



(86) Date de dépôt PCT/PCT Filing Date: 2009/10/19  
(87) Date publication PCT/PCT Publication Date: 2010/04/22  
(45) Date de délivrance/Issue Date: 2021/09/21  
(85) Entrée phase nationale/National Entry: 2011/04/13  
(86) N° demande PCT/PCT Application No.: AU 2009/001371  
(87) N° publication PCT/PCT Publication No.: 2010/043000  
(30) Priorités/Priorities: 2008/10/17 (AU2008905369);  
2009/08/05 (AU2009903644)

(51) Cl.Int./Int.Cl. *C07D 413/10* (2006.01),  
*A61K 31/16* (2006.01), *A61K 31/18* (2006.01),  
*A61K 31/343* (2006.01), *A61K 31/382* (2006.01),  
*A61K 31/397* (2006.01), *A61K 31/403* (2006.01),  
*A61K 31/41* (2006.01), *A61K 31/4164* (2006.01),  
*A61P 11/00* (2006.01), *A61P 29/00* (2006.01),  
*A61P 31/00* (2006.01), ...

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(54) Titre : MODULATEURS DES RECEPTEURS S1P ET LEUR UTILISATION

(54) Title: S1P RECEPTORS MODULATORS AND THEIR USE THEREOF

(57) Abrégé/Abstract:

The invention relates to novel compounds that have S1P receptor modulating activity. Further, the invention relates to a pharmaceutical comprising at least one compound of the invention for the treatment of diseases and/or conditions caused by or associated with inappropriate S1P receptor modulating activity or expression, for example, autoimmune response. A further aspect of the invention relates to the use of a pharmaceutical comprising at least one compound of the invention for the manufacture of a medicament for the treatment of diseases and/or conditions caused by or associated with inappropriate S1P receptor modulating activity or expression such as autoimmune response.

(51) Cl.Int./Int.Cl. (suite/continued) *A61P 31/04* (2006.01), *A61P 31/12* (2006.01), *A61P 33/00* (2006.01), *A61P 35/00* (2006.01), *A61P 37/02* (2006.01), *A61P 43/00* (2006.01), *A61P 9/00* (2006.01), *C07C 15/04* (2006.01), *C07C 215/10* (2006.01), *C07C 215/68* (2006.01), *C07C 225/16* (2006.01), *C07C 311/20* (2006.01), *C07C 9/02* (2006.01), *C07D 205/04* (2006.01), *C07D 209/04* (2006.01), *C07D 209/08* (2006.01), *C07D 215/18* (2006.01), *C07D 233/32* (2006.01), *C07D 241/12* (2006.01), *C07D 257/04* (2006.01), *C07D 295/104* (2006.01), *C07D 307/79* (2006.01), *C07D 307/81* (2006.01), *C07D 311/22* (2006.01), *C07D 333/04* (2006.01), *C07D 333/20* (2006.01), *C07D 333/54* (2006.01), *C07D 413/14* (2006.01), *C07D 491/052* (2006.01), *C07F 9/09* (2006.01)

## (12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau(43) International Publication Date  
22 April 2010 (22.04.2010)

PCT

(10) International Publication Number  
**WO 2010/043000 A1**

## (51) International Patent Classification:

<i>C07D 413/10</i> (2006.01)	<i>A61P 37/02</i> (2006.01)
<i>A61P 31/04</i> (2006.01)	<i>A61P 43/00</i> (2006.01)
<i>C07D 209/08</i> (2006.01)	<i>C07C 9/02</i> (2006.01)
<i>A61K 31/16</i> (2006.01)	<i>C07C 15/04</i> (2006.01)
<i>A61P 31/12</i> (2006.01)	<i>C07C 215/10</i> (2006.01)
<i>C07D 215/18</i> (2006.01)	<i>C07C 311/20</i> (2006.01)
<i>A61K 31/18</i> (2006.01)	<i>C07D 205/04</i> (2006.01)
<i>A61K 31/343</i> (2006.01)	<i>C07D 209/04</i> (2006.01)
<i>A61K 31/382</i> (2006.01)	<i>C07F 9/09</i> (2006.01)
<i>A61K 31/397</i> (2006.01)	<i>C07D 233/32</i> (2006.01)
<i>A61K 31/403</i> (2006.01)	<i>C07D 241/12</i> (2006.01)
<i>A61K 31/4164</i> (2006.01)	<i>C07D 257/04</i> (2006.01)
<i>A61P 9/00</i> (2006.01)	<i>C07D 307/79</i> (2006.01)
<i>A61P 11/00</i> (2006.01)	<i>C07D 311/22</i> (2006.01)
<i>A61P 29/00</i> (2006.01)	<i>C07D 333/04</i> (2006.01)
<i>A61P 31/00</i> (2006.01)	<i>C07D 333/54</i> (2006.01)
<i>C07C 225/16</i> (2006.01)	<i>C07D 413/14</i> (2006.01)
<i>C07D 295/104</i> (2006.01)	<i>C07D 491/052</i> (2006.01)
<i>C07D 333/20</i> (2006.01)	<i>C07D 307/81</i> (2006.01)
<i>A61P 33/00</i> (2006.01)	<i>A61K 31/41</i> (2006.01)
<i>A61P 35/00</i> (2006.01)	<i>C07C 215/68</i> (2006.01)

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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

## (21) International Application Number:

PCT/AU2009/001371

## (22) International Filing Date:

19 October 2009 (19.10.2009)

## (25) Filing Language:

English

## (26) Publication Language:

English

## (30) Priority Data:

2008905369	17 October 2008 (17.10.2008)	AU
2009903644	5 August 2009 (05.08.2009)	AU

(71) Applicant (for all designated States except US): **AKAAL PHARMA PTY LTD** [AU/AU]; 309-10, Level 3, Chem-

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

## Published:

— with international search report (Art. 21(3))

(54) Title: S1P RECEPTORS MODULATORS AND THEIR USE THEREOF

(57) Abstract: The invention relates to novel compounds that have S1P receptor modulating activity. Further, the invention relates to a pharmaceutical comprising at least one compound of the invention for the treatment of diseases and/or conditions caused by or associated with inappropriate S1P receptor modulating activity or expression, for example, autoimmune response. A further aspect of the invention relates to the use of a pharmaceutical comprising at least one compound of the invention for the manufacture of a medicament for the treatment of diseases and/or conditions caused by or associated with inappropriate S1P receptor modulating activity or expression such as autoimmune response.



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## **S1P RECEPTORS MODULATORS AND THEIR USE THEREOF**

### **FIELD OF INVENTION**

This invention relates to novel compounds having S1P receptors modulating activity and the use of such compounds to treat diseases associated with inappropriate S1P receptor/s activity.

### **BACKGROUND**

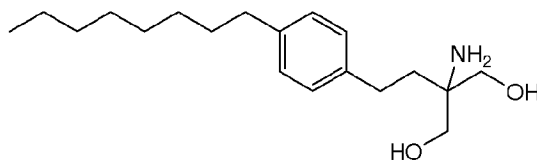
Sphingosine 1-phosphate (S1P) is a natural sphingolipid that functions as an intramolecular messenger in many types of cells and as an extracellular signalling molecule (for a recent review see Cooke et al, Annual Reports in Medicinal Chemistry, 2007, 42, pp 245 – 263 and references therein). The cellular effects induced by S1P are associated with platelet aggregation, cell morphology and proliferation, tumour cell invasion, endothelial cell chemotaxis and *in vitro* angiogenesis. The extracellular signalling occurs through interaction of S1P with G-protein-coupled receptors S1P1, S1P2, S1P3, S1P4 and S1P5. The intracellular activity of S1P and modulators has not been fully explored. S1P and its target have an essential role in lymphocyte migration through secondary lymphoid organs such the spleen, lymph nodes and mucosa-associated tissues such as the tonsils and Peyer's patches. The lymphocytes move from the peripheral circulation into the lymph nodes and mucosa associated tissues in order to generate immune responses. T and B lymphocytes are effectively sequestered within the thymus and secondary lymphoid tissue. Essentially, S1P and its receptor subtype -1 are required for lymphocytes to move out of the thymus and secondary lymphoid organs.

S1P type molecular modulators have been shown to be effective in multiple animal disease models. The S1P signalling, mainly through its receptor subtype – 1, is important in halting the T<sub>reg</sub> response and has been recommended for immunotherapy of cancer and infectious disease (Liu, G., et al, Nature Immunology, 2009, 10, 769 – 777; Wolf, A. M., et al, J. Immunology, 2009, 183, 3751-60). The S1P mediated trans-activation of insulin receptor has been reported to help treating insulin resistance and type 2 diabetes (Rapizzi E. et al, Cell Mol Life Sci, 2009, 66, 3207-18). S1P1 receptor axis has a role in the migration of neural stem cells toward the site of spinal cord injury (Kimura, A., et

al, *Stem Cells*, 2007, 25, 115-24). The S1P and its modulators supports the trafficking of hematopoietic progenitor cells and are helpful in tissue repair in myocardial infarction (Seitz, G., et al, *Ann. N. Y. Acad. Sci.*, 2005, 1044, 84 – 89; Kimura, et al, *Blood*, 2004, 103, 4478-86) and have great potential applications in regenerative medicines. S1P receptors play critical role in endothelial barrier enhancement and vasculature maturation (McVerry, B. J., et al, *Journal of Cellular Biochemistry*, 2004, 1075 -85; Allende, M. L., et al, *Blood*, 2003, 102, pp 3665-7; Paik, J., et al, *Genes and Development*, 2004, 18, 2392-2403; Garcia, J. G. N., et al, *J. Clinical Investigation*, 2001, 689-701). The vasculature normalization helps the cytotoxic T cells to access the remote and inner part of the tumour (Hamzah J. et al, *Nature*, 2008, 453, pp 410 – 414). The lymphocyte egress and endothelial barrier function is mediated through S1P1 receptor (Brinkmann, et al, *American J. of transplantation*, 2004, 4, 1019-25; McVerry B. J. et al, *Cellular Signalling*, 2005, 17, pp 131 -39). S1P type modulation reduces ischemia reperfusion injuries (Lein, Y. H., et al, *Kidney International*, 2006, 69, 1601 – 8; Tsukada, Y. T. et al, *J Cardiovascular Pharmacol*, 2007, 50, 660-9). S1P1 signalling is critical in preventing inflammation induced vascular leakage (Niessen, F. et al; *Blood*, 2009, 113, 2859-66; Wang L et al, *Microvascular Research*, 2009, 77, 39 -45; Lee, J. F., et al, *Am.J.Physiol Heart Circ Physiol*, 2009, 296, H33-H42). It also reduces a vascular leakage in models of acute lung injury (McVerry, B. J., et al, *Am J of Respiratory and Critical Care Medicine*, 2004, 170, 987-93). The S1P vasculo-protection effect, mediated by nitric oxide and prostacyclin (Rodriguez C et al, *Thromb Haemost*, 2009, 101, 66-73), prevents the development of atherosclerotic lesions (Nofer, J. R. et al, *Circulation*, 2007, 115, 501-8; Tolle, M., et al, *European J Clin Inv*, 2007, 37, 17-9; Keul, P., et al, *Arterioscler.Thromb.Vasc. Biol*, 2007, 27, 607-13). S1P prevents tumour necrosis factor alpha mediated monocyte adhesion to endothelial cells, implicated in the pathology of atherosclerosis and inflammatory diseases (Bolick, D. T. et al, *Arterioscler. Thromb. Vasc. Biol*, 2005, 25, 976-81). Recently reported target of S1P includes the family of Histone Deacetylases (HDACs) (Hait, N. C., et al, *Science*, 2009, 325, 125-7), which are known for their role in epigenetic. The S1P has been reported to help treatment of the latent mycobacterium tuberculosis infection by promoting the processing and presentation of antigens (Santucci, M. B. et al, *Biochem Biophys Res Comm*, 2007, 361, 687 -93). Additionally, the S1P

and its modulators have cardio protective effects (Means, C. K., et al, Cardiovascular Research; 2009, 82, 193-200; Hofmann, U., et al, Cardiovascular Research, 2009, 83, 285-93; Tao, R., et al, J Cardiovasc Pharmacol, 2009, 53, 486-94) and the signalling axis of S1P are important in the treatment of myocardial infarction (Yeh, C. C., et al, Am J Physiol Heart Circ Physiol; 2009, 296, H1193-9). Thus S1P like molecular modulators have a great developmental potential in wide range of cardiovascular medicines. Role of S1P receptor subtype - 1 in modulating nociception have recently been described (Selley S M J et al, Journal of Neurochemistry, 2009, 110, pp 1191 – 1202).

Fingolimod (2-amino-2-(2-[4-octylphenyl] ethyl)-1,3-propanediol) (FTY-720) is metabolised to a structural analogue of S1P and has been found to effect S1P receptors. The discovery of FTY-720 and its efficiency in animal models and clinical studies, related to many autoimmune diseases and cancer treatment, has resulted in research efforts into S1P receptors.



FTY-720

FTY-720 decreases peripheral blood lymphocyte counts (lymphopenia) reversibly, without impairing the effector function of the immune cells (Pinschewer, D. et al, J. Immunology, 2000, 164, 5761-70). FTY-720 is an emerging novel drug for Multiple Sclerosis (MS) (Kieseier, B. C., et al, Pharmacological Research, 2009, 60, 207-11; Brown, B. A., The Annals of Pharmacotherapy, 2007, 41, 1660-8) and has a direct cyto-protective and process extension effect in oligodendrocyte progenitors (Coelho, R. P. et al, J. Pharmacology and Experimental Therapeutics, 2007, 323, 626-35; Miron, V. E. et al, Ann Neurol, 2008, 63, 61 -71). It is effective against autoimmune related pathologies such as type-1 diabetes (Yang, Z., et al, Clin Immunology, 2003, 107, 30-5), arthritis (Matsuura, et al, Inflamm Res, 2000, 49, 404-10) and oxazolone stimulated colitis (Daniel, et al, Molecular Immunology, 2007, 44, 3305-16). FTY-720 interaction with cytosolic Phospholipase A2 and modulation the eicosanoids synthesis (Payne S. G. et al; Blood, 2007, 109, pp 1077 – 1085) indicates its potential as anti-inflammatory and antinociceptive agents and a safe pain killer

(Coste, O., et al, J. Cell Mol. Med., 2008, Vol 12, 995 – 1004). The anticancer activity of FTY-720 is well documented by *in vitro* apoptotic activity studies as well as numerous animal model studies. The apoptotic mechanism observed in hepatocellular carcinoma cell lines is linked to the activation of protein kinase C delta (PKC- $\delta$ ) (Hung, J. H., et al, 2008, 68, 1204-12). The apoptotic activity of FTY-720 against chronic myelogenous leukaemia and Philadelphia chromosome positive acute lymphocytic leukaemia was reported to be due to its control of Protein Phosphates 2A (PP2A) (Neviani et al, J of Clinical Investigation, 2007, 117, 24-21). Phosphorylated form of FTY-720 is speculated to be an anti-metastasis drug (Meeteren, et al, Cancer Lett., 2008, 266, 203-8). FTY-720 inhibits vascular endothelial cell growth factor induced vascular permeability (Sanchez, T., et al, J. Biological Chem., 2003, 278, 47281-90), linked to an anticancer and anti-metastatic effect in animal models (Azuma, H., et al, Cancer Res, 2002, 1410-19; Chua, C-W., et al, Int. J Cancer, 2005, 117, 1039-48; LaMontagne, K. et al, 2006, 66, 221-31). The anti-angiogenic effect of FTY-720 through its interaction with S1P receptor subtype – 1, was described recently (Schmid, G., et al, J Cellular Biochem, 2007, 101, 259-70). FTY-720 helps favourable central nervous system (CNS) gene expression and improves the blood brain barrier function (Foster, C. A., et al, Brain Pathology, 2009, 19, 254-66). Few days of treatment with FTY-720 leads to complete eradication of chronic viral infection of lymphocytic choriomeningitis (Lanier, et al, Nature, 2008, 894 – 899). Its anti-fibrotic activity was reported recently (Brunati, A. M., et al, Biochem Biophys Acta, 2008, 1783, 347-59; Delbridge, M. S., et al, Transplantation Proceedings, 2007, 39, 2992-6). FTY 720 inhibits development of atherosclerosis in low density lipoprotein receptor deficient mice (Nofer, J. R., et al, Circulation, 2007, 115, 501 -8; Tolle, M. et al, European J Clinical Investigation, 2007, 37, 171 -79). FTY720 was effective in the treatment of cerebral ischemia in the mouse model (Czech, B., et al, Biochem Biophys Res Comm, 2009, online), indicating the great potential of S1P receptors modulators in the wide range of cardiovascular medicine. The derivatives of FTY-720 were reported as pulmonary barrier enhancers and thus potential agents for the development of critical care medicines (Camp, S. M., et al, J Pharmacol Experimental Therapeutics, 2009, online).

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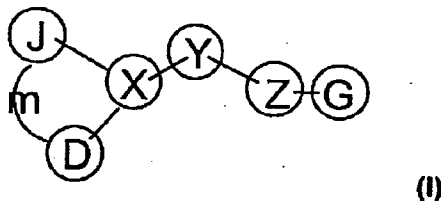
Of the classical mimics of S1P, the amino alcohols and their respective monophosphates, amino phosphonates, amino acids, alkoxyamino alcohols, alkyl carboxylates appear to be the most effective S1P receptors modulators. While an *in vivo* phosphorylation of the hydroxyl group of FTY 720 appears to be necessary for the most effective extracellular signalling and agonistic effect upon binding to S1P1-5, the apoptotic effect is limited to its non-phosphorylated form.

It is desirable to provide alternatives to FTY-720 and in particular alternative compounds with improved properties and/or activity. For example, this could include compounds with greater range of activity, altered or enhanced specificity, improved pharmacological properties or reduction in side effects.

Throughout this specification, use of the terms "comprises" or "comprising" or grammatical variations thereon shall be taken to specify the presence of stated features, integers, steps or components but does not preclude the presence or addition of one or more other features, integers, steps, components or groups thereof not specifically mentioned.

#### SUMMARY OF INVENTION

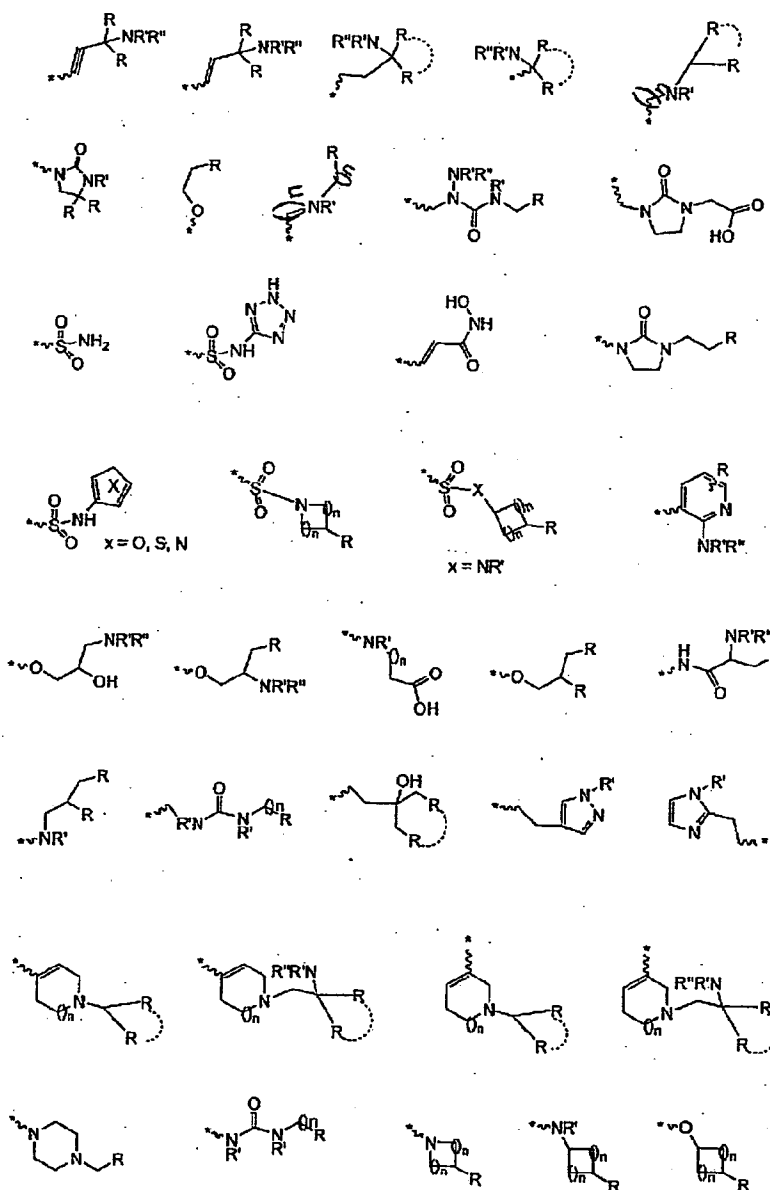
In one aspect of the present invention there is provided a compound of formula (I)



wherein G is a group selected from the following:




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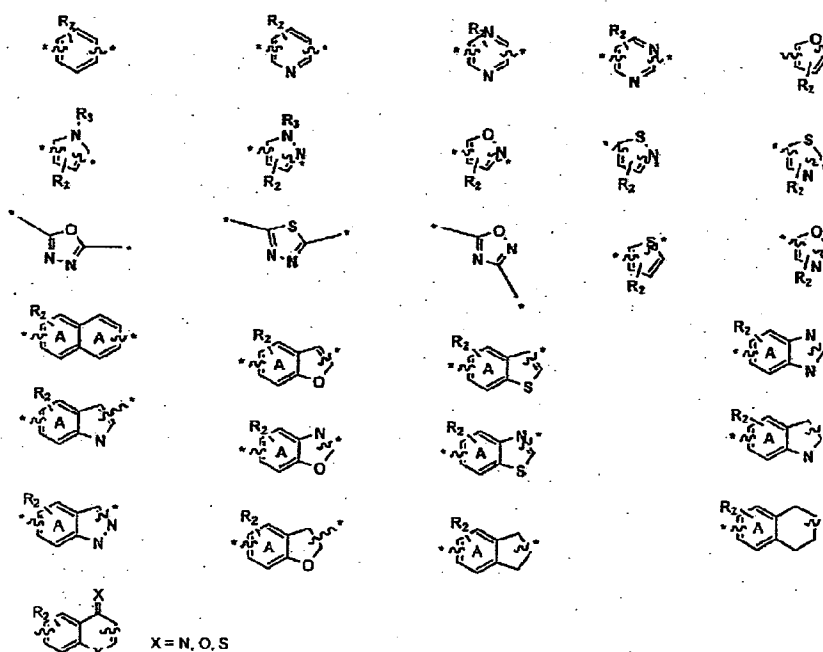
- 5 wherein R is independently selected from H, deuterium, CN, amino, alkylamino,  $\text{CH}_2\text{OH}$ , alkoxy,  $\text{CF}_3$ , an alkyl chain optionally containing one or more of deuterium, O,  $\text{NR'R''}$ , S, SO,  $\text{SO}_2$ , halogen, a carbon-carbon double bond, a carbon-carbon triple bond, a carbon-heteroatom double bond or a carbon-heteroatom triple bond, aryl, carbocycle, heterocycle, amide, sulphonamide, hydroxyl,
- 10  $-\text{CH}_2\text{COOH}$ ,  $\text{COOH}$ ,  $-\text{OPO}_3\text{H}_2$ ,  $-\text{PO}_3\text{H}_2$ , cyclic phosphate, cyclic phosphonates and/or salts, tetrazole, and n is 0-4, R' and R'' are independently selected from H, deuterium, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl,

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substituted aryl, heterocycle, substituted heterocycle, acyl, sulphonyl, benzoyl, with the proviso that if an amino group is present on the same carbon atom as R in group G, R is not hydroxyl,  represents an optional bridging group; the asterisk indicating the attachment of the group G within formula (I);

- 5 and wherein G is not  $-\text{CH}_2\text{C}(\text{H})(\text{R}_2)\text{NH}_2$ ,  $-\text{C}(\text{H})(\text{R}_2)\text{NH}_2$  or  $-\text{CH}=\text{CH}-\text{CH}_2-\text{NH}_2$  wherein  $\text{R}_2$  is hydrogen or methyl;

wherein X, Y and Z separately or in any combination, are selected from the following:

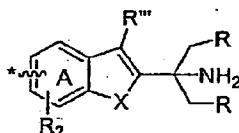


- wherein the asterisks indicate the attachment within formula (I),  $\text{R}_2$  is selected from halogen, H, deuterium, CN, amino, alkylamino, hydroxyl, alkoxy,  $\text{CF}_3$ , an alkyl chain of up to 20 carbon atoms optionally containing one or more of deuterium, O,  $\text{NR}'\text{R}''$ , (wherein  $\text{R}'$  and  $\text{R}''$  are independently selected from alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heterocycle and substituted heterocycle), S, SO,  $\text{SO}_2$ , halogen, a carbon-carbon double bond, a carbon-carbon triple bond, a carbon-heteroatom double bond or a carbon-hetero atom triple bond, carbocycle, heterocycle, amide, sulphonamide
- 15
- 20 and A represents one or more ring atoms or groups independently selected from the group consisting of C, N, O, S, CO,  $\text{C}=\text{NR}$ , wherein R is hydrogen or alkyl, SO

or SO<sub>2</sub>, R<sub>3</sub> may be a linking group or alkyl, aryl, heterocycle or an optionally substituted alkyl chain;

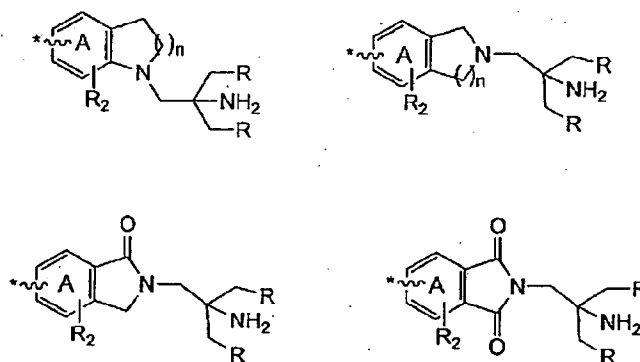
and wherein the groups J, m and D separately, or in any combination, are selected from hydrogen, deuterium, alkyl, alkoxy, alkylamino, halogen, amino, hydroxy, cyano, aryl, substituted aryl, heterocycle, substituted heterocycle, carbocycle, substituted carbocycle, alkyl chain of 1-15 carbon atom optionally containing carbon-carbon multiple bond, carbon-hetero multiple bond wherein one or more carbon atoms can be independently replaced with oxygen, sulphur, SO, SO<sub>2</sub>, NR' (wherein R' is selected from alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heterocycle and substituted heterocycle) and wherein the groups J, m and D are linked together to form a ring with X or the group m is a substituent attached to either one of J or D.

In a preferred embodiment of this aspect of the invention Y, Z and G, in combination, are selected from the following groups:



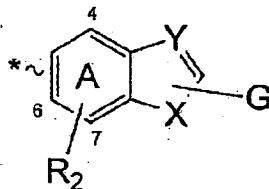
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wherein R is as defined as for group G above, wherein A is defined as above and X is selected from the group consisting of heteroatom or heteroatom containing species such as O, NR', R' defined as for NR' as above, S, SO, SO<sub>2</sub>, CO or C=NR, wherein R is hydrogen or alkyl, R''' is selected from H, deuterium, halogen, CN, NO<sub>2</sub>, amino, methyl, CF<sub>3</sub>, cyclo-alkyl, alkyl chain, optionally substituted alkyl chain, aryl, heterocycle, and R<sub>2</sub> is as defined in as above, the asterisk indicating the attachment to Y within formula (I),



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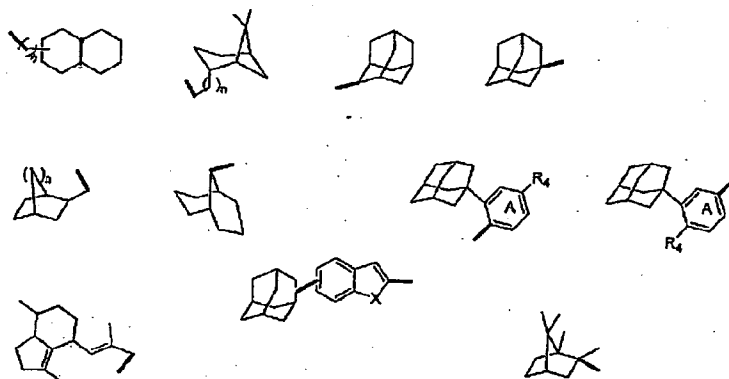
wherein R is as defined as in group G above, with the proviso that R is not OH, wherein A is defined as above and X is selected from the group consisting of heteroatom or heteroatom containing species such as O, N, S, SO, SO<sub>2</sub>, CO or C=NR, wherein R is hydrogen or alkyl; and R<sub>2</sub> is as defined as above, the  
5 asterisks indicating the attachment to Y within formula (I),



wherein A is as defined as above and X and Y are independently selected  
10 from the group consisting of heteroatom or heteroatom containing species such as O, NR', R' defined as for NR' above, S, SO, SO<sub>2</sub>, CO or C=NR and R<sub>2</sub> is as defined as above, the asterisks indicating the attachment within formula (I).

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In one embodiment the group D, when present, is selected from H, deuterium, alkyl, aryl, heterocycle or cycloalkyl. In a further embodiment the group m, when present, is selected from unsubstituted or substituted aryl, carbocycle or heterocycle. In a yet further embodiment, the group J, when present, is selected from H, alkyl or one of the following groups:



wherein A is as defined as above, n is 0-10, R<sub>4</sub> is halogen, CN, amino, alkylamino, alkoxy, CF<sub>3</sub>, an alkyl chain containing one or more of O, N, S, SO, SO<sub>2</sub>, a carbon-carbon double bond, a carbon-carbon triple bond, a carbon-heteroatom double bond or a carbon-hetero atom triple bond.

In a further aspect of the invention there is provided compounds having S1P receptor modulating activity and/or expression against target cells.

A yet further aspect of the invention provides a pharmaceutical preparation comprising at least one compound described herein in any of its stereoisomeric and/or isotopic forms or physiologically tolerable and/or therapeutically effective salts or mixtures thereof in any ratio together with a pharmaceutically acceptable carrier(s) and/or excipient(s).

In a further aspect the invention provides the use of a compound of the invention in any one of its stereoisomeric and/or isotopic forms or physiologically tolerable and/or therapeutically effective salts or mixtures thereof in any ratio, for the production of a pharmaceutical for modulation of S1P receptor activity and/or expression against target cells.

In a further aspect the invention provides the use of a compound of the invention in any one of its stereoisomeric and/or isotopic forms and mixtures thereof in any ratio and/or physiologically tolerable and/or therapeutically effective

salts for the production of a pharmaceutical for modulation of S1P receptor (extracellular and/or intracellular binders) activity and/or expression.

S1P receptors are cell surface receptors which include known receptor subtypes 1, 2, 3, 4, 5 and are regarded herein as S1P receptors. These extracellular S1P receptors may be present inside the cell on Golgi bodies, etc. There are other intracellular receptor/s, target/s, protein/s, enzyme/s where S1P interacts and are regarded as S1P receptor/s. The compounds of the invention could function as substrates of Sphingosine Kinases like SK1 and SK2 which are responsible for phosphorylation of S1P and are regarded as S1P receptor/s. Histone Deacetylase/s (HDACs) are known intra-nuclear receptors of S1P and thus are regarded as S1P receptors. In broad terms, the invention includes any receptor binder, agonists or antagonists, or inverse agonists of the S1P receptor family including S1P1, S1P2, S1P3, S1P4 and S1P5, which is responsible for direct and or indirect effect of S1P and regards them as S1P receptor/s.

Further, the invention relates to the use of a pharmaceutical comprising at least one compound of the invention in any of its stereoisomeric and/or isotopic forms or physiologically tolerable and/or therapeutically effective salts or mixtures thereof in any ratio.

Further, the invention relates to the use of a pharmaceutical comprising at least one compound of the invention in any of its stereoisomeric and/or isotopic forms or physiologically tolerable and/or therapeutically effective salts or mixtures thereof in any ratio for the treatment of diseases and/or conditions caused by or associated with inappropriate S1P receptor modulating activity or expression, for example, autoimmune disease.

A further aspect of the invention relates to the use of a pharmaceutical comprising at least one compound of the invention in any of its stereoisomeric or isotopic forms or physiologically tolerable and/or therapeutically effective salts or mixtures thereof in any ratio for the manufacture of a medicament for the treatment of diseases and/or conditions caused by or associated with inappropriate S1P receptor modulating activity or expression such as autoimmune disease.

In yet a further aspect of the invention, the compounds of the invention can be used for the prevention and/or prophylaxis and/or treatment and/or

immunotherapy of infectious diseases including any infection caused by viruses, bacteria, fungi, parasites, prions and/or any other pathogens.

Viral infections including but not limited to human immunodeficiency virus, Hepatitis (HAV, HBV, HCV), H1N1 influenza, chickenpox, cytomegalovirus infection, dengue fever, Ebola hemorrhagic fever, hand foot and mouth disease, herpes simplex, herpes zoster, HPV, influenza (Flu), Lassa fever, measles, Marburg Hemorrhagic fever, infectious mononucleosis, mumps, norovirus, poliomyelitis, progressive multifocal Leu-encephalopathy, rabies, rubella, SARS, smallpox (Variola), viral encephalitis, viral gastroenteritis, viral meningitis, viral pneumonia, west Nile disease and yellow fever.

Bacterial Infections including but not limited to actinomycosis, anaplasmosis, anthrax, bacterial meningitis, botulism, brucellosis, burkholderia infections, campylobacteriosis, cellulitis, chlamydiaceae infections, cholera, clostridium infections, coccidiomycosis, diphtheria, ehrlichiosis, empyema, gonorrhea, impetigomelioidosis legionellosis, leprosy (Hansen's Diseases), leptospirosis, listeriosis, lyme disease, bacterial endocarditis, endophthalmitis, pseudomembranous enterocolitis, erysipelas, Escherichia coli infections, necrotizing fasciitis, Fournier gangrene, furunculosis, fusobacterium infections, gram negative bacterial infections, gram positive bacterial infections, granuloma inguinale, hidradenitis suppurativa, histoplasmosis, hordeolum, impetigo, Klebsiella infections, ludwig's angina, lymphogranuloma venereum, maduromycosis, mycobacterium infections, MRSA infection, Mycoplasma infections, nocardia infections, onychomycosis, osteomyelitis, paronychia, pelvic inflammatory disease, plague pneumococcal infections, pseudomonas infections, psittacosis, puerperal infection, respiratory tract infections, retropharyngeal abscess, rheumatic fever, rhinoscleroma, rickettsia infections, rocky mountain disease, salmonella infections, scarlet fever, scrub typhus, sinusitis, shigellosis, spotted fever, bacterial skin disease, staphylococcal infections, streptococcal infections, syphilis, tetanus, trachoma, tick borne disease, epidemic typhus, tuberculosis, tularaemia, typhoid fever, urinary tract infections, whipple disease, whooping cough, vibrio infections, Yersinia infections, zoonoses, and zygomycosis,

Fungal infections including but not limited to aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, cryptococcosis, tinea pedis and histoplasmosis.

Prion infections including but not limited to transmissible spongiform encephalopathy, bovine spongiform encephalopathy, Creutzfeldt-Jakob disease, Kuru fatal Familial insomnia and Alpers Syndrome.

In a further aspect of the invention, the compounds of the invention can be used for the prevention and/or prophylaxis and/or treatment and/or immunotherapy of cancer and immune mediated diseases which include immune related and inflammatory diseases; autoimmune diseases; allergic conditions; pain; central nervous system diseases; neurodegenerative diseases, cardiovascular diseases; haematological pathologies. For example, Multiple Sclerosis, Alzheimer's, dementia, Parkinson's, Huntington's, Amyotrophic Lateral Sclerosis, Coeliac, inflammatory bowel, Crohn's, ulcerative colitis, Lupus Erythematosus, Lupus Nephritis, osteoarthritis, psoriasis, pruritus, arthritis, rheumatoid arthritis, osteoporosis, Sjogren Syndrome, uveitis, asthma, hay fever, sleep disorders, , macular degeneration, glaucoma, type1 and 2 diabetes, myasthenia gravis, non-glomerular nephrosis, autoimmune hepatitis, Behcet's, glomerulonephritis, chronic thrombocytopenia purpura, haemolytic anaemia, Wegner's granuloma and fibrosis, nervous system (spasticity), spinal cord injury, spinocerebellar ataxia, tardive dyskinesia, cognitive disorders.

The compounds of the invention can be used for the prevention and/or prophylaxis and/or treatment and/or immunotherapy of or in, Down's syndrome, schizophrenia, bipolar disorder, drug dependence, Wernicke-Korsakoff syndrome, eating disorders, depression resulting from infection, hepatic encephalopathy, lung diseases such as grain handler's, Hermansky-Pudlak Syndrome, and adult respiratory distress syndrome (ARDS, obesity, digestive tract disease, anxiety, hyperalgesia, migraine, epilepsy and neuromuscular disorder.

In another embodiment the compounds of the invention can be used for prevention and/or treatment of vascular and/or cardiovascular diseases including, but not limited to, hypoxia, atherosclerosis, diabetic blood vessel disease like inflammation, hyper vascularisation related disorders such as cancer and neoplasm, heart failure, myocardial infarction, myocarditis, ischemia, hypotension, hypertension, reperfusion injury, angina pectoris, coronary artery disease, stroke, thrombosis, artery/vein blockage or obstruction, diabetic retinopathy, sepsis and kidney failure, reperfusion or injury.



In another embodiment the compounds of the invention can be used for prevention and/or prophylaxis and/or treatment and/or immunotherapy of liver diseases including but not limited to liver cirrhosis, viral liver infections, autoimmune hepatitis, liver failure, portal hypertension, hemochromatosis, Wilson's diseases, Gaucher disease, hepatoma, primary biliary cirrhosis, primary sclerosing cholangitis, sarcoidosis and Zwellweger syndrome.

In another embodiment the compounds of the invention can be used for the prevention and/or treatment and/or immunotherapy of solid and/or haematological cancers and tumor metastasis, including but not limited to acute B-cell leukaemia, lymphoma, chronic lymphocytic leukaemia, chronic myeloid leukaemia, hairy cell leukaemia, multiple myeloma, acute lymphocytic leukaemia, acute granulocytic leukaemia, acute myelogenous leukaemia, lung cancer, adrenal gland cancer, astrocytoma, glioma, brain cancer, bile duct cancer, bladder cancer, bone cancer, bowel cancer, colorectal cancer, breast cancer, cervical cancer, endometrial cancer, oesophageal cancer, melanoma, gallbladder cancer, Kaposi sarcoma, renal cancer, laryngeal cancer, liver cancer, mesothelioma, prostate cancer, sarcoma, skin cancer, stomach cancer, testicular cancer, uterine cancer, thyroid cancer, and pancreatic cancer.

In another embodiment the compounds of the invention can be used for prevention and/or treatment and/or immunotherapy of pain including chronic pain, which could either be somatogenic (organic) or psychogenic. The somatogenic pain may be of nociceptive, inflammatory and or neuropathic origin. The pain related to nociceptive pain, peripheral neuropathy, central neuropathy, neuralgia, migraine, psychotic, inflammatory and or neurological disorders.

In another embodiment the compounds of the invention can be used for organ transplant and/or allograft and/or autograft, for example, kidney, liver, lung, heart, skin, stem cell or bone marrow transplant and in the treatment of graft versus host disease.

In another embodiment the disclosed molecules can be used for prevention and/or treatment and/or immunotherapy for the pathologies caused by bioterrorism agents.

In another embodiment the compounds of the invention can be used as a vaccine adjuvant to boost and/or enhance the action of a vaccine and/or immune agent and/or for immunization; for example antigen, tumour cell lysate, B cell

vaccine, T cell vaccine, dendritic cell vaccine boosting the immune response of cytotoxic cells, helper T cells and dendritic cells and for eradication and immunotherapy of immune related diseases and other preventable diseases such as chickenpox, cholera, diphtheria, whooping cough, meningococcal disease, hepatitis, Hemophilus influenzae type B (HIB), measles, mumps, rubella, poliomyelitis and tetanus.

In another embodiment the compounds of the invention can be used to mobilize the progenitor/ stem cells preferably towards the site of injury, ischemia, stroke etc. The compounds can be used as cyto-protective agents, cardio-protective agent, neuro-protective agents and regenerative agents that may help host/patient to repair any organ damage, grow organs like muscle, nerve, blood vessel etc and to increase immune cells number.

As used herein, "treatment" includes any effect such as lessening, reducing, modulating and/or eliminating resulting in the improvement of the condition, disease or disorder to be treated.

An appropriate concentration level in treatment is from 0.01 nM to 1 Molar.

The compounds and compositions of the invention may be administered in combination with a variety of pharmaceutical excipients, including stabilizing agents carriers and/or encapsulation formulations known in the art.

In case of treatment of autoimmune and inflammatory diseases, the compounds of the present invention can be used alone or in combination with any suitable adjuvant, non limiting examples of which include, known immunosuppressants such as cyclosporine, tacrolimus, rapamycin, azathioprine, cyclophosphamide, dexamethasone, flunisolide, prednisolone, prednisone, amcinomide desonide, methylprednisolone, triamcinolone and alclometasone.

In case of treatment of infection and or cancer the compounds of the present invention can be administered alone or in any combination with any suitable adjuvant, non limiting examples of which include, other anticancer, antiviral, antibacterial, antifungal, and/or any anti-pathogen agent, a compound which could make a delayed type hypersensitivity response.

During vaccination/s and or immunization/s the molecule/s or compounds of the present invention may be used with T cell, B cell, dendritic cell, antigen, protein, protein conjugate and or like which could be used for such immunization purpose.

**BRIEF DESCRIPTION OF THE FIGURES**

Figure 1 illustrates post-treatment lymphocyte counts

**DETAILED DESCRIPTION OF THE INVENTION**

The terms "compound", "agent", "active agent", "chemical agent", "pharmacologically active agent", "medicament", "active", "molecule" and "drug" are used interchangeably herein to refer to a chemical compound that induces a desired pharmacological and/or physiological effect. The terms also encompasses pharmaceutically acceptable and pharmacologically active ingredients of those active agents/compounds specifically mentioned herein and compounds of the invention including but not limited to salts, esters, amides, prodrugs, active metabolites, analogs and the like. When the terms "compound", "agent", "active agent", "chemical agent" "pharmacologically active agent", "medicament", "active" and "drug" are used, then it is to be understood that this includes the active agent per se as well as pharmaceutically acceptable and/or, pharmacologically active salt/s, esters, amides, prodrug/s, metabolites, analogs and the like.

The terms "effective amount" and "therapeutically effective amount" of an agent/s/compounds and compounds of the invention as used herein mean a sufficient amount of the compound to provide the desired therapeutic or physiological effect or outcome. A practitioner balances the potential benefits against the potential risks in determining what an appropriate "effective amount" is. The exact amount required will vary from subject to subject, depending on the species, age and general condition of the subject, mode of administration and the like.

A "pharmaceutically acceptable" carrier, excipient or diluent may include a pharmaceutical vehicle comprised of a material that may not be biologically active or otherwise undesirable, i.e. the material may be administered to a subject along with the selected active agent without causing any and/or a substantial adverse reaction. Carriers may include excipients and other additives such as diluents, detergents, colouring agents, wetting or emulsifying agents, pH buffering agents, preservatives, and the like.

The compositions and combination therapies of the invention may be administered in combination with a variety of pharmaceutical excipients, including

stabilizing agents, carriers or encapsulation formulations. Effective combinations are those which provide favourable synergistic effect which assist in treatment and/or prevention and/or immunotherapy better than the agents alone.

As used herein, the term "optionally substituted" means that one or more hydrogen atoms may be replaced by a group or groups selected from: -D, -F, -Cl, -Br, -I, -CF<sub>3</sub>, -OH, -OR<sub>7</sub>, -NH<sub>2</sub>, -NHR<sub>7</sub>, -NR<sub>7</sub>R<sub>8</sub>, -CN, -NO<sub>2</sub>, -SH, -SR<sub>7</sub>, -SOR<sub>7</sub>, -SO<sub>2</sub>R<sub>7</sub>, =O, =S, =NOH, =NOR<sub>7</sub>, -NHOH, -NHOR<sub>7</sub>, -CHO, where R<sub>7</sub> and R<sub>8</sub> are independently (C1-C18)alkyl, typically (C1-C12)alkyl; (C3-C18)cycloalkyl, typically (C3-C12)cycloalkyl; (C3-C18)cycloalkyl(C1-C18)alkyl, typically (C3-C12)cycloalkyl(C1-C6)alkyl; (C6-C24)aryl, typically (C6-C16)aryl; (C7-C25)aralkyl, typically (C7-C16)aralkyl; (C2-C18)alkenyl, typically (C2-C12)alkenyl; (C8-C26)aralkenyl, typically (C8-C16)aralkenyl; (C2-C18)alkynyl, typically (C2-C12)alkynyl; (C8-C26)-aralkynyl, typically (C8-C16)aralkynyl; or heterocyclic.

As used herein, the term "alkyl" includes within its meaning straight and branched chain alkyl groups. Examples of such groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, amyl, isoamyl, sec-amyl, 1,2-dimethylpropyl, 1,1-dimethyl-propyl, hexyl, 4-methylpentyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 1,2,2-trimethylpropyl, 1,1,2-trimethylpropyl, heptyl, 5-methylhexyl, 1-methylhexyl, 2,2-dimethylpentyl, 3,3-dimethylpentyl, 4,4-dimethylpentyl, 1,2-dimethylpentyl, 1,3-dimethylpentyl, 1,4-dimethyl-pentyl, 1,2,3-trimethylbutyl, 1,1,2-trimethylbutyl, 1,1,3-trimethylbutyl, octyl, 6-methylheptyl, 1-methylheptyl, 1,1,3,3-tetramethylbutyl, nonyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-methyl-octyl, 1-, 2-, 3-, 4- or 5-ethylheptyl, 1-, 2- or 3-propylhexyl, decyl, 1-, 2-, 3-, 4-, 5-, 6-, 7- or 8-methylnonyl, 1-, 2-, 3-, 4-, 5- or 6-ethyloctyl, 1-, 2-, 3- or 4-propylheptyl, undecyl, 1-, 2-, 3-, 4-, 5-, 6-, 7-, 8- or 9-methyldecyl, 1-, 2-, 3-, 4-, 5, 6- or 7-ethylnonyl, 1-, 2-, 3-, 4- or 5-propyloctyl, 1-, 2- or 3-butylheptyl, 1-pentylhexyl, dodecyl, 1-, 2-, 3-, 4-, 5-, 6-, 7-, 8-, 9- or 10-methylundecyl, 1-, 2-, 3-, 4-, 5-, 6-, 7- or 8-ethyldecyl, 1-, 2-, 3-, 4-, 5- or 6-propylnonyl, 1-, 2-, 3- or 4-butyloctyl, 1- or 2-pentylheptyl, and the like.

As used herein, the term "cycloalkyl" refers to mono- or polycyclic alkyl groups, or alkyl substituted cyclic alkyl groups. Examples of such groups include cyclopropyl, methylcyclopropyl, cyclobutyl, methylcyclobutyl, cyclopentyl, methylcyclopentyl, ethylcyclopentyl, cyclohexyl, methylcyclohexyl,

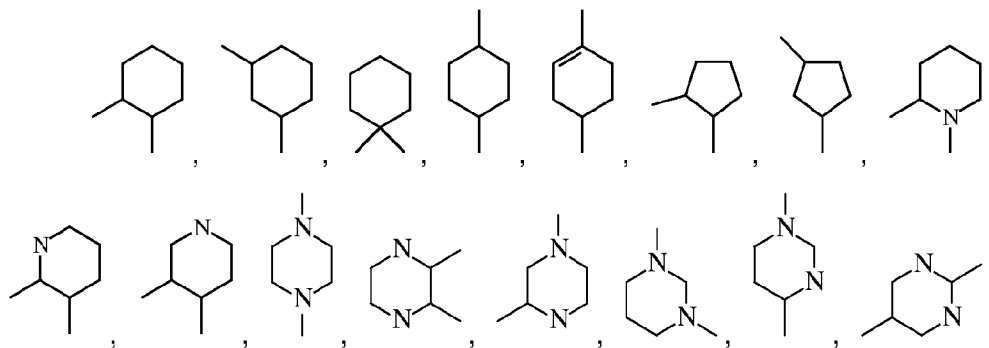
ethylcyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, cycloundecyl, cyclododecyl, decahydronaphthyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, bicyclo[3.3.2]decyl, bicyclo[4.4.3]dodecyl, bicyclo[4.4.0]octyl and the like.

As used herein, the term "cycloalkylalkyl" refers to an alkyl group substituted with a cycloalkyl group as defined above.

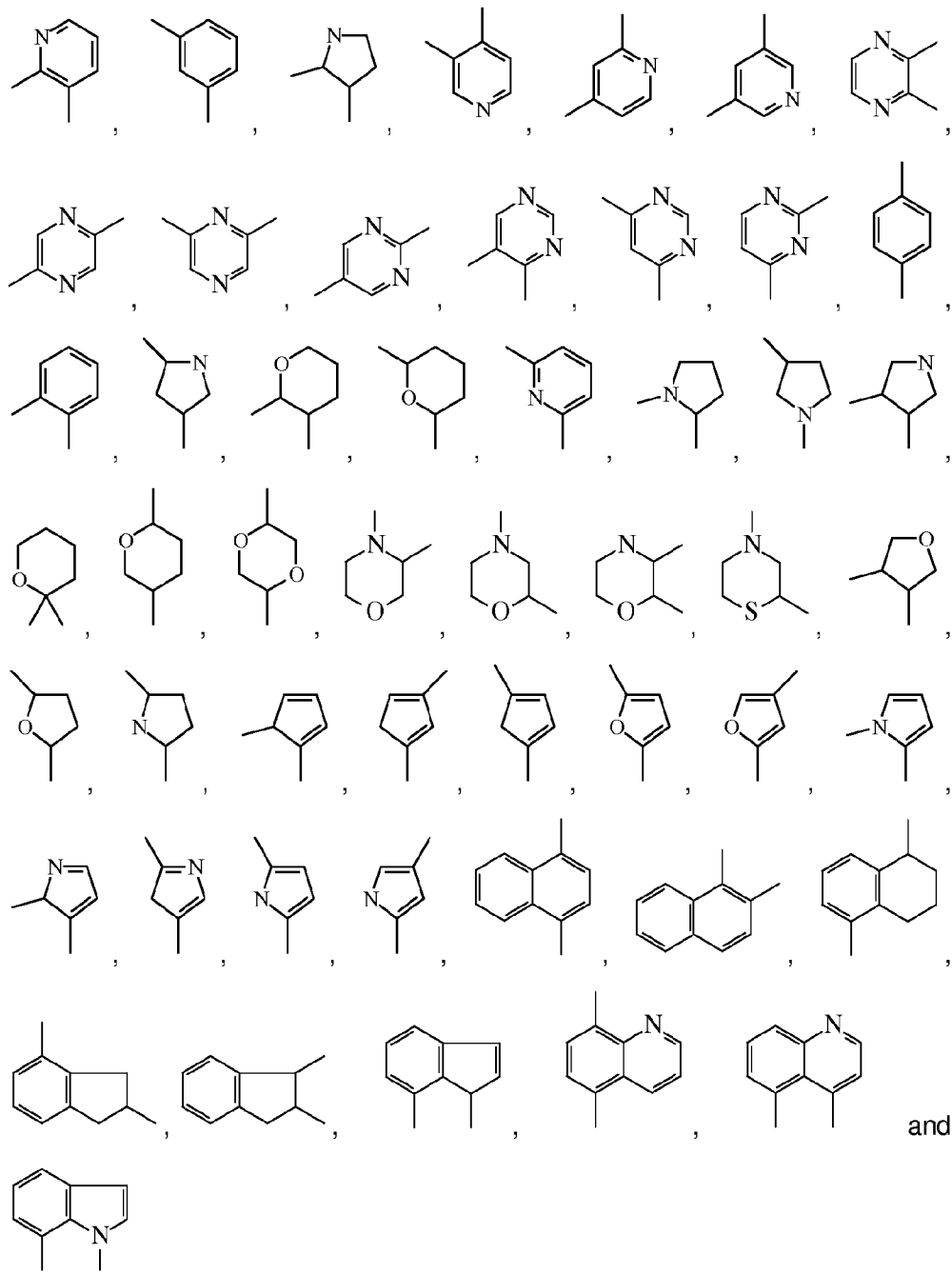
As used herein, the term "alkenyl" includes within its meaning ethylenically mono-, di- or poly-unsaturated alkyl or cycloalkyl groups as previously defined. Examples of such alkenyl groups are vinyl, allyl, 1-methylvinyl, butenyl, isobutenyl, 3-methyl-2-butenyl, 1-pentenyl, cyclopentenyl, 1-methyl-cyclopentenyl, 1-hexenyl, 3-hexenyl, cyclohexenyl, 1-heptenyl, 3-heptenyl, 1-octenyl, cyclooctenyl, 1-nonenyl, 2-nonenyl, 3-nonenyl, 1-decenyl, 3-decenyl, 1,3-butadienyl, 1,4-pentadienyl, 1,3-cyclopentadienyl, 1,3-hexadienyl, 1,4-hexadienyl, 1,3-cyclohexadienyl, 1,4-cyclohexadienyl, 1,3-cycloheptadienyl, 1,3,5-cycloheptatrienyl and 1,3,5,7-cyclooctatetraenyl.

As used herein, the term "alkynyl" includes within its meaning acetylenically unsaturated alkyl groups as previously defined. Examples of such alkynyl groups are ethynyl, propynyl, n-butynyl, n-pentynyl, 3-methyl-1-butynyl, n-hexynyl, methyl-pentynyl, (C7-C12)alkynyl and (C7-C12)cycloalkynyl.

As used herein, the term "alkylidene" refers to optionally unsaturated divalent alkyl radicals. Examples of such radicals are  $-\text{CH}_2-$ ,  $-\text{CH}_2\text{CH}_2-$ ,  $-\text{CH}=\text{CH}-$ ,  $-\text{CH}_2\text{CH}_2\text{CH}_2-$ ,  $-\text{C}(=\text{CH}_2)\text{CH}_2-$ ,  $-\text{CH}_2\text{CH}=\text{CH}-$ ,  $-(\text{CH}_2)_4-$ ,  $-\text{CH}_2\text{CH}_2\text{CH}=\text{CH}-$ ,  $-\text{CH}_2\text{CH}=\text{CHCH}_2-$ , and  $-(\text{CH}_2)_r-$  where  $r$  is 5-8. The term also refers to such radicals in which one or more of the bonds of the radical from part of a cyclic system. Examples of such radicals are groups of the structures



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and similar groups wherein any N or O atom is replaced by S or Se.

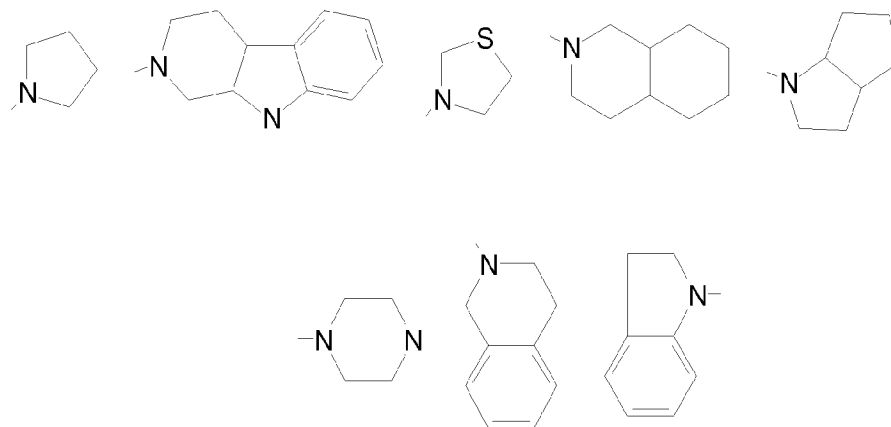
As used herein, the term "aryl" refers to single, polynuclear, conjugated and fused residues of aromatic hydrocarbons or aromatic heterocyclic ring systems. Examples of such groups are phenyl, biphenyl, terphenyl, quaterphenyl, naphthyl, tetrahydronaphthyl, anthracenyl, dihydroanthracenyl, benzanthracenyl, dibenzanthracenyl, phenanthrenyl, fluorenyl, pyrenyl, indenyl,

azulenyl, chrysenyl, pyridyl, 4-phenylpyridyl, 3-phenylpyridyl, thienyl, furyl, pyrrolyl, indolyl, pyridazinyl, pyrazolyl, pyrazinyl, thiazolyl, pyrimidinyl, quinolinyl, isoquinolinyl, benzofuranyl, benzothienyl, purinyl, quinazolinyl, phenazinyl, acridinyl, benzoxazolyl, benzothiazolyl and the like. In all cases, any available position of the fused or conjugated bicyclic system can be used for attachment to the remainder of the molecule of formula (I).

As used herein, the term "aralkyl" refers to alkyl groups substituted with one or more aryl groups as previously defined. Examples of such groups are benzyl, 2-phenylethyl and 1-phenylethyl.

As used herein, the terms "aralkenyl" and "aralkynyl" refer to alkenyl and alkynyl groups respectively, substituted with one or more aryl groups as previously defined. Examples of such groups are styryl, phenylacetylenyl and 2-phenyl-2-butenyl.

As used herein the term "saturated or unsaturated cyclic, bicyclic or fused ring system" refers to a cyclic system of up to 16 carbon atoms, up to 3 of which may be replaced by O, S or N, which ring system may be substituted with one or more of R, -NH<sub>2</sub>, -NHR, -NR<sub>2</sub>, -CHO, -C(O)R, -CN, halo, -CF<sub>3</sub>, -SR, -S(O)R, -S(O)<sub>2</sub>R, -CONH<sub>2</sub>, -CONHR, -CONR<sub>2</sub>, -NHOH, -NHOL, -NO<sub>2</sub>, =O, =S or -NHNH<sub>2</sub>; wherein each R are independently as previously defined. Examples of such ring systems are those cyclic alkylidene groups exemplified above and



As used herein, the term "heterocyclic" refers to any 3- to 16-membered monocyclic, bicyclic or polycyclic ring containing, for 3- and 4-membered rings, one heteroatom; for 5-membered rings, one or two heteroatoms; for 6- and 7-membered rings, one to three heteroatoms; for 8- and 9-membered rings, from

one to four heteroatoms; for 10- and 11-membered rings, from one to five heteroatoms; for 12- and 13-membered rings, from one to six heteroatoms; for 14- and 15-membered rings, from one to seven heteroatoms; and for 16-membered rings, from one to eight heteroatoms; the heteroatom(s) being independently selected from oxygen, nitrogen and sulphur. The term "heterocyclic" includes any group in which a heterocyclic ring is fused to a benzene ring. Examples of heterocyclics are pyrrol, pyrimidinyl, quinolinyl, isoquinolinyl, indolyl, piperidinyl, pyridinyl, furyl, thiophenyl, tetrahydrofuryl, imidazolyl, oxazolyl, thiazolyl, pyrenyl, oxazolidinyl, isoxazolyl, isothiazolyl, isoxazolidinyl, imidazolidinyl, morpholinyl, pyrrolidinyl, pyrazolyl, pyrazolinyl, furfuryl, thienyl, benzothienyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzoisothiazolyl, benzothiadiazolyl, tetrazolyl, triazolyl, thiadiazolyl, benzimidazolyl, pyrrolinyl, quinuclidinyl, azanorbornyl, isoquinuclidinyl and the like. Nitrogen-containing heterocyclics may be substituted at nitrogen with an oxygen atom. Sulfur-containing heterocyclics may be substituted at sulfur with one or two oxygen atoms.

Configurations which result in unstable heterocyclics are not included within the scope of the definition of "heterocyclic" or "saturated or unsaturated cyclic, bicyclic or fused ring system".

As used herein, the term "alkylheterocyclic" refers to a heterocyclic group as defined above, which is substituted with an alkyl group as defined above.

As used herein, the term "heterocyclic-oxy-alkyl" refers to a group of the formula heterocyclic-O-alkyl, wherein the heterocyclic and alkyl are as defined above.

As used herein, the term "alkoxy" refers to a group of the formula alkyl-O-, wherein the alkyl group is as defined above.

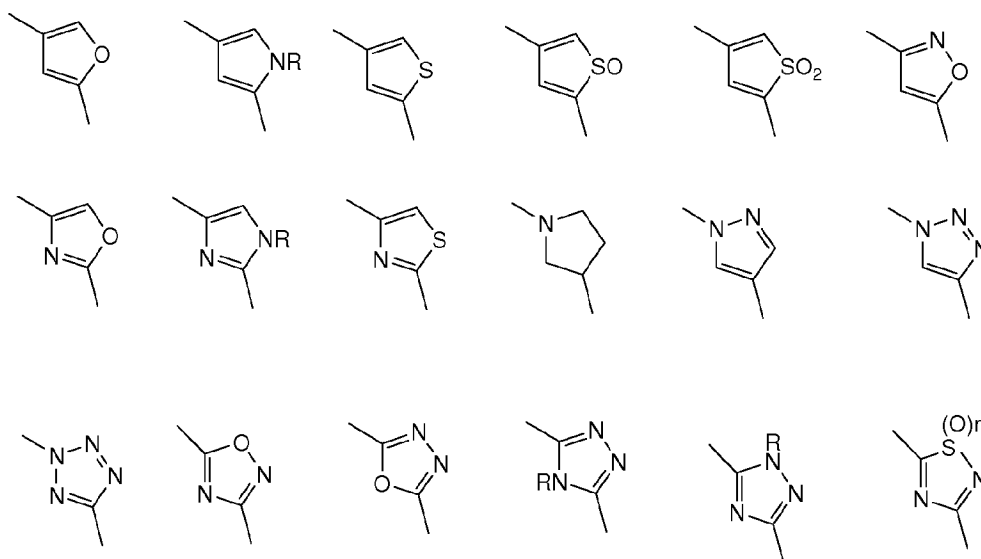
As used herein, the term "aryloxy" refers to a group of the formula aryl-O-, wherein the aryl group is as defined above.

As used herein, the term "alkanoyloxy" refers to a group of the formula alkyl-C(O)O-, wherein the alkyl group is as defined above.

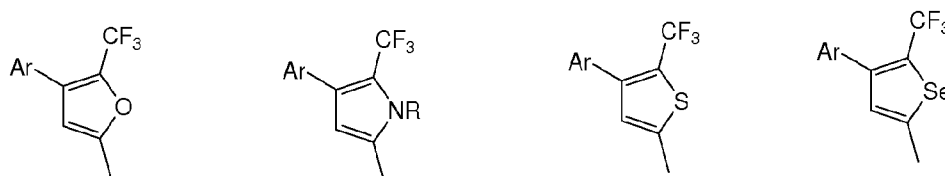
As used herein, the term group (a) refers to five member saturated or unsaturated cyclic or heterocyclic ring systems. Examples of such ring systems are:



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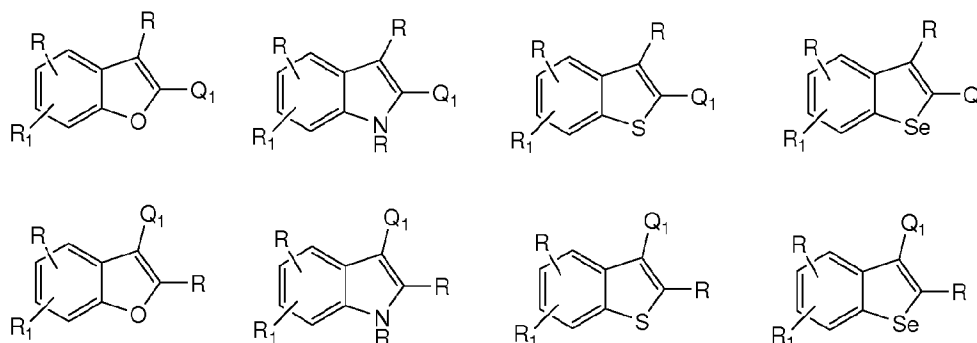


As used herein, the term group (b) refers to five member unsaturated cyclic or heterocyclic ring systems. Examples of such ring systems are:



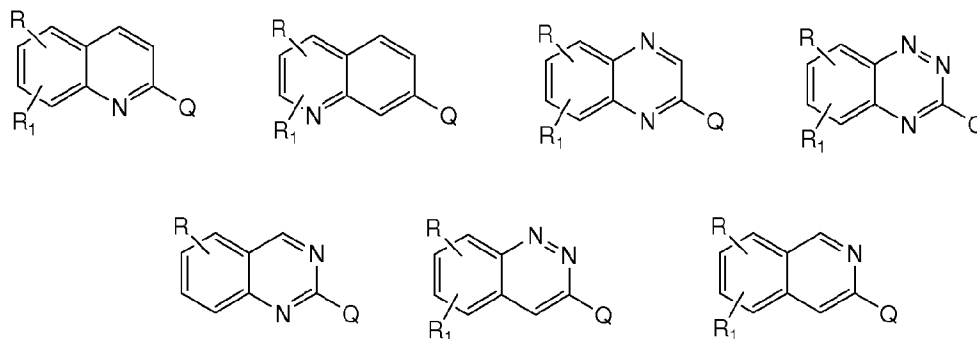
wherein each Ar and R are independently as previously defined and S and Se can be in the oxidized form S(O), S(O)<sub>2</sub> and Se(O) and Se(O)<sub>2</sub> respectively.

As used herein, the term group (c) refers to five-six bicyclic member ring systems. Examples of such ring systems are:



wherein each R, R<sub>1</sub> and Q<sub>1</sub> are independently as previously defined and S and Se can be in the oxidized form such as S(O), S(O)<sub>2</sub> and Se(O) and Se(O)<sub>2</sub> respectively.

As used herein, the term group (d) refers to six-six hetero-bicyclic member ring system. Examples of such ring systems are:

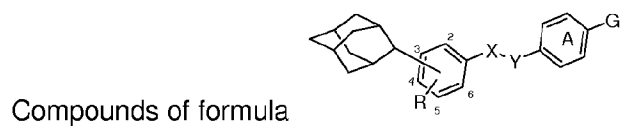


wherein each R, R<sub>1</sub> and Q are independently as previously defined.

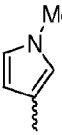
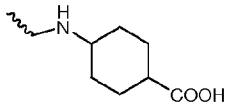
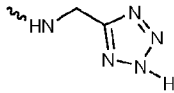
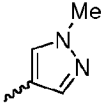

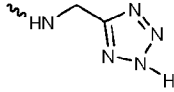
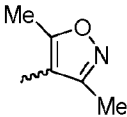


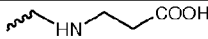
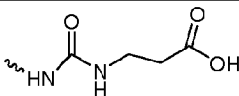


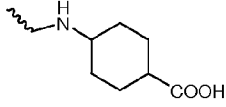

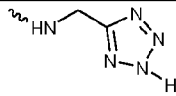
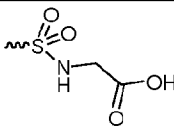
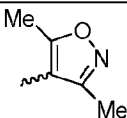
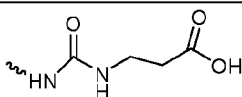
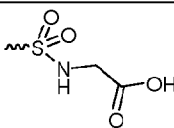
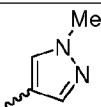
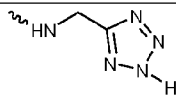
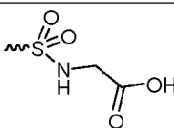
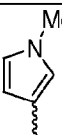
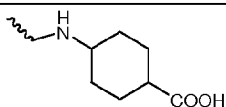

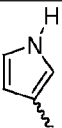
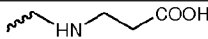
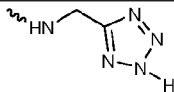
The compound preparations illustrated can be carried out by generally known methods as exemplified hereinafter. The starting materials and intermediates used in the synthesis of compounds of this invention are generally commercially available or may be prepared by conventional methods of organic chemistry. Suitable methods for the synthesis of compounds of this invention and intermediates thereof are described, for example, in Houben-Weyl, *Methoden der Organischen Chemie*; J. March, *Advanced Organic Chemistry*, 3rd Edition (John Wiley & Sons, New York, 1985); D. C. Liotta and M. Volmer, eds, *Organic Syntheses Reaction Guide* (John Wiley & Sons, Inc., New York, 1991); R. C. Larock, *Comprehensive Organic Transformations* (VCH, New York, 1989), H. O. House, *Modern Synthetic Reactions* 2nd Edition (W. A. Benjamin, Inc., Menlo Park, 1972); N. S. Simpkins, ed. *100 Modern Reagents* (The Royal Society of Chemistry, London, 1989); A. H. Haines *Methods for the Oxidation of Organic Compounds* (Academic Press, London, 1988) and B. J. Wakefield *Organolithium Methods* (Academic Press, London, 1988).

Representative compounds in accordance with the invention are described in the following Tables.


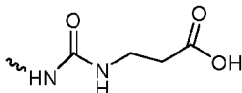
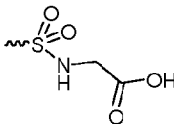

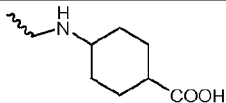


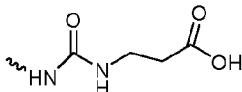
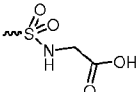



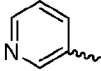
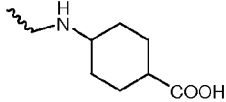
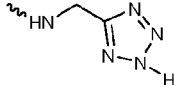

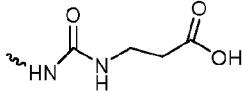

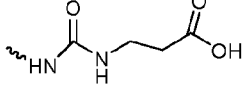
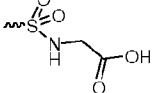
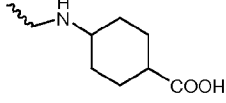

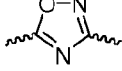

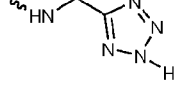
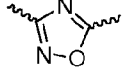
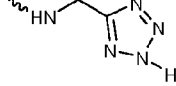
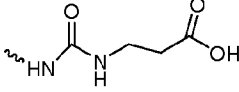
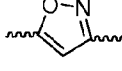
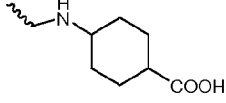
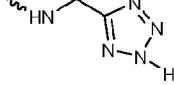
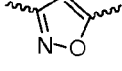
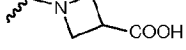
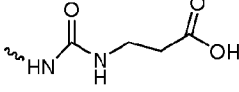
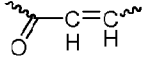

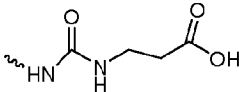
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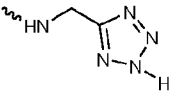
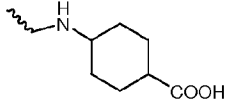
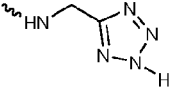

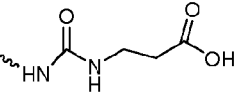

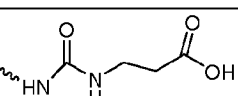
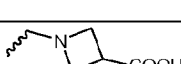
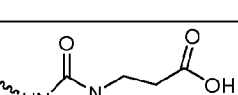
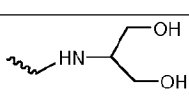
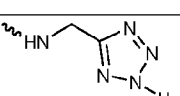
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2	Me	-O-(CH <sub>2</sub> ) <sub>3</sub> -		
3	CH <sub>2</sub> CF <sub>3</sub>	-CH <sub>2</sub> -O-		
4	Ph	-CH <sub>2</sub> -O-		
5		-CH <sub>2</sub> -CH <sub>2</sub>		
6		CH <sub>2</sub> -CH <sub>2</sub> -		
7		-CH <sub>2</sub> -O-		
8		-CH <sub>2</sub> -O-		
9		-CH <sub>2</sub> -O-		
10		-CH <sub>2</sub> -O-		
11		-CH <sub>2</sub> -O-		

S. N.	R	X-Y	G1	G2
12		-CH <sub>2</sub> -O-		
13		-CH <sub>2</sub> -O-		
14		-CH <sub>2</sub> -O-		
15	-CH <sub>2</sub> -CF <sub>3</sub>	-NH-SO <sub>2</sub> -		
16	-CF <sub>3</sub>			
17	-CH <sub>2</sub> -CF <sub>3</sub>	-C≡C-		
18	Me	$\begin{array}{c} \text{—C=C—} \\ \text{H H} \end{array}$		
19		-C≡C-		
20		-C≡C-		
21		-C≡C-		
22		-C≡C-		

25

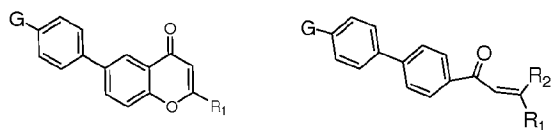
S. N.	R	X-Y	G1	G2
23		$-\text{C}\equiv\text{C}-$		
24		$-\text{C}\equiv\text{C}-$		
25		$-\text{C}\equiv\text{C}-$		
26		$-\text{C}\equiv\text{C}-$		
27		$-\text{C}\equiv\text{C}-$		
28		$-\text{C}\equiv\text{C}-$		
29	OMe	$-\text{CH}_2\text{-O}-$		
30	OCH <sub>2</sub> CF <sub>3</sub>	$-\text{CH}_2\text{-O}-$		
31	OMe			
32	OCH <sub>2</sub> CF <sub>3</sub>			
33	OMe			
34	OMe			
35	OCH <sub>2</sub> CF <sub>3</sub>			


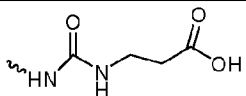
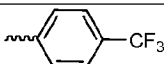
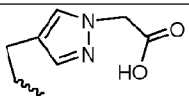
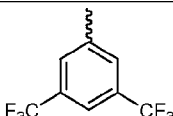
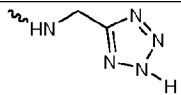
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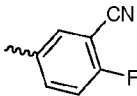

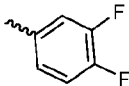


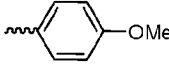

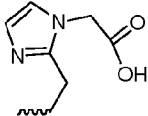


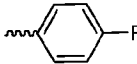

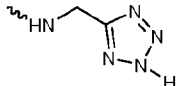
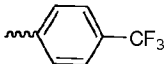

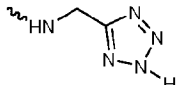
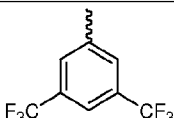





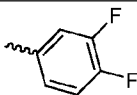

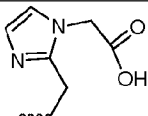
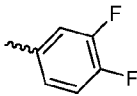

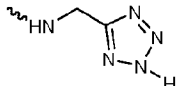




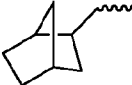

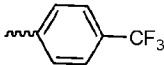
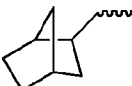
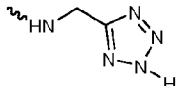
S. N.	R	X-Y	G1	G2
36	CF <sub>3</sub>	-OCH <sub>2</sub> - CH <sub>2</sub> O-		
37	CN	-CH <sub>2</sub> O-		
38	N(Me) <sub>2</sub>	-CH <sub>2</sub> -CH <sub>2</sub> -		
39	OEt	-CH <sub>2</sub> O-		
40	OPr	-CH <sub>2</sub> O-		
41	OPr	-CH <sub>2</sub> O-, -CH <sub>2</sub> CH <sub>2</sub> -		

and variations thereof.

G1 and G2 represent alternative groups for G

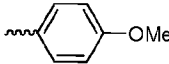
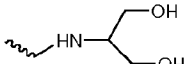

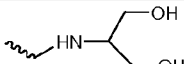
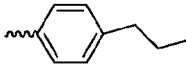
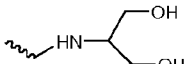
**Table 2:** Compounds of Formula

S. N.	R1	R2	G
1		-CH <sub>3</sub>	
2		-CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	
3		-CH <sub>3</sub>	

S. N.	R1	R2	G
4		-CH3	
5			
6			
7	-CH2CF3	Ph	
8	-Me	Ph	
9			
10			
11			
12			
13			
14			
15			
16			
17			

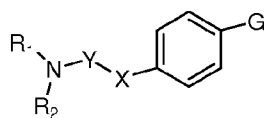
S. N.	R1	R2	G
18			
19			
20			
21			
22			
23			
24			
25			
26		-CH2CF3	
27		-CH2CF3	
28		-CH2CF3	
29		-CH2CF3	
30		-CH2CF3	





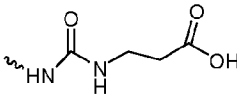
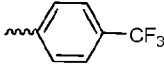

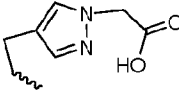
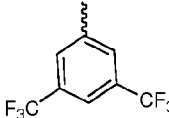

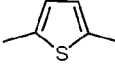
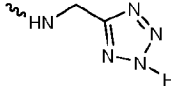
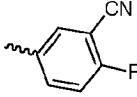


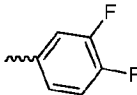


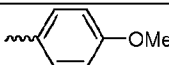

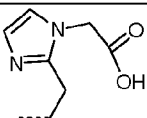
S. N.	R1	R2	G
31		H, Me	
32		H, Me	
33		H, Me	

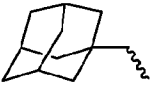

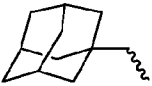
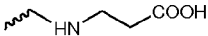


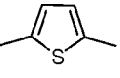
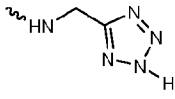
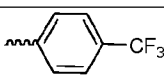

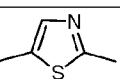
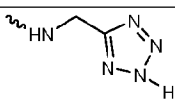
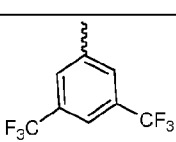

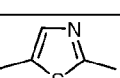
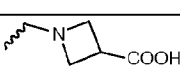
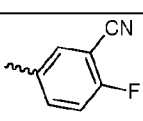

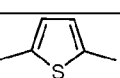

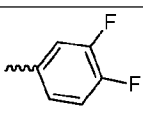

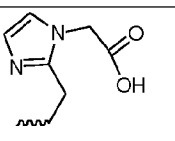
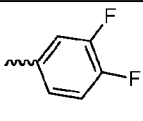

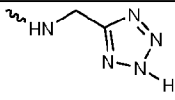
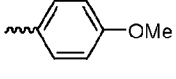

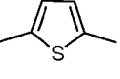
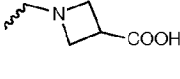
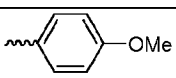
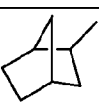
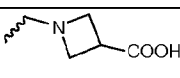
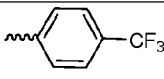
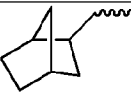
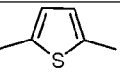
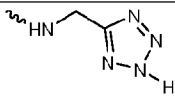
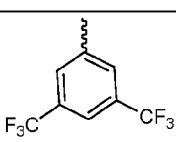
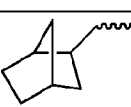
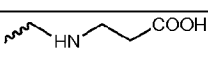
and variations thereof.

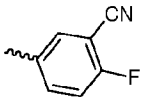
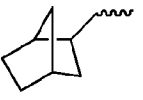
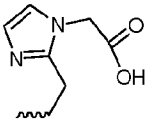
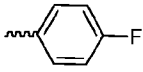
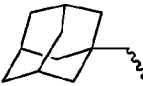
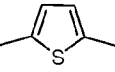

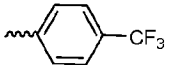
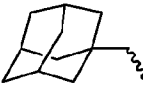
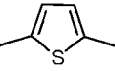
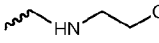
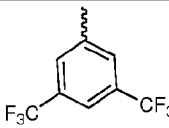

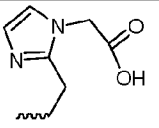
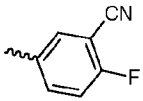
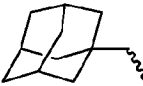
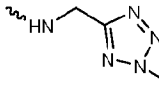
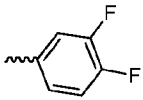
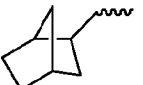
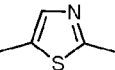
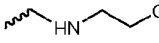
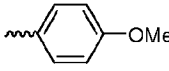

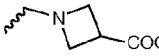
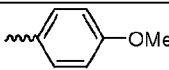
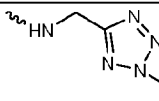
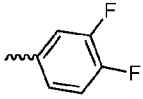
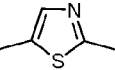
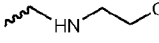
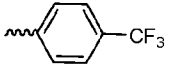
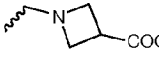
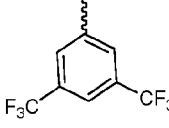
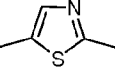
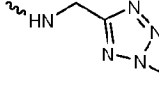
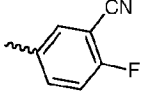
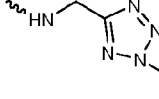
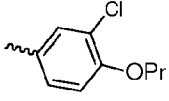
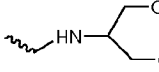
**Table 3:**



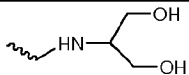
Compounds of formula

S. N.	R1	R2	X	Y	G
1			-CH2-	Ph	
2			CH2	Ph	
3			CH2		
4			-SO2-	Ph	
5			-CO-	Ph	
6			-CH2-	-CH2CH2-	

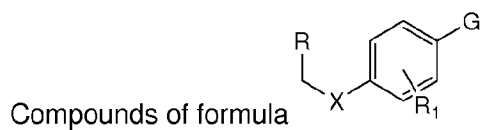
S. N.	R1	R2	X	Y	G
7	-CH <sub>2</sub> CF <sub>3</sub>		-CH <sub>2</sub> -	Ph	
8	-Me		-CH <sub>2</sub> -	Ph	
9			-CH <sub>2</sub> -		
10			-CH <sub>2</sub> -		
11			-CH <sub>2</sub> -		
12			-CO-		
13			-CH <sub>2</sub> -	-CH <sub>2</sub> CH <sub>2</sub> -	
14			-CO-	-CH <sub>2</sub> CH <sub>2</sub> -	
15			-CH <sub>2</sub> -		
16			-CH <sub>2</sub> -	-CH <sub>2</sub> CH <sub>2</sub> -	
17			-CH <sub>2</sub> -		
18			-CH <sub>2</sub> -	-CH <sub>2</sub> CH <sub>2</sub> -	

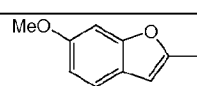
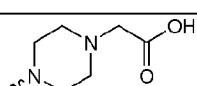
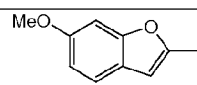
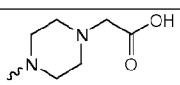
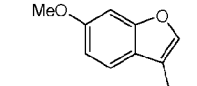
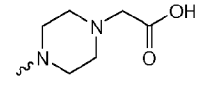
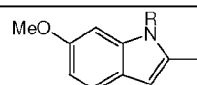
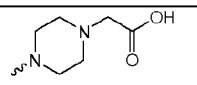
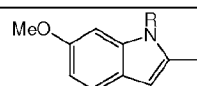
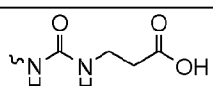
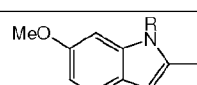
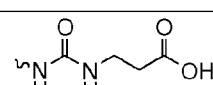
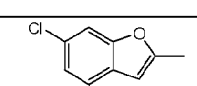

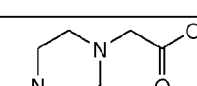
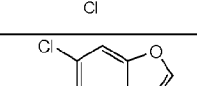
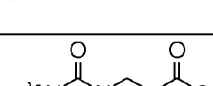
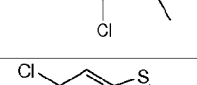
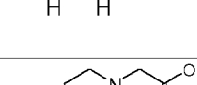
S. N.	R1	R2	X	Y	G
19			-CH2-	-CH2CH2-	
20			-CH2-		
21			-CH2-		
22			-SO2-	Ph	
23			-CH2-	-CH2CH2-	
24			-CH2-		
25			-CH2-	-CH2CH2-	
26		-CH2CF3	-CO-	-CH2CH2-	
27		-CH2CF3	-CH2-		
28		-CH2CF3	-SO2-	Ph	
29		-CH2CF3	-CH2-		
30		-CH2CF3	-CH2-	Ph	
31		Me	-CH2-	-CH2-	

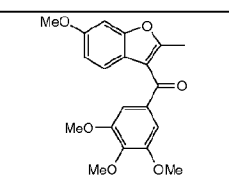
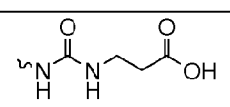
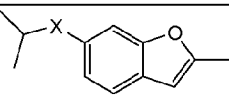
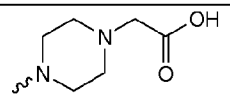
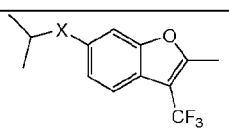
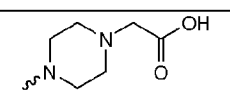
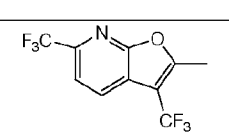
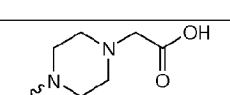
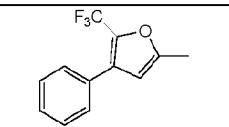
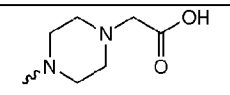
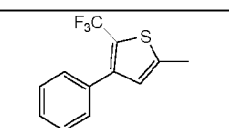
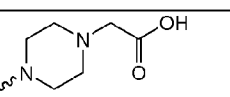
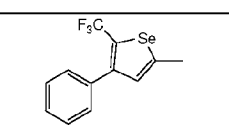
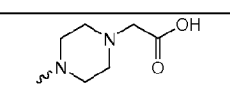
32

S. N.	R1	R2	X	Y	G
32	n-Hexyl	Me	CH2-	CH2-	

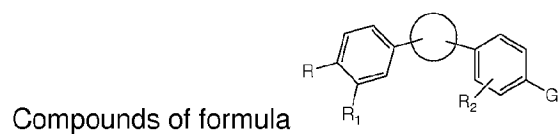
and variations thereof.

**Table 4:**

Compound No.	R	X	R1	G
1		-CH <sub>2</sub> -	H	
2		-CH <sub>2</sub> -	Cl	
3		-CH <sub>2</sub> -	CF <sub>3</sub>	
4		-CH <sub>2</sub> -	CF <sub>3</sub>	
5		-O-	iPr	
6		-S-	H	
7		-O-		
8		-CH <sub>2</sub> -	Me	
9		-O-	H	


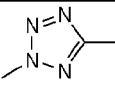
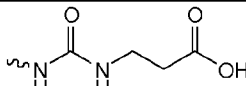
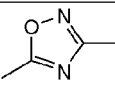

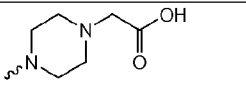
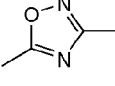
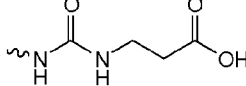
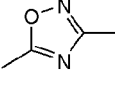
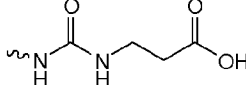
Compound No.	R	X	R1	G
10		-CH <sub>2</sub> -	H	
11		-O-	CF <sub>3</sub>	
12		-O- -CH <sub>2</sub> - -S-	H	
13		-O-	Cl	
14		-O-	F	
15		-O-	CF <sub>3</sub> CF <sub>2</sub>	
16		-O-	F	

and variations thereof.

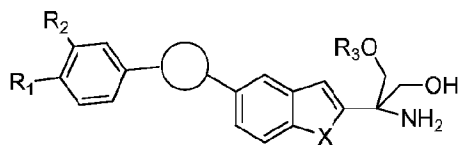
**Table 5:**

Compound No.		R	R1	R2	G
1		iPrO-		H	
2		iPrO-		H	
3		iPrO-		3-CF <sub>3</sub>	
4		MeO-	Cl	3-F	
5		Cl	Cl	2-Me	
6		Me	CF <sub>3</sub>	CF <sub>3</sub>	
7		i-Pr	CF <sub>3</sub>	H	
8		n-Bu	F	3-Cl	
9			Br	H	
10		iPrO-		H	
11		Cl	Cl	2-Me	

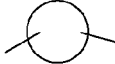
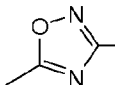
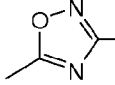
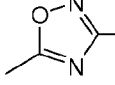
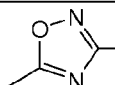
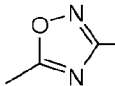
35


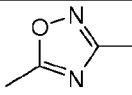
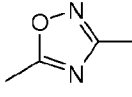
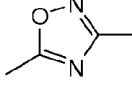
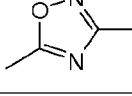
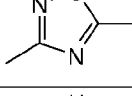
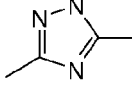
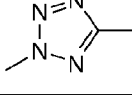
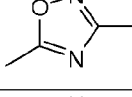
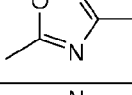
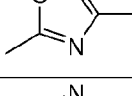
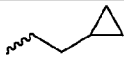
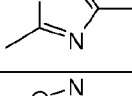

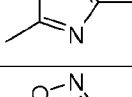
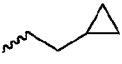
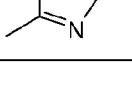
Compound No.		R	R1	R2	G
12		i-Pr	CF <sub>3</sub>	2-Me	
13			CF <sub>3</sub>	H	
14		n-Pr	CN	3-Me	
15		nPr	H	2-isoPr	

and variations thereof.

**Table 6:**

Compounds of formula

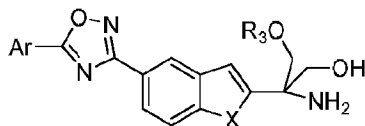
Compound No.		X	R1	R2	R3
1		O	OEt	OEt	H
2		N	OEt	OEt	H
3		O	-OEt	-OEt	-OP(O)(OH) <sub>2</sub> - and or salt of choice
4		O	-OiPr	-Cl	-H
5		S	-O-Et	-OEt	-H

Compound No.		X	R1	R2	R3
6		O	-O-Pr	-OMe	-H
7		O	-OEt	-CN	-H
8		O	-OPr	-CF <sub>3</sub>	-H
9		O	-OPr	-Br	-H
10		O	-OPr	-Me	-H
11		O	-OBut	-H	-H
12		O	-O-pentyl	-H	-H
13		O	-cyclohexyl	-H	-H
14		O	-N(Et) <sub>2</sub>	-H	-H
15		O	-OEt		-H
16		O	-OMe		-H
17		O		-H	-H
18		S	-nPr	-H	-H

and variations thereof.



Table 7:



Compound of formula

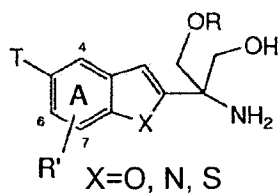
X = O, N, S

Compound No.	Ar	X	R3
1		O	H
2		N	H
3		O	H
4		O	H
5		S	H
6		O	H
7		O	H
8		O	H
9		O	H
10		O	H
11		O	H

Compound No.	Ar	X	R3
12		O	H
13		O	H
14		O	H
15		O	H
16		O	H

and variations thereof.

**Table 8:**



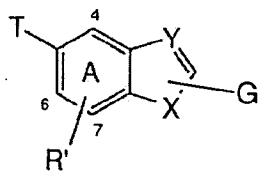
Compound No.	T	R	R'
1		H	6-Cl
2		H	7-isoprpyl
3		H	6-Cl
4		H	H
5		H	7-Me

6		H	7-Et
7		H	
8		H	6-Cl
9		H	6-Cl
10		H	H
11		H	H
12		H	H
13	n-Octyl	H	n-Octyl

And variations thereof.

s represents a ring substituent.

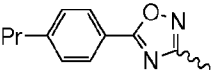
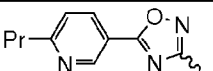
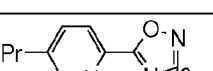
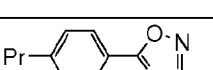
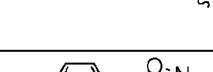
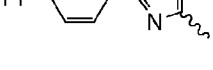
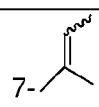
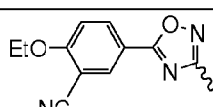
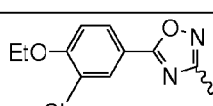
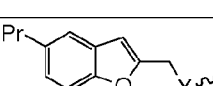
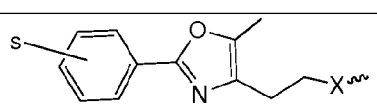
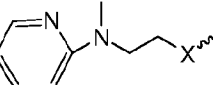
**Table 9:** Compound of formula



X, Y and G are as defined for formula (I).

Compound No.	T	R	R'
1		OH	6-Cl

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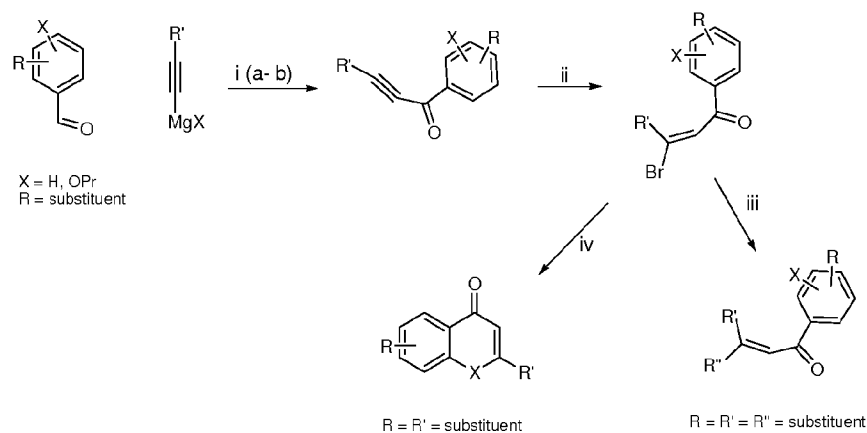
2		OH	7-isoprpyl
3		OH	6-Cl
4		OH	H
5		OH	7-Me
6		OH	7-Et
7		OH	
8		OH	6-Cl
9		OH	6-Cl
10		OH	H
11		OH	H
12		OH	H
13	n-Octyl	OH	n-Octyl

And variations thereof.

s represents a ring substituent.

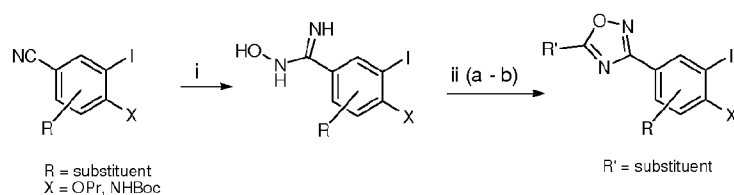
**Methods of Synthesis:**

The examples (28) to (30) were prepared by the use of following procedure as in Scheme - 1



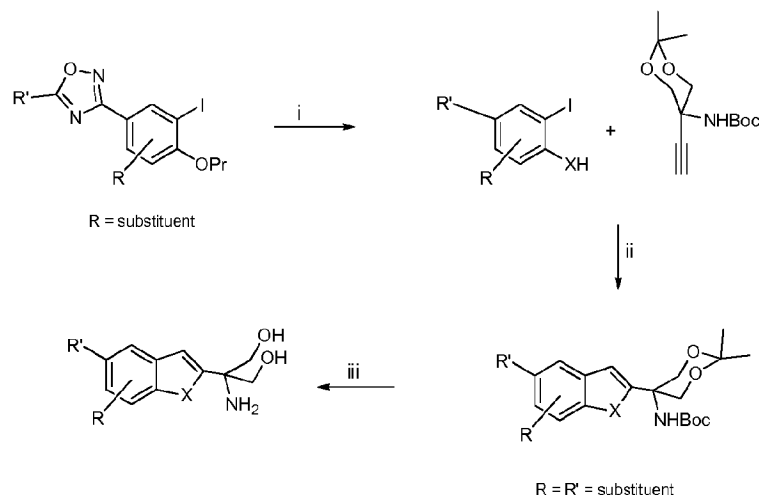
Scheme - 1 (i a) THF, stirring; (i b)  $MnO_2$  /Dioxane reflux; (ii)  $HBr$  /  $AcOH$ ; (iii)  $Pd(PPh_3)_2$ ,  $RB(OH)_2$ ,  $NaHCO_3$  /Dioxane,  $H_2O$ ,  $80^\circ C$  - reflux; (iv)  $K_2CO_3$ .

The examples (36) to (52) were prepared by the use of following procedure as in Scheme – 2 (a – b).



Scheme – 2a (i)  $Na_2CO_3$ ,  $NH_2OH.HCl$  /  $EtOH$  or  $DIEA$ ,  $NH_2OH.HCl$  /  $EtOH$ ; (ii a)  $EDC$  /  $DMF$ ; (ii b)  $TBAF$  /  $DMF$ .

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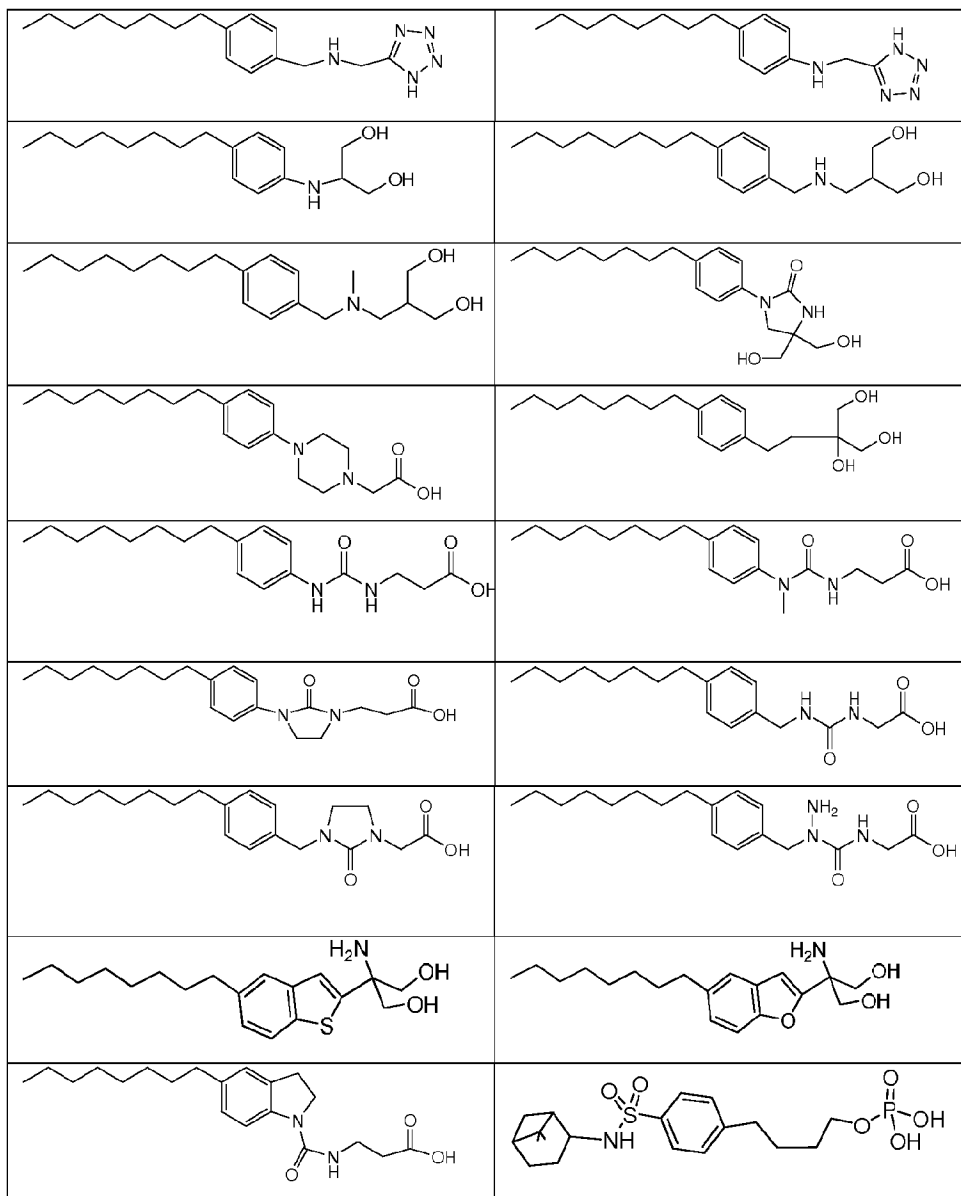


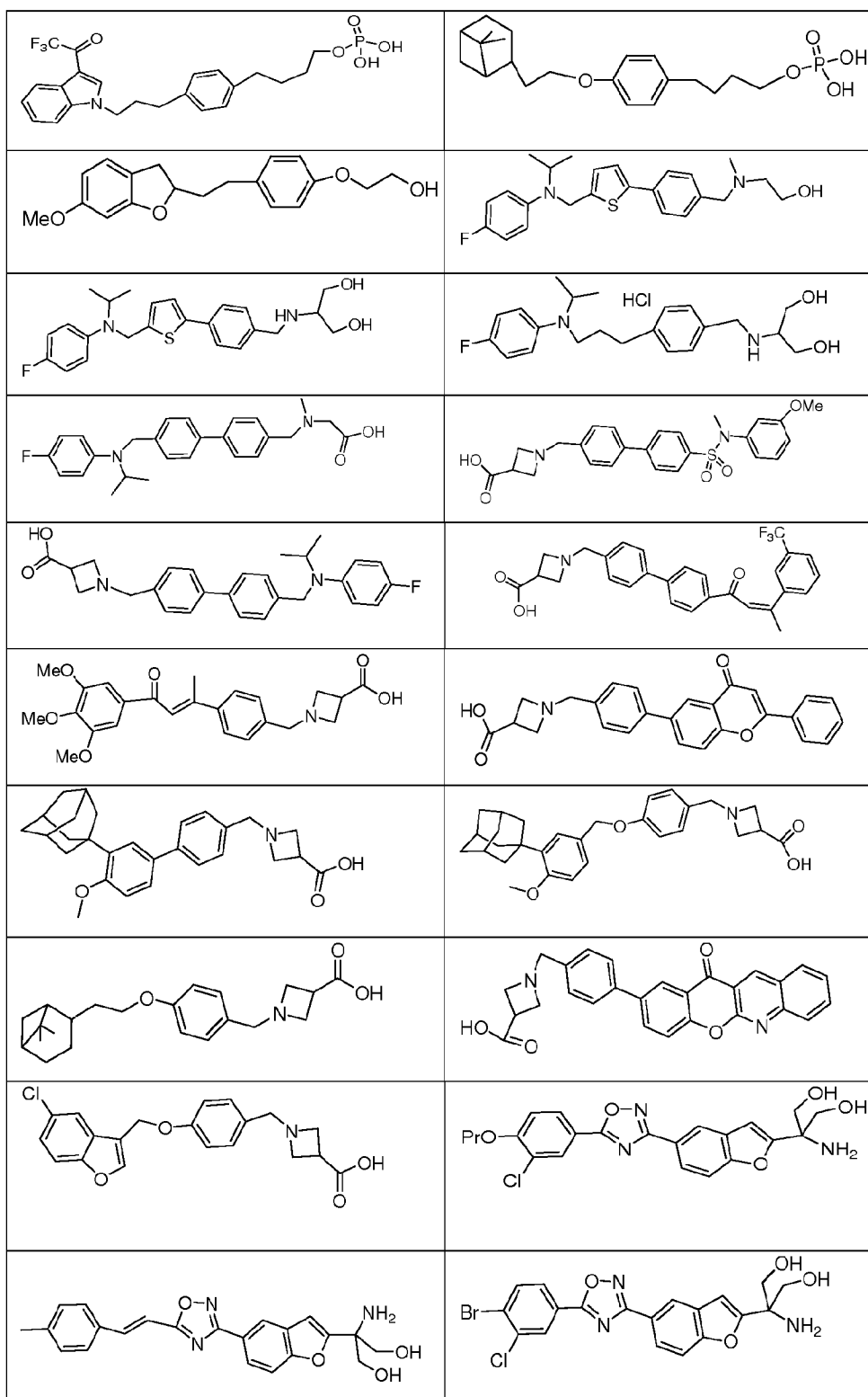
Scheme – 2b (i)  $\text{BCl}_3$ /  $\text{CH}_2\text{Cl}_2$  or  $\text{AlCl}_3$ /  $\text{CH}_2\text{Cl}_2$ ; (ii)  $\text{Cl}_2\text{PdPPh}_3$ /  $\text{CuI}$ ,  $\text{DMF/DIEA}$ ; (iii)  $\text{TFA}$  /  $\text{CH}_2\text{Cl}_2$ .

The other compounds of invention including intermediates were prepared by using various known synthesis methods like reductive amination etc. The compound preparations illustrated can be carried out by generally known methods as exemplified hereinafter. The starting materials and intermediates used in the synthesis of compounds of this invention are generally commercially available or may be prepared by conventional methods of organic chemistry. Suitable methods for the synthesis of compounds of this invention and intermediates thereof are described, for example, in Houben-Weyl, Methoden der Organischen Chemie; J. March, Advanced Organic Chemistry, 3rd Edition (John Wiley & Sons, New York, 1985); D. C. Liotta and M. Volmer, eds, Organic Syntheses Reaction Guide (John Wiley & Sons, Inc., New York, 1991); R. C. Larock, Comprehensive Organic Transformations (VCH, New York, 1989), H. O. House, Modern Synthetic Reactions 2nd Edition (W. A. Benjamin, Inc., Menlo Park, 1972); N. S. Simpkins, ed. 100 Modern Reagents (The Royal Society of Chemistry, London, 1989); A. H. Haines Methods for the Oxidation of Organic Compounds (Academic Press, London, 1988) and B. J. Wakefield Organolithium Methods (Academic Press, London, 1988). Some important Lit ref are Kim S et al, Synthesis, 2006, 5, 753 – 755.

**EXAMPLES**

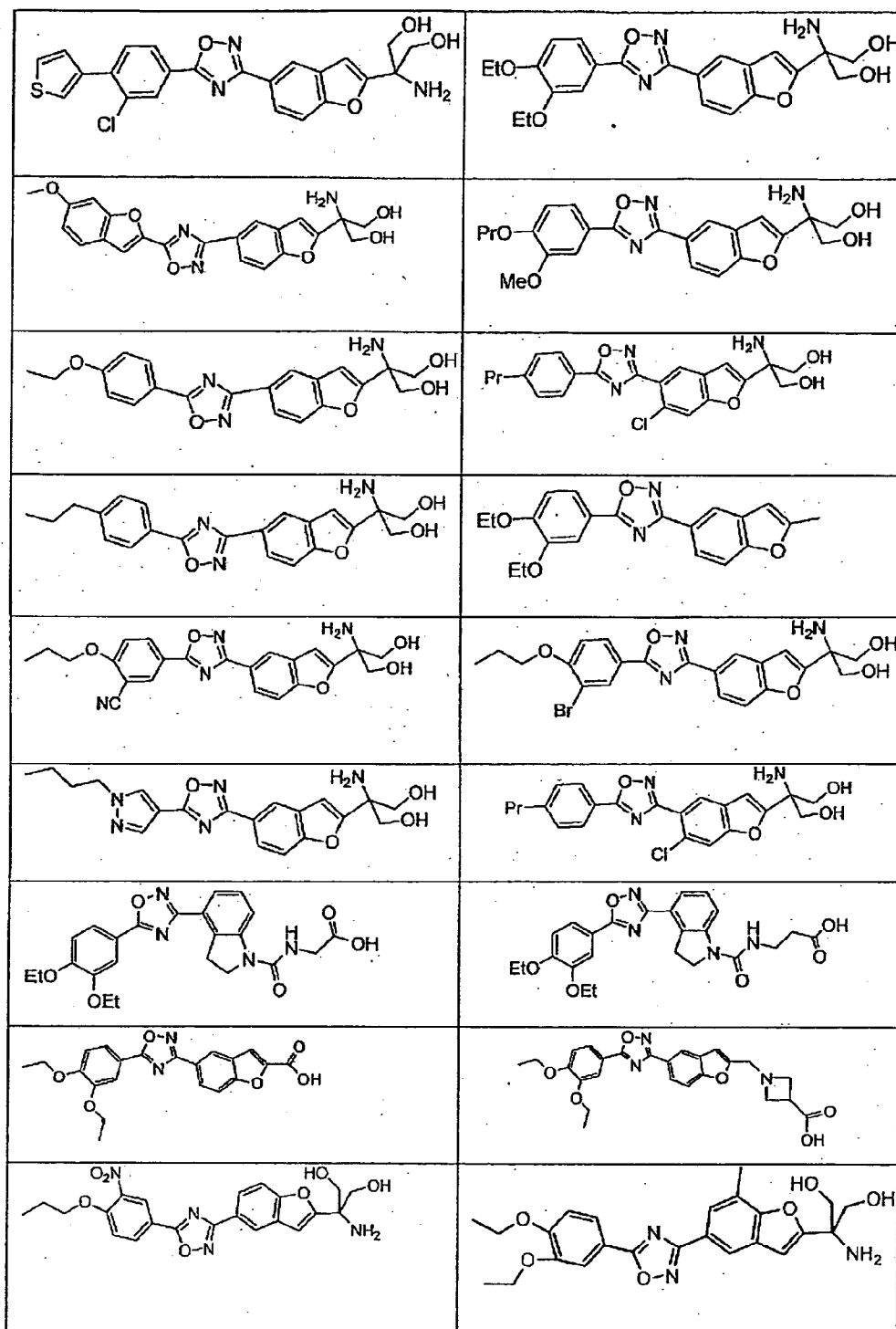
The following Examples describe the preparation of compounds according to the invention and are intended to illustrate the invention. The Examples are not be construed as limiting in any way the scope of the present invention. Proton NMR spectra were recorded at 300MHz on a Bruker EM 300 spectrometer in CDCl<sub>3</sub> unless otherwise stated. Chemical shifts for proton NMR are ppm downfield from tetramethylsilane.



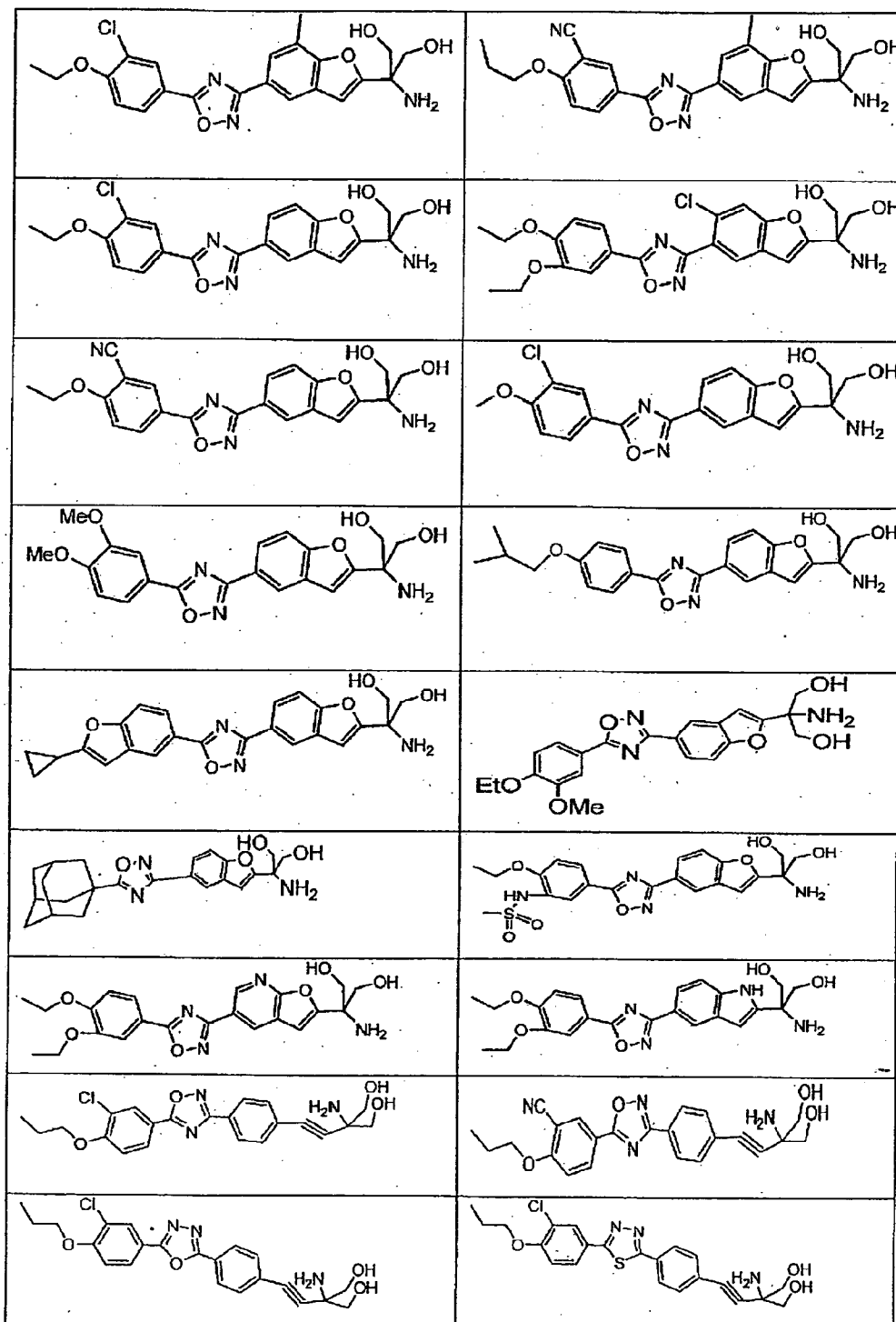




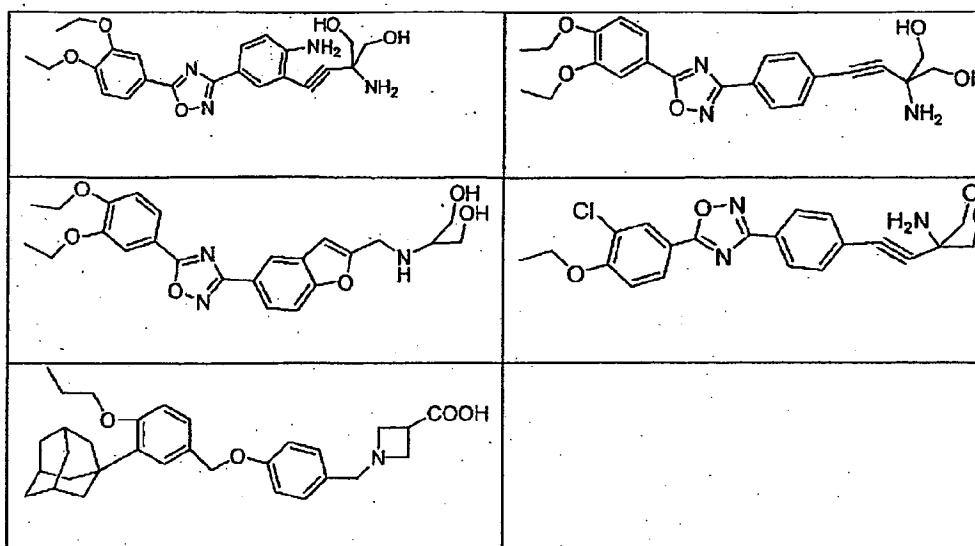
45



45/1



45/2

**Example 1****5-(5-(3,4-Diethoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-carboxylic acid**

5      *Step A: Step A: 4-Hydroxy-3-iodobenzonitrile:* To a solution of 4-hydroxybenzonitrile (0.5 g; 4.18 mmol) in 25%  $\text{NH}_4\text{OH}$  (22 ml) a solution of  $\text{I}_2$  (1.06 g; 4.18 mmol) and KI (3.41 g; 20.54 mmol) in  $\text{H}_2\text{O}$  (5 ml) was added at once with stirring. The stirring was continued for 6 h, during which time the mixture turn from black into colourless. The precipitate formed was filtered off and filtrate was

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evaporated to dryness under reduced pressure. The residue was treated with H<sub>2</sub>O (3 ml). The precipitate formed was filtered off, washed with cold H<sub>2</sub>O (3 x 2 ml), and dried *in vacuo* to give the title compound (0.82 g; 80%), as colourless solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 7.96 (d, 1H, 1.9 Hz); 7.53 (dd, 1H, J = 1.9 Hz, 8.5 Hz); 7.03 (d, 1H, J = 8.5 Hz); 6.03 (s, 1H);

*Step B: 2-(Hydroxymethyl)benzofuran-5-carbonitrile:* Propargyl alcohol (0.24 ml; 5.2 mmol) was added drop wise during 30 min to a refluxed suspension of the product of Step A (0.48 g; 1.96 mmol) and Cu<sub>2</sub>O (0.28 g; 1.96 mmol) in anhydrous pyridine (4 ml) with stirring under N<sub>2</sub>. After additional reflux for 15 min, the mixture was cooled to room temperature, diluted to 20 ml with ethyl acetate (EtOAc) and insoluble material was removed by filtration. The filtrate was evaporated to dryness under reduced pressure and the residue was diluted to 20 ml with EtOAc, washed with diluted HCl (10 ml). The insoluble material formed was filtered off and the organic phase was washed with H<sub>2</sub>O (5 ml), brine, dried over anhydrous MgSO<sub>4</sub>, filtered and the filtrate evaporated to dryness. The residue was purified by flash column chromatography (FCC) (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub> and EtOAc, 9 : 1) to give the title compound (0.23 g; 67%) as a colourless solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 7.86 (m, 1H); 7.49 – 7.55 (m, 2H); 6.72 (d, 1H, J = 3 Hz); 4.8 (d, 2H, J = 3 Hz); 2.18 (broad s, 1H);

*Step C: N-Hydroxy-2-(hydroxymethyl)benzofuran-5-carboximidamide:* A mixture of the product of Step B (0.22 g; 1.27 mmol) and HCl x NH<sub>2</sub>OH (0.18 g; 2.59 mmol) and N,N-diisopropylethylamine (DIPEA) (0.67 ml; 3.82 mmol) in ethanol (EtOH) (2 ml) was stirred for 3 h at ~ 71 °C. The solvents were removed *in vacuo* and the residue was treated with H<sub>2</sub>O (3 ml) and the product was taken up by EtOAc (3 x 15 ml). The combined organic phase was washed with brine, dried over anhydrous MgSO<sub>4</sub>, filtered and filtrate evaporated to dryness to give the title compound (0.2 g; 76%), as colourless solid, which was used in the next step without further purification.

*Step D: (5-(5-(3,4-Diethoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)methanol:* A mixture of 3,4-diethoxybenzoic acid (0.21 g; 1 mmol), the product of Step C (0.2 g; 0.97 mmol) and hydrochloride salt of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) (0.22 g; 1.15 mmol) in anhydrous dimethylsulfoxide (DMSO) (2 ml) was stirred for 20 min at ~ 40°C under N<sub>2</sub>. To it 1 M tetra-n-butylammonium fluoride (TBAF) in tetrahydrofuran (THF) (0.4 ml) was

added and the resulting mixture was stirred for 1 h at ~ 120 °C, then overnight at room temperature. The solvents were removed in vacuo and the residue was partitioned between EtOAc (15 ml) and H<sub>2</sub>O (5 ml). The organic phase was washed with brine, dried over anhydrous MgSO<sub>4</sub> and filtered. The filtrate was evaporated to dryness under reduced pressure and the residue was purified by FCC (SiO<sub>2</sub>; CH<sub>2</sub>Cl<sub>2</sub>) to give the title compound (0.13 g; 34%), as greyish solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.36 (d, 1H, J = 3 Hz); 8.09 (dd, 1H, J = 3, 9 Hz); 7.79 (dd, 1H, J = 3, 9 Hz); 7.68 (d, 1H, J = 3 Hz); 7.55 (d, 1H, J = 9 Hz); 6.98 (d, 1H, J = 9 Hz); 6.73 (s, 1H); 4.8 (s, 2H); 4.2 (m, 4H); 2.02 (s, 1H); 1.51 (m, 6H);

*Step E: 5-(5-(3,4-Diethoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-carbaldehyde:* A suspension of the product of Step D (0.13 g; 0.34 mmol) and MnO<sub>2</sub> (0.15 g; 1.7 mmol) in dioxane (4 ml) was refluxed for 1 h with stirring. After cooling to room temperature, the insoluble material was removed by filtration, washed with EtOAc (20 ml) and combined filtrates were evaporated to dryness to give the title compound (0.13 g; 100%), as greyish solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 9.91 (s, 1H); 8.59 (s, 1H); 8.33 (dd, 1H, J = 2, 9 Hz); 7.63 – 7.82 (m, 4H); 6.99 (d, 1H, J = 9 Hz); 4.14 – 4.26 (m, 4H); 1.4 – 1.57 (m, 6H + H<sub>2</sub>O).

*Step F: 5-(5-(3,4-Diethoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-carboxylic acid:* To a suspension of the product of Step E (0.009 g; 0.024 mmol) and AgNO<sub>3</sub> (0.06 g; 0.14 mmol) in EtOH (0.2 ml) H<sub>2</sub>O (0.1 ml) was added at room temperature, followed by 10% KOH (0.1 ml). The resulting black suspension was stirred for 1h at ~ 50 °C and cooled to room temperature and filtered. The insoluble material was washed with H<sub>2</sub>O (2 x 0.2 ml). The combined filtrates were acidified to pH = 1 with HCl and the product was taken up by extraction with EtOAc (2 x 5 ml). The organic phase was washed with brine, dried over anhydrous MgSO<sub>4</sub>, filtered and filtrate evaporated to dryness. The residue was purified by FCC (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/ acetic acid (AcOH) 98/2) to give the title compound (0.00012 g; 12.8 %), as a creamy solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub> + CD<sub>3</sub>OD) 8.48 (s, 1H); 8.22 (m, 1H); 7.77 (m, 1H); 7.64 – 7.66 (m, 2H); 7.58 (s, 1H); 6.96 (d, 1H, J = 6 Hz); 4.19 (m, 4H); 1.4 – 1.54 (m, 6H).

**Example 2****1-((5-(5-(3,4-Diethoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)methyl)azetidine-3-carboxylic acid**

*Step A: Methyl 1-((5-(5-(3,4-diethoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)methyl)azetidine-3-carboxylate:* A mixture the product of Example 1, Step E (0.07 g; 0.85 mmol), azetidine-3-methylcarboxylate hydrochloride (0.03 g; 0.199 mmol) and DIPEA (0.035 ml, 0.2 mmol) in 1,2-dichloroethane (1 ml) and methanol (MeOH) (3 ml) was sonicated for 30 min at room temperature, then evaporated to dryness. The yellowish residue was suspended in 1,2-dichloroethane (1 ml) and NaBH(OAc)<sub>3</sub> (0.12 g; 0.57 mmol) was added, followed by AcOH (0.01 ml). This was stirred for 1 h at room temperature and diluted to 15 ml with EtOAc, washed with 10% KOH (2 x 3 ml); brine, dried over anhydrous MgSO<sub>4</sub>, filtered and the filtrate evaporated to dryness. The residue was purified by FCC (SiO<sub>2</sub>, EtOAc) to give the title compound (0.06 g; 68%), as creamy syrup. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.33 (d, 1H, J = 3 Hz); 8.06 (dd, 1H, J = 3, 9 Hz); 7.78 (dd, 1H, J = 3, 9 Hz); 6.87 (d, 1H, J = 2 Hz); 6.63 (s, 1H); 4.14 – 4.22 (m, 4H); 3.6 – 3.7 (m, 5H); 3.48 – 3.34 (m, 2H); 1.49 (m, 6H).

*Step B: 1-((5-(5-(3,4-Diethoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)methyl)azetidine-3-carboxylic acid:* A mixture of the product of Step A (0.06 g; 0.126 mmol) and 10 % KOH (0.1 ml) in dioxane (2 ml) was refluxed for 1 h and solvents were evaporated to dryness. The residue was treated with AcOH (0.5 ml) and evaporated to dryness *in vacuo*. The residue was purified by FCC (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub> saturated with concentrated NH<sub>4</sub>OH and MeOH, 85 : 15) to give the title compound (0.032 g; 55%), as a colourless solid. <sup>1</sup>H-NMR (CD<sub>3</sub>OD + CDCl<sub>3</sub>) 8.37 (d, 1H, J = 3 Hz); 8.09 (dd, 1H, J = 3, 6 Hz); 7.77 (dd, 1H, J = 3, 9 Hz); 7.68 (s, 1H); 7.6 (d, 1H, J = 9 Hz); 7.02 – 7.07 (m, 2H); 4.38 (s, 2H); 4.05 – 4.21 (m, 8H); 1.44 – 1.49 (m, 6H).

**Example 3****N-(1H-Tetrazol-5-yl)methyl-4-octylbenzylamine**

*Step A: 4-n-Octylbenzaldehyde:* A mixture of n-octylbenzene (1.2 g; 6.3 mmol) hexamethylenetetramine (0.97 g; 6.93 mmol) in trifluoroacetic acid (TFA) was refluxed for 4 h, cooled to room temperature and evaporated to dryness under reduced pressure. The residue was neutralized with 5% NaHCO<sub>3</sub> and

extracted with diethyl ether ( $\text{Et}_2\text{O}$ ) (3 x 5ml). The combined organic phase was washed with  $\text{H}_2\text{O}$ , brine, dried over anhydrous  $\text{MgSO}_4$  and filtered. The filtrate was evaporated under reduced pressure and the residue was purified by FCC ( $\text{SiO}_2$ , hexane) to give the title compound (0.4 g; 29%) as a colourless oil and starting n-octylbenzene (0.8 g; 67 %).  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) 9.96 (s, 1H); 7.77 (d, 2H,  $J = 8.1$  Hz); 7.31 (d, 2H,  $J = 8.1$  Hz); 2.67 (t, 2H,  $J = 7.9$  Hz); 1.6 (m, 2H); 1.26 (m, 10H); 0.86 (t, 3H,  $J = 6.9$  Hz);

*Step B: 2-(4-Octylbenzylamino)acetonitrile:* To a suspension of the product of Step A (0.17 g; 0.78 mmol) and aminoacetonitrile bisulphate (0.18 g; 1.17 mmol) and  $\text{NaBH}(\text{OAc})_3$  in 1,2 dichloroethane (3 ml), DIPEA (0.2 ml; 1.17 mmol) was added at room temperature followed by AcOH (0.045 ml; 0.78 mmol). The resulting mixture was stirred over a weekend at room temperature under  $\text{N}_2$  and quenched by an addition of 1 M NaOH (0.5 ml). This was diluted to 15 ml with  $\text{Et}_2\text{O}$ , washed with  $\text{H}_2\text{O}$ , brine, dried over anhydrous  $\text{MgSO}_4$  and filtered. The filtrate was evaporated to dryness under reduced pressure and the residue was diluted to 3 ml with anhydrous MeOH and to it  $\text{NaBH}_4$  (0.1 g; 2.6 mmol) was added portion wise at room temperature with stirring. After stirring overnight, the mixture was evaporated to dryness and the residue was diluted to 15 ml with  $\text{Et}_2\text{O}$ , washed with 1N NaOH,  $\text{H}_2\text{O}$ , brine, dried over anhydrous  $\text{MgSO}_4$  and filtered. The filtrate was evaporated under reduced pressure and the residue was purified by FCC ( $\text{SiO}_2$ , hexane/ $\text{EtOAc}$  6:4) to give the title compound (0.07 g; 28%) as a colourless syrup.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) 7.23 (d, 2H,  $J = 8.01$  Hz); 7.14 (d, 2H,  $J = 8.01$  Hz); 3.88 (s, 2H); 3.55 (s, 2H); 2.58 (t, 2H,  $J = 7.94$  Hz); 1.6 (m, 3H); 1.27 (m, 10H); 0.86 (t, 3H,  $J = 6.93$  Hz).

*Step C: N-(1H-Tetrazol-5-yl)methyl-4-n-octylbenzylamine:* A mixture of the product of Step B (0.07 g; 0.271 mmol) and  $\text{Me}_3\text{SiN}_3$  (0.36 ml; 2.71 mmol) and 1M TBAF in THF (0.27 ml; 0.271 mmol) was stirred at  $75 \pm 5^\circ\text{C}$  for 8 h in sealed flask. After cooling to room temperature, the mixture was diluted to 1 ml with MeOH, refluxed for 30 min under  $\text{N}_2$  and left overnight in refrigerator. The precipitate formed was filtered off, washed with  $\text{Et}_2\text{O}$  and dried to give a title compound (0.069 g; 84%) as colourless solid.  $^1\text{H-NMR}$  ( $\text{CD}_3\text{OD}$ ) 7.32 (d, 2H,  $J = 8.0$  Hz); 7.21 (d, 2H,  $J = 8.0$  Hz); 4.72 (s,  $\text{CD}_3\text{OH}$ ); 4.34 (s, 2H); 4.16 (s, 2H); 2.59 (t, 2H,  $J = 7.76$  Hz); 1.57 (t, 2H,  $J = 7.19$  Hz); 1.25 (m, 10H); 0.84 (t, 3H,  $J = 6.93$  Hz);

**Example 4****N-((1H-Tetrazol-5-yl)methyl)-4-n-octylaniline**

*Step A: 2-(4-Octylphenylamino)acetonitrile:* A mixture of 4-n-octylaniline (0.21 g; 1 mmol), BrCH<sub>2</sub>CN (0.156 mmol; 1.3 mmol) and K<sub>2</sub>CO<sub>3</sub> (0.28 g; 2 mmol) in anhydrous CH<sub>3</sub>CN (3 ml) was stirred overnight at ~60 °C under N<sub>2</sub>, then concentrated under reduced pressure. The residue was partitioned between CH<sub>2</sub>Cl<sub>2</sub> (20 ml) and H<sub>2</sub>O (10 ml). The organic phase was dried over anhydrous MgSO<sub>4</sub> and filtered. The filtrate was evaporated to dryness under reduced pressure and the residue was purified by crystallization from hexane to give the title compound (0.18 g; 74%) as creamy solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 7.06 (d, 2H, J = 8.48 Hz); 6.63 (d, 2H, J = 8.48 Hz); 4.06 (d, 2H, J = 5.75 Hz); 3.83 (broad m, 1H); 2.51 (t, 2H, J = 7.92 Hz); 1.55 (m, 3H); 1.27 (m, 10H); 0.86 (t, 3H, J = 6.87 Hz).

*Step B: N-((1H-Tetrazol-5-yl)methyl)-4-n-octylaniline:* When the product of Step A was substituted for 2-(4-octylbenzylamino)acetonitrile in Example 3, Step C, the identical process afforded the title compound in 77% yield, as creamy solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 6.94 (d, 2H, J = 8.37 Hz); 6.61 (broad s, 2H); 6.49 (d, 2H, J = 8.37 Hz); 4.68 (m, 2H); 2.44 (t, 2H, J = 7.94 Hz); 1.49 (t, 2H, J = 7.55 Hz); 1.24 (m, 10H); 0.85 (t, 3H, J = 6.95 Hz).

**Example 5****2-(4-Octylphenylamino)propane-1,3-diol**

*Step A: 2,2-Dimethyl-N-(4-octylphenyl)-1,3-dioxan-5-amine:* To a mixture of 4-n-octylaniline (0.205 g; 1 mmol) and 2,2-dimethyl-1,3-dioxan-5-one (Helvetica Chimica Acta, 2003, 86, 2467; 0.13 g; 1 mmol) and NaBH(OAc)<sub>3</sub> in 1,2-dichloroethane (3.5 ml), AcOH (0.06 ml; 1 mmol) was added and the mixture was stirred for 2h at room temperature under N<sub>2</sub>, diluted to 20 ml with Et<sub>2</sub>O and washed with 1N NaOH, H<sub>2</sub>O, brine, dried over anhydrous MgSO<sub>4</sub> and filtered. The filtrate was evaporated under reduced pressure and the residue was purified by crystallization from hexane to give the title compound (0.2 g; 63%) as a colourless solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 6.97 (d, 2H, J = 8.4 Hz); 6.54 (d, 2H, J = 8.4 Hz); 4.1 (dd, broad s, 3H, J = 4.2, 11.9 Hz); 3.74 (dd, 2H, J = 4.2, 11.9 Hz); 3.4 (m, 1H); 2.47 (t, 2H, J = 7.91 Hz); 1.55 (m, 2H + H<sub>2</sub>O); 1.46 (s, 3H); 1.43 (s, 3H); 1.25 (m, 10H); 0.86 (m, 3H).



*Step B: 2-(4-octylphenylamino)propane-1,3-diol:* To a solution of the product of Step A (0.1 g; 0.31 mmol) in MeOH (1 ml) Me<sub>3</sub>SiCl (0.5 ml) was added at room temperature. After stirring for 1 h, the mixture was evaporated to dryness under reduced pressure to give a hydrochloride salt of the title compound (0.1 g; 100 %) as a colourless solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 10.66 (bs, 2H); 7.53 (d, 2H, J = 7.98 Hz); 7.18 (d, 2H, J = 7.98 Hz); 4.82 (broad s, 2H); 3.98 (broad m, 4H); 3.51 (broad m, 1H); 2.58 (t, 2H, J = 7.68 Hz); 1.56 (m, 2H); 1.43 (s, 3H); 1.27 (m, 10H); 0.86 (t, 3H, J = 6.96 Hz).

### Example 6

#### 2-((4-n-Octylbenzylamino)methyl)propane-1,3-diol

*Step A: 4-n-Octylbenzyl alcohol:* NaBH<sub>4</sub> (0.04 g; 1.06 mmol) was added portion wise to a solution of the product of Example 3, Step A in MeOH (5 ml) at room temperature, with vigorous stirring. After 30 min of stirring, the mixture was evaporated to dryness, diluted to 10 ml with Et<sub>2</sub>O and washed with 1N NaOH, H<sub>2</sub>O, brine, dried over anhydrous MgSO<sub>4</sub> and filtered. The filtrate was evaporated under reduced pressure to give the title compound (0.082 g; 100%), as colourless syrup, which was used in next step without further purification. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 7.26 (d, 2H, J = 8 Hz); 7.15 (d, 2H, J = 8 Hz); 4.64 (s, 2H); 2.58 (t, 2H, J = 7.9 Hz); 1.56 (m, 3H); 1.26 (m, 10H); 0.86 (t, 3H, J = 6.9 Hz).

*Step B: 4-n-octylbenzyl bromide:* PBr<sub>3</sub> (0.23 ml) was added drop wise to a stirred solution of the product of Step A (0.082 g; 0.37 mmol) in Et<sub>2</sub>O (2 ml) at -15°C. The mixture was allowed to warm up to room temperature and the stirring was continued for 4 h. This was poured onto ice (5 g) and the product was extracted with fresh Et<sub>2</sub>O (2 x 10 ml). The combined extracts were washed with 5%NaHCO<sub>3</sub>, H<sub>2</sub>O, brine, dried over anhydrous MgSO<sub>4</sub> and filtered. The filtrate was evaporated under reduced pressure and the residue was purified by FCC (SiO<sub>2</sub>, hexane) to give the title compound (0.04 g; 40%) as a colourless solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 7.28 (d, 2H, J = 8 Hz); 7.13 (d, 2H, J = 8 Hz); 4.48 (s, 2H); 2.57 (t, 2H, J = 7.9 Hz); 1.57 (m, 2H); 1.26 (m, 10H); 0.86 (t, 3H, J = 7 Hz).

*Step C: 4-n-Octylbenzylamine:* To a solution of the product of Step B (0.13 g; 0.459 mmol) in anhydrous hexamethylenedisilazane (HMDSA) 1M NaHMDSA in THF was added at room temperature under N<sub>2</sub> with stirring. After stirring overnight at room temperature solvents were removed under reduced pressure

and the residue was diluted to 5 ml with MeOH and 1 drop of concentrated HCl was added. This was evaporated under reduced pressure, diluted to 15 ml with Et<sub>2</sub>O and washed with 1N NaOH, brine, dried over anhydrous MgSO<sub>4</sub> and filtered. The filtrate was evaporated under reduced pressure to give the title compound (0.1 g; 100%), as colourless oil, which was used in the next step without further purification. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 7.2 (d, 2H, J = 8 Hz); 7.13 (d, 2H, J = 8 Hz); 3.82 (s, 2H); 2.57 (t, 2H, J = 7.9 Hz); 1.58 (m, 2H); 1.41 (s, 2H); 1.26 (m, 10H); 0.86 (t, 3H, J = 7 Hz).

*Step D: (2,2-Dimethyl-1,3-dioxan-5-yl)-N-(4-octylbenzyl)methylamine:*

When the product of Step C was substituted for 4-n-octylaniline in Example 5, Step A, the identical process afforded the title compound in 86% yield, as a colourless syrup. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 7.23 (d, 2H, J = 8 Hz); 7.11 (d, 2H, J = 8 Hz); 3.96 (dd, 2H, J = 5.57, 11.73 Hz); 11.73 Hz); 3.83 (s, 2H); 3.75 (dd, 2H, J = 5.57, 2.69 (m, 1H); 2.56 (t, 2H, J = 7.88 Hz); 1.81 (broad s, 1H + H<sub>2</sub>O); 1.4 (m, 5H); 1.25 (m, 13H); 0.86 (t, 3H, J = 6.96 Hz).

*Step E: 2-((4-n-Octylbenzylamino)methyl)propane-1,3-diol:* A solution of the product of Step D (0.6 g; 0.13 mmol) in 60% trifluoroacetic acid (TFA) in CH<sub>2</sub>Cl<sub>2</sub> (2 ml) was stirred for 15 min at room temperature and the mixture was diluted to 5 ml with MeOH and evaporated to dryness under reduced pressure. The residue was dissolved in iso-propanol (iPrOH) (2 ml) and one drop of concentrated HCl was added. This was evaporated under reduced pressure and treated with anhydrous Et<sub>2</sub>O. The precipitate formed was filtered off, dried *in vacuo* for 1 h to give a hydrochloride salt of the title compound (0.04 g; 85%), as a colourless solid. <sup>1</sup>H-NMR (D<sub>2</sub>O) 7.32 (d, 2H, J = 7.56 Hz); 7.21 (d, 2H, J = 7.56 Hz); 4.2 (s, 2H); 4.66 (DHO); 3.69 (s, 4H); 3.36 (s, 2H); 2.52 (t, 2H, J = 7.47 Hz); 1.49 (s, 2H); 1.16 (m, 10H); 0.74 (m, 3H).

## Example 7

### 2-((Methyl(4-octylbenzyl)amino)methyl)propane-1,3-diol

*Step A: (2,2-dimethyl-1,3-dioxan-5-yl)-N-methyl-N-(4-octylbenzyl)methylamine:* When the product of Example 6, Step D is substituted for 4-n-octylaniline and 30% aqueous HCHO is substituted for 2,2-dimethyl-1,3-dioxan-5-one in Example 3, Step A, the identical process afforded the title compound in 100% yield, as a colourless syrup. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 7.2 (d, 2H, J = 7.75 Hz); 7.11 (d,

2H,  $J = 7.75$  Hz); 3.83 (s, 2H); 3.94 (m, 4H); 3.64 (s, 2H); 2.83 (m, 1H); 2.56 (d, 2H,  $J = 7.3$  Hz); 2.29 (s, 3H); 1.58 (m, 2H + H<sub>2</sub>O); 1.25 – 1.42 (m, 18H); 0.86 (m, 3H).

*Step B: 2-((Methyl(4-octylbenzyl)amino)methyl)propane-1,3-diol:* When the product of Step A is substituted for (2,2-dimethyl-1,3-dioxan-5-yl)-N-(4-octylbenzyl) methylamine in Example 6, Step E, the identical process afforded the title compound in 79% yield, as a glassy solid. <sup>1</sup>H-NMR (D<sub>2</sub>O) 7.3 (d, 2H,  $J = 7.8$  Hz); 6.96 (d, 2H,  $J = 7.8$  Hz); 4.66 (DHO); 4.24 (s, 2H); 3.73 (m, 4H); 3.32 (m, 1H); 2.7 (s, 3H); 2.3 (t, 2H,  $J = 7.63$  Hz); 1.36 (m, 2H); 1.15 (s, 2H); 1.15 (m, 10H); 0.73 (t, 3H,  $J = 6.73$  Hz).

### Example 8

#### 4,4-Bis(hydroxymethyl)-1-(4-octylphenyl)imidazolidin-2-one

*Step A: tert-Butyl 2,2-dimethyl-5-((4-octylphenylamino)methyl)-1,3-dioxan-5-ylcarbamate:* To a mixture of 4-n-octylaniline (0.21 g; 1 mmol), tert-butyl 5-formyl-2,2-dimethyl-1,3-dioxan-5-ylcarbamate (Ooii et al, J.Org.Chem., 2004, 69, 7765; 0.26 g; 1 mmol) and NaBH(OAc)<sub>3</sub> (0.3g; 1.4 mmol) in 1,2-dichloroethane (3.5 ml) AcOH (.06 ml; 1 mmol) was added at room temperature with stirring under N<sub>2</sub>. After stirring for 2 h, the mixture was diluted to 20 ml with Et<sub>2</sub>O, washed with 1.M NaOH (2 x 5 ml), brine and dried over anhydrous MgSO<sub>4</sub> and filtered. The filtrate was evaporated to dryness under reduced pressure. The residue was dissolved in hexane (5 ml) and kept in the freezer (-18°C) overnight. The crystals formed were filtered off, washed with small volume of hexane and dried to give the title compound (0.32g; 71%), as colourless crystals. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 6.96 (d, 2H,  $J = 8.4$  Hz); 6.58(d, 2H,  $J = 8.4$  Hz); 4.84 (broad s, 1H); 4.01(d, 2H,  $J = 11.9$ ); 3.85 (broad s, 1H); 3.8 (d, 2H,  $J = 11.9$  Hz); 3.44 (s, 2H); 2.46 (t, 2H,  $J = 7.9$  Hz); 1.5(m, 2H); 1.45(s, 3H); 1.43 (s, 9H); 1.42 (s, 3H); 1.26 (m, 10H); 0.86 (t, 2H,  $J = 6.95$  Hz).

*Step B: 4,4-(2,2-Dimethyl-1,3-dioxanyl)-1-(4-octylphenyl)imidazolidin-2-one:* A solution of the product of Step A (0.17 g; 0.38 mmol) and 60% NaH in mineral oil (0.043 g; 1.14 mmol) in anhydrous DMF (4 ml) was stirred overnight at ~55°C under N<sub>2</sub>. After removal of solvent *in vacuo*, the residue was diluted to 15 ml with Et<sub>2</sub>O, washed with 10% citric acid, H<sub>2</sub>O, brine, dried over anhydrous MgSO<sub>4</sub> and filtered. The filtrate was evaporated under reduced pressure and the

residue was purified by FCC (SiO<sub>2</sub>, hexane/EtOAc 8:2) to give the title compound (0.06 g; 42%) as a colourless solid and starting material (0.1 g; 58 %). <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 7.41 (d, 2H, J = 8.58 Hz); 7.12 (d, 2H, J = 8.58 Hz); 5.27 (broad s, 1H); 3.84 (d, 2H, J = 11.3 Hz); 3.78 (d, 2H, J = 11.3 Hz); 3.68 (s, 2H); 2.55 (t, 2H, J = 7.83 Hz); 1.56 (m, 2H); 1.28 (m, 10H); 0.84 (t, 3H, J = 6.76 Hz).

*Step C: 4,4-Bis(hydroxymethyl)-1-(4-octylphenyl)imidazolidin-2-one:* When the product of Step B is substituted for (2,2-dimethyl-1,3-dioxan-5-yl)-N-(4-octylbenzyl)methylamine in Example 6, Step E, the identical process afforded the title compound in 74% yield, as a colourless solid, after purification by FCC (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub> saturated with concentrated NH<sub>4</sub>OH/MeOH; 98:2). <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 7.30 (d, 2H, J = 8.49 Hz); 7.02 (d, 2H, J = 8.49 Hz); 6.53 (s, 1H); 4.65 (broad s, 2H); 3.48 -3.62 (m, 6H); 2.47 (t, 2H, J = 7.94 Hz); 1.51 (m, 2H); 1.25 (m, 10H); 0.87 (t, 3H, J = 6.94 Hz).

## Example 9

### 2-(4-(4-n-Octylphenyl)piperazin-1-yl)acetic acid

*Step A: 4-n-Octyliodobenzene:* To a suspension of n-octylbenzene (1 g; 5.2 mmol) and CF<sub>3</sub>SO<sub>3</sub>Ag (1.35 g; 5.2 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (15 ml) I<sub>2</sub> was added at 0 °C. The resulting mixture was allowed to warm up to room temperature and stirred for additional 1h, then filtered through a pad of Celite, washed with fresh CH<sub>2</sub>Cl<sub>2</sub> (2 x 15 ml) and combined filtrates washed with 5% Na<sub>2</sub>SO<sub>3</sub>, H<sub>2</sub>O, brine, dried over anhydrous MgSO<sub>4</sub> and filtered. The filtrate was evaporated under reduced pressure to give the title product and 2-iodo isomer (1.64 g; 100%), as creamy oil, which was used in the next step without further purification. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 7.7 – 7.8 (m, 0.3H); 7.56 (d, 1.7 H, J = 8.3 Hz); 7.29 -7.16 (m, 0.6H); 6.9 (d, 1.4H, J = 8.3 Hz); 6.85 – 6.82 (m, 0.3H); 2.68 (t, 0.6, J = 8.01 Hz); 2.52 (t, 1.4H, J = 7.89 Hz); 1.56 (m, 2H); 1.25 (m, 10H); 0.86 (m, 3H).

*Step B: tert-Butyl 4-(benzoyloxy)piperazine-1-carboxylate:* To a suspension of benzoyl peroxide + 15% H<sub>2</sub>O (1.47 g; 4.55 mmol) and K<sub>2</sub>HPO<sub>4</sub> (1.19 g; 6.8 mmol) in DMF (11.36 ml) N-BOC piperazine (Sengmany et al, Tetrahedron, 2007, 63, 3672; 1 g; 5.4 mmol) was added and the mixture was stirred for 1 h at room temperature. To it, H<sub>2</sub>O (20 ml) was added and the resulting mixture was vigorously stirred until homogenous. This was extracted with EtOAc (15 ml). The organic phase was washed with H<sub>2</sub>O and combined

aqueous phase was extracted with fresh EtOAc (3 x 10 ml). The combined organic phase was washed with H<sub>2</sub>O, brine, dried over anhydrous MgSO<sub>4</sub> and filtered. The filtrate was evaporated under reduced pressure to give the title product (0.9 g; 65%), as a colourless solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8 - 7.96 (m, 2H); 7.59 – 7.53 (m, 1H); 7.45 – 7.38 (m, 2H); 4.01 (m, 2H); 3.41 – 3.2 (m, 4H); 2.9 (m, 2H); 1.46 (s, 9H).

*Step C: tert-Butyl 4-(4-octylphenyl)piperazine-1-carboxylate:* To a solution of the product of Step A (0.32 g; 1.01 mmol) in anhydrous THF (2 ml) 2 M iPrMgCl in THF (0.56 ml; 1.11 mmol) was added at -15 °C under N<sub>2</sub>, followed 1.27 M solution of anhydrous ZnCl<sub>2</sub> in THF (0.41 ml; 0.52 mmol), after stirring for 1 h at 0°C. The resulting mixture was stirred for 30 min on ice-bath under N<sub>2</sub> and the solution of the product of Step B (0.16 g; 0.51 mmol) and CuCl<sub>2</sub> (2.5 mol%) in anhydrous THF (10 ml) was added. The resulting mixture was allowed to warm up to room temperature and stirred for additional 10 min. This was diluted to 20 ml with Et<sub>2</sub>O and washed with 5% NaHCO<sub>3</sub>, H<sub>2</sub>O, brine, dried over anhydrous MgSO<sub>4</sub> and filtered. The filtrate was evaporated under reduced pressure and the residue was purified by FCC (SiO<sub>2</sub>, hexane/EtOAc 9:1) to give the title compound (0.06 g; 31%), as a creamy syrup. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 7.07 (d, 2H, J = 8.6 Hz); 6.84 (d, 2H, J = 8.6 Hz); 3.55 (t, 4H, J = 5 Hz); 3.06 (t, 4H, J = 5 Hz); 2.51 (t, 2H, J = 7.94 Hz); 1.55 – 1.38 (m, 11H); 1.26 (m, 10H); 0.86 (t, 3H, J = 6.93 Hz).

*Step D: 1-(4-n-Octylphenyl)piperazine:* A solution of the product of Step C (0.06 g; 0.16 mmol) in 60% TFA in CH<sub>2</sub>Cl<sub>2</sub> (2 ml) was stirred for 15 min at room temperature and the mixture was diluted to 5 ml with EtOH and evaporated to dryness under reduced pressure and kept in vacuo for 1h, to give a TFA salt of the title compound (0.07 g; 100%). <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 9.5 (broad s, 2H); 7.29 (m, 4H); 3.8 – 3.16 (m, 8H); 2.6 (t, 2H, J = 8 Hz); 1.58 (m, 2H); 1.26 (m, 10H); 0.86 (t, 3H, J = 6.9 Hz).

*Step E: tert-Butyl 2-(4-(4-octylphenyl)piperazin-1-yl)acetate:* To a solution of the product of Step D (0.04 g, 0.146 mmol) and tert-butyl bromoacetate (0.026 ml; 0.16 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1 ml) DIPEA (0.052 ml; 0.32 mmol) was added at room temperature under N<sub>2</sub>. The mixture was stirred overnight at room temperature, diluted to 5 ml with Et<sub>2</sub>O and washed with 0.1 N HCl, H<sub>2</sub>O, brine, dried over anhydrous MgSO<sub>4</sub> and filtered. The filtrate was evaporated under reduced pressure and the residue was purified by FCC (SiO<sub>2</sub>, hexane/EtOAc 7:3)

to give the title compound (0.05 g; 88%), as a colourless heavy syrup.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) 7.05 (d, 2H,  $J = 8.6$  Hz); 6.83 (d, 2H,  $J = 8.6$  Hz); 3.32 – 3.15 (m, 6H); 2.73 (m, 4H); 2.5 (t, 2H,  $J = 7.9$  Hz); 1.55 (m, 2H); 1.46 (s, 9H); 1.26 (m, 10H); 0.86 (m, 3H).

*Step F: 2-(4-(4-*n*-Octylphenyl)piperazin-1-yl)acetic acid:* A solution of the product of Step E (0.05 g; 0.129 mmol) in 60% TFA in  $\text{CH}_2\text{Cl}_2$  (5 ml) was refluxed for 2 h, cooled to room temperature then diluted to 7 ml with EtOH. The resulting mixture was evaporated to dryness under reduced pressure kept *in vacuo* for 1 h. The residue was treated dissolved in EtOH (2 ml) and 3 drops of concentrated  $\text{NH}_4\text{OH}$  was added. The resulting mixture was partially concentrated under reduced pressure and the precipitate, formed was filtered off, washed with  $\text{Et}_2\text{O}$  and dried to give the titled compound (0.02 g; 47%) as colourless solid.  $^1\text{H-NMR}$  ( $\text{CD}_3\text{OD} + \text{CDCl}_3$ ) 7.07 (d, 2H,  $J = 8.6$  Hz); 6.86 (d, 2H,  $J = 8.6$  Hz); 4.63 (s,  $\text{CD}_3\text{OH}$ ); 3.58 (s, 2H); 3.38 (m, 8H); 2.49 (t, 2H,  $J = 7.8$  Hz); 1.53 (m, 2H); 1.24 (m, 10H); 0.83 (m, 3H).

### Example 10

#### 2-(4-Octylphenethyl)propane-1,2,3-triol

*Step A: 1-Ethynyl-4-octylbenzene:* A mixture of Example 3, Step A (0.1 g; 0.46 mmol), dimethyl(1-diazo-2-oxoprpyl)phosphonate (0.11 g, 0.57 mmol) and anhydrous  $\text{K}_2\text{CO}_3$  (0.14 g, 1.01 mmol) in dry MeOH (5 ml) was stirred for 8 h under  $\text{N}_2$ . After removing solvent under reduced pressure, the residue was diluted to 15 ml with  $\text{Et}_2\text{O}$  and washed with  $\text{H}_2\text{O}$  (2 x 10 ml) and dried over anhydrous  $\text{MgSO}_4$  and filtered. The filtrate was evaporated to dryness under reduced pressure and the residue was purified by FCC ( $\text{SiO}_2$ , hexane) to give the title compound (0.05 g; 51%) as colourless oil.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) 7.38 (d, 2H,  $J = 8.1$  Hz); 7.11 (d, 2H,  $J = 8.1$  Hz); 3.0 (s, 1H); 2.58 (t, 2H,  $J = 7.8$  Hz); 1.58 (t, 3H,  $J = 6.96$  Hz); 1.27 (m, 10H); 0.86 (t, 3H,  $J = 6.96$  Hz).

*Step B: 2,2-Dimethyl-5-((4-octylphenyl)ethynyl)-1,3-dioxan-5-ol:* To a solution of the product of Step A (0.05 g; 0.233 mmol) in anhydrous THF (2 ml) 2 M *n*-butyllithium in cyclohexane (0.13 ml; 0.26 mmol) was added drop wise at  $-15^\circ\text{C}$  under  $\text{N}_2$ . After stirring for 15 min at  $-15^\circ\text{C}$ , 2,2-dimethyl-1,3-dioxan-5-one (0.034 g; 0.26 mmol) was added and the resulting mixture was allowed to warm up to room temperature, diluted to 15 ml with  $\text{Et}_2\text{O}$  and washed with  $\text{H}_2\text{O}$  (2 x 10

ml), brine and dried over anhydrous  $\text{MgSO}_4$  and filtered. The filtrate was evaporated to dryness under reduced pressure and the residue was purified by FCC ( $\text{SiO}_2$ , hexane/ EtOAc 95 : 5) to give the title compound (0.03 g; 63%) as colourless oil.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) 7.33 (d, 2H,  $J = 8.09$  Hz); 7.09 (d, 2H,  $J = 8.09$  Hz); 4.11 (d, 2H,  $J = 11.76$  Hz); 3.83 (d, 2H,  $J = 11.76$  Hz); 3.99 (s, 1H); 2.57 (t, 2H,  $J = 7.88$  Hz); 1.56 (t, 3H,  $J = 6.94$  Hz); 1.49 (s, 3H); 1.46 (s, 3H); 1.26 (m, 10H); 0.86 (t, 3H,  $J = 6.96$  Hz).

*Step C: 2-(4-Octylphenethyl)propane-1,2,3-triol:* A mixture of the product of Step B (0.03 g; 0.087 mmol) and 10% Pd/C (0.05 g) in 5% TFA in EtOH (10 ml) was stirred for 1 h under  $\text{H}_2$  (balloon) at room temperature, then filtered through a pad of Celite, washed with  $\text{CH}_2\text{Cl}_2$  (2 x 10 ml). The combined filtrates were evaporated to dryness under reduced pressure and dried *in vacuo* for 1 h to give title compound (0.027 g; 99%) as a colourless solid.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) 7.05 (s, 4H); 3.66 (broad m, 7H); 2.61 (m, 2H); 2.51 (t, 2H,  $J = 7.92$  Hz); 1.73 (m, 2H); 1.55 (t, 3H,  $J = 6.93$  Hz); 1.26 (m, 10H); 0.87 (t, 3H,  $J = 6.93$  Hz).

### Example 11

#### 3-(3-(4-n-Octylphenyl)ureido)propanoic acid

*Step A: Ethyl 3-(3-(4-octylphenyl)ureido)propanoate:* To 4-n-octylaniline (0.1 g; 0.49 mmol) ethyl 3-isocyanatopropionate (0.08 g; 0.54 mmol) was added at room temperature. The resulting mixture was diluted to 1 ml with  $\text{CH}_2\text{Cl}_2$ , refluxed for 30 min and evaporated to dryness. The residue was treated with  $\text{Et}_2\text{O}$  (5 ml) and the solid formed was filtered off and dried to give the title compound (0.15 g; 87%), as colourless crystals.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) 7.22 – 7.07 (m, 4H); 6.34 (broad s, 1H); 5.34 (m, 1H); 4.15 – 4.07 (m, 2H); 3.54 – 3.46 (m, 2H); 2.73 (m, 4H); 2.57 – 2.51 (m, 4H); 1.58 (m, 2H); 1.27 – 1.19 (m, 13H); 0.86 (m, 3H).

*Step B: 3-(3-(4-n-Octylphenyl)ureido)propanoic acid:* To a solution of the product of Step A (0.05 g; 0.143 mmol) in dioxane (1 ml) 2N KOH (0.36 ml; 0.72 mmol) was added and the mixture was refluxed for 15 min, cooled to room temperature and evaporated to dryness under reduced pressure. The residue was diluted to 2 ml with  $\text{H}_2\text{O}$  and filtered. The filtrate was acidified to pH ~4 with citric acid. The solid formed was filtered off, washed with  $\text{H}_2\text{O}$  (3 x 2 ml), dried *in vacuo* to give the title compound (0.03 g; 65%), as a colourless solid.  $^1\text{H-NMR}$  ( $\text{CD}_3\text{OD} + \text{CDCl}_3$ ) 7.16 (d, 2H,  $J = 8.4$  Hz); 7.0 (d, 2H,  $J = 8.4$  Hz); 4.21 (s,  $\text{CD}_3\text{OH}$

); 3.4 (t, 2H, J = 6.7 Hz); 2.73 (m, 4H); 2.5 – 2.44 (m, 4H); 1.5 (m, 2H); 1.2 (m, 10H); 0.81 (m, 3H).

### Example 12

#### 3-(3-Methyl-3-(4-octylphenyl)ureido)propanoic acid

*Step A: tert-Butyl 4-n-octylphenyl(methyl)carbamate:* A mixture of 4-n-octylaniline (0.09 g; 0.44 mmol) and di-tert-butyl dicarbonate (0.1 g; 0.46 mmol) and a few drops of triethylamine was stirred at ~50°C for 1 h under N<sub>2</sub>, cooled to room temperature and kept *in vacuo* for 30 min. The residue was dissolved in anhydrous DMF (2 ml) and %60 NaH in mineral oil (0.02 g; 0.47 mmol) was added to it, followed by MeI (0.03 ml; 0.47 mmol), after stirring for 30 min under N<sub>2</sub>. The resulting mixture was stirred for 3 h at room temperature and solvent was removed *in vacuo*. The residue was diluted to 15 ml with Et<sub>2</sub>O and washed with 5% Na<sub>2</sub>SO<sub>3</sub>, H<sub>2</sub>O, brine, dried over anhydrous MgSO<sub>4</sub> and filtered. The filtrate was evaporated under reduced pressure to give the title compound (0.14 g; 100%), as a creamy solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 7.14 - 6.99 (m, 4H); 3.22 (s, 3H); 2.55 (m, 2H); 1.56 (m, 2H); 1.43 (s, 9H); 1.26 (m, 10H); 0.86 (m, 3H).

*Step B: N-Methyl-4-n-octylaniline:* A solution of the product of Step A (0.14 g; 0.44 mmol) in 60% TFA in CH<sub>2</sub>Cl<sub>2</sub> (5 ml) was stirred for 30 min at room temperature and the mixture was diluted to 5 ml with EtOH and a few drops of concentrated HCl was added. This was evaporated to dryness under reduced pressure, kept *in vacuo* for 1h and the residue was partitioned between saturated NaHCO<sub>3</sub> (5 ml) and Et<sub>2</sub>O (15 ml). The organic phase was dried over anhydrous MgSO<sub>4</sub> and filtered. The filtrate was evaporated under reduced pressure and the residue was purified by FCC (SiO<sub>2</sub>, hexane/EtOAc 9:1) to give the title compound (0.055 g; 57%), as a creamy solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 7.01 (d, 2H, J = 8.2 Hz); 6.55 (d, 2H, J = 8.2 Hz); 3.55 (broad s, 1H); 2.81 (s, 3H); 2.49 (t, 2H, J = 7.9 Hz); 1.56 (m, 2H); 1.28 (m, 10H); 0.88 (t, 3H, J = 6.8 Hz).

*Step C: Ethyl 3-(3-methyl-3-(4-octylphenyl)ureido)propanoate:* When the product of Step B is substituted for 4-n-octylaniline in Example 11, Step A, , the identical process afforded the title compound in 99% yield, as a colourless solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 7.15 (d, 2H, J = 8.2 Hz); 7.05 (d, 2H, J = 8.2 Hz); 4.77 (m, 1H); 4.03 (q, 2H, J = 7.14 Hz); 3.54 (m, 2H); 3.37 (qr, 2H, J = 6.1 Hz); 3.18 (s, 3H);



2.55 (t, 2H, J = 7.5 Hz); 2.44 (t, 2H, J = 6.1 Hz); 1.57 (m, 2H); 1.25 (m, 10H); 1.13 (t, 3H, J = 7.14 Hz); 0.83 (t, 3H, J = 6.9 Hz).

*Step D: 3-(3-Methyl-3-(4-octylphenyl)ureido)propanoic acid:* When the product of Step C is substituted for ethyl 3-(3-(4-octylphenyl)ureido)propanoate in Example 11, Step B, the identical process afforded the title compound in 84% yield, as a colourless solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 7.19 (d, 2H, J = 8.3 Hz); 7.09 (d, 2H, J = 8.3 Hz); 4.83 (m, 1H); 3.54 (m, 2H); 3.4 (m, 2H); 3.22 (s, 3H); 2.6 – 2.5 (m, 4H); 1.59 (m, 2H); 1.27 (m, 10H); 0.86 (t, 3H, J = 7 Hz).

### Example 13

#### 3-(3-(4-Octylphenyl)-2-oxoimidazolidin-1-yl)propanoic acid

*Step A: Ethyl 3-(3-(4-octylphenyl)-2-oxoimidazolidin-1-yl)propanoate:* To a solution of the product of Example 11, Step A (0.05 g; 0.143 mmol) in anhydrous DMF (2 ml) 60% NaH in mineral oil (0.014 g; 0.344 mmol) was added at room temperature. After stirring for 1 h, to it 1,2-dibromoethane (0.172 ml; 0.2 mmol) was added. This was stirred at ~50°C for 1 h under N<sub>2</sub>, cooled to room and solvents were removed *in vacuo*. The residue was diluted to 15 ml with Et<sub>2</sub>O, washed with H<sub>2</sub>O, brine, dried over anhydrous MgSO<sub>4</sub> and filtered. The filtrate was evaporated under reduced pressure and the residue was purified by FCC (SiO<sub>2</sub>, hexane/EtOAc 9.5:0.5) to give the title compound (0.02 g; 37%) as a colourless solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 7.4 (d, 2H, J = 8.5 Hz); 7.1 (d, 2H, J = 8.5 Hz); 4.13 (q, 2H, J = 7.1 Hz); 3.76 (m, 2H); 3.57 (t, 2H, J = 6.7 Hz); 3.5 (m, 2H); 2.6 (t, 2H, J = 6.7 Hz); 2.53 (t, 2H, J = 7.9 Hz); 1.55 (m, 2H); 1.24 (m, 13H); 0.85 (t, 3H, J = 6.9 Hz).

*Step B: 3-(3-(4-Octylphenyl)-2-oxoimidazolidin-1-yl)propanoic acid:* When the product of Step A is substituted for ethyl 3-(3-(4-octylphenyl)ureido)propanoate in Example 11, Step B, the identical process afforded the title compound in 33% yield, as a colourless solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 7.39 (d, 2H, J = 8.4 Hz); 7.11 (d, 2H, J = 8.4 Hz); 3.78 (t, 2H, J = 7.3 Hz); 3.6 – 3.4 (m, 4H); 3.22 (s, 3H); 2.66 (t, 2H, J = 6.5 Hz); 2.53 (t, 2H, J = 7.7 Hz); 1.55 (m, 2H); 1.25 (m, 10H); 0.85 (t, 3H, J = 6.9 Hz).

**Example 14****2-(3-(4-Octylbenzyl)ureido)acetic acid**

*Step A: Ethyl 2-(3-(4-octylbenzyl)ureido)acetate:* When the product of Example 6, Step C was substituted for 4-n-octylaniline and ethyl 2-isocyanatoacetate was substituted for ethyl 3-isocyanatopropionate in Example 11, Step A, the identical process afforded the title compound in 75 % yield, as a colourless solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 7.18 (d, 2H, J = 8 Hz); 7.11 (d, 2H, J = 8 Hz); 4.86 (m, 1H); 4.78 (m, 1H); 4.32 (d, 2H, J = 5.6 Hz); 4.16 (q, 2H, J = 7.1 Hz); 3.97 (d, 2H, J = 5.3 Hz); 2.56 (t, 2H, J = 8 Hz); 1.56 (m, 2H); 1.25 (m, 13H); 0.86 (t, 3H, J = 6.9 Hz).

*Step B: 2-(3-(4-Octylbenzyl)ureido)acetic acid:* When the product of Step A was substituted for ethyl 3-(3-(4-octylphenyl)ureido)propanoate in Example 11, Step B, the identical process afforded the title compound in 87% yield, as a colourless solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub> + CD<sub>3</sub>OD) 7.15 (d, 2H, J = 8 Hz); 7.07 (d, 2H, J = 8 Hz); 4.63 (CD<sub>3</sub>OH); 4.26 (s, 2H); 3.86 (s, 2H); 2.52 (t, 2H, J = 7.8 Hz); 1.54 (m, 2H); 1.22 (m, 10H); 0.83 (t, 3H, J = 7 Hz).

**Example 15****2-(3-(4-Octylbenzyl)-2-oxoimidazolidin-1-yl)acetic acid**

*Step A: tert-Butyl 2-(2-oxoimidazolidin-1-yl)acetate:* To a solution of imidazolidin-2-one (0.2 g; 2.3 mmol) in anhydrous DMF (5 ml) 60% NaH in mineral oil (0.18 g; 4.6 mmol) was added at room temperature, under N<sub>2</sub>. After stirring for 1 h, tert-butyl 2-bromoacetate (0.35 ml; 2.3 mmol) was added. The resulting mixture was stirred for additional 2h and solvents were removed *in vacuo*. The residue was diluted to 15 ml with EtOAc, washed with H<sub>2</sub>O, brine, dried over anhydrous MgSO<sub>4</sub> and filtered. The filtrate was evaporated under reduced pressure and the residue was purified by FCC (SiO<sub>2</sub>, EtOAc) to give the title compound (0.12 g; 26%) as a colourless solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 4.61 (broad s, 1H); 3.83 (s, 2H); 3.58 – 3.41 (m, 4H); 1.44 (s, 9H).

*Step B: tert-Butyl 2-(3-(4-octylbenzyl)-2-oxoimidazolidin-1-yl)acetate:* To a solution of the product of Step A (0.03 g; 0.15 mmol) in anhydrous DMF (5 ml) 60% NaH in mineral oil (0.006 g; 0.15 mmol) was added at room temperature, under N<sub>2</sub>. After stirring for 1 h, the product of Example 4, Step B (0.042 g; 0.15 mmol) was added. The resulting mixture was stirred for additional 4h and solvents

were removed *in vacuo*. The residue was diluted to 10 ml with EtOAc, washed with H<sub>2</sub>O, brine, dried over anhydrous MgSO<sub>4</sub> and filtered. The filtrate was evaporated under reduced pressure and the residue was purified by FCC (SiO<sub>2</sub>, hexane/EtOAc) to give the title compound (0.01 g; 16%) as a colourless solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 7.16 (d, 2H, J = 8.1 Hz); 7.11 (d, 3H, J = 8.1 Hz); 4.34 (s, 2H); 3.95 (s, 2H); 3.4 (m, 2H); 3.21 (m, 2H); 2.56 (t, 3H, J = 7.9 Hz); 1.65 (m, 2H); 1.43 (s, 9H); 1.26 (m, 10H); 0.86 (t, 3H, J = 7 Hz).

*Step C: 2-(3-(4-Octylbenzyl)-2-oxoimidazolidin-1-yl)acetic acid:* When the product of Step B was substituted for tert-butyl 2-(4-(4-octylphenyl)piperazin-1-yl)acetate in Example 9, Step F, the identical process afforded the title compound in 46% yield, as a colourless solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub> + CD<sub>3</sub>OD) 7.0 (m, 4H); 4.42 (s, 2H); 3.72 (s, 2H); 3.31 (m, 2H); 3.11 (m, 2H); 2.44 (t, 2H, J = 7.8 Hz); 1.43 (m, 2H); 1.13 (m, 10H); 0.73 (t, 3H, J = 7 Hz).

### Example 16

#### 2-(1-(4-Octylbenzyl)hydrazine-carboxamido)acetic acid

*Step A: tert-Butyl 2-(4-octylbenzylidene)hydrazinecarboxylate:* To a mixture of Example 3, Step A (0.1 g; 0.46 mmol) and tert-butyl carbazate (0.06 g; 0.46 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (5 ml) anhydrous MgSO<sub>4</sub> was added and the resulting suspension was vigorously stirred for 2 h at room temperature and filtered. The filtrate was evaporated to dryness under reduced pressure to give the title compound (0.13 g; 87%) as yellowish solid, which was used in next step without further purification. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 7.8 (broad s, 1H); 7.56 (d, 2H, J = 8.1 Hz); 7.15 (d, 2H, J = 8.1 Hz); 2.58 (t, 2H, J = 7.9 Hz); 1.59 (m, 2H); 1.52 (s, 9H); 1.26 (m, 10H); 0.86 (t, 3H, J = 7 Hz).

*Step B: tert-Butyl 2-(4-octylbenzyl)hydrazinecarboxylate:* To a solution of the product of Step A (0.13 g; 0.391 mmol) in anhydrous THF (1 ml) and glacial AcOH (0.6 ml) NaBH<sub>3</sub>CN (0.06 g; 0.95 mmol) was added at ~0°C (ice bath). The resulting mixture was stirred overnight at room temperature then diluted to 15 ml with Et<sub>2</sub>O. This was washed with 5% NaHCO<sub>3</sub>, H<sub>2</sub>O, brine, dried over anhydrous MgSO<sub>4</sub> and filtered. The filtrate was evaporated under reduced pressure to give the title compound (0.01 g; 16%) as a colourless syrup, which was used in the next step without further purification. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 7.23 (d, 2H, J = 8 Hz); 7.12

(d, 3H, J = 8 Hz); 6.0 (s, 1H); 4.1 (broad s, 2H); 3.94 (s, 2H); 2.57 (t, 3H, J = 7.9 Hz); 1.56 (m, 2H); 1.45 (s, 9H); 1.26 (m, 10H); 0.86 (t, 3H, J = 7 Hz).

*Step C: tert-Butyl 2-(2-ethoxy-2-oxoethylcarbamoyl)-2-(4-octylbenzyl)-hydrazine-carboxylate:* When the product of Step B was substituted for 4-n-octylbenzylamine in Example 14, Step A, the identical process afforded the title compound in 84% yield, as a colourless solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 7.14 (m, 4H); 5.95 (s, 1H); 5.87 (t, 1H, J = 5 Hz); 4.5 (broad s, 1H); 4.19 (q, 2H, J = 7.1 Hz); 4.03 (d, 2H, J = 5 Hz); 2.57 (t, 2H, J = 7.9 Hz); 1.56 (m, 2H); 1.44 (s, 9H); 1.27 (m, 13H); 0.86 (t, 3H, J = 7 Hz).

*Step D: Ethyl 2-(1-(4-octylbenzyl)hydrazinecarboxamido)acetate:* When the product of Step C was substituted for tert-butyl 4-n-octylphenyl(methyl)carbamate in Example 12, Step B, the identical process afforded the title compound in 89% yield, as a creamy solid, which was used in the next step without further purification. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 7.15 (m, 4H); 6.84 (broad m, 1H); 4.66 (s, 2H); 4.2 (q, 2H, J = 7.14 Hz); 4.02 (d, 2H, J = 5.8 Hz); 3.42 (bs, 2H); 2.57 (t, 2H, J = 7.9 Hz); 1.57 (m, 2H); 1.27 (m, 13H); 0.86 (t, 3H, J = 6.9 Hz).

*Step E: 2-(1-(4-Octylbenzyl)hydrazinecarboxamido)acetic acid:* When the product of Step D is substituted for ethyl 3-(3-(4-octylphenyl)ureido)propanoate in Example 11, Step B, the identical process afforded the title compound in 78% yield, as a colourless solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 7.15 (m, 4H); 6.91 (t, 1H, J = 5.7 Hz); 4.66 (s, 2H); 4.02 (d, 2H, J = 5.7 Hz); 3.56 (bs, 3H); 2.57 (t, 2H, J = 7.9 Hz); 1.58 (m, 2H); 1.26 (m, 10H); 0.86 (t, 3H, J = 7 Hz).

## Example 17

### 3-(5-Octylindoline-1-carboxamido)propanoic acid

*Step A: 5-iodoindoline:* To a solution of 5-iodoindole (0.2 g; 0.82 mmol) in AcOH (5 ml) NaBH<sub>3</sub>CN (0.2 g; 3.8 mmol) was added at ~10°C under N<sub>2</sub>. After stirring for 1 h at room temperature the solvent was removed *in vacuo* and the residue was diluted to 30 ml with Et<sub>2</sub>O and washed with 1 N NaOH (5 ml), H<sub>2</sub>O (2 x 5 ml), brine, dried over anhydrous MgSO<sub>4</sub> and filtered. The filtrate was evaporated to dryness under reduced pressure to give the title compound (0.2g; 99%), which was used in next step without further purification. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 7.35 (s, 1H); 7.25 (d, 1H, J = 8.15 Hz); 6.43 (d, 1H, J = 8.15 Hz); 5.21 (bs, 1H); 3.54 (t, 2H, J = 8.36 Hz); 2.99 (t, 2H, J = 8.36 Hz).

*Step B: Ethyl 3-(5-iodoindoline-1-carboxamido)propanoate:* When the product of Step A was substituted for 4-n-octylaniline in Example 11, Step A, the identical process afforded the title compound in 99% yield, as a colourless solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 7.67 (d, 1H, J = 8.3 Hz); 7.4 (m, 2H); 5.34 (m, 1H); 4.14 (q, 2H, J = 7.1 Hz); 3.86 (t, 2H, J = 8.8 Hz); 3.56 (q, 2H, J = 5.9 Hz); 3.13 (t, 2H, J = 8.6 Hz); 2.58 (t, 2H, J = 5.7 Hz); 1.26 (t, 3H, J = 7.1 Hz).

*Step C: Ethyl 3-(5-(oct-1-ynyl)indoline-1-carboxamido)propanoate:* A mixture of the product of Step B (0.16 g; 0.41 mmol), 1-octyne (0.073 ml; 0.49 mmol), Cl<sub>2</sub>Pd(PPh<sub>3</sub>)<sub>2</sub> (0.02 g; 0.028 mmol) and CuI (0.005 g; 0.026 mmol) was degassed under reduced pressure and saturated with dry N<sub>2</sub>. After addition of DIPEA (0.5 ml), the resulting mixture was stirred for 2 h at room temperature under N<sub>2</sub>. The solvents were removed in vacuo and the residue was diluted to 15 ml with EtOAc and washed with 5% citric acid, 5% NaHCO<sub>3</sub>, H<sub>2</sub>O, brine and dried over anhydrous MgSO<sub>4</sub> and filtered. The filtrate was evaporated to dryness under reduced pressure and the residue was purified by FCC (SiO<sub>2</sub>; CH<sub>2</sub>Cl<sub>2</sub>) to give the title compound (0.1 g; 65%) as a brownish solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 7.75 (d, 1H, J = 8.4 Hz); 7.16 (d, 1H, J = 8.4 Hz); 7.1 (s, 1H); 5.34 (t, 1H, J = 5.8 Hz); 4.11 (q, 2H, J = 7.1 Hz); 3.82 (t, 2H, J = 8.8 Hz); 3.52 (m, 2H); 3.06 (t, 2H, J = 8.8 Hz); 2.56 (t, 2H, J = 5.8 Hz); 2.33 (t, 2H, J = 7.1 Hz); 1.53 (m, 2H); 1.52 (m, 2H); 1.26 (m, 6H); 1.23 (t, 2H, J = 7.1 Hz); 0.86 (t, 3H, J = 6.9 Hz).

*Step D: Ethyl 3-(5-octylindoline-1-carboxamido)propanoate:* A mixture of the product of Step C (0.1 g; 0.27 mmol) and 10% Pd/C (0.1 g) in EtOH (15 ml) was stirred at room temperature for 1 h under H<sub>2</sub> (balloon). The catalyst was removed by filtration through the Celite pad, washed with CH<sub>2</sub>Cl<sub>2</sub> (2 x 10 ml) and combined filtrates were evaporated to dryness under reduced pressure to give a title compound (0.09 g; 90%), as colourless solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 7.71 (d, 1H, J = 8.8 Hz); 6.94 (d, 1H, J = 8.8 Hz); 6.93 (s, 1H); 5.29 (m, 1H); 4.14 (q, 2H, J = 7 Hz); 3.82 (t, 2H, J = 8.8 Hz); 3.57 (q, 2H, J = 5.9 Hz); 3.11 (t, 2H, J = 8.6 Hz); 2.59 (t, 2H, J = 5.7 Hz); 2.51 (t, 2H, J = 7.7 Hz); 1.57 (m, 2H); 1.26 (m, 13H); 0.86 (t, 3H, J = 7 Hz).

*Step E: 3-(5-Octylindoline-1-carboxamido)propanoic acid:* When the product of Step D was substituted for ethyl 3-(3-(4-octylphenyl)ureido)propanoate in Example 11, Step B, the identical process afforded the title compound in 84% yield, as a colourless solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 7.68 (d, 1H, J = 8.7 Hz); 6.94 (m,

2H); 5.24 (t, 1H, J = 5.9 Hz); 3.86 (t, 2H, J = 8.7 Hz); 3.58 (q, 2H, J = 5.9 Hz); 3.11 (t, 2H, J = 8.5 Hz); 2.67 (t, 2H, J = 5.8 Hz); 2.5 (t, 2H, J = 8 Hz); 1.54 (m, 2H); 1.25 (m, 10H); 0.86 (t, 3H, J = 6.8 Hz).

### Example 18

#### 4-(4-(N-(6,6-Dimethylbicyclo[3.1.1]heptan-2-yl)sulfamoyl)phenyl)butyl-dihydrogen phosphate:

**Step A:** *4-Bromo-N-(6,6-dimethylbicyclo[3.1.1]heptan-2-yl)benzene sulfonamide:* To a stirred solution of 4-bromo-benzenesulphonyl chloride (0.6 g, 2.34 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (5 ml) and Et<sub>3</sub>N (0.65 ml, excess) at 0 °C was added (-) cis-myrtaniline (0.36 g, 2.34 mmol) and the stirring was continued overnight at room temperature. The reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (15 ml) and washed with H<sub>2</sub>O (2 x 100 ml). The organic layer was separated and dried over MgSO<sub>4</sub> and the solvent was distilled to afford the title compound (0.87 g, 100%), as pale paste, which was solidified on standing. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 7.70 (d, 2H, J = 6.78 Hz); 6.64 (d, 2H, J = 6.90 Hz); 2.91 (t, 2H, J = 7.59 Hz); 2.32 – 2.29 (m, 1H); 2.11 – 2.06 (m, 1H); 1.91 – 1.81 (m, 6H); 1.39 – 1.31 (m, 1H); 1.11 (s, 3H); 0.86 (s, 3H).

**Step B:** *N-(6,6-Dimethylbicyclo[3.1.1]heptan-2-yl)-4-(4-hydroxybut-1-ynyl)benzene sulfonamide:* A solution of the product of Step A (0.37 g, 0.5 mmol) and but-3-yn-1-ol (0.12 ml, excess) in a mixture of DMF (5 ml) and DIPEA (0.5 ml) was degassed with N<sub>2</sub> and Cl<sub>2</sub>Pd(PPh<sub>3</sub>)<sub>2</sub> (0.07 g) was added, followed by catalytic amount of CuI and the mixture was stirred for 16 h at room temperature. The reaction was quenched with saturated NH<sub>4</sub>Cl solution and diluted with H<sub>2</sub>O followed by the extraction with EtOAc (100 ml). The organic layer was separated, dried over MgSO<sub>4</sub>, filtered and the filtrate was evaporated to dryness and the residue was purified by FCC (SiO<sub>2</sub>, hexane/EtOAc) to give the product (0.11 g, 60%), as creamy paste. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 7.66 (d, 2H, J = 8.43 Hz); 7.51 (d, 2H, J = 8.43 Hz); 3.81 (b, 2H); 3.01 – 2.86 (m, 2H); 2.71 – 2.67 (m, 4H); 2.50 – 2.10 (m, 2H); 1.94 – 1.82 (m, 5H); 1.52 – 1.48 (m, 1H); 1.18 (s, 3H); 1.02 (s, 3H).

**Step C:** *N-(6,6-Dimethylbicyclo[3.1.1]heptan-2-yl)-4-(4-hydroxybutyl)benzene sulfonamide:* A mixture of the product of Step B (0.11 g, 0.3 mmol) and 10% Pd/C (0.06 g) in EtOH (10 ml) was stirred for 16 h under H<sub>2</sub>. The catalyst was filtered through Celite pad and the filtrate evaporated to dryness to give the

title compound (0.11 g, 100%,) as creamy gum.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) 7.74 (d, 2H,  $J = 7.89$  Hz); 7.29 (d, 2H,  $J = 8.01$  Hz); 4.9 (bs, 1H, NH); 3.71 – 3.65 (m, 2H); 2.92 – 2.87 (m, 2H); 2.70 (t, 2H,  $J = 7.74$  Hz); 2.45 – 2.30 (m, 1H); 2.25 – 2.10 (m, 1H); 1.86 – 1.58 (m, 9H); 1.3 – 1.1 (m, 2H); 1.08 (s, 3H); 0.83 (s, 3H).

*Step D: 4-(4-(N-(6,6-Dimethylbicyclo[3.1.1]heptan-2-yl)sulfamoyl)phenyl)butyl-dihydrogen phosphate:* To a stirred solution of  $\text{POCl}_3$  (0.006 ml, 0.66 mmol) in anhydrous  $\text{CH}_2\text{Cl}_2$  (3 ml) a solution of tert-butanol (0.062 ml, 0.65 mmol) and  $\text{Et}_3\text{N}$  (0.09 ml, 0.65 mmol) was added drop wise at 0 °C under  $\text{N}_2$ . The mixture was stirred for 0.5 h and to it a solution of the product of Step C (0.08 g, 0.22 mmol) in a mixture of anhydrous  $\text{CH}_2\text{Cl}_2$  (1 ml) and  $\text{Et}_3\text{N}$  (0.03 ml) was added drop wise. The mixture was stirred for 1 h at room temperature. The solvent was evaporated under reduced pressure and the residue was treated dropwise with a solution of 10% NaOH until the mixture become homogenous. This was washed with  $\text{CH}_2\text{Cl}_2$  (2 x 10 ml), and the aqueous phase was acidified with 2M HCl. The product was extracted with  $\text{CH}_2\text{Cl}_2$  (20 ml) and dried over  $\text{MgSO}_4$  and filtered. The filtrate was evaporated to dryness to give the title compound (0.065 g, 65%) as pale paste.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) 7.67 (d, 2H,  $J = 7.13$  Hz); 7.23 (d, 2H); 3.94 (bs, 1H, NH); 3.86 (d, 2H,  $J = 7.67$  Hz); 2.58 (b, 2H); 2.28 (b, 1H); 2.13 (b, 1H); 1.84 – 1.82 (b, 5H); 1.35 (b, 4H); 1.22 – 1.24 (b, 2H); 0.96 (s, 3H); 0.86 (s, 3H).

### Example 19

#### **4-(4-(3-(3-(2,2,2-trifluoroacetyl)-1H-indol-1-yl)propyl)phenyl)butyl-dihydrogen phosphate**

*Step A: 2,2,2-Trifluoro-1-(1H-indol-3-yl)ethenone:* To a stirred solution of indole (0.5 g, 4.3 mmol) in anhydrous  $\text{Et}_2\text{O}$  (10 ml) anhydrous pyridine (0.5 ml) was added at 0 °C, followed by drop wise addition of  $(\text{CF}_3\text{CO})_2\text{O}$  (0.87 ml, 5.16 mmol). The mixture was stirred for 15 min and the solvent was evaporated to dryness. The residue was diluted to 20 ml with  $\text{EtOAc}$ , washed with  $\text{H}_2\text{O}$ , dried over  $\text{MgSO}_4$ , filtered and the filtrate was evaporated to dryness. The residue was crystallized from  $\text{CH}_3\text{OH}$  to give the title compound (0.56 g; 61%), as colourless solid.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) 9.04 (broad s, 1H); 8.40 (t, 1H,  $J = 4.11$  Hz); 8.06 (s, 1H); 7.48 - 7.45 (m, 1H); 7.40 - 7.35 (m, 2H).

*Step B: 2,2,2-Trifluoro-1-(1-(prop-2-ynyl)-1H-indol-3-yl)ethanone:* A mixture of product of Step A (0.55 g, 2.58 mmol),  $\text{K}_2\text{CO}_3$  (0.43 g, 3.11 mmol) and propargyl

bromide (2 ml) in anhydrous DMF (8 ml). was stirred for 4 h. The mixture was quenched with  $\text{NH}_4\text{Cl}$  solution and diluted to 50 ml with EtOAc. The organic layer separated and washed with  $\text{H}_2\text{O}$ , dried over  $\text{MgSO}_4$  and filtered. The filtrate was evaporated to give the title compound (0.57 g, 88%), as yellow crystalline material.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) 8.41 – 8.38 (b, 1H); 7.99 (s, 1H); 7.48 – 7.31 (m, 3H); 4.96 (d, 2H,  $J = 2.55$  Hz); 2.58 (t, 1H,  $J = 2.55$  Hz).

*Step C: 2,2,2-Trifluoro-1-(1-(3-(4-iodophenyl)prop-2-ynyl)-1H-indol-3-yl)ethanone:* A mixture of product of Step B (0.25 g, 1 mmol), 1,4 di-iodobenzene (0.4 g, 1.2 mmol)  $\text{Cl}_2\text{Pd}(\text{PPh}_3)_2$  (0.06 g) and catalytic amount of CuI in a mixture of DMF:DIPEA (10 ml: 0.5 ml) at room temperature was degassed under reduced pressure and saturated with  $\text{N}_2$ . This was stirred overnight at room temperature, quenched with  $\text{NaHCO}_3$  solution and diluted to 50 ml with EtOAc. The organic layer was separated and washed with  $\text{H}_2\text{O}$ , dried over  $\text{MgSO}_4$  and filtered. The filtrate was evaporated to dryness and the residue was purified by FCC ( $\text{SiO}_2$ , hexane/EtOAc) to give the title compound (0.28 g, 51%), as light yellow solid.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) 8.43 – 8.40 (b, 1H); 8.12 (b, 1H); 7.66 (t, 2H,  $J = 8.36$  Hz); 7.55 – 7.51 (m, 1H); 7.44 – 7.38 (m, 2H); 7.14 (d, 2H,  $J = 8.30$  Hz); 5.16 (s, 2H).

*Step D: 2,2,2-Trifluoro-1-(1-(3-(4-(4-hydroxybut-1-ynyl)phenyl)prop-2-ynyl)-1H-indol-3-yl)ethanone:* When the product of Step C was substituted for 4-bromo-N-(6,6-dimethylbicyclo[3.1.1] heptan-2-yl) benzene sulphonamide in Example 18, Step B, the identical process afforded the title compound in 84% yield, as creamy paste.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) 8.43 – 8.40 (m, 1H); 8.14 (s, 1H); 7.56 – 7.53 (m, 1H); 7.44-7.37 (m, 2H); 7.37 (s, 4H); 5.19 (s, 2H); 3.8 (t, 2H,  $J = 6.24$  Hz); 2.69 (t, 2H,  $J = 6.24$  Hz); 1.76 (bs, 1H).

*Step E: 2,2,2-Trifluoro-1-(1-(3-(4-(4-hydroxybutyl)phenyl)propyl)-1H-indol-3-yl)ethanone:* When the product of Step D was substituted for N-(6,6-dimethylbicyclo[3.1.1]heptan-2-yl)-4-(4-hydroxybut-1-ynyl) benzene sulphonamide in Example 18, Step C, the identical process afforded the title compound in 92% yield, as pale paste.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) 8.40 (broad s, 1H); 7.86 (s, 1H); 7.37 – 7.32 (m, 3H); 7.11 (d, 2H,  $J = 8.07$  Hz); 7.05 (d, 2H,  $J = 8.07$  Hz); 4.19 (t, 2H,  $J = 7.17$  Hz); 3.72 – 3.63 (m, 4H); 2.66 – 2.59 (m, 4H); 1.68 – 1.60 (m, 4H).

*Step F: 4-(4-(3-(3-(2,2,2-trifluoroacetyl)-1H-indol-1-yl)propyl)phenyl)butyl-dihydrogen phosphate:* When the product of Step E was substituted for N-(6,6-dimethylbicyclo[3.1.1]heptan-2-yl)-4-(4-hydroxy butyl)benzene sulphonamide in



Example 18, Step D, the similar process afforded the title compound in 73% yield, as pale paste.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) 8.35 (broad s, 1H); 7.83 (s, 1H); 7.36 – 7.30 (m, 3H); 7.10 – 6.93 (m, 4H); 3.98 (m, 2H); 2.55 – 2.50 (m, 6H); 2.23 – 2.15 (m, 2H); 1.59 (b, 4H).

### Example 20

#### **4-(4-(2-(6,6-Dimethylbicyclo[3.1.1]heptan-2-yl)ethoxy)phenyl)butyl-dihydrogen phosphate**

*Step A: 2-(2-(4-iodophenoxy)ethyl)-6,6-dimethylbicyclo[3.1.1]heptane:* To a stirred suspension of 4-iodophenol (0.5 g; 2.27 mmol) and 60% NaH (0.16 g, 2.3 mmol) in anhydrous DMF (5 ml) 2-(2-bromoethyl)-6,6-dimethylbicyclo[3.1.1]heptane (0.5 g, 2.2 mmol) was added and the mixture was stirred for 3 h at room temperature. After addition of more of 2-(2-bromoethyl)-6,6-dimethylbicyclo[3.1.1]heptane (0.2 g) the mixture was stirred for additional 2 h, quenched with  $\text{NH}_4\text{Cl}$  solution and diluted to 20 ml with EtOAc. The organic layer was separated, dried over  $\text{MgSO}_4$  and filtered. The filtrate was evaporated to dryness and the residue was purified by FCC ( $\text{SiO}_2$ , hexane/EtOAc) to give the title compound (0.61 g, 73%), as a colourless paste.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) 7.51 (d, 2H,  $J = 8.91$  Hz); 6.64 (d, 2H,  $J = 8.88$  Hz); 3.88 (t, 2H,  $J = 3.21$  Hz); 2.34 – 1.84 (m, 10H); 1.17 (s, 3H); 1.01 (s, 3H).

*Step B: 4-(4-(2-(6,6-Dimethylbicyclo[3.1.1]heptan-2-yl)ethoxy)phenyl)but-3-yn-1-ol:* When the product of Step A was substituted for 4-bromo-N-(6,6-dimethylbicyclo[3.1.1]heptan-2-yl)benzene sulphonamide in Example 18, Step B, the similar process afforded the title compound in 78% yield, as pale paste.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) 7.29 (d, 2H,  $J = 8.76$  Hz); 6.78 (d, 2H,  $J = 8.82$  Hz); 3.80 – 3.76 (m, 2H); 3.92 (t, 2H,  $J = 1.89$  Hz); 2.65 (t, 2H,  $J = 6.21$  Hz); 1.92 – 1.81 (m, 10H); 1.18 (s, 3H); 1.01 (s, 3H).

*Step C: 4-(4-(2-(6,6-Dimethylbicyclo[3.1.1]heptan-2-yl)ethoxy)phenyl)butan-1-ol:* When the product of Step B was substituted for N-(6,6-dimethylbicyclo[3.1.1]heptan-2-yl)-4-(4-hydroxybut-1-ynyl)benzene sulphonamide in Example 18, Step C, the similar process afforded the title compound in 99% yield, as a colourless paste.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) 7.05 (d, 2H,  $J = 8.54$  Hz); 6.78 (d, 2H,  $J = 8.58$  Hz); 3.91 (t, 2H,  $J = 6.81$  Hz); 3.64 (t, 2H,  $J = 6.02$  Hz); 2.57 – 2.53 (m, 2H); 1.90 – 1.57 (m, 14 H); 1.18 (s, 3H); 1.01 (s, 3H).

**Step D:** *4-(4-(2-(6,6-Dimethylbicyclo[3.1.1]heptan-2-yl)ethoxy)phenyl)butyl-di-hydrogen phosphate:* When the product of Step C was substituted for N-(6,6-dimethylbicyclo[3.1.1]heptan-2-yl)-4-(4-hydroxybutyl) benzene sulfonamide in Example 18, Step D, the similar process afforded the title compound in 60% yield, as pale paste. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 7.05 (d, 2H, J = 8.31 Hz); 6.74 (d, 2H, J = 8.16 Hz); 3.93 – 3.84 (m, 4H); 2.53 – 2.15 (m, 16H); 1.15 (s, 3H); 0.99 (s, 3H).

### Example 21

#### 2-(4-(2-(6-Methoxy-2,3-dihydrobenzofuran-2-yl)ethyl)phenoxy)ethanol

**Step A:** *4-((6-Methoxybenzofuran-2-yl)ethynyl)phenyl acetate:* When 4-iodophenyl acetate and 2-ethynyl-6-methoxybenzofuran were substituted for 4-bromo-N-(6,6-dimethylbicyclo [3.1.1] heptan-2-yl)benzene sulphonamide and but-3-yn-1-ol respectively in Example 18, Step B, the similar process afforded the title compound in 56% yield, as creamy paste. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 7.56 (d, 2H, J = 8.67 Hz); 7.41 (d, 1H, J = 8.58 Hz); 7.10 (d, 2H, J = 8.7 Hz); 6.97 (d, 1H, J = 1.92 Hz); 6.9 (s, 1H); 6.88 (bd, 1H, J = 8.61 Hz); 3.85 (s, 3H); 2.3 (s, 3H).

**Step B:** *4-(2-(6-Methoxy-2,3-dihydrobenzofuran-2-yl)ethyl)phenol:* When the product of Step A was substituted for N-(6,6-dimethyl bicyclo[3.1.1]heptan-2-yl)-4-(4-hydroxybut-1-ynyl)benzenesulphonamide in Example 18, Step C, the similar process (higher pressure of H<sub>2</sub>) afforded the title compound in 96% yield, as creamy paste. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 7.25 – 7.19 (m, 2H); 7.02 – 6.97 (m, 3H); 6.38 – 6.35 (m, 2H); 4.81 – 4.72 (m, 1H); 3.75 (s, 3H); 3.24 – 3.16 (m, 1H); 2.83 – 2.73 (m, 3H); 2.27 (s, 3H); 2.13 – 2.07 (m, 1H); 2.06 – 1.92 (m, 1H).

**Step C:** *Ethyl 2-(4-(2-(6-methoxy-2,3-dihydrobenzofuran-2-yl)ethyl) phenoxy) acetate:* To a stirred solution of the product of Step A (0.05 g, 0.19 mmol) and K<sub>2</sub>CO<sub>3</sub> (0.05 g, 0.36 mmol) in anhydrous DMF (5 ml) ethyl-bromo acetate (0.025 ml, 0.22 mmol) was added at room temperature. The mixture was stirred for 2 h and quenched with saturated NH<sub>4</sub>Cl solution, extracted in EtOAc (100 ml) and washed with H<sub>2</sub>O. The organic layer was separated and dried over MgSO<sub>4</sub> and filtered. The filtrate was evaporated to dryness to give the title compound (0.07 g; 100%), as pale oil. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 7.10 (d, 2H, J = 8.39 Hz); 6.97 (d, 1H, J = 8.46 Hz); 6.80 (t, 2H, J = 8.36 Hz); 6.35 – 6.33 (m, 2H); 4.75 – 4.71 (m, 1H); 4.56 (s, 2H); 4.22 (q, 2H, J = 14.36, 7.17 Hz); 3.72 (s, 3H, OMe); 3.2 – 3.13 (m, 1H); 2.79 – 2.69 (m, 3H); 2.0 – 1.87 (m, 2H); 1.26 (t, 3H, J = 7.12 Hz).

**Step D:** *2-(4-(2-(6-Methoxy-2,3-dihydrobenzofuran-2-yl)ethyl)phenoxy) ethanol:* To the stirred slurry of  $\text{LiAlH}_4$  (0.01 g, 0.026 mmol) in anhydrous  $\text{Et}_2\text{O}$  (5 ml) the solution of the product of Step C (0.04 g, 0.11 mmol) in anhydrous  $\text{Et}_2\text{O}$  (2 ml) was added drop wise and stirring was continued for 0.5 h at room temperature. The reaction mixture was quenched with  $\text{EtOAc}:\text{H}_2\text{O}:\text{MeOH}$  mixture (7 ml: 3 ml: 1 ml), diluted to 20 ml with  $\text{EtOAc}$  and filtered through Celite. The filtrate was evaporated under reduced pressure and dried *in vacuo* to give the title compound (0.032 g, 94%), as colourless solid.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) 7.13 (d, 2H,  $J = 8.54$  Hz); 6.99 (d, 1H,  $J = 8.56$  Hz); 6.84 (d, 2H,  $J = 8.58$  Hz); 6.38 – 6.34 (m, 2H); 4.79 – 4.74 (m, 1H); 4.65 (t, 2H,  $J = 4.14$  Hz); 3.96 – 3.90 (m, 2H); 3.75 (s, 3H); 3.22 – 3.14 (m, 1H); 2.82 – 2.68 (m, 2H); 2.11 – 1.91 (m, 3H).

## Example 22

### **2-((4-(5-(((4-Fluorophenyl)(isopropyl)amino)methyl)thiophen-2-yl)benzyl)(methyl) amino)ethanol**

**Step A:** *4-(5-(Hydroxymethyl)thiophen-2-yl)benzaldehyde:* The thiophene-5-al-2-boronic acid (0.47 g, 2.97 mmol) was reduced with  $\text{NaBH}_4$  (0.15 g, 3.95 mmol) in  $\text{MeOH}$  (3 ml) and solvent was evaporated to dryness. The residue was taken in 1,4-dioxane (12 ml) and 4-bromobenzaldehyde (0.65 g, 3.5 mmol) was added. To this  $\text{Pd}(\text{PPh}_3)_4$  (0.05 g) was added with stirring at  $80^\circ\text{C}$ , followed by the addition of a solution of  $\text{NaHCO}_3$  (0.6 g) in  $\text{H}_2\text{O}$  (2 ml). The mixture was stirred at reflux for 1 h and the solvents were evaporated to dryness under reduced pressure. The residue was diluted to 100 ml with  $\text{EtOAc}$  and washed with  $\text{H}_2\text{O}$ . The organic layer was separated, dried over  $\text{MgSO}_4$  and filtered. The filtrate was evaporated to dryness and the residue was purified by FCC ( $\text{SiO}_2$ , hexane/ $\text{EtOAc}$ ) to give the title compound (0.61 g, 80%), as creamy paste.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) 9.98 (s, 1H, CHO); 7.87 (d, 2H,  $J = 8.3$  Hz); 7.72 (d, 2H,  $J = 8.31$  Hz); 7.31 (d, 1H,  $J = 3.74$  Hz); 7.0 (d, 2H,  $J = 3.7$  Hz); 4.84 (s, 2H).

**Step B:** *4-(5-(((4-Fluorophenyl)(isopropyl)amino)methyl)thiophen-2-yl) benzaldehyde:* To a stirred solution of the product of Step A (0.436 g, 2 mmol) in anhydrous  $\text{CH}_2\text{Cl}_2$  (10 ml) and  $\text{Et}_3\text{N}$  (0.3 ml) mesyl chloride (0.4 ml) was added at  $0^\circ\text{C}$  and stirring was continued for 1 h. The solvents were evaporated to dryness under reduced pressure and the residue was diluted to 50 ml with  $\text{EtOAc}$  and washed with  $\text{H}_2\text{O}$ . The organic layer was separated and dried over  $\text{MgSO}_4$  and

filtered. The filtrate was evaporated to give the crude product (0.63 g) as pale paste, which was taken up in anhydrous toluene and 4-fluoro-*N*-isopropylaniline (0.5 ml) was added to it. The mixture was stirred overnight at reflux and the solvent was evaporated. The residue was purified by FCC (SiO<sub>2</sub>, hexane/EtOAc) to give the title compound (0.14 g, 20%), as light creamy paste. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 9.98 (s, 1H); 7.82 (d, 2H, J = 8.31 Hz); 7.66 (d, 2H, J = 8.31 Hz); 7.28 (d, 1H, J = 3.69 Hz); 6.93 – 6.86 (m, 3H); 6.81 – 6.76 (m, 2H); 4.79 (s, 2H); 4.08 – 3.99 (m, 1H); 1.22 (d, 6H, J = 6.6 Hz).

**Step C:** *Methyl-2-((4-(5-(((4-fluorophenyl)(isopropyl)amino)methyl)thiophen-2-yl)benzyl) (methyl)amino) acetate:* To a stirred solution of the product of Step B (0.09 g, 0.26 mmol) and sarcosine hydrochloride (0.07 g, 0.5 mmol) in 1,2-dichloroethane (5 ml) was added DIPEA (0.1 ml) and 10 drops of AcOH, followed by NaBH(OAc)<sub>3</sub> (0.11 g, 0.51 mmol). The mixture was stirred overnight at room temperature and diluted to 20 ml with CH<sub>2</sub>Cl<sub>2</sub>. The organic layer was washed with NaHCO<sub>3</sub> solution, H<sub>2</sub>O and dried over MgSO<sub>4</sub> and filtered. The filtrate was evaporated to dryness and the residue was purified by FCC (SiO<sub>2</sub>, hexane/EtOAc) to give the title compound (0.113 g, 100%) as creamy paste. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 7.47 (d, 2H, J = 8.19 Hz); 7.28 (d, 2H, J = 8.18 Hz); 7.10 (d, 1H, J = 3.62 Hz); 6.88 – 6.85 (m, 3H); 6.85 – 6.77 (m, 2H); 4.44 (s, 2H); 4.07 – 3.98 (m, 1H); 3.69 (s, 3H); 3.24 (s, 2H); 2.37 (s, 3H); 1.21 (d, 6H, J = 6.6 Hz).

**Step D:** *2-((4-(5-(((4-Fluorophenyl)(isopropyl)amino)methyl)thiophen-2-yl)benzyl) (methyl) amino)ethanol:* When the product of Step C was substituted for ethyl-2-(4-(2-(6-methoxy-2,3-dihydrobenzofuran-2-yl)ethyl)phenoxy)acetate in Example 21, Step D, the similar process afforded the title compound in 28% yield, as light yellow paste. <sup>1</sup>H NMR (CDCl<sub>3</sub>) 7.47 (d, 2H, J = 8.05 Hz); 7.24 (d, 2H, J = 8.04 Hz); 7.10 (d, 1H, J = 3.60 Hz); 6.91 – 6.85 (m, 3H); 6.81 – 6.76 (m, 2H); 4.44 (s, 2H); 4.07 – 3.98 (m, 1H); 3.61 (t, 2H, J = 5.31 Hz); 3.53 (s, 3H); 2.58 (t, 2H, J = 5.31 Hz); 2.21 (s, 3H); 1.21 (d, 6H, J = 6.56 Hz).

### Example 23

#### **2-(4-(5-(((4-Fluorophenyl)(isopropyl)amino)methyl)thiophen-2-yl)benzylamino) propane-1,3-diol**

**Step A:** *N-(4-(5-(((4-Fluorophenyl)(isopropyl)amino)methyl)thiophen-2-yl)benzyl) -2,2-dimethyl-1,3-dioxan-5-amine:* When 2,2-dimethyl-1,3-dioxan-5-

amine was substituted for sarcosine hydrochloride in Example 22, Step C, the similar process afforded the the title compound in 90% yield, as creamy paste.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) 7.47 (d, 2H, J = 8.2 Hz); 7.29 (d, 2H, J = 8.2 Hz); 7.0 (d, 1H, J = 3.61 Hz); 6.9 – 6.85 (m, 3H); 6.82 – 6.76 (m, 2H); 4.38 (s, 2H); 4.07 – 4.0 (m, 1H); 3.96 (dd, 2H, J = 11.7, 3.5 Hz); 3.81 (s, 2H); 3.72 (dd, 2H, J = 11.8, 5.34 Hz); 2.68 – 2.63 (m, 1H); 1.41 (s, 3H); 1.4 (s, 3H); 1.21 (d, 6H, J = 6.6 Hz).

*Step B: 2-(4-(5-(((4-Fluorophenyl)(isopropyl)amino)methyl)thiophen-2-yl)benzylamino) propane-1,3-diol:* A solution of the product of Step A (0.025 g, 0.05 mmol) in a mixture of solvents ( $\text{CH}_3\text{OH}$ ,  $\text{CH}_2\text{Cl}_2$ , 30% HCl: 1 ml, 3 ml, 15 drops) was stirred for 3 h at room temperature. The solvents were evaporated and co-evaporated with iPrOH to give the title compound (0.012 g, 48%) as creamy paste.  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ ) 7.45 (d, 2H, J = 8.12 Hz); 7.23 – 7.33 (m, 4H); 7.16 – 7.09 (m, 3H); 6.88 (d, 2H, J = 3.68 Hz); 4.95 (bs, 1H); 4.21 (s, 2H); 4.07 – 4.02 (m, 1H); 3.92 – 3.68 (m, 6H); 3.29 – 3.26 (m, 1H); 1.03 (d, 6H, J = 6.6 Hz).

#### Example 24

##### **2-(4-(3-((4-Fluorophenyl)(isopropyl)amino)propyl)benzylamino)propane-1,3-diol hydrochloride**

*Step A: N-(3-(4-(Diethoxymethyl)phenyl)prop-2-ynyl)-4-fluorobenzenamine:* When 4-bromo-benzene-diethylacetal and 4-fluoro-N-propylpyridylamine was substituted for 4-bromo-N-(6,6-dimethylbicyclo[3.1.1] heptan-2-yl)benzene sulphonamide and but-3-yn-1-ol, respectively, in Example 18, Step B, the similar process afforded the title compound in 36% yield, as pale paste.  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ ) 7.38 (d, 2H, J = 8.7 Hz); 6.84 (d, 2H, J = 8.6 Hz); 6.92 (t, 2H, J = 7.8 Hz); 6.68 – 6.64 (m, 2H); 5.46 (s, 1H); 4.10 (s, 3H); 3.62 – 3.44 (m, 4H); 1.21 (t, 6H, J = 7.04 Hz).

*Step B: N-(3-(4-(Diethoxymethyl)phenyl)propyl)-4-fluorobenzenamine:* When the product of Step A was substituted for N-(6,6-dimethylbicyclo[3.1.1]heptan-2-yl)-4-(4-hydroxybut-1-ynyl)benzene sulphonamide in Example 18, Step C, the similar process afforded the title crude product (0.195 g; 96%) as creamy paste.  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ ) 7.35 (d, 2H, J = 8.01 Hz); 7.14 (d, 2H, J = 8.1 Hz); 6.85 (t, 2H, J = 7.54 Hz); 6.51 – 6.45 (m, 2H); 5.46 (s, 1H); 3.73 – 3.48 (m, 4H); 3.07 (t, 2H, J = 6.97 Hz); 2.71 (t, 2H, 7.45 Hz); 1.96 – 1.85 (m, 2H); 1.22 (t, 6H, J = 7.07 Hz).

*Step C: 4-(3-((4-Fluorophenyl)(isopropyl)amino)propyl)benzaldehyde:* A mixture of 4-(3-(4-fluorophenylamino)propyl)benzaldehyde (0.09 g, 0.35 mmol) [prepared from the product of Step B by stirring in acidified  $\text{CHCl}_3$ ] and 2-bromopropane (0.2 ml) and  $\text{K}_2\text{CO}_3$  (0.1 g; 0.73 mmol) was stirred at reflux in anhydrous DMF (5 ml) for 6 h. The solvent was evaporated under reduced pressure and the residue was diluted to 50 ml with EtOAc and washed with  $\text{H}_2\text{O}$ . The organic layer separated and dried over  $\text{MgSO}_4$  and filtered. The filtrate was evaporated to dryness and the residue was purified by FCC ( $\text{SiO}_2$ , hexane/EtOAc), to give the title compound (0.078 g, 83%) as creamy paste.  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ ) 10 (s, 1H); 7.78 (d, 2H,  $J = 8.13$  Hz); 7.32 (d, 2H,  $J = 8.07$  Hz); 6.93 – 6.86 (m, 2H); 6.82 – 6.66 (m, 2H); 3.07 (t, 2H,  $J = 7.5$  Hz); 2.71 (t, 2H,  $J = 7.5$  Hz); 2.71 (t, 2H, 7.62 Hz); 2.27 – 2.21 (m, 1H); 1.86 – 1.83 (m, 1H); 1.08 (d, 6H,  $J = 6.6$  Hz).

*Step D: N-(4-(3-((4-Fluorophenyl)(isopropyl)amino)propyl)benzyl)-2,2-dimethyl-1,3-dioxan-5-amine:* When the product of Step C and 2,2-dimethyl-1,3-dioxan-5-amine were substituted for 4-(5-((4-fluorophenyl)(isopropyl)amino)methyl)-thiophen-2-yl benzaldehyde and sarcosine hydrochloride in Example 22, Step C, the similar process afforded the title compound in 48% yield, as creamy paste.  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ ) 7.24 (d, 2H,  $J = 7.92$  Hz), 7.11 (d, 2H,  $J = 7.92$  Hz), 6.87 (t, 2H,  $J = 8.9$  Hz), 6.69 – 6.62 (m, 2H), 3.95 (dd, 2H,  $J = 11.7, 3.6$  Hz), 3.83 – 3.69 (m, 4H), 3.06 (t, 2H,  $J = 7.54$  Hz), 2.66 – 2.58 (m, 3H), 1.83 – 1.76 (m, 3H), 1.41 (s, 3H), 1.4 (s, 3H), 1.08 (d, 2H,  $J = 6.59$  Hz).

*Step E: 2-(4-(3-((4-Fluorophenyl)(isopropyl)amino)propyl)benzylamino)propane-1,3-diol hydrochloride salt:* When the product of Step D was substituted for N-(4-(5-((4-fluorophenyl)(isopropyl)amino)methyl)thiophen-2-yl)benzyl)-2,2-dimethyl-1,3-dioxan-5-amine in Example 23, Step B, the identical process afforded the title compound in 67% yield, as a creamy paste.  $^1\text{H}$ -NMR ( $\text{CDCl}_3$ ) 7.39 – 7.19 (m, 6H); 7.11 (d, 2H,  $J = 7.99$  Hz); 4.21 (s, 2H); 3.94 – 3.67 (m, 5H); 3.4 – 3.7 (m, 2H); 3.3 – 3.26 (m, 1H); 2.56 (b, 2H); 1.68 (b, 1H); 1.22 (b, 1H); 1.04 (d, 6H,  $J = 6.2$  Hz).

**Example 25****1-((4'-(N-(3-methoxyphenyl)-N-methylsulfamoyl)biphenyl-4-yl)methyl)azetidine-3-carboxylic acid**

*Step A: 4-Bromo-N-(3-methoxyphenyl)benzenesulfonamide:* To a stirred solution of 3-methoxyaniline (0.48 g, 3.92 mmol) in anhydrous pyridine (5 ml) 4-bromobenzene-sulphonyl chloride (0.5 g, 1.96 mmol) was added and the mixture was stirred for 0.5 h. The solvent was removed *in vacuo* and the residue was purified by FCC (SiO<sub>2</sub>, hexane/EtOAc) to give the title compound (0.51 g, 37%) as creamy paste. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 7.65 (d, 2H, J = 8.57 Hz); 7.52 (d, 2H, J = 8.57 Hz); 7.10 (t, 1H, J = 8.09 Hz); 6.69 – 6.61 (m, 2H); 4.37 (s, 2H); 3.71 (s, 3H, OMe).

*Step B: 4-Bromo-N-(3-methoxyphenyl)-N-methylbenzenesulfonamide:* To a stirred mixture of the product of Step A (0.5 g 1.46 mmol) and K<sub>2</sub>CO<sub>3</sub> (0.5 g) in anhydrous DMF (7 ml) was added CH<sub>3</sub>I (1 ml) and the stirring continued for 0.5 h at 50 °C. The mixture was diluted to 50 ml with H<sub>2</sub>O and extracted with EtOAc (50 ml). The organic layer was washed with H<sub>2</sub>O and dried over MgSO<sub>4</sub>, passed through silica gel bead and the filtrate was evaporated to dryness to give the title compound (0.5 g, 96%) as pale solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 7.58 (d, 2H, J = 8.64 Hz); 7.40 (d, 2H, J = 8.67 Hz); 7.18 (t, 1H, J = 8.15 Hz); 6.80 (dd, 1H, J = 8.34, 2.5 Hz); 6.69 (t, 1H, J = 2.20 Hz); 6.58 (bd, 1H); 3.75 (s, 3H, OMe); 3.14 (s, 3H, N-Me).

*Step C: 4'-Formyl-N-(3-methoxyphenyl)-N-methylbiphenyl-4-sulfonamide:* When the product of Step B and 4-carbaldehyde-boronic acid were substituted for 4-bromobenzaldehyde and 5-(hydroxymethyl)thiophen-2-ylboronic acid, respectively, in Example 22, Step A, the similar process afforded the title compound in 73% yield, as pale solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 10.07 (s, 1H); 7.98 (d, 2H, J = 6.56 Hz); 7.75 (d, 2H, J = 8.24 Hz); 7.7 (d, 2H, J = 8.82 Hz); 7.66 (d, 2H, J = 8.75 Hz); 7.19 (t, 1H, J = 8.13 Hz); 6.81 (dd, 1H, J = 8.30, 2.45 Hz); 6.74 (t, 1H, J = 2.17 Hz); 6.65 (dd, 1H, J = 7.96, 1.24 Hz); 3.76 (s, 3H); 3.20 (s, 3H).

*Step D: Methyl-1-((4'-(N-(3-methoxyphenyl)-N-methylsulfamoyl)biphenyl-4-yl)methyl) azetidine-3-carboxylate:* When the product of Step C and azetidine 3 methylcarboxylate hydrochloride were substituted for 4-(5-(((4-fluorophenyl)(isopropyl)amino)methyl)thiophen-2-yl)benzaldehyde and sarcosine hydrochloride, respectively, in Example 22, Step C, the similar process the title

compound in 69% yield, as pale paste. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 7.64 (d, 2H, J = 8.8 Hz); 7.58 (d, 2H, J = 8 Hz); 7.54 (d, 2H, J = 8.15 Hz); 7.36 (d, 2H, J = 8.12 Hz); 7.17 (t, 1H, J = 8.14 Hz); 6.80 (dd, 1H, J = 8.07, 2.21 Hz); 6.72 (t, 1H, J = 2.10 Hz); 6.64 (dd, 1H, J = 7.80, 1.67 Hz); 3.74 (s, 3H); 3.71 (s, 2H); 3.69 (s, 3H); 3.64 - 3.58 (m, 2H); 3.42 - 3.36 (m, 4H); 3.18 (s, 3H).

*Step E: 1-((4'-(N-(3-methoxyphenyl)-N-methylsulfamoyl)biphenyl-4-yl)methyl)azetidine-3-carboxylic acid:* To a stirred solution of the product of Step D (0.06 g, 0.13 mmol) in THF (3 ml) a solution of LiOH (0.006 g, 0.25 mmol) in H<sub>2</sub>O (1 ml) was added at 80 °C. The mixture was stirred for 0.5 h and solvents were evaporated to dryness. The residue was purified by FCC (SiO<sub>2</sub>) to give the title compound (0.0026 g, 43%) as creamy solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>:CD<sub>3</sub>OD) 7.58 (s, 4H); 7.58 (d, 2H, J = 8 Hz); 7.56 (d, 2H, J = 7.23 Hz); 7.49 (d, 2H, J = 8.25 Hz); 7.13 (t, 1H, J = 8.14 Hz); 6.76 (dd, 1H, J = 8.33, 2.05 Hz); 6.68 (t, 1H, J = 2.15 Hz); 6.58 (dd, 1H, J = 7.94, 1.32 Hz); 4.25 (s, 2H); 4.21 - 4.02 (m, 4H); 3.70 (s, 3H); 3.38 - 3.32 (m, 3H); 3.13 (s, 3H).

## Example 26

### **2-(((4'-(((4-Fluorophenyl)(isopropyl)amino)methyl)biphenyl-4-yl)methyl)(methyl) amino)acetic acid**

*Step A: 4-Fluoro-N-isopropylaniline:* A mixture of 4-fluoro-aniline (1.12 g; 10 mmol), 2-bromopropane (1.13 ml) and K<sub>2</sub>CO<sub>3</sub> (1.38 g, 10 mmol) in anhydrous DMF (6 ml) was stirred for 5 h at reflux. The mixture was cooled to room temperature, diluted to 100 ml with H<sub>2</sub>O and extracted with EtOAc (50 ml). The organic layer was washed with H<sub>2</sub>O (2 x 20 ml) and dried over MgSO<sub>4</sub> and filtered. The filtrate was evaporated to dryness and the residue was purified by FCC (SiO<sub>2</sub>, hexane/EtOAc) to give the title compound (0.65 g; 43%), as light yellow oil. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 6.89 - 6.82 (m, 2H); 6.53 - 6.47 (m, 2H); 3.58 - 3.49 (m, 1H); 1.18 (d, 6H, J = 6.25 Hz).

*Step B: N-(4-Bromobenzyl)-4-fluoro-N-isopropylbenzenamine:* When the product of Step A and 4-bromobenzaldehyde were substituted for sarcosine hydrochloride salt and 4-(5-(((4-fluorophenyl) isopropyl)amino)methyl)thiophen-2-yl)benzaldehyde, respectively, in Example 22, Step C, the similar process afforded the title compound in 93% yield, as a pale paste. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 7.39



(d, 2H, J = 8.18 Hz); 7.14 (d, 2H, J = 8.08 Hz); 6.91 – 6.81 (m, 2H); 6.62 – 6.57 (m, 2H); 4.26 (s, 2H); 4.11 – 4.04 (m, 1H); 1.18 (d, 2H, J = 5.34 Hz).

**Step C:** *4'-(((4-Fluorophenyl)(isopropyl)amino)methyl)biphenyl-4-carbaldehyde:* When the product of Step B and 4-carbaldehyde-boronic acid were substituted for 4-bromobenzaldehyde and 5-(hydroxymethyl) thiophen-2-ylboronic acid, respectively, in Example 22, Step A, the similar process afforded the title compound in 65% yield, as creamy gum. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 10.03 (s, 1H); 7.92 (d, 2H, J = 7.97 Hz); 7.56 (d, 2H, J = 7.95 Hz); 7.38 (d, 2H, J = 8.29 Hz); 6.86 (t, 2H, J = 8.46 Hz); 6.67 – 6.62 (m, 2H); 4.38 (s, 2H); 4.17 – 4.12 (m, 1H); 1.2 (d, 6H, J = 6.96 Hz).

**Step D:** *Methyl-2-(((4'-(((4-fluorophenyl)(isopropyl)amino)methyl)biphenyl-4-yl)methyl)(methyl)amino) acetate:* When the product of Step C was substituted for 4-(5-(((4-fluorophenyl))isopropyl) amino)methyl thiophen-2-yl)benzaldehyde in Example 22, Step C, the similar process afforded the title compound in 96% yield, as a creamy paste. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 7.54 – 7.49 (m, 4H); 7.38 – 7.31 (m, 4H); 6.86 (t, 2H, J = 8.45 Hz); 6.83 – 6.64 (m, 2H); 4.37 (s, 2H); 4.19 – 4.09 (m, 1H); 3.70 (s, 3H); 3.69 (s, 2H); 3.28 (s, 2H); 2.4 (s, 3H); 1.17 (d, 6H, J = 7.71 Hz).

**Step E:** *2-(((4'-(((4-Fluorophenyl)(isopropyl)amino)methyl)biphenyl-4-yl)methyl) (methyl)amino)acetic acid:* When the product of Step D was substituted for methyl-1-(4-((5-chlorobenzofuran-3-yl)methoxy) benzyl) azetidine-3-carboxylate in Example 25, Step E, the similar process afforded the title compound in 87% yield, as creamy solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub> + CD<sub>3</sub>OD) 7.40 – 7.18 (m, 8H); 6.76 (t, 2H, J = 8.82 Hz); 6.61 – 6.56 (m, 2H); 4.25 (s, 2H); 4.16 (s, 2H); 4.07 – 4.01 (m, 1H); 2.59 (s, 3H); 1.11 (d, 6H, J = 6.48 Hz).

## Example 27

### **1-((4'-(((4-Fluorophenyl)(isopropyl)amino)methyl)biphenyl-4-yl)methyl)azetidine-3-carboxylic acid:**

**Step A:** *Methyl-1-((4'-(((4-fluorophenyl)(isopropyl)amino)methyl)biphenyl-4-yl)methyl) azetidine-3-carboxylate:* When 4'-(((4-Fluorophenyl)(isopropyl) amino)methyl)biphenyl-4-carbaldehyde and azetidine 3-methylcarboxylate hydrochloride were substituted for 4-(5-(((4-fluorophenyl))isopropyl) amino)-methyl)thiophen-2-yl)benzaldehyde and sarcosine hydrochloride, respectively, in Example 22, Step C, the similar process afforded the title compound in 65% yield,

as creamy paste. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 7.53 (d, 2H, J = 8.12 Hz); 7.48 (d, 2H, J = 8.2 Hz); 6.85 (t, 2H, J = 9.09 Hz); 6.67 – 6.62 (m, 2H); 4.37 (s, 2H); 4.16 – 4.11 (m, 1H); 3.86 (bs, 4H); 3.69 (s, 3H); 3.58 – 3.51 (m, 1H); 1.19 (d, 6H, J = 6.63 Hz).

**Step B:** *1-((4'-(((4-Fluorophenyl)(isopropyl)amino)methyl)biphenyl-4-yl)methyl) azetidine-3-carboxylic acid:* When the product of Step A was substituted for methyl-1-(4-((5-chlorobenzofuran-3-yl)methoxy) benzyl) azetidine-3-carboxylate in Example 25, Step E, the similar process afforded the title compound in 60% yield, as creamy solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub> + CD<sub>3</sub>OD) 7.66 (d, 2H, J = 8.13 Hz); 7.62 – 7.57 (m, 4H); 7.41 (d, 2H, J = 8.07 Hz); 6.95 – 6.85 (m, 2H); 6.85 – 6.75 (m, 2H); 4.44 (s, 2H); 4.39 (s, 2H); 4.39 – 4.2 (m, 2H); 3.5 – 3.45 (m, 1H); 1.26 (d, 6H, J = 6.54 Hz).

### Example 28

#### **1-(4-(4-Oxo-4-(3,4,5-trimethoxyphenyl)but-2-en-2-yl)benzyl)azetidine-3-carboxylic acid**

**Step A:** *3-Bromo-1-(3,4,5-trimethoxyphenyl)but-2-en-1-one:* 1-(3,4,5-trimethoxyphenyl) but-2-yn-1-one (0.5 g, 2.58 mmol) was dissolved in AcOH (5 ml) and 48% HBr (5 drops) was added to it. The mixture was stirred for 2 h at 50 °C. This was evaporated to dryness and the residue was diluted to 50 ml with EtOAc, washed with NaHCO<sub>3</sub> solution and H<sub>2</sub>O. The organic layer was dried over MgSO<sub>4</sub> and filtered. The filtrate was evaporated to dryness and dried *in vacuo* to give the title compound (0.53 g, 65%), as a pale solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 7.30 (s, 1H); 7.03 (s, 2H); 3.91 (s, 9H); 2.79 (s, 3H).

**Step B:** *4-(4-Oxo-4-(3,4,5-trimethoxyphenyl)but-2-en-2-yl)benzaldehyde:* When the product of Step A and 4-carbaldehyde-boronic acid were substituted for 5-(hydroxymethyl) thiophen-2-ylboronic acid and 4-bromobenzaldehyde, respectively, in Example 22, Step A, the similar process afforded the title compound in 81% yield, as creamy gum. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 10.05 (s, 1H); 7.92 (d, 2H, J = 8.25 Hz); 7.68 (d, 2H, J = 8.28 Hz); 7.23 (s, 2H); 7.10 (s, 1H); 3.91 (s, 9H); 2.55 (s, 3H).

**Step C:** *Methyl-1-(4-(4-oxo-4-(3,4,5-trimethoxyphenyl)but-2-en-2-yl)benzyl) azetidine-3-carboxylate:* When the product of Step B and azetidine 3 methylcarboxylate hydrochloride were substituted for 4-(5-(((4-fluorophenyl)) isopropyl)amino) methyl thiophen-2-yl)benzaldehyde and sarcosine

hydrochloride, respectively, in Example 22, Step-C, the similar process afforded the title compound in 66% yield, as pale paste. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 7.49 (d, 2H, J = 8.28 Hz); 7.30 (d, 2H, J = 8.29 Hz); 7.22 (s, 2H), 7.06 (s, 1H); 3.90 (s, 9H); 3.68 (s, 3H); 3.64 (s, 2H); 3.56 - 3.52 (m, 2H); 3.37 - 3.32 (m, 3H).

*Step D: 1-(4-(4-oxo-4-(3,4,5-trimethoxyphenyl)but-2-en-2-yl)benzyl)azetidine-3-carboxylic acid:* When the product of Step C was substituted for methyl-1-(4-((5-chlorobenzofuran-3-yl)methoxy) benzyl) azetidine-3-carboxylate in Example 25, Step E, the similar process afforded the title compound in 53% yield, as light yellow solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub> + CD<sub>3</sub>OD) 7.31 (d, 2H, J = 8.18 Hz); 7.28 (d, 2H, J = 8.28 Hz); 6.71 (s, 2H); 6.62 (s, 1H); 4.24 (s, 2H); 4.17 - 4.04 (m, 4H); 3.55 - 3.38 (s, 1H); 2.15 (s, 3H).

### Example 29

#### **1-((4'-(3-(3-(Trifluoromethyl)phenyl)but-2-enoyl)biphenyl-4-yl)methyl)azetidine-3-carboxylic acid:**

*Step A: 1-(4-Bromophenyl)but-2-yn-1-one:* To an ice cold solution of 4-bromobenzaldehyde (1.3 g, 7 mmol) 0.5 M solution of propynyl magnesium bromide in THF (15 ml, 7.5 mmol) was added under N<sub>2</sub>. The mixture was stirred for 10 min, quenched with saturated NH<sub>4</sub>Cl solution and diluted to 50 ml with EtOAc. The organic layer was washed with H<sub>2</sub>O, dried over MgSO<sub>4</sub> and filtered. The filtrate was evaporated to dryness and the residue was dissolved in 1,4-dioxane (25 ml). To it MnO<sub>2</sub> (2 g) was added and the resulting suspension was stirred for 4 h at reflux. The mixture was filtered through Celite pad and the filtrate was evaporated to dryness and dried *in vacuo* to give the title compound (1.29 g, 83%) as a pale solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 7.97 (d, 2H, J = 9 Hz); 7.61 (d, 2H, J = 9 Hz); 2.14 (s, 3H).

*Step B: 4'-But-2-ynoylbiphenyl-4-carbaldehyde:* When the product of Step A and 4-carbaldehyde-boronic acid were substituted for 4-bromobenzaldehyde and 5-(hydroxymethyl)thiophen-2-ylboronic acid, respectively, in Example 22, Step A, the similar procedure afforded the title compound in 58% yield, as a creamy gum. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 10.07 (s, 1H); 8.23 (d, 2H, J = 8.4 Hz); 7.98 (d, 2H, J = 8.4 Hz); 7.78 (d, 2H, J = 8.24 Hz); 7.72 (d, 2H, J = 8.54 Hz); 2.18 (s, 3H).

*Step C: 4'-(3-Bromobut-2-enoyl)biphenyl-4-carbaldehyde:* When the product of Step B was substituted for 1-(3,4,5-trimethoxyphenyl) but-2-yn-1-one in

Example 28, Step A, the similar process afforded the title compound in 56% yield, as pale solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 10.07 (s, 1H); 8.03 – 7.96 (m, 4H); 7.79 – 7.71 (m, 4H); 7.41 (s, 1H); 2.84 (s, 3H).

*Step D: 4'-(3-(3-(Trifluoromethyl)phenyl)but-2-enoyl)biphenyl-4-carbaldehyde:* When the product of Step C and 3-trifluoromethyl-boronic acid were substituted for 4-bromo benzaldehyde and 5-(hydroxymethyl) thiophen-2-ylboronic acid, respectively, in Example 22, Step A, the similar procedure afforded the title compound in 73% yield, as creamy gum. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 10.07 (s, 1H); 8.1 (d, 2H, J = 8.5 Hz); 7.99 – 7.93 (m, 3H); 7.8 – 7.57 (m, 5H); 7.18 (s, 1H); 2.61 (s, 3H).

*Step E: Methyl-1-((4'-(3-(3-(trifluoromethyl)phenyl)but-2-enoyl)biphenyl-4-yl)methyl) azetidine-3-carboxylate:* When the product of Step D and azetidine 3 methylcarboxylate hydrochloride were substituted for 4-(5-(((4-fluorophenyl)) isopropyl)amino) methyl) thiophen-2-yl)benzaldehyde and sarcosine hydrochloride, respectively, in Example 22, Step C, the similar procedure afforded the title compound in 58% yield, as a pale paste. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.04 (d, 2H, J = 8.4 Hz); 7.78 – 7.51 (m, 8H); 7.4 (d, 2H, J = 8.2 Hz); 7.16 (d, 1H, J = 1.21 Hz); 3.76 (s, 2H); 3.7 (s, 3H); 3.73 – 3.62 (m, 4H); 3.47 – 3.41 (m, 3H); 2.58 (bs, 3H).

*Step F: 1-((4'-(3-(3-(Trifluoromethyl)phenyl)but-2-enoyl)biphenyl-4-yl)methyl) azetidine-3-carboxylic acid:* When the product of Step E was substituted for methyl-1-(4-((5-chlorobenzofuran-3-yl)methoxy) benzyl) azetidine-3-carboxylate in Example 25, Step E, the similar process afforded the title compound in 62% yield, as a light yellow solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub> + CD<sub>3</sub>OD) 7.84 (d, 2H, J = 8.34 Hz); 7.59 – 7.33 (m, 6H); 4.7 (d, 2H); 3.96 – 3.92 (m, 4H); 3.19 – 3.14 (m, 1H); 2.36 (s, 3H).

### Example 30

#### **1-(4-(4-Oxo-2-phenyl-4H-chromen-6-yl)benzyl)azetidine-3-carboxylic acid:**

*Step A: 5-Bromo-2-isopropoxybenzaldehyde:* To a stirred solution of 2-isopropoxybenzaldehyde (0.51 g, 3.1 mmol), in DMF (10 ml) NBS (0.55 g, 3.1 mmol) was added and the reaction mixture was stirred overnight at room temperature. The reaction was quenched with NaHCO<sub>3</sub> solution and extracted in EtOAc (50 ml). The organic layer was washed with H<sub>2</sub>O, dried over MgSO<sub>4</sub> and

filtered. The filtrate was evaporated to dryness to give the title compound (0.62 g, 82%) as light yellow oil. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 10.37 (s, 1H); 7.89 (d, 1H, J = 2.52 Hz); 7.55 (dd, 1H, J = 8.85, 2.58 Hz); 6.87 (d, 1H, J = 8.88 Hz); 4.67 – 4.58 (m, 1H); 1.35 (d, 6H, J = 6.03 Hz).

**Step B: 1-(5-Bromo-2-isopropoxyphenyl)-3-phenylprop-2-yn-1-one:** To a stirred solution of phenyl-acetylene (0.27 ml, 2.46 mmol) in anhydrous THF (3 ml) 2M iPrMgCl in THF (1.25 ml) was added drop wise at 0 °C under N<sub>2</sub>. After stirring for 15 min, the solution of product of Step A (0.5 g, 2.06 mmol) in anhydrous THF (2 ml) was added drop wise and the mixture was stirred for 1 h at room temperature. The mixture was quenched with saturated NH<sub>4</sub>Cl and extracted with EtOAc (50 ml). The organic layer was washed with H<sub>2</sub>O, dried over MgSO<sub>4</sub> and filtered. The filtrate was evaporated to dryness to give a creamy paste (0.59 g; 83%). [<sup>1</sup>H-NMR (CDCl<sub>3</sub>) 7.68 (d, 1H, J = 2.49 Hz); 7.46 – 7.43 (m, 2H); 7.36 (dd, 1H, J = 8.75, 2.54 Hz); 7.32-7.28 (m, 3H); 6.79 (d, 1H, J = 6.77 Hz); 5.79 (d, 1H, J = 5.23 Hz); 4.64 – 4.58 (m, 1H); 3.13 (d, 1H, J = 5.91 Hz); 1.37 (d, 6H)]. This was dissolved in dioxane (10 ml) and MnO<sub>2</sub> (1 g) was added to it. The resulting suspension was stirred for 6 h at reflux, then filtered through Celite\* and the solvent was evaporated to dryness to give the title compound (0.54 g, 76.5%), as light yellow paste. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.00 (d, 1H, J = 2.61 Hz); 7.61 – 7.52 (m, 3H); 7.44 – 7.35 (m, 3H); 6.88 (d, 1H, J = 8.91 Hz); 4.68 – 4.60 (m, 1H); 1.36 (d, 6H).

**Step C: 4-(4-oxo-2-phenyl-4H-chromen-6-yl)benzaldehyde:** A solution of the product of Step B (0.3 g, 0.88 mmol), was treated with HBr/ AcOH, as described in Example 28, Step A, to give a light creamy solid (0.18 g, 68%). <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.36 (d, 1H, J = 2.43 Hz); 7.92 – 7.88 (m, 2H); 7.77 (dd, 1H, J = 8.88, 2.46 Hz); 7.58 – 7.50 (m, 3H); 7.47 (d, 1H, J = 8.86 Hz); 6.83 (s, 1H)], which was reacted with 4-carbaldehyde-boronic acid in Example 22, Step A, to give the title compound (0.078 g, 48%), as creamy solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 10.07 (s, 1H); 8.5 (d, 1H, J = 2.31 Hz); 8.00 – 7.93 (m, 2H); 7.84 (d, 2H, J = 8.22 Hz); 7.71 – 7.63 (m, 3H); 7.56 – 7.48 (m, 3H); 6.87 (s, 1H).

**Step D: Methyl 1-(4-(4-oxo-2-phenyl-4H-chromen-6-yl)benzyl)azetidine-3-carboxylate:** When the product of Step C and azetidine 3 methylcarboxylate hydrochloride were substituted for -(5-(((4-fluorophenyl) isopropyl)amino) methyl) thiophen-2-yl)benzaldehyde and sarcosine hydrochloride, respectively, as in Example 22, Step C, the similar procedure afforded the title compound in 31%

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yield, as light green paste.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) 8.43 (d, 1H,  $J = 2.29$  Hz); 7.96 - 7.91 (m, 3H); 7.63 (d, 3H); 7.54 - 7.39 (m, 3H); 7.38 (d, 2H,  $J = 8.18$  Hz); 6.85 (s, 1H); 3.73 (s, 3H); 3.71 (s, 2H); 3.71 - 3.62 (broad, 2H); 3.42 - 3.35 (b, 3H).

**Step E:** *1-(4-(4-Oxo-2-phenyl-4H-chromen-6-yl)benzyl)azetidine-3-carboxylic acid*: When the product of Step D was substituted for methyl-1-(4-((5-chlorobenzofuran-3-yl)methoxy) benzyl) azetidine-3-carboxylate in Example 25, Step E, the similar process afforded the title compound in 36% yield, as creamy solid.  $^1\text{H-NMR}$  ( $\text{CDCl}_3 + \text{CD}_3\text{OD}$ ) 8.31 (broad s, 1H); 7.86 (broad s, 3H); 7.77 - 7.52 (m, 7H); 6.69 (s, 1H); 4.21 (broad s, 2H); 4.18 - 4.02 (m, 4H); 3.3 (s, 1H).

### Example 31

#### **3'-(1-Admantanyl)-4'methoxybiphenyl-4-yl)methyl)azetidine-3-carboxylic acid:**

**Step A:** *2-(1-Admantanyl)-4-bromophenol*: To a stirred solution of 4-bromophenol (1 g; 5.8 mmol) and adamant-1-ol (0.88 g; 5.8 mmol) in AcOH (5 ml) concentrated  $\text{H}_2\text{SO}_4$  (1 ml) was added drop wise and stirring was continued for 50 h. The solvent was distilled to half of the volume and the mixture was poured onto ice cold  $\text{H}_2\text{O}$  (100 ml) and extracted with EtOAc (150 ml). The organic layer was washed with  $\text{NaHCO}_3$  solution, dried over  $\text{MgSO}_4$  and filtered. The filtrate was evaporated to dryness and the residue was purified by FCC ( $\text{SiO}_2$ , hexane/EtOAc) to give the title compound (0.976 g, 55%), as a colourless solid.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) 7.27 (d, 1H,  $J = 2.43$ Hz); 7.13 (dd, 1H,  $J = 8.4 - 2.43$  Hz); 6.51 (d, 1H,  $J = 8.37$  Hz); 4.76 (s, 1H, OH); 2.07 (s, 10H); 1.75 (b, 5H).

**Step B:** *2-(1-Admantanyl)-4-bromomethoxybenzene*: To a stirred mixture of the product of Step A (0.5 g; 1.62 mmol) and  $\text{K}_2\text{CO}_3$  (0.335 g; 2.42 mmol) in anhydrous DMF (5 ml)  $\text{CH}_3\text{I}$  (1 ml) was added. The reaction mixture was stirred for 2 h and then diluted to 100 ml with  $\text{H}_2\text{O}$  and extracted with EtOAc (100 ml). The organic layer was dried over  $\text{MgSO}_4$  and filtered. The filtrate was passed through silica gel bead. The filtrate was evaporated to dryness to give the title compound (0.49 g, 94%), as light yellow green solid.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) 7.27 - 7.22 (m, 2H); 6.31 (d, 1H,  $J = 6.5$  Hz); 3.78 (s, 3H); 2.04 (s, 10H); 1.74 (b, 5H).

**Step C:** *3'-(1-Admantanyl)4'methoxy-4-carbaldehyde*: When the product of Step B and 4-carbaldehyde-boronic acid were substituted for 4-bromobenzaldehyde and 5-(hydroxymethyl)thiophen-2-ylboronic acid,

respectively, in Example 22, Step A, the similar process afforded the title compound in 42% yield, as pale solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 10.02 (s, 1H); 7.90 (d, 2H, J = 8.22 Hz); 7.70 (d, 2H, J = 8.22 Hz); 7.51 (d, 1H, J = 2.31 Hz); 7.46 (dd, 1H, J = 8.4 – 2.3 Hz); 6.95 (d, 1H, J = 8.4 Hz); 3.88 (s, 3H); 2.14 (b, 6H); 2.07 (b, 3H); 1.8 (b, 6H).

**Step D:** *Methyl-1-3'-(1-admantanyl)-4-methoxybiphenyl-4-yl)methyl)azetidine-3-carboxylate*: When the product of Step C and azetidine 3 methylcarboxylate hydrochloride were substituted for 4-(5-(((4-fluorophenyl)) isopropyl)amino)methyl)thiophen-2-yl)benzaldehyde and sarcosine hydrochloride, respectively in Example 22, Step C, the similar procedure afforded the title compound in 82% yield, as pale paste. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 7.48 (d, 2H, J = 8.16 Hz); 7.42 (d, 1H, J = 2.3 Hz); 7.37 (dd, 1H, J = 8.4 – 2.3 Hz); 7.28 (d, 2H, J = 8.15 Hz); 6.91 (d, 1H, J = 8.4 Hz); 3.85 (s, 3H); 3.7 (s, 3H); 3.62 (s, 2H); 3.56 – 3.52 (m, 2H); 3.35 – 3.31 (m, 3H); 2.13 (b, 5H); 2.06 (b, 3H); 1.77 (b, 5H); 1.65 (b, 2H).

**Step E:** *3'-(1-Admantanyl)-4-methoxybiphenyl-4-yl)methyl)azetidine-3-carboxylic acid*: When the product of Step D was substituted for methyl-1-(4-((5-chlorobenzofuran-3-yl)methoxy) benzyl) azetidine-3-carboxylate in Example 25, Step E, the similar procedure afforded title compound in 37% yield, as creamy solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub> + CD<sub>3</sub>OD) 7.53 (broad s, 4H); 7.36 (d, 1H, J = 2.1 Hz); 7.31 (broad d, 1H, J = 8.35 Hz); 6.87 (d, 2H, J = 8.47 Hz); 4.3 (s, 2H); 4.19 – 4.15 (m, 4H); 3.81 (s, 3H); 3.54 – 3.51 (m, 1H); 2.07 – 2.00 (m, 9H); 1.73 – 1.71 (m, 6H).

## Example 32

### **1-(4-(3-(1-Admantnyl)-4-methoxybenzyloxy)benzyl)azetidine-3-carboxylic acid:**

**Step A:** *3-(1-Admantanyl)-4-methoxybenzaldehyde*: When 4-hydroxybenzaldehyde was substituted for 4-bromophenol in Example 31, Step A, the similar procedure afforded 3-(1-admantanyl)-4-hydroxybenzaldehyde in 56% yield, as a pale white solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 9.84 (s, 1H); 7.78 (d, 1H, J = 2.07 Hz); 7.61 (dd, 1H, J = 8.13, 2.01 Hz); 6.77 (d, 1H, J = 8.16 Hz); 5.88 (bs, 1H); 2.12 (s, 6H); 2.09 (s, 3H); 1.78 (s, 6H). This was methylated by similar procedure as described in Example 31, Step B, to give the title compound in 64% yield, as light yellow solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 9.86 (s, 1H); 7.76 (d, 1H, J = 2.07 Hz); 7.7 (dd,

1H, J = 8.4, 2.1 Hz); 6.95 (d, 1H, J = 8.4 Hz); 3.91 (s, 3H); 2.09 (s, 9H); 1.76 (s, 6H).

*Step B: 4-(3-(1-Admantnyl)-4-methoxybenzyloxy)benzaldehyde:* To a stirred suspension of product of Step A (0.09 g, 0.32 mmol) in MeOH (5 ml) NaBH<sub>4</sub> (0.018 g, 0.47 mmol) was added and the mixture was stirred for 0.5 h. The solvent was evaporated to dryness and the residue was taken in NaHCO<sub>3</sub> solution and extracted with EtOAc (25 ml). The organic layer was separated, dried over MgSO<sub>4</sub>, and filtered. The filtrate was evaporated and the residue was dried *in vacuo* to give a relevant benzyl alcohol (0.095 g; 100%), as a creamy gum. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 7.21 (d, 1H, J = 2.17 Hz); 7.16 (dd, 1H, J = 8.21, 2.17 Hz); 6.83 (d, 1H, J = 8.21 Hz); 4.59 (bd, 2H, J = 4.24 Hz); 3.82 (s, 3H, OMe); 2.08 (s, 6H); 2.05 (s, 3H); 1.76 (s, 6H). To a stirred solution of above product in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (5 ml) CBr<sub>4</sub> (0.14 g, 0.42 mmol) was added, followed by PPh<sub>3</sub> (0.11 g, 0.42 mmol). The mixture was stirred for 1 h at room temperature and the solvent was distilled off. The residue was taken in EtOAc (10 ml) and the insoluble material was filtered off. The filtrate was evaporated to give the relevant benzyl bromide (0.14 g), which was added as a solution in DMF (2 ml) to a stirred suspension of 4-hydroxybenzaldehyde (0.069 g, 0.57 mmol) and K<sub>2</sub>CO<sub>3</sub> (0.080 g, 0.58 mmol) in anhydrous DMF (3 ml) and this was stirred for 2 h at 70 °C. The mixture was quenched with saturated NH<sub>4</sub>Cl solution and extracted with EtOAc (50 ml). The organic layer was dried over MgSO<sub>4</sub> and filtered. The filtrate was evaporated to dryness and the residue was purified by FCC (SiO<sub>2</sub>, hexane/EtOAc) to give the title compound (0.05 g, 31.4%), as colourless solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 9.88 (s, 1H); 7.82 (d, 2H, J = 8.78 Hz); 7.26 – 7.21 (m, 3H); 7.01 (d, 2H, J = 8.7 Hz); 6.87 (d, 1H, J = 8.2 Hz); 5.04 (s, 2H); 3.83 (s, 3H); 2.08 (s, 6H); 2.05 (s, 3H); 1.76 (s, 6H).

*Step C: Methyl 1-(4-(3-(1-admantanyl)-4-methoxybenzyloxy)benzyl)azetidine-3-carboxylate:* When the product of Step B and azatidine 3 methylcaboxylate hydrochloride were substituted for 4-(5-(((4-fluorophenyl))-isopropyl)amino)methyl thiophen-2-yl)benzaldehyde and sarcosine hydrochloride, respectively, in Example 22, Step C, the similar procedure afforded the title compound in 69% yield, as a pale paste. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 7.24 – 7.20 (m, 2H); 7.16 (d, 2H, J = 8.55 Hz); 6.91 (d, 2H, J = 8.62 Hz); 6.85 (d, 1H, J =



8.17 Hz); 4.92 (s, 2H); 3.82 (s, 3H); 3.69 (s, 3H); 3.52 (s, 2H); 3.49 (s, 1H); 3.47 (s, 2H); 3.31 – 3.24 (m, 3H); 2.08 (s, 6H); 2.04 (s, 3H); 1.75 (s, 6H).

*Step D: 1-(4-(3-(1-Admantnyl)-4-methoxybenzyloxy)benzyl)azetidine-3-carboxylic acid:* When the product of Step C was substituted for methyl-1-(4-((5-chlorobenzofuran-3-yl)methoxy) benzyl) azetidine-3-carboxylate in Example 25, Step E, the similar procedure afforded the title compound in 61% yield, as creamy solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>:CD<sub>3</sub>OD) 7.33 (d, 2H, J = 8.59 Hz); 7.17 – 7.12 (m, 2H); 6.92 (d, 2H, J = 8.64 Hz); 6.79 (d, 1H, J = 8.21 Hz); 4.87 (s, 2H); 4.13 (s, 2H); 4.08 – 4.02 (m, 4H); 2.0 (s, 6H); 1.97 (s, 3H); 1.68 (s, 6H).

### Example 33

#### **1-(4-(2-(6,6-Dimethylbicyclo[3.1.1]heptan-2-yl)ethoxy)benzyl)azetidine-3-carboxylic acid:**

*Step A: 4-(2-(6,6-Dimethylbicyclo[3.1.1]heptan-2-yl)ethoxy)benzaldehyde:* (6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl)ethanol was brominated as described in Example 32, Step B and the bromination product was used in next step without further purification, where it was treated with 4-hydroxybenzaldehyde as described in Example 32, Step B to afford the title compound in 91% yield, as creamy paste.

*Step B: Methyl-1-(4-(2-(6,6-dimethylbicyclo[3.1.1]heptan-2-yl)ethoxy)benzyl) azetidine-3-carboxylate:* When the product of Step A and azetidine 3 methylcarboxylate hydrochloride were substituted for 4-(5-(((4-fluorophenyl))- isopropyl)amino)methyl)thiophen-2-yl)benzaldehyde and sarcosine hydrochloride, respectively, in Example 22, Step C, the similar procedure afforded the title compound in 76% yield, as light yellow paste. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 7.17 (d, 2H, J = 8.56 Hz); 6.81 (d, 2H, J = 8.61 Hz); 3.91 (t, 2H, J = 1.98 Hz); 3.71 – 3.65 (m, 7H); 3.44 – 3.41 (m, 3H); 2.03 – 1.17 (m, 10H); 1.17 (s, 3H); 1.01 (s, 3H).

*Step C: 1-(4-(2-(6,6-Dimethylbicyclo[3.1.1]heptan-2-yl)ethoxy)benzyl) azetidine-3-carboxylic acid:* When the product of Step B was substituted for methyl-1-(4-((5-chlorobenzofuran-3-yl)methoxy)benzyl) azetidine-3-carboxylate in Example 25, Step E, the similar procedure afforded the title compound in 87% yield, as creamy paste. <sup>1</sup>H-NMR (CDCl<sub>3</sub> + CD<sub>3</sub>OD) 7.21 (d, 2H, J = 7.98 Hz); 6.79

(d, 2H,  $J = 7.99$  Hz); 3.94 – 3.71 (m, 8H); 3.27 – 3.25 (m, 1H); 2.36 – 1.20 (m, 10H); 1.14 (s, 3H); 0.97 (s, 3H).

#### Example 34

##### **1-(4-(12-Oxo-12H-chromeno[2,3-b]quinolin-2-yl)benzyl)azetidine-3-carboxylic acid:**

*Step A: 6-Bromo-4-oxo-2-(phenylamino)-4H-chromene-3-carbaldehyde:* To a stirred solution of 6-bromo-4-oxo-4H-chromene-3-carbaldehyde (2 g, 7.93 mmol) in anhydrous benzene (15 ml) phenyl-hydroxylamine (0.95 g, 8.71 mmol) was added. The solution was kept for 1 h at room temperature when the crystalline solid appeared. To this glacial AcOH (0.5 ml) was added and the mixture was stirred for 5 h at reflux. The solvent was distilled off and the residue was crystallized from MeOH to give the title compound (2.1 g, 78%), as yellow crystalline solid.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) 12.43 (broad s, 1H); 10.28 (s, 1H); 8.34 (d, 1H,  $J = 2.46$  Hz); 7.69 (dd, 1H,  $J = 8.76, 2.49$  Hz); 7.46 – 7.29 (m, 6H).

*Step B: 2-Bromo-12H-chromeno[2,3-b]quinolin-12-one:* To the product of Step A (1 g; 2.92 mmol) concentrated  $\text{H}_2\text{SO}_4$  (1 ml) was gently added with stirring. The mixture was kept in sealed vial for 24 h, at room temperature, than poured onto ice water and extracted with  $\text{CH}_2\text{Cl}_2$  (50 ml). The organic layer was washed with  $\text{NaHCO}_3$  solution,  $\text{H}_2\text{O}$ , dried over  $\text{MgSO}_4$  and filtered. The filtrate was distilled off and the residue was crystallized from  $\text{CH}_3\text{CN}$  to give the title compound (0.73 g, 77%), as green yellow solid.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) 9.28 (s, 1H); 8.44 (d, 1H,  $J = 2.1$  Hz); 8.1 – 8.06 (m, 2H); 7.94 – 7.84 (m, 2H); 7.63 (t, 1H,  $J = 7.88$  Hz); 7.51 (d, 1H,  $J = 8.83$  Hz).

*Step C: 4-(12-Oxo-12H-chromeno[2,3-b]quinolin-2-yl)benzaldehyde:* When the product of Step B and 4-carbaldehyde-boronic were substituted for 4-bromobenzaldehyde and 5-(hydroxymethyl)thiophen-2-ylboronic acid, respectively, in Example 22, Step A, the similar procedure afforded the title compound in 52% yield, as off white solid.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ) 10.08 (s, 1H); 9.33 (s, 1H); 8.6 (d, 1H,  $J = 2.34$  Hz); 8.14 – 8.05 (m, 3H); 8.00 (d, 2H,  $J = 8.25$  Hz); 7.96 – 7.89 (m, 1H); 7.85 (d, 2H,  $J = 8.22$  Hz); 7.74 (d, 1H,  $J = 8.7$  Hz); 7.64 (t, 1H,  $J = 7.8$  Hz).

*Step D: Methyl-1-(4-(12-oxo-12H-chromeno[2,3-b]quinolin-2-yl)benzyl)azetidine-3-carboxylate:* When the product of Step C and azetidine 3

methylcaboxylate hydrochloride were substituted for 4-(5-(((4-fluorophenyl)isopropyl)amino) methyl) thiophen-2-yl) benzaldehyde and sarcosine hydrochloride, respectively, in Example 22, Step C, the similar procedure afforded the title compound in 48% yield, as pale paste. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 9.32 (s, 1H); 8.53 (s, 1H); 8.12 – 8.07 (m, 2H); 8.00 (dd, 1H, J = 8.7, 2.4 Hz); 7.91 (t, 1H, J = 5.55 Hz); 7.7 – 7.6 (m, 4H); 7.38 (d, 2H, J = 8.22 Hz); 3.71 (s, 3H); 3.67 (s, 2H); 3.57 – 3.53 (m, 2H); 3.39 – 3.35 (m, 3H).

*Step E: 1-(4-(12-Oxo-12H-chromeno[2,3-b]quinolin-2-yl)benzyl)azetidine-3-carboxylic acid:* When the product of Step D was substituted for methyl-1-(4-((5-chlorobenzofuran-3-yl)methoxy)benzyl) azetidine-3-carboxylate in Example 25, Step E, the similar procedure afforded the title compound in 50% yield, as yellow solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub> + CD<sub>3</sub>OD) 9.25 (broad s, 1H); 8.44 (m, 2H); 7.76 – 7.54 (m, 5H); 4.31 – 4.07 (m, 4H); 4.27 – 3.95 (m, 2H).

### Example 35

#### 1-(4-((5-chlorobenzofuran-3-yl)methoxy)benzyl)azetidine-3-carboxylic acid

*Step A: (5-Chlorobenzofuran-3-yl)methanol:* To a mixture of 4-chloro-2-iodophenol (1 g, 3.92 mmol), tert-butyl(3-(tert-butyldimethylsilyl)prop-2-ynyloxy)-dimethylsilane (1.93 g, 6.8 mmol), LiCl (0.15 g; 3.5 mmol) and Na<sub>2</sub>CO<sub>3</sub> (0.636 g; 6 mmol) in anhydrous DMF (10 ml) Pd(OAc)<sub>2</sub> (0.3 g) was added at 100 °C under N<sub>2</sub> and heating was continued for 1.5 h. The solvent was removed *in vacuo* and the residue was diluted to 100 ml with EtOAc, washed with H<sub>2</sub>O, dried over MgSO<sub>4</sub> and filtered. The filtrate was evaporated to dryness and the residue was purified by FCC (SiO<sub>2</sub>, hexane/EtOAc) to give the coupling product (0.64 g; 26%). This was dissolved in THF (5 ml) and 1M TBAF in THF (2 ml) was added to it and the mixture was stirred for 4 h at reflux. The solvent was distilled off and the residue was dilute to 50 ml with EtOAc, washed with 1M HCl, H<sub>2</sub>O, dried over MgSO<sub>4</sub> and filtered. The filtrate was evaporated to dryness and the residue was purified by FCC (SiO<sub>2</sub>, hexane/EtOAc) to give the title compound (0.33 g; 99%), as creamy paste. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 7.63 (d, 1H, J = 2.11 Hz); 6.60 (b, 1H); 7.37 (d, 1H, J = 8.72 Hz); 7.25 (dd, 1H, J = 8.71, 2.13 Hz); 4.79 (s, 2H).

*Step B: 4-((5-Chlorobenzofuran-3-yl)methoxy)benzaldehyde:* When the product of Step A was substituted for 3-(1-admantanyl)-4-methoxy benzaldehyde in Example 32, Step B, the similar procedure afforded the title compound in 9%

yield, as pale paste. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 9.89 (s, 1H); 7.84 (d, 2H, J = 8.74 Hz); 7.72 (s, 1H); 7.60 (d, 1H, J = 2.07 Hz); 7.41 (d, 1H, J = 8.76 Hz); 7.28 (dd, 1H, J = 8.75, 2.09 Hz); 7.09 (d, 2H, J = 8.73 Hz); 5.23 (s, 2H).

*Step C: Methyl-1-(4-((5-chlorobenzofuran-3-yl)methoxy)benzyl) azetidine-3-carboxylate:* When the product of Step B and azetidine 3-methylcarboxylate hydrochloride were substituted for 4-(5-((4-fluorophenyl)(isopropyl)amino)methyl)-thiophen-2-yl) benzaldehyde and sarcosine hydrochloride, respectfully, in Example 22, Step C, the similar procedure afforded the title compound in 45% yield, as off white solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 7.68 (s, 1H); 7.60 (bs, 1H); 7.39 (d, 2H, J = 8.77 Hz); 7.28 – 7.18 (m, 3H); 6.93 (d, 2H, J = 6.62 Hz); 5.12 (s, 2H); 3.69 (s, 3H); 3.54 – 3.47 (m, 5H); 3.36 – 3.28 (m, 4H).

*Step D: 1-(4-((5-chlorobenzofuran-3-yl)methoxy)benzyl)azetidine-3-carboxylic acid:* When the product of Step C was substituted for methyl-1-(4-((5-chlorobenzofuran-3-yl)methoxy) benzyl) azetidine-3-carboxylate in Example 25, Step E, the similar procedure afforded the title compound in 57% yield, as creamy solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub> + CD<sub>3</sub>OD) 7.78 (s, 1H); 7.57 (d, 2H, J = 2.06 Hz); 7.53 (s, 1H); 7.39 (d, 1H, J = 8.8 Hz); 7.36 (d, 2H, J = 8.66 Hz); 7.24 (dd, 1H, J = 8.75, 2.12 Hz); 7.04 (d, 2H, J = 8.67 Hz); 5.18 (s, 2H); 4.20 – 4.06 (m, 6H); 3.36 – 3.27 (m, 1H).

### Example 36

#### **2-Amino-2-(5-(5-(3-chloro-4-propoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)propane-1,3-diol**

*Step A: N-Hydroxy-3-iodo-4-isopropoxybenzimidamide:* A suspension of 3-iodo-4-isopropoxybenzonitrile (0.576 g; 2 mmol), HCl x NH<sub>2</sub>OH (0.276 g; 4 mmol) and DIPEA (0.69 ml; 4 mmol) in EtOH (50 ml) was stirred for 18 h at 50 °C. The solvent was distilled off and the residue was diluted to 50 ml with EtOAc and washed with H<sub>2</sub>O. The organic layer was separated, dried over MgSO<sub>4</sub> and filtered. The filtrate was distilled off to give the title product (0.61 g; 95%), as colourless solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.0 (d, 1H, J = 2.22 Hz); 7.55 (dd, 1H, J = 9.54, 2.28 Hz); 6.77 (d, 1H, J = 8.7 Hz); 4.95 (b, 2H); 4.69 – 4.63 (m, 1H); 1.42 (d, 6H).

*Step B: 5-(3-Chloro-4-propoxyphenyl)-3-(3-iodo-4-isopropoxyphenyl)-1,2,4-oxadiazole:* A mixture of 3-chloro-4-propoxybenzoic acid (0.298 g, 0.93 mmol),

the product of Step A (0.2 g, 0.93 mmol) and EDC (0.214 g, 1.1 mmol) in anhydrous DMF (3 ml) was stirred overnight at 45 °C. 1 M TBAF in THF (0.3 ml) was added and this was stirred for 2.5 h at 110 °C. The reaction mixture was diluted to 20 ml with H<sub>2</sub>O and extracted with EtOAc (2 x 15 ml). The organic layer was separated, dried over MgSO<sub>4</sub> and filtered. The filtrate was distilled off and the residue was purified by FCC (SiO<sub>2</sub>, hexane/EtOAc) to give the title compound (0.22 g, 47.4%), as a colourless solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.56 (d, 1H, J = 2.04 Hz); 8.21 (d, 1H, J = 2.37 Hz); 8.07 – 8.02 (m, 2H); 7.00 (d, 1H, J = 8.73 Hz); 6.87 (d, 1H, J = 8.67 Hz); 4.68 – 4.63 (m, 1H); 4.08 (t, 2H, J = 6.45 Hz); 1.93 – 1.87 (m, 2H); 1.36 (d, 6H, J = 6.06 Hz); 1.09 (t, 3H, J = 7.44 Hz).

*Step C: 4-(5-(3-Chloro-4-propoxyphenyl)-1,2,4-oxadiazol-3-yl)-2-iodophenol:* To a solution of the product of Step B (0.2 g, 0.4 mmol) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (2 ml) 1 M BCl<sub>3</sub> in CH<sub>2</sub>Cl<sub>2</sub> (3 ml) was added drop wise at rt. After 1 h, more of 1M BCl<sub>3</sub> in CH<sub>2</sub>Cl<sub>2</sub> (1 ml) was added and this was stirred for 1 h. The reaction mixture was quenched with saturated NH<sub>4</sub>Cl solution and extracted with CH<sub>2</sub>Cl<sub>2</sub> (20 ml). The organic layer was separated, dried over MgSO<sub>4</sub> and filtered. The filtrates was evaporated to dryness and the residue was crystallized from MeOH to give the title compound (0.145 g, 79%), as colourless solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.47 (d, 1H, J = 1.95 Hz); 8.21 (d, 1H, J = 2.1 Hz); 8.06 – 8.04 (m, 1H); 8.03 – 8.02 (m, 1H); 7.07 (d, 1H, J = 8.49 Hz); 7.00 (d, 1H, J = 8.7 Hz); 4.08 (t, 2H, J = 6.45 Hz); 1.94 – 1.87 (m, 2H); 1.09 (t, 3H, J = 7.44 Hz).

*Step D: tert-Butyl 5-(5-(5-(3-chloro-4-propoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)-2,2-dimethyl-1,3-dioxan-5-ylcarbamate:* A solution of the product of Step C (0.1 g; 0.22 mmol) and *tert*-butyl 5-ethynyl-2,2-dimethyl-1,3-dioxan-5-ylcarbamate (0.056 g; 0.22 mmol) in a mixture of DMF and DIPEA (3 ml: 0.3 ml) was degassed with N<sub>2</sub> and Cl<sub>2</sub>Pd(PPh<sub>3</sub>)<sub>4</sub> (0.025 g) was added, followed by catalytic amount of Cul. The mixture was stirred overnight at 45 °C under N<sub>2</sub>, diluted to 20 ml with saturated NH<sub>4</sub>Cl and extracted with EtOAc (40 ml). The organic layer was separated, dried over MgSO<sub>4</sub> and filtered. The filtrate was distilled off and the residue was purified by FCC (SiO<sub>2</sub>, hexane/EtOAc) to give the title compound (0.11 g, 78%), as pale paste. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.34 (d, 1H, J = 1.29 Hz); 8.24 (d, 1H, J = 2.13 Hz); 8.08 (t, 1H, J = 1.56 Hz); 8.05 (t, 1H, J = 1.56 Hz); 7.53 (d, 1H, J = 8.67 Hz); 7.03 (d, 1H, J = 8.67 Hz); 6.75 (s, 1H); 4.26 – 4.19

(m, 4H); 4.06 (t, 2H, J = 5.49 Hz); 1.94 – 1.87 (m, 2H); 1.41 (s, 9H); 1.36 (s, 6H); 1.1 (t, 3H, J = 7.44 Hz).

**Step E:** *2-Amino-2-(5-(5-(3-chloro-4-propoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)propane-1,3-diol*: To a stirred solution of product of Step D (0.1 g, 0.17 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (0.5 ml) TFA (1 ml) was added. After stirring for 1 h at room temperature, EtOH (2 ml) was added and stirring was continued for additional 1 h. The mixture was evaporated to dryness and the residue was purified by FCC (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub> saturated with concentrated NH<sub>4</sub>OH/MeOH; 98:2) to give the title product (0.035 g, 46%) as colourless solid. <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) 8.3 (d, 1H, J = 1.11 Hz); 8.15 (d, 1H, J = 2.01 Hz); 8.09 (dd, 1H, J = 8.67, 2.04 Hz); 7.94 (dd, 1H, J = 8.58, 1.53 Hz); 7.68 (d, 1H, J = 8.61 Hz); 7.37 (d, 1H, J = 8.76 Hz); 6.92 (s, 1H); 4.91 (b, 2H); 4.14 (t, 2H, J = 6.36 Hz); 3.69 (d, 2H, J = 10.6 Hz); 3.59 (d, 2H, J = 10.6 Hz); 1.83 – 1.72 (m, 2H); 0.97 (t, 3H, J = 7.41 Hz).

### Example 37

#### **(E)-2-Amino-2-(5-(5-(4-methylstyryl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)propane-1,3-diol**

**Step A:** *(E)-3-(3-Iodo-4-isopropoxyphenyl)-5-(4-methylstyryl)-1,2,4-oxadiazole*: When (E)-3-p-tolylacrylic acid was substituted for 3-chloro-4-propoxybenzoic acid in Example 36, Step B, the similar process afforded the title compound in 52% yield, as colourless solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.53 (d, 1H, J = 2.07 Hz); 8.01 (dd, 1H, J = 8.58, 2.1 Hz); 7.82 (d, 1H, J = 16.35 Hz); 7.49 (d, 1H, J = 8.1 Hz); 6.97 (d, 1H, J = 16.38 Hz); 6.87 (d, 1H, J = 8.76 Hz); 4.69 – 4.6 (m, 1H); 1.4 (d, 6H, J = 5.85 Hz).

**Step B:** *(E)-2-Iodo-4-(5-(4-methylstyryl)-1,2,4-oxadiazol-3-yl)phenol*: When the product of Step A was substituted for 5-(3-chloro-4-propoxyphenyl)-3-(3-iodo-4-isopropoxyphenyl)-1,2,4-oxadiazole in Example 36, Step C, the similar procedure afforded the title compound in 53% yield, as colourless solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.44 (d, 1H, J = 1.95 Hz); 8.0 (dd, 1H, J = 8.49, 2.01 Hz); 7.84 (d, 1H, J = 16.35 Hz); 7.49 (d, 1H, J = 8.16 Hz); 7.07 (d, 1H, J = 8.49 Hz); 6.98 (d, 1H, J = 16.83 Hz); 5.61 (s, 1H).

**Step C:** *(E)-tert-Butyl 2,2-dimethyl-5-(5-(5-(4-methylstyryl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)-1,3-dioxan-5-ylcarbamate*: When the product of Step B was substituted for 4-(5-(3-chloro-4-propoxy phenyl)- 1,2,4- oxadiazol-3-yl)- 2-

iodophenol in Example 36, Step D, the similar process afforded the title compound in 68% yield, as pale paste. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.30 (d, 1H, J = 1.32 Hz); 8.03 (dd, 1H, J = 8.61, 1.68 Hz); 7.84 (d, 1H, J = 16.38 Hz); 7.53 – 7.49 (m, 3H); 7.21 (d, 2H, J = 5.34 Hz); 7.0 (d, 1H, J = 15.15 Hz); 5.28 (s, 1H); 4.24 (b, 4H); 2.39 (s, 3H); 1.46 – 1.39 (m, 15H).

*Step D: (E)-2-Amino-2-(5-(5-(4-methylstyryl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)propane-1,3-diol:* When the product of Step C was substituted for tert-butyl 5-(5-(3-chloro-4-propoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)-2,2-dimethyl-1,3-dioxan-5-yl carbamate in Example 36, Step E, the similar procedure afforded the title compound in 48% yield, as colourless solid. <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) 8.23 (b, 1H); 7.9 – 7.85 (m, 2H); 7.72 – 7.64 (m, 3H); 7.33 (d, 1H, J = 16.2 Hz); 7.25 (d, 2H, J = 6.3 Hz); 6.87 (s, 1H); 4.77 (b, 2H); 3.63 (b, 2H); 3.56 (b, 2H); 2.32 (s, 3H); 1.95 (b, 2H).

### Example 38

#### **2-Amino-2-(5-(5-(4-bromo-3-chlorophenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)propane-1,3-diol**

*Step A: 5-(4-Bromo-3-chlorophenyl)-3-(3-iodo-4-isopropoxyphenyl)-1,2,4-oxadiazole:* When 4-bromo-3-chlorobenzoic acid was substituted for 3-chloro-4-propoxybenzoic acid in Example 36, Step B, the similar procedure afforded the title compound in 72% yield, as creamy solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.55 (d, 1H, J = 2.07 Hz); 8.27 (d, 1H, J = 1.89 Hz); 8.04 (dd, 1H, J = 8.61, 2.04 Hz); 7.91 (dd, 1H, J = 8.34, 1.95 Hz); 7.79 (d, 1H, J = 8.37 Hz); 6.87 (d, 1H, J = 8.67 Hz); 4.7 – 4.6 (m, 1H); 1.4 (d, 6H, J = 5.94 Hz).

*Step B: 4-(5-(4-Bromo-3-chlorophenyl)-1,2,4-oxadiazol-3-yl)-2-iodophenol:* When the product of Step A was substituted for 5-(3-chloro-4-propoxyphenyl)-3-(3-iodo-4-isopropoxyphenyl)-1,2,4-oxadiazole in Example 36, Step C, the similar procedure afforded the title compound in 86% yield, as creamy solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.47 (d, 1H, J = 1.98 Hz); 8.28 (d, 1H, J = 1.95 Hz); 8.03 (dd, 1H, J = 8.49, 1.98 Hz); 7.92 (dd, 1H, J = 8.37, 1.98 Hz); 7.84 (d, 1H, J = 8.37 Hz); 7.08 (d, 1H, J = 8.52 Hz); 5.65 (b, 1H).

*Step C: tert-Butyl 5-(5-(5-(4-bromo-3-chlorophenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)-2,2-dimethyl-1,3-dioxan-5-ylcarbamate:* When the product of Step B was substituted for 4-(5-(3-chloro-4-propoxyphenyl)-1,2,4-oxadiazol-3-yl)-

2-iodophenol in Example 36, Step D, the similar procedure afforded the title compound in 58% yield, as pale paste. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.34 (d, 1H, J = 1.53 Hz); 8.31 (d, 1H, J = 1.95 Hz); 8.06 (dd, 1H, J = 8.61, 1.68 Hz); 7.94 (dd, 1H, J = 8.37, 1.98 Hz); 7.8 (d, 1H, J = 8.37 Hz); 7.54 (d, 1H, J = 8.61 Hz); 6.76 (s, 1H); 5.34 (bs, 1H); 4.3 – 4.24 (m, 4H); 1.55 (s, 9H); 1.47(s, 6H).

*Step D: 2-Amino-2-(5-(5-(4-bromo-3-chlorophenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)propane-1,3-diol:* When the product of Step C was substituted for tert-butyl 5-(5-(5-(3-chloro-4-propoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)-2,2-dimethyl-1,3-dioxan-5-ylcarbamate in Example 36, Step E, the similar procedure afforded the title compound in 39% yield, as creamy solid. <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) 8.31 (b, 2H); 8.05 (d, 1H, J = 8.52 Hz); 8.00 (d, 1H, J = 8.49 Hz); 7.94 (d, 1H, J = 8.58 Hz); 7.68 (d, 1H, J = 8.46 Hz); 6.91 (s, 1H); 4.88 (bs, 1H); 3.66 (bs, 2H); 3.58 (bs, 2H).

### Example 39

#### **2-Amino-2-(5-(5-(3-chloro-4-(thiophen-3-yl)phenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)propane-1,3-diol**

*Step A: tert-Butyl 5-(5-(5-(3-chloro-4-(thiophen-3-yl)phenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)-2,2-dimethyl-1,3-dioxan-5-ylcarbamate:* To a stirred mixture of the product of Example 38, Step C (0.09 g, 0.15 mmol) and 3-thiophene-boronic acid (0.028 g, 0.22 mmol) in a mixture of dioxane and H<sub>2</sub>O (5 ml:1 ml), Pd(PPh<sub>3</sub>)<sub>4</sub> (0.03 g) was added at 80 °C, followed by the NaHCO<sub>3</sub> solution (0.065 g in 1 ml H<sub>2</sub>O) and this was stirred for 2 h. The solvent was distilled off and the residue was diluted to 20 ml with EtOAc, washed with H<sub>2</sub>O, dried over MgSO<sub>4</sub> and filtered. The filtrate was evaporated and the residue was purified by FCC (SiO<sub>2</sub>, hexane/EtOAc), to give the title compound (0.065 g, 71 %), as pale paste. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.45 (d, 1H, J = 1.53 Hz); 8.25 – 8.22 (m, 2H); 7.94 (dd, 1H, J = 8.7, 1.8 Hz); 7.55 – 7.42 (m, 3H); 7.38 – 7.37 (m, 2H); 6.78 (s, 1H); 5.43 (bs, 1H); 4.29 – 4.13 (m, 4H); 1.46 (s, 9H); 1.27 (b, 6H).

*Step B: 2-Amino-2-(5-(5-(3-chloro-4-(thiophen-3-yl)phenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)propane-1,3-diol:* When the product of Step A was substituted for tert-butyl 5-(5-(5-(3-chloro-4-propoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)-2,2-dimethyl-1,3-dioxan-5-ylcarbamate in Example 36, Step E, the similar procedure afforded the title compound in 48% yield, as colourless



solid. <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) 8.42 (s, 1H); 8.28 (s, 1H); 8.2 (d, 1H, J = 8.41 Hz); 8.11 (d, 1H, J = 8.1 Hz); 7.82 (s, 1H); 7.64 – 7.61 (m, 3H); 7.4 (b, 1H); 6.92 (s, 1H); 4.9 (bs, 2H); 3.66 (b, 2H); 3.59 (b, 2H).

#### Example 40

#### **2-Amino-2-(5-(5-(3,4-diethoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)propane-1,3-diol**

*Step A: 5-(3,4-Diethoxyphenyl)-3-(3-iodo-4-isopropoxyphenyl)-1,2,4-oxadiazole:* When 3,4-diethoxy benzoic acid was substituted for 3-chloro-4-propoxybenzoic acid in Example 36, Step B, the similar procedure afforded the title compound in 60% yield, as colourless solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.57 (d, 1H, J = 2.05 Hz); 8.05 (dd, 1H, J = 8.58, 2.03 Hz); 8.02 (d, 1H, J = 2.07 Hz); 7.76 (dd, 1H, J = 8.41, 1.94 Hz); 7.66 (d, 1H, J = 1.93 Hz); 6.96 (d, 1H, J = 8.5 Hz); 6.87 (d, 1H, J = 8.69 Hz); 4.67 – 4.63 (m, 1H); 4.24 – 4.14 (m, 4H); 1.53 – 1.4 (m, 6H); 1.38 (d, 6H, J = 6.64 Hz).

*Step B: 4-(5-(3,4-Diethoxyphenyl)-1,2,4-oxadiazol-3-yl)-2-iodophenol:* When the product of Step A was substituted for 5-(3-chloro-4-propoxyphenyl)-3-(3-iodo-4-isopropoxyphenyl)-1,2,4-oxadiazole in Example 36, Step C, the similar procedure afforded the title compound in 84% yield, as a creamy solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.48 (d, 1H, J = 2.05 Hz); 8.04 (dd, 1H, J = 8.46, 1.98 Hz); 7.76 (dd, 1H, J = 8.43, 2.0 Hz); 7.65 (d, 1H, J = 1.98 Hz); 7.07 (d, 1H, J = 8.5 Hz); 6.96 (d, 1H, J = 8.46 Hz); 5.63 (bs, 1H); 4.24 – 4.09 (m, 4H); 1.56 – 1.42 (m, 6H).

*Step C: tert-Butyl 5-(5-(5-(3,4-diethoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)-2,2-dimethyl-1,3-dioxan-5-ylcarbamate:* When the product of Step B was substituted for 4-(5-(3-chloro-4-propoxyphenyl)-1,2,4-oxadiazol-3-yl)-2-iodophenol in Example 36, Step D, the similar procedure afforded the title compound in 66% yield, as creamy paste. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.35 (d, 1H, J = 1.57 Hz); 8.08 (dd, 1H, J = 8.62, 1.68 Hz); 7.79 (dd, 1H, J = 8.44, 1.94 Hz); 7.69 (d, 1H, J = 1.93 Hz); 7.52 (d, 1H, J = 8.54 Hz); 6.96 (d, 1H, J = 8.5 Hz); 6.75 (s, 1H); 5.32 (b, 1H); 4.36 – 4.15 (m, 8H); 3.95 (s, 2H); 1.54 – 1.47 (m, 21H).

*Step D: 2-Amino-2-(5-(5-(3,4-diethoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)propane-1,3-diol:* When the product of Step C was substituted for tert-butyl 5-(5-(5-(3-chloro-4-propoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)-2,2-dimethyl-1,3-dioxan-5-yl carbamate in Example 36, Step E, the similar

procedure afforded the title compound in 61% yield, as creamy solid. <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) 8.27 (s, 1H); 7.92 (d, 1H, J = 8.23 Hz); 7.75 – 7.61 (m, 3H); 7.17 (d, 1H, J = 8.34 Hz); 6.88 (s, 1H); 4.78 (b, 2H); 4.15 – 4.00 (b, 4H); 3.65 – 3.64 (b, 2H); 3.57 – 3.55 (b, 2H); 1.35(b, 6H).

#### Example 41

##### **2-Amino-2-(5-(5-(4-propoxy-3-methoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)propane-1,3-diol**

*Step A: 5-(4-Propoxy-3-methoxyphenyl)-3-(3-iodo-4-isopropoxyphenyl)-1,2,4-oxadiazole:* When 4-propoxy-3-methoxybenzoic acid was substituted for 3-chloro-4-propoxybenzoic acid in Example 36, Step B, the similar procedure afforded the title compound in 58% yield, as creamy solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.58 (d, 1H, J = 2.01 Hz); 8.06 (dd, 1H, J = 8.61, 2.07 Hz); 7.77 (dd, 1H, J = 8.43, 1.98 Hz); 7.66 (d, 1H, J = 1.92 Hz); 6.97 (d, 1H, J = 8.46 Hz); 6.88 (d, 1H, J = 8.7 Hz); 4.69 – 4.61 (m, 1H); 4.06 (t, 2H, J = 6.81 Hz); 3.98 (s, 3H); 1.93 – 1.88 (m, 2H); 1.06 (t, 3H, J = 7.38 Hz).

*Step B: 4-(5-(4-Propoxy-3-methoxyphenyl)-1,2,4-oxadiazol-3-yl)-2-iodophenol:* When the product of Step A was substituted for 5-(3-chloro-4-propoxyphenyl)-3-(3-iodo-4-isopropoxyphenyl)-1,2,4-oxadiazole in Example 36, Step C, the similar procedure afforded the title compound in 80% yield, as creamy solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.48 (d, 1H, J = 1.98 Hz); 8.04 (dd, 1H, J = 8.46, 1.98 Hz); 7.7 (dd, 1H, J = 8.43, 2.01 Hz); 7.65 (d, 1H, J = 1.95 Hz); 7.07 (d, 1H, J = 8.49 Hz); 6.97 (d, 1H, J = 8.46 Hz); 5.63 (s, 1H); 4.06 (t, 2H, J = 6.8 Hz); 4.02 (s, 3H); 1.94 – 1.87 (m, 2H); 1.06 (t, 3H, J = 7.41 Hz).

*Step C: tert-Butyl 5-(5-(5-(4-propoxy-3-methoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)-2,2-dimethyl-1,3-dioxan-5-ylcarbamate:* When the product of Step B was substituted for 4-(5-(3-chloro-4-propoxyphenyl)-1,2,4-oxadiazol-3-yl)-2-iodophenol in Example 36, Step D, the similar procedure afforded the title compound in 68% yield, as pale paste. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.35 (d, 1H, J = 1.23 Hz); 8.08 (dd, 1H, J = 8.61, 1.68 Hz); 7.8 (dd, 1H, J = 8.41, 1.98 Hz); 7.68 (d, 1H, J = 1.92 Hz); 7.52 (d, 1H, J = 8.64 Hz); 6.98 (d, 1H, J = 8.49 Hz); 6.75 (s, 1H); 5.32 (bs, 1H); 4.26 (b, 4H); 4.06 (t, 2H, J = 6.81 Hz); 3.98 (s, 3H); 1.93 – 1.88 (m, 2H); 1.49 (s, 9H); 1.44 (s, 6H); 1.06 (t, 3H, J = 7.38 Hz).

*Step D: 2-Amino-2-(5-(5-(4-Propoxy-3-methoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)propane-1,3-diol:* When the product of Step C was substituted for tert-butyl 5-(5-(3-chloro-4-propoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)-2,2-dimethyl-1,3-dioxan-5-ylcarbamate in Example 36, Step E, the similar procedure afforded the title compound in 57% yield, as colourless solid. <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) 8.28 (s, 1H); 7.92 (d, 1H, J = 2.82 Hz); 7.61 (m, 3H); 7.16 (d, 1H, J = 8.53 Hz); 6.88 (s, 1H); 4.78 (b, 2H); 4.01 (t, 2H, J = 6.03 Hz); 3.99 (s, 3H); 3.77 – 3.57 (m, 4H); 1.78 – 1.71 (m, 2H); 0.96 (t, 3H, J = 7.29 Hz).

### Example 42

#### 5-(3,4-Diethoxyphenyl)-3-(2-methylbenzofuran-5-yl)-1,2,4-oxadiazole

*Step A: 2-Methylbenzofuran-5-carbonitrile:* 2-Iodo-4-cynophenol (0.25 g, 1 mmol) and saccharin (0.1 g) in HMDSA (2 ml) was refluxed for 2 h under N<sub>2</sub>, until the solution became clear. The solvent was distilled off under reduced pressure and the residue was dissolved in anhydrous THF (2 ml). This was added to a solution made by mixing anhydrous ZnCl<sub>2</sub> (0.3 g; 2.2 mmol) with 0.5 M 1-propynyl magnesium bromide in THF (7.8 ml) in anhydrous THF (5 ml) at room temperature under N<sub>2</sub>. To it, Pd (PPh<sub>3</sub>)<sub>4</sub> (0.15 g) was added at room temperature under N<sub>2</sub> followed by catalytic amount of CuI. The mixture was stirred at room temperature for 3 h and quenched with saturated NH<sub>4</sub>Cl solution. The mixture was diluted to 50 ml with EtOAc and washed with H<sub>2</sub>O. The organic layer was separated, dried over MgSO<sub>4</sub> and filtered. The filtrate was evaporated and the residue was dissolved in 1,4-dioxane (4 ml) and 1 M TBAF in THF (0.3 ml) was added and this was stirred for 4 h at reflux. The solvent was distilled off and the residue was purified by FCC (SiO<sub>2</sub>, hexane/EtOAc) to give the title compound (0.145 g, 91 %), as colourless solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 7.78 (s, 1H); 7.46 – 7.44 (m, 2H); 6.41 (bs, 1H); 2.47 (s, 3H).

*Step B: 5-(3,4-Diethoxyphenyl)-3-(2-methylbenzofuran-5-yl)-1,2,4-oxadiazole:* The product Step A was converted to *N*-hydroxy-2-methylbenzofuran-5-carboximidamide by method described for Example 36, Step A. When *N*-hydroxy-2-methylbenzofuran-5-carboximidamide and 3,4-diethoxybenzoic acid were substituted for *N*-hydroxy-3-iodo-4-isopropoxybenzimidamide and 3-chloro-4-propoxybenzoic acid, respectively, in Example 36, Step B, the similar procedure afforded the title compound in 6% yield, as colourless solid. <sup>1</sup>H-NMR

(CDCl<sub>3</sub>) 8.28 (bs, 1H); 8.00 (dd, 1H, J = 8.55, 1.68 Hz); 7.8 (dd, 1H, J = 8.4, 1.98 Hz); 7.68 (d, 1H, J = 1.92 Hz); 7.47 (d, 1H, J = 8.58 Hz); 6.97 (d, 1H, J = 8.46 Hz); 6.45 (s, 1H); 4.23 – 4.16 (m, 4H); 2.48 (3H); 1.52 – 1.47 (m, 6H).

#### Example 43

#### **2-Amino-2-(5-(5-(6-methoxybenzofuran-2-yl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)propane-1,3-diol**

*Step A: Ethyl 2-(2-formyl-5-methoxyphenoxy)acetate:* A mixture of 2-hydroxy-4-methoxybenzaldehyde (1 g; 6.58 mmol), BrCH<sub>2</sub>CO<sub>2</sub>Et (0.806 ml; 7.24 mmol) and K<sub>2</sub>CO<sub>3</sub> (1 g, 7.24 mmol) in anhydrous DMF (5 ml) was stirred overnight at room temperature. The mixture was diluted with EtOAc (100 ml) and H<sub>2</sub>O (100 ml). The organic layer was separated and dried over MgSO<sub>4</sub>, and filtrate evaporated, to give the product (1.29 g; 97%), as colourless solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 1.28 (tr, 3H, J = 7.11 Hz); 3.84 (s, 3H); 4.25 (q, 2H, J = 7.14, 14.28 Hz); 4.69 (s, 2H); 6.30 (d, 1H, J = 2.16 Hz); 6.58 (dd, 1H, J = 1.77, 8.73 Hz); 7.83 (d, 1H, J = 8.7 Hz); 10.36 (s, 1H).

*Step B: Ethyl 6-methoxybenzofuran-2-carboxylate:* A mixture of the product of Step A (1.28 g, 5.37 mmol) and DBU (0.3 ml) was heated for 3 h at 160 °C with stirring, cooled to room temperature and dissolved in EtOAc: MeOH mixture (99:1). The mixture was filtered through the silica bead and the filtrate was evaporated to give the title compound (1.11 g; 77%), as colourless solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 1.40 (tr, 3H, J = 7.13 Hz); 3.85 (s, 3H); 4.40 (q, 2H, J = 7.13, 14.25 Hz); 4.45 (s, 1H); 6.91 (dd, 1H, J = 2.25, 8.68 Hz); 7.04 (d, 1H, J = 1.87 Hz); 7.51 (d, 1H, J = 5.17 Hz),

*Step C: 6-Methoxybenzofuran-2-carboxylic acid:* To a stirred solution of Product of Step B (0.25 g, 1.21 mmol) in a mixture of THF, MeOH and H<sub>2</sub>O (5 ml : 2 ml : 1 ml), LiOH (0.145 g, 6 mmol) in H<sub>2</sub>O (0.5 ml) was added and the mixture was stirred for 3 h at room temp. The solvents were distilled off and the residue was portioned between EtOAc (20 ml) and 1M HCl (2 ml). The organic layer was washed with H<sub>2</sub>O, dried over MgSO<sub>4</sub> and filtered. The filtrate was evaporated to dryness to give the title compound (0.21 g, 91 %), as a colourless solid. <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) 7.61 (d, 1H, J = 8.67 Hz); 7.54 (s, 1H); 7.24 (d, 1H, J = 1.59 Hz); 6.93 (dd, 1H, J = 8.67, 2.4 Hz); 3.8 (s, 3H).

*Step D: 3-(3-iodo-4-isopropoxyphenyl)-5-(6-methoxybenzofuran-2-yl)-1,2,4-oxadiazole:* When the product of Step C was substituted for 3-chloro-4-propoxybenzoic acid in Example 36, Step B, the similar procedure afforded the title compound in 67% yield, as colourless solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.6 (d, 1H, J = 2.04 Hz); 8.08 (dd, 1H, J = 8.58, 2.1 Hz); 7.63 (b, 1H); 7.57 (d, 1H, J = 8.7 Hz); 7.13 (d, 1H, J = 1.8 Hz); 6.97 (dd, 1H, J = 8.7, 2.19 Hz); 6.87 (d, 1H, J = 8.73 Hz); 4.69 – 4.59 (m, 1H); 3.88 (s, 3H); 1.4 (d, 6H, J = 6.33 Hz).

*Step E: 2-Iodo-4-(5-(6-methoxybenzofuran-2-yl)-1,2,4-oxadiazol-3-yl)phenol:* When the product of Step D was substituted for 5-(3-chloro-4-propoxyphenyl)-3-(3-iodo-4-isopropoxyphenyl)-1,2,4-oxadiazole in Example 36, Step C, the similar procedure afforded the title compound in 65% yield, as colourless solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.53 (d, 1H, J = 2.01 Hz); 8.06 (dd, 1H, J = 8.49, 2.01 Hz); 7.64 (b, 1H); 7.6 (d, 1H, J = 8.7 Hz); 7.13 (b, 1H); 7.08 (d, 1H, J = 8.46 Hz); 6.98 (dd, 1H, J = 8.7, 2.22 Hz); 3.89 (s, 3H).

*Step F: tert-Butyl 5-(5-(5-(6-methoxybenzofuran-2-yl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)-2,2-dimethyl-1,3-dioxan-5-ylcarbamate:* When the product of Step E was substituted for 4-(5-(3-chloro-4-propoxyphenyl)-1,2,4-oxadiazol-3-yl)-2-iodophenol in Example 36, Step D, the similar procedure afforded the title compound in 64 % yield, as pale paste..

*Step G: 2-Amino-2-(5-(5-(6-methoxybenzofuran-2-yl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)propane-1,3-diol:* When the product of Step F was substituted for tert-butyl 5-(5-(5-(3-chloro-4-propoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)-2,2-dimethyl-1,3-dioxan-5-ylcarbamate in Example 36, Step E, the similar procedure afforded the title compound in 26% yield, as creamy green solid. <sup>1</sup>H-NMR (CD<sub>3</sub>OD) 8.39 (d, 1H, J = 1.74 Hz); 8.08 (dd, 1H, J = 8.73, 1.89 Hz); 7.68 (b, 1H); 7.63 (d, 1H, J = 8.73 Hz); 7.58 (d, 1H, J = 8.7 Hz); 7.14 (d, 1H, J = 1.8 Hz); 7.03 (s, 1H); 6.92 (dd, 1H, J = 8.7, 2.22 Hz); 3.98 (d, 2H, J = 11.00 Hz); 3.88 (d, 2H, J = 11.01 Hz); 3.85 (s, 3H).

**Example 44****2-Amino-2-(5-(5-(4-propylphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)propane-1,3-diol**

*Step A: 3-(3-Iodo-4-isopropoxyphenyl)-5-(4-propylphenyl)-1,2,4-oxadiazole:* When 4-propylbenzoic acid was substituted for 3-chloro-4-propoxy benzoic acid in Example 36, Step B, the similar procedure afforded the title compound in 82% yield, as colourless solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.58 (d, 1H, J = 2.04 Hz); 8.11 – 8.05 (m, 3H); 7.34 (d, 2H, J = 8.25 Hz); 6.88 (d, 1H, J = 8.73 Hz); 4.7 – 4.59 (m, 1H); 2.67 (t, 2H, J = 7.83 Hz); 1.72 – 1.41 (m, 2H); 0.95 (t, 3H, J = 7.29 Hz).

*Step B: 2-Iodo-4-(5-(4-propylphenyl)-1,2,4-oxadiazol-3-yl)phenol:* When the product of Step A was substituted for 5-(3-chloro-4-propoxyphenyl)-3-(3-iodo-4-isopropoxyphenyl)-1,2,4-oxadiazole in Example 36, Step C, the similar procedure afforded the title compound in 82% yield, as colourless solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.48 (d, 1H, J = 1.98 Hz); 8.08 (d, 2H, J = 8.25 Hz); 8.03 (dd, 1H, J = 8.49, 2.01 Hz); 7.33 (d, 2H, J = 8.25 Hz); 7.07 (d, 1H, J = 8.49 Hz); 2.66 (t, 2H, J = 7.5 Hz); 1.71 – 1.61 (m, 2H); 0.95 (t, 3H, J = 7.29 Hz).

*Step C: tert-Butyl 2,2-dimethyl-5-(5-(4-propylphenyl)-1,2,4-oxadiazol-3-yl)benzo-furan-2-yl)-1,3-dioxan-5-ylcarbamate:* When the product of Step B was substituted for 4-(5-(3-chloro-4-propoxyphenyl)-1,2,4-oxadiazol-3-yl)-2-iodophenol in Example 36, Step D, the similar procedure afforded the title compound in 35% yield, as pale paste. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.35 (s, 1H); 8.13 – 8.06 (m, 3H); 7.52 (d, 1H, J = 8.64 Hz); 7.34 (d, 2H, J = 8.22 Hz); 6.75 (s, 1H); 5.35 (s, 1H); 4.26 (b, 4H); 2.67 (t, 2H, J = 7.41 Hz); 1.74 – 1.67 (m, 2H); 1.64 (s, 6H); 1.5 (s, 9H); 0.96 (t, 2H, J = 7.29 Hz).

*Step D: 2-Amino-2-(5-(5-(4-propylphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)propane -1,3-diol:* When the product of Step C was substituted for tert-butyl 5-(5-(5-(3-chloro-4-propoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)-2,2-dimethyl-1,3-dioxan-5-ylcarbamate in Example 36, Step E, the similar procedure afforded the title compound in 28% yield, as creamy solid. <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) 8.30 (s, 1H); 8.08 (d, 2H, J = 6.6 Hz); 7.94 (d, 1H, J = 7.5 Hz); 7.68 (d, 1H, J = 7.5 Hz); 7.46 (d, 2H, J = 7.5 Hz); 6.92 (s, 1H); 3.67 (b, 2H); 3.59 (b, 2H); 2.65 (b, 2H); 1.63 – 1.6 (m, 2H); 0.88 (t, 2H, J = 6.3 Hz).

**Example 45****2-Amino-2-(5-(5-(4-ethoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)propane-1,3-diol**

*Step A: 5-(4-Ethoxyphenyl)-3-(3-iodo-4-isopropoxyphenyl)-1,2,4-oxadiazole:* When 4-ethoxybenzoic acid was substituted for 3-chloro-4-propoxy benzoic acid in Example 36, Step B, the similar procedure afforded the title compound in 53% yield, as white solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.57 (d, 1H, J = 2.04 Hz); 8.11 (d, 2H, J = 8.88 Hz); 8.05 (dd, 1H, J = 8.58, 2.04 Hz); 6.99 (d, 2H, J = 8.88 Hz); 6.87 (d, 1H, J = 8.67 Hz); 4.69 – 4.61 (m, 1H); 4.11 (q, 2H, J = 6.99, 13.98 Hz); 1.45 (t, 3H, J = 6.99 Hz).

*Step B: 4-(5-(4-Ethoxyphenyl)-1,2,4-oxadiazol-3-yl)-2-iodophenol:* When the product of Step A was substituted for 5-(3-chloro-4-propoxyphenyl)-3-(3-iodo-4-isopropoxyphenyl)-1,2,4-oxadiazole in Example 36, Step C, the similar procedure afforded the title compound in 87% yield, as white solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.47 (d, 1H, J = 1.95 Hz); 8.11 (d, 2H, J = 8.94 Hz); 8.03 (dd, 1H, J = 8.46, 2.01 Hz); 7.07 (d, 2H, J = 8.49 Hz); 4.11 (q, 2H, J = 6.96, 13.98 Hz); 1.45 (t, 3H, J = 6.96 Hz).

*Step C: tert-Butyl 5-(5-(5-(4-ethoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)-2,2-dimethyl-1,3-dioxan-5-ylcarbamate:* When the product of Step B was substituted for 4-(5-(3-chloro-4-propoxyphenyl)-1,2,4-oxadiazol-3-yl)-2-iodophenol in Example 36, Step D, the similar procedure afforded the title compound in 60% yield, as pale paste. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.34 (s, 1H); 8.14 (d, 2H, J = 8.88 Hz); 8.07 (dd, 1H, J = 8.61, 1.68 Hz); 7.51 (d, 1H, J = 8.52 Hz); 7.00 (d, 2H, J = 8.94 Hz); 6.75 (s, 1H); 5.34 (s, 1H); 4.3 – 4.14 (b, 4H); 4.1 (t, 2H, J = 7.02 Hz); 1.44 – 1.39 (b, 18H).

*Step D: 2-Amino-2-(5-(5-(4-ethoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)propane-1,3-diol:* When the product of Step C was substituted for tert-butyl 5-(5-(5-(3-chloro-4-propoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)-2,2-dimethyl-1,3-dioxan-5-ylcarbamate in Example 36, Step E, the similar procedure afforded the title compound in 32% yield, as light yellow solid. <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) 8.09 (s, 1H); 7.96 (d, 2H, J = 8.4 Hz); 7.7 (d, 1H, J = 8.4 Hz); 7.15 (d, 2H, J = 9 Hz); 6.98 (s, 1H); 5.1 (b, 2H); 4.13 (q, 2H, J = 6.9, 13.8 Hz); 3.73 (d, 2H, J = 8.1 Hz); 3.64 (d, 2H, J = 8.1 Hz); 1.34 (t, 3H, J = 6.9 Hz).

**Example 46****2-Amino-2-(6-chloro-5-(5-(4-propylphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)propane-1,3-diol**

**Step A: 2-Chloro-N-hydroxy-5-iodo-4-isopropoxybenzimidamide:** To a stirred solution of 2-chloro-4-isopropoxybenzonitrile (0.8 g, 4.1 mmol) and  $\text{Cf}_3\text{CO}_2\text{Ag}$  (1.3 g, 5.1 mmol) in  $\text{CH}_2\text{Cl}_2$  (50 ml)  $\text{I}_2$  (1 g, 4 mmol) was added and the mixture was stirred for 6 h at reflux. This was filtered through the Celite\* bead and the washed with  $\text{CH}_2\text{Cl}_2$ . The combined filtrates were evaporated to dryness and the residue was purified by FCC ( $\text{SiO}_2$ , hexane/EtOAc) to give 2-chloro-5-iodo-4-isopropoxybenzonitrile (0.335 g, 26%), as white solid.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) 7.99 (s, 1H); 6.82 (s, 1H); 4.66 – 4.58 (m, 1H); 1.41 (d, 6H,  $J = 6.03$  Hz). This (0.32 g, 1 mmol) was converted to the title compound (0.335 g; 95 %) according to the procedure of Example 36 Step A.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) 7.89 (s, 1H); 6.79 (s, 1H); 4.86 – 4.49 (m, 1H); 1.4 (d, 6H)

**Step B: 3-(2-Chloro-5-iodo-4-isopropoxyphenyl)-5-(4-propylphenyl)-1,2,4-oxadiazole:** When the product of Step A and 4-propylbenzoic acid were substituted for N-hydroxy-3-iodo-4-isopropoxybenzimidamide and 3-chloro-4-propoxybenzoic acid in Example 36, Step B, the similar procedure afforded the title compound in 20% yield, as white solid.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) 8.46 (s, 1H); 8.10 (d, 2H,  $J = 8.25$  Hz); 7.34 (d, 2H,  $J = 8.28$  Hz); 6.92 (s, 1H); 7.67 – 7.59 (m, 1H); 2.67 (t, 2H,  $J = 7.35$  Hz); 1.72 – 1.65 (m, 2H); 1.43 (d, 6H,  $J = 6.06$  Hz); 0.96 (t, 3H,  $J = 7.32$  Hz).

**Step C: 5-Chloro-2-iodo-4-(5-(4-propylphenyl)-1,2,4-oxadiazol-3-yl)phenol:** When the product of Step B was substituted for 5-(3-chloro-4-propoxyphenyl)-3-(3-iodo-4-isopropoxyphenyl)-1,2,4-oxadiazole in Example 36, Step C, the similar procedure afforded the title compound in 55% yield, as creamy solid.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) 8.37 (s, 1H); 8.10 (d, 2H,  $J = 8.25$  Hz); 7.33 (d, 2H,  $J = 8.25$  Hz); 7.16 (s, 1H); 5.78 (b, 1H); 2.67 (t, 2H,  $J = 7.38$  Hz); 1.74 – 1.56 (m, 2H); 0.96 (t, 3H,  $J = 7.32$  Hz).

**Step D: 2-Amino-2-(6-chloro-5-(5-(4-propylphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)propane-1,3-diol:** When tert-butyl 5-(5-(3-chloro-4-propoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)-2,2-dimethyl-1,3-dioxan-5-ylcarbamate was replaced with the tert-butyl 5-(6-chloro-5-(5-(4-propylphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)-2,2-dimethyl-1,3-dioxan-5-ylcarbamate

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(obtained as crude via a process as described in Example 36, Step D) the similar procedure as in Example 36, Step E gave the title compound (0.006 g, 40%) as white solid.  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ ) 8.12 (d, 2H,  $J = 8.28$  Hz); 8.12 (s, 1H); 7.75 (s, 1H); 7.43 (d, 2H,  $J = 8.31$  Hz); 6.9 (s, 1H); 3.88 (d, 2H,  $J = 10.9$  Hz); 3.78 (d, 1H,  $J = 10.9$  Hz); 2.7 (t, 2H,  $J = 7.41$  Hz); 1.76 – 1.64 (m, 2H); 0.97 (t, 3H,  $J = 7.32$  Hz).

#### Example 47

##### **2-Amino-2-(5-(5-(1-butyl-1H-pyrazol-4-yl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)propane-1,3-diol**

*Step A: 1-Butyl-1H-pyrazole-4-carboxylic acid:* To a stirred suspension of 4-iodopyrazole (0.3 g, 1.55 mmol) and 60% NaH (0.08 g, 2 mmol) in anhydrous THF (1 ml) butyl bromide (0.5 ml) was added and the mixture was stirred overnight at 70 °C. The mixture was quenched with saturated  $\text{NH}_4\text{Cl}$  and extracted with EtOAc (50 ml). The organic layer was washed with  $\text{H}_2\text{O}$ , dried over  $\text{MgSO}_4$  and filtered. The filtrate was distilled off and the residue was dried *in vacuo* to give 1-butyl-4-iodo-1H-pyrazole (0.39 g, 100%), as colourless oil.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) 7.47 (s, 1H); 7.39 (s, 1H); 4.09 (t, 2H,  $J = 7.14$  Hz); 1.85 – 1.75 (m, 2H); 1.35 – 1.23 (m, 2H); 0.91 (t, 3H,  $J = 7.32$  Hz). To a stirred solution of the above product (0.36 g, 1.44 mmol) in anhydrous THF (0.5 ml) 2M  $i\text{PrMgCl}$  in THF (2 ml) was added at 0 °C and after warming up to room temperature anhydrous DMF (1 ml) was added to it. This was stirred for 1 h at room temperature, then quenched with saturated  $\text{NH}_4\text{Cl}$  and extracted with EtOAc (30 ml). The organic layer was washed with  $\text{H}_2\text{O}$ , dried over  $\text{MgSO}_4$  and filtered. The filtrate was evaporated to dryness to give 1-butyl-1H-pyrazole-4-carbaldehyde (0.27 g; 100%), as pale oil.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) 9.82 (s, 1H); 7.93 (s, 1H); 7.89 (s, 1H); 4.13 (t, 2H,  $J = 7.11$  Hz); 1.9 – 1.8 (m, 2H); 1.4 – 1.22 (m, 2H); 0.92 (t, 3H,  $J = 7.29$  Hz). To a stirred solution of above aldehyde (0.22 g, 1.44 mmol) in the mixture of dioxane and  $\text{H}_2\text{O}$  (15ml : 3 ml)  $\text{KMnO}_4$  (0.25 g; 1.58 mmol) was added over a period of 30 min. The mixture was evaporated to dryness and the residue was treated in the mixture of EtOAc and MeOH (20 ml: 5 ml) and filtered through Celite pad. The filtrate was evaporated to dryness to give the title compound (0.24 g; 100%), as creamy crystalline solid.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) 7.8 (s, 1H); 7.56 (b, 1H); 4.05 (b, 2H); 1.7 (b, 2H); 1.18 (b, 2H); 0.83 (b, 3H).

*Step B: 5-(1-Butyl-1H-pyrazol-4-yl)-3-(3-iodo-4-isopropoxyphenyl)-1,2,4-oxadiazole:* When the product of Step A was substituted for 3-chloro-4-propoxybenzoic acid in Example 36, Step B the similar procedure afforded the title compound in 17% yield, as creamy gum. <sup>1</sup>H NMR (CDCl<sub>3</sub>) 8.53 (d, 1H, J = 2.07 Hz); 8.1 (s, 1H); 8.08 (s, 1H); 8.00 (dd, 1H, J = 8.61, 2.16 Hz); 8.87 (d, 1H, J = 8.73 Hz); 4.68 – 4.6 (m, 2H); 4.2 (t, 2H, J = 7.11 Hz); 2.02 – 1.85 (m, 2H); 1.42 – 1.32 (m, 2H); 0.95 (t, 3H, J = 7.32 Hz).

*Step C: 4-(5-(1-Butyl-1H-pyrazol-4-yl)-1,2,4-oxadiazol-3-yl)-2-iodophenol:* When the product of Step B was substituted for 5-(3-chloro-4-propoxy phenyl)-3-(3-iodo-4-isopropoxy phenyl)-1,2,4-oxadiazole in Example 36, Step C, the similar procedure afforded the title compound in 72% yield, as creamy solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) 8.45 (d, 1H, J = 1.98 Hz); 8.12 (s, 1H); 8.09 (s, 1H); 7.99 (dd, 1H, J = 8.49, 2.01 Hz); 7.06 (d, 1H, J = 8.49 Hz); 4.2 (t, 2H, J = 7.08 Hz); 2.02 – 1.85 (m, 2H); 1.42 – 1.26 (m, 2H); 0.95 (t, 3H, J = 7.29 Hz).

*Step D: tert-Butyl 5-(5-(5-(1-butyl-1H-pyrazol-4-yl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)-2,2-dimethyl-1,3-dioxan-5-ylcarbamate:* When the product of Step C was substituted for 4-(5-(3-chloro-4-propoxyphenyl)-1,2,4-oxadiazol-3-yl)-2-iodophenol in Example 36, Step D, the similar procedure afforded the title compound in 68% yield, as pale paste. <sup>1</sup>H NMR (CDCl<sub>3</sub>) 8.3 (s, 1H); 8.13 (s, 1H); 8.01 (s, 1H); 7.51 (d, 1H, J = 8.7 Hz); 6.74 (s, 1H); 5.32 (s, 1H); 4.29 – 4.18 (m, 6H); 2.02 – 1.91 (m, 2H); 1.54 – 1.34 (b, 17 H); 0.96 (t, 3H, J = 7.35 Hz).

*Step E: 2-Amino-2-(5-(5-(1-butyl-1H-pyrazol-4-yl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)propane-1,3-diol:* When the product of Step D was substituted for tert-butyl 5-(5-(5-(3-chloro-4-propoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)-2,2-dimethyl-1,3-dioxan-5-ylcarbamate in Example 36, Step E, the similar procedure afforded the title compound in 46% yield, as light creamy solid. <sup>1</sup>H NMR (CD<sub>3</sub>OD) 8.46 (broad s, 1H); 8.32 (broad s, 1H); 8.13 (broad s, 1H); 8.02 (d, 1H, J = 7.98 Hz); 7.62 (d, 1H, J = 8.31 Hz); 6.97 (s, 1H); 4.25 (t, 2H, J = 6.21 Hz); 3.93 (b, 4H); 1.91 – 1.86 (m, 2H); 1.36 – 1.31 (m, 2H); 0.95 (t, 3H, J = 7.02 Hz).

**Example 48****2-Amino-2-(5-(5-(3-nitro-4-propoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)propane-1,3-diol**

*Step A: 3-Nitro-4-propoxybenzoic acid:* To a stirred solution of 3-nitro-4-propoxymethylbenzoate (0.35 g, 1.46 mmol) in a mixture of THF and EtOH (3 ml : 1 ml) the solution of LiOH (0.345 g; 15 mmol) in H<sub>2</sub>O (1ml) was added and the mixture was stirred for 4 h at room temperature. The solvent was distilled off and the residue was treated with 1 M HCl and extracted with EtOAc (50 ml). The organic layer was washed with H<sub>2</sub>O, dried over MgSO<sub>4</sub> and filtered. The filtrate was evaporated to dryness to give the title compound (0.32g, 97%); as creamy solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) 8.53 (d, 1H, J = 1.65 Hz); 8.21 (dd, 1H, J = 8.79, 1.62 Hz); 7.12 (d, 1H, J = 8.82 Hz); 4.14 (t, 2H, J = 6.39 Hz); 1.94 – 1.82 (m, 2H); 1.07 (t, 3H, J = 7.35 Hz).

*Step B: 3-(3-Iodo-4-isopropoxyphenyl)-5-(3-nitro-4-propoxyphenyl)-1,2,4-oxadiazole:* When the product of Step A was substituted for 3-chloro-4-propoxybenzoic acid in Example 36, Step B, the similar procedure afforded the title compound in 66% yield, as creamy solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) 8.64 (d, 1H, J = 2.13 Hz); 8.55 (d, 1H, J = 2.1 Hz); 8.3 (dd, 1H, J = 8.82, 2.16 Hz); 8.2 (dd, 1H, J = 8.58, 2.01 Hz); 7.2 (d, 1H, J = 8.88 Hz); 6.96 (d, 1H, J = 8.85 Hz); 4.7 – 4.62 (m, 1H); 4.16 (t, 2H, J = 6.39 Hz); 1.94 – 1.84 (m, 2H); 1.42 (d, 6H, J = 6.03 Hz); 1.08 (t, 3H, J = 7.35 Hz).

*Step C: 2-Iodo-4-(5-(3-nitro-4-propoxyphenyl)-1,2,4-oxadiazol-3-yl)phenol:* When the product of Step B was substituted for 5-(3-chloro-4-propoxyphenyl)-3-(3-iodo-4-isopropoxyphenyl)-1,2,4-oxadiazole in Example 36, Step C, the similar procedure afforded the title compound in 77% yield, as creamy solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) 8.65 (d, 1H, J = 2.16 Hz); 8.47 (d, 1H, J = 1.95 Hz); 8.3 (dd, 1H, J = 8.82, 2.19 Hz); 8.03 (dd, 1H, J = 8.49, 2.01 Hz); 7.21 (d, 1H, J = 8.88 Hz); 7.08 (d, 1H, J = 8.49 Hz); 4.17 (t, 2H, J = 6.39 Hz); 1.96 – 1.84 (m, 2H); 1.09 (t, 3H, J = 7.38 Hz).

*Step D: tert-Butyl 2,2-dimethyl-5-(5-(5-(3-nitro-4-propoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)-1,3-dioxan-5-ylcarbamate:* When the product of Step C was substituted for 4-(5-(3-chloro-4-propoxyphenyl)-1,2,4-oxadiazol-3-yl)-2-iodophenol in Example 36, Step D, the similar procedure afforded the title compound in 54% yield, as pale solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) 8.68 (d, 1H, J = 2.16 Hz);

8.35 – 8.31 (m, 2H); 8.06 (dd, 1H, J = 8.64, 1.71 Hz); 7.54 (d, 1H, J = 8.64 Hz); 7.21 (d, 1H, J = 8.97 Hz); 6.76 (s, 1H); 5.33 (s, 1H); 4.3 – 3.95 (m, 6H); 2.41 – 1.87 (m, 2H); 1.58 – 1.21 (m, 15H); 1.09 (t, 3H, J = 7.44 Hz).

**Step E:** *2-Amino-2-(5-(5-(3-nitro-4-propoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)propane-1,3-diol*: When the product of Step D was substituted for tert-butyl 5-(5-(5-(3-chloro-4-propoxy phenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)-2,2-dimethyl-1,3-dioxan-5-ylcarbamate in Example 36, Step E, the similar procedure afforded the title compound in 49% yield, as creamy solid. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) 8.6 (s, 1H); 8.37 (d, 1H, J = 8.37 Hz); 8.31 (s, 1H); 7.94 (d, 1H, J = 8.52 Hz); 7.68 (d, 1H, J = 8.52 Hz); 7.59 (d, 1H, J = 8.82 Hz); 6.91 (s, 1H); 4.87 (b, 2H); 4.23 (t, 2H, J = 5.82 Hz); 3.67 (d, 2H, J = 10.05 Hz); 3.58 (d, 2H, J = 9.96 Hz); 1.78 – 1.71 (m, 2H); 0.97 (t, 3H, J = 7.26 Hz).

#### Example 49

##### **5-(3-(2-(2-Amino-1,3-dihydroxypropan-2-yl)benzofuran-5-yl)-1,2,4-oxadiazol-5-yl)-2-propoxybenzonitrile**

**Step A:** *3-Cyano-4-propoxybenzoic acid*: To a stirred solution of 3-bromo-4-propoxybenzaldehyde (0.6 g, 2.47 mmol) in anhydrous DMF (5 ml) CuCN (0.67 g; 7.4 mmol) was added and the mixture was stirred for 4 h at reflux. After cooling to room temperature, the mixture was treated with EtOAc (50 ml) and 1M HCl (10 ml) and stirred for 15 min. The organic layer was separated, dried over MgSO<sub>4</sub> and filtered. The filtrate was evaporated to dryness to give 5-formyl-2-propoxybenzonitrile (0.41 g; 88%), as yellow oil <sup>1</sup>H NMR (CDCl<sub>3</sub>) 9.87 (s, 1H); 8.07 (d, 1H, J = 1.95 Hz); 8.03 (dd, 1H, J = 8.67, 2.1 Hz); 7.06 (d, 1H, J = 8.7 Hz); 4.13 (t, 2H, J = 6.45 Hz); 1.97 – 1.85 (m, 2H); 1.1 (t, 3H, J = 7.35 Hz). The above benzaldehyde was oxidised via a similar procedure as described in Example 47 Step A, to give the title compound (0.29 g; 68%), as white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) 8.3 (d, 1H, J = 1.71 Hz); 8.23 (dd, 1H, J = 8.88, 2.1 Hz); 7.00 (d, 1H, J = 7.62 Hz); 4.12 (t, 2H, J = 6.48 Hz); 1.97 – 1.85 (m, 2H); 1.09 (t, 3H, J = 7.38 Hz).

**Step B:** *5-(3-(3-Iodo-4-isopropoxyphenyl)-1,2,4-oxadiazol-5-yl)-2-propoxy benzonitrile*: When the product of Step A was substituted for 3-chloro-4-propoxybenzoic acid in Example 36, Step B, the similar procedure afforded the title compound in 57% yield, as creamy solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) 8.55 (d, 1H, J = 2.1 Hz); 8.4 (d, 1H, J = 2.1 Hz); 8.31 (dd, 1H, J = 8.85, 2.16 Hz); 8.04 (dd, 1H, J =

8.61, 2.1 Hz); 7.09 (d, 1H, J = 8.94 Hz); 6.88 (d, 1H, J = 8.7 Hz); 4.7 – 4.6 (m, 1H); 4.14 (t, 2H, J = 6.48 Hz); 1.98 – 1.87 (m, 2H); 1.42 (d, 6H, J = 6.06 Hz); 1.18(t, 3H, J = 7.38 Hz).

*Step C: 5-(3-(4-Hydroxy-3-iodophenyl)-1,2,4-oxadiazol-5-yl)-2-propoxy benzonitrile:* When the product of Step B was substituted for 5-(3-chloro-4-propoxyphenyl)-3-(3-iodo-4-isopropoxyphenyl)-1,2,4-oxadiazole in Example 36, Step C, the similar procedure afforded the title compound in 74% yield, as creamy solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) 8.46 (d, 1H, J = 1.95 Hz); 8.4 (d, 1H, J = 2.13 Hz); 8.31 (dd, 1H, J = 8.88, 2.19 Hz); 8.02 (dd, 1H, J = 8.49, 1.68 Hz); 7.1 (d, 1H, J = 8.94 Hz); 7.09 (d, 1H, J = 8.49 Hz); 5.64 (bs, 1H); 4.12 (t, 2H, J = 6.48 Hz); 2.02 – 1.86 (m, 2H); 1.1 (t, 3H, J = 7.38 Hz).

*Step D: tert-Butyl 5-(5-(5-(3-cyano-4-propoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)-2,2-dimethyl-1,3-dioxan-5-ylcarbamate:* When the product of Step C was substituted for 4-(5-(3-chloro-4-propoxyphenyl)-1,2,4-oxadiazol-3-yl)-2-iodophenol in Example 36, Step D, the similar procedure afforded the title compound in 44% yield, as pale paste. <sup>1</sup>H NMR (CDCl<sub>3</sub>) 8.42 (d, 1H, J = 2.16 Hz); 8.34 (dd, 1H, J = 6.63, 2.19 Hz); 8.06 (dd, 1H, J = 8.61, 1.71 Hz); 7.99 (b, 1H); 7.52 (d, 1H, J = 8.58 Hz); 7.1 (d, 1H, J = 8.94 Hz); 6.76 (s, 1H); 5.33 (s, 1H); 4.26 (t, 4H, J = 11.4 Hz); 4.15 (t, 2H, J = 11.4 Hz); 4.15 (t, 2H, J = 6.48 Hz); 2.02 – 1.87 (m, 2H); 1.56 – 1.38 (m, 15H); 1.1 (t, 3H, J = 7.38 Hz).

*Step E: 5-(3-(2-(2-Amino-1,3-dihydroxypropan-2-yl)benzofuran-5-yl)-1,2,4-oxadiazol-5-yl)-2-propoxy benzonitrile:* When product of Step D was substituted for tert-butyl 5-(5-(5-(3-chloro-4-propoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)-2,2-dimethyl-1,3-dioxan-5-ylcarbamate (obtained as crude via a process as described in Example 36, Step D) in Example 36, Step E, the similar procedure afforded the title compound in 29% yield, as off white solid. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) 8.49 (d, 1H, J = 2.22 Hz); 8.39 (dd, 1H, J = 8.91, 2.22 Hz); 8.28 (d, 1H, J = 1.41 Hz); 7.93 (dd, 1H, J = 8.55, 1.71 Hz); 7.68 (d, 1H, J = 8.58 Hz); 7.48 (d, 1H, J = 9.06 Hz); 6.89 (s, 1H); 4.78 (b, 2H); 4.22 (t, 2H, J = 6.42 Hz); 3.68 – 3.52 (m, 4H); 1.84 – 1.73 (m, 2H); 1.0(t, 3H, J = 7.41 Hz).

**Example 50****2-Amino-2-(5-(5-(3-bromo-4-propoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)propane-1,3-diol**

*Step A: 3-Bromo-4-propoxybenzoic acid:* 3-Bromo-4-propoxybenzaldehyde was oxidized by  $\text{KMnO}_4$ , according to the procedure as described in Example 47, Step A, to give the title compound in 96%, as white solid.  $^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ ) 0.98 (t, 3H,  $J = 7.32$  Hz); 1.68 - 1.79 (m, 2H); 4.06 (t, 2H,  $J = 6.39$  Hz); 7.14 (d, 1H,  $J = 8.7$  Hz); 7.87 (dd, 1H,  $J = 2.07, 8.61$  Hz); 8.01 (d, 1H,  $J = 2.04$  Hz); 11.2 (broad s, 1H).

*Step B: 4-(5-(3-Bromo-4-propoxyphenyl)-1,2,4-oxadiazol-3-yl)-2-iodophenol:* When the product of Step A was substituted for 3-chloro-4-propoxybenzoic acid in Example 36, Step B, the similar procedure afforded the title compound in 70% yield, as white solid.  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ) 8.47 (s, 1H); 8.38 (s, 1H); 8.08 (d, 1H,  $J = 9.09$  Hz); 8.03 (d, 1H,  $J = 8.79$  Hz); 7.7 (d, 1H,  $J = 8.55$  Hz); 6.98 (d, 1H,  $J = 8.67$  Hz); 4.08 (t, 2H,  $J = 6.39$  Hz); 1.96 - 1.84 (m, 2H); 1.1 (t, 3H,  $J = 7.35$  Hz).

*Step C: tert-Butyl 5-(5-(5-(3-bromo-4-propoxy-phenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)-2,2-dimethyl-1,3-dioxan-5-yl-carbamate:* When with the product of Step C was substituted for 4-(5-(3-chloro-4-propoxyphenyl)-1,2,4-oxadiazol-3-yl)-2-iodophenol in Example 36, Step D, the similar procedure afforded the title compound in 98% yield, as pale paste.

*Step D: 2-Amino-2-(5-(5-(3-bromo-4-propoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)propane-1,3-diol:* When the product of Step C is substituted for tert-butyl 5-(5-(5-(3-chloro-4-propoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)-2,2-dimethyl-1,3-dioxan-5-ylcarbamate in Example 36, Step E, the similar procedure afforded the title compound in 10% yield, as light yellow solid.  $^1\text{H NMR}$  ( $\text{CD}_3\text{OD}$ ) 8.32 (b, 2H); 8.1 (d, 1H,  $J = 8.46$  Hz); 8.00 (d, 1H,  $J = 8.52$  Hz); 7.59 (d, 1H,  $J = 8.61$  Hz); 7.18 (d, 1H,  $J = 8.58$  Hz); 6.91 (s, 1H); 4.1 (t, 2H,  $J = 6.06$  Hz); 3.91 (d, 2H,  $J = 10.98$  Hz); 3.03 (d, 2H,  $J = 10.95$  Hz); 3.32 (b, 2H); 1.9 - 1.8 (m, 2H); 1.1 (t, 3H,  $J = 7.35$  Hz).

**Example 51****2-Amino-2-(5-octylbenzo[b]thiophen-2-yl)propane-1,3-diol**

*Step A: 2-Iodo-4-octylaniline:* To a stirred mixture of 4-octyl aniline (0.33 g, 1.6 mmol) and H<sub>2</sub>O<sub>2</sub> (30 %, 0.5 ml) in CH<sub>3</sub>OH (1.5 ml) was added I<sub>2</sub> (0.2 g, 0.8 mmol) and the mixture was stirred overnight at room temperature. The solvent was distilled off and the residue was diluted to 10 ml with CH<sub>2</sub>Cl<sub>2</sub>, washed with H<sub>2</sub>O, dried over MgSO<sub>4</sub> and filtered. The filtrate was evaporated to dryness to give the title compound (0.46 g, 86%) as yellow paste. <sup>1</sup>H NMR (CDCl<sub>3</sub>) 7.44 (d, 1H, J = 1.83 Hz); 6.93 (dd, 1H, J = 8.07, 1.86 Hz); 6.65 (d, 1H, J = 8.1 Hz); 4.1 (b, 2H); 2.43 (t, 2H, J = 7.5 Hz); 1.54 – 1.49 (m, 2H); 1.26 (b, 10H); 0.87 (t, 3H, J = 6.39 Hz).

*Step B: 2-Iodo-4-octylbenzenethiol:* To a stirred mixture of the product of Step A (0.4 g; 1.21 mmol) in 35% HCl (0.2 ml) an ice cold solution of NaNO<sub>2</sub> (0.1 g, 1.3 mmol) in H<sub>2</sub>O (1 ml) was added at 0°C, followed by a solution of K-ethylxanthate, freshly prepared by rapid stirring of a mixture of KOH (0.085 g, 1.5 mmol) and CS<sub>2</sub> (0.173 g, 1.5 mmol) in a mixture of EtOH and H<sub>2</sub>O (1ml : 1.5 ml) for 2.5 h at room temperature. The resulting mixture was stirred for 5 h at 55 °C, then cooled to room temperature and extracted with EtOAc (50 ml). The organic layer was separated, washed with H<sub>2</sub>O, dried over MgSO<sub>4</sub> and filtered. The filtrate was evaporated and the residue was diluted to 20 ml with EtOH and KOH (0.5 g, 3.62 mmol) was added. This was stirred for 5 h at reflux and the mixture was evaporated to dryness and the residue was treated with 1M HCl and extracted with EtOAc (20 ml). The organic layer was separated, dried over MgSO<sub>4</sub> and filtered. The filtrate was evaporated and the residue was purified by FCC (SiO<sub>2</sub>; hexane/EtOAc) to give the title compound (0.1 g, 24%), as a yellow paste, which was used as such in next step. <sup>1</sup>H NMR (CDCl<sub>3</sub>) 7.75 (b, 1H); 7.28 (d, 1H, J = 7.95 Hz); 7.00 (dd, 1H, J = 7.95, 2.0 Hz); 7.02 (s, 1H); 2.51 – 2.45 (m, 2H); 1.53 (b, 2H); 1.25 (b, 10H); 0.86 (t, 3H, J = 6.42 Hz).

*Step C: tert-Butyl 2,2-dimethyl-5-(5-octylbenzo[b]thiophen-2-yl)-1,3-dioxan-5-ylcarbamate* When with the product of Step B was substituted for 4-(5-(3-chloro-4-propoxyphenyl)-1,2,4-oxadiazol-3-yl)-2-iodophenol in Example 36, Step D, the similar procedure afforded the title compound in 24% yield, as white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) 7.65 (d, 1H, J = 8.16 Hz); 7.47 (s, 1H); 7.1 (d, 1H, J = 6.18 Hz);

7.1 (s, 1H); 5.44 (b, 1H); 4.16 (b, 4H); 2.66 (t, 2H, J = 7.5 Hz); 1.6 – 1.1 (m, 27 H); 0.86 (t, 3H, J = 6.18 Hz).

**Step D: 2-Amino-2-(5-octylbenzo[b]thiophen-2-yl)propane-1,3-diol:** When tert-butyl 5-(5-(5-(3-chloro-4-propoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)-2,2-dimethyl-1,3-dioxan-5-ylcarbamate was replaced with the product of Step C the similar procedure as described in Example 36, Step E gave the title compound (0.008 g, 38%) as light yellow solid. <sup>1</sup>H NMR (CD300) 7.74 (d, 1H, J = 8.28 Hz); 7.6 (s, 1H); 7.4 (s, 1H); 7.2 (dd, 2H, J = 8.34, 1.59 Hz); 4.0 (d, 2H, J = 11.46 Hz); 3.94 (d, 2H, J = 11.46 Hz); 2.7 (t, 2H, J = 7.53 Hz); 1.64 (b, 2H); 1.34 – 1.26 (b, 10H); 0.85 (t, 3H, J = 4.8 Hz).

## Example 52

### 2-Amino-2-(5-octylbenzofuran-2-yl)propane-1,3-diol

**Step A: 2-Iodo-4-octylphenol:** A mixture of 4-octyl phenol (0.15 g, 0.73 mmol), Cf3C02Ag (0.25 g, 1 mmol) and 12 (0.185 g, 0.73 mmol) in CH2Cl2 (10 ml) was stirred for 0.5 h at O QC , then for 0.5 h at room temperature. The solution was filtered through Celite\* bead and washed with CH2Cl2 (30 ml). The filtrates were

evaporated to dryness to give the title compound (0.21 g, 87%) as fawn oil. <sup>1</sup>H NMR (CDCb) 7.32 (d, 1H, J = 8.34 Hz); 7.28 (d, 1H, J = 1.26 Hz); 6.98 (dd, 1H, 8.37, 1.71 Hz); 6.62 (s, 1H); 4.69 (t, 2H, J = 5.88 Hz); 3.62 – 3.38 (m, 4H); 2.59 (t, 2H, J = 7.29 Hz); 1.56 – 1.51 (m, 2H); 1.34 – 1.2 (m, 10H); 0.81 (t, 3H, J = 6.48 Hz).

**Step B: tert-Butyl 2,2-dimethyl-5-(5-octylbenzofuran-2-yl)-1,3-dioxan-5-ylcarbamate:** When with the product of Step A was substituted for 4-(5-(3-chloro-4-propoxyphenyl)-1,2,4-oxadiazol-3-yl)-2-iodophenol in Example 36, Step D, the similar procedure afforded the title compound in 53% yield, as a light yellow paste. <sup>1</sup>H NMR (CDCl3) 7.33 (d, 1H, J = 6.27 Hz); 7.32 (s, 1H); 7.01 (dd, 1H, J = 8.4, 1.71 Hz); 6.59 (s, 1H); 5.3 (s, 1H); 4.17 (s, 4H); 2.64 (t, 2H, J = 7.77 Hz); 1.62 – 1.24 (m, 27H); 0.86 (t, 3H, J = 6.42 Hz).

**Step C: 2-Amino-2-(5-octylbenzofuran-2-yl)propane-1,3-diol:** When the product of Step B was substituted for tert-butyl 5-(5-(5-(3-chloro-4-propoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)-2,2-dimethyl-1,3-dioxan-5-ylcarbamate in Example 36, Step E, the similar procedure afforded the title compound in 51% yield, as off white solid. <sup>1</sup>H NMR (DMSO-d5) 7.44 (d, 1H, J =

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1.98 Hz); 7.0 (dd, 1H, J = 8.28, 1.98 Hz); 6.87 (d, 1H, J = 8.22 Hz); 5.11(s, 1H); 2.47 (t, 2H, J = 7.5 Hz); 1.56 – 1.51 (m, 2H); 1.27 – 1.26 (m, 10H); 0.87 (t, 3H, J = 6.45 Hz).

### Example 53

#### **2-(4-(5-(3,4-Diethoxyphenyl)-1,2,4-oxadiazol-3-yl)indoline-1-carboxamido)acetic acid**

*Step A: N-Hydroxy-1H-indole-4-carboximidamide:* A mixture of 4-cyanoindole (0.64 g; 4.5 mmol), HCl x H<sub>2</sub>NOH (1.1 g; 15.8 mmol), and Na<sub>2</sub>CO<sub>3</sub> (0.79 g; 7.43 mmol) in H<sub>2</sub>O (8 ml) and EtOH (2 ml) was gently stirred for 15 min, then refluxed for 6h under N<sub>2</sub>. After cooling most of the EtOH was removed under reduced pressure and the product was extracted with EtOAc (3 x 10 ml). The organic phase was separated, dried over anhydrous MgSO<sub>4</sub> and filtered. The filtrate was evaporated to dryness under reduced pressure to give the title compound (0.74 g; 94%), as a creamy foam. <sup>1</sup>H-NMR (DMSO-d<sub>6</sub> + CDCl<sub>3</sub> + CD<sub>3</sub>OD) 7.4 – 7.3 (m, 1H); 7.2 – 7.12 (m, 2H); 7.01 (t, 1H, J = 7.8 Hz); 6.74 (d, 1H, J = 3.1 Hz); 3.68 (HDO); 1.71 (broad s, H<sub>2</sub>O).

*Step B: 5-(3,4-Diethoxyphenyl)-3-(1H-indol-4-yl)-1,2,4-oxadiazole* To a solution of 3,4-diethoxybenzoic acid (0.11 g; 0.52 mmol), and the product of Step A (0.09 g; 0.51 mmol) in anhydrous THF (2 ml), PyBroP (0.25 g; 0.54 mmol) was added followed by DIPEA (0.21 ml; 1.22 mmol), with stirring, at room temperature under N<sub>2</sub>. After 2 h of stirring, the mixture was diluted to 15 ml with EtOAc, washed with saturated NH<sub>4</sub>Cl (2 x 5 ml), brine, dried over anhydrous MgSO<sub>4</sub> and filtered. The filtrate was evaporated to dryness under reduced pressure and the residue was suspended in anhydrous toluene (10 ml). To it 1M TBAF in THF (0.5 ml) was added and the reaction mixture was refluxed for 3 h under N<sub>2</sub>, cooled to room temperature and solvents were removed under reduced pressure. The residue was washed with H<sub>2</sub>O (5 ml) and the solid was purified by FCC (SiO<sub>2</sub>; CH<sub>2</sub>Cl<sub>2</sub>) to give the title compound (0.06 g; 34%) as colourless solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.42 (s, 1H); 8.06 (dd, 1H, J = 2, 8.4 Hz); 7.83 (d, 1H, J = 8.4Hz); 7.74 (d, 1H, J = 2 Hz); 7.54 (d, 1H, J = 8.1 Hz); 7.37 – 7.31 (m, 3H); 6.98 (d, 1H, J = 8.5 Hz); 4.26 – 4.16 (m, 4H); 1.5 (m, 6H).

*Step C: 5-(3,4-Diethoxyphenyl)-3-(indolin-4-yl)-1,2,4-oxadiazole:* To a solution of the product of Step B (0.06 g; 0.172 mmol) in 1M BH<sub>3</sub> in THF (0.35 ml;

0.35 mmol) TFA (0.4 ml) was added drop wise at 0°C with stirring. After the addition was completed (~5 min), the reaction was quenched with H<sub>2</sub>O (0.5 ml) and solvents were removed under reduced pressure. The residue was diluted to 10 ml with EtOAc and was washed with 10% NaOH (2 x 2 ml), brine and dried over anhydrous MgSO<sub>4</sub> and filtered. The filtrate was evaporated to dryness under reduced pressure to give the title compound (0.026 g; 43%) as a creamy foam, which was used in the next step without further purification. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 7.78 (dd, 1H, J = 1.9, 7.2 Hz); 7.68 (d, 1H, J = 1.9 Hz); 7.52 (d, 1H, J = 7.2 Hz); 7.17 (t, 1H, J = 7.7); 6.97 (d, 1H, J = 8.5 Hz); 6.75 (d, 1H, J = 7.7 Hz); 4.19 (m, 4H); 3.65 (t, 2H, J = 8.9 Hz); 3.45 (tr, 2H, J = 8.9 Hz); 1.7 (broad s, 1H + H<sub>2</sub>O); 1.49 (m, 6H).

*Step D: Ethyl 2-(4-(5-(3,4-diethoxyphenyl)-1,2,4-oxadiazol-3-yl)indoline-1-carboxamido)acetate:* When the product of Step E was substituted for n-octylaniline and ethyl isocyanatoacetate was substituted for ethyl 3-isocyanatopropionate in Example 11, Step A the similar process afforded the title compound in 61 %, as colourless solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.11 (d, 1H, J = 7.4 Hz); 7.78 (dd, 2H, J = 2, 7.1 Hz); 7.67 (d, 1H, J = 2 Hz); 7.31 (t, 1H, J = 8 Hz); 6.97 (d, 1H, J = 8.5 Hz); 5.13 (t, 1H, J = 5.1 Hz); 4.28 – 4.04 (m, 10 H); 3.61 (t, 1H, J = 8.6 Hz); 1.52 – 1.47 (m, 6H); 1.32 (t, 3H, J = 7.1 Hz);

*Step E: 2-(4-(5-(3,4-Diethoxyphenyl)-1,2,4-oxadiazol-3-yl)indoline-1-carboxamido)acetic acid:* When the product of Step D was substituted for ethyl 3-(3-(4-octylphenyl)ureido)propanoate in Example 11, Step B the identical process afforded the title compound in 75 % yield. <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) 8.03 (d, 1H, J = 9 Hz); 7.73 (dd, 1H, J = 2, 8 Hz); 7.61 – 7.59 (m, 2H); 7.29 (t, 1H, J = 7.9 Hz); 7.17 (d, 1H, J = 8.6 Hz); 7.09 (broad m, 1H); 4.17 – 4.0 (m, 4H); 3.98 (t, 2H, J = 5.8 Hz); 3.74 (d, 2H, J = 5.2 Hz); 3.47 (t, 2H, J = 9 Hz); 1.38 – 1.32 (m, 6H).

#### Example 54

##### **3-(4-(5-(3,4-Diethoxyphenyl)-1,2,4-oxadiazol-3-yl)indoline-1-carboxamido)propanoic acid**

*Step A: Ethyl 3-(4-(5-(3,4-diethoxyphenyl)-1,2,4-oxadiazol-3-yl)indoline-1-carboxamido)propanoate:* When the product of Example 16 Step C was substituted for n-octylaniline in Example 11, Step A the identical process afforded the title compound in 52 % yield. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.1 (d, 1H, J = 9 Hz); 7.79 –

7.75 (m, 2H); 7.67 (d, 1H, J = 2 Hz); 7.31 (t, 1H, J = 8 Hz); 6.97 (d, 1H, J = 8.5 Hz); 5.38 (tr, 1H, J = 5.7 Hz); 4.24 – 4.12 (m, 6H); 3.98 (t, 2H, J = 8.6 Hz); 3.63 – 3.55 (m, 4H); 2.61 (t, 2H, J = 5.9 Hz); 1.27 (t, 3H, J = 9 Hz);

Step B: 3-(4-(5-(3,4-Diethoxyphenyl)-1,2,4-oxadiazol-3-yl)indoline-1-carboxamido)propanoic acid: When the product of Step A was substituted for ethyl 3-(3-(4-octylphenyl)ureido)propanoate in Example 11, Step B the identical process afforded the title compound in 61 % yield. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.03 (d, 1H, J = 9 Hz); 7.72 (dd, 1H, J = 1.9, 8.4 Hz); 7.59 – 7.56 (m, 2H); 7.27 (t, 1H, J = 7.9 Hz); 7.16 (d, 1H, J = 8.6 Hz); 6.76 (t, 1H, J = 5.3 Hz); 4.04 – 4.16 (m, 4H); 3.92 (t, 2H, J = 8.6 Hz); 3.43 (tr, 2H, J = 8.4 Hz); 3.36 – 3.28 (m, 2H + H<sub>2</sub>O); 2.48 – 2.42 (m, 2H); 1.37 – 1.32 (m, 6H).

#### Example 55

2-Amino-2-(5-(5-(2-cyclopropylbenzofuran-5-yl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)propane-1,3-diol

Step A: 5-(2-Cyclopropylbenzofuran-5-yl)-3-(3-iodo-4-isopropoxyphenyl)-1,2,4-oxadiazole: When 3-chloro-4-propoxybenzoic acid was substituted for 2-cyclopropylbenzofuran-5-carboxylic acid in Example 36, Step B, the similar process afforded the title compound in 47% yield, as brown gum. <sup>1</sup>H NMR (CDCl<sub>3</sub>) 8.59 (d, 1H, J = 2.04 Hz), 8.29(d, 1H, J = 1.44 Hz), 8.09 – 8.02(m, 2H), 7.46 (d, 1H, J = 8.61 Hz), 6.9 (d, 1H, J = 8.7 Hz), 6.45(s, 1H), 4.7 – 4.6 (m, 1H), 2.1 – 2.0(m, 1H), 1.42(d, 6H, J = 5.97 Hz), 1.0 (b, 4H).

Step B: 4-(5-(2-Cyclopropylbenzofuran-5-yl)-1,2,4-oxadiazol-3-yl)-2-iodophenol: When the product of Step A was substituted for 5-(3-chloro-4-propoxyphenyl)-3-(3-iodo-4-isopropoxyphenyl)-1,2,4-oxadiazole in Example 36, Step C, the similar procedure afforded the title compound in 69% yield, as white solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.5 (d, 1H, J = 1.98 Hz), 8.29(d, 1H, J = 1.59 Hz), 8.07 – 8.02(m, 2H), 7.47(d, 1H, J = 8.58 Hz), 7.08(d, 1H, J = 8.49 Hz), 6.45(s, 1H), 5.63(s, 1H), 2.1 – 2.0(m, 1H), 1.0(b, 4H).

Step C: 2-Amino-2-(5-(5-(2-cyclopropylbenzofuran-5-yl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)propane-1,3-diol: When tert-butyl 5-(5-(2-cyclopropylbenzofuran-5-yl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)-2,2-dimethyl-1,3-dioxan-5-ylcarbamate (obtained via a similar procedure as described in Example 36, Step D when the product of above Step B was replaced with 4-(5-(3-

Chloro-4-propoxyphenyl)-1,2,4-oxadiazol-3-yl)-2-iodophenol) tert-butyl-5-(5-(3-chloro-4-propoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)-2,2-dimethyl-1,3-dioxan-5-yl carbamate in Example 36, Step E, the similar procedure afforded the title compound in 48% yield, as colourless solid. <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) 8.33 (bs, 1H), 7.99(bs, 2H), 7.7(bs, 2H), 6.97(s, 1H), 6.75(bs, 1H), 5.04(bs, 2H), 3.71(bs, 2H), 3.66(bs, 2H), 2.15(bs, 1H), 0.95(d, 4H).

**Example 56****2-Amino-2-(5-(5-(4-isobutoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)propane-1,3-diol**

**Step A:** 3-(3-Iodo-4-isopropoxyphenyl)-5-(4-isobutoxyphenyl)-1,2,4-oxadiazole: When 3-chloro-4-propoxybenzoic acid was substituted for 4-isobutoxybenzoic acid [<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) 7.77(b, 2H), 6.98(b, 2H), 3.78(b, 2H), 1.99(b, 1H), 0.94(d, 6H, J = 6.06 Hz)] in Example 36, Step B, the similar process afforded the title compound in 54% yield, as creamy paste. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.57 (d, 1H, J = 2.07 Hz), 8.1(d, 2H, J = 6.93 Hz), 8.04 (dd, 1H, J = 8.55, 2.01 Hz), 6.99(d, 2H, J = 8.91 Hz), 6.87 (d, 1H, J = 8.73 Hz), 4.69 – 4.6(m, 1H), 3.79(d, 2H, J = 6.54 Hz), 2.18 – 2.06(m, 1H), 1.41(d, 6H, J = 6.03 Hz), 1.04(d, 6H, J = 6.72 Hz).

**Step B:** 2-Iodo-4-(5-(4-isobutoxyphenyl)-1,2,4-oxadiazol-3-yl)phenol : When the product of Step A was substituted for 5-(3-chloro-4-propoxyphenyl)-3-(3-iodo-4-isopropoxyphenyl)-1,2,4-oxadiazole in Example 36, Step C, the similar procedure afforded the title compound in 84% yield, as white solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.47 (d, 1H, J = 1.98 Hz), 8.1(d, 2H, J = 8.91 Hz), 8.03 (dd, 1H, J = 8.46, 1.98 Hz), 7.07 (d, 1H, J = 8.5 Hz), 7.0(d, 2H, J = 8.94 Hz), 3.79 (d, 2H, J = 6.54 Hz), 2.14 – 2.07 (m, 1H), 1.04 (d, 6H, J = 6.69 Hz).

**Step C:** tert-Butyl 5-(5-(5-(4-isobutoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)-2,2-dimethyl-1,3-dioxan-5-ylcarbamate: When the product of Step B was substituted for 4-(5-(3-chloro-4-propoxy phenyl)- 1,2,4- oxadiazol-3-yl)- 2-iodophenol in Example 36, Step D, the similar process afforded the title compound in 61% yield, as pale paste. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.34 (d, 1H, J = 1.38 Hz), 8.13(d, 2H, J = 8.91 Hz), 8.07 (dd, 1H, J = 8.67, 1.71 Hz), 7.52(d, 1H, J = 8.61 Hz), 7.02(d, 2H, J = 8.91 Hz), 6.75(s, 1H), 5.33(s, 1H), 4.29 – 4.24(m, 4H),

3.8(d, 2H, J = 6.54 Hz), 2.2 – 2.5 (m, 1H), 1.56(s, 6H), 1.52(s, 9H), 1.04(d, 6H, J = 6.72 Hz).

Step D: **2-Amino-2-(5-(5-(4-isobutoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)propane-1,3-diol**: When the product of Step D was substituted for *tert*-butyl 5-(5-(5-(3-chloro-4-propoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)-2,2-dimethyl-1,3-dioxan-5-yl carbamate in Example 36, Step E, the similar procedure afforded the title compound in 46% yield, as colourless solid. <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) 8.27 (s, 1H), 8.08 (d, 2H, J = 7.23 Hz), 7.92 (d, 1H, J = 7.59 Hz), 7.66 (d, 1H, J = 7.62 Hz), 7.15 (d, 1H, J = 7.62 Hz), 6.88 (s, 1H), 4.78 (bs, 2H), 3.84 (d, 2H, J = 5.4 Hz), 3.64 (bs, 2H), 3.56 (bs, 1H), 2.02(b, 1H), 0.96(d, 6H, J = 5.49 Hz).

#### Example 57

**2-Amino-2-(6-chloro-5-(5-(3,4-diethoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)propane-1,3-diol**

Step A: **3-(2-Chloro-5-iodo-4-isopropoxyphenyl)-5-(3,4-diethoxyphenyl)-1,2,4-oxadiazole**: When 3-propylbenzoic acid was substituted for 3,4-diethoxybenzoic acid and in Example 46, Step B, the similar process afforded the title compound in 35% yield, as creamy solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.45 (s, 1H), 7.77 (dd, 1H, J = 8.43, 2.01 Hz), 7.66 (d, 1H, J = 1.98 Hz), 6.97 (d, 1H, J = 8.5 Hz), 6.92 (s, 1H), 4.67 – 4.56 (m, 1H), 4.23 – 4.14 (m, 6H), 1.52 – 1.46 (m, 6H), 1.42 (d, 6H, J = 6.06 Hz).

Step B: **5-Chloro-4-(5-(3,4-diethoxyphenyl)-1,2,4-oxadiazol-3-yl)-2-iodophenol**: When the product of Step A was substituted for 5-(3-chloro-4-propoxyphenyl)-3-(3-iodo-4-isopropoxyphenyl)-1,2,4-oxadiazole in Example 36, Step C, the similar procedure afforded the title compound in 64% yield, as white solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.35 (s, 1H), 7.77 (dd, 1H, J = 8.43, 2.01 Hz), 7.65 (d, 1H, J = 2.01 Hz), 7.16 (s, 1H), 6.97(d, 1H, J = 8.49 Hz), 4.23 – 4.14 (m, 4H), 1.52 – 1.46 (m, 6H).

Step C: ***tert*-Butyl 5-(6-chloro-5-(5-(3,4-diethoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)-2,2-dimethyl-1,3-dioxan-5-ylcarbamate**: When the product of Step B was substituted for 4-(5-(3-chloro-4-propoxy phenyl)- 1,2,4- oxadiazol-3-yl)- 2-iodophenol in Example 36, Step D, the similar process afforded the title compound in 57% yield, as creamy solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.11(s, 1H), 7.79 (dd,

1H, J = 8.43, 1.92 Hz), 7.67 (d, 1H, J = 1.95 Hz), 7.63 (s, 1H), 6.97 (d, 1H, J = 8.55 Hz), 6.73(s, 1H), 5.3(s, 1H), 4.28 – 4.16(m, 8H), 1.54 – 1.39 (m, 21 H).

Step D: 2-Amino-2-(6-chloro-5-(5-(3,4-diethoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)propane-1,3-diol: When the product of Step C was substituted  
5 for tert-butyl-5-(5-(5-(3-chloro-4-propoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)-2,2-dimethyl-1,3-dioxan-5-yl carbamate in Example 36, Step E, the similar procedure afforded the title compound in 42% yield, as creamy solid. <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) 8.12 (bs 1H), 7.9(bs, 1H), 7.74(bs, 1H), 7.59(bs, 1H), 7.18(bs, 1H), 6.88(bs, 1H), 4.82(bs, 2H), 4.12(bs, 4H), 3.64(b, 4H), 1.34(b, 6H).

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**Example 58****2-Amino-2-(5-(5-(3-chloro-4-methoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)propane-1,3-diol**

Step A: 5-(3-Chloro-4-methoxyphenyl)-3-(3-iodo-4-isopropoxyphenyl)-1,2,4-  
15 oxadiazole: When 3-chloro-4-propoxybenzoic acid was substituted for 3-chloro-4-methoxybenzoic acid in Example 36, Step B, the similar process afforded the title compound in 59% yield, as pale paste. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.56 (d, 1H, J = 2.04 Hz), 8.21 (d, 1H, J = 2.1 Hz), 8.07 (dd, 1H), 7.55 (dd, 1H, J = 8.61, 2.04 Hz), 7.04(d, 1H, J = 8.67 Hz), 6.88 (d, 1H, J = 8.7 Hz), 4.69 – 4.59 (m, 1H), 3.99(s, 20 3H), 1.42(d, 6H, J = 6.03 Hz).

Step B: 4-(5-(3-Chloro-4-methoxyphenyl)-1,2,4-oxadiazol-3-yl)-2-iodophenol: When the product of Step A was substituted for 5-(3-chloro-4-propoxyphenyl)-3-(3-iodo-4-isopropoxyphenyl)-1,2,4-oxadiazole in Example 36, Step C, the similar procedure afforded the title compound in 62% yield, as white solid. <sup>1</sup>H-NMR  
25 (CDCl<sub>3</sub>) 8.46 (d, 1H, J = 1.89 Hz), 8.21 (d, 1H, J = 2.01 Hz), 8.01 (dd, 1H, J = 8.76, 1.98 Hz), 7.52 (dd, 1H, J = 8.58, 1.95 Hz), 7.06(d, 1H, J = 8.28 Hz), 7.01(d, 1H, J = 8.61 Hz), 3.99(s, 3H).

Step C: 2-Amino-2-(5-(5-(3-chloro-4-methoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)propane-1,3-diol: When tert-butyl-5-(5-(5-(3-chloro-4-methoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)-2,2-dimethyl-1,3-dioxan-5-ylcarbamate (obtained via a similar procedure as described in Example 36, Step D when the product of above Step B was replaced with 4-(5-(3-Chloro-4-propoxyphenyl)-1,2,4-oxadiazol-3-yl)-2-iodophenol) was replaced with tert-butyl-5-(5-(5-(3-chloro-4-propoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)-2,2-

dimethyl-1,3-dioxan-5-yl carbamate in Example 36, Step E, the similar procedure afforded the title compound in 32% yield, as white solid. <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) 8.31 (s, 1H), 8.16 – 8.1 (m, 2H), 7.95 (d, 1H, J = 8.22 Hz), 7.69 (d, 1H, J = 8.37 Hz), 7.39 (d, 1H, J = 8.7 Hz), 6.94 (s, 1H), 4.96(bs, 2H), 3.96(s, 3H), 3.68(bs, 2H), 3.64(bs, 2H).

#### Example 59

#### 2-Amino-2-(5-(5-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)propane-1,3-diol

**Step A:** 5-(3,4-Dimethoxyphenyl)-3-(3-iodo-4-isopropoxyphenyl)-1,2,4-oxadiazole: When 3-chloro-4-propoxybenzoic acid was substituted for 3,4-dimethoxybenzoic acid in Example 36, Step B, the similar process afforded the title compound in 78% yield, as crude pale solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.58 (d, 1H, J = 2.07 Hz), 8.06 (dd, 1H, J = 8.58, 2.07 Hz), 7.8 (dd, 1H, J = 8.4, 1.95 Hz), 7.66 (d, 1H, J = 1.89 Hz), 6.98(d, 1H, J = 8.46 Hz), 6.88 (d, 1H, J = 8.73 Hz), 4.69 – 4.57 (m, 1H), 4.0(s, 3H), 3.96(s, 3H), 1.41(d, 6H, J = 6.09 Hz).

**Step B:** 4-(5-(3,4-Dimethoxyphenyl)-1,2,4-oxadiazol-3-yl)-2-iodophenol: When the product of Step A was substituted for 5-(3-chloro-4-propoxyphenyl)-3-(3-iodo-4-isopropoxyphenyl)-1,2,4-oxadiazole in Example 36, Step C, the similar procedure afforded the title compound in 55% yield, as white solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.49 (d, 1H, J = 1.83 Hz), 8.04 (dd, 1H, J = 8.58, 2.04 Hz), 7.81 (dd, 1H, J = 8.22, 1.59 Hz), 7.66 (d, 1H, J = 1.71 Hz), 7.07(d, 1H), 6.98(d, 1H), 4.0(s, 3H), 3.97(s, 3H).

**Step C:** 2-Amino-2-(5-(5-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)propane-1,3-diol: When tert-butyl 5-(5-(5-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)-2,2-dimethyl-1,3-dioxan-5-ylcarbamate (obtained via a similar procedure as described in Example 36, Step D when the product of above Step B was replaced with 4-(5-(3-Chloro-4-propoxyphenyl)-1,2,4-oxadiazol-3-yl)-2-iodophenol) was replaced with tert-butyl 5-(5-(5-(3-chloro-4-propoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)-2,2-dimethyl-1,3-dioxan-5-yl carbamate in Example 36, Step E, the similar procedure afforded the title compound in 15% yield, as white solid. <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) 8.32 (bs, 1H), 7.95 (b, 1H), 7.76(b, 1H), 7.7(b, 1H), 7.2(b, 1H), 6.95(b, 1H), 5.03(b, 2H), 3.86(b, 6H), 3.65(b, 4H).

**Example 60****2-Amino-2-(5-(5-(3-chloro-4-ethoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)propane-1,3-diol**

5        *Step A: 5-(3-Chloro-4-ethoxyphenyl)-3-(3-iodo-4-isopropoxyphenyl)-1,2,4-oxadiazole:* When 3-chloro-4-propoxybenzoic acid was substituted for 3-chloro-4-methoxybenzoic acid in Example 36, Step B, the similar process afforded the title compound in 64% yield, as pale paste. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.56 (d, 1H, J = 2.01 Hz), 8.21 (d, 1H, J = 2.04 Hz), 8.07 – 8.24 (m, 2H), 7.02 (d, 1H, J = 8.67 Hz), 6.87  
10 (d, 1H, J = 8.67 Hz), 4.72 – 4.6 (m, 1H), 4.19 (q, 2H, J = 6.96, 13.95 Hz), 1.52 (t, 3H, J = 6.93 Hz), 1.42 (d, 6H, J = 6.03 Hz).

*Step B: 4-(5-(3-Chloro-4-ethoxyphenyl)-1,2,4-oxadiazol-3-yl)-2-iodophenol:* When the product of Step A was substituted for 5-(3-chloro-4-propoxyphenyl)-3-(3-iodo-4-isopropoxyphenyl)-1,2,4-oxadiazole in Example 36, Step C, the similar  
15 procedure afforded the title compound in 68% yield, as white solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.47 (d, 1H, J = 1.95 Hz), 8.21 (d, 1H, J = 2.1 Hz), 8.05 – 8.01 (m, 2H), 7.08 (d, 1H, J = 8.49 Hz), 7.02 (d, 1H, J = 8.67 Hz), 4.2 (q, 2H, J = 6.96, 13.98 Hz), 1.52 (t, 3H, J = 6.99 Hz).

*Step C: tert-Butyl 5-(5-(5-(3-chloro-4-ethoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)-2,2-dimethyl-1,3-dioxan-5-ylcarbamate:* When the product of  
20 Step B was substituted for 4-(5-(3-chloro-4-propoxy phenyl)-1,2,4-oxadiazol-3-yl)-2-iodophenol in Example 36, Step D, the similar process afforded the title compound in 55% yield, as pale paste. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.33 (d, 1H, J = 1.38 Hz), 8.24 (d, 1H, J = 2.13 Hz), 8.08 – 8.05 (m, 2H), 7.52 (d, 1H, J = 8.76 Hz), 7.0  
25 (d, 1H, J = 8.7 Hz), 6.75 (s, 1H), 5.32 (bs, 2H), 4.22 (q, 2H, J = 5.94, 12.78 Hz), 1.54 – 1.36 (m, 18H).

*Step D: 2-Amino-2-(5-(5-(3-chloro-4-ethoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)propane-1,3-diol:* When the product of Step C was substituted  
for tert-butyl 5-(5-(5-(3-chloro-4-propoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-  
30 2-yl)-2,2-dimethyl-1,3-dioxan-5-yl carbamate in Example 36, Step E, the similar procedure afforded the title compound in 35% yield, as creamy solid. <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) 8.3 (d, 1H, J = 1.35 Hz), 8.16 (d, 1H, J = 2.04 Hz), 8.1 (dd, 1H, J = 8.64, 2.1 Hz), 7.94 (dd, 1H, J = 8.64, 1.71 Hz), 7.68 (d, 1H, J = 8.46 Hz), 7.38 (d,



1H, J = 8.7 Hz), 6.91 (s, 1H), 4.86 (bs, 2H), 4.24 (q, 2H, J = 6.93, 13.89 Hz), 3.7 – 3.65 (m, 2H), 3.6 – 3.29 (m, 2H), 1.38 (t, 3H, J = 6.96 Hz).

**Example 61****5-(3-(2-(2-amino-1,3-dihydroxypropan-2-yl)benzofuran-5-yl)-1,2,4-oxadiazol-5-yl)-2-ethoxybenzonitrile**

*Step A:* 2-Ethoxy-5-(3-(3-iodo-4-isopropoxyphenyl)-1,2,4-oxadiazol-5-yl)benzonitrile: When 3-chloro-4-propoxybenzoic acid was substituted for 3-cyano-4-ethoxybenzoic acid [<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) 7.13 (b, 1H), 6.26 (b, 1H), 5.9 (b, 1H), 3.13 (b, 2H), 0.41 (b, 3H)] in Example 36, Step B, the similar process afforded the title compound in 78% yield, as creamy paste. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.6 (b, 1H), 8.51 (b, 1H), 8.33 (dd, 1H, J = 8.85, 2.16 Hz), 8.04 (dd, 1H, J = 8.58, 2.13 Hz), 7.1 (d, 1H, J = 8.94 Hz), 6.88 (d, 1H, J = 8.73 Hz), 4.69 – 4.57 (m, 1H), 4.25 (q, 2H, J = 6.99, 14.01 Hz), 1.55 – 1.5 (m, 9H).

*Step B:* 2-ethoxy-5-(3-(4-hydroxy-3-iodophenyl)-1,2,4-oxadiazol-5-yl)benzonitrile: When the product of Step A was substituted for 5-(3-chloro-4-propoxyphenyl)-3-(3-iodo-4-isopropoxyphenyl)-1,2,4-oxadiazole in Example 36, Step C, the similar procedure afforded the title compound in 56% yield, as white solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.47 (d, 1H, J = 1.98 Hz), 8.4 (d, 1H, J = 2.16 Hz), 8.32 (dd, 1H, J = 8.9, 2.19 Hz), 8.02 (dd, 1H, J = 8.49, 2.01 Hz), 7.12 – 7.07 (m, 2H), 4.26 (q, 2H, J = 7.02, 14.01 Hz), 1.53 (t, 3H, J = 7.02 Hz).

*Step C:* 5-(3-(2-(2-Amino-1,3-dihydroxypropan-2-yl)benzofuran-5-yl)-1,2,4-oxadiazol-5-yl)-2-ethoxybenzonitrile: When tert-butyl 5-(5-(5-(3-cyano-4-ethoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)-2,2-dimethyl-1,3-dioxan-5-ylcarbamate (obtained via a similar procedure as described in Example 36, Step D when the product of above Step B was replaced with 4-(5-(3-Chloro-4-propoxyphenyl)-1,2,4-oxadiazol-3-yl)-2-iodophenol) was replaced with tert-butyl 5-(5-(5-(3-chloro-4-propoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)-2,2-dimethyl-1,3-dioxan-5-yl carbamate in Example 36, Step E, the similar procedure afforded the title compound in 32% yield, as pale solid. <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) 8.48 (s, 1H), 8.39 (d, 1H, J = 8.61 Hz), 8.31 (s, 1H), 7.95 (d, 1H, J = 7.77 Hz), 7.69 (d, 1H, J = 8.61 Hz), 7.48 (d, 1H, J = 9.06 Hz), 6.94 (s, 1H), 4.99 (bs, 2H), 4.31 (bd, 2H, J = 6.84 Hz), 3.69 (bs, 2H), 3.63 (bs, 2H), 1.39 (bs, 3H).

**Example 62****2-amino-2-(5-(5-(3-chloro-4-ethoxyphenyl)-1,2,4-oxadiazol-3-yl)-7-methylbenzofuran-2-yl)propane-1,3-diol**

- Step A: N-Hydroxy-3-iodo-4-isopropoxy-5-methylbenzimidamide:* (a) 4-Bromo-2-methylphenol: To a stirred solution of 2-methylphenol (1gm, 9.3 mmol) in DCM (20 mL) at 0 °C was added bromine (500 µL, 9.3 mmol) drop wise. The solution was stirred for 1 hr, quenched with sodium bicarbonate solution and was diluted with DCM (30 mL). The organic layer was washed with sodium thiosulphate solution and dried over magnesium sulphate. The solvent was distilled to gave the product (1.62 gm, 93%) as creamy solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 7.16 (dd, 1H, J = 8.43, 2.4 Hz), 6.63 (d, 1H, J = 8.46 Hz), 5.03 (s, 1H), 2.2 (s, 3H).
- (b) 4-Hydroxy-3-methylbenzonitrile: The above product (1.2 gm, 6.42 mmol) was dissolved in dry DMF (5 mL) and CuCN (820 mg, 9 mmol) was added to it. The content was stirred at reflux for 7 hrs, brought to room temperature, poured in 1M HCl (100 mL), stirred for 0.5 hr and diluted with ethyl acetate (100 mL). The organic layer was separated and dried over magnesium sulphate, passed through silica gel bead and the solvent was distilled to gave the product (920 mg) as pale oil. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.0(s, 1H), 7.37 – 7.31 (m, 2H), 6.85 (d, 1H, J = 8.28 Hz), 2.22 (s, 1H).
- (c) 3-Iodo-4-isopropoxy-5-methylbenzonitrile: To a stirred solution of above product (850 mg, 6.4 mmol) in ammonium hydroxide solution (30 mL) was added a solution of Iodine (1.62 gm, 6.4 mmol) and KI (3.2 gm, 19.2 mmol) in water (5 mL) and the mixture was stirred for overnight. The solvent was distilled and the crude was taken in 1M HCl (5 mL) and extracted with ethyl acetate (50 mL). The organic layer was separated and dried over magnesium sulphate and the solvent was distilled to gave the product (1.1 gm, 66%) as pale paste which was dissolved in dry DMF (8 mL), potassium carbonate (700 mg, 5 mmol) was added followed by the addition of 2 bromo propane (1.5 mL, excess) and the mixture was stirred at reflux for 3 hrs. The content was diluted with water (30 mL) and extracted with ethyl acetate (50 mL x 2). The organic layer was washed with water and dried over magnesium sulphate. The solvent was distilled to gave the product (990 mg, 78%) as pale oil. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 7.9 (d, 1H, J = 1.95 Hz), 7.42 (d, 1H, J = 1.29 Hz), 4.62 – 4.53 (m, 1H), 2.3 (s, 3H), 1.34(d, 6H, J = 6.15 Hz).
- (d) *N-Hydroxy-3-iodo-4-isopropoxy-5-methylbenzimidamide:* The above product (890 mg, 3.3 mmol), hydroxylamine hydrochloride (350 mg, 5 mmol) and

sodium carbonate (530 mg, 5 mmol) were stirred in ethanol (40 mL) for 36 hrs at room temperature. The solution was filtered and the solvent was distilled to gave the pale paste (1.13 gm) which solidified on standing. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 7.86 (d, 1H, J = 2.04 Hz), 7.4 (d, 1H, J = 1.62 Hz), 4.79 (b, 2H), 4.54 – 4.46 (m, 1H), 2.29 (s, 3H), 1.33(d, 6H, J = 6.15 Hz).

Step B: 5-(3-Chloro-4-ethoxyphenyl)-3-(3-iodo-4-isopropoxy-5-methylphenyl)-1,2,4-oxadiazole: When 3-chloro-4-propoxybenzoic acid was substituted for 3-chloro-4-ethoxybenzoic acid and N-hydroxy-3-iodo-4-isopropoxybenzimidamide with the product of Step A in Example 36, Step B, the similar process afforded the title compound in 37% yield, as creamy paste, <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.41 (d, 1H, J = 1.8 Hz), 8.21(d, 1H, J = 1.8 Hz), 8.04(d, 1H, J = 2.1 Hz), 8.03(s, 1H), 7.02(d, 1H, J = 8.67 Hz), 4.61 – 4.47 (m, 1H), 4.23 – 4.14 (m, 2H), 2.36 (s, 3H), 1.36 (t, 3H, J = 5.22 Hz).

Step C: 4-(5-(3-Chloro-4-ethoxyphenyl)-1,2,4-oxadiazol-3-yl)-2-iodo-6-methylphenol: When the product of Step B was substituted for 5-(3-chloro-4-propoxyphenyl)-3-(3-iodo-4-isopropoxyphenyl)-1,2,4-oxadiazole in Example 36, Step C, the similar procedure afforded the title compound in 77% yield, as creamy solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.29 (d, 1H, J = 1.74 Hz), 8.21(d, 1H, J = 1.8 Hz), 8.03(dd, 1H, J = 8.64, 2.13 Hz), 7.89(s, 1H), 7.0(d, 1H, J = 8.64 Hz), 5.58 (s, 1H), 4.2(q, 2H, J = 13.92, 6.9 Hz), 2.37(s, 3H), 1.51(t, 3H, J = 7.02 Hz).

Step D: tert-Butyl 5-(5-(5-(3-chloro-4-ethoxyphenyl)-1,2,4-oxadiazol-3-yl)-7-methylbenzofuran-2-yl)-2,2-dimethyl-1,3-dioxan-5-ylcarbamate: When the product of Step C was substituted for 4-(5-(3-chloro-4-propoxy phenyl)-1,2,4-oxadiazol-3-yl)-2-iodophenol in Example 36, Step D, the similar process afforded the title compound in 57% yield, as pale paste. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.25 (d, 1H, J = 2.13 Hz), 8.16 (d, 1H, J = 1.11 Hz), 8.06 (dd, 1H), 7.88(s, 1H), 7.03(d, 2H, J = 8.7 Hz), 6.73(s, 1H), 5.32(s, 1H), 4.3 – 3.91(m, 6H), 2.55(s, 3H), 1.53 – 1.39(m, 18H).

Step E: 2-Amino-2-(5-(5-(5-(3-chloro-4-ethoxyphenyl)-1,2,4-oxadiazol-3-yl)-7-methylbenzofuran-2-yl))propane-1,3-diol: When the product of Step D was substituted for tert-butyl-5-(5-(5-(3-chloro-4-propoxyphenyl)-1,2,4-oxadiazol-3-yl))benzofuran-2-yl)-2,2-dimethyl-1,3-dioxan-5-yl carbamate in Example 36, Step E, the similar procedure afforded the title compound in 45% yield, as creamy solid. <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) 8.17 – 8.12 (m, 3H), 7.79 (s, 1H), 7.37 (d, 1H, J = 8.76

Hz), 6.9(s, 1H), 4.9(s, H), 4.24(t, 2H), 3.68(b, 2H), 3.63 (b, 2H), 2.52 (s, 3H), 1.38(t, 3H, J = 6.93 Hz).

### Example 63

#### 5 2-Amino-2-(5-(5-(3,4-diethoxyphenyl)-1,2,4-oxadiazol-3-yl)-7-methylbenzofuran-2-yl)propane-1,3-diol

Step A: 5-(3,4-Diethoxyphenyl)-3-(3-iodo-4-isopropoxy-5-methylphenyl)-1,2,4-oxadiazole: When 3-chloro-4-ethoxybenzoic acid was substituted for 3,5-diethoxybenzoic acid in Example 62, Step B, the similar process afforded the title compound in 59% yield, as colourless paste. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.43 (d, 1H, J = 1.98 Hz), 7.93 (d, 1H, J = 1.56 Hz), 7.76 (dd, 1H, J = 8.43, 1.98 Hz), 7.66 (d, 1H, J = 1.95 Hz), 6.96 (d, 1H, J = 8.49 Hz), 4.61 – 4.53 (m, 1H), 4.24 – 4.06 (m, 4H), 2.37 (s, 3H), 1.52 – 1.49 (m, 6H), 1.37 (d, 6H, J = 6.21 Hz).

Step B: 4-(5-(3,4-Diethoxyphenyl)-1,2,4-oxadiazol-3-yl)-2-iodo-6-methylphenol: When the product of Step A was substituted for 5-(3-chloro-4-propoxyphenyl)-3-(3-iodo-4-isopropoxyphenyl)-1,2,4-oxadiazole in Example 36, Step C, the similar procedure afforded the title compound in 54% yield, as white solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.3 (d, 1H, J = 2.9 Hz), 7.89 (d, 1H, J = 1.11 Hz), 7.76 (dd, 1H, J = 8.43, 1.98 Hz), 7.65 (d, 1H, J = 1.98 Hz), 6.96 (d, 1H, J = 8.46 Hz), 5.58 (s, 1H), 4.24 – 4.09 (m, 4H), 2.37 (s, 3H), 1.53 – 1.39 (m, 6H).

Step C: *tert*-Butyl 5-(5-(5-(3,4-diethoxyphenyl)-1,2,4-oxadiazol-3-yl)-7-methylbenzofuran-2-yl)-2,2-dimethyl-1,3-dioxan-5-ylcarbamate: When the product of Step B was substituted for 4-(5-(3-chloro-4-propoxy phenyl)- 1,2,4- oxadiazol-3-yl)- 2-iodophenol in Example 36, Step D, the similar process afforded the title compound in 47% yield, as creamy paste. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.18 (d, 1H, J = 1.41 Hz), 7.89 (s, 1H), 7.79(dd, 1H, J = 8.49, 2.01 Hz), 7.69 (d, 1H, J = 1.95 Hz), 6.98 – 6.96 (m, 2H), 6.73 (s, 1H), 5.32(s, 1H), 4.3 – 4.14(m, 8H), 2.55(s, 3H), 1.51 – 1.39 (m, 21 H).

Step D: 2-Amino-2-(5-(5-(3,4-diethoxyphenyl)-1,2,4-oxadiazol-3-yl)-7-methylbenzofuran-2-yl)propane-1,3-diol: When the product of Step C was substituted for *tert*-butyl 5-(5-(5-(3-chloro-4-propoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)-2,2-dimethyl-1,3-dioxan-5-yl carbamate in Example 36, Step E, the similar procedure afforded the title compound in 59% yield, as creamy solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.15 (s, 1H), 7.8(s, 1H), 7.74(d, 1H, J = 8.55 Hz), 7.61 (s,

1H), 7.17 (d, 1H, J = 8.52 Hz), 6.94(s, 1H), 5.09(b, 2H), 4.13(q, 2H, J = 6.75, 13.1 Hz), 3.73 (b, 2H), 3.68(b, 2H), 2.53(s, 3H), 1.38 – 1.32(m, 6H).

**Example 64****5-(3-(2-(2-Amino-1,3-dihydroxypropan-2-yl)-7-methylbenzofuran-5-yl)-1,2,4-oxadiazol-5-yl)-2-propoxybenzonitrile**

*Step A: 5-(3-(3-Iodo-4-isopropoxy-5-methylphenyl)-1,2,4-oxadiazol-5-yl)-2-propoxybenzonitrile:* When 3-chloro-4-ethoxybenzoic acid was substituted for 3,5-diethoxybenzoic acid in Example 62, Step B, the similar process afforded the title compound in 75% yield, as yellow brown paste. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.4 – 8.39 (m, 2H), 8.31(dd, 1H, J = 8.88, 2.16 Hz), 7.91(d, 1H, J = 1.41 Hz), 7.09 (d, 1H, J = 8.94 Hz), 4.61 – 4.53(m, 1H), 4.14(t, 2H, J = 7.32 Hz), 2.36 (s, 3H), 1.95 – 1.86 (m, 2H), 1.36 (d, 6H, J = 6.18 Hz), 1.1 (t, 3H, J = 7.41 Hz).

*Step B: 5-(3-(4-Hydroxy-3-iodo-5-methylphenyl)-1,2,4-oxadiazol-5-yl)-2-propoxybenzonitrile:* When the product of Step A was substituted for 5-(3-chloro-4-propoxyphenyl)-3-(3-iodo-4-isopropoxyphenyl)-1,2,4-oxadiazole in Example 36, Step C, the similar procedure afforded the title compound in 54.4% yield, as creamy white solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.4 (d, 1H, J = 2.16 Hz), 8.33 – 8.28(m, 2H), 7.87(d, 1H, J = 1.02 Hz), 7.1 (d, 1H, J = 8.94 Hz), 5.61(s, 1H), 4.14(t, 2H, J = 6.45 Hz), 2.37 (s, 3H), 1.96 – 1.89 (m, 2H), 1.1(t, 3H, J = 7.38 Hz).

*Step C: 5-(3-(2-(2-Amino-1,3-dihydroxypropan-2-yl)-7-methylbenzofuran-5-yl)-1,2,4-oxadiazol-5-yl)-2-propoxybenzonitrile:* When tert-butyl 5-(5-(3-cyano-4-propoxyphenyl)-1,2,4-oxadiazol-3-yl)-7-methylbenzofuran-2-yl)-2,2-dimethyl-1,3-dioxan-5-ylcarbamate (obtained via a similar procedure as described in Example 36, Step D when the product of above Step B was replaced with 4-(5-(3-Chloro-4-propoxyphenyl)-1,2,4-oxadiazol-3-yl)-2-iodophenol) was replaced with tert-butyl 5-(5-(3-chloro-4-propoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)-2,2-dimethyl-1,3-dioxan-5-yl carbamate in Example 36, Step E, the similar procedure afforded the title compound in 43% yield, as creamy solid. <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) 8.46 (d, 1H, J = 2.04 Hz), 8.37(dd, 1H, J = 8.85, 1.92 Hz), 8.12 (s, 1H), 7.77(s, 1H), 7.46(d, 1H, J = 9.06 Hz), 6.89(s, 1H), 4.93(bs, 2H), 4.2(t, 2H), 3.69(d, 2H, J = 10.53 Hz), 3.61(d, 2H, J = 10.53 Hz), 2.51(s, 3H), 1.84 – 1.72(m, 2H), 0.99(t, 3H, J = 7.38 Hz).

**Example 65****2-amino-2-((4-(5-(3,4-diethoxyphenyl)-1,2,4-oxadiazol-3-yl)phenyl) ethynyl) propane-1,3-diol**

*Step A: 4-Bromo-N-hydroxybenzimidamide:* A mixture of 4-cyano-  
5 bromobenzene (0.5 g, 2.75 mmol),  $\text{HCINH}_2\text{OH}$  (0.476 g, 6.9 mmol) and  $\text{Na}_2\text{CO}_3$   
(0.731 g, 6.9 mmol) in a mixture of solvent (EtOH:  $\text{H}_2\text{O}$ ; 25 mL: 5 mL) was stirred  
at reflux for 7 h. The solvent was distilled and the crude was taken in ethyl  
acetate and washed with  $\text{H}_2\text{O}$ . The organic layer was separated and dried over  
 $\text{MgSO}_4$ . The solvent was distilled to give the product as white solid (0.51 g, 87%).  
10  $^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ ) 5.81 (b, 2H); 7.53 (d, 2H,  $J = 6.66$  Hz); 7.58 (d, 2H,  $J = 6.54$   
Hz); 9.69 (s, 1H).

*Step B: 3-(4-Bromophenyl)-5-(3,4-diethoxyphenyl)-1,2,4-oxadiazole:* When  
product of Step A and 3,5-diethoxybenzoic acid were treated as in Example 36,  
Step B, the similar process afforded the title compound in 58% yield.  $^1\text{H-NMR}$   
15 ( $\text{CDCl}_3$ ) 1.47 - 1.53 (m, 6H); 4.14 - 4.24 (m, 4H); 6.97 (d, 1H,  $J = 8.48$  Hz); 7.61 -  
7.66 (m, 3H); 7.77 (dd, 1H,  $J = 1.98, 8.42$  Hz); 8.00 (d, 2H,  $J = 8.55$  Hz).

*Step C: tert-butyl 5-((4-(5-(3,4-diethoxyphenyl)-1,2,4-oxadiazol-3-yl)phenyl)  
ethynyl) -2,2-dimethyl-1,3-dioxan-5-ylcarbamate:* The product of step B (150 mg,  
0.39 mmol) and tert-butyl 5-ethynyl-2,2-dimethyl-1,3-dioxan-5-ylcarbamate (120  
20 mg, 0.47 mmol) were dissolved in a mixture of dry DMF (4 mL) and DIEA (0.7 mL)  
and degassed with nitrogen gas. The  $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$  (20 mg) was added followed  
by the addition of catalytic amount of  $\text{Cu(I)}$  and mixture was stirred at 60 °C for 1  
hr and then at room temperature for overnight. The mixture was quenched with  
saturated ammonium chloride solution (2 mL) and extracted by ethyl acetate (30  
25 mL). The organic layer was washed with water, separated and dried over  
magnesium sulphate. The solvent was distilled to gave the crude product which  
was purified over silica gel column to gave the desired product (85 mg, 39%) as  
light yellow solid.  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ) 8.1 (d, 2H,  $J = 8.46$  Hz), 7.77 (dd, 1H,  $J =$   
8.43, 1.98 Hz), 7.66 (d, 1H,  $J = 1.95$  Hz), 7.53 (d, 2H,  $J = 8.49$  Hz), 6.97 (d, 1H,  $J$   
30 = 8.49 Hz), 5.22 (s, 1H), 4.24 - 4.0 (m, 8H), 1.5 - 1.38 (m, 21H).

*Step D: 2-amino-2-((4-(5-(3,4-diethoxyphenyl)-1,2,4-oxadiazol-3-yl)phenyl)  
ethynyl)propane-1,3-diol hydrochloride:* When the product of Step C was  
substituted for tert-butyl 5-(5-(3-chloro-4-propoxyphenyl)-1,2,4-oxadiazol-3-  
yl)benzofuran-2-yl)-2,2-dimethyl-1,3-dioxan-5-yl carbamate in Example 36, Step

E, the similar procedure afforded the title compound (25 mg, 42%) which was dissolved in dry methanol (1.5 mL) and TMSCl (100  $\mu$ L) was added to it and mixture was stirred at room temperature for 0.5 hr and then the solvent was distilled to gave the product (30 mg, quantitative) as off white solid.  $^1\text{H}$  NMR (D<sub>2</sub>O) 7.23 – 7.16 (m, 4H), 6.75 (d, 1H, J = 8.1 Hz), 6.64 (s, 1H), 6.18 (d, 1H, J = 8.61 Hz), 3.8 (s, 4H), 3.65 (b, 2H), 3.43 (b, 2H), 1.18 (t, 3H, J = 6.78 Hz), 1.1 (t, 3H, J = 6.57 Hz).

#### Example 66

#### 10 2-amino-2-((2-amino-5-(5-(3,4-diethoxyphenyl)-1,2,4-oxadiazol-3-yl)phenyl)ethynyl)propane-1,3-diol

Step A: 4-cyano-2-iodo-bis(1,1-dimethylethoxycarbonyl)aniline: To a stirred solution of 2-iodo-4-cyno aniline (860 mg, 3.5 mmol) in dry THF (5 mL) was added (Boc)<sub>2</sub>O (990 mg, 4.35 mmol) followed by the addition of DMAP (30 mg) and DIEA (770  $\mu$ L, 4.5 mmol) and the mixture was stirred at room for overnight when more (Boc)<sub>2</sub>O (990 mg, 4.35 mmol) was added and reaction was stirred at room temperature for 48 hours. The solvent was distilled and the crude was taken in ethyl acetate (100 mL) and washed with sodium-bi-carbonate solution. The organic layer was separated and dried over magnesium sulphate and the solvent was distilled to gave the product (1.22 gm, 62%) as a yellow solid.  $^1\text{H}$  NMR (CDCl<sub>3</sub>) 8.11 (d, 1H, J = 1.8 Hz), 7.63 (dd, 1H, J = 8.13, 1.83 Hz), 7.29 (d, 1H, J = 8.13 Hz), 1.39 (s, 9H).

Step B: 4-(N-hydroxycarbamimidoyl)- 2-iodo-bis(1,1-dimethylethoxy carbonyl)aniline: The product of Step I (1.2 gm 2.7 mmol) was taken in dry ethanol (50 mL) and hydroxylamine hydrochloride (480 mg, 7 mmol) was added followed by the addition of DIEA (1.2 mL, 7 mmol). The mixture was stirred at 60 °C for 4 hrs and solvent was distilled. The crude was taken in ethyl acetate (100 mL) and washed with water. The organic layer was separated and dried over magnesium sulphate and the solvent was distilled to gave the product (1.3 gm, quantitative) as yellow solid.  $^1\text{H}$  NMR (CDCl<sub>3</sub>) 11.2 (bs, 1H), 8.1 (d, 1H, J = 1.95 Hz), 7.6 (dd, 1H, J = 8.19, 1.92 Hz), 7.18 (d, 1H, J = 8.22 Hz), 4.94 (s, 1H), 1.39 (s, 9H).

Step C: 4-(5-(3,4-diethoxyphenyl)-1,2,4-oxadiazol-3-yl)-2-iodo-bis(1,1-dimethylethoxycarbonyl)aniline When 3-chloro-4-propoxybenzoic acid was

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substituted for 3,4-diethoxy benzoic acid and N-hydroxy-3-iodo-4-isopropoxybenzimidamide was replaced with the product of Step-B as in Example 36, Step B, the similar process afforded the title compound in (210 mg, 29%) as light yellow gum. <sup>1</sup>H NMR (CDCl<sub>3</sub>) 8.65 (d, 1H, J = 1.83 Hz), 8.13 (dd, 1H, J = 8.19, 1.86 Hz), 7.77 (dd, 1H, J = 8.43, 2.01 Hz), 7.66 (d, 1H, J = 1.95 Hz), 7.3 (d, 1H, J = 8.19 Hz), 6.97 (d, 1H, J = 8.49 Hz), 4.24 – 4.16 (m, 4H), 1.59 – 1.46 (m, 6H), 1.39 (s, 9H).

Step D: 2-amino-2-((2-amino-5-(5-(3,4-diethoxyphenyl)-1,2,4-oxadiazol-3-yl)phenyl)ethynyl)propane-1,3-diol: (a) 4-(5-(3,4-diethoxyphenyl)-1,2,4-oxadiazol-3-yl)-2-iodobenzenamine: The product of Step C was de protected with trifluoro acetic acid (neat 1 mL) by stirring at room temperature for 3 hrs. The solvent was distilled and the crude was purified over silica gel column to gave the product (85 mg, 19%) as pale paste. (b) The above product was treated according to the procedure as described in Step C; Example 65 to gave the product (35 mg, 34%) as pale paste. (c) This product (30 mg, 0.05 mmol) was dissolved in dry acetonitrile (1.5 mL) and NaI (35 mg, 0.23 mmol) was added to it. The mixture was degassed with nitrogen gas and TMSCl (0.5 mL, excess) was added to it drop wise. The mixture was stirred for 0.5 hr and solvent was distilled to gave the crude product which was purifies over silica gel column to afford the title compound in 36% yield, as dirty brown solid. <sup>1</sup>H NMR (CD<sub>3</sub>OD) 7.93 (d, 1H, J = 1.95 Hz), 7.79 – 7.7 (m, 2H), 7.64 (d, 1H, J = 1.86 Hz), 7.08 (d, 1H, J = 8.12 Hz), 6.8 (d, 1H, J = 8.58 Hz), 4.18 – 4.11 (m, 4H), 3.74 (s, 4H), 1.46 – 1.4 (m, 6H).

#### Example 67

25 **1-(4-(3-(1-admantyl)-4-propoxybenzyloxy)benzyl)azetidine-3-carboxylic acid**

Step A: 3-(1-admantyl)-4-propoxybenzaldehyde: When methyl iodide was replaced with propyl-bromide as in Example 32, Step A, the similar process afforded the title compound (410 mg, 88%) as a creamy solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) 9.8(s, 1H), 7.74 (d, 1H, J = 2.07 Hz), 7.66 (dd, 1H, J = 8.4, 2.07 Hz), 6.92 (d, 1H, J = 8.43 Hz), 4.01 (t, 2H, J = 6.39 Hz), 2.1 (b, 9H), 1.91 – 1.81 (m, 2H), 1.75 (b, 6H), 1.11 (t, 3H, J = 7.41 Hz).

Step B: 4-(3-(1-admantyl)-4-propoxybenzyloxy)benzaldehyde: (a) 3-(1-admantyl)-4-propoxybenzyl alcohol: When 3-(1-admantyl)-4-methylbenzaldehyde was replaced with product of Step A as in Example 32, Step B, the similar



process afforded the title compound in (320 mg, 80%) as a pale foam. <sup>1</sup>H NMR (CDCl<sub>3</sub>) 7.2 (d, 1H, J = 2.13 Hz), 7.13 (dd, 1H, J = 8.25, 2.1 Hz), 6.82 (d, 1H, J = 8.25 Hz), 4.59 (s, 2H), 3.93 (t, 2H, J = 6.38 Hz), 2.12 (b, 9H), 1.91 – 1.84 (m, 2H), 1.76 (bs, 6H), 1.1 (t, 3H, J = 7.41 Hz). (b) 3-(1-admantyl)-4-propoxybenzyl chloride: When 3-(1-admantyl)-4-methylbenzyl alcohol was replaced with the above product as in Example 32, Step B, the similar process afforded the crude compound in (300 mg) as a pale solid. (c) The above product was treated with 4-hydroxy benzaldehyde adopting a similar procedure as described in Step A to afford the title compound (180 mg, 57%) as pale solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) 9.87 (s, 1H), 7.82 (d, 2H, J = 8.76 Hz), 7.25 (d, 1H, J = 2.19 Hz), 7.2 (dd, 1H, J = 8.28, 2.19 Hz), 7.07 (d, 2H, J = 8.73 Hz), 6.85 (d, 1H, J = 8.31 Hz), 5.02 (s, 2H), 3.96 (b, 2H), 2.11 (b, 9H), 1.92 – 1.85 (m, 2H), 1.76 (bs, 6H), 1.1 (t, 3H, J = 7.38 Hz).

*Step C: Methyl 1-(4-(3-(1-admantyl)-4-propoxybenzyloxy)benzyl)azetidine-3-carboxylate*: When 4-(3-(1-admantyl)-4-methylbenzyloxy) benzaldehyde was replaced with product of Step B as in Example 32, Step C, the similar process afforded the title compound (90 mg, 74%) as a pale paste. <sup>1</sup>H NMR (CDCl<sub>3</sub>) 7.24 – 7.16 (m, 4H), 6.9 (d, 2H, J = 8.61 Hz), 6.83 (d, 1H, J = 8.28 Hz), 4.92 (s, 2H), 3.93 (t, 2H, J = 6.39 Hz), 3.69 (s, 3H), 3.53 – 3.48 (b, 4H), 3.31 – 3.28 (b, 3H), 2.1 – 2.04 (b, 9H), 1.88 – 1.75 (m, 2H), 1.75 – 1.69 (b, 6H), 1.1 (t, 3H, J = 7.38 Hz).

*Step D: 1-(4-(3-(1-admantyl)-4-propoxybenzyloxy)benzyl)azetidine-3-carboxylic acid*: When methyl-1-(4-(3-(1-admantyl)-4-methylbenzyloxy)benzyl)azetidine-3-carboxylate was replaced with product of Step C as in Example 32, Step D, the similar process afforded the title compound (36 mg, 49%) as a white solid. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) 7.18 – 7.12 (m, 4H), 6.9 – 6.87 (m, 3H), 4.91 (s, 2H), 3.9 (t, 2H, J = 6.12 Hz), 3.44 – 3.32 (b, 4H), 3.14 (b, 3H), 2.0 (b, 9H), 1.87 – 1.69 (m, 8H), 1.04 (t, 3H, J = 7.32 Hz).

#### Example 68

**N-(5-(3-(2-(2-Amino-1,3-dihydroxypropan-2-yl)benzofuran-5-yl)-1,2,4-oxadiazol-5-yl)-2-ethoxyphenyl)methanesulfonamide**

*Step A: 4-Ethoxy-3-nitrobenzoic acid*: A mixture of 4-hydroxy-3-nitrobenzoic acid (0.22 g, 1.2 mmol), K<sub>2</sub>CO<sub>3</sub> (0.17 g, 1.23 mmol) and EtI (0.29 ml, 3.69 mmol) in anhydrous DMF (5 ml) was stirred at ~ 50°C for three days under N<sub>2</sub>. The mixture was concentrated in vacuo to about 2 ml, diluted to 30 ml with

Et<sub>2</sub>O, washed with H<sub>2</sub>O (3 x 10 ml), brine and dried over anhydrous MgSO<sub>4</sub>, filtered and filtrate evaporated to dryness to give ethyl 4-ethoxy-3-nitro benzoate (0.27 g, 94%), as a creamy solid, which was used in the next step without further purification. <sup>1</sup>H NMR (CDCl<sub>3</sub>) 8.44 (d, 1H, J = 2 Hz), 8.16 (dd, 1H, (m, 1H, J = 2, 8.8 Hz); 7.08 (d, 1H, J = 8.85 Hz); 4.32 – 4.41 (m, 2H); 4.19 – 4.27 (m, 2H); 1.41 – 1.48 (m, 3H); 1.33 – 1.37 (m, 3H). The mixture of ethyl 4-ethoxy-3-nitro benzoate (0.27 g, 1.13 mmol), KOH (0.19 g, 3.39 mmol) and H<sub>2</sub>O (5 ml) in dioxane (10 ml) was refluxed for 1.2 h and evaporated to dryness under reduced pressure. The residue diluted to 10 ml with H<sub>2</sub>O, filtered and the filtrate acidified to pH ~ 3 with concentrated HCl. The product was taken up with EtOAc (20 ml). The organic phase was dried over anhydrous MgSO<sub>4</sub>, filtered and filtrate evaporated to dryness to give the title compound (0.22 g, 92 %), as colourless solid, which was used in the next step without further purification. <sup>1</sup>H NMR (CDCl<sub>3</sub>) 8.53 (d, 1H, J = 3 Hz), 8.24 (dd, 1H, J = 3, 9 Hz), 7.13 (d, 1H, J = 9 Hz), 4.26 (q, 2H, J = 6Hz), 1.5 (tr, 3H, J = 6 Hz).

*Step B: 4-Ethoxy-3-(methylsulfonamido)benzoic acid:* A mixture of the product of Step A (0.22 g, 1.05 mmol), 10% Pd/C (0.2 g) in EtOH (20 ml) was vigorously stirred for 1 h at room temperature under H<sub>2</sub> (balloon). The catalyst was removed by filtration, washed with CH<sub>2</sub>Cl<sub>2</sub>, and combined filtrates were evaporated to dryness to give 3-amino-4-ethoxybenzoic acid (0.19 g, 100%), as colourless solid, which was used in the next step without further purification. To a solution of above product (0.19 g, 1.05 g) and Na<sub>2</sub>CO<sub>3</sub> (0.13 g, 1.22 mmol) in H<sub>2</sub>O (3 ml) CH<sub>3</sub>SO<sub>2</sub>Cl (0.095 ml, 1.22 mmol) was added at 0°C, with vigorous stirring. The mixture was additionally stirred for 2 h at room temperature, acidified to pH ~ 3 with concentrated HCl and the solid formed was filtered off, washed with fresh H<sub>2</sub>O (2 x 1 ml) and dried in vacuo to give the title compound (0.12 g, 44%), as colourless solid, which was used in the next step without further purification. <sup>1</sup>H NMR (CDCl<sub>3</sub>) 8.21 (d, 1H, J = 2.1 Hz), 7.89 (dd, 1H, J = 2.1, 8.6 Hz), 6.94 (d, 1H, J = 8.6 Hz), 6.86 (s, 1H), 4.2 (q, 2H, J = 7 Hz), 3.5 (s, 3H), 3.02 (s, 3H), 1.45 (tr, 3H, J = 6.6 Hz). <sup>1</sup>H NMR (CD<sub>3</sub>OD) 8.03 (d, 1H, 2.1 Hz), 7.85 (dd, 1H, J = 2.1, 8.6 Hz), 4.2 (q, 2H, J = 7 Hz), 1.46 (tr, 3H, J = 7 Hz).

*Step C: N-(2-Ethoxy-5-(3-(3-iodo-4-isopropoxyphenyl)-1,2,4-oxadiazol-5-yl)phenyl)methanesulfonamide:* A mixture of the product of Step B (0.12 g, 0.46 mmol), the product of Example 36, Step A (0.15 g, 0.47 mmol) and EDC (0.13 g,

0.7 mmol) in anhydrous DMSO (3 ml) was stirred for 2 h at  $-40^{\circ}\text{C}$  under  $\text{N}_2$ . To this 1M TBAF in THF (0.5 ml) was added and the mixture was stirred for 1 h at  $\sim 120^{\circ}\text{C}$ , cooled to room temperature and diluted to 80 ml with EtOAc. This was washed with  $\text{H}_2\text{O}$  (5 x 10 ml), brine, dried over anhydrous  $\text{MgSO}_4$  and filtered.

- 5 The filtrate was evaporated to dryness and the residue was purified by FCC ( $\text{SiO}_2$ ,  $\text{CH}_2\text{Cl}_2/\text{EtOAc}$  7/3) to give the title compound (0.08 g, 32%), as colourless foam.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) 8.56 (s, 1H), 8.06 (d, 1H,  $J = 8.6$  Hz); 7.96 (d, 1H,  $J = 8.6$  Hz); 7.02 (d, 1H,  $J = 8.6$  Hz), 6.9 (broad s, 1H); 6.87 (d, 1H,  $J = 8.6$  Hz); 4.61 – 4.7 (m, 1H); 4.17 – 4.25 (m, 2H); 3.06 (s, 3H); 1.4 – 1.6 (m, 9H +  $\text{H}_2\text{O}$ ).

- 10 **Step D:** *N*-(2-Ethoxy-5-(3-(3-iodo-4-hydroxyphenyl)-1,2,4-oxadiazol-5-yl)phenyl)methanesulfonamide: To a solution of the product of Step C (0.08 g, 0.147 mmol) in anhydrous  $\text{CH}_2\text{Cl}_2$  (0.5 ml) 1M  $\text{BCl}_3$  in  $\text{CH}_2\text{Cl}_2$  (0.44 ml, 0.44 mmol) was added at  $0^{\circ}\text{C}$ . The mixture was allowed to warm up to room temperature, with stirring for 1 h. To this  $\text{H}_2\text{O}$  (1 ml) was added and the mixture  
15 was diluted to 20 ml with EtOAc, washed with  $\text{H}_2\text{O}$  (2 x 5 ml), brine, dried over anhydrous  $\text{MgSO}_4$ , filtered and the filtrate evaporated to dryness to give the title compound (0.07 g, 97%), as colourless foam, which was used in the next step without further purification.  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ ) 8.41 (m, 2H), 8.2 (d, 1H,  $J = 2.1$  Hz), 7.98 (dd, 1H,  $J = 2.1, 8.6$  Hz), 7.15 (d, 1H,  $J = 8.7$  Hz), 6.93 (s, 1H), 4.7  
20 ( $\text{H}_2\text{O}$ ), 4.25 (q, 2H,  $J = 7$  Hz), 3.0 (s, 3H), 1.48 (tr, 3H,  $J = 7$  Hz).

- Step E:** *tert*-Butyl 5-(5-(5-(4-ethoxy-3-(methylsulfonamido)phenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)-2,2-dimethyl-1,3-dioxan-5-ylcarbamate: A  
suspension of the product of Step D (0.07 g, 0.14 mmol), *tert*-butyl 5-ethynyl-2,2-dimethyl-1,3-dioxan-5-yl carbamate (0.04 g, 0.16 mmol) and anhydrous  $\text{Cu}_2\text{O}$   
25 (0.02 g, 0.14 mmol) in anhydrous pyridine (1 ml) was degassed under reduced pressure and saturated with  $\text{N}_2$ . This was stirred for 5 h at  $\sim 110^{\circ}\text{C}$ , under  $\text{N}_2$ , cooled to room temperature, diluted to 20 ml with EtOAc and filtered. The filtrate was washed with 5% solution of  $\text{NH}_4\text{Cl}$  (pH 8, adjusted with  $\text{NH}_4\text{OH}$ ),  $\text{H}_2\text{O}$ , brine and dried over anhydrous  $\text{MgSO}_4$  and filtered. The filtrate was evaporated to  
30 dryness and the residue was purified by FCC ( $\text{SiO}_2$ ,  $\text{CH}_2\text{Cl}_2/\text{EtOAc}$  7/3) to give the title compound (0.03 g, 34%), as colourless foam.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) 8.35 (m, 2H), 8.07 (dd, 1H,  $J = 1.7, 8.6$  Hz), 7.97 (dd, 1H,  $J = 2.1$  Hz), 7.52 (d, 1H,  $J = 8.6$  Hz), 7.03 (d, 1H,  $J = 8.6$  Hz), 6.94 (broad s, 1H), 6.75 (s, 1H), 5.35 (broad s, 1H), 3.06 (s, 1H), 1.36 – 1.63 (m, 18H +  $\text{H}_2\text{O}$ ).

**Step F:** *N*-(5-(3-(2-(2-Amino-1,3-dihydroxypropan-2-yl)benzofuran-5-yl)-1,2,4-oxadiazol-5-yl)-2-ethoxyphenyl)methanesulfonamide: To a solution of the product of Step E (0.03 g, 0.048 mmol), NaI (0.032 g, 0.216 mmol) in anhydrous CH<sub>3</sub>CN (1 ml) Me<sub>3</sub>SiCl (0.1 ml) was added and the mixture was stirred for 1 h at room temperature under N<sub>2</sub>. After evaporation of solvents under reduced pressure, the residue was diluted to 2 ml with EtOH, and re evaporated to dryness. The residue was purified by FCC (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub> saturated with NH<sub>4</sub>OH/MeOH 9/1) to give the title compound (0.008 g, 35%), as colourless solid. <sup>1</sup>H NMR (CD<sub>3</sub>OD) 8.29 (s, 1H), 8.2 (s, 1H), 7.99 (d, 1H, J = 8.4 Hz), 7.56 (d, 1H, J = 8.4 Hz), 7.19 (d, 1H, J = 8.7 Hz), 6.87 (broad s, 1H, J = 8.4 Hz), 4.23 (q, 2H, J = 6.8 Hz), 3.86 (broad s, 1H), 3.0 (s, 3H), 1.48 (tr, 3H, J = 6.8 Hz).

#### Example 69

**2-Amino-2-(5-(5-(3,4-diethoxyphenyl)-1,2,4-oxadiazol-3-yl)-1H-indol-2-yl)propane-1,3-diol**

**Step A:** *4-Amino-3-iodobenzonitrile*: To a solution of 4-aminobenzonitrile (2.4 g 20 mmol) and ~30% H<sub>2</sub>O<sub>2</sub> (not titrated before use) in MeOH (30 ml) a solution of I<sub>2</sub> (5.05 g, 12 mmol) in MeOH (50 ml) was added at room temperature and the resulting mixture was stirred for 48 h, while a fresh H<sub>2</sub>O<sub>2</sub> (2 ml) was added every day. The mixture was concentrated under reduced pressure and treated with saturated solution of Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> until most of the colour disappeared. The solid formed was filtered off, diluted to 300 ml with EtOAc, washed with saturated, H<sub>2</sub>O, brine, dried over anhydrous MgSO<sub>4</sub>, filtered and the filtrate evaporated to dryness. The residue was purified by crystallization from EtOH to give the title compound (3 g). The residue was recrystallised from the mixture of CH<sub>2</sub>Cl<sub>2</sub>/hexane to give more of the title compound (1.4 g). Total yield 4.4 g (88%). <sup>1</sup>H NMR (CDCl<sub>3</sub>) 7.87 (d, 1H, J = 1.8 Hz); 7.37 (dd, 1H, J = 1.8, 8.4), 6.68 (d, 1H, J = 8.4 Hz), 4.62 (broad s, 2H).

**Step B:** *N*-(4-Cyano-2-iodophenyl)acetamide: A solution of the product of Step A (0.32 g, 1.31 mmol) and 1M NaN(SiMe<sub>3</sub>)<sub>2</sub> in THF (2.62 ml) in anhydrous THF (2 ml) was stirred at ~-5°C for 30 min under N<sub>2</sub>. To it acetyl chloride (0.11 ml, 1.44 mmol) was added and the mixture was stirred overnight at room temperature, then evaporated to dryness under reduced pressure. The residue was diluted to 50 ml with EtOAc, washed with H<sub>2</sub>O, brine, dried over anhydrous MgSO<sub>4</sub>, filtered

and the filtrate evaporated to dryness. The residue was purified by crystallization from MeOH to give the title compound (0.26 g, 70%), as colourless solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) 8.46 (d, 1H, J = 9 Hz), 8.03 (s, 1H), 7.58 – 7.63 (m, 2H), 2.27 (s, 3H).

5        *Step C: N-(4-(N-(Hydroxymethyl)carbamimidoyl)-2-iodophenyl) acetamide:*

A mixture of the product of Step B (0.26 g, 0.91 mmol), HClxH<sub>2</sub>NOH (0.13 g, 1.87 mmol) and DIPEA (0.47 ml; 2.7 mmol) in EtOH (3 ml) was stirred at room temperature for 6 h under N<sub>2</sub>. The solvents were removed under reduced pressure and the residue was partitioned between EtOAc (50 ml) and H<sub>2</sub>O (5 ml).  
10    The organic phase was washed with brine, dried over anhydrous MgSO<sub>4</sub>, filtered and filtrate evaporated to dryness to give the title compound (0.24 g, 82%), as colourless solid, which was used in the next step without further purification.

*Step D: N-(4-(5-(3,4-diethoxyphenyl)-1,2,4-oxadiazol-3-yl)-2-iodophenyl) acetamide:* To a mixture of the product of Step C (0.24 g, 0.74 mmol) and 3,4-diethoxybenzoyl chloride (0.17 g, 0.74 mmol) in 50% solution of EtOAc in CH<sub>2</sub>Cl<sub>2</sub> (5 ml) DIPEA (0.14 ml, 0.81 mmol) was added at room temperature. This was  
15    refluxed for 2 h, diluted to 80 ml with EtOAc and washed with H<sub>2</sub>O, brine, dried over anhydrous MgSO<sub>4</sub>, filtered and filtrate evaporated to dryness to give the coupling product (0.26 g, 68%) as creamy solid. This was diluted to 2 ml with  
20    anhydrous DMSO and 1M TBAF in THF was added. The mixture was stirred at for 1 h at ~110°C under N<sub>2</sub>, cooled to room temperature and H<sub>2</sub>O (4 ml) was added. The solid formed, was filtered off, washed with fresh H<sub>2</sub>O (2 x 2 ml) and dried to give the title compound (0.24 g; 94%), as colourless solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) 8.57 (d, 1H, J = 1.9 Hz), 8.41 (d, 1H, J = 8.4 Hz), 8.12 (dd, 1H, 1.9, 8.6 Hz), 7.77 (dd, 1H, J = 2, 8.4 Hz), 7.66 (d, 1H, J = 2 Hz), 7.58 (s, 1H); 6.96 (d, 1H, J = 8.5 Hz), 4.14 – 4.24 (m, 4H), 2.27 (s, 3H), 1.47 – 1.55 (m, 6H + H<sub>2</sub>O).  
25

*Step E: tert-Butyl 5-((2-acetamido-5-(5-(3,4-diethoxyphenyl)-1,2,4-oxadiazol-3-yl)phenyl)ethynyl)-2,2-dimethyl-1,3-dioxan-5-ylcarbamate:* A mixture of the product of Step D (0.24 g, 0.49 mmol) tert-butyl 5-ethynyl-2,2-dimethyl-1,3-dioxan-5-yl carbamate (0.15 g, 0.59 mmol), PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (0.02 g) and CuI (0.01 g) in anhydrous DMF (2ml) was degassed *in vacuo*, and saturated with N<sub>2</sub>.  
30    To it DIPEA (0.8 ml) was added and the mixture was stirred for 7 h at room temperature. The solvents were removed *in vacuo* and the residue was diluted to 30 ml with EtOAc, washed with H<sub>2</sub>O, NH<sub>4</sub>Cl solution, brine, dried over anhydrous

MgSO<sub>4</sub>, filtered and filtrate evaporated to dryness. Under reduced pressure. The residue was purified by FCC (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/EtOAc 9/1) to give the title compound (0.15 g, 49%), as colourless solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) 9.05 (s, 1H), 8.65 (d, 1H, J = 8.6 Hz), 8.08 – 8.13 (m, 2H), 7.77 (dd, 1H, J = 1.9, 8.4 Hz), 7.66 (d, 1H, J = 1.9 Hz), 6.96 (d, 1H, J = 8.5 Hz), 5.51 (s, 1H), 4.01 – 4.24 (m, 8H), 2.38 (s, 3H), 1.46 – 1.56 (m, 21H + H<sub>2</sub>O).

Step F: *N*-(5-(5-(5-(3,4-Diethoxyphenyl)-1,2,4-oxadiazol-3-yl)-1H-indol-2-yl)-2,2-dimethyl-1,3-dioxan-5-yl)acetamide: A mixture of the product of Step E (0.09 g, 0.145 mmol) and 1 M TBAF in THF in anhydrous THF (3 ml) was refluxed under N<sub>2</sub> for 30 h. After cooling to room temperature the solvent was removed under reduced pressure and the residue was diluted to 30 ml with EtOAc. This was washed with H<sub>2</sub>O (2 x 5 ml), brine, dried over anhydrous MgSO<sub>4</sub>, filtered and filtrate evaporated to dryness under reduced pressure. The residue was purified by FCC (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/EtOAc 9/1) to give the title compound (0.02 g, 27%), as colourless solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) 8.39 (s, 1H), 7.98 (dd, 1H, J = 2, 8.6 Hz), 7.79 (dd, 1H, J = 2, 8.4 Hz), 7.69 (d, 1H, J = 2 Hz), 7.44 (d, 1H, J = 8.5 Hz), 6.97 (d, 1H, J = 8.5 Hz), 6.32 (d, 1H, J = 1.2 Hz), 6.18 (s, 1H), 4.47 (d, 2H, J = 11.9 Hz), 4.07 – 4.23 (m, 6H), 2.13 (s, 3H), 1.46 – 1.69 (m, 12H + H<sub>2</sub>O). MS 521 (M + 1).

Step G: 2-Amino-2-(5-(5-(3,4-diethoxyphenyl)-1,2,4-oxadiazol-3-yl)-1H-indol-2-yl)propane-1,3-diol: A mixture of the product of Step F (0.02 g, 0.038 mmol) and TFA (0.1 ml) in EtOH (2 ml) was stirred for 15 min at room temperature and solvent were removed under reduced pressure and the residue kept in vacuo for 1 h. This was diluted to 2 ml with iPrOH and solid KOH (0.1 g) was added. The resulting mixture was refluxed for 6 h and solvent was removed under reduced pressure. The residue was purified by FCC (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub> saturated with NH<sub>4</sub>OH/MeOH 9/1) to give the title compound (0.006 g, 37%), as colourless solid. <sup>1</sup>H NMR (CD<sub>3</sub>OD) 8.28 (d, 1H, J = 1 Hz), 7.7 – 7.83 (m, 3H), 7.45 (d, 1H, J = 8.5 Hz), 7.1 (d, 1H, J = 8.5 Hz), 6.52 (s, 1H), 4.15 – 4.2 (m, 4H), 3.81 (s, 4H), 1.42 – 1.49 (m, 6H). MS 439 (M + 1).

**Example 70****2-Amino-2-(5-(5-(3,4-diethoxyphenyl)-1,2,4-oxadiazol-3-yl)furo[2,3-b]pyridin-2-yl)propane-1,3-diol**

*Step A: 2-Amino-4-iodopyridine:* A mixture of 2-aminopyridine (2.4 g, 25 mmol), NaIO<sub>4</sub> (0.8 g, 3.75 mmol), and I<sub>2</sub> (2.7 g, 10.7 mmol) in a pre mixed solution of AcOH (60 ml), H<sub>2</sub>O (3 ml) and concentrated H<sub>2</sub>SO<sub>4</sub> (0.5 ml) was stirred for 4 h at 80°C. This was poured onto 10% Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (100 ml) and resulting solution was extracted with EtOAc (3 x 50 ml). The organic phase was washed with 10% NaOH solution (3 x 30 ml), brine, dried over anhydrous MgSO<sub>4</sub>, filtered and filtrate evaporated to dryness under reduced pressure. The residue was purified by crystallization from EtOH to give the title compound (3.5 g, 63%), as yellowish solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) 10.5 (broad s, 2 H), 8.05 (d, 1H, J = 2 Hz), 7.62 (dd, 1H, J = 2, 8.8 Hz); 6.34 (d, 1H, J = 8.8 Hz).

*Step B: 2-Amino-4-cyanopyridine:* A suspension of the product of Step A (4 g, 18.2 mmol) and anhydrous CuCN (1.82 g, 20.3 mmol) in anhydrous pyridine (5 ml) was refluxed for 30 min. The solvent was removed in vacuo and the residue was partitioned between EtOAc (150 ml) and 10% NH<sub>4</sub>Cl (pH ~ 9, adjusted with NH<sub>4</sub>OH; 50 ml). The organic phase was washed with brine, dried over anhydrous MgSO<sub>4</sub>, filtered and the filtrate evaporated to dryness to give the title compound (1.8 g, 82%), as yellowish solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) 8.34 (d, 1H, J = 2 Hz), 7.59 (dd, 1H, J = 2, 8.7 Hz), 6.48 (dd, 1H, J = 0.6, 8.6 Hz), 4.98 (broad s, 2H).

*Step C: 2-Hydroxy-4-cyanopyridine:* NaNO<sub>2</sub> (0.99 g, 14.3 mmol) was added in small portions to a well stirred solution of the product of Step B (0.96 g, 8.1 mmol) in a premixed solution of concentrated H<sub>2</sub>SO<sub>4</sub> (1.2 ml) and H<sub>2</sub>O (11.5 ml) while the temperature of the reaction mixture was kept at ) 0 – 5°C. The clear solution became heterogenous with evolution of N<sub>2</sub>. The mixture was allowed to warm up to room temperature with stirring, than heated on the water bath (reflux) for 30 min and cooled to room temperature. The solid formed was filtered off, washed with H<sub>2</sub>O and dried in vacuo to give the title product (0.9 g, 92%) as colourless solid. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) 8.21 (d, 1H, J = 2.4 Hz), 7.61 (dd, 1H, J = 2.4, 9.6 Hz), 6.38 (d, 1H, J = 9.6 Hz), 3.3 (broad s, 1H + 2H<sub>2</sub>O).

*Step D: 2-Hydroxy-3-iodo-4-iodopyridine:* A solution of the product of Step C (0.2 g, 1.67 mmol) and N-iodosuccinimide (0.41 g, 1.83 mmol) in anhydrous DMF (30 ml) was stirred for 4 h at ~ 90°C, concentrated in vacuo to ~ 5 ml and

this was poured onto ice. The solid formed was filtered off, washed with H<sub>2</sub>O (2 x 15 ml) and dried in vacuo to give the title compound (0.3 g, 73%), as brownish solid, which was used in the next step without further purification. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) 8.33 (d, 1H, J = 2.3 Hz), 8.28 (d, 1H, J = 2.3 Hz), 3.28 (broad s, 1H + 11 H<sub>2</sub>O).

Step E: *N*,6-dihydroxy-5-iodonicotinimidamide: A mixture of the product of Step D (0.3 g, 1.22 mmol), HCl x H<sub>2</sub>NOH (0.18 g, 2.5 mmol) and DIPEA (1 ml) in EtOH (1 ml) was stirred overnight at room temperature and solvents were removed in vacuo. The residue was treated with H<sub>2</sub>O (2 ml). The precipitate formed was filtered off, washed with fresh cold H<sub>2</sub>O and dried in vacuo to give the title compound (0.31 g, 92%) as colourless solid, which was used in the next step without further purification.

Step F: 5-(5-(3,4-Diethoxyphenyl)-1,2,4-oxadiazol-3-yl)-3-iodopyridin-2-ol: A mixture of the product of Step E (0.31 g, 1.1 mmol) 3,4-diethoxybenzoic acid (0.24 g, 1.1 mmol) and EDC (0.32 g, 1.67 mmol) in anhydrous DMSO (1.5 ml) was stirred for 2 h at ~ 40°C. To it 1M TBAF in THF (0.5 ml) and the mixture was degassed in vacuo and saturated with N<sub>2</sub>, then stirred for 1 h at ~ 110°C. A fresh portion of 1M TBAF (0.5 ml) was added and stirring was continued for 2 more h and the mixture was cooled to room temperature. This was partitioned between EtOAc (150 ml) and H<sub>2</sub>O (20 ml). The organic phase was washed with brine, dried over anhydrous MgSO<sub>4</sub>, filtered and the filtrate evaporated under reduced pressure and the residue was purified by FCC (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/EtOAc 1/1) to give the title compound (0.161 g, 25%), as colourless solid. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) 8.49 (s, 1H), 8.09 (s, 1H), 7.69 (d, 1H, J = 6 Hz), 7.55 (s, 1H), 7.13 (d, 1H, J = 6 Hz), 4.11 (broad s, 4H), 1.33 (broad s, 6H).

Step G: *tert*-Butyl 5-(5-(5-(3,4-diethoxyphenyl)-1,2,4-oxadiazol-3-yl)furo[2,3-*b*]pyridin-2-yl)-2,2-dimethyl-1,3-dioxan-5-ylcarbamate: A mixture of the product of Step F (0.1076 g, 0.24 mmol) and *tert*-butyl 5-ethynyl-2,2-dimethyl-1,3-dioxan-5-yl carbamate (0.07 g, 0.27 mmol) and anhydrous Cu<sub>2</sub>O (0.04 g, 0.28 mmol) in anhydrous pyridine (1 ml) was degassed under reduced pressure and saturated with N<sub>2</sub> and stirred for 1.5 h at ~110°C. This was cooled to room temperature, diluted to 50 ml with EtOAc and filtered. The filtrate was washed with 10% NH<sub>4</sub>Cl solution (pH = 9, adjusted with NH<sub>4</sub>OH), brine, dried over anhydrous MgSO<sub>4</sub>, filtered and the filtrate evaporated to dryness under reduced



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pressure. The residue was purified by FCC (SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>/EtOAc 9/1) to give the title compound (0.06 g, 43%), as a creamy solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) 9.08 (d, 1H, J = 2 Hz), 8.61 (d, 1H, J = 2 Hz), 7.80 (dd, 1H, J = 2, 8.4 Hz), 7.68 (d, 1H, J = 2 Hz), 6.98 (d, 1H, J = 8.5 Hz); 6.81 (s, 1H), 5.33 (broad s, 1H), 4.34 (d, 2H, J = 12.5 Hz), 4.13 – 4.28 (m, 6H), 1.29 – 1.54 (m, 21H + H<sub>2</sub>O).

*Step H: 2-Amino-2-(5-(5-(3,4-diethoxyphenyl)-1,2,4-oxadiazol-3-yl)furo[2,3-b]pyridin-2-yl)propane-1,3-diol:* To a solution of the product of Step G (0.09 g, 0.155 mmol) and NaI (0.09 g, 0.62 mmol) in anhydrous CH<sub>3</sub>CN (3 ml) Me<sub>3</sub>SiCl (0.3 ml) was added at room temperature under N<sub>2</sub>. After stirring for 30 min solvents were removed under reduced pressure and the residue was diluted to 5 ml with MeOH and re evaporated to dryness. The residue was suspended in H<sub>2</sub>O (2 ml) and the pH was adjusted to ~ 9 with diluted NH<sub>4</sub>OH. The precipitate formed was filtered off, washed with Et<sub>2</sub>O (5 x 1 ml) and dried to give the title compound (0.056 g, 91%), as colourless solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) 8.98 (d, 1H, J = 1.8 Hz), 8.53 (d, 1H, J = 1.2 Hz), 7.74 (dd, 1H, J = 2, 8.4 Hz), 7.62 (d, 1H, J = 2 Hz), 6.94 (d, 1H, J = 8.5 Hz), 6.8 (s, 1H), 4.13 – 4.23 (m, 4H), 3.95 (broad s, 4H), 2.11 (broad s, 4H + 1/2H<sub>2</sub>O), 1.47 – 1.53 (m, 6H).

#### Example 71

**2-Amino-2-(5-(5-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)propane-1,3-diol.HCl**

*Step A: 5-(4-ethoxy-3-methoxyphenyl)-3-(3-iodo-4-isopropoxyphenyl)-1,2,4-oxadiazole:* When 3-chloro-4-propoxy benzoic acid was substituted for 3-methoxy-4-ethoxy benzoic acid in Example 36, Step B, the similar procedure afforded the title compound (220 mg, 49%) as a pale solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.58 (d, 1H, J = 2.04 Hz); 8.06 (dd, 1H, J = 8.55, 2.04 Hz); 7.77 (dd, 1H, J = 8.43, 1.98 Hz); 7.66 (d, 1H, J = 1.89 Hz); 6.96 (d, 1H, J = 8.46 Hz); 6.87 (d, 1H, J = 8.7 Hz); 4.69 – 4.61 (m, 1H); 4.18 (q, 2H, J = 13.98, 6.99 Hz); 3.99 (s, 3H); 1.5 (t, 3H, J = 6.96 Hz); 1.4 (d, 6H, J = 6.06 Hz).

*Step B: 4-(5-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-3-yl)-2-iodophenol:* When the product of above Step A was substituted for the product of Step B, Example 36, the similar procedure as described in Example 36, Step C, afforded the title compound (135 mg, 90%) as off white solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.48 (d, 1H, J = 1.95 Hz); 8.3 (dd, 1H, J = 8.46, 1.95 Hz); 7.77 (dd, 1H, J = 8.4,

1.98 Hz); 7.65 (d, 1H, J = 1.92 Hz); 7.07 (d, 1H, J = 8.46 Hz); 6.97 (d, 1H, J = 8.49 Hz); 5.72 (s, 1H); 4.18 (q, 2H, J = 14.01, 6.99 Hz); 3.99 (s, 3H); 1.5 (t, 3H, J = 6.99 Hz).

5      **Step C:** *tert-butyl 5-(5-(5-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)-2,2-dimethyl-1,3-dioxan-5-ylcarbamate*: When the product of above Step B was substituted for the product of Example 36, Step C, the similar procedure as described in Example 36, Step D afforded the title compound (90 mg, 53%) as a creamy paste. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.35 (d, 1H, J = 1.23 Hz); 8.08 (dd, 1H, J = 8.64, 1.59 Hz); 7.8 (dd, 1H, J = 8.4, 1.92 Hz); 7.69 (d, 1H, J = 1.83 Hz); 7.52 (d, 1H, J = 8.64 Hz); 6.98 (d, 1H, J = 8.49 Hz); 6.75 (s, 1H); 5.32 (bs, 1H); 4.30 – 4.15 (m, 6H); 3.99 (s, 3H); 1.53 – 1.5 (m, 18H).

15      **Step D:** *2-amino-2-(5-(5-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)propane-1,3-diol.HCl*: When the product of above Step C was substituted for the product of Example 36, Step D, the similar procedure as described in Example 36, Step E afforded the title compound as a free base which was turned to HCl salt (30 mg, 44%) by TMSCl to afford a white solid. <sup>1</sup>H-NMR (DMDO-d<sub>6</sub>) 8.67 (bs, 3H); 8.42 (, 1H); 8.03 (d, 1H, J = 10.02 Hz); 7.75 (d, 2H, J = 8.55 Hz); 7.62 (s, 1H); 7.18 (d, 1H, J = 8.7 Hz); 7.16 (s, 1H); 5.66 (b, 2H); 4.14 (d, 2H, J = 6.78 Hz); 4.1 (d, 2H, J = 7.05 Hz); 3.87 (bs, 6H); 1.35 (t, 3H, J = 6.9 Hz).

## Example 72

### 2-Amino-2-(5-(5-(1-admantyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)propane-1,3-diol.HCl

25      **Step A:** *5-(1-admantyl)-3-(3-iodo-4-isopropoxyphenyl)-1,2,4-oxadiazole*: When 3-chloro-4-propoxy benzoic acid was substituted for 1-admananylchloride similar procedure as described in Example 36, Step B without using the EDC.HCl afforded the title compound (290 mg, crude 55%). <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.47 (d, 1H, J = 2.07 Hz); 7.97 (dd, 1H, J = 8.96, 2.65 Hz); 6.83 (d, 1H, J = 8.67 Hz); 4.67 – 4.57 (m, 1H); 2.11 – 1.69 (m, 15H); 1.4 (d, 6H, J = 6.06 Hz).

30      **Step B:** *4-(5-(1-admantyl)-1,2,4-oxadiazol-3-yl)-2-iodophenol*: When the product of above Step A was substituted for the product of Example 36, Step B, the similar procedure as described in Example 36, Step C afforded the title compound (110 mg, 42%) as off white solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.38 (d, 1H, J =

1.62 Hz); 7.95 (dd, 1H, J = 8.49, 1.68 Hz); 7.03 (d, 1H, J = 8.46 Hz); 5.58 (bs, 1H); 2.11 (s, 9H); 1.8 (s, 6H).

Step C: *tert-butyl 5-(5-(5-(1-admantyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)-2,2-dimethyl-1,3-dioxan-5-ylcarbamate*: When the product of above Step B  
5 was substituted for the product of Example 36, Step C, the similar procedure as described in Example 36, Step D afforded the title compound (60 mg, 55%) as a yellow paste. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.26 (d, 1H, J = 1.47 Hz); 7.99 (dd, 1H, J = 8.58, 1.65 Hz); 7.48 (d, 1H, J = 8.58 Hz); 6.71 (s, 1H); 5.31 (bs, 1H); 4.23 (broad, 4H); 2.14 (s, 9H); 1.8 (s, 6H); 1.53 (s, 6H); 1.5 (s, 9H).

Step D: *2-amino-2-(5-(5-(1-admantyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)propane-1,3-diol.HCl*: When the product of above Step C was substituted for the product of Example 36, Step D, the similar procedure as described in Example 36, Step E afforded the title compound (25 mg, 63%) which was turned to HCl salt (15 mg) as a white solid. <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) 8.17 (d, 1H, J = 1.41  
15 Hz); 8.82 (d, 1H, J = 8.7 Hz); 7.76 (dd, 1H, J = 8.7, 1.8 Hz); 7.21 (s, 1H); 4.06 (d, 2H, J = 11.49 Hz); 4.02 (d, 2H, J = 11.52 Hz); 2.07 (s, 9H); 1.8 (s, 6H).

### Example 73

2-((5-(5-(3,4-Diethoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)methyl  
20 amino)propane-1,3-diol.HCl

Step A: *N-((5-(5-(3,4-diethoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)methyl)-2,2-dimethyl-1,3-dioxan-5-amine*: When azetidine-3-methyl  
carboxylate was substituted with 2,2-dimethyl-1,3-dioxo-5-aminocyclohexane the  
similar procedure as described in Example 2, Step A, afforded the title compound  
25 (35 mg, 55 %) as colourless paste. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.33 (d, 1H, J = 1.32 Hz); 8.05 (dd, 1H, J = 8.61, 1.65 Hz); 7.78 (dd, 1H, J = 8.4, 1.89 Hz); 7.68 (d, 1H, J = 1.89 Hz); 7.52 (d, 1H, J = 8.58 Hz); 6.96 (d, 1H, J = 8.46 Hz); 6.67 (s, 1H); 4.24 – 4.13 (m, 4H); 4.02 – 3.97 (m, 4H); 3.78 – 3.72 (m, 2H); 2.76 – 2.70 (m, 1H); 1.52 – 1.41 (m, 12H).

Step B: *2-((5-(5-(3,4-diethoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)methylamino)propane-1,3-diol.HCl*: To a stirred solution of product of above  
Step A in ordinary wet methanol (2 mL) and TMSCl (200 µL, excess) was added  
and the solution was stirred at room temperature for 2 hours. The solution was  
clear when the solvent was distilled and the residue was dried in oven at 60 °C for

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2 hours to afford the title compound (34 mg, quantitative) as white solid. <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) 9.22 (bs, 3H); 8.43 (s, 1H); 8.05 (d, 1H, J = 8.76 Hz); 7.79 – 7.3 (m, 2H); 7.6 (s, 1H); 7.26 (s, 1H); 7.17 (d, 1H, J = 8.52 Hz); 5.34 (s, 1H); 4.49 (b, 2H); 4.15 – 4.08 (m, 4H); 3.68 (b, 4H); 3.17 (b, 2H); 1.35 – 1.32 (m, 6H).

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**Example 74****2-Amino-2-((4-(5-(3-chloro-4-propoxyphenyl)-1,3,4-oxadiazol-2-yl)phenyl)ethynyl)propane-1,3-diol.HCl**

*Step A: 3-chloro-N'-(4-iodobenzoyl)-4-propoxybenzohydrazide:* A mixture of 4-iodobenzoic acid (500 mg, 2 mmol), EDC.HCl (450 mg, 2.3 mmol) and catalytic amount HOBT was stirred at 50 °C in dry DMF (3 mL) for 1 hour when 3-chloro-4-propoxybenzohydrazide (460 mg, 2 mmol) {<sup>1</sup>H-NMR (CDCl<sub>3</sub>) 7.78 (s, 1H), 7.6 (d, 1H, J = 7.9 Hz), 7.45 (bs, 2H), 4.02 (t, 2H, J = 6.48 Hz), 1.94 – 1.8 (m, 1H), 1.06 (t, 3H, J = 7.38 Hz)} was added to it as a solid and mixture was stirred at 50 °C for additional 2 hours. The mixture was diluted with water when white solid separated out which was extracted with ethyl acetate (50 mL). The organic layer was washed with 1M HCl and dried over magnesium sulphate and the solvent was distilled and co-distilled with toluene to afford the title compound (460 mg, 50%) as a dirty white solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 9.64 (bs, 1H); 9.51 (bs, 1H); 7.86 (d, 1H, J = 2.13 Hz); 7.75 (d, 2H, J = 8.46 Hz); 7.7 (dd, 1H, J = 8.61, 2.19 Hz); 7.54 (d, 2H, J = 8.46 Hz); 6.87 (d, 1H, J = 8.64 Hz); 4.02 (t, 2H, J = 6.48 Hz); 1.9 - 1.8 (m, 2H); 1.07 (t, 3H, J = 7.38 Hz).

*Step B: 2-(3-chloro-4-propoxyphenyl)-5-(4-iodophenyl)-1,3,4-oxadiazole:* The product of above Step A (200 mg, 0.44 mmol) was taken in dry RBF (10 mL capacity) and POCl<sub>3</sub> (0.5 mL) was added to it. The mixture was stirred at 140 °C for half hour, cooled to room temperature, treated with sodium bicarbonate solution (100 ml, nearly saturated) and extracted with ethyl acetate (50 mL). The organic layer was separated and dried over magnesium sulphate. The solvent as distilled and the crude was crystallized from methanol to afford the title compound (90 mg, 47%) as dirty white solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.1 (d, 1H, J = 2.13 Hz); 7.98 (dd, 1H, J = 8.61, 2.13 Hz); 7.88 (d, 2H, J = 6.57 Hz); 7.85 (d, 2H, J = 7.17 Hz); 7.01 (d, 1H, J = 8.67 Hz); 4.07 (t, 2H, J = 6.48 Hz); 1.96 - 1.84 (m, 2H); 1.1 (t, 3H, J = 7.38 Hz).

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**Step C:** *tert-butyl 5-((4-(5-(3-chloro-4-propoxyphenyl)-1,3,4-oxadiazol-2-yl)phenyl)ethynyl)-2,2-dimethyl-1,3-dioxan-5-ylcarbamate*: When the product of above Step B was substituted for the product of Example 36, Step C the similar procedure as described in Example 36, Step D to afford the title compound (90 mg, 88%) as a pale solid, <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.1 (d, 1H, J = 2.13 Hz); 8.04 (d, 1H, J = 8.52 Hz); 7.98 (dd, 1H, J = 8.64, 2.16 Hz); 7.56 (d, 2H, J = 8.52 Hz); 7.0 (d, 1H, J = 8.67 Hz); 5.22 (bs, 1H); 4.13 – 4.02 (m, 6H); 1.95 – 1.83 (m, 2H); 1.5 (s, 3H); 1.48 (s, 9H); 1.44 (s, 3H); 1.08 (t, 3H, J = 7.38 Hz).

**Step D:** *2-amino-2-((4-(5-(3-chloro-4-propoxyphenyl)-1,3,4-oxadiazol-2-yl)phenyl)ethynyl)propane-1,3-diol.HCl*: The product of above Step C (80 mg, 0.14 mmol) was taken in a mixture of solvent DCM:MeOH (2 mL: 1 mL) and 10 drops of concentrated HCl was added to it. The mixture was stirred for 6 hours at room temperature when the solvent was distilled and co-distilled with isopropyl alcohol. The residue was taken in isopropyl alcohol (2 mL) and sonicated. The solid as filtered and washed with isopropyl alcohol to gave a off white solid which was dried under high vacuum to afford the title compound (40 mg, 62%) as off white solid. <sup>1</sup>H-NMR (DMDO-d<sub>6</sub>) 8.51 (bs, 3H); 8.19 – 8.13 (m, 3H); 8.03 (dd, 1H, J = 8.67, 2.16 Hz); 7.67 (d, 2H, J = 8.55 Hz); 7.36 (d, 1H, J = 8.79 Hz); 5.8 (t, 2H, J = 5.67 Hz); 4.12 (t, 2H, J = 6.42 Hz); 3.74 (d, 2H, J = 11.76 Hz); 3.67 (d, 2H, J = 11.79 Hz); 1.83 – 1.71 (m, 2H); 0.99 (t, 3H, J = 7.41 Hz).

#### Example 75

##### **2-Amino-2-((4-(5-(3-chloro-4-propoxyphenyl)-1,3,4-thiadiazol-2-yl)phenyl)ethynyl)propane-1,3-diol.HCl**

**Step A:** *2-(3-chloro-4-propoxyphenyl)-5-(4-iodophenyl)-1,3,4-thiadiazole*: To a product of Example 74, Step A (140 mg, 0.31 mmol) in dry toluene (5 mL) was added Lawssen's reagent (125 mg, 0.31 mmol) and the mixture was stirred at reflux for 2 hours. The solvent was distilled and the crude was taken in ethyl acetate (50 mL) and washed with sodium bicarbonate solution. The organic layer was separated and dried over magnesium sulphate to gave the crude product which was crystallized from methanol to afford the title compound (135 mg, 96%) as a white solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.0 (d, 1H, J = 2.16 Hz); 7.86 – 7.82 (m, 3H); 7.7 (d, 2H, J = 8.55 Hz); 7.0 (d, 2H, J = 8.79 Hz); 4.06 (t, 2H, J = 6.48 Hz); 1.95 – 1.85 (m, 2H); 1.08 (t, 3H, J = 7.38 Hz).

Step B: *tert*-butyl 5-((4-(5-(3-chloro-4-propoxyphenyl)-1,3,4-thiadiazol-2-yl)phenyl)ethynyl)-2,2-dimethyl-1,3-dioxan-5-ylcarbamate: When the product of above Step A was substituted for the product of Example 36, Step C the similar procedure as described in Example 36, Step D afforded the title compound (70 mg, 60%) as a white solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.0 (d, 1H, J = 2.22 Hz); 7.91 (d, 1H, J = 8.49 Hz); 7.84 (dd, 1H, J = 8.58, 2.19 Hz); 7.51 (d, 2H, J = 8.46 Hz); 6.99 (d, 1H, J = 8.64 Hz); 5.21 (bs, 1H); 4.13 – 4.03 (m, 6H); 1.95 – 1.83 (m, 2H); 1.5 (s, 3H); 1.48 (s, 9H); 1.45 (s, 3H); 1.08 (t, 3H, J = 7.41 Hz).

Step C: 2-amino-2-((4-(5-(3-chloro-4-propoxyphenyl)-1,3,4-thiadiazol-2-yl)phenyl)ethynyl)propane-1,3-diol.HCl: When the product of above Step B was substituted for the product of Example 74, Step C the similar procedure as described in Example 74, Step D afforded the title compound (18 mg, 31%) as a dirty pale cream solid. <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) 8.56 (bs, 3H); 8.05 – 8.01 (m, 3H); 7.91 (dd, 1H, J = 8.61, 2.19 Hz); 7.64 (d, 2H, J = 8.46 Hz); 7.31 (d, 1H, J = 8.82 Hz); 4.1 (t, 2H, J = 6.42 Hz); 3.7 (t, 4H, J = 12.57 Hz); 1.87 – 1.7 (m, 2H); 0.99 (t, 3H, J = 7.44 Hz).

#### Example 76

2-Amino-2-((4-(5-(3-chloro-4-ethoxyphenyl)-1,2,4-oxadiazol-3-yl)phenyl)ethynyl)propane-1,3-diol.HCl

Step A: 3-(4-bromophenyl)-5-(3-chloro-4-ethoxyphenyl)-1,2,4-oxadiazole: When *N*-hydroxy-3-iodo-4-isopropoxybenzimidamide was substituted with *N*-hydroxy-4-bromobenzimidamide and 3-chloro-4-propoxy benzoic acid with 3-chloro-4-ethoxy benzoic acid the similar procedure as described in Example 36, Step B afforded the title compound (135 mg, 35%) as a creamy solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.21 (d, 1H, J = 2.1 Hz); 8.06 – 7.99 (m, 3H); 7.63 (d, 2H, J = 8.52 Hz); 7.2 (q, 2H, J = 13.98, 6.99 Hz); 1.51 (t, 3H, J = 6.96 Hz).

Step B: *tert*-butyl 5-((4-(5-(3-chloro-4-ethoxyphenyl)-1,2,4-oxadiazol-3-yl)phenyl)ethynyl)-2,2-dimethyl-1,3-dioxan-5-ylcarbamate: When the product of above Step A was substituted for the product of Example 36, Step C the similar procedure as described in Example 36, Step D afforded the title compound (95 mg, 54%) as a pale paste. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.21 (d, 1H, J = 2.1 Hz); 8.09 – 8.02 (m, 3H); 7.53 (d, 2H, J = 8.58 Hz); 7.02 (d, 1H, J = 8.7 Hz); 5.21 (bs, 1H); 4.19 (q,

2H, J = 13.98, 6.99 Hz); 4.14 – 4.03 (m, 4H); 1.5 – 1.43 (m, 15 H); 1.24 (t, 3H, J = 7.17 Hz).

Step C: 2-amino-2-((4-(5-(3-chloro-4-ethoxyphenyl)-1,2,4-oxadiazol-3-yl)phenyl)ethynyl)propane-1,3-diol.HCl: When the product of above Step B was substituted for the product of Example 36, Step D the similar procedure as described in Example 36, Step E afforded the free base (20 mg, 37%) which was turned to HCl salt (20 mg, quantitative) as a dirty white solid. <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) 8.51 (bs, 3H); 8.16 – 8.07 (m, 4H); 7.66 (d, 2H, J = 8.4 Hz); 7.38 (d, 1H, J = 8.76 Hz); 5.79 (t, 2H, J = 5.55 Hz); 4.24 (q, 2H, J = 13.98, 6.99 Hz); 3.71 (b, 2H); 3.7 (b, 2H); 1.38 (t, 3H, J = 6.93 Hz).

#### Example 77

**5-(3-(4-(3-Amino-4-hydroxy-3-(hydroxymethyl)but-1-ynyl)phenyl)-1,2,4-oxadiazol-5-yl)-2-propoxybenzonitrile.HCl**

Step A: 5-(3-(4-bromophenyl)-1,2,4-oxadiazol-5-yl)-2-propoxy benzonitrile: When N-hydroxy-3-iodo-4-isopropoxybenzimidamide was substituted for N-hydroxy-4-bromobenzimidamide and 3-chloro-4-propoxy benzoic acid for 3-cyno-4-propoxy benzoic acid the similar procedure as described in Example 36, Step B afforded the title compound (190 mg, 43%) as a white solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.4 (d, 1H, J = 2.13 Hz); 8.31 (dd, 1H, J = 8.88, 2.19 Hz); 8.0 (d, 2H, J = 6.69 Hz); 7.63 (d, 2H, J = 6.75 Hz); 7.11 (d, 1H, J = 8.91 Hz); 4.14 (t, 2H, J = 6.45 Hz); 1.99 – 1.87 (m, 2H); 1.1 (t, 3H, J = 7.38 Hz).

Step B: tert-butyl 5-((4-(5-(3-chloro-4-propoxyphenyl)-1,2,4-oxadiazol-3-yl)phenyl)ethynyl)-2,2-dimethyl-1,3-dioxan-5-ylcarbamate: When the product of above Step A was substituted for the product of Example 36, Step C the similar procedure as described in Example 36, Step D afforded the title compound (110 mg, 45%) as a pale paste. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.4 (d, 1H, J = 2.13 Hz); 8.32 (dd, 1H, J = 8.85, 2.19 Hz); 8.06 (d, 2H, J = 8.49 Hz); 7.54 (d, 2H, J = 8.49 Hz); 5.22 (bs, 1H); 4.16 – 4.02 (m, 6H); 1.98 – 1.86 (m, 2H); 1.48 (s, 3H); 1.45 (s, 9H); 1.44 (s, 3H); 1.1 (t, 3H, J = 7.38 Hz).

Step C: 5-(3-(4-(3-amino-4-hydroxy-3-(hydroxymethyl)but-1-ynyl)phenyl)-1,2,4-oxadiazol-5-yl)-2-propoxybenzonitrile.HCl: When the product of above Step B was substituted for the product of Example 36, Step D the similar procedure as described in Example 36, Step E afforded the title compound as free base (50

mg, 60%) which was turned to HCl salt (50 mg, quantitative) as a off white solid. <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) 8.57 (bs, 3H); 8.47 (d, 1H, J = 2.22 Hz); 8.38 (dd, 1H, J = 8.94, 2.22 Hz); 8.1 (d, 2H, J = 8.46 Hz); 7.67 (d, 2H, J = 8.46 Hz); 7.48 (d, 1H, J = 9.09 Hz); 5.8 (b, 2H); 4.21 (t, 2H, J = 6.42 Hz); 3.71 (b, 4H); 1.84 – 1.72 (m, 2H);  
5 0.99 (t, 3H, J = 7.41 Hz).

### Example 78

#### 2-Amino-2-((4-(5-(3-chloro-4-propoxyphenyl)-1,2,4-oxadiazol-3-yl)phenyl)ethynyl)propane-1,3-diol.HCl

10 Step A: 3-(4-bromophenyl)-5-(3-chloro-4-propoxyphenyl)-1,2,4-oxadiazole: When *N*-hydroxy-3-iodo-4-isopropoxybenzimidamide was substituted for *N*-hydroxy-4-bromobenzimidamide in Example 36, Step B the similar procedure afforded the title compound (190 mg, 38%) as a white solid. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.2 (d, 1H, J = 2.13 Hz); 8.06 – 8.0 (m, 3H); 7.63 (d, 2H, J = 6.75 Hz); 7.02 (d, 1H, J =  
15 8.67 Hz); 4.08 (t, 2H, J = 6.45 Hz); 1.97 – 1.84 (m, 2H); 1.09 (t, 3H, J = 7.38 Hz).

Step B: *tert*-butyl 5-((4-(5-(3-chloro-4-propoxyphenyl)-1,2,4-oxadiazol-3-yl)phenyl)ethynyl)-2,2-dimethyl-1,3-dioxan-5-ylcarbamate: When the product of above Step A was substituted for the product of Example 36, Step C the similar procedure as described in Example 36, Step D afforded the title compound (120  
20 mg, 47%) as a pale paste. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 8.2 (d, 1H, J = 2.1 Hz); 8.09 – 8.02 (m, 3H); 7.53 (d, 2H, J = 8.55 Hz); 7.0 (d, 1H, J = 8.7 Hz); 5.21 (bs, 1H); 4.13 – 4.02 (m, 6H); 1.94 – 1.84 (m, 2H); 1.54 (s, 3H); 1.48 (s, 9H); 1.44 (s, 3H); 1.09 (t, 3H, J = 7.35 Hz).

Step C: 2-amino-2-((4-(5-(3-chloro-4-propoxyphenyl)-1,2,4-oxadiazol-3-yl)phenyl)ethynyl)propane-1,3-diol.HCl: The product of above Step B (120 mg, 0.2 mmol) was taken in a mixture of solvent DCM:MeOH (1 mL: 1 mL) and 5 drops of concentrated HCl was added to it. The mixture was stirred for 2 hours at room temperature when the solvent was distilled and co-distilled with isopropyl alcohol. The residue was taken in isopropyl alcohol (1.5 mL) and sonicated. The  
25 solid as filtered and washed with isopropyl alcohol to afford the title compound (60 mg, 65%) as a off white solid. <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) 8.55 (bs, 3H); 8.15 – 8.08 (m, 4H); 7.66 (d, 2H, J = 8.19 Hz); 7.37 (d, 1H, J = 8.76 Hz); 5.8 (s, 1H); 4.14 (t, 2H, J = 6.18 Hz); 3.71 (bs, 4H); 1.8 – 1.73 (m, 2H); 0.99 (t, 3H, J = 7.29 Hz).  
30



**Example 79****S1P receptors activity evaluation**

Selected Compounds of the Examples were evaluated at Millipore Corporation, USA, using S1P1 receptor, [<sup>35</sup>S]-GTPgammaS binding assay. A  
 5 [35S]-GTPgammaS binding assay at Millipore was conducted by GPCR Profiler™ Custom Service Laboratory, Temecula, CA, Millipore, Inc. to monitor dose-dependent agonist selectivity for selected Examples against the S1P1 receptors. The assay was completed with sample compounds subjected to an eight-point, four-fold dose response curve with starting concentration of 10 μM. Selectivity was  
 10 determined upon initial addition of compounds followed by a 30 minute incubation at 30°C. Following compound incubation, bounded [35S]-GTPgammaS was determined by filtration and scintillation counting. Percentage activation and inhibition values were determined relative to the reference agonist at S1P1 and are shown in Table 10.

15 Independently, selected compounds were evaluated for S1P1 and S1P3 agonistic activity. The S1P1 assay system was GTPgamma-S35 binding in membranes from CHO K1 cells, expressing S1P1 human receptor. The S1P3 assay system was calcium mobilization in CHO K1 cells expressing S1P3 human receptor. There was no significant background response to S1P in the CHO K1  
 20 cells with either assay. Compounds were tested initially at a concentration of 10 μM. Those compounds with significant efficacy (Emax > 0.15 relative to S1P) at either receptor type were used to generate concentration-effect (dose response) curves at that receptor. These analyses provided efficacy (Emax) and potency (EC<sub>50</sub>) of the compounds relative to S1P, shown in Table 10.

25

**Table 10: S1P1 and S1P3 agonistic activity of selected compounds of Formula (I)**

Entry Number	Example	EC <sub>50</sub> (μM) S1P1	EC <sub>50</sub> S1P1/EC <sub>50</sub> S1P	Efficacy (% of maximum)	EC <sub>50</sub> (μM) S1P3
1	3	0.29	135.5	102.5	ND
2	9	1.63	761.7	88	ND

140.

Entry Number	Example	EC <sub>50</sub> ( $\mu$ M) S1P1	EC <sub>50</sub> S <sub>1</sub> P <sub>1</sub> / EC <sub>50</sub> S <sub>1</sub> P	Efficacy (% of maximum)	EC <sub>50</sub> ( $\mu$ M) S <sub>1</sub> P <sub>3</sub>
3	11	0.46	215	96	ND
4	13	3.21	1500	58	ND
5	17	1.76	542	97	ND
6	19	5.99	2799	130	ND
7	27	0.6	280.4	127	ND
8	29	0.2	93.46	102	ND
9	32	0.06	28	107	ND
10	33	0.14	65.42	97	ND
11	36	0.047	4.18	101	NA
12	37	1.82	160.8	40	NA
13	38	0.26	28.17	74	NA
14	39	3.46	305	16	NA
15	40	0.057	4.75	106	0.38
16	1	2.08	104	54	NA
17	2	0.026	1.3	64	0.467
18	42	10.31	845	34	NA
19	43	>96	>7950	30	NA
20	44	2.08	172	93	NA
21	45	2.02	202	89	NA
22	46	17.1	3373	42	NA
23	47	12.34	2436	39	NA
24	48	0.052	10.26	13	514
25	49	0.0246	2.46	100.8	NA
26	50	0.086	8.62	96	NA
27	51	>523	>123262	35	NA
28	52	>4.68	>1103	27	NA
29	55	5.48	1046	85	NA
30	56	5.03	960.5	108	NA
31	57	17.99	2571.47	81	NA
32	58	0.238	52.82	123	12.98

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Entry Number	Example	EC <sub>50</sub> ( $\mu$ M) S1P1	EC <sub>50</sub> S <sub>1</sub> P <sub>1</sub> / EC <sub>50</sub> S <sub>1</sub> P	Efficacy (% of maximum)	EC <sub>50</sub> ( $\mu$ M) S <sub>1</sub> P <sub>3</sub>
33	59	0.782	149	103	>26.45
34	60	0.255	36.45	128	>198
35	61	0.0126	2.8	111	>1.14
36	62	0.038	5.46	123	NA
37	63	0.37	53	125	0.0026
38	64	0.076	10.9	122	>9.5

NA = no activity; ND = not determined.

**Example 80****Lymphopenia Assay**

- 5 The study was performed at vivoPharm Pty Ltd, Adelaide, Australia, to determine the ability of the compounds of invention to induce lymphopenia in female BALB/c mice. On day 0, 27 female BALB/c mice were randomised based on body weight into nine groups of three mice each. Animals received a single i.p. administration of Test compounds and blood was collected by cardiac puncture
- 10 either 6 or 24 h after administration. Treatment with 3 mg/kg of Example 40 was shown to decrease lymphocyte counts at both 6 and 24 h, compared to untreated animals (Figure 1). Changes to other haematological parameters were not observed.

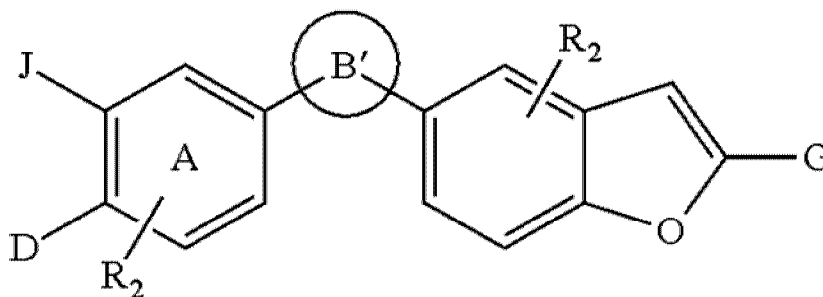
- 15 The reduction in lymphocyte count was observed by administering a single oral dose of vehicle or drug in B57.BL/6 mice and blood was taken at 6 and 24 hour time point. The direct comparison in reduction of lymphocyte count in vehicle and drug treated mice in case of example no 40 and 56 at 24 hr time point is given below in table.

Entry No	Example No	Dose mg/Kg	Reduction in lymphocyte count at 24 hr
1	40	0.25 mg/Kg	-70.6%
2	56	6 mg/Kg	-17.4%

THE CLAIMS:

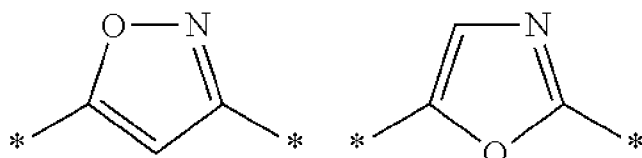
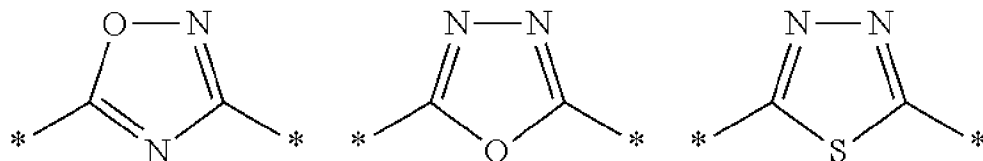
1. A compound of formula (II) or a salt thereof:

(II)



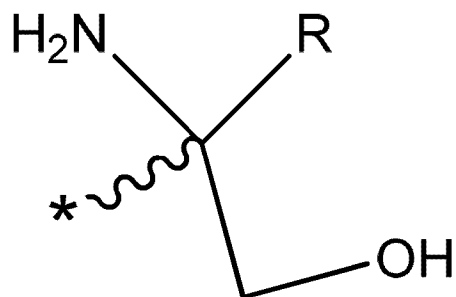
wherein

B' is a five-membered heterocyclic ring selected from one of the following:



the asterisks indicating the attachment within formula (II);

G represents



R is selected from hydrogen, deuterium, alkylamino, CH<sub>2</sub>OH, alkoxy, a C<sub>1-5</sub> alkyl chain optionally containing one or more of deuterium, O, NR'R'', S, halogen, heterocycle, amide, sulphonamide, COOH, —OPO<sub>3</sub>H<sub>2</sub> and —PO<sub>3</sub>H<sub>2</sub>;

A ring is phenyl or pyridinyl;

R<sub>2</sub> independently is selected from halogen, hydrogen, deuterium, CN, amino, alkylamino, alkoxy, CF<sub>3</sub>, a C<sub>2-4</sub> alkyl chain containing a carbon-carbon double bond, a carbon-carbon triple bond, a carbon-heteroatom double bond or a carbon-heteroatom triple bond, a C<sub>1-4</sub> alkyl chain optionally containing one or more of deuterium, OH, NR'R'', S, SO<sub>2</sub>, carbocycle, heterocycle, amide and sulphonamide; and

the groups J and D each are independently selected from hydrogen, deuterium, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> alkylamino, halogen, amino, hydroxyl, cyano, aryl, heterocycle, carbocycle or a C<sub>2-10</sub> alkyl containing a carbon-carbon double bond, a carbon-carbon triple bond, a carbon-heteroatom double bond or a carbon-heteroatom triple bond wherein one or more carbon atoms of the C<sub>2-10</sub> alkyl are optionally independently replaced with oxygen, sulphur, SO, SO<sub>2</sub>, NR', carbocycle or heterocycle; and

R' and R'' each are independently selected from alkyl, cycloalkyl, aryl or heterocycle.

2. The compound of claim 1 or the salt thereof,  
wherein

D is selected from C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> alkylamino, aryl, heterocycle, carbocycle or a C<sub>2-7</sub> alkyl chain containing a carbon-carbon double bond, a carbon-carbon triple bond or a carbon-heteroatom double bond wherein one or more carbon atoms are optionally independently replaced with oxygen, sulphur, SO, SO<sub>2</sub>, NR', carbocycle or heterocycle;

J is selected from H, deuterium, C<sub>1-4</sub> alkyl, C<sub>1-4</sub> alkoxy, C<sub>1-4</sub> alkylamino, halogen, amino, hydroxy, cyano or a C<sub>2-5</sub> alkyl chain containing a carbon-carbon double bond, a carbon-carbon triple bond or a carbon-heteroatom double bond wherein one or more carbon atoms are optionally independently replaced with oxygen, sulphur, SO, SO<sub>2</sub>, NR', carbocycle or heterocycle; and

R' is selected from alkyl, cycloalkyl, aryl or heterocycle.

3. The compound of claim 1 selected from the group consisting of:

2-amino-2-(5-(5-(3-chloro-4-propoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)propane-1,3-diol,  
2-amino-2-(5-(5-(4-bromo-3-chlorophenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)propane-1,3-diol,  
2-amino-2-(5-(5-(3-chloro-4-(thiophen-3-yl)phenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)propane-1,3-diol,  
2-amino-2-(5-(5-(3,4-diethoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)propane-1,3-diol,  
2-amino-2-(5-(5-(4-propoxy-3-methoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)propane-1,3-diol,  
2-amino-2-(5-(5-(6-methoxybenzofuran-2-yl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)propane-1,3-diol,  
2-amino-2-(5-(5-(4-propylphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)propane-1,3-diol,  
2-amino-2-(5-(5-(4-ethoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)propane-1,3-diol,  
2-amino-2-(6-chloro-5-(5-(4-propylphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)propane-1,3-diol,  
2-amino-2-(5-(5-(1-butyl-1H-pyrazol-4-yl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)propane-1,3-diol,  
2-amino-2-(5-(5-(3-nitro-4-propoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)propane-1,3-diol,  
5-(3-(2-(2-amino-1,3-dihydroxypropan-2-yl)benzofuran-5-yl)-1,2,4-oxadiazol-5-yl)-2-propoxybenzonitrile,  
2-amino-2-(5-(5-(3-bromo-4-propoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)propane-1,3-diol,  
2-amino-2-(5-(2-(2-(4-fluorophenyl)-4-methyloxazol-5-yl)ethyl)benzofuran-2-yl)propane-1,3-diol,

2-amino-2-(5-(2-(2-(4-fluorophenyl)-4-methylthiazol-5-yl)ethyl)benzofuran-2-yl)propane-1,3-diol,  
2-amino-2-(5-(2-(methyl(pyridin-2-yl)amino)ethoxy)benzofuran-2-yl)propane-1,3-diol,  
2-amino-2-(5-(2-(2-(4-fluorophenyl)-5-methyloxazol-4-yl)ethyl)benzofuran-2-yl)propane-1,3-diol,  
2-amino-2-(5-(3-(methyl(pyridin-2-yl)amino)propyl)benzofuran-2-yl)propane-1,3-diol,  
2-amino-2-(5-(5-(2-cyclopropylbenzofuran-5-yl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)propane-1,3-diol,  
2-amino-2-(5-(5-(4-isobutoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)-1,3-diol,  
2-amino-2-(6-chloro-5-(5-(3,4-diethoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)propane-1,3-diol,  
2-amino-2-(5-(5-(3-chloro-4-methoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)propane-1,3-diol,  
2-amino-2-(5-(5-(3,4-dimethoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)propane-1,3-diol,  
2-amino-2-(5-(5-(3-chloro-4-ethoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)propane-1,3-diol,  
5-(3-(2-(2-amino-1,3-dihydroxypropan-2-yl)benzofuran-5-yl)-1,2,4-oxadiazol-5-yl)-2-ethoxybenzonitrile,  
2-amino-2-(5-(5-(3-chloro-4-ethoxyphenyl)-1,2,4-oxadiazol-3-yl)-7-methylbenzofuran-2-yl)propane-1,3-diol,  
2-amino-2-(5-(5-(3,4-diethoxyphenyl)-1,2,4-oxadiazol-3-yl)-7-methylbenzofuran-2-yl)propane-1,3-diol,  
5-(3-(2-(2-amino-1,3-dihydroxypropan-2-yl)-7-methylbenzofuran-5-yl)-1,2,4-oxadiazol-5-yl)-2-propoxybenzonitrile,  
N-(5-(3-(2-(2-amino-1,3-dihydroxypropan-2-yl)benzofuran-5-yl)-1,2,4-oxadiazol-5-yl)-2-ethoxyphenyl)methanesulfonamide,  
2-amino-2-(5-(5-(3,4-diethoxyphenyl)-1,2,4-oxadiazol-3-yl)furo[2,3-b]pyridin-2-yl)propane-1,3-diol,

2-amino-2-(5-(5-(4-ethoxy-3-methoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)propane-1,3-diol,

2-amino-2-((5-(5-(3,4-diethoxyphenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)methylamino)propane-1,3-diol, and

2-amino-2-(5-(5-(4-propoxy-3-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)benzofuran-2-yl)propane-1,3-diol.

4. A pharmaceutical composition, comprising at least one compound as claimed in any one of claims 1 to 3 together with one or more pharmaceutically acceptable carriers or excipients.

5. At least one compound as claimed in any one of claims 1 to 3 for use in the treatment of sepsis, stroke, epilepsy, autoimmune disease or for use in the treatment or immunotherapy of cancer, solid tumours, haematological disorders, infections, immunological and immune mediated disorders, pain, vascular disease, cardiovascular disease, liver disease/injury, lung pathologies/injury, hypoxia or allograft or autograft rejection.

6. The compound as claimed in any one of claims 1 to 3 for use according to claim 5 wherein the autoimmune disease is Multiple Sclerosis.

7. The compound as claimed in any one of claims 1 to 3 for use according to claim 5 wherein the immune mediated disorders is an inflammatory disease.

8. At least one compound as claimed in any one of claims 1 to 3 for use in the mobilization of progenitor/stem cells for regeneration of tissue or organs.

9. At least one compound as claimed in any one of claims 1 to 3 for use in boosting the action of immunization or vaccination.



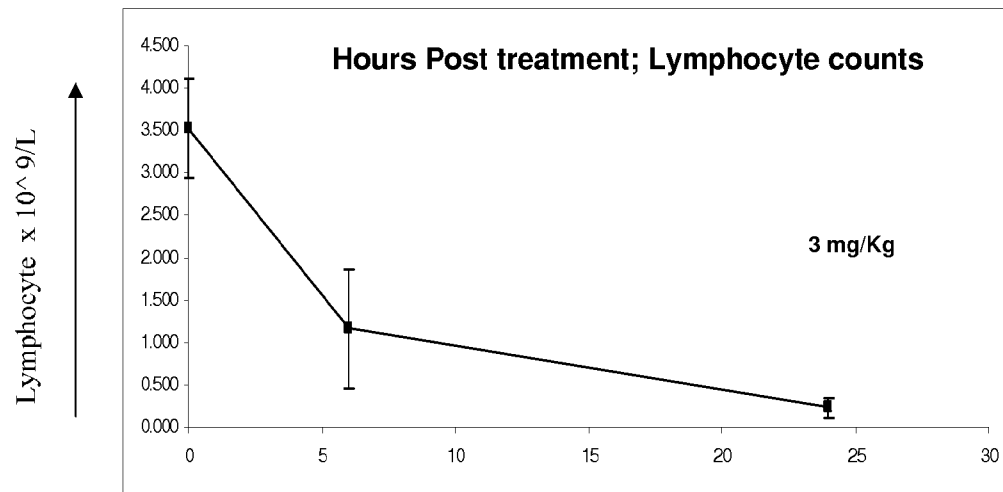
10. The compound as claimed in any one of claims 1 to 3 for use in the treatment of auto immune or inflammatory disease, wherein the compound is in combination with an adjuvant.

11. The compound as claimed in claim 10 wherein the adjuvant is selected from the group consisting of cyclosporine, tacrolimus, rapamycin, azathioprine, cyclophosphamide, dexamethasone, flunisolide, prednisolone, prednisone, amcinonide, desonide, methylprednisolone, triamcinolone and alclometasone.

12. The compound as claimed in any one of claims 1 to 3 for use in the treatment of infection or cancer, wherein the compound is in combination with an adjuvant.

13. The compound as claimed in claim 12 wherein the adjuvant is selected from the group consisting of anticancer, antiviral, antibacterial, antifungal and anti-pathogen agents.

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**Figure: 1**