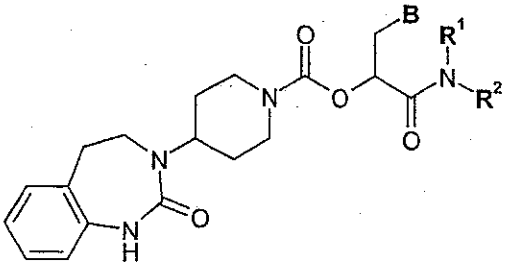
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2-Oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl-piperidines used as CGRP antagonists

The present invention relates to new CGRP antagonists of general formula I



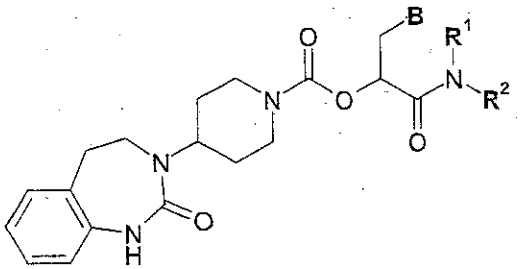
wherein **B**, $\mathbf{R^1}$ and $\mathbf{R^2}$ are defined as in claim 1, the tautomers, the isomers, the diastereomers, the enantiomers, the hydrates, the mixtures thereof and the salts thereof as well as the hydrates of the salts, particularly the physiologically acceptable salts thereof with inorganic or organic acids or bases, pharmaceutical compositions containing these compounds, the use thereof and processes for the preparation thereof.

BACKGROUND TO THE INVENTION

In International Patent Applications PCT/EP03/11762 and PCT/EP2005/003094 and in US 2005/0215576, CGRP antagonists have already been described for the treatment of migraine.

SUMMARY

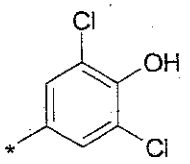
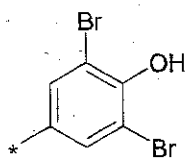
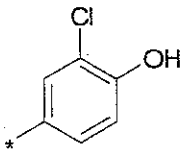
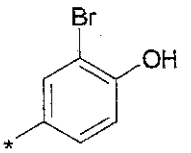
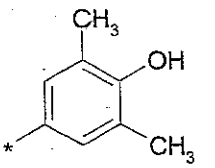
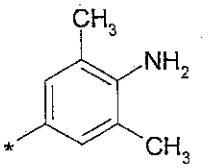
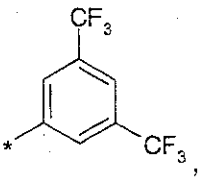
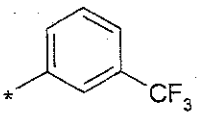
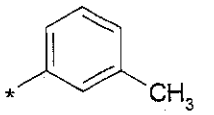
According to a first aspect, there is provided CGRP antagonists of general formula I



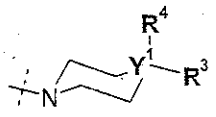
,

wherein

B denotes a group selected from


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,

,

and

,

R^1 and **R^2** together with the enclosed nitrogen atom denote a group of general formula **II**



,

wherein

Y^1 denotes the carbon atom or, if R^4 denotes a free pair of electrons, it may also denote the nitrogen atom,

R^3 denotes a cyclopentyl, cyclohexyl or cycloheptyl group or

R^3 denotes a heterocycle selected from a morpholin-4-yl, 1,1-dioxo-thiomorholin-4-yl, piperidin-1-yl, piperidin-4-yl, piperazin-1-yl or pyrrolidin-1-yl group,

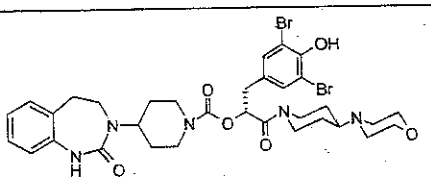
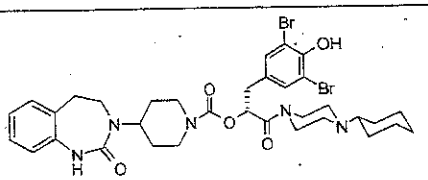
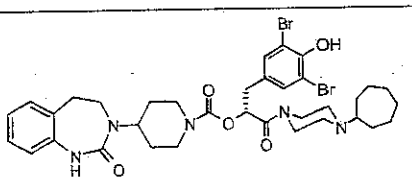
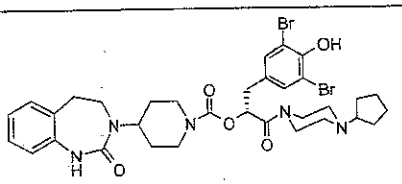
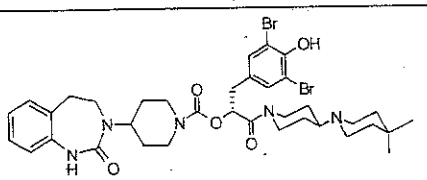
wherein the above-mentioned monocyclic heterocycles in the ring may be mono- or disubstituted by hydroxy, methyl, ethyl, trifluoromethyl, hydroxymethyl or hydroxyethyl groups, or may optionally additionally be monosubstituted by a hydroxycyclopropyl, trifluoromethylcarbonylmethyl, amino, carboxy-carbonyl, methoxycarbonyl, ethoxycarbonyl-carbonyl, carboxymethyl, carboxyethyl, ethoxycarbonylmethyl, ethoxycarbonylethyl, carboxy-ethylcarbonyl, ethoxycarbonyl-ethylcarbonyl, aminosulphonyl, methylaminosulphonyl, dimethylaminosulphonyl, methylsulphonyl, ethylsulphonyl, isopropylsulphonyl, cyclopropylsulphonyl, (hydroxyamino)-carbonylmethyl, hydroxy-(methyl)-aminocarbonyl-methyl or methoxyaminocarbonyl-methyl group, wherein the substituents may be identical or different and may be bound to a ring carbon or ring nitrogen atom, or

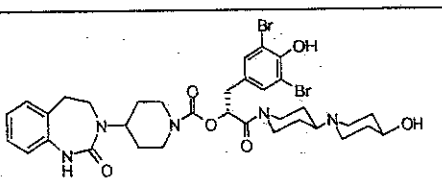
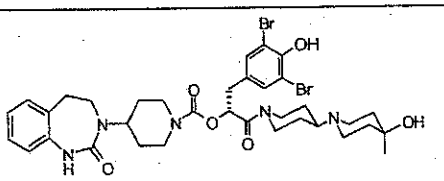
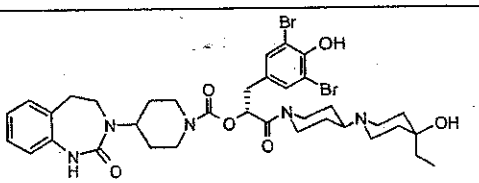
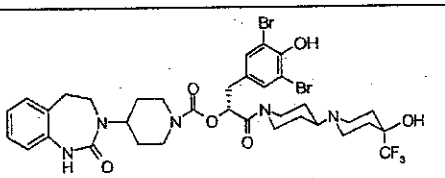
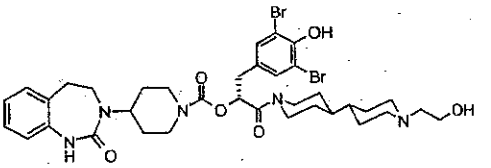
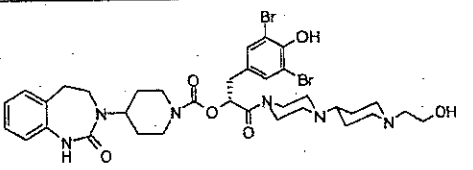
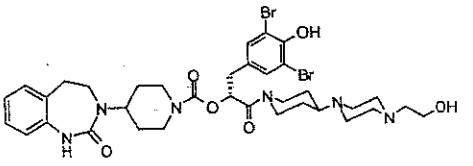
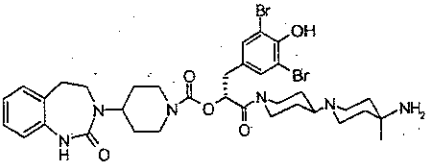
the above-mentioned monocyclic heterocycles in the ring may be monosubstituted by a carboxy group, if this carboxy group is not bound via a nitrogen atom, and

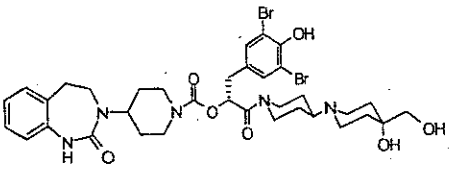
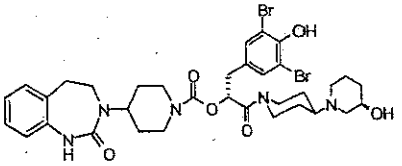
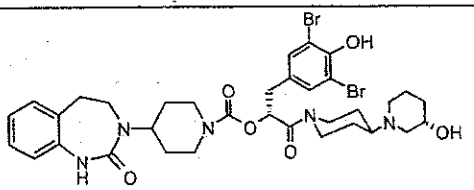
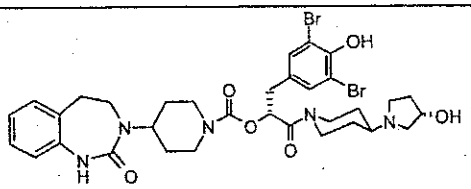
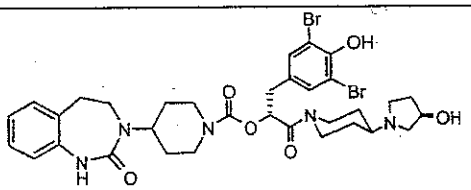
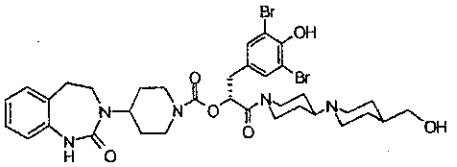
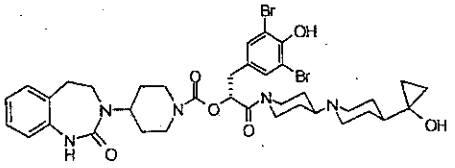
R^4 denotes the hydrogen atom, if Y^1 denotes the carbon atom, or

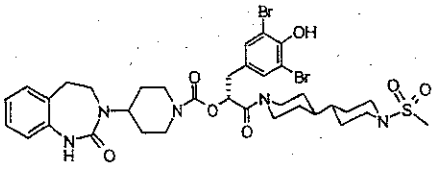
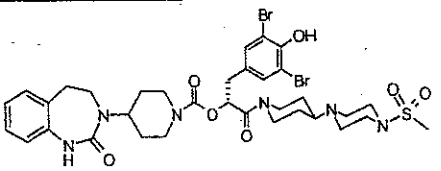
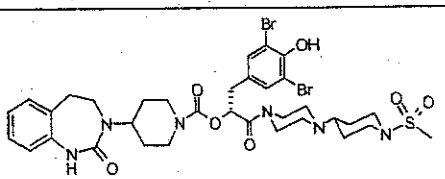
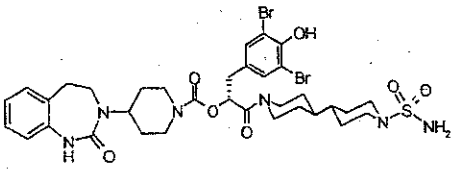
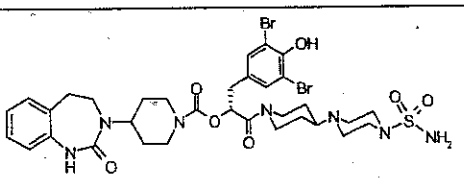
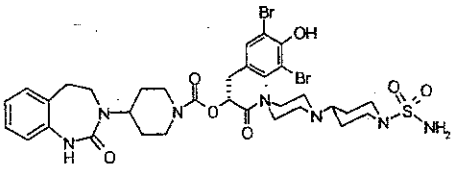
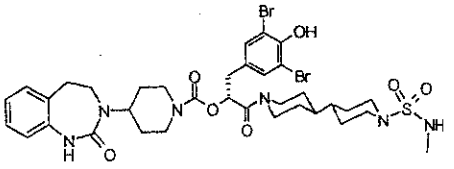
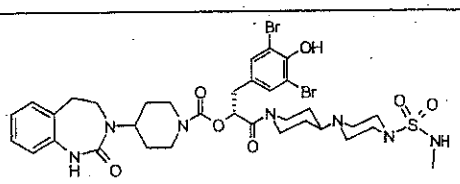
R^4 denotes a free pair of electrons, if Y^1 denotes the nitrogen atom,

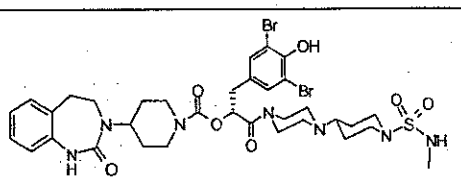
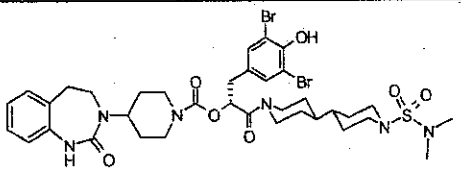
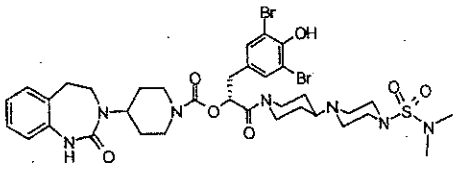
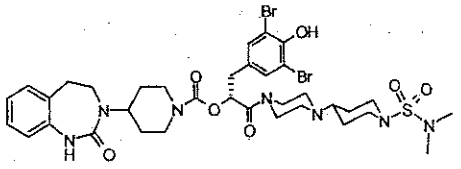
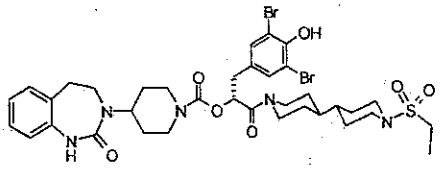
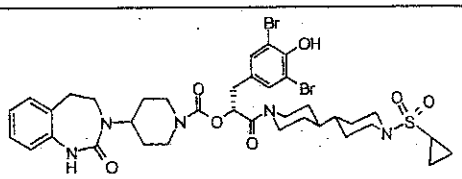
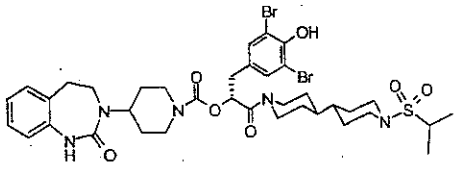
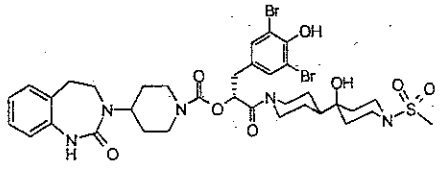
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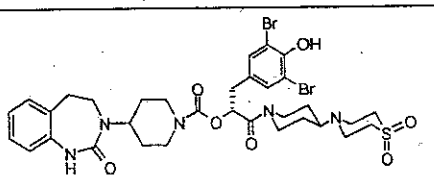
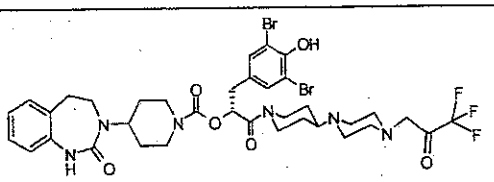
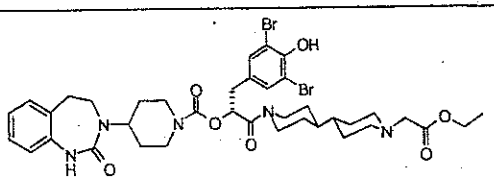
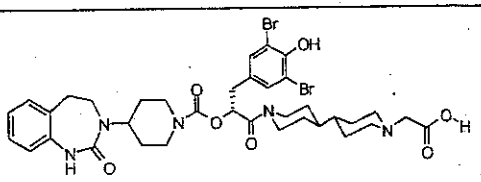
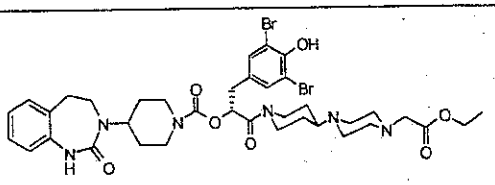
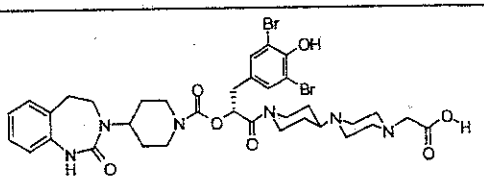
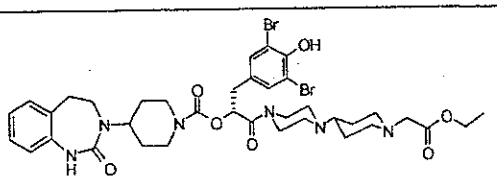
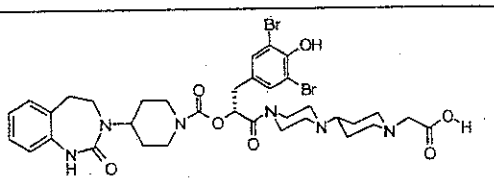
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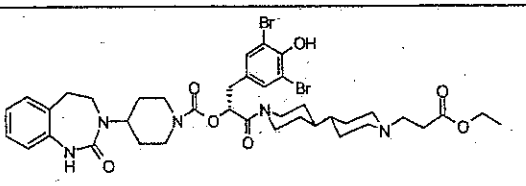
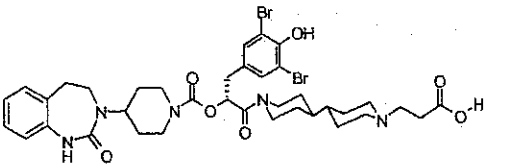
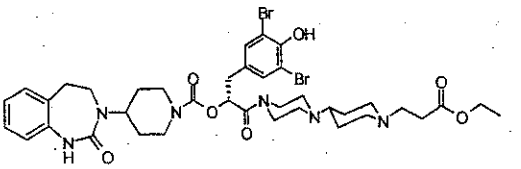
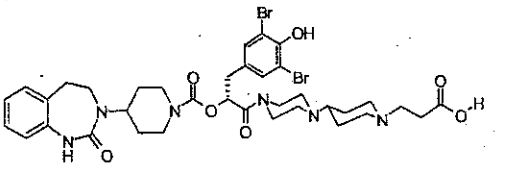
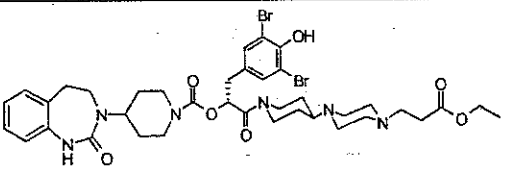
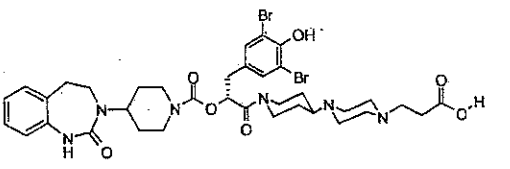
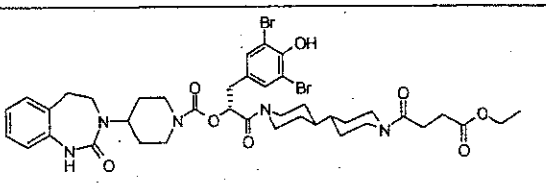
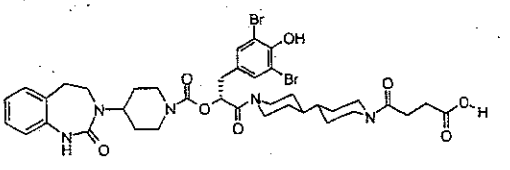
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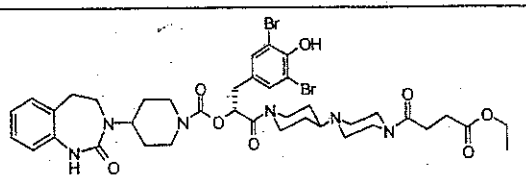
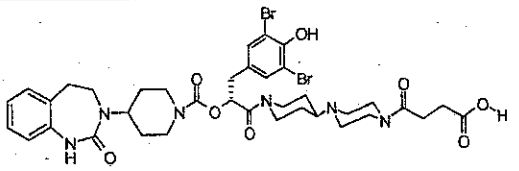
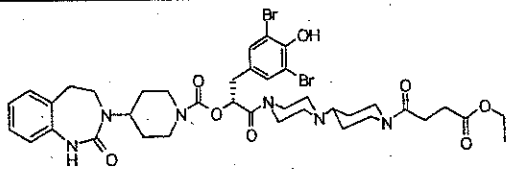
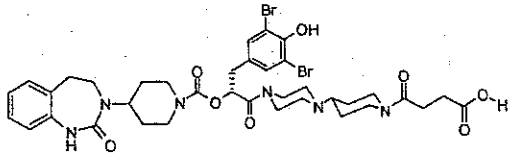
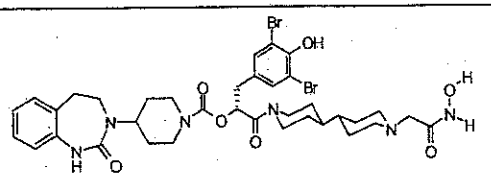
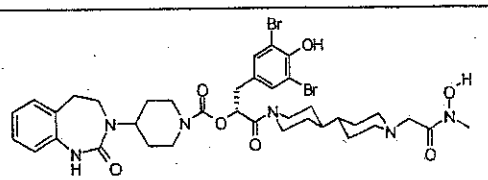
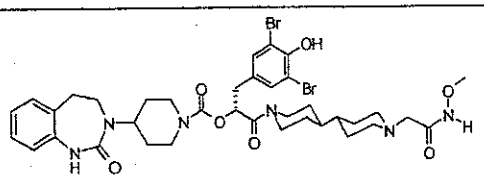
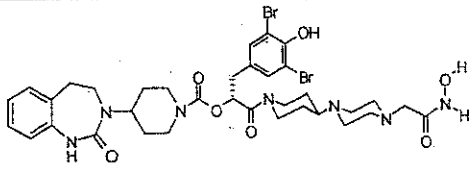
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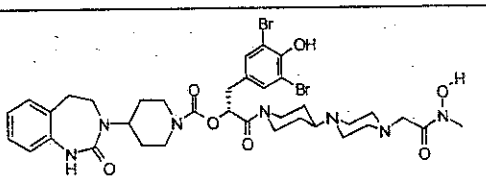
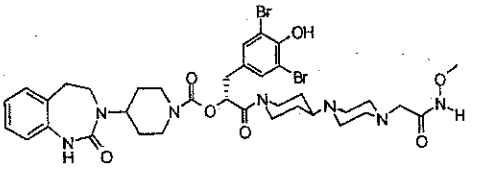
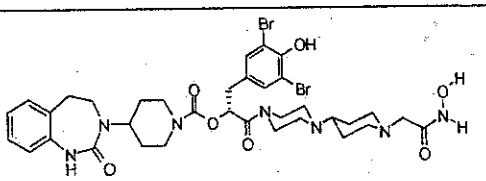
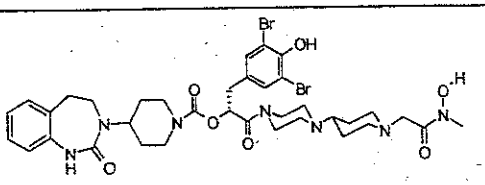
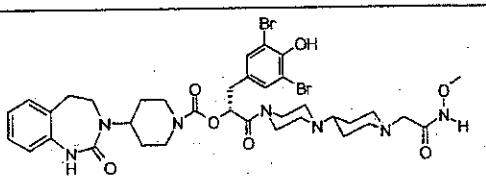
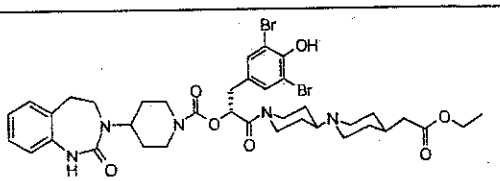
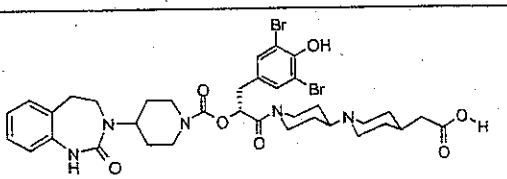
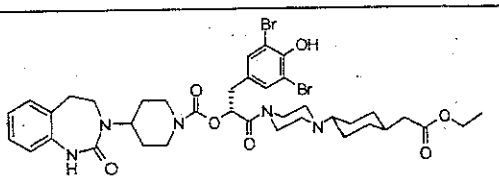
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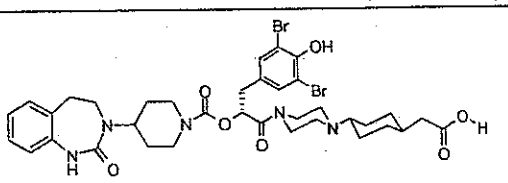
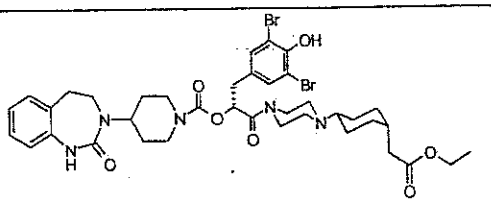
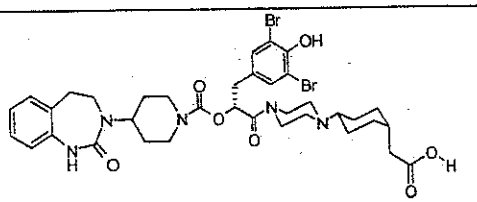
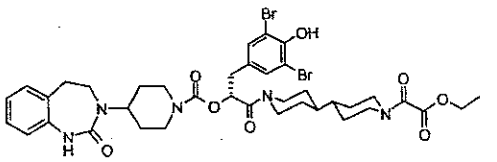
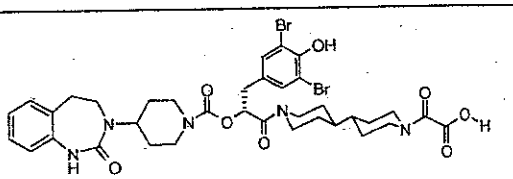
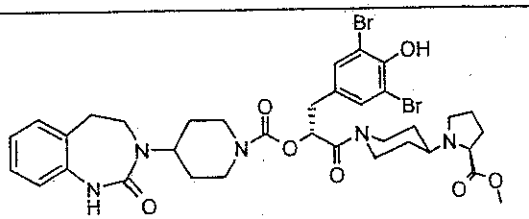
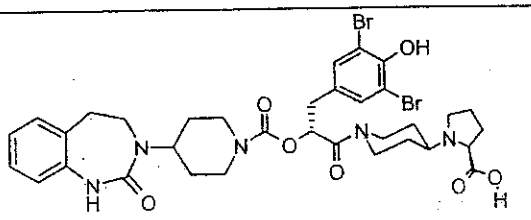
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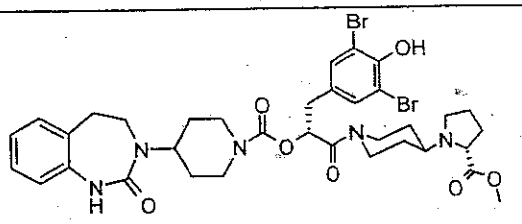
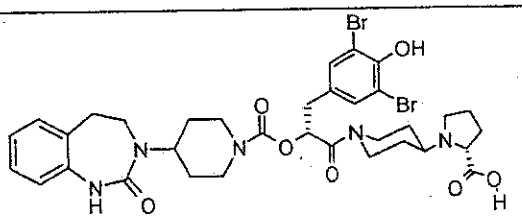
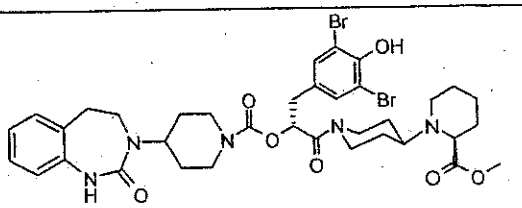
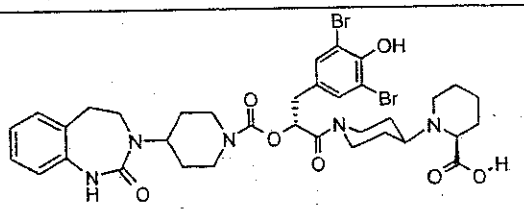
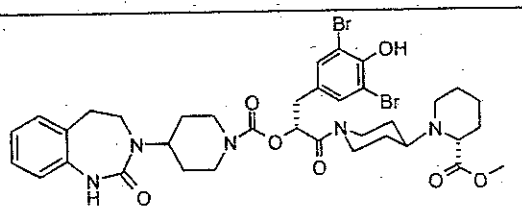
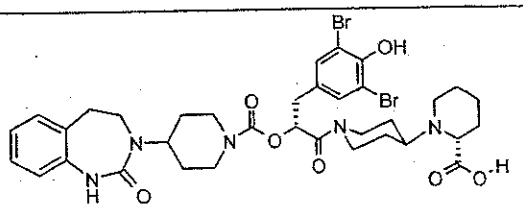
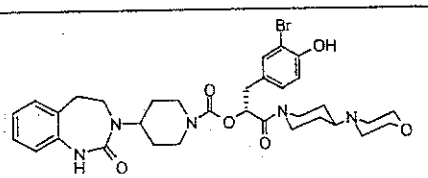
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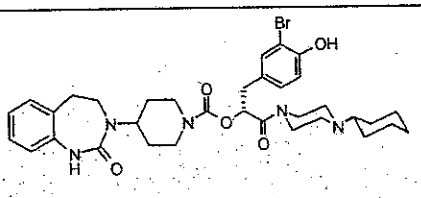
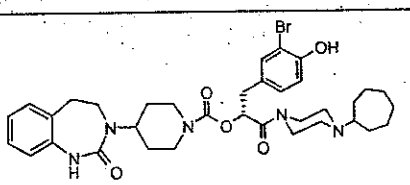
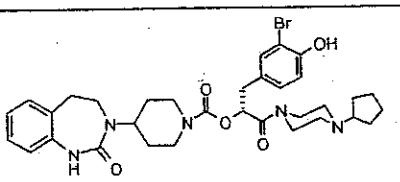
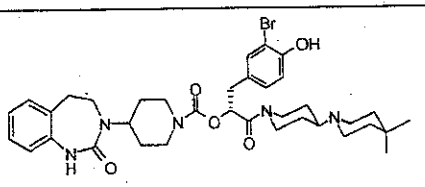
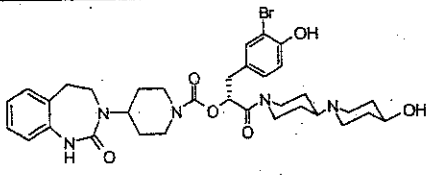
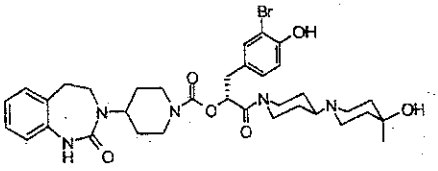
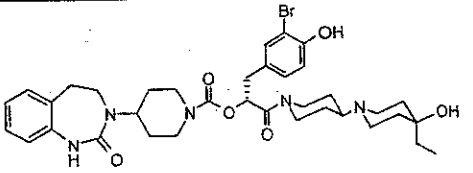
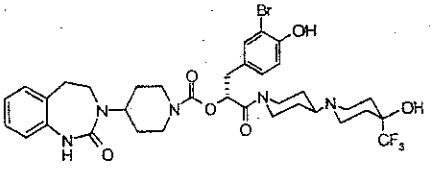
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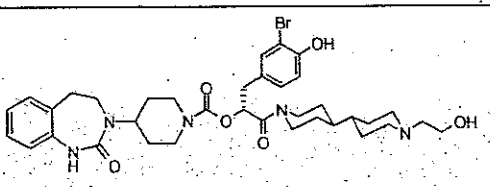
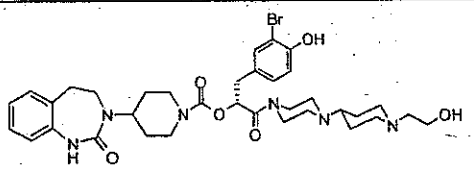
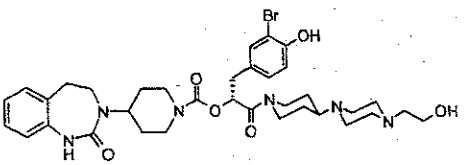
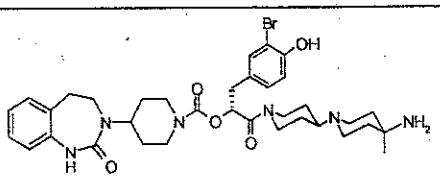
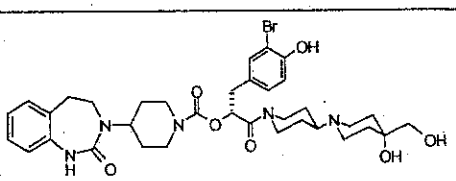
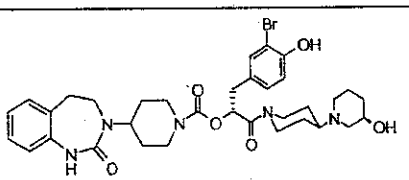
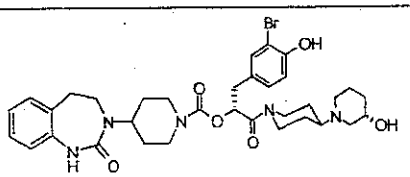
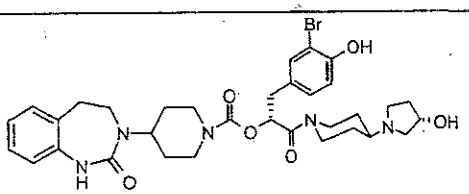
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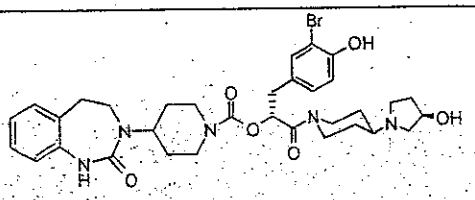
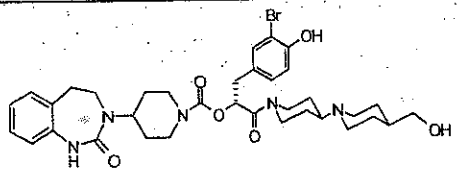
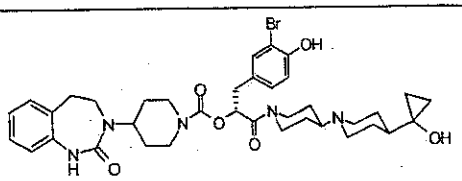
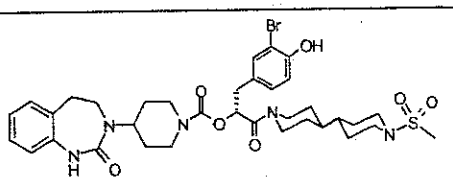
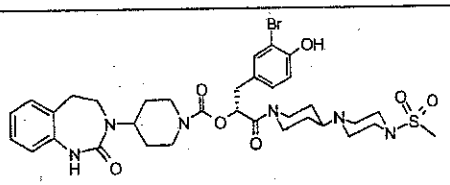
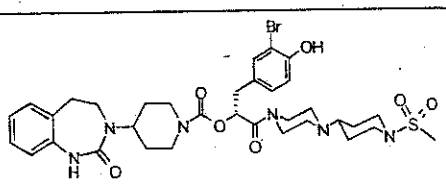
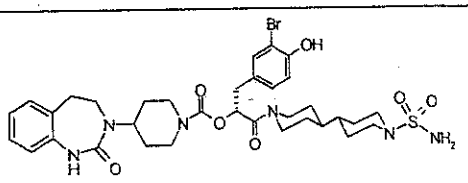
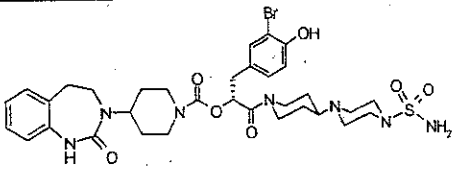
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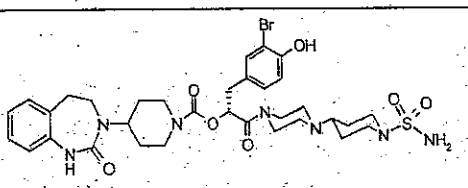
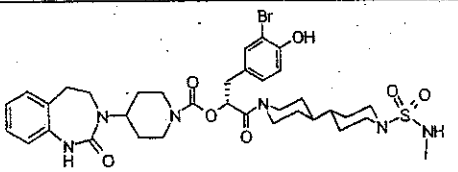
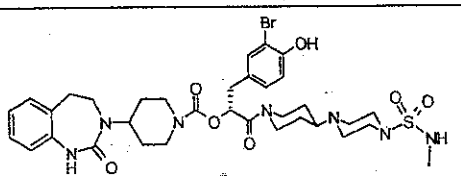
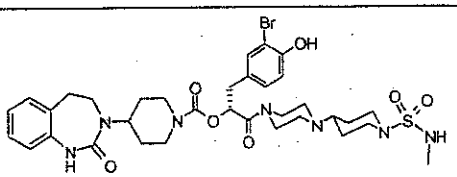
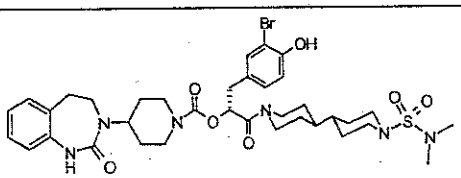
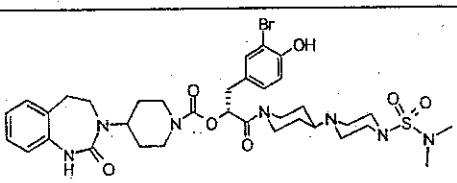
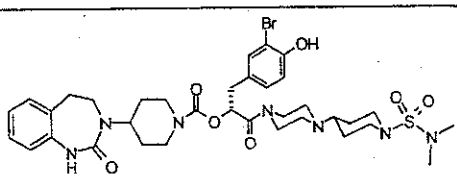
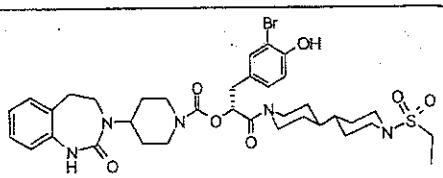
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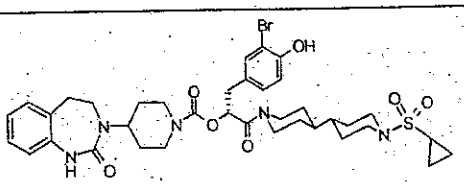
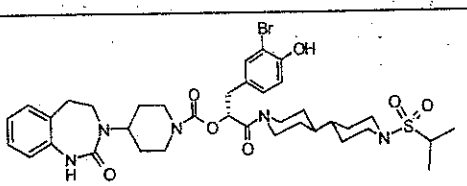
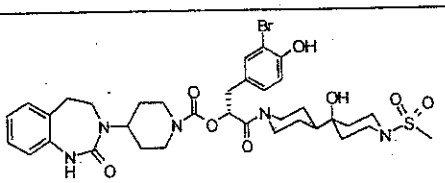
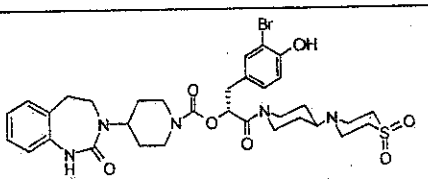
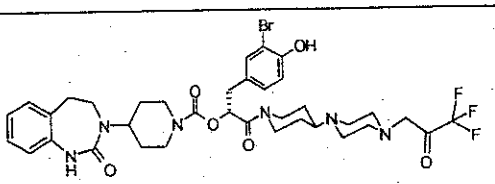
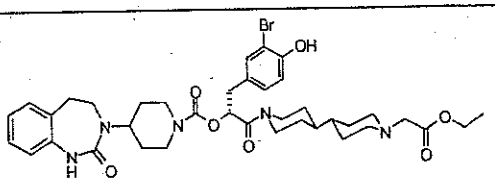
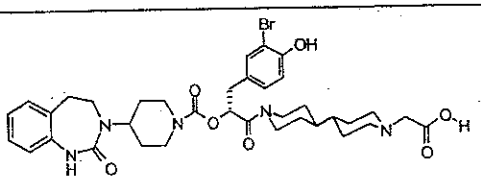
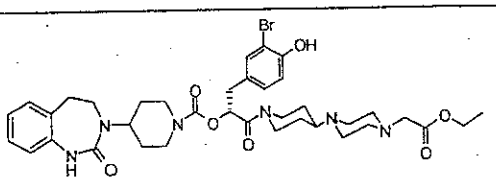
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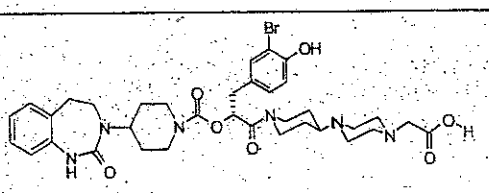
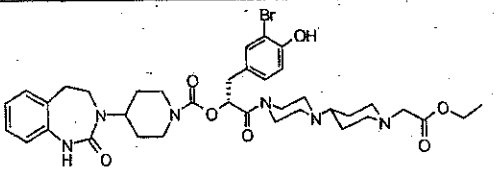
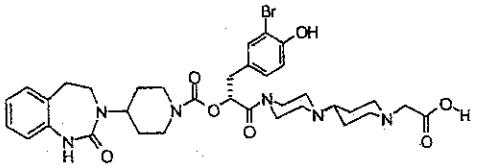
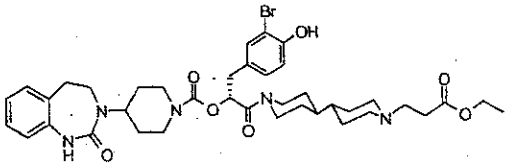
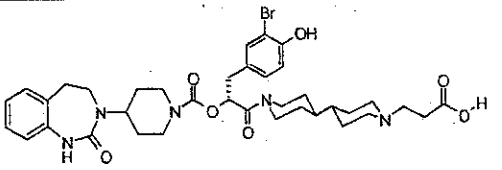
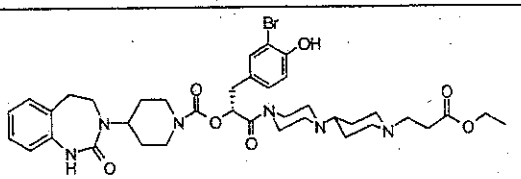
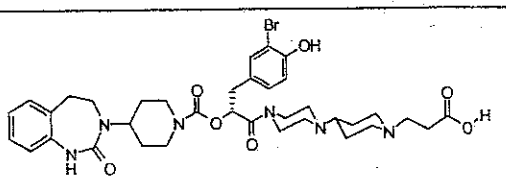
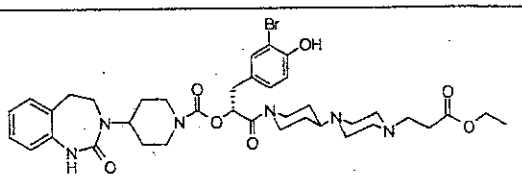
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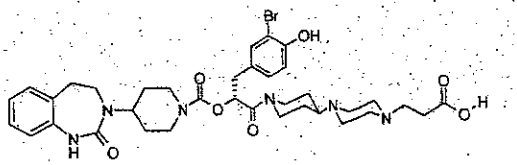
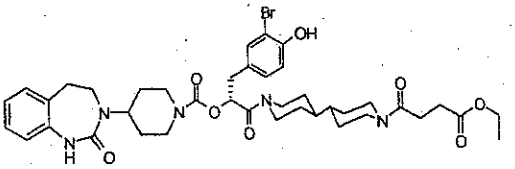
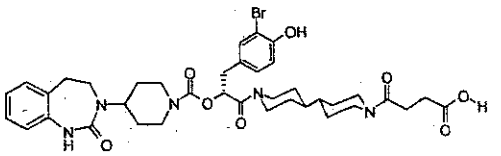
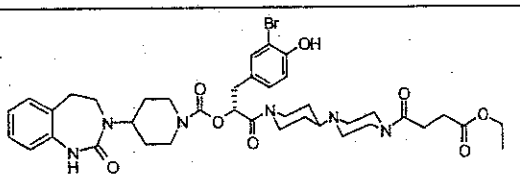
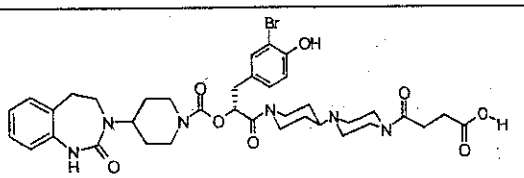
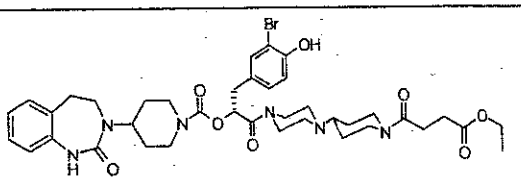
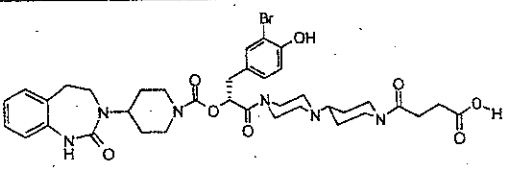
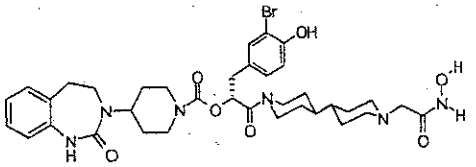
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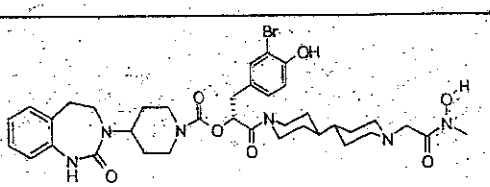
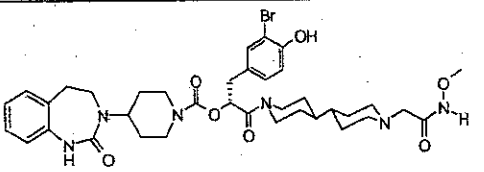
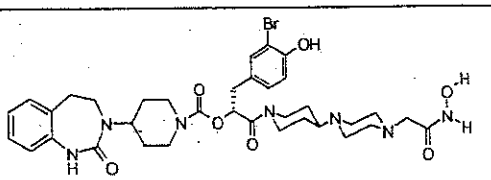
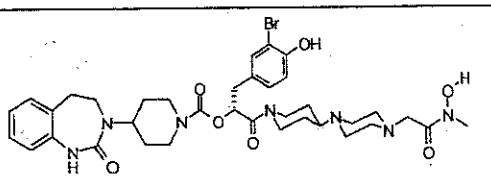
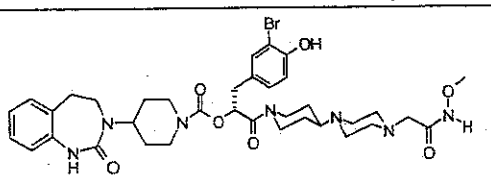
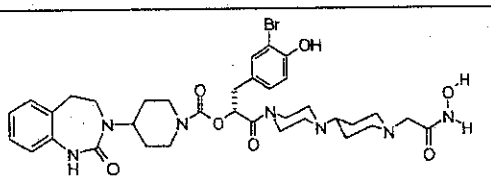
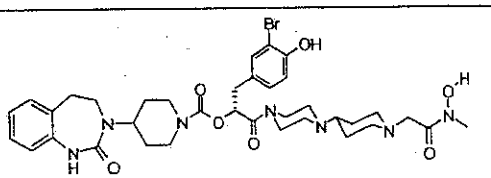
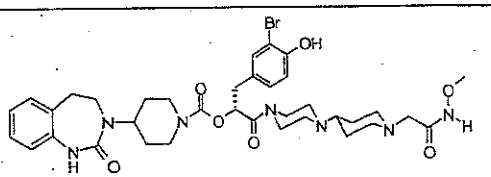
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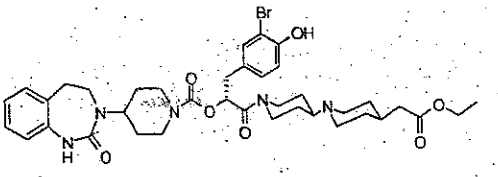
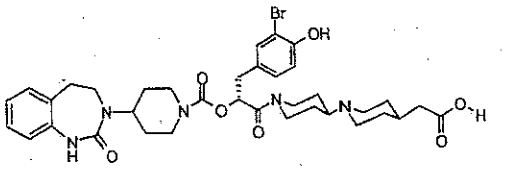
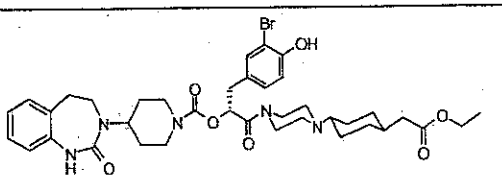
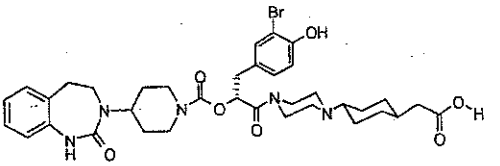
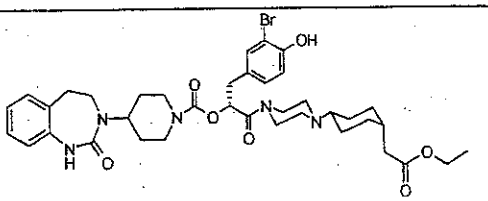
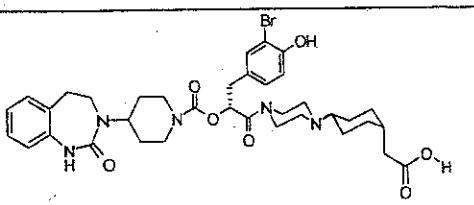
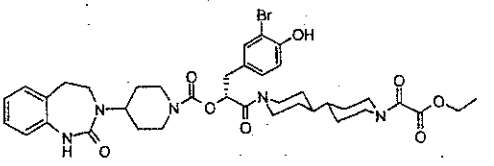
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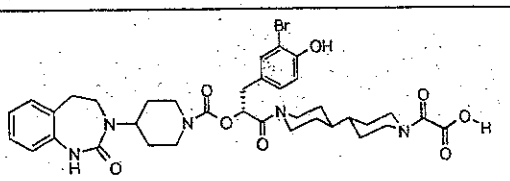
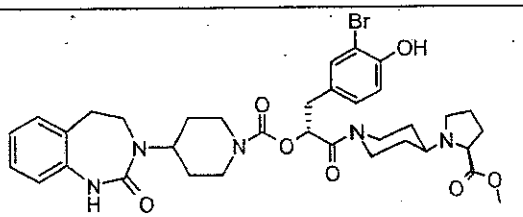
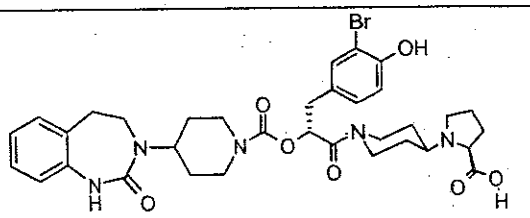
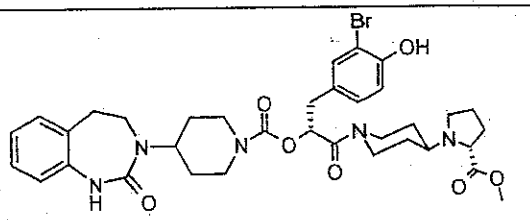
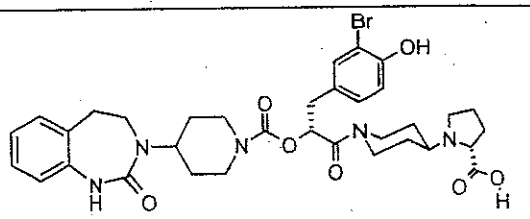
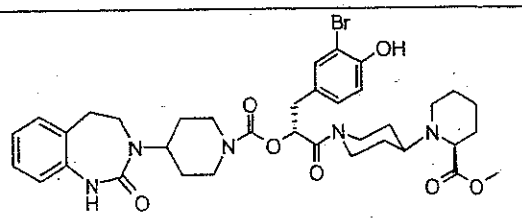
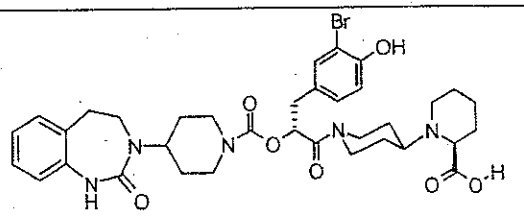
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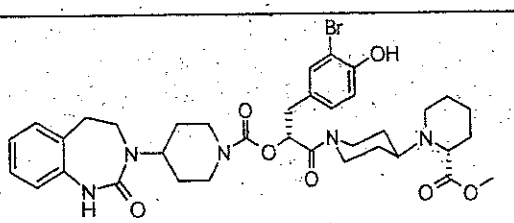
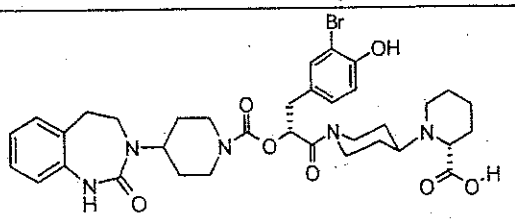
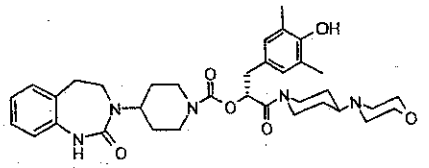
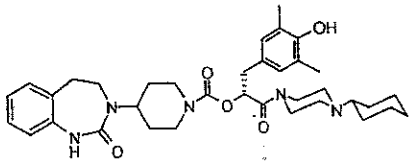
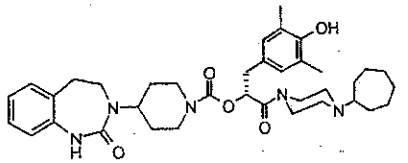
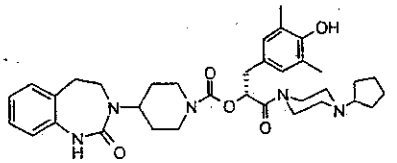
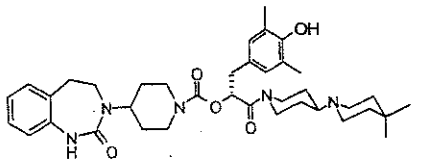
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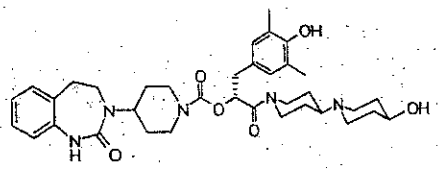
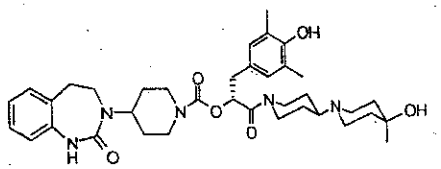
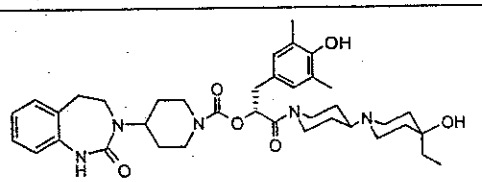
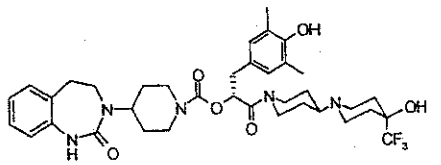
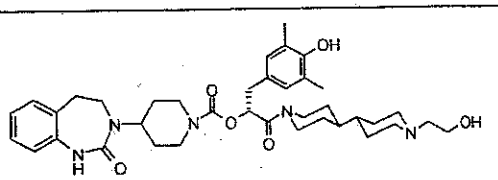
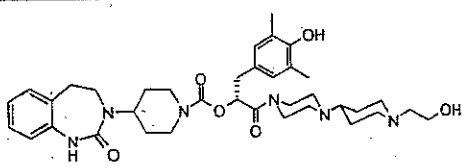
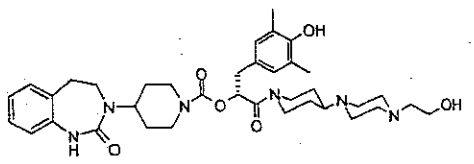
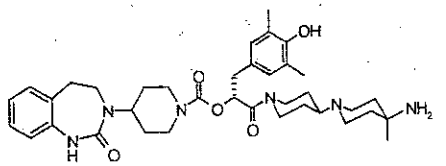
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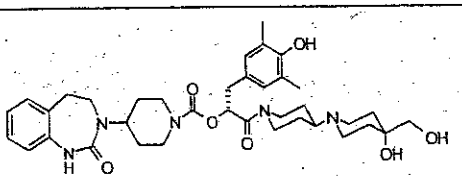
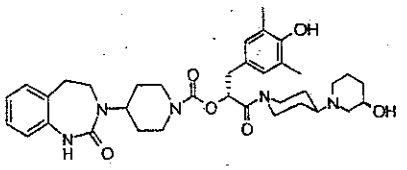
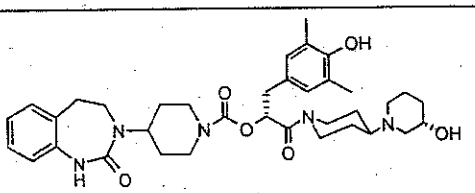
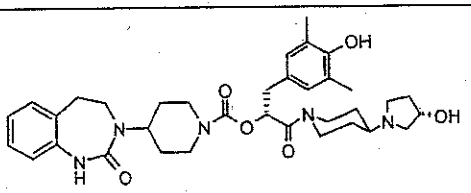
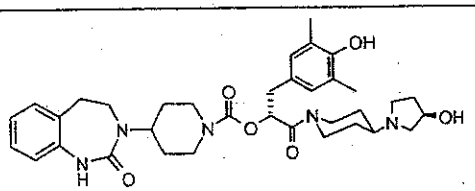
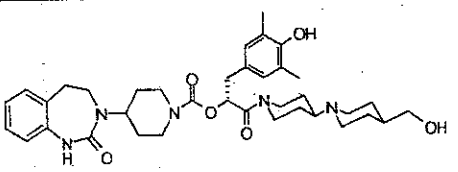
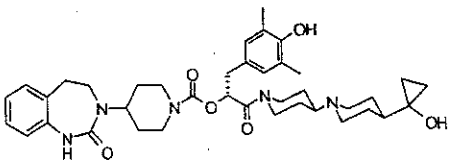
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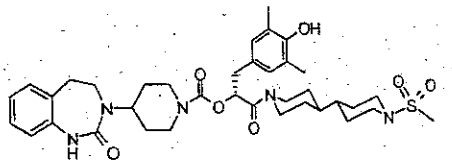
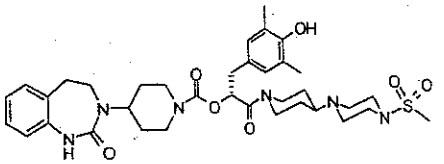
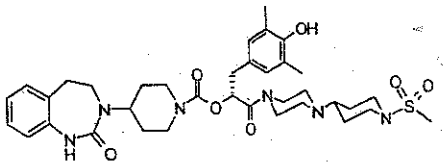
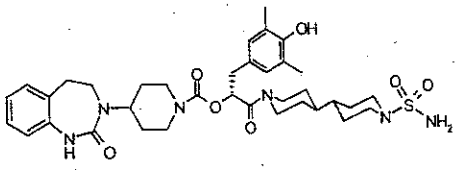
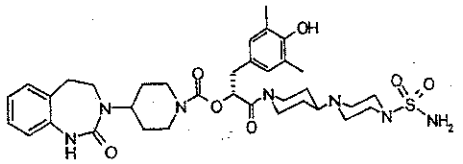
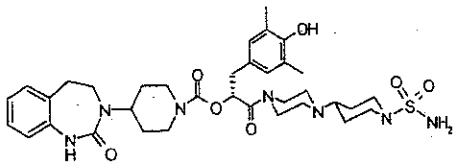
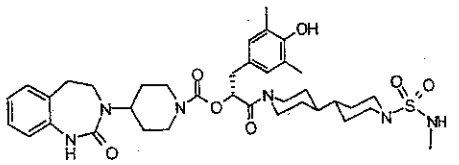
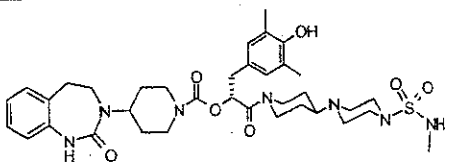
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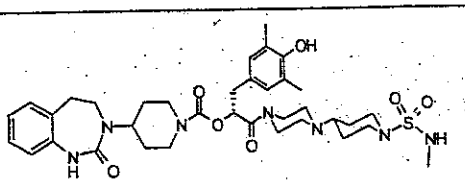
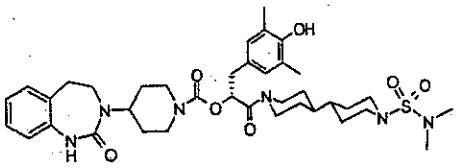
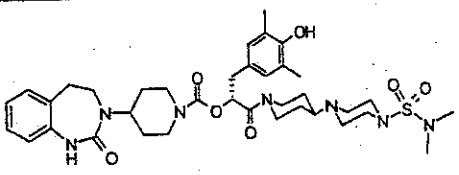
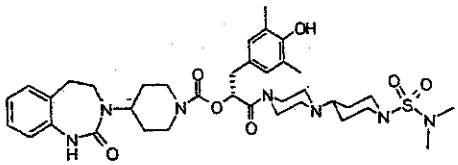
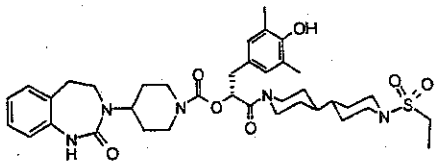
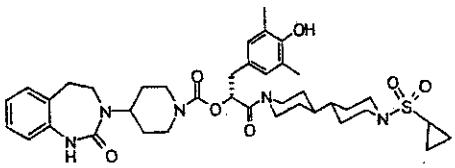
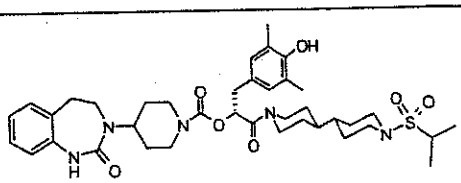
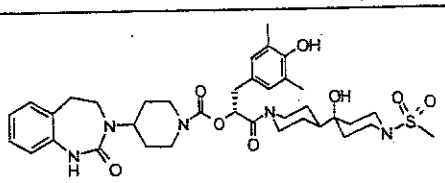
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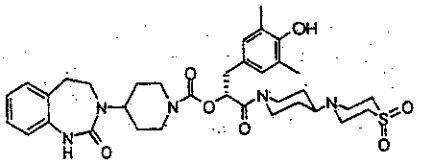
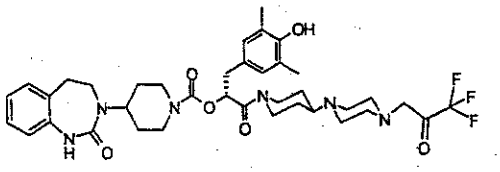
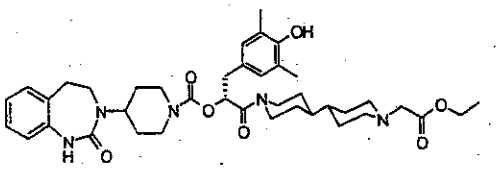
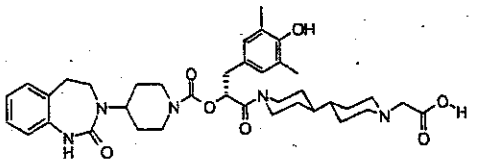
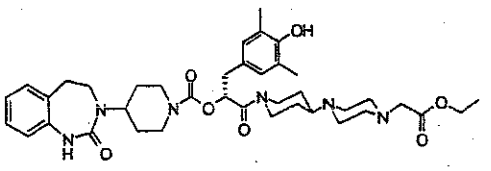
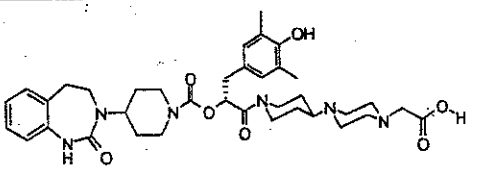
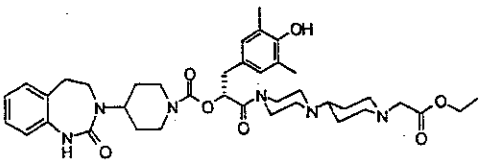
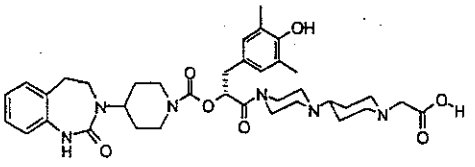
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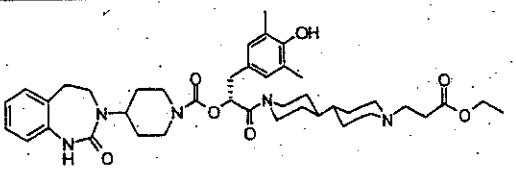
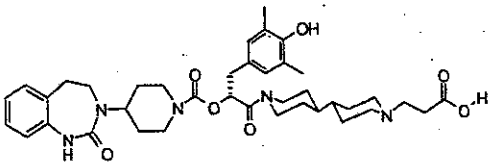
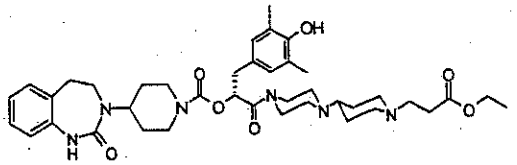
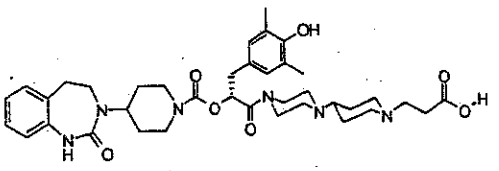
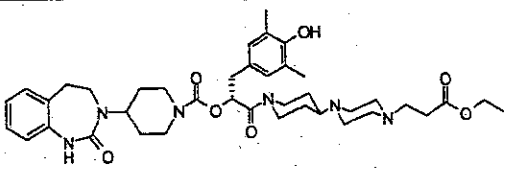
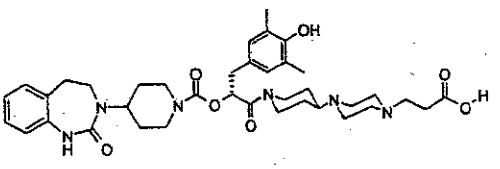
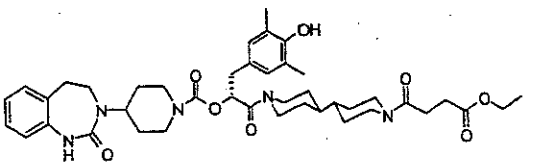
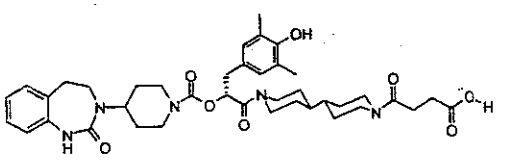
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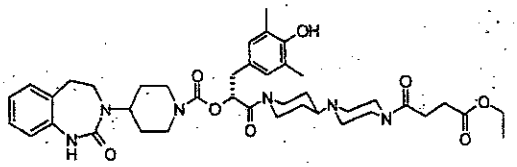
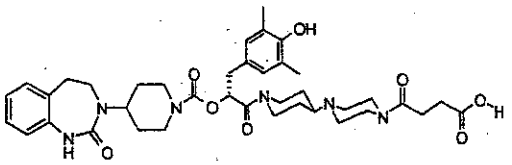
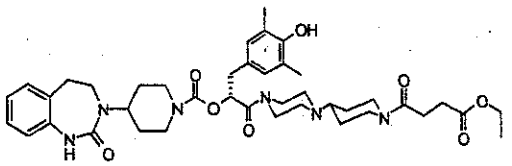
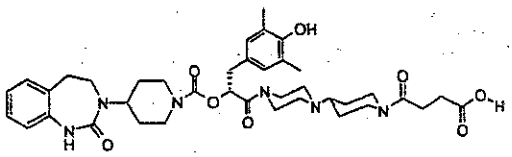
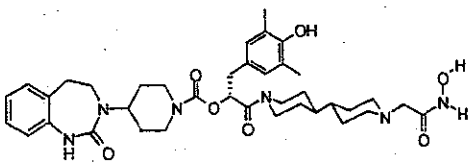
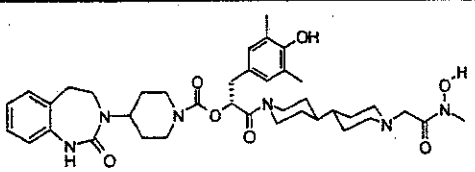
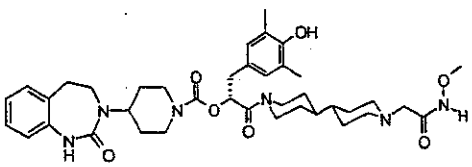
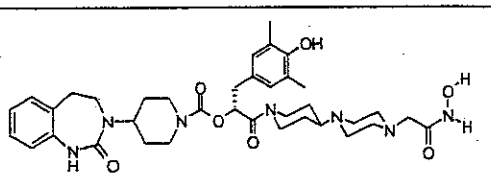
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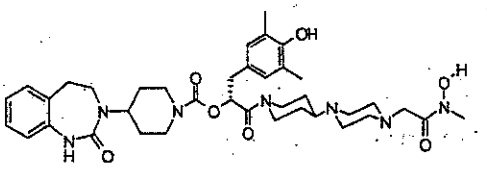
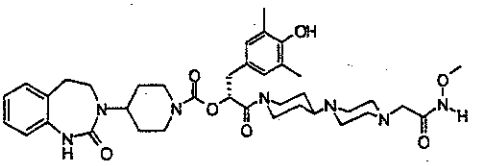
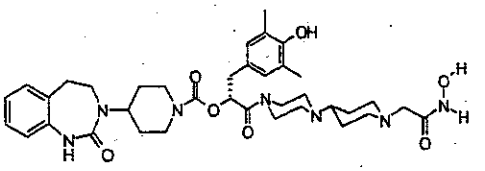
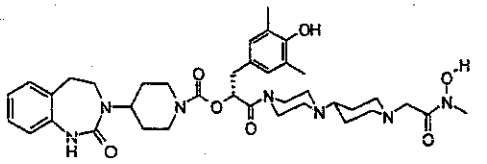
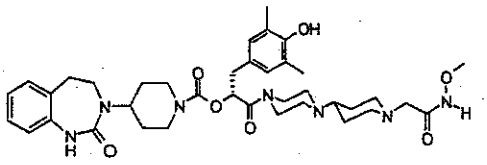
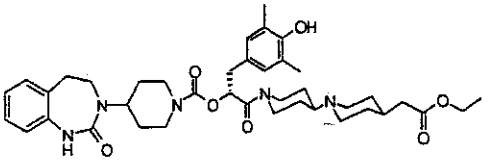
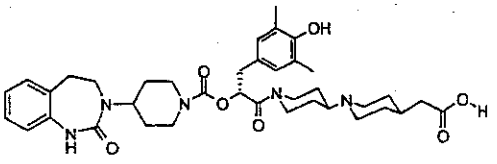
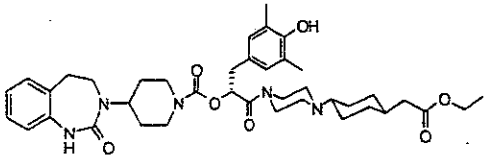
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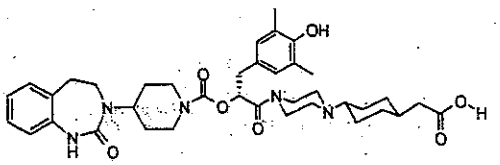
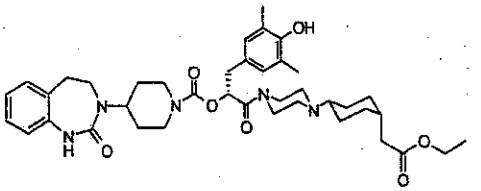
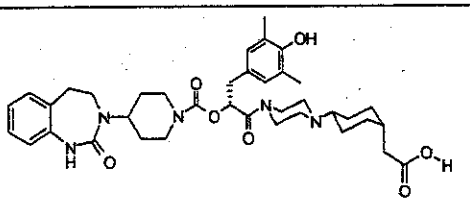
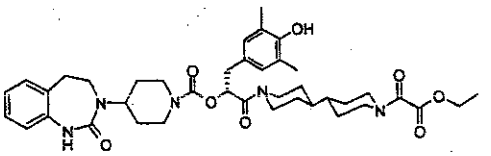
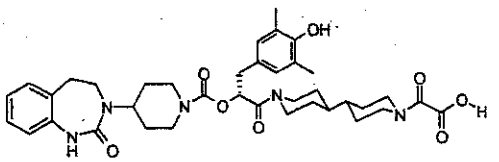
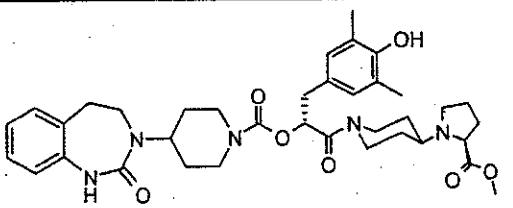
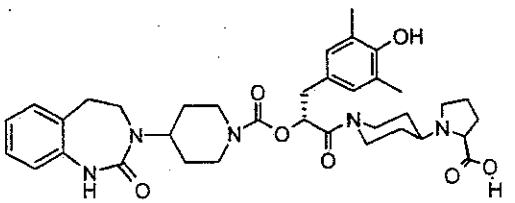
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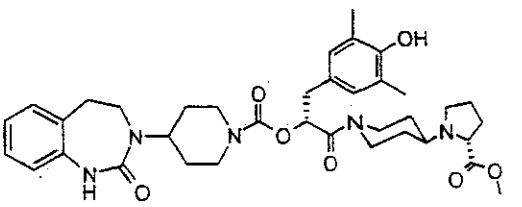
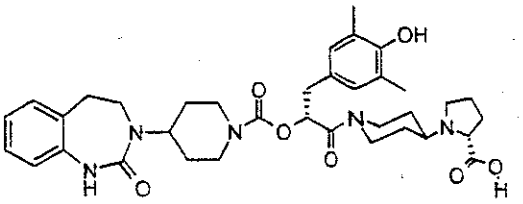
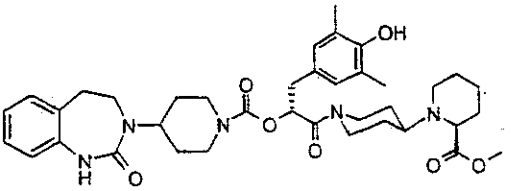
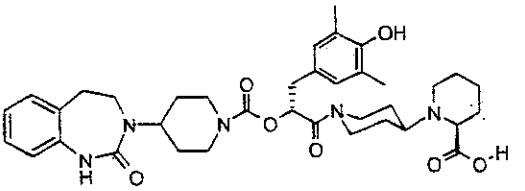
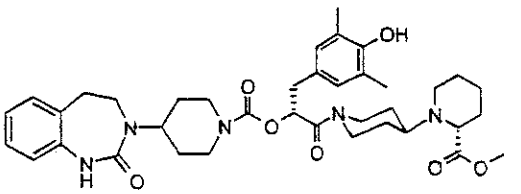
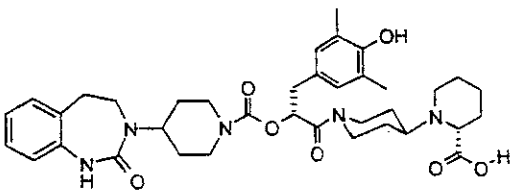
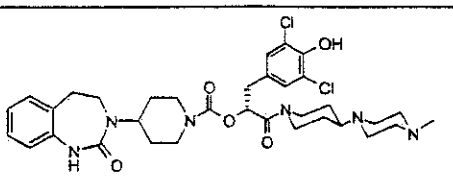
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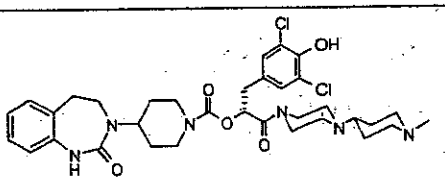
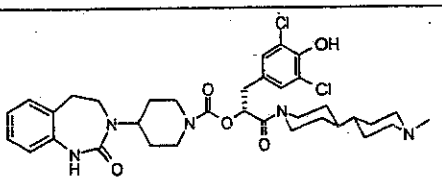
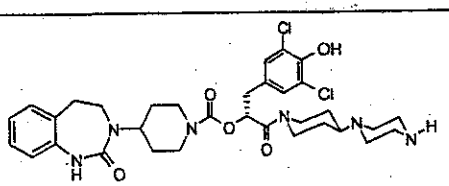
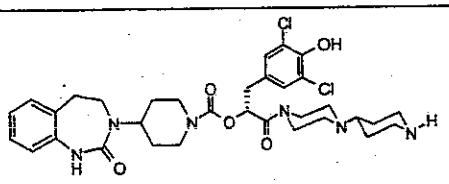
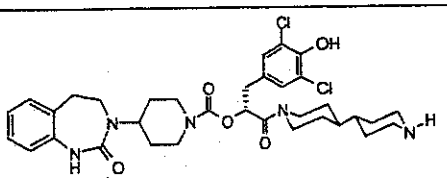
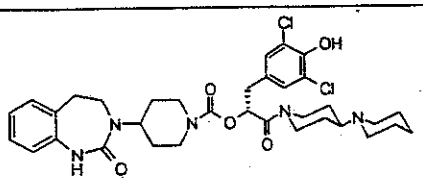
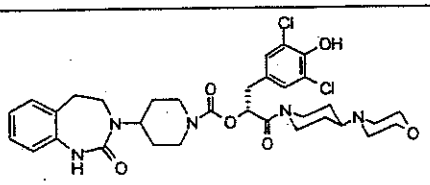
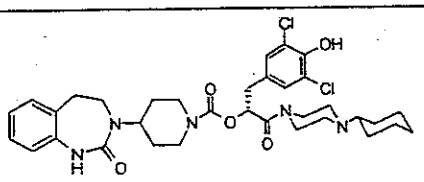
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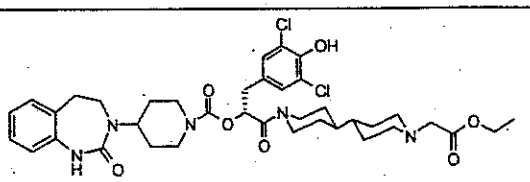
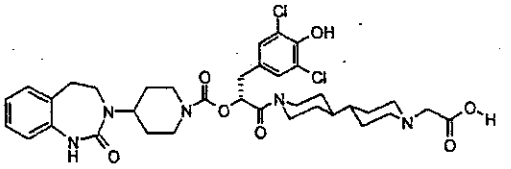
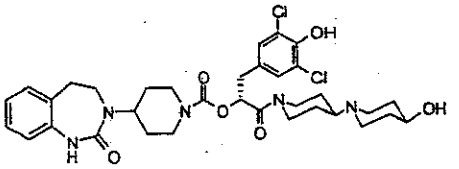
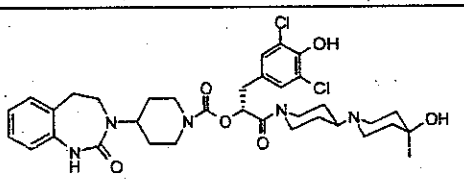
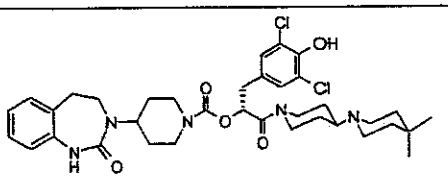
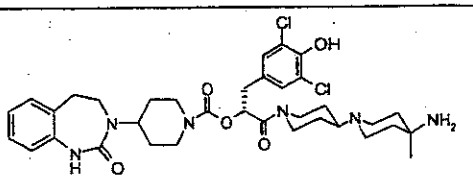
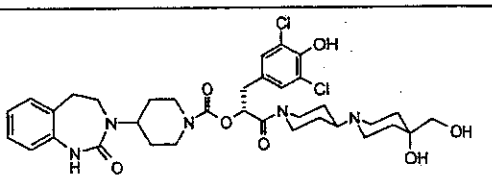
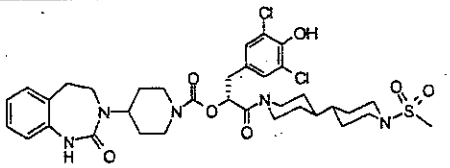
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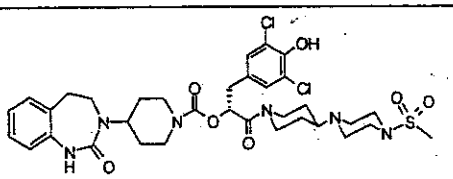
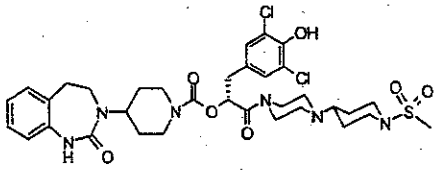
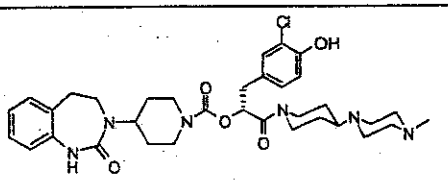
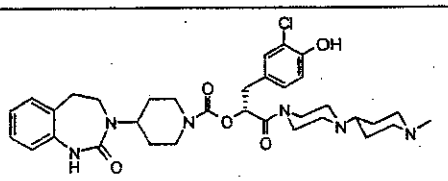
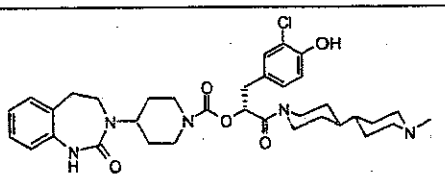
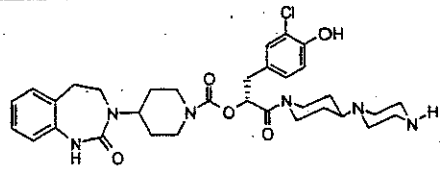
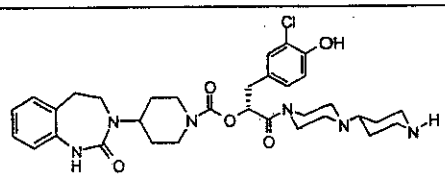
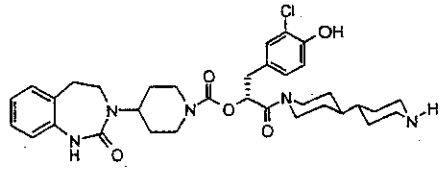
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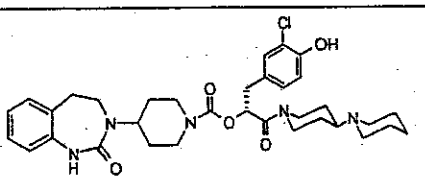
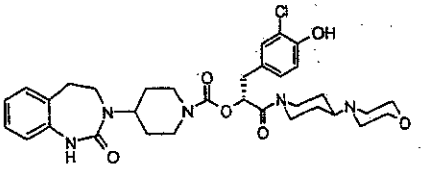
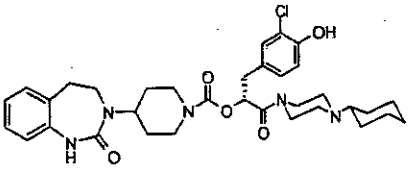
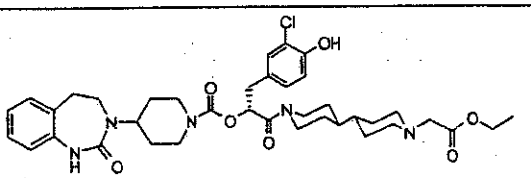
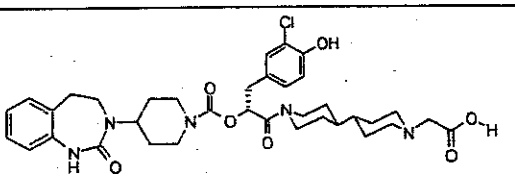
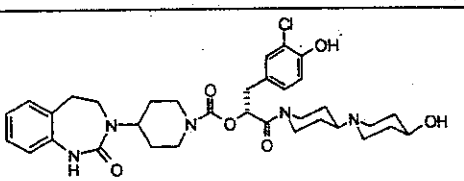
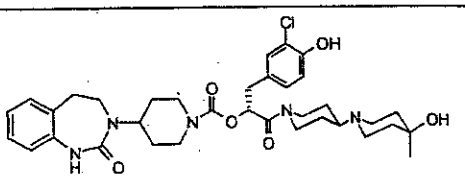
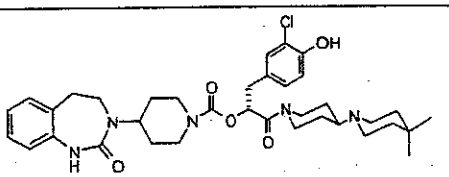
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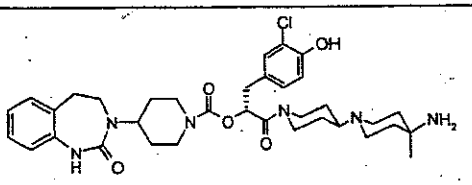
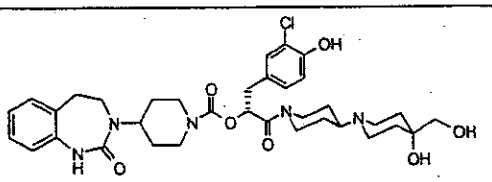
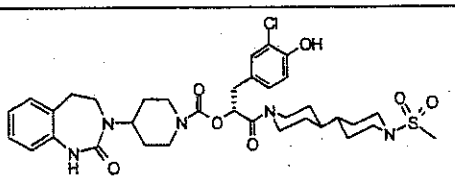
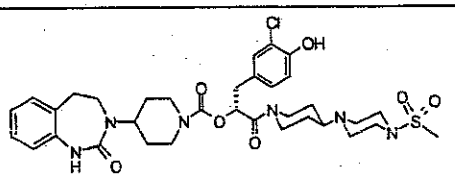
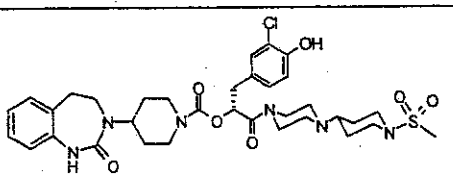
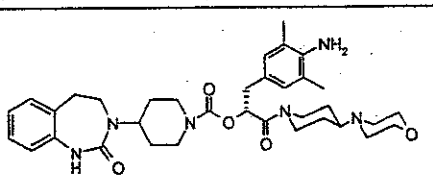
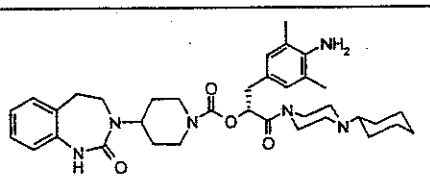
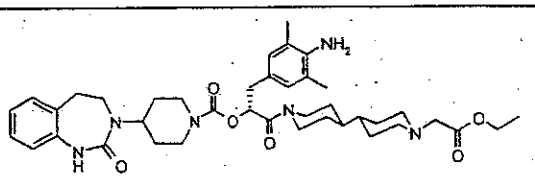
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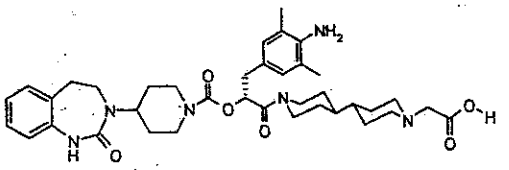
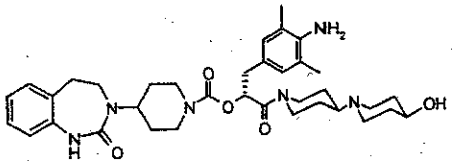
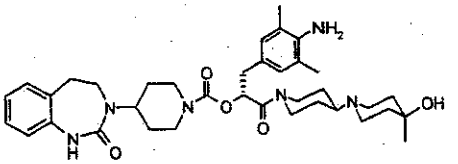
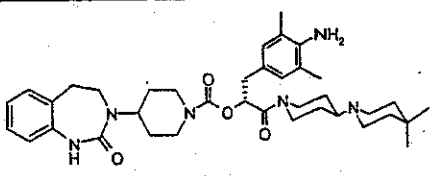
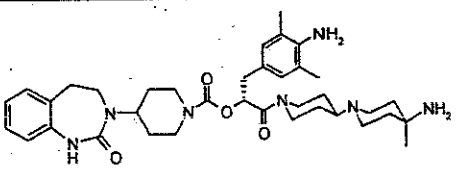
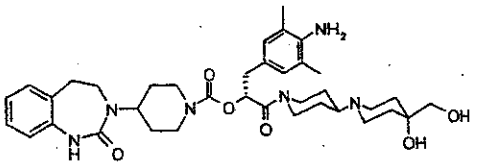
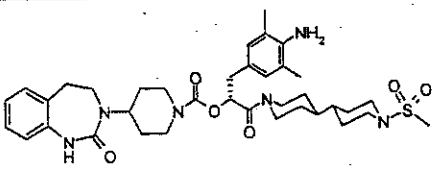
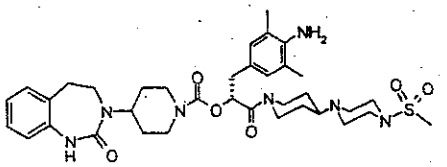
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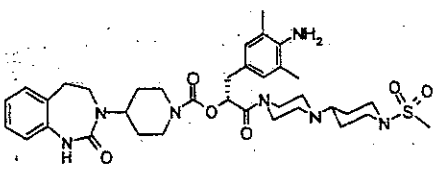
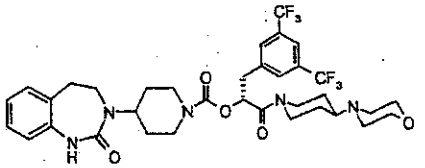
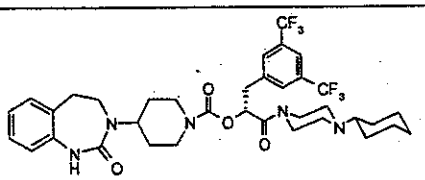
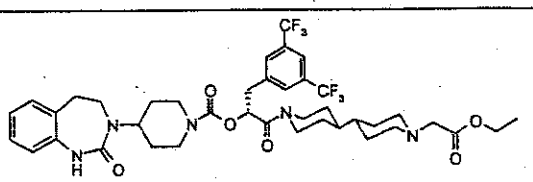
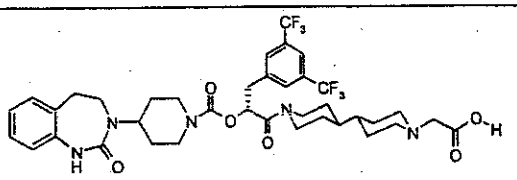
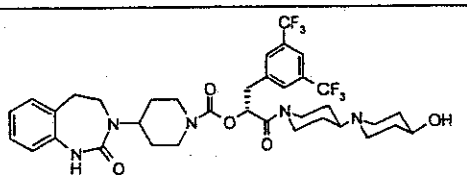
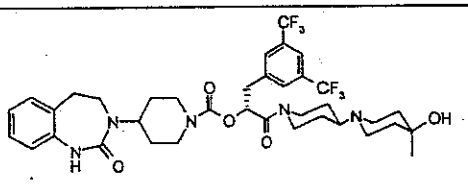
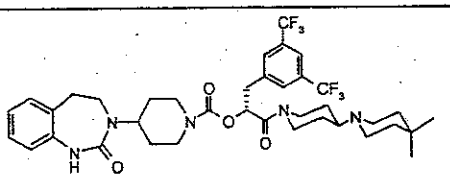
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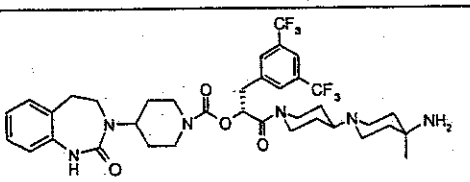
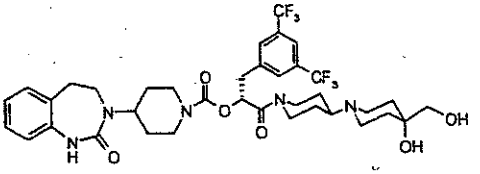
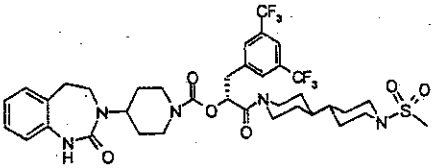
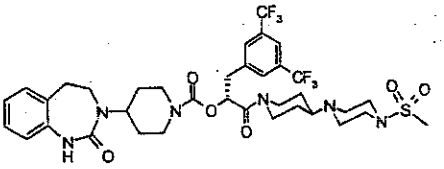
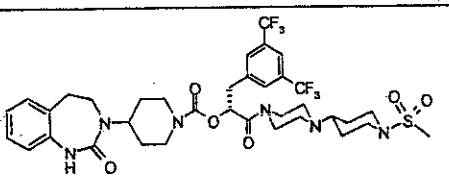
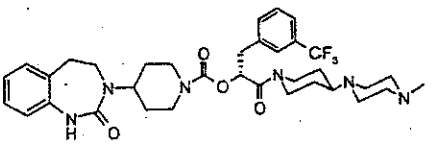
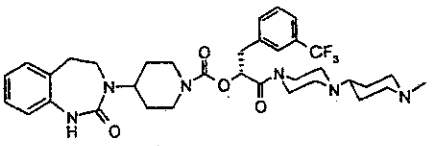
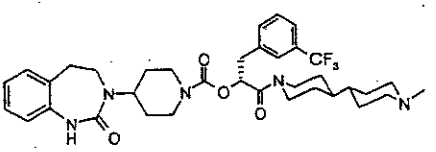
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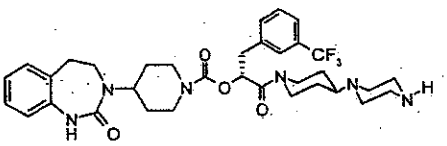
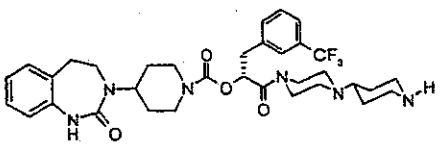
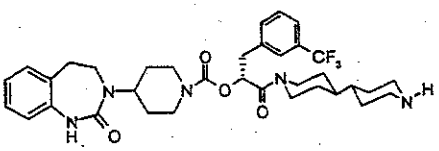
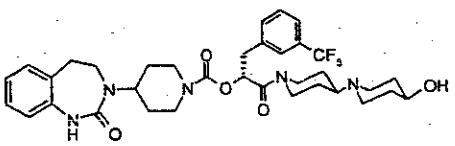
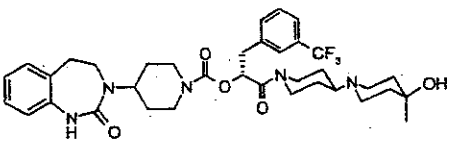
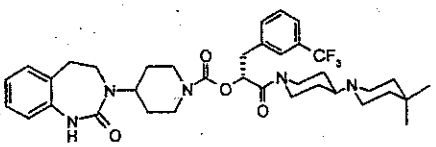
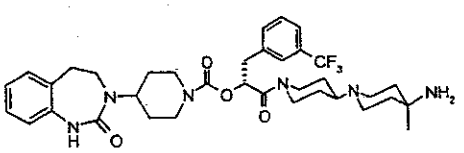
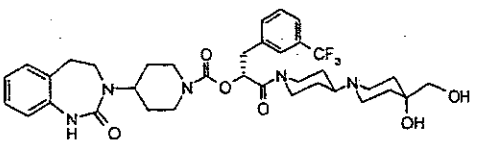
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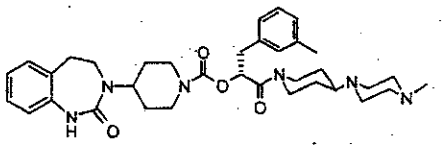
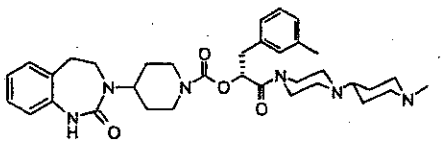
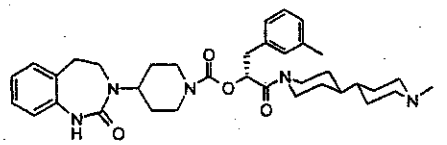
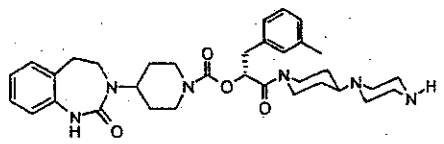
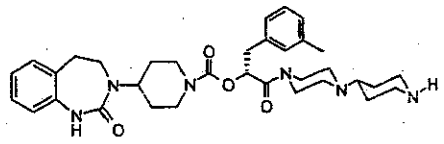
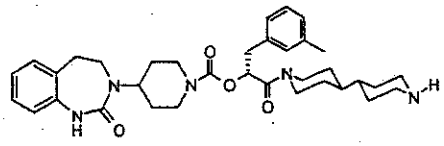
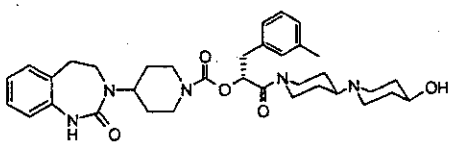
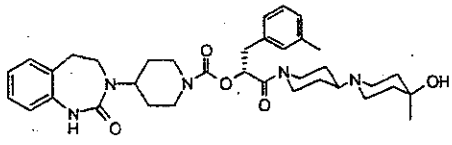
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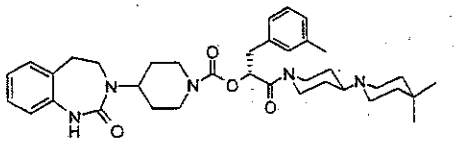
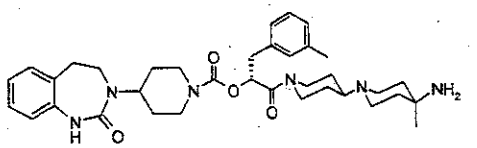
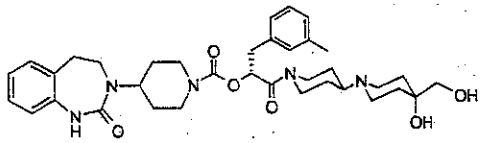
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the enantiomers, the diastereomers, the hydrates, the mixtures thereof and the salts thereof as well as the hydrates of the salts, particularly the physiologically acceptable salts thereof with inorganic or organic acids or bases.

According to a second aspect, there is provided physiologically acceptable salts of the compounds as defined above with inorganic or organic acids or bases.

According to a third aspect, there is provided pharmaceutical compositions, containing a compound as defined above or a physiologically acceptable salt as defined above optionally together with one or more inert carriers and/or diluents.

According to a fourth aspect, there is provided the use of a compound as defined above for preparing a pharmaceutical composition for the acute and prophylactic treatment of headaches, particularly migraine or cluster headaches, for the treatment of non-insulin-dependent diabetes mellitus ("NIDDM"), complex regional pain syndrome (CRPS1), cardiovascular diseases, morphine tolerance, diarrhoea caused by clostridium toxin, skin diseases, particularly thermal and radiation-

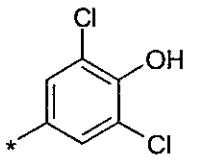
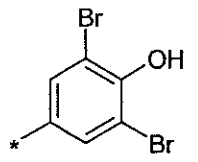
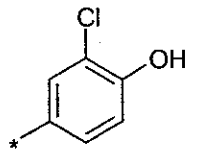
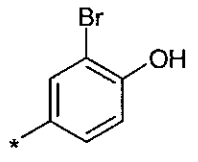
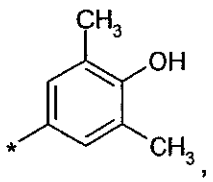
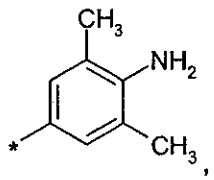
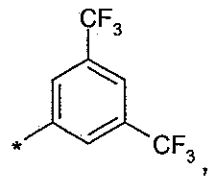
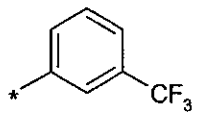
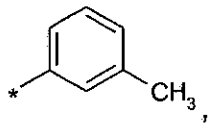
induced skin damage including sunburn, inflammatory diseases, e.g. inflammatory diseases of the joints (arthritis), neurogenic inflammation of the oral mucosa, inflammatory lung diseases, allergic rhinitis, asthma, diseases accompanied by excessive vasodilatation and resultant reduced circulation of the blood, e.g. shock and sepsis, for alleviating pain or for preventive or acute therapeutic treatment of the symptoms of menopausal hot flushes caused by vasodilatation and increased blood flow in oestrogen-deficient women and hormone-treated patients with prostate carcinoma.

According to a fifth aspect, there is provided a process for preparing a pharmaceutical composition as defined above, characterised in that a compound as defined above is incorporated in one or more inert carriers and/or diluents by a non-chemical method.

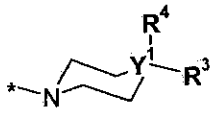
DETAILED DESCRIPTION OF THE INVENTION

In the above general formula **I** in a first embodiment

B denotes a group selected from









and


R^1 and R^2 together with the enclosed nitrogen atom denote a group of general formula **II**



wherein

Y^1 denotes the carbon atom or, if R^4 denotes a free pair of electrons, it also denotes the nitrogen atom,

R^3 denotes a cyclopentyl, cyclohexyl or cycloheptyl group or

R^3 denotes a heterocycle selected from a morpholin-4-yl, 1,1-dioxo-thiomorholin-4-yl, piperidin-1-yl, piperidin-4-yl, piperazin-1-yl or pyrrolidin-1-yl group,

wherein the above-mentioned monocyclic heterocycles in the ring may be mono- or disubstituted by hydroxy, methyl, ethyl, trifluoromethyl, hydroxymethyl or hydroxyethyl groups, or may optionally additionally be monosubstituted by a hydroxycyclopropyl, trifluoromethylcarbonylmethyl, amino, carboxy-carbonyl, methoxycarbonyl, ethoxycarbonyl-carbonyl,

carboxymethyl, carboxyethyl, ethoxycarbonylmethyl, ethoxycarbonylethyl, carboxy-ethylcarbonyl, ethoxycarbonyl-ethylcarbonyl, aminosulphonyl, methylaminosulphonyl, dimethylaminosulphonyl, methylsulphonyl, ethylsulphonyl, isopropylsulphonyl, cyclopropylsulphonyl, (hydroxyamino)-carbonylmethyl, hydroxy-(methyl)-aminocarbonyl-methyl or methoxyaminocarbonyl-methyl group, wherein the substituents may be identical or different and may be bound to a ring carbon or ring nitrogen atom, or

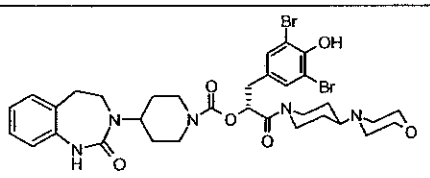
the above-mentioned monocyclic heterocycles in the ring may be monosubstituted by a carboxy group, if this carboxy group is not bound via a nitrogen atom, and

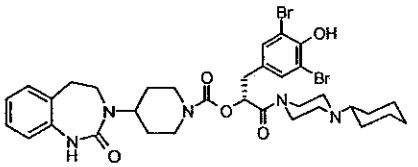
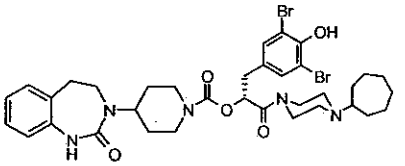
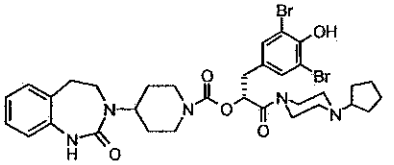
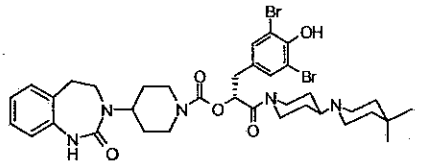
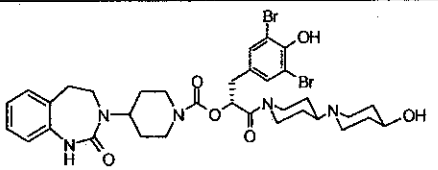
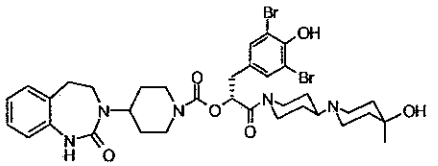
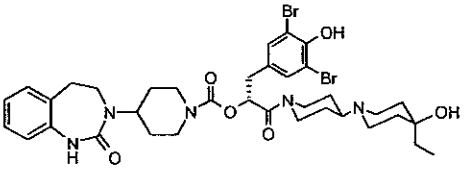
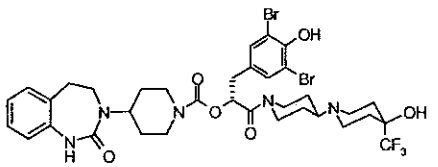
R^4 denotes the hydrogen atom, if Y^1 denotes the carbon atom, or

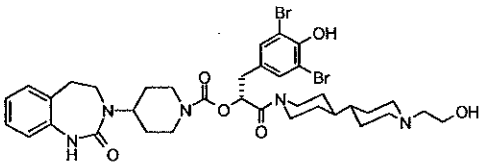
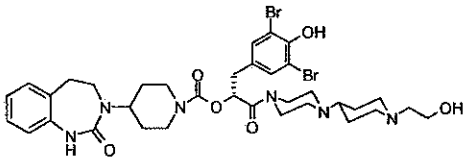
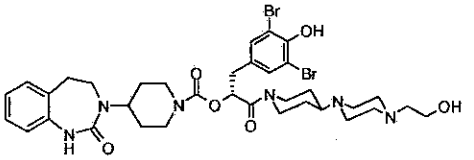
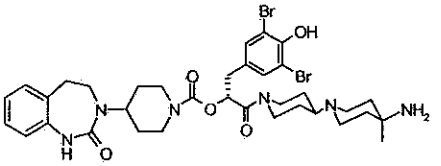
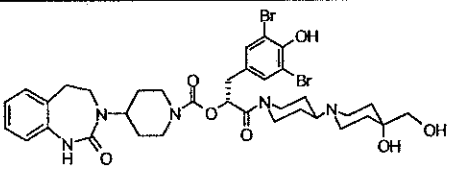
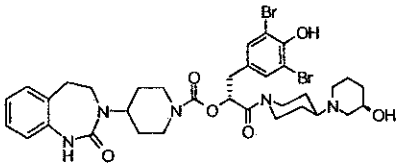
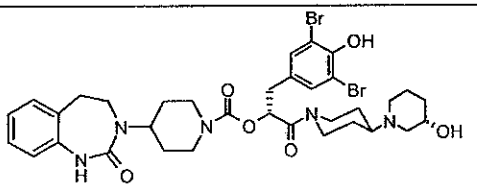
R^4 denotes a free pair of electrons, if Y^1 denotes the nitrogen atom,

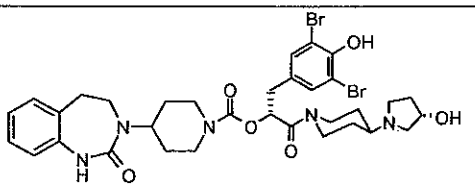
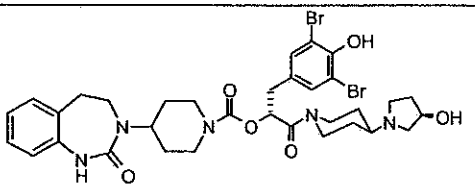
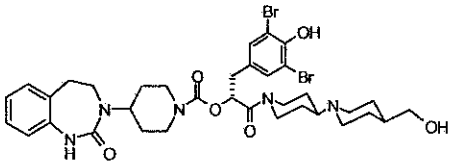
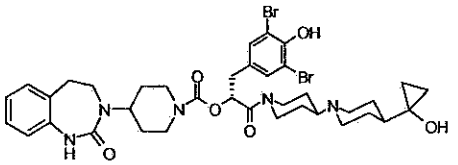
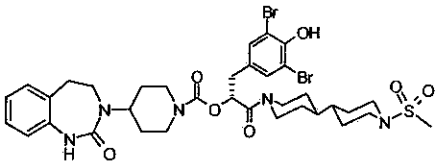
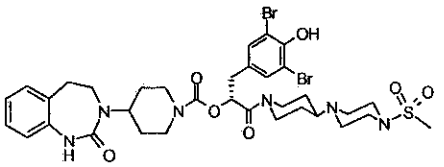
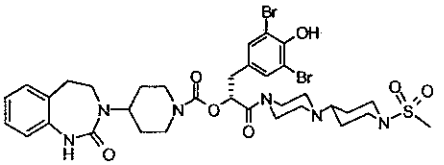
the tautomers, the diastereomers, the enantiomers, the hydrates, the mixtures thereof and the salts thereof as well as the hydrates of the salts, particularly the physiologically acceptable salts thereof with inorganic or organic acids or bases.

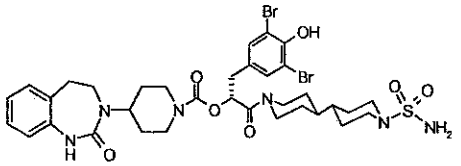
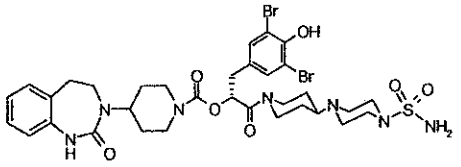
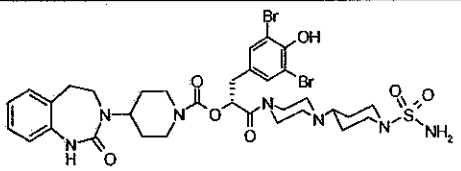
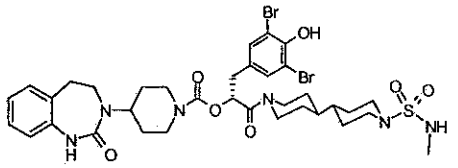
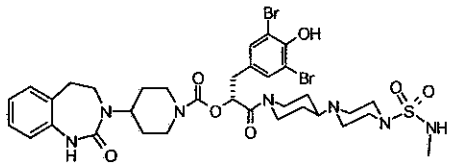
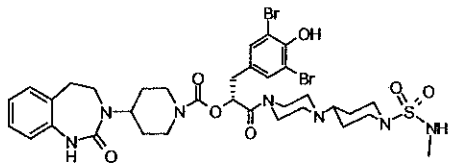
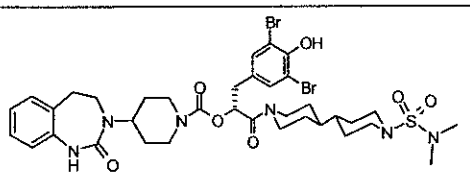
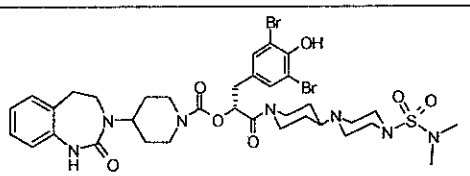
The following compounds are mentioned for example as most particularly preferred compounds of the above general formula **I**:

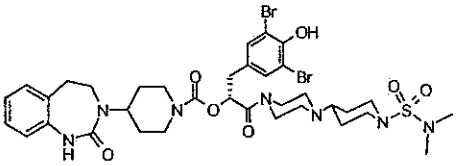
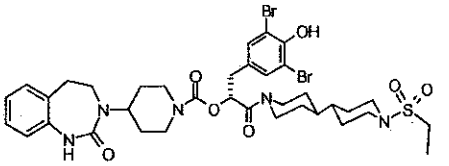
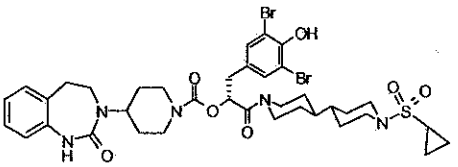
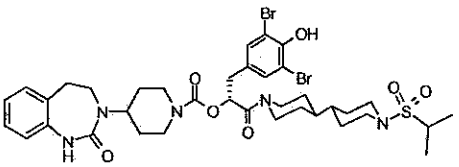
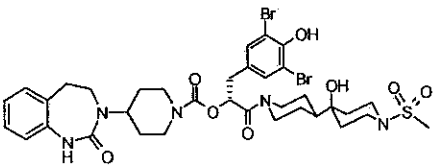
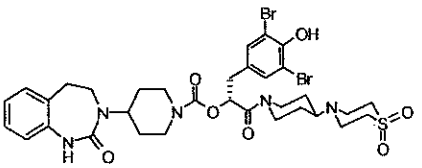
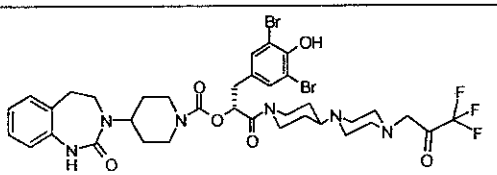
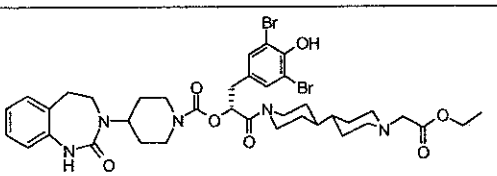
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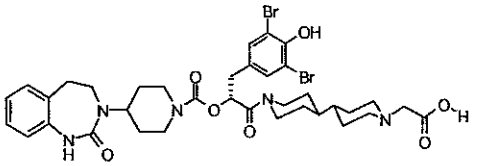
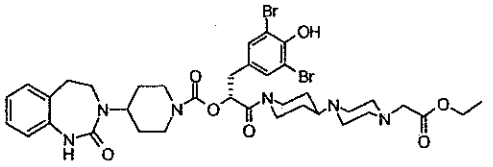
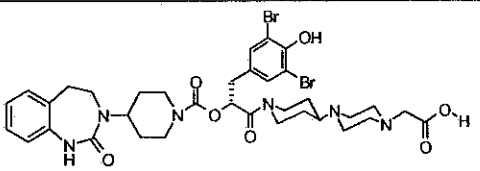
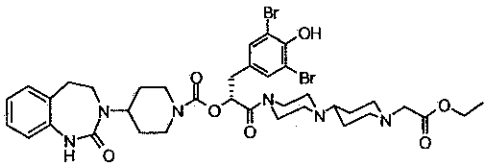
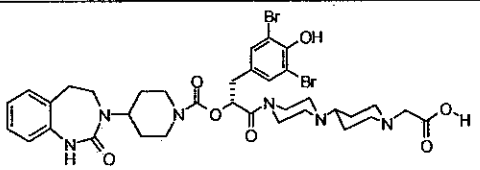
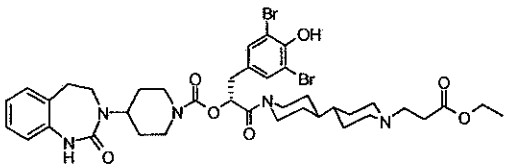
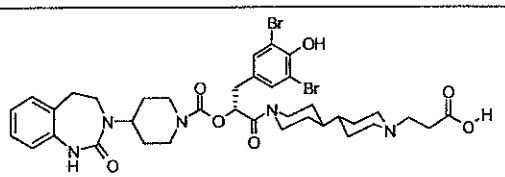
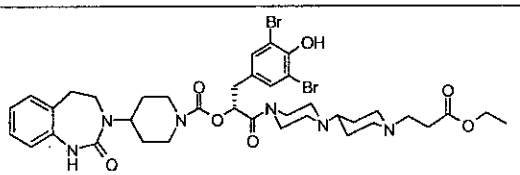
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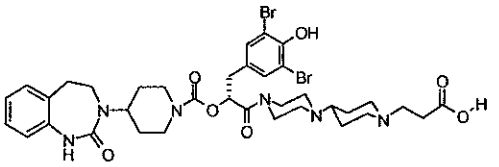
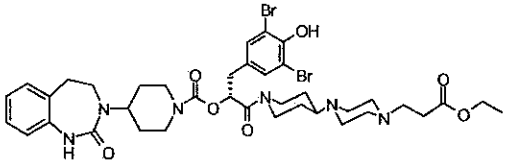
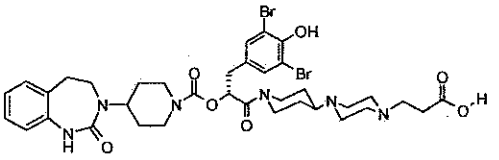
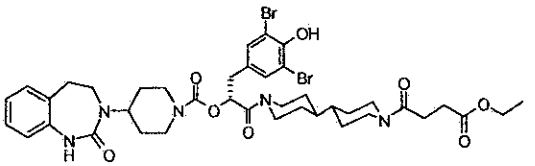
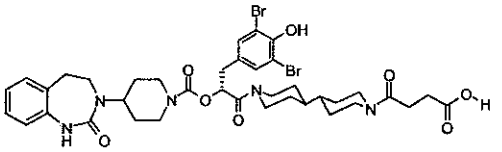
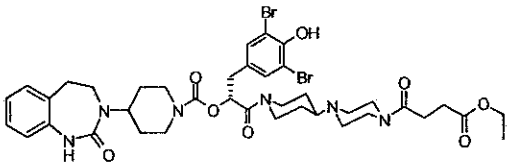
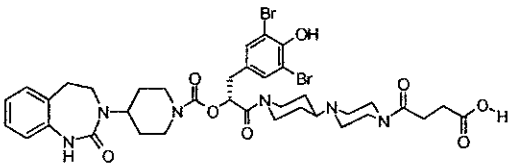
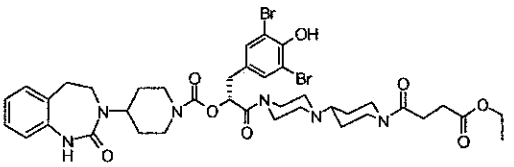
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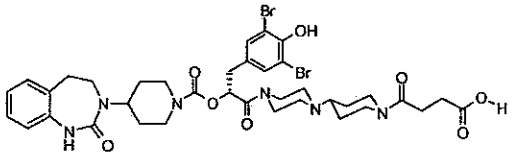
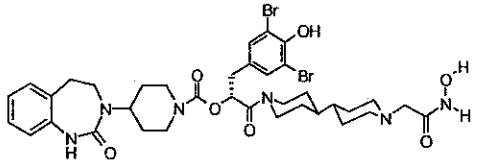
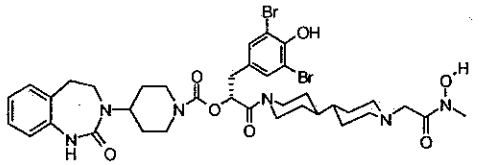
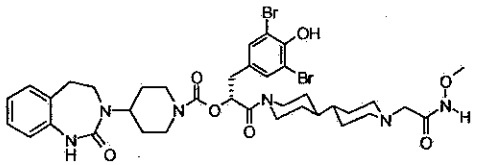
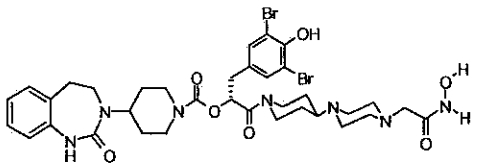
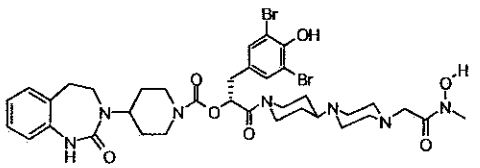
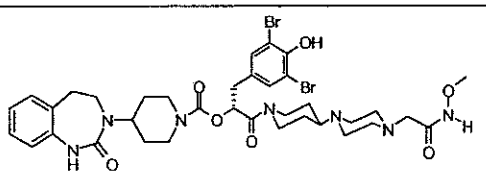
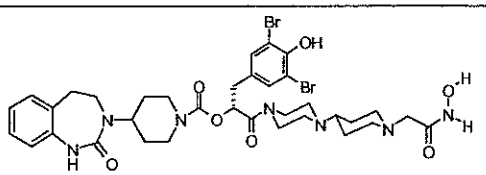
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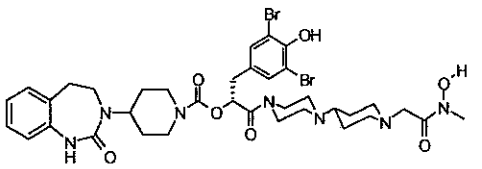
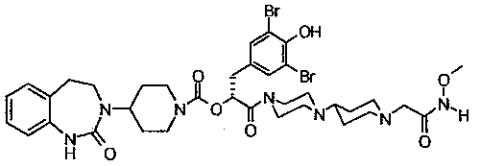
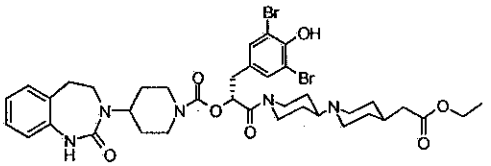
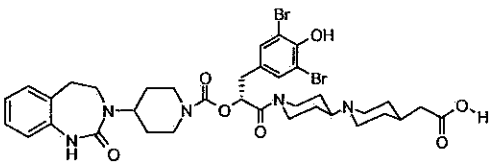
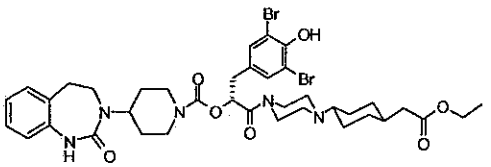
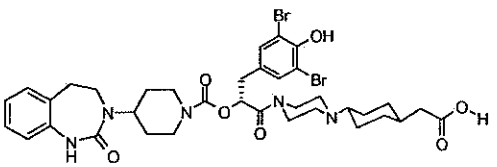
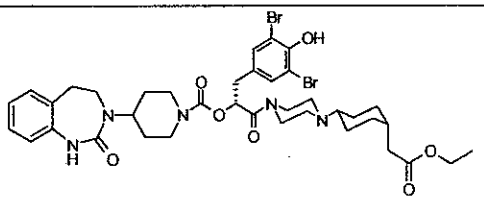
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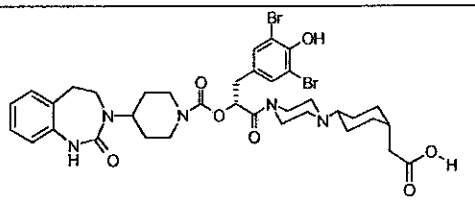
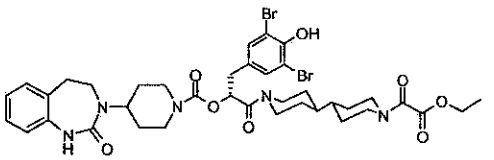
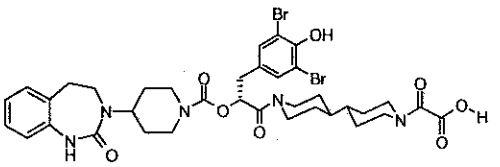
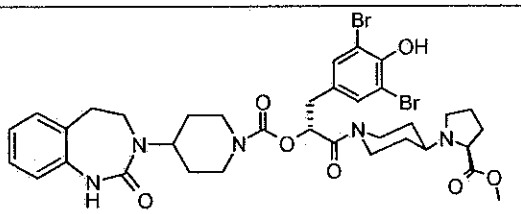
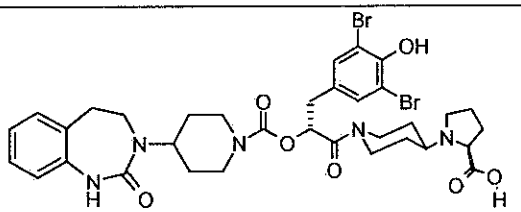
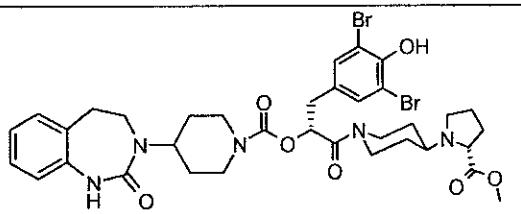
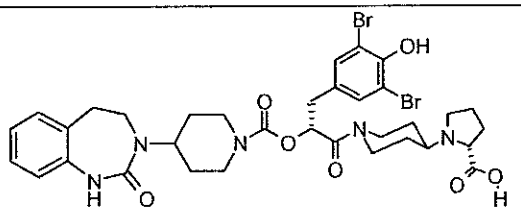
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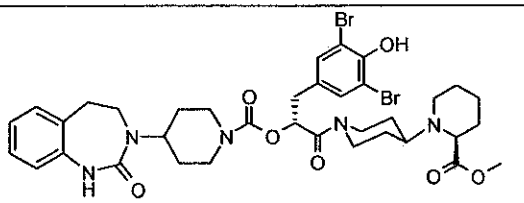
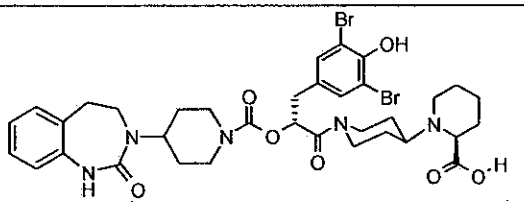
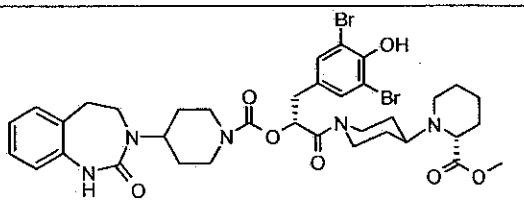
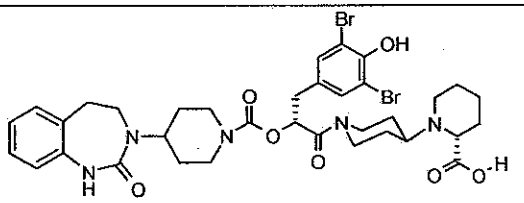
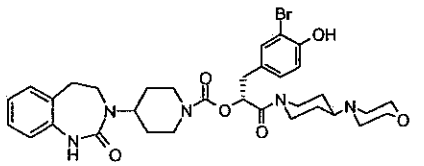
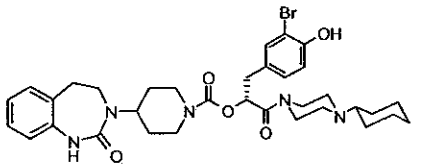
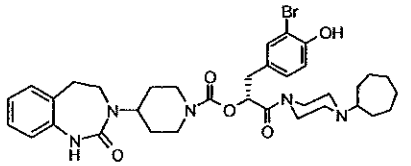
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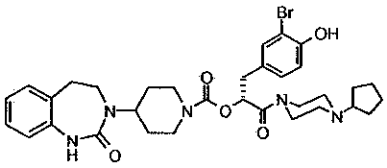
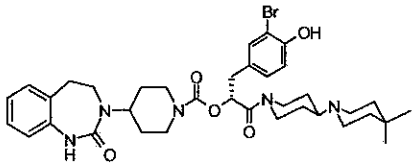
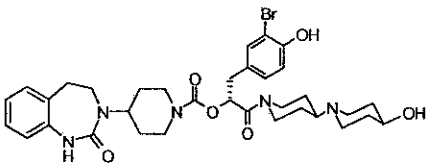
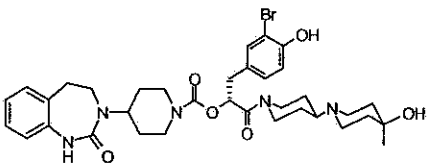
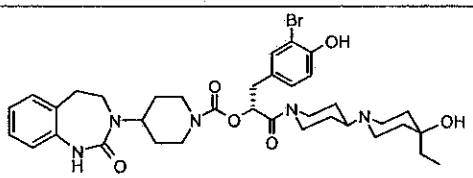
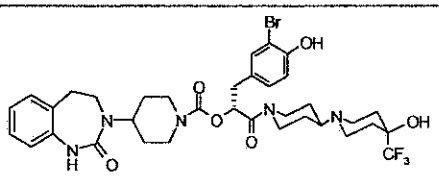
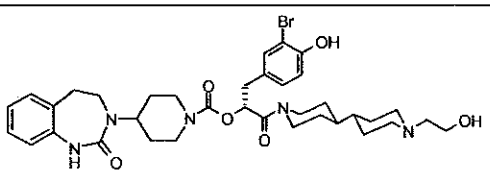
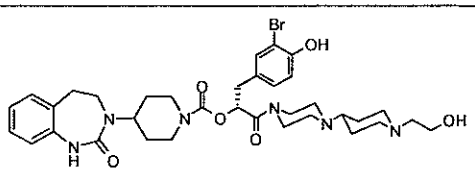
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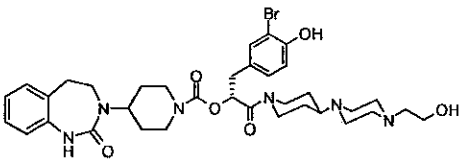
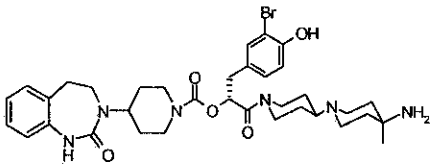
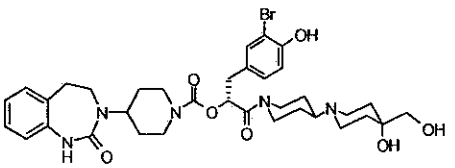
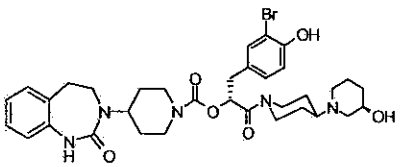
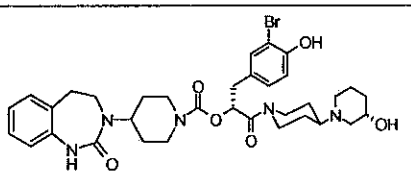
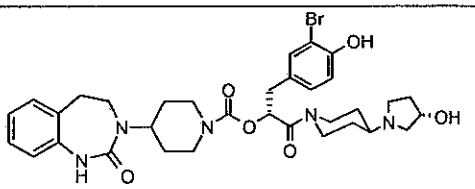
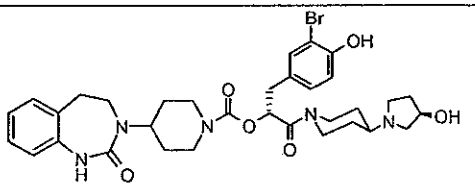
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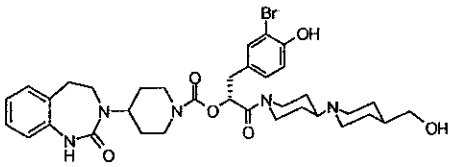
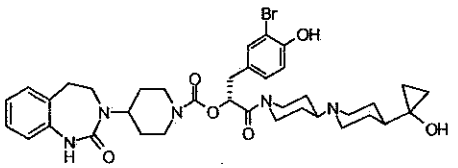
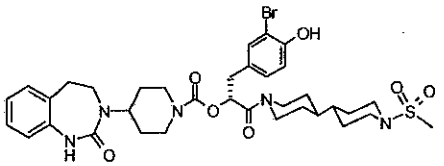
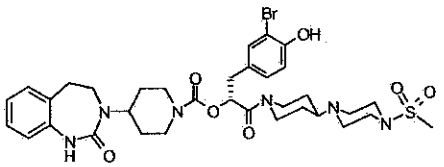
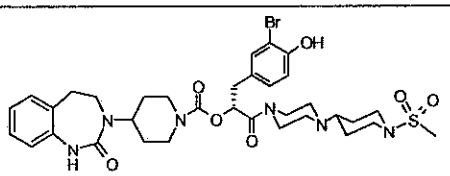
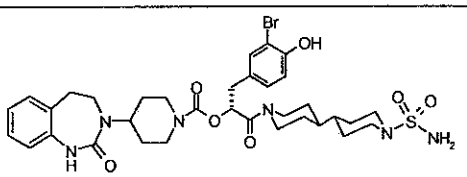
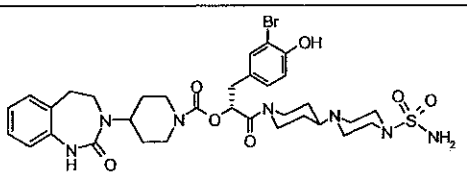
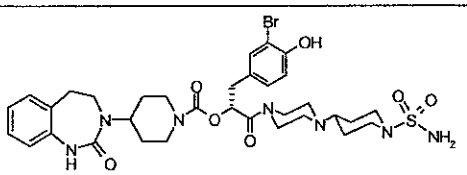
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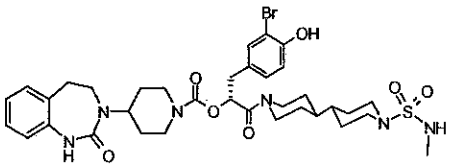
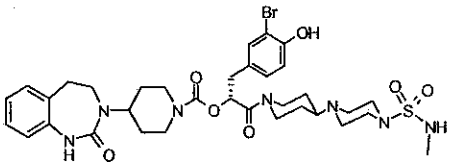
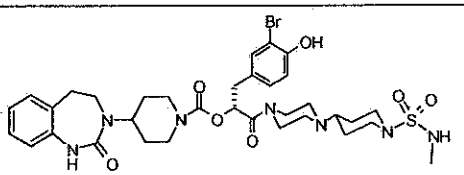
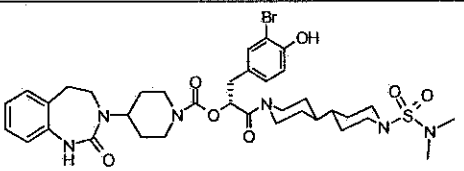
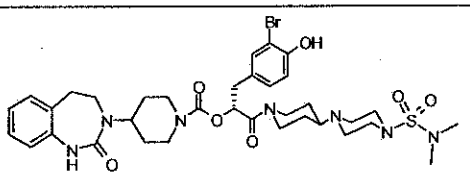
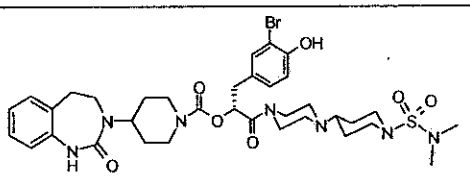
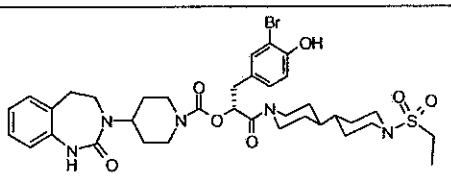
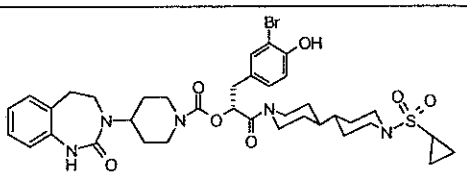
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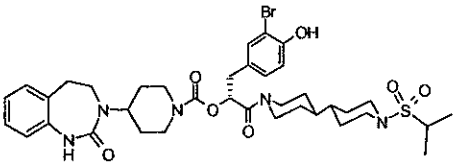
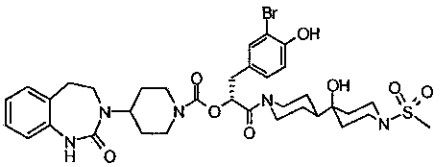
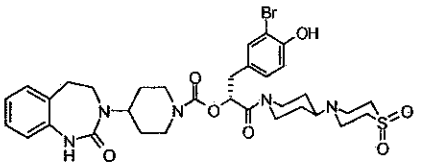
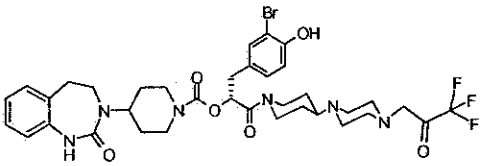
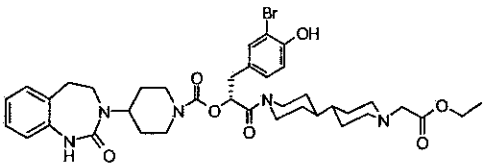
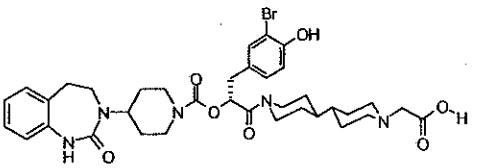
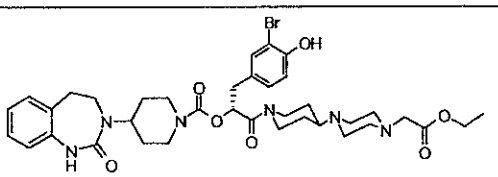
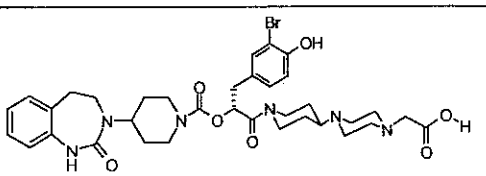
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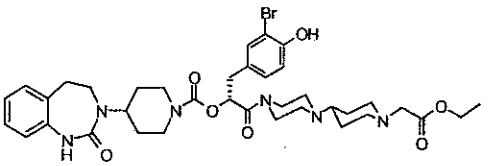
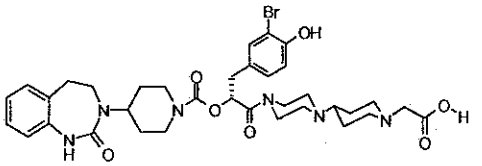
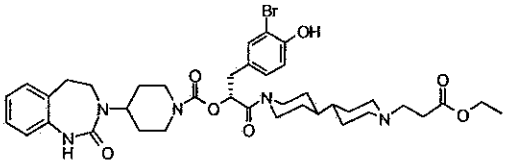
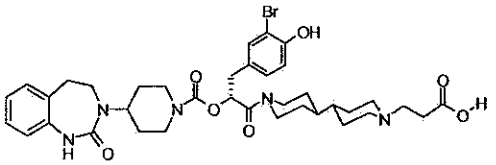
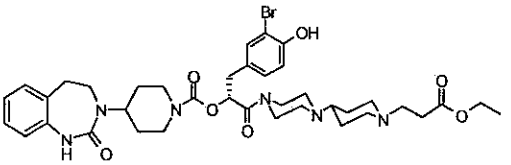
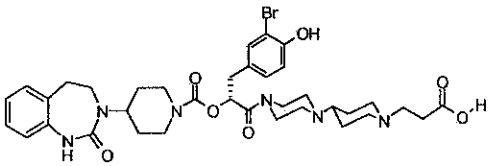
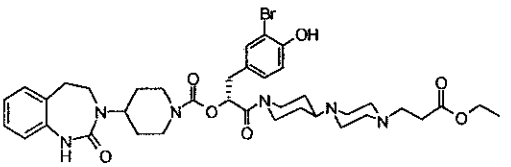
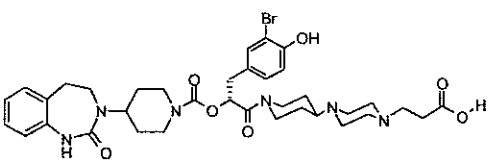
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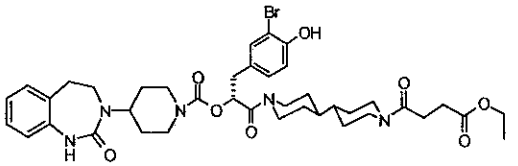
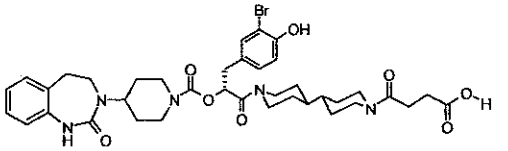
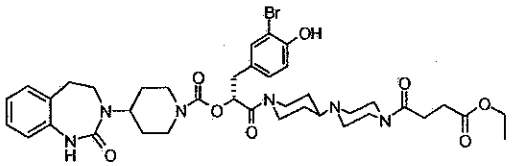
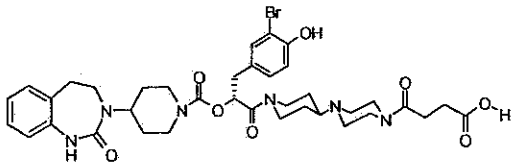
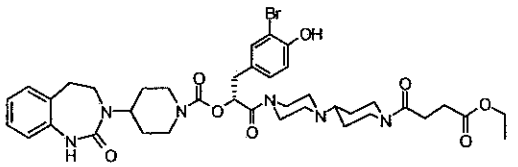
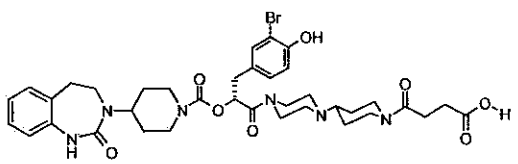
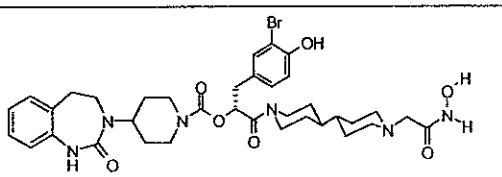
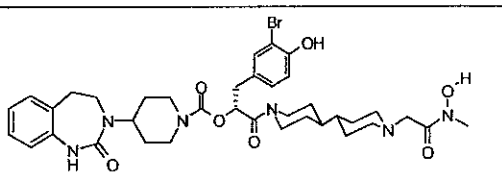
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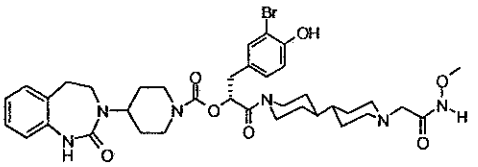
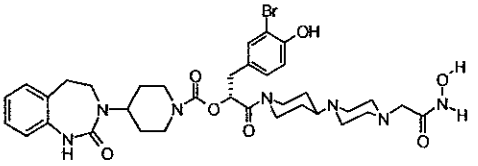
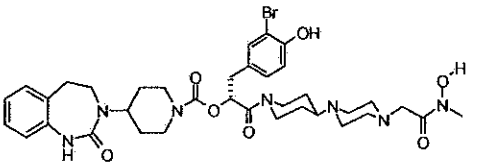
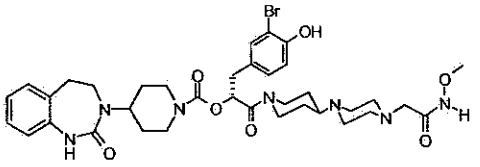
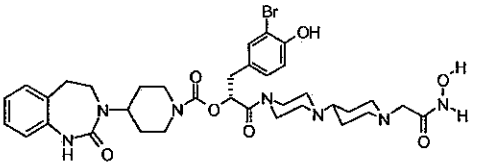
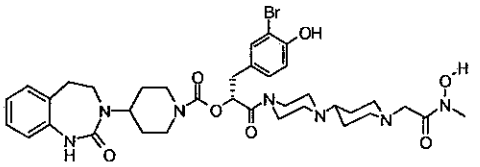
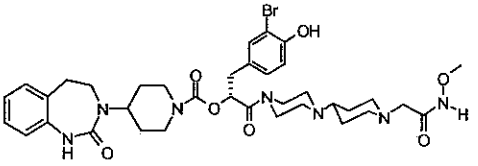
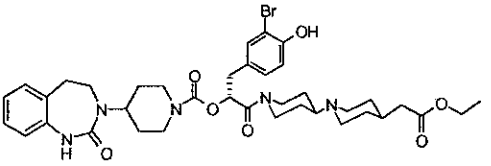
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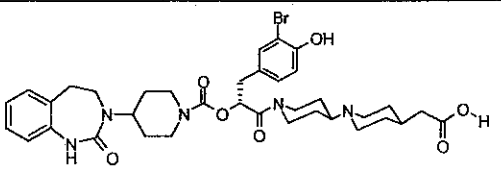
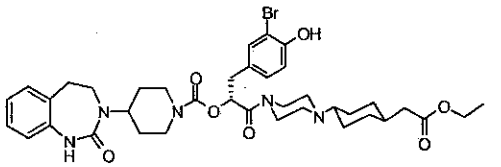
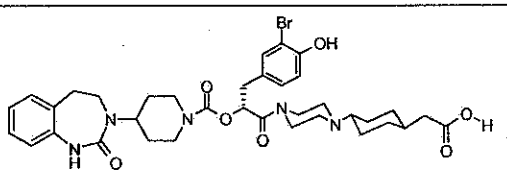
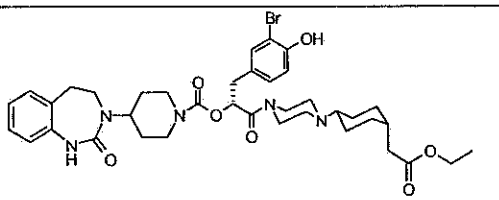
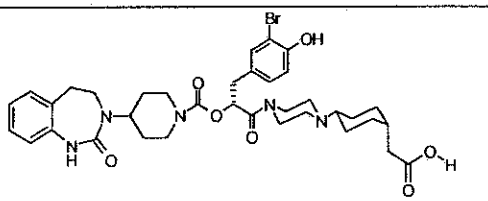
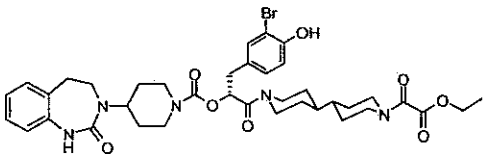
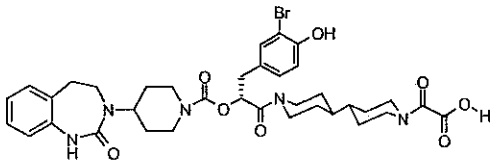
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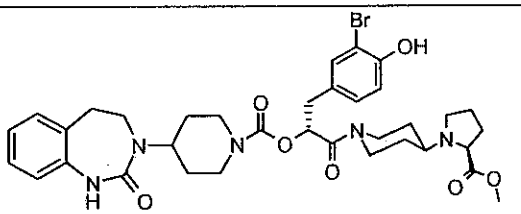
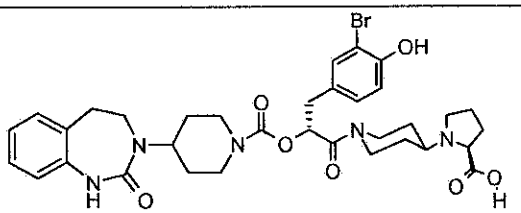
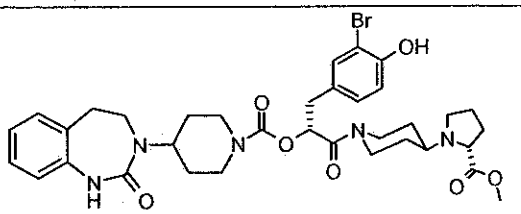
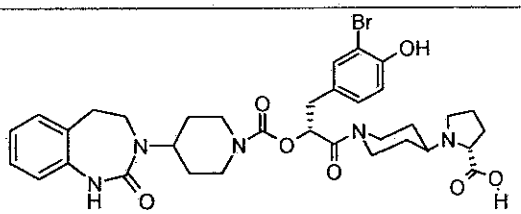
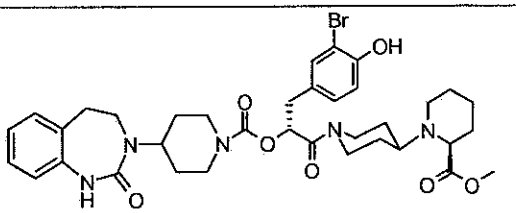
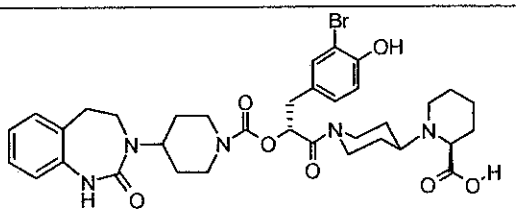
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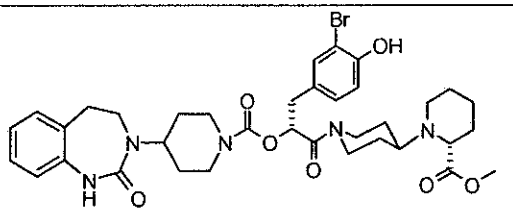
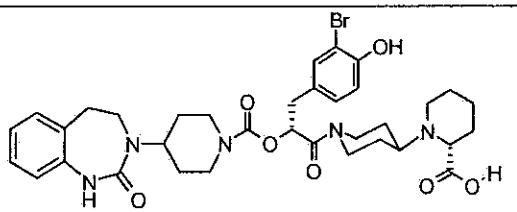
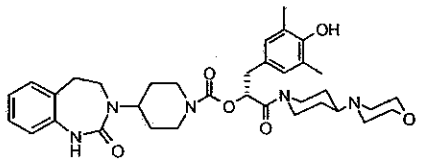
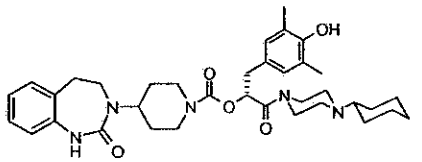
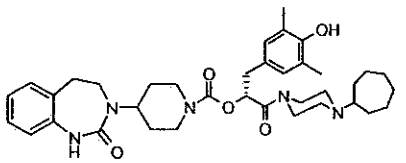
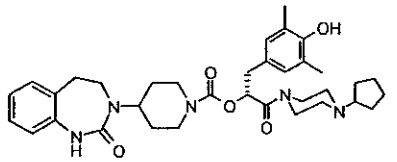
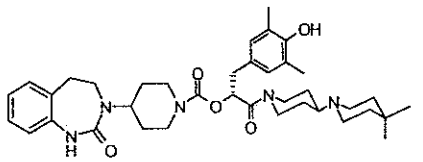
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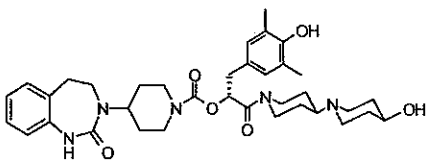
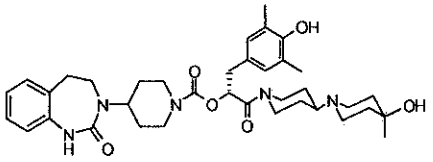
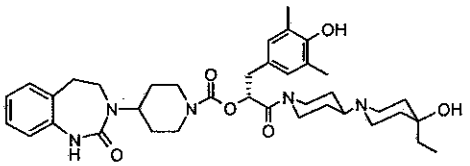
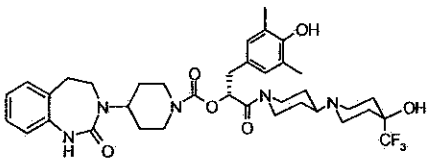
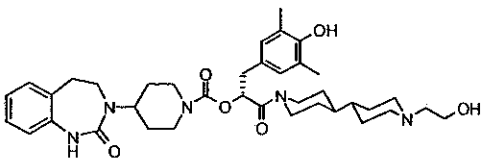
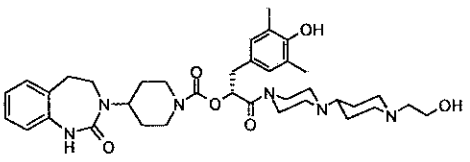
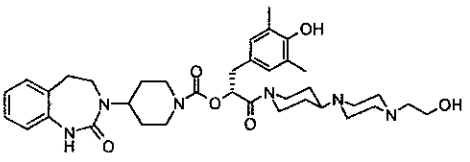
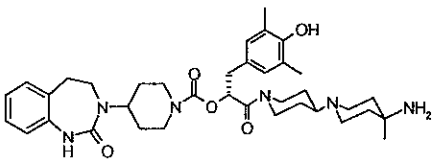
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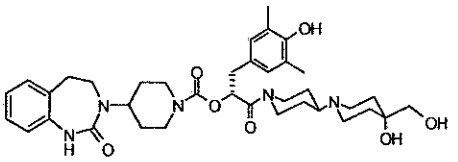
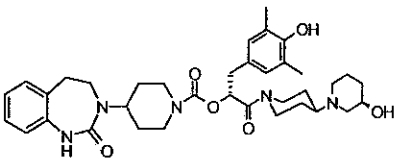
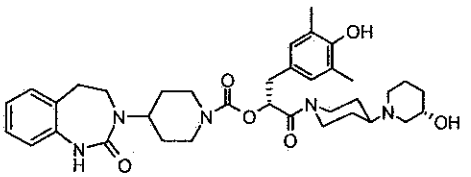
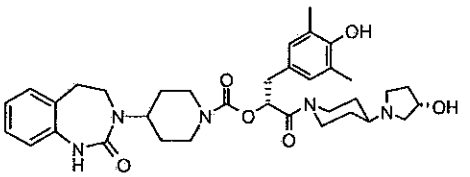
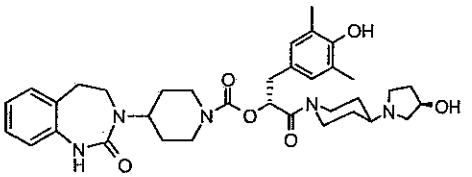
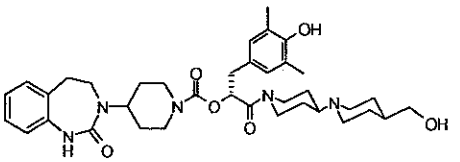
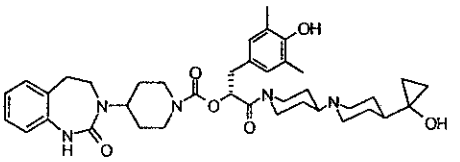
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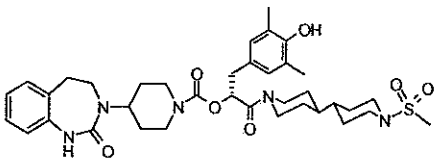
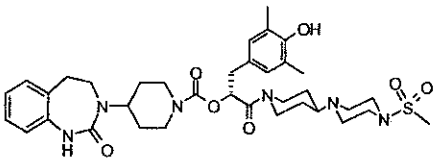
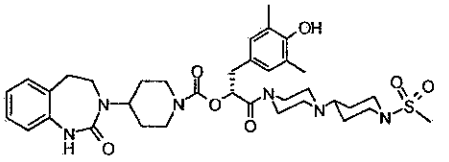
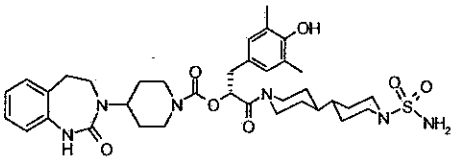
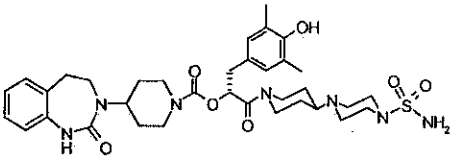
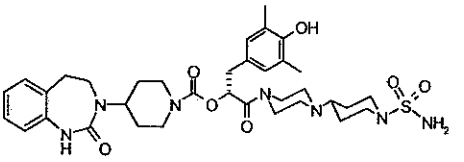
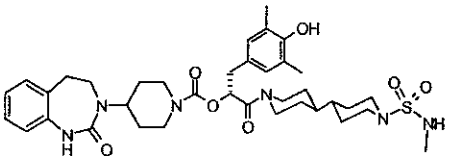
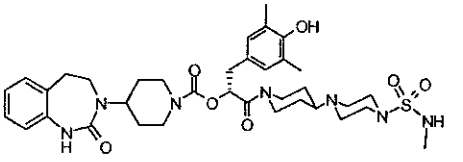
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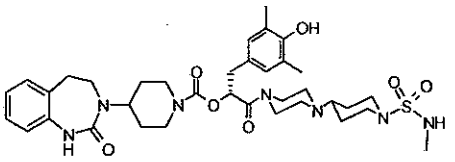
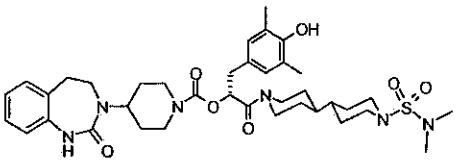
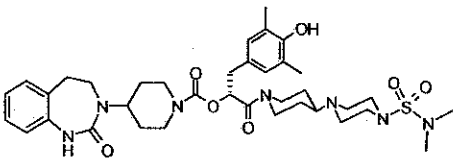
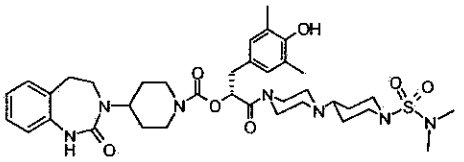
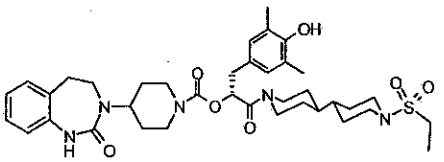
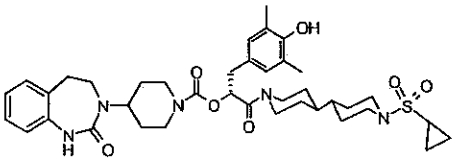
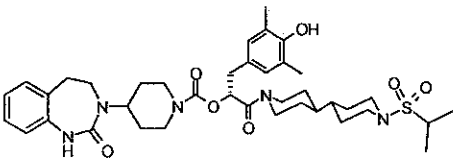
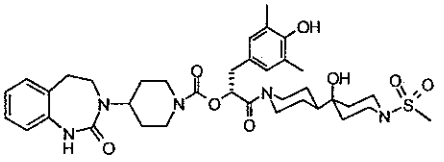
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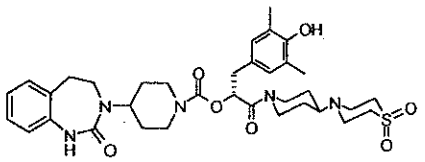
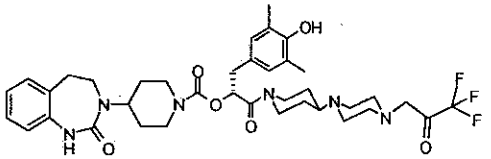
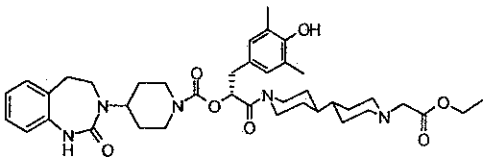
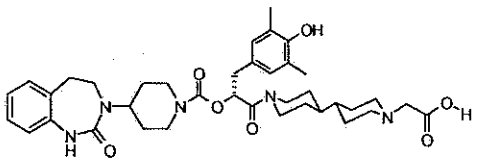
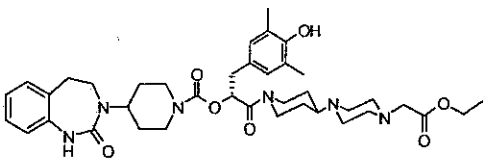
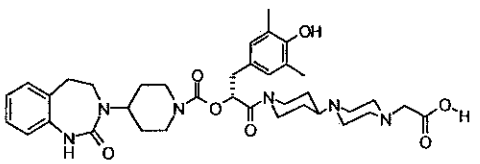
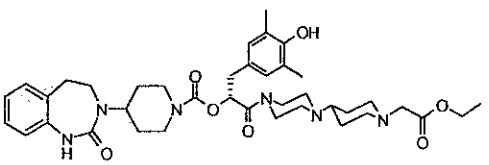
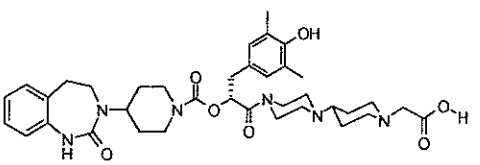
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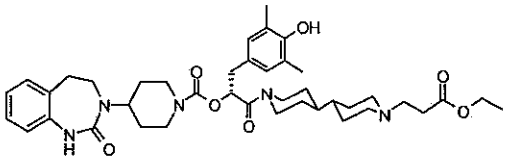
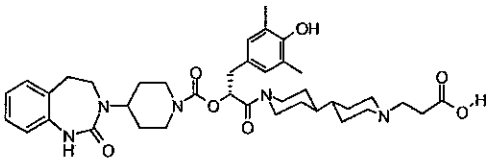
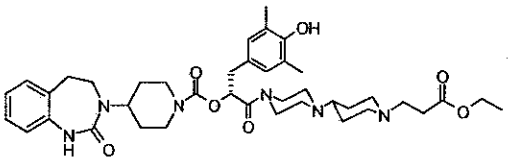
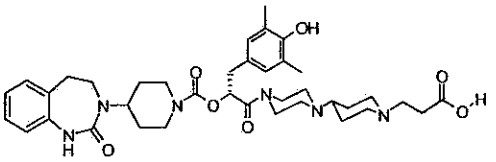
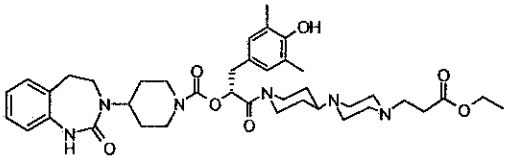
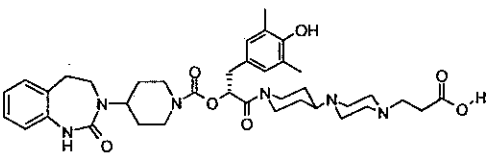
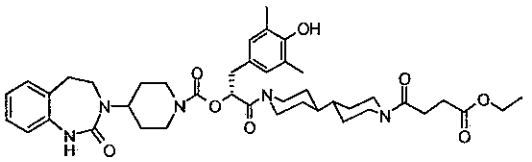
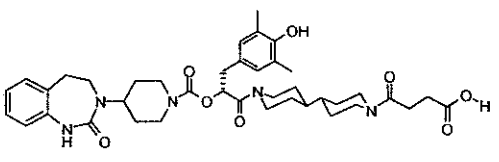
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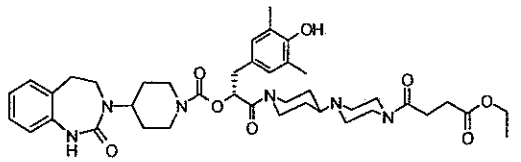
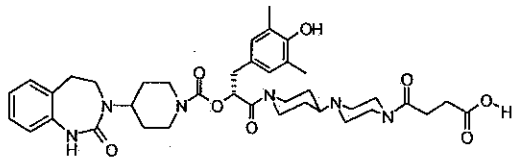
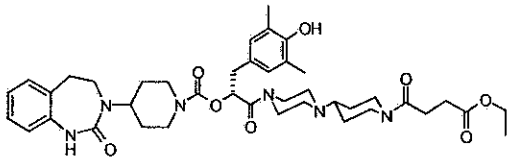
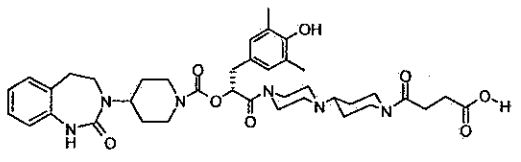
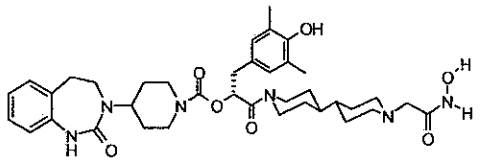
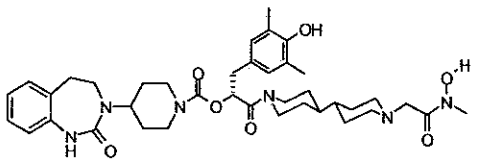
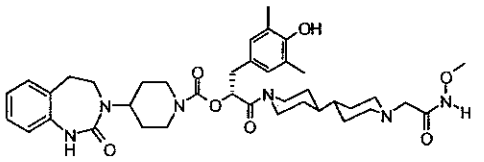
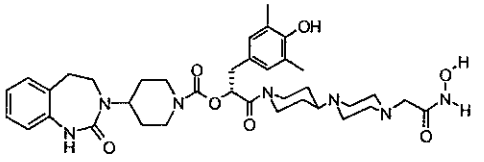
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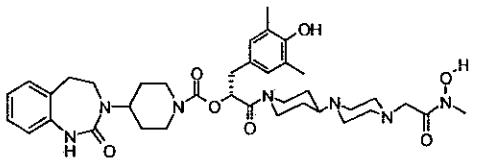
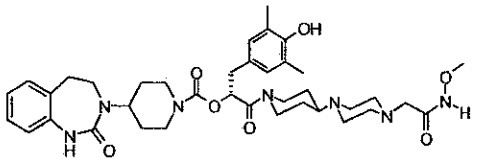
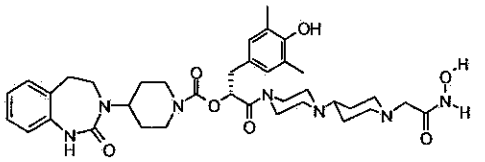
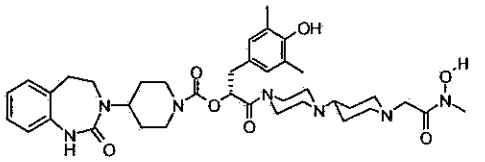
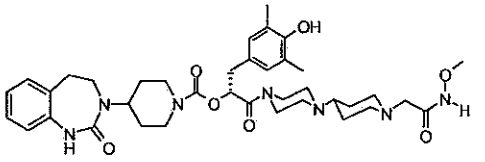
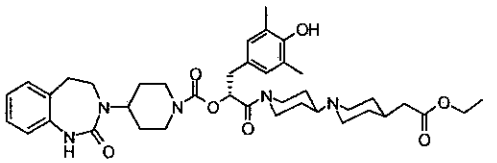
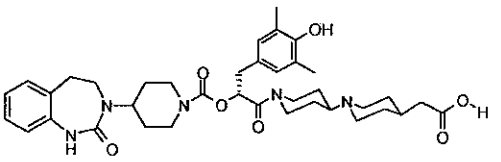
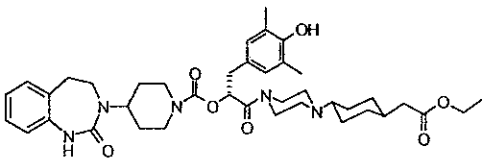
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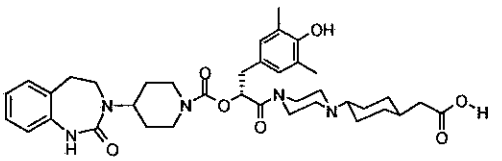
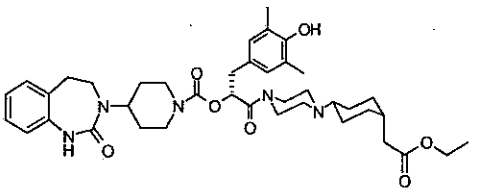
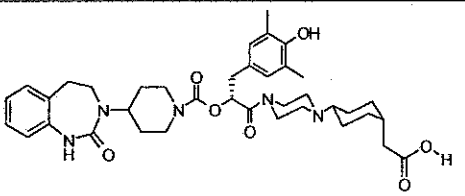
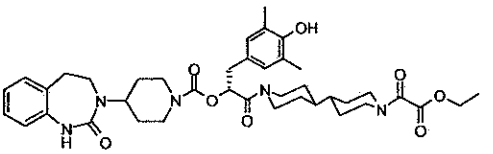
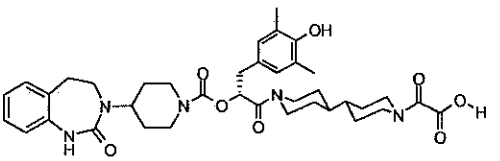
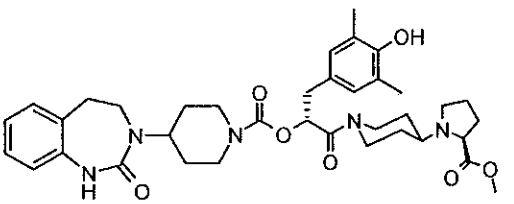
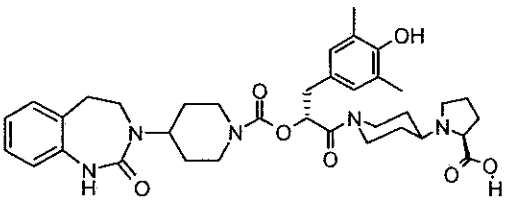
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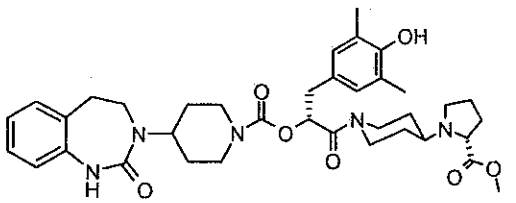
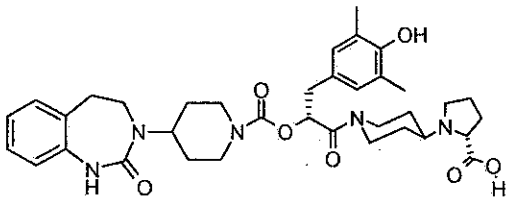
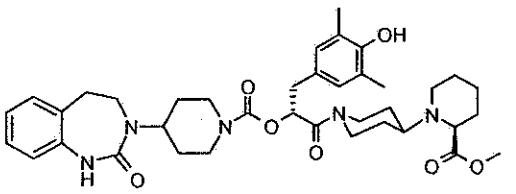
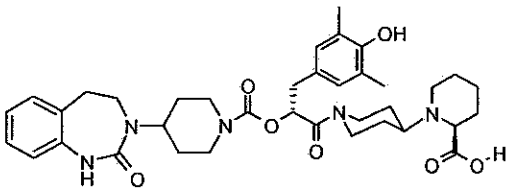
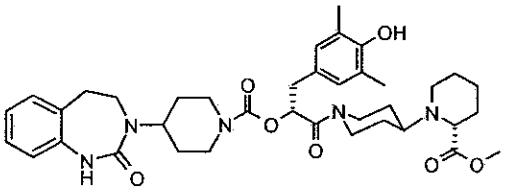
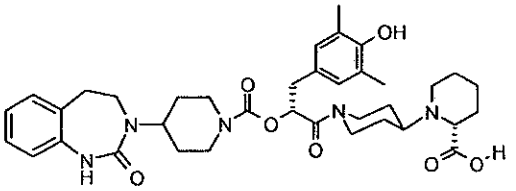
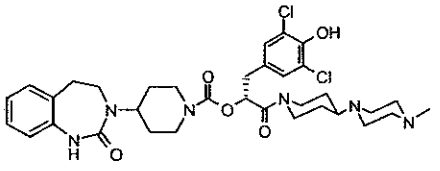
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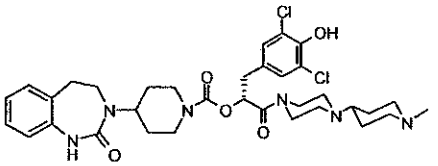
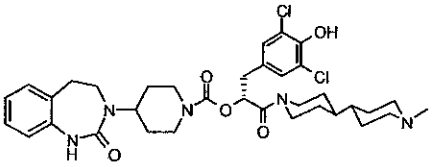
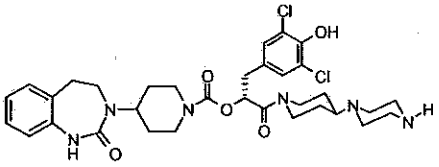
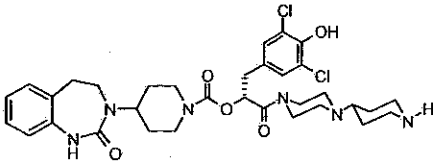
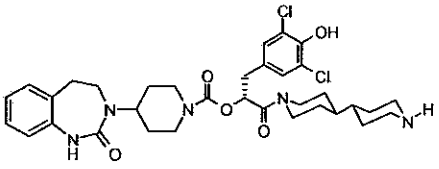
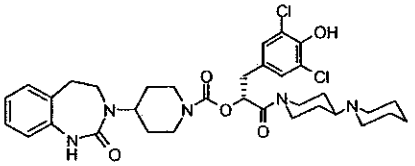
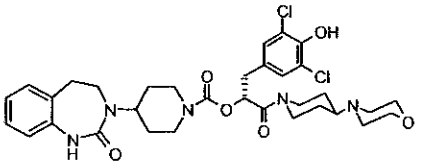
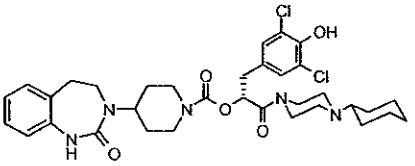
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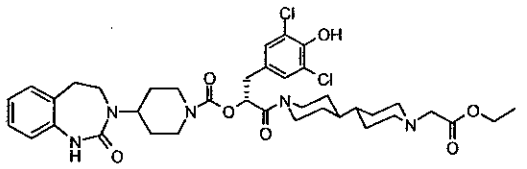
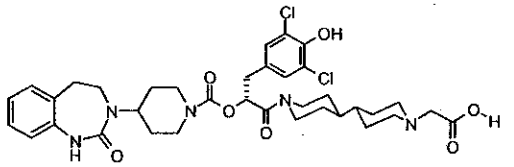
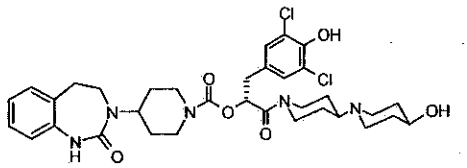
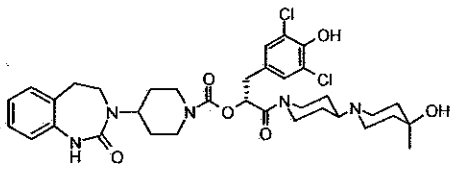
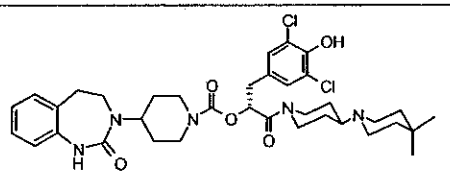
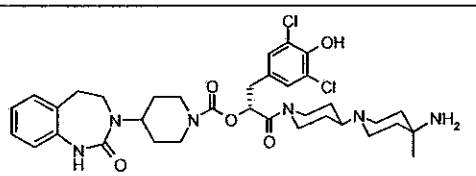
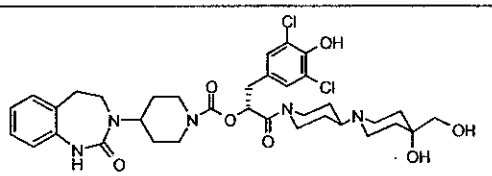
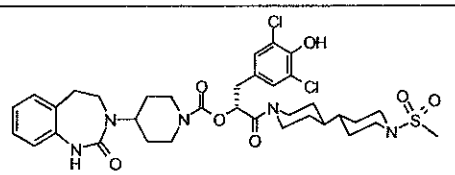
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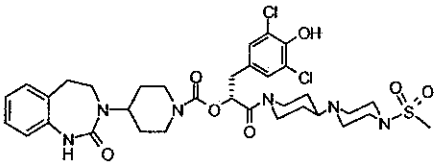
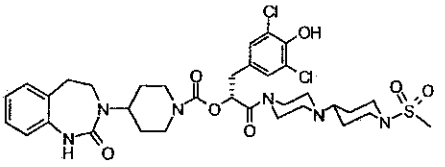
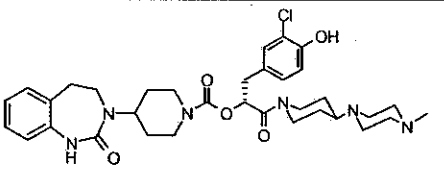
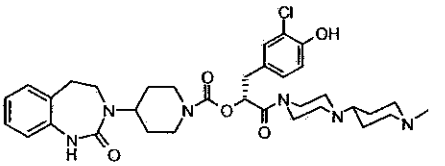
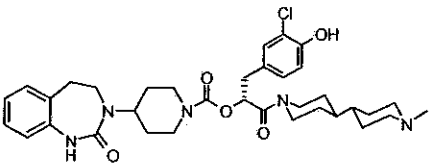
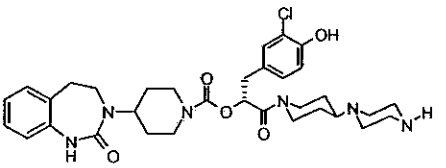
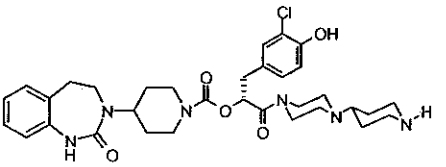
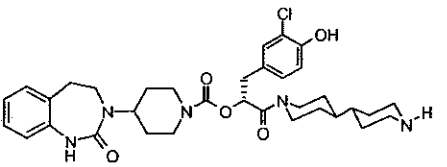
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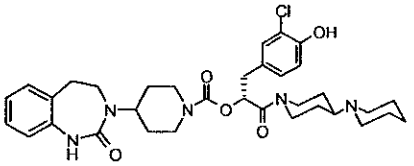
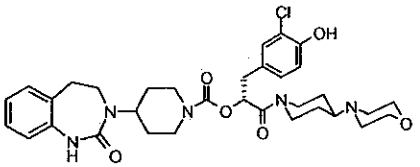
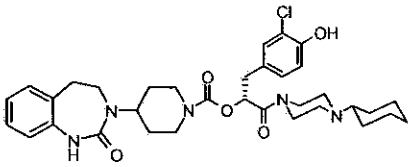
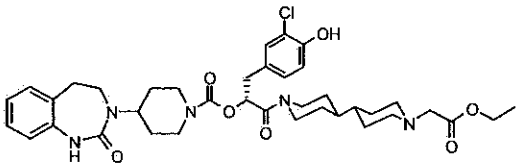
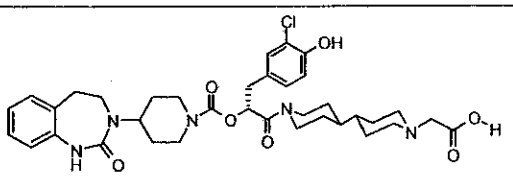
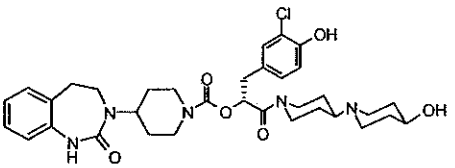
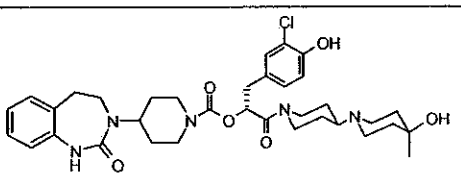
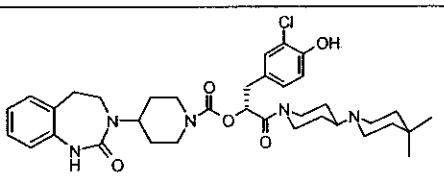
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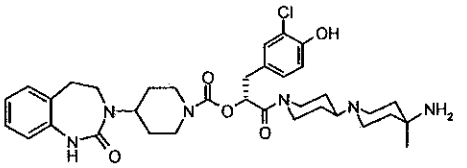
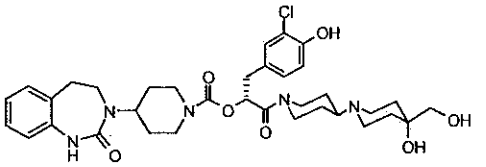
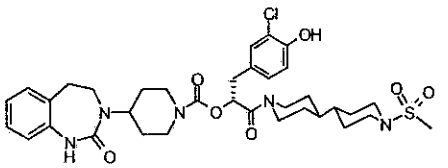
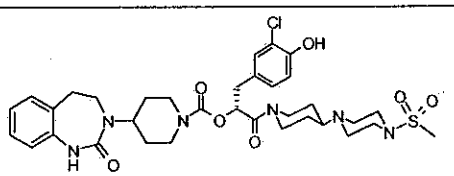
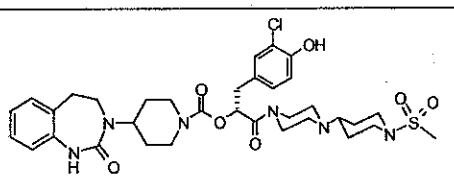
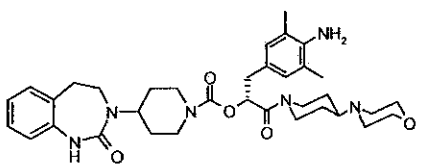
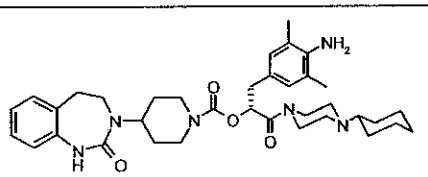
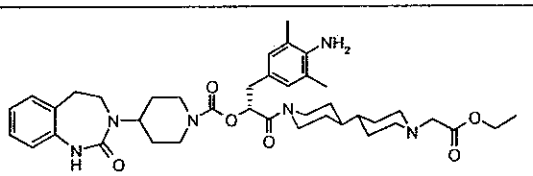
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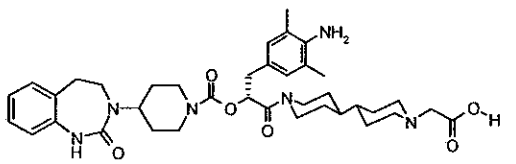
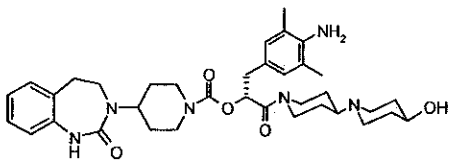
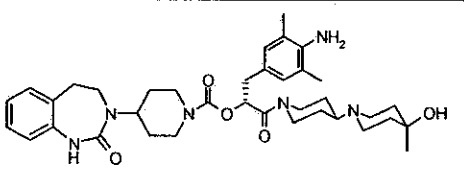
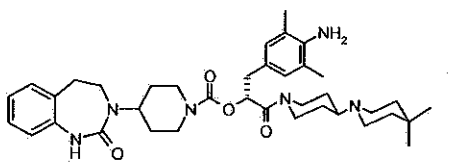
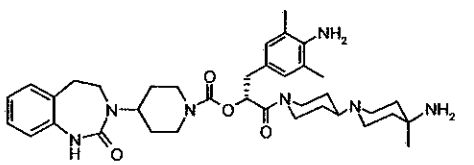
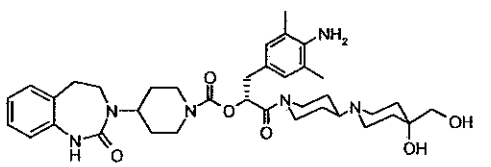
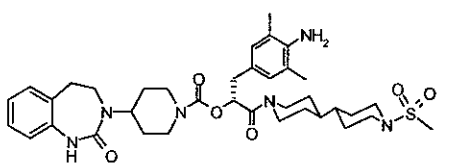
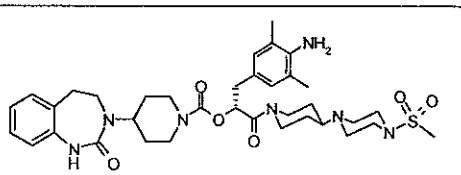
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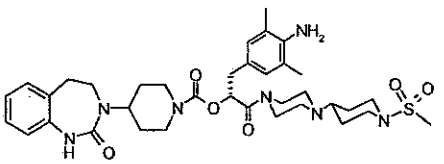
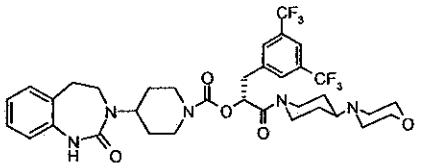
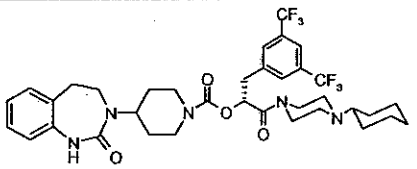
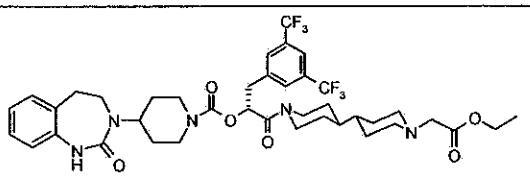
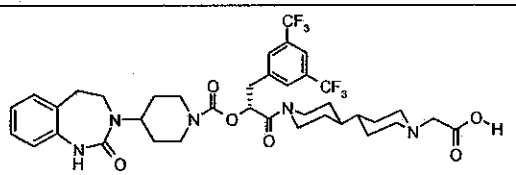
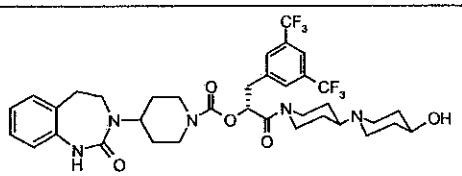
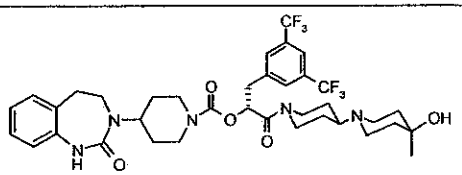
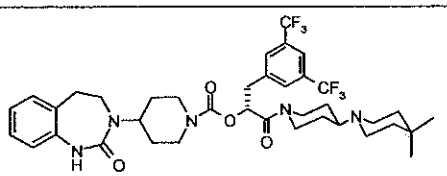
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(260)	

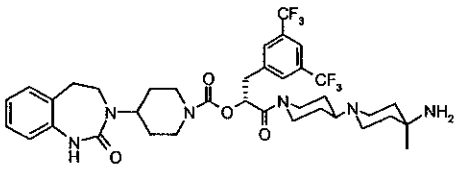
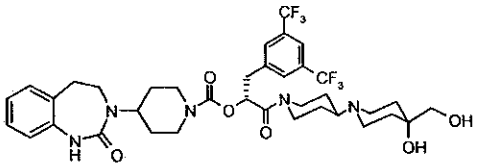
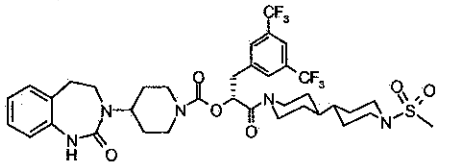
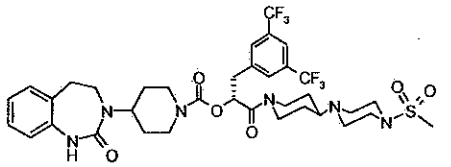
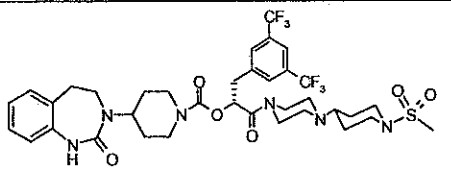
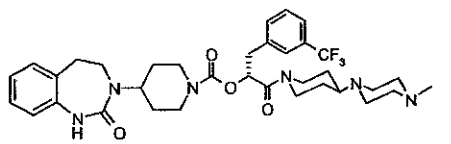
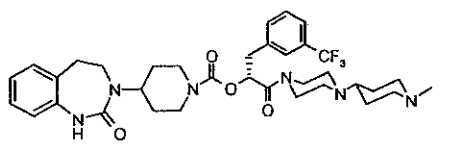
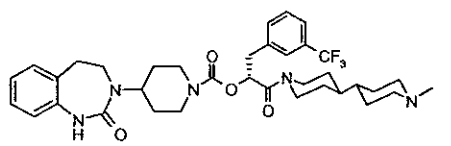
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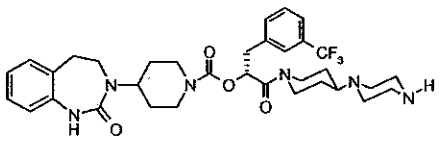
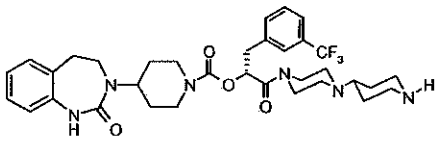
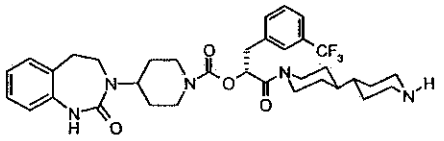
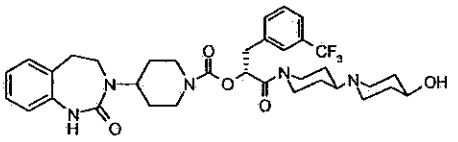
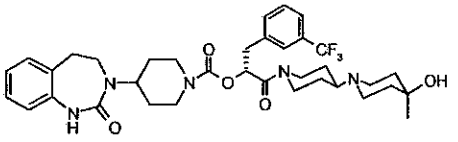
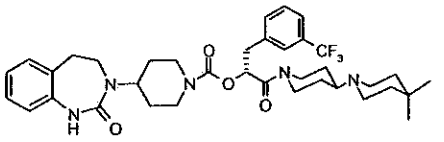
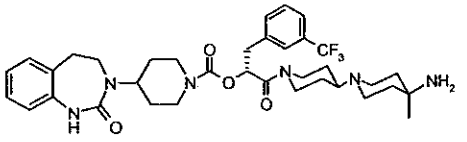
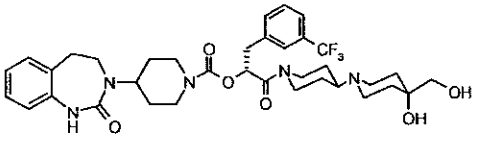
No.	Structure
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(274)	
(275)	
(276)	

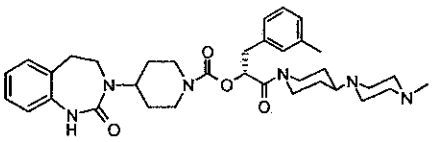
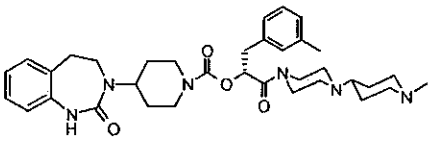
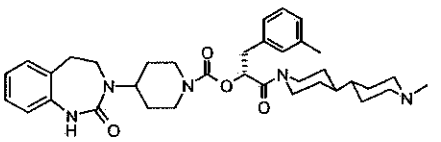
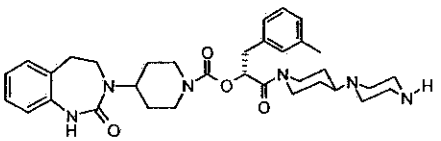
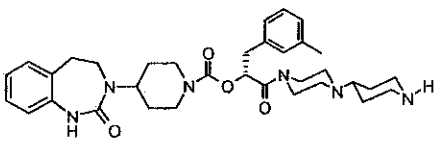
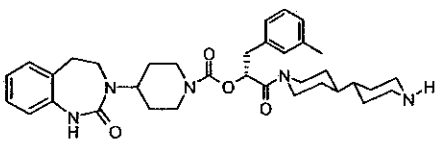
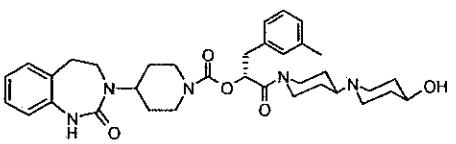
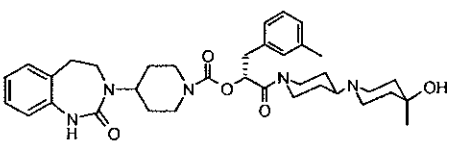
No.	Structure
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(283)	
(284)	

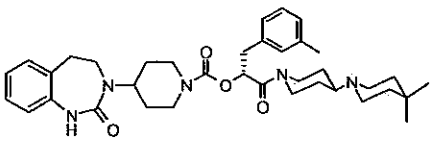
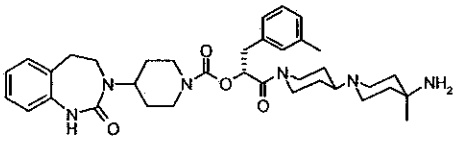
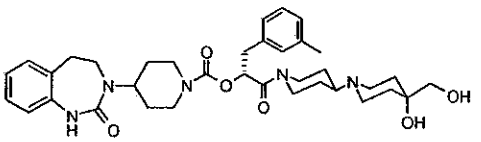
No.	Structure
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(290)	
(291)	
(292)	

No.	Structure
(293)	
(294)	
(295)	
(296)	
(297)	
(298)	
(299)	
(300)	

No.	Structure
(301)	
(302)	
(303)	
(304)	
(305)	
(306)	
(307)	
(308)	

No.	Structure
(309)	
(310)	
(311)	
(312)	
(313)	
(314)	
(315)	
(316)	

No.	Structure
(317)	
(318)	
(319)	
(320)	
(321)	
(322)	
(323)	
(324)	

No.	Structure
(325)	
(326)	
(327)	

the enantiomers, the diastereomers, the hydrates, the mixtures thereof and the salts thereof as well as the hydrates of the salts, particularly the physiologically acceptable salts thereof with inorganic or organic acids or bases.

Examples of other preferred compounds of the above general formula **I** are the following compounds, which are selected from the group consisting of:

(1), (2), (3), (4), (5), (6), (7), (8), (9), (10), (11), (12), (13), (14), (15), (16), (17), (18), (19), (20), (21), (22), (23), (24), (25), (26), (27), (28), (29), (30), (31), (32), (33), (34), (35), (36), (37), (38), (39), (40), (41), (42), (43), (44), (45), (46), (47), (48), (49), (50), (51), (52), (53), (54), (55), (56), (57), (58), (59), (60), (61), (62), (63), (64), (65), (66), (67), (68), (69), (70), (71), (72), (73), (74), (75), (76), (77), (78), (79), (80) and (81),

the enantiomers thereof, the diastereomers thereof, the hydrates thereof, the mixtures thereof and the salts thereof, as well as the hydrates of the salts,

particularly the physiologically acceptable salts thereof with inorganic or organic acids or bases.

Examples of other preferred compounds of the above general formula **I** are the following compounds, which are selected from the group consisting of:

(82), (83), (84), (85), (86), (87), (88), (89), (90), (91), (92), (93), (94), (95), (96), (97), (98), (99), (100), (101), (102), (103), (104), (105), (106), (107), (108), (109), (110), (111), (112), (113), (114), (115), (116), (117), (118), (119), (120), (121), (122), (123), (124), (125), (126), (127), (128), (129), (130), (131), (132), (133), (134), (135), (136), (137), (138), (139), (140), (141), (142), (143), (144), (145), (146), (147), (148), (149), (150), (151), (152), (153), (154), (155), (156), (157), (158), (159), (160), (161), and (162),

the enantiomers thereof, the diastereomers thereof, the hydrates thereof, the mixtures thereof and the salts thereof, as well as the hydrates of the salts, particularly the physiologically acceptable salts thereof with inorganic or organic acids or bases.

Examples of other preferred compounds of the above general formula **I** are the following compounds, which are selected from the group consisting of:

(163), (164), (165), (166), (167), (168), (169), (170), (171), (172), (173), (174), (175), (176), (177), (178), (179), (180), (181), (182), (183), (184), (185), (186), (187), (188), (189), (190), (191), (192), (193), (194), (195), (196), (197), (198), (199), (200), (201), (202), (203), (204), (205), (206), (207), (208), (209), (210), (211), (212), (213), (214), (215), (216), (217), (218), (219), (220), (221), (222), (223), (224), (225), (226), (227), (228), (229), (230), (231), (232), (233), (234), (235), (236), (237), (238), (239), (240), (241), (242) and (243),

the enantiomers thereof, the diastereomers thereof, the hydrates thereof, the mixtures thereof and the salts thereof, as well as the hydrates of the salts, particularly the physiologically acceptable salts thereof with inorganic or organic acids or bases.

Examples of other preferred compounds of the above general formula I are the following compounds, which are selected from the group consisting of:

(244), (245), (246), (247), (248), (249, (250), (251), (252), (253), (254), (255), (256), (257), (258), (259), (260), (261) and (262),

the enantiomers thereof, the diastereomers thereof, the hydrates thereof, the mixtures thereof and the salts thereof, as well as the hydrates of the salts, particularly the physiologically acceptable salts thereof with inorganic or organic acids or bases.

Examples of other preferred compounds of the above general formula I are the following compounds, which are selected from the group consisting of:

(263), (264), (265), (266), (267), (268), (269), (270), (271), (272), (273), (274), (275), (276), (277), (278), (279), (280) and (281),

the enantiomers thereof, the diastereomers thereof, the hydrates thereof, the mixtures thereof and the salts thereof, as well as the hydrates of the salts, particularly the physiologically acceptable salts thereof with inorganic or organic acids or bases.

Examples of other preferred compounds of the above general formula I are the following compounds, which are selected from the group consisting of:

(282), (283), (284), (285), (286), (287), (288), (289), (290), (291), (292) and (293),

the enantiomers thereof, the diastereomers thereof, the hydrates thereof, the mixtures thereof and the salts thereof, as well as the hydrates of the salts, particularly the physiologically acceptable salts thereof with inorganic or organic acids or bases.

Examples of other preferred compounds of the above general formula **I** are the following compounds, which are selected from the group consisting of:

(294), (295), (296), (297), (298), (299), (300), (301), (302), (303), (304) and (305),

the enantiomers thereof, the diastereomers thereof, the hydrates thereof, the mixtures thereof and the salts thereof, as well as the hydrates of the salts, particularly the physiologically acceptable salts thereof with inorganic or organic acids or bases.

Examples of other preferred compounds of the above general formula **I** are the following compounds, which are selected from the group consisting of:

(306), (307), (308), (309), (310), (311), (312), (313), (314), (315) and (316),

the enantiomers thereof, the diastereomers thereof, the hydrates thereof, the mixtures thereof and the salts thereof, as well as the hydrates of the salts, particularly the physiologically acceptable salts thereof with inorganic or organic acids or bases.

Examples of other preferred compounds of the above general formula **I** are the following compounds, which are selected from the group consisting of:

(317), (318), (319), (320), (321), (322), (323), (324), (325), (326) and (327),

the enantiomers thereof, the diastereomers thereof, the hydrates thereof, the mixtures thereof and the salts thereof, as well as the hydrates of the salts, particularly the physiologically acceptable salts thereof with inorganic or organic acids or bases.

TERMS AND DEFINITIONS USED

Within the scope of this application, in the definition of possible substituents, these may also be represented in the form of a structural formula. An asterisk (*) in the structural formula of the substituent is to be understood as being the linking point to the rest of the molecule.

Also included in the subject matter of this invention are the compounds according to the invention, including the salts thereof, in which one or more hydrogen atoms, for example one, two, three, four or five hydrogen atoms, are replaced by deuterium.

Compounds of general formula **I** may have acid groups, mainly carboxyl groups, and/or basic groups such as e.g. amino functions. Compounds of general formula **I** may therefore be present as internal salts, as salts with pharmaceutically useable inorganic acids such as for example hydrobromic acid, phosphoric acid, nitric acid, hydrochloric acid, sulphuric acid, methanesulphonic acid, ethanesulphonic acid, benzenesulphonic acid, *p*-toluenesulphonic acid or organic acids such as for example malic acid, succinic acid, acetic acid, fumaric acid, maleic acid, mandelic acid, lactic acid, tartaric acid, citric acid or as salts with pharmaceutically useable bases such as alkali or alkaline earth metal hydroxides, for example sodium hydroxide or potassium hydroxide, or carbonates, ammonia, zinc or ammonium hydroxides or organic amines such as e.g. diethylamine, triethylamine, ethanolamine, diethanolamine, triethanolamine, cyclohexylamine, dicyclohexylamine, *inter alia*.

As mentioned hereinbefore, the compounds of formula I may be converted into the salts thereof, particularly for pharmaceutical use, into the physiologically and pharmacologically acceptable salts thereof. These salts may on the one hand be in the form of the physiologically and pharmacologically acceptable acid addition salts of the compounds of formula I with inorganic or organic acids. On the other hand, if **B** contains a phenolic OH group, the compound of formula I may also be converted by reaction with inorganic bases into physiologically and pharmacologically acceptable salts with alkali or alkaline earth metal cations as counter ion. The acid addition salts may be prepared for example using hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, acetic acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid or maleic acid. It is also possible to use mixtures of the above-mentioned acids. The alkali and alkaline earth metal salts of the compound of formula I are preferably the alkali and alkaline earth metal hydroxides and hydrides thereof, of which the hydroxides and hydrides of the alkaline earth metals, particularly of sodium and potassium, are preferred and sodium and potassium hydroxide are particularly preferred.

The compounds according to the invention may occur as racemates if they have only one chiral element, but they may also be obtained as pure enantiomers, i.e. in the (*R*) or (*S*) form. Preferred compounds are those which occur as racemates or as the (*R*) form.

However, the application also includes the individual diastereomeric pairs of antipodes or the mixtures thereof which are present when there is more than one chiral element in the compounds of general formula I, as well as the individual optically active enantiomers of which the above-mentioned racemates are made up.

The invention relates to the compounds in question, optionally in the form of the individual optical isomers, mixtures of the individual enantiomers or racemates, in

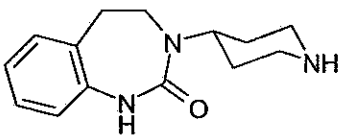
the form of the tautomers as well as in the form of the free bases or the corresponding acid addition salts with pharmacologically acceptable acids - such as for example acid addition salts with hydrohalic acids - for example hydrochloric or hydrobromic acid or organic acids – such as for example oxalic, fumaric, diglycolic or methanesulphonic acid.

PREPARATION METHODS

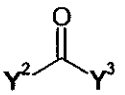
The compounds of general formula **I** are prepared by methods known in principle. The following methods have proved particularly suitable for preparing the compounds of general formula **I** according to the invention:

(a) In order to prepare compounds of general formula I wherein all the groups are as hereinbefore defined:

reacting a piperidine of formula **III**

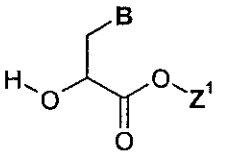


with a carbonic acid derivative of general formula **IV**



wherein Y^2 and Y^3 represent nucleofugic groups which may be identical or different, preferably the chlorine atom, the *p*-nitrophenoxy or trichloromethoxy group,

and with a compound of general formula **V**



wherein **B** is as hereinbefore defined and Z^1 denotes a protective group for a carboxy group, for example a C_{1-6}-alkyl or benzyl group, wherein the alkyl groups may be straight-chain or branched and the benzyl group may be substituted by one or two methoxy groups. Preferably Z^1 denotes the methyl, ethyl, *tert*-butyl or benzyl group.

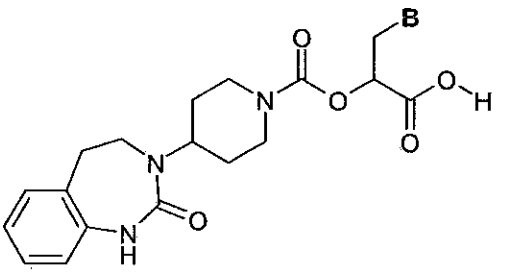
In a first step the compounds of general formula **III** are reacted in a solvent, for example in dichloromethane, THF, pyridine or mixtures thereof, at a temperature from -20 to 50°C in the presence of a base, for example triethylamine, pyridine or ethyldiisopropylamine, with the carbonic acid derivatives of general formula **IV**. The resulting intermediate may be purified or further reacted without purification. The reaction of these intermediates with compounds of general formula **V** is also carried out in one of the above-mentioned solvents, and at the temperatures specified hereinbefore, in the presence of a base, such as triethylamine or pyridine, with or without the addition of an activating reagent, such as e.g. 4-dimethylaminopyridine. To activate them the compounds of general formula **V** may also be deprotonated by means of a metal hydride such as e.g. NaH or KH, in which case there is no need for the presence of the base or the activating reagent.

The starting compounds of formula **III** and **IV** are either commercially available, known from the literature or may be prepared using methods known from the literature.

Processes for preparing compounds of general formula **III** are described for example in EP 1 619 187 A1.

(b) In order to prepare compounds of general formula I wherein all the groups are as hereinbefore defined:

coupling a carboxylic acid of general formula **VI**



wherein **B** is as hereinbefore defined, with an amine of general formula **VII**

$$H\text{-}NR^1R^2,$$

wherein R^1 and R^2 are as hereinbefore defined. Before the reaction is carried out any carboxylic acid functions, primary or secondary amino functions or hydroxy functions present in the groups R^1 and R^2 of the amine of general formula **VII** may be protected by conventional protecting groups and any protecting groups used may be cleaved again after the reaction using methods familiar to the skilled man.

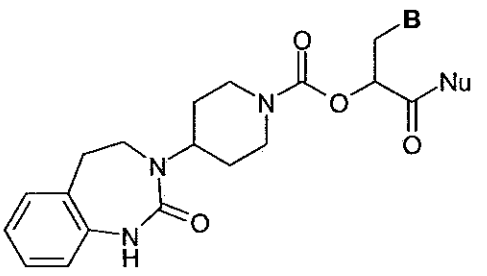
The coupling is preferably carried out using methods known from peptide chemistry (cf. e.g. Houben-Weyl, Methoden der Organischen Chemie, Vol. 15/2), for example using carbodiimides such as e.g. dicyclohexylcarbodiimide (DCC), diisopropyl carbodiimide (DIC) or ethyl-(3-dimethylaminopropyl)-carbodiimide, *O*-(1H-benzotriazol-1-yl)- *N,N-N',N'*-tetramethyluronium hexafluorophosphate (HBTU) or tetrafluoroborate (TBTU) or 1*H*-benzotriazol-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate (BOP). By adding 1-hydroxybenzotriazole (HOBt) or 3-hydroxy-4-oxo-3,4-dihydro-1,2,3-benzotriazine (HOObt) the reaction speed can be increased. The couplings are normally carried out with equimolar amounts of the coupling components as well as the coupling

reagent in solvents such as dichloromethane, tetrahydrofuran, acetonitrile, dimethyl formamide (DMF), dimethyl acetamide (DMA), *N*-methylpyrrolidone (NMP) or mixtures thereof and at temperatures between -30°C and +30°C, preferably -20°C and +25°C. If necessary, *N*-ethyl-diisopropylamine (Hünig base) is preferably used as an additional auxiliary base.

The so-called "anhydride process" is used as a further coupling method for synthesising compounds of general formula **I** (cf. also: M. Bodanszky, "Peptide Chemistry", Springer-Verlag 1988, p. 58-59; M. Bodanszky, "Principles of Peptide Synthesis", Springer-Verlag 1984, p. 21-27). The Vaughan variant of the "mixed anhydride process" is preferred (J.R. Vaughan Jr., J. Amer. Chem. Soc. 73, 3547 (1951)), in which the mixed anhydride of the carboxylic acid of general formula **VI** which is to be coupled and monoisobutyl carbonate is obtained, using isobutyl chlorocarbonate in the presence of bases such as 4-methylmorpholine or 4-ethylmorpholine. The preparation of this mixed anhydride and the coupling with amines of general formula **VII** are carried out in a one-pot process, using the above-mentioned solvents and at temperatures between -20 and +25°C, preferably between 0°C and +25°C.

(c) In order to prepare compounds of general formula **I** wherein all the groups are as hereinbefore defined:

coupling a compound of general formula **VIII**



wherein **B** is as hereinbefore defined and **Nu** denotes a leaving group, for example a halogen atom, such as the chlorine, bromine or iodine atom, an alkylsulphonyloxy group with 1 to 10 carbon atoms in the alkyl moiety, a phenylsulphonyloxy or naphthylsulphonyloxy group optionally mono-, di- or trisubstituted by chlorine or bromine atoms or by methyl or nitro groups, wherein the substituents may be identical or different, a 1*H*-imidazol-1-yl, optionally substituted by one or two methyl groups in the carbon skeleton, a 1*H*-pyrazol-1-yl, a 1*H*-1,2,4-triazol-1-yl, 1*H*-1,2,3-triazol-1-yl, 1*H*-1,2,3,4-tetrazol-1-yl, a vinyl, propargyl, *p*-nitrophenyl, 2,4-dinitrophenyl, trichlorophenyl, pentachlorophenyl, pentafluorophenyl, pyranyl or pyridinyl, a dimethylaminyloxy, 2(1*H*)-oxopyridin-1-yl-oxy, 2,5-dioxopyrrolidin-1-yloxy, phthalimidyloxy, 1*H*-benzo-triazol-1-yloxy or azide group, with an amine of general formula **VII**

$$H\text{-}NR^1R^2,$$

wherein R^1 and R^2 are as hereinbefore defined.

Before the reaction any carboxylic acid functions, primary or secondary amino functions or hydroxy functions present in the groups R^1 and R^2 of the amine of general formula **VII** may be protected by conventional protecting groups and after the reaction any protecting groups used may be cleaved again using methods familiar to those skilled in the art.

The reaction is carried out under Schotten-Baumann or Einhorn conditions, i.e. the components are reacted in the presence of at least one equivalent of an auxiliary base at temperatures between -50°C and +120°C, preferably -10°C and +30°C, and optionally in the presence of solvents. The auxiliary bases used are preferably alkali metal and alkaline earth metal hydroxides, e.g. sodium hydroxide, potassium hydroxide or barium hydroxide, alkali metal carbonates, e.g. sodium carbonate, potassium carbonate or caesium carbonate, alkali metal acetates, e.g. sodium or potassium acetate, as well as tertiary amines, e.g. pyridine, 2,4,6-trimethylpyridine,

quinoline, triethylamine, *N*-ethyl-diisopropylamine, *N*-ethyl-dicyclohexylamine, 1,4-diazabicyclo[2,2,2]octane or 1,8-diazabicyclo[5,4,0]undec-7-ene, the solvents used may be, for example, dichloromethane, tetrahydrofuran, 1,4-dioxane, acetonitrile, dimethyl formamide, dimethyl acetamide, *N*-methyl-pyrrolidone or mixtures thereof; if alkali metal or alkaline earth metal hydroxides, alkali metal carbonates or acetates are used as the auxiliary bases, water may also be added to the reaction mixture as cosolvent.

The new compounds of general formula **I** according to the invention contain one or more chiral centres. If for example there are two chiral centres the compounds may occur in the form of two pairs of diastereomeric antipodes. The invention covers the individual isomers as well as the mixtures thereof.

The diastereomers may be separated on the basis of their different physico-chemical properties, e.g. by fractional crystallisation from suitable solvents, by high pressure liquid or column chromatography, using chiral or preferably non-chiral stationary phases.

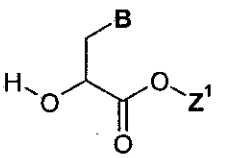
Racemates covered by general formula **I** may be separated for example by HPLC on suitable chiral stationary phases (e.g. Chiral AGP, Chiralpak AD). Racemates which contain a basic or acidic function can also be separated via the diastereomeric, optically active salts which are produced on reacting with an optically active acid, for example (+) or (-)-tartaric acid, (+) or (-)-diacetyl tartaric acid, (+) or (-)-monomethyl tartrate or (+) or (-)-camphorsulphonic acid, or an optically active base, for example with (*R*)-(+)-1-phenylethylamine, (S)-(-)-1-phenylethylamine or (S)-brucine.

According to a conventional method of separating isomers, the racemate of a compound of general formula **I** is reacted with one of the above-mentioned optically active acids or bases in equimolar amounts in a solvent and the resulting

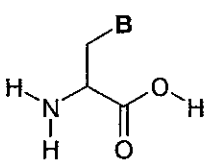
crystalline, diastereomeric, optically active salts thereof are separated using their different solubilities. This reaction may be carried out in any type of solvent provided that it is sufficiently different in terms of the solubility of the salts. Preferably, methanol, ethanol or mixtures thereof, for example in a ratio by volume of 50:50, are used. Then each of the optically active salts is dissolved in water, carefully neutralised with a base such as sodium carbonate or potassium carbonate, or with a suitable acid, e.g. dilute hydrochloric acid or aqueous methanesulphonic acid, and in this way the corresponding free compound is obtained in the (+) or (-) form.

The (*R*) or (S) enantiomer alone or a mixture of two optically active diastereomeric compounds covered by general formula **I** may also be obtained by performing the syntheses described above with a suitable reaction component in the (*R*) or (S) configuration.

The hydroxycarboxylic acids of general formula **V** needed for the synthesis



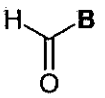
wherein **B** is as hereinbefore defined and $\mathbf{Z^1}$ denotes a protective group for a carboxy group, for example a C_{1-6}-alkyl or benzyl group, wherein the alkyl groups may be straight-chain or branched and the benzyl group may be substituted by one or two methoxy groups, wherein $\mathbf{Z^1}$ preferably denotes the methyl, ethyl, *tert*-butyl or benzyl group, may be obtained from compounds of general formula **IX**



wherein **B** is as hereinbefore defined.

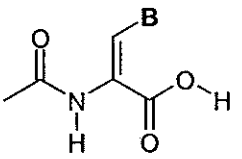
By diazotising compounds of general formula **IX** with a suitable diazotising reagent, preferably sodium nitrite in an acid medium, it is possible to obtain the compounds of general formula **V**. When enantiomerically pure compounds are used the corresponding enantiomerically pure hydroxycarboxylic acid compounds are obtained, the reaction taking place with retention of configuration.

An alternative method of obtaining compounds of general formula **V** comprises reacting aldehydes of general formula **X**



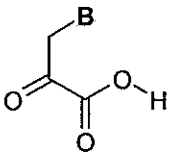
wherein **B** is as hereinbefore defined, with *N*-acetylglycine in acetic anhydride as solvent in the presence of alkali metal acetate, preferably sodium or potassium acetate, at a suitable temperature, preferably at 80 to 130°C.

The azlactones obtained as primary product are hydrolysed without being isolated to form the compounds of general formula **XI**



wherein **B** is as hereinbefore defined.

By further reaction in the presence of aqueous inorganic acids, such as for example sulphuric, phosphoric or hydrochloric acid, but preferably hydrochloric acid, compounds of general formula **XII**

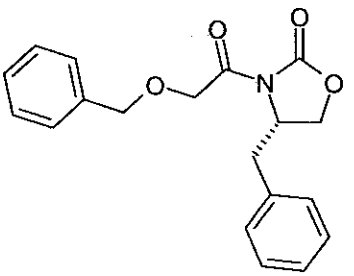


are obtained wherein **B** is as hereinbefore defined. These are then converted with suitable reducing agents into the compounds of general formula **V**.

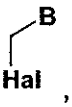
Suitable reducing agents are alkali metal borohydrides, such as sodium or potassium borohydride. Other suitable reducing agents are chlorodialkylboranes, such as chlorodicyclohexylborane. If chiral chlorodialkylboranes, such as e.g. B-chlorodiisopinocampheylborane, are used, the compounds of general formula **V** may be isolated in enantiomerically pure form.

The further reaction of compounds of general formula **V**, wherein Z^1 denotes the hydrogen atom, to compounds of general formula **V**, wherein Z^1 is as hereinbefore defined, takes place in an alcoholic medium, preferably in methanol or ethanol, in the presence of a suitable acid, such as hydrochloric acid. The reaction may alternatively be carried out by reaction in alcoholic solvents, preferably methanol, with thionyl chloride.

Another method of obtaining compounds of general formula **V** comprises alkylating a compound of formula **XIII**



with an aryl- or heteroaryl-methylhalide of general formula **XIV**



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wherein **Hal** denotes a chlorine, bromine or iodine atom, and **B** is as hereinbefore defined, analogously to methods known from the literature (Michael T. Crimmins, Kyle A. Emmitte and Jason D. Katz, Org. Lett. 2, 2165-2167 [2000]).

The diastereomeric products obtained may then be separated using physicochemical methods, preferably by chromatographic methods or recrystallisation. The hydrolytic cleaving of the chiral auxiliary and cleaving the benzyl protecting group also provides a method of obtaining enantiomerically pure hydroxycarboxylic acid compounds of general formula **V**.

All the compounds of general formula **I** which contain primary or secondary amino, hydroxy or hydroxycarbonyl functions are preferably obtained from precursors provided with protective groups. Examples of protective groups for amino functions include for example a benzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, 4-nitro-benzyloxycarbonyl, 4-methoxy-benzyloxycarbonyl, 2-chloro-benzyloxycarbonyl, 3-chloro-benzyloxycarbonyl, 4-chloro-benzyloxycarbonyl, 4-biphenylyl-α,α-dimethyl-benzyloxycarbonyl or 3,5-dimethoxy-α,α-dimethyl-benzyloxycarbonyl group, an alkoxycarbonyl group with a total of 1 to 5 carbon atoms in the alkyl moiety, for example the methoxycarbonyl, ethoxycarbonyl, *n*-propoxycarbonyl, isopropoxycarbonyl, *n*-butoxycarbonyl, 1-methylpropoxycarbonyl, 2-methylpropoxy-carbonyl or *tert*-butyloxycarbonyl group, the allyloxycarbonyl, 2,2,2-trichloro-(1,1-dimethylethoxy)carbonyl or 9-fluorenylmethoxycarbonyl group or a formyl, acetyl or trifluoroacetyl group.

Examples of protective groups for hydroxy functions include a trimethylsilyl, triethylsilyl, triisopropyl, *tert*-butyldimethylsilyl or *tert*-butyldiphenylsilyl group, a *tert*-butyl, benzyl, 4-methoxybenzyl or 3,4-dimethoxybenzyl group.

A protective group for hydroxycarbonyl functions might be, for example, an alkyl group with a total of 1 to 5 carbon atoms, for example the methyl, ethyl, *n*-propyl,

isopropyl, *n*-butyl, *tert*-butyl, allyl, 2,2,2-trichloroethyl, benzyl or 4-methoxybenzyl group.

The new compounds of general formula I and the physiologically acceptable salts thereof have valuable pharmacological properties, based on their selective CGRP-antagonistic properties. The invention further relates to pharmaceutical compositions containing these compounds, their use and the preparation thereof.

The new compounds mentioned above and the physiologically acceptable salts thereof have CGRP-antagonistic properties and exhibit good affinities in CGRP receptor binding studies. The compounds display CGRP-antagonistic properties in the pharmacological test systems described hereinafter.

The following experiments were carried out to demonstrate the affinity of the above-mentioned compounds for human CGRP-receptors and their antagonistic properties:

A. Binding studies with SK-N-MC cells (expressing the human CGRP receptor)

SK-N-MC cells are cultivated in "Dulbecco's modified Eagle medium". The medium is removed from confluent cultures. The cells are washed twice with PBS buffer (Gibco 041-04190 M), detached by the addition of PBS buffer mixed with 0.02% EDTA, and isolated by centrifuging. After resuspension in 20 ml of "Balanced Salts Solution" [BSS (in mM): NaCl 120, KCl 5.4, $NaHCO_3$ 16.2, $MgSO_4$ 0.8, $NaHPO_4$ 1.0, $CaCl_2$ 1.8, D-glucose 5.5, HEPES 30, pH 7.40] the cells are centrifuged twice at 100 x g and resuspended in BSS. After the number of cells has been determined, the cells are homogenised using an Ultra-Turrax and centrifuged for 10 minutes at 3000 x g. The supernatant is discarded and the pellet is recentrifuged in Tris buffer (10 mM Tris, 50 mM NaCl, 5 mM $MgCl_2$, 1 mM EDTA, pH 7.40) enriched with 1% bovine serum albumin and 0.1% bacitracin, and

resuspended (1 ml / 1000000 cells). The homogenised product is frozen at -80°C. The membrane preparations are stable for more than 6 weeks under these conditions.

After thawing, the homogenised product is diluted 1:10 with assay buffer (50 mM Tris, 150 mM NaCl, 5 mM $MgCl_2$, 1 mM EDTA, pH 7.40) and homogenised for 30 seconds with an Ultra-Turrax. 230 µl of the homogenised product are incubated for 180 minutes at ambient temperature with 50 pM ^{125}I-iodotyrosyl-Calcitonin-Gene-Related Peptide (Amersham) and increasing concentrations of the test substances in a total volume of 250 µl. The incubation is ended by rapid filtration through GF/B glass fibre filters treated with polyethyleneimine (0.1%) using a cell harvester. The protein-bound radioactivity is measured using a gamma counter. Non-specific binding is defined as the bound radioactivity in the presence of 1 µM human CGRP-alpha during incubation.

The concentration binding curves are analysed using computer-aided non-linear curve matching.

The compounds mentioned hereinbefore show IC_{50} values ≤ 10000 nM in the test described.

B. CGRP Antagonism in SK-N-MC cells

SK-N-MC cells (1 million cells) are washed twice with 250 µl incubation buffer (Hanks' HEPES, 1 mM 3-isobutyl-1-methylxanthine, 1% BSA, pH 7.4) and pre-incubated at 37°C for 15 minutes. After the addition of CGRP (10 µl) as agonist in increasing concentrations (10^{-11} to 10^{-6} M), or additionally the substance in 3 to 4 different concentrations, the mixture is incubated for another 15 minutes.

Intracellular cAMP is then extracted by the addition of 20 µl of 1M HCl and centrifugation (2000 x g, 4°C, for 15 minutes). The supernatants are frozen in liquid nitrogen and stored at -20°C.

The cAMP contents of the samples are determined by radioimmunoassay (Messrs. Amersham) and the pA_2 values of antagonistically acting substances are determined graphically.

The compounds according to the invention exhibit CGRP-antagonistic properties in the *in vitro* test model described, in a dosage range between 10^{-12} and 10^{-5} M.

TYPES OF INDICATIONS

In view of their pharmacological properties the compounds according to the invention and the salts thereof with physiologically acceptable acids are thus suitable for the acute and prophylactic treatment of headaches, particularly migraine, cluster headaches and tension headaches. Moreover, the compounds according to the invention also have a positive effect on the following diseases: non-insulin-dependent diabetes mellitus ("NIDDM"), cardiovascular diseases, morphine tolerance, diarrhoea caused by clostridium toxin, skin diseases, particularly thermal and radiation-induced skin damage including sunburn, lichen, prurigo, pruriginous toxidermies and severe itching, inflammatory diseases, e.g. inflammatory diseases of the joints (osteoarthritis, rheumatoid arthritis, neurogenic arthritis), generalised soft tissue rheumatism (fibromyalgia), neurogenic inflammation of the oral mucosa, inflammatory lung diseases, allergic rhinitis, asthma, COPD, diseases accompanied by excessive vasodilatation and resultant reduced blood supply to the tissues, e.g. shock and sepsis, chronic pain, such as e.g. diabetic neuropathies, neuropathies induced by chemotherapy, HIV-induced neuropathies, post-herpetic neuropathies, neuropathies induced by tissue trauma, trigeminal neuralgias, temporomandibular dysfunctions, CRPS (complex regional pain syndrome), back pain and visceral diseases such as for example irritable

bowel syndrome (IBS), inflammatory bowel syndrome. In addition, the compounds according to the invention have a general pain-relieving effect. The symptoms of menopausal hot flushes caused by vasodilatation and increased blood flow in oestrogen-deficient women and hormone-treated patients with prostate carcinoma and castrated men are favourably affected by the CGRP antagonists of the present application in a preventive and acute-therapeutic capacity, this therapeutic approach being distinguished from hormone replacement by the absence of side effects.

Preferably, the compounds according to the invention are suitable for the acute and preventive treatment of migraine and cluster headaches, for treating irritable bowel syndrome (IBS) and for the preventive and acute therapeutic treatment of hot flushes in oestrogen-deficient women.

The dosage required to achieve a corresponding effect is conveniently 0.0001 to 3 mg/kg of body weight, preferably 0.01 to 1 mg/kg of body weight, when administered intravenously or subcutaneously, and 0.01 to 10 mg/kg of body weight, preferably 0.1 to 10 mg/kg of body weight when administered orally, nasally or by inhalation, 1 to 3 times a day in each case.

If the treatment with CGRP antagonists and/or CGRP release inhibitors is given as a supplement to conventional hormone replacement, it is advisable to reduce the doses specified above, in which case the dosage may be from 1/5 of the lower limits mentioned above up to 1/1 of the upper limits specified.

The invention further relates to the use of the compounds according to the invention as valuable adjuvants for the production and purification (by affinity chromatography) of antibodies as well as in RIA and ELISA assays, after suitable radioactive labelling, for example by tritiation of suitable precursors, for example by catalytic hydrogenation with tritium or replacing halogen atoms with tritium, and as a diagnostic or analytical adjuvant in neurotransmitter research.

COMBINATIONS

Categories of active substance which may be used in the combination include e.g. antiemetics, prokinetics, neuroleptics, antidepressants, neurokinin antagonists, anticonvulsants, histamine-H1-receptor antagonists, β-blockers, α-agonists and α-antagonists, ergot alkaloids, mild analgesics, non-steroidal antiinflammatories, corticosteroids, calcium antagonists, 5-$HT_{1B/1D}$-agonists or other anti-migraine agents which may be formulated together with one or more inert conventional carriers and/or diluents, e.g. with corn starch, lactose, glucose, microcrystalline cellulose, magnesium stearate, polyvinyl pyrrolidone, citric acid, tartaric acid, water, water/ethanol, water/glycerol, water/sorbitol, water/polyethylene glycol, propylene glycol, cetylstearyl alcohol, carboxymethylcellulose or fatty substances such as hard fat or suitable mixtures thereof, into conventional galenic preparations such as plain or coated tablets, capsules, powders, suspensions, solutions, metered dose aerosols or suppositories.

Thus, other active substances which may be used for the combinations mentioned above include for example the non-steroidal antiinflammatories aceclofenac, acemetacin, acetylsalicylic acid, acetaminophen (paracetamol), azathioprine, diclofenac, diflunisal, fenbufen, fenoprofen, flurbiprofen, ibuprofen, indometacin, ketoprofen, leflunomide, lornoxicam, mefenamic acid, naproxen, phenylbutazone, piroxicam, sulphasalazine, zomepirac or the pharmaceutically acceptable salts thereof as well as meloxicam and other selective COX2-inhibitors, such as for example rofecoxib, valdecoxib, parecoxib, etoricoxib and celecoxib, as well as substances which inhibit earlier or later stages in prostaglandin synthesis or prostaglandin receptor antagonists such as e.g. EP2-receptor antagonists and IP-receptor antagonists.

It is also possible to use ergotamine, dihydroergotamine, metoclopramide, domperidone, diphenhydramine, cyclizine, promethazine, chlorpromazine, vigabatrin, timolol, isometheptene, pizotifen, botox, gabapentin, pregabaline,

duloxetine, topiramate, riboflavin, montelukast, lisinopril, micardis, prochloroperazine, dexamethasone, flunarizine, dextropropoxyphene, meperidine, metoprolol, propranolol, nadolol, atenolol, clonidine, indoramin, carbamazepine, phenytoin, valproate, amitryptiline, imipramine, venlafaxine, lidocaine or diltiazem and other 5-$HT_{1B/1D}$-agonists such as, for example, almotriptan, avitriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan and zolmitriptan.

In addition, CGRP-antagonists may be combined with vanilloid receptor antagonists, such as e.g. VR-1 antagonists, glutamate receptor antagonists, such as e.g. mGlu5-receptor antagonists, mGlu1-receptor antagonists, iGlu5-receptor antagonists, AMPA-receptor antagonists, purine receptor blockers, such as e.g. P2X3 antagonists, NO-synthase inhibitors, such as e.g. iNOS inhibitors, calcium channel blockers, such as e.g. PQ-type blockers, N-type blockers, potassium channel openers, such as e.g. KCNQ channel openers, sodium channel blockers, such as e.g. PN3 channel blockers, NMDA-receptor antagonists, acid-sensing ion channel antagonists, such as e.g. ASIC3 antagonists, bradykinin receptor antagonists such as e.g. B1-receptor antagonists, cannabinoid receptor agonists, such as e.g. CB2 agonists, CB1 agonists, somatostatin receptor agonists, such as e.g. sst2 receptor agonists.

The dosage for these active substances is conveniently 1/5 of the normally recommended dose to 1/1 of the normally recommended dose, i.e. for example 20 to 100 mg sumatriptan.

FORMULATIONS

The compounds prepared according to the invention may be administered either on their own or optionally in combination with other active substances for the treatment of migraine by intravenous, subcutaneous, intramuscular, intra-articular, intrarectal or intranasal route, by inhalation, topically, transdermally or orally, while aerosol formulations are particularly suitable for inhalation. The combinations may

be administered either simultaneously or sequentially.

Suitable forms for administration include for example tablets, capsules, solutions, syrups, emulsions or inhalable powders or aerosols. The proportion of pharmaceutically active compound or compounds should be in the range from 0.1 to 90% by weight, preferably 0.5 to 50% by weight of the total composition, i.e. in amounts which are sufficient to achieve the dosage range mentioned hereinbefore.

The preparations may be given orally in the form of tablets, powders, powders in capsules (e.g. hard gelatine capsules), or as solutions or suspensions. When taken by inhalation the active substance combination may be administered as a powder, an aqueous or aqueous-ethanolic solution or by means of a propellant gas formulation.

Preferably, therefore, pharmaceutical formulations are characterised in that they contain one or more compounds of formula I according to the preferred embodiments described hereinbefore.

It is particularly preferable if the compounds of formula I are administered orally, and it is most preferable if they are administered once or twice a day. Suitable tablets may be obtained, for example, by mixing the active substances with known excipients, for example inert diluents such as calcium carbonate, calcium phosphate or lactose, disintegrants such as corn starch or alginic acid, binders such as starch or gelatine, lubricants such as magnesium stearate or talc and/or agents for delaying release, such as carboxymethyl cellulose, cellulose acetate phthalate, or polyvinyl acetate. The tablets may also comprise several layers.

Coated tablets may be prepared accordingly by coating cores produced analogously to the tablets with substances normally used for tablet coatings, for example collidone or shellac, gum arabic, talc, titanium dioxide or sugar. To achieve delayed release or prevent incompatibilities the core may also consist of a number of layers. Similarly the tablet coating may consist of a number or layers to

achieve delayed release, possibly using the excipients mentioned above for the tablets.

Syrups containing the active substances or combinations thereof according to the invention may additionally contain a sweetener such as saccharine, cyclamate, glycerol or sugar and a flavour enhancer, e.g. a flavouring such as vanillin or orange extract. They may also contain suspension adjuvants or thickeners such as sodium carboxymethyl cellulose, wetting agents such as, for example, condensation products of fatty alcohols with ethylene oxide, or preservatives such as *p*-hydroxybenzoates.
Capsules containing one or more active substances or combinations of active substances may for example be prepared by mixing the active substances with inert carriers such as lactose or sorbitol and packing them into gelatine capsules.
Suitable suppositories may be made for example by mixing with carriers provided for this purpose, such as neutral fats or polyethyleneglycol or the derivatives thereof.

Excipients which may be used include, for example, water, pharmaceutically acceptable organic solvents such as paraffins (e.g. petroleum fractions), vegetable oils (e.g. groundnut or sesame oil), mono- or polyfunctional alcohols (e.g. ethanol or glycerol), carriers such as e.g. natural mineral powders (e.g. kaolins, clays, talc, chalk), synthetic mineral powders (e.g. highly dispersed silicic acid and silicates), sugars (e.g. cane sugar, lactose and glucose), emulsifiers (e.g. lignin, spent sulphite liquors, methylcellulose, starch and polyvinylpyrrolidone) and lubricants (e.g. magnesium stearate, talc, stearic acid and sodium lauryl sulphate).

For oral use the tablets may obviously contain, in addition to the carriers specified, additives such as sodium citrate, calcium carbonate and dicalcium phosphate together with various additional substances such as starch, preferably potato starch, gelatin and the like. Lubricants such as magnesium stearate, sodium lauryl sulphate and talc may also be used to produce the tablets. In the case of aqueous suspensions the active substances may be combined with various flavour enhancers or colourings in addition to the abovementioned excipients.

It is also preferred if the compounds of formula I are administered by inhalation, particularly preferably if they are administered once or twice a day. For this purpose, the compounds of formula I have to be made available in forms suitable for inhalation. Inhalable preparations include inhalable powders, propellant-containing metered-dose aerosols or propellant-free inhalable solutions which are optionally in admixture with conventional physiologically acceptable excipients.

Within the scope of the present invention, the term propellant-free inhalable solutions also includes concentrates or sterile inhalable solutions ready for use. The formulations which may be used within the scope of the present invention are described in more detail in the next part of the specification.

EXPERIMENTAL SECTION

As a rule, ^{1}H-NMR and/or mass spectra have been obtained for the compounds prepared. Unless otherwise stated, R_f values are obtained using ready-made silica gel TLC plates 60 F254 (E. Merck, Darmstadt, Item no. 1.05714) without chamber saturation.

The ratios given for the eluants relate to units by volume of the solvents in question. The units by volume specified for NH_3 refer to a concentrated solution of NH_3 in water.

Unless otherwise stated, the acid, base and salt solutions used for working up the reaction solutions are aqueous systems of the specified concentrations.

For chromatographic purification, silica gel made by Millipore (MATREX^{TM}, 35-70 µm) is used.

The HPLC data given are measured using the parameters shown below:

Method A:

time (min)	percent by volume of water (with 0.1% formic acid)	percent by volume of acetonitrile (with 0.1% formic acid)
0	95	5
4.5	10	90
5	10	90
5.5	90	10

Analytical column: Zorbax column (Agilent Technologies), SB (Stable Bond) C18; 3.5 µm; 4.6 x 75 mm; column temperature: 30°C; flow: 1.6 mL / min; injection volume: 5 µL; detection at 254 nm

Method B:

time (min)	percent by volume of water (with 0.1% formic acid)	percent by volume of acetonitrile (with 0.1% formic acid)
0	95	5
9	10	90
10	10	90
11	95	5

Analytical column: Zorbax column (Agilent Technologies), SB (Stable Bond) C18; 3.5 µm; 4.6 x 75 mm; column temperature: 30°C; flow: 0.8 mL / min; injection volume: 5 µL; detection at 254 nm

Method C:

time (min)	percent by volume of water (with 0.1% formic acid)	percent by volume of acetonitrile (with 0.1% formic acid)

0	95	5
4	50	50
4.5	10	90
5	10	90
5.5	90	10

Analytical column: Zorbax column (Agilent Technologies), SB (Stable Bond) C18; 3.5 µm; 4.6 x 75 mm; column temperature: 30°C; flow: 1.6 mL / min; injection volume: 5 µL; detection at 254 nm

Method D:

time (min)	percent by volume of water (with 0.04% TFA)	percent by volume of acetonitrile (with 0.04% TFA)
0	80	20
30	20	80

Analytical column: Waters Symmetry C8, 5 µm, 4.6 X 150 mm; column temperature: 25°C, flow: 1.3 ml/min, injection volume: 5 µl, detection at 254 nm.

Method E:

time (min)	percent by volume of water (with 0.04% TFA)	percent by volume of acetonitrile (with 0.04% TFA)
0	80	20
15	20	80
17	20	80

Analytical column: Symmetry C8 Waters – 4.6 X 150 mm; 5 micron, flow: 1.3 ml/min, column temperature: 25°C, detection at 254 nm.

In preparative HPLC purifications as a rule the same gradients are used as were used to collect the analytical HPLC data.
The products are collected under mass control and the fractions containing the product are combined and freeze-dried.
If no detailed information is given as to the configuration, it is not clear whether it is a pure enantiomer or whether partial or even complete racemisation has occurred.

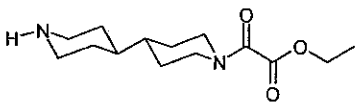
The following abbreviations are used in the description of the experiments:

Cyc	cyclohexane
DCM	dichloromethane
DIPE	diisopropylether
DMF	*N*,*N*-dimethylformamide
EtOAc	ethyl acetate
EtOH	ethanol
HATU	*O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium-hexafluoro-phosphate
AcOH	acetic acid
i.vac.	*in vacuo* (under vacuum)
MeOH	methanol
MTBE	*tert*-butylmethylether
NaOAc	sodium acetate
NMP	*N*-methylpyrroldinone
PE	petroleum ether
RT	ambient temperature
TBTU	*O*-(benzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium-tetrafluoroborate
TFA	trifluoroacetic acid
THF	tetrahydrofuran

Preparation of the starting compounds:

Amine A1

Ethyl [4,4']bipiperidinyl-1-yl-oxo-acetate



A1a) *tert*-butyl 1'-ethoxyoxalyl-[4,4']bipiperidinyl-1-carboxylate

1.68 mL (15.0 mmol) ethyl chloro-oxo-acetate were slowly added dropwise to a solution of 4.0 g (14.9 mmol) *tert*-butyl [4,4']bipiperidinyl-1-carboxylate and 2.15 mL (15.4 mmol) triethylamine in 80 mL DCM while cooling with ice and the reaction mixture was stirred for 1 h at RT. A little water was added to the reaction solution, the organic phase was separated off and dried over Na_2SO_4. After the desiccant and solvent had been eliminated the residue was taken up in EtOAc and filtered through silica gel, wherein the product was eluted with EtOAc. After evaporation i.vac. the product was obtained, which was further reacted without purification.

Yield: 3.1 g (57% of theory)

ESI-MS: $(M+NH_4)^+ = 386$

A1b) Ethyl [4,4']bipiperidinyl-1-yl-oxo-acetate

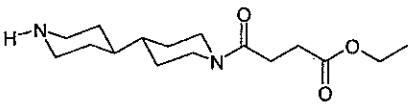
5 mL TFA were added dropwise to a solution of 3.08 g (8.36 mmol) *tert*-butyl 1'-ethoxyoxalyl-[4,4']bipiperidinyl-1-carboxylate in 40 mL DCM and the reaction mixture was stirred for 4 h at RT. The mixture was evaporated down i.vac., the residue was taken up in 50 mL DCM and this solution was slowly stirred into an ice-cooled solution of 4 g Na_2CO_3 in 20 mL water. After the addition had ended the mixture was stirred for a further 15 min, the organic phase was separated off, the aqueous phase was extracted twice more with DCM and the combined organic phases were dried over Na_2SO_4. After the desiccant and solvent had been eliminated the product was obtained as the hydrogen carbonate salt.

Yield: 2.33 g (84% of theory)

ESI-MS: $(M+H)^+ = 269$

Amine A2

ethyl 4-[4,4']bipiperidinyl-1-yl-4-oxo-butanoate



A2a) *tert*-butyl 1'-(3-carboxy-propionyl)-[4,4']bipiperidinyl-1-carboxylate

A solution of 4.07 g (41.0 mmol) succinic anhydride in 50 mL THF was slowly added dropwise to a solution of 10.0 g (37.0 mmol) *tert*-butyl [4,4']bipiperidinyl-1-carboxylate in 100 mL THF and the reaction mixture was stirred overnight at RT. To complete the reaction a further 2.0 g (20.0 mmol) succinic anhydride were added, the reaction mixture was stirred for 4 h at 50°C and overnight at RT. The mixture was carefully combined with 200 mL 7.5% K_2CO_3 solution and 200 mL EtOAc, the organic phase was separated off, extracted again with 100 mL 7.5% K_2CO_3 solution and the combined aqueous phases were acidified with 10% citric acid solution. The aqueous phase was extracted with 300 mL EtOAc, the organic phase was separated off and the solvent was eliminated i.vac..

Yield: 11.7 g (85% of theory)

ESI-MS: $(M-H)^-$ = 367

A2b) ethyl 4-[4,4']bipiperidinyl-1-yl-4-oxo-butanoate

A solution of 11.7 g (31.7 mmol) *tert*-butyl 1'-(3-carboxy-propionyl)-[4,4']bipiperidinyl-1-carboxylate in 250 mL ethanolic HCl (1.25 M) was stirred overnight at RT. The mixture was evaporated to dryness i.vac., the residue was taken up in 100 mL EtOAc and 100 mL 15% K_2CO_3 solution, the organic phase was separated off and dried over Na_2SO_4. After the desiccant and solvent had been eliminated the product was further reacted without purification.

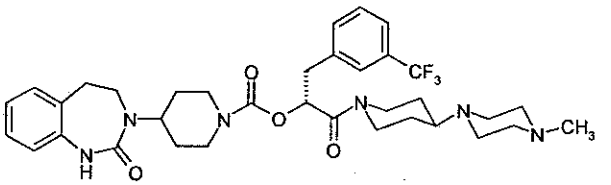
Yield: 4.3 g (46% of theory)

ESI-MS: $(M+H)^+$ = 297

Preparation of the final compounds:

Example 1

(*R*)-2-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-2-oxo-1-(3-trifluoromethyl-benzyl)-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate



1a) (*Z*,*E*)-2-acetylamino-3-(3-trifluoromethyl-phenyl)-acrylic acid

A solution of 15.8 g (115 mmol) 3-trifluoromethyl-benzaldehyde and 21.3 g (182 mmol) *N*-acetylglycine in 60 mL acetic anhydride was heated for 4 h to 120°C (bath temperature). After cooling 40 mL water were slowly added and the mixture was stirred for 1 h at 80°C. After cooling it was combined with 400 mL water and 150 mL toluene, stirred for 1 h, the precipitate formed was filtered off, washed with toluene and dried at 50°C.

Yield: 16.7 g (53% of theory)

ESI-MS: $(M+H)^+ = 274$

R_f = 0.4 (silica gel, DCM/MeOH/AcOH 90:10:1)

1b) 2-oxo-3-(3-trifluoromethyl-phenyl)-propionic acid

200 mL 4 M HCL were added dropwise to a suspension of 16.6 g (60.8 mmol) (*Z*,*E*)-2-acetylamino-3-(3-trifluoromethyl-phenyl)-acrylic acid in 200 mL 1,4-dioxane heated to 80°C (bath temperature), the reaction mixture was refluxed for 1.5 h and then stirred overnight at RT. To complete the reaction the mixture was refluxed for a further 4 h. The organic solvent was eliminated i.vac., the aqueous residue was combined with NaOH until an alkaline reaction occurred, washed with MTBE and acidified with HCl. The mixture was extracted exhaustively with EtOAc and the combined organic phases were dried over $MgSO_4$. After the desiccant and solvent

had been eliminated the desired product was obtained, which was further reacted without purification.

Yield: 5.7 g (40% of theory)

ESI-MS: $(M-H)^-$ = 231

R_f = 0.19 (silica gel, DCM/MeOH/Cyc/NH_3 70:15:15:2)

1c) (*R*)-2-hydroxy-3-(3-trifluoromethyl-phenyl)-propionic acid

Under a nitrogen atmosphere a solution of 11.8 g (36.8 mmol) (1*R*)-B-chlorodiisopinocampheylborane in 40 mL THF was added dropwise to a solution, cooled to -35°C, of 5.70 g (24.6 mmol) 2-oxo-3-(3-trifluoromethyl-phenyl)-propionic acid and 4.4 mL (31.4 mmol) triethylamine in 60 mL THF, within 15 min, and the reaction solution was stirred overnight at RT. Then the reaction solution was carefully made alkaline with 20 mL 1 M NaOH while cooling with ice and stirred for 30 min. 40 mL EtOAc was added, the aqueous phase was separated off, the organic phase was washed three times with 15 mL 1 M NaOH solution and once with 15 mL water. The combined aqueous phases were acidified with semiconcentrated HCl, extracted twice with 40 mL EtOAc and the combined organic phases were dried over $MgSO_4$. After the desiccant and solvent had been eliminated the product was obtained, which was further reacted without purification.

Yield: 4.25 g (74% of theory)

ESI-MS: $(M-H)^-$ = 233

R_f = 0.35 (silica gel, DCM/MeOH/Cyc/NH_3 70:15:15:2)

1d) methyl (*R*)-2-hydroxy-3-(3-trifluoromethyl-phenyl)-propionate

A solution of 4.20 g (17.9 mmol) (*R*)-2-hydroxy-3-(3-trifluoromethyl-phenyl)-propionic acid in 80 mL methanolic HCl was stirred for 70 h at RT. The reaction solution was evaporated down i.vac., the residue was taken up in water and exhaustively extracted with EtOAc. The combined organic phases were washed three times with 15% K_2CO_3 solution and once with water and dried over $MgSO_4$.

After the desiccant and solvent had been eliminated the residue was further reacted without purification.

Yield: 2.47 g (55% of theory)

ESI-MS: $(M+H)^+ = 249$

R_f = 0.73 (silica gel, DCM/MeOH/Cyc/NH_3 70:15:15:2)

1e) (*R*)-1-methoxycarbonyl-2-(3-trifluoromethyl-phenyl)-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate

Under a nitrogen atmosphere 2.10 g (10.4 mmol) 4-nitrophenyl chloroformate were added to a solution of 1.64 g (13.4 mmol) 4-dimethylaminopyridine in 40 mL pyridine and stirred for 3 h at RT. Then 2.47 g (9.95 mmol) methyl (*R*)-2-hydroxy-3-(3-trifluoromethyl-phenyl)-propionate in 20 mL pyridine were added and the reaction mixture was stirred for 2.5 h at RT. The reaction solution was combined with 4.1 g (10.9 mmol) 3-piperidin-4-yl-1,3,4,5-tetrahydro-1,3-benzodiazepin-2-one (purity 65%) and stirred for 20 h at RT. The mixture was evaporated down i.vac., the residue was taken up in 60 mL EtOAc, the organic phase was washed twice with 15% K_2CO_3 solution, four times with saturated $NaHCO_3$ solution and dried over Na_2SO_4. After the desiccant and solvent had been eliminated the residue was purified by chromatography (silica gel, Cyc/EtOAc 1:2).

Yield: 3.16 g (61% of theory)

ESI-MS: $(M+H)^+ = 520$

R_f = 0.93 (silica gel, EtOAc/MeOH/NH_3 80:20:2)

1f) (*R*)-1-carboxy-2-(3-trifluoromethyl-phenyl)-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate

A solution of 0.22 g (9.00 mmol) LiOH in 40 mL water was added to a solution of 3.10 g (5.97 mmol) (*R*)-1-methoxycarbonyl-2-(3-trifluoro-methyl-phenyl)-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate in 80 mL THF and the reaction mixture was stirred for 1 h at RT. The organic solvent was eliminated i.vac., the aqueous residue was combined with 80 mL water and

acidified with 1 M HCl. The precipitate formed was suction filtered and dried overnight at 35°C.

Yield: 2.80 g (93% of theory)

ESI-MS: $(M+H)^+ = 506$

R_f = 0.58 (silica gel, EtOAc/MeOH/NH_3 70:30:3)

1g) (*R*)-2-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-2-oxo-1-(3-trifluoromethyl-benzyl)-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate

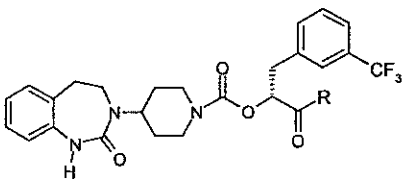
30 mg (0.16 mmol) 1-methyl-4-piperidin-4-yl-piperazine were added at RT to a solution of 80.0 mg (0.16 mmol) (*R*)-1-carboxy-2-(3-trifluoromethyl-phenyl)-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate, 61 mg (0.19 mmol) TBTU and 27 µL (0.20 mmol) triethylamine in 1 mL DMF and the reaction solution was stirred for 70 h at RT. This was purified by HPLC without any further working up; the fractions containing the product were combined and lyophilised.

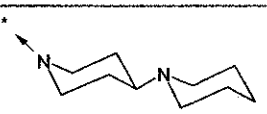
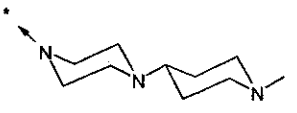
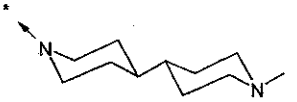
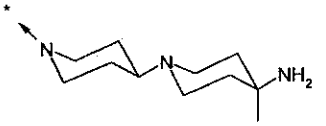
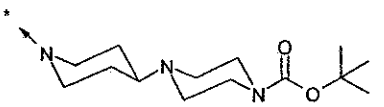
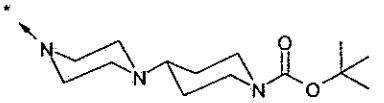
Yield: 67 mg (63% of theory)

ESI-MS: $(M+H)^+ = 671$

R_f = 0.4 (silica gel, DCM/MeOH/Cyc/NH_3 70:15:15:2)

The following compounds were prepared analogously from in each case 80 mg (Examples 1.1 to 1.4) or 140 mg (Examples 1.5 and 1.6) (*R*)-1-carboxy-2-(3-trifluoro-methyl-phenyl)-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate and the corresponding amount of amine:

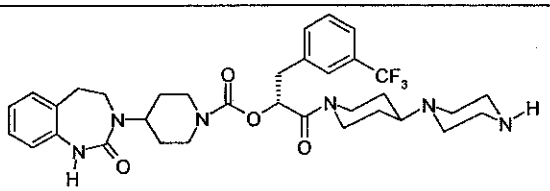


Example	R	Yield (%)	Mass spectrum	R_f ##) (method)
1.1		93	656 $[M+H]^+$	0.68
1.2		64	671 $[M+H]^+$	0.35
1.3		74	670 $[M+H]^+$	0.53
1.4		48	685 $[M+H]^+$	5.1 min (B)
1.5		62	757 $[M+H]^+$	0.51
1.6		71	757 $[M+H]^+$	0.50

##) (silica gel, DCM/MeOH/ Cyc/NH_3 70:15:15:2) or retention time HPLC

Example 1.7

(*R*)-1-(3-methyl-benzyl)-2-oxo-2-(4-piperazin-1-yl-piperidin-1-yl)-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate



A solution of 131 mg (0.17 mmol) *tert*-butyl 4-{1-[(*R*)-2-[4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carbonyloxy]-3-(3-trifluoromethyl-phenyl)-propionyl]-piperidin-4-yl}-piperazine-1-carboxylate (Example 1.5) in 1.5 mL 4 M HCl was stirred overnight at RT. The reaction solution was purified by HPLC

without any further working up. The fractions containing the product were combined and lyophilised.

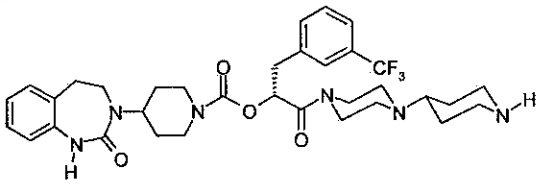
Yield: 75 mg (67% of theory)

ESI-MS: $(M+H)^+ = 657$

R_f = 0.38 (silica gel, DCM/MeOH/Cyc/NH_3 70:15:15:2)

Example 1.8

(*R*)-2-oxo-2-(4-piperidin-4-yl-piperazin-1-yl)-1-(3-trifluoromethyl-benzyl)-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate



Analogously to Example 1.7 the product was obtained from 149 mg (0.20 mmol) (*R*)-1-(3-trifluoromethyl-benzyl)-2-[4-(1-*tert*-butoxy-carbonyl-piperidin-4-yl)-piperazin-1-yl]-2-oxo-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate (Example 1.6).

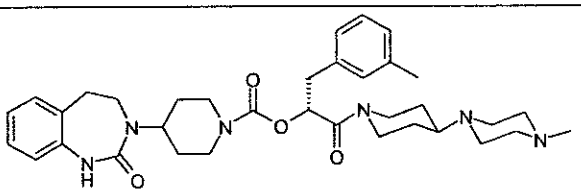
Yield: 66 mg (51% of theory)

ESI-MS: $(M+H)^+ = 657$

R_f = 0.18 (silica gel, DCM/MeOH/Cyc/NH_3 70:15:15:2)

Example 2

(*R*)-2-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-2-oxo-1-(3-methyl-benzyl)-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate



2a) (*Z,E*)-2-acetylamino-3-*m*-tolyl-acrylic acid

Analogously to Example 1a the product could be obtained from 25.0 g (212 mmol) 3-methyl-benzaldehyde and 24.9 g (212 mmol) *N*-acetylglycine.

Yield:	26.0 g (56% of theory)
ESI-MS:	$(M+H)^+ = 220$
retention time (HPLC):	5.4 min (method B)

2b) 2-oxo-3-*m*-tolyl-propionic acid

400 mL 4 M HCl were added to a solution of 13.0 g (59.3 mmol) (*Z,E*)-2-acetylamino-3-*m*-tolyl-acrylic acid in 200 mL 1,4-dioxane and the reaction mixture was refluxed for 2.5 h. The organic solvent was evaporated down i.vac., the precipitate formed was suction filtered and dried. This was taken up in 300 mL EtOAc, the organic phase was washed twice with 200 mL water and dried over Na_2SO_4. After the desiccant and solvent had been eliminated the residue was reacted further without purification.

Yield:	9.2 g (88% of theory)
ESI-MS:	$(M-H)^- = 177$
retention time (HPLC):	7.3 min (method B)

2c) (*R*)-2-hydroxy-3-*m*-tolyl-propionic acid

Analogously to Example 1c the product could be obtained from 9.24 g (51.9 mmol) 2-oxo-3-*m*-tolyl-propionic acid and 24.0 g (74.8 mmol) (1*R*)-B-chlorodiisopinocampheylborane.

Yield:	8.4 g (90% of theory)
ESI-MS:	$(M-H)^- = 179$
retention time (HPLC):	7.2 min (method B)

2d) methyl (*R*)-2-hydroxy-3-*m*-tolyl-propionate

3.74 mL (51.28 mmol) $SOCl_2$ were slowly added dropwise to a solution, cooled to 0°C, of 8.40 g (46.6 mmol) (*R*)-2-hydroxy-3-*m*-tolyl-propionic acid in 200 mL MeOH and after the addition had ended the reaction mixture was stirred for 1 h at

RT. The mixture was evaporated down i.vac. and the residue was purified by chromatography (silica gel, Cyc/EtOAc 3:1).

Yield: 6.28 g (69% of theory)

ESI-MS: $(M+H)^+ = 195$

retention time (HPLC): 6.9 min (method B)

2e) (*R*)-1-methoxycarbonyl-2-*m*-tolyl-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate

Analogously to Example 1e the product could be obtained from 1.12 g (5.76 mmol) methyl (*R*)-2-hydroxy-3-*m*-tolyl-propionate and 1.41 g (5.76 mmol) 3-piperidin-4-yl-1,3,4,5-tetrahydro-1,3-benzodiazepin-2-one.

Yield: 2.07 g (77% of theory)

ESI-MS: $(M+H)^+ = 466$

retention time (HPLC): 9.0 min (method B)

2f) (*R*)-1-carboxy-2-*m*-tolyl-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate

Analogously to Example 1f the product could be obtained from 2.07 g (4.45 mmol) (*R*)-1-methoxycarbonyl-2-*m*-tolyl-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate and 0.16 g (6.72 mmol) LiOH.

Yield: 1.86 g (93% of theory)

ESI-MS: $(M+H)^+ = 452$

retention time (HPLC): 8.0 min (method B)

2g) (*R*)-2-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-2-oxo-1-(3-methyl-benzyl)-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate

A solution of 80.0 mg (0.18 mmol) (*R*)-1-carboxy-2-*m*-tolyl-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate, 57 mg (0.18 mmol) TBTU and 31 µL (0.22 mmol) triethylamine in 1 mL DMF were stirred for 1 h at RT. Then 33 mg (0.18 mmol) 1-methyl-4-piperidin-4-yl-piperazine were added to the

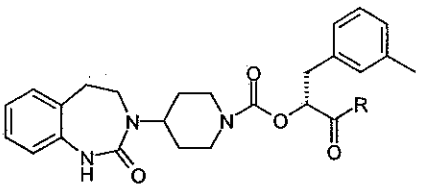
reaction solution, which was then stirred overnight at RT. It was purified by HPLC without any further working up; the fractions containing the product were combined and lyophilised.

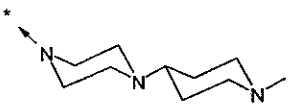
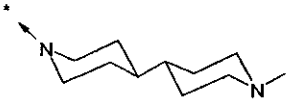
Yield: 46.7 mg (43% of theory)

ESI-MS: $(M+H)^+ = 617$

retention time (HPLC): 5.5 min (method B)

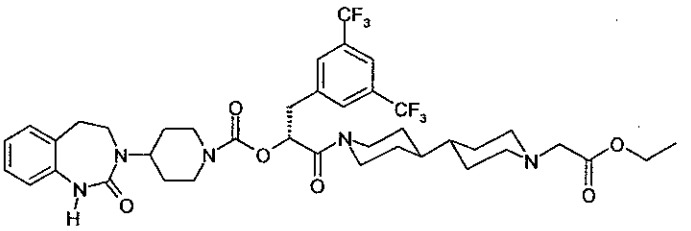
The following compounds were prepared analogously from in each case 80 mg (*R*)-1-carboxy-2-*m*-tolyl-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate and the corresponding amount of amine:



Example	R	Yield (%)	Mass spectrum	retention time HPLC (method)
2.1		80	617 $[M+H]^+$	5.0 min (B)
2.2		75	616 $[M+H]^+$	6.2 min (B)

Example 3

(*R*)-1-(3,5-bis-trifluoromethyl-benzyl)-2-(1'-ethoxycarbonylmethyl-4,4'-bipiperidinyl-1-yl)-2-oxo-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate



3a) methyl 2-acetylamino-3-(3,5-bis-trifluoromethyl-phenyl)acrylate

Under a nitrogen atmosphere 50.0 g (171 mmol) 3,5-bis-(trifluoromethyl)-bromobenzene and 25.0 g (171 mmol) methyl 2-acetylamino-acrylate in 475 mL triethylamine and 250 mL acetonitrile were combined with 3.9 g (12.4 mmol) tri-*o*-tolyl-phosphane and 2.8 g (12.5 mmol) $Pd(OAc)_2$ and stirred for 18 h at 80°C. After the reaction had ended the reaction mixture was evaporated down i.vac. to approx. 200 mL, combined with 400 mL EtOAc and 400 mL water, the precipitate was suction filtered and the phases were separated. The organic phase was dried over Na_2SO_4, combined with activated charcoal, filtered and evaporated to dryness. The residue was stirred with DIPE, suction filtered and dried i.vac..

Yield: 19.5 g (32 % of theory)

ESI-MS: $(M+H)^+ = 356$

R_f = 0.76 (silica gel, PE/EtOAc 1:1)

3b) 3-(3,5-bis-trifluoromethyl-phenyl)-2-oxo-propionic acid

19.5 g (54.9 mmol) methyl 2-acetylamino-3-(3,5-bis-trifluoromethyl-phenyl)-acrylate in 100 mL 1,4-dioxane were heated to 100°C bath temperature, combined with 100 mL 4 M HCl and stirred for 8 h at 100°C bath temperature. The reaction mixture was evaporated down i.vac., the crystals were suction filtered, washed with water and dried in the drying cupboard at 50°C.

Yield: 16.1 g (98 % of theory)

ESI-MS: $(M-H)^- = 299$

R_f = 0.18 (silica gel, EtOAc)

3c) (*R*)-3-(3,5-bis-trifluoromethyl-phenyl)-2-hydroxy-propionic acid

16.1 g (53.6 mmol) 3-(3,5-bis-trifluoromethyl-phenyl)-2-oxo-propionic acid in 9.5 (70.0 mmol) triethylamine and 100 mL THF were combined at -35°C with a solution of 26.0 (81.1 mmol) (1R)-B-chlorodiisopinocampheylborane in 40 mL THF within 30 min, stirred for 1 h at this temperature and stirred overnight at RT. After the reaction had ended the reaction mixture was made alkaline at 0°C with 160 mL 1 M NaOH, stirred for 15 min, combined with 100 mL MTBE and the phases were separated. The organic phase was washed with 50 mL water and 50 mL 1 M NaOH. The combined aqueous phases were acidified with 4 M HCl, exhaustively extracted with MTBE, the combined organic phases were dried over Na_2SO_4, suction filtered through activated charcoal and evaporated down i.vac.. The product was reacted further without purification.

Yield: 12.5 g (77% of theory)

ESI-MS: $(M-H)^-$ = 301

R_f = 0.45 (silica gel, EtOAc)

3d) methyl (*R*)-3-(3,5-bis-trifluoromethyl-phenyl)-2-hydroxy-propionate

12.5 g (41.4 mmol) of (*R*)-3-(3,5-bis-trifluoromethyl-phenyl)-2-hydroxy-propionic acid in 150 mL methanolic HCl (1.25 M) were stirred for 4 h at RT and then evaporated down i.vac.. The residue was taken up in EtOAc and washed with saturated $NaHCO_3$ solution, the organic phase was dried over Na_2SO_4, suction filtered through activated charcoal and evaporated down i.vac.. The residue was stirred with PE, suction filtered and evaporated down i.vac.. The product was reacted further without purification.

Yield: 11.4 g (87% of theory)

ESI-MS: $(M+H)^+$ = 316

R_f = 0.80 (silica gel, PE/EtOAc 1:1)

3e) (*R*)-2-(3,5-bis-trifluoromethyl-phenyl)-1-methoxycarbonyl-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate

Analogously to Example 1e the product was obtained from 6.0 g (8.2 mmol)

methyl (*R*)-3-(3,5-bis-trifluoromethyl-phenyl)-2-hydroxy-propionate and 5.13 g (20.9 mmol) 3-piperidin-4-yl-1,3,4,5-tetrahydro-1,3-benzodiazepin-2-one. Purification was carried out by chromatography (silica gel, gradient PE/EtOAc 1:1 to 1:9).

Yield: 5.1 g (46 % of theory)

ESI-MS: $(M+H)^+ = 588$

R_f = 0.63 (silica gel, DCM/MeOH/cyc/NH_3 70:15:15:2)

3f) (*R*)-2-(3,5-bis-trifluoromethyl-phenyl)-1-carboxy-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate

A solution of 307 mg (12.8 mmol) LiOH in 5 mL water was added to a solution of 5.0 g (8.5 mmol) of (*R*)-2-(3,5-bis-trifluoromethyl-phenyl)-1-methoxy-carbonyl-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate in 50 mL THF and the reaction mixture was stirred overnight at RT. The mixture was evaporated down i.vac., the residue was taken up in water, acidified with 1 M HCl, the precipitate was filtered off and dried in the vacuum drying cupboard at 40°C.

Yield: 4.5 g (92% of theory)

ESI-MS: $(M+H)^+ = 574$

R_f = 0.32 (silica gel,DCM/MeOH/cyc/NH_3 70:15:15:2)

3g) (*R*)-1-(3,5-bis-trifluoromethyl-benzyl)-2-(1'-ethoxycarbonylmethyl-4,4'-bipiperidinyl-1-yl)-2-oxo-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate

50 mg (0.20 mmol) ethyl [4,4']bipiperidinyl-1-yl-acetate were added at RT to a solution of 100 mg (0.17 mmol) (*R*)-2-(3,5-bis-trifluoromethyl-phenyl)-1-carboxy-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-benzodiazepin-3-yl)-piperidine-1-carboxylate, 61 mg (0.20 mmol) TBTU and 33 µL (0.16 mmol) ethyldiisopropylamine in 1 mL DMF and the reaction mixture was stirred overnight at RT. The reaction solution was filtered through a syringe filter and purified directly by HPLC without any further working up. The fractions containing the product were combined and lyophilised.

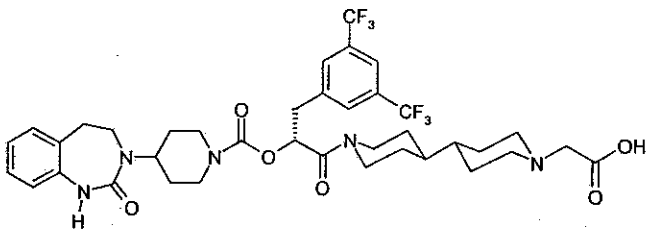
Yield: 55 mg (39% of theory)

ESI-MS: $(M+H)^+ = 810$

retention time (HPLC-MS): 7.3 min (method B)

Example 3.1

(*R*)-1-(3,5-bis-trifluoromethyl-benzyl)-2-(1'-carboxymethyl-4,4'-bipiperidinyl-1-yl)-2-oxo-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate



A solution of 1.5 mg (0.06 mmol) LiOH in 1 mL water was added to a solution of 35 mg (0.04 mmol) (*R*)-1-(3,5-bis-trifluoromethyl-benzyl)-2-(1'-ethoxycarbonylmethyl-4,4'-bipiperidinyl-1-yl)-2-oxo-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate (Example 3g) in 5 mL THF and the reaction solution was stirred overnight at RT. The mixture was evaporated down i.vac., the residue was taken up in water, acidified with 1 N HCl, the precipitate was filtered off and dried in the vacuum drying cupboard.

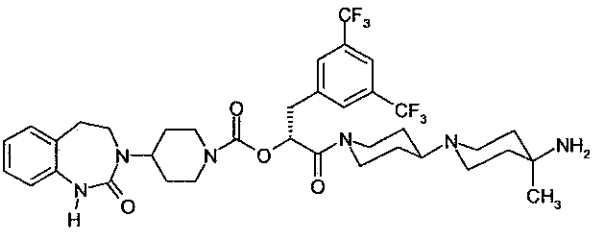
Yield: 15 mg (44% of theory)

ESI-MS: $(M+H)^+ = 782$

R_f = 0.41 (silica gel, DCM/MeOH/Cyc/NH_3 70:15:15:2)

Example 3.2

(*R*)-2-(4-amino-4-methyl-1,4'-bipiperidinyl-1'-yl)-1-(3,5-bis-trifluoromethyl-benzyl)-2-oxo-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate

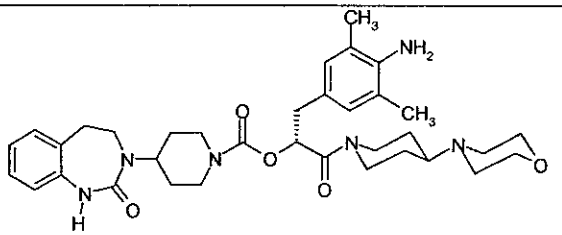


52 mg (0.14 mmol) *tert*-butyl (4-methyl-[1,4']bipiperidinyl-4-yl)-carbamate (used as the bis-hydrochloride salt) were added at RT to a solution of 80.0 mg (0.14 mmol) (*R*)-2-(3,5-bis-trifluoromethyl-phenyl)-1-carboxy-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate, 58 mg (0.18 mmol) TBTU and 140 µL (1.00 mmol) triethylamine in 1.8 mL DMF and the reaction solution was shaken overnight at RT. It was purified by HPLC without any further working up; the fractions containing the product were combined and lyophilised. The coupling product was dissolved in 4 mL DCM, the solution was combined with 0.5 mL TFA, stirred for 5 h at RT and then left overnight at RT during which time the solvent evaporated. The residue was taken up in 2 mL 15% K_2CO_3 solution, extracted twice with 2 mL DCM and the combined organic phases were shaken overnight during which time the solvent evaporated. The residue was purified by HPLC; the fractions containing the product were combined and lyophilised, and the product was obtained as the formate salt.

Yield:	47 mg (42% of theory)
ESI-MS:	$(M+H)^+ = 753$
retention time (HPLC):	5.4 min (method B)

Example 4

(*R*)-1-(4-amino-3,5-dimethyl-benzyl)-2-(4-morpholin-4-yl-piperidin-1-yl)-2-oxo-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate



4a) methyl (*Z,E*)-2-acetylamino-3-(4-amino-3,5-dimethyl-phenyl)-acrylate

Under a nitrogen atmosphere first of all a solution of 90.0 g (441 mmol) 4-bromo-2,6-dimethyl-phenylamine in 200 mL acetonitrile was added to a mixture of 7.2 g (32.1 mmol) $Pd(OAc)_2$ and 10.1 g (32.1 mmol) tri-*o*-tolyl-phosphane in 1.2 L triethylamine and 600 mL acetonitrile and then a solution of 65.0 g (445 mmol) methyl 2-acetylamino-acrylate in 200 mL acetonitrile was added dropwise. After the addition had ended the mixture was stirred for 18 h at 80°C. To complete the reaction the reaction mixture was again combined with 4.0 g (17.8 mmol) $Pd(OAc)_2$ and 5.0 g (16.4 mmol) tri-*o*-tolyl-phosphane and kept for another 5 h at 80°C. The mixture was evaporated down i.vac to approx. 200 mL, the residue was combined with 400 mL EtOAc, the residue (A) was filtered and the organic phase was dried over Na_2SO_4. After elimination of the desiccant by filtration over activated charcoal the filtrate was evaporated down to about 100 mL, the precipitated substance was suction filtered, washed with 30 mL EtOAc and dried. The above residue A was combined with 1 L DCM, Na_2SO_4 and activated charcoal and filtered through Celite. The filtrate was evaporated down, the residue was combined with 350 mL diethyl ether, the precipitate formed was suction filtered, then washed with 100 mL diethyl ether and dried. The two product fractions were combined.

Yield:	74.8 g (65% of theory)
ESI-MS:	$(M+H)^+ = 263$
R_f =	0.51 (silica gel, EtOAc)

4b) 3-(4-amino-3,5-dimethyl-phenyl)-2-oxo-propionic acid

A suspension of 74.0 g (282 mmol) methyl (Z,E)-2-acetylamino-3-(4-amino-3,5-dimethyl-phenyl)-acrylate in 500 mL 1,4-dioxane was heated to 100°C and combined with 460 mL 4 M HCl, whereupon a solution was formed. The mixture was heated for another 8 h at 100°C and the cooled solution was evaporated down i.vac. to approx. 200 mL, during which time the product crystallised out. It was filtered, the residue was washed with 50 mL water and the product was dried at 50°C.

Yield:	43.6 g (63% of theory)
ESI-MS:	$(M+H)^+$ = 208
R_f =	0.68 (silica gel, PE/EtOAc 1:1)

4c) methyl (*R*)-3-(4-amino-3,5-dimethyl-phenyl)-2-hydroxy-propionate

Under a nitrogen atmosphere a mixture of 20.0 g (82.1 mmol) 3-(4-amino-3,5-dimethyl-phenyl)-2-oxo-propionic acid and 25.7 mL (189 mmol) triethylamine in 400 mL THF was cooled to -35°C. Then a solution of 40.0 g (125 mmol) (1*R*)-B-chlorodiisopinocampheylborane in 100 mL THF was added dropwise so that the reaction temperature remained between -35°C and -25°C. The reaction mixture was kept for 1 h at this temperature, the cooling bath was removed and the reaction mixture was stirred overnight at RT. THF was evaporated off i.vac., the residue was combined with methanolic HCl (1.25 M) and stirred for 2 h at RT. It was evaporated down i.vac., the residue was taken up in 2 M HCl and extracted exhaustively with EtOAc. The aqueous phase was made alkaline with semiconcentrated NaOH and exhaustively extracted with EtOAc. The combined organic phases were dried over Na_2SO_4, suction filtered through activated charcoal and evaporated down. The product was obtained as a brown oil.

Yield:	8.3 g (45% of theory)
ESI-MS:	$(M+H)^+$ = 224
R_f =	0.46 (silica gel, PE/EtOAc 1:1)

4d) (*R*)-2-(4-amino-3,5-dimethyl-phenyl)-1-methoxycarbonyl-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate

Analogously to Example 1e the desired product was obtained from 4.0 g (17.9 mmol) methyl (*R*)-3-(4-amino-3,5-dimethyl-phenyl)-2-hydroxy-propionate and 4.8 g (19.6 mmol) 3-piperidin-4-yl-1,3,4,5-tetrahydro-1,3-benzodiazepin-2-one.

Yield:	3.2 g (36% of theory)
ESI-MS:	$(M+H)^+$ = 495
R_f =	0.35 (silica gel, DCM/MeOH/NH_3 90:10:1)

4e) (*R*)-2-(4-amino-3,5-dimethyl-phenyl)-1-carboxy-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate

A solution of 500 mg (20.9 mmol) LiOH in 10 mL water was added to a solution of 6.7 g (13.6 mmol) of (*R*)-2-(4-amino-3,5-dimethyl-phenyl)-1-methoxycarbonyl-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate in 50 mL THF and the reaction mixture was stirred overnight at RT. To complete the reaction another 300 mg (12.5 mmol) LiOH were added and the reaction solution was stirred for 3 h at 40°C. It was evaporated down i.vac., the residue was taken up in 15% K_2CO_3 solution and extracted exhaustively with DCM. The aqueous phase was acidified with 4 M HCl, exhaustively extracted with DCM and the combined organic phases were dried over Na_2SO_4. After the desiccant and solvent had been eliminated the residue was reacted further without purification.

Yield:	4.2 g (65% of theory)
ESI-MS:	$(M+H)^+$ = 481
R_f =	0.21 (silica gel, DCM/MeOH/cyc/NH_3 70:15:15:2)

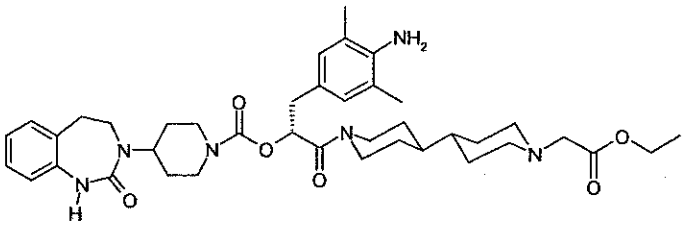
4f) (*R*)-1-(4-amino-3,5-dimethyl-benzyl)-2-(4-morpholin-4-yl-piperidin-1-yl)-2-oxo-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate

Analogously to Example 3g the product was obtained from 80 mg (0.17 mmol) (*R*)-2-(4-amino-3,5-dimethyl-phenyl)-1-carboxy-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate and 32 mg (0.19 mmol) 4-piperidin-4-yl-morpholine.

Yield:	52 mg (49% of theory)
ESI-MS:	$(M+H)^+$ = 633
retention time (HPLC):	4.9 min (method B)

Example 4.1

(*R*)-1-(4-amino-3,5-dimethyl-benzyl)-2-(1'-ethoxycarbonylmethyl-4,4'-bipiperidinyl-1-yl)-2-oxo-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate

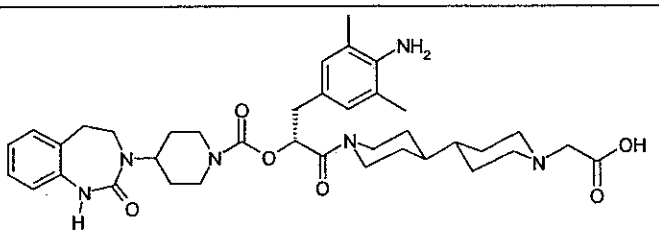


Analogously to Example 3g the product was obtained from 100 mg (0.21 mmol) (*R*)-2-(4-amino-3,5-dimethyl-phenyl)-1-carboxy-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate and 59 mg (0.23 mmol) ethyl [4,4']bipiperidinyl-1-yl-acetate.

Yield:	58 mg (39% of theory)
ESI-MS:	$(M+H)^+$ = 717
retention time (HPLC):	4.7 min (method B)

Example 4.2

(*R*)-1-(4-amino-3,5-dimethyl-benzyl)-2-(1'-carboxymethyl-4,4'-bipiperidinyl-1-yl)-2-oxo-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate



A solution of 3.1 mg (0.13 mmol) LiOH in 1 mL water was added to a solution of 55 mg (0.08 mmol) (*R*)-1-(4-amino-3,5-dimethyl-benzyl)-2-(1'-ethoxycarbonylmethyl-4,4'-bipiperidinyl-1-yl)-2-oxo-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate (Example 4.1) in 5 mL THF and the reaction mixture

was stirred overnight at RT. The mixture was evaporated down i.vac., the residue was taken up in 1 mL DMF and the crude product was purified by HPLC. The fractions containing the product were combined and lyophilised.

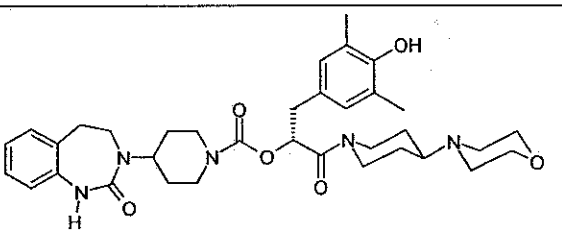
Yield: 22 mg (42% of theory)

ESI-MS: $(M+H)^+$ = 689

retention time (HPLC): 4.8 min (method B)

Example 5

(*R*)-1-(4-hydroxy-3,5-dimethyl-benzyl)-2-(4-morpholin-4-yl-piperidin-1-yl)-2-oxo-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate



5a) 2-benzyloxy-5-bromo-1,3-dimethylbenzene

39.9 g (286 mmol) K_2CO_3 were added to a solution of 50.0 g (249 mmol) 2,6-dimethyl-4-bromophenol in 500 mL DMF and stirred for 20 min. Then 34.0 mL (286 mmol) benzylchloride were slowly added dropwise and the reaction mixture was stirred for 3 h at 100°C bath temperature. After the reaction had ended the mixture was poured onto 500 mL water and exhaustively extracted with EtOAc. The organic phases were combined, dried over Na_2SO_4 and evaporated down i.vac..

Yield: quantitative

GC-MS: (M^+) = 290/292 (Br)

R_f = 0.87 (silica gel, cyc/EtOAc 3:1)

5b) methyl 2-acetylamino-3-(4-benzyloxy-3,5-dimethyl-phenyl)-acrylate

Under a nitrogen atmosphere a mixture of 40.0 g (137 mmol) 2-benzyloxy-5-

bromo-1,3-dimethylbenzene and 24.1 g (165 mmol) methyl 2-acetylamino-acrylate in 420 mL triethylamine and 200 mL acetonitrile was combined with 3.5 g (11.2 mmol) tri-*o*-tolyl-phosphane and 2.5 g (11.1 mmol) $Pd(OAc)_2$ and the mixture was stirred for 18 h at 80°C. The precipitate was suction filtered, the filtrate was evaporated down i.vac. and combined with 800 mL DCM and 800 mL water. The organic phase was separated off, suction filtered over Na_2SO_4, the solvent was removed i.vac., the residue was stirred with EtOAc, suction filtered and dried i.vac..

Yield:	31.1 g (64% of theory)
ESI-MS:	$(M+H)^+ = 354$
retention time (HPLC-MS):	8.6 min (method B)

5c) 3-(4-benzyloxy-3,5-dimethyl-phenyl)-2-oxo-propionic acid

31.1 g (88.1 mmol) methyl 2-acetylamino-3-(4-benzyloxy-3,5-dimethyl-phenyl)-acrylate in 150 mL 1,4-dioxane were combined with 125 mL 4 M HCl, stirred for 7 h at reflux temperature and stirred overnight at RT. The precipitate was suction filtered, washed with water and dried at 45°C in the vacuum drying cupboard.

Yield:	14.3 g (54 % of theory)
EI-MS:	$(M)^+ = 298$
retention time (HPLC-MS):	9.0 min (method B)

5d) (*R*)-3-(4-benzoyl-3,5-dimethyl-phenyl)-2-hydroxy-propionic acid

Under a nitrogen atmosphere a solution of 14.3 g (47.8 mmol) 3-(4-benzyloxy-3,5-dimethyl-phenyl)-2-oxo-propionic acid and 8.3 mL (59.8 mmol) triethylamine in 170 mL THF at -35°C was combined with a solution of 22.1 (69.0 mmol) (1*R*)-B-chlorodiisopinocampheylborane in 70 mL THF within 30 min. After the addition had ended the cooling bath was removed and the reaction solution was stirred overnight at RT. The reaction mixture was made alkaline at 0°C with 70 mL 1 M NaOH, combined with 100 mL MTBE, stirred for 15 min and the phases were separated. The organic phase was washed with 50 mL water and three times with 50 mL 1 M NaOH. The combined aqueous phases were acidified with semiconc.

HCl, exhaustively extracted with EtOAc and the combined organic phases were dried over Na_2SO_4. After the desiccant and solvent had been eliminated the residue was reacted further without purification.

Yield:	14.0 g (98% of theory)
ESI-MS:	$(M-H)^-$ = 299
retention time (HPLC-MS):	7.9 min (method B)

5e) methyl (*R*)-3-(4-benzyloxy-3,5-dimethyl-phenyl)-2-hydroxy-propionate

To a solution cooled to 0°C of 14.0 g (23.3 mmol) of (*R*)-3-(4-benzoyl-3,5-dimethyl-phenyl)-2-hydroxy-propionic acid in 150 mL MeOH, 2.0 mL (27.4 mmol) $SOCl_2$ were added dopwise and the reaction mixture was stirred for 1 h at RT. The reaction solution was evaporated down i.vac. and the residue was purified by chromatography (silica gel, cyc/EtOAc 3:1).

Yield:	5.7 g (78% of theory)
ESI-MS:	$(M+NH_4)^+$ = 332
retention time (HPLC-MS):	9.1 min (method B)

5f) (*R*)-2-(4-benzyloxy-3,5-dimethyl-phenyl)-1-methoxycarbonyl-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate

Under a nitrogen atmosphere 1.93 g (9.58 mmol) 4-nitrophenyl chloroformate was added to a solution of 1.17 g (9.58 mmol) 4-dimethylaminopyridine in 50 mL pyridine, stirred for 1.5 h at RT, combined with 3.0 g (9.58 mmol) methyl (*R*)-3-(4-benzyloxy-3,5-dimethyl-phenyl)-2-hydroxy-propionate and stirred for 20 min at RT. Then 2.35 g (9.58 mmol) 3-piperidin-4-yl-1,3,4,5-tetrahydro-1,3-benzodiazepin-2-one were added and the mixture was stirred for 20 h at RT. The reaction mixture was evaporated down i.vac., the residue was taken up in EtOAc, the organic phase was washed with 10% $KHSO_4$ and saturated $NaHCO_3$ solution and dried over Na_2SO_4. After the desiccant and solvent had been eliminated the residue was purified by chromatography (silica gel, gradient cyc/EtOAc 1:1 to 1:2).

Yield:	3.21 g (57% of theory)
ESI-MS:	$(M+H)^+$ = 586

retention time (HPLC-MS): 10.4 min (method A)

5g) (*R*)-2-(4-benzyloxy-3,5-dimethyl-phenyl)-1-carboxy-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate

A solution of 3.21 g (5.48 mmol) of (*R*)-2-(4-benzyloxy-3,5-dimethyl-phenyl)-1-methoxy-carbonyl-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate in 80 mL THF was combined with a solution of 200 mg (8.35 mmol) LiOH in 40 mL water and stirred for 1 h at RT. The reaction mixture was evaporated down i.vac., the residue was taken up in 100 mL water, acidified with 2 M HCl, the precipitate was suction filtered and dried in the vacuum drying cupboard at 40°C.

Yield: quantitative

ESI-MS: $(M+H)^+ = 572$

retention time (HPLC-MS): 9.2 min (method B)

5h) (*R*)-2-(4-hydroxy-3,5-dimethyl-phenyl)-1-carboxy-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate

3.72 g (6.51 mmol) of (*R*)-2-(4-benzyloxy-3,5-dimethyl-phenyl)-1-carboxy-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate in 50 mL DCM were combined with 300 mg 10% Pd/C and shaken at RT and 3000 hPa hydrogen pressure until the reaction came to a stop. The catalyst was suction filtered and the solvent was evaporated down i.vac.. The residue was triturated with DIPE and suction filtered.

Yield: 2.41 g (77% of theory)

ESI-MS: $(M+H)^+ = 482$

retention time (HPLC-MS): 7.0 min (method B)

5i) (*R*)-1-(4-hydroxy-3,5-dimethyl-benzyl)-2(4-morpholin-4-yl-piperidin-1-yl)-2-oxo-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate

A solution of 70 mg (0.15 mmol) of (*R*)-2-(4-hydroxy-3,5-dimethyl-phenyl)-1-carboxy-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate, 51 mg (0.16 mmol) TBTU and 26 µL (0.18 mmol) triethylamine in 1 mL DMF was stirred for 1 h at RT. Then 25 mg (0.15 mmol) 4-piperidin-4-yl-morpholine was added to the reaction solution, which was then stirred for 16 h at RT. The reaction solution was purified by HPLC without any further working up; the fractions containing the product were combined and lyophilised.

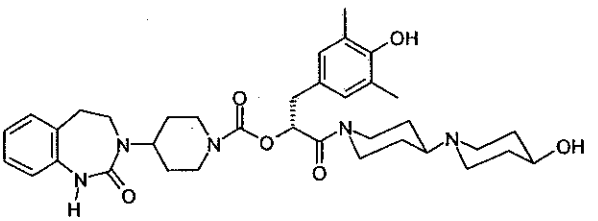
Yield: 35 mg (38% of theory)

ESI-MS: $(M+H)^+ = 634$

retention time (HPLC-MS): 5.6 min (method B)

Example 5.1

(*R*)-2-(4-hydroxy-1,4'-bipiperidinyl-1'-yl)-1-(4-hydroxy-3,5-dimethyl-benzyl)-2-oxo-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate



Analogously to Example 5i the product was obtained from 70 mg (0.15 mmol) (*R*)-2-(4-hydroxy-3,5-dimethyl-phenyl)-1-carboxy-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate and 27 mg (0.15 mmol) [1,4']bipiperidinyl-4-ol.

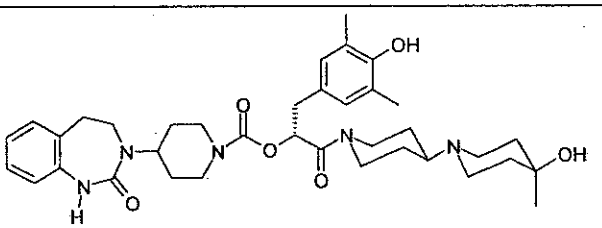
Yield: 35 mg (37% of theory)

ESI-MS: $(M+H)^+ = 648$

retention time (HPLC): 5.5 min (method B)

Example 5.2

(*R*)-1-(4-hydroxy-3,5-dimethyl-benzyl)-2-(4-hydroxy-4-methyl-[1,4']bipiperidinyl-1'-yl)-2-oxo-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate



5.2a) (*R*)-1-(4-hydroxy-3,5-dimethyl-benzyl)-2-oxo-2-(4-oxo-piperidin-1-yl)-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate

130 mg (0.83 mmol) piperidin-4-one (used as the hydrate of the hydrochloride salt) were added at RT to a solution of 400 mg (0.83 mmol) (*R*)-2-(4-hydroxy-3,5-dimethyl-phenyl)-1-carboxy-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate, 320 mg (1.00 mmol) TBTU and 260 µL (1.87 mmol) triethylamine in 10 mL DMF and the reaction mixture was stirred for 16 h at RT. The mixture was evaporated down i.vac., the residue was taken up in EtOAc, the organic phase was washed with semisaturated $NaHCO_3$ solution and dried over Na_2SO_4. After the desiccant and solvent had been eliminated the residue was purified by chromatography (silica gel, EtOAc). The fractions containing the product were evaporated down, the residue stirred with DIPE, suction filtered and dried.

Yield: 333 mg (71% of theory)

ESI-MS: $(M+H)^+ = 563$

retention time (HPLC-MS): 6.9 min (method B)

5.2b) (*R*)-1-(4-hydroxy-3,5-dimethyl-benzyl)-2-(4-hydroxy-4-methyl-[1,4']bipiperidinyl-1'-yl)-2-oxo-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate

A solution of 50 mg (0.09 mmol) (*R*)-1-(4-hydroxy-3,5-dimethyl-benzyl)-2-oxo-2-(4-oxo-piperidin-1-yl)-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate in 1.5 mL DCM was combined with 21 mg (0.18 mmol) 4-methyl-piperidin-4-ol and 10.3 µL (0.19 mmol) AcOH, cooled to 0°C cooled and stirred for 2 h. Then 28 mg (0.19 mmol) sodium-triacetoxyborohydride were added and the mixture was stirred overnight at 0°C. After the solvent had been eliminated the residue was combined with 2 mL DMF and purified by HPLC. The fractions containing the product were combined and lyophilised.

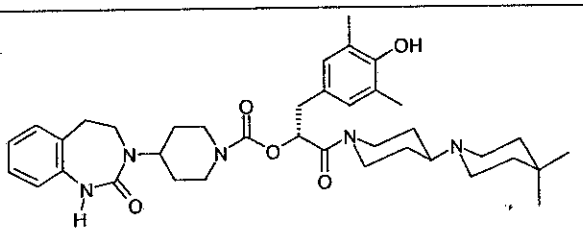
Yield: 25 mg (42% of theory)

ESI-MS: $(M+H)^+ = 662$

retention time (HPLC-MS): 2.90 min (method A)

Example 5.3

(*R*)-2-(4,4-dimethyl-[1,4']bipiperidinyl-1'-yl)-1-(4-hydroxy-3,5-dimethyl-benzyl)-2-oxo-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate



Analogously to Example 5.2b the product could be obtained from 50.0 mg (0.09 mmol) (*R*)-1-(4-hydroxy-3,5-dimethyl-benzyl)-2-oxo-2-(4-oxo-piperidin-1-yl)-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate (Example 5.2a) and 31.0 mg (0.18 mmol) 4,4-dimethylpiperidin.

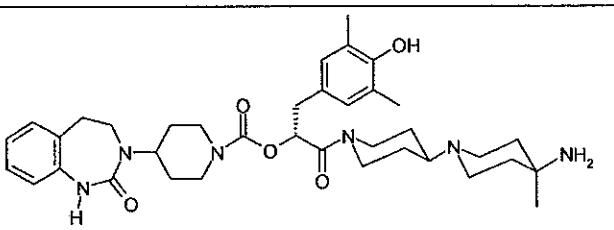
Yield: 18.3 mg (31% of theory)

ESI-MS: $(M+H)^+ = 660$

retention time (HPLC-MS): 3.2 min (method A)

Example 5.4

(*R*)-2-(4-amino-4-methyl-[1,4']bipiperidinyl-1'-yl)-1-(4-hydroxy-3,5-dimethyl-benzyl)-2-oxo-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate



A solution of 150 mg (0.27 mmol) (*R*)-1-(4-hydroxy-3,5-dimethyl-benzyl)-2-oxo-2-(4-oxo-piperidin-1-yl)-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate (Example 5.2a) in 4 mL DCM was combined with 120 mg (0.53 mmol) *tert*-butyl (4-methyl-piperidin-4-yl)-carbamate and 31 µL (0.56 mmol) AcOH, cooled to 0°C and stirred for 2 h. Then 85 mg (0.56 mmol) sodium triacetoxyborohydride were added and the mixture was stirred overnight at 0°C. Then the reaction solution was combined with 0.5 mL TFA and again stirred overnight at RT. After elimination of the solvents the residue was dissolved in 2 mL DMF and purified by HPLC. The fractions containing the product were combined and lyophilised, wherein the product was obtained as the TFA salt.

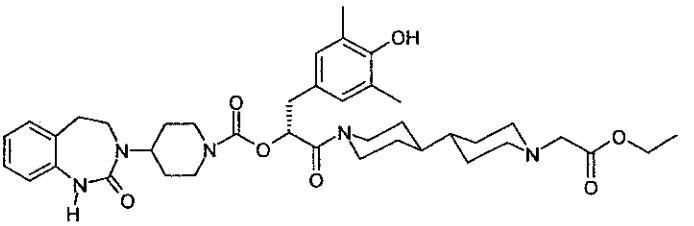
Yield: 94 mg (46% of theory)

ESI-MS: $(M+H)^+ = 661$

retention time (HPLC-MS): 2.5 min (method A)

Example 5.5

(*R*)-2-(1'-ethoxycarbonylmethyl-4,4'-bipiperidinyl-1-yl)-1-(4-hydroxy-3,5-dimethyl-benzyl)-2-oxo-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate

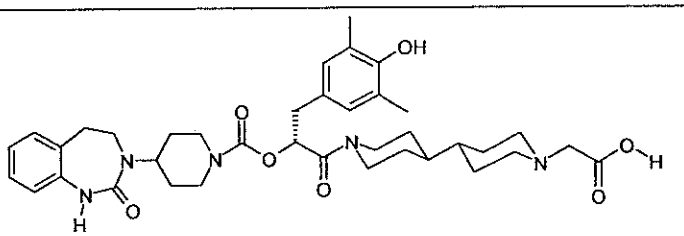


117 mg (0.46 mmol) ethyl [4,4']bipiperidinyl-1-yl-acetate were added at RT to a solution of 200 mg (0.42 mmol) (*R*)-2-(4-hydroxy-3,5-dimethyl-phenyl)-1-carboxy-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate (Example 5h), 148 mg (0.46 mmol) TBTU and 64 µL (0.46 mmol) triethylamine in 10 mL THF and 1 mL DMF and the reaction mixture was shaken overnight at RT. The reaction solution was evaporated down i.vac., the residue was taken up in MeOH and purified by HPLC. The fractions containing the product were combined, evaporated down i.vac., the residue was triturated with DIPE, suction filtered and dried.

Yield:	222 mg (74% of theory)
ESI-MS:	$(M+H)^+$ = 718
retention time (HPLC):	3.1 min (method A)

Example 5.6

(*R*)-2-(1'-carboxymethyl-4,4'-bipiperidinyl-1-yl)-1-(4-hydroxy-3,5-dimethyl-benzyl)-2-oxo-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate



A solution of 3.8 mg (0.16 mmol) LiOH in 1 mL water was added to a solution of 100 mg (0.14 mmol) (*R*)-2-(1'-ethoxycarbonylmethyl-4,4'-bipiperidinyl-1-yl)-1-(4-hydroxy-3,5-dimethyl-benzyl)-2-oxo-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate in 3 mL THF and the reaction

solution was stirred overnight at RT. The organic solvent was removed in the nitrogen stream, the residue was combined with 1 mL water and acetonitrile and acidified with formic acid. The product was purified by HPLC; the fractions containing the product were combined and lyophilised.

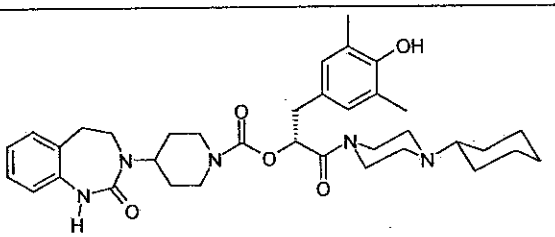
Yield: 56 mg (58% of theory)

ESI-MS: $(M-H)^-$ = 688

retention time (HPLC): 3.0 min (method A)

Example 5.7

(*R*)-2-(4-cyclohexyl-piperazin-1-yl)-1-(4-hydroxy-3,5-dimethyl-benzyl)-2-oxo-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate



Analogously to Example 3g the product could be obtained from 69 mg (0.14 mmol) (*R*)-2-(4-hydroxy-3,5-dimethyl-phenyl)-1-carboxy-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate (Example 5h) and 24 mg (0.14 mmol) 1-cyclohexyl-piperazine.

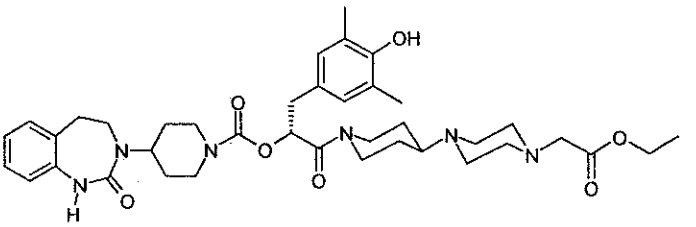
Yield: 51 mg (91% of theory)

ESI-MS: $(M+H)^+$ = 632

retention time (HPLC): 3.1 min (method A)

Example 5.8

(*R*)-2-[4-(4-ethoxycarbonylmethyl-piperazin-1-yl)-piperidin-1-yl]-1-(4-hydroxy-3,5-dimethyl-benzyl)-2-oxo-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate



Analogously to Example 5i the product could be obtained from 150 mg (0.31 mmol) (*R*)-2-(4-hydroxy-3,5-dimethyl-phenyl)-1-carboxy-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate (Example 5h) and 87 mg (0.34 mmol) ethyl (4-piperidin-4-yl-piperazin-1-yl)-acetate.

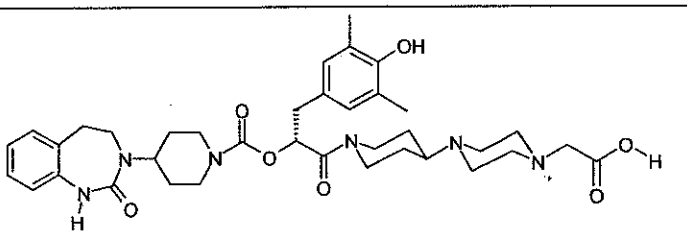
Yield: 64 mg (28% of theory)

ESI-MS: $(M+H)^+ = 719$

retention time (HPLC): 3.6 min (method A)

Example 5.9

(*R*)-2-[4-(4-carboxymethyl-piperazin-1-yl)-piperidin-1-yl]-1-(4-hydroxy-3,5-dimethyl-benzyl)-2-oxo-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate



A solution of 2.3 mg (0.09 mmol) LiOH in 5 mL water was added to a solution of 40.0 mg (0.06 mmol) (*R*)-2-[4-(4-ethoxycarbonylmethyl-piperazin-1-yl)-piperidin-1-yl]-1-(4-hydroxy-3,5-dimethyl-benzyl)-2-oxo-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate in 5 mL THF and the reaction mixture was stirred for 2 h at RT. The mixture was evaporated down i.vac., the residue was taken up in 1 mL DMF and purified by HPLC; the fractions containing the product were combined and lyophilised.

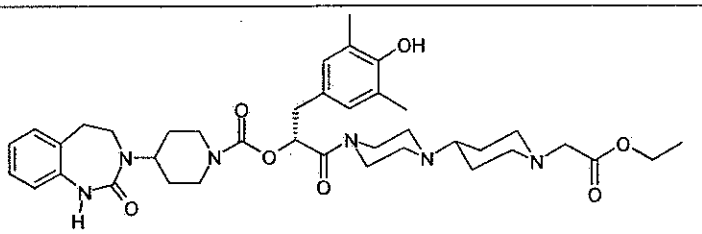
Yield: 20 mg (38% of theory)

ESI-MS: $(M+H)^+ = 691$

retention time (HPLC): 2.6 min (method A)

Example 5.10

(*R*)-2-[4-(1-ethoxycarbonylmethyl-piperidin-4-yl)-piperazin-1-yl]-1-(4-hydroxy-3,5-dimethyl-benzyl)-2-oxo-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate



5.10a) (*R*)-1-(4-benzyloxy-3,5-dimethyl-benzyl)-2-[4-(1-ethoxycarbonylmethyl-piperidin-4-yl)-piperazin-1-yl]-2-oxo-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate

A solution of 8.00 g (14.0 mmol) (*R*)-2-(4-benzyloxy-3,5-dimethyl-phenyl)-1-carboxy-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate (Example 5g), 5.17 g (16.1 mmol) TBTU and 8.84 mL (63.0 mmol) triethylamine in 100 mL DMF was stirred for 1 h at RT. Then 5.28 g (16.1 mmol) ethyl (4-piperazin-1-yl-piperidin-1-yl)-acetate (used as the bis-hydrochloride salt) was added to the reaction mixture, which was then stirred for 1 h at RT. 150 mL of 15% K_2CO_3 solution were added, the mixture was extracted with 200 mL EtOAc, the organic phase was separated off and extracted with 150 mL 10% citric acid solution. The aqueous phase was made alkaline with K_2CO_3, extracted with 200 mL EtOAc and the organic phase was dried over Na_2SO_4. After the desiccant and solvent had been eliminated the residue was purified by chromatography (silica gel, EtOH). The fractions containing the product were combined, evaporated down i.vac., the residue was stirred with DIPE, suction filtered and dried.

Yield: 8.58 g (76% of theory)

ESI-MS: $(M+H)^+ = 809$

retention time (HPLC): 3.7 min (method A)

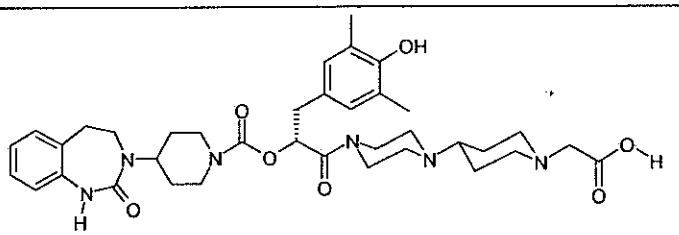
5.10b) (*R*)-2-[4-(1-ethoxycarbonylmethyl-piperidin-4-yl)-piperazin-1-yl]-1-(4-hydroxy-3,5-dimethyl-benzyl)-2-oxo-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate

A suspension of 4.00 g (4.94 mmol) (*R*)-1-(4-benzyloxy-3,5-dimethyl-benzyl)-2-[4-(1-ethoxycarbonylmethyl-piperidin-4-yl)-piperazin-1-yl]-2-oxo-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate and 400 mg 10% Pd/C in 50 mL EtOH was hydrogenated at RT and 3000 hPa hydrogen pressure until the theoretical hydrogen uptake had occurred. The catalyst was filtered off, the filtrate was evaporated down i.vac., the residue was stirred with DIPE, suction filtered and dried.

Yield:	3.40 g (96% of theory)
ESI-MS:	$(M+H)^+ = 719$
retention time (HPLC):	2.5 min (method A)

Example 5.11

(*R*)-2-[4-(1-carboxymethyl-piperidin-4-yl)-piperazin-1-yl]-1-(4-hydroxy-3,5-dimethyl-benzyl)-2-oxo-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate



A solution of 126 mg (5.25 mmol) LiOH in 10 mL water was added at RT to a solution of 2.50 g (3.48 mmol) (*R*)-2-[4-(1-ethoxycarbonylmethyl-piperidin-4-yl)-piperazin-1-yl]-1-(4-hydroxy-3,5-dimethyl-benzyl)-2-oxo-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate in 30 mL THF and the reaction mixture was stirred overnight at RT. The mixture was evaporated to dryness i.vac. and the residue was purified by chromatography (silica gel, gradient DCM to DCM/MeOH/NH_3 70:30:3). The fractions containing the product were

combined, evaporated down i.vac., the residue was triturated with DIPE, suction filtered and dried.

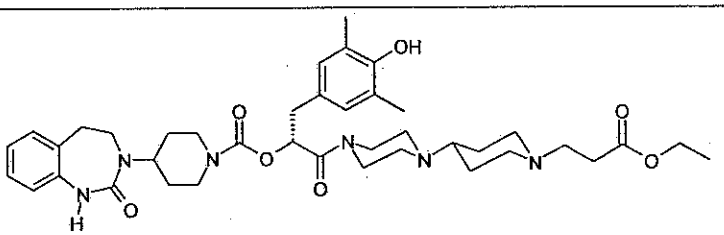
Yield: 1.80 g (75% of theory)

ESI-MS: $(M+H)^+ = 691$

R_f = 0.10 (silica gel, DCM/MeOH/Cyc/NH_3 70:15:15:2)

Example 5.12

(*R*)-2-{4-[1-(2-ethoxycarbonyl-ethyl)-piperidin-4-yl]-piperazin-1-yl}-1-(4-hydroxy-3,5-dimethyl-benzyl)-2-oxo-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate



352 mg (0.93 mmol) ethyl 3-(4-piperazin-1-yl-piperidin-1-yl)-propionate (used as the bis-Hydrochloride salt) were added to a solution of 400 mg (0.83 mmol) (*R*)-2-(4-hydroxy-3,5-dimethyl-phenyl)-1-carboxy-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate, 299 mg (0.93 mmol) TBTU and 477 µL (3.40 mmol) triethylamine in 5 mL DMF and the reaction mixture was stirred for 2 h at RT. The reaction solution was combined with 15% K_2CO_3 solution, exhaustively extracted with DCM and the combined organic phases were dried over Na_2SO_4. After the desiccant and solvent had been eliminated the residue was purified by HPLC; the fractions containing the product were combined and lyophilised.

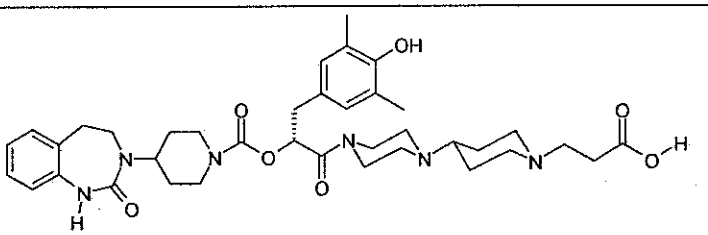
Yield: 305 mg (50% of theory)

ESI-MS: $(M+H)^+ = 733$

retention time (HPLC): 2.6 min (method A)

Example 5.13

(*R*)-2-{4-[1-(2-carboxy-ethyl)-piperidin-4-yl]-piperazin-1-yl}-1-(4-hydroxy-3,5-dimethyl-benzyl)-2-oxo-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate



Analogously to Example 5.11 the product could be obtained from 2.60 g (3.55 mmol) (*R*)-2-{4-[1-(2-ethoxycarbonyl-ethyl)-piperidin-4-yl]-piperazin-1-yl}-1-(4-hydroxy-3,5-dimethyl-benzyl)-2-oxo-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate and 128 mg (5.33 mmol) LiOH.

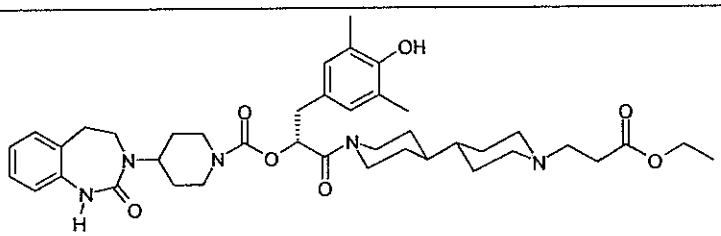
Yield: 1.60 g (64% of theory)

ESI-MS: $(M+H)^+ = 705$

R_f = 0.07 (silica gel, DCM/MeOH/Cyc/NH_3 70:15:15:2)

Example 5.14

(*R*)-2-[1'-(2-ethoxycarbonyl-ethyl)-4,4'-bipiperidinyl-1-yl]-1-(4-hydroxy-3,5-dimethyl-benzyl)-2-oxo-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate



A solution of 80 mg (0.17 mmol) (*R*)-2-(4-hydroxy-3,5-dimethyl-phenyl)-1-carboxy-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate (Example 5h), 59 mg (0.18 mmol) TBTU and 76 µL (0.54 mmol) triethylamine in 1 mL DMF was stirred for 1 h at RT. Then 49 mg (0.18 mmol) ethyl 3-

[4,4']bipiperidinyl-1-yl-propionate were added to the reaction mixture, which was then stirred for 2 h at RT. This was purified by HPLC without any further working up; the fractions containing the product were combined and lyophilised.

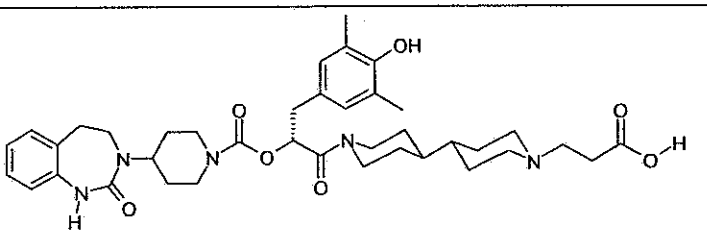
Yield: 11 mg (9% of theory)

ESI-MS: $(M+H)^+ = 732$

retention time (HPLC): 3.4 min (method C)

Example 5.15

(*R*)-2-[1'-(2-carboxy-ethyl)-4,4'-bipiperidinyl-1-yl]-1-(4-hydroxy-3,5-dimethyl-benzyl)-2-oxo-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate



Analogously to Example 5.11 the product could be obtained from 2.50 g (3.42 mmol) (*R*)-2-[1'-(2-ethoxycarbonyl-ethyl)-4,4'-bipiperidinyl-1-yl]-1-(4-hydroxy-3,5-dimethyl-benzyl)-2-oxo-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate and 128 mg (5.33 mmol) LiOH.

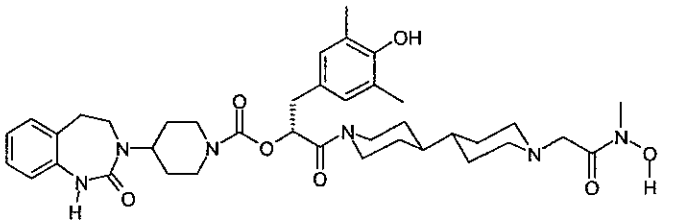
Yield: 1.70 g (71% of theory)

ESI-MS: $(M+H)^+ = 704$

R_f = 0.20 (silica gel, DCM/MeOH/Cyc/NH_3 70:15:15:2)

Example 5.16

(*R*)-1-(4-hydroxy-3,5-dimethyl-benzyl)-2-{1'-[(hydroxy-methyl-carbamoyl)-methyl]-4,4'-bipiperidinyl-1-yl}-2-oxo-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate

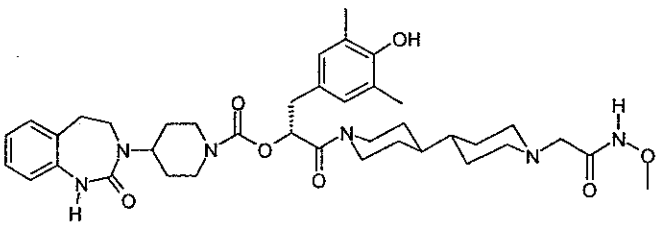


A solution of 80.0 mg (0.12 mmol) (*R*)-2-(1'-carboxymethyl-4,4'-bipiperidinyl-1-yl)-1-(4-hydroxy-3,5-dimethyl-benzyl)-2-oxo-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate (Example 5.6), 44.6 mg (0.14 mmol) TBTU and 64.6 µL (0.46 mmol) triethylamine in 1.2 mL DMF was stirred for 1 h at RT. Then 29.1 mg (0.35 mmol) *N*-methylhydroxylamine (used as the hydrochloride salt) was added to the reaction mixture, which was then stirred for 20 h at RT. To the reaction mixture were added 5 drops of AcOH, the mixture was filtered through a syringe filter and purified by HPLC. The fractions containing the product were combined, 30 mL EtOAc and 5% $NaHCO_3$ solution were added, the organic phase was separated off and dried over Na_2SO_4. After the desiccant and solvent had been eliminated the residue was purified by chromatography (silica gel, DCM/MeOH/NH_3 90:10:1). The fractions containing the product were combined, evaporated down i.vac., the residue was triturated with DIPE, suction filtered and dried in the air until a constant weight was obtained.

Yield:	12.4 mg (15% of theory)
ESI-MS:	$(M+H)^+$ = 719
R_f =	0.16 (silica gel, DCM/MeOH/NH_3 90:10:1)
retention time (HPLC):	3.0 min (method A)

Example 5.17

(*R*)-1-(4-hydroxy-3,5-dimethyl-benzyl)-2-[1'-(methoxycarbamoyl-methyl)-4,4'-bipiperidinyl-1-yl]-2-oxo-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate

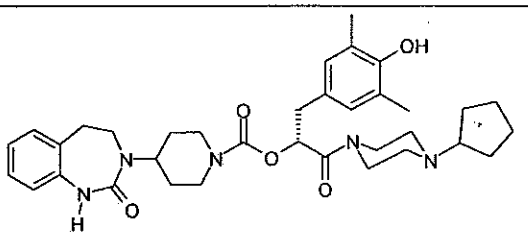


Analogously to Example 5.16 the product could be obtained from 80.0 mg (0.12 mmol) (*R*)-2-(1'-carboxymethyl-4,4'-bipiperidinyl-1-yl)-1-(4-hydroxy-3,5-dimethyl-benzyl)-2-oxo-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate (Example 5.6) and 29.1 mg (0.35 mmol) O-methylhydroxyamine (used as the hydrochloride salt).

Yield:	13.0 mg (16% of theory)
ESI-MS:	$(M+H)^+$ = 719
R_f =	0.27 (silica gel, DCM/MeOH/NH_3 90:10:1)
retention time (HPLC):	3.0 min (method A)

Example 5.18

(*R*)-2-(4-cyclopentyl-piperazin-1-yl)-1-(4-hydroxy-3,5-dimethyl-benzyl)-2-oxo-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate



5.18a) (*R*)-1-(4-benzyloxy-3,5-dimethyl-benzyl)-2-(4-benzyl-piperazin-1-yl)-2-oxo-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate

A solution of 1.54 g (2.69 mmol) (*R*)-2-(4-benzyloxy-3,5-dimethyl-phenyl)-1-carboxy-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate (Example 5g), 0.95 g (2.96 mmol) TBTU and 0.47 mL (3.37 mmol) triethylamine in 20 mL THF and 2 ml DMF was stirred for 1 h at RT. Then 0.52 mL (2.96 mmol) *N*-benzylpiperazine were added to the reaction mixture, which was

then stirred for 14 h at RT. 30 mL EtOAc were added to the reaction mixture, it was washed with semisaturated $NaHCO_3$ solution and the organic phase was dried over Na_2SO_4. After the desiccant and solvent had been eliminated the residue was purified by chromatography (silica gel, EtOAc/Cyc 95:5). The fractions containing the product were evaporated down, the residue was triturated with DIPE, suction filtered and dried.

Yield:	1.62 g (82% of theory)
ESI-MS:	$(M+H)^+ = 730$
retention time (HPLC):	4.3 min (method A)

5.18b) (*R*)-1-(4-hydroxy-3,5-dimethyl-benzyl)-2-oxo-2-piperazin-1-yl-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate

A suspension of 1.62 g (2.22 mmol) (*R*)-1-(4-benzyloxy-3,5-dimethyl-benzyl)-2-(4-benzyl-piperazin-1-yl)-2-oxo-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate and 150 mg 10% Pd/C in 40 mL MeOH was hydrogenated at RT and 3000 hPa hydrogen pressure until the theoretical hydrogen uptake had occurred. The catalyst was suction filtered, the solvent was evaporated down i.vac. and the residue was purified by chromatography (silica gel, EtOAc + 15% MeOH/NH_3 9:1).

Yield:	1.03 g (85% of theory)
ESI-MS:	$(M+H)^+ = 550$
retention time (HPLC):	2.7 min (method A)

5.18c) (*R*)-2-(4-cyclopentyl-piperazin-1-yl)-1-(4-hydroxy-3,5-dimethyl-benzyl)-2-oxo-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate

A solution of 100 mg (0.18 mmol) (*R*)-1-(4-hydroxy-3,5-dimethyl-benzyl)-2-oxo-2-piperazin-1-yl-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate, 48 µL (0.55 mmol) cyclopentanone and 20 µL (0.37 mmol) AcOH in 2 mL THF/MeOH (2:1) was stirred overnight at RT. Then 24 mg (0.36 mmol) sodium cyanoborohydride was added to the reaction solution which had been

cooled to 0°C, and this was then stirred for 4 h at 0°C and overnight at RT. The solvents were eliminated at 40°C, the residue was dissolved in 1 mL DMF and purified by HPLC; the fractions containing the product were combined and lyophilised.

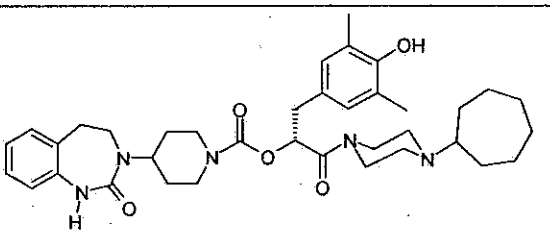
Yield: 48 mg (43% of theory)

ESI-MS: $(M+H)^+ = 618$

retention time (HPLC): 3.2 min (method A)

Example 5.19

(*R*)-2-(4-cycloheptyl-piperazin-1-yl)-1-(4-hydroxy-3,5-dimethyl-benzyl)-2-oxo-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate



Analogously to Example 5.18c the product could be obtained from 100 mg (0.18 mmol) (*R*)-1-(4-hydroxy-3,5-dimethyl-benzyl)-2-oxo-2-piperazin-1-yl-ethyl -(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate, 40.8 mg (0.36 mmol) cycloheptanone and 12 mg (0.18 mmol) sodium cyanoborohydride.

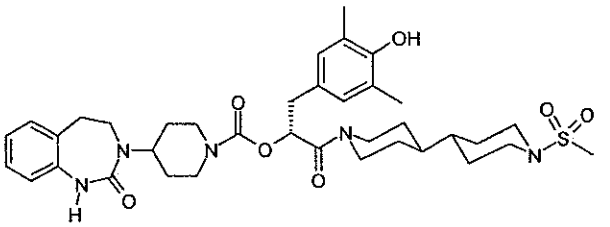
Yield: 21 mg (18% of theory)

ESI-MS: $(M+H)^+ = 646$

retention time (HPLC): 3.5 min (method A)

Example 5.20

(*R*)-1-(4-hydroxy-3,5-dimethyl-benzyl)-2-(1'-methanesulphonyl-4,4'-bipiperidinyl-1-yl)-2-oxo-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate



A solution of 100 mg (0.21 mmol) (*R*)-1-carboxy-2-(4-hydroxy-3,5-dimethyl-phenyl)-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate, 73 mg (0.23 mmol) TBTU and 36 µL (0.26 mmol) triethylamine in 1 mL DMF was stirred for 1 h at RT. Then 56 mg (0.23 mmol) 1-methanesulphonyl-[4,4']bipiperidinyl was added to the reaction mixture, which was then stirred for 5 h at RT. The reaction mixture was purified by HPLC without any further working up; the fractions containing the product were combined and lyophilised.

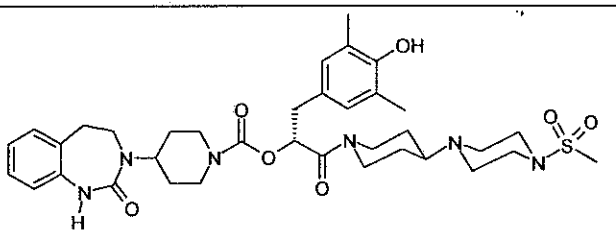
Yield: 63 mg (43% of theory)

ESI-MS: $(M-H)^-$ = 708

retention time (HPLC): 4.0 min (method A)

Example 5.21

(*R*)-1-(4-hydroxy-3,5-dimethyl-benzyl)-2-[4-(4-methanesulphonyl-piperazin-1-yl)-piperidin-1-yl]-2-oxo-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate



Analogously to Example 5.20 the product could be obtained from 100 mg (0.21 mmol) (*R*)-1-carboxy-2-(4-hydroxy-3,5-dimethyl-phenyl)-ethyl and 57 mg (0.23 mmol) 1-methanesulphonyl-4-piperidin-4-yl-piperazine 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate.

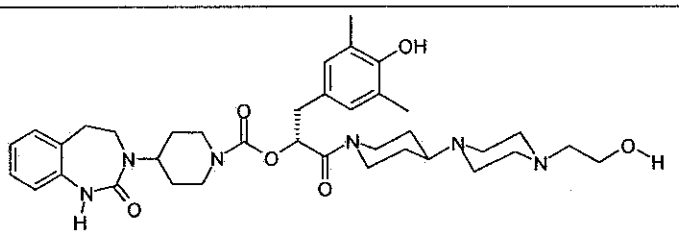
Yield: 43 mg (29% of theory)

ESI-MS: $(M+H)^+$ = 711

retention time (HPLC): 3.1 min (method A)

Example 5.22

(*R*)-1-(4-hydroxy-3,5-dimethyl-benzyl)-2-{4-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-piperidin-1-yl}-2-oxo-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate



Analogously to Example 5.20 the product could be obtained from 80 mg (0.17 mmol) (*R*)-1-carboxy-2-(4-hydroxy-3,5-dimethyl-phenyl)-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate and 52 mg (0.18 mmol) 2-(4-piperidin-4-yl-piperazin-1-yl)-ethanol.

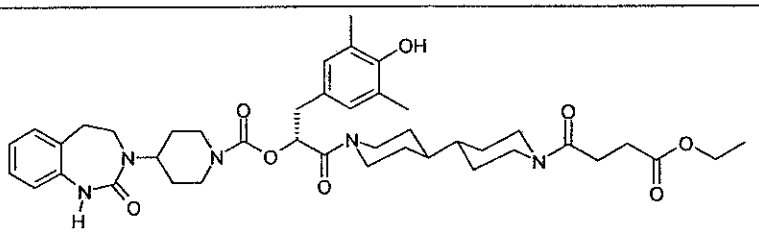
Yield: 63 mg (56% of theory)

ESI-MS: $(M+H)^+ = 677$

retention time (HPLC): 2.4 min (method A)

Example 5.23

(*R*)-2-[1'-(3-ethoxycarbonyl-propionyl)-4,4'-bipiperidinyl-1-yl]-1-(4-hydroxy-3,5-dimethyl-benzyl)-2-oxo-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate



207 mg (0.70 mmol) ethyl 4-[4,4']bipiperidinyl-1-yl-4-oxo-butyrate (amine A2) were added at RT to a solution of 300 mg (0.62 mmol) (*R*)-1-carboxy-2-(4-hydroxy-3,5-

dimethyl-phenyl)-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate, 225 mg (0.70 mmol) TBTU and 97 µL (0.70 mmol) triethylamine in 5 mL DMF and the reaction mixture was shaken overnight at RT. It was directly purified by HPLC without any further working up; the fractions containing the product were combined and lyophilised.

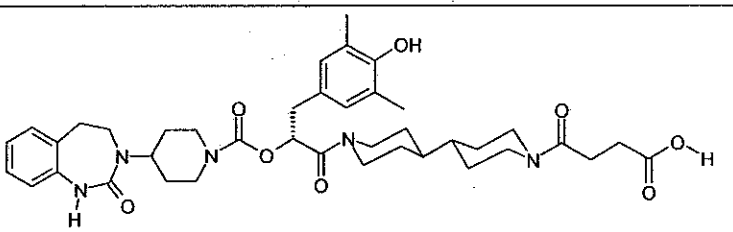
Yield: 170 mg (36% of theory)

ESI-MS: $(M+H)^+$ = 760

retention time (HPLC): 4.1 min (method A)

Example 5.24

(*R*)-2-[1'-(3-carboxy-propionyl)-4,4'-bipiperidinyl-1-yl]-1-(4-hydroxy-3,5-dimethyl-benzyl)-2-oxo-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate



A solution 0.96 mg (0.04 mmol) LiOH in 1 mL water was added to a solution of 20.0 mg (0.03 mmol) (*R*)-2-[1'-(3-ethoxycarbonyl-propionyl)-4,4'-bipiperidinyl-1-yl]-1-(4-hydroxy-3,5-dimethyl-benzyl)-2-oxo-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate in 1 mL THF and the reaction mixture was stirred for 2 h at RT. The solvents were eliminated in a nitrogen stream, the residue was taken up in water/acetonitrile and lyophilised. The product was obtained as the Li salt.

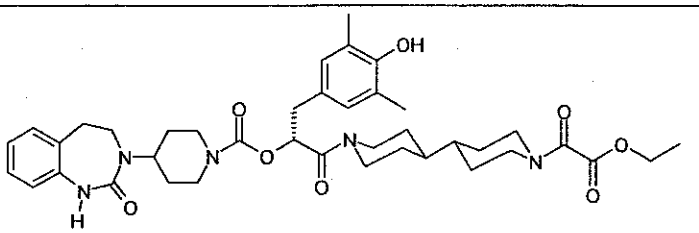
Yield: 17 mg (88% of theory)

ESI-MS: $(M+H)^+$ = 732

R_f = 0.13 (silica gel, DCM/MeOH/NH_3 90:10:1)

Example 5.25

(*R*)-2-(1'-ethoxyoxalyl-4,4'-bipiperidinyl-1-yl)-1-(4-hydroxy-3,5-dimethyl-benzyl)-2-oxo-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate

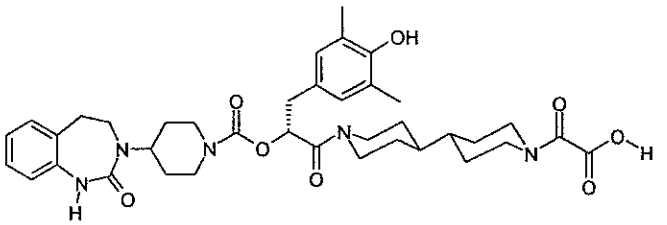


231 mg (0.70 mmol) ethyl [4,4']bipiperidinyl-1-yl-oxo-acetate (amine A1, used as the hydrogen carbonate salt) were added at RT to a solution of 300 mg (0.62 mmol) (*R*)-1-carboxy-2-(4-hydroxy-3,5-dimethyl-phenyl)-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate, 225 mg (0.70 mmol) TBTU and 197 µL (1.40 mmol) triethylamine in 5 mL DMF and the reaction mixture was stirred for 3 h at RT. The mixture was evaporated down i.vac., the residue was taken up in DCM, the organic phase was washed with 15% K_2CO_3 solution and dried over Na_2SO_4. After the desiccant and solvent had been eliminated the residue was purified by HPLC; the fractions containing the product were combined, evaporated down i.vac., the residue was triturated with DIPE, suction filtered and dried.

Yield:	360 mg (79% of theory)
ESI-MS:	$(M+H)^+$ = 732
retention time (HPLC):	4.0 min (method A)

Example 5.26

(*R*)-1-(4-hydroxy-3,5-dimethyl-benzyl)-2-(1'-oxalyl-4,4'-bipiperidinyl-1-yl)-2-oxo-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate



A solution 0.96 mg (0.04 mmol) LiOH in 1 mL water was added to a solution of 20.0 mg (0.03 mmol) (*R*)-2-(1'-ethoxyoxalyl-4,4'-bipiperidinyl-1-yl)-1-(4-hydroxy-3,5-dimethyl-benzyl)-2-oxo-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate in 1 mL THF and the reaction mixture was stirred for 2 h at RT. The solvents were eliminated in a nitrogen stream, the residue was taken up in water/acetonitrile and lyophilised. The product was obtained as the Li salt.

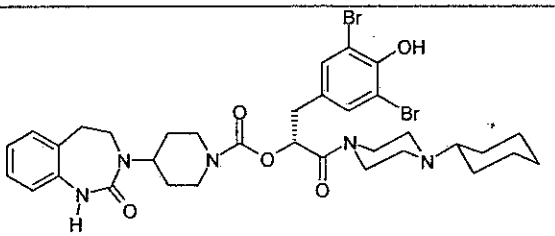
Yield: 19 mg (99% of theory)

ESI-MS: $(M+H)^+ = 704$

R_f = 0.10 (silica gel, DCM/MeOH/NH_3 90:10:1)

Example 6

(*R*)-2-(4-cyclohexyl-piperazin-1-yl)-1-(3,5-dibromo-4-hydroxy-benzyl)-2-oxo-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate



6a) (*Z*,*E*)-3-(4-acetoxy-3,5-dibromo-phenyl)-2-acetylamino-acrylic acid

Under a nitrogen atmosphere a mixture of 30.0 g (107 mmol) 3,5-dibromo-4-hydroxy-benzaldehyde, 18.8 g (268 mmol) *N*-acetylglycine and 13.2 g (161 mmol) NaOAc in 120 mL acetic anhydride was heated to 130°C for 1.5 h. The mixture was cooled to 90°C and 15 mL water was slowly added dropwise thereto in such a way that the temperature did not exceed 100°C. After the addition had ended the mixture was kept for a further 2 h at 90°C, cooled to 70°C, combined with 300 mL

water and stirred for 30 min. The precipitate was filtered off, washed with water and dried at 50°C. The crude product was further reacted without purification.

Yield: 35.7 g (79% of theory)

ESI-MS: $(M+H)^+$ = 420/422/424 (2 Br)

R_f = 0.20 (silica gel, DCM/MeOH/AcOH 90:10:1)

6b) 3-(3,5-dibromo-4-hydroxy-phenyl)-2-oxo-propionic acid

While cooling with ice 325 mL of 4 M HCl was added to a solution of 35.7 g (84.8 mmol) (*Z*,*E*)-3-(4-acetoxy-3,5-dibromo-phenyl)-2-acetylamino-acrylic acid in 290 mL NMP and the reaction mixture was heated to 120°C (bath temperature) for 1.5 h. The mixture was cooled to 0°C, combined with 1.4 L water and stirred for a further 30 min. The precipitate formed was filtered off and dried.

Yield: 20.5 g (72% of theory)

ESI-MS: $(M-H)^-$ = 335/337/339 (2 Br)

R_f = 0.35 (silica gel, DCM/MeOH/AcOH 80:20:2)

6c) (*R*)-3-(3,5-dibromo-4-hydroxy-phenyl)-2-hydroxy-propionic acid

Under an argon atmosphere 6 mL (43.1 mmol) triethylamine was added to a solution of 14.5 g (42.9 mmol) 3-(3,5-dibromo-4-hydroxy-phenyl)-2-oxo-propionic acid in 250 mL THF and the mixture was cooled to -32°C. Then a solution of 22.6 g (70.5 mmol) (1*R*)-*B*-chlorodiisopinocampheylborane in 90 mL THF was added dropwise such that the temperature did not exceed -20°C. The reaction mixture was stirred for 30 min at -30°C and allowed to heat up to 0°C within 2.5 h. To complete the reaction the mixture was again cooled to -32°C, a solution of 5.8 g (18.1 mmol) (1*R*)-*B*-chlorodiisopinocampheylborane in 40 mL THF was added dropwise such that the temperature did not exceed -20°C and then the reaction mixture was stirred overnight in the ice bath. After cooling again to -32°C a further 2.5 g (7.8 mmol) (1*R*)-*B*-chlorodiisopinocampheylborane in 20 mL THF were added dropwise, the reaction mixture was stirred for 30 min at this temperature, heated to 0°C within 2.5 h and then stirred for 66 h at RT. 100 mL 10% NaOH were added to the reaction solution such that the temperature did not exceed

25°C, stirred for a further 30 min, combined with MTBE, the organic phase was separated off and again extracted with 20 mL 10% NaOH solution. The combined aqueous phases were washed several times with MTBE, acidified with 20% HCl and exhaustively extracted with diethyl ether/EtOAc (1:1). The combined organic phases were combined with activated charcoal and filtered. The product was further reacted without purification.

Yield: 12.7 g (87% of theory)

ESI-MS: $(M-H)^-$ = 337/339/341 (2 Br)

R_f = 0.4 (silica gel, DCM/MeOH/AcOH 80:20:2)

retention time (HPLC-MS): 6.4 min (method D)

6d) methyl (*R*)-3-(3,5-dibromo-4-hydroxy-phenyl)-2-hydroxy-propionate

A solution of 14.0 g (34.8 mmol) (*R*)-3-(3,5-dibromo-4-hydroxy-phenyl)-2-hydroxy-propionic acid in 100 mL methanolic HCl (6 M) was stirred for 3 h at RT. The mixture was evaporated down i.vac. and the residue was purified by chromatography (silica gel, n-hexane/EtOAc 7:3).

Yield: 7.0 g (57% of theory)

ESI-MS: $(M-H)^-$ = 351/353/355 (2 Br)

retention time (HPLC-MS): 9.8 min (method D)

6e) methyl (*R*)-3-[3,5-dibromo-4-(2-trimethylsilanyl-ethoxymethoxy)-phenyl]-2-hydroxy-propionate

Under a nitrogen atmosphere 11.1 g (76.6 mmol) 40% KF/Al_2O_3 were added to a solution of 6.78 g (19.2 mmol) methyl (*R*)-3-(3,5-dibromo-4-hydroxy-phenyl)-2-hydroxy-propionate in 100 mL acetonitrile and the resulting suspension was stirred for a few min at RT. Then a solution of 4.07 mL (23.0 mmol) (2-chloromethoxy-ethyl)-trimethylsilane in 20 mL acetonitrile was added and the reaction mixture was stirred for 20 h at RT. The mixture was filtered through Celite, the solvent was evaporated down i.vac. and the residue was purified by chromatography (silica gel, *n*-hexane/EtOAc 7:3).

Yield: 5.49 g (59% of theory)

R_f = 0.45 (silica gel, *n*-hexane/EtOAc 1:1)

6f) (*R*)-2-[3,5-dibromo-4-(2-trimethylsilanyl-ethoxymethoxy)-phenyl]-1-methoxy-carbonyl-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate

Under a nitrogen atmosphere 1.23 g (10.0 mmol) 4-dimethylaminopyridine was added to a solution of 1.99 g (9.56 mmol) 4-nitrophenyl chloroformate in 80 mL acetonitrile cooled to 15°C. The resulting suspension was cooled to -7°C and slowly combined with a solution of 4.63 g (9.56 mmol) methyl (*R*)-3-[3,5-dibromo-4-(2-trimethylsilanyl-ethoxymethoxy)-phenyl]-2-hydroxy-propionate in 20 mL acetonitrile. The mixture was stirred for a further 15 min at this temperature, 2.35 g (9.56 mmol) 3-piperidin-4-yl-1,3,4,5-tetrahydro-1,3-benzodiazepin-2-one was added and the reaction mixture was stirred for 2.5 h at RT. The mixture was evaporated down i.vac., the residue was taken up in EtOAc, the organic phase was washed with 10% citric acid and 10% Na_2CO_3 solution and dried over Na_2SO_4. After the desiccant and solvent had been eliminated the residue was purified by chromatography (silica gel, gradient n-hexane/EtOAc 1:1 to 2:8).

Yield: 4.35 g (69% of theory)

ESI-MS: $(M+H)^+$ = 754/756/758 (2 Br)

retention time (HPLC): 29.2 min (method D)

6g) (*R*)-2-(3,5-dibromo-4-hydroxy-phenyl)-1-methoxycarbonyl-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate

Under a nitrogen atmosphere 5.46 mL methanolic H_2SO_4 (0.5 M) were added to a solution of 4.30 g (5.69 mmol) (*R*)-2-[3,5-dibromo-4-(2-trimethylsilanyl-ethoxymethoxy)-phenyl]-1-methoxy-carbonyl-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate in 40 mL THF and 40 mL MeOH and the reaction solution was stirred for 6 h at RT. The reaction mixture was evaporated down i.vac. and the residue was further reacted without purification.

Yield: quantitative

ESI-MS: $(M+H)^+$ = 624/626/628 (2 Br)

retention time (HPLC): 17.3 min (method D)

6h) (*R*)-1-carboxy-2-(3,5-dibromo-4-hydroxy-phenyl)-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate

A solution of 0.51 g (21.3 mmol) LiOH was added to a solution of (*R*)-2-(3,5-dibromo-4-hydroxy-phenyl)-1-methoxycarbonyl-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate (crude product from Example 6g) in 80 mL THF and the reaction mixture was stirred for 3 h at RT. The THF was eliminated i.vac., the aqueous phase was washed with EtOAc, acidified with 10% HCl and the aqueous phase was exhaustively extracted with EtOAc. The combined organic phases were evaporated down i.vac., suspended in diethyl ether, filtered, the residue was dried and then purified by chromatography (silica gel, DCM/MeOH/AcOH 90:10:1).

Yield: 3.5 g (100% of theory)

ESI-MS: $(M+H)^+$ = 610/612/614 (2 Br)

retention time (HPLC): 14.1 min (method D)

6i) (*R*)-2-(4-cyclohexyl-piperazin-1-yl)-1-(3,5-dibromo-4-hydroxy-benzyl)-2-oxo-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate

30 mg (0.18 mmol) 1-cyclohexyl-piperazine were added at RT to a solution of 100 mg (0.16 mmol) (*R*)-1-carboxy-2-(3,5-dibromo-4-hydroxy-phenyl)-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate, 58 mg (0.18 mmol) TBTU and 25 µL (0.18 mmol) triethylamine in 1 mL DMF and the reaction mixture was stirred overnight at RT. The reaction solution was filtered through a syringe filter and directly purified by HPLC without any further working up. The fractions containing the product were combined and lyophilised.

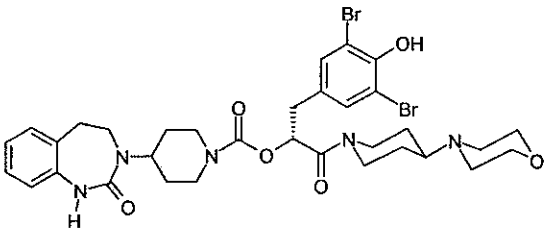
Yield: 64 mg (51% of theory)

ESI-MS: $(M+H)^+$ = 760/762/764 (2 Br)

retention time (HPLC-MS): 3.3 min (method A)

Example 6.1

(*R*)-1-(3,5-dibromo-4-hydroxy-benzyl)-2-(4-morpholin-4-yl-piperidin-1-yl)-2-oxo-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate



Analogously to Example 6i the product could be obtained from 100 mg (0.16 mmol) (*R*)-1-carboxy-2-(3,5-dibromo-4-hydroxy-phenyl)-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate and 31 mg (0.18 mmol) 4-piperidin-4-yl-morpholine.

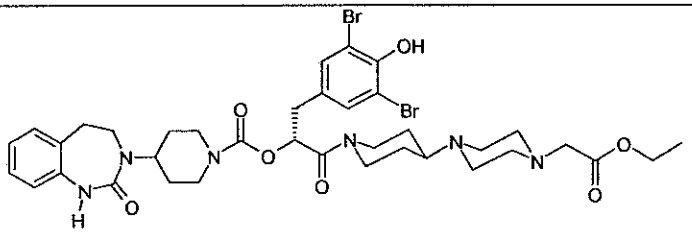
Yield: 72 mg (58% of theory)

ESI-MS: $(M+H)^+$ = 762/764/766 (2 Br)

retention time (HPLC-MS): 3.1 min (method A)

Example 6.2

(*R*)-1-(3,5-dibromo-4-hydroxy-benzyl)-2-[4-(4-ethoxycarbonylmethyl-piperazin-1-yl)-piperidin-1-yl]-2-oxo-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate



Analogously to Example 6i the product could be obtained from 100 mg (0.16 mmol) (*R*)-1-carboxy-2-(3,5-dibromo-4-hydroxy-phenyl)-ethyl 4-(2-oxo-1,2,4,5-

tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate and 46 mg (0.18 mmol) ethyl (4-piperidin-4-yl-piperazin-1-yl)-acetate.

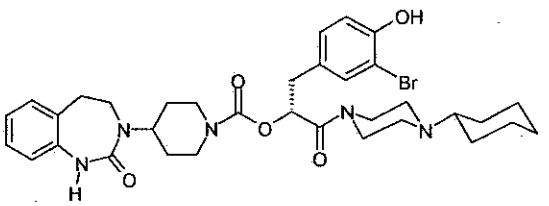
Yield: 5 mg (4% of theory)

ESI-MS: $(M+H)^+$ = 847/849/851 (2 Br)

retention time (HPLC-MS): 2.9 min (method A)

Example 7

(*R*)-1-(3-bromo-4-hydroxy-benzyl)-2-(4-cyclohexyl-piperazin-1-yl)-2-oxo-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate



7a) (*Z*,*E*)-3-(4-acetoxy-3-bromo-phenyl)-2-acetylamino-acrylic acid

Prepared analogously to Example 6a from 75.0 g (366 mmol) 3-bromo-4-hydroxy-benzaldehyde and 64.2 g (548 mmol) *N*-acetylglycine. After cooling of the reaction mixture the product precipitated out and was filtered, washed with water and dried.

Yield: 69.8 g (56% of theory)

retention time (HPLC): 7.6 min (method D)

7b) 3-(3-bromo-4-hydroxy-phenyl)-2-oxo-propionic acid

While cooling with ice, 750 mL 4 M HCl was added to a solution of 69.7 g (204 mmol) (*Z*,*E*)-3-(4-acetoxy-3-bromo-phenyl)-2-acetylamino-acrylic acid in 300 mL NMP and the reaction mixture was heated to 95°C heated (bath temperature) for 2.5 h. It was cooled overnight to RT, combined with 2 L water, extracted three times with 300 mL EtOAc, the combined organic phases were washed twice with 1 L water and dried over Na_2SO_4. After the desiccant and solvent had been eliminated the residue was reacted further without purification.

Yield: 45.8 g (87% of theory)

retention time (HPLC): 7.8 min (method D)

7c) (*R*)-3-(3-bromo-4-hydroxy-phenyl)-2-hydroxy-propionic acid

Under an argon atmosphere 29 mL (356 mmol) triethylamine was added to a solution of 45.0 g (174 mmol) 3-(3-bromo-4-hydroxy-phenyl)-2-oxo-propionic acid in 350 mL THF and the mixture was cooled to -27°C. Then a solution and 114 g (356 mmol) (1*R*)-*B*-chlorodiisopinocampheylborane in 200 mL THF was added dropwise such that the temperature did not exceed -20°C. The reaction mixture was stirred for 15 min at -30°C and allowed to warm up to RT within 1 h. 200 mL 10% NaOH were added to the reaction solution such that the temperature did not exceed 25°C, stirred for a further 15 min, diluted with 400 mL water, combined with 400 mL MTBE and the aqueous phase was separated off. It was washed with 400 mL MTBE, acidified with 150 mL 4 M HCl, extracted twice with 400 mL EtOAc, the combined organic phases were washed with saturated NaCl solution and dried over Na_2SO_4. After the desiccant and solvent had been eliminated the residue was reacted further without purification.

Yield: 53.7 g (89% of theory)

retention time (HPLC): 4.0 min (method D)

7d) methyl (*R*)-3-(3-bromo-4-hydroxy-phenyl)-2-hydroxy-propionate

2.5 mL concentrated sulphuric acid were added to a solution of 53.6 g (154 mmol) (*R*)-3-(3-bromo-4-hydroxy-phenyl)-2-hydroxy-propionic acid in 250 mL MeOH and the reaction mixture was stirred for 4 h at RT. The mixture was evaporated down i.vac., the residue was taken up in 250 mL EtOAc, the organic phase was washed twice with 100 mL saturated $NaHCO_3$ and saturated NaCl solution and dried over Na_2SO_4. After the desiccant and solvent had been eliminated the residue was reacted further without purification.

Yield: quantitative

retention time (HPLC): 6.8 min (method D)

7e) methyl (*R*)-3-[3-bromo-4-(2-trimethylsilanyl-ethoxymethoxy)-phenyl]-2-hydroxy-propionate

6.7 mL (39.1 mmol) ethyldiisopropylamine were added to a solution of 10.2 g (34.6 mmol) methyl (*R*)-3-(3-bromo-4-hydroxy-phenyl)-2-hydroxy-propionate in 100 mL DCM and the reaction mixture was cooled in the ice bath. Then a solution of 7.9 mL (44.6 mmol) (2-chloromethoxy-ethyl)-trimethylsilane in 20 mL DCM was added. The reaction mixture was stirred for 3 h at RT and then to complete the reaction combined with another 0.67 mL ethyldiisopropylamine and 0.8 mL (4.5 mmol) (2-chloromethoxy-ethyl)-trimethylsilane and stirred for 1.5 h at RT. The reaction mixture was washed with 5% Na_2CO_3 and saturated NaCl solution and dried over Na_2SO_4. After the desiccant and solvent had been eliminated the residue was purified by chromatography (silica gel, Cyc/EtOAc 75:25).

Yield: 9.6 g (68% of theory)

retention time (HPLC): 15.1 min (method E)

7f) (*R*)-2-[3-bromo-4-(2-trimethylsilanyl-ethoxymethoxy)-phenyl]-1-methoxycarbonyl-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate

Prepared analogously to Example 6f from 4.55 g (11.2 mmol) methyl (*R*)-3-[3-bromo-4-(2-trimethylsilanyl-ethoxymethoxy)-phenyl]-2-hydroxy-propionate and 2.75 g (11.2 mmol) 3-piperidin-4-yl-1,3,4,5-tetrahydro-1,3-benzodiazepin-2-one.

Yield: 5.46 g (72% of theory)

retention time (HPLC): 16.5 min (method E)

7g) (*R*)-2-(3-bromo-4-hydroxy-phenyl)-1-methoxycarbonyl-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate

Prepared analogously to Example 6g from 5.40 g (7.98 mmol) (*R*)-2-[3-bromo-4-(2-trimethylsilanyl-ethoxy-methoxy)-phenyl]-1-methoxycarbonyl-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate and 7.7 mL (4.2 mmol) methanolic sulphuric acid (0.5 M). The crude product (5.44 g) was further reacted without purification.

retention time (HPLC): 9.9 min (method E)

7h) (*R*)-2-(3-bromo-4-hydroxy-phenyl)-1-carboxy-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate

A solution of 0.84 g (34.1 mmol) LiOH in 20 mL water was added to a solution of 5.44 g of the crude product from Example 7g in 80 mL THF and the reaction mixture was stirred for 1 h at RT. The organic solvent was eliminated i.vac., the aqueous phase was washed with EtOAc, acidified with 10% HCl and exhaustively extracted with EtOAc. The combined organic phases were washed with saturated NaCl solution and dried over Na_2SO_4. After the desiccant and solvent had been eliminated the residue was triturated with 90 mL diethyl ether, filtered, the solid was washed with diethyl ether and dried at 45°C.

Yield: 4.10 g (89% of theory over 2 steps)

retention time (HPLC): 8.2 min (method E)

7i) (*R*)-1-(3-bromo-4-hydroxy-benzyl)-2-oxo-2-[4-(tetrahydro-pyran-4-yl)-piperazin-1-yl]-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate

Prepared analogously to Example 5.20 from 100 mg (0.19 mmol) (*R*)-2-(3-bromo-4-hydroxy-phenyl)-1-carboxy-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate and 35 mg (0.21 mmol) 1-cyclohexyl-piperazine.

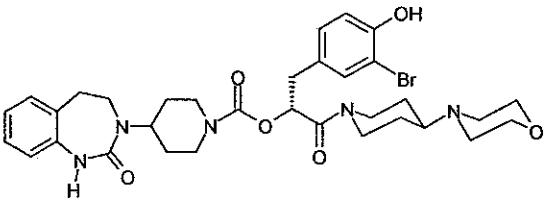
Yield: 62 mg (49% of theory)

ESI-MS: $(M+H)^+$ = 682/684 (Br)

retention time (HPLC-MS): 3.2 min (method A)

Example 7.1

(*R*)-1-(3-bromo-4-hydroxy-benzyl)-2-(4-morpholin-4-yl-piperidin-1-yl)-2-oxo-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate



Prepared analogously to Example 5.20 from 100 mg (0.19 mmol) (*R*)-2-(3-bromo-4-hydroxy-phenyl)-1-carboxy-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate and 36 mg (0.21 mmol) 4-piperidin-4-yl-morpholine.

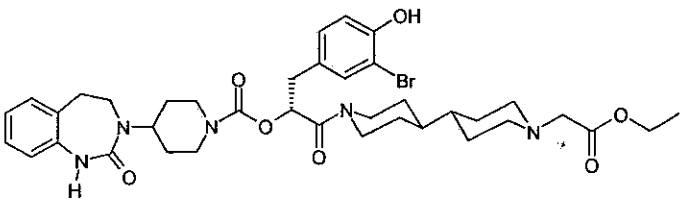
Yield: 66 mg (51% of theory)

ESI-MS: $(M+H)^+$ = 684/686 (Br)

retention time (HPLC-MS): 2.9 min (method A)

Example 7.2

(*R*)-1-(3-bromo-4-hydroxy-benzyl)-2-(1'-ethoxycarbonylmethyl-4,4'-bipiperidinyl-1-yl)-2-oxo-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate



Prepared analogously to Example 5.20 from 150 mg (0.28 mmol) (*R*)-2-(3-bromo-4-hydroxy-phenyl)-1-carboxy-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate and 79 mg (0.31 mmol) ethyl [4,4']bipiperidinyl-1-yl-acetate.

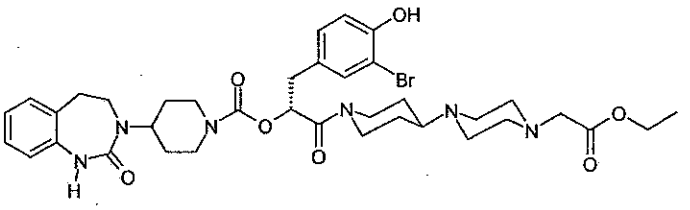
Yield: 63 mg (29% of theory)

ESI-MS: $(M+H)^+$ = 768/770 (Br)

retention time (HPLC-MS): 3.2 min (method A)

Example 7.3

(*R*)-1-(3-bromo-4-hydroxy-benzyl)-2-[4-(4-ethoxycarbonylmethyl-piperazin-1-yl)-piperidin-1-yl]-2-oxo-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate



Prepared analogously to Example 5.20 from 150 mg (0.28 mmol) (*R*)-2-(3-bromo-4-hydroxy-phenyl)-1-carboxy-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate and 79 mg (0.31 mmol) ethyl (4-piperidin-4-yl-piperazin-1-yl)-acetate.

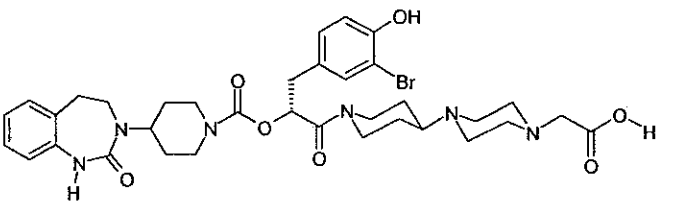
Yield: 82 mg (38% of theory)

ESI-MS: $(M+H)^+$ = 769/771 (Br)

retention time (HPLC-MS): 3.1 min (method A)

Example 7.4

(*R*)-1-(3-bromo-4-hydroxy-benzyl)-2-[4-(4-carboxymethyl-piperazin-1-yl)-piperidin-1-yl]-2-oxo-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate



A solution of 3.0 mg (0.12 mmol) LiOH in 5 mL water was added at RT to a solution of 50 mg (0.07 mol) (*R*)-1-(3-bromo-4-hydroxy-benzyl)-2-[4-(4-ethoxy-carbonylmethyl-piperazin-1-yl)-piperidin-1-yl]-2-oxo-ethyl 4-(2-oxo-1,2,4,5-

tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate in 5 mL THF and the reaction mixture was stirred for 1 h. The organic solvent was eliminated i.vac., the aqueous residue was acidified with 1 M HCl and again evaporated down i.vac.. The residue was purified by HPLC; the fractions containing the product were combined and lyophilised.

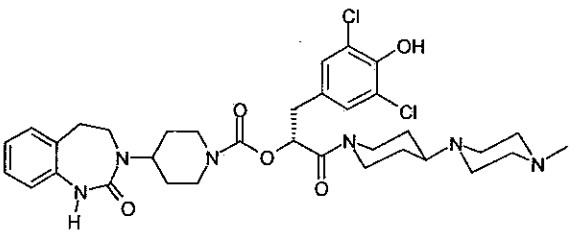
Yield: 28 mg (59% of theory)

ESI-MS: $(M+H)^+$ = 741/743 (Br)

retention time (HPLC-MS): 2.5 min (method A)

Example 8

(*R*)-1-(3,5-dichloro-4-hydroxy-benzyl)-2-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-2-oxo-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate



8a) 2,6-dichloro-4-iodo-phenol

Solutions of 40.7 g (245 mmol) sodium iodide in 160 mL water and 9.6 mL (143 mmol) ethane-1,2-diamine in 16 mL water were added to a solution of 40.0 g (245 mmol) 2,6-dichloro-phenol in 180 mL EtOH and the mixture was stirred for 15 min at RT. Then 62.3 g (245 mmol) iodine was added in small batches to the reaction mixture. To complete the reaction, after 3 h at RT, a further 31.1 g (122 mmol) iodine and 4.8 mL (72 mmol) ethane-1,2-diamine were added and the reaction mixture was stirred overnight at RT. Saturated $NaHSO_3$ solution was added until an acidic reaction occurred, the mixture was extracted three times with 400 mL EtOAc, the combined organic phases were washed with saturated NaCl solution

and dried over Na_2SO_4. After the desiccant and solvent had been eliminated the residue was reacted further without purification.

Yield: 69.0 g (97% of theory)

R_f = 0.5 (silica gel, n-hexane/EtOAc 4:1)

8b) [2-(2,6-dichloro-4-iodo-phenoxymethoxy)-ethyl]-trimethylsilane

Under a nitrogen atmosphere 33.5 g (242 mmol) K_2CO_3 and 20.7 mL (117 mmol) (2-chloromethoxy-ethyl)-trimethylsilan were added to a solution of 28.0 g (96.9 mmol) 2,6-dichloro-4-iodo-phenol in 800 mL acetonitrile and the reaction mixture was refluxed for 1 h. The reaction mixture was evaporated down i.vac., the residue was taken up in 300 mL water, extracted three times with 300 mL EtOAc and dried over Na_2SO_4. After the desiccant and solvent had been eliminated the residue was reacted further without purification.

Yield: 38.4 g (95% of theory)

R_f = 0.83 (silica gel, n-hexane/EtOAc 4:1)

8c) 3,5-dichloro-4-hydroxy-benzaldehyde

Under an argon atmosphere 39.4 mL (78.8 mmol) isopropylmagnesium chloride (2 M in THF), diluted with 50 mL THF, was slowly added dropwise to a solution of 30.0 g (71.6 mmol) [2-(2,6-dichloro-4-iodo-phenoxymethoxy)-ethyl]-trimethylsilane in 200 mL THF, cooled to -20°C. After the addition had ended 11.0 mL (143 mmol) DMF were added at -10°C and the reaction mixture was allowed to come up slowly to RT. After the reaction had ended (monitored by TLC) 100 mL of 2 M HCL were added and the reaction solution was stirred overnight at RT. It was extracted twice with 300 mL EtOAc, the combined organic phases were washed with saturated NaCl solution and dried over Na_2SO_4. After the desiccant and solvent had been eliminated the residue was purified by recrystallising twice from Cyc/EtOAc (1:1).

Yield: 12.0 g (88% of theory)

8d) (*Z,E*)-3-(4-acetoxy-3,5-dichloro-phenyl)-2-acetylamino-acrylic acid

A mixture of 12.2 g (64 mmol) 3,5-dichloro-4-hydroxy-benzaldehyde, 11.2 g (96 mmol) *N*-acetylglycine and 7.86 g (96 mmol) sodium acetate in 50 mL acetic anhydride was heated to 130°C (bath temperature) for 3 h. The reaction mixture was cooled to 90°C and 5 mL water were added such that the internal temperature did not exceed 100°C. The mixture was stirred for 2 h at 90°C and 200 mL water were added, whereupon a precipitate formed. This was filtered off, thoroughly washed with water and dried.

Yield: 12.0 g (57% of theory)

R_f = 0.84 (silica gel, Cyc/EtOAc 1:1)

8e) 3-(3,5-dichloro-4-hydroxy-phenyl)-2-oxo-propionic acid

131 mL 4 M HCl were added at RT to a solution of 12.0 g (36.1 mmol) (*Z,E*)-3-(4-acetoxy-3,5-dichloro-phenyl)-2-acetylamino-acrylic acid in 70 mL NMP and the reaction mixture was heated to 130°C (bath temperature) for 4 h. After cooling to 0°C 200 mL water were added and the mixture was stirred overnight, whereupon a precipitate formed. This was filtered off and dried (2.9 g; purity 95%). The filtrate was extracted three times with 300 mL Cyc/EtOAc (1:3), the combined organic phases were dried and evaporated down i.vac.. After the desiccant and solvent had been eliminated 4 g of the product (purity: 80%) were obtained.

Yield: 6.0 g (66% of theory)

ESI-MS: $(M+H)^+$ = 250/252/254 (2Cl)

R_f = 0.30 (silica gel, DCM/MeOH/AcOH 90:10:1)

8f) (*R*)-3-(3,5-dichloro-4-hydroxy-phenyl)-2-hydroxy-propionic acid

Prepared analogously to Example 7c from 3.00 g (10.0 mmol) 3-(3,5-dichloro-4-hydroxy-phenyl)-2-oxo-propionic acid (purity: 80%) and 6.34 g (20.0 mmol) (1*R*)-B-chlorodiisopinocampheylborane. The crude product (1.9 g) was further reacted without purification.

8g) methyl (*R*)-3-(3,5-dichloro-4-hydroxy-phenyl)-2-hydroxy-propionate

2 mL concentrated sulphuric acid were added to a solution, cooled to 0°C, of the crude product from Example 8f in 30 mL MeOH and the reaction mixture was stirred for 2 h at this temperature. The mixture was neutralised with solid $KHCO_3$, diluted with water and extracted exhaustively with EtOAc. The combined organic phases were washed with saturated NaCl solution and dried over Na_2SO_4. After the desiccant and solvent had been eliminated the product was further reacted without purification.

Yield: 1.8 g (75% of theory over 2 steps)

8h) methyl (*R*)-3-[3,5-dichloro-4-(2-trimethylsilanyl-ethoxymethoxy)-phenyl]-2-hydroxy-propionate

Under a nitrogen atmosphere 5.79 g (76.6 mmol) 40% KF/Al_2O_3 were added to a solution of 2.64 g (9.96 mmol) methyl (*R*)-3-(3,5-dichloro-4-hydroxy-phenyl)-2-hydroxy-propionate in 20 mL acetonitrile and the resulting suspension was stirred for a few min at RT. Then a solution of 2.12 mL (12.0 mmol) (2-chloromethoxy-ethyl)-trimethylsilane in 20 mL acetonitrile was added and the reaction mixture was stirred for 20 h at RT. The mixture was filtered through Celite and the solvent was evaporated down i.vac.. The residue was further reacted without purification.

Yield: 3.80 g (97% of theory)

8i) (*R*)-2-[3,5-dichloro-4-(2-trimethylsilanyl-ethoxymethoxy)-phenyl]-1-methoxycarbonyl-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate

Prepared analogously to Example 6f from 3.80 g (8.65 mmol) methyl (*R*)-3-[3,5-dichloro-4-(2-trimethylsilanyl-ethoxymethoxy)-phenyl]-2-hydroxy-propionate and 2.12 g (8.65 mmol) 3-piperidin-4-yl-1,3,4,5-tetrahydro-1,3-benzodiazepin-2-one. The product was purified by chromatography (silica gel, DCM/MeOH 98:2).

Yield: 3.10 g (54% of theory)

8k) (*R*)-2-(3,5-dichloro-4-hydroxy-phenyl)-1-methoxycarbonyl-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate

Prepared analogously to Example 6g from 3.10 g (4.65 mmol) (*R*)-2-[3,5-dichloro-4-(2-trimethyl-silanyl-ethoxy-methoxy)-phenyl]-1-methoxycarbonyl-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate and 4.48 mL methanolic sulphuric acid (0.5 M).

Yield: 2.49 g (100% of theory)

8l) (*R*)-1-carboxy-2-(3,5-dichloro-4-hydroxy-phenyl)-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate

A solution of 0.42 g (17.3 mmol) LiOH in 20 mL water was added to a solution of 2.49 g (4.64 mmol) (*R*)-2-(3,5-dichloro-4-hydroxy-phenyl)-1-methoxycarbonyl-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate in 50 mL THF and the reaction mixture was stirred for 1 h at RT. The organic solvent was eliminated i.vac., the aqueous phase was washed with EtOAc, acidified with 10% HCl, exhaustively extracted with EtOAc, the combined organic phases were washed with saturated NaCl solution and dried over Na_2SO_4. After the desiccant and solvent had been eliminated the residue was triturated with diethyl ether, suction filtered and dried.

Yield: 1.60 g (66% of theory)

R_f = 0.05 (silica gel, DCM/MeOH 9:1)

8m) (*R*)-1-(3,5-dichloro-4-hydroxy-benzyl)-2-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-2-oxo-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate

Under a nitrogen atmosphere a mixture of 150 mg (0.29 mmol) (*R*)-1-carboxy-2-(3,5-dichloro-4-hydroxy-phenyl)-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate, 63.8 mg (0.34 mmol) 1-methyl-4-piperidin-4-yl-piperazine and 0.17 mL (0.98 mmol) ethyldiisopropylamine in 10 mL DMF was stirred for 5 min at RT. Then 124 mg (0.32 mmol) HATU was added to the reaction mixture, which was then stirred for 4 h. This was evaporated down

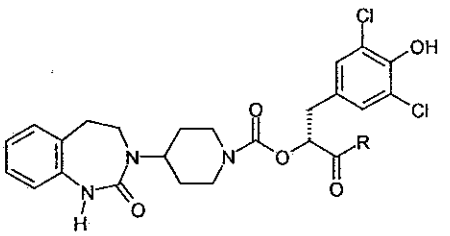
i.vac. and the residue was purified by chromatography (silica gel, gradient DCM to DCM/MeOH 85:15). The fractions containing the product were combined, evaporated down i.vac. and filtered through aluminium oxide, wherein the product was eluted with DCM/MeOH 9:1. The mixture was evaporated down i.vac., the residue was triturated with diethyl ether, and the product was filtered and dried.

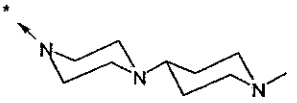
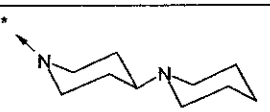
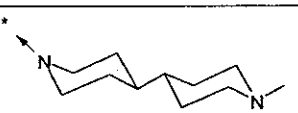
Yield: 43 mg (22% of theory)

ESI-MS: $(M+H)^+$ = 687/689 (2Cl)

retention time (HPLC-MS): 2.8 min (method A)

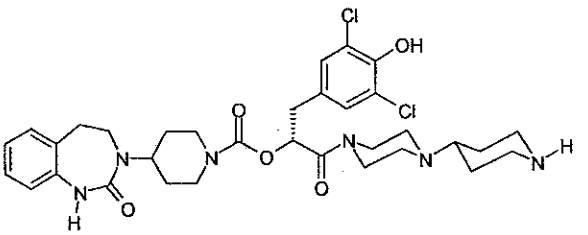
The following compounds were prepared analogously from in each case 150 mg (*R*)-1-carboxy-2-(3,5-dichloro-4-hydroxy-phenyl)-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate and the corresponding amount of amine:



Example	R	Yield (%)	Mass spectrum	retention time HPLC (method)
8.1		21	687/689 $[M+H]^+$	2.6 (A)
8.2		39	672/74 $[M+H]^+$	3.1 (A)
8.3		38	686/688 $[M+H]^+$	3.1 (A)

Example 8.4

(*R*)-1-(3,5-dichloro-4-hydroxy-benzyl)-2-oxo-2-(4-piperidin-4-yl-piperazin-1-yl)-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate



Under a nitrogen atmosphere a mixture of 150 mg (0.29 mmol) (*R*)-1-carboxy-2-(3,5-dichloro-4-hydroxy-phenyl)-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate, 105 mg (0.34 mmol) *tert*-butyl 4-piperazin-1-yl-piperidine-1-carboxylate (used as the hydrochloride salt) and 0.17 mL (0.98 mmol) ethyldiisopropylamine in 10 mL DMF was stirred at RT for 5 min. Then 124 mg (0.32 mmol) HATU was added to the reaction mixture, which was then stirred for 4 h. This was evaporated down i.vac. and the residue was purified by chromatography (silica gel, gradient DCM to DCM/MeOH 85:15). The fractions containing the product were combined and evaporated down i.vac.. The residue was taken up in 10 mL formic acid and stirred for 3 h at RT. The mixture was evaporated down i.vac., the residue was taken up in saturated NH_3 solution, extracted exhaustively with EtOAc, the combined organic phases were washed with saturated NaCl solution and dried over Na_2SO_4. After the desiccant and solvent had been eliminated the residue was triturated with diethyl ether, suction filtered and dried.

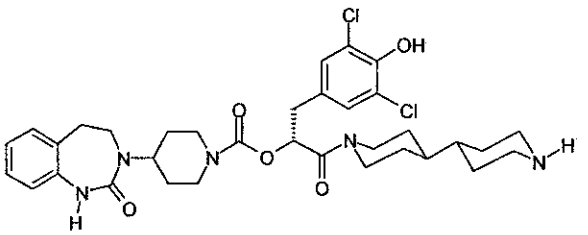
Yield: 47 mg (24% of theory)

ESI-MS: $(M+H)^+$ = 673/675 (2Cl)

retention time (HPLC-MS): 2.6 min (method A)

Example 8.5

(*R*)-2-4,4'-bipiperidinyl-1-yl-1-(3,5-dichloro-4-hydroxy-benzyl)-2-oxo-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate



Prepared analogously to Example 8.4 from 150 mg (0.29 mmol) (*R*)-1-carboxy-2-(3,5-dichloro-4-hydroxy-phenyl)-ethyl 4-(2-oxo-1,2,4,5-tetrahydro-1,3-benzodiazepin-3-yl)-piperidine-1-carboxylate and 92 mg (0.34 mmol) *tert*-butyl [4,4']bipiperidinyl-1-carboxylate.

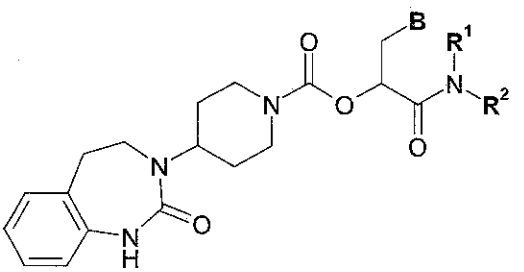
Yield: 84 mg (44% of theory)

ESI-MS: $(M+H)^+$ = 672/674 (2Cl)

retention time (HPLC-MS): 3.1 min (method A)

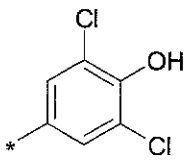
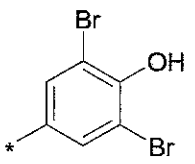
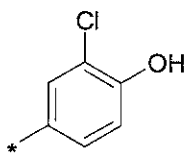
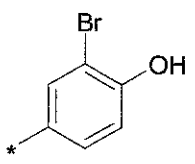
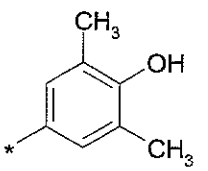
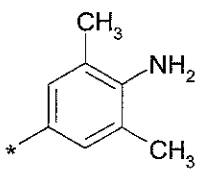
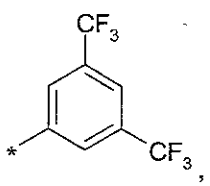
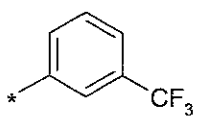
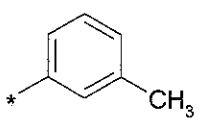
PATENT CLAIMS

1. CGRP antagonists of general formula **I**

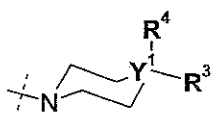


wherein

B denotes a group selected from









and


R^1 and **R^2** together with the enclosed nitrogen atom denote a group of general formula **II**



wherein

Y^1 denotes the carbon atom or, if R^4 denotes a free pair of electrons, it may also denote the nitrogen atom,

R^3 denotes a cyclopentyl, cyclohexyl or cycloheptyl group or

R^3 denotes a heterocycle selected from a morpholin-4-yl, 1,1-dioxo-thiomorholin-4-yl, piperidin-1-yl, piperidin-4-yl, piperazin-1-yl or pyrrolidin-1-yl group,

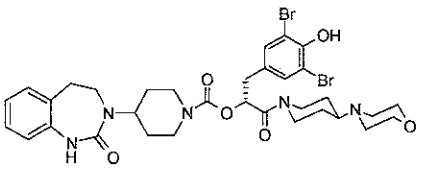
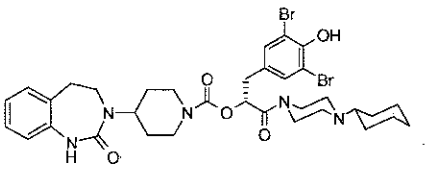
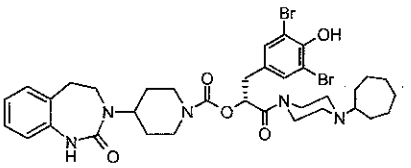
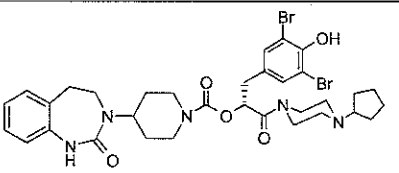
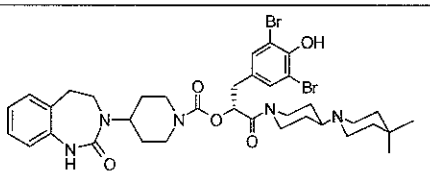
wherein the above-mentioned monocyclic heterocycles in the ring may be mono- or disubstituted by hydroxy, methyl, ethyl, trifluoromethyl, hydroxymethyl or hydroxyethyl groups, or may optionally additionally be monosubstituted by a hydroxycyclopropyl, trifluoromethylcarbonylmethyl, amino, carboxy-carbonyl, methoxycarbonyl, ethoxycarbonyl-carbonyl, carboxymethyl, carboxyethyl, ethoxycarbonylmethyl, ethoxycarbonylethyl, carboxy-ethylcarbonyl, ethoxycarbonyl-ethylcarbonyl, aminosulphonyl, methylaminosulphonyl, dimethylaminosulphonyl, methylsulphonyl, ethylsulphonyl, isopropylsulphonyl, cyclopropylsulphonyl, (hydroxyamino)-carbonylmethyl, hydroxy-(methyl)-aminocarbonyl-methyl or methoxyaminocarbonyl-methyl group, wherein the substituents may be identical or different and may be bound to a ring carbon or ring nitrogen atom, or

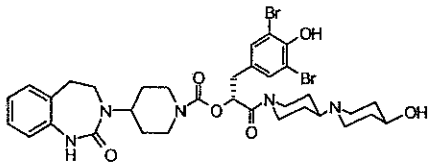
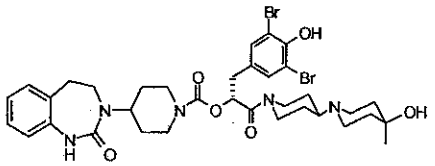
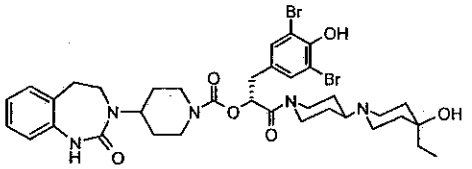
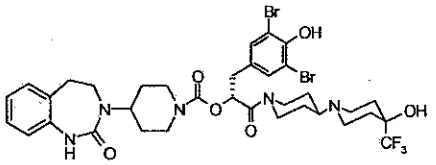
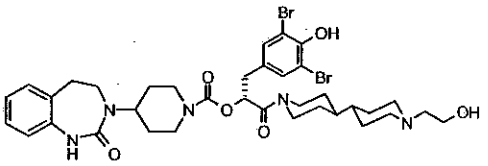
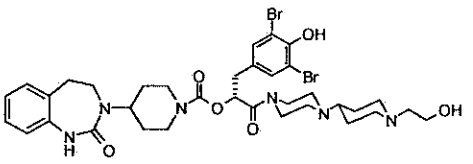
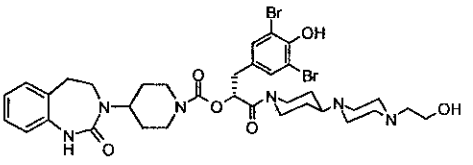
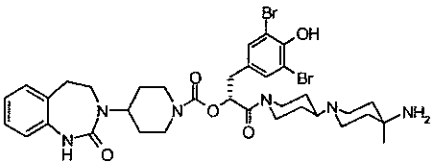
the above-mentioned monocyclic heterocycles in the ring may be monosubstituted by a carboxy group, if this carboxy group is not bound via a nitrogen atom, and

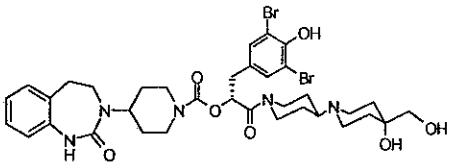
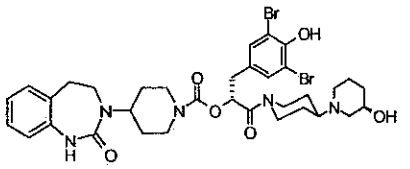
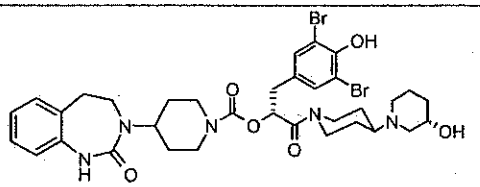
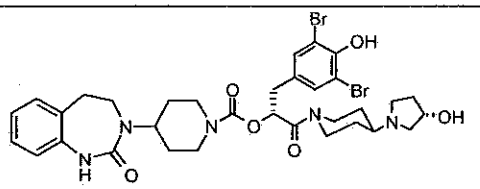
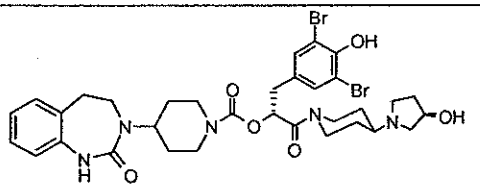
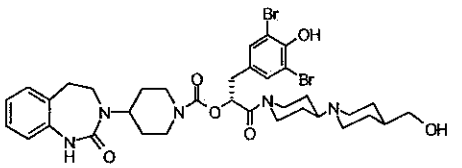
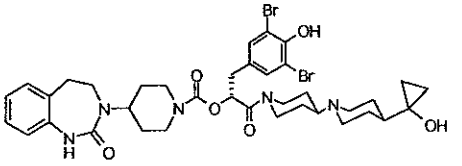
R^4 denotes the hydrogen atom, if Y^1 denotes the carbon atom, or

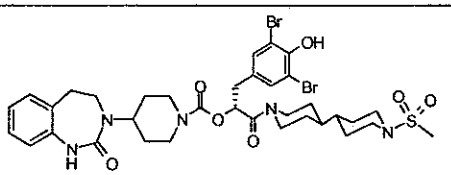
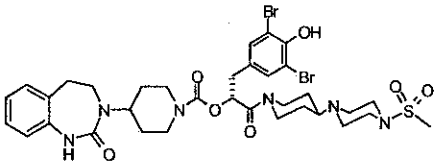
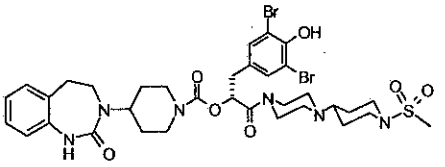
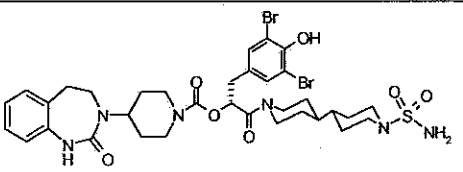
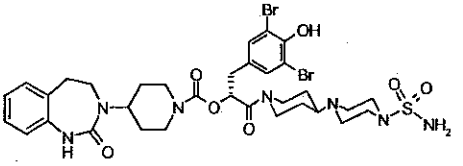
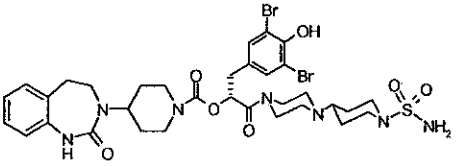
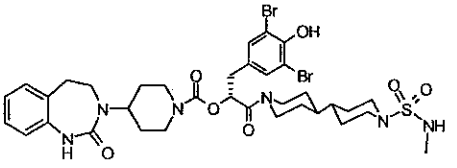
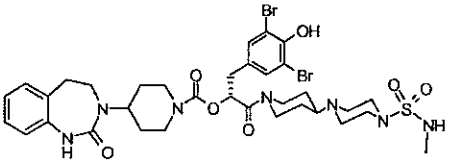
R^4 denotes a free pair of electrons, if Y^1 denotes the nitrogen atom,

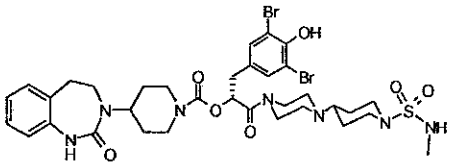
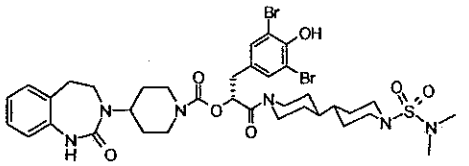
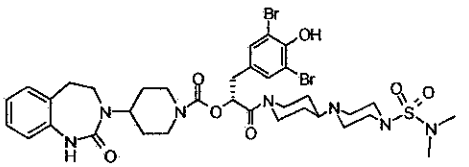
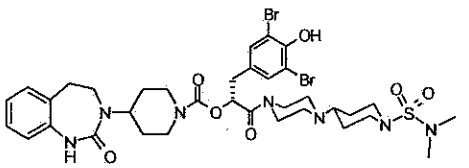
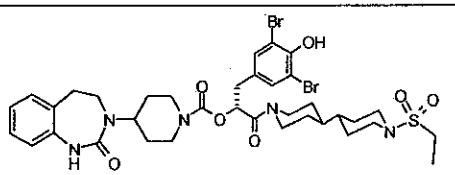
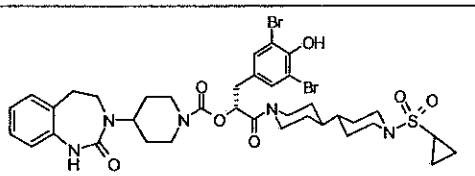
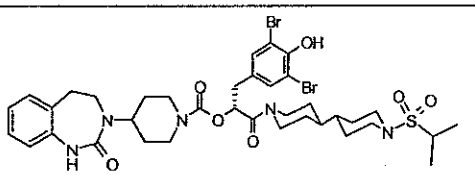
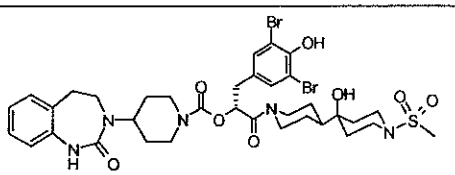
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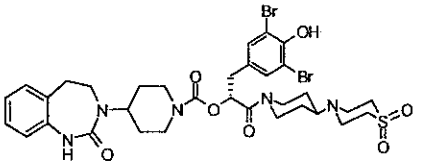
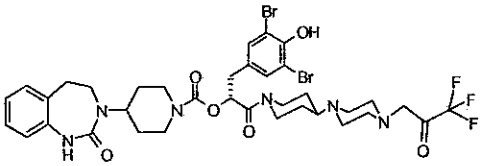
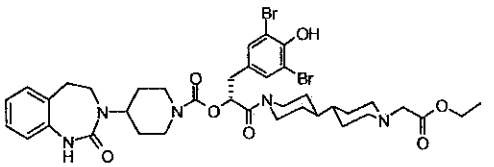
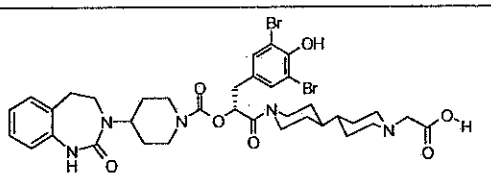
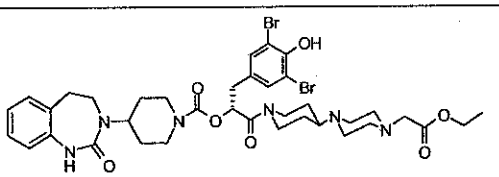
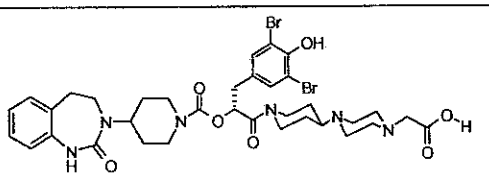
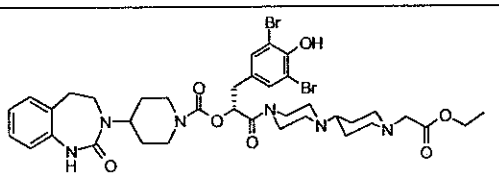
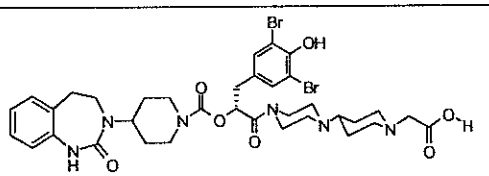
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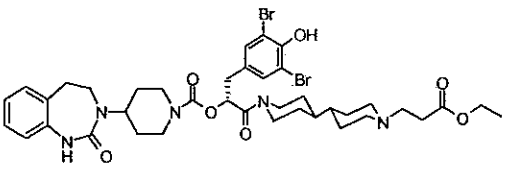
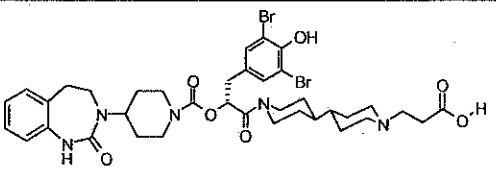
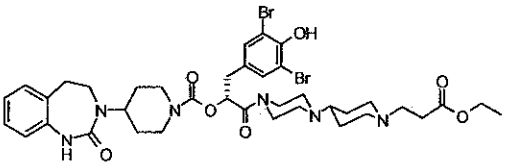
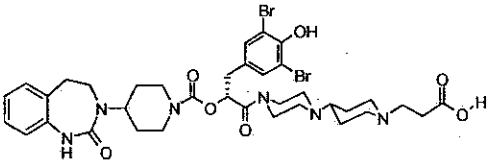
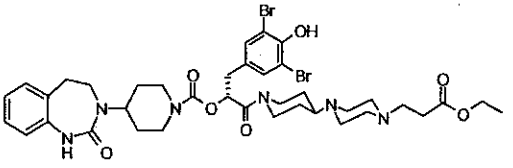
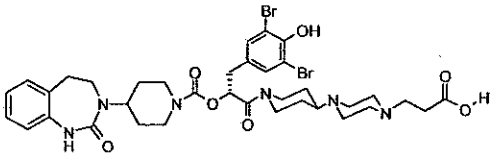
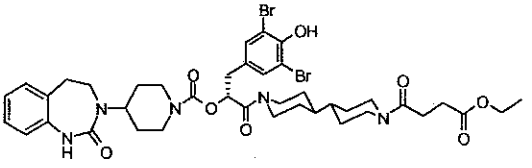
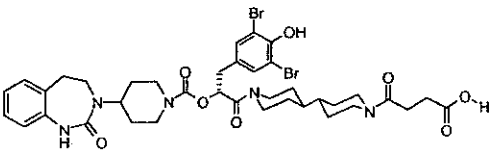
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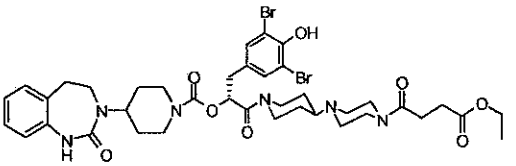
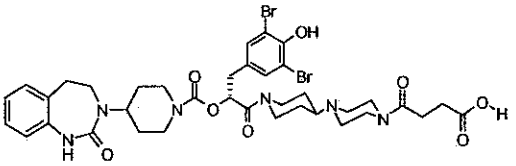
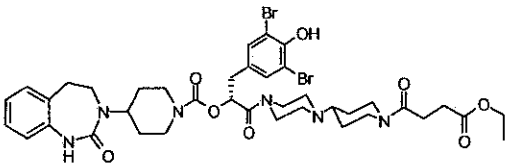
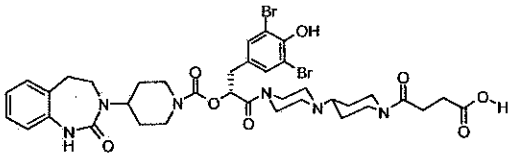
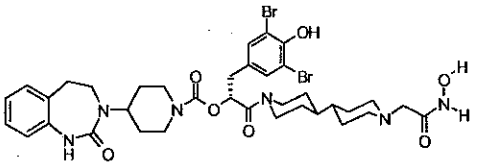
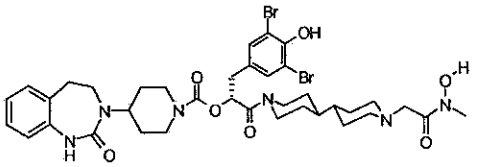
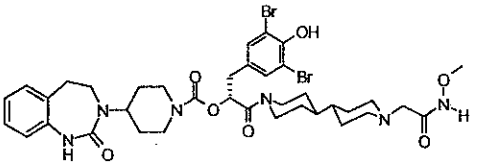
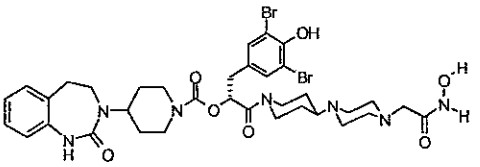
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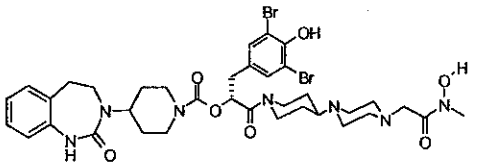
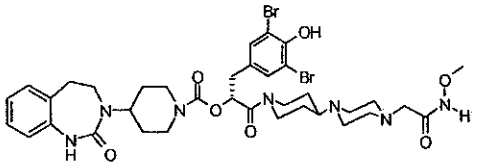
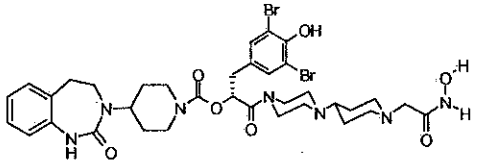
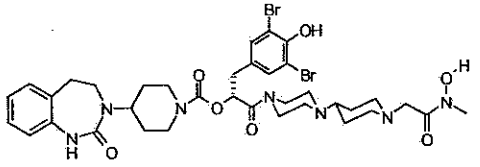
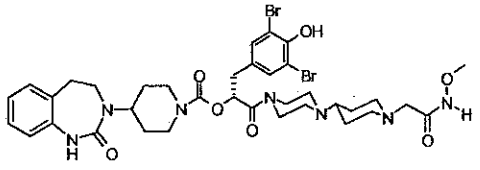
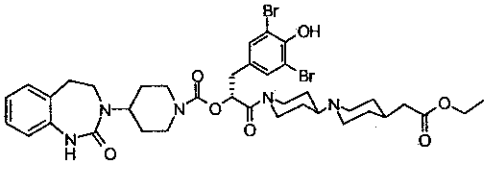
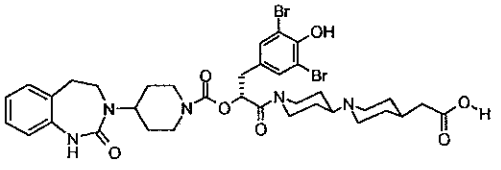
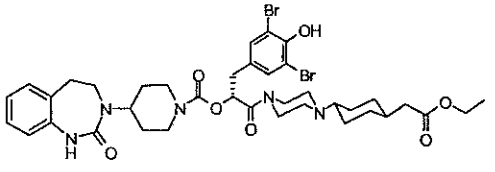
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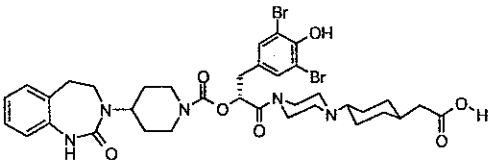
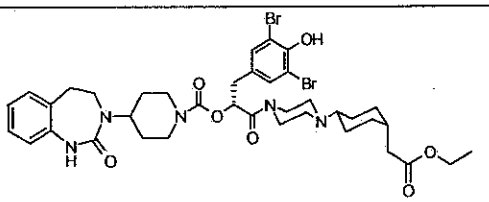
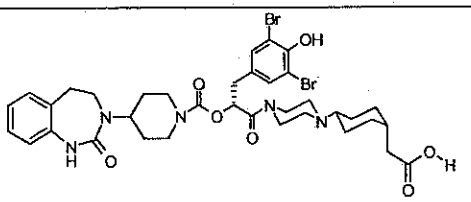
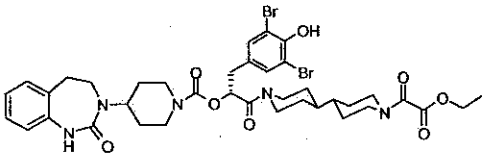
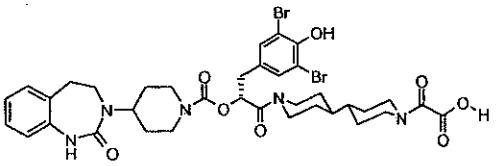
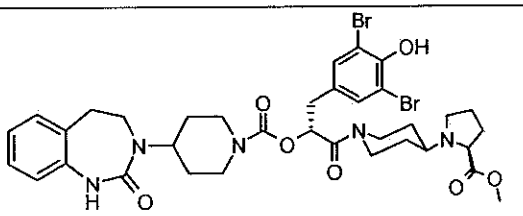
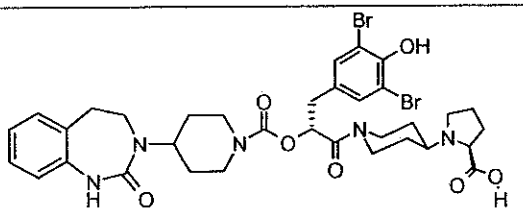
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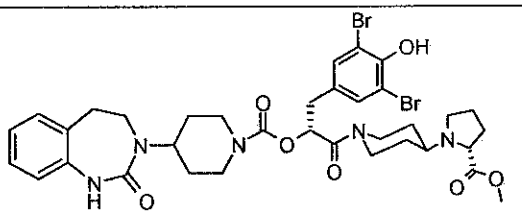
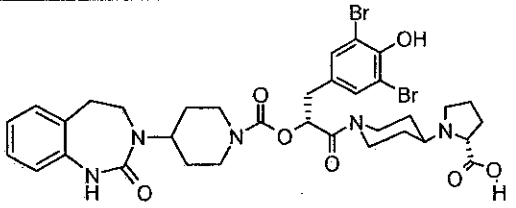
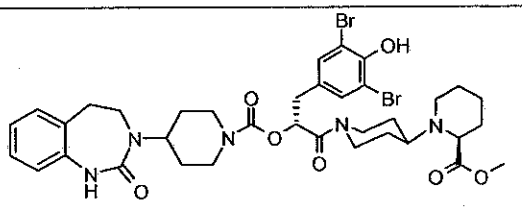
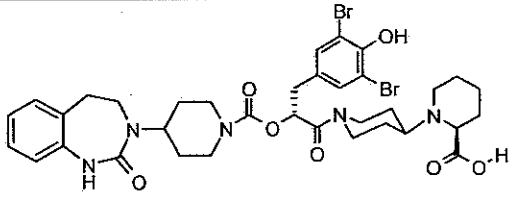
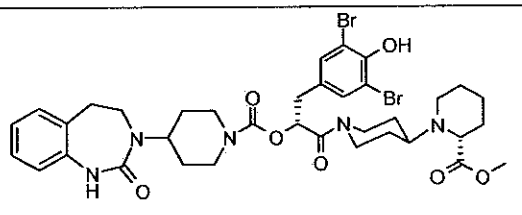
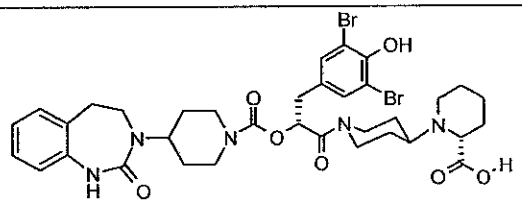
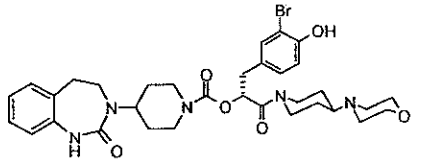
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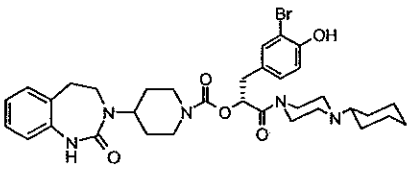
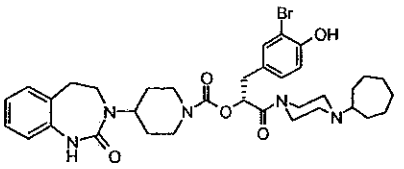
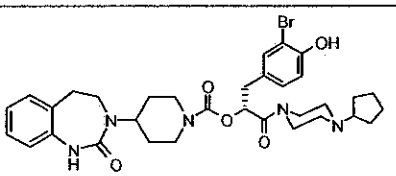
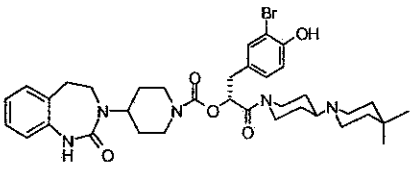
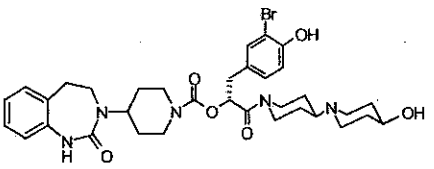
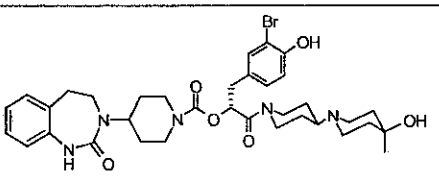
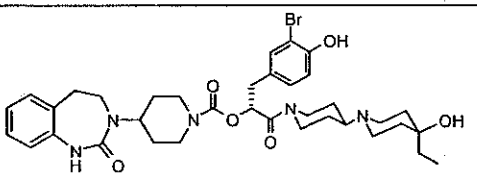
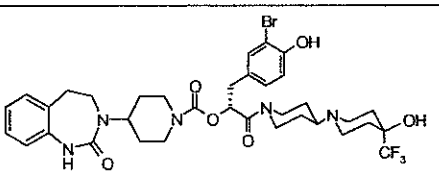
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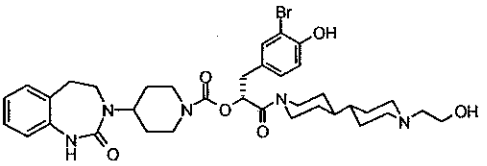
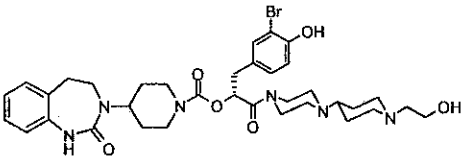
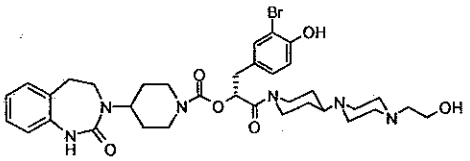
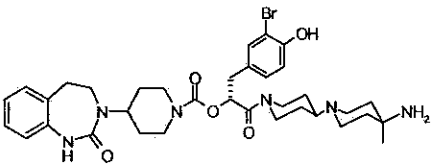
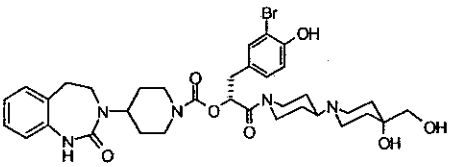
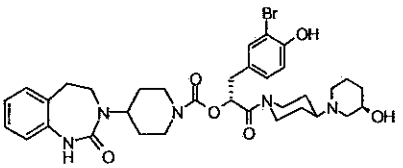
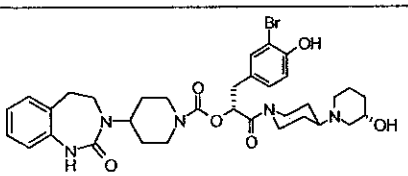
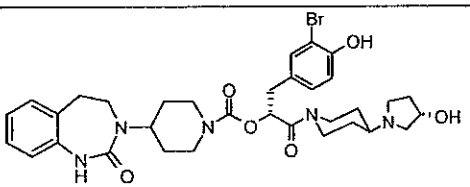
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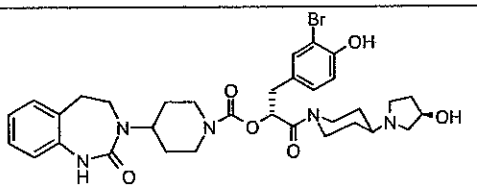
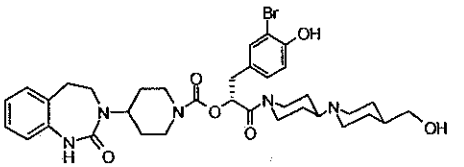
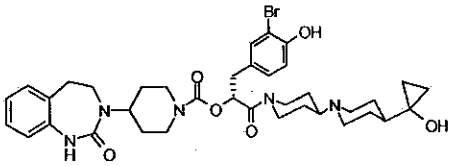
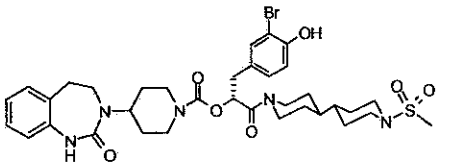
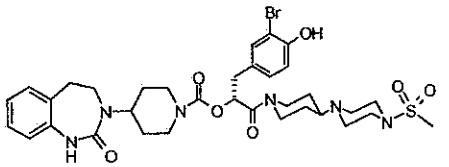
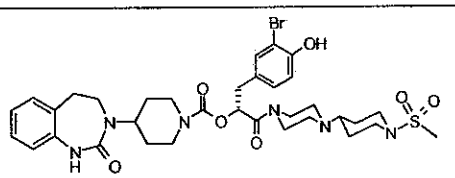
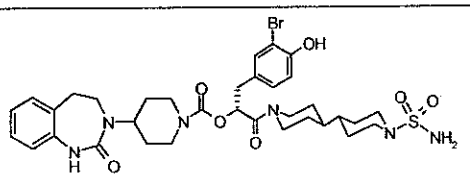
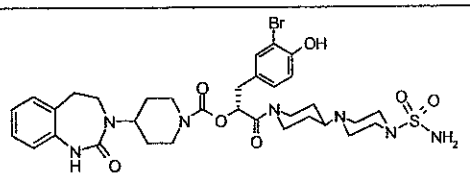
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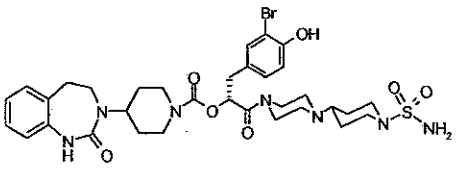
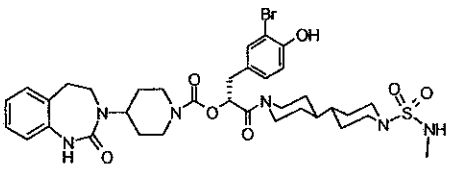
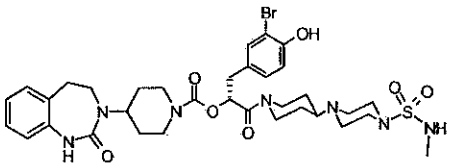
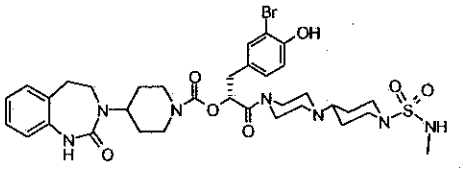
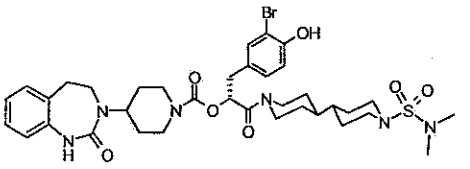
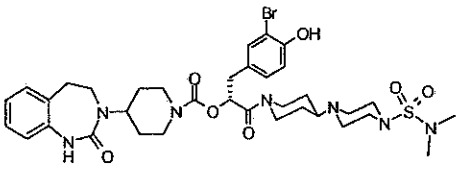
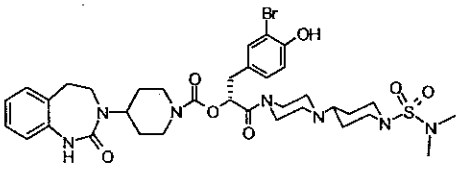
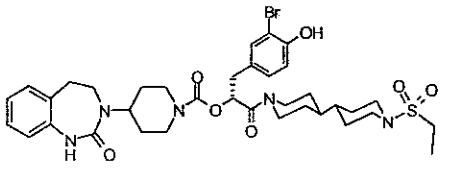
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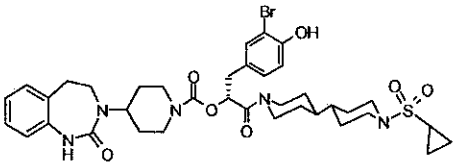
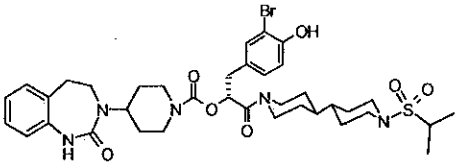
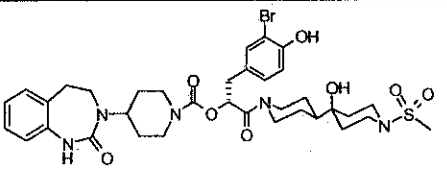
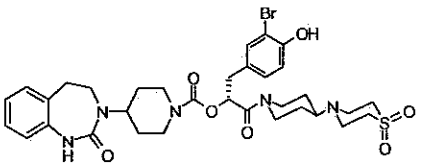
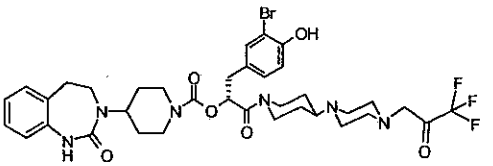
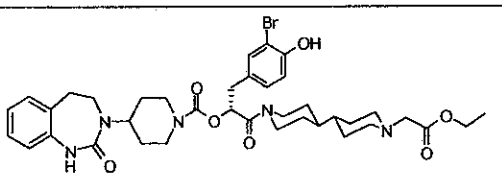
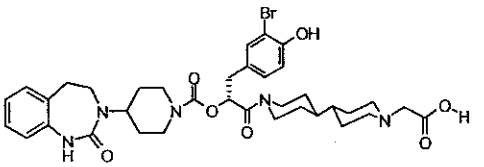
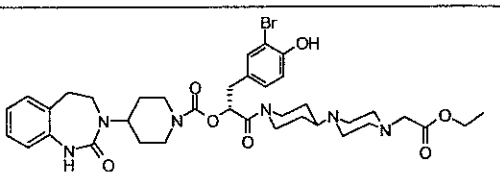
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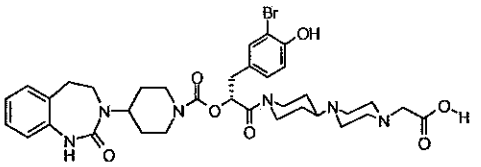
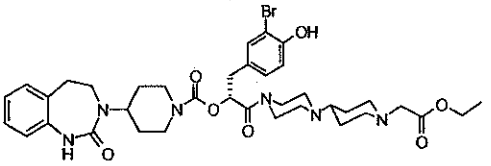
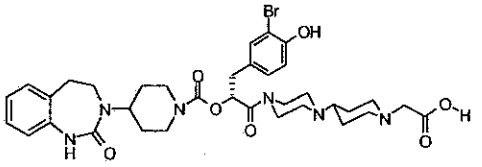
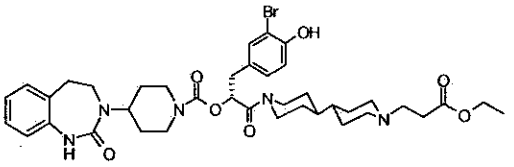
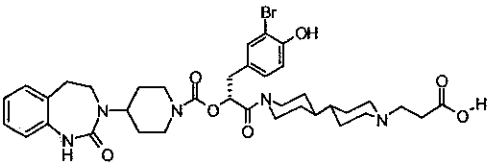
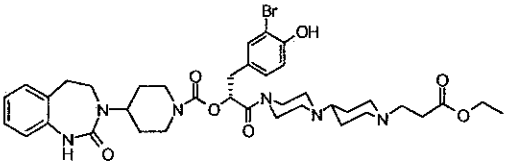
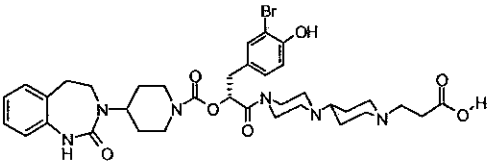
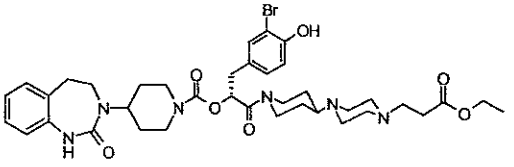
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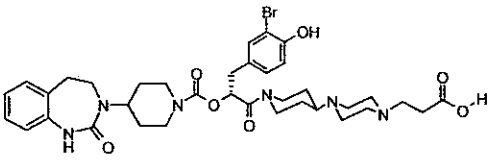
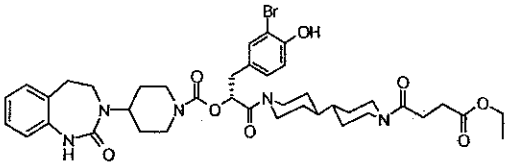
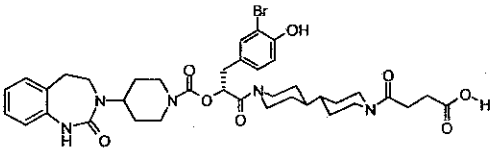
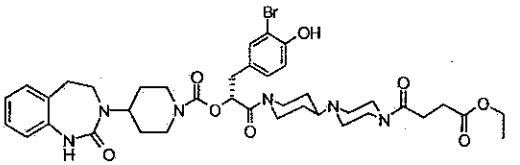
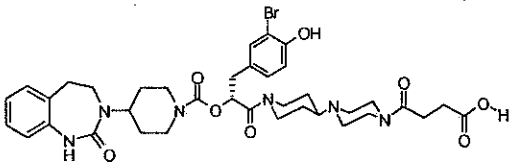
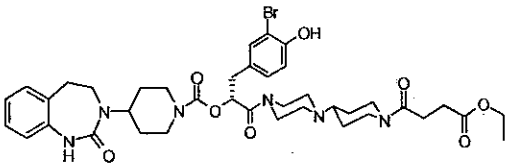
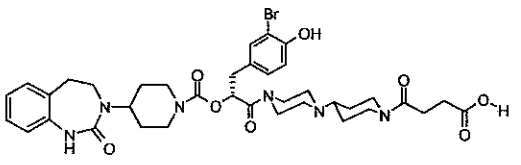
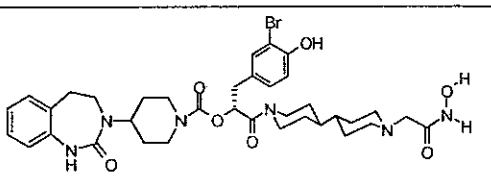
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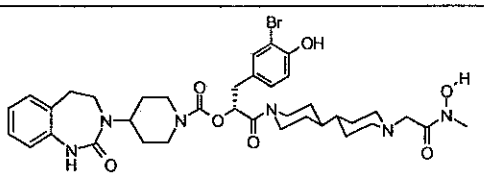
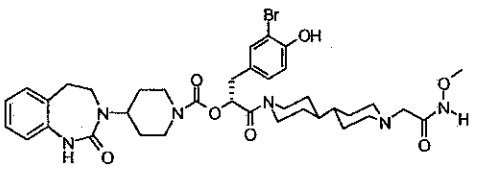
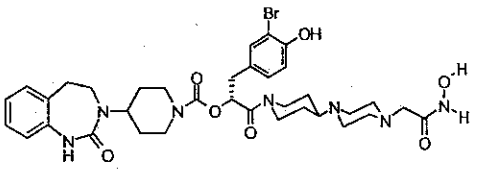
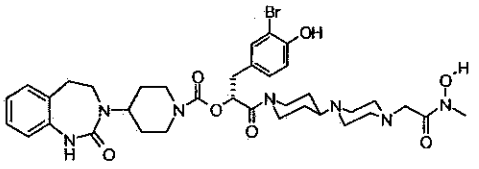
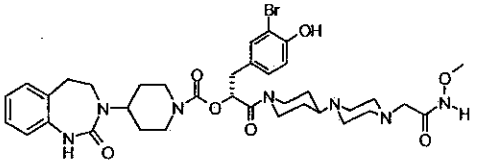
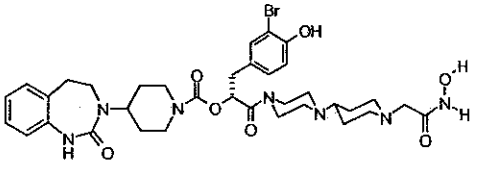
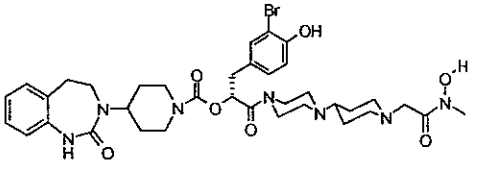
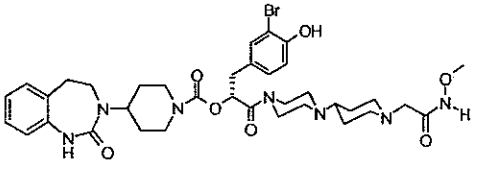
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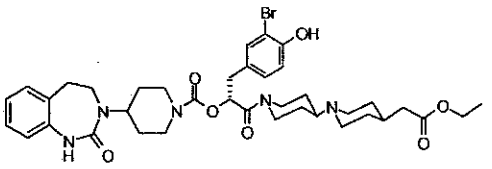
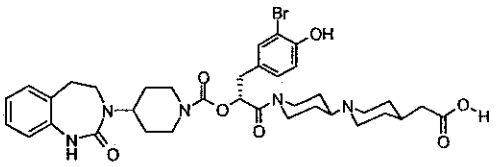
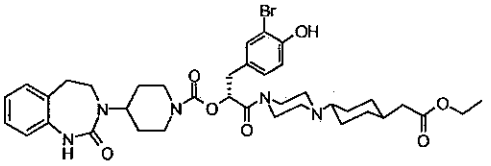
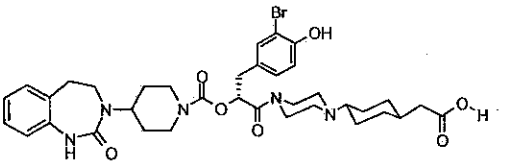
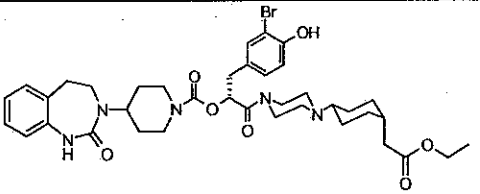
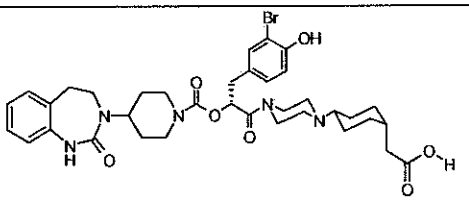
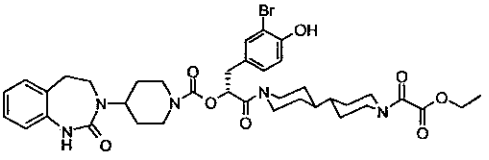
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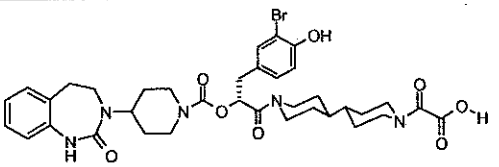
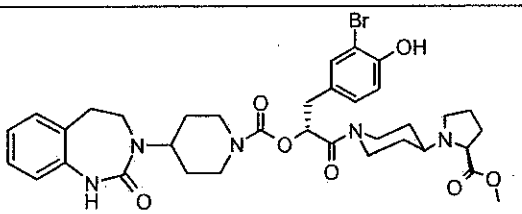
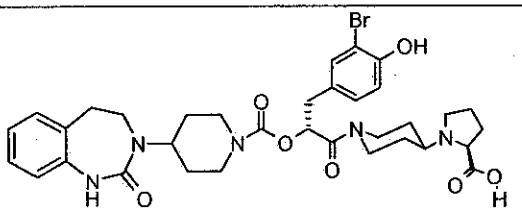
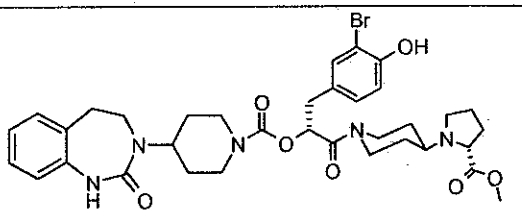
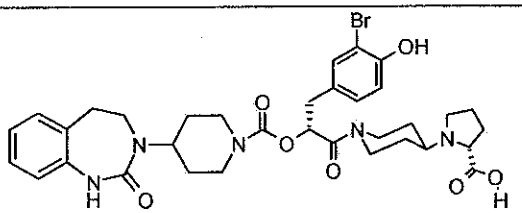
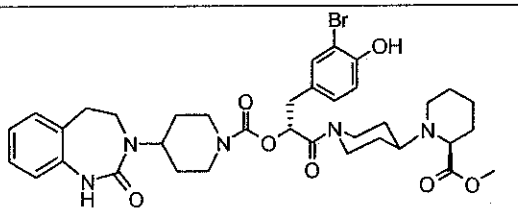
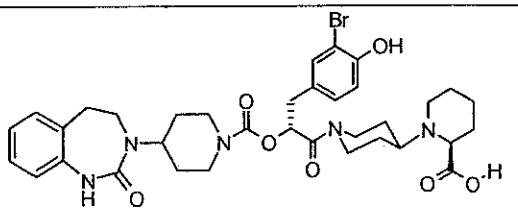
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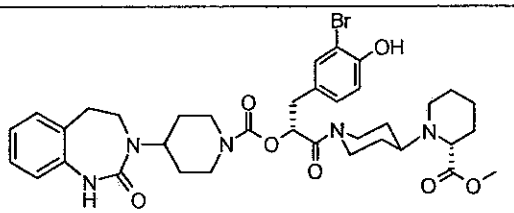
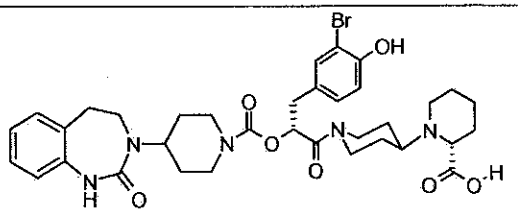
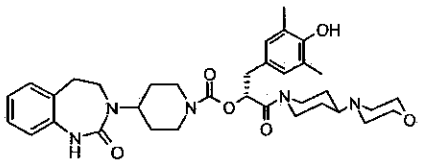
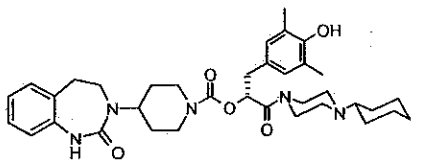
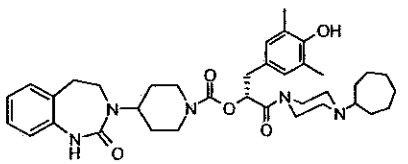
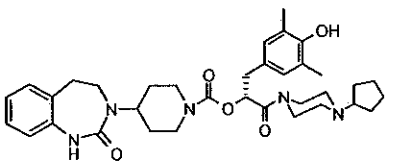
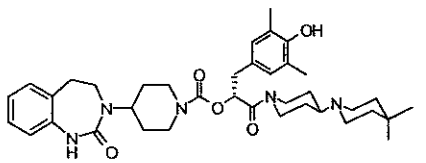
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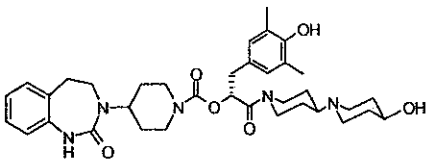
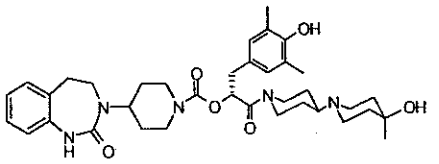
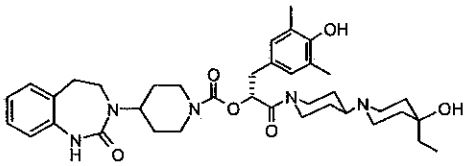
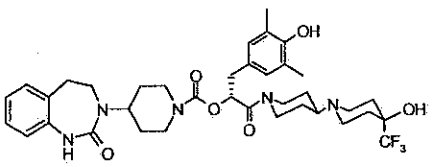
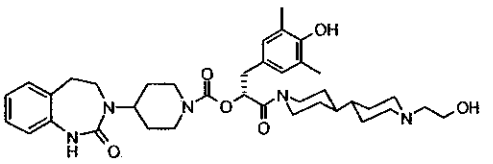
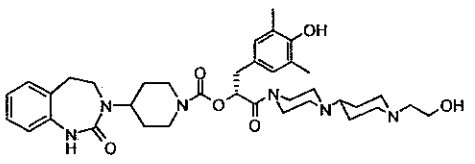
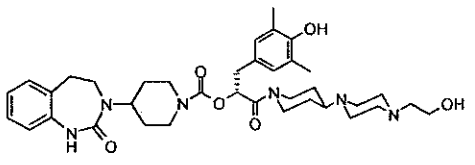
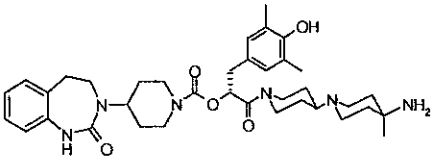
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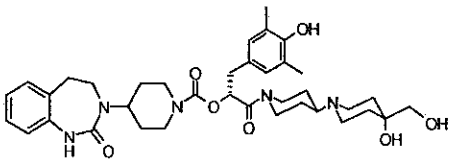
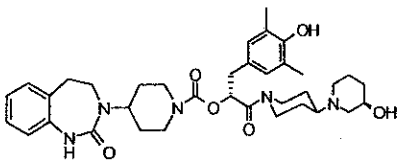
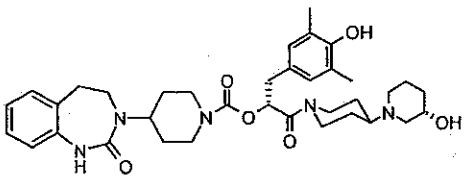
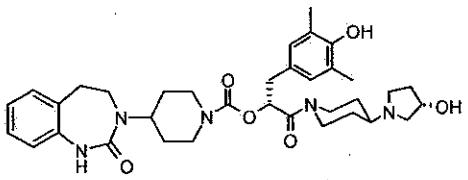
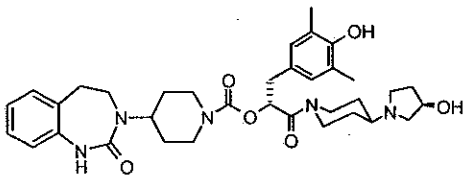
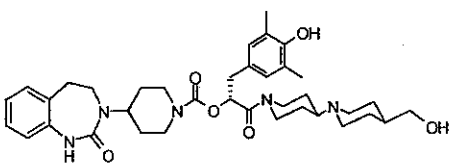
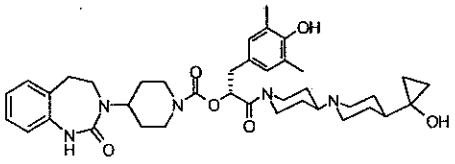
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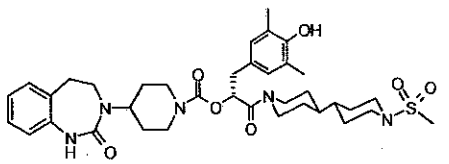
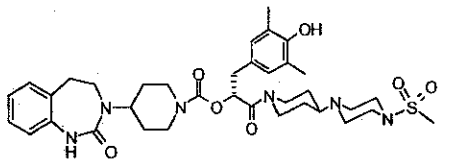
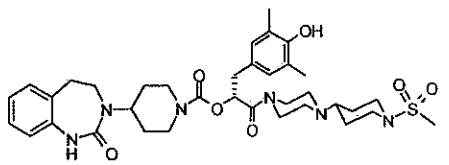
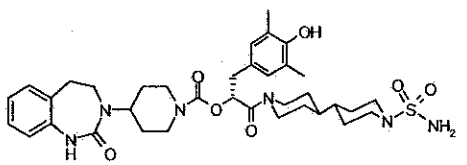
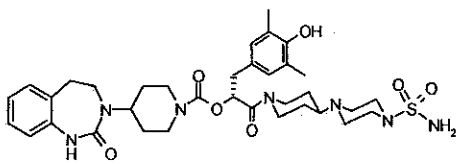
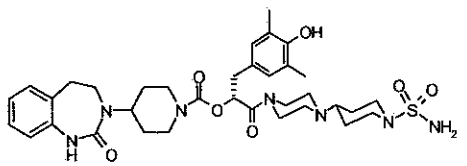
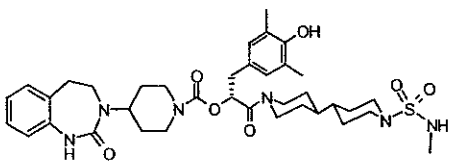
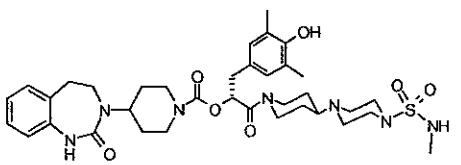
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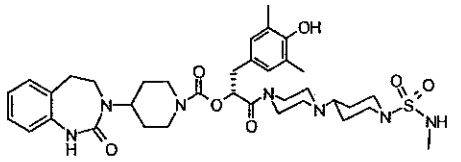
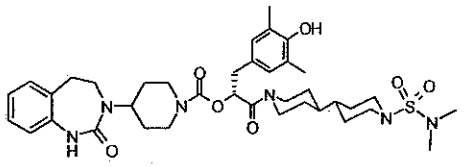
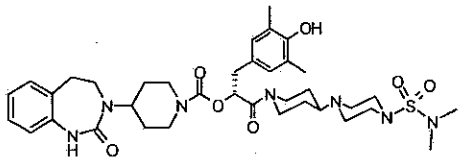
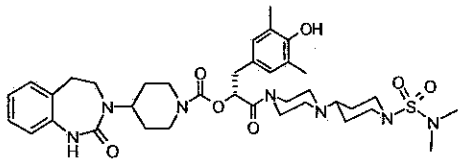
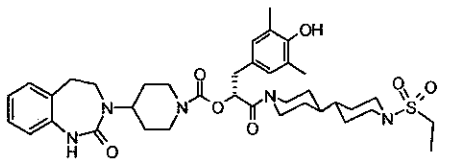
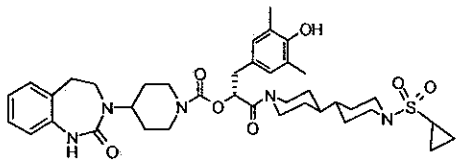
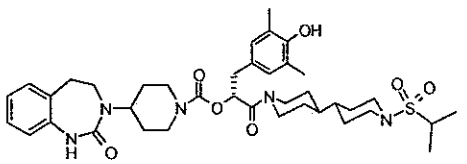
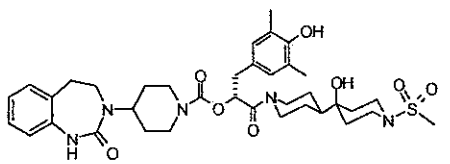
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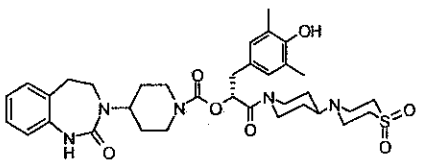
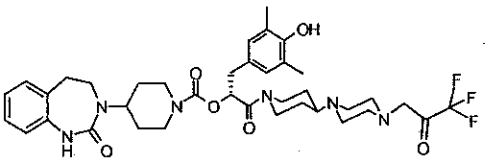
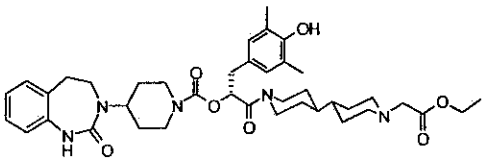
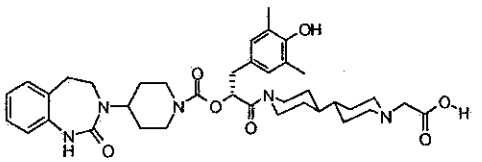
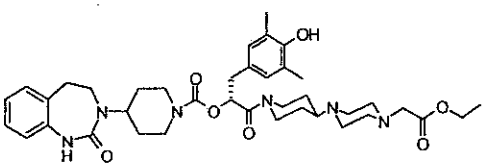
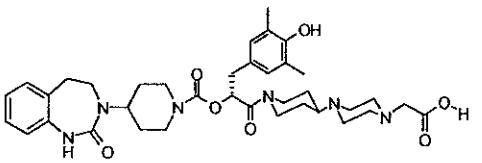
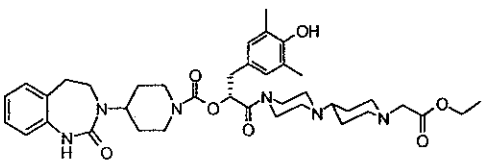
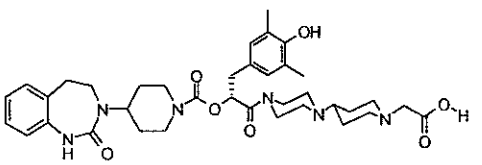
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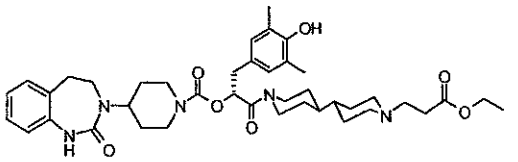
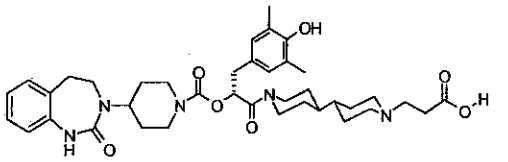
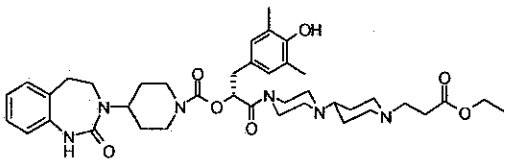
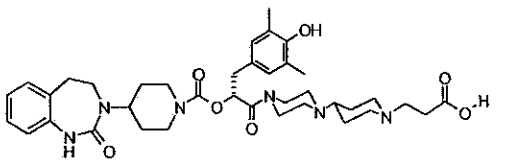
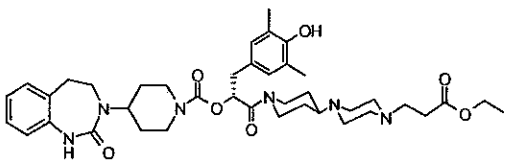
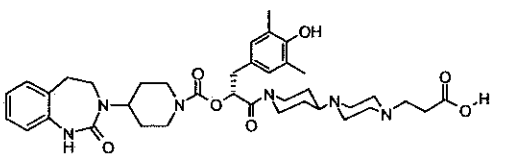
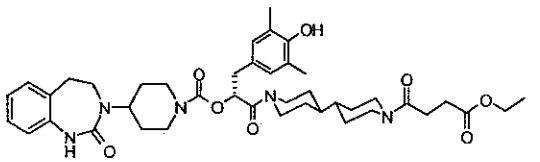
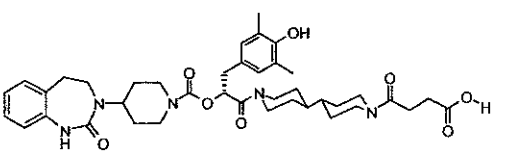
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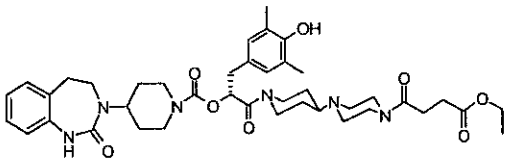
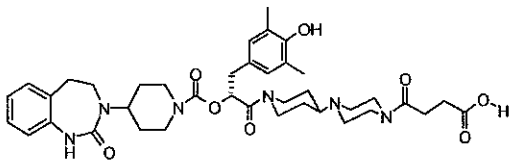
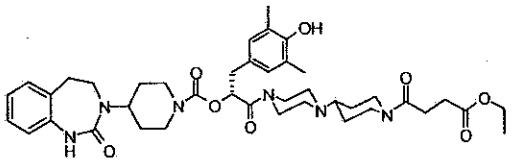
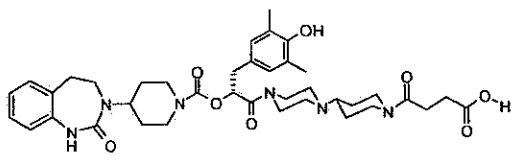
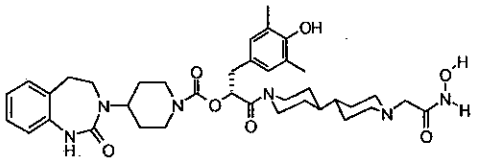
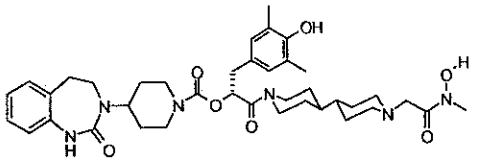
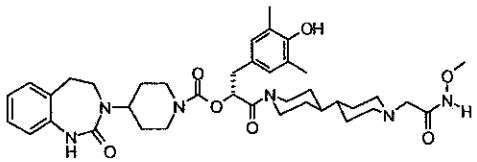
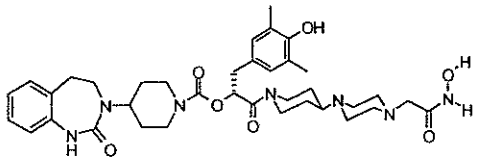
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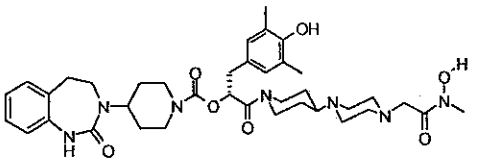
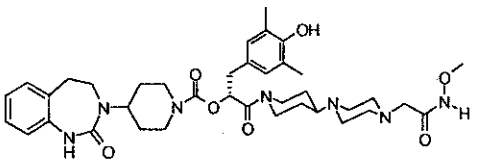
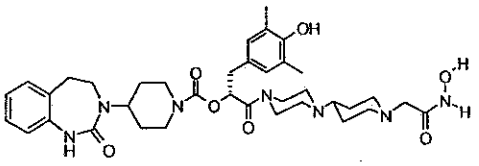
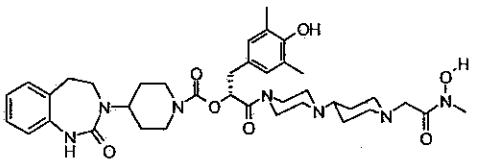
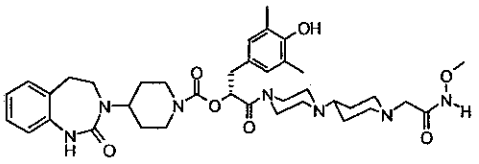
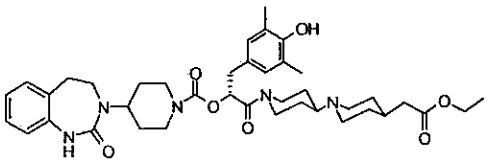
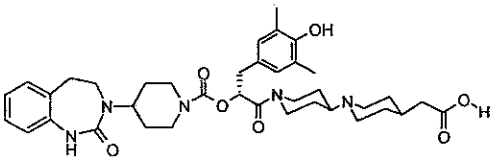
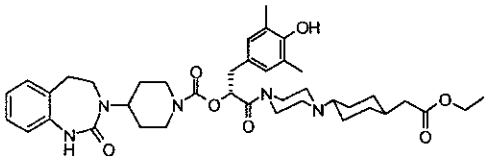
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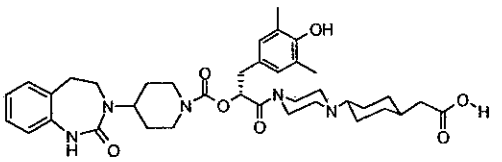
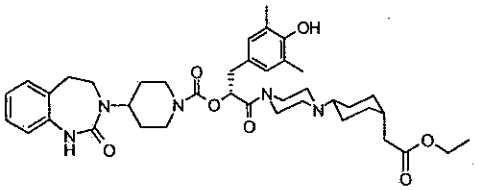
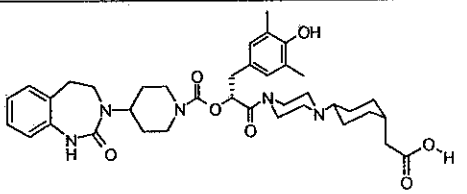
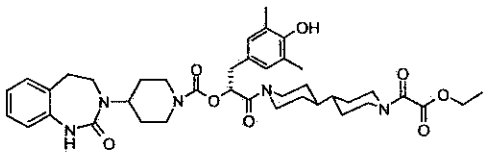
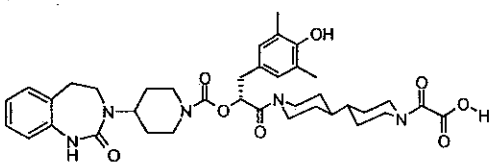
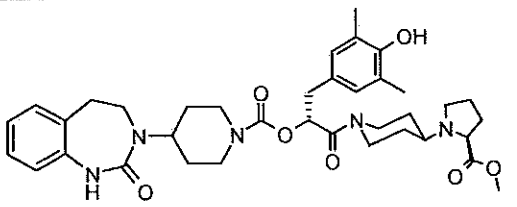
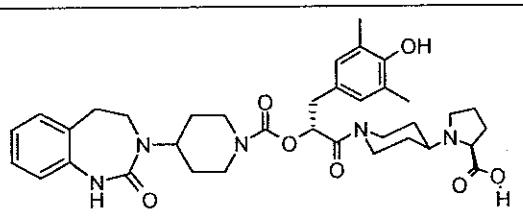
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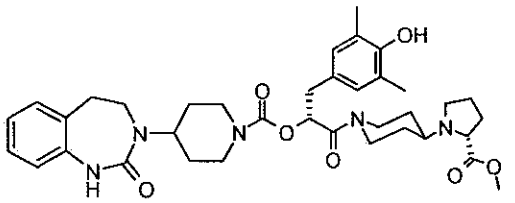
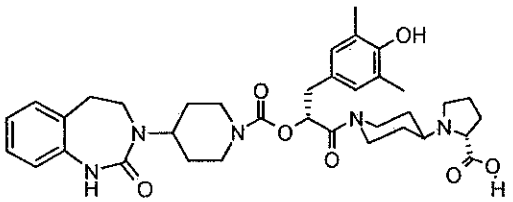
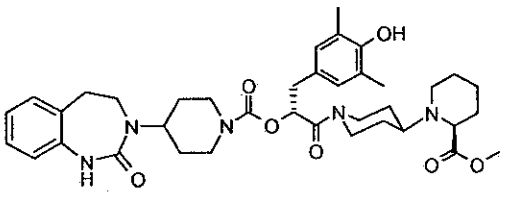
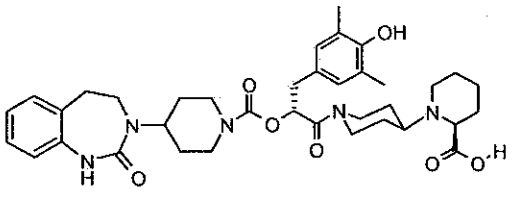
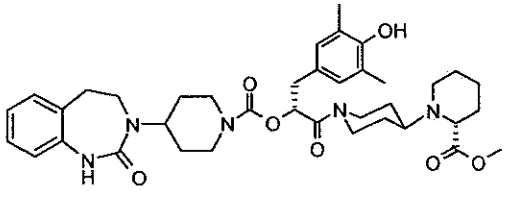
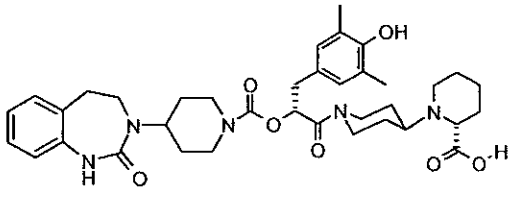
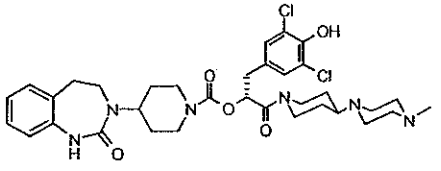
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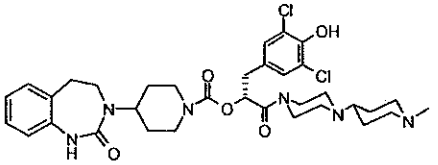
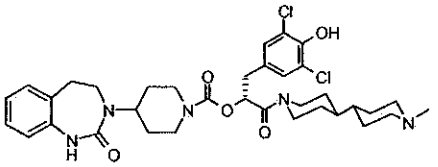
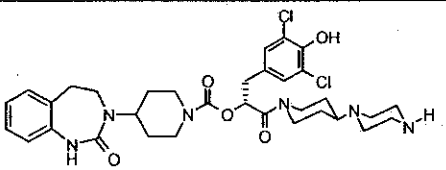
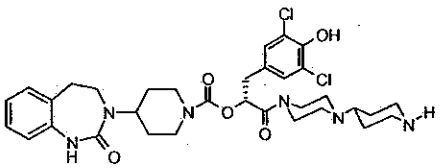
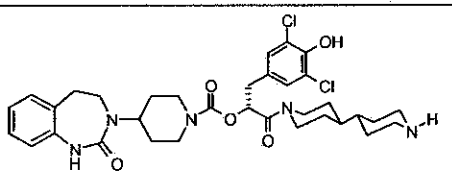
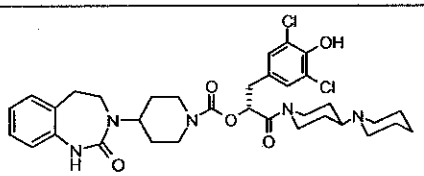
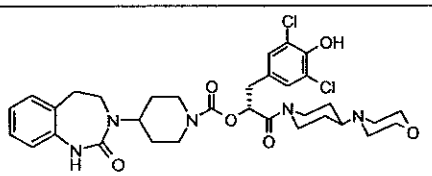
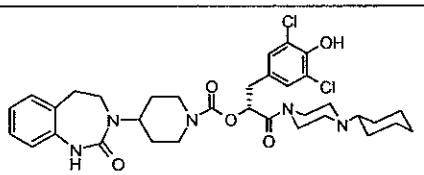
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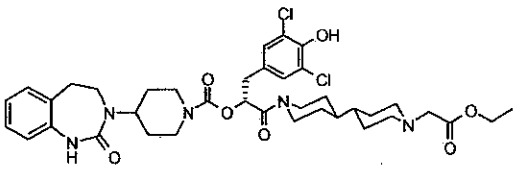
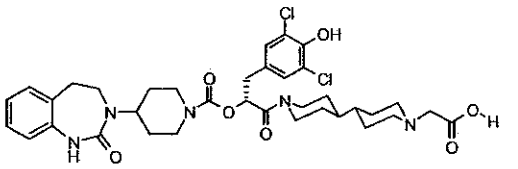
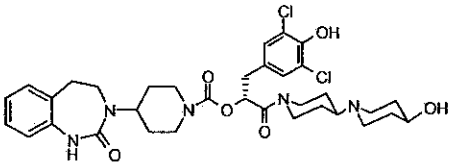
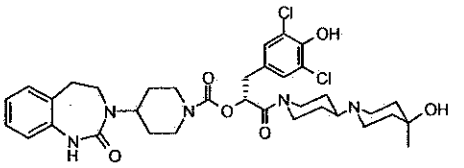
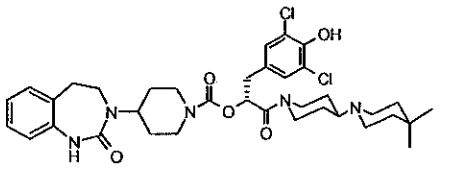
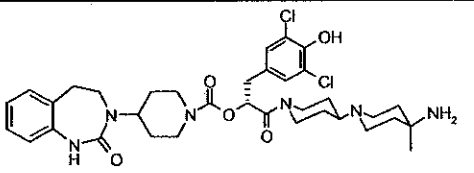
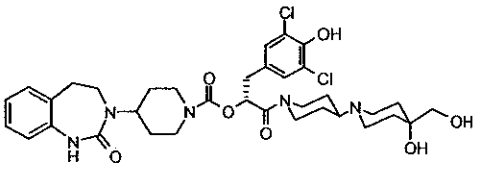
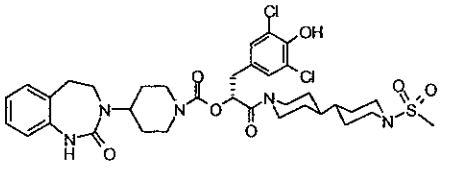
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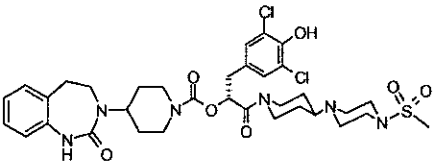
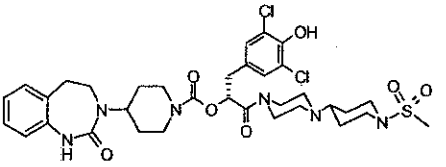
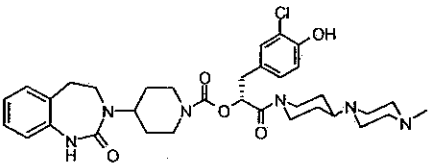
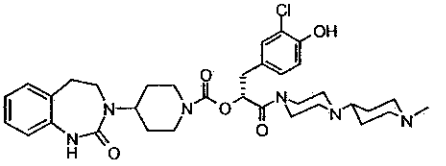
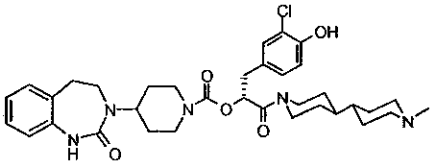
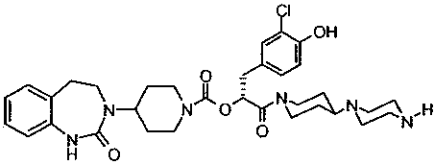
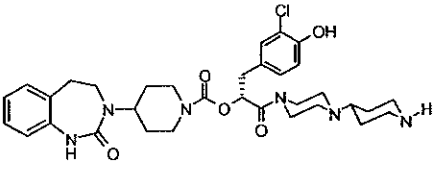
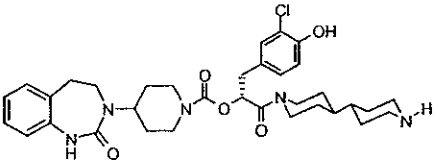
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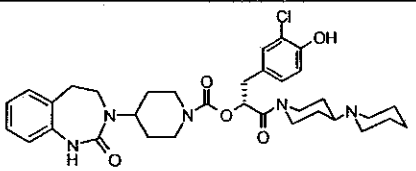
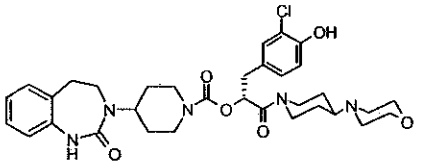
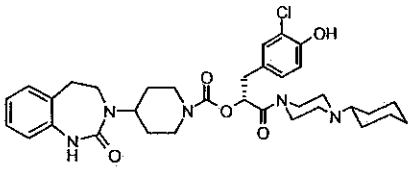
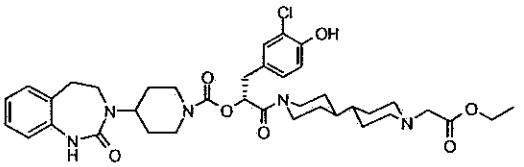
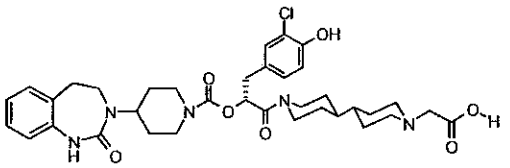
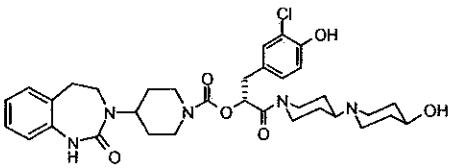
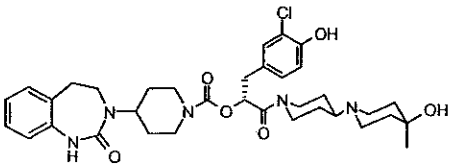
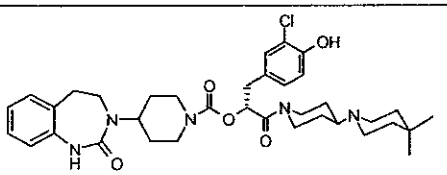
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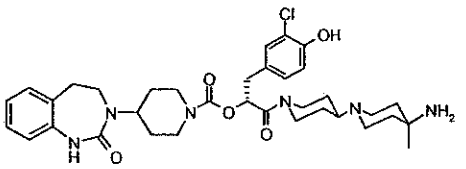
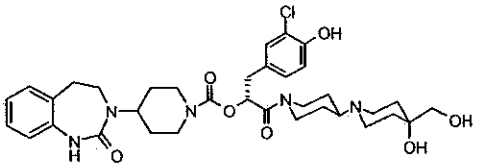
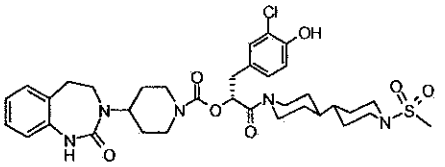
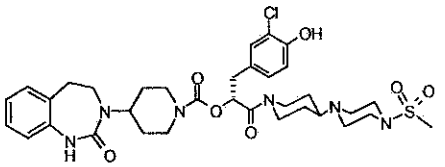
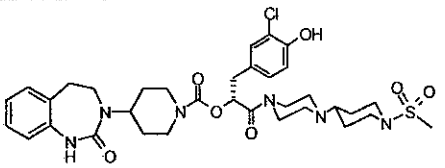
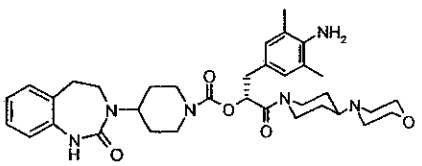
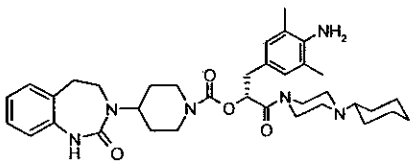
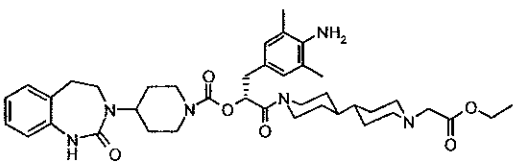
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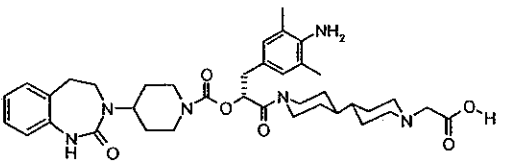
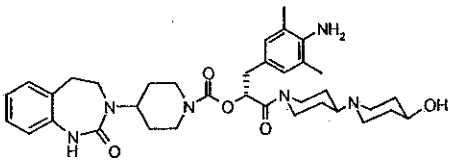
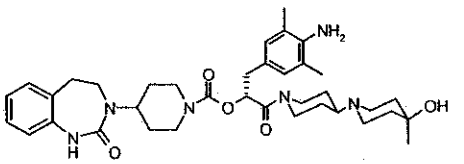
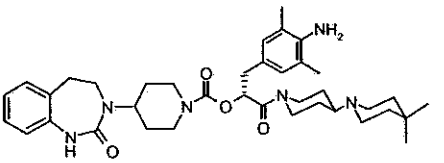
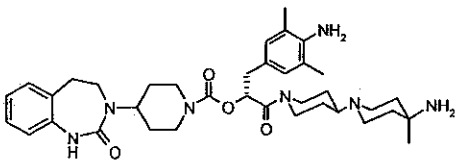
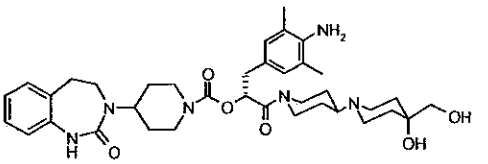
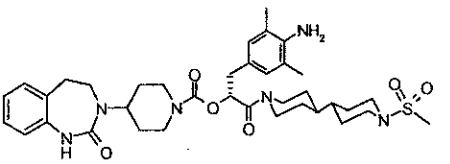
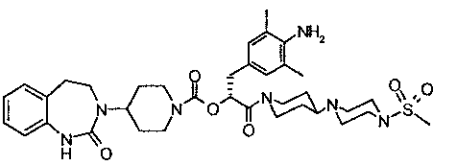
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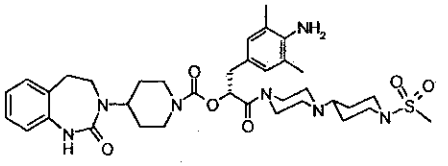
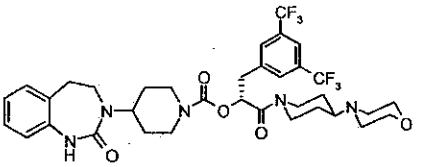
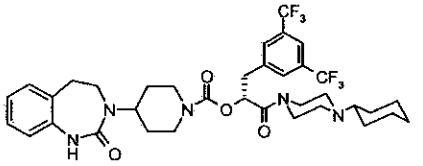
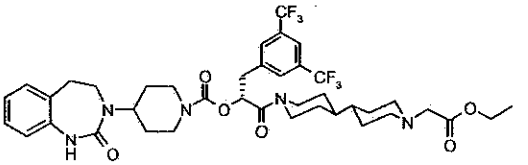
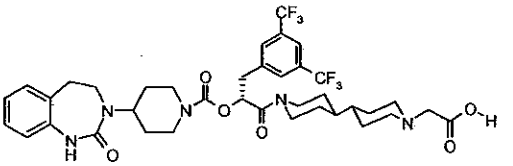
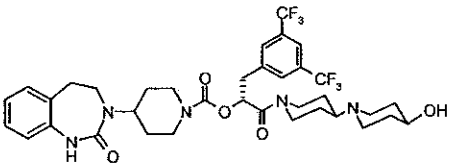
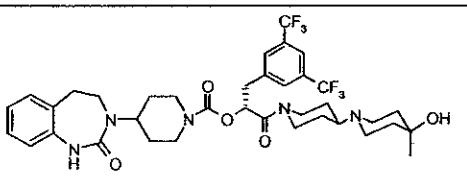
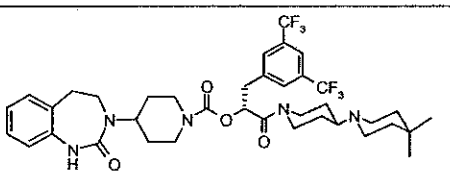
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(260)	

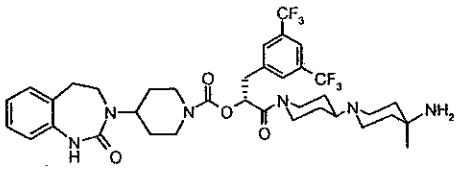
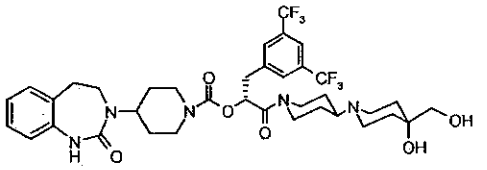
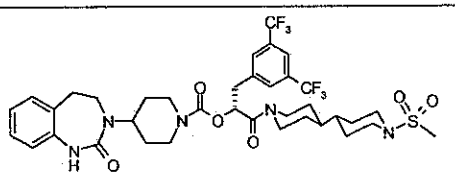
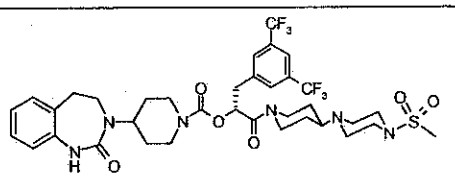
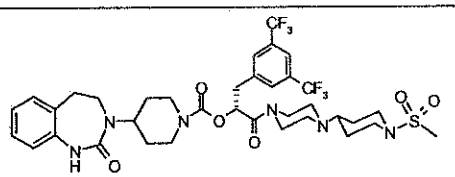
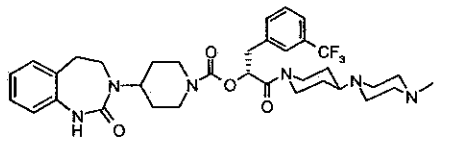
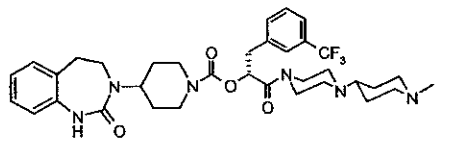
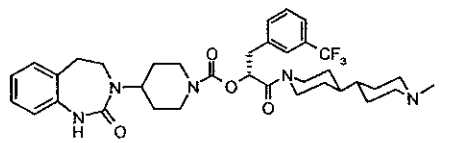
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(264)	
(265)	
(266)	
(267)	
(268)	

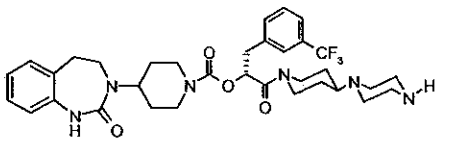
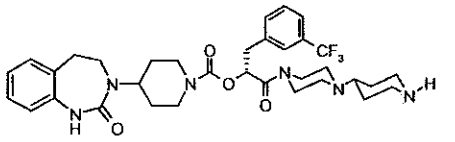
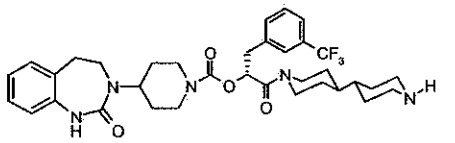
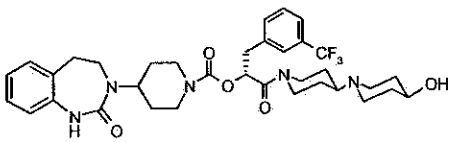
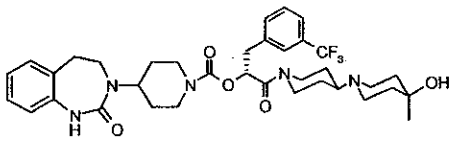
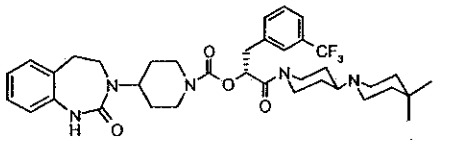
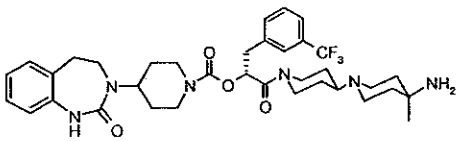
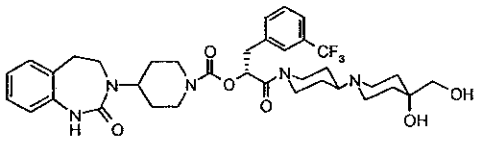
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(272)	
(273)	
(274)	
(275)	
(276)	

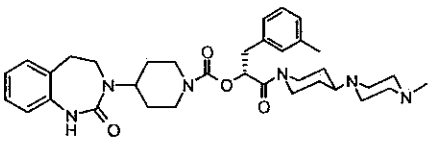
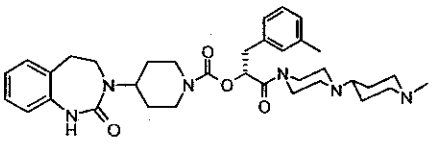
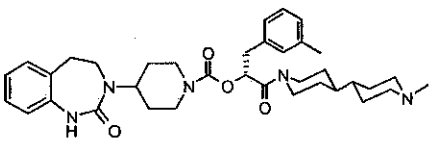
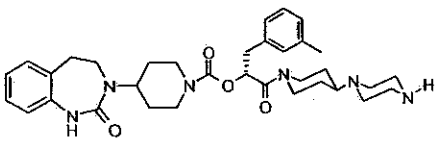
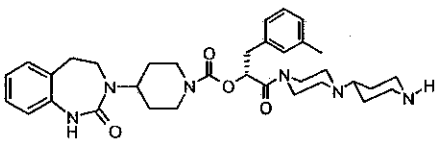
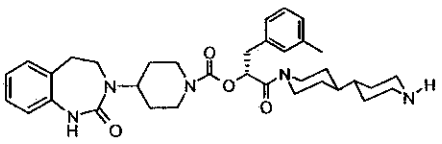
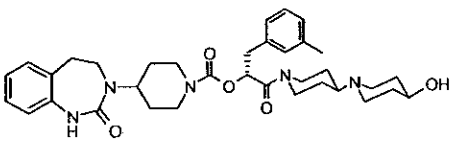
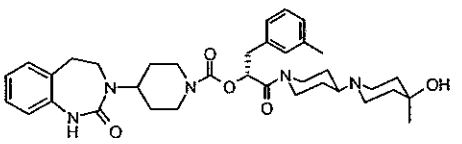
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(280)	
(281)	
(282)	
(283)	
(284)	

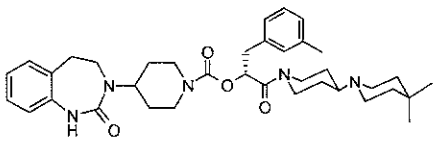
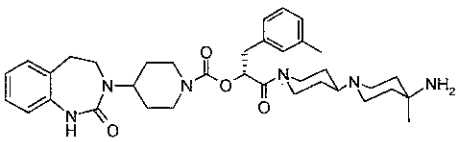
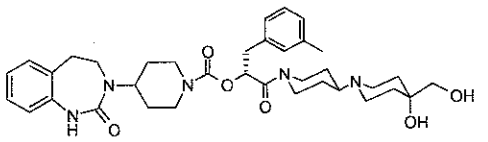
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(287)	
(288)	
(289)	
(290)	
(291)	
(292)	

No.	Structure
(293)	
(294)	
(295)	
(296)	
(297)	
(298)	
(299)	
(300)	

No.	Structure
(301)	
(302)	
(303)	
(304)	
(305)	
(306)	
(307)	
(308)	

No.	Structure
(309)	
(310)	
(311)	
(312)	
(313)	
(314)	
(315)	
(316)	

No.	Structure
(317)	
(318)	
(319)	
(320)	
(321)	
(322)	
(323)	
(324)	

No.	Structure
(325)	
(326)	
(327)	

the enantiomers, the diastereomers, the hydrates, the mixtures thereof and the salts thereof as well as the hydrates of the salts, particularly the physiologically acceptable salts thereof with inorganic or organic acids or bases.

2. The following CGRP antagonists of general formula I according to claim 1, which are selected from the group consisting of:

(1), (2), (3), (4), (5), (6), (7), (8), (9), (10), (11), (12), (13), (14), (15), (16), (17), (18), (19), (20), (21), (22), (23), (24), (25), (26), (27), (28), (29), (30), (31), (32), (33), (34), (35), (36), (37), (38), (39), (40), (41), (42), (43), (44), (45), (46), (47), (48), (49), (50), (51), (52), (53), (54), (55), (56), (57), (58), (59), (60), (61), (62), (63), (64), (65), (66), (67), (68), (69), (70), (71), (72), (73), (74), (75), (76), (77), (78), (79), (80) and (81),

the enantiomers thereof, the diastereomers thereof, the hydrates thereof, the mixtures thereof and the salts thereof, as well as the hydrates of the salts,

particularly the physiologically acceptable salts thereof with inorganic or organic acids or bases.

3. The following CGRP antagonists of general formula I according to claim 1, which are selected from the group consisting of:

(82), (83), (84), (85), (86), (87), (88), (89), (90), (91), (92), (93), (94), (95), (96), (97), (98), (99), (100), (101), (102), (103), (104), (105), (106), (107), (108), (109), (110), (111), (112), (113), (114), (115), (116), (117), (118), (119), (120), (121), (122), (123), (124), (125), (126), (127), (128), (129), (130), (131), (132), (133), (134), (135), (136), (137), (138), (139), (140), (141), (142), (143), (144), (145), (146), (147), (148), (149), (150), (151), (152), (153), (154), (155), (156), (157), (158), (159), (160), (161), and (162),

the enantiomers thereof, the diastereomers thereof, the hydrates thereof, the mixtures thereof and the salts thereof, as well as the hydrates of the salts, particularly the physiologically acceptable salts thereof with inorganic or organic acids or bases.

4. The following CGRP antagonists of general formula I according to claim 1, which are selected from the group consisting of:

(163), (164), (165), (166), (167), (168), (169), (170), (171), (172), (173), (174), (175), (176), (177), (178), (179), (180), (181), (182), (183), (184), (185), (186), (187), (188), (189), (190), (191), (192), (193), (194), (195), (196), (197), (198), (199), (200), (201), (202), (203), (204), (205), (206), (207), (208), (209), (210), (211), (212), (213), (214), (215), (216), (217), (218), (219), (220), (221), (222), (223), (224), (225), (226), (227), (228), (229), (230), (231), (232), (233), (234), (235), (236), (237), (238), (239), (240), (241), (242) and (243),

the enantiomers thereof, the diastereomers thereof, the hydrates thereof, the mixtures thereof and the salts thereof, as well as the hydrates of the salts, particularly the physiologically acceptable salts thereof with inorganic or organic acids or bases.

5. The following CGRP antagonists of general formula I according to claim 1, which are selected from the group consisting of:

(244), (245), (246), (247), (248), (249, (250), (251), (252), (253), (254), (255), (256), (257), (258), (259), (260), (261) and (262),

the enantiomers thereof, the diastereomers thereof, the hydrates thereof, the mixtures thereof and the salts thereof, as well as the hydrates of the salts, particularly the physiologically acceptable salts thereof with inorganic or organic acids or bases.

6. The following CGRP antagonists of general formula I according to claim 1, which are selected from the group consisting of:

(263), (264), (265), (266), (267), (268), (269), (270), (271), (272), (273), (274), (275), (276), (277), (278), (279), (280) and (281),

the enantiomers thereof, the diastereomers thereof, the hydrates thereof, the mixtures thereof and the salts thereof, as well as the hydrates of the salts, particularly the physiologically acceptable salts thereof with inorganic or organic acids or bases.

7. The following CGRP antagonists of general formula I according to claim 1, which are selected from the group consisting of:

(282), (283), (284), (285), (286), (287), (288), (289), (290), (291), (292) and (293),

the enantiomers thereof, the diastereomers thereof, the hydrates thereof, the mixtures thereof and the salts thereof, as well as the hydrates of the salts, particularly the physiologically acceptable salts thereof with inorganic or organic acids or bases.

8. The following CGRP antagonists of general formula I according to claim 1, which are selected from the group consisting of:

(294), (295), (296), (297), (298), (299), (300), (301), (302), (303), (304) and (305),

the enantiomers thereof, the diastereomers thereof, the hydrates thereof, the mixtures thereof and the salts thereof, as well as the hydrates of the salts, particularly the physiologically acceptable salts thereof with inorganic or organic acids or bases.

9. The following CGRP antagonists of general formula I according to claim 1, which are selected from the group consisting of:

(306), (307), (308), (309), (310), (311), (312), (313), (314), (315) and (316),

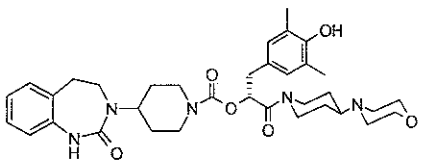
the enantiomers thereof, the diastereomers thereof, the hydrates thereof, the mixtures thereof and the salts thereof, as well as the hydrates of the salts, particularly the physiologically acceptable salts thereof with inorganic or organic acids or bases.

10. The following CGRP antagonists of general formula I according to claim 1, which are selected from the group consisting of:

(317), (318), (319), (320), (321), (322), (323), (324), (325), (326) and (327),

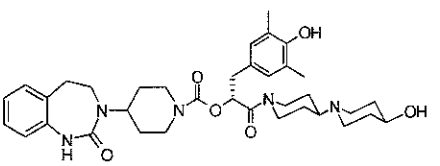
the enantiomers thereof, the diastereomers thereof, the hydrates thereof, the mixtures thereof and the salts thereof, as well as the hydrates of the salts, particularly the physiologically acceptable salts thereof with inorganic or organic acids or bases.

11. The following CGRP antagonist of general formula I according to claim 1:

(163)	

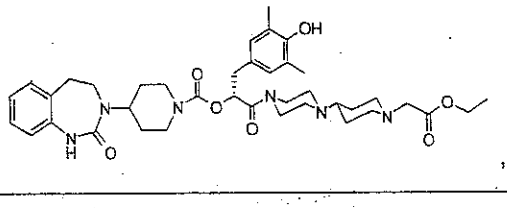
the enantiomers thereof, the diastereomers thereof, the hydrates thereof, the mixtures thereof and the salts thereof, as well as the hydrates of the salts, particularly the physiologically acceptable salts thereof with inorganic or organic acids or bases.

12. The following CGRP antagonist of general formula I according to claim 1:

(168)	

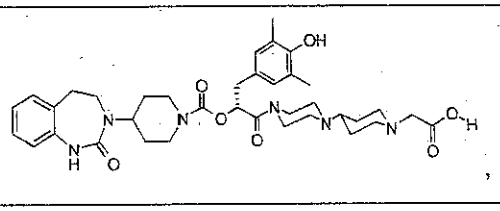
the enantiomers thereof, the diastereomers thereof, the hydrates thereof, the mixtures thereof and the salts thereof, as well as the hydrates of the salts, particularly the physiologically acceptable salts thereof with inorganic or organic acids or bases.

13. The following CGRP antagonist of general formula I according to claim 1:

(205)	

the enantiomers thereof, the diastereomers thereof, the hydrates thereof, the mixtures thereof and the salts thereof, as well as the hydrates of the salts, particularly the physiologically acceptable salts thereof with inorganic or organic acids or bases.

14. The following CGRP antagonist of general formula I according to claim 1:

(206)	

the enantiomers thereof, the diastereomers thereof, the hydrates thereof, the mixtures thereof and the salts thereof, as well as the hydrates of the salts, particularly the physiologically acceptable salts thereof with inorganic or organic acids or bases.

15. Physiologically acceptable salts of the compounds according to one of claims 1 to 14 with inorganic or organic acids or bases.

16. Pharmaceutical compositions, containing a compound according to one of claims 1 to 14 or a physiologically acceptable salt according to claim 15 optionally together with one or more inert carriers and/or diluents.

17. Use of a compound according to one of claims 1 to 15 for preparing a pharmaceutical composition for the acute and prophylactic treatment of headaches, particularly migraine or cluster headaches, for the treatment of

non-insulin-dependent diabetes mellitus ("NIDDM"), complex regional pain syndrome (CRPS1), cardiovascular diseases, morphine tolerance, diarrhoea caused by clostridium toxin, skin diseases, particularly thermal and radiation-induced skin damage including sunburn, inflammatory diseases, e.g. inflammatory diseases of the joints (arthritis), neurogenic inflammation of the oral mucosa, inflammatory lung diseases, allergic rhinitis, asthma, diseases accompanied by excessive vasodilatation and resultant reduced circulation of the blood, e.g. shock and sepsis, for alleviating pain or for preventive or acute therapeutic treatment of the symptoms of menopausal hot flushes caused by vasodilatation and increased blood flow in oestrogen-deficient women and hormone-treated patients with prostate carcinoma.

18. Process for preparing a pharmaceutical composition according to claim 16, characterised in that a compound according to one of claims 1 to 15 is incorporated in one or more inert carriers and/or diluents by a non-chemical method.