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**Pyrazolyl substituted carbonic acid derivatives as modulators of the prostacyclin (PGI<sub>2</sub>) receptor useful for the treatment of disorders related thereto**

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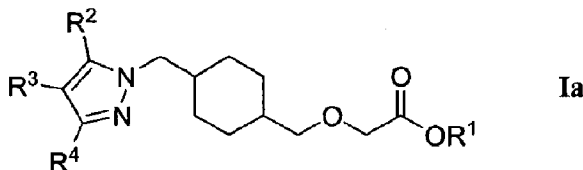
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(54) Title: PYRAZOLYL SUBSTITUTED CARBONIC ACID DERIVATIVES AS MODULATORS OF THE PROSTACYCLIN (PGI<sub>2</sub>) RECEPTOR USEFUL FOR THE TREATMENT OF DISORDERS RELATED THERETO



(57) Abstract: Pyrazole derivatives of Formula Ia and pharmaceutical compositions thereof that modulate the activity of the PGI<sub>2</sub> receptor. Compounds of the present invention and pharmaceutical compositions thereof are directed to methods useful in the treatment of: pulmonary arterial hypertension (PAH) and related disorders; platelet aggregation; coronary artery disease; myocardial infarction; transient ischemic attack; angina; stroke; ischemia-reperfusion injury; restenosis; atrial fibrillation; blood clot formation in an angioplasty or coronary bypass surgery individual or in an individual suffering from atrial fibrillation; atherosclerosis; atherothrombosis; asthma or a symptom thereof; a diabetic-related disorder such as diabetic peripheral neuropathy, diabetic nephropathy or diabetic retinopathy; glaucoma or other disease of the eye with abnormal intraocular pressure; hypertension; inflammation; psoriasis; psoriatic arthritis; rheumatoid arthritis; Crohn's disease; transplant rejection; multiple sclerosis; systemic lupus erythematosus (SLE); ulcerative colitis; ischemia-reperfusion injury; restenosis; atherosclerosis; acne; type 1 diabetes; type 2 diabetes; sepsis; and chronic obstructive pulmonary disorder (COPD).

PYRAZOLYL SUBSTITUTED CARBONIC ACID DERIVATIVES AS MODULATORS OF THE PROSTACYCLIN (PGI<sub>2</sub>) RECEPTOR USEFUL FOR THE TREATMENT OF DISORDERS RELATED THERETO

### FIELD OF THE INVENTION

5           The present invention relates to certain compounds of Formula **Ia** and pharmaceutical compositions thereof that modulate the activity of the PGI<sub>2</sub> receptor. Compounds of the present invention and pharmaceutical compositions thereof are directed to methods useful in the treatment of: pulmonary arterial hypertension (PAH); idiopathic PAH; familial PAH; PAH associated with: a collagen vascular disease, a congenital heart disease, portal hypertension, HIV  
10   infection, ingestion of a drug or toxin, hereditary hemorrhagic telangiectasia, splenectomy, pulmonary veno-occlusive disease (PVOD) or pulmonary capillary hemangiomatosis (PCH); PAH with significant venous or capillary involvement; platelet aggregation; coronary artery disease; myocardial infarction; transient ischemic attack; angina; stroke; ischemia-reperfusion injury; restenosis; atrial fibrillation; blood clot formation in an angioplasty or coronary bypass  
15   surgery individual or in an individual suffering from atrial fibrillation; atherothrombosis; asthma or a symptom thereof; a diabetic-related disorder such as diabetic peripheral neuropathy, diabetic nephropathy or diabetic retinopathy; glaucoma or other disease of the eye with abnormal intraocular pressure; hypertension; inflammation; psoriasis; psoriatic arthritis; rheumatoid arthritis; Crohn's disease; transplant rejection; multiple sclerosis; systemic lupus  
20   erythematosus (SLE); ulcerative colitis; atherosclerosis; acne; type 1 diabetes; type 2 diabetes; sepsis; and chronic obstructive pulmonary disorder (COPD).

### BACKGROUND OF THE INVENTION

          Prostacyclin (PGI<sub>2</sub>) is a lipid molecule derived from arachidonic acid through the  
25   cyclooxygenase pathway. It is a potent vasodilator, antiproliferative, anti-thrombotic and antiplatelet agent that mediates its effects as an agonist of a G protein-coupled receptor (PGI<sub>2</sub> receptor; *e.g.*, human PGI<sub>2</sub> receptor, GenBank® Accession No. NP\_000951 and alleles thereof). It is known that the binding of PGI<sub>2</sub> (or other such agonist) to the PGI<sub>2</sub> receptor leads to coupling with the G<sub>s</sub> protein and increases intracellular cAMP levels. (See, *e.g.*, Zhang *et al.*,  
30   Arch. Biochem. Biophys., 2006, 454:80-88.)

          Pulmonary arterial hypertension (PAH) is a life-threatening disease characterized by a progressive pulmonary vasculopathy leading to right ventricular hypertrophy. Right heart failure occurs if left untreated. Prostacyclin, which has vasodilatory and antiproliferative effects on the pulmonary vasculature has been found to be low in patients with PAH compared with normal  
35   controls. Exogenous administration of prostacyclin or an analog of prostacyclin (*i.e.*, an agonist of the PGI<sub>2</sub> receptor) has become an important strategy in the treatment of PAH. (See, *e.g.*, Tuder *et al.*, Am. J. Respir. Crit. Care. Med., 1999, 159:1925-1932; Humbert *et al.*, J. Am. Coll.

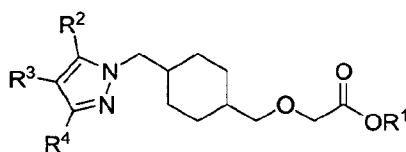
Cardiol., 2004, 43:13S-24S; Rosenzweig, Expert Opin. Emerging Drugs, 2006, 11:609-619; McLaughlin *et al.*, Circulation, 2006, 114:1417-1431; Rosenkranz, Clin. Res. Cardiol., 2007, 96:527-541; Driscoll *et al.*, Expert Opin. Pharmacother., 2008, 9:65-81.)

Trepstinil and iloprost are FDA-approved analogs of prostacyclin which, like  
5 prostacyclin, are not orally-active. Beraprost is an orally-active analog of prostacyclin approved for the treatment of PAH in Japan, but it has failed registration for the treatment of PAH in Europe and in the US. Of the three FDA-approved drugs, prostacyclin is the best studied in PAH patients. The approximate annual cost of treating PAH with these drugs is \$25,000 to \$200,000 depending on the dose. At present, many experts consider intravenous prostacyclin to be the  
10 most reliable agent for managing the sickest PAH patients. Due to the short half-life of prostacyclin, intravenous treatment is complicated by the need for a continuous infusion. Patients are at risk for potentially fatal rebound pulmonary hypertension if the infusion is abruptly disrupted, as well as significant risk of catheter-related complications including sepsis. (See, *e.g.*, Rosenzweig, Expert Opin. Emerging Drugs, 2006, 11:609-619; Naeije *et al.*, Expert  
15 Opin. Pharmacother., 2007, 8:2247-2265; Strauss *et al.*, Clin. Chest. Med., 2007, 28:127-142; Driscoll *et al.*, Expert Opin. Pharmacother., 2008, 9:65-81.)

There is considerable interest in developing prostacyclin analogs (*i.e.*, agonists of the PGI<sub>2</sub> receptor) for use in the treatment of other diseases, such as atherothrombosis. Developing stable, orally-active analogs of prostacyclin (*i.e.*, stable, orally-active agonists of the PGI<sub>2</sub>  
20 receptor) is a rate-limiting step in achieving this goal (see, *e.g.*, Arehart *et al.*, Curr. Med. Chem., 2007, 14:2161-2169; Arehart *et al.*, Circ. Res., 2008, 102(8), 986-93, as well as in the improved management of PAH.

## SUMMARY OF THE INVENTION

25 One aspect of the present invention encompasses certain cyclohexane derivatives selected from compounds of Formula **Ia** and pharmaceutically acceptable salts, solvates and hydrates thereof:



**Ia**

wherein:

30  $R^1$  is selected from: H and C<sub>1</sub>-C<sub>6</sub> alkyl;

and

$R^2$ ,  $R^3$ , and  $R^4$  are each independently selected from: H, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfinyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfonyl, C<sub>1</sub>-C<sub>6</sub> alkylthio, aryl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl



and heteroaryl; wherein said C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfinyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfonyl, C<sub>1</sub>-C<sub>6</sub> alkylthio, aryl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl and heteroaryl are each optionally substituted with one or more groups selected from: C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfinyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfonyl, C<sub>1</sub>-C<sub>6</sub> alkylthio, aryl, amino, carboxamide, cyano, C<sub>1</sub>-C<sub>6</sub> haloalkyl, halogen and hydroxy;

or

R<sup>2</sup> and R<sup>3</sup> together with the pyrazole ring to which they are both attached to form a tricyclic heteroaryl; and R<sup>4</sup> is selected from: H, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfinyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfonyl, C<sub>1</sub>-C<sub>6</sub> alkylthio, aryl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl and heteroaryl; wherein said C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfinyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfonyl, C<sub>1</sub>-C<sub>6</sub> alkylthio, aryl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl and heteroaryl are each optionally substituted with one or more groups selected from: C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfinyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfonyl, C<sub>1</sub>-C<sub>6</sub> alkylthio, aryl, cyano, C<sub>1</sub>-C<sub>6</sub> haloalkyl, halogen and hydroxy.

One aspect of the present invention pertains to methods for the treatment of a PGI<sub>2</sub> receptor mediated disorder in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

One aspect of the present invention pertains to methods for the treatment of PAH in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

One aspect of the present invention pertains to methods for the treatment of idiopathic PAH in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

One aspect of the present invention pertains to methods for the treatment of familial PAH in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

One aspect of the present invention pertains to methods for the treatment of PAH associated with a collagen vascular disease in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

One aspect of the present invention pertains to methods for the treatment of PAH associated with a collagen vascular disease selected from: scleroderma, CREST syndrome,

systemic lupus erythematosus (SLE), rheumatoid arthritis, Takayasu's arteritis, polymyositis, and dermatomyositis in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

5           One aspect of the present invention pertains to methods for the treatment of PAH associated with a congenital heart disease in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

10           One aspect of the present invention pertains to methods for the treatment of PAH associated with a congenital heart disease selected from: atrial septic defect (ASD), ventricular septic defect (VSD) and patent ductus arteriosus in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

15           One aspect of the present invention pertains to methods for the treatment of PAH associated with portal hypertension in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

20           One aspect of the present invention pertains to methods for the treatment of PAH associated with HIV infection in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

25           One aspect of the present invention pertains to methods for the treatment of PAH associated with ingestion of a drug or toxin in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

30           One aspect of the present invention pertains to methods for the treatment of PAH associated with hereditary hemorrhagic telangiectasia in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

35           One aspect of the present invention pertains to methods for the treatment of PAH associated with splenectomy in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

          One aspect of the present invention pertains to methods for the treatment of PAH associated with significant venous or capillary involvement in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

One aspect of the present invention pertains to methods for the treatment of PAH associated with pulmonary veno-occlusive disease (PVOD) in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

5        One aspect of the present invention pertains to methods for the treatment of PAH associated with pulmonary capillary hemangiomatosis (PCH) in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

10        One aspect of the present invention pertains to methods for the treatment of platelet aggregation in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

15        One aspect of the present invention pertains to methods for the treatment of: coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke, ischemia-reperfusion injury, restenosis or atrial fibrillation in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

20        One aspect of the present invention pertains to methods for the treatment of blood clot formation in an angioplasty or coronary bypass surgery individual comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

25        One aspect of the present invention pertains to methods for the treatment of blood clot formation in an individual suffering from atrial fibrillation comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

30        One aspect of the present invention pertains to methods for the treatment of atherosclerosis in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

35        One aspect of the present invention pertains to methods for the treatment of atherothrombosis in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

One aspect of the present invention pertains to methods for the treatment of asthma in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

One aspect of the present invention pertains to methods for the treatment of a symptom of asthma in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

5           One aspect of the present invention pertains to methods for the treatment of a diabetic-related disorder in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

10           One aspect of the present invention pertains to methods for the treatment of diabetic peripheral neuropathy in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

15           One aspect of the present invention pertains to methods for the treatment of diabetic nephropathy in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

20           One aspect of the present invention pertains to methods for the treatment of diabetic retinopathy in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

One aspect of the present invention pertains to methods for the treatment of glaucoma or other disease of the eye with abnormal intraocular pressure in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

25           One aspect of the present invention pertains to methods for the treatment of hypertension in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

30           One aspect of the present invention pertains to methods for the treatment of hypertension intended to confer protection against cerebral ischemia in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

35           One aspect of the present invention pertains to methods for the treatment of inflammation in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

One aspect of the present invention pertains to methods for the treatment of an inflammatory disease in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

5           One aspect of the present invention pertains to methods for the treatment of an inflammatory disease selected from: psoriasis, psoriatic arthritis, rheumatoid arthritis, Crohn's disease, transplant rejection, multiple sclerosis, systemic lupus erythematosus (SLE), ulcerative colitis, ischemia-reperfusion injury, restenosis, atherosclerosis, acne, type 1 diabetes, type 2 diabetes, sepsis, chronic obstructive pulmonary disorder (COPD) and asthma in an individual,  
10           comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

One aspect of the present invention pertains to methods of modulating the activity of a PGI<sub>2</sub> receptor by contacting the receptor with a compound of the present invention.

One aspect of the present invention pertains to methods of agonizing a PGI<sub>2</sub> receptor by  
15           contacting the receptor with a compound of the present invention.

One aspect of the present invention pertains to methods for the treatment of PAH selected from: idiopathic PAH; familial PAH; PAH associated with a collagen vascular disease selected from: scleroderma, CREST syndrome, systemic lupus erythematosus (SLE), rheumatoid arthritis, Takayasu's arteritis, polymyositis, and dermatomyositis; PAH associated  
20           with a congenital heart disease selected from: atrial septic defect (ASD), ventricular septic defect (VSD) and patent ductus arteriosus in an individual; PAH associated with portal hypertension; PAH associated with HIV infection; PAH associated with ingestion of a drug or toxin; PAH associated with hereditary hemorrhagic telangiectasia; PAH associated with splenectomy; PAH associated with significant venous or capillary involvement; PAH associated  
25           with pulmonary veno-occlusive disease (PVOD); and PAH associated with pulmonary capillary hemangiomatosis (PCH) in an individual comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

One aspect of the present invention pertains to methods for the treatment of a disorder  
30           selected from: platelet aggregation, coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke, ischemia-reperfusion injury, restenosis, atrial fibrillation, blood clot formation, atherosclerosis, atherothrombosis, asthma, a symptom of asthma, a diabetic-related disorder, diabetic peripheral neuropathy, diabetic nephropathy, diabetic retinopathy, glaucoma or other disease of the eye with abnormal intraocular pressure, hypertension,  
35           inflammation, psoriasis, psoriatic arthritis, rheumatoid arthritis, Crohn's disease, transplant rejection, multiple sclerosis, systemic lupus erythematosus (SLE), ulcerative colitis, ischemia-reperfusion injury, restenosis, atherosclerosis, acne, type 1 diabetes, type 2 diabetes, sepsis and

chronic obstructive pulmonary disorder (COPD) in an individual comprising administering to said individual in need thereof, a therapeutically effective amount of a compound of the present invention or a pharmaceutical composition thereof.

5 One aspect of the present invention pertains to the use of a compound of the present invention in the manufacture of a medicament for the treatment of a PGI2 receptor mediated disorder.

One aspect of the present invention pertains to the use of a compound of the present invention in the manufacture of a medicament for the treatment of PAH.

10 One aspect of the present invention pertains to the use of a compound of the present invention in the manufacture of a medicament for the treatment of idiopathic PAH.

One aspect of the present invention pertains to the use of a compound of the present invention in the manufacture of a medicament for the treatment of familial PAH.

15 One aspect of the present invention pertains to the use of a compound of the present invention in the manufacture of a medicament for the treatment of PAH associated with collagen vascular disease.

One aspect of the present invention pertains to the use of a compound of the present invention in the manufacture of a medicament for the treatment of PAH associated with a collagen vascular disease selected from: scleroderma, CREST syndrome, systemic lupus erythematosus (SLE), rheumatoid arthritis, Takayasu's arteritis, polymyositis, and  
20 dermatomyositis.

One aspect of the present invention pertains to the use of a compound of the present invention in the manufacture of a medicament for the treatment of PAH associated with a congenital heart disease.

25 One aspect of the present invention pertains to the use of a compound of the present invention in the manufacture of a medicament for the treatment of PAH associated with a congenital heart disease selected from: atrial septic defect (ASD), ventricular septic defect (VSD) and patent ductus arteriosus.

One aspect of the present invention pertains to the use of a compound of the present invention in the manufacture of a medicament for the treatment of PAH associated with portal  
30 hypertension.

One aspect of the present invention pertains to the use of a compound of the present invention in the manufacture of a medicament for the treatment of PAH associated with HIV infection.

35 One aspect of the present invention pertains to the use of a compound of the present invention in the manufacture of a medicament for the treatment of PAH associated with ingestion of a drug or toxin.

One aspect of the present invention pertains to the use of a compound of the present invention in the manufacture of a medicament for the treatment of PAH associated with hereditary hemorrhagic telangiectasia.

5 One aspect of the present invention pertains to the use of a compound of the present invention in the manufacture of a medicament for the treatment of PAH associated with splenectomy.

One aspect of the present invention pertains to the use of a compound of the present invention in the manufacture of a medicament for the treatment of PAH associated with significant venous or capillary involvement.

10 One aspect of the present invention pertains to the use of a compound of the present invention in the manufacture of a medicament for the treatment of PAH associated with pulmonary veno-occlusive disease (PVOD).

15 One aspect of the present invention pertains to the use of a compound of the present invention in the manufacture of a medicament for the treatment of PAH associated with pulmonary capillary hemangiomatosis (PCH).

One aspect of the present invention pertains to the use of a compound of the present invention in the manufacture of a medicament for the treatment of platelet aggregation.

20 One aspect of the present invention pertains to the use of a compound of the present invention in the manufacture of a medicament for the treatment of a PGI<sub>2</sub> receptor mediated disorder selected from: coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke, ischemia-reperfusion injury, restenosis and atrial fibrillation.

One aspect of the present invention pertains to the use of a compound of the present invention in the manufacture of a medicament for the treatment of blood clot formation in an angioplasty or coronary bypass surgery individual.

25 One aspect of the present invention pertains to the use of a compound of the present invention in the manufacture of a medicament for the treatment of blood clot formation in an individual suffering from atrial fibrillation.

One aspect of the present invention pertains to the use of a compound of the present invention in the manufacture of a medicament for the treatment of atherosclerosis.

30 One aspect of the present invention pertains to the use of a compound of the present invention in the manufacture of a medicament for the treatment of atherothrombosis.

One aspect of the present invention pertains to the use of a compound of the present invention in the manufacture of a medicament for the treatment of asthma.

35 One aspect of the present invention pertains to the use of a compound of the present invention in the manufacture of a medicament for the treatment of a symptom of asthma.

One aspect of the present invention pertains to the use of a compound of the present invention in the manufacture of a medicament for the treatment of a diabetic-related disorder.

One aspect of the present invention pertains to the use of a compound of the present invention in the manufacture of a medicament for the treatment of diabetic peripheral neuropathy.

5 One aspect of the present invention pertains to the use of a compound of the present invention in the manufacture of a medicament for the treatment of diabetic nephropathy.

One aspect of the present invention pertains to the use of a compound of the present invention in the manufacture of a medicament for the treatment of diabetic retinopathy.

10 One aspect of the present invention pertains to the use of a compound of the present invention in the manufacture of a medicament for the treatment of glaucoma or other disease of the eye with abnormal intraocular pressure.

One aspect of the present invention pertains to the use of a compound of the present invention in the manufacture of a medicament for the treatment of hypertension.

15 One aspect of the present invention pertains to the use of a compound of the present invention in the manufacture of a medicament for the treatment of hypertension intended to confer protection against cerebral ischemia.

One aspect of the present invention pertains to the use of a compound of the present invention in the manufacture of a medicament for the treatment of inflammation.

One aspect of the present invention pertains to the use of a compound of the present invention in the manufacture of a medicament for the treatment of an inflammatory disease.

20 One aspect of the present invention pertains to the use of a compound of the present invention in the manufacture of a medicament for the treatment of an inflammatory disease selected from: psoriasis, psoriatic arthritis, rheumatoid arthritis, Crohn's disease, transplant rejection, multiple sclerosis, systemic lupus erythematosus (SLE), ulcerative colitis, ischemia-reperfusion injury, restenosis, atherosclerosis, acne, type 1 diabetes, type 2 diabetes, sepsis,  
25 chronic obstructive pulmonary disorder (COPD) and asthma.

One aspect of the present invention pertains to the use of a compound of the present invention in the manufacture of a medicament for modulating the activity of a PGI<sub>2</sub> receptor.

One aspect of the present invention pertains to the use of a compound of the present invention in the manufacture of a medicament for agonizing a PGI<sub>2</sub> receptor.

30 One aspect of the present invention pertains to the use of a compound of the present invention in the manufacture of a medicament for the treatment of PAH selected from: idiopathic PAH; familial PAH; PAH associated with a collagen vascular disease selected from: scleroderma, CREST syndrome, systemic lupus erythematosus (SLE), rheumatoid arthritis, Takayasu's arteritis, polymyositis, and dermatomyositis; PAH associated with a congenital heart  
35 disease selected from: atrial septic defect (ASD), ventricular septic defect (VSD) and patent ductus arteriosus in an individual; PAH associated with portal hypertension; PAH associated with HIV infection; PAH associated with ingestion of a drug or toxin; PAH associated with



hereditary hemorrhagic telangiectasia; PAH associated with splenectomy; PAH associated with significant venous or capillary involvement; PAH associated with pulmonary veno-occlusive disease (PVOD); and PAH associated with pulmonary capillary hemangiomatosis (PCH).

One aspect of the present invention pertains to the use of a compound of the present invention in the manufacture of a medicament for the treatment of a disorder selected from: platelet aggregation, coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke, ischemia-reperfusion injury, restenosis, atrial fibrillation, blood clot formation, atherosclerosis, atherothrombosis, asthma, a symptom of asthma, a diabetic-related disorder, diabetic peripheral neuropathy, diabetic nephropathy, diabetic retinopathy, glaucoma or other disease of the eye with abnormal intraocular pressure, hypertension, inflammation, psoriasis, psoriatic arthritis, rheumatoid arthritis, Crohn's disease, transplant rejection, multiple sclerosis, systemic lupus erythematosus (SLE), ulcerative colitis, ischemia-reperfusion injury, restenosis, atherosclerosis, acne, type 1 diabetes, type 2 diabetes, sepsis and chronic obstructive pulmonary disorder (COPD).

One aspect of the present invention pertains to compounds of the present invention for use in a method of treatment of the human or animal body by therapy.

One aspect of the present invention pertains to compounds of the present invention for use in a method of treatment of a PGI<sub>2</sub> receptor mediated disorder.

One aspect of the present invention pertains to compounds of the present invention for use in a method of treatment of PAH.

One aspect of the present invention pertains to compounds of the present invention for use in a method of treatment of idiopathic PAH.

One aspect of the present invention pertains to compounds of the present invention for use in a method of treatment of familial PAH

One aspect of the present invention pertains to compounds of the present invention for use in a method of treatment of PAH associated with a collagen vascular disease.

One aspect of the present invention pertains to compounds of the present invention for use in a method of treatment of PAH associated with a collagen vascular disease selected from: scleroderma, CREST syndrome, systemic lupus erythematosus (SLE), rheumatoid arthritis, Takayasu's arteritis, polymyositis, and dermatomyositis.

One aspect of the present invention pertains to compounds of the present invention for use in a method of treatment of PAH associated with a congenital heart disease.

One aspect of the present invention pertains to compounds of the present invention for use in a method of treatment of PAH associated with a congenital heart disease selected from: atrial septic defect (ASD), ventricular septic defect (VSD) and patent ductus arteriosus.

One aspect of the present invention pertains to compounds of the present invention for use in a method of treatment of PAH associated with portal hypertension.

One aspect of the present invention pertains to compounds of the present invention for use in a method of treatment of PAH associated with HIV infection.

One aspect of the present invention pertains to compounds of the present invention for use in a method of treatment of PAH associated with ingestion of a drug or toxin.

5        One aspect of the present invention pertains to compounds of the present invention for use in a method of treatment of PAH associated with hereditary hemorrhagic telangiectasia.

One aspect of the present invention pertains to compounds of the present invention for use in a method of treatment of PAH associated with splenectomy.

10       One aspect of the present invention pertains to compounds of the present invention for use in a method of treatment of PAH associated with significant venous or capillary involvement.

One aspect of the present invention pertains to compounds of the present invention for use in a method of treatment of PAH associated with pulmonary veno-occlusive disease (PVOD).

15       One aspect of the present invention pertains to compounds of the present invention for use in a method of treatment of PAH associated with pulmonary capillary hemangiomatosis (PCH).

One aspect of the present invention pertains to compounds of the present invention for use in a method of treatment of platelet aggregation.

20       One aspect of the present invention pertains to compounds of the present invention for use in a method of treatment of: coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke, ischemia-reperfusion injury, restenosis or atrial fibrillation.

25       One aspect of the present invention pertains to compounds of the present invention for use in a method of treatment of blood clot formation in an angioplasty or coronary bypass surgery individual.

One aspect of the present invention pertains to compounds of the present invention for use in a method of treatment of blood clot formation in an individual suffering from atrial fibrillation.

30       One aspect of the present invention pertains to compounds of the present invention for use in a method of treatment of atherosclerosis.

One aspect of the present invention pertains to compounds of the present invention for use in a method of treatment of atherothrombosis.

One aspect of the present invention pertains to compounds of the present invention for use in a method of treatment of asthma.

35       One aspect of the present invention pertains to compounds of the present invention for use in a method of treatment of a symptom of asthma.

One aspect of the present invention pertains to compounds of the present invention for use in a method of treatment of a diabetic-related disorder.

One aspect of the present invention pertains to compounds of the present invention for use in a method of treatment of diabetic peripheral neuropathy.

5 One aspect of the present invention pertains to compounds of the present invention for use in a method of treatment of diabetic nephropathy.

One aspect of the present invention pertains to compounds of the present invention for use in a method of treatment of diabetic retinopathy.

10 One aspect of the present invention pertains to compounds of the present invention for use in a method of treatment of glaucoma or other disease of the eye with abnormal intraocular pressure.

One aspect of the present invention pertains to compounds of the present invention for use in a method of treatment of hypertension.

15 One aspect of the present invention pertains to compounds of the present invention for use in a method of treatment of hypertension intended to confer protection against cerebral ischemia.

One aspect of the present invention pertains to compounds of the present invention for use in a method of treatment of inflammation.

20 One aspect of the present invention pertains to compounds of the present invention for use in a method of treatment of an inflammatory disease.

One aspect of the present invention pertains to compounds of the present invention for use in a method of treatment of an inflammatory disease selected from: psoriasis, psoriatic arthritis, rheumatoid arthritis, Crohn's disease, transplant rejection, multiple sclerosis, systemic lupus erythematosus (SLE), ulcerative colitis, ischemia-reperfusion injury, restenosis, atherosclerosis, acne, type 1 diabetes, type 2 diabetes, sepsis, chronic obstructive pulmonary disorder (COPD) and asthma.

One aspect of the present invention pertains to compounds of the present invention for use in a method of modulating the activity of a PGI<sub>2</sub> receptor.

30 One aspect of the present invention pertains to compounds of the present invention for use in a method of agonizing a PGI<sub>2</sub> receptor.

One aspect of the present invention pertains to compounds of the present invention for use in a method of treatment of PAH selected from: idiopathic PAH; familial PAH; PAH associated with a collagen vascular disease selected from: scleroderma, CREST syndrome, systemic lupus erythematosus (SLE), rheumatoid arthritis, Takayasu's arteritis, polymyositis, and dermatomyositis; PAH associated with a congenital heart disease selected from: atrial septic defect (ASD), ventricular septic defect (VSD) and patent ductus arteriosus in an individual; PAH associated with portal hypertension; PAH associated with HIV infection; PAH associated

with ingestion of a drug or toxin; PAH associated with hereditary hemorrhagic telangiectasia; PAH associated with splenectomy; PAH associated with significant venous or capillary involvement; PAH associated with pulmonary veno-occlusive disease (PVOD); and PAH associated with pulmonary capillary hemangiomatosis (PCH).

5 One aspect of the present invention pertains to compounds of the present invention for use in a method of treatment of a disorder selected from: platelet aggregation, coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke, ischemia-reperfusion injury, restenosis, atrial fibrillation, blood clot formation, atherosclerosis, atherothrombosis, asthma, a symptom of asthma, a diabetic-related disorder, diabetic peripheral neuropathy,  
10 diabetic nephropathy, diabetic retinopathy, glaucoma or other disease of the eye with abnormal intraocular pressure, hypertension, inflammation, psoriasis, psoriatic arthritis, rheumatoid arthritis, Crohn's disease, transplant rejection, multiple sclerosis, systemic lupus erythematosus (SLE), ulcerative colitis, ischemia-reperfusion injury, restenosis, atherosclerosis, acne, type 1 diabetes, type 2 diabetes, sepsis and chronic obstructive pulmonary disorder (COPD).

15 One aspect of the present invention pertains to compounds for preparing a composition comprising admixing a compound of the present invention and a pharmaceutically acceptable carrier.

These and other aspects of the invention disclosed herein will be set forth in greater detail as the patent disclosure proceeds.

20

#### BRIEF DESCRIPTION OF THE DRAWINGS

**Figure 1** shows the results of an experiment which measured the ability of Compound 14 to inhibit the right ventricle hypertrophic response to MCT-induced pulmonary arterial hypertension in rat.

25 **Figure 2** shows the results of an experiment which measured the ability of Compound 31 to inhibit the right ventricle hypertrophic response to MCT-induced pulmonary arterial hypertension in rat.

**Figure 3** depicts a general method for the preparation of compounds of the present invention. First, cyclohexane-1,4-dicarboxylic acid is esterified and then reduced to give the  
30 corresponding diol. The diol is mono-alkylated with *tert*-butyl bromoacetate and the free hydroxyl is activated as a sulfonate ester. Coupling of the sulfonate ester with a pyrazole followed by acid hydrolysis affords compounds of Formula Ia.

**Figure 4** depicts an alternative general method for the preparation of compounds of the present invention. In this method the sulfonate ester shown in **Figure 3** is reacted in the presence  
35 of a base with a pyrazole bearing a halogen at a position equivalent to R<sup>3</sup>. The product then undergoes a Suzuki coupling with a boronic acid derivative and then acid hydrolysis affords compounds of Formula Ia.

**Figure 5** depicts a method of preparing an intermediate useful in the synthesis of certain dihydroxy compounds of the present invention. First, a 3-oxobutanoyl derivative is reacted with allyl bromide in the presence of base to give a 3-oxohept-6-enoyl derivative. Reaction with hydrazine hydrate gives a 5-(but-3-enyl)-1*H*-pyrazole which is converted to the diol with AD-mix-β and then protected with 2,2-dimethoxypropane.

**Figure 6** depicts a number of methods for synthesizing intermediates useful in the preparation of compounds of the present invention. In the first of these methods, a ketone derivative is reacted with carbon disulfide in the presence of base, followed by an alkyl halide, followed by hydrazine hydrate to give a 2-(alkylthio)-substituted pyrazole intermediate. In the second of these methods, a methyl ketone is reacted with carbon disulfide in the presence of base, followed by an alkyl halide, followed by hydrazine hydrate to give a 2-(alkylthio)-substituted pyrazole intermediate in which R<sup>3</sup> is hydrogen. This may then be converted to the corresponding iodide by treatment with sodium iodide and base. In the third of these methods, a 3-oxo-3-propoxypropanoyl derivative is treated with hydrazine hydrate to afford a 1*H*-pyrazol-5(4*H*)-one. Mitsunobu reaction followed by bromination affords 2-alkoxy-3-bromo pyrazole intermediates. In the fourth of these methods, a methyl ketone is reacted with an acid chloride in the presence of base, then hydrazine hydrate and finally bromine or sodium iodide in the presence of base to give 3-halo-2-alkyl- or 3-halo-2-cycloalkyl-pyrazole intermediates.

**Figure 7** depicts three methods for the synthesis of certain intermediates useful in the preparation of compounds of the present invention. In the first of these methods a ketone derivative is reacted first with carbon disulfide and methylene bromide in the presence of base, then hydrazine hydrate and finally bromo acetonitrile to give a 2-(cyanomethylthio)-pyrazole intermediate. In the second of these methods, a ketone derivative is converted to a 2-(tetrahydro-2*H*-pyran-2-yloxy)ethylthio-pyrazole. The transformation may be accomplished by either reaction with carbon disulfide, methylene bromide and base, followed by hydrazine hydrate, followed by 2-(2-bromoethoxy)tetrahydro-2*H*-pyran, or reaction with carbon disulfide and base, then 2-(2-bromoethoxy)tetrahydro-2*H*-pyran and finally hydrazine hydrate. The third method describes the preparation of substituted 4,5-dihydro-3*H*-benzo[e]indazole and 1,8-dihydroindeno[2,1-*c*]pyrazole intermediates from 3,4-dihydronaphthalen-2(1*H*)-one or 1*H*-inden-2(3*H*)-one respectively via reaction with an acid chloride in the presence of base followed by reaction with hydrazine hydrate.

**Figure 8** depicts a method of preparing certain di-substituted compounds of the present invention. β-Keto aldehydes derived from chalcone epoxides by Lewis acid-catalyzed rearrangement are reacted with hydrazine hydrate to give di-substituted pyrazoles. These are reacted with the sulfonate esters described in **Figure 3** to give di-substituted compounds of Formula Ia as mixtures of regioisomers.

**Figure 9** depicts a general method of preparing compounds of the present invention. Starting from 4-(hydroxymethyl)cyclohexanecarboxylic acid the acid group is esterified and the alcohol is protected with a benzyl group. Next, the ester is reduced and reoxidized to the aldehyde. The aldehyde undergoes reductive amination to give a Boc-protected hydrazine which is subsequently deprotected and then coupled with an aldehyde to give an imine. This is reacted with a nitroalkene in the presence of base to form the pyrazole ring. Next, the benzyl protecting group is removed reductively, the alcohol is reacted with *tert*-butyl 2-diazoacetate in the presence of rhodium acetate to give the 2-*tert*-butoxy-2-oxoethoxy derivative which is finally converted to a compound of Formula **Ia** by treatment with acid.

## DETAILED DESCRIPTION OF THE INVENTION

### DEFINITIONS

For clarity and consistency, the following definitions will be used throughout this patent document.

The term **"agonists"** is intended to mean moieties that interact and activate the receptor, such as, the PGI<sub>2</sub> receptor and initiate a physiological or pharmacological response characteristic of that receptor. For example, when moieties activate the intracellular response upon binding to the receptor, or enhance GTP binding to membranes.

The term **"contact or contacting"** is intended to mean bringing the indicated moieties together, whether in an *in vitro* system or an *in vivo* system. Thus, "contacting" a PGI<sub>2</sub> receptor with a compound of the invention includes the administration of a compound of the present invention to an individual, preferably a human, having a PGI<sub>2</sub> receptor, as well as, for example, introducing a compound of the invention into a sample containing a cellular or more purified preparation containing a PGI<sub>2</sub> receptor.

The term **"hydrate"** as used herein means a compound of the invention or a salt thereof, that further includes a stoichiometric or non-stoichiometric amount of water bound by non-covalent intermolecular forces.

The terms **"including"** and **"such as"** are illustrative and not limitative.

The term **"in need of treatment"** and the term **"in need thereof,"** when referring to treatment are used interchangeably to mean a judgment made by a caregiver (*e.g.* physician, nurse, nurse practitioner, etc. in the case of humans; veterinarian in the case of animals, including non-human mammals) that an individual or animal requires or will benefit from treatment. This judgment is made based on a variety of factors that are in the realm of a caregiver's expertise, but that includes the knowledge that the individual or animal is ill, or will become ill, as the result of a disease, condition or disorder that is treatable by the compounds of the invention. Accordingly, the compounds of the invention can be used in a protective or

preventive manner; or compounds of the invention can be used to alleviate, inhibit or ameliorate the disease, condition or disorder.

The term “**individual**” is intended to mean any animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates and most  
5 preferably humans.

The term “**modulate or modulating**” is intended to mean an increase or decrease in the amount, quality, response or effect of a particular activity, function or molecule.

The term “**pharmaceutical composition**” is intended to mean a composition comprising at least one active ingredient; including but not limited to, salts, solvates and hydrates of  
10 compounds of the present invention; whereby the composition is amenable to investigation for a specified, efficacious outcome in a mammal (for example, without limitation, a human). Those of ordinary skill in the art will understand and appreciate the techniques appropriate for determining whether an active ingredient has a desired efficacious outcome based upon the needs of the artisan.

The term “**solvate**” as used herein means a compound of the invention or a salt, thereof,  
15 that further includes a stoichiometric or non-stoichiometric amount of a solvent bound by non-covalent intermolecular forces. Preferred solvents are volatile, non-toxic, and/or acceptable for administration to humans in trace amounts.

The term “**therapeutically effective amount**” is intended to mean the amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue,  
20 system, animal, individual or human that is being sought by a researcher, veterinarian, medical doctor or other clinician or caregiver; or in an individual, which includes one or more of the following:

(1) Preventing the disease; for example, preventing a disease, condition or disorder in an individual that may be predisposed to the disease, condition or disorder but does not yet  
25 experience or display the pathology or symptomatology of the disease;

(2) Inhibiting the disease; for example, inhibiting a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (*i.e.*, arresting further development of the pathology and/or symptomatology); and

30 (3) Ameliorating the disease; for example, ameliorating a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (*i.e.*, reversing the pathology and/or symptomatology).

#### **CHEMICAL GROUP, MOIETY OR RADICAL**

35 The term “**AD-mix- $\alpha$** ” is intended to mean a mixture of potassium osmate, potassium ferricyanide, potassium carbonate and hydroquinine 1,4-phthalazinediyl diether.

The term “**AD-mix-β**” is intended to mean a mixture of potassium osmate, potassium ferricyanide, potassium carbonate and hydroquinidine 1,4-phthalazinediyl diether.

The term “**C<sub>1</sub>-C<sub>6</sub> alkoxy**” is intended to mean a C<sub>1</sub>-C<sub>6</sub> alkyl radical, as defined herein, attached directly to an oxygen atom. Some embodiments are 1 to 5 carbons; some embodiments are 1 to 4 carbons; some embodiments are 1 to 3 carbons; and some embodiments are 1 or 2 carbons. Examples include methoxy, ethoxy, *n*-propoxy, isopropoxy, *n*-butoxy, *t*-butoxy, isobutoxy, *sec*-butoxy and the like.

The term “**C<sub>1</sub>-C<sub>6</sub> alkyl**” is intended to mean a straight or branched carbon radical containing 1 to 6 carbons. Some embodiments are 1 to 5 carbons. Some embodiments are 1 to 4 carbons. Some embodiments are 1 to 3 carbons. Some embodiments are 1 or 2 carbons. Some embodiments are 1 carbon. Examples of an alkyl include, but are not limited to, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl, isobutyl, *t*-butyl, pentyl, isopentyl, *t*-pentyl, *neo*-pentyl, 1-methylbutyl [*i.e.*, -CH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>], 2-methylbutyl [*i.e.*, -CH<sub>2</sub>CH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>3</sub>], *n*-hexyl and the like.

The term “**C<sub>1</sub>-C<sub>6</sub> alkylsulfinyl**” is intended to mean a C<sub>1</sub>-C<sub>6</sub> alkyl radical attached to the sulfur of a sulfoxide radical having the formula: -S(O)- wherein the alkyl radical has the same definition as described herein. Examples include, but are not limited to, methylsulfinyl, ethylsulfinyl, *n*-propylsulfinyl, isopropylsulfinyl, *n*-butylsulfinyl, *sec*-butylsulfinyl, isobutylsulfinyl, *t*-butylsulfinyl, and the like.

The term “**C<sub>1</sub>-C<sub>6</sub> alkylsulfonyl**” is intended to mean a C<sub>1</sub>-C<sub>6</sub> alkyl radical attached to the sulfur of a sulfone radical having the formula: -S(O)<sub>2</sub>- wherein the alkyl radical has the same definition as described herein. Examples include, but are not limited to, methylsulfonyl, ethylsulfonyl, *n*-propylsulfonyl, isopropylsulfonyl, *n*-butylsulfonyl, *sec*-butylsulfonyl, isobutylsulfonyl, *t*-butylsulfonyl, and the like.

The term “**C<sub>1</sub>-C<sub>6</sub> alkylthio**” is intended to mean a C<sub>1</sub>-C<sub>6</sub> alkyl radical attached to a sulfur atom (*i.e.*, -S-) wherein the alkyl radical has the same definition as described herein. Examples include, but are not limited to, methylsulfanyl (*i.e.*, CH<sub>3</sub>S-), ethylsulfanyl, *n*-propylsulfanyl, *iso*-propylsulfanyl, *n*-butylsulfanyl, *sec*-butylsulfanyl, *iso*-butylsulfanyl, *t*-butylsulfanyl, and the like.

The term “**amino**” is intended to mean the group -NH<sub>2</sub>.

The term “**aryl**” is intended to mean an aromatic ring radical containing 6 to 10 ring carbons. Examples include phenyl and naphthyl. In some embodiments aryl is intended to mean phenyl.

The term “**carboxamide**” is intended to mean the group -CONH<sub>2</sub>.

The term “**cyano**” is intended to mean the group -CN.

The term “**C<sub>3</sub>-C<sub>7</sub> cycloalkyl**” is intended to mean a saturated ring radical containing 3 to 7 carbons. Some embodiments contain 3 to 6 carbons. Some embodiments contain 3 to 5



carbons Some embodiments contain 5 to 7 carbons. Some embodiments contain 3 to 4 carbons. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and the like.

The term “**C<sub>1</sub>-C<sub>6</sub> haloalkyl**” is intended to mean a C<sub>1</sub>-C<sub>6</sub> alkyl group, defined herein, wherein the alkyl is substituted with one halogen up to fully substituted and a fully substituted C<sub>1</sub>-C<sub>6</sub> haloalkyl can be represented by the formula C<sub>n</sub>L<sub>2n+1</sub> wherein L is a halogen and “n” is 1, 2, 3, 4, 5 or 6. When more than one halogen is present then they may be the same or different and selected from the group consisting of F, Cl, Br and I, preferably F. Some embodiments are 1 to 5 carbons, some embodiments are 1 to 4 carbons, some embodiments are 1 to 3 carbons, and some embodiments are 1 or 2 carbons. Examples of haloalkyl groups include, but are not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, chlorodifluoromethyl, 2,2,2-trifluoroethyl, pentafluoroethyl and the like.

The term “**halogen**” or “**halo**” is intended to mean to a fluoro, chloro, bromo or iodo group.

The term “**heteroaryl**” is intended to mean an aromatic ring system containing 5 to 14 aromatic ring atoms that may be a single ring, two fused rings or three fused rings wherein at least one aromatic ring atom is a heteroatom selected from, but not limited to, the group consisting of O, S and N wherein the N can be optionally substituted with H, C<sub>1</sub>-C<sub>4</sub> acyl or C<sub>1</sub>-C<sub>4</sub> alkyl. Some embodiments contain 5 to 6 ring atoms for example furanyl, thienyl, pyrrolyl, imidazolyl, oxazolyl, thiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl and the like. Some embodiments contain 8 to 14 ring atoms for example carbazolyl, quinoliziny, quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, triazinyl, indolyl, isoindolyl, indazolyl, indoliziny, purinyl, naphthyridinyl, pteridinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, benzoxazolyl, benzothiazolyl, 1*H*-benzimidazolyl, imidazopyridinyl, benzothienyl, benzofuranyl, isobenzofuran and the like.

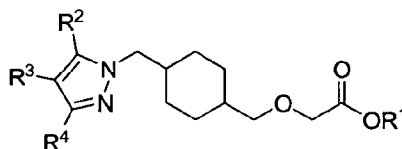
The term “**hydroxyl**” or “**hydroxy**” is intended to mean the group -OH.

The term “**MP-carbonate**” is intended to mean macroporous triethylammonium methylpolystyrene carbonate.

## 30 COMPOUNDS OF THE INVENTION:

One aspect of the present invention pertains to certain compounds as shown in Formula

**Ia:**



**Ia**

and pharmaceutically acceptable salts, solvates and hydrates thereof;  
wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> have the same definitions as described herein, *supra* and *infra*.

It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single  
5 embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable subcombination. All combinations of the embodiments pertaining to the chemical groups represented by the variables (*e.g.*, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup>) contained within the generic chemical formulae described herein, for example, **Ia**, **Ic**, **Ie**, **Ig**, **Ii**, etc., are specifically embraced by the  
10 present invention just as if each and every combination was individually explicitly recited, to the extent that such combinations embrace compounds that result in stable compounds (*i.e.*, compounds that can be isolated, characterized and tested for biological activity). In addition, all subcombinations of the chemical groups listed in the embodiments describing such variables, as well as all subcombinations of uses and medical indications described herein, are also  
15 specifically embraced by the present invention just as if each and every subcombination of chemical groups and subcombination of uses and medical indications was individually and explicitly recited herein.

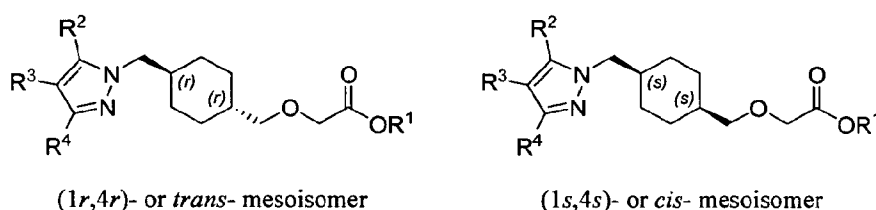
As used herein, "substituted" indicates that at least one hydrogen atom of the chemical group is replaced by a non-hydrogen substituent or group, the non-hydrogen substituent or  
20 group can be monovalent or divalent. When the substituent or group is divalent, then it is understood that this group is further substituted with another substituent or group. When a chemical group herein is "substituted" it may have up to the full valance of substitution; for example, a methyl group can be substituted by 1, 2, or 3 substituents, a methylene group can be substituted by 1 or 2 substituents, a phenyl group can be substituted by 1, 2, 3, 4, or 5  
25 substituents, a naphthyl group can be substituted by 1, 2, 3, 4, 5, 6, or 7 substituents and the like. Likewise, "substituted with one or more substituents" refers to the substitution of a group with one substituent up to the total number of substituents physically allowed by the group. Further, when a group is substituted with more than one group they can be identical or they can be different.

30 Compounds of the invention can also include tautomeric forms, such as keto-enol tautomers and the like. Tautomeric forms can be in equilibrium or sterically locked into one form by appropriate substitution. It is understood that the various tautomeric forms are within the scope of the compounds of the present invention.

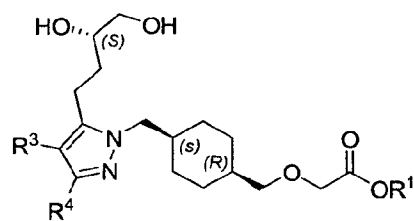
Compounds of the invention can also include all isotopes of atoms occurring in the  
35 intermediates and/or final compounds. Isotopes include those atoms having the same atomic number but different mass numbers. For example, isotopes of hydrogen include deuterium and tritium.

It is understood and appreciated that compounds of Formula **Ia** and formulae related thereto may have one or more chiral centers and therefore can exist as enantiomers and/or diastereoisomers. The invention is understood to extend to and embrace all such enantiomers, diastereoisomers and mixtures thereof, including but not limited to racemates. It is understood  
5 that compounds of Formula **Ia** and formulae used throughout this disclosure are intended to represent all individual enantiomers and mixtures thereof, unless stated or shown otherwise.

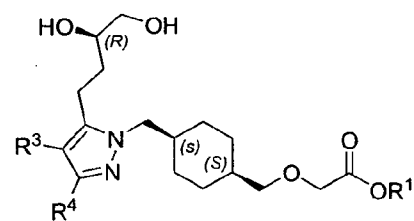
It is understood and appreciated that compounds of Formula **Ia** exist as meso isomers. Such meso isomers may be referred to as *cis* and *trans*. Certain *cis* meso isomers of compounds of Formula **Ia** are named herein using the prefix (1*s*,4*s*) and certain *trans* meso isomers of  
10 compounds of Formula **Ia** are named herein using the prefix (1*r*,4*r*) as shown below.



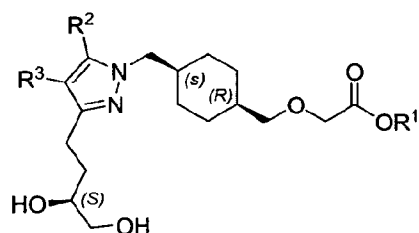
It is further understood and appreciated that certain compounds of Formula **Ia** bear a 3,4-dihydroxybutyl substituent on the pyrazole ring. When the absolute stereochemistry of the dihydroxybutyl group is (*S*) then certain *cis* compounds of Formula **Ia** are named herein using  
15 the prefix (1*R*,4*s*). When the absolute stereochemistry of the dihydroxybutyl group is (*R*) then certain *cis* compounds of Formula **Ia** are named herein using the prefix (1*S*,4*s*) as shown below.



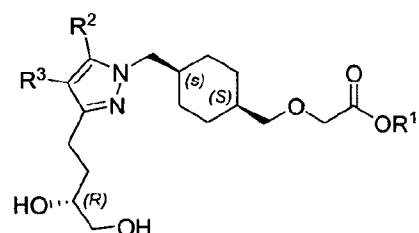
(1*R*,4*s*)- or *cis*-



(1*S*,4*s*)- or *cis*-

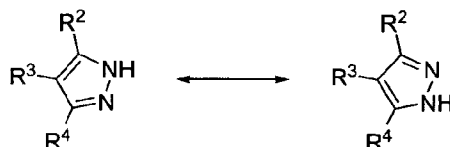


(1*R*,4*s*)- or *cis*-



(1*S*,4*s*)- or *cis*-

It is well understood and appreciated in the art that pyrazoles can exist in various  
5 tautomeric forms. Two possible tautomeric forms of certain intermediates useful in the  
preparation of compounds of the present invention are illustrated below:



It is further understood that tautomeric forms can also have corresponding nomenclature  
for each represented tautomer. The present invention includes all tautomers and the various  
10 nomenclature designations.

The Group R<sup>1</sup>:

In some embodiments, R<sup>1</sup> is selected from: H and C<sub>1</sub>-C<sub>6</sub> alkyl.

In some embodiments, R<sup>1</sup> is H.

15 In some embodiments, R<sup>1</sup> is C<sub>1</sub>-C<sub>6</sub> alkyl.

In some embodiments, R<sup>1</sup> is methyl.

The Group R<sup>2</sup>:

In some embodiments, R<sup>2</sup> is selected from: H, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfinyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfonyl, C<sub>1</sub>-C<sub>6</sub> alkylthio, aryl and C<sub>3</sub>-C<sub>7</sub> cycloalkyl; wherein said C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfinyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfonyl, C<sub>1</sub>-C<sub>6</sub> alkylthio, aryl and C<sub>3</sub>-C<sub>7</sub> cycloalkyl are each optionally substituted with one or more groups selected from: C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfinyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfonyl, C<sub>1</sub>-C<sub>6</sub> alkylthio, amino, carboxamide, cyano, halogen and hydroxy.

In some embodiments, R<sup>2</sup> is selected from: H, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfinyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfonyl, C<sub>1</sub>-C<sub>6</sub> alkylthio, aryl and C<sub>3</sub>-C<sub>7</sub> cycloalkyl; wherein said C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfinyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfonyl, C<sub>1</sub>-C<sub>6</sub> alkylthio, aryl and C<sub>3</sub>-C<sub>7</sub> cycloalkyl are each optionally substituted with one or more groups selected from: amino, carboxamide, chloro, cyano, ethoxy, fluoro, hydroxy, methoxy, methyl, methylsulfinyl, methylsulfonyl and methylthio.

In some embodiments, R<sup>2</sup> is selected from: H, butyl, cyclopropyl, ethoxy, ethyl, ethylsulfinyl, ethylthio, isopropyl, methoxy, methyl, methylsulfinyl, methylsulfonyl, methylthio, phenyl, propyl and propylthio; wherein said butyl, cyclopropyl, ethoxy, ethyl, ethylsulfinyl, ethylthio, isopropyl, methoxy, methyl, methylsulfinyl, methylsulfonyl, methylthio, phenyl, propyl and propylthio are each optionally substituted with one or more groups selected from: amino, carboxamide, chloro, cyano, ethoxy, fluoro, hydroxy, methoxy, methyl, methylsulfinyl, methylsulfonyl and methylthio.

In some embodiments, R<sup>2</sup> is selected from: H, 2-(methylsulfinyl)ethyl, 2-(methylsulfonyl)ethyl, 2-(methylthio)ethyl, 2,3-difluorophenyl, 2-aminoethylthio, 2-amino-2-oxoethoxy, 2-cyanoethyl, 2-ethoxyethylthio, 2-fluoro-4-methoxyphenyl, 2-fluorophenyl, 2-hydroxyethyl, 2-hydroxyethylsulfinyl, 2-hydroxyethylthio, 2-methoxyethyl, 2-methoxyethylthio, 3,4-difluorophenyl, 3,4-dihydroxybutyl, 3-chloro-2-fluorophenyl, 3-fluoro-5-methoxyphenyl, 3-fluorophenyl, 3-hydroxypropyl, 3-hydroxypropylthio, 3-methoxyphenyl, 4-chloro-3-fluorophenyl, 4-chlorophenyl, 4-fluorophenyl, 4-methoxyphenyl, cyanomethoxy, cyanomethylthio, cyclopropyl, ethoxy, ethyl, ethylthio, isopropyl, methyl, methylsulfinyl, methylsulfonyl, methylthio, *m*-tolyl, *n*-propyl, phenyl and trifluoromethyl.

In some embodiments, R<sup>2</sup> is selected from: H, 2-(methylsulfinyl)ethyl, 2-(methylsulfonyl)ethyl, 2-(methylthio)ethyl, 2,3-difluorophenyl, 2-aminoethylthio, 2-amino-2-oxoethoxy, 2-cyanoethyl, 2-ethoxyethylthio, 2-fluoro-4-methoxyphenyl, 2-fluorophenyl, 2-hydroxyethyl, 2-hydroxyethylsulfinyl, 2-hydroxyethylthio, 2-methoxyethyl, 2-methoxyethylthio, 3,4-difluorophenyl, 3,4-dihydroxybutyl, 3-chloro-2-fluorophenyl, 3-fluoro-5-methoxyphenyl, 3-fluorophenyl, 3-hydroxypropyl, 3-hydroxypropylthio, 3-methoxyphenyl, 4-chloro-3-fluorophenyl, 4-chlorophenyl, 4-fluorophenyl, 4-methoxyphenyl, cyanomethoxy, cyanomethylthio, cyclopropyl, ethoxy, ethyl, ethylthio, isopropyl, methyl, methylsulfinyl, methylsulfonyl, methylthio, *m*-tolyl, *n*-propyl, phenyl, *p*-tolyl and trifluoromethyl.

- In some embodiments,  $R^2$  is H.
- In some embodiments,  $R^2$  is 2-(methylsulfinyl)ethyl.
- In some embodiments,  $R^2$  is 2-(methylsulfonyl)ethyl.
- In some embodiments,  $R^2$  is 2-(methylthio)ethyl.
- 5 In some embodiments,  $R^2$  is 2,3-difluorophenyl.
- In some embodiments,  $R^2$  is 2-aminoethylthio.
- In some embodiments,  $R^2$  is 2-amino-2-oxoethoxy.
- In some embodiments,  $R^2$  is 2-cyanoethyl.
- In some embodiments,  $R^2$  is 2-ethoxyethylthio.
- 10 In some embodiments,  $R^2$  is 2-fluoro-4-methoxyphenyl.
- In some embodiments,  $R^2$  is 2-fluorophenyl.
- In some embodiments,  $R^2$  is 2-hydroxyethyl.
- In some embodiments,  $R^2$  is 2-hydroxyethylsulfinyl.
- In some embodiments,  $R^2$  is 2-hydroxyethylthio.
- 15 In some embodiments,  $R^2$  is 2-methoxyethyl.
- In some embodiments,  $R^2$  is 2-methoxyethylthio.
- In some embodiments,  $R^2$  is 3,4-difluorophenyl.
- In some embodiments,  $R^2$  is 3,4-dihydroxybutyl.
- In some embodiments,  $R^2$  is 3-chloro-2-fluorophenyl.
- 20 In some embodiments,  $R^2$  is 3-fluoro-5-methoxyphenyl.
- In some embodiments,  $R^2$  is 3-fluorophenyl.
- In some embodiments,  $R^2$  is 3-hydroxypropyl.
- In some embodiments,  $R^2$  is 3-hydroxypropylthio.
- In some embodiments,  $R^2$  is 3-methoxyphenyl.
- 25 In some embodiments,  $R^2$  is 4-chloro-3-fluorophenyl.
- In some embodiments,  $R^2$  is 4-chlorophenyl.
- In some embodiments,  $R^2$  is 4-fluorophenyl.
- In some embodiments,  $R^2$  is 4-chlorophenyl.
- In some embodiments,  $R^2$  is 4-chlorophenyl.
- 30 In some embodiments,  $R^2$  is 4-methoxyphenyl.
- In some embodiments,  $R^2$  is cyanomethoxy.
- In some embodiments,  $R^2$  is 4-chlorophenyl.
- In some embodiments,  $R^2$  is cyanomethylthio.
- In some embodiments,  $R^2$  is cyclopropyl.
- 35 In some embodiments,  $R^2$  is ethoxy.
- In some embodiments,  $R^2$  is ethyl.
- In some embodiments,  $R^2$  is ethylthio.

- In some embodiments, R<sup>2</sup> is isopropyl.  
In some embodiments, R<sup>2</sup> is methyl.  
In some embodiments, R<sup>2</sup> is methylsulfinyl.  
In some embodiments, R<sup>2</sup> is methyl.  
5 In some embodiments, R<sup>2</sup> is methylsulfonyl.  
In some embodiments, R<sup>2</sup> is methylthio.  
In some embodiments, R<sup>2</sup> is *m*-tolyl.  
In some embodiments, R<sup>2</sup> is *n*-propyl.  
In some embodiments, R<sup>2</sup> is phenyl.  
10 In some embodiments, R<sup>2</sup> is *p*-tolyl.  
In some embodiments, R<sup>2</sup> is trifluoromethyl.

The Group R<sup>3</sup>:

- In some embodiments, R<sup>3</sup> is selected from: C<sub>1</sub>-C<sub>6</sub> alkyl, aryl and heteroaryl; wherein  
15 said C<sub>1</sub>-C<sub>6</sub> alkyl, aryl and heteroaryl are each optionally substituted with one or more groups  
selected from: C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkyl, aryl, cyano, C<sub>1</sub>-C<sub>6</sub> haloalkyl, halogen and hydroxy.

- In some embodiments, R<sup>3</sup> is selected from: C<sub>1</sub>-C<sub>6</sub> alkyl, aryl and heteroaryl; wherein  
said C<sub>1</sub>-C<sub>6</sub> alkyl, aryl and heteroaryl are each optionally substituted with one or more groups  
selected from: chloro, cyano, ethoxy, fluoro, hydroxy, isopropoxy, methoxy, methyl, phenyl and  
20 trifluoromethyl.

- In some embodiments, R<sup>3</sup> is selected from: furan-2-yl, methyl, phenyl, pyridin-3-yl,  
pyridin-4-yl, thiophen-2-yl and thiophen-3-yl; wherein said furan-2-yl, methyl, phenyl, pyridin-  
3-yl, pyridin-4-yl, thiophen-2-yl and thiophen-3-yl are each optionally substituted with one or  
more groups selected from: chloro, cyano, ethoxy, fluoro, hydroxy, isopropoxy, methoxy,  
25 methyl, phenyl and trifluoromethyl.

- In some embodiments, R<sup>3</sup> is selected from: 2,3-difluorophenyl, 2,4-difluorophenyl, 2,5-  
difluorophenyl, 2-chlorophenyl, 2-fluoro-3-hydroxyphenyl, 2-fluoro-3-methoxyphenyl, 2-  
fluoro-3-methylphenyl, 2-fluoro-4-methylphenyl, 2-fluorophenyl, 2-methoxyphenyl, 2-  
methoxypyridin-4-yl, 3-(trifluoromethyl)phenyl, 3,4-difluorophenyl, 3-chloro-2-fluorophenyl, 3-  
30 chloro-4-fluorophenyl, 3-chlorophenyl, 3-fluoro-5-methoxyphenyl, 3-fluoro-5-methylphenyl, 3-  
fluorophenyl, 3-hydroxyphenyl, 3-isopropoxyphenyl, 3-methoxyphenyl, 4-chlorophenyl, 4-  
fluorophenyl, 4-methoxyphenyl, 5-cyano-2-fluorophenyl, 5-fluoropyridin-3-yl, 5-  
methoxypyridin-3-yl, 5-methylthiophen-2-yl, 6-methoxypyridin-3-yl, benzhydryl, furan-2-yl, *m*-  
tolyl, phenyl, *p*-tolyl, thiophen-2-yl and thiophen-3-yl.

- 35 In some embodiments, R<sup>3</sup> is 2,3-difluorophenyl.  
In some embodiments, R<sup>3</sup> is 2,4-difluorophenyl.  
In some embodiments, R<sup>3</sup> is 2,5-difluorophenyl.

- In some embodiments, R<sup>3</sup> is 2-chlorophenyl.  
In some embodiments, R<sup>3</sup> is 2-fluoro-3-hydroxyphenyl.  
In some embodiments, R<sup>3</sup> is 2-fluoro-3-methoxyphenyl.  
In some embodiments, R<sup>3</sup> is 2-fluoro-3-methylphenyl.  
5 In some embodiments, R<sup>3</sup> is 2-fluoro-4-methylphenyl.  
In some embodiments, R<sup>3</sup> is 2-fluorophenyl.  
In some embodiments, R<sup>3</sup> is 2-methoxyphenyl.  
In some embodiments, R<sup>3</sup> is 2-methoxypyridin-4-yl.  
In some embodiments, R<sup>3</sup> is 3-(trifluoromethyl)phenyl.  
10 In some embodiments, R<sup>3</sup> is 3,4-difluorophenyl.  
In some embodiments, R<sup>3</sup> is 3-chloro-2-fluorophenyl.  
In some embodiments, R<sup>3</sup> is 3-chloro-4-fluorophenyl.  
In some embodiments, R<sup>3</sup> is 3-chlorophenyl.  
In some embodiments, R<sup>3</sup> is 3-fluoro-5-methoxyphenyl.  
15 In some embodiments, R<sup>3</sup> is 3-fluoro-5-methylphenyl.  
In some embodiments, R<sup>3</sup> is 3-fluorophenyl.  
In some embodiments, R<sup>3</sup> is 3-hydroxyphenyl.  
In some embodiments, R<sup>3</sup> is 3-isopropoxyphenyl.  
In some embodiments, R<sup>3</sup> is 3-methoxyphenyl.  
20 In some embodiments, R<sup>3</sup> is 4-chlorophenyl.  
In some embodiments, R<sup>3</sup> is 4-fluorophenyl.  
In some embodiments, R<sup>3</sup> is 4-methoxyphenyl.  
In some embodiments, R<sup>3</sup> is 5-cyano-2-fluorophenyl.  
In some embodiments, R<sup>3</sup> is 5-fluoropyridin-3-yl.  
25 In some embodiments, R<sup>3</sup> is 5-methoxypyridin-3-yl.  
In some embodiments, R<sup>3</sup> is 5-methylthiophen-2-yl.  
In some embodiments, R<sup>3</sup> is 6-methoxypyridin-3-yl.  
In some embodiments, R<sup>3</sup> is benzhydryl, furan-2-yl.  
In some embodiments, R<sup>3</sup> is *m*-tolyl.  
30 In some embodiments, R<sup>3</sup> is phenyl.  
In some embodiments, R<sup>3</sup> is *p*-tolyl.  
In some embodiments, R<sup>3</sup> is thiophen-2-yl.  
In some embodiments, R<sup>3</sup> is thiophen-3-yl.
- 35 The Group R<sup>4</sup>:  
In some embodiments, R<sup>4</sup> is H, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkylthio, aryl and C<sub>3</sub>-C<sub>7</sub> cycloalkyl; wherein said C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkylthio, aryl and C<sub>3</sub>-C<sub>7</sub>



cycloalkyl are each optionally substituted with one or more groups selected from: C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkyl, carboxamide, cyano, halogen and hydroxy.

In some embodiments, R<sup>4</sup> is selected from: H, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkylthio, aryl and C<sub>3</sub>-C<sub>7</sub> cycloalkyl; wherein said C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkylthio, aryl and C<sub>3</sub>-C<sub>7</sub> cycloalkyl are each optionally substituted with one or more groups selected from:  
5 carboxamide, chloro, cyano, ethoxy, fluoro, hydroxy, methoxy, methyl and trifluoromethyl.

In some embodiments, R<sup>4</sup> is selected from: H, butyl, cyclopropyl, ethyl, ethylthio, isopropyl, methoxy, methyl, methylthio, phenyl and propyl; wherein said butyl, cyclopropyl, ethyl, ethylthio, isopropyl, methoxy, methyl, methylthio, phenyl and propyl are each optionally  
10 substituted with one or more groups selected from: carboxamide, chloro, cyano, ethoxy, fluoro, hydroxy, methoxy, methyl and trifluoromethyl.

In some embodiments, R<sup>4</sup> is selected from: H, 2,3-difluorophenyl, 2,4-difluorophenyl, 2-amino-2-oxoethoxy, 2-cyanoethyl, 2-ethoxyethylthio, 2-fluoro-4-methoxyphenyl, 2-fluoro-4-methylphenyl, 2-fluorophenyl, 2-hydroxyethylthio, 2-methoxyethyl, 2-methoxyethylthio, 3,4-difluorophenyl, 3,4-dihydroxybutyl, 3-chloro-2-fluorophenyl, 3-chlorophenyl, 3-fluoro-5-methoxyphenyl, 3-fluorophenyl, 3-methoxyphenyl, 4-chloro-2-fluorophenyl, 4-chloro-3-fluorophenyl, 4-chlorophenyl, 4-fluorophenyl, 4-hydroxyphenyl, 4-methoxyphenyl, cyanomethylthio, cyclopropyl, ethyl, isopropyl, methyl, methylthio, *m*-tolyl, *n*-propyl, phenyl, *p*-tolyl and trifluoromethyl.

In some embodiments, R<sup>4</sup> is selected from: H, 2,3-difluorophenyl, 2,4-difluorophenyl, 2-amino-2-oxoethoxy, 2-cyanoethyl, 2-ethoxyethylthio, 2-fluoro-4-methoxyphenyl, 2-fluoro-4-methylphenyl, 2-fluorophenyl, 2-hydroxyethyl, 2-hydroxyethylthio, 2-methoxyethyl, 2-methoxyethylthio, 3,4-difluorophenyl, 3,4-dihydroxybutyl, 3-chloro-2-fluorophenyl, 3-chlorophenyl, 3-fluoro-5-methoxyphenyl, 3-fluorophenyl, 3-hydroxypropyl, 3-methoxyphenyl, 4-chloro-2-fluorophenyl, 4-chloro-3-fluorophenyl, 4-chlorophenyl, 4-fluorophenyl, 4-hydroxyphenyl, 4-methoxyphenyl, cyanomethylthio, cyclopropyl, ethyl, isopropyl, methyl, methylthio, *m*-tolyl, *n*-propyl, phenyl, *p*-tolyl and trifluoromethyl.  
20  
25

In some embodiments, R<sup>4</sup> is H.

In some embodiments, R<sup>4</sup> is 2,3-difluorophenyl.

30 In some embodiments, R<sup>4</sup> is 2,4-difluorophenyl.

In some embodiments, R<sup>4</sup> is 2-amino-2-oxoethoxy.

In some embodiments, R<sup>4</sup> is 2-cyanoethyl.

In some embodiments, R<sup>4</sup> is 2-ethoxyethylthio.

In some embodiments, R<sup>4</sup> is 2-fluoro-4-methoxyphenyl.

35 In some embodiments, R<sup>4</sup> is 2-fluoro-4-methylphenyl.

In some embodiments, R<sup>4</sup> is 2-fluorophenyl.

In some embodiments, R<sup>4</sup> is 2-hydroxyethyl.

- In some embodiments, R<sup>4</sup> is 2-hydroxyethylthio.  
In some embodiments, R<sup>4</sup> is 2-methoxyethyl.  
In some embodiments, R<sup>4</sup> is 2-methoxyethylthio.  
In some embodiments, R<sup>4</sup> is 3,4-difluorophenyl.  
5 In some embodiments, R<sup>4</sup> is 3,4-dihydroxybutyl.  
In some embodiments, R<sup>4</sup> is 3-chloro-2-fluorophenyl.  
In some embodiments, R<sup>4</sup> is 3-chlorophenyl.  
In some embodiments, R<sup>4</sup> is 3-fluoro-5-methoxyphenyl.  
In some embodiments, R<sup>4</sup> is 3-fluorophenyl.  
10 In some embodiments, R<sup>4</sup> is 3-hydroxypropyl.  
In some embodiments, R<sup>4</sup> is 3-methoxyphenyl.  
In some embodiments, R<sup>4</sup> is 4-chloro-2-fluorophenyl.  
In some embodiments, R<sup>4</sup> is 4-chloro-3-fluorophenyl.  
In some embodiments, R<sup>4</sup> is 4-chlorophenyl.  
15 In some embodiments, R<sup>4</sup> is 4-fluorophenyl.  
In some embodiments, R<sup>4</sup> is 4-hydroxyphenyl.  
In some embodiments, R<sup>4</sup> is 4-methoxyphenyl.  
In some embodiments, R<sup>4</sup> is cyanomethylthio.  
In some embodiments, R<sup>4</sup> is cyclopropyl.  
20 In some embodiments, R<sup>4</sup> is ethyl.  
In some embodiments, R<sup>4</sup> is isopropyl.  
In some embodiments, R<sup>4</sup> is methyl.  
In some embodiments, R<sup>4</sup> is methylthio.  
In some embodiments, R<sup>4</sup> is *m*-tolyl.  
25 In some embodiments, R<sup>4</sup> is *n*-propyl.  
In some embodiments, R<sup>4</sup> is phenyl.  
In some embodiments, R<sup>4</sup> is *p*-tolyl.  
In some embodiments, R<sup>4</sup> is trifluoromethyl.
- 30 Certain Combinations of the Present Invention:  
In some embodiments, R<sup>2</sup>, R<sup>3</sup>, and R<sup>4</sup> are each independently selected from: H, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfinyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfonyl, C<sub>1</sub>-C<sub>6</sub> alkylthio, aryl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl and heteroaryl; wherein said C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfinyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfonyl, C<sub>1</sub>-C<sub>6</sub> alkylthio, aryl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl and heteroaryl are each optionally  
35 substituted with one or more groups selected from: C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfinyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfonyl, C<sub>1</sub>-C<sub>6</sub> alkylthio, aryl, amino, carboxamide, cyano, C<sub>1</sub>-C<sub>6</sub> haloalkyl, halogen and hydroxy.

In some embodiments, R<sup>2</sup>, R<sup>3</sup>, and R<sup>4</sup> are each independently selected from: H, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfinyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfonyl, C<sub>1</sub>-C<sub>6</sub> alkylthio, aryl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl and heteroaryl; wherein said C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfinyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfonyl, C<sub>1</sub>-C<sub>6</sub> alkylthio, aryl, C<sub>3</sub>-C<sub>7</sub> cycloalkyl and heteroaryl are each optionally substituted with one or more groups selected from: amino, carboxamide, chloro, cyano, ethoxy, fluoro, hydroxy, isopropoxy, methoxy, methyl, methylsulfinyl, methylsulfonyl, methylthio, phenyl and trifluoromethyl.

In some embodiments, R<sup>2</sup>, R<sup>3</sup>, and R<sup>4</sup> are each independently selected from: H, butyl, cyclopropyl, ethoxy, ethyl, ethylsulfinyl, ethylthio, furan-2-yl, isopropyl, methoxy, methyl, methylsulfinyl, methylsulfonyl, methylthio, phenyl, propyl, propylthio, pyridin-3-yl, pyridin-4-yl, thiophen-2-yl and thiophen-3-yl; wherein said butyl, cyclopropyl, ethoxy, ethyl, ethylsulfinyl, ethylthio, furan-2-yl, isopropyl, methoxy, methyl, methylsulfinyl, methylsulfonyl, methylthio, phenyl, propyl, propylthio, pyridin-3-yl, pyridin-4-yl, thiophen-2-yl and thiophen-3-yl are each optionally substituted with one or more groups selected from: amino, carboxamide, chloro, cyano, ethoxy, fluoro, hydroxy, isopropoxy, methoxy, methyl, methylsulfinyl, methylsulfonyl, methylthio, phenyl and trifluoromethyl.

In some embodiments, R<sup>2</sup>, R<sup>3</sup>, and R<sup>4</sup> are each independently selected from: H, 2-(methylsulfinyl)ethyl, 2-(methylsulfonyl)ethyl, 2-(methylthio)ethyl, 2,3-difluorophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, 2-aminoethylthio, 2-amino-2-oxoethoxy, 2-chlorophenyl, 2-cyanoethyl, 2-ethoxyethylthio, 2-fluoro-3-hydroxyphenyl, 2-fluoro-3-methoxyphenyl, 2-fluoro-3-methylphenyl, 2-fluoro-4-methoxyphenyl, 2-fluoro-4-methylphenyl, 2-fluorophenyl, 2-hydroxyethyl, 2-hydroxyethylsulfinyl, 2-hydroxyethylthio, 2-methoxyethyl, 2-methoxyethylthio, 2-methoxyphenyl, 2-methoxypyridin-4-yl, 3-(trifluoromethyl)phenyl, 3,4-difluorophenyl, 3,4-dihydroxybutyl, 3-chloro-2-fluorophenyl, 3-chloro-4-fluorophenyl, 3-chlorophenyl, 3-fluoro-5-methoxyphenyl, 3-fluoro-5-methylphenyl, 3-fluorophenyl, 3-hydroxyphenyl, 3-hydroxypropyl, 3-hydroxypropylthio, 3-isopropoxyphenyl, 3-methoxyphenyl, 4-chloro-2-fluorophenyl, 4-chloro-3-fluorophenyl, 4-chlorophenyl, 4-fluorophenyl, 4-hydroxyphenyl, 4-methoxyphenyl, 5-cyano-2-fluorophenyl, 5-fluoropyridin-3-yl, 5-methoxypyridin-3-yl, 5-methylthiophen-2-yl, 6-methoxypyridin-3-yl, benzhydryl, cyanomethoxy, cyanomethylthio, cyclopropyl, ethoxy, ethyl, ethylthio, furan-2-yl, isopropyl, methyl, methylsulfinyl, methylsulfonyl, methylthio, *m*-tolyl, *n*-propyl, phenyl, *p*-tolyl, thiophen-2-yl, thiophen-3-yl and trifluoromethyl.

In some embodiments, R<sup>2</sup> and R<sup>3</sup> together with the pyrazole ring to which they are both attached to form a tricyclic heteroaryl.

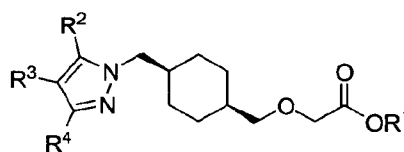
In some embodiments, wherein R<sup>2</sup> and R<sup>3</sup> together with the pyrazole ring to which they are both attached to form 4,5-dihydro-3*H*-benzo[e]indazol-3-yl or indeno[2,1-*c*]pyrazol-1(8*H*)-yl.

In some embodiments, wherein R<sup>2</sup> and R<sup>3</sup> together with the pyrazole ring to which they are both attached to form 4,5-dihydro-3*H*-benzo[e]indazol-3-yl.

In some embodiments, wherein R<sup>2</sup> and R<sup>3</sup> together with the pyrazole ring to which they are both attached to form indeno[2,1-*c*]pyrazol-1(8*H*)-yl.

5

One aspect of the present invention encompasses certain pyrazole derivatives selected from compounds of Formula **Ic** and pharmaceutically acceptable salts, solvates and hydrates thereof:



**Ic**

10

wherein:

R<sup>1</sup> is selected from: H and C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sup>2</sup> is selected from: H, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfinyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfonyl, C<sub>1</sub>-C<sub>6</sub> alkylthio, aryl and C<sub>3</sub>-C<sub>7</sub> cycloalkyl; wherein said C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfinyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfonyl, C<sub>1</sub>-C<sub>6</sub> alkylthio, aryl and C<sub>3</sub>-C<sub>7</sub> cycloalkyl are each optionally substituted with one or more groups selected from: C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfinyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfonyl, C<sub>1</sub>-C<sub>6</sub> alkylthio, amino, carboxamide, cyano, halogen and hydroxy;

15

R<sup>3</sup> is selected from: C<sub>1</sub>-C<sub>6</sub> alkyl, aryl and heteroaryl; wherein said C<sub>1</sub>-C<sub>6</sub> alkyl, aryl and heteroaryl are each optionally substituted with one or more groups selected from: C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkyl, aryl, cyano, C<sub>1</sub>-C<sub>6</sub> haloalkyl, halogen and hydroxy;

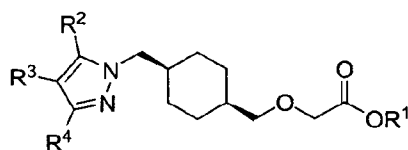
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and

R<sup>4</sup> is selected from: H, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkylthio, aryl and C<sub>3</sub>-C<sub>7</sub> cycloalkyl; wherein said C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkylthio, aryl and C<sub>3</sub>-C<sub>7</sub> cycloalkyl are each optionally substituted with one or more groups selected from: C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkyl, carboxamide, cyano, halogen and hydroxy.

25

One aspect of the present invention encompasses certain pyrazole derivatives selected from compounds of Formula **Ic** and pharmaceutically acceptable salts, solvates and hydrates thereof:



1c

wherein:

R<sup>1</sup> is selected from: H and methyl;

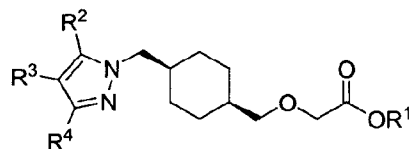
R<sup>2</sup> is selected from: H, 2-(methylsulfinyl)ethyl, 2-(methylsulfonyl)ethyl, 2-(methylthio)ethyl, 2,3-difluorophenyl, 2-aminoethylthio, 2-amino-2-oxoethoxy, 2-cyanoethyl, 2-ethoxyethylthio, 2-fluoro-4-methoxyphenyl, 2-fluorophenyl, 2-hydroxyethyl, 2-hydroxyethylsulfinyl, 2-hydroxyethylthio, 2-methoxyethyl, 2-methoxyethylthio, 3,4-difluorophenyl, 3,4-dihydroxybutyl, 3-chloro-2-fluorophenyl, 3-fluoro-5-methoxyphenyl, 3-fluorophenyl, 3-hydroxypropyl, 3-hydroxypropylthio, 3-methoxyphenyl, 4-chloro-3-fluorophenyl, 4-chlorophenyl, 4-fluorophenyl, 4-methoxyphenyl, cyanomethoxy, cyanomethylthio, cyclopropyl, ethoxy, ethyl, ethylthio, isopropyl, methyl, methylsulfinyl, methylsulfonyl, methylthio, *m*-tolyl, *n*-propyl, phenyl and trifluoromethyl;

R<sup>3</sup> is selected from: 2,3-difluorophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, 2-chlorophenyl, 2-fluoro-3-hydroxyphenyl, 2-fluoro-3-methoxyphenyl, 2-fluoro-3-methylphenyl, 2-fluoro-4-methylphenyl, 2-fluorophenyl, 2-methoxyphenyl, 2-methoxypyridin-4-yl, 3-(trifluoromethyl)phenyl, 3,4-difluorophenyl, 3-chloro-2-fluorophenyl, 3-chloro-4-fluorophenyl, 3-chlorophenyl, 3-fluoro-5-methoxyphenyl, 3-fluoro-5-methylphenyl, 3-fluorophenyl, 3-hydroxyphenyl, 3-isopropoxyphenyl, 3-methoxyphenyl, 4-chlorophenyl, 4-fluorophenyl, 4-methoxyphenyl, 5-cyano-2-fluorophenyl, 5-fluoropyridin-3-yl, 5-methoxypyridin-3-yl, 5-methylthiophen-2-yl, 6-methoxypyridin-3-yl, benzhydryl, furan-2-yl, *m*-tolyl, phenyl, *p*-tolyl, thiophen-2-yl and thiophen-3-yl;

and

R<sup>4</sup> is selected from: H, 2,3-difluorophenyl, 2,4-difluorophenyl, 2-amino-2-oxoethoxy, 2-cyanoethyl, 2-ethoxyethylthio, 2-fluoro-4-methoxyphenyl, 2-fluoro-4-methylphenyl, 2-fluorophenyl, 2-hydroxyethylthio, 2-methoxyethyl, 2-methoxyethylthio, 3,4-difluorophenyl, 3,4-dihydroxybutyl, 3-chloro-2-fluorophenyl, 3-chlorophenyl, 3-fluoro-5-methoxyphenyl, 3-fluorophenyl, 3-methoxyphenyl, 4-chloro-2-fluorophenyl, 4-chloro-3-fluorophenyl, 4-chlorophenyl, 4-fluorophenyl, 4-hydroxyphenyl, 4-methoxyphenyl, cyanomethylthio, cyclopropyl, ethyl, isopropyl, methyl, methylthio, *m*-tolyl, *n*-propyl, phenyl, *p*-tolyl and trifluoromethyl.

One aspect of the present invention encompasses certain pyrazole derivatives selected from compounds of Formula **Ic** and pharmaceutically acceptable salts, solvates and hydrates thereof:



**Ic**

5           wherein:

$R^1$  is selected from: H and methyl;

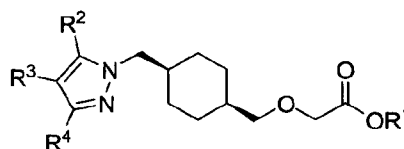
$R^2$  is selected from: H, 2-(methylsulfinyl)ethyl, 2-(methylsulfonyl)ethyl, 2-(methylthio)ethyl, 2,3-difluorophenyl, 2-aminoethylthio, 2-amino-2-oxoethoxy, 2-cyanoethyl, 2-ethoxyethylthio, 2-fluoro-4-methoxyphenyl, 2-fluorophenyl, 2-hydroxyethyl, 2-hydroxyethylsulfinyl, 2-hydroxyethylthio, 2-methoxyethyl, 2-methoxyethylthio, 3,4-difluorophenyl, 3,4-dihydroxybutyl, 3-chloro-2-fluorophenyl, 3-fluoro-5-methoxyphenyl, 3-fluorophenyl, 3-hydroxypropyl, 3-hydroxypropylthio, 3-methoxyphenyl, 4-chloro-3-fluorophenyl, 4-chlorophenyl, 4-fluorophenyl, 4-methoxyphenyl, cyanomethoxy, cyanomethylthio, cyclopropyl, ethoxy, ethyl, ethylthio, isopropyl, methyl, methylsulfinyl, methylsulfonyl, methylthio, *m*-tolyl, *n*-propyl, phenyl, *p*-tolyl and trifluoromethyl;

$R^3$  is selected from: 2,3-difluorophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, 2-chlorophenyl, 2-fluoro-3-hydroxyphenyl, 2-fluoro-3-methoxyphenyl, 2-fluoro-3-methylphenyl, 2-fluoro-4-methylphenyl, 2-fluorophenyl, 2-methoxyphenyl, 2-methoxypyridin-4-yl, 3-(trifluoromethyl)phenyl, 3,4-difluorophenyl, 3-chloro-2-fluorophenyl, 3-chloro-4-fluorophenyl, 3-chlorophenyl, 3-fluoro-5-methoxyphenyl, 3-fluoro-5-methylphenyl, 3-fluorophenyl, 3-hydroxyphenyl, 3-isopropoxyphenyl, 3-methoxyphenyl, 4-chlorophenyl, 4-fluorophenyl, 4-methoxyphenyl, 5-cyano-2-fluorophenyl, 5-fluoropyridin-3-yl, 5-methoxypyridin-3-yl, 5-methylthiophen-2-yl, 6-methoxypyridin-3-yl, benzhydryl, furan-2-yl, *m*-tolyl, phenyl, *p*-tolyl, thiophen-2-yl and thiophen-3-yl;

25           and

$R^4$  is selected from: H, 2,3-difluorophenyl, 2,4-difluorophenyl, 2-amino-2-oxoethoxy, 2-cyanoethyl, 2-ethoxyethylthio, 2-fluoro-4-methoxyphenyl, 2-fluoro-4-methylphenyl, 2-fluorophenyl, 2-hydroxyethyl, 2-hydroxyethylthio, 2-methoxyethyl, 2-methoxyethylthio, 3,4-difluorophenyl, 3,4-dihydroxybutyl, 3-chloro-2-fluorophenyl, 3-chlorophenyl, 3-fluoro-5-methoxyphenyl, 3-fluorophenyl, 3-hydroxypropyl, 3-methoxyphenyl, 4-chloro-2-fluorophenyl, 4-chloro-3-fluorophenyl, 4-chlorophenyl, 4-fluorophenyl, 4-hydroxyphenyl, 4-methoxyphenyl, cyanomethylthio, cyclopropyl, ethyl, isopropyl, methyl, methylthio, *m*-tolyl, *n*-propyl, phenyl, *p*-tolyl and trifluoromethyl.

One aspect of the present invention encompasses certain pyrazole derivatives selected from compounds of Formula **Ic** and pharmaceutically acceptable salts, solvates and hydrates thereof:



**Ic**

wherein:

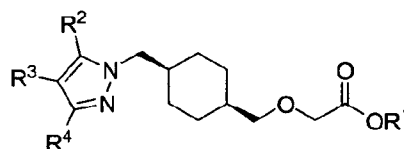
R<sup>1</sup> is selected from: H and C<sub>1</sub>-C<sub>6</sub> alkyl;

R<sup>2</sup> and R<sup>3</sup> together with the pyrazole ring to which they are both attached to form a tricyclic heteroaryl;

and

R<sup>4</sup> is selected from: H, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkylthio, aryl and C<sub>3</sub>-C<sub>7</sub> cycloalkyl; wherein said C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkylthio, aryl and C<sub>3</sub>-C<sub>7</sub> cycloalkyl are each optionally substituted with one or more groups selected from: C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkyl, carboxamide, cyano, halogen and hydroxy.

One aspect of the present invention encompasses certain pyrazole derivatives selected from compounds of Formula **Ic** and pharmaceutically acceptable salts, solvates and hydrates thereof:



**Ic**

wherein:

R<sup>1</sup> is selected from: H and methyl;

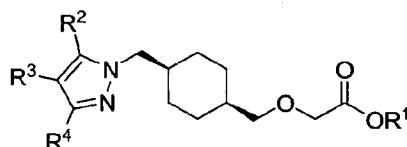
R<sup>2</sup> and R<sup>3</sup> together with the pyrazole ring to which they are both attached to form 4,5-dihydro-3*H*-benzo[e]indazol-3-yl or indeno[2,1-*c*]pyrazol-1(8*H*)-yl;

and

R<sup>4</sup> is selected from: H, 2,3-difluorophenyl, 2,4-difluorophenyl, 2-amino-2-oxoethoxy, 2-cyanoethyl, 2-ethoxyethylthio, 2-fluoro-4-methoxyphenyl, 2-fluoro-4-methylphenyl, 2-fluorophenyl, 2-hydroxyethylthio, 2-methoxyethyl, 2-methoxyethylthio, 3,4-difluorophenyl, 3,4-dihydroxybutyl, 3-chloro-2-fluorophenyl, 3-chlorophenyl, 3-fluoro-5-methoxyphenyl, 3-fluorophenyl, 3-methoxyphenyl, 4-chloro-2-fluorophenyl, 4-chloro-3-fluorophenyl, 4-

chlorophenyl, 4-fluorophenyl, 4-hydroxyphenyl, 4-methoxyphenyl, cyanomethylthio, cyclopropyl, ethyl, isopropyl, methyl, methylthio, *m*-tolyl, *n*-propyl, phenyl, *p*-tolyl and trifluoromethyl.

- 5 One aspect of the present invention encompasses certain pyrazole derivatives selected from compounds of Formula **Ic** and pharmaceutically acceptable salts, solvates and hydrates thereof:

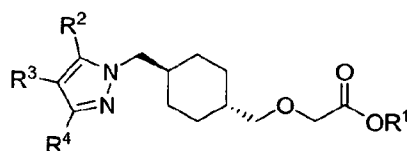


**Ic**

wherein:

- 10  $R^1$  is selected from: H and methyl;  
 $R^2$  and  $R^3$  together with the pyrazole ring to which they are both attached to form 4,5-dihydro-3*H*-benzo[e]indazol-3-yl or indeno[2,1-*c*]pyrazol-1(8*H*)-yl;  
 and  
 $R^4$  is selected from: H, 2,3-difluorophenyl, 2,4-difluorophenyl, 2-amino-2-oxoethoxy, 2-  
 15 cyanoethyl, 2-ethoxyethylthio, 2-fluoro-4-methoxyphenyl, 2-fluoro-4-methylphenyl, 2-fluorophenyl, 2-hydroxyethyl, 2-hydroxyethylthio, 2-methoxyethyl, 2-methoxyethylthio, 3,4-difluorophenyl, 3,4-dihydroxybutyl, 3-chloro-2-fluorophenyl, 3-chlorophenyl, 3-fluoro-5-methoxyphenyl, 3-fluorophenyl, 3-hydroxypropyl, 3-methoxyphenyl, 4-chloro-2-fluorophenyl, 4-chloro-3-fluorophenyl, 4-chlorophenyl, 4-fluorophenyl, 4-hydroxyphenyl, 4-methoxyphenyl,  
 20 cyanomethylthio, cyclopropyl, ethyl, isopropyl, methyl, methylthio, *m*-tolyl, *n*-propyl, phenyl, *p*-tolyl and trifluoromethyl.

- One aspect of the present invention encompasses certain pyrazole derivatives selected from compounds of Formula **Ie** and pharmaceutically acceptable salts, solvates and hydrates  
 25 thereof:



**Ie**

wherein:

$R^1$  is selected from: H and  $C_1$ - $C_6$  alkyl;



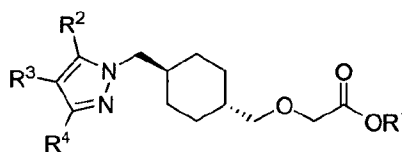
$R^2$  is selected from: H, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfinyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfonyl, C<sub>1</sub>-C<sub>6</sub> alkylthio, aryl and C<sub>3</sub>-C<sub>7</sub> cycloalkyl; wherein said C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfinyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfonyl, C<sub>1</sub>-C<sub>6</sub> alkylthio, aryl and C<sub>3</sub>-C<sub>7</sub> cycloalkyl are each optionally substituted with one or more groups selected from: C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfinyl, C<sub>1</sub>-C<sub>6</sub> alkylsulfonyl, C<sub>1</sub>-C<sub>6</sub> alkylthio, amino, carboxamide, cyano, halogen and hydroxy;

$R^3$  is selected from: C<sub>1</sub>-C<sub>6</sub> alkyl, aryl and heteroaryl; wherein said C<sub>1</sub>-C<sub>6</sub> alkyl, aryl and heteroaryl are each optionally substituted with one or more groups selected from: C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkyl, aryl, cyano, C<sub>1</sub>-C<sub>6</sub> haloalkyl, halogen and hydroxy;

and

$R^4$  is selected from: H, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkylthio, aryl and C<sub>3</sub>-C<sub>7</sub> cycloalkyl; wherein said C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkylthio, aryl and C<sub>3</sub>-C<sub>7</sub> cycloalkyl are each optionally substituted with one or more groups selected from: C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkyl, carboxamide, cyano, halogen and hydroxy.

One aspect of the present invention encompasses certain pyrazole derivatives selected from compounds of Formula **Ie** and pharmaceutically acceptable salts, solvates and hydrates thereof:



**Ie**

wherein:

$R^1$  is selected from: H and methyl;

$R^2$  is selected from: H, 2-(methylsulfinyl)ethyl, 2-(methylsulfonyl)ethyl, 2-(methylthio)ethyl, 2,3-difluorophenyl, 2-aminoethylthio, 2-amino-2-oxoethoxy, 2-cyanoethyl, 2-ethoxyethylthio, 2-fluoro-4-methoxyphenyl, 2-fluorophenyl, 2-hydroxyethyl, 2-hydroxyethylsulfinyl, 2-hydroxyethylthio, 2-methoxyethyl, 2-methoxyethylthio, 3,4-difluorophenyl, 3,4-dihydroxybutyl, 3-chloro-2-fluorophenyl, 3-fluoro-5-methoxyphenyl, 3-fluorophenyl, 3-hydroxypropyl, 3-hydroxypropylthio, 3-methoxyphenyl, 4-chloro-3-fluorophenyl, 4-chlorophenyl, 4-fluorophenyl, 4-methoxyphenyl, cyanomethoxy, cyanomethylthio, cyclopropyl, ethoxy, ethyl, ethylthio, isopropyl, methyl, methylsulfinyl, methylsulfonyl, methylthio, *m*-tolyl, *n*-propyl, phenyl and trifluoromethyl;

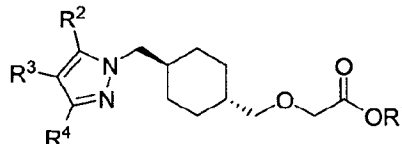
$R^3$  is selected from: 2,3-difluorophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, 2-chlorophenyl, 2-fluoro-3-hydroxyphenyl, 2-fluoro-3-methoxyphenyl, 2-fluoro-3-methylphenyl, 2-fluoro-4-methylphenyl, 2-fluorophenyl, 2-methoxyphenyl, 2-methoxypyridin-4-yl, 3-

(trifluoromethyl)phenyl, 3,4-difluorophenyl, 3-chloro-2-fluorophenyl, 3-chloro-4-fluorophenyl, 3-chlorophenyl, 3-fluoro-5-methoxyphenyl, 3-fluoro-5-methylphenyl, 3-fluorophenyl, 3-hydroxyphenyl, 3-isopropoxyphenyl, 3-methoxyphenyl, 4-chlorophenyl, 4-fluorophenyl, 4-methoxyphenyl, 5-cyano-2-fluorophenyl, 5-fluoropyridin-3-yl, 5-methoxypyridin-3-yl, 5-methylthiophen-2-yl, 6-methoxypyridin-3-yl, benzhydryl, furan-2-yl, *m*-tolyl, phenyl, *p*-tolyl, thiophen-2-yl and thiophen-3-yl;

and

$R^4$  is selected from: H, 2,3-difluorophenyl, 2,4-difluorophenyl, 2-amino-2-oxoethoxy, 2-cyanoethyl, 2-ethoxyethylthio, 2-fluoro-4-methoxyphenyl, 2-fluoro-4-methylphenyl, 2-fluorophenyl, 2-hydroxyethylthio, 2-methoxyethyl, 2-methoxyethylthio, 3,4-difluorophenyl, 3,4-dihydroxybutyl, 3-chloro-2-fluorophenyl, 3-chlorophenyl, 3-fluoro-5-methoxyphenyl, 3-fluorophenyl, 3-methoxyphenyl, 4-chloro-2-fluorophenyl, 4-chloro-3-fluorophenyl, 4-chlorophenyl, 4-fluorophenyl, 4-hydroxyphenyl, 4-methoxyphenyl, cyanomethylthio, cyclopropyl, ethyl, isopropyl, methyl, methylthio, *m*-tolyl, *n*-propyl, phenyl, *p*-tolyl and trifluoromethyl.

One aspect of the present invention encompasses certain pyrazole derivatives selected from compounds of Formula **Ie** and pharmaceutically acceptable salts, solvates and hydrates thereof:



**Ie**

20

wherein:

$R^1$  is selected from: H and methyl;

$R^2$  is selected from: H, 2-(methylsulfinyl)ethyl, 2-(methylsulfonyl)ethyl, 2-(methylthio)ethyl, 2,3-difluorophenyl, 2-aminoethylthio, 2-amino-2-oxoethoxy, 2-cyanoethyl, 2-ethoxyethylthio, 2-fluoro-4-methoxyphenyl, 2-fluorophenyl, 2-hydroxyethyl, 2-hydroxyethylsulfinyl, 2-hydroxyethylthio, 2-methoxyethyl, 2-methoxyethylthio, 3,4-difluorophenyl, 3,4-dihydroxybutyl, 3-chloro-2-fluorophenyl, 3-fluoro-5-methoxyphenyl, 3-fluorophenyl, 3-hydroxypropyl, 3-hydroxypropylthio, 3-methoxyphenyl, 4-chloro-3-fluorophenyl, 4-chlorophenyl, 4-fluorophenyl, 4-methoxyphenyl, cyanomethoxy, cyanomethylthio, cyclopropyl, ethoxy, ethyl, ethylthio, isopropyl, methyl, methylsulfinyl, methylsulfonyl, methylthio, *m*-tolyl, *n*-propyl, phenyl, *p*-tolyl and trifluoromethyl;

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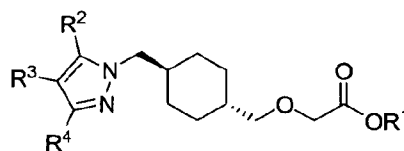
$R^3$  is selected from: 2,3-difluorophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, 2-chlorophenyl, 2-fluoro-3-hydroxyphenyl, 2-fluoro-3-methoxyphenyl, 2-fluoro-3-methylphenyl,

2-fluoro-4-methylphenyl, 2-fluorophenyl, 2-methoxyphenyl, 2-methoxypyridin-4-yl, 3-(trifluoromethyl)phenyl, 3,4-difluorophenyl, 3-chloro-2-fluorophenyl, 3-chloro-4-fluorophenyl, 3-chlorophenyl, 3-fluoro-5-methoxyphenyl, 3-fluoro-5-methylphenyl, 3-fluorophenyl, 3-hydroxyphenyl, 3-isopropoxyphenyl, 3-methoxyphenyl, 4-chlorophenyl, 4-fluorophenyl, 4-methoxyphenyl, 5-cyano-2-fluorophenyl, 5-fluoropyridin-3-yl, 5-methoxypyridin-3-yl, 5-methylthiophen-2-yl, 6-methoxypyridin-3-yl, benzhydryl, furan-2-yl, *m*-tolyl, phenyl, *p*-tolyl, thiophen-2-yl and thiophen-3-yl;

and

$R^4$  is selected from: H, 2,3-difluorophenyl, 2,4-difluorophenyl, 2-amino-2-oxoethoxy, 2-cyanoethyl, 2-ethoxyethylthio, 2-fluoro-4-methoxyphenyl, 2-fluoro-4-methylphenyl, 2-fluorophenyl, 2-hydroxyethyl, 2-hydroxyethylthio, 2-methoxyethyl, 2-methoxyethylthio, 3,4-difluorophenyl, 3,4-dihydroxybutyl, 3-chloro-2-fluorophenyl, 3-chlorophenyl, 3-fluoro-5-methoxyphenyl, 3-fluorophenyl, 3-hydroxypropyl, 3-methoxyphenyl, 4-chloro-2-fluorophenyl, 4-chloro-3-fluorophenyl, 4-chlorophenyl, 4-fluorophenyl, 4-hydroxyphenyl, 4-methoxyphenyl, cyanomethylthio, cyclopropyl, ethyl, isopropyl, methyl, methylthio, *m*-tolyl, *n*-propyl, phenyl, *p*-tolyl and trifluoromethyl.

One aspect of the present invention encompasses certain pyrazole derivatives selected from compounds of Formula **Ie** and pharmaceutically acceptable salts, solvates and hydrates thereof:



**Ie**

wherein:

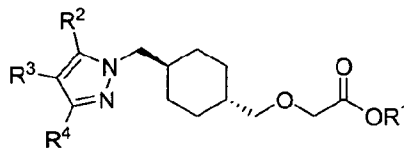
$R^1$  is selected from: H and  $C_1$ - $C_6$  alkyl;

$R^2$  and  $R^3$  together with the pyrazole ring to which they are both attached to form a tricyclic heteroaryl;

and

$R^4$  is selected from: H,  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkylthio, aryl and  $C_3$ - $C_7$  cycloalkyl; wherein said  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkylthio, aryl and  $C_3$ - $C_7$  cycloalkyl are each optionally substituted with one or more groups selected from:  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_6$  alkyl, carboxamide, cyano, halogen and hydroxy.

One aspect of the present invention encompasses certain pyrazole derivatives selected from compounds of Formula **Ie** and pharmaceutically acceptable salts, solvates and hydrates thereof:



**Ie**

5 wherein:

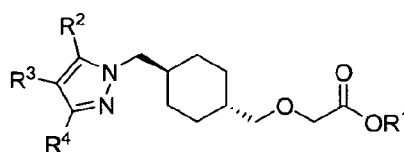
$R^1$  is selected from: H and methyl;

$R^2$  and  $R^3$  together with the pyrazole ring to which they are both attached to form 4,5-dihydro-3*H*-benzo[e]indazol-3-yl or indeno[2,1-*c*]pyrazol-1(8*H*)-yl;

and

10  $R^4$  is selected from: H, 2,3-difluorophenyl, 2,4-difluorophenyl, 2-amino-2-oxoethoxy, 2-cyanoethyl, 2-ethoxyethylthio, 2-fluoro-4-methoxyphenyl, 2-fluoro-4-methylphenyl, 2-fluorophenyl, 2-hydroxyethylthio, 2-methoxyethyl, 2-methoxyethylthio, 3,4-difluorophenyl, 3,4-dihydroxybutyl, 3-chloro-2-fluorophenyl, 3-chlorophenyl, 3-fluoro-5-methoxyphenyl, 3-fluorophenyl, 3-methoxyphenyl, 4-chloro-2-fluorophenyl, 4-chloro-3-fluorophenyl, 4-chlorophenyl, 4-fluorophenyl, 4-hydroxyphenyl, 4-methoxyphenyl, cyanomethylthio, 15 cyclopropyl, ethyl, isopropyl, methyl, methylthio, *m*-tolyl, *n*-propyl, phenyl, *p*-tolyl and trifluoromethyl.

20 One aspect of the present invention encompasses certain pyrazole derivatives selected from compounds of Formula **Ie** and pharmaceutically acceptable salts, solvates and hydrates thereof:



**Ie**

wherein:

$R^1$  is selected from: H and methyl;

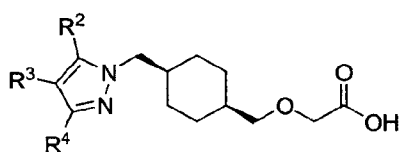
25  $R^2$  and  $R^3$  together with the pyrazole ring to which they are both attached to form 4,5-dihydro-3*H*-benzo[e]indazol-3-yl or indeno[2,1-*c*]pyrazol-1(8*H*)-yl;

and

$R^4$  is selected from: H, 2,3-difluorophenyl, 2,4-difluorophenyl, 2-amino-2-oxoethoxy, 2-cyanoethyl, 2-ethoxyethylthio, 2-fluoro-4-methoxyphenyl, 2-fluoro-4-methylphenyl, 2-

fluorophenyl, 2-hydroxyethyl, 2-hydroxyethylthio, 2-methoxyethyl, 2-methoxyethylthio, 3,4-difluorophenyl, 3,4-dihydroxybutyl, 3-chloro-2-fluorophenyl, 3-chlorophenyl, 3-fluoro-5-methoxyphenyl, 3-fluorophenyl, 3-hydroxypropyl, 3-methoxyphenyl, 4-chloro-2-fluorophenyl, 4-chloro-3-fluorophenyl, 4-chlorophenyl, 4-fluorophenyl, 4-hydroxyphenyl, 4-methoxyphenyl,  
5 cyanomethylthio, cyclopropyl, ethyl, isopropyl, methyl, methylthio, *m*-tolyl, *n*-propyl, phenyl, *p*-tolyl and trifluoromethyl.

One aspect of the present invention encompasses certain pyrazole derivatives selected from compounds of Formula **Ig** and pharmaceutically acceptable salts, solvates and hydrates  
10 thereof:



**Ig**

wherein:

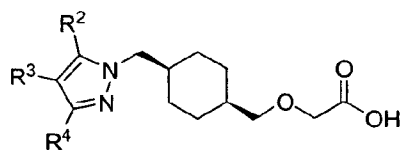
$R^2$  is selected from: H,  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkylsulfinyl,  $C_1$ - $C_6$  alkylsulfonyl,  $C_1$ - $C_6$  alkylthio, aryl and  $C_3$ - $C_7$  cycloalkyl; wherein said  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkylsulfinyl,  $C_1$ - $C_6$  alkylsulfonyl,  $C_1$ - $C_6$  alkylthio, aryl and  $C_3$ - $C_7$  cycloalkyl are  
15 each optionally substituted with one or more groups selected from:  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkylsulfinyl,  $C_1$ - $C_6$  alkylsulfonyl,  $C_1$ - $C_6$  alkylthio, amino, carboxamide, cyano, halogen and hydroxy;

$R^3$  is selected from:  $C_1$ - $C_6$  alkyl, aryl and heteroaryl; wherein said  $C_1$ - $C_6$  alkyl, aryl and heteroaryl are each optionally substituted with one or more groups selected from:  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_6$  alkyl, aryl, cyano,  $C_1$ - $C_6$  haloalkyl, halogen and hydroxy;  
20

and

$R^4$  is selected from: H,  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkylthio, aryl and  $C_3$ - $C_7$  cycloalkyl; wherein said  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkylthio, aryl and  $C_3$ - $C_7$  cycloalkyl  
25 are each optionally substituted with one or more groups selected from:  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_6$  alkyl, carboxamide, cyano, halogen and hydroxy.

One aspect of the present invention encompasses certain pyrazole derivatives selected from compounds of Formula **Ig** and pharmaceutically acceptable salts, solvates and hydrates  
30 thereof:



**Ig**

wherein:

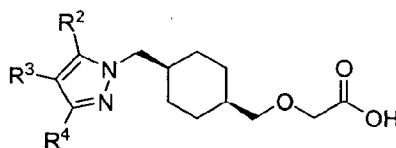
$R^2$  is selected from: H, 2-(methylsulfinyl)ethyl, 2-(methylsulfonyl)ethyl, 2-(methylthio)ethyl, 2,3-difluorophenyl, 2-aminoethylthio, 2-amino-2-oxoethoxy, 2-cyanoethyl, 2-ethoxyethylthio, 2-fluoro-4-methoxyphenyl, 2-fluorophenyl, 2-hydroxyethyl, 2-hydroxyethylsulfinyl, 2-hydroxyethylthio, 2-methoxyethyl, 2-methoxyethylthio, 3,4-difluorophenyl, 3,4-dihydroxybutyl, 3-chloro-2-fluorophenyl, 3-fluoro-5-methoxyphenyl, 3-fluorophenyl, 3-hydroxypropyl, 3-hydroxypropylthio, 3-methoxyphenyl, 4-chloro-3-fluorophenyl, 4-chlorophenyl, 4-fluorophenyl, 4-methoxyphenyl, cyanomethoxy, cyanomethylthio, cyclopropyl, ethoxy, ethyl, ethylthio, isopropyl, methyl, methylsulfinyl, methylsulfonyl, methylthio, *m*-tolyl, *n*-propyl, phenyl and trifluoromethyl;

$R^3$  is selected from: 2,3-difluorophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, 2-chlorophenyl, 2-fluoro-3-hydroxyphenyl, 2-fluoro-3-methoxyphenyl, 2-fluoro-3-methylphenyl, 2-fluoro-4-methylphenyl, 2-fluorophenyl, 2-methoxyphenyl, 2-methoxypyridin-4-yl, 3-(trifluoromethyl)phenyl, 3,4-difluorophenyl, 3-chloro-2-fluorophenyl, 3-chloro-4-fluorophenyl, 3-chlorophenyl, 3-fluoro-5-methoxyphenyl, 3-fluoro-5-methylphenyl, 3-fluorophenyl, 3-hydroxyphenyl, 3-isopropoxyphenyl, 3-methoxyphenyl, 4-chlorophenyl, 4-fluorophenyl, 4-methoxyphenyl, 5-cyano-2-fluorophenyl, 5-fluoropyridin-3-yl, 5-methoxypyridin-3-yl, 5-methylthiophen-2-yl, 6-methoxypyridin-3-yl, benzhydryl, furan-2-yl, *m*-tolyl, phenyl, *p*-tolyl, thiophen-2-yl and thiophen-3-yl;

and

$R^4$  is selected from: H, 2,3-difluorophenyl, 2,4-difluorophenyl, 2-amino-2-oxoethoxy, 2-cyanoethyl, 2-ethoxyethylthio, 2-fluoro-4-methoxyphenyl, 2-fluoro-4-methylphenyl, 2-fluorophenyl, 2-hydroxyethylthio, 2-methoxyethyl, 2-methoxyethylthio, 3,4-difluorophenyl, 3,4-dihydroxybutyl, 3-chloro-2-fluorophenyl, 3-chlorophenyl, 3-fluoro-5-methoxyphenyl, 3-fluorophenyl, 3-methoxyphenyl, 4-chloro-2-fluorophenyl, 4-chloro-3-fluorophenyl, 4-chlorophenyl, 4-fluorophenyl, 4-hydroxyphenyl, 4-methoxyphenyl, cyanomethylthio, cyclopropyl, ethyl, isopropyl, methyl, methylthio, *m*-tolyl, *n*-propyl, phenyl, *p*-tolyl and trifluoromethyl.

One aspect of the present invention encompasses certain pyrazole derivatives selected from compounds of Formula **Ig** and pharmaceutically acceptable salts, solvates and hydrates thereof:



**Ig**

wherein:

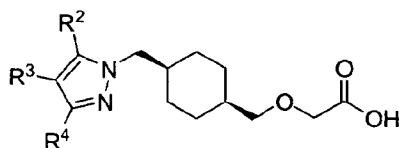
$R^2$  is selected from: H, 2-(methylsulfinyl)ethyl, 2-(methylsulfonyl)ethyl, 2-(methylthio)ethyl, 2,3-difluorophenyl, 2-aminoethylthio, 2-amino-2-oxoethoxy, 2-cyanoethyl, 2-ethoxyethylthio, 2-fluoro-4-methoxyphenyl, 2-fluorophenyl, 2-hydroxyethyl, 2-hydroxyethylsulfinyl, 2-hydroxyethylthio, 2-methoxyethyl, 2-methoxyethylthio, 3,4-difluorophenyl, 3,4-dihydroxybutyl, 3-chloro-2-fluorophenyl, 3-fluoro-5-methoxyphenyl, 3-fluorophenyl, 3-hydroxypropyl, 3-hydroxypropylthio, 3-methoxyphenyl, 4-chloro-3-fluorophenyl, 4-chlorophenyl, 4-fluorophenyl, 4-methoxyphenyl, cyanomethoxy, cyanomethylthio, cyclopropyl, ethoxy, ethyl, ethylthio, isopropyl, methyl, methylsulfinyl, methylsulfonyl, methylthio, *m*-tolyl, *n*-propyl, phenyl, *p*-tolyl and trifluoromethyl;

$R^3$  is selected from: 2,3-difluorophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, 2-chlorophenyl, 2-fluoro-3-hydroxyphenyl, 2-fluoro-3-methoxyphenyl, 2-fluoro-3-methylphenyl, 2-fluoro-4-methylphenyl, 2-fluorophenyl, 2-methoxyphenyl, 2-methoxypyridin-4-yl, 3-(trifluoromethyl)phenyl, 3,4-difluorophenyl, 3-chloro-2-fluorophenyl, 3-chloro-4-fluorophenyl, 3-chlorophenyl, 3-fluoro-5-methoxyphenyl, 3-fluoro-5-methylphenyl, 3-fluorophenyl, 3-hydroxyphenyl, 3-isopropoxyphenyl, 3-methoxyphenyl, 4-chlorophenyl, 4-fluorophenyl, 4-methoxyphenyl, 5-cyano-2-fluorophenyl, 5-fluoropyridin-3-yl, 5-methoxypyridin-3-yl, 5-methylthiophen-2-yl, 6-methoxypyridin-3-yl, benzhydryl, furan-2-yl, *m*-tolyl, phenyl, *p*-tolyl, thiophen-2-yl and thiophen-3-yl;

and

$R^4$  is selected from: H, 2,3-difluorophenyl, 2,4-difluorophenyl, 2-amino-2-oxoethoxy, 2-cyanoethyl, 2-ethoxyethylthio, 2-fluoro-4-methoxyphenyl, 2-fluoro-4-methylphenyl, 2-fluorophenyl, 2-hydroxyethyl, 2-hydroxyethylthio, 2-methoxyethyl, 2-methoxyethylthio, 3,4-difluorophenyl, 3,4-dihydroxybutyl, 3-chloro-2-fluorophenyl, 3-chlorophenyl, 3-fluoro-5-methoxyphenyl, 3-fluorophenyl, 3-hydroxypropyl, 3-methoxyphenyl, 4-chloro-2-fluorophenyl, 4-chloro-3-fluorophenyl, 4-chlorophenyl, 4-fluorophenyl, 4-hydroxyphenyl, 4-methoxyphenyl, cyanomethylthio, cyclopropyl, ethyl, isopropyl, methyl, methylthio, *m*-tolyl, *n*-propyl, phenyl, *p*-tolyl and trifluoromethyl.

One aspect of the present invention encompasses certain pyrazole derivatives selected from compounds of Formula **Ig** and pharmaceutically acceptable salts, solvates and hydrates thereof:



**Ig**

wherein:

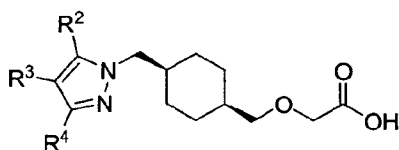
R<sup>2</sup> and R<sup>3</sup> together with the pyrazole ring to which they are both attached to form a tricyclic heteroaryl;

5 and

R<sup>4</sup> is selected from: H, C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkylthio, aryl and C<sub>3</sub>-C<sub>7</sub> cycloalkyl; wherein said C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkylthio, aryl and C<sub>3</sub>-C<sub>7</sub> cycloalkyl are each optionally substituted with one or more groups selected from: C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkyl, carboxamide, cyano, halogen and hydroxy.

10

One aspect of the present invention encompasses certain pyrazole derivatives selected from compounds of Formula **Ig** and pharmaceutically acceptable salts, solvates and hydrates thereof:



**Ig**

15 wherein:

R<sup>2</sup> and R<sup>3</sup> together with the pyrazole ring to which they are both attached to form 4,5-dihydro-3*H*-benzo[e]indazol-3-yl or indeno[2,1-*c*]pyrazol-1(8*H*)-yl;

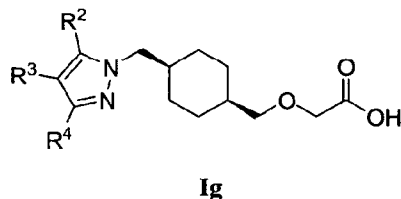
and

R<sup>4</sup> is selected from: H, 2,3-difluorophenyl, 2,4-difluorophenyl, 2-amino-2-oxoethoxy, 2-cyanoethyl, 2-ethoxyethylthio, 2-fluoro-4-methoxyphenyl, 2-fluoro-4-methylphenyl, 2-fluorophenyl, 2-hydroxyethylthio, 2-methoxyethyl, 2-methoxyethylthio, 3,4-difluorophenyl, 3,4-dihydroxybutyl, 3-chloro-2-fluorophenyl, 3-chlorophenyl, 3-fluoro-5-methoxyphenyl, 3-fluorophenyl, 3-methoxyphenyl, 4-chloro-2-fluorophenyl, 4-chloro-3-fluorophenyl, 4-chlorophenyl, 4-fluorophenyl, 4-hydroxyphenyl, 4-methoxyphenyl, cyanomethylthio, cyclopropyl, ethyl, isopropyl, methyl, methylthio, *m*-tolyl, *n*-propyl, phenyl, *p*-tolyl and trifluoromethyl.

20  
25



One aspect of the present invention encompasses certain pyrazole derivatives selected from compounds of Formula **Ig** and pharmaceutically acceptable salts, solvates and hydrates thereof:



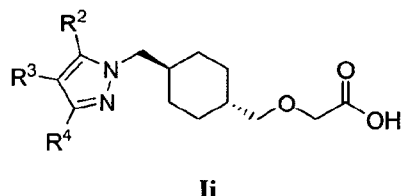
5            wherein:

$R^2$  and  $R^3$  together with the pyrazole ring to which they are both attached to form 4,5-dihydro-3*H*-benzo[e]indazol-3-yl or indeno[2,1-*c*]pyrazol-1(8*H*)-yl;

and

$R^4$  is selected from: H, 2,3-difluorophenyl, 2,4-difluorophenyl, 2-amino-2-oxoethoxy, 2-cyanoethyl, 2-ethoxyethylthio, 2-fluoro-4-methoxyphenyl, 2-fluoro-4-methylphenyl, 2-fluorophenyl, 2-hydroxyethyl, 2-hydroxyethylthio, 2-methoxyethyl, 2-methoxyethylthio, 3,4-difluorophenyl, 3,4-dihydroxybutyl, 3-chloro-2-fluorophenyl, 3-chlorophenyl, 3-fluoro-5-methoxyphenyl, 3-fluorophenyl, 3-hydroxypropyl, 3-methoxyphenyl, 4-chloro-2-fluorophenyl, 4-chloro-3-fluorophenyl, 4-chlorophenyl, 4-fluorophenyl, 4-hydroxyphenyl, 4-methoxyphenyl, 15 cyanomethylthio, cyclopropyl, ethyl, isopropyl, methyl, methylthio, *m*-tolyl, *n*-propyl, phenyl, *p*-tolyl and trifluoromethyl.

One aspect of the present invention encompasses certain pyrazole derivatives selected from compounds of Formula **II** and pharmaceutically acceptable salts, solvates and hydrates thereof:



wherein:

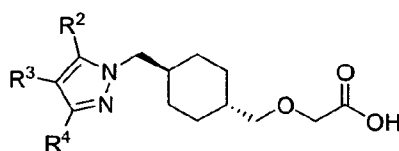
$R^2$  is selected from: H,  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkylsulfinyl,  $C_1$ - $C_6$  alkylsulfonyl,  $C_1$ - $C_6$  alkylthio, aryl and  $C_3$ - $C_7$  cycloalkyl; wherein said  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkylsulfinyl,  $C_1$ - $C_6$  alkylsulfonyl,  $C_1$ - $C_6$  alkylthio, aryl and  $C_3$ - $C_7$  cycloalkyl are each optionally substituted with one or more groups selected from:  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkylsulfinyl,  $C_1$ - $C_6$  alkylsulfonyl,  $C_1$ - $C_6$  alkylthio, amino, carboxamide, cyano, halogen and hydroxy;

$R^3$  is selected from:  $C_1$ - $C_6$  alkyl, aryl and heteroaryl; wherein said  $C_1$ - $C_6$  alkyl, aryl and heteroaryl are each optionally substituted with one or more groups selected from:  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_6$  alkyl, aryl, cyano,  $C_1$ - $C_6$  haloalkyl, halogen and hydroxy;

and

- 5  $R^4$  is selected from: H,  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkylthio, aryl and  $C_3$ - $C_7$  cycloalkyl; wherein said  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkylthio, aryl and  $C_3$ - $C_7$  cycloalkyl are each optionally substituted with one or more groups selected from:  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_6$  alkyl, carboxamide, cyano, halogen and hydroxy.

- 10 One aspect of the present invention encompasses certain pyrazole derivatives selected from compounds of Formula **II** and pharmaceutically acceptable salts, solvates and hydrates thereof:



**II**

wherein:

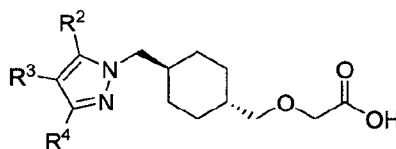
- 15  $R^2$  is selected from: H, 2-(methylsulfinyl)ethyl, 2-(methylsulfonyl)ethyl, 2-(methylthio)ethyl, 2,3-difluorophenyl, 2-aminoethylthio, 2-amino-2-oxoethoxy, 2-cyanoethyl, 2-ethoxyethylthio, 2-fluoro-4-methoxyphenyl, 2-fluorophenyl, 2-hydroxyethyl, 2-hydroxyethylsulfanyl, 2-hydroxyethylthio, 2-methoxyethyl, 2-methoxyethylthio, 3,4-difluorophenyl, 3,4-dihydroxybutyl, 3-chloro-2-fluorophenyl, 3-fluoro-5-methoxyphenyl, 3-fluorophenyl, 3-hydroxypropyl, 3-hydroxypropylthio, 3-methoxyphenyl, 4-chloro-3-fluorophenyl, 4-chlorophenyl, 4-fluorophenyl, 4-methoxyphenyl, cyanomethoxy, cyanomethylthio, cyclopropyl, ethoxy, ethyl, ethylthio, isopropyl, methyl, methylsulfinyl, methylsulfonyl, methylthio, *m*-tolyl, *n*-propyl, phenyl and trifluoromethyl;

- 25  $R^3$  is selected from: 2,3-difluorophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, 2-chlorophenyl, 2-fluoro-3-hydroxyphenyl, 2-fluoro-3-methoxyphenyl, 2-fluoro-3-methylphenyl, 2-fluoro-4-methylphenyl, 2-fluorophenyl, 2-methoxyphenyl, 2-methoxypyridin-4-yl, 3-(trifluoromethyl)phenyl, 3,4-difluorophenyl, 3-chloro-2-fluorophenyl, 3-chloro-4-fluorophenyl, 3-chlorophenyl, 3-fluoro-5-methoxyphenyl, 3-fluoro-5-methylphenyl, 3-fluorophenyl, 3-hydroxyphenyl, 3-isopropoxyphenyl, 3-methoxyphenyl, 4-chlorophenyl, 4-fluorophenyl, 4-methoxyphenyl, 5-cyano-2-fluorophenyl, 5-fluoropyridin-3-yl, 5-methoxypyridin-3-yl, 5-methylthiophen-2-yl, 6-methoxypyridin-3-yl, benzhydryl, furan-2-yl, *m*-tolyl, phenyl, *p*-tolyl, thiophen-2-yl and thiophen-3-yl;

and

$R^4$  is selected from: H, 2,3-difluorophenyl, 2,4-difluorophenyl, 2-amino-2-oxoethoxy, 2-cyanoethyl, 2-ethoxyethylthio, 2-fluoro-4-methoxyphenyl, 2-fluoro-4-methylphenyl, 2-fluorophenyl, 2-hydroxyethylthio, 2-methoxyethyl, 2-methoxyethylthio, 3,4-difluorophenyl, 3,4-dihydroxybutyl, 3-chloro-2-fluorophenyl, 3-chlorophenyl, 3-fluoro-5-methoxyphenyl, 3-fluorophenyl, 3-methoxyphenyl, 4-chloro-2-fluorophenyl, 4-chloro-3-fluorophenyl, 4-chlorophenyl, 4-fluorophenyl, 4-hydroxyphenyl, 4-methoxyphenyl, cyanomethylthio, cyclopropyl, ethyl, isopropyl, methyl, methylthio, *m*-tolyl, *n*-propyl, phenyl, *p*-tolyl and trifluoromethyl.

One aspect of the present invention encompasses certain pyrazole derivatives selected from compounds of Formula **II** and pharmaceutically acceptable salts, solvates and hydrates thereof:



**II**

wherein:

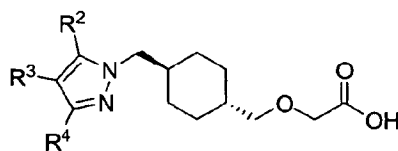
$R^2$  is selected from: H, 2-(methylsulfinyl)ethyl, 2-(methylsulfonyl)ethyl, 2-(methylthio)ethyl, 2,3-difluorophenyl, 2-aminoethylthio, 2-amino-2-oxoethoxy, 2-cyanoethyl, 2-ethoxyethylthio, 2-fluoro-4-methoxyphenyl, 2-fluorophenyl, 2-hydroxyethyl, 2-hydroxyethylsulfinyl, 2-hydroxyethylthio, 2-methoxyethyl, 2-methoxyethylthio, 3,4-difluorophenyl, 3,4-dihydroxybutyl, 3-chloro-2-fluorophenyl, 3-fluoro-5-methoxyphenyl, 3-fluorophenyl, 3-hydroxypropyl, 3-hydroxypropylthio, 3-methoxyphenyl, 4-chloro-3-fluorophenyl, 4-chlorophenyl, 4-fluorophenyl, 4-methoxyphenyl, cyanomethoxy, cyanomethylthio, cyclopropyl, ethoxy, ethyl, ethylthio, isopropyl, methyl, methylsulfinyl, methylsulfonyl, methylthio, *m*-tolyl, *n*-propyl, phenyl, *p*-tolyl and trifluoromethyl;

$R^3$  is selected from: 2,3-difluorophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, 2-chlorophenyl, 2-fluoro-3-hydroxyphenyl, 2-fluoro-3-methoxyphenyl, 2-fluoro-3-methylphenyl, 2-fluoro-4-methylphenyl, 2-fluorophenyl, 2-methoxyphenyl, 2-methoxypyridin-4-yl, 3-(trifluoromethyl)phenyl, 3,4-difluorophenyl, 3-chloro-2-fluorophenyl, 3-chloro-4-fluorophenyl, 3-chlorophenyl, 3-fluoro-5-methoxyphenyl, 3-fluoro-5-methylphenyl, 3-fluorophenyl, 3-hydroxyphenyl, 3-isopropoxyphenyl, 3-methoxyphenyl, 4-chlorophenyl, 4-fluorophenyl, 4-methoxyphenyl, 5-cyano-2-fluorophenyl, 5-fluoropyridin-3-yl, 5-methoxypyridin-3-yl, 5-methylthiophen-2-yl, 6-methoxypyridin-3-yl, benzhydryl, furan-2-yl, *m*-tolyl, phenyl, *p*-tolyl, thiophen-2-yl and thiophen-3-yl;

and

$R^4$  is selected from: H, 2,3-difluorophenyl, 2,4-difluorophenyl, 2-amino-2-oxoethoxy, 2-cyanoethyl, 2-ethoxyethylthio, 2-fluoro-4-methoxyphenyl, 2-fluoro-4-methylphenyl, 2-fluorophenyl, 2-hydroxyethyl, 2-hydroxyethylthio, 2-methoxyethyl, 2-methoxyethylthio, 3,4-difluorophenyl, 3,4-dihydroxybutyl, 3-chloro-2-fluorophenyl, 3-chlorophenyl, 3-fluoro-5-methoxyphenyl, 3-fluorophenyl, 3-hydroxypropyl, 3-methoxyphenyl, 4-chloro-2-fluorophenyl, 4-chloro-3-fluorophenyl, 4-chlorophenyl, 4-fluorophenyl, 4-hydroxyphenyl, 4-methoxyphenyl, cyanomethylthio, cyclopropyl, ethyl, isopropyl, methyl, methylthio, *m*-tolyl, *n*-propyl, phenyl, *p*-tolyl and trifluoromethyl.

One aspect of the present invention encompasses certain pyrazole derivatives selected from compounds of Formula **II** and pharmaceutically acceptable salts, solvates and hydrates thereof:



**II**

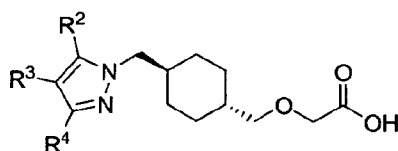
wherein:

$R^2$  and  $R^3$  together with the pyrazole ring to which they are both attached to form a tricyclic heteroaryl;

and

$R^4$  is selected from: H,  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkylthio, aryl and  $C_3$ - $C_7$  cycloalkyl; wherein said  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkylthio, aryl and  $C_3$ - $C_7$  cycloalkyl are each optionally substituted with one or more groups selected from:  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_6$  alkyl, carboxamide, cyano, halogen and hydroxy.

One aspect of the present invention encompasses certain pyrazole derivatives selected from compounds of Formula **II** and pharmaceutically acceptable salts, solvates and hydrates thereof:



**II**

wherein:

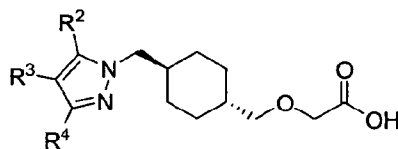
$R^2$  and  $R^3$  together with the pyrazole ring to which they are both attached to form 4,5-dihydro-3*H*-benzo[*e*]indazol-3-yl or indeno[2,1-*c*]pyrazol-1(8*H*)-yl;

and

$R^4$  is selected from: H, 2,3-difluorophenyl, 2,4-difluorophenyl, 2-amino-2-oxoethoxy, 2-cyanoethyl, 2-ethoxyethylthio, 2-fluoro-4-methoxyphenyl, 2-fluoro-4-methylphenyl, 2-fluorophenyl, 2-hydroxyethylthio, 2-methoxyethyl, 2-methoxyethylthio, 3,4-difluorophenyl, 3,4-dihydroxybutyl, 3-chloro-2-fluorophenyl, 3-chlorophenyl, 3-fluoro-5-methoxyphenyl, 3-fluorophenyl, 3-methoxyphenyl, 4-chloro-2-fluorophenyl, 4-chloro-3-fluorophenyl, 4-chlorophenyl, 4-fluorophenyl, 4-hydroxyphenyl, 4-methoxyphenyl, cyanomethylthio, cyclopropyl, ethyl, isopropyl, methyl, methylthio, *m*-tolyl, *n*-propyl, phenyl, *p*-tolyl and trifluoromethyl.

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One aspect of the present invention encompasses certain pyrazole derivatives selected from compounds of Formula **II** and pharmaceutically acceptable salts, solvates and hydrates thereof:



**II**

15

wherein:

$R^2$  and  $R^3$  together with the pyrazole ring to which they are both attached to form 4,5-dihydro-3*H*-benzo[*c*]indazol-3-yl or indeno[2,1-*c*]pyrazol-1(8*H*)-yl;

and

$R^4$  is selected from: H, 2,3-difluorophenyl, 2,4-difluorophenyl, 2-amino-2-oxoethoxy, 2-cyanoethyl, 2-ethoxyethylthio, 2-fluoro-4-methoxyphenyl, 2-fluoro-4-methylphenyl, 2-fluorophenyl, 2-hydroxyethyl, 2-hydroxyethylthio, 2-methoxyethyl, 2-methoxyethylthio, 3,4-difluorophenyl, 3,4-dihydroxybutyl, 3-chloro-2-fluorophenyl, 3-chlorophenyl, 3-fluoro-5-methoxyphenyl, 3-fluorophenyl, 3-hydroxypropyl, 3-methoxyphenyl, 4-chloro-2-fluorophenyl, 4-chloro-3-fluorophenyl, 4-chlorophenyl, 4-fluorophenyl, 4-hydroxyphenyl, 4-methoxyphenyl, cyanomethylthio, cyclopropyl, ethyl, isopropyl, methyl, methylthio, *m*-tolyl, *n*-propyl, phenyl, *p*-tolyl and trifluoromethyl.

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Some embodiments of the present invention include every combination of one or more compounds selected from the following group shown in TABLE A.

TABLE A

| Cpd No. | Chemical Structure | Chemical Name   |
|---------|--------------------|---|
| 1       |                    | 2-(((1 <i>r</i> ,4 <i>r</i> )-4-((5-(4-fluorophenyl)-3-(methylthio)-4-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid |
| 2       |                    | 2-(((1 <i>r</i> ,4 <i>r</i> )-4-((3-(4-fluorophenyl)-5-(methylthio)-4-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid |
| 3       |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((3,4-diphenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid                               |
| 4       |                    | 2-(((1 <i>r</i> ,4 <i>r</i> )-4-((1-phenyl-4,5-dihydro-3 <i>H</i> -benzo[e]indazol-3-yl)methyl)cyclohexyl)methoxy)acetic acid               |
| 5       |                    | 2-(((1 <i>r</i> ,4 <i>r</i> )-4-((3-phenylindeno[2,1-c]pyrazol-1(8 <i>H</i> )-yl)methyl)cyclohexyl)methoxy)acetic acid                      |
| 6       |                    | 2-(((1 <i>r</i> ,4 <i>r</i> )-4-((4-(3-methoxyphenyl)-3-methyl-5-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid      |
| 7       |                    | 2-(((1 <i>r</i> ,4 <i>r</i> )-4-((4-(3-methoxyphenyl)-5-methyl-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid      |

| Cpd No. | Chemical Structure | Chemical Name   |
|---------|--------------------|---|
| 8       |                    | 2-(((1 <i>r</i> ,4 <i>r</i> )-4-((3,4-diphenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid                               |
| 9       |                    | 2-(((1 <i>r</i> ,4 <i>r</i> )-4-((4,5-diphenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid                               |
| 10      |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((3-(4-fluorophenyl)-5-(methylthio)-4-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid |
| 11      |                    | 2-(((1 <i>r</i> ,4 <i>r</i> )-4-((5-methyl-3,4-diphenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid                      |
| 12      |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((5-(4-fluorophenyl)-3-(methylthio)-4-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid |
| 13      |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((4-(3-methoxyphenyl)-3-methyl-5-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid      |
| 14      |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((4-(3-methoxyphenyl)-5-methyl-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid      |

| Cpd No. | Chemical Structure | Chemical Name  |
|---------|--------------------|--|
| 15      |                    | 2-(((1s,4s)-4-((3-methyl-4,5-diphenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid                    |
| 16      |                    | 2-(((1s,4s)-4-((5-methyl-3,4-diphenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid                    |
| 17      |                    | 2-(((1s,4s)-4-((4-benzhydryl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid                             |
| 18      |                    | 2-(((1r,4r)-4-((4-benzhydryl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid                             |
| 19      |                    | 2-(((1s,4s)-4-((3-methyl-5-phenyl-4-m-tolyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid              |
| 20      |                    | 2-(((1s,4s)-4-((4-(2,5-difluorophenyl)-5-methyl-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid |
| 21      |                    | 2-(((1s,4s)-4-((4-(4-chlorophenyl)-3-methyl-5-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid     |
| 22      |                    | 2-(((1s,4s)-4-((4-(4-fluorophenyl)-5-methyl-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid     |



| Cpd No. | Chemical Structure | Chemical Name   |
|---------|--------------------|---|
| 23      |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((4-(3-chlorophenyl)-5-methyl-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid     |
| 24      |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((5-methyl-3-phenyl-4- <i>m</i> -tolyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid     |
| 25      |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((4-(4-fluorophenyl)-3-methyl-5-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid     |
| 26      |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((4-(2,3-difluorophenyl)-3-methyl-5-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid |
| 27      |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((4-(2,3-difluorophenyl)-5-methyl-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid |
| 28      |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((4-(4-chlorophenyl)-5-methyl-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid     |
| 29      |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((4-(2,5-difluorophenyl)-3-methyl-5-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid |

| Cpd No. | Chemical Structure | Chemical Name   |
|---------|--------------------|---|
| 30      |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((4-(3-methoxyphenyl)-3-(methylthio)-5-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid    |
| 31      |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((4-(3-methoxyphenyl)-5-(methylthio)-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid    |
| 32      |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((5-(3-methoxyphenyl)-3-methyl-4-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid          |
| 33      |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((3-(3-methoxyphenyl)-5-methyl-4-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid          |
| 34      |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((5-(3-fluoro-5-methoxyphenyl)-3-methyl-4-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid |
| 35      |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((3-(3-fluoro-5-methoxyphenyl)-5-methyl-4-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid |

| Cpd No. | Chemical Structure | Chemical Name  |
|---------|--------------------|--|
| 36      |                    | 2-(((1s,4s)-4-((5-(4-methoxyphenyl)-3-(methylthio)-4-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid    |
| 37      |                    | 2-(((1s,4s)-4-((3-(4-methoxyphenyl)-5-(methylthio)-4-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid    |
| 38      |                    | 2-(((1s,4s)-4-((4-(4-methoxyphenyl)-5-methyl-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid          |
| 39      |                    | 2-(((1s,4s)-4-((4-(3-fluoro-5-methoxyphenyl)-5-methyl-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid |
| 40      |                    | 2-(((1s,4s)-4-((4-(3-fluorophenyl)-5-methyl-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid           |
| 41      |                    | 2-(((1s,4s)-4-((4-(3-chlorophenyl)-3-methyl-5-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid           |
| 42      |                    | 2-(((1s,4s)-4-((4-(4-methoxyphenyl)-3-methyl-5-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid          |

| Cpd No. | Chemical Structure | Chemical Name  |
|---------|--------------------|--|
| 43      |                    | 2-(((1s,4s)-4-((4-(3-fluoro-5-methoxyphenyl)-3-methyl-5-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid |
| 44      |                    | 2-(((1s,4s)-4-((4-(2-chlorophenyl)-5-methyl-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid           |
| 45      |                    | 2-(((1s,4s)-4-((4-(2-chlorophenyl)-3-methyl-5-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid           |
| 46      |                    | 2-(((1s,4s)-4-((4-(3-fluorophenyl)-3-methyl-5-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid           |
| 47      |                    | 2-(((1s,4s)-4-((5-methyl-3-phenyl-4-p-tolyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid                    |
| 48      |                    | 2-(((1s,4s)-4-((4-(2,4-difluorophenyl)-5-methyl-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid       |
| 49      |                    | 2-(((1s,4s)-4-((4-(4-chlorophenyl)-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid                    |
| 50      |                    | 2-(((1s,4s)-4-((4-(3-fluorophenyl)-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid                    |

| Cpd No. | Chemical Structure | Chemical Name   |
|---------|--------------------|---|
| 51      |                    | 2-(((1s,4s)-4-((4-(4-fluorophenyl)-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid                   |
| 52      |                    | 2-(((1s,4s)-4-((4-(3-chloro-2-fluorophenyl)-5-methyl-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid |
| 53      |                    | 2-(((1s,4s)-4-((4-(2,4-difluorophenyl)-3-methyl-5-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid      |
| 54      |                    | 2-(((1s,4s)-4-((4-(3-chloro-2-fluorophenyl)-3-methyl-5-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid |
| 55      |                    | 2-(((1s,4s)-4-((3-methyl-5-phenyl-4-p-tolyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid                   |
| 56      |                    | 2-(((1s,4s)-4-((4-(3-chloro-4-fluorophenyl)-3-methyl-5-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid |
| 57      |                    | 2-(((1s,4s)-4-((4-(3-chloro-4-fluorophenyl)-5-methyl-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid |
| 58      |                    | 2-(((1s,4s)-4-((4-(4-methoxyphenyl)-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid                  |

| Cpd No. | Chemical Structure | Chemical Name  |
|---------|--------------------|--|
| 59      |                    | 2-(((1s,4s)-4-((4-(2-methoxyphenyl)-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid |
| 60      |                    | 2-(((1s,4s)-4-((3-phenyl-4-m-tolyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid           |
| 61      |                    | 2-(((1s,4s)-4-((3-phenyl-4-p-tolyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid           |
| 62      |                    | 2-(((1s,4s)-4-((4-(3-chlorophenyl)-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid  |
| 63      |                    | 2-(((1s,4s)-4-((4-(2-fluorophenyl)-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid  |
| 64      |                    | 2-(((1s,4s)-4-((3-methyl-4-phenyl-5-m-tolyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid  |
| 65      |                    | 2-(((1s,4s)-4-((5-methyl-4-phenyl-3-m-tolyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid  |

| Cpd No. | Chemical Structure | Chemical Name   |
|---------|--------------------|---|
| 66      |                    | 2-(((1s,4s)-4-((3-(3-chlorophenyl)-5-methyl-4-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid          |
| 67      |                    | 2-(((1s,4s)-4-((5-(3-fluorophenyl)-3-methyl-4-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid          |
| 68      |                    | 2-(((1s,4s)-4-((3-(3-fluorophenyl)-5-methyl-4-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid          |
| 69      |                    | 2-(((1s,4s)-4-((5-(3-chloro-2-fluorophenyl)-3-methyl-4-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid |
| 70      |                    | 2-(((1s,4s)-4-((3-(3-chloro-2-fluorophenyl)-5-methyl-4-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid |
| 71      |                    | 2-(((1s,4s)-4-((5-(2-fluorophenyl)-3-methyl-4-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid          |
| 72      |                    | 2-(((1s,4s)-4-((3-(2-fluorophenyl)-5-methyl-4-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid          |

| Cpd No. | Chemical Structure | Chemical Name  |
|---------|--------------------|--|
| 73      |                    | 2-(((1s,4s)-4-((5-(2,3-difluorophenyl)-3-methyl-4-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid           |
| 74      |                    | 2-(((1s,4s)-4-((3-(2,3-difluorophenyl)-5-methyl-4-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid           |
| 75      |                    | 2-(((1s,4s)-4-((3-(methylthio)-4,5-diphenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid                        |
| 76      |                    | 2-(((1s,4s)-4-((5-(methylthio)-3,4-diphenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid                        |
| 77      |                    | 2-(((1s,4s)-4-((4-(2,5-difluorophenyl)-3-(methylthio)-5-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid     |
| 78      |                    | 2-(((1s,4s)-4-((4-(2,5-difluorophenyl)-5-(methylthio)-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid     |
| 79      |                    | 2-(((1s,4s)-4-((4-(5-cyano-2-fluorophenyl)-5-(methylthio)-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid |



| Cpd No. | Chemical Structure | Chemical Name   |
|---------|--------------------|---|
| 80      |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((4-(3,4-difluorophenyl)-5-ethoxy-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid       |
| 81      |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((5-ethoxy-3,4-diphenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid                          |
| 82      |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((4-(2,3-difluorophenyl)-3-(methylthio)-5-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid |
| 83      |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((4-(2,3-difluorophenyl)-5-(methylthio)-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid |
| 84      |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((4-(3-isopropoxyphenyl)-3-(methylthio)-5-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid |
| 85      |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((4-(3-isopropoxyphenyl)-5-(methylthio)-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid |

| Cpd No. | Chemical Structure | Chemical Name  |
|---------|--------------------|--|
| 86      |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((4-(2,3-difluorophenyl)-5-(methylsulfonyl)-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid  |
| 87      |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((4-(2,5-difluorophenyl)-5-(methylsulfonyl)-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid  |
| 88      |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((5-(ethylthio)-3,4-diphenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid                          |
| 89      |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((5-(ethylthio)-4-(3-methoxyphenyl)-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid          |
| 90      |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((5-(ethylthio)-4-(2-fluoro-3-methoxyphenyl)-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid |
| 91      |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((4-(3-fluorophenyl)-5-(methylthio)-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid          |

| Cpd No. | Chemical Structure | Chemical Name   |
|---------|--------------------|---|
| 92      |                    | 2-(((1s,4s)-4-((4-(2-fluoro-3-methoxyphenyl)-5-(methylthio)-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid  |
| 93      |                    | 2-(((1s,4s)-4-((4-(3-fluoro-5-methoxyphenyl)-5-(methylthio)-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid  |
| 94      |                    | 2-(((1s,4s)-4-((4-(4-fluorophenyl)-5-(methylthio)-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid            |
| 95      |                    | 2-(((1s,4s)-4-((4-(3-chlorophenyl)-5-(methylthio)-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid            |
| 96      |                    | 2-(((1s,4s)-4-((5-(methylthio)-3-phenyl-4-(3-(trifluoromethyl)phenyl)-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid |
| 97      |                    | 2-(((1s,4s)-4-((4-(4-chlorophenyl)-5-(methylthio)-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid            |
| 98      |                    | 2-(((1s,4s)-4-((3-ethyl-4-(3-methoxyphenyl)-5-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid                  |

| Cpd No. | Chemical Structure | Chemical Name  |
|---------|--------------------|--|
| 99      |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((5-ethyl-4-(3-methoxyphenyl)-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid          |
| 100     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((3-ethyl-4,5-diphenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid                          |
| 101     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((5-ethyl-3,4-diphenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid                          |
| 102     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((3-ethyl-4-(3-fluorophenyl)-5-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid           |
| 103     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((5-ethyl-4-(3-fluorophenyl)-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid           |
| 104     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((3-ethyl-4-(2-fluoro-3-methoxyphenyl)-5-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid |
| 105     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((5-ethyl-4-(2-fluoro-3-methoxyphenyl)-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid |

| Cpd No. | Chemical Structure | Chemical Name  |
|---------|--------------------|--|
| 106     |                    | 2-(((1s,4s)-4-((4-(2,3-difluorophenyl)-3-ethyl-5-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid           |
| 107     |                    | 2-(((1s,4s)-4-((4-(2,3-difluorophenyl)-5-ethyl-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid           |
| 108     |                    | 2-(((1s,4s)-4-((5-(methylthio)-3-phenyl-4-(thiophen-2-yl)-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid         |
| 109     |                    | 2-(((1s,4s)-4-((4-(furan-2-yl)-5-(methylthio)-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid            |
| 110     |                    | 2-(((1s,4s)-4-((5-(methylthio)-3-phenyl-4-(thiophen-3-yl)-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid         |
| 111     |                    | 2-(((1s,4s)-4-((5-(methylthio)-4-(5-methylthiophen-2-yl)-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid |
| 112     |                    | 2-(((1s,4s)-4-((3-isopropyl-4,5-diphenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid                          |

| Cpd No. | Chemical Structure | Chemical Name  |
|---------|--------------------|--|
| 113     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((4-(3-fluorophenyl)-5-isopropyl-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid         |
| 114     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((4-(3-methoxyphenyl)-5-(methylsulfinyl)-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid |
| 115     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((4-(3-chlorophenyl)-3-ethyl-5-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid             |
| 116     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((4-(3-chlorophenyl)-5-ethyl-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid             |
| 117     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((4-(2,3-difluorophenyl)-5-isopropyl-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid     |
| 118     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((5-(ethylthio)-4-(2-fluorophenyl)-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid       |

| Cpd No. | Chemical Structure | Chemical Name  |
|---------|--------------------|--|
| 119     |                    | 2-(((1s,4s)-4-((5-(ethylthio)-4-(3-fluoro-5-methoxyphenyl))-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid |
| 120     |                    | 2-(((1s,4s)-4-((5-cyclopropyl-4-(3-methoxyphenyl))-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid          |
| 121     |                    | 2-(((1s,4s)-4-((3-cyclopropyl-4,5-diphenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid                           |
| 122     |                    | 2-(((1s,4s)-4-((5-cyclopropyl-3,4-diphenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid                           |
| 123     |                    | 2-(((1s,4s)-4-((3-isopropyl-4-(3-methoxyphenyl)-5-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid             |
| 124     |                    | 2-(((1s,4s)-4-((4-(3-chlorophenyl)-3-isopropyl-5-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid              |

| Cpd No. | Chemical Structure | Chemical Name   |
|---------|--------------------|---|
| 125     |                    | 2-(((1s,4s)-4-((4-(2-fluoro-3-methoxyphenyl)-3-isopropyl-5-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid   |
| 126     |                    | 2-(((1s,4s)-4-((5-cyclopropyl-4-(2-fluoro-3-methoxyphenyl)-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid |
| 127     |                    | 2-(((1s,4s)-4-((5-cyclopropyl-4-(2,3-difluorophenyl)-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid       |
| 128     |                    | 2-(((1s,4s)-4-((5-isopropyl-4-(3-methoxyphenyl)-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid            |
| 129     |                    | 2-(((1s,4s)-4-((4-(3-chlorophenyl)-5-isopropyl-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid             |
| 130     |                    | 2-(((1s,4s)-4-((4-(2-fluoro-3-methoxyphenyl)-5-isopropyl-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid   |
| 131     |                    | methyl 2-(((1s,4s)-4-((5-(methylthio)-3,4-diphenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate                      |



| Cpd No. | Chemical Structure | Chemical Name  |
|---------|--------------------|--|
| 132     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((4-(3-chlorophenyl)-3-cyclopropyl-5-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid           |
| 133     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((4-(3-chlorophenyl)-5-cyclopropyl-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid           |
| 134     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((4-(3-fluoro-5-methylphenyl)-5-(methylthio)-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid |
| 135     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((4-(5-fluoropyridin-3-yl)-5-(methylthio)-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid    |
| 136     |                    | methyl 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((4-(3-methoxyphenyl)-5-methyl-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate            |
| 137     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((3-(4-fluorophenyl)-5-methyl-4-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid                |
| 138     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((3-(4-chlorophenyl)-5-methyl-4-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid                |

| Cpd No. | Chemical Structure | Chemical Name   |
|---------|--------------------|---|
| 139     |                    | 2-(((1s,4s)-4-((5-methyl-4-phenyl-3-p-tolyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid                   |
| 140     |                    | 2-(((1s,4s)-4-((3-(4-methoxyphenyl)-5-methyl-4-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid         |
| 141     |                    | 2-(((1s,4s)-4-((3-(2,4-difluorophenyl)-5-methyl-4-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid      |
| 142     |                    | 2-(((1s,4s)-4-((4-(2,3-difluorophenyl)-5-(ethylthio)-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid |
| 143     |                    | 2-(((1s,4s)-4-((3-(2-fluoro-4-methylphenyl)-5-methyl-4-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid |
| 144     |                    | 2-(((1s,4s)-4-((3-(4-chloro-2-fluorophenyl)-5-methyl-4-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid |

| Cpd No. | Chemical Structure | Chemical Name  |
|---------|--------------------|--|
| 145     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((3-(2-fluoro-4-methoxyphenyl)-5-methyl-4-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid  |
| 146     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((5-(2-hydroxyethylthio)-3,4-diphenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid             |
| 147     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((4-(5-fluoropyridin-3-yl)-5-methyl-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid      |
| 148     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((5-(ethylthio)-4-(5-fluoropyridin-3-yl)-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid |
| 149     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((5-ethyl-4-(5-fluoropyridin-3-yl)-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid       |
| 150     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((1-phenyl-4,5-dihydro-3 <i>H</i> -benzo[e]indazol-3-yl)methyl)cyclohexyl)methoxy)acetic acid                    |

| Cpd No. | Chemical Structure | Chemical Name  |
|---------|--------------------|--|
| 151     |                    | 2-(((1s,4s)-4-((3,4-diphenyl-5-(trifluoromethyl)-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid                 |
| 152     |                    | 2-(((1s,4s)-4-((3-phenyl-4-p-tolyl-5-(trifluoromethyl)-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid           |
| 153     |                    | 2-(((1s,4s)-4-((4-(3-hydroxyphenyl)-5-methyl-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid            |
| 154     |                    | 2-(((1s,4s)-4-((4-(3-methoxyphenyl)-5-phenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid |
| 155     |                    | 2-(((1s,4s)-4-((4-(3-methoxyphenyl)-3-phenyl-5-(trifluoromethyl)-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid |
| 156     |                    | 2-(((1R,4s)-4-((3-((S)-3,4-dihydroxybutyl)-4,5-diphenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid          |

| Cpd No. | Chemical Structure | Chemical Name  |
|---------|--------------------|--|
| 157     |                    | 2-(((1 <i>R</i> ,4 <i>S</i> )-4-((5-(( <i>S</i> )-3,4-dihydroxybutyl)-3,4-diphenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid                    |
| 158     |                    | 2-(((1 <i>R</i> ,4 <i>S</i> )-4-((5-(( <i>S</i> )-3,4-dihydroxybutyl)-4-(3-fluorophenyl)-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid     |
| 159     |                    | 2-(((1 <i>R</i> ,4 <i>S</i> )-4-((4-(3,4-difluorophenyl)-3-(( <i>S</i> )-3,4-dihydroxybutyl)-5-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid |
| 160     |                    | 2-(((1 <i>R</i> ,4 <i>S</i> )-4-((4-(3,4-difluorophenyl)-5-(( <i>S</i> )-3,4-dihydroxybutyl)-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid |
| 161     |                    | 2-(((1 <i>R</i> ,4 <i>S</i> )-4-((5-(( <i>S</i> )-3,4-dihydroxybutyl)-4-(3-hydroxyphenyl)-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid    |

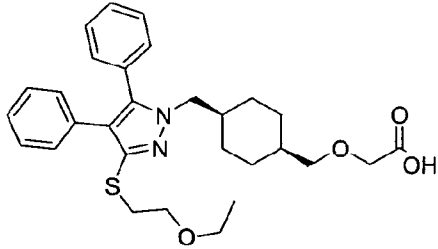
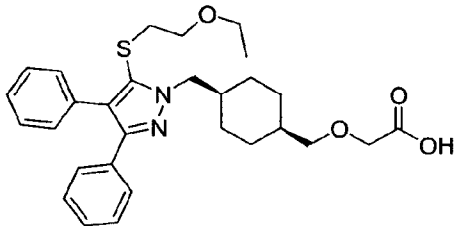
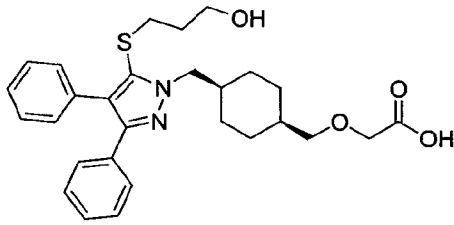
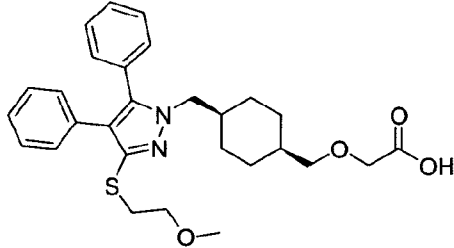
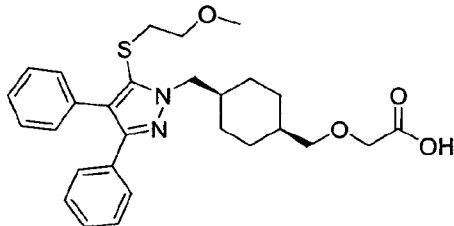
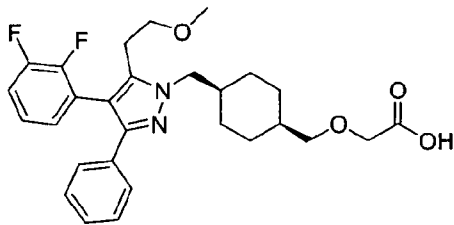
| Cpd No. | Chemical Structure | Chemical Name  |
|---------|--------------------|--|
| 162     |                    | 2-(((1 <i>R</i> ,4 <i>S</i> )-4-((4-(3-chlorophenyl)-5-(( <i>S</i> )-3,4-dihydroxybutyl)-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid |
| 163     |                    | 2-(((1 <i>S</i> ,4 <i>S</i> )-4-((3-(4-chlorophenyl)-5-ethyl-4-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid                             |
| 164     |                    | 2-(((1 <i>S</i> ,4 <i>S</i> )-4-((5-ethyl-3-(4-fluorophenyl)-4-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid                             |
| 165     |                    | 2-(((1 <i>S</i> ,4 <i>S</i> )-4-((5-ethyl-3-(2-fluoro-4-methoxyphenyl)-4-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid                   |
| 166     |                    | 2-(((1 <i>S</i> ,4 <i>S</i> )-4-((5-ethyl-3-(4-methoxyphenyl)-4-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid                            |
| 167     |                    | 2-(((1 <i>S</i> ,4 <i>S</i> )-4-((5-ethyl-3-(2-fluoro-4-methylphenyl)-4-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid                    |

| Cpd No. | Chemical Structure | Chemical Name  |
|---------|--------------------|--|
| 168     |                    | 2-(((1 <i>S</i> ,4 <i>S</i> )-4-((5-ethyl-4-phenyl-3- <i>p</i> -tolyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid                                 |
| 169     |                    | 2-(((1 <i>S</i> ,4 <i>S</i> )-4-((5-(( <i>R</i> )-3,4-dihydroxybutyl)-4-(3-fluorophenyl)-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid     |
| 170     |                    | 2-(((1 <i>S</i> ,4 <i>S</i> )-4-((4-(3,4-difluorophenyl)-5-(( <i>R</i> )-3,4-dihydroxybutyl)-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid |
| 171     |                    | 2-(((1 <i>S</i> ,4 <i>S</i> )-4-((4-(3-chlorophenyl)-5-(( <i>R</i> )-3,4-dihydroxybutyl)-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid     |
| 172     |                    | 2-(((1 <i>S</i> ,4 <i>S</i> )-4-((5-ethyl-4-(3-hydroxyphenyl)-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid                                |
| 173     |                    | 2-(((1 <i>S</i> ,4 <i>S</i> )-4-((4-(3-hydroxyphenyl)-5-(methylthio)-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid                         |

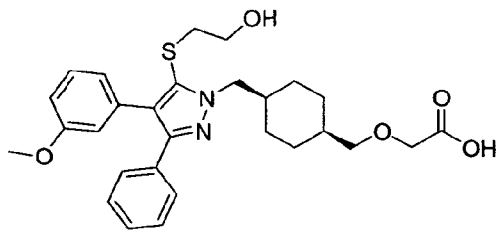
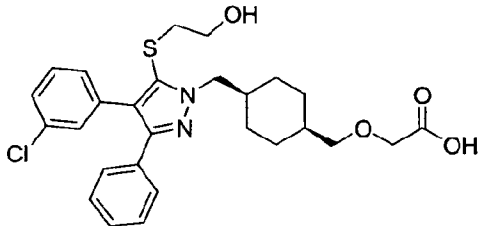
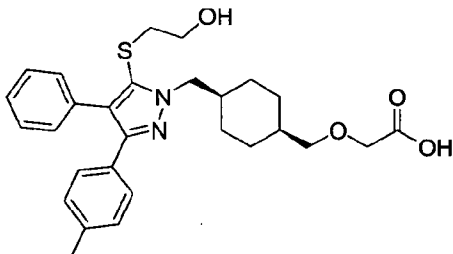
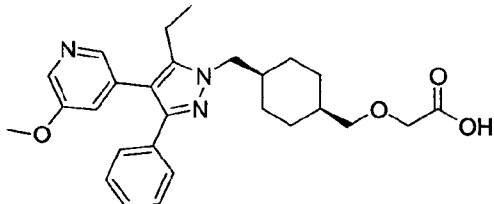
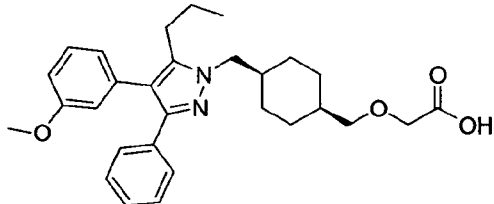
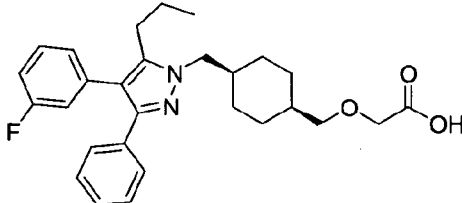
| Cpd No. | Chemical Structure | Chemical Name  |
|---------|--------------------|--|
| 174     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((5-(ethylthio)-4-(2-fluoro-3-hydroxyphenyl)-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid |
| 175     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((5-ethyl-3-(4-hydroxyphenyl)-4-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid                |
| 176     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((3-(4-chloro-3-fluorophenyl)-5-ethyl-4-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid        |
| 177     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((5-(ethylthio)-4-(3-hydroxyphenyl)-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid          |
| 178     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((5-(2-methoxyethyl)-3,4-diphenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid                     |
| 179     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((5-(2-methoxyethyl)-4-(3-methoxyphenyl)-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid     |



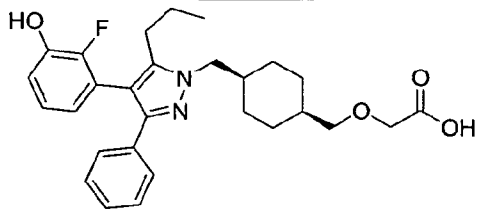
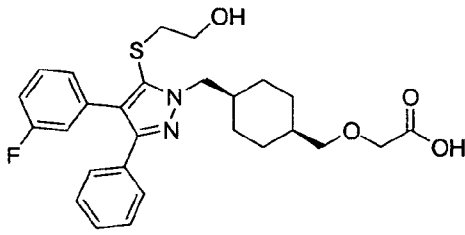
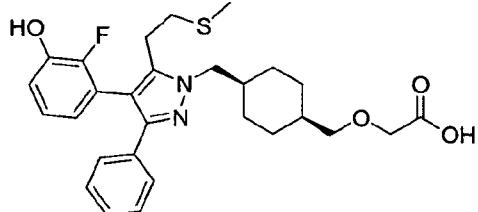
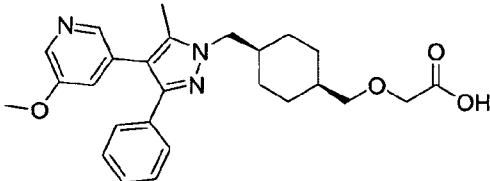
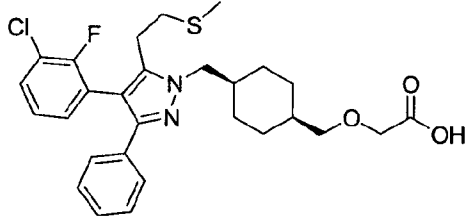
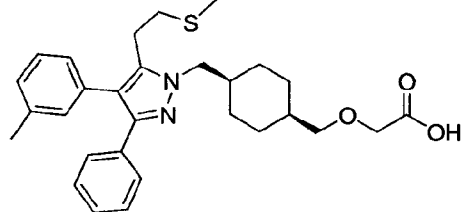
| Cpd No. | Chemical Structure | Chemical Name  |
|---------|--------------------|--|
| 180     |                    | 2-(((1s,4s)-4-((4-(3-hydroxyphenyl)-5-(2-methoxyethyl)-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid          |
| 181     |                    | 2-(((1s,4s)-4-((5-(2-methoxyethyl)-4-(6-methoxypyridin-3-yl)-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid    |
| 182     |                    | 2-(((1s,4s)-4-((4-(2-fluoro-3-hydroxyphenyl)-5-(2-methoxyethyl)-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid |
| 183     |                    | 2-(((1s,4s)-4-((3-(cyanomethylthio)-4,5-diphenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid                         |
| 184     |                    | 2-(((1s,4s)-4-((5-(cyanomethylthio)-3,4-diphenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid                         |

| Cpd No. | Chemical Structure  | Chemical Name  |
|---------|---|--|
| 185     |    | 2-(((1s,4s)-4-((3-(2-ethoxyethylthio)-4,5-diphenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid                 |
| 186     |    | 2-(((1s,4s)-4-((5-(2-ethoxyethylthio)-3,4-diphenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid                 |
| 187     |   | 2-(((1s,4s)-4-((5-(3-hydroxypropylthio)-3,4-diphenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid               |
| 188     |  | 2-(((1s,4s)-4-((3-(2-methoxyethylthio)-4,5-diphenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid                |
| 189     |  | 2-(((1s,4s)-4-((5-(2-methoxyethylthio)-3,4-diphenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid                |
| 190     |  | 2-(((1s,4s)-4-((4-(2,3-difluorophenyl)-5-(2-methoxyethyl)-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid |

| Cpd No. | Chemical Structure | Chemical Name  |
|---------|--------------------|--|
| 191     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((4-(3-chloro-2-fluorophenyl)-5-(2-methoxyethyl)-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid |
| 192     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((4-(2-fluoro-3-methylphenyl)-5-(2-methoxyethyl)-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid |
| 193     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((5-(2-methoxyethyl)-3-phenyl-4- <i>m</i> -tolyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid          |
| 194     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((4-(3-fluorophenyl)-5-(2-methoxyethyl)-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid          |
| 195     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((4-(2-methoxypyridin-4-yl)-5-methyl-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid             |
| 196     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((5-ethyl-4-(2-methoxypyridin-4-yl)-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid              |
| 197     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((4-(3-chlorophenyl)-5-(2-methoxyethyl)-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid          |

| Cpd No. | Chemical Structure   | Chemical Name  |
|---------|--|--|
| 198     |    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((5-(2-hydroxyethylthio)-4-(3-methoxyphenyl)-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid |
| 199     |    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((4-(3-chlorophenyl)-5-(2-hydroxyethylthio)-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid  |
| 200     |    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((5-(2-hydroxyethylthio)-4-phenyl-3- <i>p</i> -tolyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid  |
| 201     |  | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((5-ethyl-4-(5-methoxypyridin-3-yl)-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid          |
| 202     |  | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((4-(3-methoxyphenyl)-3-phenyl-5-propyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid               |
| 203     |   | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((4-(3-fluorophenyl)-3-phenyl-5-propyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid                |

| Cpd No. | Chemical Structure | Chemical Name  |
|---------|--------------------|--|
| 204     |                    | 2-(((1s,4s)-4-((4-(3-chlorophenyl)-3-phenyl-5-propyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid           |
| 205     |                    | 2-(((1s,4s)-4-((3-phenyl-5-propyl-4-m-tolyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid                    |
| 206     |                    | 2-(((1s,4s)-4-((4-(2-fluoro-3-methoxyphenyl)-3-phenyl-5-propyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid |
| 207     |                    | 2-(((1s,4s)-4-((4-(2,3-difluorophenyl)-3-phenyl-5-propyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid       |
| 208     |                    | 2-(((1s,4s)-4-((4-(3-chloro-2-fluorophenyl)-3-phenyl-5-propyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid  |
| 209     |                    | 2-(((1s,4s)-4-((4-(2-fluoro-3-methylphenyl)-3-phenyl-5-propyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid  |
| 210     |                    | 2-(((1s,4s)-4-((5-(2-hydroxyethylthio)-3-phenyl-4-m-tolyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid      |

| Cpd No. | Chemical Structure   | Chemical Name  |
|---------|--|--|
| 211     |    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((4-(2-fluoro-3-hydroxyphenyl)-3-phenyl-5-propyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid                |
| 212     |     | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((4-(3-fluorophenyl)-5-(2-hydroxyethylthio)-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid            |
| 213     |    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((4-(2-fluoro-3-hydroxyphenyl)-5-(2-(methylthio)ethyl)-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid |
| 214     |  | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((4-(5-methoxypyridin-3-yl)-5-methyl-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid                   |
| 215     |   | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((4-(3-chloro-2-fluorophenyl)-5-(2-(methylthio)ethyl)-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid  |
| 216     |   | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((5-(2-(methylthio)ethyl)-3-phenyl-4- <i>m</i> -tolyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid           |

| Cpd No. | Chemical Structure | Chemical Name   |
|---------|--------------------|---|
| 217     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((4-(3-chlorophenyl)-5-(2-hydroxyethylsulfinyl)-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid           |
| 218     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((4-(2-fluoro-3-methylphenyl)-5-(2-(methylthio)ethyl)-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid     |
| 219     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((4-(3-chloro-2-fluorophenyl)-5-(2-(methylsulfinyl)ethyl)-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid |
| 220     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((5-(2-(methylsulfinyl)ethyl)-3-phenyl-4- <i>m</i> -tolyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid          |
| 221     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((4-(3-hydroxyphenyl)-5-(2-(methylthio)ethyl)-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid             |
| 222     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((4-(3-fluorophenyl)-5-(2-(methylthio)ethyl)-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid              |

| Cpd No. | Chemical Structure | Chemical Name  |
|---------|--------------------|--|
| 223     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((5-(4-fluorophenyl)-4-phenyl-3-propyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid          |
| 224     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((3-(4-fluorophenyl)-4-phenyl-5-propyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid          |
| 225     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((5-(4-chloro-3-fluorophenyl)-4-phenyl-3-propyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid |
| 226     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((3-(4-chloro-3-fluorophenyl)-4-phenyl-5-propyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid |
| 227     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((5-(4-chlorophenyl)-4-phenyl-3-propyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid          |
| 228     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((3-(4-chlorophenyl)-4-phenyl-5-propyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid          |



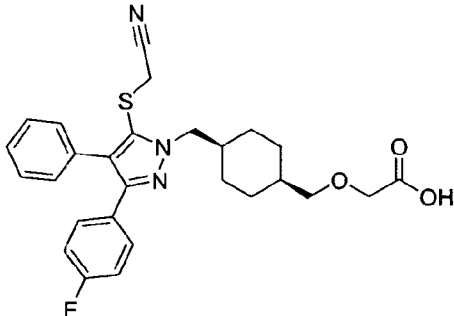
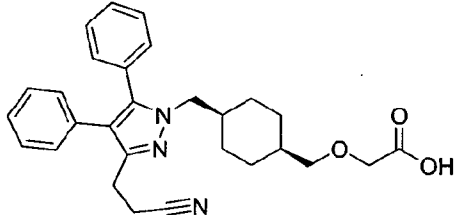
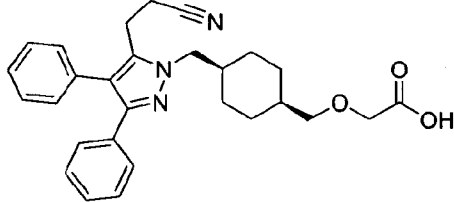
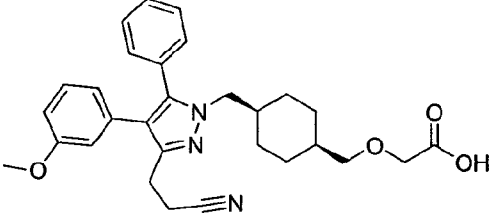
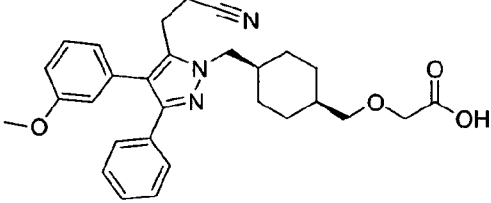
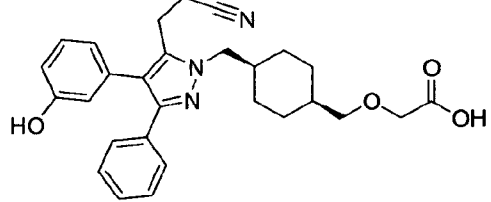
| Cpd No. | Chemical Structure | Chemical Name   |
|---------|--------------------|---|
| 229     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((5-(3,4-difluorophenyl)-4-phenyl-3-propyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid       |
| 230     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((3-(3,4-difluorophenyl)-4-phenyl-5-propyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid       |
| 231     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((5-(2-fluoro-4-methoxyphenyl)-4-phenyl-3-propyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid |
| 232     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((3-(2-fluoro-4-methoxyphenyl)-4-phenyl-5-propyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid |
| 233     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((5-(4-methoxyphenyl)-4-phenyl-3-propyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid          |

| Cpd No. | Chemical Structure | Chemical Name   |
|---------|--------------------|---|
| 234     |                    | 2-(((1s,4s)-4-((3-(4-methoxyphenyl)-4-phenyl-5-propyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid                   |
| 235     |                    | 2-(((1s,4s)-4-((5-(2-fluoro-4-methylphenyl)-4-phenyl-3-propyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid           |
| 236     |                    | 2-(((1s,4s)-4-((3-(2-fluoro-4-methylphenyl)-4-phenyl-5-propyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid           |
| 237     |                    | 2-(((1s,4s)-4-((4-(3-chlorophenyl)-5-(2-(methylthio)ethyl)-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid     |
| 238     |                    | 2-(((1s,4s)-4-((5-(2-(methylthio)ethyl)-3,4-diphenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid                    |
| 239     |                    | 2-(((1s,4s)-4-((5-(2-fluoro-4-methylphenyl)-3-(2-methoxyethyl)-4-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid |

| Cpd No. | Chemical Structure | Chemical Name   |
|---------|--------------------|---|
| 240     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((3-(2-fluoro-4-methylphenyl)-5-(2-methoxyethyl)-4-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid      |
| 241     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((4-(2-fluoro-4-methylphenyl)-5-(2-methoxyethyl)-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid      |
| 242     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((4-(2-fluoro-4-methylphenyl)-5-(2-(methylthio)ethyl)-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid |
| 243     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((4-(3-methoxyphenyl)-5-(2-(methylthio)ethyl)-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid         |
| 244     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((4-(2,3-difluorophenyl)-5-(2-(methylthio)ethyl)-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid      |
| 245     |                    | 2-(((1 <i>r</i> ,4 <i>r</i> )-4-((3-(cyanomethylthio)-4-(3-methoxyphenyl)-5-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid             |

| Cpd No. | Chemical Structure | Chemical Name   |
|---------|--------------------|---|
| 246     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((5-(cyanomethylthio)-4-(3-methoxyphenyl)-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid                 |
| 247     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((3-(2-methoxyethyl)-5-(3-methoxyphenyl)-4-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid                  |
| 248     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((5-(2-methoxyethyl)-3-(3-methoxyphenyl)-4-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid                  |
| 249     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((4-(3-chloro-2-fluorophenyl)-5-(2-(methylsulfonyl)ethyl)-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid |
| 250     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((5-(2-aminoethylthio)-4-phenyl-3- <i>p</i> -tolyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid                 |
| 251     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((5-(2-hydroxyethyl)-3,4-diphenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid                                  |

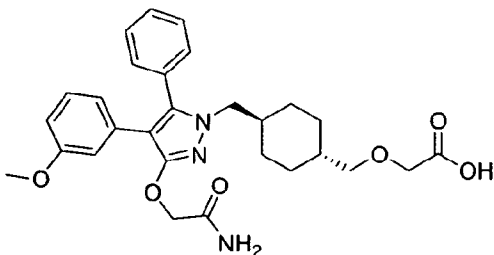
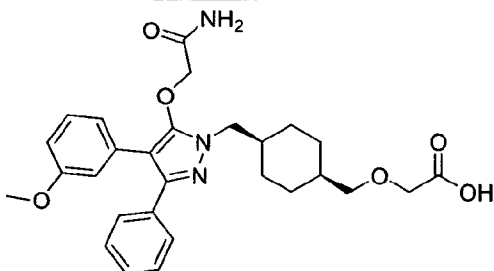
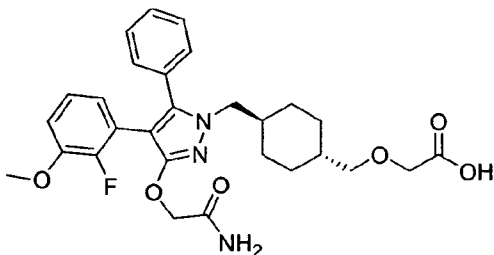
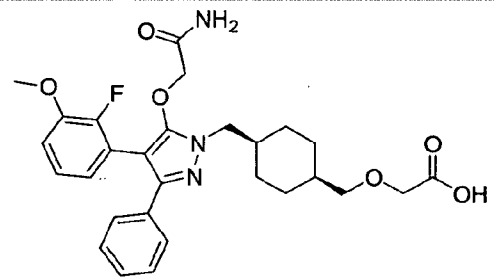
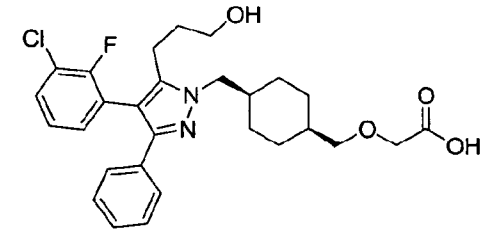
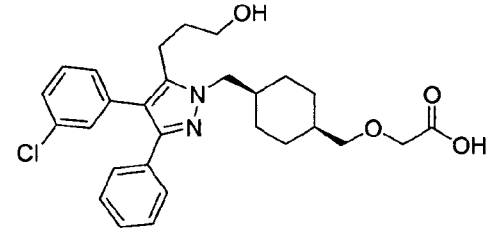
| Cpd No. | Chemical Structure | Chemical Name   |
|---------|--------------------|---|
| 252     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((5-(2-hydroxyethyl)-4-(3-methoxyphenyl)-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid    |
| 253     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((4-(2,3-difluorophenyl)-5-(2-hydroxyethyl)-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid |
| 254     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((4-(3-fluorophenyl)-5-(2-hydroxyethyl)-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid     |
| 255     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((3-(4-fluorophenyl)-5-(2-hydroxyethylthio)-4-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid |
| 256     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((5-(4-fluorophenyl)-3-(2-hydroxyethylthio)-4-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid |
| 257     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((5-(cyanomethylthio)-4-phenyl-3- <i>p</i> -tolyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid    |

| Cpd No. | Chemical Structure   | Chemical Name  |
|---------|--|--|
| 258     |     | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((5-(cyanomethylthio)-3-(4-fluorophenyl)-4-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid |
| 259     |     | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((3-(2-cyanoethyl)-4,5-diphenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid                   |
| 260     |    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((5-(2-cyanoethyl)-3,4-diphenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid                   |
| 261     |  | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((3-(2-cyanoethyl)-4-(3-methoxyphenyl)-5-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid   |
| 262     |  | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((5-(2-cyanoethyl)-4-(3-methoxyphenyl)-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid   |
| 263     |  | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((5-(2-cyanoethyl)-4-(3-hydroxyphenyl)-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid   |

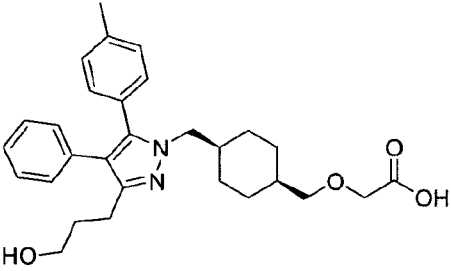
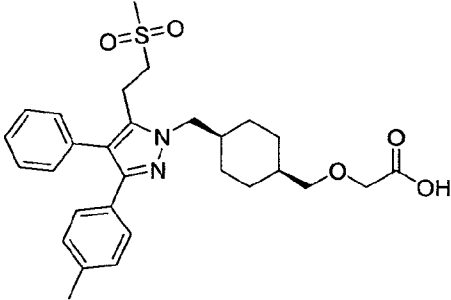
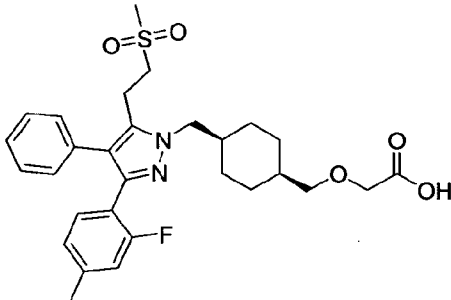
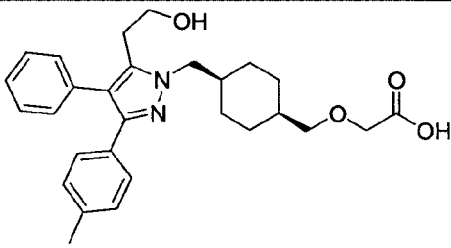
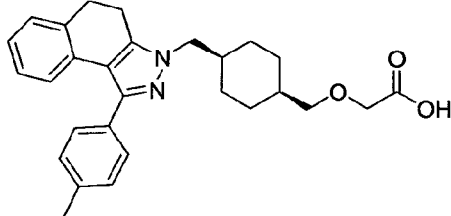
| Cpd No. | Chemical Structure | Chemical Name  |
|---------|--------------------|--|
| 264     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((4-(3-chlorophenyl)-3-(2-cyanoethyl)-5-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid          |
| 265     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((4-(3-chlorophenyl)-5-(2-cyanoethyl)-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid          |
| 266     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((3-(2-cyanoethyl)-4-(3-fluorophenyl)-5-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid          |
| 267     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((5-(2-cyanoethyl)-4-(3-fluorophenyl)-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid          |
| 268     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((3-(2-cyanoethyl)-4-(3-hydroxyphenyl)-5-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid         |
| 269     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((4-(3-chloro-2-fluorophenyl)-3-(2-cyanoethyl)-5-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid |
| 270     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((4-(3-chloro-2-fluorophenyl)-5-(2-cyanoethyl)-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid |

| Cpd No. | Chemical Structure | Chemical Name   |
|---------|--------------------|---|
| 271     |                    | 2-(((1s,4s)-4-((5-(3-hydroxypropyl)-3,4-diphenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid                        |
| 272     |                    | 2-(((1s,4s)-4-((5-(3-methoxyphenyl)-4-(3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid                         |
| 273     |                    | 2-(((1s,4s)-4-((4-(2,3-difluorophenyl)-5-(3-hydroxypropyl)-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid     |
| 274     |                    | 2-(((1s,4s)-4-((4-(3-fluorophenyl)-5-(3-hydroxypropyl)-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid         |
| 275     |                    | 2-(((1s,4s)-4-((4-(3-chlorophenyl)-5-(cyanomethylthio)-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid         |
| 276     |                    | 2-(((1s,4s)-4-((4-(3-chloro-2-fluorophenyl)-5-(2-hydroxyethyl)-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid |



| Cpd No. | Chemical Structure   | Chemical Name  |
|---------|--|--|
| 277     |    | 2-(((1 <i>r</i> ,4 <i>r</i> )-4-((3-(2-amino-2-oxoethoxy)-4-(3-methoxyphenyl)-5-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid          |
| 278     |    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((5-(2-amino-2-oxoethoxy)-4-(3-methoxyphenyl)-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid          |
| 279     |   | 2-(((1 <i>r</i> ,4 <i>r</i> )-4-((3-(2-amino-2-oxoethoxy)-4-(2-fluoro-3-methoxyphenyl)-5-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid |
| 280     |  | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((5-(2-amino-2-oxoethoxy)-4-(2-fluoro-3-methoxyphenyl)-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid |
| 281     |  | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((4-(3-chloro-2-fluorophenyl)-5-(3-hydroxypropyl)-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid      |
| 282     |  | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((4-(3-chlorophenyl)-5-(3-hydroxypropyl)-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid               |

| Cpd No. | Chemical Structure | Chemical Name  |
|---------|--------------------|--|
| 283     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((5-(cyanomethoxy)-4-(3-methoxyphenyl)-3-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid           |
| 284     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((3-(3,4-difluorophenyl)-5-ethyl-4-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid                 |
| 285     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((5-(2-fluoro-4-methylphenyl)-3-(2-hydroxyethyl)-4-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid |
| 286     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((5-(2-fluoro-4-methylphenyl)-3-methyl-4-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid           |
| 287     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((3-(2-fluoro-4-methylphenyl)-5-(2-hydroxyethyl)-4-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid |
| 288     |                    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((5-(3-hydroxypropyl)-4-phenyl-3- <i>p</i> -tolyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid         |

| Cpd No. | Chemical Structure   | Chemical Name   |
|---------|--|---|
| 289     |    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((3-(3-hydroxypropyl)-4-phenyl-5- <i>p</i> -tolyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid                  |
| 290     |    | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((5-(2-(methylsulfonyl)ethyl)-4-phenyl-3- <i>p</i> -tolyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid          |
| 291     |   | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((3-(2-fluoro-4-methylphenyl)-5-(2-(methylsulfonyl)ethyl)-4-phenyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid |
| 292     |  | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((5-(2-hydroxyethyl)-4-phenyl-3- <i>p</i> -tolyl-1 <i>H</i> -pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid                   |
| 293     |  | 2-(((1 <i>s</i> ,4 <i>s</i> )-4-((1- <i>p</i> -tolyl-4,5-dihydro-3 <i>H</i> -benzo[e]indazol-3-yl)methyl)cyclohexyl)methoxy)acetic acid                           |

Additionally, individual compounds and chemical genera of the present invention, for example those compounds found in TABLE A including diastereoisomers and enantiomers thereof, encompass all pharmaceutically acceptable salts, solvates and particularly hydrates, thereof.

5           The compounds of the Formula Ia of the present invention may be prepared according to relevant published literature procedures that are used by one skilled in the art. Exemplary reagents and procedures for these reactions appear hereinafter in the working Examples. Protection and deprotection may be carried out by procedures generally known in the art (see, for example, Greene, T. W. and Wuts, P. G. M., *Protecting Groups in Organic Synthesis*, 3<sup>rd</sup>  
10       Edition, 1999 [Wiley]; incorporated herein by reference in its entirety).

It is understood that the present invention embraces each diastereoisomer, each enantiomer and mixtures thereof of each compound and generic formulae disclosed herein just as if they were each individually disclosed with the specific stereochemical designation for each chiral carbon. Separation of the individual isomers (such as, by chiral HPLC, recrystallization of  
15       diastereoisomeric mixtures and the like) or selective synthesis (such as, by enantiomeric selective syntheses and the like) of the individual isomers is accomplished by application of various methods which are well known to practitioners in the art.

#### INDICATIONS AND METHODS OF PROPHYLAXIS AND/OR TREATMENT

20           In addition to the foregoing beneficial uses for the modulators of PGI2 receptor activity disclosed herein, the compounds disclosed herein are useful in the treatment of several additional diseases and disorders, and in the amelioration of symptoms thereof. Without limitation, these include the following:

##### 1. Pulmonary Arterial Hypertension (PAH)

25           Pulmonary arterial hypertension (PAH) has a multifactorial pathobiology. Vasoconstriction, remodeling of the pulmonary vessel wall, and thrombosis contribute to increased pulmonary vascular resistance in PAH (Humbert *et al.*, J. Am. Coll. Cardiol., 2004, 43:13S-24S.)

The compounds of the present invention disclosed herein are useful in the treatment of pulmonary arterial hypertension (PAH) and symptoms thereof. PAH shall be understood to  
30       encompass the following forms of pulmonary arterial hypertension described in the 2003 World Health Organization (WHO) clinical classification of pulmonary arterial hypertension: idiopathic PAH (IPAH); familial PAH (FPAH); PAH associated with other conditions (APAH), such as PAH associated with collagen vascular disease, PAH associated with congenital systemic-to-pulmonary shunts, PAH associated with portal hypertension, PAH associated with HIV infection,  
35       PAH associated with drugs or toxins, or PAH associated with Other; and PAH associated with significant venous or capillary involvement.

Idiopathic PAH refers to PAH of undetermined cause.

Familial PAH refers to PAH for which hereditary transmission is suspected or documented.

PAH associated with collagen vascular disease shall be understood to encompass PAH associated with scleroderma, PAH associated with CREST (calcinosis cutis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasias) syndrome, PAH  
5 associated with systemic lupus erythematosus (SLE), PAH associated with rheumatoid arthritis, PAH associated with Takayasu's arteritis, PAH associated with polymyositis, and PAH associated with dermatomyositis.

PAH associated with congenital systemic-to-pulmonary shunts shall be understood to encompass PAH associated with atrial septic defect (ASD), PAH associated with ventricular septic  
10 defect (VSD) and PAH associated with patent ductus arteriosus.

PAH associated with drugs or toxins shall be understood to encompass PAH associated with ingestion of aminorex, PAH associated with ingestion of a fenfluramine compound (*e.g.*, PAH associated with ingestion of fenfluramine or PAH associated with ingestion of dexfenfluramine),  
PAH associated with ingestion of certain toxic oils (*e.g.*, PAH associated with ingestion of rapeseed  
15 oil), PAH associated with ingestion of pyrrolizidine alkaloids (*e.g.*, PAH associated with ingestion of bush tea) and PAH associated with ingestion of monocrotaline.

PAH associated with Other shall be understood to encompass PAH associated with a thyroid disorder, PAH associated with glycogen storage disease, PAH associated with Gaucher disease, PAH associated with hereditary hemorrhagic telangiectasia, PAH associated with a  
20 hemoglobinopathy, PAH associated with a myeloproliferative disorder, and PAH associated with splenectomy.

PAH associated with significant venous or capillary involvement shall be understood to encompass PAH associated with pulmonary veno-occlusive disease (PVOD) and PAH associated with pulmonary capillary hemangiomatosis (PCH).

25 (See, *e.g.*, Simonneau *et al.*, J. Am. Coll. Cardiol., 2004, 43:5S-12S; McGoon *et al.*, Chest, 2004, 126:14S-34S; Rabinovitch, Annu. Rev. Pathol. Mech. Dis., 2007, 2:369-399; McLaughlin *et al.*, Circulation, 2006, 114:1417-1431; Strauss *et al.*, Clin. Chest. Med., 2007, 28:127-142; Taichman *et al.*, Clin. Chest. Med., 2007, 28:1-22.)

Evidence for the association of PAH with scleroderma and the beneficial effect of an  
30 agonist of the PGI<sub>2</sub> receptor on PAH is given by Badesch *et al.* (Badesch *et al.*, Ann. Intern. Med., 2000, 132:425-434). Evidence for the association of PAH with the collagen vascular diseases mixed connective tissue disease (MCTD), systemic lupus erythematosus (SLE), Sjögren's syndrome and CREST syndrome and the beneficial effect of an agonist of the PGI<sub>2</sub> receptor on  
PAH is given by Humbert *et al.* (Eur. Respir. J., 1999, 13:1351-1356). Evidence for the association  
35 of PAH with CREST syndrome and the beneficial effect of an agonist of the PGI<sub>2</sub> receptor on PAH is given by Miwa *et al.* (Int. Heart J., 2007, 48:417-422). Evidence for the association of PAH with SLE and the beneficial effect of an agonist of the PGI<sub>2</sub> receptor on PAH is given by Robbins *et al.*

(Chest, 2000, 117:14-18). Evidence for the association of PAH with HIV infection and the beneficial of an agonist of the PGI<sub>2</sub> receptor on PAH is given by Aguilar *et al.* (Am. J. Respir. Crit. Care Med., 2000, 162:1846-1850). Evidence for the association of PAH with congenital heart defects (including ASD, VSD and patent ductus arteriosus) and the beneficial effect of an agonist of the PGI<sub>2</sub> receptor on PAH is given by Rosenzweig *et al.* (Circulation, 1999, 99:1858-1865). Evidence for the association of PAH with fenfluramine and with dexfenfluramine, anorexigens, is given by Archer *et al.* (Am. J. Respir. Crit. Care Med., 1998, 158:1061-1067). Evidence for the association of PAH with hereditary hemorrhagic telangiectasia is given by McGoon *et al.* (Chest, 2004, 126:14-34). Evidence for the association of PAH with splenectomy is given by Hoeper *et al.* (Ann. Intern. Med., 1999, 130:506-509). Evidence for the association of PAH with portal hypertension and the beneficial effect of an agonist of the PGI<sub>2</sub> receptor on PAH is given by Hoeper *et al.* (Eur. Respir. J., 2005, 25:502-508).

Symptoms of PAH include dyspnea, angina, syncope and edema (McLaughlin *et al.*, Circulation, 2006, 114:1417-1431). The compounds of the present invention disclosed herein are useful in the treatment of symptoms of PAH.

Tawara *et al.* have demonstrated that long-term inhibition of Rho-kinase, an effector of the small GTPase Rho, ameliorates monocrotaline-induced PAH in rats and hypoxia-induced PAH in mice. The same group also reported that prostacyclin and its oral analog, beraprost sodium (BPS), may lack direct inhibitory effect on Rho-kinase in vitro, suggesting that combination therapy with a Rho-kinase inhibitor and BPS is effective for the treatment of PAH. Thus, male Sprague-Dawley rats were given a s.c. injection of monocrotaline (60 mg/kg) and maintained with or without the treatment with a Rho-kinase inhibitor, fasudil (30 mg/kg/day), BPS (200 µg/kg/day), or a combination of both drugs for three weeks. The combination therapy, when compared with each monotherapy, showed significantly more improvement in PAH, right ventricular hypertrophy, and pulmonary medial thickness without any adverse effects. (See, Tawara *et al.*, Journal of Cardiovascular Pharmacology (2007), 50(2), 195-200.)

The PGI<sub>2</sub> receptor agonists disclosed herein, alone or in combination with a Rho-kinase inhibitor, are useful in the treatment of pulmonary arterial hypertension (PAH) and symptoms thereof.

The enzyme tryptophan hydroxylase (TPH), has two known isoforms: TPH1, which is expressed in the periphery, and TPH2, which is expressed primarily in the brain. Mice genetically deficient for the TPH1 gene ("knockout mice") have been reported. In one case, the mice reportedly expressed normal amounts of serotonin in classical serotonergic brain regions, but largely lacked serotonin in the periphery. Walther, D. J., *et al.*, Science 299:76 (2003). In another, the knockout mice exhibited abnormal cardiac activity, which was attributed to a lack of peripheral serotonin. Cote, F., *et al.*, PNAS 100(23):13525-13530 (2003).

Recently, TPH knockout mice were studied in a hypoxia-induced pulmonary arterial hypertension model. Morecroft, I., *et al.*, Hypertension 49:232-236 (2007). The results of those studies suggest that TPH1 and peripheral serotonin play an essential role in the development of hypoxia-induced elevations in pulmonary pressures and hypoxia-induced pulmonary vascular remodeling.

The PGI2 receptor agonists disclosed herein, alone or in combination with a tryptophan hydroxylase inhibitor, are useful in the treatment of pulmonary arterial hypertension (PAH) and symptoms thereof.

## 2. Antiplatelet Therapies (Conditions related to platelet aggregation)

Antiplatelet agents (antiplatelets) are prescribed for a variety of conditions. For example, in coronary artery disease they are used to help prevent myocardial infarction or stroke in patients who are at risk of developing obstructive blood clots (*e.g.*, coronary thrombosis).

In a myocardial infarction ("MI" or "heart attack"), the heart muscle does not receive enough oxygen-rich blood as a result of a blockage in the coronary blood vessels. If taken while an attack is in progress or immediately afterward (preferably within 30 min), antiplatelets can reduce the damage to the heart.

A transient ischemic attack ("TIA" or "mini-stroke") is a brief interruption of oxygen flow to the brain due to decreased blood flow through arteries, usually due to an obstructing blood clot. Antiplatelet drugs have been found to be effective in preventing TIAs.

Angina is a temporary and often recurring chest pain, pressure or discomfort caused by inadequate oxygen-rich blood flow (ischemia) to some parts of the heart. In patients with angina, antiplatelet therapy can reduce the effects of angina and the risk of myocardial infarction.

Stroke is an event in which the brain does not receive enough oxygen-rich blood, usually due to blockage of a cerebral blood vessel by a blood clot. In high-risk patients, taking antiplatelets regularly has been found to prevent the formation of blood clots that cause first or second strokes.

Angioplasty is a catheter based technique used to open arteries obstructed by a blood clot. Whether or not stenting is performed immediately after this procedure to keep the artery open, antiplatelets can reduce the risk of forming additional blood clots following the procedure(s).

Coronary bypass surgery is a surgical procedure in which an artery or vein is taken from elsewhere in the body and grafted to a blocked coronary artery, rerouting blood around the blockage and through the newly attached vessel. After the procedure, antiplatelets can reduce the risk of secondary blood clots.

Atrial fibrillation is the most common type of sustained irregular heart rhythm (arrhythmia). Atrial fibrillation affects about two million Americans every year. In atrial fibrillation, the atria (the heart's upper chambers) rapidly fire electrical signals that cause them to quiver rather than contract normally. The result is an abnormally fast and highly irregular heartbeat. When given

after an episode of atrial fibrillation, antiplatelets can reduce the risk of blood clots forming in the heart and traveling to the brain (embolism).

There is evidence that a PGI2 receptor agonist will inhibit platelet aggregation and thus be a potential treatment as an antiplatelet therapy (see, *e.g.*, Moncada *et al.*, *Lancet*, 1977, 1:18-20). It has been shown that genetic deficiency of the PGI2 receptor in mice leads to an increased propensity towards thrombosis (Murata *et al.*, *Nature*, 1997, 388:678-682).

PGI2 receptor agonists can be used to treat, for example, claudication or peripheral artery disease as well as cardiovascular complications, arterial thrombosis, atherosclerosis, vasoconstriction caused by serotonin, ischemia-reperfusion injury, and restenosis of arteries following angioplasty or stent placement. (See, *e.g.*, Fetalvero *et al.*, *Prostaglandins Other Lipid Mediat.*, 2007, 82:109-118; Arehart *et al.*, *Curr. Med. Chem.*, 2007, 14:2161-2169; Davi *et al.*, *N. Engl. J. Med.*, 2007, 357:2482-2494; Fetalvero *et al.*, *Am. J. Physiol. Heart. Circ. Physiol.*, 2006, 290:H1337-H1346; Murata *et al.*, *Nature*, 1997, 388:678-682; Wang *et al.*, *Proc. Natl. Acad. Sci. USA*, 2006, 103:14507-14512; Xiao *et al.*, *Circulation*, 2001, 104:2210-2215; McCormick *et al.*, *Biochem. Soc. Trans.*, 2007, 35:910-911; Arehart *et al.*, *Circ. Res.*, 2008, 102(8), 986-93.)

PGI2 receptor agonists can also be used alone or in combination with thrombolytic therapy, for example, tissue-type plasminogen activator (t-PA), to provide cardioprotection following MI or postischemic myocardial dysfunction or protection from ischemic injury during percutaneous coronary intervention, and the like, including complications resulting therefrom. PGI2 receptor agonists can also be used in antiplatelet therapies in combination with, for example, alpha-tocopherol (vitamin E), echistatin (a disintegrin) or, in states of hypercoagulability, heparin. (See, *e.g.*, Chan., *J. Nutr.*, 1998, 128:1593-1596; Mardla *et al.*, *Platelets*, 2004, 15:319-324; Bernabei *et al.*, *Ann. Thorac. Surg.*, 1995, 59:149-153; Gainza *et al.*, *J. Nephrol.*, 2006, 19:648-655.)

The PGI2 receptor agonists disclosed herein provide beneficial improvement in microcirculation to patients in need of antiplatelet therapy by antagonizing the vasoconstrictive products of the aggregating platelets in, for example and not limited to the indications described above. Accordingly, in some embodiments, the present invention provides methods for reducing platelet aggregation in a patient in need thereof, comprising administering to the patient a composition comprising a PGI2 receptor agonist disclosed herein. In further embodiments, the present invention provides methods for treating coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke, atrial fibrillation, or a symptom of any of the foregoing in a patient in need of the treatment, comprising administering to the patient a composition comprising a PGI2 receptor agonist disclosed herein.

In further embodiments, the present invention provides methods for reducing risk of blood clot formation in an angioplasty or coronary bypass surgery patient, or a patient suffering from



atrial fibrillation, comprising administering to the patient a composition comprising a PGI2 receptor agonist disclosed herein at a time where such risk exists.

### 3. Atherosclerosis

Atherosclerosis is a complex disease characterized by inflammation, lipid accumulation,  
5 cell death and fibrosis. It is the leading cause of mortality in many countries, including the United States. Atherosclerosis, as the term is used herein, shall be understood to encompass disorders of large and medium-sized arteries that result in the progressive accumulation within the intima of smooth muscle cells and lipids.

It has been shown that an agonist of the PGI2 receptor can confer protection from  
10 atherosclerosis, such as from atherothrombosis (Arehart *et al.*, Curr. Med. Chem., 2007, 14:2161-2169; Stitham *et al.*, Prostaglandins Other Lipid Mediat., 2007, 82:95-108; Fries *et al.*, Hematology Am. Soc. Hematol. Educ. Program, 2005, :445-451; Egan *et al.*, Science, 2004, 306:1954-1957; Kobayashi *et al.*, J. Clin. Invest., 2004, 114:784-794; Arehart *et al.*, Circ. Res., 2008, 102(8), 986-93).

15 It has been shown that defective PGI2 receptor signaling appears to accelerate atherothrombosis in humans, *i.e.* that an agonist of the PGI2 receptor can confer protection from atherothrombosis in humans (Arehart *et al.*, Circ. Res., 2008, 102(8), 986-93).

The compounds of the present invention disclosed herein are useful in the treatment of atherosclerosis, and the treatment of the symptoms thereof. Accordingly, in some embodiments, the  
20 present invention provides methods for treating atherosclerosis in a patient in need of the treatment, comprising administering to the patient a composition comprising a PGI2 receptor agonist disclosed herein. In further embodiments, methods are provided for treating a symptom of atherosclerosis in a patient in need of the treatment, comprising administering to the patient a composition comprising a PGI2 receptor agonist disclosed herein.

### 25 4. Asthma

Asthma is a lymphocyte-mediated inflammatory airway disorder characterized by airway eosinophilia, increased mucus production by goblet cells, and structural remodeling of the airway wall. The prevalence of asthma has dramatically increased worldwide in recent decades. It has been shown that genetic deficiency of the PGI2 receptor in mice augments allergic airway inflammation  
30 (Takahashi *et al.*, Br J Pharmacol, 2002, 137:315-322). It has been shown that an agonist of the PGI2 receptor can suppress not only the development of asthma when given during the sensitization phase, but also the cardinal features of experimental asthma when given during the challenge phase (Idzko *et al.*, J. Clin. Invest., 2007, 117:464-472; Nagao *et al.*, Am. J. Respir. Cell Mol. Biol., 2003, 29:314-320), at least in part through markedly interfering with the function of antigen-presenting  
35 dendritic cells within the airways (Idzko *et al.*, J. Clin. Invest., 2007, 117:464-472; Zhou *et al.*, J. Immunol., 2007, 178:702-710; Jaffar *et al.*, J. Immunol., 2007, 179:6193-6203; Jozefowski *et al.*, Int. Immunopharmacol., 2003, 3:865-878). These cells are crucial for both the initiation and the

maintenance phases of allergic asthma, as depletion of airway dendritic cells during secondary challenge in sensitized mice abolished all characteristic features of asthma, an effect that could be completely restored by adoptive transfer of wild-type dendritic cells (van Rijt *et al.*, J. Exp. Med., 2005, 201:981-991). It has also been shown that an agonist of the PGI2 receptor can inhibit  
5 proinflammatory cytokine secretion by human alveolar macrophages (Raychaudhuri *et al.*, J. Biol. Chem., 2002, 277:33344-33348). The compounds of the present invention disclosed herein are useful in the treatment of asthma, and the treatment of the symptoms thereof. Accordingly, in some embodiments, the present invention provides methods for treating asthma in a patient in need of the treatment, comprising administering to the patient a composition comprising a PGI2 receptor  
10 agonist disclosed herein. In further embodiments, methods are provided for treating a symptom of asthma in a patient in need of the treatment, comprising administering to the patient a composition comprising a PGI2 receptor agonist disclosed herein.

### 5. Diabetic-Related Pathologies

Although hyperglycemia is the major cause for the pathogenesis of diabetic  
15 complications such as diabetic peripheral neuropathy (DPN), diabetic nephropathy (DN) and diabetic retinopathy (DR), enhanced vasoconstriction and platelet aggregation in diabetic patients has also been implicated to play a role in disease progression (Cameron *et al.*, Naunyn Schmiedebergs Arch. Pharmacol., 2003, 367:607-614). Agonists of the PGI2 receptor promote vasodilation and inhibit platelet aggregation. Improving microvascular blood flow is able to  
20 benefit diabetic complications (Cameron, Diabetologia, 2001, 44:1973-1988).

It has been shown that an agonist of the PGI2 receptor can prevent and reverse motor and sensory peripheral nerve conduction abnormalities in streptozotocin-diabetic rats (Cotter *et al.*, Naunyn Schmiedebergs Arch. Pharmacol., 1993, 347:534-540). Further evidence for the beneficial effect of an agonist of the PGI2 receptor in the treatment of diabetic peripheral  
25 neuropathy is given by Hotta *et al.* (Diabetes, 1996, 45:361-366), Ueno *et al.* (Jpn. J. Pharmacol., 1996, 70:177-182), Ueno *et al.* (Life Sci., 1996, 59:PL105-PL110), Hotta *et al.* (Prostaglandins, 1995, 49:339-349), Shindo *et al.* (Prostaglandins, 1991, 41:85-96), Okuda *et al.* (Prostaglandins, 1996, 52:375-384), and Koike *et al.* (FASEB J., 2003, 17:779-781). Evidence for the beneficial effect of an agonist of the PGI2 receptor in the treatment of diabetic  
30 nephropathy is given by Owada *et al.* (Nephron, 2002, 92:788-796) and Yamashita *et al.* (Diabetes Res. Clin. Pract., 2002, 57:149-161). Evidence for the beneficial effect of an agonist of the PGI2 receptor in the treatment of diabetic retinopathy is given by Yamagishi *et al.* (Mol. Med., 2002, 8:546-550), Burnette *et al.* (Exp. Eye Res., 2006, 83:1359-1365), and Hotta *et al.* (Diabetes, 1996, 45:361-366). It has been shown that an agonist of the PGI2 receptor can reduce  
35 increased tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) levels in diabetic patients, implying that an agonist of the PGI2 receptor may contribute to the prevention of progression in diabetic complications (Fujiwara *et al.*, Exp. Clin. Endocrinol. Diabetes, 2004, 112:390-394).

## 6. Glaucoma

Evidence that topical administration of an agonist of the PGI<sub>2</sub> receptor can result in a decrease in intraocular pressure (IOP) in rabbits and dogs and thereby have beneficial effect in the treatment of glaucoma is given by Hoyng *et al.* (Hoyng *et al.*, Invest. Ophthalmol. Vis. Sci., 5 1987, 28:470-476).

## 7. Hypertension

Agonists of the PGI<sub>2</sub> receptor have been shown to have activity for regulation of vascular tone, for vasodilation, and for amelioration of pulmonary hypertension (see, e.g., Strauss *et al.*, Clin Chest Med, 2007, 28:127-142; Driscoll *et al.*, Expert Opin. Pharmacother., 10 2008, 9:65-81). Evidence for a beneficial effect of an agonist of the PGI<sub>2</sub> receptor in the treatment of hypertension is given by Yamada *et al.* (Peptides, 2008, 29:412-418). Evidence that an agonist of the PGI<sub>2</sub> receptor can protect against cerebral ischemia is given by Dogan *et al.* (Gen. Pharmacol., 1996, 27:1163-1166) and Fang *et al.* (J. Cereb. Blood Flow Metab., 2006, 26:491-501).

## 8. Anti-Inflammation Therapies

Anti-inflammation agents are prescribed for a variety of conditions. For example, in an inflammatory disease they are used to interfere with and thereby reduce an underlying deleterious condition. There is evidence that a PGI<sub>2</sub> receptor agonist can inhibit inflammation and thus be a potential treatment as an anti-inflammation therapy. It has been shown that an agonist of the 20 PGI<sub>2</sub> receptor can inhibit pro-inflammatory cytokine and chemokine (interleukin-12 (IL-12), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), IL-1 $\alpha$ , IL-6, macrophage inflammatory protein-1 $\alpha$  (MIP-1 $\alpha$ ), monocyte chemoattractant protein-1 (MCP-1)) production and T cell stimulatory function of dendritic cells (Jozefowski *et al.*, Int. Immunopharmacol., 2003, 865-878; Zhou *et al.*, J. Immunol., 2007, 178:702-710; Nagao *et al.*, Am. J. Respir. Cell Mol. Biol., 2003, 29:314-320; 25 Idzko *et al.*, J. Clin. Invest., 2007, 117:464-472). It has been shown that an agonist of the PGI<sub>2</sub> receptor can inhibit pro-inflammatory cytokine (TNF- $\alpha$ , IL-1 $\beta$ , IL-6, granulocyte macrophage stimulating factor (GM-CSF)) production by macrophages (Raychaudhuri *et al.*, J. Biol. Chem., 2002, 277:33344-33348; Czeslick *et al.*, Eur. J. Clin. Invest., 2003, 33:1013-1017; Di Renzo *et al.*, Prostaglandin Leukot. Essent. Fatty Acids, 2005, 73:405-410; Shinomiya *et al.*, Biochem. 30 Pharmacol., 2001, 61:1153-1160). It has been shown that an agonist of the PGI<sub>2</sub> receptor can stimulate anti-inflammatory cytokine (IL-10) production by dendritic cells (Jozefowski *et al.*, Int. Immunopharmacol., 2003, 865-878; Zhou *et al.*, J. Immunol., 2007, 178:702-710). It has been shown that an agonist of the PGI<sub>2</sub> receptor can stimulate anti-inflammatory cytokine (IL-10) production by macrophages (Shinomiya *et al.*, Biochem. Pharmacol., 2001, 61:1153-1160). 35 It has been shown that an agonist of the PGI<sub>2</sub> receptor can inhibit a chemokine (CCL17)-induced chemotaxis of leukocytes (CD4<sup>+</sup> Th2 T cells) (Jaffar *et al.*, J. Immunol., 2007, 179:6193-6203). It has been shown that an agonist of the PGI<sub>2</sub> receptor can confer protection

from atherosclerosis, such as from atherothrombosis (Arehart *et al.*, Curr. Med. Chem., 2007, 14:2161-2169; Stitham *et al.*, Prostaglandins Other Lipid Mediat., 2007, 82:95-108; Fries *et al.*, Hematology Am. Soc. Hematol. Educ. Program, 2005, :445-451; Egan *et al.*, Science, 2004, 306:1954-1957; Kobayashi *et al.*, J. Clin. Invest., 2004, 114:784-794; Arehart *et al.*, Circ. Res., 5 2008, 102(8), 986-93). It has been shown that an agonist of the PGI<sub>2</sub> receptor can attenuate asthma (Idzko *et al.*, J. Clin. Invest., 2007, 117:464-472; Jaffar *et al.*, J. Immunol., 2007, 179:6193-6203; Nagao *et al.*, Am. J. Respir. Cell. Mol. Biol., 2003, 29:314-320). It has been shown that an agonist of the PGI<sub>2</sub> receptor can decrease TNF- $\alpha$  production in type 2 diabetes patients (Fujiwara *et al.*, Exp. Clin. Endocrinol. Diabetes, 2004, 112:390-394; Goya *et al.*, 10 Metabolism, 2003, 52:192-198). It has been shown that an agonist of the PGI<sub>2</sub> receptor can inhibit ischemia-reperfusion injury (Xiao *et al.*, Circulation, 2001, 104:2210-2215). It has been shown that an agonist of the PGI<sub>2</sub> receptor can inhibit restenosis (Cheng *et al.*, Science, 2002, 296:539-541). It has been shown that an agonist of the PGI<sub>2</sub> receptor can attenuate pulmonary vascular injury and shock in a rat model of septic shock (Harada *et al.*, Shock, 2008, Feb 21 15 Epub ahead of print). It has been shown that an agonist of the PGI<sub>2</sub> receptor can reduce the serum levels of TNF- $\alpha$  *in vivo* in patients with rheumatoid arthritis, and this is associated with improvement in the clinical course of the disease (Gao *et al.*, Rheumatol. Int., 2002, 22:45-51; Boehme *et al.*, Rheumatol. Int., 2006, 26:340-347).

The compounds of the present invention disclosed herein provide beneficial reduction of 20 inflammation. The compounds of the present invention disclosed herein provide beneficial reduction of a deleterious inflammatory response associated with an inflammatory disease. Accordingly, in some embodiments, the present invention provides methods for reducing inflammation in a patient in need thereof, comprising administering to the patient a composition comprising a PGI<sub>2</sub> receptor agonist disclosed herein. In some embodiments, the present 25 invention provides methods for decreasing IL-12, TNF- $\alpha$ , IL-1 $\alpha$ , IL-1 $\beta$ , IL-6, MIP-1 $\alpha$  or MCP-1 production in a patient in need thereof, comprising administering to the patient a composition comprising a PGI<sub>2</sub> receptor agonist disclosed herein. In some embodiments, the present invention provides methods for decreasing TNF- $\alpha$  production in a patient in need thereof, comprising administering to the patient a composition comprising a PGI<sub>2</sub> receptor agonist 30 disclosed herein. In some embodiments, the present invention provides methods for increasing IL-10 production in a patient in need thereof, comprising administering to the patient a composition comprising a PGI<sub>2</sub> receptor agonist disclosed herein. In some embodiments, the present invention provides methods for reducing a deleterious inflammatory response associated with an inflammatory disease in a patient in need thereof, comprising administering to the 35 patient a composition comprising a PGI<sub>2</sub> receptor agonist disclosed herein. In some embodiments, the present invention provides methods for treating an inflammatory disease or a symptom thereof in a patient in need of the treatment comprising administering to the patient a

composition comprising a PGI2 receptor agonist disclosed herein. In some embodiments, the present invention provides methods for treating an inflammatory disease or a symptom thereof in a patient in need of the treatment comprising administering to the patient a composition comprising a PGI2 receptor agonist disclosed herein. In some embodiments, the present invention provides methods for treating an inflammatory disease or a symptom thereof in a patient in need of the treatment comprising administering to the patient a composition comprising a PGI2 receptor agonist disclosed herein, wherein the inflammatory disease is selected from the group consisting of psoriasis, psoriatic arthritis, rheumatoid arthritis, Crohn's disease, transplant rejection, multiple sclerosis, systemic lupus erythematosus (SLE), ulcerative colitis, ischemia-reperfusion injury, restenosis, atherosclerosis, acne, diabetes (including type 1 diabetes and type 2 diabetes), sepsis, chronic obstructive pulmonary disease (COPD), and asthma.

### 9. Traumatic Brain Injury

Prostacyclin production is known to increase after brain trauma, and in a recent study, the importance of prostacyclin for posttraumatic hemodynamic alterations and neuron survival was investigated. Prostacyclin receptor-deficient ( $IP^{-/-}$ ) mice were compared to mice with functional prostacyclin receptors ( $IP^{+/+}$ ) after a controlled cortical injury. Contusion volume was increased in  $IP^{-/-}$  mice compared with  $IP^{+/+}$  mice. Three hours after trauma, cortical blood flow was decreased in the injured cortex of both groups and the reduction in blood flow in the cortex of the  $IP^{-/-}$  mice persisted from 3 to 24 h, whereas blood flow approached normal values in the  $IP^{+/+}$  mice after 24 h. (See, *e.g.*, Lundblad *et al.* Journal of Cerebral Blood Flow & Metabolism (2008) 28, 367–376).

The PGI2 receptor agonists disclosed herein provide beneficial improvement in neuron survival after brain trauma. Accordingly, in some embodiments, the present invention provides methods for treating a traumatic brain injury in a patient in need thereof, comprising administering to the patient a composition comprising a PGI2 receptor agonist disclosed herein.

### PHARMACEUTICAL COMPOSITIONS

A further aspect of the present invention pertains to pharmaceutical compositions comprising one or more compounds as described herein and one or more pharmaceutically acceptable carriers. Some embodiments pertain to pharmaceutical compositions comprising a compound of the present invention and a pharmaceutically acceptable carrier.

Some embodiments of the present invention include a method of producing a pharmaceutical composition comprising admixing at least one compound according to any of the compound embodiments disclosed herein and a pharmaceutically acceptable carrier.

Formulations may be prepared by any suitable method, typically by uniformly mixing the active compound(s) with liquids or finely divided solid carriers, or both, in the required proportions and then, if necessary, forming the resulting mixture into a desired shape.

Conventional excipients, such as binding agents, fillers, acceptable wetting agents, 5  
tableting lubricants and disintegrants may be used in tablets and capsules for oral administration. Liquid preparations for oral administration may be in the form of solutions, emulsions, aqueous or oily suspensions and syrups. Alternatively, the oral preparations may be in the form of dry powder that can be reconstituted with water or another suitable liquid vehicle before use. Additional additives such as suspending or emulsifying agents, non-aqueous vehicles 10  
(including edible oils), preservatives and flavorings and colorants may be added to the liquid preparations. Parenteral dosage forms may be prepared by dissolving the compound of the invention in a suitable liquid vehicle and filter sterilizing the solution before filling and sealing an appropriate vial or ampule. These are just a few examples of the many appropriate methods well known in the art for preparing dosage forms.

15 A compound of the present invention can be formulated into pharmaceutical compositions using techniques well known to those in the art. Suitable pharmaceutically-acceptable carriers, outside those mentioned herein, are known in the art; for example, see Remington, *The Science and Practice of Pharmacy*, 20<sup>th</sup> Edition, 2000, Lippincott Williams & Wilkins, (Editors: Gennaro *et al.*)

20 While it is possible that, for use in the prophylaxis or treatment, a compound of the invention may, in an alternative use, be administered as a raw or pure chemical, it is preferable however to present the compound or active ingredient as a pharmaceutical formulation or composition further comprising a pharmaceutically acceptable carrier.

Pharmaceutical formulations include those suitable for oral, rectal, nasal, topical 25  
(including buccal and sub-lingual), vaginal or parenteral (including intramuscular, sub-cutaneous and intravenous) administration or in a form suitable for administration by inhalation, insufflation or by a transdermal patch. Transdermal patches dispense a drug at a controlled rate by presenting the drug for absorption in an efficient manner with minimal degradation of the drug. Typically, transdermal patches comprise an impermeable backing layer, a single pressure 30  
sensitive adhesive and a removable protective layer with a release liner. One of ordinary skill in the art will understand and appreciate the techniques appropriate for manufacturing a desired efficacious transdermal patch based upon the needs of the artisan.

The compounds of the invention, together with a conventional adjuvant, carrier, or diluent, may thus be placed into the form of pharmaceutical formulations and unit dosages 35  
thereof and in such form may be employed as solids, such as tablets or filled capsules, or liquids such as solutions, suspensions, emulsions, elixirs, gels or capsules filled with the same, all for oral use, in the form of suppositories for rectal administration; or in the form of sterile injectable

solutions for parenteral (including subcutaneous) use. Such pharmaceutical compositions and unit dosage forms thereof may comprise conventional ingredients in conventional proportions, with or without additional active compounds or principles and such unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended  
5 daily dosage range to be employed.

For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are capsules, tablets, powders, granules or a suspension, with  
10 conventional additives such as lactose, mannitol, corn starch or potato starch; with binders such as crystalline cellulose, cellulose derivatives, acacia, corn starch or gelatins; with disintegrators such as corn starch, potato starch or sodium carboxymethyl-cellulose; and with lubricants such as talc or magnesium stearate. The active ingredient may also be administered by injection as a composition wherein, for example, saline, dextrose or water may be used as a suitable  
15 pharmaceutically acceptable carrier.

Compounds of the present invention or a solvate, hydrate or physiologically functional derivative thereof can be used as active ingredients in pharmaceutical compositions, specifically as PGI<sub>2</sub> receptor modulators. By the term "active ingredient" is defined in the context of a  
20 "pharmaceutical composition" and is intended to mean a component of a pharmaceutical composition that provides the primary pharmacological effect, as opposed to an "inactive ingredient" which would generally be recognized as providing no pharmaceutical benefit.

The dose when using the compounds of the present invention can vary within wide limits and as is customary and is known to the physician, it is to be tailored to the individual conditions in each individual case. It depends, for example, on the nature and severity of the  
25 illness to be treated, on the condition of the patient, on the compound employed or on whether an acute or chronic disease state is treated or prophylaxis is conducted or on whether further active compounds are administered in addition to the compounds of the present invention. Representative doses of the present invention include, but not limited to, about 0.001 mg to about 5000 mg, about 0.001 mg to about 2500 mg, about 0.001 mg to about 1000 mg, 0.001 mg  
30 to about 500 mg, 0.001 mg to about 250 mg, about 0.001 mg to 100 mg, about 0.001 mg to about 50 mg and about 0.001 mg to about 25 mg. Multiple doses may be administered during the day, especially when relatively large amounts are deemed to be needed, for example 2, 3 or 4 doses. Depending on the individual and as deemed appropriate from the patient's physician or caregiver it may be necessary to deviate upward or downward from the doses described herein.

35 The amount of active ingredient, or an active salt or derivative thereof, required for use in treatment will vary not only with the particular salt selected but also with the route of administration, the nature of the condition being treated and the age and condition of the patient

and will ultimately be at the discretion of the attendant physician or clinician. In general, one skilled in the art understands how to extrapolate *in vivo* data obtained in a model system, typically an animal model, to another, such as a human. In some circumstances, these extrapolations may merely be based on the weight of the animal model in comparison to  
5 another, such as a mammal, preferably a human, however, more often, these extrapolations are not simply based on weights, but rather incorporate a variety of factors. Representative factors include the type, age, weight, sex, diet and medical condition of the patient, the severity of the disease, the route of administration, pharmacological considerations such as the activity, efficacy, pharmacokinetic and toxicology profiles of the particular compound employed,  
10 whether a drug delivery system is utilized, on whether an acute or chronic disease state is being treated or prophylaxis is conducted or on whether further active compounds are administered in addition to the compounds of the present invention and as part of a drug combination. The dosage regimen for treating a disease condition with the compounds and/or compositions of this invention is selected in accordance with a variety factors as cited above. Thus, the actual dosage  
15 regimen employed may vary widely and therefore may deviate from a preferred dosage regimen and one skilled in the art will recognize that dosage and dosage regimen outside these typical ranges can be tested and, where appropriate, may be used in the methods of this invention.

The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example, as two, three, four or more sub-doses per day.  
20 The sub-dose itself may be further divided, *e.g.*, into a number of discrete loosely spaced administrations. The daily dose can be divided, especially when relatively large amounts are administered as deemed appropriate, into several, for example 2, 3 or 4 part administrations. If appropriate, depending on individual behavior, it may be necessary to deviate upward or downward from the daily dose indicated.

25 The compounds of the present invention can be administered in a wide variety of oral and parenteral dosage forms. It will be obvious to those skilled in the art that the following dosage forms may comprise, as the active component, either a compound of the invention or a pharmaceutically acceptable salt, solvate or hydrate of a compound of the invention.

For preparing pharmaceutical compositions from the compounds of the present  
30 invention, the selection of a suitable pharmaceutically acceptable carrier can be either solid, liquid or a mixture of both. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

35 In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component.



In tablets, the active component is mixed with the carrier having the necessary binding capacity in suitable proportions and compacted to the desired shape and size.

The powders and tablets may contain varying percentage amounts of the active compound. A representative amount in a powder or tablet may contain from 0.5 to about 90 percent of the active compound; however, an artisan would know when amounts outside of this range are necessary. Suitable carriers for powders and tablets are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as carrier providing a capsule in which the active component, with or without carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets and lozenges can be used as solid forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as an admixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool and thereby to solidify.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Liquid form preparations include solutions, suspensions and emulsions, for example, water or water-propylene glycol solutions. For example, parenteral injection liquid preparations can be formulated as solutions in aqueous polyethylene glycol solution. Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds according to the present invention may thus be formulated for parenteral administration (e.g. by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The pharmaceutical compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles and may

contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilization from solution, for constitution with a suitable vehicle, *e.g.* sterile, pyrogen-free water, before use.

5           Aqueous formulations suitable for oral use can be prepared by dissolving or suspending the active component in water and adding suitable colorants, flavors, stabilizing and thickening agents, as desired.

          Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins,  
10   methylcellulose, sodium carboxymethylcellulose, or other well-known suspending agents.

          Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants,  
15   thickeners, solubilizing agents and the like.

          For topical administration to the epidermis the compounds according to the invention may be formulated as ointments, creams or lotions, or as a transdermal patch.

          Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with  
20   an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilizing agents, dispersing agents, suspending agents, thickening agents, or coloring agents.

          Formulations suitable for topical administration in the mouth include lozenges comprising active agent in a flavored base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerin or sucrose and  
25   acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

          Solutions or suspensions are applied directly to the nasal cavity by conventional means, for example with a dropper, pipette or spray. The formulations may be provided in single or multi-dose form. In the latter case of a dropper or pipette, this may be achieved by the patient administering an appropriate, predetermined volume of the solution or suspension. In the case of  
30   a spray, this may be achieved for example by means of a metering atomizing spray pump.

          Administration to the respiratory tract may also be achieved by means of an aerosol formulation in which the active ingredient is provided in a pressurized pack with a suitable propellant. If the compounds of the present invention or pharmaceutical compositions comprising them are administered as aerosols, for example as nasal aerosols or by inhalation,  
35   this can be carried out, for example, using a spray, a nebulizer, a pump nebulizer, an inhalation apparatus, a metered inhaler or a dry powder inhaler. Pharmaceutical forms for administration of the compounds of the present invention as an aerosol can be prepared by processes well known

to the person skilled in the art. For their preparation, for example, solutions or dispersions of the compounds of the present invention in water, water/alcohol mixtures or suitable saline solutions can be employed using customary additives, for example benzyl alcohol or other suitable preservatives, absorption enhancers for increasing the bioavailability, solubilizers, dispersants and others and, if appropriate, customary propellants, for example include carbon dioxide, CFCs, such as, dichlorodifluoromethane, trichlorofluoromethane, or dichlorotetrafluoroethane; and the like. The aerosol may conveniently also contain a surfactant such as lecithin. The dose of drug may be controlled by provision of a metered valve.

In formulations intended for administration to the respiratory tract, including intranasal formulations, the compound will generally have a small particle size for example of the order of 10 microns or less. Such a particle size may be obtained by means known in the art, for example by micronization. When desired, formulations adapted to give sustained release of the active ingredient may be employed.

Alternatively the active ingredients may be provided in the form of a dry powder, for example, a powder mix of the compound in a suitable powder base such as lactose, starch, starch derivatives such as hydroxypropylmethyl cellulose and polyvinylpyrrolidone (PVP). Conveniently the powder carrier will form a gel in the nasal cavity. The powder composition may be presented in unit dose form for example in capsules or cartridges of, e.g., gelatin, or blister packs from which the powder may be administered by means of an inhaler.

The pharmaceutical preparations are preferably in unit dosage forms. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

Tablets or capsules for oral administration and liquids for intravenous administration are preferred compositions.

The compounds according to the invention may optionally exist as pharmaceutically acceptable salts including pharmaceutically acceptable acid addition salts prepared from pharmaceutically acceptable non-toxic acids including inorganic and organic acids. Representative acids include, but are not limited to, acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethenesulfonic, dichloroacetic, formic, fumaric, gluconic, glutamic, hippuric, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, oxalic, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, oxalic, p-toluenesulfonic and the like. Certain compounds of the present invention which contain a carboxylic acid functional group may optionally exist as pharmaceutically acceptable salts containing non-toxic, pharmaceutically acceptable metal cations and cations

derived from organic bases. Representative metals include, but are not limited to, aluminium, calcium, lithium, magnesium, potassium, sodium, zinc and the like. In some embodiments the pharmaceutically acceptable metal is sodium. Representative organic bases include, but are not limited to, benzathine ( $N^1, N^2$ -dibenzylethane-1,2-diamine), chloroprocaine (2-  
5 (diethylamino)ethyl 4-(chloroamino)benzoate), choline, diethanolamine, ethylenediamine, meglumine ((2*R*,3*R*,4*R*,5*S*)-6-(methylamino)hexane-1,2,3,4,5-pentaol), procaine (2-(diethylamino)ethyl 4-aminobenzoate), and the like. Certain pharmaceutically acceptable salts are listed in Berge, *et al.*, *Journal of Pharmaceutical Sciences*, 66:1-19 (1977), incorporated herein by reference in its entirety.

10 The acid addition salts may be obtained as the direct products of compound synthesis. In the alternative, the free base may be dissolved in a suitable solvent containing the appropriate acid and the salt isolated by evaporating the solvent or otherwise separating the salt and solvent. The compounds of this invention may form solvates with standard low molecular weight solvents using methods known to the skilled artisan.

15 Compounds of the present invention can be converted to "pro-drugs." The term "pro-drugs" refers to compounds that have been modified with specific chemical groups known in the art and when administered into an individual these groups undergo biotransformation to give the parent compound. Pro-drugs can thus be viewed as compounds of the invention containing one or more specialized non-toxic protective groups used in a transient manner to alter or to  
20 eliminate a property of the compound. In one general aspect, the "pro-drug" approach is utilized to facilitate oral absorption. A thorough discussion is provided in T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems* Vol. 14 of the A.C.S. Symposium Series; and in *Bioreversible Carriers in Drug Design*, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are hereby incorporated by reference in their entirety.

25 Some embodiments of the present invention include a method of producing a pharmaceutical composition for "combination-therapy" comprising admixing at least one compound according to any of the compound embodiments disclosed herein, together with at least one known pharmaceutical agent as described herein and a pharmaceutically acceptable carrier.

30 It is noted that when the PGI2 receptor modulators are utilized as active ingredients in a pharmaceutical composition, these are not intended for use only in humans, but in other non-human mammals as well. Indeed, recent advances in the area of animal health-care mandate that consideration be given for the use of active agents, such as PGI2 receptor modulators, for the treatment of an PGI2-associated disease or disorder in companionship animals (*e.g.*, cats, dogs,  
35 *etc.*) and in livestock animals (*e.g.*, cows, chickens, fish, *etc.*) Those of ordinary skill in the art are readily credited with understanding the utility of such compounds in such settings.

## HYDRATES AND SOLVATES

It is understood that when the phrase pharmaceutically acceptable salts, solvates and hydrates is used in referring to a particular formula herein, it is intended to embrace solvates and/or hydrates of compounds of the particular formula, pharmaceutically acceptable salts of compounds of the particular formula as well as solvates and/or hydrates of pharmaceutically acceptable salts of compounds of the particular formula.

The compounds of the present invention can be administered in a wide variety of oral and parenteral dosage forms. It will be apparent to those skilled in the art that the following dosage forms may comprise, as the active component, either a compound of the invention or a pharmaceutically acceptable salt or as a solvate or hydrate thereof. Moreover, various hydrates and solvates of the compounds of the invention and their salts will find use as intermediates in the manufacture of pharmaceutical compositions. Typical procedures for making and identifying suitable hydrates and solvates, outside those mentioned herein, are well known to those in the art; see for example, pages 202-209 of K.J. Guillory, "Generation of Polymorphs, Hydrates, Solvates, and Amorphous Solids," in: *Polymorphism in Pharmaceutical Solids*, ed. Harry G. Brittan, Vol. 95, Marcel Dekker, Inc., New York, 1999, incorporated herein by reference in its entirety. Accordingly, one aspect of the present invention pertains to hydrates and solvates of compounds of Formula **Ia** and/or their pharmaceutical acceptable salts, as described herein, that can be isolated and characterized by methods known in the art, such as, thermogravimetric analysis (TGA), TGA-mass spectroscopy, TGA-Infrared spectroscopy, powder X-ray diffraction (XRPD), Karl Fisher titration, high resolution X-ray diffraction, and the like. There are several commercial entities that provide quick and efficient services for identifying solvates and hydrates on a routine basis. Example companies offering these services include Wilmington PharmaTech (Wilmington, DE), Avantium Technologies (Amsterdam) and Aptuit (Greenwich, CT).

## OTHER UTILITIES

Another object of the present invention relates to radio-labeled compounds of the present invention that would be useful not only in radio-imaging but also in assays, both *in vitro* and *in vivo*, for localizing and quantitating the PGI2 receptor in tissue samples, including human and for identifying PGI2 receptor ligands by inhibition binding of a radio-labeled compound. It is a further object of this invention to develop novel PGI2 receptor assays of which comprise such radio-labeled compounds.

The present invention embraces isotopically-labeled compounds of the present invention. Isotopically or radio-labeled compounds are those which are identical to compounds disclosed herein, but for the fact that one or more atoms are replaced or substituted by an atom having an atomic mass or mass number different from the atomic mass or mass number most

commonly found in nature. Suitable radionuclides that may be incorporated in compounds of the present invention include but are not limited to  $^2\text{H}$  (also written as D for deuterium),  $^3\text{H}$  (also written as T for tritium),  $^{11}\text{C}$ ,  $^{13}\text{C}$ ,  $^{14}\text{C}$ ,  $^{15}\text{N}$ ,  $^{15}\text{N}$ ,  $^{17}\text{O}$ ,  $^{18}\text{O}$ ,  $^{18}\text{F}$ ,  $^{35}\text{S}$ ,  $^{36}\text{Cl}$ ,  $^{75}\text{Br}$ ,  $^{76}\text{Br}$ ,  $^{77}\text{Br}$ ,  $^{82}\text{Br}$ ,  $^{123}\text{I}$ ,  $^{124}\text{I}$ ,  $^{125}\text{I}$  and  $^{131}\text{I}$ . The radionuclide that is incorporated in the instant radio-labeled

5 compounds will depend on the specific application of that radio-labeled compound. For example, for *in vitro* PGI2 receptor labeling and competition assays, compounds that incorporate  $^3\text{H}$ ,  $^{14}\text{C}$ ,  $^{82}\text{Br}$ ,  $^{125}\text{I}$ ,  $^{131}\text{I}$  or  $^{35}\text{S}$  will generally be most useful. For radio-imaging applications  $^{11}\text{C}$ ,  $^{18}\text{F}$ ,  $^{125}\text{I}$ ,  $^{123}\text{I}$ ,  $^{124}\text{I}$ ,  $^{131}\text{I}$ ,  $^{75}\text{Br}$ ,  $^{76}\text{Br}$  or  $^{77}\text{Br}$  will generally be most useful.

It is understood that a "radio-labeled" or "labeled compound" is a compound of  
10 Formula Ia, Ic, Ie, Ig, or Ii that has incorporated at least one radionuclide; in some embodiments the radionuclide is selected from the group consisting of  $^3\text{H}$ ,  $^{14}\text{C}$ ,  $^{125}\text{I}$ ,  $^{35}\text{S}$  and  $^{82}\text{Br}$ .

Certain isotopically-labeled compounds of the present invention are useful in compound and/or substrate tissue distribution assays. In some embodiments the radionuclide  $^3\text{H}$  and/or  $^{14}\text{C}$   
15 isotopes are useful in these studies. Further, substitution with heavier isotopes such as deuterium (*i.e.*,  $^2\text{H}$ ) may afford certain therapeutic advantages resulting from greater metabolic stability (*e.g.*, increased *in vivo* half-life or reduced dosage requirements) and hence may be preferred in some circumstances. Isotopically labeled compounds of the present invention can generally be prepared by following procedures analogous to those disclosed in the Drawings and Examples  
20 *infra*, by substituting an isotopically labeled reagent for a non-isotopically labeled reagent. Other synthetic methods that are useful are discussed *infra*. Moreover, it should be understood that all of the atoms represented in the compounds of the invention can be either the most commonly occurring isotope of such atoms or the scarcer radio-isotope or nonradioactive isotope.

25 Synthetic methods for incorporating radio-isotopes into organic compounds are applicable to compounds of the invention and are well known in the art. These synthetic methods, for example, incorporating activity levels of tritium into target molecules, are as follows:

A. Catalytic Reduction with Tritium Gas: This procedure normally yields high specific  
30 activity products and requires halogenated or unsaturated precursors.

B. Reduction with Sodium Borohydride [ $^3\text{H}$ ]: This procedure is rather inexpensive and requires precursors containing reducible functional groups such as aldehydes, ketones, lactones, esters and the like.

C. Reduction with Lithium Aluminum Hydride [ $^3\text{H}$ ]: This procedure offers products at  
35 almost theoretical specific activities. It also requires precursors containing reducible functional groups such as aldehydes, ketones, lactones, esters and the like.

D. Tritium Gas Exposure Labeling: This procedure involves exposing precursors containing exchangeable protons to tritium gas in the presence of a suitable catalyst.

E. *N*-Methylation using Methyl Iodide [ $^3\text{H}$ ]: This procedure is usually employed to prepare *O*-methyl or *N*-methyl ( $^3\text{H}$ ) products by treating appropriate precursors with high specific activity methyl iodide ( $^3\text{H}$ ). This method in general allows for higher specific activity, such as for example, about 70-90 Ci/mmol.

Synthetic methods for incorporating activity levels of  $^{125}\text{I}$  into target molecules include:

A. Sandmeyer and like reactions: This procedure transforms an aryl amine or a heteroaryl amine into a diazonium salt, such as a diazonium tetrafluoroborate salt and subsequently to  $^{125}\text{I}$  labeled compound using  $\text{Na}^{125}\text{I}$ . A represented procedure was reported by Zhu, G-D. and co-workers in *J. Org. Chem.*, 2002, 67, 943-948.

B. Ortho  $^{125}\text{I}$  iodination of phenols: This procedure allows for the incorporation of  $^{125}\text{I}$  at the ortho position of a phenol as reported by Collier, T. L. and co-workers in *J. Labelled Compd. Radiopharm.*, 1999, 42, S264-S266.

C. Aryl and heteroaryl bromide exchange with  $^{125}\text{I}$ : This method is generally a two step process. The first step is the conversion of the aryl or heteroaryl bromide to the corresponding tri-alkyltin intermediate using for example, a Pd catalyzed reaction [*i.e.*  $\text{Pd}(\text{Ph}_3\text{P})_4$ ] or through an aryl or heteroaryl lithium, in the presence of a tri-alkyltinhalide or hexaalkylditin [*e.g.*,  $(\text{CH}_3)_3\text{SnSn}(\text{CH}_3)_3$ ]. A representative procedure was reported by Le Bas, M.-D. and co-workers in *J. Labelled Compd. Radiopharm.* 2001, 44, S280-S282.

A radiolabeled PGI<sub>2</sub> receptor compound of Formula **Ia** can be used in a screening assay to identify/evaluate compounds. In general terms, a newly synthesized or identified compound (*i.e.*, test compound) can be evaluated for its ability to reduce binding of the "radio-labeled compound of Formula **Ia**" to the PGI<sub>2</sub> receptor. Accordingly, the ability of a test compound to compete with the "radio-labeled compound of Formula **Ia**" for the binding to the PGI<sub>2</sub> receptor directly correlates to its binding affinity.

The labeled compounds of the present invention bind to the PGI<sub>2</sub> receptor. In one embodiment the labeled compound has an  $\text{IC}_{50}$  less than about 500  $\mu\text{M}$ , in another embodiment the labeled compound has an  $\text{IC}_{50}$  less than about 100  $\mu\text{M}$ , in yet another embodiment the labeled compound has an  $\text{IC}_{50}$  less than about 10  $\mu\text{M}$ , in yet another embodiment the labeled compound has an  $\text{IC}_{50}$  less than about 1  $\mu\text{M}$  and in still yet another embodiment the labeled inhibitor has an  $\text{IC}_{50}$  less than about 0.1  $\mu\text{M}$ .

Other uses of the disclosed receptors and methods will become apparent to those skilled in the art based upon, *inter alia*, a review of this disclosure.

As will be recognized, the steps of the methods of the present invention need not be performed any particular number of times or in any particular sequence. Additional objects, advantages and novel features of this invention will become apparent to those skilled in the art

upon examination of the following examples thereof, which are intended to be illustrative and not intended to be limiting.

## EXAMPLES

### 5 Example 1: Syntheses of compounds of the present invention.

Illustrated syntheses for compounds of the present invention are shown in Figures 3 through 9 where the symbols have the same definitions as used throughout this disclosure.

The compounds of the invention and their syntheses are further illustrated by the following examples. The following examples are provided to further define the invention  
10 without, however, limiting the invention to the particulars of these examples. The compounds described herein, *supra* and *infra*, are named according to the CS ChemDraw Ultra Version 7.0.1, AutoNom version 2.2, or CS ChemDraw Ultra Version 9.0.7. In certain instances common names are used and it is understood that these common names would be recognized by those skilled in the art.

15 **Chemistry:** Proton nuclear magnetic resonance (<sup>1</sup>H NMR) spectra were recorded on a Bruker Avance-400 equipped with a QNP (Quad Nucleus Probe) or a BBI (Broad Band Inverse) and z-gradient. Chemical shifts are given in parts per million (ppm) with the residual solvent signal used as reference. NMR abbreviations are used as follows: s = singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dt = doublet of triplets, t = triplet, td =  
20 triplet of doublets, tt = triplet of triplets, q = quartet, m = multiplet, bs = broad singlet, bt = broad triplet. Microwave irradiations were carried out using a Smith Synthesizer™ or an Emrys Optimizer™ (Biotage). Thin-layer chromatography (TLC) was performed on silica gel 60 F<sub>254</sub> (Merck), preparatory thin-layer chromatography (prep TLC) was performed on PK6F silica gel 60 A 1 mm plates (Whatman) and column chromatography was carried out on a silica gel  
25 column using Kieselgel 60, 0.063-0.200 mm (Merck). Evaporation was done under reduced pressure on a Büchi rotary evaporator.

LCMS spec: HPLC-pumps: LC-10AD VP, Shimadzu Inc.; HPLC system controller: SCL-10A VP, Shimadzu Inc; UV-Detector: SPD-10A VP, Shimadzu Inc; Autosampler: CTC HTS, PAL, Leap Scientific; Mass spectrometer: API 150EX with Turbo Ion Spray source,  
30 AB/MDS Sciex; Software: Analyst 1.2.

### Example 1.1: Preparation of *t*-Butyl 2-(((1*s*,4*s*)-4-(Tosyloxymethyl)cyclohexyl)methoxy)acetate.

#### Step A: Preparation of (1*s*,4*s*)-Diethyl Cyclohexane-1,4-dicarboxylate.

To a solution of (1*s*,4*s*)-cyclohexane-1,4-dicarboxylic acid (25 g, 145 mmol) in ethanol  
35 (150 mL) was added concentrated H<sub>2</sub>SO<sub>4</sub> (1 mL). The reaction was refluxed for 16 h, cooled to room temperature and concentrated. The residue was extracted with EtOAc and saturated NaHCO<sub>3</sub>, washed with brine, dried over MgSO<sub>4</sub>, and filtered. The filtrate was concentrated to



provide the title compound as a colorless oil (30.5 g). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 1.25 (t, *J* = 7.14 Hz, 6H), 1.64-1.70 (m, 4H), 1.87-1.92 (m, 4H), 2.44-2.46 (m, 2H), 4.11-1.46 (quartet, *J* = 7.12 Hz, 4H).

**Step B: Preparation of (1*s*,4*s*)-Cyclohexane-1,4-diylldimethanol.**

5 To a solution of (1*s*,4*s*)-diethyl cyclohexane-1,4-dicarboxylate (13.0 g, 56.9 mmol) in THF (500 mL) was added lithium aluminum hydride (4.54 g, 120 mmol) in portions at 0 °C. The mixture was stirred at that temperature for 2 h and quenched with cold water, filtered and concentrated to give the title compound as a colorless oil (8.2 g). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.27-1.42 (m, 8H), 1.46-1.54 (m, 2H), 3.26-3.31 (m, 4H), 4.27-4.30 (t, *J* = 5.31 Hz, 2H).

10 **Step C: Preparation of *tert*-Butyl 2-(((1*s*,4*s*)-4-(Hydroxymethyl)cyclohexyl)methoxy)acetate.**

To a solution of (1*s*,4*s*)-cyclohexane-1,4-diylldimethanol (18.2 g, 126 mmol) in toluene (200 mL) was added NaOH (50% aqueous, 60 mL) and tetrabutylammonium iodide (2.331 g, 6.31 mmol), followed by *tert*-butyl-2-bromoacetate (20.50 mL, 139 mmol) at room temperature. The  
15 reaction mixture was stirred vigorously at room temperature for 2 h and diluted with ethyl acetate and water. After separation, the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layers were dried over MgSO<sub>4</sub>, concentrated, and purified by silica gel column chromatography to give the title compound as a colorless oil (13.5 g). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 1.35-1.47 (m, 4H), 1.48 (s, 9H), 1.50-1.60 (m, 4H), 1.63-1.74 (m, 1H), 1.79-1.92 (m, 1H), 3.42  
20 (d, *J* = 6.95 Hz, 2H), 3.55 (d, *J* = 6.82 Hz, 2H), 3.93 (s, 1H), 3.94 (s, 2H).

**Step D: Preparation of *tert*-Butyl 2-(((1*s*,4*s*)-4-(Tosyloxymethyl)cyclohexyl)methoxy)acetate.**

To a solution of *tert*-butyl 2-(((1*s*,4*s*)-4-(hydroxymethyl)cyclohexyl)methoxy)acetate (12.0 g, 46.4 mmol) in dichloromethane (150 mL) were added triethylamine (4.70 g, 46.4 mmol) and 4-  
25 (dimethylamino)pyridine (0.567 g, 4.64 mmol), followed by 4-methylbenzene-1-sulfonyl chloride (8.86 g, 46.4 mmol). The reaction was stirred at room temperature for 16 h. The solvent was removed and the residue was extracted with EtOAc/H<sub>2</sub>O. The organic extracts were dried over MgSO<sub>4</sub>, and concentrated. The residue was purified by silica gel column chromatography to give the title compound as a pale liquid (9.5 g). LCMS *m/z* = 413.1 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ  
30 ppm 1.28-1.43 (m, 4H), 1.46-1.48 (m, 9H), 1.49-1.56 (m, 4H), 1.76-1.91 (m, 2H), 2.45 (s, 3H), 3.36 (d, *J* = 6.95 Hz, 2H), 3.92 (d, *J* = 7.05 Hz, 2H), 3.92 (s, 2H), 7.35 (d, *J* = 8.46 Hz, 2H), 7.78 (d, *J* = 8.34 Hz, 2H).

**Example 1.2: Preparation of 2-(((1*s*,4*s*)-4-((4-(3-Chlorophenyl)-5-(methylthio)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 95).**

**Step A: Preparation of 4-(3-Chlorophenyl)-5-(methylthio)-3-phenyl-1*H*-pyrazole**

To a solution of 2-(3-chlorophenyl)-1-phenylethanone (5 g, 21.67 mmol) in anhydrous THF (10 mL) was added a solution of 1.0 M KO-*t*-Bu in THF. The reaction was stirred for 15 min at room temperature, then CS<sub>2</sub> (1.782 g, 23.41 mmol) was added. After 10 min, iodomethane (6.77 g, 47.7 mmol) was added and the reaction was stirred for 4 h. The reaction was washed with saturated NaHCO<sub>3</sub> solution and dried over MgSO<sub>4</sub>. The filtrate was concentrated under reduced pressure and the residue was triturated with 10% ethyl acetate. The solid was suspended in ethanol and hydrazine hydrate (5.43 g, 108 mmol) was added at room temperature. The reaction was refluxed for 4 h. The reaction mixture was concentrated under reduced pressure and the residue was triturated with ethyl acetate / hexane to give the title compound as a white solid (4.9 g). LCMS *m/z* = 301.1 [M+H]<sup>+</sup>.

**Step B: Preparation of 2-(((1*s*,4*s*)-4-((4-(3-Chlorophenyl)-5-(methylthio)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid.**

To a solution of 4-(3-chlorophenyl)-5-(methylthio)-3-phenyl-1*H*-pyrazole (4.98 g, 16.62 mmol) in DMF (2 mL) was added sodium hydride (0.399 g, 16.62 mmol) at 0 °C. After stirring for 10 min, *tert*-butyl 2-(((1*s*,4*s*)-4-(tosyloxymethyl)cyclohexyl)methoxy)acetate (6.86 g, 16.62 mmol) was added and warmed to 40 °C. After stirring for 12 h, the mixture was extracted with ethyl acetate. The organic extract was concentrated under reduced pressure and the residue was treated with 4.0 M HCl for 8 h. The mixture was concentrated under reduced pressure and purified by HPLC to give the title compound (3.89 g). LCMS *m/z* = 486.1 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.31-1.50 (m, 8H), 1.74 (m, 1H), 2.14 (m, 1H), 2.31 (s, 3H), 3.52 (d, *J* = 7.0 Hz, 2H), 3.58 (s, 2H), 4.25 (d, *J* = 7.5 Hz, 2H), 7.25-7.51 (m, 9H).

**Example 1.3: Preparation of 2-(((1*s*,4*s*)-4-((4-(3,4-Difluorophenyl)-5-ethoxy-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 80).**

**Step A: Preparation of 3-Phenyl-1*H*-pyrazol-5(4*H*)-one.**

To a solution of propyl 3-oxo-3-phenylpropanoate (10 g, 48.5 mmol) in ethanol (100 mL) was added hydrazine hydrate (9.71 g, 194 mmol) at room temperature. The reaction was heated to 80 °C for 2 h, cooled to room temperature and concentrated. The residue was crystallized from 20% ethyl acetate/hexane to give the title compound (6.58 g). LCMS *m/z* = 161.08 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm, 2.32 (br, 2H), 7.32-7.78 (m, 5H), 12.1 (s, 1H).

**Step B: Preparation of 5-Ethoxy-3-phenyl-1*H*-pyrazole.**

To a solution of 3-phenyl-1*H*-pyrazol-5(4*H*)-one (1.0 g, 6.24 mmol), ethanol (0.288 g, 6.24 mmol) and triphenylphosphine (1.638 g, 6.24 mmol) in *N*-methylmorpholine (7 mL) was added diethylazo dicarboxylate (0.988 mL, 6.24 mmol) dropwise at 0 °C. The reaction was warmed to room temperature and stirred for 2 h. The reaction was poured into H<sub>2</sub>O and extracted with ethyl acetate. The extract was dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give the title

compound (0.89 g). LCMS  $m/z$  = 189.19  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.32 (t,  $J$  = 4.2 Hz, 3H), 4.32 (q,  $J$  = 4.2 Hz, 2H), 6.45 (s, 1H), 7.41-7.94 (m, 5H), 11.3 (s, 1H).

**Step C: Preparation of 4-Bromo-5-ethoxy-3-phenyl-1H-pyrazole**

To a solution of 5-ethoxy-3-phenyl-1H-pyrazole (1.0 g, 5.31 mmol) in dichloromethane (20 mL), was added bromine (0.849 g, 5.31 mmol) dropwise at room temperature. The reaction was stirred for 2 h, washed with saturated NaHCO<sub>3</sub> solution and concentrated under reduced pressure. The residue was triturated with 10% ethyl acetate/hexane to give the title compound as a yellowish solid (1.20 g). LCMS  $m/z$  = 268.07  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.38 (t,  $J$  = 4.2 Hz, 3H), 4.39 (q,  $J$  = 4.2 Hz, 2H), 7.45-7.85 (m, 5H), 12.4 (s, 1H).

**Step D: Preparation of *tert*-Butyl 2-(((1*s*,4*s*)-4-((4-Bromo-5-ethoxy-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate.**

To a solution of 4-bromo-5-ethoxy-3-phenyl-1H-pyrazole (1.5 g, 5.62 mmol) in DMF (5 mL) was added sodium hydride (0.135 g, 5.62 mmol) at room temperature. After stirring for 10 min, a solution of *tert*-butyl 2-(((1*s*,4*s*)-4-(tosyloxymethyl)cyclohexyl)methoxy)acetate (2.317 g, 5.62 mmol) in DMF (1 mL) was added at room temperature. The reaction was stirred at 45 °C for 8 h. The mixture was poured into H<sub>2</sub>O and extracted with ethyl acetate. The organic extract was dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The residue was purified by silica gel to give the title compound (1.45 g). LCMS  $m/z$  = 508.35  $[M+H]^+$ .

**Step E: Preparation of 2-(((1*s*,4*s*)-4-((4-(3,4-Difluorophenyl)-5-ethoxy-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid.**

To a solution of *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-ethoxy-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate (110 mg, 0.217 mmol) in dioxane (2 mL) were added 3,4-difluorophenylboronic acid (34.2 mg, 0.217 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (12.52 mg, 10.84  $\mu$ mol), and K<sub>2</sub>CO<sub>3</sub> (59.9 mg, 0.434 mmol) at room temperature. The reaction was irradiated under microwave for 1.5 h at 150 °C. The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was treated with 4.0 M HCl (5 mL). After stirring for 10 h, the reaction was concentrated under reduced pressure and purified by HPLC to give the title compound (85 mg). LCMS  $m/z$  = 485.3  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.21 (t,  $J$  = 4.1 Hz, 3H), 1.30-1.41 (m, 8H), 1.63-1.74 (m, 1H), 2.18-2.23 (m, 1H), 3.49 (d,  $J$  = 7.1 Hz, 2H), 3.71 (s, 2H), 3.85 (q,  $J$  = 4.1 Hz, 2H), 4.12 (d,  $J$  = 7.4 Hz, 2H), 7.76-7.32 (m, 8H).

**Example 1.4: Preparation of 2-(((1*s*,4*s*)-4-((4-(5-Cyano-2-fluorophenyl)-5-(methylthio)-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 79).**

**Step A: Preparation of 5-(Methylthio)-3-phenyl-1H-pyrazole.**

To a solution of acetophenone (5.0 g, 41.6 mmol) and CS<sub>2</sub> (3.17 g, 41.6 mmol) in THF (150 mL) was added sodium hydride (1.997 g, 83 mmol) at 0 °C. After 30 min at 0 °C, the reaction was warmed to room temperature and stirred for 1 h, then refluxed for 4 h. The reaction was cooled to

room temperature, added iodomethane (16.23 g, 104 mmol), and refluxed for another 12 h. The reaction was cooled and extracted with ethyl acetate. The organic extracts were concentrated under reduced pressure. The residue was diluted with ethanol (200 mL), added hydrazine (1.334 g, 41.6 mmol), and refluxed for 4 h. After cooling, the mixture was concentrated under reduced pressure and extracted with ethyl acetate. The organic extracts were dried over  $\text{MgSO}_4$  and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound (6.02 g). LCMS  $m/z = 191.37$   $[\text{M}+\text{H}]^+$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  ppm 2.31 (s, 3H), 6.21 (s, 1H), 7.38-7.56 (m, 5H), 12.2 (s, 1H).

**Step B: Preparation of 4-Iodo-5-(methylthio)-3-phenyl-1H-pyrazole.**

To a solution of 5-(methylthio)-3-phenyl-1H-pyrazole (1.5 g, 7.88 mmol) in THF (20 mL) and water (20 mL), were added sodium iodide (1.182 g, 7.88 mmol), iodine (3.00 g, 11.83 mmol), and  $\text{K}_2\text{CO}_3$  (1.634 g, 11.83 mmol) at room temperature. The reaction was warmed to 100 °C and stirred for 2 h. The reaction was quenched with 2.0 M aqueous sodium thiosulfite and concentrated under reduced pressure. The mixture was extracted with ethyl acetate and washed with  $\text{NaHCO}_3$  solution. The organic extracts were dried over  $\text{MgSO}_4$  and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound (2.35 g). LCMS  $m/z = 317.02$   $[\text{M}+\text{H}]^+$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  ppm 2.43 (s, 3H), 7.43-7.79 (m, 5H), 13.5 (s, 1H).

**Step C: Preparation of *tert*-Butyl 2-(((1*s*,4*s*)-4-((4-Iodo-5-(methylthio)-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate.**

To a solution of 5-(methylthio)-3,4-diphenyl-1H-pyrazole (100 mg, 0.375 mmol) in DMF (3 mL), was added sodium hydride (9.01 mg, 0.375 mmol) at room temperature. After stirring for 10 min, a solution of *tert*-butyl 2-(((1*s*,4*s*)-4-(tosyloxymethyl)cyclohexyl)methoxy)acetate (154 mg, 0.375 mmol) in DMF (1 mL) was added at room temperature. The reaction was heated to 45 °C and stirred for 8 h. The reaction was poured into  $\text{H}_2\text{O}$  and extracted with ethyl acetate. The organic extract was dried over  $\text{MgSO}_4$  and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound (2.98 g). LCMS  $m/z = 557.48$   $[\text{M}+\text{H}]^+$ .

**Step D: Preparation of 2-(((1*s*,4*s*)-4-((4-(5-Cyano-2-fluorophenyl)-5-(methylthio)-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid.**

To a solution of *tert*-butyl 2-(((1*s*,4*s*)-4-((4-iodo-5-(methylthio)-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate (110 mg, 0.198 mmol) in dioxane (2 mL), were added 5-cyano-2-fluorophenylboronic acid (32.6 mg, 0.198 mmol),  $\text{Pd}(\text{PPh}_3)_4$  (11.42 mg, 9.88  $\mu\text{mol}$ ), and  $\text{K}_2\text{CO}_3$  (54.6 mg, 0.395 mmol) at room temperature. The reaction was heated under microwave irradiation for 1.5 h at 150 °C. The mixture was filtered and concentrated under reduced pressure. The residue was treated with 4.0 M HCl (5 mL) for 10 h. The mixture was concentrated under reduced pressure and purified by HPLC to give the title compound (68 mg). LCMS  $m/z = 494.5$   $[\text{M}+\text{H}]^+$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  ppm 1.31-1.40 (m, 8H), 1.60-1.78 (m, 1H), 2.18-2.20

(m, 1H), 2.38 (s, 3H), 3.51 (d,  $J = 7.0$  Hz, 2H), 3.79 (s, 2H), 4.19 (d,  $J = 7.5$  Hz, 2H), 7.21-7.34 (m, 5H), 7.80-7.41 (m, 3H).

**Example 1.5: Preparation of 2-(((1*s*,4*s*)-4-((4-(Furan-2-yl)-5-(methylthio)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 109).**

To a solution of *tert*-butyl 2-(((1*s*,4*s*)-4-((4-iodo-5-(methylthio)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate (150 mg, 0.270 mmol) in dioxane (1 mL), was added furan-2-yl boronic acid (31.23 mg, 0.270 mmol) followed by Pd(PPh<sub>3</sub>)<sub>4</sub> (15.57 mg, 0.013 mmol) and K<sub>2</sub>CO<sub>3</sub> (74.5 mg, 0.539 mmol) at room temperature. The reaction was heated under microwave at 120 °C for 1.5 h. The mixture was extracted with ethyl acetate and the organic extract was concentrated under reduced pressure. The residue was treated with 4.0 M HCl (3.37 mL, 13.48 mmol) for 5 h. The reaction was concentrated under reduced pressure and purified by HPLC to give the title compound (88 mg). LCMS  $m/z = 441.3$  [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  ppm 1.24-1.39 (m, 8H), 1.64-1.80 (m, 1H), 2.12-2.17 (m, 1H), 2.34 (s, 3H), 3.49 (d,  $J = 7.0$  Hz, 2H), 3.78 (s, 2H), 4.19 (d,  $J = 7.5$  Hz, 2H), 7.31-7.45 (m, 8H).

**Example 1.6: Preparation of 2-(((1*s*,4*s*)-4-((4-(5-Fluoropyridin-3-yl)-5-(methylthio)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 135).**

To a solution of *tert*-butyl 2-(((1*s*,4*s*)-4-((4-iodo-5-(methylthio)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate (500 mg, 0.898 mmol) in dioxane (5 mL) was added 5-fluoropyridin-3-ylboronic acid (127 mg, 0.898 mmol) followed by Pd(PPh<sub>3</sub>)<sub>4</sub> (51.9 mg, 0.045 mmol) and K<sub>2</sub>CO<sub>3</sub> (248 mg, 1.797 mmol) at room temperature. The reaction was heated under microwave irradiation at 120 °C for 1.5 h. The reaction mixture was extracted with ethyl acetate and the organic extracts were concentrated under reduced pressure. The residue was treated with 4.0 M HCl (11.23 mL, 44.9 mmol) in dioxane for 5 h. The mixture was concentrated under reduced pressure and the residue was purified by HPLC to give the title compound as a solid. The solid was dissolved in acetonitrile (1 mL) and water (2 mL) and added 1.0 eq. of NaOH in H<sub>2</sub>O (1 mL). The mixture was concentrated under reduced pressure to give the sodium salt of the title compound (210 mg). LCMS  $m/z = 470.2$  [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  ppm 1.39-1.58 (m, 8H), 1.74-1.80 (m, 1H), 2.20 (s, 3H), 2.21-2.31 (m, 1H), 3.31 (d,  $J = 7.0$  Hz, 2H), 3.73 (s, 2H), 4.32 (d,  $J = 7.5$  Hz, 2H), 6.65-7.40 (m, 5H), 7.76-7.70 (m, 1H), 8.34 (s, 1H), 8.55 (s, 1H).

**Example 1.7: Preparation of 2-(((1*s*,4*s*)-4-((5-(Methylthio)-4-(5-methylthiophen-2-yl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 111).**

To a solution of *tert*-butyl 2-(((1*s*,4*s*)-4-((4-iodo-5-(methylthio)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate (500 mg, 0.981 mmol) in dioxane (5 mL) was added 5-methylthiophen-2-ylboronic acid (139 mg, 0.981 mmol) followed by Pd(PPh<sub>3</sub>)<sub>4</sub> (56.7 mg, 0.049

mmol) and  $K_2CO_3$  (271 mg, 1.963 mmol) at room temperature. The reaction was heated under microwave at 120 °C for 1.5 h. The mixture was extracted with ethyl acetate and concentrated under reduced pressure. The residue was treated with HCl (4.0 M in dioxane) for 5 h. The mixture was concentrated under reduced pressure and the residue was purified by HPLC to give the title compound as a solid. The solid was dissolved in acetonitrile (1 mL) and water (2 mL) and added 1.0 eq. of NaOH in  $H_2O$  (1 mL). The mixture was concentrated under reduced pressure to give the sodium salt of the title compound (158 mg). LCMS  $m/z = 470.1$   $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.21-1.49 (m, 8H), 1.63-1.79 (m, 1H), 2.08-2.13 (m, 1H), 2.15 (s, 3H), 2.35 (s, 3H), 3.54 (d,  $J = 7.0$  Hz, 2H), 3.88 (s, 2H), 4.20 (d,  $J = 7.5$  Hz, 2H), 7.23-7.48 (m, 7H).

**Example 1.8: Preparation of 2-(((1*s*,4*s*)-4-((4-(3-Methoxyphenyl)-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 14).**

To a solution of *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate (1.5 g, 3.14 mmol) in dioxane (12 mL) was added 3-methoxyphenylboronic acid (0.477 g, 3.14 mmol) followed by  $Pd(PPh_3)_4$  (0.182 g, 0.157 mmol) and  $K_2CO_3$  (0.868 g, 6.28 mmol) at room temperature. The reaction was heated under microwave irradiation at 150 °C for 1 h. The reaction was extracted with ethyl acetate and the organic extracts were concentrated under reduced pressure. The residue was treated with HCl (4.0 M in dioxane) for 5 h. The mixture was concentrated under reduced pressure and the residue was purified by HPLC to give the title compound as the free acid. The free acid was treated with NaOH in 30% acetonitrile/ $H_2O$  and the mixture was concentrated under reduced pressure to give the sodium salt of the title compound (0.687 g). LCMS  $m/z = 449.2$   $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.30-1.52 (m, 8H), 1.71-1.83 (m, 1H), 2.01-2.11 (m, 1H), 2.20 (s, 3H), 3.41 (d,  $J = 7.0$  Hz, 2H), 3.78 (s, 2H), 3.85 (s, 3H), 4.13 (d,  $J = 7.5$  Hz, 2H), 6.65-7.40 (m, 9H).

**Example 1.9: Preparation of 2-(((1*R*,4*s*)-4-((5-((*S*)-3,4-Dihydroxybutyl)-4-(3-hydroxyphenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 161).**

**Step A: Preparation of 1-Phenylhept-6-ene-1,3-dione.**

To a solution of 1-phenylbutane-1,3-dione (5 g, 30.8 mmol) in THF (50 mL) was added sodium hydride (0.740 g, 30.8 mmol) at 0 °C. After warming and stirring at room temperature for 30 min, LDA, which was made by adding BuLi (1.975 g, 30.8 mmol) to a solution of diisopropylamine (4.39 mL, 30.8 mmol) in THF (50 mL) at -45 °C, was added at 0 °C. After stirring for 30 min at the same temperature, 3-bromoprop-1-ene (3.73 g, 30.8 mmol) was added at 0 °C. After stirring for 1 h, the reaction was quenched with 1.0 M HCl and extracted with ethyl acetate. The organic extract was dried over  $MgSO_4$  and concentrated under reduced pressure to give the title compound without further purification. LCMS  $m/z = 203.19$   $[M+H]^+$ .

**Step B: Preparation of 5-(But-3-enyl)-3-phenyl-1H-pyrazole.**

To a solution of 1-phenylhept-6-ene-1,3-dione (3 g, 14.83 mmol) in ethanol (50 mL) was added hydrazine hydrate (2.228 g, 44.5 mmol) at room temperature. The reaction was refluxed for 10 h, cooled to room temperature and concentrated under reduced pressure. The residue was  
5 extracted with ethyl acetate. The organic extract was dried over MgSO<sub>4</sub> and concentrated under reduced pressure to give the title compound without further purification. LCMS  $m/z$  = 199.3 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  ppm 2.65-2.78 (m, 2H), 4.01-4.12 (m, 2H), 4.83-4.95 (m, 2H), 5.82-5.93 (m, 1H), 6.42 (s, 1H), 7.23-7.82 (m, 5H), 12.6 (s, 1H).

**Step C: Preparation of (S)-4-(3-Phenyl-1H-pyrazol-5-yl)butane-1,2-diol.**

10 To a solution of 5-(but-3-enyl)-3-phenyl-1H-pyrazole (1 g, 5.04 mmol) in H<sub>2</sub>O (25 mL), and isopropanol (25 mL) was added AD-mix- $\beta$  (5 g, 5.04 mmol) at room temperature. The reaction was stirred for 48 h, quenched with Na<sub>2</sub>SO<sub>3</sub> and extracted with ethyl acetate. The organic extract was dried over MgSO<sub>4</sub> and concentrated under reduced pressure to give the title compound (1.02 g) without further purification. LCMS  $m/z$  = 232.9 [M+H]<sup>+</sup>.

15 **Step D: Preparation of (S)-5-(2-(2,2-Dimethyl-1,3-dioxolan-4-yl)ethyl)-3-phenyl-1H-pyrazole.**

To a solution of (S)-4-(3-phenyl-1H-pyrazol-5-yl)butane-1,2-diol (2.5 g, 10.76 mmol) in acetone (50 mL) were added 2,2-dimethoxypropane (11.21 g, 108 mmol) and *p*-toluenesulfonic acid (0.185g, 1.076 mmol) at room temperature. After stirring for 3 h, the reaction was concentrated  
20 under reduced pressure. The residue was extracted with ethyl acetate. The organic extract was dried over MgSO<sub>4</sub> and concentrated under reduced pressure to give the title compound (2.70 g) without further purification. LCMS  $m/z$  = 273.0 [M+H]<sup>+</sup>.

**Step E: Preparation of (S)-4-Bromo-5-(2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethyl)-3-phenyl-1H-pyrazole.**

25 To a solution of (S)-5-(2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethyl)-3-phenyl-1H-pyrazole (1.1 g, 4.04 mmol) and MP-carbonate in CH<sub>2</sub>Cl<sub>2</sub> (50 mL) was added bromine (0.645 g, 4.04 mmol) dropwise at 0 °C. After stirring for 1 h, MP-carbonate (12.4 g, 40.4mmol) was filtered off and washed with CH<sub>2</sub>Cl<sub>2</sub>. The combined filtrate was poured into water, extracted with CH<sub>2</sub>Cl<sub>2</sub>, dried over MgSO<sub>4</sub>, and concentrated under reduced pressure. The residue was purified by silica gel  
30 column chromatography to give the title compound as an oil (1.129 g). LCMS  $m/z$  = 351.1 [M+H]<sup>+</sup>.

**Step F: Preparation of *tert*-Butyl 2-(((1*R*,4*s*)-4-((4-Bromo-5-(2-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)ethyl)-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate.**

To a solution of (S)-4-bromo-5-(2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethyl)-3-phenyl-1H-pyrazole (1.23 g, 3.50 mmol) in DMF (10 mL) was added sodium hydride (0.084 g, 3.50 mmol) at  
35 room temperature. After stirring for 30 min, *tert*-butyl 2-(((1*s*,4*s*)-4-(tosyloxymethyl)cyclohexyl)methoxy)acetate (1.44 g, 3.50 mmol) was added and the reaction was heated to 45 °C. After stirring for 12 h at the same temperature, the reaction was poured into H<sub>2</sub>O

and extracted with ethyl acetate. The organic extract was dried over  $\text{MgSO}_4$  and concentrated under reduced pressure to give the title compound without further purification. LCMS  $m/z = 592.1$   $[\text{M}+\text{H}]^+$ .

**Step G: Preparation of 2-(((1*R*,4*s*)-4-((5-((*S*)-3,4-Dihydroxybutyl)-4-(3-hydroxyphenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid.**

To a solution of *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-(2-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)ethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate (150 mg, 0.254 mmol) in dioxane (1 mL) was added 3-hydroxyphenylboronic acid (35.0 mg, 0.254 mmol) followed by  $\text{Pd}(\text{PPh}_3)_4$  (14.65 mg, 0.013 mmol) and  $\text{K}_2\text{CO}_3$  (70.1 mg, 0.507 mmol) at room temperature. The reaction was heated under microwave at 120 °C for 1.5 h. The reaction was extracted with ethyl acetate and concentrated under reduced pressure. The residue was treated with HCl (4.0 M in dioxane) for 5 h. The mixture was concentrated under reduced pressure and purified by HPLC to give the title compound (59 mg). LCMS  $m/z = 509.3$   $[\text{M}+\text{H}]^+$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  ppm 1.20-1.62 (m, 12H), 1.75-1.80 (m, 1H), 2.10-2.15 (m, 1H), 2.45-2.70 (m, 1H), 3.14-3.20 (m, 2H), 3.39 (d,  $J = 7.0$  Hz, 2H), 3.83 (s, 2H), 4.05 (d,  $J = 7.5$  Hz, 2H), 6.50-7.35 (m, 9H).

**Example 1.10: Preparation of 2-(((1*s*,4*s*)-4-((5-(Cyanomethylthio)-3,4-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 184).**

**Step A: Preparation of 3,4-Diphenyl-1*H*-pyrazole-5(4*H*)-thione.**

To a solution of 1,2-diphenylethanone (10 g, 51.0 mmol) in acetone (250 mL) were added  $\text{K}_2\text{CO}_3$  (21.1 g, 153 mmol),  $\text{CS}_2$  (11.62 g, 153 mmol), and dibromomethane (26.5 g, 153 mmol) at room temperature. The reaction was stirred for 48 h at 40 °C. The reaction mixture was extracted with ethyl acetate, dried over  $\text{MgSO}_4$ , and concentrated under reduced pressure. The resulting residue was diluted with ethanol (125 mL) and hydrazine hydrate (2.55 g, 50.9 mmol) was added at room temperature. The reaction was refluxed for 4 h, cooled, and concentrated under reduced pressure. The residue was triturated with isopropanol and dried under reduced pressure to give the title compound as a white solid (8.25 g). LCMS  $m/z = 253.1$   $[\text{M}+\text{H}]^+$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  ppm 3.14 (bs, 1H), 7.34-7.54 (m, 10H), 12.5 (s, 1H).

**Step B: Preparation of 2-(3,4-Diphenyl-1*H*-pyrazol-5-ylthio)acetonitrile.**

To a solution of 3,4-diphenyl-1*H*-pyrazole-5(4*H*)-thione (0.5 g, 1.981 mmol) in DMF (5 mL), were added 2-bromoacetonitrile (0.238 g, 1.981 mmol) and  $\text{K}_2\text{CO}_3$  (0.274 g, 1.981 mmol) at room temperature. After stirring at the same temperature for 1 h, the reaction was extracted with ethyl acetate, which was dried over  $\text{MgSO}_4$  and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound (0.38 g). LCMS  $m/z = 292.0$   $[\text{M}+\text{H}]^+$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  ppm 3.20 (s, 2H), 7.35-7.45 (m, 10H), 13.7 (s, 1H).



**Step C: Preparation of 2-(((1*s*,4*s*)-4-((5-(Cyanomethylthio)-3,4-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid.**

To a solution of 2-(3,4-diphenyl-1*H*-pyrazol-5-ylthio)acetonitrile (330 mg, 1.133 mmol) in DMF (2 mL) was added sodium hydride (27.2 mg, 1.133 mmol) at 0 °C. After stirring for 10 min, *tert*-butyl 2-(((1*s*,4*s*)-4-(tosyloxymethyl)cyclohexyl)methoxy)acetate (467 mg, 1.133 mmol) was added. The reaction was warmed to 40 °C and stirred for 12 h. The reaction mixture was extracted with ethyl acetate. The organic extract was concentrated under reduced pressure and the residue was treated with 4.0 M HCl for 8 h. The mixture was concentrated under reduced pressure and the residue was purified by HPLC to give the title compound (92 mg). LCMS  $m/z$  = 476.3 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.31-1.53 (m, 8H), 1.63 (m, 1H), 2.15 (m, 1H), 3.32 (d,  $J$  = 7.0 Hz, 2H), 3.63 (s, 2H), 3.73 (s, 2H), 4.25 (d,  $J$  = 7.5 Hz, 2H), 7.21-7.35 (m, 10H).

**Example 1.11: Preparation of 2-(((1*s*,4*s*)-4-((5-(Methylthio)-3,4-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 76).**

**Step A: Preparation 5-(Methylthio)-3,4-diphenyl-1*H*-pyrazole.**

To a solution of 1,2 -diphenylethanone (5 g, 25.5 mmol) in anhydrous THF (10 mL) was added a solution of 1.0 M KO-*t*-Bu in THF (108 mL). The reaction was stirred for 15 min at room temperature, then CS<sub>2</sub> (2.09 g, 27.5 mmol) was added. After 10 min, iodomethane (7.96 g, 56.1 mmol) was added and the reaction was stirred for 4 h. The reaction was washed with saturated NaHCO<sub>3</sub> solution and dried over MgSO<sub>4</sub>. The filtrate was concentrated under reduced pressure and the residue was triturated with 10% ethyl acetate. The solid was suspended in ethanol and hydrazine hydrate (5.10 g, 102 mmol) was added at room temperature. The reaction was refluxed for 4 h. The reaction mixture was concentrated under reduced pressure and the residue was triturated with ethyl acetate / hexane to give the title compound as a white solid (5.2 g). LCMS  $m/z$  = 267.27 [M+H]<sup>+</sup>.

**Step B: Preparation of 2-(((1*s*,4*s*)-4-((5-(Methylthio)-3,4-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid.**

To a solution of 5-(methylthio)-3,4-diphenyl-1*H*-pyrazole (100 mg, 0.375 mmol) in DMF (3 mL) was added sodium hydride (9.01 mg, 0.375 mmol) at room temperature. After stirring for 10 min, a solution of *tert*-butyl 2-(((1*s*,4*s*)-4-(tosyloxymethyl)cyclohexyl)methoxy)acetate (155 mg, 0.375 mmol) in DMF (1 mL) was added. The reaction was heated to 45 °C and stirred for 8 h. The reaction mixture was poured into H<sub>2</sub>O and extracted with ethyl acetate. The organic extract was dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The residue was treated with HCl (4.0 M in dioxane) overnight. The mixture was concentrated under reduced pressure and the residue was purified by HPLC to give the title compound (98 mg). LCMS  $m/z$  = 451.47 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.33-1.55 (m, 8H), 2.12 (s, 3H) 1.69- 1.81 (m, 1H), 2.14-2.26 (m, 1H), 3.39 (d,  $J$  = 7.0 Hz, 2H), 3.80 (s, 2H), 4.28 (d,  $J$  = 7.5 Hz, 2H), 7.21-7.43 (m, 10H).

**Example 1.12: Preparation of 2-(((1*s*,4*s*)-4-((4-(4-Chlorophenyl)-3-methyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 21).**

**Step A: Preparation of 5-Methyl-3-phenyl-1*H*-pyrazole.**

To a solution of acetophenone (10 g, 83 mmol) in anhydrous toluene (10 mL) was added  
5 LiHMDS (1.0 M in THF, 83 mL, 83 mmol) via syringe at 0 °C under argon. After 5 min, acetyl  
chloride (6.53 g, 83 mmol) was added in one portion via syringe. The ice bath was removed and  
glacial AcOH (5 mL), EtOH (50 mL), and hydrazine hydrate (12.50 g, 250 mmol) were added. The  
mixture was refluxed for 2 h. After cooled to room temperature, the reaction was neutralized to pH 7  
by adding 1.0 M NaOH solution. The mixture was extracted with EtOAc, washed with brine, dried  
10 over MgSO<sub>4</sub>, and concentrated. The residue was purified by silica gel column chromatography to  
give the title compound as a pale yellow oil (12.05 g). LCMS *m/z* = 159.0 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400  
MHz, DMSO-*d*<sub>6</sub>) δ ppm 2.25 (s, 3H), 6.42 (s, 1H), 7.20-7.44 (m, 3H), 7.67-7.82 (m, 2H), 12.53 (bs,  
1H).

**Step B: Preparation of 4-Bromo-5-methyl-3-phenyl-1*H*-pyrazole.**

15 To a solution of 5-methyl-3-phenyl-1*H*-pyrazole (8.0 g, 50.6 mmol) in dichloromethane  
(150 mL) was added bromine (8.08 g, 50.6 mmol) dropwise at 0 °C. The reaction was stirred at that  
temperature for 30 min and continued at room temperature for 2 h. After the reaction was quenched  
with an aqueous solution of Na<sub>2</sub>SO<sub>3</sub> (10% w/w, 10 mL), the organic solvent was removed and the  
aqueous mixture was extracted with EtOAc, washed with brine, dried over MgSO<sub>4</sub>, and  
20 concentrated. The residue was purified by silica gel column chromatography to give the title  
compound as a yellow oil (9.5 g). LCMS *m/z* = 236.9 (M+H<sup>+</sup>). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ  
ppm 2.26 (s, 3H), 7.30-7.57 (m, 5H), 13.12 (s, 1H).

**Step C: Preparation of *tert*-Butyl 2-(((1*s*,4*s*)-4-((4-Bromo-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate.**

25 To a solution of 4-bromo-5-methyl-3-phenyl-1*H*-pyrazole (2.0 g, 8.44 mmol) in DMF (5  
mL) was added sodium hydride (0.202 g, 8.44 mmol) in portions at 0 °C. The reaction was stirred at  
0 °C for 1 h and *tert*-butyl 2-(((1*s*,4*s*)-4-(tosyloxymethyl)cyclohexyl)methoxy)acetate (3.48 g, 8.44  
mmol) was added. The reaction was heated to 42 °C, stirred for 16 h, and quenched with H<sub>2</sub>O (2  
mL). The mixture was extracted with ethyl acetate, dried over MgSO<sub>4</sub> and concentrated under  
30 reduced pressure. The residue was purified by silica gel column chromatography to give the title  
compound as a colorless liquid (3.05 g). LCMS *m/z* = 477.3 (M+H<sup>+</sup>). <sup>1</sup>H NMR (400 MHz, DMSO-  
*d*<sub>6</sub>) δ ppm 1.26-1.50 (m, 8H), 1.43 (s, 9H), 1.66-1.78 (m, 1H), 1.97-2.09 (m, 1H), 2.30 (s, 3H), 3.39  
(d, *J* = 6.82 Hz, 2H), 3.94 (s, 2H), 4.06 (d, *J* = 7.58 Hz, 2H), 7.30-7.50 (m, 3H), 7.74-7.85 (m, 2H).

**Step D: Preparation of 2-(((1*s*,4*s*)-4-((4-(4-Chlorophenyl)-3-methyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid.**

35 To a solution of *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate (100 mg, 0.19 mmol) in dioxane (3 mL) were added 4-

chlorophenylboronic acid (29.8 mg, 0.19 mmol), tetrakis(triphenylphosphine)palladium (22 mg, 0.019 mmol), and K<sub>2</sub>CO<sub>3</sub> (2 M aqueous, 0.2 mL). The reaction was heated to 150 °C under microwave irradiation for 4 h. The reaction mixture was filtered and the filtrate was concentrated. The residue was treated with HCl (4 M in dioxane, 5 mL) at room temperature for 10 h. The mixture was concentrated and the residue was purified by HPLC to give the title compound (13.5 mg). LCMS *m/z* = 453.4 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.01-1.19 (m, 4H), 1.21-1.36 (m, 4H), 1.54-1.66 (m, 1H), 1.86-1.98 (m, 1H), 2.22 (s, 3H), 3.19 (d, *J* = 6.95 Hz, 2H), 3.89 (d, *J* = 7.45 Hz, 2H), 3.91 (s, 2H), 7.04-7.11 (m, 2H), 7.21-7.31 (m, 5H), 7.39-7.47 (m, 2H).

**Example 1.13: Preparation of 2-(((1*s*,4*s*)-4-((5-(Ethylthio)-4-(2-fluoro-3-methoxyphenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 90).**

From 5-(ethylthio)-3-phenyl-1*H*-pyrazole, using a similar method to the one described in Example 1.4, the title compound was obtained. LCMS *m/z* = 513.1. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 0.96 (t, *J* = 7.33 Hz, 3H), 1.30-1.52 (m, 8H), 1.68-1.80 (m, 1H), 2.14-2.26 (m, 1H), 2.53 (q, *J* = 7.33 Hz, 2H), 3.37 (d, *J* = 6.95 Hz, 2H), 3.68 (s, 2H), 3.84 (s, 3H), 4.28 (d, *J* = 7.58 Hz, 2H), 6.76-6.94 (m, 2H), 7.13-7.40 (m, 6H).

**Example 1.14: Preparation of 2-(((1*s*,4*s*)-4-((5-Ethyl-4-(3-methoxyphenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 99).**

**Step A: Preparation of 5-Ethyl-3-phenyl-1*H*-pyrazole.**

To a solution of acetophenone (10 g, 83 mmol) in anhydrous toluene (10 mL) added LiHMDS (85.0 mL, 1.0 M in THF, 85.0 mmol) via syringe at 0 °C under argon. After 5 min, propionyl chloride (7.70 g, 83 mmol) was added in one portion via syringe. The ice bath was removed after 10 min and AcOH (2 mL), EtOH (50 mL), and hydrazine hydrate (8.35 g, 116 mmol) were added. The mixture was refluxed for 2 h. The resulting solution was added to 1.0 M NaOH solution, extracted with EtOAc, washed with brine, dried over MgSO<sub>4</sub>, and concentrated. The residue was purified by silica gel column chromatography to give the title compound as a clear yellowish liquid (12.05 g). LCMS *m/z* = 173.3 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.23 (t, *J* = 7.58 Hz, 3H), 2.64 (q, *J* = 7.07 Hz, 2H), 6.46 (s, 1H), 7.20-7.52 (m, 3H), 7.77 (d, *J* = 6.32 Hz, 2H), 12.55 (s, 1H).

**Step B: Preparation of 4-Bromo-5-ethyl-3-phenyl-1*H*-pyrazole.**

To a solution of 5-ethyl-3-phenyl-1*H*-pyrazole (10.0 g, 58.1 mmol) in DCM (150 mL) was added dropwise bromine (9.28 g, 58.1 mmol) at 0 °C. The reaction was stirred at that temperature for 30 min and continued for 2 h at room temperature and then quenched with aqueous Na<sub>2</sub>SO<sub>3</sub> solution (10% w/w, 10 mL). DCM was removed and the residue was extracted with EtOAc, washed with brine, dried over MgSO<sub>4</sub>, and concentrated. The residue was purified by silica gel column chromatography to give the title compound as a yellow liquid (9.5 g). LCMS *m/z* = 250.9 [M+H]<sup>+</sup>;

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.22 (t, *J* = 7.58 Hz, 3H), 2.66 (q, *J* = 7.58 Hz, 2H), 7.40-7.56 (m, 3H), 7.82 (d, *J* = 7.58 Hz, 2H), 13.15 (s, 1H).

**Step C: Preparation of *tert*-Butyl 2-(((1*s*,4*s*)-4-((4-Bromo-5-ethyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate.**

5 To a solution of 4-bromo-5-ethyl-3-phenyl-1*H*-pyrazole (3.0 g, 11.95 mmol) in DMF (5 mL) was added sodium hydride (0.287 g, 11.95 mmol) followed by *tert*-butyl 2-(((1*s*,4*s*)-4-(tosyloxymethyl)cyclohexyl)methoxy)acetate (4.93 g, 11.95 mmol). The reaction was heated at 45 °C overnight, quenched with water (2 mL), and the mixture was extracted with EtOAc. The organic phase was washed with brine, dried over MgSO<sub>4</sub>, and concentrated. The residue was purified by  
10 silica gel column chromatography to give the title compound as a clear liquid (4.5 g). LCMS *m/z* = 491.2 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 1.25 (t, *J* = 7.20 Hz, 3H), 1.31-1.43 (m, 4H), 1.49 (s, 9H), 1.51-1.60 (m, 4H), 1.76-1.90 (m, 1H), 2.12-2.24 (m, 1H), 2.72 (q, *J* = 7.75 Hz, 2H), 3.46 (d, *J* = 6.82 Hz, 2H), 3.92 (s, 2H), 4.01 (d, *J* = 7.58 Hz, 2H), 7.31-7.43 (m, 3H), 7.86 (d, *J* = 7.33 Hz, 2H).

**Step D: Preparation of 2-(((1*s*,4*s*)-4-((5-Ethyl-4-(3-methoxyphenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid.**

A mixture of 3-methoxyphenylboronic acid (0.141 g, 0.929 mmol), *tert*-butyl 2-(((1*s*,4*s*)-4-((5-ethyl-4-iodo-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate (0.5 g, 0.929 mmol), tetrakis(triphenylphosphine)palladium (0.107 g, 0.093 mmol), K<sub>2</sub>CO<sub>3</sub> (2 M aqueous, 0.5 mL) and dioxane (10 mL) was heated to 150 °C under microwave for 4 h. The reaction mixture was  
20 filtered and the filtrate was concentrated. The residue was treated with HCl (4 M in dioxane, 5 mL) at room temperature for 10 h. The mixture was concentrated and the residue was purified by HPLC to give the title compound (0.135 g). LCMS *m/z* = 463.2 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.04 (t, *J* = 7.45 Hz, 3H), 1.35-1.55 (m, 8H), 1.71-1.83 (m, 1H), 2.06-2.18 (m, 1H), 2.60 (q, *J* =  
25 7.58 Hz, 2H), 3.40 (d, *J* = 6.95 Hz, 2H), 3.70 (s, 3H), 3.72 (s, 2H), 4.02 (d, *J* = 7.45 Hz, 2H), 6.69-6.78 (m, 2H), 6.85-6.91 (m, 1H), 7.15-7.36 (m, 6H).

**Example 1.15: Preparation of 2-(((1*s*,4*s*)-4-((4-(3-Fluorophenyl)-5-isopropyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 113).**

**Step A: Preparation of 5-Isopropyl-3-phenyl-1*H*-pyrazole.**

30 To a solution of acetophenone (1.21 g, 10.07 mmol) in dry toluene (5 mL) was added LiHMDS (11.0 mL, 1.0 M in THF, 11.0 mmol) via syringe at 0 °C under argon. After 5 min, isobutyryl chloride (1.073 g, 10.07 mmol) was added in one portion via syringe. The ice bath was removed and AcOH (2 mL), EtOH (50 mL) and THF (5 mL) were added to form a homogeneous  
35 mixture. Hydrazine hydrate (2 mL, 10.07 mmol) was added and the reaction was refluxed for 2 h. The reaction was cooled to room temperature and concentrated. The residue was extracted with EtOAc, washed with brine, dried over MgSO<sub>4</sub>, and concentrated. The residue was purified by silica

gel column chromatography to give the title compound as a colorless oil (0.70 g). LCMS  $m/z$  = 187.3  $[M+H]^+$ ;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  ppm 1.33 (d,  $J$  = 6.82 Hz, 6H), 2.94-3.13 (m, 1H), 6.38 (s, 1H), 7.17-7.45 (m, 5H), 10.14 (bs, 1H).

**Step B: Preparation of 4-Iodo-5-isopropyl-3-phenyl-1H-pyrazole.**

5 To a solution of 5-isopropyl-3-phenyl-1H-pyrazole (0.64 g, 3.44 mmol) in THF (20 mL) and water (20.00 mL) were added sodium iodide (0.515 g, 3.44 mmol), iodine (1.308 g, 5.15 mmol), and potassium carbonate (0.712 g, 5.15 mmol) at room temperature. The reaction was refluxed for 2 h, cooled to room temperature and quenched with 10% aqueous  $Na_2SO_3$ . The organic solvent was removed under reduced pressure and the aqueous residue was extracted with EtOAc. The organic  
10 extract was washed with  $NaHCO_3$  solution, brine, dried over  $MgSO_4$ , and concentrated. The residue was purified by silica gel column chromatography to give the title compound as a clear liquid (0.42 g). LCMS  $m/z$  = 313.2  $[M+H]^+$ ;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  ppm 1.17 (d,  $J$  = 7.07 Hz, 6H), 3.02 (septet,  $J$  = 7.07 Hz, 1H), 7.23-7.32 (m, 3H), 7.60-7.67 (m, 2H), 11.81 (bs, 1H).

**Step C: Preparation of *tert*-Butyl 2-(((1*s*,4*s*)-4-((4-Iodo-5-isopropyl-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate.**

To a solution of 4-iodo-5-isopropyl-3-phenyl-1H-pyrazole (0.35 g, 1.121 mmol) in DMF (5 mL) was added sodium hydride (0.027 g, 1.121 mmol) at room temperature. The reaction was stirred at room temperature for 1 h and *tert*-butyl 2-(((1*s*,4*s*)-4-(tosyloxymethyl)cyclohexyl)methoxy)acetate (0.463 g, 1.121 mmol) was added. The reaction was  
20 heated at 50 °C for 16 h, cooled to room temperature, and quenched with water (2 mL). The mixture was extracted with EtOAc. The organic extract was dried over  $MgSO_4$  and concentrated. The residue was purified by silica gel column chromatography to give the title compound as a clear liquid (0.52 g). LCMS  $m/z$  = 553.2  $[M+H]^+$ ;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  ppm 0.99-1.20 (m, 4H), 1.25-1.42 (m, 4H), 1.46 (d,  $J$  = 7.20 Hz, 6H), 1.48 (s, 9H), 1.82-1.94 (m, 1H), 2.07-2.19 (m, 1H),  
25 3.16-3.28 (m, 1H), 3.45 (d,  $J$  = 7.07 Hz, 2H), 3.95 (s, 2H), 4.07 (d,  $J$  = 7.71 Hz, 2H), 7.30-7.46 (m, 3H), 7.63-7.79 (m, 2H).

**Step C: Preparation of 2-(((1*s*,4*s*)-4-((4-(3-Fluorophenyl)-5-isopropyl-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid.**

A mixture of 3-fluorophenylboronic acid (25.3 mg, 0.181 mmol), *tert*-butyl 2-(((1*s*,4*s*)-4-((4-iodo-5-isopropyl-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate (100 mg, 0.181 mmol), tetrakis(triphenylphosphine)palladium (10.0 mg, 0.009 mmol),  $K_2CO_3$  (2 M aqueous, 0.2 mL) and dioxane (4 mL) was heated to 150 °C under microwave irradiation for 4 h. The mixture was filtered and the filtrate was concentrated. The residue was treated with HCl (4 M in dioxane, 5 mL) at room temperature for 10 h. The mixture was concentrated and the residue was purified by  
35 HPLC to give the title compound (15.5 mg). LCMS  $m/z$  = 465.3  $[M+H]^+$ ;  $^1H$  NMR (400 MHz,  $DMSO-d_6$ )  $\delta$  ppm 1.10 (d,  $J$  = 7.07 Hz, 6H), 1.34-1.59 (m, 8H), 1.72-1.85 (m, 1H), 2.06-2.19 (m,

1H), 3.09-3.22 (m, 1H), 3.44 (d,  $J = 7.07$  Hz, 2H), 4.00 (s, 2H), 4.08 (d,  $J = 7.58$  Hz, 2H), 7.00-7.10 (m, 2H), 7.14-7.28 (m, 5H), 7.37-7.46 (m, 2H).

**Example 1.16: Preparation of 2-(((1*s*,4*s*)-4-((3-Cyclopropyl-4,5-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 121).**

**Step A: Preparation of 5-Cyclopropyl-3-phenyl-1*H*-pyrazole.**

To a solution of acetophenone (5.0 g, 41.6 mmol) in dry toluene (5 mL) was added LiHMDS (42.0 mL, 1.0 M in THF, 42.0 mmol) via syringe at 0 °C under argon. After 5 min, cyclopropanecarbonyl chloride (4.35 g, 41.6 mmol) was added in one portion via syringe. The ice bath was removed and AcOH (2 mL), EtOH (50 mL), and hydrazine hydrate (10 mL, 64% aqueous, 127.8 mmol) was added. The mixture was refluxed for 30 min, cooled to room temperature, and concentrated. The residue was extracted with EtOAc, washed with brine, dried over MgSO<sub>4</sub>, and purified by silica gel column chromatography to give the title compound as a colorless oil (4.5 g). LCMS  $m/z = 184.7$  [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  ppm 0.71-0.80 (m, 2H), 0.89-1.00 (m, 2H), 1.81-1.98 (m, 1H), 6.22 (s, 1H), 7.11-7.56 (m, 5H), 10.50 (bs, 1H).

**Step B: Preparation of 5-Cyclopropyl-4-iodo-3-phenyl-1*H*-pyrazole.**

To a solution of 5-cyclopropyl-3-phenyl-1*H*-pyrazole (3.0 g, 16.28 mmol) in THF (20 mL) and water (20 mL) were added sodium iodide (2.441 g, 16.28 mmol), iodine (6.20 g, 24.43 mmol), and potassium carbonate (3.38 g, 24.43 mmol) at room temperature. The reaction was refluxed for 2 h (100 °C). The reaction was cooled to room temperature and quenched with 10% aqueous Na<sub>2</sub>SO<sub>3</sub>. The organic solvent was removed under reduced pressure and the aqueous phase was extracted with EtOAc, washed with NaHCO<sub>3</sub> solution, brine, dried over MgSO<sub>4</sub>, and concentrated. The residue was purified by silica gel column chromatography (2.7 g). LCMS  $m/z = 310.8$  [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  ppm 0.75-0.81 (m, 2H), 0.83-0.88 (m, 2H), 2.46-2.56 (m, 1H), 7.33-7.47 (m, 3H), 7.62-7.71 (m, 2H), 12.91 (s, 1H).

**Step C: Preparation of *tert*-Butyl 2-(((1*s*,4*s*)-4-((3-Cyclopropyl-4-iodo-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate.**

A solution of 5-cyclopropyl-4-iodo-3-phenyl-1*H*-pyrazole (3.5 g, 11.29 mmol) in DMF (5 mL) was treated with sodium hydride (0.271 g, 11.29 mmol) at room temperature for 1 h, then *tert*-butyl 2-(((1*s*,4*s*)-4-(tosyloxymethyl)cyclohexyl)methoxy)acetate (4.66 g, 11.29 mmol) was added. The reaction mixture was heated to 50 °C for 16 h and quenched with water (2 mL). The mixture was extracted by EtOAc, dried over MgSO<sub>4</sub>, and concentrated. The residue was purified by silica gel column chromatography to give the title compound as a colorless oil (4.5 g). LCMS  $m/z = 551.1$  [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  ppm 1.04-1.19 (m, 4H), 1.33-1.44 (m, 4H), 1.46 (s, 9H), 1.47 (d,  $J = 8.08$  Hz, 4H), 1.67-1.77 (m, 1H), 1.85-1.91 (m, 1H), 1.90-1.99 (m, 1H), 3.25 (d,  $J = 7.07$  Hz, 2H), 3.87 (s, 2H), 3.91 (d,  $J = 7.58$  Hz, 2H), 7.28-7.54 (m, 5H).

**Step D: Preparation of 2-(((1*s*,4*s*)-4-((3-Cyclopropyl-4,5-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid.**

A mixture of phenylboronic acid (25.3 mg, 0.181 mmol), *tert*-butyl 2-(((1*s*,4*s*)-4-((3-cyclopropyl-4-iodo-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate (100 mg, 0.181 mmol), tetrakis(triphenylphosphine)palladium (10.0 mg, 0.009 mmol), K<sub>2</sub>CO<sub>3</sub> (2 M aqueous, 0.2 mL) and dioxane (4 mL) was heated to 150 °C under microwave irradiation for 4 h. The mixture was filtered and the filtrate was concentrated. The residue was treated with HCl (4 M in dioxane, 5 mL) at room temperature for 10 h. The mixture was concentrated and the residue was purified by HPLC to give the title compound (23.5 mg). LCMS *m/z* = 445.1 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.32-1.55 (m, 8H), 1.71-1.82 (m, 1H), 2.04-2.17 (m, 1H), 2.28 (s, 3H), 2.93 (t, *J* = 6.82 Hz, 2H), 3.16 (s, 3H), 3.40 (t, *J* = 6.63 Hz, 2H), 3.41 (d, *J* = 6.69 Hz, 2H), 3.87 (s, 2H), 4.07 (d, *J* = 7.45 Hz, 2H), 6.87-6.98 (m, 2H), 7.07-7.13 (m, 2H), 7.16-7.31 (m, 5H).

**Example 1.17: Preparation of 2-(((1*s*,4*s*)-4-((3-(2-Fluoro-4-methylphenyl)-5-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 143).**

**Step A: Preparation of 3-Iodo-5-methyl-4-phenyl-1*H*-pyrazole.**

To a solution of 5-methyl-4-phenyl-1*H*-pyrazole (5.0 g, 31.6 mmol) in THF (40 mL) and water (40 mL) were added sodium iodide (4.74 g, 31.6 mmol), iodine (12.03 g, 47.4 mmol), and K<sub>2</sub>CO<sub>3</sub> (4.37 g, 31.6 mmol) at room temperature. The reaction was refluxed for 2 h and then quenched with aqueous Na<sub>2</sub>SO<sub>3</sub> (10%). The mixture was extracted with ethyl acetate, dried over MgSO<sub>4</sub>, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound as a colorless oil (2.5 g). LCMS *m/z* = 284.7 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 2.26 (s, 3H), 7.24-7.54 (m, 5H), 13.13 (s, 1H).

**Step B: Preparation of *tert*-Butyl 2-(((1*s*,4*s*)-4-((3-Iodo-5-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate.**

A solution of 3-iodo-5-methyl-4-phenyl-1*H*-pyrazole (2.0 g, 7.04 mmol) in DMF (5 mL) was treated with sodium hydride (0.169 g, 7.04 mmol) at room temperature for 1 h, then *tert*-butyl 2-(((1*s*,4*s*)-4-(tosyloxymethyl)cyclohexyl)methoxy)acetate (2.9 g, 7.04 mmol) was added. The reaction mixture was heated to 50 °C for 16 h before it was quenched by addition of water (2 mL). The mixture was extracted with EtOAc, dried over MgSO<sub>4</sub> and concentrated. The residue was purified by silica gel column chromatography to give the title compound as a colorless oil (1.5 g). LCMS *m/z* = 525.0 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.27-1.52 (m, 8H), 1.44 (s, 9H), 1.68-1.80 (m, 1H), 1.95-2.07 (m, 1H), 1.99 (s, 3H), 3.40 (d, *J* = 6.82 Hz, 2H), 3.96 (s, 2H), 4.03 (d, *J* = 7.33 Hz, 2H), 7.28-7.46 (m, 5H).

**Step C: Preparation of 2-(((1*s*,4*s*)-4-((3-(2-Fluoro-4-methylphenyl)-5-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid.**

A solution of 2-fluoro-4-methylphenylboronic acid (29.4 mg, 0.191 mmol), *tert*-butyl 2-(((1*s*,4*s*)-4-((3-iodo-5-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate (100 mg, 0.191 mmol), tetrakis(triphenylphosphine)palladium (22.03 mg, 0.019 mmol), and K<sub>2</sub>CO<sub>3</sub> (2 M aqueous, 0.5 mL) in dioxane (3 mL) was heated to 150 °C under microwave irradiation for 2 h. The mixture was filtered and the filtrate was concentrated. The residue was treated with HCl (4 M in dioxane, 3 mL) at room temperature for 16 h. The mixture was concentrated and the residue was purified by HPLC (Varian ProStar; Prep Column: Phenomenex™ 00G-4253-V0, Luna™ C18(2), 10 μm, 100Å, 250 × 50 mm ID; Eluent: 40-65% ACN/ H<sub>2</sub>O with 0.1% TFA over 15 min, and then 65% ACN/H<sub>2</sub>O with 0.1% FTA isocratic over 50 min) to give the title compound (retention time: 41 min, 25.0 mg). LCMS *m/z* = 451.1 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.32-1.52 (m, 8H), 1.69-1.79 (m, 1H), 2.02-2.13 (m, 1H), 2.28 (s, 3H), 2.30 (s, 3H), 3.39 (d, *J* = 6.95 Hz, 2H), 3.99 (s, 2H), 4.06 (d, *J* = 7.45 Hz, 2H), 6.91(d, *J* = 11 Hz, 1H), 6.98(d, *J* = 7.8 Hz, 1H), 7.05 (m, 1H), 7.07 (m, 1H), 7.15-7.31 (m, 4H). A compound eluting at 37 min under the same HPLC conditions was collected and identified as the regioisomer of the title compound, 2-(((1*s*,4*s*)-4-((5-(2-fluoro-4-methylphenyl)-3-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid (25.0 mg). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.07-1.20 (m, 4H), 1.21-1.39 (m, 4H), 1.60-1.75 (m, 1H), 1.90-1.99 (m, 1H), 2.23 (s, 3H), 2.35 (s, 3H), 3.21 (d, *J* = 6.95 Hz, 2H), 3.80 (bs, 2H), 4.92 (s, 2H), 7.05-7.27 (m, 8H).

**Example 1.18: Preparation of 2-(((1*s*,4*s*)-4-((3-(4-Chloro-2-fluorophenyl)-5-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 144).**

A solution of 4-chloro-2-fluorophenylboronic acid (33.2 mg, 0.191 mmol), *tert*-butyl 2-(((1*s*,4*s*)-4-((3-iodo-5-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate (100 mg, 0.191 mmol), tetrakis(triphenylphosphine)palladium (22.03 mg, 0.019 mmol), and K<sub>2</sub>CO<sub>3</sub> (2 M aqueous, 0.5 mL) in dioxane (3 mL) was heated to 150 °C under microwave irradiation for 2 h. The mixture was filtered and the filtrate was concentrated. The residue was treated with HCl (4 M in dioxane, 3 mL) at room temperature for 16 h. The mixture was concentrated and the residue was purified by HPLC to give the title compound (23.0 mg). LCMS *m/z* = 471.1 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.32-1.53 (m, 8H), 1.70-1.80 (m, 1H), 2.02-2.12 (m, 1H), 2.29 (s, 3H), 3.39 (d, *J* = 6.95 Hz, 2H), 3.82 (s, 2H), 4.07 (d, *J* = 7.45 Hz, 2H), 7.03-7.10 (m, 2H), 7.18-7.41 (m, 6H).

**Example 1.19: Preparation of 2-(((1*s*,4*s*)-4-((5-(2-Hydroxyethylthio)-3,4-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 146).**

**Step A: Preparation of 2-(1,3-Dithietan-2-ylidene)-1,2-diphenylethanone.**

To a solution of 1,2-diphenylethanone (10.0 g, 51.0 mmol) in anhydrous THF (100 mL) was added KO<sup>t</sup>Bu (1M in THF, 51.0 mL, 51.0 mmol). The mixture was stirred for 30 min at room temperature, and carbon disulfide (7.76 g, 102 mmol) was added. After 10 min, dibromomethane



(17.72 g, 102 mmol) was added and the reaction was stirred for 4 h at room temperature. The reaction was quenched with water (10 mL) and diluted with EtOAc. The organic layer was separated, dried over  $\text{MgSO}_4$ , and concentrated to give the title compound as a yellow solid (13.0 g). LCMS  $m/z = 285.0$   $[\text{M}+\text{H}]^+$ .

5 **Step B: Preparation of 3,4-Diphenyl-1H-pyrazole-5-thiol.**

To a suspension of 2-(1,3-dithietan-2-ylidene)-1,2-diphenylethanone (1.88 g, 6.61 mmol) in ethanol (50 mL) was added hydrazine hydrate (0.496 g, 9.92 mmol). The reaction was refluxed for 16 h, cooled to room temperature and concentrated. The residue was neutralized with HCl (1.0 M) to pH 6-7 and extracted with EtOAc/ $\text{H}_2\text{O}$ . The organic extract was dried over  $\text{MgSO}_4$  and concentrated to give the title compound (1.5 g). LCMS  $m/z = 253.4$   $[\text{M}+\text{H}]^+$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 4.01-4.19 (m, 1H), 6.92-7.58 (m, 10H).

**Step C: Preparation of 3,4-Diphenyl-5-(2-(tetrahydro-2H-pyran-2-yloxy)ethylthio)-1H-pyrazole.**

To a solution of 3,4-diphenyl-1H-pyrazole-5-thiol (1.2 g, 4.76 mmol) and 2-(2-bromoethoxy)tetrahydro-2H-pyran (0.994 g, 4.76 mmol) in DMF (5 mL) was added  $\text{K}_2\text{CO}_3$  (1.0 g, 7.23 mmol). The reaction was stirred at 60 °C for 2 h, cooled to room temperature, and quenched with  $\text{H}_2\text{O}$  (5 mL). The mixture was extracted with EtOAc, dried over  $\text{MgSO}_4$ , and concentrated. The residue was purified by silica gel column chromatography to give the title compound as a colorless oil (1.7 g). LCMS  $m/z = 381.2$   $[\text{M}+\text{H}]^+$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  ppm 1.32-1.50 (m, 4H), 1.50-1.73 (m, 2H), 2.99-3.13 (m, 1H), 3.21-3.44 (m, 2H), 3.46-3.59 (m, 1H), 3.61-3.82 (m, 2H), 4.44-4.59 (m, 1H), 7.16-7.40 (m, 10H), 13.32 (bs, 1H).

**Step D: Preparation of *tert*-Butyl 2-(((1*s*,4*s*)-4-((3,4-Diphenyl-5-(2-(tetrahydro-2H-pyran-2-yloxy)ethylthio)-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate.**

To a solution of 3,4-diphenyl-5-(2-(tetrahydro-2H-pyran-2-yloxy)ethylthio)-1H-pyrazole (2.0 g, 5.26 mmol) in DMF (5 mL) was added sodium hydride (0.126 g, 5.26 mmol) slowly at room temperature. The reaction was stirred at room temperature for 30 min, and *tert*-butyl 2-(((1*s*,4*s*)-4-(tosyloxymethyl)cyclohexyl)methoxy)acetate (2.168 g, 5.26 mmol) was added. The reaction was gently heated to 60 °C for 16 h. After cooled to room temperature, the reaction was quenched with  $\text{H}_2\text{O}$  (5 mL). The mixture was extracted with EtOAc, dried over  $\text{MgSO}_4$ , and concentrated. The residue was purified by silica gel column chromatography to give the title compound as a colorless oil (2.5 g). LCMS  $m/z = 621.4$   $[\text{M}+\text{H}]^+$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 1.26-1.43 (m, 4H), 1.44-1.54 (m, 4H), 1.47 (s, 9H), 1.54-1.62 (m, 2H), 1.76-1.92 (m, 4H), 2.23-2.36 (m, 2H), 2.63 (t,  $J = 6.69$  Hz, 2H), 3.21-3.32 (m, 1H), 3.36 (d,  $J = 6.95$  Hz, 2H), 3.38-3.44 (m, 1H), 3.56-3.64 (m, 1H), 3.73 (t,  $J = 11.18$  Hz, 1H), 3.91 (s, 2H), 3.93 (d,  $J = 7.07$  Hz, 2H), 4.33 (t,  $J = 7.71$  Hz, 1H), 7.20-7.43 (m, 6H), 7.75-7.81 (m, 4H).

**Step E: Preparation of 2-(((1*s*,4*s*)-4-((5-(2-Hydroxyethylthio)-3,4-diphenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid.**

A mixture of *tert*-butyl 2-(((1*s*,4*s*)-4-((3,4-diphenyl-5-(2-(tetrahydro-2*H*-pyran-2-ylloxy)ethylthio)-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate (100 mg, 0.21 mmol) and HCl (4.0 M in dioxane, 4 mL) was stirred at room temperature for 16 h. The reaction mixture was concentrated and the residue was purified by HPLC to give the title compound. LCMS *m/z* = 481.4  
5 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.02-1.20 (m, 4H), 1.22-1.37 (m, 4H), 1.55-1.64 (m, 1H), 1.88-1.99 (m, 1H), 3.03 (t, *J* = 6.82 Hz, 2H), 3.20 (d, *J* = 6.82 Hz, 2H), 3.61 (t, *J* = 6.82 Hz, 2H), 3.91 (s, 2H), 3.93 (d, *J* = 7.20 Hz, 2H), 7.06-7.32 (m, 10H), 12.51 (br. s., 1H).

**Example 1.20: Preparation of 2-(((1*s*,4*s*)-4-((4-(3-Hydroxyphenyl)-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 153).**

**Step A: Preparation of 5-Methyl-3-phenyl-1*H*-pyrazole.**

To a solution of acetophenone (10 g, 83 mmol) in anhydrous toluene (10 mL) was added LiHMDS (1.0 M in THF, 83 mL, 83 mmol) via syringe at 0 °C under argon. After 5 min, acetyl chloride (6.53 g, 83 mmol) was added via syringe in one portion. The ice bath was removed and  
15 AcOH (5 mL, glacial), EtOH (50 mL), and hydrazine hydrate (12.50 g, 250 mmol) were added. The mixture was refluxed for 2 h, cooled to room temperature, and neutralized to pH 7 by adding 1.0 M NaOH solution. The mixture was extracted with EtOAc, washed with brine, dried over MgSO<sub>4</sub>, and concentrated. The residue was purified by silica gel column chromatography to give the title compound as a pale yellow oil (12.05 g). LCMS *m/z* = 159.0 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 2.25 (s, 3H), 6.42 (s, 1H), 7.20-7.44 (m, 3H), 7.67-7.82 (m, 2H), 12.53 (bs, 1H).  
20

**Step B: Preparation of 4-Bromo-5-methyl-3-phenyl-1*H*-pyrazole.**

To a solution of 5-methyl-3-phenyl-1*H*-pyrazole (8.0 g, 50.6 mmol) in dichloromethane (150 mL) was added bromine (8.08 g, 50.6 mmol) dropwise at 0 °C. The reaction was stirred at 0 °C for 30 min and then at room temperature for 2 h before quenching with aqueous Na<sub>2</sub>SO<sub>3</sub> (10% w/w,  
25 10 mL). The organic solvent was removed and the aqueous phase was extracted with EtOAc, washed with brine, dried over MgSO<sub>4</sub>, and concentrated. The residue was purified by silica gel column chromatography to give the title compound as a yellow oil (9.5 g). LCMS *m/z* = 236.9 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 2.26 (s, 3H), 7.30-7.57 (m, 5H), 13.12 (s, 1H).

**Step C: Preparation of *tert*-Butyl 2-(((1*s*,4*s*)-4-((4-Bromo-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate.**

To a solution of 4-bromo-5-methyl-3-phenyl-1*H*-pyrazole (2.0 g, 8.44 mmol) in DMF (5 mL) were added sodium hydride (0.202 g, 8.44 mmol) in portions at 0 °C. The reaction was stirred at that temperature for 1 h and *tert*-butyl 2-(((1*s*,4*s*)-4-(tosyloxymethyl)cyclohexyl)methoxy)acetate (3.48 g, 8.44 mmol) was added. The reaction was gently heated to 42 °C for 16 h, cooled to room  
35 temperature, and quenched with H<sub>2</sub>O (2 mL). The mixture was extracted with ethyl acetate, dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound as a colorless liquid (3.05 g). LCMS *m/z* = 477.3

[M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.26-1.50 (m, 8H), 1.43 (s, 9H), 1.66-1.78 (m, 1H), 1.97-2.09 (m, 1H), 2.30 (s, 3H), 3.39 (d, *J* = 6.82 Hz, 2H), 3.94 (s, 2H), 4.06 (d, *J* = 7.58 Hz, 2H), 7.30-7.50 (m, 3H), 7.74-7.85 (m, 2H).

**Step D: Preparation of 2-(((1*s*,4*s*)-4-((4-(3-Hydroxyphenyl)-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid.**

To a solution of *tert*-butyl 2-(((1*s*,4*s*)-4-((4-iodo-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate (100 mg, 0.191 mmol) in dioxane (3 mL) was added 3-hydroxyphenylboronic acid (26.3 mg, 0.191 mmol), tetrakis(triphenylphosphine)palladium (22.03 mg, 0.019 mmol), and K<sub>2</sub>CO<sub>3</sub> (2 M aqueous, 0.2 mL, 0.4 mmol). The mixture was heated to 150 °C under microwave irradiation for 4 h, filtered through a plug of silica gel, and concentrated. The residue was treated with HCl (4 M in dioxane, 3 mL) for 10 h. The mixture was concentrated and the residue was purified by HPLC to give the title compound (25.6 mg). LCMS *m/z* = 435.2 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.31-1.54 (m, 8H), 1.70-1.81 (m, 1H), 2.03-2.13 (m, 1H), 2.19 (s, 3H), 3.42 (d, *J* = 7.07 Hz, 2H), 3.99 (s, 2H), 4.03 (d, *J* = 7.45 Hz, 2H), 6.52-6.73 (m, 4H), 7.11-7.39 (m, 5H), 9.44 (bs, 1H).

**Example 1.21: Preparation of 2-(((1*s*,4*s*)-4-((5-(2-Methoxyethyl)-3,4-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 178).**

**Step A: Preparation of 5-(2-Methoxyethyl)-3-phenyl-1*H*-pyrazole.**

To a solution of acetophenone (3.5 g, 29.1 mmol) in dry toluene (10 mL) was added LiHMDS (1.0 M in toluene) via syringe at 0 °C under argon. After 5 min, 3-methoxypropanoyl chloride (3.57 g, 29.1 mmol) was added in one portion via syringe. The ice bath was removed and AcOH (2 mL), EtOH (100 mL), and hydrazine hydrate (4.37 g, 87 mmol) were added. The reaction was refluxed for 2 h, cooled to room temperature, and concentrated. The residue was extracted with EtOAc/H<sub>2</sub>O, washed with brine, dried over MgSO<sub>4</sub>, and concentrated. The resulting residue was purified by silica gel column chromatography to give the title compound as a pale yellow oil (2.0 g). LCMS *m/z* = 203.1 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 2.85 (bs, 2H), 3.27 (s, 3H), 3.59 (t, *J* = 6.82 Hz, 2H), 6.49 (s, 1H), 7.21-7.46 (m, 3H), 7.74 (m, 2H), 12.56 (s, 1H).

**Step B: Preparation of 4-Bromo-5-(2-methoxyethyl)-3-phenyl-1*H*-pyrazole.**

To a solution of 5-(2-methoxyethyl)-3-phenyl-1*H*-pyrazole (2.0 g, 9.89 mmol) in DCM (100 mL) was added bromine (4.74 g, 29.7 mmol) dropwise at 0 °C. The reaction was stirred at 0 °C for 1 h and then at room temperature for 2 h before quenching with Na<sub>2</sub>SO<sub>3</sub> (10% aqueous). The organic phase was removed and the aqueous layer was extracted with DCM (2 × 50 mL). The organic layers were combined, washed with brine, dried over MgSO<sub>4</sub>, and concentrated to give the title compound (2.5 g). LCMS *m/z* = 281.1 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 2.87 (t, *J* = 6.82 Hz, 2H), 3.27 (s, 3H), 3.62 (t, *J* = 6.82 Hz, 2H), 5.75 (s, 1H), 7.35-7.51 (m, 3H), 7.75-7.82 (m, 2H).

**Step C: Preparation of *tert*-Butyl 2-(((1*s*,4*s*)-4-((4-Bromo-5-(2-methoxyethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate.**

To a solution of 4-bromo-5-(2-methoxyethyl)-3-phenyl-1*H*-pyrazole (3.0 g, 10.67 mmol) in DMF (5 mL) was added sodium hydride (0.256 g, 10.67 mmol), followed by *tert*-butyl 2-(((1*s*,4*s*)-4-(tosyloxymethyl)cyclohexyl)methoxy)acetate (4.40 g, 10.67 mmol). The reaction was gently heated to 45 °C overnight. After quenching with water (5 mL), the mixture was extracted with EtOAc, washed with brine, dried over MgSO<sub>4</sub>, and concentrated. The residue was purified by silica gel column chromatography to give the title compound (4.5 g). LCMS *m/z* = 523.4 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.69-1.80 (m, 4H), 1.81-1.89 (m, 4H), 1.91 (s, 9H), 2.19-2.30 (m, 2H), 2.90 (s, 3H), 3.46 (t, *J* = 6.63 Hz, 2H), 3.89 (d, *J* = 6.95 Hz, 2H), 4.02 (t, *J* = 6.32 Hz, 2H), 4.43 (s, 2H), 4.56 (d, *J* = 7.45 Hz, 2H), 7.81-7.99 (m, 3H), 8.24-8.32 (m, 2H).

**Step D: Preparation of 2-(((1*s*,4*s*)-4-((5-(2-Methoxyethyl)-3,4-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid.**

To a solution of *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-(2-methoxyethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate (100 mg, 0.192 mmol) in dioxane (3 mL) was added phenylboronic acid (23.4 mg, 0.192 mmol), tetrakis(triphenylphosphine)palladium (22.03 mg, 0.019 mmol), and K<sub>2</sub>CO<sub>3</sub> (2 M aqueous, 0.5 mL). The reaction was heated under microwave irradiation at 150 °C for 4 h, filtered through a plug of silica gel and concentrated. The residue was treated with HCl (4M in dioxane, 3 mL) for 10 h, and the mixture was purified by HPLC to give the title compound (23.5 mg). LCMS *m/z* = 463.3 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.33-1.56 (m, 8H), 1.71-1.84 (m, 1H), 2.05-2.20 (m, 1H), 2.84 (t, *J* = 6.82 Hz, 2H), 3.13 (s, 3H), 3.35 (t, *J* = 6.82 Hz, 2H), 3.39 (d, *J* = 7.07 Hz, 2H), 3.67 (s, 2H), 4.06 (d, *J* = 7.33 Hz, 2H), 7.15-7.42 (m, 10H).

**Example 1.22: Preparation of 2-(((1*s*,4*s*)-4-((5-(2-Methoxyethyl)-4-(3-methoxyphenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 179).**

To a solution of *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-(2-methoxyethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate (100 mg, 0.192 mmol) in dioxane (3 mL) was added 3-methoxyphenylboronic acid (23.4 mg, 0.192 mmol), tetrakis(triphenylphosphine)palladium (22.03 mg, 0.019 mmol), and K<sub>2</sub>CO<sub>3</sub> (2 M aqueous, 0.5 mL). The reaction was heated under microwave irradiation at 150 °C for 4 h, filtered through a plug of silica gel and concentrated. The residue was treated with HCl (4M in dioxane, 3 mL) for 10 h. The mixture was purified by HPLC to give the title compound (23.5 mg). LCMS *m/z* = 493.4 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.32-1.56 (m, 8H), 1.72-1.85 (m, 1H), 2.06-2.18 (m, 1H), 2.85 (t, *J* = 6.69 Hz, 2H), 3.16 (s, 3H), 3.36-3.38 (m, 2H), 3.40 (d, *J* = 3.03 Hz, 2H), 3.66 (s, 2H), 3.70 (s, 3H), 4.05 (d, *J* = 7.33 Hz, 2H), 6.71-6.80 (m, 2H), 6.85-6.91 (m, 1H), 7.16-7.35 (m, 6H).

**Example 1.23: Preparation of 2-(((1*s*,4*s*)-4-((4-(3-Chloro-2-fluorophenyl)-5-(2-(methylthio)ethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 215).**

**Step A: Preparation of 5-(2-(Methylthio)ethyl)-3-phenyl-1*H*-pyrazole.**

5 To a solution of acetophenone (5.0 g, 41.6 mmol) in dry toluene (10 mL) was added LiHMDS (1.0 M in toluene, 42 mL, 42 mmol) via syringe at 0 °C under argon. After 5 min, 3-(methylthio)propanoyl chloride (5.77 g, 41.6 mmol) was added in one portion via syringe. The ice bath was removed and AcOH (5 mL), EtOH (100 mL), and hydrazine hydrate (6.25 g, 125 mmol) were added. The mixture was refluxed for 2 h, cooled to room temperature, and concentrated. The  
10 residue was partitioned between EtOAc and water, and the organic phase was washed with brine, dried over MgSO<sub>4</sub>, and concentrated. The resulting residue was purified by silica gel column chromatography to give the title compound as a pale yellow oil (6.5 g). LCMS *m/z* = 219.2 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 2.09 (s, 3H), 2.77 (t, *J* = 7.71 Hz, 2H), 2.84-2.95 (m, 2H), 6.53 (s, 1H), 7.18-7.50 (m, 3H), 7.63-7.84 (m, 2H), 12.60 (bs, 1H).

**Step B: Preparation of 4-Bromo-5-(2-(methylthio)ethyl)-3-phenyl-1*H*-pyrazole.**

To a solution of 5-(2-(methylthio)ethyl)-3-phenyl-1*H*-pyrazole (4.0 g, 18.32 mmol) in methanol (20 mL) was added *N*-bromosuccinimide (3.26 g, 18.32 mmol) slowly at 0 °C. The reaction was stirred at 0 °C for 2 h. The mixture was concentrated and purified by silica gel column chromatography to give the title compound (3.4 g). LCMS *m/z* = 297.0 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400  
20 MHz, DMSO-*d*<sub>6</sub>) δ ppm 2.11 (s, 3H), 2.79 (t, *J* = 7.83 Hz, 2H), 2.83-2.97 (m, 2H), 7.32-7.56 (m, 3H), 7.67-7.88 (m, 2H), 13.20 (bs, 1H).

**Step C: Preparation of *tert*-Butyl 2-(((1*s*,4*s*)-4-((4-Bromo-5-(2-(methylthio)ethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate.**

To a solution of 4-bromo-5-(2-(methylthio)ethyl)-3-phenyl-1*H*-pyrazole (3.4 g, 11.44  
25 mmol) in DMF (5 mL) was added sodium hydride (0.275 g, 11.44 mmol) at room temperature, followed by *tert*-butyl 2-(((1*s*,4*s*)-4-(tosyloxymethyl)cyclohexyl)methoxy)acetate (4.72 g, 11.44 mmol). The reaction was heated to 45 °C overnight, cooled to room temperature, and quenched with water (5 mL). The mixture was extracted with EtOAc, washed with brine, dried over MgSO<sub>4</sub>, and concentrated. The residue was purified by silica gel column chromatography to give the title  
30 compound (3.5 g). LCMS *m/z* = 539.1 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.30-1.40 (m, 4H), 1.43 (s, 9H), 1.44-1.52 (m, 4H), 1.70-1.80 (m, 1H), 2.03-2.11 (m, 1H), 2.14 (s, 3H), 2.72 (t, *J* = 7.07 Hz, 2H), 3.00 (t, *J* = 7.20 Hz, 2H), 3.40 (d, *J* = 6.95 Hz, 2H), 3.94 (s, 2H), 4.09 (d, *J* = 7.45 Hz, 2H), 7.32-7.51 (m, 3H), 7.75-7.84 (m, 2H).

**Step D: Preparation of 2-(((1*s*,4*s*)-4-((4-(3-Chloro-2-fluorophenyl)-5-(2-(methylthio)ethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid.**

To a solution of *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-(2-(methylthio)ethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate (100 mg, 0.19 mmol) in dioxane (3 mL) were

added 2-fluoro-3-chlorophenylboronic acid (32.4 mg, 0.19 mmol),  
tetrakis(triphenylphosphine)palladium (22 mg, 0.019 mmol), and K<sub>2</sub>CO<sub>3</sub> (2 M aqueous, 0.2 mL).  
The reaction mixture was heated to 150 °C under microwave irradiation for 4 h. The mixture was  
then filtered through a plug of silica gel and concentrated, and the residue was treated with HCl (4  
5 M in dioxane, 5 mL) at room temperature for 10 h. The mixture was concentrated and the residue  
was purified by HPLC to give the title compound (24.5 mg). LCMS *m/z* = 531.2 [M+H]<sup>+</sup>; <sup>1</sup>H NMR  
(400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.32-1.55 (m, 8H), 1.71-1.83 (m, 1H), 1.86 (s, 3H), 2.06-2.19 (m, 1H),  
2.50 (t, *J* = 7.83 Hz, 2H), 2.85 (t, *J* = 7.39 Hz, 2H), 3.40 (d, *J* = 6.95 Hz, 2H), 3.71 (s, 2H), 4.09 (d, *J*  
= 7.33 Hz, 2H), 7.15-7.38 (m, 6H), 7.54-7.65 (m, 2H).

10

**Example 1.24: Preparation of 2-(((1*s*,4*s*)-4-((4-(3-Methoxyphenyl)-5-(methylthio)-3-phenyl-  
1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 31).**

**Step A: Preparation of 2-(3-Methoxyphenyl)-3,3-bis(methylthio)-1-phenylprop-2-  
en-1-one.**

15 To a solution of 2-(3-methoxyphenyl)-1-phenylethanone (5.0 g, 22.10 mmol) in  
anhydrous THF (44.0 mL) was added a solution of potassium *tert*-butoxide (1 M in THF, 46.0  
mL, 46.0 mmol). The reaction mixture was stirred for 15 min at room temperature, and then CS<sub>2</sub>  
(1.45 mL, 24.05 mmol) was added. After several minutes, MeI (3.40 mL, 54.4 mmol) was added  
and the reaction was stirred for 5 h. Upon completion, the reaction mixture was diluted with  
20 saturated NaHCO<sub>3</sub> and extracted with EtOAc. The combined organic layers were washed with  
H<sub>2</sub>O, brine, dried over MgSO<sub>4</sub> and concentrated to give the title compound as an orange oil.

**Step B: Preparation of 4-(3-Methoxyphenyl)-5-(methylthio)-3-phenyl-1*H*-pyrazole.**

To a solution of 2-(3-methoxyphenyl)-3,3-bis(methylthio)-1-phenylprop-2-en-1-one in  
EtOH (100 mL) was added hydrazine hydrate (5.36 mL, 110 mmol). The reaction mixture was  
25 refluxed overnight, additional hydrazine hydrate (1.00 mL, 20.6 mmol) was added, and the  
mixture was refluxed until the reaction was complete. The mixture was concentrated under  
reduced pressure, washed with H<sub>2</sub>O and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers  
were washed with H<sub>2</sub>O, brine, dried over MgSO<sub>4</sub> and concentrated to give the title compound  
(6.67 g). LCMS *m/z* = 397 [M+H]<sup>+</sup>.

30 **Step C: Preparation of *tert*-Butyl 2-(((1*s*,4*s*)-4-((4-(3-Methoxyphenyl)-5-  
(methylthio)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate.**

In a reaction vial was placed 4-(3-methoxyphenyl)-5-(methylthio)-3-phenyl-1*H*-  
pyrazole (2.241 g, 7.56 mmol) and NaH (357.4 mg, 8.94 mmol) in DMF (36.0 mL). The mixture  
was stirred at room temperature for 15 min then a solution of *tert*-butyl 2-(((1*s*,4*s*)-4-  
35 (tosyloxymethyl)cyclohexyl)methoxy)acetate (3.0415 g, 7.37 mmol) in DMF (10.0 mL) was  
added. The reaction was heated at 45 °C for 15 h. Upon completion, the reaction mixture was  
quenched with H<sub>2</sub>O and extracted with EtOAc. The combined organic layers were washed with

brine, dried over  $\text{MgSO}_4$ , and concentrated. The residue was purified by silica gel column chromatography to give the title compound.

**Step D: Preparation of 2-(((1*s*,4*s*)-4-((4-(3-Methoxyphenyl)-5-(methylthio)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid.**

5 To *tert*-butyl 2-(((1*s*,4*s*)-4-((4-(3-methoxyphenyl)-5-(methylthio)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate obtained above was added 4 M HCl in dioxane. The reaction was stirred at room temperature overnight. Upon completion, the reaction was basified with 10% NaOH and organic impurities were extracted out with MTBE. The aqueous layer was then acidified with 1 M HCl and extracted with MTBE. The combined organic layers were dried  
10 over  $\text{MgSO}_4$  and concentrated. The residue obtained was dissolved in ACN and 1 N NaOH solution (2.45 mL, 2.45 mmol) was added. The mixture was lyophilized to give a solid which was recrystallized from isopropyl alcohol to give the sodium salt of the title compound as an off-white solid (897.6 mg). LCMS  $m/z = 481$   $[\text{M}+\text{H}]^+$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  1.17-1.80 (m, 10H), 2.14 (s, 3H), 3.34 (d,  $J = 7.0$  Hz, 2H), 3.50 (s, 2H), 3.71 (s, 3H), 4.27 (d,  $J = 7.5$   
15 Hz, 2H), 6.80-6.85 (m, 2H), 6.89-6.94 (m, 1H), 7.21-7.37 (m, 6H).

**Example 1.25: Preparation of 2-(((1*s*,4*s*)-4-((5-(2-Hydroxyethylthio)-4-(3-methoxyphenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 198).**

**Step A: Preparation of 4-(3-Methoxyphenyl)-3-phenyl-5-(2-(tetrahydro-2*H*-pyran-2-yloxy)ethylthio)-1*H*-pyrazole.**  
20

To a stirred solution of 2-(3-methoxyphenyl)-1-phenylethanone (1.25 g, 5.52 mmol) in THF (11.05 mL) was added potassium *tert*-butoxide (11.49 mL, 11.49 mmol). After 30 min,  $\text{CS}_2$  (0.363 mL, 6.02 mmol) was added and the mixture was stirred for 10 min before 2-(2-bromoethoxy)tetrahydro-2*H*-pyran (2.086 mL, 13.81 mmol) was added and the reaction was  
25 stirred overnight. The mixture was diluted with ethanol (11.05 mL). Acetic acid (1.898 mL, 33.1 mmol) was added followed by hydrazine hydrate (2.71 mL, 55.2 mmol). The reaction was stirred at 85 °C overnight and concentrated under reduced pressure. The residue was extracted with  $\text{EtOAc}/\text{H}_2\text{O}$  (twice). The organic phases were combined and washed with brine, dried over  $\text{MgSO}_4$  and concentrated. The residue was purified by silica gel column chromatography to give  
30 the title compound as a white solid (1.681 g).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 1.52-1.64 (m, 3H), 1.65-1.93 (m, 3H), 3.06 (t,  $J = 5.94$  Hz, 2H), 3.49-3.57 (m, 1H), 3.65-3.71 (m, 1H), 3.72 (s, 3H), 3.88-3.95 (m, 1H), 3.97-4.05 (m, 1H), 4.66-4.69 (m, 1H), 6.79-6.90 (m, 3H), 7.19-7.26 (m, 1H), 7.26-7.33 (m, 3H), 7.37-7.45 (m, 2H), 10.91 (bs, 1H).

**Step B: Preparation of *tert*-Butyl 2-(((1*s*,4*s*)-4-((4-(3-Methoxyphenyl)-3-phenyl-5-(2-(tetrahydro-2*H*-pyran-2-yloxy)ethylthio)-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-Butyl 2-(((1*s*,4*s*)-4-((4-(3-Methoxyphenyl)-5-phenyl-3-(2-(tetrahydro-2*H*-pyran-2-yloxy)ethylthio)-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate.**  
35

To a stirred solution of 4-(3-methoxyphenyl)-3-phenyl-5-(2-(tetrahydro-2H-pyran-2-yloxy)ethylthio)-1H-pyrazole (0.123 g, 0.3 mmol) was added 60% NaH (0.012 g, 0.300 mmol). After 20 min, *tert*-butyl 2-(((1*s*,4*s*)-4-(tosyloxymethyl)cyclohexyl)methoxy)acetate (0.124 g, 0.300 mmol) was added. The reaction was heated to 70 °C for 18 h, cooled to room temperature, and diluted with water. The mixture was extracted three times with EtOAc. The combined extracts were washed with brine, dried over MgSO<sub>4</sub> and concentrated. The residue was purified by silica gel column chromatography to give the title compound as a mixture of regioisomers (46 mg). LCMS *m/z* = 651.7 [M+H]<sup>+</sup>.

**Step C: Preparation of 2-(((1*s*,4*s*)-4-((5-(2-Hydroxyethylthio)-4-(3-methoxyphenyl)-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid.**

To a stirred solution of *tert*-butyl 2-(((1*s*,4*s*)-4-((4-(3-methoxyphenyl)-3-phenyl-5-(2-(tetrahydro-2H-pyran-2-yloxy)ethylthio)-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate (46 mg, 0.071 mmol) and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-(3-methoxyphenyl)-5-phenyl-3-(2-(tetrahydro-2H-pyran-2-yloxy)ethylthio)-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate (a mixture of regioisomers) in DCM (214 µL) was added water (21.42 µL), triethylsilane (113 µL, 0.707 mmol), and TFA (109 µL, 1.413 mmol). The reaction was stirred overnight, further TFA (0.5 mL) was added and the reaction was stirred for an additional 1 h. The solvent was evaporated. The residue was taken up in 70% acetonitrile/water and purified by HPLC (50% acetonitrile/water; isocratic) to give the title compound as a solid. LCMS *m/z* = 511.5 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.31-1.45 (m, 4H), 1.45-1.54 (m, 4H), 1.69-1.80 (m, *J* = 4.55 Hz, 1H), 2.18 (bs, 1H), 2.51-2.56 (m, 2H), 2.60 (t, *J* = 6.69 Hz, 2H), 2.60 (t, *J* = 6.69 Hz, 1H), 3.41 (d, *J* = 7.07 Hz, 2H), 3.71 (s, 3H), 3.96-4.01 (m, 2H), 4.29 (d, *J* = 7.58 Hz, 2H), 6.79-6.84 (m, 2H), 6.88-6.95 (m, 1H), 7.23-7.30 (m, 4H), 7.30-7.37 (m, 2H).

**Example 1.26: Preparation of 2-(((1*s*,4*s*)-4-((5-(2-Hydroxyethylthio)-4-phenyl-3-*p*-tolyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 200).**

**Step A: Preparation of 4-Phenyl-5-(2-(tetrahydro-2H-pyran-2-yloxy)ethylthio)-3-*p*-tolyl-1H-pyrazole.**

From 2-phenyl-1-*p*-tolylethanone, using a similar method to the one described in

**Example 1.25, step A,** the title compound was obtained as a white solid. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 1.54-1.64 (m, 3H), 1.66-1.90 (m, 3H), 2.33 (s, 3H), 3.05 (t, *J* = 5.43 Hz, 2H), 3.47-3.56 (m, 1H), 3.64-3.72 (m, 1H), 3.86-3.94 (m, 1H), 3.95-4.01 (m, 1H), 4.63-4.67 (m, 1H), 7.10 (d, *J* = 8.08 Hz, 2H), 7.25-7.30 (m, 5H), 7.30-7.39 (m, 2H).

**Step B: Preparation of *tert*-Butyl 2-(((1*s*,4*s*)-4-((4-Phenyl-5-(2-(tetrahydro-2H-pyran-2-yloxy)ethylthio)-3-*p*-tolyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate**



From 4-phenyl-5-(2-(tetrahydro-2H-pyran-2-yloxy)ethylthio)-3-*p*-tolyl-1H-pyrazole, using a similar method to the one described in **Example 1.25, step B**, the title compound was obtained as a clear solid. LCMS  $m/z$  = 635.6  $[M+H]^+$ .

**Step C: Preparation of 2-(((1*s*,4*s*)-4-((5-(2-Hydroxyethylthio)-4-phenyl-3-*p*-tolyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid.**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-phenyl-5-(2-(tetrahydro-2H-pyran-2-yloxy)ethylthio)-3-*p*-tolyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate, using a method similar to the one described in **Example 1.25, Step C**, the title compound was obtained as a white solid. LCMS  $m/z$  = 495.3  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.32-1.45 (m, 4H), 1.45-1.52 (m, 4H), 1.68-1.80 (m, 1H), 2.13-2.22 (m, 1H), 2.25 (s, 3H), 2.56 (t,  $J$  = 6.69 Hz, 2H), 3.23-3.29 (m, 2H), 3.41 (d,  $J$  = 6.82 Hz, 2H), 3.98-4.01 (m, 2H), 4.28 (d,  $J$  = 7.58 Hz, 2H), 4.75 (bs, 1H), 7.06 (d,  $J$  = 7.83 Hz, 2H), 7.20 (d,  $J$  = 8.08 Hz, 2H), 7.23-7.28 (m, 2H), 7.30-7.43 (m, 3H), 12.52 (bs, 1H).

**Example 1.27: Preparation of 2-(((1*r*,4*r*)-4-((3,4-Diphenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 8) and 2-(((1*r*,4*r*)-4-((4,5-Diphenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 9).**

**Step A: Preparation of 3,4-Diphenyl-1H-pyrazole.**

Phenyl(3-phenyloxiran-2-yl)methanone (5.0 g, 22.3 mmol) was suspended in dry Et<sub>2</sub>O (40 mL) under an argon balloon. Boron trifluoride diethyl etherate (3.00 mL, 23.7 mmol) was added slowly via syringe. The reaction was refluxed at 50 °C for an hour, then cooled and extracted with 60 mL each of H<sub>2</sub>O and Et<sub>2</sub>O/EtOAc. The aqueous layer was extracted again with EtOAc (60 mL). The combined organic layer was dried and concentrated to give 3-oxo-2,3-diphenylpropanal.

3-Oxo-2,3-diphenylpropanal (5.00 g, 22.3 mmol) was dissolved in EtOH (40 mL). Hydrazine monohydrate (2.0 mL, 38.7 mmol) was added slowly via syringe. The reaction was stirred at room temperature for an hour. The solvent was evaporated and the residue was purified by silica gel column chromatography to yield the title compound as a light purple solid (2.75g). LCMS  $m/z$  = 221.1  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 6.99-7.57 (m, 10H), 7.66-8.09 (bs, 1H), 13.15 (bs, 1H).

**Step B: Preparation of 2-(((1*r*,4*r*)-4-((3,4-Diphenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid and 2-(((1*r*,4*r*)-4-((4,5-Diphenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid.**

3,4-Diphenyl-1H-pyrazole (16.02 mg, 0.073 mmol) was dissolved in DMF (0.4 mL). NaH (1.745 mg, 0.073 mmol) was added and the reaction was stirred at room temperature for 15 min. *tert*-Butyl-2-(((1*r*,4*r*)-4-(tosyloxymethyl)cyclohexyl)methoxy)acetate (prepared in a similar manner to **Example 1.1**) (30.0 mg, 0.073 mmol) was added and the reaction was stirred at room

temperature for an hour. After this time, the reaction was partitioned between with H<sub>2</sub>O (2 mL) and EtOAc (2 mL). The aqueous layer was extracted with EtOAc (2 mL). The organic layers were combined, dried and concentrated. The resulting oil was redissolved in HCl (4 M in dioxane) (400  $\mu$ L, 1.600 mmol) and stirred overnight. The solvent was evaporated and the residue was purified by preparative LC/MS (50% acetonitrile/water; isocratic) to yield Compound 8 as a white solid (6.5 mg); LCMS  $m/z$  = 405.5 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  ppm 0.86-1.12 (m, 4H), 1.44-1.58 (m, 1H), 1.61-1.71 (m, 2H), 1.73-1.80 (m, 2H), 1.80-1.91 (m, 1H), 3.26 (d,  $J$  = 6.32 Hz, 2H), 3.95 (s, 2H), 4.00 (d,  $J$  = 7.07 Hz, 2H), 7.20-7.27 (m, 3H), 7.27-7.36 (m, 5H), 7.36-7.44 (m, 2H), 7.92 (s, 1H); and Compound 9 as a white solid (1.0 mg); LCMS  $m/z$  = 405.6 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  ppm 0.68-0.88 (m, 4H), 1.33-1.50 (m,  $J$  = 9.98 Hz, 3H), 1.57-1.78 (m, 3H), 3.20 (d,  $J$  = 6.32 Hz, 2H), 3.78 (d,  $J$  = 7.20 Hz, 2H), 3.92 (s, 2H), 7.07-7.16 (m, 3H), 7.16-7.22 (m, 2H), 7.30-7.36 (m, 2H), 7.47-7.56 (m, 3H), 7.83 (s, 1H).

**Example 1.28: Preparation of 2-(((1*s*,4*s*)-4-((1-Phenyl-4,5-dihydro-3*H*-benzo[e]indazol-3-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 150).**

**Step A: Preparation of 1-Phenyl-4,5-dihydro-3*H*-benzo[e]indazole.**

3,4-Dihydronaphthalen-2(1*H*)-one (2.080 g, 14.23 mmol) was dissolved in toluene (15 mL) and the solution was cooled on an ice bath. LiHMDS (7.470 mL, 7.470 mmol) was added with vigorous stirring. One minute later benzoyl chloride (0.8258 mL, 7.114 mmol) was added. The reaction was removed from the ice bath and stirred for another minute. AcOH (4 mL) was added with stirring, followed by EtOH (10 mL), THF (5 mL), and hydrazine monohydrate (5 mL, 96.8 mmol). After 10 min, the solution was poured into a separatory funnel loaded with 1M NaOH (30 mL) and extracted with additional H<sub>2</sub>O (70 mL) and EtOAc (100 mL). The aqueous layer was extracted again with EtOAc (100 mL). The combined organic layer was dried and concentrated. The residue was purified by silica gel column chromatography to yield the title compound as a light-purple colored solid. LCMS  $m/z$  = 247.2 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  ppm 2.72-2.86 (m, 2H), 2.90-3.00 (m, 2H), 6.99-7.09 (m, 2H), 7.11-7.21 (m, 1H), 7.23-7.29 (m, 1H), 7.37-7.61 (m, 5H), 12.75 (s, 0.7H), 12.97 (s, 0.3H).

**Step B: Preparation of 2-(((1*s*,4*s*)-4-((1-Phenyl-4,5-dihydro-3*H*-benzo[e]indazol-3-yl)methyl)cyclohexyl)methoxy)acetic Acid.**

1-Phenyl-4,5-dihydro-3*H*-benzo[e]indazole (100 mg, 0.406 mmol) was dissolved in DMF (0.4 mL). Sodium hydride (9.74 mg, 0.406 mmol) was added. The reaction was stirred at room temperature for 10 min and then *tert*-butyl 2-(((1*s*,4*s*)-4-(tosyloxymethyl)cyclohexyl)methoxy)acetate (167 mg, 0.406 mmol), pre-dissolved in DMF (0.2 mL) was added. The reaction was stirred for 1 h at 50 °C. After this time, more NaH (10 mg) was added. The reaction was again stirred for 1 h at 50 °C. The mixture was extracted with 15 mL each of H<sub>2</sub>O and

EtOAc. The aqueous layer was extracted again with EtOAc (15 mL). The combined organic layer was dried and concentrated. The residue was redissolved in HCl (4 M in dioxane) (507  $\mu$ L, 2.030 mmol) and stirred overnight at room temperature. The solvent was evaporated and the residue was purified by preparative LC/MS to give the title compound as a light-tan solid (35 mg). LCMS  $m/z$  = 431.4  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.28-1.54 (m, 8H), 1.69-1.80 (m, 1H), 2.00-2.10 (m, 1H), 2.85 (d,  $J$  = 7.83 Hz, 2H), 2.97 (t,  $J$  = 7.33 Hz, 2H), 3.41 (d,  $J$  = 6.95 Hz, 2H), 3.99 (s, 2H), 4.04 (d,  $J$  = 7.58 Hz, 2H), 6.98-7.08 (m, 2H), 7.10-7.18 (m, 1H), 7.22-7.30 (m, 1H), 7.35-7.50 (m, 3H), 7.54-7.60 (m, 2H).

**Example 1.29: Preparation of 2-(((1*s*,4*s*)-4-((3-(2-Fluoro-4-methylphenyl)-5-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 143).**

**Step A: Preparation of (1*s*,4*s*)-Ethyl 4-(Hydroxymethyl)cyclohexanecarboxylate.**

To a solution of (1*s*,4*s*)-4-(hydroxymethyl)cyclohexanecarboxylic acid (10 g, 63.2 mmol) in ethanol (100 mL), was added sulfuric acid (0.31 g, 3.16 mmol) at room temperature. After heating for 10 h at 85  $^{\circ}$ C, the reaction was cooled to room temperature and concentrated under reduced pressure. The residue was extracted with ethyl acetate, dried over  $MgSO_4$ , and then concentrated under reduced pressure to give the title compound (4.98 g).  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.15 (t,  $J$  = 7.1 Hz, 3H), 1.40-1.54 (m, 7H), 2.55 (m, 1H), 1.82 (m, 2H), 3.21 (d,  $J$  = 6.4 Hz, 2H), 4.01 (q,  $J$  = 7.1 Hz, 2H).

**Step B: Preparation of ((1*s*,4*s*)-4-(Benzyloxymethyl)cyclohexyl)methanol.**

To a solution of (1*s*,4*s*)-ethyl 4-(hydroxymethyl)cyclohexanecarboxylate (5 g, 26.8 mmol) in DMF (50 mL) was added (bromomethyl)benzene (4.59 g, 26.8 mmol) followed by NaH (0.644 g, 26.8 mmol) at 0  $^{\circ}$ C. After stirring for 4 h at room temperature, the mixture was poured into water and extracted with ethyl acetate. The extract was dried over  $MgSO_4$  and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give (1*s*,4*s*)-ethyl 4-(benzyloxymethyl)cyclohexanecarboxylate (3.2 g, 13.66 mmol). The above material was dissolved in THF (50 mL) and lithium aluminum hydride (1.02 g, 26.8 mmol) was added at 0  $^{\circ}$ C. After stirring for 1 h at room temperature, the reaction was quenched with  $H_2O$  (5 mL) at 0  $^{\circ}$ C. After stirring at room temperature for 1 h, the resulting precipitate was filtered off. The filtrate was dried over  $MgSO_4$  and concentrated under reduced pressure to give the title compound (3.2 g).  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 0.84-0.99 (m, 7H), 1.35 (m, 1H), 1.46 (m, 1H), 1.52 (m, 1H), 3.23 (d,  $J$  = 7.0 Hz, 2H), 3.25 (d,  $J$  = 5.7 Hz, 2H), 4.45 (s, 2H), 7.21-7.40 (m, 5H).

**Step C: Preparation of (1*s*,4*s*)-4-(Benzyloxymethyl)cyclohexanecarbaldehyde.**

To a solution of DMSO (1.32 mL, 18.78 mmol) in  $CH_2Cl_2$  (50 mL) was added oxalyl dichloride (1.19 g, 9.39 mmol) dropwise at -50  $^{\circ}$ C. After stirring for 10 min, ((1*s*,4*s*)-4-(benzyloxymethyl)cyclohexyl)methanol (2.0 g, 8.53 mmol) and triethylamine (4.32 g, 42.7 mmol) were added at the same temperature. After stirring for 1 h at room temperature, the reaction was

extracted with CH<sub>2</sub>Cl<sub>2</sub> and dried over MgSO<sub>4</sub>. The organic layer was concentrated under reduced pressure to give the title compound (1.9 g). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 0.91-1.21 (m, 6H), 1.45 (m, 1H), 1.75-1.95 (m, 2H), 2.25 (m, 1H), 3.25 (d, *J* = 7.1 Hz, 2H), 4.42 (s, 2H), 7.25-7.42 (m, 5H), 9.52 (s, 1H).

5           **Step D: Preparation of *tert*-Butyl 2-(((1*s*,4*s*)-4-(Benzyloxymethyl)cyclohexyl)methyl)hydrazinecarboxylate.**

To a solution of (1*s*,4*s*)-4-(benzyloxymethyl)cyclohexanecarbaldehyde (1.2 g, 5.17 mmol) in MeOH (50 mL) was added *tert*-butyl hydrazinecarboxylate (0.68 g, 5.17 mmol) at room temperature. After stirring for 1 h, the reaction was concentrated under reduced pressure. The residue was dissolved in MeOH (25 mL) and acetic acid (25 mL). NaCNBH<sub>3</sub> (0.33 g, 5.17 mmol) was added at 0 °C. After stirring for 30 min, the reaction was concentrated under reduced pressure. The residue was dissolved in ethyl acetate and washed with 0.1 M NaOH. The extract was dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound (0.85 g). LCMS *m/z* = 349.4 [M+H]<sup>+</sup>.

15           **Step E: Preparation of 1-(((1*s*,4*s*)-4-(Benzyloxymethyl)cyclohexyl)methyl)-2-(2-fluoro-4-methylbenzylidene)hydrazine.**

To a solution of *tert*-butyl 1-(((1*s*,4*s*)-4-(benzyloxymethyl)cyclohexyl)methyl)hydrazinecarboxylate (1.0 g, 2.87 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL), was added TFA (5.0 mL) at room temperature. After stirring for 3 h at the same temperature, the reaction was concentrated under reduced pressure. The residue was dissolved in THF (10 mL) and 2-fluoro-4-methylbenzaldehyde (0.40 g, 2.87 mmol) was added. After stirring for 30 min, the reaction was washed with saturated NaHCO<sub>3</sub>. The organics were dried over MgSO<sub>4</sub> and concentrated under reduced pressure to give the title compound (0.96 g). LCMS *m/z* = 369.3 [M+H]<sup>+</sup>.

25           **Step F: Preparation of 1-(((1*s*,4*s*)-4-(Benzyloxymethyl)cyclohexyl)methyl)-3-(2-fluoro-4-methylphenyl)-5-methyl-4-phenyl-1*H*-pyrazole.**

To a solution of 1-(((1*s*,4*s*)-4-(benzyloxymethyl)cyclohexyl)methyl)-2-(2-fluoro-4-methylbenzylidene)hydrazine (0.5 g, 1.357 mmol) and (2-nitroprop-1-enyl)benzene (0.22 g, 1.36 mmol) in THF (5 mL) at -78 °C, was added potassium butan-1-olate (0.152 g, 1.357 mmol) dropwise. After 10 min, TFA (0.21 mL, 2.71 mmol) was added at the same temperature and maintained for 2 h. After warming to room temperature, the reaction was extracted with ethyl acetate, dried over MgSO<sub>4</sub>, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound (0.49 g). LCMS *m/z* = 483.3 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.34-1.52 (m, 8H), 1.85 (m, 1H), 2.15 (m, 1H), 2.25 (s, 3H), 2.31 (s, 3H), 3.34 (d, *J* = 7.0 Hz, 2H), 4.25 (d, *J* = 7.4 Hz, 2H), 4.51 (s, 2H), 6.92-7.38 (m, 4H), 7.39-7.45 (m, 9H).

**Step G: Preparation of ((1*s*,4*s*)-4-((3-(2-Fluoro-4-methylphenyl)-5-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methanol.**

To a solution of 1-(((1*s*,4*s*)-4-(benzyloxymethyl)cyclohexyl)methyl)-3-(2-fluoro-4-methylphenyl)-5-methyl-4-phenyl-1*H*-pyrazole (100 mg, 0.21 mmol) in MeOH (5 mL), was added ammonium formate (261 mg, 4.14 mmol) followed by 10% Pd/C (5 mg). The reaction was heated to 80 °C for 10 h. After filtration of insoluble material, the reaction was concentrated under reduced pressure to give the title compound as a colorless oil (78 mg). LCMS  $m/z$  = 393.3  $[M+H]^+$ .

**Step H: Preparation of *tert*-Butyl 2-(((1*s*,4*s*)-4-((3-(2-Fluoro-4-methylphenyl)-5-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate.**

To a solution of ((1*s*,4*s*)-4-((3-(2-fluoro-4-methylphenyl)-5-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methanol (20 mg, 0.051 mmol) and  $(Rh(OAc)_2)_2$  (2.25 mg, 5.10  $\mu$ mol) in  $CH_2Cl_2$  (2 mL), was added a solution of *tert*-butyl 2-diazoacetate (7.24 mg, 0.051 mmol) in  $CH_2Cl_2$  (0.5 mL) dropwise for 10 min at -10 °C. The reaction was stirred for 1 h at the same temperature. The solid material was filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound (20 mg). LCMS  $m/z$  = 507.5  $[M+H]^+$ ;  $^1H$  NMR (400 MHz,  $DMSO-d_6$ )  $\delta$  ppm 1.30-1.45 (m, 17H), 1.75 (m, 1H), 2.11 (m, 1H), 2.28 (s, 3H), 2.30 (s, 3H), 3.52 (d,  $J$  = 7.0 Hz, 2H), 3.95 (s, 2H), 4.05 (d,  $J$  = 7.3 Hz, 2H), 6.90 (d,  $J$  = 11.5 Hz, 1H), 6.95 (d,  $J$  = 7.7 Hz, 1H), 7.05-7.33 (m, 6H).

**Step I: Preparation of 2-(((1*s*,4*s*)-4-((3-(2-Fluoro-4-methylphenyl)-5-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid.**

*tert*-Butyl 2-(((1*s*,4*s*)-4-((3-(2-fluoro-4-methylphenyl)-5-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate (250 mg, 0.49 mmol) was treated with HCl (4.0 M in dioxane, 10 mL) at room temperature. After stirring for 12 h, the reaction was concentrated in vacuo and purified by HPLC. The free acid was dissolved in acetonitrile (5 mL) and  $H_2O$  (2 mL), added into a solution of sodium hydroxide (19.74 mg, 0.49 mmol) in  $H_2O$  (10 mL), and dried under reduced pressure to give the sodium salt of the title compound (149 mg). LCMS  $m/z$  = 451.2  $[M+H]^+$ ;  $^1H$  NMR (400 MHz,  $DMSO-d_6$ )  $\delta$  ppm 1.32-1.52 (m, 8H), 1.71-1.81 (m, 1H), 2.02-2.13 (m, 1H), 2.28 (s, 3H), 2.30 (s, 3H), 3.37 (d,  $J$  = 6.7 Hz, 2H), 3.61 (s, 2H), 4.05 (d,  $J$  = 7.3 Hz, 2H), 6.91 (d,  $J$  = 11.2 Hz, 1H), 6.98 (d,  $J$  = 7.9 Hz, 1H), 7.05 (s, 1H), 7.07 (s, 1H), 7.16-7.32 (m, 4H).

**Example 1.30: Preparation of 2-(((1*s*,4*s*)-4-((4-(3-Chlorophenyl)-5-(2-hydroxyethylthio)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 199).**

**Step A: Preparation of 4-(3-Chlorophenyl)-3-phenyl-5-(2-(tetrahydro-2*H*-pyran-2-yloxy)ethylthio)-1*H*-pyrazole.**

From 2-(3-chlorophenyl)-1-phenethanone, using a similar method to the one described in **Example 1.25, Step A**, the title compound was obtained as a yellow solid.  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  ppm 1.51-1.65 (m, 3H), 1.66-1.92 (m, 3H), 3.07 (t,  $J$  = 5.81 Hz, 2H), 3.49-3.59

(m, 1H), 3.66-3.75 (m, 1H), 3.87-3.96 (m, 1H), 3.97-4.04 (m, 1H), 4.68 (dd,  $J = 4.29, 3.03$  Hz, 1H), 7.09-7.15 (m, 1H), 7.23-7.27 (m, 2H), 7.28-7.33 (m, 4H), 7.34-7.42 (m, 2H), 10.95 (bs, 1H).

**Step B: Preparation of *tert*-Butyl 2-(((1*s*,4*s*)-4-((4-(3-Chlorophenyl)-3-phenyl-5-(2-(tetrahydro-2*H*-pyran-2-yloxy)ethylthio)-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-Butyl 2-(((1*s*,4*s*)-4-((4-(3-Chlorophenyl)-5-phenyl-3-(2-(tetrahydro-2*H*-pyran-2-yloxy)ethylthio)-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a Mixture of Regioisomers.**

From 4-(3-chlorophenyl)-3-phenyl-5-(2-(tetrahydro-2*H*-pyran-2-yloxy)ethylthio)-1*H*-pyrazole, using a similar method to the one described in **Example 1.25, Step B**, the title compound was obtained as a clear oil (a mixture of regioisomers). LCMS  $m/z = 655.4$   $[M+H]^+$ .

**Step C: Preparation of 2-(((1*s*,4*s*)-4-((4-(3-Chlorophenyl)-5-(2-hydroxyethylthio)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid.**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-(3-chlorophenyl)-3-phenyl-5-(2-(tetrahydro-2*H*-pyran-2-yloxy)ethylthio)-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-(3-chlorophenyl)-5-phenyl-3-(2-(tetrahydro-2*H*-pyran-2-yloxy)ethylthio)-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers, using a similar method to the one described in **Example 1.25, Step C**, the title compound was obtained as a clear solid. LCMS  $m/z = 515.5$   $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.32-1.54 (m, 8H), 1.71-1.79 (m, 1H), 2.11-2.23 (m, 1H), 2.51-2.55 (m, 2H), 2.61 (t,  $J = 6.57$  Hz, 2H), 3.30 (t,  $J = 6.57$  Hz, 1H), 3.41 (d,  $J = 6.82$  Hz, 2H), 3.98 (s, 2H), 4.30 (d,  $J = 7.58$  Hz, 2H), 7.18-7.23 (m, 1H), 7.25-7.34 (m, 6H), 7.38-7.44 (m, 2H).

**Example 1.31: Preparation of 2-(((1*s*,4*s*)-4-((5-(2-Hydroxyethylthio)-3-phenyl-4-*m*-tolyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 210).**

**Step A: Preparation of 3-Phenyl-5-(2-(tetrahydro-2*H*-pyran-2-yloxy)ethylthio)-4-*m*-tolyl-1*H*-pyrazole.**

From 1-phenyl-2-*m*-tolylethanone, using a similar method to the one described in **Example 1.25, Step A**, the title compound was obtained as a white solid.  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.30-1.51 (m, 4H), 1.52-1.73 (m, 2H), 2.26 (s, 3H), 3.10 (t,  $J = 6.82$  Hz, 2H), 3.32-3.45 (m, 1H), 3.53-3.67 (m, 1H), 3.68-3.76 (m, 1H), 3.76-3.84 (m, 1H), 4.55 (t,  $J = 3.16$  Hz, 1H), 6.97 (d,  $J = 7.33$  Hz, 1H), 7.04 (s, 1H), 7.08-7.14 (m, 1H), 7.20-7.27 (m, 2H), 7.29-7.37 (m, 4H), 13.30 (s, 1H).

**Step B: Preparation of *tert*-Butyl 2-(((1*s*,4*s*)-4-((3-Phenyl-5-(2-(tetrahydro-2*H*-pyran-2-yloxy)ethylthio)-4-*m*-tolyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-Butyl 2-(((1*s*,4*s*)-4-((5-Phenyl-3-(2-(tetrahydro-2*H*-pyran-2-yloxy)ethylthio)-4-*m*-tolyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a Mixture of Regioisomers.**

From 3-phenyl-5-(2-(tetrahydro-2H-pyran-2-yloxy)ethylthio)-4-*m*-tolyl-1H-pyrazole, using a similar method to the one described in **Example 1.25, Step B**, the title compound was obtained as a clear oil (a mixture of regioisomers). LCMS  $m/z$  = 635.7  $[M+H]^+$ .

**Step C: Preparation of 2-(((1*s*,4*s*)-4-((5-(2-Hydroxyethylthio)-3-phenyl-4-*m*-tolyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid.**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((3-phenyl-5-(2-(tetrahydro-2H-pyran-2-yloxy)ethylthio)-4-*m*-tolyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((5-phenyl-3-(2-(tetrahydro-2H-pyran-2-yloxy)ethylthio)-4-*m*-tolyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers, using a similar method to the one described in **Example 1.25, Step C**, the title compound was obtained as a yellow oily solid. LCMS  $m/z$  = 495.4  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.33-1.44 (m, 4H), 1.44-1.53 (m, 4H), 1.68-1.80 (m, 1H), 2.13-2.23 (m, 1H), 2.30 (s, 3H), 2.58 (t,  $J$  = 6.69 Hz, 2H), 3.17 (d,  $J$  = 5.05 Hz, 1H), 3.26-3.35 (m, 2H), 3.41 (d,  $J$  = 7.07 Hz, 2H), 3.99 (s, 2H), 4.29 (d,  $J$  = 7.58 Hz, 2H), 7.02 (d,  $J$  = 7.58 Hz, 1H), 7.10 (s, 1H), 7.16 (d,  $J$  = 7.83 Hz, 1H), 7.22-7.29 (m, 4H), 7.30-7.35 (m, 2H).

**Example 1.32: Preparation of 2-(((1*s*,4*s*)-4-((4-(3-Fluorophenyl)-5-(2-hydroxyethylthio)-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 212).**

**Step A: Preparation of 4-(3-Fluorophenyl)-3-phenyl-5-(2-(tetrahydro-2H-pyran-2-yloxy)ethylthio)-1H-pyrazole.**

From 2-(3-fluorophenyl)-1-phenethanone, using a similar method to the one described in **Example 1.25, Step A**, the title compound was obtained as a white solid.  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.31-1.51 (m, 4H), 1.50-1.75 (m, 2H), 3.12 (t,  $J$  = 6.69 Hz, 2H), 3.33-3.43 (m, 1H), 3.52-3.66 (m, 1H), 3.67-3.76 (m, 1H), 3.76-3.84 (m, 1H), 4.55 (t,  $J$  = 3.28 Hz, 1H), 6.96-7.05 (m, 2H), 7.08-7.15 (m, 1H), 7.23-7.44 (m, 6H), 13.41 (s, 1H).

**Step B: Preparation of *tert*-Butyl 2-(((1*s*,4*s*)-4-((4-(3-Fluorophenyl)-3-phenyl-5-(2-(tetrahydro-2H-pyran-2-yloxy)ethylthio)-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-Butyl 2-(((1*s*,4*s*)-4-((4-(3-Fluorophenyl)-5-phenyl-3-(2-(tetrahydro-2H-pyran-2-yloxy)ethylthio)-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a Mixture of Regioisomers.**

From 4-(3-fluorophenyl)-3-phenyl-5-(2-(tetrahydro-2H-pyran-2-yloxy)ethylthio)-1H-pyrazole, using a similar method to the one described in **Example 1.25, Step B**, the title compound was obtained as a clear oil (a mixture of regioisomers). LCMS  $m/z$  = 639.5  $[M+H]^+$ .

**Step C: Preparation of 2-(((1*s*,4*s*)-4-((4-(3-Fluorophenyl)-5-(2-hydroxyethylthio)-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid.**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-(3-fluorophenyl)-3-phenyl-5-(2-(tetrahydro-2H-pyran-2-yloxy)ethylthio)-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-

(((1*s*,4*s*)-4-((4-(3-fluorophenyl)-5-phenyl-3-(2-(tetrahydro-2*H*-pyran-2-yloxy)ethylthio)-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers, using a similar method to the one described in **Example 1.25, Step C**, the title compound was obtained as a clear oily solid. LCMS  $m/z$  = 499.6  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.34-1.45 (m, 4H), 1.45-1.53 (m, 4H), 1.69-1.81 (m, 1H), 2.11-2.22 (m, 1H), 2.43-2.56 (m, 2H), 2.60 (t,  $J$  = 6.69 Hz, 1H), 3.21-3.33 (m, 2H), 3.41 (d,  $J$  = 7.07 Hz, 2H), 3.99-4.00 (m, 2H), 4.30 (d,  $J$  = 7.58 Hz, 2H), 7.05-7.12 (m, 2H), 7.13-7.22 (m, 1H), 7.23-7.34 (m, 5H), 7.38-7.46 (m, 1H), 12.52 (s, 1H).

**Example 1.33: Preparation of 2-(((1*s*,4*s*)-4-((4-(3-Chlorophenyl)-5-(2-hydroxyethylsulfinyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 217).**

To a solution of 2-(((1*s*,4*s*)-4-((4-(3-chlorophenyl)-5-(2-hydroxyethylthio)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid (18.3 mg, 0.036 mmol) in DCM (178  $\mu$ L) was added mCPBA (5.82 mg, 0.034 mmol). The reaction was stirred for 20 min and concentrated under reduced pressure. The residue was taken up in ACN/H<sub>2</sub>O and purified via preparative HPLC to give the title compound (9.7 mg) as a white solid. LCMS  $m/z$  = 531.3  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.33-1.55 (m,  $J$  = 4.29 Hz, 8H), 1.72-1.80 (m, 1H), 2.26 (bs, 1H), 2.98-3.10 (m, 1H), 3.25-3.28 (m, 2H), 3.40 (d,  $J$  = 7.20 Hz, 1H), 3.57-3.66 (m, 1H), 3.68-3.77 (m, 1H), 3.99 (s, 2H), 4.28-4.50 (m, 2H), 5.08 (bs, 1H), 7.21-7.27 (m, 1H), 7.27-7.33 (m, 5H), 7.38-7.46 (m, 3H), 12.51 (s, 1H).

**Example 1.34: Preparation of 2-(((1*s*,4*s*)-4-((5-(2-Aminoethylthio)-4-phenyl-3-*p*-tolyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 250).**

**Step A: Preparation of *tert*-Butyl 2-(4-Phenyl-3-*p*-tolyl-1*H*-pyrazol-5-ylthio)ethylcarbamate.**

From 2-phenyl-1-*p*-tolylethanone and *tert*-butyl 2-bromoethylcarbamate, using a similar method to the one described in **Example 1.25, Step A**, the title compound was obtained as a light yellow solid.  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.36 (s, 9H), 2.28 (s, 3H), 2.71-2.78 (m, 1H), 2.94 (t,  $J$  = 7.07 Hz, 2H), 3.13-3.21 (m, 2H), 6.88 (t,  $J$  = 5.68 Hz, 1H), 7.13-7.23 (m, 6H), 7.32-7.37 (m, 2H), 13.26 (s, 1H).

**Step B: Preparation of *tert*-Butyl 2-(((1*s*,4*s*)-4-((5-(2-(*tert*-Butoxycarbonylamino)ethylthio)-4-phenyl-3-*p*-tolyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-Butyl 2-(((1*s*,4*s*)-4-((3-(2-(*tert*-Butoxycarbonylamino)ethylthio)-4-phenyl-5-*p*-tolyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a Mixture of Regioisomers.**



From *tert*-butyl 2-(4-phenyl-3-*p*-tolyl-1*H*-pyrazol-5-ylthio)ethylcarbamate, using a similar method to the one described in **Example 1.25, Step B**, the title compound was obtained as a clear oil (a mixture of regioisomers). LCMS  $m/z$  = 650.7  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.34 (s, 9H), 1.36-1.46 (m, 3H), 1.43 (s, 9H), 1.45-1.52 (m, 3H), 1.68-1.80 (m, 1H), 2.12-2.21 (m, 1H), 2.25 (s, 3H), 2.51-2.55 (m, 2H), 2.83 (q,  $J$  = 6.61 Hz, 2H), 3.14-3.19 (m, 2H), 3.40 (d,  $J$  = 6.82 Hz, 2H), 3.95 (s, 2H), 4.26 (d,  $J$  = 7.58 Hz, 2H), 6.64-6.75 (m, 1H), 7.05 (d,  $J$  = 7.96 Hz, 2H), 7.20 (d,  $J$  = 8.08 Hz, 2H), 7.23-7.27 (m, 2H), 7.30-7.42 (m, 3H).

**Step C: Preparation of 2-(((1*s*,4*s*)-4-((5-(2-Aminoethylthio)-4-phenyl-3-*p*-tolyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid.**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((5-(2-(*tert*-butoxycarbonylamino)ethylthio)-4-phenyl-3-*p*-tolyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((3-(2-(*tert*-butoxycarbonylamino)ethylthio)-4-phenyl-5-*p*-tolyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers, using a similar method to the one described in **Example 1.25, Step C**, the title compound was obtained as a white solid. LCMS  $m/z$  = 494.5  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.30-1.46 (m,  $J$  = 23.31, 5.62 Hz, 4H), 1.46-1.54 (m, 4H), 1.70-1.85 (m, 1H), 2.14-2.23 (m, 1H), 2.26 (s, 3H), 2.57-2.74 (m, 4H), 3.42 (d,  $J$  = 7.07 Hz, 2H), 4.00 (s, 2H), 4.28 (d,  $J$  = 7.45 Hz, 2H), 7.07 (d,  $J$  = 7.96 Hz, 2H), 7.20 (d,  $J$  = 8.08 Hz, 2H), 7.24-7.29 (m, 2H), 7.31-7.45 (m, 3H), 7.64 (bs, 2H), 12.54 (s, 1H).

**Example 1.35: Preparation of 2-(((1*s*,4*s*)-4-((3-(4-Fluorophenyl)-5-(2-hydroxyethylthio)-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 255).**

**Step A: Preparation of 3-(4-Fluorophenyl)-4-phenyl-5-(2-(tetrahydro-2*H*-pyran-2-yloxy)ethylthio)-1*H*-pyrazole**

From 1-(4-fluorophenyl)-2-phenethanone, using a similar method to the one described in **Example 1.25, Step A**, the title compound was obtained as a white solid.  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.32-1.51 (m, 3H), 1.52-1.75 (m, 3H), 3.10 (t,  $J$  = 6.63 Hz, 2H), 3.33-3.44 (m, 1H), 3.53-3.66 (m, 1H), 3.68-3.83 (m, 2H), 4.52-4.57 (m, 1H), 7.11 (t,  $J$  = 8.27 Hz, 1H), 7.21 (t,  $J$  = 8.97 Hz, 3H), 7.24-7.43 (m, 5H), 13.34 (s, 1H).

**Step B: Preparation of *tert*-butyl 2-(((1*s*,4*s*)-4-((3-(4-Fluorophenyl)-4-phenyl-5-(2-(tetrahydro-2*H*-pyran-2-yloxy)ethylthio)-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-Butyl 2-(((1*s*,4*s*)-4-((5-(4-Fluorophenyl)-4-phenyl-3-(2-(tetrahydro-2*H*-pyran-2-yloxy)ethylthio)-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a Mixture of Regioisomers.**

From 4-(3-fluorophenyl)-3-phenyl-5-(2-(tetrahydro-2*H*-pyran-2-yloxy)ethylthio)-1*H*-pyrazole, using a similar method to the one described in **Example 1.25, Step B**, the title compound was obtained as a clear oil (a mixture of regioisomers). LCMS  $m/z$  = 639.6  $[M+H]^+$ ;  $^1H$  NMR (400

MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.30-1.42 (m, 4H), 1.43 (s, 9H), 1.45-1.54 (m, 7H), 1.56-1.79 (m, 3H), 2.14-2.24 (m, 1H), 2.65-2.72 (m, 2H), 3.20-3.28 (m, 2H), 3.31-3.37 (m, 1H), 3.39 (d, *J* = 6.82 Hz, 2H), 3.47-3.56 (m, 1H), 3.58-3.66 (m, 1H), 3.95 (s, 2H), 4.30 (dd, *J* = 7.39, 3.09 Hz, 2H), 4.34-4.36 (m, 1H), 7.06-7.13 (m, 2H), 7.24-7.28 (m, 2H), 7.29-7.44 (m, 5H).

5           **Step C: Preparation of 2-(((1*s*,4*s*)-4-((3-(4-Fluorophenyl)-5-(2-hydroxyethylthio)-4-phenyl)-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid.**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((3-(4-fluorophenyl)-4-phenyl-5-(2-(tetrahydro-2*H*-pyran-2-yloxy)ethylthio)-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((5-(4-fluorophenyl)-4-phenyl-3-(2-(tetrahydro-2*H*-pyran-2-yloxy)ethylthio)-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate, using a similar method to the one described in  
10           **Example 1.25, Step C**, the title compounds were obtained as clear oily solids. LCMS *m/z* = 499.7 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.29-1.45 (m, 4H), 1.45-1.53 (m, 4H), 1.69-1.80 (m, 1H), 2.14-2.22 (m, 1H), 2.57 (t, *J* = 6.69 Hz, 2H), 3.25-3.29 (m, 2H), 3.28-3.32 (m, 1H), 3.40 (d, *J* = 6.95 Hz, 2H), 3.97 (s, 2H), 4.29 (d, *J* = 7.45 Hz, 2H), 7.06-7.14 (m, 2H),  
15           7.23-7.28 (m, 2H), 7.30-7.43 (m, 5H).

**Example 1.36: Preparation of 2-(((1*s*,4*s*)-4-((5-(4-Fluorophenyl)-3-(2-hydroxyethylthio)-4-phenyl)-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 256).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((3-(4-fluorophenyl)-4-phenyl-5-(2-(tetrahydro-2*H*-pyran-2-yloxy)ethylthio)-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((5-(4-fluorophenyl)-4-phenyl-3-(2-(tetrahydro-2*H*-pyran-2-yloxy)ethylthio)-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate, using a similar method to the one described in  
20           **Example 1.25, Step C**, the title compound was obtained as clear oil solid. LCMS *m/z* = 499.7 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 0.81-0.99 (m, 2H), 1.01-1.14 (m, 2H), 1.46-1.59 (m, 1H), 1.65 (dd, *J* = 13.20, 2.08 Hz, 2H), 1.76 (dd, *J* = 12.44, 2.08 Hz, 2H), 1.86-1.97 (m, 1H), 2.56 (t, *J* = 6.63 Hz, 2H), 3.27 (dd, *J* = 13.52, 6.69 Hz, 4H), 3.91 (s, 2H), 4.20 (d, *J* = 7.20 Hz, 2H), 4.76 (bs, 1H), 7.07-7.14 (m, 2H), 7.25-7.28 (m, 2H), 7.31-7.43 (m, 5H).

30           **Example 1.37: Preparation of 2-(((1*s*,4*s*)-4-((5-(2-Hydroxyethyl)-3,4-diphenyl)-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 251).**

**Step A: Preparation of 2-(3-Phenyl-1*H*-pyrazol-5-yl)ethanol.**  
5-(2-(Benzyloxy)ethyl-3-phenyl-1*H*-pyrazole (2.1 g, 7.54 mmol) was dissolved in acetic acid (10 mL) and THF (10 mL). Palladium on carbon (0.080 g, 0.754 mmol) was added and the reaction was stirred for 4 days under hydrogen atmosphere on the Parr shaker at 55 psi. After  
35           this time, the reaction was filtered through celite and washed with EtOAc. The solvents were evaporated. The reaction progress was checked by TLC and shown to be ~50-60% complete. The reaction was set up on the Parr shaker again. After three more days on the Parr shaker, the

reaction was stopped. The reaction was filtered through celite and the solvents removed. The reaction was extracted (70 mL each of H<sub>2</sub>O and EtOAc). The aqueous layer was extracted again with EtOAc (70 mL). The combined organic layer was dried and concentrated, and the residue was purified by column chromatography to give the title compound (665 mg) as a white solid.

5 LCMS  $m/z$  = 189.4 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  ppm 2.68-2.82 (m, 2H), 3.60-3.71 (m, 2H), 4.73-4.81 (m, 1H), 6.48 (s, 1H), 7.20-7.49 (m, 3H), 7.55-7.96 (m, 2H), 12.53 (s, 1H).

**Step B: Preparation of 2-(4-Bromo-3-phenyl-1H-pyrazol-5-yl)ethanol.**

2-(3-Phenyl-1H-pyrazol-5-yl)ethanol (664 mg, 3.53 mmol) was dissolved in dry DCM (40 mL) and THF (10 mL). The reaction was cooled in an ice bath and Br<sub>2</sub> (363  $\mu$ L, 7.06 mmol), pre-dissolved in DCM (3 mL), was added slowly dropwise via addition funnel. The reaction was stirred for 2 h in an ice bath, then the reaction was quenched by the addition of Na<sub>2</sub>SO<sub>3</sub> (20 mL of 10% solution; the reaction went from reddish-brown to clear and some bubbling was observed). The reaction was extracted (100 mL each of H<sub>2</sub>O and DCM). The aqueous layer was extracted again with DCM (100 mL). The combined organic layer was back extracted again with H<sub>2</sub>O (200 mL). The organic layer was dried and concentrated to yield the title compound (880 mg) as a light yellow solid. LCMS  $m/z$  = 267.1 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  ppm 2.78 (t,  $J$  = 7.14 Hz, 2H), 3.66 (t,  $J$  = 7.14 Hz, 2H), 7.35-7.42 (m, 1H), 7.43-7.51 (m, 2H), 7.72-7.84 (m, 2H).

20 **Step C: Preparation of *tert*-Butyl 2-(((1*s*,4*s*)-4-((4-Bromo-5-(2-hydroxyethyl)-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate.**

2-(4-Bromo-3-phenyl-1H-pyrazol-5-yl)ethanol (880 mg, 3.29 mmol), *tert*-butyl 2-(((1*s*,4*s*)-4-(tosyloxymethyl)cyclohexyl)methoxy)acetate (1359 mg, 3.29 mmol), and cesium carbonate (2147 mg, 6.59 mmol) were added to DMF (15 mL). The reaction was heated to 80 °C and stirred at this temperature for 1 h. The reaction was cooled and extracted (50 mL each of H<sub>2</sub>O and EtOAc). The aqueous layer was extracted again with EtOAc (50 mL). The combined organic layer was back extracted with H<sub>2</sub>O (100 mL). The organic layer was dried, concentrated, and the residue was purified by chromatography to yield the title compound (640 mg) as a light yellow oil. LCMS  $m/z$  = 507.4 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  ppm 1.28-1.53 (m, 17H), 1.69-1.81 (m,  $J$  = 5.31 Hz, 1H), 2.02-2.14 (m, 1H), 2.87 (t,  $J$  = 6.76 Hz, 2H), 3.39 (d,  $J$  = 6.95 Hz, 2H), 3.56-3.66 (m, 2H), 3.94 (s, 2H), 4.10 (d,  $J$  = 7.45 Hz, 2H), 4.92 (t,  $J$  = 5.43 Hz, 1H), 7.33-7.40 (m, 1H), 7.40-7.49 (m, 2H), 7.75-7.85 (m, 2H).

**Step D: Preparation of 2-(((1*s*,4*s*)-4-((5-(2-Hydroxyethyl)-3,4-diphenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid.**

35 *tert*-Butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-(2-hydroxyethyl)-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate (30 mg, 0.059 mmol), phenyl boronic acid (1.1 eq), tetrakis(triphenyl)phosphinepalladium (3.42 mg, 2.96  $\mu$ mol), and K<sub>2</sub>CO<sub>3</sub> (16.34 mg, 0.118 mmol)

were added to a vial with dioxane (300  $\mu$ L). The reaction was heated in a microwave at 150  $^{\circ}$ C for 1 h. After this time, the reaction was filtered through a plug of  $\text{MgSO}_4$ . The solvent was removed and the resulting oil (t-butyl ester intermediate) was re-dissolved in HCl (500  $\mu$ L, 2.000 mmol). The reaction was stirred overnight at room temperature. The next day, the solvent  
5 was removed and the product was purified by preparative LC/MS to give the title compound (4.2 mg) as a white solid. LCMS  $m/z$  = 449.3  $[\text{M}+\text{H}]^+$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  ppm 1.33-1.59 (m, 8H), 1.73-1.82 (m, 1H), 2.09-2.21 (m, 1H), 2.75 (t,  $J$  = 7.14 Hz, 2H), 3.40-3.46 (m, 4H), 3.98-4.00 (m, 2H), 4.06-4.09 (m, 2H), 7.15-7.25 (m, 5H), 7.26-7.34 (m, 3H), 7.34-7.42 (m, 2H).

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**Example 1.38: Preparation of 2-(((1*s*,4*s*)-4-((5-(2-Hydroxyethyl)-4-(3-methoxyphenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 252).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-(2-hydroxyethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and 3-methoxyphenylboronic acid, using a similar  
15 method to the one described in **Example 1.37**, the title compound was obtained as a white solid. LCMS  $m/z$  = 479.6  $[\text{M}+\text{H}]^+$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  ppm 1.32-1.59 (m, 8H), 1.71-1.86 (m, 1H), 2.06-2.22 (m, 1H), 2.76 (t,  $J$  = 6.19 Hz, 2H), 3.41-3.50 (m, 4H), 3.70 (s, 3H), 4.00 (s, 2H), 4.07 (d,  $J$  = 6.32 Hz, 2H), 6.73-6.80 (m, 2H), 6.85-6.92 (m, 1H), 7.14-7.36 (m, 6H).

20 **Example 1.39: Preparation of Sodium 2-(((1*s*,4*s*)-4-((5-(2-Hydroxyethyl)-4-(3-methoxyphenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate.**

2-(((1*s*,4*s*)-4-((5-(2-Hydroxyethyl)-4-(3-methoxyphenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid (8.2 mg, 0.017 mmol) was dissolved in ACN (0.2 mL). NaOH (5.71  $\mu$ L, 0.017 mmol) was added, followed by  $\text{H}_2\text{O}$  (0.2 mL), and the reaction was  
25 stirred for an hour. After this time, the reaction was frozen and lyophilized to give the title compound (8.5 mg) as a white solid. LCMS  $m/z$  = 479.4  $[\text{M}-\text{Na}+\text{H}]^+$ .

**Example 1.40: Preparation of 2-(((1*s*,4*s*)-4-((4-(2,3-Difluorophenyl)-5-(2-hydroxyethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 253).**

30 From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-(2-hydroxyethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and 2,3-difluorophenylboronic acid, using a similar method to the one described in **Example 1.37**, the title compound was obtained as a white solid. LCMS  $m/z$  = 485.4  $[\text{M}+\text{H}]^+$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  ppm 1.31-1.55 (m, 8H), 1.73-1.83 (m, 1H), 2.09-2.19 (m, 1H), 2.73 (t,  $J$  = 7.01 Hz, 2H), 3.37-3.45 (m, 4H), 4.00 (s, 2H), 4.10  
35 (d,  $J$  = 7.45 Hz, 2H), 7.10-7.17 (m, 1H), 7.19-7.32 (m, 6H), 7.38-7.49 (m, 1H).

**Example 1.41: Preparation of 2-(((1*s*,4*s*)-4-((4-(3-Fluorophenyl)-5-(2-hydroxyethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 254).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-(2-hydroxyethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and 3-fluorophenylboronic acid, using a similar method to the one described in **Example 1.37**, the title compound was obtained as a white solid. LCMS  $m/z = 467.6$   $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.32-1.59 (m, 8H), 1.77 (dd,  $J = 9.92, 4.48$  Hz, 1H), 2.09-2.19 (m, 1H), 2.77 (t,  $J = 7.01$  Hz, 2H), 3.41-3.48 (m, 4H), 4.00 (s, 2H), 4.08 (d,  $J = 7.45$  Hz, 2H), 6.99-7.08 (m, 2H), 7.10-7.18 (m, 1H), 7.18-7.32 (m, 5H), 7.35-7.45 (m, 1H).

**Example 1.42: Preparation of 2-(((1*s*,4*s*)-4-((4-(3-Chloro-2-fluorophenyl)-5-(2-hydroxyethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 276).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-(2-hydroxyethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and 3-chloro-2-fluorophenylboronic acid, using a similar method to the one described in **Example 1.37**, the title compound was obtained as a white solid. LCMS  $m/z = 501.5$   $[M+H]^+$ .

**Example 1.43: Preparation of 2-(((1*s*,4*s*)-4-((5-(3-Hydroxypropyl)-3,4-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 271).**

**Step A: Preparation of 5-(But-3-enyl)-3-phenyl-1*H*-pyrazole.**

Acetophenone (4.92 mL, 42.2 mmol) was dissolved in toluene (50 mL). The reaction was cooled on an ice bath. LiHMDS (42.2 mL, 42.2 mmol) was added via syringe and the reaction was stirred for 2 min. Pent-4-enoyl chloride (4.66 mL, 42.2 mmol) was added and then the reaction was stirred for 2 more min. Hydrazine hydrate (8.18 mL, 169 mmol) was then added, along with AcOH (2 mL) and EtOH (2 mL). The reaction was warmed to room temperature and then heated in an oil bath to 80 °C for 1 h. After this time, the reaction was cooled and an extraction was performed (200 mL each of H<sub>2</sub>O and EtOAc). The aqueous layer was extracted again with EtOAc (200 mL). The combined organic layer was dried, concentrated, and the residue was purified by column chromatography to give the title compound (5.4 g) as a yellow oil. LCMS  $m/z = 199.3$   $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 2.39 (q,  $J = 7.28$  Hz, 2H), 2.61-2.76 (m, 2H), 5.00 (d,  $J = 9.98$  Hz, 1H), 5.04-5.13 (m, 1H), 5.78-5.95 (m, 1H), 6.47 (s, 1H), 7.21-7.33 (m, 1H), 7.33-7.48 (m, 2H), 7.65-7.81 (m, 2H), 12.56 (s, 1H).

**Step B: Preparation of 3-(3-Phenyl-1*H*-pyrazol-5-yl)propan-1-ol.**

5-(But-3-enyl)-3-phenyl-1*H*-pyrazole (5.4 g, 27.2 mmol) was dissolved in MeOH (40 mL) and DCM (10 mL). The reaction was cooled on a dry-ice/acetone bath and ozone was bubbled through the solution for ~2 h. The reaction was transferred into an ice bath and NaBH<sub>4</sub>

(1.546 g, 40.9 mmol) was added slowly portion-wise (bubbling was observed). Upon complete addition, the reaction was removed from the ice bath and stirred at room temperature for 1 h. Excess solvent was evaporated and the reaction was extracted (100 mL each of H<sub>2</sub>O and EtOAc). The aqueous layer was extracted again with EtOAc (100 mL). The combined organic layer was dried, concentrated, and the residue was purified by column chromatography to yield the title compound (3.0 g) as a white solid. LCMS  $m/z$  = 203.3 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  ppm 1.72-1.82 (m, 2H), 2.54-2.69 (m, 2H), 3.46 (q,  $J$  = 6.11 Hz, 2H), 4.40-4.54 (m, 1H), 6.45 (s, 1H), 7.21-7.45 (m, 3H), 7.66-7.79 (m,  $J$  = 7.45 Hz, 2H), 12.53 (s, 1H).

**Step C: Preparation of 3-(4-Bromo-3-phenyl-1H-pyrazol-5-yl)propan-1-ol.**

3-(3-Phenyl-1H-pyrazol-5-yl)propan-1-ol (3.0 g, 14.83 mmol) was dissolved in dry DCM (40 mL) and THF (15 mL). The reaction was cooled in an ice bath and Br<sub>2</sub> (1.146 mL, 22.25 mmol) pre-dissolved in DCM (10 mL) was added slowly dropwise via addition funnel. The reaction was stirred for 2 h in an ice bath. The reaction was quenched by the addition of Na<sub>2</sub>SO<sub>3</sub> (20 mL of 10% solution; the reaction went from reddish-brown to clear and some bubbling was observed). The reaction was extracted (100 mL each of H<sub>2</sub>O and DCM). The aqueous layer was extracted again with DCM (100 mL). The combined organic layer was back extracted again with H<sub>2</sub>O (200 mL). The organic layer was dried and concentrated to give the title compound (4.08 g) as a yellow solid. LCMS  $m/z$  = 281.3 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  ppm 1.72-1.83 (m, 2H), 2.61-2.68 (m, 2H), 3.47 (t,  $J$  = 6.44 Hz, 2H), 7.39 (t,  $J$  = 7.33 Hz, 1H), 7.47 (t,  $J$  = 7.45 Hz, 2H), 7.78 (d,  $J$  = 7.07 Hz, 2H).

**Step D: Preparation of *tert*-Butyl 2-(((1*s*,4*s*)-4-((4-Bromo-5-(3-hydroxypropyl)-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate.**

3-(4-Bromo-3-phenyl-1H-pyrazol-5-yl)propan-1-ol, *tert*-butyl 2-(((1*s*,4*s*)-4-(tosyloxymethyl)cyclohexyl)methoxy)acetate (2.93 g, 7.11 mmol), and cesium carbonate (4.64 g, 14.23 mmol) were dissolved in DMF (35 mL). The reaction was heated to 80 °C in an oil bath and stirred at this temperature for an hour. The reaction was cooled and extracted (100 mL each of H<sub>2</sub>O and EtOAc). The aqueous layer was extracted again with EtOAc (100 mL). The combined organic layer was back extracted once with H<sub>2</sub>O (200 mL). The organic layer was dried, concentrated, and the residue was purified by column chromatography to give the title compound (1.54 g) as a light yellow oil. LCMS  $m/z$  = 521.7 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  ppm 0.97-1.05 (m, 4H), 1.26-1.55 (m, 13H), 1.65-1.79 (m, 3H), 2.01-2.12 (m, 1H), 2.71-2.77 (m, 2H), 3.39 (d,  $J$  = 6.95 Hz, 2H), 3.46 (t,  $J$  = 6.19 Hz, 2H), 3.94 (s, 2H), 4.06 (d,  $J$  = 7.45 Hz, 2H), 7.32-7.39 (m, 1H), 7.40-7.48 (m, 2H), 7.77-7.82 (m,  $J$  = 8.34, 1.14 Hz, 2H).

**Step E: Preparation of 2-(((1*s*,4*s*)-4-((5-(3-Hydroxypropyl)-3,4-diphenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid.**

*tert*-Butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-(3-hydroxypropyl)-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate (50 mg, 0.096 mmol), phenylboronic acid (1.1 eq),

tetrakis(triphenylphosphine)palladium(0) (11.08 mg, 9.59  $\mu\text{mol}$ ), and  $\text{K}_2\text{CO}_3$  (26.5 mg, 0.192 mmol) were added to a vial with dioxane (0.4 mL). The reaction was heated in a microwave at 150 °C for 2 h. After this time, the reaction was filtered through a plug of  $\text{MgSO}_4$ . The solvent was removed and the ester intermediate obtained was re-dissolved in HCl (4M in dioxane) (503  $\mu\text{L}$ , 2.013 mmol). The reaction was stirred overnight at room temperature. The next day, the solvent was removed and the residue was purified by preparative LC/MS. After lyophilizing the reaction, there was observed the side-product formation of the TFA-ester off of the side chain alcohol. Therefore, the product was dissolved in THF (0.3 mL). Then 3M LiOH (50  $\mu\text{L}$ ) was added. The reactions were stirred at room temperature overnight. The next day, 1 M HCl (200  $\mu\text{L}$ ) was added to make the reaction acidic. The reactions were extracted (2 mL each of HCl/ $\text{H}_2\text{O}$  and EtOAc). The aqueous layer was extracted again with EtOAc (2 mL). The combined organic layer was dried and concentrated. The resulting oil was re-dissolved in ACN (0.3 mL) and  $\text{H}_2\text{O}$  (0.2 mL). The mixture was frozen and lyophilized to give the title compound (8.9 mg) as a white solid. LCMS  $m/z = 463.5$   $[\text{M}+\text{H}]^+$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  ppm 1.32-1.60 (m, 10H), 1.71-1.84 (m, 1H), 2.08-2.19 (m, 1H), 2.59-2.65 (m, 2H), 3.31 (t,  $J = 6.19$  Hz, 2H), 3.43-3.44 (m, 2H), 3.99 (s, 2H), 4.05 (d,  $J = 7.33$  Hz, 2H), 7.14-7.25 (m, 5H), 7.26-7.40 (m, 5H).

**Example 1.44: Preparation of 2-(((1*s*,4*s*)-4-((5-(3-Hydroxypropyl)-4-(3-methoxyphenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 272).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-(3-hydroxypropyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and 3-methoxyphenylboronic acid, using a similar method to the one described in **Example 1.43**, the title compound was obtained as a white solid. LCMS  $m/z = 493.6$   $[\text{M}+\text{H}]^+$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  ppm 1.32-1.61 (m, 10H), 1.72-1.83 (m, 1H), 2.08-2.18 (m, 1H), 2.60-2.66 (m, 2H), 3.33 (t,  $J = 6.19$  Hz, 2H), 3.42 (d,  $J = 6.82$  Hz, 2H), 3.70 (s, 3H), 3.99 (s, 2H), 4.04 (d,  $J = 7.33$  Hz, 2H), 6.70-6.75 (m, 2H), 6.87 (dd,  $J = 7.96, 2.15$  Hz, 1H), 7.16-7.37 (m, 6H).

**Example 1.45: Preparation of 2-(((1*s*,4*s*)-4-((4-(2,3-Difluorophenyl)-5-(3-hydroxypropyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 273).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-(3-hydroxypropyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and 2,3-difluorophenylboronic acid, using a similar method to the one described in **Example 1.43**, the title compound was obtained as a white solid. LCMS  $m/z = 499.7$   $[\text{M}+\text{H}]^+$ .

**Example 1.46: Preparation of 2-(((1*s*,4*s*)-4-((4-(3-Fluorophenyl)-5-(3-hydroxypropyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 274).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-(3-hydroxypropyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and 3-fluorophenylboronic acid, using a similar method to the one described in **Example 1.43**, the title compound was obtained as a white solid. LCMS  $m/z = 481.3$   $[M+H]^+$ .

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**Example 1.47: Preparation of 2-(((1*s*,4*s*)-4-((4-(3-Chloro-2-fluorophenyl)-5-(3-hydroxypropyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 281).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-(3-hydroxypropyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and 3-chloro-2-fluorophenylboronic acid, using a similar method to the one described in **Example 1.43**, the title compound was obtained as a white solid. LCMS  $m/z = 515.5$   $[M+H]^+$ .

**Example 1.48: Preparation of 2-(((1*s*,4*s*)-4-((4-(3-Chlorophenyl)-5-(3-hydroxypropyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 282).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-(3-hydroxypropyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and 3-chlorophenylboronic acid, using a similar method to the one described in **Example 1.43**, the title compound was obtained as a white solid. LCMS  $m/z = 497.5$   $[M+H]^+$ .

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**Example 1.49: Preparation of 2-(((1*s*,4*s*)-4-((5-(3-hydroxypropyl)-4-phenyl-3-*p*-tolyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 288).**

**Step A: Preparation of 5-(But-3-enyl)-4-phenyl-3-*p*-tolyl-1*H*-pyrazole.**

2-Phenyl-1-*p*-tolylethanone (1.0 g, 4.76 mmol) was dissolved in Toluene (20 mL). The reaction was cooled in an ice bath and then LiHMDS (4.76 mL, 4.76 mmol) was added slowly via syringe. The reaction was stirred at this temperature for 5 min and then pent-4-enoyl chloride (0.564 g, 4.76 mmol) was added. The reaction was warmed to room temperature and stirred at this temperature for 20 min. After this time EtOH (10 mL), AcOH (2 mL), and hydrazine hydrate (0.231 mL, 4.76 mmol) were added to the reaction. The reaction was heated to 80 °C and stirred at this temperature for an hour. After this time, the reaction was cooled and extracted (50 mL each of EtOAc and 1M NaOH). The aqueous layer was extracted again with EtOAc (50 mL). The combined organic layer was dried, concentrated, and the residue was purified by silica gel column chromatography to give the title compound (355 mg) as a colorless oil. LCMS  $m/z = 289.0$   $[M+H]^+$ ;  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 2.22-2.32 (m, 5H), 2.55-2.69 (m, 2H), 4.86-5.02 (m, 2H), 5.75 (s, 1H), 6.99-7.24 (m, 6H), 7.25-7.31 (m, 1H), 7.33-7.39 (m, 2H), 12.74 (s, 1H).

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**Step B: Preparation of 3-(4-Phenyl-3-*p*-tolyl-1*H*-pyrazol-5-yl)propan-1-ol.**



5-(But-3-enyl)-4-phenyl-3-*p*-tolyl-1*H*-pyrazole (360 mg, 1.248 mmol) was dissolved in MeOH (20 mL) and DCM (5 mL). The reaction was cooled to -78 °C and ozone was bubbled through the solution. After the starting material was consumed, the reaction was cooled in an ice bath. Sodium borohydride (70.8 mg, 1.872 mmol) was added to the reaction. The reaction was warmed to room temperature and stirred for an hour. The solvent was removed under reduced pressure and the reaction was extracted (50mL each of H<sub>2</sub>O and EtOAc). The aqueous layer was extracted again with EtOAc (50 mL). The combined organic layer was dried, concentrated, and the residue was purified by silica gel column chromatography to give the title compound (130 mg) as a white solid. LCMS *m/z* = 293.1 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.60-1.74 (m, 2H), 2.25 (s, 3H), 2.54-2.62 (m, 2H), 3.33-3.44 (m, 2H), 4.44 (br. s., 1H), 7.16 (t, *J* = 6.44 Hz, 6H), 7.24-7.30 (m, 1H), 7.32-7.38 (m, 2H), 12.71 (s, 1H).

**Step C: Preparation of 2-(((1*s*,4*s*)-4-((5-(3-Hydroxypropyl)-4-phenyl-3-*p*-tolyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid.**

3-(4-Phenyl-3-*p*-tolyl-1*H*-pyrazol-5-yl)propan-1-ol (50 mg, 0.171 mmol), *tert*-butyl 2-(((1*s*,4*s*)-4-(tosyloxymethyl)cyclohexyl)methoxy)acetate (70.5 mg, 0.171 mmol), and Cs<sub>2</sub>CO<sub>3</sub> (111 mg, 0.342 mmol) were suspended in DMF (0.5 mL). The reaction was heated at 80 °C for an hour. The mixture was cooled and extracted (2 mL each of H<sub>2</sub>O and EtOAc). The aqueous layer was extracted again with EtOAc (2 mL). The combined organic layer was filtered through a plug of MgSO<sub>4</sub>. The solvents were removed, then the resulting oil was re-dissolved in HCl (4M in dioxane) (0.5 mL, 2.000 mmol). The reaction was stirred at room temperature overnight. The mixture was purified by preparative LC/MS. After lyophilization, the product was re-dissolved in THF (0.3 mL) and stirred with 1M NaOH (100 µL) overnight. The reaction was then made acidic by addition of 1M HCl (200 µL). The reaction was extracted (2 mL each of H<sub>2</sub>O and EtOAc). The aqueous layer was extracted again with EtOAc (2 mL). The combined organic layer was filtered through a plug of MgSO<sub>4</sub> and concentrated to give the title compound (3.5 mg), one of the two regioisomers, as a colorless oil. LCMS *m/z* = 477.4 [M+H]<sup>+</sup>.

**Example 1.50: Preparation of 2-(((1*s*,4*s*)-4-((3-(3-Hydroxypropyl)-4-phenyl-5-*p*-tolyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 289).**

The title compound was isolated as one of the two regioisomers from Example 1.49, Step C, to give an oil. LCMS *m/z* = 477.5 [M+H]<sup>+</sup>.

**Example 1.51: Preparation of 2-(((1*s*,4*s*)-4-((5-(2-fluoro-4-methylphenyl)-3-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 286).**

**Step A: Preparation of *tert*-Butyl 2-(((1*s*,4*s*)-4-((5-(2-Fluoro-4-methylphenyl)-3-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate.**

3-(2-Fluoro-4-methylphenyl)-5-methyl-4-phenyl-1*H*-pyrazole (2.82 g, 10.59 mmol) was dissolved in dry DMF (40 mL). Cs<sub>2</sub>CO<sub>3</sub> (6.90 g, 21.18 mmol) and *tert*-butyl 2-(((1*s*,4*s*)-4-(tosyloxymethyl)cyclohexyl)methoxy)acetate (4.37 g, 10.59 mmol) were added. The reaction was heated to 80 °C and stirred at this temperature for 1 h. The reaction was cooled and  
5 extracted (100 mL each of H<sub>2</sub>O and EtOAc). The aqueous layer was extracted again with EtOAc (100 mL). The combined organic layer was back extracted once with H<sub>2</sub>O/Brine (200 mL). The organic layer was dried, concentrated, and the residue was purified by chromatography to give the title compound (3.2 g), a mixture of regioisomers, as a colorless oil. LCMS *m/z* = 507.2 [M+H]<sup>+</sup>.

10 **Step B: Preparation of 2-(((1*s*,4*s*)-4-((5-(2-Fluoro-4-methylphenyl)-3-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid.**

*tert*-Butyl 2-(((1*s*,4*s*)-4-((3-(2-fluoro-4-methylphenyl)-5-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate (3.2 g, 6.32 mmol) was dissolved in HCl (4*M* in dioxane) (50.0 mL, 200 mmol). The reaction was stirred overnight at room temperature. The  
15 solvent was removed and the residue was purified by HPLC to give the title compound as a colorless oil (746 mg). LCMS *m/z* = 451.3 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.08-1.20 (m, 4H), 1.22-1.37 (m, 4H), 1.57-1.69 (m, 1H), 1.90-1.97 (m, 1H), 2.23 (s, 3H), 2.35 (s, 3H), 3.22 (d, *J* = 6.82 Hz, 2H), 3.71-3.87 (m, 2H), 3.92 (s, 2H), 7.04-7.11 (m, 4H), 7.11-7.20 (m, 2H), 7.24 (t, *J* = 7.33 Hz, 2H).

20 **Example 1.52: Preparation of 2-(((1*s*,4*s*)-4-((3-(4-Chlorophenyl)-5-ethyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 163).**

**Step A: Preparation of 1-(Dimethylamino)-2-phenylpent-1-en-3-one.**

To a solution of 1-phenylbutan-2-one (5.00 g, 33.7 mmol) in DMF (80.0 mL) was added  
25 1,1-dimethoxy-*N,N*-dimethylmethanamine (6.03 g, 50.6 mmol). The resulting mixture was stirred at 90 °C for 16 h. Upon completion, the reaction mixture was quenched with water (40.0 mL), extracted with EtOAc (4 × 50.0 mL), and washed with brine. The combined organics were dried over MgSO<sub>4</sub>, filtered, and concentrated to give a brown oil. This brown oil was purified by flash chromatography to give the title compound as a yellow oil (3.32 g). <sup>1</sup>H NMR (400 MHz,  
30 CDCl<sub>3</sub>) δ ppm 0.97 (t, *J* = 7.32 Hz, 3H), 2.19 (q, *J* = 7.49 Hz, 2H), 2.67 (s, 6H), 7.14-7.41 (m, 5H), 7.61 (s, 1H).

**Step B: Preparation of 5-Ethyl-4-phenyl-1*H*-pyrazole.**

To a mixture of 1-(dimethylamino)-2-phenylpent-1-en-3-one (3.32 g, 16.33 mmol) in EtOH (80.0 mL) was added hydrazine hydrate (1.58 mL, 32.66 mmol). The resulting mixture  
35 was stirred at 80 °C for 3 h. The reaction mixture was cooled to room temperature and concentrated to give a solid. The solid was re-crystallized, using 20% ethanol in water to give the title compound as a white solid (2.81 g). LCMS *m/z* = 173 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz,

CDCl<sub>3</sub>)  $\delta$  ppm 1.31 (t,  $J$  = 7.58 Hz, 3H), 2.88 (q,  $J$  = 7.58 Hz, 2H), 7.22-7.30 (m, 1H), 7.35-7.42 (m, 4H).

**Step C: Preparation of 3-Bromo-5-ethyl-4-phenyl-1H-pyrazole.**

To a solution of 5-ethyl-4-phenyl-1H-pyrazole (3.34 g, 19.39 mmol) in dichloromethane (111.0 mL), was added bromine (1.49 mL, 29.09 mmol) at 25 °C. The reaction was stirred at room temperature for 72 h and quenched with NaOH (aq.) to pH 12. The organics were separated. The aqueous layer was extracted again with DCM (3  $\times$ ). The combined organics were washed with brine, dried (MgSO<sub>4</sub>), filtered and concentrated to give a red oil. This oil was purified by flash chromatography to give the title compound as a yellow oil (2.84 g). LCMS  $m/z$  = 251.2 [M+H]<sup>+</sup>.

**Step D: Preparation of *tert*-Butyl 2-(((1*s*,4*s*)-4-((3-Bromo-5-ethyl-4-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate.**

To a solution of 3-bromo-5-ethyl-4-phenyl-1H-pyrazole (0.364 g, 1.451 mmol) in DMF (5.0 mL), was slowly added 60% sodium hydride (0.070 g, 1.740 mmol). The solution was allowed to stir for a total of 20 min, before a mixture of *tert*-butyl 2-(((1*s*,4*s*)-4-(tosyloxymethyl)cyclohexyl)methoxy)acetate (0.598 g, 1.450 mmol) in DMF (1.0 mL) was added. The reaction mixture was then stirred at 45 °C for 12 h. Upon completion, the reaction mixture was quenched with water and extracted with EtOAc (4  $\times$ ). The combined organics were dried over MgSO<sub>4</sub>, filtered, and concentrated to give a brown oil. This brown oil was purified by flash chromatography to give the title compound as a yellow oil (0.213 g). LCMS  $m/z$  = 491.4, 493.5 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  ppm 1.13-1.29 (m, 4H), 1.27-1.41 (m, 2H), 1.43-1.62 (m, 13H), 1.79-1.93 (m, 2H), 2.09-2.25 (m, 1H), 2.76 (q,  $J$  = 7.58 Hz, 2H), 3.39-3.50 (m, 2H), 3.84-4.05 (m, 4H), 7.20-7.28 (m, 2H), 7.33-7.39 (m, 1H), 7.45-7.54 (m, 2H).

**Step E: Preparation of *tert*-Butyl 2-(((1*s*,4*s*)-4-((3-(4-Chlorophenyl)-5-ethyl-4-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate.**

To a solution of 4-chlorophenylboronic acid (0.019 g, 0.122 mmol), *tert*-butyl 2-(((1*s*,4*s*)-4-((3-bromo-5-ethyl-4-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate (0.060 g, 0.122 mmol), tetrakis(triphenylphosphine)palladium (0) (0.004 g, .004 mmol) in benzene (3.0 mL) and EtOH (1.0 mL) was added sodium carbonate (0.122 mL, 0.244 mmol). The reaction mixture was then heated in a microwave at 130 °C for 1 h. Upon completion, the reaction mixture was diluted with water and extracted with EtOAc (3  $\times$ ). The combined organics were dried over MgSO<sub>4</sub>, filtered, and concentrated to give a yellow oil. This yellow oil was re-suspended in ACN/H<sub>2</sub>O and purified by HPLC to give the title compound as a white solid (0.032 g). LCMS  $m/z$  = 523.4, 525.8 [M+H]<sup>+</sup>.

**Step F: Preparation of 2-(((1*s*,4*s*)-4-((3-(4-Chlorophenyl)-5-ethyl-4-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid.**

To a solution of *tert*-butyl 2-(((1*s*,4*s*)-4-((3-(4-chlorophenyl)-5-ethyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate (0.032 g, 0.060 mmol) in DCM (2.0 mL) was added 4M HCl in dioxane (0.151 mL, 0.602 mmol). The resulting reaction mixture was stirred at 25 °C for 16 h. The reaction was concentrated to give a yellow oil. This yellow oil was then re-suspended in ACN/H<sub>2</sub>O and purified by HPLC to give the title compound as a white solid (0.004 g). LCMS *m/z* = 467.5 [M+H]<sup>+</sup>.

**Example 1.53: Preparation of 2-(((1*s*,4*s*)-4-((3-(3,4-difluorophenyl)-5-ethyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 284).**

**Step A: Preparation of *tert*-Butyl 2-(((1*s*,4*s*)-4-((3-(3,4-Difluorophenyl)-5-ethyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate.**

From 3,4-difluorophenylboronic acid and *tert*-butyl 2-(((1*s*,4*s*)-4-((3-bromo-5-ethyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate, using a similar method to the one described in **Example 1.52, Step E**, the title compound was obtained as a white solid. LCMS *m/z* = 525.5 [M+H]<sup>+</sup>.

**Step B: 2-(((1*s*,4*s*)-4-((3-(3,4-Difluorophenyl)-5-ethyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid.**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((3-(3,4-difluorophenyl)-5-ethyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate, using a similar method to the one described in **Example 1.52, Step F**, the title compound was obtained as a white solid. LCMS *m/z* = 469.5 [M+H]<sup>+</sup>.

**Example 1.54: Preparation of 2-(((1*s*,4*s*)-4-((5-Ethyl-3-(4-fluorophenyl)-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 164).**

**Step A: Preparation of *tert*-Butyl 2-(((1*s*,4*s*)-4-((5-Ethyl-3-(4-fluorophenyl)-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate.**

From 4-difluorophenylboronic acid and *tert*-butyl 2-(((1*s*,4*s*)-4-((3-bromo-5-ethyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate, using a similar method to the one described in **Example 1.52, Step E**, the title compound was obtained as a white solid. LCMS *m/z* = 507.4 [M+H]<sup>+</sup>.

**Step B: Preparation of 2-(((1*s*,4*s*)-4-((5-Ethyl-3-(4-fluorophenyl)-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid.**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((5-ethyl-3-(4-fluorophenyl)-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate, using a similar method to the one described in **Example 1.52, Step F**, the title compound was obtained as a white solid. LCMS *m/z* = 451.3 [M+H]<sup>+</sup>.

**Example 1.55: Preparation of 2-(((1*s*,4*s*)-4-((5-Ethyl-3-(2-fluoro-4-methoxyphenyl)-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 165).**

**Step A: Preparation of *tert*-Butyl 2-(((1*s*,4*s*)-4-((5-Ethyl-3-(2-fluoro-4-methoxyphenyl)-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate.**

To a solution of 2-fluoro-4-methoxyphenylboronic acid (0.021 g, 0.122 mmol), *tert*-butyl 2-(((1*s*,4*s*)-4-((3-bromo-5-ethyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate (0.060 g, 0.122 mmol), aq. Na<sub>2</sub>CO<sub>3</sub> (2 M solution, 0.122 mL, 0.244 mmol), and Pd(PPh<sub>3</sub>)<sub>4</sub> (0.004 g, 0.004 mmol) in EtOH (1.0 mL) and benzene (3.0 mL). The reaction mixture was then heated in a microwave at 130 °C for 1 h. Upon completion, the reaction mixture was quenched with H<sub>2</sub>O and extracted with EtOAc (2 ×). The combined organics layers were dried over MgSO<sub>4</sub>, filtered and concentrated to give the title compound as a yellow oil without further purification. LCMS *m/z* = 537.5 [M+H]<sup>+</sup>.

**Step B: Preparation of 2-(((1*s*,4*s*)-4-((5-Ethyl-3-(2-fluoro-4-methoxyphenyl)-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid**

To *tert*-butyl 2-(((1*s*,4*s*)-4-((5-ethyl-3-(2-fluoro-4-methoxyphenyl)-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate obtained was added 4 M HCl (0.610 mL, 2.44 mmol) in 1,4-dioxane. The reaction mixture was stirred at 40 °C for 6 h. The reaction mixture was concentrated and the residue was purified by HPLC to give the title compound (0.005 g) as a white solid. LCMS *m/z* = 481.2 [M+H]<sup>+</sup>.

**Example 1.56: Preparation of 2-(((1*s*,4*s*)-4-((5-Ethyl-3-(4-methoxyphenyl)-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 166).**

From 4-methoxyphenylboronic acid and *tert*-butyl 2-(((1*s*,4*s*)-4-((3-bromo-5-ethyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate, using a similar method to the one described in **Example 1.55**, the title compound was obtained as a white solid. LCMS *m/z* = 463.4 [M+H]<sup>+</sup>.

**Example 1.57: Preparation of 2-(((1*s*,4*s*)-4-((5-Ethyl-3-(2-fluoro-4-methylphenyl)-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 167).**

From 2-fluoro-4-methylphenylboronic acid and *tert*-butyl 2-(((1*s*,4*s*)-4-((3-bromo-5-ethyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate, using a similar method to the one described in **Example 1.55**, the title compound was obtained as a white solid. LCMS *m/z* = 465.2 [M+H]<sup>+</sup>.

**Example 1.58: Preparation of 2-(((1*s*,4*s*)-4-((5-Ethyl-4-phenyl-3-*p*-tolyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 168).**

From *p*-tolylboronic acid and *tert*-butyl 2-(((1*s*,4*s*)-4-((3-bromo-5-ethyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate, using a similar method to the one described in **Example 1.55**, the title compound was obtained as a white solid. LCMS *m/z* = 447.5 [M+H]<sup>+</sup>.

**Example 1.59: Preparation of 2-(((1*s*,4*s*)-4-((5-Ethyl-3-(4-hydroxyphenyl)-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 175).**

From 4-hydroxyphenylboronic acid and *tert*-butyl 2-(((1*s*,4*s*)-4-((3-bromo-5-ethyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate, using a similar method to the one described in **Example 1.55**, The title compound was obtained as a white solid. LCMS  $m/z$  = 449.3  $[M+H]^+$ .

**Example 1.60: Preparation of 2-(((1*s*,4*s*)-4-((3-(4-Chloro-3-fluorophenyl)-5-ethyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 176).**

From 4-chloro-3-fluorophenylboronic acid and *tert*-butyl 2-(((1*s*,4*s*)-4-((3-bromo-5-ethyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate, using a similar method to the one described in **Example 1.55**, The title compound was obtained as a white solid. LCMS  $m/z$  = 485.4  $[M+H]^+$ .

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**Example 1.61: Preparation of 2-(((1*s*,4*s*)-4-((4-(3-Methoxyphenyl)-3-phenyl-5-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 202).**

**Step A: Preparation of 3-Phenyl-5-propyl-1*H*-pyrazole.**

To a solution of acetophenone (4.87 mL, 41.6 mmol) in dry toluene (5.0 mL) cooled to 0 °C was added LiHMDS (41.6 mL, 41.6 mmol). The resulting mixture was stirred at 0 °C for 5 min before butyryl chloride (4.36 mL, 41.6 mmol) was added in portions. After the addition of the butyryl chloride, the ice bath was then removed before AcOH (2.0 mL) and EtOH (10.0 mL) were added to form a homogenous mixture, then hydrazine hydrate (3.03 mL, 62.4 mmol) was added. The resulting mixture was heated to reflux. After 30 min, the reaction mixture was quenched with 1.0 M NaOH solution, extracted with EtOAc and washed with brine. The combined organics were dried over MgSO<sub>4</sub>, filtered, and concentrated to give an orange oil. This orange oil was purified by silica gel flash chromatography to give the title compound as a yellow oil (3.83 g). LCMS  $m/z$  = 187.2  $[M+H]^+$ ; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  ppm 0.92 (t,  $J$  = 7.33 Hz, 3H), 1.58-1.71 (m, 2H), 2.57 (t,  $J$  = 7.58 Hz, 2H), 6.34 (s, 1H), 7.22-7.39 (m, 3H), 7.72 (d,  $J$  = 7.83 Hz, 2H).

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**Step B: Preparation of 4-Bromo-3-phenyl-5-propyl-1*H*-pyrazole.**

To a solution of 3-phenyl-5-propyl-1*H*-pyrazole (3.83 g, 20.56 mmol) in dichloromethane (118.0 mL) was added bromine (1.05 mL, 20.56 mmol) at 25 °C. The reaction mixture was stirred at room temperature for 16 h. The reaction mixture was then quenched with 2 M Na<sub>2</sub>CO<sub>3</sub> (aq.) to pH 12 and the organics were separated. The aqueous layer was extracted with DCM (thrice). The combined organics were washed with brine, dried over MgSO<sub>4</sub>, filtered and concentrated to give a red oil. This oil was purified by silica gel flash chromatography to

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give the title compound as a yellow oil (3.44 g). LCMS  $m/z$  = 265.1, 267.1  $[M+H]^+$ ;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  ppm 0.97 (t,  $J$  = 7.33 Hz, 3H), 1.63-1.74 (m, 2H), 2.57 (t,  $J$  = 7.58 Hz, 2H), 7.37-7.48 (m, 3H), 7.77-7.82 (m, 2H).

**Step C: Preparation of *tert*-Butyl 2-(((1*s*,4*s*)-4-((4-Bromo-3-phenyl-5-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate.**

To a solution of 4-bromo-3-phenyl-5-propyl-1*H*-pyrazole (1.00 g, 3.77 mmol) in DMF (13.0 mL) was slowly added 60% sodium hydride (0.181 g, 4.53 mmol). The solution was allowed to stir for a total of 20 min, before a mixture of *tert*-butyl 2-(((1*s*,4*s*)-4-(tosyloxymethyl)cyclohexyl)methoxy)acetate (1.556 g, 3.77 mmol) in DMF (2.0 mL) was added. The reaction mixture was then stirred at 45 °C for 12 h, quenched with water and extracted with EtOAc (4 times). The combined organics were dried over  $MgSO_4$ , filtered, and concentrated to give a brown oil. This brown oil was purified by silica gel flash chromatography to give the title compound as a yellow oil (1.501 g). LCMS  $m/z$  = 505.4, 507.4  $[M+H]^+$ ;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  ppm 1.02 (t,  $J$  = 7.45 Hz, 3H), 1.29-1.41 (m, 2H), 1.43-1.59 (m, 15H), 1.65 (d,  $J$  = 7.83 Hz, 2H), 1.82-1.94 (m, 1H), 2.13-2.24 (m, 1H), 2.66 (t,  $J$  = 7.83 Hz, 2H), 3.46 (d,  $J$  = 7.07 Hz, 2H), 3.95 (s, 2H), 4.00 (d,  $J$  = 7.58 Hz, 2H), 7.33 (d,  $J$  = 7.58 Hz, 1H), 7.40 (t,  $J$  = 7.45 Hz, 2H), 7.84-7.89 (m, 2H).

**Step D: Preparation of *tert*-Butyl 2-(((1*s*,4*s*)-4-((4-(3-Methoxyphenyl)-3-phenyl-5-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate.**

To a solution of 3-methoxyphenylboronic acid (0.029 g, 0.194 mmol), *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-phenyl-5-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate (0.098 g, 0.194 mmol), aq.  $Na_2CO_3$  (2 M solution, 0.194 mL, 0.388 mmol), and  $Pd(PPh_3)_4$  (0.004 g, 0.007 mmol) in EtOH (1.0 mL) and benzene (3.0 mL). The reaction mixture was then heated in a microwave at 130 °C for 1 h, quenched with  $H_2O$  and extracted with EtOAc (2  $\times$ ). The combined organics layers were dried over  $MgSO_4$ , filtered and concentrated to give the title compound as a yellow oil without purification. LCMS  $m/z$  = 533.4  $[M+H]^+$ .

**Step E: Preparation of 2-(((1*s*,4*s*)-4-((4-(3-Methoxyphenyl)-3-phenyl-5-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid.**

To *tert*-butyl 2-(((1*s*,4*s*)-4-((4-(3-methoxyphenyl)-3-phenyl-5-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate obtained was added 4 M HCl (0.969 mL, 3.88 mmol) in 1,4-dioxane. The resulting reaction mixture was stirred at 25 °C for 4 h. The reaction was concentrated to give a yellow oil. This yellow oil was purified by HPLC to give the title compound (0.026 g) as a white solid. LCMS  $m/z$  = 477.4  $[M+H]^+$ ;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  ppm 0.87 (t,  $J$  = 7.33 Hz, 3H), 1.33-1.62 (m, 9H), 1.86-1.97 (m, 1H), 2.17-2.29 (m, 1H), 2.54-2.62 (m, 2H), 3.50-3.55 (m, 2H), 3.72 (s, 3H), 3.86 (s, 1H), 4.02-4.13 (m, 4H), 6.70-6.86 (m, 3H), 7.15-7.27 (m, 4H), 7.34-7.43 (m, 2H).

**Example 1.62: Preparation of 2-(((1*s*,4*s*)-4-((4-(3-Fluorophenyl)-3-phenyl-5-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 203).**

From 3-fluorophenylboronic acid *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-phenyl-5-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate, using a similar method to the one described in **Example 1.61, Step D & E**, the title compound was obtained as a white solid. LCMS  $m/z = 465.2$   $[M+H]^+$ .

**Example 1.63: Preparation of 2-(((1*s*,4*s*)-4-((4-(3-Chlorophenyl)-3-phenyl-5-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 204).**

From 3-chlorophenylboronic acid and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-phenyl-5-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate, using a similar method to the one described in **Example 1.62**, the title compound was obtained as a white solid. LCMS  $m/z = 481.3$   $[M+H]^+$ .

**Example 1.64: Preparation of 2-(((1*s*,4*s*)-4-((3-Phenyl-5-propyl-4-*m*-tolyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 205).**

From *m*-tolylboronic acid and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-phenyl-5-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate, using a similar method to the one described in **Example 1.62**, the title compound was obtained as a white solid. LCMS  $m/z = 461.5$   $[M+H]^+$ .

**Example 1.65: Preparation of 2-(((1*s*,4*s*)-4-((4-(2-Fluoro-3-methoxyphenyl)-3-phenyl-5-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 206).**

From 2-fluoro-3-methoxyphenylboronic acid and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-phenyl-5-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate, using a similar method to the one described in **Example 1.62**, the title compound was obtained as a white solid. LCMS  $m/z = 495.5$   $[M+H]^+$ .

**Example 1.66: Preparation of 2-(((1*s*,4*s*)-4-((4-(2,3-Difluorophenyl)-3-phenyl-5-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 207).**

From 2,3-difluorophenylboronic acid and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-phenyl-5-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate, using a similar method to the one described in **Example 1.62**, the title compound was obtained as a white solid. LCMS  $m/z = 483.4$   $[M+H]^+$ .

**Example 1.67: Preparation of 2-(((1*s*,4*s*)-4-((4-(3-Chloro-2-fluorophenyl)-3-phenyl-5-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 208).**



From 3-chloro-2-fluorophenylboronic acid and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-phenyl-5-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate, using a similar method to the one described in **Example 1.62**, the title compound was obtained as a white solid. LCMS  $m/z = 499.7$   $[M+H]^+$ .

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**Example 1.68: Preparation of 2-(((1*s*,4*s*)-4-((4-(2-Fluoro-3-methylphenyl)-3-phenyl-5-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 209).**

From 2-fluoro-3-methylphenylboronic acid and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-phenyl-5-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate, using a similar method to the one described in **Example 1.62**, the title compound was obtained as a white solid. LCMS  $m/z = 479.6$   $[M+H]^+$ .

**Example 1.69: Preparation of 2-(((1*s*,4*s*)-4-((4-(2-Fluoro-3-hydroxyphenyl)-3-phenyl-5-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 211).**

From 2-fluoro-3-hydroxyphenylboronic acid and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-phenyl-5-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate, using a similar method to the one described in **Example 1.62**, the title compound was obtained as a white solid. LCMS  $m/z = 481.3$   $[M+H]^+$ .

**Example 1.70: Preparation of 2-(((1*s*,4*s*)-4-((5-(4-Fluorophenyl)-4-phenyl-3-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 223).**

**Step A: Preparation of 1-(Dimethylamino)-2-phenylhex-1-en-3-one.**

To a solution of 1-phenylpentan-2-one (5.00 g, 30.8 mmol) in dry DMF (80.0 mL) was added 1,1-dimethoxy-*N,N*-dimethylmethanamine (6.16 mL, 46.2 mmol). The resulting mixture was heated at 90 °C. After 16 h, the reaction mixture was quenched with water, extracted with EtOAc (3 ×) and washed with brine. The combined organics were dried over MgSO<sub>4</sub>, filtered, and concentrated to give a yellow oil. This yellow oil was purified by silica gel flash chromatography to give the title compound as a yellow oil (3.51 g). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 0.76-0.83 (m, 3H), 0.83-0.89 (m, 2H), 2.11-2.19 (m, 2H), 2.62-2.71 (m, 6H), 7.15-7.42 (m, 5H), 7.61 (s, 1H).

**Step B: Preparation of 4-Phenyl-5-propyl-1*H*-pyrazole.**

To a solution of 1-(dimethylamino)-2-phenylhex-1-en-3-one (3.51 g, 16.2 mmol) in ethanol (80.0 mL), was added hydrazine hydrate (1.57 mL, 32.4 mmol). The reaction mixture was stirred at 80 °C. After 3 h, the reaction mixture was cooled to room temperature, concentrated under reduced pressure and crystallized in 20% ethanol / H<sub>2</sub>O to give the title compound as a white solid (3.01 g). LCMS  $m/z = 187.1$   $[M+H]^+$ ; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 0.92-1.00 (m, 3H), 1.64-1.76 (m, 2H), 2.75-2.84 (m, 2H), 7.36-7.41 (m, 5H), 7.65 (s, 1H).

**Step C: Preparation of 3-Bromo-4-phenyl-5-propyl-1H-pyrazole.**

To a solution of 4-phenyl-5-propyl-1H-pyrazole (1.43 g, 7.68 mmol) in acetonitrile (38.0 mL), was added *N*-bromosuccinimide (1.50 g, 8.45 mmol). The reaction mixture was stirred at 82 °C. After 16 h, the reaction mixture was quenched with 2 M Na<sub>2</sub>CO<sub>3</sub> (aq.) to pH 12 and the organics were separated. The aqueous layer was extracted with EtOAc (3 ×). The combined organics were dried over MgSO<sub>4</sub>, filtered and concentrated to give a dark oil. This oil was purified by silica gel flash chromatography to give the title compound as a yellow oil (0.310 g). LCMS *m/z* = 265.1, 267.1 [M+H]<sup>+</sup>.

**Step D: Preparation of *tert*-Butyl 2-(((1*s*,4*s*)-4-((3-Bromo-4-phenyl-5-propyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-Butyl 2-(((1*s*,4*s*)-4-((5-Bromo-4-phenyl-3-propyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate.**

To a solution of 3-bromo-4-phenyl-5-propyl-1H-pyrazole (0.940 g, 3.55 mmol) in DMF (12.0 mL), was slowly added 60% sodium hydride (0.170 g, 4.25 mmol). The solution was stirred for a total of 20 min, before a mixture of *tert*-butyl 2-(((1*s*,4*s*)-4-(tosyloxymethyl)cyclohexyl)methoxy)acetate (1.463 g, 3.55 mmol) in DMF (2.0 mL) was added. The reaction mixture was then stirred at 45 °C for 12 h, quenched with water and extracted with EtOAc (4 ×). The combined organics were dried over MgSO<sub>4</sub>, filtered, and concentrated to give a brown oil. This brown oil was purified by silica gel flash chromatography to give a mixture of regioisomers, the title compounds as a yellow oil (1.219 g). LCMS *m/z* = 505.4 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 0.85 (t, *J* = 7.33 Hz, 3H), 1.32-1.63 (m, 18H), 1.76-1.93 (m, 2H), 2.17-2.29 (m, 1H), 2.56-2.64 (m, 2H), 3.45 (d, *J* = 6.82 Hz, 2H), 3.95 (s, 2H), 4.05-4.14 (m, 2H), 7.28-7.35 (m, 3H), 7.36-7.43 (m, 2H).

**Step E: Preparation of *tert*-Butyl 2-(((1*s*,4*s*)-4-((5-(4-Fluorophenyl)-4-phenyl-3-propyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-Butyl 2-(((1*s*,4*s*)-4-((3-(4-Fluorophenyl)-4-phenyl-5-propyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate.**

To a solution of 4-fluorophenylboronic acid (0.032 g, 0.231 mmol), a mixture of regioisomers, *tert*-butyl 2-(((1*s*,4*s*)-4-((3-bromo-4-phenyl-5-propyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((5-bromo-4-phenyl-3-propyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate (0.117 g, 0.231 mmol), aq. Na<sub>2</sub>CO<sub>3</sub> (2 M solution, 0.231 mL, 0.463 mmol), and Pd(PPh<sub>3</sub>)<sub>4</sub> (0.008 g, 0.007 mmol) in EtOH (1.0 mL) and benzene (3.0 mL). The reaction mixture was then heated under microwave at 130 °C for 1 h, quenched with H<sub>2</sub>O and extracted with EtOAc (2 ×). The combined organics layers were dried over MgSO<sub>4</sub>, filtered and concentrated to give a mixture of regioisomers, the title compounds as a yellow oil without further purification. LCMS *m/z* = 521.7 [M+H]<sup>+</sup>.

**Step F: Preparation of 2-(((1*s*,4*s*)-4-((5-(4-Fluorophenyl)-4-phenyl-3-propyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid.**

To a mixture of regioisomers, *tert*-Butyl 2-(((1*s*,4*s*)-4-((5-(4-Fluorophenyl)-4-phenyl-3-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-Butyl 2-(((1*s*,4*s*)-4-((3-(4-Fluorophenyl)-4-phenyl-5-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate obtained was added 4 M HCl (1.16 mL, 4.63 mmol) in 1,4-dioxane. The resulting reaction mixture was stirred at 25 °. After 4 h, the reaction mixture concentrated to give a yellow oil. This yellow oil was purified by HPLC to give the title compound (0.019 g) as a white solid. LCMS  $m/z$  = 465.3  $[M+H]^+$ .

**Example 1.71: Preparation of 2-(((1*s*,4*s*)-4-((3-(4-Fluorophenyl)-4-phenyl-5-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 224).**

From a mixture of regioisomers, *tert*-butyl 2-(((1*s*,4*s*)-4-((5-(4-fluorophenyl)-4-phenyl-3-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((3-(4-fluorophenyl)-4-phenyl-5-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate, using a similar method to the one described in **Example 1.70, Step F**, the title compound was obtained as a second isomer. LCMS  $m/z$  = 465.3  $[M+H]^+$ ;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  ppm 0.87 (t,  $J$  = 7.26 Hz, 3H), 1.16-1.30 (m, 1H), 1.33-1.68 (m, 8H), 1.94 (s, 2H), 2.21 (s, 1H), 2.52-2.64 (m, 2H), 3.53 (d,  $J$  = 6.95 Hz, 2H), 3.97-4.19 (m, 4H), 6.91 (t,  $J$  = 8.72 Hz, 2H), 7.13-7.19 (m, 2H), 7.28-7.39 (m, 5H).

**Example 1.72: Preparation of 2-(((1*s*,4*s*)-4-((5-(4-Chloro-3-fluorophenyl)-4-phenyl-3-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 225).**

From 4-chloro-3-fluorophenylboronic acid and a mixture of regioisomers, *tert*-butyl 2-(((1*s*,4*s*)-4-((3-bromo-4-phenyl-5-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((5-bromo-4-phenyl-3-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate, using a similar method to the one described in **Example 1.70, Step E & F**, the title compound was obtained as a white solid. LCMS  $m/z$  = 499.6  $[M+H]^+$ .

**Example 1.73: Preparation of 2-(((1*s*,4*s*)-4-((3-(4-Chloro-3-fluorophenyl)-4-phenyl-5-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 226).**

From 4-chloro-3-fluorophenylboronic acid and a mixture of regioisomers, *tert*-butyl 2-(((1*s*,4*s*)-4-((3-bromo-4-phenyl-5-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((5-bromo-4-phenyl-3-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate, using a similar method to the one described in **Example 1.72**, the title compound was obtained as an isomer. LCMS  $m/z$  = 499.7  $[M+H]^+$ .

**Example 1.74: Preparation of 2-(((1*s*,4*s*)-4-((5-(4-Chlorophenyl)-4-phenyl-3-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 227).**

From 4-chlorophenylboronic acid and a mixture of regioisomers, *tert*-butyl 2-(((1*s*,4*s*)-4-((3-bromo-4-phenyl-5-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((5-bromo-4-phenyl-3-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate, using a similar method to the one described in **Example 1.72**, the title compound was obtained as a white solid. LCMS  $m/z = 481.2$   $[M+H]^+$ .

**Example 1.75: Preparation of 2-(((1*s*,4*s*)-4-((3-(4-Chlorophenyl)-4-phenyl-5-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 228).**

From 4-chlorophenylboronic acid and a mixture of regioisomers, *tert*-butyl 2-(((1*s*,4*s*)-4-((3-bromo-4-phenyl-5-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((5-bromo-4-phenyl-3-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate, using a similar method to the one described in **Example 1.72**, the title compound was obtained as a white solid. LCMS  $m/z = 481.4$   $[M+H]^+$ .

**Example 1.76: Preparation of 2-(((1*s*,4*s*)-4-((5-(3,4-Difluorophenyl)-4-phenyl-3-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 229).**

From 3,4-difluorophenylboronic acid and a mixture of regioisomers, *tert*-butyl 2-(((1*s*,4*s*)-4-((3-bromo-4-phenyl-5-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((5-bromo-4-phenyl-3-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate, using a similar method to the one described in **Example 1.72**, the title compound was obtained as a white solid. LCMS  $m/z = 483.4$   $[M+H]^+$ .

**Example 1.77: Preparation of 2-(((1*s*,4*s*)-4-((3-(3,4-Difluorophenyl)-4-phenyl-5-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 230).**

From 3,4-difluorophenylboronic acid and a mixture of regioisomers, *tert*-butyl 2-(((1*s*,4*s*)-4-((3-bromo-4-phenyl-5-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((5-bromo-4-phenyl-3-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate, using a similar method to the one described in **Example 1.72**, the title compound was obtained as a white solid. LCMS  $m/z = 483.4$   $[M+H]^+$ .

**Example 1.78: Preparation of 2-(((1*s*,4*s*)-4-((5-(2-Fluoro-4-methoxyphenyl)-4-phenyl-3-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 231).**

From 2-fluoro-4-methoxyphenylboronic acid and a mixture of regioisomers, *tert*-butyl 2-(((1*s*,4*s*)-4-((3-bromo-4-phenyl-5-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((5-bromo-4-phenyl-3-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate, using a similar method to the one described in **Example 1.72**, the title compound was obtained as a white solid. LCMS  $m/z = 495.6$   $[M+H]^+$ .

**Example 1.79: Preparation of 2-(((1*s*,4*s*)-4-((3-(2-Fluoro-4-methoxyphenyl)-4-phenyl-5-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 232).**

From 2-fluoro-4-methoxyphenylboronic acid and a mixture of regioisomers, *tert*-butyl 2-(((1*s*,4*s*)-4-((3-bromo-4-phenyl-5-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((5-bromo-4-phenyl-3-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate, using a similar method to the one described in **Example 1.72**, the title compound was obtained as a white solid. LCMS  $m/z$  = 495.5 [M+H]<sup>+</sup>.

**Example 1.80: Preparation of 2-(((1*s*,4*s*)-4-((5-(4-Methoxyphenyl)-4-phenyl-3-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 233).**

From 4-methoxyphenylboronic acid and a mixture of regioisomers, *tert*-butyl 2-(((1*s*,4*s*)-4-((3-bromo-4-phenyl-5-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((5-bromo-4-phenyl-3-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate, using a similar method to the one described in **Example 1.72**, the title compound was obtained as a white solid. LCMS  $m/z$  = 477.4 [M+H]<sup>+</sup>.

**Example 1.81: Preparation of 2-(((1*s*,4*s*)-4-((3-(4-Methoxyphenyl)-4-phenyl-5-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 234).**

From 4-methoxyphenylboronic acid and a mixture of regioisomers, *tert*-butyl 2-(((1*s*,4*s*)-4-((3-bromo-4-phenyl-5-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((5-bromo-4-phenyl-3-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate, using a similar method to the one described in **Example 1.72**, the title compound was obtained as a white solid. LCMS  $m/z$  = 477.5 [M+H]<sup>+</sup>.

**Example 1.82: Preparation of 2-(((1*s*,4*s*)-4-((5-(2-Fluoro-4-methylphenyl)-4-phenyl-3-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 235).**

From 2-fluoro-4-methylphenylboronic acid and a mixture of regioisomers, *tert*-butyl 2-(((1*s*,4*s*)-4-((3-bromo-4-phenyl-5-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((5-bromo-4-phenyl-3-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate, using a similar method to the one described in **Example 1.72**, the title compound was obtained as a white solid. LCMS  $m/z$  = 479.5 [M+H]<sup>+</sup>.

**Example 1.83: Preparation of 2-(((1*s*,4*s*)-4-((3-(2-Fluoro-4-methylphenyl)-4-phenyl-5-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 236).**

From 2-fluoro-4-methylphenylboronic acid and a mixture of regioisomers, *tert*-butyl 2-(((1*s*,4*s*)-4-((3-bromo-4-phenyl-5-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate

and *tert*-butyl 2-(((1*s*,4*s*)-4-((5-bromo-4-phenyl-3-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate, using a similar method to the one described in **Example 1.72**, the title compound was obtained as a white solid. LCMS  $m/z$  = 479.4  $[M+H]^+$ .

**5 Example 1.84: Preparation of 2-(((1*s*,4*s*)-4-((5-(Cyanomethylthio)-4-phenyl-3-*p*-tolyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 257).**

**Step A: Preparation of 2-(1,3-Dithietan-2-ylidene)-2-phenyl-1-*p*-tolylethanone**

To a solution of 2-phenyl-1-*p*-tolylethanone (3.00 g, 14.27 mmol) in THF (50.0 mL) was added KOtBu (30.0 mL, 30.0 mmol), CS<sub>2</sub> (0.862 mL, 14.27 mmol) and dibromomethane  
10 (0.994 mL, 14.27 mmol). The reaction was stirred at 25 °C for 12 h, quenched with water (40.0 mL) and extracted with EtOAc (3 × 50.0 mL). The combined organics were dried over MgSO<sub>4</sub>, filtered, and concentrated to give the title compound as a brown oil without further purification. LCMS  $m/z$  = 299.2  $[M+H]^+$ .

**15 Step B: Preparation of A Mixture of 4-Phenyl-3-*p*-tolyl-1*H*-pyrazole-5(4*H*)-thione and 1,2-Bis(4-phenyl-3-*p*-tolyl-1*H*-pyrazol-5-yl)disulfane.**

To a solution of 2-(1,3-dithietan-2-ylidene)-2-phenyl-1-*p*-tolylethanone dissolved in isopropanol (25.0 mL) was added hydrazine (7.00 mL, 143.0 mmol). The reaction was stirred at 100 °C for 16 h. After cooling to room temperature, a precipitate was formed. The precipitate was filtered and washed with isopropanol and dried under reduced pressure to give the title  
20 compounds as a mixture of 4-phenyl-3-*p*-tolyl-1*H*-pyrazole-5(4*H*)-thione and 1,2-bis(4-phenyl-3-*p*-tolyl-1*H*-pyrazol-5-yl)disulfane as a white solid (2.24 g). LCMS  $m/z$  = 267.2  $[M+H]^+$ ; 531.3  $[M+H]^+$ ; <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  ppm 2.31 (s, 3H), 7.04 (d,  $J$  = 7.58 Hz, 2H), 7.10-7.16 (m, 1H), 7.17-7.27 (m, 5H), 7.39 (d,  $J$  = 7.33 Hz, 2H).

**Step C: Preparation of 2-(4-Phenyl-3-*p*-tolyl-1*H*-pyrazol-5-ylthio)acetonitrile.**

To a mixture of 4-phenyl-3-*p*-tolyl-1*H*-pyrazole-5(4*H*)-thione and 1,2-bis(4-phenyl-3-*p*-tolyl-1*H*-pyrazol-5-yl)disulfane (0.500 g, 1.88 mmol) in DMF (12.5 mL) was added 2-bromoacetonitrile (0.125 mL, 1.88 mmol) and K<sub>2</sub>CO<sub>3</sub> (0.259 g, 1.88 mmol). The reaction was stirred at 25 °C for 72 h, quenched with water (40.0 mL) and extracted with EtOAc (4 × 50.0 mL) and washed with brine. The combined organics were dried over MgSO<sub>4</sub>, filtered, and  
30 concentrated to give the title compound as a yellow oil (0.547 g). LCMS  $m/z$  = 306.2  $[M+H]^+$ .

**Step C: Preparation of *tert*-Butyl 2-(((1*s*,4*s*)-4-((5-(Cyanomethylthio)-4-phenyl-3-*p*-tolyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate.**

To a solution of 2-(4-phenyl-3-*p*-tolyl-1*H*-pyrazol-5-ylthio)acetonitrile (0.250 g, 0.819 mmol) in anhydrous DMF (4.0 mL) was added cesium carbonate (0.533 g, 1.64 mmol) and *tert*-butyl 2-(((1*s*,4*s*)-4-(tosyloxymethyl)cyclohexyl)methoxy)acetate (0.338 g, 0.819 mmol) in DMF  
35 (1.0 mL). The reaction was heated at 80 °C for 1 h, quenched with water and extracted with

EtOAc (2 ×). The combined organics were dried over MgSO<sub>4</sub>, filtered, and concentrated to give the title compound as a yellow oil without further purification. LCMS *m/z* = 546.4 [M+H]<sup>+</sup>.

**Step D: Preparation of 2-(((1*s*,4*s*)-4-((5-(Cyanomethylthio)-4-phenyl-3-*p*-tolyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid.**

5 To *tert*-butyl 2-(((1*s*,4*s*)-4-((5-(cyanomethylthio)-4-phenyl-3-*p*-tolyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate obtained above was added 4 M HCl (4.09 mL, 16.37 mmol) in 1,4-dioxane. The reaction was stirred at 25 °C for 16 h and concentrated to give a yellow oil. This yellow oil was purified by HPLC to give the title compound as a white solid (0.013 g). LCMS *m/z* = 490.5 [M+H]<sup>+</sup>.

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**Example 1.85: Preparation of 2-(((1*r*,4*r*)-4-((3-(Cyanomethylthio)-4-(3-methoxyphenyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 245).**

**Step A: Preparation of 2-(4-(3-Methoxyphenyl)-3-phenyl-1*H*-pyrazol-5-ylthio)acetonitrile.**

15 To a solution of 4-(3-methoxyphenyl)-3-phenyl-1*H*-pyrazole-5(4*H*)-thione (0.200 g, 0.708 mmol) in DMF (5.0 mL) was added 2-bromoacetonitrile (0.047 mL, 0.708 mmol) and K<sub>2</sub>CO<sub>3</sub> (0.098 g, 0.708 mmol). The mixture was stirred at 25 °C for 72 h, quenched with water (40.0 mL), extracted with EtOAc (4 × 50.0 mL) and washed with brine. The combined organics were dried over MgSO<sub>4</sub>, filtered, and concentrated to give a brown oil. This brown oil was  
20 purified by silica gel flash chromatography to give the title compound as a white solid (0.158 g). LCMS *m/z* = 332.3 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 3.67 (s, 2H), 3.74 (s, 3H), 6.82-6.89 (m, 3H), 7.23-7.29 (m, 1H), 7.34 (s, 5H).

**Step B: Preparation of *tert*-Butyl 2-(((1*r*,4*r*)-4-((3-(Cyanomethylthio)-4-(3-methoxyphenyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-Butyl  
25 2-(((1*s*,4*s*)-4-((5-(Cyanomethylthio)-4-(3-methoxyphenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate**

To a solution of 2-(4-(3-methoxyphenyl)-3-phenyl-1*H*-pyrazol-5-ylthio)acetonitrile (0.158 g, 0.492 mmol) in DMF (2.0 mL) at 0 °C was slowly added 60% sodium hydride (0.022 g, 0.541 mmol). The solution was allowed to stir for a total of 20 min, before a mixture of *tert*-butyl 2-  
30 (((1*s*,4*s*)-4-(tosyloxymethyl)cyclohexyl)methoxy)acetate (0.203 g, 0.492 mmol) in DMF (1.0 mL) was added. The reaction mixture was then stirred at 40 °C for 16 h, quenched with water and extracted with EtOAc (2 ×). The combined organics were dried over MgSO<sub>4</sub>, filtered, and concentrated to give a mixture of *tert*-butyl 2-(((1*r*,4*r*)-4-((3-(cyanomethylthio)-4-(3-methoxyphenyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-  
35 (((1*s*,4*s*)-4-((5-(cyanomethylthio)-4-(3-methoxyphenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate without further purification. LCMS *m/z* = 562.4 [M+H]<sup>+</sup>.

**Step C: Preparation of 2-(((1*r*,4*r*)-4-((3-(Cyanomethylthio)-4-(3-methoxyphenyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid.**

To the mixture of *tert*-butyl 2-(((1*r*,4*r*)-4-((3-(cyanomethylthio)-4-(3-methoxyphenyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((5-(cyanomethylthio)-4-(3-methoxyphenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate obtained above was added 4 M HCl (2.46 mL, 9.83 mmol) in 1,4-dioxane. The reaction was stirred at 25 °C for 16 h and concentrated to give a yellow oil. This yellow oil was purified by HPLC to give the title compound (0.042 g) as a white solid. LCMS  $m/z$  = 506.5 [M+H]<sup>+</sup>.

10

**Example 1.86: Preparation of 2-(((1*s*,4*s*)-4-((5-(Cyanomethylthio)-4-(3-methoxyphenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 246).**

From a mixture of regioisomers *tert*-butyl 2-(((1*r*,4*r*)-4-((3-(cyanomethylthio)-4-(3-methoxyphenyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((5-(cyanomethylthio)-4-(3-methoxyphenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate, using a similar method to the one described in **Example 1.85, Step C**, the title compound was also isolated as a white solid. LCMS  $m/z$  = 506.4 [M+H]<sup>+</sup>.

15

**Example 1.87: Preparation of 2-(((1*s*,4*s*)-4-((5-(Cyanomethylthio)-3-(4-fluorophenyl)-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 258).**

20

From 1-(4-fluorophenyl)-2-phenylethanone, using a similar method to the one described in **Example 1.85**, the title compound was obtained as a white solid. LCMS  $m/z$  = 494.5 [M+H]<sup>+</sup>.

**Example 1.88: Preparation of 2-(((1*s*,4*s*)-4-((4-(3-Chlorophenyl)-5-(cyanomethylthio)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 275).**

25

From 2-(3-chlorophenyl)-1-phenylethanone, using a similar method to the one described in **Example 1.85**, the title compound was obtained as a white solid. LCMS  $m/z$  = 510.3 [M+H]<sup>+</sup>.

**Example 1.89: Preparation of 2-(((1*r*,4*r*)-4-((3-(2-Amino-2-oxoethoxy)-4-(3-methoxyphenyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 277).**

30

**Step A: Preparation of 2-(3-Phenyl-1*H*-pyrazol-5-yloxy)acetonitrile**

To a solution of 3-phenyl-1*H*-pyrazol-5(4*H*)-one (1.00 g, 6.24 mmol) in DMF (5.0 mL) was added 2-bromoacetonitrile (0.520 mL, 7.80 mmol) and K<sub>2</sub>CO<sub>3</sub> (0.863 g, 6.24 mmol). The reaction was stirred at 25 °C for 12 h, quenched with water (40.0 mL), extracted with EtOAc (3 × 50.0 mL) and washed with brine. The combined organics were dried over MgSO<sub>4</sub>, filtered, and concentrated to give the title compound as a yellow oil. This yellow oil was purified by

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silica gel flash chromatography to give the title compound as a clear oil (0.990 g). LCMS  $m/z$  = 200.3  $[M+H]^+$ .

**Step B: Preparation of 2-(4-Bromo-3-phenyl-1H-pyrazol-5-yloxy)acetonitrile.**

To a solution of 2-(3-phenyl-1H-pyrazol-5-yloxy)acetonitrile (0.500 g, 2.51 mmol) in  
5 dichloromethane (15.0 mL), was added bromine (0.129 mL, 2.51 mmol) at 25 °C. The reaction  
was stirred at room temperature for 1 h and quenched with 2 M Na<sub>2</sub>CO<sub>3</sub> (aq.) to pH 12. The  
organics were separated. The aqueous layer was extracted with DCM (3 ×). The combined  
organics were washed with brine, dried (MgSO<sub>4</sub>), filtered and concentrated to give a red oil.  
This oil was purified by silica gel flash chromatography to give the title compound as a yellow  
10 solid (0.360 g). LCMS  $m/z$  = 278.1, 280.2  $[M+H]^+$ ; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 5.21  
(s, 2H), 7.39-7.61 (m, 3H), 7.70-7.77 (m, 2H), 13.04 (s, 1H).

**Step C: Preparation of *tert*-Butyl 2-(((1*s*,4*s*)-4-((4-Bromo-5-(cyanomethoxy)-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-Butyl 2-(((1*s*,4*s*)-4-((4-Bromo-3-(cyanomethoxy)-5-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate.**

To a solution of 2-(4-bromo-3-phenyl-1H-pyrazol-5-yloxy)acetonitrile (0.570 g, 2.50  
15 mmol) in anhydrous DMF (18.0 mL) was added cesium carbonate (1.34 g, 4.10 mmol) and a  
mixture of *tert*-butyl 2-(((1*s*,4*s*)-4-(tosyloxymethyl)cyclohexyl)methoxy)acetate (0.846 g, 2.50  
mmol) in DMF (2.0 mL). The reaction was heated at 80 °C for 1 h, quenched with water and  
extracted with EtOAc (3 ×). The combined organics were dried over MgSO<sub>4</sub>, filtered, and  
20 concentrated to give a yellow oil. This oil was purified by silica gel flash chromatography to  
give the title compound as a clear oil (0.386 g). LCMS  $m/z$  = 518.4, 520.5  $[M+H]^+$ ; <sup>1</sup>H NMR  
(400 MHz, CDCl<sub>3</sub>) δ ppm 1.09-1.22 (m, 1H), 1.28-1.57 (m, 13H), 1.61 (s, 1H), 1.69-1.91 (m,  
2H), 1.95-2.08 (m, 1H), 2.45 (s, 2H), 3.26 (d, *J* = 6.82 Hz, 1H), 3.36 (d, *J* = 6.82 Hz, 1H), 3.83-  
3.97 (m, 3H), 4.97 (d, 2H), 7.31-7.38 (m, 2H), 7.45-7.51 (m, 1H), 7.78 (d, *J* = 8.34 Hz, 2H).

**Step D: Preparation of *tert*-Butyl 2-(((1*s*,4*s*)-4-((3-(Cyanomethoxy)-4-(3-methoxyphenyl)-5-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-Butyl 2-(((1*s*,4*s*)-4-((5-(Cyanomethoxy)-4-(3-methoxyphenyl)-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate.**

To a solution of 3-methoxyphenylboronic acid (0.019 g, 0.123 mmol), *tert*-butyl 2-(((1*s*,4*s*)-  
30 4-((4-bromo-5-(cyanomethoxy)-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate  
(0.064 g, 0.123 mmol), aq. Na<sub>2</sub>CO<sub>3</sub> (2 M solution, 0.123 mL, 0.247 mmol), and Pd(PPh<sub>3</sub>)<sub>4</sub> (0.004 g,  
0.004 mmol) in EtOH (1.0 mL) and benzene (3.0 mL). The reaction mixture was then heated in a  
microwave at 130 °C for 1 h, quenched with H<sub>2</sub>O and extracted with EtOAc (2 ×). The combined  
organics layers were dried over MgSO<sub>4</sub>, filtered and concentrated to give the title compounds as a  
35 dark solid mixture without further purification. LCMS  $m/z$  = 546.5  $[M+H]^+$ .

**Step E: Preparation of 2-(((1*s*,4*s*)-4-((3-(2-Amino-2-oxoethoxy)-4-(3-methoxyphenyl)-5-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid.**

To *tert*-butyl 2-(((1*r*,4*r*)-4-((3-(2-Amino-2-oxoethoxy)-4-(3-methoxyphenyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((5-(2-Amino-2-oxoethoxy)-4-(3-methoxyphenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate obtained was added 4 M HCl (0.309 mL, 1.23 mmol) in 1,4-dioxane. The reaction was stirred at 25 °C for 16 h, and concentrated to give a yellow oil. This yellow oil was purified by HPLC to give the title compound (0.004 g) as a white solid. LCMS  $m/z$  = 508.3 [M+H]<sup>+</sup>.

**Example 1.90: Preparation of 2-(((1*s*,4*s*)-4-((5-(2-Amino-2-oxoethoxy)-4-(3-methoxyphenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 278).**

From the same mixture of *tert*-butyl 2-(((1*s*,4*s*)-4-((3-(cyanomethoxy)-4-(3-methoxyphenyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((5-(cyanomethoxy)-4-(3-methoxyphenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate obtained, using a similar method to the one described in **Example 1.89, Step E**, the title compound was also isolated as a white solid. LCMS  $m/z$  = 509.4 [M+H]<sup>+</sup>.

**Example 1.91: Preparation of 2-(((1*r*,4*r*)-4-((3-(2-Amino-2-oxoethoxy)-4-(2-fluoro-3-methoxyphenyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 279).**

From 2-fluoro-3-methoxyphenylboronic acid and a mixture of *tert*-Butyl 2-(((1*s*,4*s*)-4-((4-Bromo-5-(cyanomethoxy)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-Butyl 2-(((1*s*,4*s*)-4-((4-Bromo-3-(cyanomethoxy)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate, using a similar method to the one described in **Example 1.89, Step D&E**, the title compound was obtained as a white solid. LCMS  $m/z$  = 526.8 [M+H]<sup>+</sup>.

**Example 1.92: Preparation of 2-(((1*s*,4*s*)-4-((5-(2-Amino-2-oxoethoxy)-4-(2-fluoro-3-methoxyphenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 280).**

From 2-fluoro-3-methoxyphenylboronic acid and a mixture of *tert*-butyl 2-(((1*s*,4*s*)-4-((4-Bromo-5-(cyanomethoxy)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-Bromo-3-(cyanomethoxy)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate, using a similar method to the one described in **Example 1.89, Step D&E**, the title compound was obtained as a white solid. LCMS  $m/z$  = 527.6 [M+H]<sup>+</sup>.

**Example 1.93: Preparation of 2-(((1*s*,4*s*)-4-((5-(Cyanomethoxy)-4-(3-methoxyphenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 283).**

From 3-methoxyphenylboronic acid, using a similar method to the one described in Example 1.89, Step D&E, the title compound was obtained as a white solid. LCMS  $m/z$  = 490.5  $[M+H]^+$ .

**Example 1.94: Preparation of 2-(((1*s*,4*s*)-4-((4-Benzhydryl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 17).**

A mixture of 4-benzhydryl-1*H*-pyrazole (30 mg, 0.128 mmol), *tert*-butyl 2-(((1*s*,4*s*)-4-((methylsulfonyloxy)methyl)cyclohexyl)methoxy)acetate (43.1 mg, 0.128 mmol), potassium *tert*-butoxide (28.7 mg, 0.256 mmol) and 18-Crown-6 (6.77 mg, 0.026 mmol) was stirred at room temperature overnight. The mixture was purified by preparative LCMS to give the title compound (one of the two regioisomers separated). LCMS  $m/z$  = 419.3  $[M+H]^+$ ;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  ppm 7.36-7.27 (m, 5H), 7.23 (m, 2H), 7.17 (m, 4H), 7.03 (s, 1H), 5.34 (s, 1H), 4.07 (m, 4H), 3.46 (d, 2H,  $J$  = 5.6 Hz), 2.06 (m, 1H), 1.85 (m, 1H), 1.58-1.44 (m, 6H), 1.28 (m, 2H).

**Example 1.95: Preparation of 2-(((1*r*,4*r*)-4-((4-Benzhydryl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 18).**

A mixture of 4-benzhydryl-1*H*-pyrazole (30 mg, 0.128 mmol), *tert*-butyl 2-(((1*s*,4*s*)-4-((methylsulfonyloxy)methyl)cyclohexyl)methoxy)acetate (43.1 mg, 0.128 mmol), potassium *tert*-butoxide (28.7 mg, 0.256 mmol) and 18-Crown-6 (6.77 mg, 0.026 mmol) was stirred at room temperature overnight. The mixture was purified by preparative LCMS to give the title compound (one of the two regioisomers separated). LCMS  $m/z$  = 419.3  $[M+H]^+$ ;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  ppm 7.31-7.27 (m, 5H), 7.23 (d, 2H,  $J$  = 7 Hz), 7.17 (m, 4H), 6.97 (s, 1H), 5.34 (s, 1H), 4.08 (s, 2H), 3.93 (d, 2H,  $J$  = 6.8 Hz), 3.36 (d, 2H,  $J$  = 6.3 Hz), 1.83 (m, 3H), 1.63 (m, 3H), 0.99 (m, 4H).

**Example 1.96: Preparation of 2-(((1*s*,4*s*)-4-((3,4-Diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 3).**

A mixture of 3,4-diphenyl-1*H*-pyrazole (50 mg, 0.227 mmol), *tert*-butyl 2-(((1*s*,4*s*)-4-((methylsulfonyloxy)methyl)cyclohexyl)methoxy)acetate (76 mg, 0.227 mmol), potassium *tert*-butoxide (76 mg, 0.681 mmol) and 18-Crown-6 (12.00 mg, 0.045 mmol) in DMF (2 mL) was stirred at 25 °C for 18 h. The mixture was purified by HPLC to give the title compound. LCMS  $m/z$  = 405.3  $[M+H]^+$ ;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  ppm 7.47 (m, 3H), 7.30 (m, 4H), 7.26 (m, 4H), 4.16 (d, 2H,  $J$  = 7.6 Hz), 4.11 (s, 2H), 3.50 (d, 2H,  $J$  = 6.8 Hz), 2.22 (m, 1H), 1.90 (m, 1H), 1.58 (m, 6H), 1.40 (m, 2H).

**Example 1.97: Preparation of 2-(((1*s*,4*s*)-4-((3-Methyl-5-phenyl-4-*m*-tolyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 19).**

**Step A: Preparation of (1*s*,4*s*)-Diethyl Cyclohexane-1,4-dicarboxylate.**

5 To a solution of (1*s*,4*s*)-cyclohexane-1,4-dicarboxylic acid (25 g, 145 mmol) in ethanol (150 mL) was added concentrated H<sub>2</sub>SO<sub>4</sub> (1 mL). The reaction was refluxed for 16 h, cooled to room temperature and concentrated. The residue was extracted with EtOAc and saturated NaHCO<sub>3</sub>, washed with brine, dried over MgSO<sub>4</sub>, and filtered. The filtrate was concentrated to provide the title compound as a colorless oil (30.5 g). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 1.25  
10 (t, *J* = 7.14 Hz, 6H), 1.64-1.70 (m, 4H), 1.87-1.92 (m, 4H), 2.44-2.46 (m, 2H), 4.11-1.46 (quartet, *J* = 7.12 Hz, 4H).

**Step B: Preparation of (1*s*,4*s*)-Cyclohexane-1,4-diyl dimethanol.**

To a solution of (1*s*,4*s*)-diethyl cyclohexane-1,4-dicarboxylate (13.0 g, 56.9 mmol) in THF (500 mL) was added lithium aluminum hydride (4.54 g, 120 mmol) in portions at 0 °C. The mixture  
15 was stirred at that temperature for 2 h and quenched with cold water, filtered and concentrated to give the title compound as colorless oil (8.2 g). <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.27-1.42 (m, 8H), 1.46-1.54 (m, 2H), 3.26-3.31 (m, 4H), 4.27-4.30 (t, *J* = 5.31 Hz, 2H).

**Step C: Preparation of *tert*-Butyl 2-(((1*s*,4*s*)-4-(Hydroxymethyl)cyclohexyl)methoxy)acetate.**

20 To a solution of (1*s*,4*s*)-cyclohexane-1,4-diyl dimethanol (18.2 g, 126 mmol) in toluene (200 mL) was added NaOH (50% aq., 60 mL) and tetrabutylammonium iodide (2.331 g, 6.31 mmol), followed by *tert*-butyl-2-bromoacetate (20.50 mL, 139 mmol) at room temperature. The reaction mixture was stirred violently at room temperature for 2 h and diluted with ethyl acetate and water. After separation, the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic  
25 layers were dried over MgSO<sub>4</sub>, concentrated, and purified by silica gel column chromatography to give the title compound as colorless oil (13.5 g). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 1.35-1.47 (m, 4H), 1.48 (s, 9H), 1.50-1.60 (m, 4H), 1.63-1.74 (m, 1H), 1.79-1.92 (m, 1H), 3.42 (d, *J* = 6.95 Hz, 2H), 3.55 (d, *J* = 6.82 Hz, 2H), 3.93 (s, 1H), 3.94 (s, 2H).

**Step D: Preparation of *tert*-Butyl 2-(((1*s*,4*s*)-4-(Tosyloxymethyl)cyclohexyl)methoxy)acetate.**

30 To a solution of *tert*-butyl 2-(((1*s*,4*s*)-4-(hydroxymethyl)cyclohexyl)methoxy)acetate (12.0 g, 46.4 mmol) in dichloromethane (150 mL) were added triethylamine (4.70 g, 46.4 mmol) and 4-(dimethylamino)pyridine (0.567 g, 4.64 mmol), followed by 4-methylbenzene-1-sulfonyl chloride (8.86 g, 46.4 mmol). The reaction was stirred at room temperature for 16 h. The solvent was  
35 removed and the residue was extracted with EtOAc / H<sub>2</sub>O. The organic extracts were dried over MgSO<sub>4</sub>, and concentrated. The residue was purified by silica gel column chromatography to give the title compound as pale liquid (9.5 g). LCMS *m/z* = 413.1 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ

ppm 1.28-1.43 (m, 4H), 1.46-1.48 (m, 9H), 1.49-1.56 (m, 4H), 1.76-1.91 (m, 2H), 2.45 (s, 3H), 3.36 (d,  $J = 6.95$  Hz, 2H), 3.92 (d,  $J = 7.05$  Hz, 2H), 3.92 (s, 2H), 7.35 (d,  $J = 8.46$  Hz, 2H), 7.78 (d,  $J = 8.34$  Hz, 2H).

**Step E: Preparation of 5-Methyl-3-phenyl-1H-pyrazole.**

5 To a solution of acetophenone (10 g, 83 mmol) in anhydrous toluene (10 mL) was added LiHMDS (1.0 M in THF, 83 mL, 83 mmol) via syringe at 0 °C under argon. After 5 min, acetyl chloride (6.53 g, 83 mmol) was added in one portion via syringe. The ice bath was removed and glacial AcOH (5 mL), EtOH (50 mL), and hydrazine hydrate (12.50 g, 250 mmol) were added. The mixture was refluxed for 2 h. After cooled to room temperature, the reaction was neutralized to pH 7  
10 by adding 1.0 M NaOH solution. The mixture was extracted with EtOAc, washed with brine, dried over MgSO<sub>4</sub>, and concentrated. The residue was purified by silica gel column chromatography to give the title compound as pale yellow oil (12.05 g). LCMS  $m/z = 159.0$  [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 2.25 (s, 3H), 6.42 (s, 1H), 7.20-7.44 (m, 3H), 7.67-7.82 (m, 2H), 12.53 (bs, 1H).

15 **Step F: Preparation of 4-Bromo-5-methyl-3-phenyl-1H-pyrazole.**

To a solution of 5-methyl-3-phenyl-1H-pyrazole (8.0 g, 50.6 mmol) in dichloromethane (150 mL) was added bromine (8.08 g, 50.6 mmol) dropwise at 0 °C. The reaction was stirred at that temperature for 30 min and continued at room temperature for 2 h. After quenched with aqueous solution of Na<sub>2</sub>SO<sub>3</sub> (10 % wt aq., 10 mL), the organic solvent was removed and the aqueous mixture  
20 was extracted with EtOAc, washed with brine, dried over MgSO<sub>4</sub>, and concentrated. The residue was purified by silica gel column chromatography to give the title compound as yellow oil (9.5 g). LCMS  $m/z = 236.9$  [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 2.26 (s, 3H), 7.30-7.57 (m, 5H), 13.12 (s, 1H).

25 **Step G: Preparation of *tert*-Butyl 2-(((1*s*,4*s*)-4-((4-Bromo-3-methyl-5-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-Butyl 2-(((1*s*,4*s*)-4-((4-Bromo-5-methyl-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a Mixture of Regioisomers.**

To a solution of 4-bromo-5-methyl-3-phenyl-1H-pyrazole (2.0 g, 8.44 mmol) in DMF (5 mL) were added sodium hydride (0.202 g, 8.44 mmol) in portions at 0 °C. The reaction was stirred  
30 at that temperature for 1 h and *tert*-butyl 2-(((1*s*,4*s*)-4-(tosyloxymethyl)cyclohexyl)methoxy)acetate (3.48 g, 8.44 mmol) was added. The reaction was heated to 42 °C, stirred for 16 h, and quenched with H<sub>2</sub>O (2 mL). The mixture was extracted with ethyl acetate, dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound as a colorless liquid (3.05 g) (mixture of two isomers). LCMS  $m/z = 477.3$  [M+H]<sup>+</sup>.

35 **Step H: Preparation of 2-(((1*s*,4*s*)-4-((3-Methyl-5-phenyl-4-*m*-tolyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid.**

To a solution of *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-methyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers (100 mg, 0.19 mmol) in dioxane (3 mL) were added *m*-tolylboronic acid (25.8 mg, 0.19 mmol),  
5 tetrakis(triphenylphosphine)palladium (22 mg, 0.019 mmol), and K<sub>2</sub>CO<sub>3</sub> (2 M aq., 0.2 mL). The reaction was heated to 150 °C under microwave irradiation for 4 h. The reaction mixture was filtered and concentrated. The residue was treated with HCl (4 M in dioxane, 5 mL) at room temperature for 10 h. The mixture was concentrated and purified by HPLC to give the title compound (13.5 mg) as a white solid. LCMS *m/z* = 433.2 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.01-1.19 (m, 4H),  
10 1.21-1.36 (m, 4H), 1.54-1.66 (m, 1H), 1.86-1.98 (m, 1H), 2.22 (s, 3H), 3.19 (d, *J* = 6.95 Hz, 2H), 3.89 (d, *J* = 7.45 Hz, 2H), 3.91 (s, 2H), 7.04-7.11 (m, 2H), 7.21-7.31 (m, 5H), 7.39-7.47 (m, 2H).

**Example 1.98: Preparation of 2-(((1*s*,4*s*)-4-((2,5-Difluorophenyl)-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 20).**

15 From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-methyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers, and 2,5-difluorophenylboronic acid, the title compound was obtained using a similar method to the one described in **Example 1.97**. LCMS *m/z* = 455.2 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm  
20 0.99-1.21 (m, 4H), 1.21-1.38 (m, 4H), 1.54-1.66 (m, 1H), 1.88-2.02 (m, 1H), 2.13 (s, 3H), 3.20 (d, *J* = 7.07 Hz, 2H), 3.91 (s, 2H), 3.93 (d, *J* = 7.07 Hz, 2H), 6.93-7.00 (m, 1H), 7.05-7.27 (m, 5H), 7.38-7.43 (m, 2H).

**Example 1.99: Preparation of 2-(((1*s*,4*s*)-4-((4-Fluorophenyl)-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 22).**

25 From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-methyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 4-fluorophenylboronic, the title compound was obtained using a similar method to the one described  
30 in **Example 1.97**. LCMS *m/z* = 437.2 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.33-1.54 (m, 8H), 1.71-1.82 (m, 1H), 2.05-2.15 (m, 1H), 2.20 (s, 3H), 3.43 (d, *J* = 7.07 Hz, 2H), 4.00 (s, 2H), 4.05 (d, *J* = 7.58 Hz, 2H), 7.17-7.21 (m, 3H), 7.21-7.28 (m, 3H), 7.29-7.34 (m, 3H).

**Example 1.100: Preparation of 2-(((1*s*,4*s*)-4-((3-Chlorophenyl)-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 23).**

35 From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-methyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-methyl-3-phenyl-

1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 3-chlorophenylboronic acid, the title compound was obtained using a similar method to the one described in **Example 1.97**. LCMS  $m/z$  = 453.3  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.34-1.55 (m, 8H), 1.73-1.82 (m, 1H), 2.04-2.16 (m, 1H), 2.23 (s, 3H), 3.43 (d,  $J$  = 7.07 Hz, 2H),  
5 4.01 (s, 2H), 4.06 (d,  $J$  = 7.58 Hz, 2H), 7.09-7.14 (m, 1H), 7.18-7.41 (m, 8H).

**Example 1.101: Preparation of 2-(((1*s*,4*s*)-4-((5-Methyl-3-phenyl-4-*m*-tolyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 24).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-methyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and *m*-tolylboronic acid, the title compound was obtained using a similar method to the one described in **Example 1.97**. LCMS  $m/z$  = 433.2  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.33-1.55 (m, 8H), 1.72-1.82 (m, 1H), 2.07-2.15 (m, 1H), 2.19 (s, 3H), 2.28 (s, 3H), 3.43 (d,  $J$  = 6.82 Hz, 2H),  
15 4.00 (s, 2H), 4.05 (d,  $J$  = 7.58 Hz, 2H), 6.88-7.14 (m, 3H), 7.15-7.29 (m, 3H), 7.29-7.39 (m, 3H).

**Example 1.102: Preparation of 2-(((1*s*,4*s*)-4-((4-(4-Fluorophenyl)-3-methyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 25).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-methyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 4-fluorophenylboronic acid, the title compound was obtained using a similar method to the one described in **Example 1.97**. LCMS  $m/z$  = 437.2  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.01-1.20 (m, 4H), 1.21-1.36 (m, 4H), 1.52-1.67 (m, 1H), 1.86-2.00 (m, 1H), 2.20 (s, 3H), 3.19 (d,  $J$  = 6.82 Hz, 2H), 3.88 (d,  $J$  = 7.58 Hz, 2H), 3.91 (s, 2H), 6.96-7.17 (m, 4H), 7.18-7.31 (m, 2H), 7.34-7.48 (m, 3H).

**Example 1.103: Preparation of 2-(((1*s*,4*s*)-4-((2,3-Difluorophenyl)-3-methyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 26).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-methyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 2,3-difluorophenylboronic acid, the title compound was obtained using a similar method to the one described in **Example 1.97**. LCMS  $m/z$  = 455.2  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 0.98-1.20 (m, 4H), 1.21-1.38 (m, 4H), 1.53-1.69 (m, 1H), 1.88-2.02 (m, 1H), 2.13 (s, 3H), 3.19 (d,  $J$  = 7.07 Hz, 2H), 3.91 (s, 2H), 3.94 (d,  $J$  = 7.33 Hz, 2H), 6.91-6.97 (m, 1H), 7.05-7.12 (m, 1H), 7.20-7.25 (m, 3H), 7.37-7.42 (m, 3H).

**Example 1.104: Preparation of 2-(((1s,4s)-4-((4-(2,3-Difluorophenyl)-5-methyl-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 27).**

From *tert*-butyl 2-(((1s,4s)-4-((4-bromo-3-methyl-5-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1s,4s)-4-((4-bromo-5-methyl-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 2,3-difluorophenylboronic acid, the title compound was obtained using a similar method to the one described in **Example 1.97**. LCMS  $m/z = 455.2$   $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.31-1.54 (m, 8H), 1.71-1.81 (m, 1H), 2.05-2.15 (m, 1H), 2.17 (s, 3H), 3.42 (d,  $J = 7.07$  Hz, 2H), 3.99 (s, 2H), 4.07 (d,  $J = 7.58$  Hz, 2H), 7.02-7.09 (m, 2H), 7.19-7.32 (m, 4H), 7.34-7.46 (m, 2H).

**Example 1.105: Preparation of 2-(((1s,4s)-4-((4-(4-Chlorophenyl)-5-methyl-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 28).**

From *tert*-butyl 2-(((1s,4s)-4-((4-bromo-3-methyl-5-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1s,4s)-4-((4-bromo-5-methyl-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 4-chlorophenylboronic acid, the title compound was obtained using a similar method to the one described in **Example 1.97**. LCMS  $m/z = 453.2$   $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.31-1.57 (m, 8H), 1.70-1.83 (m, 1H), 2.03-2.14 (m, 1H), 2.21 (s, 3H), 3.42 (d,  $J = 6.95$  Hz, 2H), 4.00 (s, 2H), 4.05 (d,  $J = 7.58$  Hz, 2H), 7.14-7.20 (m, 2H), 7.22-7.34 (m, 5H), 7.38-7.44 (m, 2H).

**Example 1.106: Preparation of 2-(((1s,4s)-4-((4-(2,5-Difluorophenyl)-3-methyl-5-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 29).**

From *tert*-butyl 2-(((1s,4s)-4-((4-bromo-3-methyl-5-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1s,4s)-4-((4-bromo-5-methyl-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 2,5-difluorophenylboronic acid, the title compound was obtained using a similar method to the one described in **Example 1.97**. LCMS  $m/z = 455.2$   $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 0.99-1.21 (m, 4H), 1.21-1.38 (m, 4H), 1.54-1.66 (m, 1H), 1.88-2.02 (m, 1H), 2.13 (s, 3H), 3.20 (d,  $J = 7.07$  Hz, 2H), 3.91 (s, 2H), 3.93 (d,  $J = 7.07$  Hz, 2H), 6.93-7.00 (m, 1H), 7.05-7.27 (m, 5H), 7.38-7.43 (m, 2H).

**Example 1.107: Preparation of 2-(((1s,4s)-4-((5-(3-Methoxyphenyl)-3-methyl-4-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 32).**

**Step A: Preparation of 3-Bromo-5-methyl-4-phenyl-1H-pyrazole.**

To a solution of 5-methyl-4-phenyl-1H-pyrazole (3.0 g, 18.96 mmol) in acetic acid (glacial, 100 mL) was added bromine (1.457 mL, 28.4 mmol) at room temperature. The reaction was stirred



at room temperature for 2 h. After quenched with aqueous solution of Na<sub>2</sub>SO<sub>3</sub> (10 % wt aq., 10 mL), the reaction was concentrated and extracted with EtOAc, washed with brine, dried over MgSO<sub>4</sub>, and purified by silica gel column chromatography to give the title compound as yellow oil (2.8 g).

LCMS  $m/z$  = 236.9 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  ppm 2.26 (s, 3H), 7.24-7.54 (m, 5H),  
5 13.13 (s, 1H).

**Step B: Preparation of *tert*-Butyl 2-(((1*s*,4*s*)-4-((5-Bromo-3-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-Butyl 2-(((1*s*,4*s*)-4-((3-Bromo-5-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a Mixture of Regioisomers.**

10 A solution of 3-bromo-5-methyl-4-phenyl-1*H*-pyrazole (2.0 g, 7.04 mmol) in DMF (10 mL) was treated with sodium hydride (0.169 g, 7.04 mmol) at 0 °C for 1 h, then a solution of *tert*-butyl 2-(((1*s*,4*s*)-4-(tosyloxymethyl)cyclohexyl)methoxy)acetate (2.90 g, 7.04 mmol) in DMF (5 mL) was added. The reaction mixture was gently warmed to 60 °C for 16 h and quenched by water (2 mL). The mixture was extracted by EtOAc, dried over MgSO<sub>4</sub>, and purified by silica gel column  
15 chromatography to give the title compound (2.25 g) (mixture of two regioisomers). LCMS  $m/z$  = 477.3 [M+H]<sup>+</sup>.

**Step C: Preparation of 2-(((1*s*,4*s*)-4-((3-(3-Methoxyphenyl)-3-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid.**

To a solution of *tert*-butyl 2-(((1*s*,4*s*)-4-((5-bromo-3-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((3-bromo-5-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers (100 mg, 0.19 mmol) in dioxane (3 mL) were added 3-methoxyphenylboronic acid (28.9 mg, 0.19 mmol), tetrakis(triphenylphosphine)palladium (22 mg, 0.019 mmol), and K<sub>2</sub>CO<sub>3</sub> (2 M aq., 0.2 mL). The reaction was heated to 150 °C under microwave irradiation for 4 h. The reaction mixture was filtered  
25 and concentrated. The residue was treated with HCl (4.0 M in dioxane, 5 mL) at room temperature for 10 h. The mixture was concentrated and purified by HPLC to give the title compound (one of the two regioisomers separated) as a white solid. LCMS  $m/z$  = 449.2 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  ppm 1.09-1.20 (m, 4H), 1.22-1.38 (m, 4H), 1.57-1.69 (m, 1H), 1.89-1.99 (m, 1H), 2.21 (s, 3H), 3.23 (d, *J* = 6.82 Hz, 2H), 3.77 (s, 3H), 3.86 (d, *J* = 7.33 Hz, 2H), 3.92 (s, 2H), 6.94-6.99  
30 (m, 2H), 7.04-7.10 (m, 2H), 7.11-7.19 (m, 3H), 7.20-7.26 (m, 2H).

**Example 1.108: Preparation of 2-(((1*s*,4*s*)-4-((3-(3-Methoxyphenyl)-5-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 33).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((5-bromo-3-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((3-bromo-5-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 3-methoxyphenylboronic acid, the title compound (one of the two regioisomers separated) was  
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obtained using a similar method to the one described in **Example 1.107**. LCMS  $m/z$  = 449.2  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.32-1.54 (m, 8H), 1.71-1.80 (m, 1H), 2.04-2.14 (m, 1H), 2.19 (s, 3H), 3.42 (d,  $J$  = 6.82 Hz, 2H), 3.71 (s, 3H), 3.99 (s, 2H), 4.03 (d,  $J$  = 7.58 Hz, 2H), 6.77-6.84 (m, 2H), 7.12-7.19 (m, 2H), 7.20-7.31 (m, 3H), 7.32-7.39 (m, 2H).

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**Example 1.109: Preparation of 2-(((1*s*,4*s*)-4-((5-(3-Fluoro-5-methoxyphenyl)-3-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 34).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((5-bromo-3-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((3-bromo-5-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 3-fluoro-5-methoxyphenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.107**. LCMS  $m/z$  = 467.3  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.09-1.22 (m, 4H), 1.23-1.39 (m, 4H), 1.56-1.69 (m, 1H), 1.88-2.00 (m, 1H), 2.20 (s, 3H), 3.24 (d,  $J$  = 6.32 Hz, 2H), 3.72 (s, 3H), 3.79 (d,  $J$  = 7.57 Hz, 2H), 3.93 (s, 2H), 6.60-6.92 (m, 3H), 7.05-7.35 (m, 5H).

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**Example 1.110: Preparation of 2-(((1*s*,4*s*)-4-((3-(3-Fluoro-5-methoxyphenyl)-5-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 35).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((5-bromo-3-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((3-bromo-5-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 3-fluoro-5-methoxyphenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.107**. LCMS  $m/z$  = 467.3  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.33-1.54 (m, 8H), 1.71-1.81 (m, 1H), 2.05-2.14 (m, 1H), 2.18 (s, 3H), 3.42 (d,  $J$  = 6.82 Hz, 2H), 3.59 (s, 3H), 3.99 (s, 2H), 4.05 (d,  $J$  = 7.58 Hz, 2H), 6.62-6.71 (m, 4H), 7.17-7.23 (m, 1H), 7.29-7.44 (m, 3H).

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**Example 1.111: Preparation of 2-(((1*s*,4*s*)-4-((4-(4-Methoxyphenyl)-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 38).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-methyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 4-methoxyphenylboronic acid (26.6 mg, 0.19 mmol), the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.97**. LCMS  $m/z$  = 449.2  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.31-1.54 (m, 8H), 1.71-1.81 (m, 1H), 2.04-2.14 (m, 1H), 2.17 (s, 3H), 3.42 (d,  $J$  = 6.82 Hz, 2H), 3.77 (s, 3H), 4.00 (s, 2H), 4.04 (d,  $J$  = 7.58 Hz, 2H), 6.90-6.96 (m, 2H), 7.04-7.11 (m, 2H), 7.16-7.27 (m, 3H), 7.30-7.37 (m, 2H).

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**Example 1.112: Preparation of 2-(((1*s*,4*s*)-4-((4-(3-Fluoro-5-methoxyphenyl)-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 39).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-methyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 3-fluoro-5-methoxyphenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.97**. LCMS  $m/z = 467.2$   $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.31-1.55 (m, 8H), 1.70-1.82 (m, 1H), 2.03-2.14 (m, 1H), 2.23 (s, 3H), 3.42 (d,  $J = 7.07$  Hz, 2H), 3.70 (s, 3H), 3.99 (s, 2H), 4.04 (d,  $J = 7.58$  Hz, 2H), 6.39-6.81 (m, 3H), 7.19-7.36 (m, 5H).

**Example 1.113: Preparation of 2-(((1*s*,4*s*)-4-((4-(3-Fluorophenyl)-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 40).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-methyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 3-fluorophenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.97**. LCMS  $m/z = 437.2$   $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.34-1.53 (m, 8H), 1.72-1.81 (m, 1H), 2.04-2.15 (m, 1H), 2.23 (s, 3H), 3.43 (d,  $J = 7.07$  Hz, 2H), 4.00 (s, 2H), 4.06 (d,  $J = 7.58$  Hz, 2H), 6.93-7.01 (m, 2H), 7.08-7.15 (m, 1H), 7.20-7.35 (m, 5H), 7.35-7.44 (m, 1H).

**Example 1.114: Preparation of 2-(((1*s*,4*s*)-4-((4-(3-Chlorophenyl)-3-methyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 41).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-methyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 3-chlorophenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.97**. LCMS  $m/z = 453.3$   $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.02-1.20 (m, 4H), 1.21-1.35 (m, 4H), 1.54-1.65 (m, 1H), 1.88-1.98 (m, 1H), 2.24 (s, 3H), 3.20 (d,  $J = 6.82$  Hz, 2H), 3.89 (d,  $J = 7.58$  Hz, 2H), 3.91 (s, 2H), 7.00-7.08 (m, 2H), 7.17-7.30 (m, 5H), 7.40-7.48 (m, 2H).

**Example 1.115: Preparation of 2-(((1*s*,4*s*)-4-((4-(4-Methoxyphenyl)-3-methyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 42).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-methyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 4-methoxyphenylboronic acid, the title compound (one of the two regioisomers separated) was  
5 obtained using a similar method to the one described in **Example 1.97**. LCMS  $m/z$  = 449.2  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.01-1.19 (m, 4H), 1.20-1.35 (m, 4H), 1.54-1.64 (m, 1H), 1.86-1.97 (m, 1H), 2.19 (s, 3H), 3.19 (d,  $J$  = 6.82 Hz, 2H), 3.69 (s, 3H), 3.87 (d,  $J$  = 7.33 Hz, 2H), 3.91 (s, 2H), 6.76-6.82 (m, 2H), 6.95-7.02 (m, 2H), 7.19-7.26 (m, 2H), 7.35-7.45 (m, 3H).

10 **Example 1.116: Preparation of 2-(((1*s*,4*s*)-4-((4-(3-Fluoro-5-methoxyphenyl)-3-methyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 43).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-methyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 3-fluoro-5-  
15 methoxyphenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.97**. LCMS  $m/z$  = 467.2  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.01-1.20 (m, 4H), 1.21-1.36 (m, 4H), 1.56-1.64 (m, 1H), 1.88-1.97 (m, 1H), 2.25 (s, 3H), 3.20 (d,  $J$  = 7.07 Hz, 2H), 3.60 (s, 3H), 3.87 (d,  $J$  = 7.33 Hz, 2H), 3.91 (s, 2H), 6.36-6.65 (m, 4H), 7.20-7.52 (m, 4H).

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**Example 1.117: Preparation of 2-(((1*s*,4*s*)-4-((4-(2-Chlorophenyl)-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 44).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-methyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 2-  
25 chlorophenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.97**. LCMS  $m/z$  = 453.2  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.32-1.53 (m, 8H), 1.71-1.82 (m, 1H), 2.08 (s, 3H), 2.08-2.17 (m, 1H), 3.42 (d,  $J$  = 6.82 Hz, 2H), 3.99 (s, 2H), 4.06 (d,  $J$  = 7.58 Hz, 2H), 7.16-7.30 (m, 4H), 7.33-7.44 (m, 3H), 7.52-7.59 (m, 2H).

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**Example 1.118: Preparation of 2-(((1*s*,4*s*)-4-((4-(2-Chlorophenyl)-3-methyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 45).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-methyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 2-  
35 chlorophenylboronic acid, the title compound (one of the two regioisomers separated) was obtained

using a similar method to the one described in **Example 1.97**. LCMS  $m/z$  = 453.2  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.00-1.20 (m, 4H), 1.20-1.37 (m, 4H), 1.55-1.64 (m, 1H), 1.91-2.00 (m, 1H), 2.03 (s, 3H), 3.18 (d,  $J$  = 6.82 Hz, 2H), 3.90 (s, 2H), 3.95 (d,  $J$  = 7.58 Hz, 2H), 7.14-7.29 (m, 4H), 7.31-7.39 (m, 3H), 7.41-7.45 (m, 2H).

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**Example 1.119: Preparation of 2-(((1*s*,4*s*)-4-((4-(3-Fluorophenyl)-3-methyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 46).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-methyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 3-fluorophenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.97**. LCMS  $m/z$  = 437.2  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.02-1.19 (m, 4H), 1.21-1.36 (m, 4H), 1.55-1.66 (m, 1H), 1.87-1.98 (m, 1H), 2.24 (s, 3H), 3.20 (d,  $J$  = 7.07 Hz, 2H), 3.88 (d,  $J$  = 7.33 Hz, 2H), 3.91 (s, 2H), 6.79-7.01 (m, 3H), 7.22-7.30 (m, 3H), 7.40-7.47 (m, 3H).

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**Example 1.120: Preparation of 2-(((1*s*,4*s*)-4-((5-Methyl-3-phenyl-4-*p*-tolyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 47).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-methyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and *p*-tolylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.97**. LCMS  $m/z$  = 433.2  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.34-1.53 (m, 8H), 1.71-1.80 (m, 1H), 2.04-2.14 (m, 1H), 2.18 (s, 3H), 2.32 (s, 3H), 3.42 (d,  $J$  = 7.07 Hz, 2H), 3.99 (s, 2H), 4.04 (d,  $J$  = 7.58 Hz, 2H), 7.02-7.07 (m, 2H), 7.14-7.27 (m, 5H), 7.30-7.35 (m, 2H).

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**Example 1.121: Preparation of 2-(((1*s*,4*s*)-4-((2,4-Difluorophenyl)-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 48).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-methyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 2,4-difluorophenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.97**. LCMS  $m/z$  = 455.2  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.33-1.53 (m, 8H), 1.72-1.81 (m, 1H), 2.06-2.13 (m, 1H), 2.14 (s, 3H), 3.43 (d,  $J$  = 7.07 Hz, 2H), 4.00 (s, 2H), 4.07 (d,  $J$  = 7.58 Hz, 2H), 7.07-7.15 (m, 2H), 7.19-7.34 (m, 6H).

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**Example 1.122: Preparation of 2-(((1*s*,4*s*)-4-((4-(4-Chlorophenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 49).**

**Step A: Preparation of 4-Bromo-3-phenyl-1*H*-pyrazole.**

5 To a solution of 3-phenyl-1*H*-pyrazole-4-carbaldehyde (10.0 g, 58.1 mmol) in acetic acid (100 mL, 58.1 mmol) was added bromine (10 mL, 195 mmol) dropwise at room temperature. The reaction was stirred at room temperature for 2 h. After quenched with aqueous solution of Na<sub>2</sub>SO<sub>3</sub> (10 % wt aq., 10 mL), the reaction was concentrated and extracted with EtOAc, washed with brine, dried over MgSO<sub>4</sub>, and purified by silica gel column chromatography to give the title compound as  
10 yellow oil (10.2 g). LCMS *m/z* = 223.0 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 7.37-7.53 (m, 3H), 7.76-7.84 (m, 2H), 7.91 (s, 1H).

**Step B: Preparation of *tert*-Butyl 2-(((1*s*,4*s*)-4-((4-Bromo-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-Butyl 2-(((1*s*,4*s*)-4-((4-Bromo-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a Mixture of Regioisomers.**

15 A solution of 3-bromo-5-methyl-4-phenyl-1*H*-pyrazole (2.0 g, 7.04 mmol) in DMF (10 mL) was treated with sodium hydride (0.169 g, 7.04 mmol) at 0 °C for 1 h, then a solution of *tert*-butyl 2-(((1*s*,4*s*)-4-(tosyloxymethyl)cyclohexyl)methoxy)acetate (2.90 g, 7.04 mmol) in DMF (5 mL) was added. The reaction mixture was gently warmed to 60 °C for 16 h and quenched by water (2 mL). The mixture was extracted by EtOAc, dried over MgSO<sub>4</sub>, and concentrated. The residue was  
20 purified by column chromatography to give the title compound as a mixture of regioisomers (2.25 g). LCMS *m/z* = 462.2 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.22-1.33 (m, 4H), 1.35-1.48 (m, 4H), 1.43 (s, 9H), 1.65-1.79 (m, 1H), 2.02-2.15 (m, 1H), 3.37 (d, *J* = 6.82 Hz, 2H), 3.95 (s, 2H), 4.09 (d, *J* = 7.58 Hz, 2H), 7.34-7.51 (m, 3H), 7.76-7.84 (m, 2H), 8.08 (s, 1H).

**Step C: Preparation of 2-(((1*s*,4*s*)-4-((4-(4-Chlorophenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid.**

25 To a solution of *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers (100 mg, 0.22 mmol) in dioxane (3 mL) were added 4-chlorophenylboronic acid (34.4 mg, 0.22 mmol),  
30 tetrakis(triphenylphosphine)palladium (25 mg, 0.022 mmol), and K<sub>2</sub>CO<sub>3</sub> (2 M aq., 0.2 mL). The reaction was heated to 150 °C under microwave irradiation for 4 h. The reaction mixture was filtered and concentrated. The residue was treated with HCl (4.0 M in dioxane, 5 mL) at room temperature for 10 h. The mixture was concentrated and purified by HPLC to give the title compound (one of the two regioisomers separated) as a white solid. LCMS *m/z* = 438.2 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz,  
35 DMSO-*d*<sub>6</sub>) δ ppm 1.29-1.52 (m, 8H), 1.71-1.79 (m, 1H), 2.07-2.19 (m, 1H), 3.40 (d, *J* = 6.82 Hz, 2H), 3.99 (s, 2H), 4.09 (d, *J* = 7.83 Hz, 2H), 7.21-7.27 (m, 2H), 7.29-7.42 (m, 7H), 7.98 (s, 1H).

**Example 1.123: Preparation of 2-(((1*s*,4*s*)-4-((4-(3-Fluorophenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 50).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 3-fluorophenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.122**. LCMS  $m/z$  = 423.2  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.27-1.55 (m, 8H), 1.67-1.84 (m, 1H), 2.07-2.22 (m, 1H), 3.41 (d,  $J$  = 6.82 Hz, 2H), 4.00 (s, 2H), 4.10 (d,  $J$  = 7.58 Hz, 2H), 6.99-7.10 (m, 3H), 7.29-7.43 (m, 6H), 8.04 (s, 1H).

**Example 1.124: Preparation of 2-(((1*s*,4*s*)-4-((4-(4-Fluorophenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 51).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 4-fluorophenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.122**. LCMS  $m/z$  = 423.2  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.28-1.53 (m, 8H), 1.70-1.80 (m, 1H), 2.08-2.18 (m, 1H), 3.40 (d,  $J$  = 6.82 Hz, 2H), 3.99 (s, 2H), 4.09 (d,  $J$  = 7.58 Hz, 2H), 7.10-7.17 (m, 2H), 7.22-7.36 (m, 5H), 7.36-7.41 (m, 2H), 7.93 (s, 1H).

**Example 1.125: Preparation of 2-(((1*s*,4*s*)-4-((4-(3-Chloro-2-fluorophenyl)-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 52).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-methyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 3-chloro-2-fluorophenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.97**. LCMS  $m/z$  = 470.1  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.30-1.54 (m, 8H), 1.71-1.82 (m, 1H), 2.05-2.14 (m, 1H), 2.16 (s, 3H), 3.43 (d,  $J$  = 7.07 Hz, 2H), 4.00 (s, 2H), 4.07 (d,  $J$  = 7.58 Hz, 2H), 7.16-7.36 (m, 6H), 7.50-7.63 (m, 2H).

**Example 1.126: Preparation of 2-(((1*s*,4*s*)-4-((4-(2,4-Difluorophenyl)-3-methyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 53).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-methyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 2,4-

5 difluorophenylboronic acid, the title compound was obtained using a similar method to the one described in **Example 1.97**. LCMS  $m/z = 455.2$   $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.02-1.18 (m, 4H), 1.21-1.35 (m, 4H), 1.55-1.64 (m, 1H), 1.89-1.99 (m, 1H), 2.10 (s, 3H), 3.19 (d,  $J = 7.07$  Hz, 2H), 3.91 (s, 2H), 3.93 (d,  $J = 7.33$  Hz, 2H), 6.94-7.02 (m, 2H), 7.11-7.24 (m, 3H), 7.34-7.43 (m, 3H).

**Example 1.127: Preparation of 2-(((1*s*,4*s*)-4-((4-(3-Chloro-2-fluorophenyl)-3-methyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 54).**

10 From *tert*-butyl 2-(((1*s*,4*s*)-4-(4-bromo-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-methyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 3-chloro-2-fluorophenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.97**. LCMS  $m/z = 470.1$   $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.01-1.20 (m, 4H), 1.21-1.39 (m, 4H), 1.54-1.66 (m, 1H), 1.90-2.00 (m, 1H), 2.12 (s, 3H), 3.20 (d,  $J = 6.82$  Hz, 2H), 3.91 (s, 2H), 3.94 (d,  $J = 7.58$  Hz, 2H), 7.05-7.30 (m, 4H), 7.34-7.53 (m, 4H).

**Example 1.128: Preparation of 2-(((1*s*,4*s*)-4-((3-Methyl-5-phenyl-4-*p*-tolyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 55).**

20 From *tert*-butyl 2-(((1*s*,4*s*)-4-(4-bromo-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-methyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and *p*-tolylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.97**. LCMS  $m/z = 433.2$   $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.25-1.50 (m, 8H), 1.68-1.79 (m, 1H), 1.98-2.08 (m, 1H), 2.07 (s, 3H), 2.31 (s, 3H), 3.40 (d,  $J = 7.07$  Hz, 2H), 3.98 (s, 2H), 4.06 (d,  $J = 7.58$  Hz, 2H), 7.33-7.39 (m, 2H), 7.40-7.47 (m, 4H), 7.77-7.82 (m, 3H).

30 **Example 1.129: Preparation of 2-(((1*s*,4*s*)-4-((4-(3-Chloro-4-fluorophenyl)-3-methyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 56).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-(4-bromo-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-methyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 3-chloro-4-fluorophenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.97**. LCMS  $m/z = 471.1$   $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.02-1.18 (m, 4H), 1.21-1.36 (m, 4H), 1.55-1.65 (m, 1H), 1.87-1.98



(m, 1H), 2.23 (s, 3H), 3.20 (d,  $J = 6.82$  Hz, 2H), 3.89 (d,  $J = 7.58$  Hz, 2H), 3.91 (s, 2H), 7.01-7.08 (m, 1H), 7.18-7.29 (m, 4H), 7.41-7.48 (m, 3H).

**Example 1.130: Preparation of 2-(((1*s*,4*s*)-4-((4-(3-Chloro-4-fluorophenyl)-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 57).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-methyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 3-chloro-4-fluorophenylboronic acid, the title compound was obtained using a similar method to the one described in **Example 1.97**. LCMS  $m/z = 471.1$   $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.33-1.55 (m, 8H), 1.72-1.83 (m, 1H), 2.05-2.15 (m, 1H), 2.22 (s, 3H), 3.44 (d,  $J = 7.07$  Hz, 2H), 4.01 (s, 2H), 4.06 (d,  $J = 7.58$  Hz, 2H), 7.10-7.17 (m, 1H), 7.21-7.42 (m, 7H).

**Example 1.131: Preparation of 2-(((1*s*,4*s*)-4-((4-(4-Methoxyphenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 58).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers (100 mg, 0.22 mmol) and 4-methoxyphenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.122**. LCMS  $m/z = 435.3$   $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.26-1.54 (m, 8H), 1.65-1.81 (m, 1H), 2.03-2.19 (m, 1H), 3.40 (d,  $J = 6.82$  Hz, 2H), 3.75 (s, 3H), 3.99 (s, 2H), 4.07 (d,  $J = 7.58$  Hz, 2H), 6.85-6.92 (m, 2H), 7.11-7.18 (m, 2H), 7.23-7.34 (m, 3H), 7.37-7.43 (m, 2H), 7.84 (s, 1H).

**Example 1.132: Preparation of 2-(((1*s*,4*s*)-4-((4-(2-Methoxyphenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 59).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 2-methoxyphenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.122**. LCMS  $m/z = 435.3$   $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.29-1.52 (m, 8H), 1.69-1.80 (m, 1H), 2.13 (dd,  $J = 6.57, 3.79$  Hz, 1H), 3.40 (d,  $J = 6.82$  Hz, 2H), 3.52 (s, 3H), 3.99 (s, 2H), 4.09 (d,  $J = 7.58$  Hz, 2H), 6.85-6.93 (m, 2H), 7.08-7.13 (m, 2H), 7.18-7.31 (m, 3H), 7.32-7.38 (m, 2H), 7.77 (s, 1H).

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**Example 1.133: Preparation of 2-(((1*s*,4*s*)-4-((3-Phenyl-4-*m*-tolyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 60).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and *m*-tolylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.122**. LCMS  $m/z$  = 419.3  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.29-1.53 (m, 8H), 1.70-1.81 (m, 1H), 2.07-2.18 (m, 1H), 2.25 (s, 3H), 3.40 (d,  $J$  = 7.07 Hz, 2H), 3.99 (s, 2H), 4.09 (d,  $J$  = 7.58 Hz, 2H), 6.96-7.08 (m, 2H), 7.09-7.21 (m, 2H), 7.25-7.35 (m, 3H), 7.38-7.44 (m, 2H), 7.90 (s, 1H).

**Example 1.134: Preparation of 2-(((1*s*,4*s*)-4-((3-Phenyl-4-*p*-tolyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 61).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and *p*-tolylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.122**. LCMS  $m/z$  = 419.3  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.28-1.51 (m, 8H), 1.70-1.80 (m, 1H), 2.08-2.18 (m, 1H), 2.29 (s, 3H), 3.40 (d,  $J$  = 7.07 Hz, 2H), 3.99 (s, 2H), 4.08 (d,  $J$  = 7.58 Hz, 2H), 7.10-7.16 (m, 3H), 7.26-7.36 (m, 3H), 7.37-7.44 (m, 3H), 7.88 (s, 1H).

**Example 1.135: Preparation of 2-(((1*s*,4*s*)-4-((4-(3-Chlorophenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 62).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 3-chlorophenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.122**. LCMS  $m/z$  = 439.2  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.29-1.53 (m, 8H), 1.70-1.79 (m, 1H), 2.08-2.19 (m, 1H), 3.40 (d,  $J$  = 7.07 Hz, 2H), 4.00 (s, 2H), 4.10 (d,  $J$  = 7.58 Hz, 2H), 7.15-7.19 (m, 1H), 7.25-7.42 (m, 8H), 8.05 (s, 1H).

**Example 1.136: Preparation of 2-(((1*s*,4*s*)-4-((4-(2-Fluorophenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 63).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 2-fluorophenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.122**. LCMS  $m/z$  = 423.2  $[M+H]^+$ ;  $^1H$  NMR (400 MHz,

DMSO-*d*<sub>6</sub>) δ ppm 1.29-1.53 (m, 8H), 1.71-1.81 (m, 1H), 2.09-2.20 (m, 1H), 3.41 (d, *J* = 7.07 Hz, 2H), 4.00 (s, 2H), 4.12 (d, *J* = 7.83 Hz, 2H), 7.13-7.40 (m, 9H), 7.92 (s, 1H).

**Example 1.137: Preparation of 2-(((1*s*,4*s*)-4-((3-Methyl-4-phenyl-5-*m*-tolyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 64).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((5-bromo-3-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((3-bromo-5-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and *m*-tolylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.107**. LCMS *m/z* = 433.2 [*M*+*H*]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 1.29-1.44 (m, 4H), 1.48 (s, 9H), 1.49-1.60 (m, 4H), 1.81-1.91 (m, 1H), 2.04 (s, 3H), 2.12-2.20 (m, 1H), 3.25 (d, *J* = 6.95 Hz, 2H), 3.87 (s, 2H), 4.02 (d, *J* = 7.58 Hz, 2H), 7.30-7.37 (m, 1H), 7.37-7.49 (m, 3H), 7.84-7.89 (m, 1H).

**Example 1.138: Preparation of 2-(((1*s*,4*s*)-4-((5-Methyl-4-phenyl-3-*m*-tolyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 65).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((5-bromo-3-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((3-bromo-5-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and *m*-tolylboronic acid, the title compound was obtained using a similar method to the one described in **Example 1.107**. LCMS *m/z* = 433.3 [*M*+*H*]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.26-1.50 (m, 8H), 1.43 (s, 9H), 1.66-1.78 (m, 1H), 1.97-2.09 (m, 1H), 2.30 (s, 3H), 3.39 (d, *J* = 6.82 Hz, 2H), 3.94 (s, 2H), 4.06 (d, *J* = 7.58 Hz, 2H), 7.30-7.50 (m, 3H), 7.74-7.85 (m, 2H).

**Example 1.139: Preparation of 2-(((1*s*,4*s*)-4-((3-(3-Chlorophenyl)-5-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 66).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((5-bromo-3-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((3-bromo-5-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 3-chlorophenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.107**. LCMS *m/z* = 453.3 [*M*+*H*]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.33-1.54 (m, 8H), 1.73-1.81 (m, 1H), 2.06-2.15 (m, 1H), 2.20 (s, 3H), 3.43 (d, *J* = 6.82 Hz, 2H), 4.00 (s, 2H), 4.06 (d, *J* = 7.58 Hz, 2H), 7.16-7.29 (m, 5H), 7.31-7.43 (m, 4H).

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**Example 1.140: Preparation of 2-(((1*s*,4*s*)-4-((5-(3-Fluorophenyl)-3-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 67).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((5-bromo-3-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((3-bromo-5-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 3-fluorophenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.107**. LCMS  $m/z$  = 437.2 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  ppm 1.04-1.20 (m, 4H), 1.22-1.37 (m, 4H), 1.56-1.64 (m, 1H), 1.86-1.96 (m, 1H), 2.21 (s, 3H), 3.22 (d,  $J$  = 6.82 Hz, 2H), 3.91 (d,  $J$  = 7.53 Hz, 2H), 3.91 (s, 2H), 7.04-7.29 (m, 7H), 7.41-7.50 (m, 2H).

**Example 1.141: Preparation of 2-(((1*s*,4*s*)-4-((3-(3-Fluorophenyl)-5-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 68).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((5-bromo-3-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((3-bromo-5-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 3-fluorophenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.107**. LCMS  $m/z$  = 437.2 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  ppm 1.33-1.54 (m, 8H), 1.71-1.81 (m, 1H), 2.05-2.15 (m, 1H), 2.19 (s, 3H), 3.42 (d,  $J$  = 7.07 Hz, 2H), 4.00 (s, 2H), 4.06 (d,  $J$  = 7.58 Hz, 2H), 6.99-7.08 (m, 2H), 7.12-7.21 (m, 3H), 7.23-7.44 (m, 4H).

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**Example 1.142: Preparation of 2-(((1*s*,4*s*)-4-((5-(3-Chloro-2-fluorophenyl)-3-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 69).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((5-bromo-3-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((3-bromo-5-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 3-chloro-2-fluorophenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.107**. LCMS  $m/z$  = 470.1 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  ppm 1.00-1.21 (m, 4H), 1.22-1.37 (m, 4H), 1.55-1.72 (m, 1H), 1.89-2.00 (m, 1H), 2.24 (s, 3H), 3.21 (d,  $J$  = 6.82 Hz, 2H), 3.67 (d,  $J$  = 7.58 Hz, 2H), 3.91 (s, 2H), 7.03-7.11 (m, 2H), 7.14-7.39 (m, 6H).

**Example 1.143: Preparation of 2-(((1*s*,4*s*)-4-((3-(3-Chloro-2-fluorophenyl)-5-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 70).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((5-bromo-3-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((3-bromo-5-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 3-chloro-2-fluorophenylboronic acid, the title compound (one of the two regioisomers separated) was obtained

using a similar method to the one described in **Example 1.107**. LCMS  $m/z$  = 470.1  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.32-1.54 (m, 8H), 1.70-1.81 (m, 1H), 2.04-2.14 (m, 1H), 2.30 (s, 3H), 3.42 (d,  $J$  = 6.82 Hz, 2H), 3.99 (s, 2H), 4.08 (d,  $J$  = 7.58 Hz, 2H), 7.05-7.11 (m, 2H), 7.16-7.34 (m, 4H), 7.48-7.56 (m, 2H).

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**Example 1.144: Preparation of 2-(((1*s*,4*s*)-4-((5-(2-Fluorophenyl)-3-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 71).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((5-bromo-3-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((3-bromo-5-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 2-fluorophenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.107**. LCMS  $m/z$  = 437.3  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.02-1.19 (m, 4H), 1.22-1.35 (m, 4H), 1.88-1.98 (m, 1H), 2.05-2.14 (m, 1H), 2.24 (s, 3H), 3.42 (d,  $J$  = 7.07 Hz, 2H), 3.99 (s, 2H), 4.07 (d,  $J$  = 7.58 Hz, 2H), 7.03-7.10 (m, 2H), 7.12-7.39 (m, 6H), 7.43-7.54 (m, 1H).

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**Example 1.145: Preparation of 2-(((1*s*,4*s*)-4-((3-(2-Fluorophenyl)-5-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 72).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((5-bromo-3-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((3-bromo-5-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 2-fluorophenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.107**. LCMS  $m/z$  = 437.3  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.35-1.53 (m, 8H), 1.72-1.80 (m, 1H), 2.04-2.14 (m, 1H), 2.30 (s, 3H), 3.41 (d,  $J$  = 7.07 Hz, 2H), 3.99 (s, 2H), 4.07 (d,  $J$  = 7.58 Hz, 2H), 7.03-7.10 (m, 3H), 7.12-7.38 (m, 6H).

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**Example 1.146: Preparation of 2-(((1*s*,4*s*)-4-((5-(2,3-Difluorophenyl)-3-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 73).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((5-bromo-3-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((3-bromo-5-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 2,3-difluorophenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.107**. LCMS  $m/z$  = 455.2  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.04-1.22 (m, 4H), 1.24-1.38 (m, 4H), 1.58-1.70 (m, 1H), 1.88-1.98 (m, 1H), 2.24 (s, 3H), 3.23 (d,  $J$  = 6.82 Hz, 2H), 3.92 (s, 2H), 3.98 (d,  $J$  = 7.58 Hz, 2H), 7.05-7.39 (m, 8H).

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**Example 1.147: Preparation of 2-(((1*s*,4*s*)-4-((3-(2,3-Difluorophenyl)-5-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 74).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((5-bromo-3-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((3-bromo-5-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 2,3-difluorophenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.107**. LCMS  $m/z$  = 455.2  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.33-1.53 (m, 8H), 1.72-1.81 (m, 1H), 2.04-2.14 (m, 1H), 2.29 (s, 3H), 3.42 (d,  $J$  = 6.82 Hz, 2H), 3.99 (s, 2H), 4.08 (d,  $J$  = 7.58 Hz, 2H), 7.01-7.35 (m, 8H).

**Example 1.148: Preparation of 2-(((1*s*,4*s*)-4-((5-Ethoxy-3,4-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 81).**

To a solution of *tert*-butyl 2-(((1*s*,4*s*)-4-((5-ethoxy-3,4-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate (100 mg, 0.20 mmol) in dioxane (4 mL) were added phenylboronic acid (24.0 mg, 0.20 mmol), tetrakis(triphenylphosphine)palladium (22.8 mg, 0.20 mmol), and  $K_2CO_3$  (2 M aq., 0.2 mL). The reaction mixture was heated to 150 °C under microwave for 4 h. The reaction mixture was filtered and concentrated. The residue was treated with HCl (4 M in dioxane, 5 mL) at room temperature for 16 h. The mixture was concentrated and purified by HPLC to give the title compound (one of the two regioisomers separated) as a white solid. LCMS  $m/z$  = 449.3  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.15-1.42 (m, 8H), 1.35 (t,  $J$  = 7.35 Hz, 3H), 1.66-1.75 (m, 1H), 1.87-1.95 (m, 1H), 3.02 (q,  $J$  = 7.35 Hz, 2H), 3.35 (d,  $J$  = 6.82 Hz, 2H), 3.99 (s, 2H), 4.08 (d,  $J$  = 7.58 Hz, 2H), 7.08-7.32 (m, 8H), 7.40-7.48 (m, 2H).

**Example 1.149: Preparation of 2-(((1*s*,4*s*)-4-((5-(Ethylthio)-3,4-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 88).**

To a solution of *tert*-butyl 2-(((1*s*,4*s*)-4-((5-(ethylthio)-4-iodo-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((3-(ethylthio)-4-iodo-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers (100 mg, 0.18 mmol) in dioxane (4 mL) were added phenylboronic acid (21.9 mg, 0.18 mmol), tetrakis(triphenylphosphine)palladium (22.8 mg, 0.20 mmol), and  $K_2CO_3$  (2 M aq., 0.2 mL). The reaction mixture was heated to 150 °C under microwave for 4 h. The reaction mixture was filtered and concentrated. The residue was treated with HCl (4 M in dioxane, 5 mL) at room temperature for 16 h. The mixture was concentrated and purified by HPLC to give the title compound (one of the two regioisomers separated) as white solid. LCMS  $m/z$  = 465.2  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.05-1.36 (m, 8H), 1.24 (t,  $J$  = 7.33 Hz, 3H), 1.56-1.65 (m, 1H), 1.87-1.99 (m,

1H), 2.92 (q,  $J = 7.33$  Hz, 2H), 3.20 (d,  $J = 6.82$  Hz, 2H), 3.91 (s, 2H), 3.94 (d,  $J = 7.58$  Hz, 2H), 7.07-7.31 (m, 8H), 7.38-7.45 (m, 2H).

**Example 1.150: Preparation of 2-(((1*s*,4*s*)-4-((5-(Ethylthio)-4-(3-methoxyphenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 89).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((5-(ethylthio)-4-iodo-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((3-(ethylthio)-4-iodo-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 3-methoxyphenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.149**. LCMS  $m/z = 495.3$   $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 0.96 (t,  $J = 7.33$  Hz, 3H), 1.32-1.55 (m, 8H), 1.70-1.81 (m, 1H), 2.15-2.25 (m, 1H), 2.53 (q,  $J = 7.58$  Hz, 2H), 3.42 (d,  $J = 7.07$  Hz, 2H), 3.70 (s, 3H), 4.00 (s, 2H), 4.28 (d,  $J = 7.58$  Hz, 2H), 6.79-6.95 (m, 4H), 7.21-7.32 (m, 3H), 7.33-7.40 (m, 2H).

**Example 1.151: Preparation of 2-(((1*s*,4*s*)-4-((4-(3-Fluoro-5-methoxyphenyl)-5-(methylthio)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 93).**

To a solution of *tert*-butyl 2-(((1*s*,4*s*)-4-((4-iodo-5-(methylthio)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-iodo-3-(methylthio)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers (100 mg, 0.18 mmol) in dioxane (3 mL) were added 3-fluoro-5-methoxyphenylboronic acid (30.6 mg, 0.18 mmol), tetrakis(triphenylphosphine)palladium (20.8 mg, 0.20 mmol), and  $K_2CO_3$  (2 M aq., 0.2 mL). The reaction mixture was heated to 150 °C under microwave for 4 h. The reaction mixture was filtered and concentrated. The residue was treated with HCl (4 M in dioxane, 5 mL) at room temperature for 16 h. The mixture was concentrated and purified by HPLC to give the title compound (one of the two regioisomers separated) as a white solid. LCMS  $m/z = 499.2$   $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.31-1.56 (m, 8H), 1.62-1.82 (m, 1H), 2.12-2.24 (m, 1H), 2.17 (s, 3H), 3.35 (d,  $J = 6.95$  Hz, 2H), 3.54 (s, 2H), 3.72 (s, 3H), 4.27 (d,  $J = 7.58$  Hz, 2H), 6.60-6.70 (m, 2H), 6.75-6.87 (m, 2H), 7.19-7.41 (m, 4H).

**Example 1.152: Preparation of 2-(((1*s*,4*s*)-4-((3-Ethyl-4-(3-methoxyphenyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 98).**

**Step A: Preparation of 5-Ethyl-3-phenyl-1*H*-pyrazole.**

To a solution of acetophenone (10 g, 83 mmol) in anhydrous toluene (10 mL) was added LiHMDS (85.0 mL, 1.0 M in THF, 85.0 mmol) via syringe at 0 °C under argon. After 5 min, propionyl chloride (7.70 g, 83 mmol) was added in one portion via syringe. The ice bath was removed after 10 min and AcOH (2 mL), EtOH (50 mL), and hydrazine hydrate (8.35 g, 116 mmol)

was added. The mixture was refluxed for 2 h. The resulting solution was added to 1.0 M NaOH solution, extracted with EtOAc, washed with brine, dried over MgSO<sub>4</sub>, and concentrated. The residue was purified by silica gel column chromatography to give the title compound as a clear yellowish liquid (12.05 g). LCMS *m/z* = 173.3 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.23 (t, *J* = 7.58 Hz, 3H), 2.64 (q, *J* = 7.07 Hz, 2H), 6.46 (s, 1H), 7.20-7.52 (m, 3H), 7.77 (d, *J* = 6.32 Hz, 2H), 12.55 (s, 1H).

**Step B: Preparation of 4-Bromo-5-ethyl-3-phenyl-1H-pyrazole.**

To a solution of 5-ethyl-3-phenyl-1H-pyrazole (10.0 g, 58.1 mmol) in DCM (150 mL) was added dropwise bromine (9.28 g, 58.1 mmol) at 0 °C. The reaction was stirred at that temperature for 30 min and continued for 2 h at room temperature before quenched with aqueous Na<sub>2</sub>SO<sub>3</sub> solution (10 % wt, 10 mL). DCM was removed and the residue was extracted with EtOAc, washed with brine, dried over MgSO<sub>4</sub>, and concentrated. The residue was purified by silica gel column chromatography to give the title compound as a yellow liquid (9.5 g). LCMS *m/z* = 250.9 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.22 (t, *J* = 7.58 Hz, 3H), 2.66 (q, *J* = 7.58 Hz, 2H), 7.40-7.56 (m, 3H), 7.82 (d, *J* = 7.58 Hz, 2H), 13.15 (s, 1H).

**Step C: Preparation of *tert*-Butyl 2-(((1*s*,4*s*)-4-((4-Bromo-3-ethyl-5-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-Butyl 2-(((1*s*,4*s*)-4-((4-Bromo-5-ethyl-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a Mixture of Regioisomers.**

To a solution of 4-bromo-5-ethyl-3-phenyl-1H-pyrazole (3.0 g, 11.95 mmol) in DMF (5 mL) was added sodium hydride (0.287 g, 11.95 mmol) followed by *tert*-butyl 2-(((1*s*,4*s*)-4-(tosyloxymethyl)cyclohexyl)methoxy)acetate (4.93 g, 11.95 mmol). The reaction was heated at 45 °C overnight. After quenched with water (2 mL), the mixture was extracted with EtOAc, washed with brine, dried over MgSO<sub>4</sub>, and concentrated. The residue was purified by silica gel column chromatography to give the title compound (a mixture of regioisomers) as a clear liquid (4.5 g). LCMS *m/z* = 491.2 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 1.25 (t, *J* = 7.20 Hz, 3H), 1.31-1.43 (m, 4H), 1.49 (s, 9H), 1.51-1.60 (m, 4H), 1.76-1.90 (m, 1H), 2.12-2.24 (m, 1H), 2.72 (q, *J* = 7.75 Hz, 2H), 3.46 (d, *J* = 6.82 Hz, 2H), 3.92 (s, 2H), 4.01 (d, *J* = 7.58 Hz, 2H), 7.31-7.43 (m, 3H), 7.86 (d, *J* = 7.33 Hz, 2H).

**Step D: Preparation of 2-(((1*s*,4*s*)-4-((3-Ethyl-4-(3-methoxyphenyl)-5-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid.**

To a solution of *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-ethyl-5-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-ethyl-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers (100 mg, 0.20 mmol) were added 3-methoxyphenylboronic acid (30.2 mg, 0.20 mmol), tetrakis(triphenylphosphine)palladium (23.1 mg, 0.20 mmol), K<sub>2</sub>CO<sub>3</sub> (2 M aq., 0.5 mL) and dioxane (3 mL) was heated to 150 °C under microwave for 4 h. The reaction mixture was filtered and concentrated. The residue was treated with HCl (4 M in dioxane, 5 mL) at room temperature for 10



h. The mixture was concentrated and purified by HPLC to give the title compound (one of the two regioisomers separated) as a white solid (13.5 mg). LCMS  $m/z$  = 463.3  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.01-1.18 (m, 4H), 1.12 (t,  $J$  = 7.58 Hz, 3H), 1.22-1.35 (m, 4H), 1.54-1.68 (m, 1H), 1.87-1.98 (m, 1H), 2.63 (q,  $J$  = 7.58 Hz, 2H), 3.20 (d,  $J$  = 6.82 Hz, 2H), 3.58 (s, 3H), 3.90 (d,  $J$  = 7.32 Hz, 2H), 3.91 (s, 2H), 6.55-6.74 (m, 3H), 7.10-7.17 (m, 2H), 7.22-7.28 (m, 2H), 7.36-7.44 (m, 2H).

**Example 1.153: Preparation of 2-(((1*s*,4*s*)-4-((3-Ethyl-4,5-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 100).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-ethyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-ethyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and phenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.152**. LCMS  $m/z$  = 433.3  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.01-1.16 (m, 4H), 1.11 (t,  $J$  = 7.58 Hz, 3H), 1.22-1.34 (m, 4H), 1.55-1.66 (m, 1H), 1.83-1.96 (m, 1H), 2.60 (q,  $J$  = 7.83 Hz, 2H), 3.20 (d,  $J$  = 6.82 Hz, 2H), 3.90 (s, 2H), 3.94 (d,  $J$  = 7.33 Hz, 2H), 7.04-7.26 (m, 5H), 7.35-7.57 (m, 5H).

**Example 1.154: Preparation of 2-(((1*s*,4*s*)-4-((5-Ethyl-3,4-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 101).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-ethyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-ethyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and phenylboronic acid, the title compound was obtained using a similar method to the one described in **Example 1.152**. LCMS  $m/z$  = 433.3  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.02 (t,  $J$  = 7.58 Hz, 3H), 1.30-1.57 (m, 8H), 1.72-1.83 (m, 1H), 2.08-2.18 (m, 1H), 2.59 (q,  $J$  = 7.49 Hz, 2H), 3.44 (d,  $J$  = 7.07 Hz, 2H), 4.00 (s, 2H), 4.03 (d,  $J$  = 7.33 Hz, 2H), 7.15-7.25 (m, 4H), 7.28-7.47 (m, 6H).

**Example 1.155: Preparation of 2-(((1*s*,4*s*)-4-((3-Ethyl-4-(3-fluorophenyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 102).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-ethyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-ethyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 3-fluorophenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.152**. LCMS  $m/z$  = 451.3  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.00-1.19 (m, 4H), 1.12 (t,  $J$  = 7.45 Hz, 3H), 1.21-1.35 (m, 4H),

1.53-1.64 (m, 1H), 1.88-1.98 (m, 1H), 2.64 (q,  $J = 7.58$  Hz, 2H), 3.20 (d,  $J = 7.07$  Hz, 2H), 3.91 (d,  $J = 7.33$  Hz, 2H), 3.91 (s, 2H), 6.80-7.02 (m, 3H), 7.22-7.46 (m, 6H).

**Example 1.156: Preparation of 2-(((1s,4s)-4-((5-Ethyl-4-(3-fluorophenyl)-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 103).**

From *tert*-butyl 2-(((1s,4s)-4-((4-bromo-3-ethyl-5-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1s,4s)-4-((4-bromo-5-ethyl-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 3-fluorophenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.152**. LCMS  $m/z = 451.3$   $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.03 (t,  $J = 7.58$  Hz, 3H), 1.34-1.56 (m, 8H), 1.74-1.82 (m, 1H), 2.09-2.18 (m, 1H), 2.63 (q,  $J = 7.58$  Hz, 2H), 3.44 (d,  $J = 7.07$  Hz, 2H), 4.00 (s, 2H), 4.04 (d,  $J = 7.33$  Hz, 2H), 6.95-7.04 (m, 2H), 7.10-7.18 (m, 1H), 7.18-7.33 (m, 5H), 7.37-7.45 (m, 1H).

**Example 1.157: Preparation of 2-(((1s,4s)-4-((3-Ethyl-4-(2-fluoro-3-methoxyphenyl)-5-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 104).**

From *tert*-butyl 2-(((1s,4s)-4-((4-bromo-3-ethyl-5-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1s,4s)-4-((4-bromo-5-ethyl-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 2-fluoro-3-methoxyphenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.152**. LCMS  $m/z = 481.3$   $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.06 (t,  $J = 7.58$  Hz, 3H), 1.06-1.19 (m, 4H), 1.26-1.39 (m, 4H), 1.54-1.63 (m, 1H), 1.88-1.98 (m, 1H), 2.64 (q,  $J = 7.41$  Hz, 2H), 3.19 (d,  $J = 6.82$  Hz, 2H), 3.77 (s, 3H), 3.96 (d,  $J = 7.58$  Hz, 2H), 3.99 (s, 2H), 6.95-7.04 (m, 2H), 7.18-7.29 (m, 3H), 7.32-7.42 (m, 3H).

**Example 1.158: Preparation of 2-(((1s,4s)-4-((5-Ethyl-4-(2-fluoro-3-methoxyphenyl)-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 105).**

From *tert*-butyl 2-(((1s,4s)-4-((4-bromo-3-ethyl-5-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1s,4s)-4-((4-bromo-5-ethyl-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 2-fluoro-3-methoxyphenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.152**. LCMS  $m/z = 481.3$   $[M+H]^+$ ;  $^1H$  NMR (400 MHz, CD $_3$ OD)  $\delta$  ppm 1.24 (t,  $J = 7.58$  Hz, 3H), 1.32-1.70 (m, 8H), 1.85-1.99 (m, 1H), 2.15-2.27 (m, 1H), 2.65 (q,  $J = 7.45$  Hz, 2H), 3.53 (d,  $J = 7.07$  Hz, 2H), 3.87 (s, 3H), 4.07 (s, 2H), 4.10 (d,  $J = 7.71$  Hz, 2H), 6.68-6.74 (m, 1H), 7.04-7.10 (m, 1H), 7.18-7.24 (m, 2H), 7.29-7.38 (m, 2H), 7.45-7.55 (m, 2H).

**Example 1.159: Preparation of 2-(((1*s*,4*s*)-4-((4-(2,3-Difluorophenyl)-3-ethyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 106).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-ethyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-ethyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 2,3-difluorophenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.152**. LCMS  $m/z$  = 469.3  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.00 (t,  $J$  = 7.45 Hz, 3H), 1.03-1.13 (m, 4H), 1.22-1.32 (m, 4H), 1.54-1.65 (m, 1H), 1.81-1.90 (m, 1H), 2.58 (q,  $J$  = 7.58 Hz, 2H), 3.18 (d,  $J$  = 6.82 Hz, 2H), 3.90 (s, 2H), 3.95 (d,  $J$  = 7.83 Hz, 2H), 7.07-7.14 (m, 1H), 7.19-7.32 (m, 3H), 7.36-7.58 (m, 4H).

**Example 1.160: Preparation of 2-(((1*s*,4*s*)-4-((4-(2,3-Difluorophenyl)-5-ethyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 107).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-ethyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-ethyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 2,3-difluorophenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.152**. LCMS  $m/z$  = 469.3  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, CD $_3$ OD)  $\delta$  ppm 1.08 (t,  $J$  = 7.58 Hz, 3H), 1.38-1.68 (m, 8H), 1.85-1.95 (m, 1H), 2.17-2.27 (m, 1H), 2.66 (q,  $J$  = 7.58 Hz, 2H), 3.53 (d,  $J$  = 7.07 Hz, 2H), 4.08 (s, 2H), 4.12 (d,  $J$  = 7.58 Hz, 2H), 6.96-7.02 (m, 1H), 7.11-7.18 (m, 1H), 7.20-7.26 (m, 3H), 7.28-7.33 (m, 3H).

**Example 1.161: Preparation of 2-(((1*s*,4*s*)-4-((3-Isopropyl-4,5-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 112).**

**Step A: Preparation of 5-Isopropyl-3-phenyl-1*H*-pyrazole (15):**

To a solution of acetophenone (1.21 g, 10.07 mmol) in dry toluene (5 mL) was added LiHMDS (11.0 mL, 1.0 M in THF, 11.0 mmol) via syringe at 0 °C under argon. After 5 min, isobutyryl chloride (1.073 g, 10.07 mmol) was added in one portion via syringe. The ice bath was removed and AcOH (2 mL), EtOH (50 mL) and THF (5 mL) were added to form a homogeneous mixture. Hydrazine hydrate (2 mL, 10.07 mmol) was added and the reaction was refluxed for 2 h. After cooled to room temperature, the reaction was concentrated and extracted with EtOAc, washed with brine, dried over MgSO $_4$ , and concentrated. The residue was purified by silica gel column chromatography to give the title compound as colorless oil (0.70 g). LCMS  $m/z$  = 187.3  $[M+H]^+$ ;  $^1H$

NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 1.33 (d,  $J = 6.82$  Hz, 6H), 2.94-3.13 (m, 1H), 6.38 (s, 1H), 7.17-7.45 (m, 5H), 10.14 (bs, 1H).

**Step B: Preparation of 4-Iodo-5-isopropyl-3-phenyl-1H-pyrazole.**

To a solution of 5-isopropyl-3-phenyl-1H-pyrazole (0.64 g, 3.44 mmol) in THF (20 mL) and water (20.00 mL) were added sodium iodide (0.515 g, 3.44 mmol), iodine (1.308 g, 5.15 mmol), and potassium carbonate (0.712 g, 5.15 mmol) at room temperature. The reaction was refluxed for 2 h, cooled to room temperature and quenched with 10% aq.  $\text{Na}_2\text{SO}_3$ . The organic solvent was removed under reduced pressure and the aqueous residue was extracted with EtOAc. The organic extract was washed with  $\text{NaHCO}_3$  solution, brine, dried over  $\text{MgSO}_4$ , and concentrated. The residue was purified by silica gel column chromatography to give the title compound as a clear liquid (0.42 g). LCMS  $m/z = 313.2$   $[\text{M}+\text{H}]^+$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 1.17 (d,  $J = 7.07$  Hz, 6H), 3.02 (septet,  $J = 7.07$  Hz, 1H), 7.23-7.32 (m, 3H), 7.60-7.67 (m, 2H), 11.81 (bs, 1H).

**Step C: Preparation of *tert*-Butyl 2-(((1*s*,4*s*)-4-((4-Iodo-5-isopropyl-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-Butyl 2-(((1*s*,4*s*)-4-((4-Iodo-3-isopropyl-5-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a Mixture of Regioisomers.**

To a solution of 4-iodo-5-isopropyl-3-phenyl-1H-pyrazole (0.35 g, 1.121 mmol) in DMF (5 mL) was added sodium hydride (0.027 g, 1.121 mmol) at room temperature. The reaction was stirred at room temperature for 1 h and *tert*-butyl 2-(((1*s*,4*s*)-4-(tosyloxymethyl)cyclohexyl)methoxy)acetate (0.463 g, 1.121 mmol) was added. The reaction was heated at 50 °C for 16 h, cooled to room temperature, and quenched with water (2 mL). The mixture was extracted with EtOAc. The organic extract was dried over  $\text{MgSO}_4$  and concentrated. The residue was purified by silica gel column chromatography to give the title compound (a mixture of two regioisomers) as a clear liquid (0.52 g). LCMS  $m/z = 553.2$   $[\text{M}+\text{H}]^+$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  ppm 0.99-1.20 (m, 4H), 1.25-1.42 (m, 4H), 1.46 (d,  $J = 7.20$  Hz, 6H), 1.48 (s, 9H), 1.82-1.94 (m, 1H), 2.07-2.19 (m, 1H), 3.16-3.28 (m, 1H), 3.45 (d,  $J = 7.07$  Hz, 2H), 3.95 (s, 2H), 4.07 (d,  $J = 7.71$  Hz, 2H), 7.30-7.46 (m, 3H), 7.63-7.79 (m, 2H).

**Step D: Preparation of 2-(((1*s*,4*s*)-4-((3-Isopropyl-4,5-diphenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid.**

A mixture of phenylboronic acid (21.9 mg, 0.18 mmol), *tert*-butyl 2-(((1*s*,4*s*)-4-((4-iodo-5-isopropyl-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-iodo-3-isopropyl-5-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers (100 mg, 0.18 mmol), tetrakis(triphenylphosphine)palladium (10.0 mg, 0.009 mmol),  $\text{K}_2\text{CO}_3$  (2 M aq., 0.2 mL) and dioxane (4 mL) was heated to 150 °C under microwave irradiation for 4 h. The mixture was filtered and concentrated. The residue was treated with HCl (4 M in dioxane, 5 mL) at room temperature for 10 h. The mixture was concentrated and purified by HPLC to give the title compound (one of the two regioisomers separated) as a white solid (15.5 mg).

LCMS  $m/z$  = 447.3  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.05-1.15 (m, 4H), 1.17 (d,  $J$  = 6.82 Hz, 6H), 1.21-1.35 (m, 4H), 1.55-1.63 (m, 1H), 1.84-1.95 (m, 1H), 2.96-3.04 (m, 1H), 3.20 (d,  $J$  = 6.82 Hz, 2H), 3.91 (s, 2H), 3.93 (d,  $J$  = 7.58 Hz, 2H), 7.05-7.10 (m, 2H), 7.12-7.19 (m, 2H), 7.19-7.27 (m, 3H), 7.32-7.40 (m, 3H).

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**Example 1.162: Preparation of 2-(((1*s*,4*s*)-4-((4-(3-Chlorophenyl)-3-ethyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 115).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-ethyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-ethyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 3-chlorophenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.152**. LCMS  $m/z$  = 467.2  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  ppm 1.08-1.23 (m, 4H), 1.21 (t,  $J$  = 7.58 Hz, 3H), 1.27-1.45 (m, 4H), 1.68-1.79 (m, 1H), 1.94-2.04 (m, 1H), 2.77 (q,  $J$  = 7.54 Hz, 2H), 3.31 (d,  $J$  = 6.57 Hz, 2H), 4.02 (s, 2H), 4.12 (d,  $J$  = 7.58 Hz, 2H), 6.88-6.95 (m, 2H), 7.06-7.23 (m, 5H), 7.35-7.44 (m, 2H).

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**Example 1.163: Preparation of 2-(((1*s*,4*s*)-4-((4-(3-Chlorophenyl)-5-ethyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 116).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-ethyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-ethyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 3-chlorophenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.152**. LCMS  $m/z$  = 467.2  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  ppm 1.13 (t,  $J$  = 7.52 Hz, 3H), 1.32-1.46 (m, 4H), 1.48-1.66 (m, 4H), 1.87-1.99 (m, 1H), 2.13-2.26 (m, 1H), 2.66 (q,  $J$  = 7.58 Hz, 2H), 3.52 (d,  $J$  = 6.69 Hz, 2H), 4.10 (s, 2H), 4.17 (d,  $J$  = 7.45 Hz, 2H), 7.02-7.08 (m, 2H), 7.18-7.38 (m, 7H).

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**Example 1.164: Preparation of 2-(((1*s*,4*s*)-4-((4-(2,3-Difluorophenyl)-5-isopropyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 117).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-iodo-5-isopropyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-iodo-3-isopropyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 2,3-difluorophenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.161**. LCMS  $m/z$  = 483.3  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.14 (d,  $J$  = 7.07 Hz, 6H), 1.20-1.36 (m, 8H), 1.56-1.64 (m, 1H), 1.87-1.97 (m, 1H), 2.78-2.88 (m, 1H), 3.20 (d,  $J$  = 7.07 Hz, 2H), 3.91 (s, 2H), 3.98 (d,  $J$  = 7.58 Hz, 2H), 6.96-7.14 (m, 2H), 7.19-7.26 (m, 3H), 7.32-7.41 (m, 3H).

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**Example 1.165: Preparation of 2-(((1*s*,4*s*)-4-((5-(Ethylthio)-4-(2-fluorophenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 118).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((5-(ethylthio)-4-iodo-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((3-(ethylthio)-4-iodo-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 3-fluorophenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.149**. LCMS  $m/z$  = 483.2  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 0.95 (t,  $J$  = 7.33 Hz, 3H), 1.32-1.56 (m, 8H), 1.72-1.82 (m, 1H), 2.17-2.28 (m, 1H), 2.53 (q,  $J$  = 7.33 Hz, 2H), 3.42 (d,  $J$  = 6.82 Hz, 2H), 4.01 (s, 2H), 4.30 (d,  $J$  = 7.58 Hz, 2H), 7.20-7.30 (m, 5H), 7.32-7.39 (m, 2H), 7.40-7.49 (m, 2H).

**Example 1.166: Preparation of 2-(((1*s*,4*s*)-4-((5-(Ethylthio)-4-(3-fluoro-5-methoxyphenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 119).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((5-(ethylthio)-4-iodo-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((3-(ethylthio)-4-iodo-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 3-fluoro-5-methoxyphenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.149**. LCMS  $m/z$  = 513.3  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 0.99 (t,  $J$  = 7.33 Hz, 3H), 1.33-1.56 (m, 8H), 1.72-1.82 (m, 1H), 2.17-2.27 (m, 1H), 2.57 (q,  $J$  = 7.33 Hz, 2H), 3.42 (d,  $J$  = 6.82 Hz, 2H), 3.73 (s, 3H), 4.01 (s, 2H), 4.28 (d,  $J$  = 7.58 Hz, 2H), 6.62-6.70 (m, 2H), 6.76-6.83 (m, 1H), 7.23-7.41 (m, 5H).

**Example 1.167: Preparation of 2-(((1*s*,4*s*)-4-((5-Cyclopropyl-4-(3-methoxyphenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 120).**

**Step A: Preparation of 5-Cyclopropyl-3-phenyl-1*H*-pyrazole.**

To a solution of acetophenone (5.0 g, 41.6 mmol) in dry toluene (5 mL) was added LiHMDS (42.0 mL, 1.0 M in THF, 42.0 mmol) via syringe at 0 °C under argon. After 5 min, cyclopropanecarbonyl chloride (4.35 g, 41.6 mmol) was added in one portion via syringe. The ice bath was removed and AcOH (2 mL), EtOH (50 mL), and hydrazine hydrate (10 mL, 64% aq., 127.8 mmol) was added. The mixture was refluxed for 30 min, cooled to room temperature, and concentrated. The residue was extracted with EtOAc, washed with brine, dried over  $MgSO_4$ , and purified by silica gel column chromatography to give the title compound as colorless oil (4.5 g). LCMS  $m/z$  = 184.7  $[M+H]^+$ ;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  ppm 0.71-0.80 (m, 2H), 0.89-1.00 (m, 2H), 1.81-1.98 (m, 1H), 6.22 (s, 1H), 7.11-7.56 (m, 5H), 10.50 (bs, 1H).

**Step B: Preparation of 5-Cyclopropyl-4-iodo-3-phenyl-1*H*-pyrazole.**

To a solution of 5-cyclopropyl-3-phenyl-1*H*-pyrazole (3.0 g, 16.28 mmol) in THF (20 mL) and water (20 mL) were added sodium iodide (2.441 g, 16.28 mmol), iodine (6.20 g, 24.43 mmol), and potassium carbonate (3.38 g, 24.43 mmol) at room temperature. The reaction was brought to reflux for 2 h at 100 °C. The reaction was cooled to room temperature and quenched with 10% aq. Na<sub>2</sub>SO<sub>3</sub>. The organic solvent was removed under reduced pressure and the aqueous was extracted with EtOAc, washed with NaHCO<sub>3</sub> solution, brine, dried over MgSO<sub>4</sub>, and concentrated. The residue was purified by silica gel column chromatography to give the title compound (2.7 g). LCMS *m/z* = 310.8 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 0.75-0.81 (m, 2H), 0.83-0.88 (m, 2H), 2.46-2.56 (m, 1H), 7.33-7.47 (m, 3H), 7.62-7.71 (m, 2H), 12.91 (s, 1H).

**Step C: Preparation of *tert*-Butyl 2-(((1*s*,4*s*)-4-((3-Cyclopropyl-4-iodo-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-Butyl 2-(((1*s*,4*s*)-4-((5-Cyclopropyl-4-iodo-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a Mixture of Regioisomers.**

A solution of 5-cyclopropyl-4-iodo-3-phenyl-1*H*-pyrazole (3.5 g, 11.29 mmol) in DMF (5 mL) was treated with sodium hydride (0.271 g, 11.29 mmol) at room temperature for 1 h, then *tert*-butyl 2-(((1*s*,4*s*)-4-(tosyloxymethyl)cyclohexyl)methoxy)acetate (4.66 g, 11.29 mmol) was added. The reaction mixture was heated to 50 °C for 16 h and quenched by water (2 mL). The mixture was extracted by EtOAc, dried over MgSO<sub>4</sub>, and concentrated. The residue was purified by silica gel column chromatography to give the title compound (a mixture of two regioisomers) as colorless oil (4.5 g). LCMS *m/z* = 551.1 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 1.04-1.19 (m, 4H), 1.33-1.44 (m, 4H), 1.46 (s, 9H), 1.47 (d, *J* = 8.08 Hz, 4H), 1.67-1.77 (m, 1H), 1.85-1.91 (m, 1H), 1.90-1.99 (m, 1H), 3.25 (d, *J* = 7.07 Hz, 2H), 3.87 (s, 2H), 3.91 (d, *J* = 7.58 Hz, 2H), 7.28-7.54 (m, 5H).

**Step D: Preparation of 2-(((1*s*,4*s*)-4-((5-Cyclopropyl-4-(3-methoxyphenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid.**

A mixture of 3-methoxyphenylboronic acid (27.4 mg, 0.18 mmol), *tert*-butyl 2-(((1*s*,4*s*)-4-((3-cyclopropyl-4-iodo-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((5-cyclopropyl-4-iodo-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers (100 mg, 0.18 mmol), tetrakis(triphenylphosphine)palladium (10.0 mg, 0.009 mmol), K<sub>2</sub>CO<sub>3</sub> (2 M aq., 0.2 mL) and dioxane (4 mL) was heated to 150 °C under microwave irradiation for 4 h. The mixture was filtered and concentrated. The residue was treated with HCl (4 M in dioxane, 5 mL) at room temperature for 10 h. The mixture was concentrated and purified by HPLC to give the title compound (one of the two regioisomers separated) as white solid (23.5 mg). LCMS *m/z* = 475.3 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD) δ ppm 0.35-0.48 (m, 2H), 0.86-0.99 (m, 2H), 1.44-1.80 (m, 8H), 1.83-2.01 (m, 1H), 2.29-2.41 (m, 1H), 2.67-2.76 (m, 1H), 3.57 (d, *J* = 6.95 Hz, 2H), 3.74 (s, 3H), 4.13 (s, 2H), 4.30 (d, *J* = 7.33 Hz, 2H), 6.70-7.00 (m, 4H), 7.17-7.55 (m, 5H).

**Example 1.168: Preparation of 2-(((1*s*,4*s*)-4-((5-Cyclopropyl-3,4-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 122).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((3-cyclopropyl-4-iodo-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((5-cyclopropyl-4-iodo-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and phenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.167**. LCMS  $m/z$  = 445.4  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 0.20-0.27 (m, 2H), 0.74-0.81 (m, 2H), 1.36-1.56 (m, 8H), 1.70-1.81 (m, 1H), 1.81-1.91 (m, 1H), 2.13-2.28 (m, 1H), 3.42 (d,  $J$  = 6.95 Hz, 2H), 4.00 (s, 2H), 4.17 (d,  $J$  = 7.45 Hz, 2H), 7.16-7.25 (m, 5H), 7.25-7.37 (m, 5H).

**Example 1.169: Preparation of 2-(((1*s*,4*s*)-4-((3-Isopropyl-4-(3-methoxyphenyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 123).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-iodo-5-isopropyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-iodo-3-isopropyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers, and 3-methoxyphenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.161**. LCMS  $m/z$  = 477.3  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  ppm 1.10-1.26 (m, 4H), 1.29 (d,  $J$  = 6.95 Hz, 6H), 1.30-1.45 (m, 4H), 1.66-1.76 (m, 1H), 1.95-2.06 (m, 1H), 3.10-3.22 (m, 1H), 3.29 (d,  $J$  = 6.95 Hz, 2H), 3.66 (s, 3H), 4.00 (s, 2H), 4.10 (d,  $J$  = 7.71 Hz, 2H), 6.60-6.81 (m, 3H), 7.13-7.31 (m, 3H), 7.33-7.46 (m, 3H).

**Example 1.170: Preparation of 2-(((1*s*,4*s*)-4-((4-(3-Chlorophenyl)-3-isopropyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 124).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-iodo-5-isopropyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-iodo-3-isopropyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 3-chlorophenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.161**. LCMS  $m/z$  = 481.3  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.18 (d,  $J$  = 6.82 Hz, 6H), 1.21-1.35 (m, 4H), 1.37-1.56 (m, 4H), 1.83-1.95 (m, 1H), 2.06-2.17 (m, 1H), 2.96-3.06 (m, 1H), 3.20 (d,  $J$  = 7.07 Hz, 2H), 3.91 (s, 2H), 3.93 (d,  $J$  = 7.83 Hz, 2H), 7.01-7.09 (m, 1H), 7.15-7.31 (m, 5H), 7.35-7.44 (m, 3H).

**Example 1.171: Preparation of 2-(((1*s*,4*s*)-4-((4-(2-Fluoro-3-methoxyphenyl)-3-isopropyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 125).**



From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-iodo-5-isopropyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-iodo-3-isopropyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 2-fluoro-3-methoxyphenylboronic acid, the title compound (one of the two regioisomers separated) was  
5 obtained using a similar method to the one described in **Example 1.161**. LCMS  $m/z$  = 495.3 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  ppm 1.24 (d,  $J$  = 6.82 Hz, 6H), 1.25-1.33 (m, 4H), 1.34-1.43 (m, 4H), 1.72-1.82 (m, 1H), 2.07-2.15 (m, 1H), 2.98-3.08 (m, 1H), 3.42 (d,  $J$  = 6.82 Hz, 2H), 3.77 (s, 3H), 3.99 (s, 2H), 4.01 (d,  $J$  = 7.59 Hz, 2H), 6.81-6.88 (m, 1H), 6.96-7.04 (m, 2H), 7.22-7.30 (m, 2H), 7.32-7.40 (m, 3H).

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**Example 1.172: Preparation of 2-(((1*s*,4*s*)-4-((5-Cyclopropyl-4-(2-fluoro-3-methoxyphenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 126).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((3-cyclopropyl-4-iodo-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((5-cyclopropyl-4-iodo-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 2-fluoro-3-methoxyphenylboronic acid, the title compound was obtained using a similar method to the one described in **Example 1.167**. LCMS  $m/z$  = 493.3 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  ppm 0.38-0.45 (m, 2H), 0.82-0.90 (m, 2H), 1.49-1.71 (m, 8H), 1.82-1.90 (m, 1H), 1.90-2.00 (m, 1H),  
15 2.29-2.40 (m, 1H), 3.57 (d,  $J$  = 6.95 Hz, 2H), 3.93 (s, 3H), 4.13 (s, 2H), 4.31 (d,  $J$  = 7.58 Hz, 2H), 6.66-6.77 (m, 2H), 7.01-7.15 (m, 3H), 7.22-7.39 (m, 3H).

**Example 1.173: Preparation of 2-(((1*s*,4*s*)-4-((5-Cyclopropyl-4-(2,3-difluorophenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 127).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((3-cyclopropyl-4-iodo-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((5-cyclopropyl-4-iodo-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 2,3-difluorophenylboronic acid, the title compound was obtained using a similar method to the one described in **Example 1.167**. LCMS  $m/z$  = 481.2 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  ppm  
25 0.36-0.42 (m, 2H), 0.85-0.94 (m, 2H), 1.48-1.72 (m, 8H), 1.84-1.91 (m, 1H), 1.89-1.97 (m, 1H), 2.29-2.40 (m, 1H), 3.56 (d,  $J$  = 6.95 Hz, 2H), 4.12 (s, 2H), 4.31 (d,  $J$  = 7.70 Hz, 2H), 6.92-7.04 (m, 2H), 7.09-7.19 (m, 2H), 7.19-7.40 (m, 4H).

**Example 1.174: Preparation of 2-(((1*s*,4*s*)-4-((5-Isopropyl-4-(3-methoxyphenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 128).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-iodo-5-isopropyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-iodo-3-isopropyl-5-phenyl-

1 *H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 3-methoxyphenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.161**. LCMS  $m/z$  = 477.3 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD)  $\delta$  ppm 1.23 (d,  $J$  = 7.07 Hz, 6H), 1.44-1.75 (m, 8H), 1.90-2.00 (m, 1H), 2.17-2.27 (m, 1H), 3.19-3.30 (m, 1H), 3.58 (d,  $J$  = 7.07 Hz, 2H), 3.78 (s, 3H), 4.13 (s, 2H), 4.17 (d,  $J$  = 7.58 Hz, 2H), 6.78-6.97 (m, 3H), 7.20-7.25 (m, 3H), 7.27-7.37 (m, 3H).

**Example 1.175: Preparation of 2-(((1*s*,4*s*)-4-((4-(3-Chlorophenyl)-5-isopropyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 129).**

10 From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-iodo-5-isopropyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-iodo-3-isopropyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 3-chlorophenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.161**. LCMS  $m/z$  = 481.3 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  ppm 1.09 (d,  $J$  = 7.07 Hz, 6H), 1.34-1.57 (m, 8H), 1.74-1.83 (m, 1H), 2.06-2.17 (m, 1H), 2.95-3.05 (m, 1H), 3.43 (d,  $J$  = 7.07 Hz, 2H), 3.99 (s, 2H), 4.07 (d,  $J$  = 7.33 Hz, 2H), 7.01-7.08 (m, 1H), 7.12-7.27 (m, 4H), 7.32-7.54 (m, 4H).

20 **Example 1.176: Preparation of 2-(((1*s*,4*s*)-4-((4-(2-Fluoro-3-methoxyphenyl)-5-isopropyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 130).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-iodo-5-isopropyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-iodo-3-isopropyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 2-fluoro-3-methoxyphenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.161**. LCMS  $m/z$  = 495.3 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  ppm 1.12 (d,  $J$  = 7.07 Hz, 6H), 1.39-1.55 (m, 8H), 1.70-1.82 (m, 1H), 1.86-1.97 (m, 1H), 2.75-2.85 (m, 1H), 3.20 (d,  $J$  = 7.07 Hz, 2H), 3.77 (s, 3H), 3.91 (s, 2H), 3.96 (d,  $J$  = 7.83 Hz, 2H), 6.97-7.05 (m, 1H), 7.13-7.30 (m, 4H), 7.31-7.40 (m, 3H).

30 **Example 1.177: Preparation of Methyl 2-(((1*s*,4*s*)-4-((5-(Methylthio)-3,4-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl) Methoxy)acetate (Compound 131).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-iodo-5-(methylthio)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and phenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.151**. LCMS  $m/z$  = 451.2 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  ppm 1.32-1.53 (m, 8H), 1.70-1.80 (m, 1H), 2.12 (s, 3H), 2.15-2.25 (m, 1H), 3.39 (d,  $J$  = 6.95 Hz, 2H), 3.80 (s, 2H), 4.28 (d,  $J$  = 7.45 Hz, 2H), 7.22-7.29 (m, 5H), 7.30-7.43 (m, 5H).

**Example 1.178: Preparation of 2-(((1*s*,4*s*)-4-((4-(3-Chlorophenyl)-3-cyclopropyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 132).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((3-cyclopropyl-4-iodo-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((5-cyclopropyl-4-iodo-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 3-chlorophenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.167**. LCMS  $m/z$  = 479.3  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 0.54-0.62 (m, 4H), 0.76-0.92 (m, 4H), 0.95-1.10 (m, 4H), 1.30-1.41 (m, 1H), 1.53-1.60 (m, 1H), 1.60-1.69 (m, 1H), 2.95 (d,  $J$  = 6.82 Hz, 2H), 3.61 (d,  $J$  = 7.33 Hz, 2H), 3.67 (s, 2H), 6.85-6.93 (m, 2H), 6.95-7.07 (m, 4H), 7.08-7.23 (m, 3H).

**Example 1.179: Preparation of 2-(((1*s*,4*s*)-4-((4-(3-Chlorophenyl)-5-cyclopropyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 133).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((3-cyclopropyl-4-iodo-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((5-cyclopropyl-4-iodo-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 3-chlorophenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.167**. LCMS  $m/z$  = 479.3  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  ppm 0.34-0.41 (m, 2H), 0.87-0.95 (m, 2H), 1.37-1.65 (m, 8H), 1.71-1.80 (m, 1H), 1.88-1.97 (m, 1H), 2.23-2.33 (m, 1H), 3.53 (d,  $J$  = 6.95 Hz, 2H), 4.11 (s, 2H), 4.31 (d,  $J$  = 7.58 Hz, 2H), 7.00-7.05 (m, 1H), 7.19-7.30 (m, 6H), 7.30-7.36 (m, 2H).

**Example 1.180: Preparation of Methyl 2-(((1*s*,4*s*)-4-((4-(3-Methoxyphenyl)-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl) Methoxy)acetate (Compound 136).**

To a solution of *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-methyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers (100 mg, 0.19 mmol) in dioxane (3 mL) were added 3-methoxyphenylboronic acid (28.9 mg, 0.19 mmol), tetrakis(triphenylphosphine)palladium (22 mg, 0.019 mmol), and K<sub>2</sub>CO<sub>3</sub> (2 M aq., 0.2 mL). The reaction was heated to 150 °C under microwave irradiation for 4 h. The reaction mixture was filtered and concentrated. The residue was treated with HCl (4.0 M in dioxane, 5 mL) at room temperature for 10 h. The mixture was concentrated and purified by HPLC to give 2-(((1*s*,4*s*)-4-((4-(3-methoxyphenyl)-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid. The title compound (15.4 mg) was obtained by treating the above acid with anhydrous methanol for 1 h. LCMS  $m/z$  = 463.3  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.31-1.53 (m, 8H), 1.69-1.80 (m, 1H), 2.03-2.13 (m, 1H), 2.21 (s, 3H), 3.36 (d,  $J$  = 7.07 Hz, 2H), 3.56 (s, 3H), 3.68 (s, 3H), 3.82

(s, 2H), 4.04 (d,  $J = 7.45$  Hz, 2H), 6.67-6.75 (m, 2H), 6.83-6.88 (m, 1H), 7.20-7.30 (m, 4H), 7.30-7.35 (m, 2H).

**Example 1.181: Preparation of 2-(((1*s*,4*s*)-4-((3-(4-Fluorophenyl)-5-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 137).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((3-bromo-3-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((3-bromo-5-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 4-fluorophenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.107**. LCMS  $m/z = 437.2$   $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.35-1.53 (m, 8H), 1.72-1.81 (m, 1H), 2.05-2.13 (m, 1H), 2.20 (s, 3H), 3.42 (d,  $J = 6.95$  Hz, 2H), 3.99 (s, 2H), 4.05 (d,  $J = 7.58$  Hz, 2H), 7.03-7.18 (m, 4H), 7.25-7.42 (m, 5H).

**Example 1.182: Preparation of 2-(((1*s*,4*s*)-4-((3-(4-Chlorophenyl)-5-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 138).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((3-bromo-3-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((3-bromo-5-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 4-chlorophenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.107**. LCMS  $m/z = 453.2$   $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.33-1.53 (m, 8H), 1.71-1.82 (m, 1H), 2.03-2.14 (m, 1H), 2.20 (s, 3H), 3.42 (d,  $J = 6.95$  Hz, 2H), 3.99 (s, 2H), 4.05 (d,  $J = 7.45$  Hz, 2H), 7.13-7.19 (m, 3H), 7.28-7.34 (m, 3H), 7.35-7.41 (m, 3H).

**Example 1.183: Preparation of 2-(((1*s*,4*s*)-4-((5-Methyl-4-phenyl-3-*p*-tolyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 139).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((3-bromo-3-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((3-bromo-5-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and *p*-tolylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.107**. LCMS  $m/z = 433.3$   $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.35-1.53 (m, 8H), 1.72-1.80 (m, 1H), 2.04-2.13 (m, 1H), 2.19 (s, 3H), 2.25 (s, 3H), 3.42 (d,  $J = 6.95$  Hz, 2H), 3.99 (s, 2H), 4.03 (d,  $J = 7.45$  Hz, 2H), 7.00-7.07 (m, 2H), 7.11-7.22 (m, 4H), 7.24-7.40 (m, 3H).

**Example 1.184: Preparation of 2-(((1*s*,4*s*)-4-((3-(4-Methoxyphenyl)-5-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 140).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((5-bromo-3-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((3-bromo-5-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 4-methoxyphenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.107**. LCMS  $m/z$  = 449.3 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  ppm 1.34-1.53 (m, 8H), 1.71-1.80 (m, 1H), 2.04-2.14 (m, 1H), 2.19 (s, 3H), 3.42 (d,  $J$  = 7.07 Hz, 2H), 3.71 (s, 3H), 3.99 (s, 2H), 4.02 (d,  $J$  = 7.45 Hz, 2H), 6.77-6.85 (m, 2H), 7.12-7.19 (m, 2H), 7.18-7.41 (m, 5H).

**Example 1.185: Preparation of 2-(((1*s*,4*s*)-4-((3-(2,4-Difluorophenyl)-5-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 141).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((5-bromo-3-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((3-bromo-5-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 2,4-difluorophenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.107**. LCMS  $m/z$  = 454.2 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  ppm 1.31-1.53 (m, 8H), 1.70-1.81 (m, 1H), 2.03-2.14 (m, 1H), 2.29 (s, 3H), 3.41 (d,  $J$  = 6.95 Hz, 2H), 3.99 (s, 2H), 4.07 (d,  $J$  = 7.45 Hz, 2H), 7.04-7.08 (m, 2H), 7.08-7.24 (m, 3H), 7.25-7.43 (m, 3H).

**Example 1.186: Preparation of 2-(((1*s*,4*s*)-4-((4-(2,3-Difluorophenyl)-5-(ethylthio)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 142).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((5-(ethylthio)-4-iodo-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and 2,3-difluoro-methoxyphenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.149**. LCMS  $m/z$  = 501.2 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  ppm 0.95 (t,  $J$  = 7.33 Hz, 3H), 1.30-1.53 (m, 8H), 1.69-1.81 (m, 1H), 2.15-2.27 (m, 1H), 2.56 (q,  $J$  = 7.33 Hz, 2H), 3.38 (d,  $J$  = 6.95 Hz, 2H), 3.75 (s, 2H), 4.29 (d,  $J$  = 7.45 Hz, 2H), 7.14-7.21 (m, 1H), 7.23-7.37 (m, 6H), 7.42-7.52 (m, 1H).

**Example 1.187: Preparation of 2-(((1*s*,4*s*)-4-((3-(2-Fluoro-4-methoxyphenyl)-5-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 145).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((5-bromo-3-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((3-bromo-5-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 2-fluoro-4-

methoxyphenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.107**. LCMS  $m/z$  = 467.2  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.34-1.53 (m, 8H), 1.70-1.80 (m, 1H), 2.05-2.14 (m, 1H), 2.29 (s, 3H), 3.42 (d,  $J$  = 6.82 Hz, 2H), 3.66 (s, 3H), 3.99 (s, 2H), 4.07 (d,  $J$  = 7.58 Hz, 2H), 5 6.79-6.91 (m, 2H), 6.97-7.12 (m, 3H), 7.15-7.33 (m, 3H).

**Example 1.188: Preparation of 2-(((1*s*,4*s*)-4-((4-(5-Fluoropyridin-3-yl)-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 147).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-methyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 5-fluoropyridin-3-ylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.97**. LCMS  $m/z$  = 438.2  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.30-1.54 (m, 8H), 1.70-1.81 (m, 1H), 2.02-2.14 (m, 1H), 10 2.27 (s, 3H), 3.42 (d,  $J$  = 6.95 Hz, 2H), 3.99 (s, 2H), 4.08 (d,  $J$  = 7.58 Hz, 2H), 7.22-7.32 (m, 3H), 15 7.33-7.40 (m, 1H), 7.54-7.61 (m, 1H), 7.69-7.74 (m, 1H), 8.18-8.23 (m, 1H), 8.50 (d,  $J$  = 2.78 Hz, 1H).

**Example 1.189: Preparation of 2-(((1*s*,4*s*)-4-((5-(Ethylthio)-4-(5-fluoropyridin-3-yl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 148).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((5-(ethylthio)-4-iodo-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and 5-fluoropyridin-3-ylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.149**. LCMS  $m/z$  = 484.2  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 0.95 (t,  $J$  = 7.33 Hz, 3H), 1.34-1.54 (m, 8H), 1.70-1.81 (m, 1H), 2.16-2.26 (m, 1H), 2.58 (q,  $J$  = 7.33 Hz, 2H), 25 3.41 (d,  $J$  = 6.95 Hz, 2H), 4.00 (s, 2H), 4.30 (d,  $J$  = 7.58 Hz, 2H), 7.27-7.35 (m, 5H), 7.65-7.71 (m, 1H), 8.29 (t,  $J$  = 1.64 Hz, 1H), 8.55 (d,  $J$  = 2.78 Hz, 1H).

**Example 1.190: Preparation of 2-(((1*s*,4*s*)-4-((5-Ethyl-4-(5-fluoropyridin-3-yl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 149).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-ethyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-ethyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 5-fluoropyridin-3-ylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.152**. LCMS  $m/z$  = 452.2  $[M+H]^+$ ;  $^1H$  NMR (400 35 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.00-1.07 (m, 3H), 1.35-1.57 (m, 8H), 1.73-1.83 (m, 1H), 2.07-2.19 (m,

1H), 2.66 (q,  $J = 7.49$  Hz, 2H), 3.44 (d,  $J = 7.07$  Hz, 2H), 4.00 (s, 2H), 4.06 (d,  $J = 7.45$  Hz, 2H), 7.23-7.31 (m, 5H), 7.57-7.62 (m, 1H), 8.23 (t,  $J = 1.71$  Hz, 1H), 8.53 (d,  $J = 2.78$  Hz, 1H).

**Example 1.191: Preparation of 2-(((1*s*,4*s*)-4-((3,4-Diphenyl-5-(trifluoromethyl)-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 151).**

**Step A: Preparation of 3-Phenyl-5-(trifluoromethyl)-1*H*-pyrazole.**

To a stirred mixture of 4,4,4-trifluoro-1-phenylbutane-1,3-dione (5.0 g, 23.13 mmol) in dry ethanol (100 mL) was added hydrazine hydrate (1.737 g, 34.7 mmol) dropwise. The resulting solution was refluxed for 16 h. The reaction was cooled to room temperature and concentrated. The oil was diluted with saturated NaHCO<sub>3</sub> solution and extracted with EtOAc, washed with brine, dried over MgSO<sub>4</sub> and concentrated. The residue was purified by silica gel column chromatography to give the title compound as a clear liquid which was crystallized in hexanes/ethyl acetate (3.25 g). LCMS  $m/z = 213.1$  [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  ppm 6.77 (s, 1H), 7.36-7.51 (m, 3H), 7.53-7.64 (m, 2H), 11.59 (s, 1H).

**Step B: Preparation of 4-Iodo-3-phenyl-5-(trifluoromethyl)-1*H*-pyrazole.**

To a mixture of 3-phenyl-5-(trifluoromethyl)-1*H*-pyrazole (4.0 g, 18.85 mmol) in THF (50 mL) and water (50 mL) were added sodium iodide (2.83 g, 18.85 mmol), iodine (7.18 g, 28.3 mmol), and K<sub>2</sub>CO<sub>3</sub> (2.61 g, 18.85 mmol) at room temperature. The reaction was refluxed for 16 h, quenched with sodium thiosulfite (2.0 M aq. 10 mL) and concentrated under reduced pressure. The reaction was extracted with ethyl acetate and washed with NaHCO<sub>3</sub>, brine, dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give the title compound as white solid (4.0 g). LCMS  $m/z = 338.8$  [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  ppm 7.39-7.62 (m, 3H), 7.70-7.75 (m, 1H), 7.82-7.88 (m, 1H), 14.11 (s, 1H).

**Step C: Preparation of *tert*-Butyl 2-(((1*s*,4*s*)-4-((4-Iodo-5-phenyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-Butyl 2-(((1*s*,4*s*)-4-((4-Iodo-3-phenyl-5-(trifluoromethyl)-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a Mixture of Regioisomers.**

To a solution of 4-iodo-3-phenyl-5-(trifluoromethyl)-1*H*-pyrazole (2.0 g, 5.92 mmol) in DMF (6 mL) was added sodium hydride (0.14 g, 5.92 mmol) in portions at 0 °C. The reaction was stirred at that temperature for 1 h and *tert*-butyl 2-(((1*s*,4*s*)-4-(tosyloxymethyl)cyclohexyl)methoxy)acetate (2.44 g, 5.92 mmol) was added. The reaction was gently heated to 60 °C for 16 h, quenched with water (2 mL), extracted with ethyl acetate, dried over MgSO<sub>4</sub>, and concentrated. The residue was purified by silica gel column chromatography to give the title compound (a mixture of two regioisomers) as a colorless liquid (2.7 g). LCMS  $m/z = 579.1$  [M+H]<sup>+</sup>.

**Step D: Preparation of 2-(((1*s*,4*s*)-4-((3,4-Diphenyl-5-(trifluoromethyl)-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid.**

In a solution of *tert*-butyl 2-(((1*s*,4*s*)-4-((4-iodo-5-phenyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-iodo-3-phenyl-5-(trifluoromethyl)-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers (100 mg, 0.17 mmol) in dioxane (3 mL) were added phenylboronic acid (21.0 mg, 0.17 mmol),  
5 tetrakis(triphenylphosphine)palladium (22 mg, 0.019 mmol), and K<sub>2</sub>CO<sub>3</sub> (2 M aq., 0.2 mL). The reaction was heated to 150 °C under microwave irradiation for 4 h. The reaction mixture was filtered and concentrated. The residue was treated with HCl (4.0 M in dioxane, 4 mL) at room temperature for 10 h. The mixture was concentrated and purified by HPLC to give the title compound as a white solid (16.4 mg). LCMS *m/z* = 473.2 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.35-1.54 (m, 8H), 1.73-1.82 (m, 1H), 2.13-2.21 (m, 1H), 3.42 (d, *J* = 7.07 Hz, 2H), 3.99 (s, 2H), 4.27 (d, *J* = 7.45 Hz, 2H), 7.23-7.29 (m, 5H), 7.37-7.43 (m, 5H), 12.30-12.76 (m, 1H).  
10

**Example 1.192: Preparation of 2-(((1*s*,4*s*)-4-((3-Phenyl-4-*p*-tolyl-5-(trifluoromethyl)-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 152).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-iodo-5-phenyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-iodo-3-phenyl-5-(trifluoromethyl)-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and *p*-tolylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.191**. LCMS *m/z* = 487.2 [M+H]<sup>+</sup>; <sup>1</sup>H  
15 NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.34-1.54 (m, 8H), 1.73-1.83 (m, 1H), 2.12-2.21 (m, 1H), 2.34 (s, 3H), 3.42 (d, *J* = 7.07 Hz, 2H), 3.99 (s, 2H), 4.26 (d, *J* = 7.45 Hz, 2H), 7.09-7.15 (m, 2H), 7.18-7.23 (m, 2H), 7.23-7.30 (m, 5H), 12.47 (s, 1H).  
20

**Example 1.193: Preparation of 2-(((1*s*,4*s*)-4-((4-(3-Methoxyphenyl)-5-phenyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 154).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-iodo-5-phenyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-iodo-3-phenyl-5-(trifluoromethyl)-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers  
25 and 3-methoxyphenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.191**. LCMS *m/z* = 503.2 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.01-1.22 (m, 4H), 1.23-1.41 (m, 4H), 1.54-1.70 (m, 1H), 1.86-2.02 (m, 1H), 3.15 (d, *J* = 6.82 Hz, 2H), 3.49 (s, 2H), 3.62 (s, 3H), 4.03 (d, *J* = 7.07 Hz, 2H), 6.63-6.87 (m, 4H), 7.13-7.24 (m, 2H), 7.29-7.53 (m, 3H).  
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**Example 1.194: Preparation of 2-(((1*s*,4*s*)-4-((4-(3-Methoxyphenyl)-3-phenyl-5-(trifluoromethyl)-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 155).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-iodo-5-phenyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-iodo-3-phenyl-5-(trifluoromethyl)-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 3-methoxyphenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.191**. LCMS  $m/z$  = 503.2  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.34-1.53 (m, 8H), 1.69-1.82 (m, 1H), 2.11-2.19 (m, 1H), 3.35 (d,  $J$  = 7.58 Hz, 2H), 3.53 (s, 2H), 3.71 (s, 3H), 4.26 (d,  $J$  = 7.96 Hz, 2H), 6.77-6.83 (m, 2H), 6.94-7.01 (m, 2H), 7.22-7.35 (m, 5H).

**Example 1.195: Preparation of 2-(((1*s*,4*s*)-4-((5-Ethyl-4-(3-hydroxyphenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 172).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-ethyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-ethyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 3-hydroxyphenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.152**. LCMS  $m/z$  = 449.2  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.03 (t,  $J$  = 7.45 Hz, 3H), 1.31-1.56 (m, 8H), 1.69-1.83 (m, 1H), 2.03-2.19 (m, 1H), 2.58 (q,  $J$  = 7.41 Hz, 2H), 3.40 (d,  $J$  = 7.07 Hz, 2H), 3.79 (s, 2H), 4.01 (d,  $J$  = 7.58 Hz, 2H), 6.54-6.63 (m, 2H), 6.67-6.75 (m, 1H), 7.09-7.38 (m, 6H).

**Example 1.196: Preparation of 2-(((1*s*,4*s*)-4-((4-(3-Hydroxyphenyl)-5-(methylthio)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 173).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-iodo-5-(methylthio)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and phenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.151**. LCMS  $m/z$  = 467.2  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.31-1.53 (m, 8H), 1.70-1.80 (m, 1H), 2.13 (s, 3H), 2.15-2.25 (m, 1H), 3.38 (d,  $J$  = 7.07 Hz, 2H), 3.80 (s, 2H), 4.26 (d,  $J$  = 7.33 Hz, 2H), 6.63-6.78 (m, 3H), 7.13-7.20 (m, 1H), 7.21-7.30 (m, 3H), 7.33-7.38 (m, 2H).

**Example 1.197: Preparation of 2-(((1*s*,4*s*)-4-((5-(Ethylthio)-4-(2-fluoro-3-hydroxyphenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 174).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((5-(ethylthio)-4-iodo-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and 2-fluoro-3-hydroxyphenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one

described in **Example 1.149**. LCMS  $m/z = 499.2$   $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 0.97 (t,  $J = 7.33$  Hz, 3H), 1.31-1.53 (m, 8H), 1.68-1.81 (m, 1H), 2.14-2.25 (m, 1H), 2.54 (q,  $J = 7.33$  Hz, 2H), 3.38 (d,  $J = 6.82$  Hz, 2H), 3.74 (s, 2H), 4.27 (d,  $J = 7.33$  Hz, 2H), 6.64-6.73 (m, 1H), 6.95-7.06 (m, 2H), 7.19-7.30 (m, 2H), 7.34-7.40 (m, 2H), 7.41-7.53 (m, 1H).

5

**Example 1.198: Preparation of 2-(((1*s*,4*s*)-4-((5-(Ethylthio)-4-(3-hydroxyphenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 177).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((5-(ethylthio)-4-iodo-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and 3-hydroxyphenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.149**. LCMS  $m/z = 489.2$   $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 0.97 (t,  $J = 7.33$  Hz, 3H), 1.31-1.53 (m, 8H), 1.70-1.81 (m, 1H), 2.14-2.25 (m, 1H), 2.53 (q,  $J = 7.33$  Hz, 2H), 3.41 (d,  $J = 7.07$  Hz, 2H), 4.00 (s, 2H), 4.26 (d,  $J = 7.58$  Hz, 2H), 6.63-6.76 (m, 2H), 7.14-7.21 (m, 2H), 7.21-7.30 (m, 3H), 7.32-7.39 (m, 2H).

15

**Example 1.199: Preparation of 2-(((1*s*,4*s*)-4-((4-(3-Hydroxyphenyl)-5-(2-methoxyethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 180).**

**Step A: Preparation of 5-(2-Methoxyethyl)-3-phenyl-1*H*-pyrazole.**

To a solution of acetophenone (3.5 g, 29.1 mmol) in dry toluene (10 mL) was added LiHMDS (1.0 M in toluene) via syringe at 0 °C under argon. After 5 min, 3-methoxypropanoyl chloride (3.57 g, 29.1 mmol) was added in one portion via syringe. The ice bath was removed and AcOH (2 mL), EtOH (100 mL), and hydrazine hydrate (4.37 g, 87 mmol) were added. The reaction was refluxed for 2 h, cooled to room temperature, and concentrated. The residue was extracted with EtOAc/H<sub>2</sub>O, washed with brine, dried over MgSO<sub>4</sub>, and concentrated. The resulting residue was purified by silica gel column chromatography to give the title compound as pale yellow oil (2.0 g). LCMS  $m/z = 203.1$   $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 2.85 (bs, 2H), 3.27 (s, 3H), 3.59 (t,  $J = 6.82$  Hz, 2H), 6.49 (s, 1H), 7.21-7.46 (m, 3H), 7.74 (m, 2H), 12.56 (s, 1H).

25

**Step B: Preparation of 4-Bromo-5-(2-methoxyethyl)-3-phenyl-1*H*-pyrazole.**

To a solution of 5-(2-methoxyethyl)-3-phenyl-1*H*-pyrazole (2.0 g, 9.89 mmol) in DCM (100 mL) was added bromine (4.74 g, 29.7 mmol) dropwise at 0 °C. The reaction was stirred at that temperature for 1 h and continued at room temperature for 2 h before quenched with Na<sub>2</sub>SO<sub>3</sub> (10% aq.). The organics were separated, and the aqueous layer was extracted with DCM (2 × 50 mL). The combined organics were washed with brine, dried over MgSO<sub>4</sub>, and concentrated to give the title compound (2.5 g). LCMS  $m/z = 281.1$   $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 2.87 (t,  $J = 6.82$  Hz, 2H), 3.27 (s, 3H), 3.62 (t,  $J = 6.82$  Hz, 2H), 5.75 (s, 1H), 7.35-7.51 (m, 3H), 7.75-7.82 (m, 2H).

35

**Step C: Preparation of *tert*-Butyl 2-(((1*s*,4*s*)-4-((4-Bromo-5-(2-methoxyethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-Butyl 2-(((1*s*,4*s*)-4-((4-Bromo-3-(2-methoxyethyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a Mixture of Regioisomers.**

5 To a solution of 4-bromo-5-(2-methoxyethyl)-3-phenyl-1*H*-pyrazole (3.0 g, 10.67 mmol) in DMF (5 mL) was added sodium hydride (0.256 g, 10.67 mmol), followed by *tert*-butyl 2-(((1*s*,4*s*)-4-(tosyloxymethyl)cyclohexyl)methoxy)acetate (4.40 g, 10.67 mmol). The reaction was gently heated to 45 °C overnight. After quenched with water (5 mL), the mixture was extracted with EtOAc, washed with brine, dried over MgSO<sub>4</sub>, and concentrated. The residue was purified by silica gel  
10 column chromatography to give the title compound (a mixture of two regioisomers, 4.5 g). LCMS *m/z* = 523.4 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.69-1.80 (m, 4H), 1.81-1.89 (m, 4H), 1.91 (s, 9H), 2.19-2.30 (m, 2H), 2.90 (s, 3H), 3.46 (t, *J* = 6.63 Hz, 2H), 3.89 (d, *J* = 6.95 Hz, 2H), 4.02 (t, *J* = 6.32 Hz, 2H), 4.43 (s, 2H), 4.56 (d, *J* = 7.45 Hz, 2H), 7.81-7.99 (m, 3H), 8.24-8.32 (m, 2H).

15 **Step D: Preparation of 2-(((1*s*,4*s*)-4-((4-(3-Hydroxyphenyl)-5-(2-methoxyethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid.**

To a solution of *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-(2-methoxyethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-(2-methoxyethyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of  
20 regioisomers (100 mg, 0.192 mmol) in dioxane (3 mL) were added 3-hydroxyphenylboronic acid (26.5 mg, 0.192 mmol), tetrakis(triphenylphosphine)palladium (22 mg, 0.019 mmol), and K<sub>2</sub>CO<sub>3</sub> (2 M aq., 0.2 mL). The reaction was heated to 150 °C under microwave irradiation for 4 h. The reaction mixture was filtered and concentrated. The residue was treated with HCl (4.0 M in dioxane, 5 mL) at room temperature for 10 h. The mixture was concentrated and purified by HPLC to give  
25 the title compound (one of the two regioisomers separated) as a white solid (12.8 mg). LCMS *m/z* = 479.3 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.32-1.57 (m, 8H), 1.73-1.82 (m, 1H), 2.07-2.18 (m, 1H), 2.83 (t, *J* = 6.95 Hz, 2H), 3.15 (s, 3H), 3.35 (t, *J* = 6.95 Hz, 2H), 3.43 (d, *J* = 7.07 Hz, 2H), 4.00 (s, 2H), 4.05 (d, *J* = 7.58 Hz, 2H), 6.56-6.75 (m, 3H), 7.14-7.26 (m, 4H), 7.30-7.37 (m, 2H).

30

**Example 1.200: Preparation of 2-(((1*s*,4*s*)-4-((5-(2-Methoxyethyl)-4-(6-methoxypyridin-3-yl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 181).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-(2-methoxyethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-(2-methoxyethyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 6-methoxypyridin-3-ylboronic acid, the title compound (one of the two regioisomers separated) was  
35 obtained using a similar method to the one described in **Example 1.199**. LCMS *m/z* = 494.3

[M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.33-1.57 (m, 8H), 1.74-1.84 (m, 1H), 2.09-2.18 (m, 1H), 2.83 (t, *J* = 6.69 Hz, 2H), 3.16 (s, 3H), 3.38 (t, *J* = 6.69 Hz, 2H), 3.43 (d, *J* = 7.07 Hz, 2H), 3.87 (s, 3H), 4.00 (s, 2H), 4.06 (d, *J* = 7.33 Hz, 2H), 6.83 (d, *J* = 8.59 Hz, 1H), 7.19-7.33 (m, 5H), 7.51 (dd, *J* = 8.46, 2.40 Hz, 1H), 8.01 (d, *J* = 2.02 Hz, 1H).

5

**Example 1.201: Preparation of 2-(((1*s*,4*s*)-4-((4-(2-Fluoro-3-hydroxyphenyl)-5-(2-methoxyethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 182).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-(2-methoxyethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-(2-methoxyethyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 2-fluoro-3-hydroxyphenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.199**. LCMS *m/z* = 497.2 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.31-1.54 (m, 8H), 1.72-1.84 (m, 1H), 2.06-2.19 (m, 1H), 2.79 (t, *J* = 6.32 Hz, 2H), 3.12 (s, 3H), 3.31 (t, *J* = 6.95 Hz, 2H), 3.40 (d, *J* = 6.82 Hz, 2H), 3.68 (s, 2H), 4.07 (d, *J* = 7.07 Hz, 2H), 6.59-6.65 (m, 1H), 6.94-7.04 (m, 2H), 7.16-7.27 (m, 3H), 7.31-7.37 (m, 2H).

**Example 1.202: Preparation of 2-(((1*s*,4*s*)-4-((4-(2,3-Difluorophenyl)-5-(2-methoxyethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 190).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-(2-methoxyethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-(2-methoxyethyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 2,3-difluoro-phenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.199**. LCMS *m/z* = 499.2 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.31-1.56 (m, 8H), 1.71-1.83 (m, 1H), 2.07-2.19 (m, 1H), 2.83 (t, *J* = 6.32 Hz, 2H), 3.11 (s, 3H), 3.33 (t, *J* = 6.57 Hz, 2H), 3.39 (d, *J* = 6.82 Hz, 2H), 3.67 (s, 2H), 4.09 (d, *J* = 7.33 Hz, 2H), 7.10-7.18 (m, 1H), 7.19-7.33 (m, 6H), 7.38-7.48 (m, 1H).

**Example 1.203: Preparation of 2-(((1*s*,4*s*)-4-((4-(3-Chloro-2-fluorophenyl)-5-(2-methoxyethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 191).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-(2-methoxyethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-(2-methoxyethyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 3-chloro-2-fluorophenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.199**. LCMS *m/z* = 515.2

[M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.28-1.55 (m, 8H), 1.71-1.85 (m, 1H), 2.07-2.19 (m, 1H), 2.81 (t, *J* = 5.68 Hz, 2H), 3.11 (s, 3H), 3.32 (t, *J* = 6.44 Hz, 2H), 3.40 (d, *J* = 6.82 Hz, 2H), 3.68 (s, 2H), 4.09 (d, *J* = 7.33 Hz, 2H), 7.18-7.34 (m, 6H), 7.55-7.63 (m, 2H).

5 **Example 1.204: Preparation of 2-(((1*s*,4*s*)-4-((4-(2-Fluoro-3-methylphenyl)-5-(2-methoxyethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 192).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-(2-methoxyethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-(2-methoxyethyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 2-  
10 fluoro-3-methylphenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.199**. LCMS *m/z* = 495.3  
[M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.32-1.56 (m, 8H), 1.72-1.83 (m, 1H), 2.06-2.17 (m, 1H), 2.23 (s, 3H), 2.78 (t, *J* = 5.94 Hz, 2H), 3.11 (s, 3H), 3.30 (t, *J* = 6.06 Hz, 2H), 3.40 (d, *J* =  
15 6.57 Hz, 2H), 3.71 (s, 2H), 4.07 (d, *J* = 6.82 Hz, 2H), 7.05-7.16 (m, 3H), 7.16-7.34 (m, 5H).

**Example 1.205: Preparation of 2-(((1*s*,4*s*)-4-((5-(2-Methoxyethyl)-3-phenyl-4-*m*-tolyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 193).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-(2-methoxyethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-(2-methoxyethyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and *m*-  
20 tolylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.199**. LCMS *m/z* = 477.3 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.32-1.54 (m, 8H), 1.72-1.84 (m, 1H), 2.06-2.18 (m, 1H), 2.28 (s, 3H), 2.82  
25 (t, *J* = 6.82 Hz, 2H), 3.14 (s, 3H), 3.35 (t, *J* = 6.82 Hz, 2H), 3.40 (d, *J* = 7.07 Hz, 2H), 3.69 (s, 2H), 4.06 (d, *J* = 7.33 Hz, 2H), 6.97 (d, *J* = 7.58 Hz, 1H), 7.04 (s, 1H), 7.13 (d, *J* = 7.58 Hz, 1H), 7.17-7.35 (m, 6H).

30 **Example 1.206: Preparation of 2-(((1*s*,4*s*)-4-((4-(3-Fluorophenyl)-5-(2-methoxyethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 194).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-(2-methoxyethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-(2-methoxyethyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 3-  
fluorophenylboronic acid, the title compound (one of the two regioisomers separated) was obtained  
35 using a similar method to the one described in **Example 1.199**. LCMS *m/z* = 481.3 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.32-1.56 (m, 8H), 1.73-1.83 (m, 1H), 2.07-2.18 (m, 1H), 2.87 (t, *J* = 6.69 Hz, 2H), 3.15 (s, 3H), 3.37 (t, *J* = 6.69 Hz, 2H), 3.41 (d, *J* = 7.07 Hz, 2H), 3.83 (s, 2H),

4.07 (d,  $J = 7.33$  Hz, 2H), 7.01-7.06 (m, 2H), 7.11-7.18 (m, 1H), 7.19-7.33 (m, 4H), 7.37-7.45 (m, 2H).

**Example 1.207: Preparation of 2-(((1*s*,4*s*)-4-((4-(2-Methoxypyridin-4-yl)-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 195).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-methyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 2-methoxypyridin-4-ylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.97**. LCMS  $m/z = 450.2$   $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.32-1.54 (m, 8H), 1.71-1.80 (m, 1H), 2.04-2.13 (m, 1H), 2.28 (s, 3H), 3.42 (d,  $J = 7.07$  Hz, 2H), 3.85 (s, 3H), 3.99 (s, 2H), 4.06 (d,  $J = 7.33$  Hz, 2H), 6.62 (s, 1H), 6.74 (dd,  $J = 5.31, 1.26$  Hz, 1H), 7.26-7.35 (m, 5H), 8.10 (d,  $J = 5.31$  Hz, 1H).

**Example 1.208: Preparation of 2-(((1*s*,4*s*)-4-((5-Ethyl-4-(2-methoxypyridin-4-yl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 196).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-ethyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-ethyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 2-methoxypyridin-4-ylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.152**. LCMS  $m/z = 464.3$   $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.06 (t,  $J = 7.58$  Hz, 3H), 1.32-1.57 (m, 8H), 1.71-1.83 (m, 1H), 2.07-2.18 (m, 1H), 2.67 (q,  $J = 7.49$  Hz, 2H), 3.43 (d,  $J = 6.82$  Hz, 2H), 3.85 (s, 3H), 4.00 (s, 2H), 4.04 (d,  $J = 7.33$  Hz, 2H), 6.61 (s, 1H), 6.76 (dd,  $J = 5.31, 1.26$  Hz, 1H), 7.22-7.34 (m, 5H), 8.12 (d,  $J = 5.31$  Hz, 1H).

**Example 1.209: Preparation of 2-(((1*s*,4*s*)-4-((4-(3-Chlorophenyl)-5-(2-methoxyethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 197).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-(2-methoxyethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-(2-methoxyethyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 3-chlorophenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.199**. LCMS  $m/z = 497.2$   $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.33-1.56 (m, 8H), 1.73-1.84 (m, 1H), 2.06-2.18 (m, 1H), 2.86 (t,  $J = 6.69$  Hz, 2H), 3.15 (s, 3H), 3.37 (d,  $J = 6.82$  Hz, 2H), 3.39 (t,  $J = 7.07$  Hz, 2H), 3.75 (s, 2H), 4.06 (d,  $J = 7.58$  Hz, 2H), 7.14-7.19 (m, 1H), 7.20-7.31 (m, 6H), 7.35-7.43 (m, 2H).

**Example 1.210: Preparation of 2-(((1*s*,4*s*)-4-((5-Ethyl-4-(5-methoxypyridin-3-yl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 201).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-ethyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-ethyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 5-methoxypyridin-3-ylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.152**. LCMS  $m/z$  = 464.3  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.05 (t,  $J$  = 7.52 Hz, 3H), 1.36-1.58 (m, 8H), 1.74-1.83 (m, 1H), 2.10-2.19 (m, 1H), 2.67 (q,  $J$  = 7.45 Hz, 2H), 3.44 (d,  $J$  = 7.07 Hz, 2H), 3.84 (s, 3H), 4.00 (s, 2H), 4.07 (d,  $J$  = 7.45 Hz, 2H), 7.23-7.33 (m, 5H), 7.47 (dd,  $J$  = 2.65, 1.64 Hz, 1H), 8.09 (d,  $J$  = 1.64 Hz, 1H), 8.38 (d,  $J$  = 2.78 Hz, 1H).

**Example 1.211: Preparation of 2-(((1*s*,4*s*)-4-((4-(2-Fluoro-3-hydroxyphenyl)-5-(2-(methylthio)ethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 213).**

**Step A: Preparation of 5-(2-(Methylthio)ethyl)-3-phenyl-1*H*-pyrazole.**

To a solution of acetophenone (5.0 g, 41.6 mmol) in dry toluene (10 mL) was added LiHMDS (1.0 M in toluene, 42 mL, 42 mmol) via syringe at 0 °C under argon. After 5 min, 3-(methylthio)propanoyl chloride (5.77 g, 41.6 mmol) was added in one portion via syringe. The ice bath was removed and AcOH (5 mL), EtOH (100 mL), and hydrazine hydrate (6.25 g, 125 mmol) were added. The mixture was refluxed for 2 h, cooled to room temperature, and concentrated. The residue was extracted with EtOAc/H<sub>2</sub>O, washed with brine, dried over MgSO<sub>4</sub>, and concentrated. The resulting residue was purified by silica gel column chromatography to give the title compound as a pale yellow oil (6.5 g). LCMS  $m/z$  = 219.2  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 2.09 (s, 3H), 2.77 (t,  $J$  = 7.71 Hz, 2H), 2.84-2.95 (m, 2H), 6.53 (s, 1H), 7.18-7.50 (m, 3H), 7.63-7.84 (m, 2H), 12.60 (bs, 1H).

**Step B: Preparation of 4-Bromo-5-(2-(methylthio)ethyl)-3-phenyl-1*H*-pyrazole.**

To a solution of 5-(2-(methylthio)ethyl)-3-phenyl-1*H*-pyrazole (4.0 g, 18.32 mmol) in methanol (20 mL) was added *N*-bromosuccinimide (3.26 g, 18.32 mmol) slowly at 0 °C. The reaction was stirred at 0 °C for 2 h. The mixture was concentrated and purified by silica gel column chromatography to give the title compound (3.4 g). LCMS  $m/z$  = 297.0  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 2.11 (s, 3H), 2.79 (t,  $J$  = 7.83 Hz, 2H), 2.83-2.97 (m, 2H), 7.32-7.56 (m, 3H), 7.67-7.88 (m, 2H), 13.20 (bs, 1H).

**Step C: Preparation of *tert*-Butyl 2-(((1*s*,4*s*)-4-((4-Bromo-5-(2-(methylthio)ethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-Butyl 2-(((1*s*,4*s*)-4-((4-Bromo-3-(2-(methylthio)ethyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a Mixture of Regioisomers.**

To a solution of 4-bromo-5-(2-(methylthio)ethyl)-3-phenyl-1H-pyrazole (3.4 g, 11.44 mmol) in DMF (5 mL) was added sodium hydride (0.275 g, 11.44 mmol) at room temperature, followed by *tert*-butyl 2-(((1*s*,4*s*)-4-(tosyloxymethyl)cyclohexyl)methoxy)acetate (4.72 g, 11.44 mmol). The reaction was heated to 45 °C overnight, cooled to room temperature, and quenched with water (5 mL). The mixture was extracted with EtOAc, washed with brine, dried over MgSO<sub>4</sub>, and concentrated. The residue was purified by silica gel column chromatography to give the title compound (a mixture of two regioisomers, 3.5 g). LCMS *m/z* = 539.1 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.30-1.40 (m, 4H), 1.43 (s, 9H), 1.44-1.52 (m, 4H), 1.70-1.80 (m, 1H), 2.03-2.11 (m, 1H), 2.14 (s, 3H), 2.72 (t, *J* = 7.07 Hz, 2H), 3.00 (t, *J* = 7.20 Hz, 2H), 3.40 (d, *J* = 6.95 Hz, 2H), 3.94 (s, 2H), 4.09 (d, *J* = 7.45 Hz, 2H), 7.32-7.51 (m, 3H), 7.75-7.84 (m, 2H).

**Step D: Preparation of 2-(((1*s*,4*s*)-4-((4-(2-Fluoro-3-hydroxyphenyl)-5-(2-(methylthio)ethyl)-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid.**

To a solution of *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-(2-(methylthio)ethyl)-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-(2-(methylthio)ethyl)-5-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers (100 mg, 0.19 mmol) in dioxane were added 2-fluoro-3-hydroxyphenylboronic acid (29.6 mg, 0.19 mmol), tetrakis(triphenylphosphine)palladium (22 mg, 0.019 mmol), and K<sub>2</sub>CO<sub>3</sub> (2 M aq., 0.2 mL). The reaction was heated to 150 °C under microwave irradiation for 4 h. The reaction mixture was filtered and concentrated. The residue was treated with HCl (4.0 M in dioxane, 5 mL) at room temperature for 10 h. The mixture was concentrated and purified by HPLC to give the title compound (one of the two regioisomers separated) as a white solid (15.5 mg). LCMS *m/z* = 513.2 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.32-1.57 (m, 8H), 1.74-1.82 (m, 1H), 1.88 (s, 3H), 2.08-2.18 (m, 1H), 2.46 (t, *J* = 7.71 Hz, 2H), 2.82 (t, *J* = 7.20 Hz, 2H), 3.43 (d, *J* = 7.07 Hz, 2H), 4.00 (s, 2H), 4.08 (d, *J* = 7.45 Hz, 2H), 6.65-6.72 (m, 1H), 6.91-7.04 (m, 3H), 7.17-7.28 (m, 3H), 7.31-7.37 (m, 1H).

**Example 1.212: Preparation of 2-(((1*s*,4*s*)-4-((4-(5-Methoxypyridin-3-yl)-5-methyl-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 214).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-methyl-5-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-methyl-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers, and 5-methoxypyridin-3-ylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.97**. LCMS *m/z* = 450.2 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.35-1.55 (m, 8H), 1.72-1.82 (m, 1H), 2.05-2.15 (m, 1H), 2.27 (s, 3H), 3.42 (d, *J* = 7.07 Hz, 2H), 3.81 (s, 3H), 4.00 (s, 2H), 4.08 (d, *J* = 7.45 Hz, 2H), 7.23-7.33 (m, 5H), 7.39 (dd, *J* = 2.65, 1.64 Hz, 1H), 8.04 (d, *J* = 1.52 Hz, 1H), 8.32 (d, *J* = 2.78 Hz, 1H).



**Example 1.213: Preparation of 2-(((1*s*,4*s*)-4-((5-(2-(Methylthio)ethyl)-3-phenyl-4-*m*-tolyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 216).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-(2-(methylthio)ethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-(2-(methylthio)ethyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and *m*-tolylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.211**. LCMS *m/z* = 493.3 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.33-1.56 (m, 8H), 1.70-1.82 (m, 1H), 1.89 (s, 3H), 2.07-2.16 (m, 1H), 2.29 (s, 3H), 2.50 (t, *J* = 7.06 Hz, 2H), 2.86 (t, *J* = 7.33 Hz, 2H), 3.40 (d, *J* = 6.80 Hz, 2H), 3.77 (s, 2H), 4.06 (d, *J* = 7.45 Hz, 2H), 6.98 (d, *J* = 7.71 Hz, 1H), 7.07 (s, 1H), 7.13 (d, *J* = 7.58 Hz, 1H), 7.17-7.28 (m, 4H), 7.29-7.35 (m, 2H).

**Example 1.214: Preparation of 2-(((1*s*,4*s*)-4-((4-(2-Fluoro-3-methylphenyl)-5-(2-(methylthio)ethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 218).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-(2-(methylthio)ethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-(2-(methylthio)ethyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 2-fluoro-3-methylphenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.211**. LCMS *m/z* = 511.2 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.33-1.56 (m, 8H), 1.73-1.81 (m, 1H), 1.85 (s, 3H), 2.09-2.17 (m, 1H), 2.23 (s, 3H), 2.46 (t, *J* = 7.71 Hz, 2H), 2.81 (t, *J* = 7.07 Hz, 2H), 3.41 (d, *J* = 6.95 Hz, 2H), 3.81 (s, 2H), 4.08 (d, *J* = 7.45 Hz, 2H), 7.07-7.14 (m, 2H), 7.18-7.26 (m, 3H), 7.26-7.35 (m, 3H).

**Example 1.215: Preparation of 2-(((1*s*,4*s*)-4-((4-(3-Chloro-2-fluorophenyl)-5-(2-(methylsulfinyl)ethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 219).**

2-(((1*s*,4*s*)-4-((4-(3-Chloro-2-fluorophenyl)-5-(2-(methylthio)ethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid (16.4 mg, 0.031 mmol) was dissolved in DCM (2 mL) and 3-chloroperbenzoic acid (5.33 mg, 0.031 mmol) was added. After stirred at room temperature for 30 min, the reaction mixture was concentrated and purified by HPLC to give the title compound as a white solid (10.8 mg). LCMS *m/z* = 547.2 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.33-1.56 (m, 8H), 1.74-1.82 (m, 1H), 2.10-2.20 (m, 1H), 2.46 (s, 3H), 2.66-2.77 (m, 2H), 2.83-3.00 (m, 2H), 3.43 (d, *J* = 7.07 Hz, 2H), 3.99 (s, 2H), 4.08-4.14 (m, 2H), 7.20-7.30 (m, 6H), 7.30-7.36 (m, 1H), 7.56-7.64 (m, 1H).

**Example 1.216: Preparation of 2-(((1*s*,4*s*)-4-((5-(2-(Methylsulfinyl)ethyl)-3-phenyl-4-*m*-tolyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 220).**

To a solution of 2-(((1*s*,4*s*)-4-((5-(2-(methylthio)ethyl)-3-phenyl-4-*m*-tolyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid (19.7 mg, 0.040 mmol) in DCM (2 mL) was added 3-chloroperbenzoic acid (6.9 mg, 0.040 mmol). After stirred at room temperature for 30 min, the reaction mixture was concentrated and purified by HPLC to give the title compound as a white solid (14.2 mg). LCMS  $m/z$  = 509.2  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.31-1.55 (m, 8H), 1.71-1.81 (m, 1H), 2.08-2.18 (m, 1H), 2.27 (s, 3H), 2.44 (s, 3H), 2.68-2.79 (m, 2H), 2.82-2.99 (m, 2H), 3.43 (d,  $J$  = 7.07 Hz, 2H), 3.98 (s, 2H), 4.04-4.10 (m, 2H), 6.97 (d,  $J$  = 7.58 Hz, 1H), 7.05 (s, 1H), 7.13 (d,  $J$  = 7.58 Hz, 1H), 7.17-7.27 (m, 4H), 7.28-7.33 (m, 2H).

**Example 1.217: Preparation of 2-(((1*s*,4*s*)-4-((4-(3-Hydroxyphenyl)-5-(2-(methylthio)ethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 221).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-(2-(methylthio)ethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-(2-(methylthio)ethyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 3-hydroxyphenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.211**. LCMS  $m/z$  = 495.2  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.34-1.55 (m, 8H), 1.74-1.82 (m, 1H), 1.91 (s, 3H), 2.09-2.16 (m, 1H), 2.51 (t,  $J$  = 6.82 Hz, 2H), 2.86 (t,  $J$  = 7.33 Hz, 2H), 3.43 (d,  $J$  = 7.07 Hz, 2H), 4.00 (s, 2H), 4.06 (d,  $J$  = 7.45 Hz, 2H), 6.57-6.75 (m, 3H), 7.15-7.27 (m, 4H), 7.32-7.37 (m, 2H).

**Example 1.218: Preparation of 2-(((1*s*,4*s*)-4-((4-(3-Fluorophenyl)-5-(2-(methylthio)ethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 222).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-(2-(methylthio)ethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-(2-(methylthio)ethyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 3-fluorophenylboronic acid, the title compound was obtained using a similar method to the one described in **Example 1.211**. LCMS  $m/z$  = 497.2  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.34-1.59 (m, 8H), 1.74-1.82 (m, 1H), 1.90 (s, 3H), 2.09-2.18 (m, 1H), 2.52 (t,  $J$  = 6.82 Hz, 2H), 2.91 (t,  $J$  = 7.33 Hz, 2H), 3.44 (d,  $J$  = 6.95 Hz, 2H), 4.00 (s, 2H), 4.08 (d,  $J$  = 7.45 Hz, 2H), 7.02-7.09 (m, 2H), 7.12-7.19 (m, 1H), 7.19-7.33 (m, 5H), 7.38-7.47 (m, 1H).

**Example 1.219: Preparation of 2-(((1*s*,4*s*)-4-((4-(3-Chlorophenyl)-5-(2-(methylthio)ethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 237).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-(2-(methylthio)ethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-(2-(methylthio)ethyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 3-chlorophenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.211**. LCMS *m/z* = 513.2 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.35-1.55 (m, 8H), 1.74-1.82 (m, 1H), 1.90 (s, 3H), 2.09-2.17 (m, 1H), 2.53 (t, *J* = 7.20 Hz, 2H), 2.90 (t, *J* = 7.45 Hz, 2H), 3.43 (d, *J* = 7.07 Hz, 2H), 3.96 (s, 2H), 4.07 (d, *J* = 7.45 Hz, 2H), 7.15-7.19 (m, 2H), 7.22-7.32 (m, 5H), 7.37-7.41 (m, 2H).

**Example 1.220: Preparation of 2-(((1*s*,4*s*)-4-((5-(2-(Methylthio)ethyl)-3,4-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 238).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-(2-(methylthio)ethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-(2-(methylthio)ethyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and phenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.211**. LCMS *m/z* = 479.2 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.34-1.56 (m, 8H), 1.73-1.81 (m, 1H), 1.88 (s, 3H), 2.08-2.18 (m, 1H), 2.50 (t, *J* = 7.33 Hz, 2H), 2.87 (t, *J* = 7.33 Hz, 2H), 3.42 (d, *J* = 7.07 Hz, 2H), 3.88 (s, 2H), 4.07 (d, *J* = 7.45 Hz, 2H), 7.16-7.25 (m, 5H), 7.28-7.41 (m, 5H).

**Example 1.221: Preparation of 2-(((1*s*,4*s*)-4-((5-(2-Fluoro-4-methylphenyl)-3-(2-methoxyethyl)-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 239).**

**Step A: Preparation of 5-(2-Methoxyethyl)-4-phenyl-1*H*-pyrazole.**

To a solution of 2-phenylacetaldehyde (4.0 g, 33.3 mmol) in toluene (10 mL), were added LiHMDS (33.3 mL, 33.3 mmol) at 0 °C. After stirring for 10min, 3-methoxypropanoyl chloride (4.08 g, 33.3 mmol) was added and continued stirring for 30 min at 0 °C. The reaction was quenched with acetic acid (glacial, 2 mL), diluted with ethanol (75mL), and hydrazine hydrate (5.00 g, 100 mmol) was added. The reaction was brought to reflux for 4hrs. After cooling to room temperature, the reaction was concentrated and extracted with EtOAc, dried over MgSO<sub>4</sub>, and purified by column chromatography to give the title compound as yellowish oil (2.5 g). LCMS *m/z* = 203.1 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 2.85 (t, *J* = 6.69 Hz, 2H), 3.17 (s, 3H), 3.48 (t, *J* = 6.63 Hz, 2H), 5.75 (s, 1H), 7.31-7.38 (m, 3H), 7.41-7.47 (m, 2H), 13.08 (s, 1H).

**Step B: Preparation of 3-Bromo-5-(2-methoxyethyl)-4-phenyl-1*H*-pyrazole.**

To a solution of 5-(2-methoxyethyl)-4-phenyl-1*H*-pyrazole (1.0 g, 4.94 mmol) in methanol (20 mL) was added *N*-bromosuccinimide (0.880 g, 4.94 mmol) in portions at room temperature.

After stirred at room temperature for 16 h, the reaction was concentrated and extracted with EtOAc/H<sub>2</sub>O, purified by column chromatography to give the title compound as yellow oil (1.0 g). LCMS  $m/z$  = 281.3 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 2.97 (t, *J* = 6.63 Hz, 2H), 3.22 (s, 3H), 3.57 (t, *J* = 7.07 Hz, 2H), 7.20-7.27 (m, 2H), 7.35-7.45 (m, 3H), 12.67 (bs, 1H).

5           **Step C: Preparation of *tert*-Butyl 2-(((1*s*,4*s*)-4-((3-Bromo-5-(2-methoxyethyl)-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-Butyl 2-(((1*s*,4*s*)-4-((5-Bromo-3-(2-methoxyethyl)-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a Mixture of Regioisomers.**

To a solution of 3-bromo-5-(2-methoxyethyl)-4-phenyl-1*H*-pyrazole (1.0 g, 3.6 mmol) in DMF (5 mL) were added cesium carbonate (1.16 g, 3.6 mmol), followed by *tert*-butyl 2-(((1*s*,4*s*)-4-(tosyloxymethyl)cyclohexyl)methoxy)acetate (1.47 g, 3.6 mmol). The reaction was gently heated to 80 °C for 10 h. After cooled to room temperature, the reaction was quenched with water (2 mL), extracted with EtOAc, dried over MgSO<sub>4</sub>, and purified by column chromatography to give the title compound as clear oil. LCMS  $m/z$  = 521.5 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.33-1.42 (m, 4H), 1.43 (s, 9H), 1.44-1.52 (m, 4H), 1.70-1.81 (m, 1H), 2.04-2.14 (m, 1H), 2.91 (t, *J* = 6.57 Hz, 2H), 3.14 (s, 3H), 3.41 (d, *J* = 6.95 Hz, 2H), 3.47 (t, *J* = 7.20 Hz, 2H), 3.95 (s, 2H), 4.04 (d, *J* = 7.07 Hz, 2H), 7.32-7.39 (m, 3H), 7.40-7.50 (m, 2H).

**Step D: Preparation of 2-(((1*s*,4*s*)-4-((5-(2-Fluoro-4-methylphenyl)-3-(2-methoxyethyl)-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid.**

20           To a solution of *tert*-butyl 2-(((1*s*,4*s*)-4-((3-bromo-5-(2-methoxyethyl)-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((5-bromo-3-(2-methoxyethyl)-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers (100 mg, 0.19 mmol) in dioxane (3 mL) were added 2-fluoro-4-methylphenylboronic acid (29.3 mg, 0.19 mmol), tetrakis(triphenylphosphine)palladium (22 mg, 0.019 mmol), and K<sub>2</sub>CO<sub>3</sub> (2 M aq., 0.2 mL). The reaction was heated to 150 °C under microwave irradiation for 4 h. After filtered and concentrated, the residue was treated with HCl (4.0 M in dioxane, 5 mL) at room temperature for 10 h. The mixture was concentrated and purified by HPLC to give the title compound as white solid (15.6 mg). LCMS  $m/z$  = 495.4 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.05-1.18 (m, 4H), 1.21-1.36 (m, 4H), 1.56-1.67 (m, 1H), 1.85-1.97 (m, 1H), 2.33 (s, 3H), 2.84 (t, *J* = 7.45 Hz, 2H), 3.18 (s, 3H), 3.19 (d, *J* = 7.07 Hz, 2H), 3.53 (t, *J* = 7.39 Hz, 2H), 3.74 (s, 2H), 3.81 (d, *J* = 7.83 Hz, 2H), 7.03-7.13 (m, 5H), 7.13-7.20 (m, 2H), 7.22-7.28 (m, 2H).

**Example 1.222: Preparation of 2-(((1*s*,4*s*)-4-((3-(2-Fluoro-4-methylphenyl)-5-(2-methoxyethyl)-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 240).**

35           From *tert*-butyl 2-(((1*s*,4*s*)-4-((3-bromo-5-(2-methoxyethyl)-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((5-bromo-3-(2-methoxyethyl)-4-

phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 2-fluoro-4-methylphenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.221**. LCMS  $m/z$  = 495.4 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.32-1.55 (m, 8H), 1.71-1.82 (m, 1H), 2.04-2.17 (m, 1H), 2.28 (s, 3H), 2.93 (t,  $J$  = 6.82 Hz, 2H), 3.16 (s, 3H), 3.40 (t,  $J$  = 6.63 Hz, 2H), 3.41 (d,  $J$  = 6.69 Hz, 2H), 3.87 (s, 2H), 4.07 (d,  $J$  = 7.45 Hz, 2H), 6.87-6.98 (m, 2H), 7.07-7.13 (m, 2H), 7.16-7.31 (m, 5H).

**Example 1.223: Preparation of 2-(((1*s*,4*s*)-4-((4-(2-Fluoro-4-methylphenyl)-5-(2-methoxyethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 241).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-(2-methoxyethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-(2-methoxyethyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 2-fluoro-4-methylphenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.199**. LCMS  $m/z$  = 495.2 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.31-1.57 (m, 8H), 1.73-1.83 (m, 1H), 2.08-2.18 (m, 1H), 2.36 (s, 3H), 2.78 (t,  $J$  = 6.76 Hz, 2H), 3.12 (s, 3H), 3.30 (t,  $J$  = 6.82 Hz, 2H), 3.42 (d,  $J$  = 7.07 Hz, 2H), 3.92 (s, 2H), 4.07 (d,  $J$  = 7.45 Hz, 2H), 7.03-7.10 (m, 2H), 7.13-7.27 (m, 4H), 7.30-7.34 (m, 2H).

**Example 1.224: Preparation of 2-(((1*s*,4*s*)-4-((4-(2-Fluoro-4-methylphenyl)-5-(2-(methylthio)ethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 242).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-(2-(methylthio)ethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-(2-(methylthio)ethyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 2-fluoro-4-methylphenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.211**. LCMS  $m/z$  = 511.1 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.34-1.55 (m, 8H), 1.73-1.82 (m, 1H), 1.88 (s, 3H), 2.08-2.18 (m, 1H), 2.36 (s, 3H), 2.48 (t,  $J$  = 7.58 Hz, 2H), 2.82 (t,  $J$  = 7.20 Hz, 2H), 3.43 (d,  $J$  = 7.07 Hz, 2H), 3.95 (s, 2H), 4.08 (d,  $J$  = 7.45 Hz, 2H), 7.03-7.11 (m, 2H), 7.15-7.27 (m, 4H), 7.30-7.35 (m, 2H).

**Example 1.225: Preparation of 2-(((1*s*,4*s*)-4-((4-(3-Methoxyphenyl)-5-(2-(methylthio)ethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 243).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-(2-(methylthio)ethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-(2-(methylthio)ethyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 3-methoxyphenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.211**. LCMS  $m/z$  = 509.7  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.34-1.56 (m, 8H), 1.74-1.82 (m, 1H), 1.91 (s, 3H), 2.09-2.18 (m, 1H), 2.52 (t,  $J$  = 8.46 Hz, 2H), 2.89 (t,  $J$  = 8.21 Hz, 2H), 3.43 (d,  $J$  = 6.95 Hz, 2H), 3.70 (s, 3H), 3.98 (s, 2H), 4.06 (d,  $J$  = 7.33 Hz, 2H), 6.74-6.80 (m, 2H), 6.87-6.92 (m, 1H), 7.17-7.36 (m, 6H).

**Example 1.226: Preparation of 2-(((1*s*,4*s*)-4-((4-(2,3-Difluorophenyl)-5-(2-(methylthio)ethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 244).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-(2-(methylthio)ethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-(2-(methylthio)ethyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers (100 mg, 0.19 mmol) and 2,3-difluorophenylboronic acid (30.0 mg, 0.19 mmol), the title compound was obtained using a similar method to the one described in **Example 1.211**. LCMS  $m/z$  = 515.4  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.34-1.58 (m, 8H), 1.73-1.82 (m, 1H), 1.86 (s, 3H), 2.09-2.19 (m, 1H), 2.50 (t,  $J$  = 7.20 Hz, 2H), 2.86 (t,  $J$  = 7.20 Hz, 2H), 3.42 (d,  $J$  = 7.07 Hz, 2H), 3.90 (s, 2H), 4.09 (d,  $J$  = 7.45 Hz, 2H), 7.13-7.20 (m, 1H), 7.20-7.34 (m, 6H), 7.39-7.49 (m, 1H).

**Example 1.227: Preparation of 2-(((1*s*,4*s*)-4-((3-(2-Methoxyethyl)-5-(3-methoxyphenyl)-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 247).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((3-bromo-5-(2-methoxyethyl)-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((5-bromo-3-(2-methoxyethyl)-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 3-methoxyphenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.221**. LCMS  $m/z$  = 493.1  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.06-1.20 (m, 4H), 1.22-1.37 (m, 4H), 1.55-1.69 (m, 1H), 1.86-1.99 (m, 1H), 2.82 (t,  $J$  = 7.39 Hz, 2H), 3.17 (s, 3H), 3.21 (d,  $J$  = 6.69 Hz, 2H), 3.51 (t,  $J$  = 7.33 Hz, 2H), 3.68 (s, 3H), 3.84 (s, 2H), 3.94 (d,  $J$  = 7.45 Hz, 2H), 6.74-6.82 (m, 2H), 6.91-6.97 (m, 1H), 7.06-7.34 (m, 6H).

**Example 1.228: Preparation of 2-(((1*s*,4*s*)-4-((5-(2-Methoxyethyl)-3-(3-methoxyphenyl)-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 248).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((3-bromo-5-(2-methoxyethyl)-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((5-bromo-3-(2-methoxyethyl)-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 3-methoxyphenylboronic acid, the title compound (one of the two regioisomers separated) was  
5 obtained using a similar method to the one described in **Example 1.221**. LCMS  $m/z$  = 493.1  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.32-1.57 (m, 8H), 1.73-1.83 (m, 1H), 2.05-2.19 (m, 1H), 2.83 (t,  $J$  = 6.76 Hz, 2H), 3.13 (s, 3H), 3.34 (t,  $J$  = 6.76 Hz, 2H), 3.43 (d,  $J$  = 6.95 Hz, 2H), 3.55 (s, 3H), 3.93 (s, 2H), 4.06 (d,  $J$  = 7.45 Hz, 2H), 6.72-6.81 (m, 2H), 6.90-6.97 (m, 1H), 7.09-7.25 (m, 3H), 7.29-7.42 (m, 3H).

10

**Example 1.229: Preparation of 2-(((1*s*,4*s*)-4-((4-(3-Chloro-2-fluorophenyl)-5-(2-(methylsulfonyl)ethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 249).**

To a solution of 2-(((1*s*,4*s*)-4-((4-(3-chloro-2-fluorophenyl)-5-(2-(methylthio)ethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid (16.4 mg, 0.031 mmol) in DCM (2  
15 mL) was added 3-chloroperbenzoic acid (16.0 mg, 0.093 mmol) was added. After stirred at room temperature for 30 min, the reaction mixture was concentrated and purified on prep HPLC to give the title compound as white solid (12.3 mg). LCMS  $m/z$  = 563.3  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.34-1.58 (m, 8H), 1.73-1.84 (m, 1H), 2.11-2.23 (m, 1H), 2.95 (s, 3H), 3.01 (t,  $J$  =  
20 8.02 Hz, 2H), 3.24 (t,  $J$  = 8.02 Hz, 2H), 3.43 (d,  $J$  = 6.95 Hz, 2H), 4.00 (s, 2H), 4.12 (d,  $J$  = 7.33 Hz, 2H), 7.21-7.32 (m, 6H), 7.32-7.39 (m, 1H), 7.58-7.65 (m, 1H).

**Example 1.230: Preparation of 2-(((1*s*,4*s*)-4-((3-(2-Cyanoethyl)-4,5-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 259).**

25 **Step A: Preparation of 3-(3-Phenyl-1*H*-pyrazol-5-yl)propanenitrile.**

To a solution of acetophenone (5.0 g, 41.6 mmol) in dry toluene (10 mL) was added LiHMDS (1.0 M in toluene) via syringe at 0 °C under argon. The reaction was allowed to stir at that temperature for 5 min and 3-cyanopropanoyl chloride (4.89 g, 41.6 mmol) was added via syringe in one portion. The ice bath was removed and AcOH (glacial, 5 mL), EtOH (100 mL), and hydrazine  
30 hydrate (6.25 g, 125 mmol) were added. The mixture was brought to reflux for 16 h. After cooled to room temperature, the reaction was concentrated, extracted with EtOAc, dried over MgSO<sub>4</sub>, and purified by column chromatography to give the title compound as yellowish oil (2.5 g). LCMS  $m/z$  = 198.1  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 2.87 (t,  $J$  = 4.42 Hz, 2H), 2.92 (t,  $J$  = 4.04 Hz, 2H), 6.59 (s, 1H), 7.25-7.48 (m, 3H), 7.63-7.81 (m, 2H), 13.06 (bs, 1H).

35 **Step B: Preparation of 3-(4-Bromo-3-phenyl-1*H*-pyrazol-5-yl)propanenitrile.**

To a solution of 3-(3-phenyl-1*H*-pyrazol-5-yl)propanenitrile (2.0 g, 10.14 mmol) in methanol (20 mL) was added *N*-bromosuccinimide (1.80 g, 10.14 mmol) in portions at room

temperature. After stirred at room temperature for 16 h, the reaction was concentrated and extracted with EtOAc/H<sub>2</sub>O, purified by column chromatography to give the title compound as yellow oil (2.4 g). LCMS  $m/z$  = 276.0 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 2.90 (t,  $J$  = 4.80 Hz, 2H), 2.92 (t,  $J$  = 4.29 Hz, 2H), 7.33-7.59 (m, 3H), 7.76 (d,  $J$  = 7.07 Hz, 2H), 13.45 (bs, 1H).

5           **Step C: Preparation of *tert*-Butyl 2-(((1*s*,4*s*)-4-((4-Bromo-3-(2-cyanoethyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-Butyl 2-(((1*s*,4*s*)-4-((4-Bromo-5-(2-cyanoethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a Mixture of Regioisomers.**

To a solution of 3-(4-bromo-3-phenyl-1*H*-pyrazol-5-yl)propanenitrile (2.0 g, 7.24 mmol) in  
10 DMF (5 mL) were added cesium carbonate (1.16 g, 3.6 mmol), followed by *tert*-butyl 2-(((1*s*,4*s*)-4-(tosyloxymethyl)cyclohexyl)methoxy)acetate (2.36 g, 7.24 mmol). The reaction was gently heated to 80 °C for 10 h. After cooled to room temperature, the reaction was quenched with water (2 mL), extracted with EtOAc, dried over MgSO<sub>4</sub>, and purified by column chromatography to give the title compound as clear oil (2.4 g) (mixture of two isomers). LCMS  $m/z$  = 516.2 [M+H]<sup>+</sup>.

15           **Step D: Preparation of 2-(((1*s*,4*s*)-4-((3-(2-Cyanoethyl)-4,5-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid.**

To a solution of *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-(2-cyanoethyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-(2-cyanoethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers (100 mg,  
20 0.19 mmol) in dioxane (3 mL) were added phenylboronic acid (29.3 mg, 0.19 mmol), tetrakis(triphenylphosphine)palladium (22 mg, 0.019 mmol), and K<sub>2</sub>CO<sub>3</sub> (2 M aq., 0.2 mL). The reaction was heated to 150 °C under microwave irradiation for 4 h. After filtered and concentrated, the residue was treated with HCl (4.0 M in dioxane, 5 mL) at room temperature for 10 h. The mixture was concentrated and purified by HPLC to give the title compound as white solid (13.5 mg).  
25 LCMS  $m/z$  = 458.3 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.03-1.19 (m, 4H), 1.22-1.36 (m, 4H), 1.55-1.66 (m, 1H), 1.88-1.99 (m, 1H), 2.79 (t,  $J$  = 6.95 Hz, 2H), 2.93 (t,  $J$  = 7.07 Hz, 2H), 3.20 (d,  $J$  = 6.95 Hz, 2H), 3.91 (s, 2H), 3.95 (d,  $J$  = 7.45 Hz, 2H), 7.06-7.13 (m, 2H), 7.15-7.30 (m, 5H), 7.36-7.45 (m, 3H).

30           **Example 1.231: Preparation of 2-(((1*s*,4*s*)-4-((5-(2-Cyanoethyl)-3,4-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 260).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-(2-cyanoethyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-(2-cyanoethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and  
35 phenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.230**. LCMS  $m/z$  = 458.3 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.33-1.59 (m, 8H), 1.74-1.84 (m, 1H), 2.06-2.18 (m, 1H), 2.58 (t,  $J$  = 7.39



Hz, 2H), 2.97 (t,  $J = 7.39$  Hz, 2H), 3.45 (d,  $J = 7.07$  Hz, 2H), 4.00 (s, 2H), 4.10 (d,  $J = 7.45$  Hz, 2H), 7.19-7.27 (m, 5H), 7.28-7.32 (m, 2H), 7.34-7.44 (m, 3H).

**Example 1.232: Preparation of 2-(((1*s*,4*s*)-4-((3-(2-Cyanoethyl)-4-(3-methoxyphenyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 261).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-(2-cyanoethyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-(2-cyanoethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 3-methoxyphenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.230**. LCMS  $m/z = 488.3$  [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  ppm 1.05-1.20 (m, 4H), 1.22-1.36 (m, 4H), 1.56-1.66 (m, 1H), 1.89-2.01 (m, 1H), 2.80 (t,  $J = 7.20$  Hz, 2H), 2.95 (t,  $J = 7.07$  Hz, 2H), 3.21 (d,  $J = 6.95$  Hz, 2H), 3.60 (s, 3H), 3.91 (s, 2H), 3.94 (d,  $J = 7.45$  Hz, 2H), 6.59-6.64 (m, 1H), 6.69 (d,  $J = 7.71$  Hz, 1H), 6.75 (dd,  $J = 8.02, 2.21$  Hz, 1H), 7.17 (t,  $J = 7.96$  Hz, 1H), 7.23-7.30 (m, 2H), 7.38-7.46 (m, 3H).

**Example 1.233: Preparation of 2-(((1*s*,4*s*)-4-((5-(2-Cyanoethyl)-4-(3-methoxyphenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 262).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-(2-cyanoethyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-(2-cyanoethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 3-methoxyphenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.230**. LCMS  $m/z = 488.3$  [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  ppm 1.33-1.59 (m, 8H), 1.76-1.84 (m, 1H), 2.08-2.18 (m, 1H), 2.61 (t,  $J = 7.33$  Hz, 2H), 2.99 (t,  $J = 7.33$  Hz, 2H), 3.45 (d,  $J = 7.20$  Hz, 2H), 3.72 (s, 3H), 4.00 (s, 2H), 4.10 (d,  $J = 7.45$  Hz, 2H), 6.79 (s, 1H), 6.80 (d,  $J = 1.64$  Hz, 1H), 6.90-6.94 (m, 1H), 7.19-7.27 (m, 3H), 7.28-7.37 (m, 3H).

**Example 1.234: Preparation of 2-(((1*s*,4*s*)-4-((5-(2-Cyanoethyl)-4-(3-hydroxyphenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 263).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-(2-cyanoethyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-(2-cyanoethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 3-hydroxyphenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.230**. LCMS  $m/z = 474.2$  [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>)  $\delta$  ppm 1.31-1.59 (m, 8H), 1.73-1.84 (m, 1H), 2.07-2.17 (m, 1H), 2.58 (t,  $J = 7.39$  Hz, 2H), 2.97 (t,  $J = 7.39$  Hz, 2H), 3.45 (d,  $J = 7.07$  Hz, 2H), 4.00 (s, 2H),

4.09 (d,  $J = 7.45$  Hz, 2H), 6.59-6.62 (m, 1H), 6.68 (d,  $J = 7.58$  Hz, 1H), 6.73-6.78 (m, 1H), 7.17-7.28 (m, 5H), 7.31-7.37 (m, 1H).

**Example 1.235: Preparation of 2-(((1*s*,4*s*)-4-((4-(3-Chlorophenyl)-3-(2-cyanoethyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 264).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-(2-cyanoethyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-(2-cyanoethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 3-chlorophenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.230**. LCMS  $m/z = 492.2$   $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.04-1.20 (m, 4H), 1.22-1.36 (m, 4H), 1.55-1.66 (m, 1H), 1.90-2.01 (m, 1H), 2.82 (t,  $J = 6.95$  Hz, 2H), 2.95 (t,  $J = 6.95$  Hz, 2H), 3.21 (d,  $J = 6.95$  Hz, 2H), 3.92 (s, 2H), 3.95 (d,  $J = 7.45$  Hz, 2H), 7.04-7.09 (m, 2H), 7.11-7.14 (m, 1H), 7.21-7.32 (m, 4H), 7.40-7.47 (m, 2H).

**Example 1.236: Preparation of 2-(((1*s*,4*s*)-4-((4-(3-Chlorophenyl)-5-(2-cyanoethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 265).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-(2-cyanoethyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-(2-cyanoethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 3-chlorophenylboronic acid, the title compound was obtained using a similar method to the one described in **Example 1.230**. LCMS  $m/z = 492.2$   $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.32-1.60 (m, 8H), 1.76-1.84 (m, 1H), 2.09-2.18 (m, 1H), 2.63 (t,  $J = 7.26$  Hz, 2H), 3.00 (t,  $J = 7.33$  Hz, 2H), 3.45 (d,  $J = 7.07$  Hz, 2H), 4.01 (s, 2H), 4.10 (d,  $J = 7.45$  Hz, 2H), 7.19-7.33 (m, 7H), 7.40-7.44 (m, 2H).

**Example 1.237: Preparation of 2-(((1*s*,4*s*)-4-((3-(2-Cyanoethyl)-4-(3-fluorophenyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 266).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-(2-cyanoethyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-(2-cyanoethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 3-fluorophenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.230**. LCMS  $m/z = 476.2$   $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.04-1.22 (m, 4H), 1.23-1.36 (m, 4H), 1.57-1.67 (m, 1H), 1.91-2.00 (m, 1H), 2.82 (t,  $J = 7.20$  Hz, 2H), 2.97 (t,  $J = 7.07$  Hz, 2H), 3.22 (d,  $J = 6.82$  Hz, 2H), 3.92 (s, 2H), 3.96 (d,  $J = 7.58$  Hz, 2H), 6.86-6.96 (m, 2H), 6.97-7.05 (m, 1H), 7.24-7.33 (m, 3H), 7.40-7.46 (m, 3H).

**Example 1.238: Preparation of 2-(((1*s*,4*s*)-4-((5-(2-Cyanoethyl)-4-(3-fluorophenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 267).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-(2-cyanoethyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-(2-cyanoethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 3-fluorophenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.230**. LCMS  $m/z = 476.2$   $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.33-1.61 (m, 8H), 1.75-1.86 (m, 1H), 2.09-2.19 (m, 1H), 2.62 (t,  $J = 7.33$  Hz, 2H), 3.01 (t,  $J = 7.33$  Hz, 2H), 3.46 (d,  $J = 7.07$  Hz, 2H), 4.01 (s, 2H), 4.11 (d,  $J = 7.58$  Hz, 2H), 7.05-7.11 (m, 2H), 7.14-7.21 (m, 1H), 7.21-7.34 (m, 5H), 7.40-7.48 (m, 1H).

**Example 1.239: Preparation of 2-(((1*s*,4*s*)-4-((3-(2-Cyanoethyl)-4-(3-hydroxyphenyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 268).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-(2-cyanoethyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-(2-cyanoethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 3-hydroxyphenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.230**. LCMS  $m/z = 474.2$   $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.03-1.19 (m, 4H), 1.20-1.36 (m, 4H), 1.54-1.67 (m, 1H), 1.87-1.97 (m, 1H), 2.78 (t,  $J = 7.01$  Hz, 2H), 2.91 (t,  $J = 7.01$  Hz, 2H), 3.20 (d,  $J = 6.82$  Hz, 2H), 3.91 (s, 2H), 3.93 (d,  $J = 8.08$  Hz, 2H), 6.46-6.54 (m, 2H), 6.59 (dd,  $J = 8.15, 1.58$  Hz, 1H), 7.04 (t,  $J = 7.83$  Hz, 2H), 7.22-7.28 (m, 2H), 7.38-7.46 (m, 2H).

**Example 1.240: Preparation of 2-(((1*s*,4*s*)-4-((4-(3-Chloro-2-fluorophenyl)-3-(2-cyanoethyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 269).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-(2-cyanoethyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-(2-cyanoethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 3-chloro-2-fluorophenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.230**. LCMS  $m/z = 510.2$   $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 0.99-1.15 (m, 4H), 1.16-1.34 (m, 4H), 1.55-1.67 (m, 1H), 1.81-1.93 (m, 1H), 2.82-2.94 (m, 4H), 3.16 (d,  $J = 6.95$  Hz, 2H), 3.68 (s, 2H), 3.98 (d,  $J = 7.45$  Hz, 2H), 7.39-7.46 (m, 3H), 7.48-7.60 (m, 5H).

**Example 1.241: Preparation of 2-(((1*s*,4*s*)-4-((4-(3-Chloro-2-fluorophenyl)-5-(2-cyanoethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 270).**

From *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-3-(2-cyanoethyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-bromo-5-(2-cyanoethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a mixture of regioisomers and 3-chloro-2-fluorophenylboronic acid, the title compound (one of the two regioisomers separated) was obtained using a similar method to the one described in **Example 1.230**. LCMS  $m/z$  = 510.2  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.27-1.56 (m, 8H), 1.71-1.83 (m, 1H), 2.00-2.11 (m, 1H), 2.83 (t,  $J$  = 7.20 Hz, 2H), 3.11 (t,  $J$  = 7.26 Hz, 2H), 3.41 (d,  $J$  = 7.20 Hz, 2H), 3.81 (s, 2H), 4.11 (d,  $J$  = 7.58 Hz, 2H), 7.35-7.42 (m, 2H), 7.42-7.49 (m, 3H), 7.79-7.85 (m, 3H).

**Example 1.242: Preparation of 2-(((1*s*,4*s*)-4-((3-(2-Fluoro-4-methylphenyl)-5-(2-hydroxyethyl)-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 287).**

**Step A: Preparation of Ethyl 3-(2-Fluoro-4-methylphenyl)-3-oxo-2-phenylpropanoate.**

2-Fluoro-4-methylbenzoyl chloride was made 2 h before the reaction by adding oxalyl chloride (3.20 mL, 36.5 mmol) to a solution of 2-fluoro-4-methylbenzoic acid (4.69 g, 30.5 mmol) in DCM (5 mL) at room temperature. After stirring for 2 h, the resulting solution was concentrated to dryness and dissolved in THF (10 mL), used as it was without further purification.

The solution of ethyl 2-phenylacetate (5 g, 30.5 mmol) in THF (20 mL) was cooled to -78 °C and LiHMDS (30.5 mL, 30.5 mmol) was added, followed by prior made solution of 2-fluoro-4-methylbenzoyl chloride in THF (10 mL). The reaction was allowed to warm to room temperature slowly and stirred for 4 h. Quenched with AcOH (2 mL), extracted with EtOAc, washed with brine, dried over  $MgSO_4$ , and purified by column chromatography to give the title compound as clear liquid (7.10 g). LCMS  $m/z$  = 301.2  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.14 (t,  $J$  = 7.07 Hz, 3H), 2.32 (s, 3H), 4.22 (q,  $J$  = 7.07 Hz, 2H), 5.77 (s, 1H), 7.03-7.17 (m, 3H), 7.24-7.40 (m, 4H), 7.82 (t,  $J$  = 8.21 Hz, 1H).

**Step B: Preparation of 1-(2-Fluoro-4-methylphenyl)-2-phenylethanone.**

Ethyl 3-(2-fluoro-4-methylphenyl)-3-oxo-2-phenylpropanoate (8.0 g, 26.6 mmol) was dissolved in THF (20 mL) and hydrogen chloride (37 % wt., 32.0 mL, 400 mmol) was added. The reaction was brought to reflux overnight. After cooled to room temperature, the reaction was diluted with  $H_2O$  (100 mL) and neutralized to pH 8 with NaOH (4.0 M aq.). The mixture was extracted with EtOAc (3  $\times$  75 mL), dried over  $MgSO_4$ , and purified by column chromatography to give the title compound as a clear oil (4.81 g). LCMS  $m/z$  = 229.1  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 2.36 (s, 3H), 4.28 (s, 2H), 7.11-7.18 (m, 2H), 7.19-7.26 (m, 3H), 7.27-7.34 (m, 2H), 7.77 (t,  $J$  = 8.21 Hz, 1H).

**Step C: Preparation of 1-(1*H*-Benzo[d][1,2,3]triazol-1-yl)but-3-en-1-one.**

Sulfurous dichloride (6.91 g, 58.1 mmol) was added to a stirred solution of 1*H*-benzo[*d*][1,2,3]triazole (27.7 g, 232 mmol) in anhydrous dichloromethane (100 mL) at room temperature under argon atmosphere. The mixture was stirred for 30 min and but-3-enoic acid (5.0 g, 58.1 mmol) was added in one portion and stirring was continued for 2 h. The resulting suspension was filtered off and washed with 2.0 M NaOH (3 × 50 mL), dried over MgSO<sub>4</sub>, and purified by column chromatography to give the title compound as white solid (5.12 g). LCMS *m/z* = 188.1 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 4.24 (d, *J* = 6.57 Hz, 2H), 5.28-5.42 (m, 2H), 6.04-6.19 (m, 1H), 7.61 (t, *J* = 7.71 Hz, 1H), 7.78 (t, *J* = 7.71 Hz, 1H), 8.24 (dd, *J* = 10.61, 8.34 Hz, 2H).

**Step D: Preparation of 5-Allyl-3-(2-fluoro-4-methylphenyl)-4-phenyl-1*H*-pyrazole.**

To a solution of 1-(2-fluoro-4-methylphenyl)-2-phenylethanone (1.0 g, 4.38 mmol) in THF (10 mL) was added LiHMDS (1.0 M in THF) (8.76 mL, 8.76 mmol) slowly via syringe at 0 °C. After stirring for 10 min, 1-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)but-3-en-1-one (0.984 g, 5.26 mmol) was added in one portion. The reaction was stirred at 0 °C for 30 min before quenched with AcOH (2 mL). To the reaction were added EtOH (30 mL), hydrazine hydrate (0.658 g, 13.14 mmol), and heated to reflux for 1 h. After cooled to room temperature, the reaction was concentrated and extracted with EtOAc/H<sub>2</sub>O, washed with brine, dried over MgSO<sub>4</sub>, and purified by column chromatography to give the title compound as clear oil (0.50 g). LCMS *m/z* = 293.2 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 2.31 (s, 3H), 3.40 (d, *J* = 5.94 Hz, 2H), 4.94-5.08 (m, 2H), 5.88-6.00 (m, 1H), 6.92-7.31 (m, 8H).

**Step E: Preparation of 2-(3-(2-Fluoro-4-methylphenyl)-4-phenyl-1*H*-pyrazol-5-yl)ethanol.**

5-Allyl-3-(2-fluoro-4-methylphenyl)-4-phenyl-1*H*-pyrazole (1.0 g, 3.42 mmol) was dissolved in methanol (40 mL) and dichloromethane (10 mL) and cooled to -78 °C on a dry-ice/acetone bath. Ozone was bubbled through the solution for ~2 h, until the solution appeared light blue. To the reaction added sodium borohydride (0.129 g, 3.42 mmol) slowly. Upon complete addition, the reaction was removed from the dry-ice bath and stirred at room temperature for 1 h. Excess solvent was removed under reduced pressure and the reaction was extracted with EtOAc/H<sub>2</sub>O, dried over MgSO<sub>4</sub>, and purified by column chromatography to give the title compound as clear oil (0.70 g). LCMS *m/z* = 297.2 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 2.30 (s, 3H), 2.79 (t, *J* = 7.20 Hz, 2H), 3.62 (t, *J* = 7.33 Hz, 2H), 6.93-7.00 (m, 1H), 7.09-7.14 (m, 2H), 7.15-7.23 (m, 3H), 7.25-7.31 (m, 2H), 12.86 (bs, 1H).

**Step F: Preparation of *tert*-Butyl 2-(((1*s*,4*s*)-4-((3-(2-Fluoro-4-methylphenyl)-5-(2-hydroxyethyl)-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate.**

To a solution of 2-(3-(2-fluoro-4-methylphenyl)-4-phenyl-1*H*-pyrazol-5-yl)ethanol (0.7 g, 2.362 mmol) in DMF (10 mL) were added cesium carbonate (0.770 g, 2.362 mmol) and *tert*-butyl 2-(((1*s*,4*s*)-4-(tosyloxymethyl)cyclohexyl)methoxy)acetate (0.974 g, 2.362 mmol). The reaction was gently heated to 60 °C for 2 h. After cooled to room temperature, the reaction mixture was extracted

with EtOAC/H<sub>2</sub>O, dried over MgSO<sub>4</sub>, and purified by column chromatography to give the title compound as a clear oil (0.75 g). LCMS  $m/z$  = 537.5 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 1.14-1.29 (m, 4H), 1.33-1.46 (m, 4H), 1.47 (s, 9H), 1.72-1.81 (m, 1H), 2.00-2.09 (m, 1H), 2.37 (s, 3H), 2.91 (t,  $J$  = 5.56 Hz, 2H), 3.30 (d,  $J$  = 7.07 Hz, 2H), 3.89 (s, 2H), 3.90 (d,  $J$  = 7.33 Hz, 2H),  
5 3.91 (t,  $J$  = 5.81 Hz, 2H), 4.68 (s, 1H), 6.89-7.01 (m, 2H), 7.04-7.10 (m, 1H), 7.13-7.27 (m, 5H).

**Step G: Preparation of 2-(((1*s*,4*s*)-4-((3-(2-Fluoro-4-methylphenyl)-5-(2-hydroxyethyl)-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 287).**

*tert*-Butyl 2-(((1*s*,4*s*)-4-((3-(2-fluoro-4-methylphenyl)-5-(2-hydroxyethyl)-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate (0.50 g, 0.932 mmol) was dissolved in hydrogen  
10 chloride (4.0 M in dioxane) (4.66 mL, 18.63 mmol) and stirred at room temperature for 16 h. The reaction was concentrated and purified by HPLC to give the title compound. LCMS  $m/z$  = 481.6 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.07-1.19 (m, 4H), 1.21-1.41 (m, 4H), 1.55-1.72 (m, 1H), 1.86-1.97 (m, 1H), 2.33 (s, 3H), 3.22 (d,  $J$  = 6.82 Hz, 2H), 3.59 (t,  $J$  = 5.81 Hz, 2H), 3.82 (t,  $J$  = 5.85 Hz, 2H), 3.91 (s, 2H), 3.93 (d,  $J$  = 7.54 Hz, 2H), 4.55 (s, 1H), 7.03-7.12 (m, 4H), 7.13-  
15 7.19 (m, 2H), 7.22-7.27 (m, 2H).

**Example 1.243: Preparation of 2-(((1*s*,4*s*)-4-((5-(2-fluoro-4-methylphenyl)-3-(2-hydroxyethyl)-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 285).**

The title compound was obtained using a similar method to the one described in Example  
20 **1.242**. LCMS  $m/z$  = 481.6 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.32-1.53 (m, 8H), 1.71-1.81 (m, 1H), 2.08-2.17 (m, 1H), 2.28 (s, 3H), 2.84 (t,  $J$  = 7.07 Hz, 2H), 3.41 (d,  $J$  = 7.07 Hz, 2H), 3.49 (t,  $J$  = 7.20 Hz, 2H), 3.93 (s, 2H), 4.08 (d,  $J$  = 7.58 Hz, 2H), 4.45 (s, 1H), 6.86-6.98 (m, 1H), 7.08-7.13 (m, 2H), 7.16-7.31 (m, 5H).

**Example 1.244: Preparation of 2-(((1*s*,4*s*)-4-((5-(2-(Methylsulfonyl)ethyl)-4-phenyl-3-*p*-tolyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 290).**

**Step A: Preparation of 1-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)-3-(methylthio)propan-1-one.**

Sulfurous dichloride (4.95 g, 41.6 mmol) was added to a stirred solution of 1*H*-benzo[*d*][1,2,3]triazole (19.83 g, 166 mmol) in anhydrous dichloromethane (300 mL) at room  
30 temperature under argon. The mixture was stirred for 30 min and 3-(methylthio)propanoic acid (5.0 g, 41.6 mmol) was added in one portion and stirring was continued for 2 h. The resulting suspension was filtered off and the filtrate was washed with 2 M NaOH (3 × 50mL), dried over MgSO<sub>4</sub>, and purified by column chromatography to give the title compound as clear oil (5.12 g). LCMS  $m/z$  = 222.1 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 2.21 (s, 3H), 3.05 (t,  $J$  = 7.07 Hz, 2H), 3.74 (t,  $J$  = 7.07 Hz, 2H), 7.42-7.54 (m, 1H), 7.56-7.69 (m, 1H), 8.08 (d,  $J$  = 8.34 Hz, 1H), 8.24 (d,  $J$  = 8.08 Hz, 1H).  
35

**Step B: Preparation of 5-(2-(Methylthio)ethyl)-4-phenyl-3-*p*-tolyl-1*H*-pyrazole.**

To a solution of 2-phenyl-1-*p*-tolylethanone (2.0 g, 9.51 mmol) in THF (10 mL) was added LiHMDS (1.0 M in THF) (19.02 mL, 19.02 mmol) slowly via syringe at 0 °C. After stirring for 10 min, 1-(1*H*-benzo[d][1,2,3]triazol-1-yl)-3-(methylthio)propan-1-one (2.53 g, 11.41 mmol) was added in one portion. The reaction was stirred at 0 °C for 30 min before quenched with AcOH (2 mL). To the reaction were added EtOH (30 mL), hydrazine hydrate (1.428 g, 28.5 mmol), and brought to reflux for 2 h. After cooled to room temperature, the reaction was concentrated and extracted with EtOAc/H<sub>2</sub>O, washed with brine, dried over MgSO<sub>4</sub>, and purified by column chromatography to give the title compound **a** as clear oil (1.50 g). LCMS *m/z* = 309.3 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 1.96 (s, 3H), 2.29 (s, 3H), 2.66 (t, *J* = 7.71 Hz, 2H), 2.90 (t, *J* = 7.58 Hz, 2H), 7.01-7.06 (m, 2H), 7.18-7.25 (m, 3H), 7.26-7.37 (m, 3H).

**Step C: Preparation of *tert*-butyl 2-(((1*s*,4*s*)-4-((5-(2-(Methylthio)ethyl)-4-phenyl-3-*p*-tolyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate.**

To a solution of 5-(2-(methylthio)ethyl)-4-phenyl-3-*p*-tolyl-1*H*-pyrazole (0.5 g, 1.621 mmol) in DMF (10 mL) were added cesium carbonate (0.528 g, 1.621 mmol) and *tert*-butyl 2-(((1*s*,4*s*)-4-(tosyloxymethyl)cyclohexyl)methoxy)acetate (0.669 g, 1.621 mmol). The reaction was gently heated to 60 °C for 2 h. After cooled to room temperature, the mixture was extracted with EtOAc/H<sub>2</sub>O, dried over MgSO<sub>4</sub>, and purified by column chromatography to give the title compound **a** as a clear oil. LCMS *m/z* = 549.5 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 1.10-1.27 (m, 4H), 1.29-1.45 (m, 4H), 1.46 (s, 9H), 1.53-1.61 (m, 1H), 1.73-1.81 (m, 1H), 2.04 (s, 3H), 2.35 (s, 3H), 2.73 (t, *J* = 7.58 Hz, 2H), 2.99 (t, *J* = 7.58 Hz, 2H), 3.28 (d, *J* = 6.82 Hz, 2H), 3.88 (s, 2H), 3.96 (d, *J* = 7.58 Hz, 2H), 7.04-7.10 (m, 4H), 7.11-7.18 (m, 3H), 7.18-7.24 (m, 2H).

**Step D: Preparation of 2-(((1*s*,4*s*)-4-((5-(2-(Methylsulfonyl)ethyl)-4-phenyl-3-*p*-tolyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 290).**

*tert*-Butyl 2-(((1*s*,4*s*)-4-((5-(2-(methylthio)ethyl)-4-phenyl-3-*p*-tolyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate (0.50 g, 0.911 mmol) was dissolved in hydrogen chloride (4.0 M in dioxane) (4.56 mL, 18.22 mmol) and stirred at room temperature for 16 h. The reaction was concentrated to dryness and dissolved in dichloromethane (5 mL) and 3-chloroperoxybenzoic acid (0.550 g, 3.19 mmol) was added. After stirred at room temperature for 1 h, the reaction was concentrated and purified on HPLC. LCMS *m/z* = 525.4 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.08-1.20 (m, 4H), 1.23-1.36 (m, 4H), 1.57-1.68 (m, 1H), 1.90-2.00 (m, 1H), 2.32 (s, 3H), 2.97 (s, 3H), 3.04 (t, *J* = 8.59 Hz, 2H), 3.22 (d, *J* = 6.82 Hz, 2H), 3.41 (t, *J* = 8.08 Hz, 2H), 3.92 (d, *J* = 7.38 Hz, 2H), 3.92 (s, 2H), 7.08-7.15 (m, 3H), 7.16-7.31 (m, 6H).

**Example 1.245: Preparation of 2-(((1*s*,4*s*)-4-((3-(2-Fluoro-4-methylphenyl)-5-(2-(methylsulfonyl)ethyl)-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 291).**

**Step A: Preparation of 3-(2-Fluoro-4-methylphenyl)-5-(2-(methylthio)ethyl)-4-phenyl-1H-pyrazole.**

To a solution of 1-(2-fluoro-4-methylphenyl)-2-phenylethanone (2.0 g, 8.76 mmol) in THF (10 mL) was added LiHMDS (1.0 M in THF) (17.52 mL, 17.52 mmol) slowly via syringe at 0 °C. After stirring for 10 min, 1-(1H-benzo[d][1,2,3]triazol-1-yl)-3-(methylthio)propan-1-one (2.327 g, 10.51 mmol) was added in one portion. The reaction was stirred at 0 °C for 30 min before quenched with AcOH (2 mL). To the reaction were added EtOH (30 mL), hydrazine hydrate (1.316 g, 26.3 mmol), and brought to reflux for 2 h. After cooled to room temperature, the reaction was concentrated and extracted with EtOAc/H<sub>2</sub>O, washed with brine, dried over MgSO<sub>4</sub>, and purified by column chromatography to give the title compound as a clear oil (1.40 g). LCMS *m/z* = 327.2 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 1.94 (s, 3H), 2.22 (s, 3H), 2.65 (t, *J* = 7.33 Hz, 2H), 2.88 (t, *J* = 7.58 Hz, 2H), 6.71 (d, *J* = 7.83 Hz, 1H), 6.80 (d, *J* = 11.87 Hz, 1H), 6.97 (t, *J* = 7.96 Hz, 1H), 7.09-7.29 (m, 5H), 9.64 (bs, 1H).

**Step B: Preparation of *tert*-Butyl 2-(((1*s*,4*s*)-4-((3-(2-Fluoro-4-methylphenyl)-5-(2-(methylthio)ethyl)-4-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate.**

To a solution of 3-(2-fluoro-4-methylphenyl)-5-(2-(methylthio)ethyl)-4-phenyl-1H-pyrazole (0.5 g, 1.532 mmol) in DMF (10 mL) were added cesium carbonate (0.499 g, 1.532 mmol) and *tert*-butyl 2-(((1*s*,4*s*)-4-(tosyloxymethyl)cyclohexyl)methoxy)acetate (0.632 g, 1.532 mmol). The reaction was gently heated to 60 °C for 2 h. After cooled to room temperature, the mixture was extracted with EtOAc/H<sub>2</sub>O, dried over MgSO<sub>4</sub>, and purified by column chromatography to give the title compound as a clear oil. LCMS *m/z* = 567.5 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 1.31-1.44 (m, 4H), 1.46 (s, 9H), 1.52-1.65 (m, 4H), 1.69-1.81 (m, 1H), 1.84-1.92 (m, 1H), 2.04 (s, 3H), 2.35 (s, 3H), 2.55 (t, *J* = 7.83 Hz, 2H), 2.74 (t, *J* = 7.58 Hz, 2H), 3.47 (d, *J* = 7.07 Hz, 2H), 3.96 (s, 2H), 4.08 (d, *J* = 7.33 Hz, 2H), 6.84-7.01 (m, 2H), 7.06-7.18 (m, 3H), 7.19-7.32 (m, 3H).

**Step C: Preparation of 2-(((1*s*,4*s*)-4-((3-(2-Fluoro-4-methylphenyl)-5-(2-(methylsulfonyl)ethyl)-4-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 291).**

*tert*-Butyl 2-(((1*s*,4*s*)-4-((3-(2-fluoro-4-methylphenyl)-5-(2-(methylthio)ethyl)-4-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate (0.50 g, 0.882 mmol) was dissolved in hydrogen chloride (4.0 M in dioxane) (4.41 mL, 17.64 mmol) and stirred at room temperature for 16 h. The reaction was concentrated and dissolved in DCM (5 mL). 3-Chloroperoxybenzoic acid (0.533 g, 3.09 mmol) was added. After stirred at room temperature for 1 h, the reaction was concentrated and the residue was purified by HPLC to give the title compound. LCMS *m/z* = 543.4 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.05-1.20 (m, 4H), 1.23-1.37 (m, 4H), 1.57-1.69 (m, 1H), 1.89-1.99 (m, 1H), 2.34 (s, 3H), 2.97 (s, 3H), 3.06 (t, *J* = 8.21 Hz, 2H), 3.22 (d, *J* = 6.82 Hz, 2H), 3.43 (t, *J* = 8.21 Hz, 2H), 3.92 (d, *J* = 7.33 Hz, 2H), 3.91 (s, 2H), 7.05-7.14 (m, 3H), 7.15-7.23 (m, 3H), 7.24-7.31 (m, 2H).



**Example 1.246: Preparation of 2-(((1*s*,4*s*)-4-((5-(2-Hydroxyethyl)-4-phenyl-3-*p*-tolyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 292).**

**Step A: Preparation of 5-Allyl-4-phenyl-3-*p*-tolyl-1*H*-pyrazole.**

5 To a solution of 2-phenyl-1-*p*-tolylethanone (1.0 g, 4.76 mmol) in THF (10 mL) added LiHMDS (1.0 M in THF) (9.51 mL, 9.51 mmol) slowly via syringe at 0 °C. After stirring for 10 min, 1-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)but-3-en-1-one (1.068 g, 5.71 mmol) was added in one portion. The reaction was stirred at 0 °C for 30 min and then quenched with AcOH (2 mL). EtOH (30 mL) and hydrazine hydrate (0.714 g, 14.27 mmol) were added, and the reaction was heated to  
10 reflux for 30 min. The reaction was cooled to room temperature, concentrated and the residue was extracted with EtOAc/H<sub>2</sub>O, washed with brine, dried over MgSO<sub>4</sub>, and purified by column chromatography to give the title compound as clear oil (0.47 g). LCMS *m/z* = 275.0 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 2.31 (s, 3H), 3.38-3.43 (m, 2H), 5.07-5.14 (m, 2H), 5.90-6.01 (m, 1H), 7.03-7.09 (m, 2H), 7.19-7.30 (m, 5H), 7.30-7.36 (m, 2H).

15 **Step B: Preparation of 2-(4-Phenyl-3-*p*-tolyl-1*H*-pyrazol-5-yl)ethanol.**

5-Allyl-4-phenyl-3-*p*-tolyl-1*H*-pyrazole (1.0 g, 3.64 mmol) was dissolved in methanol (40 mL) and dichloromethane (10 mL) and cooled to -78 °C on a dry-ice/acetone bath. Ozone was bubbled through the solution for ~2 h, until the solution appeared light blue. To the reaction was added sodium borohydride (0.138 g, 3.64 mmol) and the reaction was removed from the dry-ice bath  
20 and stirred at room temperature for 1 h. Excess solvent was removed under reduced pressure and the reaction was extracted with EtOAc/H<sub>2</sub>O, dried over MgSO<sub>4</sub>, and purified by column chromatography to give the title compound as white solid (0.54 g). LCMS *m/z* = 279.2 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 2.25 (s, 3H), 2.71 (t, *J* = 7.33 Hz, 2H), 3.57 (t, *J* = 7.33 Hz, 2H), 4.65 (bs, 1H), 7.03-7.09 (m, 2H), 7.16-7.23 (m, 3H), 7.24-7.31 (m, 2H), 7.32-7.40 (m, 2H).

25 **Step C: Preparation of *tert*-Butyl 2-(((1*s*,4*s*)-4-((5-(2-Hydroxyethyl)-4-phenyl-3-*p*-tolyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate.**

To a solution of 2-(4-phenyl-3-*p*-tolyl-1*H*-pyrazol-5-yl)ethanol (0.7 g, 2.51 mmol) in DMF (10 mL) were added cesium carbonate (0.819 g, 2.51 mmol) and *tert*-butyl 2-(((1*s*,4*s*)-4-(tosyloxymethyl)cyclohexyl)methoxy)acetate (1.037 g, 2.51 mmol). The reaction was gently heated  
30 to 60 °C for 2 h. The reaction was cooled to room temperature and extracted with EtOAc/H<sub>2</sub>O. The organic layer was dried over MgSO<sub>4</sub> and purified by column chromatography to give the title compound as clear oil (0.75 g). LCMS *m/z* = 519.5 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ ppm 1.34-1.45 (m, 4H), 1.49 (s, 9H), 1.55-1.63 (m, 4H), 1.72-1.80 (m, 1H), 1.85-1.93 (m, 1H), 2.28 (s, 3H), 2.90 (t, *J* = 6.95 Hz, 2H), 3.47 (d, *J* = 7.07 Hz, 2H), 3.66 (t, *J* = 6.44 Hz, 2H), 3.96 (s, 2H), 4.09  
35 (d, *J* = 7.58 Hz, 2H), 6.98-7.10 (m, 2H), 7.12-7.24 (m, 2H), 7.24-7.37 (m, 5H).

**Step D: Preparation of 2-(((1*s*,4*s*)-4-((5-(2-Hydroxyethyl)-4-phenyl-3-*p*-tolyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 292).**

*tert*-Butyl 2-(((1*s*,4*s*)-4-((5-(2-hydroxyethyl)-4-phenyl-3-*p*-tolyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate (0.50 g, 0.964 mmol) was dissolved in hydrogen chloride (4.0 M in dioxane) (4.82 mL, 19.28 mmol) and stirred at room temperature for 16 h. The reaction was concentrated and purified by HPLC to give the title compound. LCMS  $m/z$  = 463.4  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.31-1.57 (m, 8H), 1.73-1.83 (m, 1H), 2.09-2.19 (m, 1H), 2.24 (s, 3H), 2.75 (t,  $J$  = 7.20 Hz, 2H), 3.44 (t,  $J$  = 7.20 Hz, 2H), 3.44 (d,  $J$  = 6.82 Hz, 2H), 4.00 (s, 2H), 4.07 (d,  $J$  = 7.33 Hz, 2H), 7.00-7.05 (m, 2H), 7.16-7.22 (m, 4H), 7.27-7.40 (m, 3H).

**Example 1.247: Preparation of 2-(((1*r*,4*r*)-4-((5-(4-Fluorophenyl)-3-(methylthio)-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 1).**

**Step A: Preparation of 3-(4-Fluorophenyl)-5-(methylthio)-4-phenyl-1*H*-pyrazole**

To a solution of 1-(4-fluorophenyl)-2-phenylethanone (1.0 g, 4.67 mmol) in anhydrous THF (10 mL), was added a solution of 1.0 M KO-*t*-Bu in THF (2 mL). The reaction was stirred for 15 min at room temperature, and then quenched with CS<sub>2</sub> (0.38 g, 5.04 mmol). After stirring for 30 min, iodomethane (1.45 g, 10.22 mmol) was added to the reaction over 5 min. The reaction was maintained at the same temperature for 4 h. The reaction was poured into water and extracted with ethyl acetate. The extract was dried over MgSO<sub>4</sub> and concentrated under reduced pressure to give a yellow solid (1.02 g). To the suspension of the above-mentioned yellow solid in ethanol (10 mL), hydrazine hydrate (0.70 g, 14.0 mmol) was added at room temperature. The reaction was refluxed for 4 h. After cooling to room temperature, the mixture was concentrated under reduced pressure and extracted with ethyl acetate. The organic extract was dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The residue was poured into 10% ethyl acetate in hexane and the precipitate was filtered and dried in air to give the title compound (0.69 g) as a white solid. LCMS  $m/z$  = 285.4  $[M+H]^+$ .

**Step B: Preparation of 2-(((1*r*,4*r*)-4-((5-(4-Fluorophenyl)-3-(methylthio)-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid.**

To a solution of 3-(4-fluorophenyl)-5-(methylthio)-4-phenyl-1*H*-pyrazole (150 mg, 0.528 mmol) and *tert*-butyl 2-(((1*r*,4*r*)-4-(tosyloxymethyl)cyclohexyl)methoxy)acetate (218 mg, 0.528 mmol) in DMF (3 mL) was added sodium hydride (12.66 mg, 0.528 mmol) at room temperature. The reaction was heated at 60 °C overnight. After cooling to room temperature, the reaction was poured into water and extracted with ethyl acetate. The organic extract was concentrated under reduced pressure and the resulting residue was purified by HPLC to give the title compound (29 mg). LCMS  $m/z$  = 469.8  $[M+H]^+$ .

**Example 1.248: Preparation of 2-(((1*r*,4*r*)-4-((3-(4-Fluorophenyl)-5-(methylthio)-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 2).**

From 3-(4-fluorophenyl)-5-(methylthio)-4-phenyl-1*H*-pyrazole and *tert*-butyl 2-(((1*r*,4*r*)-4-(tosyloxymethyl)cyclohexyl)methoxy)acetate, the title compound was obtained using a similar method to the one described in **Example 1.247, Step B**. LCMS  $m/z$  = 469.5  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 0.95 (m, 2H), 1.15 (m, 2H), 1.56 (m, 1H), 1.74 (m, 2H), 1.81 (m, 2H), 1.89 (m, 1H), 2.10 (s, 3H), 3.25 (d,  $J$  = 6.4 Hz, 2H), 3.89 (s, 2H), 4.20 (d,  $J$  = 7.2 Hz, 2H), 7.12-7.20 (m, 2H), 7.23-7.49 (m, 7H).

**Example 1.249: Preparation of 2-(((1*r*,4*r*)-4-((4-(3-Methoxyphenyl)-3-methyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 6).**

**Step A: Preparation of 3-Methyl-5-phenyl-1*H*-pyrazole**

To a solution of 1-phenylbutane-1,3-dione (5.0 g, 30.8 mmol) in ethanol (50 mL), was added hydrazine hydrate (1.54 g, 30.8 mmol) at ambient temperature. The reaction was refluxed for 5 h. After cooling, the reaction was concentrated under reduced pressure and extracted with ethyl acetate. The extract was dried over  $MgSO_4$  and concentrated under reduced pressure. The residue was added 10% ethyl acetate in hexane. The precipitate was filtered and washed with hexane. The white solid was dried in air to give the title compound (3.9 g). LCMS  $m/z$  = 159.3  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 2.25 (s, 3H), 6.65 (s, 1H), 7.34 (m, 1H), 7.42 (m, 2H), 7.82 (m, 2H).

**Step B: Preparation of 4-Iodo-3-methyl-5-phenyl-1*H*-pyrazole.**

To a solution of 5-methyl-3-phenyl-1*H*-pyrazole (1.5 g, 9.48 mmol) in THF (20 mL) and water (20 mL), were added sodium iodide (1.42 g, 9.48 mmol), iodine (3.61 g, 14.22 mmol), and  $K_2CO_3$  (1.96 g, 14.22 mmol) at room temperature. The reaction was warmed to 100 °C and stirred for 10 h. After cooling to room temperature, the reaction was poured into water and extracted with ethyl acetate, which was washed with 2.0 M aq. sodium thiosulfite and saturated.  $NaHCO_3$  successively. The extract was dried over  $MgSO_4$  and concentrated under reduced pressure to give a semi-solid, which was recrystallized from 10% ethyl acetate in hexane to give the title compound (1.9 g). LCMS  $m/z$  = 285.5  $[M+H]^+$ .

**Step C: Preparation of *tert*-Butyl 2-(((1*r*,4*r*)-4-((4-Iodo-3-methyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-Butyl 2-(((1*r*,4*r*)-4-((4-Iodo-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a Mixture of Regioisomers.**

To a solution of 4-iodo-5-methyl-3-phenyl-1*H*-pyrazole (1.0 g, 3.52 mmol) in DMF (10 mL), was added sodium hydride (0.084 g, 3.52 mmol) at ambient temperature. After stirring for 10 min, a solution of *tert*-butyl 2-(((1*r*,4*r*)-4-(tosyloxymethyl)cyclohexyl)methoxy)acetate (1.45 g, 3.52 mmol) in DMF (1 mL) was added at room temperature. The reaction was heated to 45 °C and stirred for 8 h. After cooling to room temperature, the reaction was poured into  $H_2O$  and extracted with ethyl acetate, which was dried over  $MgSO_4$  and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography to give the title compound (1.25 g) as a colorless oil. LCMS  $m/z$  = 525.4  $[M+H]^+$ .

**Step D: Preparation of 2-(((1*r*,4*r*)-4-((4-(3-Methoxyphenyl)-3-methyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid.**

To a solution of regioisomers, *tert*-butyl 2-(((1*r*,4*r*)-4-((4-iodo-3-methyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*r*,4*r*)-4-((4-iodo-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate (200 mg, 0.381 mmol), in dioxane (2 mL), were added 3-methoxyphenylboronic acid (58.0 mg, 0.381 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (22.03 mg, 0.019 mmol), and a 2.0 M aqueous solution of K<sub>2</sub>CO<sub>3</sub> (105 mg, 0.763 mmol) at ambient temperature. The reaction was irradiated under microwave for 1.5 h at 150 °C. After cooling to room temperature, the reaction was poured into water, extracted with ethyl acetate, and then dried over MgSO<sub>4</sub>. The extract was concentrated under reduced pressure and the residue was treated with 4.0 M HCl (5 mL) at room temperature. After stirring for 10 h, the reaction was concentrated under reduced pressure and purified by HPLC to give the title compound (25 mg). LCMS *m/z* = 449.3 [M+H]<sup>+</sup>.

**Example 1.250: Preparation of 2-(((1*r*,4*r*)-4-((4-(3-Methoxyphenyl)-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 7).**

From a mixture of regioisomers, *tert*-butyl 2-(((1*r*,4*r*)-4-((4-iodo-3-methyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*r*,4*r*)-4-((4-iodo-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate, and 3-methoxyphenylboronic acid, the title compound was obtained using a similar method to the one described in **Example 1.250, Step D**. LCMS *m/z* = 449.5 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 0.91 (m, 2H), 1.15 (m, 2H), 1.59 (m, 1H), 1.75 (m, 2H), 1.82 (m, 2H), 1.95 (m, 1H), 2.25 (s, 3H), 2.51 (s, 3H), 3.24 (d, *J* = 6.8 Hz, 2H), 3.75 (s, 2H), 4.01 (d, *J* = 7.4 Hz, 2H), 6.65-6.89 (m, 3H), 7.26-7.49 (m, 6H).

**Example 1.251: Preparation of 2-(((1*r*,4*r*)-4-((5-Methyl-3,4-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 11).**

To a solution of regioisomers, *tert*-butyl 2-(((1*r*,4*r*)-4-((4-iodo-3-methyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*r*,4*r*)-4-((4-iodo-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate (200 mg, 0.381 mmol), in dioxane (2 mL), were added phenylboronic acid (0.046 g, 0.381 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (0.022 g, 0.019 mmol), and a 2.0 M aqueous solution of K<sub>2</sub>CO<sub>3</sub> (0.105 g, 0.763 mmol) at ambient temperature. The reaction was irradiated under microwave for 4 h at 150 °C. After cooling to room temperature, the reaction was poured into water, extracted with ethyl acetate, and then dried over MgSO<sub>4</sub>. The extract was concentrated under reduced pressure and the residue was treated with 4.0 M HCl (5 mL). After stirring for 10 h, the reaction was concentrated under reduced pressure and purified by HPLC to give the title compound (0.104 g). LCMS *m/z* = 419.3 [M+H]<sup>+</sup>.

**Example 1.252: Preparation of 2-(((1*s*,4*s*)-4-((5-(4-Fluorophenyl)-3-(methylthio)-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 12).**

To a solution of 3-(4-fluorophenyl)-5-(methylthio)-4-phenyl-1*H*-pyrazole (150.0 mg, 0.502 mmol) in DMF (5 mL), was added sodium hydride (12.66 mg, 0.528 mmol) at room temperature.

- 5 After stirring for 30 min, a solution of *tert*-butyl 2-(((1*r*,4*r*)-4-(tosyloxymethyl)cyclohexyl)methoxy)acetate (218 mg, 0.528 mmol) in DMF (1 mL) was added into the reaction at room temperature. The reaction was heated at 60 °C overnight. After cooling to room temperature, the reaction was poured into water and extracted with ethyl acetate. The extract was concentrated under reduced pressure and the residue was treated with 4.0 M HCl in dioxane (5 mL).
- 10 After standing for 10 h, the reaction was concentrated under reduced pressure and purified by HPLC to give the title compound (21.0 mg). LCMS *m/z* = 469.5 [M+H]<sup>+</sup>.

**Example 1.253: Preparation of 2-(((1*s*,4*s*)-4-((3-(4-Fluorophenyl)-5-(methylthio)-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 10).**

- 15 From 3-(4-fluorophenyl)-5-(methylthio)-4-phenyl-1*H*-pyrazole and *tert*-butyl 2-(((1*r*,4*r*)-4-(tosyloxymethyl)cyclohexyl)methoxy), the title compound was obtained using a similar method to the one described in **Example 1.252**. LCMS *m/z* = 496.4 [M+H]<sup>+</sup>.

**Example 1.254: Preparation of 2-(((1*s*,4*s*)-4-((4-(3-Methoxyphenyl)-3-methyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 13).**

- 20 **Step A: Preparation of *tert*-Butyl 2-(((1*r*,4*s*)-4-((4-Iodo-3-methyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-Butyl 2-(((1*r*,4*s*)-4-((4-Iodo-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a Mixture of Regioisomers.**

- To a solution of 4-iodo-5-methyl-3-phenyl-1*H*-pyrazole (1.0 g, 3.52 mmol) in DMF (5 mL),  
25 was added sodium hydride (0.084 g, 3.52 mmol) at room temperature. After stirring for 30 min, the reaction was treated with *tert*-butyl 2-(((1*r*,4*r*)-4-(tosyloxymethyl)cyclohexyl)methoxy)acetate (1.32 g, 0.528 mmol) in DMF (5 mL) at ambient temperature. The reaction was stirred at 60 °C for 12 h. The reaction was poured into H<sub>2</sub>O and extracted with ethyl acetate. The organic extract was dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The residue was purified by column  
30 chromatography to give the titled compounds (1.2 g) as a mixture of regioisomers. LCMS *m/z* = 525.7 [M+H]<sup>+</sup>.

**Step B: Preparation of 2-(((1*s*,4*s*)-4-((4-(3-Methoxyphenyl)-3-methyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid.**

- To a solution of regioisomers, *tert*-butyl 2-(((1*r*,4*s*)-4-((4-iodo-3-methyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*r*,4*s*)-4-((4-iodo-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate (0.2 g, 0.381 mmol), in dioxane (5  
35 mL), were added 3-methoxyphenylboronic acid (0.058 g, 0.381 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (0.022 g, 0.019

mmol), and a 2.0 M aqueous solution of  $K_2CO_3$  (0.131 g, 0.952 mmol) at ambient temperature. The reaction was irradiated under microwave for 4 h at 150 °C. After cooling to room temperature, the mixture was poured into water and extracted with ethyl acetate. The extract was concentrated under reduced pressure and the residue was treated with 4.0 M HCl in dioxane (5 mL). After standing for 10 h, the reaction was concentrated under reduced pressure and purified by HPLC to give the title compound (0.032 g). LCMS  $m/z$  = 449.2  $[M+H]^+$ .

**Example 1.255: Preparation of ((1s,4s)-4-((5-Methyl-3,4-diphenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methyl)hydrazine.**

**Step A: Preparation of (E)-1-Benzylidene-2-(((1s,4s)-4-(benzyloxymethyl)cyclohexyl)methyl)hydrazine.**

To a solution of *tert*-butyl 2-(((1s,4s)-4-(benzyloxymethyl)cyclohexyl)methyl)hydrazinecarboxylate (1.0 g, 2.87 mmol) in dichloromethane (5 mL), was added TFA (5.0 mL) at room temperature. After stirring for 3 h at the same temperature, the mixture was concentrated under reduced pressure. The resulting residue was dissolved in THF (10.0 mL) and benzaldehyde (0.31 g, 2.87 mmol) was added at room temperature. After stirring for 30 min, the reaction was poured into water and extracted with ethyl acetate. The organic layer was washed with sat.  $NaHCO_3$ , dried over  $MgSO_4$ , and concentrated under reduced pressure to give the titled compound (0.96 g) without further purification. LCMS  $m/z$  = 337.4  $[M+H]^+$ ;  $^1H$  NMR (400 MHz,  $DMSO-d_6$ )  $\delta$  ppm 1.32-1.55 (m, 8H), 1.75-1.85 (m, 2H), 3.11 (m, 2H), 3.31 (d,  $J$  = 2.5Hz, 2H), 4.45 (s, 2H), 7.21-7.54 (m, 11H).

**Step B: Preparation of 1-(((1s,4s)-4-(Benzyloxymethyl)cyclohexyl)methyl)-5-methyl-3,4-diphenyl-1H-pyrazole.**

To a solution of (E)-1-benzylidene-2-(((1s,4s)-4-(benzyloxymethyl)cyclohexyl)methyl)hydrazine (0.77 g, 2.28 mmol) and (E)-(2-nitroprop-1-enyl)benzene (0.37 g, 2.28 mmol) in THF (5 mL) at -78 °C, was added potassium butan-1-olate (0.25 g, 2.28 mmol) dropwise. After stirring for 10 min, TFA (0.35 mL, 4.58 mmol) was added at the same temperature and maintained for 2 h. After warmed to room temperature, the reaction was poured into water and extracted with ethyl acetate. The organic layer was dried over  $MgSO_4$ , and concentrated under reduced pressure. The residue was purified by silica gel to give the title compound (0.45 g). LCMS  $m/z$  = 451.3  $[M+H]^+$ ;  $^1H$  NMR (400 MHz,  $DMSO-d_6$ )  $\delta$  ppm 1.29-1.52(m, 8H), 1.75-1.80 (m, 1H), 2.11-2.15 (m, 1H), 2.22 (s, 3H), 3.30 (s, 2H), 3.42 (d,  $J$  = 2.5Hz, 2H), 4.14 (d,  $J$  = 2.4Hz, 2H), 7.23-7.42 (m, 15H).

**Step C: Preparation of ((1s,4s)-4-((5-Methyl-3,4-diphenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methanol.**

To a solution of 1-(((1s,4s)-4-(benzyloxymethyl)cyclohexyl)methyl)-5-methyl-3,4-diphenyl-1H-pyrazole (100 mg, 0.22 mmol) in MeOH (5 mL), was added ammonium formate (280 mg, 4.44

mmol) followed by 10% Pd/C (5 mg). The reaction was heated to 80 °C for 10 h. The mixture was filtered. The filtrate was concentrated under reduced pressure to give the titled compound (78 mg) as a colorless oil. LCMS  $m/z$  = 361.2  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.34-1.55 (m, 8H), 1.56-1.60 (m, 1H), 2.10-2.15 (m, 1H), 2.21 (s, 3H), 3.31 (d,  $J$  = 2.5Hz, 2H), 4.20 (d,  $J$  = 2.4Hz, 2H), 7.31-7.54 (m, 10H).

**Example 1.256: Preparation of 2-(((1*s*,4*s*)-4-((3-Methyl-4,5-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 15).**

To a solution of regioisomers, *tert*-butyl 2-(((1*r*,4*s*)-4-((4-iodo-3-methyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*r*,4*s*)-4-((4-iodo-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate (0.2 g, 0.381 mmol), in dioxane (5 mL), were added phenylboronic acid (0.183 g, 1.5 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (86.6 mg, 0.0075 mmol) and a 2.0 M aqueous solution of K<sub>2</sub>CO<sub>3</sub> (0.513 g, 3.5 mmol) at ambient temperature. The reaction was irradiated under microwave for 1.5 h at 150 °C. After cooling to room temperature, the reaction was poured into water and extracted with ethyl acetate. The organic extract was concentrated under reduced pressure and the residue was treated with 4.0 M HCl in dioxane (5 mL). After standing for 10 h, the reaction was concentrated under reduced pressure and purified by HPLC to give the title compound (0.075 g). LCMS  $m/z$  = 419.3  $[M+H]^+$ .

**Example 1.257: Preparation of 2-(((1*s*,4*s*)-4-((5-Methyl-3,4-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 16).**

From a mixture of regioisomers, *tert*-butyl 2-(((1*r*,4*s*)-4-((4-iodo-3-methyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*r*,4*s*)-4-((4-iodo-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate, and phenylboronic acid, the title compound was obtained using a similar method to the one described in **Example 1.256**. LCMS  $m/z$  = 419.4  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.25-1.64 (m, 8H), 1.75 (m, 1H), 2.11 (m, 1H), 2.20 (s, 3H), 3.45 (d,  $J$  = 7.1Hz, 2H), 4.05 (s, 2H), 4.12 (d,  $J$  = 7.3Hz, 2H), 7.23-7.46 (m, 10H).

**Example 1.258: Preparation of 2-(((1*s*,4*s*)-4-((4-(3-Methoxyphenyl)-3-(methylthio)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 30).**

**Step A: Preparation of 4-(3-Methoxyphenyl)-5-(methylthio)-3-phenyl-1*H*-pyrazole.**

To a solution of 2-(3-methoxyphenyl)-1-phenylethanone (3.0 g, 13.26 mmol) in anhydrous THF (10 mL), was added a solution of 1.0 M KO-*t*-Bu in THF (13.26 mL, 13.26 mmol). The reaction was stirred for 15 min at room temperature, and carbon disulfide (1.01 g, 13.26 mmol) was added at 0 °C. After 15 min, iodomethane (4.12 g, 29.0 mmol) was added dropwise and the reaction was maintained at the same temperature for 4 h. The reaction was poured into water and extracted with ethyl acetate. The organic extract was dried over MgSO<sub>4</sub> and concentrated under reduced

pressure. The residue was suspended in ethanol (10 mL) and added hydrazine hydrate (1.99 g, 39.8 mmol) at room temperature. The reaction was refluxed for 4 h. After cooling to room temperature, the reaction was concentrated under reduced pressure and extracted with ethyl acetate. The organic extract was dried over  $\text{MgSO}_4$  and concentrated under reduced pressure to give a semi-solid, which  
5 was recrystallized from 10% ethyl acetate in hexane to give the title compound (2.15 g). LCMS  $m/z$  = 297.5  $[\text{M}+\text{H}]^+$ .

**Step B: Preparation of 2-(((1*s*,4*s*)-4-((4-(3-Methoxyphenyl)-3-(methylthio)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid.**

To a solution of 4-(3-methoxyphenyl)-5-(methylthio)-3-phenyl-1*H*-pyrazole (100 mg, 0.337 mmol) in DMF (2 mL), was added sodium hydride (8.10 mg, 0.337 mmol) at ambient temperature.  
10 After stirring for 10 min, a solution of *tert*-butyl 2-(((1*s*,4*s*)-4-(tosyloxymethyl)cyclohexyl)methoxy)acetate (139 mg, 0.337 mmol) in DMF (1 mL) was added at room temperature. The reaction was heated to 45 °C and stirred for 8 h. After cooling to room temperature, the reaction was poured into  $\text{H}_2\text{O}$  and extracted with ethyl acetate, which was dried  
15 over  $\text{MgSO}_4$  and concentrated under reduced pressure. The resulting residue was treated with 4.0 M HCl in dioxane and stirred for overnight. The reaction was concentrated under reduced pressure and the residue was purified by HPLC to give the title compound (21 mg). LCMS  $m/z$  = 481.6  $[\text{M}+\text{H}]^+$ .

**Example 1.259: Preparation of 1-(((1*s*,4*s*)-4-(Benzyloxymethyl)cyclohexyl)methyl)-3-(4-fluorophenyl)-5-methyl-4-phenyl-1*H*-pyrazole.**

**Step A: Preparation of (E)-1-(((1*s*,4*s*)-4-(benzyloxymethyl)cyclohexyl)methyl)-2-(4-fluorobenzylidene)hydrazine.**

To a solution of *tert*-butyl 2-(((1*s*,4*s*)-4-(benzyloxymethyl)cyclohexyl)methyl)hydrazinecarboxylate (1.0 g, 2.87 mmol) in dichloromethane  
25 (5 mL), was added TFA (5.0 mL) at room temperature. After stirring for 3 h at the same temperature, the reaction was concentrated under reduced pressure. The resulting residue was dissolved in THF (10 mL) and 4-fluorobenzaldehyde (0.36 g, 2.87 mmol) was added at room temperature. After stirring for 30 min, the reaction was poured into water and extracted with ethyl acetate. The organic layer was washed with saturated  $\text{NaHCO}_3$ , dried over  $\text{MgSO}_4$ , and then  
30 concentrated under reduced pressure to give the title compound (0.96 g) without further purification. LCMS  $m/z$  = 355.3  $[\text{M}+\text{H}]^+$ .

**Step B: Preparation of 1-(((1*s*,4*s*)-4-(Benzyloxymethyl)cyclohexyl)methyl)-3-(4-fluorophenyl)-5-methyl-4-phenyl-1*H*-pyrazole.**

To a solution of (E)-1-(((1*s*,4*s*)-4-(benzyloxymethyl)cyclohexyl)methyl)-2-(4-fluorobenzylidene)hydrazine (0.97 g, 2.73 mmol) and (E)-(2-nitroprop-1-enyl)benzene (0.445 g, 2.73 mmol) in THF (5 mL) at -78 °C, was added potassium butan-1-olate (0.31 g, 2.73 mmol)  
35 dropwise. After stirring for 10 min, TFA (0.42 mL, 5.45 mmol) was added and the reaction



maintained at -78 °C for 2 h. After warmed to room temperature, the reaction was poured into water and extracted with ethyl acetate. The organic layer was dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography to give the title compound (0.2 g). LCMS *m/z* = 469.3.

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**Example 1.260: Preparation of 2-(((1*s*,4*s*)-4-((5-(4-Methoxyphenyl)-3-(methylthio)-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 36).**

**Step A: Preparation of 3-(4-Methoxyphenyl)-5-(methylthio)-4-phenyl-1*H*-pyrazole.**

To a solution of 1-(4-methoxyphenyl)-2-phenylethanone (3.7 g, 16.35 mmol) in anhydrous  
10 THF (10 mL), was added a solution of 1.0 M KO-*t*-Bu in THF at ambient temperature. The reaction was stirred for 15 min at room temperature, then CS<sub>2</sub> (1.345 g, 17.66 mmol) was added. After 5 min, iodomethane (5.08 g, 35.8 mmol) was added and the reaction was stirred for 4 h. The reaction was poured into water and extracted with ethyl acetate. The extract was dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The residue was dissolved in ethanol (10 mL) and added  
15 hydrazine hydrate (2.45 g, 49.1 mmol) at room temperature. The reaction was refluxed for 4 h. After cooling, the reaction was poured into water and extracted with ethyl acetate. The organic layer was dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The residue was purified by column chromatography to give the title compound (3.95 g) as a solid. LCMS *m/z* = 297.4 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 2.41 (s, 3H), 3.72 (s, 3H), 6.72-6.90 (m, 2H), 7.10-7.43 (m, 7H).

20 **Step B: Preparation of 2-(((1*s*,4*s*)-4-((5-(4-Methoxyphenyl)-3-(methylthio)-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid.**

To a solution of 3-(4-methoxyphenyl)-5-(methylthio)-4-phenyl-1*H*-pyrazole (100 mg, 0.337 mmol) in DMF (2 mL), was added sodium hydride (8.10 mg, 0.337 mmol) at ambient temperature. After stirring for 10 min, a solution of *tert*-butyl 2-(((1*s*,4*s*)-4-  
25 (tosyloxymethyl)cyclohexyl)methoxy)acetate (139 mg, 0.337 mmol) in DMF (1 mL) was added at room temperature. The reaction was heated to 45 °C and stirred for 8 h. After cooling to room temperature, the reaction was poured into H<sub>2</sub>O and extracted with ethyl acetate, which was dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The resulting residue was treated with 4.0 M HCl in dioxane and stirred for overnight. The reaction was concentrated under reduced pressure and  
30 the residue was purified by HPLC to give the title compound (31 mg). LCMS *m/z* = 481.6 [M+H]<sup>+</sup>.

**Example 1.261: Preparation of 2-(((1*s*,4*s*)-4-((3-(4-Methoxyphenyl)-5-(methylthio)-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 37).**

From 3-(4-methoxyphenyl)-5-(methylthio)-4-phenyl-1*H*-pyrazole and *tert*-butyl 2-(((1*s*,4*s*)-4-  
35 4-(tosyloxymethyl)cyclohexyl)methoxy)acetate, the title compound was obtained using a similar method to the one described in **Example 1.260, Step B**. LCMS *m/z* = 481.5 [M+H]<sup>+</sup>.

**Example 1.262: Preparation of 2-(((1*s*,4*s*)-4-((3-(Methylthio)-4,5-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 75).**

**Step A: Preparation of 3,3-Bis(methylthio)-1,2-diphenylprop-2-en-1-one.**

To a solution of 1,2-diphenylethanone (5.0 g, 25.5 mmol) in anhydrous THF (50 mL), was added a solution of 1.0 M KO-*t*-Bu in THF (51.0 mL, 51.0 mmol). The reaction was stirred for 15 min at room temperature, and then K<sub>2</sub>CO<sub>3</sub> (2.095 g, 27.5 mmol) was added. After 10 min, iodomethane (7.92 g, 55.8 mmol) was added and the reaction was stirred for 4 h. The reaction was poured into water and extracted with ethyl acetate. The organic layer was dried over MgSO<sub>4</sub> and concentrated under reduced pressure to give the title compound (6.9 g). LCMS *m/z* = 301.3 [M+H]<sup>+</sup>.

**Step B: Preparation of 5-(Methylthio)-3,4-diphenyl-1*H*-pyrazole.**

To a suspension of 3,3-bis(methylthio)-1,2-diphenylprop-2-en-1-one (2.5 g, 8.32 mmol) in ethanol (20 mL), was added hydrazine hydrate (1.67 g, 33.3 mmol) at room temperature. The reaction was refluxed for 6 h. After cooling, the reaction was poured into water and extracted with ethyl acetate. The organic extract was dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The residue was purified by column chromatography to give the title compound (1.98 g). LCMS *m/z* = 267.0 [M+H]<sup>+</sup>.

**Step C: Preparation of 2-(((1*s*,4*s*)-4-((3-(Methylthio)-4,5-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid.**

To a solution of 5-(methylthio)-3,4-diphenyl-1*H*-pyrazole (100 mg, 0.375 mmol) in DMF (3 mL), was added sodium hydride (9.01 mg, 0.375 mmol) at ambient temperature. After stirring for 10 min, a solution of *tert*-butyl 2-(((1*s*,4*s*)-4-(tosyloxymethyl)cyclohexyl)methoxy)acetate (155 mg, 0.375 mmol) in DMF (1 mL) was added at room temperature. The reaction was heated to 45 °C and stirred for 8 h. The reaction was poured into H<sub>2</sub>O and extracted with ethyl acetate, which was dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The resulting residue was treated with 4.0 M HCl in dioxane and stirred overnight. The reaction was concentrated under reduced pressure and purified by HPLC to give the title compound (19 mg). LCMS *m/z* = 451.6 [M+H]<sup>+</sup>.

**Example 1.263: Preparation of 2-(((1*s*,4*s*)-4-((3-(2-Methoxyethylthio)-4,5-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 188).**

**Step A: Preparation of 5-(2-Methoxyethylthio)-3,4-diphenyl-1*H*-pyrazole.**

To a solution of 3,4-diphenyl-1*H*-pyrazole-5(4*H*)-thione (0.5 g, 1.981 mmol) in DMF (5 mL), were added 1-bromo-2-methoxyethane (0.275 g, 1.981 mmol) and K<sub>2</sub>CO<sub>3</sub> (0.274 g, 1.981 mmol) at room temperature. After stirring for 4 h, the reaction was poured into water and extracted with ethyl acetate. The organic extract was dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The resulting residue was purified by column chromatography to give the title compound (0.45 g). LCMS *m/z* = 311.2 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 3.23 (s, 3H), 3.12-3.54 (m, 4H), 7.22-7.49 (m, 10H), 13.2 (s, 1H).

**Step B: Preparation of 2-(((1*s*,4*s*)-4-((3-(2-Methoxyethylthio)-4,5-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid.**

To a solution of 5-(2-methoxyethylthio)-3,4-diphenyl-1*H*-pyrazole (180 mg, 0.580 mmol) in DMF (2 mL), was added sodium hydride (13.92 mg, 0.580 mmol) in 0 °C. After stirring for 10 min, *tert*-butyl 2-(((1*s*,4*s*)-4-(tosyloxymethyl)cyclohexyl)methoxy)acetate (239 mg, 0.580 mmol) was added and the reaction was warmed to 40 °C. After stirring for 12 h, the reaction was poured into water and extracted with ethyl acetate. The organic extract was dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The residue was treated with 4.0 M HCl in dioxane (5 mL) and placed for 8 h. The mixture was concentrated under reduced pressure and purified by HPLC to give the title compound (32 mg). LCMS *m/z* = 495.7 [M+H]<sup>+</sup>.

**Example 1.264: Preparation of 2-(((1*s*,4*s*)-4-((4-(2,5-Difluorophenyl)-3-(methylthio)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 77).**

To a solution of regioisomers, *tert*-butyl 2-(((1*s*,4*s*)-4-((4-iodo-3-methylthio-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-iodo-5-methylthio-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate (110 mg, 0.198 mmol), in dioxane (2 mL), were added 2,5-difluorophenylboronic acid (31.2 mg, 0.198 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (11.42 mg, 9.88 μmol), and a 2.0 M aqueous solution of K<sub>2</sub>CO<sub>3</sub> (54.6 mg, 0.395 mmol) at ambient temperature. The reaction was irradiated under microwave for 1.5 h at 150 °C. The reaction was filtered and concentrated under reduced pressure. The residue was treated with 4.0 M HCl (5 mL). After stirring for 10 h, the reaction was concentrated under reduced pressure and purified by HPLC to give the title compound (19 mg). LCMS *m/z* = 487.4 [M+H]<sup>+</sup>.

**Example 1.265: Preparation of 2-(((1*s*,4*s*)-4-((4-(2,5-Difluorophenyl)-5-(methylthio)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 78).**

From regioisomers, *tert*-butyl 2-(((1*s*,4*s*)-4-((4-iodo-3-methylthio-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-iodo-5-methylthio-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate, and 2,5-difluorophenylboronic acid, the title compound was obtained using a similar method to the one described in Example 1.264. LCMS *m/z* = 487.8 [M+H]<sup>+</sup>.

**Example 1.266: Preparation of 2-(((1*s*,4*s*)-4-((4-(2,3-Difluorophenyl)-3-(methylthio)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 82).**

To a mixture of regioisomers, *tert*-butyl 2-(((1*s*,4*s*)-4-((4-iodo-3-methylthio-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-iodo-5-methylthio-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate (110 mg, 0.198 mmol), in dioxane (2 mL), were added 2,3-difluorophenylboronic acid (31.2 mg, 0.198 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (11.42 mg, 9.88

μmol), and a 2.0 M aqueous solution of K<sub>2</sub>CO<sub>3</sub> (54.6 mg, 0.395 mmol) at ambient temperature. The reaction was irradiated under microwave for 1.5 h at 150 °C. After cooling to room temperature, the reaction was poured into water and extracted with ethyl acetate. The organic extract was concentrated under reduced pressure and the resulting residue was treated with 4.0 M HCl in dioxane (5 mL). After standing for 10 h, the reaction was concentrated under reduced pressure and purified by HPLC to give the title compound (13 mg). LCMS *m/z* = 487.4 [M+H]<sup>+</sup>.

**Example 1.267: Preparation of 2-(((1*s*,4*s*)-4-((4-(2,3-Difluorophenyl)-5-(methylthio)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 83).**

From a mixture of regioisomers, *tert*-butyl 2-(((1*s*,4*s*)-4-((4-iodo-3-methylthio-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*r*,4*r*)-4-((4-iodo-5-methylthio-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate, and 2,3-difluorophenylboronic acid, the title compound was obtained using a similar method to the one described in **Example 1.266**. LCMS *m/z* = 487.4 [M+H]<sup>+</sup>.

**Example 1.268: Preparation of 2-(((1*s*,4*s*)-4-((4-(3-Isopropoxyphenyl)-3-(methylthio)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 84).**

To a mixture of regioisomers, *tert*-butyl 2-(((1*s*,4*s*)-4-((4-iodo-3-methylthio-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-iodo-5-methylthio-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate (110 mg, 0.198 mmol, 1:3 mixture), in dioxane (2 mL), were added 3-isopropoxyphenylboronic acid (35.6 mg, 0.198 mmol), Ph(PPh<sub>3</sub>)<sub>4</sub> (11.42 mg, 9.88 μmol), and a 2.0 M aqueous solution of K<sub>2</sub>CO<sub>3</sub> (54.6 mg, 0.395 mmol) at ambient temperature. The reaction was irradiated under microwave for 1.5 h at 150 °C. After cooling to room temperature, the reaction was poured into water and extracted with ethyl acetate. The extract was concentrated under reduced pressure and the resulting residue was treated with 4.0 M HCl in dioxane (5 mL). After standing for 10 h, the reaction was concentrated under reduced pressure and purified by HPLC to give the title compound (21 mg). LCMS *m/z* = 509.5 [M+H]<sup>+</sup>.

**Example 1.269: Preparation of 2-(((1*s*,4*s*)-4-((4-(3-Isopropoxyphenyl)-5-(methylthio)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 85).**

From a mixture of regioisomers, *tert*-butyl 2-(((1*s*,4*s*)-4-((4-iodo-3-methylthio-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*r*,4*r*)-4-((4-iodo-5-methylthio-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate, and 3-isopropoxyphenylboronic acid, the title compound was obtained using a similar method to the one described in **Example 1.268**. LCMS *m/z* = 509.8 [M+H]<sup>+</sup>.

**Example 1.270: Preparation of 2-(((1s,4s)-4-((4-(2,3-Difluorophenyl)-5-(methylsulfonyl)-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 86).**

To a solution of 2-(((1s,4s)-4-((4-(2,3-difluorophenyl)-5-(methylthio)-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid (10 mg, 0.021 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL), was added mCPBA (3.55 mg, 0.021 mmol) at room temperature. The reaction was stirred for 3 h at room temperature. The reaction was poured into water and extracted with ethyl acetate. The extract was dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The resulting residue was purified by HPLC to give the title compound (9 mg). LCMS *m/z* = 519.7 [M+H]<sup>+</sup>.

**Example 1.271: Preparation of 2-(((1s,4s)-4-((4-(2,5-Difluorophenyl)-5-(methylsulfonyl)-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 87).**

To a solution of 2-(((1s,4s)-4-((4-(2,5-difluorophenyl)-5-(methylthio)-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid (10mg, 0.021 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL), was added mCPBA (7.09 mg, 0.041 mmol) at room temperature. The reaction was stirred for 3 h at room temperature. The reaction was poured into water and extracted with ethyl acetate. The extract was dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The resulting residue was purified by HPLC to give the title compound (8 mg). LCMS *m/z* = 519.7 [M+H]<sup>+</sup>.

**Example 1.272: Preparation of 2-(((1s,4s)-4-((4-(3-Fluorophenyl)-5-(methylthio)-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 91).**

To a mixture of regioisomers, *tert*-butyl 2-(((1s,4s)-4-((4-iodo-3-methylthio-5-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1s,4s)-4-((4-iodo-5-methylthio-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate (150 mg, 0.270 mmol), in dioxane (1 mL), were added 3-fluorophenylboronic acid (37.7 mg, 0.270 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (1.56 mg, 1.348 μmol) and a 2.0 M aqueous solution of K<sub>2</sub>CO<sub>3</sub> (0.270 mL, 0.539 mmol) at ambient temperature. The reaction was heated under microwave at 120 °C for 1.5 h. The reaction was poured into water and extracted with ethyl acetate. The organic extract was dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The resulting residue was treated with hydrogen chloride (3.37 mL, 13.48 mmol) and stirred for 5 h. The mixture was concentrated under reduced pressure and purified by HPLC to give the title compound (93 mg). LCMS *m/z* = 469.3 [M+H]<sup>+</sup>.

**Example 1.273: Preparation of 2-(((1s,4s)-4-((4-(2-Fluoro-3-methoxyphenyl)-5-(methylthio)-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 92).**

To a mixture of regioisomers, *tert*-butyl 2-(((1s,4s)-4-((4-iodo-3-methylthio-5-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1s,4s)-4-((4-iodo-5-methylthio-3-phenyl-1H-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate (150 mg, 0.270 mmol), in dioxane (1

mL), were added 2-fluoro-3-methoxyphenylboronic acid (45.8 mg, 0.270 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (1.557 mg, 1.348 μmol) and a 2.0 M aqueous solution of K<sub>2</sub>CO<sub>3</sub> (0.270 mL, 0.539 mmol) at ambient temperature. The reaction was heated under microwave at 120 °C for 1.5 h. The reaction was poured into water and extracted with ethyl acetate. The organic extract was dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The resulting residue was treated with hydrogen chloride (3.37 mL, 13.48 mmol) and stirred for 5 h. The reaction was concentrated under reduced pressure and purified by HPLC to give the title compound (102 mg). LCMS *m/z* = 499.1 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.34-1.61 (m, 8H), 1.85 (m, 1H), 2.11 (s, 3H), 2.21 (m, 1H), 3.52 (d, *J* = 7.1 Hz, 2H), 3.83 (s, 3H), 3.92 (s, 2H), 4.28 (d, *J* = 7.4 Hz, 2H), 6.80-6.91 (m, 2H), 7.23-7.42 (m, 6H).

**Example 1.274: Preparation of 2-(((1*s*,4*s*)-4-((4-(4-Fluorophenyl)-5-(methylthio)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 94).**

To a mixture of regioisomers, *tert*-butyl 2-(((1*s*,4*s*)-4-((4-iodo-3-methylthio-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-iodo-5-methylthio-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate (150 mg, 0.270 mmol), in dioxane (1 mL), was added 4-fluorophenylboronic acid (37.7 mg, 0.270 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (15.57 mg, 0.013 mmol) and a 2.0 M aqueous solution of K<sub>2</sub>CO<sub>3</sub> (74.5 mg, 0.539 mmol) at ambient temperature. The reaction was heated under microwave at 120 °C for 1.5 h. The reaction was poured into water and extracted with ethyl acetate. The extract was dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The resulting residue was treated with hydrogen chloride (3.37 mL, 13.48 mmol) and stirred for 5 h. The reaction was concentrated under reduced pressure and purified by HPLC to give the title compound (96 mg). LCMS *m/z* = 469.3 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.20-1.35 (m, 8H) 1.63 (m, 1H), 1.95 (s, 3H), 2.09 (m, 1H), 3.48 (d, *J* = 7.0 Hz, 2H), 3.79 (s, 2H), 4.10 (d, *J* = 7.2 Hz, 2H), 6.94-7.09 (m, 9H).

**Example 1.275: Preparation of 2-(((1*s*,4*s*)-4-((5-(Methylthio)-3-phenyl-4-(3-(trifluoromethyl)phenyl)-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 96).**

To a mixture of regioisomers, *tert*-butyl 2-(((1*s*,4*s*)-4-((4-iodo-3-methylthio-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-iodo-5-methylthio-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate (150 mg, 0.270 mmol), in dioxane (1 mL), was added 3-(trifluoromethyl)phenylboronic acid (51.2 mg, 0.270 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (15.57 mg, 0.013 mmol) and a 2.0 M aqueous solution of K<sub>2</sub>CO<sub>3</sub> (74.5 mg, 0.539 mmol) at ambient temperature. The reaction was heated under microwave at 120 °C for 1.5 h. The reaction was poured into water and extracted with ethyl acetate. The extract was dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The resulting residue was treated with hydrogen chloride (3.37 mL, 13.48

mmol) and stirred for 5 h. The reaction was concentrated under reduced pressure and purified by HPLC to give the title compound (85 mg). LCMS  $m/z$  = 519.7  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.38-1.59 (m, 8H), 1.85 (m, 1H), 2.10 (s, 3H), 2.25 (m, 1H), 3.52 (d,  $J$  = 7.0 Hz, 2H), 4.01 (s, 2H), 4.31 (d,  $J$  = 7.2 Hz, 2H), 7.29-7.65 (m, 9H).

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**Example 1.276: Preparation of 2-(((1*s*,4*s*)-4-((4-(4-Chlorophenyl)-5-(methylthio)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 97).**

To a mixture of regioisomers, *tert*-butyl 2-(((1*s*,4*s*)-4-((4-iodo-3-methylthio-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-iodo-5-methylthio-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate (150 mg, 0.270 mmol), in dioxane (1 mL), was added 4-chlorophenylboronic acid (42.1 mg, 0.270 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (15.57 mg, 0.013 mmol) and a 2.0 M aqueous solution of K<sub>2</sub>CO<sub>3</sub> (74.5 mg, 0.539 mmol) at ambient temperature. The reaction was heated under microwave at 120 °C for 1.5 h. The reaction was poured into water and extracted with ethyl acetate. The extract was dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The resulting residue was treated with hydrogen chloride (3.37 mL, 13.48 mmol) and was stirred for 5 h. The reaction was concentrated under reduced pressure and purified by HPLC to give the title compound (98 mg). LCMS  $m/z$  = 485.1  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.21-1.45 (m, 8H), 1.68 (m, 1H), 1.99 (s, 3H), 2.10 (m, 1H), 3.35 (d,  $J$  = 7.1 Hz, 2H), 3.87 (s, 2H), 4.15 (d,  $J$  = 7.2 Hz, 2H), 7.12-7.38 (m, 9H).

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**Example 1.277: Preparation of 2-(((1*s*,4*s*)-4-((5-(Methylthio)-3-phenyl-4-(thiophen-2-yl)-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 108).**

To a mixture of regioisomers, *tert*-butyl 2-(((1*s*,4*s*)-4-((4-iodo-3-methylthio-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-iodo-5-methylthio-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate (150 mg, 0.270 mmol), in dioxane (1 mL), was added thiophen-2-ylboronic acid (34.5 mg, 0.270 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (15.57 mg, 0.013 mmol) and a 2.0 M aqueous solution of K<sub>2</sub>CO<sub>3</sub> (74.5 mg, 0.539 mmol) at ambient temperature. The reaction was heated under microwave at 120 °C for 1.5 h. The reaction was poured into water and extracted with ethyl acetate. The extract was dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The resulting residue was treated with hydrogen chloride (3.37 mL, 13.48 mmol) and was stirred for 5 h. The reaction was concentrated under reduced pressure and purified by HPLC to give the title compound (89 mg). LCMS  $m/z$  = 457.1  $[M+H]^+$ .

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**Example 1.278: Preparation of 2-(((1*s*,4*s*)-4-((5-(Methylthio)-3-phenyl-4-(thiophen-3-yl)-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 110).**

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To a mixture of regioisomers, *tert*-butyl 2-(((1*s*,4*s*)-4-((4-iodo-3-methylthio-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-iodo-5-methylthio-

3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate (150 mg, 0.270 mmol), in dioxane (1 mL), was added thiophen-3-ylboronic acid (34.5 mg, 0.270 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (15.57 mg, 0.013 mmol) and a 2.0 M aqueous solution of K<sub>2</sub>CO<sub>3</sub> (74.5 mg, 0.539 mmol) at ambient temperature. The reaction was heated under microwave at 120 °C for 1.5 h. The reaction was poured into water and  
5 extracted with ethyl acetate. The organic extract was dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The resulting residue was treated with hydrogen chloride (3.37 mL, 13.48 mmol) and stirred for 5 h. The mixture was concentrated under reduced pressure and purified by HPLC to give the title compound (106 mg). LCMS *m/z* = 457.2 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.34-1.61 (m, 8H), 1.86 (m, 1H), 1.99 (m, 1H), 2.22(s, 3H), 3.61 (d, *J* = 7.1Hz, 2H), 3.99 (s, 2H), 4.24 (d, *J* = 7.4Hz, 2H), 7.01-7.69 (m, 8H).  
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**Example 1.279: Preparation of 2-(((1*s*,4*s*)-4-((4-(3-Methoxyphenyl)-5-(methylsulfinyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 114).**

To a solution of 2-(((1*s*,4*s*)-4-((4-(3-methoxyphenyl)-5-(methylthio)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid (52 mg, 0.108 mmol) in DCM (1 mL), was added *m*CPBA (18.67 mg, 0.108 mmol) portionwise at room temperature. After stirring for 30 min, the reaction was poured into water and extracted with ethyl acetate. The extract was dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The resulting residue was purified by HPLC to provide the title compound (40 mg). LCMS *m/z* = 497.2 [M+H]<sup>+</sup>.  
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**Example 1.280: Preparation of 2-(((1*s*,4*s*)-4-((4-(3-Fluoro-5-methylphenyl)-5-(methylthio)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 134).**

To a mixture of regioisomers, *tert*-butyl 2-(((1*s*,4*s*)-4-((4-iodo-3-methylthio-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*s*,4*s*)-4-((4-iodo-5-methylthio-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate (500 mg, 0.898 mmol), in dioxane (5 mL), was added 3-fluoro-5-methylphenylboronic acid (138 mg, 0.898 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (51.9 mg, 0.045 mmol) and a 2.0 M aqueous solution of K<sub>2</sub>CO<sub>3</sub> (248 mg, 1.797 mmol) at ambient temperature. The reaction was heated under Microwave at 120 °C for 1.5 h. The reaction was poured into water and extracted with ethyl acetate. The extract was dried over MgSO<sub>4</sub> and concentrated under reduced  
25 pressure. The resulting residue was treated with 4.0 M hydrogen chloride (11.23 mL, 44.9 mmol) in dioxane and stirred for 5 h. The reaction was concentrated under reduced pressure and purified by HPLC. The lyophilized solid was dissolved in acetonitrile (1 mL) and H<sub>2</sub>O (2 mL) and added NaOH (14.6 mg, 0.367 mmol) in H<sub>2</sub>O (1 mL). The mixture was dried under reduced pressure to give the title compound (185 mg). LCMS *m/z* = 483.4 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.30-1.65 (m, 8H), 1.76 (m, 1H), 2.18 (s, 3H), 2.21 (m, 1H), 2.35(s, 3H), 3.45 (d, *J* = 7.2Hz, 2H), 3.98 (s, 2H), 4.28 (d, *J* = 7.4Hz, 2H), 6.85-7.08 (m, 3H), 7.21-7.35 (m, 5H).  
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**Example 1.281: Preparation of 2-(((1*r*,4*s*)-4-((3-((*S*)-3,4-Dihydroxybutyl)-4,5-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 156).**

**Step A: Preparation of (*R*)-4-(3-phenyl-1*H*-pyrazol-5-yl)butane-1,2-diol.**

To a solution of 5-(but-3-enyl)-3-phenyl-1*H*-pyrazole (3.0 g, 15.13 mmol) in *iso*-propanol (20 mL) and H<sub>2</sub>O (20 mL), was added AD-mix- $\alpha$  (20.0 g) at room temperature. The reaction was stirred for 48 h at room temperature. The reaction was poured into saturated Na<sub>2</sub>SO<sub>3</sub> (20 mL) and extracted with ethyl acetate. The extract was dried over MgSO<sub>4</sub> and concentrated under reduced pressure to give the title compound (2.45 g) as an oil, which was used without further purification. LCMS  $m/z$  = 232.9 [M+H]<sup>+</sup>.

**Step B: Preparation of (*R*)-5-(2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethyl)-3-phenyl-1*H*-pyrazole.**

To a solution of (*R*)-4-(3-phenyl-1*H*-pyrazol-5-yl)butane-1,2-diol (2.5 g, 10.76 mmol) in acetone (50 mL), were added 2,2-dimethoxypropane (11.21 g, 108 mmol) and PTSA (0.185 g, 1.076 mmol) at room temperature. After stirring for 3 h, the reaction was concentrated under reduced pressure. The resulting residue was poured into water and extracted with ethyl acetate. The extract was dried over MgSO<sub>4</sub> and concentrated under reduced pressure to give the title compound without further purification. LCMS  $m/z$  = 273.4 [M+H]<sup>+</sup>.

**Step C: Preparation of (*R*)-4-bromo-5-(2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethyl)-3-phenyl-1*H*-pyrazole.**

To a solution of (*R*)-5-(2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethyl)-3-phenyl-1*H*-pyrazole (2.3 g, 8.45 mmol) and MP-carbonate (26 g, 84.5 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (100 mL), was added bromine (1.350 g, 8.45 mmol) dropwise at 0 °C. After stirring for 1 h, MP-carbonate was filtered off and washed with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layer was poured into water, extracted with CH<sub>2</sub>Cl<sub>2</sub>, dried over MgSO<sub>4</sub>, and then concentrated under reduced pressure. The resulting residue was purified by column chromatography to give the title compound (2.81 g) as an oil. LCMS  $m/z$  = 351.2 [M+H]<sup>+</sup>.

**Step D: Preparation of *tert*-Butyl 2-(((1*s*,4*s*)-4-((4-Bromo-5-(2-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)ethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-Butyl 2-(((1*s*,4*s*)-4-((4-Bromo-3-(2-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)ethyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate as a Mixture of Regioisomers.**

To a solution of (*R*)-4-bromo-5-(2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethyl)-3-phenyl-1*H*-pyrazole (1.23 g, 3.50 mmol) in DMF (10 mL), was sodium hydride (0.084 g, 3.50 mmol) added at ambient temperature. After stirring for 30 min, (*R*)-*tert*-butyl 2-(((4-bromo-3-(2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate (1.45 g, 3.50 mmol) was added and the reaction was heated to 45 °C. After stirring for 12 h, the reaction was poured into H<sub>2</sub>O and extracted with ethyl acetate, which was dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The resulting residue was purified by column chromatography to give the title compounds (1.82 g, 1:3 ratio) as a mixture of regioisomers. LCMS  $m/z$  = 591.7 [M+H]<sup>+</sup>.

**Step E: Preparation of 2-(((1*r*,4*s*)-4-((3-((*S*)-3,4-dihydroxybutyl)-4,5-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid.**

To a solution of regioisomers, *tert*-butyl 2-(((1*r*,4*s*)-4-((4-bromo-3-(2-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)ethyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*r*,4*s*)-4-((4-bromo-5-(2-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)ethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate (150 mg, 0.254 mmol), in dioxane (1 mL), were added phenylboronic acid (30.9 mg, 0.254 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (14.65 mg, 0.013 mmol) and a 2.0 M aqueous solution of K<sub>2</sub>CO<sub>3</sub> (70.1 mg, 0.507 mmol) at ambient temperature. The reaction was heated under microwave at 120 °C for 1.5 h. After cooling to room temperature, the reaction was poured into water and extracted with ethyl acetate. The organic extract was dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The residue was treated with 4.0 M HCl in dioxane (5 mL). After standing for 10 h, the reaction was concentrated under reduced pressure and purified by HPLC to give the title compound (12 mg). LCMS *m/z* = 493.5 [M+H]<sup>+</sup>

**Example 1.282: Preparation of 2-(((1*r*,4*s*)-4-((5-((*S*)-3,4-Dihydroxybutyl)-3,4-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 157).**

From a mixture of regioisomers, *tert*-butyl 2-(((1*r*,4*s*)-4-((4-bromo-3-(2-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)ethyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*r*,4*s*)-4-((4-bromo-5-(2-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)ethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate, and phenylboronic acid, the title compound was obtained by using a similar method to the one described in **Example 1.281**. LCMS *m/z* = 493.7 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.30-1.78 (m, 10H), 1.86 (m, 1H), 2.10 (s, 1H), 2.63 (m, 1H), 2.71 (m, 1H), 3.10 (m, 2H), 3.12-3.22 (m, 1H), 3.35 (d, *J* = 7.2 Hz, 2H), 3.95 (s, 2H), 4.02 (d, *J* = 7.3 Hz, 2H), 7.02-7.35 (m, 10H).

**Example 1.283: Preparation of 2-(((1*r*,4*s*)-4-((5-((*S*)-3,4-Dihydroxybutyl)-4-(3-fluorophenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 158).**

To a solution of regioisomers, *tert*-butyl 2-(((1*r*,4*s*)-4-((4-bromo-3-(2-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)ethyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*r*,4*s*)-4-((4-bromo-5-(2-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)ethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate (150 mg, 0.254 mmol), in dioxane (1 mL), were added 3-fluorophenylboronic acid (35.5 mg, 0.254 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (14.65 mg, 0.013 mmol) and a 2.0 M aqueous solution of K<sub>2</sub>CO<sub>3</sub> (70.1 mg, 0.507 mmol) at ambient temperature. The reaction was heated under microwave at 120 °C for 1.5 h. The reaction was poured into water and extracted with ethyl acetate. The extract was dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The residue was treated with 4.0 M HCl in dioxane. After stirring for 5 h, the reaction was concentrated under

reduced pressure and purified by HPLC to give the title compound (45 mg). LCMS  $m/z$  = 511.5  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.10-1.77 (m, 10H), 1.78 (m, 1H), 1.98 (m, 1H), 2.72 (m, 1H), 2.80 (m, 1H), 3.20-3.40 (m, 3H), 3.38 (d,  $J$  = 7.2Hz, 2H), 3.97 (s, 2H), 3.99 (d,  $J$  = 7.3Hz, 2H), 7.15-7.38 (m, 9H).

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**Example 1.284: Preparation of 2-(((1*r*,4*s*)-4-((4-(3,4-Difluorophenyl)-3-((*S*)-3,4-dihydroxybutyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 159).**

To a solution of regioisomers, *tert*-butyl 2-(((1*r*,4*s*)-4-((4-bromo-3-(2-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)ethyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*r*,4*s*)-4-((4-bromo-5-(2-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)ethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate (150 mg, 0.254 mmol), in dioxane (1 mL), were added 3,4-difluorophenylboronic acid (40.0 mg, 0.254 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (14.65 mg, 0.013 mmol) and a 2.0 M aqueous solution of K<sub>2</sub>CO<sub>3</sub> (70.1 mg, 0.507 mmol) at ambient temperature. The reaction was heated under microwave at 120 °C for 1.5 h. After cooling to room temperature, the reaction was poured into water and extracted with ethyl acetate. The extract was concentrated under reduced pressure and the resulting residue was treated with 4.0 M HCl in dioxane (5 mL). After standing for 10 h, the reaction was concentrated under reduced pressure and purified by HPLC to give the title compound (12 mg). LCMS  $m/z$  = 529.7  $[M+H]^+$ .

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**Example 1.285: Preparation of 2-(((1*r*,4*s*)-4-((4-(3,4-Difluorophenyl)-5-((*S*)-3,4-dihydroxybutyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 160).**

From regioisomers, *tert*-butyl 2-(((1*r*,4*s*)-4-((4-bromo-3-(2-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)ethyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*r*,4*s*)-4-((4-bromo-5-(2-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)ethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate, and 3,4-difluorophenylboronic acid, the title compound was obtained by using similar method to the one described in **Example 1.284**. LCMS  $m/z$  = 529.5  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.10-1.77 (m, 10H), 1.75 (m, 1H), 2.10 (m, 1H), 2.70 (m, 1H), 2.75 (m, 1H), 3.15 (m, 1H), 3.21 (m, 1H), 3.32 (m, 1H), 3.35 (d,  $J$  = 7.2Hz, 2H), 3.97 (s, 2H), 3.98 (d,  $J$  = 7.2Hz, 2H), 6.95 (m, 1H), 7.14-7.41 (m, 7H).

**Example 1.286: Preparation of 2-(((1*r*,4*s*)-4-((4-(3-Chlorophenyl)-5-((*S*)-3,4-dihydroxybutyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 162).**

To a solution of regioisomers, *tert*-butyl 2-(((1*r*,4*s*)-4-((4-bromo-3-(2-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)ethyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl

2-(((1*r*,4*s*)-4-((4-bromo-5-(2-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)ethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate (150 mg, 0.254 mmol), in dioxane (1 mL), were added 3-chlorophenylboronic acid (39.7 mg, 0.254 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (14.65 mg, 0.013 mmol) and a 2.0 M aqueous solution of K<sub>2</sub>CO<sub>3</sub> (70.1 mg, 0.507 mmol) at ambient temperature. The reaction was heated under microwave at 120 °C for 1.5 h. The reaction was poured into water and extracted with ethyl acetate. The extract was dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The residue was treated with 4.0 M HCl in dioxane (5 mL). After stirring for 5 h, the reaction was concentrated under reduced pressure and purified by HPLC to give the title compound (65 mg). LCMS *m/z* = 528.3 [M+H]<sup>+</sup>; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ ppm 1.31-1.65 (m, 10H), 1.80 (m, 1H), 2.12 (m, 1H), 2.72 (m, 1H), 2.80 (m, 1H), 3.20 (m, 1H), 3.25 (m, 1H), 3.42 (m, 1H), 3.45 (d, *J* = 7.2 Hz, 2H), 4.00 (s, 2H), 4.05 (d, *J* = 7.2 Hz, 2H), 7.13-7.42 (m, 9H).

**Example 1.287: Preparation of 2-(((1*s*,4*s*)-4-((5-((*R*)-3,4-Dihydroxybutyl)-4-(3-fluorophenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 169).**

To a solution of regioisomers, *tert*-butyl 2-(((1*r*,4*s*)-4-((4-bromo-3-(2-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)ethyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*r*,4*s*)-4-((4-bromo-5-(2-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)ethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate (150 mg, 0.254 mmol), in dioxane (1 mL), were added 3-fluorophenylboronic acid (35.5 mg, 0.254 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (14.65 mg, 0.013 mmol) and a 2.0 M aqueous solution of K<sub>2</sub>CO<sub>3</sub> (70.1 mg, 0.507 mmol) at ambient temperature. The reaction was heated under microwave at 120 °C for 1.5 h. The reaction was poured into water and extracted with ethyl acetate. The organic extract was dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The residue was treated with 4.0 M HCl in dioxane (5 mL). After stirring for 5 h, the reaction was concentrated under reduced pressure and purified by HPLC to give the title compound (89 mg). LCMS *m/z* = 511.4 [M+H]<sup>+</sup>.

**Example 1.288: Preparation of 2-(((1*s*,4*s*)-4-((4-(3,4-Difluorophenyl)-5-((*R*)-3,4-dihydroxybutyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 170).**

To a solution of regioisomers, *tert*-butyl 2-(((1*r*,4*s*)-4-((4-bromo-3-(2-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)ethyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl 2-(((1*r*,4*s*)-4-((4-bromo-5-(2-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)ethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate (150 mg, 0.254 mmol), in dioxane (1 mL), was added 3,4-difluorophenylboronic acid (40.0 mg, 0.254 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (14.65 mg, 0.013 mmol) and a 2.0 M aqueous solution of K<sub>2</sub>CO<sub>3</sub> (70.1 mg, 0.507 mmol) at ambient temperature. The reaction was heated under microwave at 120 °C for 1.5 h. The reaction was extracted with ethyl acetate and concentrated

under reduced pressure. The residue was treated with 4.0 M HCl in dioxane and was stirred for 5 h. The reaction was concentrated under reduced pressure and purified by HPLC to give the title compound (72 mg). LCMS  $m/z$  = 529.3  $[M+H]^+$ .

5 **Example 1.289: Preparation of 2-(((1*s*,4*s*)-4-((4-(3-Chlorophenyl)-5-((*R*)-3,4-dihydroxybutyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 171).**

To a solution of regioisomers, *tert*-butyl 2-(((1*r*,4*s*)-4-((4-bromo-3-(2-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)ethyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate and *tert*-butyl  
10 2-(((1*r*,4*s*)-4-((4-bromo-5-(2-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)ethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate (150 mg, 0.254 mmol), in dioxane (1 mL), were added 3-chlorophenylboronic acid (39.7 mg, 0.254 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (14.65 mg, 0.013 mmol) and a 2.0 M aqueous solution of K<sub>2</sub>CO<sub>3</sub> (70.1 mg, 0.507 mmol) at ambient temperature. The reaction was heated under microwave at 120 °C for 1.5 h. The reaction was extracted with ethyl acetate and concentrated  
15 under reduced pressure. The residue was treated with 4.0 M HCl in dioxane and stirred for 5 h. The reaction was concentrated under reduced pressure and purified by HPLC to give the title compound (85 mg). LCMS  $m/z$  = 528.3  $[M+H]^+$ .

20 **Example 1.290: Preparation of 2-(((1*s*,4*s*)-4-((3-(Cyanomethylthio)-4,5-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 183).**

**Step A: Preparation of 2-(3,4-Diphenyl-1*H*-pyrazol-5-ylthio)acetonitrile**

To a solution of 3,4-diphenyl-1*H*-pyrazole-5(4*H*)-thione (0.49 g, 1.981 mmol) in DMF (5 mL), were added 2-bromoacetonitrile (0.253 g, 1.981 mmol) and K<sub>2</sub>CO<sub>3</sub> (0.274 g, 1.981 mmol) at room temperature. After stirring for 2 h, the reaction was poured into water and extracted with ethyl  
25 acetate. The organic extract was dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The residue was purified by column chromatography to give the title compound (0.52 g). LCMS  $m/z$  = 292.1

**Step B: Preparation of 2-(((1*s*,4*s*)-4-((3-(Cyanomethylthio)-4,5-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid.**

To a solution of 2-(3,4-diphenyl-1*H*-pyrazol-5-ylthio)acetonitrile (330 mg, 1.13 mmol) in DMF (2 mL), was added sodium hydride (27.2 mg, 1.133 mmol) in 0 °C. After stirring for 10 min, *tert*-butyl 2-(((1*s*,4*s*)-4-(tosyloxymethyl)cyclohexyl)methoxy)acetate (467 mg, 1.13 mmol) was added and the reaction was warmed to 40 °C. After stirring for 12 h, the reaction was poured into water and extracted with ethyl acetate. The extract was dried over MgSO<sub>4</sub>, concentrated under  
35 reduced pressure, and then treated with 4.0 M HCl in dioxane (5 mL). After stirring for 8 h, the mixture was concentrated under reduced pressure and purified by HPLC to give the title compound (78 mg). LCMS  $m/z$  = 476.2  $[M+H]^+$ .

**Example 1.291: Preparation of 2-(((1*s*,4*s*)-4-((5-(2-Methoxyethylthio)-3,4-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 189).**

From 5-(2-methoxyethylthio)-3,4-diphenyl-1*H*-pyrazole and *tert*-butyl 2-(((1*s*,4*s*)-4-(tosyloxymethyl)cyclohexyl)methoxy)acetate, the title compound was obtained by using similar method to the one described in **Example 1.263**. LCMS  $m/z$  = 495.7  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.35-1.52 (m, 8H), 1.85 (m, 1H), 2.31 (m, 1H), 2.43 (t,  $J$  = 2.5Hz, 2H), 2.61 (t,  $J$  = 2.5Hz, 2H), 3.05 (s, 3H), 3.46 (d,  $J$  = 7.1Hz, 2H), 3.98 (s, 2H), 4.31 (d,  $J$  = 7.2Hz, 2H), 7.31-7.54 (m, 10H).

**Example 1.292: Preparation of 2-(((1*s*,4*s*)-4-((3-(2-Ethoxyethylthio)-4,5-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 185).**

**Step A: Preparation of 5-(2-Ethoxyethylthio)-3,4-diphenyl-1*H*-pyrazole.**

To a solution of 3,4-diphenyl-1*H*-pyrazole-5(4*H*)-thione (0.5 g, 1.981 mmol) in DMF (5 mL), were added 1-bromo-2-ethoxyethane (0.303 g, 1.981 mmol) and  $K_2CO_3$  (0.274 g, 1.981 mmol) at room temperature. After stirring for 4 h, the reaction was poured into water and extracted with ethyl acetate, which was dried over  $MgSO_4$  and concentrated under reduced pressure. The residue was purified by column chromatography to give the title compound (0.45 g). LCMS  $m/z$  = 343.5  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.20 (t,  $J$  = 7.1Hz, 3H), 3.25 (m, 2H), 3.45 (m, 2H), 4.25 (q,  $J$  = 7.1Hz, 2H), 7.25-7.56 (m, 10H), 13.0 (s, 1H).

**Step B: Preparation of 2-(((1*s*,4*s*)-4-((3-(2-Ethoxyethylthio)-4,5-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid.**

To a solution of 5-(2-ethoxyethylthio)-3,4-diphenyl-1*H*-pyrazole (320 mg, 0.986 mmol) in DMF (2 mL), was added sodium hydride (23.67 mg, 0.986 mmol) at 0 °C. After stirring for 10 min, *tert*-butyl 2-(((1*s*,4*s*)-4-(tosyloxymethyl)cyclohexyl)methoxy)acetate (407 mg, 0.986 mmol) was added and the reaction was warmed to 40 °C. After stirring for 12 h, the reaction was poured into water and extracted with ethyl acetate. The extract was dried over  $MgSO_4$  and concentrated under reduced pressure. The resulting residue was treated with 4.0 M HCl in dioxane (5 mL) and stirred for 8 h. The reaction was concentrated under reduced pressure and purified by HPLC to give the title compound (70 mg). LCMS  $m/z$  = 509.5  $[M+H]^+$ .

**Example 1.293: Preparation of 2-(((1*s*,4*s*)-4-((5-(2-Ethoxyethylthio)-3,4-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 186).**

From 5-(2-ethoxyethylthio)-3,4-diphenyl-1*H*-pyrazole and *tert*-butyl 2-(((1*s*,4*s*)-4-(tosyloxymethyl)cyclohexyl)methoxy)acetate, the title compound was obtained by using a similar method to the one described in **Example 1.292**. LCMS  $m/z$  = 509.6  $[M+H]^+$ ;  $^1H$  NMR (400 MHz, DMSO- $d_6$ )  $\delta$  ppm 1.01 (t,  $J$  = 7.1Hz, 3H), 1.35-1.52 (m, 8H), 1.85 (m, 1H), 2.25 (m, 1H), 2.41 (q,  $J$

= 7.1Hz, 2H), 2.60 (t,  $J=5.0\text{Hz}$ , 2H), 3.25 (t,  $J=5.0\text{Hz}$ , 2H), 3.45 (d,  $J=7.1\text{Hz}$ , 2H), 4.00 (s, 2H), 4.35 (d,  $J=7.2\text{Hz}$ , 2H), 7.25-7.53 (m, 10H).

**Example 1.294: Preparation of 2-(((1*s*,4*s*)-4-((5-(3-Hydroxypropylthio)-3,4-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid (Compound 187).**

**Step A: Preparation of 3,4-Diphenyl-5-(2-(tetrahydro-2*H*-pyran-2-yloxy)ethylthio)-1*H*-pyrazole.**

To a solution of 3-(4-bromo-3-phenyl-1*H*-pyrazol-5-yl)propan-1-ol (1.0 g, 3.56 mmol) in THF (10 mL), was added 3,4-dihydro-2*H*-pyran (0.898 g, 10.67 mmol) followed by PTSA (0.061 g, 0.356 mmol) at room temperature. After stirring for 12 h, the reaction was poured into water and extracted with ethyl acetate. The extract was dried over  $\text{MgSO}_4$  and concentrated under reduced pressure to give the title compound (1.12 g). LCMS  $m/z = 381.2$   $[\text{M}+\text{H}]^+$ .

**Step B: Preparation of (2-(((1*s*,4*s*)-4-((5-(2-Hydroxyethylthio)-3,4-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic Acid.**

To a solution of 3,4-diphenyl-5-(3-(tetrahydro-2*H*-pyran-2-yloxy)propylthio)-1*H*-pyrazole (120 mg, 0.304 mmol) in DMF (2 mL), was added sodium hydride (7.30 mg, 0.304 mmol) at 0 °C. After stirring for 10 min, *tert*-butyl 2-(((1*s*,4*s*)-4-(tosyloxymethyl)cyclohexyl)methoxy)acetate (125 mg, 0.304 mmol) was added and the reaction was warmed to 40 °C. After stirring for 12 h, the reaction was poured into water and extracted with ethyl acetate. The extract was concentrated under reduced pressure and treated with 4.0 M HCl dioxane (5 mL) for 8 h. The mixture was concentrated under reduced pressure and purified by HPLC to give the title compound (105 mg). LCMS  $m/z = 495.6$   $[\text{M}+\text{H}]^+$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  ppm 1.35-1.52 (m, 10H), 1.83 (m, 1H), 2.22 (m, 1H), 2.46 (t,  $J=5.0\text{Hz}$ , 2H), 3.22 (t,  $J=5.0\text{Hz}$ , 2H), 3.50 (d,  $J=7.1\text{Hz}$ , 2H), 3.91 (s, 2H), 4.30 (d,  $J=7.2\text{Hz}$ , 2H), 7.23-7.50 (m, 10H).

**Example 2: Homogeneous Time-Resolved Fluorescence (HTRF®) Assay For Direct cAMP Measurement**

Compounds were screened for agonists of the human prostacyclin (PGI<sub>2</sub>) receptor using the HTRF® assay for direct cAMP measurement (Gabriel *et al.*, ASSAY and Drug Development Technologies, 1:291-303, 2003) and recombinant CHO-K1 cells stably transfected with human prostacyclin receptor. CHO-K1 cells were obtained from ATCC® (Manassas, VA; Catalog # CCL-61). An agonist of the prostacyclin receptor was detected in HTRF® assay for direct cAMP measurement as a compound which increased cAMP concentration. HTRF® assay also was used to determine EC<sub>50</sub> values for prostacyclin receptor agonists.

**Principle of the assay:** The HTRF® assay kit was purchased from Cisbio-US, Inc. (Bedford, MA; Catalog # 62AM4PEC). The HTRF® assay supported by the kit is a competitive immunoassay between endogenous cAMP produced by the CHO-K1 cells and tracer cAMP

labeled with the dye d2. The tracer binding is visualized by a monoclonal anti-cAMP antibody labeled with Cryptate. The specific signal (*i.e.*, fluorescence resonance energy transfer, FRET) is inversely proportional to the concentration of unlabeled cAMP in the standard or sample.

**Standard curve:** The fluorescence ratio (665 nm/620 nm) of the standards (0.17 to 712 nM cAMP) included in the assay was calculated and used to generate a cAMP standard curve according to the kit manufacturer's instructions. The fluorescence ratio of the samples (test compound or compound buffer) was calculated and used to deduce respective cAMP concentrations by reference to the cAMP standard curve.

**Setup of the assay:** The HTRF® assay was carried out using a two-step protocol essentially according to the kit manufacturer's instructions, in 20 µL total volume per well in 384-well plate format (ProxiPlates; PerkinElmer, Fremont, CA; catalog # 6008280). To each of the experimental wells was transferred 3000 recombinant CHO-K1 cells in 5 µL assay buffer (phosphate buffered saline containing calcium chloride and magnesium chloride (Invitrogen, Carlsbad, CA; catalog # 14040) supplemented with IBMX (100 µM) and rolipram (10 µM) (phosphodiesterase inhibitors; Sigma-Aldrich, St. Louis, MO; catalog # I5879 and catalog # R6520, respectively) and 0.1% bovine serum albumin (BSA) fraction V (Sigma-Aldrich; catalog # A3059)), followed by test compound in 5 µL assay buffer or 5 µL assay buffer. The plate was then incubated at room temperature for 1 h. To each well was then added 5 µL cAMP-d2 conjugate in lysis buffer and 5 µL Cryptate conjugate in lysis buffer according to the kit manufacturer's instructions. The plate was then further incubated at room temperature for 1 h, after which the assay plate was read.

**Assay readout:** The HTRF® readout was accomplished using a PHERAstar (BMG LABTECH Inc., Durham, NC) or EnVision™ (PerkinElmer, Fremont CA) microplate reader.

Certain compounds of the present invention and their corresponding activity values are shown in TABLE B.

TABLE B

| Compound No. | human PGI2 receptor<br>EC <sub>50</sub> (nM) (HTRF®) |
|--------------|--|
| 90           | 7  |
| 111          | 16   |
| 184          | 11   |
| 198          | 2  |

Certain other compounds of the invention had activity values ranging from about 1.3 nM to about 5 µM in this assay.

### Example 3: Human Platelet Aggregation Inhibition Test



Blood collected from healthy human volunteers in aqueous trisodium citrate solution was centrifuged at 150 g for 15 min and the upper layer was recovered to obtain platelet-rich plasma (PRP). The residual blood was centrifuged at 3000 g for 10 min and the supernatant was collected as platelet-poor plasma (PPP). Platelet concentration in the PRP was determined using the Z series Beckman Coulter particle counter (Beckman, Fullerton, CA) and adjusted to 250,000 platelets/ $\mu$ L using PPP. 480  $\mu$ L of PRP was pre-incubated at 37 °C and stirred at 1200 rpm with 10  $\mu$ L aqueous test compound solution for 1 min prior to induction of aggregation by the addition of 10  $\mu$ L of aqueous adenosine diphosphate (ADP) solution to adjust the final ADP concentration in the PRP to  $1 \times 10^{-5}$  M. The maximal amplitude of aggregation response within 3 min was determined and measured in triplicate using the Chronolog model 490 aggregometer (Chrono-log Corp., Havertown, PA). Percent inhibition of aggregation was calculated from the maximum decrease in optical density of the control (addition of water in place of the test compound solution) sample and of the samples containing test compound. The test compound was added to adjust the final concentration to the range  $10^{-9}$  to  $10^{-4}$  M, and  $IC_{50}$  values were determined by inhibition percentage of aggregation at each concentration. The results are shown in Table C.

TABLE C

| Compound No. | human PRP $IC_{50}$ (nM) |
|--------------|--------------------------|
| 184          | 20                       |
| 111          | 28                       |
| 146          | 70                       |
| 135          | 220                      |

Certain other compounds of the invention had activity values ranging from about 10.3 nM to about 810 nM in this assay.

It is apparent that the compounds of the present invention markedly inhibit platelet aggregation in human PRP.

#### Example 4: Rat Model of Pulmonary Arterial Hypertension

**Animals:** Male Wistar rats (100-150 g at start of study) (Charles River Laboratories, Wilmington, MA) were housed two per cage and maintained in a humidity- (40-60%) and temperature- (68-72 °F) controlled facility on a 12 hr:12 hr light/dark cycle (lights on at 6:30 am) with free access to food (Harlan Teklad, Orange CA, Rodent Diet 8604) and water. Rats were allowed one week of habituation to the animal facility before testing.

**Rat monocrotaline model:** The rat monocrotaline (MCT) model is a standard and well-accepted model of pulmonary arterial hypertension. MCT induces acute pulmonary endothelial

damage associated with pulmonary vascular inflammation. Subsequently, pulmonary artery smooth muscle cells proliferate, occluding small pulmonary vessels and leading to severe pulmonary arterial hypertension including right ventricular hypertrophy. (See, *e.g.*, Schermuly *et al.*, *Circ. Res.*, 2004, 94:1101-1108.)

5           Rats were randomly given a single subcutaneous injection of either 60 mg/kg MCT (Sigma, St. Louis, MO) or 0.9% saline (sham) and assigned to receive oral administration of 20% hydroxypropyl beta-cyclodextrin (vehicle) or test compound (30 mg/kg; Figures 1 and 2). 10-11 rats were used per treatment group. 24 h following MCT administration, test compound or vehicle was administered by oral gavage twice a day for 21 consecutive days. Heart chamber  
10       weights were measured on Day 22. Rats were anesthetized with intraperitoneal pentobarbital (50 mg/kg), the chest cavity was opened and the heart was excised. The right ventricle was dissected free from the septum and left ventricle and both parts were weighed. The ratio of right ventricular (RV) weight to left ventricle plus septum (LV + S) weight (this ratio is indicated as “RV/(LV + S)” in Figures 1 and 2) was calculated as an index of the hypertrophic response to  
15       the induced pulmonary arterial hypertension and, as such, as an index of a test compound's therapeutic efficacy for pulmonary arterial hypertension.

          It is apparent from inspection of Figures 1 and 2 that oral administration of Compounds 14 and 31 inhibited the hypertrophic response to the induced pulmonary arterial hypertension and, as such, evidenced therapeutic efficacy for pulmonary arterial hypertension.

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          Those skilled in the art will recognize that various modifications, additions, substitutions and variations to the illustrative examples set forth herein can be made without departing from the spirit of the invention and are, therefore, considered within the scope of the invention. All documents referenced above, including, but not limited to, printed publications  
25       and provisional and regular patent applications, are incorporated herein by reference in their entirety.

Throughout this specification the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated element, integer or step, or group of elements, integers or steps, but not the exclusion of any other element, integer or step, or group of elements, integers or steps.

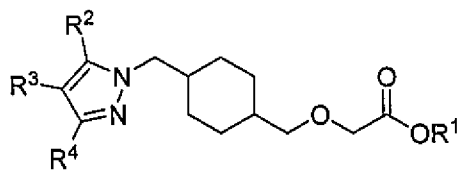
It is to be understood that any discussion of public documents, acts, materials, devices, articles or the like included herein is solely for the purpose of providing a context for the present invention. It is not to be taken as an admission that any or all of these matters were common general knowledge in the field relevant to the present invention as it existed before the priority date of any claim of this application.

#### **REFERENCE TO RELATED APPLICATIONS**

This application is the Australian national phase application of International application No. PCT/US2009/006251 filed November 24, 2009 which claims priority to United States application No. 61/200,393 filed November 26, 2008 the full contents of each of which is incorporated by reference herein.

**THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:**

1. A compound selected from compounds of Formula **Ia**:



**Ia**

or a pharmaceutically acceptable salt, solvate and hydrate thereof, wherein:

$R^1$  is selected from: H and  $C_1$ - $C_6$  alkyl;

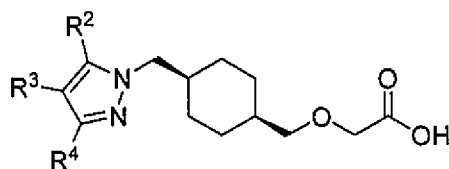
and

$R^2$ ,  $R^3$ , and  $R^4$  are each independently selected from: H,  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkylsulfinyl,  $C_1$ - $C_6$  alkylsulfonyl,  $C_1$ - $C_6$  alkylthio, aryl,  $C_3$ - $C_7$  cycloalkyl and heteroaryl; wherein said  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkylsulfinyl,  $C_1$ - $C_6$  alkylsulfonyl,  $C_1$ - $C_6$  alkylthio, aryl,  $C_3$ - $C_7$  cycloalkyl and heteroaryl are each optionally substituted with one or more groups selected from:  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkylsulfinyl,  $C_1$ - $C_6$  alkylsulfonyl,  $C_1$ - $C_6$  alkylthio, amino, aryl, carboxamide, cyano,  $C_1$ - $C_6$  haloalkyl, halogen and hydroxy;

or

$R^2$  and  $R^3$  together with the pyrazole ring to which they are both attached to form a tricyclic heteroaryl; and  $R^4$  is selected from: H,  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkylsulfinyl,  $C_1$ - $C_6$  alkylsulfonyl,  $C_1$ - $C_6$  alkylthio, aryl,  $C_3$ - $C_7$  cycloalkyl and heteroaryl; wherein said  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkylsulfinyl,  $C_1$ - $C_6$  alkylsulfonyl,  $C_1$ - $C_6$  alkylthio, aryl,  $C_3$ - $C_7$  cycloalkyl and heteroaryl are each optionally substituted with one or more groups selected from:  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkylsulfinyl,  $C_1$ - $C_6$  alkylsulfonyl,  $C_1$ - $C_6$  alkylthio, amino, aryl, cyano,  $C_1$ - $C_6$  haloalkyl, halogen and hydroxy.

2. The compound or pharmaceutically acceptable salt, solvate or hydrate thereof according to claim 1, wherein  $R^1$  is H.
3. The compound or pharmaceutically acceptable salt, solvate or hydrate thereof according to claim 1, wherein  $R^1$  is  $C_1$ - $C_6$  alkyl.
4. The compound or pharmaceutically acceptable salt, solvate or hydrate thereof according to claim 3, wherein  $R^1$  is methyl.
5. The compound according to claim 1, selected from compounds of Formula **Ig**:

**Ig**

or pharmaceutically acceptable salts, solvates or hydrates thereof, wherein:

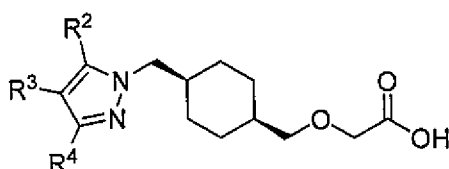
$R^2$  is selected from: H,  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkylsulfinyl,  $C_1$ - $C_6$  alkylsulfonyl,  $C_1$ - $C_6$  alkylthio, aryl and  $C_3$ - $C_7$  cycloalkyl; wherein said  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkylsulfinyl,  $C_1$ - $C_6$  alkylsulfonyl,  $C_1$ - $C_6$  alkylthio, aryl and  $C_3$ - $C_7$  cycloalkyl are each optionally substituted with one or more groups selected from:  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkylsulfinyl,  $C_1$ - $C_6$  alkylsulfonyl,  $C_1$ - $C_6$  alkylthio, amino, carboxamide, cyano, halogen and hydroxy;

$R^3$  is selected from:  $C_1$ - $C_6$  alkyl, aryl and heteroaryl; wherein said  $C_1$ - $C_6$  alkyl, aryl and heteroaryl are each optionally substituted with one or more groups selected from:  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_6$  alkyl, aryl, cyano,  $C_1$ - $C_6$  haloalkyl, halogen and hydroxy;

and

$R^4$  is selected from: H,  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkylthio, aryl and  $C_3$ - $C_7$  cycloalkyl; wherein said  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkylthio, aryl and  $C_3$ - $C_7$  cycloalkyl are each optionally substituted with one or more groups selected from:  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_6$  alkyl, carboxamide, cyano, halogen and hydroxy.

6. The compound according to claim 1, selected from compounds of Formula **Ig**:

**Ig**

or pharmaceutically acceptable salts, solvates or hydrates thereof, wherein:

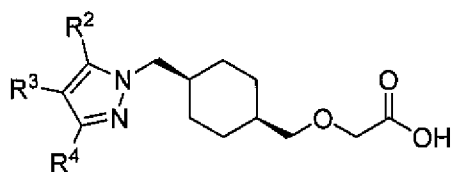
$R^2$  is selected from: H, 2-(methylsulfinyl)ethyl, 2-(methylsulfonyl)ethyl, 2-(methylthio)ethyl, 2,3-difluorophenyl, 2-aminoethylthio, 2-amino-2-oxoethoxy, 2-cyanoethyl, 2-ethoxyethylthio, 2-fluoro-4-methoxyphenyl, 2-fluorophenyl, 2-hydroxyethyl, 2-hydroxyethylsulfinyl, 2-hydroxyethylthio, 2-methoxyethyl, 2-methoxyethylthio, 3,4-difluorophenyl, 3,4-dihydroxybutyl, 3-chloro-2-fluorophenyl, 3-fluoro-5-methoxyphenyl, 3-fluorophenyl, 3-hydroxypropyl, 3-hydroxypropylthio, 3-methoxyphenyl, 4-chloro-3-fluorophenyl, 4-chlorophenyl, 4-fluorophenyl, 4-methoxyphenyl, cyanomethoxy, cyanomethylthio, cyclopropyl, ethoxy, ethyl, ethylthio, isopropyl, methyl, methylsulfinyl, methylsulfonyl, methylthio, *m*-tolyl, *n*-propyl, phenyl, *p*-tolyl and trifluoromethyl;

$R^3$  is selected from: 2,3-difluorophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, 2-chlorophenyl, 2-fluoro-3-hydroxyphenyl, 2-fluoro-3-methoxyphenyl, 2-fluoro-3-methylphenyl, 2-fluoro-4-methylphenyl, 2-fluorophenyl, 2-methoxyphenyl, 2-methoxypyridin-4-yl, 3-(trifluoromethyl)phenyl, 3,4-difluorophenyl, 3-chloro-2-fluorophenyl, 3-chloro-4-fluorophenyl, 3-chlorophenyl, 3-fluoro-5-methoxyphenyl, 3-fluoro-5-methylphenyl, 3-fluorophenyl, 3-hydroxyphenyl, 3-isopropoxyphenyl, 3-methoxyphenyl, 4-chlorophenyl, 4-fluorophenyl, 4-methoxyphenyl, 5-cyano-2-fluorophenyl, 5-fluoropyridin-3-yl, 5-methoxypyridin-3-yl, 5-methylthiophen-2-yl, 6-methoxypyridin-3-yl, benzhydryl, furan-2-yl, *m*-tolyl, phenyl, *p*-tolyl, thiophen-2-yl and thiophen-3-yl;

and

$R^4$  is selected from: H, 2,3-difluorophenyl, 2,4-difluorophenyl, 2-amino-2-oxoethoxy, 2-cyanoethyl, 2-ethoxyethylthio, 2-fluoro-4-methoxyphenyl, 2-fluoro-4-methylphenyl, 2-fluorophenyl, 2-hydroxyethyl, 2-hydroxyethylthio, 2-methoxyethyl, 2-methoxyethylthio, 3,4-difluorophenyl, 3,4-dihydroxybutyl, 3-chloro-2-fluorophenyl, 3-chlorophenyl, 3-fluoro-5-methoxyphenyl, 3-fluorophenyl, 3-hydroxypropyl, 3-methoxyphenyl, 4-chloro-2-fluorophenyl, 4-chloro-3-fluorophenyl, 4-chlorophenyl, 4-fluorophenyl, 4-hydroxyphenyl, 4-methoxyphenyl, cyanomethylthio, cyclopropyl, ethyl, isopropyl, methyl, methylthio, *m*-tolyl, *n*-propyl, phenyl, *p*-tolyl and trifluoromethyl.

7. The compound according to claim 1, selected from compounds of Formula **Ig**:



**Ig**

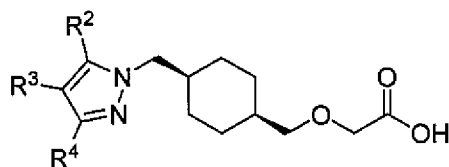
or pharmaceutically acceptable salts, solvates or hydrates thereof, wherein:

$R^2$  and  $R^3$  together with the pyrazole ring to which they are both attached to form a tricyclic heteroaryl;

and

$R^4$  is selected from: H,  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkylthio, aryl and  $C_3$ - $C_7$  cycloalkyl; wherein said  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkylthio, aryl and  $C_3$ - $C_7$  cycloalkyl are each optionally substituted with one or more groups selected from:  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_6$  alkyl, carboxamide, cyano, halogen and hydroxy.

8. The compound according to claim 1, selected from compounds of Formula **Ig**:



I g

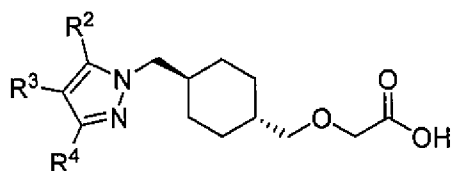
or pharmaceutically acceptable salts, solvates or hydrates thereof, wherein:

$R^2$  and  $R^3$  together with the pyrazole ring to which they are both attached to form 4,5-dihydro-3*H*-benzo[e]indazol-3-yl or indeno[2,1-*c*]pyrazol-1(8*H*)-yl;

and

$R^4$  is selected from: H, 2,3-difluorophenyl, 2,4-difluorophenyl, 2-amino-2-oxoethoxy, 2-cyanoethyl, 2-ethoxyethylthio, 2-fluoro-4-methoxyphenyl, 2-fluoro-4-methylphenyl, 2-fluorophenyl, 2-hydroxyethyl, 2-hydroxyethylthio, 2-methoxyethyl, 2-methoxyethylthio, 3,4-difluorophenyl, 3,4-dihydroxybutyl, 3-chloro-2-fluorophenyl, 3-chlorophenyl, 3-fluoro-5-methoxyphenyl, 3-fluorophenyl, 3-hydroxypropyl, 3-methoxyphenyl, 4-chloro-2-fluorophenyl, 4-chloro-3-fluorophenyl, 4-chlorophenyl, 4-fluorophenyl, 4-hydroxyphenyl, 4-methoxyphenyl, cyanomethylthio, cyclopropyl, ethyl, isopropyl, methyl, methylthio, *m*-tolyl, *n*-propyl, phenyl, *p*-tolyl and trifluoromethyl.

9. The compound according to claim 1, selected from compounds of Formula II:



II

or pharmaceutically acceptable salts, solvates or hydrates thereof, wherein:

$R^2$  is selected from: H,  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkylsulfinyl,  $C_1$ - $C_6$  alkylsulfonyl,  $C_1$ - $C_6$  alkylthio, aryl and  $C_3$ - $C_7$  cycloalkyl; wherein said  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkylsulfinyl,  $C_1$ - $C_6$  alkylsulfonyl,  $C_1$ - $C_6$  alkylthio, aryl and  $C_3$ - $C_7$  cycloalkyl are each optionally substituted with one or more groups selected from:  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkylsulfinyl,  $C_1$ - $C_6$  alkylsulfonyl,  $C_1$ - $C_6$  alkylthio, amino, carboxamide, cyano, halogen and hydroxy;

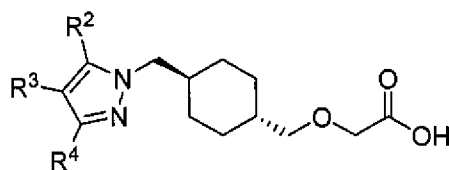
$R^3$  is selected from:  $C_1$ - $C_6$  alkyl, aryl and heteroaryl; wherein said  $C_1$ - $C_6$  alkyl, aryl and heteroaryl are each optionally substituted with one or more groups selected from:  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_6$  alkyl, aryl, cyano,  $C_1$ - $C_6$  haloalkyl, halogen and hydroxy;

and

$R^4$  is selected from: H,  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkylthio, aryl and  $C_3$ - $C_7$  cycloalkyl; wherein said  $C_1$ - $C_6$  alkoxy,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkylthio, aryl and  $C_3$ - $C_7$  cycloalkyl are

each optionally substituted with one or more groups selected from: C<sub>1</sub>-C<sub>6</sub> alkoxy, C<sub>1</sub>-C<sub>6</sub> alkyl, carboxamide, cyano, halogen and hydroxy.

10. The compound according to claim 1, selected from compounds of Formula II:



II

or pharmaceutically acceptable salts, solvates or hydrates thereof, wherein:

R<sup>2</sup> is selected from: H, 2-(methylsulfinyl)ethyl, 2-(methylsulfonyl)ethyl, 2-(methylthio)ethyl, 2,3-difluorophenyl, 2-aminoethylthio, 2-amino-2-oxoethoxy, 2-cyanoethyl, 2-ethoxyethylthio, 2-fluoro-4-methoxyphenyl, 2-fluorophenyl, 2-hydroxyethyl, 2-hydroxyethylsulfinyl, 2-hydroxyethylthio, 2-methoxyethyl, 2-methoxyethylthio, 3,4-difluorophenyl, 3,4-dihydroxybutyl, 3-chloro-2-fluorophenyl, 3-fluoro-5-methoxyphenyl, 3-fluorophenyl, 3-hydroxypropyl, 3-hydroxypropylthio, 3-methoxyphenyl, 4-chloro-3-fluorophenyl, 4-chlorophenyl, 4-fluorophenyl, 4-methoxyphenyl, cyanomethoxy, cyanomethylthio, cyclopropyl, ethoxy, ethyl, ethylthio, isopropyl, methyl, methylsulfinyl, methylsulfonyl, methylthio, *m*-tolyl, *n*-propyl, phenyl, *p*-tolyl and trifluoromethyl;

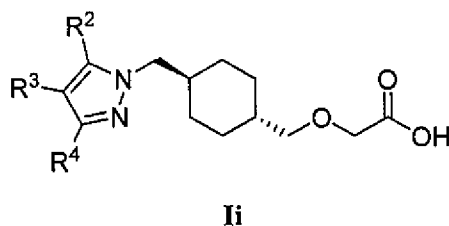
R<sup>3</sup> is selected from: 2,3-difluorophenyl, 2,4-difluorophenyl, 2,5-difluorophenyl, 2-chlorophenyl, 2-fluoro-3-hydroxyphenyl, 2-fluoro-3-methoxyphenyl, 2-fluoro-3-methylphenyl, 2-fluoro-4-methylphenyl, 2-fluorophenyl, 2-methoxyphenyl, 2-methoxypyridin-4-yl, 3-(trifluoromethyl)phenyl, 3,4-difluorophenyl, 3-chloro-2-fluorophenyl, 3-chloro-4-fluorophenyl, 3-chlorophenyl, 3-fluoro-5-methoxyphenyl, 3-fluoro-5-methylphenyl, 3-fluorophenyl, 3-hydroxyphenyl, 3-isopropoxyphenyl, 3-methoxyphenyl, 4-chlorophenyl, 4-fluorophenyl, 4-methoxyphenyl, 5-cyano-2-fluorophenyl, 5-fluoropyridin-3-yl, 5-methoxypyridin-3-yl, 5-methylthiophen-2-yl, 6-methoxypyridin-3-yl, benzhydryl, furan-2-yl, *m*-tolyl, phenyl, *p*-tolyl, thiophen-2-yl and thiophen-3-yl;

and

R<sup>4</sup> is selected from: H, 2,3-difluorophenyl, 2,4-difluorophenyl, 2-amino-2-oxoethoxy, 2-cyanoethyl, 2-ethoxyethylthio, 2-fluoro-4-methoxyphenyl, 2-fluoro-4-methylphenyl, 2-fluorophenyl, 2-hydroxyethyl, 2-hydroxyethylthio, 2-methoxyethyl, 2-methoxyethylthio, 3,4-difluorophenyl, 3,4-dihydroxybutyl, 3-chloro-2-fluorophenyl, 3-chlorophenyl, 3-fluoro-5-methoxyphenyl, 3-fluorophenyl, 3-hydroxypropyl, 3-methoxyphenyl, 4-chloro-2-fluorophenyl, 4-chloro-3-fluorophenyl, 4-chlorophenyl, 4-fluorophenyl, 4-hydroxyphenyl, 4-methoxyphenyl, cyanomethylthio, cyclopropyl, ethyl, isopropyl, methyl, methylthio, *m*-tolyl, *n*-propyl, phenyl, *p*-tolyl and trifluoromethyl.



11. The compound according to claim 1, selected from compounds of Formula **II**:



or pharmaceutically acceptable salts, solvates or hydrates thereof, wherein:

$R^2$  and  $R^3$  together with the pyrazole ring to which they are both attached to form 4,5-dihydro-3*H*-benzo[e]indazol-3-yl or indeno[2,1-*c*]pyrazol-1(8*H*)-yl;

and

$R^4$  is selected from: H, 2,3-difluorophenyl, 2,4-difluorophenyl, 2-amino-2-oxoethoxy, 2-cyanoethyl, 2-ethoxyethylthio, 2-fluoro-4-methoxyphenyl, 2-fluoro-4-methylphenyl, 2-fluorophenyl, 2-hydroxyethyl, 2-hydroxyethylthio, 2-methoxyethyl, 2-methoxyethylthio, 3,4-difluorophenyl, 3,4-dihydroxybutyl, 3-chloro-2-fluorophenyl, 3-chlorophenyl, 3-fluoro-5-methoxyphenyl, 3-fluorophenyl, 3-hydroxypropyl, 3-methoxyphenyl, 4-chloro-2-fluorophenyl, 4-chloro-3-fluorophenyl, 4-chlorophenyl, 4-fluorophenyl, 4-hydroxyphenyl, 4-methoxyphenyl, cyanomethylthio, cyclopropyl, ethyl, isopropyl, methyl, methylthio, *m*-tolyl, *n*-propyl, phenyl, *p*-tolyl and trifluoromethyl.

12. A compound or pharmaceutically acceptable salt, solvate or hydrate thereof according to claim 1 selected from the group consisting of:

2-(((1*r*,4*r*)-4-((5-(4-fluorophenyl)-3-(methylthio)-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*r*,4*r*)-4-((3-(4-fluorophenyl)-5-(methylthio)-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((3,4-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*r*,4*r*)-4-((1-phenyl-4,5-dihydro-3*H*-benzo[e]indazol-3-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*r*,4*r*)-4-((3-phenylindeno[2,1-*c*]pyrazol-1(8*H*)-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*r*,4*r*)-4-((4-(3-methoxyphenyl)-3-methyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*r*,4*r*)-4-((4-(3-methoxyphenyl)-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*r*,4*r*)-4-((3,4-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*r*,4*r*)-4-((4,5-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((3-(4-fluorophenyl)-5-(methylthio)-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*r*,4*r*)-4-((5-methyl-3,4-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((5-(4-fluorophenyl)-3-(methylthio)-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((4-(3-methoxyphenyl)-3-methyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((4-(3-methoxyphenyl)-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((3-methyl-4,5-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((5-methyl-3,4-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((4-benzhydryl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*r*,4*r*)-4-((4-benzhydryl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((3-methyl-5-phenyl-4-*m*-tolyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((4-(2,5-difluorophenyl)-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((4-(4-chlorophenyl)-3-methyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((4-(4-fluorophenyl)-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((4-(3-chlorophenyl)-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((5-methyl-3-phenyl-4-*m*-tolyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((4-(4-fluorophenyl)-3-methyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((4-(2,3-difluorophenyl)-3-methyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((4-(2,3-difluorophenyl)-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((4-(4-chlorophenyl)-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((4-(2,5-difluorophenyl)-3-methyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((4-(3-methoxyphenyl)-3-(methylthio)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((4-(3-methoxyphenyl)-5-(methylthio)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((5-(3-methoxyphenyl)-3-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((3-(3-methoxyphenyl)-5-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((5-(3-fluoro-5-methoxyphenyl)-3-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((3-(3-fluoro-5-methoxyphenyl)-5-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((5-(4-methoxyphenyl)-3-(methylthio)-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((3-(4-methoxyphenyl)-5-(methylthio)-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((4-(4-methoxyphenyl)-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((4-(3-fluoro-5-methoxyphenyl)-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((4-(3-fluorophenyl)-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((4-(3-chlorophenyl)-3-methyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((4-(4-methoxyphenyl)-3-methyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((4-(3-fluoro-5-methoxyphenyl)-3-methyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((4-(2-chlorophenyl)-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((4-(2-chlorophenyl)-3-methyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((4-(3-fluorophenyl)-3-methyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((5-methyl-3-phenyl-4-*p*-tolyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((4-(2,4-difluorophenyl)-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((4-(4-chlorophenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((4-(3-fluorophenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((4-(4-fluorophenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((4-(3-chloro-2-fluorophenyl)-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((4-(2,4-difluorophenyl)-3-methyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((4-(3-chloro-2-fluorophenyl)-3-methyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((3-methyl-5-phenyl-4-*p*-tolyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((4-(3-chloro-4-fluorophenyl)-3-methyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((4-(3-chloro-4-fluorophenyl)-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((4-(4-methoxyphenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((4-(2-methoxyphenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((3-phenyl-4-*m*-tolyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((3-phenyl-4-*p*-tolyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((4-(3-chlorophenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((4-(2-fluorophenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((3-methyl-4-phenyl-5-*m*-tolyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((5-methyl-4-phenyl-3-*m*-tolyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((3-(3-chlorophenyl)-5-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((5-(3-fluorophenyl)-3-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((3-(3-fluorophenyl)-5-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((5-(3-chloro-2-fluorophenyl)-3-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((3-(3-chloro-2-fluorophenyl)-5-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((5-(2-fluorophenyl)-3-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((3-(2-fluorophenyl)-5-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((5-(2,3-difluorophenyl)-3-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((3-(2,3-difluorophenyl)-5-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((3-(methylthio)-4,5-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((5-(methylthio)-3,4-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((4-(2,5-difluorophenyl)-3-(methylthio)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((4-(2,5-difluorophenyl)-5-(methylthio)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((4-(5-cyano-2-fluorophenyl)-5-(methylthio)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((4-(3,4-difluorophenyl)-5-ethoxy-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((5-ethoxy-3,4-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((4-(2,3-difluorophenyl)-3-(methylthio)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((4-(2,3-difluorophenyl)-5-(methylthio)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((4-(3-isopropoxyphenyl)-3-(methylthio)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((4-(3-isopropoxyphenyl)-5-(methylthio)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((4-(2,3-difluorophenyl)-5-(methylsulfonyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((4-(2,5-difluorophenyl)-5-(methylsulfonyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((5-(ethylthio)-3,4-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((5-(ethylthio)-4-(3-methoxyphenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((5-(ethylthio)-4-(2-fluoro-3-methoxyphenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((4-(3-fluorophenyl)-5-(methylthio)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((4-(2-fluoro-3-methoxyphenyl)-5-(methylthio)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((4-(3-fluoro-5-methoxyphenyl)-5-(methylthio)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((4-(4-fluorophenyl)-5-(methylthio)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((4-(3-chlorophenyl)-5-(methylthio)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((5-(methylthio)-3-phenyl-4-(3-(trifluoromethyl)phenyl)-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((4-(4-chlorophenyl)-5-(methylthio)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((3-ethyl-4-(3-methoxyphenyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((5-ethyl-4-(3-methoxyphenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((3-ethyl-4,5-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((5-ethyl-3,4-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((3-ethyl-4-(3-fluorophenyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((5-ethyl-4-(3-fluorophenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((3-ethyl-4-(2-fluoro-3-methoxyphenyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((5-ethyl-4-(2-fluoro-3-methoxyphenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((4-(2,3-difluorophenyl)-3-ethyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

- 2-(((1*s*,4*s*)-4-((4-(2,3-difluorophenyl)-5-ethyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((5-(methylthio)-3-phenyl-4-(thiophen-2-yl)-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((4-(furan-2-yl)-5-(methylthio)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((5-(methylthio)-3-phenyl-4-(thiophen-3-yl)-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((5-(methylthio)-4-(5-methylthiophen-2-yl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((3-isopropyl-4,5-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((4-(3-fluorophenyl)-5-isopropyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((4-(3-methoxyphenyl)-5-(methylsulfinyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((4-(3-chlorophenyl)-3-ethyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((4-(3-chlorophenyl)-5-ethyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((4-(2,3-difluorophenyl)-5-isopropyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((5-(ethylthio)-4-(2-fluorophenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((5-(ethylthio)-4-(3-fluoro-5-methoxyphenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((5-(cyclopropyl-4-(3-methoxyphenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((3-cyclopropyl-4,5-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((5-(cyclopropyl-3,4-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((3-isopropyl-4-(3-methoxyphenyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((4-(3-chlorophenyl)-3-isopropyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((4-(2-fluoro-3-methoxyphenyl)-3-isopropyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((5-cyclopropyl-4-(2-fluoro-3-methoxyphenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((5-cyclopropyl-4-(2,3-difluorophenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((5-isopropyl-4-(3-methoxyphenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((4-(3-chlorophenyl)-5-isopropyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((4-(2-fluoro-3-methoxyphenyl)-5-isopropyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

methyl 2-(((1*s*,4*s*)-4-((5-(methylthio)-3,4-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate;

2-(((1*s*,4*s*)-4-((4-(3-chlorophenyl)-3-cyclopropyl-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((4-(3-chlorophenyl)-5-cyclopropyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((4-(3-fluoro-5-methylphenyl)-5-(methylthio)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((4-(5-fluoropyridin-3-yl)-5-(methylthio)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

methyl 2-(((1*s*,4*s*)-4-((4-(3-methoxyphenyl)-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetate;

2-(((1*s*,4*s*)-4-((3-(4-fluorophenyl)-5-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((3-(4-chlorophenyl)-5-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((5-methyl-4-phenyl-3-*p*-tolyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((3-(4-methoxyphenyl)-5-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((3-(2,4-difluorophenyl)-5-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((4-(2,3-difluorophenyl)-5-(ethylthio)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((3-(2-fluoro-4-methylphenyl)-5-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((3-(4-chloro-2-fluorophenyl)-5-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;



- 2-(((1*s*,4*s*)-4-((3-(2-fluoro-4-methoxyphenyl)-5-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((5-(2-hydroxyethylthio)-3,4-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((4-(5-fluoropyridin-3-yl)-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((5-(ethylthio)-4-(5-fluoropyridin-3-yl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((5-ethyl-4-(5-fluoropyridin-3-yl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((1-phenyl-4,5-dihydro-3*H*-benzo[e]indazol-3-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((3,4-diphenyl-5-(trifluoromethyl)-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((3-phenyl-4-*p*-tolyl-5-(trifluoromethyl)-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((4-(3-hydroxyphenyl)-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((4-(3-methoxyphenyl)-5-phenyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((4-(3-methoxyphenyl)-3-phenyl-5-(trifluoromethyl)-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*R*,4*s*)-4-((3-((*S*)-3,4-dihydroxybutyl)-4,5-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*R*,4*s*)-4-((5-((*S*)-3,4-dihydroxybutyl)-3,4-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*R*,4*s*)-4-((5-((*S*)-3,4-dihydroxybutyl)-4-(3-fluorophenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*R*,4*s*)-4-((4-(3,4-difluorophenyl)-3-((*S*)-3,4-dihydroxybutyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*R*,4*s*)-4-((4-(3,4-difluorophenyl)-5-((*S*)-3,4-dihydroxybutyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*R*,4*s*)-4-((5-((*S*)-3,4-dihydroxybutyl)-4-(3-hydroxyphenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*R*,4*s*)-4-((4-(3-chlorophenyl)-5-((*S*)-3,4-dihydroxybutyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((3-(4-chlorophenyl)-5-ethyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

- 2-(((1*s*,4*s*)-4-((5-ethyl-3-(4-fluorophenyl)-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((5-ethyl-3-(2-fluoro-4-methoxyphenyl)-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((5-ethyl-3-(4-methoxyphenyl)-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((5-ethyl-3-(2-fluoro-4-methylphenyl)-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((5-ethyl-4-phenyl-3-*p*-tolyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*S*,4*s*)-4-((5-((*R*)-3,4-dihydroxybutyl)-4-(3-fluorophenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*S*,4*s*)-4-((4-(3,4-difluorophenyl)-5-((*R*)-3,4-dihydroxybutyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*S*,4*s*)-4-((4-(3-chlorophenyl)-5-((*R*)-3,4-dihydroxybutyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((5-ethyl-4-(3-hydroxyphenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((4-(3-hydroxyphenyl)-5-(methylthio)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((5-(ethylthio)-4-(2-fluoro-3-hydroxyphenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((5-ethyl-3-(4-hydroxyphenyl)-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((3-(4-chloro-3-fluorophenyl)-5-ethyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((5-(ethylthio)-4-(3-hydroxyphenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((5-(2-methoxyethyl)-3,4-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((5-(2-methoxyethyl)-4-(3-methoxyphenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((4-(3-hydroxyphenyl)-5-(2-methoxyethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((5-(2-methoxyethyl)-4-(6-methoxypyridin-3-yl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((4-(2-fluoro-3-hydroxyphenyl)-5-(2-methoxyethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

- 2-(((1*s*,4*s*)-4-((3-(cyanomethylthio)-4,5-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((5-(cyanomethylthio)-3,4-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((3-(2-ethoxyethylthio)-4,5-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((5-(2-ethoxyethylthio)-3,4-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((5-(3-hydroxypropylthio)-3,4-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((3-(2-methoxyethylthio)-4,5-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((5-(2-methoxyethylthio)-3,4-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((4-(2,3-difluorophenyl)-5-(2-methoxyethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((4-(3-chloro-2-fluorophenyl)-5-(2-methoxyethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((4-(2-fluoro-3-methylphenyl)-5-(2-methoxyethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((5-(2-methoxyethyl)-3-phenyl-4-*m*-tolyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((4-(3-fluorophenyl)-5-(2-methoxyethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((4-(2-methoxypyridin-4-yl)-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((5-ethyl-4-(2-methoxypyridin-4-yl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((4-(3-chlorophenyl)-5-(2-methoxyethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((5-(2-hydroxyethylthio)-4-(3-methoxyphenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((4-(3-chlorophenyl)-5-(2-hydroxyethylthio)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((5-(2-hydroxyethylthio)-4-phenyl-3-*p*-tolyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((5-ethyl-4-(5-methoxypyridin-3-yl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

- 2-(((1*s*,4*s*)-4-((4-(3-methoxyphenyl)-3-phenyl-5-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((4-(3-fluorophenyl)-3-phenyl-5-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((4-(3-chlorophenyl)-3-phenyl-5-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((3-phenyl-5-propyl-4-*m*-tolyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((4-(2-fluoro-3-methoxyphenyl)-3-phenyl-5-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((4-(2,3-difluorophenyl)-3-phenyl-5-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((4-(3-chloro-2-fluorophenyl)-3-phenyl-5-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((4-(2-fluoro-3-methylphenyl)-3-phenyl-5-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((5-(2-hydroxyethylthio)-3-phenyl-4-*m*-tolyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((4-(2-fluoro-3-hydroxyphenyl)-3-phenyl-5-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((4-(3-fluorophenyl)-5-(2-hydroxyethylthio)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((4-(2-fluoro-3-hydroxyphenyl)-5-(2-(methylthio)ethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((4-(5-methoxypyridin-3-yl)-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((4-(3-chloro-2-fluorophenyl)-5-(2-(methylthio)ethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((5-(2-(methylthio)ethyl)-3-phenyl-4-*m*-tolyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((4-(3-chlorophenyl)-5-(2-hydroxyethylsulfinyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((4-(2-fluoro-3-methylphenyl)-5-(2-(methylthio)ethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((4-(3-chloro-2-fluorophenyl)-5-(2-(methylsulfinyl)ethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((5-(2-(methylsulfinyl)ethyl)-3-phenyl-4-*m*-tolyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((4-(3-hydroxyphenyl)-5-(2-(methylthio)ethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((4-(3-fluorophenyl)-5-(2-(methylthio)ethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((5-(4-fluorophenyl)-4-phenyl-3-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((3-(4-fluorophenyl)-4-phenyl-5-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((5-(4-chloro-3-fluorophenyl)-4-phenyl-3-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((3-(4-chloro-3-fluorophenyl)-4-phenyl-5-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((5-(4-chlorophenyl)-4-phenyl-3-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((3-(4-chlorophenyl)-4-phenyl-5-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((5-(3,4-difluorophenyl)-4-phenyl-3-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((3-(3,4-difluorophenyl)-4-phenyl-5-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((5-(2-fluoro-4-methoxyphenyl)-4-phenyl-3-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((3-(2-fluoro-4-methoxyphenyl)-4-phenyl-5-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((5-(4-methoxyphenyl)-4-phenyl-3-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((3-(4-methoxyphenyl)-4-phenyl-5-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((5-(2-fluoro-4-methylphenyl)-4-phenyl-3-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((3-(2-fluoro-4-methylphenyl)-4-phenyl-5-propyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((4-(3-chlorophenyl)-5-(2-(methylthio)ethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((5-(2-(methylthio)ethyl)-3,4-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((5-(2-fluoro-4-methylphenyl)-3-(2-methoxyethyl)-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

- 2-(((1*s*,4*s*)-4-((3-(2-fluoro-4-methylphenyl)-5-(2-methoxyethyl)-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((4-(2-fluoro-4-methylphenyl)-5-(2-methoxyethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((4-(2-fluoro-4-methylphenyl)-5-(2-(methylthio)ethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((4-(3-methoxyphenyl)-5-(2-(methylthio)ethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((4-(2,3-difluorophenyl)-5-(2-(methylthio)ethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*r*,4*r*)-4-((3-(cyanomethylthio)-4-(3-methoxyphenyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((5-(cyanomethylthio)-4-(3-methoxyphenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((3-(2-methoxyethyl)-5-(3-methoxyphenyl)-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((5-(2-methoxyethyl)-3-(3-methoxyphenyl)-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((4-(3-chloro-2-fluorophenyl)-5-(2-(methylsulfonyl)ethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((5-(2-aminoethylthio)-4-phenyl-3-*p*-tolyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((5-(2-hydroxyethyl)-3,4-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((5-(2-hydroxyethyl)-4-(3-methoxyphenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((4-(2,3-difluorophenyl)-5-(2-hydroxyethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((4-(3-fluorophenyl)-5-(2-hydroxyethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((3-(4-fluorophenyl)-5-(2-hydroxyethylthio)-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((5-(4-fluorophenyl)-3-(2-hydroxyethylthio)-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((5-(cyanomethylthio)-4-phenyl-3-*p*-tolyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((5-(cyanomethylthio)-3-(4-fluorophenyl)-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

- 2-(((1*s*,4*s*)-4-((3-(2-cyanoethyl)-4,5-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((5-(2-cyanoethyl)-3,4-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((3-(2-cyanoethyl)-4-(3-methoxyphenyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((5-(2-cyanoethyl)-4-(3-methoxyphenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((5-(2-cyanoethyl)-4-(3-hydroxyphenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((4-(3-chlorophenyl)-3-(2-cyanoethyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((4-(3-chlorophenyl)-5-(2-cyanoethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((3-(2-cyanoethyl)-4-(3-fluorophenyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((5-(2-cyanoethyl)-4-(3-fluorophenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((3-(2-cyanoethyl)-4-(3-hydroxyphenyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((4-(3-chloro-2-fluorophenyl)-3-(2-cyanoethyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((4-(3-chloro-2-fluorophenyl)-5-(2-cyanoethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((5-(3-hydroxypropyl)-3,4-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((5-(3-hydroxypropyl)-4-(3-methoxyphenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((4-(2,3-difluorophenyl)-5-(3-hydroxypropyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((4-(3-fluorophenyl)-5-(3-hydroxypropyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((4-(3-chlorophenyl)-5-(cyanomethylthio)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*s*,4*s*)-4-((4-(3-chloro-2-fluorophenyl)-5-(2-hydroxyethyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;
- 2-(((1*r*,4*r*)-4-((3-(2-amino-2-oxoethoxy)-4-(3-methoxyphenyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;

2-(((1*s*,4*s*)-4-((5-(2-amino-2-oxoethoxy)-4-(3-methoxyphenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;  
 2-(((1*r*,4*r*)-4-((3-(2-amino-2-oxoethoxy)-4-(2-fluoro-3-methoxyphenyl)-5-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;  
 2-(((1*s*,4*s*)-4-((5-(2-amino-2-oxoethoxy)-4-(2-fluoro-3-methoxyphenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;  
 2-(((1*s*,4*s*)-4-((4-(3-chloro-2-fluorophenyl)-5-(3-hydroxypropyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;  
 2-(((1*s*,4*s*)-4-((4-(3-chlorophenyl)-5-(3-hydroxypropyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid; and  
 2-(((1*s*,4*s*)-4-((5-(cyanomethoxy)-4-(3-methoxyphenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid.

13. A compound according to claim 1 selected from the following compounds and pharmaceutically acceptable salts, solvates and hydrates thereof:

2-(((1*s*,4*s*)-4-((3-(3,4-difluorophenyl)-5-ethyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;  
 2-(((1*s*,4*s*)-4-((5-(2-fluoro-4-methylphenyl)-3-(2-hydroxyethyl)-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;  
 2-(((1*s*,4*s*)-4-((5-(2-fluoro-4-methylphenyl)-3-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;  
 2-(((1*s*,4*s*)-4-((3-(2-fluoro-4-methylphenyl)-5-(2-hydroxyethyl)-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;  
 2-(((1*s*,4*s*)-4-((5-(3-hydroxypropyl)-4-phenyl-3-*p*-tolyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;  
 2-(((1*s*,4*s*)-4-((3-(3-hydroxypropyl)-4-phenyl-5-*p*-tolyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;  
 2-(((1*s*,4*s*)-4-((5-(2-(methylsulfonyl)ethyl)-4-phenyl-3-*p*-tolyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;  
 2-(((1*s*,4*s*)-4-((3-(2-fluoro-4-methylphenyl)-5-(2-(methylsulfonyl)ethyl)-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;  
 2-(((1*s*,4*s*)-4-((5-(2-hydroxyethyl)-4-phenyl-3-*p*-tolyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid; and  
 2-(((1*s*,4*s*)-4-((1-*p*-tolyl-4,5-dihydro-3*H*-benzo[*e*]indazol-3-yl)methyl)cyclohexyl)methoxy)acetic acid.

14. A compound according to claim 1 selected from the following compounds and pharmaceutically acceptable salts, solvates and hydrates thereof:



2-(((1*s*,4*s*)-4-((4-(3-methoxyphenyl)-5-methyl-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;  
 2-(((1*s*,4*s*)-4-((4-(3-methoxyphenyl)-5-(methylthio)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;  
 2-(((1*s*,4*s*)-4-((5-(methylthio)-3,4-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;  
 2-(((1*s*,4*s*)-4-((4-(3-chlorophenyl)-5-(methylthio)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;  
 2-(((1*s*,4*s*)-4-((5-ethyl-4-(3-methoxyphenyl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;  
 2-(((1*s*,4*s*)-4-((5-(methylthio)-4-(5-methylthiophen-2-yl)-3-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;  
 2-(((1*s*,4*s*)-4-((3-(4-chloro-2-fluorophenyl)-5-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid;  
 2-(((1*s*,4*s*)-4-((5-(2-hydroxyethylthio)-3,4-diphenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid; and  
 2-(((1*s*,4*s*)-4-((3-(4-fluorophenyl)-5-(2-hydroxyethylthio)-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid.

15. A compound according to claim 1 selected from the following compound and pharmaceutically acceptable salts, solvates or hydrates thereof.  
 2-(((1*s*,4*s*)-4-((3-(2-fluoro-4-methylphenyl)-5-methyl-4-phenyl-1*H*-pyrazol-1-yl)methyl)cyclohexyl)methoxy)acetic acid.
16. A pharmaceutical composition comprising a compound or pharmaceutically acceptable salt, solvate or hydrate thereof according to any one of claims 1 to 15 and a pharmaceutically acceptable carrier.
17. A method for the treatment of Pulmonary Arterial Hypertension (PAH) in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound or pharmaceutically acceptable salt, solvate or hydrate thereof according to any one of claims 1 to 15 or a pharmaceutical composition according to claim 16
18. The method according to claim 17, wherein the PAH is selected from:  
 idiopathic PAH;  
 familial PAH;

PAH associated with a collagen vascular disease selected from: scleroderma, CREST syndrome, systemic lupus erythematosus (SLE), rheumatoid arthritis, Takayasu's arteritis, polymyositis, and dermatomyositis;

PAH associated with a congenital heart disease selected from: atrial septic defect (ASD), ventricular septic defect (VSD) and patent ductus arteriosus in an individual;

PAH associated with portal hypertension;

PAH associated with HIV infection;

PAH associated with ingestion of a drug or toxin;

PAH associated with hereditary hemorrhagic telangiectasia;

PAH associated with splenectomy;

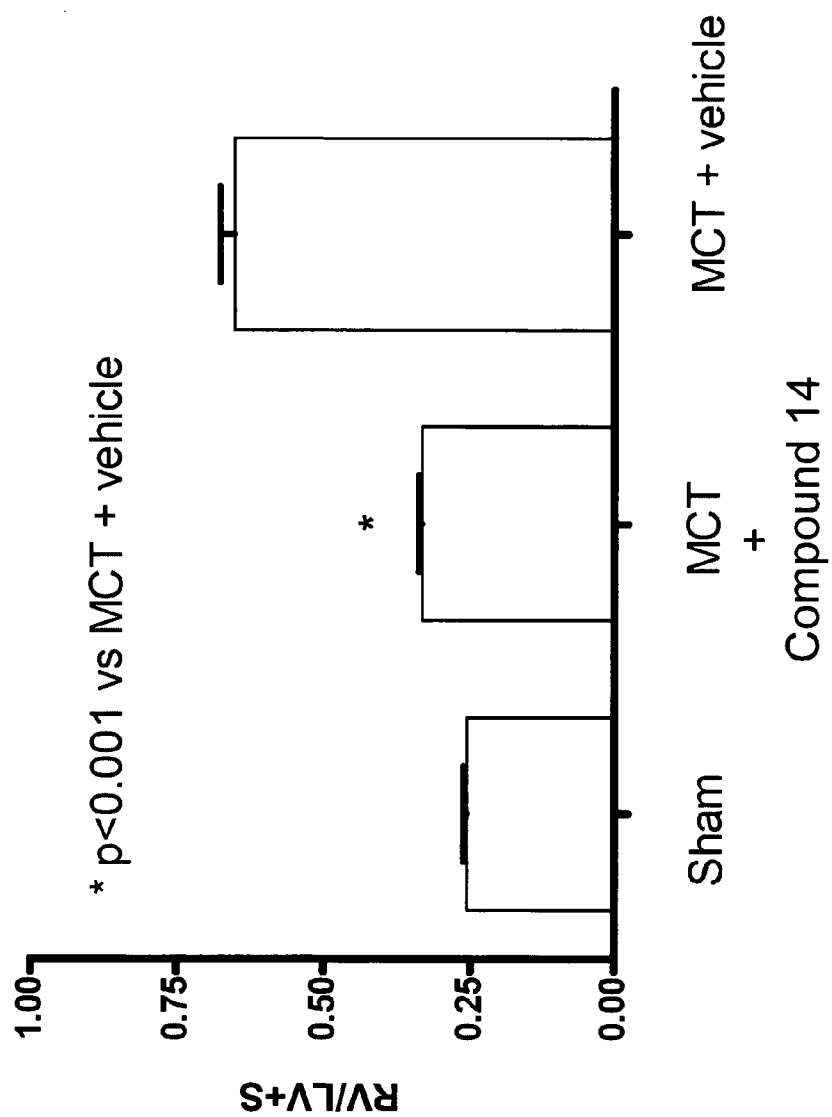
PAH associated with significant venous or capillary involvement;

PAH associated with pulmonary veno-occlusive disease (PVOD); and

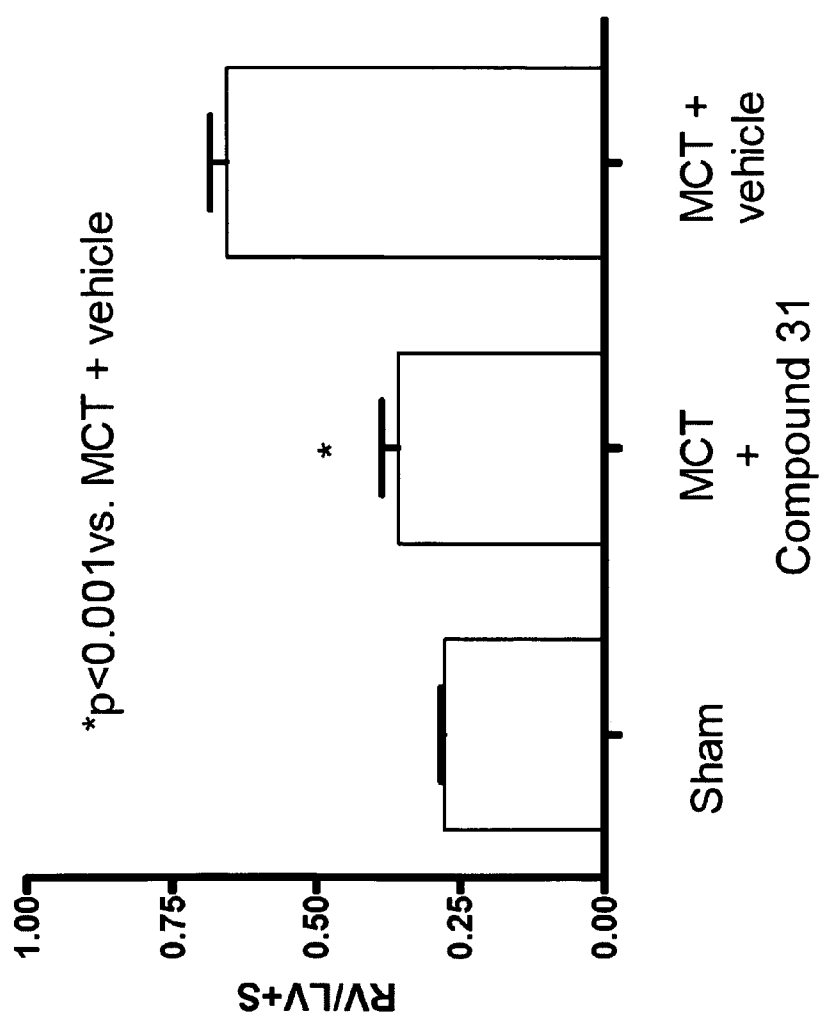
PAH associated with pulmonary capillary hemangiomatosis (PCH) in an individual.

19. A method for the treatment of a disorder selected from: platelet aggregation, coronary artery disease, myocardial infarction, transient ischemic attack, angina, stroke, ischemia-reperfusion injury, restenosis, atrial fibrillation, blood clot formation, atherosclerosis, atherothrombosis, asthma, a symptom of asthma, a diabetic-related disorder, diabetic peripheral neuropathy, diabetic nephropathy, diabetic retinopathy, glaucoma or other disease of the eye with abnormal intraocular pressure, hypertension, inflammation, psoriasis, psoriatic arthritis, rheumatoid arthritis, Crohn's disease, transplant rejection, multiple sclerosis, systemic lupus erythematosus (SLE), ulcerative colitis, ischemia-reperfusion injury, restenosis, atherosclerosis, acne, type 1 diabetes, type 2 diabetes, sepsis and chronic obstructive pulmonary disorder (COPD) in an individual, comprising administering to said individual in need thereof, a therapeutically effective amount of a compound according to any one of claims 1 to 15 or a pharmaceutical composition according to claim 16.
20. A process for preparing a composition comprising admixing a compound or pharmaceutically acceptable salt, solvate or hydrate thereof according to any one of claims 1 to 15 and a pharmaceutically acceptable carrier.
21. The compound or pharmaceutically acceptable salt, solvate or hydrate thereof, according to any one of claims 1 to 15, or the pharmaceutical composition according to claim 16, or the method according to any one of claims 17 to 19, or the process according to claim 20, substantially as hereinbefore described with reference to the Figures and/or Examples.

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**Figure 1**

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**Figure 2**

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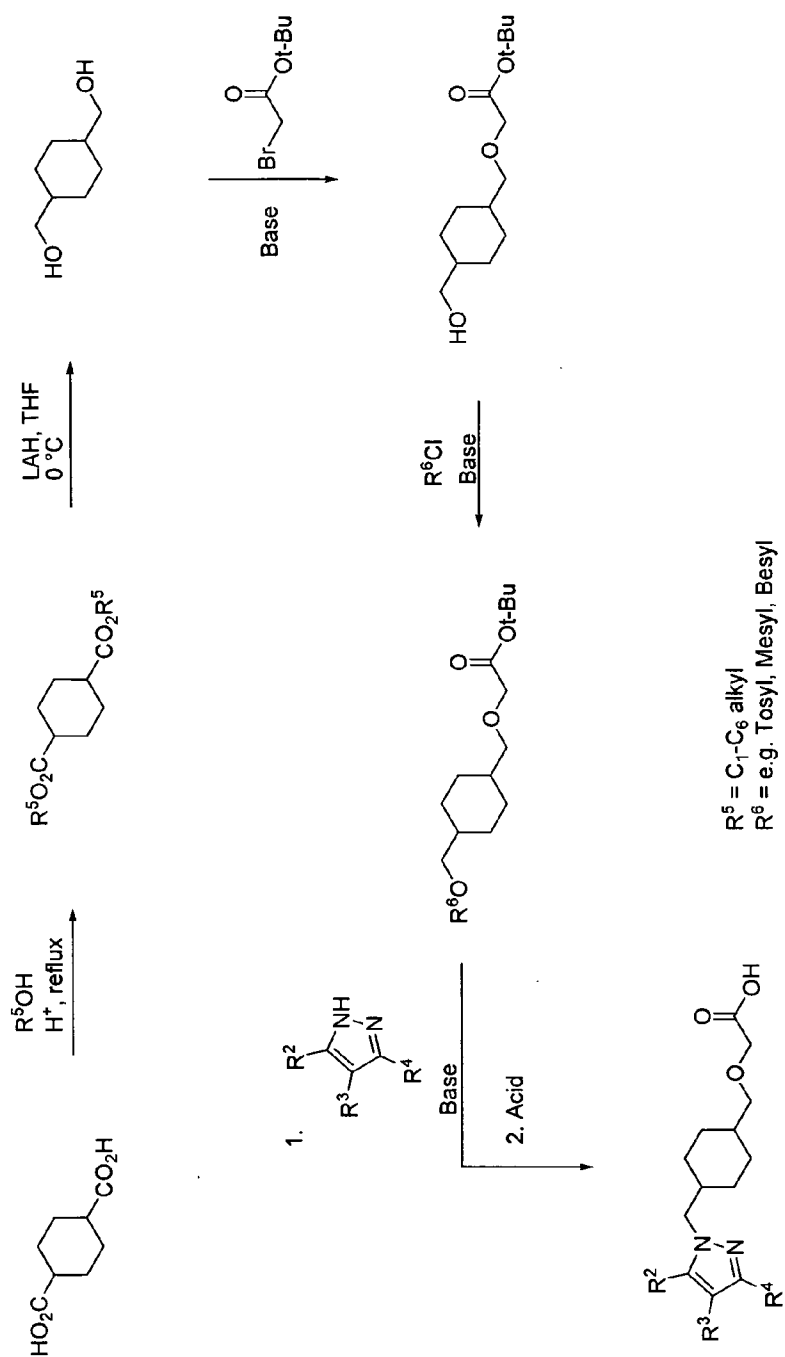


Figure 3

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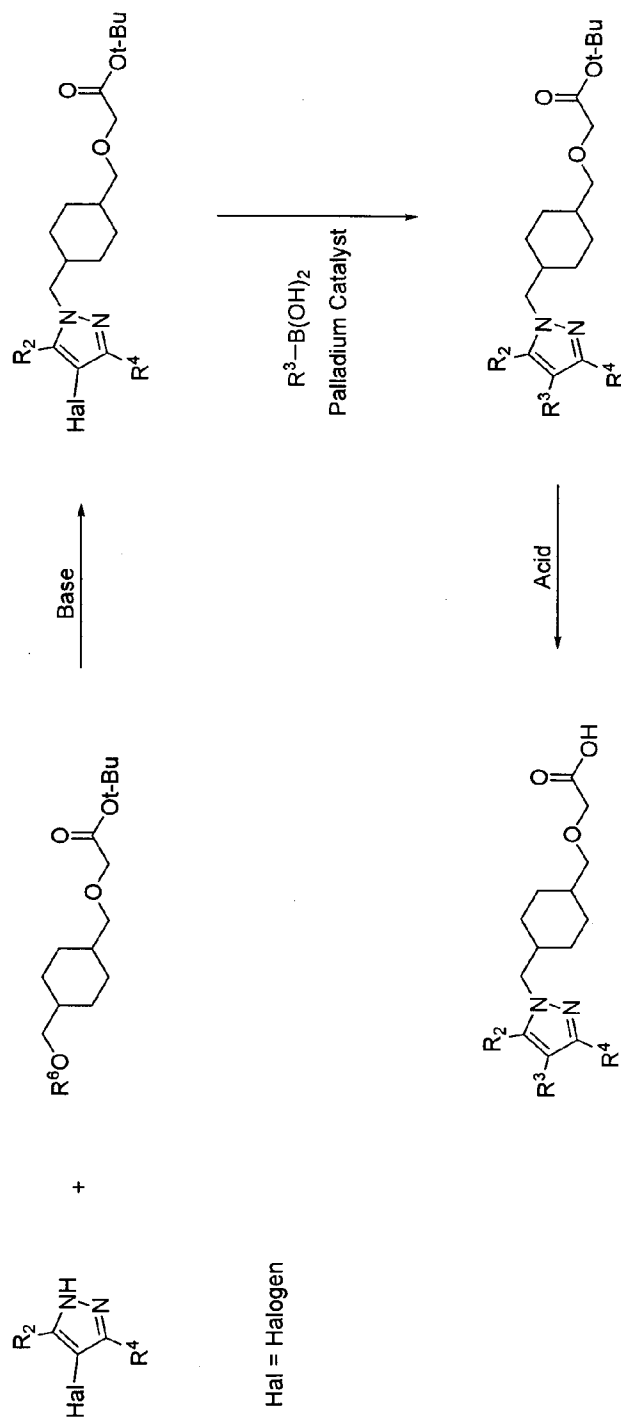


Figure 4

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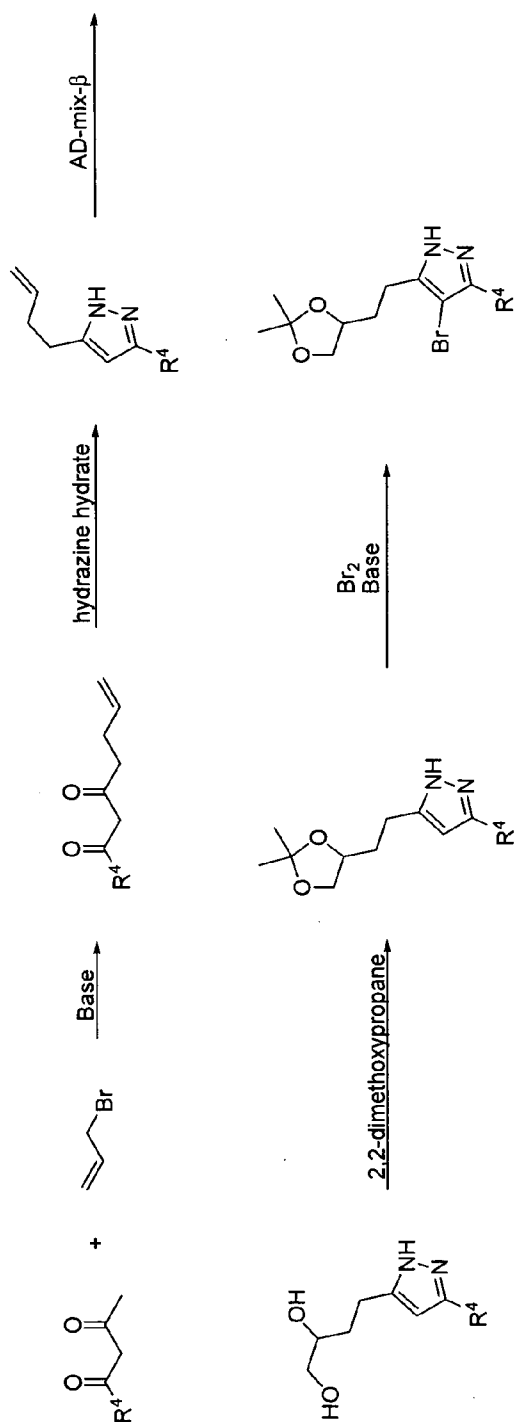


Figure 5

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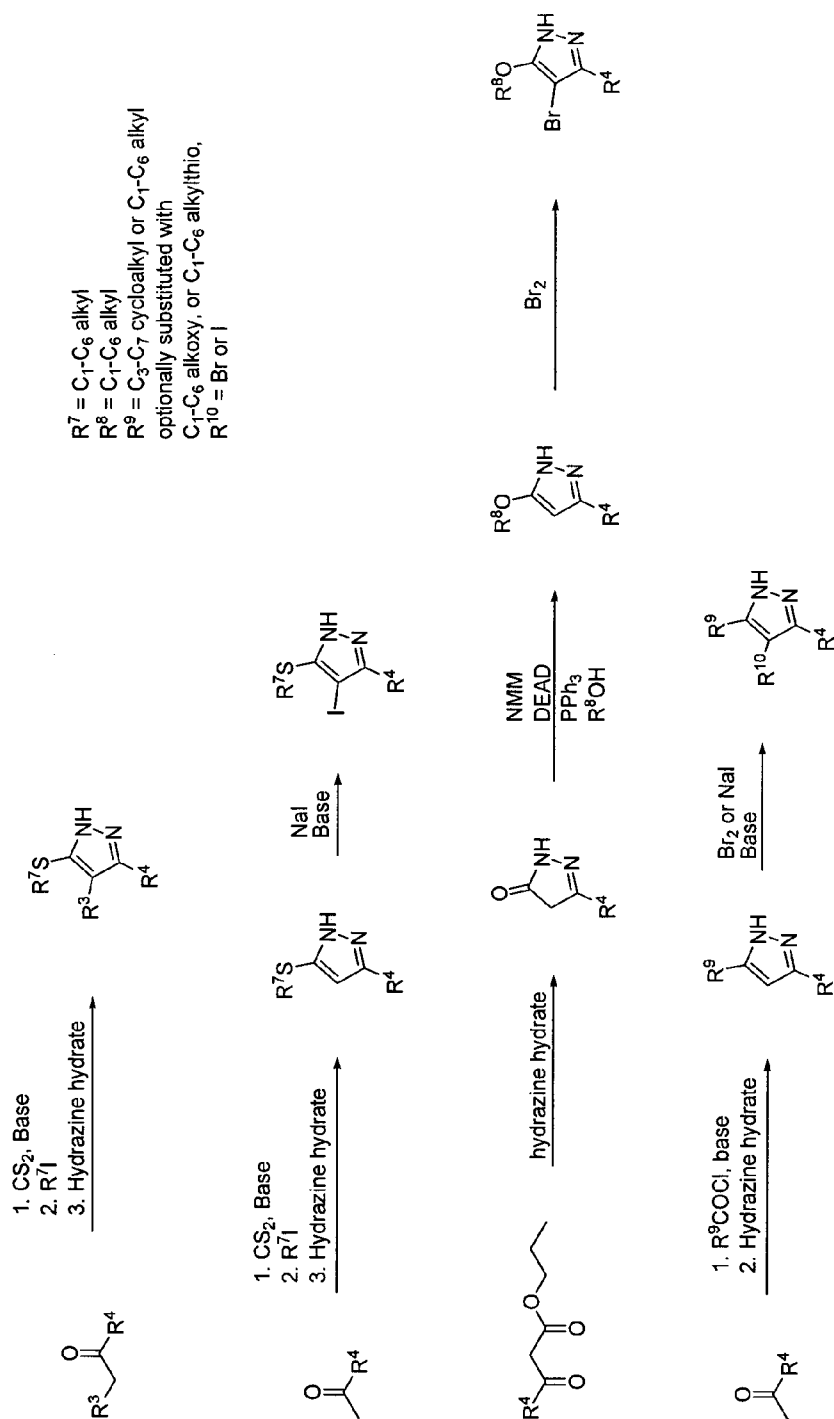


Figure 6



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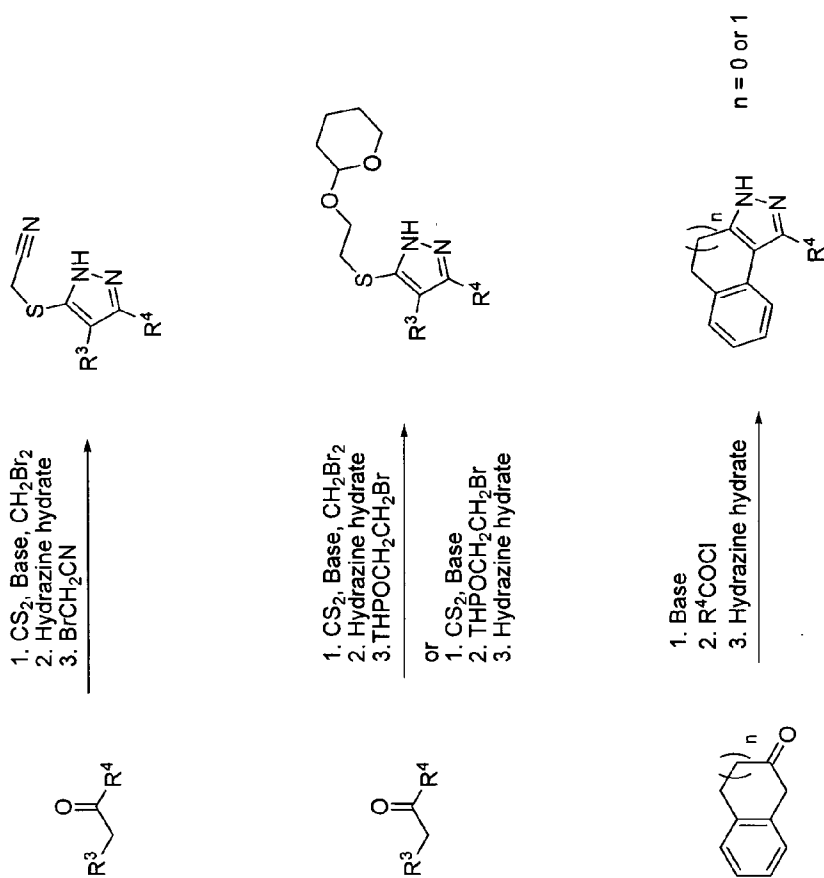


Figure 7

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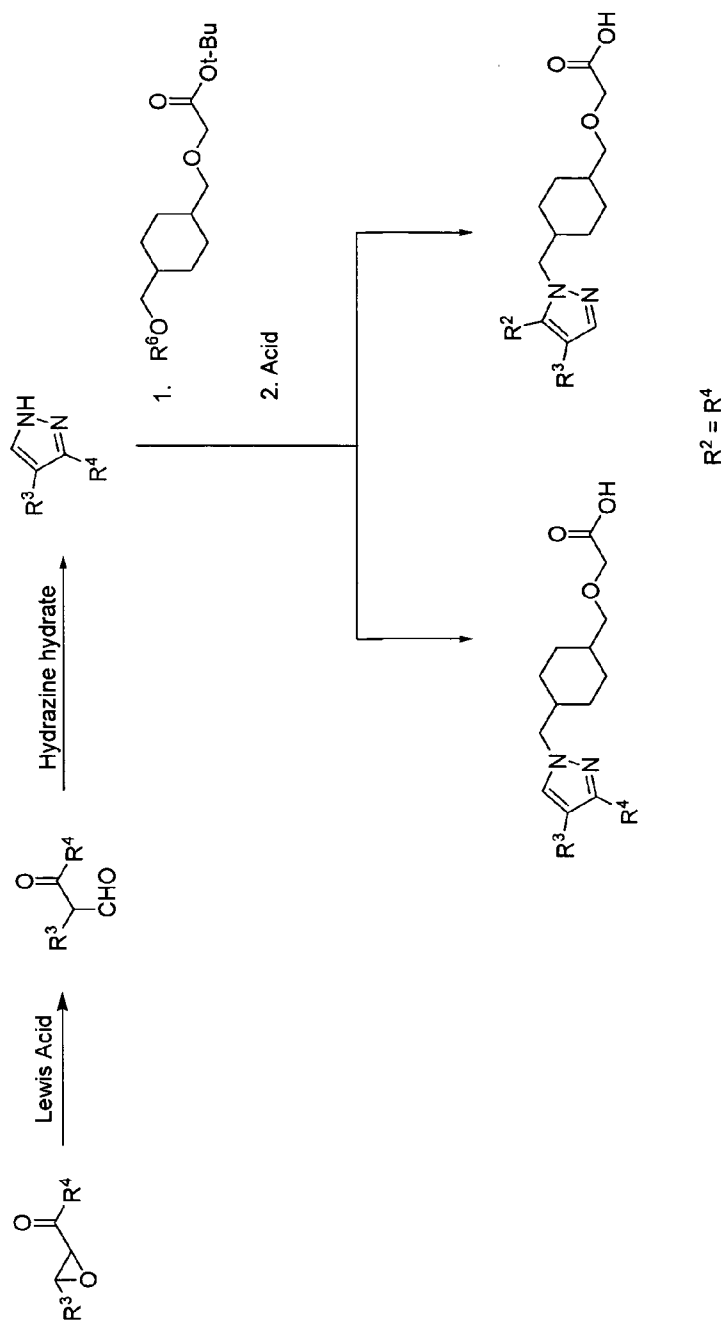


Figure 8

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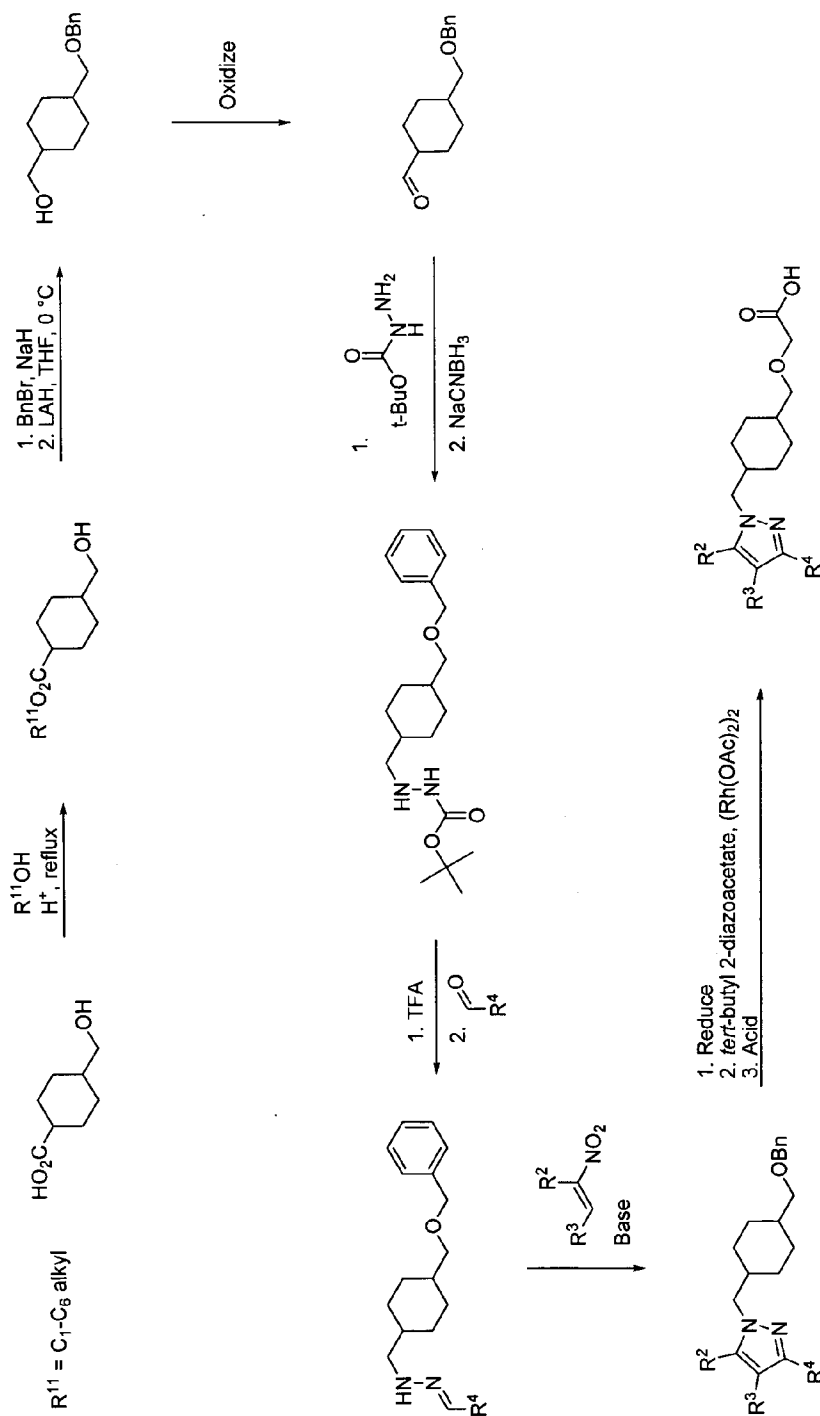


Figure 9