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(71) Applicant *(for all designated States except US)*: **GLENMARK PHARMACEUTICALS LTD.** [IN/IN]; B/2 Mahalaxmi Chambers, 22, Bhulabhai Desai Road, Mumbai-400 026 (IN).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **BALASUBRAMANIAN, Gopalan** [IN/IN]; Flat no. 54, Block B-3, Mahavir Shikar, L.B.S. Marg, Mulund (West), Mumbai 400 080 (IN). **GHARAT, Laxmikant, Atmaram** [IN/IN]; Parvati Apts., A-2, Patilwadi, Chandanwadi, Thane (West), Maharashtra 400 601 (IN). **JOSHI, Hemant, Vasant** [IN/IN]; Flat No. 2, "Mohita", 2nd Seaward Road, Valmiki Nagar, Thiruvanmiyur, Chennai 600 041 (IN).

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(54) Title: NEW TRICYCLIC COMPOUNDS USEFUL FOR THE TREATMENT OF INFLAMMATORY AND ALLERGIC DISORDERS: PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

(57) Abstract: The present invention relates to novel heterocyclic compounds, their analogs, their tautomers, their regioisomers, their stereoisomers, their enantiomers, their diastereomers, their polymorphs, their pharmaceutically acceptable salts, their appropriate oxides, their pharmaceutically acceptable solvates and their pharmaceutical compositions containing them. The present invention also relates to Phosphodiesterase type 4 (PDE4) inhibitor compounds which down regulate or inhibit the production of TNF-α and therefore are useful in the treatment of variety of allergic and inflammatory diseases including asthma and chronic obstructive pulmonary disease (COPD). The present invention also relates to a process for the preparation of the novel heterocyclic compounds.

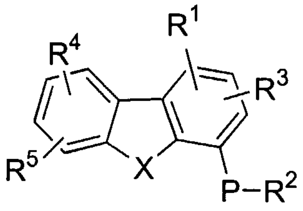
NEW TRICYCLIC COMPOUNDS USEFUL FOR THE TREATMENT OF INFLAMMATORY AND ALLERGIC DISORDERS: PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

Cross-Reference to Related Applications

This application claims priority to U.S. Provisional Patent Application **60/589,479**, filed July 19, 2004, and Indian Provisional Patent Application **809/MUM/2004** (**70/MUM-WTO/2004**), filed July 29, 2004, both of which are incorporated by reference in their entireties.

Field of the Invention

The present invention relates to novel Phosphodiesterase type 4 (PDE4) inhibitors of formula **(1)** (shown below),



(1)

wherein R^1-R^5, P, and X are as defined herein, their analogs, their tautomers, their enantiomers, their diasteromers, their regioisomers, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts, their appropriate oxides, and their pharmaceutically acceptable solvates, the pharmaceutical compositions containing them, processes for their preparation, and their use for down regulation or inhibiting the production of TNF-α and the treatment of allergic and inflammatory diseases including asthma, chronic obstructive pulmonary disease (COPD), chronic bronchitis, atopic dermatitis, urticaria, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, eosinophilic granuloma, psoriasis, rheumatoid arthritis, septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and reperfusion injury of the brain, chronic glomerulonephritis, endotoxic shock and adult respiratory distress syndrome.

Background of the Invention

Airway inflammation characterizes a number of severe lung diseases including asthma and chronic obstructive pulmonary disease (COPD). Events leading to airway obstruction include edema of airway walls, infiltration of inflammatory cells into the lung, production of various inflammatory mediators and increased mucous production. The airways of asthmatic patients are infiltrated by inflammatory leukocytes, of which the eosinophil is the most prominent component. The magnitude of asthmatic reactions is correlated with the number of eosinophils present in lungs.

The accumulation of eosinophils is found dramatically in the lungs of asthmatic patients although there are very few in the lungs of a normal individual. They are capable of lysing and activating cells and destroying tissues. When activated, they synthesize and release inflammatory cytokines such as IL-1, IL-3, TNF-α and inflammatory mediators such as PAF, LTD4 and related oxygen species that can produce edema and broncho-constriction. Tumor necrosis factor (TNF-α) was also known to be involved in the pathogenesis of a number of autoimmune and inflammatory diseases. Consequently, manipulation of the cytokine signaling or biosynthetic pathways associated with these proteins may provide therapeutic benefit in those disease states. It has been well demonstrated that TNF-α production in pro-inflammatory cells becomes attenuated by an elevation of intracellular cyclic adenosine 3',5'-monophosphate (cAMP). This second messenger is regulated by the phosphodiesterase (PDE) family of enzymes. The phosphodiesterase enzymes play an integral role in cell signaling mechanisms by hydrolyzing cAMP and cGP to their inactive 5' forms. Inhibition of PDE enzymes thus results in an elevation of cAMP and /or cGP levels and alters intracellular responses to extra cellular signals by affecting the processes mediated by cyclic nucleotides. Since eosinophilis are believed to be a critical proinflammatory target for asthma, identification of the expression of the PDE 4 gene family in eosinophils led to PDE 4 as potential therapeutic target for asthma [Rogers, D.F., Giembycz, M.A., *Trends Pharmacol. Sci.*, 19,160-164(1998); Barnes, P.J., *Trends Pharmacol. Sci.*, 19, 415-423 (1998) herein incorporated by reference in their entirety].

The mammalian cyclic nucleotide phosphodiesterases (PDEs) are classified into ten families on the basis of their amino acid sequences and/or DNA sequence, substrate specificity and sensitivity to pharmacological agents [Soderling, S.H., Bayuga, S.J., and Beavo, J.A., *Proc. Natl. Acad. Sci., USA*, 96, 7071-7076 (1999); Fujishige, K, Kotera, J., Michibata, H., Yuasa, K., Takebayashi, Si, Okamura, K. and Omori, K., *J. Biol. Chem.*, 274, 18438-18445 (1999) herein incorporated by reference in their entirety]. Many cell types express more than one PDE and distribution of isoenzymes between the cells varies markedly. Therefore development of highly isoenzyme selective PDE inhibitors provides a unique opportunity for selective manipulation of various pathophysiological processes.

Phosphodiesterase type 4 (PDE4) is an enzyme which regulates activities in cells which lead to inflammation in the lungs. PDE4, a cAMP-specific and Ca^{+2}-independent enzyme, is a key isozyme in the hydrolysis of cAMP in mast cells, basophils, eosinophils, monocytes and lymphocytes. The association between cAMP elevation in inflammatory cells with airway smooth muscle relaxation and inhibition of mediator release has led to widespread interest in the design of PDE4 inhibitors [Trophy,T.J., *Am. J. Respir. Crit. Care Med.*, 157, 351-370 (1998) herein incorporated by reference in their entirety]. Excessive or unregulated TNF-α production has been implicated in mediating or exacerbating a number of undesirable physiological conditions such as diseases including osteoarthritis, and other arthritic conditions; septic shock, endotoxic shock, respiratory distress syndrome and bone resorption diseases since TNF-α also participates in the onset and progress of autoimmune diseases, PDE4 inhibitors may find utility as therapeutic agents for rheumatoid arthritis, multiple sclerosis and Crohn's disease. [*Nature Medicine*, 1, 211-214 (1995) and *ibid.*, 244-248 herein incorporated by reference in their entirety].

Strong interest in drugs capable of selective inhibition of PDE 4 is due to several factors. Tissue distribution of PDE-4 suggests that pathologies related to the central nervous and immune systems could be treated with selective PDE-4 inhibitors. In addition, the increase in intracellular cAMP concentration, the obvious biochemical consequence of PDE-4 inhibition, has been well characterized in immuno-competent cells where it acts as a deactivating signal.

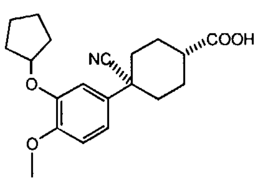
Recently the PDE4 family has grown to include four subtypes - PDE4A to PDE4D, each encoded by a distinct gene (*British Journal of Pharmacology; 1999; v.128; p.1393-1398*), herein incorporated by reference in its entirety.

It has been demonstrated that increasing cAMP levels within these cells results in suppression of cell activation, which in turn inhibits the production and release of pro-inflammatory cytokines such as TNF-α. Since eosinophilis are believed to be a critical pro-inflammatory target for asthma, identification of the expression of the PDE-4 gene family in eosinophils led to the PDE-4 as a potential therapeutic target for asthma.

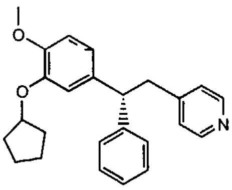
The usefulness of several PDE-4 inhibitors, unfortunately, is limited due to their undesirable side effect profile which include nausea and emesis (due to action on PDE-4 in the central nervous system) and gastric acid secretion due to action on PDE-4 in parietal cells in the gut. Barnette, M.S., Grous, M., Cieslinsky, L.B., Burman, M., Christensen, S.B., Trophy, T J., *J. Pharmacol. Exp. Ther.*, 273, 1396-1402 (1995) herein incorporated by reference in their entirety. One of the earliest PDE-4 inhibitors, Rolipram™, was withdrawn from clinical development because of its severe unacceptable side effect profile. Zeller E. et. al., *Pharmacopsychiatr.*, 17, 188-190 (1984) herein incorporated by reference in its entirety. The cause of severe side effects of several PDE-4 inhibitor molecules in human clinical trials has recently become apparent.

There exist two binding sites on mammalian PDE-4 at which inhibitor molecules may bind. Also PDE-4 exists in two distinct forms which represent different conformations. They are designated as High affinity Rolipram binding site PDE-4H and low affinity Rolipram binding site PDE-4L [Jacobitz, S., McLaughlin, M.M., Livi, G.P., Burman, M., Trophy, T.J., *Mol. Pharmaco.*, 50, 891-899 (1996) herein incorporated by reference in their entirety]. It was shown that certain side effects (vomiting and gastric acid secretion) are associated with inhibition of PDE-4H whereas some beneficial actions are associated with PDE-4L inhibition. It was also found that human recombinant PDE-4 exists in 4 isoforms A, B, C and D [Muller, T., Engels, P., Fozard, J.R., *Trends Pharmacol. Sci.*, 17, 294-298 (1996) herein incorporated by reference in its entirety]. Accordingly, compounds displaying more PDE-4D isoenzyme selectivity over the A, B or C are found to have fewer side effects than Rolipram [Hughes. B et.al., *Br. J. Pharmacol.* **1996**, 118, 1183-1191 herein incorporated by reference in their entirety]. Therefore, selective inhibitors of PDE-4 isozymes would have therapeutic effects in inflammatory diseases such as asthma and other respiratory diseases.

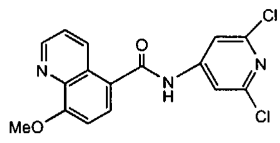
Although several research groups all over the world are working to find highly selective PDE-4 isozyme inhibitors, so far success has been limited. Various compounds have shown PDE-4 inhibition.



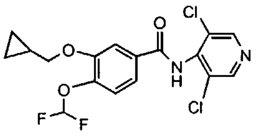
ARIFLO A



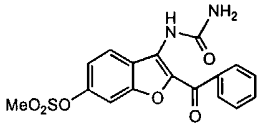
CDP-840 B



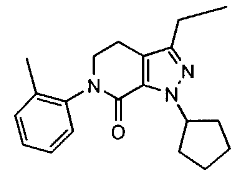
D-4418 C



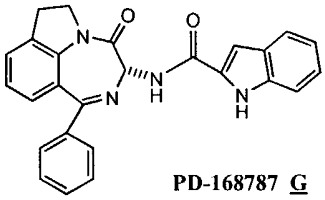
Roflumilast D



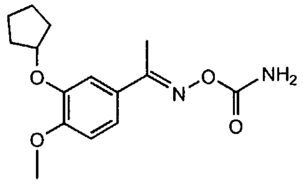
Bay-19-8004 E



CP - 220,629 F



PD-168787 G



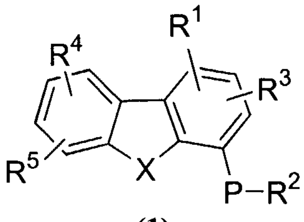
Filaminast H

SmithKline Beecham's "Ariflo" which has the formula A, Byk Gulden's Roflumilast which has the formula D and Bayer's Bay-19-8004 which has the formula E have reached advanced stage of human clinical trials. Other compounds which have shown potent PDE-4 inhibitory activity include Celltech's CDP-840 of the formula B, Schering Plough's D-4418 of the formula C, Pfizer's 5CP-220,629 which has the formula F, Parke Davis's PD-168787 which has the formula G and Wyeth's Filaminast which has the formula H. However, recently due to efficacy and side effects problems, Ariflo, CDP-840 and Bay-19-8004 were discontinued from clinical trials as a treatment for asthma. Other compounds of the formulae C and F are presently undergoing phase-1 clinical trials.

During the course of our research aimed at the development of novel anti-asthmatic compounds having potential PDE4 inhibitory activity, we have filed a WTO patent application in India bearing No. 922/MUM/2002 dated October 23, 2002 and PCT application No PCT/IB03/04442 dated October 8, 2003 which has been published on May 6,2004 as WO 2004/037805 incorporated herein by reference in their entireties, for a novel series of tricyclic compounds useful for the treatment of inflammatory and allergic disorders.

SUMMARY OF THE INVENTION:

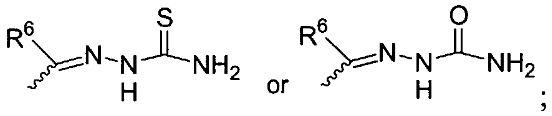
Accordingly, the present invention provides novel heterocyclic compounds of the general formula **(1)**



(1)

wherein:

R^1 is substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroarylalkyl; in which the substituents may be one or more, the same or different and are independently hydrogen, hydroxyl, halogen, cyano, nitro, carboxyl, trifluoroalkyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkoxycarbonyl, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted alkylcarbonyloxy, substituted or unsubstituted amino, mono- or di- substituted or unsubstituted alkylamino,



R^2, R^3, R^4, R^5, R^6 and R^7 may be the same or different and are independently for each occurrence selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroarylalkyl , $-NR^8R^9$, $-C(O)-R^8$, $-C(O)O-R^8$, $-C(O)NR^8R^9$, $-S(O)_m-R^8$, $-S(O)_m-NR^8R^9$, nitro, -OH, cyano, formyl, acetyl, halogen, $-OR^8$, $-SR^8$, or a protecting group, when R^1 and R^3, or R^4 and R^5 are ortho to each other then R^1 and R^3 together with the carbon atoms to which they are bound or R^4 and R^5 together with the carbon atoms to which they are bound may be joined to form a saturated or unsaturated cyclic ring, which may optionally include up to two heteroatoms selected from O, NR^a or S;

Each occurrence of R^8 and R^9 may be same or different and is independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroarylalkyl , nitro, halo, -OH, cyano, $-C(O)-R^a$, $-C(O)O-R^a$, $-C(O)NR^aR^b$, $-S(O)_m-R^a$, $-S(O)_m-NR^aR^b$, $-C(=NR^a)-R^b$, $-C(=NR^a)-NR^aR^b$, $-C(=S)-NR^aR^b$, $-C(=S)-R^a$, $-N=C(R^aR^b)$, $-NR^aR^b$, $-OR^a$, $-SR^a$, a protecting group, or R^8 and R^9 may be joined together with the atom connecting them to a form a optionally substituted saturated or unsaturated cyclic ring, which may optionally include up to two heteroatoms selected from O, NR^a or S.

Each occurrence of R^a and R^b may be same or different and is independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroarylalkyl , nitro, -OH, cyano, formyl, acetyl, halogen, a protecting group, $-C(O)-R^a$, $-C(O)O-R^a$, $-C(O)NR^aR^b$, $-S(O)_m-R^a$, $-S(O)_m-NR^aR^b$, $-NR^aR^b$,$-OR^a$, $-SR^a$, or R^a and R^b may be joined together with the atom connecting them to a form an optionally substituted saturated or unsaturated cyclic ring, which may optionally include up to two heteroatoms selected from O, NR^a or S;

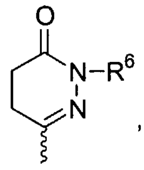
X is O, $S(O)_m$ and NR^6;

P is O or S;

each occurrence of m is 0, 1 or 2;

and their analogs, tautomers, regioisomers, stereoisomers, enantiomers, diastereomers, polymorphs, pharmaceutically acceptable salts, N-oxides, pharmaceutically acceptable solvates and pharmaceutical compositions containing them.

Preferably, R^1 is selected from



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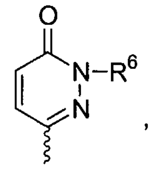

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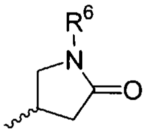

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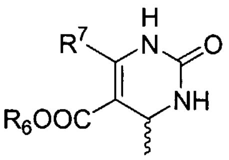

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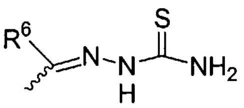

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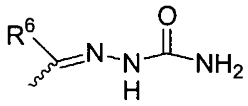

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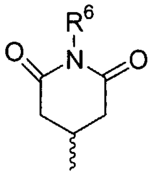

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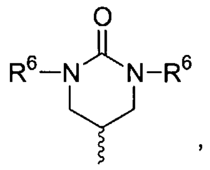

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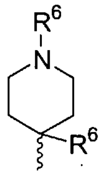

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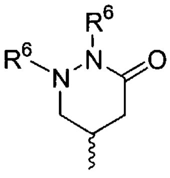

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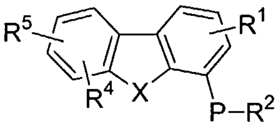
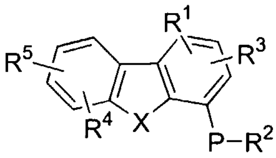
Further preferred is a compound according to formula **(2)**



(2)

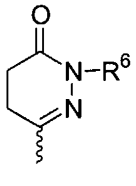
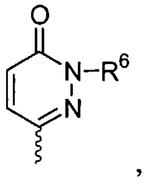
wherein R¹, R², R⁴, R⁵ and X are defined as in formula **(1)**.

Further preferred is a compound according to formula **(3)**:



(3)

where

R¹ is  or  , and

R^2-R^7, X, and P are as defined in Formula **(1)**.

Further preferred is a compound according Formula **(3)** wherein X is O.

Further preferred is a compound according Formula **(3)** wherein P is O.

Further preferred is a compound according Formula **(3)** wherein R^2 is chosen from the group consisting of alkyl, cycloalkyl and substituted alkyl.

Further preferred is a compound according to Formula **(3)** wherein R^2 is -CH_3.

Further preferred is a compound according Formula **(3)** wherein R^2 is cyclopentyl.

Further preferred is a compound according Formula **(3)** wherein R^2 is -CHF_2.

Further preferred is a compound according Formula **(3)** wherein R^3 is hydrogen.

Further preferred is a compound according Formula **(3)** wherein R^3 is bromo.

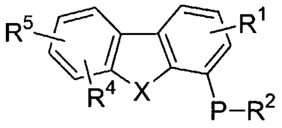
Further preferred is a compound according Formula **(3)** wherein R^6 is chosen from the group consisting of hydrogen, alkyl and substituted alkyl.

Further preferred is a compound according Formula **(3)** wherein R^6 is -CH_3.

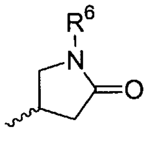
Further preferred is a compound according Formula **(3)** wherein R^6 is benzyl.

Further preferred is a compound according Formula **(3)** wherein R^5 and R^6 are hydrogen.

Further preferred is a compound according to Formula **(4)**



(4)

wherein R^1 is  and R^2- R^6, X and P as defined in Formula 1.

Further preferred is a compound according Formula **(4)** wherein X is O.

Further preferred is a compound according Formula **(4)** wherein P is O.

Further preferred is a compound according Formula **(4)** wherein R^2 is chosen from the group consisting of alkyl, cycloalkyl and substitute alkyl.

Further preferred is a compound according Formula **(4)** wherein R^2 is -CH_3.

Further preferred is a compound according Formula **(4)** wherein R^2 is cyclopentyl.

Further preferred is a compound according Formula **(4)** wherein R^2 is -CHF_2.

Further preferred is a compound according Formula **(4)** wherein R^4 and R^5 are hydrogen.

Further preferred is a compound according Formula **(4)** wherein R^4 is hydrogen and R^5 is $-NO_2$.

Further preferred is a compound according Formula **(4)** wherein R^4 is hydrogen and R^5 is $-NH_2$.

Further preferred is a compound according Formula **(4)** wherein R^4 is hydrogen and R^5 is $-NH\text{-}CO\text{-}CH_3$.

Further preferred is a compound according Formula **(4)** wherein R^4 is hydrogen and R^5 is $-NH\text{-}S(O)_2\text{-}CH_3$.

Further preferred is a compound according Formula **(4)** wherein R^4 is hydrogen and R^5 is $-NH\text{-}C(O)\text{-}(4\text{-}CH_3$.piperazin-1yl)

Further preferred is a compound according Formula **(4)** wherein R^4 is hydrogen and R^5 is $-S(O)_2\text{-}(4\text{-}CH_3$.piperazin-1yl)

Further preferred is a compound according Formula **(4)** wherein R^4 is hydrogen and R^5 is $-S(O)_2$-(morpholine)

Further preferred is a compound according Formula **(4)** wherein R^6 is chosen from the group consisting of hydrogen, formyl, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl , substituted or unsubstituted alkylcycloalkyl or substituted or unsubstituted aryl .

Further preferred is a compound according Formula **(4)** wherein R^6 is H.

Further preferred is a compound according Formula **(4)** wherein R^6 is -CH_3.

Further preferred is a compound according Formula **(4)** wherein R^6 is –$CH_2\text{-}CH_3$.

Further preferred is a compound according Formula **(4)** wherein R^6 is –$CH(CH_3)_2$.

Further preferred is a compound according Formula (4) wherein R^6 is -$(CH_2)_3$-CH_3.

Further preferred is a compound according Formula (4) wherein R^6 is Cyclopentyl.

Further preferred is a compound according Formula (4) wherein R^6 is -CH_2-Cyclopropyl.

Further preferred is a compound according Formula (4) wherein R^6 is 3-bromobenzyl.

Further preferred is a compound according Formula (4) wherein R^6 is 4-bromobenzyl.

Further preferred is a compound according Formula (4) wherein R^6 is 4-chlorobenzyl.

Further preferred is a compound according Formula (4) wherein R^6 is 2,6 dichlorobenzyl.

Further preferred is a compound according Formula (4) wherein R^6 is 4-t-butyl-benzyl.

Further preferred is a compound according Formula (4) wherein R^6 is 4-flurophenyl ethyl.

Further preferred is a compound according Formula (4) wherein R^6 is 3,5 dimethyl-phenyl.

Further preferred is a compound according Formula (4) wherein R^6 is 4-methylbenzoate.

Further preferred is a compound according Formula (4) wherein R^6 is 4-benzoic acid.

Further preferred is a compound according Formula (4) wherein R^6 is 3-benzoic acid.

Further preferred is a compound according Formula (4) wherein R^6 is 3-methoxy phenyl.

Further preferred is a compound according Formula (4) wherein R^6 is 4-methoxy phenyl.

Further preferred is a compound according Formula (4) wherein R^6 is 4-trifluro methyl phenyl.

Further preferred is a compound according Formula **(4)** wherein R^6 is 4-trifluro methyl acetamido phenyl.

Further preferred is a compound according Formula **(4)** wherein R^6 is 4-pyridine.

Further preferred is a compound according Formula **(4)** wherein R^6 is 3-methyl sulphonamido phenyl.

Further preferred is a compound according Formula **(4)** wherein R^6 is 3-fluro-4- methyl sulphonamido phenyl.

Further preferred is a compound according Formula **(4)** wherein R^6 is –$COOCH_2$-CH_3.

Further preferred is a compound according Formula **(4)** wherein R^6 is –CH2--COOH.

Further preferred is a compound according Formula **(4)** wherein R^6 is –CH2—$COOCH_2$-CH_3.

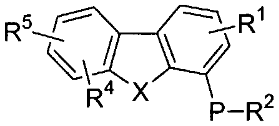
Further preferred is a compound according Formula **(4)** wherein R^6 is –CH2—CONH-CH_3.

Further preferred is a compound according Formula **(4)** wherein R^6 is formyl

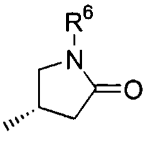
Further preferred is a compound according Formula **(4)** wherein R^6 is 2-hydroxyethyl

Further preferred is a compound according Formula **(4)** wherein R^6 is 2-methanesulphonate-ethyl.

Further preferred is a compound according to Formula **(4a)**



(4a)

wherein R^1 is  and R^2- R^6, X and P as defined in Formula 1.

Further preferred is a compound according Formula **(4a)** wherein X is O.

Further preferred is a compound according Formula **(4a)** wherein P is O.

Further preferred is a compound according Formula **(4a)** wherein R^2 is chosen from the group consisting of alkyl, cycloalkyl and substitute alkyl.

Further preferred is a compound according Formula **(4a)** wherein R^2 is -CH_3.

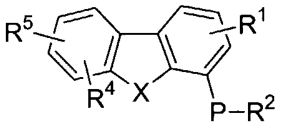
Further preferred is a compound according Formula **(4a)** wherein R^2 is cyclopentyl.

Further preferred is a compound according Formula **(4a)** wherein R^2 is -CHF_2.

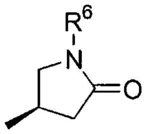
Further preferred is a compound according Formula **(4a)** wherein R^6 is chosen from the group consisting of hydrogen, formyl, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl , substituted or unsubstituted alkylcycloalkyl or substituted or unsubstituted aryl .

Further preferred is a compound according Formula **(4a)** wherein R^6 is H.

Further preferred is a compound according Formula **(4b)**



(4 b)

wherein R^1 is  and R^2- R^7, X and P as defined in Formula 1.

Further preferred is a compound according Formula **(4b)** wherein X is O.

Further preferred is a compound according Formula **(4b)** wherein P is O.

Further preferred is a compound according Formula **(4b)** wherein R^2 is chosen from the group consisting of alkyl, cycloalkyl and substitute alkyl.

Further preferred is a compound according Formula **(4b)** wherein R^2 is -CH_3.

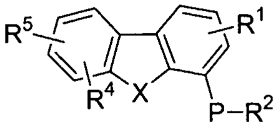
Further preferred is a compound according Formula **(4b)** wherein R^2 is cyclopentyl.

Further preferred is a compound according Formula **(4b)** wherein R^2 is -CHF_2.

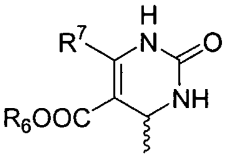
Further preferred is a compound according Formula **(4b)** wherein R^6 is chosen from the group consisting of hydrogen, formyl, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl , substituted or unsubstituted alkylcycloalkyl or substituted or unsubstituted aryl .

Further preferred is a compound according Formula **(4b)** wherein R^6 is H.

Further preferred is a compound according to Formula **(5)**



(5)

wherein R^1 is  and R^2- R^7, X and P as defined in Formula 1.

Further preferred is a compound according Formula **(5)** wherein X is O.

Further preferred is a compound according Formula **(5)** wherein P is O.

Further preferred is a compound according Formula **(5)** wherein R^2 is chosen from the group consisting of alkyl, cycloalkyl and substituted alkyl.

Further preferred is a compound according Formula **(5)** wherein R^2 is -CH_3.

Further preferred is a compound according Formula **(5)** wherein R^2 is cyclopentyl.

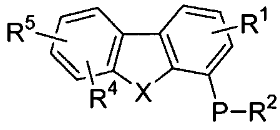
Further preferred is a compound according Formula **(5)** wherein R^2 is -CHF_2.

Further preferred is a compound according Formula **(5)** wherein R^6 is alkyl.

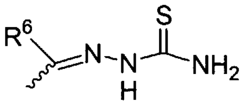
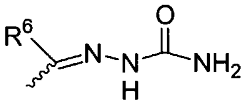
Further preferred is a compound according Formula **(5)** wherein R^7 is alkyl.

Further preferred is a compound according Formula **(5)** wherein R^4 and R^5 are hydrogen.

Further preferred is a compound according of the Formula **(6)**



(6)

wherein R^1 is chosen from the group consisting of  and  and R^2- R^6, X and P as defined in Formula 1.

Further preferred is a compound according Formula **(6)** wherein X is O.

Further preferred is a compound according Formula **(6)** wherein P is O.

Further preferred is a compound according Formula **(6)** wherein R^2 is chosen from the group consisting of hydrogen, alkyl, cycloalkyl and substituted alkyl.

Further preferred is a compound according Formula **(6)** wherein R^2 is -CH_3.

Further preferred is a compound according Formula **(6)** wherein R^2 is cyclopentyl.

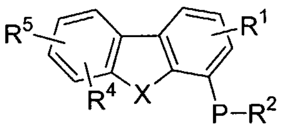
Further preferred is a compound according Formula **(6)** wherein R^2 is -CHF_2.

Further preferred is a compound according Formula **(6)** wherein R^6 is chosen from the group consisting of hydrogen and alkyl.

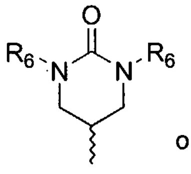
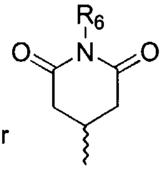
Further preferred is a compound according Formula **(6)** wherein R^6 is -CH_3.

Further preferred is a compound according Formula **(6)** wherein R^5 and R^6 are hydrogen.

Further preferred is a compound according Formula **(7)**



(7)

wherein R^1 is  or  and R^2- R^6, X and P as defined in Formula 1.

Further preferred is a compound according Formula **(7)** wherein X is O.

Further preferred is a compound according Formula **(7)** wherein P is O.

Further preferred is a compound according Formula (7) wherein R^2 is chosen from the group consisting of alkyl and substituted alkyl.

Further preferred is a compound according Formula (7) wherein R^2 is -CH_3.

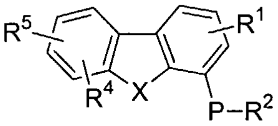
Further preferred is a compound according Formula (7) wherein R^2 is -cyclopentyl.

Further preferred is a compound according Formula (7) wherein R^2 is -CHF_2.

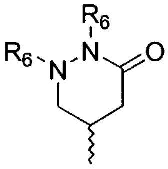
Further preferred is a compound according Formula (7) wherein R^6 is Hydrogen.

Further preferred is a compound according Formula (7) wherein R^4 and R^5 are hydrogen.

Further preferred is a compound according Formula (8)



(8)

wherein R^1 is  and R^2- R^6, X and P as defined in Formula 1.

Further preferred is a compound according Formula (8) wherein X is O.

Further preferred is a compound according Formula (8) wherein P is O.

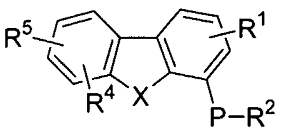
Further preferred is a compound according Formula (8) wherein R^2 is chosen from the group consisting of alkyl.

Further preferred is a compound according Formula (8) wherein R^2 is -CH_3.

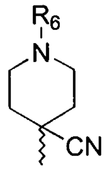
Further preferred is a compound according Formula (8) wherein R^6 is H.

Further preferred is a compound according Formula (8) wherein R^4 and R^5 are hydrogen.

Further preferred is a compound according Formula (9)



(9)

wherein R^1 is  and R^2- R^6, X and P as defined in Formula 1.

Further preferred is a compound according Formula **(9)** wherein X is O.

Further preferred is a compound according Formula **(9)** wherein P is O.

Further preferred is a compound according Formula **(9)** wherein R^2 is chosen from the group consisting of alkyl.

Further preferred is a compound according Formula **(9)** wherein R^2 is -CH_3.

Further preferred is a compound according Formula **(9)** wherein R^4 and R^5 are hydrogen.

Further preferred is a compound according Formula **(9)** wherein R^6 is –CH2-CO-NH-OH.

Further preferred are when the substituents in the 'substituted alkyl', 'substituted alkoxy', 'substituted alkenyl', 'substituted alkynyl', 'substituted cycloalkyl', 'substituted cycloalkylalkyl', 'substituted cyclocalkenyl', 'substituted arylalkyl', 'substituted aryl', 'substituted heterocyclic ring', 'substituted heteroaryl ring', 'substituted heteroarylalkyl', 'substituted heterocyclylalkyl ring', 'substituted amino', 'substituted alkoxycarbonyl', 'substituted cyclic ring', 'substituted alkylcarbonyl', and 'substituted alkylcarbonyloxy', which may be the same or different, are independently selected from hydrogen, hydroxy, halogen, carboxyl, cyano, nitro, oxo (=O), thio(=S), substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted amino, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, 'substituted heterocyclylalkyl ring' substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclic ring, substituted or unsubstiuted guanidine, $-COOR^x$, $-C(O)R^x$, $-C(S)R^x$, $-C(O)NR^xR^y$, $-C(O)ONR^xR^y$, $-NR^xCONR^yR^z$, $-N(R^x)SOR^y$, $-N(R^x)SO_2R^y$, $-(=N-N(R^x)R^y)$, $-NR^xC(O)OR^y$, $-NR^xR^y$, -

$NR^xC(O)R^y$-, $-NR^xC(S)R^y$ $-NR^xC(S)NR^yR^z$, $-SONR^xR^y$-, $-SO_2NR^xR^y$-, $-OR^x$, $-OR^xC(O)NR^yR^z$, $-OR^xC(O)OR^y$-, $-OC(O)R^x$, $-OC(O)NR^xR^y$, $-R^xNR^yC(O)R^z$, $-R^xOR^y$, $-R^xC(O)OR^y$, $-R^xC(O)NR^yR^z$, $-R^xC(O)R^x$, $-R^xOC(O)R^y$, $-SR^x$, $-SOR^x$, $-SO_2R^x$, $-ONO_2$, wherein R^x, R^y and R^z in each of the above groups are independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted. arylalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted amino, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted heterocyclylalkyl ring, substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclic ring.

The present invention also relates to a process for the preparation of the novel heterocyclic compounds of the present invention as described herein.

The compounds of formula **(1)** down regulate or inhibit the production of TNF-α as they are PDE4 inhibitors and are useful in the treatment of allergic and inflammatory diseases including asthma, chronic bronchitis, atopic dermatitis, urticaria, allergic rhinitis, allergic conjunctivitis, vernal conjuctivitis, eosinophilic granuloma, psoriasis, rheumatoid arthritis, septic shock, diabetes, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and reperfusion injury of the brain, chronic glomerulonephritis, endotoxic shock and adult respiratory distress syndrome. The compounds of the present invention are particularly useful for the treatment of asthma and chronic obstructive pulmonary disease (COPD).

DETAILED DESCRIPTION OF THE INVENTION

The term 'alkyl' refers to a straight or branched hydrocarbon chain radical containing solely of carbon and hydrogen atoms, containing no unsaturation, having from one to eight carbon atoms, and which is attached to the rest of the molecule by a single bond, e.g., methyl, ethyl, n-propyl, 1-methylethyl (isopropyl), n-butyl, n-pentyl, 1,1-dimethylethyl (t-butyl), and the like.

The term "alkenyl " refers to an aliphatic hydrocarbon group containing a carbon-carbon double bond and which may be a straight or branched chain having 2 to about 10 carbon atoms, e.g., ethenyl, 1-propenyl, 2-propenyl (allyl), iso-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl and the like.

The term “alkynyl” refers to a straight or branched chain hydrocarbyl radical having at least one carbon-carbon triple bond, and having in the range of 2 up to about 12 carbon atoms (with radicals having in the range of 2 up to about 10 carbon atoms presently being preferred), e.g., ethynyl, propynyl, butnyl and the like.

The term “alkoxy” denotes an alkyl group as defined above attached via an oxygen linkage to the rest of the molecule. Representative examples of alkoxy groups are –OCH_3, -OC_2H_5 and the like

The term “cycloalkyl” denotes a non-aromatic mono or multicyclic ring system of 3 to about 12 carbon atoms such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl. Non-limiting examples of multicyclic cycloalkyl groups include perhydronapththyl, adamantyl and norbornyl groups bridged cyclic group or sprirobicyclic groups, e.g., sprio (4,4) non-2-yl.

The term “cycloalkylalkyl” refers to a cyclic ring-containing radical containing in the range of 3 up to about 8 carbon atoms directly attached to an alkyl group which is then attached to the main structure at any carbon atom in the alkyl group that results in the creation of a stable structure such as cyclopropylmethyl, cyclobuylethyl, cyclopentylethyl, and the like.

The term “cycloalkenyl” refers to a cyclic ring-containing radical containing in the range of 3 up to about 8 carbon atoms with at least one carbon-carbon double bond such as cyclopropenyl, cyclobutenyl, cyclopentenyl and the like.

The term “aryl” refers to an aromatic radical having in the range of 6 up to 14 carbon atoms such as phenyl, naphthyl, tetrahydronapthyl, indanyl, biphenyl and the like.

The term “arylalkyl” refers to an aryl group as defined above directly bonded to an alkyl group as defined above, e.g.,-$CH_2C_6H_5$, -$C_2H_5C_6H_5$ and the like.

The term “heterocyclic ring” refers to a stable 3- to 15 membered ring radical which consists of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, phosphorus, oxygen and sulfur. For purpose of this invention, the heterocyclic ring radical may be a monocyclic, bicyclic or tricyclic ring system, which may include fused, bridged or spiro ring systems, and the nitrogen, phosphorus, carbon, oxygen or sulfur atoms in the heterocyclic ring radical may be optionally oxidized to various oxidation states. In addition, the nitrogen atom may be optionally quaternized; and the ring radical may be partially or fully saturated or aromatic. Examples of such heterocyclic ring radicals include, but are not limited to, azetidinyl, acridinyl, benzodioxolyl, benzodioxanyl, benzofurnyl, carbazolyl, cinnolinyl, dioxolanyl, indolizinyl, naphthyridinyl, perhydroazepinyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pyridyl pteridinyl, purinyl, quinazolinyl, quinoxalinyl, quinolinyl, isoquinolinyl, tetrazoyl, imidazolyl, tetrahydroisouinolyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxoazepinyl, azepinyl, pyrrolyl, 4-piperidonyl, pyrrolidinyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolinyl, oxasolidinyl, triazolyl, indanyl, isoxazolyl, isoxasolidinyl, morpholinyl, thiazolyl, thiazolinyl, thiazolidinyl, isothiazolyl, quinuclidinyl, isothiazolidinyl, indolyl, isoindolyl, indolinyl, isoindolinyl, octahydroindolyl, octahydroisoindolyl, quinolyl, isoquinolyl, decahydroisoquinolyl, benzimidazolyl, thiadiazolyl, benzopyranyl, benzothiazolyl, benzooxazolyl, furyl, tetrahydrofurtyl, tetrahydropyranyl, thienyl, benzothienyl, thiamorpholinyl, thiamorpholinyl sulfoxide thiamorpholinyl sulfone, dioxaphospholanyl , oxadiazolyl , chromanyl, isochromanyl and the like.

The term “heteroaryl” refers to a heterocyclic ring radical as defined above. The heteroaryl ring radical may be attached to the main structure at any heteroatom or carbon atom that results in the creation of a stable structure.

The term “heteroarylalkyl” refers to a heteroaryl ring radical as defined above directly bonded to an alkyl group. The heteroarylalkyl radical may be attached to the main structure at any carbon atom from alkyl group that results in the creation of a stable structure.

The term “heterocyclyl” refers to a heterocylic ring radical as defined above. The heterocylyl ring radical may be attached to the main structure at any heteroatom or carbon atom that results in the creation of a stable structure.

The term “heterocyclylalkyl” refers to a heterocylic ring radical as defined above directly bonded to an alkyl group. The heterocyclylalkyl radical may be attached to the main structure at carbon atom in the alkyl group that results in the creation of a stable structure.

The term “carbocyclic” refers to a cyclic group containing 3-10 carbon atoms.

The term “protecting group” refers to a protecting group, such as CBZ or BOC and the like.

The term “halogen” refers to radicals of fluorine, chlorine, bromine, and iodine.

The substituents in the ‘substituted alkyl’, ‘substituted alkoxy’, ‘substituted alkenyl’, ‘substituted alkynyl’, ‘substituted cycloalkyl’, 'substituted cycloalkylalkyl', 'substituted cyclocalkenyl', ‘substituted arylalkyl’, ‘substituted aryl’, ‘substituted heterocyclic ring’, ‘substituted heteroaryl ring,’ ‘substituted heteroarylalkyl’, ‘substituted heterocyclylalkyl ring’, ‘substituted amino’, ‘substituted alkoxycarbonyl’, ‘substituted alkylcarbonyl’, ‘substituted alkylcarbonyloxy’ and ‘substituted carboxylic acid’ may be the same or different and may be selected from hydrogen, hydroxy, halogen, carboxyl, cyano, amino, nitro, oxo (=O), thio (=S), formyl, alkyl, alkoxy, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, aryl, heteroaryl, heterocyclic ring, –COOR^x, -C(O)R^x, -C(S)R^x, -C(O)NR^{x}R^y, -C(O)ONR^{x}R^y, -NR^{x}CONR^{y}R^z, -N(R^x)SOR^y, -N(R^x)SO$_2$R^y, -N(R^x)CO-, -(=N-N(R^x)R^y), -N(R^x)R^{y}CO-, -NR^{x}R^{y}C(O)OR^z, -NR^{x}R^y, -NR^{x}C(O)R^y-, -NR^{x}C(S)R^y, -NR^{x}C(S)NR^{y}R^z, -N(R^x)SO-, -NR^{x}SO$_2$-, -OR^x, -OR^{x}C(O)NR^{y}R^z, -OR^{x}C(O)OR^y-, -OC(O)R^x, -OC(O)NR^{x}R^y, -R^{x}NR^{y}R^z, -R^{x}R^{y}R^z, -R^{x}CF$_3$, -R^{x}NR^{y}C(O)R^z, -R^{x}OR^y, -R^{x}C(O)OR^y, -R^{x}C(O)NR^{y}R^z, -R^{x}CS, -R^{x}C(O)R^x, -R^{x}OC(O)R^y, -SR^x, -SOR^x, -SO$_2$R^x, or -ONO$_2$ (wherein R^x, R^y and R^z in each of the above groups are independently hydrogen, substituted or unsubstituted alkyl, haloalkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted aryl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocyclic ring, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroaryl or substituted or unsubstituted heteroarylalkyl). According to one embodiment, the substituents in the aforementioned “substituted” groups cannot be further substituted. For example, when the substituent on “substituted alkyl” is “substituted aryl”, the substituent on “substituted aryl” cannot be “substituted alkenyl”.

Pharmaceutically acceptable salts forming part of this invention include salts derived from inorganic bases such as Li, Na, K, Ca, Mg, Fe, Cu, Zn, Mn; salts of organic bases such as N,N'-diacetylethylenediamine, betaine, caffeine, 2-diethylaminoethanol, 2-dimethylaminoethanol, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, hydrabamine, isopropylamine, methylglucamine, morpholine, piperazine, piperidine, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, diethanolamine, meglumine, ethylenediamine, N,N'-

diphenylethylenediamine, N,N'-dibenzylethylenediamine, N-benzyl phenylethylamine, choline, choline hydroxide, dicyclohexylamine, metformin, benzylamine, phenylethylamine, dialkylamine, trialkylamine, thiamine, aminopyrimidine, aminopyridine, purine, spermidine, and the like; salts of chiral bases like alkylphenylamine, glycinol, phenyl glycinol and the like, salts of natural amino acids such as glycine, alanine, valine, leucine, isoleucine, norleucine, tyrosine, cystine, cysteine, methionine, proline, hydroxy proline, histidine, omithine, lysine, arginine, serine, threonine, and phenylalanine; salts of unnatural amino acids such as D-isomers or substituted amino acids; salts of guanidine or substituted guanidine wherein the substituents are selected from nitro, amino, alkyl, alkenyl, alkynyl, ammonium and substituted ammonium salts; and aluminum salts. Salts may include acid addition salts where appropriate which are, sulphates, nitrates, phosphates, perchlorates, borates, hydrohalides, acetates, tartrates, fumarates, maleates, citrates, succinates, palmoates, methanesulphonates, benzoates, salicylates, hydroxynaphthoates, benzenesulfonates, ascorbates, glycerophosphates, ketoglutarates and the like. Pharmaceutically acceptable solvates may be hydrates or comprise other solvents of crystallization such as alcohols.

Another embodiment of the invention is a method of treating an inflammatory disease, disorder or condition characterized by or associated with an undesirable inflammatory immune response or a disease or condition induced by or associated with an excessive secretion of TNF-α and PDE-4 in a subject. The method includes administering to the subject a therapeutically effective amount of a compound according to Formula (1).

Another embodiment of the invention is a method of treating an inflammatory condition or immune disorder in a subject in need thereof by administering to the subject a therapeutically effective amount of a compound according to Formula (1).

Preferred inflammatory conditions and immune disorders are chosen from the group consisting of asthma, bronchial asthma, chronic obstructive pulmonary disease, allergic rhinitis, eosinophilic granuloma, nephritis, rheumatoid arthritis, cystic fibrosis, chronic bronchitis, multiple sclerosis, Crohns disease, psoraisis, uticaria, adult vernal cojunctivitis, respiratory distress syndrome, rhematoid spondylitis, osteoarthritis, gouty arthritis, uteltis, allergic conjunctivitis, inflammatory bowel conditions, ulcerative coalitis, eczema, atopic dermatitis and chronic inflammation. Further preferred are allergic inflammatory conditions.

Further preferred are inflammatory conditions and immune disorders selected from the group consisting of inflammatory conditions or immune disorders of the lungs, joints, eyes, bowels, skin and heart.

Further preferred are inflammatory conditions chosen from the group consisting of bronchial asthma, nepritis, and allergic rhinitis.

Another embodiment of the invention is a method for abating inflammation in an affected organ or tissue including delivering to the organ or tissue a therapeutically effective amount of a compound represented by a compound according to Formula 1.

Another embodiment of the invention is a method of treating a disease of the central nervous system in a subject in need thereof which comprises administering to said subject a therapeutically effective amount of a compound according to Formula 1.

Preferred diseases of the central nervous system are chosen from the group consisting of depression, amnesia, dementia, Alzheimers disease, cardiac failure, shock and cerebrovascular disease.

Another embodiment of the invention is a method of treating insulin resistant diabetes in a subject in need thereof which comprises administering to said subject a therapeutically effective amount of a compound according to Formula 1.

"Treating" or "treatment" of a state, disorder or condition includes:

(1) preventing or delaying the appearance of clinical symptoms of the state, disorder or condition developing in a mammal that may be afflicted with or predisposed to the state, disorder or condition but does not yet experience or display clinical or subclinical symptoms of the state, disorder or condition,

(2) inhibiting the state, disorder or condition, i.e., arresting or reducing the development of the disease or at least one clinical or subclinical symptom thereof, or

(3) relieving the disease, i.e., causing regression of the state, disorder or condition or at least one of its clinical or subclinical symptoms.

The benefit to a subject to be treated is either statistically significant or at least perceptible to the patient or to the physician

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

The four classic symptoms of acute inflammation are redness, elevated temperature, swelling, and pain in the affected area, and loss of function of the affected organ.

Symptoms and signs of inflammation associated with specific conditions include:

- rheumatoid arthritis- pain, swelling, warmth and tenderness of the involved joints; generalized and morning stiffness;
- insulin-dependent diabetes mellitus- insulitis; this condition can lead to a variety of complications with an inflammatory component, including: retinopathy, neuropathy, nephropathy; coronary artery disease, peripheral vascular disease, and cerebrovascular disease;
- autoimmune thyroiditis- weakness, constipation, shortness of breath, puffiness of the face, hands and feet, peripheral edema, bradycardia;
- multiple sclerosis- spasticity, blurry vision, vertigo, limb weakness, paresthesias;
- uveoretinitis- decreased night vision, loss of peripheral vision;
- lupus erythematosus- joint pain, rash, photosensitivity, fever, muscle pain, puffiness of the hands and feet, abnormal urinalysis (hematuria, cylinduria, proteinuria), glomerulonephritis, cognitive dysfunction, vessel thrombosis, pericarditis;
- scleroderma- Raynaud's disease; swelling of the hands, arms, legs and face; skin thickening; pain, swelling and stiffness of the fingers and knees, gastrointestinal dysfunction, restrictive lung disease; pericarditis,; renal failure;
- other arthritic conditions having an inflammatory component such as rheumatoid spondylitis, osteoarthritis, septic arthritis and polyarthritis- fever, pain, swelling, tenderness;
- other inflammatory brain disorders, such as meningitis, Alzheimer's disease, AIDS dementia encephalitis- photophobia, cognitive dysfunction, memory loss;
- other inflammatory eye inflammations, such as retinitis- decreased visual acuity;
- inflammatory skin disorders, such as , eczema, other dermatites (e.g., atopic, contact), psoriasis, burns induced by UV radiation (sun rays and similar UV sources)- erythema, pain, scaling, swelling, tenderness;
- inflammatory bowel disease, such as Crohn's disease, ulcerative colitis- pain, diarrhea, constipation, rectal bleeding, fever, arthritis;
- asthma- shortness of breath, wheezing;
- other allergy disorders, such as allergic rhinitis- sneezing, itching, runny nose

- conditions associated with acute trauma such as cerebral injury following stroke- sensory loss, motor loss, cognitive loss;
- heart tissue injury due to myocardial ischemia- pain, shortness of breath;
- lung injury such as that which occurs in adult respiratory distress syndrome- shortness of breath, hyperventilation, decreased oxygenation, pulmonary infiltrates;
- inflammation accompanying infection, such as sepsis, septic shock, toxic shock syndrome- fever, respiratory failure, tachycardia, hypotension, leukocytosis;
- other inflammatory conditions associated with particular organs or tissues, such as nephritis (e.g., glomerulonephritis)-oliguria, abnormal urinalysis;
- inflamed appendix- fever, pain, tenderness, leukocytosis;
- gout- pain, tenderness, swelling and erythema of the involved joint, elevated serum and/or urinary uric acid;
- inflamed gall bladder- abdominal pain and tenderness, fever, nausea, leukocytosis;
- chronic obstructive pulmonary disease- shortness of breath, wheezing;
- congestive heart failure- shortness of breath, rales, peripheral edema;
- Type II diabetes- end organ complications including cardiovascular, ocular, renal, and peripheral vascular disease ,lung fibrosis- hyperventilation, shortness of breath, decreased oxygenation;
- vascular disease, such as atherosclerosis and restenosis- pain, loss of sensation, diminished pulses, loss of function and alloimmunity leading to transplant rejection- pain, tenderness, fever.

Subclinical symptoms include without limitation diagnostic markers for inflammation the appearance of which may precede the manifestation of clinical symptoms. One class of subclinical symptoms is immunological symptoms, such as the invasion or accumulation in an organ or tissue of proinflammatory lymphoid cells or the presence locally or peripherally of activated pro-inflammatory lymphoid cells recognizing a pathogen or an antigen specific to the organ or tissue. Activation of lymphoid cells can be measured by techniques known in the art.

"Delivering" a therapeutically effective amount of an active ingredient to a particular location within a host means causing a therapeutically effective blood concentration of the active ingredient at the particular location. This can be accomplished , e.g., by local or by systemic administration of the active ingredient to the host.

"A subject" or "a patient" or "a host" refers to mammalian animals, preferably human.

Some of the representative compounds according to the present invention are specified below but should not construe to be limited thereto;

1. 3-(4-methoxydibenzo [*b,d*]furan-1-yl)-1,6-dihydro-6-pyridazinone
2. 3 - (4-methoxydibenzo [*b,d*] furan-1-yl)-1-methyl-1,6- dihydro-6-pyridazinone
3. 1-Benzyl -3-(4-methoxydibenzo [*b,d*] furan-1-yl)-1,6-dihydro-6-pyridazinone
4. 6-(4-methoxydibenzo[*b,d*]furan-1-yl)-4,5-dihydropyridazin-3(2*H*)-one
5. (±) Ethyl 4- (4- Cyclopentyloxydibenzo[*b,d* furan-1-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate
6. (±) 4-(4-methoxydibenzo[*b,d*]furan-1-yl)-2-azolanone
7. 4-methoxydibenzo [*b,d*]furan-1-carbaldehyde semicarbazone
8. 4-methoxydibenzo [*b,d*]furan-1-carbaldehyde thiosemicarbazone
9. (1*Z*)-1-(4-methoxydibenzo[*b,d*]furan-1-yl)ethan-1-one semicarbazone
10. (1*Z*)-1-(4-hydroxydibenzo [*b,d*]furan-1-yl)ethan-1-one semicarbazone
11. (1*Z*)-1-(4-Difluoromethoxydibenzo [*b,d*]furan-1-yl)ethan-1-one semicarbazone
12. 4-Difluoromethoxydibenzo [*b,d*]furan-1-carbaldehyde semicarbazone
13. 4-Difluoromethoxydibenzo [*b,d*]furan-1-carbaldehyde thiosemicarbazone
14. 4-Cyclopentyloxydibenzo [*b,d*]furan-1-carbaldehyde semicarbazone
15. 4-Cyclopentyloxydibenzo [*b,d*]furan-1-carbaldehyde thiosemicarbazone
16. 4-Methoxydibenzo [*b,d*]furan-3-carbaldehyde semicarbazone
17. 4-Methoxydibenzo [*b,d*]furan-3-carbaldehyde thiosemicarbazone
18. (±)1-methyl-4-(4-Methoxydibenzo [*b,d*]furan-1-yl)-2-azolanone
19. (±) 1-(3-bromobenzyl)-4-(4-methoxydibenzo [*b, d*] furan-1-yl)-2-azolanone
20. (±) 1-(4-tert-butyl benzyl)-4-(4-methoxydibenzo [*b, d*] furan-1-yl)-2-azolanone
21. (±) 1-(4-bromobenzyl)-4-(4-methoxydibenzo [*b, d*] furan-1-yl)-2-azolanone
22. (±) 1-(4-chlorobenzyl)-4-(4-methoxydibenzo [*b, d*] furan-1-yl)-2-azolanone
23. (±) 1-(2, 6-dichlorobenzyl)-4-(4-methoxydibenzo [*b, d*] furan-1-yl)-2-azolanone
24. (±) 1-ethyl-4-(4-methoxydibenzo [*b, d*] furan-1-yl)-2-azolanone
25. (±) 1-isopropyl-4-(4-methoxydibenzo [*b, d*] furan-1-yl)-2-azolanone
26. (±) 1-butyl-4-(4-methoxydibenzo [*b, d*] furan-1-yl)-2-azolanone

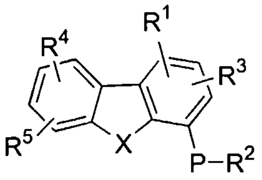
27. (±) 1-cyclopentyl-4-(4-methoxydibenzo [*b, d*] furan-1-yl)-2-azolanone
28. (±) 1-cyclopropylmethyl-4-(4-methoxydibenzo [*b, d*] furan-1-yl)-2-azolanone
29. (±) 1-(4-fluorophenethyl)-4-(1-methoxy-9H-4-fluorenyl)-2-azolanone
30. (±) Ethyl 2-[4-(4-Methoxydibenzo [*b,d*]furan-1-yl)-2-oxo-1-azolanyl]acetate
31. (±) 2-[4-(4-Methoxydibenzo [*b,d*]furan-1-yl)-2-oxo-1-azolanyl]acetic acid
32. (±) N1-methyl-2-[4-(4-Methoxydibenzo [*b,d*]furan-1-yl)-2-oxo-1-azolanyl] acetamide
33. (±) 4-(4-methoxydibenzo [*b, d*] furan-1-yl)-2-oxo-1-azolanecarbaldehyde
34. (±) Ethyl-4-(4-methoxydibenzo [*b, d*] furan-1-yl)-2-oxo-1-azolanecarboxylate
35. (±) 1-(2-hydroxyethyl)-4-(4-methoxydibenzo [*b, d*] furan-1-yl)-2-azolanone
36. (±) 2-[4-(4-methoxydibenzo [*b, d*] furan-1-yl)-2-oxo-1-azolanyl] ethyl methanesulfonate
37. (±)1-(3,5-dimethylphenyl)-4-(4-methoxydibenzo[*b,d*]furan-1-yl) pyrrolidine-2-one
38. (±)Methyl-4-[4-(4-methoxydibenzo[*b,d*]furan-1-yl)-2-pyrrolidinonyl] benzoate
39. (±)N-{3-[4-(4-methoxydibenzo[*b,d*]furan-1-yl)-2-oxo-1-azolanyl]phenyl}methanesufonamide
40. (±)4-(4-methoxydibenzo[*b,d*]furan-1-yl)-1-(3-methoxyphenyl)-2-azolanone
41. (±) 4-(4-methoxydibenzo[*b,d*]furan-1-yl)-1-(4-trifluoromethylphenyl)-2-azolanone
42. (±) N-{3-fluoro-4-[4-(4-methoxydibenzo[*b,d*]furan-1-yl)-2-oxo-1-azolanyl]phenyl}methanesufonamide
43. (±) Methyl-3-[4-(4-methoxydibenzo[*b,d*]furan-1-yl)-2-pyrrolidinonyl] benzoate
44. (±)4-(4-methoxydibenzo[*b,d*]furan-1-yl)-1-(4-methoxyphenyl)-2-azolanone
45. (±)4-(4-methoxydibenzo[*b,d*]furan-1-yl)-1-(4-trifluoromethylacetamidophenyl)-2-azolanone
46. (±)4-(4-methoxydibenzo[*b,d*]furan-1-yl)-1-(4-pyridyl)-2-azolanone
47. (±)3-[4-(4-methoxydibenzo[*b,d*]furan-1-yl)-2-oxo-1-azolanyl] benzoic acid
48. (±)4-[4-(4-methoxydibenzo[*b,d*]furan-1-yl)-2-oxo-1-azolanyl] benzoic acid
49. (±) 4-(4-difluoromethoxy-8-morpholinosulfonyldibenzo[*b,d*]furan-1-yl)-2-azolanone
50. (±) 4-[4-difluoromethoxy-8-(4-methylpiperazino)sulfonyldibenzo[*b,d*]furan-1-yl]-2-azolanone
51. (±)*N*-[6-methoxy-9-(5-oxopyrrolidin-3-yl)dibenzo[*b,d*]furan-2-yl]acetamide
52. (±) *N*-[6-methoxy-9-(5-oxopyrrolidin-3-yl) dibenzo [*b,d*]furan-2-yl]methane sulfonamide

53. (±) 2-(4-methylpiperazinocarboxamido)-6-methoxy-9-(5-oxopyrrolidin-3-yl) dibenzo[*b*,*d*]furan
54. (+) 4-[4-methoxy-8-(methylamino)dibenzo[*b*, *d*]furan-1-yl]pyrrolidin-2-one
55. (–) 4-[4-methoxy-8-(methylamino) dibenzo[*b*, *d*]furan-1-yl]pyrrolidin-2-one
56. (+) 4-(4-methoxydibenzo [b,d] furan-1-yl)-2-azolanone
57. (-)4-(4-methoxydibenzo [b,d] furan-1-yl)-2-azolanone
58. (+) 4-(4-difluoromethoxydibenzo [b,d] furan-1-yl)-2-azolanone
59. (-)4-(4-difluoromethoxydibenzo [b,d] furan-1-yl)-2-azolanone
60. (±) 5-(4-methoxydibenzo [*b*,*d*]furan-1-yl) hexahydro-3-pyridazinone
61. 5-[4-(methoxy)dibenzo[*b*, *d*]furan-1-yl]tetrahydropyrimidin-2(1*H*)-one
62. 5-[4-(difluoromethoxy)dibenzo[*b*, *d*]furan-1-yl]tetrahydropyrimidin-2(1*H*)-one
63. 4-[4-(difluoromethoxy)dibenzo[*b*, *d*]furan-1-yl]piperidine-2, 6-dione
64. 6-(3-bromo-4-methoxydibenzo[*b*,*d*]furan-1-yl)pyridazin-3(2*H*)-one:
65. N-Hydroxy-2-[4-cyano-4-(4-methoxydibenzo[b,d]furan-1-yl)piperidino] acetamide

and pharmaceutically acceptable salts of the preceding.

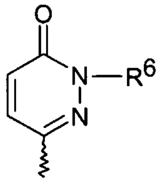
The compounds according to the present invention may be prepared by the following processes. The symbols P, X, R^1, R^2, R^3, R^4, R^5 when used in the formulae below are to be understood to present those groups described above in relation to formula **(1)** unless otherwise indicated.

The present invention discloses a process for the preparation of compounds of general formula **(1)**.



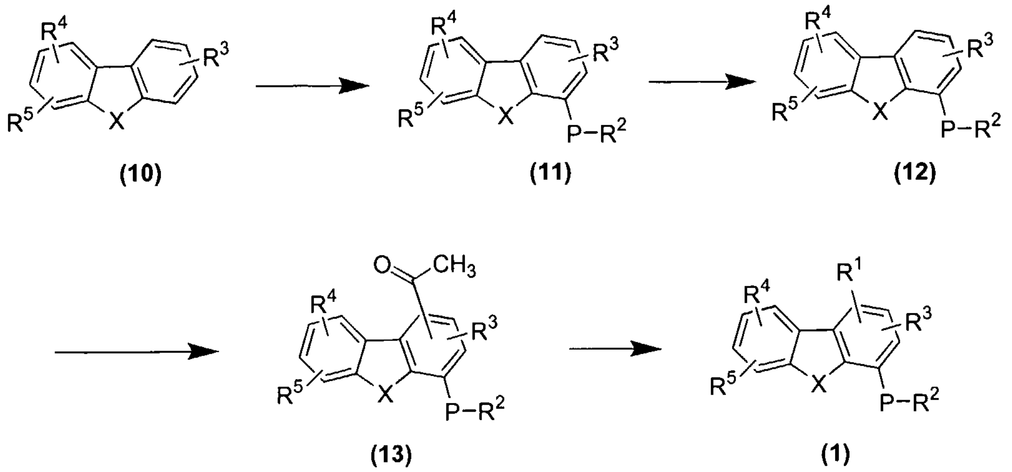
(1)

In one embodiment, the compounds of general formula **(1)** wherein P, X, R^2, R^3, R^4, R^5, R^6 are the same as described in the general description and R^1 is



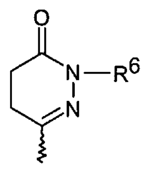
can be synthesized by using the general process described in synthetic scheme **I**.

Synthetic Scheme 1:



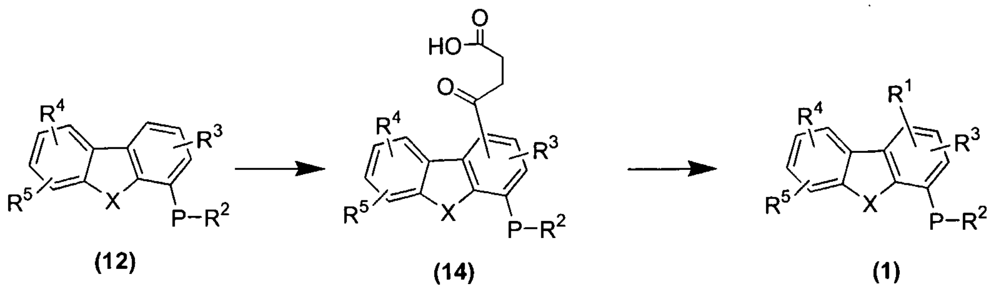
In the above mentioned scheme a compound of general formula **(11)** (wherein R^2 is H and P is O) is obtained by reacting a substituted dibenzofuran **(10)** synthesized from the commercially available dibenzofuran under basic conditions using bases such as *n*- butyl lithium in presence of an oxygen source which can be air, oxygen or peroxide, etc. The intermediate of general formula **(11)** (wherein R^2 is H and P is O)can be alkylated using an alkylating agent such as alkyl halide, alkyl sulphate under basic conditions (potassium salts in DMF or DMSO, NaH in DMF or DMSO) or potassium or sodium salts in presence of water to yield the alkylated product **(12)** (wherein R^2 is other than H). The carbonyl group is introduced by carrying out the reactions such as acylation to yield a carbonyl compound **(13)**. The acylating agent used can be acyl halide or an anhydride in presence of Lewis acid catalyst like $AlCl_3$, $TiCl_4$, $SnCl_4$, $FeCl_3$, and $ZnCl_2$. The intermediate of general formula **(13)** is then reacted with glyoxylic acid monohydrate or a glyoxylic acid ester followed by basification using ammonium hydroxide and further reaction with alkyl / aryl hydrazine yields compound of general formula **(1)**.

In another embodiment, the compounds of general formula **(1)** wherein P, X, R^2, R^3, R^4, R^5, R^6 are the same as described in the general description and R^1 is



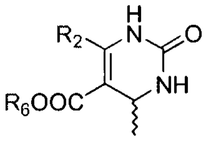
can be synthesized by using the general process described in synthetic scheme **II**

Synthetic Scheme II:



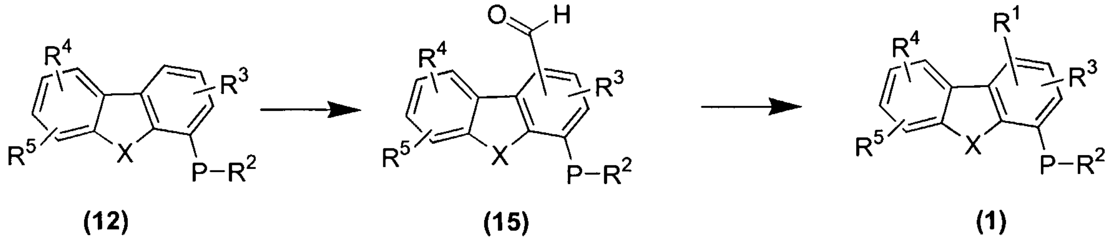
In the above mentioned scheme the compound of general formula **(12)** is acylated under Friedel- Crafts acylation conditions wherein the acylating agent is preferably succinic anhydride and the catalyst can be $AlCl_3$, $FeCl_3$, $ZnCl_2$, $SnCl_4$ and $TiCl_4$. The Oxobutanoic acid **(14)** is cyclized on reaction with substituted or unsubstituted hydrazine to obtain a compound of general formula **(1)**.

In another embodiment, the compounds of general formula **(1)** wherein P, X, R^2, R^3, R^4, R^5 are the same as described in the general description and $R^1$is



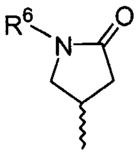
can be synthesized by using the general process described in synthetic scheme **III**.

Synthetic Scheme III:



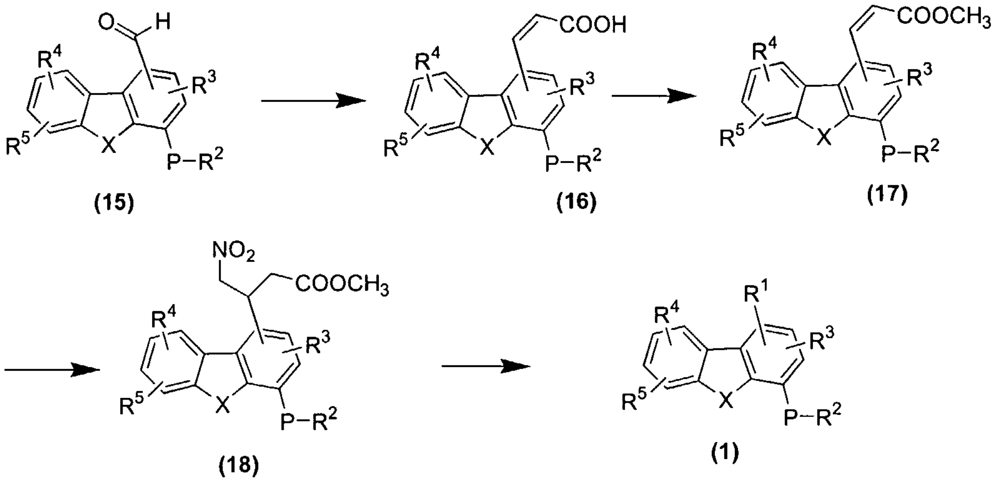
In the above mentioned scheme a compound of general formula **(15)** is obtained carrying out formylation of a intermediate compound **(12)** using dichloromethyl methyl ether in presence of Lewis acid catalyst like $AlCl_3$, $TiCl_4$, $SnCl_4$, $FeCl_3$, and $ZnCl_2$. The intermediate of general formula **(15)** is then reacted with appropriate β-ketoester like ethyl acetoacetate, urea in presence of an acid catalyst which may include $FeCl_3.6H_2O$, $NiCl_2.6H_2O$, $ZnCl_2$ to yield compound of general formula **(1)**.

In yet another embodiment, the compounds of general formula **(1)** wherein P, X, R^2, R^3, R^4, R^5 are the same as described in the general description and R^1 is



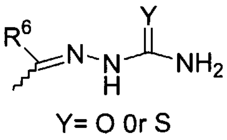
wherein R^6 is hydrogen can be synthesized by using the general process described in synthetic scheme **IV**.

Synthetic Scheme IV:



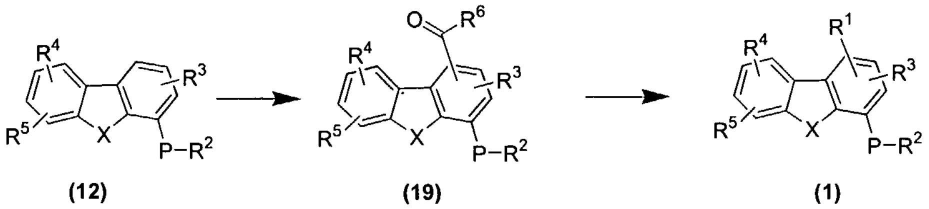
In the above mentioned scheme, an intermediate of general formula **(15)** is condensed with an active methylene compound preferably malonic acid to give the intermediate of general formula **(16)**. The Alkylation of the **(16)** is carried out under acidic conditions (alcohol, acid) or in presence of an alkyl halide under basic conditions to yield an ester of general formula **(17)**. The intermediate of general formula **(17)** is reacted with nitro methane in the presence of a base preferably 1,1,3,3-tetramethylguanidine to yield the intermediate of general formula **(18)**. The cyclization of **(18)** is carried out under reductive conditions which may include H_2/ Pd on carbon, Raney Ni / MeOH, Raney Ni / hydrazine hydrate, Zn/ Acetic acid, Fe/ HCl to obtain the compound of general formula **(1)** wherein R^6 is hydrogen. These can be further derivatised using, for example,appropriate substituted or unsubstituted alkyl, aryl, or aralkyl halides (preferably bromides of iodides), chloroformates, isocyanates, sulfonylchlorides, anhydridesin the presence of bases including, but not limited to, sodium hydride or potassium carbonate or triethylamine.

In yet another embodiment, the compounds of general formula **(1)** wherein P, X, R^2, R^3, R^4, R^5, R^6 are the same as described in the general description and R^1 is Preferably R^1 group is selected from



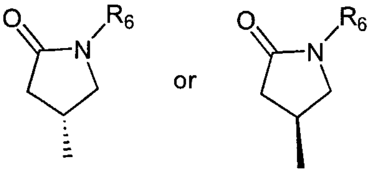
can be synthesized by using the general process described in synthetic scheme **V**.

Synthetic Scheme V:



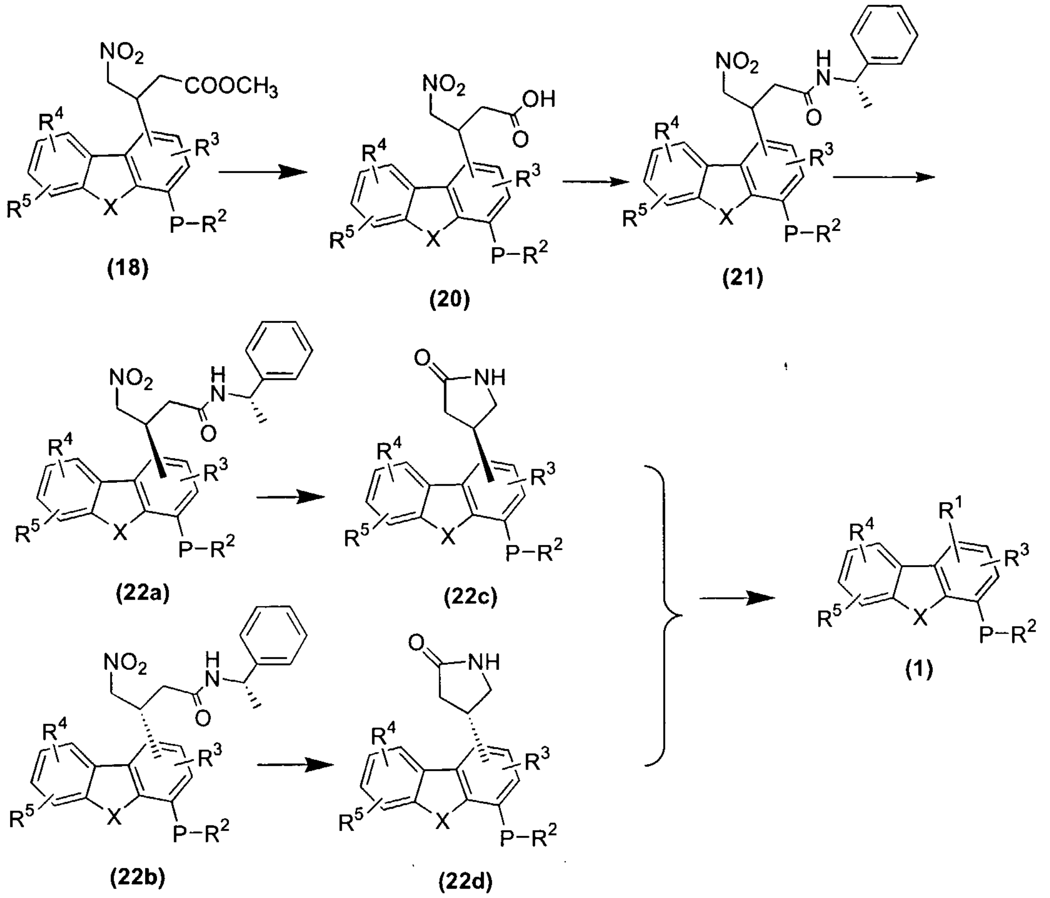
In the above mentioned scheme carbonylation of the intermediate **(12)** is done using the reactions such as acylation and formylation to yield a intermediate compound **(19)**. The acylating agent used can be acyl halide or an anhydride in presence of Lewis acid catalyst like $AlCl_3$, $TiCl_4$, $SnCl_4$, $FeCl_3$, and $ZnCl_2$. The formylating agent used is preferably dichloromethyl methyl ether. The intermediate carbonyl compound on reacting with semicarbazide hydrochloride or thiosemicarbazide in presence of a suitable solvent to obtain the compounds of general formula **(1)**.

In yet another embodiment, the compounds of general formula **(1)** wherein P, X, R^2, R^3, R^4, R^5, R^6 are the same as described in the general description and R^1 is



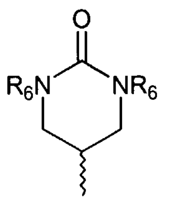
can be synthesized by using the general process described in synthetic scheme **VI**.

Synthetic Scheme VI:

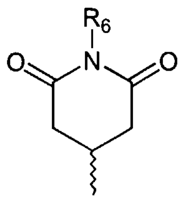


In the above mentioned scheme, an intermediate of general formula **(18)** is hydrolyzed to the acid intermediate **(20)** using aqueous methanolic sodium hydroxide. The acid intermediate **(20)** can be converted to the diasteromeric mixture **(21)** using various basic resolving agents such as (R)-(+)-1-Phenylethylamine, (S)-(+)-1-Phenylethylamine. The diasteromeric mixture **(21)** can be resolved into its respective diastereomers **(22a)** and **(22b)** which could be cyclised under reductive conditions which may include H_2/ Pd on carbon, Raney Ni / MeOH, Raney Ni / hydrazine hydrate, Zn/ Acetic acid, Fe/ HCl to obtain the compound of general formula **(22c)** and **(22d)** respectively. These can be further derivatized using, for example, appropriate alkyl, aralkyl halides (preferably bromides of iodides), chloroformates, isocyanates, sulfonylchlorides, anhydrides in the presence of bases such as sodium hydride or potassium carbonate or triethylamine to obtain the compound of general formula **(1)**.

In yet another embodiment, the compounds of general formula **(1)** wherein P, X, R^2, R^3, R^4, R^5 are the same as described in the general description and R^1 is

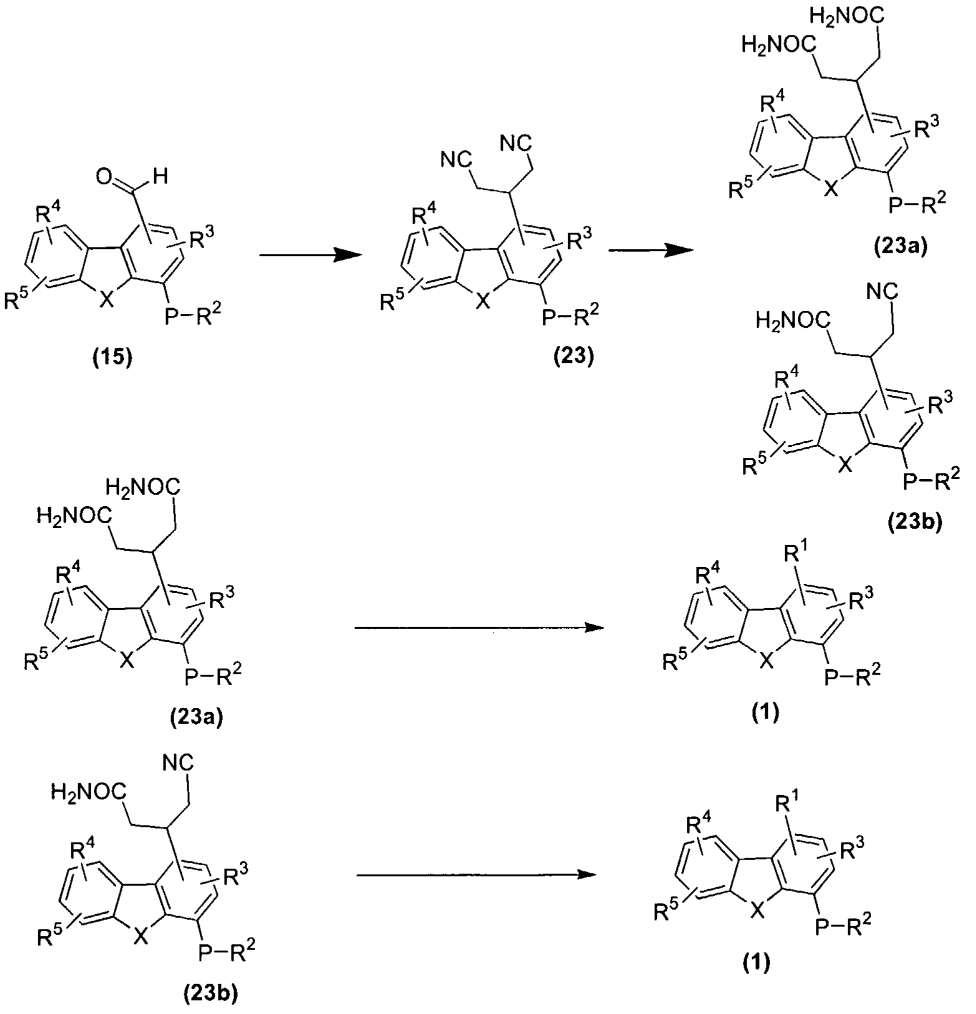


and

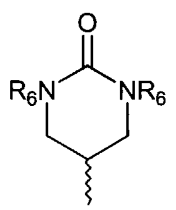


and wherein R^6 is hydrogen can be synthesized by using the general process described in synthetic scheme **VII**.

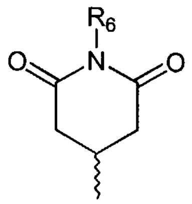
Synthetic Scheme VII:



In the above mentioned scheme, an intermediate of general formula **(23)** can be obtained by reaction of the aldehyde **(15)** with cyanoacetic acid which can be further hydrolysed to yield the intermediate **(23a)** & **(23b)** using alkaline hydrogen peroxide or acids such as sulphuric acid. Both the compound of formula **(23a)** & **(23b)** can then be cyclized to the desired compound of general formula **(1)** wherein R^1 is

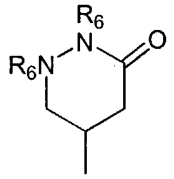


and



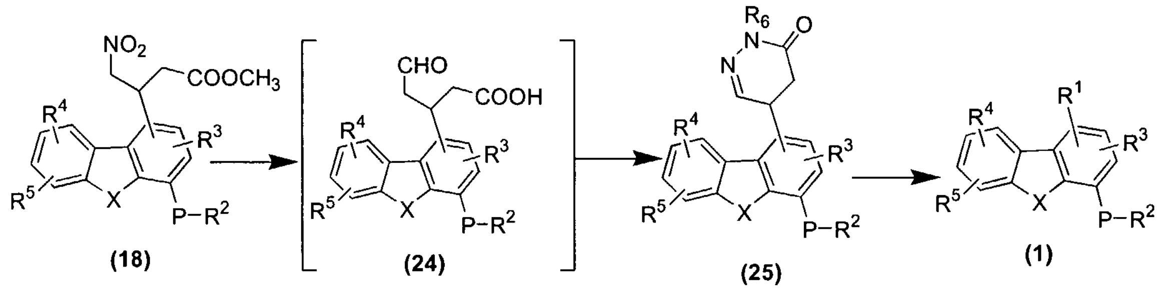
respectively, and R^6 is hydrogen using reagents such as lead tetracetate or bromine in aqueous sodium hydroxide. These can be further derivatized using, for example, appropriate alkyl, aralkyl halides (preferably bromides of iodides), chloroformates, isocyanates, sulfonylchlorides, anhydrides in the presence of bases, including but not limited to, sodium hydride or potassium carbonate or triethylamine.

In yet another embodiment, the compounds of general formula **(1)** wherein P, X, R^2, R^3, R^4, R^5 are the same as described in the general description and R^1 is



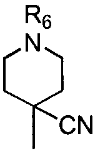
and wherein R^6 is hydrogen can be synthesized by using the general process described in synthetic scheme **VIII.**

Synthetic Scheme VIII:



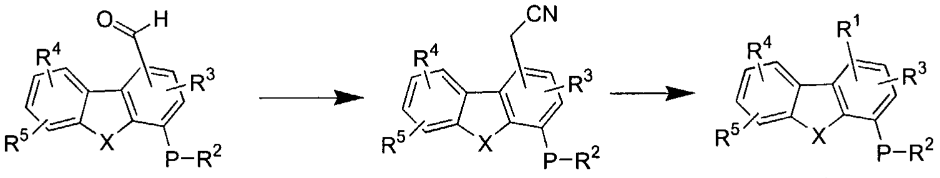
In the above mentioned scheme, an intermediate of general formula **(25)** can be obtained by reaction of the nitrobutanoate **(18)** (initially treated with dilute base such as sodium hydroxide and the like followed by treatment with concentrated sulfuric acid to give a compound of general formula **(24)**). The compound of general formula **(24)** is then reacted with Hydrazine hydrate to afford the compound of general formula **(25)**. The compound of general formula **(25)** can then be reduced to the desired compound of general formula **(1)** wherein R^6 is hydrogen using reagents such as H_2/ Pd on carbon, Raney Ni / MeOH, Raney Ni / hydrazine hydrate and the likes. These can be further derivatized using, for example, appropriate alkyl, aralkyl halides (preferably bromides of iodides), chloroformates, isocyanates, sulfonylchlorides, anhydrides in the presence of bases, including but not limited to, sodium hydride or potassium carbonate or triethylamine.

In yet another embodiment, the compounds of general formula **(1)** wherein P, X, R^2, R^3, R^4, R^5 are the same as described in the general description and R^1 is



and wherein R^6 is hydrogen can be synthesized by using the general process described in synthetic scheme **IX**.

Synthetic Scheme IX:



In the above mentioned scheme, an intermediate of general formula **(26)** can be obtained by reduction of the aldehyde **(15)** to alcohol using sodium borohydride followed by chlorination using thionylchloride and cyanation using sodium cyanide. The cyanomethyl compound of the general formula **(26)** can be converted to the desired piperidines **(1)** wherein R^6 is hydrogen, using N-BOC-N, N-bis (2-chloro ethyl) amine in presence of base such as sodium hydride and the likes followed by deprotection of the BOC group. These piperidines **(1)** can be further derivatized using, for example, appropriate alkyl, aralkyl halides (preferably bromides of iodides), chloroformates, isocyanates, sulfonylchlorides, anhydrides in the presence of bases, including but not limited to, sodium hydride or potassium carbonate or triethylamine.

The desired compounds of the formula **(1)** obtained are then converted into their salts and if desired, salts of the compounds of the formula **(1)** obtained are then converted into the free form.

The substances according to the invention are isolated and purified in a manner known per se, e.g. by distilling off the solvent in vacuum and recrystallizing the residue obtained from a suitable solvent or subjecting it to one of the customary purification methods, such as column chromatography on a suitable support material.

Salts are obtained by dissolving the free compound in a suitable solvent, e.g in a chlorinated hydrocarbon, such as methylene chloride or chloroform, or a low molecular weight aliphatic alcohol (ethanol, isopropanol) which contains the desired acid or base, or to which the desired acid or base is then added. The salts are obtained by filtering, reprecepitating, precipitating with a non-solvent for the addition salt or by evaporating the solvent. Salts obtained can be converted by basification or by acidifying into the free compounds which, in turn can be converted into salts.

In general, the ethereal solvents used in the above described processes for the preparation of compounds of the formula **(1)** are selected from diethyl ether, 1,2-dimethoxyethane, tetrahydrofuran, diisopropyl ether, 1,4 dioxane and the like. The chlorinated solvent which may be employed may be selected from dichloromethane, 1,2-dichloroethane, chloroform, carbontetrachloride and the like. The aromatic solvents which may be employed may be selected from benzene and toluene. The alchoholic solvents which may be employed may be selected from methanol, ethanol, n-propanol, iso propanol, tert-butanol and the like. The aprotic solvents which may be employed may be selected from N, N-dimethylformamide, dimethyl sulfoxide and the like.

In general, the compounds prepared in the above described processes are obtained in pure form by using well known techniques such as crystallization using solvents such as pentane, diethyl ether, isopropyl ether, chloroform, dichloromethane, ethyl acetate, acetone, methanol, ethanol, isopropanol, water or their combinations, or column chromatography using alumina or silica gel and eluting the column with solvents such as hexane, petroleum ether (pet.ether), chloroform, ethyl acetate, acetone, methanol or their combinations.

Various polymorphs of a compound of general formula **(1)** forming part of this invention may be prepared by crystallization of compound of formula **(1)** under different conditions. example, using different solvents commonly used or their mixtures for recrystallization; crystallizations at different temperatures, various modes of cooling, ranging from very fast to very slow cooling during crystallizations. Polymorphs may also be obtained by heating or melting the compound followed by gradual or fast cooling. The presence of polymorphs may be determined by solid probe NMR spectroscopy, IR spectroscopy, differential scanning calorimetry, powder X-ray diffraction or such other techniques.

The present invention provides novel heterocyclic compounds, their analogs, their tautomers, their regioisomers, their stereoisomers, their enantiomers, their diastereomers, their polymorphs, their pharmaceutically acceptable salts, their appropriate N-oxides and their pharmaceutically acceptable solvates.

The present invention also provides pharmaceutical compositions, containing compounds of general formula **(1)** as defined above, their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their enantiomers, their diasteromers, their pharmaceutically acceptable salts or their pharmaceutically acceptable solvates in combination with the usual pharmaceutically employed carriers, diluents and the like. The pharmaceutical compositions according to this invention can be used for the treatment of allergic disorders.

It will be appreciated that some of the compounds of general formula **(1)** defined above according to the invention can contain one or more asymmetrically substituted carbon atoms. The presence of one or more of these asymmetric centers in the compounds of general formula **(1)** can give rise to stereoisomers and in each case the invention is to be understood to extend to all such stereoisomers, including enantiomers and diastereomers and their mixtures, including racemic mixtures. The invention may also contain E and Z geometrical isomers wherever possible in the compounds of general formula **(1)** which includes the single isomer or mixture of both the isomers

The pharmaceutical compositions may be in the forms normally employed, such as tablets, capsules, powders, syrups, solutions, suspensions and the like and may contain flavorants, sweeteners etc. in suitable solid or liquid carriers or diluents, or in suitable sterile media to form injectable solutions or suspensions. The active compounds of formula **(1)** will be present in such pharmaceutical compositions in the amounts sufficient to provide the desired dosage in the range as described above. Thus, for oral administration, the compounds of formula **(1)** can be combined with a suitable solid, liquid carrier or diluent to form capsules, tablets, powders, syrups, solutions, suspensions and the like. The pharmaceutical compositions, may, if desired, contain additional components such as flavorants, sweeteners, excipients and the like. For parenteral administration, the compounds of the formula **(1)** can be combined with sterile aqueous or organic media to form injectable solutions or suspensions. For example, solutions in sesame or peanut oil, aqueous propylene glycol and the like can be used as well as aqueous solutions of water-soluble pharmaceutically-acceptable acid addition salts or salts with base of the compounds of formula **(1)** The injectable solutions prepared in this manner can then be administered intravenously, intraperitoneally, subcutaneously, or intramuscularly, with intramuscular administration being preferred in humans.

The compounds can also be administered by inhalation when application within the respiratory tract is intended. Formulation of the present compounds is especially significant for respiratory inhalation, wherein the compound of Formula **(1)** is to be delivered in the form of an aerosol under pressure. It is preferred to micronize the compound of Formula **(1)** after it has been homogenized, e.g., in lactose, glucose, higher fatty acids, sodium salt of dioctylsulfosuccinic acid or, most preferably, in carboxymethyl cellulose, in order to achieve a microparticle size of 5 μm or less for the majority of particles. For the inhalation formulation, the aerosol can be mixed with a gas or a liquid propellant for dispensing the active substance. An inhaler or atomizer or nebulizer may be used. Such devices are known. See, e.g., Newman et al., *Thorax*, 1985, 40:61-676; Berenberg, M., J. *Asthma USA*, 1985, 22:87-92; incorporated herein by reference in their entirety. A Bird nebulizer can also be used. See also U.S. Patents 6,402,733; 6,273,086; and 6,228,346, incorporated herein by reference in their entirety. The compound of the structure **(1)** for inhalation is preferably formulated in the form of a dry powder with micronized particles. The compounds of the invention may also be used in a metered dose inhaler using methods disclosed in U.S. Patent 6, 131,566, incorporated herein by reference in its entirety.

In addition to the compounds of formula **(1)** the pharmaceutical compositions of the present invention may also contain or be co-administered with one or more known drugs selected from other clinically useful therapeutic agents.

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

The following intermediates have been used to synthesize the representative examples of the compounds of the invention.

Intermediate 1

Dibenzo[*b,d*]furan -4-ol:

4-Hydroxy dibenzo [*b,d*]furan was prepared according to the procedure reported in *J. Org. Chem.,* 1986, 51, 1821-1829; *Helv. Chim. Acta.* 2003, 86, 2900-2907.

IR (KBr): 3277, 2950, 1637, 1603, 1478, 1437, 1311, 1250, 1193, 1164, 1080, 1051, 925, 843, 786, 744 cm^{-1}

^{1}H NMR (300 MHz, DMSO) δ 6.99 (d, 1H, *J* = 8.1 Hz), 7.19 (t, 1H, *J* = 7.8 Hz), 7.39 (t, 1H, *J* = 7.8 Hz), 7.53 (m, 2H), 7.71 (d, 1H, *J* = 8.1 Hz), 8.09 (d, 1H, *J* = 7.2 Hz), 10.24 (s, 1H)

Intermediate 2

4-methoxydibenzo[*b,d*]furan :

4-hydroxy dibenzofuran (intermediate 1) (2.5 gm, 0.0136 mol), was dissolved in 7 % sodium hydroxide solution (25 ml) and stirred at room temperature for 30 min. Dimethyl sulphate (3.4 gm, 0.02716 mol) was added drop wise to the above solution and stirred for 12 h. Reaction mixture was diluted with water (100 ml), acidified with concentrated hydrochloric acid and extracted with ethyl acetate (3 x 50 ml). The organic layer was washed with water (50 ml), saturated sodium bicarbonate solution (25 ml), brine and dried over anhydrous sodium sulphate. Removal of the organic solvent in vacuo gave the product as a white solid (2.0 gm).

^{1}H *NMR* (300 MHz, $CDCl_3$) δ 3.97 (s, 3 H), 7.15 (d, 1H, *J* = 8.4 Hz), 7.31 (t, 1H, *J* = 8.4 Hz), 7.38 (t, 1H, *J* = 8.4 Hz), 7.50 (t, 1H, *J* = 8.4 Hz), 7.67 (d, 1H, *J* = 8.1 Hz), 7.70 (d, 1H, *J* = 8.4 Hz), 8.10 (d, 1H, *J* = 6.9 Hz).

Intermediate 3

1-(4-methoxy dibenzo[*b,d*]furan-1-yl)-1-ethanone :

4-methoxy dibenzo[*b,d*]furan (intermediate 2) (2 g, 0.01 mol) was dissolved in dry 1,2-dichloroethane (20 ml) and cooled to 5°C. Anhydrous aluminum chloride (4 g, 0.03 mol) was added to the reaction mixture and was stirred for 10 min at 5°C. A solution of acetyl chloride (0.94 g, 0.012 mol) in 1,2-dichloroethane (5 ml) was added drop wise to the reaction mixture and was stirred at 5-10°C for 1 h. The reaction mixture was cooled in ice-bath, quenched with crushed ice, diluted with water (50 ml) and extracted with chloroform (2 x 25ml). The organic extract was washed with water (50 ml), saturated sodium bicarbonate solution (25 ml), brine (25 ml) and dried over anhydrous sodium sulphate. Removal of solvent under vacuo gave the product as white solid (1.1 g); mp: 180-182°C.

IR (KBr): 3052, 2938, 1819, 1672, 1569, 1448, 1395, 1281, 1202, 1128, 1092, 1011, 912, 831, 791, 749 cm^{-1}

^1H *NMR* (300 MHz, DMSO) δ 2.74 (s, 3 H), 4.12 (s, 3H), 6.97 (d, 1H, *J* = 8.7 Hz), 7.36 (t, 1H, *J* = 8.1 Hz), 7.51 (t, 1H, *J* = 8.1 Hz), 7.55 (d, 1H, *J* = 7.8 Hz), 7.86 (d, 1H, *J* = 8.4 Hz), 8.93 (d, 1H, *J* = 7.8 Hz)

Intermediate 4

4-(4-methoxydibenzo[*b,d*]furan-1-yl)-4-oxobutanoic acid:

To a solution of 4-methoxy dibenzo[*b,d*]furan (intermediate 2) (500 mg, 2.74 mmol) in dry methylene chloride anhydrous Aluminium chloride (730 mg, 5.48 mmol) is added and the mixture is stirred for half an hour at 0 ^0C. Then succinic anhydride (411 mg, 4.11 mmol) is added to it and refluxed for 24 hours. After cooling to room temperature, it is poured in ice cold 1N HCl solution and extracted with methylene chloride. Organic layer is dried over anhydrous Sodium sulphate and concentrated to afford yellowish solid (636 mg) Mp. 218 – 219 ^0C.

IR (cm^{-1}) KBr - 3423, 2922, 1713, 1671, 1600, 1566, 1448, 911, 830, 765

^1H *NMR* (DMSO d^6, 300 MHz) δ 2.685 (t, 2H, *J*=6.3Hz), 3.389 (t, 2H, *J*= 6.3Hz), 4.09 (s, 3H), 7.312 (d, 1H, *J*=8.4 Hz), 7.409 (t, 1H, *J*=7.5 Hz), 7.597 (t, 1H, *J*=7.2 Hz), 7.765 (d, 1H, *J*=8.4 Hz), 8.153 (d, 1H, *J*=8.4 Hz), 8.754 (d, 1H, *J*=7.5 Hz), 12.25 (br, 1H, exchanges with D_2O)

Mass: 297.2 [M-H]; 283.3; 253.2; 239.2; 210.2; 182.2.

Intermediate 5

4-Cyclopentyloxydibenzo[*b,d*]furan:

4-hydroxy dibenzofuran (intermediate 1) (2.5 g, 0.014 mol) was dissolved in dry DMF (25 ml). Powered anhydrous K_2CO_3 (4.7 g, 0.034 mol) was added and the reaction mixture was heated at 80°C for 30 min. To this, cyclopentyl bromide (4.02 g, 0.027 mol) was added and the resulting mixture was heated at 80°C for 3h. The reaction mixture was cooled and poured into crushed ice (200 gm) and 100ml of water was added. The reaction mixture was acidified with conc. HCl (pH 3-4) and extracted with 3 x 30 ml of ethyl acetate. The organic layer was washed with water (2 x 30 ml) and brine. The solvent was evaporated in vacuo to give 4-Cyclopentyloxydibenzo[*b,d*]furan as brown oil (3.5 g).

IR (KBr): 3060, 2960, 2871, 1634, 1585, 1498, 1451, 1428, 1333, 1310, 1270, 1192, 1170, 1090, 987, 842, 785, 744.

^{1}H *NMR* (300 MHz, DMSO): δ 1.6 to 2.1 (m, 8H), 5.08 (m, 1H), 7.14 (d, 1H, *J*= 8.1Hz), 7.31 (t, 1H, *J*= 7.7Hz), 7.4 (t, 1H, *J* =7.8 Hz), 7.53 (t, 1H, *J*= 7.7 Hz), 7.7 (d, 1H, *J*= 7.8 Hz), 7.75 (d, 1H, *J*= 8.1Hz), 8.12 (d, 2H, *J*= 7.8 Hz)

Intermediate 6

4-Cyclopentyloxydibenzo[*b,d*]furan-1-carbaldehyde:

4-Cyclopentyloxydibenzo[*b,d*]furan (intermediate 5) (3.5 g, 0.0138 mol) was dissolved in dry dichloromethane (25 ml) and the solution was cooled to -10°C. To this solution was added tin (IV) chloride (6.2 g, 0.024 mol) all at once at -10°C under nitrogen atmosphere followed by drop wise addition of a solution of dichloromethyl methyl ether (1.8 g, 0.0153 mol) in dichloromethane (10 ml) at -10°C. The reaction mixture was allowed to attain room temperature under stirring for 30 min. Cold water (20 ml) was added to the reaction mixture and extracted with chloroform (30 ml x 3). The organic layer was washed with water and dried over anhydrous sodium sulphate. The organic layer was concentrated under vacuo to give a brown solid which was purified by silica gel column chromatography using 15 % ethyl acetate in pet ether as the eluent. The product was obtained as a yellow solid (1.3g).

IR (KBr): 2943, 2859, 2734, 1678, 1625, 1599, 1566, 1449, 1395, 1278, 1183, 1100, 1033, 985, 759, 709, 635.

^{1}H *NMR* (300 MHz, DMSO): δ 1.6 to 2.1 (m, 8H), 5.24 (m, 1H), 7.45 (m, 2H), 7.64 (t, 1H, *J* = 8.4Hz), 7.84 (d, 1H, *J* = 8.4Hz), 8.04 (d, 1H, *J* = 8.7Hz), 8.93 (d, 1H, *J* = 8.0Hz), 10.19 (s, 1H)

Intermediate 7a and 7b

4-Methoxydibenzo[*b,d*]furan-1-carbaldehyde and 4-Methoxydibenzo[*b,d*]furan-3-carbaldehyde

To a stirred solution of 4-methoxydibenzo[*b,d*]furan (intermediate 2) (850 mg, 4.29 mmol) in dry dichloromethane (10 ml) was added tin(IV) chloride(1.56 g, 6.0 mmol) in one portion followed by drop-wise addition of dichloromethylmethyl ether (493 mg, 4.29 mmol) in dichloromethane (5 ml). The mixture was maintained at 0 °C for a period of 20 min and the dark mixture was quenched by the addition of ice-cold water (50 ml). The aqueous layer was extracted with dichloromethane (20 ml) and the combined organic layer was washed with water (2 x 25 ml) and brine (25 ml). The crude product obtained after evaporation of the solvent was purified by silica gel column chromatography using 25 % ethyl acetate in petroleum ether to give 260 mg of **7a** and 125 mg of **7b** as white solid.

For 7a: ^{1}H *NMR* (300 MHz, DMSO) δ 4.14 (s, 3 H), 7.09 (d, J = 8.4 Hz, 1 H), 7.40 (t, J = 7.2 Hz, 1 H), 7.53 (t, J = 7.2 Hz, 1 H), 7.65 (d, J = 8.2 Hz, 1 H), 7.80 (d, J = 8.4 Hz, 1 H), 8.97 (d, J = 7.2 Hz, 1 H), 10.18 (s, 1 H).

For 7b: mp: 103 °C; IR (KBr): 3001, 2950, 2874, 1670, 1661, 1597, 1451, 1420, 1250, 1197, 1092, 1016, 1005, 819, 781, 764 cm^{-1}.

^{1}H *NMR* (300 MHz, DMSO) δ 4.38 (s, 3 H), 7.49 (t, J = 7.5 Hz, 1 H), 7.65 (t, J = 7.8 Hz, 1 H), 7.74 (d, J = 8.4 Hz, 1 H), 7.83 (d, J = 8.4 Hz, 1 H), 7.94 (d, J = 8.1 Hz, 1 H), 8.25 (d, J = 7.8 Hz, 1 H), 10.44 (s, 1 H).

Intermediate 8

3-(4-methoxydibenzo [*b,d*]furan-1-yl)-2-propenoic acid:

4-methoxydibenzo [*b,d*]furan-1-carbaldehyde (intermediate 7) (500 mg, 2.21 mmol) was dissolved in toluene (50 ml) and added with malonic acid (280 mg, 2.64 mmol), and piperdine (0.5 ml) and refluxed at 120°C for 8 hrs. Excess of toluene was removed and fresh toluene (30 ml)was added and the toluene layer was washed with aqueous 2 N NaOH solution (25x3 ml).The aqueous layer was then acidified and filtered to get the product as a white solid (400 mg). Mp: >250°C

IR (KBr): 3073, 2998, 2841, 2671, 2534, 1682, 1634, 1618, 1597, 1514, 1451, 1398, 1316, 1301, 1221, 1206, 1099, 1013, 970, 799, 730, 555 cm^{-1}.

^{1}H *NMR* (300 MHz, DMSO): δ 4.03 (s, 3H), 6.53 (d, 1 H, J=15.6 Hz), 7.25 (d, 1H, J=8.1 Hz), 7.51 (t, 1H), 7.58 (t, 1 H), 7.81 (m, 2H), 8.08 (d, 1H, J=7.8 Hz), 8.34 (d, 1H, J=18 Hz), 12.58 (brs, 1H) .

Intermediate 9

Methyl-3-(4-methoxydibenzo [*b,d*]furan-1-yl)-2-propenoate:

3-(4-methoxydibenzo [*b,d*] furan-1-yl)-2-propenoic acid (intermediate 8) (300mg, 1.17 mmol), was dissolved in DMF (10 ml) and added with anhydrous K_2CO_3 (490 mg, 3.52 mmol) and dimethyl sulphate (340 mg, 2.64 mmol).The reaction mixture was heated at 80 °C under nitrogen atmosphere for 3 hours. The reaction mixture was cooled to room temperature and diluted with water. The compound was extracted with ethyl acetate (25x3 ml).The organic extracts were combined and washed with water and dried over anhydrous Na_2SO_4. Removal of solvent under vacuo gave the product as an off-white solid (310 mg).Mp: 162-163°C

IR (KBr): 3043, 3097, 2950, 2847, 1699, 1622, 1602, 1514, 1451, 1442, 1401, 1330, 1274, 1219, 1180, 1101, 1041, 1013, 964, 802, 742, 734 cm^{-1}.

^{1}H *NMR* (300 MHz, DMSO): δ 3.79 (s,3H), 4.04 (s, 3H), 6.73 (d, 1 H, *J*=15 Hz), 7.23 (d, 1H, *J*=9 Hz), 7.50 (t, 1H), 7.63 (t, 1 H), 7.82 (m, 2H), 8.07 (d, 1H, *J*=7.8 Hz), 8.37 (d, 1H, *J*=15 Hz).

Intermediate 10

Methyl 3-(4-methoxydibenzo [*b,d*]furan-1-yl)-4-nitrobutanoate:

Methyl -3-(4-methoxydibenzo[*b,d*]furan-1-yl)-2-propenoate (intermediate 9) (100 mg, 0.345 mmol), was dissolved in nitro methane(4 ml) at 80°C.The reaction mixture was heated at 80°C for 10 minutes and a solution of 1,1,3,3-tetramethylguanidine (20 mg) in nitro methane was added at the same temperature .The reaction mixture was heated at 80°C for 5 hours. The reaction mixture was cooled to room temperature, diluted with water and acidified to pH =5 .The compound was extracted with ethyl acetate (10x3 ml).The organic extracts were combined and washed with water and brine and dried over anhydrous Na_2SO_4. Removal of solvent under vacuo gave the crude product (100 mg), which was column chromatographed using 6%ethyl acetate in pet ether to give a white solid (80 mg) Mp: 103-104°C

IR (KBr): 3024, 2952, 2842, 1733, 1543, 1520, 1440, 1382, 1300, 1276, 1248, 1168, 1110, 1017, 891, 791, 745, 574 cm^{-1}.

^{1}H *NMR* (300 MHz, DMSO): δ 2.95 (d, 2H, *J*=7.2 Hz), 3.44 (s, 3H), 3.97 (s, 3H), 4.82 (m, 1H), 5.08 (d, 1 H, *J*=8.7 Hz), 7.16 (d, 1H, *J*=8.7 Hz), 7.40(d, 1H, *J*=9 Hz), 7.47 (t, 1H), 7.57 (t, 1 H), 7.76 (d, 1H,*J*=), 8.07 (d, 1H, *J*=7.8 Hz), 8.37 (d, 1H, *J*=15 Hz).

Intermediate 11

1-(4-hydroxydibenzo [*b,d*]furan-1-yl)-1-ethanone:

A suspension of 60 % NaH (0.5g, 0.013 mol) in dry DMF (3ml) was stirred at) 0°C in inert atmosphere. To this, a solution of ethanethiol (0.8 ml, 0.01 mol) in dry DMF (3 ml) was added over a period of 30 min at 0°C. The reaction mixture was heated at room temperature and then gradually heated to 80°C. To this preheated reaction mixture, a solution of 1-(4-methoxy dibenzo [*b,d*]furan-1-yl)-1-ethanone (Intermediate 3) (1.1gm, 0.005 mol) in dry

DMF (10ml) was slowly added. The reaction mixture was heated at 80°C for 3 hours. The reaction was quenched by adding brine solution (15 ml). The reaction mixture was extracted with ethyl acetate (3 x 20 ml) The aqueous layer was separated and acidified with 10% HCl solution and extracted with ethyl acetate and concentrated to yield 1-(4-hydroxydibenzo [*b,d*]furan-1-yl)-1-ethanone (0.83g). Decomposes above 180°C.

IR (KBr): 3423, 3128, 2924, 1654, 1596, 1581, 1544, 1404, 1256, 1240, 1199, 1085, 1017, 803, 747 cm^{-1}

^{1}H (300 MHz, DMSO-d_6) δ 2.70 (s, 3H), 7.073 (d, 1H, *J* = 8.7 Hz), 7.41 (t, 1H, *J* = 8.1 Hz) 7.6 (t, 1H, *J* = 7.5 Hz) 7.75 (d, 1H, *J* = 7.5 Hz) 7.96 (d, 1H, *J= 8.4 Hz)* 8.9 (d, 1H, *J* = 7.8 Hz) 10.22 (s, 1H, exchanges with D_2O)

Intermediate 12

1-(4-difluoromethoxydibenzo [*b,d*]furan-1-yl)-1-ethanone:

1-(4-hydroxydibenzo [*b,d*]furan-1-yl)-1-ethanone (intermediate 11) was dissolved in 10 ml of dry DMF (10 ml). To this, anhydrous K_2CO_3 (1.7 g, 0.012 mole) was added and the reaction mixture was heated at 80°C for 30 min. To the preheated reaction mixture, dry monochlorodifluoromethane gas (FREON 22) was purged for 3 hours at 90°C. The reaction mixture was cooled and poured into 10% aqeous HCl (till pH- 2-3). The reaction mixture was extracted with ethyl acetate (3 x 30 ml). The organic layer was washed with water and dried over anhydrous sodium sulphate. The organic layer was concentrated under vacuo to give buff coloured 1-(4-difluoromethoxydibenzo [*b,d*]furan-1-yl)-1-ethanone (0.81 g) Mp. 180-183°C

IR (KBr): 3208, 2947, 2879, 1645, 1580, 1497, 1438, 1381, 1284, 1272, 1209, 1012, 822, 645 cm^{-1}

^{1}H *NMR* (300 MHz, DMSO-d_6) δ 2.78 (s, 3H), 7.5 (t, 1H, *J* = 7.9 Hz), 7.6 (d, 1H, *J* = 8.4 Hz), 7.63 (t, 1H, *J* = 76.2 Hz), 7. 65 (t, 1H, *J* = 7.5 Hz), 7.85 (d, 1H, *J* = 8.4 Hz), 8.15 (d, 1H, *J* = 9.0 Hz), 8.75 (d, 1H, *J* = 7.2 Hz)

Intermediate 13

4-difluoromethoxydibenzo[*b,d*]furan-1-carbaldehyde:

Step 1.

4-Cyclopentyloxydibenzo[*b,d*]furan-1-carbaldehyde (Intermediate 6) (2.0 gm) was heated in 30-33% HBr in acetic acid (20 ml) to 80-90°C. To this solution was added 30-33% HBr in acetic acid (10 ml) over a period of 3h. After completion the reaction mixture was cooled and to this was added ice-water (50 ml)with stirring. The precipitate was filtered, washed with water and dried in oven at 60°C to give 1.1 gm of the product as white solid.

IR (KBr) 2943, 2859, 2734, 1678, 1599, 1566, 1449, 1395, 1278, 1206, 1183, 1033, 985, 759 cm^{-1}

^1H (300 MHz, DMSO-d_6) δ 7.18 (d, 1H, J = 8.4 Hz), 7.41 (t, 1H, J = 8.1 Hz) 7.63 (t, 1H, J = 7.4 Hz) 7.8 (d, 1H, J = 8.1 Hz) 7.93 (d, 1H, J= *8.7 Hz),* 8.94 (d, 1H, J = 8.1 Hz), 10. 15 (s, 1H), 11.60 (s, 1H, exchanges with D_2O)

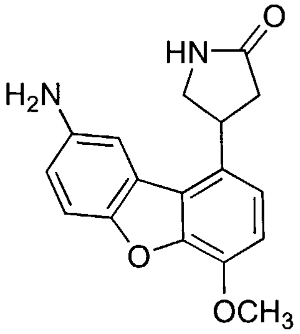
Step 2. Difluoromethoxylation was carried out in a similar way as described for intermediate 12 using 4-hydroxydibenzo[b,d]furan-1-carbaldehyde from step 1 above as the starting material.

IR (KBr): 2943, 2853, 2730, 1670, 1590, 1566, 1430, 1393, 1275, 1206,1180, 1039, 982, 757 cm^{-1}

^1H *NMR* (300 MHz, DMSO-d_6) δ 7.53 (t, 1H, J = 8.1 Hz), 7.63 (t, 1H, J = 72.6 Hz), 7.71 (t, 1H, J= 8.4 Hz), 7.89 (d, 1H, J = 8.4 Hz), , 7.95 (d, 1H, J = 8.4 Hz), 8.15 (d, 1H, J = 9.0 Hz), 8.92 (d, 1H, J = 7.2 Hz) , 10.34 (s, 1H).

Intermediate 14

(±) 4-(8-amino-4-methyldibenzo [*b,d*]furan-1-yl)-2-azolanone:



Step 1: (2*E*)-3-(4-methoxy-8-nitrodibenzo [*b,d*]furan-1-yl)acrylic acid

4-methoxy-8-nitrodibenzo [*b,d*]furan-1-carbaldehyde (obtained by process described in WO2004/037805) (3.5 mmoles) and malonic acid (5.3 mmoles) was dissolved in presence of piperazine (2 ml) in toluene(25 ml). Reaction mass was heated up to reflux temperature to remove water over a period of 4-5 hrs. Reaction was monitored by TLC. Toluene was distilled out and reaction mass dissolved in 10% aq. $NaHCO_3$, extracted with ethyl acetate to remove unreacted as well as organic impurities. On acidification to pH 4, the precipitated product was filtered, washed with water and dried.

^{1}H*NMR*-(300 MHz, DMSO): δ 4.06 (s, 3H), 6.68 (d, 1H, *J* = 15 Hz), 7.36 (d, 1H, *J*= 9.0 Hz), 7.98 (d, 1H, *J* = 8.7 Hz), 8.04 (d, 1H, *J* = 9.3 & 2.0 Hz), 8.28 (d, 1H, *J* = 18 Hz), 8.49 (dd, 1H, *J*= 9.0 and 2.0 Hz), 8.87 (d, 1H, *J*= 2.1 Hz), 12.6 (bs, 1H) D_20 exchange.

IR (KBr): 3083, 3038, 2936, 2842, 2721, 2545, 1917, 1649, 1629, 1610, 1526, 1447, 1374, 1345, 1292, 1273, 1244, 1228, 1191, 1173, 1117, 1074, 1023, 1003, 968, 955, 930-,888, 866, 844, 816, 804, 749, 731, 708, 686, 596, 577, 550, 513 cm^{-1}

Step 2: methyl (2*E*)-3-(4-methoxy-8-nitrodibenzo[*b*,*d*]furan-1-yl)acrylate

(2*E*)-3-(4-methoxy-8-nitrodibenzo [*b*,*d*]furan-1-yl)acrylic acid (from step 1) (1.36 mmoles), K_2CO_3 (2.73 mmoles) and DMF (20 ml) was heated up to 80-90 ^{O}C for 1-2 hrs. to make a salt of acid dimethylsulfate (2.04 mmoles) was slowly added in to the reaction mass at 40 ^{O}C and again heated up to 80-90 ^{O}C for 1-2 h. Reaction was cooled at room temperature and water was poured in the reaction. The precipitated solid product was filtered, washed and dried.

^{1}H*NMR*-(300 MHz, DMSO): 3.81(3H, s), 4.09 (3H, s), 6.80 (1H,d *J*= 15 Hz), 7.37 (1H, d *J* = 9.0 Hz), 7.94 (1H, d. *J* = 8.7), 8.05 (1H, d *J* = 9.3 Hz), 8.35 (1H, d, *J* = 15 Hz), 8.50 (1H, dd., *J* = 9 & 2 Hz), 8.87 (d, 1H, *J* = 2 Hz).

Step 3: (±) methyl 3-(4-methoxy-8-nitrodibenzo[*b*,*d*]furan-1-yl)-4-nitrobutanoate:

To a solution of methyl (2*E*)-3-(4-methoxy-8-nitrodibenzo [*b*,*d*]furan-1-yl)acryl ate (from step 2) (1.46 moles) in nitro methane (20 ml). Catalytic (20 microltrs) amount of 1,1,3,.3 tetramethylquanidine was added and heated up to reflux (80-90 ^{O}C) for 3-4 hrs.

^{1}H*NMR*-(300 MHz, DMSO): δ 2.98 (2H,d), 3.42 (3H, s), 3.99 (3H, s), 4.81(1H, q), 8.12 (2H, d), 7.31(1H, d, *J* = 8.4 Hz), 7.55 (1H, d, *J*= 8.4 Hz), 8.03 (1H, d, *J*= 9.3 Hz), 8.49 (1H, dd , *J* = 2 & 9 Hz).

IR (KBr) : (cm^{-1}) 3091, 2951, 2846, 2649, 1728, 1637, 1615, 1579, 1551, 1523, 1436, 1421, 1400, 1377, 1340, 1293, 1267, 1252, 1221, 1205, 1196, 1130 1120, 1104, 1074, 1024, 1005, 925, 899,.844, 824, 749, 727, 695, 658, 640, 597, 583.

Step 4: (±) 4-(8-amino-4-methyldibenzo [*b*,*d*]furan-1-yl)-2-azolanone

To a solution of Methyl 3-(4-methoxy-8-nitrodibenzo [*b*,*d*]furan-1-yl)-4-nitrobutanoate (from step 3) in methanol, Raney Nickel (50% w/w), ammonium chloride(20% w/w) was added and kept under 60 psi pressure of hydrogen for 3-4 hrs.

^{1}H*NMR*-(300 MHz, DMSO): 2.71(2H, d), 3.75(2H,dd), 3.93(3H,s), 4.27(1H, m), 5.05(2H, bs)D_2O Exchange, 6.78(1H, dd), 7.05(1H, d), 7.18 (1H, t), 7.27(1H,d), 7.39 (1H, d *J*= 8.7 Hz), 7.77(1H, bs) D_2O Exchange.

Intermediate 15

Methyl 3-(4-difluoromethoxydibenzo [*b*,*d*]furan-1-yl)-4-nitrobutanoate

Was synthesized using 4-difluoromethoxydibenzo[*b*,*d*]furan-1-carbaldehyde (intermediate 13) by the method described for intermediate 10.

Step 1: 3-(4-difluoromethoxydibenzo [b,d] furan-1-yl)-2-propenoic acid

IR (KBr): 3403, 2988, 2829, 2661, 2555, 1680, 1612, 1610, 1588, 1510, 1466, 1380, 1308, 1288, 1221, 1112, 1091, 1013, 970, 790, 730, 685 cm^{-1}.

1H *NMR* (300 MHz, DMSO -d^6): δ 6.78 (d, 1 H, *J* = 15.6 Hz), 7.37(m, 2H), 7.41 (t, 1H, *J* = 81.3 Hz), 7.46(t, 1H), 7.64 (t, 1 H), 7.82 (m, 2H), 8.19 (d, 1H, *J* = 7.8 Hz), 12.58 (brs, 1H).

Step 2: Methyl -3-(4-difluoromethoxydibenzo [b,d] furan-1-yl)-2-propenoate

IR (KBr): 3011, 3097, 2998, 2847, 1712, 1622, 1602, 1594, 1481, 1453, 1399, 1325, 1284, 1219, 1170, 1121, 1041, 980, 864, 799, 736, 725 cm^{-1}.

1H *NMR* (DMSO -d^6): δ 2.69 (s, 3H), 6.78 (d, 1 H, *J* = 15.6 Hz), 7.32(m, 2H), 7.39 (t, 1H, *J* = 81.3 Hz), 7.56(t, 1H), 7.62 (t, 1 H), 7.80 (m, 2H), 8.15 (d, 1H, *J* = 7.8 Hz).

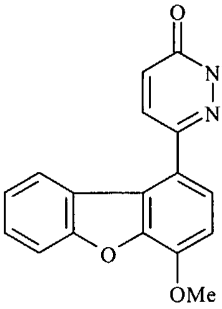
Step 3: Methyl 3-(4-difluoromethoxydibenzo [b,d] furan-1-yl)-4-nitrobutanoate

IR (KBr): 3042, 3084, 2991, 2842, 1713, 1618, 1602, 1535, 1520, 1440, 1357, 1298, 1266, 1248, 1108, 1089, 1015, 890, 780, 764 cm^{-1}.

1H *NMR* (DMSO-d^6): δ 2.65 (s, 3H), 2.68(m, 2H), 4.82(m,1H), 5.04(m,2H), 6.78 (d, 1 H, *J*=8.4 Hz), 7.39 (t, 1H, *J*=81.3 Hz), 7.56(t, 1H), 7.62 (t, 1 H), 7.80 (m, 2H), 8.15 (d, 1H, *J*=8.4 Hz).

Example 1

3-(4-methoxydibenzo [*b,d*]furan-1-yl)-1,6-dihydro-6-pyridazinone

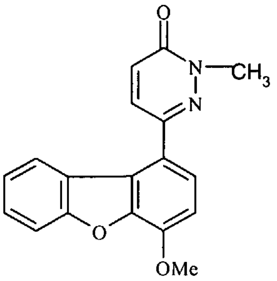


A mixture of 1-(4-methoxy dibenzo[*b,d*]furan-1-yl)-1-ethanone (intermediate 2) (900 mg, 4.01 mmol), glyoxylic acid monohydrate (122 mg, 1.34 mmol) and AcOH (10 ml) was heated at 95-100°C for 3 hours. The mixture was allowed to cool and then treated with water (15 ml) and then cooled in ice. To this, conc. Aq. NH_4OH solution was added till pH was 8. The resulting mixture was filtered to recover the unreacted starting. The filtrate obtained was further extracted with 2 successive portions of 20ml of ethyl acetate in order to remove the unreacted starting material (800 mg). The aqueous layer was heated under reflux with hydrazine hydrate (65 µL, 1.34 mmol) for 3h to give 3-(4-methoxydibenzo[*b,d*]furan-1-yl)-1,6-dihydro-6-pyridazinone (55 mg); m.p. 250°C (decomposes).

IR (KBr): 3435, 2938, 2841, 1675, 1657, 1591, 1516, 1451, 1391, 1299, 1275, 1202 cm^{-1}
^{1}H *NMR* (300 MHz, DMSO) δ 4.047 (s, 3H), 7.07 (dd, 1H, *J*= 1.8 Hz, 9.7 Hz), 7.29 (d, 1H, *J*=8.4 Hz), 7.35 (d, 1H, *J*= 8.4 Hz), 7.50 (d, 1H, *J* = 8.1 Hz), 7.55 (t, 1H, *J*= 8.7 Hz), 7.8 (d, 1H, *J*= 8.4 Hz), 7.87 (d, 1H, *J*= 9.6Hz), 8.01 (d, 1H, *J*= 7.8 Hz), 13.37 (s, 1H)

Example 2

3 - (4-methoxydibenzo [*b,d*] furan-1-yl)-1-methyl-1,6- dihydro-6-pyridazinone



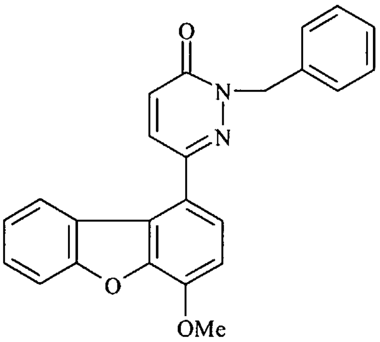
3-(4-methoxydibenzo [b,d] furan-1-yl)-1,6-dihydro-6-pyridazinone (example 1) (50 mg, 0.171 mmol), was dissolved in dry DMF (8ml) and was cooled to -10°C. To this, 14 mg of 60% NaH (0.342 mmol) was added under nitrogen atmosphere with constant stirring. The resulting suspension was stirred at -10°C for 15 min. To this, 15 µl of methyl iodide (0.205 mmol) was added drop wise. The reaction mixture was stirred at -10°C for 1h. The reaction was quenched by addition of brine (15 ml) and the reaction mixture was extracted with ethyl acetate (2 x 15 ml), washed with water, dried over anhydrous Na_2SO_4. Removal of solvent under vacuo gave the product as an off-white solid (45 mg); mp: 159-161°C.

IR (KBr): 3051, 2938, 1671, 1631, 1592, 1519, 1448, 1390, 1274, 1288, 1203, 1139, 1095, 1011, 945, 882, 829, 797, 744, 592 cm^{-1}

^{1}H *NMR* (300 MHz, DMSO) δ 3.80 (s, 3H), 4.05 (s, 3H), 7.14 (d, 1H, *J*= 9.6 Hz), 7.3 (d, 1H, *J*= 8.4Hz), 7.35 (t, 1H, *J*= 7.8 Hz), 7.49 (d, 1H, *J* = 8.7 Hz), 7.56 (t, 1H, *J*= 7.35Hz), 7.77 (d, 1H, *J*= 8.1 Hz), 7.9 (d, 1H, *J* = 9.6 Hz), 7.98 (d, 1H, *J*= 8.1 Hz)

Example 3

1-Benzyl -3-(4-methoxydibenzo [*b,d*] furan-1-yl)-1,6-dihydro-6-pyridazinone



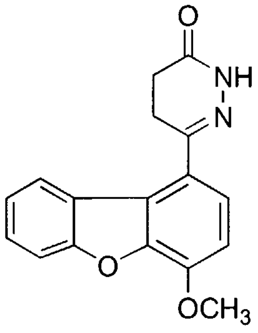
3-(4-methoxydibenzo [b,d] furan-1-yl)-1,6-dihydro-6-pyridazinone (example 1) (24 mg, 0.082 mmol), was dissolved in dry DMF (4 ml) and was cooled to -10°C. To this, 4 mg of 60% NaH (0.164 mmol) was added under nitrogen atmosphere with constant stirring. The resulting suspension was stirred at -10°C for 15 min. To this, 12 μl of benzyl bromide (0.0986 mmol) was added drop wise. The reaction mixture was stirred at -10°C for 1h. The reaction was quenched by addition of brine (15 ml) and the reaction mixture was extracted with ethyl acetate (2 x 15 ml), washed with water, dried over anhydrous Na_2SO_4. Removal of solvent under vacuo gave the product as an off-white solid (25 mg); mp: 168-172°C.

IR (KBr): 2920, 2850, 1663, 1591, 1518, 1451, 1390, 1275, 1200, 1178, 1101, 1011, 805, 775, 749, 696 cm^{-1}

^1H *NMR* (300 MHz, DMSO) δ 4.04 (s, 3H), 5.41 (s, 2H), 7.0 (t, 1H, *J* = 7.7 Hz), 7.23 (d, 1H, *J*= 9.9 Hz), 7.29 (d, 1H, *J* = 9.0 Hz), 7.36 (m, 7H), 7.5 (m, 1H), 7.73 (dd, 1H, *J*= 2.1, 8.4 Hz), 7.92 (d, 1H, *J* = 9.9 Hz)

Example 4

6-(4-methoxydibenzo[*b,d*]furan-1-yl)-4,5-dihydropyridazin-3(2*H*)-one



4-(4-methoxydibenzo[*b,d*]furan-1-yl)-4-oxobutanoic acid (intermediate 4) (100 mg, 3.3 mmol) and hydrazine hydrate (35 mg, 7.0 mmol) were refluxed in dry ethanol for 17 hours. The product which crystallizes out is filtered, washed with ethanol and dried in-vacuo (84 mg) mp - compound decomposes above 260 °C.

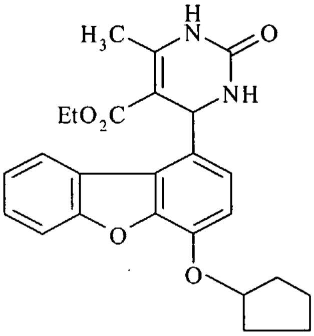
IR (cm^{-1}): KBr 3317, 2957, 1690, 1611, 1517, 1446, 907, 880, 755.

^1H *NMR* (DMSO-d^6, 300 MHz) δ 2.579 (t, 2H, *J* = 8.4 Hz), 3.079 (t, 2H, *J* = 8.4 Hz), 4.031(s, 3H), 7.242(d, 1H, *J* = 8.4 Hz), 7.338 (t, 1H, *J*=8.1Hz), 7.568 – 7.502 (m, 2H), 7.73 (d, 1H, *J* =8.1Hz), 8.453 (d, 1H, *J*=7.8 Hz),11.102 (s, 1H, exchanges with D_2O)

Mass: 295.5[M+H]; 255.2.

Example 5

(±) Ethyl 4- (4- Cyclopentyloxydibenzo[*b,d* furan-1-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate



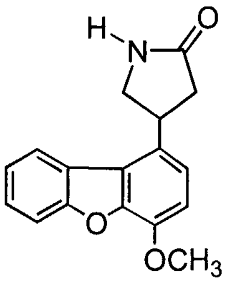
A solution of ethyl acetoacetate (0.13 g, 1.0 mmol), 4-Cyclopentyloxydibenzo[*b,d*]furan-1-carbaldehyde (intermediate 6) (1.0 mmol), urea (0.1 g, 1.5 mmol), $FeCl_3.6H_20$ (41 mg, 0.25 mmol) and 1-2 drops of conc. HCl in 20 ml of ethanol was heated under reflux for 48 hours. After cooling the reaction mixture was poured onto crushed ice with vigorous stirring. The solid obtained was filtered, washed with cold water and a mixture of ethanol and water. The residue was purified by silica gel column chromatography using 30 % ethyl acetate in petroleum ether to give pure product.(m.p.= decomposes above 245°C).

IR (KBr): 3372, 3217, 3095, 2959, 1698, 1641, 1511, 1452, 1366, 1316, 1297, 1273, 1232, 1168, 1096, 984, 804, 749, 736, 609, 510.

^1H *NMR* (300 MHz, DMSO): δ 0.61 (t, 3H, *J*= 7.2Hz), 1.6 to 2.1 (m, 8H), 2.32 (s, 3H), 3.69 (m, 2H), 5.03 (m, 1H), 6.11 (s, 1H), 7.14 (d, 1H, *J*= 9Hz), 7.19 (d, 1H, *J*= 8.4Hz), 7.41 (t, 1H, *J*= 7.4Hz), 7.53 (t, 1H, *J*= 7.7Hz), 7.75 (d, 1H, *J*= 8.1Hz), 7.81 (s, 1H), 8.25 (d, 1H, *J*= 8.1Hz), 9.27 (s, 1H).

Example 6

(±) 4-(4-methoxydibenzo[*b,d*]furan-1-yl)-2-azolanone



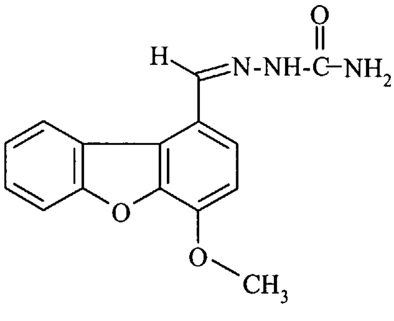
(±) Methyl 3-(4-methoxydibenzo[b,d] furan-1-yl)-4-nitrobutanoate (intermediate 10) (70 mg, 0.20 mmol), was dissolved in a mixture of 1:1 isopropanol and DMF (10ml), added with 10% Pd/C (35 mg, 50% w/w) and reduced under pressure 40 psi for 24 hrs.The reaction mixture was filtered through and the solvent was evaporated in vacuo to get the crude product which was column chromatographed using 20 % acetone in chloroform to get the product as a white solid (15 mg) Mp: 191-192°C.

IR (KBr): 3179, 3080, 2933, 2871, 1713, 1690, 1516, 1401, 1277, 1103, 1016, 817, 742, 730 cm^{-1}.

^1H *NMR* (300 MHz, DMSO): δ 2.40 (m, 1H), 2.75 (m, 1H), 3.40 (m, 1H), 3.80 (m, 1H), 3.97(s, 3H), 4.35 (m, 1 H), 7.15 (d, 1H, *J*=8.1 Hz), 7.25(d, 1H, *J*=8.1 Hz), 7.43 (t, 1H), 7.55 (t, 1 H), 7.99-7.74 (m, 2H), 8.12 (d, 1H, *J*=7.5 Hz) .

Example 7

4-methoxydibenzo [*b*,*d*]furan-1-carbaldehyde semicarbazone



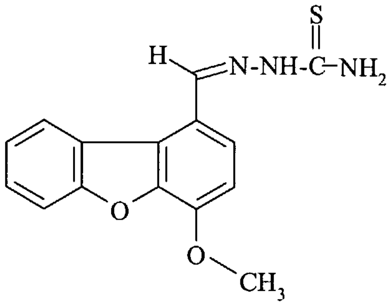
4-methoxydibenzo [*b*,*d*]furan-1-carbaldehyde (intermediate 7a) (100 mg, 442 μM) was dissolved in dry methanol (10 mL). To this, semicarbazide hydrochloride (49.3 mg, 442 μM) was added to it. The suspension after stirring for an hour became clear solution. On further stirring for further 5 hrs, crystals of 4-methoxydibenzo [*b*,*d*]furan-1-carbaldehyde semicarbazone fell out. The crystals were filtered out, washed with diethyl ether and dried in vacuo. Mp. Compound decomposes above 230 °C.

IR (KBr) : 3484, 3375, 2912, 2843, 1682,1635, 1607, 1578, 1499, 1396, 1278, 1200, 1026, 925, 888, 797, 760 cm^{-1}.

^{1}H *NMR* (DMSO-d_6): δ 4.029 (s, 3H), 6.523 (brs, 2H, exchanges with D_2O), 7.224 (d, 1H, *J* = Hz), 7.447 (t, 1H, *J* = 7.5 Hz), 7.581 (t, 1H, *J* = 7.8 Hz), 7.773 (d, 1H, *J* = 8.7 Hz), 7.971 (d, 1H, *J* = 8.7 Hz), 8.349 (d, 1H, *J* = 7.8 Hz), 8.739 (s, 1H), 10.309 (brs, 1H, exchange with D_2O).

Example 8

4-methoxydibenzo [*b*,*d*]furan-1-carbaldehyde thiosemicarbazone



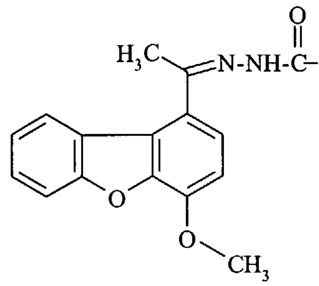
4-methoxydibenzo [*b*,*d*]furan-1-carbaldehyde (intermediate 7a) (100 mg, 442 µM) was dissolved in dry methanol (10 mL). Then thiosemicarbazide (40.3 mg, 442 µM) was added to it. The suspension, after stirring for an hour, became clear solution. On further stirring for further 39 hrs, crystals of 4-methoxydibenzo [*b*,*d*]furan-1-carbaldehyde thiosemicarbazone fell out. The crystals were filtered out, washed with diethyl ether and dried in vacuo. Mp. 281°C.

IR (KBr): 3468, 3348, 3154, 2979, 1684, 1634, 1602, 1510, 1452, 1277, 1237, 1100, 933, 839, 798, 727 cm^{-1}

^{1}H *NMR* (DMSO- d_6) δ 4.043 (s, 3H), 7.239 (d, 1H, *J* = 8.7 Hz), 7. 459 (t, 1H, *J* = 7.5 Hz), 7. 549 (t, 1H, *J* = 8.1 Hz), 7.784 (s,1H, *J* = 8.1 Hz), 8.051 (br, s, 1H, exchanges with D_2O), 8.157 (d, 1H, *J* = 8.4 Hz), 8.275 (br, s, 1H, exchanges with D_2O), 8.337 (d, 1H, *J* = 7.5 Hz), 9.024 (s, 1H), 11.491 (brs, 1H, exchanges with D_2O).

Example 9

(1*Z*)-1-(4-methoxydibenzo[*b*,*d*]furan-1-yl)ethan-1-one semicarbazone



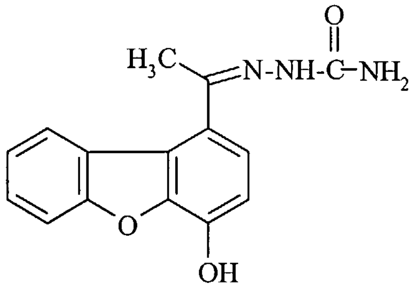
1-(4-methoxydibenzo [*b*,*d*]furan-1-yl)ethanone (intermediate 3) (100 mg, 417 μM)was dissolved in dry methanol (10 mL). Then semicarbazide hydrochloride (100 mg, 417 μM) and pyridine (65.8 mg, 834 μM) were added to it. On stirring for 42 hrs, crystals of (1*Z*)-1-(4-methoxydibenzo [*b*,*d*]furan-1-yl)ethan-1-one semicarbazone fell out. The crystals were filtered out, washed with diethyl ether and dried in vacuo. Mp. 240.7 °C.

IR (KBr): 3458, 3193, 1682, 1632, 1575, 1520, 1449, 1132, 1097, 927, 830, 735 cm^{-1}

^1H *NMR* (DMSO- d_6) δ 2.359 (s, 3H), 4.010 (s, 3H), 6.218 (br, s, 2H, exchanges with D_2O), 7.196 (d, 1H, *J* = 8.4 Hz), 7.30-7.40 (m, 2H), 7.390 (d, 1H, *J* = 8.4 Hz), 7.522 (t,1H, *J* = 7.8 Hz), 8.135 (d, 1H, *J* = 7.8 Hz), 9.501 (s, 1H, exchanges with D_2O).

Example 10

(1*Z*)-1-(4-hydroxydibenzo [*b*,*d*]furan-1-yl)ethan-1-one semicarbazone



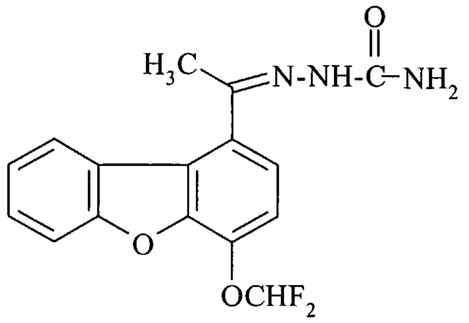
1-(4-hydroxydibenzo [*b*,*d*]furan-1-yl)ethanone (intermediate 10) (76 mg, 317 μM) was dissolved in dry methanol (10 mL). Then thiosemicarbazide (35.6 mg, 317 μM) and pyridine (65.8 mg, 634 μM) were added to it. On stirring for 48 hrs, crystals of (1*Z*)-1-(4-methoxydibenzo [*b*,*d*]furan-1-yl)ethan-1-one thiosemicarbazone fell out. The crystals were filtered out, washed with diethyl ether and dried in vacuo. Mp. 237.1 ^{0}C

IR (KBr): 3581, 3454, 3211, 1687, 1640, 1608, 1582, 1519, 1450, 1020, 902, 832 cm^{-1}

^{1}**H NMR** (DMSO- d_6): δ 2.335 (s, 3H), 6.027 (br, s, 2H, exchanges with D_2O), 6.981 (d, 1H, *J* = 8.4 Hz), 7.252 (t, 1H, *J* = 8.1 Hz), 7.304 (t, 1H, *J* = 7.5 Hz), 7.507 (t, 1H, *J* = 8.4 Hz), 7.708 (d, 1H, *J* = 8.1 Hz), 8.120 (d, 1H, *J* = 7.5 Hz), 9.449 (brs, 1H, exchanges with D_2O), 10.43 (brs, 1H, exchanges with D_2O).

Example 11

(1*Z*)-1-(4-Difluoromethoxydibenzo [*b,d*]furan-1-yl)ethan-1-one semicarbazone



Was synthesiszed in a similar manner as example 9 using 1-(4-difluoromethoxydibenzo [*b,d*]furan-1-yl)-1-ethanone (intermediate 12) as the starting material.

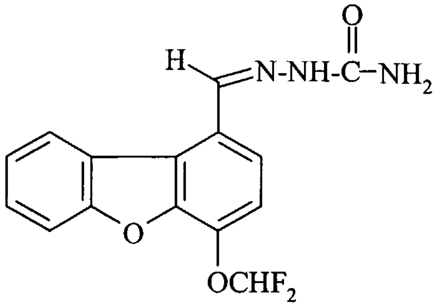
Mp: Decomposes at 235-237°C

IR (KBr): 3467, 3213 2920, 1696, 1612, 1569, 1450, 1379, 1272, 1134, 1111, 1040, 907, 750 cm^{-1}

^{1}H *NMR* (300 MHz, DMSO): δ 2.38 (s, 3H), 6.25 (br, s, 2H, exchanges with D_2O), 7. 38 (t, 1H, *J* = 8.1 Hz), 7.40-7.47 (m, 2H), 7.46 (t, 1H, *J* = 69.9 Hz), 7.55 (t, 1H, *J* = 8.1Hz), 7.8 (d, 1H, *J* = 8.1 Hz), 8.13 (d, 1H, *J*= 7.8 Hz), 9.62 (s, 1H, exchanges with D_2O)

Example 12

4-Difluoromethoxydibenzo [*b,d*]furan-1-carbaldehyde semicarbazone



Was synthesiszed in a similar manner as example 7 using 4-difluoromethoxydibenzo [*b,d*]furan-1-carbaldehyde (intermediate 13) as the starting material.

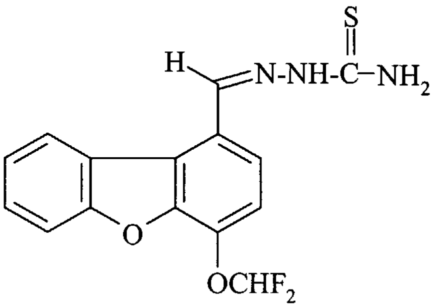
Mp: Decomposes above 196-198°C

IR (KBr): 3470, 3210, 1718, 1684, 1596, 1503, 1452, 1396, 1241, 1183, 1136, 1111, 749, 555

^{1}H *NMR* (300 MHz, DMSO): δ 6.62 (s, broad, 2H, exchanges with D_2O) 7.42 (d, 1H, *J*= 8.4 Hz) 7.49 (t, 1H, *J* = 73.5 Hz) 7.50 (t, 1H, *J* = 8.1 Hz) 7.63 (t, 1H, *J* = 8.1 Hz) 7.85 (d, 1H, *J* = 8.1 Hz) 8.08 (d, 1H, *J* = 9.0 Hz) 8.35 (d, 1H, *J* = 7.8Hz) 8.79 (s, 1H) 10.45 (s, 1H, exchanges with D_2O

Example 13

4-Difluoromethoxydibenzo [*b,d*]furan-1-carbaldehyde thiosemicarbazone



Was synthesiszed in a similar manner as example 8 using 4-difluoromethoxydibenzo [*b,d*]furan-1-carbaldehyde (intermediate 13) as the starting material.

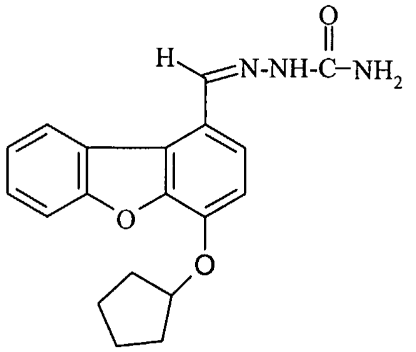
Mp: Decomposes at 196-198 °C

IR (KBr): 3304, 3016, 1594, 1545, 1506, 1452, 1375, 1239, 1186, 1156, 1110, 754, 616

^{1}H *NMR* (300 MHz, DMSO): δ 7.43 (d, 1H, *J* = 8.7 Hz) 7.515 (t, 1H, *J* = 73 Hz) 7.517 (t, 1H, *J* = 7.5 Hz) 7.65 (t, 1H, *J*= 8.4 Hz) 7.86 (d, 1H, *J* = 8.4 Hz) 8.18 (s, broad, 2H, exchanges with D_2O) 8.25 (d, 1H, *J* = 8.7 Hz) 8.35 (d, 1H, *J* = 7.54 Hz) 8.36 (s, broad, 1H, exchanges with D_2O, 9.06 (s, 1H)

Example 14

4-Cyclopentyloxydibenzo [*b,d*]furan-1-carbaldehyde semicarbazone



Was synthesiszed in a similar manner as example 7 using 4-cyclopentoxydibenzo [*b,d*]furan-1-carbaldehyde (intermediate 6) as the starting material.

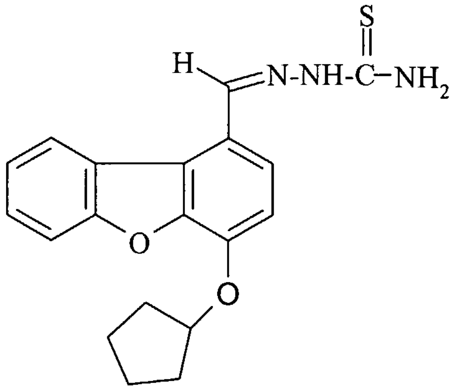
Mp: Decomposes at 215-216°C

IR (KBr): 3457, 3128, 2962, 1683, 1601, 1571, 1448, 1296, 1274, 1187, 1120, 1049, 981, 775, 750, 552.

^{1}H *NMR* (300 MHz, DMSO): δ 1.6 to 2.1 (m, broad, 8H) 5.14 (m, 1H) 6.51 (s, broad, 2H, exchanges with D_2O) 7.18 (d, 1H, J = 9.0 Hz) 7.44 (t, 1H, J = 7.2 Hz) 7.57 (t, 1H, J = 8.7 Hz) 7.8 (d, 1H, J = 8.1 Hz) 7.94 (d, 1H, J= 8.4 Hz) 8.33 (d, 1H, J = 7.8 Hz) 8.74 (s, 1H) 10.3 (s, 1H, exchanges with D_2O)

Example 15

4-Cyclopentyloxydibenzo [*b*,*d*]furan-1-carbaldehyde thiosemicarbazone



Was synthesiszed in a similar manner as example 8 using 4-cyclopentoxydibenzo [*b*,*d*]furan-1-carbaldehyde (intermediate 6) as the starting material.

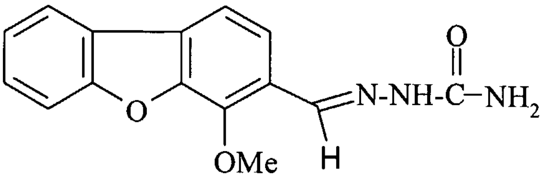
Mp: Decomposes above 250 °C

IR (KBr): 3287, 3213, 2961, 1632, 1596, 1534, 1506, 1451, 1368, 1299, 1184, 1104, 1003, 814, 748, 616

^{1}H *NMR* (300 MHz, DMSO): δ 1.6 to 2.1 (m, broad, 8H) 5.16 (m, 1H) 7.2 (d, 1H, J = 9.0Hz) 7.45 (t, 1H, J = 8.4Hz) 7.58 (t, 1H, J = 8.2 Hz) 7.81 (d, 1H, J = 8.4 Hz) 8.03 (s, broad, exchanges with D_2O 2H) 8.13 (d, 1H, J = 8.7 Hz) 8.33 (d, 1H, J = 7.8 Hz) 9.02 (s, 1H) 11.2 (s, broad, 1H, exchanges with D_2O)

Example 16

4-Methoxydibenzo [*b*,*d*]furan-3-carbaldehyde semicarbazone



Was synthesiszed in a similar manner as example 7 using 4-Methoxydibenzo [*b*,*d*]furan-3-carbaldehyde (intermediate 7b) as the starting material.

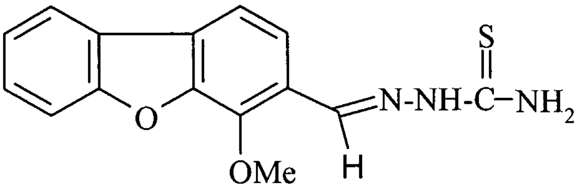
Mp: Compound decomposes above 250 ^{0}C.

IR (cm^{-1}) KBr: 3276, 3135, 2927, 1685, 1588, 1455, 1417, 1275, 1106, 1084, 970, 932, 787, 735.

^{1}H *NMR* (DMSO- d^6) δ 4.186 (s, 3H), 6.547 (br, s, 2H, exchanges with D_2O), 7.427 (t,1H, *J* = 7.8 Hz), 7.552 (t,1H, *J* = 7.8 Hz), 7.755 (d, 1H, *J* = 8.1 Hz), 7.824 (d, 1H, *J* = 8.4Hz), 8.097 (d, 1H, *J* = 8.1 Hz). 8.159 (d, 1H, *J* = 7.2 Hz), 8.159 (d, 1H, *J* = 7.2 Hz), 8.289 (s, 1H), 10.340 (s, 1H).

Example 17

4-Methoxydibenzo [*b,d*]furan-3-carbaldehyde thiosemicarbazone



Was synthesiszed in a similar manner as example 8 using 4-Methoxydibenzo [*b,d*]furan-3-carbaldehyde (intermediate 7b) as the starting material.

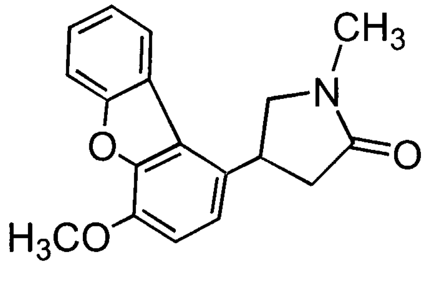
mp. Compound decomposes at 221 ^{0}C.

IR (cm^{-1}) KBr: 3388, 3234, 3152, 1595, 1516, 1467, 1454, 1270, 1104, 995, 843, 795, 748.

^{1}H *NMR* (DMSO- d^6): δ 4.201(s, 3H), 7.435 (t, 1H, *J* = 7.5 Hz), 7.566 (t, 1H, *J* = 7.5 Hz), 7.766 (d,1H, *J* = 8.1 Hz), 7.842 (d, 1H, *J* = 8.1 Hz), 8.076 (br, s, 1H, exchanges with D_2O), 8.163 – 8.235 (m, 3H), 8.527(s, 1H).

Example 18

(±)1-methyl-4-(4-Methoxydibenzo [*b,d*]furan-1-yl)-2-azolanone



To a suspension of 4-(1-methoxydibenzofuran [b,d]-4-yl)-2-azolanone (100 mg, 0.35 moles) and sodium hydride (28 mg, 0.700 mmoles), in DMF (6 ml), was added a solution of methyl iodide (99 mg,0.700 mmoles), in DMF (3 ml) at room temperature. The reaction mixture was stirred for 1 hr, at room temperature and was quenched with brine, diluted with water and the compound was extracted with ethyl acetate. The aqueous layer was washed with ethyl acetate (15x 3 times).The organic layers were combined and washed with water , brine and dried over sodium sulphate and concentrated to get a crude yellow solid which was further washed with pentane to get 4-(1-methoxydibenzofuran [b,d]-4-yl)-1-methyl-2-azolanone (35 mg). Mp: 139°C

IR (KBr): 3082, 2971, 2935, 1693, 1673, 1636, 1606, 1519, 14514, 1398, 1302, 1277, 1252, 1107, 1102, 1014, 752, cm^{-1}

^{1}H *NMR* (300 MHz, DMSO -d^6): 2.66 (1H, m), 2.85 (s, 3H), 2.98 (1H, m), 3.59 (1H, m), 3.97 (1H,m), 4.04 (s, 3H), 4.35 (m, 1H), 6.52 (d, 1H, J = 15.6 Hz), 7.21 (d, 1H, J = 8.1Hz), 7.51 (t, 1H), 7.58 (t, 1 H), 8.08 (d, 1H, J = 7.8 Hz), 8.34 (d, 1H, J = 18 Hz).

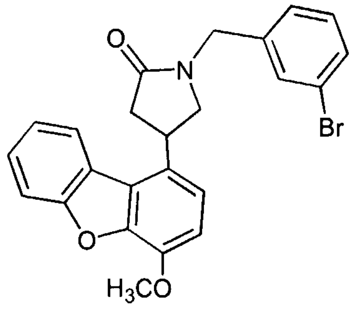
Examples 19 to 29 were synthesized using the following general process

General procedure for the alkylation:

4-(4-methoxydibenzo [*b, d*] furan-1-yl)-2-azolanone (Example 6) (0.35 mmoles) was dissolved in dry N, N'-Dimethyl formamide (5 times) and the resulting solution was cooled to 10°C. To this, sodium hydride (60% dispersion in mineral oil) (1.06 mmoles) was added slowly and the resulting solution was stirred at 10°C for 30 minutes. To this, an alkyl or aralkyl bromide/ iodide (0.426 moles) was added drop wise with vigorous stirring and the reaction mixture was allowed to come at room temperature and then heated at 80°C for 5-6h. The reaction mixture was then cooled and diluted with water (10 times) and extracted with ethyl acetate (2 X 20 ml). The organic layer was washed with water, brine and dried over anhydrous sodium sulfate. The solvent was removed by distillation under vacuum to yield the crude product which was purified by silica gel column chromatography using 20 % acetone in chloroform to get the product as a white solid.

Example 19

(±) 1-(3-bromobenzyl)-4-(4-methoxydibenzo [*b, d*] furan-1-yl)-2-azolanone



Mp: 158°C (decomposes)

IR (KBr): 3060, 2930, 2347, 2034, 1690, 1633, 1518, 1436, 1402, 1275, 1208, 1167, 1098, 1015, 787, 748, 666, 506.

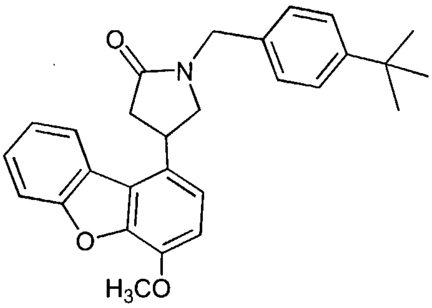
^{1}H *NMR* (300 MHz, DMSO): ^{1}H *NMR* (300 MHz, DMSO): δ 2.45 (m, 1H), 2.75 (m, 1H), 3.0 (m, 1H), 3.85 (m, 1H), 3.97 (s, 3H), 4.35 (m, 1 H), 4.5 (s,2H), 7.15 (t, 1H, *J*=8.4 Hz),7.3 to 7.6 (m, 7H), 7.75 (d, 1H, *J* = 8.1Hz), 8.05 (d, 1H, *J* = 7.8Hz)

M^{+1}: 452

HPLC purity (%): 96.389%

Example 20

(±) 1-(4-tert-butyl benzyl)-4-(4-methoxydibenzo [*b, d*] furan-1-yl)-2-azolanone



Mp: 141°C (decomposes)

IR (KBr): 3055, 2957, 2905, 2867, 1688, 1636, 1518, 1452, 1406, 1274, 1260, 1168, 1016, 933, 824, 748, 562, 542.

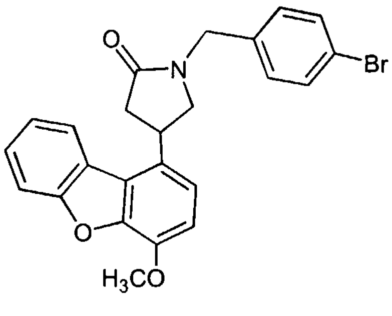
^{1}H *NMR* (300 MHz, DMSO): 1.23 (s, 9H), 2.5 (m, 1H), 2.6 (m, 1H), 2.9 (m, 1H), 3.8 (m, 1H), 3.97 (s, 3H), 4.35 (m, 1H), 4.4 (s, 2H), 7.1 (m, 3H), 7.2 (d, 1H, *J* = 6.9 Hz), 7.3 (m, 3H), 7.5 (t, 1H, *J* = 8.1 Hz), 7.7 (d, 1H, *J* = 7.8 Hz), 7.93 (d, 1H, *J* = 6.9 Hz)

M^{+1}: 428

HPLC purity (%): 94.91%

Example 21

(±) 1-(4-bromobenzyl)-4-(4-methoxydibenzo [*b, d*] furan-1-yl)-2-azolanone



Mp: 124-125°C (decomposes)

IR (KBr): 3072, 2931, 2840, 2347, 1898, 1681, 1666, 1519, 1487, 1452, 1403, 1277, 1232, 1133, 1103, 1012, 959, 913, 885, 829, 796, 750, 736, 629, 524, 483.

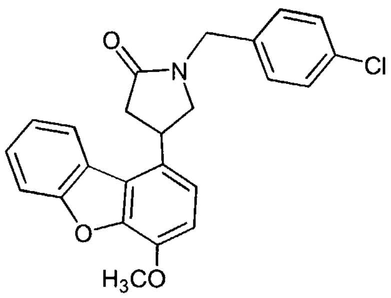
^{1}H *NMR* (300 MHz, DMSO): 2.59 (m, 1H), 2.61 (m, 1H), 2.95 (m, 1H), 3.83 (m, 1H), 3.97 (s, 3H), 4.38 (m, 1H), 4.42 (s, 2H), 7.15 (m, 2H), 7.21 (m, 2H), 7.39 (t, 1H, J = 7.5 Hz), 7.56 (m, 3H), 7.74 (d, 1H, J = 7.8Hz), 8.016 (d, 1H, J = 7.8Hz)

M^{+1}: 452

HPLC purity (%): 95.09%

Example 22

(±) 1-(4-chlorobenzyl)-4-(4-methoxydibenzo [*b, d*] furan-1-yl)-2-azolanone



Mp: 129-130°C (decomposes)

IR (KBr): 3044, 2925, 2853, 2368, 1680, 1669, 1578, 1518, 1492, 1450, 1401, 1363, 1297, 1277, 1233, 1211, 1175, 1129, 1102, 1012, 886, 829, 798, 745, 730, 675, 529, 487.

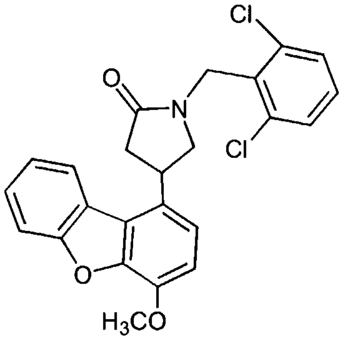
^{1}H *NMR* (300 MHz, DMSO): 2.59 (m, 1H), 2.61 (m, 1H), 2.95 (m, 1H), 3.83 (m, 1H), 3.97 (s, 3H), 4.336 (m, 1H), 4.46 (s, 2H), 7.14 (m, 2H), 7.2 (d, 1H, J = 8.4 Hz), 7.391 (m, 4H), 7.538 (t, 1H, J = Hz), 7.53 (d, 1H, J = 8.4 Hz), 8.016 (d, 1H, J = 7.5Hz)

M^{+1}: 406

HPLC purity (%): 95.94 %

Example 23

(±) 1-(2, 6-dichlorobenzyl)-4-(4-methoxydibenzo [*b, d*] furan-1-yl)-2-azolanone



Mp: 141-143°C (decomposes)

IR (KBr): 3072, 2932, 2840, 1694, 1580, 1518, 1451, 1436, 1298, 1275, 1168, 1103, 1012, 943, 829, 779, 750, 655, 536.

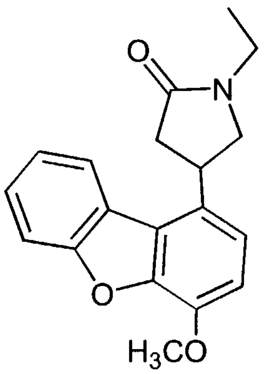
^{1}H *NMR* (300 MHz, DMSO): 2.59 (m, 1H), 2.61 (m, 1H), 2.95 (m, 1H), 3.83 (m, 1H), 3.97 (s, 3H), 4.27 (m, 1H), 4.2 to 4.8 (m, 2H), 7.062 (m, 2H), 7.38 (m, 2H), 7.52 (m, 3H), 7.73 (d, 1H, *J* = 8.4 Hz), 7.94 (m, 1H)

M^{+1}: 440

HPLC purity (%): 93.148 %

Example 24

(±) 1-ethyl-4-(4-methoxydibenzo [*b, d*] furan-1-yl)-2-azolanone



Mp: 141-143°C (decomposes)

IR (KBr): 3058, 2983, 2937, 1677, 1605, 1580, 1521, 1486, 1447, 1401, 1322, 1297, 1273, 1234, 1174, 1101, 1011, 827, 756, 736, 700.

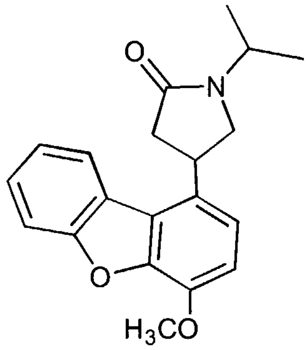
^{1}H *NMR* (300 MHz, DMSO): 1.068 (t, 3H, *J* = 7.5 Hz), 2.89 (m, 1H), 3.38 (m, 2H), 3.42 (m, 1H), 3.906 (m, 2H), 3.97 (s, 3H), 4.317 (m, 1H), 7.15 (d, 1H, *J* = 8.4 Hz), 7.226 (d, 1H, *J* = 8.4 Hz), 7.437 (t, 1H, *J* = 7.5 Hz), 7.56 (t, 1H, *J* = 8.4 Hz), 7.76 (d, 1H, *J* = 8.1 Hz), 8.1 (d, 1H, *J* = 7.5 Hz)

M^{+1}: 310

HPLC purity (%): 96.92 %

Example 25

(±) 1-isopropyl-4-(4-methoxydibenzo [*b, d*] furan-1-yl)-2-azolanone



Mp: 122-24 °C (decomposes)

IR (KBr): 3058, 2983, 2937, 1677, 1605, 1580, 1521, 1486, 1447, 1401, 1322, 1297, 1273, 1234, 1174, 1101, 1011, 827, 756, 736, 700.

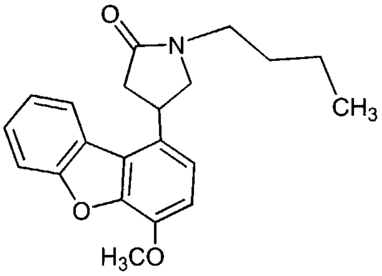
^{1}H *NMR* (300 MHz, DMSO): 1.069 (d, 3H, J = 6.9 Hz), 1.136 (d, 3H, J = 6.6 Hz), 2.447 (m, 2H), 2.9 (m, 1H), 3.86 (m, 1H), 3.97 (s, 3H), 4.25 (m, 2H), 7.193 (m, 2H), 7.442 (t, 1H, J = 7.8 Hz), 7.564 (t, 1H, J = 7.8Hz), 7.77 (d, 1H, J = 8.1 Hz), 8.098 (d, 1H, J = 8.1 Hz)

M^{+1}: 324

HPLC purity (%): 94.965 %

Example 26

(±) 1-butyl-4-(4-methoxydibenzo [*b, d*] furan-1-yl)-2-azolanone



Mp: 110-112°C (decomposes)

IR (KBr):

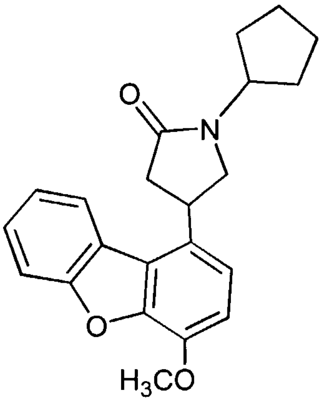
^{1}H *NMR* (300 MHz, DMSO): 0.884 (t, 3H, J = 7.2 Hz), 1.241 (m, 2H), 1.458 (m, 2H), 2.90 (m, 1H), 3.2 to 3.5 (m, 3H), 3.90 (m, 2H), 3.97 (s, 3H), 4.315 (m, 1H), 7.198 (m, 2H), 7.458 (t, 1H, J = 8.1 Hz), 7.562 (t, 1H, J = 8.4 Hz), 7.768 (d, 1H, J = 7.8 Hz), 8.11 (d, 1H, J = 7.2 Hz)

M^{+1}: 338

HPLC purity (%): 97.260 %

Example 27

(±) 1-cyclopentyl-4-(4-methoxydibenzo [*b, d*] furan-1-yl)-2-azolanone



Mp: 118-120°C (decomposes)

IR (KBr):

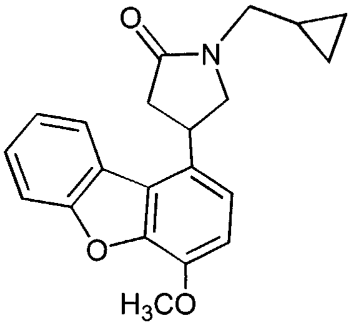
^{1}H *NMR* (300 MHz, DMSO): 1.702 (m, 8H), 2.87 (m, 1H), 3.47 (m, 2H), 3.88 (m, 1H), 3.97 (s, 3H), 4.29 (m, 1H), 4.419 (m, 1H), 7.195 (m, 2H), 7.436 (t, 1H, *J* = 7.5 Hz), 7.56 (t, 1H, *J* = 7.5 Hz), 7.768 (d, 1H, *J* = 7.8 Hz), 8.09 (d, 1H, *J* = 8.1 Hz)

M^{+1}: 336

HPLC purity (%): 95.287 %

Example 28

(±) 1-cyclopropylmethyl-4-(4-methoxydibenzo [*b, d*] furan-1-yl)-2-azolanone



Mp: 118-120°C (decomposes)

IR (KBr):

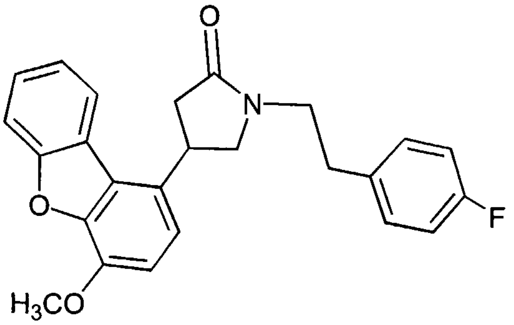
^{1}H *NMR* (300 MHz, DMSO): 0.214 (m, 2H), 0.481 (m, 2H), 0.95 (m, 1H), 2.906 (m, 1H), 3.18 (m, 2H), 3.39 (m, 1H), 3.973 (s, 3H), 4.033 (m, 2H), 4.323(m, 1H), 7.158 (d, 1H, *J* = 8.4 Hz), 7.253 (d, 1H, *J* = 8.1 Hz), 7.438 (t, 1H, *J* = 8.1 Hz), 7.563 (t, 1H, *J* = 7.2 Hz), 7.77 (d, 1H, *J* = 8.4 Hz), 8.12 (d, 1H, *J* = 7.5 Hz)

M^{+1}: 335

HPLC purity (%): 95.139 %

Example 29

(±) 1-(4-fluorophenethyl)-4-(1-methoxy-9H-4-fluorenyl)-2-azolanone



Mp: 145-146°C (decomposes)

IR (KBr):

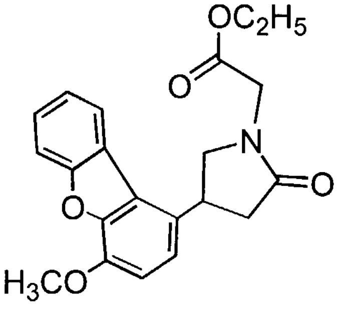
^{1}H *NMR* (300 MHz, DMSO): 2.792 (m, 4H), 3.510 (m, 3H), 3.825 (t, 1H, *J* = 8.1Hz), 3.973 (s, 3H), 4.253 (m, 1H), 7.112 (m, 1H), 7.233 (m, 1H), 7.421 (m 1H), 7.54 (t, 1H, *J* = 7.9 Hz), 7.75 (d, 1H, *J* = 8.1 Hz), 8.03 (d, 1H, *J* = 8.1Hz)

M^{+1}: 404

HPLC purity (%): 95.94

Example 30

(±) Ethyl 2-[4-(4-Methoxydibenzo [*b*,*d*]furan-1-yl)-2-oxo-1-azolanyl]acetate



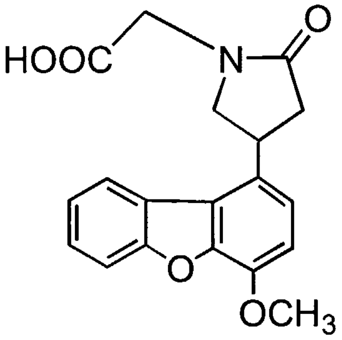
To a suspension of 4-(1-methoxydibenzofuran [b,d]-4-yl)-2-azolanone (Example 6) (300 mg,1.00 moles) and sodium hydride (85 mg, 2.00 mmoles), in DMF (6 ml), was added a solution of ethyl bromoacetate (250 mg,1.5 mmoles), in DMF (3 ml) at 0°C. The reaction mixture was stirred overnight, at room temperature. The reaction was quenched with brine, diluted with water and the compound was extracted with ethyl acetate. The aqueous layer was washed with ethyl acetate (15x 3 times).The organic layers were combined and washed with water, brine and dried over sodium sulphate and concentrated to get a crude brown oil which was further column chromatographed using 10%ethyl acetate in chloroform to get ethyl 2-[4-4-methoxydibenzo [b,d]furan-1-yl)-2-oxo-1-azolanyl]acetate (310 mg, 80% yield) as yellow solid. Mp: 138-140°C

IR (KBr): 3056, 2971, 2935, 1743, 1693, 1645, 1582, 1519, 1492, 1452, 1395, 1298, 1275, 1214, 1170, 1102, 1014, 752, cm^{-1}

^{1}H *NMR* (DMSO -d^6):1.20 (t, 3H), 2.56 (1H, m), 2.88 (1H, m), 3.59 (1H, m), 3.97 (1H, m), 4.03 (s, 2H), 4.04 (s, 3H), 4.11-4.20 (q, 2H), 4.35 (m,1H), 6.52 (d, 1 H, *J* = 7.5 Hz), 7.21 (d, 1H, *J* = 8.1 Hz), 7.51 (t, 1H), 7.58 (t, 1 H), 8.08 (d, 1H, *J* = 7.8 Hz), 8.34 (d, 1H, *J* = 8.0 Hz).

Example 31

(±) 2-[4-(4-Methoxydibenzo [*b*,*d*]furan-1-yl)-2-oxo-1-azolanyl]acetic acid



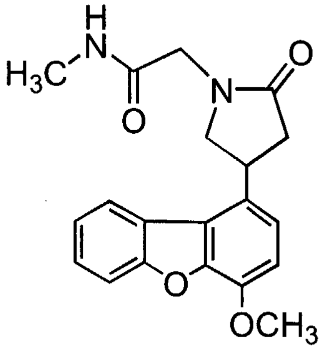
To a suspension of ethyl 2-[4-4-methoxydibenzo [b,d]furan-1-yl)-2-oxo-1-azolanyl]acetate (Example 3992) (100 mg, 0.272 mmoles), was added an aqueous solution of potassium hydroxide (30 mg, 0.544 mmoles) in methanol (5 ml). The resulting suspension was stirred at room temperature for 1 hr and the solution obtained was added to ice cold water. The precipitate obtained was washed with water and dried under vacuum to yield 2-[4-(1-methoxydibenzo [b,d]furan-4-yl)-2-oxo-1-azolanyl] acetic acid . Mp = 248°C.

IR (KBr): 2964, 2837, 2506, 1737, 1641, 1519, 1456, 1406, 1395, 1278, 1228, 1186, 1103, 1014, 886 cm^{-1}

^{1}H *NMR* (300 MHz, DMSO -d^6): 2.56 (1H, m), 2.88 (1H, m), 3.59 (1H, m), 3.97 (1H, m), 4.03 (s, 2H), 4.04 (s, 3H), 4.35 (m, 1H), 6.52 (d, 1 H, *J* =7.5 Hz), 7.21 (d, 1H, *J* = 8.1 Hz), 7.51 (t, 1H), 7.58 (t, 1 H), 8.08 (d, 1H, *J* = 7.8 Hz), 8.34 (d, 1H, *J* = 8.0 Hz), 12.58 (brs, 1H) .

Example 32

(±) N1-methyl-2-[4-(4-Methoxydibenzo [*b,d*]furan-1-yl)-2-oxo-1-azolanyl] acetamide



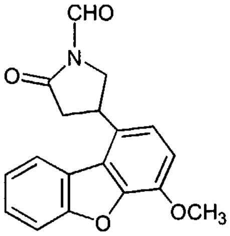
To a suspension of ethyl 2-[4-4-methoxydibenzo [b,d]furan-1-yl)-2-oxo-1-azolanyl]acetate (Example 3992) (50 mg, 0.13 mmoles), was added an aqueous solution of methyl amine (12 mg, 0.39 mmoles) in THF (12 ml). The resulting suspension was stirred overnight at room temperature and THF was evaporated .The reaction mass was diluted with water and the compound was extracted with ethyl acetate. The aqueous layer was washed with ethyl acetate (15x 3 times).The organic layers were combined and washed with water, brine and dried over sodium sulphate and concentrated to get crude yellow oil which was further column chromatographed using 5% methanol in chloroform to get N1-methyl-2-[4-1-methoxydibenzo [b,d]furan-4-yl)-2-oxo-1-azolanyl]acetamide (15 mg, low melting white solid) Mp: 68-70°C

IR (KBr): 3099, 2961, 2935, 1674, 1636, 1606, 1519, 1451, 1398, 1302, 1277, 1252, 1107, 1102, 1014, 752, cm-1

^{1}H *NMR* (300 MHz, DMSO -d^6): 2.56 (1H, m), 2.66 (d, 3H), 2.88 (1H, m), 3.59 (1H, m), 3.97 (1H,m), 4.03 (s, 2H) 4.04 (s, 3H), 4.35 (m, 1H), 7.15 (d, 1 H, J = 15.6 Hz), 7.36-7.46 (m, 2H), 7.53 (t, 1H), 7.77 (d, 1 H, J = 7.8 Hz), 7.05 (brd,1H), 8.18 (d, 1H, J = 7.8 Hz).

Example 33

(±) 4-(4-methoxydibenzo [*b, d*] furan-1-yl)-2-oxo-1-azolanecarbaldehyde



To a mixture t-BuOK (0.001067 mole) and 18-crown-6 (0.0000711mole) in dry N, N'-Dimethyl formamide (5 times) was added 4-(4-methoxydibenzo [*b, d*] furan-1-yl)-2-azolanone (0.00035 moles) at 5°C under nitrogen atmosphere. After 30 minutes, 1, 2-dibromoethane (0.0017793 mole) was added drop wise at a constant rate and the reaction mixture was heated at 80°C for 48 hours. The reaction mixture was then cooled and water (100 ml) was then added and extracted with ethyl acetate (3x 20 ml). The organic layer was washed with water, brine and dried over anhydrous sodium sulfate. The solvent was removed by distillation under vacuum to yield the crude product which was column chromatographed using 20 % acetone in chloroform to get the product as a white solid.

Mp: 170-2°C (decomposes)

IR (KBr): 3052, 2841, 2920, 2890, 2365, 2343, 1745, 1698, 1636, 1583, 1559, 1519, 1452, 1404, 1391, 1345, 1318, 1276, 1238, 1172, 1102, 1021, 1012, 887, 795, 752, 622, 523.

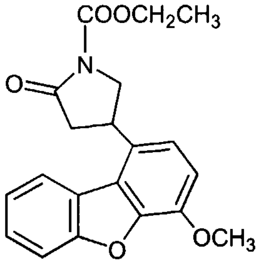
^{1}H *NMR* (300 MHz, DMSO): 2.911 (m, 1H), 3.154 (m, 1H), 3.694 (m, 1H), 3.97 (s, 3H), 4.196 (m, 1H), 4.517 (m, 1H), 7.178 (d, 1H, *J* = 8.1 Hz), 7.293 (d, 1H, *J* = 8.1 Hz), 7.445 (t, 1H, *J* = 7.8 Hz), 7.573 (t, 1H, *J* = 7.5 Hz), 7.77 (d, 1H, *J* = 8.1 Hz), 8.23 (d, 1H, *J* = 7.8 Hz), 9.077 (s, 1H)

M^{+1}: 310

HPLC purity (%): 99.605 %

Example 34

(±) Ethyl-4-(4-methoxydibenzo [*b, d*] furan-1-yl)-2-oxo-1-azolanecarboxylate



4-(4-methoxydibenzo [*b, d*] furan-1-yl)-2-azolanone (0.00035 moles) was dissolved in dry N, N'-Dimethyl formamide (5 times) and to this, sodium hydride (0.001076 moles) (60 %

dispersion in mineral oil) was added and the resulting solution was stirred at 25°C under nitrogen atmosphere. After 30 minutes, ethyl chloroformate (0.0007117 moles) dissolved in dry tetrahydrofuran was added drop wise. The reaction mixture was stirred at 25°C for 5h and then water was added and the resulting mixture was extracted with ethyl acetate (25 x 4 ml). The organic layer was washed with water, brine and dried over anhydrous Na_2SO_4. The solvent was distilled to yield a crude compound which was purified by column chromatography using silica gel (100-200 mesh) using 20% acetone in $CHCl_3$ as eluent to give pure product. HPLC purity (%): 94.70

Mp: 122-23°C (decomposes)

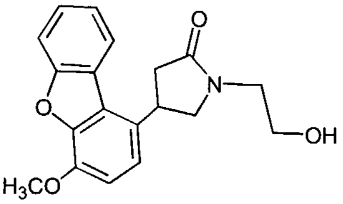
IR (KBr):

^{1}H *NMR* (300 MHz, DMSO): 1.345 (t, 3H, J = 7.2 Hz), 2.957 (m, 1H), 3.087 (m, 1H), 3.987 (m, 1H), 4.004 (s, 3H), 4.069 (m, 1H), 4.334 (m, 3H), 6.97 (d, 1H, J = 8.1 Hz), 7.14 (d, 1H, J = 8.1 Hz), 7.398 (t, 1H, J = 8.7 Hz), 7.518 (t, 3H, J = 8.4 Hz), 7.69 (d, 1H, J = 8.1 Hz), 7.91 (d, 1H, J = 7.8 Hz)

M^{+1}: 353

Example 35

(±) 1-(2-hydroxyethyl)-4-(4-methoxydibenzo [*b, d*] furan-1-yl)-2-azolanone



4-(4-methoxydibenzo [*b, d*] furan-1-yl)-2-azolanone (0.00035 moles), ethylene carbonate (0.0014 moles), anhydrous K_2CO_3 (0.00071 moles), 18-crown-6 (0.0000711 moles) and dry N, N'-Dimethyl formamide (7 times) were mixed together and heated to 80°C for 18 hours. The reaction mixture was cooled and water was added (90 ml) and the resulting mixture was extracted with ethyl acetate (3x 20 ml). The organic layer was washed with water, brine and dried over anhydrous sodium sulfate. The solvent was removed by distillation under vacuum to yield the crude product which was column chromatographed using 20 % acetone in chloroform to get the product as a white solid. HPLC purity (%): 93.075 ; Mp: 121-123°C (decomposes)

IR (KBr):

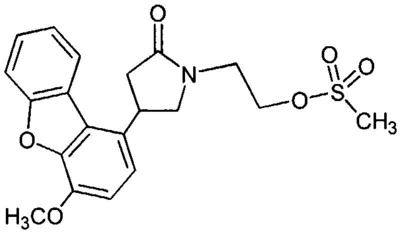
^{1}H *NMR* (300 MHz, CDCl3): 2.82 (m, 1H), 3.0 (m, 1H), 3.56 (m, 3H), 3.66 (m, 3H), 3.83 (m, 1H, exchanges with D_2O), 4.064 (s, 3H), 4.32 (m, 1H), 6.97 (d, 1H, J = 8.4 Hz), 7.17

(d, 1H, $J = 8.1$ Hz), 7.381 (t, 1H, $J = 8.1$ Hz), 7.5 (t, 1H, $J = 7.8$ Hz), 7.68 (d, 1H, $J = 8.1$ Hz), 7.91 (d, 1H, $J = 8.1$ Hz)

M^{+1}: 326

Example 36

(±) 2-[4-(4-methoxydibenzo [*b, d*] furan-1-yl)-2-oxo-1-azolanyl] ethyl methanesulfonate



1-(2-hydroxyethyl)-4-(4-methoxydibenzo [*b, d*] furan-1-yl)-2-azolanone (moles) was taken in dry pyridine (moles) and tetrahydrofuran (10 times) mixture and stirred at 0°C under nitrogen atmosphere. To this, freshly distilled methane sulfonyl chloride (0.) moles dissolved in dry tetrahydrofuran was added drop wise and the resulting mixture was stirred at 25°C for 2h. The reaction mixture was distilled to remove excess of tetrahydrofuran and then water (50 ml) was added and the resulting mixture was extracted with ethyl acetate (3x 20 ml). The organic layer was washed with water, brine and dried over anhydrous sodium sulfate. The solvent was removed by distillation under vacuum to yield the crude product which was column chromatographed using 20 % acetone in chloroform to get the product as a white solid.

Mp: 118-119°C (decomposes)

IR (KBr):

^{1}H *NMR* (300 MHz, $CDCl_3$): 2.8 (m, 1H), 2.97 (m, 1H), 3.002 (s, 3H), 3.701 (m, 3H), 4.067 (s, 3H), 4.091 (m, 1H), 4.424 (m, 3H), 6.98 (d, 1H, $J = 8.4$ Hz), 7.17 (d, 1H, $J = 8.1$ Hz), 7.395 (t, 1H, $J = 7.5$ Hz), 7.507 (t, 1H, $J = 7.2$ Hz), 7.67 (d, 1H, $J = 8.1$ Hz), 7.93 (d, 1H, $J = 7.5$ Hz)

M^{+1}: 404

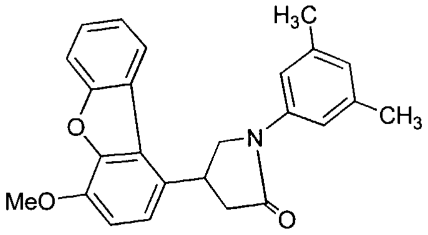
HPLC purity (%): 97.114

Examples 37 to 48 were synthesized using the following general process

A mixture of 4-(4-methoxydibenzo[*b,d*]furan-1-yl)-2-azolanone (Example 6), appropriate aryl bromide or aryl iodide (1.5 eq), Cu powder (0.16 eq) and K_2CO_3 (1.5 eq) in dry DMF was heated at 150°C for 16 h. Reaction mixture was cooled and diluted with water and extracted with ethyl acetate. Organic layer was washed with water, brine, dried over sodium sulphate and concentrated. The crude product was purified by column chromatography using appropriate solvents.

Example 37

(±)1-(3,5-dimethylphenyl)-4-(4-methoxydibenzo[*b,d*]furan-1-yl) pyrrolidine-2-one



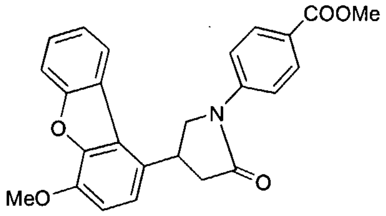
^{1}H *NMR* (300 MHz, DMSO-d^6): δ 2.3 (s, 6H), 2.78 (dd, 1H), 3.14 (dd, 1H), 3.92-3.97 (m, 4H), 4.37 (t, 1H, *J* = 8.4 Hz), 4.48 (quintet, 1H), 6.78 (s, 1H), 7.18 (d, 1H, *J* = 8.4 Hz), 7.30 (d, 3H, *J* = 8.7 Hz), 7.41 (t, 1H, *J*=7.5 Hz), 7.56 (t, 1H, *J* = 7.6 Hz), 7.76 (d, 1H, *J* = 8.7 Hz), 8.2 (d, 1H, *J* = 7.8Hz)

IR (cm^{-1}), KBr: 2957, 2924, 2853, 2581, 1737, 1663,1632, 1595, 1329, 1271, 1215, 1180, 1127, 811.

Mp; Compound melts at 167-168 ^{0}C.

Example 38

(±)Methyl-4-[4-(4-methoxydibenzo[*b,d*]furan-1-yl)-2-pyrrolidinonyl] benzoate



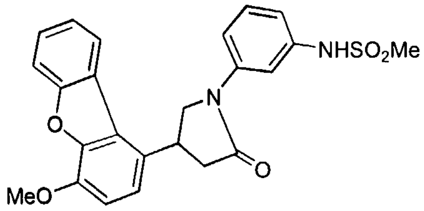
^{1}H *NMR* (300 MHz, DMSO-d^6): δ 2.8 (dd, 1H), 3.19 (dd, 1H), 3.9 (s, 3H), 4.0 (s, 3H), 4.07 (m, 1H), 4.44 (t, 3H), 4.53 (quintet, 1H), 7.18 (d, 1H, *J* = 8.4 Hz), 7.38 (d, 3H, *J* = 8.7 Hz), 7.44 (t, 1H, *J* = 7.5Hz), 7.57 (t, 1H, *J* = 7.6 Hz), 7.77 (d, 1H, *J* = 8.1Hz), 7.86 (d, 2H, *J* = 8.7 Hz), 7.93 (d, 2H, *J* = 9.0 Hz), 8.25 (d, 1H, *J* = 8.1Hz).

IR (cm-1), KBr: 2994, 2837, 2375, 1709, 1609, 1514, 1431, 1380, 1276, 1181, 1106, 789, 773.

Mp: Compound melts at 211-212 ^{0}C.

Example 39

(±)N-{3-[4-(4-methoxydibenzo[*b,d*]furan-1-yl)-2-oxo-1-azolanyl]phenyl}methanesufonamide



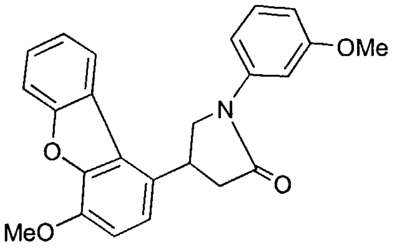
^{1}H *NMR* (300 MHz, DMSO-d^6): δ 2.8 (dd, 1H), 2.98 (s, 3H), 3.22 (dd, 1H), 3.92 (s, 3H), 4.08 (t, 1H), 4.38 (t, 1H), 4.49 (quintet, 1H), 7.13 (t, 1H, *J* = 8.1 Hz), 7.23 (d, 1H, *J* = 8.1 Hz), 7.45 (d, 1H, *J* = 8.1 Hz), 7.54 (s, 1H), 9.91 (s,1H).

IR (cm-1), KBr: 3130, 2932, 2867, 1697, 1596, 1452, 1387, 1321, 1232, 1105, 1038, 818.

MP: Compound melts at .149-151 ^{0}C.

Example 40

(±)4-(4-methoxydibenzo[*b,d*]furan-1-yl)-1-(3-methoxyphenyl)-2-azolanone



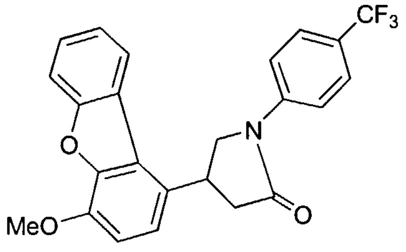
^{1}H NMR (300 MHz, DMSO-d^6): δ 2.8 (dd, 1H), 3.14 (dd, 1H), 3.75 (s, 3H), 3.97-4.02 (m, 4H), 4.38 (t, 1H), 4.5 (m, 1H), 6.73 (bd, 1H, *J*=7.5 Hz), 7.33-7.16 (m, 4H), 7.38 (s, 1H, *J* = 8.7 Hz), 7.41 (t, 1H, *J* = 7.5Hz), 7.56 (t, 1H, *J* = 7.5Hz), 7.77 (d, 1H, *J* = 8.4 Hz), 8.23 (d, 1H, *J* =7.8 Hz)

IR (cm-1), KBr: 3130, 2932, 2867, 1697, 1596, 1452, 1387, 1321, 1232, 1105, 1038, 818.

MP: Compound melts at .149-151 ^{0}C.

Example 41

(±) 4-(4-methoxydibenzo[*b,d*]furan-1-yl)-1-(4-trifluoromethylphenyl)-2-azolanone



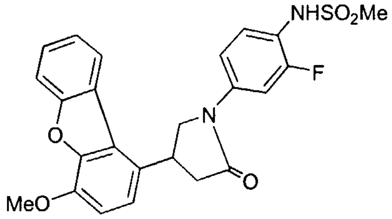
^{1}H NMR (300 MHz, DMSO-d^6): δ 2.89 (dd, 1H), 3.17 (dd, 1H), 3.97 (s, 3H), 4.06 (t, 1H, *J* = 7.95 Hz), 4.43 (t, 1H, *J* = 8.5 Hz), 4.55 (quintet, 1H), 7.17 (d, 1H, *J* = 8.4 Hz), 7.33 (d,1H, *J* = 8.1 Hz), 7.43 (t, 1H, *J* = 7.6Hz), 7.75 (t, 1H, *J* = 9.0 Hz), 8.23 (d, 1H, *J*=7.8)

IR (cm-1), KBr: 3272, 2931, 1702, 1682, 1515, 1398, 1452, 1398, 1299, 1279, 1202, 1188, 1160, 1013, 745.

Mp: Compound melts at .231-241 ^{0}C.

Example 42

(±) N-{3-fluoro-4-[4-(4-methoxydibenzo[*b,d*]furan-1-yl)-2-oxo-1-azolanyl]phenyl}methanesufonamide



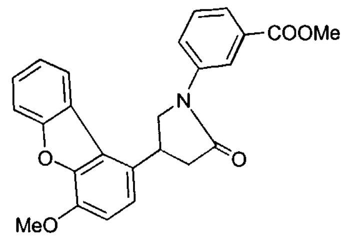
^{1}H NMR (300 MHz, DMSO-d^6): δ 2.83 (dd, 1H), 2.93 (s, 3H), 3.14 (dd, 1H), 3.97-4.02 (m, 4H), 4.37 (t, 1H), 4.43 (t, 1H), 4.51 (quintet, 1H), 7.17 (d, 1H, *J* = 8.4 Hz), 7.31-7.46 (m, 4H, *J* = 8.1Hz), 7.543 (t, 1H, *J* = 7.5 Hz), 7.76 (d, 1H, *J* = 10.0 Hz), 8.23 (d, 1H, *J* = 7.8 Hz), 9.5 (br s, 1H)

IR (cm-1), KBr: 3215, 2962, 2930, 2325, 1705, 1632, 1514, 14021, 1325, 1273, 1214,1402, 1325, 1273, 1214, 1133, 1020, 804.

Mp: Compound melts at .199.4-202.5 ^{0}C.

Example 43

(±) Methyl-3-[4-(4-methoxydibenzo[*b,d*]furan-1-yl)-2-pyrrolidinonyl] benzoate



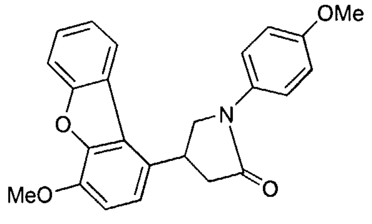
^{1}H *NMR* (300 MHz, DMSO-d^6): δ 2.84 (dd, 1H), 3.16 (dd,1H), 3.86 (s, 3H), 3.97 (s, 3H), 4.05 (t, 1H), 4.44 (t, 1H), 4.51(quintet, 1H), 7.17 (d, 1H, *J* = 8.4 Hz), 7.35 (d, 1H, *J* = 12 Hz), 7.45 (t, 1H, *J* =14.4 Hz), 7.56 (t, 1H, *J* = 7.5 Hz), 7.59 (t, 1H, *J* = 9.0 Hz), 7.85 (d, 1H, *J* = 6.0 Hz), 8.24 (d, 1H, *J* = 6.0 Hz), 8.4 (s, 1H).

IR (cm-1), KBr: 2929, 2652, 2346, 1971, 1684, 1587, 1562, 1433, 1308, 1261, 1214,1402, 1325, 1273, 1214, 1133, 1020, 804.

Mp: Compound melts at .171-176.6 ^{0}C.

Example 44

(±)4-(4-methoxydibenzo[*b,d*]furan-1-yl)-1-(4-methoxyphenyl)-2-azolanone



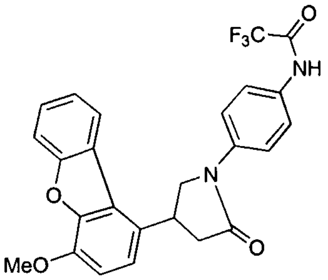
^{1}H *NMR* (300 MHz, DMSO-d^6): δ 2.97 (dd, 1H), 3.16 (dd, 1H), 3.81 (s, 3H), 4.0 (q, 1H), 4.03 (s, 3H), 4.34-4.46 (m, 2H), 6.89-6.94 (m, 2H), 6.98 (d, 1H, *J* = 5.0 Hz), 7.09 (d, 1H, *J* = 3.0 Hz), 7.38 (t, 1H, *J* = 7.5 Hz), 7.51 (d, 3H, *J* = 9.0 Hz), 7.68 (d, 1H, *J* = 9.0 Hz), 7.96 (d, 1H, *J* = 6.0 Hz).

IR (cm-1), KBr: 2959, 2365, 1678, 1510, 1393, 1275, 1103, 1034, 829.

Mp; Compound melts 168-170 ^{0}C.

Example 45

(±)4-(4-methoxydibenzo[*b,d*]furan-1-yl)-1-(4-trifluoromethylacetamidophenyl)-2-azolanone



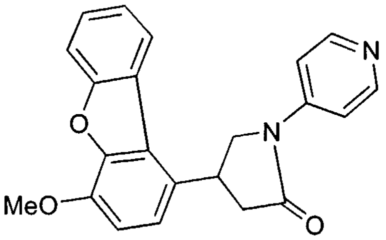
^{1}H *NMR* (300 MHz, DMSO-d^6): δ 3.0 (dd, 1H), 3.2 (dd, 1H), 4.07 (s, 4H), 4.4-4.47 (m, 2H), 6.98 (d, 1H, *J* = 8.4Hz), 7.2 (d, 1H, *J* = 7.0 Hz), 7.4 (t, 1H, *J* = 7.5 Hz), 7.5 (t, 1H, *J* = 7.05 Hz), 7.55 (d, 2H, *J* = 9.0 Hz), 7.7 (d, 2H, *J* = 6.0 Hz), 7.90 (q, 2H, *J* = 21Hz).

IR (cm-1), KBr: 3272, 2931, 2832, 1702, 1682, 1515, 1398, 1279, 1188, 1160, 1103, 1013, 745.

Mp; Compound melts >250 ^{0}C.

Example 46

(±)4-(4-methoxydibenzo[*b,d*]furan-1-yl)-1-(4-pyridyl)-2-azolanone



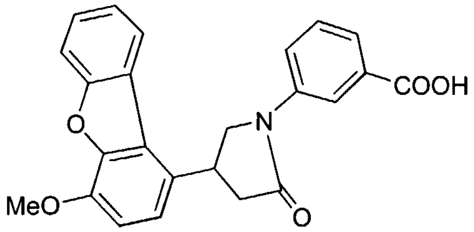
^{1}H *NMR* (300 MHz, DMSO-d^6): δ 2.86 (dd, 1H), 3.13 (dd, 1H), 3.97 (s, 3H), 4.0 (t, 1H), 4.4 (t, 1H), 4.5 (t, 1H), 7.19 (d, 1H, *J* = 8.4 Hz), 7.35-7.43 (m, 3H), 7.56 (t, 1H), 7.79 (d, 1H, *J* = 8.1Hz), 8.15 (d, 1H, *J* = 8.4 Hz), 8.25 (d, 1H, *J* = 7.8 Hz), 8.36 (s, 1H), 8.94 (s,1H).

IR (cm-1), KBr; 3074, 1707, 1585, 1486, 1452, 1397, 1275, 1218, 1168, 1101, 1012, 753..

Mp: Compound melts 175 ^{0}C.

Example 47

(±)3-[4-(4-methoxydibenzo[*b,d*]furan-1-yl)-2-oxo-1-azolanyl] benzoic acid



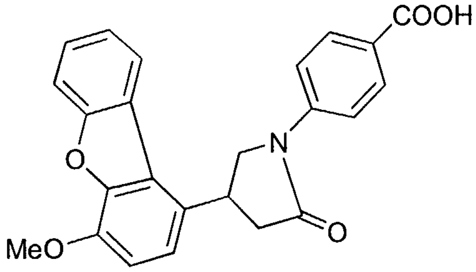
^{1}H *NMR* (300 MHz, DMSO-d^6): δ 2.80 (dd, 1H), 3.11 (dd, 1H, 3.93 (s, 3H), 4.02 (q, 1H), 4.41-4.5 (m, 2H), 7.13-7.16 (d, 1H, *J* = 8.1Hz), 7.30 (d, 1H, *J* = 8.7), 7.56-7.38 (m, 3H), 7.68 (dd, 2H, *J* = 16.95, 8.1Hz), 7.82 (d, 1H, *J* = 7.8 Hz), 8.21 (d, 1H, *J* = 7.5 Hz), 8.32 (s, 1H).

IR (cm-1), KBr: 3272, 1702, 1602, 1575, 1456, 1398, 1270, 1118, 1160, 1103, 948, 748.

Mp: Compound melts >250 ^{0}C.

Example 48

(±)4-[4-(4-methoxydibenzo[*b,d*]furan-1-yl)-2-oxo-1-azolanyl] benzoic acid



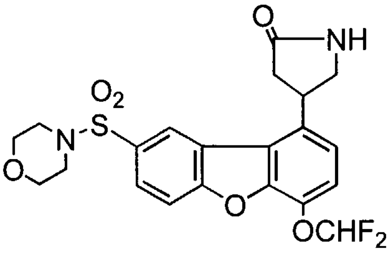
^{1}H *NMR* (300 MHz, DMSO-d^6): δ 2.85-2.92 (m, 1H), 3.13-3.21 (m, 1H), 4.02 (s, 3H), 4.04-4.07 (m, 1H), 4.44-4.47 (m, 1H), 4.50-4.54 (m, 1H), 7.18 (d, 1H, *J* = 8.4 Hz), 7.34 (d, 1H, *J* = 8.1Hz), 7.44 (t, 1H), 7.57 (t, 1H), 7.77 (d, 1H, *J* = 8.1Hz), 7.84 (d, 2H, *J* = 8.7 Hz), 7.95 (d, 2H, *J* = 8.7 Hz), 8.25 (d, 1H, *J* = 8.1Hz).

IR (cm-1), KBr: 3435, 2939, 1693, 1605, 1517, 1419, 1384, 1276, 1232, 1183, 1103, 928, 748.

Mp., Compound melts >250 ^{0}C.

Example 49

(±) 4-(4-difluoromethoxy-8-morpholinosulfonyldibenzo[*b,d*]furan-1-yl)-2-azolanone



Step 1: 4-difluoromethoxy-8-morpholinosulfonyldibenzo[*b,d*]furan-1-carbaldehyde
4-difluoromethoxydibenzo[*b,d*]furan-1-carbaldehyde (Intermediate 13) (400 mg, 1.52 mmol) was suspended in chlorosulphonic acid (5 ml) and stirred at 0°C for 30 mins and then reaction mixture was poured in water (20 ml) and extracted in ethyl acetate (25ml x 2) and concentrated under vacuum. This concentrated residue was dissolved in tetrahydrofuran (5 ml) and then morpholine (144 mg, 1.67 mmol) was added and stirred for 1 h. Water was added and precipitated solid was filtered to get the product as a white solid (250 mg).

IR (KBr): 3107, 3075, 2869, 1687, 1639, 1582, 1517, 1440, 1389, 1370, 1294, 1269, 1243, 1175, 1141, 1119, 1099, 1053, 941, 818 cm^{-1}.

^{1}H *NMR* (300 MHz, DMSO-d_6) δ 1.5 (m, 4H), 2.9 (m, 4H), 7.61 (d, 1H, *J* = 72.0 Hz), 7.67 (d, 1H, *J* = 9.0 Hz), 7.79 (d, 1H, *J* = 9.0 Hz), 7.93 (d, 1H, *J* = 9.0 Hz), 8.14 (d, 1H, *J* = 9.0 Hz), 9.22 (s, 1H), 10.29(s, 1H).

Step 2: (E)-3-(4-difluoromethoxy-8-morpholinosulfonyldibenzo[*b,d*]furan-1-yl)-2-propenoic acid
6-difluoromethoxy-8-morpholinosulfonyldibenzo[*b,d*]furan-1-carbaldehyde (from step 1) (250 mg, 0.608 mmol) was dissolved in toluene (10 ml) and added with malonic acid (75 mg, 0.729 mmol), and piperidine (0.3 ml) and refluxed at 120°C for 8 hrs. Excess of toluene was removed and fresh toluene (10 ml)was added and the toluene layer was washed with aqueous 2 N NaOH solution (10 x 3 ml).The aqueous layer was then acidified and filtered to get the product as a white solid (270 mg).

IR (KBr): 3434, 2942, 2856, 1685, 1627, 1511, 1453, 1386, 1360, 1339, 1316, 1276, 1232, 1165, 1117, 1095, 1052, 931, 819 cm^{-1}.

^{1}H *NMR* (300 MHz, DMSO-d_6) δ 1.5 (m, 4H), 2.9 (m, 4H), 6.73 (d, 1H), 7.54 (t, 1H, *J* = 72.0 Hz), 7.55 (d, 1H, *J* = 9.0 Hz), 7.91 (d, 1H, *J* = 9.0 Hz), 7.97 (d, 1H, *J* = 9.0 Hz), 8.11 (d, 1H), 8.25 (d, 1H), 8.39 (s, 1H).

Step 3: methyl (E)-3-(4-difluoromethoxy-8-morpholinosulfonyldibenzo[*b,d*]furan-1-yl)-2-propionate

(E)-3-(6-difluoromethoxy-8-morpholinosulfonyldibenzo[*b,d*]furan-1-yl)-2-propenoic acid (from step 2) (270 mg, 0.596 mmol), was suspended in methanol (10 ml) and added with conc. sulfuric acid (0.5 ml) .The reaction mixture was heated at 80 °C 3 hours. The reaction mixture was cooled to room temperature and diluted with water. The compound was extracted with ethyl acetate (25 x 3 ml).The organic extracts were combined and washed with water and dried over anhydrous Na_2SO_4. Removal of solvent under vacuo gave the product as an off-white solid (250 mg).

IR (KBr): 3075, 2869, 1687, 1639, 1582, 1517, 1440, 1389, 1370, 1294, 1269, 1175, 1141, 1119, 1099, 1053, 941, 833 cm^{-1}.

^{1}H *NMR* (300 MHz, DMSO-d_6) δ 1.5 (m, 4H), 2.9 (m, 4H), 3.8 (s, 3H), 6.80 (d, 1H), 7.56 (t, 1H, *J* = 72.0 Hz), 7.57 (d, 1H, *J* = 9.0 Hz), 7.95 (d, 1H, *J* = 9.0 Hz), 7.99 (d, 1H, *J* = 9.0 Hz), 8.12 (d, 1H), 8.32 (s, 1H), 8.39 (d,1H).

Step 4: methyl (E)-3-(4-difluoromethoxy-8-morpholinosulfonyldibenzo[*b,d*]furan-1-yl)-4-nitrobutanoate

Methyl (E)-3-(6-difluoromethoxy-8-morpholinosulfonyldibenzo[*b,d*]furan-1-yl)-2-propionate (from step 3) (250 mg, 0.535 mmol), was dissolved in nitro methane(5 ml) at 80°C.The reaction mixture was heated at 80°C for 10 minutes and a solution of 1,1,3,3-tetramethylguanidine (0.05ml) in nitro methane was added at the same temperature .The reaction mixture was heated at 80°C for 5 hours. The reaction mixture was cooled to room temperature, diluted with water and acidified to pH =5 .The compound was extracted with ethyl acetate (10x3 ml).The organic extracts were combined and washed with water and brine and dried over anhydrous Na_2SO_4. Removal of solvent under vacuo gave the crude product (100 mg), which was purified by silica gel column chromatography using 6% ethyl acetate in pet ether to give a white solid (260 mg).

IR (KBr): 2944, 2855, 1709, 1632, 1616, 1511, 1524, 1453, 225, 1165, 1115, 1066, 973, 946, 816 cm^{-1}.

^1H *NMR* (300 MHz, DMSO-d_6) δ 1.5 (m, 4H), 2.9(m, 4H), 3.2 (brd, 2H), 3.9 (s, 3H), 4.9 (m,1H), 5.2 (brd, 2H), 7.49 (t, 1H, *J* = 72.0 Hz), 7.51 (d, 1H, *J* = 9.0 Hz), 7.64 (d, 1H, *J* = 9.0 Hz), 7.95 (d, 1H, *J* = 9.0 Hz), 8.07 (d, 1H), 8.71 (s, 1H).

Step 5: (±) 4-(4-difluoromethoxy-8-morpholinosulfonyldibenzo[*b,d*]furan-1-yl)-2-azolanone

Methyl (E)-3-(4-difluoromethoxy-8-morpholinosulfonyldibenzo[*b,d*]furan-1-yl)-4-nitrobutanoate (from step 4) (260 mg, 0.492 mmol), was dissolved in a acetic acid added with zinc dust (500 mg, 200% w/w).The reaction mixture was heated at 120c for 2 hours. Reaction mass was cooled filtered to the celite filtrate was concentrated under vaccum to get the crude product which was purified by silica gel column chromatography using 20 % acetone in chloroform to get the product as a white solid (60 mg).

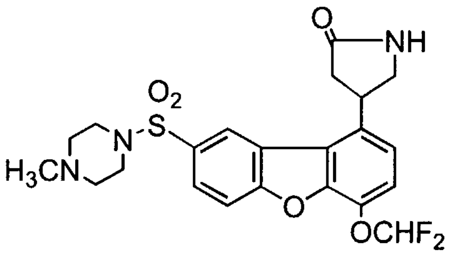
Mp: 226^{0}C

IR (KBr): 3207, 3095, 2930, 2854, 1703, 1641, 1516, 1448, 1392, 1340, 1285, 1234, 1160, 1052, 1034, 993, 815. cm^{-1}.

^1H *NMR* (300 MHz, DMSO-d_6) δ 1.62 (m, 4H), 2.81 (m, 1H), 2.86 (m, 1H), 3.01 (m, 4H), 3.47 (m,1H), 3.86 (m, 1H), 4.51 (m,1H), 7.49 (d, 1H, *J* = 9.0 Hz), 7.51 (d, 1H, *J* = 72.0 Hz), 7.57 (d, 1H, *J* = 9.0 Hz), 7.97 (s, 1H), 8.01 (d, 1H), 8.15 (d, 1H), 8.40 (s, 1H).

Example 50

(±) 4-[4-difluoromethoxy-8-(4-methylpiperazino)sulfonyldibenzo[*b,d*]furan-1-yl]-2-azolanone



Was synthesized by the method as described for Example (4002), except for using N-methylpiperazine instead of morpholine in step 1.

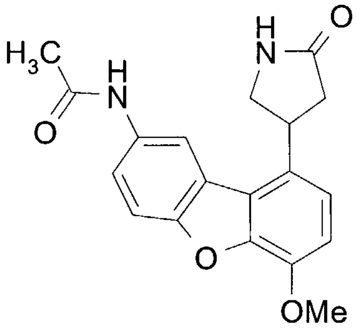
Mp: 232^{0}C

IR (KBr): 3214, 3095, 2930, 2853, 1701, 1641, 1516, 1448, 1392, 1340, 1285, 1234, 1160, 1052, 1034, 993, 815 cm^{-1}.

^{1}H *NMR*300 MHz, DMSO-d$_6$) δ 1.33 (m, 2H), 1.55 (m, 2H), 2.74 (m, 1H), 2.94 (m, 3H), 3.4 (m,1H), 3.82 (m, 1H), 4.44 (m, 1H), 7.42 (d, 1H, *J* = 9.0 Hz), 7.44 (d, 1H, *J* =72.0 Hz), 7.50 (d, 1H, *J* = 9.0 Hz), 7.90 (s, 1H), 7.95 (d, 1H), 8.09 (d, 1H), 8.33 (s, 1H).

Example 51

(±)*N*-[6-methoxy-9-(5-oxopyrrolidin-3-yl)dibenzo[*b*,*d*]furan-2-yl]acetamide



To a cooled solution 4-(8-amino-4-methyldibenzo [b,d]furan-1-yl)-2-azolanone of (intermediate 14) (0.16 mmoles),triethylamine (0.25 mmoles) in dichloromethane .Add a solution of acetic anhydride (0.20 mmoles) in dichloromethane at 0-10 ^{O}C within 15 mins. Reaction was stirred at room temperature for 1-2 hrs. The reaction mixture was diluted with water. The compound was extracted with ethyl acetate (10x3 ml).The organic extracts were combined and washed with water and brine and dried over anhydrous Na_2SO_4. Removal of solvent under vacuo gave the crude product which was purified by silica gel column chromatography

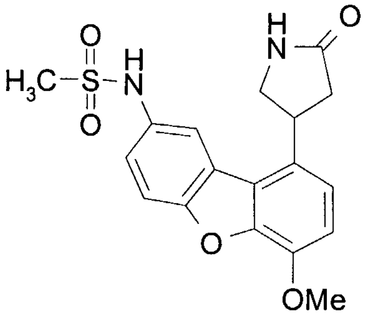
Mp: 185-200 ^{O}C .

^{1}H*NMR*-(300 MHz, DMSO): 2.08(3H,s) 2.41(1H,d), 2.71(1H,q), 3.79(1H,t), 3.96(3H,s), 4.24(1H,m), 7.14(1H,d), 7.27(1H, d), 7.71(2H,m), 7.81(1H,s), 8.38(1H,s), 10.14(1H,s).

IR (KBr) : 3423, 3327,3241, 3110, 2918, 2850, 1682, 1603, 1583, 1565, 1518, 1479, 1440, 1394, 1369, 1329 ,1294, 1284, 1265, 1238, 1169, 1108, 1051, 1023, 921, 875, 860, 835, 803, 739.

Example 52

(±) *N*-[6-methoxy-9-(5-oxopyrrolidin-3-yl) dibenzo [*b*,*d*]furan-2-yl]methane sulfonamide



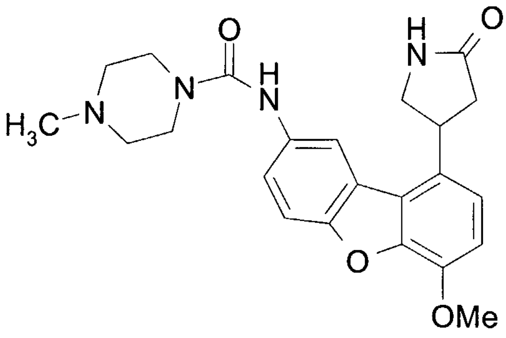
To a cooled solution 4-(8-amino-4-methyldibenzo [b,d]furan-1-yl)-2-azolanone (intermediate 14) of (0.33 mmoles), triethylamine (0.50 mmoles) in dichloromethane .Add a solution of methylsulphonyl chloride (0.37 mmoles) in dichloromethane at 0-10 ^{0}C within 15 mins. Reaction was stirred at room temperature for 1-2 h. The compound was extracted with ethyl acetate (10x3 ml).The organic extracts were combined and washed with water and brine and dried over anhydrous Na_2SO_4. Removal of solvent under vacuo gave the crude product which was purified by silica gel column chromatography M.P = 151-160 ^{0}C .

^{1}H*NMR*-(300 MHz, DMSO): δ 2.69(1H, dd), 2.95(1H, t), 3.02(3H, s), 3.97(1H, t), 4.06(3H, s), 4.36(1H, 2q), 6.18(1H, bs), D_2O Exchange, 6.99(1H, d *J*= 8.2 Hz), 7.20(1H,d *J*= 8.4 Hz), 7.41(1H, dd *J*= 2 & 8.7 Hz), 7.48(1H, s), 7.64(1H, d 8.9 hz), 7.90(1H, d. *J*= 8.7 Hz).

IR (KBr) : (cm^{-1}) 3413, 2929, 2851, 2320, 2048, 1743, 1681, 1614, 1558, 1555, 1520, 1514, 1462, 1436, 1325, 1289, 1238, 1198, 1152, 1107, 1055, 1027, 978, 904, 808, 772, 735, 608, 569, 559, 510.

Example 53

(±) 2-(4-methylpiperazinocarboxamido)-6-methoxy-9-(5-oxopyrrolidin-3-yl) dibenzo[*b*,*d*]furan



General procedure:-

To a cooled solution of phenylcarbamate of 4-(8-amino-4-methyldibenzo [b, d]furan-1-yl)-2-azolanone (0.14 mmoles), triethylamine (0.21 mmoles) in DMSO. Add slowly solution of N-methyl piperazine (0.17 mmoles) in above reaction mass at 0-10 ^{O}C within 15 mins. Reaction was stirred at room temperature for overnight. The reaction mixture was diluted with water. The compound was extracted with ethyl acetate (10x3 ml).The organic extracts were combined and washed with water and brine and dried over anhydrous Na_2SO_4. Removal of solvent under vacuo gave the crude product which was purified by silica gel column chromatography. Mp = 180-196 ^{O}C

^{1}H*NMR*-(300 MHz, DMSO): 8.68(1H, s) and 8.21(1H, s) D_2O exchange, 7.79(1H, s), 7.62(2H, m), 7.25(1H, d), 7.13(1H, d), 4.23(1H, m), 3.95(3H, s), 3.80 (1H, t), 3.46(6H, m), 2.70(1H, t), 2.41(4H, t), 2.22(3H, s).

IR-(KBr) : (cm^{-1}) 3965, 3784, 3571, 3414, 2925, 2853, 2804, 2312, 2050, 1733, 1675, 1651, 1636, 1584, 1544, 1518, 1474, 1444, 1400, 1384, 1341, 1293, 1258, 1202, 1234, 1169, 1148, 1128, 1108, 1051, 1025, 1001, 977, 958, 904, 872, 807, 753, 711, 690, 610, 624, 575, 510, 493, 460.

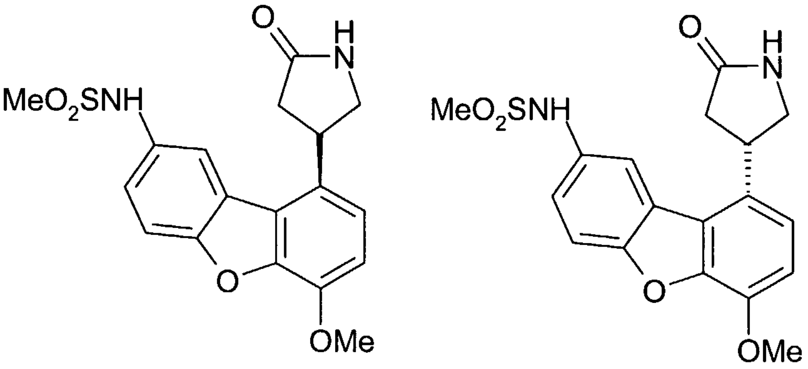
Example 54

(+) 4-[4-methoxy-8-(methylamino)dibenzo[*b, d*]furan-1-yl]pyrrolidin-2-one

and

Example 55

(–) 4-[4-methoxy-8-(methylamino) dibenzo[*b, d*]furan-1-yl]pyrrolidin-2-one

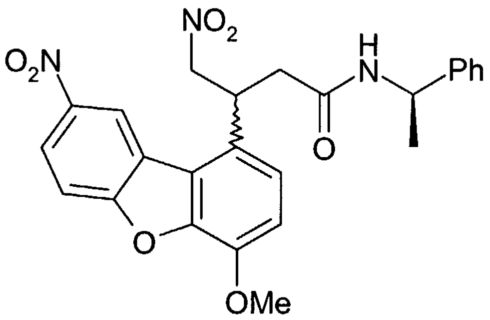


Step 1: (±) 3-(4-methoxy-8-nitrodibenzo [*b, d*]furan-1-yl)-4-nitrobutanoic acid

To a cooled solution of (±) methyl 3-(4-methoxy-8-nitrodibenzo[*b, d*]furan-1-yl)-4-nitrobutanoate (0.77 moles) in methanol 2 eq. aqueous NaOH (0.15 moles) was added slowly at 0-5 ^{o}C. Reaction mass was stirred overnight at room temperature.

^{1}H*NMR*-(300 MHz, DMSO): δ 2.87(2H, q) 4.00 3H, s), 4.77 (1H, m), 5.11 (2H, dd, *J*= 7.5 Hz), 7.31 (1H, dd , *J*= 8.4 Hz), 7.55 (1H, dd , *J* = 8.4), 8.02 (1H, dd , *J*= 7.5 Hz), 8.48 (1H, dd, *J* = 7.6 Hz), 9.20 (1H, d., *J* = 2.1), 12.30 (1H, bs),

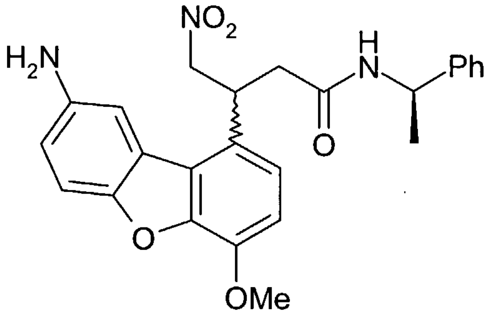
Step 2: Diastereomers of (±) 3-(4-methoxy-8-nitrodibenzo [*b, d*]furan-1-yl)-4-nitrobutanoic acid with (S)-(-)-1-Phenylethylamine



To a solution of 3-(4-methoxy-8-nitrodibenzo [*b*, *d*]furan-1-yl)-4-nitrobutanoic acid (from step 1) (2.6 mmoles), (S)-(-)-1-phenylethylamine (4.0 mmoles), EDCI (5.3 mmoles), and HOBt (1.3 moles) in DMF at 10-15 ^{O}C, triethylamine (5.3 mmoles) was added slowly and reaction mass was stirred at room temperature for 2-3 hrs.

^{1}H*NMR*-(300 MHz, DMSO): δ 1.09(3H, dd), 2.36(2H, d), 3.99(3H, s), 4.46(1H, t), .56(1H, m), 5.15 (2H, d), 5.55(2H, d), 6.49(3H, m), 7.21(2H, t), 7.55(1H, dd), 7.95(1H, dd. *J*= 9.3 Hz), 8.33 (1H, dd), ,8.28(1H, dd), 9.19(1H, s) D_2O Exchange

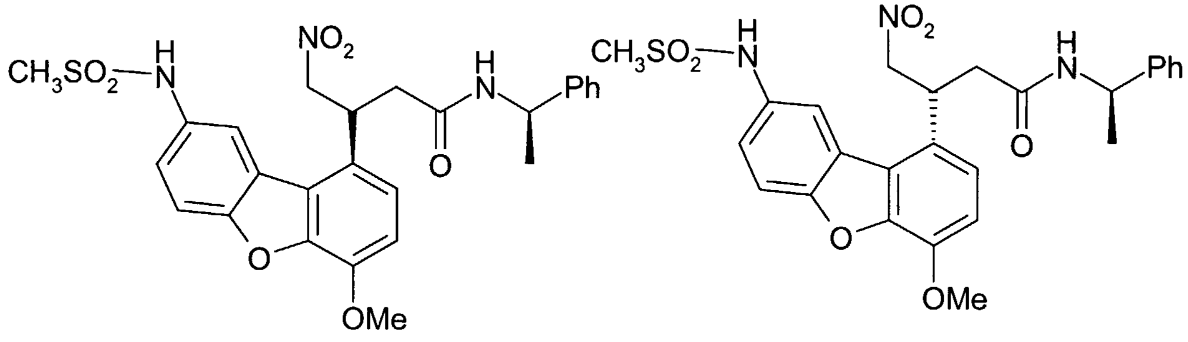
Step 3: Diastereomers of (±) 3-(4-methoxy-8-aminodibenzo [*b*, *d*]furan-1-yl)-4-nitrobutanoic acid with (S)-(-)-1-Phenylethylamine



The diastereomers from step 2 (350 mg) were reduced using 10% Pd/c (50 mg) in methanol under H2 gas at 60 psi pressure for 3 hrs.

^{1}H*NMR*-(300 MHz, DMSO): δ 1.00 (3H, dd), 2.30 (2H, d), 3.90 (3H, s), 4.66 (1H, t), 4.56(1H, m) 5.00 (2H, d) D_2O Exchange, 6.15 (2H, d), 6.40 (2H, t), 7.21(3H, m), 7.89 (1H, dd), 7.9 (1H, dd, *J*= 9.3 Hz), 8.03(1H, d), 8.23(4H, dd), 9.00 (1H, s) D_2O exchange.

Step 3: Diastereomers of (±) 3-(4-methoxy-8-methanesufonamidodibenzo [*b, d*]furan-1-yl)-4-nitrobutanoic acid with (S)-(-)-1-Phenylethylamine



To a cooled solution of above diastereomers from step 3 (0.33 mmoles), triethylamine (0.50 mmoles) in dichloromethane was added a solution of methylsulphonyl chloride (0.37 mmoles) in dichloromethane at 0-10 ^{O}C within 15 mins. Reaction was stirred at R.T for 1-2 hrs. The diastereomers were separated by silica gel column chromatography.

^{1}H*NMR*-(300 MHz, DMSO) (diastereomer 1): δ 1.40 (d 3H,), 2.73 (t 2H,), 3.00 (s, 3H,) 3.90 (s, 3H,), 4.78 (m 2H,), 5.12 (m, 2H,), 7.21(m, 7H,), 7.47 (q, 1H,), 7.36 (dd, 2H, *J* = 8.7 Hz), 8.14 (bs, 1H,), D_2O Exchange, 8.31(dd, 1H), 9.77 (bs 1H,) D_2O Exchange.

^{1}H*NMR*-(300 MHz, DMSO) (diastereomer 2): δ 1.40 (d, 3H), 2.73 (t 2H,), 3.00 (s, 3H,) 3.90 (s, 3H,), 4.78 (m, 2H), 5.12 (m, 2H), 7.25 (m, 7H), 7.51(q, 1H), 7.40 (dd, 2H, *J*= 8.7 Hz), 8.13 (bs, 1H) D_2O Exchange, 8.31(dd 1H), 9.77 (bs, 1H) D_2O Exchange.

Step 4: (+)4-[4-methoxy-8-(methylamino)dibenzo[*b, d*]furan-1-yl]-2-azolanone and (–) 4-[4-methoxy-8-(methylamino) dibenzo[*b, d*]furan-1-yl]-2-azolanone

To a solution of the separated diastereomers from step 3, (0.76 mmoles) in acetic acid Zn dust (3.8 mmoles) was added slowly at room temperature and heated to reflux for 4-6 hrs. After workup, the final products were purified by silica gel column chromatography.

^{1}H*NMR*-(300 MHz, DMSO) (+) **isomer**: δ 2.43(2H, t). 2.75(1H, q) 2.98(3H, s), 3.26 (1H, dd), 3.79(1H, t), 3.90 (3H, s), 4.25 (1H q), 7.11(1H, dd, *J*= 8.1 Hz), 7.27(1H, dd, *J*= 8.4

Hz), 7.40(1H, d), 7.42(1H, d), 7.75(1H, dd, *J*= 8.7 Hz), 7.81(1H, bs), D_2O Exchange 7.94(1H, dd), 9.72(1H bs,)D_2O Exchange.

M.P= 205 ^{O}C decompose.

^{1}H*NMR*-(300 MHz, DMSO) **(-) isomer** : δ 2.40 (2H, t). 2.54 (1H, q) 2.98 (3H, s), 3.25 (1H, dd), 3.79 (1H, t), 3.96 (3H, s), 4.25 (1H, q) 7.16(1H, dd , *J*= 8.1 Hz), 7.27(1H, dd *J* = 8.4 Hz), 7.40(1H, d), 7.43(1H, d), 7.74(1H, dd , *J* = 8.7 Hz), 7.81(1H, bs), D_2O Exchange, 7.98(1H, dd), 9.75(1H bs,)D_2O Exchange.

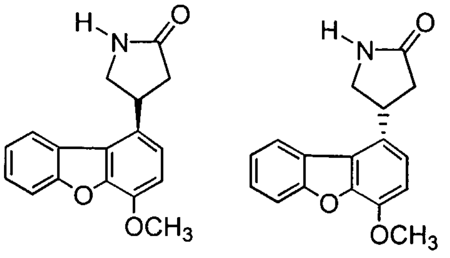
Example 56

(+) 4-(4-methoxydibenzo [b,d] furan-1-yl)-2-azolanone

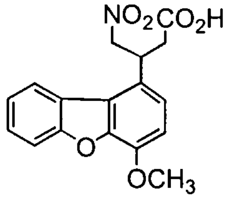
And

Example 57

(-)4-(4-methoxydibenzo [b,d] furan-1-yl)-2-azolanone



Step 1: (±)3-(4-methoxydibenzo[b,d]furan-1yl)-4-nitrobutanoicacid

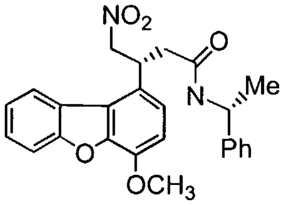


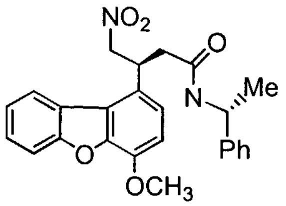
A solution of sodium hydroxide (3.49 gram, 0.086 moles), in water (150 ml), was added to a solution of Methyl 3-(4-methoxydibenzo[b,d] furan-1-yl)-4-nitrobutanoate (example 10) (15 gram, 0.043 moles), in methanol (300 ml), at 0°C. The resulting suspension was stirred overnight at room temperature .The reaction mixture was then cooled to 0°C and was acidified with 10 % aqueous hydrochloric acid. Methanol was evaporated and water was added to the reaction mixture. It was then filtered and dried under vacuum to get the product (13 gram, white solid).

IR (KBr): 3240, 3080, 2933, 2871, 1710, 1526, 1442, 1310, 1224, 1103, 1016, 817, 742, 730 cm^{-1}.

1H-*NMR* (300 MHz, DMSO-d^6): δ 2.85 (d, 2H, *J* = 7.2 Hz), 3.97 (s, 3H), 4.75 (m, 1H), 5.08 (m, 2 H), 7.15 (d, 1H, *J* = 8.7 Hz), 7.39 (d, 1H, *J* = 9 Hz), 7.45 (t, 1H), 7.55 (t, 1 H), 7.72 (d, 1H, *J* = 7.8Hz), 8.25 (d, 1H, *J* = 7.8 Hz), 12.34 (brs,1H).

Step 2: (+)(-) N1-(1-phenylethyl)- 3-(4-methoxydibenzo[b,d]furan -1-yl)-4-nitrobutanamide and (-)(-) N1-(1-phenylethyl)- 3-(4-methoxydibenzo[b,d]furan -1-yl)-4-nitrobutanamide)





Preparation of acid chloride

(±) 3-(4-methoxydibenzo[b,d]furan-1yl)-4-nitrobutanoicacid (from step 1) (13gram, 0.039 moles), was suspended in benzene (130 ml), and Thionyl chloride (26 ml), was added to it at 0-5°C. The reaction mixture was refluxed for 1 hr. Benzene was then distilled off and a fresh lot of benzene (100 ml) was added to the reaction mixture. Benzene was again distilled of and the process was repeated to ensure complete removal of thionyl chloride.

Preparation of amide

Acid chloride prepared in above manner was added with benzene (150 ml), and refluxed for 15 minutes. A mixture of solution of triethylamine (7.9 gram, 0.078 moles), and S-(-)-α-methyl benzyl amine (9.5 gram, 0.078 moles), in benzene (75 ml), was slowly added in dropwise manner, at reflux temperature, to the solution of acid chloride in benzene. The reaction mixture was refluxed for 30 more minutes. It was then cooled to room temperature and the solid obtained was filtered and washed with water,dried and then column chromatographed to get two separate diastereoisomers.

Spectral data of diastereomer 1 :

IR (KBr):3438, 3177, 2939, 1662, 1583, 1518, 1451, 1400, 1296, 1278, 1213, 1102, 1012, 804,754, 689 cm^{-1}.

1H-*NMR* ($CDCl_3$): δ 1.38 (d, 3H, *J* = 6.9 Hz), 2.80 (d, 2H, *J* = 7.2 Hz), 4.05 (s, 3H), 4.96-5.02 (m, 4H), 5.58 (brm, 1H), 6.92 (d, 1 H, *J* = 8.7 Hz), 7.08-7.06 (m, 2H), 7.22-7.24 (m, 4H), 7.39(t, 1H), 7.47 (t, 1H), 7.67 (d, 1H, *J* = 8.1 Hz), 8.13 (d, 1H, *J* = 7.8 Hz).

Spectral data of diastereomer 2:

IR (KBr): 3428, 3167, 2820, 1678, 1521, 1510, 1411, 11390, 1277, 1214, 1110, 1102, 1004, 856,786, 668 cm^{-1}.

1H-*NMR*($CDCl_3$): δ 1.33 (d, 3H, *J* = 6.9 Hz), 2.88-2.72 (m, 2H), 4.04 (s, 3H), 5.06-4.88 (m, 4H), 5.61 (brd, 1H), 6.88 (d, 1 H, *J* = 8.4 Hz), 7.03 (d, 1H, *J* = 8.1 Hz), 7.08 (m, 2H), 7.22-7.28 (m, 3H), 7.41(t, 1H), 7.51 (t, 1H), 7.66 (d, 1H, *J* =8.1 Hz), 8.16 (d, 1H, *J* = 7.8 Hz).

Step 3a: (-) 4-(4-methoxydibenzo [b,d] furan-1-yl)-2-azolanone and

(+)(-) N1-(1-phenylethyl)- 3-dibenzo[b,d]furan -1-yl-4-nitrobutanamide (from step 2) (5 gram, 0.011 moles), was dissolved in acetic acid (50 ml), and added with zinc dust (3.75 gram, 0.055 moles), at room temperature. The reaction mixture was then refluxed for 2 hrs at 130°C.It was then cooled to room temperature and added to water (1 lit).The precipitate obtained was then filtered and washed with water and column chromatographed to get product as off white solid. m.p: 192°C; $[\alpha]_D$ -29° c = 0.5 % in MeOH at 25°C.

IR (KBr): 3440, 3180, 2842, 1663, 1583, 1518, 1451, 1400, 1297, 1278, 1231, 1213, 1103, 1013, 804, 754, 690 cm^{-1}.

1H-*NMR* (DMSO-d^6): δ 2.40 (m, 1H), 2.745 (m, 1H), 3.44 (m, 1H), 3.80 (m, 1H), 3.97(s, 3H), 4.35 (m, 1 H), 7.16 (d, 1H, *J* = 8.4 Hz), 7.25(d, 1H, *J* = 8.4 Hz), 7.42 (t, 1H), 7.55 (t, 1 H), 7.77 (d,1H, *J* = 8.7 Hz), 7.99(brs, 1H), 8.11 (d, 1H, *J* = 8.1 Hz) .

Step 3b: (+) 4-(4-methoxydibenzo [b,d] furan-1-yl)-2-azolanone

The compound was obtained by the process mentioned above using (-)(-) N1-(1-phenylethyl)- 3-dibenzo[b,d]furan -1-yl-4-nitrobutanamide (from step 2) as the starting material. Mp: 191°C, $[\alpha]_D$ +20° c = 0.5 % in MeOH at 25°C.

IR (KBr): 3198, 2953, 2840, 1703,1655, 1608, 15191450, 1401, 1296,1277, 1232, 1213, 1171, 1131, 1011,748, 731, 678 cm^{-1}.

1H-*NMR* (300 MHz, DMSO-d^6): δ 2.40 (m, 1H), 2.74 (m, 1H), 3.34 (m, 1H), 3.82 (m, 1H), 3.97(s, 3H), 4.36 (m, 1 H), 7.16 (d, 1H, *J* = 8.4 Hz), 7.25(d, 1H, *J* = 8.4 Hz), 7.42 (t, 1H), 7.55 (t, 1 H), 7.77 (d,1H, *J* = 8.1 Hz), 7.80(brs, 1H), 8.12 (d, 1H, *J* = 8.1 Hz) .

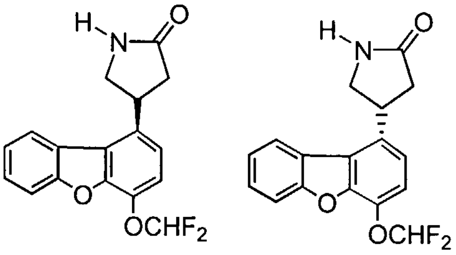
Example 58

(+) 4-(4-difluoromethoxydibenzo [b,d] furan-1-yl)-2-azolanone

and

Example 59

(-)4-(4-difluoromethoxydibenzo [b,d] furan-1-yl)-2-azolanone



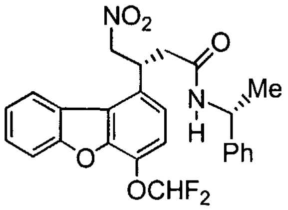
Were synthesized using intermediate 15 by the process described for synthesis of examples 3929 and 3930.

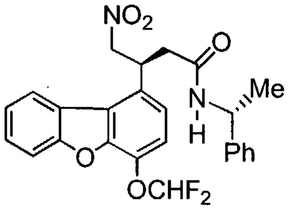
Step 1: (±)3-(4-difluoromethoxydibenzo[b,d]furan-1yl)-4-nitrobutanoicacid

IR (KBr): 3324, 3029, 2929, 1684, 1616, 1602, 1535, 1511, 1464, 1357, 1269, 1254, 1212, 1101, 1067, 1011, 790, 686 cm^{-1}.

1H *NMR* (DMSO-d^6): δ 2.66(m, 2H), 4.80(m, 1H), 5.03(m, 2H), 6.74 (d, 1 H, *J*=8.4 Hz), 7.36 (t, 1H, *J*=81.3 Hz), 7.58(t, 1H), 7.60 (t, 1 H), 7.78 (m, 2H), 8.18(d, 1H, *J*=8.4 Hz), 12.34 (brs, 1H).

Step 2: (+)(-) N1-(1-phenylethyl) - 3-(4-difluoromethoxydibenzo [b,d]furan -1-yl)-4-nitrobutanamide and (-)(-) N1-(1-phenylethyl)- 3-(4-difluoromethoxydibenzo[b,d]furan -1-yl)-4-nitrobutanamide





Spectral data of isomer 1:

IR (KBr): 3434, 3189, 2989, 1682, 15343, 1521, 1432, 1410, 1356, 1224, 1211, 1182, 1021, 956,824,756, 688 cm^{-1}.

1H *NMR* (300 MHz, DMSO-d^{6}): δ 2.62(m, 2H), 4.82(m, 1H), 5.05(m, 2H), 7.14-7.44 (m, 3H), 7.26-7.44 (m, 4H), 7.60-7.68 (m, 3H), 7.84(d, 1 H, *J* = 8.1Hz), 8.32-8.39(m, 2H).

Spectral data of isomer 2:

IR (KBr):3422, 3124, 2968, 1678, 1554, 1539, 1428, 1412, 1354, 1276, 1209, 1148, 1011, 965, 832, 756, 680 cm^{-1}.

1H *NMR*(DMSO-d^{6}): δ 2.64(m, 2H), 4.84(m, 1H), 5.04(m, 2H), 7.19-7.42 (m,3H),7.26-7.40 (m, 4H), 7.50-7.68(m, 3H), 7.82(d, 1 H, *J*=8.1Hz), 8.29(d, 1H, *J*=6.9 Hz), 8.39(d, 1H, *J*=8.1 Hz).

Step 3a: (-) 4-(4-difluoromethoxydibenzo [b,d] furan-1-yl)-2-azolanone:

[α]$_D$ -26° C = 1.0 % in chloroform at 25°C.

IR (KBr): 3371, 3186, 3094, 2924, 1694, 1587, 1515, 1451, 1396, 1300, 1268, 1233, 1159, 1137, 1112, 1026, 799, 749, 682 cm^{-1}.

1H *NMR*(DMSO-d^{6}): δ 2.46-2.52(m, 1H), 2.82(m, 1H), 3.39(m,1H), 3.83(m,1H), 4.47(m, 1H), 7.37-7.41(m, 2H), 7.48(t, 1H), 7.59-7.66(m,2H), 7.82-7.85(m, 2H), 8.19(d, 1H, *J*=7.5Hz).

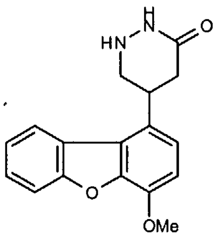
Step 3b: (+)-4-(4-difluoromethoxydibenzo [b,d] furan-1-yl)-2-azolanone:
$[\alpha]_D$ +25° C = 1.0 % in chloroform at 25°C.

IR (KBr): 3374, 3224, 3010, 2928, 1717, 1582, 1542, 1465, 1398, 1298, 1256, 1222, 1165, 1143, 1109, 1046, 780, 769, 682 cm^{-1}.

1H *NMR* (300 MHz, DMSO-d^6): δ 2.40 (m, 1H), 2.74(m, 1H),3.39(m,1H), 3.83(m,1H), 4.45(m, 1H), 7.37-7.51(m, 2H), 7.48(t, 1H), 7.59-7.66(m, 2H), 7.82-7.85(m, 2H), 8.19 (d, 1H, *J* = 7.2Hz).

Example 60

(±) 5-(4-methoxydibenzo [*b,d*]furan-1-yl) hexahydro-3-pyridazinone



Step 1: 4-(4-methoxydibenzo [*b,d*]furan-1-yl)-1,4,5,6-tetrahydro-6-pyridazinone
Methyl 3-(4-methoxydibenzo [*b,d*] furan-1-yl)-4-nitrobutanoate (intermediate 10) (80 mg) was suspended in mixture of methanol (10 ml) and water (1ml). To this, sodium hydroxide pellets (83 mg) were added and the resulting mixture was stirred at room temperature for 48 h. The clear solution obtained was added drop wise to 60% methanolic sulfuric acid (50 ml) at -10°C and the mixture was stirred at -10°C for 3h. The resulting mixture was extracted with chloroform (3x 25 ml). The organic layer was washed with water (2x25 ml), brine (2x20ml) and dried over anhydrous sodium sulphate and concentrated in vacuum to give orange colored oil (65 mg) which was directly taken to the cyclization reaction.

The above oil (60 mg) was dissolved in absolute ethanol (10 ml) and to this hydrazine hydrate (1ml) was added and the resulting mixture was refluxed for 8h. The reaction was cooled and the solvent was evaporated to remove excess of ethanol. To the residue, water (25ml) was added and was neutralized with dilute hydrochloric acid. The solid obtained was filtered and the crude product thus obtained was column chromatographed using 20% acetone in chloroform to give a white solid (50 mg)

IR (KBr): 3437, 2925, 2961, 2853, 1670, 1634, 1518, 1450, 1402, 1262, 1276, 1215, 1166, 1128, 1101, 1014, 803, 744, 732, 543 cm^{-1}

^1H NMR (300 MHz, $CDCl_3$): δ 2.6 (dd, 1H), 2.9 (dd, 1H), 4.05 (s, 3H), 4.72 (m, 1H), 7.08 (d, 1H, *J* = 8.4 Hz), 7.19 (d, 1H, *J* = 8.1Hz), 7.33 (d, 1H, *J* = 2.7 Hz), 7.447 (t, 1H, *J*= 7.5 Hz), 7.57 (t, 1H, *J*= 7.5 Hz), 7.78 (d, 1H, *J* = 8.1 Hz), 8.05 (d, 1H, *J* = 7.8 Hz), 11.037 (s, 1H, exchanges with D_2O)

Mass spectra M+1: 295

M.P. (°C): 207-208°C (compound decomposes)

Step 2: 5-(4-methoxydibenzo [*b,d*]furan-1-yl)hexahydro-3-pyridazinone

4-(4-methoxydibenzo [*b,d*]furan-1-yl)-1,4,5,6-tetrahydro-6-pyridazinone (50 mg) was suspended in absolute ethanol (10 ml) and glacial acetic acid (2-3 drops) and platinum oxide (25 mg) was added. The resulting mixture was stirred at room temperature under hydrogen (pressure 30 psi) in a parr hydrogenator for 12h. The reaction mixture was filtered and evaporated in vacuum to remove excess of ethanol. The slurry obtained was extracted with chloroform (3x15ml). The organic layer was washed with water (2x10ml), saturated $NaHCO_3$ (2x10ml) and brine (2x10ml). The organic layer was dried over anhydrous sodium sulphate and distillation of solvent under reduced pressure gave a crude product which was column chromatographed using silica gel and 20% acetone in chloroform as eluent to yield pure product (43 mg).

IR (KBr):3446, 3222, 3058, 2921, 1683, 1634, 1517, 1451, 1397, 1273, 1230, 1164, 1129, 1093, 1015, 937, 752, 513 cm^{-1}

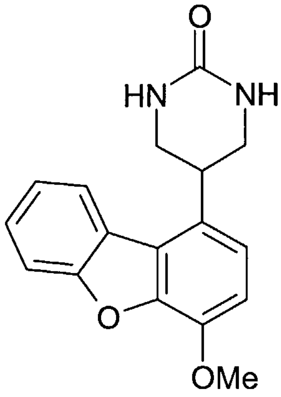
^1H NMR (300 MHz, $CDCl_3$): δ 2.6 to 2.8 (m, 2H), 2.9 to 3.2 (m, 2H), 3.97 (s, 3H), 4.078 (m, 1H), 5.37 (broad singlet, 1H, exchanges with D_2O) 7.16 (d, 1H, *J* = 8.4 Hz) 7.22 (d, 1H, *J* = 8.4 Hz) , 7.43 (t, 1H, *J* = 8.1 Hz), 7.55 (t, 1H, *J* = 8.4 Hz), 7.75 (d, 1H, *J* = 8.1 Hz), 8.26 (d, 1H, *J* = 7.8 Hz), 9.05 (s, 1H, slowly exchanges with D_2O)

Mass spectra M+1: 297

M.P. (°C): 210-212°C (compound decomposes)

Example 61

5-[4-(methoxy)dibenzo[*b, d*]furan-1-yl]tetrahydropyrimidin-2(1*H*)-one



Step 1: 3-(4-methoxydibenzo[*b*,*d*] furan-1-yl)pentanedinitrile :

To a solution of 4-methoxydibenzo[*b*,*d*]furan-1-carbaldehyde (intermediate 7a) (3 gm; 0.0133M) in pyridine (100 mL), Cyanoacetic acid (11.3 gm, 0.133 M) and piperidine (5 mL) was added and stirred for 16 hrs at 80 ^{0}C to yield 3-(4-methoxydibenzo[*b*,*d*]furan-1-yl)pentanedinitrile (86%).

1H-NMR (DMSO d^6): δ values 8.2685 (d, 1H, *J*=7.5 Hz), 7.7835 (d, 1H, *J*=8.1 Hz), 7.580 (t, 1H, *J*=7.35 Hz), 7.478 – 7.428 (m, 2H), 7.260 (d, 1H, *J*= 8.4 Hz), 4.392 (m, 1H), 4.015 (s, 3H), 3.272-3.050 (m, 4H).

IR (cm^{-1}) KBr : 3437, 2941.71, 2845, 2245, 1637, 1585, 1519, 1452, 1280, 1237, 1013, 936.

Mp. = 189 – 191 ^{0}C

Step 2: 3-(4-methoxydibenzo[*b*,*d*]furan-1-yl)pentanediamide:

To a suspension of 3-(4-methoxydibenzo[*b*,*d*] furan-1-yl)pentanedinitrile (from step **1**) (3 gm, 0.0103 M), a 10 % solution of sodium carbonate (1.0917 gm, 0.0103 M) was added. After cooling to 0 ^{0}C, hydrogen peroxide [50%, 3.502 gm, 0.103 M) was added drop-wise and stirred for 18 hrs to yield the product (62%) on purification with Silica Gel.

1H-NMR (300 MHz, DMSO d^6): δ values 8.394 (d, 1H, *J*=7.8 Hz), 7.395 (d, 1H, *J*=8.1 Hz), 7.533 (t, 1H, *J*=7.5 Hz), 7.295 (t, 3H, *J*=7.65 Hz, *2 protons exchanges with D_2O*), 7.202 (d, 1H, *J*=8.1Hz), 7.098 (d, 1H, *J*=8.4 Hz), 6.791 (s, 2H, *exchanges with D_2O*), 4.351 (m, 1H), 3.962 (s, 3H), 2.587 (q, 2H, *J*=7.35 Hz), 2.410 (q, 2H, *J*=6.6 Hz).

IR (cm^{-1}) KBr : 3463, 3427, 3340, 3210, 2934, 2909, 2839, 1654, 1619, 1519, 1449, 1401, 1278, 1235, 1222, 1131, 1101, 1013, 890.

Mp. = melts above 250 ^{0}C.

Step 3: 5-(4-methoxydibenzo[*b*,*d*]furan-1-yl)tetrahydropyrimidin-2(1*H*)-one:

To a solution of 3-(4-methoxydibenzo[*b*,*d*]furan-1-yl)pentanediamide (from step 2) (81.5 mg, 0.00025 M) in Pyridine, Lead tetra acetate (277 mg 0.000625 M) was added and stirred for 18 hrs. Water was added to RM and extracted with chloroform. On purification on Silica Gel, it yielded (41 %).

1H-NMR (DMSO d^6): δ values 8.027 (d, 1H, *J*=7.5 Hz), 7.704 (d, 1H, *J*=8.1 Hz), 7.568 (t, 1H, *J*=7.5 Hz), 7.458 (t, 1H, *J*=7.25 Hz), 7.244 (d, 1H, *J*=8.7Hz), 7.143 (d, 1H, *J*=8.4 Hz), 6.361 (s, 2H, *exchanges with D_2O*), 3.972 (s, 3H), 3.809 – 3.785 (m, 1H), 3.475 – 3.404 (m, 4H).

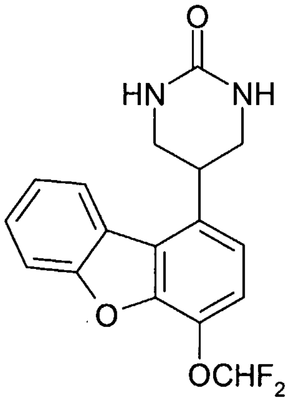
IR (cm^{-1}) KBr : 3241, 3079, 2925, 1689, 1546, 1519, 1439, 1274, 1224, 1170, 1098, 793, 742, 686.

Mass $[m+H]^+$: 297.1, 280, 251, 237.1, 211.

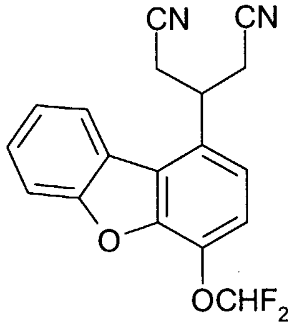
Mp. = decomposes above 250 ^{0}C.

Example 62

5-[4-(difluoromethoxy)dibenzo[*b*, *d*]furan-1-yl]tetrahydropyrimidin-2(1*H*)-one



Step 1: 3-[4-(difluoromethoxy)dibenzo[*b, d*]furan-1-yl]pentanedinitrile

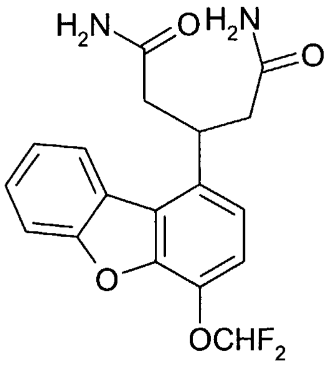


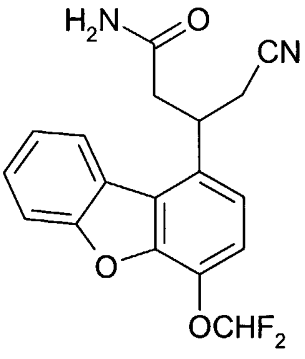
To a solution of 4-(difluoromethoxy)dibenzo[*b, d*]furan-1-carbaldehyde (intermediate 13) (0.19 mmoles) in pyridine, cyanoacetic acid (1.9 mmoles) was added slowly at room temperature. Reaction mass was slowly heated up 80-90 ^{O}C for overnight.

^{1}H*NMR*-(300 MHz, DMSO): δ 3.10 (4H, m), 4.32 (1H, q), 6.84 (1H, t, *J* = 72 Hz), 7.25(1H, d), 7.40(1H, d, *J*= 8.4 Hz), 7.47 (1H, t, *J*= 7.8 Hz), 7.60 (1H, t , *J*= 7.8 Hz), 7.73 (1H, d , *J*= 7.8 Hz), 8.75(1H d , *J*=7.8 Hz).

Mp = Above 250 ^{O}C .

Step 2: (a) 3-[4-(difluoromethoxy)dibenzo[*b, d*]furan-1-yl]pentanediamide and (b) 4-cyano-3-(4-difluoromethoxydibenzo[*b, d*]furan-1-yl) butanamide





To a cooled solution of 3-[4-(difluoromethoxy) dibenzo [*b, d*]furan-1-yl]pentanedinitrile (from step 1) (0.12 mmoles), Na_2CO_3 (0.24 mmoles) in Acetone/ water(5:1) slowly 50% H_2O_2 was added at 0-5 ^{O}C. and reaction was stirred at room temperature overnight. The two compounds were separated by column chromatography.

Mp = Above 250 ^{O}C

^{1}H-NMR-(DMSO) **(a)** : δ 2.40 (2H, t), 2.43 (2H, dd), 2.54 (1H, q), 6.83 (2H, bs) D2O Exchange, 7.27-7.50 (5H, m), 7.41 (1H, t, *J* = 72 Hz), 7.59 (1H, t), 7.80 (1H, d), 8.43 (1H , d).

^{1}HNMR-(300 MHz, DMSO) **(b)**: 2.50-2.82 (m, 2H), 2.97-3.35 (m, 2H), 4.37(t, 1H), 6.93(bs, 1H), 7.43-7.50 (m, 4H,) 7.52 (1H, s) D2O Exchange, 7.62 (t, 1H), 7.85 (d, 1H,) 8.26 (d 1H,).

Step 3: 5-[4-(difluoromethoxy)dibenzo[*b, d*]furan-1-yl]tetrahydropyrimidin-2(1*H*)-one

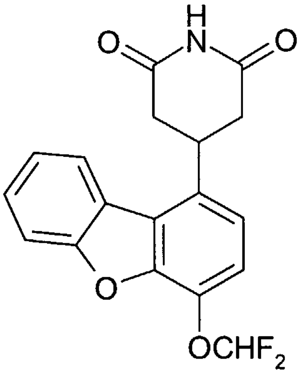
The 3-[4-(difluoromethoxy)dibenzo[*b, d*]furan-1-yl]pentanediamide [compound (a) from step 2] (2.03 mmoles) was dissolved in pyridine and Pb(OAc)$_4$ (5.08 mmoles) was added in one lot. Reaction was stirred at room temperature for 1 hrs. Removal of pyridine under vacuum, and purification of the residue by silica gel column chromatography gave the desired product as a white solid (200 mg).

^{1}HNMR-(300 MHz, DMSO): 3.47 (4H, m), 3.87 (1H, m), 6.39 (2H, s), 7.33(1H, t, *J* = 72 Hz), 7.48 (1H, d), 7.38(1H, d), 7.50 (1H, t), 7.62 (1H, t), 7.85 (1H, dd, *J*= 7.8 & 2 Hz), 8.75(1H dd, *J*=7.8 & 2 Hz)

Mp: Above 250 ^{O}C .

Example 63

4-[4-(difluoromethoxy)dibenzo[*b, d*]furan-1-yl]piperidine-2, 6-dione



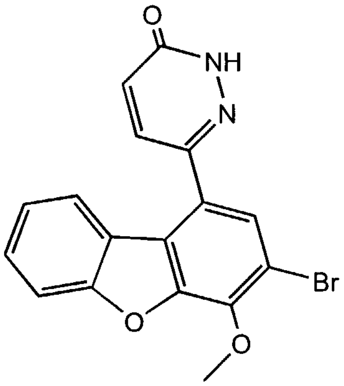
To solution of 4-cyano-3-[4-(difluoromethoxy)dibenzo[*b, d*]furan-1-yl]butanamide [compound (b) from step 2 of example 3968] (0.14 mmoles) in acetone water (5:1) phosphoric acid 85 % (0.49 mmoles) was added at 0-5 ^{O}C and stirred at room temperature overnight. Removal of pyridine under vacuum, and purification of the residue by silica gel column chromatography gave the desired product as a white solid (10 mg). Mp = Above 250 ^{O}C

^{1}H-NMR (300 MHz, DMSO): 2.93 (1H, d), 2.98 (1H, m), 3.12 (1H, d), 3.18 (1H, d), 4.25(1H, m), 6.83 (1H, t, J = 72 Hz), 7.10 (1H, d), 7.30 (1H, d), 7.43 (1H, t), 7.57 (1H, t), 7.70 (1H, d), 7.88 (1H, d), 8.07 (1H bs) D2O exchange.

IR (KBr) (cm^{-1}) 3438, 3202, 3083, 2924, 2318, 1703, 1640, 1516, 1486, 1453, 1427, 1404, 1379, 1352, 1313, 1271, 1217, 1190, 1235, 1112, 1052, 994, 925, 829, 790, 751, 732, 591, 557, 524, 467.

Example 64

6-(3-bromo-4-methoxydibenzo[*b*,*d*]furan-1-yl)pyridazin-3(2*H*)-one:



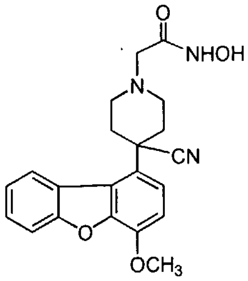
To a solution of 6-(4-methoxydibenzo[b,d]furan-1-yl))-4,5-dihydropyridazin-3(2H)-one (example 4) in acetic acid, bromine was added at 60-65°C and stirred for 6 hrs. On work up it yielded 6-(3-bromo-4-methoxydibenzo[*b*,*d*]furan-1-yl)pyridazin-3(2*H*)-one.

1H NMR: (300, MHz, DMSO-d^{6}) δ 4.22 (s, 3H); 7.08 (d, 1H, J = 9.9Hz); 7.37 (t, 1H, J = 7.8Hz); 7.61 (t, 1H, J = 7.5Hz); 7.75 (s, 1H); 7.82 (d, 1H, J = 8.1 Hz); 7.90 (d, 1H, J = 9.9Hz); 7.93 (d, 1H, J = 7.5Hz).

IR (KBr) (cm^{-1}): 3422, 2999, 1690, 1594, 1258, 844

Example 65

N-Hydroxy-2-[4-cyano-4-(4-methoxydibenzo[b,d]furan-1-yl)piperidino] acetamide



Step 1: 4-Methoxy dibenzo[*b,d*]furan-1-yl methanol

4-methoxydibenzo[*b,d*]furan-1-carbaldehyde (intermediate 7a) (500mg, 2.21 mmole) was dissolved in methanol (10ml) and a solution of sodium borohydride (500mg) in water (5.0 ml) was added slowly at 15-20 ^{0}C and stirred further at room temperature for 2.0 hours. Water (100 ml) was added to the reaction mixture and extracted with ethyl acetate (3x25 ml). The combined ethyl acetate layers were washed with water (2x25ml), dried over anhydrous sodium sulfate and concentrated under vacuo to give product as of white solid (450mg).

m.p. 124°C

IR (KBr) 3352, 1633, 1521, 1451, 1302, 1276, 1165, 1103 1001,808,747 cm^{-1};

^{1}H NMR (300 MHz, DMSO-d$_6$) δ 3.97 (s, 3H), 4.92 (d, 2H), 5.35 (t, 1H), 7.12 (d, 1H, J = 9.3 Hz), 7.30 (d, 1H, J = 8.4 Hz), 7.40 (t, 1H, J = 7.2 Hz), 7.52 (t, 1H, J = 7.2 Hz), 7.72 (d, 1H, J = 7.8 Hz), 8.12 (d, 1H, J = 7.2 Hz).

Step 2: 2-(4-Methoxy dibenzo[b,d]furan-1-yl) Acetonitrile

4-Methoxy dibenzo[*b,d*]furan-1-yl methanol (from step 1)(400mg, 1.75 mmole) was dissolved in benzene (10ml) and thionyl chloride (1.0 ml) was added slowly at 15-20 °C. The reaction mixture was then refluxed fro 3-4 hours. Excess of thionyl chloride and benzene were removed under vacuo. The traces of thionyl chloride were removed by co distillation with benzene under vacuo. The residue obtained was dissolved in dimethyl formamide (5.0ml) and finely powdered sodium cyanide (150mg, 3.25 mmole) was added. The reaction mixture was then stirred at room temperature for 10-12 hours. Water (50 ml) was added to the reaction mixture and extracted with ethyl acetate (3x30 ml). The combined ethyl acetate layer were washed with water (25ml), 4% sodium hypochlorite solution (25ml) and finally with water (25ml) and dried over anhydrous sodium sulfate. Removal of sovent under vacuo gave sticky solid, which was then purified by column chromatography on silica gel using 20% ethyl acetate in petroleum ether to give 350 mg of product as yellow solid, mp 147°C.

IR (KBr) 3440, 1629, 1574, 1359, 1283, 1181, 1002, 982 cm^{-1};
^{1}H NMR (300 MHz, DMSO-d$_6$) δ 3.99 (s, 3H), 4.51 (s, 2H), 7.21 (d, 1H, J = 9.3 Hz), 7.35 (d, 1H, J = 8.4 Hz), 7.47 (t, 1H, J = 7.2 Hz), 7.59 (t, 1H, J = 7.2 Hz), 7.79 (d, 1H, J = 7.8 Hz), 8.15 (d, 1H, J = 7.2 Hz).

Step 3: tert-Butyl-4-cyano-4-(4-methoxydibenzo[*b,d*]furan-1-yl)-1-piperidine carboxylate

Sodium hydride (128mg, 3.23 mmole) was suspended in dimethyl formamide (3.0 ml)and a solution of 2-(4-Methoxy dibenzo[b,d]furan-1-yl) acetonitrile (from step 2) (350mg, 1.47 mmole) in dimethyl formamide (2.0 ml) was added slowly at 10-15oC under stirring. The reaction mixture was then stirred at room temperature for 30 minutes. To this a solution of N-BOC-N, N-bis (2-chloro ethyl) amine in dimethyl formamide (3.0 ml) was added and stirred at 80-90oC for 6-7 hours. Reaction mixture was cooled to room temperature; water (100ml) was added. The product separated was extracted with ethyl acetate (3x25ml). The combined ethyl acetate layers were washed with water (2x25ml) and dried over anhydrous sodium sulfate. Removal of solvent under vacuo gave sticky solid, which was then purified by column chromatography on silica gel using 5% ethyl acetate in choloroform to give 250 mg of product as yellow solid, mp 147°C.

IR (KBr) 3447, 2930, 1697, 1631, 1512, 1453, 1366, 1280, 1166, 1014, 801, 751 cm-1;
^{1}H NMR (300 MHz, DMSO-d$_6$) δ 1.50 (s,9H), 2.21-2.18 (t, 3H), 2.53-2.57 (d, 2H),3.40 (t, 2H), 4.08 (s, 3H), 4.36 (d, 2H), 6.97 (d, 1H, J = 9.3 Hz), 7.29 (d, 1H, J = 8.4 Hz), 7.42 (t, 1H, J = 7.2 Hz), 7.55 (t, 1H, J = 7.2 Hz), 7.71 (d, 1H, J = 7.8 Hz), 8.24 (d, 1H, J = 7.2 Hz).

Step 4: Ethyl-2-[4-cyano-4-(4-methoxy dibenzo[*b,d*]furan-1-yl]piperidino]acetate

The tert-Butyl-4-cyano-4-(4-methoxydibenzo[*b,d*]furan-1-yl)-1-piperidine carboxylate (from step 3) (250mg) was dissolved in dichloromethane (10ml) and trifluoro acetic acid (2.0ml) was added. The reaction mixture was then stirred at reflux for 3-4 hours. Solvent was removed under vacuo, residue was diluted with ethyl acetate (25ml) and washed with water (2x25). The ethyl acetate layer was dried over anhydrous sodium sulfate and solvent was removed under vacuo to give sticky solid.

The sticky solid (~200mg, 0.65mmole) was dissolved in dimethyl formamide (5.0ml) and anhydrous potassium carbonate (160mg, 0.87mmole) was added. Ethyl bromo acetate (180mg, 1.3mmole) was added to reaction mixture and was then stirred at 60-65°C for 4-5 hours, reaction mixture was cooled to room temperature and water (30ml) was added. The product separated was extracted with ethyl acetate (3x25ml). The combined ethyl acetate layers were washed with water (2x25ml) and dried over anhydrous sodium sulfate; removal of solvent under vacuo gave stick solid, which was then purified by column chromatography on silica gel using 10% ethyl acetate in choloroform to give 100 mg of product as buff solid, mp 154°C.

IR (KBr) 3440, 2937, 1731, 1629, 1576, 1510, 1445, 1372, 1282, 1185, 1011, 751 cm-1; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.25-1.34 (t,3H), 2.35-2.43 (d,2H), 2.56-2.60 (d, 2H), 2.87-2.95 (t, 2H), 3.16-3.20 (d, 2H), 3.38 (s, 2H), 4.08 (s, 3H), 4.20-4.27 (q, 2H), 6.97 (d, 1H, *J* = 9.3 Hz), 7.29 (d, 1H, *J* = 8.4 Hz), 7.42 (t, 1H, *J* = 7.2 Hz), 7.48 (t, 1H, *J* = 7.2 Hz), 7.68 (d, 1H, *J* = 7.8 Hz), 8.43 (d, 1H, *J* = 7.2 Hz).

Step 5: N-Hydroxy-2-[4-cyano-4-(4-methoxydibenzo[b,d]furan-1-yl)piperidino] acetamide

To a solution of hydroxyl amine hydrochloride (26mg, 0.1273 mmole) in methanol (2.0ml) was added slowly a solution of potassium hydroxide (42mg, 0.75mmole) in methanol (1.0 ml) at 10-15°C. The solid separated was filtered. Ethyl-2-[4-cyano-4-(4-methoxy dibenzo[*b,d*]furan-1-yl]piperidino]acetate (from step 4) (50.0mg, 0.1273mmole) was added to the filtrate and stirred for 2.0 hours. A solution of potassium hydroxide (42mg, 0.75mmole) in methanol (1.0 ml) was added again to the reaction mixture and stirred at room temperature for 3-4 hours. Water (25ml) was added to reaction mixture, product separated was extracted with ethyl acetate (2x15ml). The combined ethyl acetate layers were washed with water (25ml), 10% aqueous sodium bicarbonate solution (5.0ml) and dried over anhydrous sodium sulfate. Removal of solvent under vacuo gave buff solid, which was then purified by column chromatography on silica gel using 10% ethyl acetate in chloroform as eluent to give 30.0mg of product as white solid, mp 167-168°C.

IR (KBr) 3439, 2927, 1748, 1632, 1577, 1512, 1449, 1394, 1360, 1220, 1100, 1017, 802, 749 cm-1;

^1H NMR (300 MHz, DMSO-d_6) δ 2.35-2.43 (t,2H), 2.56-2.60 (d, 2H), 2.87-2.95 (t, 2H), 3.16-3.20 (d, 2H), 3.40 (s, 2H), 3.78 (s, 2H), 4.08 (s, 3H), 4.20-4.27 (q, 2H), 6.97 (d, 1H, J = 9.3 Hz), 7.31 (d, 1H, J = 8.4 Hz), 7.40 (t, 1H, J = 7.2 Hz), 7.51 (t, 1H, J = 7.2 Hz), 7.68 (d, 1H, J = 7.8 Hz), 8.43 (d, 1H, J = 7.2 Hz).

$[M+H]^+$= 379.2

In vitro Studies

Inhibition of Phosphodiesterase Enzymes (PDE4)

In this assay, PDE4 enzyme converts [^{3}H] cAMP to the corresponding [^{3}H] 5'-AMP in proportion to the amount of PDE4 present. The [^{3}H] 5'-AMP then was quantitatively converted to free [^{3}H] adenosine and phosphate by the action of snake venom 5'-nucleotidase. Hence, the amount of [^{3}H] adenosine liberated is proportional to PDE4 activity.

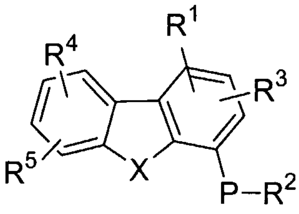
The assay was performed with modification of the method of Thompson and Appleman (Biochemistry; 1971; 10; 311-316) and Schwartz and Passoneau (Proc. Natl. Acad. Sci. U.S.A. 1974; 71; 3844-3848), both references incorporated herein by reference in their entirety, at 34°C. In a 200 µl total reaction mixture, the reaction mixture contained 12.5mM of Tris, 5 mM $MgCl_2$, 1 µM cAMP (cold) and ^{3}H cAMP (0.1 µCi), (Amersham). Stock solutions of the compounds to be investigated were prepared in DMSO in concentrations such that the DMSO content in the test samples did not exceed 0.05 % by volume to avoid affecting the PDE4 activity. Drug samples were then added in the reaction mixture (25 µl/tube). The assay was initiated by addition of enzyme mix (75 µl) and the mixture was incubated for 20 minutes at 34^0 C. The reaction was stopped by boiling the tubes for 2 mins at 100^0C in a water bath. After cooling on ice for 5 minutes and addition of 50 µg/reaction of 5'-nucleotidase snake venom from Crotalus atrox incubation was carried out again for 20 min. at 34°C. The unreacted substrate was separated from (^{3}H) Adenosine by addition of Dowex AG 1-X8 (Biorad Lab), (400 µl) which was prequilibrated (1:1:1) in water and ethanol. Reaction mixture was then thoroughly mixed, placed on ice for 15 minutes, vortexed and centrifuged at 14,000 r.p.m. for 2 mins. After centrifugation, a sample of the supernatant was taken and added in 24 well optiplates containing Scintillant (1 ml) and mixed well. The samples in the plates were then determined for radioactivity in a Top Counter and the PDE4 activity was estimated. PDE4 enzyme was present in quantities that yield <30% total hydrolysis of substrate (linear assay conditions).Additionally, activity of the compounds were tested against other Phosphodiesterase enzymes, namely, PDE 1(Ca.sup.2+/calmodulin-dependent), PDE 2(cGP-stimulated), PDE 3 (cGP-inhibited), PDE 5 (cGP-specific) and PDE 6 (cGP-specific, photoreceptor).

Results were expressed as percent inhibition (IC_{50}) in nM concentrations. The IC_{50} values were determined from the concentration curves by nonlinear regression analysis.

Compound	**IC_{50} (nM)**	**Compound**	**IC_{50} (nM)**
Example 1	226.1	Example -34	653.2
Example 2	65.96	Example -35	955
Example 3	611.9	Example -36	527.8
Example 4	147.5	Example -37	2985
Example 5	489.8	Example -38	33.87 % at 1 µM
Example 6	69.78	Example -39	0 % at 1 µM
Example 7	283.1	Example -40	1311
Example 8	24.92 % at 1 µM	Example -41	0 % at 1 µM
Example 9	289	Example -42	46.74 % at 1 µM
Examplel 0	30.19 % at 1 µM	Example -43	40.61 % at 1 µM
Examplel 1	151.2	Example -44	21.09 % at 1 µM
Examplel 2	1171	Example -45	48.88 % at 1 µM
Examplel 3	17.46 % at 1 µM	Example -46	43.33 % at 1 µM
Examplel 4	25.39 % at 1 µM	Example -47-	32.29 % at 1 µM
Examplel 5	36.23 % at 1 µM	Example -48	21.16 % at 1 µM
Examplel 6	5 % at 1 µM	Example -49	79.72
Examplel 7	26.36 % at 1 µM	Example -50	150.2
Example 18	60.79	Example -51-	151
Example 19	881.60	Example -52	40.58
Example -20	392.7	Example -53	400.4
Example -21	49.16 % at 1 µM	Example -54	68.87
Example 22	32.62 % at 1 µM	Example -55	33.85
Example -23	36.23 % at 1 µM	Example -56	36.88
Example -24	459.5	Example -57	39.69
Example -25	43.78 % at 1 uM	Example -58	79.93
3996 Example -26	1400	3961 Example -59	76.52
3994 Example -27	31.05 % at 1 uM	3944 Example -60	1166
3993 Example -28	1623	3939 Example -61	36.06
3986 Example -29	31.86 % at 1 uM	3968 Example -62	26.79
3992 Example -30	617.7	3972 Example -63	79.08
4006 Example -31	1677	3918 Example -64	1039
4005 Example -32	929.8	3947 Example -65	232.1
3995 Example -33	147.5		

What is claimed is:

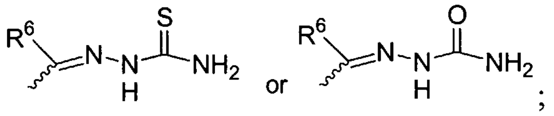
1. A compound of the general Formula 1



(1)

wherein:

R^1 is substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroarylalkyl; in which the substituents may be one or more, and the same or different and are hydrogen, hydroxyl, halogen,. cyano, nitro, carboxyl, trifluoroalkyl, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkoxycarbonyl, substituted or unsubstituted alkylcarbonyl, substituted or unsubstituted alkylcarbonyloxy, substituted or unsubstituted amino, mono- or di- substituted or unsubstituted alkylamino,



R^2, R^3, R^4, R^5, R^6 and R^7 may be the same or different and are independently for each occurrence hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroarylalkyl , $-NR^8R^9$, $-C(O)-R^8$, $-C(O)O-R^8$, $-C(O)NR^8R^9$, $-S(O)_m-R^8$, $-S(O)_m-NR^8R^9$, nitro, -OH, cyano, formyl, acetyl, halogen, $-OR^8$, $-SR^8$, or a protecting group, or when R^1 and R^3, or R^4 and R^5 or ortho to each other then R^1 and R^3 together with the carbon atoms to which they are bound or R^4 and R^5 together with the carbon atoms to which they are bound may be joined to a form a saturated or unsaturated cyclic ring, which may optionally include up to two heteroatoms selected from O, NR^a or S;

R^8 and R^9 may be same or different and are independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroarylalkyl , nitro, halo, -OH, cyano, $-C(O)-R^a$, $-C(O)O-R^a$, $-C(O)NR^aR^b$, $-S(O)_m-R^a$, $-S(O)_m-NR^aR^b$, $-C(=NR^a)-R^b$, $-C(=NR^a)-NR^aR^b$, $-C(=S)-NR^aR^b$, $-C(=S)-R^a$, $-N=C(R^aR^b)$, $-NR^aR^b$, $-OR^a$, $-SR^a$, a protecting group, or R^8 and R^9 may be joined together with the atom connecting them to a form a optionally substituted saturated or unsaturated cyclic ring, which may optionally include up to two heteroatoms selected from O, NR^a or S;

R^a and R^b may be same or different and are independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroarylalkyl , nitro, -OH, cyano, formyl, acetyl, halogen, a protecting group, $-C(O)-R^a$, $-C(O)O-R^a$, $-C(O)NR^aR^b$, $-S(O)_m-R^a$, $-S(O)_m-NR^aR^b$, $-NR^aR^b$, ,$-OR^a$, $-SR^{a,}$ or R^a and R^b may be joined together with the atom connecting them to a form a optionally substituted saturated or unsaturated cyclic ring, which may optionally include up to two heteroatoms selected from O, NR^a or S;

X is O, $S(O)_m$ and NR^6;

wherein P is O or S;

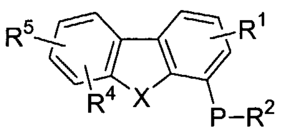
wherein m is 0, 1 or 2;

or an analog, tautomer, regioisomer, stereoisomer, enantiomer, diastereomer, polymorph, pharmaceutically acceptable salt, N-oxide, pharmaceutically acceptable solvate thereof.

2. The compound according to claim 1 wherein the substituents in the 'substituted alkyl', 'substituted alkoxy' 'substituted alkenyl' 'substituted alkynyl' 'substituted cycloalkyl' 'substituted cycloalkylalkyl' 'substituted cyclocalkenyl' 'substituted arylalkyl' 'substituted aryl' 'substituted heterocyclic ring', 'substituted

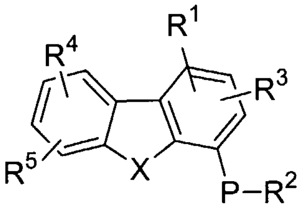
heteroaryl ring,' 'substituted heteroarylalkyl', 'substituted heterocyclylalkyl ring', 'substituted amino', 'substituted alkoxycarbonyl', 'substituted cyclic ring' 'substituted alkylcarbonyl', 'substituted alkylcarbonyloxy' and may be the same or different which one or more are selected from the groups such as hydrogen, hydroxy, halogen, carboxyl, cyano, nitro, oxo (=O), thio(=S), substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted amino, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, 'substituted heterocyclylalkyl ring' substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclic ring, substituted or unsubstituted guanidine, $-COOR^x$, $-C(O)R^x$, $-C(S)R^x$, $-C(O)NR^xR^y$, $-C(O)ONR^xR^y$, $-NR^xCONR^yR^z$, $-N(R^x)SOR^y$, $-N(R^x)SO_2R^y$, $-(=N-N(R^x)R^y)$, $-NR^xC(O)OR^y$, $-NR^xR^y$, $-NR^xC(O)R^y-$, $-NR^xC(S)R^y$ $-NR^xC(S)NR^yR^z$, $-SONR^xR^y-$, $-SO_2NR^xR^y-$, $-OR^x$, $-OR^xC(O)NR^yR^z$, $-OR^xC(O)OR^y-$, $-OC(O)R^x$, $-OC(O)NR^xR^y$, $-R^xNR^yC(O)R^z$, $-R^xOR^y$, $-R^xC(O)OR^y$, $-R^xC(O)NR^yR^z$, $-R^xC(O)R^x$, $-R^xOC(O)R^y$, $-SR^x$, $-SOR^x$, $-SO_2R^x$, $-ONO_2$, wherein R^x, R^y and R^z in each of the above groups can be hydrogen atom, substituted or unsubstituted alkyl, substituted or unsubstituted alkoxy, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted amino, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, 'substituted heterocyclylalkyl ring' substituted or unsubstituted heteroarylalkyl, substituted or unsubstituted heterocyclic ring.

3. The compound according to claim 1 of the formula **(2)**

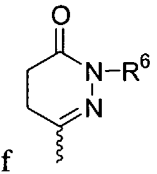


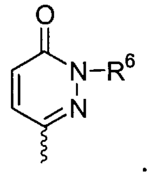
(2)

4. The compound according to claim 1 of the formula **(3)**



(3)

wherein R^1 is chosen from the group consisting of  and

.

5. The compound according to claim 4 wherein X is O.

6. The compound according to claim 4 or 5 wherein P is O.

7. The compound according to claims 4, 5 or 6 wherein R^2 is chosen from the group consisting of alkyl, cycloalkyl and substituted alkyl.

8. The compound according to claim 7 wherein R^2 is $-CH_3$

9. The compound according to claim 7 wherein R^2 is cyclopentyl.

10. The compound according to claim 7 wherein R^2 is $-CHF_2$.

11. The compound according to claim 4-9 or 10, wherein R^3 is hydrogen or Bromo.

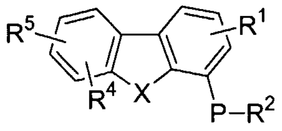
12. The compound according to claim 4-10 or 11, wherein R^6 is chosen from the group consisting of hydrogen, alkyl and substituted alkyl.

13. The compound according to claim 12, wherein R^6 is $-CH_3$.

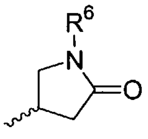
14. The compound according to claim 12, wherein R^6 is benzyl.

15. The compound according to claims 4-13 or 14, wherein R^5 and R^6 are hydrogen.

16. The compound according to claim 1, of the formula **(4)**



(4)

wherein R^1 is  .

17. The compound according to claim 16, wherein X is O.

18. The compound according to claim 16 or 17, wherein P is O.

19. The compound according to claims 16, 17 or 18, wherein R^2 is chosen from the group consisting of alkyl, cycloalkyl and substituted alkyl.

20. The compound according to claim 19, wherein R^2 is $-CH_3$.

21. The compound according to claim 19, wherein R^2 is cyclopentyl.

22. The compound according to claim 19, wherein R^2 is $-CHF_2$.

23. The compound according to claims 16-21 or 22 wherein R^4 and R^5 are hydrogen.

24. The compound according to claims 16-21 or 22 wherein R^4 is hydrogen and R^5 is chosen from the group consisting of Nitro($-NO_2$), Amino($-NH_2$),$-NH-CO-CH_3$,$-NH-S(O)_2-CH_3$,$-NH-C(O)-(4-CH_3$.piperazin-1yl),$-S(O)_2-(4-CH_3$.piperazin-1yl) or $-S(O)_2$-(morpholine).

25. The compound according to claims 15-23 or 24 wherein R^6 is chosen from the group consisting of hydrogen, formyl, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl , substituted or unsubstituted alkylcycloalkyl or substituted or unsubstituted aryl.

26. The compound according to claims 25, wherein R^6 is H.

27. The compound according to claims 25, wherein R^6 is $-CH_3$

28. The compound according to claims 25, wherein R^6 is $-CH_2-CH_3$

29. The compound according to claims 25, wherein R^6 is $-CH(CH_3)_2$.

30. The compound according to claims 25, wherein R^6 is $-(CH_2)_3-CH_3$.

31. The compound according to claims 25, wherein R^6 is Cyclopentyl.

32. The compound according to claims 25, wherein R^6 is $-CH_2$-Cyclopropyl.

33. The compound according to claims 25, wherein R^6 is 3-bromobenzyl.

34. The compound according to claims 25, wherein R^6 is 4-bromobenzyl.

35. The compound according to claims 25, wherein R^6 is 4-chlorobenzyl.

36. The compound according to claims 25, wherein R^6 is 2,6 dichlorobenzyl.

37. The compound according to claims 25, wherein R^6 is 4-t-butyl-benzyl.

38. The compound according to claims 25, wherein R^6 is 4-flurophenyl ethyl.

39. The compound according to claims 25, wherein R^6 is 3,5 dimethyl-phenyl.

40. The compound according to claims 25, wherein R^6 is 4-methylbenzoate.

41. The compound according to claims 25, wherein R^6 is 4-benzoic acid.

42. The compound according to claims 25, wherein R^6 is 3-benzoic acid.

43. The compound according to claims 25, wherein R^6 is 3-methoxy phenyl.

44. The compound according to claims 25, wherein R^6 is 4-methoxy phenyl.

45. The compound according to claims 25, wherein R^6 is 4-trifluro methyl phenyl.

46. The compound according to claims 25, wherein R^6 4-trifluro methyl acetamido phenyl.

47. The compound according to claims 25, wherein R^6 4-pyridine.

48. The compound according to claims 25, wherein R^6 3-methyl sulphonamido phenyl.

49. The compound according to claims 25, wherein R^6 3-fluro-4- methyl sulphonamido phenyl.

50. The compound according to claims 25, wherein R^6 $-COOCH_2-CH_3$.

51. The compound according to claims 25, wherein R^6 -CH2--COOH.

52. The compound according to claims 25, wherein R^6 -CH2—$COOCH_2-CH_3$.

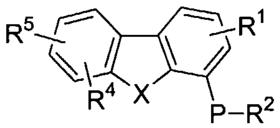
53. The compound according to claims 25, wherein R^6 -CH2—CONH-CH_3.

54. The compound according to claims 25, wherein R^6 formyl

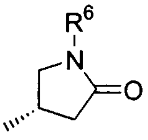
55. The compound according to claims 25, wherein R^6 2-hydroxyethyl

56. The compound according to claims 25, wherein R^6 2-methanesulphonate-ethyl.

57. The compound according to claim 16, of the formula **(4 a)**



(4 a)

wherein R^1 is  .

58. The compound according to claim 57, wherein X is O.

59. The compound according to claim 57 or 58, wherein P is O.

60. The compound according to claims 57, 58 or 59, wherein R^2 is chosen from the group consisting of alkyl, cycloalkyl and substituted alkyl.

61. The compound according to claim 60, wherein R^2 is $-CH_3$.

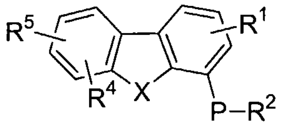
62. The compound according to claim 60, wherein R^2 is cyclopentyl.

63. The compound according to claim 60, wherein R^2 is $-CHF_2$.

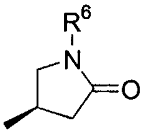
64. The compound according to claims 57-62 or 63, wherein R^4 and R^5 are chosen from a group consisting of hydrogen, Nitro($-NO_2$), Amino($-NH_2$),or $-NH-SO_2-CH_3$.

65. The compound according to claims 57-63 or 64, wherein R^6 is hydrogen.

66. The compound according to claim 16, of the formula **(4 b)**



(4 b)

wherein R^1 is  .

67. The compound according to claim 66, wherein X is O.

68. The compound according to claim 66 or 67, wherein P is O.

69. The compound according to claims 66, 67 or 68, wherein R^2 is chosen from the group consisting of alkyl, cycloalkyl and substituted alkyl.

70. The compound according to claim 69, wherein R^2 is $-CH_3$.

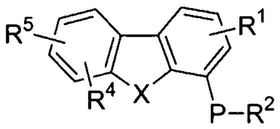
71. The compound according to claim 69, wherein R^2 is cyclopentyl.

72. The compound according to claim 69, wherein R^2 is $-CHF_2$.

73. The compound according to claims 66-71 or 72, wherein R^4 and R^5 are chosen from a group consisting of hydrogen, Nitro ($-NO_2$), Amino ($-NH_2$),or $-NH-SO_2-CH_3$.

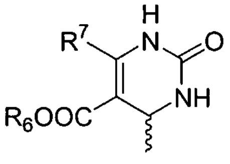
74. The compound according to claims 66-72 or 73, wherein R^6 is hydrogen.

75. The compound according to claim 1 of the formula **(5)**



(5)

wherein R^1 is



.

76. The compound according to claim 75, wherein X is O.

77. The compound according to claims 75 or 76, wherein P is O.

78. The compound according to claims 75, 76 or 77, wherein R^2 is chosen from the group consisting of alkyl, cycloalkyl and substituted alkyl.

79. The compound according to claim 78, wherein R^2 is $-CH_3$.

80. The compound according to claim 78, wherein R^2 is cyclopentyl.

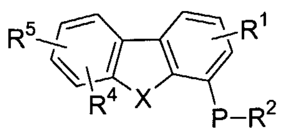
81. The compound according to claim 78, wherein R^2 is $-CHF_2$.

82. The compound according to claims 75-80 or 81, wherein R^6 is alkyl.

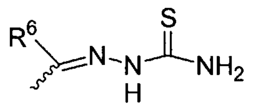
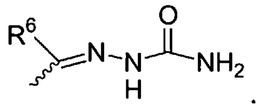
83. The compound according to claims 75-81 or 82 wherein R^7 is alkyl.

84. The compound according to claims 75-82 or 83 wherein R^4 and R^5 are hydrogen.

85. The compound according to claim 1 of the formula **(6)**



(6)

wherein R^1 is chosen from the group consisting of  and  .

86. The compound according to claim 85, wherein X is O.

87. The compound according to claim 85 or 86, wherein P is O.

88. The compound according to claims 85, 86 or 87 wherein R^2 is chosen from the group consisting of hydrogen, alkyl, cycloalkyl and substituted alkyl.

89. The compound according to claim 88, wherein R^2 is $-CH_3$.

90. The compound according to claim 88, wherein R^2 is cyclopentyl.

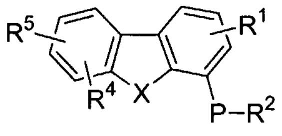
91. The compound according to claim 88, wherein R^2 is $-CHF_2$.

92. The compound according to claim 85-90 or 91, wherein R^6 is chosen from the group consisting of hydrogen and alkyl.

93. The compound according to claim 92, wherein R^6 is $-CH_3$.

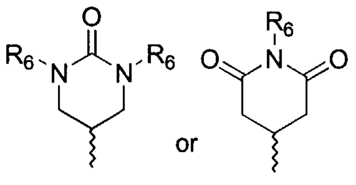
94. The compound according to claims 85-92 or 93, wherein R^5 and R^6 are hydrogen.

95. The compound according to claim 1, of the formula **(7)**



(7)

wherein R^1 is



96. The compound according to claim 95, wherein X is O.

97. The compound according to claim 95 or 96, wherein P is O.

98. The compound according to claims 95, 96 or 97, wherein R^2 is chosen from the group consisting of hydrogen, alkyl, cycloalkyl and substituted alkyl.

99. The compound according to claim 98, wherein R^2 is $-CH_3$.

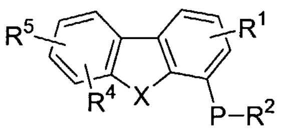
100. The compound according to claim 98, wherein R^2 is cyclopentyl.

101. The compound according to claim 98, wherein R^2 is $-CHF_2$.

102. The compound according to claim 95-100 or 101, wherein R^4 and R^5 represents hydrogen.

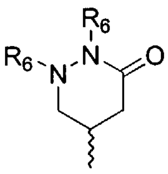
103. The compound according to claim 95-101 or 102, wherein R^6 is chosen from the group consisting of hydrogen.

104. The compound according to claim 1 of the formula **(8)**



(8)

wherein R^1 is



105. The compound according to claim 104, wherein X is O.

106. The compound according to claim 104 or 105, wherein P is O.

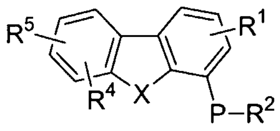
107. The compound according to claims 104, 105 or 106, wherein R^2 is chosen from the group consisting of hydrogen, alkyl.

108. The compound according to claim 107, wherein R^2 is $-CH_3$.

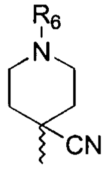
109. The compound according to claim 104-107 or 108, wherein R^4 and R^5 represents hydrogen.

110. The compound according to claim 104-108 or 109, wherein R^6 is chosen from the group consisting of hydrogen.

111. The compound according to claim 1 of the formula **(9)**



(9)

wherein R^1 is 

112. The compound according to claim 111, wherein X is O.

113. The compound according to claim 111 or 112, wherein P is O.

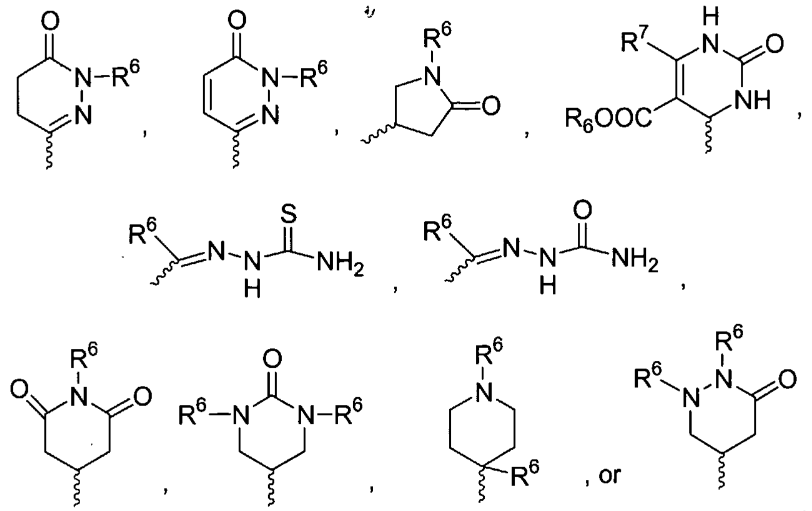
114. The compound according to claims 111, 112 or 113, wherein R^2 is chosen from the 5roup consisting of hydrogen, alkyl.

115. The compound according to claim 114, wherein R^2 is $-CH_3$.

116. The compound according to claim 111-114 or 115, wherein R^4 and R^5 represents hydrogen.

117. The compound according to claim 111-115 or 116, wherein R^6 is -CH2-CO-NH-OH.

118. The compound according to claim 1, wherein R^1 is:



119. The compound according to claim 1 chosen from the group consisting of

3-(4-methoxydibenzo [*b,d*]furan-1-yl)-1,6-dihydro-6-pyridazinone
3 - (4-methoxydibenzo [*b,d*] furan-1-yl)-1-methyl-1,6- dihydro-6-pyridazinone
1-Benzyl -3-(4-methoxydibenzo [*b,d*] furan-1-yl)-1,6-dihydro-6-pyridazinone
6-(4-methoxydibenzo[*b,d*]furan-1-yl)-4,5-dihydropyridazin-3(2*H*)-one
(±) Ethyl 4- (4- Cyclopentyloxydibenzo[*b,d* furan-1-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate
(±) 4-(4-methoxydibenzo[*b,d*]furan-1-yl)-2-azolanone
4-methoxydibenzo [*b,d*]furan-1-carbaldehyde semicarbazone
4-methoxydibenzo [*b,d*]furan-1-carbaldehyde thiosemicarbazone
(1*Z*)-1-(4-methoxydibenzo[*b,d*]furan-1-yl)ethan-1-one semicarbazone
(1*Z*)-1-(4-hydroxydibenzo [*b,d*]furan-1-yl)ethan-1-one semicarbazone
(1*Z*)-1-(4-Difluoromethoxydibenzo [*b,d*]furan-1-yl)ethan-1-one semicarbazone
4-Difluoromethoxydibenzo [*b,d*]furan-1-carbaldehyde semicarbazone
4-Difluoromethoxydibenzo [*b,d*]furan-1-carbaldehyde thiosemicarbazone
4-Cyclopentyloxydibenzo [*b,d*]furan-1-carbaldehyde semicarbazone
4-Cyclopentyloxydibenzo [*b,d*]furan-1-carbaldehyde thiosemicarbazone
4-Methoxydibenzo [*b,d*]furan-3-carbaldehyde semicarbazone
4-Methoxydibenzo [*b,d*]furan-3-carbaldehyde thiosemicarbazone
(±)1-methyl-4-(4-Methoxydibenzo [*b,d*]furan-1-yl)-2-azolanone
(±) 1-(3-bromobenzyl)-4-(4-methoxydibenzo [*b, d*] furan-1-yl)-2-azolanone

(±) 1-(4-tert-butyl benzyl)-4-(4-methoxydibenzo [*b*, *d*] furan-1-yl)-2-azolanone

(±) 1-(4-bromobenzyl)-4-(4-methoxydibenzo [*b*, *d*] furan-1-yl)-2-azolanone

(±) 1-(4-chlorobenzyl)-4-(4-methoxydibenzo [*b*, *d*] furan-1-yl)-2-azolanone

(±) 1-(2, 6-dichlorobenzyl)-4-(4-methoxydibenzo [*b*, *d*] furan-1-yl)-2-azolanone

(±) 1-ethyl-4-(4-methoxydibenzo [*b*, *d*] furan-1-yl)-2-azolanone

(±) 1-isopropyl-4-(4-methoxydibenzo [*b*, *d*] furan-1-yl)-2-azolanone

(±) 1-butyl-4-(4-methoxydibenzo [*b*, *d*] furan-1-yl)-2-azolanone

(±) 1-cyclopentyl-4-(4-methoxydibenzo [*b*, *d*] furan-1-yl)-2-azolanone

(±) 1-cyclopropylmethyl-4-(4-methoxydibenzo [*b*, *d*] furan-1-yl)-2-azolanone

(±) 1-(4-fluorophenethyl)-4-(1-methoxy-9H-4-fluorenyl)-2-azolanone

(±) Ethyl 2-[4-(4-Methoxydibenzo [*b*,*d*]furan-1-yl)-2-oxo-1-azolanyl]acetate

(±) 2-[4-(4-Methoxydibenzo [*b*,*d*]furan-1-yl)-2-oxo-1-azolanyl]acetic acid

(±) N1-methyl-2-[4-(4-Methoxydibenzo [*b*,*d*]furan-1-yl)-2-oxo-1-azolanyl] acetamide

(±) 4-(4-methoxydibenzo [*b*, *d*] furan-1-yl)-2-oxo-1-azolanecarbaldehyde

(±) Ethyl-4-(4-methoxydibenzo [*b*, *d*] furan-1-yl)-2-oxo-1-azolanecarboxylate

(±) 1-(2-hydroxyethyl)-4-(4-methoxydibenzo [*b*, *d*] furan-1-yl)-2-azolanone

(±) 2-[4-(4-methoxydibenzo [*b*, *d*] furan-1-yl)-2-oxo-1-azolanyl] ethyl methanesulfonate

(±)1-(3,5-dimethylphenyl)-4-(4-methoxydibenzo[*b*,*d*]furan-1-yl) pyrrolidine-2-one

(±)Methyl-4-[4-(4-methoxydibenzo[*b*,*d*]furan-1-yl)-2-pyrrolidinonyl] benzoate

(±)N-{3-[4-(4-methoxydibenzo[*b*,*d*]furan-1-yl)-2-oxo-1-azolanyl]phenyl}methanesufonamide

(±)4-(4-methoxydibenzo[*b*,*d*]furan-1-yl)-1-(3-methoxyphenyl)-2-azolanone

(±) 4-(4-methoxydibenzo[*b*,*d*]furan-1-yl)-1-(4-trifluoromethylphenyl)-2-azolanone

(±) N-{3-fluoro-4-[4-(4-methoxydibenzo[*b*,*d*]furan-1-yl)-2-oxo-1-azolanyl]phenyl}methanesufonamide

(±) Methyl-3-[4-(4-methoxydibenzo[*b*,*d*]furan-1-yl)-2-pyrrolidinonyl] benzoate

(±)4-(4-methoxydibenzo[*b*,*d*]furan-1-yl)-1-(4-methoxyphenyl)-2-azolanone

(±)4-(4-methoxydibenzo[*b*,*d*]furan-1-yl)-1-(4-trifluoromethylacetamidophenyl)-2-azolanone

(±)4-(4-methoxydibenzo[*b*,*d*]furan-1-yl)-1-(4-pyridyl)-2-azolanone

(±)3-[4-(4-methoxydibenzo[*b*,*d*]furan-1-yl)-2-oxo-1-azolanyl] benzoic acid

(±)4-[4-(4-methoxydibenzo[*b*,*d*]furan-1-yl)-2-oxo-1-azolanyl] benzoic acid

(±) 4-(4-difluoromethoxy-8-morpholinosulfonyldibenzo[*b*,*d*]furan-1-yl)-2-azolanone

(±) 4-[4-difluoromethoxy-8-(4-methylpiperazino)sulfonyldibenzo[*b,d*]furan-1-yl]-2-azolanone

(±)*N*-[6-methoxy-9-(5-oxopyrrolidin-3-yl)dibenzo[*b,d*]furan-2-yl]acetamide

(±) *N*-[6-methoxy-9-(5-oxopyrrolidin-3-yl) dibenzo [*b,d*]furan-2-yl]methane sulfonamide

(±) 2-(4-methylpiperazinocarboxamido)-6-methoxy-9-(5-oxopyrrolidin-3-yl) dibenzo[*b,d*]furan

(+) 4-[4-methoxy-8-(methylamino)dibenzo[*b, d*]furan-1-yl]pyrrolidin-2-one

(–) 4-[4-methoxy-8-(methylamino) dibenzo[*b, d*]furan-1-yl]pyrrolidin-2-one

(+) 4-(4-methoxydibenzo [b,d] furan-1-yl)-2-azolanone

(-)4-(4-methoxydibenzo [b,d] furan-1-yl)-2-azolanone

(+) 4-(4-difluoromethoxydibenzo [b,d] furan-1-yl)-2-azolanone

(-)4-(4-difluoromethoxydibenzo [b,d] furan-1-yl)-2-azolanone

(±) 5-(4-methoxydibenzo [*b,d*]furan-1-yl) hexahydro-3-pyridazinone

5-[4-(methoxy)dibenzo[*b, d*]furan-1-yl]tetrahydropyrimidin-2(1*H*)-one

5-[4-(difluoromethoxy)dibenzo[*b, d*]furan-1-yl]tetrahydropyrimidin-2(1*H*)-one

4-[4-(difluoromethoxy)dibenzo[*b, d*]furan-1-yl]piperidine-2, 6-dione

6-(3-bromo-4-methoxydibenzo[*b,d*]furan-1-yl)pyridazin-3(2*H*)-one:

N-Hydroxy-2-[4-cyano-4-(4-methoxydibenzo[b,d]furan-1-yl)piperidino] acetamide

or a pharmaceutically acceptable salt of any of the preceding compounds.

120. A pharmaceutical composition comprising a compound according to claims 1-118 or 119 and at least one pharmaceutically acceptable excipient.

121. A method of treating inflammatory diseases, disorders and conditions characterized by or associated with an undesirable inflammatory immune response and all disease and conditions induced by or associated with an excessive secretion of TNF-α and PDE-4 which comprises administering to a subject in need thereof a therapeutically effective amount of a compound according to claims 1-118 or 119.

122. A method of treating inflammatory conditions and immune disorders comprising administering to a subject in need thereof a therapeutically effective amount of a compound according to claims 1-118 or 119.

123. The method according to claim 122, wherein said inflammatory conditions and immune disorders are chosen from the group consisting of asthma, bronchial asthma chronic obstructive pulmonary disease, allergic rhinitis, eosinophilic granuloma, nephritis, rheumatoid arthritis, cystic fibrosis, chronic bronchitis, multiple sclerosis, Crohns disease, psoraisis, uticaria, adult vernal cojunctivitis, respiratory distress syndrome, rhematoid spondylitis, osteoarthritis, gouty arthritis, uteltis, allergic conjunctivitis, inflammatory bowel conditions, ulcerative coalitis, eczema, atopic dermatitis and chronic inflammation.

124. The method according to claim 122, wherein said inflammatory conditions and immune disorders are selected from the group consisting of inflammatory conditions or immune disorders of the lungs, joints, eyes, bowels, skin and heart.

125. The method according to claim 123, wherein said inflammatory condition is chosen from the group consisting asthma and chronic obstructive pulmonary disease.

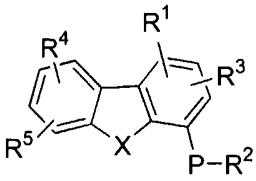
126. A method for abating inflammation in an affected organ or tissue comprising delivering to said organ or tissue a therapeutically effective amount of a compound represented by a compound according to claims 1-118 or 119.

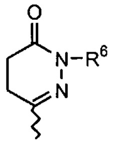
127. A method of treating diseases of the central nervous system comprising administering to a subject in need thereof a therapeutically effective amount of a compound according to claims 1-118 or 119.

128. The method according to claim 127, wherein said diseases of the central nervous system are chosen from the group consisting of depression, amnesia, dementia, Alzheimers disease, cardiac failure, shock and cerebrovascular disease

129. A method of treating insulin resistant diabetes comprising administering to a subject in need thereof a therapeutically effective amount of a compound according to claims claims 1-118 or 119.

130. A method for the preparation of compounds of the general formula I



wherein R1 is 

R^2, R^3, R^4, R^5, R^6 and R^7 may be the same or different and are independently for each occurrence hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroarylalkyl , $-NR^8R^9$, $-C(O)-R^8$, $-C(O)O-R^8$, $-C(O)NR^8R^9$, $-S(O)_m-R^8$, $-S(O)_m-NR^8R^9$, nitro, -OH, cyano, formyl, acetyl, halogen, $-OR^8$, $-SR^8$, or a protecting group, or when R^1 and R^3, or R^4 and R^5 or ortho to each other then R^1 and R^3 together with the carbon atoms to which they are bound or R^4 and R^5 together with the carbon atoms to which they are bound may be joined to a form a saturated or unsaturated cyclic ring, which may optionally include up to two heteroatoms selected from O, NR^a or S;

R^8 and R^9 may be same or different and are independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroarylalkyl , nitro, halo, -OH, cyano, $-C(O)-R^a$, $-C(O)O-R^a$, $-C(O)NR^aR^b$, $-S(O)_m-R^a$, $-S(O)_m-NR^aR^b$, $-C(=NR^a)-R^b$, $-C(=NR^a)-NR^aR^b$, $-C(=S)-NR^aR^b$, $-C(=S)-R^a$, $-N=C(R^aR^b)$, $-NR^aR^b$, $-OR^a$, $-SR^a$, a protecting group, or R^8 and R^9 may be joined together with the atom connecting them to a form a optionally substituted saturated or unsaturated cyclic ring, which may optionally include up to two heteroatoms selected from O, NR^a or S;

R^a and R^b may be same or different and are independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroarylalkyl , nitro, -OH, cyano, formyl, acetyl, halogen, a protecting group, $-C(O)-R^a$, $-C(O)O-R^a$, $-C(O)NR^aR^b$, $-S(O)_m-R^a$, $-S(O)_m-NR^aR^b$, $-NR^aR^b$, ,$-OR^a$, $-SR^a$, or R^a and R^b may be joined together with the atom connecting them to a form a optionally substituted saturated or unsaturated cyclic ring, which may optionally include up to two heteroatoms selected from O, NR^a or S;

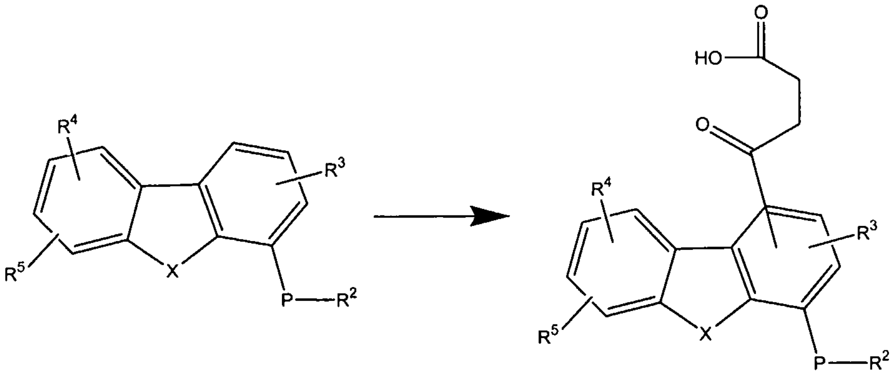
X is O, $S(O)_m$ and NR^6;

wherein P is O or S;

wherein m is 0, 1 or 2;

or an analog, tautomer, regioisomer, stereoisomer, enantiomer, diastereomer, polymorph, pharmaceutically acceptable salt, N-oxide, pharmaceutically acceptable solvate thereof comprising the steps of

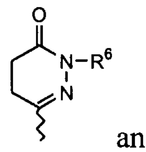
(a) acylating a compound of the general formula 12 with succinic anhydride in the presence of a Lewis acid catalyst to give a compound of the formula (14)



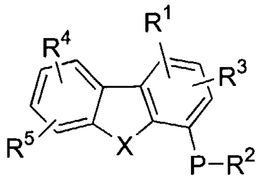
(12) (14)

wherein R^2, R^3, R^4, R^5, X and P are previously defined; and

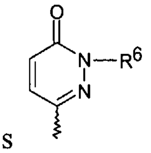
(b) reacting a compound of the general formula (14) with a substituted or unsubstituted hydrazine derivative to afford a compound of the general formula 1

wherein R^1 is  and R^6 is the same as defined above.

131. A method for the preparation of compounds of the general formula I



wherein R^1 is



R^2, R^3, R^4, R^5, R^6 and R^7 may be the same or different and are independently for each occurrence hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroarylalkyl , $-NR^8R^9$, $-C(O)-R^8$, $-C(O)O-R^8$, $-C(O)NR^8R^9$, $-S(O)_m-R^8$, $-S(O)_m-NR^8R^9$, nitro, -OH, cyano, formyl, acetyl, halogen, $-OR^8$, $-SR^8$, or a protecting group, or when R^1 and R^3, or R^4 and R^5 or ortho to each other then R^1 and R^3 together with the carbon atoms to which they are bound or R^4 and R^5 together with the carbon atoms to which they are bound may be joined to a form a saturated or unsaturated cyclic ring, which may optionally include up to two heteroatoms selected from O, NR^a or S;

R^8 and R^9 may be same or different and are independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroarylalkyl , nitro, halo, -OH, cyano, $-C(O)-R^a$, $-C(O)O-R^a$, $-C(O)NR^aR^b$, $-S(O)_m-R^a$, $-S(O)_m-NR^aR^b$, $-C(=NR^a)-R^b$, $-C(=NR^a)-NR^aR^b$, $-C(=S)-NR^aR^b$, $-C(=S)-R^a$, $-N=C(R^aR^b)$, $-NR^aR^b$, $-OR^a$, $-SR^a$, a protecting group, or R^8 and R^9 may be joined together with the atom connecting them to a form a optionally substituted saturated or unsaturated cyclic ring, which may optionally include up to two heteroatoms selected from O, NR^a or S;

R^a and R^b may be same or different and are independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroarylalkyl , nitro, -OH, cyano, formyl, acetyl, halogen, a protecting group, $-C(O)-R^a$, $-C(O)O-R^a$, $-C(O)NR^aR^b$, $-S(O)_m-R^a$, $-S(O)_m-NR^aR^b$, $-NR^aR^b$, ,$-OR^a$, $-SR^a$, or R^a and R^b may be joined together with the atom connecting them to a form a optionally substituted saturated or unsaturated cyclic ring, which may optionally include up to two heteroatoms selected from O, NR^a or S;

X is O, $S(O)_m$ and NR^6;

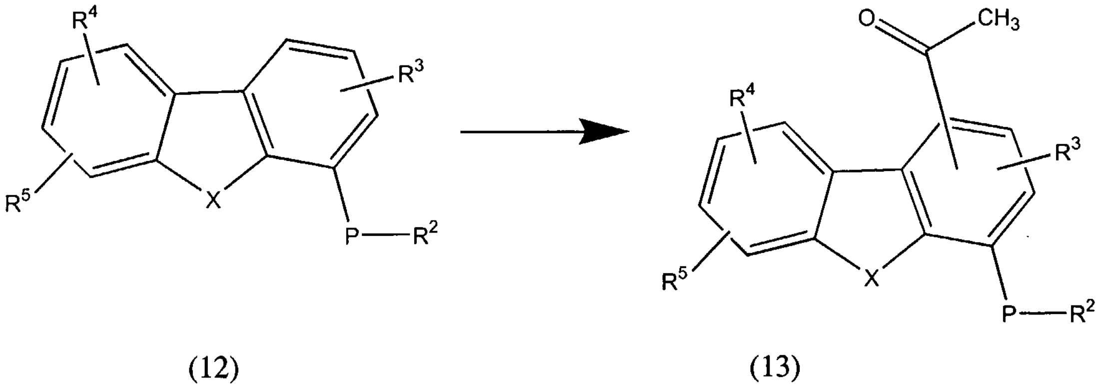
wherein P is O or S;

wherein m is 0, 1 or 2;

or an analog, tautomer, regioisomer, stereoisomer, enantiomer, diastereomer, polymorph, pharmaceutically acceptable salt, N-oxide, pharmaceutically acceptable solvate thereof

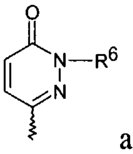
comprising the steps of

(a) acylating a compound of the general formula 12 with succinic anhydride in the presence of a Lewis acid catalyst to give a compound of the formula (14)

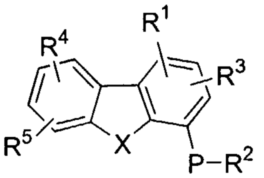


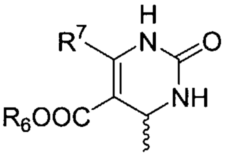
(12) (13)

wherein R^2, R^3, R^4, R^5, X and P are previously defined; and

(b) reacting a compound of the general formula (13) with a glyoxalic acid monohydrate or a glyoxalic acid ester followed by basification using ammoniumhydroxide and further reaction with alkyl or aryl hydrazine derivative to afford a compound of the general formula 1 wherein R^1 is  and R^6 is the same as defined above.

132. A method for the preparation of a compound of the general formula 1



wherein R^1 is 

R^2, R^3, R^4, R^5, R^6 and R^7 may be the same or different and are independently for each occurrence hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroarylalkyl , $-NR^8R^9$, $-C(O)-R^8$, $-C(O)O-R^8$, $-C(O)NR^8R^9$, $-S(O)_m-R^8$, $-S(O)_m-NR^8R^9$, nitro, -OH, cyano, formyl, acetyl, halogen, $-OR^8$, $-SR^8$, or a protecting group, or when R^1 and R^3, or R^4 and R^5 or ortho to each other then R^1 and R^3 together with the carbon atoms to which they are bound or R^4 and R^5 together with the carbon atoms to which they are bound may be joined to a form a saturated or unsaturated cyclic ring, which may optionally include up to two heteroatoms selected from O, NR^a or S;

R^8 and R^9 may be same or different and are independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroarylalkyl , nitro, halo, -OH, cyano, –C(O)-R^a, -C(O)O-R^a, -C(O)NR^{a}R^b, -S(O)$_m$-R^a, -S(O)$_m$-NR^{a}R^b, -C(=NR^a)-R^b, -C(=NR^a)-NR^{a}R^b, -C(=S)-NR^{a}R^b , -C(=S)-R^a, -N=C(R^{a}R^b), -NR^{a}R^b, -OR^a, -SR^a, a protecting group, or R^8 and R^9 may be joined together with the atom connecting them to a form a optionally substituted saturated or unsaturated cyclic ring, which may optionally include up to two heteroatoms selected from O, NR^a or S;

R^a and R^b may be same or different and are independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroarylalkyl , nitro, -OH, cyano, formyl, acetyl, halogen, a protecting group, –C(O)-R^a, -C(O)O-R^a, -C(O)NR^{a}R^b , -S(O)$_m$-R^a, -S(O)$_m$-NR^{a}R^b, -NR^{a}R^b, ,-OR^a, -SR^{a,} or R^a and R^b may be joined together with the atom connecting them to a form a optionally substituted saturated or unsaturated cyclic ring, which may optionally include up to two heteroatoms selected from O, NR^a or S;

X is O, S(O)$_m$ and NR^6;

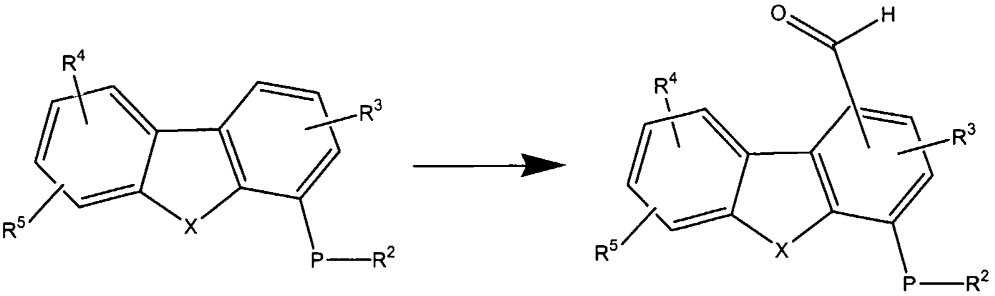
wherein P is O or S;

wherein m is 0, 1 or 2;

or an analog, tautomer, regioisomer, stereoisomer, enantiomer, diastereomer, polymorph, pharmaceutically acceptable salt, N-oxide, pharmaceutically acceptable solvate thereof

comprising the steps of

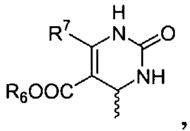
(a) formylating a compound of the general formula (12) with dichloromethyl methyl ether in the presence of a Lewis acid catalyst to give a compound of the formula (15)



(12) (15)

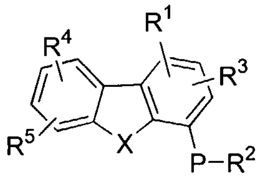
wherein R^2, R^3, R^4, R^5, X and P are as previously defined; and

(b) reacting a compound of the general formula (15) with a β ketoester, urea, and an acid catalyst to give a compound of the formula 1 wherein R^1 is

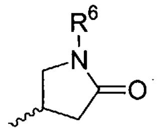


, R^6 and R^7 are the same as defined above.

133. A method for the preparation of compound of the general formula 1



wherein R^1 is



R^2, R^3, R^4, R^5, R^6 and R^7 may be the same or different and are independently for each occurrence hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroarylalkyl , $-NR^8R^9$, $-C(O)-R^8$, $-C(O)O-R^8$, $-C(O)NR^8R^9$, $-S(O)_m-R^8$, $-S(O)_m-NR^8R^9$, nitro, -OH, cyano, formyl, acetyl, halogen, $-OR^8$, $-SR^8$, or a protecting group, or when R^1 and R^3, or R^4 and R^5 or ortho to each other then R^1 and R^3 together with the carbon atoms to which they are bound or R^4 and R^5 together with the carbon atoms to which they are bound may be joined to a form a saturated or unsaturated cyclic ring, which may optionally include up to two heteroatoms selected from O, NR^a or S;

R^8 and R^9 may be same or different and are independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroarylalkyl , nitro, halo, -OH, cyano, $-C(O)-R^a$, $-C(O)O-R^a$, $-C(O)NR^aR^b$, $-S(O)_m-R^a$, $-S(O)_m-NR^aR^b$, $-C(=NR^a)-R^b$, $-C(=NR^a)-NR^aR^b$, $-C(=S)-NR^aR^b$, $-C(=S)-R^a$, $-N=C(R^aR^b)$, $-NR^aR^b$, $-OR^a$, $-SR^a$, a protecting group, or R^8 and R^9 may be joined together with the atom connecting them to a form a optionally substituted saturated or unsaturated cyclic ring, which may optionally include up to two heteroatoms selected from O, NR^a or S;

R^a and R^b may be same or different and are independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroarylalkyl , nitro, -OH, cyano, formyl, acetyl, halogen, a protecting group, $-C(O)-R^a$, $-C(O)O-R^a$, $-C(O)NR^aR^b$, $-S(O)_m-R^a$, $-S(O)_m-NR^aR^b$, $-NR^aR^b$, ,$-OR^a$, $-SR^{a,}$ or R^a and R^b may be joined together with the atom connecting them to a form a optionally substituted saturated or unsaturated cyclic ring, which may optionally include up to two heteroatoms selected from O, NR^a or S;

X is O, $S(O)_m$ and NR^6;

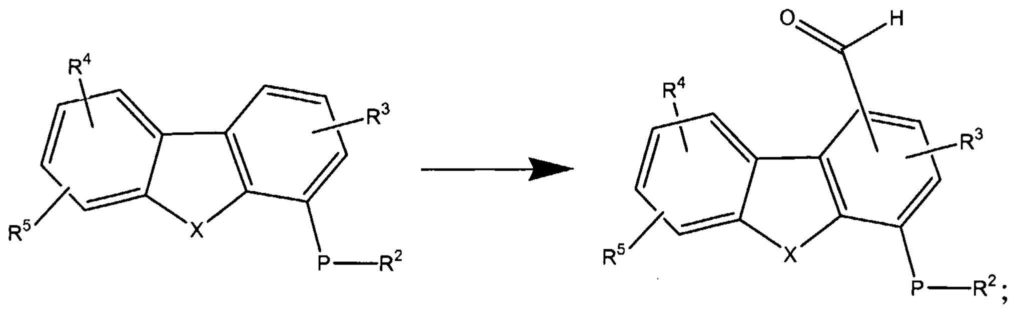
wherein P is O or S;

wherein m is 0, 1 or 2;

or an analog, tautomer, regioisomer, stereoisomer, enantiomer, diastereomer, polymorph, pharmaceutically acceptable salt, N-oxide, pharmaceutically acceptable solvate thereof

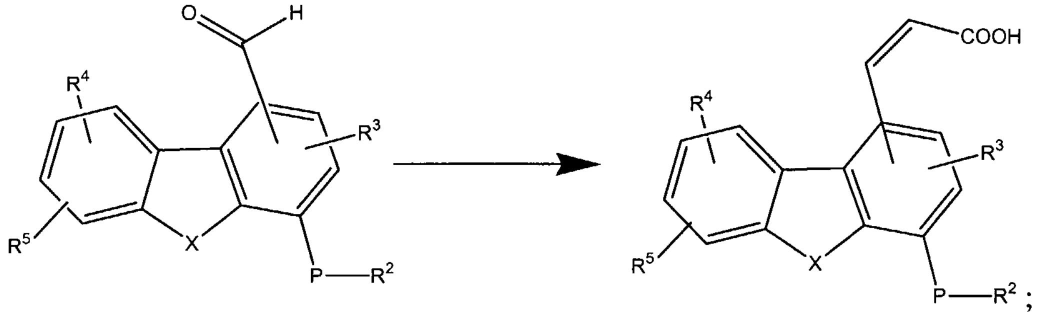
comprising the steps of

(a) formylating a compound of the general formula (12) with dichloromethyl methyl ether in the presence of a Lewis acid catalyst to give a compound of the formula (15)



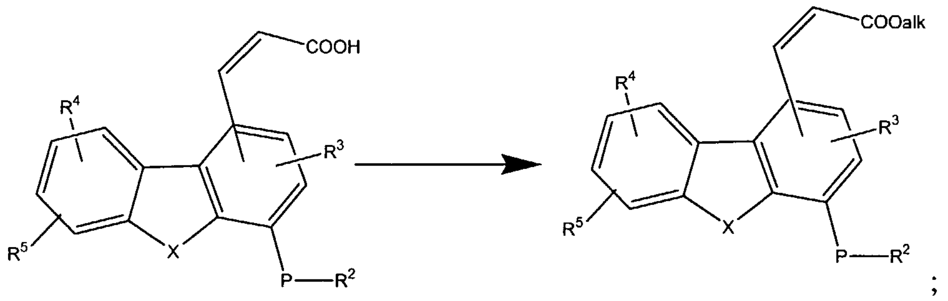
(12) (15)

(b) condensing a compound of the formula (15) with malonic acid to give a compound of the general formula (16)



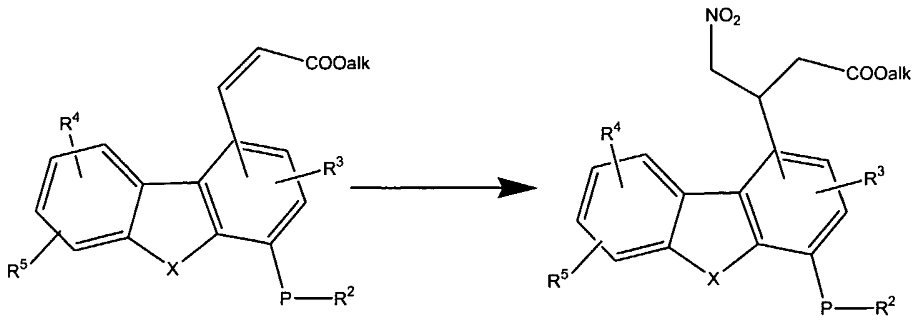
(15) (16)

(c) alkylating a compound of the formula (16) with an aklyl halide under basic conditions to give a compound of the formula (17)



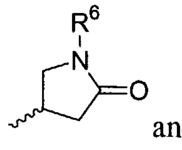
(16) (17)

(d) reacting a compound of the formula (17) with nitromethane in the presence of a base to give a compound of the formula (18)

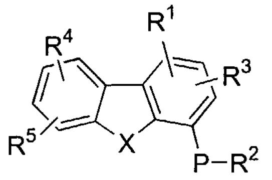


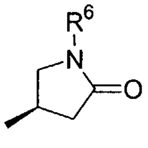
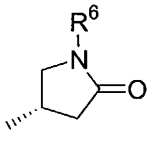
; and

(17) (18)

(e) reduction of a compound of formula 18 followed by cyclization to afford a compound of formula 1 wherein R^1 is  and R^6 is the same as defined above.

134. A method for the preparation of compound of the general formula 1



wherein R^1 is  or 

R^2, R^3, R^4, R^5, R^6 and R^7 may be the same or different and are independently for each occurrence hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroarylalkyl , $-NR^8R^9$, $-C(O)-R^8$, $-C(O)O-R^8$, $-C(O)NR^8R^9$, $-S(O)_m-R^8$, $-S(O)_m-NR^8R^9$, nitro, -OH, cyano, formyl, acetyl, halogen, $-OR^8$, $-SR^8$, or a protecting group, or when R^1 and R^3, or R^4 and R^5 or ortho to each other then R^1 and R^3 together with the carbon atoms to which they are bound or R^4 and R^5 together with the carbon atoms to which they are bound may be joined to a form a saturated or unsaturated cyclic ring, which may optionally include up to two heteroatoms selected from O, NR^a or S;

R^8 and R^9 may be same or different and are independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroarylalkyl , nitro, halo, -OH, cyano, $-C(O)-R^a$, $-C(O)O-R^a$, $-C(O)NR^aR^b$, $-S(O)_m-R^a$, $-S(O)_m-NR^aR^b$, $-C(=NR^a)-R^b$, $-C(=NR^a)-NR^aR^b$, $-C(=S)-NR^aR^b$, $-C(=S)-R^a$, $-N=C(R^aR^b)$, $-NR^aR^b$, $-OR^a$, $-SR^a$, a protecting group, or R^8 and R^9 may be joined together with the atom connecting them to a form a optionally substituted saturated or unsaturated cyclic ring, which may optionally include up to two heteroatoms selected from O, NR^a or S;

R^a and R^b may be same or different and are independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroarylalkyl , nitro, -OH, cyano, formyl, acetyl, halogen, a protecting group, $-C(O)-R^a$, $-C(O)O-R^a$, $-C(O)NR^aR^b$, $-S(O)_m-R^a$, $-S(O)_m-NR^aR^b$, $-NR^aR^b$, ,$-OR^a$, $-SR^{a,}$ or R^a and R^b may be joined together with the atom connecting them to a form a optionally substituted saturated or unsaturated cyclic ring, which may optionally include up to two heteroatoms selected from O, NR^a or S;

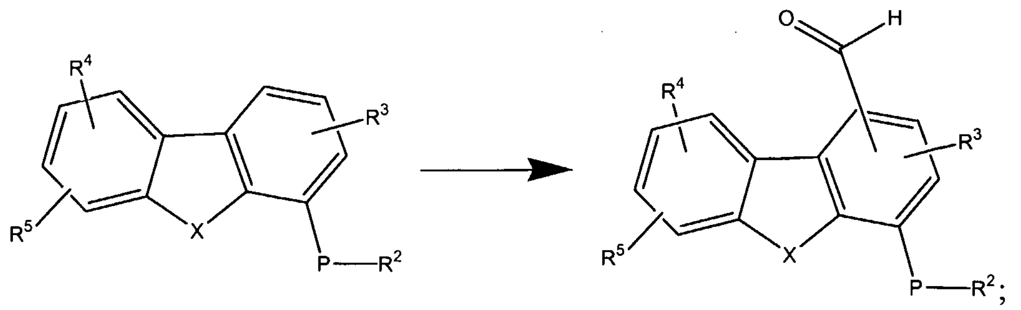
X is O, $S(O)_m$ and NR^6;

wherein P is O or S;

wherein m is 0, 1 or 2;

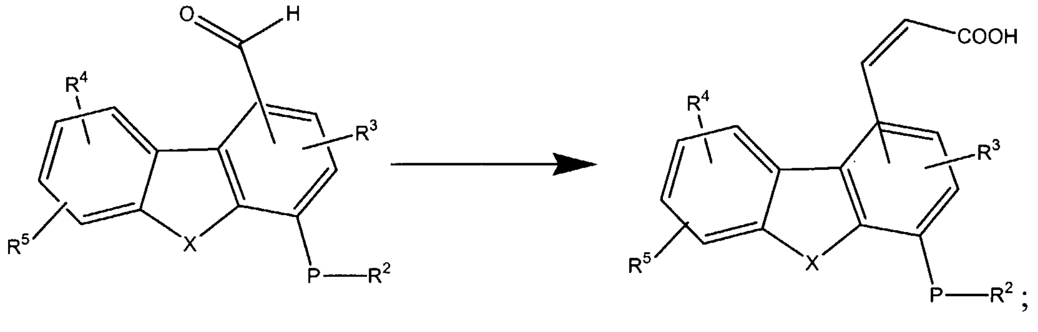
or an analog, tautomer, regioisomer, stereoisomer, enantiomer, diastereomer, polymorph, pharmaceutically acceptable salt, N-oxide, pharmaceutically acceptable solvate thereof comprising the steps of

(a) formylating a compound of the general formula (12) with dichloromethyl methyl ether in the presence of a Lewis acid catalyst to give a compound of the formula (15)



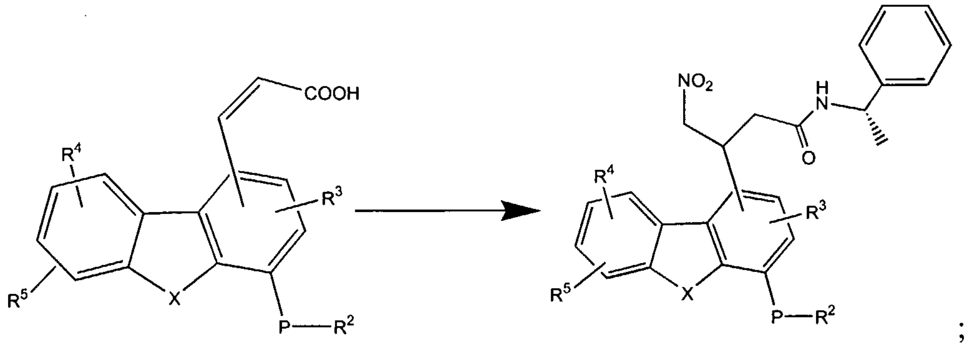
(12) (15)

(b) condensing a compound of the formula (15) with malonic acid to give a compound of the general formula (16)



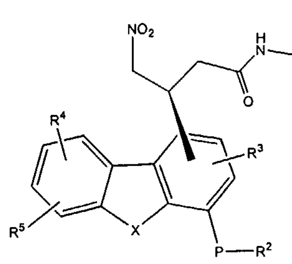
(15) (16)

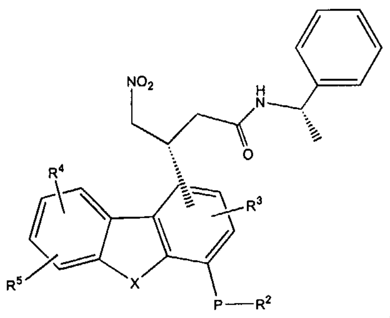
(c) The compound of the formula (16) is then converted to diasteriomeric mixture of compound (21) using basic resolving agent such as (R)-(+)-1-Phenylethylamine or (S)-(+)-1-Phenylethylamine.



(16) (21)

(d) resolving the diasteriomeric mixture of compound of general formula (21) to give the compounds of general formula 22a and 22b.

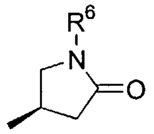




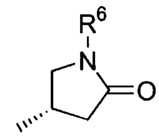
; and

(22a) and (22b)

(e) reduction of a compound of formula 22a and 22b followed by cyclization to afford a compound of formula 1 wherein R^1 is

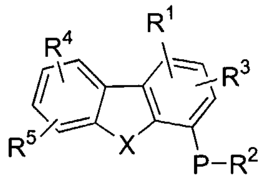


and

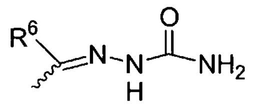


and R^6 is the same as defined above.

135. A process for the preparation of a compound of the formula 1



wherein R^1 is



R^2, R^3, R^4, R^5, R^6 and R^7 may be the same or different and are independently for each occurrence hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroarylalkyl , $-NR^8R^9$, $-C(O)-R^8$, $-C(O)O-R^8$, $-C(O)NR^8R^9$, $-S(O)_m-R^8$, $-S(O)_m-NR^8R^9$, nitro, -OH, cyano, formyl, acetyl, halogen, $-OR^8$, $-SR^8$, or a protecting group, or when R^1 and R^3, or R^4 and R^5 or ortho to each other then R^1 and R^3 together with the carbon atoms to which they are bound or R^4 and R^5 together with the carbon atoms to which they are bound may be joined to a form a saturated or unsaturated cyclic ring, which may optionally include up to two heteroatoms selected from O, NR^a or S;

R^8 and R^9 may be same or different and are independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroarylalkyl , nitro, halo, -OH, cyano, $-C(O)-R^a$, $-C(O)O-R^a$, $-C(O)NR^aR^b$, $-S(O)_m-R^a$, $-S(O)_m-NR^aR^b$, $-C(=NR^a)-R^b$, $-C(=NR^a)-NR^aR^b$, $-C(=S)-NR^aR^b$, $-C(=S)-R^a$, $-N=C(R^aR^b)$, $-NR^aR^b$, $-OR^a$, $-SR^a$, a protecting group, or R^8 and R^9 may be joined together with the atom connecting them to a form a optionally substituted saturated or unsaturated cyclic ring, which may optionally include up to two heteroatoms selected from O, NR^a or S;

R^a and R^b may be same or different and are independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroarylalkyl , nitro, -OH, cyano, formyl, acetyl, halogen, a protecting group, $-C(O)-R^a$, $-C(O)O-R^a$, $-C(O)NR^aR^b$, $-S(O)_m-R^a$, $-S(O)_m-NR^aR^b$, $-NR^aR^b$, ,$-OR^a$, $-SR^{a,}$ or R^a and R^b may be joined together with the atom connecting them to a form a optionally substituted saturated or unsaturated cyclic ring, which may optionally include up to two heteroatoms selected from O, NR^a or S;

X is O, $S(O)_m$ and NR^6;

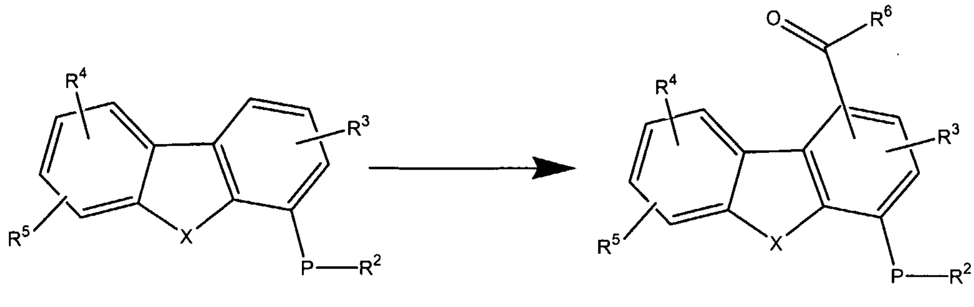
wherein P is O or S;

wherein m is 0, 1 or 2;

or an analog, tautomer, regioisomer, stereoisomer, enantiomer, diastereomer, polymorph, pharmaceutically acceptable salt, N-oxide, pharmaceutically acceptable solvate thereof

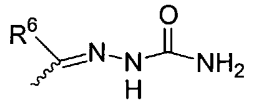
comprising steps of

(a) acylating a compound of the formula (12) with an acylating agent in the presence of a Lewis acid catalyst or a formylation agent to afford a compound of the formula (19)

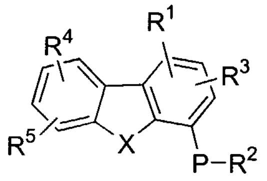


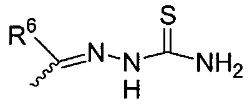
; and

(12) (19)

(b) reacting a compound of the formula (19) with semicarbazide hydrochloride to afford a compound of the formula 1 where R^1 is  and R^6 is the same as defined above.

136. A process for the preparation of a compound of the formula 1



wherein R^1 is 

R^2, R^3, R^4, R^5, R^6 and R^7 may be the same or different and are independently for each occurrence hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroarylalkyl , $-NR^8R^9$, $-C(O)-R^8$, $-C(O)O-R^8$, $-C(O)NR^8R^9$, $-S(O)_m-R^8$, $-S(O)_m-NR^8R^9$, nitro, -OH, cyano, formyl, acetyl, halogen, $-OR^8$, $-SR^8$, or a protecting group, or when R^1 and R^3, or R^4 and R^5 or ortho to each other then R^1 and R^3 together with the carbon atoms to which they are bound or R^4 and R^5 together with the carbon atoms to which they are bound may be joined to a form a saturated or unsaturated cyclic ring, which may optionally include up to two heteroatoms selected from O, NR^a or S;

R^8 and R^9 may be same or different and are independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroarylalkyl , nitro, halo, -OH, cyano, $-C(O)-R^a$, $-C(O)O-R^a$, $-C(O)NR^aR^b$, $-S(O)_m-R^a$, $-S(O)_m-NR^aR^b$, $-C(=NR^a)-R^b$, $-C(=NR^a)-NR^aR^b$, $-C(=S)-NR^aR^b$, $-C(=S)-R^a$, $-N=C(R^aR^b)$, $-NR^aR^b$, $-OR^a$, $-SR^a$, a protecting group, or R^8 and R^9 may be joined together with the atom connecting them to a form a optionally substituted saturated or unsaturated cyclic ring, which may optionally include up to two heteroatoms selected from O, NR^a or S;

R^a and R^b may be same or different and are independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroarylalkyl , nitro, -OH, cyano, formyl, acetyl, halogen, a protecting group, $-C(O)-R^a$, $-C(O)O-R^a$, $-C(O)NR^aR^b$, $-S(O)_m-R^a$, $-S(O)_m-NR^aR^b$, $-NR^aR^b$, ,$-OR^a$, $-SR^{a,}$ or R^a and R^b may be joined together with the atom connecting them to a form a optionally substituted saturated or unsaturated cyclic ring, which may optionally include up to two heteroatoms selected from O, NR^a or S;

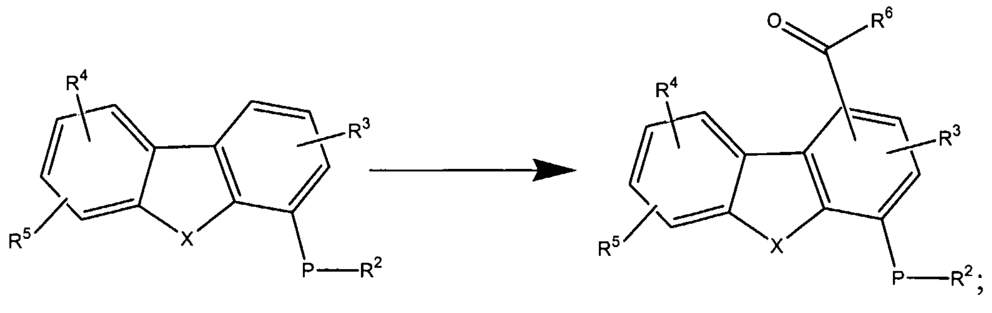
X is O, $S(O)_m$ and NR^6;

wherein P is O or S;

wherein m is 0, 1 or 2;

or an analog, tautomer, regioisomer, stereoisomer, enantiomer, diastereomer, polymorph, pharmaceutically acceptable salt, N-oxide, pharmaceutically acceptable solvate thereof comprising steps of

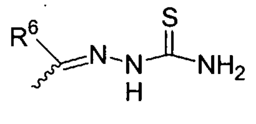
(a) acylating a compound of the formula (12) with an acylating agent in the presence of a Lewis acid catalyst or a formylation agent to afford a compound of the formula (19)



and

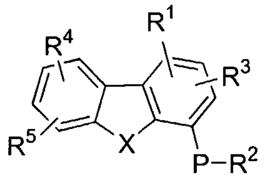
(12) (19)

(b) reacting a compound of the formula (19) with thiosemicarbanzide hydrochloride to afford a compound of the formula 1 where R^1 is

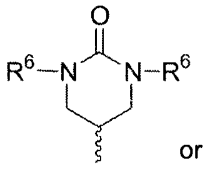


R^6 is the same as defined above.

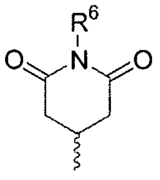
137. A process for the preparation of a compound of the formula 1



wherein R^1 is



or



R^2, R^3, R^4, R^5, R^6 and R^7 may be the same or different and are independently for each occurrence hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroarylalkyl , -NR^{8}R^9, -C(O)-R^8 , -C(O)O-R^8, -C(O)NR^{8}R^9 , -S(O)$_m$-R^8, -S(O)$_m$-NR^{8}R^9, nitro, -OH, cyano, formyl, acetyl, halogen, -OR^8, -SR^8, or a protecting group, or when R^1 and R^3, or R^4 and R^5 or ortho to each other then R^1 and R^3 together with the carbon atoms to which they are bound or R^4 and R^5 together with the carbon atoms to which they are bound may be joined to a form a saturated or unsaturated cyclic ring, which may optionally include up to two heteroatoms selected from O, NR^a or S;

R^8 and R^9 may be same or different and are independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroarylalkyl , nitro, halo, -OH, cyano, $-C(O)-R^a$, $-C(O)O-R^a$, $-C(O)NR^aR^b$, $-S(O)_m-R^a$, $-S(O)_m-NR^aR^b$, $-C(=NR^a)-R^b$, $-C(=NR^a)-NR^aR^b$, $-C(=S)-NR^aR^b$, $-C(=S)-R^a$, $-N=C(R^aR^b)$, $-NR^aR^b$, $-OR^a$, $-SR^a$, a protecting group, or R^8 and R^9 may be joined together with the atom connecting them to a form a optionally substituted saturated or unsaturated cyclic ring, which may optionally include up to two heteroatoms selected from O, NR^a or S;

R^a and R^b may be same or different and are independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroarylalkyl , nitro, -OH, cyano, formyl, acetyl, halogen, a protecting group, $-C(O)-R^a$, $-C(O)O-R^a$, $-C(O)NR^aR^b$, $-S(O)_m-R^a$, $-S(O)_m-NR^aR^b$, $-NR^aR^b$, ,$-OR^a$, $-SR^{a,}$ or R^a and R^b may be joined together with the atom connecting them to a form a optionally substituted saturated or unsaturated cyclic ring, which may optionally include up to two heteroatoms selected from O, NR^a or S;

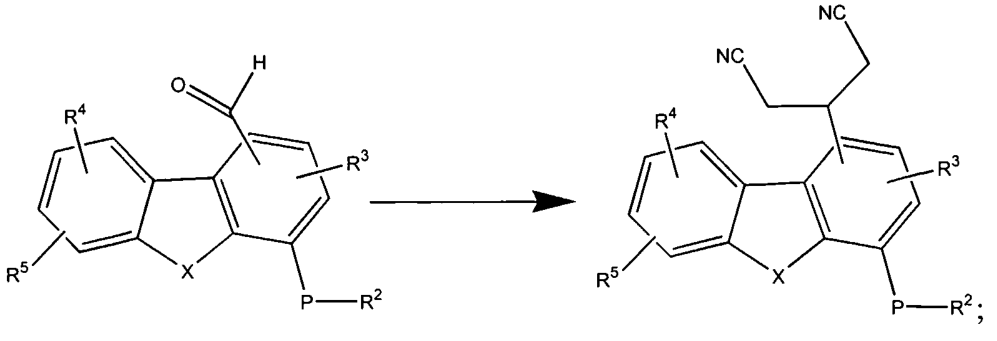
X is O, $S(O)_m$ and NR^6;

wherein P is O or S;

wherein m is 0, 1 or 2;

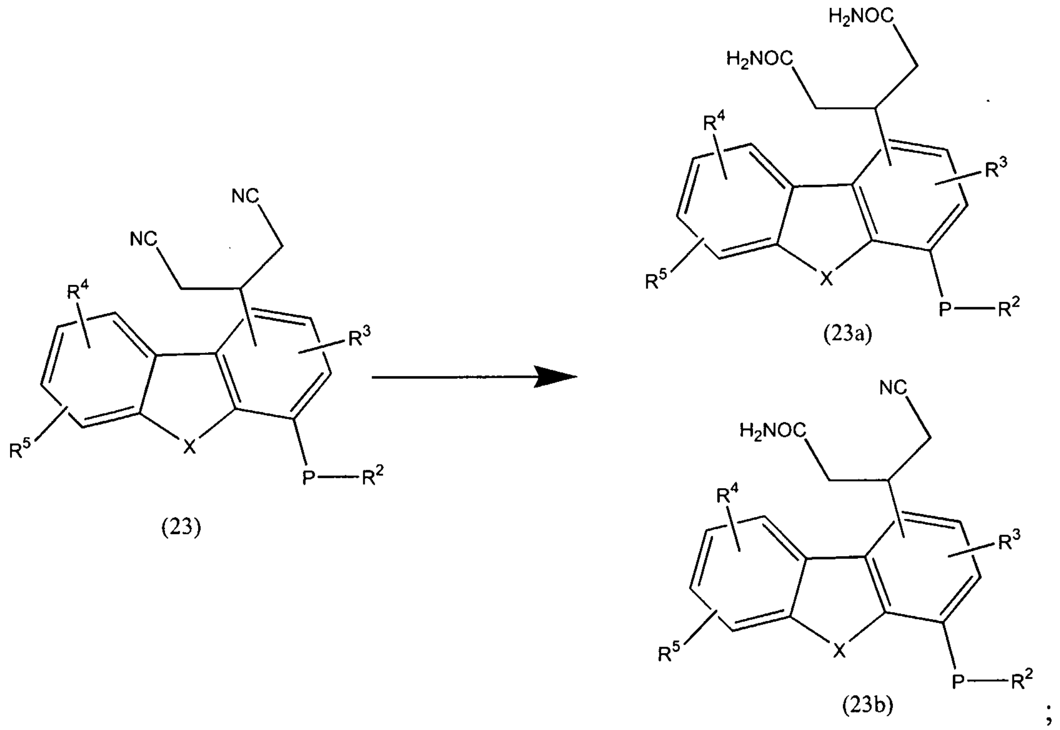
or an analog, tautomer, regioisomer, stereoisomer, enantiomer, diastereomer, polymorph, pharmaceutically acceptable salt, N-oxide, pharmaceutically acceptable solvate thereof comprising steps of

(a) Reacting a compound of the formula (15) with cyanoacetic acid to yield a compound of the formula (23)



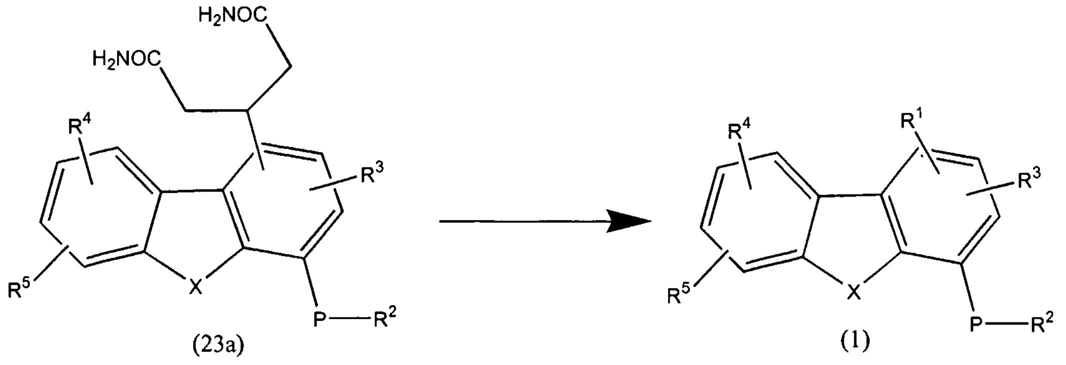
(15) (23)

(b) Hydrolysing the compound of the formula (23) using hydrogen peroxide or acid such as H_2SO_4 to afford a compound of the formula (24).

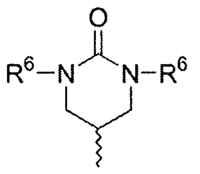


(23) (23a) (23b)

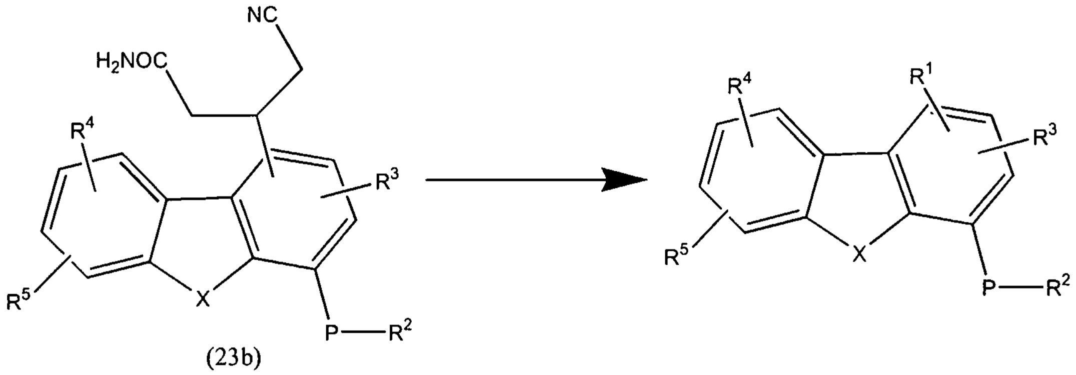
(c) Cyclising the compound of the formula (23a) using lead tetraacetate or bromine in aqueous sodium hydroxide to afford a compound of the general formula (1).



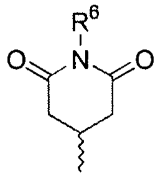
(23a) (1)

wherein R^1 is  and R^6 is the same as defined above; and

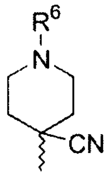
c) Cyclising the compound of the formula (23b) to afford a compound of the general formula (1)



(23b)

wherein R^1 is  and R^6 is the same as defined bove

138. A process for the preparation of a compound of the formula 1

wherein R^1 is 

R^2, R^3, R^4, R^5, R^6 and R^7 may be the same or different and are independently for each occurrence hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroarylalkyl , $-NR^8R^9$, $-C(O)-R^8$, $-C(O)O-R^8$, $-C(O)NR^8R^9$, $-S(O)_m-R^8$, $-S(O)_m-NR^8R^9$, nitro, -OH, cyano, formyl, acetyl, halogen, $-OR^8$, $-SR^8$, or a protecting group, or when R^1 and R^3, or R^4 and R^5 or ortho to each other then R^1 and R^3 together with the carbon atoms to which they are bound or R^4 and R^5 together with the carbon atoms to which they are bound may be joined to a form a saturated or unsaturated cyclic ring, which may optionally include up to two heteroatoms selected from O, NR^a or S;

R^8 and R^9 may be same or different and are independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroarylalkyl , nitro, halo, -OH, cyano, $-C(O)-R^a$, $-C(O)O-R^a$, $-C(O)NR^aR^b$, $-S(O)_m-R^a$, $-S(O)_m-NR^aR^b$, $-C(=NR^a)-R^b$, $-C(=NR^a)-NR^aR^b$, $-C(=S)-NR^aR^b$, $-C(=S)-R^a$, $-N=C(R^aR^b)$, $-NR^aR^b$, $-OR^a$, $-SR^a$, a protecting group, or R^8 and R^9 may be joined together with the atom connecting them to a form a optionally substituted saturated or unsaturated cyclic ring, which may optionally include up to two heteroatoms selected from O, NR^a or S;

R^a and R^b may be same or different and are independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroarylalkyl , nitro, -OH, cyano, formyl, acetyl, halogen, a protecting group, $-C(O)-R^a$, $-C(O)O-R^a$, $-C(O)NR^aR^b$, $-S(O)_m-R^a$, $-S(O)_m-NR^aR^b$, $-NR^aR^b$, ,$-OR^a$, $-SR^{a,}$ or R^a and R^b may be joined together with the atom connecting them to a form a optionally substituted saturated or unsaturated cyclic ring, which may optionally include up to two heteroatoms selected from O, NR^a or S;

X is O, $S(O)_m$ and NR^6;

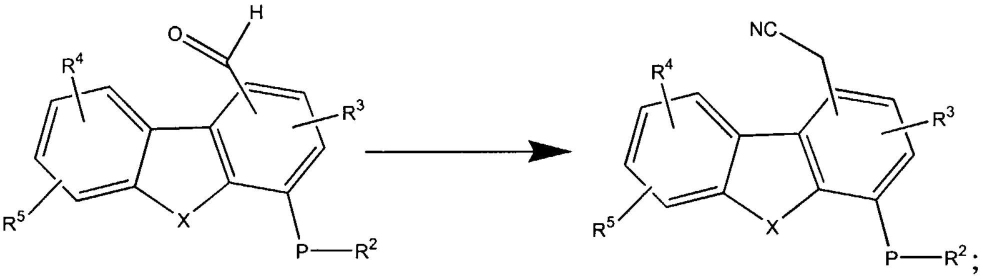
wherein P is O or S;

wherein m is 0, 1 or 2;

or an analog, tautomer, regioisomer, stereoisomer, enantiomer, diastereomer, polymorph, pharmaceutically acceptable salt, N-oxide, pharmaceutically acceptable solvate thereof

comprising steps of

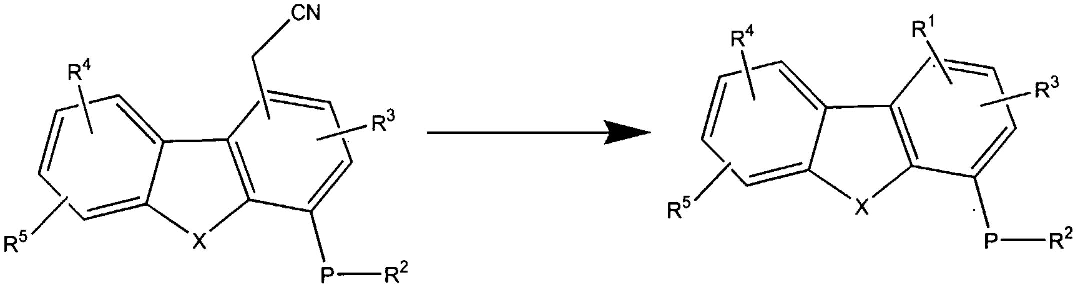
(a) converting a compound of the formula (15) to a compound of the formula (26) by reduction of aldehyde to alcohol followed by chlorination using thionyl chloride and cyanation using sodium cyanide.



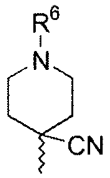
; and

(15) (26)

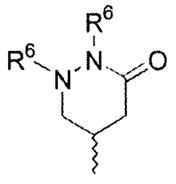
(b) Reacting the compound of the formula (26) with appropriate amine such as N-boc-N,Nbis(2-chloro ethyl) amine in the presence of a strong base such as NaH to afford a compound of the formula (1).



(24) (1)

wherein R^1 is  and R^6 is the same as defined above.

139. A process for the preparation of a compound of the formula 1

wherein R^1 is 

R^2, R^3, R^4, R^5, R^6 and R^7 may be the same or different and are independently for each occurrence hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroarylalkyl , $-NR^8R^9$, $-C(O)-R^8$, $-C(O)O-R^8$, $-C(O)NR^8R^9$, $-S(O)_m-R^8$, $-S(O)_m-NR^8R^9$, nitro, -OH, cyano, formyl, acetyl, halogen, $-OR^8$, $-SR^8$, or a protecting group, or when R^1 and R^3, or R^4 and R^5 or ortho to each other then R^1 and R^3 together with the carbon atoms to which they are bound or R^4 and R^5 together with the carbon atoms to which they are bound may be joined to a form a saturated or unsaturated cyclic ring, which may optionally include up to two heteroatoms selected from O, NR^a or S;

R^8 and R^9 may be same or different and are independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroarylalkyl , nitro, halo, -OH, cyano, $-C(O)-R^a$, $-C(O)O-R^a$, $-C(O)NR^aR^b$, $-S(O)_m-R^a$, $-S(O)_m-NR^aR^b$, $-C(=NR^a)-R^b$, $-C(=NR^a)-NR^aR^b$, $-C(=S)-NR^aR^b$, $-C(=S)-R^a$, $-N=C(R^aR^b)$, $-NR^aR^b$, $-OR^a$, $-SR^a$, a protecting group, or R^8 and R^9 may be joined together with the atom connecting them to a form a optionally substituted saturated or unsaturated cyclic ring, which may optionally include up to two heteroatoms selected from O, NR^a or S;

R^a and R^b may be same or different and are independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkylalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocyclic group, substituted or unsubstituted heterocyclylalkyl, substituted or unsubstituted heteroarylalkyl , nitro, -OH, cyano, formyl, acetyl, halogen, a protecting group, $-C(O)-R^a$, $-C(O)O-R^a$, $-C(O)NR^aR^b$, $-S(O)_m-R^a$, $-S(O)_m-NR^aR^b$, $-NR^aR^b$, ,$-OR^a$, $-SR^{a,}$ or R^a and R^b may be joined together with the atom connecting them to a form a optionally substituted saturated or unsaturated cyclic ring, which may optionally include up to two heteroatoms selected from O, NR^a or S;

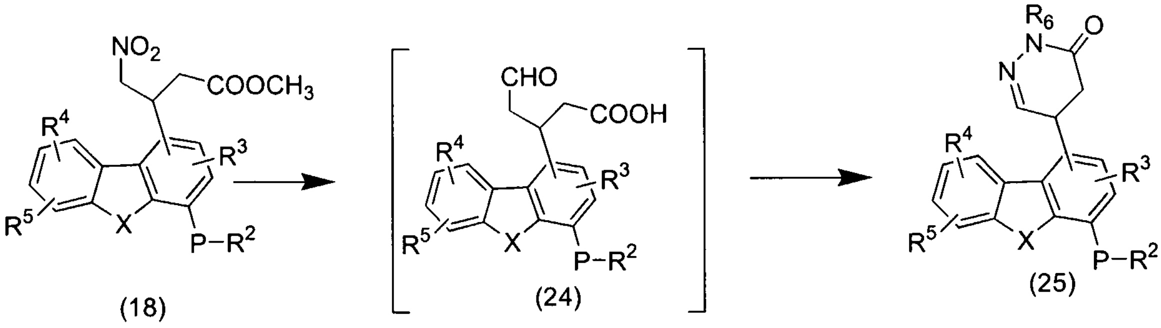
X is O, $S(O)_m$ and NR^6;

wherein P is O or S;

wherein m is 0, 1 or 2;

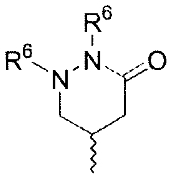
or an analog, tautomer, regioisomer, stereoisomer, enantiomer, diastereomer, polymorph, pharmaceutically acceptable salt, N-oxide, pharmaceutically acceptable solvate thereof comprising steps of

(a) reacting a compound of general formula (18) with dilute base such as sodium hydroxide and the like followed by treatment with concentrated sulfuric acid to give a compound of general formula (24) which is further reacted with Hydrazine hydrate to give a compound of general formula **(25).**



(b) reducing the copm[pound of general formula (25) using H2/Pd on

Carbon or Raney nickel in Methanol to afford a compound of the formula 1 where R^1 is



and R^6 is the same as described above.