

2-thioxanthine derivatives acting as MPO-inhibitors

FIELD OF THE INVENTION

The present invention relates to novel thioxanthine derivatives, compositions containing them and their use in therapy.

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BACKGROUND OF THE INVENTION

Myeloperoxidase (MPO) is a heme-containing enzyme found predominantly in polymorphonuclear leukocytes (PMNs). MPO is one member of a diverse protein family of mammalian peroxidases that also includes eosinophil peroxidase, thyroid peroxidase, 10 salivary peroxidase, lactoperoxidase, prostaglandin H synthase, and others. The mature enzyme is a dimer of identical halves. Each half molecule contains a covalently bound heme that exhibits unusual spectral properties responsible for the characteristic green colour of MPO. Cleavage of the disulphide bridge linking the two halves of MPO yields the hemi-enzyme that exhibits spectral and catalytic properties indistinguishable from 15 those of the intact enzyme. The enzyme uses hydrogen peroxide to oxidize chloride to hypochlorous acid. Other halides and pseudohalides (like thiocyanate) are also physiological substrates to MPO.

PMNs are of particular importance for combating infections. These cells contain MPO, 20 with well-documented microbicidal action. PMNs act non-specifically by phagocytosis to engulf microorganisms, incorporate them into vacuoles, termed phagosomes, which fuse with granules containing myeloperoxidase to form phagolysosomes. In phagolysosomes the enzymatic activity of the myeloperoxidase leads to the formation of hypochlorous acid, a potent bactericidal compound. Hypochlorous acid is oxidizing in itself, and reacts most 25 avidly with thiols and thioethers, but also converts amines into chloramines, and chlorinates aromatic amino acids. Macrophages are large phagocytic cells which, like PMNs, are capable of phagocytosing microorganisms. Macrophages can generate hydrogen peroxide and upon activation also produce myeloperoxidase. MPO and hydrogen peroxide can also be released to the outside of the cells where the reaction with chloride 30 can induce damage to adjacent tissue.

Linkage of myeloperoxidase activity to disease has been implicated in neurological diseases with a neuroinflammatory response including multiple sclerosis, Alzheimer's disease, Parkinson's disease and stroke as well as other inflammatory diseases or conditions like asthma, chronic obstructive pulmonary disease, cystic fibrosis, atherosclerosis, ischemic heart disease, heart failure, inflammatory bowel disease, renal glomerular damage and rheumatoid arthritis. Lung cancer has also been suggested to be associated with high MPO levels.

Multiple sclerosis (MS)

MPO positive cells are immensely present in the circulation and in tissue undergoing inflammation. More specifically MPO containing macrophages and microglia has been documented in the CNS during disease; multiple sclerosis (Nagra RM, et al. Journal of Neuroimmunology 1997; 78(1-2):97-107), Parkinson's disease (Choi D-K. et al. J. Neurosci. 2005; 25(28):6594-600) and Alzheimer's disease (Green PS. et al. Journal of Neurochemistry. 2004; 90(3):724-33). It is supposed that some aspects of a chronic ongoing inflammation result in an overwhelming destruction where agents from MPO reactions have an important role.

The enzyme is released both extracellularly as well as into phagolysosomes in the neutrophils (Hampton MB, Kettle AJ, Winterbourn CC. Blood 1998; 92(9): 3007-17). A prerequisite for the MPO activity is the presence of hydrogen peroxide, generated by NADPH oxidase and a subsequent superoxide dismutation. The oxidized enzyme is capable to use a plethora of different substrates of which chloride is most recognized. From this reaction the strong non-radical oxidant - hypochlorous acid (HOCl) - is formed. HOCl oxidizes sulphur containing amino acids like cysteine and methionine very efficiently (Peskin AV, Winterbourn CC. Free Radical Biology and Medicine 2001; 30(5): 572-9). It also forms chloramines with amino groups, both in proteins and other biomolecules (Peskin AV. et al. Free Radical Biology and Medicine 2004; 37(10):1622-30). It chlorinates phenols (like tyrosine) (Hazen SL. et al. Mass Free Radical Biology and Medicine 1997; 23(6): 909-16) and unsaturated bonds in lipids (Albert CJ. et al. J. Biol. Chem. 2001; 276(26): 23733-41), oxidizes iron centers (Rosen H, Klebanoff SJ. Journal of

Biological Chemistry 1982; 257(22): 13731-354) and crosslinks proteins (Fu X, Mueller DM, Heinecke JW. Biochemistry 2002; 41(4): 1293-301).

Proteolytic cascades participate both in cell infiltration through the BBB as well as the
5 destruction of BBB, myelin and nerve cells (Cuzner ML, Opdenakker G. Journal of
Neuroimmunology 1999; 94(1-2): 1-14; Yong VW. et al. Nature Reviews Neuroscience
accomplished through the action of upstream proteases in a cascade as well as through
oxidation of a disulfide bridge Fu X. et al. J. Biol. Chem. 2001; 276(44): 41279-87; Gu Z.
et al. Science 2002; 297(5584): 1186-90). This oxidation can be either a nitrosylation or
10 HOCl-mediated oxidation. Both reactions can be a consequence of MPO activity. Several
reports have suggested a role for MMP's in general and MMP-9 in particular as
influencing cell infiltration as well as tissue damage (BBB breakdown and demyelination),
both in MS and EAE (for review see Yong VW. et al, *supra*). The importance of these
specific kinds of mechanisms in MS comes from studies where increased activity and
15 presence of proteases have been identified in MS brain tissue and CSF. Supportive data has
also been generated by doing EAE studies with mice deficient in some of the proteases
implicated to participate in the MS pathology, or by using pharmacological approaches.
The demyelination is supposed to be dependent on the cytotoxic T-cells and toxic products
generated by activated phagocytes (Lassmann H. J Neurol Neurosurg Psychiatry 2003;
20 74(6): 695-7). The axonal loss is thus influenced by proteases and reactive oxygen and
nitrogen intermediates. When MPO is present it will obviously have the capability of both
activating proteases (directly as well as through disinhibition by influencing protease
inhibitors) and generating reactive species.

25 *Chronic obstructive pulmonary disease (COPD)*

Chronic obstructive pulmonary disease (COPD) is a disease state characterised by airflow
limitation that is not fully reversible. The airflow limitation is usually both progressive and
associated with an abnormal inflammatory response of the lungs to noxious particles or
gases. COPD is a major public health problem. It is the fourth leading cause of chronic
30 morbidity and mortality in the United States and is projected to rank fifth in 2020 as a
worldwide burden of disease. In the UK the prevalence of COPD is 1.7% in men and 1.4%

in women. COPD spans a range of severity from mild to very severe, with the cost of treatment rising rapidly as the severity increases.

Levels of MPO in sputum and BAL are much greater in COPD patients than normal,
5 nonsmoking controls (Keatings V.M., Barnes P.J. Am J Respir Crit Care Med 1997;
155:449-453; Pesci, A. et al. Eur Respir J 1998; 12:380-386). MPO levels are further
elevated during exacerbations of the disease (Fiorini G. et al. Biomedicine &
Pharmacotherapy 2000; 54:274-278; Crooks S.W. et al. European Respiratory Journal.
15(2): 274-80, 2000). The role of MPO is likely to be more important in exacerbations of
10 COPD (Sharon S.D. et al. Am J Respir Crit Care Med. 2001; 163: 349-355).

In addition to the destructive capacity of MPO there is a strong clinical link with vascular
disease (Baldus S. et al. Circulation 2003;108: 1440-5). Dysfunctional MPO
polymorphisms are associated with a reduced risk of mortality from coronary artery
15 disease (Nikpoor B. et al. Am Heart J 2001; 142: 336), and patients with high serum levels
of MPO have increased risk of acute coronary syndrome. The effects of MPO on vascular
disease may extend to COPD, since there is strong evidence that the pulmonary vasculature
is one of the earliest sites of involvement in the smokers' lung. Striking changes in the
intima of the pulmonary arteries have been described which show a dose relationship with
20 smoking (Hale K.A., Niewoehner D.E., Cosio M.G. Am Rev Resp Dis 1980;122: 273-8).
The physiological function of MPO is associated with innate host defence. This role,
however, is not critical as most cases of MPO deficient patients have relatively benign
symptoms (Parry M.F. et al. Ann Int Med. 1981; 95: 293-301, Yang, K.D., Hill, H.R.
Pediatr Infect Dis J. 2001; 20: 889-900). In summary, there is considerable evidence that
25 elevated MPO levels in COPD may contribute to the disease via several mechanisms. A
selective inhibitor of MPO would therefore be expected to alleviate both the acute and
chronic inflammatory aspects of COPD and may reduce the development of emphysema.

Atherosclerosis

30 An MPO inhibitor should reduce the atherosclerotic burden and/or the vulnerability of
existing atherosclerotic lesions and thereby decrease the risk of acute myocardial
infarction, unstable angina or stroke, and reduce ischemia/reperfusion injury during acute

coronary syndrome and ischemic cerebrovascular events. Several lines of data support a role for MPO in atherosclerosis. MPO is expressed in the shoulder regions and necrotic core of human atherosclerotic lesions and active enzyme has been isolated from autopsy specimens of human lesions (Daugherty, A. et al. (1994) *J Clin Invest* 94(1): 437-44). In
5 eroded and ruptured human lesions, as compared to fatty streaks, an increased number of MPO expressing macrophages have been demonstrated, suggesting a particular role for MPO in acute coronary syndromes (Sugiyama, S. et al. (2001) *Am J Pathol* 158(3): 879-91). Patients with established coronary artery disease have higher plasma and leukocyte MPO levels than healthy controls (Zhang, R. et al. (2001) *Jama* 286(17): 2136-42).
10 Moreover, in two large prospective studies plasma levels of MPO predicted the risk of future coronary events or revascularisation (Baldus, S. et al. (2003) *Circulation* 108(12):1440-5; Brennan, M. et al. (2003) *N Engl J Med* 349(17): 1595-604). Total MPO deficiency in humans has a prevalence of 1 in 2000-4000 individuals. These individuals appear principally healthy but a few cases of severe *Candida* infection have
15 been reported. Interestingly, MPO deficient humans are less affected by cardiovascular disease than controls with normal MPO levels (Kutter, D. et al. (2000) *Acta Haematol* 104(1)). A polymorphism in the MPO promoter affects expression leading to high and low MPO expressing individuals. In three different studies the high expression genotype has been associated with an increased risk of cardiovascular disease (Nikpoor, B. et al. (2001)
20 *Am Heart J* 142(2): 336-9; Makela, R., P. J. Karhunen, et al. (2003) *Lab Invest* 83(7): 919-25; Asselbergs, F. W., et al. (2004) *Am J Med* 116(6): 429-30). Data accumulated during the last ten years indicate that the proatherogenic actions of MPO include oxidation of lipoproteins, induction of endothelial dysfunction via consuming nitric oxide and destabilisation of atherosclerotic lesions by activation of proteases (Nicholls, S. J. and S. L.
25 Hazen (2005) *Arterioscler Thromb Vasc Biol* 25(6): 1102-11). Recently, several studies have focused on nitro- and chlorotyrosine modifications of LDL and HDL lipoproteins. Since chlorotyrosine modifications in vivo only can be generated by hypochlorous acid produced by MPO these modifications are regarded as specific markers of MPO activity (Hazen, S. L. and J. W. Heinecke (1997) *J Clin Invest* 99(9): 2075-81). LDL particles
30 exposed to MPO in vitro become aggregated, leading to facilitated uptake via macrophage scavenger receptors and foam cell formation (Hazzell, L. J. and R. Stocker (1993) *Biochem J* 290 (Pt 1): 165-72). Chlorotyrosine modification of apoA1, the main apolipoprotein of

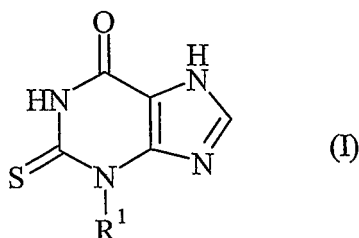
HDL cholesterol, results in impaired cholesterol acceptor function (Bergt, C., S. et al. (2004) Proc Natl Acad Sci U S A; Zheng, L. et al. (2004) J Clin Invest 114(4): 529-41).

Systematic studies of these mechanisms have shown that MPO binds to and travels with apoA1 in plasma. Moreover, MPO specifically targets those tyrosine residues of apoA1 that physically interact with the macrophage ABCA1 cassette transporter during cholesterol efflux from the macrophage (Bergt, C. et al. (2004) J Biol Chem 279(9): 7856-66; Shao, B. et al. (2005) J Biol Chem 280(7): 5983-93; Zheng et al. (2005) J Biol Chem 280(1): 38-47). Thus, MPO seems to have a dual aggravating role in atherosclerotic lesions, i.e. increasing lipid accumulation via aggregation of LDL particles and decreasing the reverse cholesterol transport via attack on the HDL protein apoA1.

The present invention discloses novel thioxanthines that display useful properties as inhibitors of the enzyme MPO. Furthermore, the novel compounds of the present invention display either one or more than one of the following: (i) improved selectivity towards TPO; (ii) unexpectedly high inhibitory activity towards MPO; (iii) improved brain permeability; (iv) improved solubility and/or (v) improved half-life; when compared to known thioxanthines. Such thioxanthines are disclosed in e.g. WO 03/089430 and WO 05/037835.

DISCLOSURE OF THE INVENTION

The present invention provides a compound according to Formula (I)



wherein

R¹ is selected from C₁-C₆ alkyl, and said C₁-C₆ alkyl is substituted with C₁-C₆ alkoxy; and at least one of said C₁-C₆ alkyl or said C₁-C₆ alkoxy is branched; or a pharmaceutically acceptable salt thereof, solvate or solvate of a salt thereof.

According to one aspect of the present invention, the C₁-C₆ alkyl of R¹ represents C₂-₄alkyl.

According to one embodiment of the present invention, said alkyl is selected from isobutyl,
5 ethyl and propyl.

According to one embodiment of the present invention, said alkyl is substituted with C₁-₃alkoxy.

10 According to one embodiment of the present invention, said alkyl is substituted with C₁-alkoxy.

According to one embodiment of the present invention, said alkyl is substituted with C₂-alkoxy.

15 According to one embodiment of the present invention, said alkyl is substituted with propoxy or iso-propoxy.

The present invention also relates to a compound selected from the group consisting of:

20 3-(2-Ethoxy-2-methylpropyl)-2-thioxanthine;
3-(2-Propoxy-2-methylpropyl)-2-thioxanthine;
3-(2-Methoxy-2-methylpropyl)-2-thioxanthine;
3-(2-isopropoxyethyl)-2-thioxanthine;
3-(2-Ethoxypropyl)-2- thioxanthine;
25 3-(2*S*-Ethoxypropyl)-2- thioxanthine;
3-(2*R*-Ethoxypropyl)-2- thioxanthine;

or a pharmaceutically acceptable salt, solvate or solvate of a salt thereof.

The compounds of Formula (I) may exist in tautomeric forms. All such tautomers and
30 mixtures of tautomers are included within the scope of the present invention.

The compounds of Formula (I) may exist in enantiomeric forms. It is to be understood that all enantiomers, diastereomers, racemates and mixtures thereof are included within the scope of the invention.

5 Unless otherwise indicated, the term "C₁-C₆ alkyl" referred to herein denotes a straight or branched chain alkyl group having from 1 to 6 carbon atoms. Examples of such groups include methyl, ethyl, n-propyl, n-butyl, iso-butyl, tert-butyl, pentyl and hexyl. The term "C₂-C₄ alkyl" is to be interpreted analogously. It is to be understood that when the alkyl denotes a C₁ or a C₂ alkyl, such alkyls cannot be branched.

10 Unless otherwise indicated, the term "C₁-C₆ alkoxy" referred to herein denotes a straight or branched chain alkoxy group having from 1 to 6 carbon atoms. Examples of such groups include methoxy, ethoxy, 1-propoxy, 2-propoxy, 1-butoxy, iso-butoxy, tert-butoxy and pentoxy. The term "C₁-C₃ alkoxy" is to be interpreted analogously. It is to be understood
15 that when the alkoxy denotes a C₁ or a C₂-alkoxy, such alkoxys cannot be branched. The present invention also relates to the use of the novel compounds of Formula (I) or a pharmaceutically acceptable salt thereof as a medicament.

A further aspect of the present invention is the use of a compound of Formula (I), or a
20 pharmaceutically acceptable salt thereof, solvate or solvate of a salt thereof, in the manufacture of a medicament, for the treatment or prophylaxis of diseases or conditions in which inhibition of the enzyme MPO is beneficial.

A further aspect of the present invention provides the use of a compound of Formula (I), or
25 a pharmaceutically acceptable salt thereof, solvate or solvate of a salt thereof, in the manufacture of a medicament, for the treatment or prophylaxis of neuroinflammatory disorders, cardio- and cerebrovascular atherosclerotic disorders and peripheral artery disease, heart failure and respiratory disorders such as chronic obstructive pulmonary disease (COPD).

30 Another further aspect of the present invention provides the use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, solvate or solvate of a salt thereof, in the

manufacture of a medicament, for the treatment or prophylaxis of multiple sclerosis.
Treatment may include slowing progression of disease.

Another further aspect of the present invention provides the use of a compound of Formula
5 (I), or a pharmaceutically acceptable salt thereof, solvate or solvate of a salt thereof, in the
manufacture of a medicament, for the treatment or prophylaxis of Parkinson's disease.
Treatment may include slowing progression of disease.

Another further aspect of the present invention provides the use of a compound of Formula
10 (I) or a pharmaceutically acceptable salt thereof, solvate or solvate of a salt thereof, in the
manufacture of a medicament, for the treatment or prophylaxis of atherosclerosis by
preventing and/or reducing the formation of new atherosclerotic lesions or plaques and/or
by preventing or slowing progression of existing lesions and plaques.

Another further aspect of the present invention provides the use of a compound of Formula
15 (I) or a pharmaceutically acceptable salt thereof, solvate or solvate of a salt thereof, in the
manufacture of a medicament, for the treatment or prophylaxis of atherosclerosis by
changing the composition of the plaques to reduce the risk of plaque rupture and
atherothrombotic events.

Another further aspect of the present invention provides the use of a compound of Formula
20 (I) or a pharmaceutically acceptable salt thereof, solvate or solvate of a salt thereof, in the
manufacture of a medicament, for the treatment or prophylaxis of respiratory disorders,
such as chronic obstructive pulmonary disease. Treatment may include slowing
25 progression of disease.

According to the present invention, there is also provided a method of treating, or reducing
the risk of, diseases or conditions in which inhibition of the enzyme MPO is beneficial
which comprises administering to a person suffering from or at risk of, said disease or
30 condition, a therapeutically effective amount of a compound of Formula (I), or a
pharmaceutically acceptable salt thereof, solvate or solvate of a salt thereof.

Further, there is also provided a method of treating, or reducing the risk of, neuroinflammatory disorders, cardio- and cerebrovascular atherosclerotic disorders or peripheral artery disease, or heart failure or respiratory disorders, such as chronic obstructive pulmonary disease (COPD), in a person suffering from or at risk of, said disease or condition, wherein the method comprises administering to the person a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, solvate or solvate of a salt thereof.

Further, there is also provided a method of treating, or reducing the risk of, multiple sclerosis in a person suffering from or at risk of, said disease or condition, wherein the method comprises administering to the person a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, solvate or solvate of a salt thereof.

Further, there is also provided a method of treating, or reducing the risk of, Parkinson's disease in a person suffering from or at risk of, said disease or condition, wherein the method comprises administering to the person a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. There is also provided a method of treating, or reducing the risk of atherosclerosis by preventing and/or reducing the formation of new atherosclerotic lesions or plaques and /or by preventing or slowing progression of existing lesions and plaques in a person suffering from or at risk of, said disease or condition, wherein the method comprises administering to the person a therapeutically effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof, solvate or solvate of a salt thereof.

There is also provided a method of treating, or reducing the risk of atherosclerosis by changing the composition of the plaques so as to reduce the risk of plaque rupture and atherothrombotic events in a person suffering from or at risk of, said disease or condition, wherein the method comprises administering to the person a therapeutically effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof, solvate or solvate of a salt thereof.

In another aspect the present invention provides a pharmaceutical formulation comprising a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, solvate or solvate of a salt thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier, for use in the treatment or
5 prophylaxis of diseases or conditions in which inhibition of the enzyme MPO is beneficial.

In a further aspect the present invention provides a pharmaceutical formulation comprising a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, solvate or solvate of a salt thereof, in admixture with a
10 pharmaceutically acceptable adjuvant, diluent or carrier, for use in the treatment or prophylaxis of neuroinflammatory disorders.

In a further aspect the present invention provides a pharmaceutical formulation comprising a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent
15 or carrier, for use in the treatment or prophylaxis of multiple sclerosis, cardio- and cerebrovascular atherosclerotic disorders and peripheral artery disease and heart failure and respiratory disorders, such as chronic obstructive pulmonary disease. In another aspect the present invention provides a pharmaceutical formulation comprising a therapeutically
20 effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, solvate or solvate of a salt thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier, for use in the treatment or prophylaxis of atherosclerosis by preventing and reducing the formation of new atherosclerotic lesions and/or plaques and/or by preventing or slowing progression of existing lesions and
25 plaques.

In another aspect the present invention provides a pharmaceutical formulation comprising a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, solvate or solvate of a salt thereof, in admixture with a
30 pharmaceutically acceptable adjuvant, diluent or carrier, for use in the treatment or prophylaxis of atherosclerosis by changing the composition of the plaques so as to reduce the risk of plaque rupture and atherothrombotic events.

The present invention further relates to therapies for the treatment of:

Neurodegenerative Disorder(s) including but not limited to Alzheimer's Disease (AD), Dementia, Cognitive Deficit in Schizophrenia (CDS), Mild Cognitive Impairment (MCI), Age-Associated Memory Impairment (AAMI), Age-Related Cognitive Decline (ARCD),
5 Cognitive Impairment No Dementia (CIND), Multiple Sclerosis, Parkinson's Disease (PD), postencephalitic parkinsonism, Huntington's Disease, amyotrophic lateral sclerosis (ALS), motor neuron diseases (MND), Multiple System Atrophy (MSA), Corticobasal Degeneration, Progressive Supranuclear Paresis, Guillain-Barré Syndrome (GBS), and Chronic Inflammatory Demyelinating Polyneuropathy (CIDP). Dementia includes, but is
10 not limited to, Down syndrome, vascular dementia, dementia with Lewy bodies, HIV dementia, Frontotemporal dementia Parkinson's Type (FTDP), Pick's Disease, Niemann-Pick's Disease, traumatic brain injury (TBI), dementia pugilistica, Creutzfeld-Jacob Disease and prion diseases.

15 The present invention further relates to therapies for the treatment of:

Neuroinflammatory Disorder(s) including but not limited to Multiple Sclerosis (MS), Parkinson's disease, Multiple System Atrophy (MSA), Corticobasal Degeneration, Progressive Supranuclear Paresis, Guillain-Barré Syndrome (GBS), chronic inflammatory demyelinating polyneuropathy (CIDP). Multiple sclerosis (MS) includes Relapse
20 Remitting Multiple Sclerosis (RRMS), Secondary Progressive Multiple Sclerosis (SPMS), and Primary Progressive Multiple Sclerosis (PPMS).

The present invention further relates to therapies for the treatment of:

Cognitive Disorder(s) including but not limited to

- 25 a) Dementia, including but not limited to Alzheimer's Disease (AD), Down syndrome, vascular dementia, Parkinson's Disease (PD), postencephalitic parkinsonism, dementia with Lewy bodies, HIV dementia, Huntington's Disease, amyotrophic lateral sclerosis (ALS), motor neuron diseases (MND), Frontotemporal dementia Parkinson's Type (FTDP), progressive supranuclear palsy (PSP), Pick's Disease, Niemann-Pick's Disease,
30 corticobasal degeneration, traumatic brain injury (TBI), dementia pugilistica, Creutzfeld-Jacob Disease and prion diseases;
- b) Cognitive Deficit in Schizophrenia (CDS);

- c) Mild Cognitive Impairment (MCI);
- d) Age-Associated Memory Impairment (AAMI);
- e) Age-Related Cognitive Decline (ARCD);
- f) Cognitive Impairment No Dementia (CIND).

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The present invention further relates to therapies for the treatment of:
Attention-Deficit and Disruptive Behavior Disorder(s) including but not limited to
attention deficit disorder (ADD), attention deficit hyperactivity disorder (ADHD) and
affective disorders.

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The present invention also relates to the treatment of the diseases and conditions below
which may be treated with the compounds of the present invention:
respiratory tract: obstructive diseases of the airways including: asthma, including
bronchial, allergic, intrinsic, extrinsic, exercise-induced, drug-induced (including aspirin
and NSAID-induced) and dust-induced asthma, both intermittent and persistent and of all
severities, and other causes of airway hyper-responsiveness; chronic obstructive pulmonary
disease (COPD); bronchitis, including infectious and eosinophilic bronchitis; emphysema;
bronchiectasis; cystic fibrosis; sarcoidosis; farmer's lung and related diseases;
hypersensitivity pneumonitis; lung fibrosis, including cryptogenic fibrosing alveolitis,
idiopathic interstitial pneumonias, fibrosis complicating anti-neoplastic therapy and
chronic infection, including tuberculosis and aspergillosis and other fungal infections;
complications of lung transplantation; vasculitic and thrombotic disorders of the lung
vasculature, and pulmonary hypertension; antitussive activity including treatment of
chronic cough associated with inflammatory and secretory conditions of the airways, and
iatrogenic cough; acute and chronic rhinitis including rhinitis medicamentosa, and
vasomotor rhinitis; perennial and seasonal allergic rhinitis including rhinitis nervosa (hay
fever); nasal polyposis; acute viral infection including the common cold, and infection due
to respiratory syncytial virus, influenza, coronavirus (including SARS) and adenovirus;
bone and joints: arthritides associated with or including osteoarthritis/osteoarthritis, both
primary and secondary to, for example, congenital hip dysplasia; cervical and lumbar
spondylitis, and low back and neck pain; rheumatoid arthritis and Still's disease;
seronegative spondyloarthropathies including ankylosing spondylitis, psoriatic arthritis,

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reactive arthritis and undifferentiated spondarthropathy; septic arthritis and other infection related arthropathies and bone disorders such as tuberculosis, including Potts' disease and Poncet's syndrome; acute and chronic crystal-induced synovitis including urate gout, calcium pyrophosphate deposition disease, and calcium apatite related tendon, bursal and synovial inflammation; Behcet's disease; primary and secondary Sjogren's syndrome; systemic sclerosis and limited scleroderma; systemic lupus erythematosus, mixed connective tissue disease, and undifferentiated connective tissue disease; inflammatory myopathies including dermatomyositis and polymyositis; polymyalgia rheumatica; juvenile arthritis including idiopathic inflammatory arthritides of whatever joint distribution and associated syndromes, and rheumatic fever and its systemic complications; vasculitides including giant cell arteritis, Takayasu's arteritis, Churg-Strauss syndrome, polyarteritis nodosa, microscopic polyarteritis, and vasculitides associated with viral infection, hypersensitivity reactions, cryoglobulins, and paraproteins; low back pain; Familial Mediterranean fever, Muckle-Wells syndrome, and Familial Hibernian Fever, Kikuchi disease; drug-induced arthralgias, tendonitis, and myopathies;

The present invention further relates to combination therapies wherein a compound of Formula (I) or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition or formulation comprising a compound of Formula (I) is administered concurrently or sequentially with therapy and/or an agent for the treatment of any one of cardio- and cerebrovascular atherosclerotic disorders and peripheral artery disease.

The present invention includes compounds of Formula (I) and also said compounds in their form of salts. Suitable salts include those formed with organic or inorganic acids or organic or inorganic bases. Such salts will normally be pharmaceutically acceptable although salts of non-pharmaceutically acceptable acids or bases may be of utility in the preparation and purification of the compound in question. Thus, acid addition salts include inter alia those formed from hydrochloric acid. Base addition salts include those in which the cation is inter alia sodium or potassium.

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The compounds of the invention and intermediates thereto may be isolated from their reaction mixtures and, if necessary further purified, by using standard techniques.

The compounds of Formula (I) may exist in enantiomeric forms. Therefore, all enantiomers, diastereomers, racemates, tautomers and mixtures thereof are included within the scope of the invention. The various optical isomers may be isolated by separation of a racemic mixture of the compounds using conventional techniques, for example, fractional
5 crystallisation, or HPLC. Alternatively, the various optical isomers may be prepared directly using optically active starting materials.

The compounds of Formula (I) and their pharmaceutically acceptable salts are useful
10 because they possess pharmacological activity as inhibitors of the enzyme MPO.

For the above-mentioned therapeutic indications, the dosage administered will, of course, vary with the compound employed, the mode of administration and the treatment desired. However, in general, satisfactory results are obtained when the compounds are
15 administered at a dosage of the solid form of between 1 mg and 2000 mg per day.

The compounds of Formula (I) and pharmaceutically acceptable derivatives thereof, may be used on their own, or in the form of appropriate pharmaceutical compositions in which the compound or derivative is in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier. Thus, another embodiment of the invention concerns a pharmaceutical
20 composition comprising a novel compound of Formula (I), or a pharmaceutically acceptable salt thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier. Administration may be by, but is not limited to, enteral (including oral, sublingual or rectal), intranasal, inhalation, intravenous, topical or other parenteral routes.

25 Conventional procedures for the selection and preparation of suitable pharmaceutical formulations are described in, for example, "Pharmaceuticals - The Science of Dosage Form Designs", M. E. Aulton, Churchill Livingstone, 1988. The pharmaceutical composition preferably comprises less than 80% and more preferably less than 50% of a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

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There is also provided a process for the preparation of such a pharmaceutical composition, which comprises mixing the ingredients.

A compound of Formula (I) or a pharmaceutically acceptable salt thereof may be administered in association with compounds from one or more of the following groups:

1) anti-inflammatory agents, for example

- a) NSAIDs (e.g. acetylsalicylic acid, Ibuprofen, naproxen, flurbiprofen, diclofenac, indometacin);
- b) leukotriene synthesis inhibitors (5-LO inhibitors e.g. AZD4407, Zileuton, licofelone, CJ13610, CJ13454; FLAP inhibitors e.g. BAY-Y-1015, DG-031, MK591, MK886, A81834; LTA4 hydrolase inhibitors e.g. SC56938, SC57461A);
- c) leukotriene receptor antagonists (e.g. CP195543, amelubant, LY293111, accolat, MK571);

2) anti-hypertensive agents, for example

- a) beta-blockers (e.g. metoprolol, atenolol, sotalol);
- b) angiotensin converting enzyme inhibitors (e.g. captopril, ramipril, quinapril, enalapril);
- c) calcium channel blockers (e.g. verapamil, diltiazem, felodipine, amlodipine);
- d) angiotensin II receptor antagonists (e.g. irbesartan, candesartan, telmisartan, losartan);

3) anti-coagulantia, for example

- a) thrombin inhibitors (e.g. ximelagatran), heparines, factor Xa inhibitors;
- b) platelet aggregation inhibitors (e.g. clopidogrel, ticlopidine, prasugrel, AZD6140);

4) modulators of lipid metabolism, for example

- a) insulin sensitizers such as PPAR agonists (e.g. pioglitazone, rosiglitazone, Galida, muraglitazar, gefemrozil, fenofibrate);
- b) HMG-CoA reductase inhibitors, statins (e.g. simvastatin, pravastatin, atorvastatin, rosuvastatin, fluvastatin);
- c) cholesterol absorption inhibitors (e.g. ezetimibe);
- d) IBAT inhibitors (e.g. AZD-7806);
- e) LXR agonists (e.g. GW-683965A, T-0901317);
- f) FXR receptor modulators;
- g) phospholipase inhibitors;

5) anti-anginal agents, for example, nitrates and nitrites;

6) modulators of oxidative stress, for example, anti-oxidants (e.g. probucol, AGI 1067).

Methods of preparation

According to the invention, we further provide a process for the preparation of compounds of Formula (I), or a pharmaceutically acceptable salt, solvate, enantiomer, diastereomer or racemate thereof wherein R¹ is defined as in Formula (I).

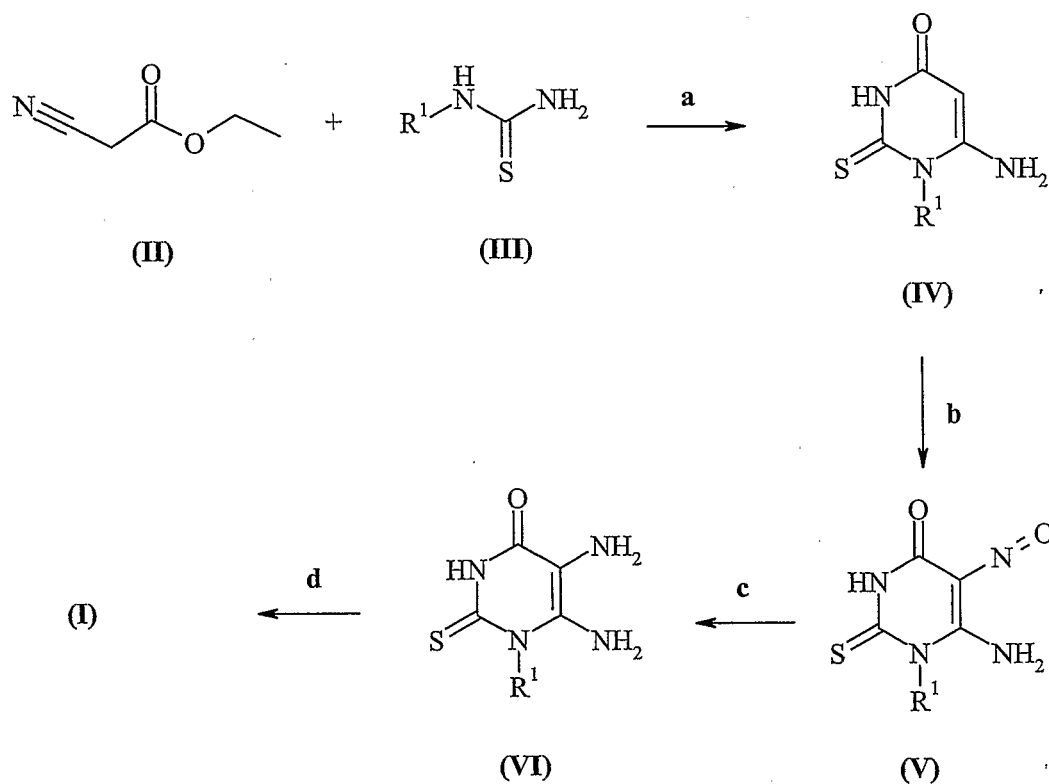
5

Throughout the following description of such processes it is to be understood that, where appropriate, suitable protecting groups will be added to, and subsequently removed from, the various reactants and intermediates in a manner that will be readily understood by one skilled in the art of organic synthesis. Conventional procedures for using such protecting groups as well as examples of suitable protecting groups are described, for example, in 10 "Protective Groups in Organic Synthesis", T.W. Green, P.G.M. Wuts, Wiley-Interscience, New York, (1999). It is also to be understood that a transformation of a group or substituent into another group or substituent by chemical manipulation can be conducted on any intermediate or final product on the synthetic path toward the final product, in 15 which the possible type of transformation is limited only by inherent incompatibility of other functionalities carried by the molecule at that stage to the conditions or reagents employed in the transformation. Such inherent incompatibilities, and ways to circumvent them by carrying out appropriate transformations and synthetic steps in a suitable order, will be readily understood to the one skilled in the art of organic synthesis. Examples of 20 transformations are given below, and it is to be understood that the described transformations are not limited only to the generic groups or substituents for which the transformations are exemplified. References and descriptions on other suitable transformations are given in "Comprehensive Organic Transformations – A Guide to Functional Group Preparations" R. C. Larock, VHC Publishers, Inc. (1989). References 25 and descriptions of other suitable reactions are described in textbooks of organic chemistry, for example, "Advanced Organic Chemistry", March 4th ed. McGraw Hill (1992) or, "Organic Synthesis", Smith, McGraw Hill, (1994). Techniques for purification of intermediates and final products include for example, straight and reversed phase chromatography on column or rotating plate, recrystallisation, distillation and liquid-liquid 30 or solid-liquid extraction, which will be readily understood by one skilled in the art. The definitions of substituents and groups are as in Formula (I) except where defined differently. The terms "room temperature" and "ambient temperature" shall mean, unless

otherwise specified, a temperature between 16 and 25 °C. The term "reflux" shall mean, unless otherwise stated, in reference to an employed solvent using a temperature at or slightly above the boiling point of the named solvent. It is understood that microwaves can be used for the heating of reaction mixtures. The terms "flash chromatography" or "flash column chromatography" shall mean preparative chromatography on silica using an organic solvent, or mixtures thereof, as mobile phase.

Preparation of end products

1. A process for preparing a compound of Formula (I), wherein R^1 is defined as in Formula (I) is shown in Scheme 1:



Scheme 1

Compounds of formula (II), (III), (IV), (V) and (VI) are useful intermediates in the preparation of compound of Formula (I) wherein R^1 is defined as in Formula (I).

Compounds of formula (II)-(VI) are either commercially available, or can be prepared from either commercially available, or in the literature described compounds (Ouwkerk *et al.* Eur. J. Org. Chem. 2002, 14, 2356).

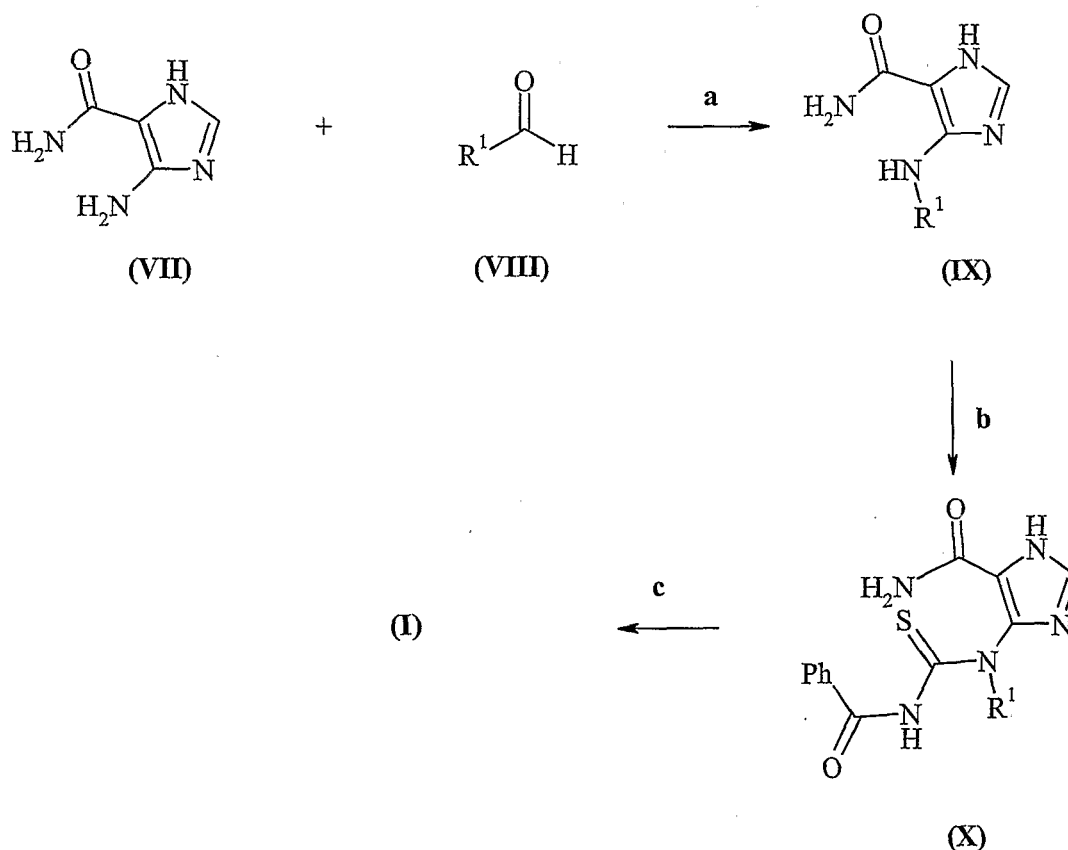
- a) Reaction of ethyl cyanoacetate (II) with a thiourea of formula (III), wherein R^1 is defined as in Formula (I). In the process, ethyl cyanoacetate (II) and an appropriate thiourea (III) are dissolved or suspended in a suitable alcohol, such as ethanol, and an alkoxide, such as sodium ethoxide, is added. The temperature is typically from 70 °C up to reflux temperature of the reaction mixture.
- b) Reaction of a thiouracil of formula (IV), wherein R^1 is defined above with sodium nitrite in an acidic solution. In the process, the thiouracil (IV) is suspended in a solvent such as acetic acid (10 to 100% in aqueous solution) and hydrochloric acid (aq. 1M) and stirred at a suitable temperature between 0 °C and 85 °C for 10 to 20 minutes before the sodium nitrite, dissolved in water, is added dropwise.
- c) Reduction of a nitroso compound of formula (V), wherein R^1 is defined above. In the process, the reduction of the nitroso compound of formula (V) may be carried out with a suitable reducing agent, such as sodium dithionite or gaseous hydrogen (H_2 (gas)), in a suitable solvent mixture such as water and ammonia solution or sodium hydroxide (aq. 1N) at a temperature range between room temperature and 75 °C for 30 minutes to 24 hours. Alternatively the sodium dithionite could be added directly to the conditions used in step b.
- d) The reaction of a diamine of formula (VI), wherein R^1 is defined above with i) formic acid, ii) formamidine acetate or with iii) trialkylorthoester is described below:
- (i) In process (d), the diamine of formula (VI) is treated with formic acid (98%), at a suitable temperature between ambient temperature and the reflux temperature of the reaction mixture. The process is continued for a suitable period of time, typically for between 20 to 30 minutes. After removal of the formic acid, treatment with a suitable aqueous base, for example, with 10% aqueous sodium hydroxide solution, then yields the compound of Formula (I). The treatment with base is carried out for a suitable time at a suitable temperature, for example for about 30 minutes to 90 minutes at a temperature between ambient temperature and the reflux temperature of the reaction mixture.
- Alternatively the reaction can be performed in a solvent such as water to which formic acid and sulphuric acid is added. The reaction is then heated under reflux overnight which after neutralization gives the compound of Formula (I).

(ii) In process (d), the diamine of formula (VI) is treated with formamidine acetate in a solvent such as (DMSO) dimethyl sulfoxide at a suitable temperature, for example 70 °C, until the reaction is complete, typically for 1-3 h.

(iii) In process (d), the diamine of formula (VI) is treated at a suitable temperature with an excess of an appropriate ortho ester such as triethylorthoformate and tripropylorthoformate, optionally in the presence of a suitable solvent such as an alcohol, until reaction is complete. The temperature is typically up to the reflux temperature of the reaction mixture, and reaction times are generally from 30 minutes to overnight.

Other methods for the conversion of a diamine of formula (VI) into a compound of Formula (I) are described in the literature and will be readily known to the person skilled in the art.

2. A process for preparing a compound of Formula (I), wherein R¹ is defined as in Formula (I) (Suzuki *et al.* Chem. Pharm. Bull. 2002, 50, 1163) is shown in Scheme 2



Scheme 2

Compounds of formula (VII), (VIII), (IX) and (X) are useful intermediates in the preparation of compounds of Formula (I) wherein R¹ is defined as in Formula (I).

Compounds of formula (VII)-(X) are either commercially available, or can be prepared from either commercially available, or in the literature described compounds.

5

a) Reaction of 5-Amino-4-imidazolecarboxamide (VII) with an appropriate aldehyde of formula (VIII), wherein R¹ is defined as in Formula (I), and a suitable borohydride, such as sodium cyanoborohydride or sodium acetoxyborohydride, in a suitable solvent such as methanol, with the optional addition of acetic acid, at room temperature or with heating up
10 10 to 50 °C gave the intermediate of formula (IX).

b) Reaction of intermediate of formula (IX), wherein R¹ is defined as in Formula (I), with an isothiocyanate such as benzoylisothiocyanate or ethoxycarbonyl isothiocyanate in a solvent such as dichloromethane and methanol at room temperature gave intermediate of
15 formula (X).

c) Reaction of intermediate of formula (X), wherein R¹ is defined as in Formula (I), with a base such as sodium hydroxide or ammonia (7N in methanol) at a temperature ambient to 80 °C and the reflux temperature of the solvent gave a compound of formula (I) wherein R¹
20 is defined as in Formula (I).

General Methods

All solvents used were analytical grade and commercially available anhydrous solvents were routinely used for reactions. Reactions were typically run under an inert atmosphere
25 of nitrogen or argon.

¹H and ¹³C NMR spectra were recorded at 400 MHz for proton and 100 MHz for carbon-13 either on a Varian Unity+ 400 NMR Spectrometer equipped with a 5mm BBO probe head with Z-gradients, or a Bruker Avance 400 NMR spectrometer equipped with a 60 µl
30 dual inverse flow probe head with Z-gradients, or a Bruker DPX400 NMR spectrometer equipped with a 4-nucleus probe head equipped with Z-gradients. Unless specifically noted in the examples, spectra were recorded at 400 MHz for proton and 100 MHz for carbon-13.

The following reference signals were used: the middle line of DMSO- d_6 δ 2.50 (^1H), δ 39.51 (^{13}C); the middle line of CD_3OD δ 3.31 (^1H) or δ 49.15 (^{13}C); acetone- d_6 2.04 (^1H), 206.5 (^{13}C); and CDCl_3 δ 7.26 (^1H), the middle line of CDCl_3 δ 77.16 (^{13}C) (unless otherwise indicated).

5

Mass spectra were recorded on a Waters LCMS consisting of an Alliance 2795 (LC), Waters PDA 2996, and ELS detector (Sedex 75) and a ZMD single quadrupole mass spectrometer. The mass spectrometer was equipped with an electrospray ion source (ES) operated in a positive or negative ion mode. The capillary voltage was 3 kV and cone
10 voltage was 30 V. The mass spectrometer was scanned between m/z 100-600 with a scan time of 0.7s. The column temperature was set to 40 °C. The Diode Array Detector was scanned from 200-400 nm. The temperature of the ELS detector was adjusted to 40 °C and the pressure was set to 1.9 bar. For LC separation a linear gradient was applied starting at 100% A (A: 10 mM ammonium acetate (NH_4OAc) in 5% acetonitrile(MeCN)) and ending
15 at 100% B (B: MeCN) after four minutes. The column used was a X-Terra MS C8, 3.0 x 50; 3.5 μm (Waters) run at 1.0 mL/min.

20

Alternatively, mass spectra was performed on a GC-MS (GC 6890, 5973N MSD) supplied by Agilent Technologies. The column used was a VF-5 MS, ID 0.25 mm x 30m, 0.25 μm (Varian Inc.). A linear temperature gradient was applied starting at 40 °C (hold 1 min) and ending at 300 °C (hold 1 min), 25 °C/minute. The MS was equipped with a CI ion source and the reactant gas was methane. The MS was scanned between m/z 50-500 and the scan speed was set to 3.25 scan/s. The MS was equipped with an EI ion source. The MS was scanned between m/z 50-500 and the scan speed was set to 3.25 scan/s. The electron
25 voltage was set to 70 eV.

30

HPLC analyses were performed on an Agilent HP1100 system consisting of G1379A Micro Vacuum Degasser, G1312A Binary Pump, G1367A Well plate auto-sampler, G1316A Thermostatted Column Compartment and G1315B Diode Array Detector.
Column: X-Terra MS, Waters, 3.0 x 100 mm, 3.5 μm . The column temperature was set to 40 °C and the flow rate to 1.0 ml/min. The Diode Array Detector was scanned from 210-300 nm, step and peak width were set to 2 nm and 0.05 min, respectively. A linear

gradient was applied, starting at 100 % A (A: 10 mM NH₄OAc in 5 % MeCN) and ending at 100% B (B: MeCN), in 6 min.

GC-MS analysis was performed on a GC 6890, 5973N MSD, supplied by Agilent Technologies. The column used was a VF-5 MS, ID 0.25 mm x 30m, 0.25 µm (Varian Inc.). A linear temperature gradient was applied starting at 40 °C (hold 1 min) and ending at 300 °C (hold 1 min), 25 °C/minute. The MS was equipped with a CI ion source and the reactant gas was methane. The MS was scanned between *m/z* 50-500 and the scan speed was set to 3.25 scan/s. The electron voltage was set to 70 eV.

Microwave heating was performed in an Initiator or Smith Synthesizer Single-mode microwave cavity producing continuous irradiation at 2450 MHz.

A typical workup procedure after a reaction consisted of extraction of the product with a solvent such as ethyl acetate, washing with water followed by drying of the organic phase over Magnesium sulphate (MgSO₄) or Sodium sulphate (Na₂SO₄) filtration and concentration of the solution *in vacuo*.

Thin layer chromatography (TLC) was performed on Merck TLC-plates (Silica gel 60 F254) and UV visualized the spots. Flash chromatography was performed on a Combi Flash® Companion™ using RediSep™ normal-phase flash columns. Typical solvents used for flash chromatography were mixtures of chloroform/methanol, dichloromethane/methanol and heptane/ethyl acetate.

Preparative chromatography was run on a Waters autopurification HPLC with a diode array detector. Column: XTerra MS C8, 19 x 300 mm, 10 µm. Narrow gradients with MeCN/(95:5 0.1M NH₄OAc:MeCN) were used at a flow rate of 20 ml/min. Alternatively, another column was used; Atlantis C18 19 x 100 mm, 5 µm column. Gradient with acetonitrile/0.1M ammonium acetate in 5% acetonitrile in MilliQ Water, run from 0% to 35-50% acetonitrile, in 15 min. Flow rate: 15 ml/min. Alternatively, purification was achieved on a semi preparative Shimadzu LC-8A HPLC with a Shimadzu SPD-10A

UVvis.-detector equipped with a Waters Symmetry® column (C18, 5 µm, 100 mm x 19 mm).

Narrow gradients with MeCN/0.1% trifluoroacetic acid in MilliQ Water were used at a
5 flow rate of 10 ml/min.

The following abbreviations have been used:

	aq.	aqueous;
	m-CPBA	3-chloroperoxybenzoic acid;
10	equiv.	equivalent;
	DEAD	diethyl azodicarboxylate
	DMF	N,N-dimethylformamide;
	DMSO	dimethylsulfoxide;
	HOAc	acetic acid;
15	NaCNBH ₃	sodium cyanoborohydride;
	Na ₂ SO ₄	sodium sulphate;
	r.t.	room temperature;
	o.n.	over night;
	THF	tetrahydrofuran;
20	Boc ₂ O	Di- <i>tert</i> -butyl dicarbonate;
	MeOH	methanol;
	EtOH	ethanol;
	EtOAc	ethylacetate;
	TFA	trifluoroacetic acid;
25	DIPEA	N,N-Diisopropylethylamine;
	CH ₂ Cl ₂	methylene chloride;
	CHCl ₃	chloroform;
	TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy;
	HCl	acetic acid

Starting materials used were either available from commercial sources or prepared according to literature procedures and had experimental data in accordance with those reported.

5 EXAMPLES

The invention is illustrated, but in no way limited, by the following examples:

Example 1 3-(2-Ethoxy-2-methylpropyl)-2-thioxanthine

(a) 2-Bromo-1,1-diethoxy-2-methylpropane

10 The product was synthesized according to a modified procedure described in US 3,652,579.

Bromine water (2.95 mL, 57.6 mmol) was added drop by drop to isobutyraldehyde (4.82 g, 66.8 mmol) in EtOH (22 mL) and the resulting mixture was stirred at r.t. for 40 minutes.

More bromine water (0.3 mL, 5.86 mmol) was added. The reaction mixture was
15 neutralized by the addition of calcium carbonate (3.5 g, 25.3 mmol). The remaining calcium carbonate was filtered off and the filtrate was poured onto ice-water mixture. The aqueous phase was extracted with CH₂Cl₂, dried Na₂SO₄, filtered and concentrated. After vacuum distillation the title product was obtained in 67% (10.10 g) yield.

¹H NMR (400 MHz, DMSO-d₆) δ ppm 4.43 (s, 1 H), 3.80-3.73 (m, 2 H), 1.64 (s, 6 H),
20 1.15 (t, 6 H).

(b) 2-Ethoxy-2-methylpropanal

The product was synthesized according to a procedure described in US 3,652,579.

2-Bromo-1,1-diethoxy-2-methylpropane (5.63 g, 25 mmol) obtained from 1a was added
25 drop by drop to potassium bitartrate (2.35 g, 12.5 mmol) in refluxing deionized water (22.5 mL) over 50 minutes. The resulting mixture was left to reflux for 1 h 10 minutes. The solvent and product was distilled off. ammonium sulphate (totally 8.5 g) was added to the product-solvent mixture. The mixture was stirred for a while. The two phases were separated and the upper phase was distilled from calcium chloride yielding 55% (1.60 g) of
30 the title product. MS (CI) m/z 117 (M+1).

(c) 4-[(2-Ethoxy-2-methylpropyl)amino]-1H-imidazole-5-carboxamide

NaCNBH₃ (0.077 g, 1.23 mmol) was added to 5-amino-4-imidazolecarboxamide hydrochloride (0.200 g, 1.23 mmol) and acetic acid (141 µL, 2.46 mmol) in methanol (1.5 mL). 2-Ethoxy-2-methylpropanal (0.286 g, 2.46 mmol) obtained from Example 1(b) was added drop by drop. After 1.5 h more 2-Ethoxy-2-methylpropanal (0.300g, 2.58 mmol) was added followed by more 2-Ethoxy-2-methylpropanal after 0.5 h (0.424 mg, 3.65 mmol). The reaction mixture was stirred at r.t. 17 h after which it was concentrated and purified by flash silica gel chromatography (CHCl₃/MeOH; 20:1-9.1), to give the title compound as an oil in 90% yield (0.251 g). MS (ESI) m/z 227 (M +1).

(d) 3-(2-Ethoxy-2-methylpropyl)-2-thioxanthine

Ethoxycarbonyl isothiocyanate (0.171 g, 1.30 mmol) was added to a stirred solution of 4-[(2-Ethoxy-2-methylpropyl)amino]-1H-imidazole-5-carboxamide (0.246 g, 1.09 mmol), which had been obtained from Example 1(c), in CH₂Cl₂ (1.1 mL) at r.t. for 0.5 h, then the reaction was left unstirred at 4 °C for 16 h. The reaction mixture was heated to r.t. for 1 h and the solvent was evaporated, the residue was dissolved in 2% sodium hydroxide (aq.) (27 mL) and the reaction was heated at 50 °C for 5.5 h. The pH was adjusted to neutral with conc. HCl and 1M HCl. The precipitate was collected by filtration, washed with water and purified by flash silica gel chromatography (CHCl₃/MeOH; 20:1), to give the title compound in 47% yield (96 mg).

¹H NMR (400 MHz, DMSO-d₆) δ ppm 13.76 (br s, 1 H), 12.42 (s, 1 H), 8.13 (s, 1 H), 4.69 (br s, 2 H), 3.54 (q, 2 H), 1.21 (s, 6 H), 1.02 (t, 3 H). MS (ESI) m/z 267 (M-1).

Example 2 3-(2-Propoxy-2-methylpropyl)-2-thioxanthine

(a) 2-Bromo-2-methyl-1,1-dipropoxypropane

2-Bromo-2-methyl-1,1-dipropoxypropane was prepared according to a modified method described in US 3,652,579.

Isobutyraldehyde (7.2 g, 0.10 mol) and 1-propanol (12 mL) were cooled in an icebath. Bromine (4.4 mL, 0.086 mol) was added drop-by-drop during 20 min. Stirring was continued at ambient temperature for 5 min and then at 55 °C for 30 min. Calcium carbonate (3 g, 0.030 mol) was added in portions. The resulting mixture was stirred at ambient temperature for 1 h. The mixture was filtered and the solids were washed with

diethyl ether. Water (15 mL) was then added. The organic phase was separated, dried over sodium sulphate and concentrated in vacuo at ambient temperature. This crude product (13.5 g, 53 %) was used in the next step without further purification.

¹H NMR (CDCl₃) δ ppm 4.40 (s, 1 H), 3.73-3.79 (m, 2H), 3.51-3.57 (m, 2H), 1.73 (s, 6H),
5 1.60-1.66 (m, 4H), 0.93-0.97 (m, 6H).

(b) 2-Methyl-2-propoxypropanal

2-Methyl-2-propoxypropanal was prepared according to a modified method described in patent US 3,652,579. A slurry consisting of 2-bromo-2-methyl-1,1-dipropoxypropane
10 obtained from Example 2(a) (6.5 g, 0.026 mol), potassium hydrogen tartrate (4.8 g, 0.026 mol) in water (75 mL) was heated at reflux for 7 h. A distillation set-up was mounted and the liquid that was distilled between 82-90 °C was collected. The organic phase was separated. The obtained crude product (1.9 g, 56 %) was used without further purification.
¹H NMR (CDCl₃) δ ppm 9.58 (s, 1H), 3.31-3.34 (m, 2H), 1.54-1.64 (m, 2H), 1.26 (s, 6H),
15 0.92-0.96 (m, 3H).

(c) 4-[(2-Methyl-2-propoxypropyl)amino]-1H-imidazole-5-carboxamide

The reaction mixture of 2-methyl-2-propoxypropanal, which was obtained from Example 2(b), (1.0 g, 8.3 mmol), 5-amino-4-imidazolecarboxamide (0.5 g, 4.0 mmol), sodium
20 cyanoborohydride (0.25 g, 4.0 mmol) and acetic acid (0.45 mL, 7.9 mmol) in 10 mL of methanol was stirred at ambient temperature for 1 h. The solvent was removed in vacuo. Water (20 mL) and ethyl acetate (20 mL) were added. The organic phase was separated and the solvent was removed in vacuo. Purification by ISCO flash (EtOAc:Heptane, gradient elution 1:1 to 100% EtOAc) gave 0.19 g (20 %) of the title compound.
¹H NMR (CDCl₃) δ ppm 6.98 (s, 1H), 6.39 (br s, 1H), 3.40 (t, 2H, J=6.7 Hz), 3.14 (d, 2H,
25 J=4.3 Hz), 1.56-1.65 (m, 2H), 1.22 (s, 6H), 0.95 (t, 3H, J=7.5 Hz); MS (ESI) m/z 241 (M+1).

(d) 3-(2-Propoxy-2-methylpropyl)-2-thioxanthine

4-[(2-Methyl-2-propoxypropyl)amino]-1H-imidazole-5-carboxamide obtained from
30 Example 2(c) was dissolved (0.19 g, 0.78 mmol) in 7 mL of dichloromethane. The obtained solution was stirred at ambient temperature. Benzoyl isothiocyanate (0.50 g, 3.1

mmol) was added in portions during 6 h. The reaction mixture was stirred over night and the solvent was then removed in vacuo. Ammonia in methanol (7 mL of 7 M solution) was added and the obtained solution was heated at 50 °C for 3 h and then at 80 °C for 3 h in a pressure flask. The cooled reaction mixture was concentrated and the crude product was purified by reverse phase HPLC. The product was obtained in 22 % (48 mg) yield.

¹H NMR (DMSO-d₆) δ ppm 13.70 (very br s, 1H), 12.39 (br s, 1H), 8.12 (s, 1H), 4.69 (br s, 2H), 3.41 (t, 2H, J=6.6 Hz), 1.36-1.44 (m, 2H), 1.21 (s, 6H), 0.81 (t, 3H, J=7.5 Hz);

¹³C NMR (DMSO-d₆) δ ppm 175.3, 152.5, 149.9, 140.7, 111.0, 75.9, 62.7, 53.5, 25.4, 23.2, 10.6; MS (ESI) m/z 283 (M+1)

Example 3 3-(2-Methoxy-2-methylpropyl)-2-thioxanthine

(a) 2-Methoxy-2-methylpropanal

The product was synthesized according to a procedure described in US 3,652,579.

(b) 4-[(2-Methoxy-2-methylpropyl)amino]-1H-imidazole-5-carboxamide

5-Amino-4-imidazolecarboxamide hydrochloride (0.162 g, 1.0 mmol) and 2-methoxy-2-methylpropanal, which was obtained from Example 3(a) (0.204 g, 2.0 mmol) were mixed in methanol (3 mL) at r.t. Acetic acid (141 µL, 2.46 mmol) mL) was then added and the mixture was allowed to stir for 30 min followed by addition of NaCNBH₃ (0.063 g, 1.0 mmol). After 3 h, additional 2-methoxy-2-methylpropanal (0.060 g, 0.59 mmol) was added. The reaction mixture was stirred at r.t. for 17 h and was then concentrated and purified by flash silica gel chromatography (CHCl₃:MeOH=5:1). The title compound was obtained as an oil in 73% yield (0.155 g). MS (ESI) m/z 213 (M+1).

(c) 3-(2-Methoxy-2-methylpropyl)-2-thioxanthine

Ethoxycarbonyl isothiocyanate (0.144 g, 1.1 mmol) was added to a stirred solution of 4-[(2-methoxy-2-methylpropyl)amino]-1H-imidazole-5-carboxamide (0.155 g, 0.73 mmol), which was obtained from Example 3(b), in CH₂Cl₂ (2.5 mL) at r.t. for 16 h. The solvent was evaporated and the residue was then dissolved in 2% aqueous sodium hydroxide (NaOH) solution (10 mL) and heated at 50 °C for 3 h. The pH was adjusted to neutral with 2 M HCl and the resulted precipitates were collected by filtration followed by prep-HPLC purification. The title compound was obtained as a white solid in 32% yield (60 mg).

¹H NMR (400 MHz, DMSO-d₆) δ ppm 12.41 (s, 1 H), 8.13 (s, 1 H), 4.68 (s, 2 H), 3.21 (s, 3 H), 1.20 (s, 6 H). MS (ESI) m/z 255 (M+1).

Example 4 3-(2-isopropoxyethyl)-2-thioxanthine

5 (a) 4-[(2-isopropoxyethyl)amino]-1H-imidazole-5-carboxamide

Trichlorocyanuric acid (1.23 g, 5.29 mmol) was added to a solution of 2-isopropoxyethanol (0.50 g, 4.80 mmol) in CH₂Cl₂ (3 mL). The reaction mixture was cooled to 0 °C and TEMPO (0.015 g, 0.09 mmol) was carefully added in small portions. The mixture was stirred at r.t. for 20 minutes and then filtrated through Celite and washed with CH₂Cl₂. The filtrate was kept cold, 0 °C, during the filtration. The obtained aldehyde solution was added to a stirred mixture of 4-amino-1H-imidazole-5-carboxamide hydrochloride (0.78 g, 4.80 mmol), which was obtained from Example 3(b), at 0 °C in MeOH (5 mL). The mixture was stirred for 20 minutes, then NaCNBH₄ (0.30 g, 4.80 mmol) was added. After stirring at r.t for 5 h the mixture was concentrated and purified by flash chromatography (CH₂Cl₂/methanol gradient; 0 to 5% methanol), to yield the title compound (0.39 g, 38%) as an oil.

¹H NMR (DMSO-d₆) δ ppm 7.58 - 7.45 (1 H, m), 6.84 - 6.66 (2 H, m), 6.23 (1 H, br s), 3.59 - 3.49 (1 H, m), 3.49 - 3.43 (2 H, m), 3.35 - 3.28 (2 H, m), 1.10-1.06 (6 H, m); MS (ESI) m/z 213 (M +1).

20

(b) 3-(2-isopropoxyethyl-2-thioxo-1,2,3,7-tetrahydro-6H-purin-6-one

4-[(2-isopropoxyethyl)amino]-1H-imidazole-5-carboxamide, which was obtained from Example 4(a) (0.37 g, 1.74 mmol) was dissolved in CH₂Cl₂ (5 mL).

Etoxycarbonylisothiocyanate (0.27 g, 2.09 mmol) was added and the mixture was stirred at r.t. for 30 minutes. The mixture was concentrated in vacuo and dissolved in 2M sodium hydroxide (2 mL). The reaction was run in the microwave at 120 °C for 10 minutes. The pH of the solution was adjusted to neutral pH with 2M HCl and the precipitate was collected by filtration and washed with water. Purified by preparative HPLC, obtaining the title compound (0.14 g, 32%) as a solid.

30 ¹H NMR (DMSO-d₆) δ ppm 13.82 (1 H, br s), 12.44 (1 H, br s), 8.16 (1 H, s), 4.72 - 4.51 (2 H, m), 3.80 - 3.67 (2 H, m), 3.67 - 3.56 (1 H, m), 1.04 (6 H, d, J=6.0 Hz); MS (ESI) m/z 255 (M +1).

Example 5 3-(2-Ethoxy-propyl)-2-thioxanthine(a) (2-Ethoxy-propyl)-thiourea

2-Ethoxy-propylamine (1.50 g, 14.5 mmol) and benzoylisothiocyanate (2.61 g, 16.0 mmol) in chloroform (50 mL) were heated at 75°C for 1 h. The solvent was removed under reduced pressure and methanol (15 mL) and water (30 mL) were added. Potassium carbonate (2.0 g, 14.5 mmol) was added and the mixture was heated at 75°C for 2 h. After cooling to room temperature, the mixture was neutralized with 2M sulphuric acid and the solvent was removed under reduced pressure. The crude product was dissolved in methanol and insoluble material was removed by filtration. The solvent was distilled off and the resulting solid was washed with dichloromethane and dissolved in ethanol. Insoluble material was removed by filtration and the solvent was removed under reduced pressure. This gave the title compound as a white solid (1.6 g, 59% yield).

¹H NMR (DMSO-d₆) δ ppm 7.52 (1 H, broad s), 7.02 (2 H, broad s), 3.58 - 3.33 (5 H, m), 1.09 (3 H, t, J=6.95 Hz), 1.03 (3 H, d, J=6.06 Hz); MS (ES) m/z 161 (M -1).

(b) 6-Amino-1-(2-ethoxy-propyl)-2-thioxo-2,3-dihydro-1H-pyrimidin-4-one

(2-Ethoxy-propyl)-thiourea (1.5 g, 1.4 mmol) obtained from Example 5(a) and ethyl cyanoacetate (1.75 g, 15.5 mmol) were added to a solution of sodium ethoxide [made from sodium (0.35 g, 15.2 mmol) and absolute ethanol (15 mL)]. The resulting mixture was refluxed for over night. After cooling to room temperature water was added and the contained mixture was neutralized with 2 M sulphuric acid. The resulting precipitate was collected by filtration and the solid was washed with water to give the desired product (1.2 g, 71% yield).

¹H NMR (DMSO-d₆) δ ppm 11.86 (1 H, broad s), 6.73 (2 H, broad s), 4.91 (1 H, s), 4.54 (1 H, broad s), 4.00 - 3.85 (1 H, m), 3.66 - 3.46 (1 H, m), 3.39 - 3.23 (2 H, m), 1.12 (3 H, d, J=6.32 Hz), 1.03 (3 H, t, J=7.07 Hz); MS (ES) m/z 230 (M +1).

(c) 6-Amino-1-(2-ethoxy-propyl)-5-nitroso-2-thioxo-2,3-dihydro-1H-pyrimidin-4-one

6-Amino-1-(2-ethoxy-propyl)-2-thioxo-2,3-dihydro-1H-pyrimidin-4-one (1.1 g, 4.8 mmol) obtained from Example 5b was suspended in 10% acetic acid (20 mL) and the mixture was stirred for 15 minutes. Sodium nitrite (0.36 g, 5.3 mmol) was added and the resulting mixture was heated at 75°C for 1 h. The reaction mixture turned pink and then purple. The

mixture was cooled to room temperature, and the purple solid was collected by filtration and washed with water to give the title compound (1.05 g, 70% yield). This solid was used in Example 5(d) without further purification.

¹H NMR (DMSO-d₆) δ ppm 13.16 (1 H, broad s), 12.61 (1 H, broad s), 4.50 (1 H, broad s), 4.24 (1 H, broad s), 3.96 - 3.84 (1 H, m), 3.56 - 3.43 (1 H, m), 3.34 - 3.20 (2 H, m), 1.13 (3 H, d, J=6.32 Hz), 0.95 (3 H, t, J=6.95 Hz); MS (ES) m/z 259 (M +1).

(d) 5,6-Diamino-1-(2-ethoxy-propyl)-2-thioxo-2,3-dihydro-1H-pyrimidin-4-one

6-Amino-1-(2-ethoxy-propyl)-5-nitroso-2-thioxo-2,3-dihydro-1H-pyrimidin-4-one (1.0 g, 3.9 mmol) obtained from Example 5(c) was suspended in 32% ammonia (5 mL) and water (10 mL) was added. This mixture was heated at 75°C and sodium dithionite (1.7 g, 9.7 mmol) was added in small portions. After heating for another 5 minutes the reaction mixture was removed from the oil bath and stirred at ambient temperature for 2 h. The pH of the mixture was adjusted to neutral pH with 2M H₂SO₄. The solid was collected by filtration and washed with water and dried to yield the diamine (0.6 g, 41% yield). This product was used in Example 5(e) without further purification.

¹H NMR (DMSO-d₆) δ ppm 5.91 (2 H, broad s), 4.59 (1 H, broad s), 4.11 (1 H, broad s), 3.99 - 3.85 (1 H, m), 3.68 - 3.42 (3 H, m), 3.39 - 3.20 (2 H, m), 1.14 (3 H, d, J=6.32 Hz), 1.03 (3 H, t, J=6.95 Hz); MS (ES) m/z 245 (M +1).

(e) 3-(2-Ethoxy-propyl)-2-thioxanthine

5,6-Diamino-1-(2-ethoxy-propyl)-2-thioxo-2,3-dihydro-1H-pyrimidin-4-one (0.60 g, 2.45 mmol) obtained from Example 5(d) was suspended in formic acid (6 mL) and the obtained solution was heated at 70°C for 2 h. Excess formic acid was evaporated off under reduced pressure. 10% sodium hydroxide (6 mL) was added to the solid and the obtained solution was heated at 70°C for 2 h. The pH of the solution was adjusted to neutral pH with 2M sulphuric acid. The obtained precipitate was collected by filtration and washed with water. Purified by preparative HPLC, the title compound (0.18 g, 29% yield) was obtained as a solid.

¹H NMR (DMSO-d₆) δ ppm 13.77 (1 H, broad s), 12.41 (1 H, broad s), 8.13 (1 H, s), 4.64 - 4.51 (1 H, m), 4.47 - 4.33 (1 H, m), 4.25 - 4.12 (1 H, m), 3.58 - 3.42 (1 H, m), 3.43 - 3.31 (1 H, m), 1.06 (3 H, d, J=6.32 Hz), 0.95 (3 H, t, J=6.95 Hz); ¹³C NMR (DMSO-d₆) □ ppm

174.22, 152.96, 150.18, 141.54, 111.16, 71.15, 63.78, 52.13, 18.33, 15.80; MS (ES) m/z 255 ($M+1$).

Example 6 3-(2*S*-Ethoxy-propyl)-2-thioxanthine and 3-(2*R*-Ethoxy-propyl)-2-thioxanthine

A solution of racemic 3-(2-Ethoxy-propyl)-2-thioxanthine (5 mg/mL) obtained from example 6 was separated into its two enantiomers by using chiral HPLC on a Chiralpak AD column (21.2 x 250 mm; 10 μ m). The mobile phase was 100% methanol and the flow rate 8 mL/min. The injection volume was 2mL.

The first eluted enantiomer was 3-(2*S*-Ethoxy-propyl)-2-thioxanthine and this enantiomer was determined by single crystal diffraction technique at 200 K, e.e. 98%; MS (ES) m/z 255 ($M+1$).

The second eluted enantiomer was 3-(2*R*-Ethoxy-propyl)-2-thioxanthine, e.e. 98%; MS (ES) m/z 255 ($M+1$).

Screens

Methods for the determination of MPO inhibitory activity are disclosed in patent application WO 02/090575. The pharmacological activity of compounds according to the invention was tested in the following screen in which the compounds were either tested alone or in the presence of added tyrosine:

Assay buffer: 20 mM sodium/potassium phosphate buffer pH 6.5 containing 10 mM taurine and 100 mM NaCl.

Developing reagent: 2 mM 3,3',5,5'-tetramethylbenzidine (TMB), 200 μ M KI, 200 mM acetate buffer pH 5.4 with 20 % DMF.

To 10 μ l of diluted compounds in assay buffer, 40 μ l of human MPO (final concentration 2.5 nM), with or without 20 μ M tyrosine (final concentration, if present, 8 μ M), was added and the mixture was incubated for 10 minutes at ambient temperature. Then 50 μ l of H₂O₂ (final concentration 100 μ M), or assay buffer alone as a control, were added. After

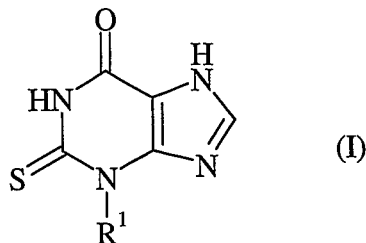
incubation for 10 minutes at ambient temperature, the reaction was stopped by adding 10 μ l 0.2 mg/ml of catalase (final concentration 18 μ g/ml). The reaction mixture was left for an additional 5 minutes before 100 μ l of TMB developing reagent was added. The amount of oxidised 3,3',5,5'-tetramethylbenzidine formed was then measured after about 5 minutes
5 using absorbance spectroscopy at about 650 nM. IC₅₀ values were then determined using standard procedures.

When tested in at least one version of the above screen, the compounds of Examples 1 to 6 gave IC₅₀ values of less than 60 μ M, indicating that they are expected to show useful
10 therapeutic activity. A representative result is shown in the following Table.

Compound	Inhibition of MPO (in the presence of tyrosine) IC ₅₀ μ M
Example 5	0.5

CLAIMS

1. A compound according to Formula (I)



R¹ is selected from C₁-C₆ alkyl, and said C₁-C₆ alkyl is substituted with C₁-C₆ alkoxy;

5 and at least one of said C₁-C₆ alkyl or said C₁-C₆ alkoxy is branched;
or a pharmaceutically acceptable salt thereof, solvate or solvate of a salt thereof.

2. A compound according to claim 1, wherein the C₁-C₆ alkyl of R¹ represents C₂-₄ alkyl.

10 3. A compound according to claim 1 or claim 2, wherein said alkyl is selected from
isobutyl, ethyl and propyl.

4. A compound according to any one of claims 1 to 3, wherein said alkyl is substituted
with C₁-₃ alkoxy.

15

5. A compound according to any one of claims 1 to 3, wherein said alkyl is substituted
with C₁-alkoxy.

6. A compound according to any one of claims 1 to 3, wherein said alkyl is substituted
20 with C₂-alkoxy.

7. A compound according to any one of claims 1 to 3, wherein said alkyl is substituted
with propoxy or iso-propoxy.

25 8. A compound, said compound being:
3-(2-Ethoxy-2-methylpropyl)-2-thioxanthine;
3-(2-Propoxy-2-methylpropyl)-2-thioxanthine;
3-(2-Methoxy-2-methylpropyl)-2-thioxanthine;

3-(2-isopropoxyethyl)-2-thioxanthine;

3-(2-Ethoxypropyl)-2- thioxanthine;

3-(2*S*-Ethoxypropyl)-2- thioxanthine;

3-(2*R*-Ethoxypropyl)-2- thioxanthine;

5 or a pharmaceutically acceptable salt, solvate or solvate of a salt thereof.

9. A compound according to any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof, for use as a medicament.

10 10. A pharmaceutical composition comprising a compound according to any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof, optionally in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

11 11. A method of treating, or reducing the risk of, diseases or conditions in which inhibition
15 of the enzyme MPO is beneficial which comprises administering to a person suffering from or at risk of, said disease or condition, a therapeutically effective amount of a compound as defined in any one of claims 1 to 8 or a pharmaceutically acceptable salt thereof.

20 12. A method of treating, or reducing the risk of inflammatory disorders which comprises administering to a person suffering from or at risk of, said disease or condition, a therapeutically effective amount of a compound as defined in any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof.

25 13. The method according to claim 12, wherein said inflammatory disorders are neuroinflammatory disorders.

14. The method according to claim 13, wherein said neuroinflammatory disorder is multiple sclerosis.

30

15. The method according to claim 13, wherein said neuroinflammatory disorder is Parkinson's disease.

16. A method according to claim 11, wherein said disease or condition is cardio- and cerebrovascular atherosclerotic disorders or peripheral artery disease, heart failure or respiratory disorders.

5 17. The method according to claim 16, wherein said disease or condition is atherosclerosis.

18. The method according to claim 16, wherein said disease or condition is chronic obstructive pulmonary disease (COPD).

10 19. The method according to claim 16, wherein said disease or condition is bronchitis, including infectious and eosinophilic bronchitis; emphysema; bronchiectasis or cystic fibrosis.

20. A method of treating, or reducing the risk of stroke which comprises administering to a
15 person suffering from or at risk of, said disease or condition, a therapeutically effective amount of a as defined in any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof.

21. Use of a compound as defined in any one of claims 1 to 8, or a pharmaceutically
20 acceptable salt thereof, in the manufacture of a medicament, for the treatment or prophylaxis of diseases or conditions in which inhibition of the enzyme MPO is beneficial.

22. Use of a compound as defined in any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament, for the treatment or
25 prophylaxis of inflammatory disorders.

23. The use according to claim 22, wherein the inflammatory disorder is neuroinflammatory disorders.

30 24. The use according to claim 23, wherein said neuroinflammatory disorder is multiple sclerosis.

25. The use according to claim 23, wherein said neuroinflammatory disorder is Parkinson's disease.

26. The use according to claim 21, wherein said disease or condition is cardio- and
5 cerebrovascular atherosclerotic disorders or peripheral artery disease, heart failure or respiratory disorders.

27. The use according to claim 26, wherein said disease or condition is atherosclerosis.

10 28. The use according to claim 26, wherein said disease or condition is chronic obstructive pulmonary disease (COPD).

29. The use according to claim 26, wherein said disease or condition is bronchitis,
including infectious and eosinophilic bronchitis; emphysema; bronchiectasis or cystic
15 fibrosis.

30. Use of a compound as defined in any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament, for the treatment or prophylaxis of stroke.