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CA 2928670 A1 2016/11/05

(21) 2 928 670

(12) DEMANDE DE BREVET CANADIEN
CANADIAN PATENT APPLICATION

(13) A1

(22) **Date de dépôt/Filing Date:** 2016/05/02

(41) **Mise à la disp. pub./Open to Public Insp.:** 2016/11/05

(30) **Priorité/Priority:** 2015/05/05 (US62/157,067)

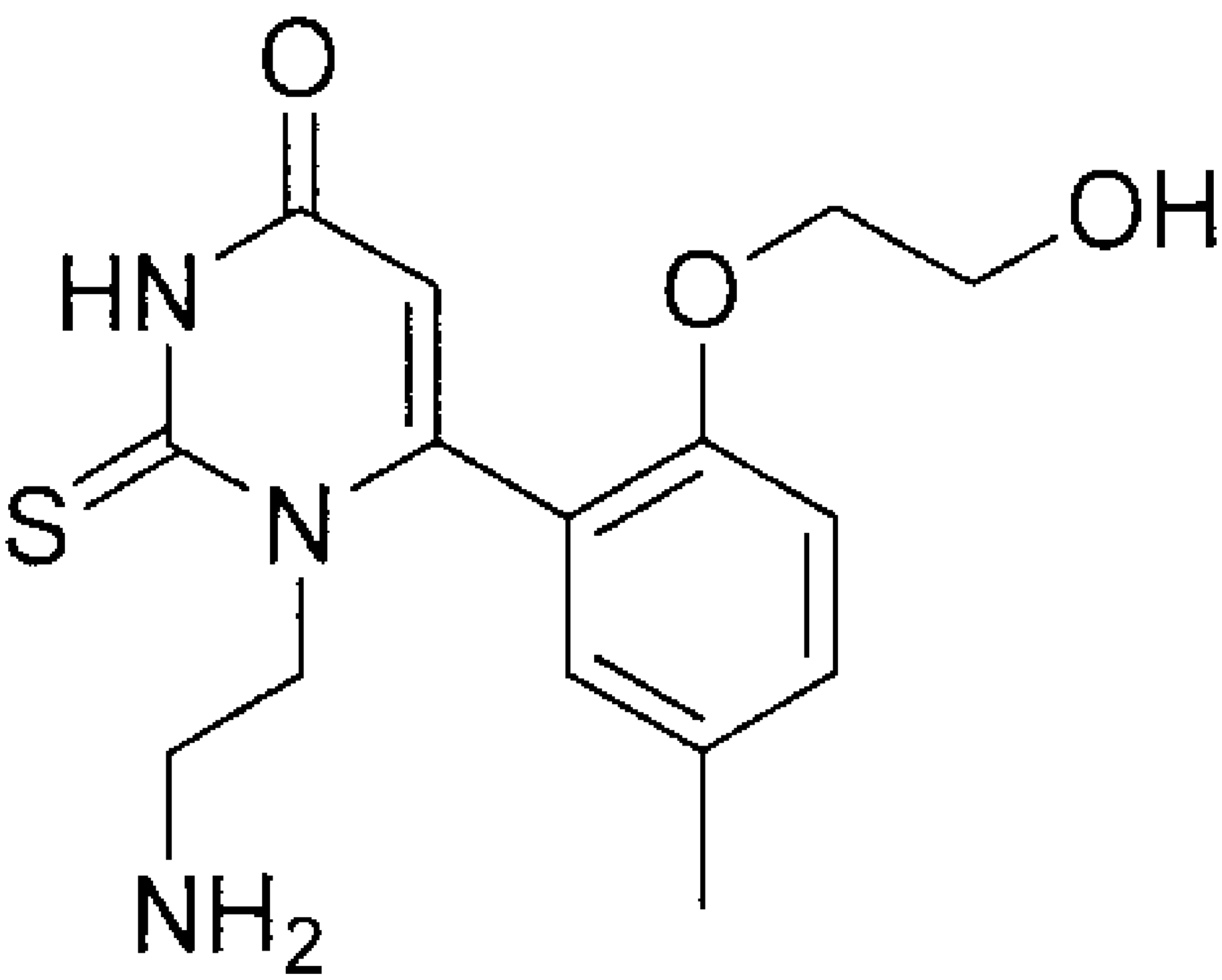
(51) **Cl.Int./Int.Cl.** ***C07D 239/56*** (2006.01),
A61K 31/513 (2006.01)

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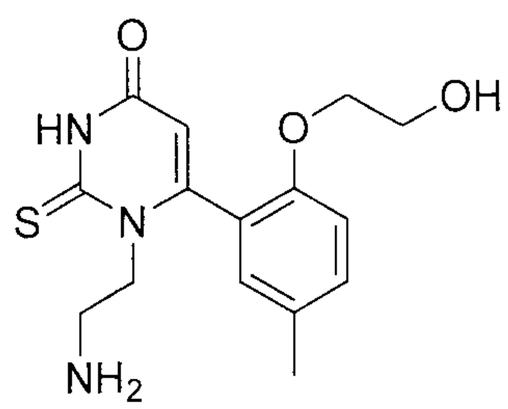
(54) **Titre : 2-THIOPYRIMIDINONES**
(54) **Title: 2-THIOPYRIMIDINONES**



(57) **Abrégé/Abstract:**
Myeloperoxidase inhibitor of Formula I: (see formula I) and pharmaceutical compositions containing the inhibitor.

ABSTRACT

Myeloperoxidase inhibitor of Formula I:



and pharmaceutical compositions containing the inhibitor.

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2-THIOPYRIMIDINONES

BACKGROUND OF THE INVENTION

This invention relates to myeloperoxidase inhibitors.

Myeloperoxidase (MPO) is a heme-containing enzyme belonging to the peroxidase superfamily. Examples of animal peroxidases are lactoperoxidase, thyroid peroxidase (TPO), eosinophil peroxidase and myeloperoxidase. Myeloperoxidase is present in primary granules of neutrophils and to a lesser extent in monocytes. It catalyzes the synthesis of hypochlorous acid from chloride and hydrogen peroxide. The hypochlorous acid formed is a powerful oxidant that reacts with a variety of cellular substrates including heme proteins, porphyrins, thiols, iron sulfur centers, nucleotides, DNA, unsaturated lipids, amines and amino acids.

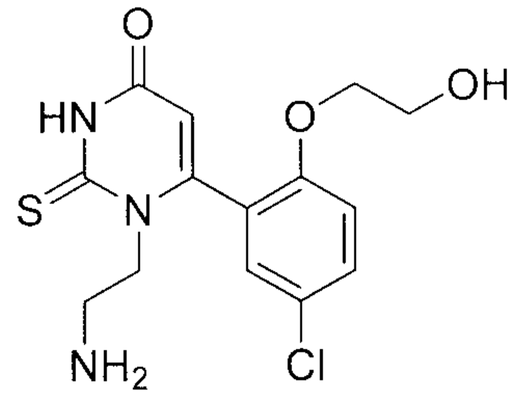
In addition, MPO-catalyzed reactions and their products have been found to exhibit pro-atherogenic biological activity during the development of atherosclerosis and cardiovascular disease. For example, the myeloperoxidase plasma content is correlated with the appearance of cardiovascular disorders in patients suffering unstable angina pectoris. Myeloperoxidase has been reported to contribute to the development of atherosclerosis by the oxidation of lipids and protein in LDL and HDL.

Furthermore, it has been observed that MPO-generated oxidants reduce the bioavailability of nitric oxide, an important vasodilator. Accordingly, high MPO plasma levels are inversely correlated with the success of therapy to establish reperfusion of occluded arteries. High MPO levels are also associated with decreased survival from congestive heart failure. Additionally, it has been shown that MPO plays a role in plaque destabilization which leads to plaque rupture and myocardial infarction.

Therefore, MPO is thought to play a role in several processes that lead to cardiovascular disease including 1) impaired cholesterol trafficking and progression of the atherosclerotic plaque towards an unstable state , 2) destabilization of the atherosclerotic plaque and plaque rupture, 3) consumption of nitric oxide leading to impaired endothelial function and blood flow, and 4) pathological tissue damage post ischemia contributing to atrial fibrillation and adverse cardiac remodeling with left ventricular hypertrophy leading to congestive heart failure, aortic aneurysm, and cerebral aneurysm.. As such inhibitors of

MPO activity may offer significant therapeutic benefit in the prevention and treatment of cardiovascular disease.

Commonly assigned related WO 2013/068875 published on May 16, 2013 discloses a series of 2-thiopyrimidinones useful as MPO inhibitors including the inhibitor compound of Example 427.



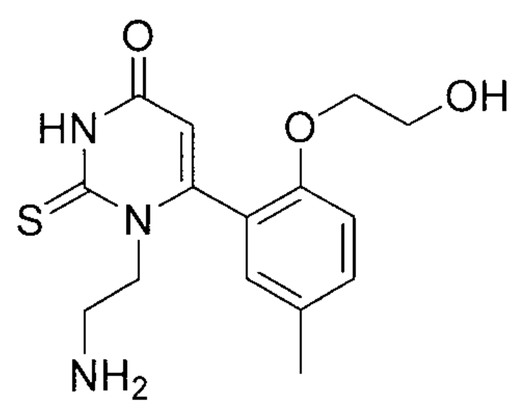
Example 427

Also related are commonly assigned U.S. patent no. 8,835,449 granted on Sept 16, 2014 and first published as US 2013123230 on May 16, 2013 which discloses 2-(6-(5-chloro-2-methoxyphenyl)-4-oxo-2-thioxo-3,4-dihydropyrimidin-1(2H)-yl)acetamide (Example 1) and commonly assigned U.S. patent no. 8,841,314 granted on May 2, 2013 and first published as US2013296351 on Nov 7, 2013 which discloses N-(2-aminoethyl)-2-[6-(2,4-dimethoxyphenyl)-4-oxo-2-thioxo-3,4-dihydropyrimidin-1(2H)-yl]acetamide (Example 241).

Nevertheless, although MPO has been implicated extensively in the etiology and progression of cardiovascular disease there is still an ongoing need for new MPO inhibitors..

SUMMARY OF THE INVENTION

The present invention is directed to a compound of the Formula I



Formula I

or a pharmaceutically acceptable salt thereof.

An especially preferred aspect of this invention is the hydrochloride salt of the compound of Formula I.

Another preferred aspect of this invention is the compound 1-(2-aminoethyl)-6-(2-(2-hydroxyethoxy)-5-methylphenyl)-2-thioxo-2,3-dihydropyrimidin-4(1H)-one (Compound A).

Also provided herein are compositions comprising a compound of the Formula I described herein and a pharmaceutically acceptable carrier, vehicle, or diluent.

All patents and patent applications referred to herein are hereby incorporated by reference.

Other features and advantages of this invention will be apparent from this specification and the appendant claims which describe the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a characteristic x-ray powder diffraction pattern showing a crystalline form of Example 1; Preparation 5 (Vertical Axis: Intensity (CPS); Horizontal Axis: Two theta (degrees)).

DETAILED DESCRIPTION OF THE INVENTION

The term Formula I compound as used herein refers to the Formula I compound and also includes the salts, polymorphs, isomers, tautomers, zwitterions, complexes, isotopes and the like as described below.

Pharmaceutically acceptable salts of the Formula I compound may include the acid addition and base salts thereof. Acid salts of the Formula I compound are preferred. Suitable acid addition salts may be formed from acids which form non-toxic salts. Examples may include the acetate, adipate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulphate/sulphate, borate, camsylate, citrate, cyclamate, edisylate, esylate, formate, fumarate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactate, malate, maleate, malonate, mesylate, methylsulphate, naphthylate, 2-napsylate, nicotinate, nitrate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, pyroglutamate,

saccharate, stearate, succinate, tannate, tartrate, tosylate, trifluoroacetate and xinofoate salts.

Suitable base salts may be formed from bases which form non-toxic salts. While base salts are not preferred, exemplary base salts may include the aluminum, arginine, calcium, choline, diethylamine, glycine, lysine, magnesium, meglumine, olamine, potassium, sodium, trimethylamine and zinc salts. Hemisalts of acids and bases may also be formed, for example, hemisulphate and hemicalcium salts. For a review on suitable salts, see Handbook of Pharmaceutical Salts: Properties, Selection, and Use by Stahl and Wermuth (Wiley-VCH, 2002).

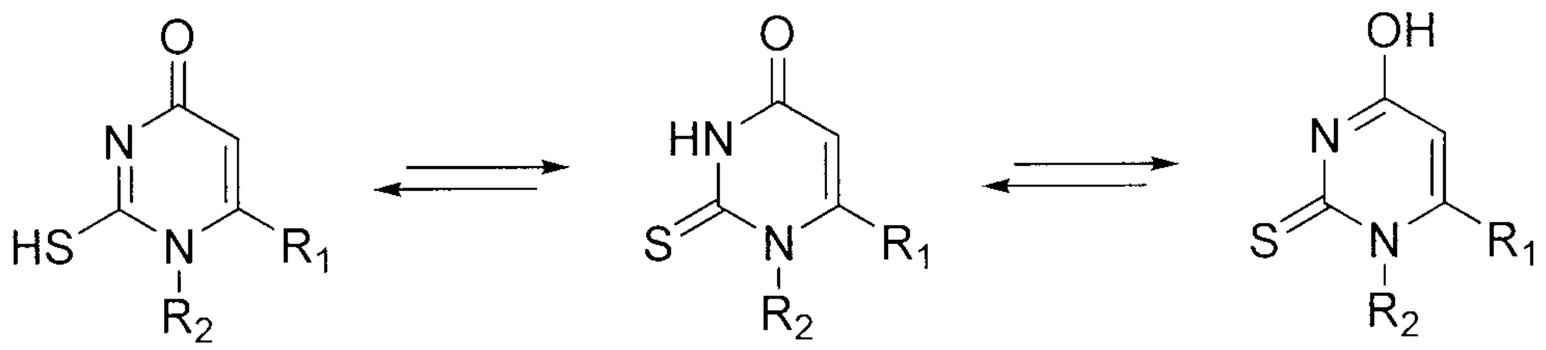
The Formula I compound may exist in both unsolvated and solvated forms. The term 'solvate' is used herein to describe a molecular complex comprising the compound of the invention and one or more pharmaceutically acceptable solvent molecules, for example, ethanol and/or water. Such solvent molecules are those commonly used in the pharmaceutical art, which are known to be innocuous, e.g., water, ethanol, and the like. Other solvents may be used as intermediate solvates in the preparation of more desirable solvates, such as methanol, methyl t-butyl ether, ethyl acetate, methyl acetate, (S)-propylene glycol, (R)-propylene glycol, 1,4-butyne-diol, and the like. The term 'hydrate' is employed when said solvent is water. Pharmaceutically acceptable solvates include hydrates (e.g., polyhydrates; monohydrates) and other solvates wherein the solvent of crystallization may be isotopically substituted, *e.g.* D_2O, d_6-acetone, d_6-DMSO. The solvates and/or hydrates preferably exist in crystalline form.

Included within the scope of the Formula I compound are complexes such as clathrates, drug-host inclusion complexes wherein, in contrast to the aforementioned solvates, the drug and host are present in stoichiometric or non-stoichiometric amounts. Also included are complexes of the active containing two or more organic and/or inorganic components which may be in stoichiometric or non-stoichiometric amounts. The resulting complexes may be ionized, partially ionized, or non-ionized. For a review of such complexes, see J Pharm Sci, 64 (8), 1269-1288 by Haleblian (August 1975).

Where the compound contains, for example, a keto or thiocarbonyl group or an aromatic moiety, tautomeric isomerism ('tautomerism') can occur. It follows that a single

compound may exhibit more than one type of isomerism. For example, the following is illustrative of tautomers of the compounds of Formula I.

Thiouracil Tautomers



most
predominant
tautomer

Included within the scope of the Formula I compound are all tautomeric forms of the Formula I compound including compounds exhibiting more than one type of isomerism, and mixtures of one or more thereof. Also included are acid addition or base salts wherein the counterion is optically active, for example, D-lactate or L-lysine, or racemic, for example, DL-tartrate or DL-arginine.

The present invention includes all pharmaceutically acceptable isotopically-labelled Formula I compounds wherein one or more atoms are replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number usually found in nature.

Examples of isotopes suitable for inclusion in the compounds of the invention include isotopes of hydrogen, such as ^{2}H and ^{3}H, carbon, such as ^{11}C, ^{13}C and ^{14}C, chlorine, such as ^{36}Cl, fluorine, such as ^{18}F, iodine, such as ^{123}I and ^{125}I, nitrogen, such as ^{13}N and ^{15}N, oxygen, such as ^{15}O, ^{17}O and ^{18}O, phosphorus, such as ^{32}P, and sulfur, such as ^{35}S.

Certain isotopically-labelled Formula I compound, for example, those incorporating a radioactive isotope, may potentially be useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, *i.e.* ^{3}H, and carbon-14, *i.e.* ^{14}C, may be particularly useful for this purpose in view of their ease of incorporation and ready means of detection.

Substitution with heavier isotopes such as deuterium, *i.e.* ^{2}H, may afford certain advantages resulting from potentially greater metabolic stability, for example, potentially

increased *in vivo* half-life or potentially reduced dosage requirements, and hence may be preferred in some circumstances.

Substitution with positron emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O and ^{13}N, may be useful in Positron Emission Tomography (PET) studies for examining substrate receptor occupancy.

An isotopically-labelled Formula I compound can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using an appropriate isotopically-labelled reagent in place of the non-labelled reagent previously employed.

As used herein, the expressions "reaction-inert solvent" and "inert solvent" refer to a solvent or a mixture thereof which does not interact with starting materials, reagents, intermediates or products in a manner which adversely affects the yield of the desired product.

By "pharmaceutically acceptable" is meant the carrier, vehicle, or diluent and/or salt must be compatible with the other ingredients of the formulation, and not deleterious to a potential recipient thereof.

The term “room temperature or ambient temperature” means a temperature between 18 to 25 °C, “HPLC” refers to high pressure liquid chromatography, “MPLC” refers to medium pressure liquid chromatography, “TLC” refers to thin layer chromatography, “MS” refers to mass spectrum or mass spectroscopy or mass spectrometry, “NMR” refers to nuclear magnetic resonance spectroscopy, “DCM” refers to dichloromethane, “DMSO” refers to dimethyl sulfoxide, “DME” refers to dimethoxyethane, ”EtOAc” refers to ethyl acetate, “MeOH” refers to methanol, “Ph” refers to the phenyl group, ”Pr” refers to propyl, ”trityl” refers to the triphenylmethyl group, “ACN” refers to acetonitrile, “DEAD” refers to diethylazodicarboxylate, and “DIAD” refers to diisopropylazodicarboxylate.

The starting materials and reagents for the above described Formula I compound are also readily available or can be easily synthesized by those skilled in the art using conventional methods of organic synthesis. For example, many of the compounds used herein, are related to, or are derived from compounds in which there is a large scientific interest and commercial need, and accordingly many such compounds are commercially

available or are reported in the literature or are easily prepared from other commonly available substances by methods which are reported in the literature.

Cis/trans isomers may be separated by conventional techniques well known to those skilled in the art, for example, chromatography and fractional crystallization.

Pharmaceutically acceptable salts of the Formula I compound may be prepared by one or more of three exemplary methods:

(i) by reacting the Formula I compound with the desired acid or base;

(ii) by removing an acid- or base-labile protecting group from a suitable precursor of the Formula I compound, for example treating an *O-tert*-butylcarbamate with acid, -or by ring-opening a suitable cyclic precursor, for example, a lactone or lactam, using the desired acid or base; or

(iii) by converting one salt of the Formula I compound to another by reaction with an appropriate acid or base or by means of a suitable ion exchange column.

All three reactions are typically carried out in solution. The resulting salt may precipitate out and be collected by filtration or may be recovered by evaporation of the solvent. The degree of ionization in the resulting salt may vary from completely ionized to almost non-ionized.

Certain processes for the manufacture of the compound of this invention are provided as further features of the invention and are described in the experimental section.

It is believed that MPO exhibits pro-atherogenic biological activity during the evolution of cardiovascular disease. Furthermore, it has been observed that MPO-generated oxidants reduce the bioavailability of nitric oxide, an important vasodilator. Additionally, it has been shown that MPO plays a role in plaque destabilization by causing the activation of metalloproteinases, leading to a weakening of the fibrous cap of the plaques and subsequent plaque destabilization and rupture. Given these wide-ranging effects of MPO, MPO has thus been implicated in a wide variety of cardiovascular diseases.

Cardiovascular complications of type 2 diabetes are also associated with deleterious levels of MPO

In addition, linkage of myeloperoxidase activity to disease has been demonstrated in neuroinflammatory and neurodegenerative conditions.

The utility of the Formula I compound as a MPO inhibitor is demonstrated by the activity of the compounds of this invention in conventional *in vitro* and *in vivo* assays described below. The *in vivo* assays (with appropriate modifications within the skill in the art) may be used to determine the activity of other agents as well as the compounds of this invention. Such assays also provide a means whereby the activities of the Formula I compound (or the other agents described herein) can be compared to each other and with the activities of other known compounds.

The following protocols may of course be varied by those skilled in the art.

Human Whole Blood Assay for Irreversible Inhibition of MPO

To measure the inhibition of MPO activity in a biological system in the present invention, bioassays were performed with human whole blood that was collected from medication-free, human volunteers in heparin treated tubes (APP Pharmaceuticals, LLC, cat # NDC#63323-047-10, #4710). Blood was aliquoted and treated with different concentrations of the MPO inhibitor or vehicle control and co-treated with or without bacterial lipopolysaccharide (LPS, InVivogen) to stimulate blood leukocytes to simultaneously generate H_20_2 (a required MPO substrate) and the release of MPO. After a 4 hour incubation at room temperature the plasma fraction was collected following a 2000Xg centrifugation at 4^0C.

The plasma fraction was divided in two for analysis of total MPO and active MPO. The total MPO content was determined using a standard sandwich ELISA (capture and detection antibodies: Cell Sciences, Cat# HP9048, and Cell Sciences, Cat# HM2164, clone 266-6K1) and calculated relative to a standard curve of purified MPO (myeloperoxidase, Calbiochem, cat# 475911) that was prepared by dilution in the autologous donor plasma. The MPO activity is determined by capturing the total MPO from plasma using the capture step as described for the above ELISA method. After washing unbound plasma material including unreacted MPO inhibitor, MPO reaction substrates were added [H_20_2 (2uM) and Amplex Red (Invitrogen, Cat# A12222)] and the Vmax of the MPO-catalyzed conversion of the Amplex Red substrate to resorufin was determined by measuring the increase in fluorescence (excitation 530 nM, emission 580 nm) using a fluorescent plate reader in a kinetic analysis. The MPO activity of the captured material was compared to that obtained

with a standard curve of purified MPO (myeloperoxidase, Calbiochem, cat# 475911) that was prepared in autologous donor plasma. The percent of 'active' myeloperoxidase for each sample was calculated from the ratio of the active myeloperoxidase in the Amplex Red assay and the total myeloperoxidase from the ELISA for each sample. A dose response curve of the compound concentration versus MPO activity was then plotted to determine the IC50 value.

hERG ASSAY

All testing was carried out in CHO cells transfected with the hERG gene purchased from Millipore (PrecisION hERG-CHO Recombinant Cell Line CYL3038). The cell line was grown in DMEM/F-12, GlutaMAX™ with 10% fetal bovine serum, 1% Penicillin-Streptomycin, 1% Geneticin and 1% of 1M HEPES buffer solution, and maintained at approximately 37°C in a humidified atmosphere containing 5% carbon dioxide. The cells were passaged every 3-5 days based on confluency. On the day of the experiment, 50%-80% confluent cells were harvested from a 175 cm^2 culture flask using Detachin™. After 10 minutes of exposure to Detachin™ at 37°C, the cells were centrifuged for 1 minute at 1000 RPM. The supernatant was removed and the cell pellet was reconstituted in 5-8 mL of serum free media with 2.5% of 1M HEPES, placed on the Qstirrer™, and allowed to recover. After a ~ 30 minute recovery period, experiments were initiated.

hERG current was elicited and recorded using the automated Qpatch HT™ system (as described in Kutchinsky J, Friis S, Asmild M, et al. Characterization of potassium channel modulators with QPatch automated patch-clamp technology: system characteristics and performance. Assay Drug Dev Technol 2003;1(5):685-93). The suspended cells in the Qstirrer™ were transferred to 48 individual recording chambers on a Qplate 48™containing extracellular recording saline composed of (in mM): 138 NaCl, 5.3 KCl, 1.3 $CaCl_2$, 0.5 $MgCl_2$, 5.6 Glucose, 5 HEPES, 0.4 $MgSO_4$, 0.44 KH_2PO_4, 4.2 $NaHCO_3$, 0.34 Na_2HPO_4, and adjusted to pH 7.4 $\pm$ 0.1 with NaOH. The intracellular recording saline was composed of (in mM): 130 KCl, 1 $MgCl_2$, 10 HEPES, 5 Mg-ATP, and 5 EGTA, and

adjusted to pH 7.2 ± 0.1 with KOH. Membrane currents were recorded at room temperature.

hERG current was elicited from a holding potential of -80 mV with a voltage step to +30 mV for 1 second, followed by a ramp back to -80 mV at 0.55 mV/ms. Test pulses were delivered at a frequency of 0.25 Hz. Up to 4 different concentrations were studied on each cell, each exposure lasting 5 minutes or until steady-state effects were observed. In a separate set of experiments, a full concentration-response relationship and an IC50 was determined for a positive control, cisapride, (Jules C. Hancox, Mark J. McPate, Aziza El Harchi, Yi hong Zhang, The hERG potassium channel and hERG screening for drug-induced torsades de pointes, Pharmacology & Therapeutics, Volume 119, Issue 2, August 2008, Pages 118-132).

Using Sophion Qpatch Assay Software, the amplitude of the peak outward hERG current upon repolarizing ramp was measured. Current amplitude was determined by taking the average of the last 5 current peaks under each treatment condition. Percent inhibition was determined by taking the ratio of the current measured at steady state in the presence of test article ($I_{Test\ article}$) versus the control current ($I_{Control}$), and expressed as: % inhibition = 100 - ($I_{Test\ article}/I_{Control}$)*100. When possible, a concentration-response curve was plotted and the data were fitted using Qpatch software to determine an IC50.

Table 1 below provides the myeloperoxidase inhibitory activity in human whole blood for the compound of this invention (as the HCL salt) and for certain Examples disclosed in commonly assigned WO 2013/068875 published on May 16, 2013 in accordance with the above-described assay. In addition, it provides the hERG activity and the resultant calculated therapeutic ratio of hERG IC50 / MPO IC50 for these compounds.

It has surprisingly been found that the Example 1 compound of this patent application has an advantage in the hERG IC50 / MPO IC50 ratio associated with cardiovascular safety in comparison to compounds C, D and E (disclosed in WO 2013/068875), as more fully described below.

In Table 1 below the MPO IC50 (as determined according to the Human Whole Blood Assay for Irreversible Inhibition of MPO provided above) reflects the compound concentration required to irreversibly inhibit 50% of the active MPO present in a sample of

human blood tested exogenously. Compound A (Example 1 in this patent application), effectively inhibits MPO in human plasma at a lower concentration than either of the compounds D or E, and so is more potent allowing for a lower plasma concentration required for a potential therapeutic benefit. In addition, it is noted that the methylphenyl analogs (compounds B and D) of the chlorophenyl substituents (compounds F and C) have increased MPO IC50. Thus, it is surprising that the methylphenyl analog (compound A) has a decreased MPO IC50 versus the chlorophenyl analog (compound E).

In addition, a significant and undesirable off-target activity for any systemically-acting pharmacologically active agent is inhibition of the hERG potassium channel. An adverse effect of inhibition of this ion channel is well known to those skilled in the art for being associated with prolongation of the QTc interval on the patient's electrocardiogram (ECG) and potentially for the triggering of "torsades de pointes" and ventricular tachycardia (Bernard Fermini, Anthony A. Fossa, Pre-Clinical Assessment of Drug-Induced QT Interval Prolongation. Current Issues and Impact on Drug Discovery, Annual Reports in Medicinal Chemistry, Academic Press, 2004, Volume 39, Pages 323-334). A greater ratio between the concentrations required to inhibit hERG and myeloperoxidase activity (in this case hERG IC50 / MPO IC50) provides an advantage as it allows for the potential of safely inhibiting MPO to a greater extent before hERG-related adverse cardiovascular effects might be encountered. This ratio is proportional to the therapeutic index (the therapeutic index is the plasma concentration where an adverse effect is observed divided by the plasma concentration where a therapeutic benefit may be realized). The therapeutic index, as related to hERG inhibitory activity, is an especially significant advantage for a myeloperoxidase inhibitor since an important potential target population for MPO inhibitors is expected to be patients that have recently suffered a heart attack and thus would be much more susceptible to cardiac arrhythmia and the adverse consequences therefrom. For this reason it may be especially advantageous to develop a drug with high cardiovascular safety profile for patients that are suffering from cardiovascular or coronary heart disease.

It is a significant advantage for a myeloperoxidase inhibitor candidate to have a larger ratio between the hERG IC50 and MPO IC50, in order to maximize the potential therapeutic benefit and safety ratio. In Table 1, compound A (Example 1 in this patent

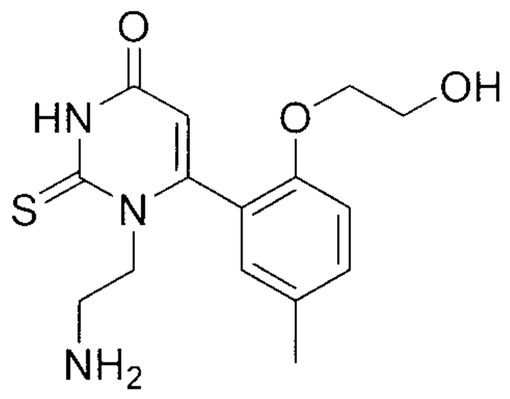
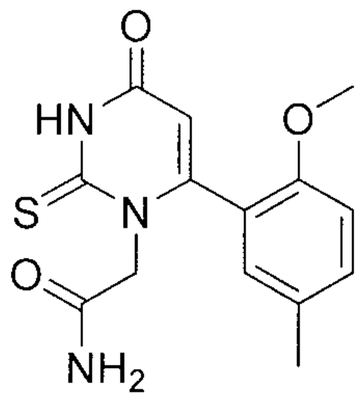
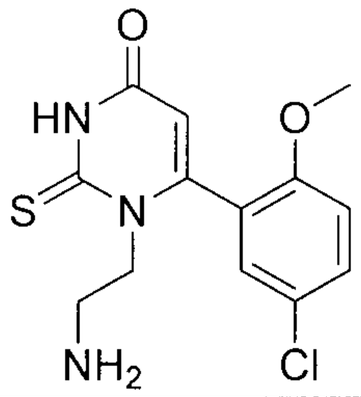
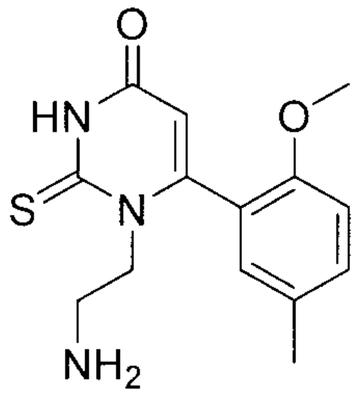
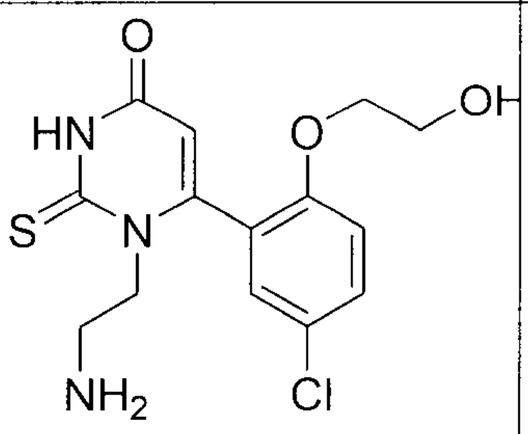
application) has a hERG IC50 /MPO IC50 ratio of 5515 (hERG IC50 = 3033 uM; extrapolated from 9% at 300 uM: [300 uM x ((100 - 9) / 9)]) in comparison to that for compound D (hERG IC50 /MPO IC50 ratio = 162; hERG IC50 = 160 uM: fit to a curve including 40% at 100 uM and 63% at 300 uM) and compound E (hERG IC50 /MPO IC50 ratio = 260; hERG IC50 = 335 uM, extrapolated from 23% at 100 uM: [100 uM x ((100 – 23) / 23)]). (Extrapolation method see "Optimizing Higher Throughput Methods to Assess Drug-Drug Interactions for CYP1A2, CYP2C9, CYP2C19, CYP2D6, rCYP2D6, and CYP3A4 In Vitro Using a Single Point IC50" *J Biomol Screen* (2002) 7:373). By a similar analysis, compound F has a hERG IC50 /MPO IC50 ratio of 900 (hERG IC50 = 1700 uM; extrapolated from 15% at 300 uM: [300 uM x ((100 - 15) / 15)]); compound C has a hERG IC50 /MPO IC50 ratio of 41 (hERG IC50 = 33 uM; fit to a curve including 49% at 30 uM and 75% at 100 uM); and compound G has a hERG IC50 /MPO IC50 ratio of 1500 (hERG IC50 = 900 uM; extrapolated from 25% at 300 uM: [300 uM x ((100 - 25) / 25)]). [Results for Compound B were not determined.]

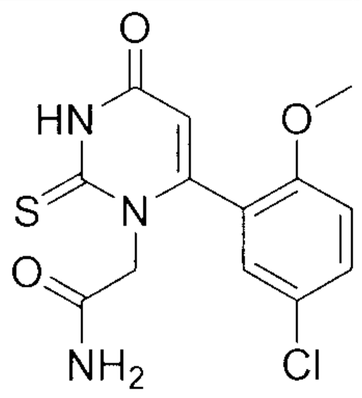
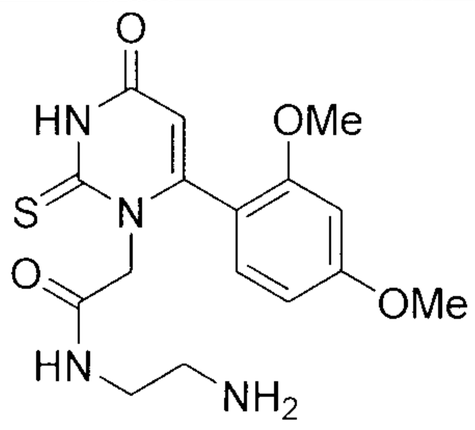
Thus, compound A (Example 1 in this patent application), has an expected 34 times (i.e., 5515/162) the hERG IC50 /MPO IC50 safety ratio over compound D and 21 times (i.e., 5515/260) the hERG IC50 /MPO IC50 safety ratio over compound E. This exceptionally high selectivity for MPO inhibition over hERG activity with compound A is unexpected and may offer a potentially significant cardiovascular safety advantage for patients that have a cardiovascular condition.

In an analogous manner, compound A (Example 1 in this patent application), has an expected 135 times (i.e., 5515/41) the hERG IC50 /MPO IC50 safety ratio over compound C, 6.1 times (i.e., 5515/900) the hERG IC50 /MPO IC50 safety ratio over compound F, and 3.7 times (i.e., 5515/1500) the hERG IC50 /MPO IC50 safety ratio over compound G.

Table 1. MPO Activity/hERG Therapeutic Ratio

Com-pound	Example No.	Structure	MPO IC50 in human whole blood	hERG IC50 (determined by curve fitting or *extrapolated* from %	Therapeutic ratio hERG IC50/ MPO IC50

				activity shown)	
A Example 1	See Example 1 in this patent application		0.55 uM	*3033 uM* (9%@ 300 uM)	5515
B	WO13068875 Example 164		2.5 uM	Not Available	Not Available
C	WO13068875 Example 63		0.80 uM	33 uM (49%@30 uM) (75%@100 uM)	41
D	WO13068875 Example 159		0.99 uM	160 uM (40%@100 uM) (63%@300 uM)	162
E	WO13068875 Example 427		1.3 uM	*335 uM* (23%@100 uM)	260

F	Example 1 in WO13068875 2-(6-(5-chloro-2-methoxyphenyl)-4-oxo-2-thioxo-3,4-dihydropyrmidin-1(2H)-yl)acetamide		1.9 uM	1700 uM (15%@ 300 uM)	900
G	WO13068875 Example 241 N-(2-aminoethyl)-2-[6-(2,4-dimethoxyphenyl)-4-oxo-2-thioxo-3,4-dihydropyrimidin-1(2H)-yl]acetamide		0.60 uM	900 uM (25%@ 300 uM)	1500

MPO Amplex Red Activity Assay.

MPO peroxidase activity was measured by monitoring the formation of resorufin generated from the oxidation of Amplex Red (10-acetyl-3,7-dihydroxyphenoxazine; Invitrogen, Carlsbad, CA) by MPO (Gomes, Fernandes et al. 2005). Assay mixtures (100 μL total volume) contained 50 mM NaPi pH 7.4, 150 mM NaCl, 1 mM DTPA (diethylenetriaminepentaacetic acid), 2% DMSO, 2 μM H_2O_2, 30 μM Amplex Red and the reaction was initiated by the addition of 100 pM MPO (purified from human polynuclear

leukocytes and purchased from Calbiochem/EMD Biosciences, Gibbstown, NJ). All assays were performed in 96-well, half-area, black, nonbinding surface, polystyrene plates (Corning) and the production of resorufin (excitation 530 nm, emission 580 nm) was monitored every 20 sec on a Spectramax M2 Microplate Spectrophotometer (Molecular Devices, Palo Alto, CA) equipped with Softmax Pro software (Molecular Devices, Palo Alto, CA). Reactions to determine the background reaction rate consisted of all assay components and 4 μL of 500 unit/mL bovine catalase (Sigma) in 50 mM KPi pH 7.0. The background rate was subtracted from each reaction progress curve. All data was analyzed using non-linear regression analysis in Microsoft Excel and Kaleidagraph (Synergy Software).

To determine inhibitor potency (k_{inact}/K_I) against MPO, the first 600 sec of the reaction progress curves were fit to equation 1, where V_o is the initial rate in RFU/sec and t is time in seconds, to obtain the first order rate constant for enzyme inactivation (k_{obs}) at each inhibitor concentration.

$$\text{Product} = \frac{V_0}{k_{obs}} [1-\exp(-k_{obs}t)] \quad (1)$$

Equation 1 is a variation of the standard equation for slow binding inhibition where the steady state velocity (V_s) is set to zero. Each k_{obs} value was corrected for auto-inactivation of the enzyme by subtracting the k_{obs} value for the uninhibited reaction. The corrected k_{obs} values were then plotted versus inhibitor concentration ([I]) and fit to equation 2

$$k_{obs} = \frac{k_{inact}[I]}{K_I + [I]} \quad (2)$$

where k_{inact} is the maximal rate of inactivation and K_I is the inhibitor concentration that yields half the rate of maximal inactivation (Copeland 2005).

Thyroid Peroxidase (TPO) Amplex Red activity assay.

TPO activity was measured using the same assay as MPO with 2 μM H_2O_2, 30 μM Amplex Red and the reactions were initiated with 1.3 μg of protein from HEK293 cell

membranes expressing human TPO. The cDNA encoding 933 amino acids of the full length human TPO was cloned into the inducible expression vector pcDNA5/frt/to (InVitrogen), stable 293 clones were selected using 100 ug/ml of hygromycin and 15 ug/ml blasticidine in DMEM w/ 10% FBS. When cells reached 50-60% confluence, TPO expression was induced in medium containing all of above plus 10 ug/ml doxycycline and 5 ug/ml hemin (Sigma). Membranes were isolated from HEK293hTPO by harvesting the cells in PBS. The cells were pelleted at 1000 x g for 5 minutes at 4^0C, resuspended in homogenization buffer (1 mM sodium bicarbonate, pH 7.4) containing EDTA-Free protease inhibitor (Roche), and incubated on ice for 10 minutes followed by Dounce homogenization. Nuclei and unlysed cells were removed by pelleting at 1000 x g for 10 minutes at 4^0C. The supernatant was then centrifuged at 25,000 x g for 20 minutes at 4^0C. The pellet was resuspended in homogenization buffer and centrifuged again at 25,000 x g for 20 minutes at 4^0C. The final pellet was resuspended in storage buffer (50 mM Tris pH 7, 150 mM NaCl) containing protease inhibitors as described above. Membrane concentration was determined using the BCA Protein Assay (Pierce). TPO activity was measured using the Amplex Red assay as described above. Aliquots were made based on the activity accordingly and stored at -80^0C.

The IC_{50} values were determined by plotting the initial rates (from the first 200 sec of each reaction progress curve) as percentage of inhibition relative to the uninhibited (DMSO) reaction as a function of inhibitor concentration. The data were fit to equation 3

$$y = \frac{100}{1 + (x/\mathrm{IC}_{50})^{z}} \qquad (3)$$

where IC_{50} is the inhibitor concentration at 50% inhibition and *z* is the Hill slope (the slope of the curve at its inflection point).

REFERENCES

Copeland, R. A. (2005). Evaluation of Enzyme Inhibitors in Drug Discovery A Guide for Medicinal Chemists and Pharmacologists. Hoboken, Wiley.

Gomes, A., E. Fernandes, et al. (2005). "Fluorescence probes used for detection of reactive oxygen species." J Biochem Biophys Methods **65**(2-3): 45-80.

A pharmaceutical composition of the Formula I compound may be prepared as a formulation comprising a Formula I compound, in association with one or more pharmaceutically acceptable excipients including carriers, vehicles and diluents. The term "excipient" herein means any substance, not itself a pharmacologically active agent, used as a diluent, adjuvant, or vehicle for potential delivery of a pharmacologically active agent to a subject or added to a pharmaceutical composition to improve its handling or storage properties or to permit or facilitate formation of a solid dosage form such as a tablet, capsule, or a solution or suspension suitable for potential oral, parenteral, intradermal, subcutaneous, or topical application. Excipients may include, by way of illustration and not limitation, diluents, disintegrants, binding agents, adhesives, wetting agents, polymers, lubricants, glidants, stabilizers, substances added to mask or counteract a disagreeable taste or odor, flavors, dyes, fragrances, and substances added to improve appearance of the composition. Acceptable excipients may include (but are not limited to) stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, magnesium carbonate, talc, gelatin, acacia gum, sodium alginate, pectin, dextrin, mannitol, sorbitol, lactose, sucrose, starches, gelatin, cellulosic materials, such as cellulose esters of alkanoic acids and cellulose alkyl esters, low melting wax, cocoa butter or powder, polymers such as polyvinyl-pyrrolidone, polyvinyl alcohol, and polyethylene glycols, and other pharmaceutically acceptable materials. Examples of excipients and their use may be found in Remington's Pharmaceutical Sciences, 20th Edition (Lippincott Williams & Wilkins, 2000).The choice of excipient will to a large extent depend on factors such as the particular mode of potential administration, the effect of the excipient on solubility and stability, and the nature of the dosage form.

The Formula I compound may be formulated for potential oral, buccal, intranasal, parenteral (e.g., intravenous, intramuscular or subcutaneous) or rectal administration or in a form suitable for potential administration by inhalation. The compounds of the invention may also be formulated for sustained delivery.

Methods of preparing various pharmaceutical compositions with a certain amount of active ingredient are known, or will be apparent in light of this disclosure, to those skilled

in this art. For examples of methods of preparing pharmaceutical compositions see Remington's Pharmaceutical Sciences, 20th Edition (Lippincott Williams & Wilkins, 2000).

Pharmaceutical compositions according to the invention may contain 0.1%-95% of the compound(s) of this invention, for example, 1%-70%.

The active ingredient may be formulated as a solution in an aqueous or non-aqueous vehicle, with or without additional solvents, co-solvents, excipients, or complexation agents selected from pharmaceutically acceptable diluents, excipients, vehicles, or carriers.

An exemplary intravenous formulation may be prepared as follows:

Formulation: Intravenous Solution

Ingredient	Quantity
Active ingredient dissolved in 5% Dextrose Injection, USP	150 mg
5% Dextrose Injection, USP	1.0 mL

The active ingredient may be formulated as a solid dispersion or as a self-emulsified drug delivery system (SEDDS) with pharmaceutically acceptable excipients.

The active ingredient may be formulated as an immediate release or modified release tablet or capsule. Alternatively, the active ingredient may be within a capsule shell, without additional excipients.

GENERAL EXPERIMENTAL PROCEDURES

All chemicals, reagents and solvents were purchased from commercial sources when available and used without further purification. Proton nuclear magnetic spectroscopy (^{1}H NMR) was recorded with 400 and 500 MHz Varian spectrometers. Chemical shifts are expressed in parts per million downfield from tetramethylsilane. The peak shapes are denoted as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br s, broad singlet. Mass spectrometry (MS) was performed via atmospheric pressure chemical ionization (APCI) or electron scatter (ES) ionization sources. Observed mass (Obs Mass) reported in the Tables correspond to the exact mass of the parent molecule plus one,

unless otherwise noted. Silica gel chromatography was performed primarily using a medium pressure Biotage or ISCO systems using columns pre-packaged by various commercial vendors including Biotage and ISCO. Microanalyses were performed by Quantitative Technologies Inc. and were within 0.4% of the calculated values. The terms "concentrated" and "evaporated" refer to the removal of solvent at reduced pressure on a rotary evaporator with a bath temperature less than 60 °C. The abbreviation "min" and "h" stand for "minutes" and "hours" respectively.

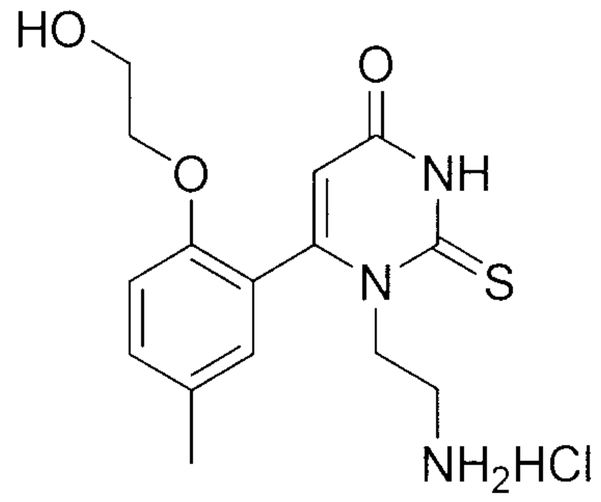
Powder X-ray Diffraction

Powder X-ray diffraction analysis was conducted using a Bruker AXS D4 Endeavor diffractometer equipped with a Cu radiation source. The divergence slit was set at 0.6 mm while the secondary optics used variable slits. Diffracted radiation was detected by a PSD-Lynx Eye detector. The X-ray tube voltage and amperage were set to 40 kV and 40 mA respectively. Data was collected in the Theta-2Theta goniometer at the Cu wavelength $K\alpha_1$ =1.54056 Å from 3.0 to 40.0 degrees 2-Theta using a step size of 0.020 degrees and a step time of 0.3 second. Samples were prepared by placing them in a silicon low background sample holder and rotated during collection. Data were collected using Bruker DIFFRAC Plus software and analysis was performed by EVA diffract plus software.

PXRD data file was not processed prior to peak searching. Using the peak search algorithm in the EVA software, peaks were selected with a threshold value of 1 and a width value of 0.3 was used to make preliminary peak assignments. The output of automated assignments was visually checked to ensure validity and adjustments manually made if necessary. Peaks with relative intensity of ≥ 3% were summarized in Table 2. The peaks which were not resolved or were consistent with noise were not selected. A typical error associated with the peak position from PXRD stated in USP and JP is up to +/- 0.2° 2-theta.

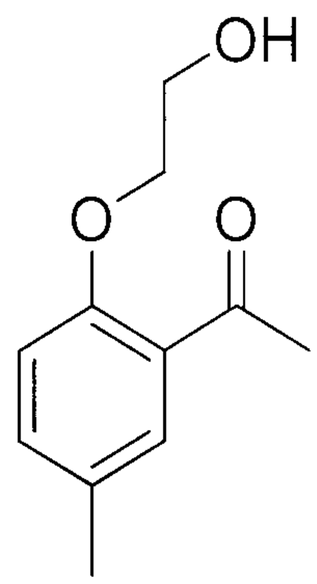
Example 1

1-(2-Aminoethyl)-6-(2-(2-hydroxyethoxy)-5-methylphenyl)-2-thioxo-2,3-dihydropyrimidin-4(1H)-one hydrochloride



Preparation 1

1-(2-(2-Hydroxyethoxy)-5-methylphenyl)ethanone

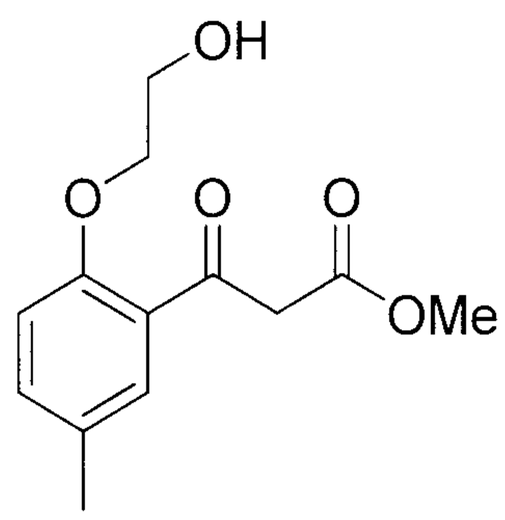


A jacketed reactor was charged with 1-(2-hydroxy-5-methylphenyl)ethanone (30.0 g, 0.200 mol, 1.0 eq) and dimethyl sulfoxide (DMSO, 210 mL), and the resulting mixture was stirred at 20 °C. Cesium carbonate (200 g, 0.608 mol, 3 eq) was added followed by 2-chloroethanol (27.0 mL, 0.40 mol, 2 eq) and the resulting mixture was stirred at 80 °C until completion of the reaction. The resulting mixture was then cooled to 15 °C before water (500 mL) was added. The resulting mixture was extracted with ethyl acetate (500 mL and then 300 mL). The combined organic layers were washed with brine (300 mL) and then treated with Darco G-60 (10 g) for 1 hour at ambient temperature, before being filtered through Celite and concentrated to afford the desired product, 1-[2-(2-hydroxyethoxy)-5-methyl-phenyl]ethanone (34.35 g, 89%) as an orange oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53-7.48 (m, 1H), 7.29-7.22 (m, 1H), 6.91-6.85 (m, 1H), 4.21-4.15 (m, 2H), 4.02-3.94 (m, 2H), 2.83 (b, 1H), 2.62 (s, 3H), 2.31 (s, 3H). ^{13}C-NMR (101 MHz, $CDCl_3$): δ = 200.11,

159.91, 134.18, 130.64, 130.44, 128.26, 113.67, 70.69, 61.23, 31.27, 20.30.

Preparation 2

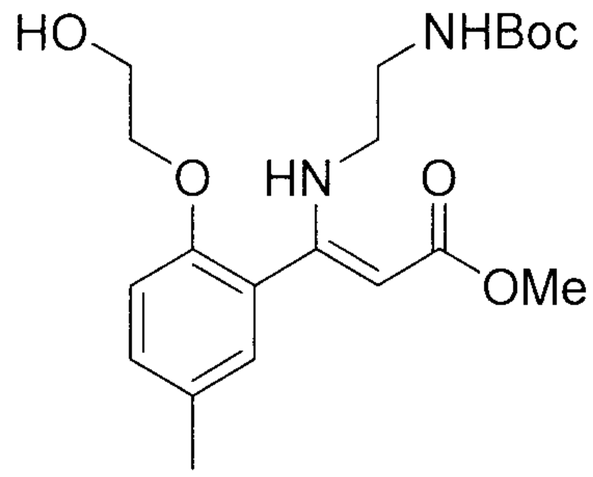
Methyl 3-(2-(2-hydroxyethoxy)-5-methylphenyl)-3-oxopropanoate



A jacketed reactor was charged with potassium tert-butoxide (48.9 g, 0.427 mol) and tetrahydrofuran (170 mL) and the resulting mixture was stirred at 20 °C as dimethyl carbonate (47.1 g, 0.523 mol, 3.0 eq) was added resulting in a mild exotherm with the formation of a white slurry. To this mixture was added a solution of 1-[2-(2-hydroxyethoxy)-5-methyl-phenyl]ethanone (33.84 g, 0.174 mol) in tetrahydrofuran (170 mL) and the resulting mixture was warmed to 30 °C. After 3h, the reaction mixture was treated with a solution of acetic acid (57.5 mL, 1.00 mol) in water (338 mL). After stirring for 1h, the reaction mixture was extracted with ethyl acetate (340 mL) and the organic phase treated with Darco (2.0 g) for 1h at room temperature before the mixture was filtered through Celite, concentrated, dissolved in isopropyl alcohol (160 mL), and then concentrated to afford a red oil. This crude product was then taken up in isopropyl alcohol (65 mL), cooled to 0 °C and then water (120 mL) was added slowly over 15 min. After stirring for 1h at 0-5 °C, additional water (240 mL) was added over 30 min, and the mixture stirred for 30 min before the resulting solid was collected by filtration, washed with water (200 mL) and dried to afford methyl 3-(2-(2-hydroxyethoxy)-5-methylphenyl)-3-oxopropanoate (37.2 g, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69-7.65 (m, 1H), 7.33-7.27 (m, 1H), 6.89-6.83 (m, 1H), 4.16-4.11 (m, 2H), 3.99 (s, 2H), 3.98-3.93 (m, 2H), 3.71 (s, 3H), 3.53-3.40 (b, 1H), 2.30 (s, 3H). ^{13}C-NMR (101 MHz, $CDCl_3$) δ 192.39, 169.63, 156.40, 135.46, 131.31, 130.46, 125.75, 112.39, 70.73, 60.85, 52.55, 50.26, 20.15 ppm. *m/z* (EI+) for $C_{13}H_{16}O_5$ 253.1 $(M+H)^+$.

Preparation 3

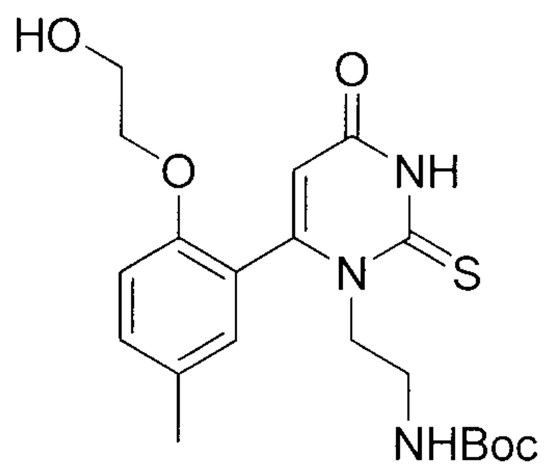
(Z)-Methyl 3-(2-(tert-butoxycarbonylamino)ethylamino)-3-(2-(2-hydroxyethoxy)-5-methylphenyl)acrylate



To a jacketed reactor was added isopropyl alcohol (250 mL), methyl 3-(2-(2-hydroxyethoxy)-5-methylphenyl)-3-oxopropanoate (36.0 g, 0.143 mol), tert-butyl 2-aminoethylcarbamate (35.0 g, 0.218 mol) and acetic acid (12.3 mL, 0.215 mol), and the mixture was heated at 84 °C. After 8h, the reaction was cooled to 15 °C and water (830 mL) was added slowly until the solution became hazy, then the addition was paused to allow solids to form over 15 min before slowly completing the water addition. The resulting slurry was stirred at 15 °C for 3 h, then filtered and the filter cake washed with water (290 mL). The solid was dried in a vacuum oven at 50 °C for 16h to afford (Z)-methyl 3-(2-(tert-butoxycarbonylamino)ethylamino)-3-(2-(2-hydroxyethoxy)-5-methylphenyl)acrylate (51.96g, 92%). ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.69-8.52 (m, 1H), 7.18 (dd, J=8.6, 1.6 Hz, 1H), 7.01-6.91 (m, 2H), 6.83 and 6.45 (b, total integration = 1H), 4.79 (t, J=5.3 Hz, 1H), 4.25 (s, 1H), 3.99 (b, 2H), 3.67 (q, J=5.3Hz, 2H), 3.53 (s, 3H), 3.17-2.80 (m, 4H), 2.24 (s, 3H), 1.36 (s, 9H). ^{13}C-NMR (101 MHz, d_6-DMSO) δ 169.48, 162.05, 155.61, 152.99, 130.92, 129.80, 129.34, 124.32, 112.21, 82.80, 77.66, 69.84, 59.46, 49.58, 43.20, 40.53, 28.17, 19.91. *m/z* (EI+) for $C_{20}H_{30}N_2O_6$ 395.3 $(M+H)^+$.

Preparation 4

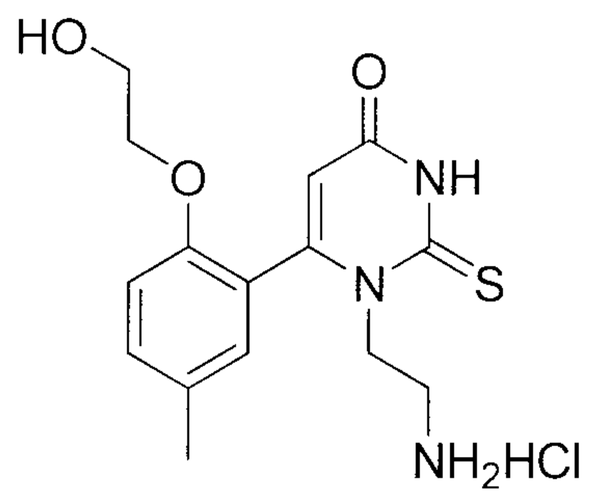
tert-Butyl 2-(6-(2-(2-hydroxyethoxy)-5-methylphenyl)-4-oxo-2-thioxo-3,4-dihydropyrimidin-1(2H)-yl)ethylcarbamate



A jacketed reactor was charged with butyl acetate (70 mL), (Z)-methyl 3-(2-(tert-butoxycarbonylamino)ethylamino)-3-(2-(2-hydroxyethoxy)-5-methylphenyl)acrylate (10.00 g, 25.35 mol) and isothiocyanatotrimethylsilane (10.0 mL, 70.98 mol). The resulting solution was heated to 80 °C and stirred for 8 hours before the reaction mixture was cooled to ambient temperature. After 12 hours, heptane (100 mL) was gradually added to the reaction mixture over a period of 10 minutes. The resulting slurry was warmed to 40 °C and stirred for 3 hours before cooling to 20 °C. After 3 hours, the solids were isolated by filtration, washing with a 1:1 solution of heptane/butyl acetate (50 mL), and allowed to dry overnight. The resulting solids (9.57 g) were mixed with butyl acetate (60 mL) and the mixture stirred at 40 °C for 3 hours, then cooled to 25 °C over 30 minutes and stirred 3 hours. The resulting solids were collected by filtration, washed with butyl acetate (20 mL) and dried in a vacuum oven at 35 °C for 24 hours to afford *tert*-butyl 2-(6-(2-(2-hydroxyethoxy)-5-methylphenyl)-4-oxo-2-thioxo-3,4-dihydropyrimidin-1(2H)-yl)ethylcarbamate (7.75 g, 72.5%). ^{1}H NMR (400 MHz, d6-DMSO) δ 12.52 (s, 1H), 7.21 (d, J=8.2Hz, 1H), 7.07 (s, 1H), 6.97 (d, J=8.6Hz, 1H), 6.51 (t, J=5.9Hz, 1H), 5.62 (d, J=2.0Hz, 1H), 4.51 (m, 1H), 3.96 (m, 2H), 3.56 (t, J=5.1Hz, 2H), 3.47 (m, 1H), 3.35 (m, 1H), 2.86 (m, 1H), 2.23 (s, 3H), 1.27 (s, 9H). ^{13}C-NMR (101 MHz, d6-DMSO) δ 177.53, 159.93, 155.77, 154.89, 152.96, 132.54, 131.00, 130.08, 122.89, 112.76, 109.22, 78.10, 70.44, 59.92, 50.94, 37.75, 28.69, 20.59. *m/z* (EI+) for $C_{20}H_{27}N_3O_5S$ 422.3 $(M+H)^+$.

Preparation 5

1-(2-Aminoethyl)-6-(2-(2-hydroxyethoxy)-5-methylphenyl)-2-thioxo-2,3-dihydropyrimidin-4(1H)-one hydrochloride



A dry 1 L round bottomed flask was charged with ethanol (515 mL) and cooled to 0 °C before acetyl chloride (160 mL, 2.25 mol) was added via an addition funnel with stirring over 20 minutes. The resulting solution was then heated at 50 °C for 30 minutes and then cooled to ambient temperature. A separate 4 L round bottomed flask equipped with a mechanical stirrer was charged with *tert*-butyl 2-(6-(2-(2-hydroxyethoxy)-5-methylphenyl)-4-oxo-2-thioxo-3,4-dihydropyrimidin-1(2H)-yl)ethylcarbamate (95.0 g, 0.23 mol) and ethanol (515 mL) to afford a white suspension. The previously prepared HCl solution in the 1 L round bottomed flask was added gradually with stirring to the suspension in the 4 L round bottomed flask. The resulting mixture was stirred at ambient temperature for 20 minutes before warming to 50 °C. After stirring for 1 h the reaction mixture was then allowed to gradually cool to ambient temperature and after stirring for 3 h ethyl acetate (550 mL) was added to the reaction mixture. The resulting slurry was stirred at ambient temperature for 1 h before the solids were collected by filtration, washing with a 1:1 mixture of ethyl acetate/heptane (2.5 L). The isolated solid was dried in a vacuum oven at 50 °C for 20 h to afford (1-(2-aminoethyl)-6-(2-(2-hydroxyethoxy)-5-methylphenyl)-2-thioxo-2,3-dihydropyrimidin-4(1H)-one hydrochloride (78.78 g, 98%).

^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.82 (br. s., 1H), 7.95 (br. s., 3H), 7.32 (dd, J=8.5, 1.5 Hz, 1H), 7.17 (d, J=1.8 Hz, 1H), 7.10 (d, J=8.8 Hz, 1H), 5.76 (s, 1H), 4.88 (t, J=5.0 Hz, 1H), 4.52 (br. s., 1H), 4.06 (t, J=5.0 Hz, 2H), 3.98-4.04 (m, 1H), 3.64 (d, J=4.7 Hz, 2H), 2.93-3.01 (m, 1H), 2.86-2.93 (m, 1H), 2.28 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 177.2, 159.3, 153.9, 152.7, 132.4, 130.1, 129.8, 121.6, 112.9, 109.3, 70.1, 59.3, 47.0, 35.9, 20.0; *m/z* (EI+) for $C_{15}H_{19}N_3O_3S$ 322.1 $(M+H)^+$.

The powder X-ray diffraction pattern PXRD for the resulting crystalline product is

provided in Figure 1.

Table 2 below provides a PXRD peak list* for the same resulting crystalline product.

Table 2: PXRD peak list* for crystalline material

Angle 2Θ (°)	Relative Intensity (%)
8.1	11
9.4	10
10.4	51
11.8	8
15.8	5
16.1	4
16.5	3
17.0	7
18.2	48
18.9	6
21.0	18
21.2	28
21.4	100
22.3	51
22.5	54
22.8	22
22.9	34
23.6	9
23.8	18
24.1	39
24.7	21
25.8	53
26.3	10
27.2	5
27.5	7
27.8	4
28.1	20
28.3	4
28.6	11
29.1	3
29.7	38
30.1	3
30.8	9
31.2	19

31.9	11
32.0	11
32.4	7
32.6	7
34.1	4
34.5	5
34.9	10
35.8	11
36.3	12
36.8	7
37.8	8
38.5	15
39.1	17

*Note: Characteristic peak positions were selected based on visual observation of peak shape and intensity.

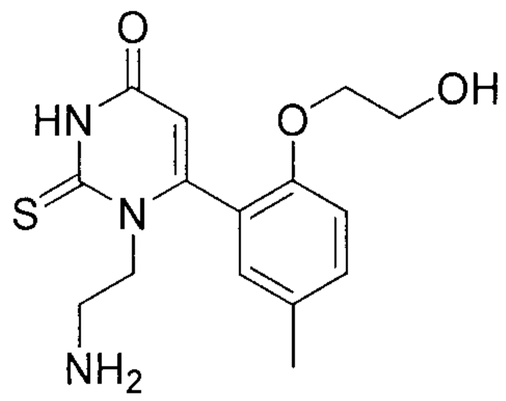
All publications, including but not limited to, issued patents, patent applications, and journal articles, cited in this application are each herein incorporated by reference in their entirety.

Although the invention has been described above with reference to the disclosed embodiments, those skilled in the art will readily appreciate that the specific experiments detailed are only illustrative of the invention. It should be understood that various modifications can be made without departing from the spirit of the invention.

What is claimed:

CLAIMS

1. A compound of the Formula I



Formula I

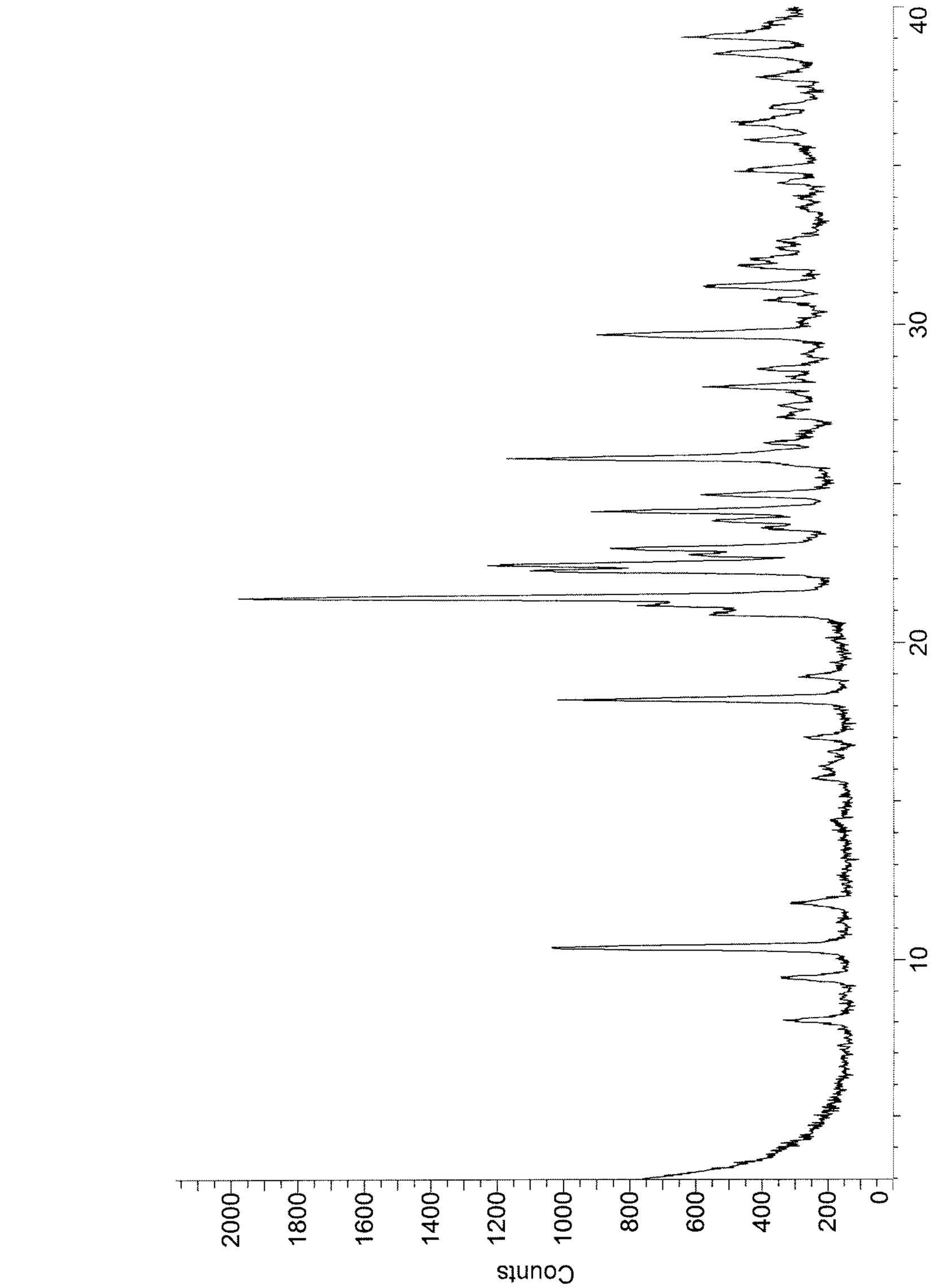
or a pharmaceutically acceptable salt thereof.

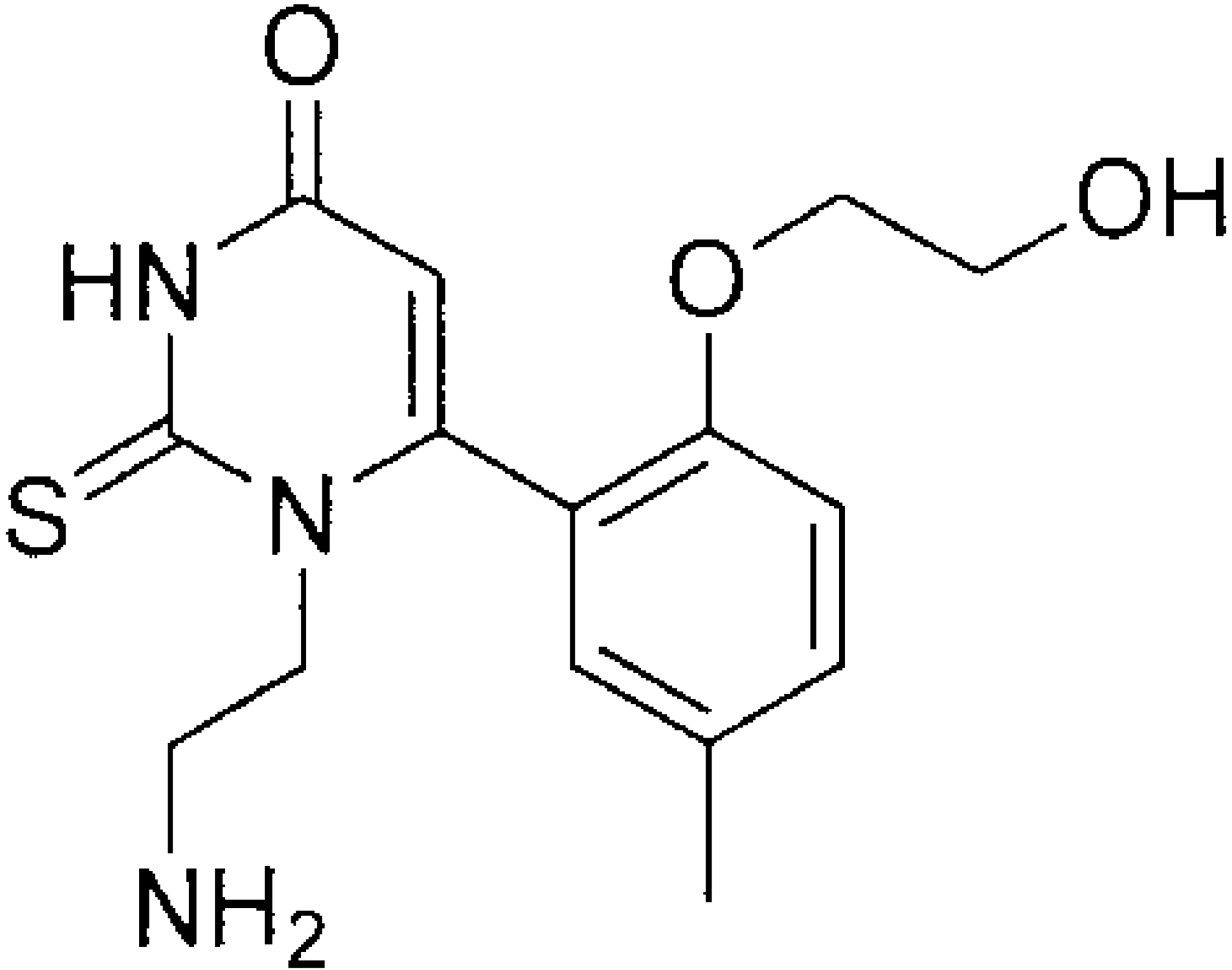
2. The hydrochloride salt of the compound of Formula I.

3. The compound 1-(2-aminoethyl)-6-(2-(2-hydroxyethoxy)-5-methylphenyl)-2-thioxo-2,3-dihydropyrimidin-4(1H)-one.

4. A pharmaceutical composition which comprises a compound of claim 1 or a pharmaceutically acceptable salt of said compound and a pharmaceutically acceptable carrier, vehicle or diluent.

Figure 1


Counts
2000
1800
1600
1400
1200
1000
800
600
400
200
0
10
20
30
40
2Theta (degrees)


O
HN
O
OH
S
N
NH2