

Noncardiotoxic Pharmaceutical Compounds

Cross-Reference to Related Applications

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This patent application claims the benefit of prior filed copending provisional application numbers 60/600,699 filed August 11, 2004, and 60/673,545 filed April 21, 2005 each titled Noncardiotoxic Pharmaceutical Compositions, which are hereby incorporated by reference in their entirety.

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Background of the Invention

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The present invention relates to novel noncardiotoxic compounds and pharmaceutical compositions useful in the treatment of a variety of disorders including the treatment of depression, allergies, psychoses, infection, cancer and gastrointestinal disorders. The compounds and pharmaceutical compositions of the present invention are useful in the prevention and/or reduction of severe cardiac conductance and cardiac rhythm disturbances and the cardiac arrhythmias such as *torsade de pointes* that lead to sudden cardiac death.

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The annual incidence of sudden cardiac death is estimated to be greater than 400,000 persons in the United States alone, and accounts for approximately 50% of all deaths from cardiovascular disease (Chugh et al. Journal American College of Cardiology 44: 1268-1275 (2004); U.S. Centers for Disease Control; Chugh et al. Circulation 102:649-654 (2000)). Although the occurrence of sudden cardiac death in the general population is high, the incidence (as a percent of the total) in patients over 64 years of age and in patients with cardiovascular disease is considerably higher (Huikuri et al. New England Journal of Medicine 345(2):1473-1482(2001); Morbidity and Mortality: 2004 Chart Book on Cardiovascular, Lung and Blood Diseases, National Institutes of Health (May 2004); and Myerburg et al. Annals of Internal Medicine 119:1187-1197 (1993)). According to the World Health Organization, the non-cardiovascular drugs most commonly associated with *torsade de pointes* between 1983 and 1999 are gastrointestinal, antiinfective, antidepressant, antihistaminic and antipsychotic agents. Moreover, antipsychotic,

antidepressant and cardiovascular drugs account for over 40% of fatalities for all pharmaceutical agents (The 2002 Annual Report of the American Association of Poison Control Centers Toxic Exposure Surveillance System (AAPCC-TESS)).

- 5 It has been reported that the incidence of sudden cardiac death is clearly associated with increasing amounts of antidepressant and antipsychotic drugs at therapeutically relevant doses (Ray, AR et al. Clinical Pharmacology and Therapeutics 75(3): 234-241 (2004); Ray, AR et al. Archives General Psychiatry 58: 1162-1167 (2001)). Although low therapeutic doses of these types of drugs (< 100 mg daily) are not associated with
- 10 sudden cardiac death, moderate and high therapeutic doses of these drugs ($\geq$ 100 mg daily) are clearly associated with sudden cardiac death. Not only is the incidence of sudden death in patients with cardiovascular disease and treated with these drugs considerably higher than patients without cardiovascular disease, the incidence of sudden death in these patients is clearly correlated with the severity of cardiovascular
- 15 disease (Ray, AR et al. Archives General Psychiatry 58: 1162-1167 (2001)).

- Antipsychotics primarily antagonize central dopaminergic D_2 receptor neurotransmission, although they also have antagonist effects at muscarinic, serotonergic, α_1 -adrenergic, and H_1 -histaminergic receptors. Because antipsychotics are also used as sedatives,
- 20 as antiemetics, to control hiccups, to treat migraine headaches, and as antidotes for drug-induced psychosis, the adverse effects of antipsychotics are not confined to psychiatric patients. Antipsychotics are capable of causing orthostatic and severe hypotension, as well as prolongation of the QTc interval and QRS which can result in arrhythmias. Antipsychotics account for about 18 % of moderate (pronounced) toxicity,
- 25 over 20% of life-threatening toxicity and 17% of the fatalities of all pharmaceuticals.

- Tricyclic antidepressants cause the overwhelming majority of antidepressant poisoning in the United States resulting in morbidity and mortality; the most severe toxicity occurs in the cardiovascular system. Antidepressants account for about 15 % of moderate
- 30 (pronounced) toxicity and 18% of life-threatening toxicity of the fatalities of all pharmaceuticals.

Antidepressants affect the prolongation of the QTc interval causing cardiotoxicity that result from direct myocardial depression, cardiac conduction disturbances, effects on peripheral vasomotor tone, and changes in the autonomic nervous system. The

interactions of tricyclic antidepressants with fast sodium channels in cardiac tissue results in slowed cardiac conduction (e.g. prolonged QRS on the ECG), impaired cardiac contractility and possible ventricular dysrhythmias and inhibition of repolarization in His-Purkinje myocytes (e.g. prolonged QTc on the ECG).

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Torsade de pointes is a particular cardiac problem associated with many therapeutic agents and has been implicated as a possible cause of sudden death, particularly in those individuals with a past history of disturbances of cardiac rhythm, myocardial infarction, congenital repolarization abnormalities and cardiac risk factors such as hyperlipidemia and age. This arrhythmia is a variant of paroxysmal ventricular tachycardia associated with a prolonged QTc interval or prominent U waves on the ECG. Although *torsade de pointes* might remit spontaneously, it is potentially lethal because it can progress to ventricular fibrillation, life-threatening arrhythmias or precipitate sudden death.

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Drug-induced QTc interval prolongation may be clinically important even if the mean increase is not very large. For example, the drug terodiline was withdrawn after causing QTc interval prolongation, *torsade de pointes*, and sudden death. In healthy volunteers, therapeutic plasma concentrations of terodiline are associated with increases in mean QTc of only 23 ms, which are similar to the increases associated with quinidine and prenylamine. Nevertheless, much larger increases occurred in a minority of patients who developed arrhythmias. These included those predisposed by existing problems such as heart disease and congenital repolarization abnormalities. Thus, benign QTc interval prolongation in one subject may indicate that another more susceptible patient might develop extreme QTc interval prolongation and arrhythmias with the same drug at the same dose. Furthermore, small increases in QTc interval might increase the risk of ventricular fibrillation/ *torsade de pointes* over a large population. The number of excess cases of sudden death in the large numbers of patients with minor QTc interval prolongation might actually exceed those in the small numbers of patients with extreme QTc interval prolongation. Nevertheless, the potential of a drug to cause QTc interval prolongation is currently believed to be the lower threshold of determining the cardiotoxicity of a therapeutic drug.

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To date, the understanding of QTc interval prolongation has focused on defective repolarization of the heart through blockade of K⁺ channels, either alone or in combination with Na⁺ channel modulation. Prevailing theories also suggest that the arrhythmogenic [potential of drugs is based on elevated plasma levels of parent drug that are not metabolized. Despite attempts to correlate the blockade of human cardiac K⁺ channels, such as the Herg channel, with *torsade de pointes* and sudden cardiac death, very little evidence exists to support this correlation. In fact, a number of severely cardiotoxic drugs that have been withdrawn from the market or denied approval by the FDA have insignificant effects on the Herg channel.

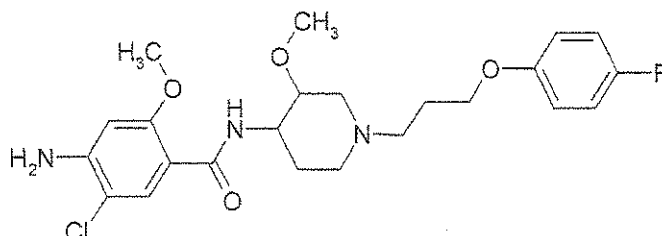
Although data has existed for decades that demonstrates adverse conductance changes and arrhythmias in patients having higher than normal plasma concentrations of drug metabolites, the cardiotoxic effects of these metabolites have received relatively little attention. These observed adverse cardiac conductance changes reflect significant changes in cardiac depolarization (QRS interval prolongation and dispersion) and atrial block (PR interval prolongation) that were correlated with elevated plasma levels of hydroxylated drug metabolites in clinical studies (Kutcher SP et al. British Journal of Psychiatry 148: 676-679 (1986); Stern SL et al. Journal of Clinical Pharmacology 11: 93-98 (1991); Vozeh S et al. American Journal of Cardiology 59: 681-684 (1987); Vozeh S et al. Clinical Pharmacology and Therapeutics 37:575-581 (1985); Drayer DE et al. Clinical Pharmacology and Therapeutics 24: 31-39 (1978)); in isolated perfused heart studies (Uematsu T et al. Archives of International Pharmacodynamics 297: 29-38 (1989); Uematsu T. et al. Journal of Pharmacological Methods 18: 179-185 (1987); and in animal studies (Pollock BG Ph.D. Dissertation University of Pittsburgh 1987; Pollack BG and Perel JM Psychopharmacology 109: 57-62 (1992); Jandhyala HS et al. European Journal of Pharmacology 42: 403-410 (1977)). Hydroxylated drug metabolites have also been reported to be responsible for severe cardiotoxic effects *in vitro* (Chem. Res. Toxicology (17: 623-632 (2004)).

A considerable number of cardiovascular and noncardiovascular therapeutic agents rely on secondary and tertiary amine structural motifs in their chemical structure that are responsible for their pharmacological activity. Many cardiovascular drugs, including antiarrhythmics, calcium channel antagonists, adrenergics and β -blockers contain essential secondary and tertiary amines in their chemical structure. Entire therapeutic

classes of non-cardiovascular drugs, including antidepressants, antihistamines and antipsychotics rely on the secondary and tertiary amine functionality for their primary activity. Others, such as gastrointestinal and anti-infective drugs do not necessarily rely on the secondary and tertiary amine group for their primary activity; but, include this structural motif as part of their chemical structure. Cardiotoxicity associated with the therapeutic use of secondary and tertiary amine-containing drugs is reflected in a variety of cardiac disturbances, including notable changes in ECG, polymorphic ventricular tachycardia, negative inotropism, drops in blood pressure, orthostatic hypotension and depressed cardiac contractility resulting in acute cardiac arrest.

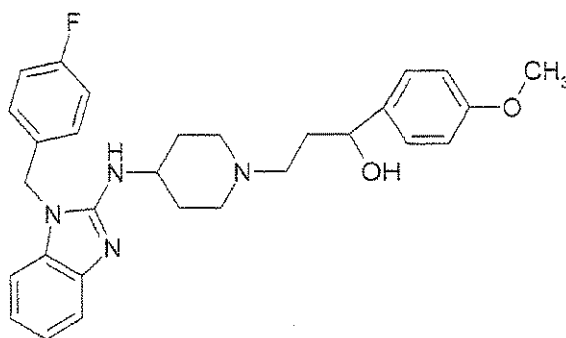
Serious cardiac arrhythmias (both fatal and non-fatal) including tachycardia, ventricular fibrillation, *torsades de pointes*, and QTc interval prolongation have been reported in patients taking individual secondary and tertiary amine-containing drugs that are oxidized by cytochrome P450 2D6 or combinations of secondary and tertiary amine-containing drugs that inhibit cytochrome P450 3A4. Drugs known to inhibit metabolism of secondary and tertiary amine-containing drugs by cytochrome P450 3A4 include, inter alia, ketoconazole, itraconazole, miconazole, troleandomycin, erythromycin, fluconazole and clarithromycin. It is generally believed that inhibition of a drug's metabolism by cytochrome P450 3A4 increases the plasma concentration of the parent amine-containing drug to toxic levels; however, this view has not been supported by rigorous examination and discrimination between plasma levels of the parent drugs and their metabolites. An alternate explanation is that inhibition of cytochrome P450 3A4 by inhibitors administered concomitantly "switches" the metabolism of the parent compound from one involving both cytochrome P450 3A4 and cytochrome P450 2D6 to the metabolism of the parent drug primarily by cytochrome P450 2D6.

Cisapride (Propulsid®), shown below, was commonly used to treat nocturnal heartburn as well as a variety of other gastrointestinal disorders:



- 5 Cisapride (Propulsid®) was recently removed from the market by the FDA because of the QTc interval prolongation and life-threatening ventricular arrhythmias such as *torsade de pointes* which produced sudden cardiac death. These cardiotoxic effects are believed to be due to cardiac conduction delays such as the specific and potent blockade of human cardiac K⁺ channels, particularly the HERG channels. The specific, high affinity block of
- 10 the human cardiac K⁺ channel HERG by cisapride (IC₅₀ of 0.045 μM) is similar to that observed for the class III antiarrhythmic agent dofetilide (IC₅₀ of .010 μM) and the nonsedating antihistamines astemizole (IC₅₀) of .001 μM) and terfenadine (IC₅₀) of 0.213 μM). It is further believed that this blockade of human cardiac K⁺ channels underlies the proarrhythmic effects of the drug observed under certain clinical settings. In guinea pig
- 15 ventricular myocytes cisapride elicited a concentration-dependent block (IC₅₀ of 46.9 μM) of L-type Ca²⁺ channels suggesting that the inhibitory effect of cisapride on calcium channels might also contribute to its cardiotoxicity under pathophysiological conditions. Cisapride is metabolized by both cytochrome P450 3A4 and cytochrome P450 2D6; however the primary metabolic route is believed to be through cytochrome P450 3A4.
- 20 When higher than normal dosages of cisapride are used or with concomitant ingestion of imidazole antifungals or macrolide antibiotics, it is believed that cisapride is metabolized to cardiotoxic metabolites through aromatic hydroxylation primarily by cytochrome P450 2D6.
- 25 Astemizole (Hismanal®) and terfenadine (Seldane®) are H₁ histamine antagonists that have also been removed from the market by the FDA because of QTc interval prolongation and ventricular arrhythmias such as *torsade de pointes* which produced sudden cardiac death.

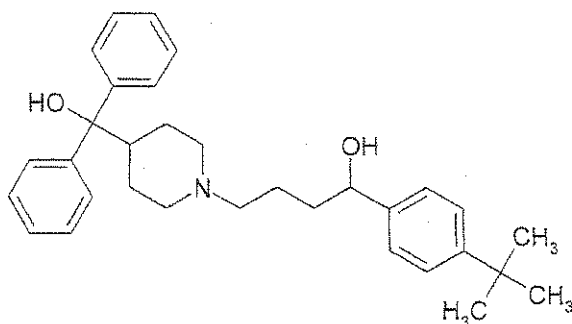
Astemizole (Hismanal®), shown below, was commonly used to treat the symptoms associated with seasonal allergic rhinitis and chronic idiopathic urticaria.



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Terfenadine (Seldane®), shown below, was commonly used to symptoms associated with seasonal allergic rhinitis such as sneezing, rhinorrhea, pruritus, and lacrimation.

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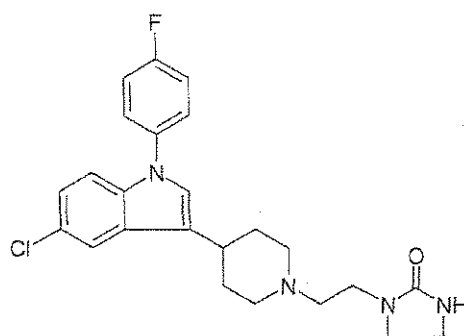
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25 Astemizole (Hismanal®) and terfenadine (Seldane®) are metabolized by both cytochrome P450 3A4 and cytochrome P450 2D6, and at least astemizole is believed to be metabolized to cardiotoxic metabolites through aromatic hydroxylation. Terfenadine is believed to be metabolized to cardiotoxic metabolites primarily through aliphatic oxidation. Terfenadine and astemizole suppress the HERG current with IC_{50} of 0.213 μM and 0.001 μM , respectively. Clinical use of astemizole and terfenadine has been associated with hypotension, QTc interval prolongation, development of early after-depolarization, *torsade de pointes*, cardiac arrest and sudden death. It is believed that *torsade de pointes* occurs when higher than normal dosages of astemizole are used or

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with concomitant ingestion of imidazole antifungals or macrolide antibiotics. Concomitant administration of astemizole with ketoconazole, itraconazole, erythromycin, clarithromycin or quinine was contraindicated. It is believed that these cardiovascular effects resulting in electrocardiographic conductance defects are associated with elevation of astemizole or its metabolites in plasma. Norastemizole is 13- to 16-fold more potent as an H1 antagonist than astemizole and 20- to 40-fold more potent in inhibiting histamine-induced bronchoconstriction.

Sertindole, shown below, was an atypical antipsychotic agent commonly used for the treatment of schizophrenia outside of the United States:



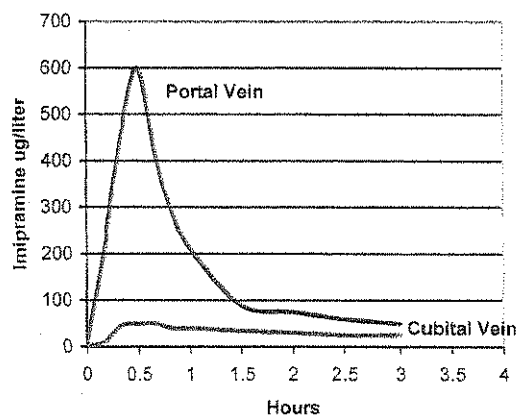
In 1996, sertindole (Serlect®) was rejected by the Food and Drug Administration because it prolonged the QTc interval and was associated with a significant number of unexplained deaths in clinical trials. Sertindole had been approved in 19 European countries, but more evidence of associated arrhythmias led to its withdrawal in Europe.

In trials involving more than 2,000 patients up to June 1996, 27 patients died while receiving sertindole, including 13 sudden deaths. Although there was no proof that the drug actually caused these deaths, sertindole was known to induce QT interval prolongation in some patients. Other antipsychotics have been associated with QT interval prolongation, and sudden death has been associated with schizophrenia.

Secondary and tertiary amines and other drug substrates for the P450 2D6 isozymes are lipophilic compounds that possess a planar component and are strong organic bases that are protonated at physiological pH. It is believed that a charged nitrogen atom on these amines is required to orient the drug correctly within the P450 2D6 active site where
5 metabolic oxidation occurs. At this site, it is believed that the secondary or tertiary amine molecule adopts a conformation in which the positively-charged nitrogen (N⁺) atom is oriented towards an anionic location (COO⁻) on the P450 2D6 protein while the aromatic ring is aligned with a relatively planar, hydrophobic region of the protein. It is believed that when this conformation is adopted the nitrogen atom and the metabolic
10 oxidation are in close proximity and metabolism of the drug occurs. Although cytochrome P450 3A4 is located both in the liver and the intestine, P450 2D6 is located in the liver and not the intestine.

Metabolic oxidation of drugs and other xenobiotic substances is a first step in a
15 biotransformation that the body relies on to distribute active drug metabolites to tissues and also to eliminate them from the body. In some cases, this metabolic oxidation involves the formation of a pharmacologically active metabolite, and in other cases it involves the formation of hydroxylated metabolites through oxidation of an aromatic ring. Although metabolic oxidation to pharmacologically active metabolites is essential,
20 metabolism of secondary and tertiary amine-containing drugs to hydroxymetabolites by cytochrome P450 2D6 and cytochrome P450 3A4 has serious cardiotoxicity implications to patients, particularly at high oral doses. We have found that the hydroxymetabolites are primarily responsible for the cardiotoxicity and not the parent secondary and tertiary amine-containing drugs. Published studies in humans (Dencker H et al. Clinical
25 Pharmacology and Therapeutics 19: 584-588 (1976)) have also shown that the concentration of the tertiary-amine drugs is highest after leaving the liver and immediately prior to reaching the heart (8-10 times the concentration in the systemic circulation). Consequently, a patient is at highest risk during the first-pass metabolism of the secondary and tertiary amine drugs when the concentration of the cardiotoxic
30 hydroxymetabolites is highest.

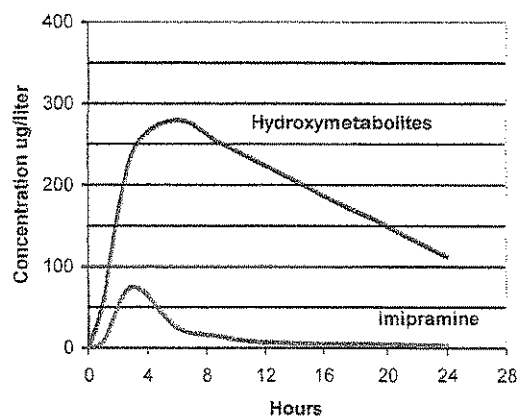
Intestinal Absorption and Metabolism of Imipramine
in Human Subjects
Adapted from Dencker et al. 1976



Ratio of Imipramine in portal vein to plasma at C_{max} = 12

Published studies in humans (Gram LF and Christiansen J Clinical Pharmacology and Therapeutics 17: 555-563 (1975) have further shown that the concentration of the hydroxymetabolites of imipramine in plasma reaches significantly higher levels than the parent compounds or their active metabolites.

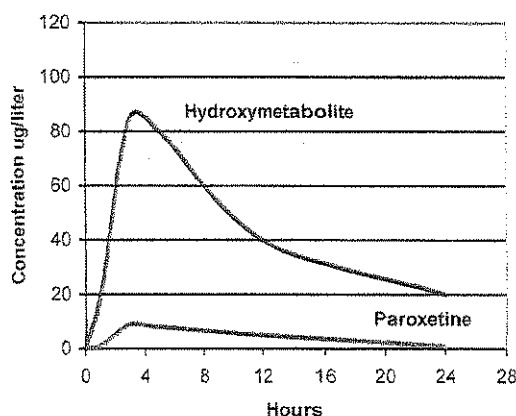
Plasma Concentration for Imipramine and
its Metabolites in Human Subjects
Adapted from Gram et al. 1975



Ratio of Hydroxymetabolites to imipramine at C_{max} = 11

Likewise, published studies (Segura M et al. Rapid Communications in Mass Spectrometry 17: 1455-1461 (2003)) report that the concentration of the hydroxymetabolites of paroxetine in human plasma reaches significantly higher levels than the parent compounds or their active metabolites.

Plasma Concentrations for Paroxetine and its Metabolite Adapted from Segura et al. 2003



Adapted from Segura et al. 2003

	Paroxetine	Hydroxylated Metabolite	Ratio of Metabolite to Paroxetine
Cmax (ug/L)	8.60	92.40	10.7
Tmax (hours)	5 (3-5)	3 (3-5)	-
AUC(0-24) (ug/L/h)	96.50	988.10	10.2

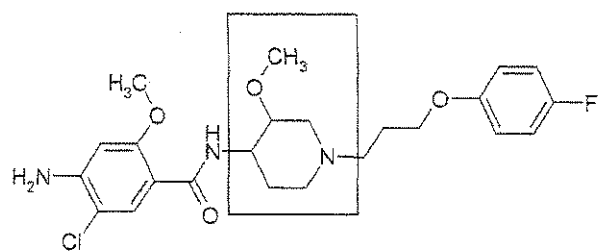
Consequently, a patient is at greatest risk during the first-pass metabolism of the secondary and tertiary amine drugs when the concentration of the cardiotoxic hydroxymetabolites is highest. We believe that reverting metabolism of secondary and tertiary amine-containing drugs to hydroxymetabolites by cytochrome P450 2D6 and cytochrome P450 3A4 is therefore important to reducing their cardiotoxicity.

Inhibition studies on a series of imipramine analogs were conducted and the analogs tested for CYP2D6 activity, the enzyme that is responsible for the formation of the cardiotoxic hydroxylated metabolites (Halliday RC et al. European Journal of Drug Metabolism and Pharmacokinetics 22: 291-294 (1997)). The analogs of imipramine that were tested were designed to have the positively charged nitrogen atom removed from the active site of CYP2D6. The three approaches were adjustment of alkyl chain length, alkyl bond rigidity (restricted bond rotation) and removing the positive charge on the tertiary nitrogen atom using the prodrug imipramine-N-oxide. Halliday et al. reported that removal of the positively charged nitrogen atom of imipramine from the active site of CYP2D6 either by lengthening the alkyl chain length or altering the pKa of imipramine with using imipramine-N-oxide abolished the metabolism of imipramine by CYP2D6 to the hydroxymetabolite.

A considerable amount of preclinical and clinical data is available that demonstrates that imipramine-N-oxide is not subject to first-pass metabolism or aromatic hydroxylation to the cardiotoxic hydroxymetabolites by cytochrome P450 2D6 and cytochrome P450 3A4. This prodrug is rapidly converted in the systemic circulation to imipramine which is then metabolized under much lower systemic plasma concentrations to the active form (desipramine) and hydroxylated metabolites that are not as likely to produce severe cardiotoxicity. In published preclinical and clinical studies imipramine-N-oxide has been shown not produce the cardiotoxicity of the tertiary amine drug imipramine. Nevertheless, formulation difficulties and the complexities of imipramine-N-oxide metabolism in plasma limits its use.

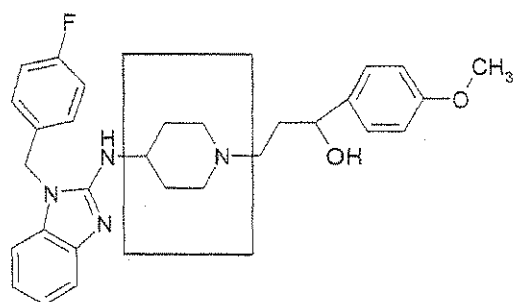
It is believed, in accordance with the present invention that the piperidine chemical group with its tertiary amine in cisapride, astemizole, sertindole, trazadone, nefazadone, buspirone and terfenadine contributes to cardiac conduction disturbances and orientation of the drugs within the binding sites of the cytochrome enzymes responsible for the responsible metabolism of these drugs by aromatic or cycloalkyl hydroxylation.

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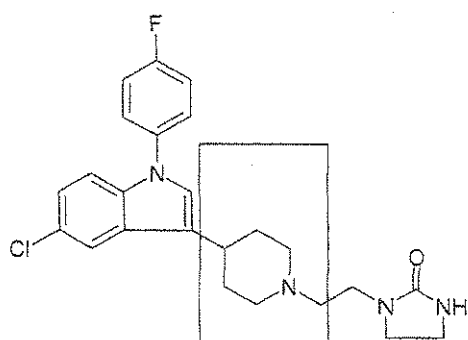
Cisapride

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Astemizole

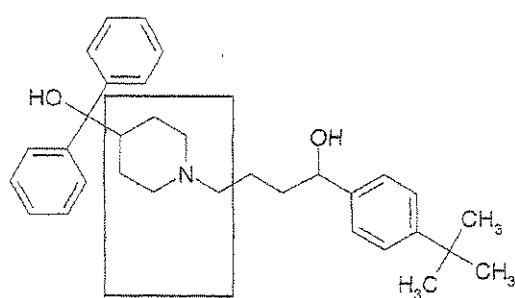
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Sertindole

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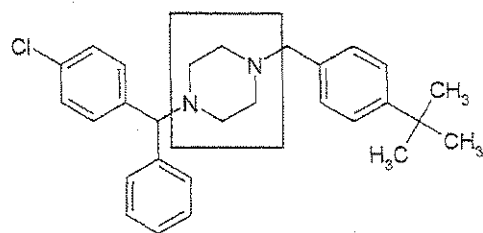
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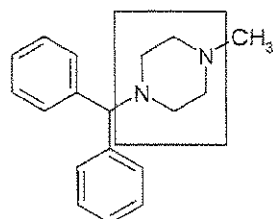
Terfenadine

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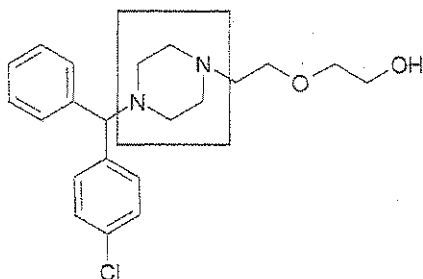
It is further believed that the chemically related piperazine chemical group with its tertiary amine contributes to cardiac conduction disturbances and orientation of the drugs within the binding sites of the cytochrome enzymes responsible for the responsible metabolism of these drugs by for aromatic or cycloalkyl hydroxylation. Pharmacologic agents containing a piperazine group known to cause cardiac conduction disturbances include buclizine, buspirone, cyclizine, doxazosin, fluphenazine, gepirone, hydroxyzine, itraconazole, ketoconazole, loxapine, meclizine, olanzapine, perphenazine, quetiapine, trazadone, nefazadone and ziprasidone. By way of example, the chemical structures of a series of pharmacological compounds containing a piperazine moiety and having antihistamine activity are shown below:



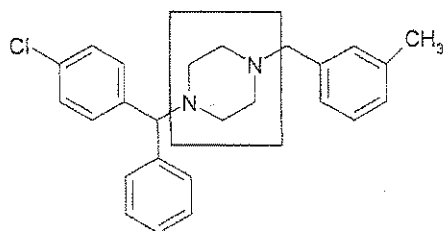
Bucizine



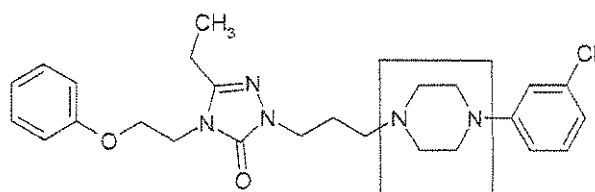
Cyclizine



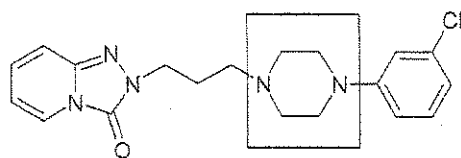
Hydroxyzine



Meclizine

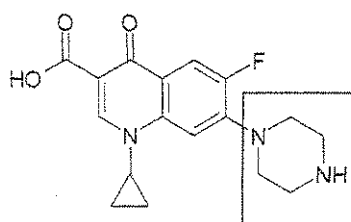


Nefazodone

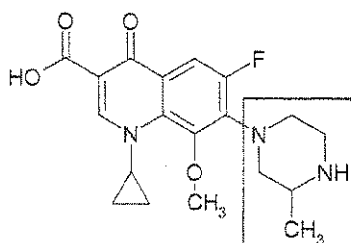


Trazadone

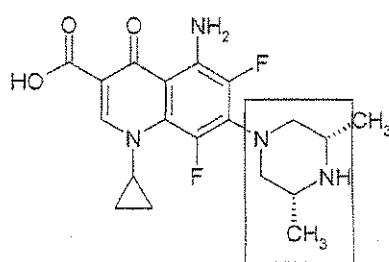
Fluoroquinolone antibiotics are pharmacologic agents containing a piperazine group known to cause serious cardiac conduction disturbances and torsade de pointes. Fluoroquinolone antibiotics approved for marketing and having a secondary amine on the piperazine ring include norfloxacin, lomefloxacin, ciprofloxacin, enoxacin, 5 gatifloxacin, sparfloxacin, temafloxacin, grepafloxacin and moxifloxacin. Several of these fluoroquinolone agents have already been removed from the market because of life-threatening cardiac conduction disturbance or torsade de pointes. By way of example, the chemical structures of a series of fluoroquinolone compounds containing a 10 secondary amine on the piperazine moiety are shown below:



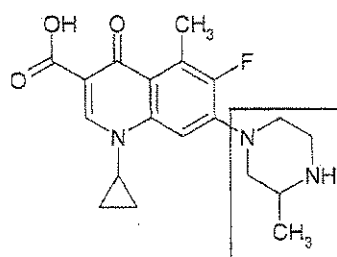
Ciprofloxacin



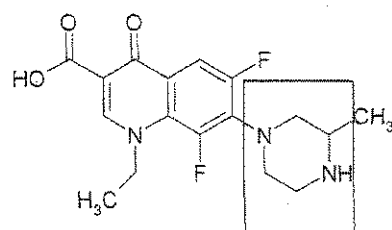
Gatifloxacin



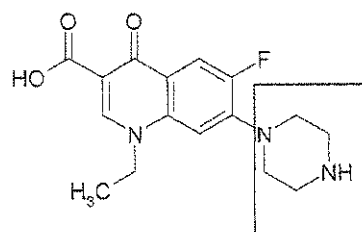
Sparfloxacin



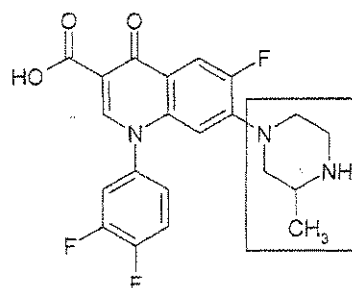
Grepafloxacin



Lomefloxacin

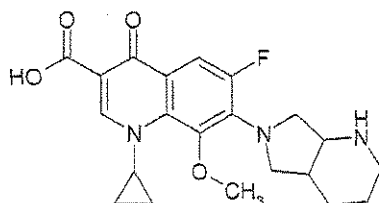


Norfloxacin



Temafloxacin

Fluoroquinolone antibiotics approved for marketing and having a secondary amine on the piperidine ring include moxifloxacin as shown below:



Moxifloxacin

It is therefore an object of the present invention to provide non-cardiotoxic pharmacologically active compounds having modulated cytochrome P 450 metabolism.

It is a further object of the invention to provide non-cardiotoxic pharmacologically active compounds having reduced metabolism by cytochrome P450 2D6.

It is a further object of the invention is to provide non-cardiotoxic prodrugs of pharmacologically active compounds having modulated cytochrome P 450 metabolism.

It is a further object of the invention to provide non-cardiotoxic pharmacologically active compounds having reduced metabolism by cytochrome P450 2D6 and cytochrome P450 3A4.

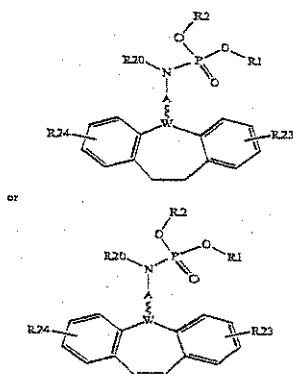
A further object of the invention is to provide non-cardiotoxic prodrugs that will modify the physicochemical properties of tertiary amine-containing drugs such that these drugs will exhibit reduced binding to the CYP2D6 metabolizing enzymes during first-pass absorption.

A further object of the invention is to provide non-cardiotoxic prodrugs that can be hydrolyzed in the plasma after absorption and be converted directly to the therapeutically active form of the parent compounds.

A further object of the invention is to provide non-cardiotoxic prodrugs that lower the pKa of the tertiary amine group to a level such that the majority of the tertiary amine is uncharged at physiological pH (pH 7.4). For example, imipramine has pKa of 9.5 and is completely ionized as it is transported through the gastrointestinal tract. After oral ingestion, imipramine is rapidly and completely absorbed from the small intestine, with peak plasma concentration within two to five hours. Imipramine is subject to extensive first-pass metabolism in the liver, and is eliminated by demethylation to the active metabolite, desipramine and to a lesser extent by aromatic hydroxylation to 2-hydroxyimipramine. Desipramine, in turn, is metabolized by aromatic hydroxylation to 2-hydroxydesipramine. The systemic availability of imipramine in healthy subjects ranges from 27% to 80% and the corresponding first-pass metabolism ranges from 20% to 73%. Imipramine-N-oxide, a nitrogen-atom prodrug of imipramine which has a pKa of about 4.7, has a systemic availability of about 100% after oral administration suggesting that there is no first pass effect. Both preclinical and clinical studies have shown that the cardiotoxicity of imipramine-N-oxide is significantly reduced over that of imipramine.

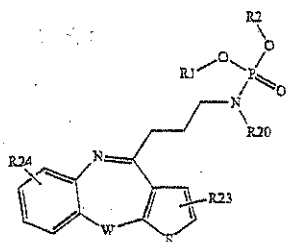
Summary

In a first aspect, there is provided a pharmaceutical composition comprising a compound having the formula



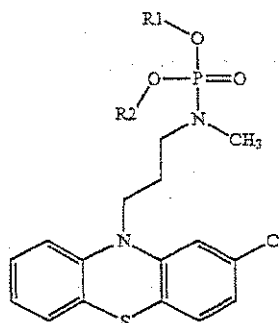
where R₁ and R₂ are independently hydrogen, alkyl having from 1 to about 7 carbon atoms, aryl, aralkyl, or cycloalkyl having from 3 to about 6 carbon atoms, A is a lower alkyl, lower heteroalkyl or cycloalkyl, R₂₀ is hydrogen, phenyl or lower alkyl, W is carbon or nitrogen, R₂₃ and R₂₄ are independently hydrogen, halogen, alkyl or alkoxy, and pharmaceutically acceptable salts thereof in combination with a pharmaceutically acceptable excipient, diluent or carrier suitable for delayed release oral administration.

In a second aspect, there is provided a pharmaceutical composition comprising a compound having the formula



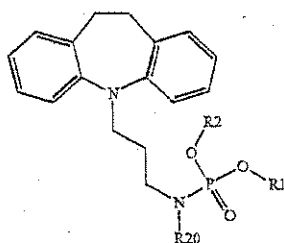
where R₁ and R₂ are independently hydrogen, alkyl having from 1 to about 7 carbon atoms, aryl, aralkyl, or cycloalkyl having from 3 to about 6 carbon atoms, R₂₀ is hydrogen, phenyl or lower alkyl, W is carbon or nitrogen, R₂₃ and R₂₄ are independently hydrogen, halogen, alkyl or alkoxy, and pharmaceutically acceptable salts thereby in combination with a pharmaceutically acceptable excipient, diluent or carrier suitable for delayed release oral administration.

In a third aspect, there is provided a pharmaceutical composition comprising a compound having the formula



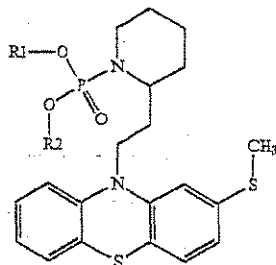
where R₁ and R₂ are independently hydrogen, alkyl having from 1 to about 7 carbon atoms, aryl, aralkyl, or cycloalkyl having from 3 to about 6 carbon atoms, and pharmaceutically acceptable salts thereof in combination with a pharmaceutically acceptable excipient, diluent or carrier suitable for delayed release oral administration.

In a fourth aspect, there is provided a pharmaceutical composition comprising a compound having the formula



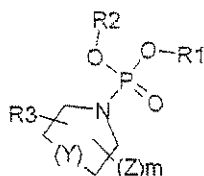
where R₁ and R₂ are independently hydrogen, alkyl having from 1 to about 7 carbon atoms, aryl, aralkyl, or cycloalkyl having from 3 to about 6 carbon atoms, R₂₀ is hydrogen phenyl or lower alkyl and pharmaceutically acceptable salts thereof in combination with a pharmaceutically acceptable excipient, diluent or carrier suitable for delayed release oral administration.

In a fifth aspect, there is provided a pharmaceutical composition comprising a compound having the formula



where R₁ and R₂ are independently hydrogen, alkyl having from 1 to about 7 carbon atoms, aryl, aralkyl, and cycloalkyl having from 3 to about 6 carbon atoms, and pharmaceutically acceptable salts thereof in combination with a pharmaceutically acceptable excipient, diluent or carrier suitable for delayed release oral administration.

- 5 In accordance with the present disclosure, disclosed are enzyme-labile compounds having the formula



- 10 where R_1 and R_2 are independently hydrogen, alkyl having from 1 to about 7 carbon atoms, aryl, aralkyl, and cycloalkyl having from about 3 to about 6 carbon atoms, Y is $(CH_2)_n$ where n is from 0 to 2, Z is alkyl, alkoxy, aryloxy, or alkylaryloxy where m is from 0 to about 4, and R_3 is selected from the group consisting of substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkylaryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkylaryloxy, substituted or unsubstituted indole, substituted or unsubstituted phenothiazine, substituted or unsubstituted dibenzoxazepine, substituted or unsubstituted dibenzothiazepine, substituted or unsubstituted oxophthalazine, substituted or unsubstituted quinoline, substituted or unsubstituted dihydroquinoline, substituted or unsubstituted benzodiazepine, substituted or unsubstituted benzocycloheptapyridine, substituted or unsubstituted carbazol, substituted or unsubstituted tetrahydrocarbazols, substituted or unsubstituted dibenzocycloheptenes, substituted or unsubstituted benzimidazoles, substituted or unsubstituted piperazines, substituted or unsubstituted benzamides, substituted or unsubstituted benzhydrol, and substituted or unsubstituted diazabenzoazulene, substituted or unsubstituted oxobenzimidazole, 3,4 pyrrolo-dihydroquinoline, carbamoyl-2,3,4,9-tetrahydro-cabazol, and pharmaceutically acceptable salts thereof.

- 30 These enzyme-labile compounds, having lower pK_a values than their corresponding secondary and tertiary amines, have significantly reduced cardiotoxicity than those secondary and tertiary amines from which they are derived. The compounds of the

present disclosure are useful as gastrointestinal, antiinfective, antidepressant, antihistaminic, antipsychotic, antineoplastic and cardiovascular therapeutic agents.

Detailed Description of the Invention

5 In accordance with the present invention, disclosed are enzyme-labile prodrugs having a modified ionization potential (pKa) of the nitrogen atoms such that they are significantly less basic than on the highly basic nitrogen atoms of the parent drugs. In accordance with the present invention we describe chemical modifications of the highly basic that amines include formation of phosphoramidates which are stable toward hydrolysis in the
10 intestine and plasma. Phosphoramidates are non-toxic organophosphorous compounds containing phosphorous-nitrogen bonds.

An unexpected advantage of these organophosphorous compounds over the N-oxides is that they are enzyme-labile and are selectively hydrolyzed after passage through the
15 intestine to the pharmacologically active drug moiety. Unlike other prodrug technologies employing esters, phosphonates and peptide bonds, which are hydrolyzed by esterases, phosphatases and peptidases in the intestine, enterocytes, hepatic cells and plasma, the organophosphorous compounds of the present invention are stable in the intestine and the enterocytes and plasma.

20 In agreement with a limited number of published studies, we have shown that the hydroxymetabolites of several secondary and tertiary amine-containing drugs are primarily responsible for the cardiotoxicity and not the parent compound. In Langendorff isolated perfused rabbit heart studies we have demonstrated that the
25 hydroxymetabolites demonstrated dose-dependent significant increases in cardiac conductance, notably in PR interval prolongation, QRS interval prolongation and QT interval prolongation at clinically relevant doses. None of these changes were accompanied by observed conductance changes associated with K⁺ channel blockade. In receptor binding studies, no differences were noted in the affinity of the
30 hydroxymetabolites and the parent drugs toward the voltage operated L-type calcium channel receptors or the Herg receptors of the K⁺ channel.

In accordance with the present invention, we describe enzyme-labile prodrugs of the secondary and tertiary amine moiety that mask the enzyme(s) primarily responsible for
35 the production of these hydroxymetabolites in the liver. We describe enzyme-labile

prodrugs of secondary and tertiary amine-containing drugs that are not substrates of cytochrome P450 CYP2D6. We describe enzyme-labile prodrugs of secondary and tertiary amine-containing drugs having minimal capacity for aromatic hydroxylation or first-pass metabolism to the cardiotoxic hydroxymetabolites. These enzyme-label

5 prodrugs are expected to be rapidly converted in the systemic circulation to the pharmacologically active form of the secondary and tertiary amine-containing drugs which are then metabolized under much lower systemic plasma concentrations that are not as likely to produce severe cardiotoxicity.

10 These enzyme-labile prodrugs modulate the physicochemical properties of secondary and tertiary amine-containing drugs such that these drugs do not bind to the cytochrome P450 2D6 metabolizing enzymes during first-pass absorption at physiological pH. The nitrogen atoms on these enzyme-labile prodrugs are significantly less basic ($pK_a < 5.4$) than on the highly basic nitrogen atoms of the parent drugs ($pK_a \sim 9.5$). Because these

15 prodrugs are enzyme-labile, they can be hydrolyzed in the body after absorption directly to the non-cardiotoxic therapeutically active compounds. It is anticipated that specific therapeutic areas covered by this technology include, among others, all types of antidepressants, antihistamines, antipsychotics, gastrointestinal and several classes of antiinfective drugs. In a preferred embodiment of the present invention, chemical

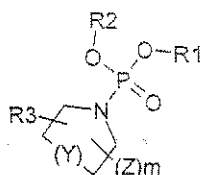
20 modification of the highly basic amines of known cardiotoxic drugs includes formation of phosphoramidates whose hydrolysis is primarily restricted to the liver and are stable in the intestine and plasma. Phosphoramidates are organophosphorous compounds containing phosphorous-nitrogen bonds.

A partial list of therapeutic compounds having a highly basic nitrogen atom that have reported cases of QT interval prolongation, *torsade de pointes* or both and their corresponding pKa values include the following: dextromethorphan (9.20), methadone (8.25), propoxyphene (8.91), tramadol (9.41), amoxapine (7.60), citalopram (9.50), clomipramine (9.50), desipramine (10.40), doxepin (8.00), duloxetine (10.00), escitalopram (9.60), femoxetine (9.00), fluoxetine (8.70), maprotiline (10.20), mianserin (8.26), mirtazapine (8.10), nefazodone (7.90), nortriptyline (10.10), paroxetine (9.90), selegiline (7.53), sertraline (9.50), venlafaxine (9.40), zimeldine (8.00), astemizole (9.90), azelastine (9.06), chlorpheniramine (9.20), chlorphenoxamine (8.21), clemastine (10.23), desloratadine (9.40), diphenhydramine (9.00), doxylamine (9.30), fexofenadine (9.53), promethazine (9.10), terfenadine (9.60), ciprofloxacin (7.68), halofantrine (9.60), levofloxacin (7.09), moxifloxacin (10.01), ofloxacin (7.09), rimantadine (11.70), tamoxifen (8.85), chlorpromazine (9.30), clozapine (8.20), loxapine (7.64), nortriptyline (10.61), olanzapine (6.37), risperidone (8.24), sertindole (9.06), thioridazine (9.50), trifluoperazine (7.98), ziprasidone (8.24), amphetamine (9.90), atomoxetine (10.12), carbamazepine (7.00), cyclobenzaprine (9.21), fenfluramine (9.92), methamphetamine (10.28), methylphenidate (8.90), oxybutynin (6.96), phenytoin (8.31), sibutramine (9.36), tolterodine (9.87), cimetidine (6.80), cisapride (7.04), cyclizine (8.35), meclizine (7.32), norcispripide (8.46), ranitidine (8.20), almotriptan (9.58), eletriptan (10.13), frovatriptan (10.63), naratriptan (9.74), rizatriptan (9.49), sumatriptan (9.50), and Zolmitriptan (9.52).

In accordance with a preferred embodiment of the present invention, the pharmaceutical formulations comprise phosphoramidate-based prodrugs having pKa of less than about 5.4. In accordance with a more preferred embodiment of the present invention, the pharmaceutical formulations comprise phosphoramidate-based prodrugs having pKa values in the range from about 1 to about 5. In yet an even more preferred embodiment of the present invention, the phosphoramidate-based prodrugs have a pKa less than 4. It will be appreciated by those skilled in the art that this reduction in pKa represents a considerable difference in the proportion of positively charged amines present at physiological pH compared to the highly basic amine parent drugs.

Pharmaceutical compounds in accordance with the present invention have considerable similarity because of the similar pharmacologic requirements for therapeutic activity. Accordingly, the chemical structures of the enzyme-labile prodrugs can be characterized by a few general structure types. The first type include those containing cyclic aliphatic groups such as piperidine and piperazine containing a secondary or tertiary nitrogen atom such as found in amoxapine, and another type includes those having and alkylamine group such as found in imipramine.

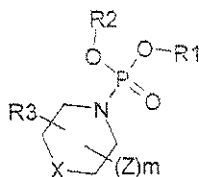
In accordance with one embodiment of the present invention, compounds have the formula



where R_1 and R_2 are independently hydrogen, alkyl having from 1 to about 7 carbon atoms, aryl, aralkyl, and cycloalkyl having from about 3 to about 6 carbon atoms, Y is $(CH_2)_n$ where n is from 0 to 2, Z is alkyl, alkoxy, aryloxy, or alkylaryloxy where m is from 0 to about 4, and R_3 is selected from the group consisting of substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkylaryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkylaryloxy, substituted or unsubstituted indole, substituted or unsubstituted phenothiazine, substituted or unsubstituted dibenzoxazepine, substituted or unsubstituted dibenzothiazepine, substituted or unsubstituted oxophthalazine, substituted or unsubstituted quinoline, substituted or unsubstituted dihydroquinoline, substituted or unsubstituted benzodiazepine, substituted or unsubstituted benzocycloheptapyridine, substituted or unsubstituted carbazol, substituted or unsubstituted tetrahydrocarbazols, substituted or unsubstituted dibenzocycloheptenes, substituted or unsubstituted benzimidazoles, substituted or unsubstituted piperazines, substituted or unsubstituted benzamides, substituted or unsubstituted benzhydrol, and substituted or unsubstituted diazabenzoazulene, substituted or unsubstituted oxobenzimidazole, 3,4 pyrrolo-dihydroquinoline, carbamoyl-2,3,4,9-tetrahydro-carbazol, and pharmaceutically acceptable salts thereof. In accordance with a preferred embodiment of the present

invention, n is 2. In a more preferred embodiment of the present invention, n is 2 and m is from 0 to 3.

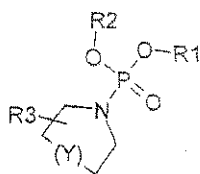
In accordance with another embodiment of the present invention, compounds have the
5 formula



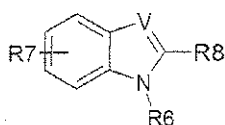
- 10 where R_1 and R_2 are independently hydrogen, alkyl having from 1 to about 7 carbon atoms, aryl, aralkyl, and cycloalkyl having from about 3 to about 6 carbon, X is oxygen, nitrogen or carbon, and m is from 0 to about 3.

Another type of compound in accordance with the present invention has the formula

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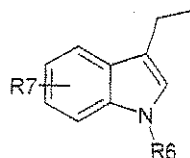


where R_3 is a group having the formula



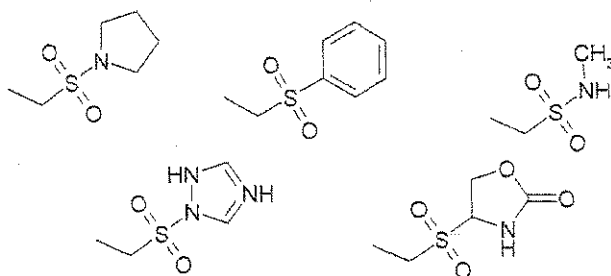
- 20 where V is carbon or nitrogen, R_6 is hydrogen, alkyl, aryl or aralkyl, R_7 is hydrogen, alkyl, aralkyl, cycloalkyl, alkylcycloalkyl, alkylsulfonylcycloalkyl, alkylsulfonylaryl, alkylsulfonylaminoalkyl or alkylsulfonylalkyl and R_8 is hydrogen, carbonyl or a direct bond.

Preferred compounds in accordance with this embodiment of the present invention include those where R_3 has the formula



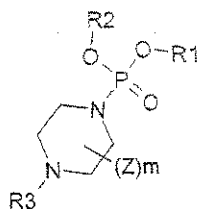
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In accordance with the present invention, R_7 is preferably selected from the group consisting of:



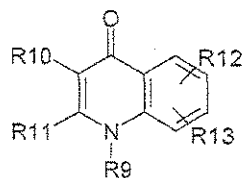
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In yet another embodiment of the present invention, the compounds have the formula



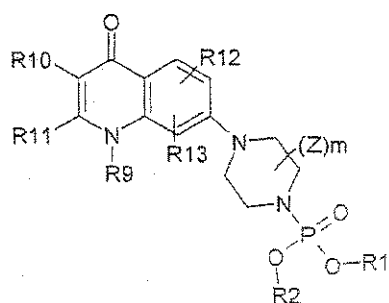
where R_3 is a group having the formula

15



where R_9 and R_{11} are hydrogen, alkyl, aryl, alkylaryl, cycloalkyl or together form a cycloalkyl or cycloheteroalkyl group, and R_{10} is hydrogen, alkyl or a carboxylic acid group, and R_{12} and R_{13} are independently hydrogen, halogen, alkyl, alkoxy or amino.

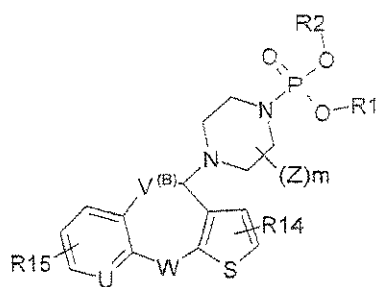
5 In a preferred embodiment of the present invention the compounds have the formula



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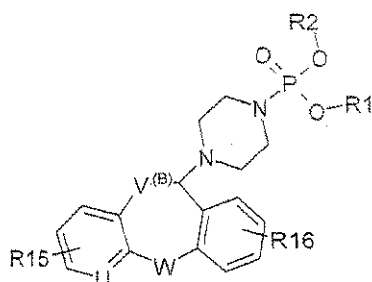
In another embodiment of the present invention the compounds have the formula



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where V is carbon or nitrogen, W is carbon, nitrogen or oxygen, U is carbon or nitrogen, B is a single or double bond, and R₁₄ and R₁₅ are independently hydrogen, halogen, or alkyl.

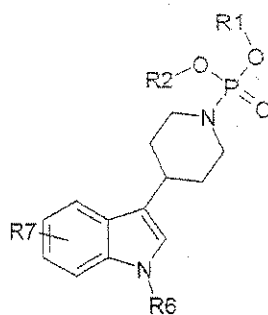
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where V is carbon or nitrogen, W is carbon, nitrogen or oxygen, U is carbon or nitrogen,
10 B is a single or double bond, and R₁₅ and R₁₆ are independently hydrogen, halogen or alkyl.

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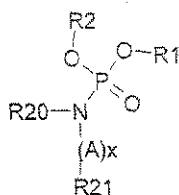
In still another embodiment of the present invention, the compounds have the formula



20

where R_6 is hydrogen, alkyl, alkylaryl or aralkyl, and R_7 is hydrogen, alkyl, aralkyl, cycloalkyl, alkylcycloalkyl, alkylsulfonylcycloalkyl, alkylsulfonylaryl, alkylsulfonylaminoalkyl or alkylsulfonylalkyl.

- 5 Another type includes those containing short linear aliphatic chains depending from a nitrogen atom such as those found with imipramine.

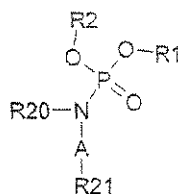


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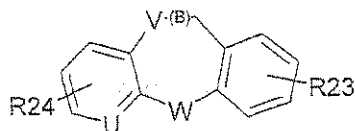
- In accordance with this aspect of the present invention, R_1 and R_2 are independently
 15 hydrogen, alkyl having from 1 to about 7 carbon atoms including but not limited to methyl, ethyl, propyl, butyl, isobutyl, and pentyl, aryl including but not limited to phenyl and pyridinyl, aralkyl such as benzyl, and cycloalkyl having from about 3 to about 6 carbon atoms including but not limited to cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl, A is a lower alkyl, lower heteroalkyl, carbonyl or cycloalkyl, X is 0 or 1, R_1
 20 and R_2 are independently hydrogen, alkyl having from 1 to about 7 carbon atoms, aryl, aralkyl, and cycloalkyl having from about 3 to about 6 carbon atoms, R_{20} is hydrogen, phenyl or lower alkyl, and R_{21} is selected from the group consisting of substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted alkylaryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted
 25 alkylaryoxy, substituted or unsubstituted indole, substituted or unsubstituted phenothiazine, substituted or unsubstituted dibenzoxazepine, substituted or unsubstituted dibenzathiazepine, substituted or unsubstituted oxophthalazine, substituted or unsubstituted quinoline, substituted or unsubstituted dihydroquinoline, substituted or unsubstituted dibenzodiazepine, substituted or unsubstituted benzocycloheptapyridine,
 30 substituted or unsubstituted carbazol, substituted or unsubstituted tetrahydrocarbazols, substituted or unsubstituted dibenzocycloheptenes, substituted or unsubstituted

benzoimidazoles, substituted or unsubstituted piperazines, substituted or unsubstituted benzamides, substituted or unsubstituted benzhydrol, and substituted or unsubstituted diazabenzazulene, substituted or unsubstituted oxobenzimidazole, 3,4 pyrrolo-dihydroquinoline, carbamoyl-2,3,4,9-tetrahydro-cabazol, and pharmaceutically acceptable salts thereof.

In accordance with another embodiment of the present invention, the compounds have the formula

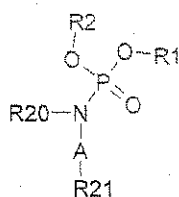


where A is a lower alkyl, lower heteroalkyl or cycloalkyl, R₂₀ is hydrogen, phenyl or lower alkyl and R₂₁ is a group having the formula



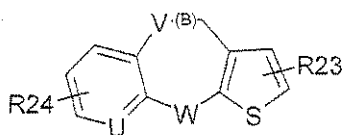
where V is carbon or nitrogen, W is carbon, nitrogen or oxygen, U is carbon or nitrogen, R₂₃ and R₂₄ are independently hydrogen, halogen, alkyl or alkoxy, and B is a single or double bond.

In accordance with another aspect of the present invention, the compounds have the formula



where A is a lower alkyl, lower heteroalkyl or cycloalkyl, R₂₀ is hydrogen, phenyl or lower alkyl and R₂₁ is a group having the formula

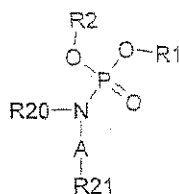
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where V is carbon or nitrogen, W is carbon, nitrogen or oxygen, U is carbon or nitrogen, R₂₃ and R₂₄ are independently hydrogen, halogen, alkyl or alkoxy, and B is a single or double bond.

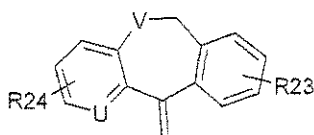
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In accordance with another embodiment of the present invention, the compounds have the formula



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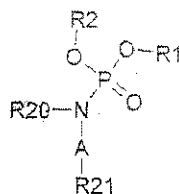
where A is a lower alkyl, lower heteroalkyl or cycloalkyl, R₂₀ is hydrogen, phenyl or lower alkyl and R₂₁ is a group having the formula



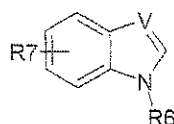
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where V is carbon or nitrogen, U is carbon or nitrogen, R₂₃ and R₂₄ are independently hydrogen, halogen, alkyl or alkoxy, and B is a single or double bond.

5 In accordance with another embodiment of the present invention, the compounds have the formula

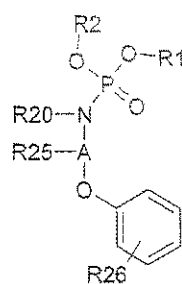


10 where A is a lower alkyl, lower heteroalkyl or cycloalkyl, R₂₀ is hydrogen, phenyl or lower alkyl and R₂₁ is a group having the formula



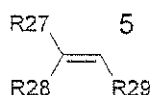
15 where V is carbon or nitrogen, R₆ is hydrogen, alkyl, aryl or aralkyl, and R₇ is hydrogen, halogen, aralkyl, cycloalkyl, alkylcycloalkyl, alkylsulfonylcycloalkyl, alkylsulfonylaryl, alkylsulfonylaminoalkyl or alkylsulfonylalkyl.

In accordance with another embodiment of the present invention, the compounds have the formula



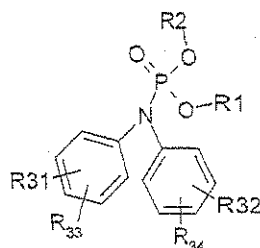
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where A is a lower alkyl, lower heteroalkyl or cycloalkyl, R₂₀ is hydrogen, phenyl or lower alkyl, R₂₆ is hydrogen, alkyl, alkoxy, alkylaryl, alkenylaryl, halogen, halogen-substituted alkyl, alkylaryloxy, alkanoyl, arylalkanoyl, or a group having the formula



where R₂₇, R₂₈ and R₂₉ are independently substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted aralkyl, substituted or unsubstituted alkylaryl, substituted or unsubstituted cycloalkyl or substituted or unsubstituted heterocycloalkyl, and R₂₅ is hydrogen, hydroxy, alkyl, alkylaryl, aryl, cycloalkyl or heteroaryl.

In accordance with another embodiment of the present invention, the compounds have the formula



where R₃₁, R₃₂, R₃₃, R₃₄ are independently hydrogen, halogen, alkyl, alkoxy or a group having the formula (CH₂)_nCOOH where n = 1 to about 5.

Unless otherwise specifically identified or claimed for preferred embodiments, the following general definitions are used in accordance with the present invention.

"Alkyl" refers to a branched or straight chain acyclic alkyl group comprising one to about ten carbon atoms, a haloalkyl group, an alkenyl group, an alkynyl group, a bridged cycloalkyl group, a cycloalkyl group or a heterocyclic ring.

"Lower alkyl" refers to a branched or straight chain acyclic alkyl group comprising one to about six carbon atoms. In accordance with the present invention, lower alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, pentyl, neopentyl, iso-amyl, hexyl, and the like.

5

"Haloalkyl" refers to a lower alkyl group, an alkenyl group, an alkynyl group, a bridged cycloalkyl group, a cycloalkyl group or a heterocyclic ring, to which is appended one or more halogens, as defined herein. Exemplary haloalkyl groups include trifluoromethyl, chloromethyl, 2-bromobutyl, 1-bromo-2-chloro-pentyl, and the like.

10

"Alkenyl" refers to a branched or straight chain C_2 - C_{10} hydrocarbon which can comprise one or more carbon-carbon double bonds. In accordance with the present invention, alkenyl groups include propylenyl, buten-1-yl, isobutenyl, penten-1-yl, 2, 2-methylbuten-1-yl, 3-methylbuten-1-yl, hexan-1-yl, hepten-1-yl, octen-1-yl, and the like.

15

"Alkynyl" refers to an unsaturated acyclic C_2 - C_{10} hydrocarbon which can comprise one or more carbon-carbon triple bonds. In accordance with the present invention, alkynyl groups include ethynyl, propynyl, butyn-1-yl, butyn-2-yl, pentyl-1-yl, pentyl-2-yl, 3-methylbutyn-1-yl, hexyl-1-yl, hexyl-2-yl, hexyl-3-yl, 3,3-dimethyl-butyn-1-yl, and the like.

20

"Cycloalkyl" refers to a saturated or unsaturated cyclic hydrocarbon comprising from about 3 to about 8 carbon atoms. Cycloalkyl groups can be unsubstituted or substituted with one, two or three substituents independently selected from alkyl, alkoxy, amino, alkylamino, dialkylamino, arylamino, diarylamino, alkylarylamino, aryl, amidyl, ester, hydroxy, halo, carboxyl, alkylcarboxylic acid, alkylcarboxylic ester, carboxamido, alkylcarboxamido, oxo and nitro. In accordance with the present invention, cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, cycloheptyl and the like.

25

30 "Heterocyclic ring or group" refers to a saturated, unsaturated, cyclic or aromatic or polycyclic hydrocarbon group having about 3 to about 7 carbon atoms where 1 to about 4 carbon atoms are replaced by one or more nitrogen, oxygen and/or sulfur atoms. Sulfur maybe in the thio, sulfinyl or sulfonyl oxidation state. The heterocyclic ring or group can be fused to an aromatic hydrocarbon group. Heterocyclic groups can be

unsubstituted or substituted with one, two or three substituents independently selected from alkyl, alkoxy, amino, alkylamino, dialkylamino, arylamino, diarylamino, alkylarylamino, hydroxy, oxo, thial, halo, carboxyl, carboxylic ester, alkylcarboxylic acid, alkylcarboxylic ester, aryl, arylcarboxylic acid, arylcarboxylic ester, amidyl, ester, 5 carboxamido, alkylcarboxamido, arylcarboxamido, sulfonic acid, sulfonic ester, sulfonamido and nitro. In accordance with the present invention, heterocyclic groups include pyrrolyl, 3-pyrrolyl, 4,5,6-trihydro-2H-pyranyl, pyridinyl, 1,4-dihydropyridinyl, pyrazolyl, triazolyl, pyrimidinyl, pyridazinyl, oxazolyl, thiazolyl, imidazolyl, indolyl, thiophenyl, furanyl, tetrahydrofuranyl, tetrazolyl, 2-pyrrolyl, 3-pyrrolyl, pyrrolidinyl, 10 oxazolindinyl, 1,3-dioxolanyl, 2,6-dioxabicydo[3,3,0]octanyl, 2-imidazonlinyl, imidazolindinyl, 2-pyrazolinyl, pyrazolidinyl, isoxazolyl, isothiazolyl, 1,2,3-oxadiazolyl, 1,2,3-triazolyl, 1,3,4-thiadiazolyl, 2H-pyranyl, 4H-pyranyl, piperidinyl, 1,4-dioxanyl, morpholinyl, 1,4-dithianyl, thiomorpholinyl, pyrazinyl, piperazinyl, 1,3,5-triazinyl, 1,3,5-trithianyl, benzo(b)thiophenyl, benzimidazolyl, quinolinyl, and the like. "Heterocyclic 15 compounds" refer to mono- and polycyclic compounds comprising at least one aryl or heterocyclic ring.

"Aryl" refers to a monocyclic, bicyclic, carbocyclic or heterocyclic ring system comprising one or two aromatic rings. In accordance with the present invention, aryl groups include 20 phenyl, pyridyl, naphthyl, quinoyl, tetrahydronaphthyl, furanyl, indanyl, indenyl, indoyl, and the like. Aryl groups (including bicyclic aryl groups) can be unsubstituted or substituted with one, two or three substituents independently selected from alkyl, alkoxy, amino, alkylamino, dialkylamino, arylamino, diarylamino, alkylarylamino, hydroxy, carboxyl, carboxylic ester, alkylcarboxylic acid, alkylcarboxylic ester, aryl, arylcarboxylic acid, 25 arylcarboxylic ester, alkylcarbonyl, arylcarbonyl, amidyl, ester, carboxamido, alkylcarboxamido, carbonyl, sulfonic acid, sulfonic ester, sulfonamido and nitro. In accordance with the present invention, substituted aryl groups include tetrafluorophenyl, pentafluorophenyl, sulfonamide, alkylsulfonyl, arylsulfonyl, and the like.

30 "Alkylaryl" refers to an alkyl group to which is appended an aryl group. In accordance with the present invention, alkylaryl groups include benzyl, phenylethyl, hydroxybenzyl, fluorobenzyl, fluorophenylethyl, and the like.

"Arylalkyl" refers to an aryl radical, attached to an alkyl radical in accordance with the present invention,

5 "Cycloalkylalkyl" refers to a cycloalkyl radical attached to an alkyl radical in accordance with the present invention,

"Alkoxy" refers to RO-, wherein R is an alkyl group in accordance with the present invention. In accordance with the present invention, alkoxy groups include methoxy, ethoxy, t-butoxy, cyclopentyloxy, and the like.

10 "Arylalkoxy or alkoxyaryl" refers to an alkoxy group, as defined herein, to which is appended an aryl group in accordance with the present invention. In accordance with the present invention, arylalkoxy groups include benzyloxy, phenylethoxy, chlorophenylethoxy, and the like.

15 "Alkoxyaryl refers to an alkoxy group, in accordance with the present invention, appended to an alkyl group. In accordance with the present invention, alkoxyaryl groups include methoxymethyl, methoxyethyl, isopropoxymethyl, and the like.

20 In accordance with the present invention, R₁ is hydrogen, an alkyl having from 1 to about 5 carbon atoms including but not limited to methyl, ethyl, propyl, butyl, isopropyl, isobutyl, and pentyl, an aryl including but not limited to phenyl, aralkyl such as benzyl, or cycloalkyl having from about 3 to about 6 carbon atoms including but not limited to
25 cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

In accordance with a preferred embodiment of the present invention R₂ is hydrogen, lower alkyl including but not limited to methoxy and ethoxy. In accordance with a more preferred embodiment of the present invention, R₂ is hydrogen or OCH₃.

30 In accordance with a preferred embodiment of the present invention R₁ and R₂ are independently hydrogen, methyl, ethyl, propyl or phenyl. In accordance with a more preferred embodiment of the present invention, R₁ is methyl, ethyl or phenyl and R₂ is

hydrogen. In accordance with a most preferred embodiment of the present invention, R₁ and R₂ are both ethyl.

5 Illustrative compounds in accordance with a most preferred embodiment of the present invention include the following:

Methyl-[2-[6-(pyrrolidine-1-sulfonylmethyl)-1H-indol-3-yl]-ethyl]-phosphoramidic acid diethyl ester

[4-(2-Chloro-dibenzo[b,f][1,4]oxazepin-11-yl)-piperazin-1-yl]-phosphonic acid diethyl ester

(1-Methyl-2-phenyl-ethyl)-phosphoramidic acid diethyl ester

Methyl-(3-phenyl-3-o-tolyloxy-propyl)-phosphoramidic acid diethyl ester

{4-[4-(3-Chloro-benzyl)-1-oxo-1H-phthalazin-2-yl]-azepan-1-yl}-phosphonic acid diethyl ester

(Dibenzo[b,f]azepine-5-carbonyl)-phosphoramidic acid diethyl ester

[3-(4-Chloro-phenyl)-3-pyridin-2-yl-propyl]-methyl-phosphoramidic acid diethyl ester

{2-[1-(4-Chloro-phenyl)-1-phenyl-ethoxy]-ethyl}-methyl-phosphoramidic acid diethyl ester

[3-(2-Chloro-phenothiazin-10-yl)-propyl]-methyl-phosphoramidic acid diethyl ester

1-Cyclopropyl-7-[4-(diethoxy-phosphoryl)-piperazin-1-yl]-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid

{3-[5-Cyano-1-(4-fluoro-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-propyl}-methyl-phosphoramidic acid diethyl ester

[4-(8-Chloro-5H-dibenzo[b,e][1,4]diazepin-11-yl)-piperazin-1-yl]-phosphonic acid diethyl ester

(3-Dibenzo[a,d]cyclohepten-5-ylidene-propyl)-methyl-phosphoramidic acid diethyl ester

[3-(10,11-Dihydro-dibenzo[b,f]azepin-5-yl)-propyl]-methyl-phosphoramidic acid diethyl ester

[4-(8-Chloro-5,6-dihydro-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)-piperidin-1-yl]-phosphonic acid diethyl ester

(6-Ethyl-8-methoxy-11-propyl-1,2,5,6-tetrahydro-4H-2,6-methano-benzo[d]azocin-3-yl)-phosphonic acid diethyl ester

{2-[(2,6-Dichloro-phenyl)-(diethoxy-phosphoryl)-amino]-phenyl}-acetic acid

[3-(6H-Dibenzo[b,e]oxepin-11-ylidene)-propyl]-methyl-phosphoramidic acid diethyl ester

Methyl-[2-(1-phenyl-1-pyridin-2-yl-ethoxy)-ethyl]-phosphoramidic acid diethyl ester

Methyl-[2-(naphthalen-1-yloxy)-2-thiophen-2-yl-ethyl]-phosphoramidic acid diethyl ester

{2-[5-(2-Benzenesulfonyl-ethyl)-1H-indol-3-ylmethyl]-pyrrolidin-1-yl}-phosphonic acid diethyl ester

(2-Hydroxy-1-methyl-2-phenyl-ethyl)-methyl-phosphoramidic acid diethyl ester

{3-[5-Cyano-1-(4-fluoro-phenyl)-1,3-dihydro- isobenzofuran-11(S)-yl]-propyl}-methyl-phosphoramidic acid diethyl ester

[3-(4-Methoxy-phenoxy-methyl)-4-phenyl-piperidin-1-yl]-phosphonic acid diethyl ester

Ethyl-[1-methyl-2-(3-trifluoromethyl-phenyl)-ethyl]-phosphoramidic acid diethyl ester

Ethyl-[2-phenyl-2-(4-trifluoromethyl-phenoxy)-ethyl]-phosphoramidic acid diethyl ester

(6-Carbamoyl-2,3,4,9-tetrahydro-1H-carbazol-3-yl)-methyl-phosphoramidic acid diethyl ester

6H-benzofuro[3a,3,2-ef][2]benzazepin-6-ol,4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-, (4aS,6-R,8aS)-phosphoramidic acid diethyl ester

1-Cyclopropyl-7-[4-(diethoxy-phosphoryl)-3-methyl-piperazin-1-yl]-6-fluoro-8-methoxy-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid

1-Cyclopropyl-7-[4-(diethoxy-phosphoryl)-3-methyl-piperazin-1-yl]-6-fluoro-5-methyl-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid

Butyl-[3-(6,8-dichloro-3-trifluoromethyl-phenanthren-9-yl)-3-hydroxy-propyl]-phosphoramidic acid diethyl ester

9-[4-(Diethoxy-phosphoryl)-piperazin-1-yl]-8-fluoro-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalene-5-carboxylic acid

7-[4-(Diethoxy-phosphoryl)-3-methyl-piperazin-1-yl]-1-ethyl-6,8-difluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid

[4-(8-Chloro-dibenzo[b,f][1,4]oxazepin-11-yl)-piperazin-1-yl]-phosphonic acid diethyl ester

[9,10-ethanoanthracene-9(10H)-propylamine]-methyl phosphoramidic acid diethyl ester

(2-Benzo[1,3]dioxol-5-yl-1-methyl-ethyl)-methyl-phosphoramidic acid diethyl ester

[4-(3-Chloro-phenyl)-piperazin-1-yl]-phosphonic acid diethyl ester

Methyl-(1-methyl-4-oxo-3,3-diphenyl-hexyl)-phosphoramidic acid diethyl ester

Methyl-(1-methyl-2-phenyl-ethyl)-phosphoramidic acid diethyl ester

[1-(Diethoxy-phosphoryl)-piperidin-2-yl]-phenyl-acetic acid methyl ester

[2-(2-Methoxy-phenyl)-1-methyl-ethyl]-phosphoramidic acid diethyl ester

(3,4,9,13b-Tetrahydro-1H-2,4a-diaza-tribenzo [a,c,e]cyclohepten-2-yl)-phosphonic acid diethyl ester

(3,4,9,13b-Tetrahydro-1H-2,4a,5-triaza-tribenzo [a,c,e]cyclohepten-2-yl)-phosphonic acid diethyl ester

1-Cyclopropyl-7-[1-(diethoxy-phosphoryl)-octahydro-pyrrolo[3,4-b]pyridin-6-yl]-6-fluoro-8-methoxy-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid

[4-(6-Methylsulfamoylmethyl-1H-indol-3-yl)-piperidin-1-yl]-phosphonic acid diethyl ester

{4-[1-(4-Fluoro-benzyl)-1H-benzimidazol-2-ylamino]-piperidin-1-yl}-phosphonic acid diethyl ester

(4-Pyrimidin-2-yl-piperazin-1-yl)-phosphonic acid diethyl ester

[4-(4-Amino-5-chloro-2-methoxy-benzoylamino)-3-methoxy-piperidin-1-yl]-phosphonic acid diethyl ester

(4-Benzhydryl-piperazin-1-yl)-phosphonic acid diethyl ester

7-[4-(Diethoxy-phosphoryl)-piperazin-1-yl]-1-ethyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid

[4-(2-Oxo-2,3-dihydro-benzimidazol-1-yl)-piperidin-1-yl]-phosphonic acid diethyl ester

[3-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidene)-propyl]-methyl-phosphoramidic acid diethyl ester

{4-[5-Chloro-1-(4-fluoro-phenyl)-1H-indol-3-yl]-piperidin-1-yl}-phosphonic acid diethyl ester

[4-(2-Methyl-4H-3-thia-4,9-diaza-benzo[f]azulen-10-yl)-piperazin-1-yl]-phosphonic acid diethyl ester

Cyclohexyl-hydroxy-phenyl-acetic acid 3-[(diethoxy-phosphoryl)-ethyl-amino]-prop-1-ynyl ester

[3-(Benzo[1,3]dioxol-5-yloxymethyl)-4-(4-fluoro-phenyl)-piperidin-1-yl]-phosphonic acid diethyl ester

(Amino-carbamimidoylimino-methyl)-phenethyl-phosphoramidic acid diethyl ester

(2,5-Dioxo-4,4-diphenyl-imidazolidin-1-yl)-phosphonic acid diethyl ester

{2-Hydroxy-3-[2-(3-phenyl-propionyl)-phenoxy]-propyl}-propyl-phosphoramidic acid diethyl ester

{2-[(2-Ethoxy-phenoxy)-phenyl-methyl]-morpholin-4-yl}-phosphonic acid diethyl ester

(1-Adamantan-1-yl-ethyl)-phosphoramidic acid diethyl ester

Methyl-[2-(5-[1,2,4]triazol-1-ylmethyl-1H-indol-3-yl)-ethyl]-phosphoramidic acid dimethyl ester(1-Methyl-2-phenyl-ethyl)-prop-2-ynyl-phosphoramidic acid diethyl ester

[4-(3,4-Dichloro-phenyl)-1,2,3,4-tetrahydro-naphthalen-1-yl]-methyl-phosphoramidic acid diethyl ester

{1-[1-(4-Chloro-phenyl)-cyclobutyl]-3-methyl-butyl}-methyl-phosphoramidic acid diethyl ester

{1-[1-(4-Chloro-phenyl)-cyclobutyl]-3-methyl-butyl}-phosphoramidic acid diethyl ester

5-Amino-1-cyclopropyl-7-[4-(diethoxy-phosphoryl)-3,5-dimethyl-piperazin-1-yl]-6,8-difluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid

Methyl-[2-(5-methylsulfamoylmethyl-1H-indol-3-yl)-ethyl]-phosphoramidic acid diethyl ester

{2-[4-(1,2-Diphenyl-but-1-enyl)-phenoxy]-ethyl}-methyl-phosphoramidic acid diethyl ester

1-(3,4-Difluoro-phenyl)-7-[4-(diethoxy-phosphoryl)-3-methyl-piperazin-1-yl]-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid

{2-[2-(2-Methylsulfanyl-phenothiazin-10-yl)-ethyl]-piperidin-1-yl}-phosphonic acid diethyl ester

[2-Hydroxy-2-(3-methoxy-phenyl)-cyclohexylmethyl]-methyl-phosphoramidic acid diethyl ester

[3-Hydroxy-2-(4-methoxy-phenyl)-3-propyl-hexyl]-methyl-phosphoramidic acid diethyl ester

[3-(4-Bromo-phenyl)-3-pyridin-3-yl-allyl]-methyl-phosphoramidic acid diethyl ester

Methyl-{2-[5-(2-oxo-oxazolidin-4-ylmethyl)-1H-indol-3-yl]-ethyl}-phosphoramidic acid diethyl ester

The compounds of the present invention can be administered alone but will generally be administered in admixture with a suitable pharmaceutical excipient, diluent or carrier selected with regard to the intended route of administration and standard pharmaceutical practice. For example, the compounds of the present invention can be administered orally, in the form of tablets, capsules, multi-particulates, elixirs, solutions or suspensions, which may contain flavoring or coloring agents, either for immediate-, delayed-, modified-, sustained-, pulsed- or controlled-release applications. Suitable formulations of the compounds of the present invention may be in coated or uncoated form, as desired.

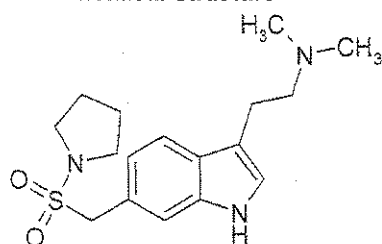
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Such solid pharmaceutical compositions, for example, tablets, may contain excipients such as microcrystalline cellulose, lactose, sodium citrate, calcium carbonate, dibasic calcium phosphate, glycine and starch (preferably corn, potato or tapioca starch), disintegrants such as sodium starch glycolate, and certain complex silicates, and granulation binders such as polyvinylpyrrolidone, hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, stearic acid, may be included.

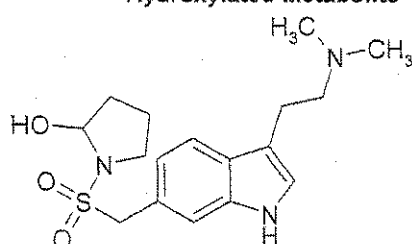
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Almotriptan (Axert®)

Chemical Structure

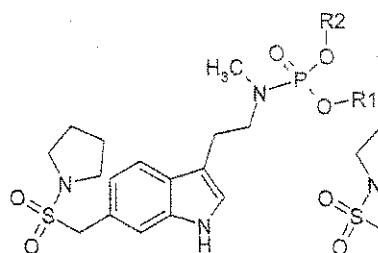


Hydroxylated Metabolite

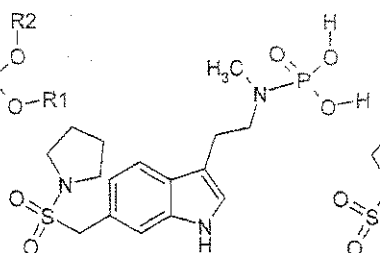


Compound	R1	R2	Chemical Name	Estimated LogP	pKa
E1229	hydrogen	hydrogen	Methyl-{2-[6-(pyrrolidine-1-sulfonylmethyl)-1H-indol-3-yl]-ethyl}-phosphoramidic acid	1.86	2.87
E1230	hydrogen	methyl	Methyl-{2-[6-(pyrrolidine-1-sulfonylmethyl)-1H-indol-3-yl]-ethyl}-phosphoramidic acid monomethyl ester	1.92	4.79
E1231	methyl	methyl	Methyl-{2-[6-(pyrrolidine-1-sulfonylmethyl)-1H-indol-3-yl]-ethyl}-phosphoramidic acid dimethyl ester	1.97	4.21
E1232	phenyl	hydrogen	Methyl-{2-[6-(pyrrolidine-1-sulfonylmethyl)-1H-indol-3-yl]-ethyl}-phosphoramidic acid monophenyl ester	3.69	4.35
E1233	phenyl	methyl	Methyl-{2-[6-(pyrrolidine-1-sulfonylmethyl)-1H-indol-3-yl]-ethyl}-phosphoramidic acid methyl ester phenyl ester	3.74	3.77

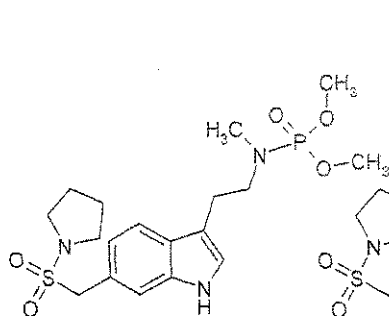
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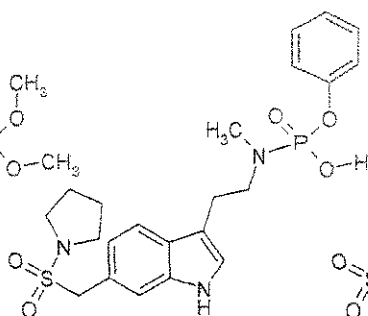
E1229



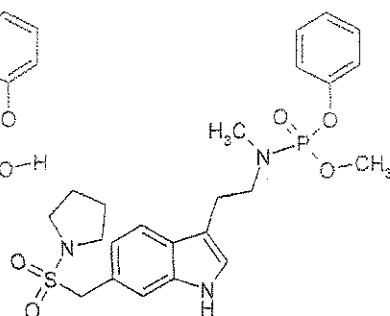
E1230



E1231



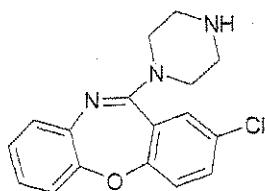
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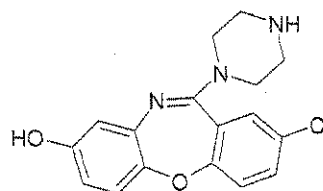
E1233

Amoxapine (Ascendin®)

Chemical Structure

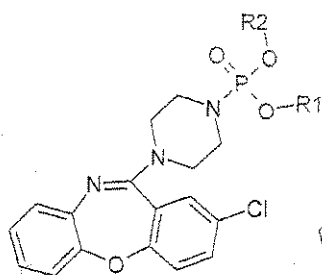


Hydroxylated Metabolite

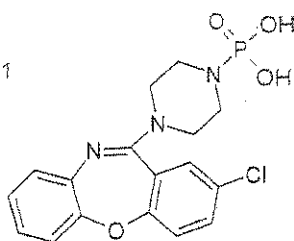


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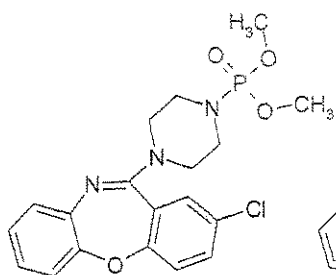
Compound	R1	R2	Chemical Name	Estimated LogP	pKa
E1121	hydrogen	hydrogen	[4-(2-Chloro-dibenzo[b,f][1,4]oxazepin-11-yl)-piperazin-1-yl]-phosphonic acid	2.97	4.83
E1122	hydrogen	methyl	[4-(2-Chloro-dibenzo[b,f][1,4]oxazepin-11-yl)-piperazin-1-yl]-phosphonic acid monomethyl ester	3.03	2.59
E1123	methyl	methyl	[4-(2-Chloro-dibenzo[b,f][1,4]oxazepin-11-yl)-piperazin-1-yl]-phosphonic acid dimethyl ester	3.93	5.90
E1124	phenyl	hydrogen	[4-(2-Chloro-dibenzo[b,f][1,4]oxazepin-11-yl)-piperazin-1-yl]-phosphonic acid monophenyl ester	5.64	2.35
E1125	phenyl	methyl	[4-(2-Chloro-dibenzo[b,f][1,4]oxazepin-11-yl)-piperazin-1-yl]-phosphonic acid methyl ester phenyl ester	5.70	6.04



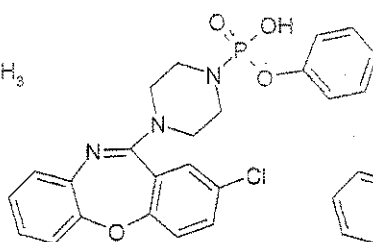
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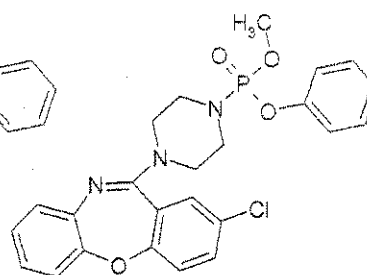
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E1123



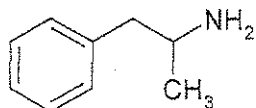
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E1125

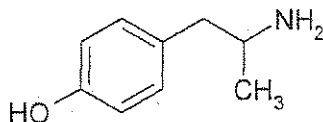
Amphetamine (Adderall®)

Chemical Structure

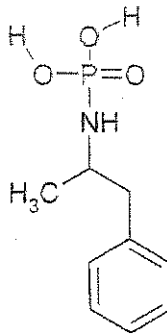
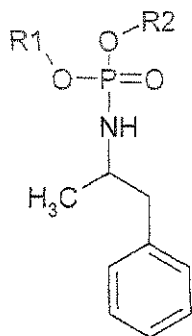


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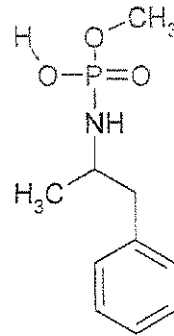
Hydroxylated Metabolite



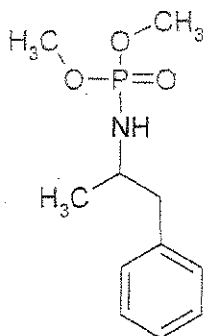
Compound	R1	R2	Chemical Name	Estimated LogP	pKa
E1222	hydrogen	hydrogen	(1-Methyl-2-phenyl-ethyl)-phosphoramidic acid	1.48	1.90
E1223	hydrogen	methyl	(1-Methyl-2-phenyl-ethyl)-phosphoramidic acid monomethyl ester	1.54	6.07
E1224	methyl	methyl	(1-Methyl-2-phenyl-ethyl)-phosphoramidic acid dimethyl ester		
E1225	phenyl	hydrogen	(1-Methyl-2-phenyl-ethyl)-phosphoramidic acid monophenyl ester	3.31	5.61
E1226	phenyl	methyl	(1-Methyl-2-phenyl-ethyl)-phosphoramidic acid cyclohexa-1,5-dienyl ester	3.36	3.36



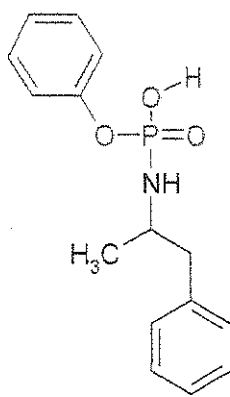
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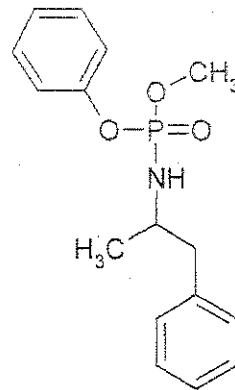
E1223



E1224



E1225

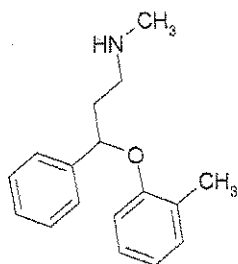


E1226

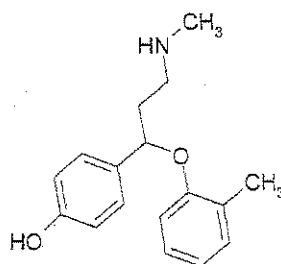
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Atomoxetine (Strattera®)

Chemical Structure

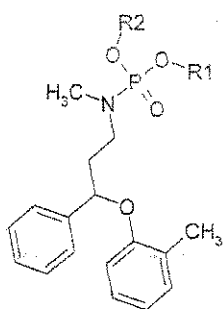


Hydroxylated Metabolite

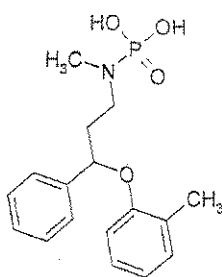


Compound	R1	R2	Chemical Name	Estimated LogP	pKa
E1021	hydrogen	hydrogen	Methyl-(3-phenyl-3-o-tolyloxy-propyl)-phosphoramidic acid	3.82	3.48
E1022	hydrogen	methyl	Methyl-(3-phenyl-3-o-tolyloxy-propyl)-phosphoramidic acid monomethyl ester	3.87	4.18
E1023	methyl	methyl	Methyl-(3-phenyl-3-o-tolyloxy-propyl)-phosphoramidic acid dimethyl ester	3.93	3.47
E1024	phenyl	hydrogen	Methyl-(3-phenyl-3-o-tolyloxy-propyl)-phosphoramidic acid monophenyl ester	5.64	3.75
E1025	phenyl	methyl	Methyl-(3-phenyl-3-o-tolyloxy-propyl)-phosphoramidic acid methyl ester phenyl ester	5.70	4.02

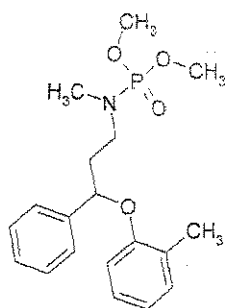
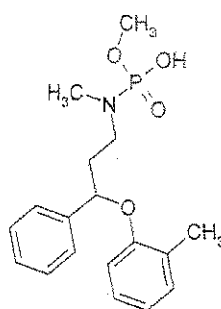
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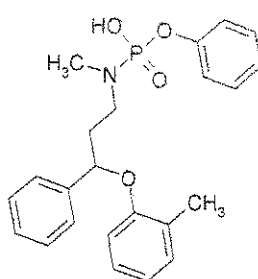
E1021



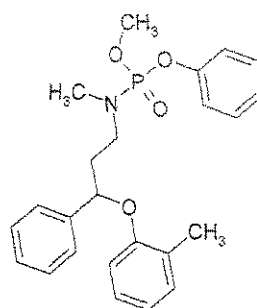
E1022



E1023



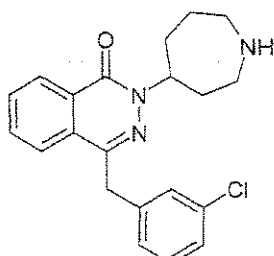
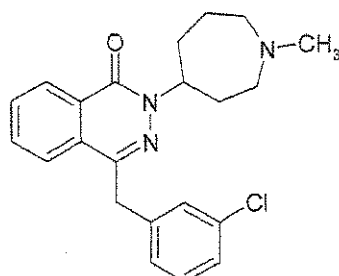
E1024



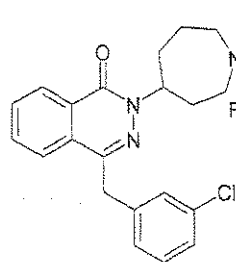
E1025

Azelastine (Azelastin®)

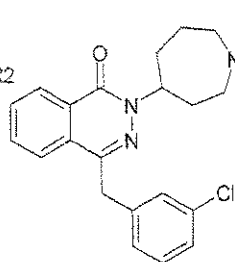
Chemical Structure Active Metabolite Structure Hydroxylated Metabolite



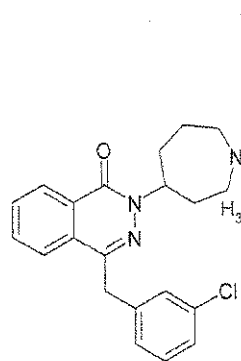
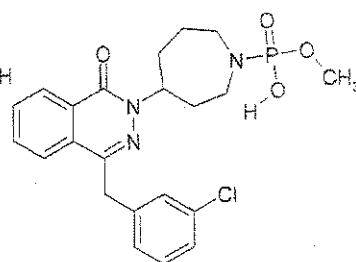
Compound	R1	R2	Chemical Name	Estimated LogP	pKa
E1234	hydrogen	hydrogen	{4-[4-(3-Chloro-benzyl)-1-oxo-1H-phthalazin-2-yl]-azepan-1-yl}-phosphonic acid	5.10	3.41
E1235	hydrogen	methyl	{4-[4-(3-Chloro-benzyl)-1-oxo-1H-phthalazin-2-yl]-azepan-1-yl}-phosphonic acid monomethyl ester	5.15	4.25
E1236	methyl	methyl	{4-[4-(3-Chloro-benzyl)-1-oxo-1H-phthalazin-2-yl]-azepan-1-yl}-phosphonic acid dimethyl ester	5.21	4.48
E1237	phenyl	hydrogen	{4-[4-(3-Chloro-benzyl)-1-oxo-1H-phthalazin-2-yl]-azepan-1-yl}-phosphonic acid monophenyl ester	6.92	3.78
E1238	phenyl	methyl	{4-[4-(3-Chloro-benzyl)-1-oxo-1H-phthalazin-2-yl]-azepan-1-yl}-phosphonic acid methyl ester phenyl ester	6.98	4.65



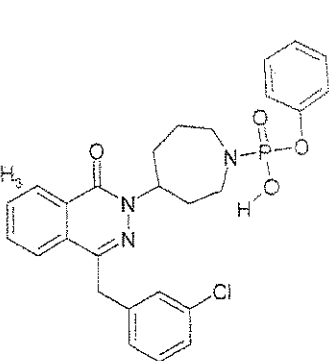
E1234



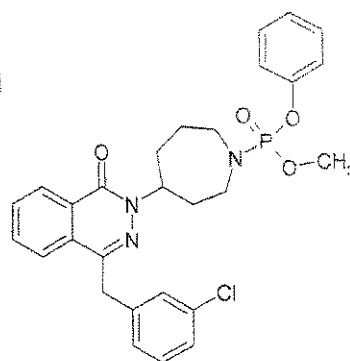
E1235



E1236



E1237

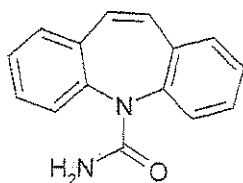


E1238

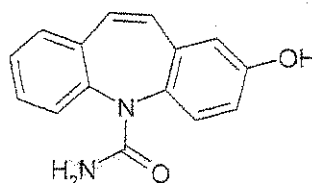
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Carbamazepine (Tegetrol®)

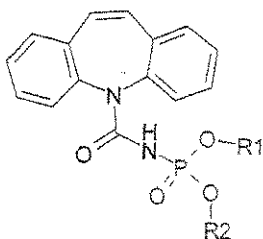
Chemical Structure



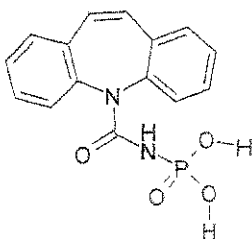
Hydroxylated Metabolite



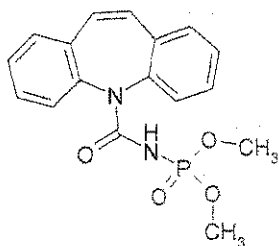
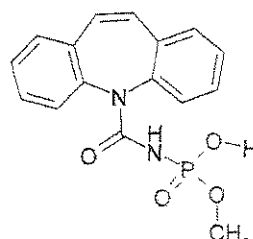
Compound	R1	R2	Chemical Name
E1179	hydrogen	hydrogen	(Dibenzo[b,f]azepine-5-carbonyl)-phosphoramidic acid
E1180	hydrogen	methyl	(Dibenzo[b,f]azepine-5-carbonyl)-phosphoramidic acid monomethyl ester
E1181	methyl	methyl	(Dibenzo[b,f]azepine-5-carbonyl)-phosphoramidic acid dimethyl ester
E1182	phenyl	hydrogen	(Dibenzo[b,f]azepine-5-carbonyl)-phosphoramidic acid monophenyl ester
E1183	phenyl	methyl	(Dibenzo[b,f]azepine-5-carbonyl)-phosphoramidic acid methyl ester phenyl ester



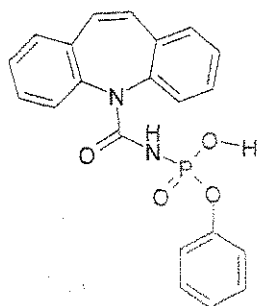
E1179



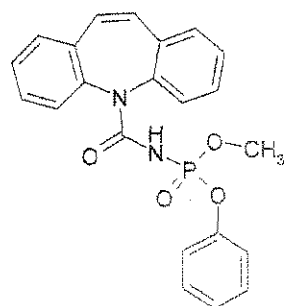
E1180



E1181



E1182



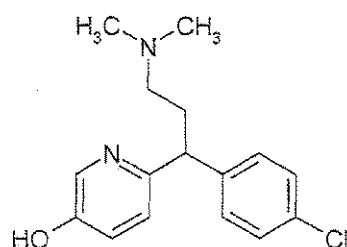
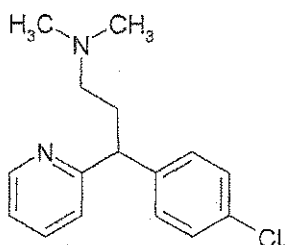
E1183

Chlorpheniramine (Chlor-Trimetron®)

Chemical Structure

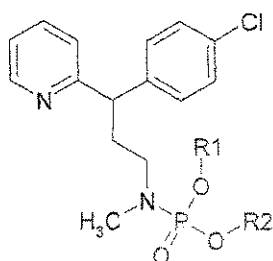
Active Metabolite Structure

Hydroxylated Metabolite

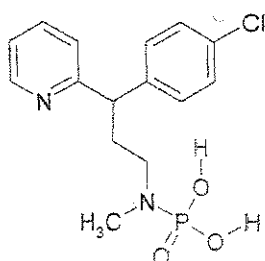


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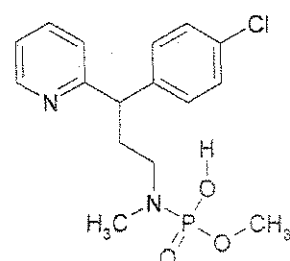
Compound	R1	R2	Chemical Name
E1349	hydrogen	hydrogen	[3-(4-Chloro-phenyl)-3-pyridin-2-yl-propyl]-methyl-phosphoramidic acid
E1350	hydrogen	methyl	[3-(4-Chloro-phenyl)-3-pyridin-2-yl-propyl]-methyl-phosphoramidic acid monomethyl ester
E1351	methyl	methyl	[3-(4-Chloro-phenyl)-3-pyridin-2-yl-propyl]-methyl-phosphoramidic acid dimethyl ester
E1352	hydrogen	phenyl	[3-(4-Chloro-phenyl)-3-pyridin-2-yl-propyl]-methyl-phosphoramidic acid monophenyl ester
E1353	methyl	phenyl	[3-(4-Chloro-phenyl)-3-pyridin-2-yl-propyl]-methyl-phosphoramidic acid methyl ester phenyl ester



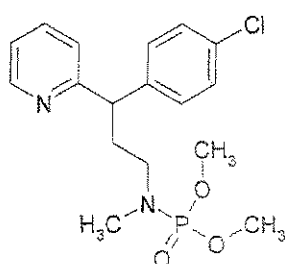
E1349



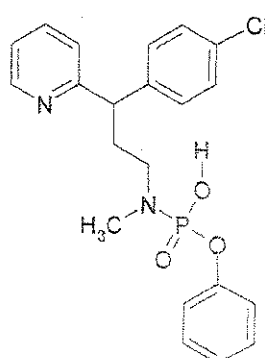
E1350



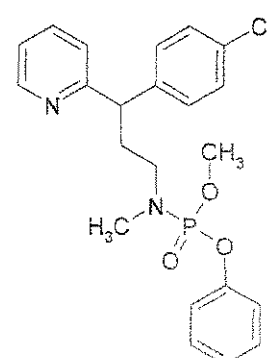
E1351



E1352

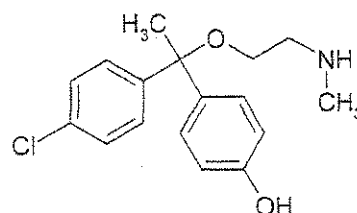
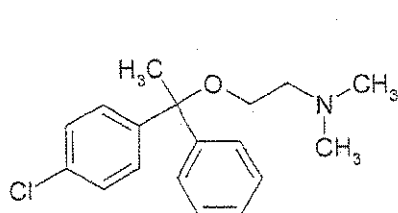


E1353



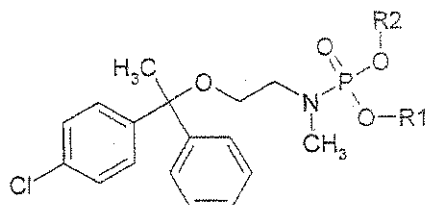
Chlorphenoxamine (Phenoxene®)

Chemical Structure Active Metabolite Structure Hydroxylated Metabolite

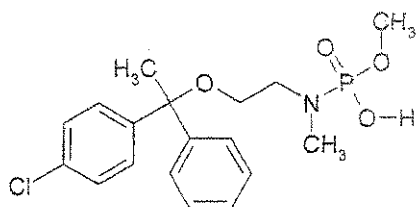


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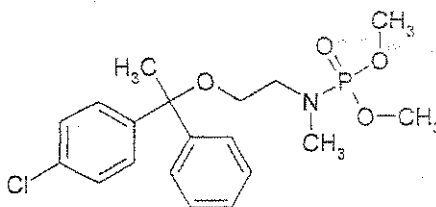
Compound	R1	R2	Chemical Name
E1354	hydrogen	hydrogen	{2-[1-(4-Chloro-phenyl)-1-phenyl-ethoxy]-ethyl}-methyl-phosphoramidic acid
E1355	hydrogen	methyl	{2-[1-(4-Chloro-phenyl)-1-phenyl-ethoxy]-ethyl}-methyl-phosphoramidic acid monomethyl ester
E1356	methyl	methyl	{2-[1-(4-Chloro-phenyl)-1-phenyl-ethoxy]-ethyl}-methyl-phosphoramidic acid dimethyl ester
E1357	phenyl	hydrogen	{2-[1-(4-Chloro-phenyl)-1-phenyl-ethoxy]-ethyl}-methyl-phosphoramidic acid monophenyl ester
E1358	phenyl	methyl	{2-[1-(4-Chloro-phenyl)-1-phenyl-ethoxy]-ethyl}-methyl-phosphoramidic acid methyl ester phenyl ester



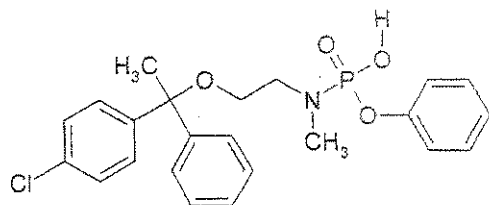
E1354



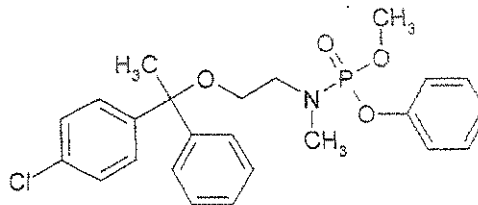
E1355



E1356



E1357

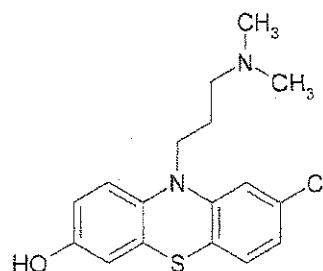
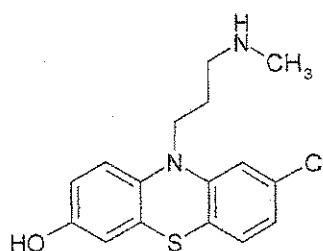
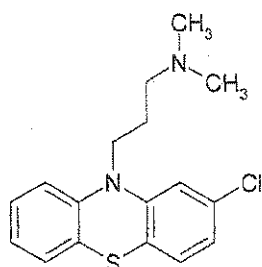


E1358

Chlorpromazine (Thorazine®)
Active Metabolite Structure

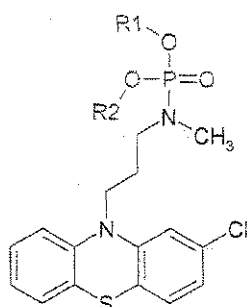
Chemical Structure

Hydroxylated Metabolite

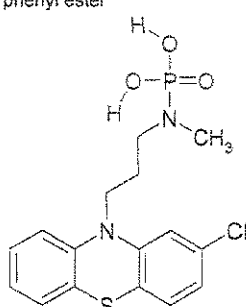


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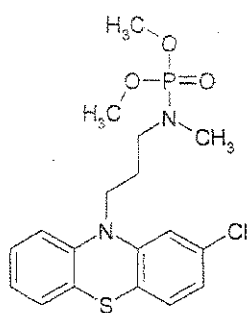
Compound	R1	R2	Chemical Name	Estimated LogP	Estimated Pka
E1154	hydrogen	hydrogen	[3-(2-Chloro-phenothiazin-10-yl)-propyl]-methyl-phosphoramidic acid	4.58	3.29
E1155	hydrogen	methyl	[3-(2-Chloro-phenothiazin-10-yl)-propyl]-methyl-phosphoramidic acid monomethyl ester	4.64	4.36
E1156	methyl	methyl	[3-(2-Chloro-phenothiazin-10-yl)-propyl]-methyl-phosphoramidic acid dimethyl ester	4.69	3.55
E1157	phenyl	hydrogen	[3-(2-Chloro-phenothiazin-10-yl)-propyl]-methyl-phosphoramidic acid monophenyl ester	6.40	3.93
E1158	phenyl	methyl	[3-(2-Chloro-phenothiazin-10-yl)-propyl]-methyl-phosphoramidic acid methyl ester phenyl ester	6.46	4.11



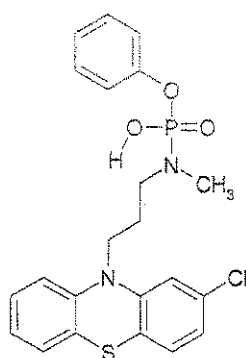
E1154



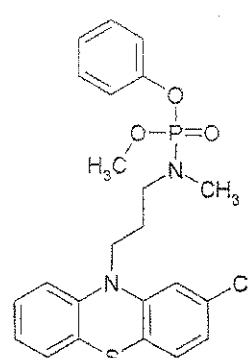
E1155



E1156



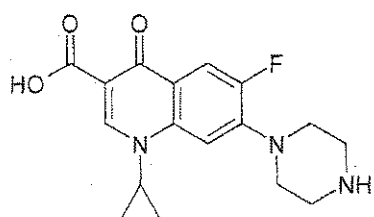
E1157



E1158

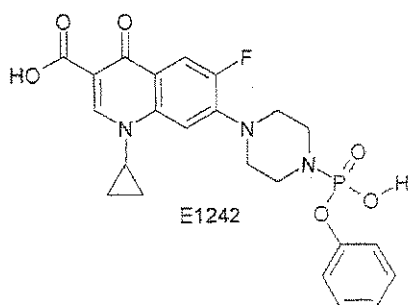
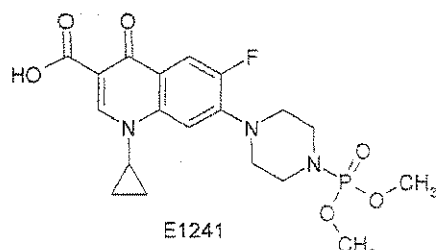
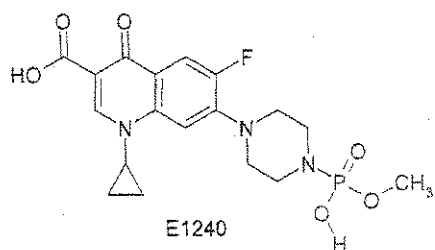
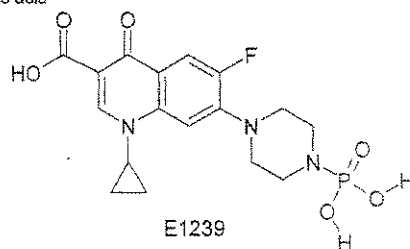
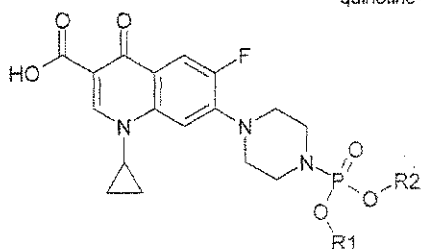
Ciprofloxacin (Cipro®)

Chemical Structure



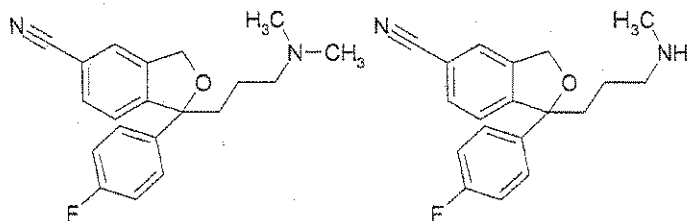
Hydroxylated Metabolite

Compound	R1	R2	Chemical Name	Estimated LogP	pKa
E1239	hydrogen	hydrogen	1-Cyclopropyl-6-fluoro-4-oxo-7-(4-phosphono-piperazin-1-yl)-1,4-dihydro-quinoline-3-carboxylic acid	1.28	5.63
E1240	hydrogen	methyl	1-Cyclopropyl-6-fluoro-7-[4-(hydroxy-methoxy-phosphoryl)-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid	1.34	2.03
E1241	methyl	methyl	1-Cyclopropyl-7-[4-(dimethoxy-phosphoryl)-piperazin-1-yl]-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid	1.40	6.70
E1242	phenyl	hydrogen	1-Cyclopropyl-6-fluoro-7-[4-(hydroxy-phenoxy-phosphoryl)-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid	3.11	1.56
E1243	phenyl	methyl	1-Cyclopropyl-6-fluoro-7-[4-(methoxy-phenoxy-phosphoryl)-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid	3.16	6.83



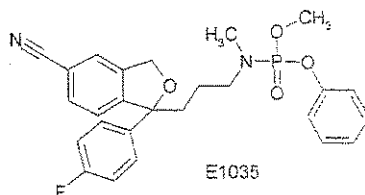
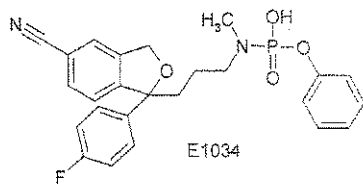
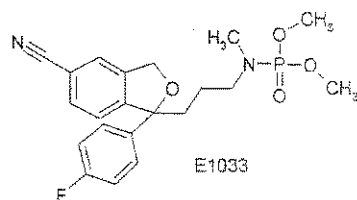
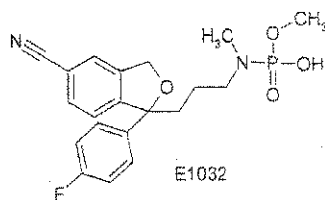
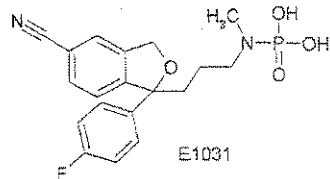
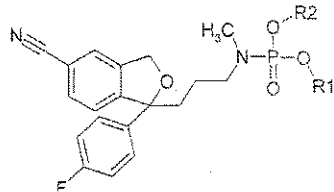
Citalopram (Celexa®)

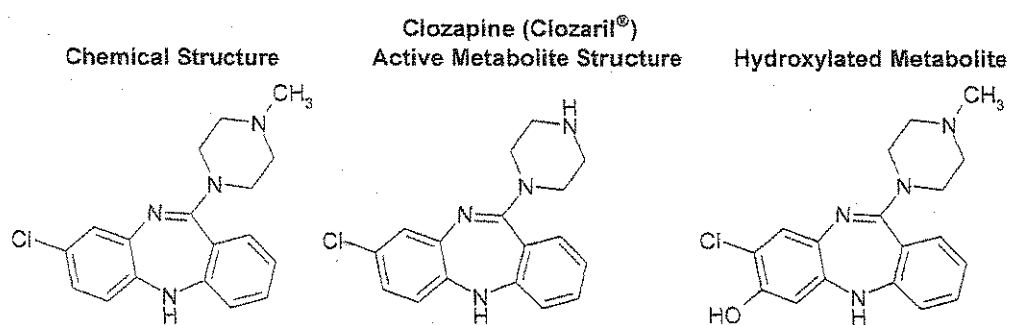
Chemical Structure Active Metabolite Structure



5

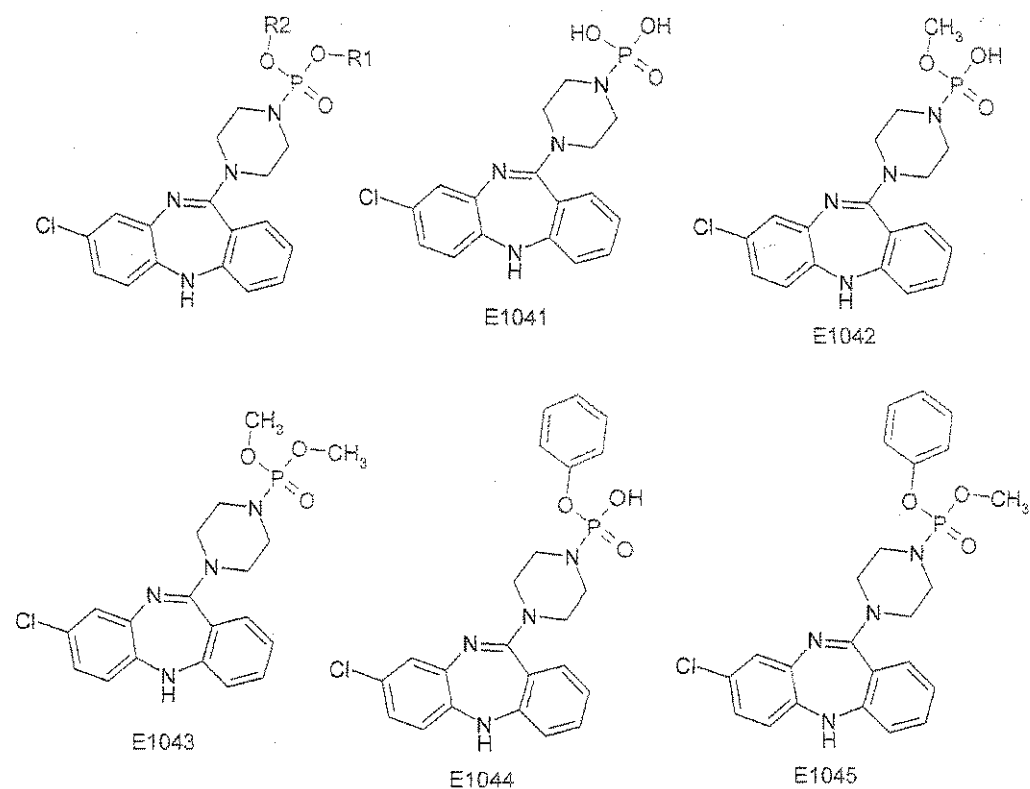
Compound	R1	R2	Chemical Name	Estimated LogP	Estimated pKa
E1031	hydrogen	hydrogen	{3-[5-Cyano-1-(4-fluoro-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-propyl}-methyl-phosphoramidic acid	3.12	3.35
E1032	hydrogen	methyl	{3-[5-Cyano-1-(4-fluoro-phenyl)-1,3{3-[5-Cyano-1-(4-fluoro-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-propyl}-methyl-phosphoramidic acid monomethyl ester	3.17	4.31
E1033	methyl	methyl	{3-[5-Cyano-1-(4-fluoro-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-propyl}-methyl-phosphoramidic acid dimethyl ester	3.23	4.43
E1034	phenyl	hydrogen	{3-[5-Cyano-1-(4-fluoro-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-propyl}-methyl-phosphoramidic acid monophenyl ester	4.94	3.86
E1035	phenyl	methyl	{3-[5-Cyano-1-(4-fluoro-phenyl)-1,3-dihydro-isobenzofuran-1-yl]-propyl}-methyl-phosphoramidic acid methyl ester phenyl ester	5.00	4.99





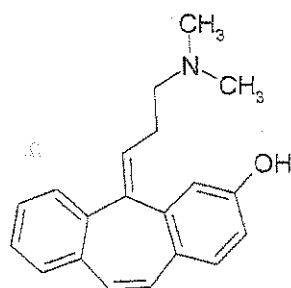
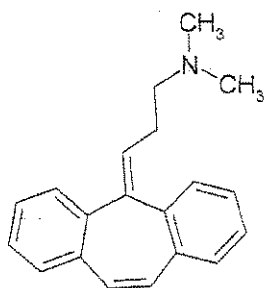
Compound	R1	R2	Chemical Name	Estimated LogP	Estimated pKa
E1041	hydrogen	hydrogen	{4-(8-Chloro-5H-dibenzo[b,e][1,4]diazepin-11-yl)-piperazin-1-yl}-phosphonic acid	2.21	4.67
E1042	hydrogen	methyl	[4-(8-Chloro-5H-dibenzo[b,e][1,4]diazepin-11-yl)-piperazin-1-yl]-phosphonic acid monomethyl ester	2.27	2.99
E1043	methyl	methyl	[4-(8-Chloro-5H-dibenzo[b,e][1,4]diazepin-11-yl)-piperazin-1-yl]-phosphonic acid dimethyl ester	2.32	5.74
E1044	phenyl	hydrogen	4-(8-Chloro-5H-dibenzo[b,e][1,4]diazepin-11-yl)-piperazin-1-yl]-phosphonic acid monophenyl ester	4.04	5.89
E1045	phenyl	methyl	[4-(8-Chloro-5H-dibenzo[b,e][1,4]diazepin-11-yl)-piperazin-1-yl]-phosphonic acid methyl ester phenyl ester	4.09	2.52

5



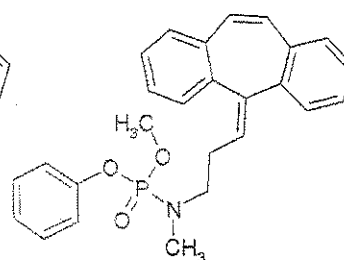
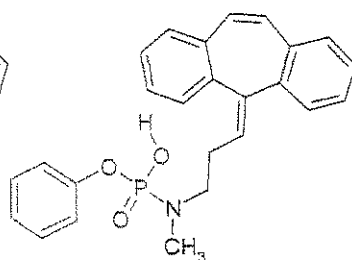
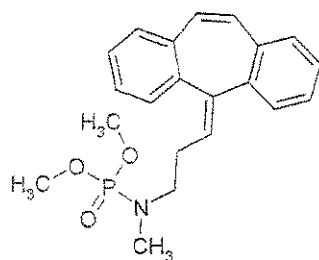
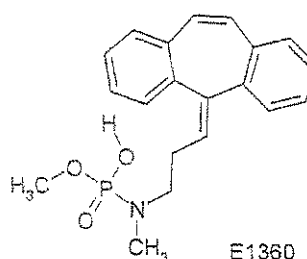
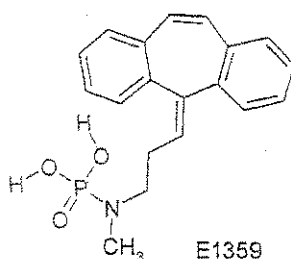
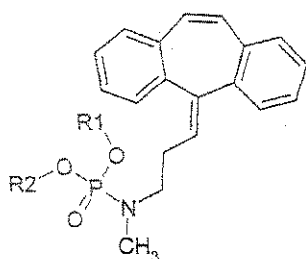
Cyclobenzaprine (Flexeril®)

Chemical Structure	Active Metabolite Structure	Hydroxylated Metabolite
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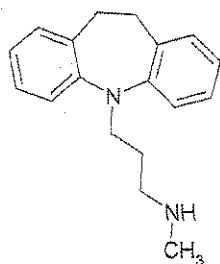
5

Compound	R1	R2	Chemical Name
E1359	hydrogen	hydrogen	(3-Dibenzo[a,d]cyclohepten-5-ylidene-propyl)-methyl-phosphoramidic acid
E1360	hydrogen	methyl	(3-Dibenzo[a,d]cyclohepten-5-ylidene-propyl)-methyl-phosphoramidic acid monomethyl ester
E1361	methyl	methyl	(3-Dibenzo[a,d]cyclohepten-5-ylidene-propyl)-methyl-phosphoramidic acid dimethyl ester
E1362	phenyl	hydrogen	(3-Dibenzo[a,d]cyclohepten-5-ylidene-propyl)-methyl-phosphoramidic acid monophenyl ester
E1363	phenyl	methyl	(3-Dibenzo[a,d]cyclohepten-5-ylidene-propyl)-methyl-phosphoramidic acid methyl ester phenyl ester

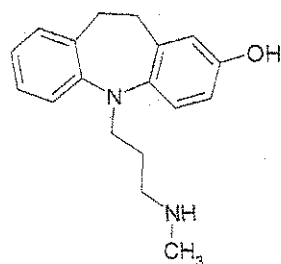


Desipramine (Norpramin®)

Chemical Structure

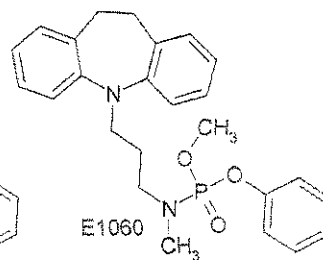
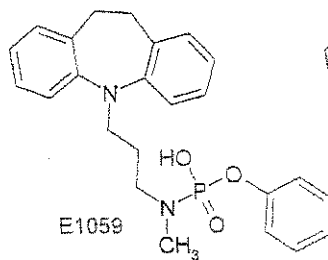
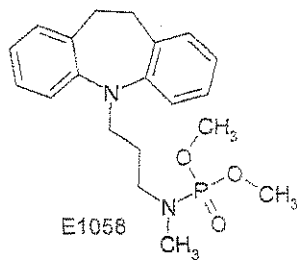
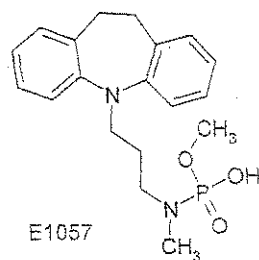
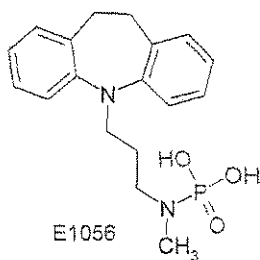
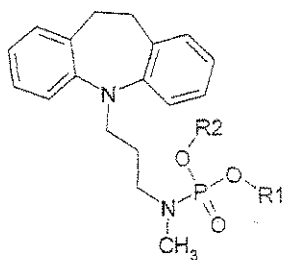


Hydroxylated Metabolite



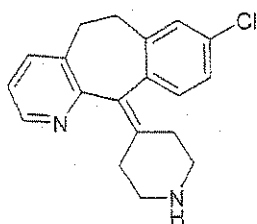
Compound	R1	R2	Chemical Name	Estimated LogP	pKa
E1056	hydrogen	hydrogen	[3-(10,11-Dihydro-dibenzo[b,f]azepin-5-yl)-propyl]-methyl-phosphoramidic acid	4.38	3.01
E1057	hydrogen	methyl	[3-(10,11-Dihydro-dibenzo[b,f]azepin-5-yl)-propyl]-methyl-phosphoramidic acid monomethyl ester	4.44	4.64
E1058	methyl	methyl	[3-(10,11-Dihydro-dibenzo[b,f]azepin-5-yl)-propyl]-methyl-phosphoramidic acid dimethyl ester	4.50	3.27
E1059	phenyl	hydrogen	[3-(10,11-Dihydro-dibenzo[b,f]azepin-5-yl)-propyl]-methyl-phosphoramidic acid monophenyl ester	6.21	4.20
E1060	phenyl	methyl	[3-(10,11-Dihydro-dibenzo[b,f]azepin-5-yl)-propyl]-methyl-phosphoramidic acid methyl ester phenyl ester	6.26	3.83

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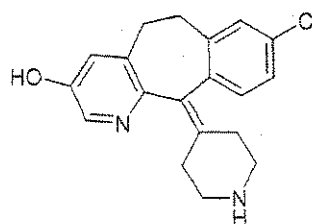


Desloratadine (Clarinet[®])

Chemical Structure

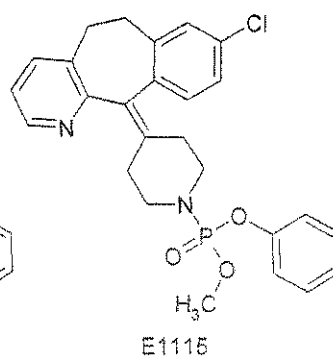
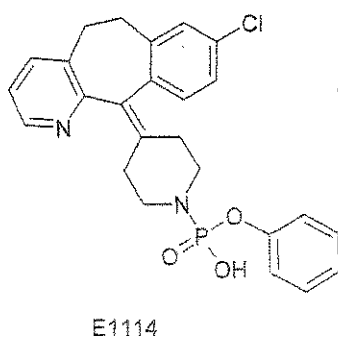
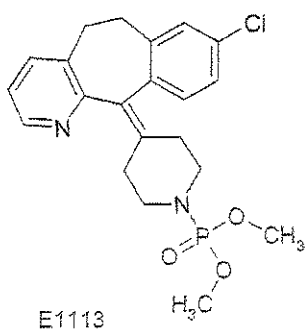
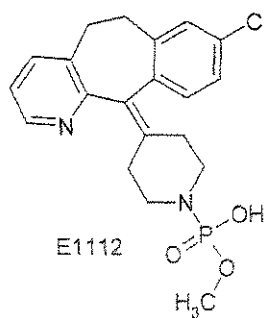
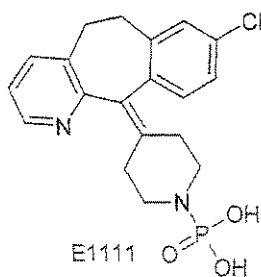
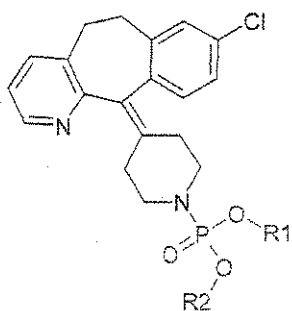


Hydroxylated Metabolite



Compound	R1	R2	Chemical Name	Estimated LogP	pKa
E1111	hydrogen	hydrogen	[4-(8-Chloro-5,6-dihydro-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)-piperidin-1-yl]-phosphonic acid	4.21	3.86
E1112	hydrogen	methyl	[4-(8-Chloro-5,6-dihydro-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)-piperidin-1-yl]-phosphonic acid monomethyl ester	4.27	3.80
E1113	methyl	methyl	[4-(8-Chloro-5,6-dihydro-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)-piperidin-1-yl]-phosphonic acid dimethyl ester	4.33	4.93
E1114	phenyl	hydrogen	[4-(8-Chloro-5,6-dihydro-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)-piperidin-1-yl]-phosphonic acid monophenyl ester	6.04	3.32
E1115	phenyl	methyl	[4-(8-Chloro-5,6-dihydro-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)-piperidin-1-yl]-phosphonic acid methyl ester phenyl ester	6.09	5.07

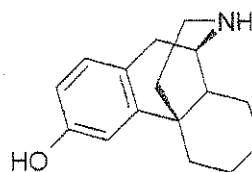
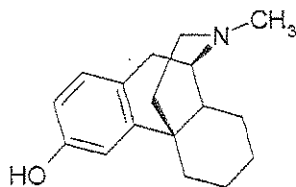
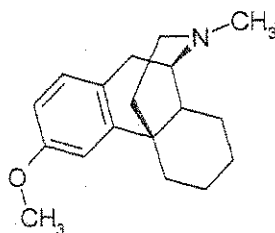
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Chemical Structure

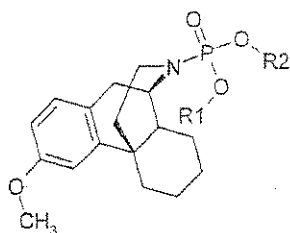
Dextromethorphan (Dextrophan®)
Active Metabolite Structure

Hydroxylated Metabolite

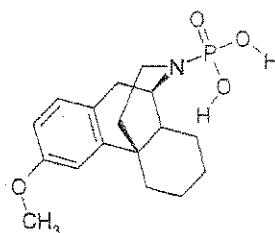


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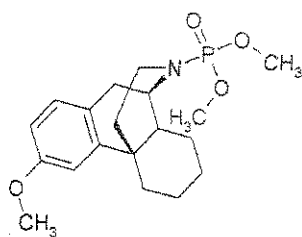
Compound	R1	R2	Chemical Name	Estimated LogP	pKa
E1244	hydrogen	hydrogen	(6-Ethyl-8-methoxy-11-propyl-1,2,5,6-tetrahydro-4H-2,6-methano-benzo[d]azocin-3-yl)-phosphonic acid	3.57	3.13
E1245	hydrogen	methyl	(6-Ethyl-8-methoxy-11-propyl-1,2,5,6-tetrahydro-4H-2,6-methano-benzo[d]azocin-3-yl)-phosphonic acid monomethyl ester	3.62	4.54
E1246	methyl	methyl	(6-Ethyl-8-methoxy-11-propyl-1,2,5,6-tetrahydro-4H-2,6-methano-benzo[d]azocin-3-yl)-phosphonic acid dimethyl ester	3.68	4.19
E1247	phenyl	hydrogen	(6-Ethyl-8-methoxy-11-propyl-1,2,5,6-tetrahydro-4H-2,6-methano-benzo[d]azocin-3-yl)-phosphonic acid monophenyl ester	5.39	4.08
E1248	phenyl	methyl	(6-Ethyl-8-methoxy-11-propyl-1,2,5,6-tetrahydro-4H-2,6-methano-benzo[d]azocin-3-yl)-phosphonic acid methyl ester phenyl ester	5.44	4.33



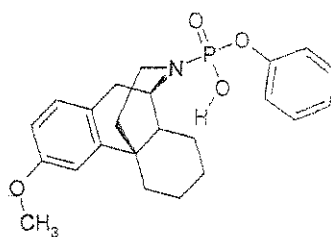
E1244



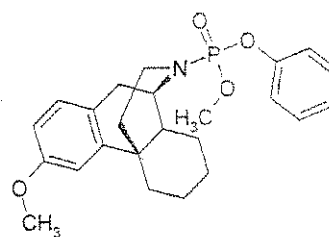
E1245



E1246



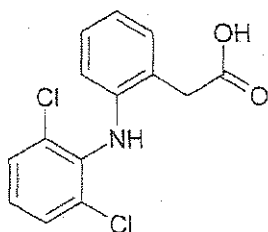
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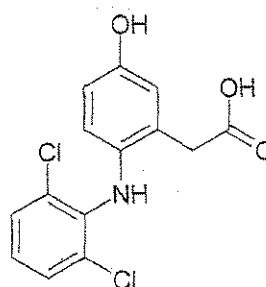
E1248

Diclofenac (Voltaren®)

Chemical Structure



Hydroxylated Metabolite

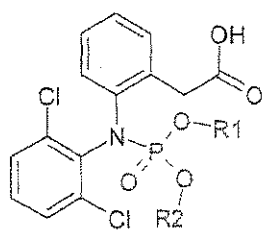


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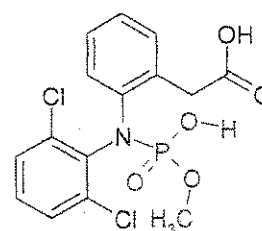
Compound	R1	R2
E1249	hydrogen	hydrogen
E1250	hydrogen	methyl
E1251	methyl	methyl
E1252	phenyl	hydrogen
E1253	phenyl	methyl

Chemical Name

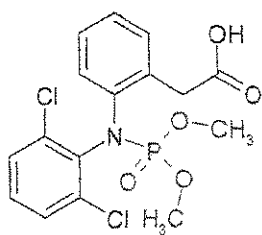
{2-[(2,6-Dichloro-phenyl)-phosphono-amino]-phenyl}-acetic acid
 {2-[(2,6-Dichloro-phenyl)-(hydroxy-methoxy-phosphoryl)-amino]-phenyl}-acetic acid
 {2-[(2,6-Dichloro-phenyl)-(dimethoxy-phosphoryl)-amino]-phenyl}-acetic acid
 {2-[(2,6-Dichloro-phenyl)-(hydroxy-phenoxy-phosphoryl)-amino]-phenyl}-acetic acid
 {2-[(2,6-Dichloro-phenyl)-(methoxy-phenoxy-phosphoryl)-amino]-phenyl}-acetic acid



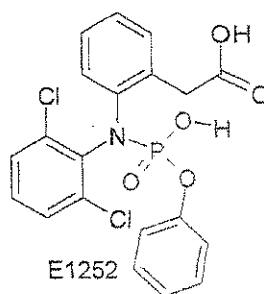
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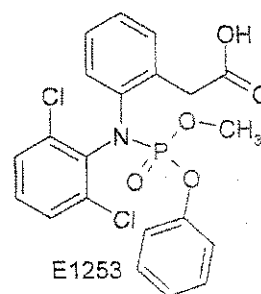
E1250



E1251

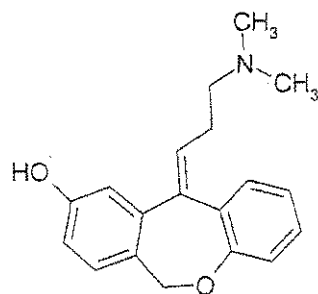
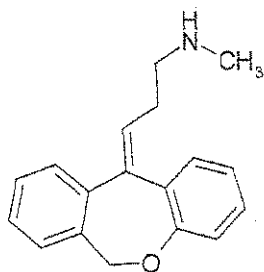
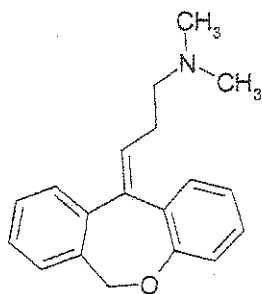


E1252



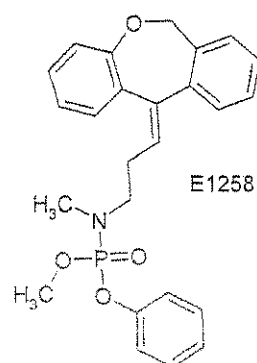
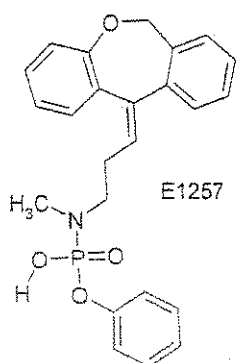
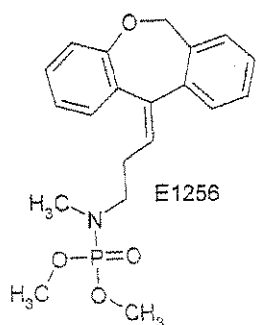
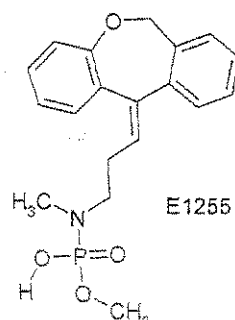
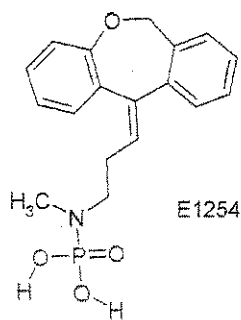
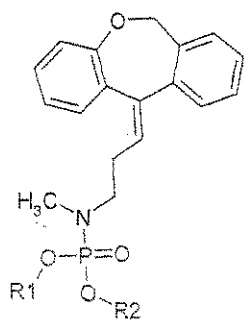
E1253

Chemical Structure Doxepin (Adapin[®], Sinequan[®])
Active Metabolite Structure Hydroxylated Metabolite

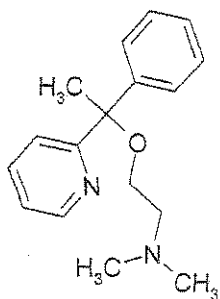


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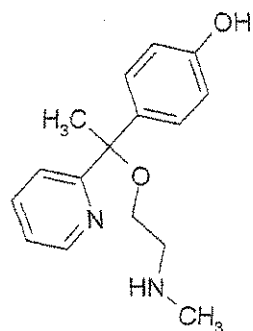
Compound	R1	R2	Chemical Name	Estimated LogP	pKa
E1254	hydrogen	hydrogen	[3-(6H-Dibenzo[b,e]oxepin-11-ylidene)-propyl]-methyl-phosphoramidic acid	3.37	2.91
E1255	hydrogen	methyl	[3-(6H-Dibenzo[b,e]oxepin-11-ylidene)-propyl]-methyl-phosphoramidic acid monomethyl ester	3.42	4.75
E1256	methyl	methyl	[3-(6H-Dibenzo[b,e]oxepin-11-ylidene)-propyl]-methyl-phosphoramidic acid dimethyl ester	3.48	3.99
E1257	phenyl	hydrogen	[3-(6H-Dibenzo[b,e]oxepin-11-ylidene)-propyl]-methyl-phosphoramidic acid monophenyl ester	5.19	4.31
E1258	phenyl	methyl	[3-(6H-Dibenzo[b,e]oxepin-11-ylidene)-propyl]-methyl-phosphoramidic acid methyl ester phenyl ester	5.25	4.54



Chemical Structure



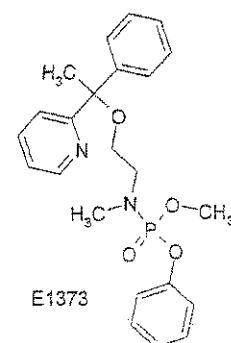
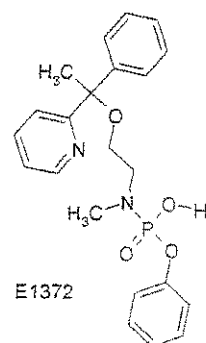
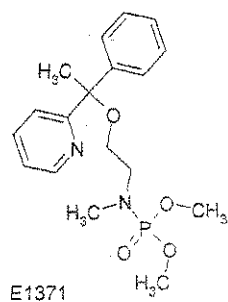
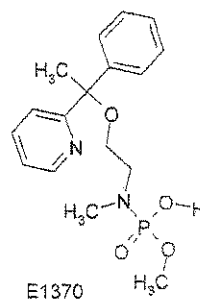
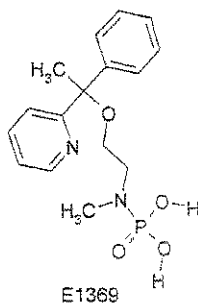
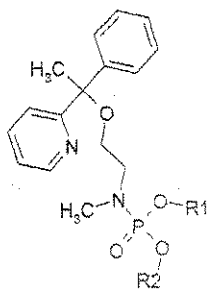
Active Metabolite Structure



Hydroxylated Metabolite

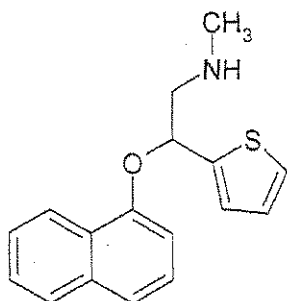
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Compound	R1	R2	Chemical Name
E1369	hydrogen	hydrogen	Methyl-[2-(1-phenyl-1-pyridin-2-yl-ethoxy)-ethyl]-phosphoramidic acid
E1370	hydrogen	methyl	Methyl-[2-(1-phenyl-1-pyridin-2-yl-ethoxy)-ethyl]-phosphoramidic acid monomethyl ester
E1371	methyl	methyl	Methyl-[2-(1-phenyl-1-pyridin-2-yl-ethoxy)-ethyl]-phosphoramidic acid dimethyl ester
E1372	phenyl	hydrogen	Methyl-[2-(1-phenyl-1-pyridin-2-yl-ethoxy)-ethyl]-phosphoramidic acid monophenyl ester
E1373	phenyl	methyl	Methyl-[2-(1-phenyl-1-pyridin-2-yl-ethoxy)-ethyl]-phosphoramidic acid methyl ester phenyl ester

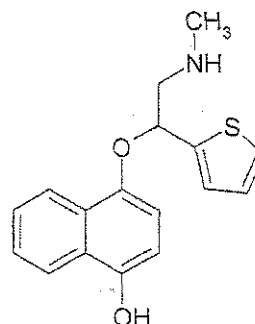


Duloxetine (Cymbalta®)

Chemical Structure

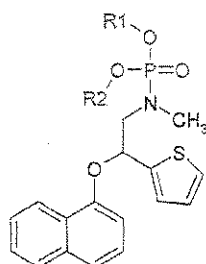


Hydroxylated Metabolite

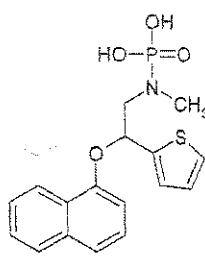


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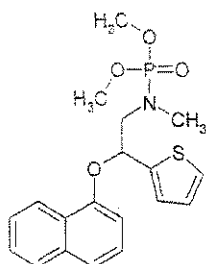
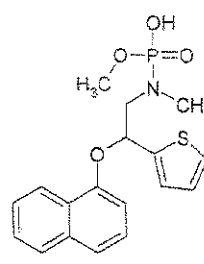
Compound	R1	R2	Chemical Name	Estimated LogP	Estimated pKa
E1106	hydrogen	hydrogen	Methyl-[2-(naphthalen-1-yloxy)-2-thiophen-2-ylethyl]-phosphoramidic acid	3.78	4.48
E1107	hydrogen	methyl	Methyl-[2-(naphthalen-1-yloxy)-2-thiophen-2-ylethyl]-phosphoramidic acid monomethyl ester	3.83	3.18
E1108	methyl	methyl	Methyl-[2-(naphthalen-1-yloxy)-2-thiophen-2-ylethyl]-phosphoramidic acid dimethyl ester	3.89	4.32
E1109	phenyl	hydrogen	Methyl-[2-(naphthalen-1-yloxy)-2-thiophen-2-ylethyl]-phosphoramidic acid monophenyl ester	5.60	2.76
E1110	phenyl	methyl	Methyl-[2-(naphthalen-1-yloxy)-2-thiophen-2-ylethyl]-phosphoramidic acid methyl ester phenyl ester	5.66	4.86



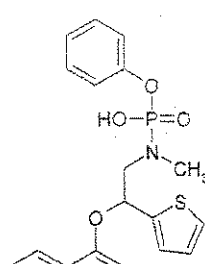
E1106



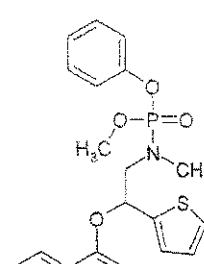
E1107



E1108

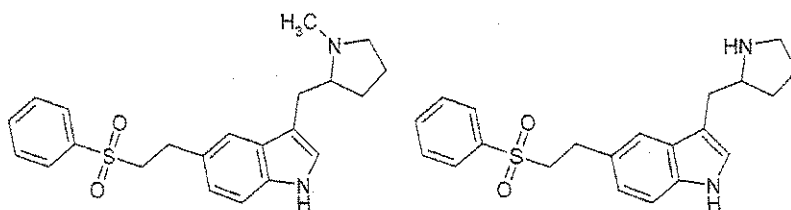


E1109



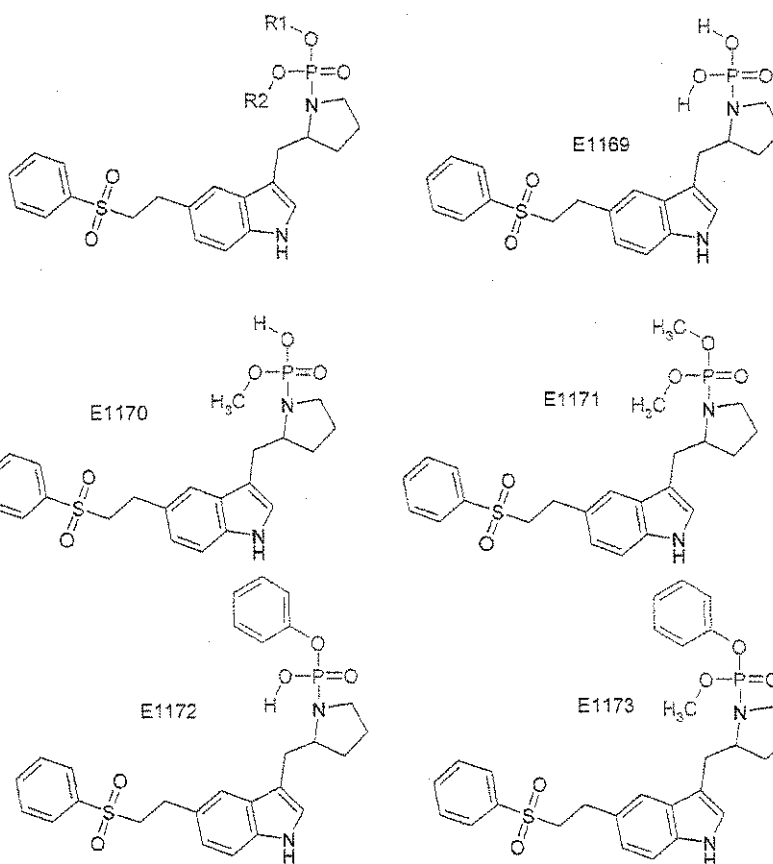
E1110

Eletriptan (Relbox®)
Chemical Structure Active Metabolite Structure Hydroxylated Metabolite



5

Compound	R1	R2	Chemical Name	Estimated LogP	pKa
E1169	hydrogen	hydrogen	{2-[5-(2-Benzenesulfonyl-ethyl)-1H-indol-3-ylmethyl]-pyrrolidin-1-yl}-phosphonic acid	3.24	2.30
E1170	hydrogen	methyl	{2-[5-(2-Benzenesulfonyl-ethyl)-1H-indol-3-ylmethyl]-pyrrolidin-1-yl}-phosphonic acid monomethyl ester	3.29	5.36
E1171	methyl	methyl	{2-[5-(2-Benzenesulfonyl-ethyl)-1H-indol-3-ylmethyl]-pyrrolidin-1-yl}-phosphonic acid dimethyl ester	3.35	4.45
E1172	phenyl	hydrogen	{2-[5-(2-Benzenesulfonyl-ethyl)-1H-indol-3-ylmethyl]-pyrrolidin-1-yl}-phosphonic acid monophenyl ester	5.06	4.88
E1173	phenyl	methyl	{2-[5-(2-Benzenesulfonyl-ethyl)-1H-indol-3-ylmethyl]-pyrrolidin-1-yl}-phosphonic acid methyl ester phenyl ester	5.12	4.52

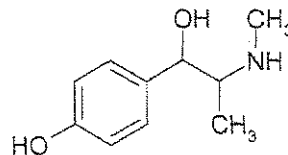
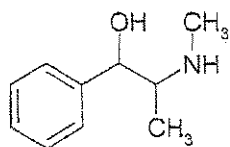


Ephedrine (Broncholate®)

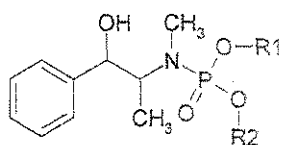
Chemical Structure

Hydroxylated Metabolite

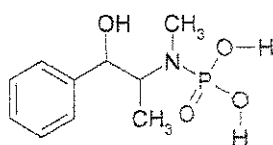
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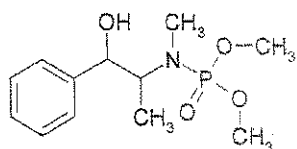
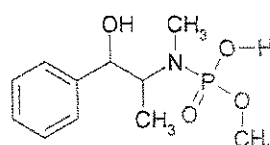
Compound	R1	R2	Chemical Name	Estimated LogP	pKa
E1334	hydrogen	hydrogen	(2-Hydroxy-1-methyl-2-phenyl-ethyl)-methyl-phosphoramidic acid	0.49	3.47
E1335	hydrogen	methyl	(2-Hydroxy-1-methyl-2-phenyl-ethyl)-methyl-phosphoramidic acid monomethyl ester	0.55	4.18
E1336	methyl	methyl	(2-Hydroxy-1-methyl-2-phenyl-ethyl)-methyl-phosphoramidic acid dimethyl ester	0.60	3.58
E1337	phenyl	hydrogen	(2-Hydroxy-1-methyl-2-phenyl-ethyl)-methyl-phosphoramidic acid monophenyl ester	2.31	3.80
E1338	phenyl	methyl	(2-Hydroxy-1-methyl-2-phenyl-ethyl)-methyl-phosphoramidic acid methyl ester phenyl ester	2.37	3.80



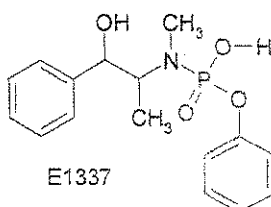
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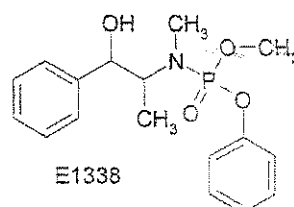
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E1336



E1337

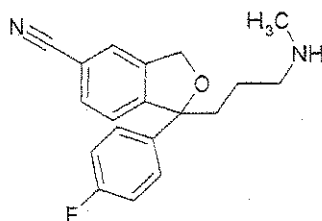
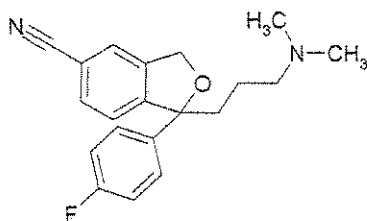


E1338

Escitalopram (Lexapro®)

Chemical Structure

Active Metabolite Structure

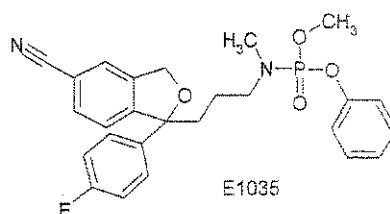
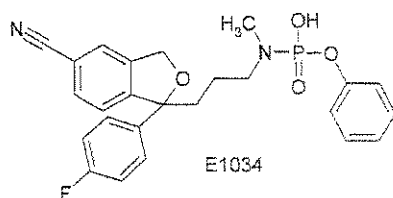
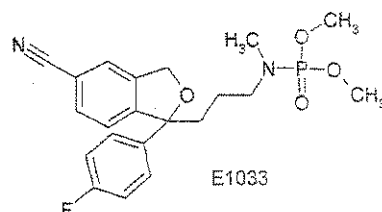
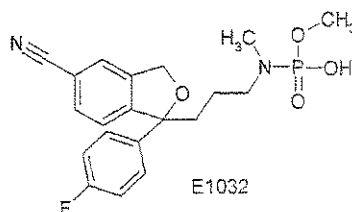
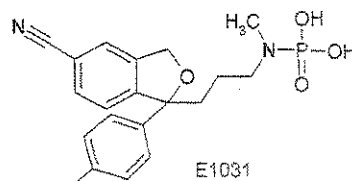
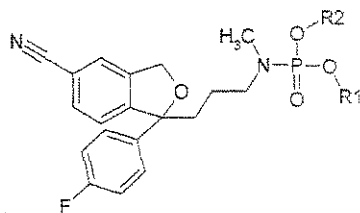


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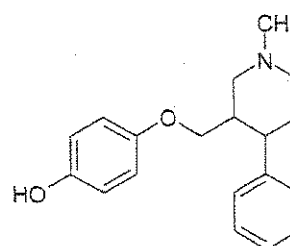
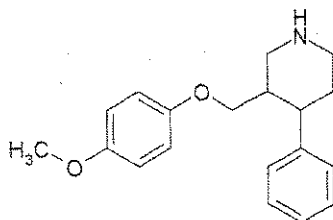
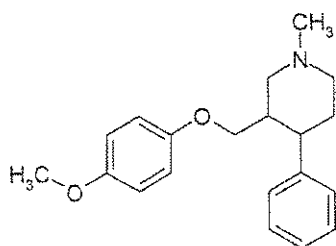
Compound	R1	R2	Chemical Name	Estimated LogP	pKa
E1031	hydrogen	hydrogen	{3-[5-Cyano-1-(4-fluoro-phenyl)-1,3-dihydro-isobenzofuran-1(S)-yl]-propyl}-methyl-phosphoramidic acid	3.12	
E1032	hydrogen	methyl	{3-[5-Cyano-1-(4-fluoro-phenyl)-1,3-dihydro-isobenzofuran-1(S)-yl]-propyl}-methyl-phosphoramidic acid monomethyl ester	3.17	
E1033	methyl	methyl	{3-[5-Cyano-1-(4-fluoro-phenyl)-1,3-dihydro-isobenzofuran-11(S)-yl]-propyl}-methyl-phosphoramidic acid dimethyl ester	3.23	
E1034	phenyl	hydrogen	{3-[5-Cyano-1-(4-fluoro-phenyl)-1,3-dihydro-isobenzofuran-11(S)-yl]-propyl}-methyl-phosphoramidic acid monophenyl ester	4.94	
E1035	phenyl	methyl	{3-[5-Cyano-1-(4-fluoro-phenyl)-1,3-dihydro-isobenzofuran-11(S)-yl]-propyl}-methyl-phosphoramidic acid methyl ester phenyl ester	5.00	



20

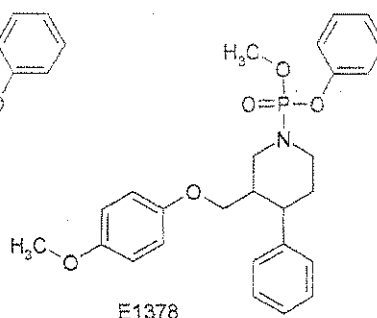
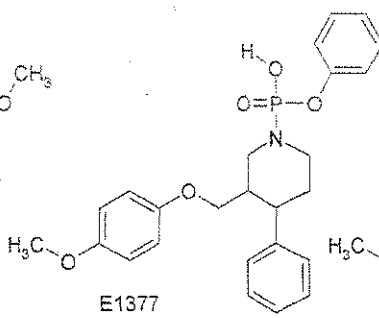
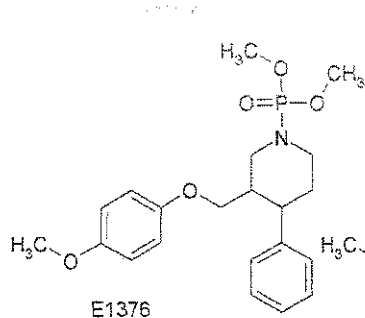
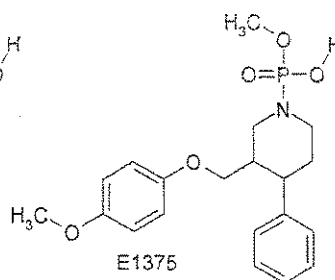
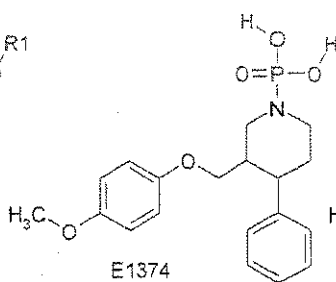
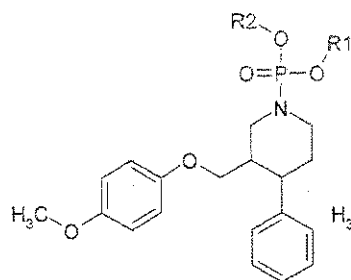
Femoxetine (Malexil®)

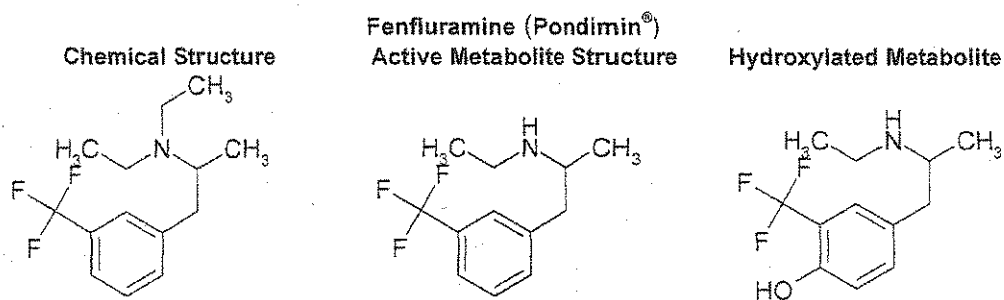
Chemical Structure Active Metabolite Structure Hydroxylated Metabolite



Compound	R1	R2	Chemical Name
E1374	hydrogen	hydrogen	[3-(4-Methoxy-phenoxy-methyl)-4-phenyl-piperidin-1-yl]-phosphonic acid
E1375	hydrogen	methyl	[3-(4-Methoxy-phenoxy-methyl)-4-phenyl-piperidin-1-yl]-phosphonic acid monomethyl ester
E1376	methyl	methyl	[3-(4-Methoxy-phenoxy-methyl)-4-phenyl-piperidin-1-yl]-phosphonic acid dimethyl ester
E1377	phenyl	hydrogen	[3-(4-Methoxy-phenoxy-methyl)-4-phenyl-piperidin-1-yl]-phosphonic acid monophenyl ester
E1378	phenyl	methyl	[3-(4-Methoxy-phenoxy-methyl)-4-phenyl-piperidin-1-yl]-phosphonic acid methyl ester phenyl ester

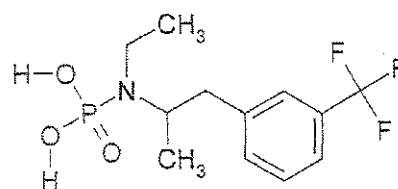
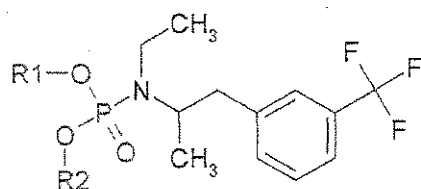
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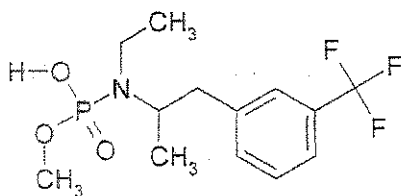


Compound	R1	R2	Chemical Name	Estimated LogP	pKa
E1314	hydrogen	hydrogen	Ethyl-[1-methyl-2-(3-trifluoromethyl-phenyl)-ethyl]-phosphoramidic acid	3.48	3.29
E1315	hydrogen	methyl	Ethyl-[1-methyl-2-(3-trifluoromethyl-phenyl)-ethyl]-phosphoramidic acid monomethyl ester	3.54	4.36
E1316	methyl	methyl	Ethyl-[1-methyl-2-(3-trifluoromethyl-phenyl)-ethyl]-phosphoramidic acid dimethyl ester	3.60	3.60
E1317	phenyl	hydrogen	Ethyl-[1-methyl-2-(3-trifluoromethyl-phenyl)-ethyl]-phosphoramidic acid monophenyl ester	5.31	4.00
E1318	phenyl	methyl	Ethyl-[1-methyl-2-(3-trifluoromethyl-phenyl)-ethyl]-phosphoramidic acid methyl ester phenyl ester	5.36	4.11

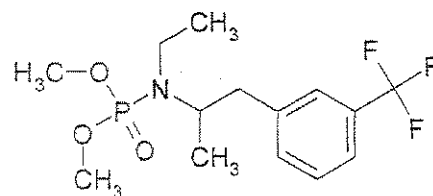
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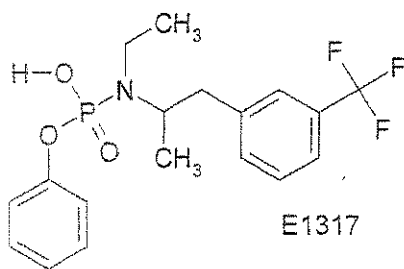
E1314



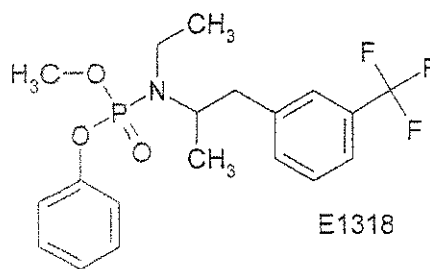
E1315



E1316



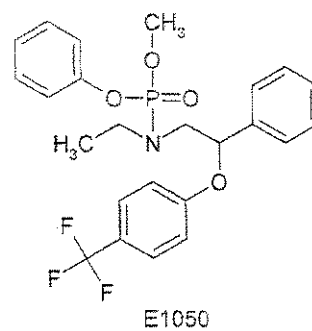
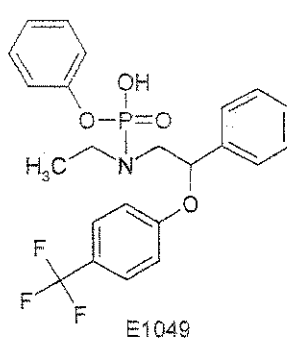
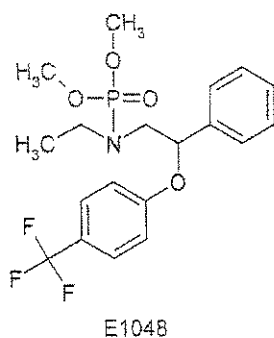
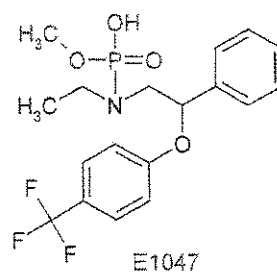
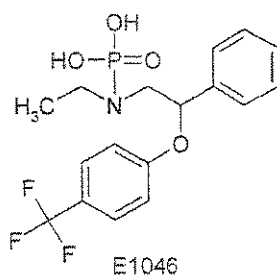
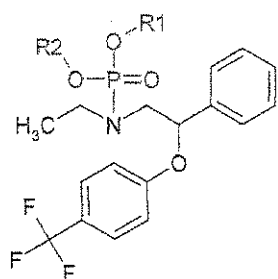
E1317



E1318

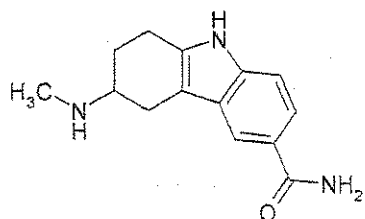
Chemical Structure			Fluoxetine (Prozac [®]) Active Metabolite Structure	Hydroxylated Metabolite	
Compound	R1	R2	Chemical Name	Estimated LogP	Estimated pKa
E1046	hydrogen	hydrogen	Ethyl-[2-phenyl-2-(4-trifluoromethyl-phenoxy)-ethyl]-phosphoramidic acid	4.23	4.64
E1047	hydrogen	methyl	Ethyl-[2-phenyl-2-(4-trifluoromethyl-phenoxy)-ethyl]-phosphoramidic acid monomethyl ester	4.29	3.02
E1048	methyl	methyl	Ethyl-[2-phenyl-2-(4-trifluoromethyl-phenoxy)-ethyl]-phosphoramidic acid dimethyl ester	4.35	3.96
E1049	phenyl	hydrogen	Ethyl-[2-phenyl-2-(4-trifluoromethyl-phenoxy)-ethyl]-phosphoramidic acid monophenyl ester	6.06	2.64
E1050	phenyl	methyl	Ethyl-[2-phenyl-2-(4-trifluoromethyl-phenoxy)-ethyl]-phosphoramidic acid methyl ester phenyl ester	6.11	4.49

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Frovatriptan (Frova®)

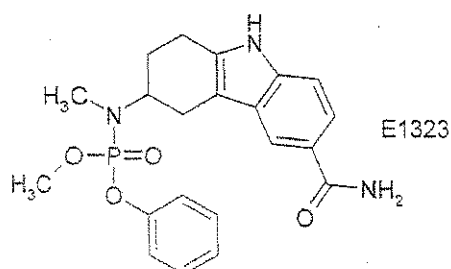
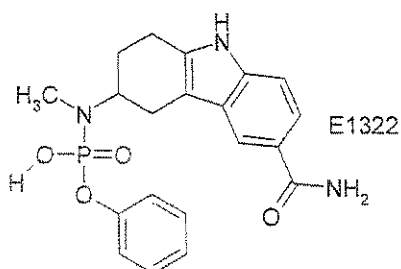
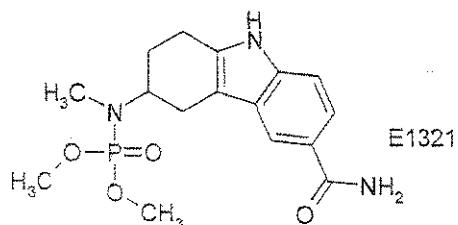
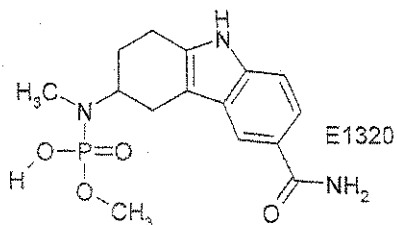
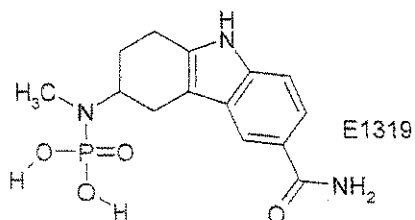
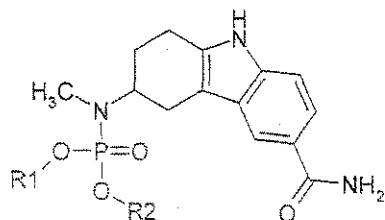
Chemical Structure



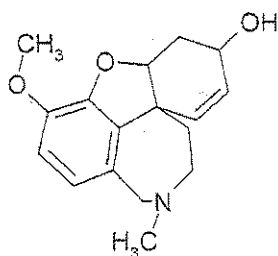
Hydroxylated Metabolite

Compound	R1	R2	Chemical Name	Estimated LogP	pKa
E1319	hydrogen	hydrogen	(6-Carbamoyl-2,3,4,9-tetrahydro-1H-carbazol-3-yl)-methyl-phosphoramidic acid	1.27	2.52
E1320	hydrogen	methyl	(6-Carbamoyl-2,3,4,9-tetrahydro-1H-carbazol-3-yl)-methyl-phosphoramidic acid monomethyl ester	1.33	5.13
E1321	methyl	methyl	(6-Carbamoyl-2,3,4,9-tetrahydro-1H-carbazol-3-yl)-methyl-phosphoramidic acid dimethyl ester	1.38	3.65
E1322	phenyl	hydrogen	(6-Carbamoyl-2,3,4,9-tetrahydro-1H-carbazol-3-yl)-methyl-phosphoramidic acid monophenyl ester	3.09	4.70
E1323	phenyl	methyl	(6-Carbamoyl-2,3,4,9-tetrahydro-1H-carbazol-3-yl)-methyl-phosphoramidic acid methyl ester phenyl ester	3.15	3.13

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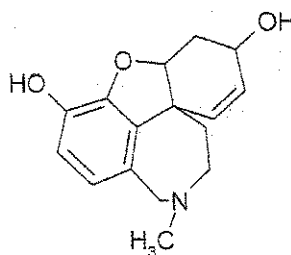


Chemical Structure



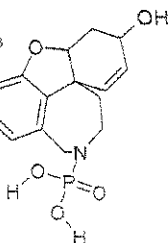
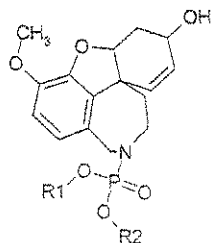
Galantamine (Reminyl®)
Active Metabolite Structure

Hydroxylated Metabolite

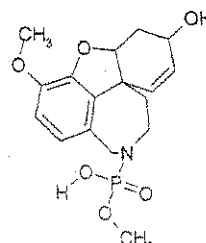


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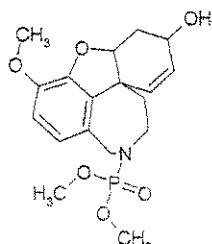
Compound	R1	R2	Chemical Name
E1259	hydrogen	hydrogen	6H-benzofuro[3a,3,2-ef][2]benzazepin-6-ol, 4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-, (4aS,6-R,8aS)-phosphoramidic acid
E1260	hydrogen	methyl	6H-benzofuro[3a,3,2-ef][2]benzazepin-6-ol, 4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-, (4aS,6-R,8aS)-phosphoramidic acid monomethyl ester
E1261	methyl	methyl	6H-benzofuro[3a,3,2-ef][2]benzazepin-6-ol, 4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-, (4aS,6-R,8aS)-phosphoramidic acid dimethyl ester
E1262	phenyl	hydrogen	6H-benzofuro[3a,3,2-ef][2]benzazepin-6-ol, 4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-, (4aS,6-R,8aS)-phosphoramidic acid monophenyl ester
E1263	phenyl	methyl	6H-benzofuro[3a,3,2-ef][2]benzazepin-6-ol, 4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-, (4aS,6-R,8aS)-phosphoramidic acid methyl ester phenyl ester



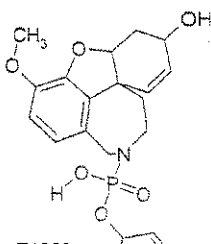
E1259



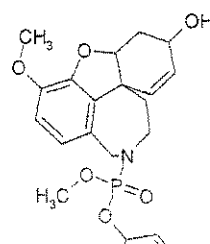
E1260



E1261



E1262

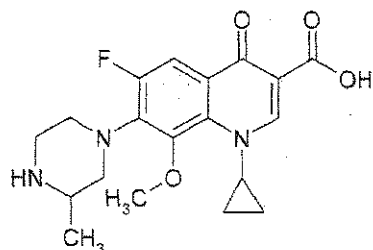


E1263

Gatifloxacin (Tequine®)

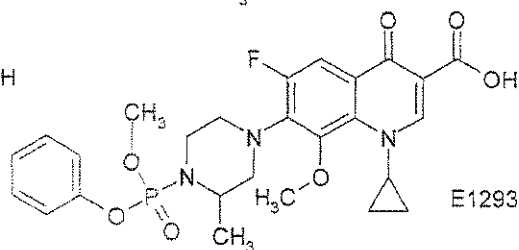
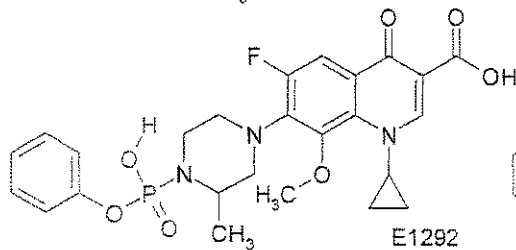
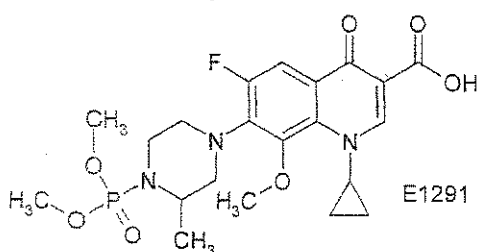
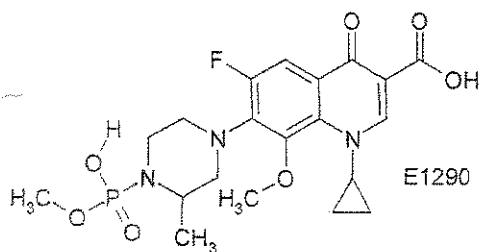
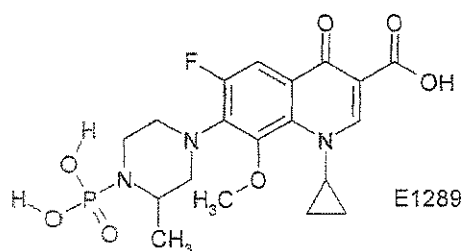
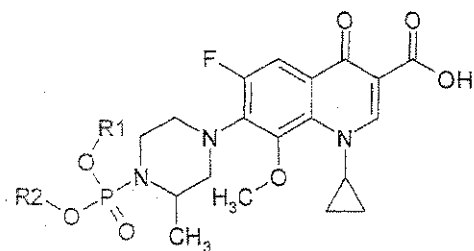
Chemical Structure

Hydroxylated Metabolite



Compound	R1	R2	Chemical Name	Estimated LogP	pKa
E1289	hydrogen	hydrogen	1-Cyclopropyl-6-fluoro-8-methoxy-7-(3-methyl-4-phosphono-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid	1.78	5.15
E1290	hydrogen	methyl	1-Cyclopropyl-6-fluoro-7-[4-(hydroxy-methoxy-phosphoryl)-3-methyl-piperazin-1-yl]-8-methoxy-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid	1.84	2.51
E1291	methyl	methyl	1-Cyclopropyl-7-[4-(dimethoxy-phosphoryl)-3-methyl-piperazin-1-yl]-6-fluoro-8-methoxy-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid	1.90	6.22
E1292	phenyl	hydrogen	1-Cyclopropyl-6-fluoro-7-[4-(hydroxy-phenoxy-phosphoryl)-3-methyl-piperazin-1-yl]-8-methoxy-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid	3.61	2.04
E1293	phenyl	methyl	1-Cyclopropyl-6-fluoro-8-methoxy-7-[4-(methoxy-phenoxy-phosphoryl)-3-methyl-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid	3.66	6.36

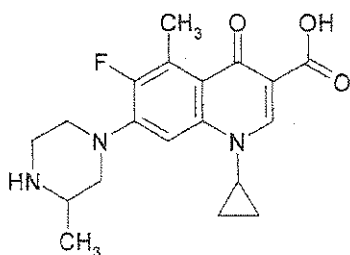
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Grepafloxacin (Raxar®)

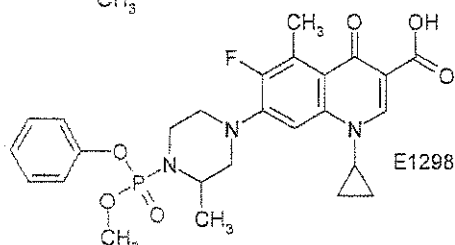
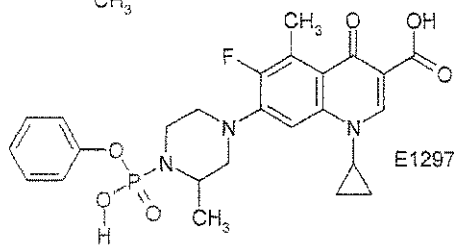
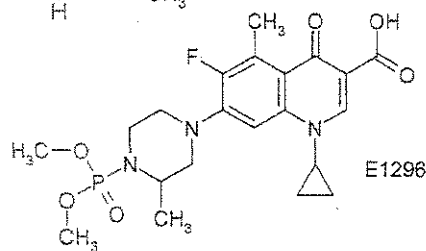
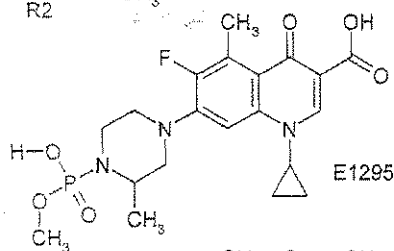
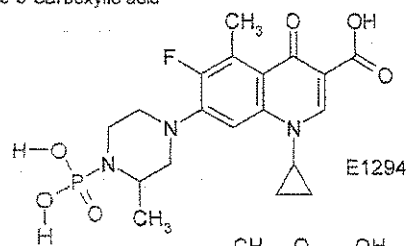
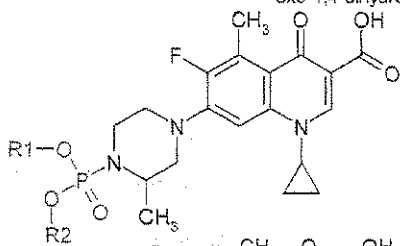
Chemical Structure

Hydroxylated Metabolite



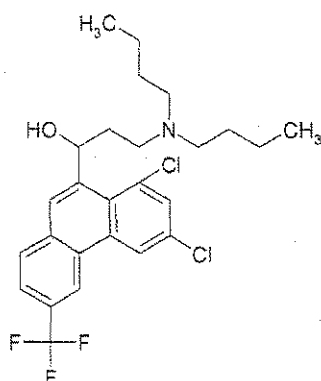
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Compound	R1	R2	Chemical Name	Estimated LogP	pKa
E1294	hydrogen	hydrogen	1-Cyclopropyl-6-fluoro-5-methyl-7-(3-methyl-4-phosphono-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid		
E1295	hydrogen	methyl	1-Cyclopropyl-6-fluoro-7-[4-(hydroxy-methoxy-phosphoryl)-3-methyl-piperazin-1-yl]-5-methyl-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid		
E1296	methyl	methyl	1-Cyclopropyl-7-[4-(dimethoxy-phosphoryl)-3-methyl-piperazin-1-yl]-6-fluoro-5-methyl-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid	2.36	6.49
E1297	phenyl	hydrogen	1-Cyclopropyl-6-fluoro-7-[4-(hydroxy-phenoxy-phosphoryl)-3-methyl-piperazin-1-yl]-5-methyl-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid	4.07	1.76
E1298	phenyl	methyl	1-Cyclopropyl-6-fluoro-7-[4-(methoxy-phenoxy-phosphoryl)-3-methyl-piperazin-1-yl]-5-methyl-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid	4.13	6.63

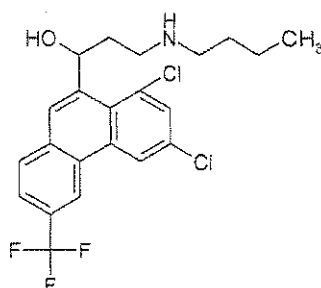


Halofantrine (Halfan®)

Chemical Structure

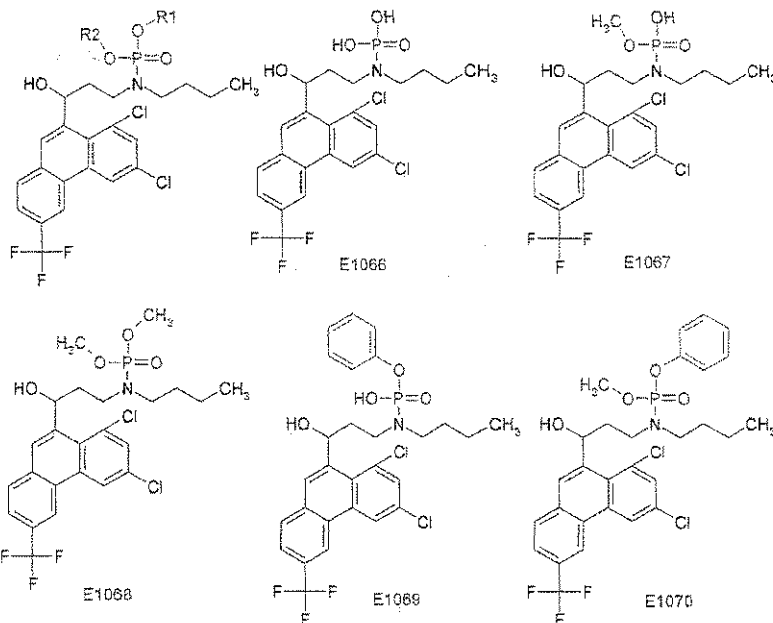


Active Metabolite Structure



Compound	R1	R2	Chemical Name	Estimated LogP	Estimated pKa
E1066	hydrogen	hydrogen	Butyl-[3-(6,8-dichloro-3-trifluoromethyl-phenanthren-9-yl)-3-hydroxy-propyl]-phosphoramidic acid	6.64	3.57
E1067	hydrogen	methyl	Butyl-[3-(6,8-dichloro-3-trifluoromethyl-phenanthren-9-yl)-3-hydroxy-propyl]-phosphoramidic acid monomethyl ester	6.70	4.09
E1068	methyl	methyl	Butyl-[3-(6,8-dichloro-3-trifluoromethyl-phenanthren-9-yl)-3-hydroxy-propyl]-phosphoramidic acid dimethyl ester	6.75	3.77
E1069	phenyl	hydrogen	Butyl-[3-(6,8-dichloro-3-trifluoromethyl-phenanthren-9-yl)-3-hydroxy-propyl]-phosphoramidic acid monophenyl ester	8.47	3.70
E1070	phenyl	methyl	Butyl-[3-(6,8-dichloro-3-trifluoromethyl-phenanthren-9-yl)-3-hydroxy-propyl]-phosphoramidic acid methyl ester phenyl ester	8.52	4.29

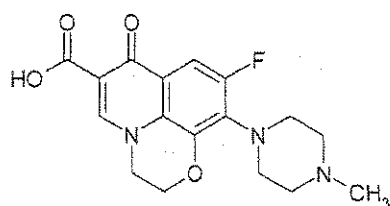
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Levofloxacin (Lеваquin®)

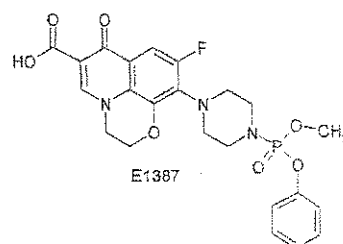
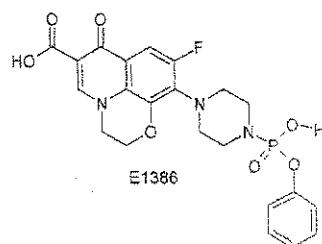
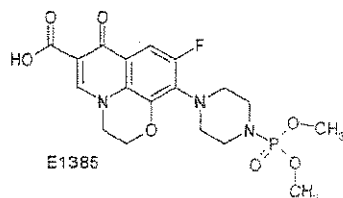
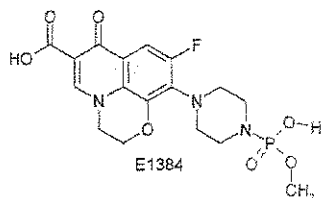
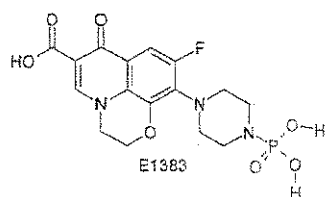
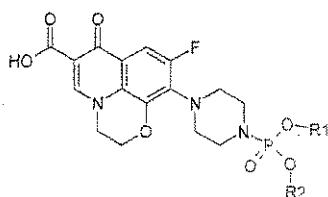
Chemical Structure

Hydroxylated Metabolite



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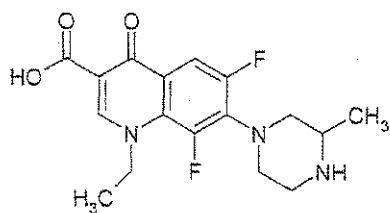
Compound	R1	R2	Chemical Name
E1383	hydrogen	hydrogen	8-Fluoro-6-oxo-9-(4-phosphono-piperazin-1-yl)-2,3-dihydro-6H-1-oxa-3a-aza-phenalene-5-carboxylic acid
E1384	hydrogen	methyl	8-Fluoro-9-[4-(hydroxy-methoxy-phosphoryl)-piperazin-1-yl]-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalene-5-carboxylic acid
E1385	methyl	methyl	9-[4-(Dimethoxy-phosphoryl)-piperazin-1-yl]-8-fluoro-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalene-5-carboxylic acid
E1386	phenyl	hydrogen	8-Fluoro-9-[4-(hydroxy-phenoxy-phosphoryl)-piperazin-1-yl]-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalene-5-carboxylic acid
E1387	phenyl	methyl	8-Fluoro-9-[4-(methoxy-phenoxy-phosphoryl)-piperazin-1-yl]-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalene-5-carboxylic acid



Lomefloxacin (Maxaquin®)

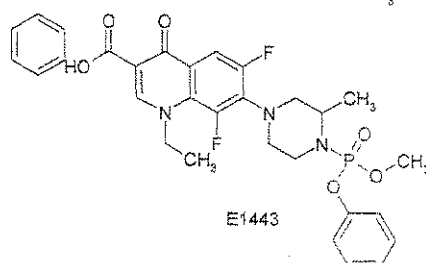
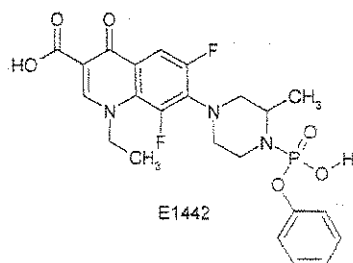
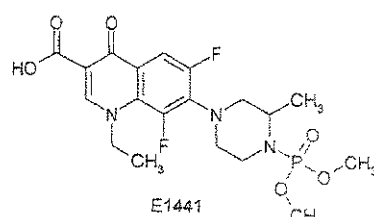
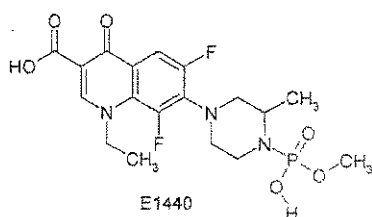
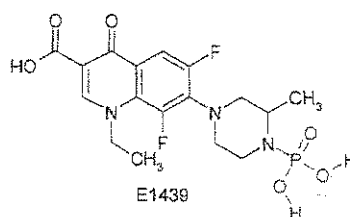
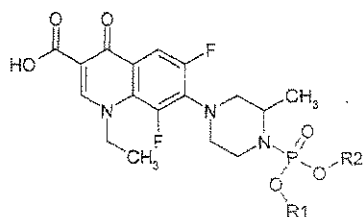
Chemical Structure

Hydroxylated Metabolite

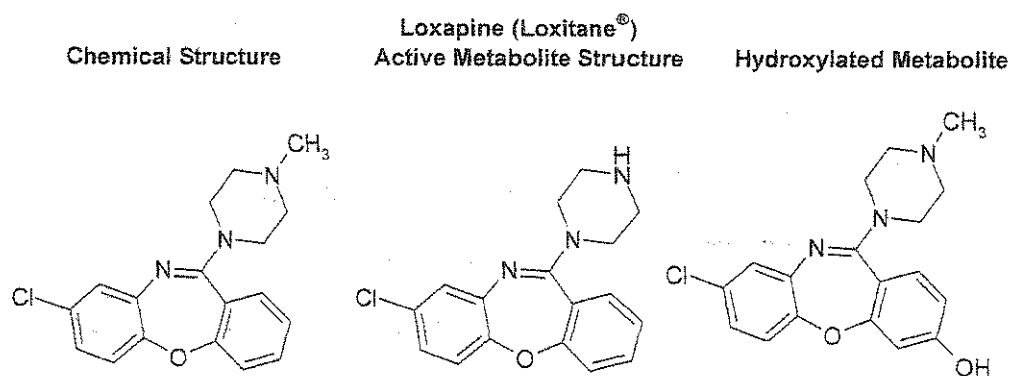


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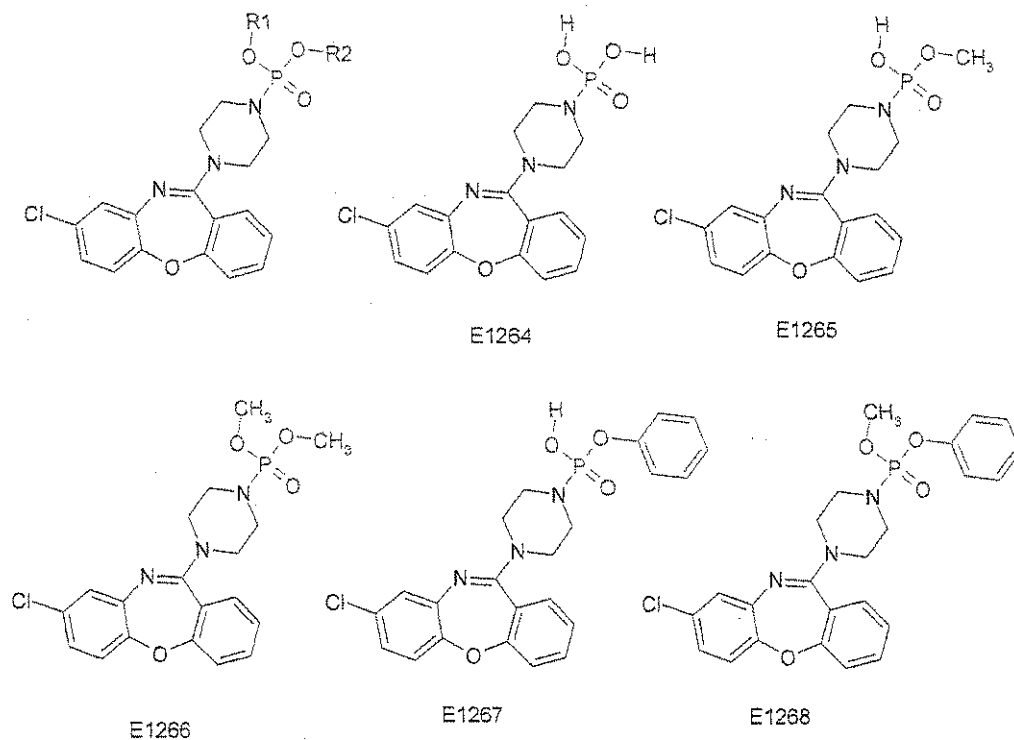
Compound	R1	R2	Chemical Name	Estimated LogP	Estimated pKa
E1439	hydrogen	hydrogen	1-Ethyl-6,8-difluoro-7-(3-methyl-4-phosphono-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid		
E1440	hydrogen	methyl	1-Ethyl-6,8-difluoro-7-[4-(hydroxy-methoxy-phosphoryl)-3-methyl-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid		
E1441	methyl	methyl	7-[4-(Dimethoxy-phosphoryl)-3-methyl-piperazin-1-yl]-1-ethyl-6,8-difluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid		
E1442	phenyl	hydrogen	1-Ethyl-6,8-difluoro-7-[4-(hydroxy-phenoxy-phosphoryl)-3-methyl-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid		
E1443	phenyl	methyl	1-Ethyl-6,8-difluoro-7-[4-(methoxy-phenoxy-phosphoryl)-3-methyl-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid; compound with benzene		



5

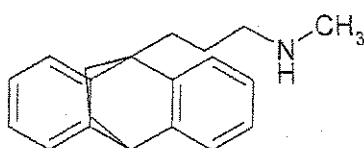


Compound	R1	R2	Chemical Name	Estimated LogP	pKa
E1264	hydrogen	hydrogen	[4-(8-Chloro-dibenzo[b,f][1,4]oxazepin-11-yl)-piperazin-1-yl]-phosphonic acid	2.47	4.81
E1265	hydrogen	methyl	[4-(8-Chloro-dibenzo[b,f][1,4]oxazepin-11-yl)-piperazin-1-yl]-phosphonic acid monomethyl ester	3.03	2.85
E1266	methyl	methyl	[4-(8-Chloro-dibenzo[b,f][1,4]oxazepin-11-yl)-piperazin-1-yl]-phosphonic acid dimethyl ester	3.08	5.88
E1267	phenyl	hydrogen	[4-(8-Chloro-dibenzo[b,f][1,4]oxazepin-11-yl)-piperazin-1-yl]-phosphonic acid monophenyl ester	4.79	2.38
E1268	phenyl	methyl	[4-(8-Chloro-dibenzo[b,f][1,4]oxazepin-11-yl)-piperazin-1-yl]-phosphonic acid methyl ester phenyl ester	4.85	6.02

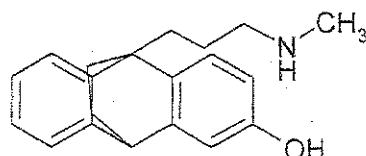


Maprotiline (Ludiomil®)

Chemical Structure

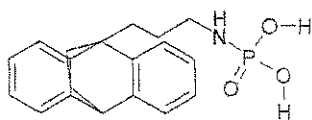
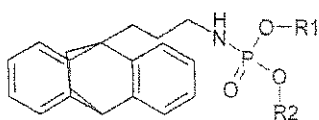


Hydroxylated Metabolite

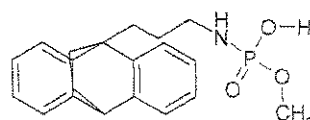


Compound	R1	R2	Chemical Name	Estimated LogP	pKa
E1344	hydrogen	hydrogen	[9,10-ethanoanthracene-9(10H)-propylamine]-methyl phosphoramidic acid	3.56	1.73
E1345	hydrogen	methyl	[9,10-ethanoanthracene-9(10H)-propylamine]-methyl phosphoramidic acid monomethyl ester	3.61	6.24
E1346	methyl	methyl	[9,10-ethanoanthracene-9(10H)-propylamine]-methyl phosphoramidic acid dimethyl ester	3.67	2.28
E1347	phenyl	hydrogen	[9,10-ethanoanthracene-9(10H)-propylamine]-methyl phosphoramidic acid monophenyl ester	5.38	5.57
E1348	phenyl	methyl	[9,10-ethanoanthracene-9(10H)-propylamine]-methyl phosphoramidic acid methyl ester phenyl ester	5.44	2.89

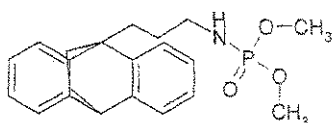
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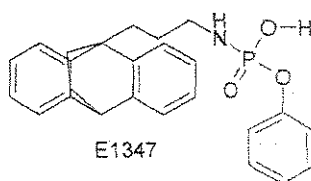
E1344



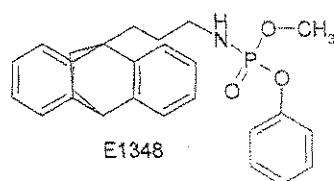
E1345



E1346



E1347

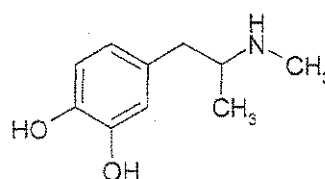
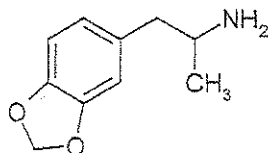
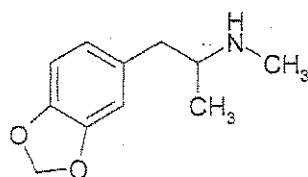


E1348

Chemical Structure

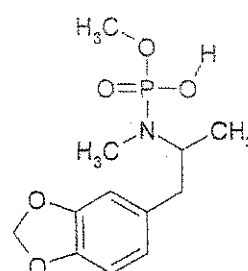
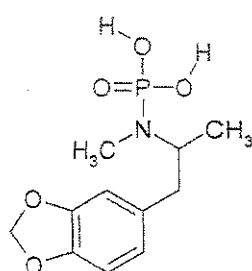
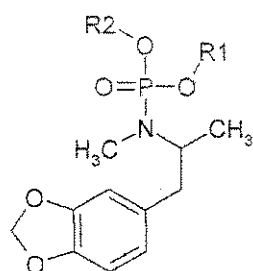
MDMA (Ecstasy®)
Active Metabolite Structure

Hydroxylated Metabolite



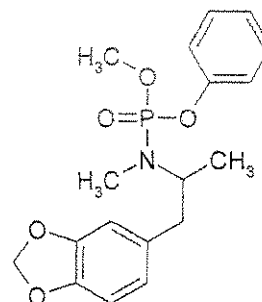
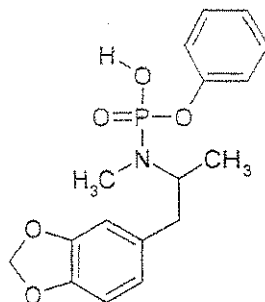
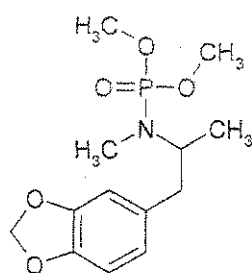
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Compound	R1	R2	Chemical Name	Estimated LogP	pKa
E1269	hydrogen	hydrogen	(2-Benzo[1,3]dioxol-5-yl-1-methyl-ethyl)-methyl-phosphoramidic acid	0.71	2.83
E1270	hydrogen	methyl	(2-Benzo[1,3]dioxol-5-yl-1-methyl-ethyl)-methyl-phosphoramidic acid monomethyl ester	0.76	4.83
E1271	methyl	methyl	(2-Benzo[1,3]dioxol-5-yl-1-methyl-ethyl)-methyl-phosphoramidic acid dimethyl ester	0.82	3.46
E1272	phenyl	hydrogen	(2-Benzo[1,3]dioxol-5-yl-1-methyl-ethyl)-methyl-phosphoramidic acid monophenyl ester	2.53	4.42
E1273	phenyl	methyl	(2-Benzo[1,3]dioxol-5-yl-1-methyl-ethyl)-methyl-phosphoramidic acid methyl ester phenyl ester	2.59	3.99



E1269

E1270



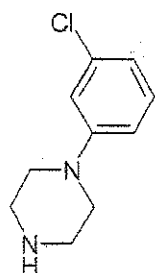
E1271

E1272

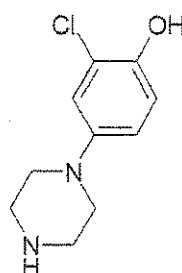
E1273

Metachlorophenylpiperazine

Chemical Structure

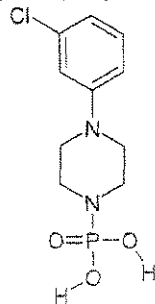
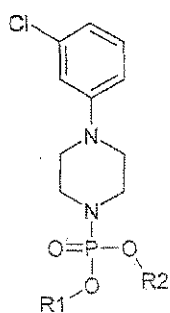


Hydroxylated Metabolite

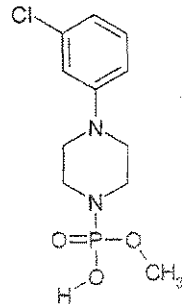


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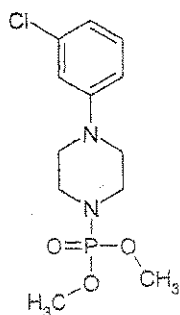
Compound	R1	R2	Chemical Name	Estimated LogP	pKa
E1195	hydrogen	hydrogen	[4-(3-Chloro-phenyl)-piperazin-1-yl]-phosphonic acid	1.77	4.99
E1196	hydrogen	methyl	[4-(3-Chloro-phenyl)-piperazin-1-yl]-phosphonic acid monomethyl ester	1.83	2.67
E1197	methyl	methyl	[4-(3-Chloro-phenyl)-piperazin-1-yl]-phosphonic acid dimethyl ester	1.89	6.06
E1198	phenyl	hydrogen	[4-(3-Chloro-phenyl)-piperazin-1-yl]-phosphonic acid monophenyl ester	3.60	2.20
E1199	phenyl	methyl	[4-(3-Chloro-phenyl)-piperazin-1-yl]-phosphonic acid methyl ester phenyl ester	3.65	6.20



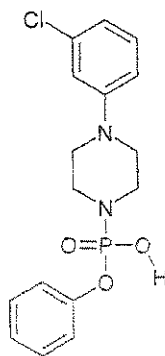
E1195



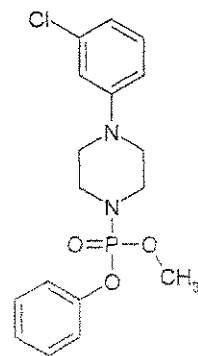
E1196



E1197

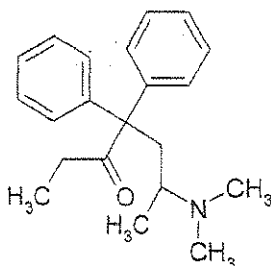


E1198



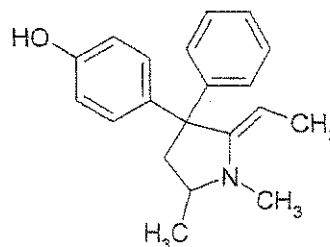
E1199

Chemical Structure



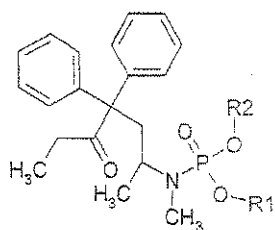
Methadone (Dolophine®)
Active Metabolite Structure

Hydroxylated Metabolite

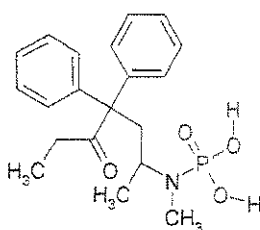


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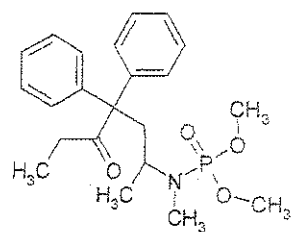
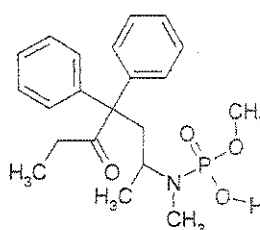
Compound	R1	R2	Chemical Name	Estimated LogP	pKa
E1299	hydrogen	hydrogen	Methyl-(1-methyl-4-oxo-3,3-diphenyl-hexyl)-phosphoramidic acid	3.54	3.26
E1300	hydrogen	methyl	Methyl-(1-methyl-4-oxo-3,3-diphenyl-hexyl)-phosphoramidic acid monomethyl ester	3.60	4.40
E1301	methyl	methyl	Methyl-(1-methyl-4-oxo-3,3-diphenyl-hexyl)-phosphoramidic acid dimethyl ester	3.65	3.36
E1302	phenyl	hydrogen	Methyl-(1-methyl-4-oxo-3,3-diphenyl-hexyl)-phosphoramidic acid monophenyl ester	5.36	4.01
E1303	phenyl	methyl	Methyl-(1-methyl-4-oxo-3,3-diphenyl-hexyl)-phosphoramidic acid methyl ester phenyl ester	5.42	4.01



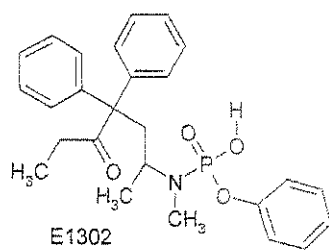
E1299



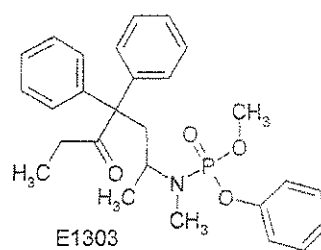
E1300



E1301



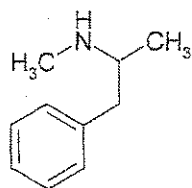
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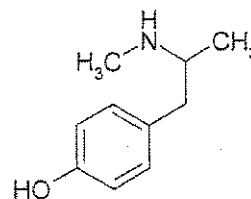
E1303

Methamphetamine (Desoxyn®)

Chemical Structure

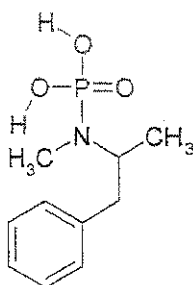
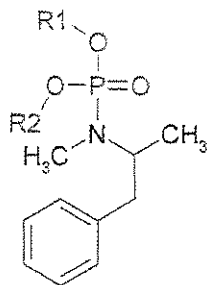


Hydroxylated Metabolite

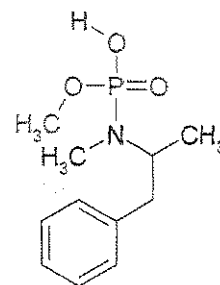


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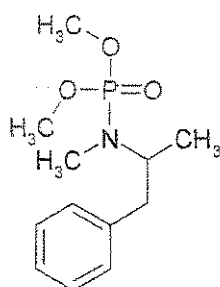
Compound	R1	R2	Chemical Name	Estimated LogP	pKa
E1217	hydrogen	hydrogen	Methyl-(1-methyl-2-phenyl-ethyl)-phosphoramidic acid	2.03	2.77
E1218	hydrogen	methyl	Methyl-(1-methyl-2-phenyl-ethyl)-phosphoramidic acid monomethyl ester	2.09	2.89
E1219	methyl	methyl	Methyl-(1-methyl-2-phenyl-ethyl)-phosphoramidic acid dimethyl ester	2.14	3.39
E1220	phenyl	hydrogen	Methyl-(1-methyl-2-phenyl-ethyl)-phosphoramidic acid monophenyl ester	3.85	4.49
E1221	phenyl	methyl	Methyl-(1-methyl-2-phenyl-ethyl)-phosphoramidic acid methyl ester phenyl ester	3.91	3.92



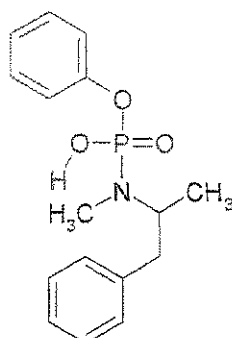
E1217



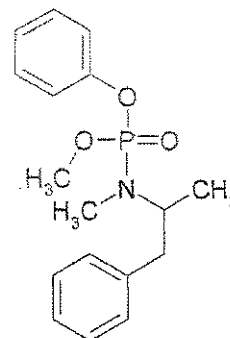
E1218



E1219



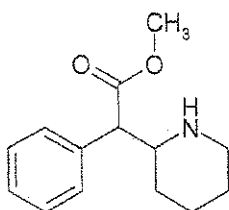
E1220



E1221

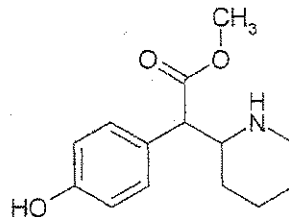
Methylphenidate (Ritalin®)

Chemical Structure



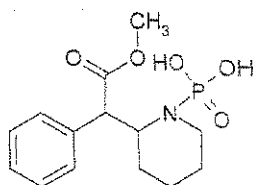
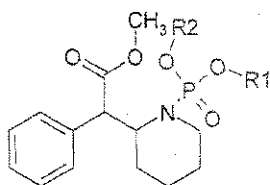
Active Metabolite Structure

Hydroxylated Metabolite

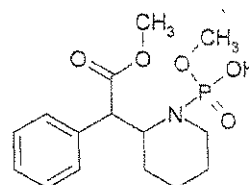


Compound	R1	R2	Chemical Name	Estimated LogP	pKa
E1086	hydrogen	hydrogen	Phenyl-(1-phosphono-piperidin-2-yl)-acetic acid methyl ester	2.37	3.57
E1087	hydrogen	methyl	[1-(Hydroxy-methoxy-phosphoryl)-piperidin-2-yl]-phenyl-acetic acid ethyl ester	2.42	4.09
E1088	methyl	methyl	[1-(Dimethoxy-phosphoryl)-piperidin-2-yl]-phenyl-acetic acid methyl ester	2.48	4.63
E1089	phenyl	hydrogen	[1-(Dimethoxy-phosphoryl)-piperidin-2-yl]-phenyl-acetic acid methyl ester	4.19	3.62
E1090	phenyl	phenyl	[1-(Methoxy-phenoxy-phosphoryl)-piperidin-2-yl]-phenyl-acetic acid methyl ester	4.25	4.78

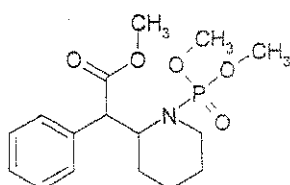
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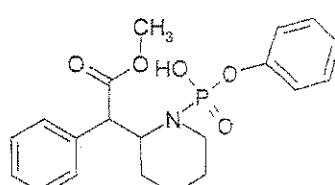
E1086



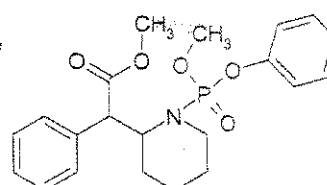
E1087



E1088



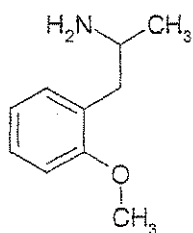
E1089



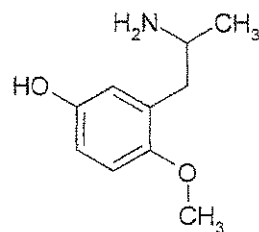
E1090

Methoxyphenamine (Orthoxinine®)

Chemical Structure

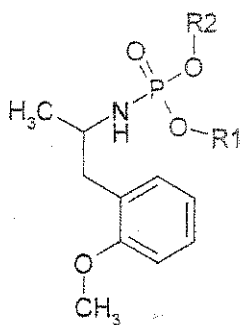


Hydroxylated Metabolite

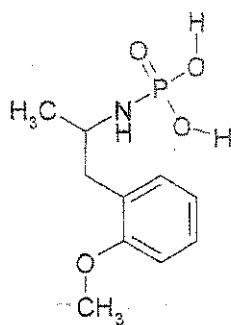


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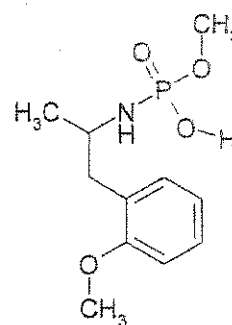
Compound	R1	R2	Chemical Name	Estimated LogP	pKa
E1304	hydrogen	hydrogen	[2-(2-Methoxy-phenyl)-1-methyl-ethyl]-phosphoramidic acid	1.56	2.29
E1305	hydrogen	methyl	[2-(2-Methoxy-phenyl)-1-methyl-ethyl]-phosphoramidic acid monomethyl ester	1.62	5.68
E1306	methyl	methyl	[2-(2-Methoxy-phenyl)-1-methyl-ethyl]-phosphoramidic acid dimethyl ester	1.68	3.03
E1307	phenyl	hydrogen	[2-(2-Methoxy-phenyl)-1-methyl-ethyl]-phosphoramidic acid monophenyl ester	3.39	5.23
E1308	phenyl	methyl	[2-(2-Methoxy-phenyl)-1-methyl-ethyl]-phosphoramidic acid methyl ester phenyl ester	3.44	3.61



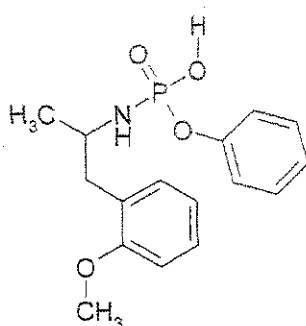
E1304



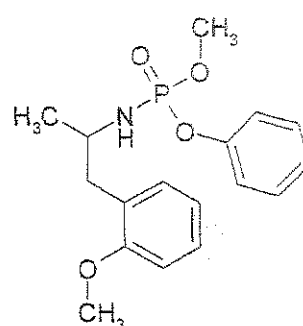
E1305



E1306

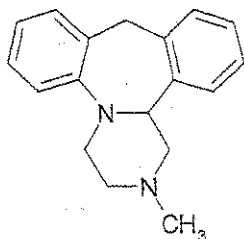


E1307

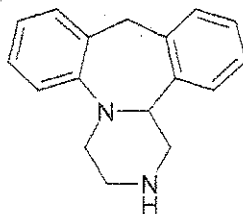


E1308

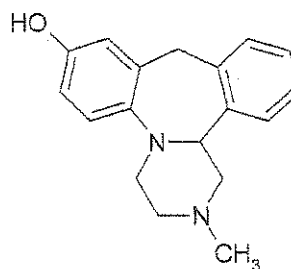
Chemical Structure



Mianserin (Tolvon®)
Active Metabolite Structure

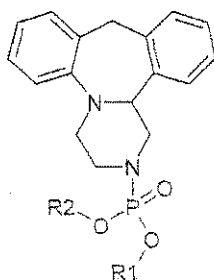


Hydroxylated Metabolite

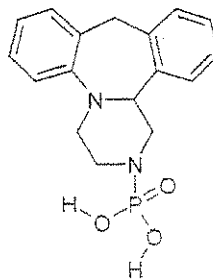


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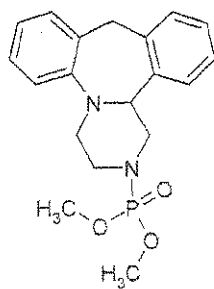
Compound	R1	R2	Chemical Name	Estimated LogP	pKa
E1164	hydrogen	hydrogen	(3,4,9,13b-Tetrahydro-1H-2,4a-diaza-tribenzo[cyclohepten-2-yl]-phosphonic acid	2.72	4.72
E1165	hydrogen	methyl	(3,4,9,13b-Tetrahydro-1H-2,4a-diaza-tribenzo[a,c,e]cyclohepten-2-yl)-phosphonic acid monomethyl ester	2.78	2.94
E1166	methyl	methyl	(3,4,9,13b-Tetrahydro-1H-2,4a-diaza-tribenzo[a,c,e]cyclohepten-2-yl)-phosphonic acid dimethyl ester	2.83	5.79
E1167	phenyl	hydrogen	(3,4,9,13b-Tetrahydro-1H-2,4a-diaza-tribenzo[a,c,e]cyclohepten-2-yl)-phosphonic acid monophenyl ester	4.55	2.46
E1168	phenyl	methyl	(3,4,9,13b-Tetrahydro-1H-2,4a-diaza-tribenzo[a,c,e]cyclohepten-2-yl)-phosphonic acid methyl ester phenyl ester	4.60	5.93



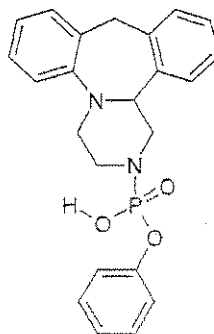
E1164



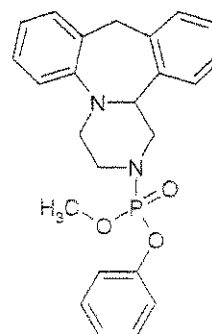
E1165



E1166



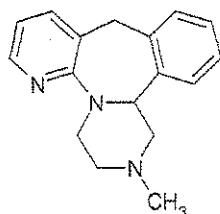
E1167



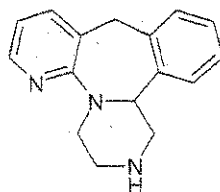
E1168

Mirtazapine (Remeron®)

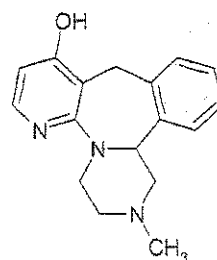
Chemical Structure



Active Metabolite Structure

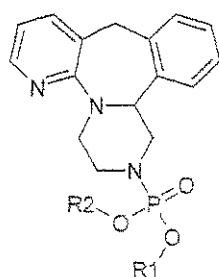


Hydroxylated Metabolite

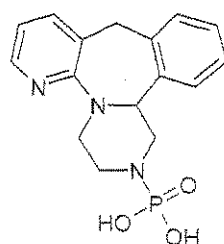


Compound	R1	R2	Chemical Name	Estimated LogP	Estimated pKa
E1061	hydrogen	hydrogen	(3,4,9,13b-Tetrahydro-1H-2,4a,5-triaza-tribenzo [a,c,e]cyclohepten-2-yl)-phosphonic acid	2.41	4.91
E1062	hydrogen	methyl	(3,4,9,13b-Tetrahydro-1H-2,4a,5-triaza-tribenzo [a,c,e]cyclohepten-2-yl)-phosphonic acid monomethyl ester	2.46	2.74
E1063	methyl	methyl	(3,4,9,13b-Tetrahydro-1H-2,4a,5-triaza-tribenzo [a,c,e]cyclohepten-2-yl)-phosphonic acid dimethyl ester	2.52	6.11
E1064	phenyl	hydrogen	(3,4,9,13b-Tetrahydro-1H-2,4a,5-triaza-tribenzo [a,c,e]cyclohepten-2-yl)-phosphonic acid monophenyl ester	4.23	2.14
E1065	phenyl	methyl	(3,4,9,13b-Tetrahydro-1H-2,4a,5-triaza-tribenzo [a,c,e]cyclohepten-2-yl)-phosphonic acid methyl ester phenyl ester	4.29	6.25

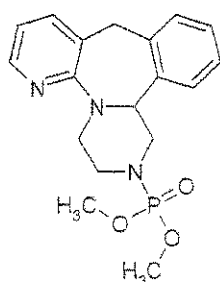
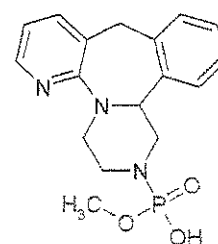
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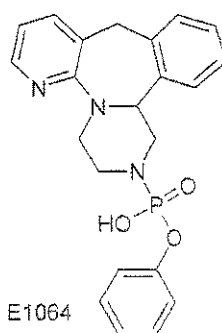
E1061



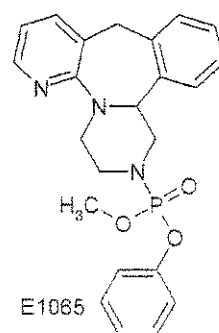
E1062



E1063



E1064

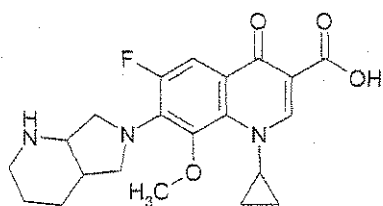


E1065

Moxifloxacin (Avalox®)

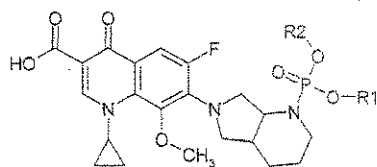
Chemical Structure

Hydroxylated Metabolite

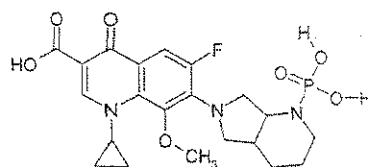


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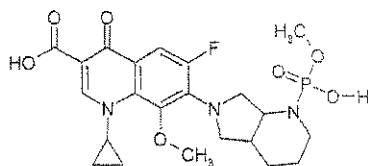
Compound	R1	R2	Chemical Name
E1434	hydrogen	hydrogen	1-Cyclopropyl-6-fluoro-8-methoxy-4-oxo-7-(1-phosphono-octahydro-pyrrolo[3,4-b]pyridin-6-yl)-1,4-dihydro-quinoline-3-carboxylic acid
E1435	hydrogen	methyl	1-Cyclopropyl-6-fluoro-7-[1-(hydroxy-methoxy-phosphoryl)-octahydro-pyrrolo[3,4-b]pyridin-6-yl]-8-methoxy-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
E1436	methyl	methyl	1-Cyclopropyl-7-[1-(dimethoxy-phosphoryl)-octahydro-pyrrolo[3,4-b]pyridin-6-yl]-6-fluoro-8-methoxy-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
E1437	phenyl	hydrogen	1-Cyclopropyl-6-fluoro-7-[1-(hydroxy-phenoxy-phosphoryl)-octahydro-pyrrolo[3,4-b]pyridin-6-yl]-8-methoxy-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
E1438	phenyl	methyl	1-Cyclopropyl-6-fluoro-8-methoxy-7-[1-(methoxy-phenoxy-phosphoryl)-octahydro-pyrrolo[3,4-b]pyridin-6-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid



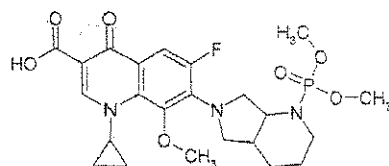
E1434



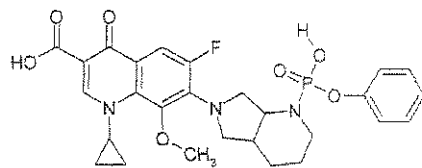
E1435



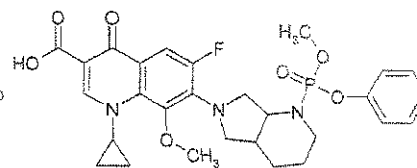
E1436



E1437



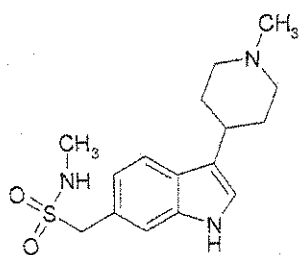
E1438



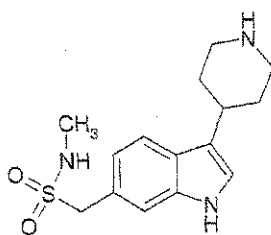
E1439

Naratriptan (Amerge®)

Chemical Structure

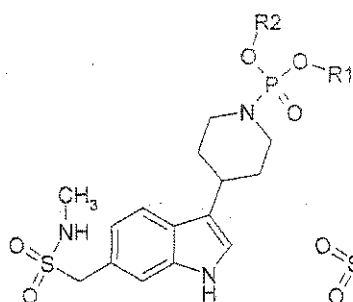


Active Metabolite Structure

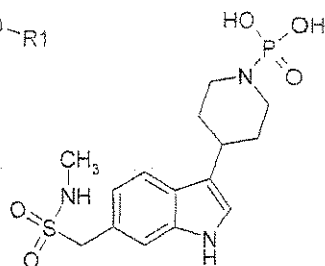


Compound	R1	R2	Chemical Name	Estimated LogP	Estimated pKa
E1091	hydrogen	hydrogen	4-(6-Methylsulfonylmethyl-1H-indol-3-yl)-piperidin-1-yl]-phosphonic acid	1.58	2.70
E1092	hydrogen	methyl	[4-(6-Methylsulfonylmethyl-1H-indol-3-yl)-piperidin-1-yl]-phosphonic acid monomethyl ester	1.63	4.95
E1093	methyl	methyl	[4-(6-Methylsulfonylmethyl-1H-indol-3-yl)-piperidin-1-yl]-phosphonic acid dimethyl ester	1.69	3.77
E1094	phenyl	hydrogen	[4-(6-Methylsulfonylmethyl-1H-indol-3-yl)-piperidin-1-yl]-phosphonic acid monophenyl ester	3.40	4.48
E1095	phenyl	methyl	[4-(6-Methylsulfonylmethyl-1H-indol-3-yl)-piperidin-1-yl]-phosphonic acid methyl ester phenyl ester	3.46	3.92

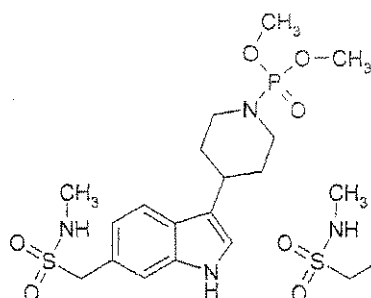
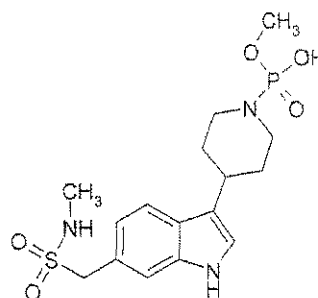
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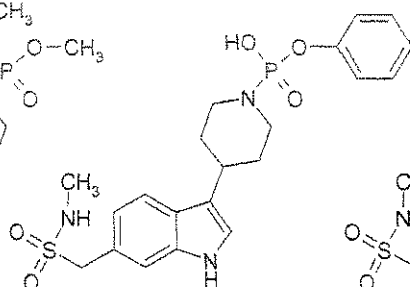
E1091



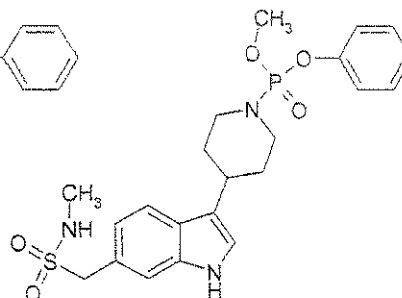
E1092



E1093



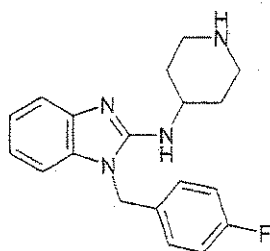
E1094



E1095

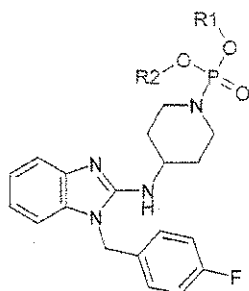
Norastemizole

Chemical Structure

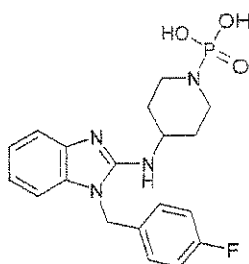


Compound	R1	R2	Chemical Name	Estimated LogP	Estimated pKa
E1101	hydrogen	hydrogen	{4-[1-(4-Fluoro-benzyl)-1H-benzimidazol-2-ylamino]-piperidin-1-yl}-phosphonic acid	3.75	3.92
E1102	hydrogen	methyl	{4-[1-(4-Fluoro-benzyl)-1H-benzimidazol-2-ylamino]-piperidin-1-yl}-phosphonic acid monomethyl ester	3.80	3.74
E1103	methyl	methyl	{4-[1-(4-Fluoro-benzyl)-1H-benzimidazol-2-ylamino]-piperidin-1-yl}-phosphonic acid dimethyl ester	3.86	4.99
E1104	phenyl	hydrogen	{4-[1-(4-Fluoro-benzyl)-1H-benzimidazol-2-ylamino]-piperidin-1-yl}-phosphonic acid monophenyl ester	5.57	3.26
E1105	phenyl	methyl	{4-[1-(4-Fluoro-benzyl)-1H-benzimidazol-2-ylamino]-piperidin-1-yl}-phosphonic acid methyl ester phenyl ester	5.63	5.13

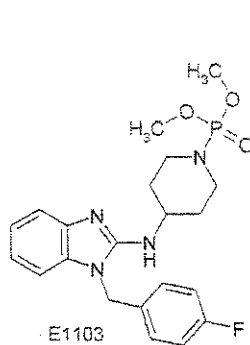
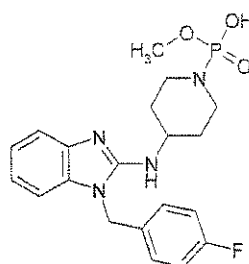
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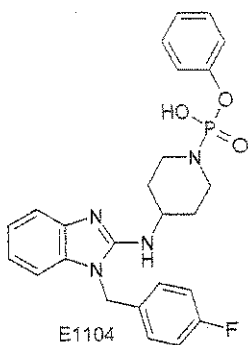
E1101



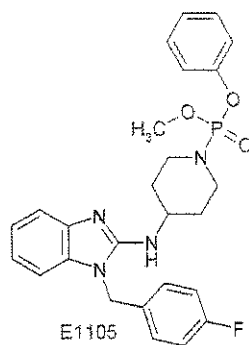
E1102



E1103



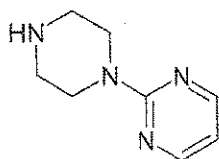
E1104



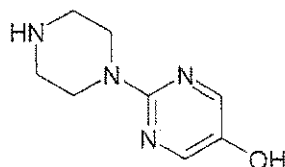
E1105

Norbuspirone

Chemical Structure

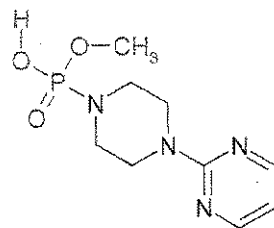
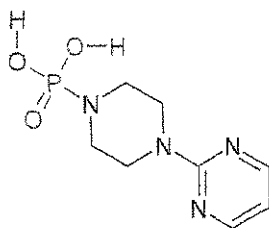
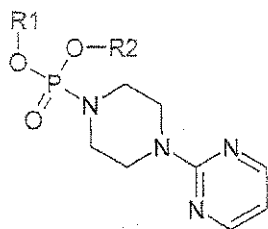


Hydroxylated Metabolite



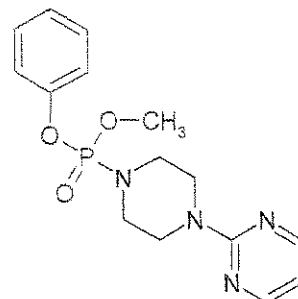
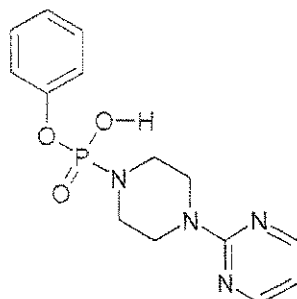
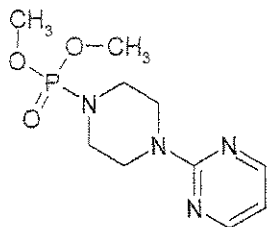
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Compound	R1	R2	Chemical Name	Estimated LogP	pKa
E1200	hydrogen	hydrogen	(4-Pyrimidin-2-yl-piperazin-1-yl)-phosphonic acid	-0.07	6.04
E1201	hydrogen	methyl	(4-Pyrimidin-2-yl-piperazin-1-yl)-phosphonic acid monomethyl ester	-0.01	1.62
E1202	methyl	methyl	(4-Pyrimidin-2-yl-piperazin-1-yl)-phosphonic acid dimethyl ester	0.05	7.10
E1203	phenyl	hydrogen	(4-Pyrimidin-2-yl-piperazin-1-yl)-phosphonic acid monophenyl ester	1.76	1.14
E1204	phenyl	methyl	(4-Pyrimidin-2-yl-piperazin-1-yl)-phosphonic acid methyl ester phenyl ester	1.81	7.25



E1200

E1201



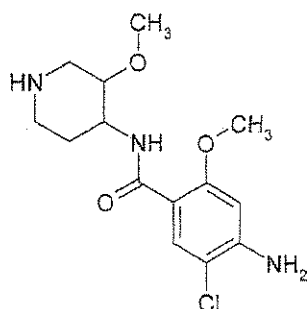
E1202

E1203

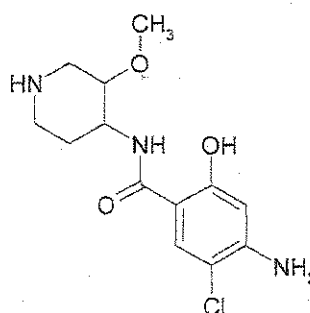
E1204

Norcisapride

Chemical Structure

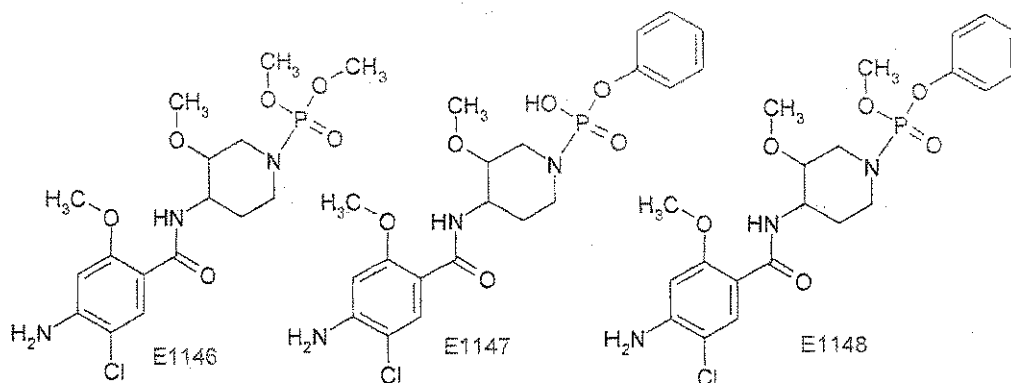
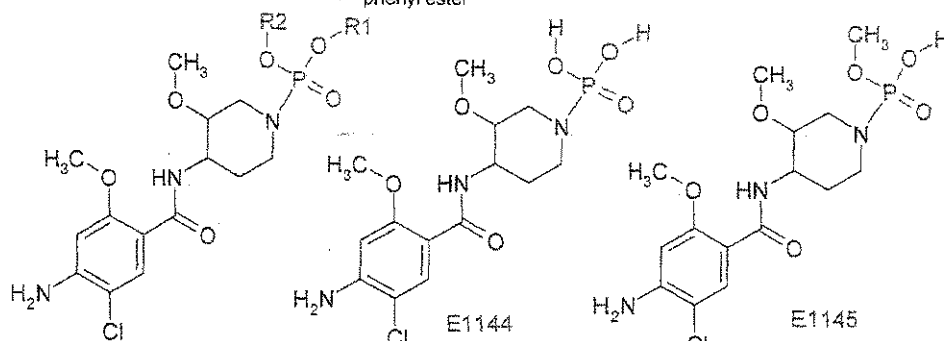


Hydroxylated Metabolite



5

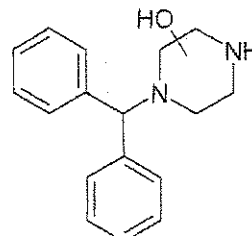
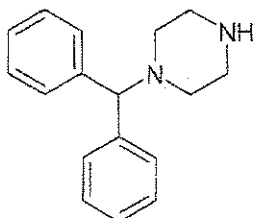
Compound	R1	R2	Chemical Name	Estimated LogP	pKa
E1144	hydrogen	hydrogen	[4-(4-Amino-5-chloro-2-methoxy-benzoylamino)-3-methoxy-piperidin-1-yl]-phosphonic acid	0.04	4.78
E1145	hydrogen	methyl	[4-(4-Amino-5-chloro-2-methoxy-benzoylamino)-3-methoxy-piperidin-1-yl]-phosphonic acid monomethyl ester	0.10	2.89
E1146	methyl	methyl	[4-(4-Amino-5-chloro-2-methoxy-benzoylamino)-3-methoxy-piperidin-1-yl]-phosphonic acid dimethyl ester	0.15	5.85
E1147	phenyl	hydrogen	[4-(4-Amino-5-chloro-2-methoxy-benzoylamino)-3-methoxy-piperidin-1-yl]-phosphonic acid monophenyl ester	1.86	2.41
E1148	phenyl	methyl	[4-(4-Amino-5-chloro-2-methoxy-benzoylamino)-3-methoxy-piperidin-1-yl]-phosphonic acid methyl ester phenyl ester	1.92	5.99



Chemical Structure

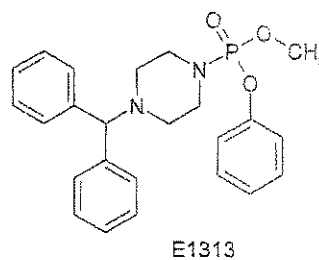
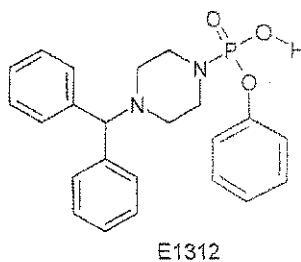
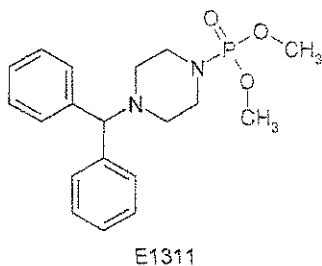
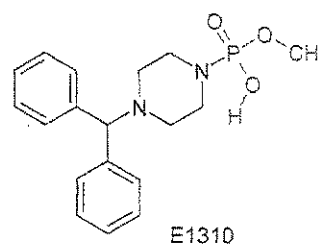
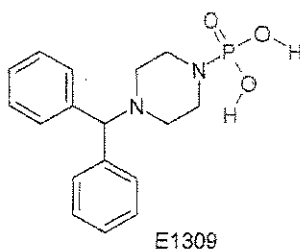
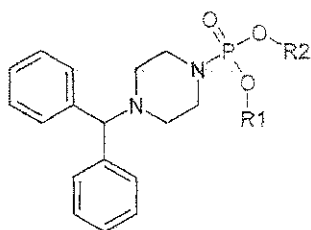
Norcyclizine

Hydroxylated Metabolite



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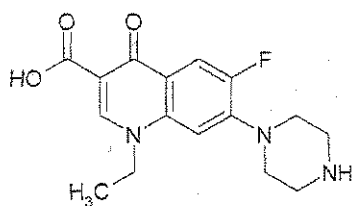
Compound	R1	R2	Chemical Name	Estimated LogP	pKa
E1309	hydrogen	hydrogen	(4-Benzhydryl-piperazin-1-yl)-phosphonic acid	2.34	4.10
E1310	hydrogen	methyl	(4-Benzhydryl-piperazin-1-yl)-phosphonic acid monomethyl ester	2.40	3.56
E1311	methyl	methyl	(4-Benzhydryl-piperazin-1-yl)-phosphonic acid dimethyl ester	2.45	5.16
E1312	phenyl	hydrogen	(4-Benzhydryl-piperazin-1-yl)-phosphonic acid monophenyl ester	4.16	3.09
E1313	phenyl	methyl	(4-Benzhydryl-piperazin-1-yl)-phosphonic acid methyl ester phenyl ester	4.22	5.31



Norfloxacin (Noroxin®)

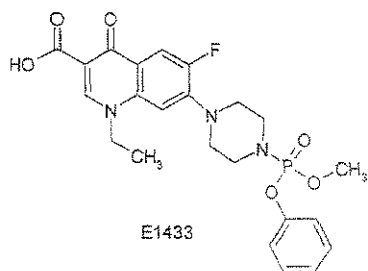
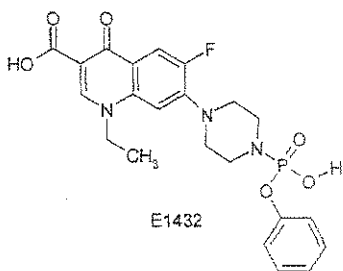
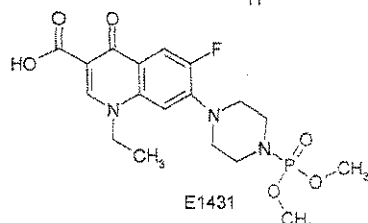
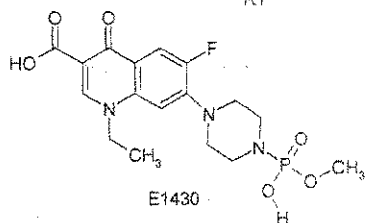
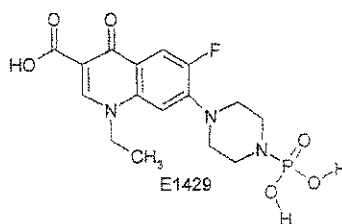
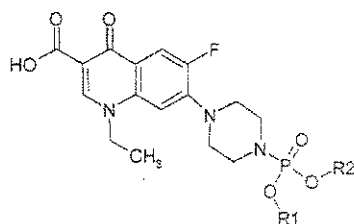
Chemical Structure

Hydroxylated Metabolite



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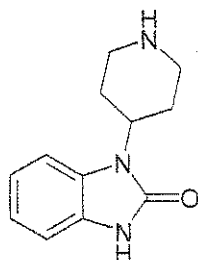
Compound	R1	R2	Chemical Name
E1429	hydrogen	hydrogen	1-Ethyl-6-fluoro-4-oxo-7-(4-phosphono-piperazin-1-yl)-1,4-dihydro-quinoline-3-carboxylic acid
E1430	hydrogen	methyl	1-Ethyl-6-fluoro-7-[4-(hydroxy-methoxy-phosphoryl)-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
E1431	methyl	methyl	7-[4-(Dimethoxy-phosphoryl)-piperazin-1-yl]-1-ethyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
E1432	phenyl	hydrogen	1-Ethyl-6-fluoro-7-[4-(hydroxy-phenoxy-phosphoryl)-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
E1433	phenyl	methyl	1-Ethyl-6-fluoro-7-[4-(methoxy-phenoxy-phosphoryl)-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid



Chemical Structure

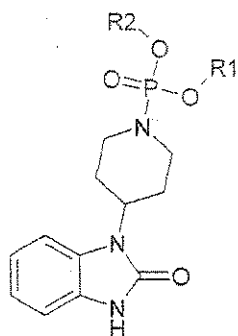
Norpimozide

Hydroxylated Metabolite

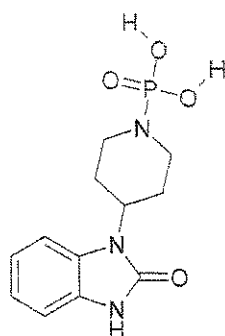


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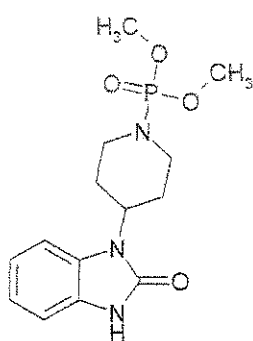
Compound	R1	R2	Chemical Name	Estimated LogP	pKa
E1279	hydrogen	hydrogen	[4-(2-Oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidin-1-yl]-phosphonic acid	0.90	2.92
E1280	hydrogen	methyl	[4-(2-Oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidin-1-yl]-phosphonic acid monomethyl ester	0.96	4.74
E1281	methyl	methyl	[4-(2-Oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidin-1-yl]-phosphonic acid dimethyl ester	1.01	3.99
E1282	phenyl	hydrogen	[4-(2-Oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidin-1-yl]-phosphonic acid monophenyl ester	2.72	4.26
E1283	phenyl	methyl	[4-(2-Oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidin-1-yl]-phosphonic acid methyl ester phenyl ester	2.78	4.13



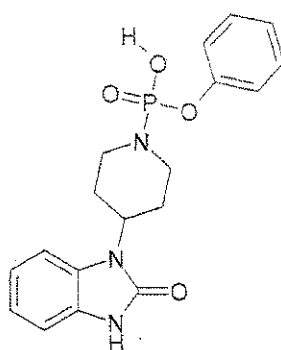
E1279



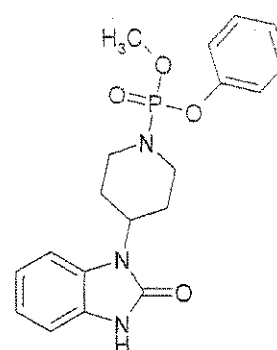
E1280



E1281



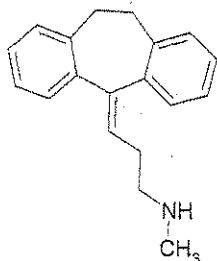
E1282



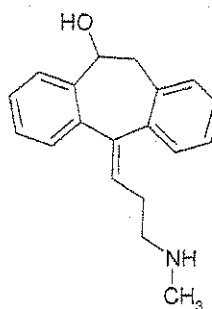
E1283

Nortriptyline (Aventyl®)

Chemical Structure

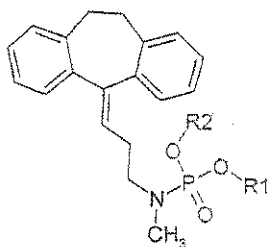


Hydroxylated Metabolite

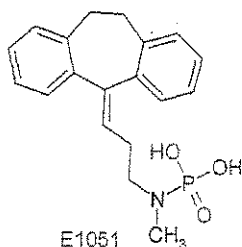


Compound	R1	R2	Chemical Name	Estimated LogP	Estimated pKa
E1051	hydrogen	hydrogen	3-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidene)-propyl]-methyl-phosphoramidic acid	4.32	2.90
E1052	hydrogen	methyl	3-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidene)-propyl]-methyl-phosphoramidic acid monomethyl ester	4.38	4.76
E1053	methyl	methyl	[3-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidene)-propyl]-methyl-phosphoramidic acid dimethyl ester	4.44	3.99
E1054	phenyl	hydrogen	[3-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidene)-propyl]-methyl-phosphoramidic acid monophenyl ester	6.15	4.32
E1055	phenyl	methyl	3-(10,11-Dihydro-dibenzo[a,d]cyclohepten-5-ylidene)-propyl]-methyl-phosphoramidic acid methyl ester phenyl ester	6.20	4.54

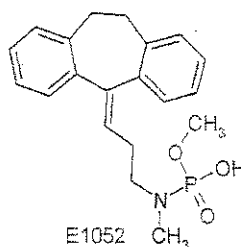
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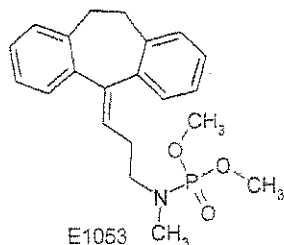
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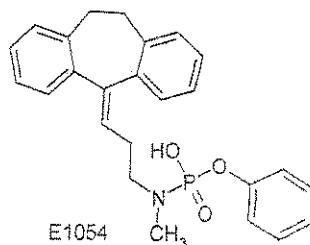
E1052



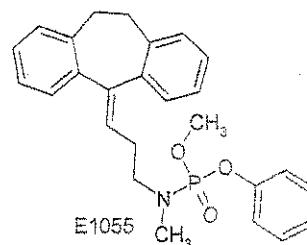
E1053



E1054



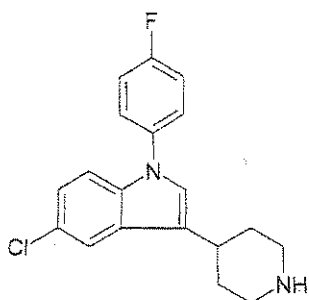
E1055



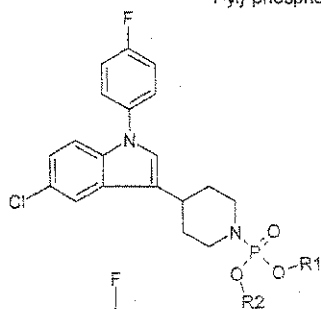
Norsertindole

Chemical Structure

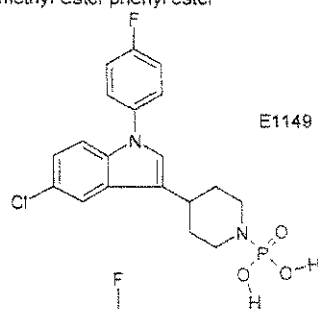
Hydroxylated Metabolite



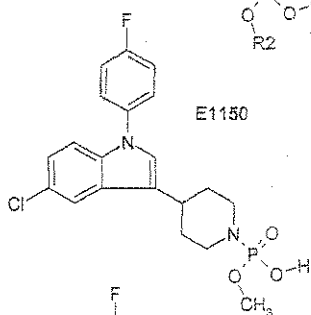
Compound	R1	R2	Chemical Name	Estimated LogP	pKa
E1149	hydrogen	hydrogen	{4-[5-Chloro-1-(4-fluoro-phenyl)-1H-indol-3-yl]-piperidin-1-yl}-phosphonic acid	5.08	2.77
E1150	hydrogen	methyl	{4-[5-Chloro-1-(4-fluoro-phenyl)-1H-indol-3-yl]-piperidin-1-yl}-phosphonic acid monomethyl ester	5.14	4.89
E1151	methyl	methyl	{4-[5-Chloro-1-(4-fluoro-phenyl)-1H-indol-3-yl]-piperidin-1-yl}-phosphonic acid dimethyl ester	5.19	3.84
E1152	phenyl	hydrogen	{4-[5-Chloro-1-(4-fluoro-phenyl)-1H-indol-3-yl]-piperidin-1-yl}-phosphonic acid monophenyl ester	6.90	4.41
E1153	phenyl	methyl	{4-[5-Chloro-1-(4-fluoro-phenyl)-1H-indol-3-yl]-piperidin-1-yl}-phosphonic acid methyl ester phenyl ester	6.96	3.98



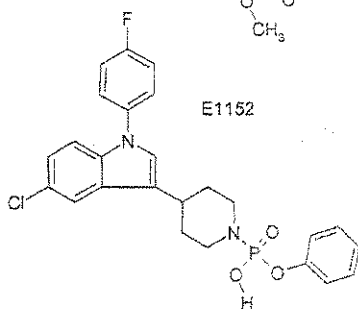
E1149



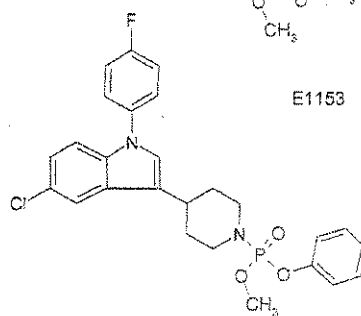
E1151

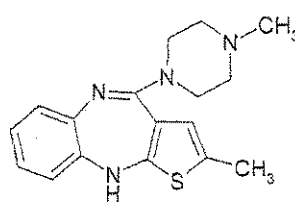
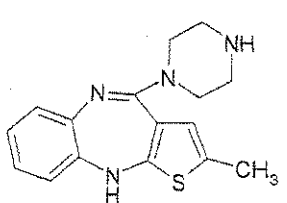
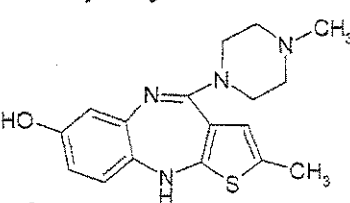


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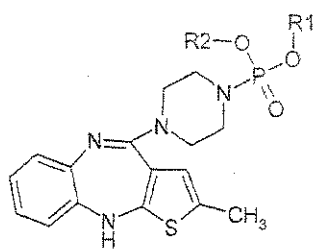


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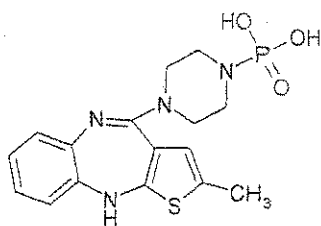


Chemical Structure			Olanzapine (Zyprexa®) Active Metabolite Structure	Hydroxylated Metabolite	
					
Compound	R1	R2	Chemical Name	Estimated LogP	Estimated pKa
E1006	hydrogen	hydrogen	[4-(2-Methyl-4H-3-thia-4,9-diaza-benzo[f]azulen-10-yl)-piperazin-1-yl]-phosphonic acid	1.94	4.96
E1007	hydrogen	methyl	[4-(2-Methyl-4H-3-thia-4,9-diaza-benzo[f]azulen-10-yl)-piperazin-1-yl]-phosphonic acid monomethyl ester	1.99	2.70
E1008	methyl	methyl	[4-(2-Methyl-4H-3-thia-4,9-diaza-benzo[f]azulen-10-yl)-piperazin-1-yl]-phosphonic acid dimethyl ester	2.05	6.02
E1009	phenyl	hydrogen	[4-(2-Methyl-4H-3-thia-4,9-diaza-benzo[f]azulen-10-yl)-piperazin-1-yl]-phosphonic acid monophenyl ester	3.76	2.22
E1010	phenyl	methyl	[4-(2-Methyl-4H-3-thia-4,9-diaza-benzo[f]azulen-10-yl)-piperazin-1-yl]-phosphonic acid methyl ester phenyl ester	3.82	6.17

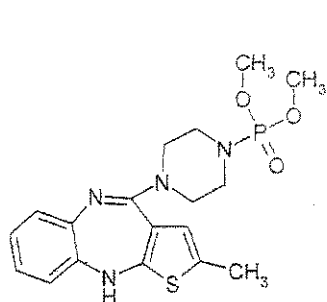
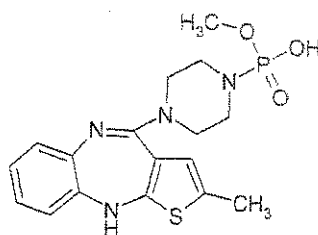
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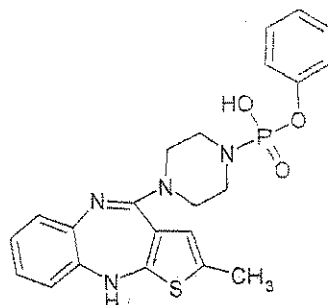
E1006



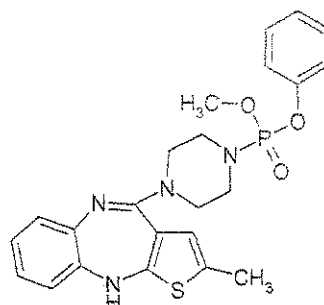
E1007



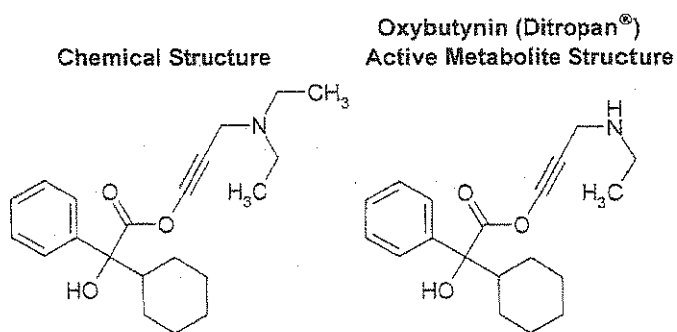
E1008



E1009

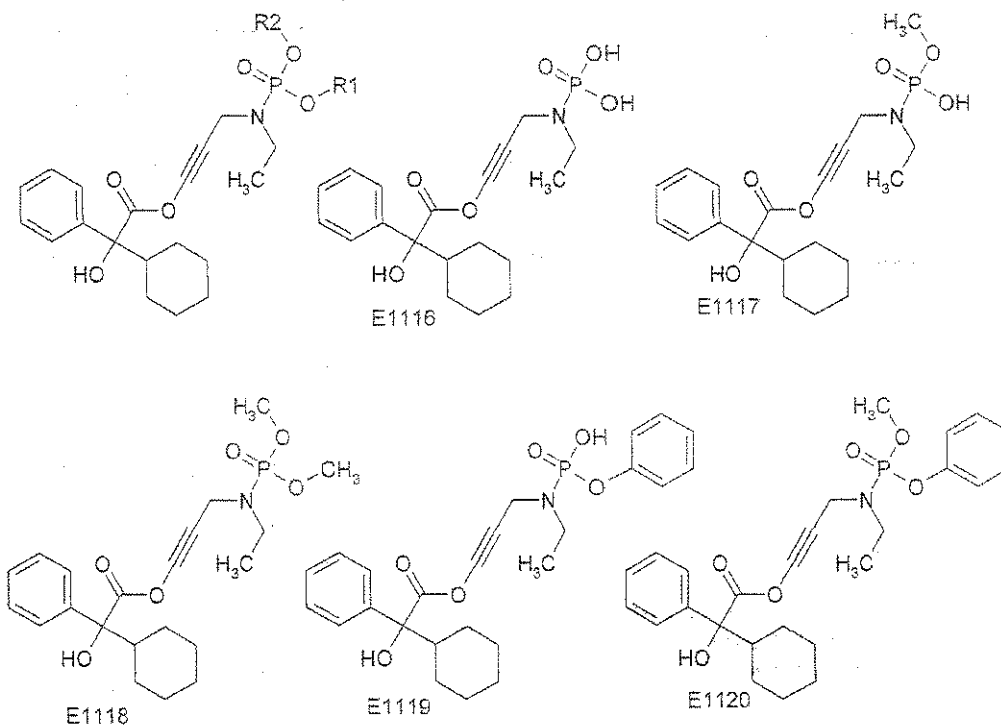


E1010

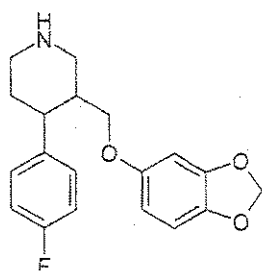


Compound	R1	R2	Chemical Name	Estimated LogP	pKa
E1116	hydrogen	hydrogen	Cyclohexyl-hydroxy-phenyl-acetic acid 3-(ethyl-phosphono-amino)-prop-1-ynyl ester	2.35	3.67
E1117	hydrogen	methyl	Cyclohexyl-hydroxy-phenyl-acetic acid 3-[ethyl-(hydroxy-methoxy-phosphoryl)-amino]-prop-1-ynyl ester	2.41	3.99
E1118	methyl	methyl	Cyclohexyl-hydroxy-phenyl-acetic acid 3-[(dimethoxy-phosphoryl)-ethyl-amino]-prop-1-ynyl ester	2.47	4.44
E1119	phenyl	hydrogen	Cyclohexyl-hydroxy-phenyl-acetic acid 3-[ethyl-(hydroxy-phenoxy-phosphoryl)-amino]-prop-1-ynyl	4.18	3.58
E1120	phenyl	methyl	Cyclohexyl-hydroxy-phenyl-acetic acid 3-[ethyl-(methoxy-phenoxy-phosphoryl)-amino]-prop-1-ynyl	4.23	4.49

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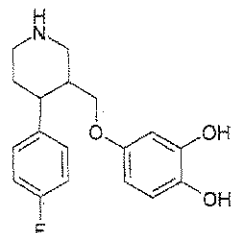
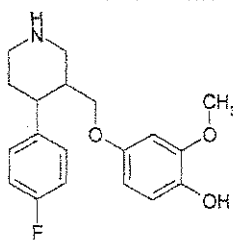


Chemical Structure



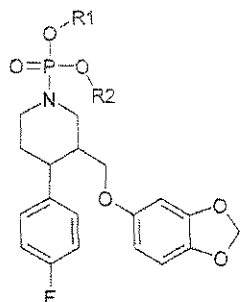
Paroxetine (Paxil®)

Active Metabolite Structure

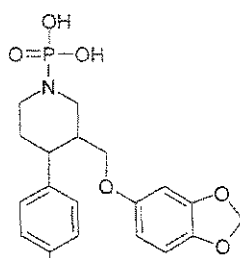


Compound	R1	R2	Chemical Name	Estimated LogP	Estimated pKa
E1001	hydrogen	hydrogen	[3-(Benzo[1,3]dioxol-5-yloxy)methyl]-4-(4-fluorophenyl)-piperidin-1-yl]-phosphonic acid	4.33	3.80
E1002	hydrogen	methyl	[3-(Benzo[1,3]dioxol-5-yloxy)methyl]-4-(4-fluorophenyl)-piperidin-1-yl]-phosphonic acid monomethyl ester	4.39	3.86
E1003	methyl	methyl	[3-(Benzo[1,3]dioxol-5-yloxy)methyl]-4-(4-fluorophenyl)-piperidin-1-yl]-phosphonic acid dimethyl ester	4.44	4.86
E1004	phenyl	hydrogen	[3-(Benzo[1,3]dioxol-5-yloxy)methyl]-4-(4-fluorophenyl)-piperidin-1-yl]-phosphonic acid monophenyl ester	6.15	4.86
E1005	phenyl	methyl	[3-(Benzo[1,3]dioxol-5-yloxy)methyl]-4-(4-fluorophenyl)-piperidin-1-yl]-phosphonic acid methyl ester phenyl ester	6.21	5.00

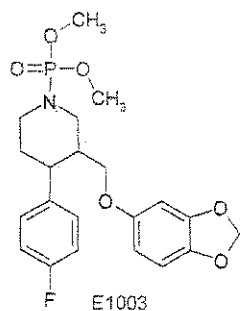
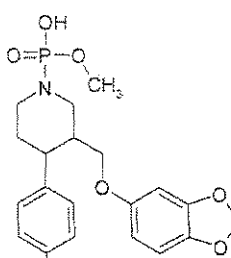
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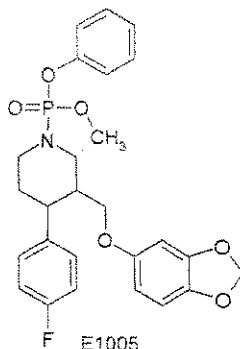
E1001



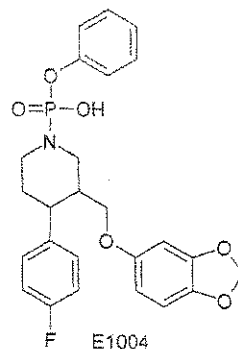
E1002



E1003

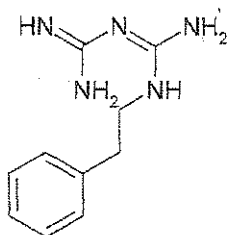


E1005



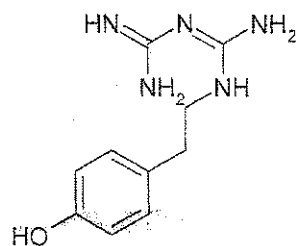
E1004

Chemical Structure



Phenformin (Dibotin®)

Hydroxylated Metabolite

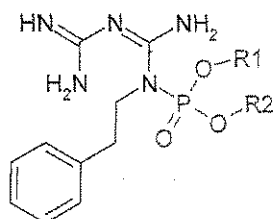


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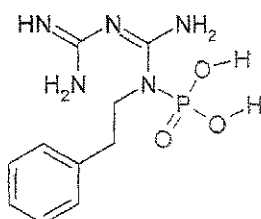
Compound	R1	R2
E1324	hydrogen	hydrogen
E1325	hydrogen	methyl
E1326	methyl	methyl
E1327	phenyl	hydrogen
E1328	phenyl	methyl

Chemical Name

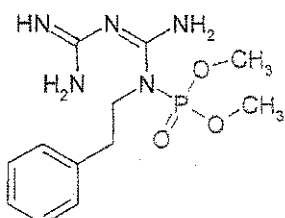
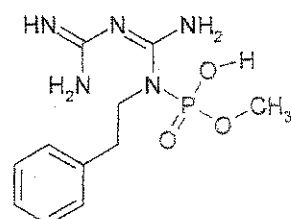
(Amino-carbamimidoylimino-methyl)-phenethyl-phosphoramidic acid
 (Amino-carbamimidoylimino-methyl)-phenethyl-phosphoramidic acid monomethyl ester
 (Amino-carbamimidoylimino-methyl)-phenethyl-phosphoramidic acid dimethyl ester
 (Amino-carbamimidoylimino-methyl)-phenethyl-phosphoramidic acid monophenyl ester
 (Amino-carbamimidoylimino-methyl)-phenethyl-phosphoramidic acid methyl ester phenyl ester



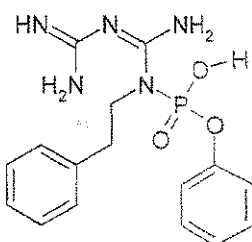
E1324



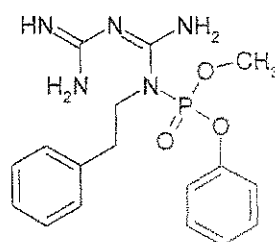
E1325



E1326



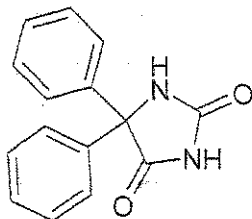
E1327



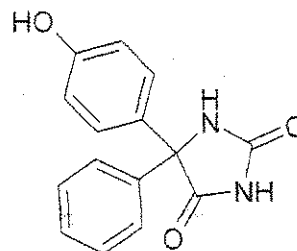
E1328

Phenytoin (Dilantin®)

Chemical Structure

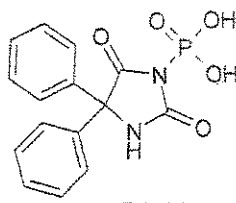
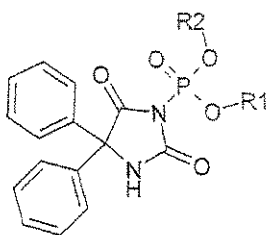


Hydroxylated Metabolite

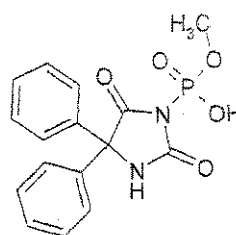


Compound	R1	R2	Chemical Name
E1126	hydrogen	hydrogen	(2,5-Dioxo-4,4-diphenyl-imidazolidin-1-yl)-phosphonic acid
E1127	hydrogen	methyl	(2,5-Dioxo-4,4-diphenyl-imidazolidin-1-yl)-phosphonic acid monomethyl ester
E1128	methyl	methyl	(2,5-Dioxo-4,4-diphenyl-imidazolidin-1-yl)-phosphonic acid dimethyl ester
E1129	phenyl	hydrogen	(2,5-Dioxo-4,4-diphenyl-imidazolidin-1-yl)-phosphonic acid monophenyl ester
E1130	phenyl	methyl	(2,5-Dioxo-4,4-diphenyl-imidazolidin-1-yl)-phosphonic acid methyl ester phenyl ester

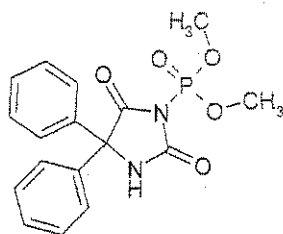
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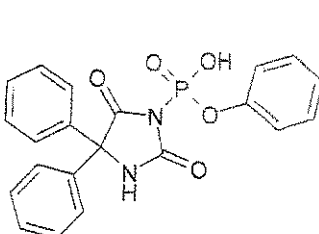
E1126



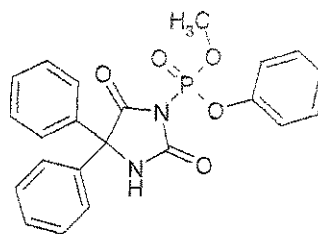
E1127



E1128



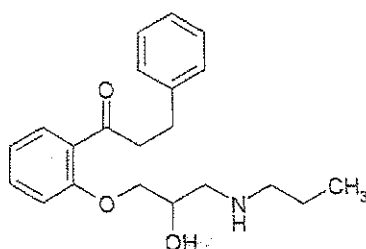
E1129



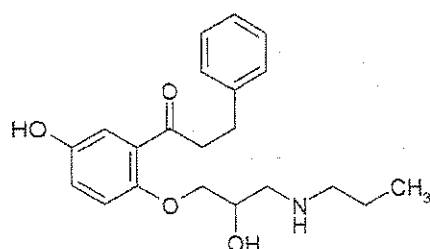
E1130

Propafenone (Rhythmol®)

Chemical Structure

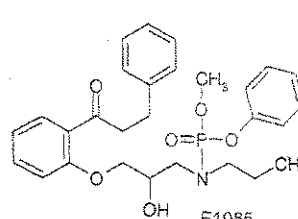
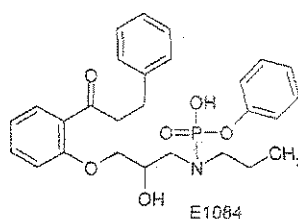
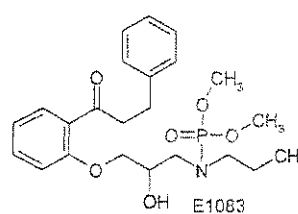
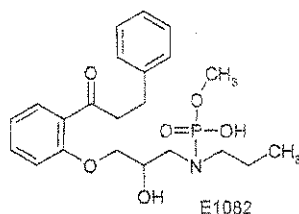
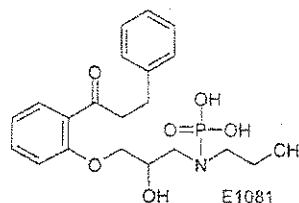
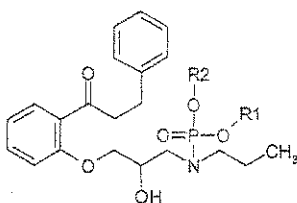


Hydroxylated Metabolite



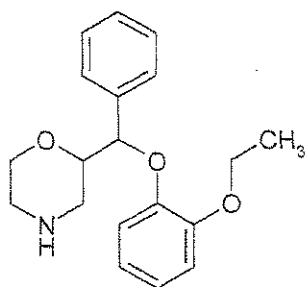
Compound	R1	R2	Chemical Name	Estimated LogP	pKa
E1081	hydrogen	hydrogen	{2-Hydroxy-3-[2-(3-phenyl-propionyl)-phenoxy]-propyl}-propyl-phosphoramidic acid	2.96	4.07
E1082	hydrogen	methyl	{2-Hydroxy-3-[2-(3-phenyl-propionyl)-phenoxy]-propyl}-propyl-phosphoramidic acid monomethyl ester	3.02	3.59
E1083	methyl	methyl	{2-Hydroxy-3-[2-(3-phenyl-propionyl)-phenoxy]-propyl}-propyl-phosphoramidic acid dimethyl ester	3.07	4.36
E1084	phenyl	hydrogen	{2-Hydroxy-3-[2-(3-phenyl-propionyl)-phenoxy]-propyl}-propyl-phosphoramidic acid monophenyl ester	4.78	3.21
E1085	phenyl	methyl	{2-Hydroxy-3-[2-(3-phenyl-propionyl)-phenoxy]-propyl}-propyl-phosphoramidic acid methyl ester phenyl ester	4.84	4.89

5

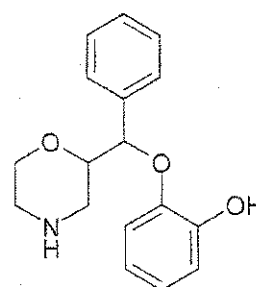


Reboxetine (Vestra®)

Chemical Structure

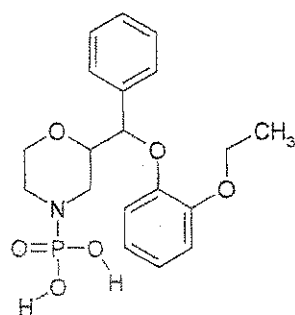
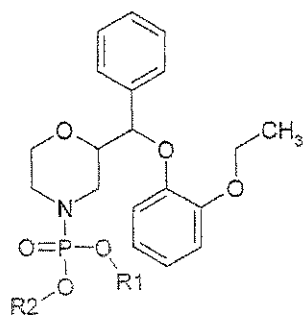


Hydroxylated Metabolite

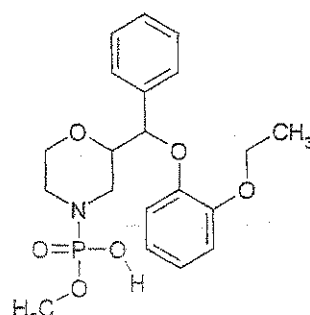


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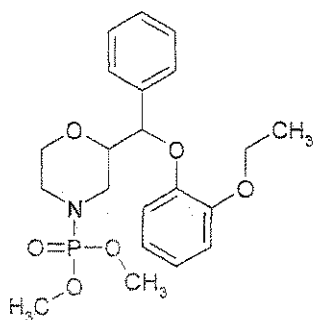
Compound	R1	R2	Chemical Name	Estimated LogP	pKa
E1284	hydrogen	hydrogen	{2-[(2-Ethoxy-phenoxy)-phenyl-methyl]-morpholin-4-yl}-phosphonic acid	2.37	5.87
E1285	hydrogen	methyl	{2-[(2-Ethoxy-phenoxy)-phenyl-methyl]-morpholin-4-yl}-phosphonic acid monomethyl ester	2.43	1.79
E1286	methyl	methyl	{2-[(2-Ethoxy-phenoxy)-phenyl-methyl]-morpholin-4-yl}-phosphonic acid dimethyl ester	2.49	6.94
E1287	phenyl	hydrogen	{2-[(2-Ethoxy-phenoxy)-phenyl-methyl]-morpholin-4-yl}-phosphonic acid monophenyl ester	4.20	1.31
E1288	phenyl	methyl	{2-[(2-Ethoxy-phenoxy)-phenyl-methyl]-morpholin-4-yl}-phosphonic acid methyl ester phenyl ester	4.25	7.09



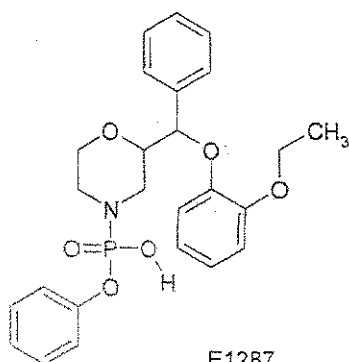
E1284



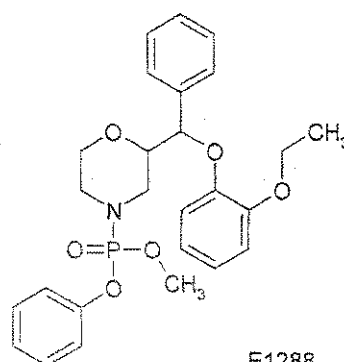
E1285



E1286

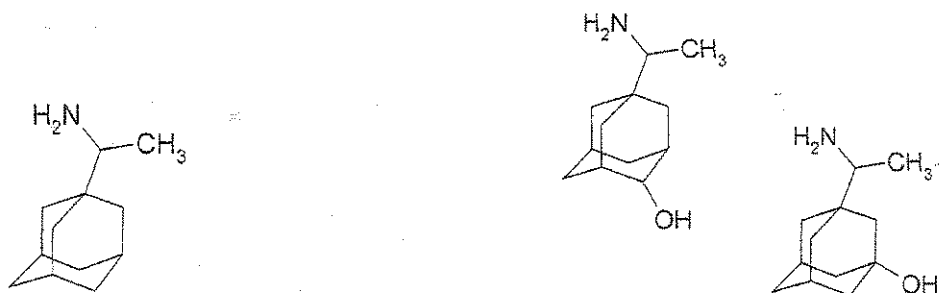


E1287



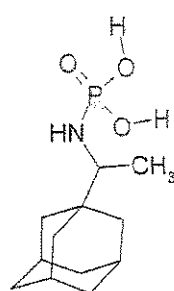
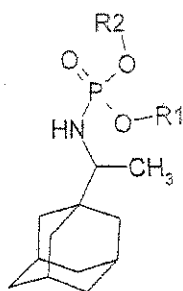
E1288

Chemical Structure Rimantadine (Flumadine®) Active Metabolite Structure Hydroxylated Metabolite

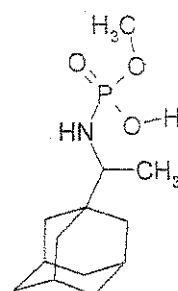


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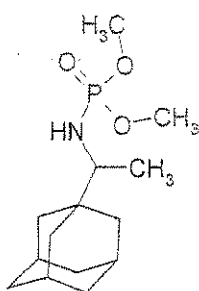
Compound	R1	R2	Chemical Name
E1403	hydrogen	hydrogen	(1-Adamantan-1-yl-ethyl)-phosphoramidic acid
E1404	hydrogen	methyl	(1-Adamantan-1-yl-ethyl)-phosphoramidic acid monomethyl ester
E1405	methyl	methyl	(1-Adamantan-1-yl-ethyl)-phosphoramidic acid dimethyl ester
E1406	phenyl	hydrogen	(1-Adamantan-1-yl-ethyl)-phosphoramidic acid monophenyl ester
E1407	phenyl	methyl	(1-Adamantan-1-yl-ethyl)-phosphoramidic acid methyl ester phenyl ester



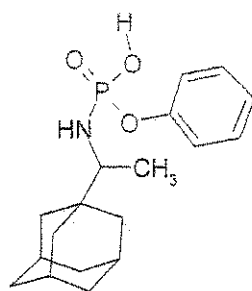
E1403



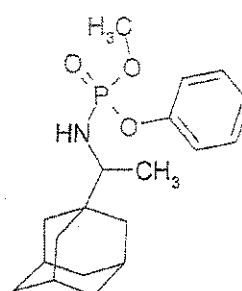
E1404



E1405



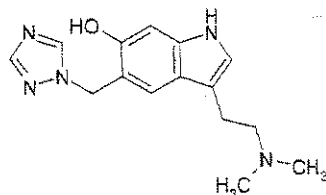
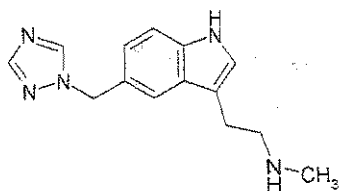
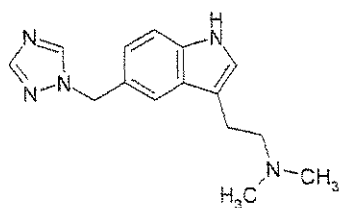
E1406



E1407

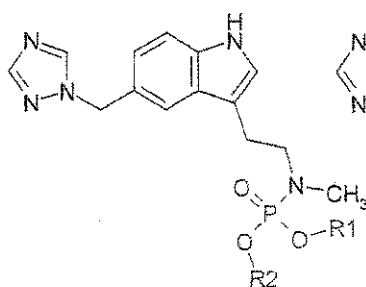
Rizatriptan (Maxalt®)

Chemical Structure Active Metabolite Structure Hydroxylated Metabolite

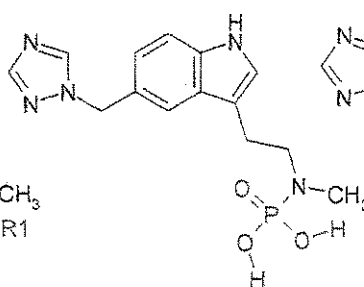


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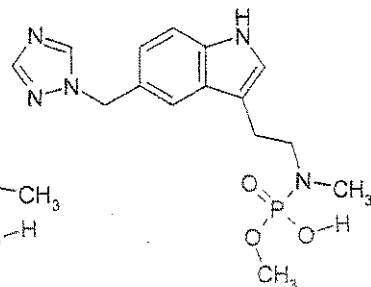
Compound	R1	R2	Chemical Name	Estimated LogP	pKa
E1174	hydrogen	hydrogen	Methyl-[2-(5-[1,2,4]triazol-1-ylmethyl-1H-indol-3-yl)-ethyl]-phosphoramidic acid	1.17	2.64
E1175	hydrogen	methyl	Methyl-[2-(5-[1,2,4]triazol-1-ylmethyl-1H-indol-3-yl)-ethyl]-phosphoramidic acid monomethyl ester	1.23	5.02
E1176	methyl	methyl	Methyl-[2-(5-[1,2,4]triazol-1-ylmethyl-1H-indol-3-yl)-ethyl]-phosphoramidic acid dimethyl ester	1.29	3.99
E1177	phenyl	hydrogen	Methyl-[2-(5-[1,2,4]triazol-1-ylmethyl-1H-indol-3-yl)-ethyl]-phosphoramidic acid monophenyl ester	3.00	4.57
E1178	phenyl	methyl	Methyl-[2-(5-[1,2,4]triazol-1-ylmethyl-1H-indol-3-yl)-ethyl]-phosphoramidic acid methyl ester phenyl ester	3.05	3.55



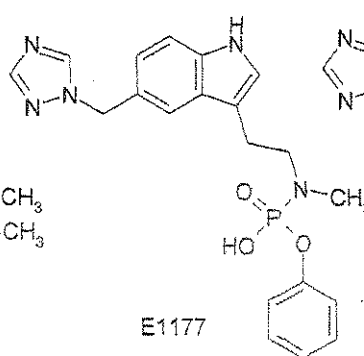
E1174



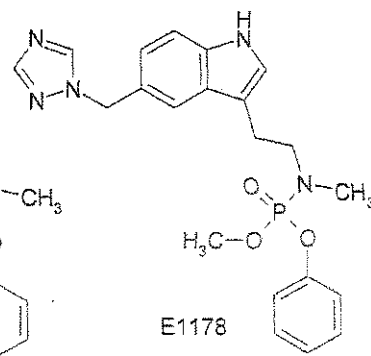
E1175



E1176



E1177

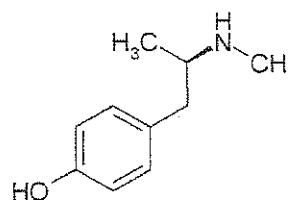
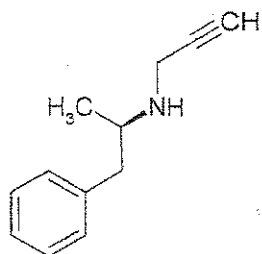
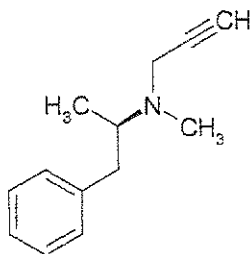


E1178

Chemical Structure

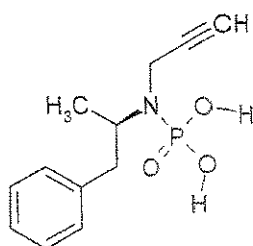
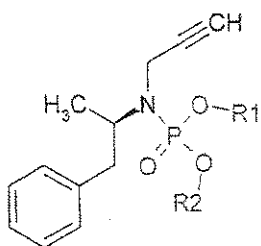
Selegiline (Eldepryl®)
Active Metabolite Structure

Hydroxylated Metabolite

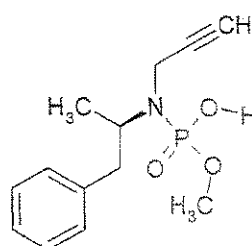


Compound	R1	R2	Chemical Name
E1444	hydrogen	hydrogen	(1-Methyl-2-phenyl-ethyl)-prop-2-ynylphosphoramidic acid
E1445	hydrogen	methyl	(1-Methyl-2-phenyl-ethyl)-prop-2-ynylphosphoramidic acid monomethyl ester
E1446	methyl	methyl	(1-Methyl-2-phenyl-ethyl)-prop-2-ynylphosphoramidic acid dimethyl ester
E1447	phenyl	hydrogen	(1-Methyl-2-phenyl-ethyl)-prop-2-ynylphosphoramidic acid monophenyl ester
E1448	phenyl	methyl	(1-Methyl-2-phenyl-ethyl)-prop-2-ynylphosphoramidic acid methyl ester phenyl ester

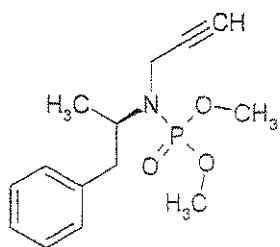
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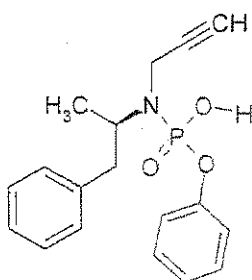
E1444



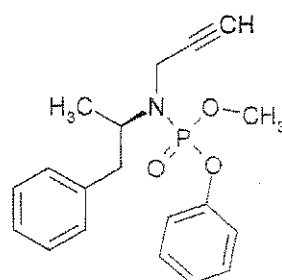
E1445



E1446



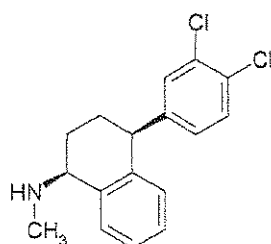
E1447



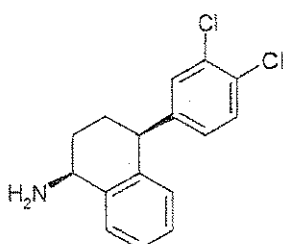
E1448

Sertraline (Zoloft®)

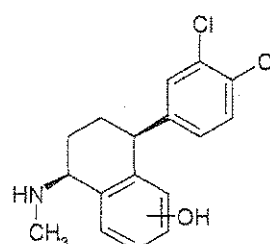
Chemical Structure



Active Metabolite Structure

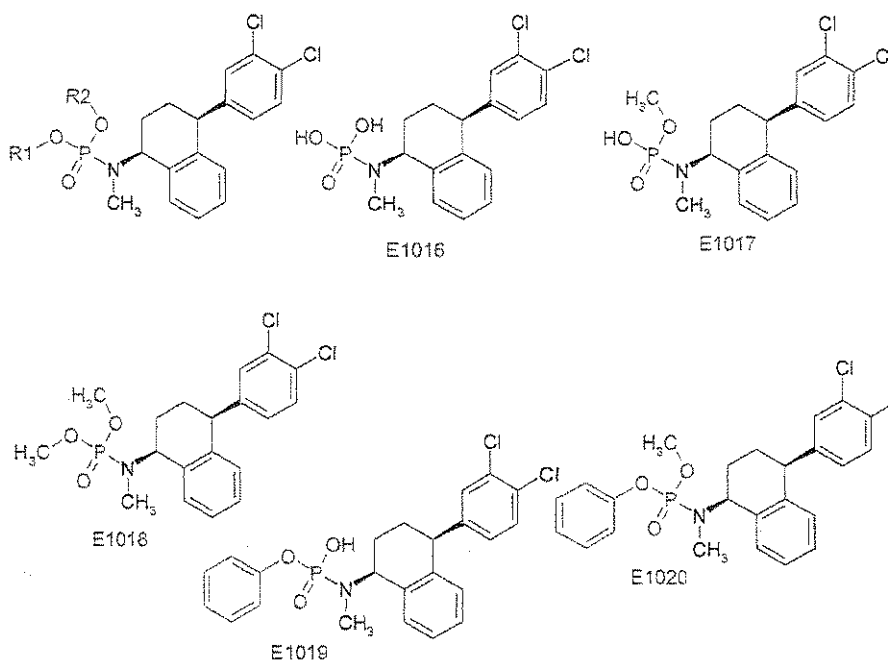


Hydroxylated Metabolite



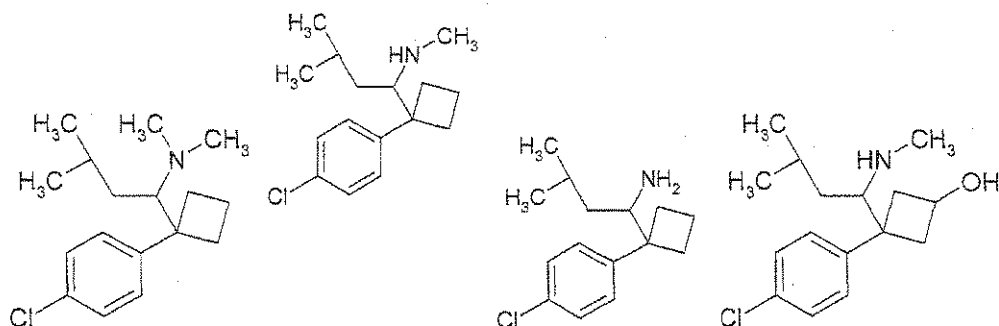
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Compound	R1	R2	Chemical Name	Estimated LogP	Estimated pKa
E1016	hydrogen	hydrogen	[4-(3,4-Dichloro-phenyl)-1,2,3,4-tetrahydronaphthalen-1-yl]-methyl-phosphoramidic acid	4.87	3.50
E1017	hydrogen	methyl	[4-(3,4-Dichloro-phenyl)-1,2,3,4-tetrahydronaphthalen-1-yl]-methyl-phosphoramidic acid monomethyl ester	4.93	4.16
E1018	methyl	methyl	[4-(3,4-Dichloro-phenyl)-1,2,3,4-tetrahydronaphthalen-1-yl]-methyl-phosphoramidic acid dimethyl ester	4.98	3.84
E1019	phenyl	hydrogen	[4-(3,4-Dichloro-phenyl)-1,2,3,4-tetrahydronaphthalen-1-yl]-methyl-phosphoramidic acid monophenyl ester	6.70	3.73
E1020	phenyl	methyl	[4-(3,4-Dichloro-phenyl)-1,2,3,4-tetrahydronaphthalen-1-yl]-methyl-phosphoramidic acid methyl ester phenyl ester	6.75	4.39

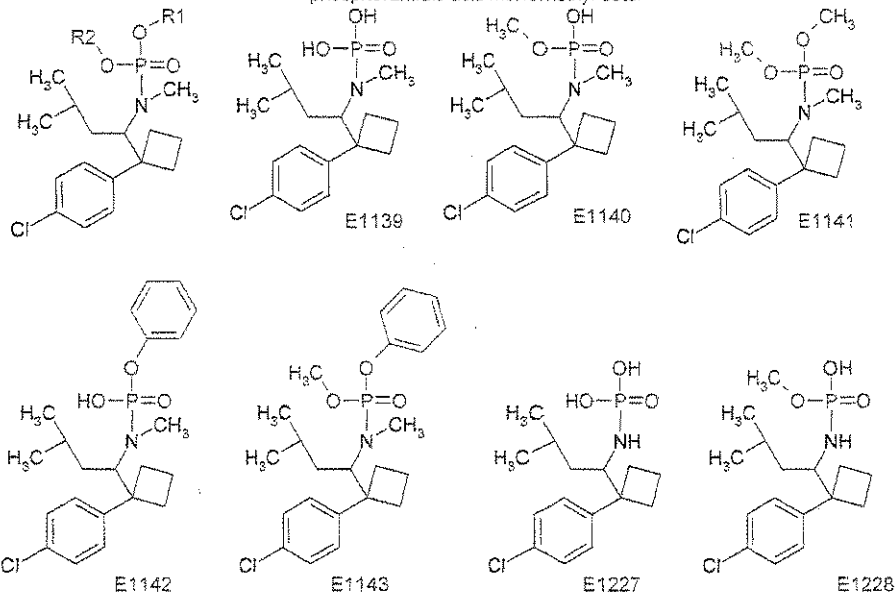


Sibutramine (Meridia®)
Chemical Structure Active Metabolite Structures Hydroxylated Metabolite

5



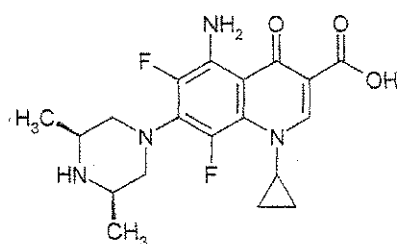
Compound	R1	R2	Chemical Name	Estimated LogP	pKa
E1139	hydrogen	hydrogen	{1-[1-(4-Chloro-phenyl)-cyclobutyl]-3-methyl-butyl}-methyl-phosphoramidic acid	5.32	3.08
E1140	hydrogen	methyl	{1-[1-(4-Chloro-phenyl)-cyclobutyl]-3-methyl-butyl}-methyl-phosphoramidic acid monomethyl ester	5.38	4.57
E1141	methyl	methyl	{1-[1-(4-Chloro-phenyl)-cyclobutyl]-3-methyl-butyl}-methyl-phosphoramidic acid dimethyl ester	5.44	3.14
E1142	phenyl	hydrogen	{1-[1-(4-Chloro-phenyl)-cyclobutyl]-3-methyl-butyl}-methyl-phosphoramidic acid monophenyl ester	7.15	4.19
E1143	phenyl	methyl	{1-[1-(4-Chloro-phenyl)-cyclobutyl]-3-methyl-butyl}-methyl-phosphoramidic acid methyl ester phenyl ester	7.2	3.67
E1227	hydrogen	hydrogen	{1-[1-(4-Chloro-phenyl)-cyclobutyl]-3-methyl-butyl}-phosphoramidic acid		
E1228	hydrogen	methyl	{1-[1-(4-Chloro-phenyl)-cyclobutyl]-3-methyl-butyl}-phosphoramidic acid monomethyl ester		



Sparfloxacin (Zagam®)

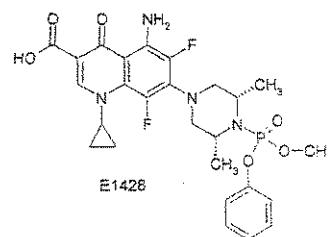
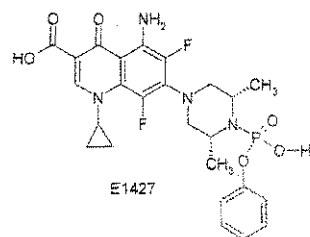
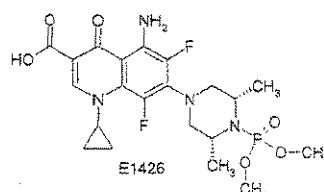
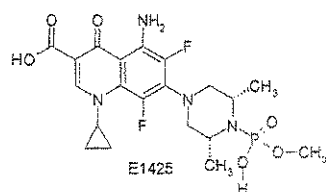
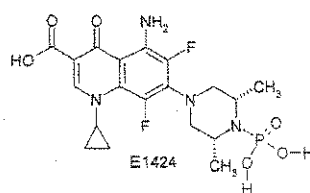
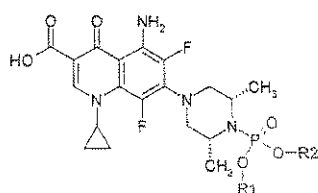
Chemical Structure

Hydroxylated Metabolite



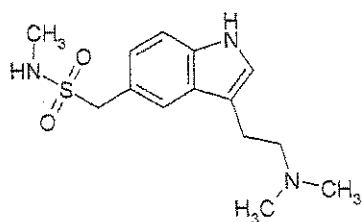
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Compound	R1	R2	Chemical Name
E1424	hydrogen	hydrogen	5-Amino-1-cyclopropyl-7-(3,5-dimethyl-4-phosphono-piperazin-1-yl)-6,8-difluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
E1425	hydrogen	methyl	5-Amino-1-cyclopropyl-6,8-difluoro-7-[4-(hydroxy-methoxy-phosphoryl)-3,5-dimethyl-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
E1426	methyl	methyl	5-Amino-1-cyclopropyl-7-[4-(dimethoxy-phosphoryl)-3,5-dimethyl-piperazin-1-yl]-6,8-difluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
E1427	phenyl	hydrogen	5-Amino-1-cyclopropyl-6,8-difluoro-7-[4-(hydroxy-phenoxy-phosphoryl)-3,5-dimethyl-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
E1428	phenyl	methyl	5-Amino-1-cyclopropyl-6,8-difluoro-7-[4-(methoxy-phenoxy-phosphoryl)-3,5-dimethyl-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid

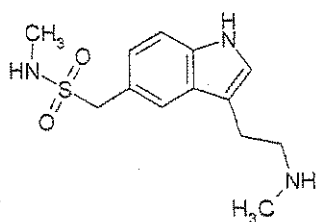


Sumatriptan (Imitrex®)

Chemical Structure

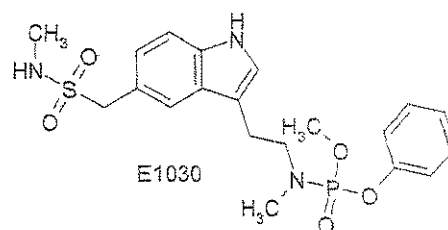
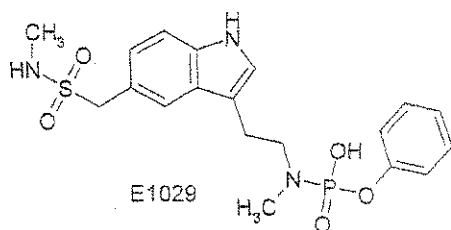
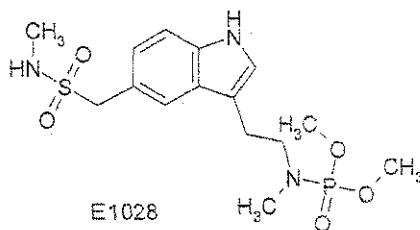
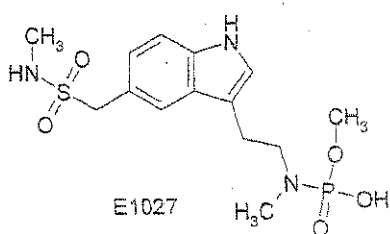
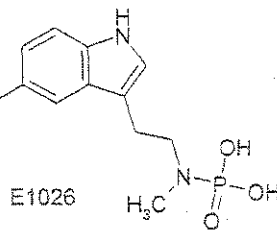
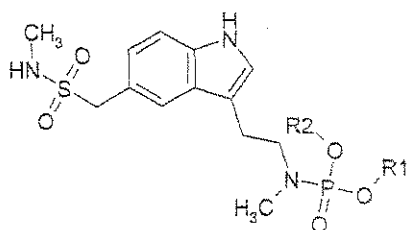


Active Metabolite Structure



Compound	R1	R2	Chemical Name	Estimated LogP	pKa
E1026	hydrogen	hydrogen	Methyl-[2-(5-methylsulfonylmethyl-1H-indol-3-yl)-ethyl]-phosphoramidic acid	0.78	2.78
E1027	hydrogen	methyl	Methyl-[2-(5-methylsulfonylmethyl-1H-indol-3-yl)-ethyl]-phosphoramidic acid monomethyl ester	0.84	4.88
E1028	methyl	methyl	Methyl-[2-(5-methylsulfonylmethyl-1H-indol-3-yl)-ethyl]-phosphoramidic acid dimethyl ester	0.89	4.13
E1029	phenyl	hydrogen	Methyl-[2-(5-methylsulfonylmethyl-1H-indol-3-yl)-ethyl]-phosphoramidic acid monophenyl ester	2.60	4.44
E1030	phenyl	methyl	Methyl-[2-(5-methylsulfonylmethyl-1H-indol-3-yl)-ethyl]-phosphoramidic acid methyl ester phenyl ester	2.66	3.69

5

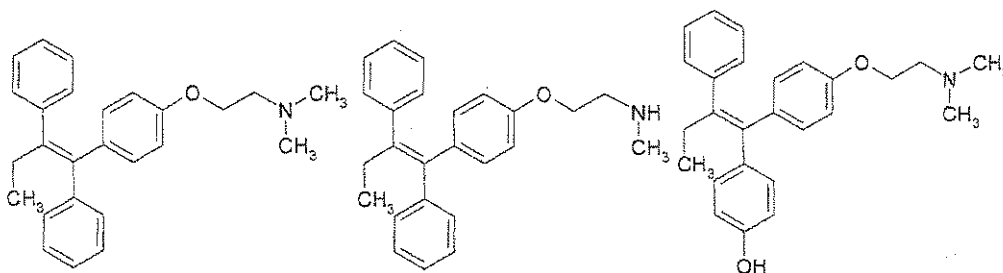


Tamoxifen (Nolvadex®)

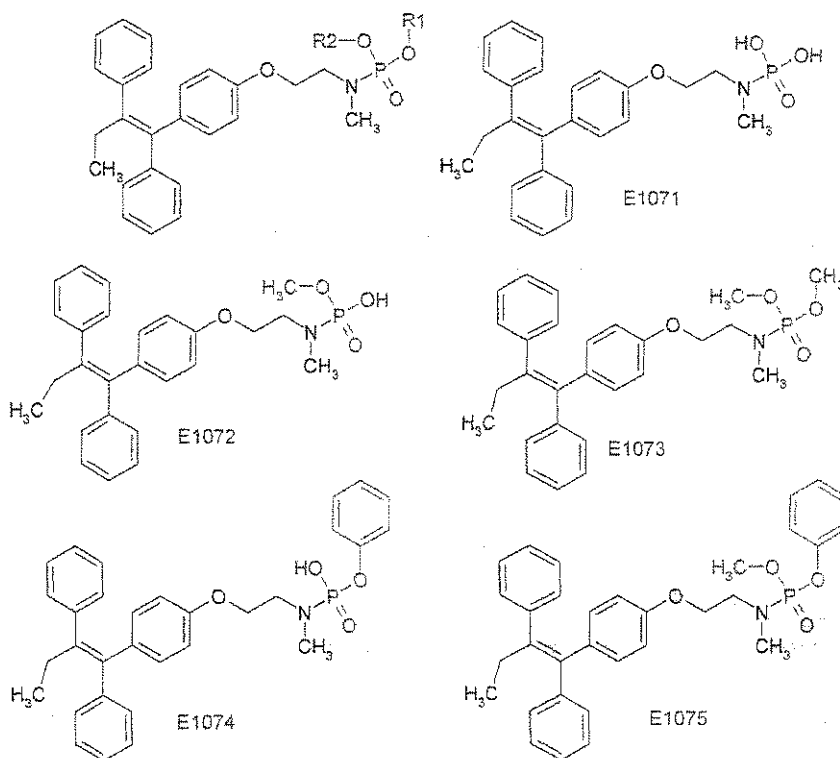
Chemical Structure

Active Metabolite Structure

Hydroxylated Metabolite



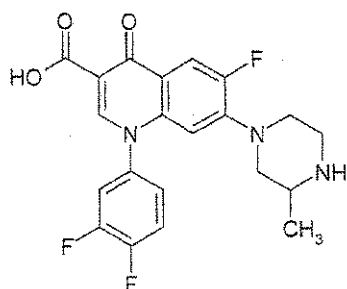
	Compound	R1	R2	Chemical Name	Estimated LogP	pKa
5	E1071	hydrogen	hydrogen	{2-[4-(1,2-Diphenyl-but-1-enyl)-phenoxy]-ethyl}-methyl-phosphoramidic acid	5.68	4.02
	E1072	hydrogen	methyl	{2-[4-(1,2-Diphenyl-but-1-enyl)-phenoxy]-ethyl}-methyl-phosphoramidic acid monomethyl ester	5.73	3.64
10	E1073	methyl	methyl	{2-[4-(1,2-Diphenyl-but-1-enyl)-phenoxy]-ethyl}-methyl-phosphoramidic acid dimethyl ester	5.79	5.37
	E1074	phenyl	hydrogen	{2-[4-(1,2-Diphenyl-but-1-enyl)-phenoxy]-ethyl}-methyl-phosphoramidic acid monophenyl ester	7.50	3.20
	E1075	phenyl	methyl	{2-[4-(1,2-Diphenyl-but-1-enyl)-phenoxy]-ethyl}-methyl-phosphoramidic acid methyl ester phenyl ester	7.56	4.94



Temafloracin (Omniflox®)

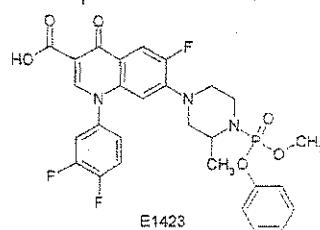
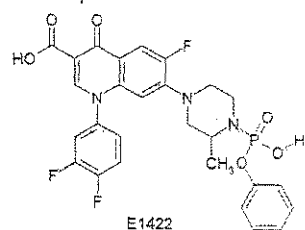
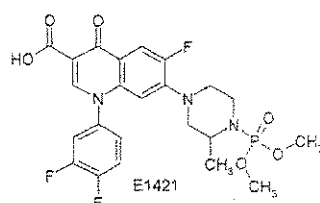
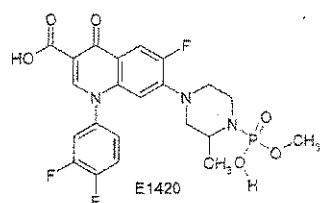
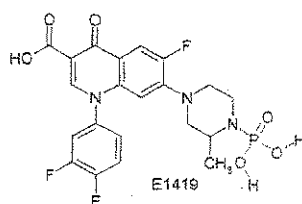
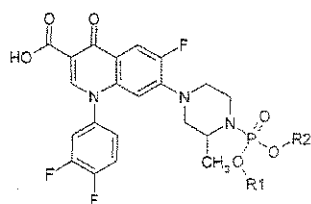
Chemical Structure

Hydroxylated Metabolite

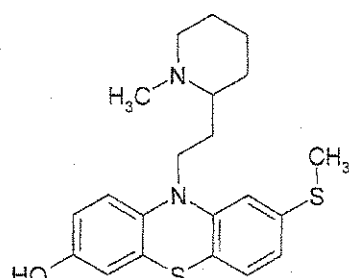
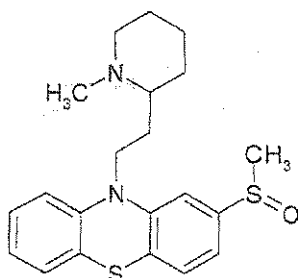
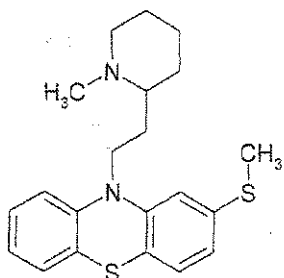


Compound	R1	R2	Chemical Name
E1419	hydrogen	hydrogen	1-(3,4-Difluoro-phenyl)-6-fluoro-7-(3-methyl-4-phosphono-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
E1420	hydrogen	methyl	1-(3,4-Difluoro-phenyl)-6-fluoro-7-[4-(hydroxy-methoxy-phosphoryl)-3-methyl-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
E1421	methyl	methyl	1-(3,4-Difluoro-phenyl)-7-[4-(dimethoxy-phosphoryl)-3-methyl-piperazin-1-yl]-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
E1422	phenyl	hydrogen	1-(3,4-Difluoro-phenyl)-6-fluoro-7-[4-(hydroxy-phenoxy-phosphoryl)-3-methyl-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
E1423	phenyl	methyl	1-(3,4-Difluoro-phenyl)-6-fluoro-7-[4-(methoxy-phenoxy-phosphoryl)-3-methyl-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid

5

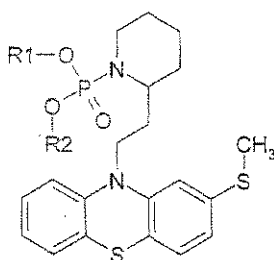


Chemical Structure Thioridazine (Mellaril®) Active Metabolite Structure Hydroxylated Metabolite

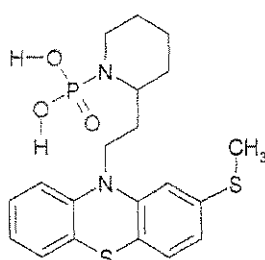


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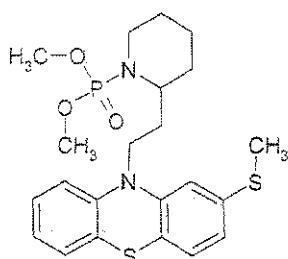
Compound	R1	R2	Chemical Name	Estimated LogP	pKa
E1159	hydrogen	hydrogen	{2-[2-(2-Methylsulfanyl-phenothiazin-10-yl)-ethyl]-piperidin-1-yl}-phosphonic acid	5.82	2.81
E1160	hydrogen	methyl	{2-[2-(2-Methylsulfanyl-phenothiazin-10-yl)-ethyl]-piperidin-1-yl}-phosphonic acid monomethyl ester	5.88	4.85
E1161	methyl	methyl	{2-[2-(2-Methylsulfanyl-phenothiazin-10-yl)-ethyl]-piperidin-1-yl}-phosphonic acid dimethyl ester	5.94	3.87
E1162	phenyl	hydrogen	{2-[2-(2-Methylsulfanyl-phenothiazin-10-yl)-ethyl]-piperidin-1-yl}-phosphonic acid monophenyl ester	7.65	4.38
E1163	phenyl	methyl	{2-[2-(2-Methylsulfanyl-phenothiazin-10-yl)-ethyl]-piperidin-1-yl}-phosphonic acid methyl ester phenyl ester	7.70	4.02



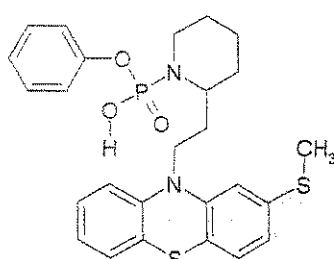
E1159



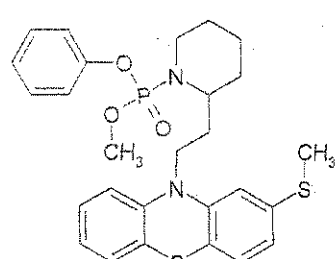
E1160



E1161

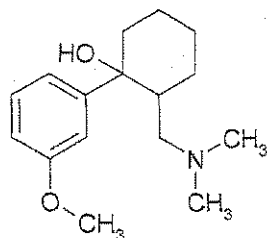


E1162

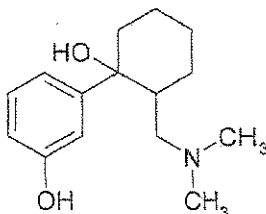


E1163

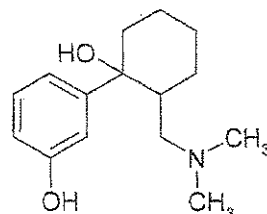
Chemical Structure



Tramadol (Ultram®)
Active Metabolite Structure

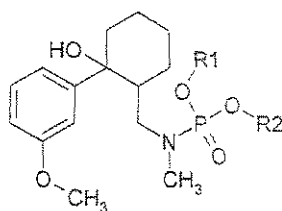


Hydroxylated Metabolite

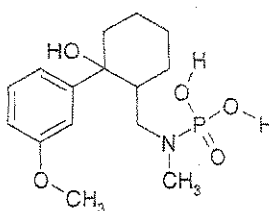


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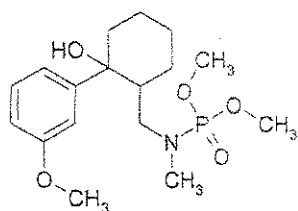
Compound	R1	R2	Chemical Name
E1329	hydrogen	hydrogen	[2-Hydroxy-2-(3-methoxy-phenyl)-cyclohexylmethyl]-methyl-phosphoramidic acid
E1330	hydrogen	methyl	[2-Hydroxy-2-(3-methoxy-phenyl)-cyclohexylmethyl]-methyl-phosphoramidic acid monomethyl ester
E1131	methyl	methyl	[2-Hydroxy-2-(3-methoxy-phenyl)-cyclohexylmethyl]-methyl-phosphoramidic acid dimethyl ester
E1332	phenyl	hydrogen	[2-Hydroxy-2-(3-methoxy-phenyl)-cyclohexylmethyl]-methyl-phosphoramidic acid monophenyl ester
E1333	phenyl	methyl	[2-Hydroxy-2-(3-methoxy-phenyl)-cyclohexylmethyl]-methyl-phosphoramidic acid methyl ester phenyl ester



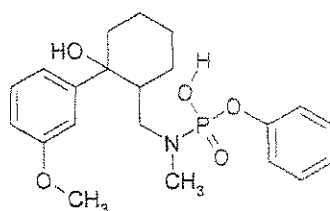
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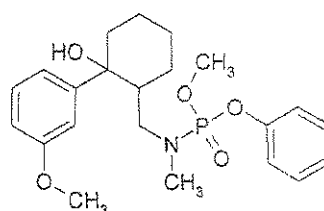
E1330



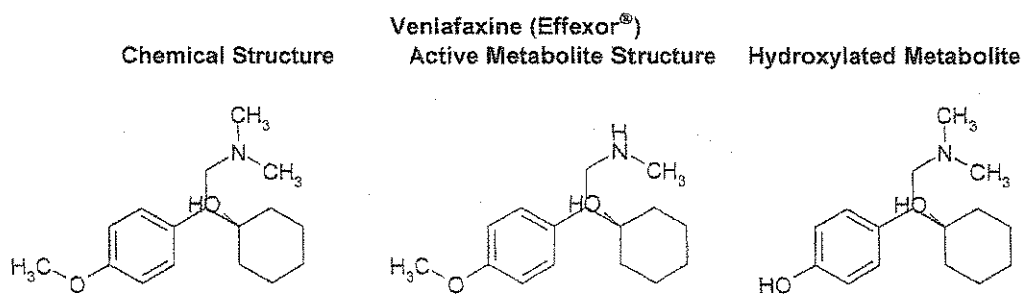
E1331



E1332



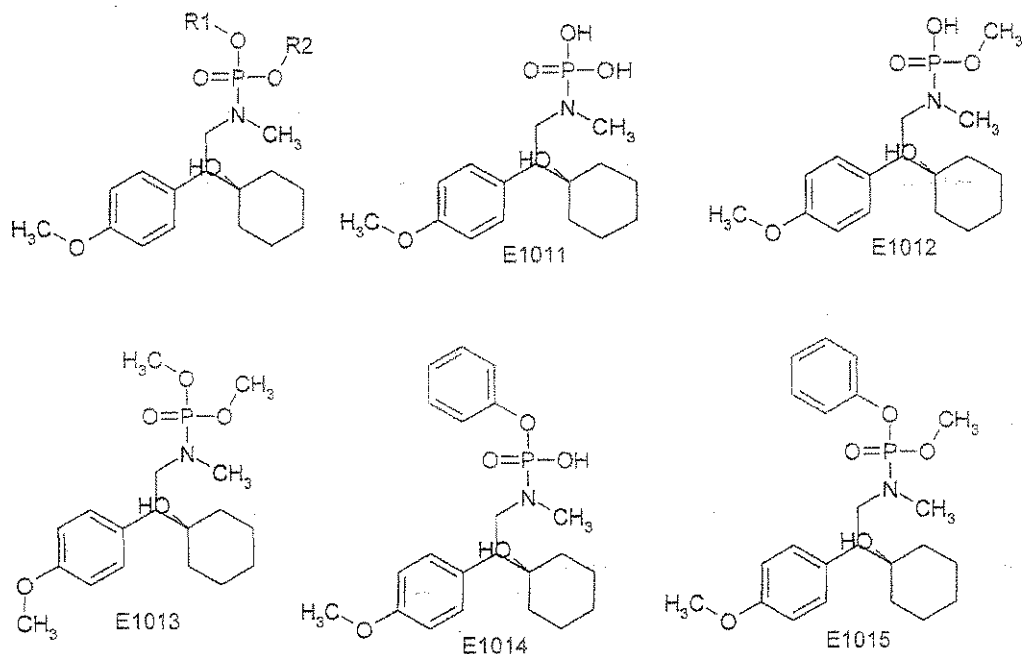
E1333



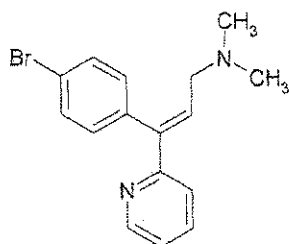
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Compound	R1	R2	Chemical Name	Estimated LogP	Estimated pKa
E1011	hydrogen	hydrogen	[2-(1-Hydroxy-cyclohexyl)-2-(4-methoxy-phenyl)-ethyl]-methyl-phosphoramidic acid	2.88	3.22
E1012	hydrogen	methyl	[2-(1-Hydroxy-cyclohexyl)-2-(4-methoxy-phenyl)-ethyl]-methyl-phosphoramidic acid monomethyl ester	2.93	4.44
E1013	methyl	methyl	[3-Hydroxy-2-(4-methoxy-phenyl)-3-propyl-hexyl]-methyl-phosphoramidic acid dimethyl ester	2.99	2.84
E1014	phenyl	hydrogen	[2-(1-Hydroxy-cyclohexyl)-2-(4-methoxy-phenyl)-ethyl]-methyl-phosphoramidic acid monophenyl ester	4.70	4.02
E1015	phenyl	methyl	[2-(1-Hydroxy-cyclohexyl)-2-(4-methoxy-phenyl)-ethyl]-methyl-phosphoramidic acid methyl ester phenyl ester	4.76	3.38

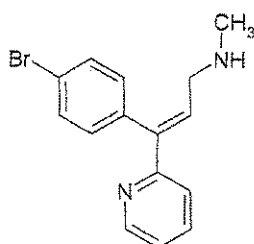
10



Chemical Structure



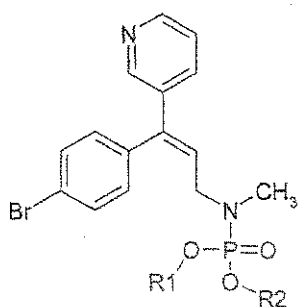
Zimeldine (Zelmid®)
Active Metabolite Structure



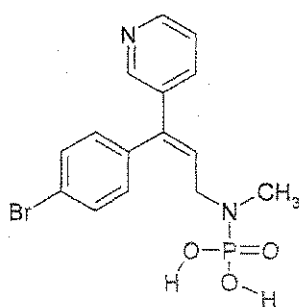
Hydroxylated Metabolite

5

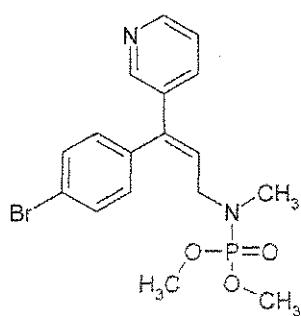
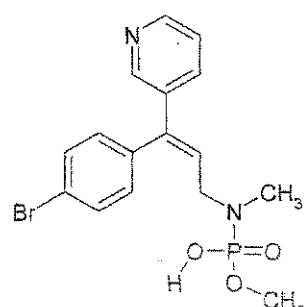
Compound	R1	R2	Chemical Name
E1449	hydrogen	hydrogen	[3-(4-Bromo-phenyl)-3-pyridin-3-yl-allyl]-methyl-phosphoramidic acid
E1450	hydrogen	methyl	[3-(4-Bromo-phenyl)-3-pyridin-3-yl-allyl]-methyl-phosphoramidic acid monomethyl ester
E1451	methyl	methyl	[3-(4-Bromo-phenyl)-3-pyridin-3-yl-allyl]-methyl-phosphoramidic acid dimethyl ester
E1452	phenyl	hydrogen	[3-(4-Bromo-phenyl)-3-pyridin-3-yl-allyl]-methyl-phosphoramidic acid monophenyl ester
E1453	phenyl	methyl	[3-(4-Bromo-phenyl)-3-pyridin-3-yl-allyl]-methyl-phosphoramidic acid methyl ester phenyl ester



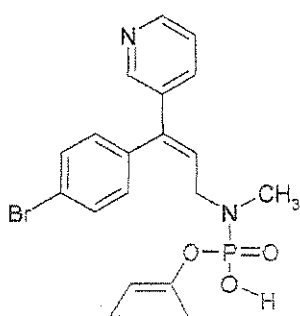
E1449



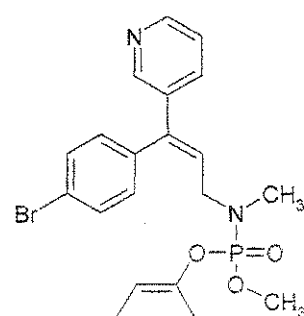
E1450



E1451



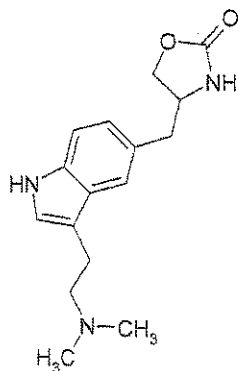
E1452



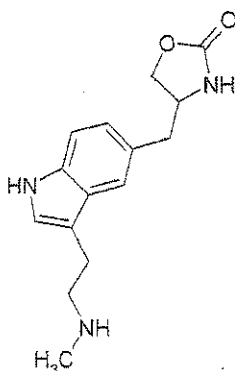
E1453

Zolmitriptan (Zomig®)

Chemical Structure

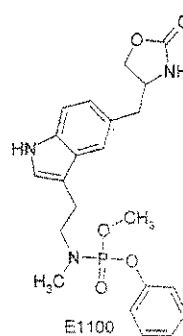
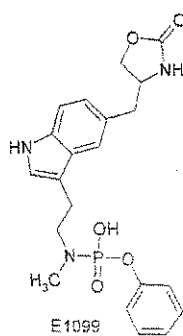
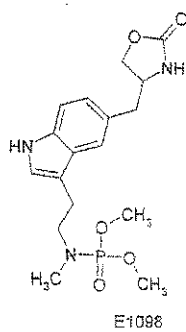
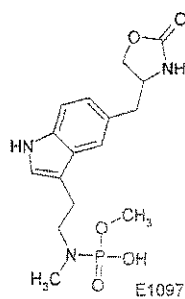
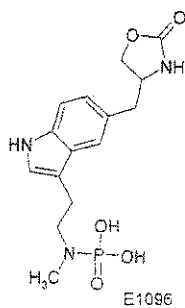
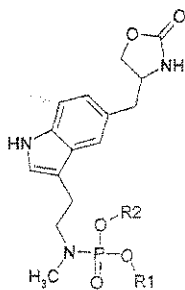


Active Metabolite Structure



Compound	R1	R2	Chemical Name	Estimated LogP	pKa
E1096	hydrogen	hydrogen	Methyl-{2-[5-(2-oxo-oxazolidin-4-ylmethyl)-1H-indol-3-yl]-ethyl}-phosphoramidic acid	1.65	2.59
E1097	hydrogen	methyl	Methyl-{2-[5-(2-oxo-oxazolidin-4-ylmethyl)-1H-indol-3-yl]-ethyl}-phosphoramidic acid monomethyl ester	1.71	5.07
E1098	methyl	methyl	Methyl-{2-[5-(2-oxo-oxazolidin-4-ylmethyl)-1H-indol-3-yl]-ethyl}-phosphoramidic acid dimethyl ester	1.76	3.93
E1099	phenyl	hydrogen	Methyl-{2-[5-(2-oxo-oxazolidin-4-ylmethyl)-1H-indol-3-yl]-ethyl}-phosphoramidic acid monophenyl ester	3.47	4.63
E1100	phenyl	methyl	Methyl-{2-[5-(2-oxo-oxazolidin-4-ylmethyl)-1H-indol-3-yl]-ethyl}-phosphoramidic acid methyl ester phenyl ester	3.53	3.49

5

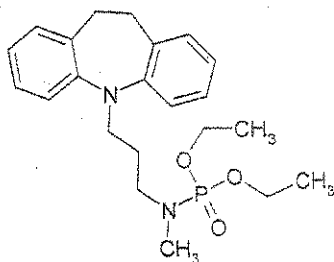


Examples of the Invention

Example 1

Synthesis of [3-(10,11-Dihydro-dibenzo[b,f]azepin-5-yl)-propyl]-methyl-phosphoramidic acid diethyl ester

5

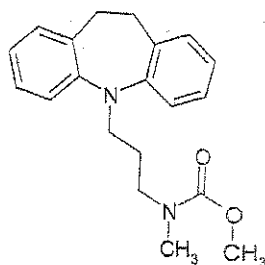


Compound Number E1413

- 10 Desipramine hydrochloride (1 equivalent, 0.5 gram) was added drop wise to a stirred solution of potassium carbonate (2 equivalents, 0.456 gram) in dry DMF at 0°C. Diethylchlorophosphate (1.2 equivalents, 0.33 ml) which had been dissolved in dry DMF was added drop wise to this mixture and stirred for 12 hours at room temperature. The reaction mixture was quenched with water, extracted with ethyl acetate, the organic layer
- 15 separated, washed with brine solution and dried over anhydrous sodium sulfate. The dried material was concentrated and purified by column chromatography to provide a pale yellow liquid (yield: 0.33 gram) and analyzed by HPLC (purity 93.1%). The FTIR, MS and ¹H NMR spectra were consistent with the assigned with the empirical formula of C₂₂H₃₁N₂O₃P.

Example 2

Synthesis of [3-(10,11-Dihydro-dibenzo[b,f]azepin-5-yl)-propyl]-methyl-carbamic acid methyl ester



5

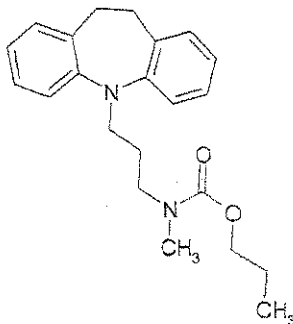
Compound Number E1414

- Desipramine hydrochloride (1 equivalent, 0.3 gram) was added drop wise to a stirred solution of potassium carbonate (2 equivalents, 0.27 gram) in dry DMF at 0°C. Methyl chloroform (1.2 equivalents, 0.1 ml) which had been dissolved in dry DMF was added drop wise to this mixture and stirred for 6 hours at room temperature. The reaction mixture was quenched with water, extracted with ethyl acetate, the organic layer separated, washed with brine solution and dried over anhydrous sodium sulfate. The dried material was concentrated and purified by column chromatography to provide a pale yellow liquid (yield: 0.18 gram) and analyzed by HPLC (purity 97.7%). The FTIR, MS and ¹H NMR spectra were consistent with the assigned with the empirical formula of C₂₀H₂₄N₂O₂.
- 10
- 15

Example 3

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Synthesis of [3-(10,11-Dihydro-dibenzo[b,f]azepin-5-yl)-propyl]-methyl-carbamic acid propyl ester



Compound Number E1415

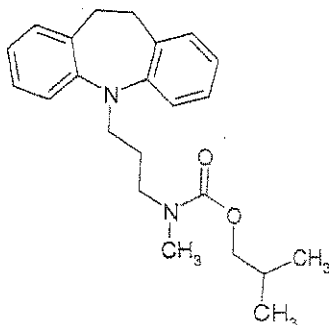
10 Desipramine hydrochloride (1 equivalent, 0.2 gram) was added drop wise to a stirred solution of potassium carbonate (5 equivalents, 0.45 gram) in dry DMF at 0°C. Propyl chloroform (1.5 equivalents, 0.1 ml) which had been dissolved in dry DMF was added drop wise to this mixture and stirred for 6 hours at room temperature. The reaction mixture was quenched with water, extracted with ethyl acetate, the organic layer separated, washed with brine solution and dried over anhydrous sodium sulfate. The dried material was concentrated and purified by column chromatography to provide a yellow liquid (yield: 0.12 gram) and by HPLC (purity 95.7%). The FTIR, MS and ¹H NMR spectra were consistent with the assigned structure with the empirical formula of C₂₂H₂₈N₂O₂.

15

Example 4

Synthesis of [3-(10,11-Dihydro-dibenzo[b,f]azepin-5-yl)-propyl]-methyl-carbamic acid isobutyl ester

5



Compound Number E1416

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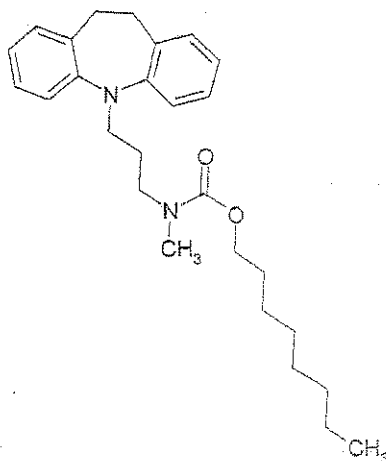
Desipramine hydrochloride (1 equivalent, 0.3 gram) was added drop wise to a stirred solution of potassium carbonate (5 equivalents, 0.68 gram) in dry DMF at 0° C. Isobutyl chloroform (1.5 equivalents, 0.18 ml) which had been dissolved in dry DMF was added drop wise to this mixture and stirred for 6 hours at room temperature. The reaction mixture was quenched with water, extracted with ethyl acetate, the organic layer separated, washed with brine solution and dried over anhydrous sodium sulfate. The dried material was concentrated and purified by column chromatography to provide a pale yellow liquid (yield: 0.18 gram) and analyzed by HPLC (purity 96.4%) The FTIR, MS and ¹H NMR spectra were consistent with the assigned structure with the empirical formula of C₂₂H₂₈N₂O₂.

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Example 5

Synthesis of [3-(10,11-Dihydro-dibenzo[b,f]azepin-5-yl)-propyl]-methyl-carbamic acid octyl ester

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Compound Number E1417

- 10 Desipramine hydrochloride (1 equivalent, 0.3 gram) was added drop wise to a stirred solution of potassium carbonate (2.5 equivalents, 0.34 gram) in dry DMF at 0° C. Octyl chloroform (1.5 equivalents, 0.429 grams) which had been dissolved in dry DMF was added drop wise to this mixture and stirred for 12 hours at room temperature. The reaction mixture was quenched with water, extracted with ethyl acetate, the organic layer
- 15 separated, washed with brine solution and dried over anhydrous sodium sulfate. The dried material was concentrated and purified by column chromatography to provide a pale yellow liquid (yield: 0.12 gram) and analyzed by HPLC (purity 95.3%) The FTIR, MS and ¹H NMR spectra were consistent with the assigned structure with the empirical formula of C₂₇H₃₈N₂O₂.

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Example 6

Stability Testing of Prodrugs in Human Plasma

5 Pooled human plasma was obtained from Bioreclamation (East Meadow, New York) by collection into sodium EDTA as the anticoagulant, and was stored at ca -20 °C prior to use. Prior to use, the plasma defrosted and was spun at ca. 3000 rpm for 5 minutes to remove any precipitate. The pH of the plasma was adjusted to pH 7.4 by careful addition of NaH_2PO_4 buffer.

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Plasma stability was assessed by incubation of 10 μM of each compound prepared in Examples 1-5 with human plasma, in duplicate, at ca. 37 °C with shaking. Each compound prepared in Examples 1-5 was also incubated at 10 μM in PBS as a control for compound heat stability. Aliquots were removed at 0, 0.5, 1 and 2 hours and stored at -20°C until analysis.

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For analysis, plasma samples were extracted in 1 part acetonitrile and isolation of the supernatant. Analysis of each compound prepared in Examples 1-5 in plasma extracts was conducted by an LC-MS method at each time interval and quantification was achieved by comparison of the response due to the sample to that of a three point standard curve. Appearance of the parent drug the hydroxymetabolites were also monitored at each time interval. The % degradation following incubation at each time point was calculated by comparison of the parent concentration to that at 0 minutes.

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The results of the stability testing in human plasma are shown in the following table:

Table 1- Stability Testing of Prodrugs in Human Plasma

Loss of parent compound in human plasma (%)					
Incubation Time (min)	RIC-02	RIC-5a	RIC-5b	RIC-5c	RIC-5d
0	0.00	0.00	0.00	0.00	0.00
30	-43	5.47	7.15	5.11	-32.74
60	9.94	15.80	6.85	-1.48	-1.44
120	7.93	26.22	21.06	25.82	49.54

Example 7

Stability Testing of Prodrugs in Rat Plasma (elevated esterase activity)

- 15 Sprague-Dawley rat plasma was obtained by collection into sodium EDTA as the anticoagulant, and was stored at ca -20 °C prior to use. Prior to use, the plasma defrosted and was spun at ca. 3000 rpm for 5 minutes to remove any precipitate. The pH of the plasma was adjusted to pH 7.4 by careful addition of NaH₂PO₄ buffer.
- 20 Plasma stability was assessed by incubation of 10 µM of each compound prepared in Examples 1-5 with rat plasma, in duplicate, at ca. 37 °C with shaking. Each compound prepared in Examples 1-5 was also incubated at 10 µM in PBS as a control for compound heat stability. Aliquots were removed at 0, 0.5, 1 and 2 hours and stored at -20°C until analysis.
- 25 For analysis, plasma samples were extracted in 1 part acetonitrile and isolation of the supernatant. Analysis of each compound prepared in Examples 1-5 in plasma extracts was conducted by an LC-MS method at each time interval and quantification was achieved by comparison of the response due to the sample to that of a three point
- 30 standard curve. Appearance of the parent drug and the hydroxymetabolites were also monitored at each time interval. The % degradation following incubation at each time point was calculated by comparison of the parent concentration to that at 0 minutes.

The results of the stability testing in rat plasma are shown in the following table:

Table 2- Stability Testing of Prodrugs in Rat Plasma

Loss of parent compound in rat plasma (%)					
Incubation Time (min)	RIC-02	RIC-5a	RIC-5b	RIC-5c	RIC-5d
0	0.00	0.00	0.00	0.00	0.00
30	4.67	8.81	7.17	-14.69	-8.16
60	11.01	23.43	8.34	-2.88	41.70
120	9.02	45.85	23.42	33.40	73.48

Example 8

Stability Testing of Prodrugs in the Stomach and Intestine

The stability of each compound prepared in Examples 1-5 was assessed in both simulated gastric fluids and intestinal fluids alone and intestinal fluids spiked with alkaline phosphatase to approximate the enzymatic activity of the intestinal wall.

The stability of each compound prepared in Examples 1-5 was assessed in duplicate by incubation of 10 μ M of each compound at ca. 37 °C and shaking with each of the following: simulated gastric fluids (saline pH approximately 1, plus pepsin); simulated intestinal fluids (phosphate pH 6 with pepsin); and alkaline phosphatase enhanced simulated intestinal fluids (phosphate pH 6 with pepsin and $\pm$ alkaline phosphatase). Aliquots were removed at 0, 0.5, 1 and 2 hours, extracted with one volume of organic solvent and stored at -20°C until analysis.

Analysis of each compound prepared in Examples 1-5 in gastric fluid and intestinal fluid extracts was conducted by an LC-MS method at each time interval and quantification was achieved by comparison of the response due to the sample to that of a three point standard curve. Appearance of the parent drug and the hydroxymetabolites were also monitored at each time interval. The % degradation following incubation at each time point was calculated by comparison of the parent concentration to that at 0 minutes.

The results of the stability testing in simulated gastric fluids are shown in the following table:

Loss of parent compound in simulated gastric fluid (%)					
Incubation Time (min)	RIC-02	RIC-5a	RIC-5b	RIC-5c	RIC-5d
0	0.00	0.00	0.00	0.00	0.00
30	49.94	13.93	58.72	70.64	13.84
60	74.67	31.78	26.67	82.77	
120	93.12	81.43	94.37	98.11	

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The results of the stability testing in simulated intestinal fluids are shown in the following table:

Loss of parent compound in simulated intestinal fluid (%)					
Incubation Time (min)	RIC-02	RIC-5a	RIC-5b	RIC-5c	RIC-5d
0	0.00	0.00	0.00	0.00	0.00
30	11.65	16.75	6.73	1.05	7.73
60	7.83	22.88	13.57	12.68	-8.72
120	9.29	35.18	25.61	21.78	4.23

No further loss of RIC-02 in simulated intestinal fluids enhanced with alkaline phosphatase was observed up to 120 minute incubation.

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Example 9

Metabolic Stability Testing of Prodrugs - Microsomal Incubations

The metabolic stability of each compound prepared in Examples 1-5 was assessed in microsomal preparations obtained from BD Gentest (Woburn, MA).

The metabolic stability of each compound prepared in Examples 1-5 was assessed in duplicate by incubation of 10 μ M compound with 0.5 mg/mL microsomal protein, 1 mM NADPH in 0.1 M phosphate buffer, pH 7.4 in the presence and absence of a CYP3A4 inhibitor (ketoconazole). The reaction mixture was pre-incubated, in the absence of the microsomes, at ca. 37 °C for 5 minutes, followed by initiation of the incubation by the addition of microsomal protein and maintained at ca. 37 °C for a further 0, 30 and 60 minutes. After the appropriate incubation time, the mixtures were quenched by the addition of one volume of acetonitrile and the supernatant was isolated by centrifugation. Positive control incubations (7-ethoxycoumarin) were performed in the same manner as the compounds from Examples 1-5 and quenched after 0 and 30 minutes. In addition,

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negative control incubations were performed for 60 minutes in the absence of NADPH to assess chemical stability.

Analysis of supernatants from each time interval was conducted for each compound prepared in Examples 1-5 by LC-MS analysis. Quantification of the disappearance on the parent drug was achieved by comparison of the sample response to that of a suitable standard curve constructed in 0.1 M phosphate buffer, pH 7.4. The standard curve ranged between $\leq 1\%$ up to $\geq 100\%$ of the dosing concentration.

The % turnover following 60 minutes of incubation was calculated by comparison of the parent concentration to that at 0 minutes. The % degradation was calculated in the same manner from the negative control incubations. Appearance of the parent drug and the hydroxymetabolites were also monitored at each time interval.

The results of the metabolic testing in microsomes without inhibitor are shown in the following table:

Loss of parent compound with no ketoconazole (%)					
Incubation Time (min)	RIC-02	RIC-5a	RIC-5b	RIC-5c	RIC-5d
30	76.17	70.94	64.76	54.01	59.12
60	91.40	87.25	82.29	76.36	74.17

The results of the metabolic testing in microsomes with ketoconazole inhibitor are shown in the following table:

Loss of parent compound with ketoconazole (%)					
Incubation Time (min)	RIC-02	RIC-5a	RIC-5b	RIC-5c	RIC-5d
30	-17.26	27.65	31.69	6.36	15.18
60	11.04	62.37	50.21	19.49	55.88

Example 10

Metabolic Stability of the Prodrugs - CYP3A4 and 2D6 Incubations

The metabolic stability of each compound prepared in Examples 1-5 was assessed in the presence of CYP2D6 and CYP3A4 obtained from BD Gentest (Woburn, MA).

The metabolic stability of each compound prepared in Examples 1-5 was assessed in duplicate by incubation of 10 μ M compound with recombinant human CYP2D6 and 3A4

using similar conditions to those in Example 12. Samples were removed for analysis at 0, 30 and 60 minutes and extracted with one volume of organic solvent. Appropriate controls were included. Quantification of the disappearance of the prodrug was conducted LC-MS. Appearance of metabolites was also monitored.

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The results of the metabolic testing in the presence of CYP3A4 isozyme are shown in the following table:

Loss of parent compound with CYP3A4 isozyme (%)					
Incubation Time (min)	RIC-02	RIC-5a	RIC-5b	RIC-5c	RIC-5d
0	0.00	0.00	0.00	0.00	0.00
30	97.05	91.32	92.32	72.07	33.66
60	98.62	97.96	95.20	90.69	60.64

- 10 The results of the metabolic testing in the presence of CYP2D6 isozyme are shown in the following table:

Loss of parent compound with CYP2D6 isozyme (%)					
Incubation Time (min)	RIC-02	RIC-5a	RIC-5b	RIC-5c	RIC-5d
0	0.00	0.00	0.00	0.00	0.00
30	13.19	73.91	19.21	43.71	18.68
60	37.11	83.13	28.01	70.07	

Example 11

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Metabolic Stability Testing - Hepatocyte Incubations

The metabolic stability of each compound prepared in Examples 1-5 was assessed in human hepatocytes obtained from In Vitro Technologies (Baltimore, MD).

- 20 The metabolic stability of each compound prepared in Examples 1-5 was assessed in duplicate by incubation of 10 μ M compound with human hepatocytes after thawing of cryopreserved suspensions. The hepatocytes were maintained in Modified Williams' E medium (HMM, Clonetics, MD) supplemented with 0.1 μ M dexamethasone, 0.1 μ M insulin and 0.05 % gentamicin immediately after thawing.

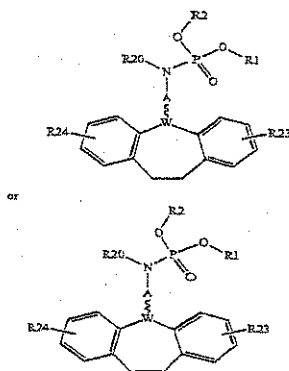
Each compound prepared in Examples 1-5 was tested by incubation in duplicate with the hepatocyte suspensions (1.0×10^6 viable cells/mL HHM media) and incubated for 0, 1, 2 and 4 hours at 37°C at 5% CO₂. Incubations were terminated by the addition of two volumes of ice-cold methanol, cell debris was removed by centrifugation and the
5 supernatant was stored at approximately -70°C prior to analysis.

Negative and positive control incubations were performed in duplicate under the same conditions as described for the prodrugs. *Negative control incubations:* An incubation of each compound prepared in Examples 1-5 in Modified Williams' E media (HHM media), in the absence of hepatocytes was performed alongside the hepatocyte incubations.
10 *Positive control incubations:* Incubations with a positive control (7-ethoxycoumarin; 100 µM) was performed with hepatocytes from each species for 1 hour alongside the prodrug incubations. Analysis of metabolic turnover was performed by HPLC. Quantification of the parent compound was achieved by comparison of the sample response to that of a suitable standard curve. The standard curve ranged between ≤1% up to ≥100% of the
15 dosing concentration. The % turnover following 1, 2 and 4 hours of incubation was calculated by comparison of the parent concentration to that at 0 minutes.

The present invention has been described in specific detail and with particular reference to its preferred embodiments; however, it will be obvious to those having skill in the art
20 that modifications and changes can be made thereto without departing from the spirit and scope of the invention.

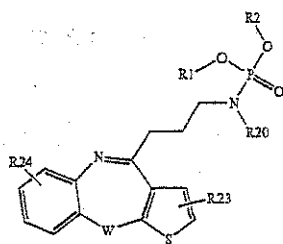
I claim:

1. A pharmaceutical composition comprising a compound having the formula



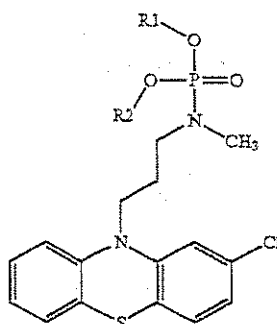
where R_1 and R_2 are independently hydrogen, alkyl having from 1 to about 7 carbon atoms, aryl, aralkyl, or cycloalkyl having from 3 to about 6 carbon atoms, A is a lower alkyl, lower heteroalkyl or cycloalkyl, R_{20} is hydrogen, phenyl or lower alkyl, W is carbon or nitrogen, R_{23} and R_{24} are independently hydrogen, halogen, alkyl or alkoxy, and pharmaceutically acceptable salts thereof in combination with a pharmaceutically acceptable excipient, diluent or carrier suitable for delayed release oral administration.

2. A pharmaceutical composition comprising a compound having the formula



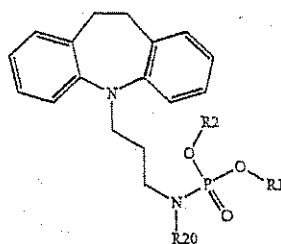
where R_1 and R_2 are independently hydrogen, alkyl having from 1 to about 7 carbon atoms, aryl, aralkyl, or cycloalkyl having from 3 to about 6 carbon atoms, R_{20} is hydrogen, phenyl or lower alkyl, W is carbon or nitrogen, R_{23} and R_{24} are independently hydrogen, halogen, alkyl or alkoxy, and pharmaceutically acceptable salts thereof in combination with a pharmaceutically acceptable excipient, diluent or carrier suitable for delayed release oral administration.

3. A pharmaceutical composition comprising a compound having the formula



where R_1 and R_2 are independently hydrogen, alkyl having from 1 to about 7 carbon atoms, aryl, aralkyl, or cycloalkyl having from 3 to about 6 carbon atoms, and pharmaceutically acceptable salts thereof in combination with a pharmaceutically acceptable excipient, diluent or carrier suitable for delayed release oral administration.

4. A pharmaceutical composition comprising a compound having the formula

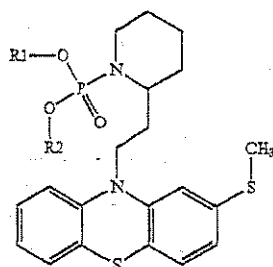


where R_1 and R_2 are independently hydrogen, alkyl having from 1 to about 7 carbon atoms, aryl, aralkyl, or cycloalkyl having from 3 to about 6 carbon atoms, R_{20} is hydrogen phenyl or lower alkyl and pharmaceutically acceptable salts thereof in combination with a pharmaceutically acceptable excipient, diluent or carrier suitable for delayed release oral administration.

5. The pharmaceutical composition of claim 4 where R_1 and R_2 are independently hydrogen and alkyl having from 1 to about 2 carbon atoms and R_{20} is hydrogen or lower alkyl.

6. The pharmaceutical composition of claim 5 where R_{20} is hydrogen or methyl.

7. A pharmaceutical composition comprising a compound having the formula



where R₁ and R₂ are independently hydrogen, alkyl having from 1 to about 7 carbon atoms, aryl, aralkyl, and cycloalkyl having from 3 to about 6 carbon atoms, and pharmaceutically acceptable salts thereof in combination with a pharmaceutically acceptable excipient, diluent or carrier suitable for delayed release oral administration.