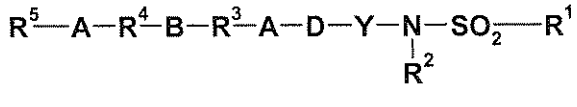
NEW COMPOUNDS

The present invention relates to compounds of general formula **I**



, (**I**)

wherein **A**, **B**, **D**, **Y**, R^1, R^2, R^3, R^4 and R^5 are defined as in claim 1, the enantiomers, diastereomers, mixtures thereof and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases, which have valuable properties, the preparation thereof, the pharmaceutical compositions containing the pharmacologically effective compounds, the preparation thereof and the use thereof.

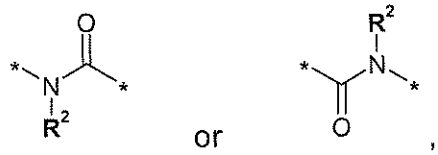
DETAILED DESCRIPTION OF THE INVENTION

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

A denotes a bond, C_{1-4}-alkylene or $-CH_2$-C(O),

B denotes a bond, C_{1-3}-alkylene, -O or –C(O),

D denotes a group of general formulae **II**



Y denotes a C_{1-6}-alkylene group optionally substituted by the group R^2, wherein a methylene group may additionally be replaced by Y^1 and

Y^1 denotes -O, -S, -S(O), -N(R^2), -N(R^2)-C(O), -C(O)-N(R^2), -C(O), -CH(aryl), C_{3-6}-cycloalkylene or -$S(O)_2$-,

R^1 denotes C_{3-7}-cycloalkyl or aryl, heteroaryl or aryl-C_{1-3}-alkyl, each of which may be substituted by one, two, three or four groups $R^{1.1}$, while the groups $R^{1.1}$ may be identical or different and

$R^{1.1}$ denotes H, F, Cl, Br, I, C_{1-3}-alkyl, F_3C, HO, C_{1-3}-alkyl-O or C_{1-3}-alkyl-O-C_{2-4}-alkylene-O-,

R^2 denotes H or C_{1-3}-alkyl, while each methylene group may be substituted by up to two and each methyl group may be substituted by up to three fluorine atoms, or also denotes H_3C-C(O),

R^3 denotes a) C_{1-6}-alkylene,
b) -N(R^2),
c) an arylene group mono- or disubstituted by $R^{3.1}$,
d) a heteroarylene group mono- or disubstituted by $R^{3.1}$,
e) a saturated 4- to 7-membered heterocyclic ring mono- or disubstituted by $R^{3.1}$,
f) an unsaturated 5- to 7-membered heterocyclic ring mono- or disubstituted by $R^{3.1}$, which is fused to one or two phenyl rings via the unsaturated bonds, or
g) a saturated 8- to 10-membered aza-heterobicyclic group mono- or disubstituted by $R^{3.1}$,

while the groups $R^{3.1}$ may be identical or different in each case and

$R^{3.1}$ denotes H, F, Cl, Br, I, C_{1-3}-alkyl, HO, C_{1-3}-alkyl-O or C_{1-3}-alkyl-O-C_{2-4}-alkylene-O-, or

R^3 also denotes -O, if **B** does not denote the group –O-,

R^4 denotes a) -O,
b) -C(O)O,
c) -C(O)NR^2,
d) -NR^2,
e) -NR^2-NR^2,
f) C_{3-7}-cycloalkylene,
g) C_{1-6}-alkylene,
h) an arylene group mono- or disubstituted by $R^{4.1}$,
i) a heteroarylene group mono- or disubstituted by $R^{4.1}$,
j) a 4- to 7-membered saturated heterocyclic ring mono- or disubstituted by $R^{4.1}$,
k) a saturated 8- to 10-membered diaza-heterobicyclic group mono- or disubstituted by $R^{4.1}$,
l) a 5- to 7-membered unsaturated heterocyclic ring mono- or disubstituted by $R^{4.1}$, which is fused to one or two phenyl rings via the unsaturated bonds, or
m) a saturated 9- to 11-membered diaza-spirocyclic group,

while the groups $R^{4.1}$ may be identical or different in each case and

$R^{4.1}$ denotes H, F, Cl, Br, I, C_{1-3}-alkyl, HO, C_{1-3}-alkyl-O or C_{1-3}-alkyl-O-C_{2-4}-alkylene-O-,

R^5 denotes H, HO, C_{1-8}-alkyl, a C_{3-7}-cycloalkyl group optionally substituted by C_{1-3}-alkyl, H_2N, C_{1-4}-alkyl-NH, (C_{3-6}-cycloalkyl)-NH, (C_{1-4}-alkyl)$_2$N, (C_{1-4}-alkyl)(C_{3-6}-cycloalkyl)N, (cyclopropylmethyl)(methyl)N, H_2N-C(O), a phenyl group mono- or disubstituted by $R^{5.1}$, a heteroaryl group mono- or disubstituted by $R^{5.1}$ or a 4- to 7-membered saturated heterocyclic ring

mono- or disubstituted by $R^{5.1}$, while the groups $R^{5.1}$ may be identical or different in each case and

$R^{5.1}$ denotes H, F, Cl, Br, I, C_{1-3}-alkyl, HO, C_{1-3}-alkyl-O, $(C_{1-3}$-alkyl$)_2N$ or C_{1-3}-alkyl-O-C_{2-4}-alkylene-O-,

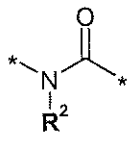
the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

A second embodiment of the present invention comprises the compounds of the above general formula **I**, wherein

A denotes a bond or C_{1-4}-alkylene,

B denotes a bond, C_{1-3}-alkylene, -O or –C(O),

D denotes a group of general formulae **II**



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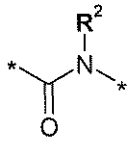

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Y denotes a C_{1-4}-alkylene group optionally substituted by the group R^2, wherein a methylene group may additionally be replaced by Y^1 and

Y^1 denotes -O, -S, -S(O), -N(R^2), -N(R^2)-C(O), -C(O)-N(R^2), -C(O), -CH(aryl) or -$S(O)_2$-,

R^1 denotes C_{3-7}-cycloalkyl or aryl, heteroaryl or aryl-C_{1-3}-alkyl, each of which may be substituted by one, two, three or four groups $R^{1.1}$, while the groups $R^{1.1}$ may be identical or different and

$R^{1.1}$ denotes H, F, Cl, Br, I, C_{1-3}-alkyl, HO, C_{1-3}-alkyl-O or C_{1-3}-alkyl-O-C_{2-4}-alkylene-O-,

R^2 denotes H or C_{1-3}-alkyl, while each methylene group may be substituted by up to two and each methyl group may be substituted by up to three fluorine atoms,

R^3 denotes C_{1-6}-alkylene, an arylene group mono- or disubstituted by $R^{3.1}$, a heteroarylene group mono- or disubstituted by $R^{3.1}$, a saturated 4- to 7-membered heterocyclic ring mono- or disubstituted by $R^{3.1}$ or a unsaturated 5- to 7-membered heterocyclic ring mono- or disubstituted by $R^{3.1}$, while the groups $R^{3.1}$ may be identical or different in each case and

$R^{3.1}$ denotes H, F, Cl, Br, I, C_{1-3}-alkyl, HO, C_{1-3}-alkyl-O or C_{1-3}-alkyl-O-C_{2-4}-alkylene-O-,

R^4 denotes -O, -C(O)O, -C(O)NR^2, -NR^2, -NR^2-NR^2, C_{3-7}-cycloalkylene, C_{1-6}-alkylene, an arylene group mono- or disubstituted by $R^{4.1}$, a heteroarylene group mono- or disubstituted by $R^{4.1}$, a 4- to 7-membered saturated heterocyclic ring mono- or disubstituted by $R^{4.1}$ or a 5- to 7-membered unsaturated heterocyclic ring mono- or disubstituted by $R^{4.1}$, while the groups $R^{4.1}$ may be identical or different in each case and

$R^{4.1}$ denotes H, F, Cl, Br, I, C_{1-3}-alkyl, HO, C_{1-3}-alkyl-O or C_{1-3}-alkyl-O-C_{2-4}-alkylene-O-,

R^5 denotes H, C_{1-8}-alkyl, a C_{3-7}-cycloalkyl group optionally substituted by C_{1-3}-alkyl, H_2N, C_{1-4}-alkyl-NH, $(C_{1-4}$-alkyl$)_2N$, H_2N-C(O),

a heteroaryl group mono- or disubstituted by $R^{5.1}$ or a 4- to 7-membered saturated heterocyclic ring mono- or disubstituted by $R^{5.1}$, while the groups $R^{5.1}$ may be identical or different in each case and

$R^{5.1}$ denotes H, F, Cl, Br, I, C_{1-3}-alkyl, HO, C_{1-3}-alkyl-O or C_{1-3}-alkyl-O-C_{2-4}-alkylene-O-,

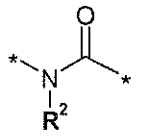
the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

A third embodiment of the present invention comprises the compounds of the above general formula **I**, wherein

A denotes a bond, C_{1-4}-alkylene or $-CH_2$-C(O),

B denotes a bond, C_{1-2}-alkylene, -O or -C(O),

D denotes a group of general formula **II**



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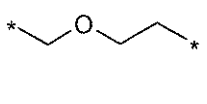
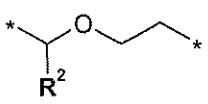
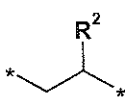
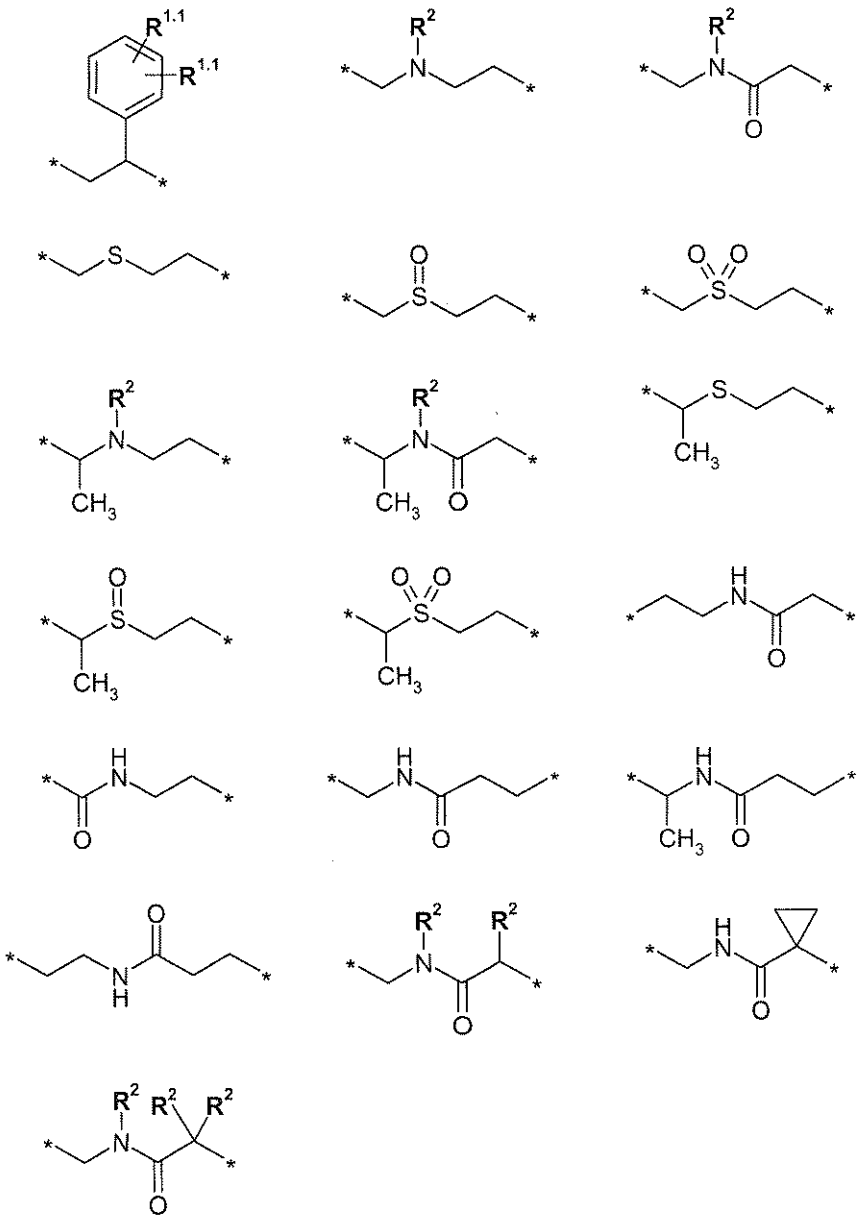
Y denotes C_{1-4}-alkylene or a group selected from







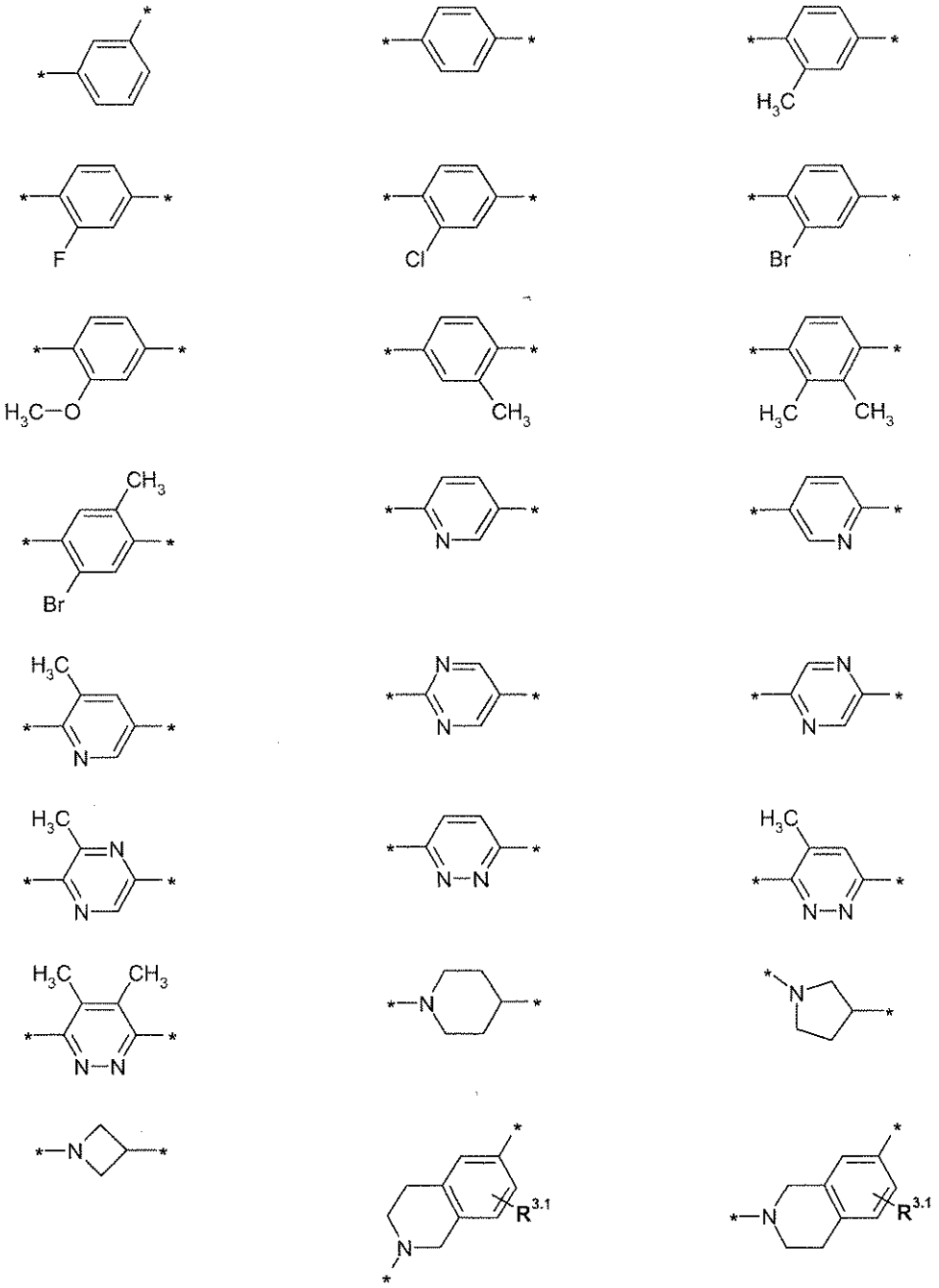


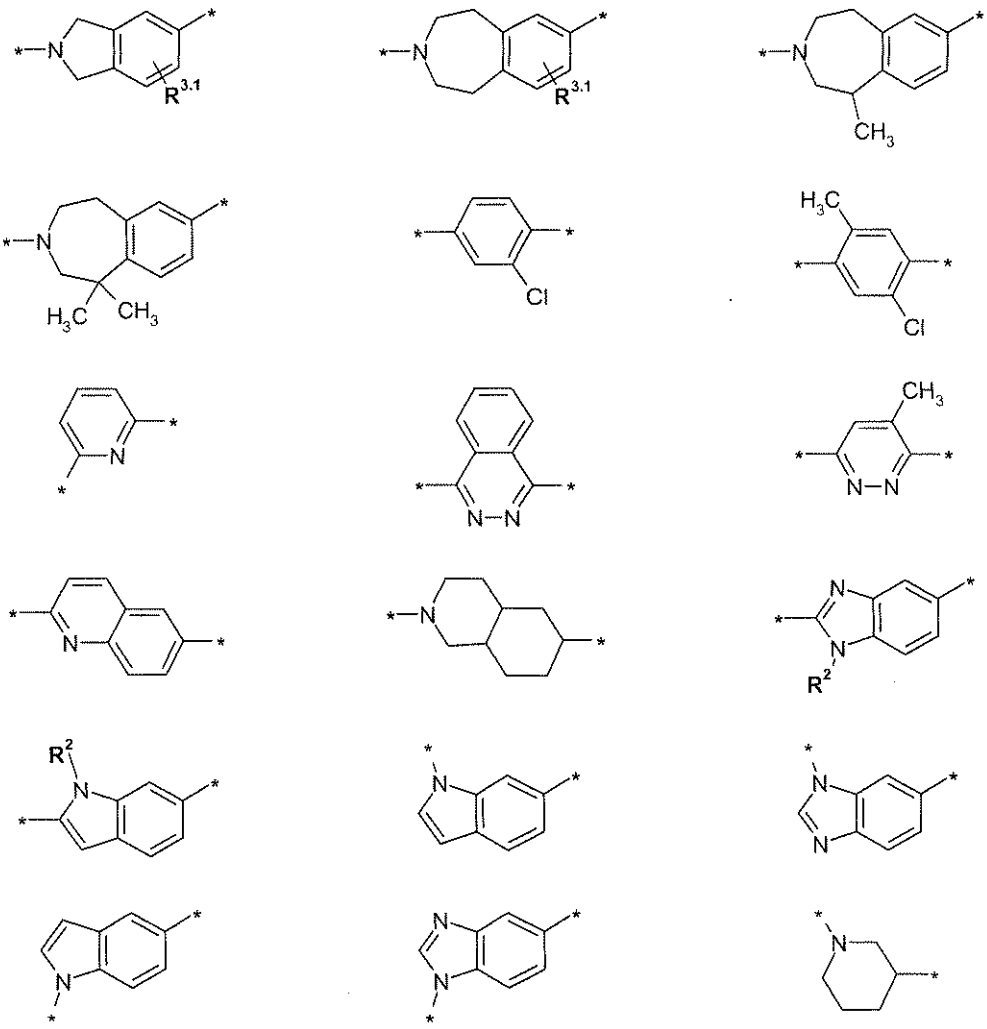
R^1 denotes aryl or heteroaryl, each of which may be substituted by one, two, three or four groups **R$^{1.1}$**, while the groups **R$^{1.1}$** may be identical or different and

R$^{1.1}$ denotes H, F, Cl, Br, I, C_{1-3}-alkyl, F_3C, HO, C_{1-3}-alkyl-O or C_{1-3}-alkyl-O-C_{2-4}-alkylene-O-,

R^2 denotes H, H_3C, H_5C_2, isopropyl, F_3C-CH_2, F_2CH-CH_2 or FH_2C-H_2C,

R^3 denotes C_{1-4}-alkylene, -N(**R^2**) or a group selected from



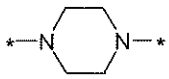
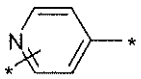
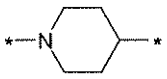


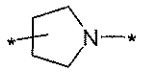
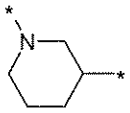
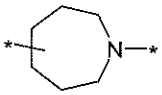
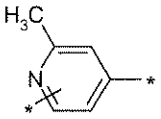
wherein

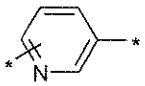
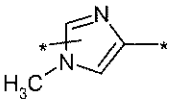
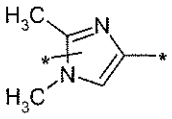
$R^{3.1}$ denotes H, F, Cl, Br, I, C_{1-3}-alkyl, HO, C_{1-3}-alkyl-O or C_{1-3}-alkyl-O-C_{2-4}-alkylene-O-, or

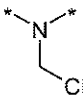
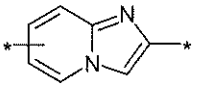
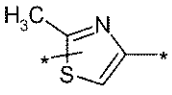
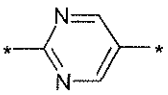
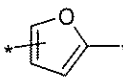
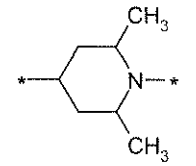
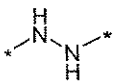
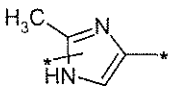
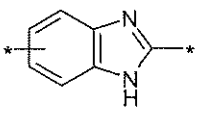
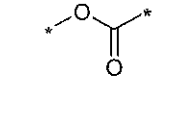
R^3 also denotes -O, if **B** does not denote the group –O- ,

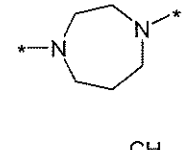
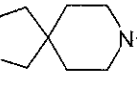
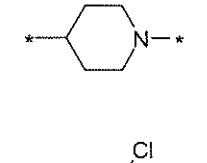
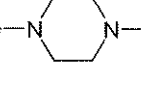
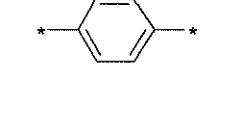
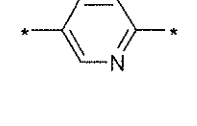
R^4 denotes C_{1-4}-alkylene, C_{3-7}-cycloalkylene, -O or a group selected from

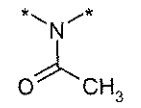
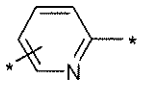
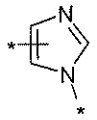
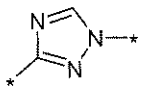
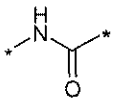
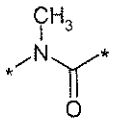
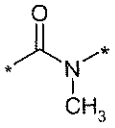
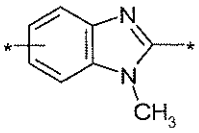
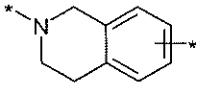




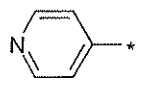
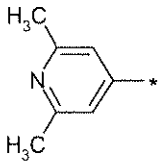
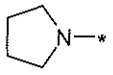
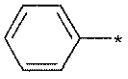
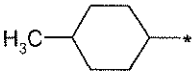
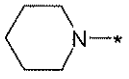
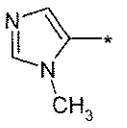
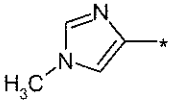
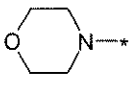
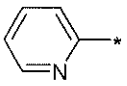
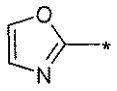
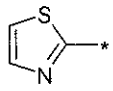
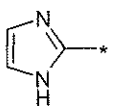
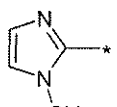
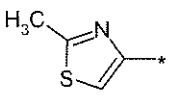











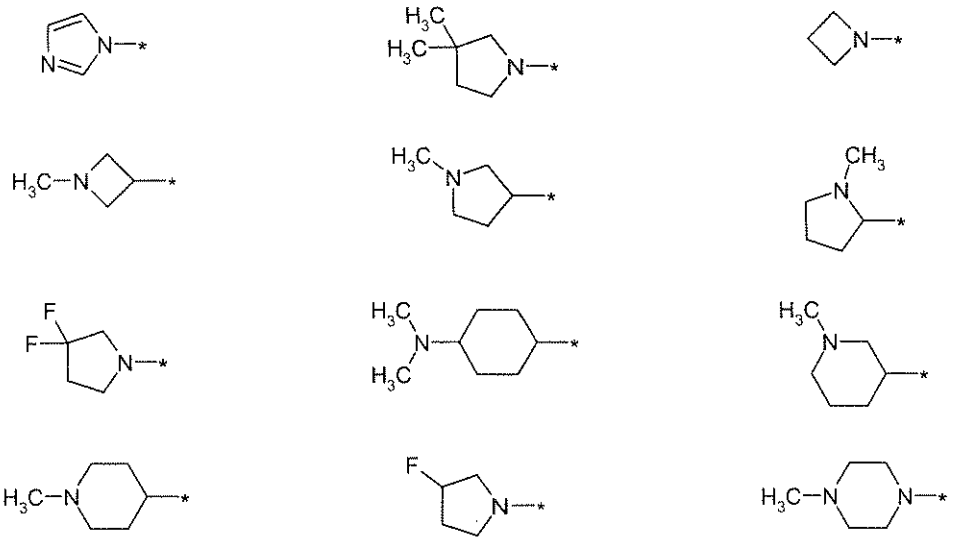







R^5 denotes H, C_{1-8}-alkyl, C_{3-7}-cycloalkyl, HO, (C_{1-3}-alkyl)-O, (C_{1-4}-alkyl)-NH, (C_{3-6}-cycloalkyl)-NH, (C_{1-4}-alkyl)$_2$N, (C_{1-4}-alkyl)(C_{3-6}-cycloalkyl)N, (cyclopropylmethyl)(methyl)N, H_2N-C(O), or

R^5 denotes a group selected from



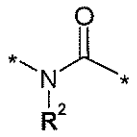
the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

A fourth embodiment of the present invention comprises the compounds of the above general formula **I**, wherein

A denotes a bond or C_{1-3}-alkylene,

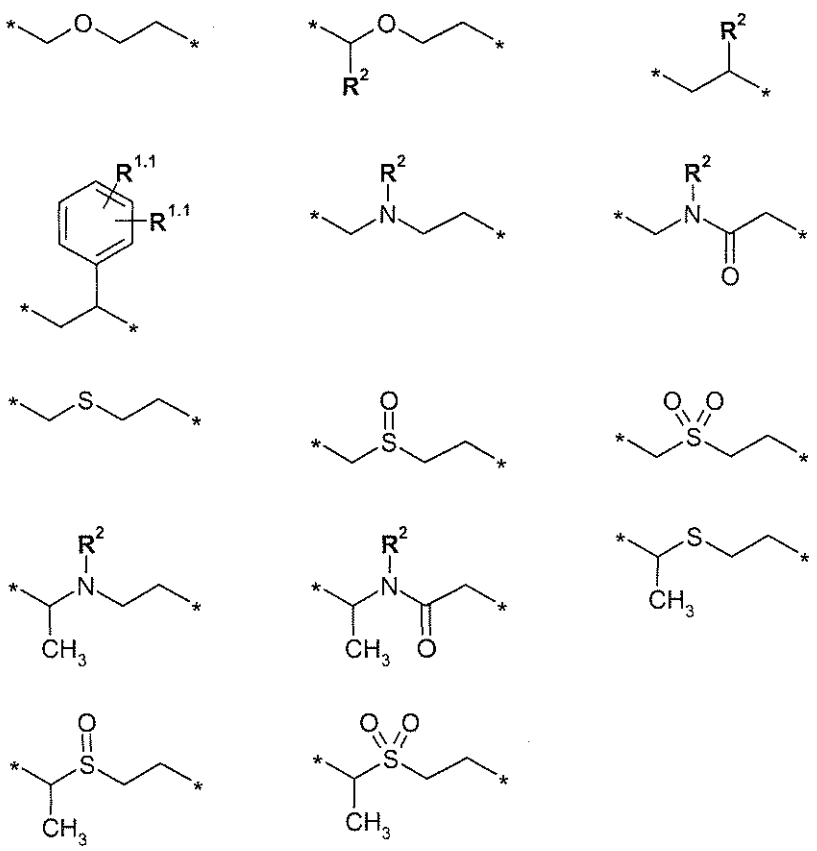
B denotes a bond, C_{1-2}-alkylene, -O or -C(O),

D denotes a group of general formula **II**



,

Y denotes C_{1-4}-alkylene or a group selected from

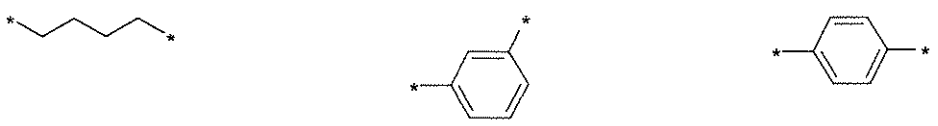


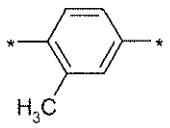
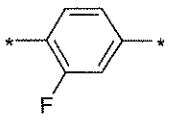
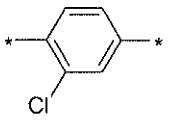
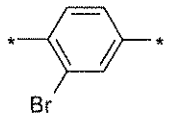
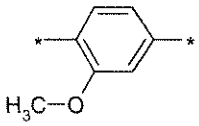
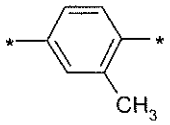
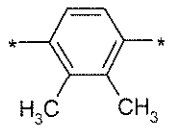
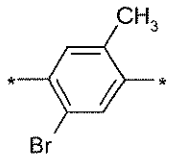
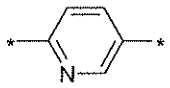
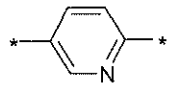
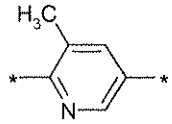
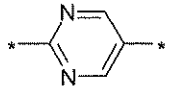
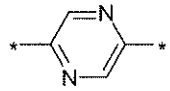
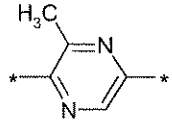
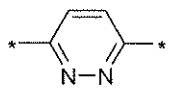
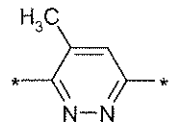
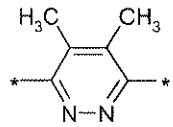
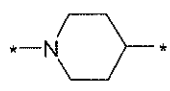
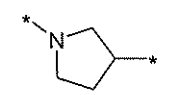
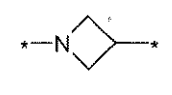
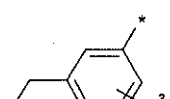
R¹ denotes aryl or heteroaryl, each of which may be substituted by one, two, three or four groups **R^1.1**, while the groups **R^1.1** may be identical or different and

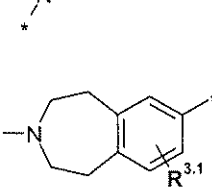
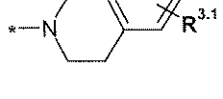
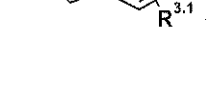
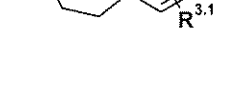
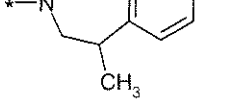
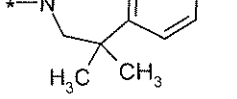
R^1.1 denotes H, F, Cl, Br, I, C_{1-3}-alkyl, HO, C_{1-3}-alkyl-O or C_{1-3}-alkyl-O-C_{2-4}-alkylene-O-,

R² denotes H, H_3C, H_5C_2, isopropyl, F_3C-CH_2, F_2CH-CH_2 or FH_2C-H_2C,

R³ denotes C_{1-4}-alkylene or a group selected from



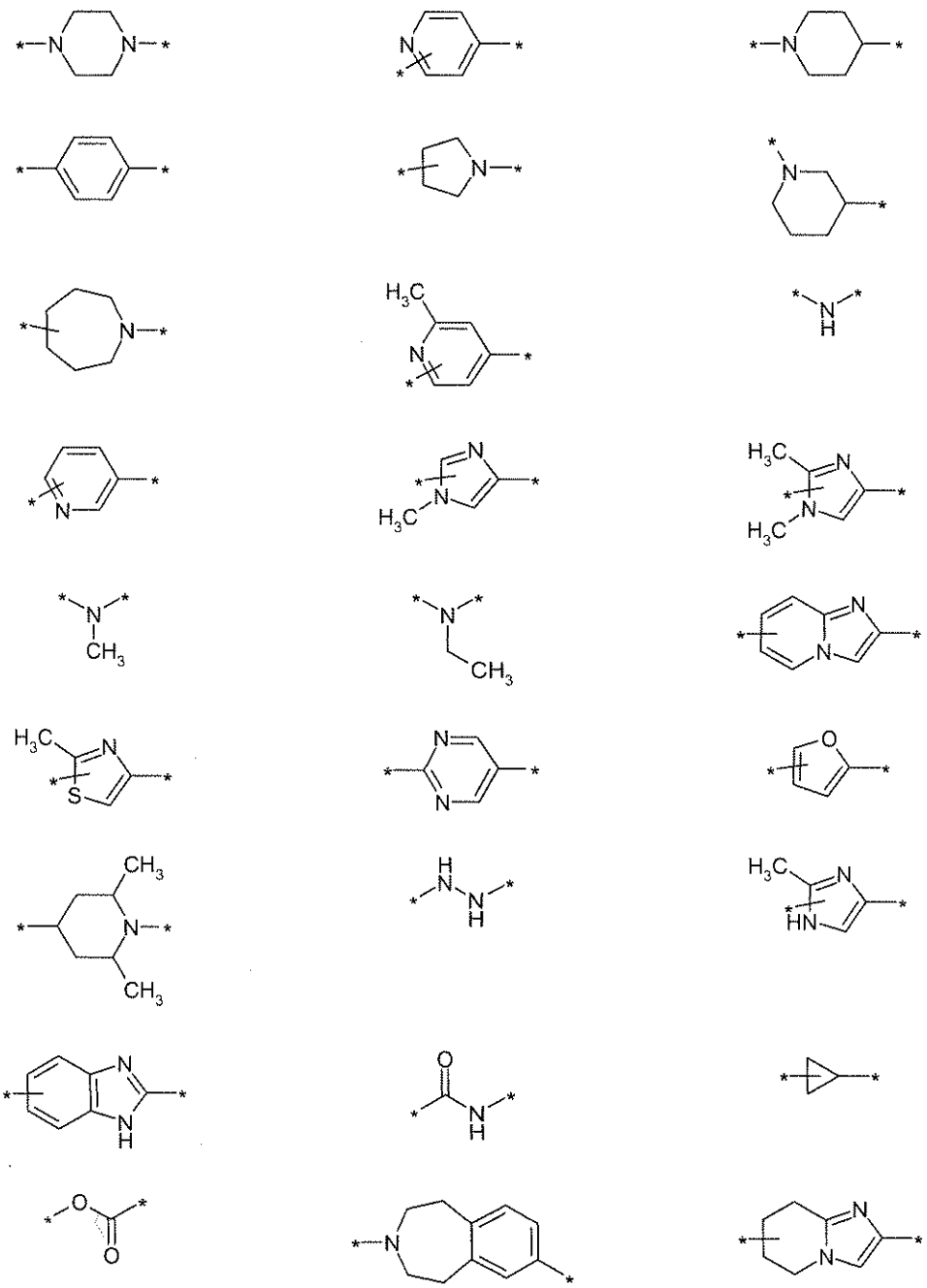






















wherein

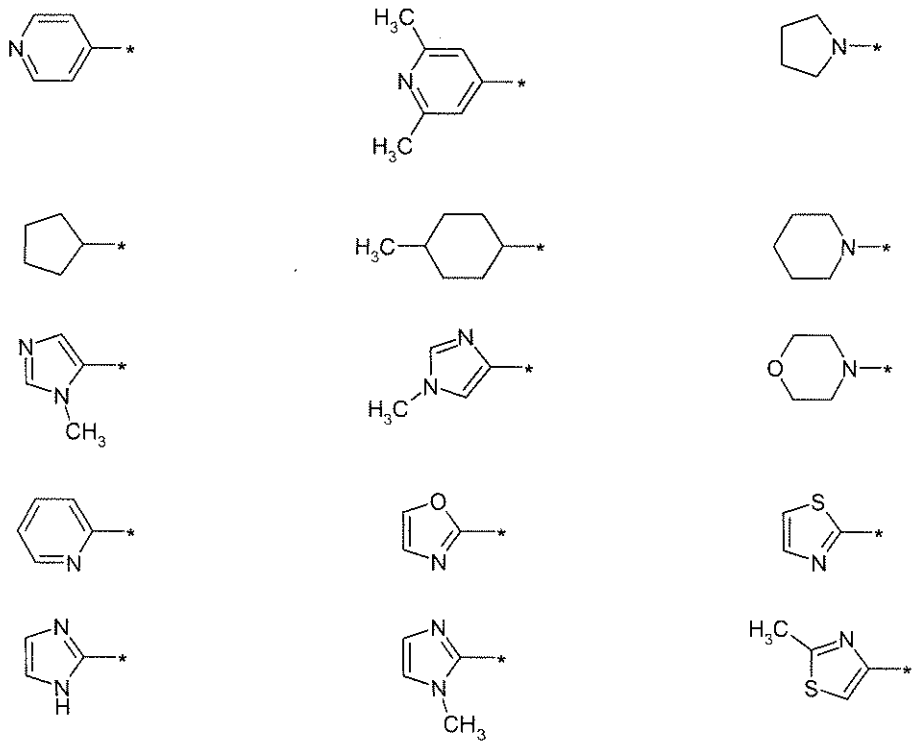
$R^{3.1}$ denotes H, F, Cl, Br, I, C_{1-3}-alkyl, HO, C_{1-3}-alkyl-O or C_{1-3}-alkyl-O-C_{2-4}-alkylene-O-,

R^4 denotes C_{1-4}-alkylene, -O or a group selected from



R^5 denotes H, C_{1-8}-alkyl, C_{3-7}-cycloalkyl, (C_{1-4}-alkyl)-NH, (C_{1-4}-alkyl)$_2$N, H_2N-C(O), or

R^5 denotes a group selected from



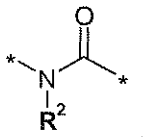
the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

A fifth embodiment of the present invention comprises the compounds of the above general formula **I**, wherein

A denotes a bond, C_{1-3}-alkylene or $-CH_2$-C(O),

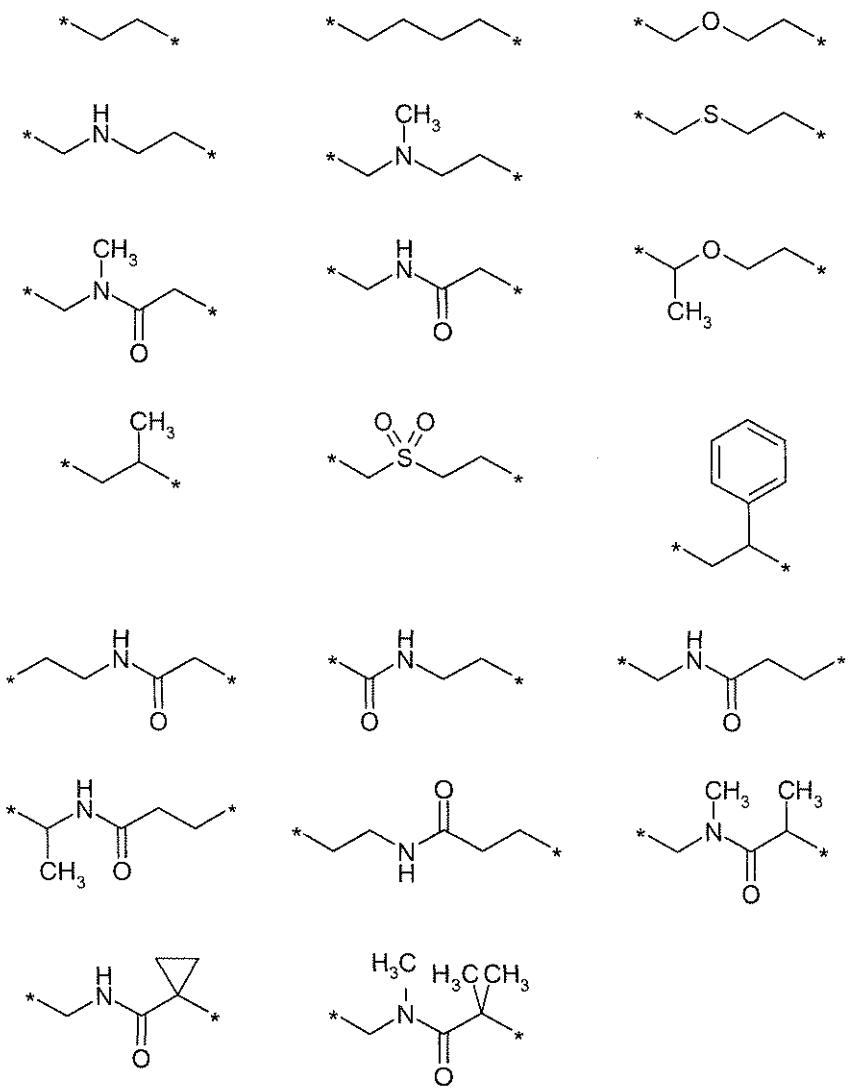
B denotes a bond, C_{1-2}-alkylene, -O or -C(O),

D denotes a group of general formula **II**

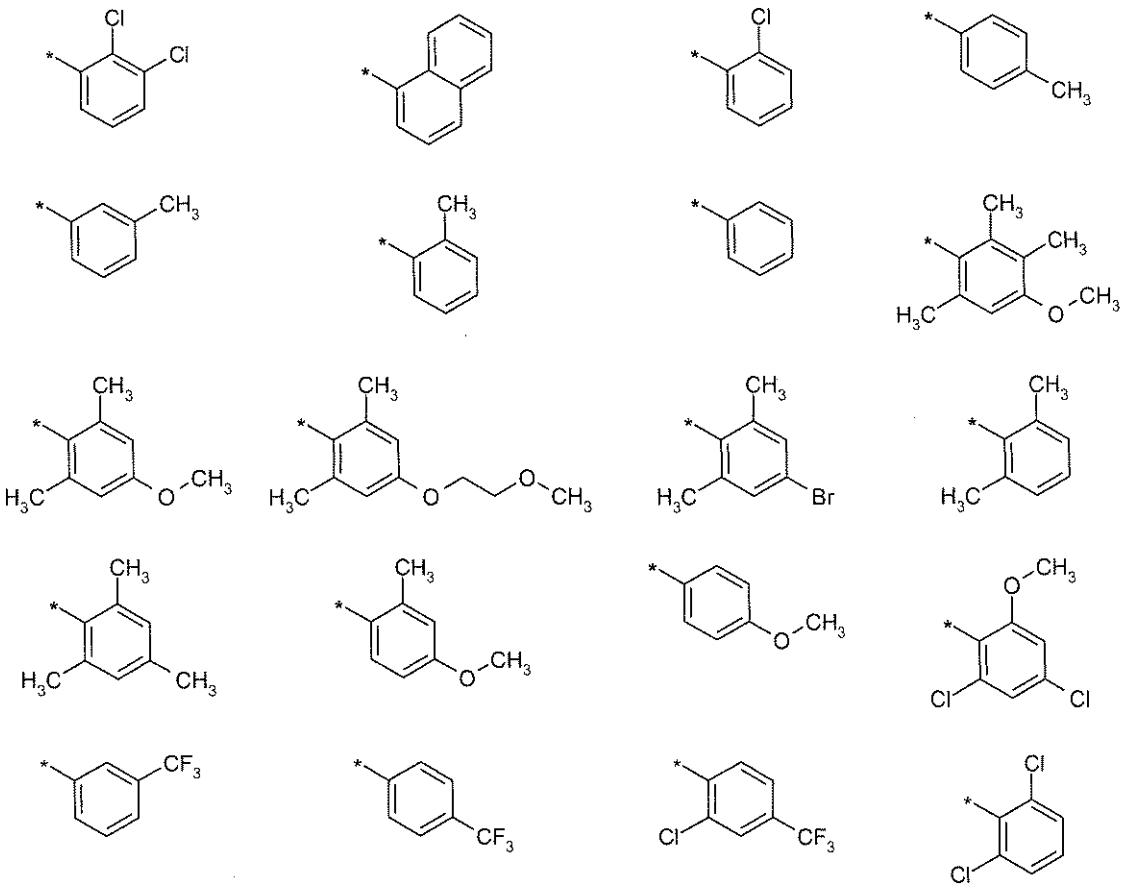


,

Y denotes a group selected from

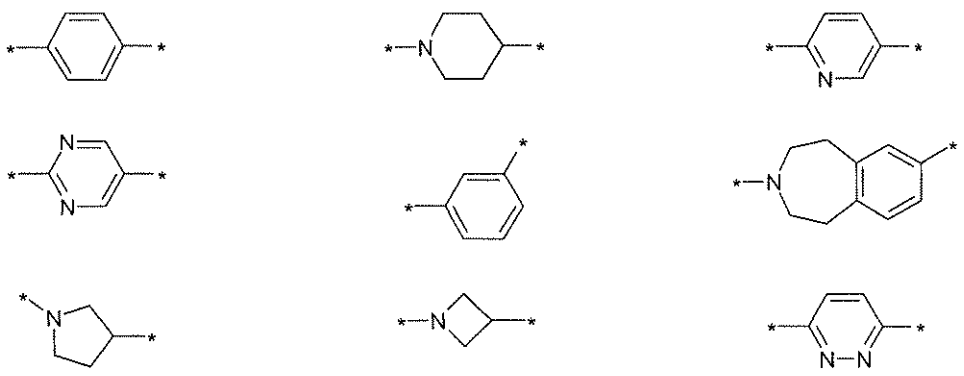


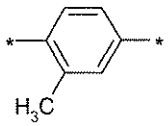
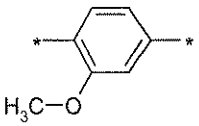
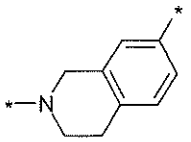
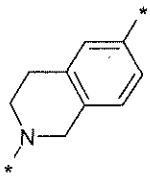
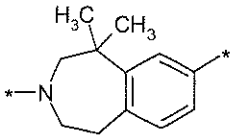
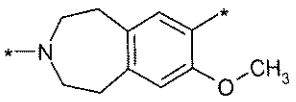
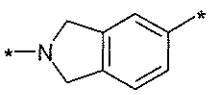
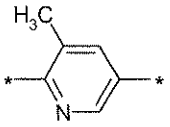
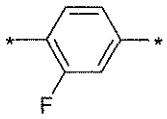
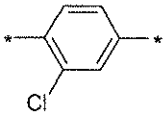
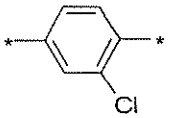
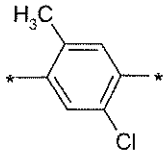
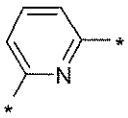
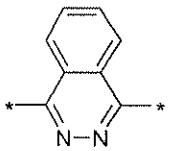
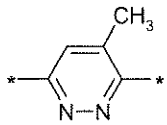
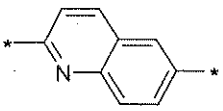
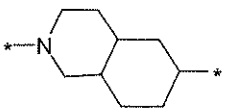
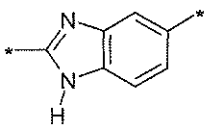
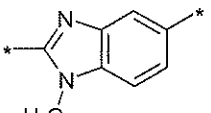
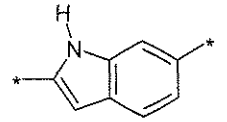
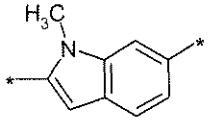
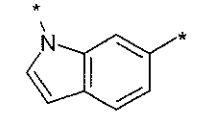
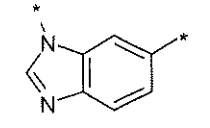
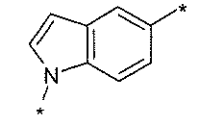
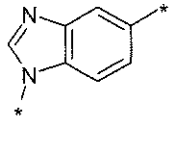
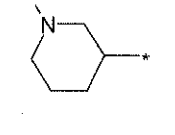
R^1 denotes a group selected from



R^2 denotes H, H_3C, H_5C_2 or FH_2C-H_2C,

R^3 denotes C_{1-4}-alkylene, -NH, -N(CH_3) or a group selected from

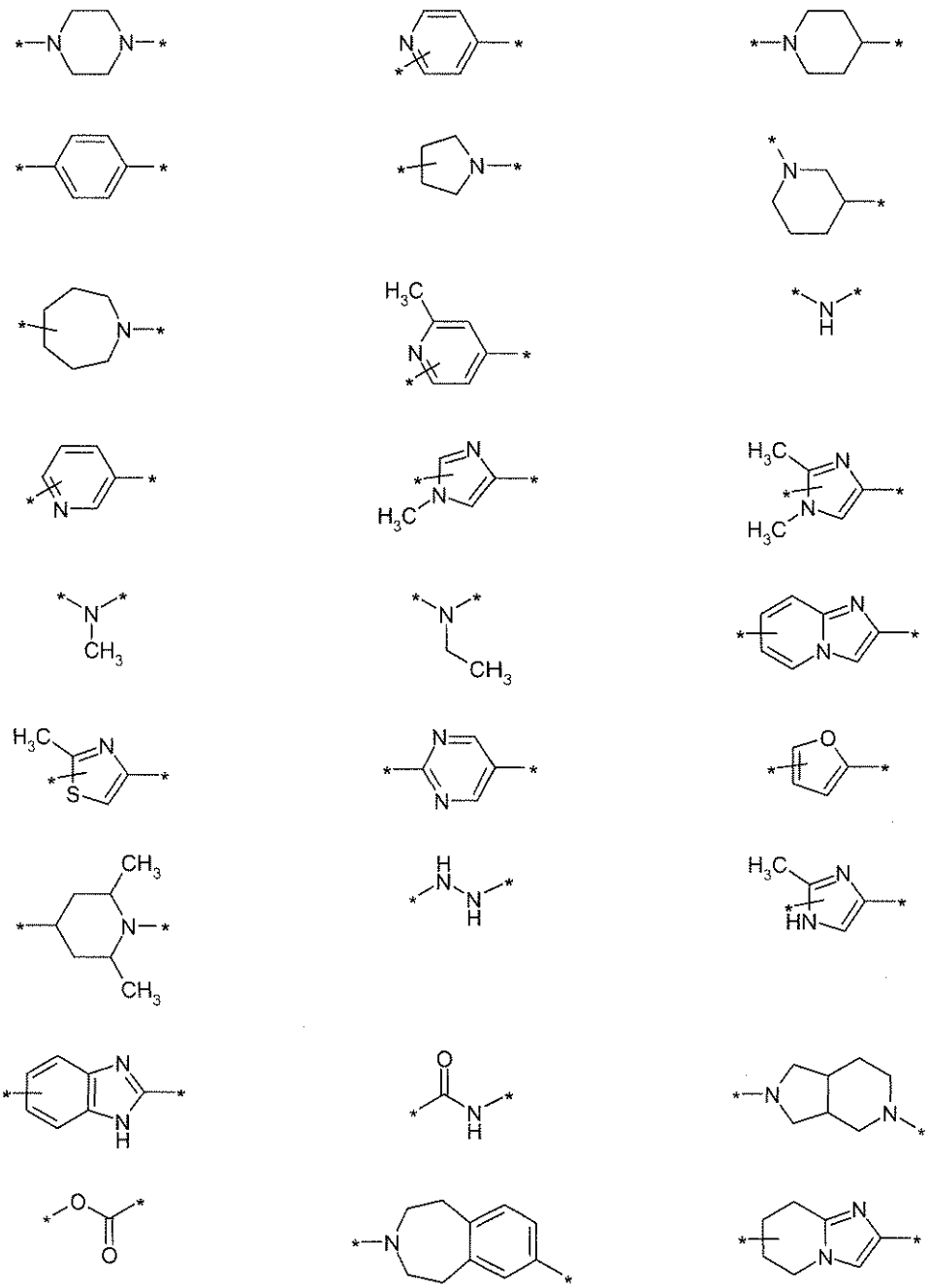


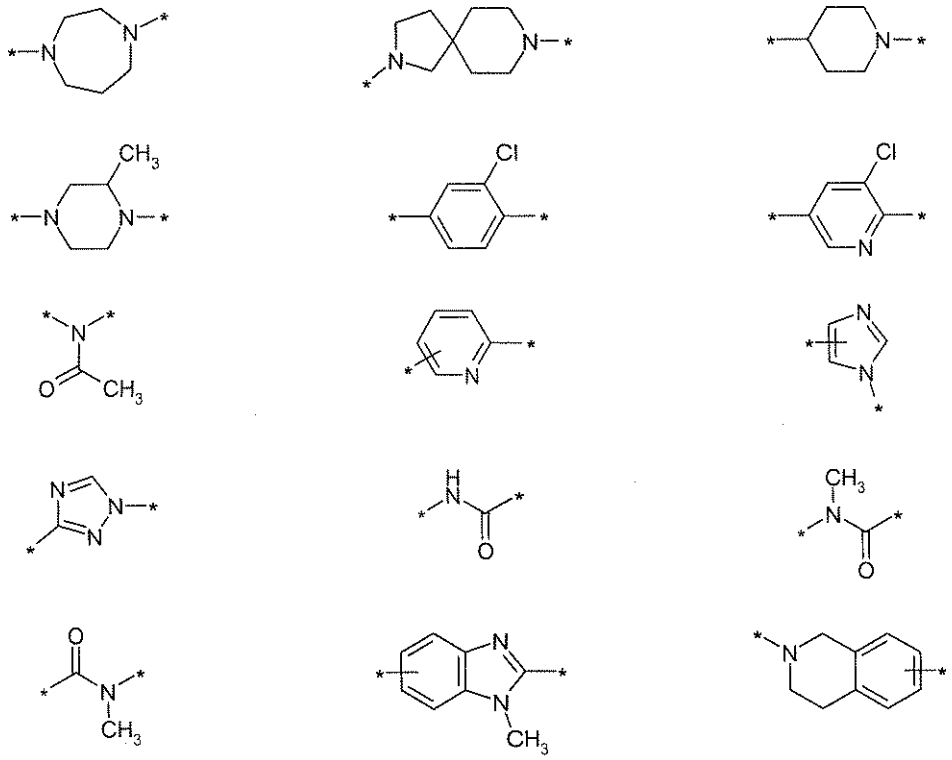



























or

R^3 also denotes -O, if **B** does not denote the group –O- ,

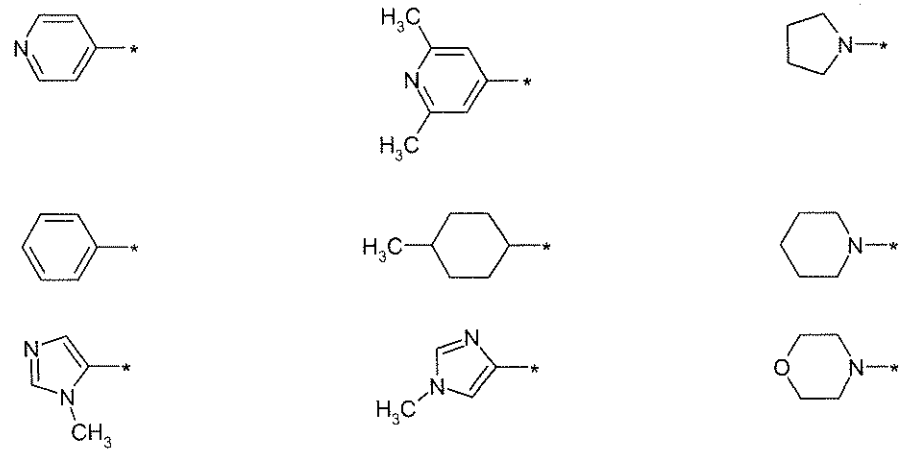
R^4 denotes C_{1-4}-alkylene, C_{3-7}-cycloalkylene, -O or a group selected from

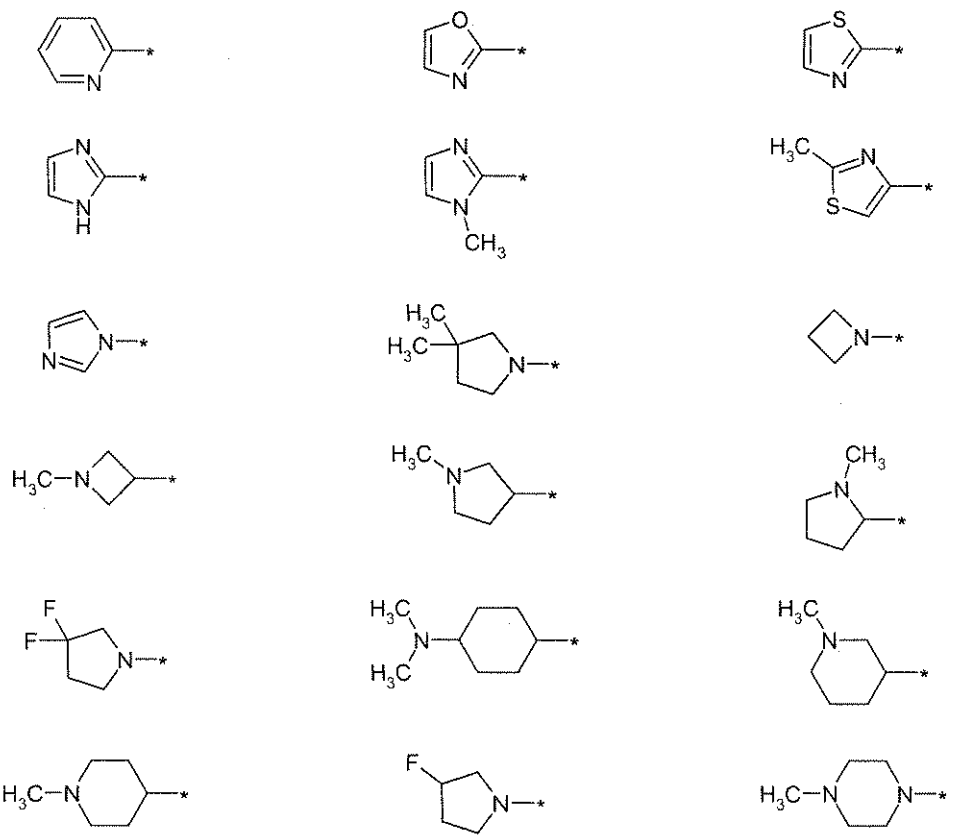




R^5 denotes H, HO, C_{1-5}-alkyl, C_{3-5}-cycloalkyl, H_2N, (C_{1-2}-alkyl)-NH, (C_{3-6}-cycloalkyl)-NH, (C_{1-2}-alkyl)$_2$N, (C_{1-4}-alkyl)(C_{3-6}-cycloalkyl)N, (cyclopropylmethyl)(methyl)N, H_2N-C(O), or

R^5 denotes a group selected from





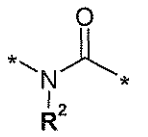
the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

A sixth embodiment of the present invention comprises the compounds of the above general formula **I**, wherein

A denotes a bond or C_{1-3}-alkylene,

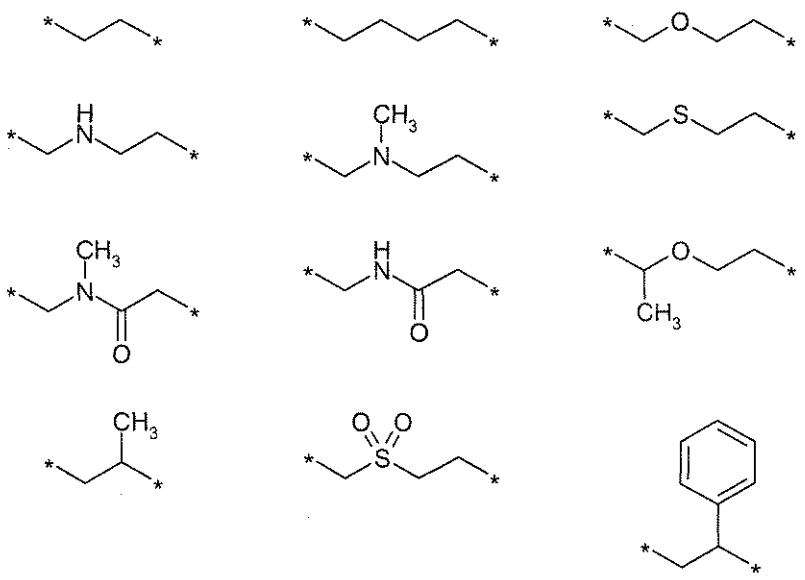
B denotes a bond, C_{1-2}-alkylene, -O or -C(O),

D denotes a group of general formula **II**

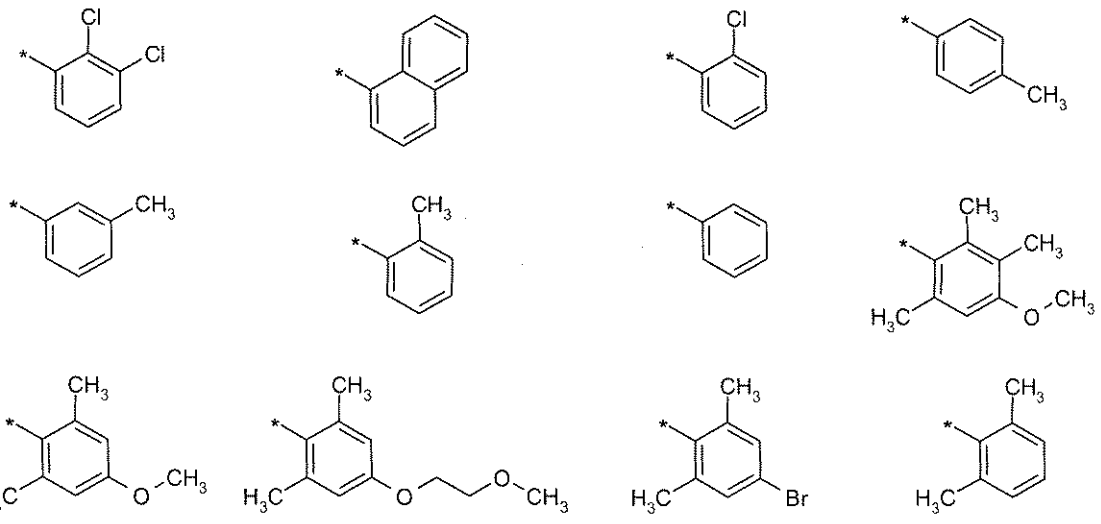


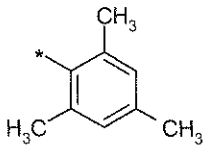
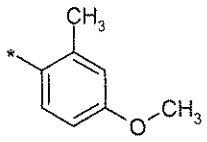
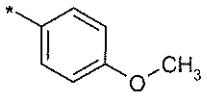
,

Y denotes a group selected from



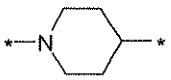
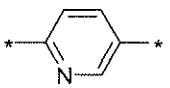
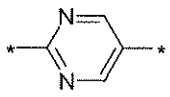
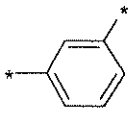
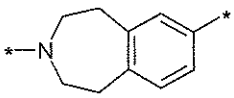
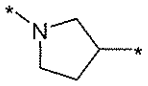
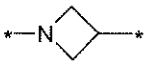
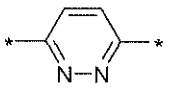
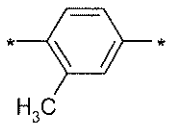
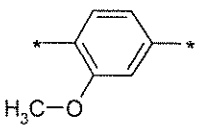
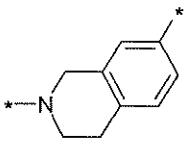
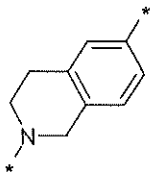
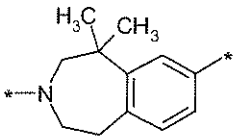
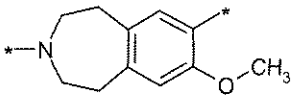
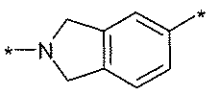
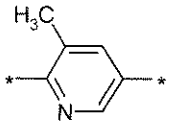
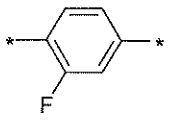
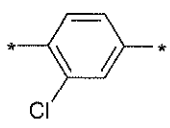
R^1 denotes a group selected from



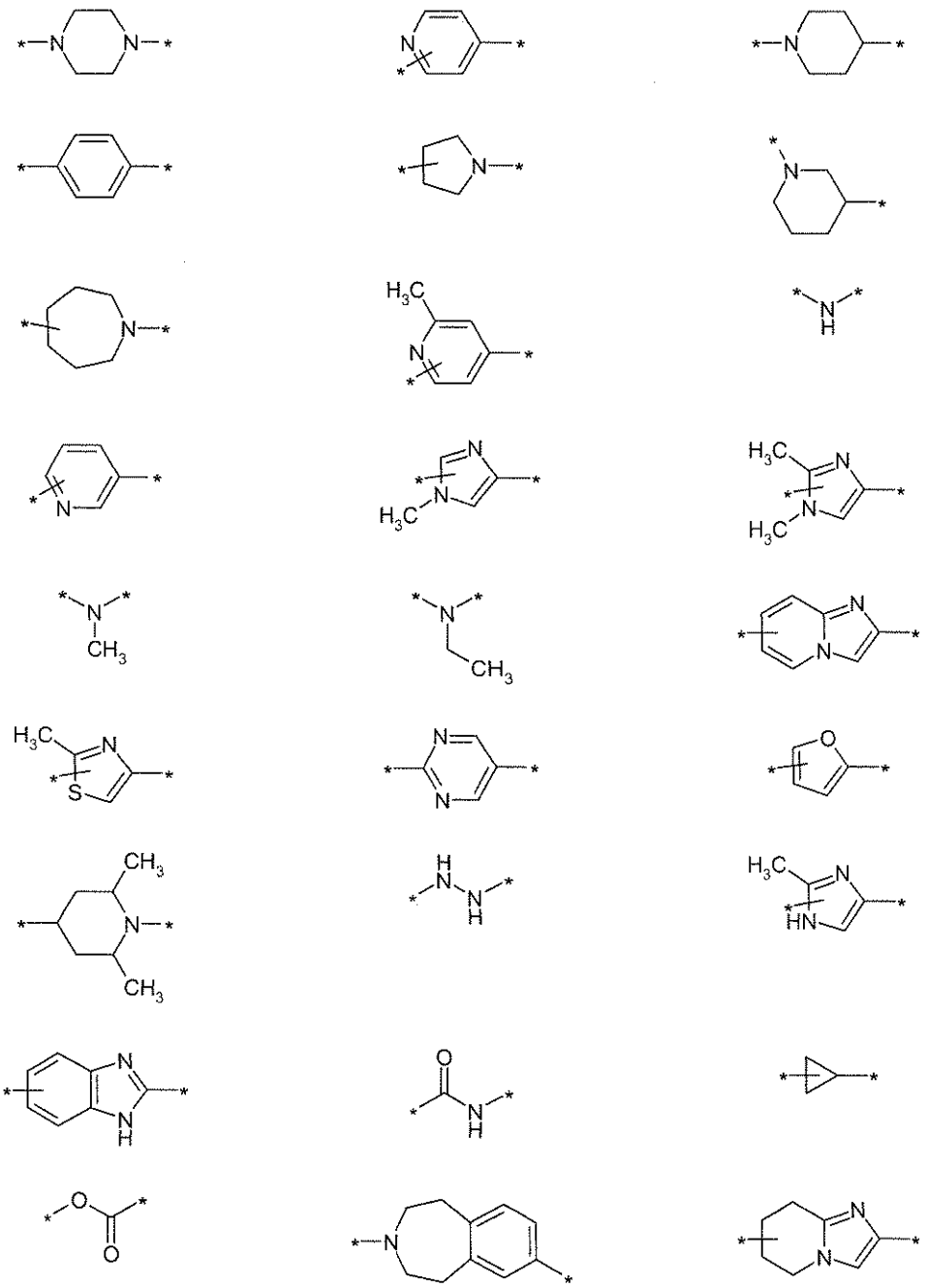




R^2 denotes H, H_3C, H_5C_2 or FH_2C-H_2C,

R^3 denotes C_{1-4}-alkylene or a group selected from

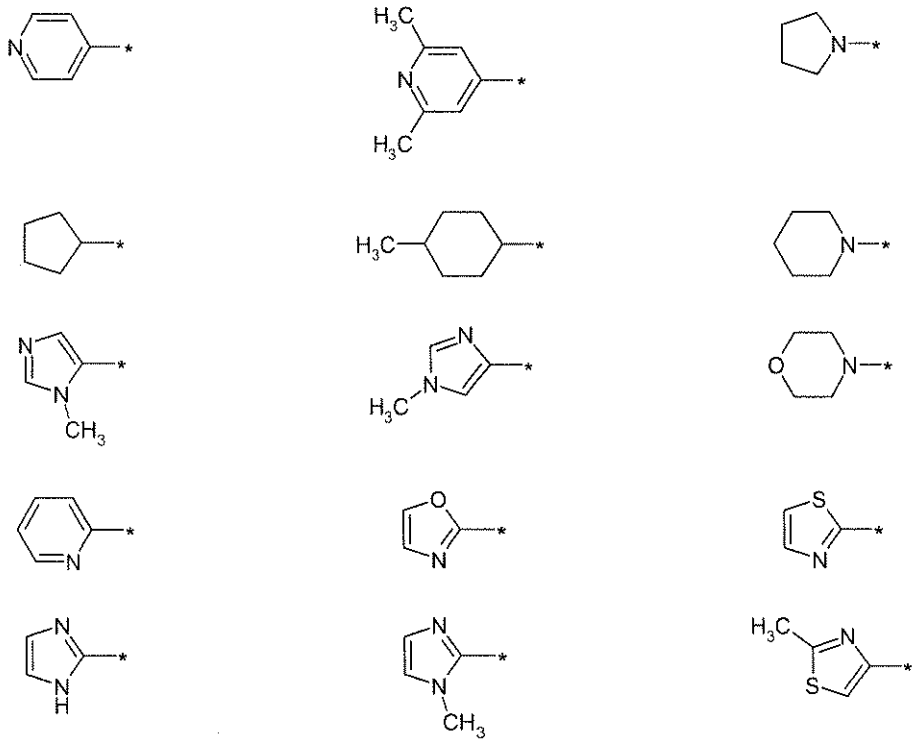



















R^4 denotes C_{1-4}-alkylene, -O or a group selected from



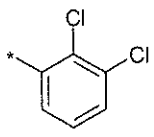
R^5 denotes H, C_{1-5}-alkyl, H_2N, (C_{1-2}-alkyl)-NH, (C_{1-2}-alkyl)$_2$N, H_2N-C(O), or

R^5 denotes a group selected from



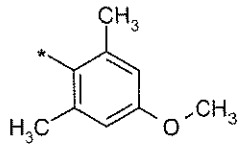
the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

A seventh embodiment of the present invention comprises the compounds of the above general formula **I**, wherein **A**, **B**, **D**, **Y**, R^2, R^3, R^4 and R^5 are defined as hereinbefore under the first to sixth embodiments and

R^1 denotes the group  ,

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

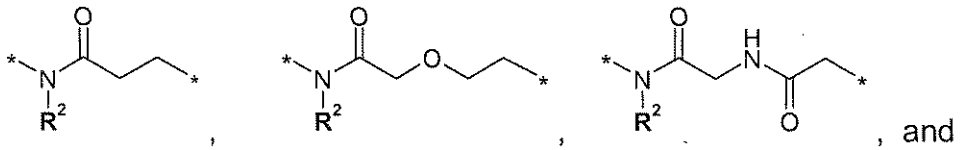
An eighth embodiment of the present invention comprises the compounds of the above general formula **I**, wherein **A**, **B**, **D**, **Y**, R^2, R^3, R^4 and R^5 are defined as hereinbefore under the first to sixth embodiments and

R^1 denotes the group  ,

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

A ninth embodiment of the present invention comprises the compounds of the above general formula **I**, wherein **A**, **B**, R^1, R^3, R^4 and R^5 are defined as hereinbefore under the first to eighth embodiments and

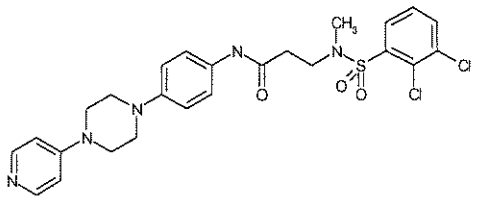
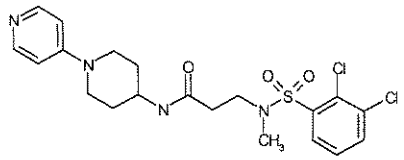
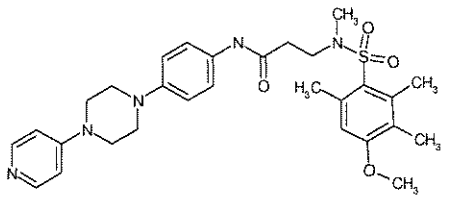
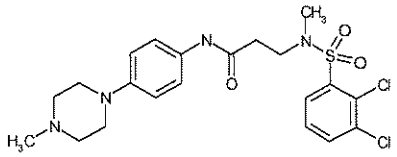
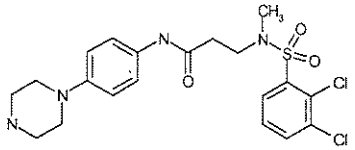
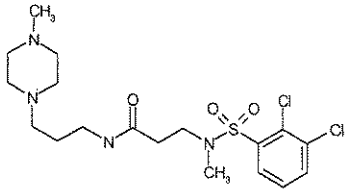
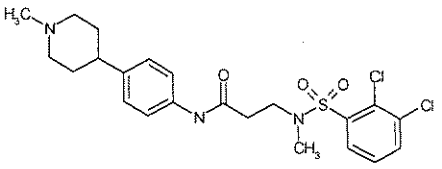
-**D**-**Y**- together denote a group selected from

 , and

R^2 denotes H or C_{1-3}-alkyl-,

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

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

Example	Structure
(1)	
(2)	
(3)	
(4)	
(5)	
(6)	
(7)	

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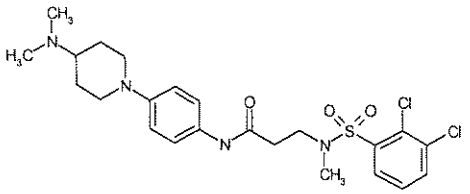
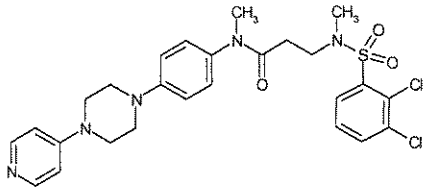
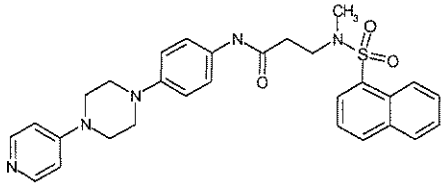
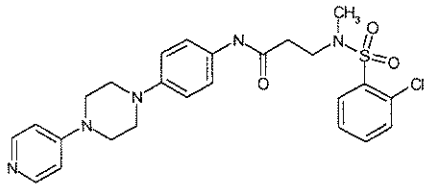
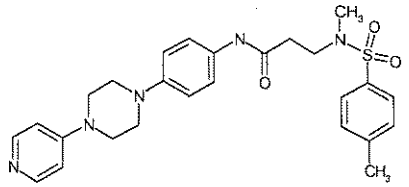
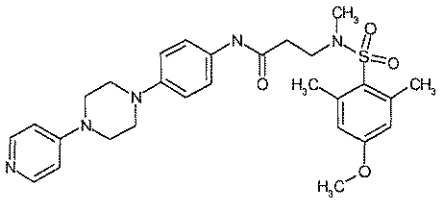
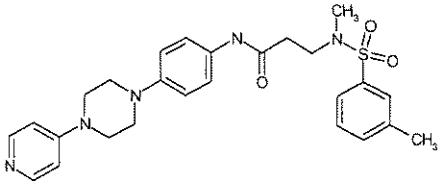
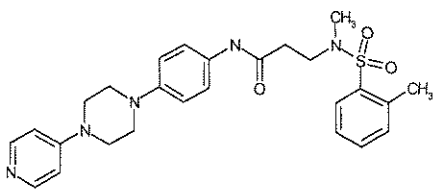
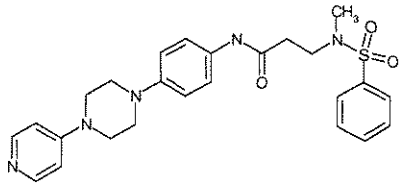
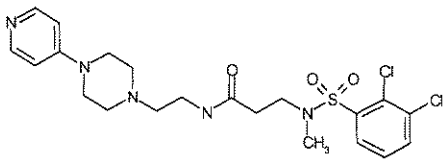
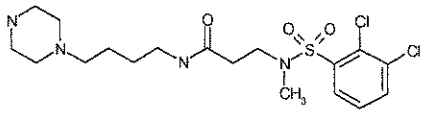
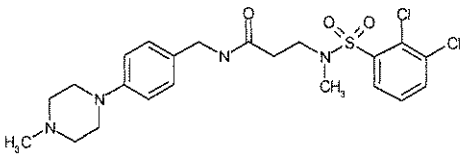
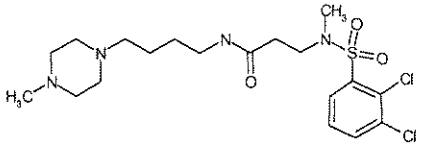
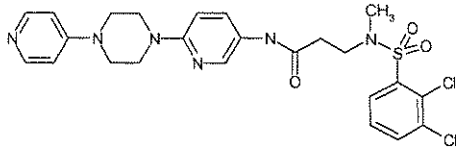
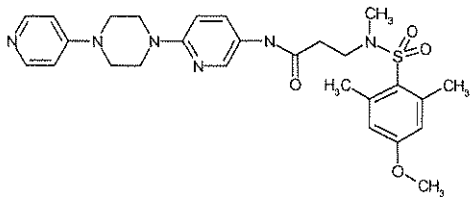
(8)	
(9)	
(10)	
(11)	
(12)	
(13)	
(14)	

Example	Structure
(15)	
(16)	
(17)	
(18)	
(19)	
(20)	
(21)	
(22)	

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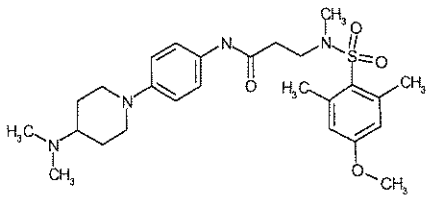
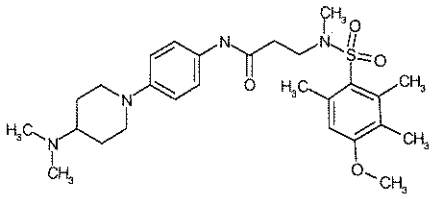
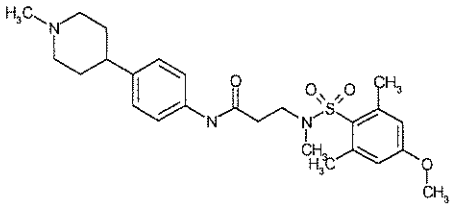
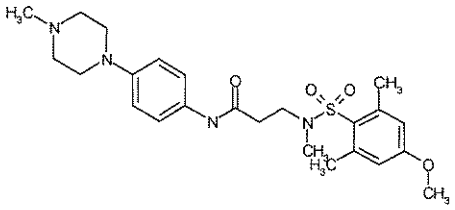
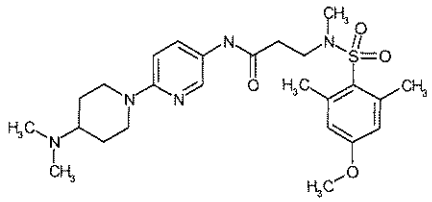
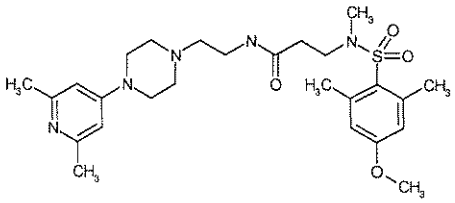
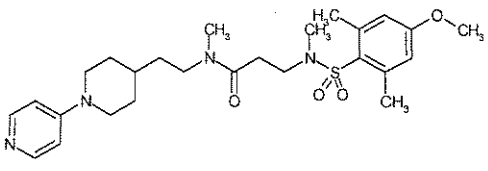
(23)	
(24)	
(25)	
(26)	
(27)	
(28)	
(29)	

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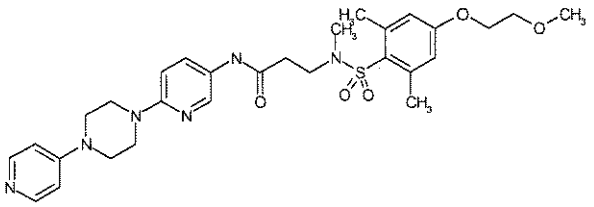
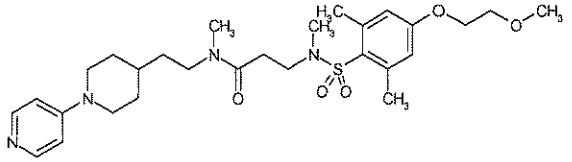
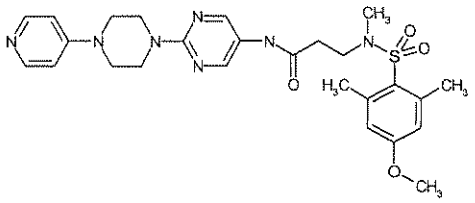
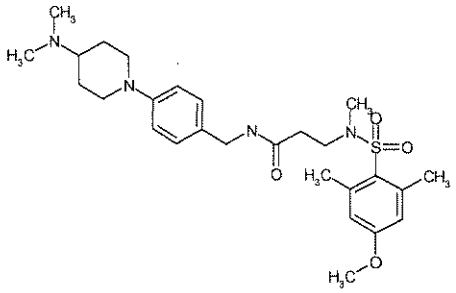
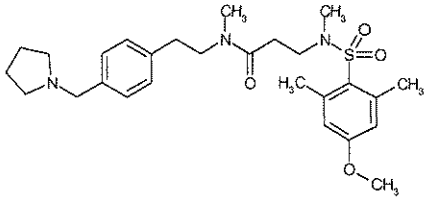
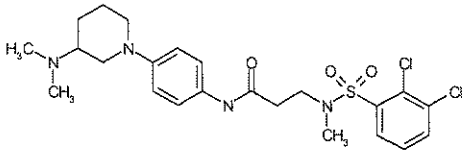
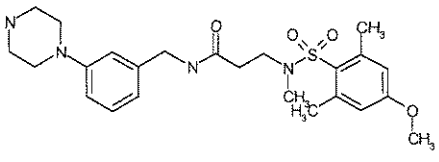
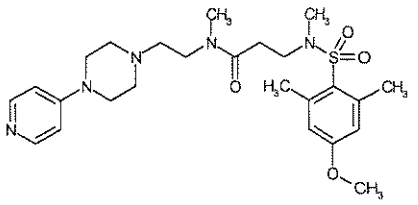
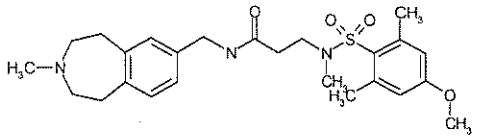
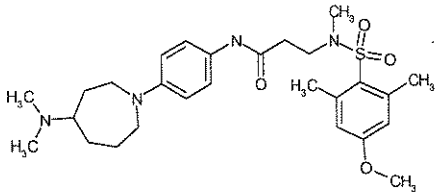
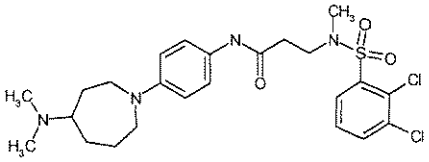
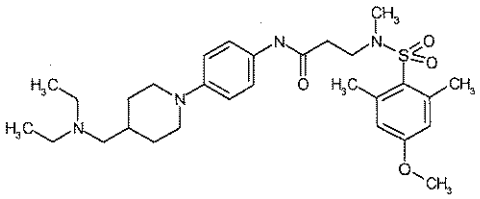
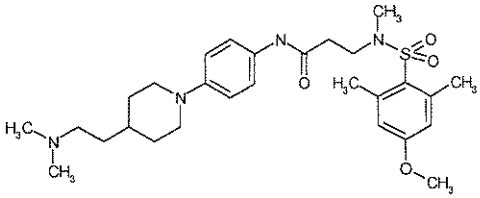
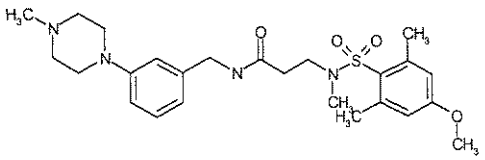
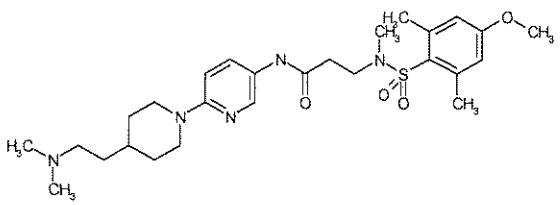
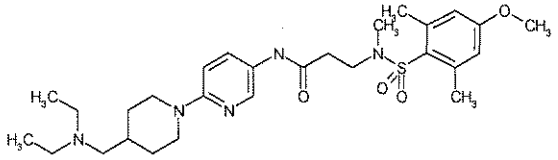
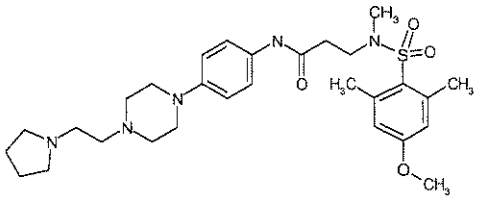
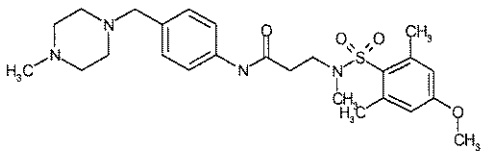
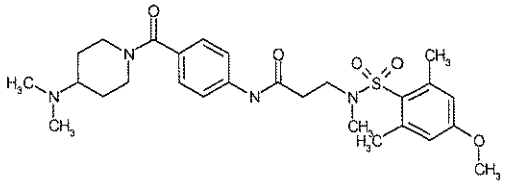
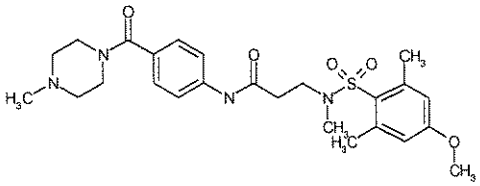
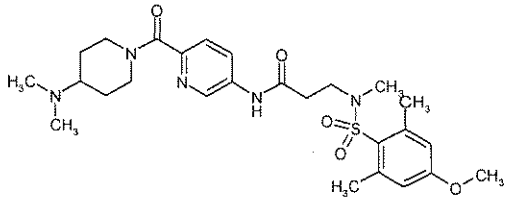
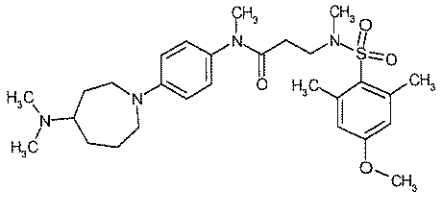
(30)	
(31)	
(32)	
(33)	
(34)	
(35)	
(36)	

Example	Structure
(37)	
(38)	
(39)	
(40)	
(41)	
(42)	
(43)	
(44)	

Example	Structure
(45)	
(46)	
(47)	
(48)	
(49)	
(50)	
(51)	

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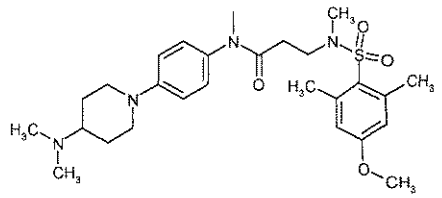
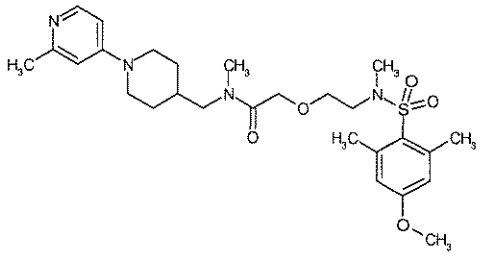
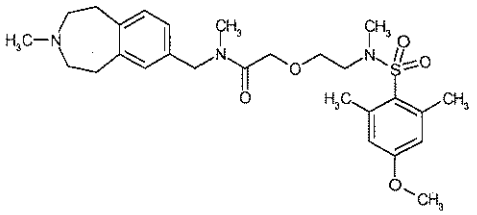
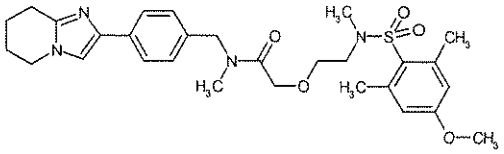
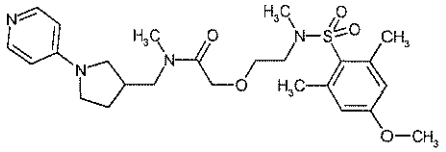
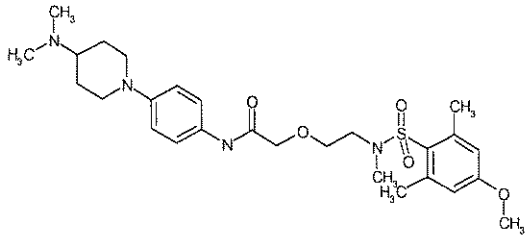
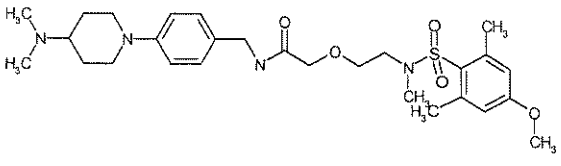
(52)	
(53)	
(54)	
(55)	
(56)	
(57)	
(58)	

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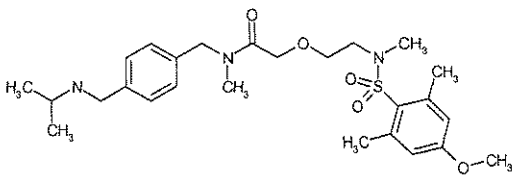
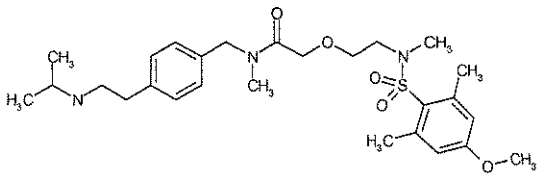
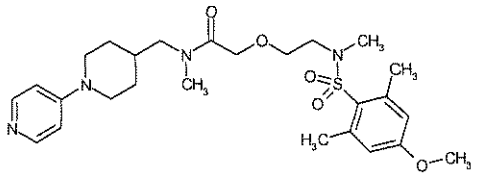
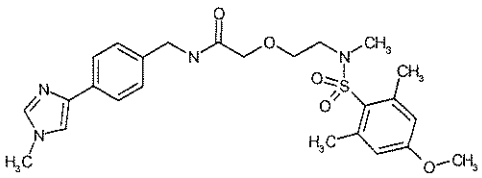
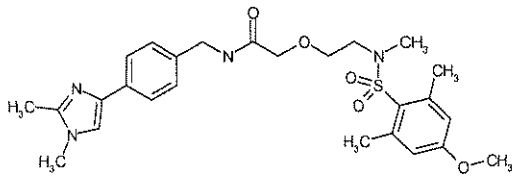
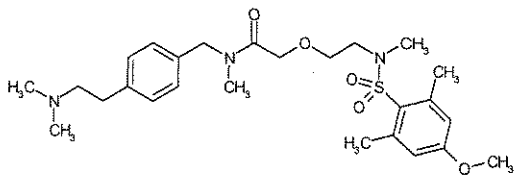
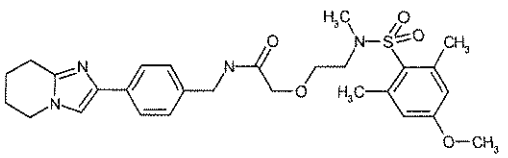
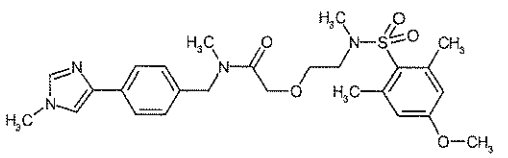
(59)	
(60)	
(61)	
(62)	
(63)	
(64)	
(65)	
(66)	

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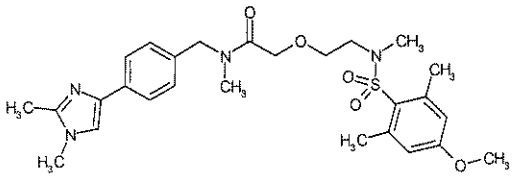
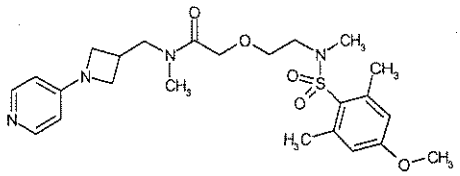
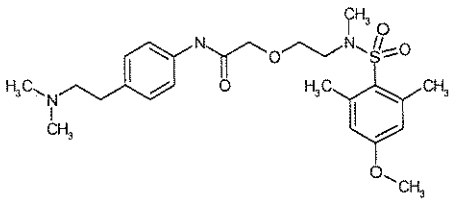
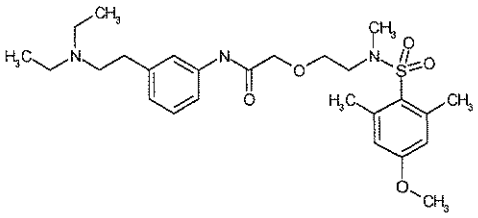
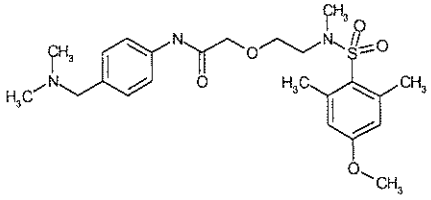
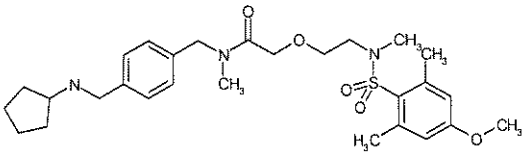
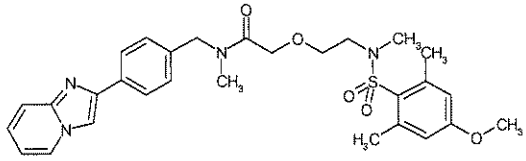
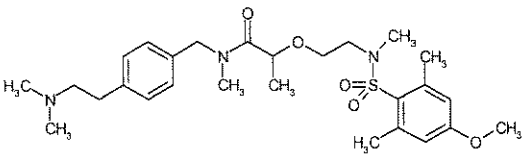
(67)	
(68)	
(69)	
(70)	
(71)	
(72)	
(73)	
(74)	

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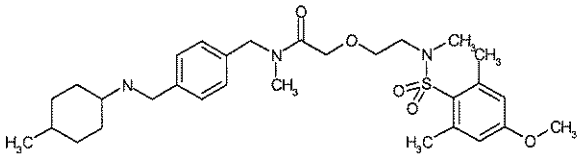
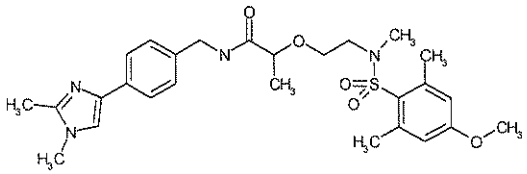
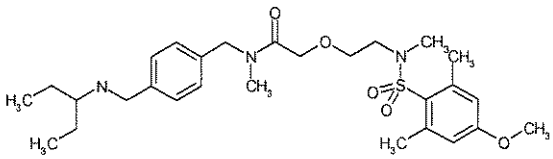
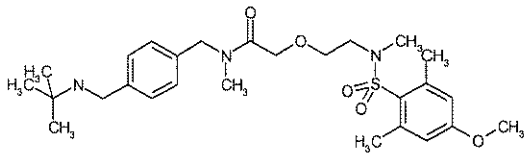
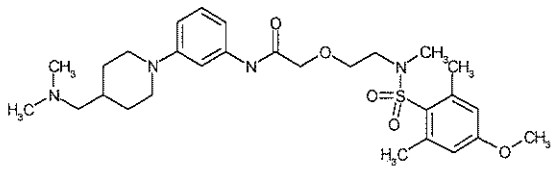
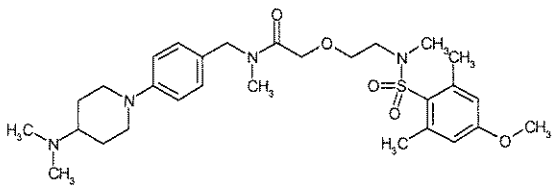
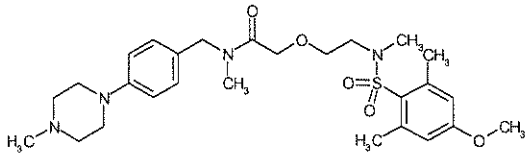
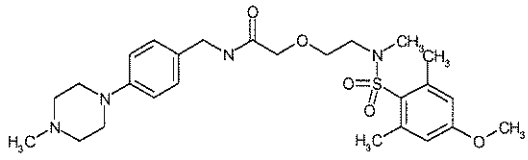
(75)	
(76)	
(77)	
(78)	
(79)	
(80)	
(81)	
(82)	

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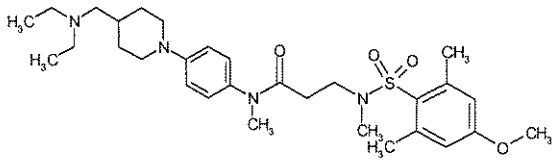
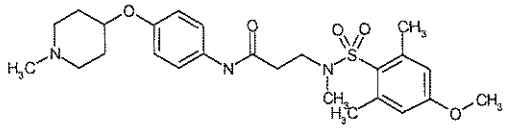
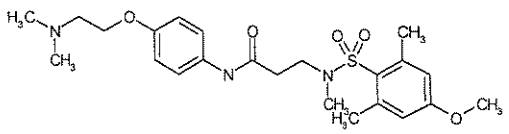
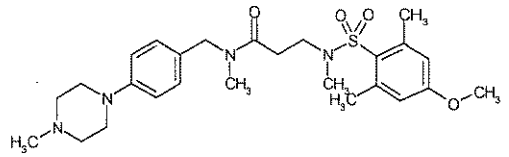
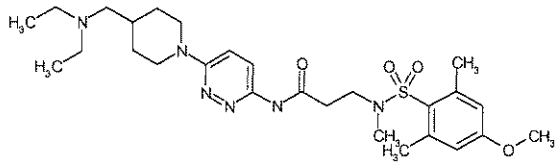
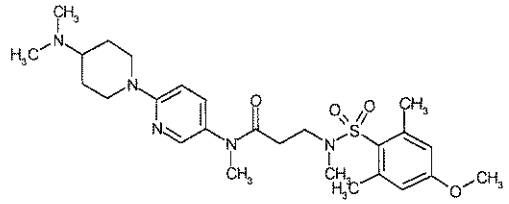
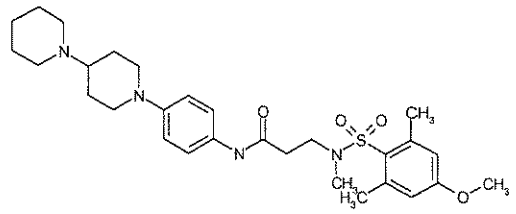
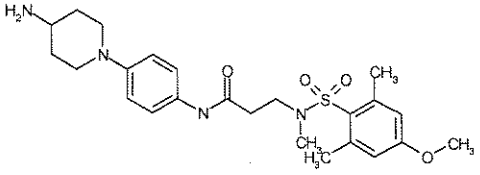
(83)	
(84)	
(85)	
(86)	
(87)	
(88)	
(89)	
(90)	

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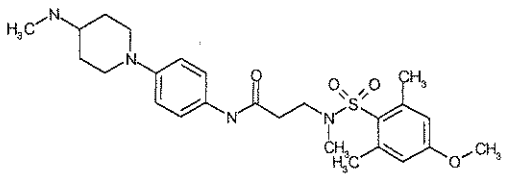
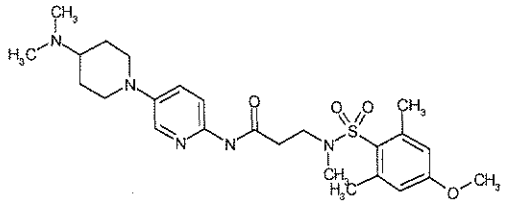
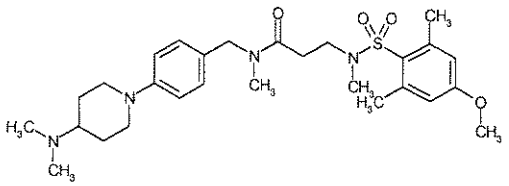
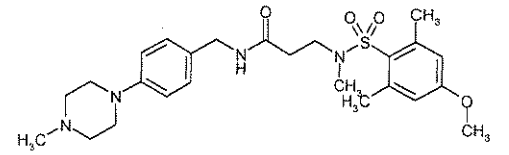
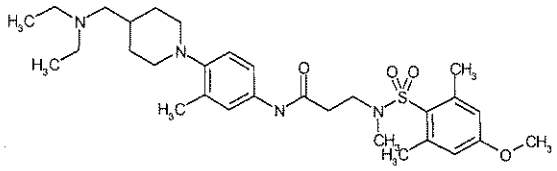
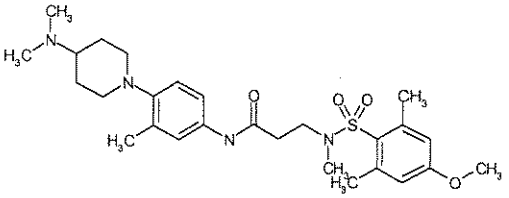
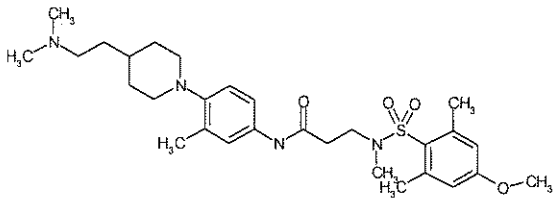
(91)	
(92)	
(93)	
(94)	
(95)	
(96)	
(97)	

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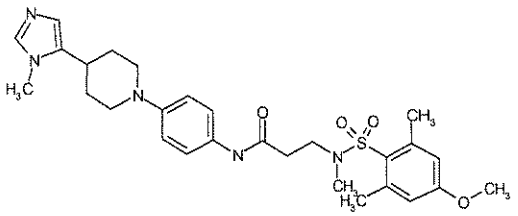
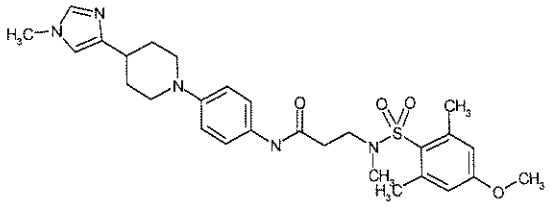
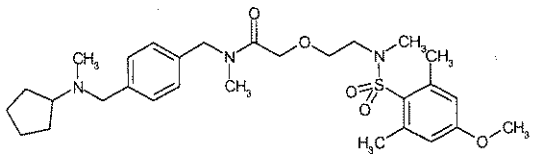
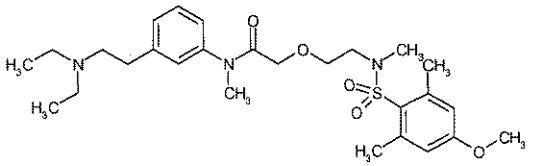
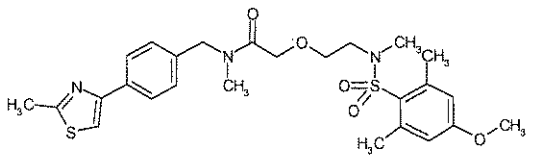
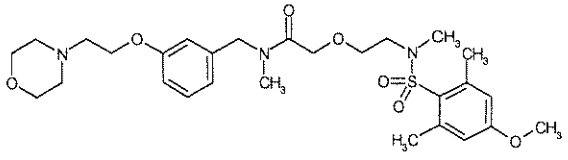
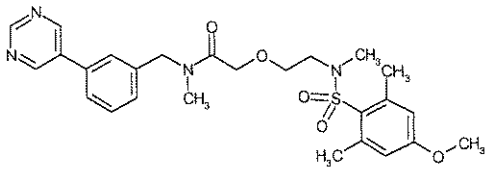
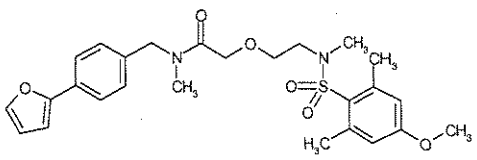
(98)	
(99)	
(100)	
(101)	
(102)	
(103)	
(104)	
(105)	

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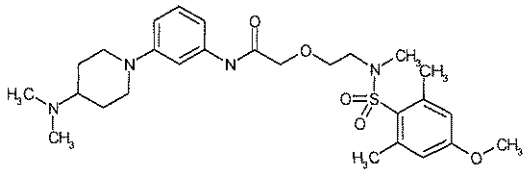
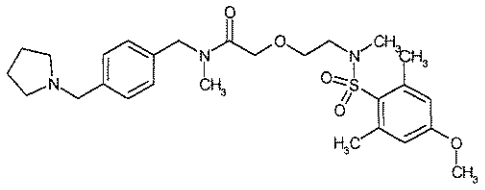
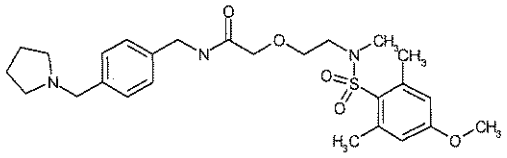
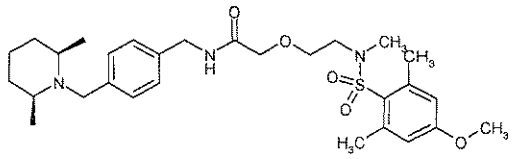
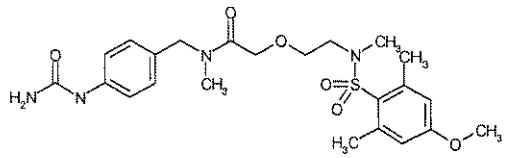
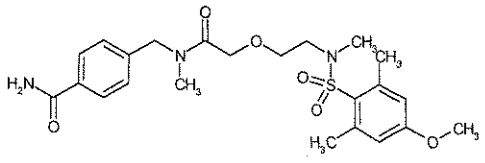
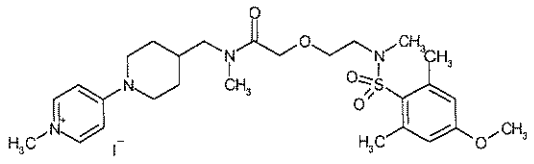
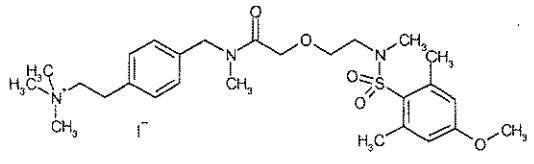
(106)	
(107)	
(108)	
(109)	
(110)	
(111)	
(112)	
(113)	

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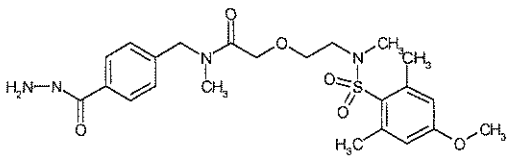
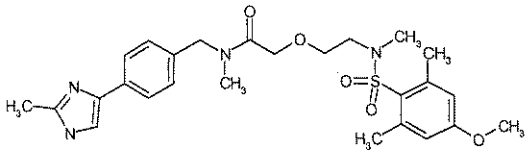
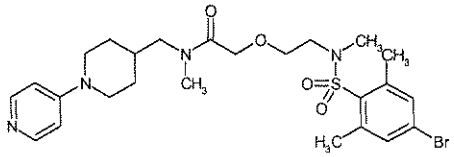
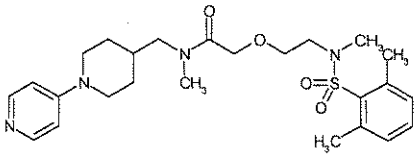
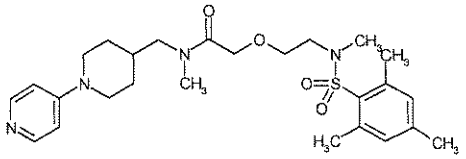
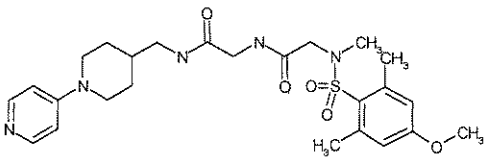
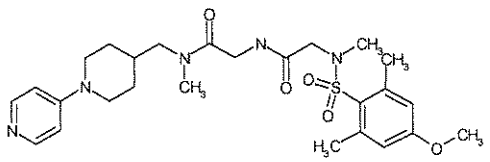
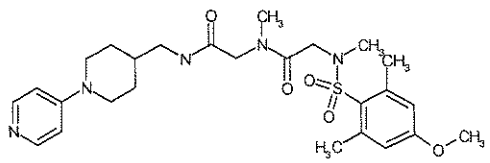
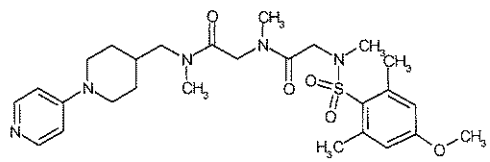
(114)	
(115)	
(116)	
(117)	
(118)	
(119)	
(120)	
(121)	
(122)	

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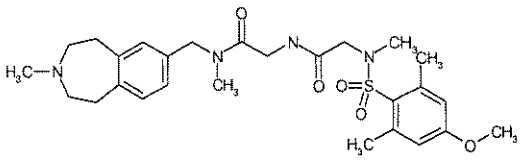
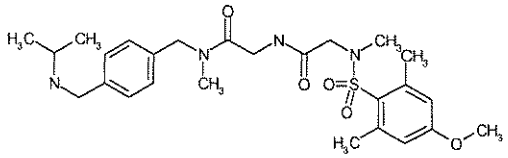
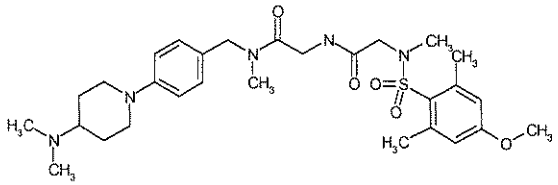
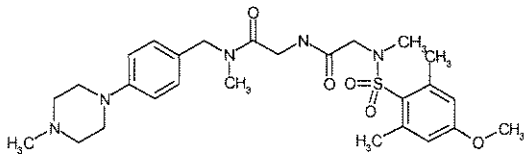
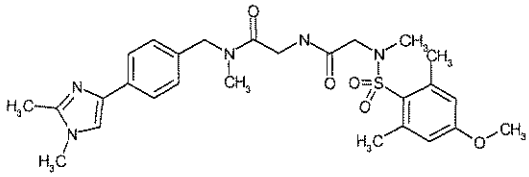
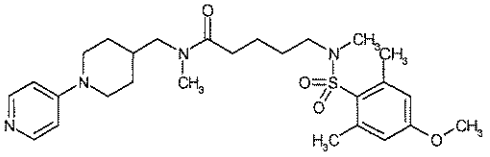
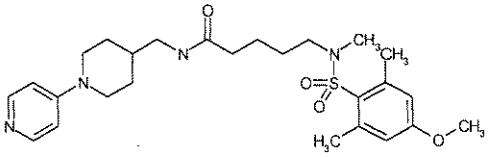
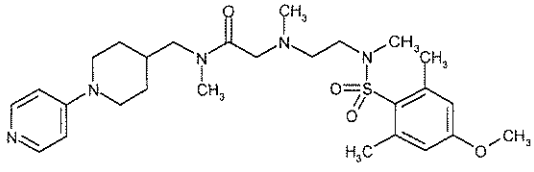
(123)	
(124)	
(125)	
(126)	
(127)	
(128)	
(129)	
(130)	

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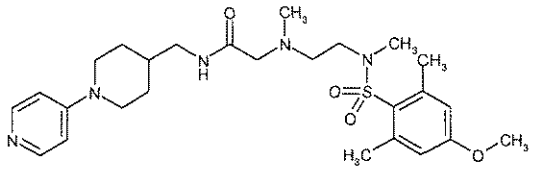
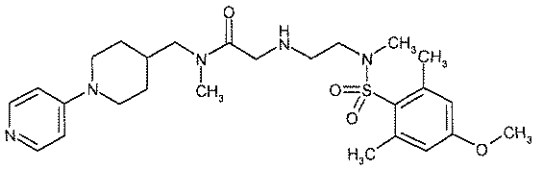
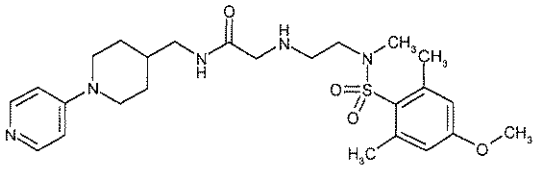
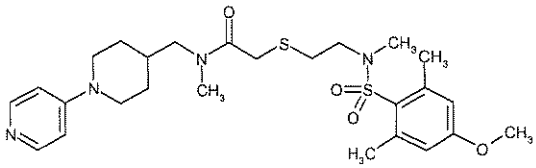
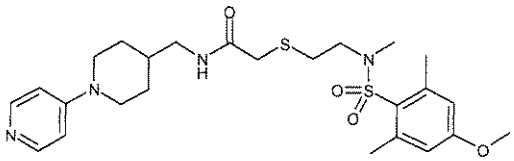
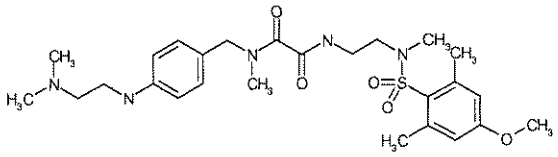
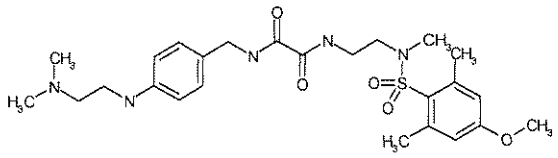
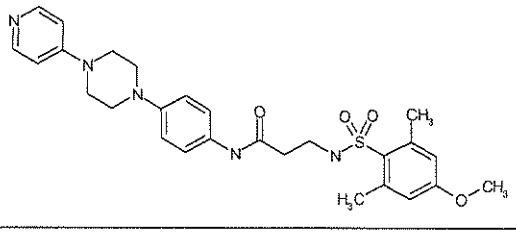
(131)	
(132)	
(133)	
(134)	
(135)	
(136)	
(137)	
(138)	

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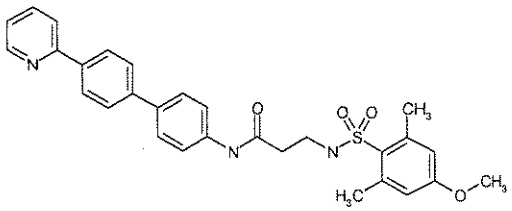
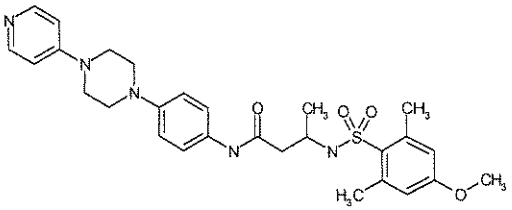
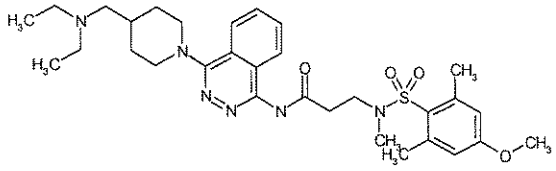
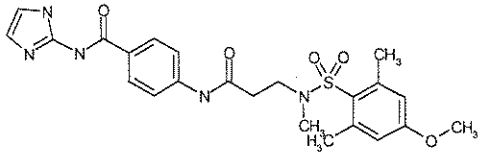
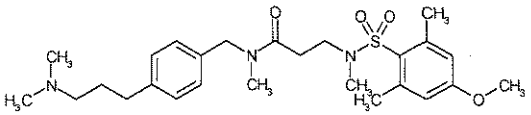
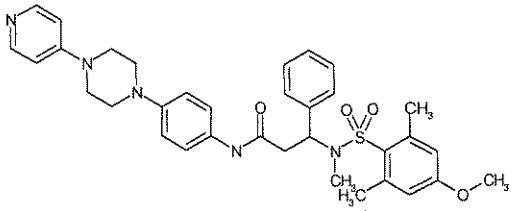
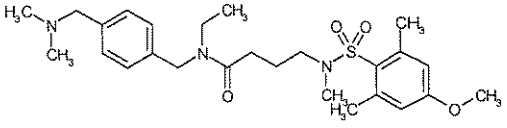
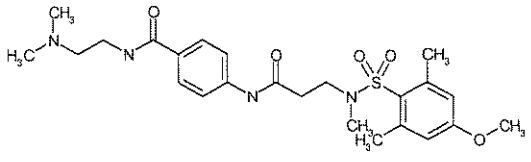
(139)	
(140)	
(141)	
(142)	
(143)	
(144)	
(145)	
(146)	

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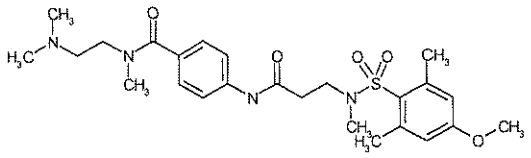
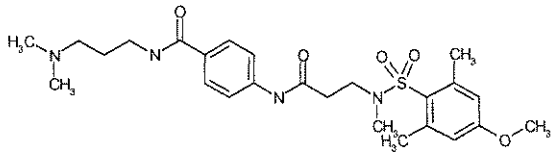
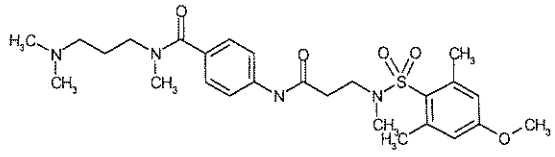
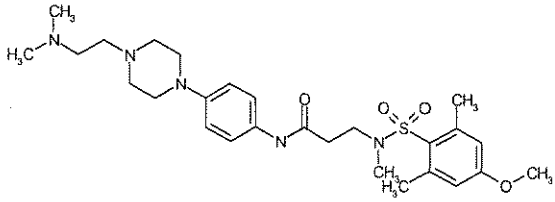
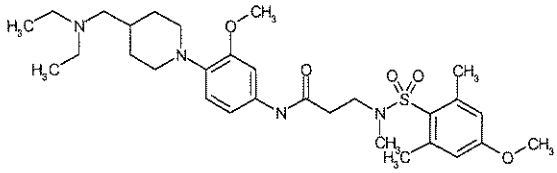
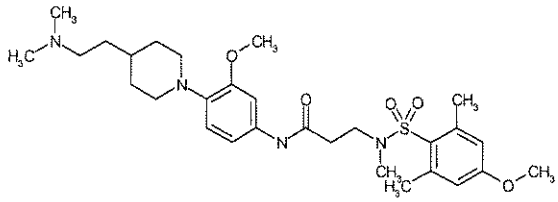
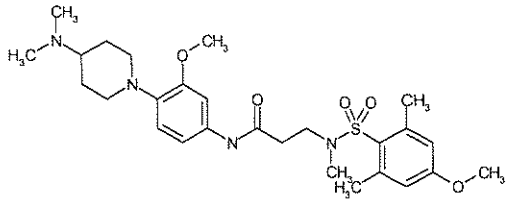
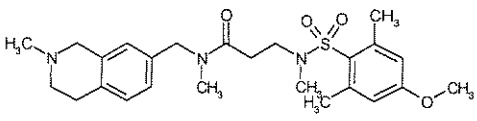
(147)	
(148)	
(149)	
(150)	
(151)	
(152)	
(153)	
(154)	

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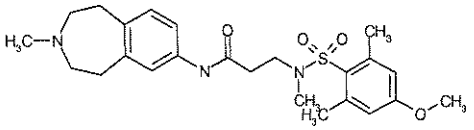
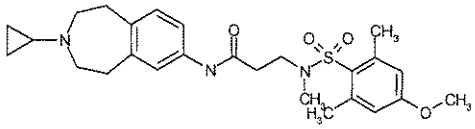
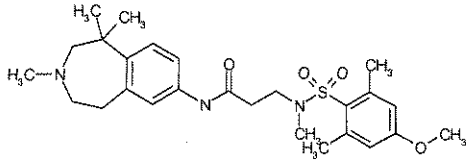
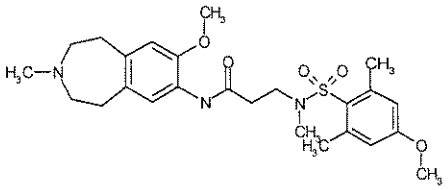
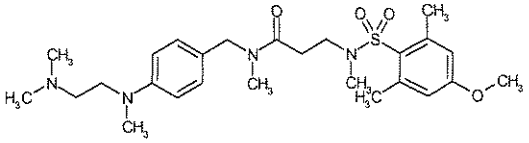
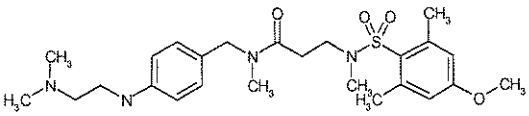
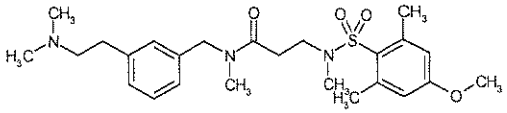
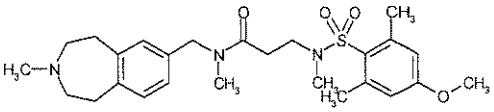
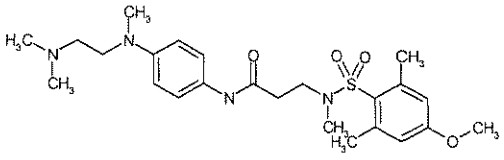
(155)	
(156)	
(157)	
(158)	
(159)	
(160)	
(161)	
(162)	
(163)	

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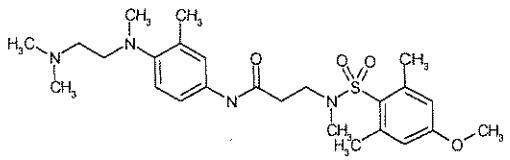
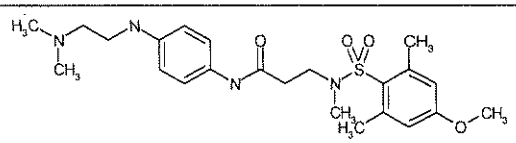
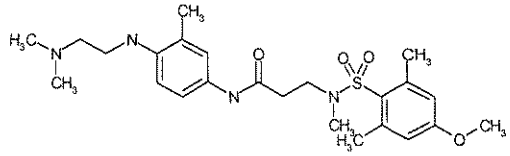
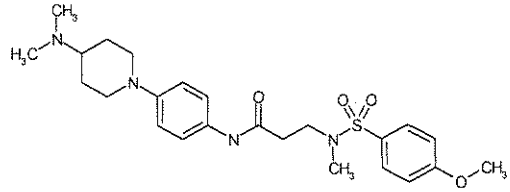
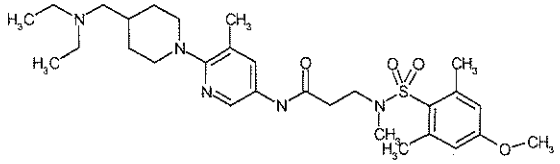
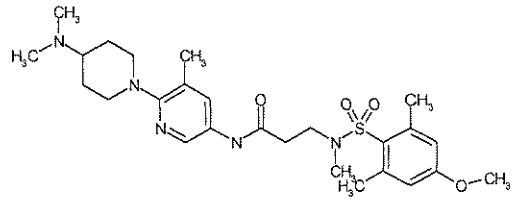
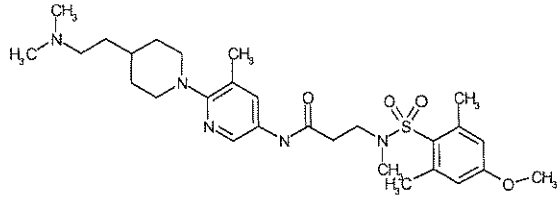
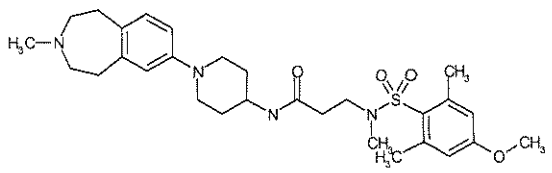
(164)	
(165)	
(166)	
(167)	
(168)	
(169)	
(170)	
(171)	

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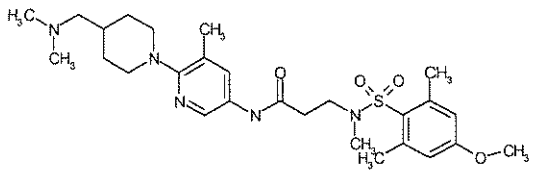
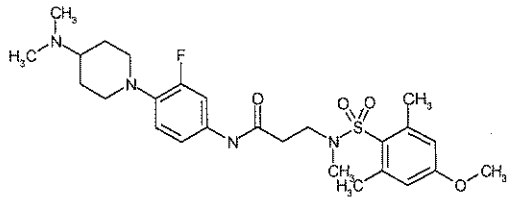
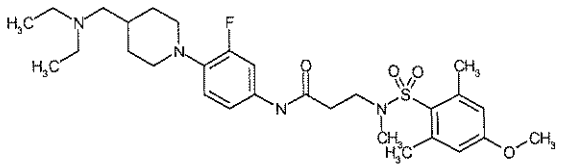
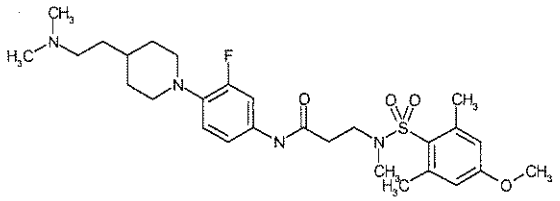
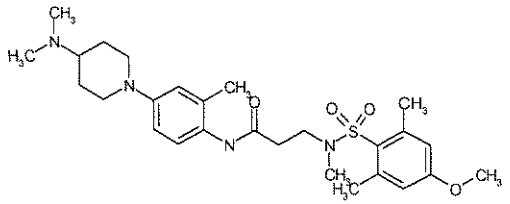
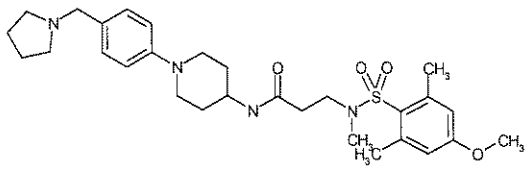
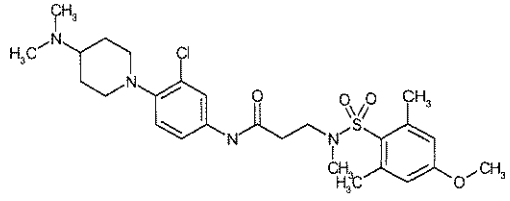
(172)	
(173)	
(174)	
(175)	
(176)	
(177)	
(178)	

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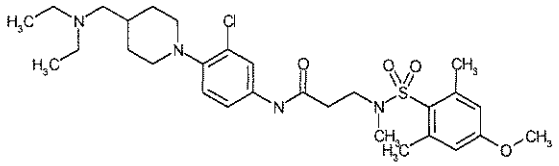
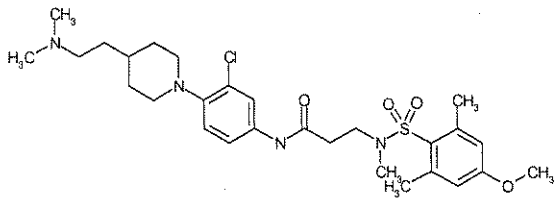
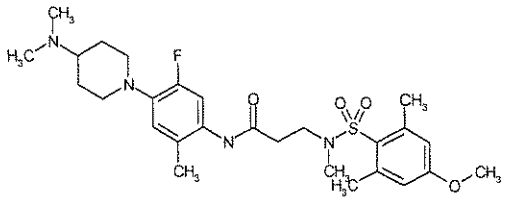
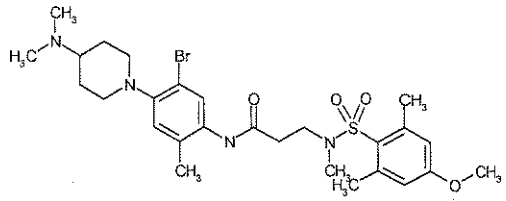
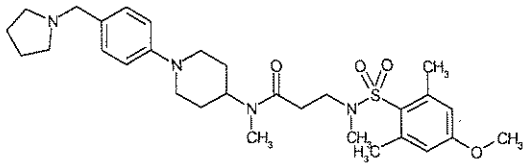
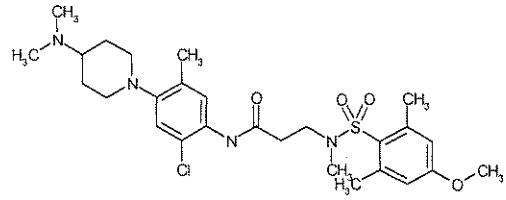
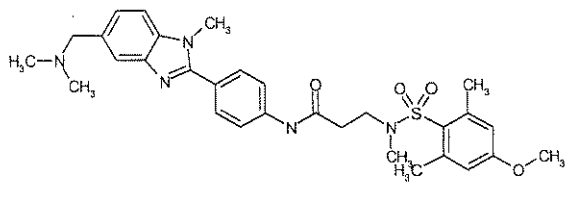
(179)	
(180)	
(181)	
(182)	
(183)	
(184)	
(185)	

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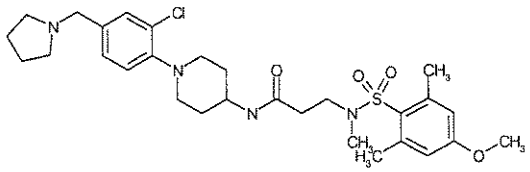
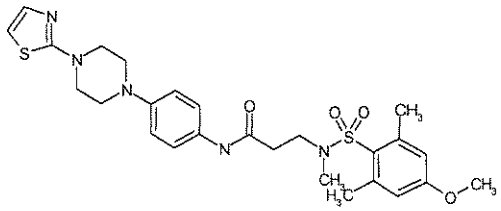
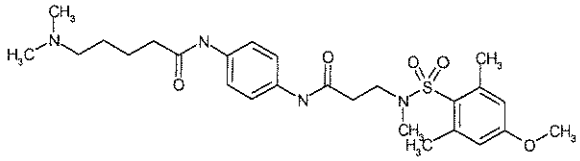
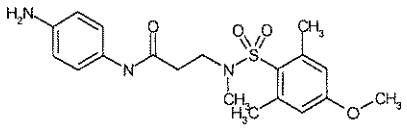
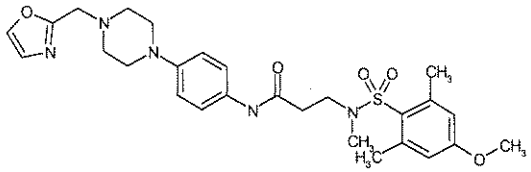
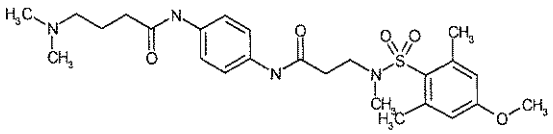
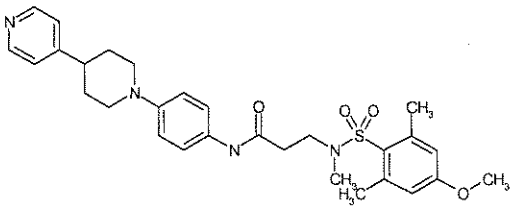
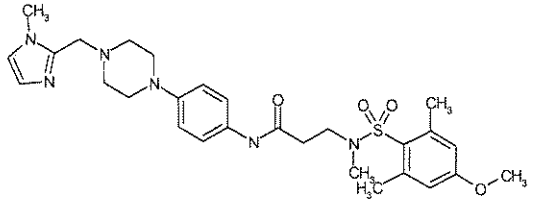
(186)	
(187)	
(188)	
(189)	
(190)	
(191)	
(192)	
(193)	

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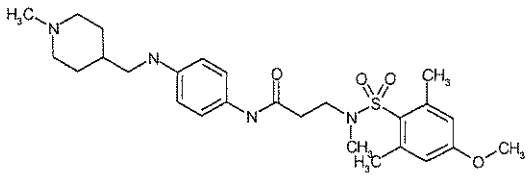
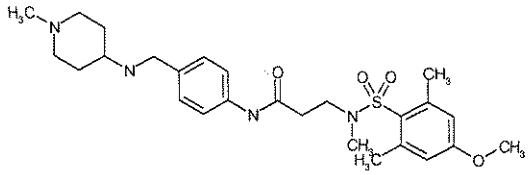
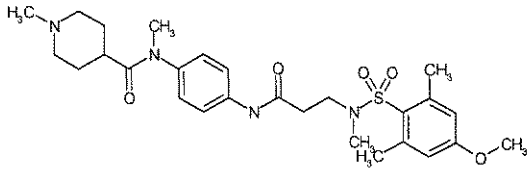
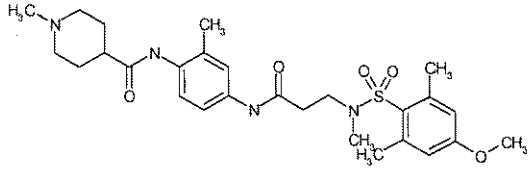
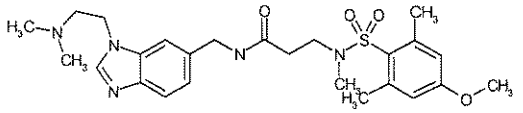
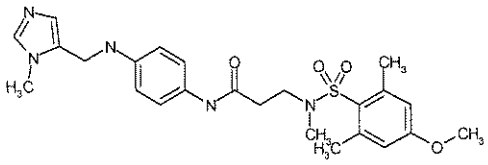
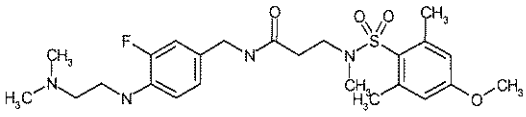
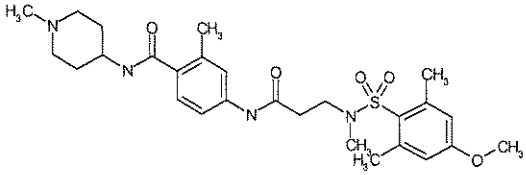
(194)	
(195)	
(196)	
(197)	
(198)	
(199)	
(200)	
(201)	

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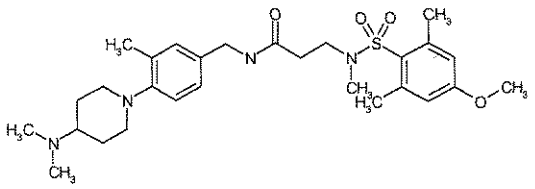
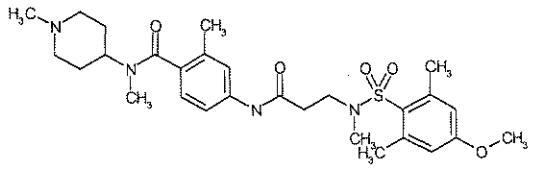
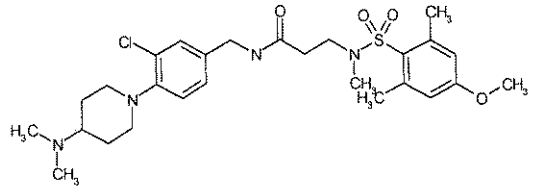
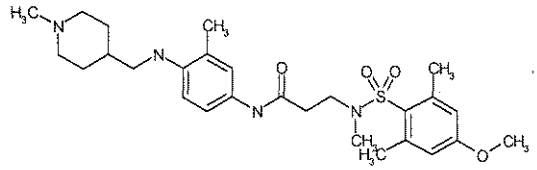
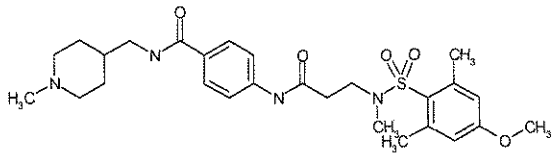
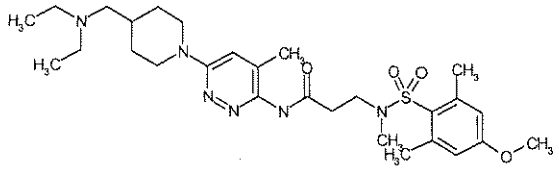
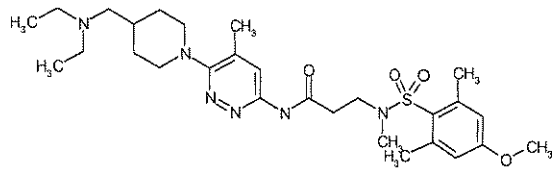
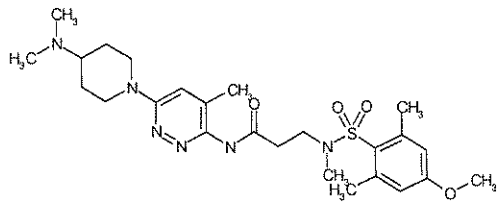
(202)	
(203)	
(204)	
(205)	
(206)	
(207)	
(208)	
(209)	

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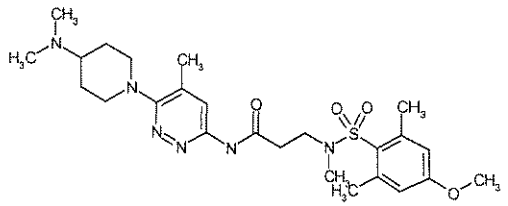
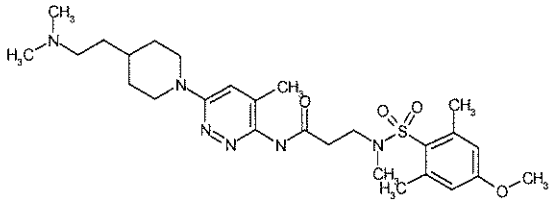
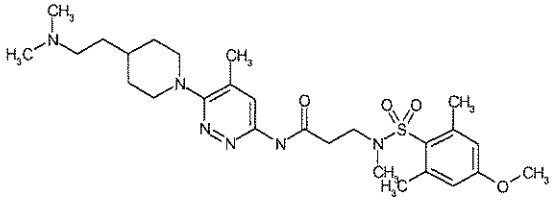
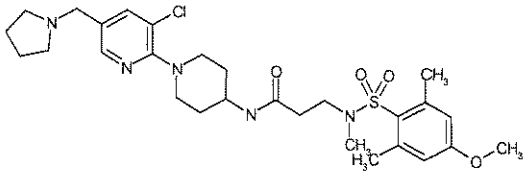
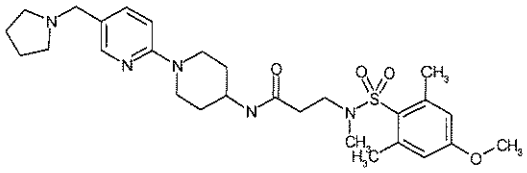
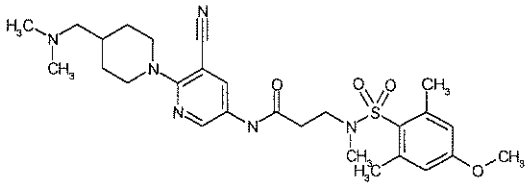
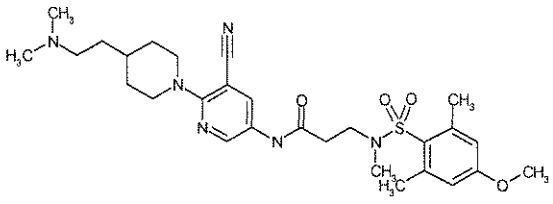
(210)	
(211)	
(212)	
(213)	
(214)	
(215)	
(216)	

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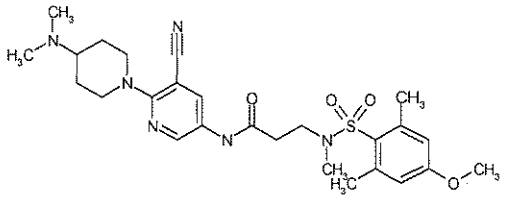
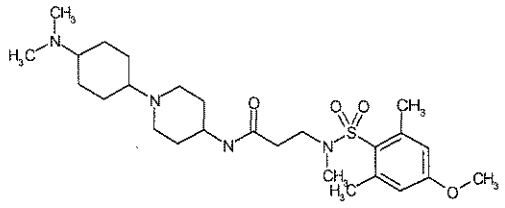
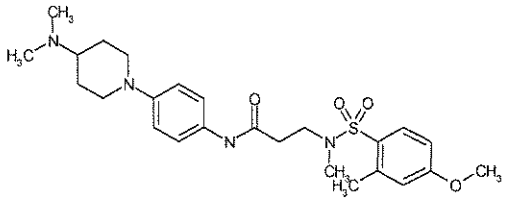
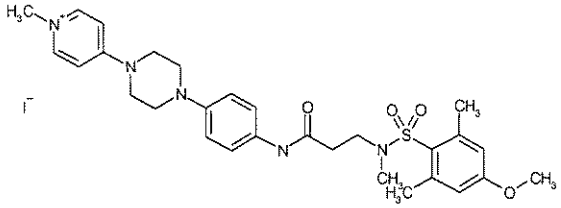
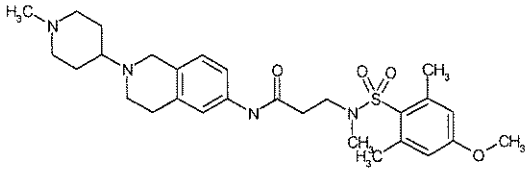
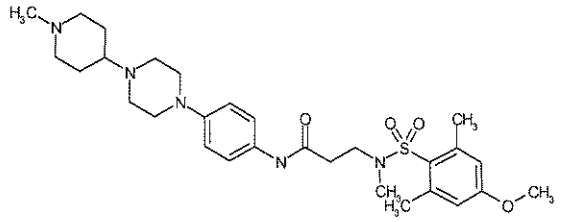
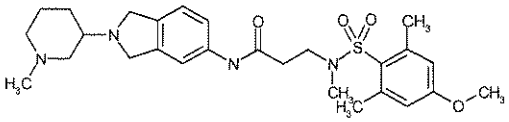
(217)	
(218)	
(219)	
(220)	
(221)	
(222)	
(223)	

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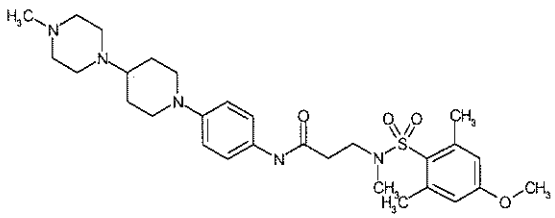
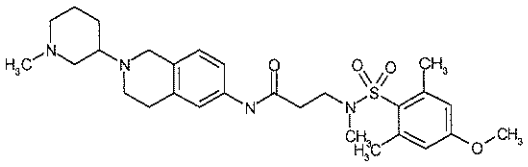
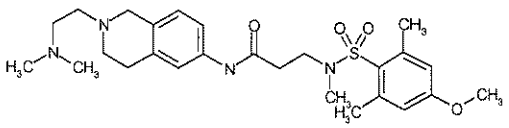
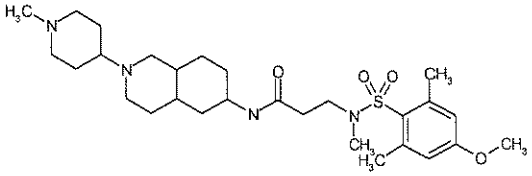
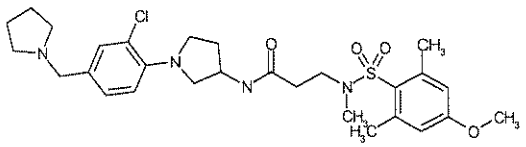
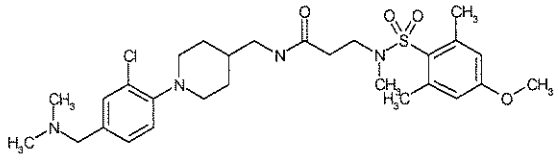
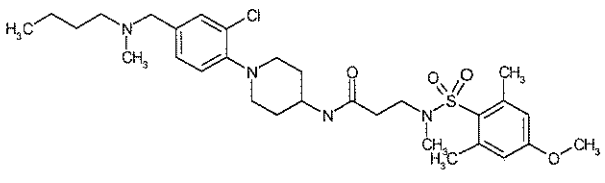
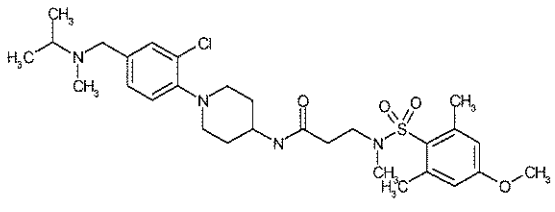
(224)	
(225)	
(226)	
(227)	
(228)	
(229)	
(230)	
(231)	

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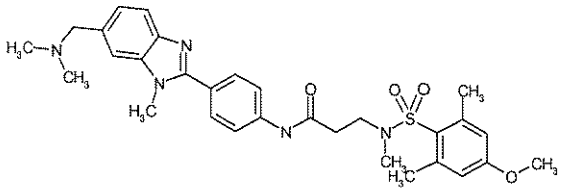
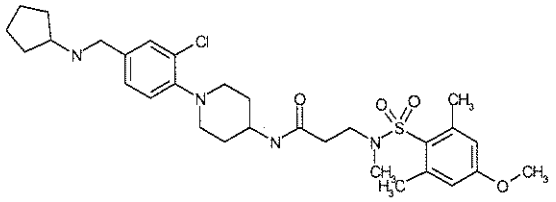
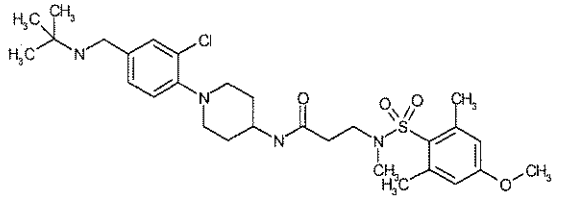
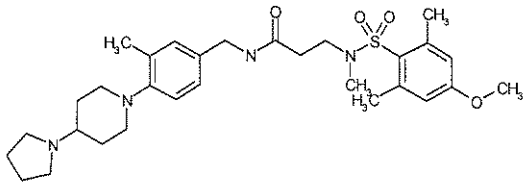
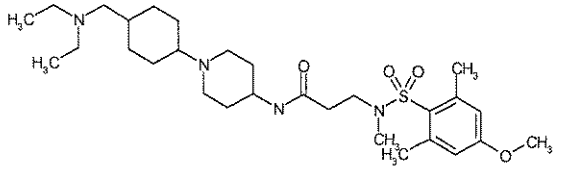
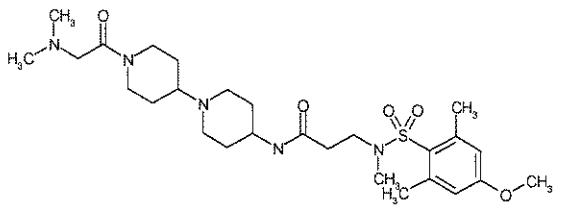
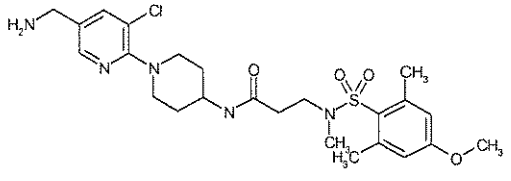
(232)	
(233)	
(234)	
(235)	
(236)	
(237)	
(238)	

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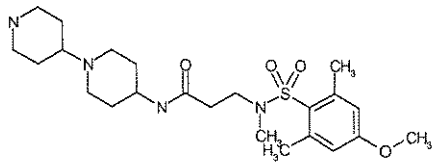
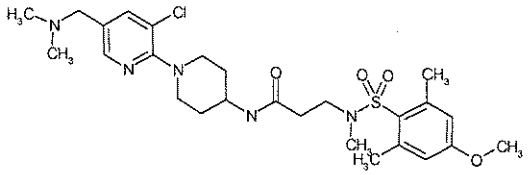
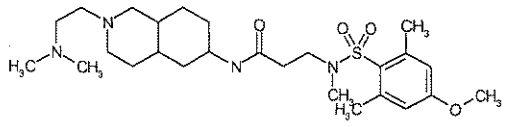
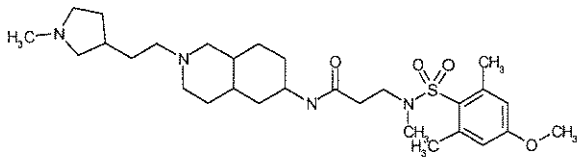
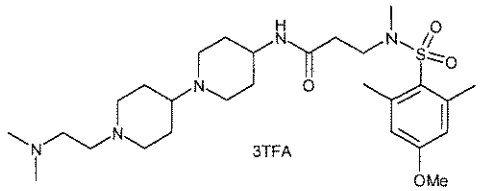
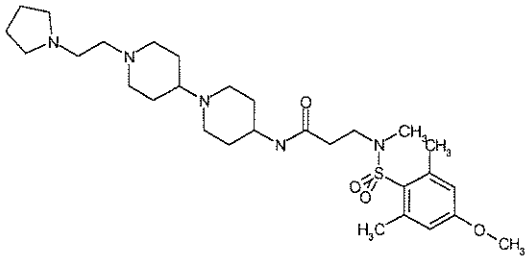
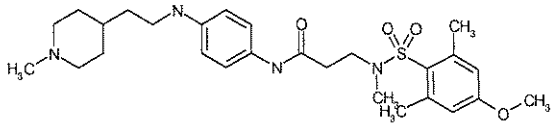
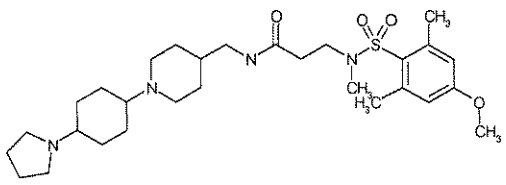
(239)	
(240)	
(241)	
(242)	
(243)	
(244)	
(245)	
(246)	

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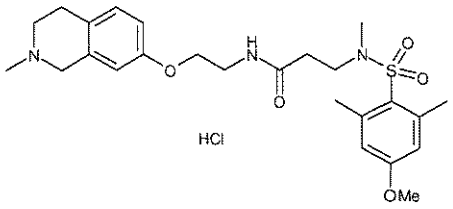
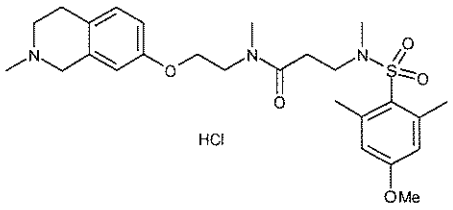
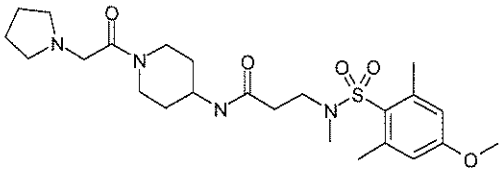
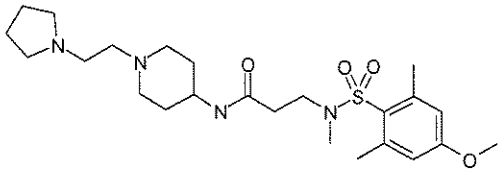
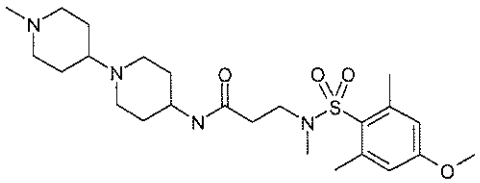
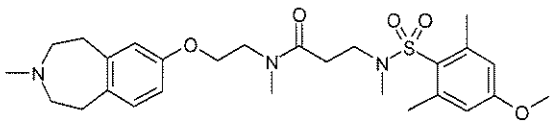
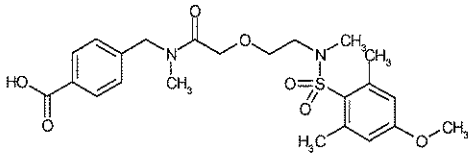
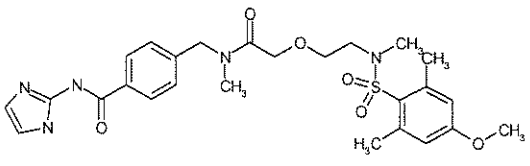
(247)	
(248)	
(249)	
(250)	
(251)	
(252)	
(253)	
(254)	

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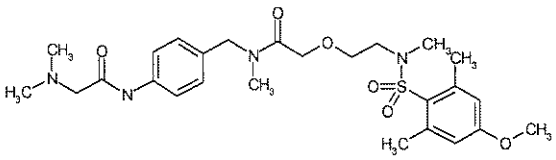
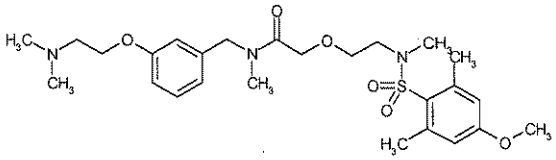
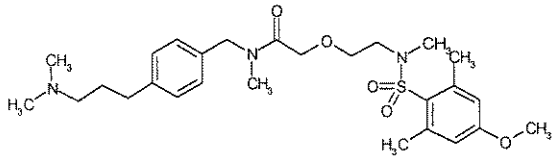
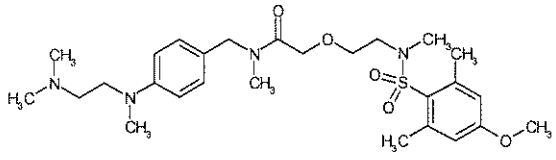
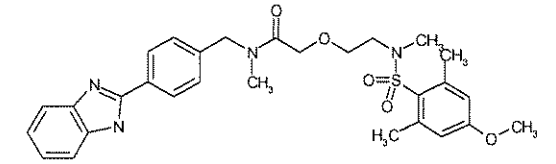
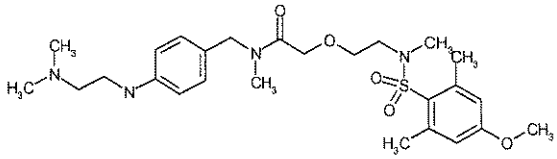
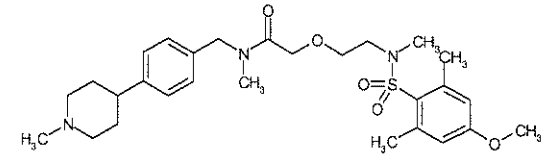
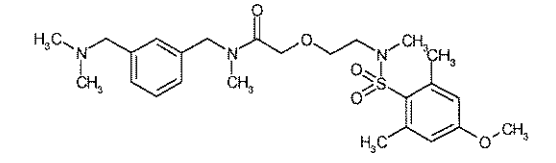
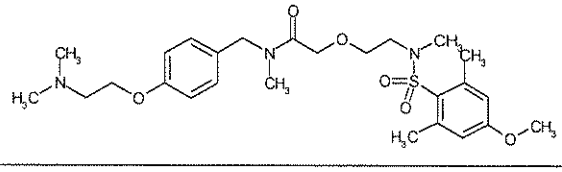
(255)	
(256)	
(257)	
(258)	
(259)	
(260)	
(261)	
(262)	
(263)	

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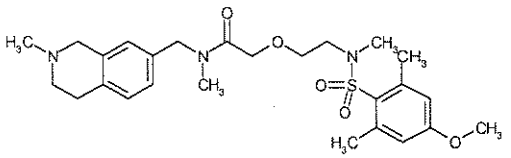
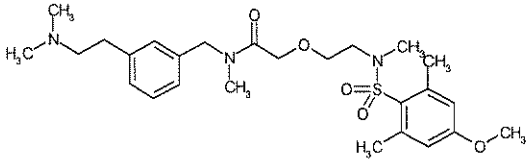
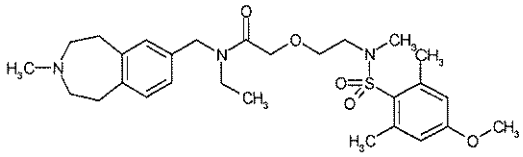
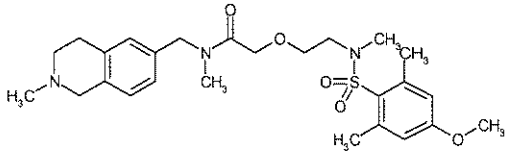
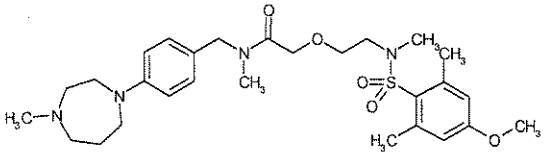
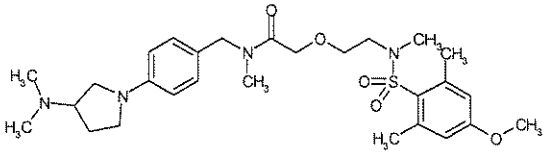
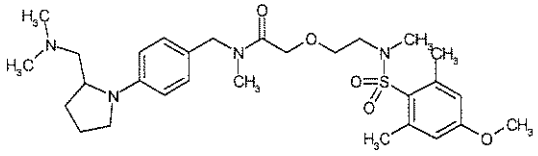
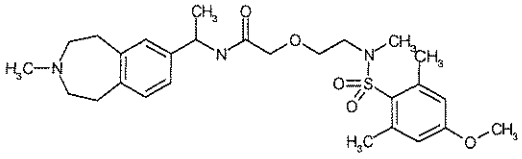
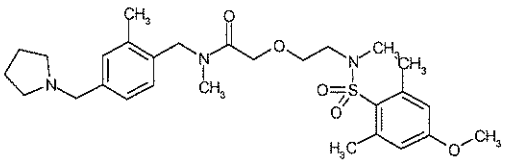
(264)	
(265)	
(266)	
(267)	
(268)	
(269)	
(270)	
(271)	
(272)	

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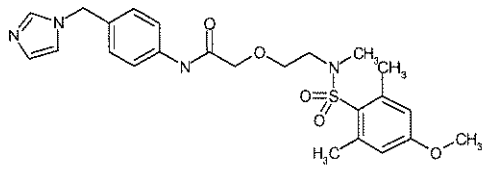
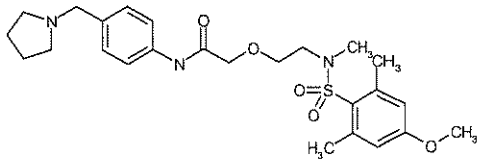
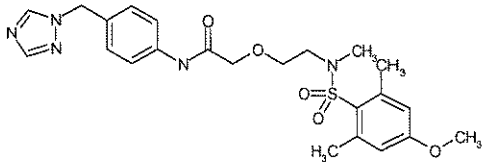
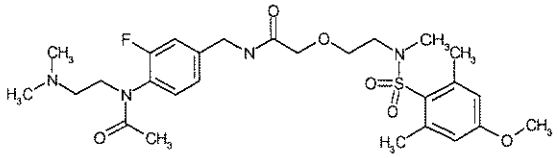
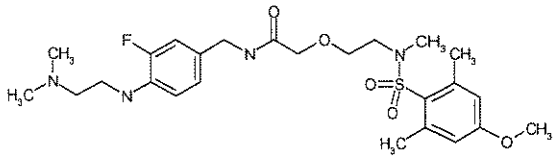
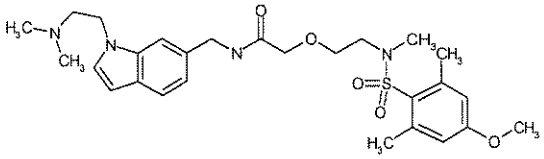
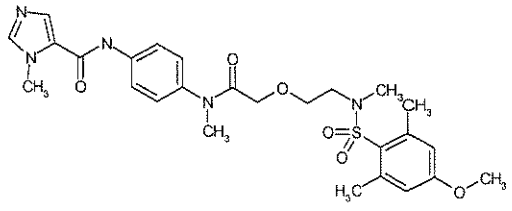
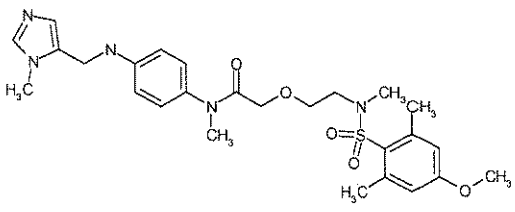
(273)	
(274)	
(275)	
(276)	
(277)	
(278)	
(279)	
(280)	

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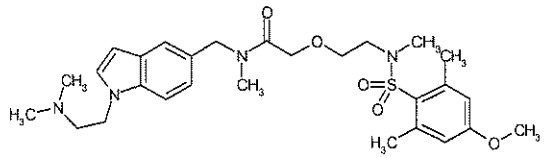
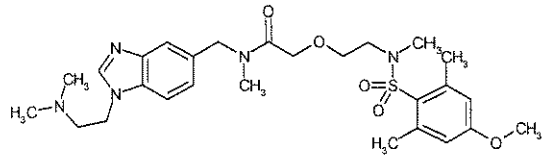
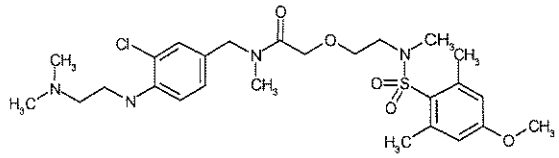
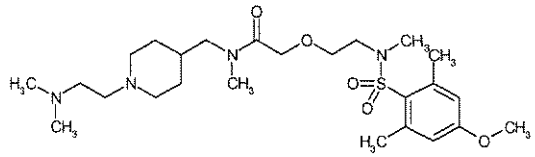
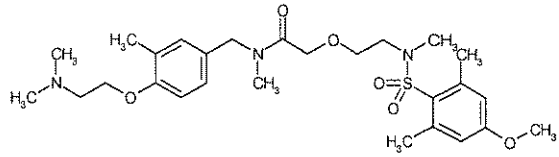
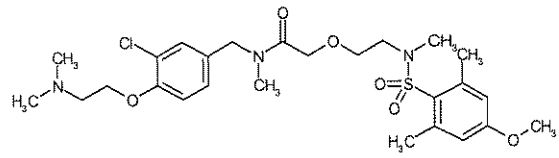
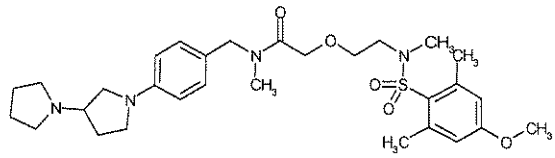
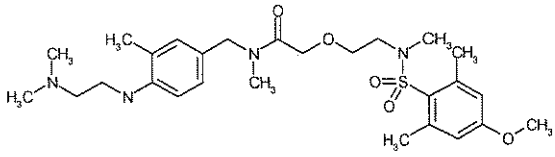
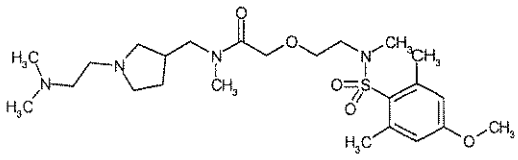
(281)	
(282)	
(283)	
(284)	
(285)	
(286)	
(287)	
(288)	
(289)	

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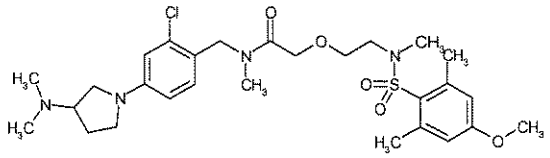
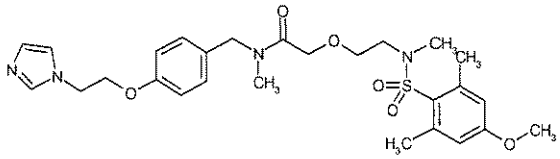
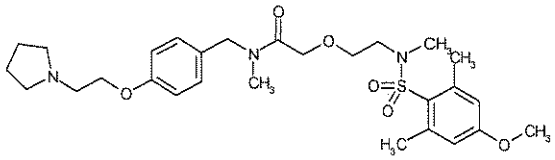
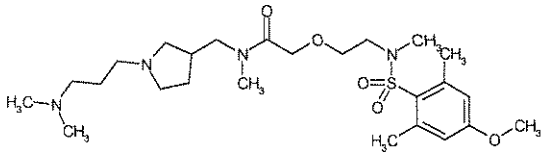
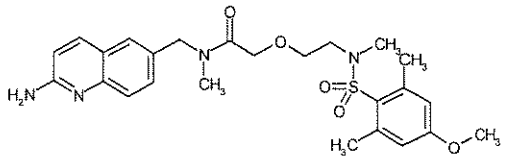
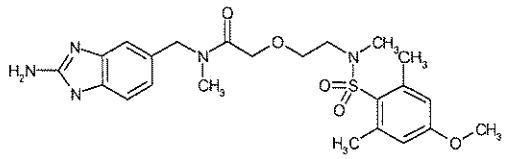
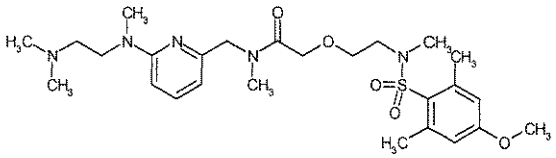
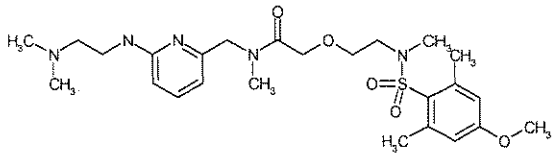
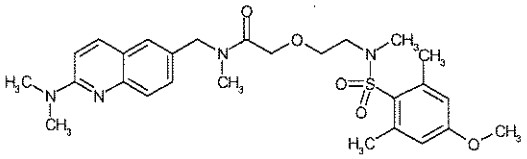
(290)	
(291)	
(292)	
(293)	
(294)	
(295)	
(296)	
(297)	
(298)	

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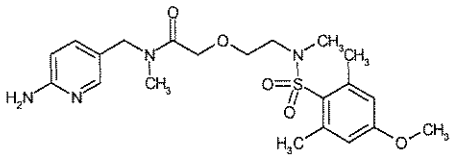
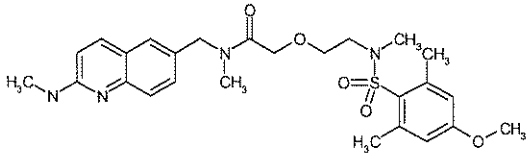
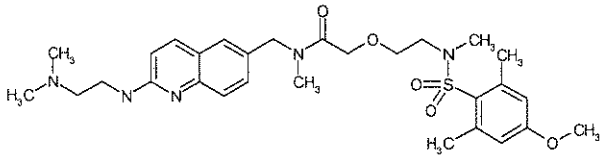
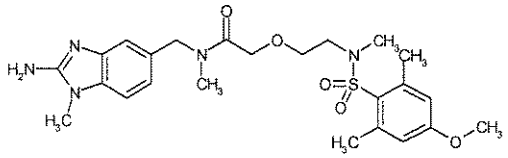
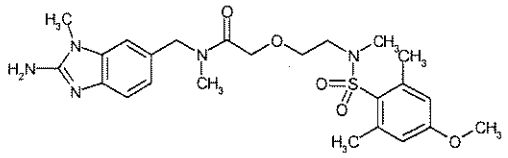
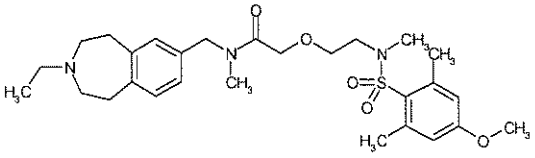
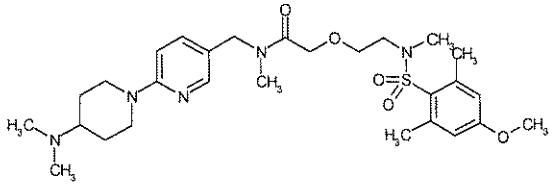
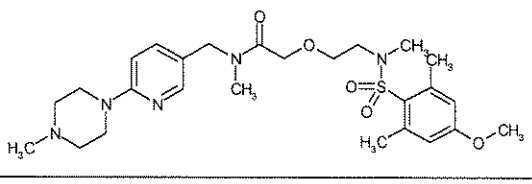
(299)	
(300)	
(301)	
(302)	
(303)	
(304)	
(305)	
(306)	

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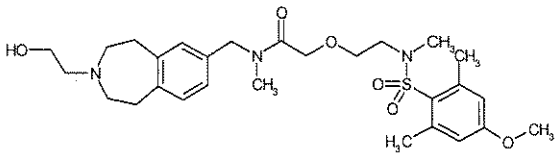
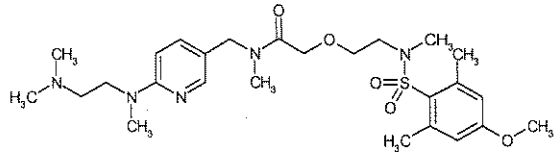
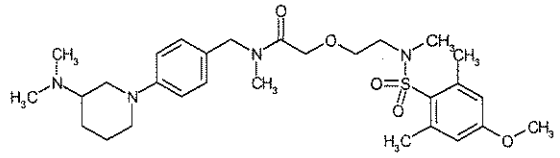
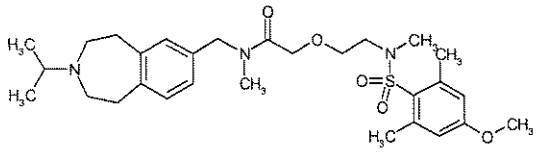
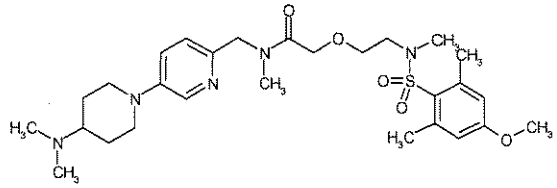
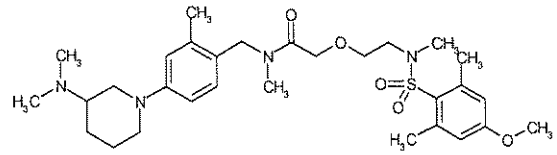
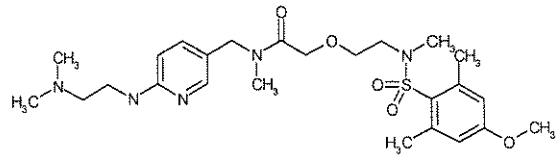
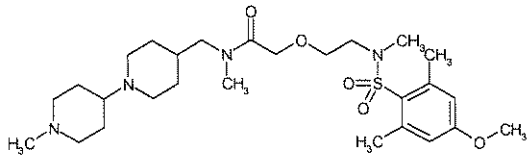
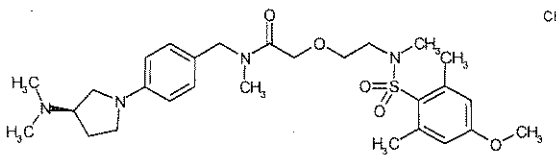
(307)	
(308)	
(309)	
(310)	
(311)	
(312)	
(313)	
(314)	
(315)	Chiral 

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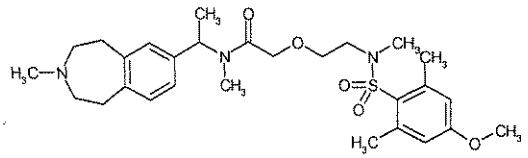
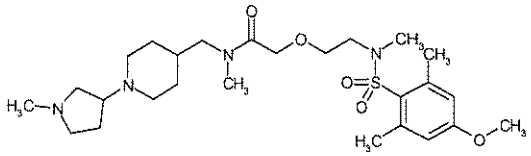
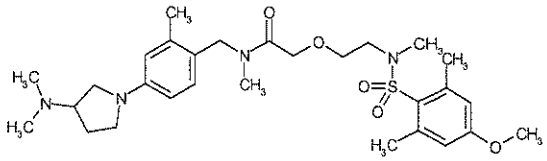
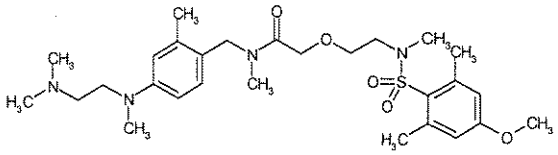
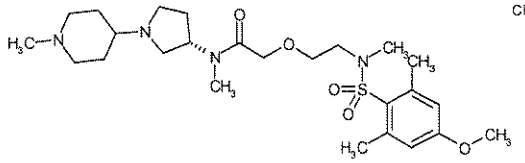
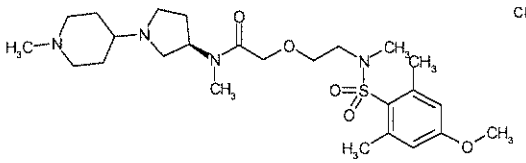
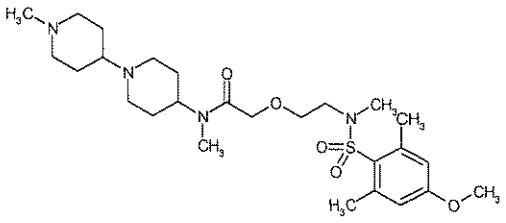
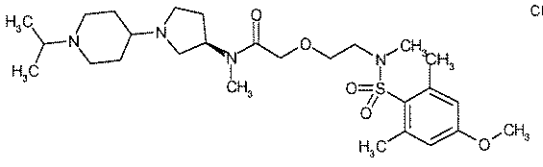
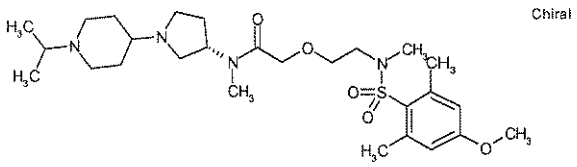
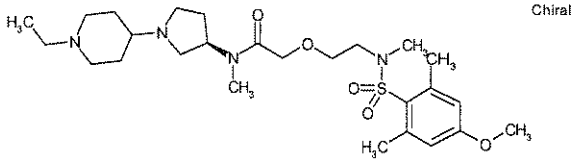
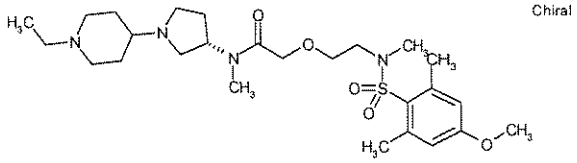
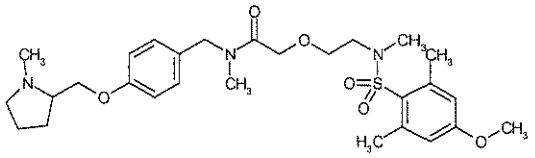
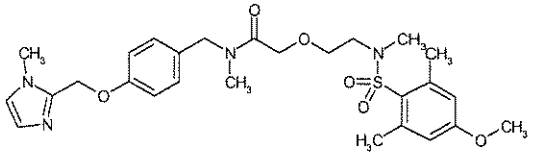
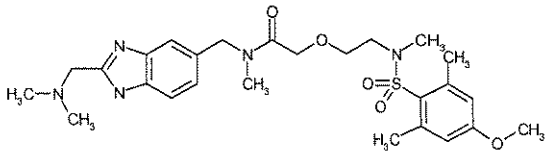
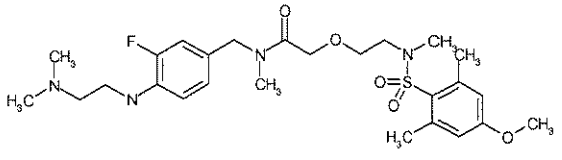
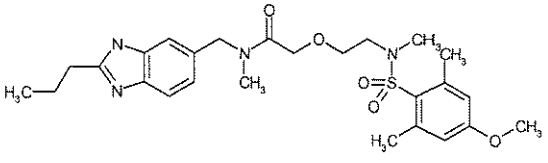
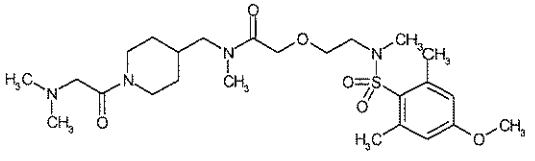
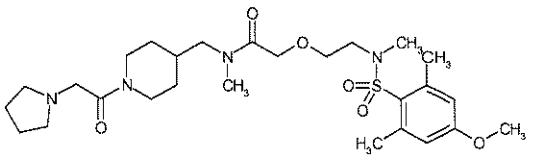
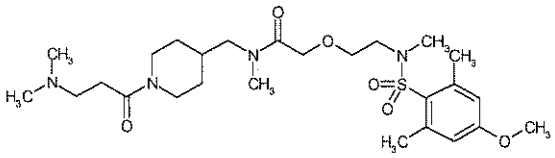
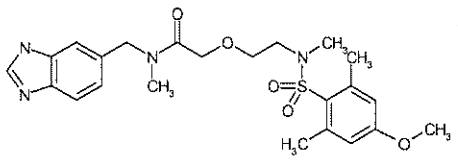
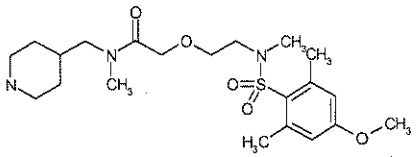
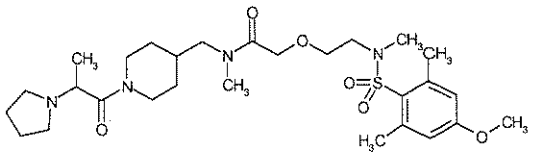
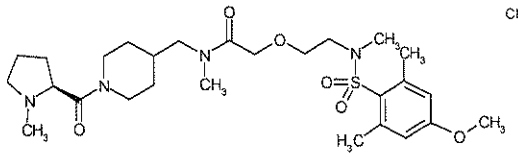
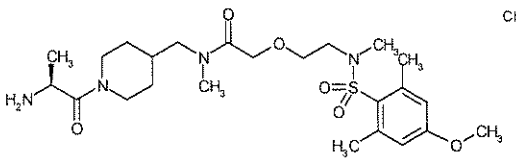
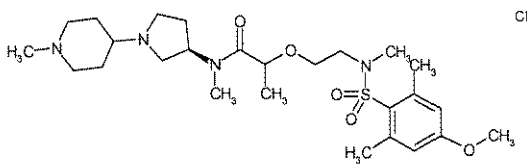
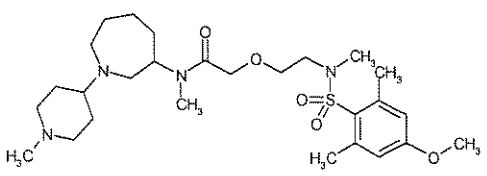
(316)	
(317)	
(318)	
(319)	
(320)	Chiral 
(321)	Chiral 
(322)	
(323)	Chiral 

Example	Structure
(324)	 Chiral
(325)	 Chiral
(326)	 Chiral
(327)	
(328)	
(329)	
(330)	
(331)	
(332)	

Example	Structure
(333)	
(334)	
(335)	
(336)	
(337)	
(338)	Chiral 
(339)	Chiral 
(340)	Chiral 
(341)	

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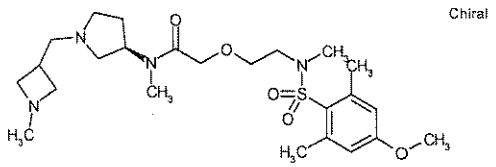
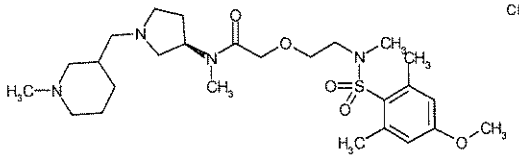
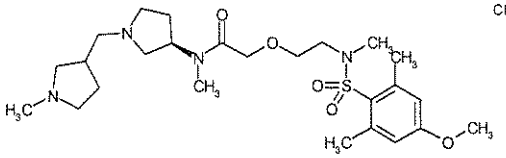
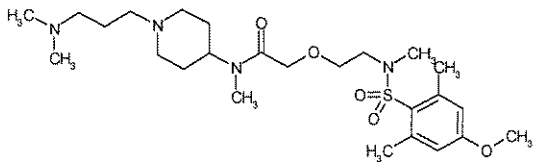
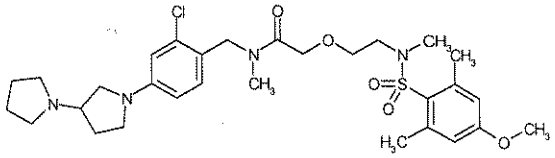
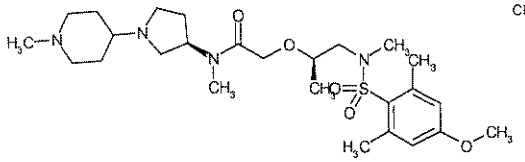
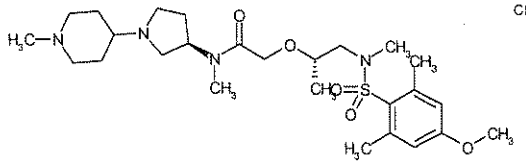
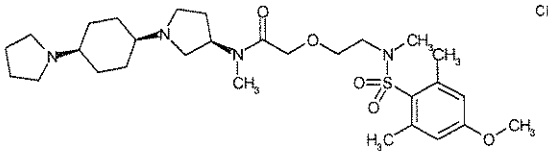
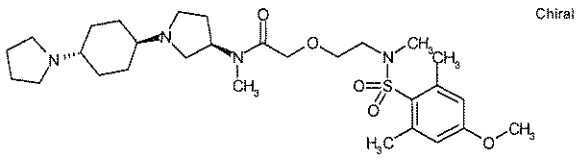
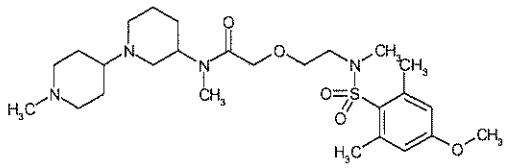
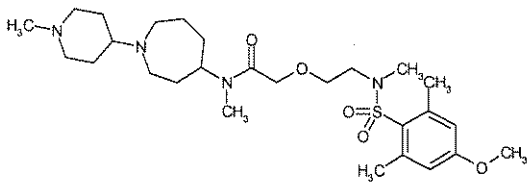
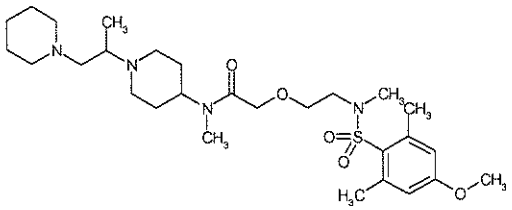
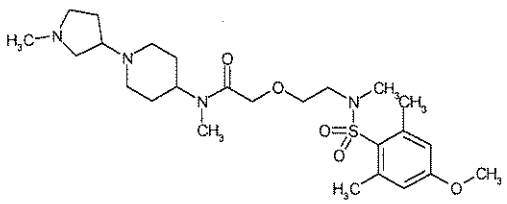
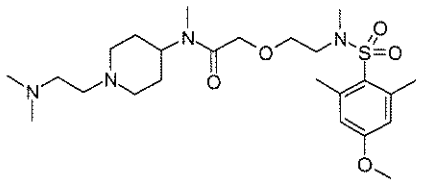
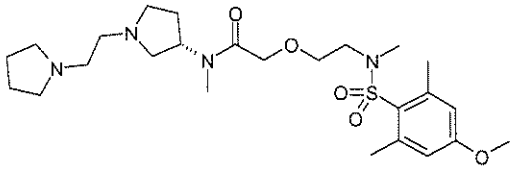
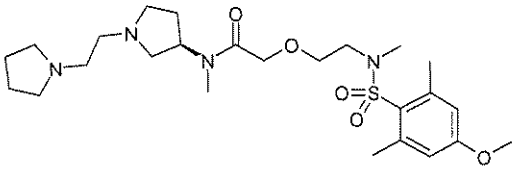
(342)	 Chiral
(343)	 Chiral
(344)	 Chiral
(345)	
(346)	
(347)	 Chiral
(348)	 Chiral
(349)	 Chiral

Example	Structure
(350)	 Chiral
(351)	
(352)	
(353)	
(354)	
(355)	
(356)	
(357)	

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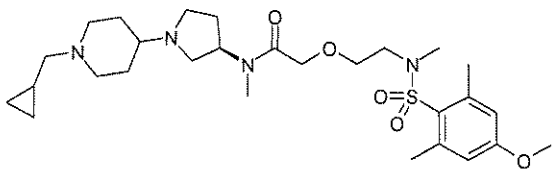
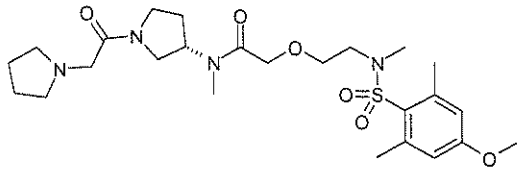
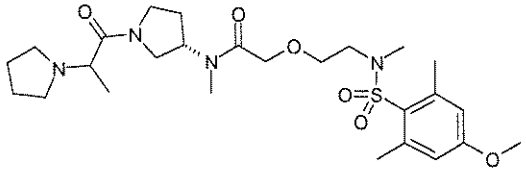
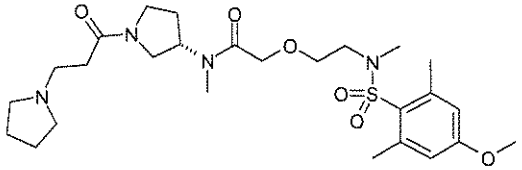
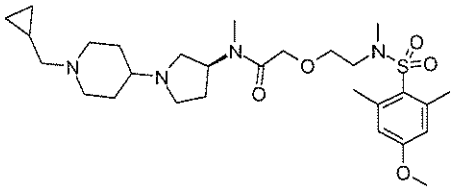
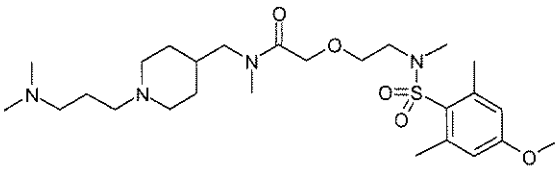
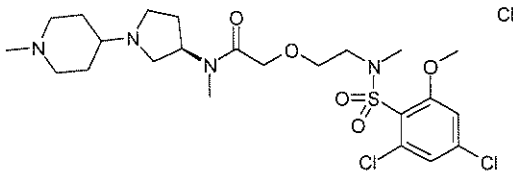
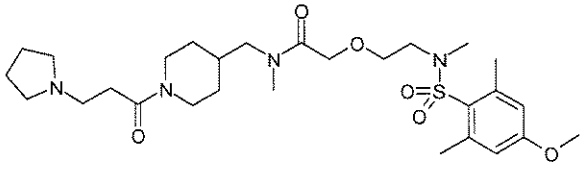
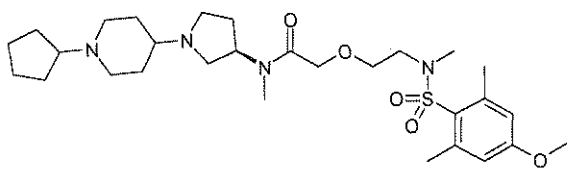
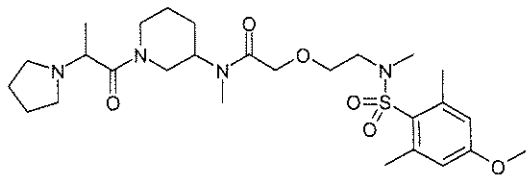
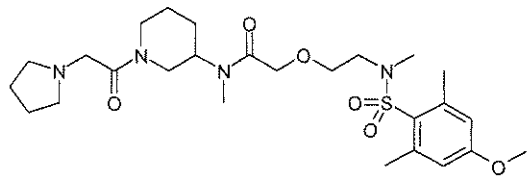
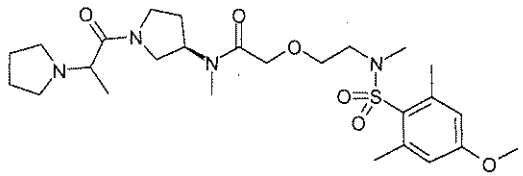
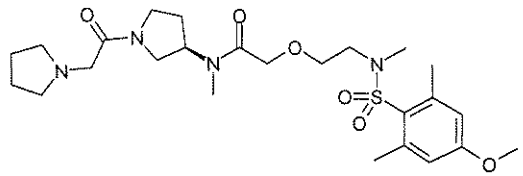
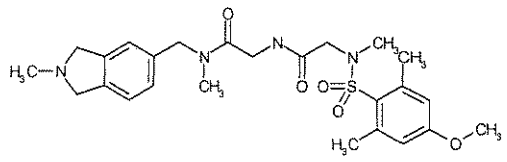
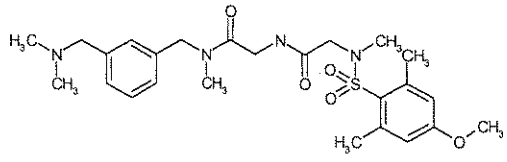
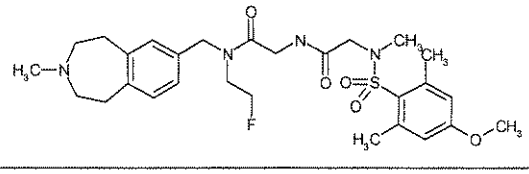
(358)	 Chiral
(359)	
(360)	
(361)	
(362)	
(363)	
(364)	 Chiral
(365)	

Example	Structure
(366)	 Chiral
(367)	
(368)	
(369)	 Chiral
(370)	 Chiral
(371)	
(372)	
(373)	

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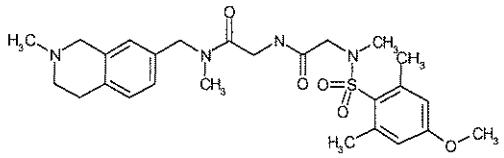
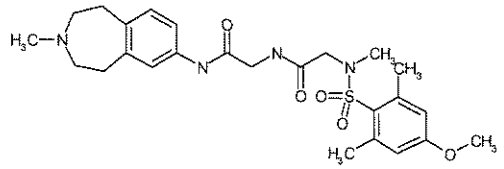
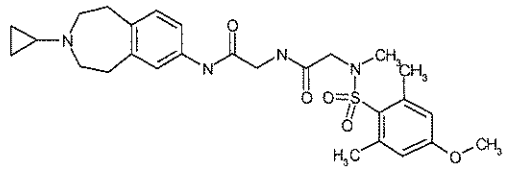
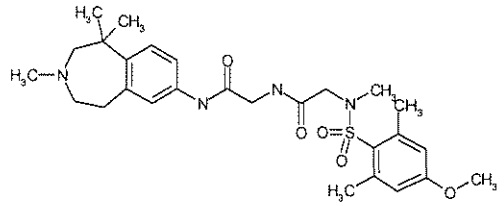
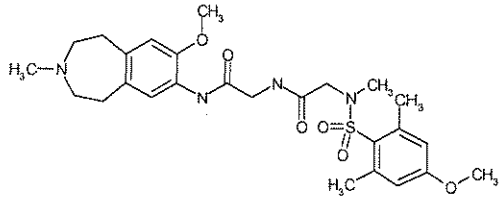
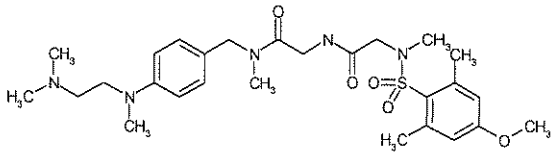
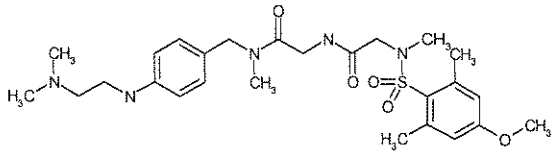
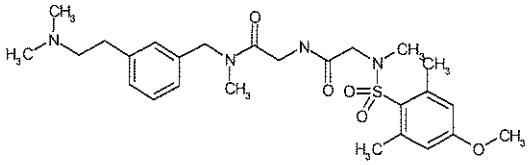
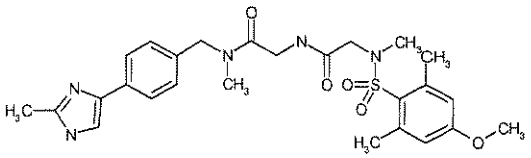
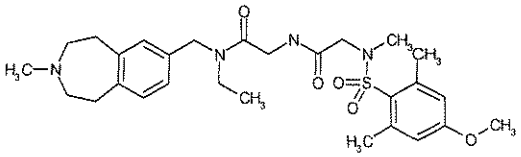
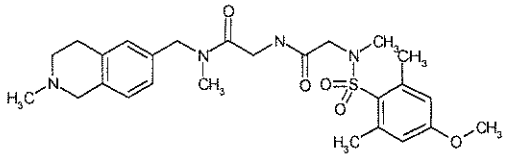
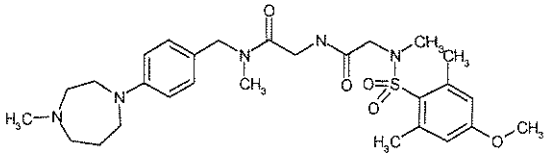
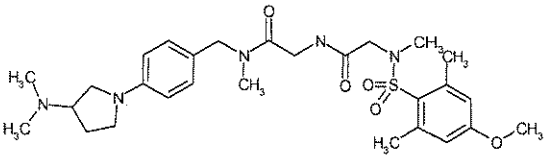
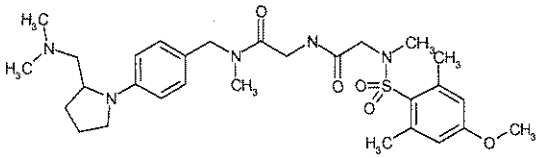
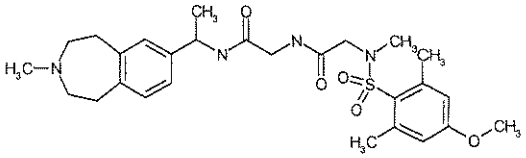
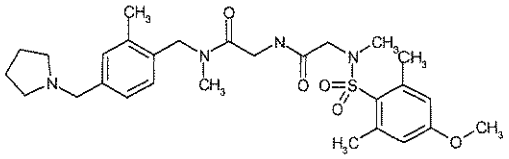
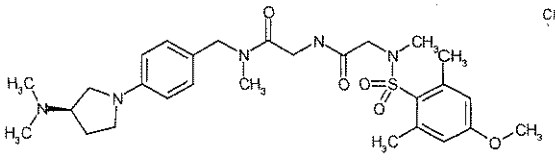
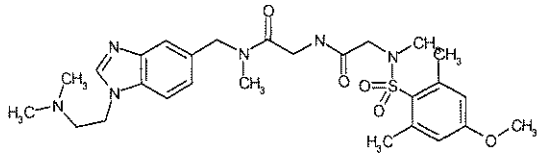
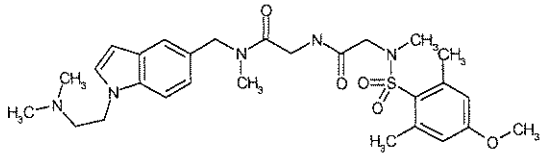
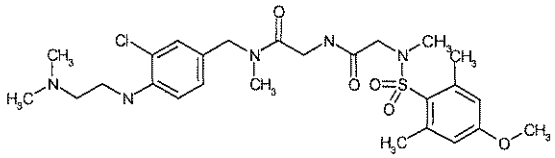
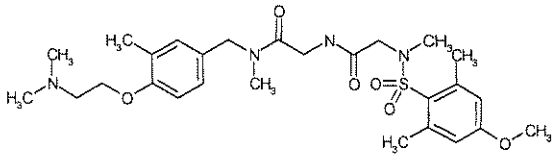
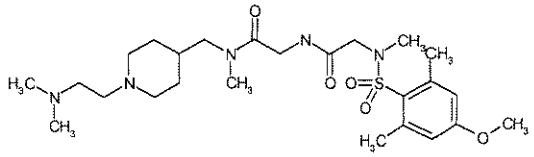
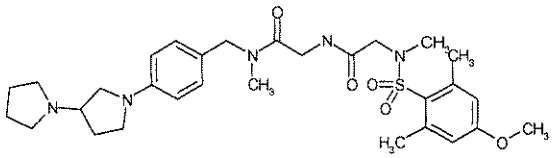
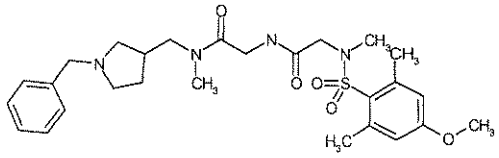
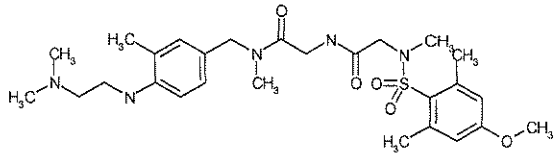
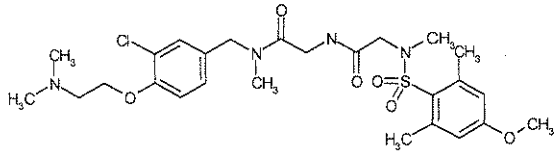
(374)	
(375)	
(376)	
(377)	
(378)	
(379)	
(380)	
(381)	

Example	Structure
(382)	
(383)	
(384)	
(385)	
(386)	
(387)	
(388)	
(389)	
(390)	Chiral 

Example	Structure
(391)	
(392)	
(393)	
(394)	
(395)	
(396)	
(397)	
(398)	
(399)	

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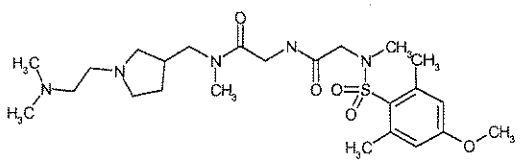
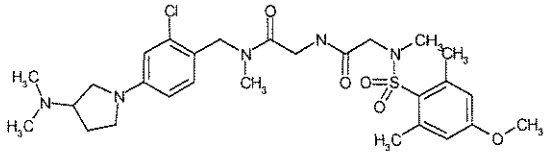
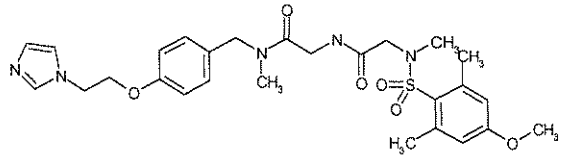
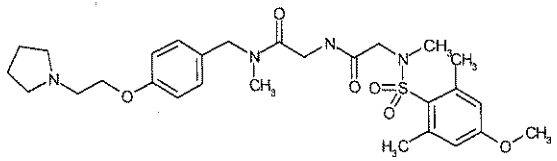
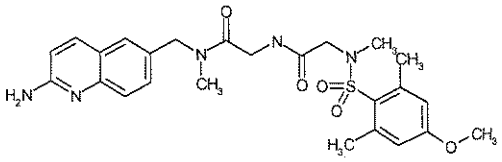
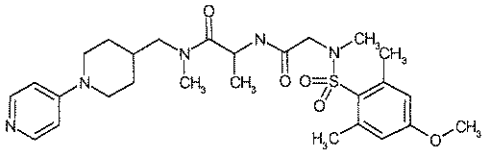
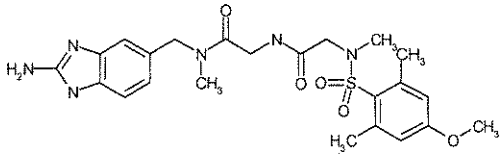
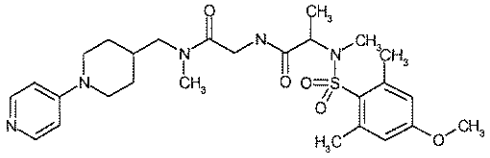
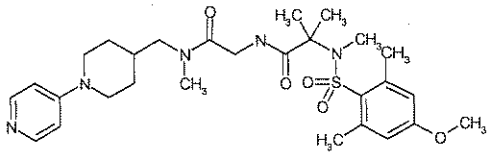
(400)	
(401)	
(402)	
(403)	
(404)	
(405)	
(406)	
(407)	
(408)	

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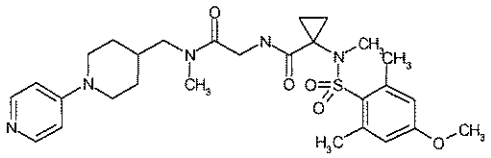
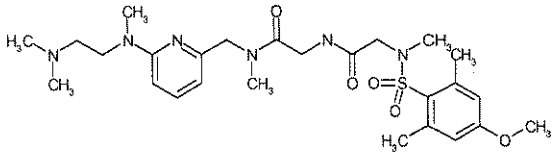
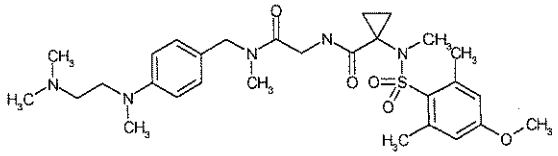
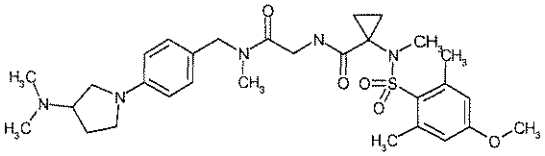
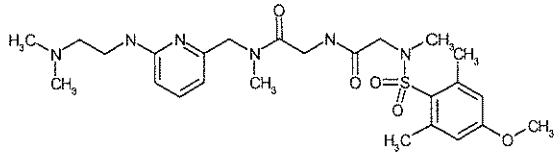
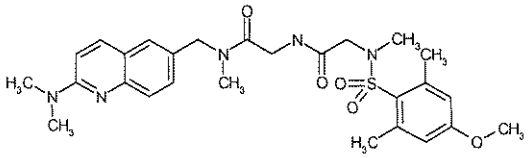
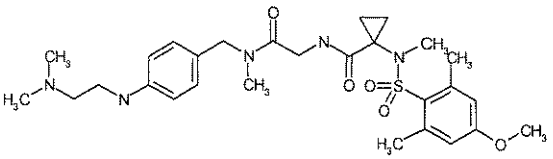
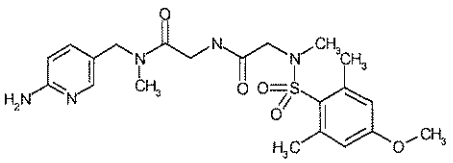
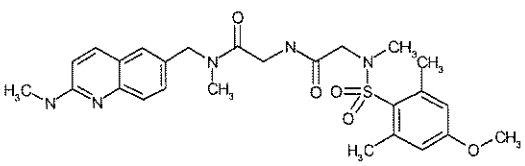
(409)	
(410)	
(411)	
(412)	
(413)	
(414)	
(415)	
(416)	
(417)	

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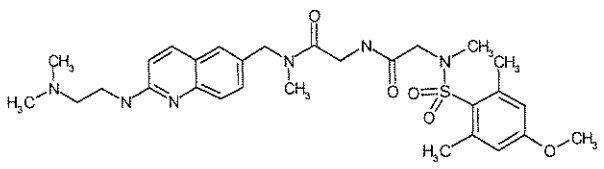
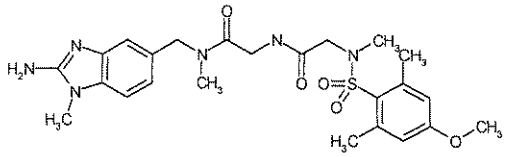
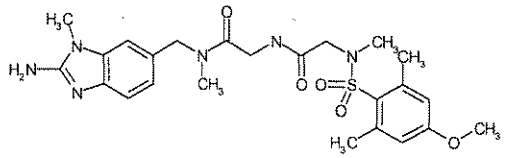
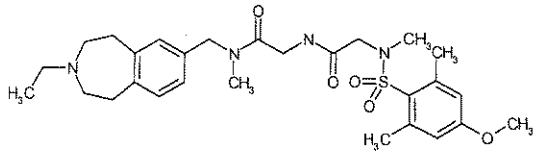
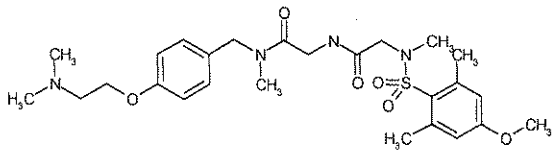
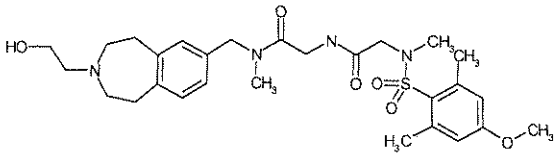
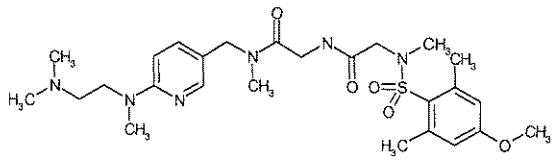
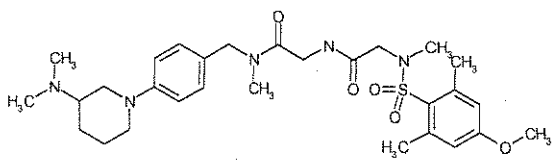
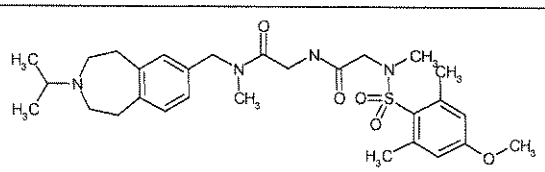
(418)	
(419)	
(420)	
(421)	
(422)	
(423)	
(424)	
(425)	
(426)	

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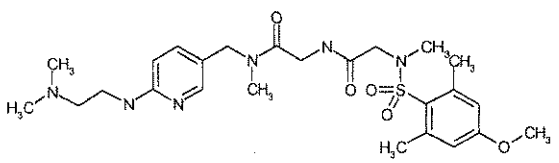
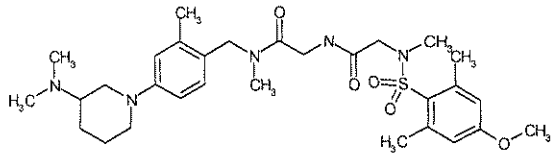
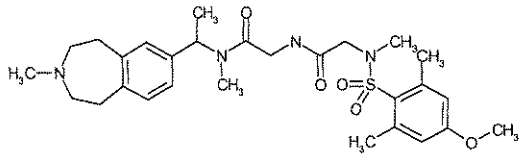
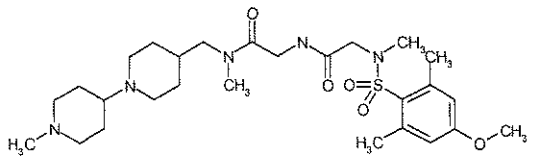
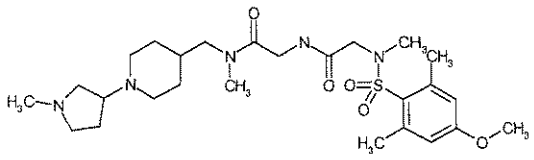
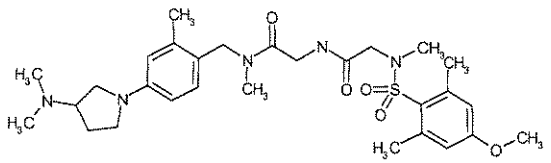
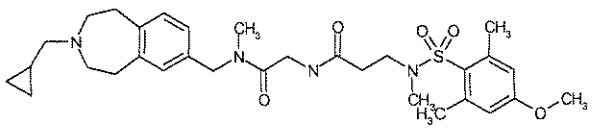
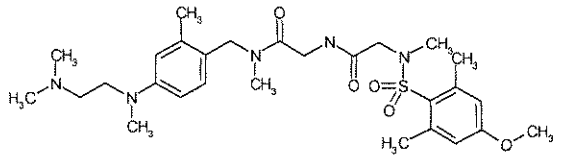
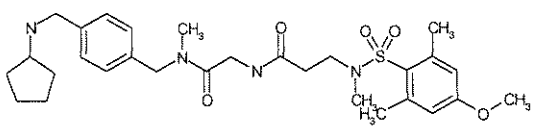
(427)	
(428)	
(429)	
(430)	
(431)	
(432)	
(433)	
(434)	
(435)	

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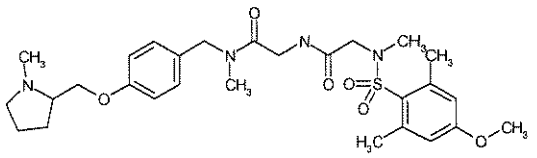
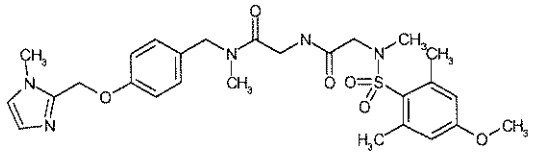
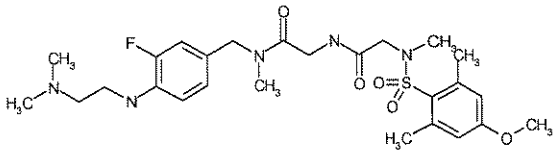
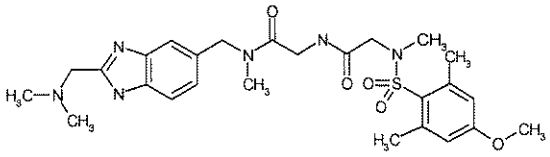
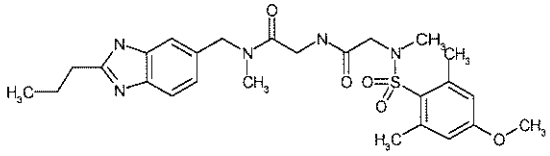
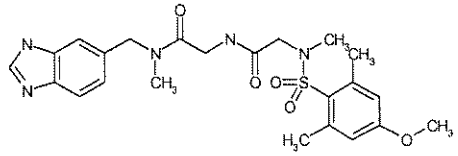
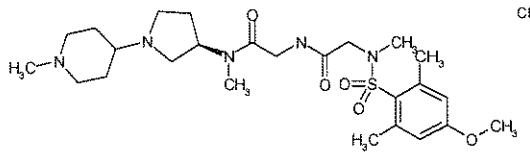
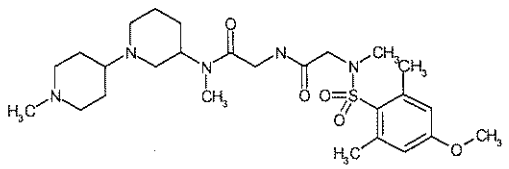
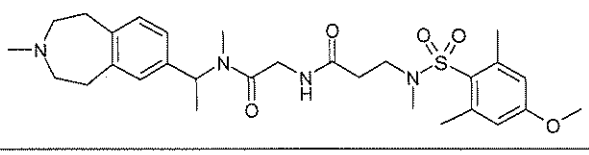
(436)	
(437)	
(438)	
(439)	
(440)	
(441)	
(442)	Chiral 
(443)	
(444)	

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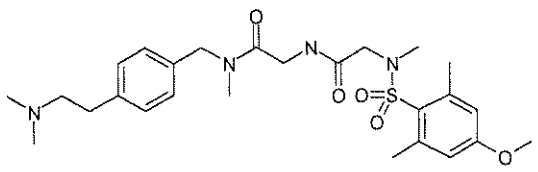
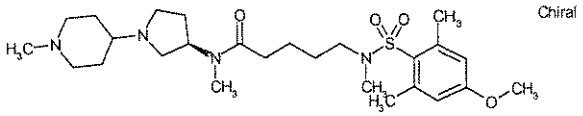
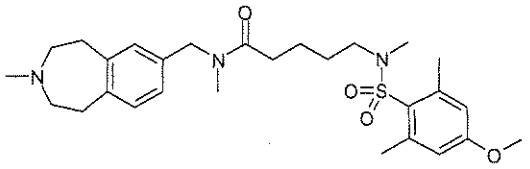
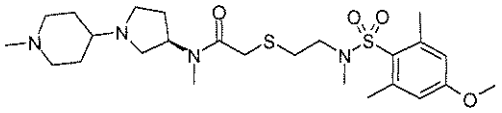
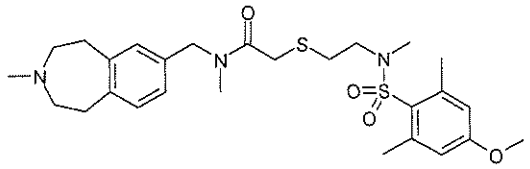
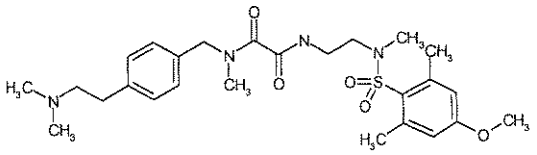
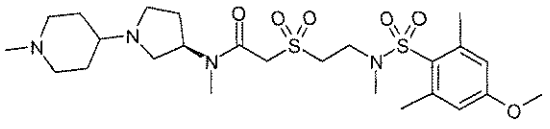
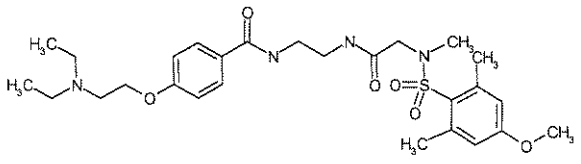
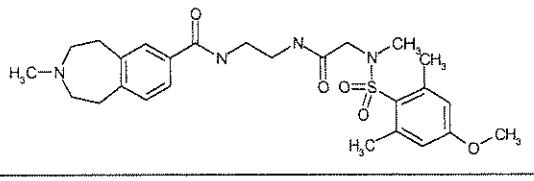
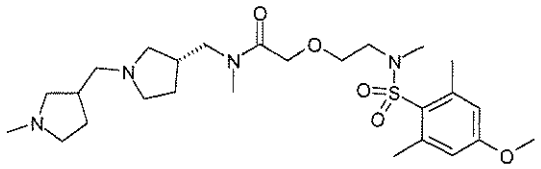
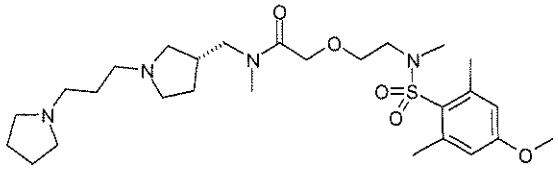
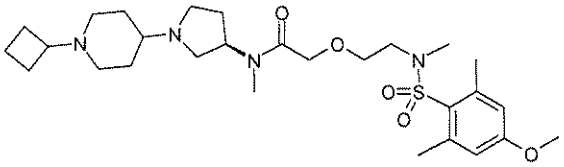
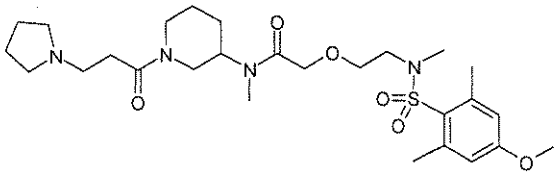
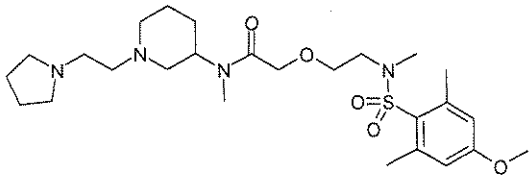
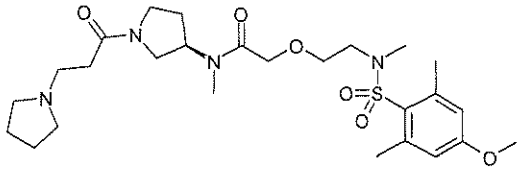
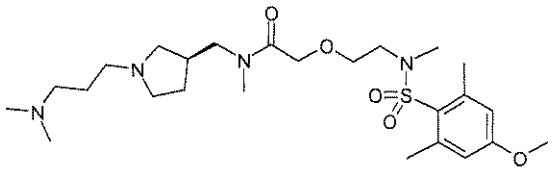
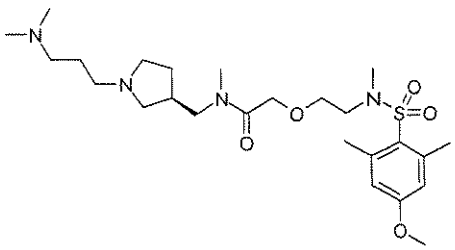
(445)	
(446)	 Chiral
(447)	
(448)	
(449)	
(450)	
(451)	
(452)	
(453)	

Example	Structure
(454)	
(455)	
(456)	
(457)	
(458)	
(459)	
(460)	
(461)	

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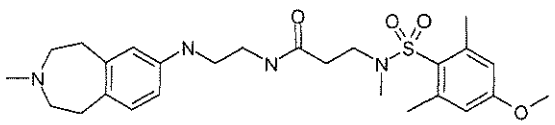
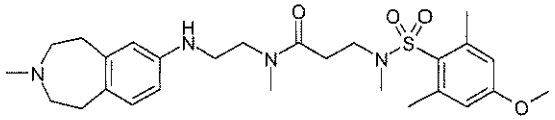
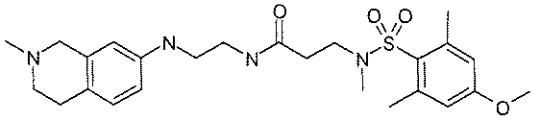
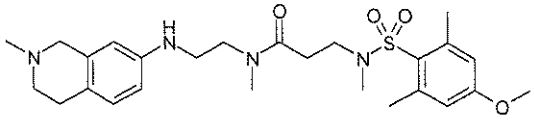
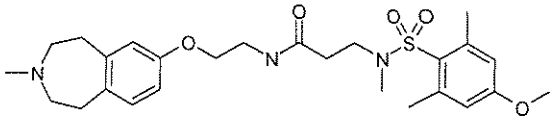
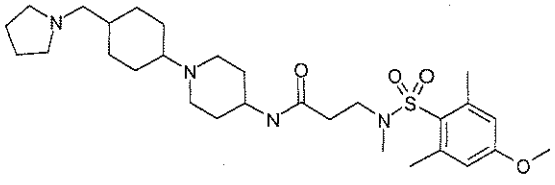
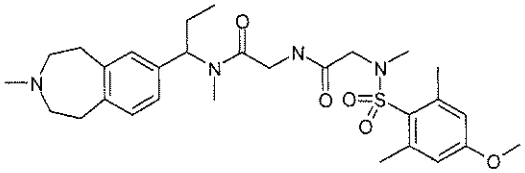
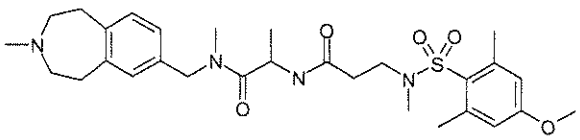
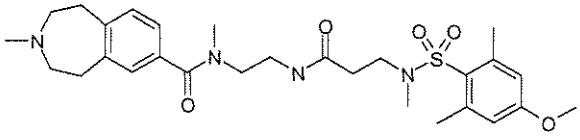
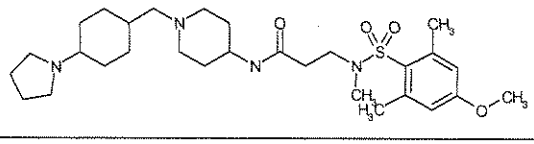
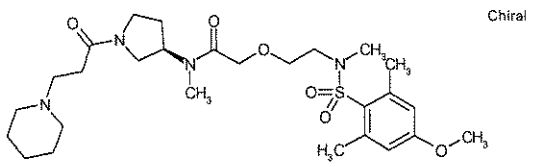
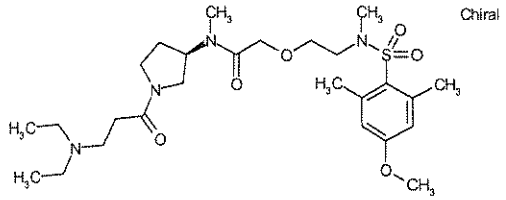
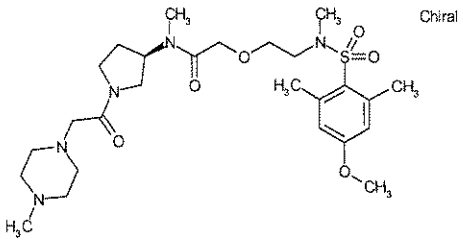
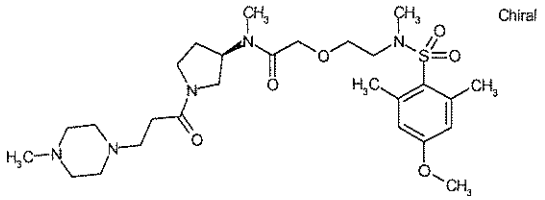
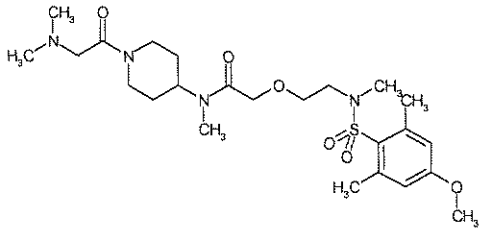
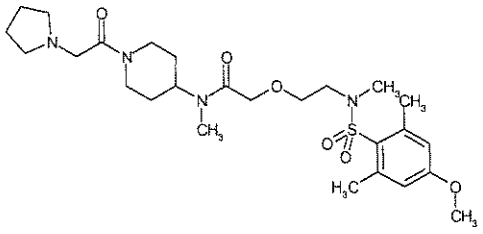
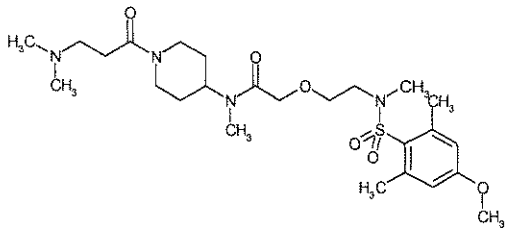
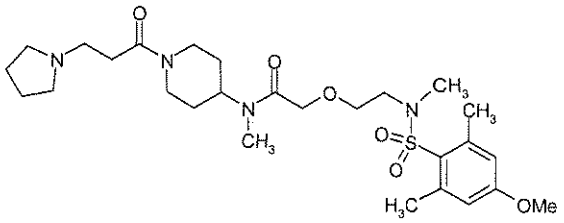
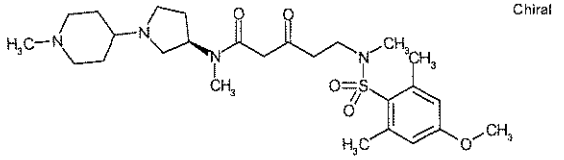
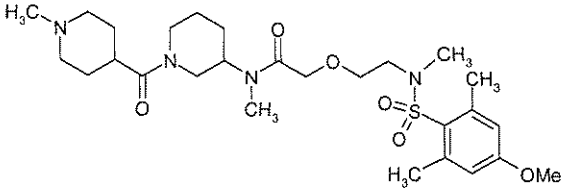
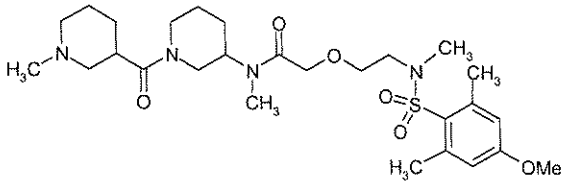
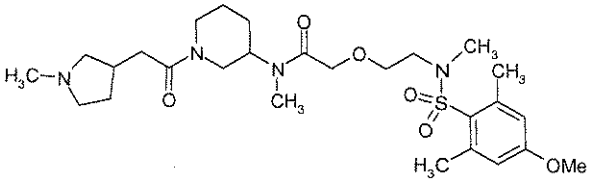
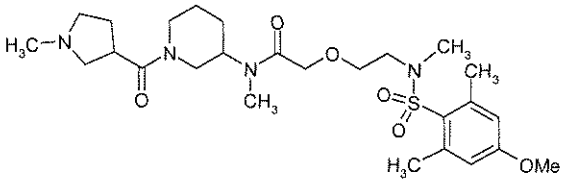
(462)	
(463)	
(464)	
(465)	
(466)	
(467)	
(468)	
(469)	
(470)	
(471)	

Example	Structure
(472)	 Chiral
(473)	 Chiral
(474)	 Chiral
(475)	 Chiral
(476)	
(477)	

Example	Structure
(478)	
(479)	
(480)	 Chiral
(481)	
(482)	
(483)	
(484)	

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

TERMS AND DEFINITIONS USED

Unless otherwise stated, all the substituents are independent of one another. If for example there are a plurality of C_{1-6}-alkyl groups as substituents in one group, in the case of three C_{1-6}-alkyl substituents, independently of one another, one may represent methyl, one *n*-propyl and one *tert*-butyl.

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

The subject-matter of this invention also includes the compounds according to the invention, including the salts thereof, wherein one or more hydrogen atoms, for example one, two, three, four or five hydrogen atoms, are replaced by deuterium.

By the term "C_{1-2}-alkyl" (including those which are part of other groups) are meant alkyl groups with 1 to 2 carbon atoms, by the term "C_{1-3}-alkyl" are meant branched and unbranched alkyl groups with 1 to 3 carbon atoms, by the term "C_{1-4}-alkyl" are meant branched and unbranched alkyl groups with 1 to 4 carbon atoms, by the term "C_{1-5}-alkyl" are meant branched and unbranched alkyl groups with 1 to 5 carbon atoms, by the term "C_{1-6}-alkyl" are meant branched and unbranched alkyl groups with 1 to 6 carbon atoms and by the term "C_{1-8}-alkyl" are meant branched and unbranched alkyl groups with 1 to 8 carbon atoms. Examples include: methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, *n*-pentyl, *iso*-pentyl, *neo*-pentyl, hexyl, heptyl and octyl. The following abbreviations may optionally also be used for the above-mentioned groups: Me, Et, *n*-Pr, *i*-Pr, *n*-Bu, *i*-

Bu, *t*-Bu, etc. Unless stated otherwise, the definitions propyl, butyl, pentyl, hexyl, heptyl and octyl include all the possible isomeric forms of the groups in question. Thus, for example, propyl includes *n*-propyl and *iso*-propyl, butyl includes *iso*-butyl, *sec*-butyl and *tert*-butyl etc..

Moreover, the terms mentioned above also include those groups wherein each methylene group may be substituted by up to two fluorine atoms and each methyl group may be substituted by up to three fluorine atoms.

By the term "C_{1-2}-alkylene" are meant branched and unbranched alkylene groups with 1 or 2 carbon atoms, by the term "C_{1-3}-alkylene" (including those which are part of other groups) are meant branched and unbranched alkylene groups with 1 to 3 carbon atoms, by the term "C_{1-4}-alkylene" are meant branched and unbranched alkylene groups with 1 to 4 carbon atoms, by the term "C_{1-6}-alkylene" are meant branched and unbranched alkylene groups with 1 to 6 carbon atoms and by the term "C_{2-4}-alkylene" are meant branched and unbranched alkylene groups with 2 to 4 carbon atoms. Examples include: methylene, ethylene, ethane-1,1-diyl, propylene, propane-2,2-diyl, 1-methylethylene, butylene, 1-methylpropylene, 1,1-dimethylethylene, 1,2-dimethylethylene. Unless stated otherwise, the definitions propylene and butylene include all the possible isomeric forms with the same number of carbons. Thus, for example, propyl also includes 1-methylethylene and butylene includes 1-methylpropylene, 1,1-dimethylethylene, 1,2-dimethylethylene.

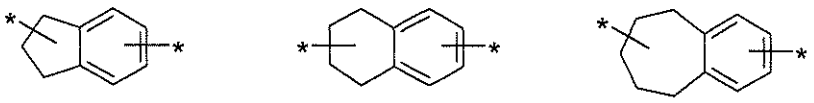
In addition, the terms mentioned above also include those groups wherein each methylene group may be substituted by up to two fluorine atoms.

By the term "C_{3-5}-cycloalkyl" are meant cyclic alkyl groups with 3 to 5 carbon atoms, by the term "C_{3-6}-cycloalkyl" are meant cyclic alkyl groups with 3 to 6 carbon atoms and by the term "C_{3-7}-cycloalkyl" (including those which are part of other groups) are meant cyclic alkyl groups with 3 to 7 carbon atoms. Examples include: cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl. Unless otherwise stated, the cyclic alkyl groups may be substituted by one or more groups

selected from among methyl, ethyl, *iso*-propyl, *tert*-butyl, hydroxy, fluorine, chlorine, bromine and iodine.

By the term "C_{3-6}-cycloalkylene" (including those which are part of other groups) are meant cyclic alkylene groups with 3 to 6 carbon atoms, by the term "C_{3-7}-cycloalkylene" are meant cyclic alkylene groups with 3 to 7 carbon atoms and by the term "C_{4-6}-cycloalkylene" are meant cyclic alkylene groups with 4 to 6 carbon atoms. Examples include: cyclopropylene, cyclobutylene, cyclopentylene, cyclohexylene or cycloheptylene. Unless otherwise stated, the cyclic alkylene groups may be substituted by one or more groups selected from among methyl, ethyl, *iso*-propyl, *tert*-butyl, hydroxy, fluorine, chlorine, bromine and iodine.
A C_4- or a C_5-cycloalkylene group may be linked to the remainder of the molecule in the 1,2 position or in the 1,3 position, preferably in the 1,3 position. A C_6- or a C_7-cycloalkylene group may be linked to the remainder of the molecule in the 1,2 position, in the 1,3 position or in the 1,4 position, preferably in the 1,3 position.

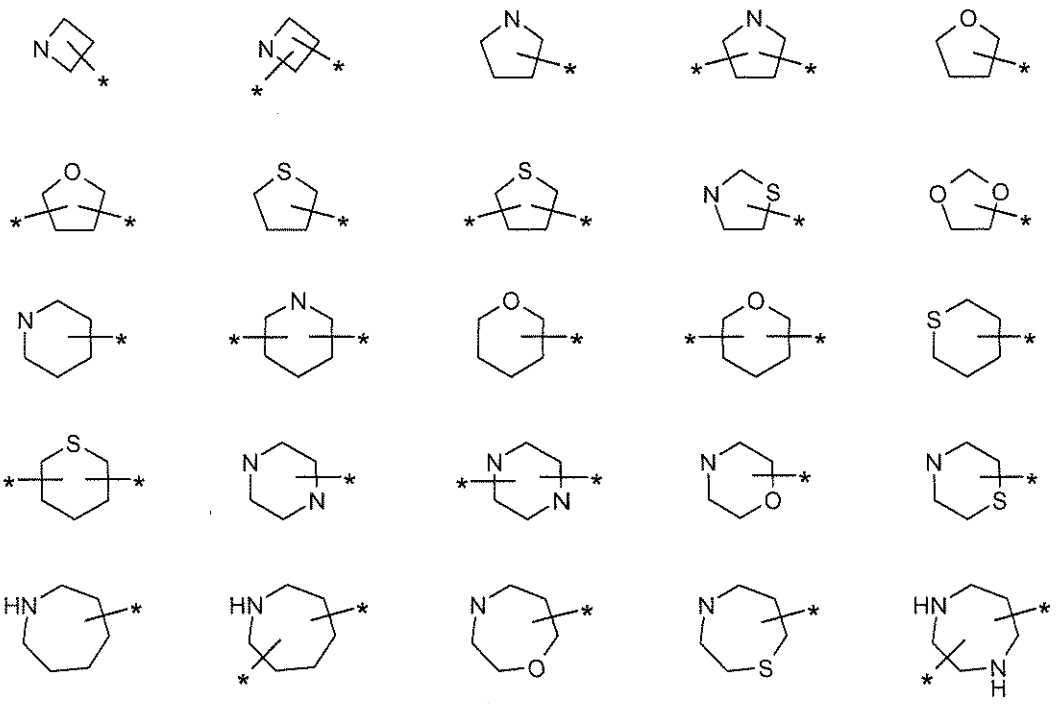
By the term "C_{5-7}-cycloalkenylene" (including those which are part of other groups) are meant cyclic alkenyl groups with 5 to 7 carbon atoms, which contain an unsaturated bond and which are fused to a phenyl ring via this unsaturated bond. Examples include: cyclopentenyl, cyclohexenyl or cycloheptenyl:



Unless otherwise stated, the cyclic alkenyl groups may be substituted by one or more groups selected from among methyl, ethyl, *iso*-propyl, *tert*-butyl, hydroxy, fluorine, chlorine, bromine and iodine.

By the term " saturated heterocyclic rings" are meant four, five, six or seven membered heterocyclic rings which may contain one, two or three heteroatoms

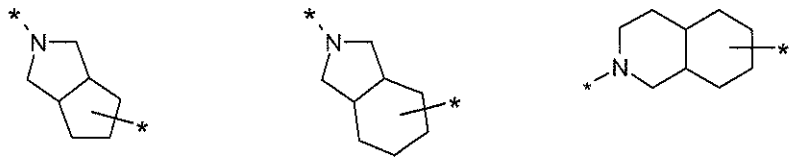
selected from among oxygen, sulphur and nitrogen. The ring may be attached to the molecule through a carbon atom and/or - if present - through a nitrogen atom or also through two carbon atoms or through two nitrogen atoms. Although it is encompassed by the term "heterocyclic rings", the term "heterocyclic non-aromatic rings" denotes five, six or seven membered saturated rings. Examples include:



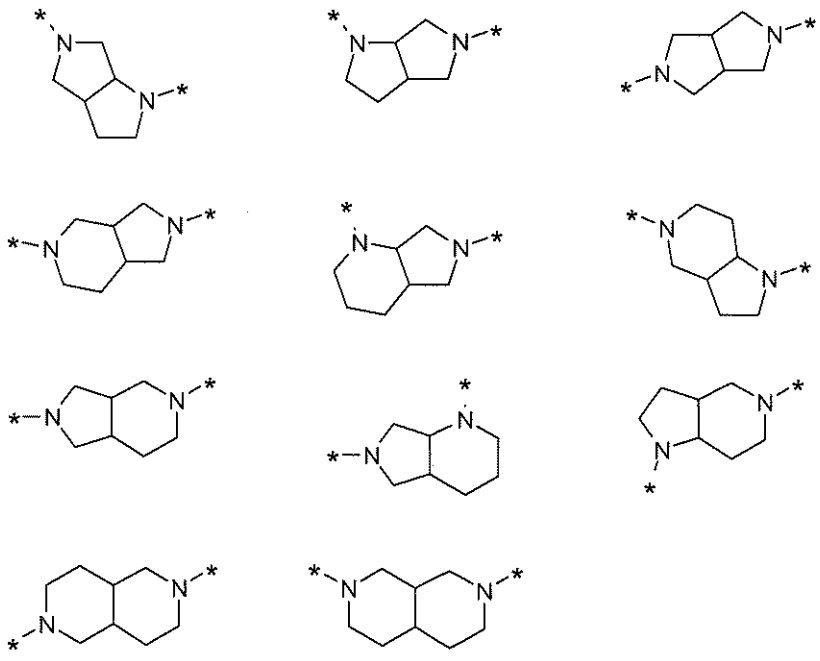
By the term "saturated diaza-heterocycles" are meant six or seven membered heterocyclic rings which contain two nitrogen atoms. The ring is linked to the remainder of the molecule through both nitrogen atoms. Examples include:

By the term "saturated aza-heterobicycles" are meant eight, nine or ten membered heterobicyclic rings which contain a nitrogen atom. The ring is linked to the

remainder of the molecule through a carbon atom and the nitrogen atom. Examples include:

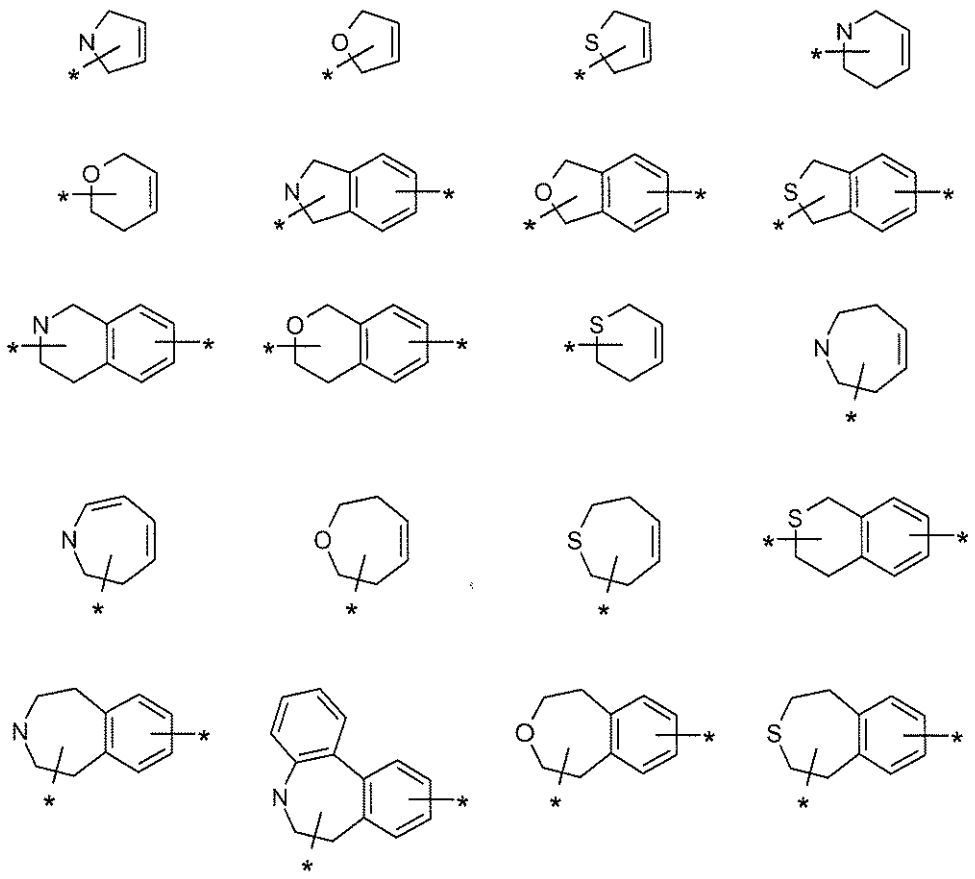


By the term "saturated diaza-heterobicycles" are meant eight, nine or ten membered heterobicyclic rings which contain two nitrogen atoms. The ring is linked to the remainder of the molecule through both nitrogen atoms. Examples include:

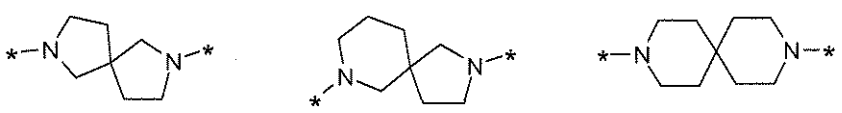


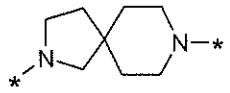
By the term "unsaturated heterocyclic rings" are meant five-, six- or seven-membered, mono- or diunsaturated heterocyclic rings which may contain one, two or three heteroatoms, selected from among oxygen, sulphur and nitrogen and condensed through the unsaturated bonds with one or two phenyl rings. The

heterocyclic ring may be linked to the molecule through a carbon atom and/or - if present - through a nitrogen atom or through two carbon atoms or through two nitrogen atoms. Examples include:



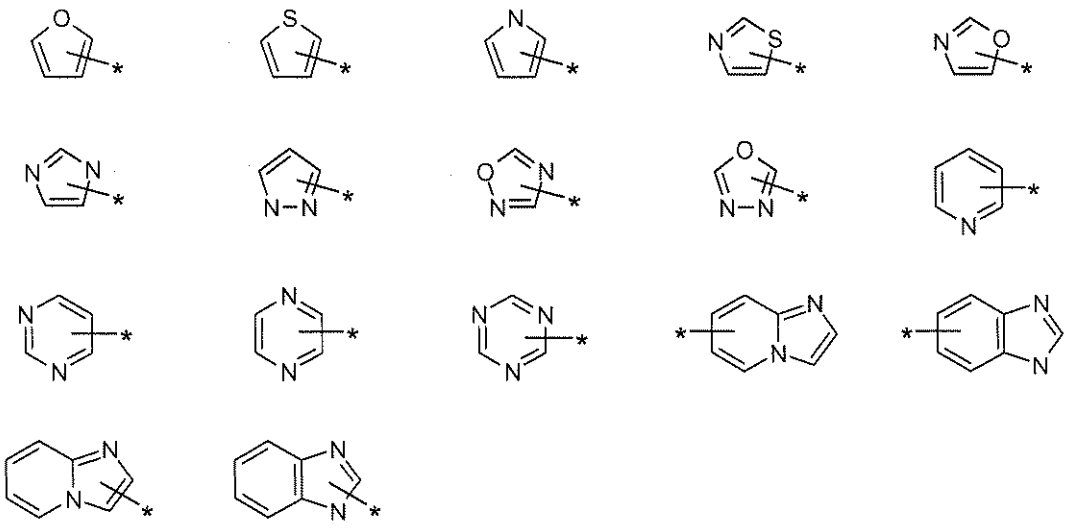
By the term "saturated diaza-spirocycles" are meant nine-, ten- or eleven-membered spirocyclic rings which contain two nitrogen atoms. The spirocyclic group is linked to the remainder of the molecule through the two nitrogen atoms. Examples include:





By the term "aryl" (including those which are part of other groups) are meant aromatic ring systems with 6 or 10 carbon atoms. Examples of these are phenyl, 1-naphthyl or 2-naphthyl; preferred aryl groups are phenyl and 1-naphthyl; the particularly preferred aryl group is phenyl. Unless otherwise stated, the aromatic groups may be substituted by one or more groups selected from among methyl, ethyl, *n*-propyl, *iso*-propyl, *tert*-butyl, hydroxy, methoxy, trifluoromethoxy, fluorine, chlorine, bromine and iodine, while the groups may be identical or different.

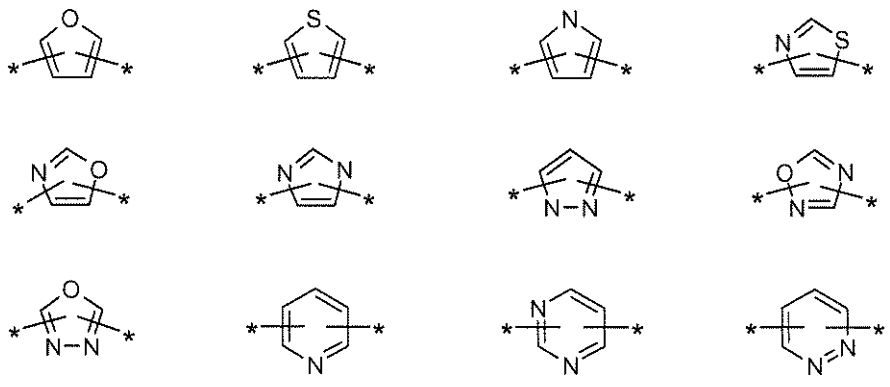
By the term "heteroaryl" are meant five- or six-membered heterocyclic aromatic groups or 9-11 membered bicyclic heteroaryl rings, which may contain one, two or three heteroatoms, selected from among oxygen, sulphur and nitrogen, and additionally contain sufficient conjugated double bonds to form an aromatic system. Examples of five- or six-membered heterocyclic aromatic groups are as follows:

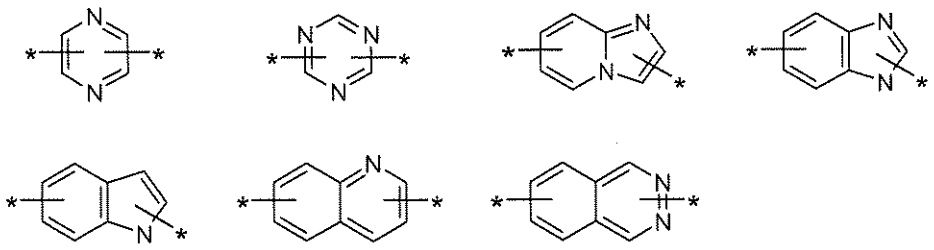


Unless otherwise stated, the heteroaryls mentioned previously may be substituted by one or more groups selected from among methyl, ethyl, *n*-propyl, *iso*-propyl, *tert*-butyl, hydroxy, methoxy, trifluoromethoxy, fluorine, chlorine, bromine and iodine, while the groups may be identical or different. Bicyclic heteroaryl rings may preferably be substituted in the phenyl group.

By the term "arylene" (including those which are part of other groups) are meant aromatic ring systems with 6 or 10 carbon atoms. Examples include: phenylene, 1-naphthylene or 2-naphthylene, the preferred arylene group being phenylene. Unless otherwise stated, the aromatic groups may be substituted by one or more groups selected from among methyl, ethyl, *n*-propyl, *iso*-propyl, *tert*-butyl, hydroxy, methoxy, trifluoromethoxy, fluorine, chlorine, bromine and iodine.
These aromatic ring systems are linked to the rest of the molecule at two places independently of one another through a carbon atom in each case.

By the term "heteroarylene" are meant five- or six-membered heterocyclic aromatic groups or 9-11 membered bicyclic heteroaryl rings which may contain one, two or three heteroatoms selected from among oxygen, sulphur and nitrogen, and additionally sufficient conjugated double bonds to form an aromatic system. These heterocyclic aromatic groups are linked at two points independently of one another either through carbon and/or nitrogen.
The following are examples of five- or six-membered heterocyclic aromatic groups:





Unless otherwise stated, the heteroaromatic groups may be substituted by one or more groups selected from among methyl, ethyl, *n*-propyl, *iso*-propyl, *tert*-butyl, hydroxy, methoxy, trifluoromethoxy, fluorine, chlorine, bromine and iodine. Preferably, the substituents in the above-mentioned 5-10 membered bicyclic heteroaryl rings are in the phenyl ring.

If they contain suitable basic functions, for example amino groups, compounds of general formula **I** may be converted, particularly for pharmaceutical use, into the physiologically acceptable salts thereof with inorganic or organic acids. Examples of inorganic acids for this purpose include hydrobromic acid, phosphoric acid, nitric acid, hydrochloric acid, sulphuric acid, methanesulphonic acid, ethanesulphonic acid, benzenesulphonic acid or *p*-toluenesulphonic acid, while organic acids that may be used include malic acid, succinic acid, acetic acid, fumaric acid, maleic acid, mandelic acid, lactic acid, tartaric acid or citric acid. In addition, any tertiary amino groups present in the molecule may be quaternised. Alkyl halides are used for the reaction. According to the invention methyl iodide is preferably used for the quaternisation.

In addition, the compounds of general formula **I**, if they contain suitable carboxylic acid functions, may if desired be converted into the addition salts thereof with inorganic or organic bases. Examples of inorganic bases include alkali or alkaline earth metal hydroxides, e.g. sodium hydroxide or potassium hydroxide, or carbonates, ammonia, zinc or ammonium hydroxides; examples of organic amines include diethylamine, triethylamine, ethanolamine, diethanolamine, triethanolamine, cyclohexylamine or dicyclohexylamine.

The compounds according to the invention may be present as racemates, provided that they have only one chiral element, but may also be obtained as pure enantiomers, i.e. in the (*R*) or (*S*) form.

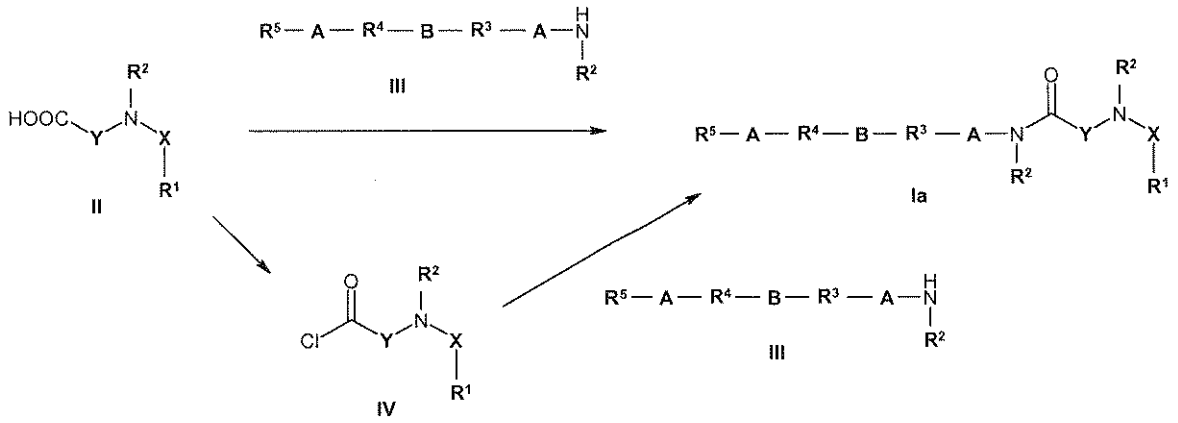
However, the application also includes the individual diastereomeric pairs of antipodes or mixtures thereof, which are obtained if there is more than one chiral element in the compounds of general formula **I**, as well as the individual optically active enantiomers of which the above-mentioned racemates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

METHODS OF PREPARATION

According to the invention the compounds of general formula I are obtained by methods known *per se*, for example by the following methods:

Scheme 1



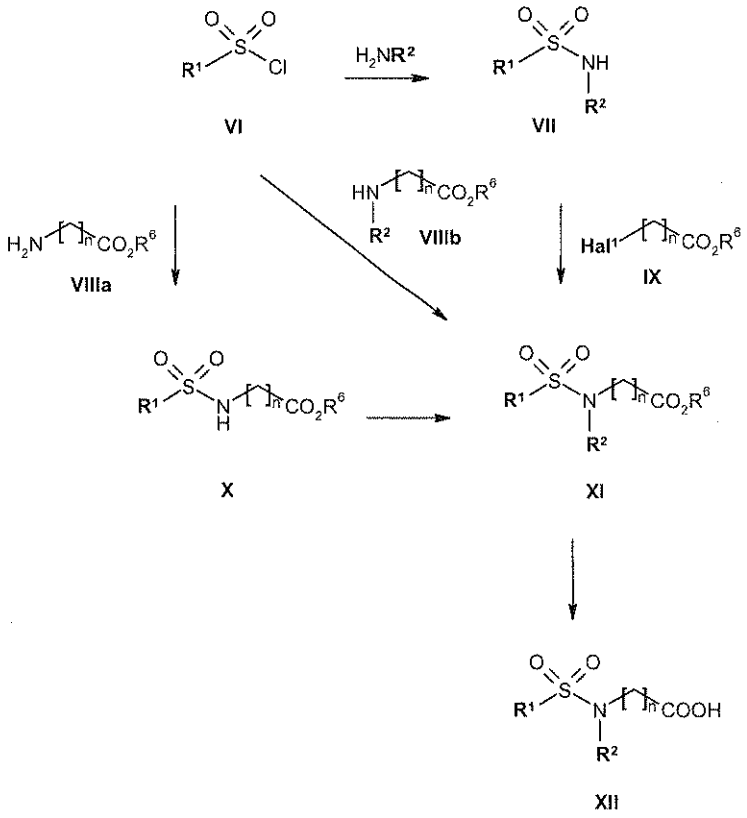
The linking of carboxylic acids of general formula **III** shown in Scheme 1 wherein all the groups are as hereinbefore defined, with amines of general formula **IV**, wherein all the groups are as hereinbefore defined, forming carboxylic acid amides of general formula **Ia**, wherein all the groups are as hereinbefore defined, may be carried out using conventional methods of amide formation.

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.

An alternative method of attachment consists in converting a carboxylic acid of general formula **III**, wherein all the groups are as hereinbefore defined, into a carboxylic acid chloride of general formula **V**, wherein all the groups are as hereinbefore defined, and subsequent reaction with an amine of general formula **IV**, wherein all the groups are as hereinbefore defined. The synthesis of a carboxylic acid chloride of general formula **V** is carried out using methods known from the literature (see e.g. Houben-Weyl, Methoden der Organischen Chemie, vol. E5/1).

The carboxylic acids of general formula **III** used as starting materials, wherein all the groups are as hereinbefore defined, is obtained using methods known per se from the literature, for example by the methods of synthesis shown in Schemes 2 to 7.

Scheme 2

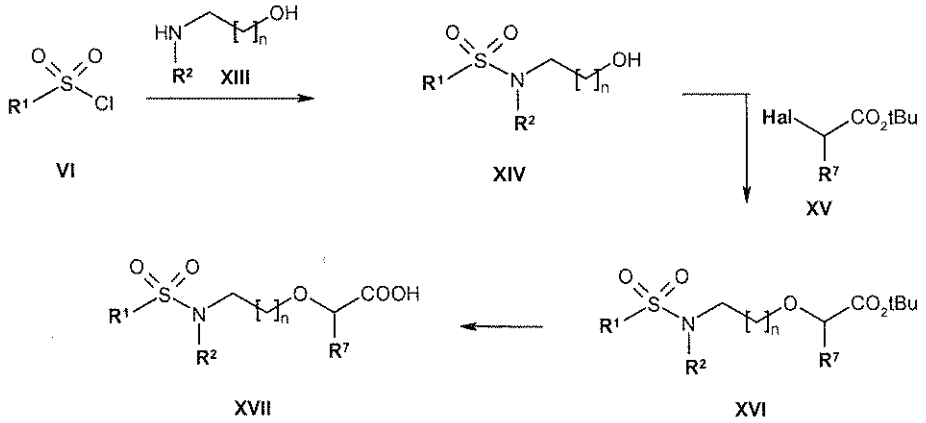


The sulphonic acid chlorides of general formula **VI**, wherein R^1 is as hereinbefore defined, are either known from the literature or commercially obtainable. They are reacted under standard reaction conditions with an amine of general formulae H_2N-R^2, **VIIIa** or **VIIIb** to obtain sulphonic acid amides of general formulae **VII**, **X** or **XI**, wherein R^1 and R^2 are hereinbefore defined and **n** denotes a number 1, 2, 3 or 4 and R^6 denotes a C_{1-6}-alkyl group. The reaction is optionally carried out in the presence of a base such as triethylamine, DIPEA or pyridine and an inert solvent such as dichloromethane or tetrahydrofuran at a temperature of 0°C to 100°C with a typical reaction time of one to 24 hours.

The reaction of the sulphonic acid amides of general formula **VII** with a halide of general formula **IX**, wherein **Hal**^{1} denotes chlorine or bromine, is carried out using methods known from the literature, for example with the aid of a base such as potassium or sodium carbonate in dimethylformamide or tetrahydrofuran at 0°C to 100°C.

The hydrolysis of the carboxylic acid esters of general formula **XI**, wherein R^1 and R^2 are as hereinbefore defined, **n** denotes a number 1, 2, 3 or 4 and R^6 denotes a C_{1-3}-alkyl group, to obtain carboxylic acids of general formula **XII**, wherein R^1 and R^2 are as hereinbefore defined and **n** denotes a number 1, 2, 3 or 4 and R^6 denotes a C_{1-3}-alkyl group, is carried out under known conditions, for example with lithium or sodium carbonate and water in methanol and/or tetrahydrofuran.

Scheme 3



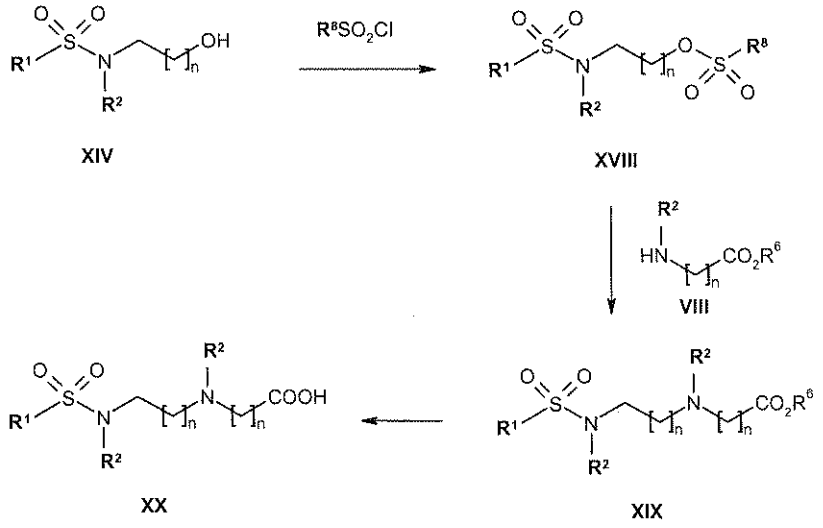
The preparation of sulphonic acid amides of general formula **XIV** is carried out as described under Scheme 2.

The alkylation of the hydroxyl function of the sulphonic acid amides of general formula **XIV**, wherein R^1 and R^2 are as hereinbefore defined with the proviso that R^2 does not denote a hydrogen atom, and **n** denotes a number 1, 2, 3 or 4 and R^6 denotes a C_{1-3}-alkyl group, is carried out under reaction conditions known from the literature, for example under 2-phase conditions using a phase transfer catalyst in the presence of a strong inorganic base such as sodium hydroxide solution or

potassium hydroxide solution and in an inert solvent such as toluene at 0°C to 100°C.

The cleaving of the tert-butylester of general formula **XVI**, wherein $\mathbf{R^1}$ and $\mathbf{R^2}$ are as hereinbefore defined, **n** denotes a number 1, 2, 3 or 4 and $\mathbf{R^6}$ denotes a C_{1-3}-alkyl group and $\mathbf{R^7}$ denotes a hydrogen atom or a C_{1-3}-alkyl group, is carried out using methods known from the literature (see e.g. Philip J. Kocieński, Protecting Groups, 3rd Edition, 2005, published by Georg Thieme).

Scheme 4

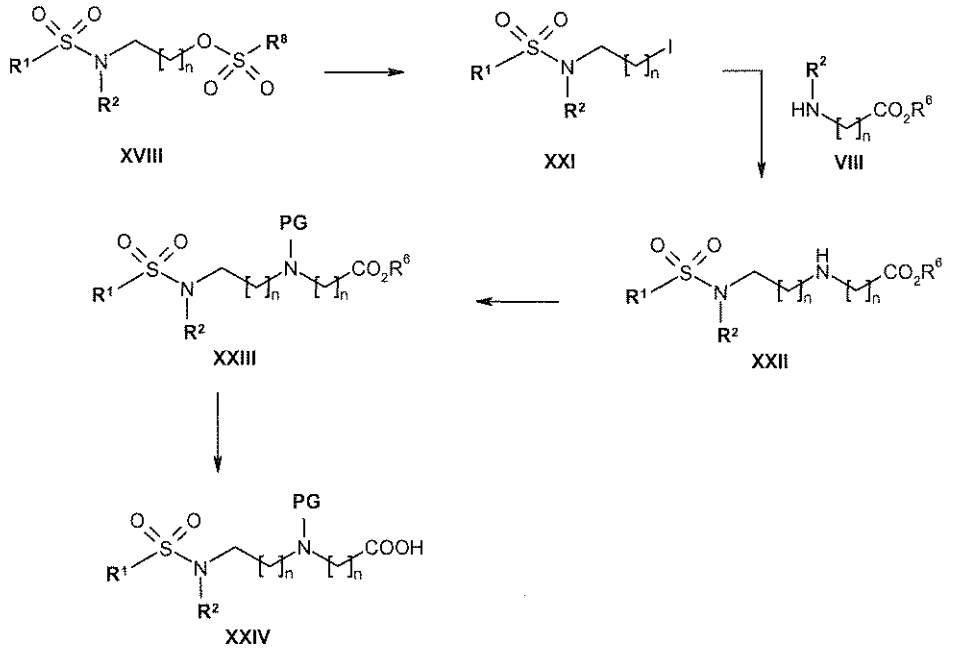


The sulphonation of the hydroxyl function of a compound of general formula **XIV**, wherein $\mathbf{R^1}$ and $\mathbf{R^2}$ are as hereinbefore defined, with the proviso that $\mathbf{R^2}$ does not denote a hydrogen atom, and **n** denotes a number 1, 2, 3 or 4 and $\mathbf{R^6}$ denotes a C_{1-3}-alkyl group, with a sulphonic acid chloride of general formula $\mathbf{R^8SO_2Cl}$, wherein $\mathbf{R^8}$ denotes a C_{1-3}-alkyl group or a phenyl group optionally substituted by a C_{1-3}-alkyl group, to form compounds of general formula **XVIII**, wherein all the groups are as hereinbefore defined, is carried out under standard reaction conditions, typically in the presence of a base such as DMAP and/or pyridine and an inert solvent such as dichloromethane or THF at -5°C to 35°C. A liquid base such as pyridine may be used as the base and solvent simultaneously.

The subsequent alkylation of the amines of general formula **VII** to form compounds of general formula **XIX**, wherein R^1 and R^2 are as hereinbefore defined, **n** denotes a number 1, 2, 3 or 4 and R^6 denotes a C_{1-3}-alkyl group and R^6 denotes a C_{1-6}-alkyl group, is conveniently carried out in a solvent such as toluene, chlorobenzene, dimethylformamide, dimethylsulphoxide (DMSO), dichloromethane, acetonitrile or pyridine, for example at temperatures between 0°C and 150°C and conveniently in the presence of bases such as pyridine, triethylamine, DIPEA, potassium carbonate, potassium-tert-butoxide or sodium methoxide, the alkylsulphonate serving as the leaving group.

The hydrolysis of the carboxylic acid esters of general formula **XIX** to form carboxylic acids of general formula **XX** is carried out as described under Scheme 2.

Scheme 5



The Finkelstein reaction of compounds of general formula **XVIII**, wherein R^1 and R^2 are as hereinbefore defined, **n** denotes a number 1, 2, 3 or 4 and R^6 denotes a C_{1-3}-alkyl group and R^8 denotes a C_{1-3}-alkyl group or a phenyl group optionally substituted by a C_{1-3}-alkyl group, to form halides of general formula **XXI**, wherein

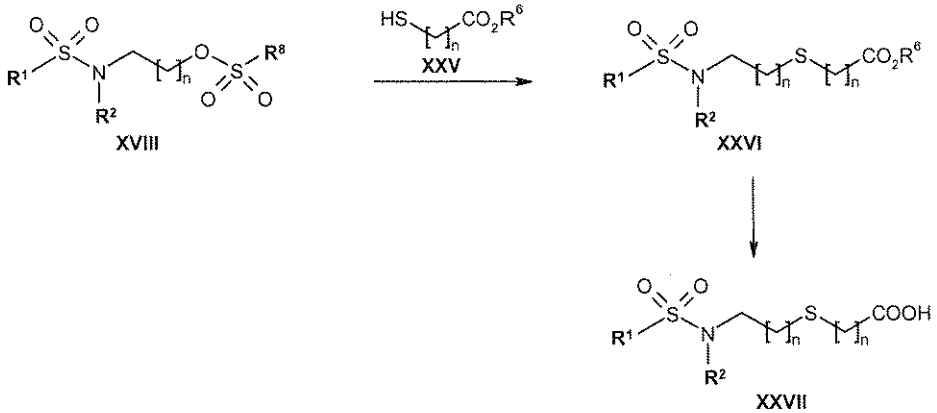
R^1 and R^2 are as hereinbefore defined and **n** denotes a number 1, 2, 3 or 4 and R^6 denotes a C_{1-3}-alkyl group, is carried out under known reaction conditions (see e.g. H. Finkelstein, Berichte der Deutschen Chemischen Gesellschaft **43**, 1910, 1528).

The subsequent alkylation of the glycine ester is carried out as described under Scheme 4 ($R^2 \neq H$).

The amino function in the compounds of general formula **XXIII** is protected by a conventional protective group **PG** by known methods. The selected protective group is one which can be cleaved under non-hydrogenolytic conditions. A preferred protective group is the Boc group. An overview of the chemistry of protective groups can be found in Theodora W. Greene and Peter G. M. Wuts, Protective Groups in Organic Synthesis, Second Edition, 1991, published by John Wiley and Sons, and in Philip J. Kocieński, Protecting Groups, 3rd Edition, 2005, published by Georg Thieme.

The cleaving of the carboxylic acid esters of general formula **XXIII** to form carboxylic acids of general formula **XXIV** is carried out as described under Scheme 2.

Scheme 6

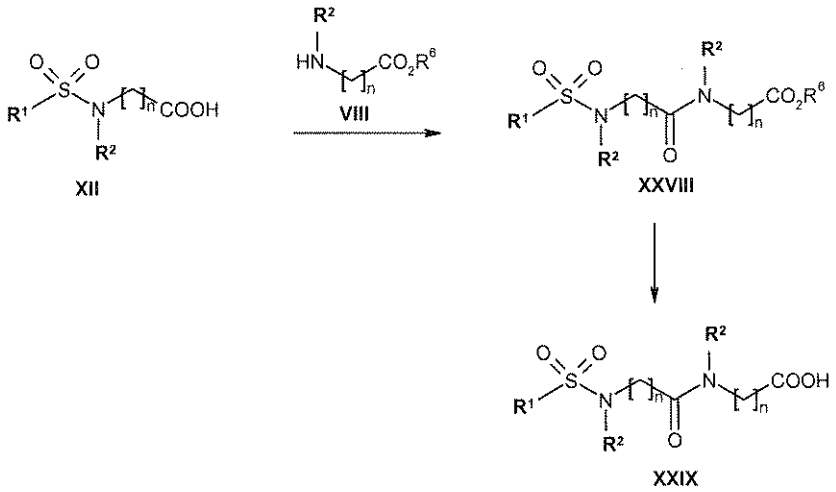


The alkylation of a thiol of general formula **XXV**, wherein **n** denotes a number 1, 2, 3 or 4 and R^6 denotes a C_{1-6}-alkyl group, to obtain compounds of general formula

XXVI, wherein R^1 and R^2 are as hereinbefore defined, **n** denotes a number 1, 2, 3 or 4 and R^6 denotes a C_{1-6}-alkyl group, is conveniently carried out in a solvent such as toluene, chlorobenzene, DMF, DMSO, dichloromethane, acetonitrile or pyridine, for example at temperatures between 0°C and 150°C and conveniently in the presence of bases such as pyridine, triethylamine, DIPEA, potassium carbonate, potassium-tert-butoxide or sodium methoxide, while the alkylsulphonate serves as leaving group.

The hydrolysis of the carboxylic acid esters of general formula **XXVI** to form carboxylic acids of general formula **XXVII**, wherein all the groups are as hereinbefore defined, is carried out as described under Scheme 2.

Scheme 7

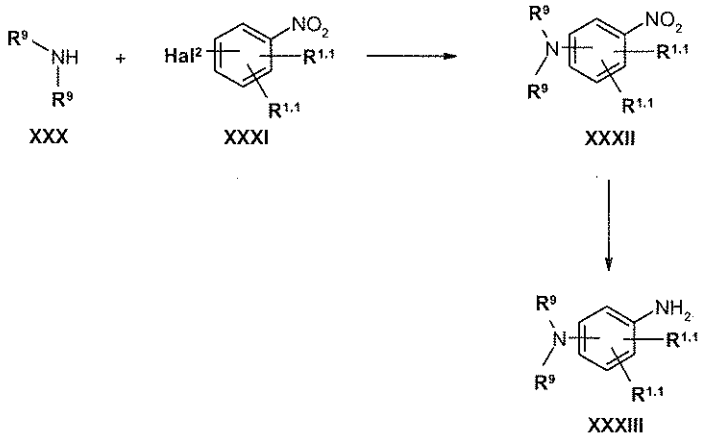


The amide linking of carboxylic acids of general formula **XII**, wherein R^1 and R^2 are as hereinbefore defined and **n** denotes a number 1, 2, 3 or 4, and amino acids of general formula **VIII**, wherein R^1 and R^2 are as hereinbefore defined, **n** denotes a number 1, 2, 3 or 4 and R^6 denotes a C_{1-6}-alkyl group, to obtain carboxylic acid amides of general formula **XXVIII**, wherein R^1 and R^2 are as hereinbefore defined, **n** denotes a number 1, 2, 3 or 4 and R^6 denotes a C_{1-6}-alkyl group, is carried out as described under Scheme 1.

As mentioned under Scheme 2, the carboxylic acid ester of general formula **XXVIII** is cleaved to form carboxylic acid of general formula **XXIX**, wherein R^1 and R^2 are as hereinbefore defined and **n** denotes a number 1, 2, 3 or 4.

The amines of general formula **IV** used as starting materials are either commercially obtainable, or are obtained using methods known per se from the literature, for example by the methods of synthesis represented in Schemes 8 to 12, wherein $R^{1.1}$ is as hereinbefore defined, Hal^1 denotes a chlorine or bromine atom and Hal^2 denotes a fluorine, chlorine or bromine atom or a group R^9.

Scheme 8

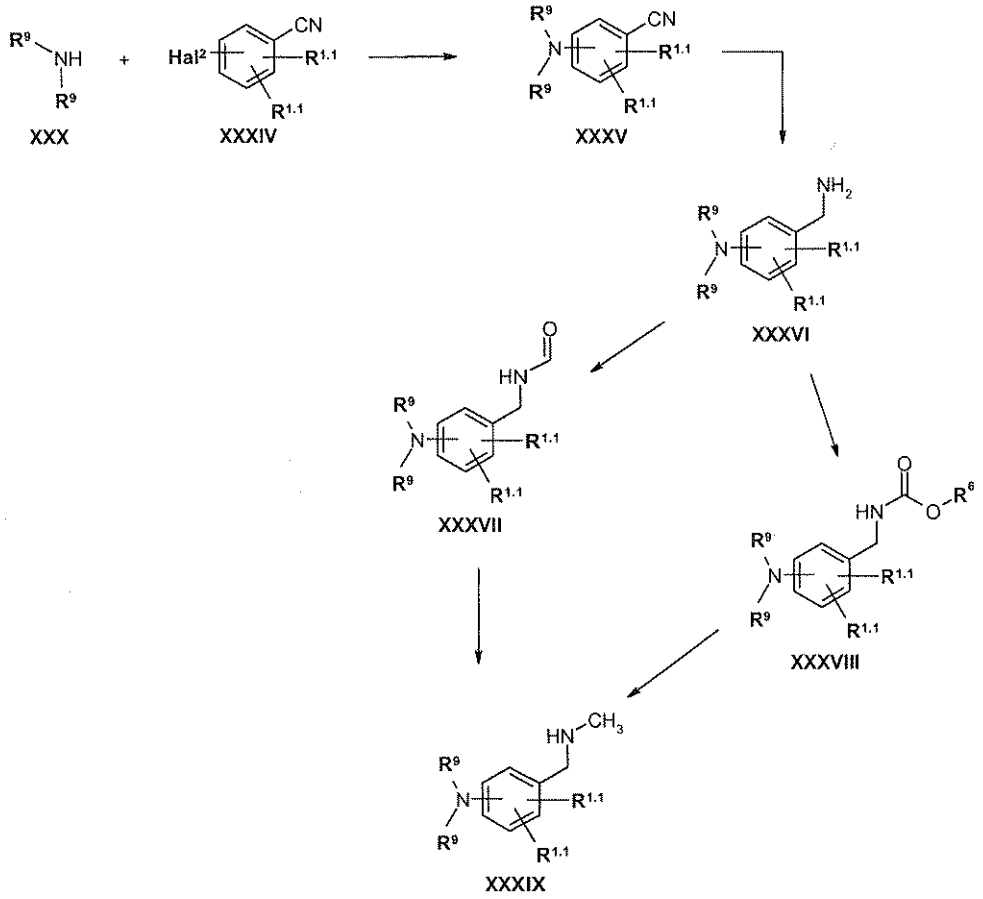


The reaction of an amine of general formula **XXX**, wherein R^9 denotes a C_{1-3}-alkyl group, with a halo-nitrobenzene of general formula **XXXI**, wherein $R^{1.1}$ is as hereinbefore defined and Hal^2 denotes a fluorine, chlorine or bromine atom or a group R^9, is carried out using known methods, for example in a solvent such as tetrahydrofuran, dimethylformamide or dimethylsulphoxide and conveniently in the presence of a suitable base such as triethylamine or potassium carbonate, at a temperature of 20°C to 160°C. If the amine of general formula **XXX** is liquid, the reaction may also be carried out without a solvent and additional base.

The reduction of the nitro group to form anilines of general formula **XXXIII**, wherein $R^{1.1}$ is as hereinbefore defined and R^9 denotes a C_{1-3}-alkyl group, is carried out under standard reaction conditions (see e.g. Richard C. Larock, Comprehensive

Organic Transformations, 1989, VCH), preferably under standard conditions of catalytic hydrogenolysis with a catalyst such as palladium on charcoal or Raney nickel in a solvent such as methanol or ethanol.

Scheme 9



The reaction of compounds of general formulae **XXX**, wherein R^9 denotes a C_{1-3}-alkyl group, with a compound of general formula **XXXIV**, wherein $R^{1.1}$ is as hereinbefore defined and **Hal**^{2} denotes a fluorine, chlorine or bromine atom or a group R^9, to obtain compounds of general formula **XXXV**, wherein $R^{1.1}$ is as hereinbefore defined and R^9 denotes a C_{1-3}-alkyl group, is carried out as described under Scheme 8.

The reduction of a nitrile of general formula **XXXV** to form an amine of general formula **XXXVI**, wherein $R^{1.1}$ is as hereinbefore defined and R^9 denotes a C_{1-3}-alkyl

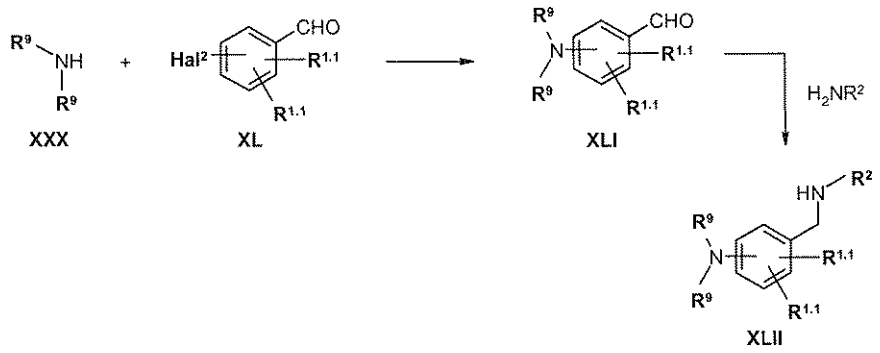
group, may be carried out under standard conditions of catalytic hydrogenolysis with a catalyst such as for example Raney nickel in a solvent such as ammoniacal methanol or ethanol or with a reducing agent such as lithium aluminium hydride or sodium borohydride in a solvent such as tetrahydrofuran, optionally in the presence of aluminium chloride.

The formylation of an amine of general formula **XXXVI** to obtain a compound of general formula **XXXVII**, wherein $\mathbf{R^{1.1}}$ is as hereinbefore defined and $\mathbf{R^9}$ denotes a C_{1-3}-alkyl group, is conveniently carried out in a solvent such as dichloromethane, for example at temperatures from 40°C to 70°C and in the presence of acetic anhydride and formic acid.

The carbamate formation to obtain compounds of general formula **XXXVIII**, wherein $\mathbf{R^{1.1}}$ is as hereinbefore defined, $\mathbf{R^6}$ denotes a C_{1-6}-alkyl and $\mathbf{R^9}$ denotes a C_{1-3}-alkyl group is carried out by known methods, for example with a chloroformic acid ester or Boc-anhydride in the presence of a base such as triethylamine or sodium hydroxide solution and a solvent such as THF or dioxane.

The reduction of the formyl or of the carbamate to obtain compounds of general formula **XXXIX**, wherein $\mathbf{R^{1.1}}$ is as hereinbefore defined and $\mathbf{R^9}$ denotes a C_{1-3}-alkyl group, is carried out under standard reaction conditions, preferably with a reducing agent such as lithium aluminium hydride and in a solvent such as tetrahydrofuran at a temperature of 50°C to 100°C.

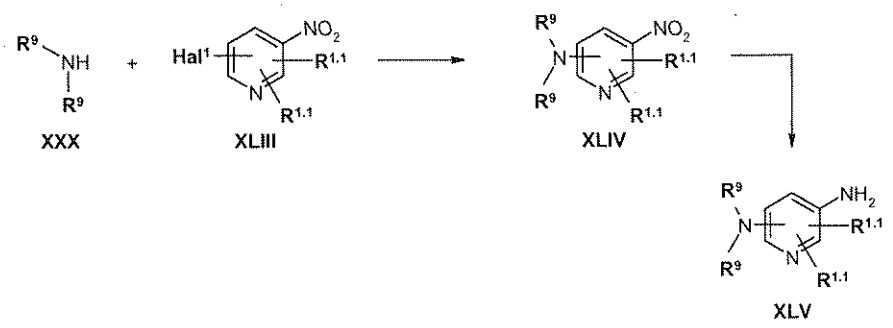
Scheme 10



The halogen-nitrogen exchange in compounds of general formulae **XXX**, wherein R^9 denotes a C_{1-3}-alkyl group, and **XL**, wherein $R^{1.1}$ is as hereinbefore defined and Hal^2 denotes a fluorine, chlorine or bromine atom or a group R^9, for preparing compounds of general formula **XLI**, wherein $R^{1.1}$ is as hereinbefore defined and R^9 denotes a C_{1-3}-alkyl group, is carried out as described under Scheme 8.

The reaction of benzaldehydes of general formula **XLI**, wherein $R^{1.1}$ is as hereinbefore defined and R^9 denotes a C_{1-3}-alkyl group, with an amine of general formula H_2NR^2, wherein R^2 is as hereinbefore defined, to obtain a compound of general formula **XLII**, wherein $R^{1.1}$ and R^2 are as hereinbefore defined and R^9 denotes a C_{1-3}-alkyl group, is a reductive amination. It is carried out by known methods, for example with a reducing agent such as sodium triacetoxyborohydride, sodium borohydride or sodium cyanoborohydride, conveniently in a solvent such as tetrahydrofuran or dichloromethane, optionally with the addition of acetic acid.

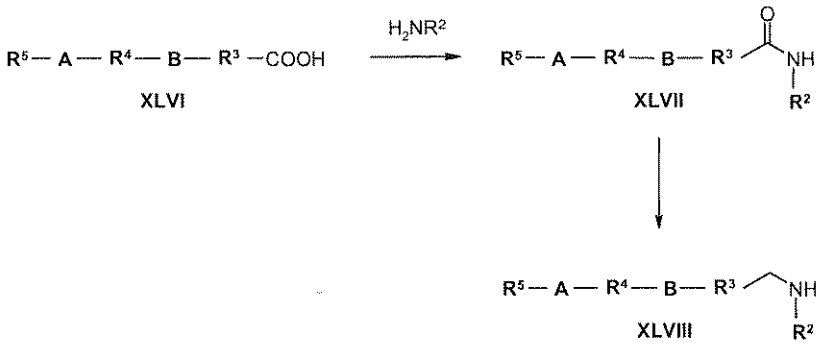
Scheme 11



The reaction of an amine of general formula **XXX**, wherein R^9 denotes a C_{1-3}-alkyl group, with a halogen-nitropyridine of general formula **XLIII**, wherein $R^{1.1}$ is as hereinbefore defined and Hal^1 denotes a chlorine or bromine atom, is carried out by known methods, for example in a solvent such as tetrahydrofuran, dichloromethane, methanol or DMSO and conveniently in the presence of a suitable base such as triethylamine, sodium hydroxide solution or potassium carbonate and at a temperature of 20°C to 100°C.

The subsequent reduction of the nitro group of a compound of general formula **XLIV**, wherein $R^{1.1}$ is as hereinbefore defined and R^9 denotes a C_{1-3}-alkyl group, to obtain compounds of general formula **XLV**, wherein $R^{1.1}$ is as hereinbefore defined and R^9 denotes a C_{1-3}-alkyl group, is carried out as described under Scheme 8.

Scheme 12



The amide linking of carboxylic acids of general formula **XLVI**, wherein all the groups are as hereinbefore defined, and amines of general formula H_2NR^2, wherein R^2 is as hereinbefore defined, to form carboxylic acid amides of general formula **XLVII**, wherein all the groups are as hereinbefore defined, is carried out as described under Scheme 1.

The reduction of carboxylic acid amides of general formula **XLVII** to obtain amines of general formula **XLVIII**, wherein all the groups are as hereinbefore defined, is carried out under standard reaction conditions, preferably in the presence of a

reducing agent such as lithium aluminium hydride and a solvent such as tetrahydrofuran at 40°C to 100°C.

Description of the method of hBK1 receptor binding

CHO cells expressing the hBK1 receptor are cultivated in Dulbecco's modified medium. The medium from confluent cultures is removed and the cells are washed with PBS buffer, scraped off and isolated by centrifugation. The cells are then homogenized in suspension and the homogenate is centrifuged and resuspended. The protein content is determined and the membrane preparation obtained in this manner is then frozen at -80°C.

After thawing, 200 µl of the homogenate (50 to 100 µg of proteins/assay) are incubated at room temperature with 0.5 to 1.0 nM of kallidin (DesArg10, Leu9), [3,4-prolyl-3,43H(N)] and increasing concentrations of the test substance in a total volume of 250 µl for 60 minutes. The incubation is terminated by rapid filtration through GF/B glass fibre filters which had been pretreated with polyethyleneimine (0.3%). The protein-bound radioactivity is measured in a TopCount NXT. Non-specific binding is defined as radioactivity bound in the presence of 1.0 µM of kallidin (DesArg10, Leu9), [3,4-prolyl-3,43H(N)]. The concentration/binding curve is analysed using a computer-assisted nonlinear curve fitting. The K_i which corresponds to the test substance is determined using the data obtained in this manner.

To demonstrate that the compounds of general formula I with different structural elements show good to very good bradykinin-B1-receptor antagonistic effects, the following Table gives the K_i values obtained according to the test method described above. It is pointed out that the compounds were selected for their different structural elements and not in order to emphasis specific compounds:

Example	K_i [nM]
(1)	6.2
(13)	2.1
(22)	7
(53)	2.4
(55)	0.7
(59)	6.3
(61)	3.3
(66)	4.6
(67)	0.4
(72)	2.8
(73)	6.8
(77)	8.7
(78)	5.8
(95)	6.7
(100)	5.0
(107)	6.0
(112)	4.4
(115)	0.99
(128)	5.7
(178)	5.2
(179)	7.1
(180)	4.8
(181)	6.6
(182)	1.3
(184)	3.4
(186)	9.4

Example	K_i [nM]
(213)	4.9
(220)	4.8
(235)	7.8
(258)	2.8
(260)	0.94
(261)	6.5
(269)	8.65
(270)	9.37
(272)	1.11
(286)	9.2
(287)	6.1
(290)	8.8
(292)	3.5
(294)	4.4
(295)	7.4
(298)	2.4
(300)	2.7
(301)	1.52
(302)	3.8
(312)	8.1
(314)	9.3
(315)	6.4
(316)	6.3
(319)	3.7
(320)	1.6
(321)	1.04

Example	K_i [nM]
(322)	7.5
(323)	0.74
(324)	3
(325)	0.79
(326)	2.7
(327)	9.3
(329)	2.8
(346)	5.6
(349)	0.82
(352)	9
(358)	4.3
(362)	3.8
(364)	8
(365)	2.4
(366)	1
(380)	3.2
(455)	0.85
(456)	0.34
(459)	6.2
(472)	3.4
(473)	8
(479)	5.5

INDICATIONS

By virtue of their pharmacological properties, the novel compounds and their physiologically acceptable salts are suitable for treating diseases and symptoms of diseases caused at least to some extent by stimulation of bradykinin-B1 receptors.

In view of their pharmacological effect the substances are suitable for the treatment of

(a) **acute pain** such as e.g. toothache, peri- and postoperative pain, traumatic pain, muscle pain, the pain caused by burns, sunburn, trigeminal neuralgia, pain caused by colic, as well as spasms of the gastro-intestinal tract or uterus;

(b) **visceral pain** such as e.g. chronic pelvic pain, gynaecological pain, pain before and during menstruation, pain caused by pancreatitis, peptic ulcers, interstitial cystitis, renal colic, angina pectoris, pain caused by irritable bowel, non-ulcerative dyspepsia and gastritis, non-cardiac thoracic pain and pain caused by myocardial ischaemia and cardiac infarct;

(c) **neuropathic pain** such as e.g. painful neuropathies, pain of diabetic neuropathy, AIDS-associated neuropathic pain, pain of lumbago, non-herpes-associated neuralgia, post-zoster neuralgia, nerve damage, cerebro-cranial trauma, pain of nerve damage caused by toxins or chemotherapy, phantom pain, pain of multiple sclerosis, nerve root tears and painful traumatically-caused damage to individual nerves;

(d) **inflammatory / pain receptor-mediated pain** in connection with diseases such as osteoarthritis, rheumatoid arthritis, rheumatic fever, tendo-synovitis, tendonitis, gout, vulvodynia, damage to and diseases of the muscles and fascia (muscle injury, fibromyalgia), osteoarthritis, juvenile arthritis, spondylitis, gout-arthritis, psoriasis-arthritis, fibromyalgia, myositis, migraine, dental disease, influenza and other virus infections such as colds, systemic lupus erythematodes,

(e) **tumour pain** associated with cancers such as lymphatid or myeloid leukaemia, Hodgkin's disease, non-Hodgkin's lymphomas, lymphogranulomatosis, lymphosarcomas, solid malignant tumours and extensive metastases;

(f) **headache diseases** such as e.g. headache of various origins, cluster headaches, migraine (with or without aura) and tension headaches.

The compounds are also suitable for treating

(g) inflammatory changes connected with diseases of the airways such as bronchial asthma, including allergic asthma (atopic and non-atopic) as well as bronchospasm on exertion, occupationally induced asthma, viral or bacterial exacerbation of an existing asthma and other non-allergically induced asthmatic diseases;

chronic obstructive pulmonary disease (COPD) including pulmonary emphysema, acute adult respiratory distress syndrome (ARDS), bronchitis, lung inflammation, allergic rhinitis (seasonal and all year round), vasomotor rhinitis and diseases caused by dust in the lungs such as aluminosis, anthracosis, asbestosis, chalicosis, siderosis, silicosis, tabacosis and byssinosis;

(h) inflammatory phenomena caused by sunburn and burns, oedema after burns trauma, cerebral oedema and angiooedema, intestinal complaints including Crohn's diseases and ulcerative colitis, irritable bowel syndrome, pancreatitis, nephritis, cystitis (interstitial cystitis), uveitis; inflammatory skin diseases (such as e.g. psoriasis and eczema), vascular diseases of the connective tissue, lupus, sprains and fractures;

(i) diabetes mellitus and its effects (such as e.g. diabetic vasculopathy, diabetic neuropathy, diabetic retinopathy) and diabetic symptoms in insulitis (e.g. hyperglycaemia, diuresis, proteinuria and increased renal excretion of nitrite and kallikrein);

(j) neurodegenerative diseases such as Parkinson´s disease and Alzheimer's disease;

(k) sepsis and septic shock after bacterial infections or after trauma;

(l) syndromes that cause itching and allergic skin reactions;

(m) osteoporosis;
(n) epilepsy;
(o) damage to the central nervous system;
(p) wounds and tissue damage;
(q) inflammation of the gums;
(r) benign prostatic hyperplasia and hyperactive bladder;
(s) pruritus;
(t) vitiligo;
(u) disorders of the motility of respiratory, genito-urinary, gastro-intestinal or vascular regions and
(v) post-operative fever.

In addition to being suitable as human therapeutic agents, these substances are also useful in the veterinary treatment of domestic animals, exotic animals and farm animals.
For treating pain, it may be advantageous to combine the compounds according to the invention with stimulating substances such as caffeine or other pain-alleviating active compounds. If active compounds suitable for treating the cause of the pain are available, these can be combined with the compounds according to the invention. If, independently of the pain treatment, other medical treatments are also indicated, for example for high blood pressure or diabetes, the active compounds required can be combined with the compounds according to the invention.

The following compounds may be used for combination therapy, for example:

Non-steroidal antirheumatics (NSAR): COX-2 inhibitors such as propionic acid derivatives (alminoprofen, benoxaprofen, bucloxic acid, carprofen, fenhufen, fenoprofen, fiuprofen, fiulbiprofen, ibuprofen, indoprofen, ketoprofen, miroprofen, naproxen, oxaprozin, pirprofen, pranoprofen, suprofen, tiaprofenic acid, tioxaprofen), acetic acid derivatives (indomethacin, acemetacin, alcofenac,

isoxepac, oxpinax, sulindac, tiopinac, tolmetin, zidometacin, zomepirac) fenamic derivatives (meclofenamic acid, mefenamic acid, tolfenamic acid), biphenyl-carboxylic acid derivatives, oxicams (isoxicam, meloxicam, piroxicam, sudoxicam and tenoxicam), salicylic acid derivatives (acetylsalicylic acid, sulphasalazin, why not also mesalazin, olsalazin, and pyrazolone (apazone, bezpiperylone, feprazone, mofebutazone, oxyphenbutazone, phenylbutazone, why not also propyphenazone and metamizol, and coxibs (celecoxib, valecoxib, rofecoxib, etoricoxib).

Opiate receptor agonists such as e.g. morphine, propoxyphen (Darvon), tramadol, buprenorphine.

Cannabinoid agonists such as e.g. GW-1000, KDS-2000, SAB-378, SP-104, NVP001-GW-843166, GW-842166X, PRS-211375.

Sodium channel blockers such as e.g. carbamazepine, mexiletin, lamotrigin, pregabalin, tectin, NW-1029, CGX-1002.

N-type calcium channel blockers such as e.g. ziconitide, NMED-160, SP1-860.

Serotonergic and noradrenergic modulators such as e.g. SR-57746, paroxetine, duloxetine, clonidine, amitriptyline, citalopram.

Corticosteroids such as e.g. betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone and triamcinolone.

Histamine H1-receptor antagonists such as e.g. bromopheniramine, chloropheniramine, dexchlorpheniramine, triprolidine, clemastine, diphenhydramine, diphenylpyraline, tripelennamine, hydroxyzine, methdilazine, promethazine, trimeprazine azatadine, cyproheptadine, antazoline, pheniramine, pyrilamine, astemizole, terfenadine, loratadine, cetirizine, desloratadine, fexofenadine, levocetirizine.

Histamine H2-receptor antagonists such as e.g. cimetidine, famotidine, and ranitidine.

Proton pump inhibitors such as e.g. omeprazole, pantoprazole, esomeprazole.

Leukotriene antagonists and 5-lipoxygenasehemmer such as e.g. zafirlukast, montelukast, pranlukast and zileuton.

Local anaesthetics such as e.g. ambroxol, lidocaine.
VR1 agonists and antagonists such as e.g. NGX-4010, WL-1002, ALGRX-4975, WL-10001, AMG-517.
Nicotine receptor agonists such as e.g. ABT-202, A-366833, ABT-594, BTG-102, A-85380, CGX1204.
P2X3-receptor antagonists such as e.g. A-317491, ISIS-13920, AZD-9056.
NGF agonists and antagonists such as e.g. RI-724, RI-1024, AMG-819, AMG-403, PPH 207.
NK1 and NK2 antagonists such as e.g. DA-5018, R-116301, CP-728663, ZD-2249.
NMDA antagonists such as e.g. NER-MD-11, CNS-5161, EAA-090, AZ-756, CNP-3381.
potassium channel modulators such as e.g. CL-888, ICA-69673, retigabin.
GABA modulators such as e.g. lacosamide.
Serotonergic and noradrenergic modulators such as e.g. SR-57746, paroxetine, duloxetine, clonidine, amitriptyline, citalopram, flibanserine.
Anti-migraine drugs such as e.g. sumatriptan, zolmitriptan, naratriptan, eletriptan.

The dosage necessary for obtaining a pain-alleviating effect is, in the case of intravenous administration, expediently from 0.01 to 3 mg/kg of body weight, preferably from 0.1 to 1 mg/kg, and, in the case of oral administration, from 0.1 to 8 mg/kg of body weight, preferably from 0.5 to 3 mg/kg, in each case 1 to 3 times per day. The compounds prepared according to the invention can be administered intravenously, subcutaneously, intramuscularly, intrarectally, intranasally, by inhalation, transdermally or orally, aerosol formulations being particularly suitable for inhalation. They can be incorporated into customary pharmaceutical preparations, such as tablets, coated tablets, capsules, powders, suspensions, solutions, metered-dose aerosols or suppositories, if appropriate together with one or more customary inert carriers and/or diluents, for example with maize starch, lactose, cane sugar, microcrystalline cellulose, magnesium stearate, polyvinylpyrrolidone, citric acid, tartaric acid, water, water/ethanol, water/glycerol,

water/sorbitol, water/polyethylene glycol, propylene glycol, cetylstearyl alcohol, carboxymethylcellulose or fatty substances, such as hardened fat, or suitable mixtures thereof.

EXPERIMENTAL SECTION

Generally, there are IR, ^{1}H NMR and/or mass spectra for the compounds that were prepared. The ratios given for the eluants are in volume units of the solvents in question. For ammonia, the given volume units are based on a concentrated solution of ammonia in water.

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

For chromatographic purification, silica gel from Millipore (MATREX™, 35-70 µm) or Alox (E. Merck, Darmstadt, Alumina 90 standardized, 63-200 µm, article No. 1.01097.9050) are used.

In the descriptions of the experiments, the following abbreviations are used:

CDI	1,1'-carbonyldiimidazole
TLC	thin layer chromatogram
DIPEA	diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethylsulphoxide
HATU	*O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N'*,*N'*-tetramethyluronium hexafluorophosphate
tert	tertiary
TBTU	2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium-tetrafluoroborate
THF	tetrahydrofuran

The following analytical HPLC methods were used:

Method 1: column: XTerra™ MS C18, 2.5 µM, 4.6 x 30 mm
detection: 210 – 420 nm
eluant A: water / 0.1 % formic acid
eluant B: acetonitrile / 0.1 % formic acid
gradient:

time in min	%A	%B	flow rate in mL/min
0.0	95.0	5.0	1.0
0.1	95.0	5.0	1.0
3.1	2.0	98.0	1.0
4.5	2.0	98.0	1.0
5.0	95.0	5.0	1.0

Method 2: column: Microsorb C18, 3 µM, 4.6 x 50 mm
detection: 220 – 320 nm
eluant A: water / 0.1 % TFA
eluant B: acetonitrile / 0.1 % TFA
gradient:

time in min	%A	%B	flow rate in mL/min
0.0	95.0	5.0	1.5
0.5	95.0	5.0	1.5
3.8	2.0	98.0	1.5
4.3	2.0	98.0	1.5
4.35	95.0	5.0	1.5
4.6	95.0	5.0	1.5

Method 3: column: XTerra™ MS C18, 3.5 µM, 4.6 x 50 mm
detection: 210 – 420 nm
eluant A: water / 0.1 % formic acid
eluant B: acetonitrile / 0.1 % formic acid

gradient:

time in min	%A	%B	flow rate in mL/min
0.0	95.0	5.0	1.0
0.1	95.0	5.0	1.0
7.1	2.0	98.0	1.0
7.9	2.0	98.0	1.0
8.0	95.0	5.0	1.0

Method 4: column: Zorbax Stable Bond C18, 3.5 µM, 4.6 x 75 mm
detection: 230 - 360 nm
eluant A: water / 0.1 % formic acid
eluant B: acetonitrile / 0.1 % formic acid
gradient:

time in min	%A	%B	flow rate in mL/min
0.0	95.0	5.0	1.6
0.1	95.0	5.0	1.6
4.5	10.0	90.0	1.6
5.09	10.0	90.0	1.6
5.5	90.0	10.0	1.6

Method 5: column: Interchim Strategy C18, 5 µM, 4.6 x 50 mm
detection: 220 – 320 nm
eluant A: water / 0.1 % TFA
eluant B: acetonitrile
gradient:

time in min	%A	%B	flow rate in mL/min
0.0	95.0	5.0	3.0
0.3	95.0	5.0	3.0
2.0	2.0	98.0	3.0
2.4	2.0	98.0	3.0
2.45	95.0	5.0	3.0

time in min	%A	%B	flow rate in mL/min
2.8	95.0	5.0	3.0

Method 6: column: Merck Cromolith Speed ROD RP18e, 4.6 x 50 mm
detection: 190 – 400 nm
eluant A: water / 0.1 % formic acid
eluant B: acetonitrile / 0.1 % formic acid
gradient:

time in min	%A	%B	flow rate in mL/min
0.0	90.0	10.0	1.5
4.5	10.0	90.0	1.5
5.0	10.0	90.0	1.5
5.5	90.0	10.0	1.5

Method 7: column: Waters SunFire C18, 3.5 µM, 4.6 x 50 mm
detection: 210 – 500 nm
eluant A: water / 0.1 % TFA
eluant B: acetonitrile / 0.1 % TFA
gradient:

time in min	%A	%B	flow rate in mL/min
0.0	95.0	5.0	1.5
2.0	2.0	98.0	1.5
3.0	2.0	98.0	1.5
3.4	95.0	5.0	1.5

Method 8: column: Waters XBridge C18, 3.5 µM, 4.6 x 50 mm
detection: 210 – 500 nm
eluant A: water / 0.1 % TFA
eluant B: acetonitrile / 0.1 % TFA
gradient:

time in min	%A	%B	flow rate in mL/min
0.0	95.0	5.0	1.0
0.1	95.0	5.0	1.0
5.1	2.0	98.0	1.0
6.5	2.0	98.0	1.0
7.0	95.0	5.0	1.0

Method 9: column: Merck Chromolith™ Flash RP18e, 4.6 x 25 mm
detection: 190 – 400 nm
eluant A: water / 0.1 % formic acid
eluant B: acetonitrile / 0.1 % formic acid
gradient:

time in min	%A	%B	flow rate in mL/min
0.0	90.0	10.0	1.6
2.7	10.0	90.0	1.6
3.0	10.0	90.0	1.6
3.3	90.0	10.0	1.6

Method 10: column: Merck Chromolith™ Flash RP18e, 4.6 x 25 mm
detection: 210 – 400 nm
eluant A: water / 0.1 % TFA
eluant B: acetonitrile / 0.1 % TFA
gradient:

time in min	%A	%B	flow rate in mL/min
0.0	95.0	5.0	2.5
0.2	95.0	5.0	2.5
1.5	2.0	98.0	2.5
1.7	2.0	98.0	2.5

time in min	%A	%B	flow rate in mL/min
1.9	95.0	5.0	2.5
2.2	95.0	5.0	2.5

Method 11: column: Waters XBridge C18, 3.5 µM, 4.6 x 50 mm
detection: 210 – 500 nm
eluant A: water / 0.1 % TFA
eluant B: acetonitrile / 0.1 % TFA
gradient:

time in min	%A	%B	flow rate in mL/min
0.0	95.0	5.0	1.5
2.0	0.0	100.0	1.5
3.0	0.0	100.0	1.5
3.4	95.0	5.0	1.5

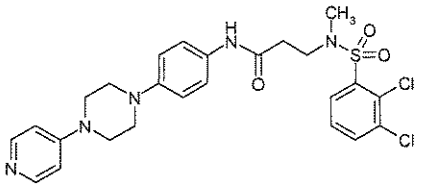
Method 12: column: YMC-Pack ODS-AQ, 3.0 µM, 4.6 x 75 mm
detection: 230 – 360 nm
eluant A: water / 0.1 % formic acid
eluant B: acetonitrile / 0.1 % formic acid
gradient:

time in min	%A	%B	flow rate in mL/min
0.0	95.0	5.0	1.6
4.5	10.0	90.0	1.6
5.0	10.0	90.0	1.6
5.5	90.0	10.0	1.6

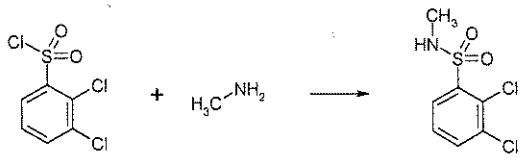
The following microwave apparatus was used: Biotage EmrysOptimizer™

Preparation of the End Compounds

Example 1



1a)



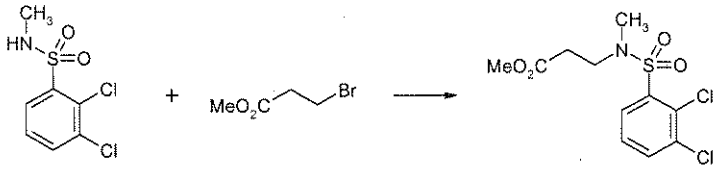
A mixture of 1.0 g (4.07 mmol) of 2,3-dichlorobenzenesulphonic acid chloride, 0.33 g (4.89 mmol) of methylamine hydrochloride, 2.73 ml (19.55 mmol) of triethylamine and 20 ml dichloromethane is stirred overnight at ambient temperature. The reaction mixture is then washed once with 1N HCl, saturated sodium hydrogen carbonate solution, water and saturated sodium chloride solution, dried on sodium sulphate and then evaporated to dryness.

$C_7H_7Cl_2NO_2S$ (240.11)

[M+H]+ = 240/242/244

TLC: silica gel, petroleum ether / ethyl acetate 2:1, Rf value = 0.50

1b)



A mixture of 0.9 g (3.75 mmol) of product from 1a and 20 ml DMF is taken and combined with 1.55 g (11.24 mmol) of potassium carbonate and 0.49 ml (4.50 mmol) of ethyl 3-bromopropionate. The reaction mixture is stirred overnight at ambient temperature and then mixed with water. It is extracted twice with ethyl

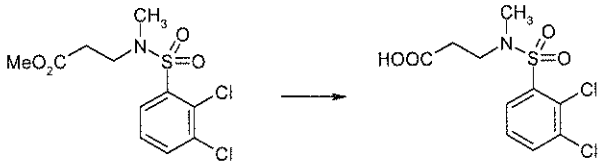
acetate. The organic extracts are washed three times with water and once with saturated sodium chloride solution, dried on sodium sulphate and evaporated to dryness.

$C_{11}H_{13}Cl_2NO_4S$ (326.20)

[M+H]+ = 326/328/330

TLC: silica gel, petroleum ether / ethyl acetate 2:1, Rf value = 0.45

1c)



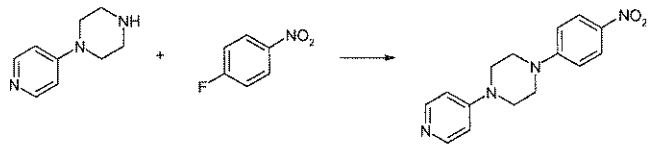
A mixture of 1.15 g (3.53 mmol) of product from 1b, 0.74 g (17.63 mmol) of lithium hydroxide monohydrate, 15 ml THF and 15 ml of water is stirred for one hour at ambient temperature. Then the THF is eliminated in vacuo and the residue is acidified with concentrated HCl. The reaction mixture is then extracted three times with ethyl acetate. The organic extracts are washed with saturated sodium chloride solution, dried on sodium sulphate and evaporated to dryness. The crude product is triturated with diethyl ether and suction filtered.

$C_{10}H_{11}Cl_2NO_4S$ (312.17)

[M+H]+ = 310/312/314

TLC: silica gel, petroleum ether / ethyl acetate 2:1, Rf value = 0.03

1d)



A mixture of 5.0 g (30.63 mmol) of 1-pyridin-4-yl-piperazine, 4.32 g (30.63 mmol) of 1-fluoro-4-nitrobenzene (Aldrich), 10.62 ml (76.59 mmol) of triethylamine and 100 ml DMF is heated for 50 min at reflux temperature and then evaporated to dryness. The crude product thus obtained is purified by column chromatography

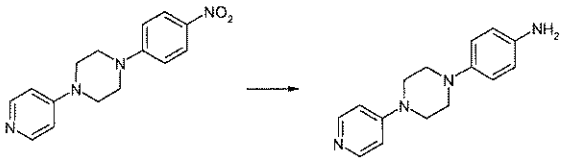
through silica gel (eluant: dichloromethane / ethanol / ammonia 12:1:0.1 to 10:1:0.1).

$C_{15}H_{16}N_4O_2$ (284.31)

[M+H]+ = 285

TLC: silica gel, dichloromethane / methanol / ammonia 9:1:0.1, Rf value = 0.52

1e)

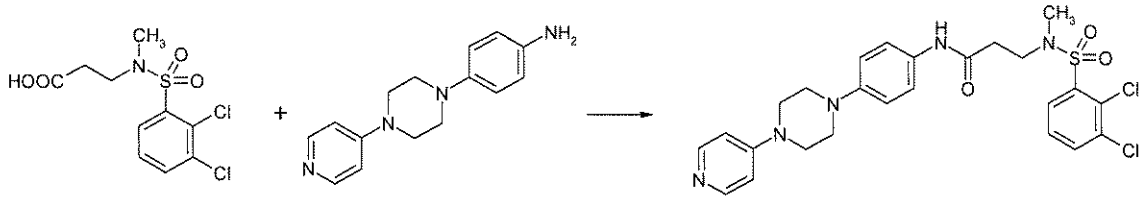


A mixture of 4.95 g (17.41 mmol) of product from 1d, 0.6 g palladium on charcoal (10%), 120 ml dichloromethane and 20 ml of methanol is hydrogenated for five hours in the autoclave at ambient temperature. Then the mixture is suction filtered and the filter cake is decocted another six times with dichloromethane / methanol 1:1 and suction filtered again. The combined filtrates are evaporated to dryness in vacuo.

$C_{15}H_{18}N_4$ (254.33)

[M+H]+ = 255

1f)



A mixture of 1.25 g (4.00 mmol) of product from 1c, 2.0 ml (14.34 mmol) of triethylamine, 1.28 g (4.00 mmol) of TBTU and 7 ml DMF is stirred for 45 min at ambient temperature. Then 1.0 g (3.93 mmol) of product from 1e is added and the mixture is stirred overnight at ambient temperature. Then the reaction mixture is poured into water and extracted with dichloromethane. The organic extracts are washed with water, dried on Na_2SO_4 and evaporated to dryness. The crude

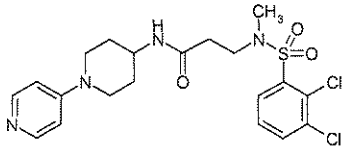
product thus obtained was purified by column chromatography through silica gel (eluant: dichloromethane with 5-20 % methanol).

$C_{25}H_{27}Cl_2N_5O_3S$ (548.49)

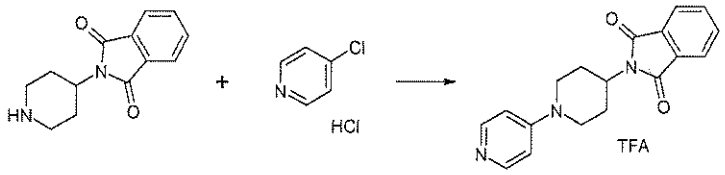
[M+H]+ = 548/550/552

TLC: silica gel, dichloromethane / methanol 4:1, Rf value = 0.65

Example 2



2a)



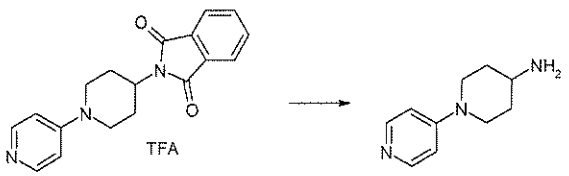
A mixture of 0.5 g (2.17 mmol) of *N*-(1-benzylpiperidin-4-yl)-phthalimide (Bioorg. Med. Chem. Lett. 11, 2001, 2325-2330), 0.33 g (2.17 mmol) of 4-chloropyridine hydrochloride, 1.2 ml (8.69 mmol) of triethylamine and 2.4 ml of absolute ethanol is heated in the microwave to 150°C for one hour. The reaction mixture is then diluted with ethanol, the precipitate formed is filtered off. The filtrates are evaporated to dryness and the crude product is purified by preparative HPLC.

$C_{18}H_{17}N_3O_2 \times C_2HF_3O_2$ (421.37)

[M+H]+ = 308

HPLC (Method 1): retention time = 2.07 min

2b)

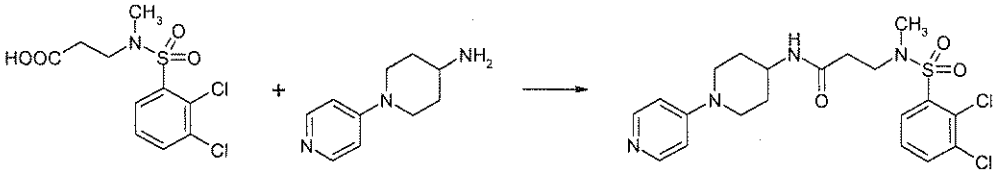


A mixture of 0.3 g (0.71 mmol) of product from 2a, 0.09 g (1.42 mmol) of hydrazine hydrate 80% and 6 ml of absolute ethanol is refluxed for four hours. The reaction mixture is then cooled to 0°C, the precipitate formed is filtered off. The filtrates are evaporated to dryness.

$C_{10}H_{15}N_3$ (177.25)

[M+H]+ = 178

2c)



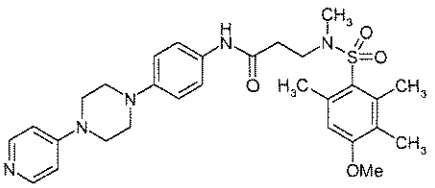
Example 2 is prepared analogously to 1f from 0.22 g (0.71 mmol) of product from 1c, 0.24 g (1.35 mmol) of product from 2b, 0.3 ml (2.13 mmol) of triethylamine and 0.23 g (0.71 mmol) of TBTU in 5.5 ml DMF.

$C_{20}H_{24}Cl_2N_4O_3S$ (471.40)

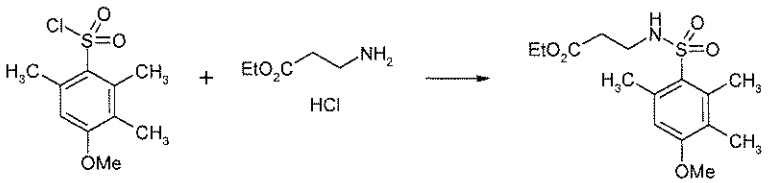
[M+H]+ = 471/473/475

TLC: silica gel, dichloromethane / methanol 9:1, Rf value = 0.2

Example 3



3a)



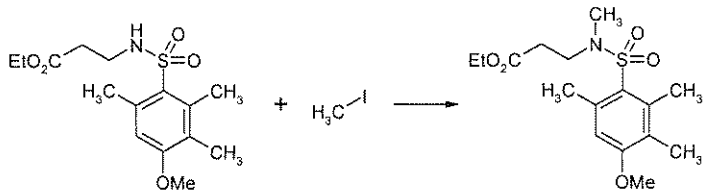
A mixture of 0.99 g (4.00 mmol) of 4-methoxy-2,3,6-trimethyl-benzenesulphonyl chloride, 0.69 g (4.51 mmol) of ß-alanine ethylester hydrochloride, 2.23 ml (15.98 mmol) of triethylamine and 20 ml dichloromethane is stirred overnight at ambient temperature. The reaction mixture is then washed with 0.5 M HCl, saturated sodium hydrogen carbonate solution, water and saturated sodium chloride solution, dried on sodium sulphate and evaporated to dryness in vacuo.

$C_{15}H_{23}NO_5S$ (329.41)

[M+H]+ = 330

TLC: silica gel, petroleum ether / ethyl acetate 2:1, Rf value = 0.43

3b)



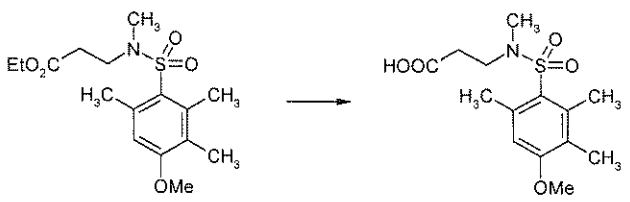
A mixture of 1.24 g (3.76 mmol) of product from 3a, 0.84 ml (13.55 mmol) of methyl iodide, 1.04 g (7.53 mmol) of anhydrous potassium carbonate and 10 ml DMF is stirred for five hours at ambient temperature. The reaction mixture is then evaporated to dryness in vacuo, the residue is taken up in ethyl acetate. It is washed with water, saturated sodium hydrogen carbonate solution and saturated sodium chloride solution, dried on sodium sulphate and evaporated to dryness in vacuo.

$C_{16}H_{25}NO_5S$ (343.44)

[M+H]+ = 344

TLC: silica gel, petroleum ether / ethyl acetate 2:1, Rf value = 0.52

3c)



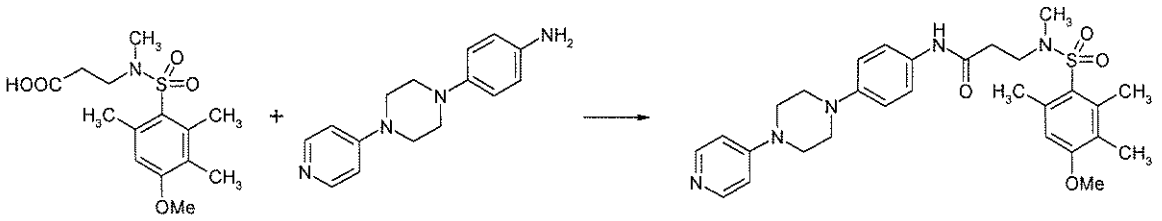
The acid is prepared analogously to 1c from 1.29 g (3.76 mmol) of product from 3b, 0.79 g (18.80 mmol) of lithium hydroxide monohydrate, 15 ml THF and 15 ml of water.

$C_{14}H_{21}NO_5S$ (315.39)

[M+H]+ = 316

TLC: silica gel, petroleum ether / ethyl acetate 2:1, Rf value = 0.07

3d)



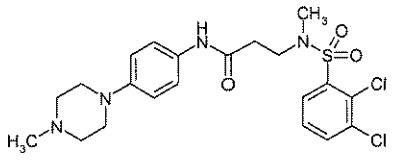
Example 3 is prepared analogously to 1f from 0.15 g (0.47 mmol) of product from 3c, 0.12 g (0.47 mmol) of product from 1e, 0.2 ml (1.43 mmol) of triethylamine and 0.15 g (0.48 mmol) of TBTU in 8 ml DMF.

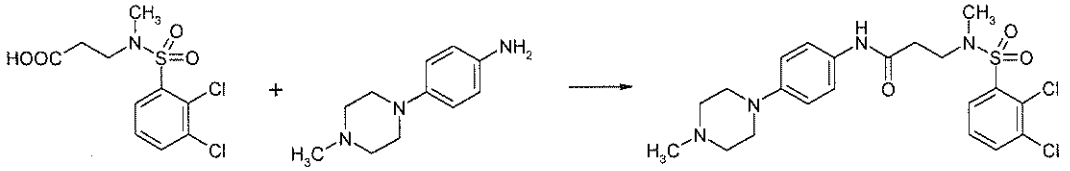
$C_{29}H_{37}N_5O_4S$ (551.70)

[M+H]+ = 552

TLC: silica gel, dichloromethane / methanol 9:1, Rf value = 0.38

Example 4





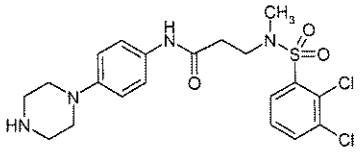
Example 4 is prepared analogously to 1f from 0.39 g (1.26 mmol) of product from 1c, 0.24 g (1.26 mmol) of 4-(4-methylpiperazin-1-yl)-aniline (J. Med. Chem. SIR 48, 7, 2005, 2371-2387), 0.35 ml (2.51 mmol) of triethylamine and 0.50 g (1.32 mmol) of HATU in 5 ml DMF.

$C_{21}H_{26}CL_2N_4O_3S$ (485.43)

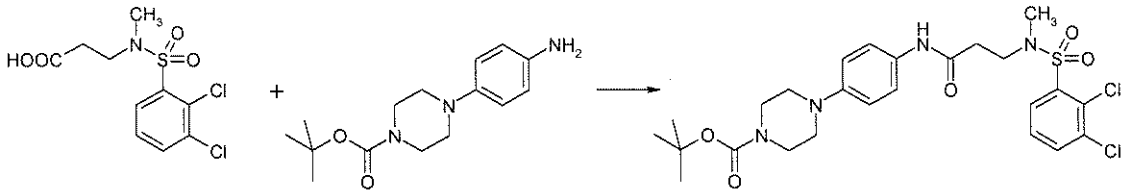
[M+H]+ = 485/487/489

HPLC (Method 2): retention time = 2.64 min

Example 5



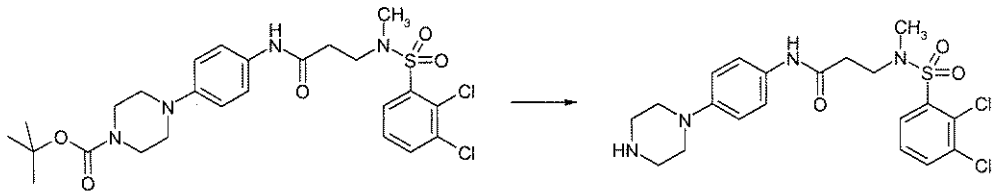
5a)



5a is prepared analogously to 1f from 0.39 g (1.26 mmol) of product from 1c, 0.24 g (1.26 mmol) of 4-(4-methylpiperazin-1-yl)-aniline (J. Med. Chem. SIR 48, 7, 2005, 2371-2387), 0.35 ml (2.51 mmol) of triethylamine and 0.50 g (1.32 mmol) of HATU in 5 ml DMF.

$C_{25}H_{32}CL_2N_4O_5S$ (571.52)

5b)



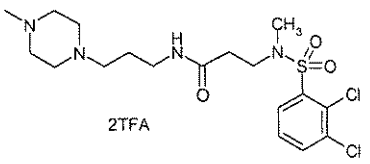
A mixture of 0.60 g (1.05 mmol) of product from 5a, 3 ml TFA and 3 ml dichloromethane is stirred for two hours at ambient temperature. The reaction mixture is evaporated to dryness and the crude product is purified by preparative HPLC.

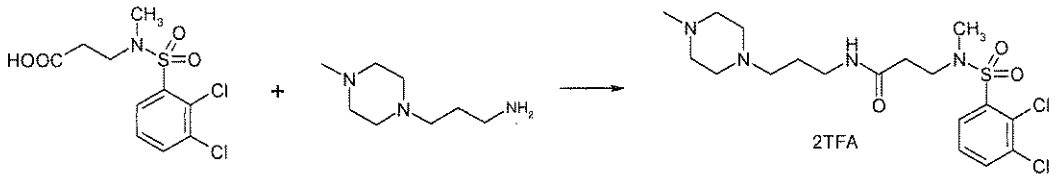
$C_{20}H_{24}Cl_2N_4O_3S$ (471.40)

[M+H]+ = 471/473/475

HPLC (Method 2): retention time = 2.58 min

Example 6





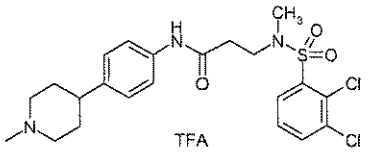
Example 6 is prepared analogously to 1f from 0.22 g (0.71 mmol) of product from 1c, 0.12 g (0.78 mmol) of 3-(4-methylpiperazin-1-yl)-propylamine (Bioorg. Med. Chem. Lett. 13, 2003, 2131-2136), 0.30 ml (2.13 mmol) of triethylamine and 0.23 g (0.71 mmol) of TBTU in 5.5 ml THF.

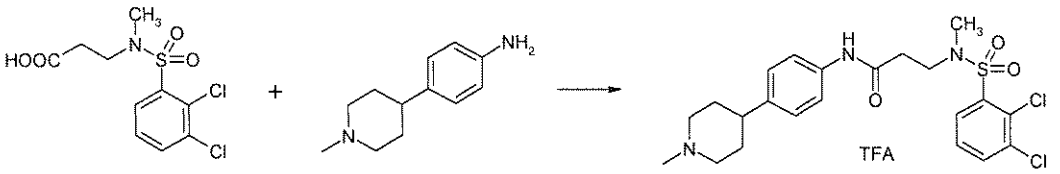
$C_{18}H_{28}Cl_2N_4O_3S \times 2C_2HF_3O_2$ (679.46)

[M+H]+ = 451/453/455

HPLC (Method 5): retention time = 1.37 min

Example 7





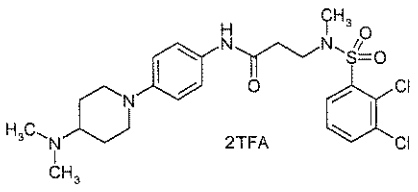
Example 7 is prepared analogously to 1f from 0.22 g (0.71 mmol) of product from 1c, 0.14 g (0.71 mmol) of 4-(1-methylpiperidin-4-yl)-aniline (JW Pharmlab), 0.30 ml (2.13 mmol) of triethylamine and 0.23 g (0.71 mmol) of TBTU in 5.5 ml THF.

$C_{22}H_{27}Cl_2N_3O_3S \times C_2HF_3O_2$ (598.46)

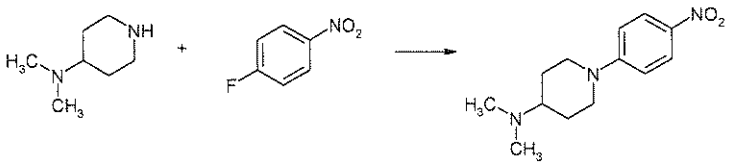
[M+H]+ = 484/486/488

HPLC (Method 5): retention time = 1.57 min

Example 8



8a)

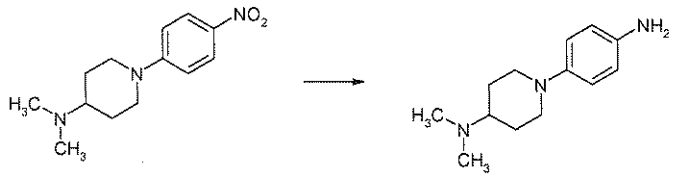


8a is prepared analogously to 1d from 0.5 g (3.90 mmol) of 4-dimethylamino-piperidine (Alfa Aesar), 0.44 g (4.18 mmol) of 1-fluoro-4-nitrobenzene (Aldrich) and 1.33 ml (76.59 mmol) of triethylamine in 12 ml DMF.

$C_{13}H_{19}N_3O_2$ (249.31)

[M+H]+ = 250

8b)



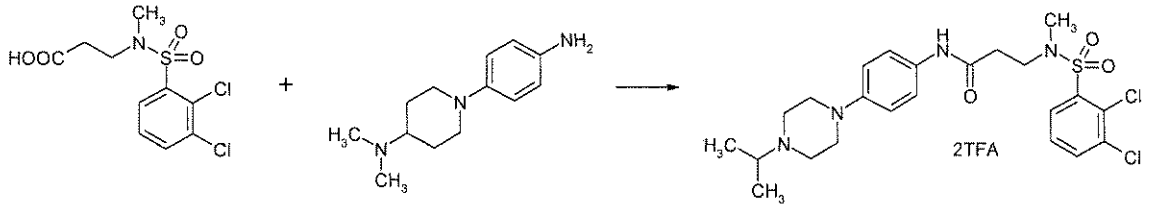
A mixture of 1.66 g (6.67 mmol) of product from 8a, 0.17 g palladium on charcoal (5%) and 132 ml of ethanol is hydrogenated in the autoclave at ambient temperature. Then the catalyst is removed by suction filtering and the filtrate is evaporated to dryness in vacuo.

$C_{13}H_{21}N_3$ (219.33)

[M+H]+ = 220

TLC: silica gel, dichloromethane / methanol 9:1, Rf value = 0.1

8c)



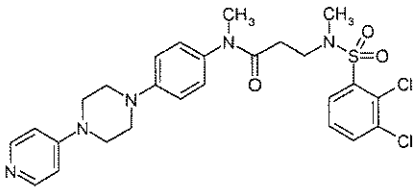
Example 8 is prepared analogously to 1f from 0.22 g (0.71 mmol) of product from 1c, 0.16 g (0.71 mmol) of product from 8b, 0.30 ml (2.13 mmol) of triethylamine and 0.23 g (0.71 mmol) of TBTU in 5.5 ml THF.

$C_{23}H_{30}Cl_2N_4O_3S \times 2C_2HF_3O_2$ (741.53)

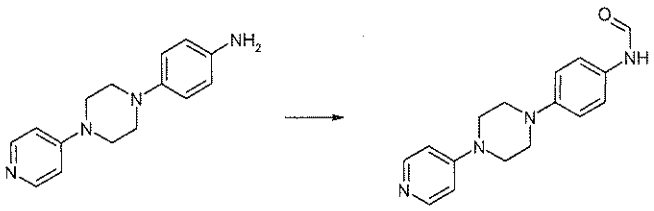
[M+H]+ = 513/515/517

HPLC (Method 5): retention time = 1.46 min

Example 9



9a)

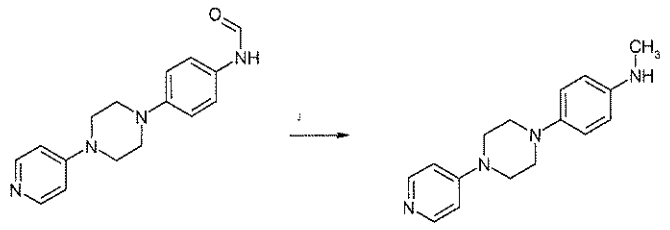


13 ml acetic anhydride are taken and 8 ml formic acid are slowly added thereto. The reaction mixture is heated for 1.5 hours to 50°C and then combined with 80 ml dichloromethane. While cooling with the ice bath 5.0 g (19.66 mmol) are then added. The mixture is stirred for one hour at ambient temperature and then evaporated to dryness. The residue is combined with semisaturated sodium hydrogen carbonate solution and extracted twice with dichloromethane. The organic extracts are washed with saturated sodium chloride solution, dried on sodium sulphate and evaporated to dryness. The crude product thus obtained is purified by column chromatography through silica gel (eluant: dichloromethane / methanol / ammonia 9:1:0.1).

$C_{16}H_{18}N_4O$ (282.34)

[M+H]+ = 283

9b)

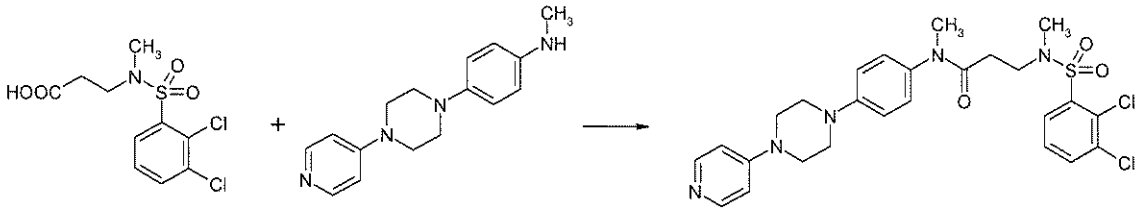


At 60°C a mixture of 10.63 ml lithium aluminium hydride 2 M in THF (21.25 mmol) and 50 ml THF is slowly combined with 3.0 g (10.63 mmol) of product from 9a.

The reaction mixture is stirred for eight hours at 60°C and four hours at ambient temperature. While cooling with the ice bath 20 ml of water are then added. The mixture is filtered through Celite and washed with THF and dichloromethane. The filtrate is evaporated to dryness. The residue is combined with dichloromethane, washed with water and 1 M sodium hydroxide solution, dried on sodium sulphate solution and evaporated to dryness. The crude product thus obtained is purified by column chromatography through silica gel (eluant: dichloromethane / methanol / ammonia 9:1:0.1).

$C_{16}H_{20}N_4$ (268.36)

9c)



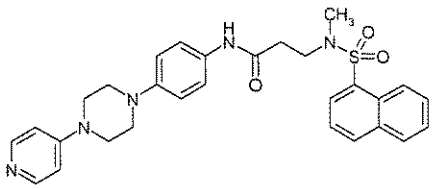
Example 9 is prepared analogously to 1f from 0.15 g (0.48 mmol) of product from 1c, 0.14 g (0.51 mmol) of product from 9b, 0.13 ml (0.96 mmol) of triethylamine and 0.19 g (0.51 mmol) of HATU in 5 ml DMF.

$C_{26}H_{29}Cl_2N_5O_3S$ (562.51)

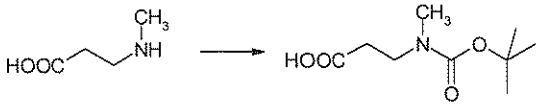
[M+H]+ = 562/564/566

HPLC (Method 2): retention time = 2.86 min

Example 10



10a)

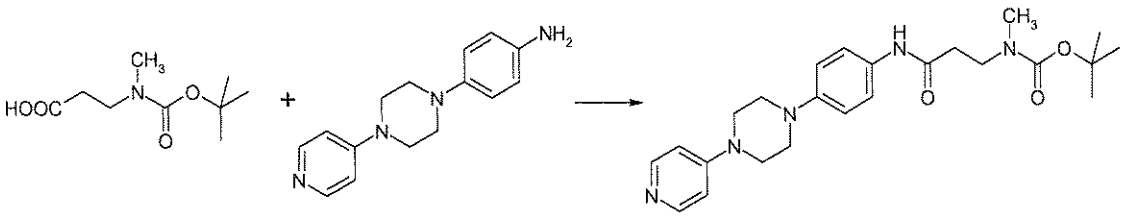


A mixture of 1.0 g (9.70 mmol) of N-methyl-ß-alanine (Convertex), 24 ml dioxane, 12 ml of water and 2.68 g (19.38 mmol) of anhydrous potassium carbonate is combined with 2.33 g (10.66 mmol) of Boc-anhydride while cooling with an ice bath. The reaction mixture is stirred for three days at ambient temperature. Then the dioxane is eliminated in vacuo. The aqueous residue is extracted with ethyl acetate (ethyl acetate phases are discarded), then acidified slightly with 1 M hydrochloric acid and then extracted with dichloromethane. The organic dichloromethane extracts are washed with saturated sodium chloride solution, dried on sodium sulphate and evaporated to dryness.

$C_9H_{17}NO_4$ (203.24)

[M+H]+ = 204

10b)



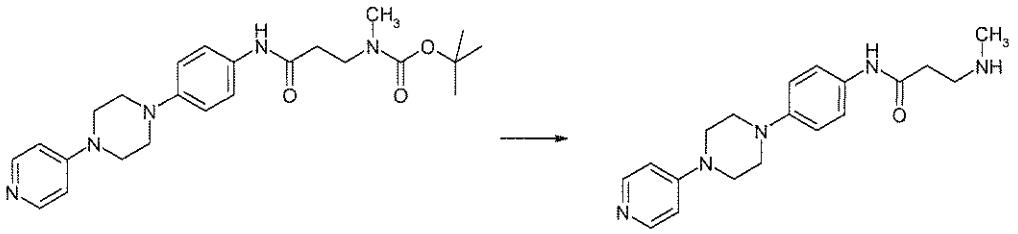
10b is prepared analogously to 1f from 1.85 g (9.10 mmol) of product from 10a, 2.32 g (9.10 mmol) of product from 1e, 3.81 ml (27.31 mmol) of triethylamine and 2.92 g (9.10 mmol) of TBTU in 80 ml DMF.

$C_{24}H_{33}N_5O_3$ (439.55)

[M+H]+ = 440

TLC: silica gel, dichloromethane / methanol 9:1, Rf value = 0.49

10c)



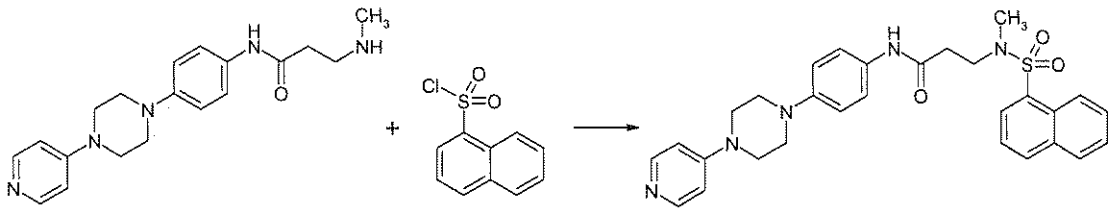
A mixture of 3.20 g (7.28 mmol) of product from 10b, 20 ml TFA and 60 ml dichloromethane is stirred for 30 min at ambient temperature. Then the reaction mixture is evaporated to dryness in vacuo. The crude product thus obtained is purified by column chromatography through silica gel (eluant: dichloromethane / ethanol / ammonia 9:1:0.1 to 4:1:0.1).

$C_{19}H_{25}N_5O$ (339.43)

[M+H]+ = 340

TLC: silica gel, dichloromethane / methanol / ammonia 9:1:0.1, Rf value = 0.25

10d)



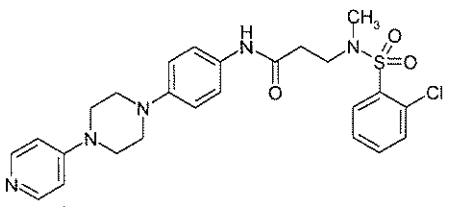
A mixture of 0.1 g (0.30 mmol) of product from 10c, 0.056 g (0.25 mmol) of 1-naphthylsulphonic acid chloride, 0.137 ml (0.98 mmol) of triethylamine and 5 ml dichloromethane is stirred overnight at ambient temperature. Then the reaction mixture is evaporated to dryness in vacuo. The crude product thus obtained is purified by column chromatography through silica gel (eluant: dichloromethane / ethanol / ammonia 12:1:0.1).

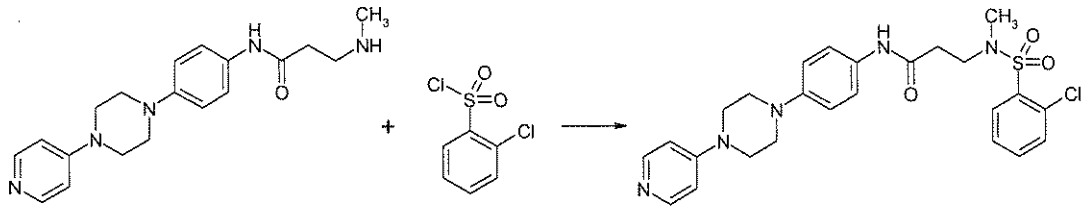
$C_{29}H_{31}N_5O_3S$ (529.65)

[M+H]+ = 530

TLC: silica gel, dichloromethane / methanol / ammonia 9:1:0.1, Rf value = 0.44

Example 11





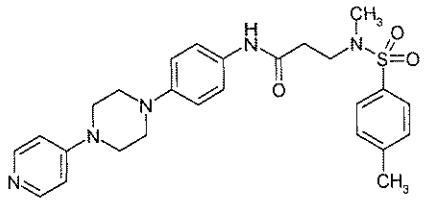
Example 11 is prepared analogously to 10d from 0.10 g (0.30 mmol) of product from 10c, 0.052 g (0.25 mmol) of 2-chlorobenzenesulphonic acid chloride, 0.14 ml (98 mmol) of triethylamine in 5 ml dichloromethane.

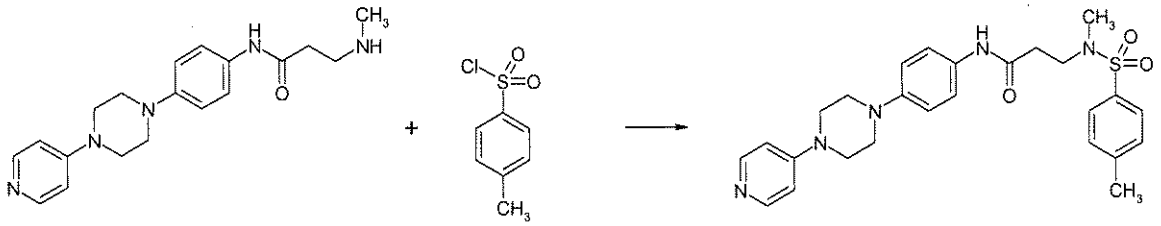
$C_{25}H_{28}ClN_5O_3S$ (514.04)

[M+H]+ = 514/516

TLC: silica gel, dichloromethane / methanol / ammonia 9:1:0.1, Rf value = 0.47

Example 12





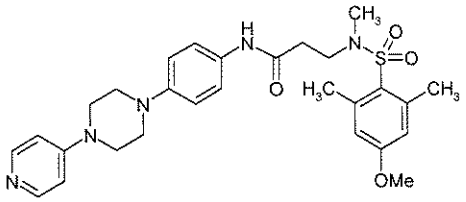
Example 12 is prepared analogously to 10d from 0.10 g (0.30 mmol) of product from 10c, 0.047 g (0.25 mmol) of p-toluenesulphonic acid chloride, 0.14 ml (98 mmol) of triethylamine in 5 ml dichloromethane.

$C_{26}H_{31}N_5O_3S$ (493.62)

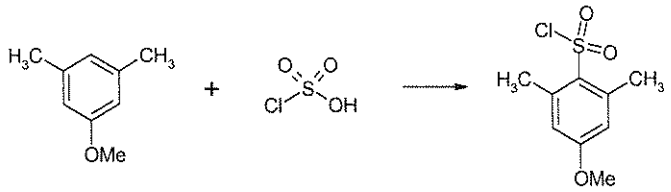
[M+H]+ = 494

TLC: silica gel, dichloromethane / methanol / ammonia 9:1:0.1, Rf value = 0.43

Example 13



13a)



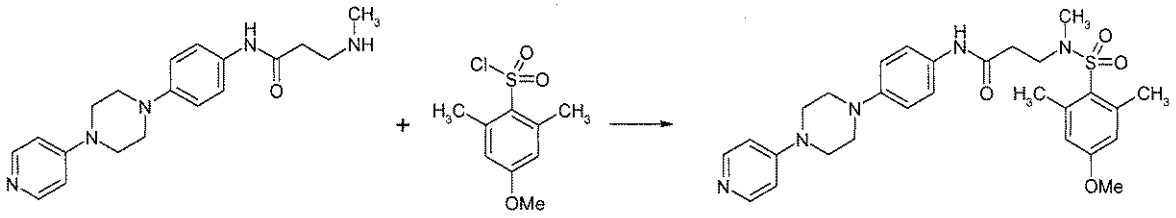
A mixture of 2.0 g (14.69 mmol) of 3,5-dimethylanisol and 20 ml dichloromethane is combined with 5.85 ml (88.0 mmol) of chlorosulphonic acid while cooling with an ice bath. The reaction mixture is then stirred for 20 min at ambient temperature and then poured onto 50 ml ice water. The mixture is extracted with 100 ml dichloromethane. The organic extracts are washed with 5% sodium hydrogen carbonate solution, dried on sodium sulphate and evaporated to dryness.

$C_9H_{11}ClO_3S$ (234.70)

[M+H]+ = 234/236

TLC: silica gel, petroleum ether / ethyl acetate 9:1, Rf value = 0.46

13b)



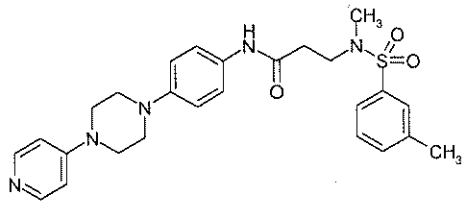
Example 13 is prepared analogously to 10d from 0.10 g (0.30 mmol) of product from 10c, 0.058 g (0.25 mmol) of product from 13a, 0.14 ml (98 mmol) of triethylamine in 5 ml dichloromethane.

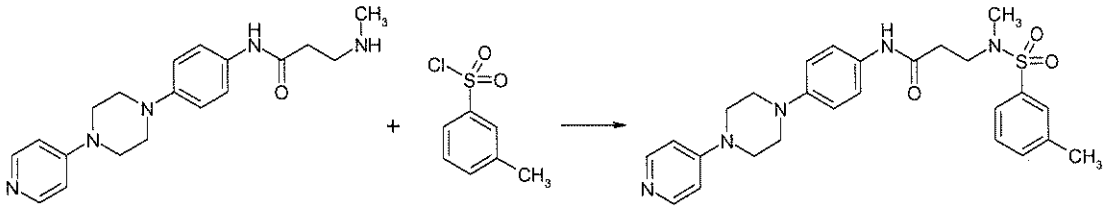
$C_{28}H_{35}N_5O_4S$ (537.67)

[M+H]+ = 538

TLC: silica gel, dichloromethane / methanol / ammonia 9:1:0.1, Rf value = 0.62

Example 14





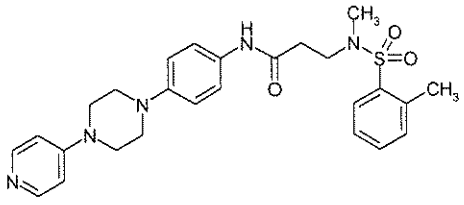
Example 14 is prepared analogously to 10d from 0.10 g (0.30 mmol) of product from 10c, 0.047 g (0.25 mmol) of m-toluenesulphonic acid chloride, 0.14 ml (98 mmol) of triethylamine in 5 ml dichloromethane.

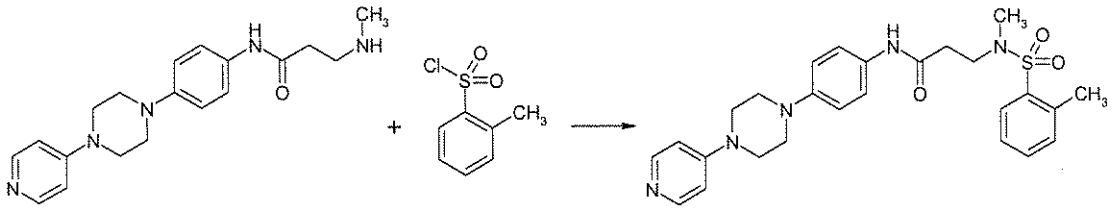
$C_{26}H_{31}N_5O_3S$ (493.62)

[M+H]+ = 494

TLC: silica gel, dichloromethane / methanol / ammonia 9:1:0.1, Rf value = 0.47

Example 15





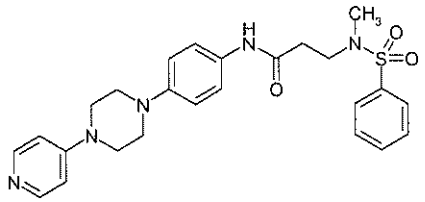
Example 15 is prepared analogously to 10d from 0.10 g (0.30 mmol) of product from 10c, 0.047 g (0.25 mmol) of o-toluenesulphonic acid chloride, 0.14 ml (98 mmol) of triethylamine in 5 ml dichloromethane.

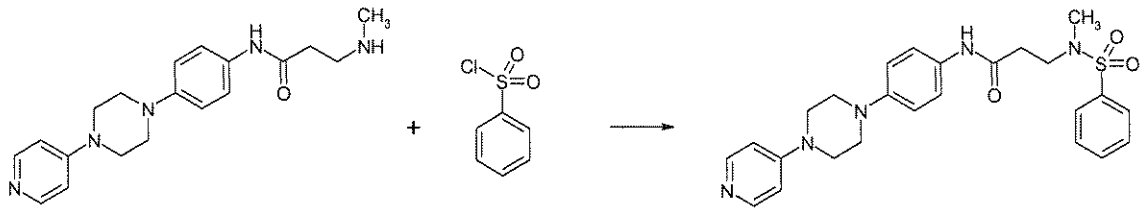
$C_{26}H_{31}N_5O_3S$ (493.62)

[M+H]+ = 494

HPLC (Method 1): retention time = 2.37 min

Example 16





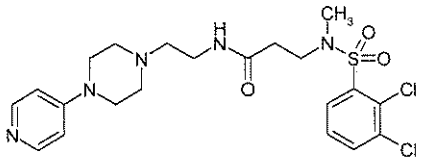
Example 16 is prepared analogously to 10d from 0.10 g (0.30 mmol) of product from 10c, 0.043 g (0.25 mmol) of benzenesulphonic acid chloride, 0.14 ml (98 mmol) of triethylamine in 5 ml dichloromethane.

$C_{25}H_{29}N_5O_3S$ (479.60)

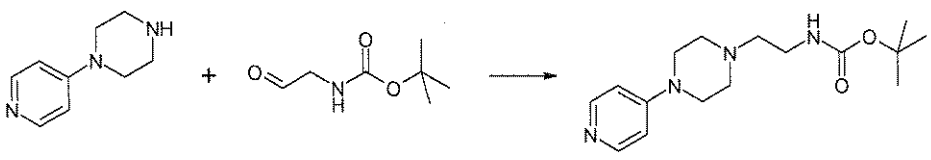
[M+H]+ = 480

HPLC (Method 1): retention time = 2.40 min

Example 17



17a)

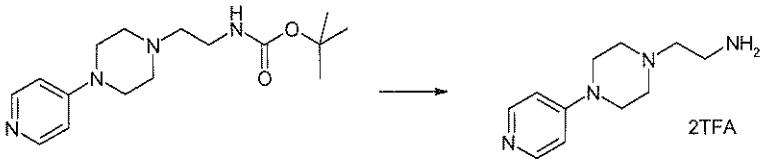


A mixture of 1.03 g (6.28 mmol) of 1-(4-pyridyl)-piperazine (Girindus) and 50 ml dichloromethane is combined with 1.0 g (6.28 mmol) of *tert*-butyl-N-(2-oxoethyl)-carbamate (Aldrich). The reaction mixture is then stirred for 30 min at ambient temperature, then combined with 2.66 g (12.56 mmol) of sodium-triacetoxyborohydride while cooling with an ice bath and then stirred overnight at ambient temperature. Another 60 ml dichloromethane are added and the reaction mixture is washed with saturated sodium hydrogen carbonate solution and saturated sodium chloride solution. The organic phase is dried on sodium sulphate and evaporated to dryness. The crude product thus obtained is purified by column chromatography through silica gel (eluant: dichloromethane / ethanol / ammonia 14:1:0.1 to 10:1:0.1).

$C_{16}H_{26}N_4O_2$ (306.40)

[M+H]+ = 307

17b)



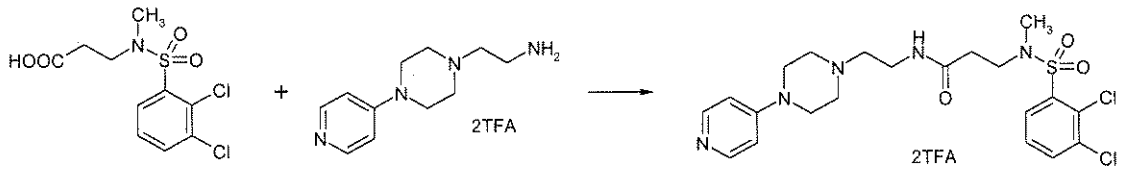
A mixture of 0.36 g (1.19 mmol) of product from 17a, 1.19 ml (15.50 mmol) of TFA and 2 ml dichloromethane is stirred for two hours at ambient temperature. Then the reaction mixture is evaporated to dryness in vacuo.

$C_{11}H_{18}N_4 \times 2C_2HF_3O_2$ (434.33)

[M+H]+ = 207

HPLC (Method 2): retention time = 0.98 min

17c)



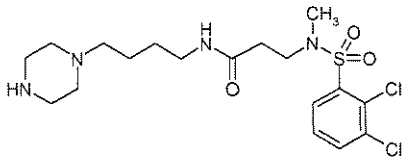
Example 17 is prepared analogously to 1f from 0.22 g (0.71 mmol) of product from 1c, 0.34 g (0.78 mmol) of product from 17b, 0.50 ml (3.56 mmol) of triethylamine and 0.23 g (0.71 mmol) of TBTU in 5.5 ml THF.

$C_{21}H_{27}Cl_2N_5O_3S \times 2C_2HF_3O_2$ (728.49)

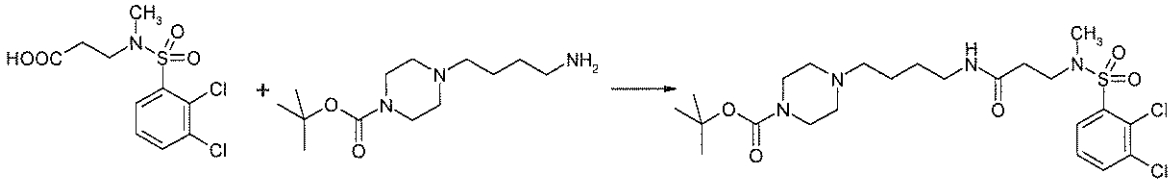
[M+H]+ = 500/502/504

HPLC (Method 2): retention time = 3.14 min

Example 18



18a)



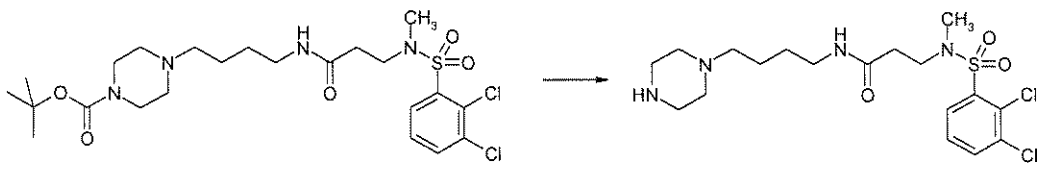
18a is prepared analogously to 1f from 0.20 g (0.64 mmol) of product from 1c, 0.17 g (0.64 mmol) of tert-butyl 4-(4-aminobutyl)-piperazine-1-carboxylate (J. Med. Chem. 47, 2004, 4300-4315), 0.27 ml (1.92 mmol) of triethylamine and 0.21 g (0.64 mmol) of TBTU in 5 ml THF.

$C_{23}H_{36}CL_2N_4O_5S$ (551.53)

M+H]+ = 551/553/555

TLC: silica gel, dichloromethane / methanol 30:1, Rf value = 0.1

18b)



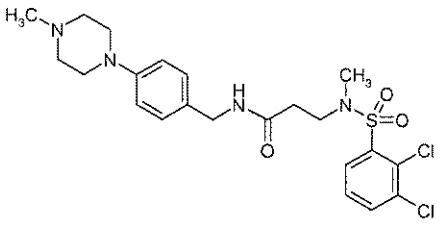
A mixture of 0.29 g (0.53 mmol) of product from 18a, 0.53 ml TFA and 1 ml dichloromethane is stirred for two hours at ambient temperature. The reaction mixture is washed with saturated sodium hydrogen carbonate solution. After the phase separation the aqueous phase is extracted three times more with dichloromethane. The organic extracts are dried on sodium sulphate and evaporated to dryness in vacuo.

$C_{18}H_{28}Cl_2N_4O_3S$ (451.41)

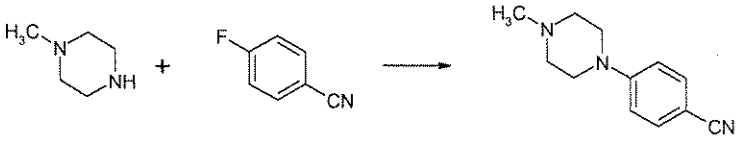
[M+H]+ = 451/453/455

HPLC (Method 2): retention time = 2.22 min

Example 19



19a)



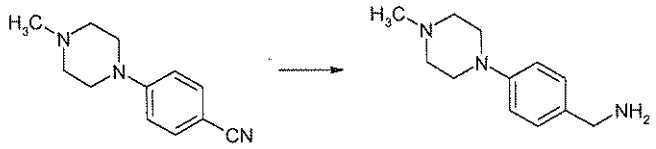
A mixture of 5.0 ml (45.13 mmol) of *N*-methylpiperazine and 0.73 g (6.00 mmol) of 4-fluorobenzonitrile (Aldrich) is heated for 12 hours to 80°C. Then it is evaporated to dryness and the residue is mixed with water. It is extracted three times with ethyl acetate. The organic extracts are dried on sodium sulphate and evaporated to dryness in vacuo.

$C_{12}H_{15}N_3$ (201.27)

M+H]+ = 202

TLC: silica gel, dichloromethane / ethanol 95:5, Rf value = 0.31

19b)

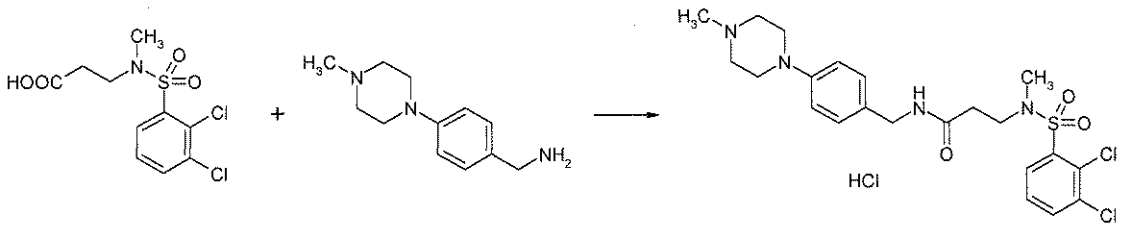


A mixture of 1.17 g (5.81 mmol) of product from 19a, 0.3 g Raney nickel and 50 ml of methanolic ammonia solution is hydrogenated at 50°C in the autoclave. Then the catalyst is filtered off and the filtrate is evaporated to dryness in vacuo.

$C_{12}H_{19}N_3$ (205.30)

M+H]+ = 206

19c)



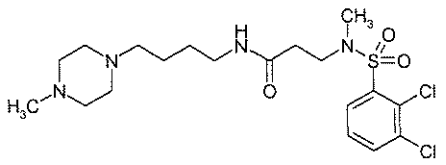
Example 19 is prepared analogously to 1f from 0.16 g (0.50 mmol) of product from 1c, 0.10 g (0.50 mmol) of product from 19b, 0.14 ml (1.00 mmol) of triethylamine and 0.16 g (0.50 mmol) of TBTU in 3 ml DMF.

$C_{22}H_{28}Cl_2N_4O_3S$ x HCl (535.91)

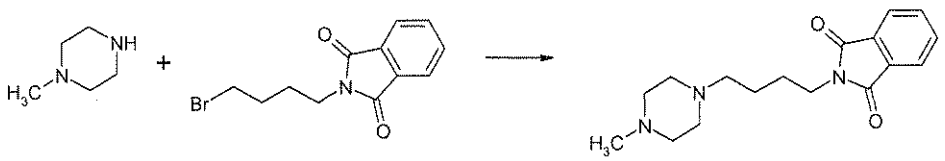
[M+H]+ = 499/501/503

HPLC (Method 3): retention time = 3.49 min

Example 20



20a)

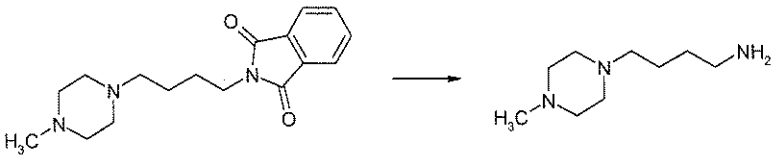


A mixture of 0.5 g (4.99 mmol) of *N*-methylpiperazine (Aldrich), 1.41 g (4.99 mmol) of N-(4-bromobutyl)-phthalimide (Fluka), 0.86 ml (4.99 mmol) of DIPEA and 9.3 ml acetonitrile is heated for 45 min in the microwave to 120°C. Then it is evaporated to dryness. The crude product thus obtained is purified by column chromatography through silica gel (eluant: dichloromethane / methanol 98:2).

$C_{17}H_{23}N_3O_2$ (301.38)

M+H]+ = 302

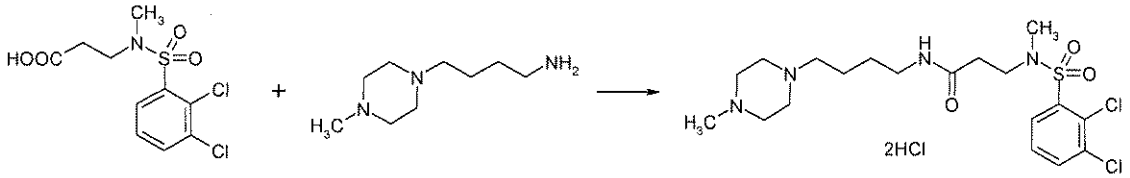
20b)



A mixture of 1.94 g (6.44 mmol) of product from 20a, 1.61 g (25.75 mmol) of hydrazine hydrate hydrate and 15 ml of absolute ethanol is heated for 5.5 hours in the autoclave to 120°C. The precipitate formed is filtered off. Then the filtrate is evaporated to dryness.

$C_9H_{21}N_3$ (171.28)

20c)



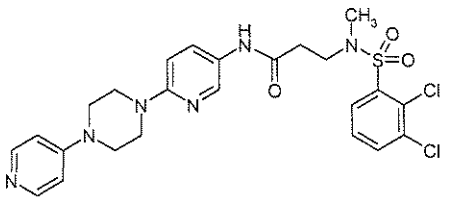
Example 20 is prepared analogously to 1f from 0.50 g (1.61 mmol) of product from 1c, 0.55 g (3.22 mmol) of product from 20b, 0.67 ml (4.83 mmol) of triethylamine and 0.52 g (1.61 mmol) of TBTU in 30 ml DMF.

$C_{19}H_{30}Cl_2N_4O_3S$ x 2HCl (538.36)

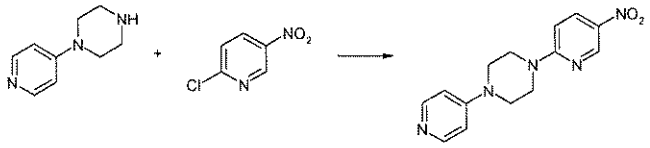
[M+H]+ = 465/467/469

HPLC (Method 1): retention time = 2.15 min

Example 21



21a)



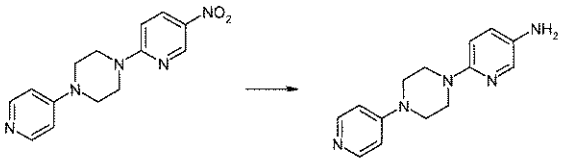
A mixture of 2.06 g (12.62 mmol) of 1-pyridin-4-yl-piperazine (Girindus), 2.00 g (12.62 mmol) of 2-chloro-5-nitropyridine (Fluka) and 50 ml dichloromethane is stirred for 15 min at ambient temperature and then combined with 6.31 ml (12.62 mmol) of 2 M sodium hydroxide solution. The reaction mixture is stirred for 20 hours at ambient temperature and then combined with 300 ml dichloromethane and 100 ml 5% sodium hydrogen carbonate solution. After the phase separation the organic phase is dried on sodium sulphate and evaporated to dryness in vacuo. The crude product is stirred with 100 ml diethyl ether / ethanol 2:1, filtered off and dried.

$C_{14}H_{15}N_5O_2$ (285.30)

[M+H]+ = 286

TLC: silica gel, dichloromethane / ethanol 9:1, Rf value = 0.10

21b)



A mixture of 1.75 g (6.13 mmol) of product from 21a, 0.4 g palladium on charcoal (10%), 100 ml dichloromethane and 50 ml of methanol is hydrogenated for five hours in the autoclave at ambient temperature. Then the catalyst is removed by suction filtering and the filtrate is evaporated to dryness in vacuo. The residue is stirred with 100 ml diethyl ether / ethanol 2:1 and suction filtered. The crude

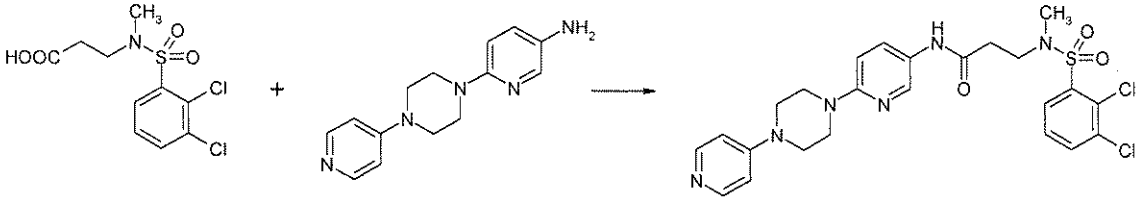
product thus obtained is purified by column chromatography through silica gel (eluant: dichloromethane / methanol / ammonia 95:5:0.5).

$C_{14}H_{17}N_5$ (255.32)

[M+H]+ = 256

TLC: silica gel, dichloromethane / methanol / ammonia 9:1:0.1, Rf value = 0.37

21c)



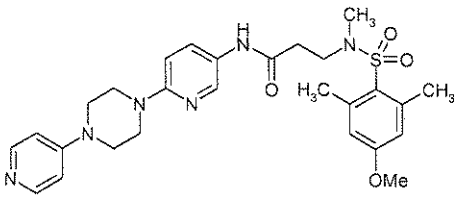
Example 21 is prepared analogously to 1f from 0.11 g (0.35 mmol) of product from 1c, 0.089 g (0.35 mmol) of product from 21b, 0.098 ml (0.70 mmol) of triethylamine and 0.13 g (0.42 mmol) of TBTU in 15 ml THF.

$C_{24}H_{26}Cl_2N_6O_3S$ (549.47)

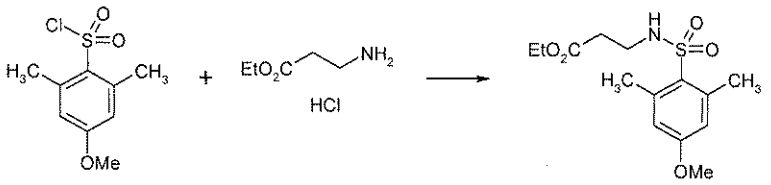
[M+H]+ = 549/551/553

HPLC (Method 4): retention time = 2.7 min

Example 22



22a)



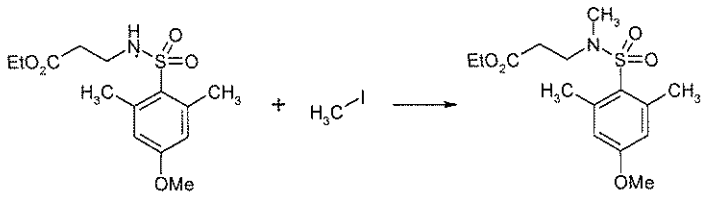
22a is prepared analogously to 3a from 3.00 g (12.78 mmol) of product from 13a, 2.16 g (14.06 mmol) of ß-alanine ethylester hydrochloride, 7.13 ml (51.13 mmol) of triethylamine in 70 ml dichloromethane.

$C_{14}H_{21}NO_5S$ (315.39)

[M+H]+ = 316

TLC: silica gel, petroleum ether / ethyl acetate 2:1, Rf value = 0.23

22b)



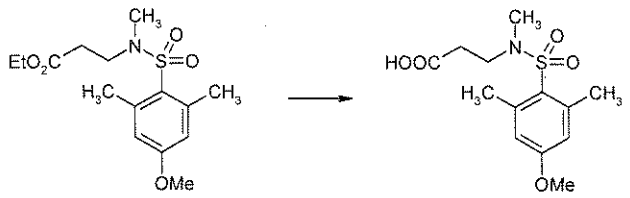
22b is prepared analogously to 3b from 4.06 g (12.87 mmol) of product from 22a, 2.40 ml (38.62 mmol) of methyl iodide, 3.56 g (25.75 mmol) of potassium carbonate anhydrous in 40 ml DMF.

$C_{15}H_{23}NO_5S$ (329.41)

[M+H]+ = 330

TLC: silica gel, petroleum ether / ethyl acetate 2:1, Rf value = 0.36

22c)



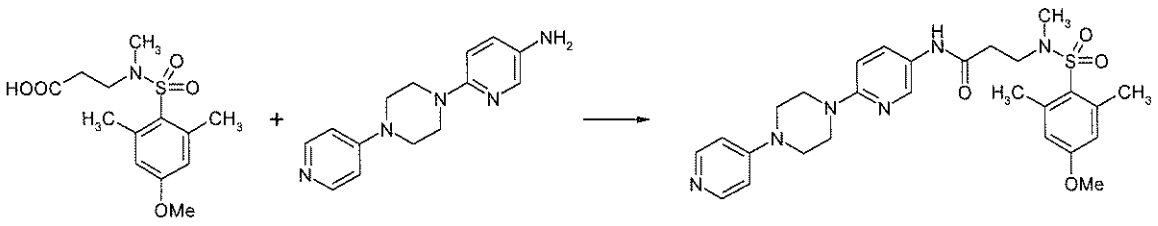
The acid is prepared analogously to 1c from 3.83 g (11.63 mmol) of product from 22b, 2.44 g (58.13 mmol) of lithium hydroxide monohydrate in 30 ml THF and 30 ml of water.

$C_{13}H_{19}NO_5S$ (301.36)

[M+H]+ = 302

TLC: silica gel, petroleum ether / ethyl acetate 1:1, Rf value = 0.12

22d)



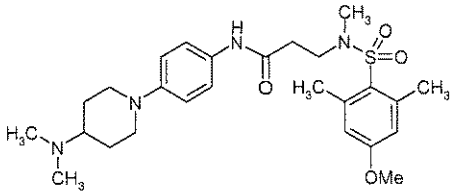
Example 22 is prepared analogously to 1f from 0.13 g (0.42 mmol) of product from 22c, 0.089 g (0.35 mmol) of product from 21b, 0.098 ml (0.70 mmol) of triethylamine and 0.13 g (0.42 mmol) of TBTU in 15 ml THF.

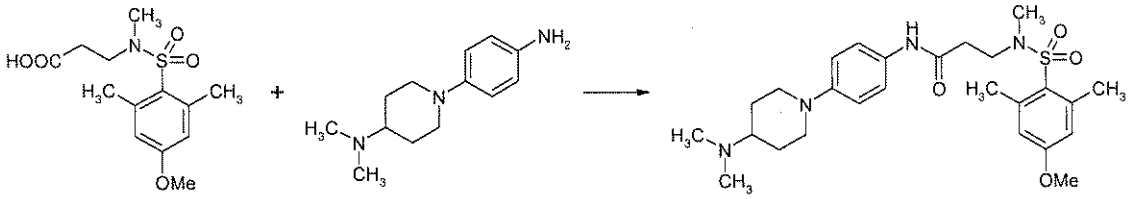
$C_{27}H_{34}N_6O_4S$ (538.66)

[M+H]+ = 539

HPLC (Method 4): retention time = 2.6 min

Example 23





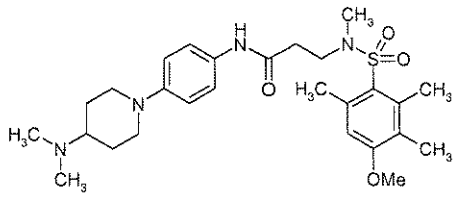
Example 23 is prepared analogously to 1f from 0.30 g (1.00 mmol) of product from 22c, 0.22 g (1.00 mmol) of product from 8b, 0.42 ml (2.99 mmol) of triethylamine and 0.32 g (1.00 mmol) of TBTU in 15 ml DMF.

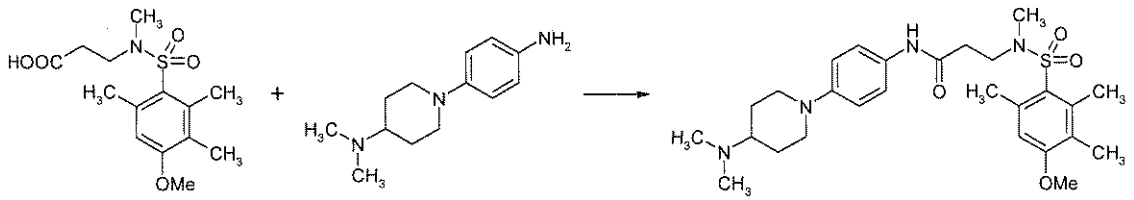
$C_{26}H_{38}N_4O_4S$ (502.67)

[M+H]+ = 503

HPLC (Method 1): retention time = 2.47 min

Example 24





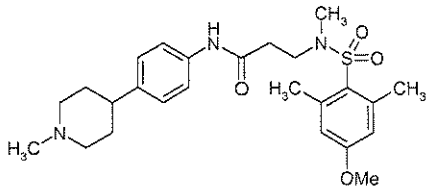
Example 24 is prepared analogously to 1f from 0.25 g (0.80 mmol) of product from 3c, 0.18 g (0.80 mmol) of product from 8b, 0.33 ml (2.39 mmol) of triethylamine and 0.26 g (0.80 mmol) of TBTU in 10 ml DMF.

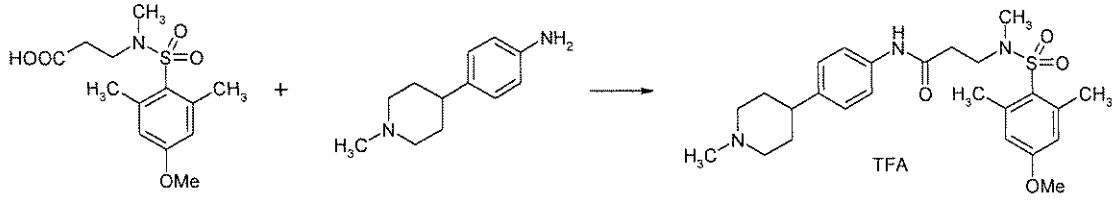
$C_{27}H_{40}N_4O_4S$ (516.70)

[M+H]+ = 517

HPLC (Method 1): retention time = 2.50 min

Example 25





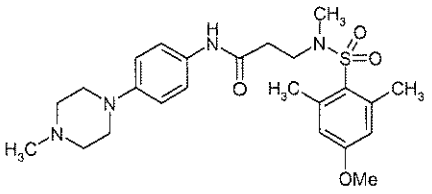
Example 25 is prepared analogously to 1f from 0.20 g (0.66 mmol) of product from 22c, 0.14 g (0.73 mmol) of 4-(1-methylpiperidin-4-yl)-aniline (JW Pharmlab), 0.28 ml (1.99 mmol) of triethylamine and 0.21 g (0.66 mmol) of TBTU in 50 ml THF.

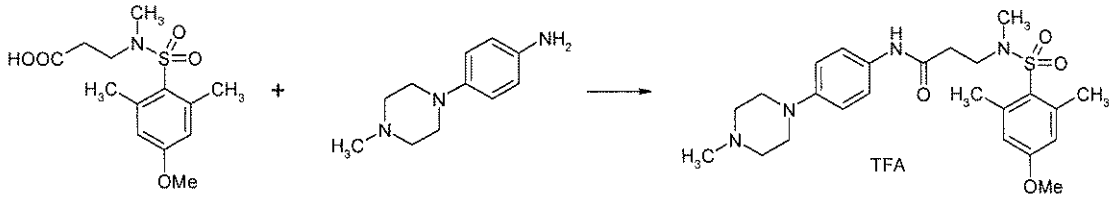
$C_{27}H_{40}N_4O_4S \times C_2HF_3O_2$ (587.65)

[M+H]+ = 474

HPLC (Method 2): retention time = 3.03 min

Example 26





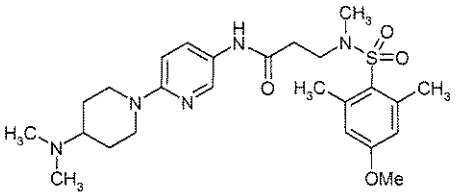
Example 26 is prepared analogously to 1f from 0.20 g (0.66 mmol) of product from 22c, 0.14 g (0.73 mmol) of 4-(4-methylpiperazin-1-yl)-aniline (J. Med. Chem. SIR 48, 7, 2005, 2371-2387), 0.28 ml (1.99 mmol) of triethylamine and 0.21 g (0.66 mmol) of TBTU in 5 ml THF.

$C_{24}H_{34}N_4O_4S \times C_2HF_3O_2$ (588.65)

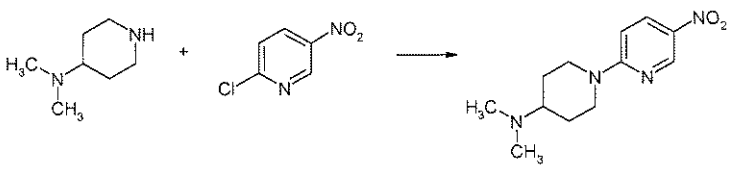
[M+H]+ = 475

HPLC (Method 5): retention time = 1.50 min

Example 27



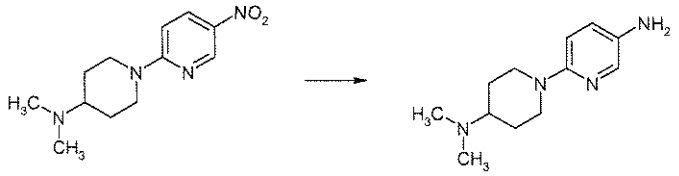
27a)



A mixture of 1.00 g (6.31 mmol) of 2-chloro-5-nitropyridine (Fluka), 1.32 ml (9.46 mmol) of triethylamine and 2 ml of methanol is taken and slowly combined with 1.13 g (8.83 mmol) of 4-dimethylamino-piperidine (Alfa Aesar). The reaction solution is then quenched with semisaturated sodium chloride, the precipitate formed is suction filtered and dried.

$C_{12}H_{18}N_4O_2$ (250.30)

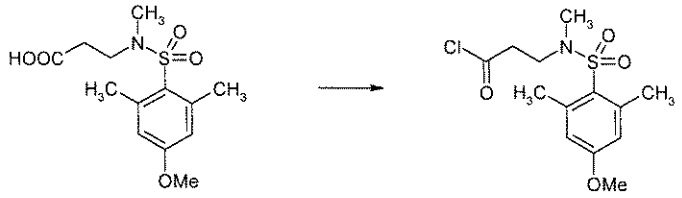
27b)



27b is prepared analogously to 8b from 1.50 g (5.99 mmol) of product from 27a, 0.20 g palladium on charcoal (10%) and 15 ml of methanol.

$C_{12}H_{20}N_4$ (220.31)

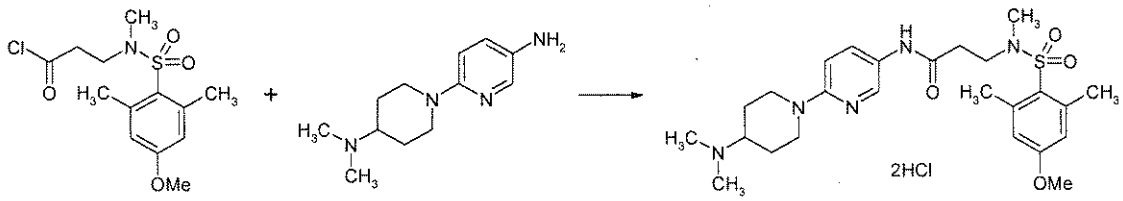
27c)



A mixture of 0.11 g (0.35 mmol) of product from 22c and 2.0 ml of thionyl chloride is stirred for two hours at ambient temperature. The reaction mixture is then evaporated to dryness in vacuo.

$C_{13}H_{18}ClNO_4S$ (319.81)

27d)



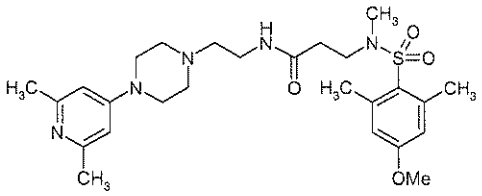
A mixture of 0.11 g (0.34 mmol) of product from 27c, 0.091 g (0.41 mmol) of product from 27b, 0.18 ml (1.03 mmol) of DIPEA and 45 ml THF is stirred for two hours at ambient temperature. The reaction mixture is then evaporated to dryness in vacuo. The crude product is purified by preparative HPLC. Then the hydrochloride is prepared using 4 M HCl in dioxane.

$C_{25}H_{37}N_5O_4S$ x 2HCl (576.58)

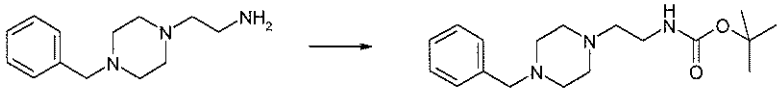
[M+H]+ = 504

HPLC (Method 2): retention time = 2.73 min

Example 28



28a)

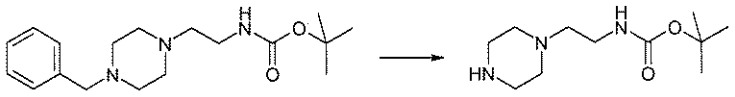


A mixture of 1.50 g (6.84 mmol) of 1-(2-aminoethyl)-4-benzylpiperazine (Maybridge), 1.64 g (7.52 mmol) of Boc-anhydride and 30 ml dichloromethane is stirred for one hour at ambient temperature. Then the reaction solution is diluted with 100 ml dichloromethane and washed with 1 M sodium hydroxide solution and water. The organic phase is dried on sodium sulphate and evaporated to dryness in vacuo.

$C_{18}H_{29}N_3O_2$ (319.44)

HPLC (Method 4): retention time = 2.6 min

28b)



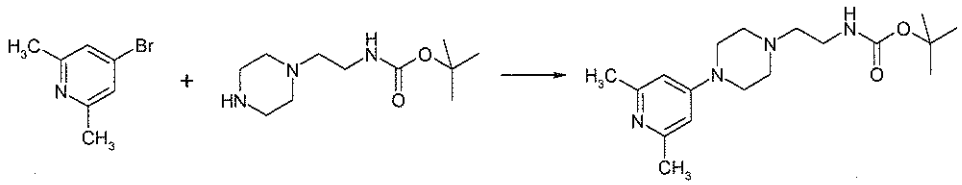
A mixture of 2.10 g (6.57 mmol) of product from 28a, 0.25 g palladium on charcoal (10%) and 30 ml of methanol is hydrogenated for 15 hours at ambient temperature in the autoclave. Then the catalyst is removed by suction filtering and the filtrate is evaporated to dryness in vacuo.

$C_{11}H_{23}N_3O_4$ (229.32)

[M+H]+ = 230

TLC: silica gel, dichloromethane / ethanol 9:1, Rf value = 0.08

28c)



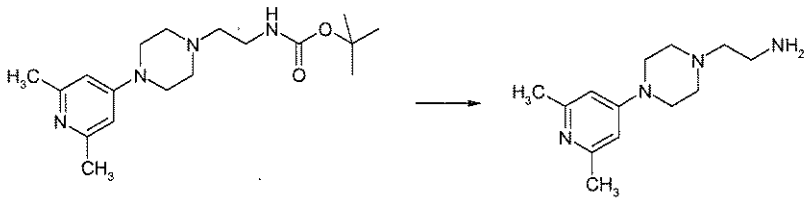
A mixture of 1.18 g (6.32 mmol) of 4-bromo-2,6-dimethylpyridine (Acta Chem. Scand. Ser. B 42, 1988, 373-377), 1.45 g (6.32 mmol) of product from 28b and 2.2 ml DIPEA is heated for 50 min to 130°C in the microwave. The reaction mixture is combined with ethyl acetate and semisaturated potassium carbonate solution and then the phases are separated. The organic phase is dried on sodium sulphate and evaporated to dryness in vacuo. The crude product thus obtained is purified by column chromatography through silica gel (eluant: dichloromethane / methanol / ammonia 95:5:0.5).

$C_{18}H_{30}N_4O_2S$ (334.46)

[M+H]+ = 335

TLC: silica gel, dichloromethane / methanol / ammonia 9:1:0.1, Rf value = 0.37

28d)



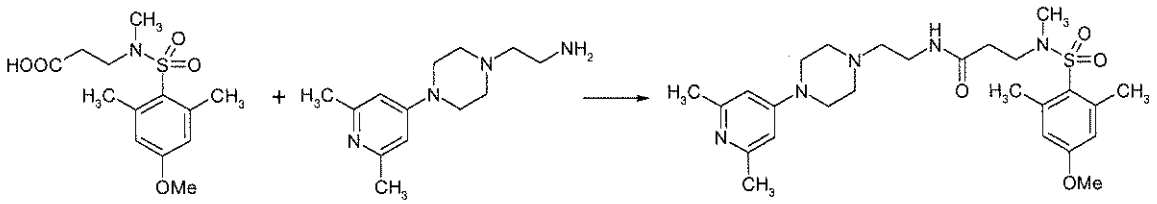
A mixture of 1.61 g (4.81 mmol) of product from 28c, 3.70 ml TFA and 30 ml dichloromethane is stirred for six hours at ambient temperature. The reaction mixture is then diluted with dichloromethane and washed with 5% sodium hydrogen carbonate solution. The aqueous phase is extracted twice more with ethyl acetate. The combined organic phases are dried on sodium sulphate and evaporated to dryness in vacuo. The crude product thus obtained is purified by column chromatography through silica gel (eluant: dichloromethane / methanol / ammonia 90:10:1).

$C_{13}H_{22}N_4$ (234.34)

[M+H]+ = 235

TLC: silica gel, dichloromethane / methanol / ammonia 9:1:0.1, Rf value = 0.10

28e)



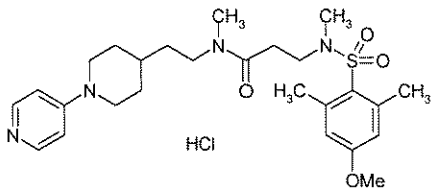
Example 28 is prepared analogously to 1f from 0.11 g (0.35 mmol) of product from 22c, 0.082 g (0.35 mmol) of product from 28d, 0.098 ml (0.70 mmol) of triethylamine and 0.13 g (0.42 mmol) of TBTU in 7 ml THF and 1 ml DMF.

$C_{26}H_{39}N_5O_4S$ (517.69)

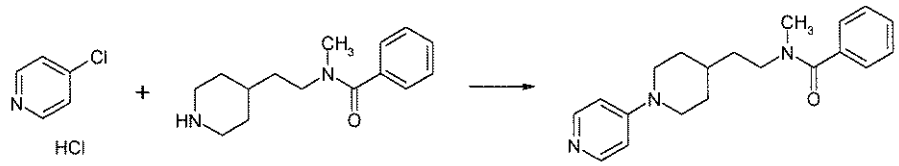
[M+H]+ = 518

HPLC (Method 4): retention time = 2.4 min

Example 29



29a)

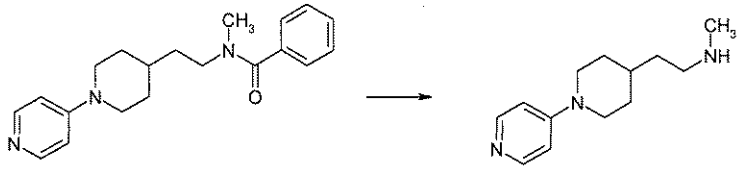


29a is prepared analogously to 28c from 0.12 g (0.80 mmol) of 4-chloropyridine hydrochloride (Aldrich), 0.20 g (0.80 mmol) of *N*-methyl-N-(2-piperidin-4-yl-ethyl)-benzamide (J. Med. Chem. 33, 1990, 1880-1887), 0.23 ml (1.68 mmol) of triethylamine in 5 ml of ethanol.

$C_{20}H_{25}N_3O$ (323.43)

[M+H]+ = 324

29b)



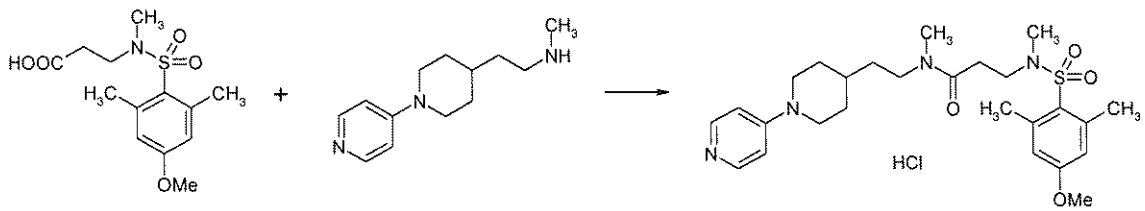
A mixture of 0.52 g (1.61 mmol) of product from 29a, 10 ml of 2 M potassium hydroxide solution and 10 ml of ethanol is refluxed for 30 hours. The reaction mixture is evaporated down by half in vacuo and then extracted with dichloromethane. The organic extracts are dried on sodium sulphate and evaporated to dryness in vacuo.

$C_{13}H_{21}N_3$ (219.33)

[M+H]+ = 220

TLC: silica gel, dichloromethane / methanol / ammonia 8:2:0.01, Rf value = 0.46

29c)



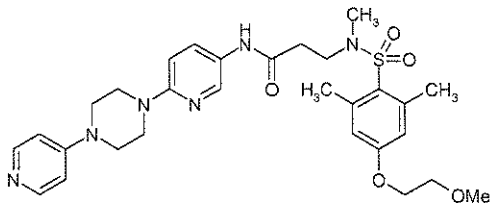
Example 29 is prepared analogously to 1f from 0.14 g (0.46 mmol) of product from 22c, 0.10 g (0.46 mmol) of product from 29b, 0.15 ml (1.09 mmol) of triethylamine and 0.16 g (0.50 mmol) of TBTU in 30 ml THF and 5 ml DMF.

$C_{26}H_{38}N_4O_4S$ x HCl (539.13)

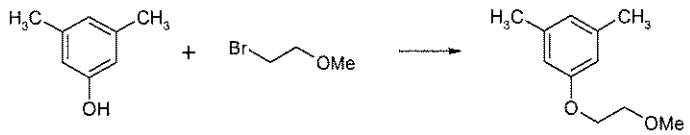
[M+H]+ = 503

TLC: silica gel, dichloromethane / methanol / ammonia 8:2:0.01, Rf value = 0.41

Example 30



30a)



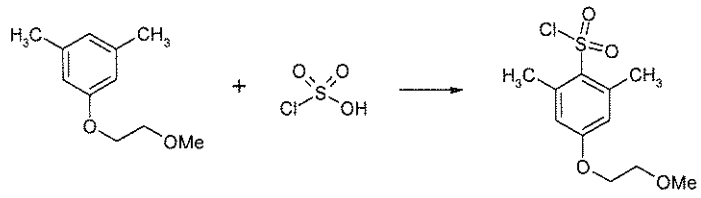
A mixture of 3.25 g (26.60 mmol) of 3,5-dimethylphenol (Aldrich), 3.20 g (28.52 mmol) of potassium-*tert*-butoxide and 40 ml DMSO is stirred for one hour at ambient temperature. Then 3.80 g (27.34 mmol) of bromoethylmethylether (Aldrich) is added dropwise thereto and the mixture is stirred for another two hours at ambient temperature. The reaction mixture is poured onto water and extracted with diethyl ether. The organic extracts are washed with water and saturated sodium chloride solution, dried on sodium sulphate and evaporated to dryness in vacuo.

$C_{11}H_{16}O_2$ (180.24)

[M+H]+ = 181

TLC: silica gel, petroleum ether/ethyl acetate 9:1, Rf value = 0.31

30b)

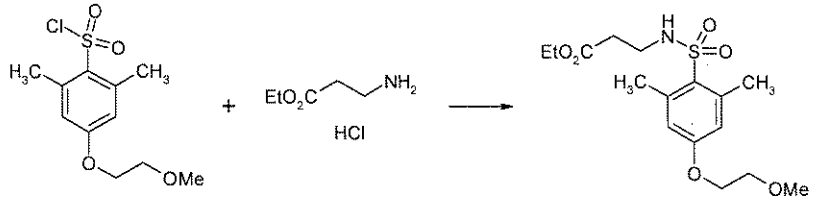


30b is prepared analogously to 13a from 4.30 g (23.86 mmol) of product from 30a and 5.60 g (48.06 mmol) of chlorosulphonic acid in 100 ml dichloromethane.

$C_{11}H_{15}ClO_4S$ (278.75)

TLC: silica gel, petroleum ether/ethyl acetate 9:1, Rf value = 0.06

30c)



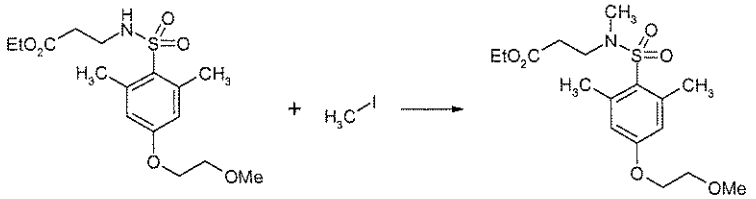
30a is prepared analogously to 3a from 1.70 g (6.10 mmol) of product from 30b, 1.20 g (7.81 mmol) of ß-alanine ethylester hydrochloride, 2.60 ml (18.65 mmol) of triethylamine in 30 ml dichloromethane.

$C_{16}H_{25}NO_6S$ (359.44)

[M+H]+ = 360

TLC: silica gel, dichloromethane / methanol 19:1, Rf value = 0.51

30d)

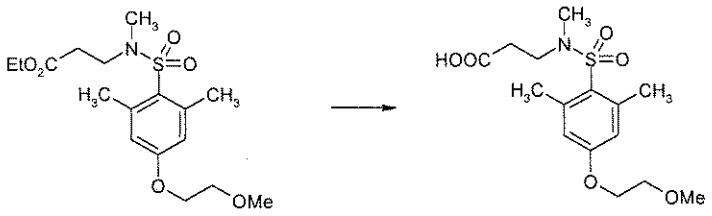


30d is prepared analogously to 3b from 1.90 g (5.29 mmol) of product from 30c, 1.10 g (7.75 mmol) of methyl iodide, 1.50 g (10.85 mmol) of anhydrous potassium carbonate in 30 ml DMF.

$C_{17}H_{27}NO_6S$ (373.47)

[M+H]+ = 374

30e)

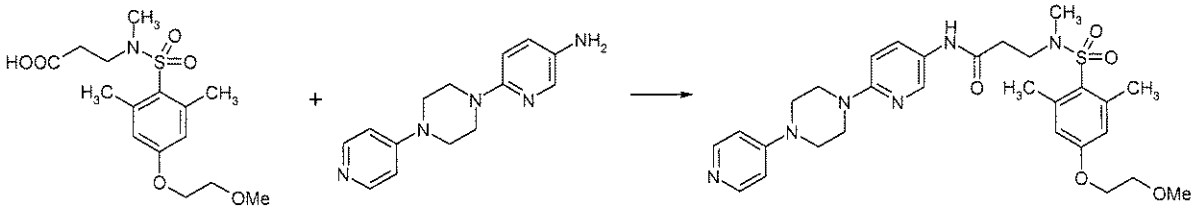


The acid is prepared analogously to 1c from 1.70 g (4.55 mmol) of product from 30d, 0.80 g (20.00 mmol) of sodium hydroxide in 30 ml of ethanol and 10 ml of water.

$C_{15}H_{23}NO_6S$ (345.41)

[M+H]+ = 346

30f)



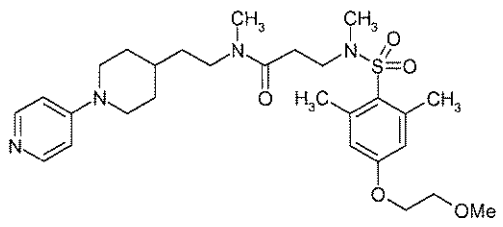
Example 30 is prepared analogously to 1f from 0.14 g (0.39 mmol) of product from 30e, 0.10 g (0.39 mmol) of product from 21b, 0.10 ml (0.99 mmol) of triethylamine and 0.14 g (0.44 mmol) of TBTU in 30 ml THF and 5 ml DMF.

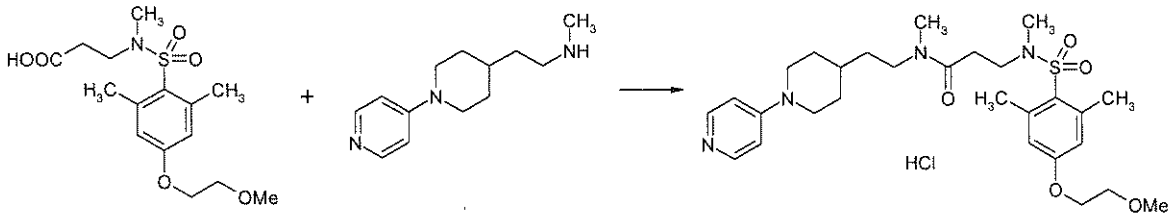
$C_{29}H_{38}N_6O_5S$ (582.72)

[M+H]+ = 583

TLC: silica gel, dichloromethane / methanol / ammonia 8:2:0.01, Rf value = 0.44

Example 31





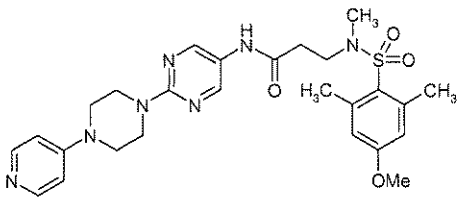
Example 31 is prepared analogously to 1f from 0.16 g (0.46 mmol) of product from 30e, 0.10 g (0.46 mmol) of product from 29b, 0.11 ml (1.09 mmol) of triethylamine and 0.16 g (0.50 mmol) of TBTU in 30 ml THF and 5 ml DMF.

$C_{28}H_{42}N_4O_5S$ x HCl (583.18)

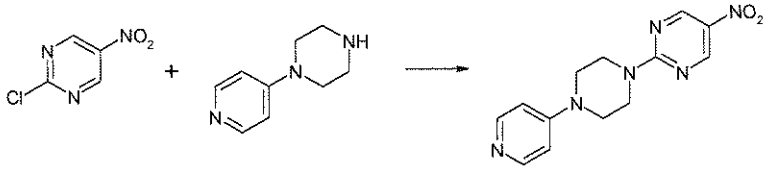
[M+H]+ = 547

TLC: silica gel, dichloromethane / methanol / ammonia 8:2:0.01, Rf value = 0.52

Example 32



32a)



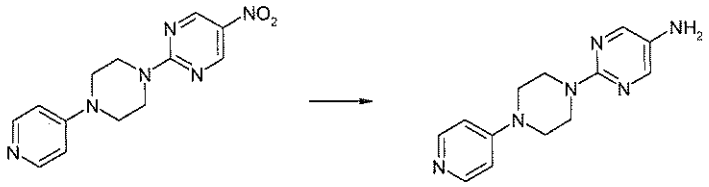
A mixture of 3.00 g (18.81 mmol) of 2-chloro-5-nitropyrimidine (Apin), 3.07 g (18.81 mmol) of 1-(4-pyridyl)-piperazine (Girindus), 9.40 ml (18.81 mmol) of 2 M sodium hydroxide solution in 80 ml dichloromethane is stirred for 2.5 hours at ambient temperature. Then the reaction mixture is diluted with 100 ml dichloromethane and washed with 5% sodium hydrogen carbonate solution. The organic phase is dried on sodium sulphate and evaporated to dryness in vacuo. The crude product is triturated with a mixture of 50 ml of water and 30 ml ethyl acetate, filtered off and dried.

$C_{13}H_{14}N_6O_2$ (286.29)

[M+H]+ = 287

HPLC (Method 4): retention time = 2.6 min

32b)



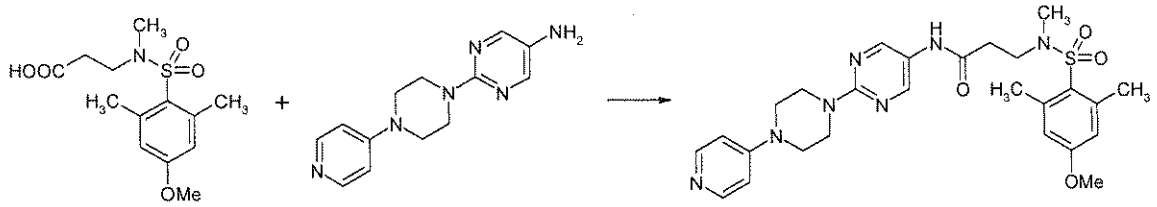
32b is prepared analogously to 21b from 1.93 g (6.74 mmol) of product from 32a and 0.3 g palladium on charcoal (10 %) in 60 ml dichloromethane and 30 ml of methanol.

$C_{13}H_{16}N_6$ (256.31)

[M+H]+ = 257

TLC: silica gel, dichloromethane / methanol 8:2, Rf value = 0.11

32c)



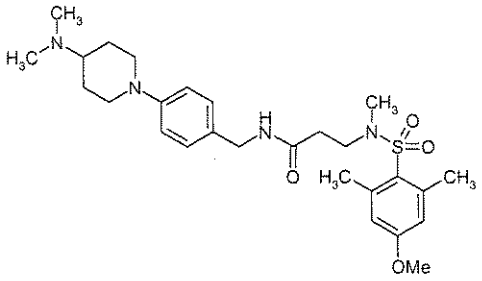
Example 32 is prepared analogously to 1f from 0.11 g (0.35 mmol) of product from 22c, 0.090 g (0.35 mmol) of product from 32b, 0.098 ml (0.70 mmol) of triethylamine and 0.13 g (0.42 mmol) of TBTU in 7 ml THF and 1 ml DMF.

$C_{26}H_{33}N_7O_4S$ (539.65)

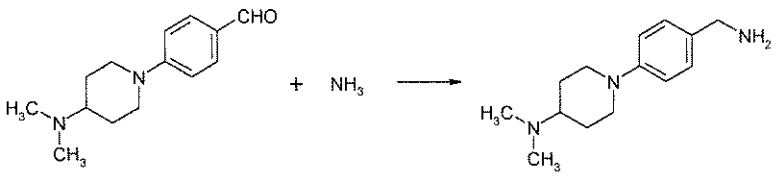
[M+H]+ = 540

HPLC (Method 4): retention time = 2.9 min

Example 33



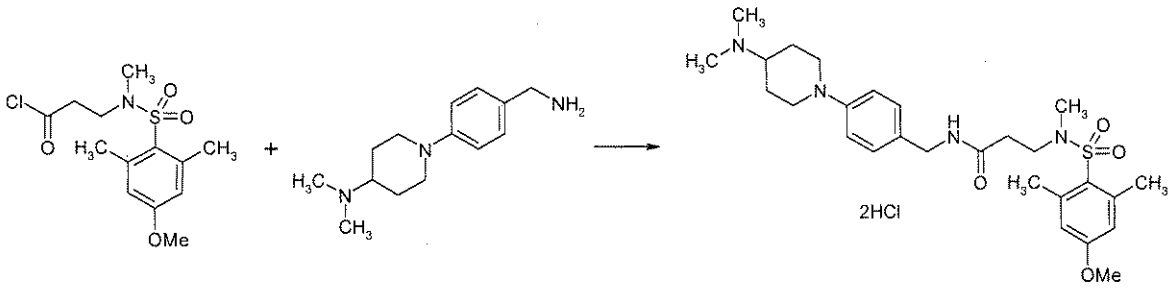
33a)



A mixture of 0.68 g (2.91 mmol) of 4-(4-dimethylamino-piperidin-1-yl)-benzaldehyde (Tetrahedron 57, 2001, 4781-4785), 15 ml of 2 M ammonia in ethanol and 0.10 g Raney nickel is hydrogenated at ambient temperature in the autoclave. Then the catalyst is filtered off and the filtrate is evaporated to dryness in vacuo.

$C_{14}H_{23}N_3$ (233.35)

33b)



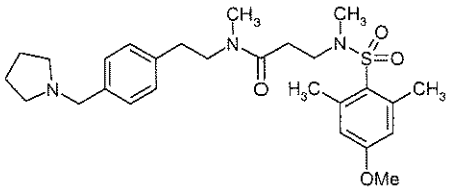
Example 33 is prepared analogously to 27d from 0.27 g (0.84 mmol) of product from 27c, 0.63 g (2.68 mmol) of product from 33a, 0.22 ml (1.26 mmol) of DIPEA in 3 ml dichloromethane.

$C_{27}H_{40}N_4O_4S$ x 2HCl (589.62)

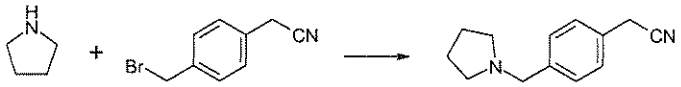
[M+H]+ = 517

HPLC (Method 5): retention time = 1.46 min

Example 34



34a)



A mixture of 4.97 ml (59.50 mmol) of pyrrolidine and 100 ml dichloromethane is slowly combined with 5.00 g (23.80 mmol) of (4-bromomethyl-phenyl)-acetonitrile (Tetrahedron 47, 1991, 3969-3980) while cooling with an ice bath. Then the reaction mixture is heated to ambient temperature, washed with water, dried on magnesium sulphate and evaporated to dryness in vacuo.

$C_{13}H_{16}N_2$ (200.28)

[M+H]+ = 201

TLC: silica gel, dichloromethane / methanol / ammonia 9:1:0.1, Rf value = 0.58

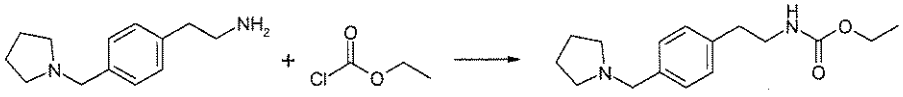
34b)

A mixture of 4.70 g (23.47 mmol) of product from 34a, 0.5 g Raney nickel and 50 ml of methanolic ammonia solution is hydrogenated in the autoclave at 50°C. Then the catalyst is filtered off and the filtrate is evaporated to dryness in vacuo.

$C_{13}H_{20}N_2$ (204.31)

[M+H]+ = 205

34c)

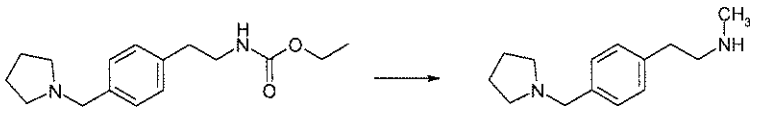


A mixture of 4.09 g (20.00 mmol) of product from 34b, 5.62 ml (40.00 mmol) of triethylamine and 100 ml dichloromethane is slowly combined with 2.17 ml (22.00 mmol) of ethyl chloroformate (Aldrich) while cooling with an ice bath. Then the mixture is stirred for five hours at ambient temperature. The reaction mixture is then quenched with water and extracted with MTB-ether. The organic extracts are washed twice with water, dried on magnesium sulphate and evaporated to dryness in vacuo. The crude product thus obtained is purified by column chromatography through silica gel (eluant: dichloromethane / methanol / ammonia 9:1:0.1).

$C_{16}H_{24}N_2O_2$ (276.37)

[M+H]+ = 277

34d)

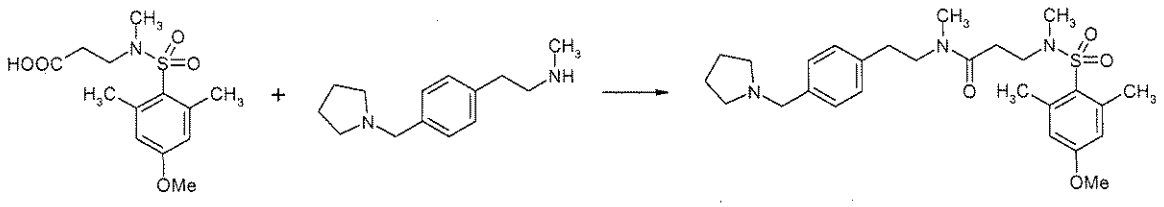


A mixture of 3.60 g (13.03 mmol) of product from 34c and 25 ml THF is slowly combined with 51.05 ml (51.05 mmol) of 1 M lithium aluminium hydride in THF (Aldrich). Then the mixture is stirred for two hours at ambient temperature and two hours at 70°C. The reaction mixture is then quenched with water and 15% sodium hydroxide solution and stirred for another hour at ambient temperature. The precipitate formed is filtered off and the filtrate is evaporated to dryness in vacuo. The crude product thus obtained is purified by column chromatography through silica gel (eluant: dichloromethane / methanol / ammonia 9:1:0.1).

$C_{14}H_{22}N_2$ (218.34)

[M+H]+ = 219

34e)



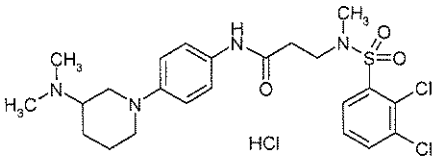
Example 34 is prepared analogously to 1f from 0.11 g (0.35 mmol) of product from 22c, 0.076 g (0.35 mmol) of product from 34d, 0.098 ml (0.70 mmol) of triethylamine and 0.13 g (0.42 mmol) of TBTU in 7 ml THF and 1 ml DMF.

$C_{27}H_{39}N_3O_4S$ (501.68)

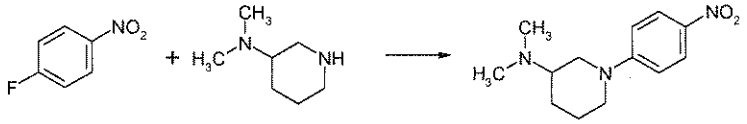
[M+H]+ = 502

HPLC (Method 4): retention time = 3.1 min

Example 35



35a)



A mixture of 0.33 g (2.34 mmol) of 1-fluoro-4-nitrobenzene (Aldrich), 0.30 g (2.34 mmol) of 3-dimethylamino-piperidine (Chess), 0.46 ml (3.27 mmol) of triethylamine and 4 ml DMF is stirred for six hours at ambient temperature. The reaction mixture is then quenched with water and extracted with dichloromethane. The organic extracts are washed with saturated sodium chloride solution, dried on sodium sulphate and evaporated to dryness in vacuo.

$C_{13}H_{19}N_3O_2$ (249.31)

[M+H]+ = 250

TLC: silica gel, dichloromethane / methanol / ammonia 9:1:0.1, Rf value = 0.56

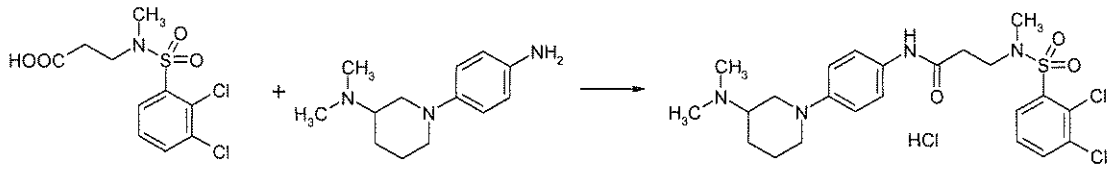
35b)

A mixture of 0.25 g (1.00 mmol) of product from 35a, 30 mg Raney nickel and 10 ml ethyl acetate is hydrogenated in the autoclave at ambient temperature. The catalyst is filtered off and the filtrate is evaporated to dryness in vacuo.

$C_{13}H_{21}N_3$ (219.33)

TLC: silica gel, dichloromethane / methanol / ammonia 9:1:0.1, Rf value = 0.25

35c)



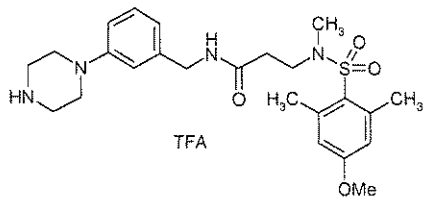
Example 35 is prepared analogously to 1f from 0.16 g (0.50 mmol) of product from 1c, 0.11 g (0.50 mmol) of product from 35b, 0.14 ml (1.00 mmol) of triethylamine and 0.16 g (0.50 mmol) of TBTU in 3 ml DMF.

$C_{23}H_{30}Cl_2N_4O_3S$ x HCl (539.14)

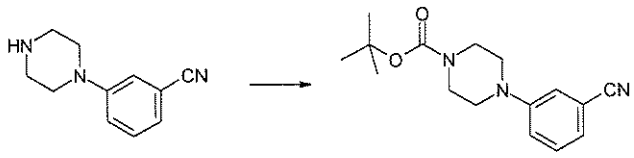
[M+H]+ = 513/515/517

HPLC (Method 1): retention time = 2.43 min

Example 36



36a)



A mixture of 2.50 g (13.35 mmol) of 3-piperazin-1-yl-benzonitrile (Tetrahedron 55, 1999, 13285-13300), 3.00 g (13.75 mmol) of Boc-anhydride, 2.40 ml (13.78 mmol) of DIPEA and 50 ml THF is stirred for four hours at ambient temperature and then

evaporated to dryness in vacuo. The residue is taken up in water and extracted with diethyl ether. The organic extracts are dried on sodium sulphate and evaporated to dryness in vacuo.

$C_{16}H_{21}N_3O_2$ (287.36)

[M+Na]+ = 310

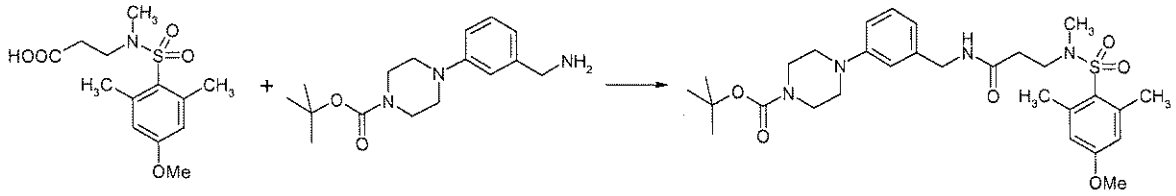
36b)

36b is prepared analogously to 34b from 4.40 g (15.31 mmol) of product from 36a, 0.7 g Raney nickel and 45 ml of methanolic ammonia solution.

$C_{16}H_{25}N_3O_2$ (291.39)

[M+H]+ = 292

36c)



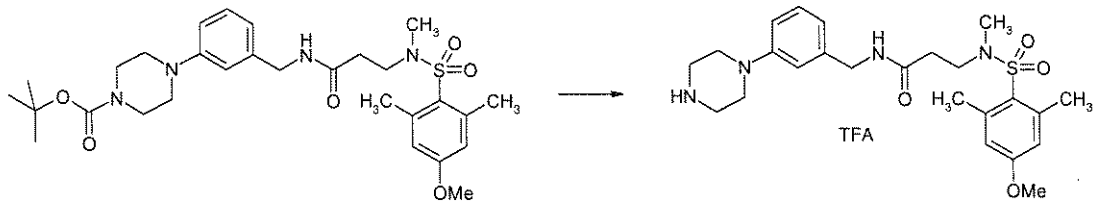
36c is prepared analogously to 1f from 0.40 g (1.33 mmol) of product from 22c, 0.43 g (1.46 mmol) of product from 36b, 0.56 ml (3.98 mmol) of triethylamine and 0.43 g (1.33 mmol) of TBTU in 10 ml THF.

$C_{29}H_{42}N_4O_6S$ (574.73)

M+H]+ = 575

TLC: silica gel, dichloromethane / methanol 9:1, Rf value = 0.53

36d)



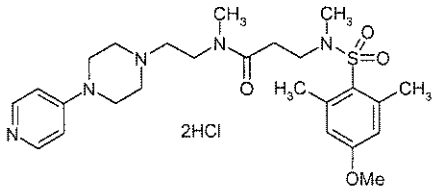
Example 36 is prepared analogously to 18b from 0.50 g (0.57 mmol) of product from 36c, 0.44 ml TFA in 5 ml dichloromethane.

$C_{18}H_{28}Cl_2N_4O_3S \times C_2HF_3O_2$ (588.64)

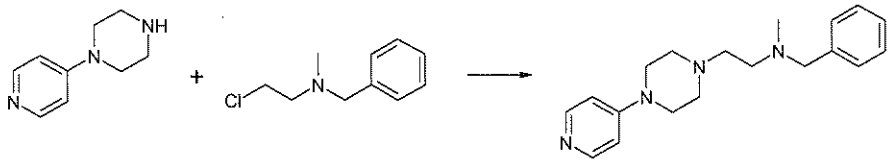
[M+H]+ = 475

HPLC (Method 2): retention time = 2.95 min

Example 37



37a)



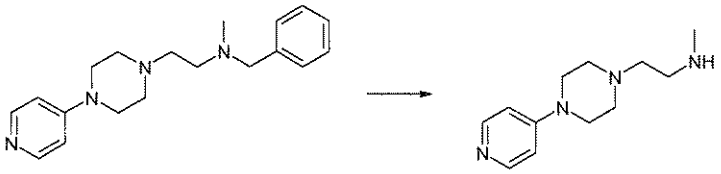
A mixture of 2.00 g (12.25 mmol) of 1-(4-pyridyl)-piperazine (Girindus), 1.65 g (14.70 mmol) of potassium-tert-butoxide and 50 ml DMSO is stirred for 30 min at ambient temperature and then combined with 2.25 g (12.25 mmol) of 1-benzylmethylamino-2-chloroethane (Chem. Pharm. Bull. 45, 1997, 996-1007). The reaction mixture is stirred overnight at ambient temperature and then poured onto ice water. It is extracted four times with dichloromethane. The organic extracts are dried on sodium sulphate and evaporated to dryness in vacuo. The crude product thus obtained is purified by column chromatography through silica gel (eluant: dichloromethane / methanol / ammonia 9:1:0.1).

$C_{19}H_{26}N_4$ (310.44)

[M+H]+ = 311

TLC: silica gel, dichloromethane / methanol / ammonia 9:1:0.1, Rf value = 0.22

37b)



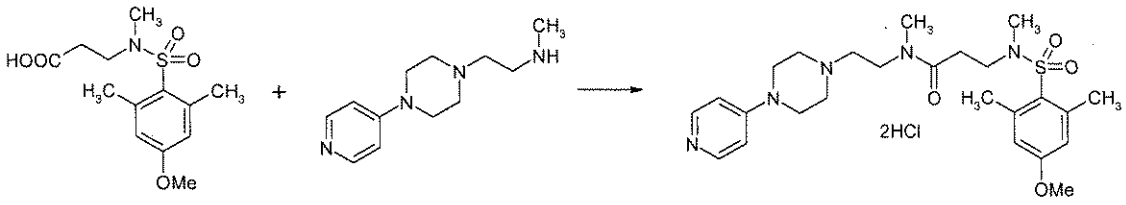
A mixture of 1.78 g (5.73 mmol) of product from 37a, 0.40 g palladium hydroxide and 50 ml of methanol is hydrogenated at 40°C in the autoclave. The catalyst is filtered off and the filtrate is evaporated to dryness in vacuo. The crude product thus obtained is purified by column chromatography through silica gel (eluant: dichloromethane / methanol / ammonia 9:1:0.1).

$C_{12}H_{20}N_4$ (220.31)

[M+H]+ = 221

TLC: silica gel, dichloromethane / methanol / ammonia 9:1:0.1, Rf value = 0.13

37c)



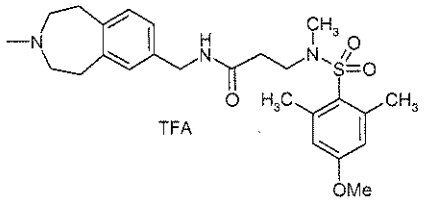
Example 37 is prepared analogously to 1f from 0.11 g (0.35 mmol) of product from 22c, 0.072 g (0.35 mmol) of product from 37b, 0.098 ml (0.70 mmol) of triethylamine and 0.13 g (0.42 mmol) of TBTU in 7 ml THF.

$C_{25}H_{37}N_5O_4S$ x 2HCl (576.58)

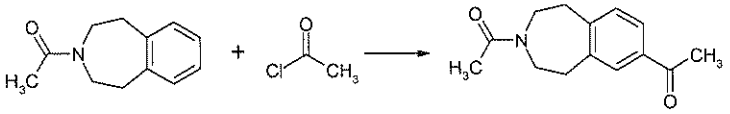
[M+H]+ = 504

HPLC (Method 4): retention time = 2.5 min

Example 38



38a)

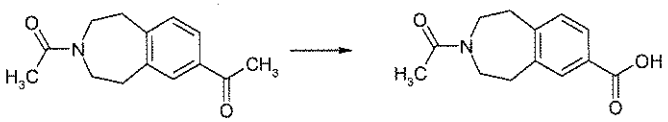


A mixture of 4.44 g (33.29 mmol) of aluminium chloride (Merck) and 16 ml of dichloroethane is taken and 1.24 ml (17.44 mmol) of acetyl chloride (Aldrich) is slowly added while cooling with an ice bath. The mixture is stirred for 30 min at ambient temperature. Then 3.00 g (15.85 mmol) of 1-(1,2,4,5-tetrahydrobenzo[d]azepin-3-yl)-ethanone (J. Med. Chem. 46, 2003, 4952-4964) in 7 ml of dichloroethane slowly added to the reaction mixture. After two hours' stirring at ambient temperature the reaction mixture is poured onto a mixture of 6 M HCl and ice. After the phase separation the aqueous phase is extracted another three times with dichloromethane. The combined organic phases are washed with water, dried on sodium sulphate and evaporated to dryness in vacuo. The crude product thus obtained is triturated with diethyl ether, filtered off and dried.

$C_{14}H_{17}NO_2$ (231.29)

[M+H]+ = 232

38b)



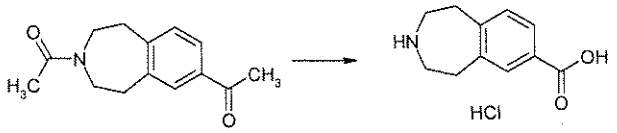
A mixture of 2.86 g (12.37 mmol) of product from 38a and 79 ml 2.5 M sodium hydroxide solution is slowly combined at ambient temperature with 2.48 ml (48.23 mmol) of bromine. The reaction mixture is then stirred for one hour at ambient temperature. The precipitate formed is filtered off and the filtrate is extracted with

MTB-ether. The aqueous phase is then mixed with concentrated HCl and a little sodium disulphite solution while cooling with an ice bath. The precipitate formed is filtered off and dried in the circulating air dryer at 30°C.

$C_{13}H_{15}NO_3$ (233.26)

[M+H]+ = 234

38c)

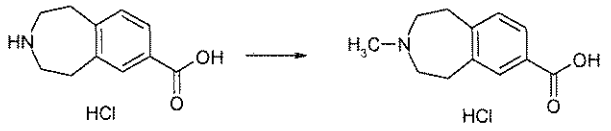


A mixture of 2.12 g (9.09 mmol) of product from 38b and 20 ml 6 M HCl is heated for 3.5 days to 100°C. The reaction mixture is then cooled with a mixture of ice and ethanol. The precipitate formed is filtered off, washed with a little cooled acetone and diethyl ether and dried in the desiccator.

$C_{11}H_{13}NO_2$ x HCl (227.69)

[M+H]+ = 192

38d)

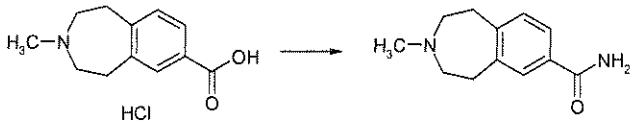


First 0.94 ml (17.83 mmol) of 50% sodium hydroxide solution, then 2.66 ml (35.66 mmol) of 37% formalin solution are slowly added to a mixture of 2.03 g (8.92 mmol) of product from 38c and 3.36 ml (89.16 mmol) of formic acid. The reaction mixture is heated for two hours to 70°C and then evaporated to dryness in vacuo. The residue is combined with water and concentrated HCl and again evaporated to dryness. The crude product is triturated with a little ice-cold water, filtered off and dried in the circulating air dryer at 60°C.

$C_{12}H_{15}NO_2$ x HCl (241.71)

[M+H]+ = 206

38e)



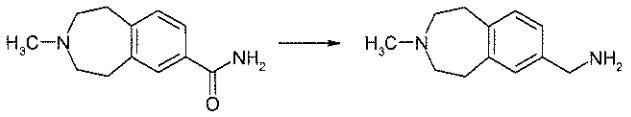
38e is prepared analogously to 1f from 2.00 g (8.27 mmol) of product from 38d, 18.20 ml (9.10 mmol) of ammonia 0.5 M in dioxane (Aldrich), 3.46 ml (24.82 mmol) of triethylamine and 3.19 g (9.93 mmol) of TBTU in 30 ml THF.

$C_{12}H_{16}N_2O$ (204.27)

[M+H]+ = 205

HPLC (Method 2): retention time = 1.54 min

38f)



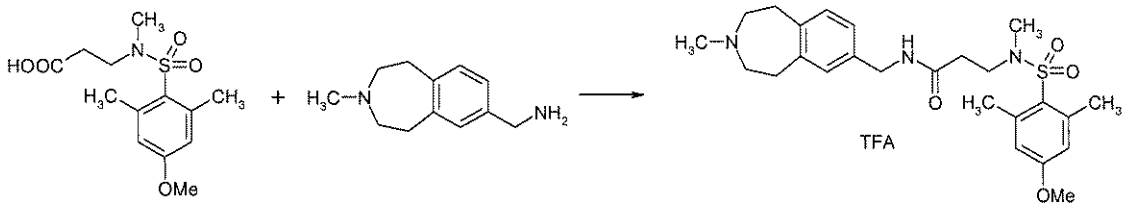
A mixture of 5.20 ml (5.20 mmol) of lithium aluminium hydride 1 M in THF (Aldrich) and 18 ml THF is heated to 50°C and slowly combined with 0.84 g (2.64 mmol) of product from 38e. The reaction mixture is then stirred for 30 min at 50°C. It is then cooled to -20°C and the reaction mixture is quenched first with a mixture of water and THF, then with 2 M sodium hydroxide solution. It is stirred for one hour at ambient temperature. The precipitate formed is filtered off, the filtrate is evaporated to dryness in vacuo. The residue is taken up in dichloromethane and washed with saturated sodium hydrogen sulphate solution. The organic phase is dried on sodium sulphate and evaporated to dryness in vacuo.

$C_{12}H_{18}N_2$ (190.28)

[M+H]+ = 191

HPLC (Method 2): retention time = 2.21 min

38g)



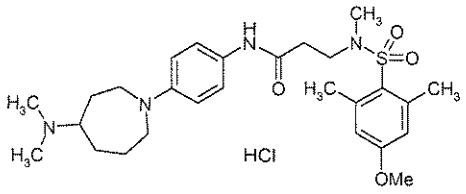
Example 38 is prepared analogously to 1f from 0.19 g (0.63 mmol) of product from 22c, 0.12 g (0.63 mmol) of product from 38f, 0.26 ml (1.89 mmol) of triethylamine and 0.20 g (0.63 mmol) of TBTU in 5 ml THF.

$C_{25}H_{35}N_3O_4S \times C_2HF_3O_2$ (587.65)

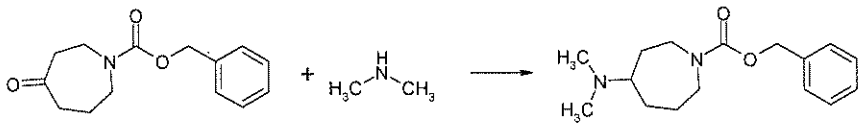
[M+H]+ = 474

HPLC (Method 4): retention time = 2.98 min

Example 39



39a)



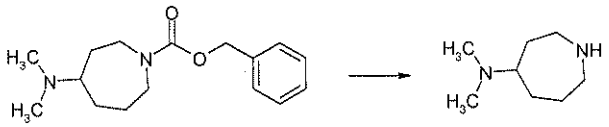
A mixture of 1.50 g (6.07 mmol) of benzyl 4-oxo-azepan-1-carboxylate (Tyger), 20 ml (40.00 mmol) of dimethylamine 2 M in THF (Aldrich) and 0.34 ml (6.07 mmol) of acetic acid is stirred for 20 min at ambient temperature and then combined with 3.82 g (18.00 mmol) of sodium triacetoxyborohydride (Aldrich). The mixture is stirred overnight at ambient temperature. The reaction mixture is then mixed with saturated sodium hydrogen carbonate solution and extracted with ethyl acetate. The organic extracts are washed with saturated sodium chloride solution, dried on sodium sulphate and evaporated to dryness in vacuo. The crude product thus obtained is purified by column chromatography through silica gel (eluant: dichloromethane / 4-12 % (methanol + 10% ammonia)).

$C_{16}H_{24}N_2O_2$ (276.37)

[M+H]+ = 277

HPLC (Method 1): retention time = 2.12 min

39b)



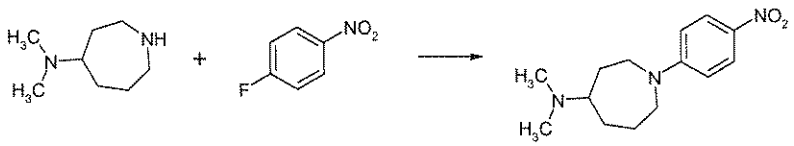
A mixture of 1.00 g (3.62 mmol) of product from 39a, 0.10 g palladium on charcoal (10%) and 30 ml of methanol is hydrogenated at ambient temperature in the autoclave. The catalyst is then filtered off, the filtrate is evaporated to dryness in vacuo.

$C_8H_{18}N_2$ (142.24)

[M+H]+ = 143

TLC: silica gel, dichloromethane / methanol / ammonia 9:1:0.1, Rf value = 0.12

39c)



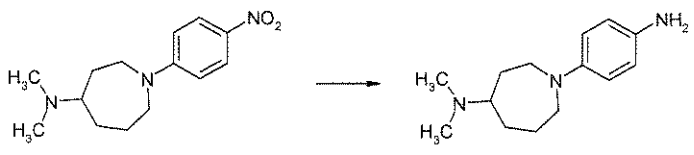
39c is prepared analogously to 1d from 0.56 g (4.37 mmol) of product from 39b, 0.64 g (4.50 mmol) of 4-fluoro-nitrobenzene (Aldrich), 0.65 ml (4.60 mmol) of triethylamine in 5 ml DMF.

$C_{14}H_{21}N_3O_2$ (263.34)

[M+H]+ = 264

TLC: silica gel, dichloromethane / methanol / ammonia 9:1:0.1, Rf value = 0.60

39d)

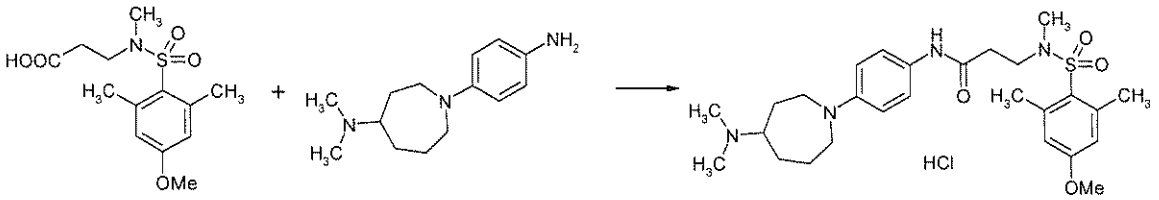


39d is prepared analogously to 8b from 0.94 g (3.55 mmol) of product from 39c and 0.10 g palladium on charcoal (10%) in 30 ml of methanol.

$C_{14}H_{23}N_3O_2$ (233.35)

TLC: silica gel, dichloromethane / methanol / ammonia 9:1:0.1, Rf value = 0.15

39e)



Example 39 is prepared analogously to 1f from 0.30 g (1.00 mmol) of product from 22c, 0.23 g (1.00 mmol) of product from 39d, 0.42 ml (3.00 mmol) of triethylamine and 0.32 g (1.00 mmol) of TBTU in 15 ml DMF.

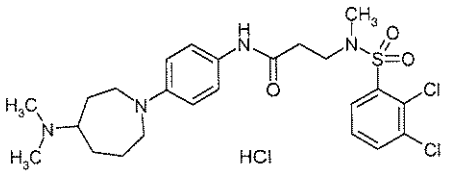
$C_{27}H_{40}N_4O_4S$ x HCl (553.16)

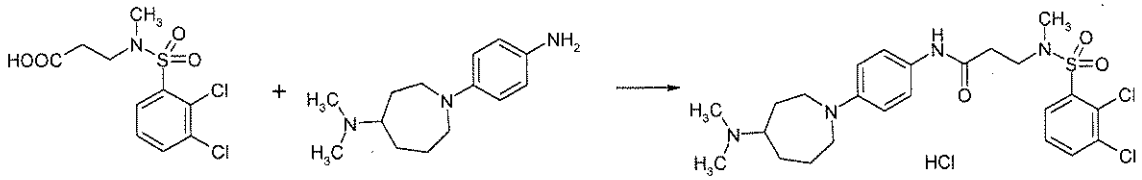
[M+H]+ = 517

TLC: silica gel, dichloromethane / methanol / ammonia 9:1:0.1, Rf value = 0.42

HPLC (Method 5): retention time = 1.50 min

Example 40





Example 40 is prepared analogously to 1f from 0.16 g (0.50 mmol) of product from 1c, 0.12 g (0.50 mmol) of product from 39d, 0.21 ml (1.50 mmol) of triethylamine and 0.16 g (0.50 mmol) of TBTU in 5 ml DMF.

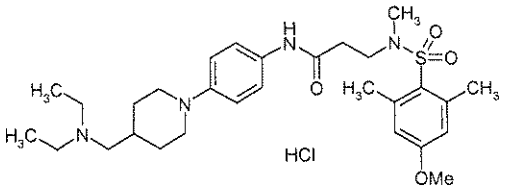
$C_{24}H_{32}Cl_2N_4O_3S$ x HCl (563.97)

[M+H]+ = 527/529/531

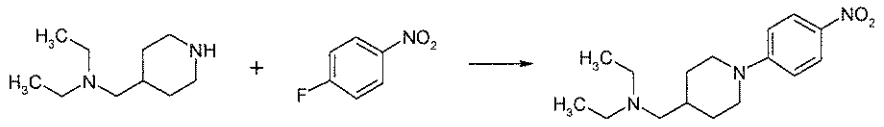
TLC: silica gel, dichloromethane / methanol / ammonia 6:1:0.2, Rf value = 0.48

HPLC (Method 5): retention time = 1.53 min

Example 41



41a)



41a is prepared analogously to 1d from 1.00 g (5.87 mmol) of diethyl-piperidin-4-ylmethyl-amine (Chem. Pharm. Bull. 42, 1994, 74-84), 0.83 g (5.87 mmol) of 4-fluoro-nitrobenzene (Aldrich), 1.14 ml (8.20 mmol) of triethylamine in 12 ml DMF.

$C_{16}H_{25}N_3O_2$ (291.39)

[M+H]+ = 292

TLC: silica gel, dichloromethane / ethanol 9:1, Rf value = 0.5

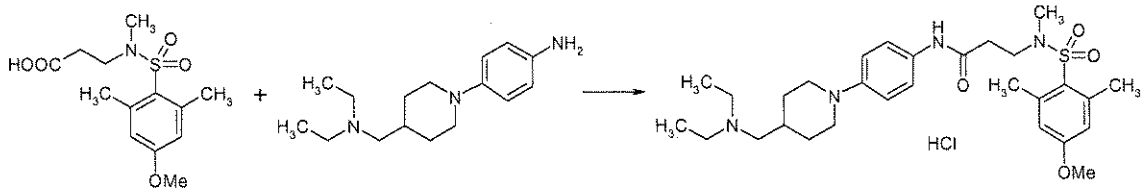
41b)

A mixture of 0.40 g (1.37 mmol) of product from 41a, 0.10 g palladium on charcoal (10%) and 30 ml of methanol is hydrogenated at ambient temperature in the autoclave. The catalyst is then filtered off, the filtrate is evaporated to dryness in vacuo.

$C_{16}H_{27}N_3$ (261.41)

TLC: silica gel, dichloromethane / ethanol 9:1, Rf value = 0.1

41c)



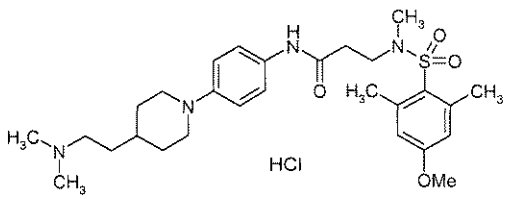
Example 41 is prepared analogously to 1f from 0.40 g (1.34 mmol) of product from 22c, 0.35 g (1.34 mmol) of product from 41b, 0.47 ml (3.35 mmol) of triethylamine and 0.43g (1.34 mmol) of TBTU in 7 ml THF and 1 ml DMF.

$C_{29}H_{44}N_4O_4S$ x HCl (581.21)

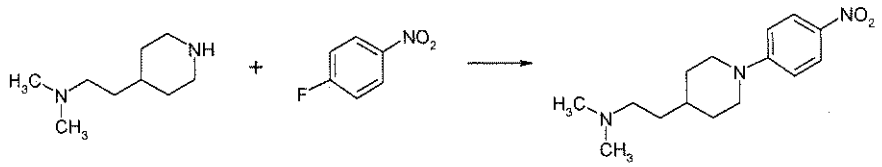
[M+H]+ = 545

HPLC (Method 5): retention time = 1.42 min

Example 42



42a)



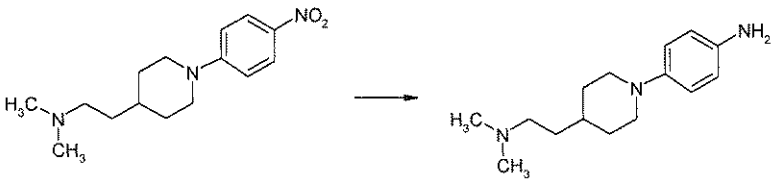
42a is prepared analogously to 1d from 1.88 g (12.00 mmol) of dimethyl-(2-piperidin-4-yl-ethyl)-amine (J. Med. Chem. 36, 1993, 162-165), 1.69 g (12.00 mmol) of 4-fluoro-nitrobenzene (Aldrich), 2.37 ml (17.00 mmol) of triethylamine in 15 ml DMF.

$C_{15}H_{23}N_3O_2$ (277.36)

[M+H]+ = 278

TLC: silica gel, dichloromethane / ethanol 9:1, Rf value = 0.2

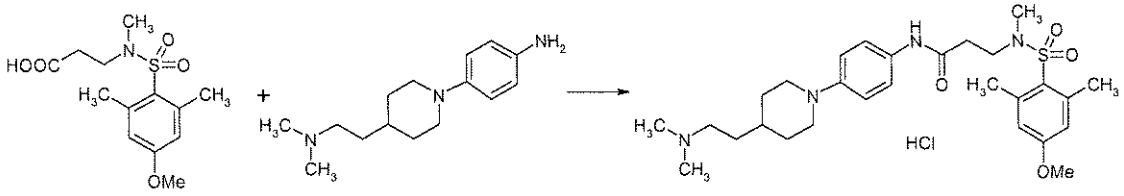
42b)



A mixture of 0.30 g (1.08 mmol) of product from 42a, 0.10 g palladium on charcoal (10%) and 30 ml of methanol is hydrogenated at ambient temperature in the autoclave. The catalyst is then filtered off, the filtrate is evaporated to dryness in vacuo.

$C_{15}H_{25}N_3$ (247.38)

42c)



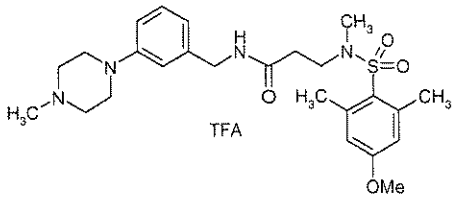
Example 42 is prepared analogously to 1f from 0.33 g (1.08 mmol) of product from 22c, 0.27 g (1.08 mmol) of product from 42b, 0.38 ml (2.70 mmol) of triethylamine and 0.35g (1.08 mmol) of TBTU in 7 ml THF and 1 ml DMF.

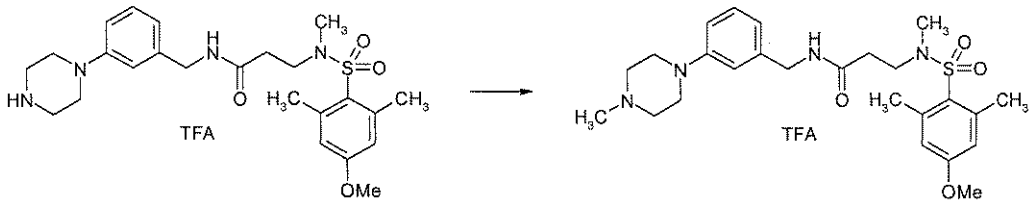
$C_{28}H_{42}N_4O_4S$ (530.72)

[M+H]+ = 531

HPLC (Method 5): retention time = 1.41 min

Example 43





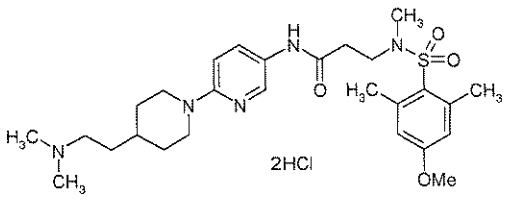
A mixture of 0.15 g (0.25 mmol) of product from 36d, 0.025 ml (0.40 mmol) of methyl iodide (Aldrich), 0.10 ml (0.75 mmol) of potassium carbonate and 5 ml acetonitrile is stirred overnight at ambient temperature. The reaction mixture is then combined with 10% TFA, the product is separated off by preparative HPLC.

$C_{25}H_{36}N_4O_4S \times C_2HF_3O_2$ (602.67)

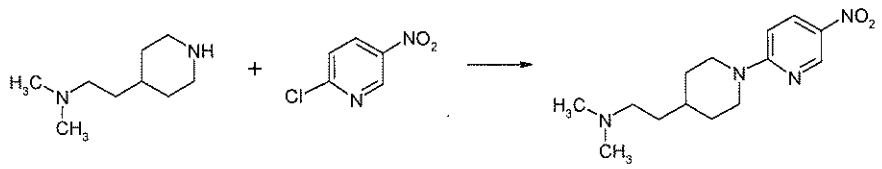
[M+H]+ = 489

HPLC (Method 2): retention time = 2.99 min

Example 44



44a)

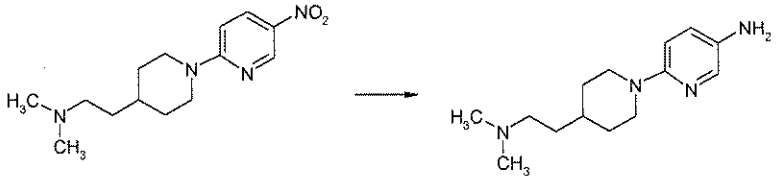


A mixture of 0.72 g (4.61 mmol) of dimethyl-(2-piperidin-4-yl-ethyl)-amine (J. Med. Chem. 36, 1993, 162-165), 0.73 g (4.61 mmol) of 2-chloro-5-nitropyridine (Fluka), 1.30 g (9.41 mmol) of potassium carbonate and 100 ml THF is stirred at ambient temperature over the weekend. The precipitate is filtered off, the filtrate is evaporated to dryness in vacuo. The crude product thus obtained is purified by column chromatography through silica gel (eluant: dichloromethane / methanol 19:1 to 4:1).

$C_{14}H_{22}N_4O_2$ (278.35)

[M+H]+ = 279

44b)

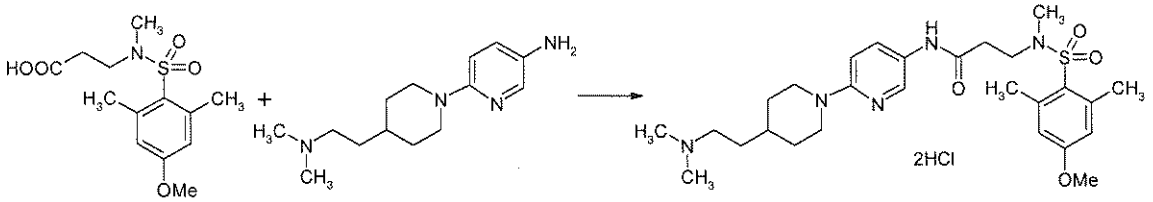


A mixture of 0.26 g (0.93 mmol) of product from 44a, 0.05 g palladium on charcoal (10%) and 30 ml of methanol is hydrogenated at ambient temperature in the autoclave. The catalyst is then filtered off, the filtrate is evaporated to dryness in vacuo.

$C_{14}H_{24}N_4$ (248.37)

[M+H]+ = 249

44c)



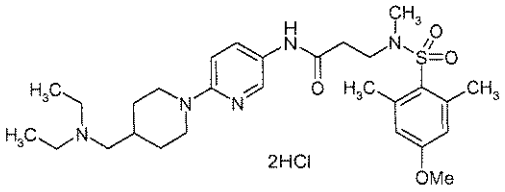
Example 44 is prepared analogously to 1f from 0.12 g (0.40 mmol) of product from 22c, 0.10 g (0.40 mmol) of product from 44b, 0.069 ml (0.50 mmol) of triethylamine and 0.14g (0.44 mmol) of TBTU in 40 ml THF and 5 ml DMF.

$C_{27}H_{41}N_5O_4S$ x 2HCl (604.63)

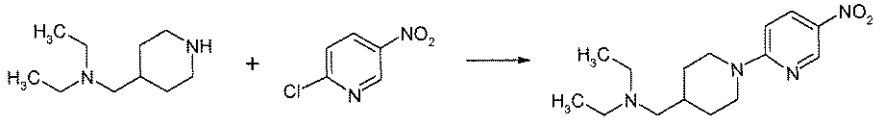
[M+H]+ = 532

HPLC (Method 5): retention time = 1.40 min

Example 45



45a)

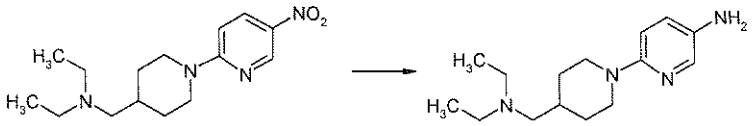


45a is prepared analogously to 44a from 1.00 g (5.87 mmol) of diethyl-piperidin-4-ylmethyl-amine (Chem. Pharm. Bull. 42, 1994, 74-84), 0.93 g (5.87 mmol) of 2-chloro-5-nitropyridine (Fluka) and 1.70 g (12.30 mmol) of potassium carbonate in 100 ml THF.

$C_{15}H_{24}N_4O_2$ (292.38)

[M+H]+ = 293

45b)

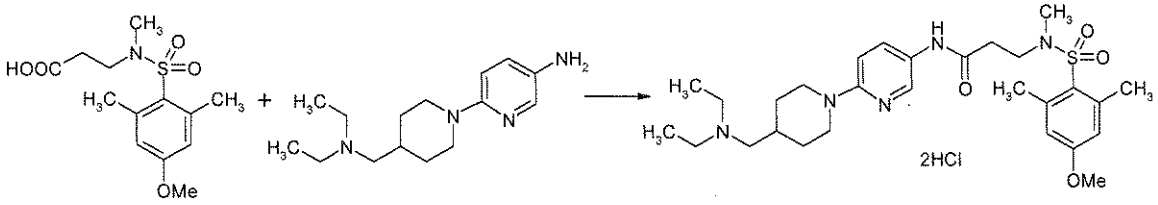


A mixture of 0.20 g (0.68 mmol) of product from 45a, 0.03 g palladium on charcoal (10%) and 30 ml of methanol is hydrogenated at ambient temperature in the autoclave. The catalyst is then filtered off, the filtrate is evaporated to dryness in vacuo.

$C_{15}H_{26}N_4$ (262.39)

[M+H]+ = 263

45c)



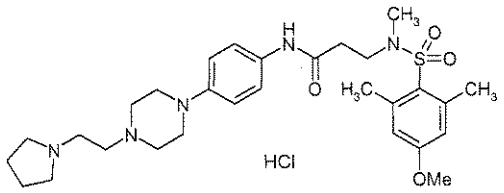
Example 45 is prepared analogously to 1f from 0.16 g (0.53 mmol) of product from 22c, 0.14 g (0.53 mmol) of product from 45b, 0.096 ml (0.69 mmol) of triethylamine and 0.19 g (0.58 mmol) of TBTU in 40 ml THF and 5 ml DMF.

$C_{28}H_{43}N_5O_4S$ x 2HCl (618.66)

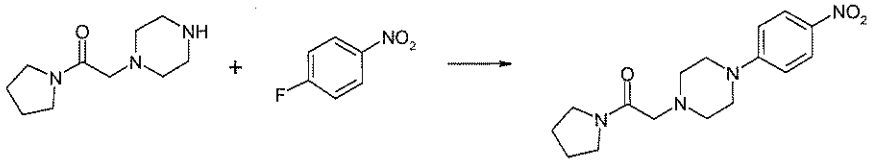
[M+H]+ = 546

HPLC (Method 5): retention time = 1.40 min

Example 46



46a)



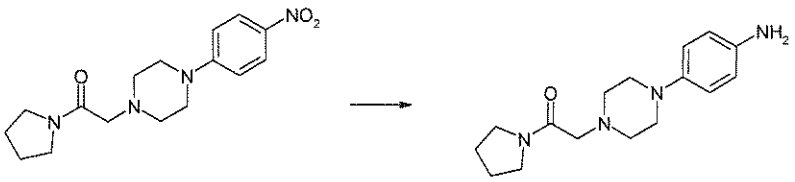
46a is prepared analogously to 1d from 3.00 g (15.21 mmol) of 2-piperazin-1-yl-1-pyrrolidin-1-yl-ethanone (Chess), 2.15 g (15.21 mmol) of 1-fluoro-4-nitrobenzene (Aldrich) and 3.07 ml (22.00 mmol) of triethylamine in 25 ml DMF.

$C_{16}H_{22}N_4O_3$ (318.37)

[M+H]+ = 319

TLC: silica gel, dichloromethane / ethanol 9:1, Rf value = 0.4

46b)

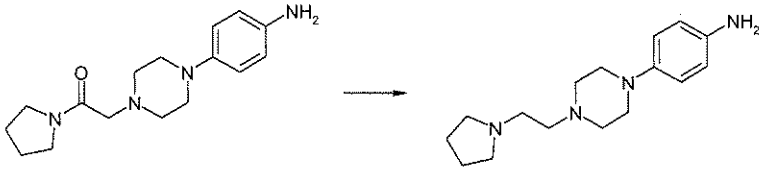


A mixture of 3.00 g (9.42 mmol) of product from 46a, 0.30 g palladium on charcoal (10%) and 200 ml of methanol is hydrogenated at ambient temperature in the autoclave. The catalyst is then filtered off, the filtrate is evaporated to dryness in vacuo.

$C_{16}H_{24}N_4O$ (288.39)

TLC: silica gel, dichloromethane / ethanol 9:1, Rf value = 0.42

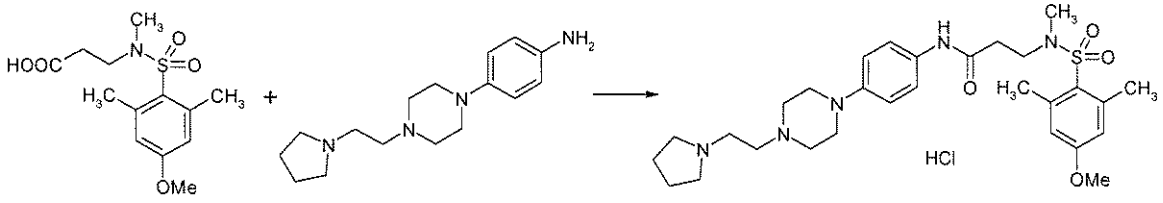
46c)



30.00 ml (30.00 mmol) of lithium aluminium hydride 1 M in THF (Aldrich) is placed in 50 ml THF and at ambient temperature combined with a mixture of 2.70 g (9.36 mmol) of product from 46b and 20 ml THF. The reaction mixture is then stirred for three hours at ambient temperature and then combined with 20% sodium hydroxide solution while cooling with an ice bath. The precipitate formed is filtered off, the filtrate is evaporated to dryness in vacuo.

$C_{16}H_{26}N_4$ (274.40)

46d)



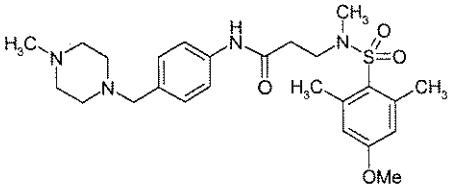
Example 46 is prepared analogously to 1f from 0.30 g (1.00 mmol) of product from 22c, 0.27 g (1.00 mmol) of product from 46c, 0.35 ml (2.50 mmol) of triethylamine and 0.32 g (1.00 mmol) of TBTU in 7 ml THF and 1 ml DMF.

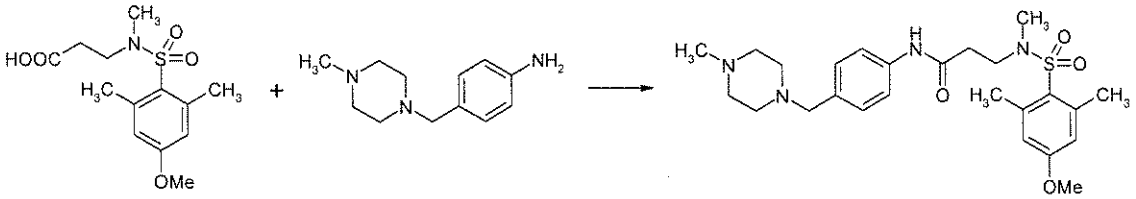
$C_{29}H_{43}N_5O_4S$ x HCl (594.21)

[M+H]+ = 558

HPLC (Method 5): retention time = 1.43 min

Example 47





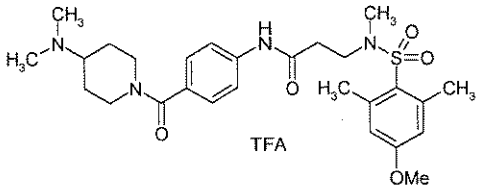
Example 47 is prepared analogously to 1f from 0.20 g (0.66 mmol) of product from 22c, 0.14 g (0.66 mmol) of 4-(4-methyl-piperazin-1-ylmethyl)-phenylamine (Med. Chem. Res. 9, 1999, 149-161), 0.28 ml (1.99 mmol) of triethylamine and 0.21 g (0.66 mmol) of TBTU in 5 ml THF.

$C_{25}H_{36}N_4O_4S$ (488.64)

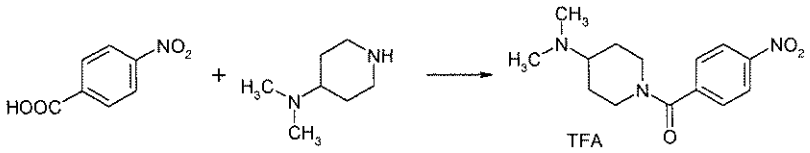
[M+H]+ = 489

HPLC (Method 5): retention time = 1.42 min

Example 48



48a)



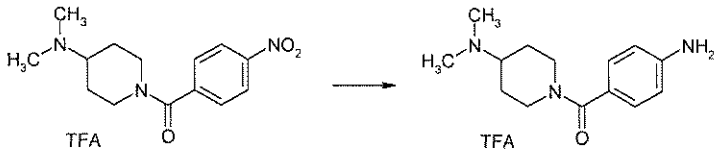
48a is prepared analogously to 1f from 0.24 g (1.45 mmol) of 4-nitrobenzoic acid (Aldrich), 0.19 g (1.45 mmol) of 4-dimethylamino-piperidine (Alfa Aesar), 0.21 ml (1.52 mmol) of triethylamine and 0.49 g (1.52 mmol) of TBTU in 8 ml DMF.

$C_{14}H_{19}N_3O_3 \times C_2HF_3O_2$ (391.34)

[M+H]+ = 278

HPLC (Method 2): retention time = 2.29 min

48b)



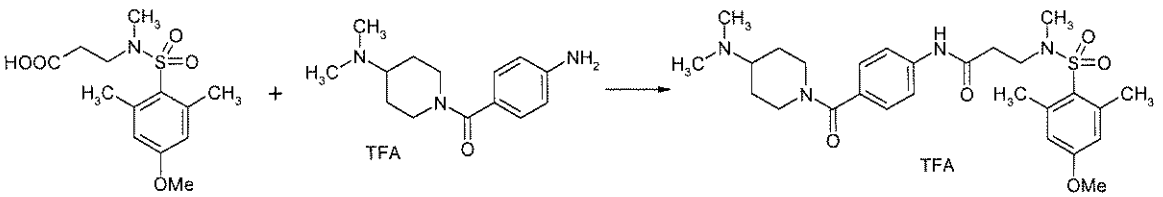
A mixture of 0.36 g (0.92 mmol) of product from 48a, 0.092 g palladium on charcoal (10%) and 5 ml of methanol is hydrogenated at ambient temperature in the autoclave. The catalyst is then filtered off, the filtrate is evaporated to dryness in vacuo.

$C_{14}H_{21}N_3O \times C_2HF_3O_2$ (361.36)

[M+H]+ = 248

HPLC (Method 2): retention time = 0.66 min

48c)



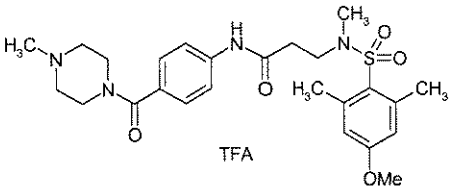
Example 48 is prepared analogously to 1f from 0.15 g (0.50 mmol) of product from 22c, 0.18 g (0.50 mmol) of product from 48b, 0.21 ml (1.49 mmol) of triethylamine and 0.16 g (0.50 mmol) of TBTU in 3 ml THF.

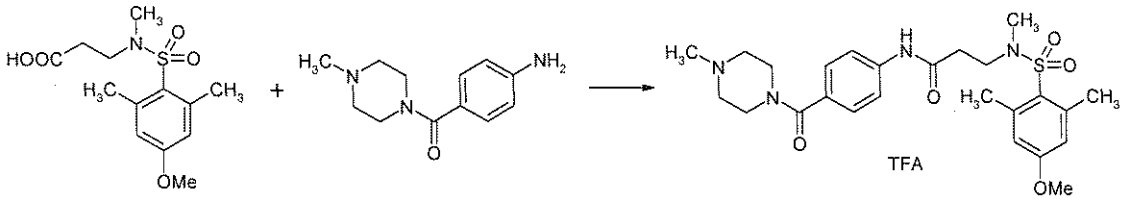
$C_{27}H_{38}N_4O_5S \times C_2HF_3O_2$ (644.70)

[M+H]+ = 531

HPLC (Method 5): retention time = 1.48 min

Example 49





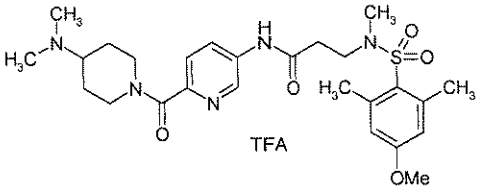
Example 49 is prepared analogously to 1f from 0.15 g (0.50 mmol) of product from 22c, 0.11 g (0.50 mmol) of (4-aminophenyl)-(4-methylpiperazin-1-yl)-methanone (J. Org. Chem. 24, 1959, 459-463), 0.21 ml (1.49 mmol) of triethylamine and 0.16 g (0.50 mmol) of TBTU in 3 ml THF.

$C_{25}H_{34}N_4O_5S \times C_2HF_3O_2$ (616.65)

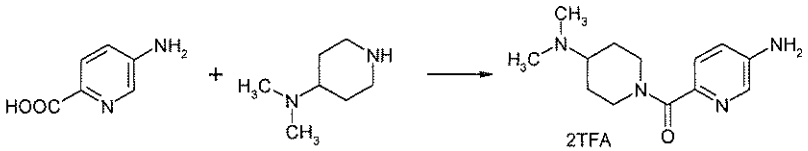
[M+H]+ = 503

HPLC (Method 5): retention time = 1.47 min

Example 50



50a)

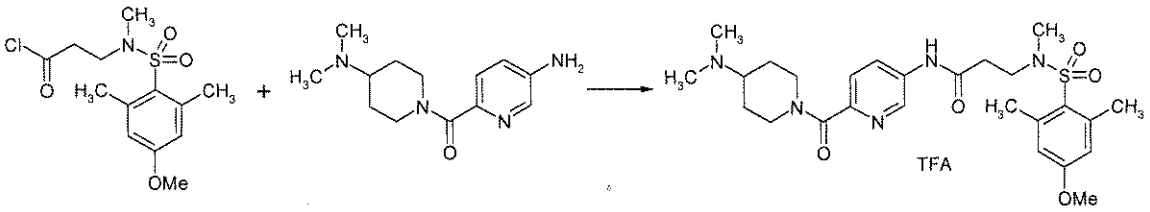


50a is prepared analogously to 1f from 0.60 g (4.34 mmol) of 5-amino-pyridine-2-carboxylic acid (Pharm. Acta Helv. 44, 1969, 637-643), 0.56 g (4.34 mmol) of 4-dimethylamino-piperidine (Alfa Aesar), 0.64 ml (4.56 mmol) of triethylamine and 1.46 g (4.56 mmol) of TBTU in 24 ml DMF.

$C_{13}H_{20}N_4O \times 2C_2HF_3O_2$ (476.37)

HPLC (Method 2): retention time = 0.65 min

50b)



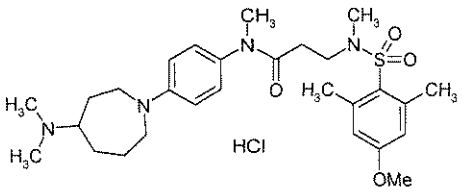
A mixture of 0.64 g (1.99 mmol) of product from 27c, 1.90 g (2.39 mmol) of product from 50a, 0.08 g (0.33 mmol) of DMAP and 16 ml chlorobenzene is heated to 15°C for 39 hours. The reaction mixture is then evaporated to dryness in vacuo. The product is obtained by preparative HPLC.

$C_{26}H_{37}N_5O_5S \times C_2HF_3O_2$ (645.69)

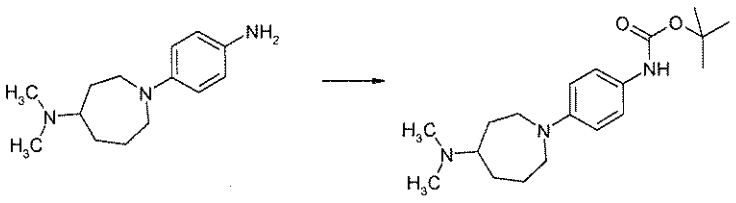
[M+H]+ = 532

HPLC (Method 5): retention time = 1.44 min

Example 51



51a)



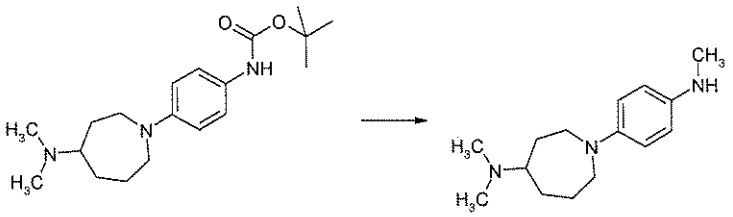
A mixture of 0.26 g (1.11 mmol) of product from 39d, 0.27 g (1.22 mmol) of Boc-anhydride, 0.17 ml (1.22 mmol) of triethylamine and 15 ml dichloromethane is stirred overnight at ambient temperature. Then the reaction mixture is diluted with dichloromethane, washed with saturated sodium hydrogen carbonate solution and saturated sodium chloride solution, dried on sodium sulphate and evaporated to dryness in vacuo.

$C_{19}H_{31}N_3O_2$ (333.47)

[M+H]+ = 334

HPLC (Method 1): retention time = 2.40 min

51b)

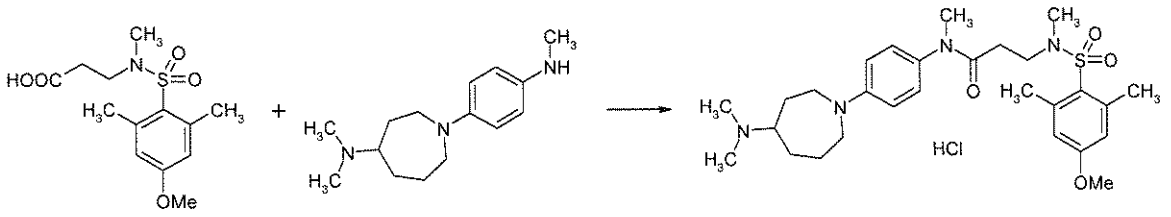


0.13 g (3.40 mmol) of lithium aluminium hydride are placed in 5 ml THF, heated to 60°C and combined with 0.38 g (1.14 mmol) of product from 51a in 5 ml THF. The reaction mixture is then refluxed for four hours and stirred overnight at ambient temperature. Then the reaction mixture is quenched with water and 1 M sodium hydroxide solution. The precipitate formed is filtered off through Celite, the filtrate is evaporated to dryness in vacuo.

$C_{15}H_{25}N_3$ (247.38)

TLC: silica gel, dichloromethane / methanol / ammonia 4:1:0.2, Rf value = 0.68

51c)



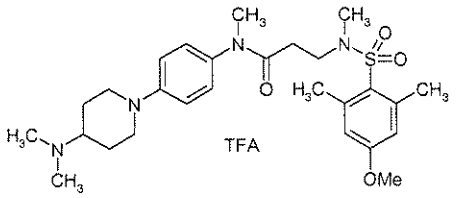
Example 51 is prepared analogously to 1f from 0.15 g (0.50 mmol) of product from 22c, 0.12 g (0.50 mmol) of product from 51b, 0.21 ml (1.50 mmol) of triethylamine and 0.18 g (0.55 mmol) of TBTU in 8 ml DMF.

$C_{28}H_{42}N_4O_4S$ x HCl (567.18)

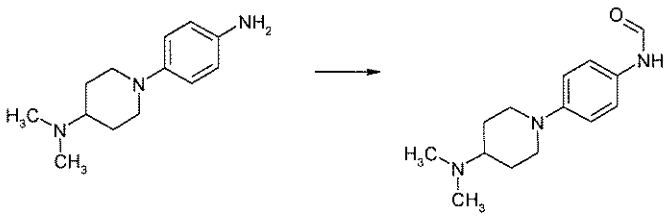
[M+H]+ = 531

HPLC (Method 1): retention time = 2.5 min

Example 52



52a)



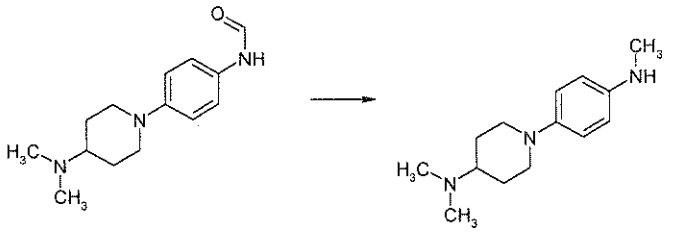
0.70 ml (7.36 mmol) of acetic anhydride are placed under a nitrogen atmosphere and slowly combined with 0.42 ml (9.06 mmol) of formic acid while cooling with an ice bath. The reaction mixture is heated for two hours to 50-60°C and then combined with 0.50 g (2.28 mmol) of product from 8b in 7 ml dichloromethane while cooling with an ice bath. After 20 minutes' stirring at ambient temperature the reaction mixture is evaporated to dryness in vacuo. The crude product thus obtained is purified by column chromatography through silica gel (eluant: dichloromethane / methanol / ammonia 9:1:0.1).

$C_{14}H_{21}N_3O$ (247.34)

[M+H]+ = 248

HPLC (Method 5): retention time = 0.50 min

52b)

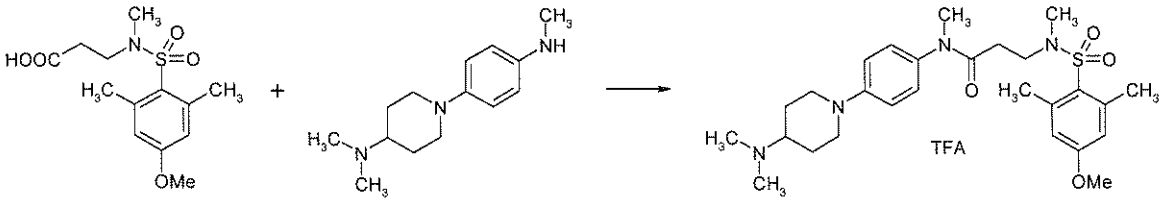


52b is prepared analogously to 51b from 0.17 g (4.51mmol) of lithium aluminium hydride and 0.58 g (2.34 mmol) of product from 52a in 10 ml THF.

$C_{14}H_{23}N_3$ (233.35)

TLC: silica gel, dichloromethane / methanol / ammonia 9:1:0.1, Rf value = 0.5

52c)



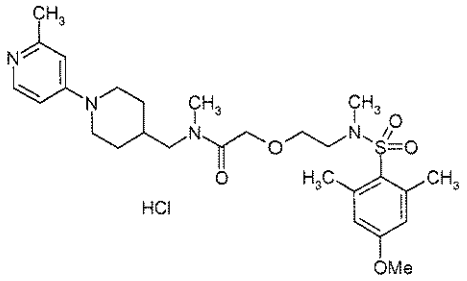
Example 52 is prepared analogously to 1f from 0.21 g (0.68 mmol) of product from 22c, 0.24 g (0.68 mmol) of product from 52b, 0.28 ml (2.04 mmol) of triethylamine and 0.22 g (0.68 mmol) of TBTU in 4 ml THF.

$C_{27}H_{40}N_4O_4S \times C_2HF_3O_2$ (630.72)

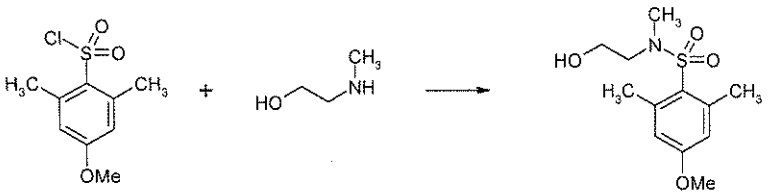
[M+H]+ = 517

HPLC (Method 5): retention time = 1.50 min

Example 53



53a)



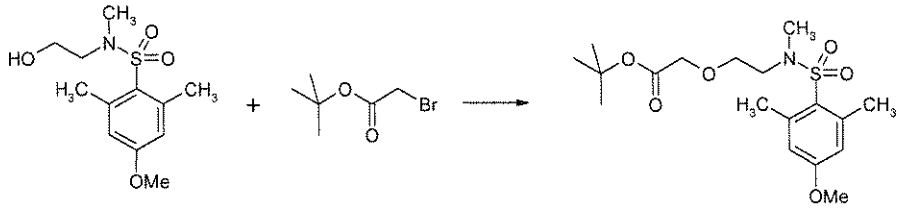
53a is prepared analogously to 3a from 4.50 g (19.17 mmol) of product from 13a, 1.69 g (21.10 mmol) of N-methylaminoethanol (BASF), 6.68 ml (47.90 mmol) of triethylamine in 150 ml dichloromethane.

$C_{12}H_{19}NO_4S$ (273.35)

[M+H]+ = 274

TLC: silica gel, dichloromethane / ethanol 19:1, Rf value = 0.43

53b)



First 100 ml 35% sodium hydroxide solution, then 4.18 ml (28.26 mmol) of tert-butyl bromoacetate in 20 ml of toluene are added to a mixture of 5.15 g (18.84 mmol) of product from 53a, 1.75 g (6.60 mmol) of tetrabutylammonium chloride (Fluka) and 80 ml of toluene at 0°C. The reaction mixture is then stirred for 1.5 hours at ambient temperature, then diluted with diethyl ether. After the phase separation the organic phase is washed four times with water until neutral, dried on sodium sulphate and evaporated to dryness in vacuo. The crude product thus

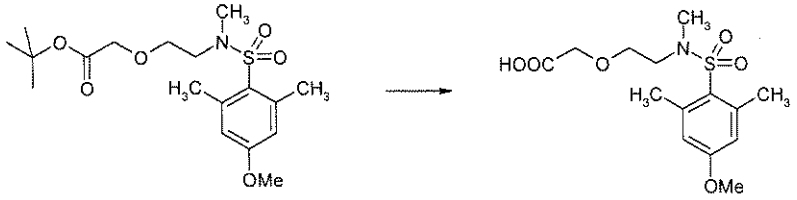
obtained is purified by column chromatography through silica gel (eluant: petroleum ether / ethyl acetate 4:1).

$C_{18}H_{29}NO_6S$ (387.49)

[M+H]+ = 388

TLC: silica gel, petroleum ether / ethyl acetate 7:3, Rf value = 0.59

53c)



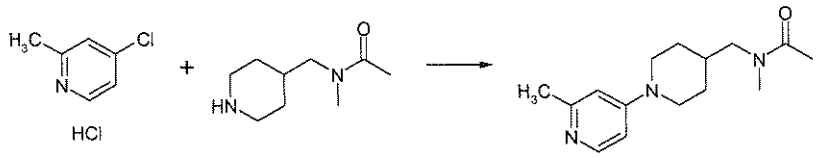
A mixture of 6.80 g (17.55 mmol) of product from 53b, 8 ml TFA and 100 ml dichloromethane is stirred for 2.5 hours at ambient temperature. The reaction mixture is then evaporated to dryness in vacuo. The residue is combined with 1 M sodium hydroxide solution and extracted twice with ethyl acetate (organic extracts are discarded). The aqueous phase is acidified with 2 M HCl, then extracted again with ethyl acetate. The organic extracts are washed with water, dried on sodium sulphate and evaporated to dryness in vacuo.

$C_{14}H_{21}NO_6S$ (331.29)

[M+H]+ = 332

HPLC (Method 4): retention time = 3.4 min

53d)



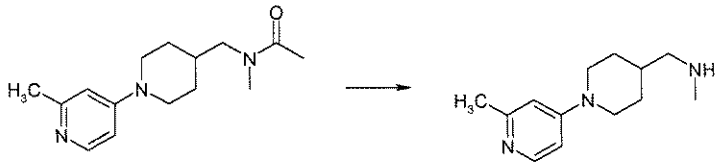
53d is prepared analogously to 28c from 1.00 g (6.10 mmol) of 4-chloro-2-methylpyridine hydrochloride (Alfa Aesar) and 2.08 g (12.20 mmol) of N-methyl-N-piperidin-4-ylmethyl-acetamide (DE 1100635, Rhône-Poulenc, 1961).

$C_{15}H_{23}N_3O$ (261.36)

[M+H]+ = 262

HPLC (Method 4): retention time = 1.9 min

53e)



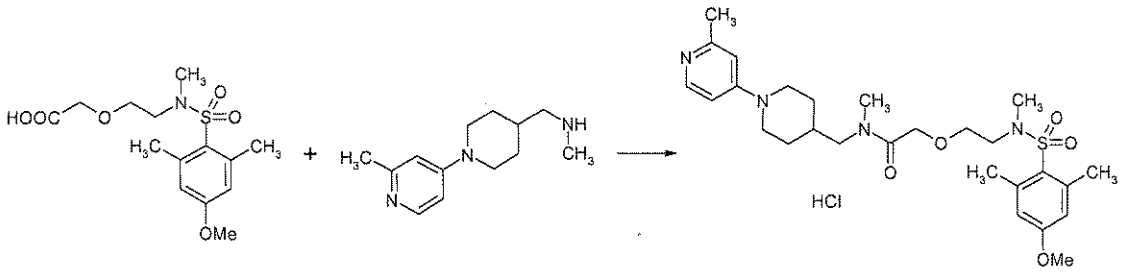
A mixture of 1.37 g (5.24 mmol) of product from 53d and 15 ml semiconcentrated HCl is refluxed for four days. The reaction mixture is made alkaline with 20% sodium hydroxide solution and extracted with dichloromethane. The organic extracts are dried on sodium sulphate and evaporated to dryness in vacuo.

$C_{13}H_{21}N_3$ (219.33)

[M+H]+ = 220

TLC: silica gel, dichloromethane / methanol / ammonia 8:2:0.2, Rf value = 0.48

53f)



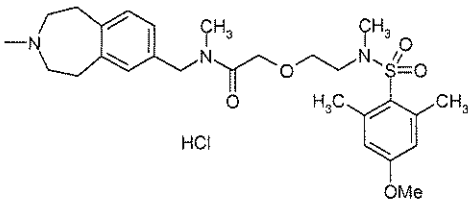
Example 53 is prepared analogously to 1f from 0.099 g (0.30 mmol) of product from 53c, 0.066 g (0.30 mmol) of product from 53e, 0.10 ml (0.75 mmol) of triethylamine and 0.12 g (0.36 mmol) of TBTU in 8 ml THF and 1 ml DMF.

$C_{27}H_{40}N_4O_5S$ x HCl (569.16)

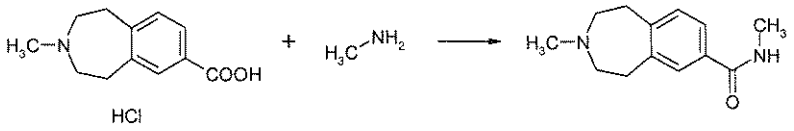
[M+H]+ = 533

HPLC (Method 4): retention time = 3.1 min

Example 54



54a)



54a is prepared analogously to 1f from 2.00 g (8.27 mmol) of product from 38d, 8.28 ml (16.55 mmol) of methylamine 2 M in THF (Aldrich), 3.46 ml (24.82 mmol) of triethylamine and 3.19 g (9.93 mmol) of TBTU in 30 ml THF.

$C_{13}H_{18}N_2O$ (218.29)

$[M+H]^+$ = 219

TLC: silica gel, dichloromethane / methanol 8:2, Rf value = 0.14

54b)

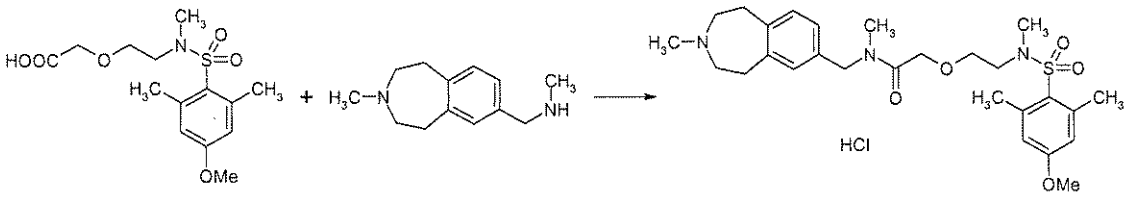
54b is prepared analogously to 38f from 1.00 g (4.58 mmol) of product from 54a and 9.00 ml (9.00 mmol) of lithium aluminium hydride 1 M in THF (Aldrich) in 30 ml THF.

$C_{13}H_{20}N_2$ (204.31)

$[M+H]^+$ = 205

TLC: silica gel, dichloromethane / methanol 8:2, Rf value = 0.07

54c)



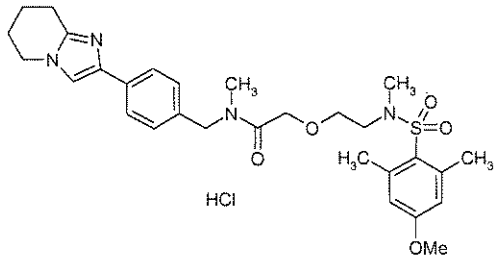
Example 54 is prepared analogously to 1f from 0.099 g (0.30 mmol) of product from 53c, 0.088 g (0.30 mmol) of product from 54b, 0.10 ml (0.75 mmol) of triethylamine and 0.12 g (0.36 mmol) of TBTU in 7 ml THF and 1 ml DMF.

$C_{27}H_{39}N_3O_5S$ x HCl (554.14)

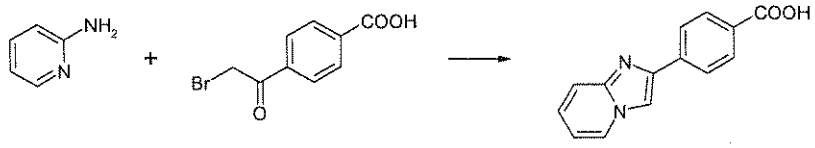
[M+H]+ = 518

HPLC (Method 4): retention time = 3.1 min

Example 55



55a)

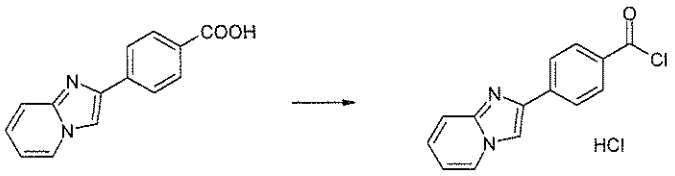


A mixture of 3.20 g (34.00 mmol) of 2-aminopyridine (Aldrich), 2.75 g (11.31 mmol) of 4-bromoacetylbenzoic acid (Fluorochem) and 100 ml of ethanol is refluxed for six hours at reflux temperature and stirred overnight at ambient temperature. The precipitate formed is filtered off and dried.

$C_{14}H_{10}N_2O_2$ (238.24)

[M+H]+ = 239

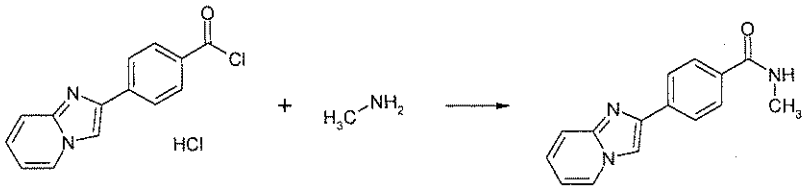
55b)



55b is prepared analogously to 27c from 1.7 g (7.14 mmol) of product from 55a and 30 ml of thionyl chloride.

$C_{14}H_9ClN_2O$ x HCl (293.15)

55c)

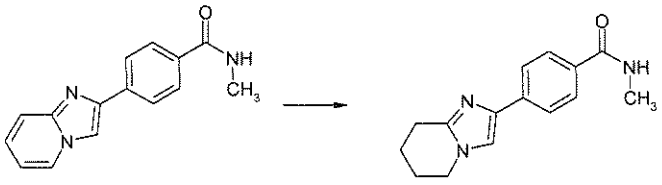


2.10 g (7.14 mmol) of product from 55b in 100 ml dichloromethane are combined with 25 ml (50.00 mmol) of methylamine 2 M in THF (Aldrich) while cooling with an ice bath. The reaction mixture is then stirred for two hours at ambient temperature and then evaporated to dryness in vacuo. The residue is triturated with water, filtered off and dried. The crude product thus obtained is purified by column chromatography through silica gel (eluant: dichloromethane / methanol 97:3).

$C_{15}H_{13}N_3O$ (251.28)

[M+H]+ = 252

55d)

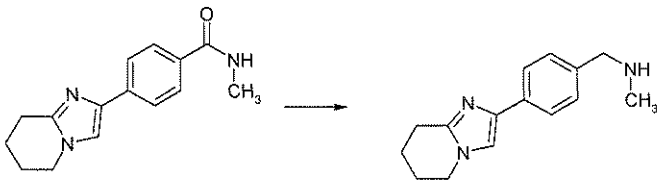


A mixture of 0.70 g (2.79 mmol) of product from 55c, 0.15 g palladium on charcoal (20%), 100 ml of methanol and 30 ml dichloromethane is hydrogenated at ambient temperature in the autoclave. The catalyst is filtered off, the filtrate is evaporated to dryness in vacuo.

$C_{15}H_{17}N_3O$ (255.32)

[M+H]+ = 256

55e)

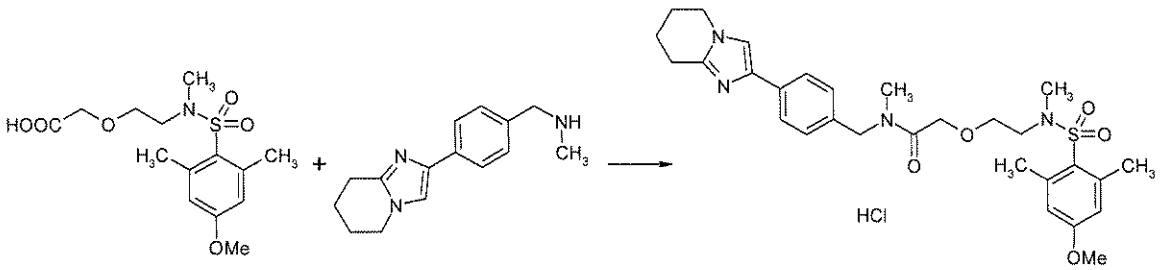


55e is prepared analogously to 38f from 0.80 g (3.13 mmol) of product from 55d and 20.00 ml (20.00 mmol) of lithium aluminium hydride 1 M in THF (Aldrich) in 50 ml of pyridine.

$C_{15}H_{19}N_3$ (241.33)

[M+H]+ = 242

55f)



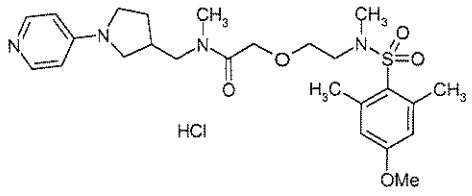
Example 55 is prepared analogously to 1f from 0.14 g (0.42 mmol) of product from 53c, 0.10 g (0.41 mmol) of product from 55e, 0.14 ml (0.99 mmol) of triethylamine and 0.15 g (0.46 mmol) of TBTU in 30 ml THF and 5 ml DMF.

$C_{29}H_{38}N_4O_5S$ x HCl (591.16)

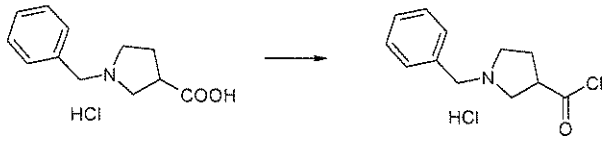
[M+H]+ = 555

TLC: silica gel, dichloromethane / methanol 9:1, Rf value = 0.26

Example 56



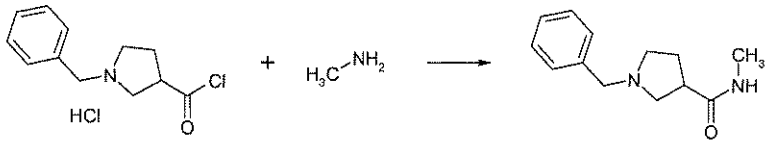
56a)



56a is prepared analogously to 27c from 1.35 g (5.59 mmol) of 1-benzyl-pyrrolidine-3-carboxylic acid (J. Org. Chem. 33, 1968, 3637-3639) and 10 ml of thionyl chloride.

$C_{12}H_{14}ClNO$ x HCl (260.16)

56b)

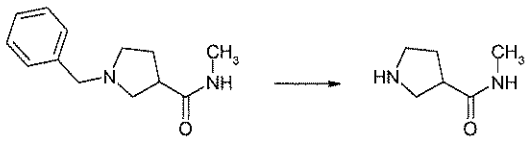


56b is prepared analogously to 55c from 1.45 g (5.57 mmol) of product from 56a, 10 ml (50.00 mmol) of methylamine 2 M in THF (Aldrich) in 50 ml THF.

$C_{13}H_{18}N_2O$ (218.29)

[M+H]+ = 219

56c)

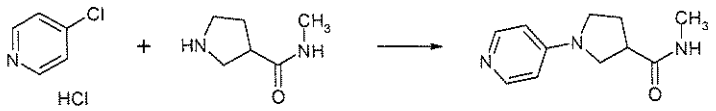


A mixture of 1.10 g (5.04 mmol) of product from 56b, 0.20 g palladium hydroxide and 40 ml of methanol is hydrogenated at 50°C in the autoclave. The catalyst is filtered off, the filtrate is evaporated to dryness in vacuo.

$C_6H_{12}N_2O$ (128.17)

[M+H]+ = 129

56d)



56d is prepared analogously to 28c from 0.76 g (5.08 mmol) of 4-chloropyridine hydrochloride (Aldrich), 0.65 g (5.07 mmol) of product from 56c and 1.52 ml (10.88 mmol) of triethylamine in 10 ml of ethanol.

$C_{11}H_{15}N_3O$ (205.26)

[M+H]+ = 206

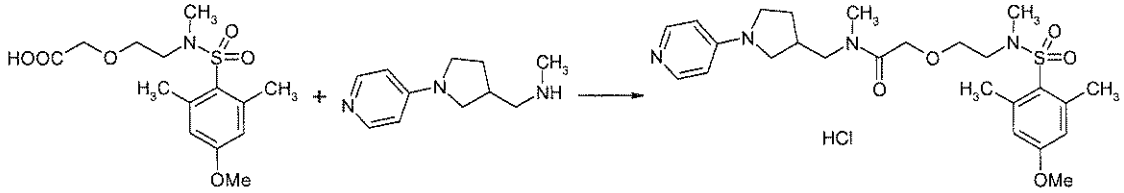
56e)

56e is prepared analogously to 38f from 0.45 g (2.19 mmol) of product from 56d and 7.00 ml (7.00 mmol) of lithium aluminium hydride 1 M in THF (Aldrich) in 30 ml THF.

$C_{11}H_{17}N_3$ (191.27)

[M+H]+ = 192

56f)



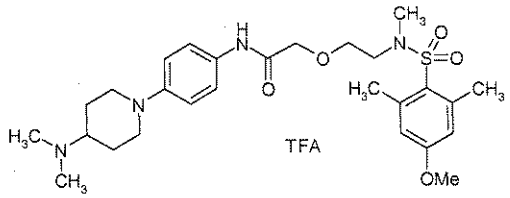
Example 56 is prepared analogously to 1f from 0.14 g (0.42 mmol) of product from 53c, 0.10 g (0.42 mmol) of product from 56e, 0.18 ml (1.29 mmol) of triethylamine and 0.18 g (0.56 mmol) of TBTU in 30 ml THF and 5 ml DMF.

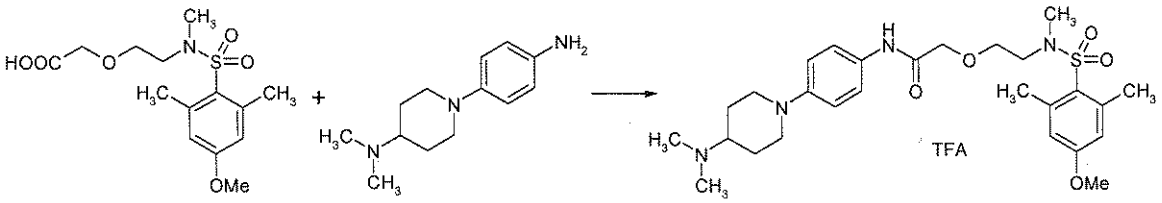
$C_{25}H_{36}N_4O_5S$ x HCl (541.10)

[M+H]+ = 505

HPLC (Method 5): retention time = 1.51 min

Example 57





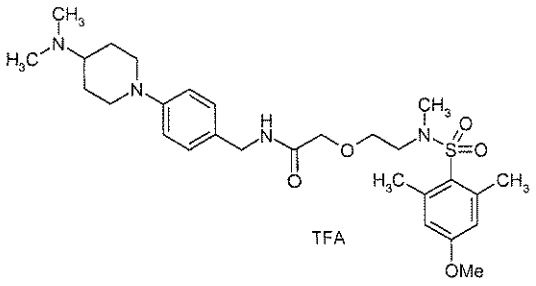
Example 57 is prepared analogously to 1f from 0.10 g (0.30 mmol) of product from 53c, 0.066 g (0.30 mmol) of product from 8b, 0.13 ml (0.91 mmol) of triethylamine and 0.097 g (0.30 mmol) of TBTU in 5 ml DMF.

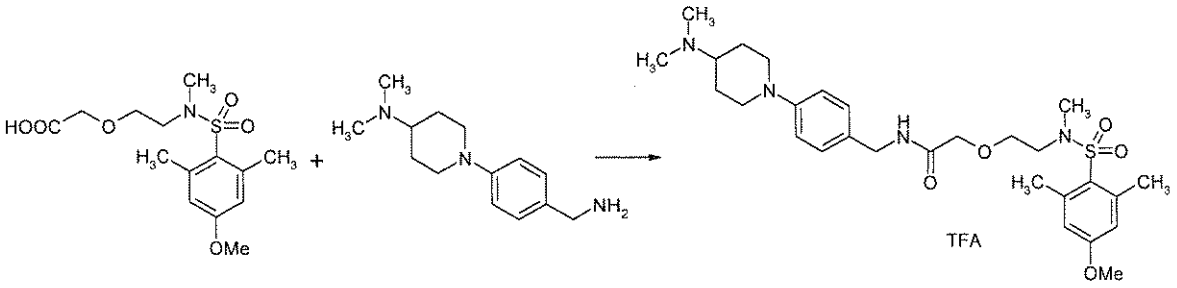
$C_{27}H_{40}N_4O_5S \times C_2HF_3O_2$ (646.72)

[M+H]+ = 533

HPLC (Method 5): retention time = 1.51 min

Example 58





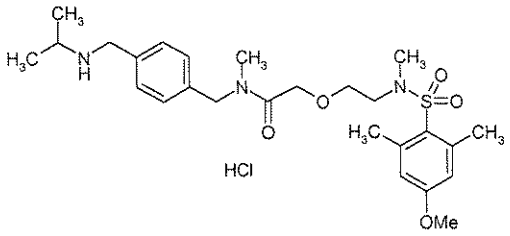
Example 58 is prepared analogously to 1f from 0.10 g (0.30 mmol) of product from 53c, 0.07 g (0.30 mmol) of product from 33a, 0.13 ml (0.91 mmol) of triethylamine and 0.097 g (0.30 mmol) of TBTU in 5 ml DMF.

$C_{28}H_{42}N_4O_5S \times C_2HF_3O_2$ (660.75)

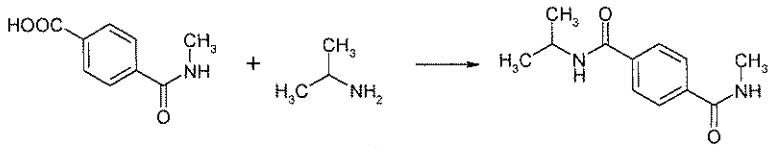
[M+H]+ = 547

HPLC (Method 5): retention time = 1.48 min

Example 59



59a)



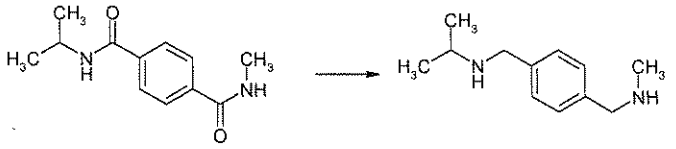
59a is prepared analogously to 1f from 2.00 g (11.16 mmol) of terephthalic acid monomethylamide (EMKA), 1.90 ml (22.32 mmol) of isopropylamine (Aldrich), 3.11 ml (22.32 mmol) of triethylamine and 4.30 g (13.40 mmol) of TBTU in 60 ml THF.

$C_{12}H_{16}N_2O_2$ (220.27)

[M+H]+ = 221

HPLC (Method 4): retention time = 2.3 min

59b)



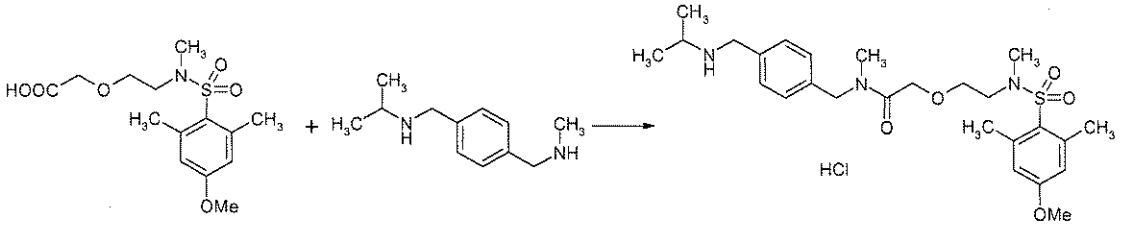
59b is prepared analogously to 38f from 1.34 g (6.08 mmol) of product from 59a and 25.00 ml (25.00 mmol) of lithium aluminium hydride 1 M in THF (Aldrich) in 150 ml THF.

$C_{12}H_{20}N_2$ (192.30)

[M+H]+ = 193

TLC: silica gel, dichloromethane / methanol / ammonia 9:1:0.1, Rf value = 0.17

59c)



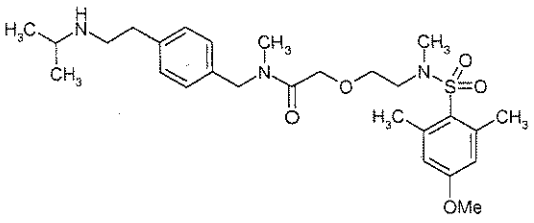
Example 59 is prepared analogously to 1f from 0.099 g (0.30 mmol) of product from 53c, 0.058 g (0.30 mmol) of product from 59b, 0.10 ml (0.75 mmol) of triethylamine and 0.12 g (0.36 mmol) of TBTU in 8 ml THF.

$C_{26}H_{39}N_3O_5S$ x HCl (542.13)

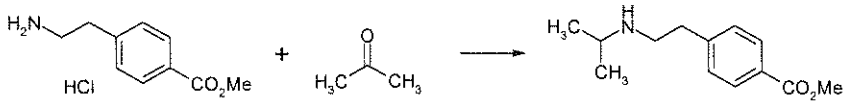
[M+H]+ = 506

HPLC (Method 4): retention time = 3.1 min

Example 60



60a)



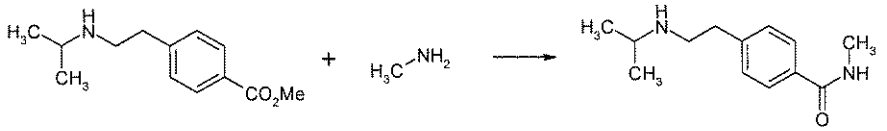
A mixture of 3.00 g (13.91 mmol) of methyl 4-aminoethylbenzoate (EMKA), 1.94 ml (13.91 mmol) of triethylamine and 50 ml THF is stirred for 10 min at ambient temperature and then combined with 1.13 ml (15.30 mmol) of acetone. The reaction mixture is stirred for another 30 min at ambient temperature, then 3.24 g (15.30 mmol) of sodium triacetoxyborohydride and 1.19 ml (20.86 mmol) of acetic acid are added. The mixture is stirred for 16 hours at ambient temperature. The reaction mixture is evaporated to dryness in vacuo, the residue is taken up in 1 M HCl and extracted with ethyl acetate (organic phase is discarded). The aqueous phase is made alkaline with saturated potassium carbonate solution and extracted with ethyl acetate. The organic extracts are dried on sodium sulphate and evaporated to dryness in vacuo.

$C_{13}H_{19}NO_2$ (221.30)

[M+H]+ = 222

HPLC (Method 4): retention time = 2.2 min

60b)



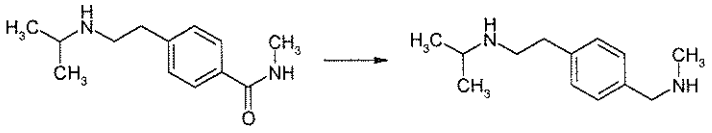
A mixture of 2.52 g (11.39 mmol) of product from 60a, 11.40 ml (22.80 mmol) of methylamine 2 M in THF (Aldrich), 0.54 g (5.70 mmol) of magnesium chloride (Aldrich) and 100 ml THF is stirred for 17 hours at 120°C in the autoclave. The reaction mixture is filtered, the filtrate is evaporated to dryness in vacuo. The crude product thus obtained is purified by column chromatography through silica gel (eluant: dichloromethane / methanol / ammonia 9:1:0.1).

$C_{13}H_{20}N_2O$ (220.31)

[M+H]+ = 221

TLC: silica gel, dichloromethane / methanol / ammonia 9:1:0.1, Rf value = 0.21

60c)



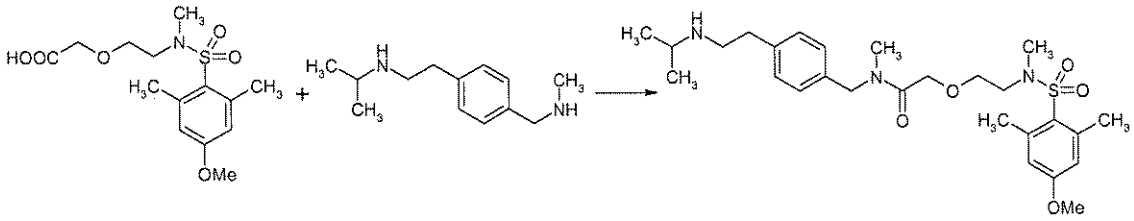
60c is prepared analogously to 38f from 1.49 g (6.76 mmol) of product from 60b and 10.00 ml (10.00 mmol) of lithium aluminium hydride 1 M in THF (Aldrich) in 60 ml THF.

$C_{13}H_{22}N_2$ (206.33)

[M+H]+ = 207

TLC: silica gel, dichloromethane / methanol / ammonia 9:1:0.1, Rf value = 0.10

60d)



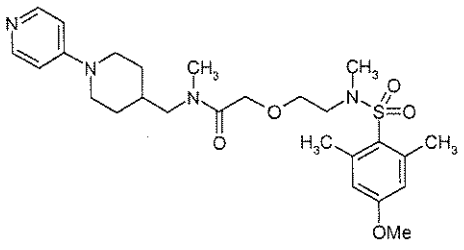
Example 60 is prepared analogously to 1f from 0.099 g (0.30 mmol) of product from 53c, 0.062 g (0.30 mmol) of product from 60c, 0.083 ml (0.60 mmol) of triethylamine and 0.12 g (0.36 mmol) of TBTU in 8 ml THF.

$C_{27}H_{41}N_3O_5S$ (519.70)

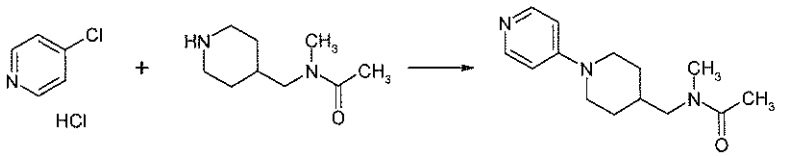
[M+H]+ = 520

HPLC (Method 4): retention time = 3.2 min

Example 61



61a)

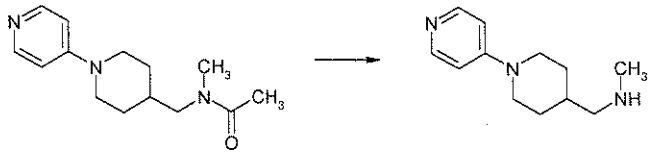


61a is prepared analogously to 28c from 1.00 g (6.67 mmol) of 4-chloropyridine hydrochloride (Aldrich) and 2.55 g (15.00 mmol) of N-methyl-N-piperidin-4-ylmethyl-acetamide (DE 110635, Rhône-Poulenc, 1961) in 1 ml of water.

$C_{14}H_{21}N_3O$ (247.34)

$[M+H]^+ = 248$

61b)

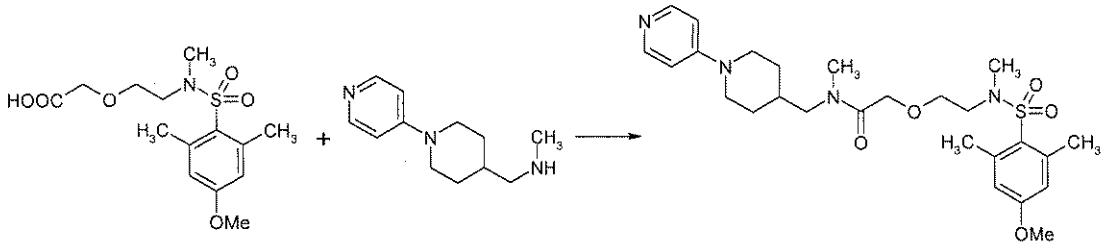


A mixture of 1.00 g (4.04 mmol) of product from 61a and 10 ml semiconcentrated HCl is refluxed for three days. The reaction mixture is then diluted with water, made alkaline with 20% sodium hydroxide solution and extracted with ethyl acetate. The organic extracts are dried on sodium sulphate and evaporated to dryness in vacuo.

$C_{12}H_{19}N_3$ (205.30)

TLC: silica gel, dichloromethane / ethanol 9:1, Rf value = 0.2

61c)



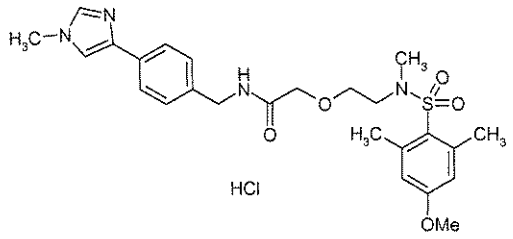
Example 61 is prepared analogously to 1f from 0.099 g (0.30 mmol) of product from 53c, 0.062 g (0.30 mmol) of product from 61b, 0.083 ml (0.60 mmol) of triethylamine and 0.12 g (0.36 mmol) of TBTU in 8 ml THF and 1 ml DMF.

$C_{26}H_{38}N_4O_5S$ (518.67)

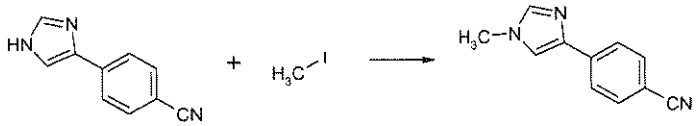
[M+H]+ = 519

HPLC (Method 4): retention time = 3.2 min

Example 62



62a)



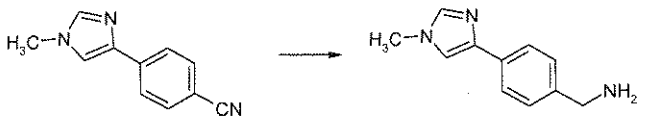
A mixture of 1.69 g (10.00 mmol) of 4-(1H-imidazol-4-yl)-benzonitrile (J. Am. Chem. Soc. 93, 1971, 4256-4263), 1.12 g (10.00 mmol) of potassium-tert-butoxide and 25 ml DMSO is first stirred for 30 min at ambient temperature, then slowly combined with 0.62 ml (10.00 mmol) of methyl iodide and stirred for another 2.5 hours at ambient temperature. The reaction mixture is then added to water, the precipitate formed is filtered off and dried in vacuo. The crude product thus obtained is purified by column chromatography through silica gel (eluant: dichloromethane / ethanol 19:1).

$C_{11}H_9N_3$ (183.21)

[M+H]+ = 184

HPLC (Method 4): retention time = 1.9 min

62b)

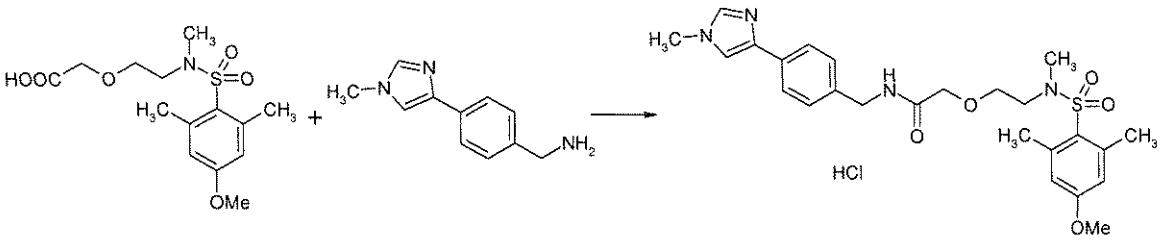


62b is prepared analogously to 34b from 1.02 g (5.57 mmol) of product from 62a, 0.20 g Raney nickel and 30 ml of methanolic ammonia solution.

$C_{11}H_{13}N_3$ (187.24)

TLC: silica gel, dichloromethane / methanol / ammonia 9:1:0.1, Rf value = 0.27

62c)



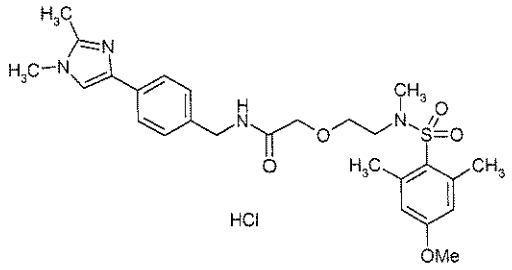
Example 62 is prepared analogously to 1f from 0.099 g (0.30 mmol) of product from 53c, 0.056 g (0.30 mmol) of product from 62b, 0.083 ml (0.60 mmol) of triethylamine and 0.12 g (0.36 mmol) of TBTU in 7 ml THF and 1 ml DMF.

$C_{25}H_{32}N_4O_5S$ x HCl (537.07)

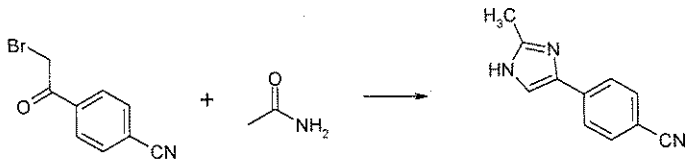
[M+H]+ = 501

HPLC (Method 4): retention time = 3.2 min

Example 63



63a)



5.00 g (22.32 mmol) of 2-bromo-4`-cyano-acetophenone (Aldrich) and 10.00 g (169.29 mmol) of acetamide (Merck) are heated together with stirring for two hours to 210°C. After cooling, the reaction mixture is stirred into water and acidified with 2 M HCl. The precipitate is filtered off and discarded. The filtrate is made alkaline

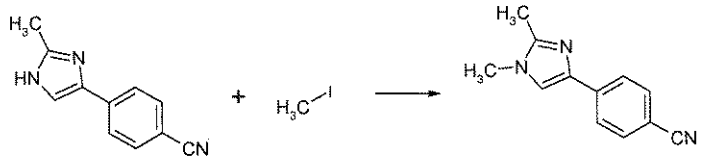
with concentrated ammonia solution, the precipitate is filtered off and dried in vacuo. The crude product thus obtained is purified by column chromatography through silica gel (eluant: dichloromethane / ethanol 9:1).

$C_{11}H_9N_3$ (183.21)

[M-H]- = 182

HPLC (Method 4): retention time = 1.9 min

63b)



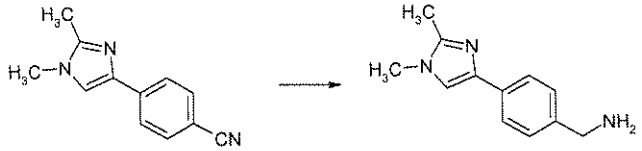
63b is prepared analogously to 62a from 2.39 g (13.05 mmol) of product from 63a, 1.46 g (13.05 mmol) of potassium-tert-butoxide and 0.81 ml (13.05 mmol) of methyl iodide in 50 ml DMSO.

$C_{12}H_{11}N_3$ (197.24)

[M+H]+ = 198

HPLC (Method 4): retention time = 1.9 min

63c)

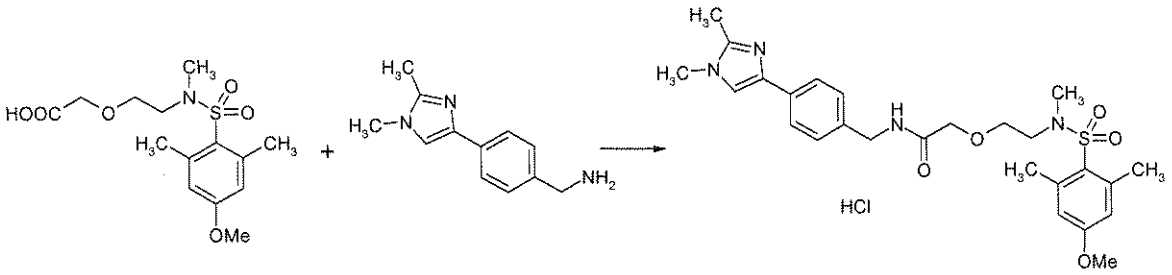


63c is prepared analogously to 34b from 2.04 g (10.34 mmol) of product from 63b, 0.40 g Raney nickel and 50 ml of methanolic ammonia solution.

$C_{12}H_{15}N_3$ (201.27)

TLC: silica gel, dichloromethane / methanol / ammonia 9:1:0.1, Rf value = 0.19

63d)



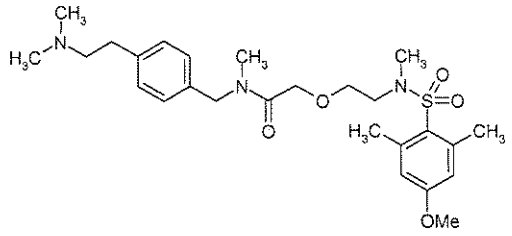
Example 63 is prepared analogously to 1f from 0.099 g (0.30 mmol) of product from 53c, 0.060 g (0.30 mmol) of product from 63c, 0.083 ml (0.60 mmol) of triethylamine and 0.12 g (0.36 mmol) of TBTU in 7 ml THF and 1 ml DMF.

$C_{26}H_{34}N_4O_5S$ x HCl (551.10)

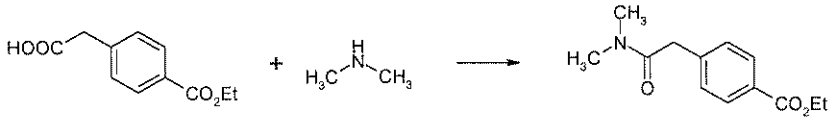
[M+H]+ = 515

HPLC (Method 4): retention time = 3.2 min

Example 64



64a)



64a is prepared analogously to 1f from 4.00 g (19.21 mmol) of ethyl 4-carboxymethyl-benzoate (J. Med. Chem. 41, 1998, 5219-5246), 19.21 ml (38.42 mmol) of dimethylamine 2 M in THF (Aldrich), 5.36 ml (38.42 mmol) of triethylamine and 7.39 g (23.00 mmol) of TBTU in 100 ml THF.

$C_{13}H_{17}NO_3$ (235.28)

[M+H]+ = 236

HPLC (Method 4): retention time = 3.3 min

64b)

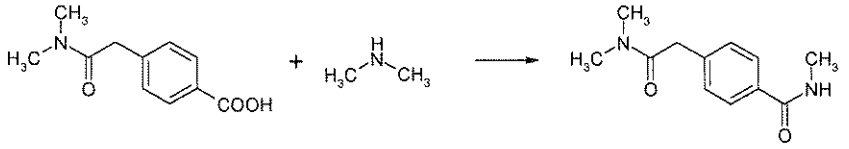
A mixture of 3.07 g (13.05 mmol) of product from 64a, 9.75 ml (39.00 mmol) of 4 M sodium hydroxide solution, 9.75 ml of water and 50 ml of ethanol is stirred overnight at ambient temperature. Then the ethanol is eliminated in vacuo. The aqueous residue is acidified with 4 M HCl and extracted with ethyl acetate. The organic extracts are dried on sodium sulphate and evaporated to dryness in vacuo. The product thus obtained is triturated with diethyl ether and dried.

$C_{11}H_{13}NO_3$ (207.23)

[M+H]+ = 208

HPLC (Method 4): retention time = 2.3 min

64c)



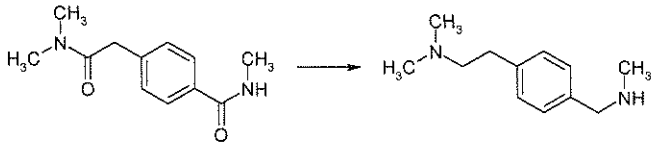
64c is prepared analogously to 1f from 2.30 g (11.10 mmol) of product from 64b, 11.10 ml (22.20 mmol) of dimethylamine 2 M in THF (Aldrich), 3.09 ml (22.20 mmol) of triethylamine and 4.28 g (13.32 mmol) of TBTU in 70 ml THF.

$C_{12}H_{16}N_2O_2$ (220.27)

[M+H]+ = 221

TLC: silica gel, dichloromethane / methanol / ammonia 9:1:0.1, Rf value = 0.44

64d)



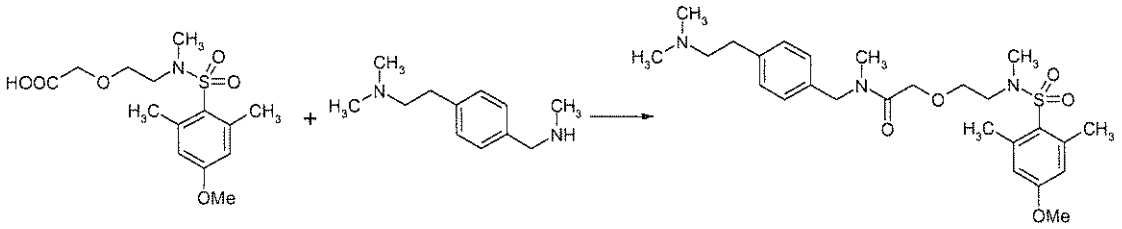
64d is prepared analogously to 38f from 1.92 g (8.72 mmol) of product from 64c and 40.00 ml (40.00 mmol) of lithium aluminium hydride 1 M in THF (Aldrich) in 150 ml THF.

$C_{12}H_{20}N_2$ (192.30)

[M+H]+ = 193

TLC: silica gel, dichloromethane / methanol / ammonia 9:1:0.1, Rf value = 0.10

64e)



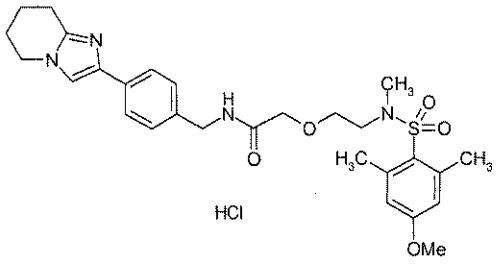
Example 64 is prepared analogously to 1f from 0.099 g (0.30 mmol) of product from 53c, 0.058 g (0.30 mmol) of product from 64d, 0.083 ml (0.60 mmol) of triethylamine and 0.12 g (0.36 mmol) of TBTU in 7 ml THF and 1 ml DMF.

$C_{26}H_{39}N_3O_5S$ (505.67)

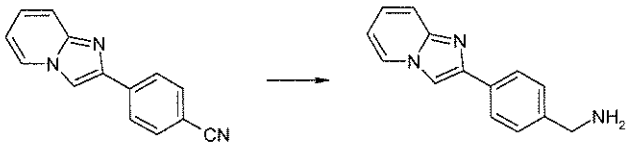
[M+H]+ = 508

HPLC (Method 4): retention time = 3.0 min

Example 65



65a)



65a is prepared analogously to 34b from 0.40 g (1.82 mmol) of 4-imidazo[1,2-a]pyridin-2-yl-benzonitrile (J. Med. Chem. 41, 1998, 4317-4328), 0.10 g Raney nickel and 40 ml of methanolic ammonia solution.

$C_{14}H_{13}N_3$ (223.27)

[M+H]+ = 224

TLC: silica gel, dichloromethane / methanol 9:1, Rf value = 0.06

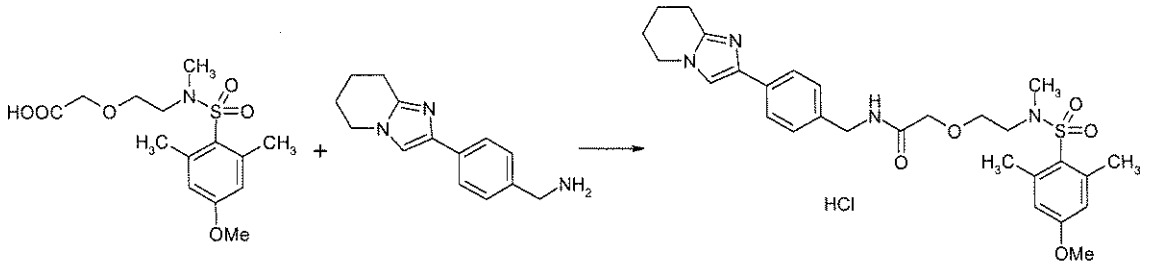
65b)

A mixture of 0.40 g (1.79 mmol) of product from 65a, 0.05 g platinum oxide and 40 ml of methanol is hydrogenated at 50°C in the autoclave. The catalyst is filtered off, the filtrate is evaporated to dryness in vacuo.

$C_{14}H_{17}N_3$ (227.30)

[M+H]+ = 228

65c)



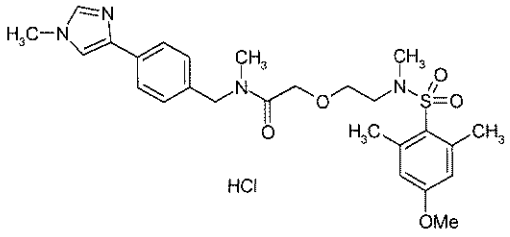
Example 65 is prepared analogously to 1f from 0.15 g (0.44 mmol) of product from 53c, 0.10 g (0.44 mmol) of product from 65b, 0.15 ml (1.09 mmol) of triethylamine and 0.16 g (0.48 mmol) of TBTU in 30 ml THF and 10 ml DMF.

$C_{28}H_{36}N_4O_5S$ x HCl (577.14)

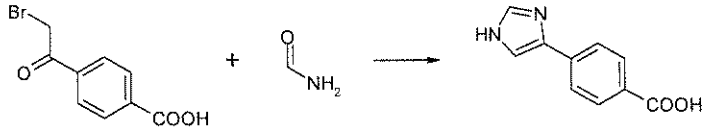
[M+H]+ = 541

HPLC (Method 5): retention time = 1.57 min

Example 66



66a)

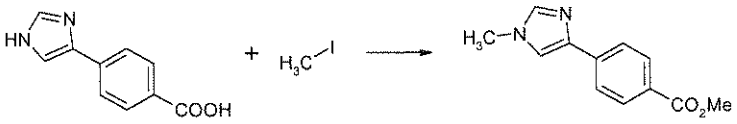


A mixture of 0.50 g (2.06 mmol) of 4-bromoacetylbenzoic acid (Fluorochem) and 5 ml formamide is stirred for one hour at 150°C in the microwave. After cooling the precipitated product is filtered off, washed with diethyl ether and dried.

$C_{10}H_8N_2O_2$ (188.18)

[M+H]+ = 189

66b)

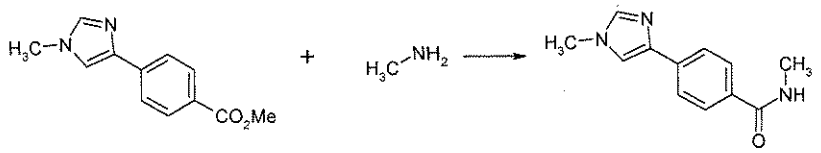


A mixture of 1.60 g (8.50 mmol) of product from 66a, 5.40 g (38.04 mmol) of methyl iodide, 7.00 g (25.33 mmol) of potassium carbonate and 30 ml DMF is stirred overnight at ambient temperature. The reaction mixture is filtered, the filtrate is evaporated to dryness in vacuo. The crude product thus obtained is purified by column chromatography through silica gel (eluant: dichloromethane / methanol 100:1 to 75:1).

$C_{12}H_{12}N_2O_2$ (216.24)

[M+H]+ = 217

66c)

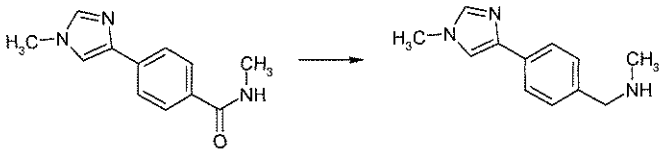


A mixture of 0.75 g (3.47 mmol) of product from 66b and 20 ml methylamine 33% in ethanol (Fluka) is heated to 160°C overnight in the autoclave. The reaction mixture is evaporated to dryness in vacuo. The crude product thus obtained is purified by column chromatography through silica gel (eluant: dichloromethane / methanol 50:1 to 25:1).

$C_{12}H_{13}N_3O$ (215.25)

[M+H]+ = 216

66d)



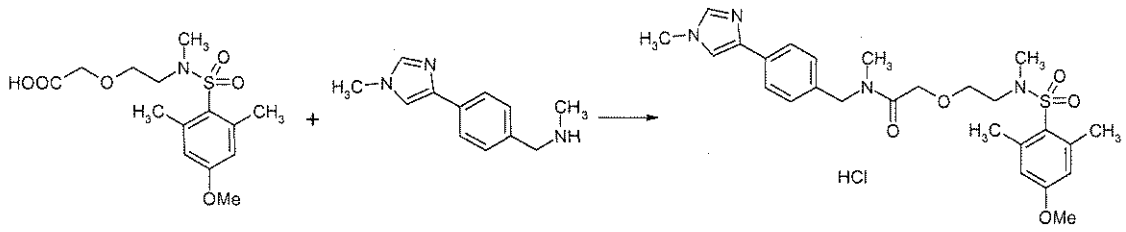
66d is prepared analogously to 38f from 0.41 g (1.91 mmol) of product from 66c and 3.00 ml (3.00 mmol) of lithium aluminium hydride 1 M in THF (Aldrich) in 70 ml THF.

$C_{12}H_{15}N_3$ (201.27)

[M+H]+ = 202

TLC: silica gel, dichloromethane / methanol / ammonia 8:2:0.01, Rf value = 0.16

66e)



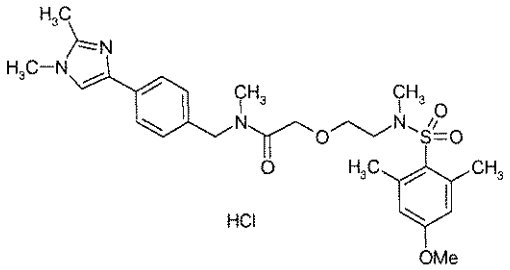
Example 66 is prepared analogously to 1f from 0.15 g (0.45 mmol) of product from 53c, 0.09g (0.45 mmol) of product from 66d, 0.11 ml (1.09 mmol) of triethylamine and 0.16 g (0.50 mmol) of TBTU in 30 ml THF and 5 ml DMF.

$C_{26}H_{34}N_4O_5S$ x HCl (551.10)

[M+H]+ = 515

TLC: silica gel, dichloromethane / methanol 9:1, Rf value = 0.52

Example 67



67a)

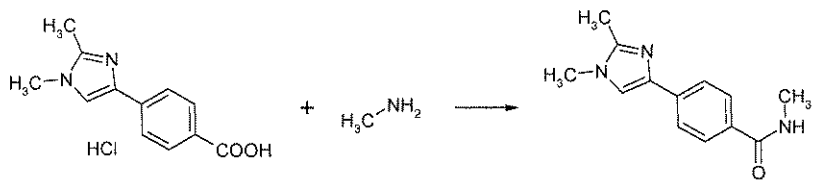
A mixture of 1.21 g (6.14 mmol) of product from 63b, 20 ml 20% sodium hydroxide solution and 40 ml of ethanol is refluxed overnight with stirring. The ethanol is eliminated in vacuo. The residue is diluted with water and acidified with 4 M HCl. The precipitated product is filtered off and dried at 50°C in the circulating air dryer.

$C_{12}H_{12}N_2O_2$ (252.70)

[M+H]+ = 217

HPLC (Method 4): retention time = 1.7 min

67b)



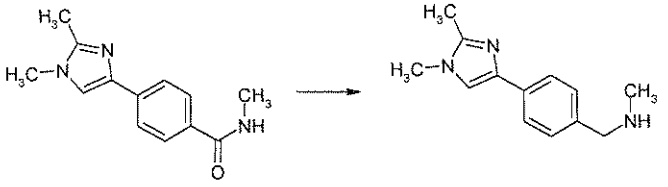
67b is prepared analogously to 1f from 1.55 g (6.13 mmol) of product from 67a, 4.60 ml (9.20 mmol) of methylamine 2 M in THF (Aldrich), 1.71 ml (12.30 mmol) of triethylamine and 2.38 g (7.40 mmol) of TBTU in 50 ml THF.

$C_{13}H_{15}N_3O$ (229.28)

[M+H]+ = 230

TLC: silica gel, dichloromethane / methanol 9:1, Rf value = 0.47

67c)



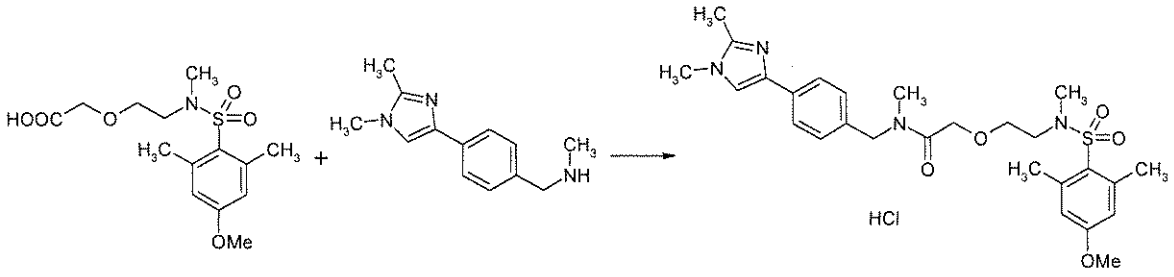
67c is prepared analogously to 38f from 1.33 g (5.80 mmol) of product from 67b and 15.00 ml (15.00 mmol) of lithium aluminium hydride 1 M in THF (Aldrich) in 80 ml THF.

$C_{13}H_{17}N_3$ (215.29)

[M+H]+ = 216

TLC: silica gel, dichloromethane / methanol / ammonia 9:1:0.1, Rf value = 0.29

67d)



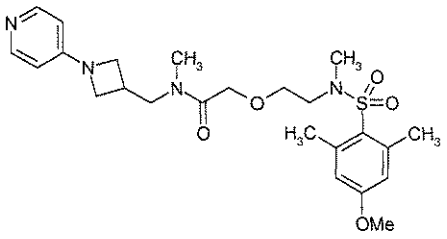
Example 67 is prepared analogously to 1f from 0.099 g (0.30 mmol) of product from 53c, 0.065 g (0.30 mmol) of product from 67c, 0.083 ml (0.60 mmol) of triethylamine and 0.12 g (0.36 mmol) of TBTU in 7 ml THF and 1 ml DMF.

$C_{27}H_{36}N_4O_5S$ x HCl (565.13)

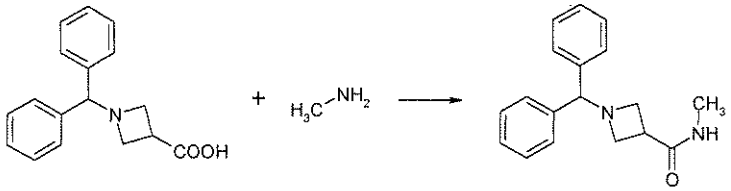
[M+H]+ = 529

HPLC (Method 4): retention time = 3.1 min

Example 68



68a)

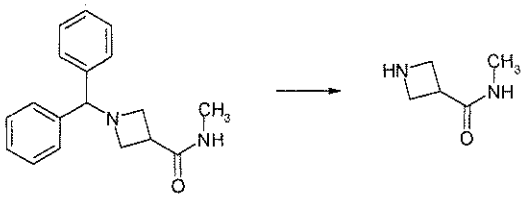


68a is prepared analogously to 1f from 5.39 g (20.16 mmol) of 1-benzhydryl-azetidine-3-carboxylic acid (Acros), 15 ml (30.00 mmol) of methylamine 2 M in THF (Aldrich), 5.58 ml (40.00 mmol) of triethylamine and 7.71 g (24.00 mmol) of TBTU in 150 ml THF.

$C_{18}H_{20}N_2O$ (280.36)

HPLC (Method 4): retention time = 2.5 min

68b)

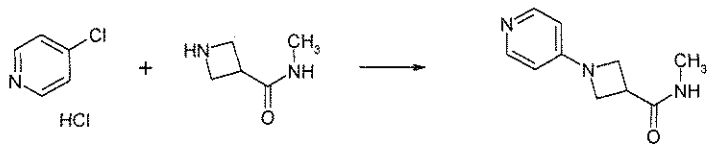


A mixture of 5.32 g (18.98 mmol) of product from 68a, 0.50 g palladium on charcoal (10%) and 100 ml of methanol is hydrogenated for 24 hours at ambient temperature in the autoclave. The catalyst is filtered off, the filtrate is evaporated to dryness in vacuo. The crude product thus obtained is purified by column chromatography through silica gel (eluant: dichloromethane / methanol / ammonia 70:30:3).

$C_5H_{10}N_2O$ (114.15)

TLC: silica gel, dichloromethane / methanol / ammonia 7:3:0.3, Rf value = 0.17

68c)



68c is prepared analogously to 28c from 1.31 g (8.76 mmol) of 4-chloropyridine hydrochloride (Aldrich), 1.00 g (8.76 mmol) of product from 68b and 2.40 ml (17.22 mmol) of triethylamine in 5 ml of ethanol.

$C_{10}H_{13}N_3O$ (191.23)

[M+H]+ = 192

TLC: silica gel, dichloromethane / methanol / ammonia 9:1:0.1, Rf value = 0.25

68d)

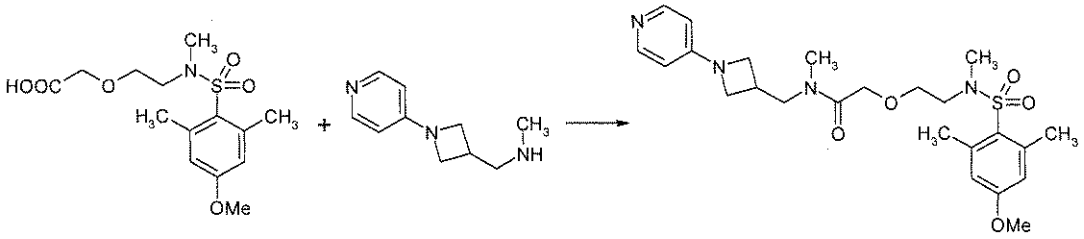
68d is prepared analogously to 38f from 0.46 g (2.41 mmol) of product from 68c and 5.00 ml (5.00 mmol) of lithium aluminium hydride 1 M in THF (Aldrich) in 20 ml THF.

$C_{10}H_{15}N_3$ (177.25)

[M+H]+ = 178

TLC: silica gel, dichloromethane / methanol / ammonia 8:2:0.2, Rf value = 0.40

68e)



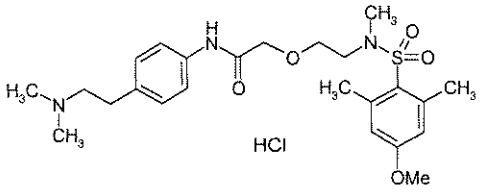
Example 68 is prepared analogously to 1f from 0.083 g (0.25 mmol) of product from 53c, 0.044 g (0.25 mmol) of product from 68d, 0.070 ml (0.50 mmol) of triethylamine and 0.096 g (0.30 mmol) of TBTU in 7 ml THF and 1 ml DMF.

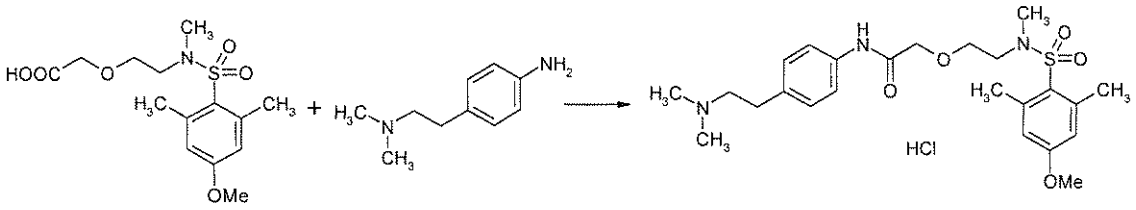
$C_{24}H_{34}N_4O_5S$ (490.62)

[M+H]+ = 491

HPLC (Method 4): retention time = 2.9 min

Example 69





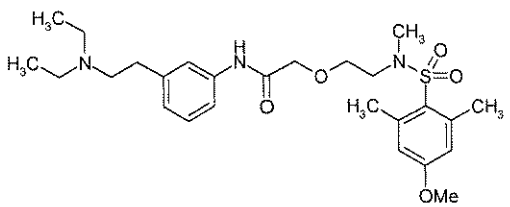
Example 69 is prepared analogously to 1f from 0.083 g (0.25 mmol) of product from 53c, 0.041 g (0.25 mmol) of 4-(2-dimethylamino-ethyl)-phenylamine (JW Pharmlab), 0.070 ml (0.50 mmol) of triethylamine and 0.096 g (0.30 mmol) of TBTU in 7 ml THF and 1 ml DMF.

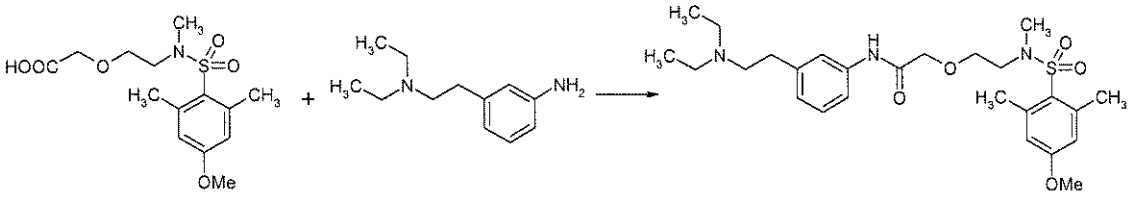
$C_{24}H_{35}N_3O_5S$ x HCl (514.08)

[M+H]+ = 478

HPLC (Method 4): retention time = 3.1 min

Example 70





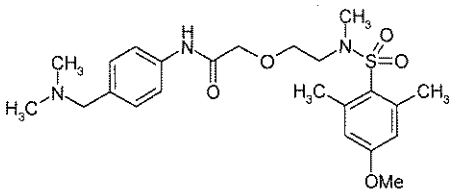
Example 70 is prepared analogously to 1f from 0.083 g (0.25 mmol) of product from 53c, 0.048 g (0.25 mmol) of 3-(2-diethylamino-ethyl)-phenylamine (analogously to J. Med. Chem. 28, 1985, 1533-1536), 0.070 ml (0.50 mmol) of triethylamine and 0.096 g (0.30 mmol) of TBTU in 7 ml THF and 1 ml DMF.

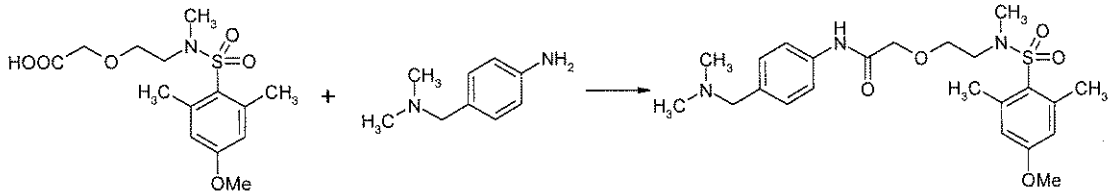
$C_{26}H_{39}N_3O_5S$ (505.67)

$[M+H]^+$ = 506

HPLC (Method 4): retention time = 3.4 min

Example 71





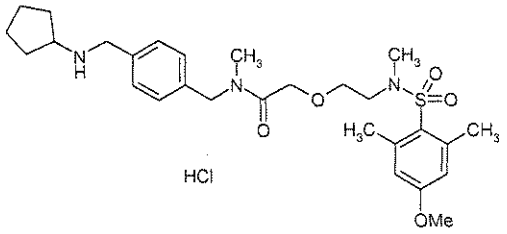
Example 71 is prepared analogously to 1f from 0.083 g (0.25 mmol) of product from 53c, 0.038 g (0.25 mmol) of 4-dimethylaminomethyl-phenylamine (J. Chem. Soc. 1935, 871), 0.070 ml (0.50 mmol) of triethylamine and 0.096 g (0.30 mmol) of TBTU in 7 ml THF and 1 ml DMF.

$C_{23}H_{33}N_3O_5S$ (463.59)

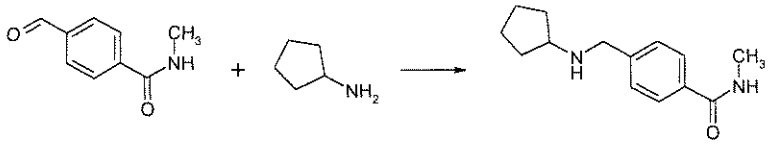
$[M+H]^+$ = 464

HPLC (Method 4): retention time = 3.1 min

Example 72



72a)



72a is prepared analogously to 60a from 0.82 g (5.00 mmol) of 4-formyl-benzoic acid methylamide (EMKA), 0.50 ml (5.00 mmol) of cyclopentylamine (Aldrich), 0.37 ml (6.50 mmol) of acetic acid and 1.59 g (7.50 mmol) of sodium triacetoxyborohydride in 30 ml THF.

$C_{14}H_{20}N_2O$ (232.32)

TLC: silica gel, dichloromethane / ethanol 9:1, Rf value = 0.15

72b)

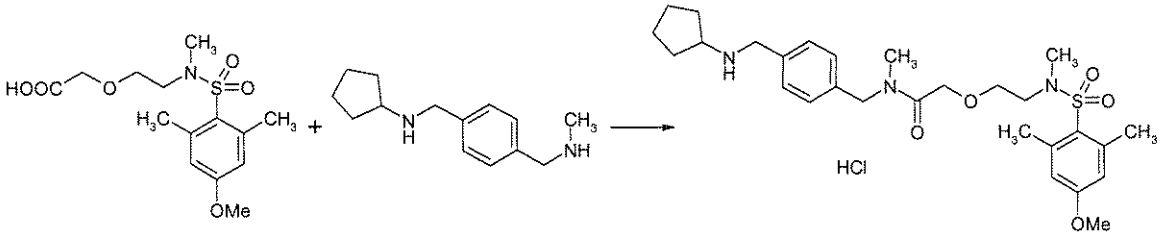
72b is prepared analogously to 38f from 1.00 g (4.30 mmol) of product from 72a and 9.00 ml (9.00 mmol) of lithium aluminium hydride 1 M in THF (Aldrich) in 40 ml THF.

$C_{14}H_{22}N_2$ (218.34)

[M+H]+ = 219

TLC: silica gel, dichloromethane / ethanol 9:1, Rf value = 0.2

72c)



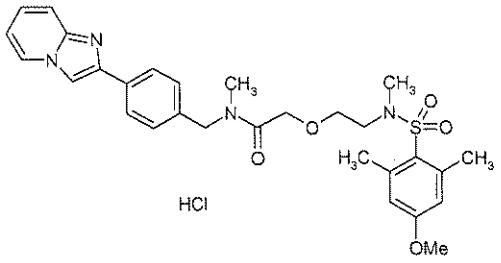
Example 72 is prepared analogously to 1f from 0.20 g (0.60 mmol) of product from 53c, 0.13 g (0.60 mmol) of product from 72b, 0.21 ml (1.50 mmol) of triethylamine and 0.23 g (0.72 mmol) of TBTU in 10 ml THF.

$C_{28}H_{41}N_3O_5S$ x HCl (568.17)

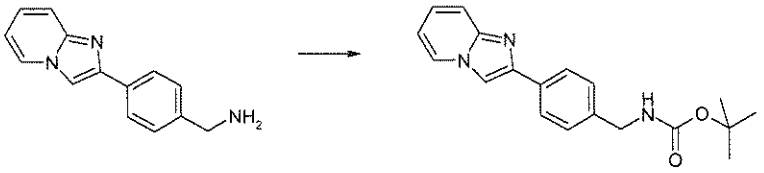
[M+H]+ = 532

HPLC (Method 5): retention time = 1.60 min

Example 73



73a)



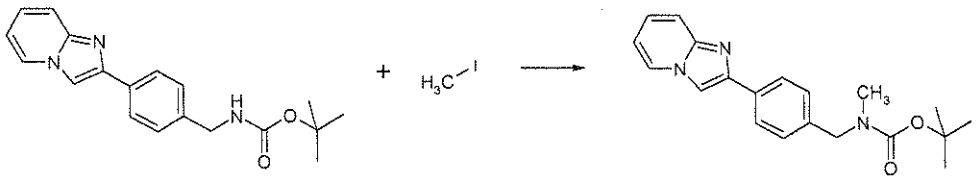
A mixture of 2.60 g (11.65 mmol) of product from 65a, 2.55 g (11.68 mmol) of Boc-anhydride and 100 ml DMF is stirred for two hours at ambient temperature. Then 100 ml of water are slowly added thereto. The precipitated product is filtered off, washed with water and petroleum ether and dried.

$C_{19}H_{21}N_3O_2$ (323.39)

[M+H]+ = 324

TLC: silica gel, dichloromethane / methanol 9:1, Rf value = 0.78

73b)

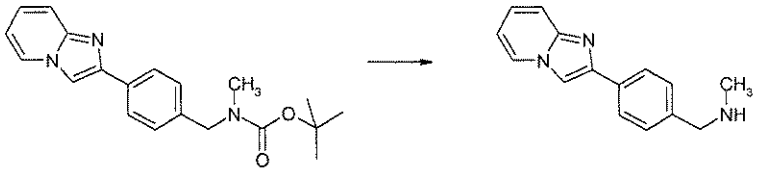


73b is prepared analogously to 62a from 1.00 g (3.09 mmol) of product from 73a, 0.70 g (6.24 mmol) of potassium-tert-butoxide and 0.98 ml (6.90 mmol) of methyl iodide in 30 ml DMSO.

$C_{17}H_{17}N_3O_2$ (295.34)

[M+H]+ = 296

73c)

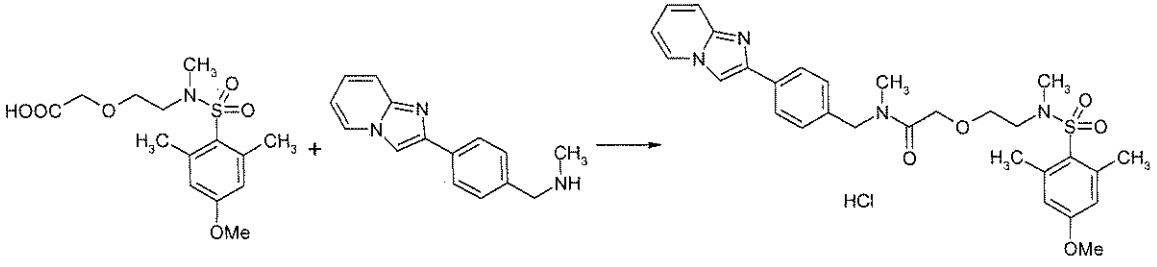


A mixture of 0.59 g (1.75 mmol) of product from 73b, 2 ml TFA and 30 ml dichloromethane is stirred for three hours at ambient temperature. The reaction mixture is then washed with water, dried on sodium sulphate and evaporated to dryness in vacuo.

$C_{15}H_{15}N_3$ (237.30)

[M+H]+ = 238

73d)



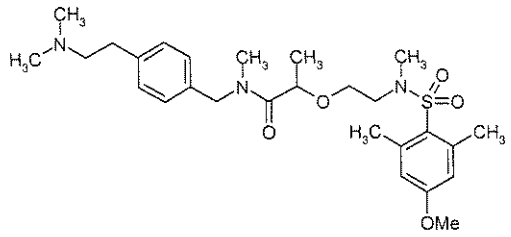
Example 73 is prepared analogously to 1f from 0.14 g (0.42 mmol) of product from 53c, 0.10 g (0.42 mmol) of product from 73c, 0.10 ml (0.99 mmol) of triethylamine and 0.15 g (0.46 mmol) of TBTU in 30 ml THF and 5 ml DMF.

$C_{29}H_{34}N_4O_5S$ x HCl (587.13)

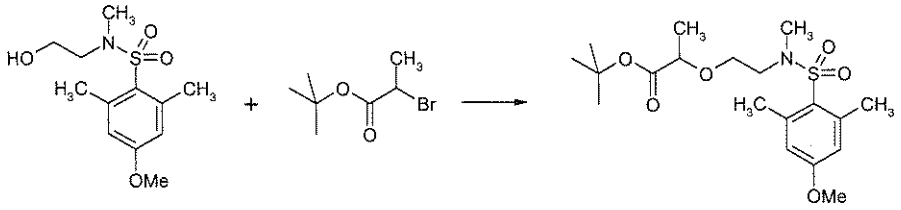
[M+H]+ = 551

HPLC (Method 5): retention time = 1.58 min

Example 74



74a)



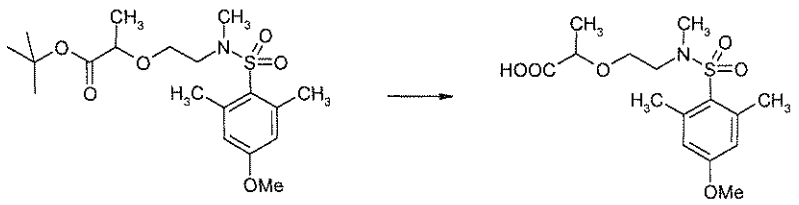
74a is prepared analogously to 53b from 4.08 g (14.93 mmol) of product from 53a, 4.68 g (22.39 mmol) of tert-butyl 2-bromopropionate (TCI), 1.38 g (4.98 mmol) of tetrabutylammonium chloride (Fluka) and 70 ml of 35% sodium hydroxide solution in 70 ml of toluene.

$C_{19}H_{31}NO_6S$ (401.52)

[M+H]+ = 402

TLC: silica gel, petroleum ether / ethyl acetate 7:3, Rf value = 0.69

74b)



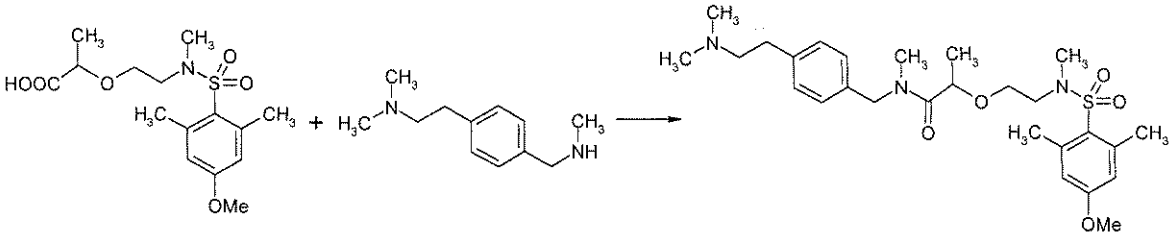
74b is prepared analogously to 53c from 5.12 g (12.75 mmol) of product from 74a and 5.89 ml TFA in 80 ml dichloromethane.

$C_{15}H_{23}NO_6S$ (345.41)

[M+H]+ = 346

TLC: silica gel, dichloromethane / ethanol 19:1, Rf value = 0.25

74c)



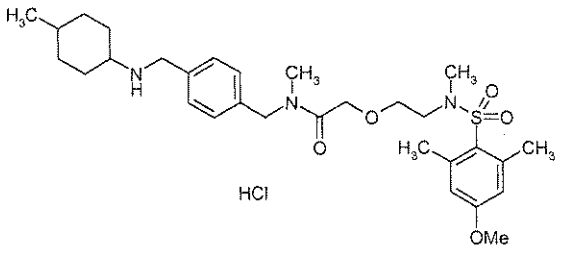
Example 74 is prepared analogously to 1f from 0.10 g (0.30 mmol) of product from 74b, 0.058 g (0.30 mmol) of product from 64d, 0.084 ml (0.60 mmol) of triethylamine and 0.12 g (0.36 mmol) of TBTU in 7 ml THF and 1 ml DMF.

$C_{27}H_{41}N_3O_5S$ (519.70)

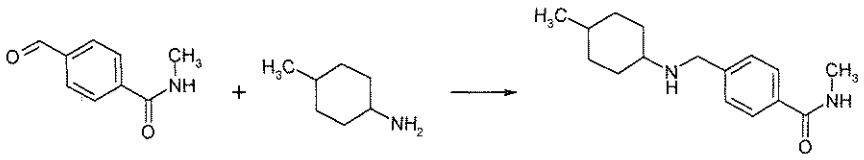
[M+H]+ = 520

HPLC (Method 4): retention time = 3.1 min

Example 75



75a)

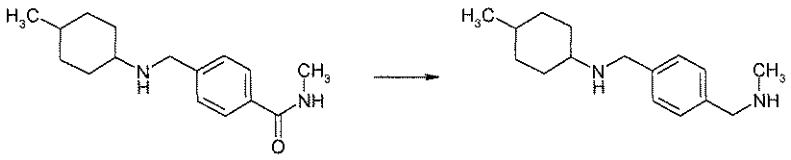


75a is prepared analogously to 60a from 0.82 g (5.00 mmol) of 4-formyl-benzoic acid methylamide (EMKA), 0.67 ml (5.00 mmol) of 4-methylcyclohexylamine cis/trans mixture (Acros), 0.37 ml (6.50 mmol) of acetic acid and 1.59 g (7.50 mmol) of sodium triacetoxyborohydride in 30 ml THF.

$C_{16}H_{24}N_2O$ (260.37)

TLC: silica gel, dichloromethane / ethanol 9:1, Rf value = 0.25

75b)

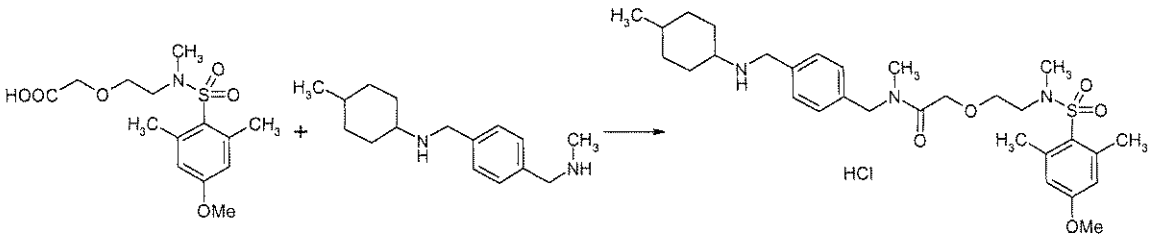


75b is prepared analogously to 38f from 1.30 g (4.99 mmol) of product from 75a and 10.00 ml (10.00 mmol) of lithium aluminium hydride 1 M in THF (Aldrich) in 50 ml THF.

$C_{16}H_{26}N_2$ (246.39)

TLC: silica gel, dichloromethane / ethanol 9:1, Rf value = 0.2

75c)



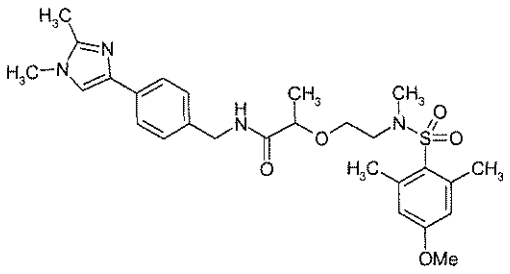
Example 75 is prepared analogously to 1f from 0.20 g (0.60 mmol) of product from 53c, 0.15 g (0.60 mmol) of product from 75b, 0.21 ml (1.50 mmol) of triethylamine and 0.23 g (0.72 mmol) of TBTU in 10 ml THF.

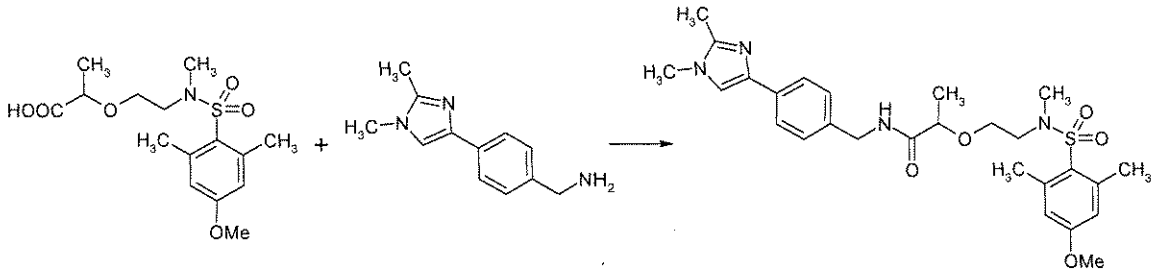
$C_{30}H_{45}N_3O_5S$ x HCl (596.22)

[M+H]+ = 560

HPLC (Method 5): retention time = 1.65 min

Example 76





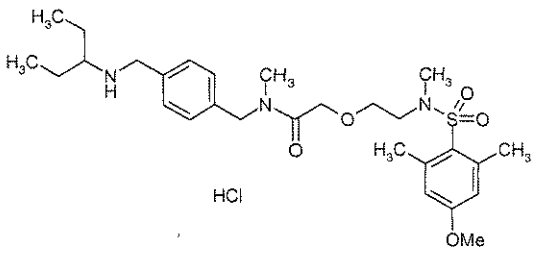
Example 76 is prepared analogously to 1f from 0.10 g (0.30 mmol) of product from 74b, 0.060 g (0.30 mmol) of product from 63c, 0.084 ml (0.60 mmol) of triethylamine and 0.12 g (0.36 mmol) of TBTU in 7 ml THF and 1 ml DMF.

$C_{27}H_{36}N_4O_5S$ (528.66)

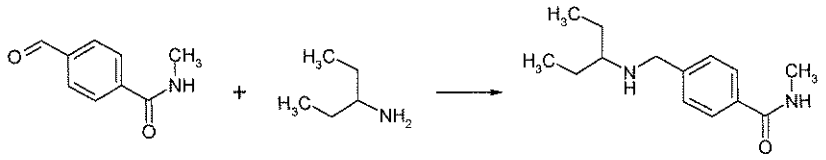
[M+H]+ = 529

HPLC (Method 4): retention time = 3.2 min

Example 77



77a)



77a is prepared analogously to 60a from 0.82 g (5.00 mmol) of 4-formyl-benzoic acid methylamide (EMKA), 0.58 ml (5.00 mmol) of 3-pentylamine (Aldrich), 0.37 ml (6.50 mmol) of acetic acid and 1.59 g (7.50 mmol) of sodium triacetoxyborohydride in 30 ml THF.

$C_{14}H_{22}N_2O$ (234.34)

[M+H]+ = 235

TLC: silica gel, dichloromethane / ethanol 9:1, Rf value = 0.4

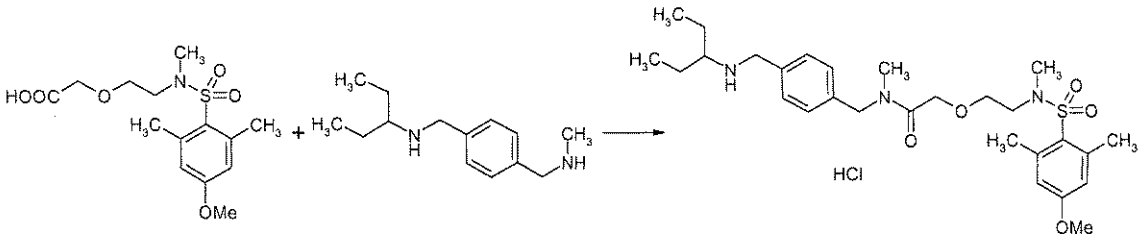
77b)

77b is prepared analogously to 38f from 1.10 g (4.69 mmol) of product from 77a and 9.40 ml (9.40 mmol) of lithium aluminium hydride 1 M in THF (Aldrich) in 40 ml THF.

$C_{14}H_{24}N_2$ (220.35)

TLC: silica gel, dichloromethane / ethanol 9:1, Rf value = 0.1

77c)



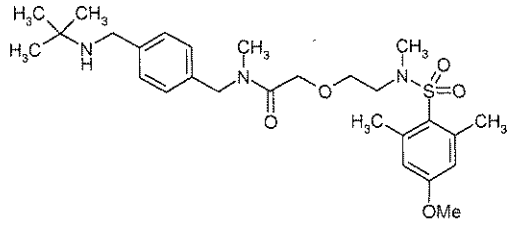
Example 77 is prepared analogously to 1f from 0.20 g (0.60 mmol) of product from 53c, 0.13 g (0.60 mmol) of product from 77b, 0.21 ml (1.50 mmol) of triethylamine and 0.23 g (0.72 mmol) of TBTU in 10 ml THF.

$C_{28}H_{43}N_3O_5S$ x HCl (570.18)

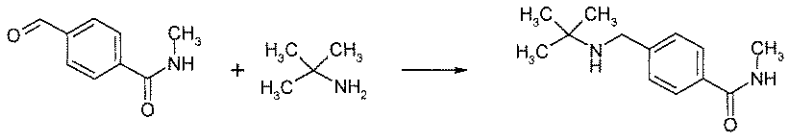
[M+H]+ = 534

TLC: silica gel, dichloromethane / ethanol 9:1, Rf value = 0.45

Example 78



78a)



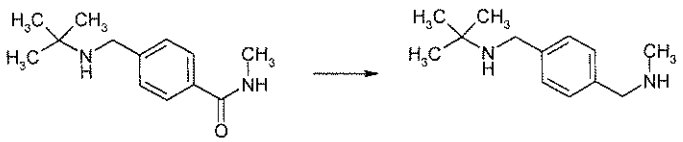
78a is prepared analogously to 60a from 0.82 g (5.00 mmol) of 4-formyl-benzoic acid methylamide (EMKA), 0.53 ml (5.00 mmol) of tert-butylamine (Fluka), 0.37 ml (6.50 mmol) of acetic acid and 1.59 g (7.50 mmol) of sodium triacetoxyborohydride in 30 ml THF.

$C_{13}H_{20}N_2O$ (220.31)

[M+H]+ = 221

TLC: silica gel, dichloromethane / ethanol 9:1, Rf value = 0.15

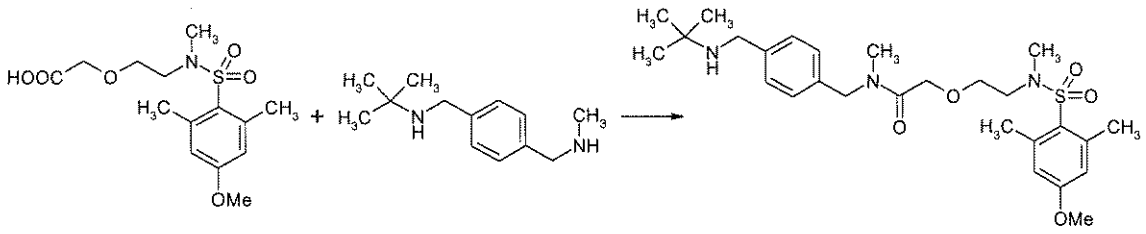
78b)



78b is prepared analogously to 38f from 1.00 g (4.54 mmol) of product from 78a and 9.10 ml (9.10 mmol) of lithium aluminium hydride 1 M in THF (Aldrich) in 40 ml THF.

$C_{13}H_{22}N_2$ (206.33)

78c)



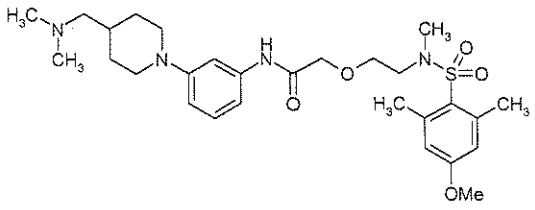
Example 78 is prepared analogously to 1f from 0.20 g (0.60 mmol) of product from 53c, 0.12 g (0.60 mmol) of product from 78b, 0.21 ml (1.50 mmol) of triethylamine and 0.23 g (0.72 mmol) of TBTU in 10 ml THF.

$C_{27}H_{41}N_3O_5S$ (519.70)

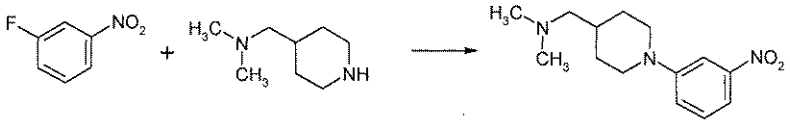
[M+H]+ = 520

HPLC (Method 5): retention time = 1.58 min

Example 79



79a)



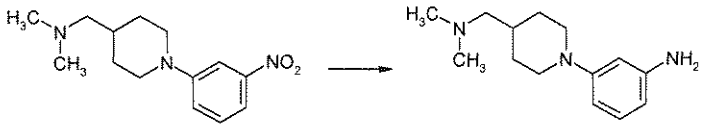
A mixture of 0.50 ml (4.70 mmol) of 1-fluoro-3-nitrobenzene (Fluka), 1.34 g (9.39 mmol) of 4-(N,N-dimethylaminomethyl)-piperidine (Eur. J. Med.Chem. Chim. Ther. 37, 2002, 487-502), 0.65 g (4.70 mmol) of potassium carbonate and 6.6 ml DMSO is stirred for five days at 110°C. The reaction mixture is then poured onto ice, the precipitate formed is filtered off. The product thus obtained is dried overnight in the vacuum desiccator.

$C_{14}H_{21}N_3O_2$ (263.34)

[M+H]+ = 264

TLC: silica gel, dichloromethane / methanol 9:1, Rf value = 0.20

79b)

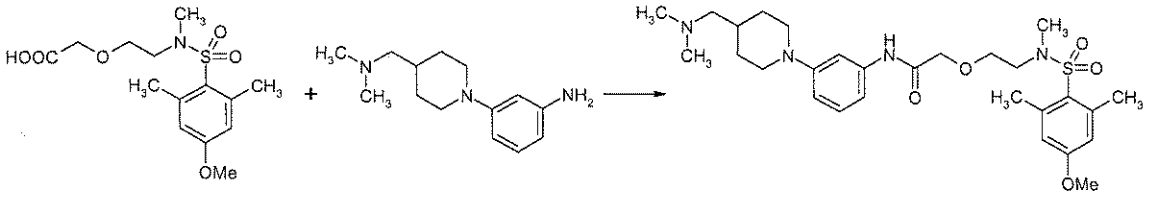


A mixture of 0.95 ml (3.60 mmol) of product from 79a, 0.095 g palladium on charcoal (5%) and 72 ml of ethanol is hydrogenated at ambient temperature in the autoclave. The catalyst is filtered off, the filtrate is evaporated to dryness in vacuo.

$C_{14}H_{23}N_3$ (233.35)

[M+H]+ = 234

79c)



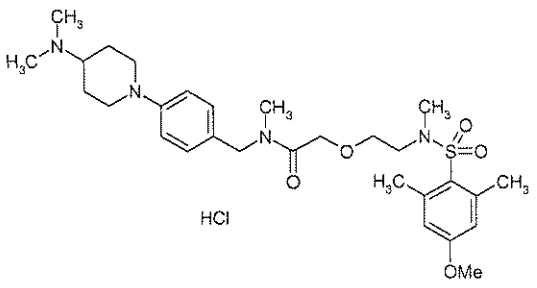
Example 79 is prepared analogously to 1f from 0.15 g (0.46 mmol) of product from 53c, 0.11 g (0.46 mmol) of product from 79b, 0.084 ml (0.60 mmol) of triethylamine and 0.18 g (0.56 mmol) of TBTU in 3 ml DMF.

$C_{28}H_{42}N_4O_5S$ (546.72)

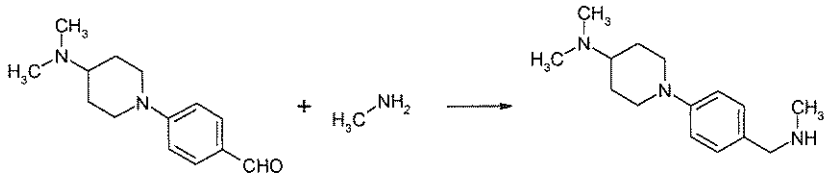
[M+H]+ = 547

HPLC (Method 5): retention time = 1.49 min

Example 80



80a)



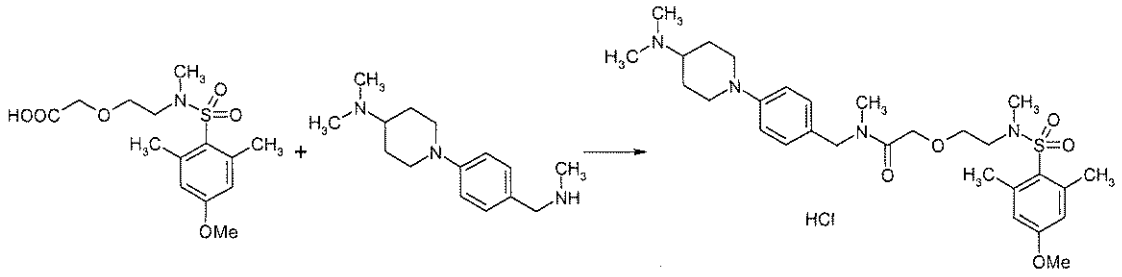
80a is prepared analogously to 33a from 0.70 g (3.01 mmol) of 4-(4-dimethylamino-piperidin-1-yl)-benzaldehyde (Tetrahedron 57, 2001, 4781-4785), 3.00 ml (31.88 mmol) of methylamine 33% in ethanol (Aldrich), 0.20 g Raney nickel in 25 ml of ethanol.

$C_{15}H_{25}N_3$ (247.38)

[M+H]+ = 248

TLC: silica gel, dichloromethane / methanol / ammonia 9:1:0.1, Rf value = 0.16

80b)



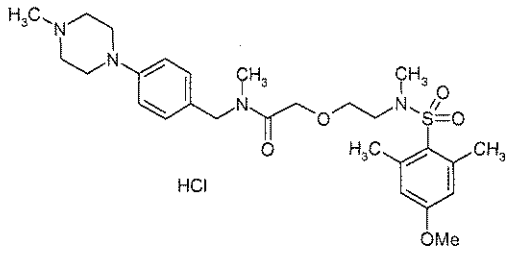
Example 80 is prepared analogously to 1f from 0.15 g (0.45 mmol) of product from 53c, 0.11 g (0.45 mmol) of product from 80a, 0.13 ml (0.90 mmol) of triethylamine and 0.17 g (0.54 mmol) of TBTU in 5 ml DMF.

$C_{29}H_{44}N_4O_5S$ x HCl (597.21)

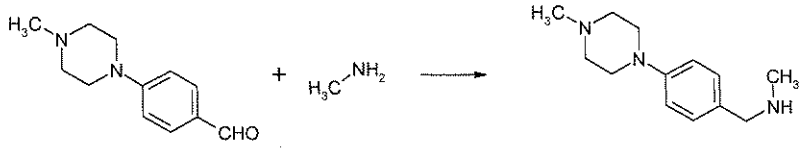
[M+H]+ = 561

HPLC (Method 1): retention time = 2.33 min

Example 81



81a)



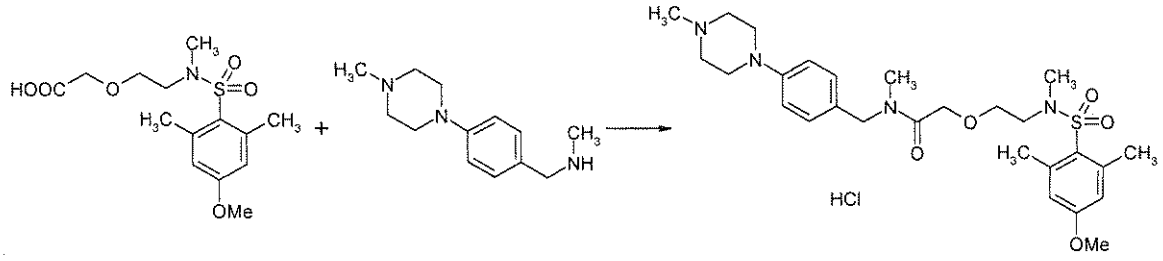
81a is prepared analogously to 33a from 1.00 g (4.90 mmol) of 4-(4-methyl-piperazin-1-yl)-benzaldehyde (Chem. Pharm Bull. 45, 1997, 1458-1469), 4.00 ml (42.50 mmol) of methylamine 33% in ethanol (Aldrich), 0.20 g Raney nickel in 30 ml of ethanol.

$C_{13}H_{21}N_3$ (219.33)

[M+H]+ = 220

TLC: silica gel, dichloromethane / methanol / ammonia 9:1:0.1, Rf value = 0.15

81b)



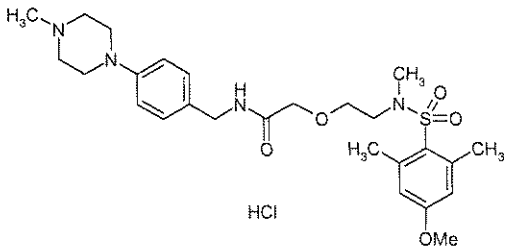
Example 81 is prepared analogously to 1f from 0.15 g (0.45 mmol) of product from 53c, 0.099 g (0.45 mmol) of product from 81a, 0.13 ml (0.90 mmol) of triethylamine and 0.17 g (0.54 mmol) of TBTU in 5 ml DMF.

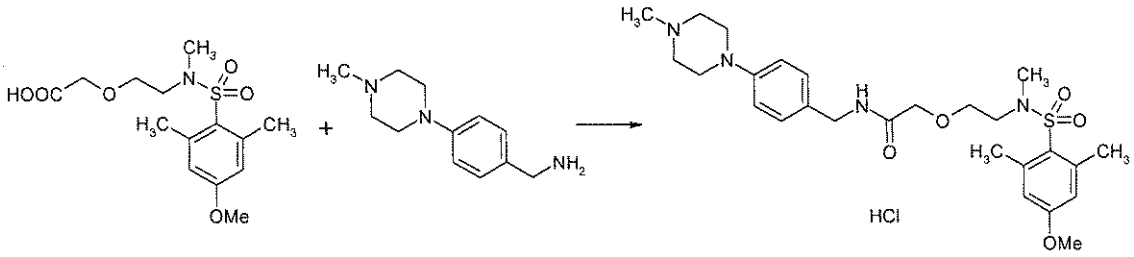
$C_{27}H_{40}N_4O_5S$ x HCl (569.16)

[M+H]+ = 533

HPLC (Method 1): retention time = 2.28 min

Example 82





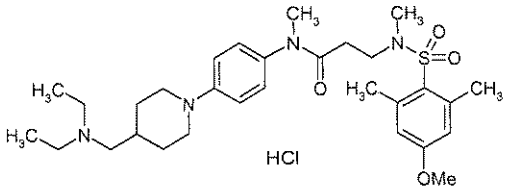
Example 82 is prepared analogously to 1f from 0.15 g (0.45 mmol) of product from 53c, 0.092 g (0.45 mmol) of product from 19b, 0.13 ml (0.90 mmol) of triethylamine and 0.17 g (0.54 mmol) of TBTU in 5 ml DMF.

$C_{26}H_{38}N_4O_5S$ x HCl (555.13)

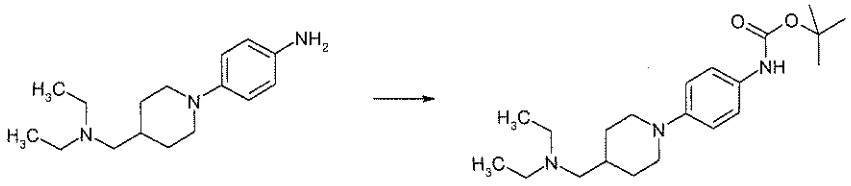
[M+H]+ = 519

HPLC (Method 1): retention time = 2.29 min

Example 83



83a)



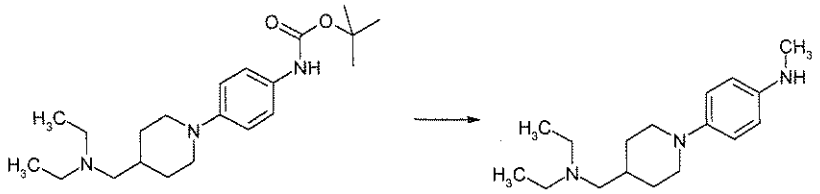
83a is prepared analogously to 51a from 1.35 g (5.16 mmol) of product from 41b, 1.24 g (5.68 mmol) of Boc-anhydride and 0.80 ml (5.68 mmol) of triethylamine in 50 ml dichloromethane.

$C_{21}H_{35}N_3O_2$ (361.52)

[M+H]+ = 362

TLC: silica gel, dichloromethane / methanol / ammonia 9:1:0.1, Rf value = 0.42

83b)



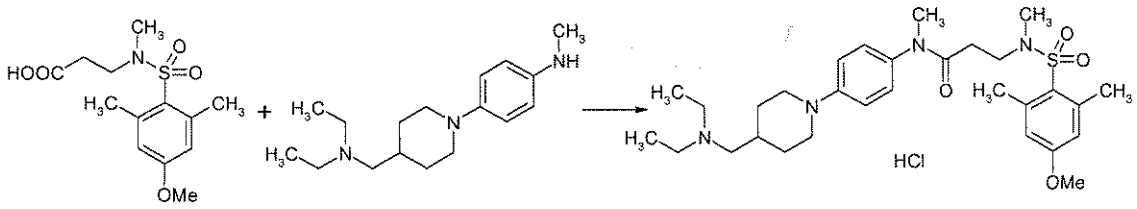
83b is prepared analogously to 51b from 1.80 g (4.98 mmol) of product from 83a and 0.57 g (15.00 mmol) of lithium aluminium hydride (Aldrich) in 25 ml THF.

$C_{17}H_{29}N_3$ (275.43)

[M+H]+ = 276

HPLC (Method 1): retention time = 1.77 min

83c)



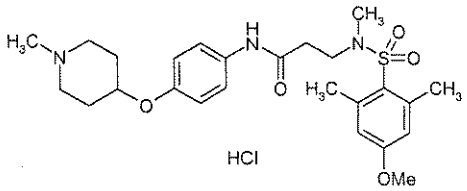
Example 83 is prepared analogously to 1f from 0.14 g (0.50 mmol) of product from 22c, 0.15 g (0.50 mmol) of product from 83b, 0.14 ml (1.00 mmol) of triethylamine and 0.18 g (0.55 mmol) of TBTU in 6 ml DMF.

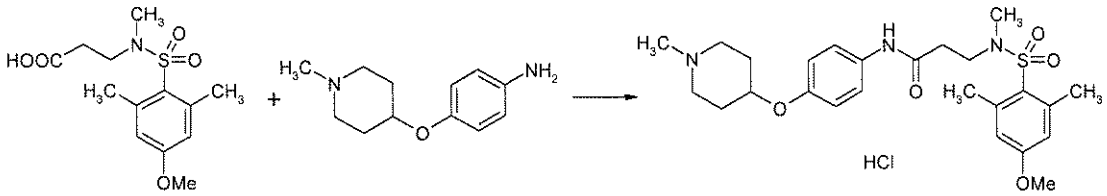
$C_{30}H_{46}N_4O_4S$ x HCl (595.24)

[M+H]+ = 559

HPLC (Method 1): retention time = 2.46 min

Example 84





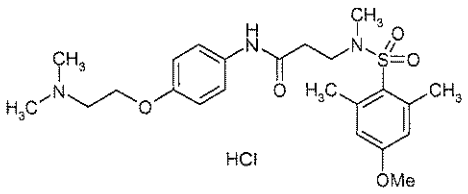
Example 84 is prepared analogously to 1f from 0.15 g (0.50 mmol) of product from 22c, 0.10 g (0.50 mmol) of 4-(1-methylpiperidin-4-yloxy)-phenylamine (ART-CHEM), 0.14 ml (1.00 mmol) of triethylamine and 0.18 g (0.55 mmol) of TBTU in 6 ml DMF.

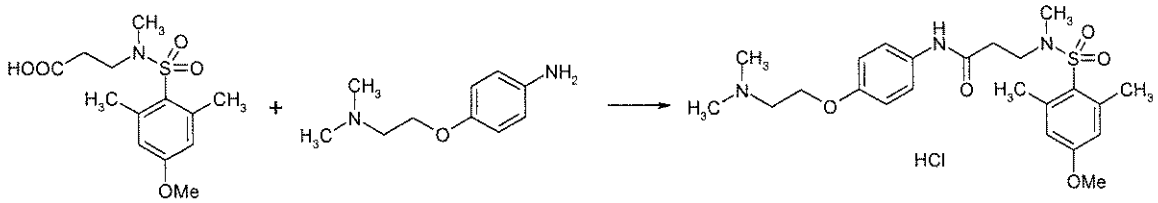
$C_{25}H_{35}N_3O_5S$ x HCl (526.09)

[M+H]+ = 490

HPLC (Method 1): retention time = 2.40 min

Example 85





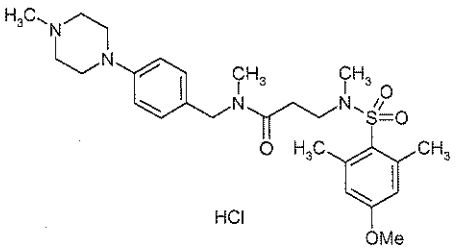
Example 85 is prepared analogously to 1f from 0.15 g (0.50 mmol) of product from 22c, 0.09 g (0.50 mmol) of 4-(2-dimethylamino-ethoxy)-phenylamine (Collect. Czech. Chem. Commun. 55, 1990, 282-295), 0.14 ml (1.00 mmol) of triethylamine and 0.18 g (0.55 mmol) of TBTU in 6 ml DMF.

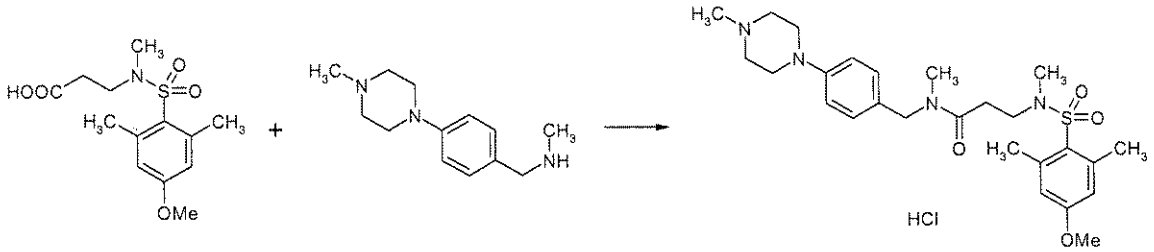
$C_{23}H_{33}N_3O_5S$ x HCl (500.05)

[M+H]+ = 464

HPLC (Method 1): retention time = 2.35 min

Example 86





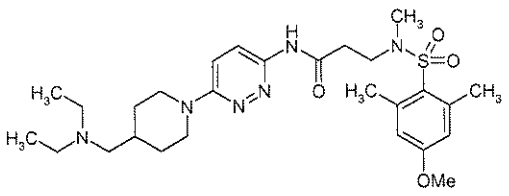
Example 86 is prepared analogously to 1f from 0.14 g (0.45 mmol) of product from 22c, 0.099 g (0.45 mmol) of product from 81a, 0.13 ml (0.90 mmol) of triethylamine and 0.17 g (0.54 mmol) of TBTU in 5 ml DMF.

$C_{26}H_{38}N_4O_5S$ x HCl (539.13)

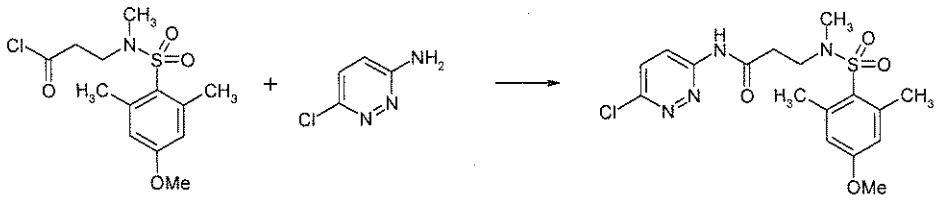
[M+H]+ = 503

HPLC (Method 1): retention time = 2.43 min

Example 87



87a)

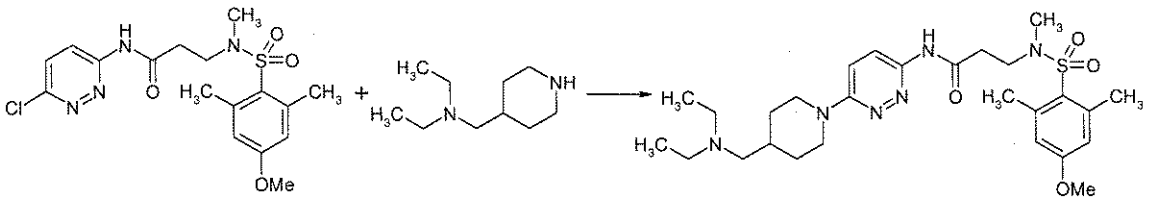


A mixture of 0.11 g (0.33 mmol) of product from 27c, 0.043 g (0.33 mmol) of 3-amino-6-chloropyridazine (Acros), 0.12 ml (0.66 mmol) of DIPEA and 10 ml dichloromethane is refluxed for three days with stirring. The precipitate is then filtered off. The filtrate is evaporated to dryness in vacuo and the crude product is purified by preparative HPLC.

$C_{17}H_{21}ClN_4O_4S$ (412.89)

[M+H]+ = 413/415

87b)



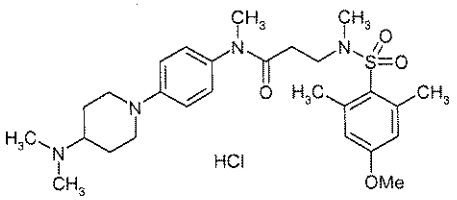
A mixture of 0.03 g (0.073 mmol) of product from 87a and 0.013 g (0.073 mmol) of diethyl-piperidin-4-ylmethyl-amine (Chem. Pharm. Bull. 42, 1994, 74-84) is melted at 173°C. The product is then recovered from the reaction mixture by preparative HPLC.

$C_{27}H_{42}N_6O_4S$ (546.73)

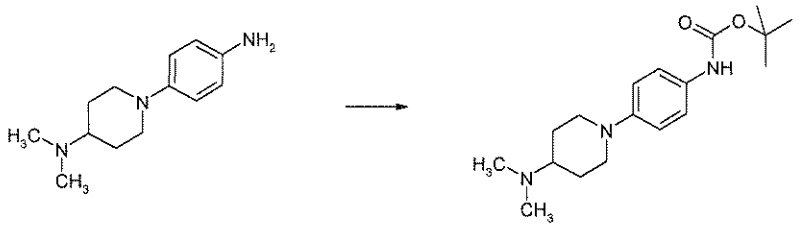
[M+H]+ = 547

HPLC (Method 6): retention time = 2.12 min

Example 88



88a)



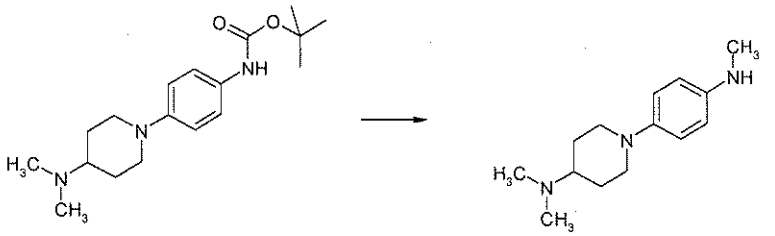
88a is prepared analogously to 51a from 0.70 g (3.18 mmol) of product from 27b, 0.80 g (3.65 mmol) of Boc-anhydride and 5.50 ml (11.00 mmol) of 2 M sodium hydroxide solution in 40 ml dioxane and 20 ml of water.

$C_{17}H_{28}N_4O_2$ (320.43)

[M+H]+ = 321

TLC: silica gel, dichloromethane / methanol / ammonia 4:1:0.2, Rf value = 0.83

88b)



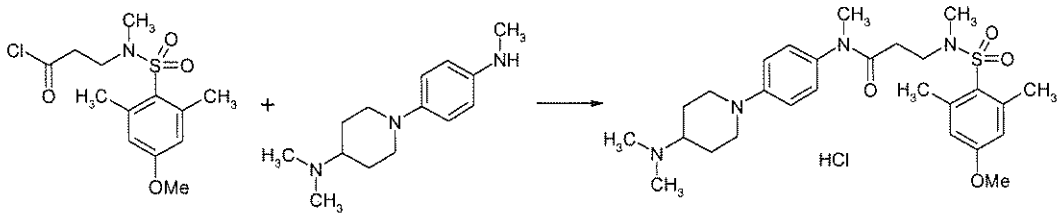
88b is prepared analogously to 51b from 0.60 g (1.87 mmol) of product from 88a and 0.21 g (5.60 mmol) of lithium aluminium hydride (Aldrich) in 20 ml THF.

$C_{13}H_{22}N_4$ (234.34)

[M+H]+ = 235

TLC: silica gel, dichloromethane / methanol / ammonia 4:1:0.2, Rf value = 0.62

88c)



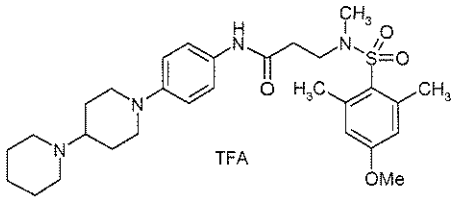
Example 88 is prepared analogously to 27d from 0.16 g (0.50 mmol) of product from 27c, 0.12 g (0.50 mmol) of product from 88b and 0.17 ml (1.00 mmol) of DIPEA in 5 ml THF.

$C_{26}H_{39}N_5O_4S$ x HCl (554.15)

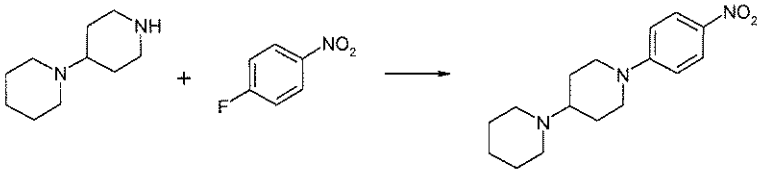
[M+H]+ = 518

TLC: silica gel, dichloromethane / methanol / ammonia 9:1:0.1, Rf value = 0.61

Example 89



89a)



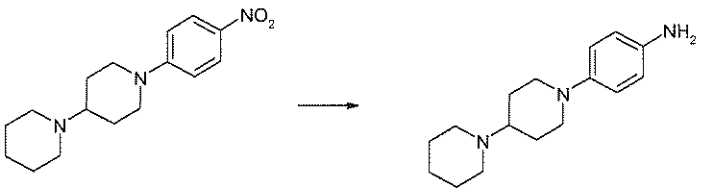
89a is prepared analogously to 8a from 0.70 g (4.18 mmol) of 4-piperidinopiperidine (Aldrich), 0.44 ml (4.18 mmol) of 1-fluoro-4-nitrobenzene (Acros) and 1.33 ml (9.61 mmol) of triethylamine in 12 ml DMF.

$C_{16}H_{23}N_3O_2$ (289.37)

[M+H]+ = 290

TLC: silica gel, dichloromethane / methanol / ammonia 9:1:0.1, Rf value = 0.3

89b)



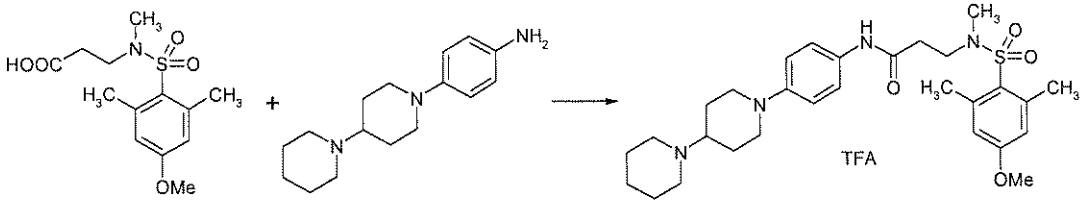
89b is prepared analogously to 8b from 0.96 g (3.32 mmol) of product from 89a and 0.093 g palladium on charcoal (5%) in 45 ml of ethanol.

$C_{16}H_{25}N_3$ (259.39)

[M+H]+ = 260

TLC: silica gel, dichloromethane / methanol / ammonia 9:1:0.1, Rf value = 0.2

89c)



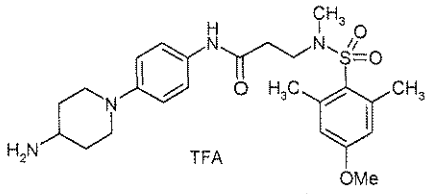
Example 89 is prepared analogously to 1f from 0.10 g (0.33 mmol) of product from 22c, 0.086 g (0.33 mmol) of product from 89b, 0.14 ml (1.00 mmol) of triethylamine and 0.11 g (0.33 mmol) of TBTU in 2 ml THF.

$C_{29}H_{42}N_4O_4S \times C_2HF_3O_2$ (656.76)

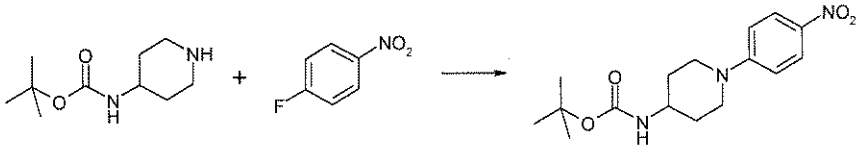
[M+H]+ = 543

HPLC (Method 5): retention time = 1.47 min

Example 90



90a)

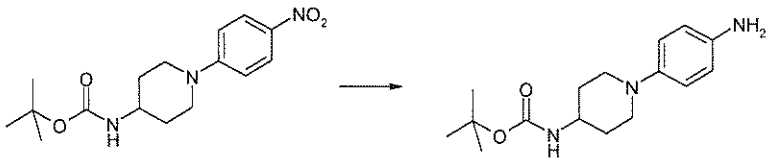


90a is prepared analogously to 8a from 0.84 g (4.18 mmol) of 4-N-Boc-aminopiperidine (Acros), 0.44 ml (4.18 mmol) of 1-fluoro-4-nitrobenzene (Acros) and 1.33 ml (9.61 mmol) of triethylamine in 12 ml DMF.

$C_{16}H_{23}N_3O_4$ (321.37)

[M+H]+ = 322

90b)

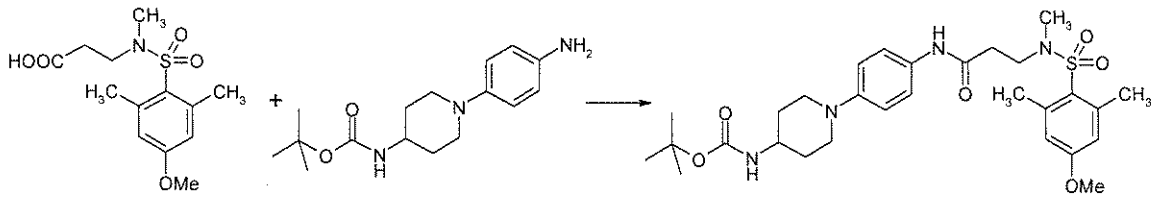


90b is prepared analogously to 8b from 1.01 g (3.43 mmol) of product from 90a and 0.11 g palladium on charcoal (5%) in 45 ml of ethanol.

$C_{16}H_{25}N_3O_2$ (291.39)

[M+H]+ = 292

90c)



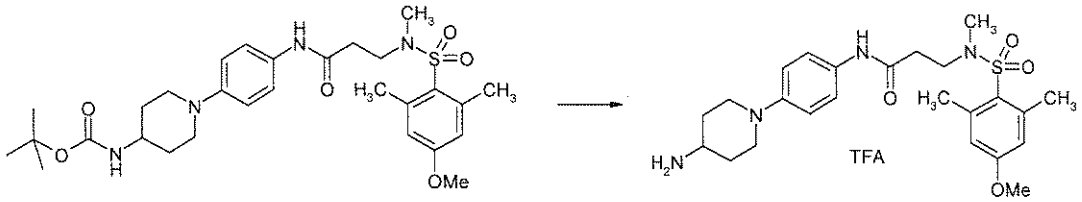
90c is prepared analogously to 1f from 0.10 g (0.33 mmol) of product from 22c, 0.097 g (0.33 mmol) of product from 90b, 0.14 ml (1.00 mmol) of triethylamine and 0.11 g (0.33 mmol) of TBTU in 2 ml THF.

$C_{29}H_{42}N_4O_6S$ (574.73)

[M+H]+ = 575

HPLC (Method 5): retention time = 1.62 min

90d)



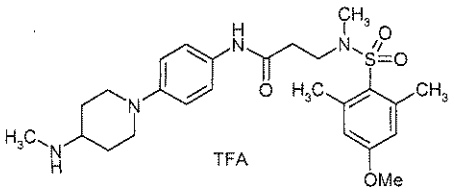
Example 90 is prepared analogously to 18b from 0.19 g (0.33 mmol) of product from 90c and 0.33 ml TFA in 0.5 ml dichloromethane.

$C_{24}H_{34}N_4O_4S \times C_2HF_3O_2$ (588.64)

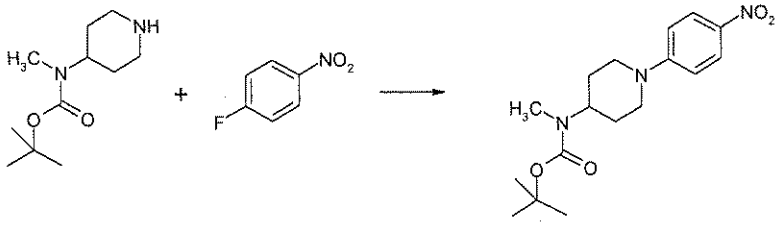
[M+H]+ = 475

HPLC (Method 5): retention time = 1.41 min

Example 91



91a)



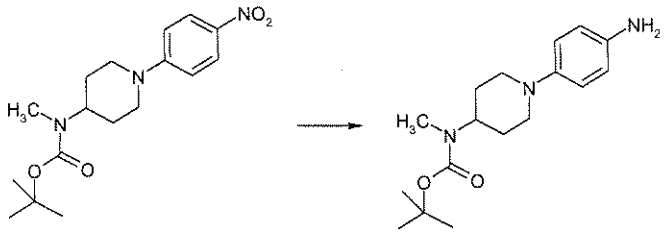
91a is prepared analogously to 8a from 0.90 g (4.18 mmol) of tert-butyl methyl-piperidin-4-yl-carbamate (Fluorochem), 0.44 ml (4.18 mmol) of 1-fluoro-4-nitrobenzene (Acros) and 1.33 ml (9.61 mmol) of triethylamine in 12 ml DMF.

$C_{17}H_{25}N_3O_4$ (335.40)

[M+H]+ = 336

TLC: silica gel, dichloromethane / methanol 30:1, Rf value = 0.6

91b)



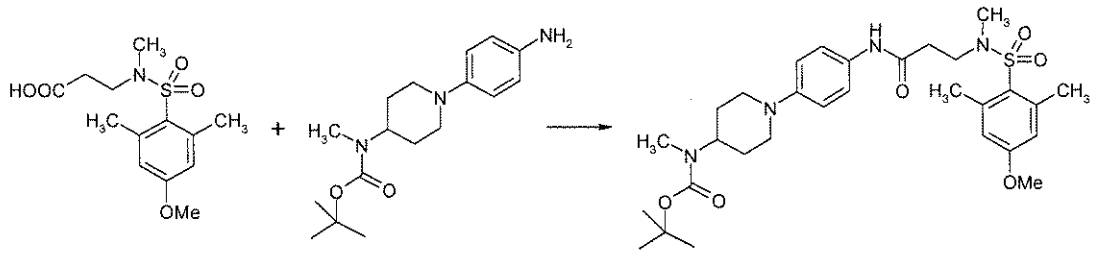
91b is prepared analogously to 8b from 1.08 g (3.22 mmol) of product from 91a and 0.11 g palladium on charcoal (5%) in 45 ml of ethanol.

$C_{17}H_{27}N_3O_2$ (305.42)

[M+H]+ = 306

TLC: silica gel, dichloromethane / methanol 30:1, Rf value = 0.4

91c)



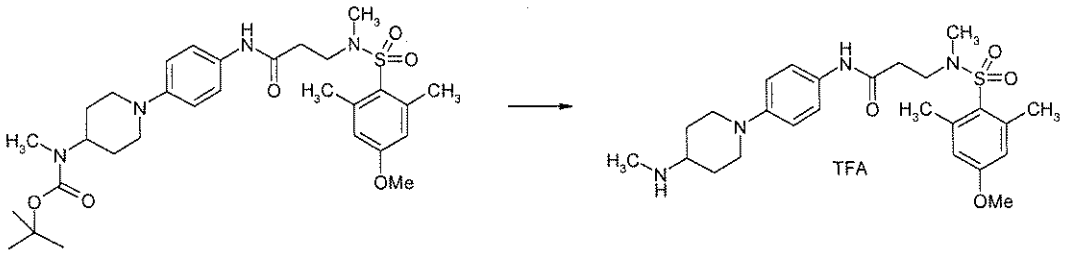
91c is prepared analogously to 1f from 0.10 g (0.33 mmol) of product from 22c, 0.10 g (0.33 mmol) of product from 91b, 0.14 ml (1.00 mmol) of triethylamine and 0.11 g (0.33 mmol) of TBTU in 2 ml THF.

$C_{30}H_{44}N_4O_6S$ (588.76)

[M+H]+ = 589

HPLC (Method 5): retention time = 1.69 min

91d)



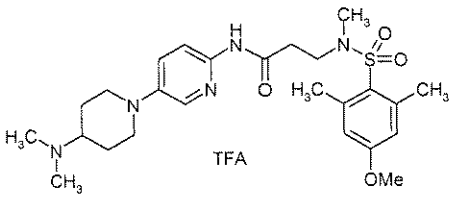
Example 91 is prepared analogously to 18b from 0.21 g (0.36 mmol) of product from 91c and 0.36 ml TFA in 0.6 ml dichloromethane.

$C_{25}H_{36}N_4O_4S \times C_2HF_3O_2$ (602.67)

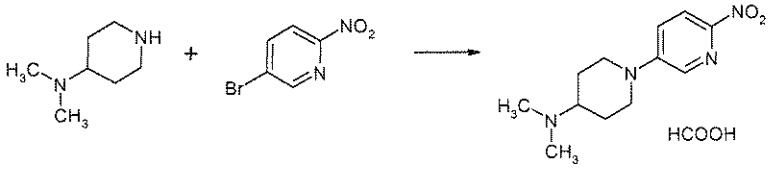
[M+H]+ = 489

HPLC (Method 5): retention time = 1.42 min

Example 92



92a)

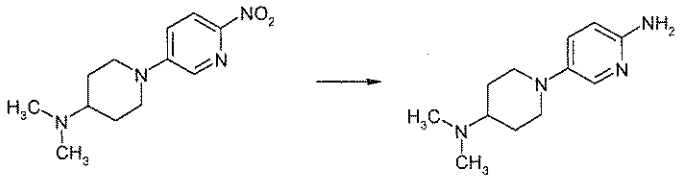


A mixture of 0.88 g (6.88 mmol) of 4-dimethylamino-piperidine (Alfa Aesar), 1.00 g (4.93 mmol) of 3-bromo-6-nitropyriridine (Aldrich), 0.18 g (0.49 mmol) of tetrabutyl-ammonium iodide, 0.74 g (5.33 mmol) of potassium carbonate and 5 ml DMSO is stirred for two hours at 80°C. Then the reaction mixture is poured onto water and extracted with dichloromethane. The organic extracts are washed with saturated sodium hydrogen carbonate solution and saturated sodium chloride solution, dried on sodium sulphate and evaporated to dryness in vacuo. The crude product thus obtained is purified by preparative HPLC.

$C_{12}H_{18}N_4O_2 \times CH_2O_2$ (296.32)

HPLC (Method 1): retention time = 1.49 min

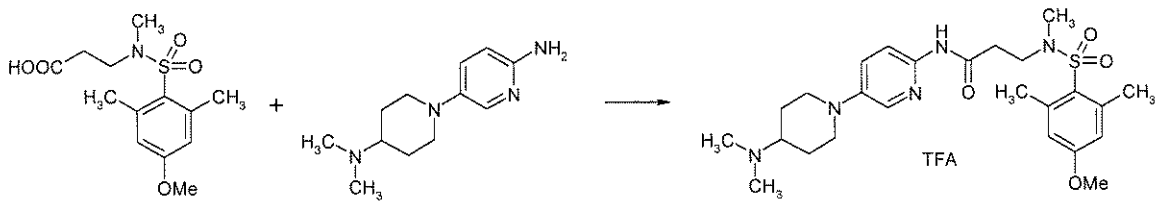
92b)



92b is prepared analogously to 8b from 0.50 g (2.00 mmol) of product from 94a and 0.08 g palladium on charcoal (10%) in 40 ml of methanol.

$C_{12}H_{20}N_4$ (220.31)

92c)



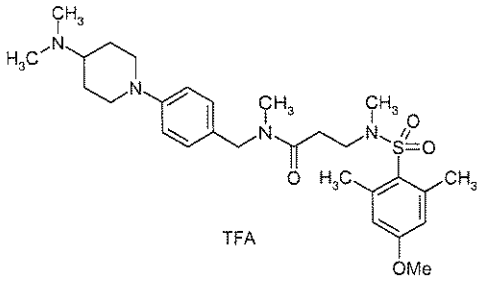
A mixture of 0.63 g (2.10 mmol) of product from 22c, 0.91 g (9.00 mmol) of N-methylmorpholine, 0.45 g (2.04 mmol) of product from 92b and 50 ml THF is stirred for 10 minutes at ambient temperature and then combined with 5.22 ml (9.00 mmol) of propylphosphonic anhydride 50% in ethyl acetate (Fluka). The reaction mixture is stirred overnight at ambient temperature and then evaporated to dryness in vacuo. The residue is combined with 2 N potassium carbonate solution and extracted with dichloromethane. The organic extracts are washed with water and saturated sodium chloride solution, dried on sodium sulphate and evaporated to dryness in vacuo. The crude product thus obtained is purified by preparative HPLC.

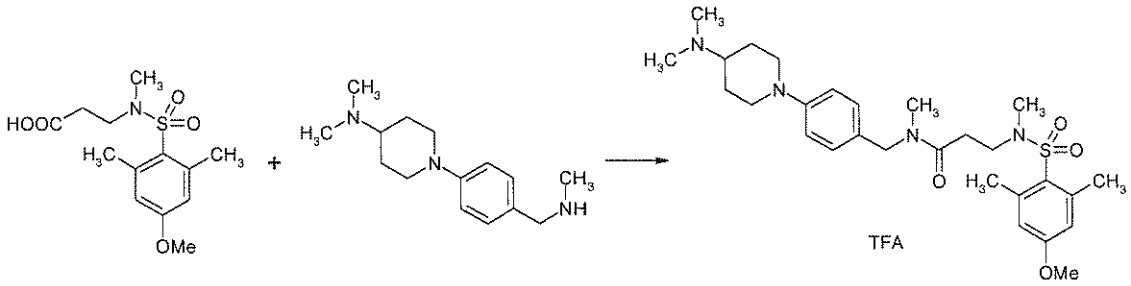
$C_{25}H_{37}N_5O_4S \times C_2HF_3O_2$ (617.68)

[M+H]+ = 504

HPLC (Method 5): retention time = 1.38 min

Example 93





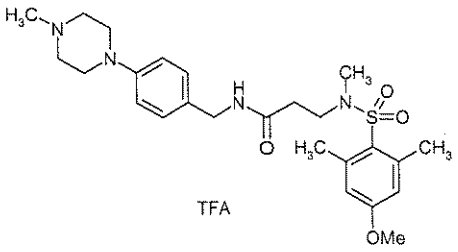
Example 93 is prepared analogously to 1f from 0.08 g (0.27 mmol) of product from 22c, 0.066 g (0.27 mmol) of product from 80a, 0.11 ml (0.80 mmol) of triethylamine and 0.085 g (0.27 mmol) of TBTU in 2 ml THF.

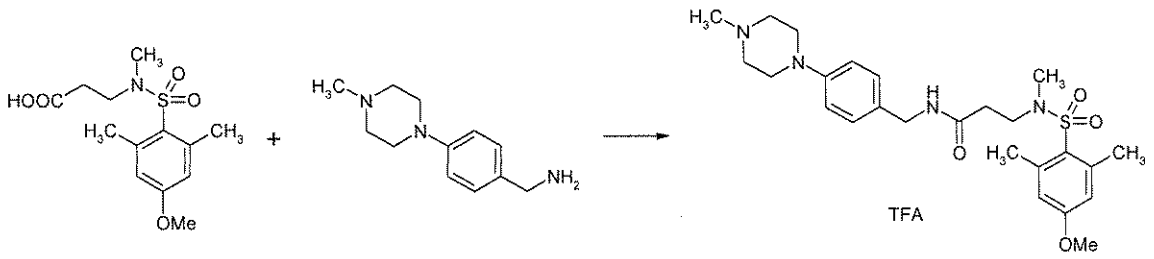
$C_{28}H_{42}N_4O_4S \times C_2HF_3O_2$ (644.75)

[M+H]+ = 531

HPLC (Method 5): retention time = 1.50 min

Example 94





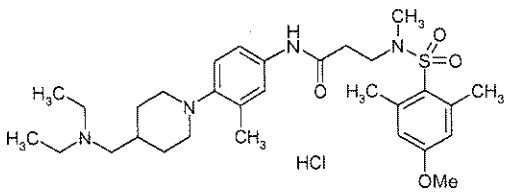
Example 94 is prepared analogously to 1f from 0.08 g (0.27 mmol) of product from 22c, 0.054 g (0.27 mmol) of product from 19b, 0.11 ml (0.80 mmol) of triethylamine and 0.085 g (0.27 mmol) of TBTU in 2 ml THF.

$C_{25}H_{36}N_4O_4S \times C_2HF_3O_2$ (602.67)

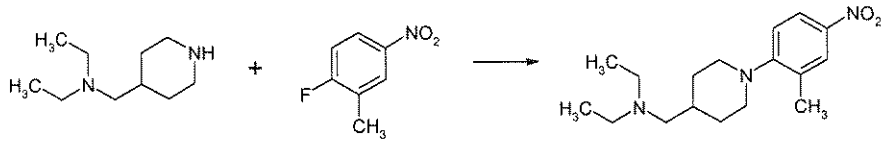
[M+H]+ = 489

HPLC (Method 5): retention time = 1.49 min

Example 95



95a)

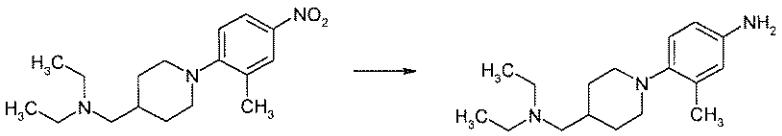


95a is prepared analogously to 8a from 1.00 g (5.87 mmol) of diethyl-piperidin-4-ylmethyl-amine (Chem. Pharm. Bull. 42, 1994, 74-84), 0.91 g (5.87 mmol) of 1-fluoro-2-methyl-4-nitrobenzene (ABCR) and 1.14 ml (8.20 mmol) of triethylamine in 12 ml DMF.

$C_{17}H_{27}N_3O_2$ (305.42)

[M+H]+ = 306

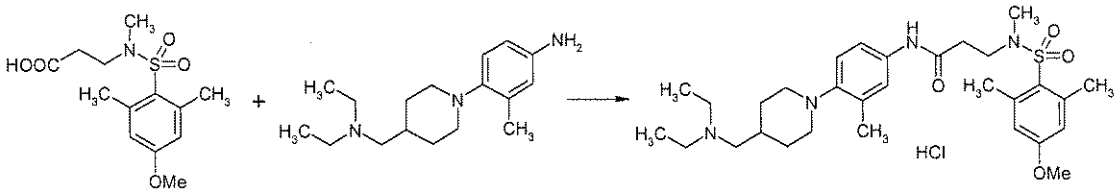
95b)



95b is prepared analogously to 8b from 0.91 g (2.98 mmol) of product from 95a and 0.20 g palladium on charcoal (10%) in 50 ml of methanol.

$C_{17}H_{29}N_3$ (275.43)

95c)



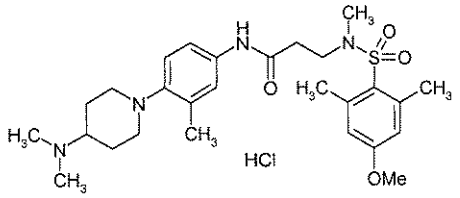
Example 95 is prepared analogously to 1f from 0.15 g (0.50 mmol) of product from 22c, 0.14 g (0.50 mmol) of product from 95b, 0.21 ml (1.50 mmol) of triethylamine and 0.16 g (0.50 mmol) of TBTU in 7 ml THF and 1 ml DMF.

$C_{30}H_{46}N_4O_4S$ x HCl (595.24)

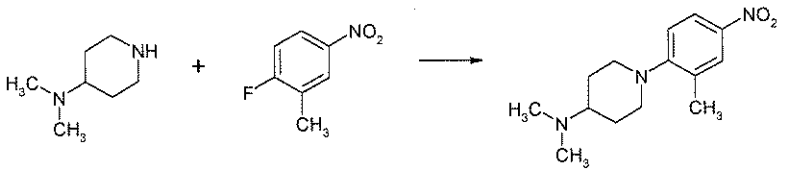
[M+H]+ = 559

HPLC (Method 5): retention time = 1.44 min

Example 96



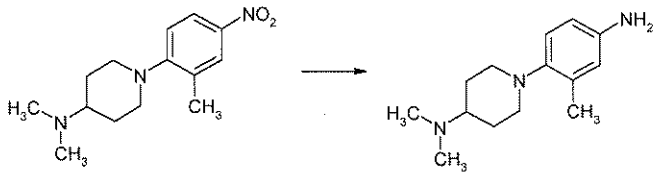
96a)



96a is prepared analogously to 8a from 0.75 g (5.87 mmol) of 4-dimethylamino-piperidine (Alfar Aesar), 0.91 g (5.87 mmol) of 1-fluoro-2-methyl-4-nitrobenzene (ABCR) and 1.14 ml (8.20 mmol) of triethylamine in 12 ml DMF.

$C_{14}H_{21}N_3O_2$ (263.34)

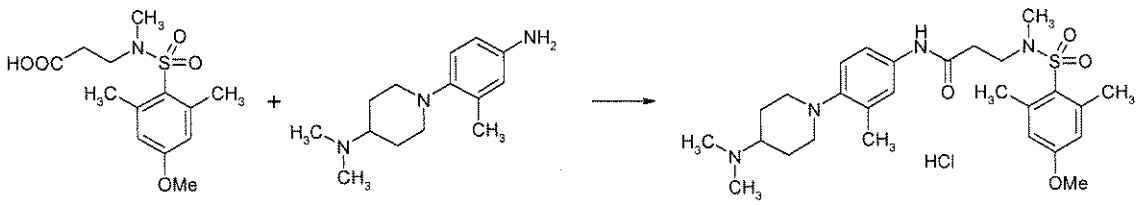
96b)



96b is prepared analogously to 8b from 0.30 g (1.14 mmol) of product from 96a and 0.10 g palladium on charcoal (10%) in 25 ml of methanol.

$C_{14}H_{23}N_3$ (233.35)

96c)



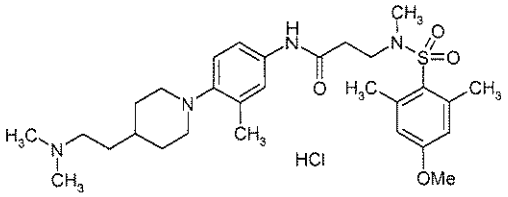
Example 96 is prepared analogously to 1f from 0.32 g (1.07 mmol) of product from 22c, 0.25 g (1.07 mmol) of product from 96b, 0.42 ml (3.00 mmol) of triethylamine and 0.34 g (1.07 mmol) of TBTU in 7 ml THF and 1 ml DMF.

$C_{27}H_{40}N_4O_4S$ x HCl (553.16)

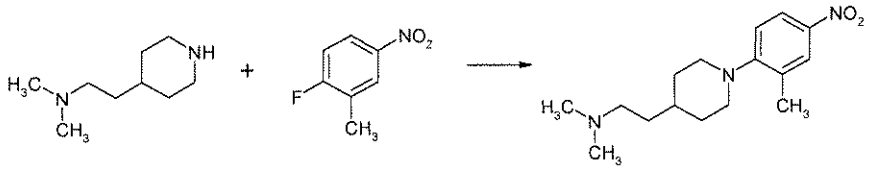
[M+H]+ = 517

HPLC (Method 5): retention time = 1.52 min

Example 97



97a)

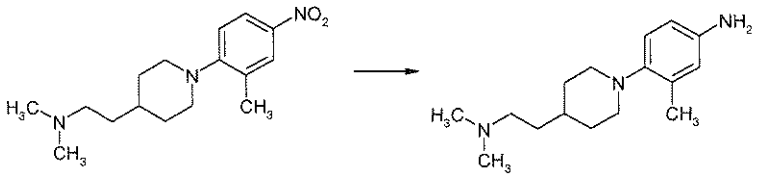


97a is prepared analogously to 8a from 0.92 g (5.87 mmol) of dimethyl-(2-piperidin-4-yl-ethyl)-amine (J. Med. Chem. 36, 1993, 162-165), 0.91 g (5.87 mmol) of 1-fluoro-2-methyl-4-nitrobenzene (ABCR) and 2.49 g (18.00 mmol) of potassium carbonate in 12 ml DMF.

$C_{16}H_{25}N_3O_2$ (291.39)

[M+H]+ = 292

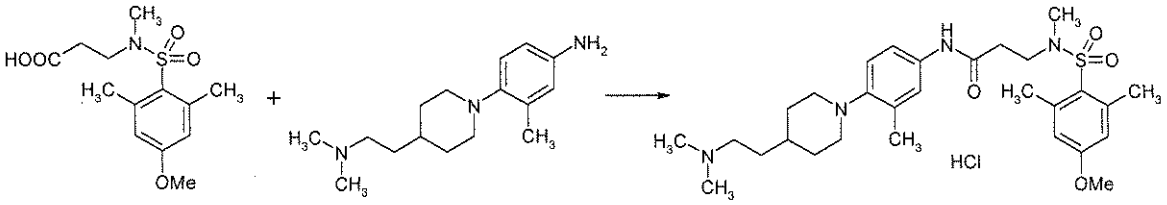
97b)



97b is prepared analogously to 8b from 0.60 g (1.14 mmol) of product from 97a and 0.20 g palladium on charcoal (10%) in 50 ml of methanol.

$C_{16}H_{27}N_3$ (261.41)

97c)



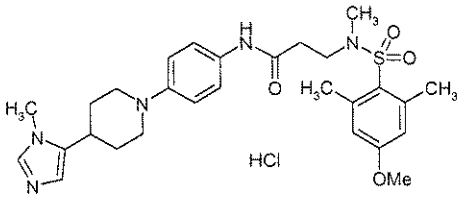
Example 97 is prepared analogously to 1f from 0.15 g (0.50 mmol) of product from 22c, 0.13 g (0.50 mmol) of product from 97b, 0.21 ml (1.50 mmol) of triethylamine and 0.16 g (0.50 mmol) of TBTU in 7 ml THF and 1 ml DMF.

$C_{29}H_{44}N_4O_4S$ x HCl (581.21)

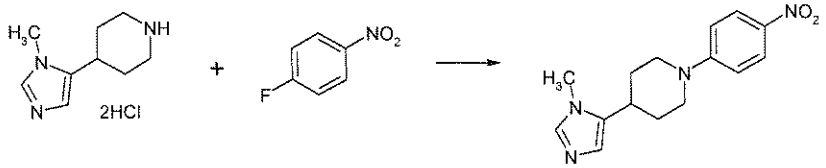
[M+H]+ = 545

HPLC (Method 5): retention time = 1.42 min

Example 98



98a)

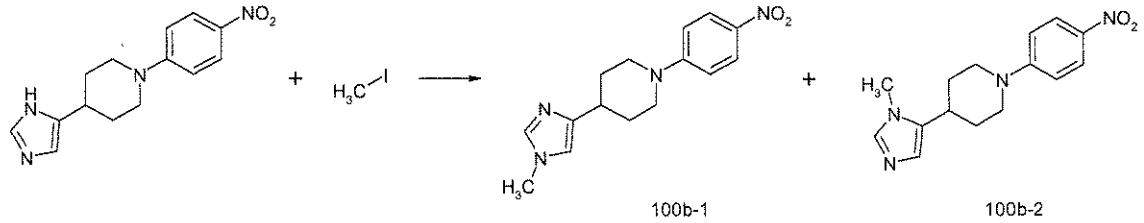


980a is prepared analogously to 8a from 1.00 g (4.47 mmol) of 4-(3-methyl-3H-imidazol-4-yl)-piperidine (J. Med. Chem. 46, 2003, 5445-5457), 0.63 g (4.47 mmol) of 4-fluoro-nitrobenzene (ABCR) and 2.10 g (15.20 mmol) of potassium carbonate in 50 ml DMF.

$C_{14}H_{16}N_4O_2$ (272.30)

[M+H]+ = 273

98b)



98b-1 and 98b-2 are prepared analogously to 62a from 1.10 g (4.04 mmol) of product from 98a, 0.60 g (4.23 mmol) of methyl iodide and 0.46 g (4.10 mmol) of potassium-tert-butoxide in 50 ml DMSO. The resulting mixture of isomers is separated by column chromatography through silica gel (eluant: dichloromethane / methanol 100:1 to 30:1).

98b-1: $C_{15}H_{18}N_4O_2$ (286.33)

[M+H]+ = 287

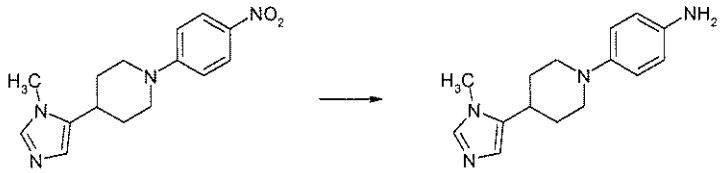
TLC: silica gel, dichloromethane / methanol 9:1, Rf value = 0.50

98b-2: $C_{15}H_{18}N_4O_2$ (286.33)

[M+H]+ = 287

TLC: silica gel, dichloromethane / methanol 9:1, Rf value = 0.38

98c)

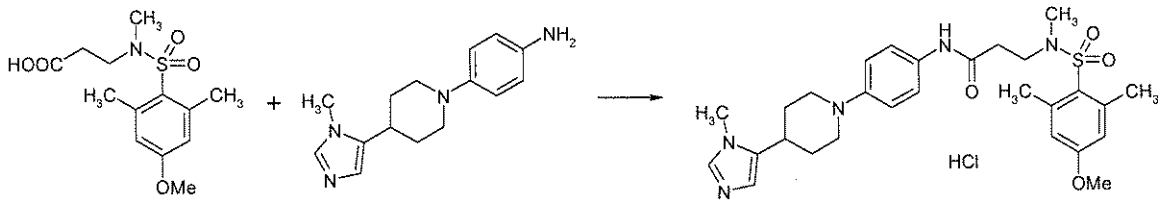


98c is prepared analogously to 8b from 0.10 g (0.35 mmol) of 98b-2 and 0.20 g palladium on charcoal (10%) in 30 ml of methanol.

$C_{15}H_{20}N_4$ (256.35)

TLC: silica gel, dichloromethane / methanol 9:1, Rf value = 0.10

98d)



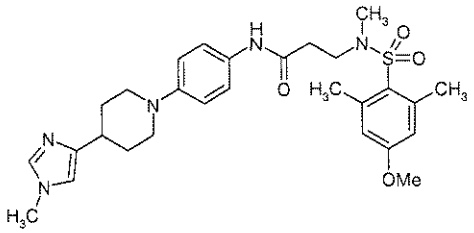
Example 98 is prepared analogously to 1f from 0.085 g (0.28 mmol) of product from 22c, 0.070 g (0.27 mmol) of product from 98c, 0.048 ml (0.35 mmol) of triethylamine and 0.095 g (0.30 mmol) of TBTU in 20 ml THF and 3 ml DMF.

$C_{28}H_{37}N_5O_4S$ x HCl (576.15)

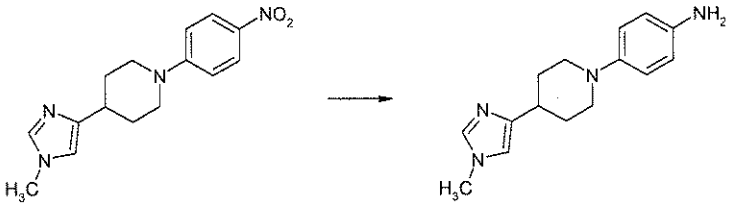
[M+H]+ = 540

HPLC (Method 5): retention time = 1.41 min

Example 99



99a)

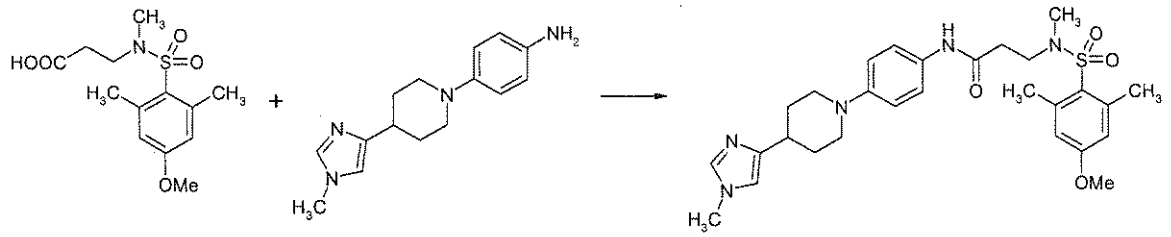


99a is prepared analogously to 8b from 0.35 g (1.22 mmol) of 98b-1 and 0.50 g palladium on charcoal (10%) in 50 ml of methanol.

$C_{15}H_{20}N_4$ (256.35)

TLC: silica gel, dichloromethane / methanol 9:1, Rf value = 0.14

99b)



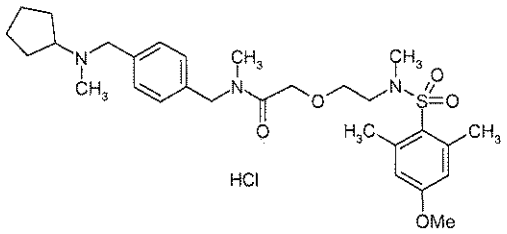
Example 99 is prepared analogously to 1f from 0.12 g (0.40 mmol) of product from 22c, 0.10 g (0.39 mmol) of product from 99a, 0.05 ml (0.50 mmol) of triethylamine and 0.14 g (0.42 mmol) of TBTU in 30 ml THF and 5 ml DMF.

$C_{28}H_{37}N_5O_4S$ (539.69)

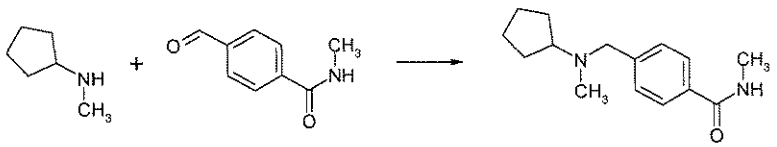
[M+H]+ = 540

TLC: silica gel, dichloromethane / methanol 9:1, Rf value = 0.47

Example 100



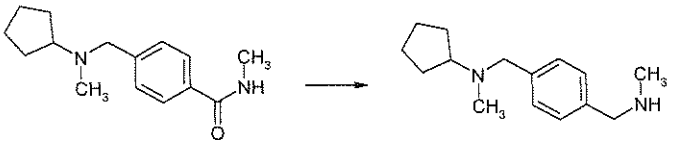
100a)



100a is prepared analogously to 60a from 0.50 g (5.00 mmol) of N-methylcyclohexylamine (CHESS), 0.82 g (5.00 mmol) of 4-formyl-benzoic acid methylamide (EMKA), 1.59 g (7.50 mmol) of sodium triacetoxyborohydride and 0.37 ml (6.50 mmol) of acetic acid in 30 ml THF.

$C_{15}H_{22}N_2$ (246.35)

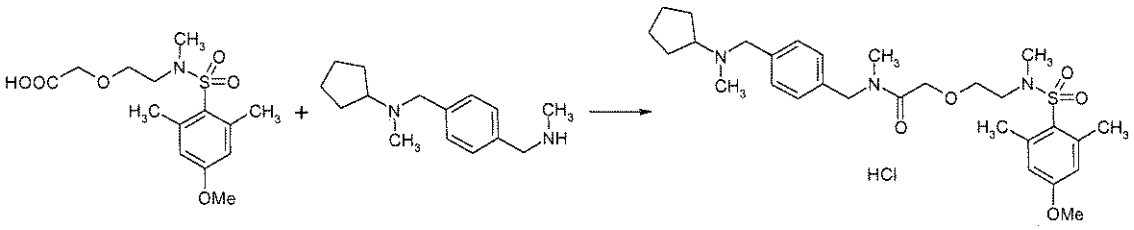
100b)



100b is prepared analogously to 38f from 1.06 g (4.30 mmol) of product from 100a and 8.60 ml (8.60 mmol) of lithium aluminium hydride 1 M in THF (Aldrich) in 40 ml THF.

$C_{15}H_{24}N_2$ (232.36)

100c)



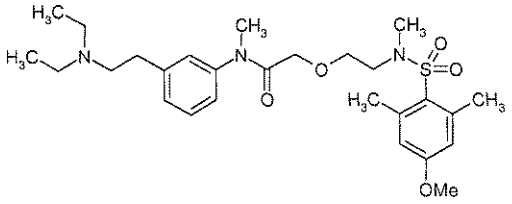
Example 100 is prepared analogously to 1f from 0.20 g (0.60 mmol) of product from 53c, 0.14 g (0.60 mmol) of product from 102b, 0.21 ml (1.50 mmol) of triethylamine and 0.23 g (0.72 mmol) of TBTU in 10 ml THF.

$C_{29}H_{43}N_3O_5S$ x HCl (582.20)

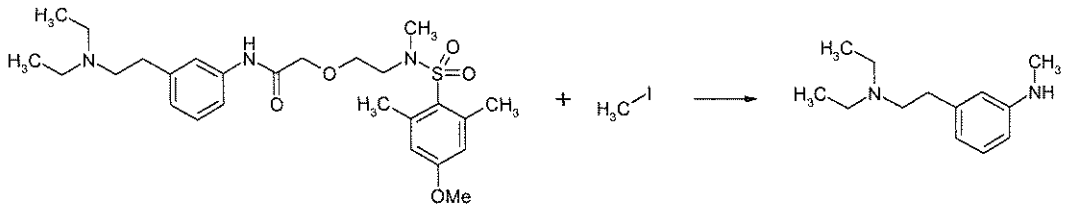
$[M+H]^+$ = 546

HPLC (Method 5): retention time = 1.58 min

Example 101



101a)

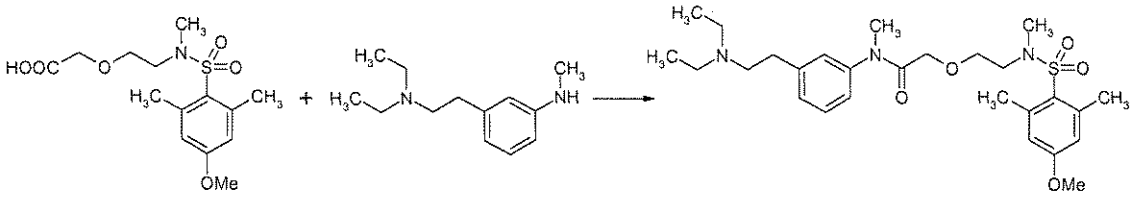


A mixture of 0.04 g (0.079 mmol) of 70, 4.8 mg (0.12 mmol) of sodium hydride 60%, 1 ml THF and 0.5 ml DMF is stirred for 30 minutes at ambient temperature. Then 4.9 µl (0.079 mmol) of methyl iodide are added and the mixture is stirred for a further two hours at ambient temperature. The reaction mixture is then evaporated to dryness in vacuo, the residue is mixed with water and extracted with ethyl acetate. The organic extracts are dried on sodium sulphate and evaporated to dryness in vacuo. The crude product thus obtained is purified by column chromatography (eluant: dichloromethane / methanol / ammonia 95:5:0.5).

$C_{13}H_{22}N_2$ (206.33)

[M+H]+ = 207

101b)



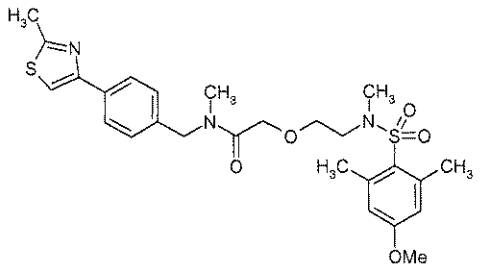
Example 101 is prepared analogously to 1f from 0.08 g (0.24 mmol) of product from 53c, 0.05 g (0.24 mmol) of product from 101a, 0.067 ml (0.48 mmol) of triethylamine and 0.093 g (0.29 mmol) of TBTU in 7 ml THF and 1 ml DMF.

$C_{27}H_{41}N_3O_5S$ (519.70)

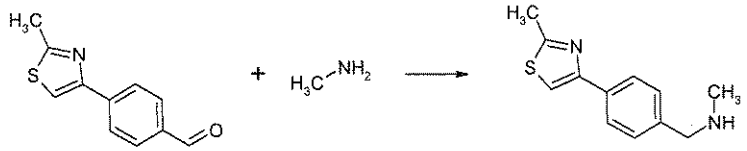
[M+H]+ = 520

HPLC (Method 4): retention time = 3.2 min

Example 102



102a)

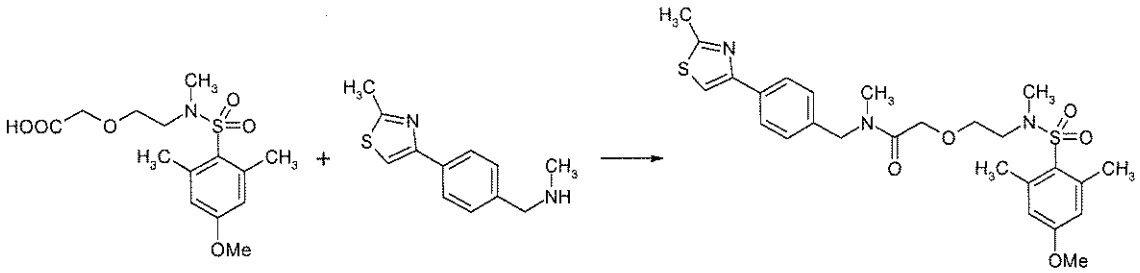


102a is prepared analogously to 60a from 0.35 g (1.72 mmol) of 4-(2-methyl-1.3-thiazol-4-yl)-benzaldehyde (Maybridge), 1.50 ml (3.00 mmol) of methylamine 2 M in THF (Acros), 0.70 g (3.30 mmol) of sodium triacetoxyborohydride and 0.23 ml (4.00 mmol) of acetic acid in 20 ml THF.

$C_{12}H_{14}N_2S$ (218.32)

[M+H]+ = 219

102b)



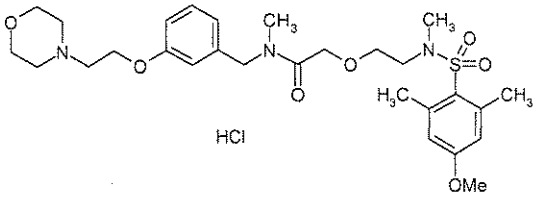
Example 102 is prepared analogously to 1f from 0.16 g (0.47 mmol) of product from 53c, 0.10 g (0.46 mmol) of product from 102a, 0.11 ml (1.09 mmol) of triethylamine and 0.16 g (0.48 mmol) of TBTU in 30 ml THF and 5 ml DMF.

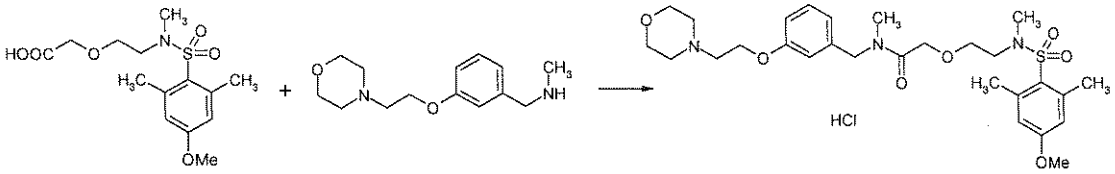
$C_{26}H_{33}N_3O_5S_2$ (531.69)

[M+H]+ = 532

TLC: silica gel, dichloromethane / methanol 9:1, Rf value = 0.66

Example 103





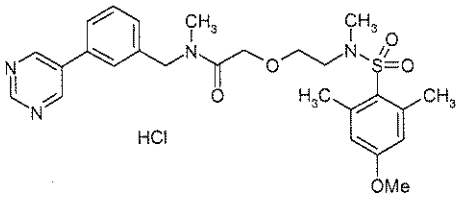
Example 103 is prepared analogously to 1f from 0.14 g (0.41 mmol) of product from 53c, 0.10 g (0.40 mmol) of methyl-[3-(2-morpholin-4-yl-ethoxy)-benzyl]-amine (Maybridge), 0.14 ml (0.99 mmol) of triethylamine and 0.14 g (0.44 mmol) of TBTU in 30 ml THF and 5 ml DMF.

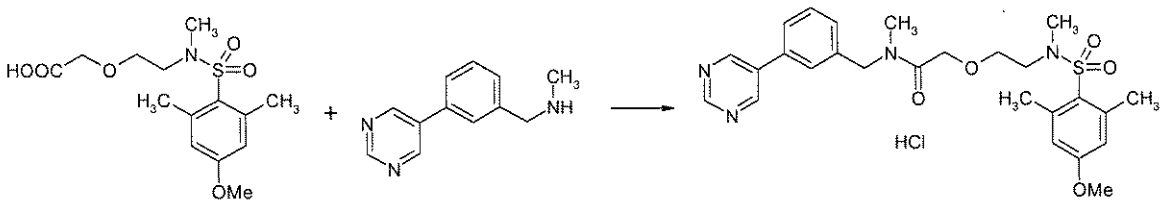
$C_{28}H_{41}N_3O_7S$ x HCl (600.17)

$[M+H]^+$ = 564

TLC: silica gel, dichloromethane / methanol 9:1, Rf value = 0.59

Example 104





Example 104 is prepared analogously to 1f from 0.17 g (0.51 mmol) of product from 53c, 0.10 g (0.50 mmol) of methyl-(3-pyrimidin-5-yl-benzyl)-amine

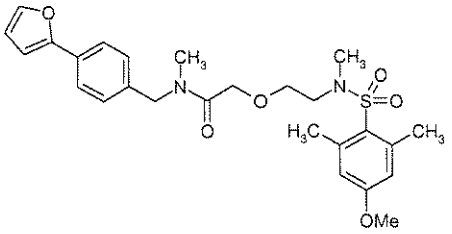
(Maybridge), 0.17 ml (1.19 mmol) of triethylamine and 0.17 g (0.53 mmol) of TBTU in 30 ml THF and 5 ml DMF.

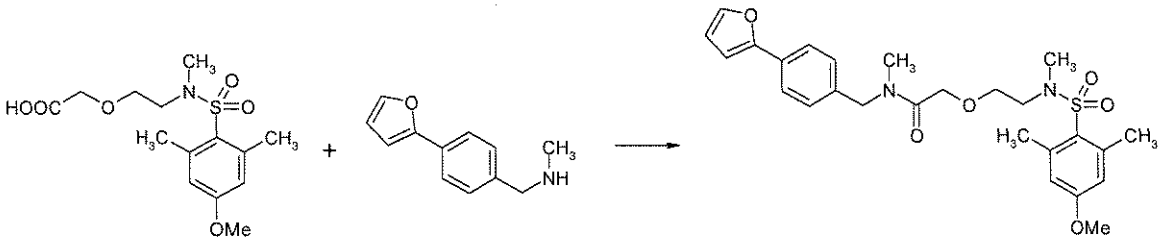
$C_{26}H_{32}N_4O_5S$ x HCl (549.08)

[M+H]+ = 513

HPLC (Method 5): retention time = 1.78 min

Example 105





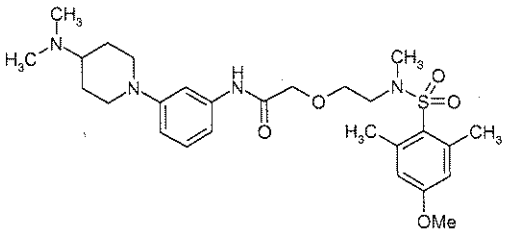
Example 105 is prepared analogously to 1f from 0.18 g (0.54 mmol) of product from 53c, 0.10 g (0.53 mmol) of (4-furan-2-yl-benzyl)-methyl-amine (Maybridge), 0.18 ml (1.29 mmol) of triethylamine and 0.18 g (0.56 mmol) of TBTU in 30 ml THF and 5 ml DMF.

$C_{26}H_{32}N_2O_6S$ (500.61)

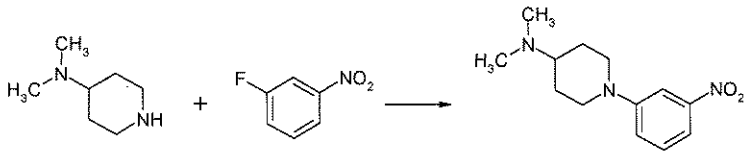
[M+H]+ = 501

HPLC (Method 5): retention time = 2.09 min

Example 106



106a)

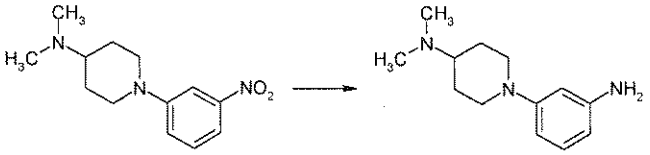


106a is prepared analogously to 79a from 2.41 g (18.78 mmol) of 4-dimethylamino-piperidine (Alfa Aesar), 1.00 ml (9.39 mmol) of 1-fluoro-3-nitrobenzene (Fluka) and 1.30 g (9.39 mmol) of potassium carbonate in 15 ml DMSO.

$C_{13}H_{19}N_3O_2$ (249.31)

[M+H]+ = 250

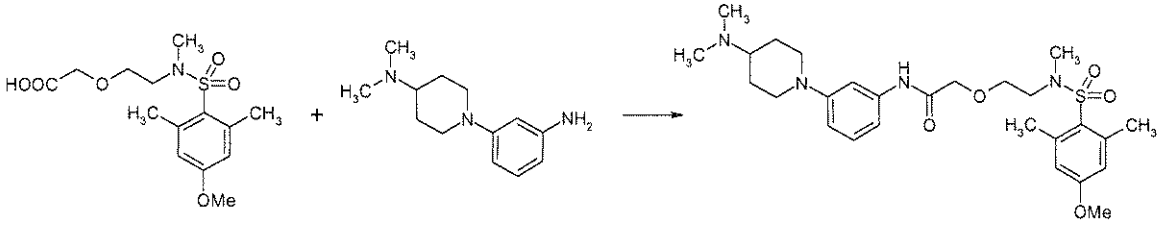
106b)



A mixture of 1.74 g (6.98 mmol) of product from 106a, 12.00 g (68.92 mmol) of sodium dithionite, 10.00 g (72.35 mmol) of potassium carbonate, 60 ml THF and 30 ml of water six hours is heated to 80°C. After cooling the organic phase is separated off, washed with saturated sodium chloride solution, dried on sodium sulphate and evaporated to dryness in vacuo.

$C_{13}H_{21}N_3$ (219.33)

106c)



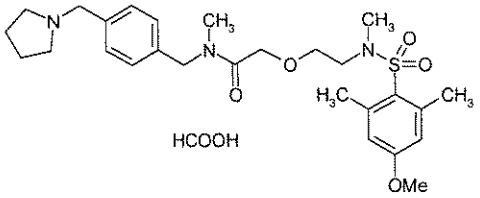
Example 106 is prepared analogously to 1f from 0.13 g (0.40 mmol) of product from 53c, 0.10 g (0.47 mmol) of product from 106b, 0.067 ml (0.48 mmol) of triethylamine and 0.15 g (0.48 mmol) of TBTU in 5 ml DMF.

$C_{27}H_{40}N_4O_5S$ (532.70)

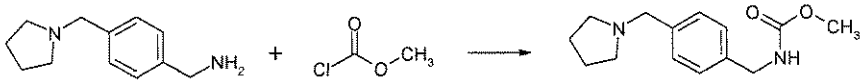
[M+H]+ = 533

HPLC (Method 5): retention time = 1.56 min

Example 107



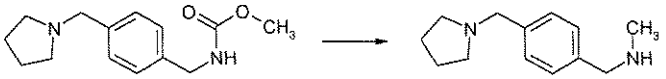
107a)



A mixture of 0.59 g (3.12 mmol) of 4-pyrrolidin-1-ylmethyl-benzylamine (Enamine-BB), 0.29 ml (3.75 mmol) of methyl chloroformate (Fluka), 0.52 ml (3.75 mmol) of triethylamine and 10 ml dichloromethane is stirred for two hours at ambient temperature. The reaction mixture is diluted with 10 ml dichloromethane, washed twice with water, dried on sodium sulphate and evaporated to dryness in vacuo.

$C_{14}H_{20}N_2O_2$ (248.32)

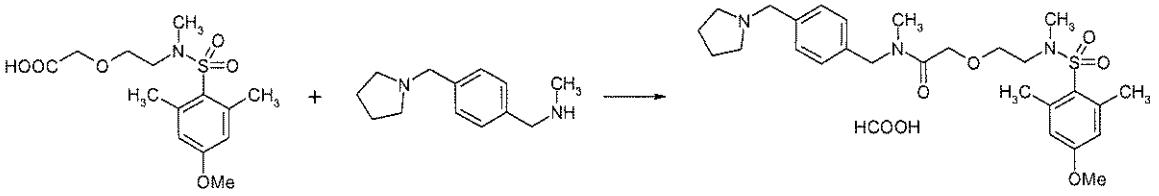
107b)



107b is prepared analogously to 51b from 0.61 g (2.44 mmol) of product from 107a and 5.00 ml (5.00 mmol) of lithium aluminium hydride 1 M in THF (Aldrich) in 5 ml THF.

$C_{13}H_{20}N_2$ (204.31)

107c)



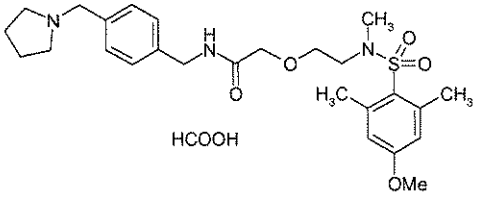
Example 107 is prepared analogously to 1f from 0.18 g (0.54 mmol) of product from 53c, 0.17 g (0.81 mmol) of product from 107b, 0.15 ml (1.07 mmol) of triethylamine and 0.21 g (0.65 mmol) of TBTU in 4 ml DMF.

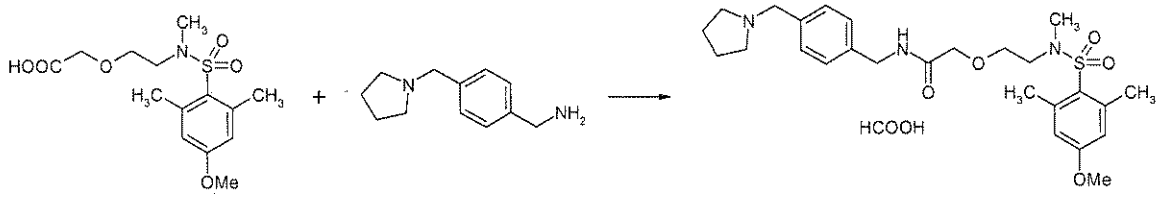
$C_{27}H_{39}N_3O_5S \times CH_2O_2$ (631.71)

[M+H]+ = 518

HPLC (Method 5): retention time = 1.56 min

Example 108





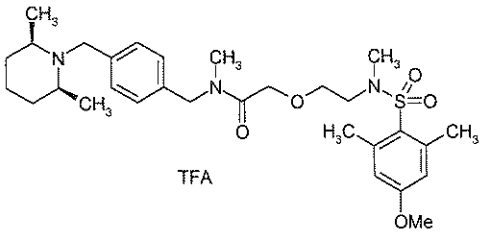
Example 108 is prepared analogously to 1f from 0.12 g (0.36 mmol) of product from 53c, 0.096 g (0.51 mmol) of 4-pyrrolidin-1-ylmethyl-benzylamine (Enamine-BB), 0.10 ml (0.72 mmol) of triethylamine and 0.14 g (0.44 mmol) of TBTU in 4 ml DMF.

$C_{26}H_{37}N_3O_5S \times CH_2O_2$ (617.68)

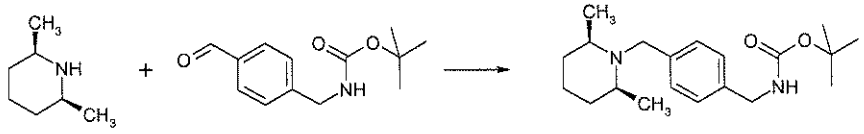
[M+H]+ = 504

HPLC (Method 5): retention time = 1.56 min

Example 109



109a)



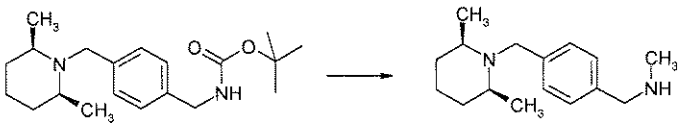
A mixture of 1.00 g (4.25 mmol) of tert-butyl (4-formylbenzyl)-carbamate (Acros) and 10 ml dichloromethane is combined successively with 1.15 ml (8.50 mmol) of cis-2,6-dimethylpiperidine (Aldrich) and 1.80 g (8.50 mmol) of sodium triacetoxyborohydride while cooling with an ice bath. The reaction mixture is stirred for three days at ambient temperature, then slowly quenched with saturated sodium hydrogen carbonate solution and extracted with dichloromethane. The organic extracts are washed with water and saturated sodium chloride solution, dried on sodium sulphate and evaporated to dryness in vacuo. The crude product thus obtained is purified by column chromatography (eluant: dichloromethane / methanol 93:7).

$C_{20}H_{32}N_2O_2$ (332.48)

[M+H]+ = 333

HPLC (Method 5): retention time = 1.47 min

109b)



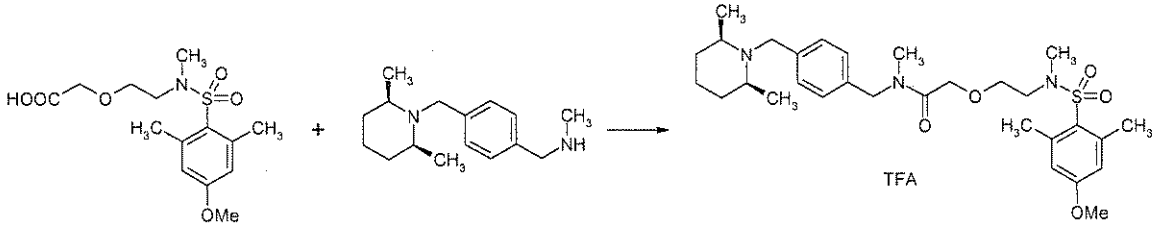
109b is prepared analogously to 51b from 0.92 g (2.76 mmol) of product from 109a and 8.27 ml (8.27 mmol) of lithium aluminium hydride 1 M in THF (Aldrich) in 30 ml THF.

$C_{16}H_{26}N_2$ (246.39)

[M+H]+ = 247

HPLC (Method 5): retention time = 1.03 min

109c)



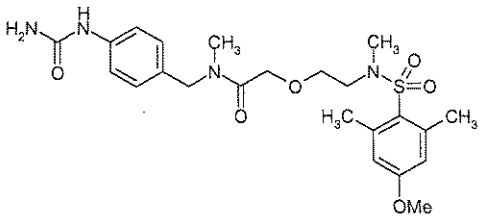
Example 109 is prepared analogously to 1f from 0.08 g (0.24 mmol) of product from 53c, 0.059 g (0.24 mmol) of product from 109b, 0.10 ml (0.72 mmol) of triethylamine and 0.078 g (0.24 mmol) of TBTU in 2 ml THF.

$C_{30}H_{45}N_3O_5S \times C_2HF_3O_2$ (673.78)

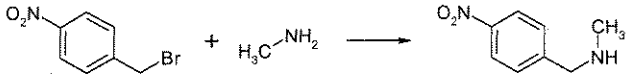
[M+H]+ = 560

HPLC (Method 5): retention time = 1.59 min

Example 110



110a)



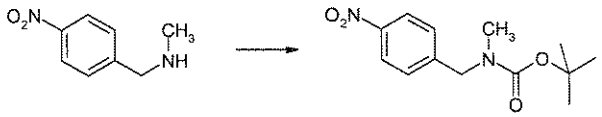
250.00 ml (500.00 mmol) of methylamine 2 M in methanol (Fluka) are slowly combined with 54.00 g (250.00 mmol) of 4-nitrobenzylbromide (Fluka) while

cooling with an ice bath. The reaction mixture is stirred for one hour while cooling with an ice bath and for 30 minutes at ambient temperature and then evaporated to dryness in vacuo. The residue is stirred with diethyl ether and filtered off. The filtrate is evaporated to dryness in vacuo, combined with sodium carbonate solution and extracted with diethyl ether. The organic extracts are dried on sodium sulphate and evaporated to dryness in vacuo. The crude product thus obtained is purified by column chromatography (eluant: dichloromethane / methanol 5:0 to 5:1).

$C_8H_{10}N_2O_2$ (166.18)

[M+H]+ = 167

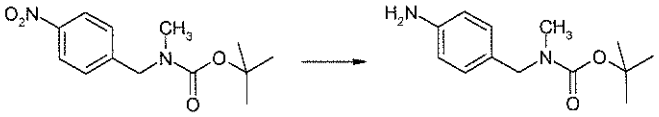
110b)



A mixture of 13.40 g (80.64 mmol) of product from 110a and 25 ml ethyl acetate is slowly combined with 17.68 g (81.00 mmol) of Boc-anhydride while cooling with an ice bath. The reaction mixture is stirred for three hours at ambient temperature, then washed with water, dried on sodium sulphate and evaporated to dryness in vacuo.

$C_{13}H_{18}N_2O_4$ (266.29)

110c)



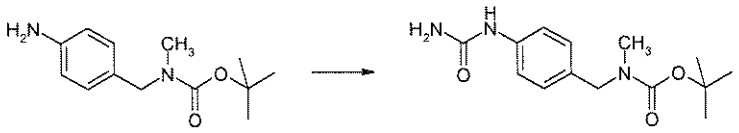
A mixture of 23.00 g (86.37 mmol) of product from 110b, 2.30 g Raney nickel, 230 ml of ethanol and 230 ml ethyl acetate is hydrogenated in the autoclave at ambient temperature. The catalyst is filtered off, the filtrate is evaporated to dryness in vacuo. The crude product thus obtained is purified by column chromatography (eluant: petroleum ether / ethyl acetate 1:1).

$C_{13}H_{20}N_2O_2$ (236.31)

[M+H]+ = 237

TLC: silica gel, petroleum ether / ethyl acetate 1:1, Rf value = 0.55

110d)

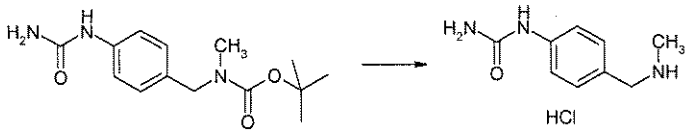


A mixture of 0.50 g (2.12 mmol) of product from 110c, 0.48 g (3.56 mmol) of trimethylsilyl isocyanate (Fluka) and 15 ml THF is refluxed over the weekend with stirring. Then the reaction mixture is evaporated to dryness in vacuo.

$C_{14}H_{21}N_3O_3$ (279.33)

[2M+H]+ = 559

110e)

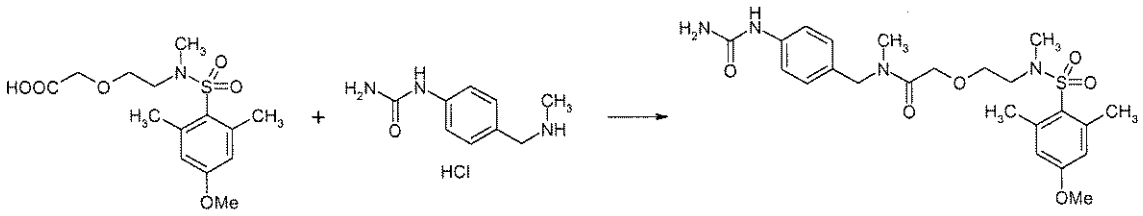


A mixture of 0.64 g (2.29 mmol) of product from 1100 and 10 ml of methanolic HCl is stirred for three hours at ambient temperature and for two hours at 50°C. Then the reaction mixture is evaporated to dryness in vacuo. The residue is dried overnight in vacuo.

$C_9H_{13}N_3$ x HCl (215.68)

[M+H]+ = 180

110f)



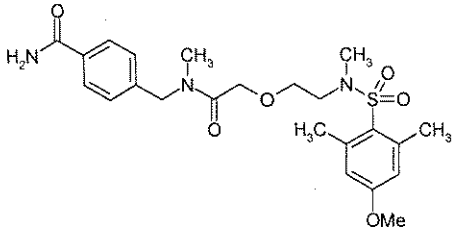
Example 110 is prepared analogously to 1f from 0.20 g (0.60 mmol) of product from 53c, 0.13 g (0.60 mmol) of product from 110e, 0.42 ml (3.02 mmol) of triethylamine and 0.22 g (0.66 mmol) of TBTU in 4 ml DMF.

$C_{23}H_{32}N_4O_6S$ (492.59)

[M+H]+ = 493

HPLC (Method 6): retention time = 2.93 min

Example 111



111a)

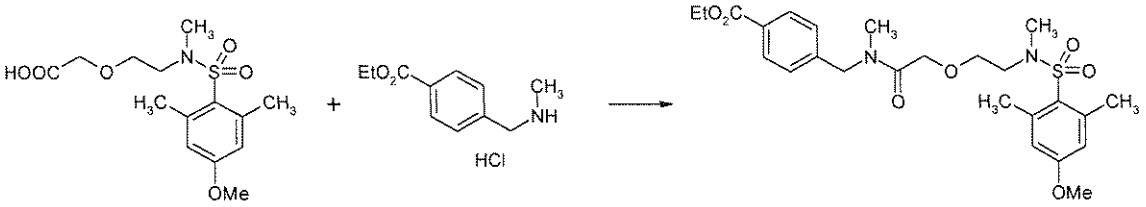
A mixture of 2.00 g (9.92 mmol) of 4-methylaminomethyl-benzoic acid hydrochloride (J. Med. Chem. 26, 1983, 309-312) and 25 ml of ethanolic HCl is stirred for 1.5 hours at reflux temperature. Then the reaction mixture is evaporated to dryness in vacuo.

$C_{11}H_{15}NO_2$ x HCl (229.70)

[M+H]+ = 194

HPLC (Method 6): retention time = 1.39 min

111b)



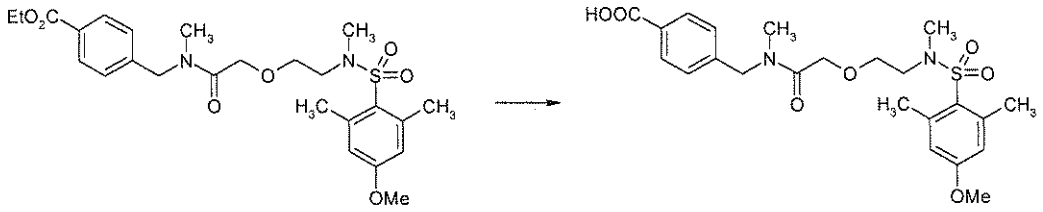
111b is prepared analogously to 1f from 0.70 g (2.11 mmol) of product from 53c, 0.49 g (2.11 mmol) of product from 111a, 0.88 ml (6.34 mmol) of triethylamine and 0.78 g (2.32 mmol) of TBTU in 12 ml DMF.

$C_{25}H_{34}N_2O_7S$ (506.61)

[M+H]+ = 507

HPLC (Method 6): retention time = 3.95 min

111c)



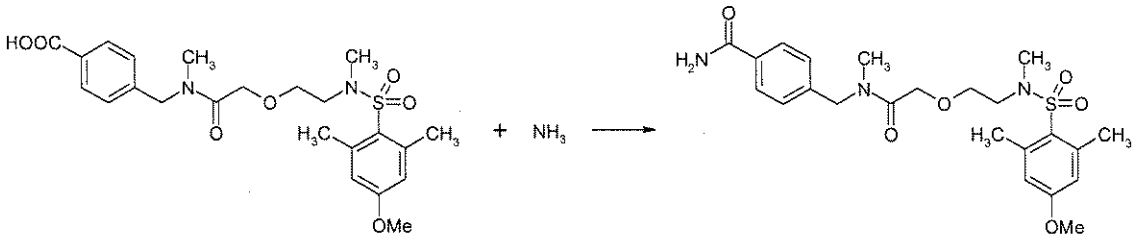
A mixture of 1.06 g (2.09 mmol) of product from 133b, 7.00 ml (7.00 mmol) of 1 M sodium hydroxide solution, 15 ml THF and 1.5 ml of ethanol is stirred for four hours at 50°C. The reaction mixture is then combined with 7 ml 1 M HCl and evaporated to dryness in vacuo. The residue is taken up in acetone, dried on magnesium sulphate and evaporated to dryness in vacuo.

$C_{23}H_{30}N_2O_7S$ (478.56)

[M+H]+ = 479

HPLC (Method 6): retention time = 3.21 min

111d)



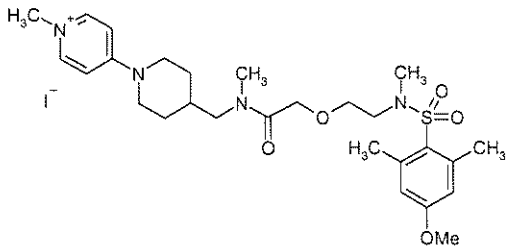
Example 111 is prepared analogously to 1f from 0.50 g (1.05 mmol) of product from 111c, 4.00 ml (2.00 mmol) of ammonia 0.5 M in dioxane, 0.44 ml (3.14 mmol) of triethylamine and 0.38 g (1.15 mmol) of TBTU in 4 ml DMF.

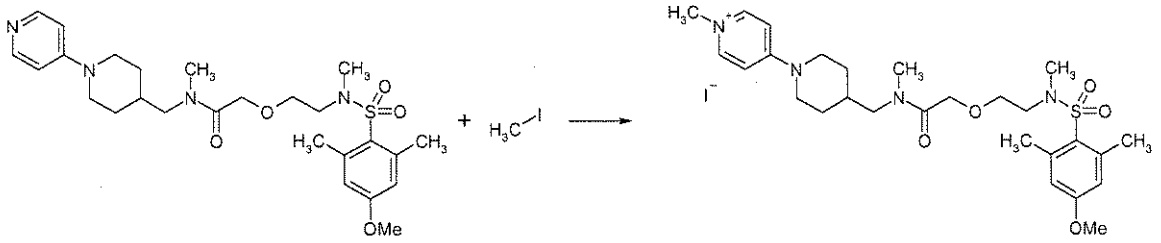
$C_{23}H_{31}N_3O_6S$ (477.57)

[M+H]+ = 478

HPLC (Method 6): retention time = 2.92 min

Example 112





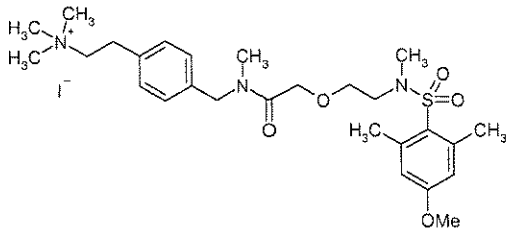
A mixture of 0.075 g (0.15 mmol) of 61, 0.1 g (0.71 mmol) of methyl iodide and 5 ml dichloromethane is stirred overnight at ambient temperature. The reaction mixture is then evaporated to dryness in vacuo.

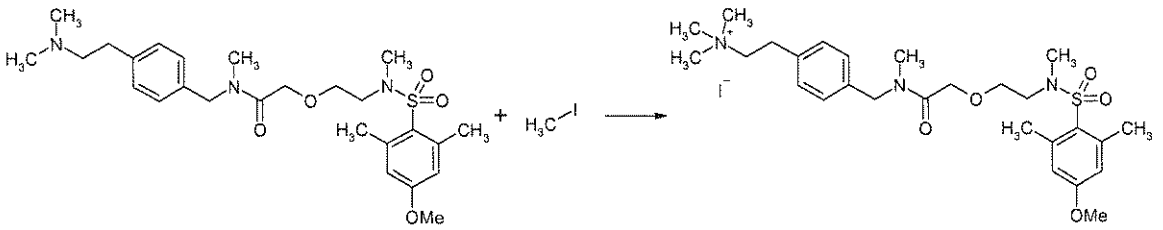
$C_{27}H_{41}N_4O_5S$ x I (660.61)

[M+H]+ = 533

HPLC (Method 5): retention time = 1.55 min

Example 113





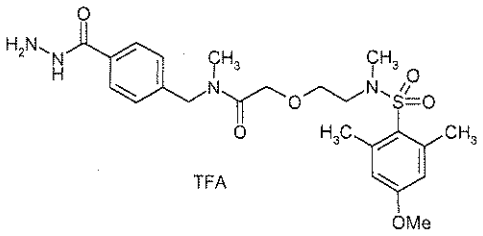
Example 113 is prepared analogously to 112 from 0.03 g (0.059 mmol) of 64 and 0.05 g (0.35 mmol) of methyl iodide in 5 ml dichloromethane.

$C_{27}H_{42}N_3O_5S \times I$ (647.61)

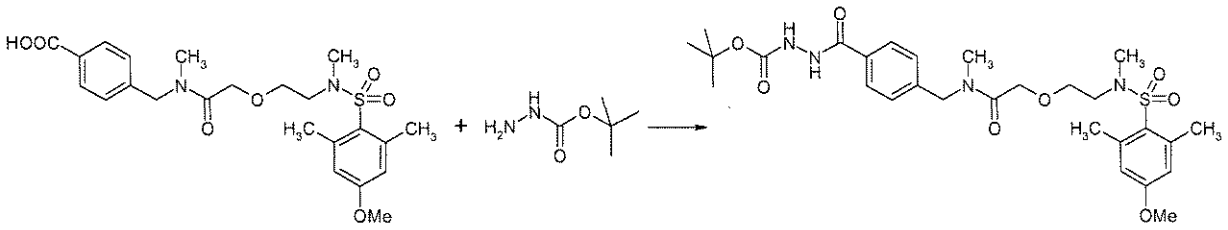
[M+H]+ = 520

HPLC (Method 5): retention time = 1.55 min

Example 114



114a)



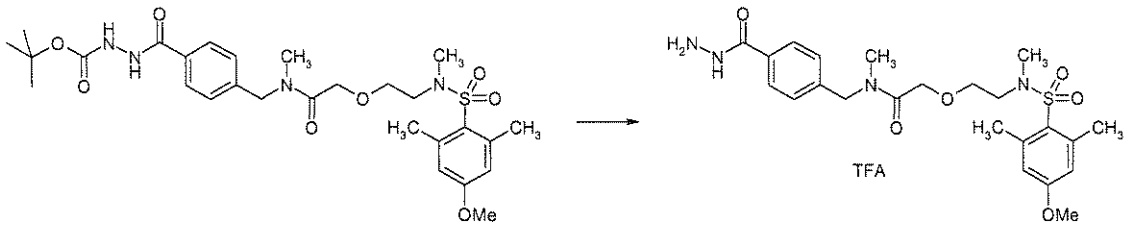
114a is prepared analogously to 1f from 0.50 g (1.05 mmol) of product from 111c, 0.14 g (1.05 mmol) of tert-butyl hydrazine carboxylate (Aldrich), 0.58 ml (4.18 mmol) of triethylamine and 0.38 g (1.15 mmol) of TBTU in 6 ml DMF.

$C_{28}H_{40}N_4O_8S$ (592.71)

[M+H]+ = 593

HPLC (Method 6): retention time = 3.46 min

114b)



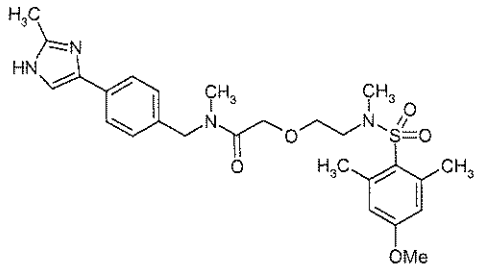
Example 114 is prepared analogously to 110e from 0.68 g (1.15 mmol) of product from 114a and 10 ml of methanolic HCl.

$C_{23}H_{32}N_4O_6S \times C_2HF_3O_2$ (606.61)

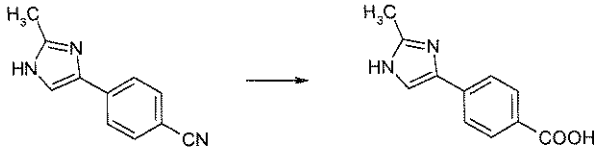
$[M+H]^+ = 493$

HPLC (Method 6): retention time = 3.46 min

Example 115



115a)

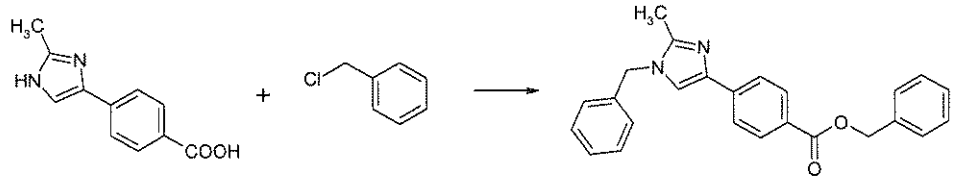


A mixture of 3.20 g (17.47 mmol) of product from 63a, 50 ml 20% sodium hydroxide solution and 50 ml of ethanol is refluxed overnight with stirring. Then the ethanol is eliminated in vacuo and the aqueous residue is neutralised with concentrated HCl. The precipitate formed is filtered off and dried.

$C_{11}H_{10}N_2O_2$ (202.21)

$[M+H]^+ = 203$

115b)



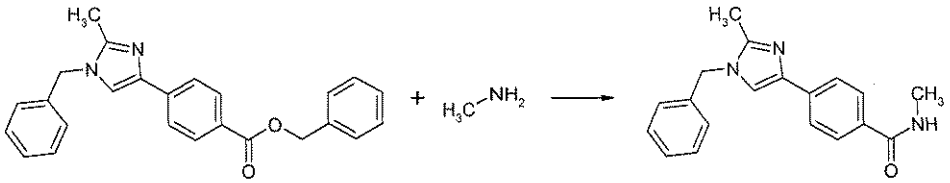
A mixture of 2.70 g (13.35 mmol) of product from 115a, 8.00 g (57.89 mmol) of potassium carbonate and 100 ml DMF is stirred for one hour at 60°C. After cooling the reaction mixture is combined with 3.50 g (27.65 mmol) of benzyl chloride (Aldrich) at ambient temperature and then stirred over the weekend at 60°C. The reaction mixture is poured onto water and stirred for one hour at ambient temperature. The precipitate formed is filtered off and dried.

$C_{25}H_{22}N_2O_2$ (382.45)

[M+H]+ = 383

TLC: silica gel, dichloromethane / methanol 9:1, Rf value = 0.64

115c)

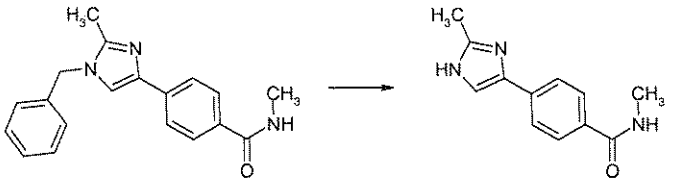


A mixture of 1.80 g (4.71 mmol) of product from 115b and 100 ml methylamine 33% in ethanol (Aldrich) is stirred for six hours at 180°C and overnight at 160°C in the autoclave. The reaction mixture is then evaporated to dryness in vacuo. The crude product thus obtained is purified by column chromatography (eluant: dichloromethane / methanol 19:1).

$C_{19}H_{19}N_3O$ (305.37)

[M+H]+ = 306

115d)

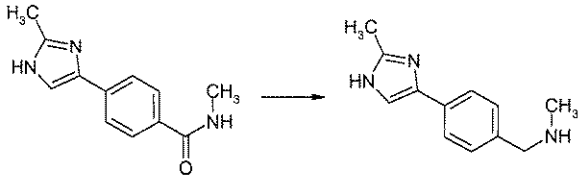


A mixture of 1.20 g (3.93 mmol) of product from 115c, 0.20 g palladium on charcoal (20%) and 50 ml of methanol is hydrogenated at 50°C in the autoclave. The catalyst is filtered off, the filtrate is evaporated to dryness in vacuo.

$C_{12}H_{13}N_3O$ (215.25)

[M+H]+ = 216

115e)

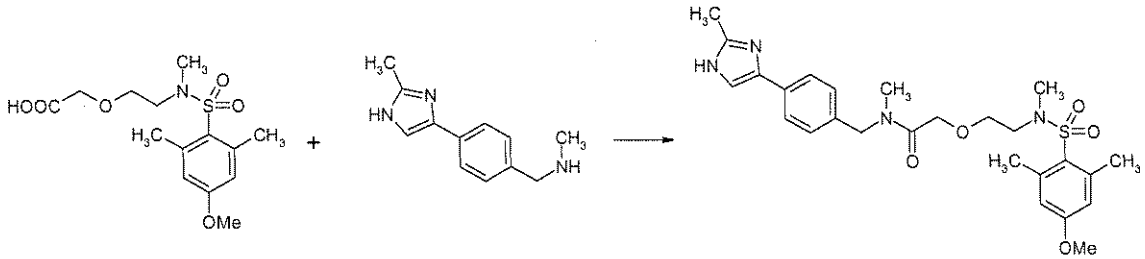


115e is prepared analogously to 38f from 0.70 g (3.25 mmol) of product from 115d and 10.00 ml (10.00 mmol) of lithium aluminium hydride 1 M in THF (Aldrich) in 200 ml THF.

$C_{12}H_{15}N_3$ (201.27)

[M+H]+ = 202

115f)



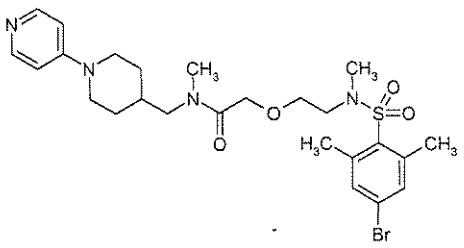
Example 115 is prepared analogously to 1f from 0.17 g (0.51 mmol) of product from 53c, 0.10 g (0.50 mmol) of product from 115e, 0.17 ml (1.19 mmol) of triethylamine and 0.17 g (0.53 mmol) of TBTU in 30 ml THF and 5 ml DMF.

$C_{26}H_{34}N_4O_5S$ (514.64)

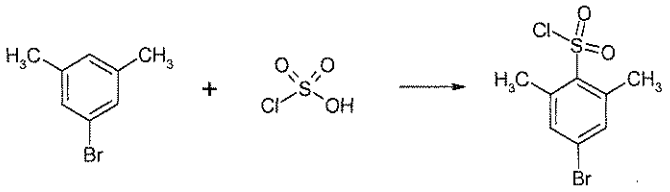
[M+H]+ = 515

TLC: silica gel, dichloromethane / methanol 9:1, Rf value = 0.28

Example 116



116a)

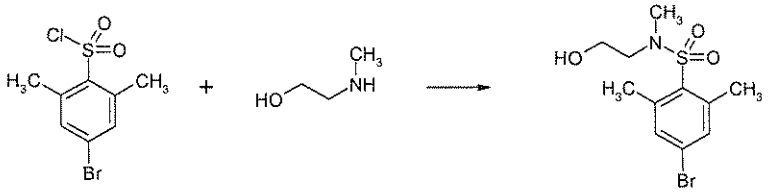


116a is prepared analogously to 13a from 0.75 g (4.05 mmol) of 5-bromo-*m*-xylene (Aldrich), 0.55 ml (8.30 mmol) of chlorosulphonic acid (Aldrich) and 10 ml dichloromethane.

$C_8H_8BrClO_2S$ (283.57)

HPLC (Method 6): retention time = 4.76 min

116b)

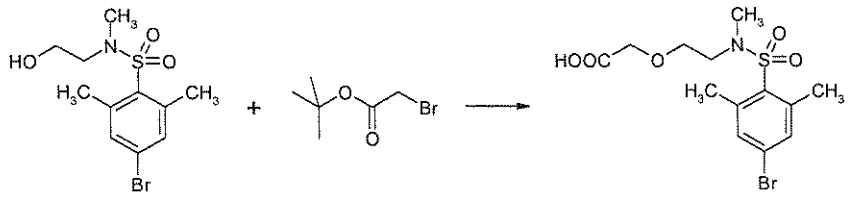


116b is prepared analogously to 3a from 0.65 g (2.29 mmol) of product from 116a and 0.28 ml (3.44 mmol) of N-methylaminoethanol (BASF) in 5 ml THF.

$C_{11}H_{16}BrNO_3S$ (322.22)

HPLC (Method 6): retention time = 3.38 min

116c)

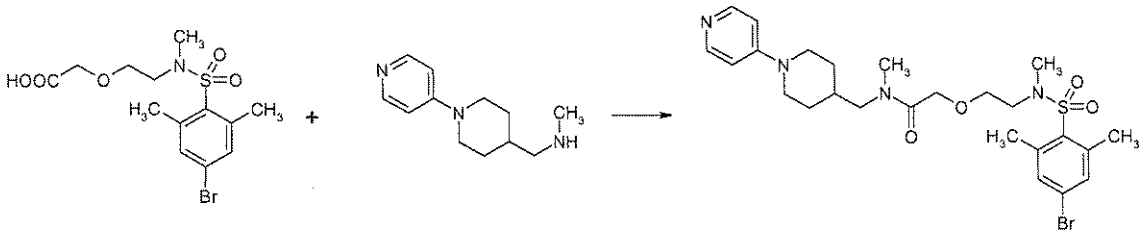


116c is first prepared analogously to 53b from 0.74 g (2.29 mmol) of product from 116b, 0.75 g (5.06 mmol) of tert-butyl 2-bromopropionate (Fluka), 0.42 g (1.14 mmol) of tetrabutylammonium iodide (Aldrich) and 8.67 g (75.90 mmol) of 35% sodium hydroxide solution in 40 ml of toluene. The tert-butyl ester is then stirred overnight together with 2 ml HCl 4 M in dioxane (Aldrich) in 4 ml dioxane at ambient temperature. The product is then obtained by evaporating the reaction mixture in vacuo.

$C_{13}H_{18}BrNO_5S$ (380.26)

HPLC (Method 6): retention time = 3.48 min

116d)



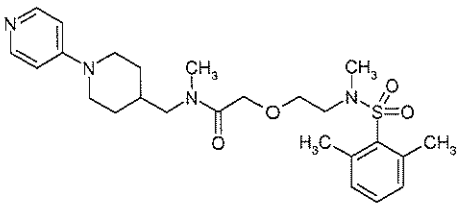
Example 116 is prepared analogously to 1f from 0.10 g (0.26 mmol) of product from 116c, 0.054 g (0.26 mmol) of product from 61b, 0.11 ml (0.79 mmol) of triethylamine and 0.084 g (0.26 mmol) of TBTU in 10 ml THF and 3 ml DMF.

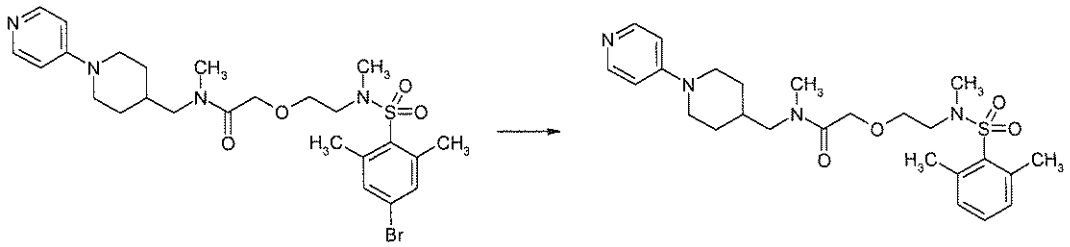
$C_{25}H_{35}BrN_4O_4S$ (567.54)

$[M+H]^+$ = 568/569/571

HPLC (Method 6): retention time = 2.77 min

Example 117





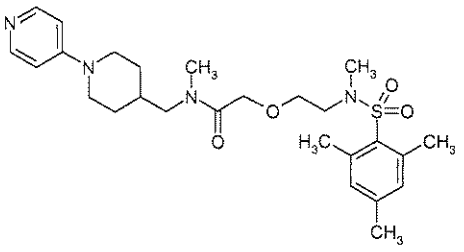
A mixture of 0.03 g (0.053 mmol) of 116 and 0.03 g palladium on charcoal in 5 ml of methanol is hydrogenated in the autoclave at ambient temperature. The catalyst is filtered off, the filtrate is evaporated to dryness in vacuo. The crude product thus obtained is purified by preparative HPLC.

$C_{25}H_{36}N_4O_4S$ (488.64)

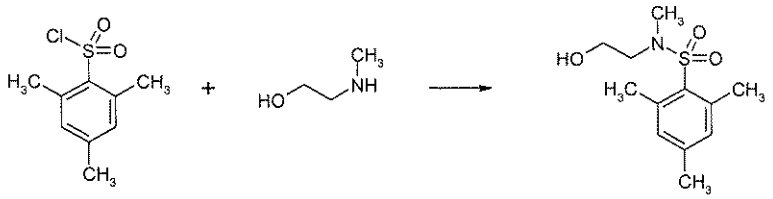
[M+H]+ = 489

HPLC (Method 6): retention time = 2.45 min

Example 118



118a)

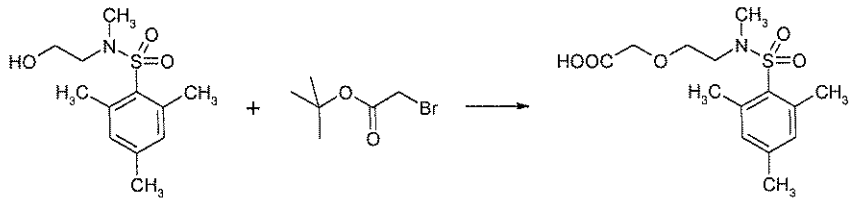


118a is prepared analogously to 3a from 0.50 g (2.29 mmol) of 2,4,6-trimethylbenzene-sulphonic acid chloride (Fluka) and 0.19 g (2.52 mmol) of N-methylaminoethanol (BASF) in 5 ml THF.

$C_{12}H_{19}NO_3S$ (257.35)

[M+H]+ = 258

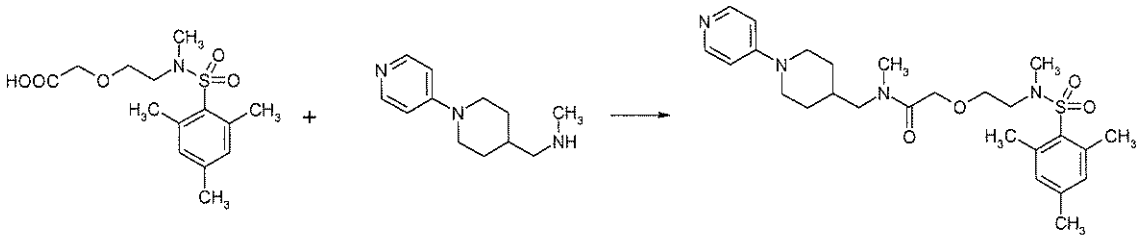
118b)



118b is prepared analogously to 116c from 0.56 g (2.18 mmol) of product from 118a, 0.48 ml (3.26 mmol) of tert-butyl 2-bromopropionate (Fluka), 0.18 g (0.65 mmol) of tetrabutylammonium chloride (Fluka) and 7.46 g (65.28 mmol) of 35% sodium hydroxide solution in 20 ml of toluene and subsequent stirring in 2 ml HCl 4 M in dioxane.

$C_{14}H_{21}NO_5S$ (315.39)

118c)



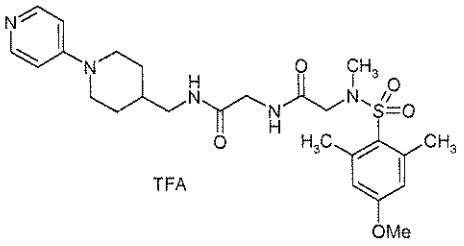
Example 118 is prepared analogously to 1f from 0.10 g (0.32 mmol) of product from 118b, 0.065 g (0.32 mmol) of product from 61b, 0.13 ml (0.95 mmol) of triethylamine and 0.20 g (0.63 mmol) of TBTU in 10 ml THF.

$C_{26}H_{38}N_4O_4S$ (502.67)

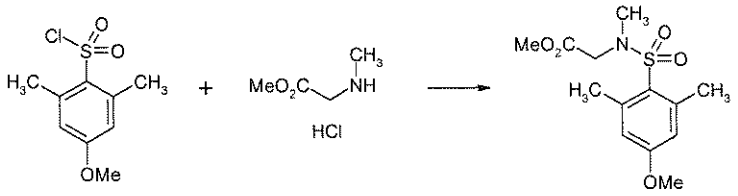
[M+H]+ = 503

HPLC (Method 5): retention time = 1.57 min

Example 119



119a)

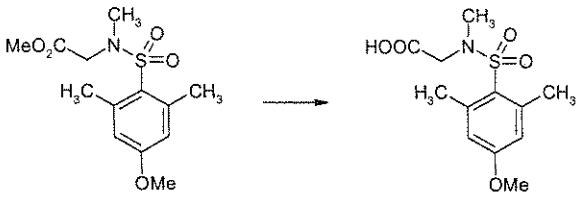


A mixture of 0.98 g (7.05 mmol) of sarcosine methylester hydrochloride (Fluka), 1.65 g (7.05 mmol) of product from 13a and 50 ml of pyridine is stirred for one hour at ambient temperature. The reaction mixture is then evaporated to dryness in vacuo. The residue is then taken up in 1 M HCl and extracted with ethyl acetate. The organic extracts are dried on sodium sulphate and evaporated to dryness in vacuo.

$C_{13}H_{19}NO_5S$ (301.36)

$[M+H]^+$ = 302

119b)

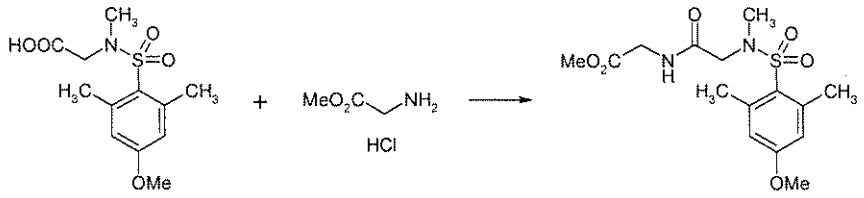


A mixture of 1.90 g (6.29 mmol) of product from 119a, 6.45 ml (12.90 mmol) of 2 M sodium hydroxide solution and 9 ml of methanol is stirred for three days at ambient temperature. The methanol is eliminated in vacuo, the aqueous residue is poured onto 1 M HCl. The precipitate formed is filtered off and dried overnight in the vacuum desiccator.

$C_{12}H_{17}NO_5S$ (287.33)

[M+H]+ = 288

119c)



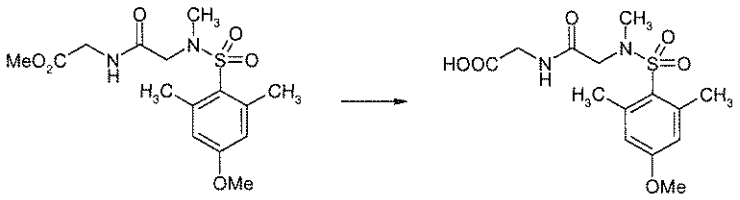
119c is prepared analogously to 1f from 0.20 g (0.70 mmol) of product from 119b, 0.087 g (0.70 mmol) of glycine methylester hydrochloride (Aldrich), 0.29 ml (2.09 mmol) of triethylamine and 0.22 g (0.70 mmol) of TBTU in 5 ml THF.

$C_{15}H_{22}N_2O_6S$ (358.41)

[M+H]+ = 359

HPLC (Method 5): retention time = 1.72 min

119d)

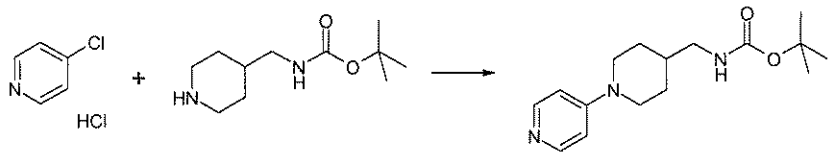


119d is prepared analogously to 119b from 0.23 g (0.63 mmol) of product from 119c and 0.64ml (1.29 mmol) of 2 M sodium hydroxide solution in 1 ml of methanol.

$C_{14}H_{20}N_2O_6S$ (344.38)

[M+H]+ = 345

119e)



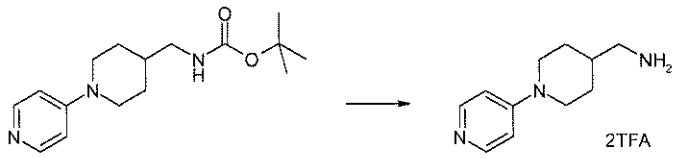
119e is prepared analogously to 28c from 3.00 g (14.00 mmol) of tert-butyl piperidine-4-ylmethyl-carbamate (EMKA), 2.10 g (14.00 mmol) of 4-chloropyridine hydrochloride (Aldrich) and 7.80 ml (56.32 mmol) of triethylamine in 15 ml isopropanol.

$C_{16}H_{25}N_3O_2$ (291.39)

[M+H]+ = 292

HPLC (Method 5): retention time = 1.40 min

119f)



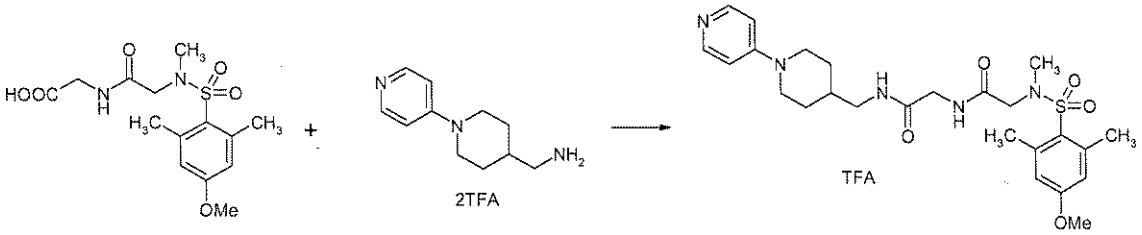
119f is prepared analogously to 18b from 1.44 g (4.95 mmol) of product from 119e and 4.95 ml TFA in 8 ml dichloromethane.

$C_{11}H_{17}N_3 \times 2C_2HF_3O_2$ (419.32)

[M+H]+ = 192

HPLC (Method 5): retention time = 0.36 min

119g)



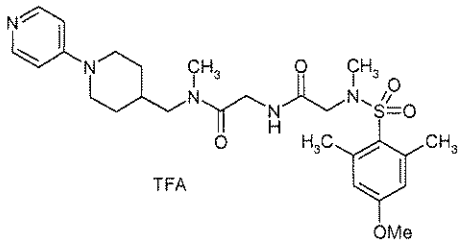
Example 119 is prepared analogously to 1f from 0.09 g (0.26 mmol) of product from 119d, 0.11 g (0.26 mmol) of product from 119f, 0.15 ml (1.05 mmol) of triethylamine and 0.084 g (0.26 mmol) of TBTU in 1.9 ml THF.

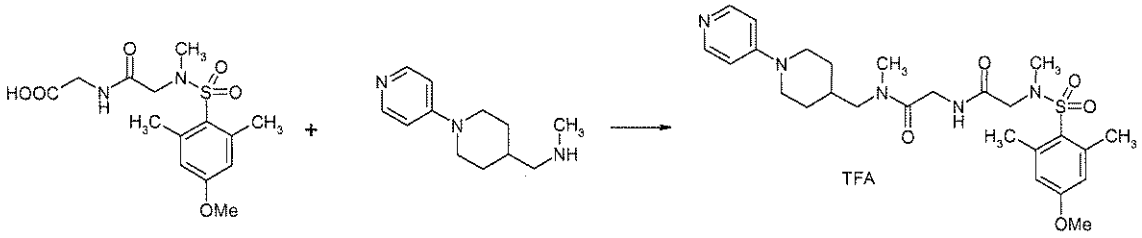
$C_{25}H_{35}N_5O_5S \times C_2HF_3O_2$ (631.67)

[M+H]+ = 518

HPLC (Method 5): retention time = 1.46 min

Example 120





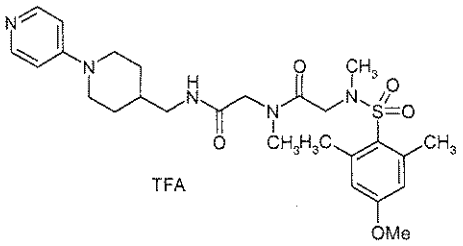
Example 120 is prepared analogously to 1f from 0.09 g (0.26 mmol) of product from 119d, 0.054 g (0.26 mmol) of product from 61b, 0.11 ml (0.78 mmol) of triethylamine and 0.084 g (0.26 mmol) of TBTU in 1.9 ml THF.

$C_{26}H_{37}N_5O_5S \times C_2HF_3O_2$ (645.69)

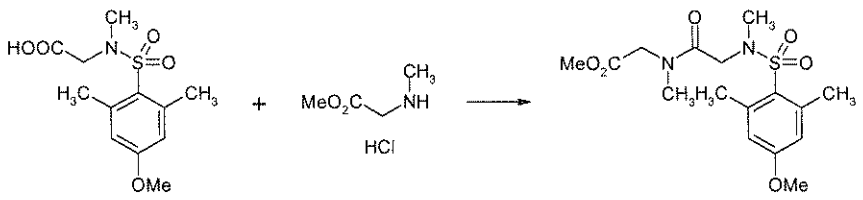
$[M+H]^+ = 532$

HPLC (Method 5): retention time = 1.50 min

Example 121



121a)



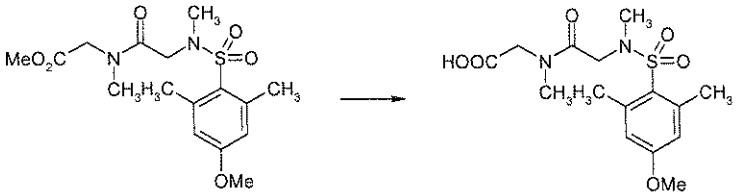
121a is prepared analogously to 1f from 0.20 g (0.70 mmol) of product from 119b, 0.097 g (0.70 mmol) of sarcosine methylester hydrochloride (Fluka), 0.29 ml (2.09 mmol) of triethylamine and 0.22 g (0.70 mmol) of TBTU in 5 ml THF.

$C_{16}H_{24}N_2O_6S$ (372.44)

[M+H]+ = 373

HPLC (Method 5): retention time = 1.78 min

121b)

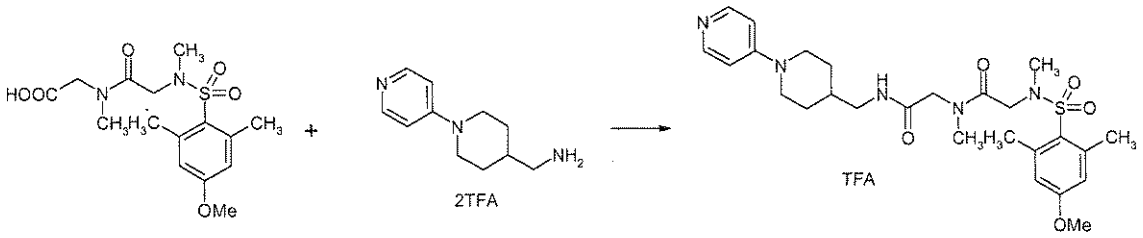


121b is prepared analogously to 119b from 0.23 g (0.60 mmol) of product from 121a and 0.62 ml (1.24 mmol) of 2 M sodium hydroxide solution in 1 ml of methanol.

$C_{15}H_{22}N_2O_6S$ (258.41)

[M+H]+ = 359

121c)



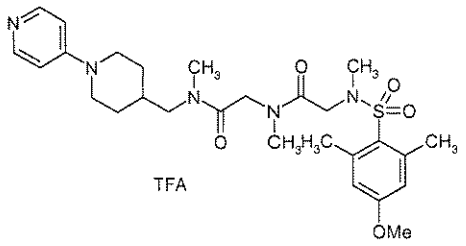
Example 121 is prepared analogously to 1f from 0.094 g (0.26 mmol) of product from 121b, 0.11 g (0.26 mmol) of product from 119f, 0.15 ml (1.05 mmol) of triethylamine and 0.084 g (0.26 mmol) of TBTU in 1.9 ml THF.

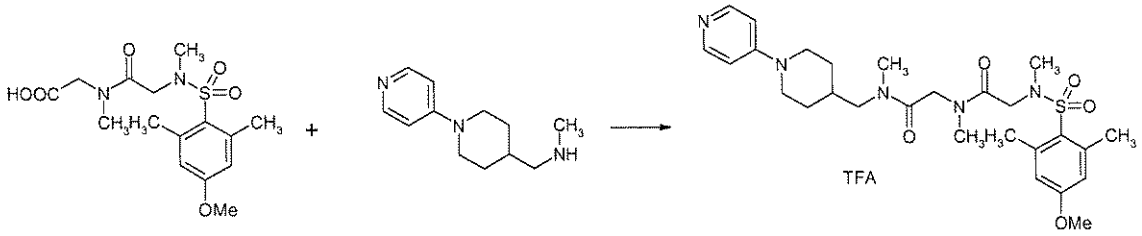
$C_{26}H_{37}N_5O_5S \times C_2HF_3O_2$ (645.69)

[M+H]+ = 532

HPLC (Method 5): retention time = 1.47 min

Example 122





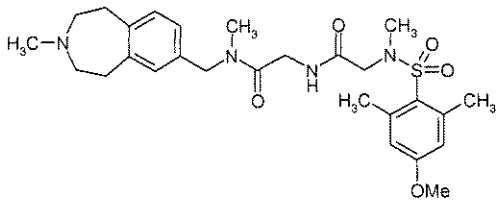
Example 122 is prepared analogously to 1f from 0.094 g (0.26 mmol) of product from 121b, 0.054 g (0.26 mmol) of product from 61b, 0.11 ml (0.78 mmol) of triethylamine and 0.084 g (0.26 mmol) of TBTU in 1.9 ml THF.

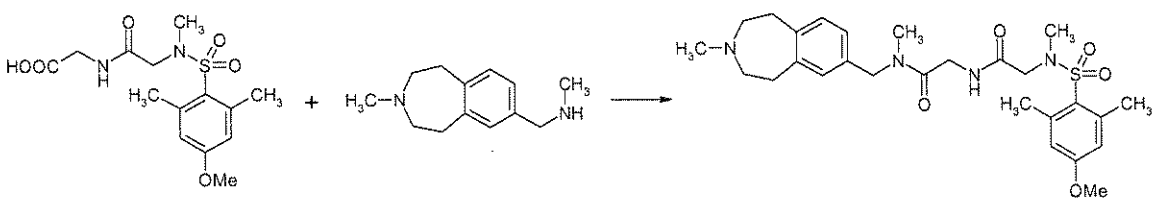
$C_{27}H_{39}N_5O_5S \times C_2HF_3O_2$ (659.72)

$[M+H]^+ = 548$

HPLC (Method 5): retention time = 1.49 min

Example 123





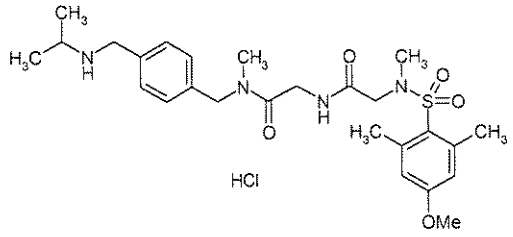
Example 123 is prepared analogously to 1f from 0.09 g (0.26 mmol) of product from 119d, 0.076 g (0.26 mmol) of product from 54b, 0.11 ml (0.78 mmol) of triethylamine and 0.084 g (0.26 mmol) of TBTU in 1.9 ml THF.

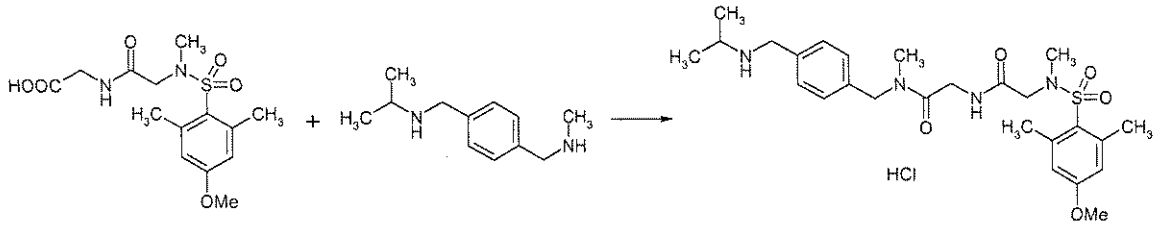
$C_{27}H_{38}N_4O_5S$ (530.68)

[M+H]+ = 531

HPLC (Method 1): retention time = 2.43 min

Example 124





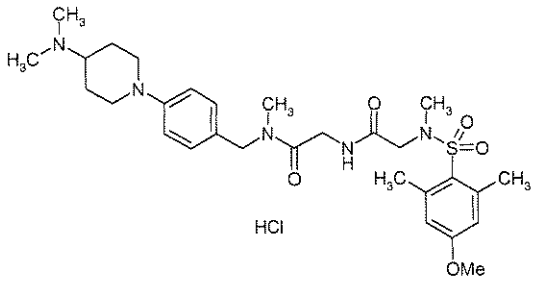
Example 124 is prepared analogously to 1f from 0.09 g (0.26 mmol) of product from 119d, 0.05 g (0.26 mmol) of product from 59b, 0.11 ml (0.78 mmol) of triethylamine and 0.084 g (0.26 mmol) of TBTU in 1.9 ml THF.

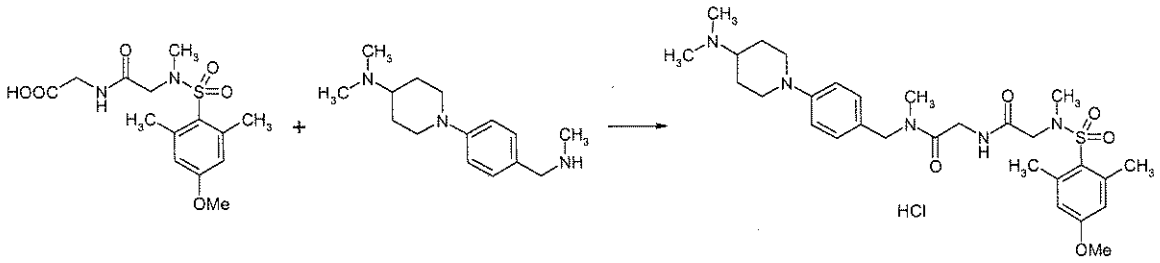
$C_{26}H_{38}N_4O_5S$ x HCl (555.13)

[M+H]+ = 519

HPLC (Method 1): retention time = 2.42 min

Example 125





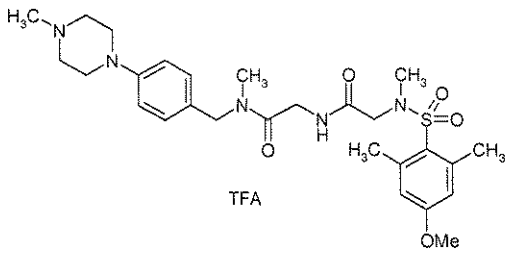
Example 125 is prepared analogously to 1f from 0.09 g (0.26 mmol) of product from 119d, 0.065 g (0.26 mmol) of product from 80a, 0.11 ml (0.78 mmol) of triethylamine and 0.084 g (0.26 mmol) of TBTU in 1.9 ml THF.

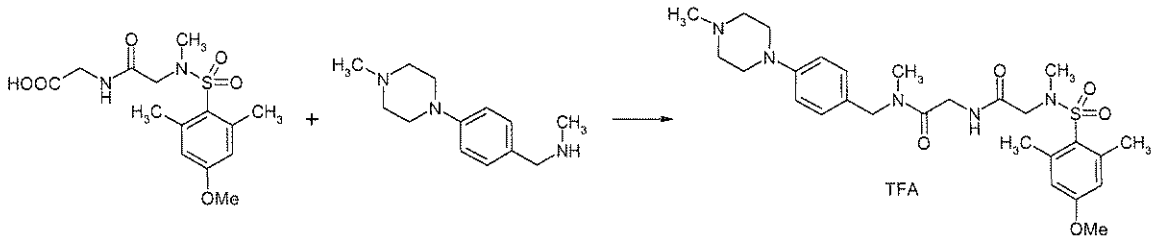
$C_{29}H_{43}N_5O_5S$ x HCl (610.21)

[M+H]+ = 574

HPLC (Method 1): retention time = 2.38 min

Example 126





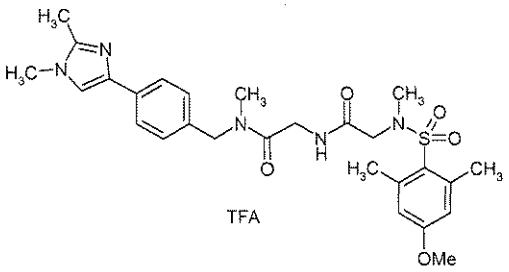
Example 126 is prepared analogously to 1f from 0.09 g (0.26 mmol) of product from 119d, 0.057 g (0.26 mmol) of product from 81a, 0.11 ml (0.78 mmol) of triethylamine and 0.084 g (0.26 mmol) of TBTU in 1.9 ml THF.

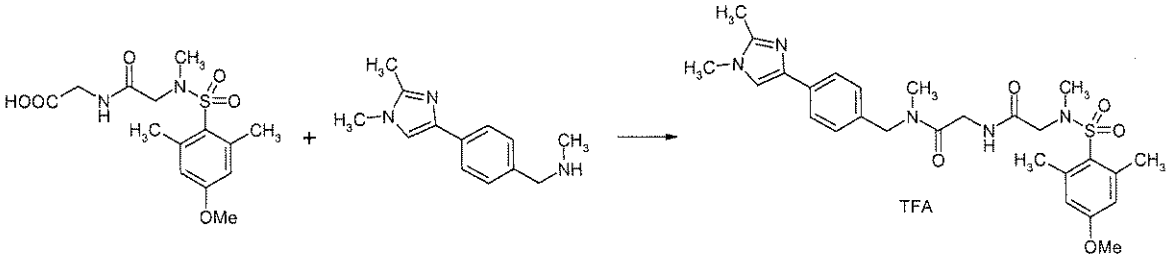
$C_{27}H_{39}N_5O_5S \times C_2HF_3O_2$ (610.21)

[M+H]+ = 546

HPLC (Method 5): retention time = 1.51 min

Example 127





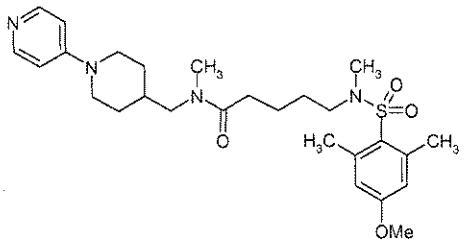
Example 127 is prepared analogously to 1f from 0.09 g (0.26 mmol) of product from 119d, 0.056 g (0.26 mmol) of product from 67c, 0.11 ml (0.78 mmol) of triethylamine and 0.084 g (0.26 mmol) of TBTU in 1.9 ml THF.

$C_{27}H_{35}N_5O_5S \times C_2HF_3O_2$ (655.69)

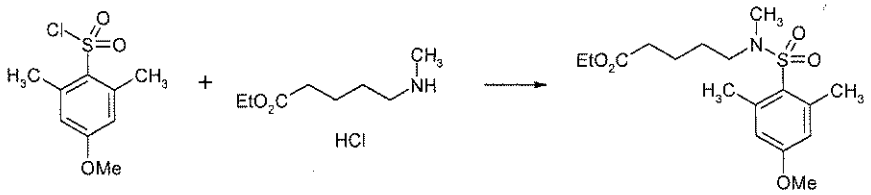
[M+H]+ = 542

HPLC (Method 5): retention time = 1.52 min

Example 128



128a)



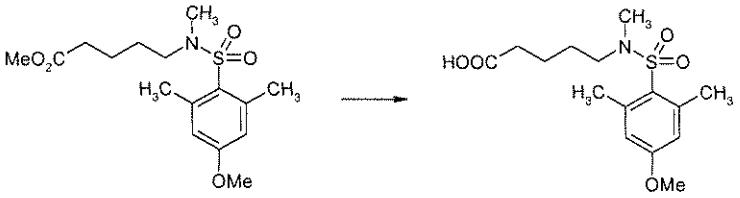
128a is prepared analogously to 10d from 0.50 g (2.13 mmol) of product from 13a, 0.42 g (2.13 mmol) of ethyl 5-methylaminovalerate (J. Am. Chem. Soc. 55, 1933, 1233-1241) and 1.18 ml (8.52 mmol) of triethylamine in 15 ml THF.

$C_{17}H_{27}NO_5S$ (357.47)

[M+H]+ = 358

HPLC (Method 6): retention time = 4.10 min

128b)



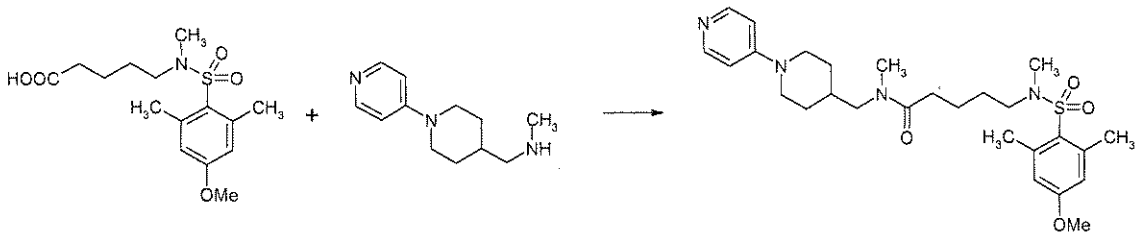
128b is prepared analogously to 119b from 0.62 g (1.73 mmol) of product from 128a and 7.00 ml (7.00 mmol) of 1 M sodium hydroxide solution in 1.5 ml of methanol and 15 ml THF.

$C_{15}H_{23}NO_5S$ (329.41)

[M+H]+ = 330

HPLC (Method 6): retention time = 3.24 min

128c)



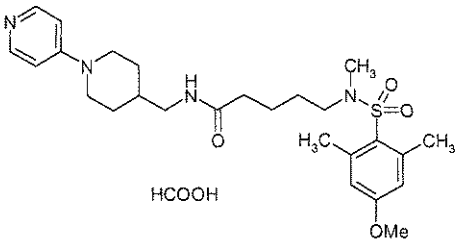
Example 128 is prepared analogously to 1f from 0.18 g (0.54 mmol) of product from 128b, 0.10 g (0.49 mmol) of product from 61b, 0.14 ml (0.97 mmol) of triethylamine and 0.18 g (0.54 mmol) of TBTU in 3 ml DMF.

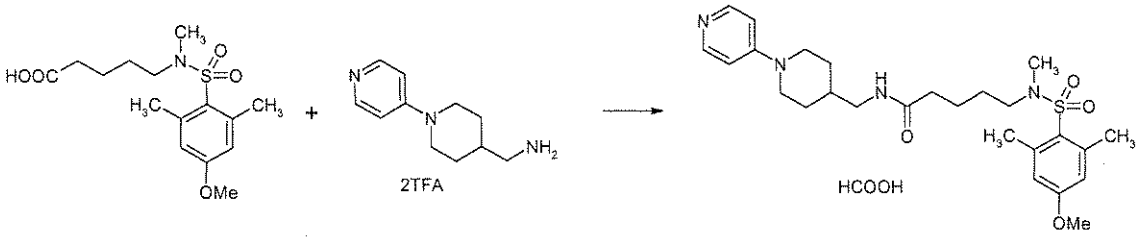
$C_{27}H_{40}N_4O_4S$ (516.70)

[M+H]+ = 517

HPLC (Method 6): retention time = 2.65 min

Example 129





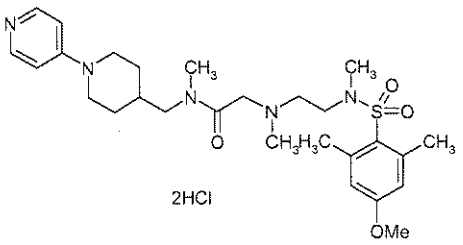
Example 129 is prepared analogously to 1f from 0.069 g (0.21 mmol) of product from 128b, 0.088 g (0.21 mmol) of product from 119f, 0.087 ml (0.63 mmol) of triethylamine and 0.077 g (0.23 mmol) of TBTU in 1 ml DMF.

$C_{26}H_{38}N_4O_4S \times CH_2O_2$ (548.71)

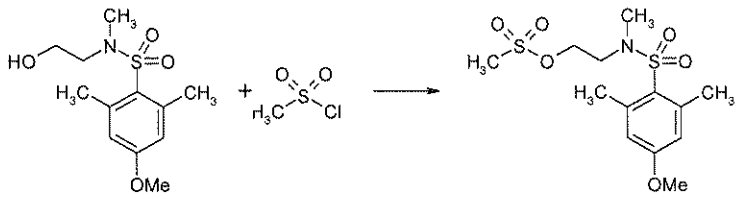
[M+H]+ = 503

HPLC (Method 6): retention time = 2.52 min

Example 130



130a)



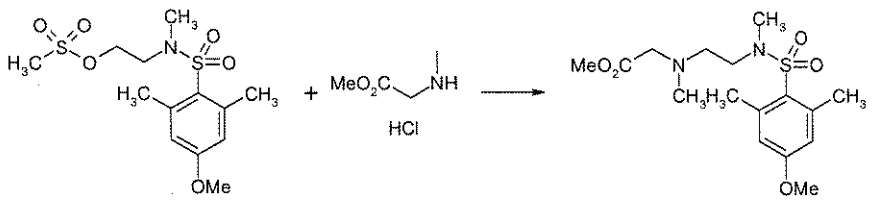
A mixture of 2.50 g (9.15 mmol) of product from 53a, 1.39 ml (10.00 mmol) of triethylamine and 50 ml THF is combined at ambient temperature with 0.77 ml (10.00 mmol) of methanesulphonic acid chloride (Aldrich). The reaction mixture is then stirred overnight at ambient temperature. The precipitate formed is filtered off. The filtrate is evaporated to dryness in vacuo. The residue is taken up in ethyl acetate and washed with water and saturated sodium chloride solution, dried on sodium sulphate and evaporated to dryness in vacuo.

$C_{13}H_{21}NO_6S_2$ (351.44)

[M+H]+ = 352

TLC: silica gel, dichloromethane / methanol 9.5:0.5, Rf value = 0.95

130b)



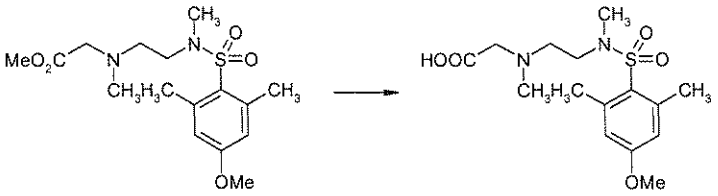
A mixture of 0.50 g (1.42 mmol) of product from 130a, 0.20 g (1.42 mmol) of sarcosine methylester hydrochloride (Aldrich), 0.52 ml (3.00 mmol) of DIPEA and 5 ml DMF is stirred for 24 hours at 80°C. The reaction mixture is evaporated down

in vacuo. The residue is taken up in dichloromethane and washed with water and saturated sodium hydrogen carbonate solution, dried on sodium sulphate and evaporated to dryness in vacuo. The crude product thus obtained is purified by column chromatography (eluant: dichloromethane / 0-3 % methanol).

$C_{16}H_{26}N_2O_5S$ (358.45)

[M+H]+ = 359

130c)

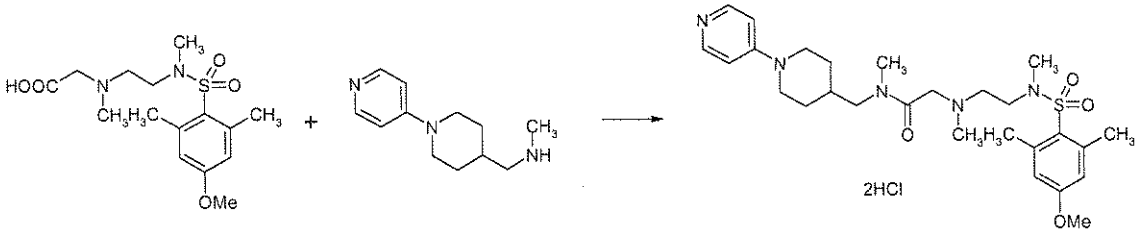


130c is prepared analogously to 1c from 0.29 g (0.81 mmol) of product from 130b and 0.17 g (4.00 mmol) of lithium hydroxide monohydrate (Aldrich) in 5 ml THF and 4 ml of water.

$C_{15}H_{24}N_2O_5S$ (344.43)

HPLC (Method 1): retention time = 2.32 min

130d)



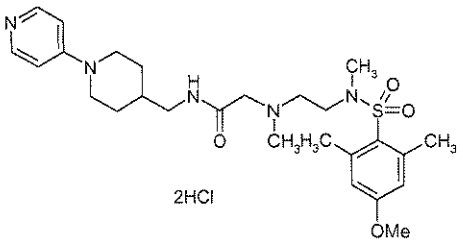
Example 130 is prepared analogously to 1f from 0.10 g (0.29 mmol) of product from 130c, 0.06 g (0.29 mmol) of product from 61b, 0.084 ml (0.60 mmol) of triethylamine and 0.096 g (0.30 mmol) of TBTU in 10 ml DMF.

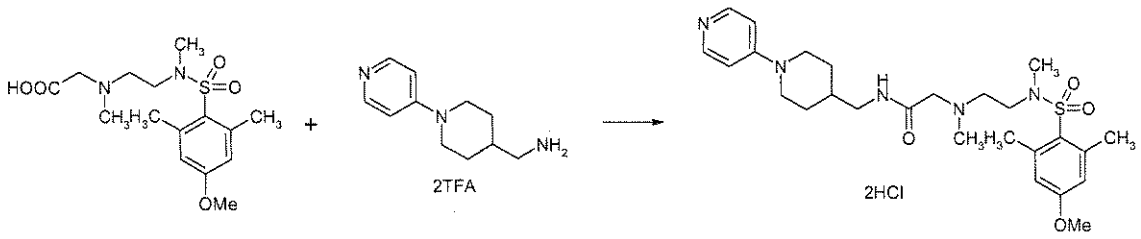
$C_{27}H_{41}N_5O_4S$ x 2HCl (604.63)

[M+H]+ = 532

HPLC (Method 5): retention time = 1.39 min

Example 131





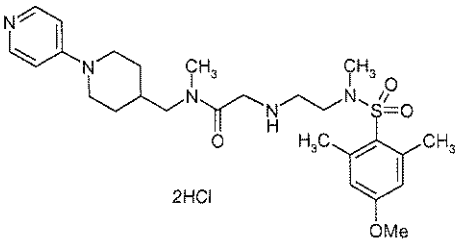
Example 131 is prepared analogously to 1f from 0.10 g (0.29 mmol) of product from 130c, 0.12 g (0.29 mmol) of product from 119f, 0.17 ml (1.20 mmol) of triethylamine and 0.096 g (0.30 mmol) of TBTU in 60 ml DMF.

$C_{26}H_{39}N_5O_4S$ x 2HCl (590.61)

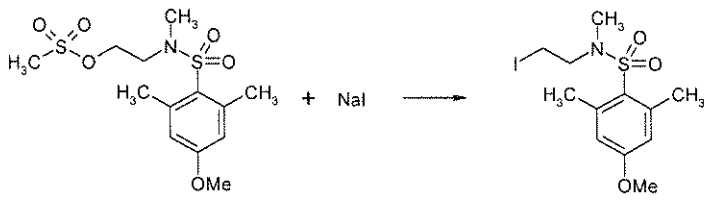
[M+H]+ = 518

HPLC (Method 5): retention time = 1.37 min

Example 132



132a)



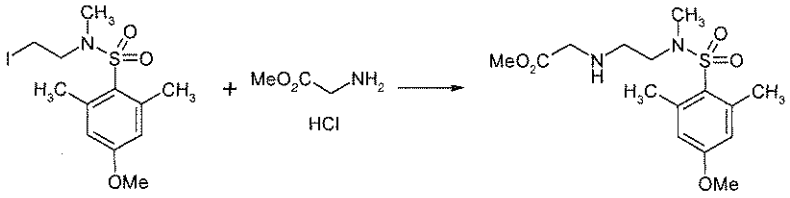
A mixture of 1.60 g (4.55 mmol) of product from 130a, 2.10 g (14.00 mmol) of sodium iodide and 30 ml acetone is stirred for eight hours at reflux temperature. The reaction mixture is then filtered through silica gel. The filtrate is evaporated to dryness in vacuo. The residue is taken up in ethyl acetate, washed with water, dried on sodium sulphate and evaporated to dryness in vacuo.

$C_{12}H_{18}INO_3S$ (383.25)

[M+H]+ = 384

HPLC (Method 1): retention time = 3.75 min

132b)



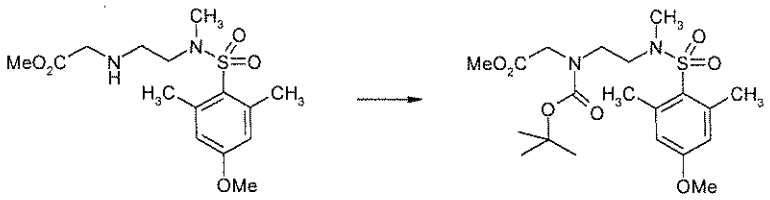
132b is prepared analogously to 130b from 1.30 g (3.39 mmol) of product from 132a, 1.28 g (10.20 mmol) of glycine methylester hydrochloride (Aldrich) and 3.48 ml (20.00 mmol) of DIPEA in 15 ml acetonitrile.

$C_{15}H_{24}N_2O_5S$ (344.43)

[M+H]+ = 345

TLC: silica gel, dichloromethane / methanol 9.5:0.5, Rf value = 0.38

132c)



A mixture of 0.46 g (1.34 mmol) of product from 132b, 0.33 g (1.50 mmol) of Boc-anhydride, 0.21 ml (1.50 mmol) of triethylamine and 30 ml dichloromethane is stirred overnight at ambient temperature. The reaction mixture is then diluted with dichloromethane and washed with saturated sodium hydrogen carbonate solution

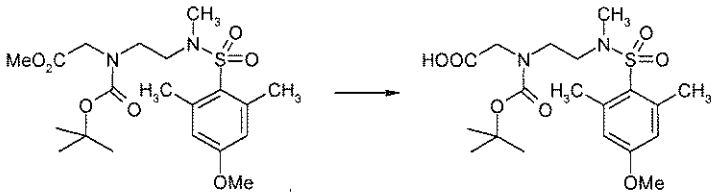
and saturated sodium chloride solution, dried on sodium sulphate and evaporated to dryness in vacuo.

$C_{20}H_{32}N_2O_7S$ (444.54)

[M+H]+ = 445

TLC: silica gel, dichloromethane / methanol 9.5:0.5, Rf value = 0.45

132d)

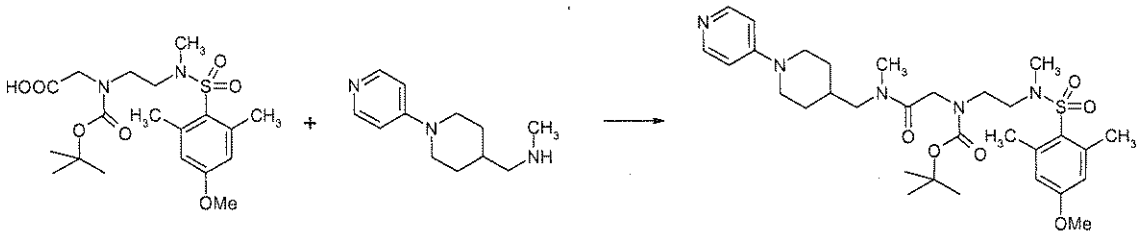


132d is prepared analogously to 1c from 0.59 g (1.33 mmol) of product from 132c and 0.28 g (6.60 mmol) of lithium hydroxide monohydrate (Aldrich) in 7 ml THF and 6.6 ml of water.

$C_{19}H_{30}N_2O_7S$ (430.52)

[M+H]+ = 431

132e)



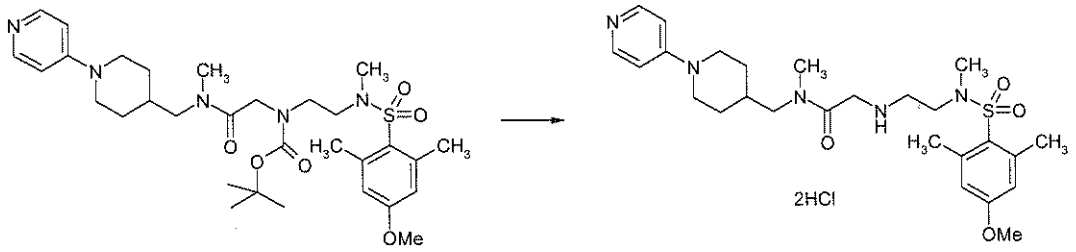
132e is prepared analogously to 1f from 0.15 g (0.35 mmol) of product from 132d, 0.072 g (0.35 mmol) of product from 61b, 0.098 ml (0.70 mmol) of triethylamine and 0.11 g (0.35 mmol) of TBTU in 7 ml DMF.

$C_{31}H_{47}N_5O_6S$ (617.80)

[M+H]+ = 618

HPLC (Method 1): retention time = 2.62 min

132f)



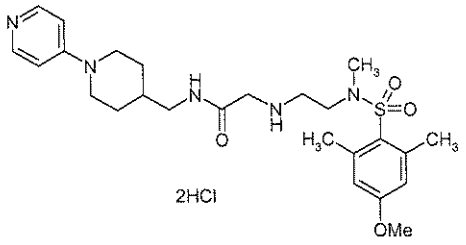
Example 132 is prepared analogously to 18b from 0.16 g (0.26 mmol) of product from 132e and 3 ml TFA in 3 ml dichloromethane.

$C_{26}H_{39}N_5O_4S$ x 2HCl (590.61)

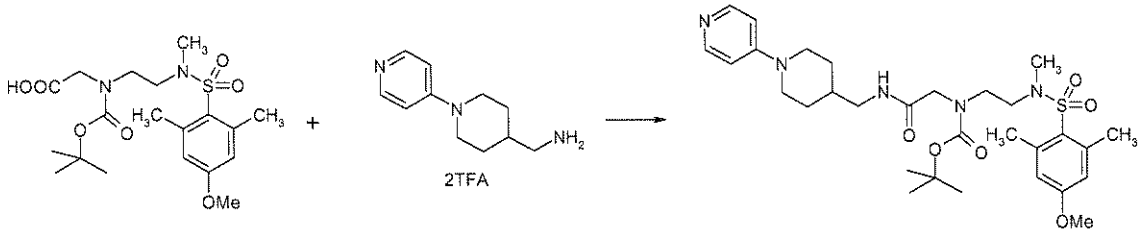
[M+H]+ = 518

HPLC (Method 5): retention time = 1.40 min

Example 133



133a)



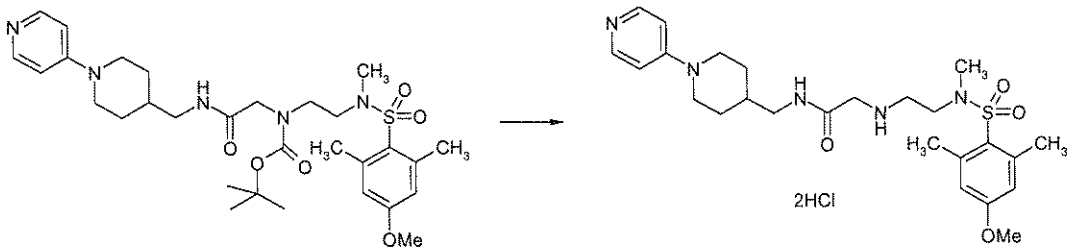
133a is prepared analogously to 1f from 0.15 g (0.35 mmol) of product from 132d, 0.15 g (0.35 mmol) of product from 119f, 0.20 ml (1.40 mmol) of triethylamine and 0.11 g (0.35 mmol) of TBTU in 7 ml DMF.

$C_{30}H_{45}N_5O_6S$ (603.77)

[M+H]+ = 604

TLC: silica gel, dichloromethane / methanol / ammonia 9:1:0.1, Rf value = 0.48

133b)



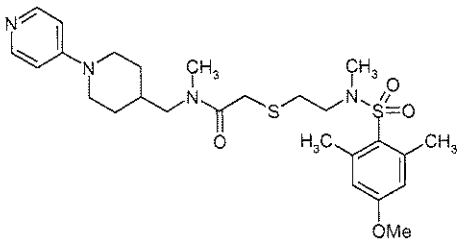
Example 133 is prepared analogously to 18b from 0.16 g (0.27 mmol) of product from 133a and 5 ml TFA in 5 ml dichloromethane.

$C_{25}H_{37}N_5O_4S$ x 2HCl (576.58)

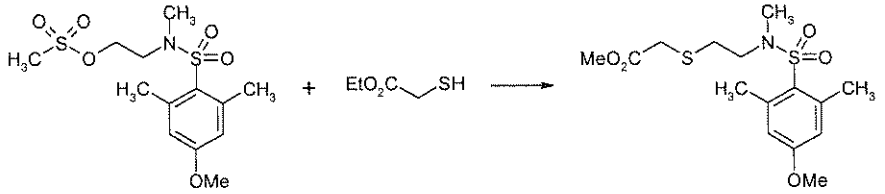
[M+H]+ = 504

HPLC (Method 1): retention time = 2.17 min

Example 134



134a)

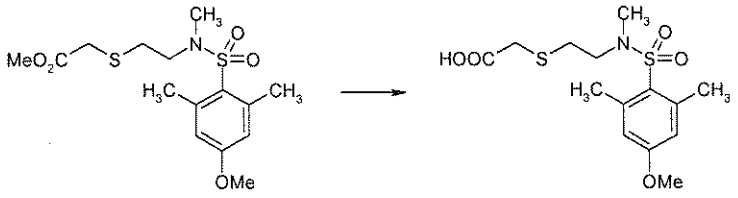


A mixture of 0.21 g (0.60 mmol) of product from 130a, 0.065 ml (0.60 mmol) of ethyl mercaptoacetate (Aldrich), 0.17 g (1.20 mmol) of potassium carbonate and 10 ml acetonitrile is stirred for 24 hours at ambient temperature. The precipitate is filtered off, the filtrate is evaporated down in vacuo. The crude product thus obtained is purified by preparative HPLC.

$C_{16}H_{25}NO_5S_2$ (375.51)

[M+H]+ = 376

134b)

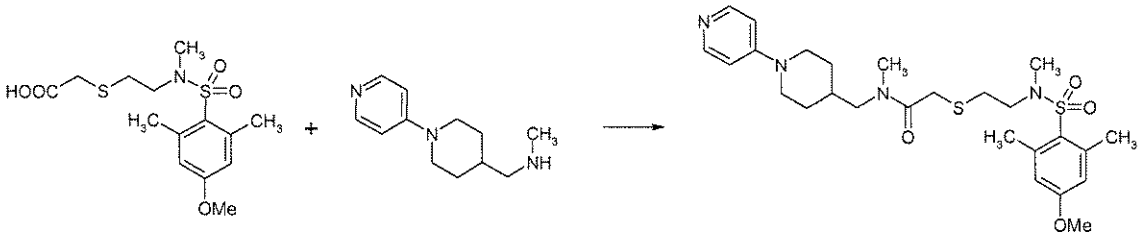


134b is prepared analogously to 119b from 0.070 g (0.19 mmol) of product from 134a and 2.00 ml (2.00 mmol) of 1 M sodium hydroxide solution in 5 ml THF.

$C_{14}H_{21}NO_5S_2$ (347.45)

[M+H]+ = 348

134c)



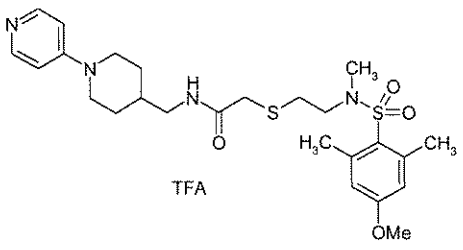
Example 134 is prepared analogously to 1f from 0.064 g (0.18 mmol) of product from 134b, 0.038 g (0.18 mmol) of product from 61b, 0.079 ml (0.46 mmol) of DIPEA and 0.059 g (0.18 mmol) of TBTU in 5 ml DMF.

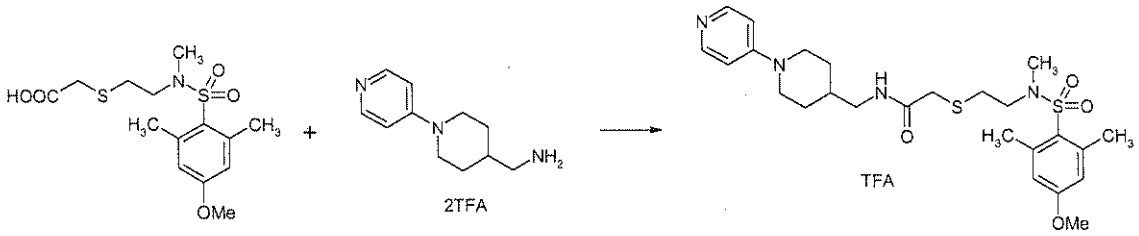
$C_{26}H_{38}N_4O_4S_2$ (534.74)

[M+H]+ = 535

HPLC (Method 6): retention time = 2.68 min

Example 135





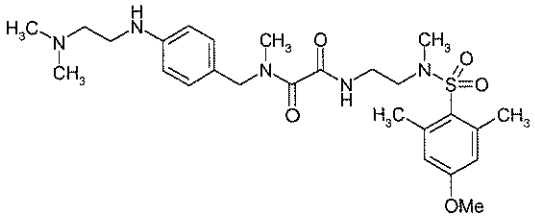
Example 135 is prepared analogously to 1f from 0.073 g (0.21 mmol) of product from 134b, 0.088 g (0.21 mmol) of product from 119f, 0.11 ml (0.63 mmol) of DIPEA and 0.087 g (0.27 mmol) of TBTU in 5 ml DMF.

$C_{25}H_{36}N_4O_4S_2 \times C_2HF_3O_2$ (634.73)

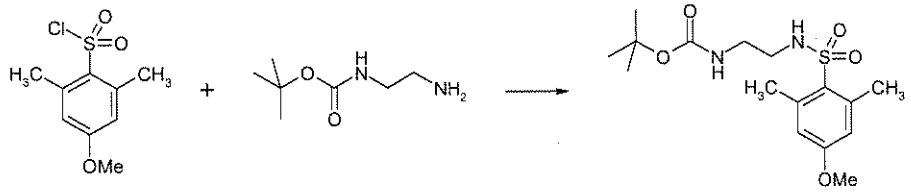
[M+H]+ = 521

HPLC (Method 6): retention time = 2.57 min

Example 136



136a)



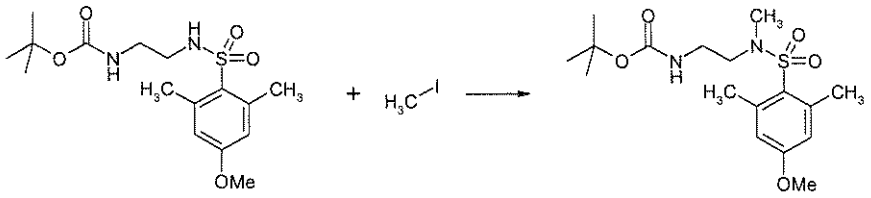
136a is prepared analogously to 3a from 2.0 g (8.52 mmol) of product of 13a, 1.37 g (8.55 mmol) of N-Boc-ethylenediamine (Fluka) and 1.0 g (9.89 mmol) of triethylamine in 50 ml THF.

$C_{16}H_{26}N_2O_5S$ (358.45)

[M-H]- = 357

HPLC (Method 6): retention time = 3.63 min

136b)



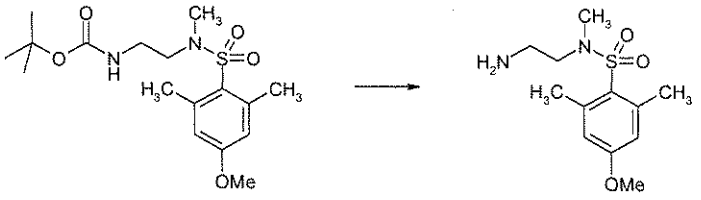
136b is prepared analogously to 3b from 3.38 g (9.43 mmol) of the product of 136a, 0.53 ml (8.55 mmol) of methyl iodide, 1.77 g (12.83 mmol) of potassium carbonate under anhydrous conditions in 30 ml DMSO.

$C_{17}H_{28}N_2O_5S$ (372.48)

[M+H]+ = 373

HPLC (Method 6): retention time = 3.89 min

136c)



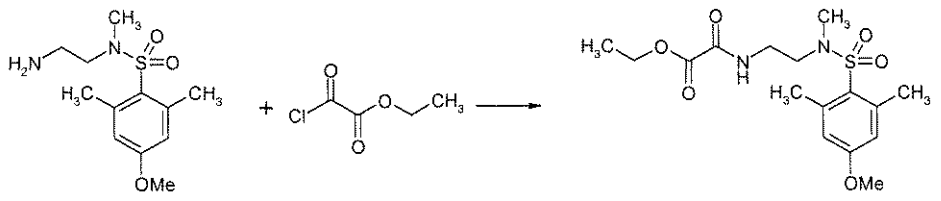
136b is prepared analogously to 28d from 3.61 g (9.69 mmol) of the product of 136b and 10 ml TFA in 50 ml dichloromethane.

$C_{127}H_{20}N_2O_3S$ (272.36)

[M+H]+ = 273

HPLC (Method 6): retention time = 1.95 min

136d)

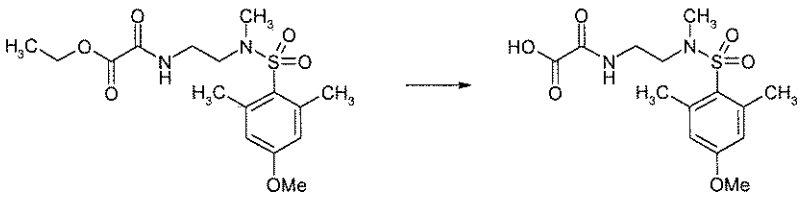


A mixture of 0.50 g (1.84 mmol) of the product of 136c, 0.56 ml (5.51 mmol) of triethylamine and 25 ml dichloromethane is combined with 0.38 ml (2.75 mmol) of monoethyl oxalate chloride (Fluka) in 5 ml dichloromethane while cooling with an ice bath and the mixture is stirred for two hours at ambient temperature. The reaction mixture is then diluted with dichloromethane, washed with 10% aqueous citric acid solution, saturated sodium sulphate solution and with water, dried on sodium sulphate and evaporated to dryness in vacuo.

$C_{16}H_{24}N_2O_6S$ (372.44)

[M+H]+ = 373

136e)

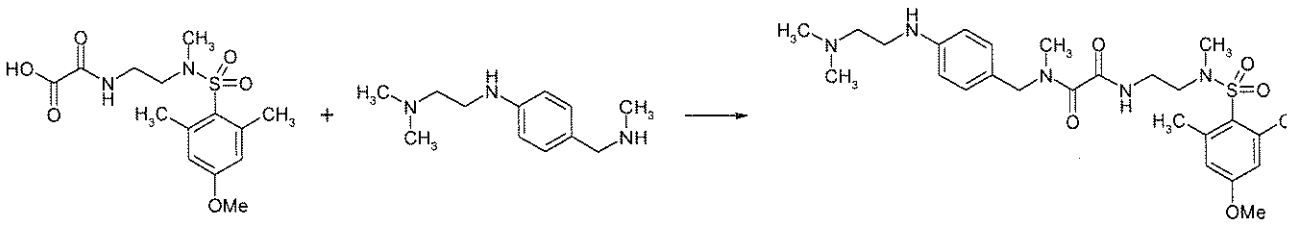


A mixture of 0.60 g (1.60 mmol) of the product of 136d, 5.6 ml 1 M sodium hydroxide solution and 6 ml of ethanol is stirred for four hours at ambient temperature and then evaporated to dryness in vacuo. The residue is combined with 8 ml 1 M hydrochloric acid and extracted with ethyl acetate. The combined organic extracts are washed with water and saturated sodium chloride solution, dried on sodium sulphate and evaporated to dryness in vacuo.

$C_{14}H_{20}N_2O_6S$ (344.38)

[M+H]+ = 345

136f)



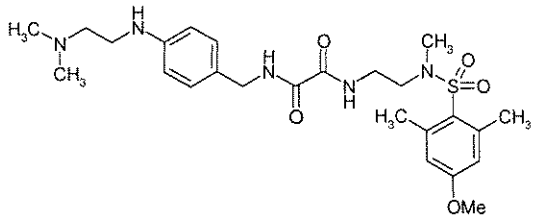
Example 136 is prepared analogously to 1f from 40.0 mg (0.12 mmol) of the product of 136e, 48.2 mg (0.12 mmol) of N,N-dimethyl-N'-(4-methylaminomethyl-phenyl)-ethan-1,2-diamine (analogously to J. Chem. Soc 1960, 3163-3165), 0.038 ml (0.29 mmol) of DIPEA and 38.9 mg (0.12 mmol) of TBTU in 1.5 ml DMF.

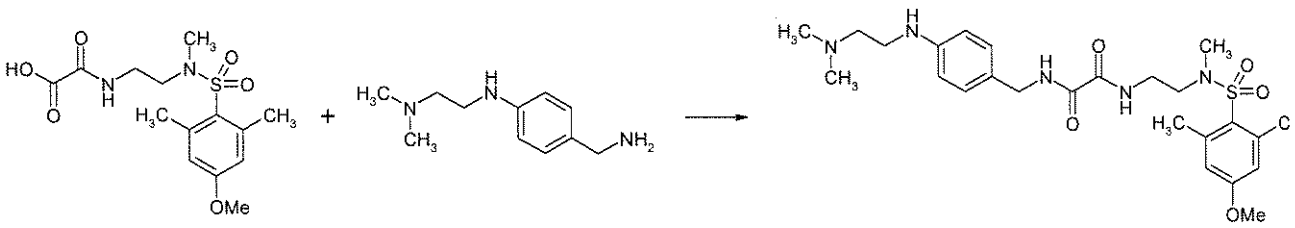
$C_{26}H_{39}N_5O_5S$ (533.68)

[M+H]+ = 534

HPLC (Method 6): retention time = 1.61 min

Example 137





Example 137 is prepared analogously to 1f from 40.0 mg (0.12 mmol) of the product of 136e, 22.5 mg (0.12 mmol) of N-(4-aminomethyl-phenyl)-N',N'-dimethylethan-1,2-diamine (analogously to J. Chem. Soc 1960, 3163-3165), 0.038 ml (0.29 mmol) of DIPEA and 38.9 mg (0.12 mmol) of TBTU in 1.5 ml DMF.

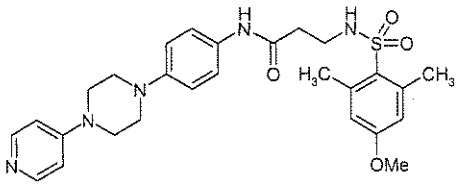
$C_{25}H_{37}N_5O_5S$ (519.66)

[M+H]+ = 520

HPLC (Method 6): retention time = 1.53 min

The following compounds were prepared analogously to Example 22:

Example 138

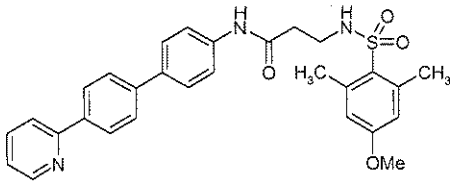


$C_{27}H_{33}N_5O_4S \times C_2HF_3O_2$ (637.67)

[M+H]+ = 524

HPLC (Method 6): retention time = 2.43 min

Example 139

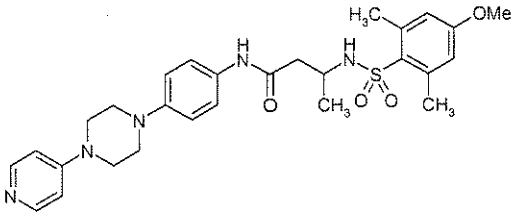


$C_{29}H_{29}N_3O_4S \times C_2HF_3O_2$ (629.65)

[M+H]+ = 516

HPLC (Method 6): retention time = 3.39 min

Example 140

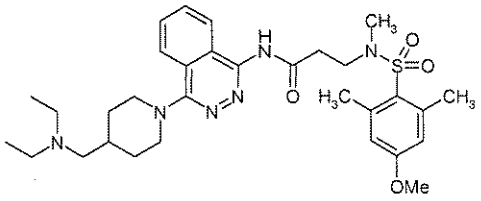


$C_{28}H_{35}N_5O_4S$ (537.67)

[M+H]+ = 538

HPLC (Method 6): retention time = 2.45 min

Example 141

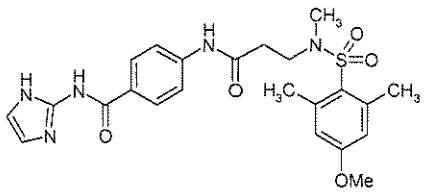


$C_{31}H_{44}N_6O_4S$ x $C_2HF_3O_2$ (710.81)

[M+H]+ = 597

HPLC (Method 6): retention time = 2.30 min

Example 142

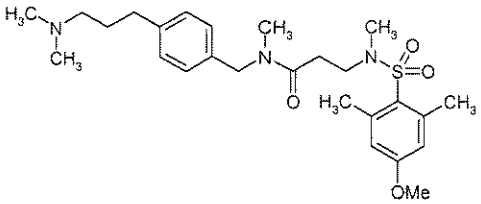


$C_{23}H_{27}N_5O_5S$ x $C_2HF_3O_2$ (599.58)

[M+H]+ = 486

HPLC (Method 6): retention time = 2.46 min

Example 143

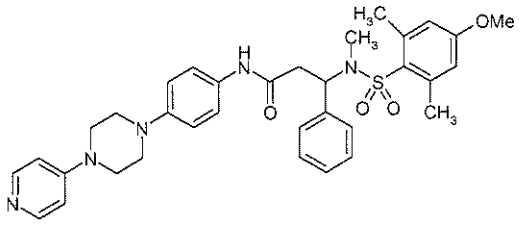


$C_{26}H_{39}N_3O_4S$ (489.67)

[M+H]+ = 490

HPLC (Method 6): retention time = 2.66 min

Example 144

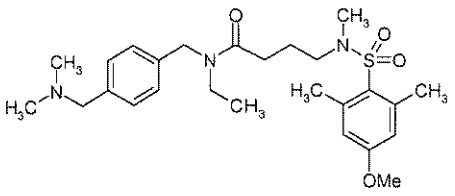


$C_{34}H_{39}N_5O_4S$ (613.77)

[M+H]+ = 614

HPLC (Method 6): retention time = 3.07 min

Example 145

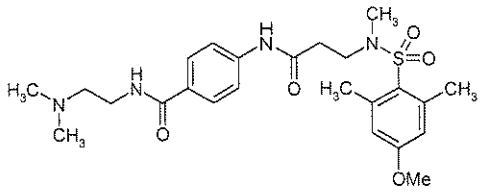


$C_{26}H_{39}N_3O_4S \times C_2HF_3O_2$ (603.70)

[M+H]+ = 490

HPLC (Method 6): retention time = 2.60 min

Example 146

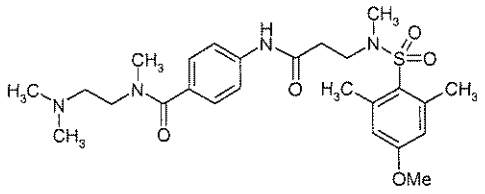


$C_{24}H_{34}N_4O_5S \times CH_2O_2$ (536.64)

[M+H]+ = 491

HPLC (Method 6): retention time = 2.29 min

Example 147

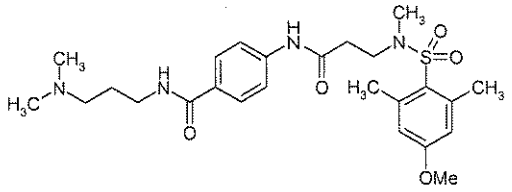


$C_{25}H_{36}N_4O_5S \times CH_2O_2$ (550.67)

[M+H]+ = 505

HPLC (Method 6): retention time = 2.32 min

Example 148

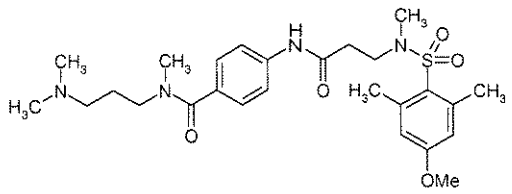


$C_{25}H_{36}N_4O_5S$ (504.64)

[M+H]+ = 505

HPLC (Method 6): retention time = 2.31 min

Example 149



$C_{26}H_{38}N_4O_5S \times CH_2O_2$ (564.70)

[M+H]+ = 519

HPLC (Method 6): retention time = 2.34 min

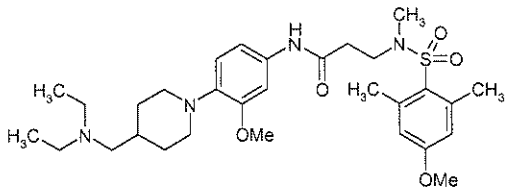
Example 150

$C_{27}H_{41}N_5O_4S \times 2C_2HF_3O_2$ (759.76)

[M+H]+ = 532

HPLC (Method 5): retention time = 1.40 min

Example 151

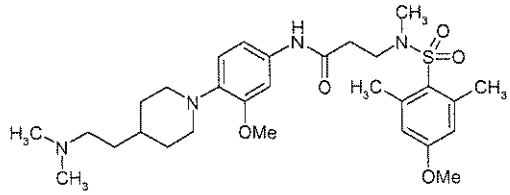


$C_{30}H_{46}N_4O_5S \times HCl$ (611.24)

[M+H]+ = 575

HPLC (Method 1): retention time = 2.12 min

Example 152

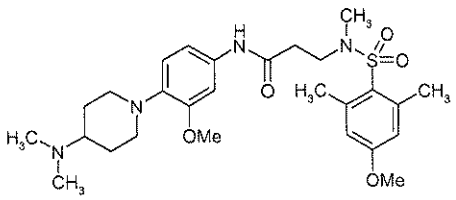


$C_{29}H_{44}N_4O_5S \times HCl$ (597.21)

[M+H]+ = 561

HPLC (Method 8): retention time = 3.12 min

Example 153

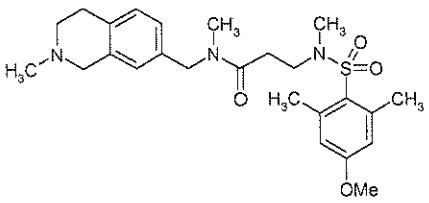


$C_{27}H_{40}N_4O_5S$ x HCl (569.16)

[M+H]+ = 533

HPLC (Method 11): retention time = 1.67 min

Example 154

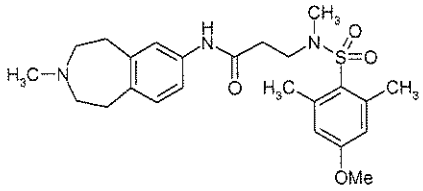


$C_{25}H_{35}N_3O_4S$ x HCl (510.09)

[M+H]+ = 474

HPLC (Method 7): retention time = 1.90 min

Example 155

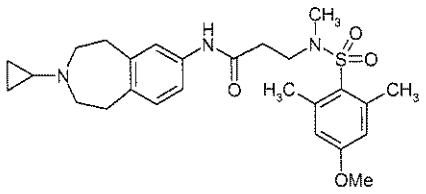


$C_{24}H_{33}N_3O_4S$ x $C_2HF_3O_2$ (573.63)

[M+H]+ = 460

HPLC (Method 5): retention time = 1.52 min

Example 156

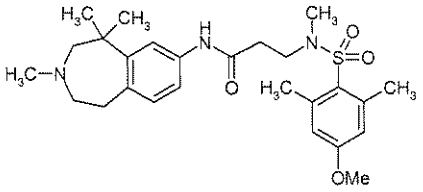


$C_{26}H_{35}N_3O_4S \times C_2HF_3O_2$ (599.66)

[M+H]+ = 486

HPLC (Method 5): retention time = 1.55 min

Example 157

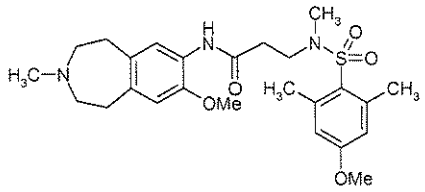


$C_{26}H_{37}N_3O_4S \times C_2HF_3O_2$ (601.68)

[M+H]+ = 488

HPLC (Method 5): retention time = 1.54 min

Example 158

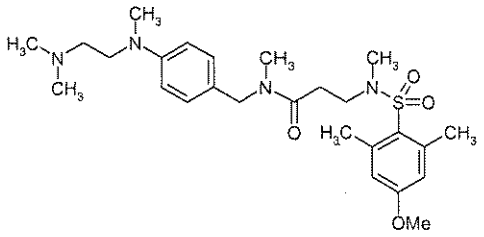


$C_{25}H_{35}N_3O_5S \times C_2HF_3O_2$ (603.65)

[M+H]+ = 490

HPLC (Method 5): retention time = 1.54 min

Example 159

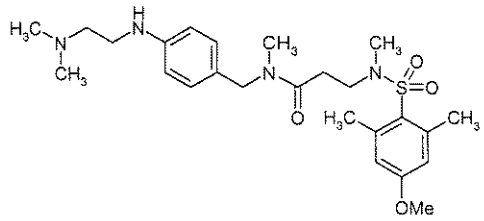


$C_{26}H_{40}N_4O_4S$ x HCl (541.15)

[M+H]+ = 505

HPLC (Method 5): retention time = 1.59 min

Example 160

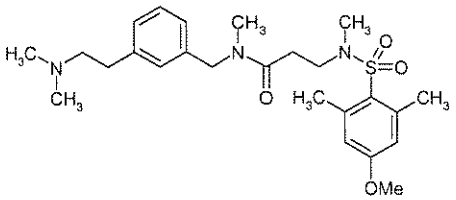


$C_{25}H_{38}N_4O_4S$ x HCl (527.12)

[M+H]+ = 491

HPLC (Method 5): retention time = 1.55 min

Example 161

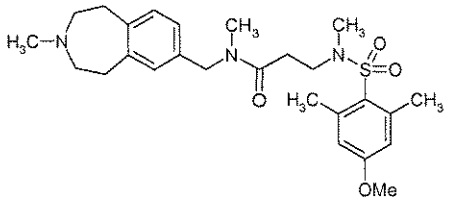


$C_{25}H_{37}N_3O_4S$ x HCl (512.11)

[M+H]+ = 476

HPLC (Method 5): retention time = 1.56 min

Example 162

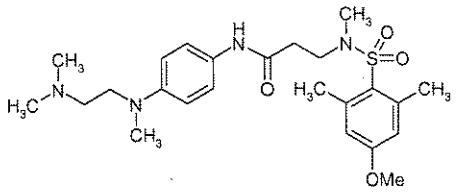


$C_{26}H_{37}N_3O_4S$ x HCl (524.12)

[M+H]+ = 488

HPLC (Method 5): retention time = 1.54 min

Example 163

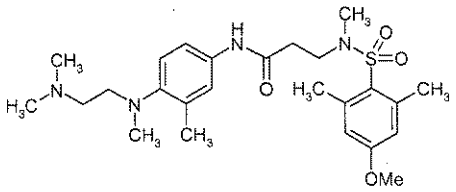


$C_{24}H_{36}N_4O_4S$ x HCl (513.09)

[M+H]+ = 477

HPLC (Method 7): retention time = 1.88 min

Example 164

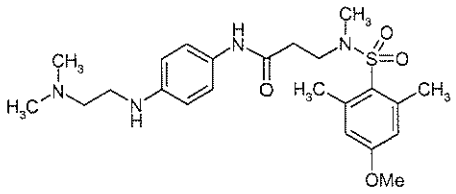


$C_{25}H_{38}N_4O_4S$ x HCl (527.12)

[M+H]+ = 491

HPLC (Method 7): retention time = 1.92 min

Example 165

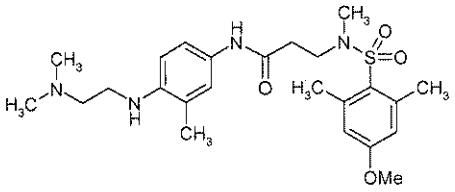


$C_{23}H_{34}N_4O_4S$ x HCl (499.07)

[M+H]+ = 463

HPLC (Method 7): retention time = 1.79 min

Example 166

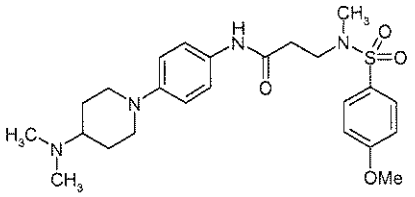


$C_{24}H_{36}N_4O_4S$ x HCl (513.09)

[M+H]+ = 477

HPLC (Method 7): retention time = 1.86 min

Example 167

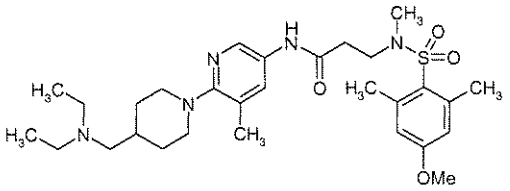


$C_{24}H_{34}N_4O_4S$ x $C_2HF_3O_2$ (588.64)

[M+H]+ = 475

HPLC (Method 5): retention time = 1.39 min

Example 168

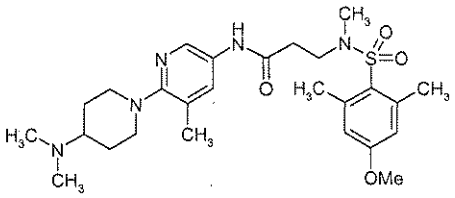


$C_{29}H_{45}N_5O_4S$ x 2HCl (632.69)

[M+H]+ = 560

DC: silica gel, dichloromethane / ethanol 9:1, Rf value = 0.22

Example 169

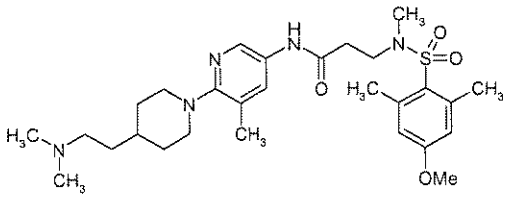


$C_{26}H_{39}N_5O_4S$ x 2HCl (590.61)

[M+H]+ = 518

DC: silica gel, dichloromethane / ethanol 4:1, Rf value = 0.68

Example 170

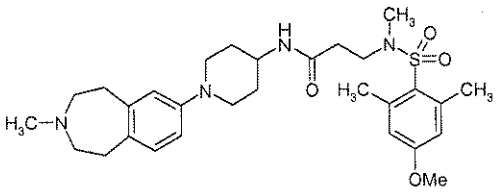


$C_{28}H_{43}N_5O_4S$ x 2HCl (618.66)

[M+H]+ = 546

HPLC (Method 5): retention time = 1.26 min

Example 171

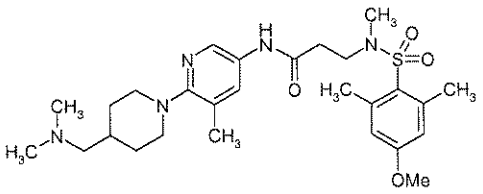


$C_{29}H_{42}N_4O_4S$ (542.73)

[M+H]+ = 543

HPLC (Method 4): retention time = 2.8 min

Example 172

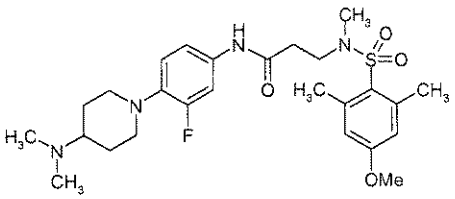


$C_{27}H_{41}N_5O_4S$ x 2HCl (604.63)

[M+H]+ = 532

HPLC (Method 5): retention time = 1.39 min

Example 173

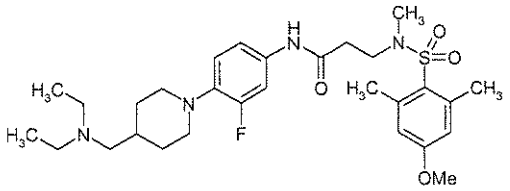


$C_{26}H_{37}FN_4O_4S$ x HCl (557.12)

[M+H]+ = 521

DC: silica gel, dichloromethane / ethanol 9:1, Rf value = 0.25

Example 174

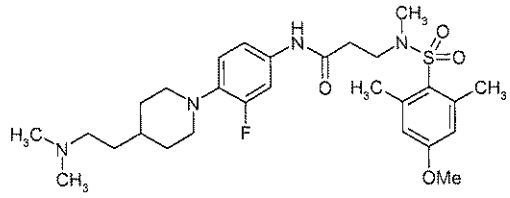


$C_{29}H_{43}FN_4O_4S$ x HCl (599.20)

[M+H]+ = 563

DC: silica gel, dichloromethane / ethanol 9:1, Rf value = 0.40

Example 175

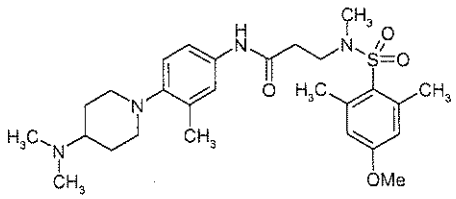


$C_{28}H_{41}FN_4O_4S$ x HCl (585.17)

[M+H]+ = 549

DC: silica gel, dichloromethane / ethanol 9:1, Rf value = 0.35

Example 176

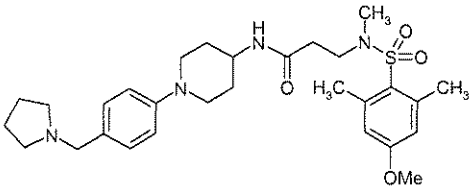


$C_{27}H_{40}N_4O_4S$ (516.70)

[M+H]+ = 517

DC: silica gel, dichloromethane / ethanol / ammonia 8:2:0.01, Rf value = 0.41

Example 177

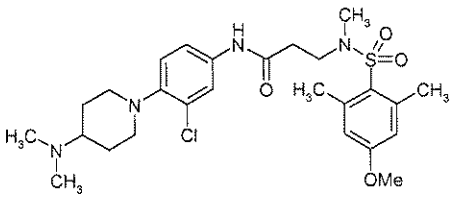


$C_{29}H_{42}N_4O_4S$ x HCl (579.19)

[M+H]+ = 543

DC: silica gel, dichloromethane / ethanol / ammonia 8:2:0.01, Rf value = 0.47

Example 178

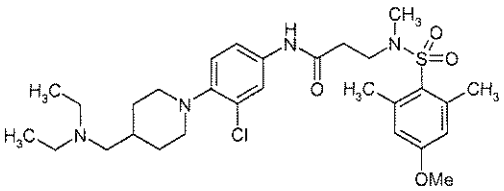


$C_{26}H_{37}ClN_4O_4S$ x HCl (573.58)

[M+H]+ = 537/539

DC: silica gel, dichloromethane / ethanol 9:1, Rf value = 0.26

Example 179

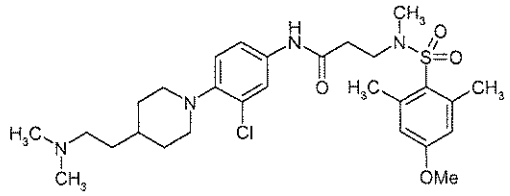


$C_{29}H_{43}ClN_4O_4S$ x HCl (615.66)

[M+H]+ = 579/581

DC: silica gel, dichloromethane / ethanol 9:1, Rf value = 0.45

Example 180

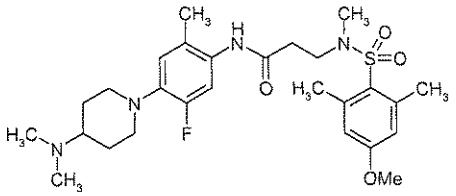


$C_{28}H_{41}ClN_4O_4S$ x HCl (601.63)

[M+H]+ = 565/567

DC: silica gel, dichloromethane / ethanol 9:1, Rf value = 0.30

Example 181

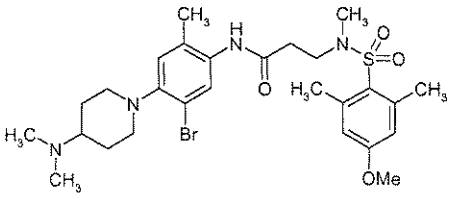


$C_{27}H_{39}FN_4O_4S$ x HCl (571.15)

[M+H]+ = 535

DC: silica gel, dichloromethane / ethanol / ammonia 8:2:0.01, Rf value = 0.26

Example 182

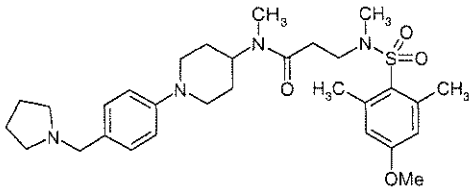


$C_{27}H_{39}BrN_4O_4S$ x HCl (632.05)

[M+H]+ = 595/597

DC: silica gel, dichloromethane / ethanol / ammonia 8:2:0.01, Rf value = 0.51

Example 183

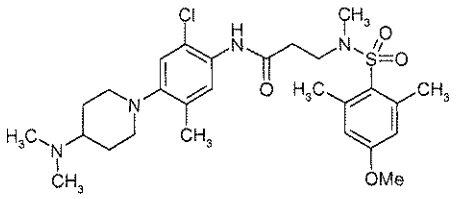


$C_{30}H_{44}N_4O_4S$ x HCl (593.22)

[M+H]+ = 557

DC: silica gel, dichloromethane / ethanol / ammonia 8:2:0.01, Rf value = 0.63

Example 184

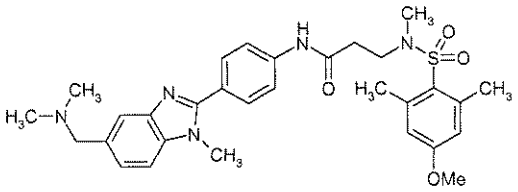


$C_{27}H_{39}ClN_4O_4S$ x HCl (587.60)

[M+H]+ = 551

DC: silica gel, dichloromethane / ethanol / ammonia 8:2:0.01, Rf value = 0.58

Example 185

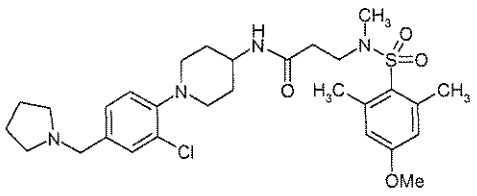


$C_{30}H_{37}N_5O_4S$ x HCl (600.17)

[M+H]+ = 564

HPLC (Method 4): retention time = 3.0 min

Example 186

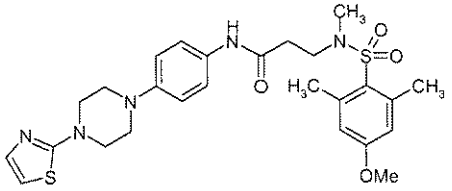


$C_{29}H_{41}ClN_4O_4S$ x HCl (613.64)

[M+H]+ = 577/579

DC: silica gel, dichloromethane / methanol 9:1, Rf value = 0.24

Example 187

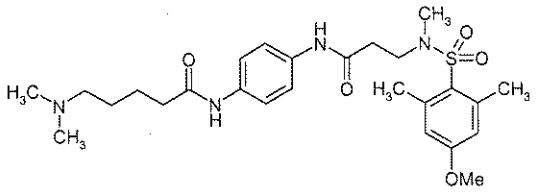


$C_{26}H_{33}N_5O_4S_2$ (543.70)

[M+H]+ = 544

HPLC (Method 6): retention time = 3.11 min

Example 188

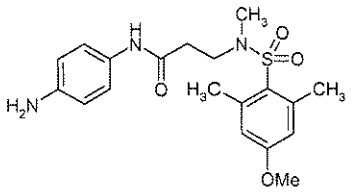


$C_{26}H_{38}N_4O_5S$ (518.67)

[M+H]+ = 519

HPLC (Method 6): retention time = 2.44 min

Example 189

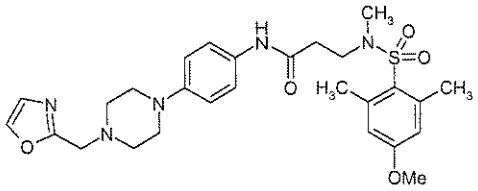


$C_{19}H_{25}N_3O_4S \times C_2HF_3O_2$ (505.51)

[M+H]+ = 392

HPLC (Method 6): retention time = 2.04 min

Example 190

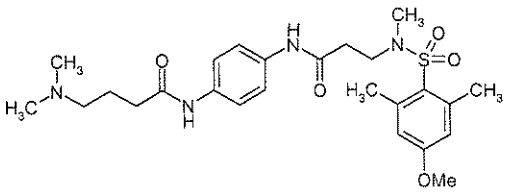


$C_{27}H_{35}N_5O_5S$ (541.66)

[M+H]+ = 542

HPLC (Method 6): retention time = 2.51 min

Example 191

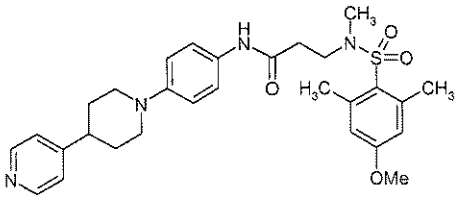


$C_{25}H_{36}N_4O_5S$ (504.64)

[M+H]+ = 505

HPLC (Method 6): retention time = 2.43 min

Example 192

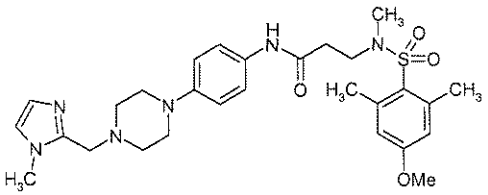


$C_{29}H_{36}N_4O_4S$ (536.69)

[M+H]+ = 537

HPLC (Method 6): retention time = 2.19 min

Example 193

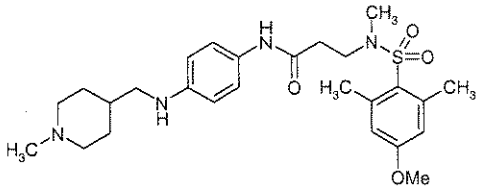


$C_{28}H_{38}N_6O_4S$ (554.71)

[M+H]+ = 555

HPLC (Method 6): retention time = 2.37 min

Example 194

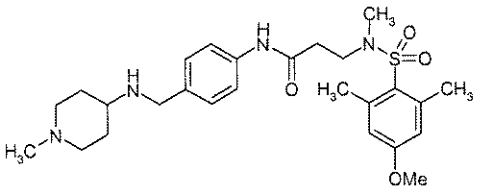


$C_{26}H_{38}N_4O_4S$ (502.67)

[M+H]+ = 503

HPLC (Method 6): retention time = 2.35 min

Example 195

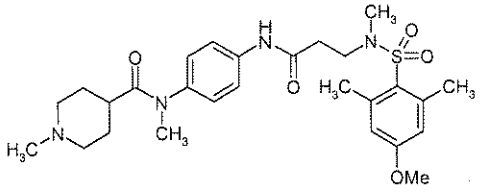


$C_{26}H_{38}N_4O_4S$ (502.67)

[M+H]+ = 503

HPLC (Method 6): retention time = 2.00 min

Example 196

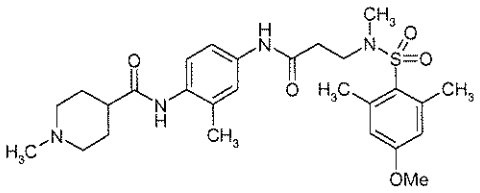


$C_{27}H_{38}N_4O_5S \times C_2HF_3O_2$ (644.70)

[M+H]+ = 531

HPLC (Method 6): retention time = 2.45 min

Example 197

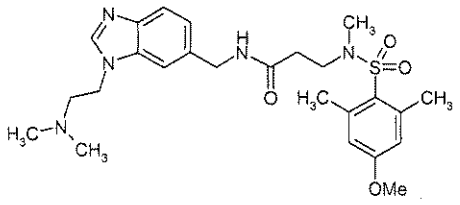


$C_{27}H_{38}N_4O_5S$ (530.68)

[M+H]+ = 531

HPLC (Method 6): retention time = 2.53 min

Example 198

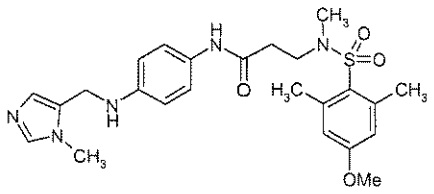


$C_{25}H_{35}N_5O_4S$ (501.64)

[M+H]+ = 502

HPLC (Method 6): retention time = 2.05 min

Example 199

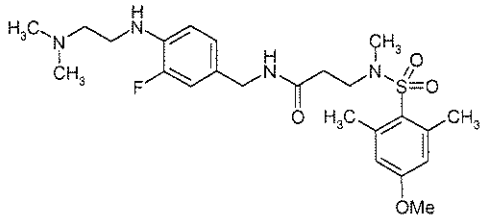


$C_{24}H_{31}N_5O_4S$ (485.60)

[M+H]+ = 486

HPLC (Method 6): retention time = 2.41 min

Example 200

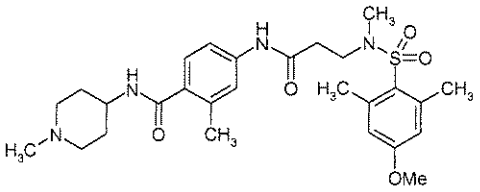


$C_{24}H_{35}FN_4O_4S \times CH_2O_2$ (540.65)

[M+H]+ = 495

HPLC (Method 6): retention time = 2.50 min

Example 201

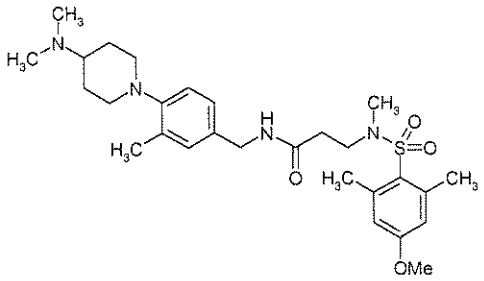


$C_{27}H_{38}N_4O_5S$ (530.68)

[M+H]+ = 531

HPLC (Method 6): retention time = 2.36 min

Example 202

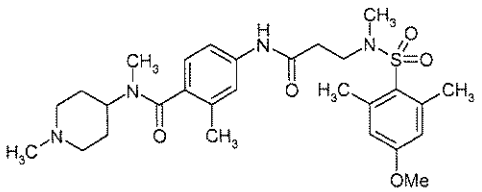


$C_{28}H_{42}N_4O_4S$ (530.72)

[M+H]+ = 531

HPLC (Method 6): retention time = 2.60 min

Example 203

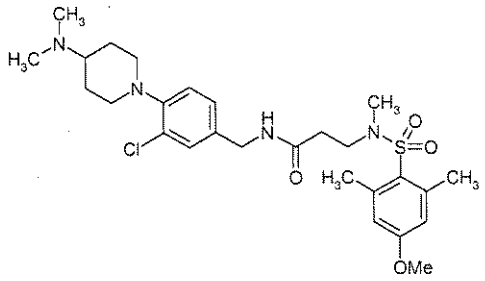


$C_{28}H_{40}N_4O_5S$ (544.71)

[M+H]+ = 545

HPLC (Method 6): retention time = 2.21 min

Example 204

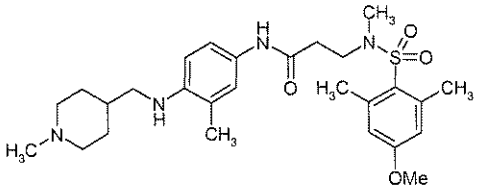


$C_{27}H_{39}ClN_4O_4S$ (551.14)

[M+H]+ = 551/553

HPLC (Method 6): retention time = 2.65 min

Example 205

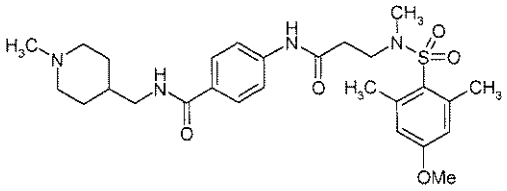


$C_{27}H_{40}N_4O_4S \times C_2HF_3O_2$ (630.72)

[M+H]+ = 517

HPLC (Method 6): retention time = 2.51 min

Example 206

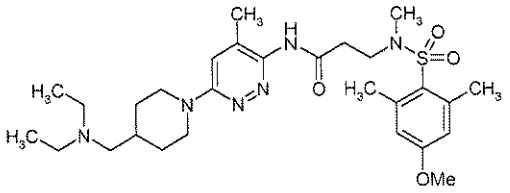


$C_{27}H_{38}N_4O_5S \times CH_2O_2$ (576.71)

[M+H]+ = 531

HPLC (Method 6): retention time = 2.33 min

Example 207

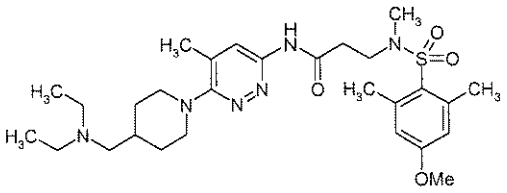


$C_{28}H_{44}N_6O_4S \times C_2HF_3O_2$ (674.78)

[M+H]+ = 561

HPLC (Method 6): retention time = 2.14 min

Example 208

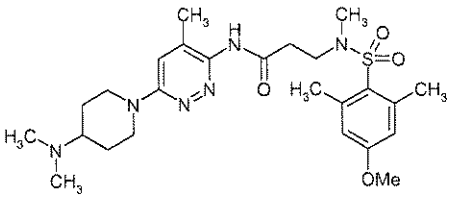


$C_{28}H_{44}N_6O_4S \times C_2HF_3O_2$ (674.78)

[M+H]+ = 561

HPLC (Method 6): retention time = 2.43 min

Example 209

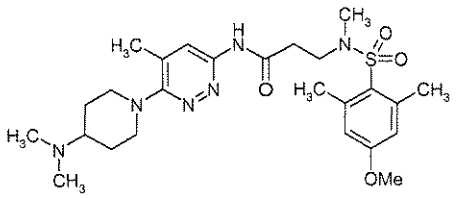


$C_{25}H_{38}N_6O_4S \times C_2HF_3O_2$ (632.70)

[M+H]+ = 519

HPLC (Method 6): retention time = 2.11 min

Example 210

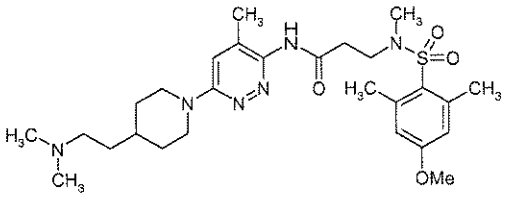


$C_{25}H_{38}N_6O_4S \times C_2HF_3O_2$ (632.70)

[M+H]+ = 519

HPLC (Method 6): retention time = 2.30 min

Example 211

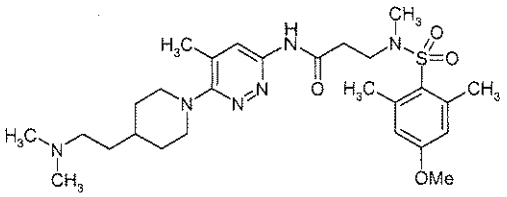


$C_{27}H_{42}N_6O_4S \times C_2HF_3O_2$ (660.75)

[M+H]+ = 547

HPLC (Method 6): retention time = 2.08 min

Example 212

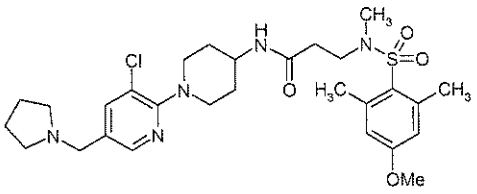


$C_{27}H_{42}N_6O_4S \times C_2HF_3O_2$ (660.75)

[M+H]+ = 547

HPLC (Method 6): retention time = 2.34 min

Example 213

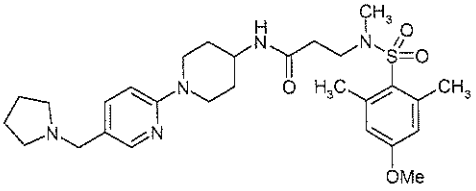


$C_{28}H_{40}ClN_5O_4S \times CH_2O_2$ (624.19)

[M+H]+ = 578/580

HPLC (Method 6): retention time = 2.64 min

Example 214

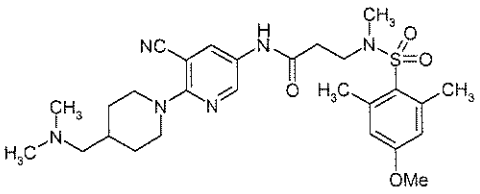


$C_{28}H_{41}N_5O_4S \times CH_2O_2$ (589.75)

[M+H]+ = 544

HPLC (Method 6): retention time = 2.09 min

Example 215

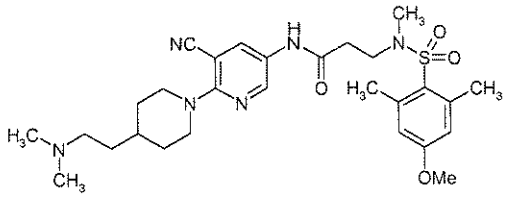


$C_{27}H_{38}N_6O_4S \times CH_2O_2$ (588.72)

[M+H]+ = 543

HPLC (Method 9): retention time = 1.67 min

Example 216

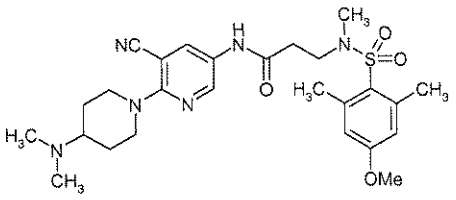


$C_{28}H_{40}N_6O_4S$ (556.72)

[M+H]+ = 557

HPLC (Method 9): retention time = 1.71 min

Example 217

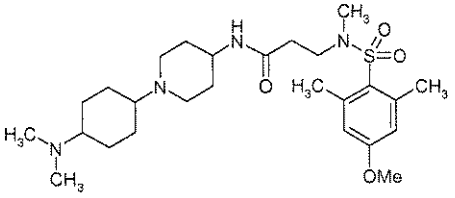


$C_{26}H_{36}N_6O_4S \times CH_2O_2$ (574.69)

[M+H]+ = 529

HPLC (Method 9): retention time = 1.61 min

Example 218

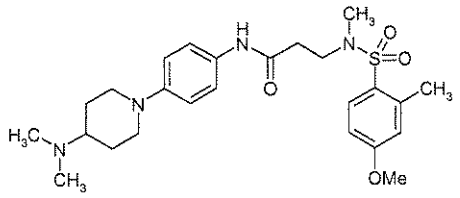


$C_{26}H_{44}N_4O_4S$ (508.72)

[M+H]+ = 509

HPLC (Method 9): retention time = 1.23 min

Example 219

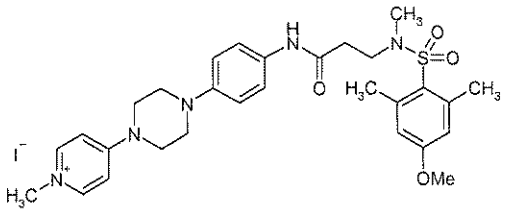


$C_{25}H_{36}N_4O_4S \times C_2HF_3O_2$ (602.67)

[M+H]+ = 489

HPLC (Method 5): retention time = 1.39 min

Example 220

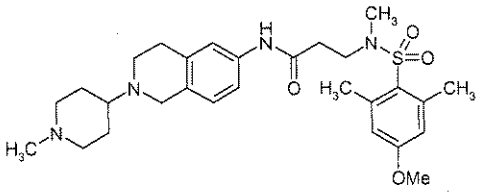


$C_{29}H_{38}N_5O_4S \times I$ (679.61)

[M+H]+ = 552

HPLC (Method 5): retention time = 1.55 min

Example 221

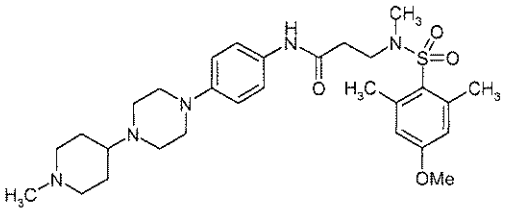


$C_{28}H_{40}N_4O_4S \times 2HCl$ (601.63)

[M+H]+ = 529

HPLC (Method 5): retention time = 1.41 min

Example 222

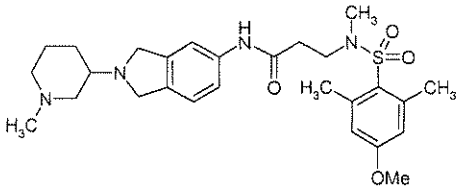


$C_{29}H_{43}N_5O_4S$ (557.75)

[M+H]+ = 558

HPLC (Method 1): retention time = 1.90 min

Example 223

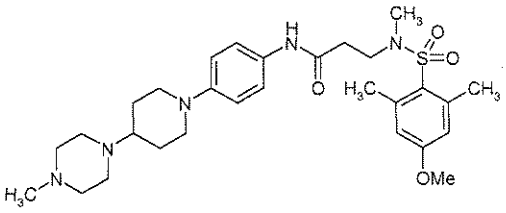


$C_{27}H_{38}N_4O_4S$ (610.68)

[M+H]+ = 515

HPLC (Method 5): retention time = 1.41 min

Example 224

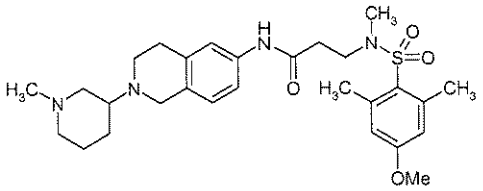


$C_{29}H_{43}N_5O_4S$ (557.75)

[M+H]+ = 558

HPLC (Method 5): retention time = 1.43 min

Example 225

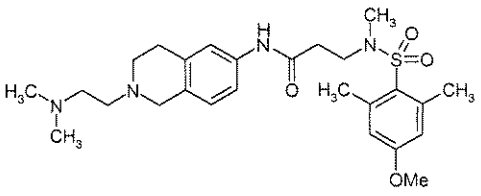


$C_{28}H_{40}N_4O_4S \times 2C_2HF_3O_2$ (756.75)

[M+H]+ = 529

HPLC (Method 5): retention time = 1.42 min

Example 226

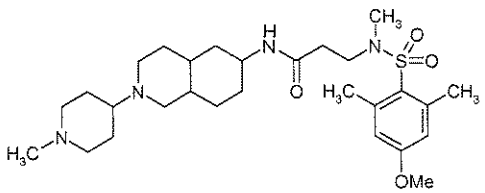


$C_{26}H_{38}N_4O_4S \times 2C_2HF_3O_2$ (730.72)

[M+H]+ = 503

HPLC (Method 5): retention time = 1.40 min

Example 227

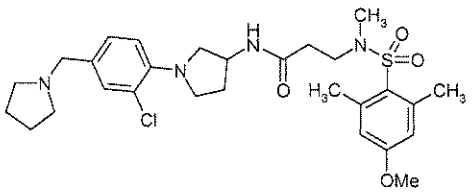


$C_{28}H_{46}N_4O_4S \times 2HCl$ (607.68)

[M+H]+ = 535

HPLC (Method 5): retention time = 1.10 min

Example 228

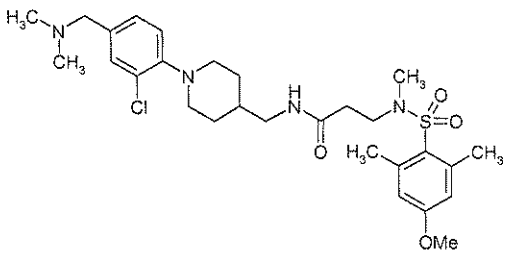


$C_{28}H_{39}ClN_4O_4S$ x HCl (599.61)

[M+H]+ = 563/565

HPLC (Method 5): retention time = 1.59 min

Example 229

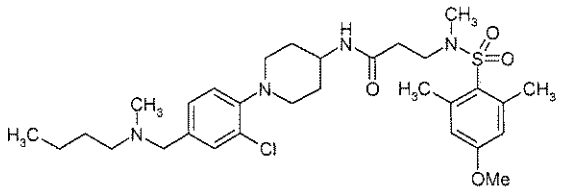


$C_{28}H_{41}ClN_4O_4S$ x HCl (601.63)

[M+H]+ = 565/567

DC: silica gel, dichloromethane / methanol / ammonia 9:1:0.1, Rf value = 0.46

Example 230

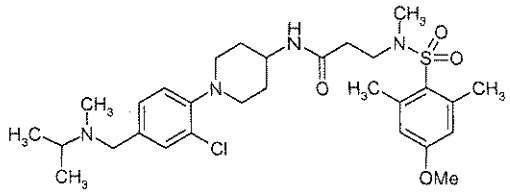


$C_{30}H_{45}ClN_4O_4S$ x HCl (629.68)

[M+H]+ = 593/595

DC: silica gel, dichloromethane / methanol 9:1, Rf value = 0.42

Example 231

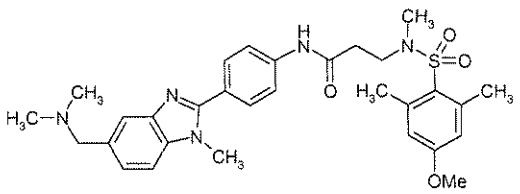


$C_{29}H_{43}ClN_4O_4S$ x HCl (615.66)

[M+H]+ = 579/581

DC: silica gel, dichloromethane / methanol 9:1, Rf value = 0.23

Example 232

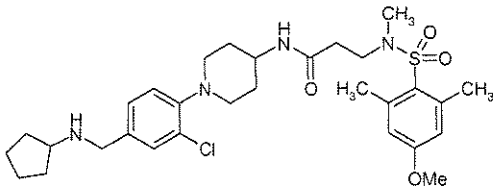


$C_{30}H_{37}N_5O_4S$ x HCl (600.17)

[M+H]+ = 564

DC: silica gel, dichloromethane / methanol / ammonia 8:2:0.1, Rf value = 0.67

Example 233

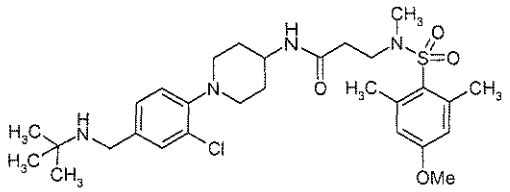


$C_{30}H_{43}ClN_4O_4S$ x HCl (627.67)

[M+H]+ = 591/593

DC: silica gel, dichloromethane / methanol 9:1, Rf value = 0.20

Example 234

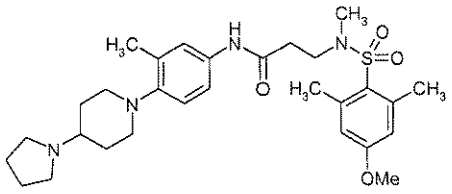


$C_{29}H_{43}ClN_4O_4S$ x HCl (615.66)

[M+H]+ = 579/581

DC: silica gel, dichloromethane / methanol 9:1, Rf value = 0.17

Example 235

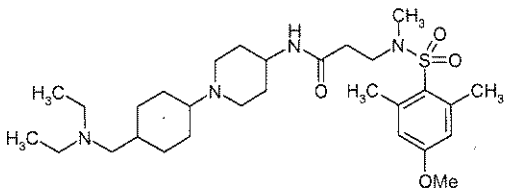


$C_{309}H_{44}N_4O_4S$ (556.76)

[M+H]+ = 557

HPLC (Method 9): retention time = 1.71 min

Example 236

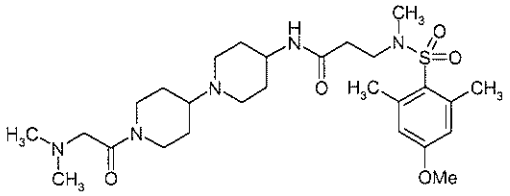


$C_{29}H_{50}N_4O_4S$ x CH_2O_2 (596.82)

[M+H]+ = 551

HPLC (Method 9): retention time = 1.31 min

Example 237

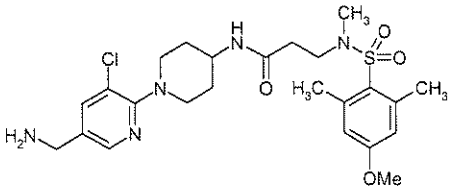


$C_{27}H_{45}N_5O_5S \times C_2HF_3O_2$ (665.77)

[M+H]+ = 552

HPLC (Method 9): retention time = 1.18 min

Example 238

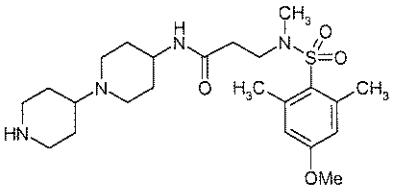


$C_{24}H_{34}ClN_5O_4S$ (524.08)

[M+H]+ = 524/526

HPLC (Method 9): retention time = 1.60 min

Example 239

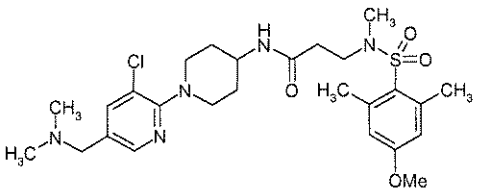


$C_{23}H_{38}N_4O_4S \times 2C_2HF_3O_2$ (694.69)

[M+H]+ = 467

HPLC (Method 9): retention time = 1.16 min

Example 240

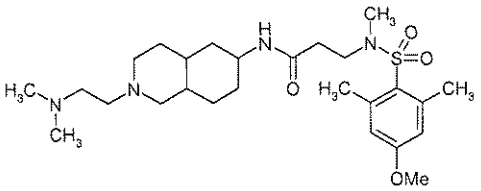


$C_{26}H_{38}ClN_5O_4S \times C_2HF_3O_2$ (666.15)

[M+H]+ = 552/554

HPLC (Method 9): retention time = 1.68 min

Example 241

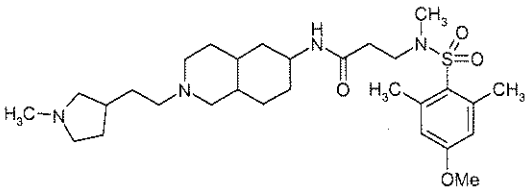


$C_{26}H_{44}N_4O_4S \times 2HCl$ (581.64)

[M+H]+ = 509

HPLC (Method 5): retention time = 1.36 min

Example 242

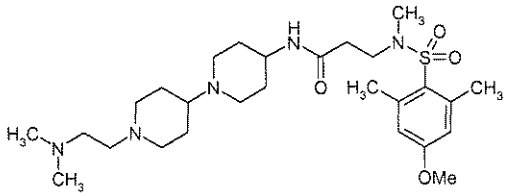


$C_{29}H_{48}N_4O_4S \times 2HCl$ (621.70)

[M+H]+ = 549

HPLC (Method 5): retention time = 1.38 min

Example 243

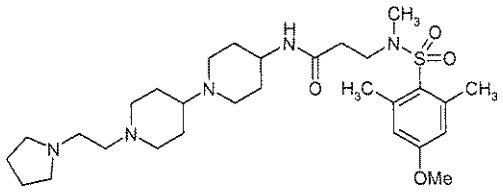


$C_{27}H_{47}N_5O_4S \times 3C_2HF_3O_2$ (879.83)

[M+H]+ = 538

HPLC (Method 5): retention time = 1.33 min

Example 244

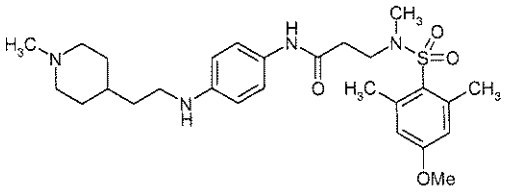


$C_{29}H_{49}N_5O_4S \times 3C_2HF_3O_2$ (905.87)

[M+H]+ = 564

HPLC (Method 5): retention time = 1.08 min

Example 245

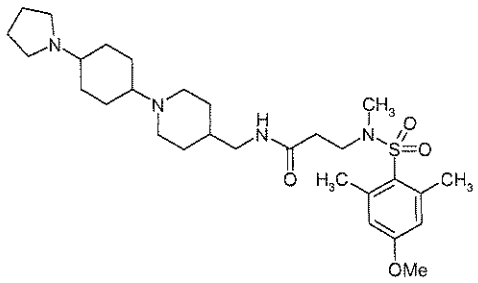


$C_{27}H_{40}N_4O_4S \times C_2HF_3O_4$ (630.72)

[M+H]+ = 517

HPLC (Method 9): retention time = 1.40 min

Example 246

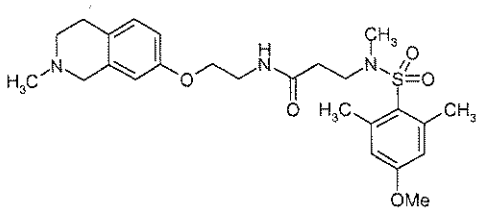


$C_{29}H_{48}N_4O_4S$ (548.78)

[M+H]+ = 549

HPLC (Method 6): retention time = 1.24 min

Example 247

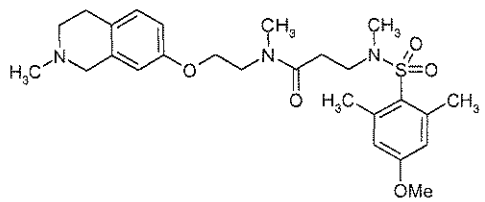


$C_{25}H_{35}N_3O_5S$ x HCl (526.09)

[M+H]+ = 490

HPLC (Method 10): retention time = 1.16 min

Example 248

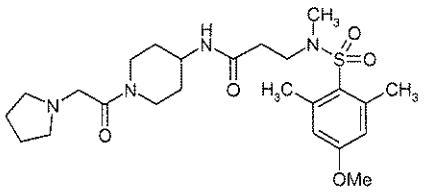


$C_{26}H_{37}N_3O_5S$ x HCl (540.12)

[M+H]+ = 504

HPLC (Method 10): retention time = 1.22 min

Example 249

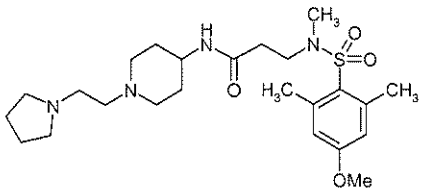


$C_{24}H_{38}N_4O_5S \times C_2HF_3O_2$ (608.67)

[M+H]+ = 495

HPLC (Method 9): retention time = 1.47 min

Example 250

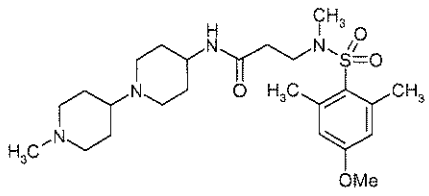


$C_{24}H_{40}N_4O_4S$ (480.66)

[M+H]+ = 481

HPLC (Method 9): retention time = 1.21 min

Example 251

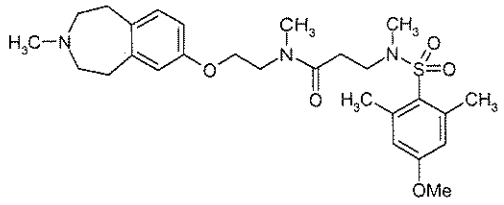


$C_{24}H_{40}N_4O_4S \times C_2HF_3O_2$ (594.69)

[M+H]+ = 481

HPLC (Method 9): retention time = 1.19 min

Example 252

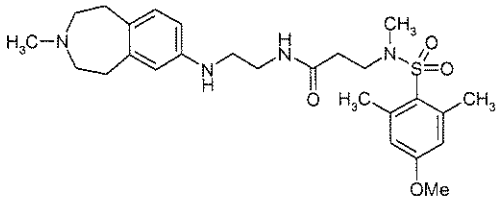


$C_{27}H_{39}N_3O_5S$ x HCl (554.14)

[M+H]+ = 518

HPLC (Method 5): retention time = 1.36 min

Example 462

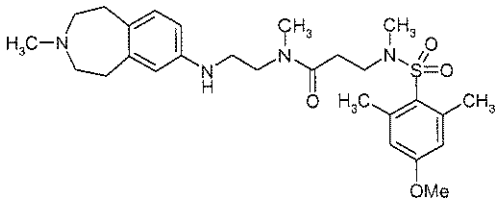


$C_{26}H_{38}N_4O_4S$ x HCl (539.13)

[M+H]+ = 503

HPLC (Method 5): retention time = 1.29 min

Example 463

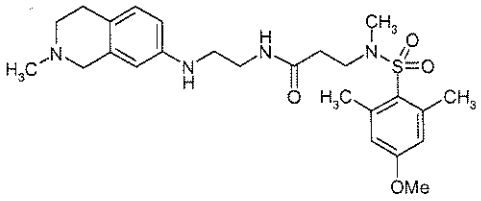


$C_{27}H_{40}N_4O_4S$ x HCl (553.16)

[M+H]+ = 517

HPLC (Method 5): retention time = 1.35 min

Example 464

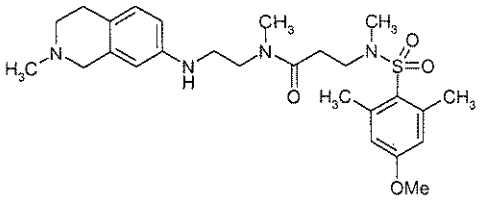


$C_{25}H_{36}N_4O_4S$ x HCl (525.10)

[M+H]+ = 489

HPLC (Method 5): retention time = 1.31 min

Example 465

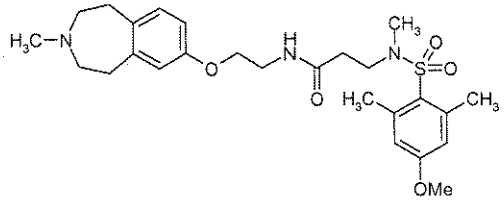


$C_{26}H_{38}N_4O_4S$ x HCl (539.13)

[M+H]+ = 503

HPLC (Method 5): retention time = 1.35 min

Example 466

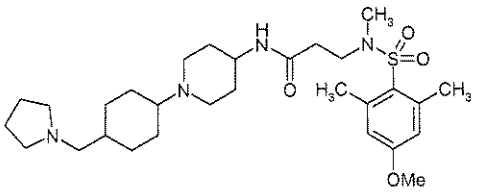


$C_{26}H_{37}N_3O_5S$ x HCl (540.12)

[M+H]+ = 504

HPLC (Method 10): retention time = 1.18 min

Example 467

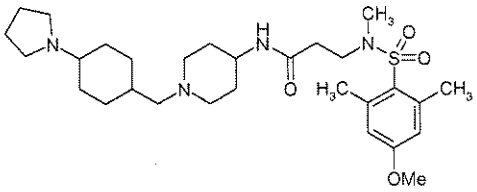


$C_{29}H_{48}N_4O_4S \times C_2HF_3O_2$ (662.81)

[M+H]+ = 549

HPLC (Method 9): retention time = 1.27 min

Example 471



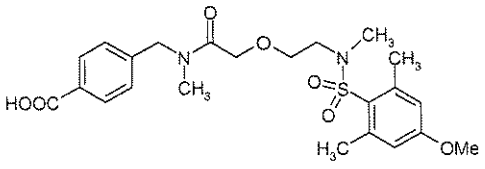
$C_{29}H_{48}N_4O_4S \times C_2HF_3O_2$ (662.81)

[M+H]+ = 549

HPLC (Method 9): retention time = 1.30 min

The following compounds were prepared analogously to Example 53:

Example 253

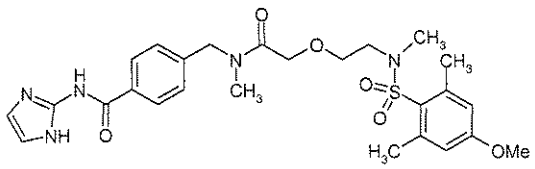


$C_{23}H_{30}N_2O_7S$ (478.56)

[M+H]+ = 479

HPLC (Method 6): retention time = 3.21 min

Example 254

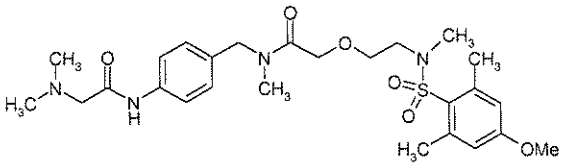


$C_{26}H_{33}N_5O_6S$ (543.64)

[M+H]+ = 544

HPLC (Method 6): retention time = 2.51 min

Example 255

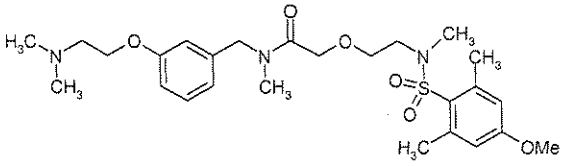


$C_{26}H_{38}N_4O_6S$ (534.67)

[M+H]+ = 535

HPLC (Method 6): retention time = 2.48 min

Example 256

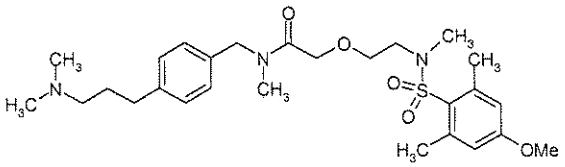


$C_{26}H_{398}N_3O_6S$ (521.67)

[M+H]+ = 522

HPLC (Method 6): retention time = 2.60 min

Example 257

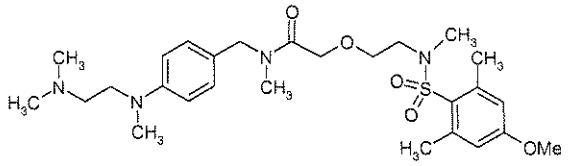


$C_{27}H_{41}N_3O_5S$ (519.70)

[M+H]+ = 520

HPLC (Method 6): retention time = 2.61 min

Example 258

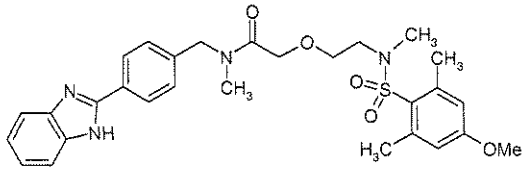


$C_{27}H_{42}N_4O_5S$ x HCl (571.17)

[M+H]+ = 535

HPLC (Method 5): retention time = 1.57 min

Example 259

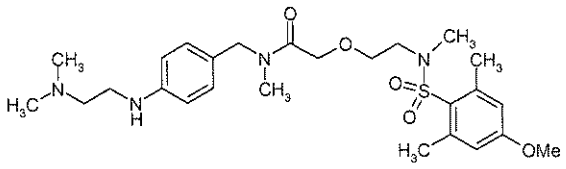


$C_{29}H_{34}N_4O_5S$ x $C_2HF_3O_2$ (664.69)

[M+H]+ = 551

HPLC (Method 5): retention time = 1.60 min

Example 260

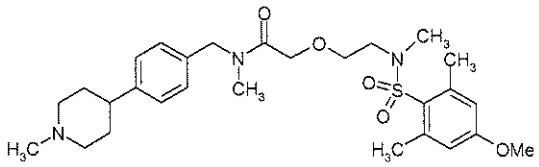


$C_{26}H_{40}N_4O_5S$ x HCl (557.15)

[M+H]+ = 521

HPLC (Method 5): retention time = 1.53 min

Example 261

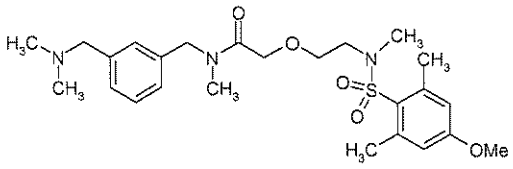


$C_{28}H_{41}N_3O_5S$ x $C_2HF_3O_2$ (645.73)

[M+H]+ = 532

HPLC (Method 5): retention time = 1.54 min

Example 262

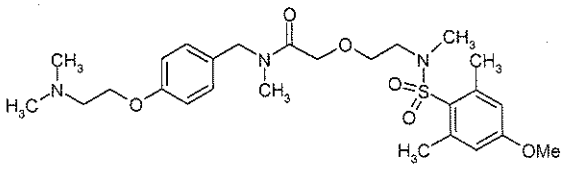


$C_{25}H_{37}N_3O_5S$ x HCl (528.11)

[M+H]+ = 492

HPLC (Method 5): retention time = 1.53 min

Example 263

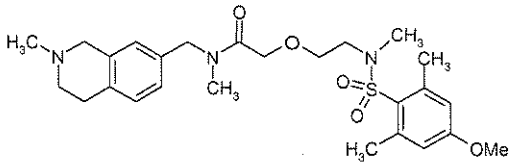


$C_{26}H_{39}N_3O_6S \times C_2HF_3O_2$ (635.69)

[M+H]+ = 522

HPLC (Method 5): retention time = 1.53 min

Example 264

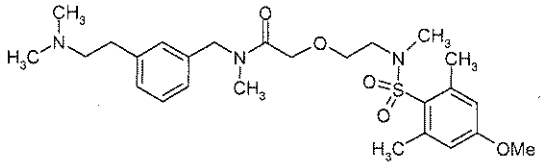


$C_{26}H_{37}N_3O_5S \times HCl$ (540.12)

[M+H]+ = 504

HPLC (Method 7): retention time = 1.93 min

Example 265

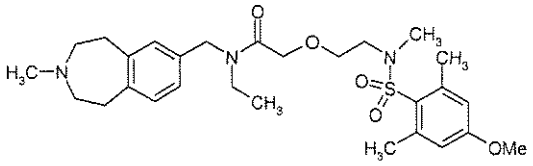


$C_{26}H_{39}N_3O_5S \times HCl$ (542.13)

[M+H]+ = 506

HPLC (Method 5): retention time = 1.54 min

Example 266

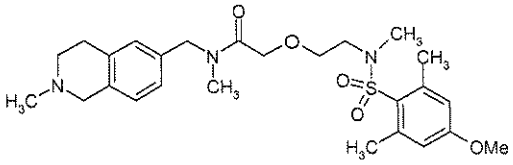


$C_{28}H_{41}N_3O_5S$ x HCl (568.17)

[M+H]+ = 532

DC: silica gel, dichloromethane / methanol / ammonia 9:1:0.1, Rf value = 0.30

Example 267

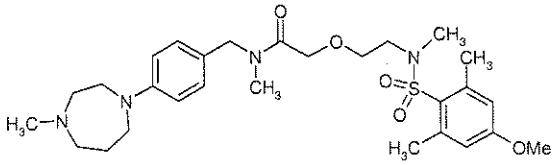


$C_{26}H_{37}N_3O_5S$ x HCl (540.12)

[M+H]+ = 504

HPLC (Method 5): retention time = 1.51 min

Example 268

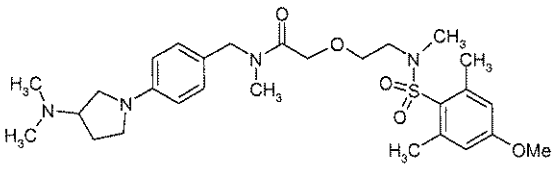


$C_{28}H_{42}N_4O_5S$ x HCl (583.18)

[M+H]+ = 547

HPLC (Method 5): retention time = 1.54 min

Example 269

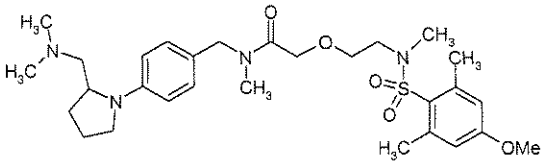


$C_{28}H_{42}N_4O_5S$ x HCl (583.18)

[M+H]+ = 547

HPLC (Method 10): retention time = 1.24 min

Example 270

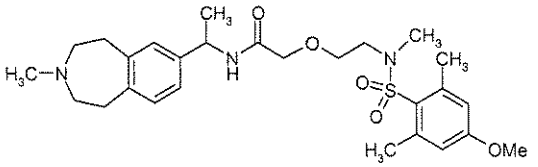


$C_{29}H_{44}N_4O_5S$ x HCl (597.21)

[M+H]+ = 561

HPLC (Method 5): retention time = 1.55 min

Example 271

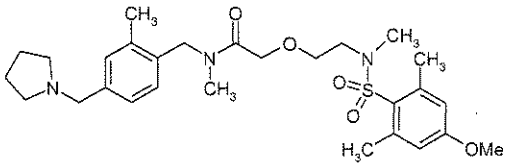


$C_{27}H_{39}N_3O_5S$ x HCl (554.14)

[M+H]+ = 518

HPLC (Method 4): retention time = 3.4 min

Example 272

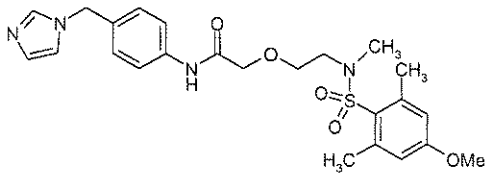


$C_{28}H_{41}N_3O_5S$ x HCl (568.17)

[M+H]+ = 532

DC: silica gel, dichloromethane / methanol 9:1, Rf value = 0.14

Example 273

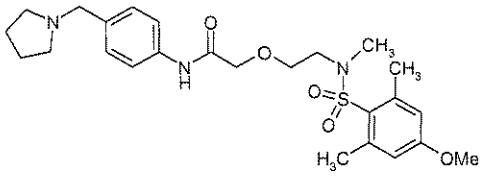


$C_{24}H_{30}N_4O_5S$ x $C_2HF_3O_2$ (600.61)

[M+H]+ = 487

HPLC (Method 6): retention time = 2.58 min

Example 274

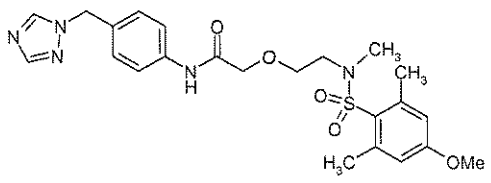


$C_{25}H_{35}N_3O_5S$ x $C_2HF_3O_2$ (603.65)

[M+H]+ = 490

HPLC (Method 6): retention time = 2.61 min

Example 275

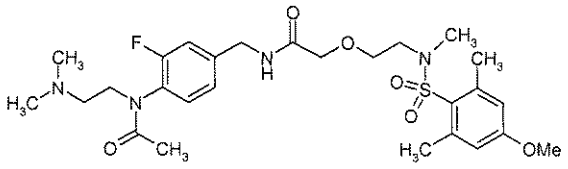


$C_{23}H_{29}N_5O_5S \times C_2HF_3O_2$ (601.60)

[M+H]+ = 488

HPLC (Method 6): retention time = 3.28 min

Example 276

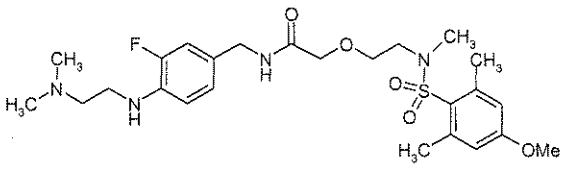


$C_{27}H_{39}FN_4O_6S$ (566.69)

[M+H]+ = 567

HPLC (Method 6): retention time = 2.59 min

Example 277

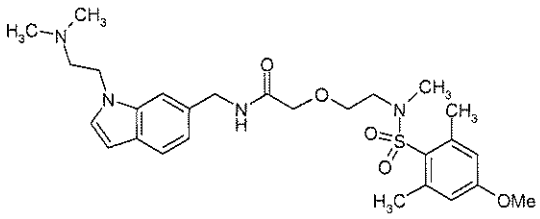


$C_{25}H_{37}FN_4O_5S$ (524.65)

[M+H]+ = 525

HPLC (Method 6): retention time = 2.59 min

Example 278

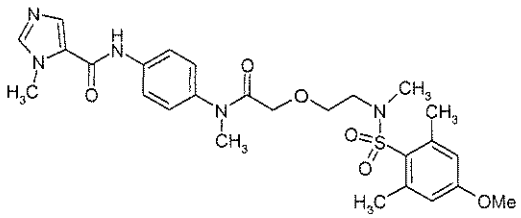


$C_{27}H_{38}N_4O_5S$ (530.68)

[M+H]+ = 531

HPLC (Method 6): retention time = 2.65 min

Example 279

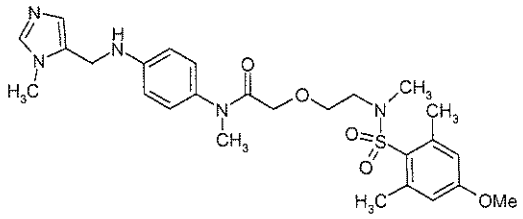


$C_{26}H_{33}N_5O_6S$ (543.64)

[M+H]+ = 544

HPLC (Method 6): retention time = 2.39 min

Example 280

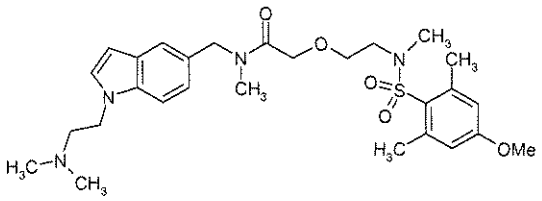


$C_{26}H_{35}N_5O_5S$ (529.65)

[M+H]+ = 530

HPLC (Method 6): retention time = 2.43 min

Example 281

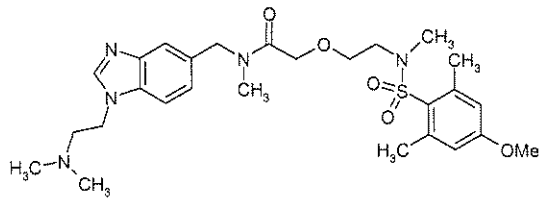


$C_{28}H_{40}N_4O_5S$ (544.71)

[M+H]+ = 545

HPLC (Method 6): retention time = 2.65 min

Example 282

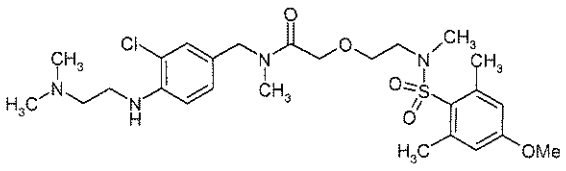


$C_{27}H_{39}N_5O_5S$ (545.70)

[M+H]+ = 546

HPLC (Method 6): retention time = 2.19 min

Example 283

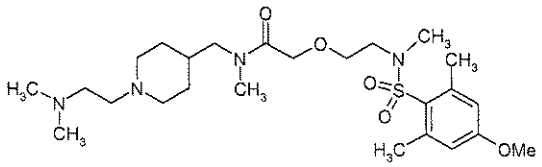


$C_{26}H_{39}ClN_4O_5S$ (555.13)

[M+H]+ = 555/557

HPLC (Method 6): retention time = 2.63 min

Example 284

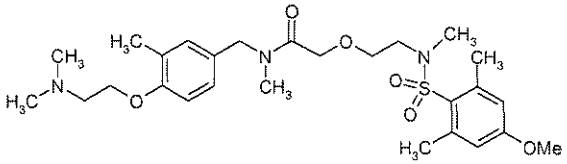


$C_{25}H_{44}N_4O_5S$ (512.71)

[M+H]+ = 513

HPLC (Method 6): retention time = 1.94 min

Example 285

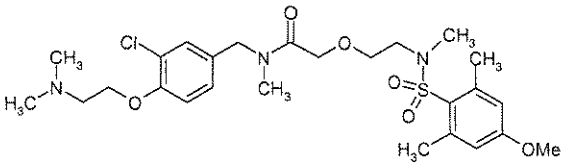


$C_{27}H_{41}N_3O_6S$ (535.70)

[M+H]+ = 536

HPLC (Method 6): retention time = 2.56 min

Example 286

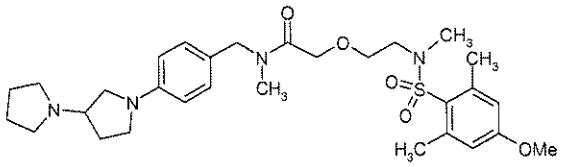


$C_{26}H_{38}ClN_3O_6S \times CH_2O_2$ (602.14)

[M+H]+ = 556/558

HPLC (Method 6): retention time = 2.65 min

Example 287

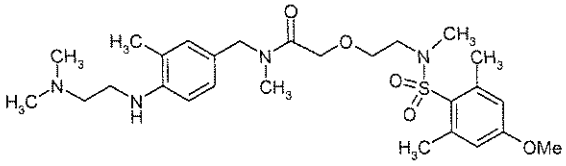


$C_{30}H_{44}N_4O_5S$ (572.76)

[M+H]+ = 573

HPLC (Method 6): retention time = 2.69 min

Example 288

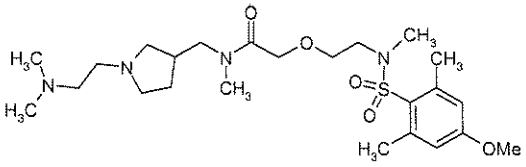


$C_{27}H_{42}N_4O_5S$ (534.71)

[M+H]+ = 535

HPLC (Method 6): retention time = 2.54 min

Example 289

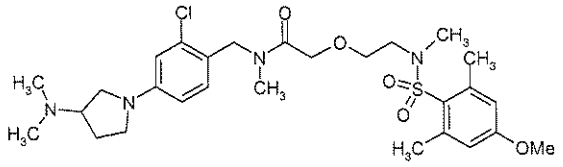


$C_{24}H_{42}N_4O_5S$ (498.68)

[M+H]+ = 499

HPLC (Method 6): retention time = 1.95 min

Example 290

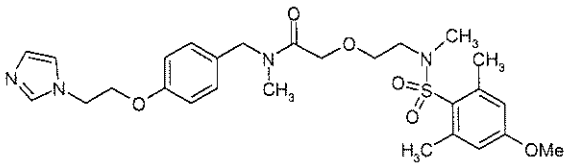


$C_{28}H_{41}ClN_4O_5S$ (581.17)

[M+H]+ = 581/583

HPLC (Method 6): retention time = 2.77 min

Example 291

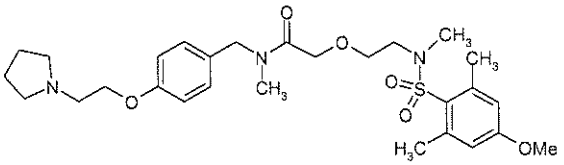


$C_{27}H_{36}N_4O_6S$ (544.66)

[M+H]+ = 545

HPLC (Method 6): retention time = 2.59 min

Example 292

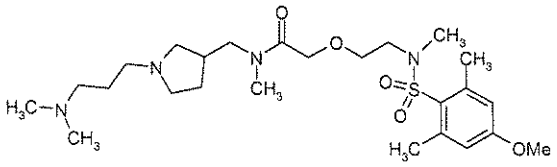


$C_{28}H_{41}N_3O_6S$ (547.71)

[M+H]+ = 548

HPLC (Method 6): retention time = 2.59 min

Example 293

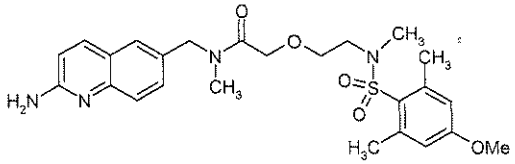


$C_{25}H_{44}N_4O_5S$ (512.71)

[M+H]+ = 513

HPLC (Method 6): retention time = 1.94 min

Example 294

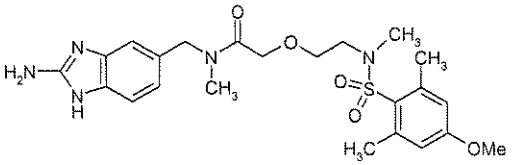


$C_{25}H_{32}N_4O_5S$ (500.61)

[M+H]+ = 501

HPLC (Method 6): retention time = 2.41 min

Example 295

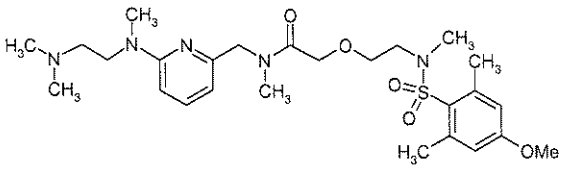


$C_{23}H_{31}N_5O_5S$ (489.59)

[M+H]+ = 490

HPLC (Method 6): retention time = 2.46 min

Example 296

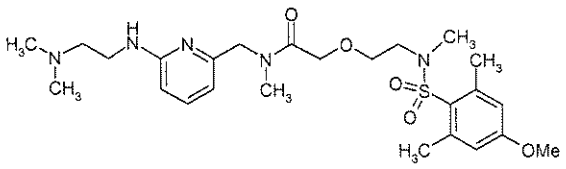


$C_{26}H_{41}N_5O_5S \times CH_2O_2$ (581.73)

[M+H]+ = 536

HPLC (Method 6): retention time = 2.58 min

Example 297

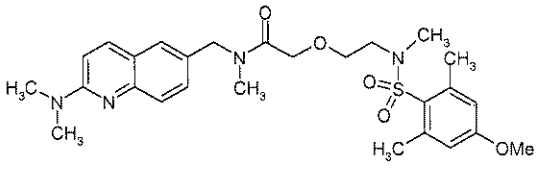


$C_{25}H_{39}N_5O_5S \times CH_2O_2$ (567.70)

[M+H]+ = 522

HPLC (Method 6): retention time = 2.31 min

Example 298

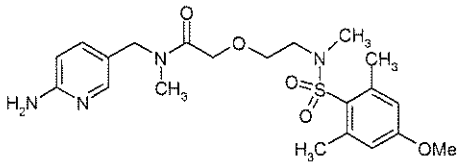


$C_{27}H_{36}N_4O_5S \times C_2HF_3O_2$ (642.69)

[M+H]+ = 529

HPLC (Method 6): retention time = 2.56 min

Example 299

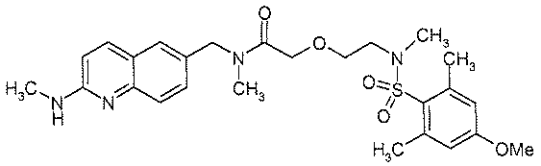


$C_{21}H_{30}N_4O_5S$ (450.55)

[M+H]+ = 451

HPLC (Method 6): retention time = 2.31 min

Example 300

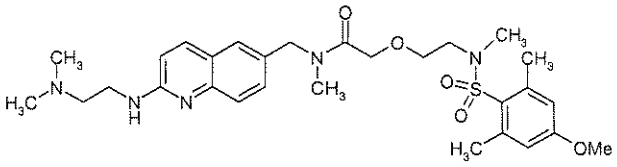


$C_{26}H_{34}N_4O_5S$ (514.64)

[M+H]+ = 515

HPLC (Method 6): retention time = 2.51 min

Example 301

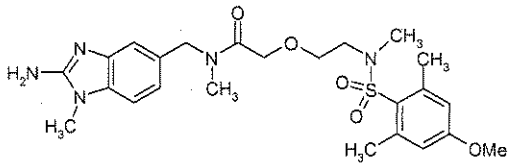


$C_{29}H_{41}N_5O_5S \times C_2HF_3O_2$ (685.76)

[M+H]+ = 572

HPLC (Method 6): retention time = 2.14 min

Example 302

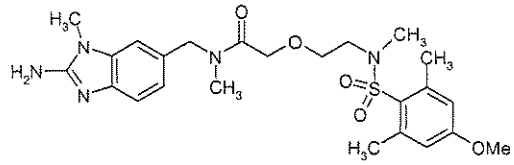


$C_{24}H_{33}N_5O_5S \times C_2HF_3O_2$ (617.64)

[M+H]+ = 504

HPLC (Method 9): retention time = 1.61 min

Example 303

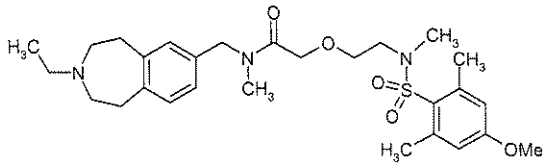


$C_{24}H_{33}N_5O_5S \times C_2HF_3O_2$ (617.64)

[M+H]+ = 504

HPLC (Method 9): retention time = 1.59 min

Example 304

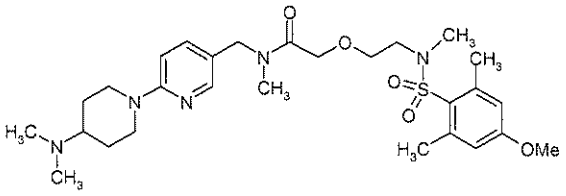


$C_{28}H_{41}N_3O_5S \times C_2HF_3O_2$ (645.73)

[M+H]+ = 532

HPLC (Method 5): retention time = 1.56 min

Example 305

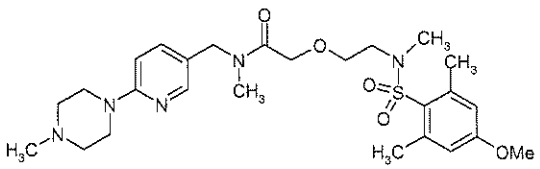


$C_{28}H_{43}N_5O_5S \times C_2HF_3O_2$ (675.76)

[M+H]+ = 562

HPLC (Method 5): retention time = 1.41 min

Example 306

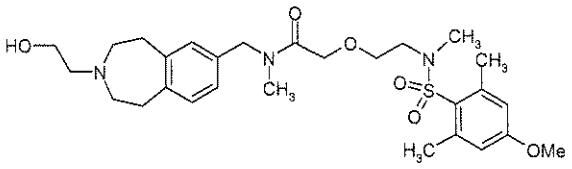


$C_{26}H_{39}N_5O_5S \times C_2HF_3O_2$ (647.71)

[M+H]+ = 534

HPLC (Method 5): retention time = 1.42 min

Example 307

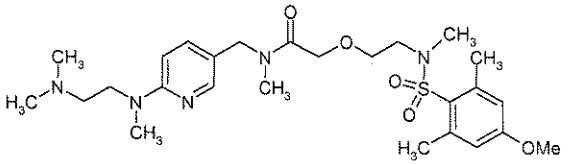


$C_{28}H_{41}N_3O_6S$ (547.71)

[M+H]+ = 548

HPLC (Method 5): retention time = 1.53 min

Example 308

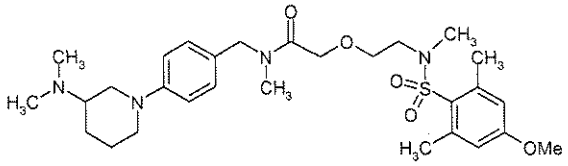


$C_{26}H_{41}N_5O_5S$ (535.70)

[M+H]+ = 536

HPLC (Method 5): retention time = 1.42 min

Example 309

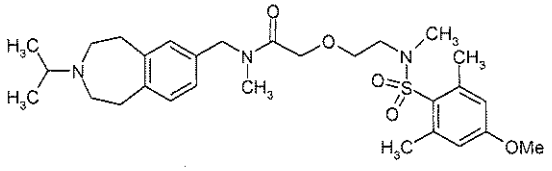


$C_{29}H_{44}N_4O_5S$ x HCl (597.21)

[M+H]+ = 561

HPLC (Method 7): retention time = 1.91 min

Example 310

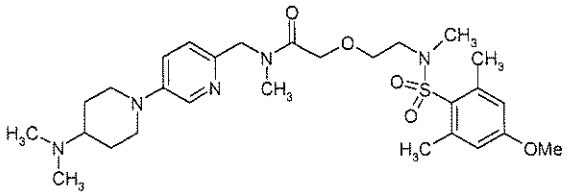


$C_{29}H_{43}N_3O_5S$ x $C_2HF_3O_2$ (659.76)

[M+H]+ = 546

HPLC (Method 5): retention time = 1.59 min

Example 311

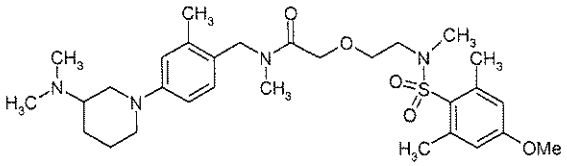


$C_{28}H_{43}N_5O_5S \times 2C_2HF_3O_2$ (789.78)

[M+H]+ = 562

HPLC (Method 5): retention time = 1.40 min

Example 312

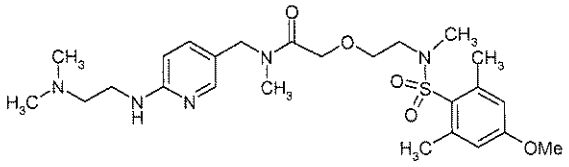


$C_{30}H_{46}N_4O_5S \times C_2HF_3O_2$ (688.80)

[M+H]+ = 575

HPLC (Method 5): retention time = 1.56 min

Example 313

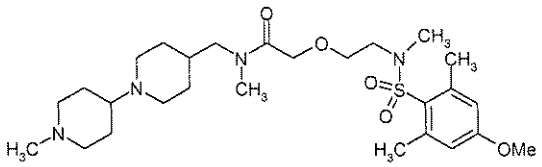


$C_{25}H_{39}N_5O_5S \times 2HCl$ (594.60)

[M+H]+ = 522

HPLC (Method 5): retention time = 1.40 min

Example 314

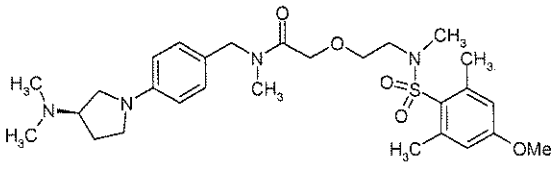


$C_{27}H_{46}N_4O_5S$ x HCl (575.20)

[M+H]+ = 539

DC: silica gel, dichloromethane / methanol / ammonia 8:2:0.01, Rf value = 0.35

Example 315

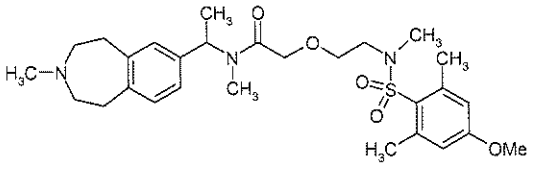


$C_{28}H_{42}N_4O_5S$ x HCl (583.18)

[M+H]+ = 547

DC: silica gel, dichloromethane / methanol / ammonia 9:1:0.1, Rf value = 0.32

Example 316

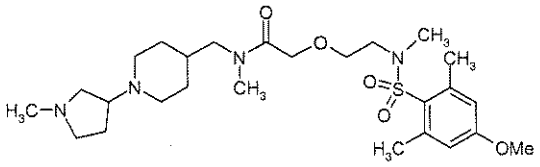


$C_{28}H_{41}N_3O_5S$ x HCl (568.17)

[M+H]+ = 532

DC: silica gel, dichloromethane / methanol / ammonia 9:1:0.1, Rf value = 0.35

Example 317

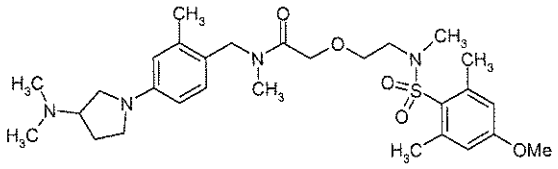


$C_{26}H_{44}N_4O_5S$ x HCl (561.18)

[M+H]+ = 525

DC: silica gel, dichloromethane / methanol / ammonia 8:2:0.01, Rf value = 0.12

Example 318

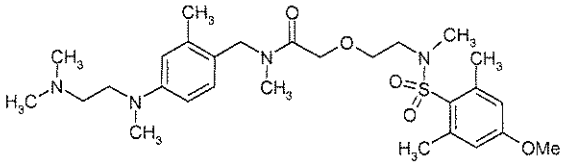


$C_{29}H_{44}N_4O_5S$ x HCl (597.21)

[M+H]+ = 561

DC: silica gel, dichloromethane / methanol 9:1, Rf value = 0.30

Example 319

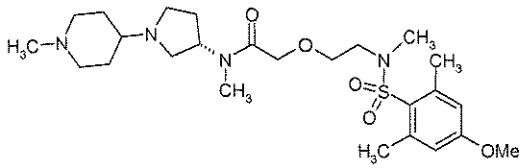


$C_{28}H_{44}N_4O_5S$ x HCl (585.20)

[M+H]+ = 549

DC: silica gel, dichloromethane / methanol 9:1, Rf value = 0.15

Example 320

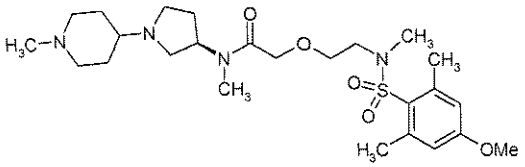


$C_{25}H_{42}N_4O_5S$ x 2HCl (583.61)

[M+H]+ = 511

DC: silica gel, dichloromethane / ethanol / ammonia 9:1:0.1, Rf value = 0.22

Example 321

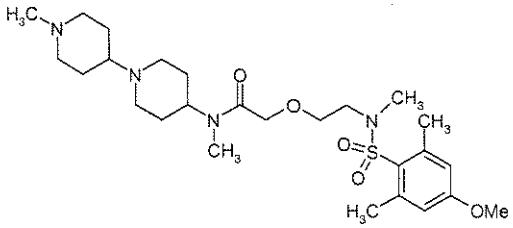


$C_{25}H_{42}N_4O_5S$ x 2HCl (583.61)

[M+H]+ = 511

HPLC (Method 5): retention time = 1.37 min

Example 322

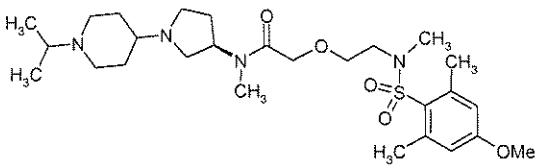


$C_{26}H_{44}N_4O_5S$ x 2HCl (597.64)

[M+H]+ = 525

DC: silica gel, dichloromethane / methanol / ammonia 8:2:0.2, Rf value = 0.52

Example 323

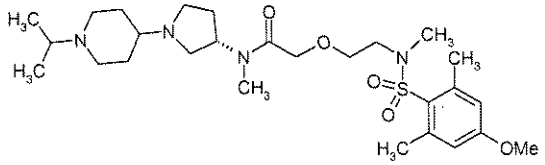


$C_{27}H_{46}N_4O_5S$ x 2HCl (611.67)

[M+H]+ = 539

HPLC (Method 12): retention time = 2.45 min

Example 324

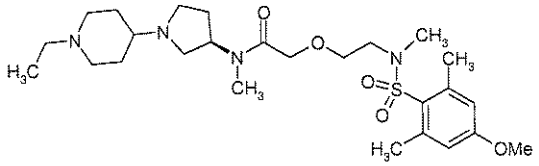


$C_{27}H_{46}N_4O_5S$ x 2HCl (611.67)

[M+H]+ = 539

HPLC (Method 12): retention time = 2.35 min

Example 325

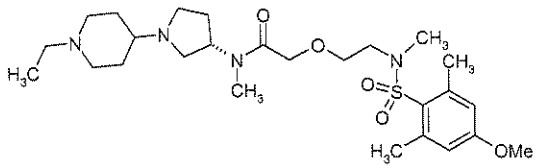


$C_{26}H_{44}N_4O_5S$ x 2HCl (597.64)

[M+H]+ = 525

HPLC (Method 12): retention time = 2.3 min

Example 326

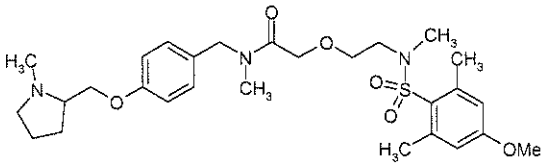


$C_{26}H_{44}N_4O_5S$ x 2HCl (597.64)

[M+H]+ = 525

HPLC (Method 12): retention time = 2.3 min

Example 327

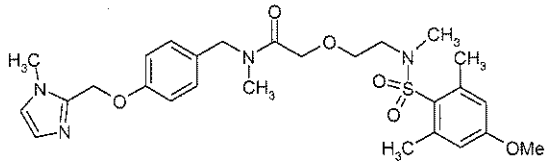


$C_{28}H_{41}N_3O_6S$ (547.71)

[M+H]+ = 548

HPLC (Method 9): retention time = 1.7 min

Example 328

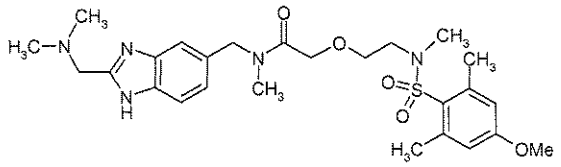


$C_{27}H_{36}N_4O_6S$ (544.66)

[M+H]+ = 545

HPLC (Method 9): retention time = 1.69 min

Example 329

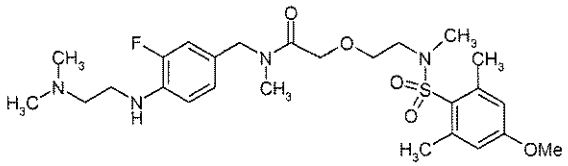


$C_{26}H_{37}N_5O_5S$ (531.67)

[M+H]+ = 532

HPLC (Method 6): retention time = 1.56 min

Example 330

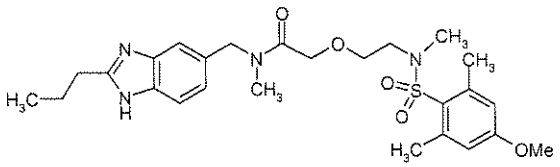


$C_{26}H_{39}FN_4O_5S$ (538.68)

[M+H]+ = 539

HPLC (Method 6): retention time = 2.60 min

Example 331

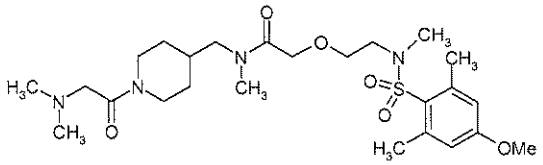


$C_{26}H_{36}N_4O_5S$ (516.65)

[M+H]+ = 517

HPLC (Method 9): retention time = 1.65 min

Example 332

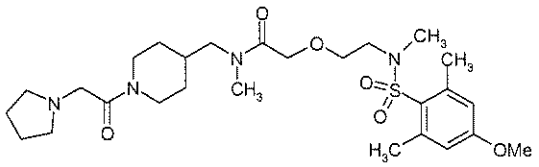


$C_{25}H_{42}N_4O_6S \times C_2HF_3O_2$ (640.71)

[M+H]+ = 527

HPLC (Method 9): retention time = 1.55 min

Example 333

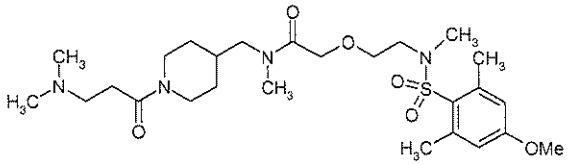


$C_{27}H_{44}N_4O_6S \times C_2HF_3O_2$ (666.75)

[M+H]+ = 553

HPLC (Method 9): retention time = 1.57 min

Example 334

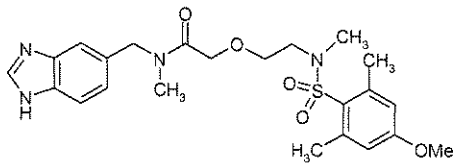


$C_{26}H_{44}N_4O_6S \times C_2HF_3O_2$ (654.74)

[M+H]+ = 541

HPLC (Method 9): retention time = 1.57 min

Example 335

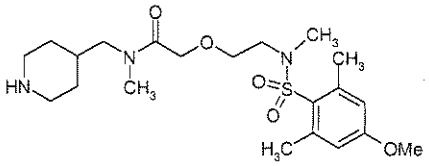


$C_{23}H_{30}N_4O_5S$ (474.57)

[M+H]+ = 475

HPLC (Method 9): retention time = 1.53 min

Example 336

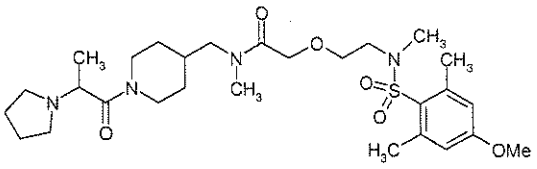


$C_{21}H_{35}N_3O_5S$ (441.59)

[M+H]+ = 442

HPLC (Method 9): retention time = 1.48 min

Example 337

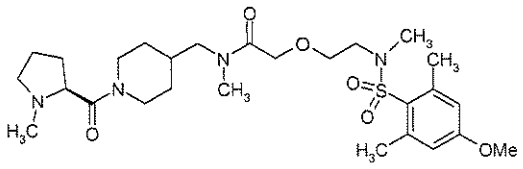


$C_{28}H_{46}N_4O_6S \times C_2HF_3O_2$ (680.78)

[M+H]+ = 567

HPLC (Method 9): retention time = 1.60 min

Example 338

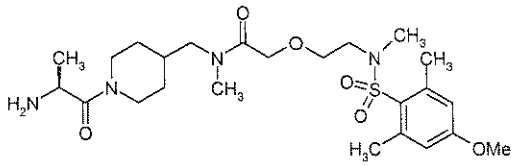


$C_{27}H_{44}N_4O_6S$ x $C_2HF_3O_2$ (666.75)

[M+H]+ = 553

HPLC (Method 9): retention time = 1.57 min

Example 339

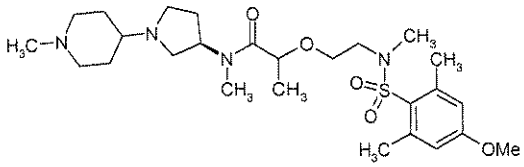


$C_{24}H_{40}N_4O_6S$ x $C_2HF_3O_2$ (626.69)

[M+H]+ = 513

HPLC (Method 9): retention time = 1.53 min

Example 340

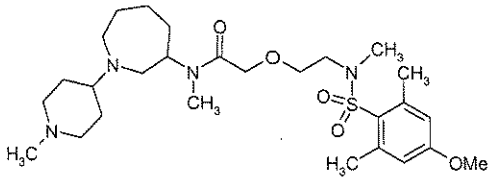


$C_{26}H_{44}N_4O_5S$ x 2HCl (597.64)

[M+H]+ = 525

HPLC (Method 12): retention time = 2.3 min

Example 341

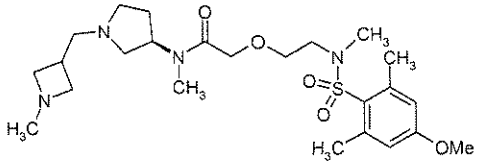


$C_{27}H_{46}N_4O_5S$ x 2HCl (611.67)

[M+H]+ = 539

DC: silica gel, dichloromethane / methanol / ammonia 8:2:0.2, Rf value = 0.65

Example 342

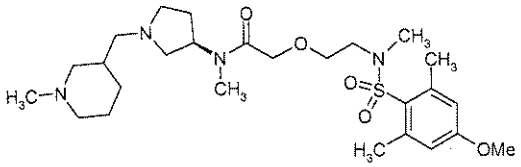


$C_{24}H_{40}N_4O_5S$ x CH_2O_2 (542.69)

[M+H]+ = 497

HPLC (Method 9): retention time = 1.25 min

Example 343

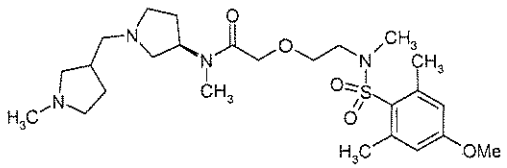


$C_{26}H_{44}N_4O_5S$ x CH_2O_2 (570.74)

[M+H]+ = 525

HPLC (Method 9): retention time = 1.31 min

Example 344

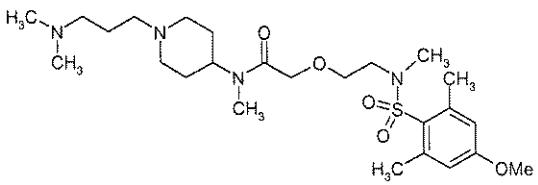


$C_{25}H_{42}N_4O_5S \times CH_2O_2$ (556.72)

[M+H]+ = 511

HPLC (Method 9): retention time = 1.31 min

Example 345

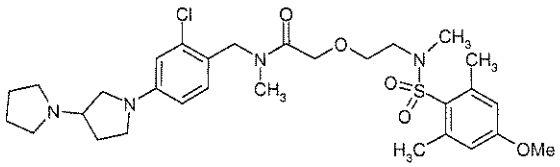


$C_{25}H_{44}N_4O_5S \times C_2HF_3O_2$ (626.73)

[M+H]+ = 513

HPLC (Method 9): retention time = 1.29 min

Example 346

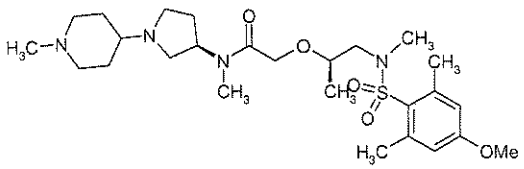


$C_{30}H_{43}ClN_4O_5S$ (607.21)

[M+H]+ = 608

HPLC (Method 6): retention time = 1.80 min

Example 347

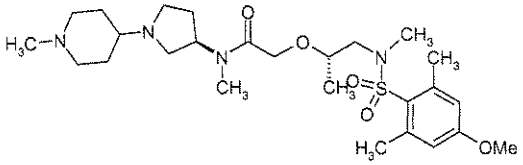


$C_{26}H_{44}N_4O_5S$ x 2HCl (597.64)

[M+H]+ = 525

HPLC (Method 12): retention time = 2.4 min

Example 348

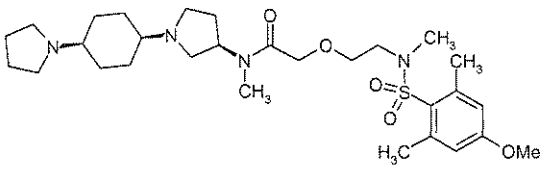


$C_{26}H_{44}N_4O_5S$ x 2HCl (597.64)

[M+H]+ = 525

HPLC (Method 12): retention time = 2.4 min

Example 349

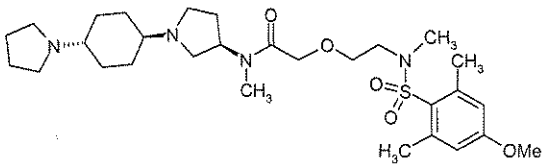


$C_{29}H_{48}N_4O_5S$ x 2HCl (637.70)

[M+H]+ = 565

HPLC (Method 12): retention time = 2.3 min

Example 350

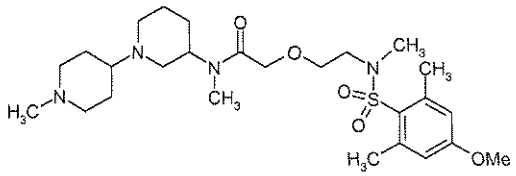


$C_{29}H_{48}N_4O_5S$ x 2HCl (637.70)

[M+H]+ = 565

HPLC (Method 12): retention time = 2.92 min

Example 351

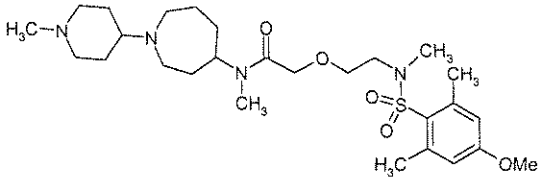


$C_{26}H_{44}N_4O_5S$ x 2HCl (597.64)

[M+H]+ = 525

DC: silica gel, dichloromethane / methanol / ammonia 8:2:0.2, Rf value = 0.60

Example 352

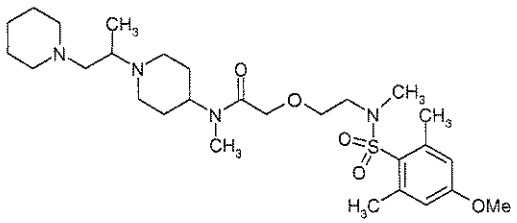


$C_{27}H_{46}N_4O_5S$ x 2HCl (611.67)

[M+H]+ = 539

DC: silica gel, dichloromethane / methanol / ammonia 8:2:0.2, Rf value = 0.62

Example 353

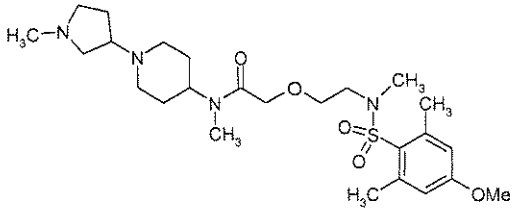


$C_{28}H_{48}N_4O_5S$ x 2HCl (625.69)

[M+H]+ = 553

HPLC (Method 12): retention time = 2.45 min

Example 354

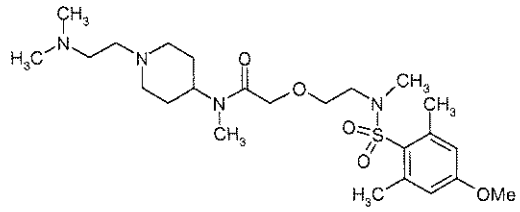


$C_{25}H_{42}N_4O_5S$ x 2HCl (583.61)

[M+H]+ = 511

HPLC (Method 12): retention time = 2.33 min

Example 355

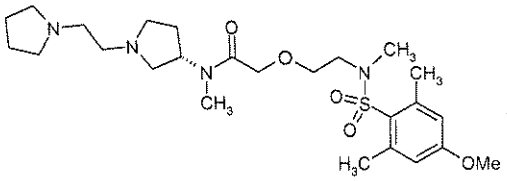


$C_{24}H_{42}N_4O_5S$ x $C_2HF_3O_2$ (612.70)

[M+H]+ = 499

HPLC (Method 9): retention time = 1.32 min

Example 356

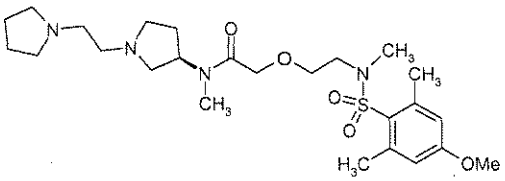


$C_{25}H_{42}N_4O_5S \times 2C_2HF_3O_2$ (738.74)

[M+H]+ = 511

HPLC (Method 9): retention time = 1.24 min

Example 357

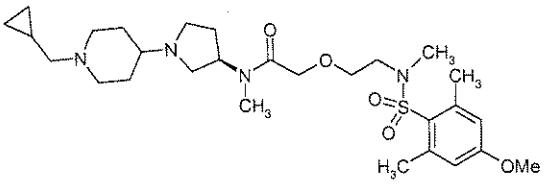


$C_{25}H_{42}N_4O_5S \times 2C_2HF_3O_2$ (738.74)

[M+H]+ = 511

HPLC (Method 9): retention time = 1.27 min

Example 358

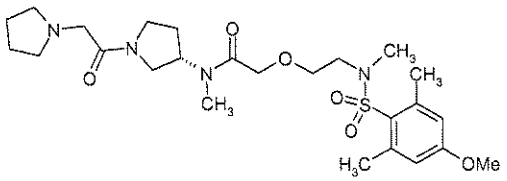


$C_{28}H_{46}N_4O_5S \times CH_2O_2$ (596.78)

[M+H]+ = 551

HPLC (Method 6): retention time = 1.31 min

Example 359

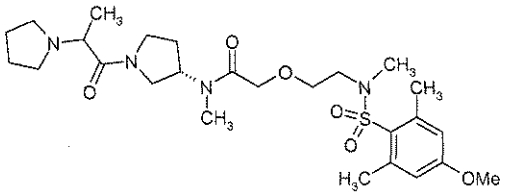


$C_{25}H_{40}N_4O_6S \times C_2HF_3O_2$ (638.70)

[M+H]+ = 525

HPLC (Method 9): retention time = 1.49 min

Example 360

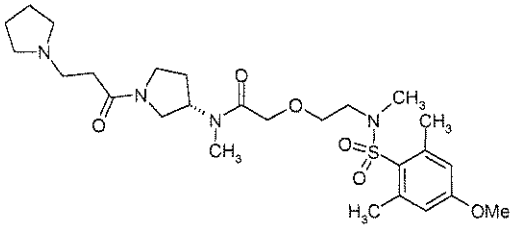


$C_{26}H_{42}N_4O_6S \times C_2HF_3O_2$ (652.72)

[M+H]+ = 539

HPLC (Method 9): retention time = 1.51 min

Example 361

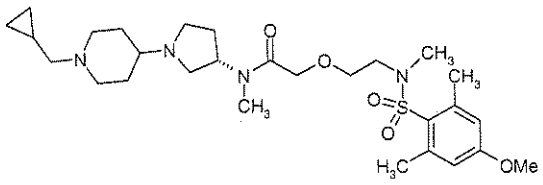


$C_{26}H_{42}N_4O_6S \times C_2HF_3O_2$ (652.72)

[M+H]+ = 539

HPLC (Method 9): retention time = 1.52 min

Example 362

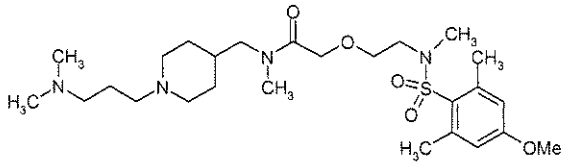


$C_{28}H_{46}N_4O_5S \times CH_2O_2$ (596.78)

[M+H]+ = 551

HPLC (Method 6): retention time = 1.32 min

Example 363

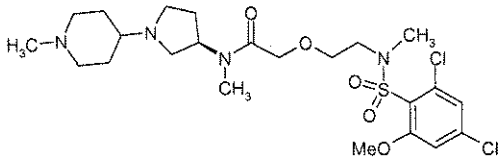


$C_{26}H_{46}N_4O_5S$ (526.73)

[M+H]+ = 527

HPLC (Method 9): retention time = 1.27 min

Example 364

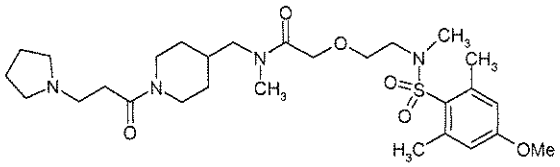


$C_{23}H_{36}Cl_2N_4O_5S$ (551.53)

[M+H]+ = 551/553/555

HPLC (Method 9): retention time = 1.30 min

Example 365

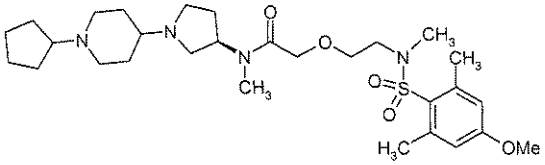


$C_{28}H_{46}N_4O_6S \times C_2HF_3O_2$ (680.78)

[M+H]+ = 567

HPLC (Method 9): retention time = 1.60 min

Example 366

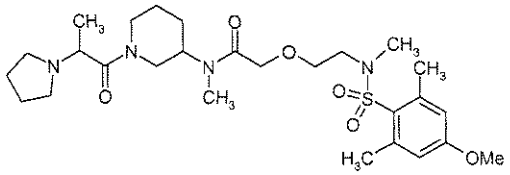


$C_{29}H_{48}N_4O_5S \times 2HCl$ (637.70)

[M+H]+ = 565

HPLC (Method 12): retention time = 2.4 min

Example 367

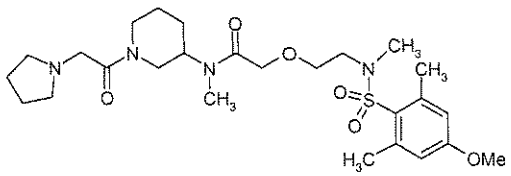


$C_{27}H_{44}N_4O_6S \times C_2HF_3O_2$ (666.75)

[M+H]+ = 553

HPLC (Method 9): retention time = 1.61 min

Example 368

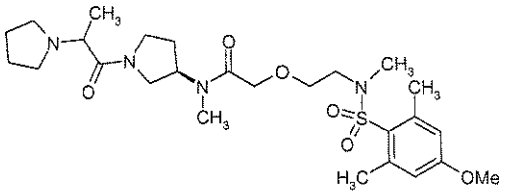


$C_{26}H_{42}N_4O_6S \times C_2HF_3O_2$ (652.72)

[M+H]+ = 539

HPLC (Method 9): retention time = 1.60 min

Example 369

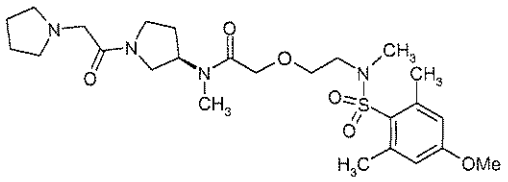


$C_{26}H_{42}N_4O_6S$ (538.70)

[M+H]+ = 539

HPLC (Method 9): retention time = 1.47 min

Example 370

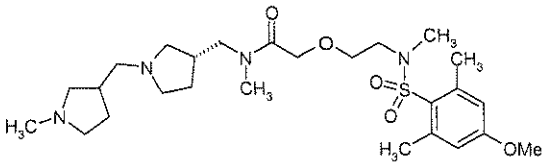


$C_{25}H_{40}N_4O_6S$ (524.67)

[M+H]+ = 525

HPLC (Method 9): retention time = 1.48 min

Example 454

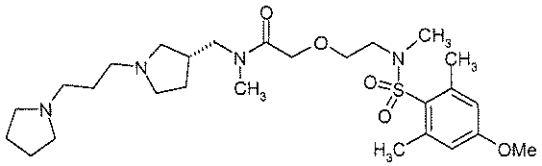


$C_{26}H_{44}N_4O_5S$ (524.72)

[M+H]+ = 525

HPLC (Method 9): retention time = 1.30 min

Example 455

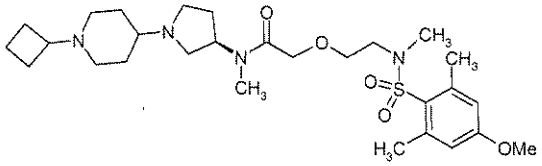


$C_{27}H_{46}N_4O_5S$ (538.74)

[M+H]+ = 539

HPLC (Method 9): retention time = 1.34 min

Example 456

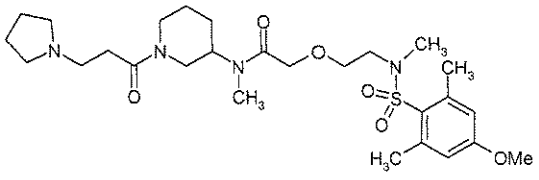


$C_{28}H_{46}N_4O_5S$ x 2HCl (623.68)

[M+H]+ = 551

DC: silica gel, dichloromethane / methanol / ammonia 8:2:0.2, Rf value = 0.71

Example 457

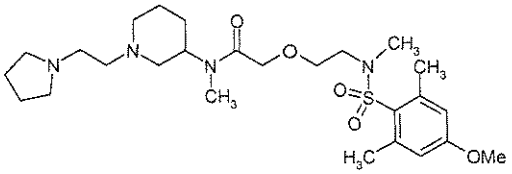


$C_{27}H_{44}N_4O_6S \times C_2HF_3O_2$ (666.75)

[M+H]+ = 553

HPLC (Method 9): retention time = 1.62 min

Example 458

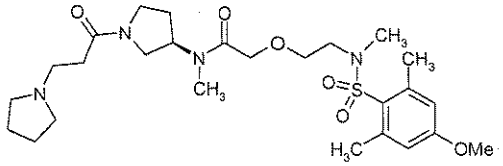


$C_{26}H_{44}N_4O_5S \times 2C_2HF_3O_2$ (752.76)

[M+H]+ = 525

HPLC (Method 9): retention time = 1.33 min

Example 459

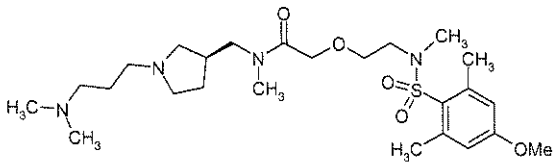


$C_{26}H_{42}N_4O_6S \times C_2HF_3O_2$ (652.72)

[M+H]+ = 539

HPLC (Method 9): retention time = 1.50 min

Example 460

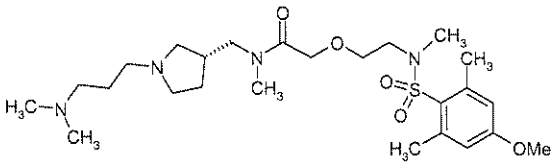


$C_{25}H_{44}N_4O_5S$ (512.71)

[M+H]+ = 513

HPLC (Method 9): retention time = 1.27 min

Example 461

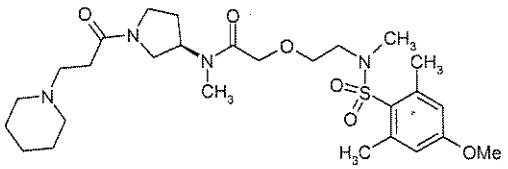


$C_{25}H_{44}N_4O_5S$ (512.71)

[M+H]+ = 513

HPLC (Method 9): retention time = 1.35 min

Example 472

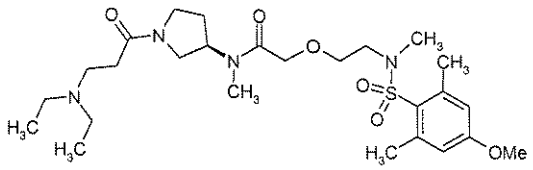


$C_{27}H_{44}N_4O_6S \times C_2HF_3O_2$ (666.76)

[M+H]+ = 553

HPLC (Method 9): retention time = 1.57 min

Example 473

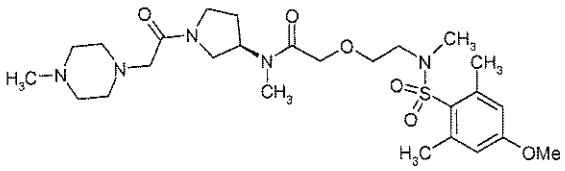


$C_{26}H_{44}N_4O_6S \times C_2HF_3O_2$ (654.75)

[M+H]+ = 541

HPLC (Method 9): retention time = 1.56 min

Example 474

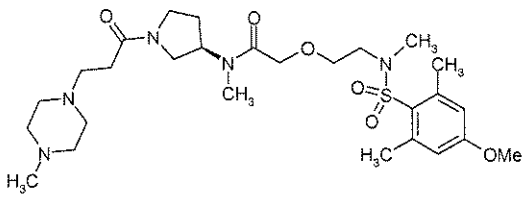


$C_{26}H_{43}N_5O_6S \times C_2HF_3O_2$ (667.74)

[M+H]+ = 554

HPLC (Method 9): retention time = 1.00 min

Example 475

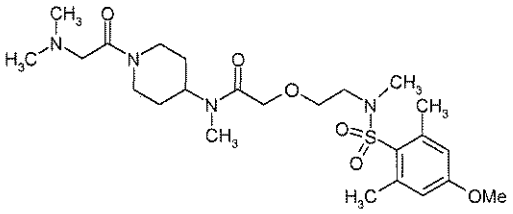


$C_{27}H_{45}N_5O_6S \times C_2HF_3O_2$ (681.77)

[M+H]+ = 568

HPLC (Method 9): retention time = 1.03 min

Example 476

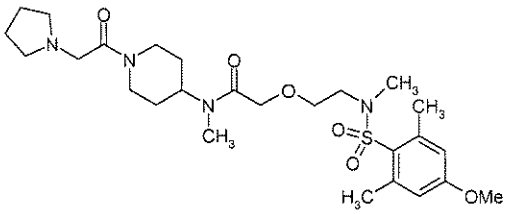


$C_{24}H_{40}N_4O_6S \times C_2HF_3O_2$ (626.69)

[M+H]+ = 513

HPLC (Method 9): retention time = 1.50 min

Example 477

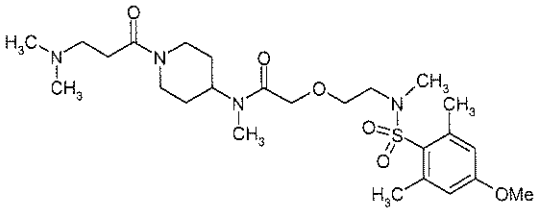


$C_{26}H_{42}N_4O_6S \times C_2HF_3O_2$ (654.72)

[M+H]+ = 539

HPLC (Method 9): retention time = 1.55 min

Example 478

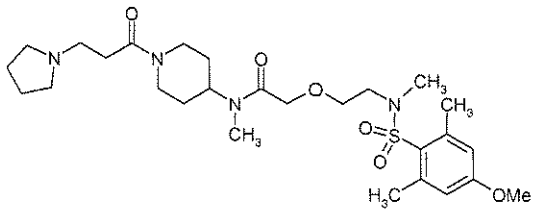


$C_{25}H_{42}N_4O_6S \times C_2HF_3O_2$ (640.71)

[M+H]+ = 527

HPLC (Method 9): retention time = 1.63 min

Example 479

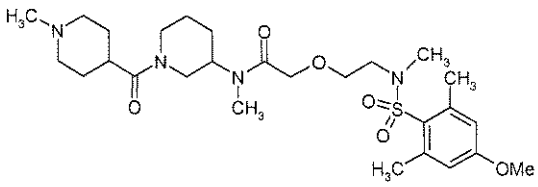


$C_{27}H_{44}N_4O_6S$ (552.73)

[M+H]+ = 553

HPLC (Method 9): retention time = 1.65 min

Example 481

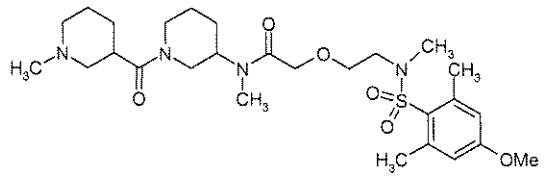


$C_{27}H_{44}N_4O_6S$ x $C_2HF_3O_2$ (666.75)

[M+H]+ = 553

HPLC (Method 9): retention time = 1.59 min

Example 482

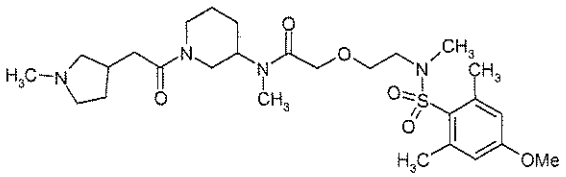


$C_{27}H_{44}N_4O_6S$ x $C_2HF_3O_2$ (666.75)

[M+H]+ = 553

HPLC (Method 9): retention time = 1.61 min

Example 483

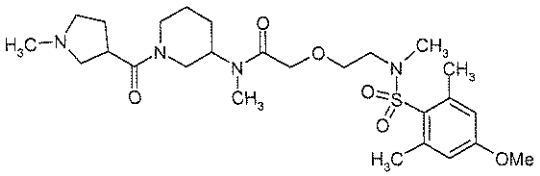


$C_{27}H_{44}N_4O_6S \times C_2HF_3O_2$ (666.75)

[M+H]+ = 553

HPLC (Method 9): retention time = 1.55 min

Example 484



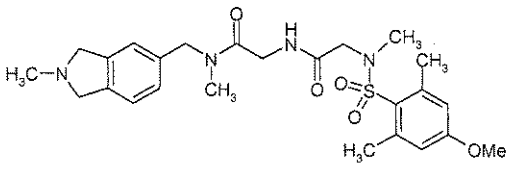
$C_{26}H_{42}N_4O_6S \times C_2HF_3O_2$ (652.72)

[M+H]+ = 539

HPLC (Method 9): retention time = 1.55 min

The following compounds were prepared analogously to Example 119:

Example 371

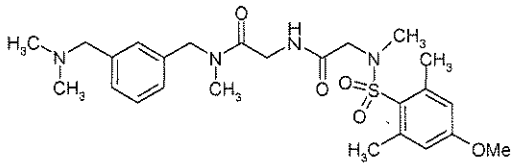


$C_{25}H_{34}N_4O_5S \times C_2HF_3O_2$ (616.65)

[M+H]+ = 503

HPLC (Method 6): retention time = 2.30 min

Example 372

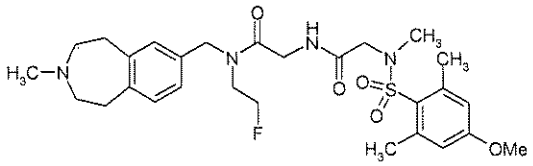


$C_{25}H_{36}N_4O_5S$ x HCl (541.10)

[M+H]+ = 505

HPLC (Method 5): retention time = 1.49 min

Example 373

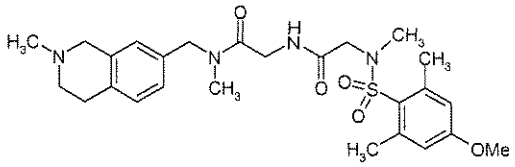


$C_{28}H_{39}FN_4O_5S$ x $C_2HF_3O_2$ (676.72)

[M+H]+ = 563

HPLC (Method 5): retention time = 1.55 min

Example 374

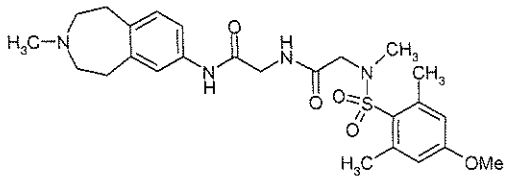


$C_{26}H_{36}N_4O_5S$ x HCl (553.11)

[M+H]+ = 517

HPLC (Method 11): retention time = 1.73 min

Example 375

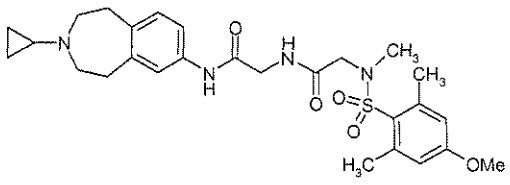


$C_{25}H_{34}N_4O_5S \times C_2HF_3O_2$ (616.65)

[M+H]+ = 503

HPLC (Method 5): retention time = 1.49 min

Example 376

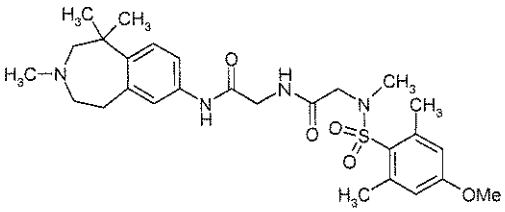


$C_{27}H_{36}N_4O_5S \times C_2HF_3O_2$ (642.69)

[M+H]+ = 529

HPLC (Method 5): retention time = 1.50 min

Example 377

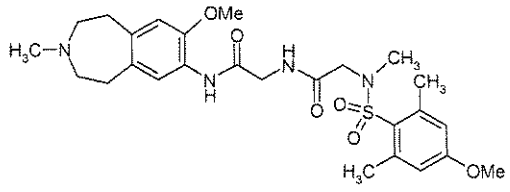


$C_{27}H_{38}N_4O_5S \times C_2HF_3O_2$ (644.70)

[M+H]+ = 531

HPLC (Method 5): retention time = 1.54 min

Example 378

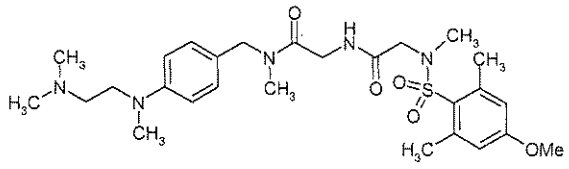


$C_{26}H_{36}N_4O_6S$ x $C_2HF_3O_2$ (646.68)

[M+H]+ = 533

HPLC (Method 5): retention time = 1.51 min

Example 379

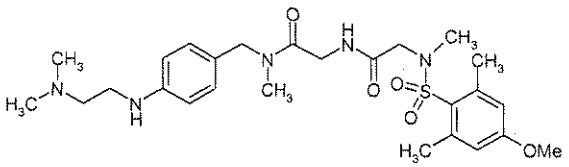


$C_{27}H_{41}N_5O_5S$ x HCl (584.17)

[M+H]+ = 548

HPLC (Method 5): retention time = 1.53 min

Example 380

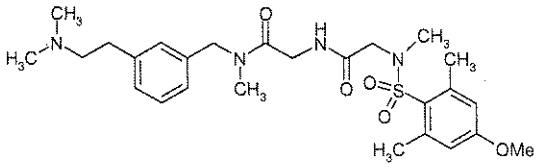


$C_{26}H_{39}N_5O_5S$ x HCl (570.15)

[M+H]+ = 534

HPLC (Method 5): retention time = 1.52 min

Example 381

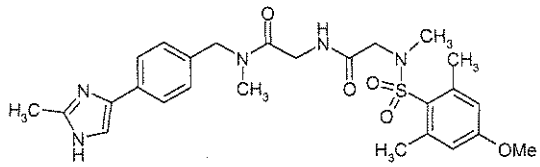


$C_{26}H_{38}N_4O_5S$ x HCl (555.13)

[M+H]+ = 519

HPLC (Method 5): retention time = 1.51 min

Example 382

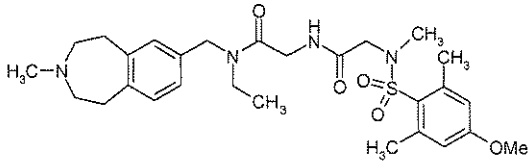


$C_{26}H_{33}N_5O_5S$ (527.64)

[M+H]+ = 528

HPLC (Method 4): retention time = 3.0 min

Example 383

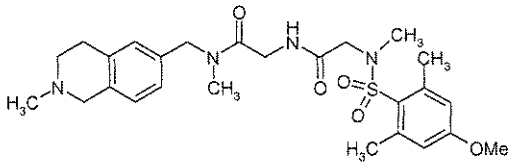


$C_{28}H_{40}N_4O_5S$ x HCl (581.17)

[M+H]+ = 545

HPLC (Method 4): retention time = 3.1 min

Example 384

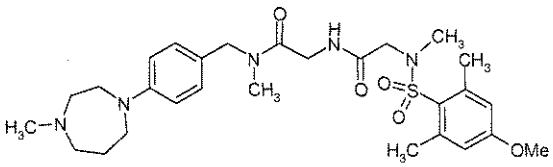


$C_{26}H_{36}N_4O_5S$ x HCl (553.11)

[M+H]+ = 517

HPLC (Method 5): retention time = 1.48 min

Example 385

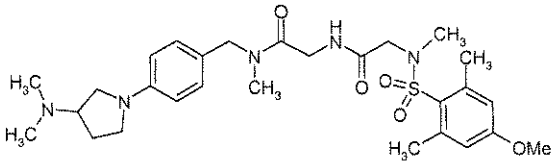


$C_{28}H_{41}N_5O_5S$ x HCl (596.18)

[M+H]+ = 560

HPLC (Method 5): retention time = 1.52 min

Example 386

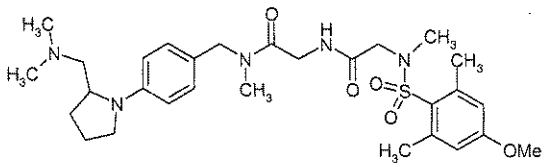


$C_{28}H_{41}N_5O_5S$ x HCl (596.18)

[M+H]+ = 560

HPLC (Method 5): retention time = 1.52 min

Example 387

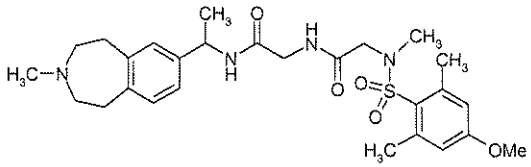


$C_{29}H_{43}N_5O_5S$ x HCl (610.21)

[M+H]+ = 574

HPLC (Method 5): retention time = 1.57 min

Example 388

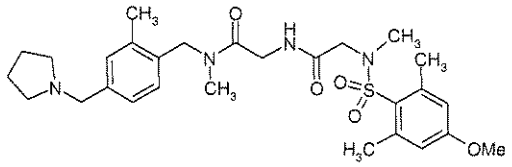


$C_{27}H_{38}N_4O_5S$ x HCl (567.14)

[M+H]+ = 531

HPLC (Method 4): retention time = 3.0 min

Example 389

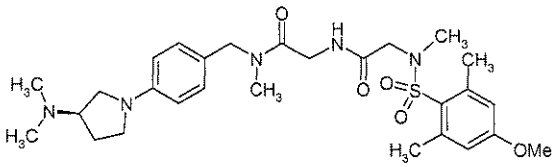


$C_{28}H_{40}N_4O_5S$ x HCl (581.17)

[M+H]+ = 545

DC: silica gel, dichloromethane / methanol 9:1, Rf value = 0.18

Example 390

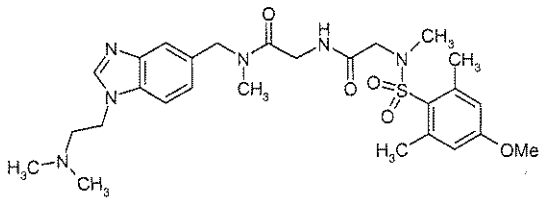


$C_{28}H_{41}N_5O_5S$ x HCl (596.18)

[M+H]+ = 560

DC: silica gel, ethyl acetate / methanol / ammonia 9:1:0.1, Rf value = 0.42

Example 391

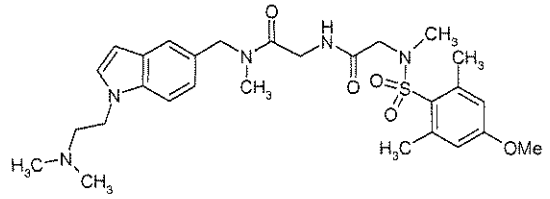


$C_{27}H_{38}N_6O_5S$ (558.69)

[M+H]+ = 559

HPLC (Method 6): retention time = 2.23 min

Example 392

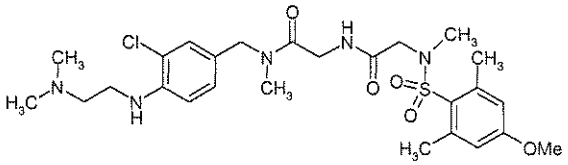


$C_{28}H_{39}N_5O_5S$ (557.71)

[M+H]+ = 558

HPLC (Method 6): retention time = 2.35 min

Example 393

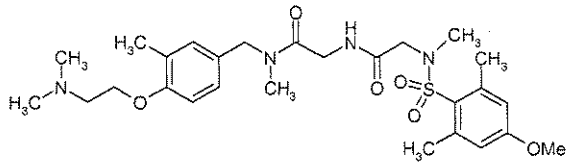


$C_{26}H_{38}ClN_5O_5S \times CH_2O_2$ (614.16)

[M+H]+ = 568/570

HPLC (Method 6): retention time = 2.55 min

Example 394

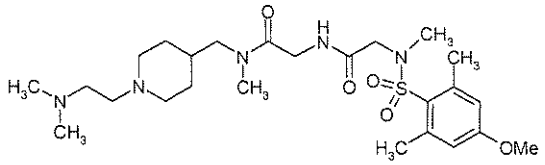


$C_{27}H_{40}N_4O_6S$ (548.70)

[M+H]+ = 549

HPLC (Method 6): retention time = 2.49 min

Example 395

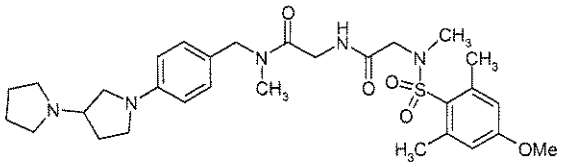


$C_{25}H_{43}N_5O_5S$ (525.71)

[M+H]+ = 526

HPLC (Method 6): retention time = 1.85 min

Example 396

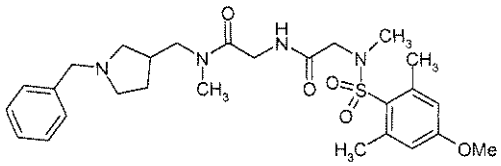


$C_{30}H_{43}N_5O_5S$ (585.76)

[M+H]+ = 586

HPLC (Method 6): retention time = 2.66 min

Example 397

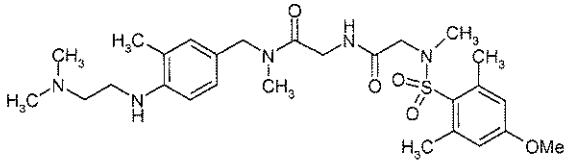


$C_{27}H_{38}N_4O_5S$ (530.68)

[M+H]+ = 531

HPLC (Method 6): retention time = 2.52 min

Example 398

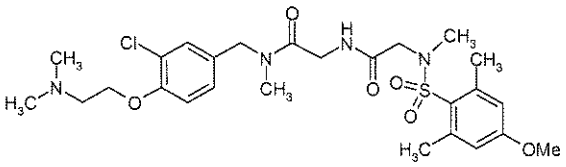


$C_{27}H_{41}N_5O_5S$ (547.71)

[M+H]+ = 548

HPLC (Method 6): retention time = 2.44 min

Example 399

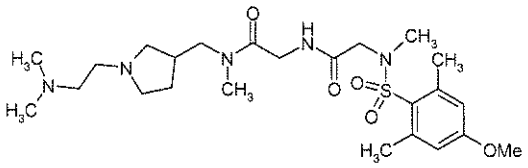


$C_{26}H_{37}ClN_4O_6S$ (569.11)

[M+H]+ = 570

HPLC (Method 6): retention time = 2.56 min

Example 400

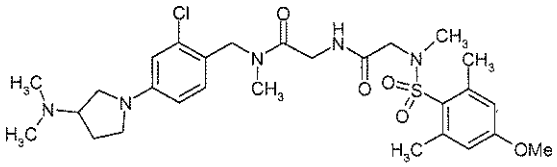


$C_{24}H_{41}N_5O_5S$ (511.68)

[M+H]+ = 512

HPLC (Method 6): retention time = 1.80 min

Example 401

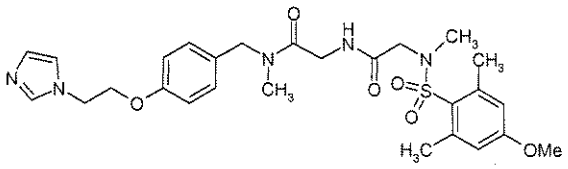


$C_{28}H_{40}ClN_5O_5S$ (594.17)

[M+H]+ = 594/596

HPLC (Method 6): retention time = 2.68 min

Example 402

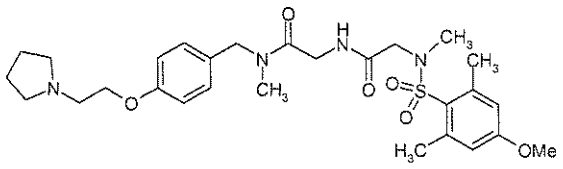


$C_{27}H_{35}N_5O_6S$ (557.66)

[M+H]+ = 558

HPLC (Method 6): retention time = 2.51 min

Example 403

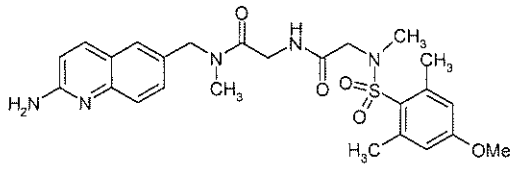


$C_{28}H_{40}N_4O_6S$ (560.71)

[M+H]+ = 561

HPLC (Method 6): retention time = 2.51 min

Example 404

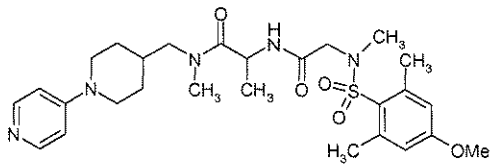


$C_{25}H_{31}N_5O_5S$ (513.61)

[M+H]+ = 514

HPLC (Method 6): retention time = 2.35 min

Example 405

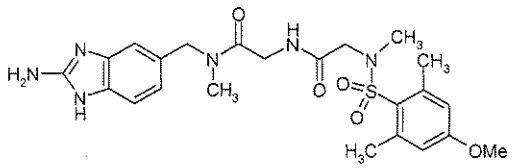


$C_{27}H_{39}N_5O_5S \times C_2HF_3O_2$ (659.72)

[M+H]+ = 546

HPLC (Method 6): retention time = 2.44 min

Example 406

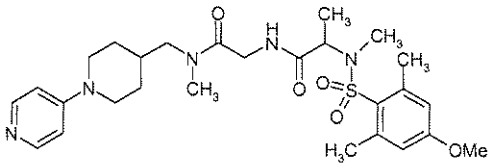


$C_{23}H_{30}N_6O_5S$ (502.59)

[M+H]+ = 503

HPLC (Method 6): retention time = 2.37 min

Example 407

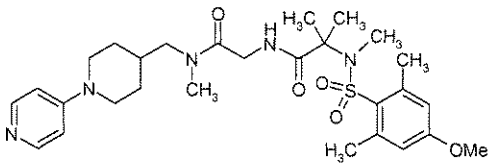


$C_{27}H_{39}N_5O_5S \times C_2HF_3O_2$ (659.72)

[M+H]+ = 546

HPLC (Method 6): retention time = 2.52 min

Example 408

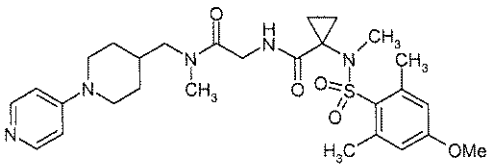


$C_{28}H_{41}N_5O_5S \times C_2HF_3O_2$ (673.75)

[M+H]+ = 560

HPLC (Method 6): retention time = 2.58 min

Example 409

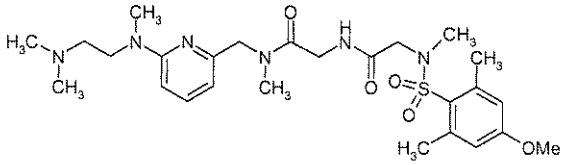


$C_{28}H_{39}N_5O_5S \times C_2HF_3O_2$ (671.73)

[M+H]+ = 558

HPLC (Method 6): retention time = 2.57 min

Example 410

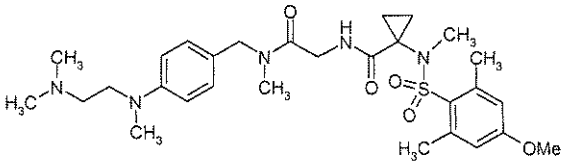


$C_{26}H_{40}N_6O_5S$ (548.70)

[M+H]+ = 549

HPLC (Method 6): retention time = 2.52 min

Example 411

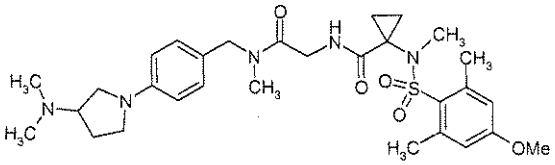


$C_{29}H_{43}N_5O_5S \times C_2HF_3O_2$ (687.77)

[M+H]+ = 574

HPLC (Method 6): retention time = 2.72 min

Example 412

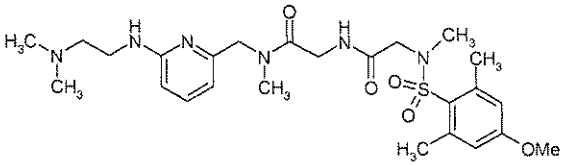


$C_{30}H_{43}N_5O_5S$ (585.76)

[M+H]+ = 586

HPLC (Method 6): retention time = 2.70 min

Example 413

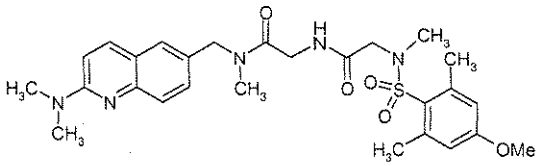


$C_{25}H_{38}N_6O_5S \times CH_2O_2$ (580.70)

[M+H]+ = 535

HPLC (Method 6): retention time = 2.16 min

Example 414

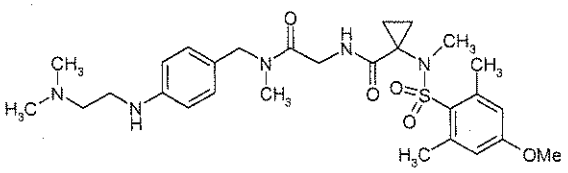


$C_{27}H_{35}N_5O_5S \times C_2HF_3O_2$ (655.69)

[M+H]+ = 542

HPLC (Method 6): retention time = 2.48 min

Example 415

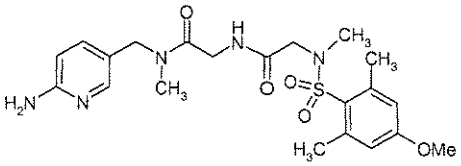


$C_{28}H_{41}N_5O_5S \times C_2HF_3O_2$ (673.75)

[M+H]+ = 560

HPLC (Method 6): retention time = 2.61 min

Example 416

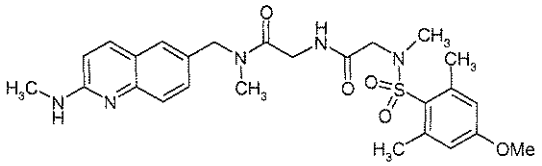


$C_{21}H_{29}N_5O_5S$ (463.55)

[M+H]+ = 464

HPLC (Method 9): retention time = 1.47 min

Example 417

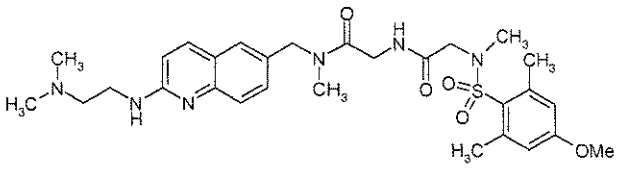


$C_{26}H_{33}N_5O_5S$ (527.64)

[M+H]+ = 528

HPLC (Method 9): retention time = 1.60 min

Example 418

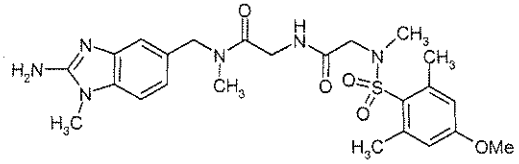


$C_{29}H_{40}N_6O_5S$ (584.73)

[M+H]+ = 585

HPLC (Method 9): retention time = 1.37 min

Example 419

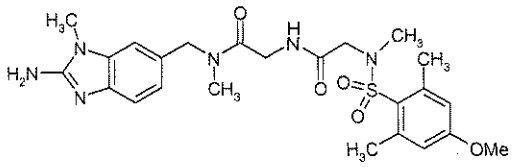


$C_{24}H_{32}N_6O_5S \times C_2HF_3O_2$ (630.64)

[M+H]+ = 517

HPLC (Method 9): retention time = 1.58 min

Example 420

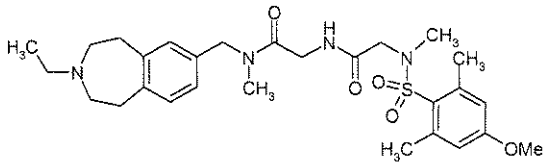


$C_{24}H_{32}N_6O_5S$ x $C_2HF_3O_2$ (630.64)

[M+H]+ = 517

HPLC (Method 9): retention time = 1.57 min

Example 421

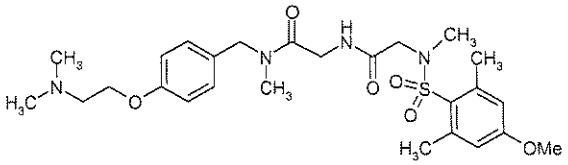


$C_{28}H_{40}N_4O_5S$ x $C_2HF_3O_2$ (658.73)

[M+H]+ = 545

HPLC (Method 5): retention time = 1.53 min

Example 422

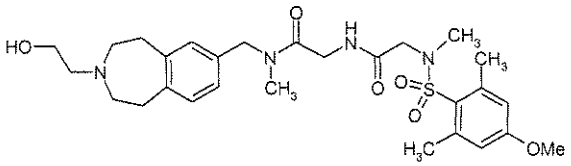


$C_{26}H_{38}N_4O_6S$ x $C_2HF_3O_2$ (648.69)

[M+H]+ = 535

HPLC (Method 5): retention time = 1.43 min

Example 423

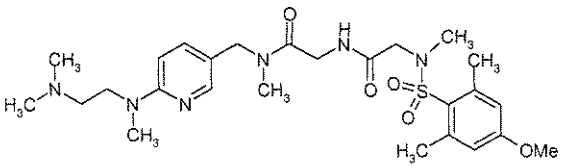


$C_{28}H_{40}N_4O_6S$ (560.71)

[M+H]+ = 561

HPLC (Method 5): retention time = 1.50 min

Example 424

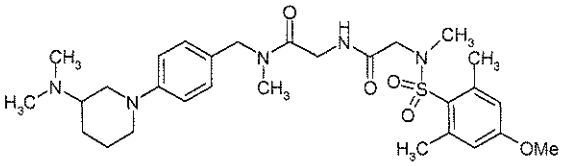


$C_{26}H_{40}N_6O_5S$ (548.70)

[M+H]+ = 549

HPLC (Method 5): retention time = 1.39 min

Example 425

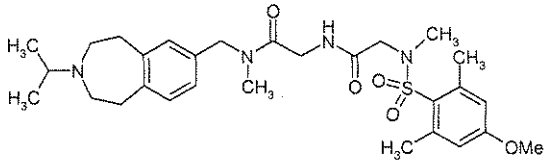


$C_{29}H_{43}N_5O_5S$ x HCl (610.21)

[M+H]+ = 574

HPLC (Method 7): retention time = 1.88 min

Example 426

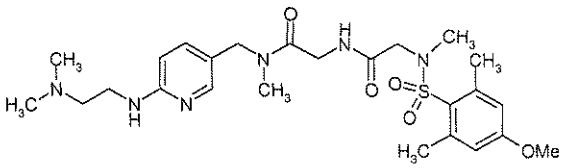


$C_{29}H_{42}N_4O_5S \times C_2HF_3O_2$ (672.76)

[M+H]+ = 559

HPLC (Method 5): retention time = 1.55 min

Example 427

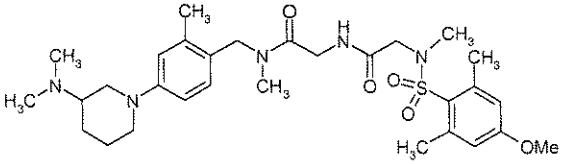


$C_{25}H_{38}N_6O_5S \times 2HCl$ (607.59)

[M+H]+ = 535

HPLC (Method 5): retention time = 1.39 min

Example 428

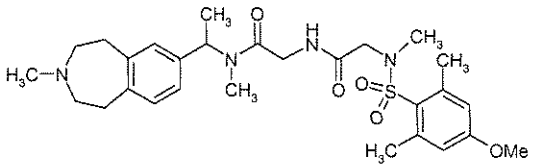


$C_{30}H_{45}N_5O_5S \times C_2HF_3O_2$ (701.80)

[M+H]+ = 588

HPLC (Method 5): retention time = 1.55 min

Example 429

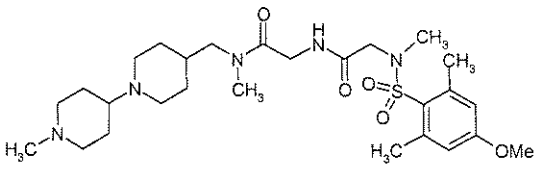


$C_{28}H_{40}N_4O_5S$ x HCl (581.17)

[M+H]+ = 545

HPLC (Method 4): retention time = 3.3 min

Example 430

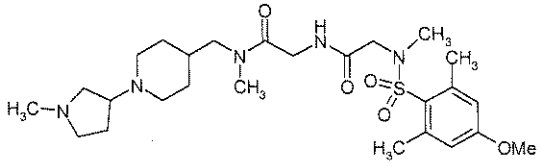


$C_{27}H_{45}N_5O_5S$ x 2HCl (624.66)

[M+H]+ = 552

DC: silica gel, dichloromethane / methanol / ammonia 8:2:0.01, Rf value = 0.25

Example 431

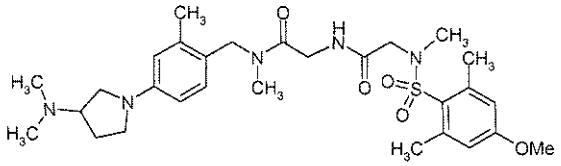


$C_{26}H_{43}N_5O_5S$ x HCl (574.18)

[M+H]+ = 538

DC: silica gel, dichloromethane / methanol / ammonia 8:2:0.01, Rf value = 0.10

Example 432

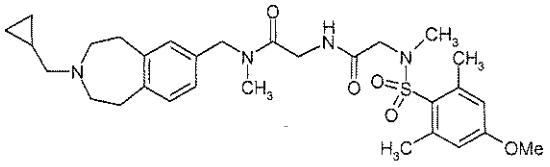


$C_{29}H_{43}N_5O_5S$ x HCl (610.21)

[M+H]+ = 574

DC: silica gel, dichloromethane / methanol 9:1, Rf value = 0.25

Example 433

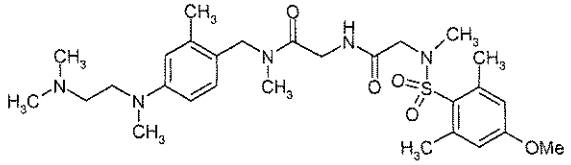


$C_{31}H_{44}N_4O_5S$ x HCl (621.23)

[M+H]+ = 585

HPLC (Method 12): retention time = 3.0 min

Example 434

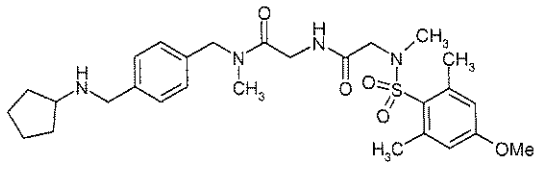


$C_{28}H_{43}N_5O_5S$ x HCl (598.20)

[M+H]+ = 562

DC: silica gel, dichloromethane / methanol 9:1, Rf value = 0.14

Example 435

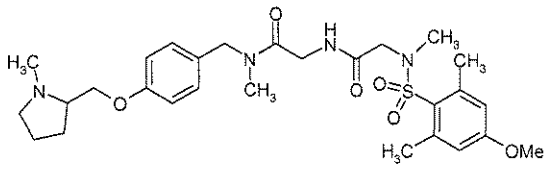


$C_{29}H_{42}N_4O_5S$ x HCl (595.19)

[M+H]+ = 559

DC: silica gel, dichloromethane / methanol / ammonia 9:1:0.1, Rf value = 0.32

Example 436

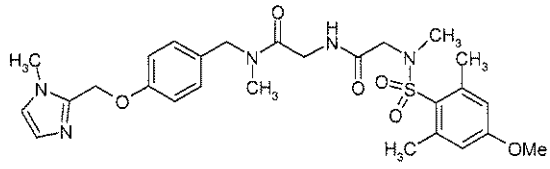


$C_{28}H_{40}N_4O_6S$ (560.71)

[M+H]+ = 561

HPLC (Method 9): retention time = 1.66 min

Example 437

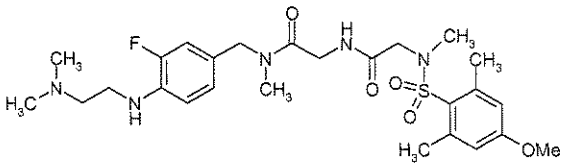


$C_{27}H_{35}N_5O_6S$ (557.66)

[M+H]+ = 558

HPLC (Method 9): retention time = 1.64 min

Example 438

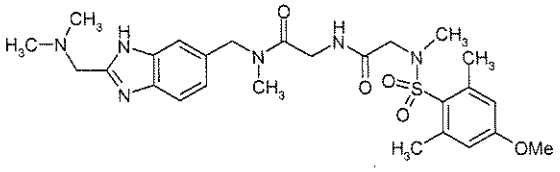


$C_{26}H_{38}FN_5O_5S$ (551.68)

[M+H]+ = 552

HPLC (Method 6): retention time = 2.30 min

Example 439

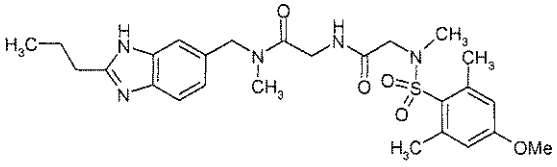


$C_{26}H_{36}N_6O_5S$ (544.67)

[M+H]+ = 545

HPLC (Method 6): retention time = 1.48 min

Example 440

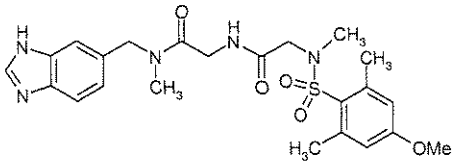


$C_{26}H_{35}N_5O_5S$ (529.65)

[M+H]+ = 530

HPLC (Method 9): retention time = 1.61 min

Example 441

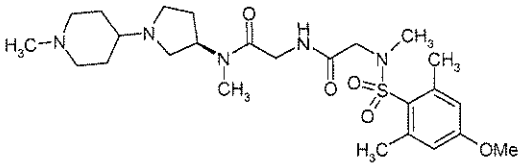


$C_{23}H_{29}N_5O_5S$ (487.57)

[M+H]+ = 488

HPLC (Method 9): retention time = 1.53 min

Example 442

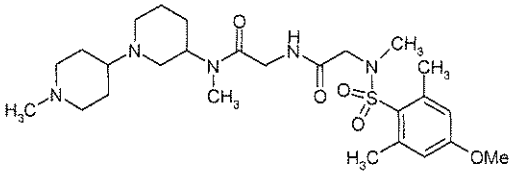


$C_{25}H_{41}N_5O_5S$ x 2HCl (596.61)

[M+H]+ = 524

HPLC (Method 12): retention time = 2.3 min

Example 443

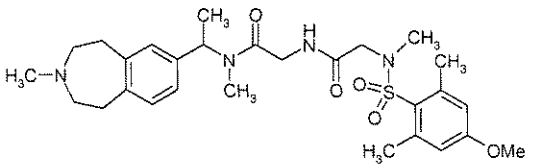


$C_{26}H_{43}N_5O_5S$ x 2HCl (610.64)

[M+H]+ = 538

DC: silica gel, dichloromethane / methanol / ammonia 8:2:0.2, Rf value = 0.53

Example 444

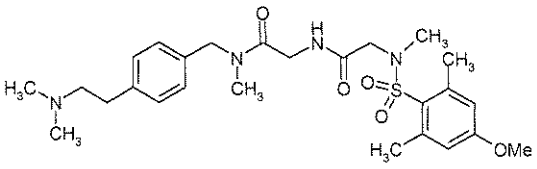


$C_{29}H_{42}N_4O_5S$ x HCl (595.19)

[M+H]+ = 559

HPLC (Method 12): retention time = 2.8 min

Example 445

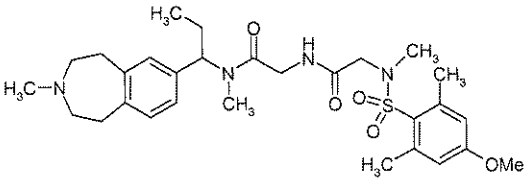


$C_{26}H_{38}N_4O_5S$ x $C_2HF_3O_2$ (632.69)

[M+H]+ = 519

HPLC (Method 9): retention time = 1.61 min

Example 468

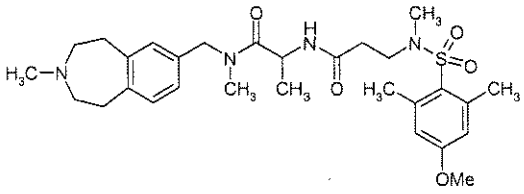


$C_{29}H_{42}N_4O_5S$ x HCl (595.19)

[M+H]+ = 559

HPLC (Method 12): retention time = 3.1 min

Example 469



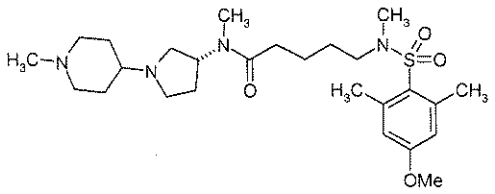
$C_{29}H_{42}N_4O_5S$ x HCl (595.19)

[M+H]+ = 559

DC: silica gel, dichloromethane / methanol / ammonia 8:2:0.01, Rf value = 0.68

The following compounds were prepared analogously to Example 128:

Example 446

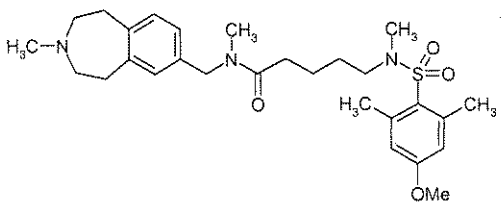


$C_{26}H_{44}N_4O_4S$ x $2C_2HF_3O_2$ (736.76)

[M+H]+ = 509

HPLC (Method 6): retention time = 1.36 min

Example 447



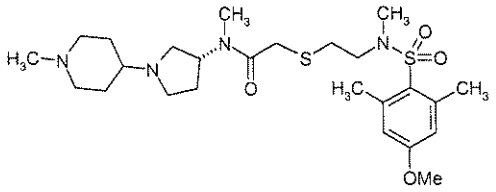
$C_{28}H_{41}N_3O_4S$ x $C_2HF_3O_2$ (629.73)

[M+H]+ = 516

HPLC (Method 6): retention time = 1.77 min

The following compounds were prepared analogously to Example 134:

Example 448

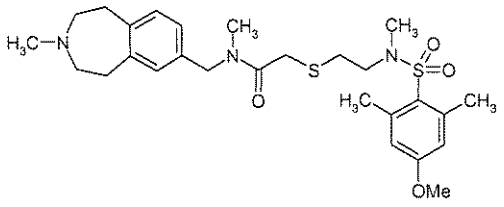


$C_{25}H_{42}N_4O_4S_2 \times C_2HF_3O_2$ (640.78)

[M+H]+ = 527

HPLC (Method 6): retention time = 1.35 min

Example 449



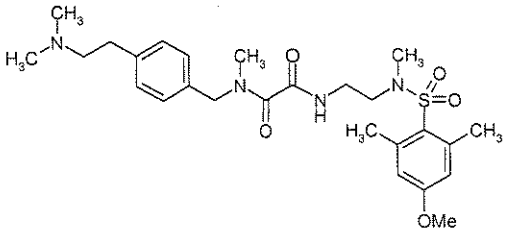
$C_{27}H_{39}N_3O_4S_2$ (533.75)

[M+H]+ = 534

HPLC (Method 6): retention time = 1.74 min

The following compound was prepared analogously to Example 138:

Example 450

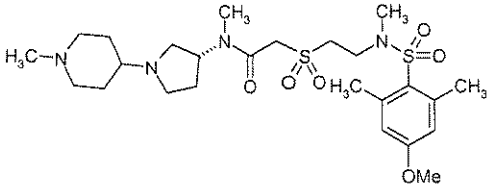


$C_{26}H_{38}N_4O_5S \times CH_2O_2$ (564.70)

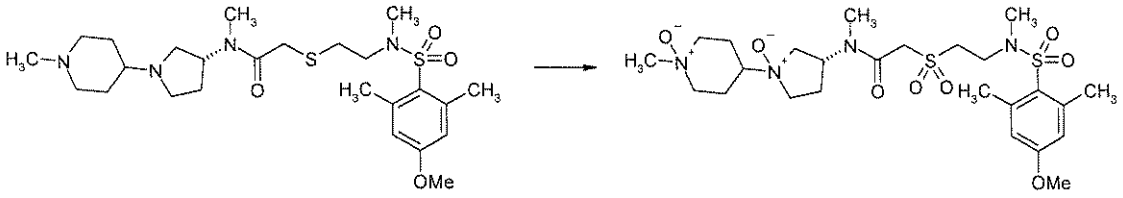
[M+H]+ = 519

HPLC (Method 6): retention time = 2.33 min

Example 451



451a)

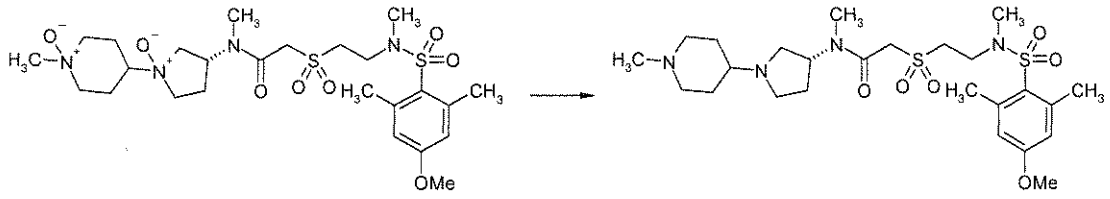


A mixture of 88.0 mg (0.167 mmol) of 448, 0.15 g (0.61 mmol) of 70 % *m*-chloroper-benzoic acid (Fluka) and 3 ml dichloromethane is stirred for 30 minutes at ambient temperature and then evaporated to dryness in vacuo. The residue is dissolved in methanol and membrane-filtered. The product is then obtained by preparative HPLC from the filtrate.

$C_{25}H_{42}N_4O_8S_2$ (590.76)

[M+H]+ = 591

451b)



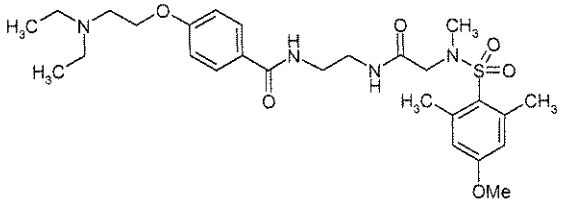
A mixture of 90.0 mg (0.15 mmol) of the product of 451a, 20.0 mg Raney nickel and 10 ml THF is stirred for one hour in the autoclave at ambient temperature. Then the catalyst is filtered off and the filtrate is evaporated to dryness in vacuo. The crude product thus obtained is purified by preparative HPLC.

$C_{25}H_{42}N_4O_6S_2 \times CH_2O_2$ (604.78)

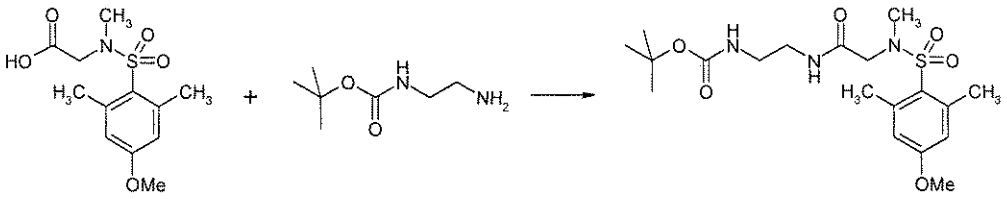
[M+H]+ = 559

HPLC (Method 6): retention time = 1.33 min

Example 452



452a)

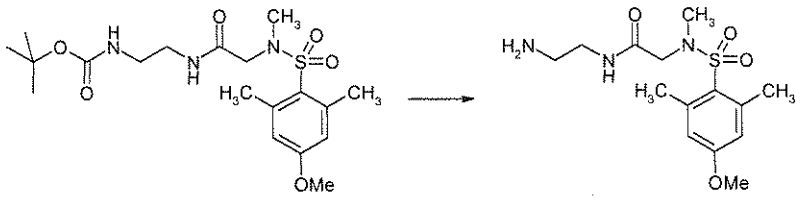


452a is prepared analogously to 1f from 2.16 g (7.50 mmol) of the product of 119b, 1.20 g (7.50 mmol) of N-Boc-ethylenediamine (Fluka), 3.14 ml (22.50 mmol) of triethylamine and 2.41 g (7.50 mmol) of TBTU in 28 ml THF and 4 ml DMF.

$C_{19}H_{31}N_3O_6S$ (429.53)

DC: silica gel, dichloromethane / ethanol 19:1, Rf value = 0.35

452b)

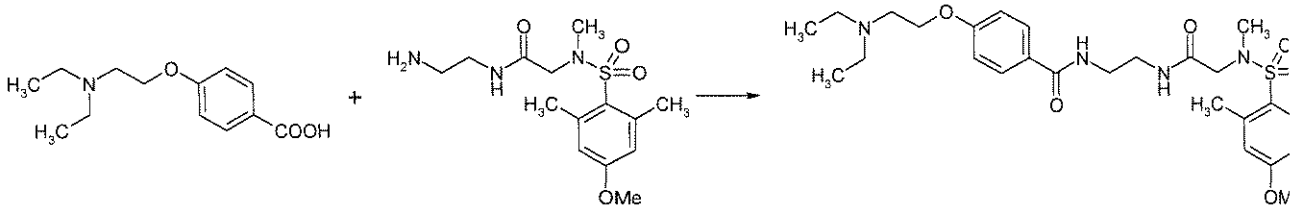


452b is prepared analogously to 28d from 2.70 g (6.29 mmol) of the product of 452a and 7 ml TFA in 50 ml dichloromethane.

$C_{14}H_{23}N_3O_4S$ (329.42)

DC: silica gel, dichloromethane / ethanol 9:1, Rf value = 0.15

452c)



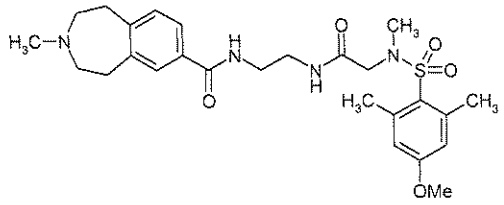
Example 452 is prepared analogously to 1f from 0.119 g (0.50 mmol) of 4-(2-diethylaminoethoxy)-benzoic acid (J. Med. Chem. 14, 1971, 836-842), 0.165 g (0.50 mmol) of the product of 452b, 0.21 ml (1.50 mmol) of triethylamine and 0.16 g (0.50 mmol) of TBTU in 7 ml THF and 1 ml DMF.

$C_{27}H_{40}N_4O_6S$ x HCl (585.16)

HPLC (Method 5): retention time = 1.44 min

The following compounds were prepared analogously to Example 452:

Example 453

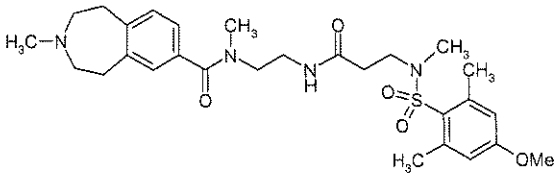


$C_{26}H_{36}N_4O_5S$ x HCl (553.11)

[M+H]+ = 517

HPLC (Method 5): retention time = 1.40 min

Example 470

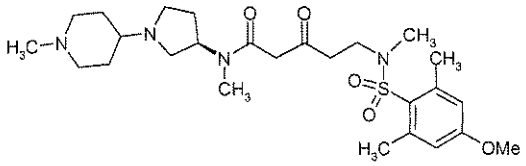


$C_{28}H_{40}N_4O_5S$ x HCl (581.17)

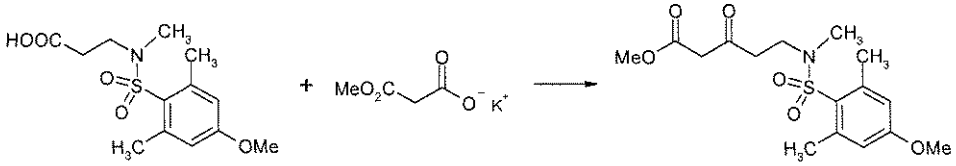
[M+H]+ = 545

HPLC (Method 12): retention time = 3.51 min

Example 480



480a)



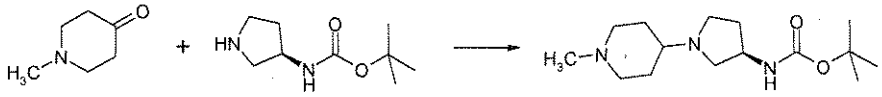
A mixture of 0.78 g (4.98 mmol) of monomethylmalonate potassium salt (Fluka), 0.52 g (5.47 mmol) of magnesium chloride and 30 ml THF is stirred for four hours at 50°C. A second mixture of 1.00 g (3.32 mmol) of the product of 22c, 0.65 g (3.98 mmol) of CDI and 20 ml THF is stirred first for one hour at RT and then added to the first mixture. The mixture is stirred overnight at RT and then the precipitate formed is filtered off. The filtrate is evaporated to dryness in vacuo. The crude product thus obtained is triturated with water, filtered off and dried at 45°C in the vacuum dryer.

$C_{16}H_{23}NO_6S$ (357.42)

[M+H]+ = 358

HPLC (Method 9): retention time = 2.19 min

480b)

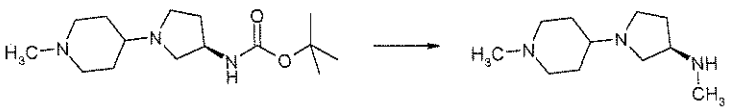


480b is prepared analogously to 60a from 0.47 ml (4.07 mmol) of 1-methyl-4-piperidone (Fluka), 0.76 g .(4.07 mmol) of (R)-3-(Boc-amino)-pyrrolidine (Fluka), 1.72 g (8.13 mmol) of sodium triacetoxyborohydride and 0.23 ml (4.07 mmol) of acetic acid in 10 ml dichloromethane.

$C_{15}H_{29}N_3O_2$ (283.41)

[M+H]+ = 284

480c)

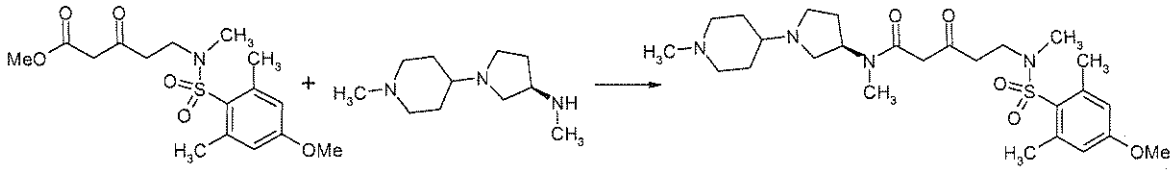


480c is prepared analogously to 38f from 0.90 g (3.18 mmol) of the product of 480b and 5.0 ml (10.00 mmol) of lithium aluminium hydride (2M in THF) in 15 ml THF.

$C_{11}H_{23}N_3$ (197.32)

[M+H]+ = 198

480d)



A mixture of 0.56 g (1.58 mmol) of the product of 480a, 0.54 g (2.73 mmol) of the product of 480c and 5 ml of toluene is heated to 120°C for 24 hours. Then the reaction mixture is evaporated to dryness in vacuo. The crude product thus obtained is purified by preparative HPLC.

$C_{26}H_{42}N_4O_5S$ (522.70)

[M+H]+ = 523

HPLC (Method 9): retention time = 1.33 min

The following Examples describe pharmaceutical formulations which contain as active substance any desired compound of general formula I:

Example I

Dry ampoule with 75 mg of active compound per 10 ml

Composition:

Active compound	75.0 mg
Mannitol	50.0 mg
Water for injection	ad 10.0 ml

Production:

Active compound and mannitol are dissolved in water. The charged ampoules are

freeze dried. Water for injection is used to dissolve to give the solution ready for use.

Example II

Tablet with 50 mg of active compound

Composition:

(1) Active compound	50.0 mg
(2) Lactose	98.0 mg
(3) Maize starch	50.0 mg
(4) Polyvinylpyrrolidone	15.0 mg
(5) Magnesium stearate	2.0 mg
	215.0 mg

Production:

(1), (2) and (3) are mixed and granulated with an aqueous solution of (4). (5) is admixed to the dry granules. Tablets are compressed from this mixture, biplanar with a bevel on both sides and dividing groove on one side.
Diameter of the tablets: 9 mm.

Example III

Tablet with 350 mg of active compound

Composition:

(1) Active compound	350.0 mg
(2) Lactose	136.0 mg

(3) Maize starch	80.0 mg
(4) Polyvinylpyrrolidone	30.0 mg
(5) Magnesium stearate	4.0 mg
	600.0 mg

Production:

(1), (2) and (3) are mixed and granulated with an aqueous solution of (4). (5) is admixed to the dry granules. Tablets are compressed from this mixture, biplanar with a bevel on both sides and dividing groove on one side.

Diameter of the tablets: 12 mm.

Example IV

Capsule with 50 mg of active compound

Composition:

(1) Active compound	50.0 mg
(2) Maize starch dried	58.0 mg
(3) Lactose powdered	50.0 mg
(4) Magnesium stearate	2.0 mg
	160.0 mg

Production:

(1) is triturated with (3). This trituration is added to the mixture of (2) and (4) with vigorous mixing.

This powder mixture is packed into hard gelatine two-piece capsules of size 3 in a capsule-filling machine.

Example V

Capsules with 350 mg of active compound

Composition:

(1) Active compound	350.0 mg
(2) Maize starch dried	46.0 mg
(3) Lactose powdered	30.0 mg
(4) Magnesium stearate	4.0 mg
	430.0 mg

Production:

(1) is triturated with (3). This trituration is added to the mixture of (2) and (4) with vigorous stirring.

This powder mixture is packed into hard gelatine two-piece capsules of size 0 in a capsule-filling machine.

Example VI

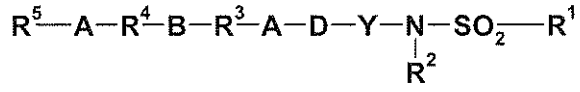
Suppositories with 100 mg of active compound

1 suppository comprises:

Active compound	100.0 mg
Polyethylene glycol (M.W. 1500)	600.0 mg
Polyethylene glycol (M.W. 6000)	460.0 mg
Polyethylene sorbitan monostearate	840.0 mg
	2000.0 mg

PATENT CLAIMS

1. Compounds of general formula **I**



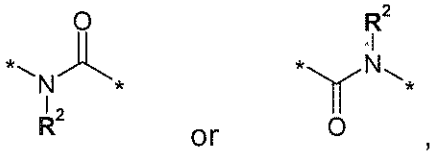
, (I)

wherein

A denotes a bond, C_{1-4}-alkylene or $-CH_2$-C(O),

B denotes a bond, C_{1-3}-alkylene, -O or –C(O),

D denotes a group of general formulae **II**



or

,

Y denotes a C_{1-6}-alkylene group optionally substituted by the group $\mathbf{R^2}$, wherein a methylene group may additionally be replaced by $\mathbf{Y^1}$ and

$\mathbf{Y^1}$ denotes -O, -S, -S(O), -N($\mathbf{R^2}$), -N($\mathbf{R^2}$)-C(O), -C(O)-N($\mathbf{R^2}$), -C(O), -CH(aryl), C_{3-6}-cycloalkylene or -$S(O)_2$-,

$\mathbf{R^1}$ denotes C_{3-7}-cycloalkyl or aryl, heteroaryl or aryl-C_{1-3}-alkyl, each of which may be substituted by one, two, three or four groups $\mathbf{R^{1.1}}$, while the groups $\mathbf{R^{1.1}}$ may be identical or different and

$\mathbf{R^{1.1}}$ denotes H, F, Cl, Br, I, C_{1-3}-alkyl, F_3C, HO, C_{1-3}-alkyl-O or C_{1-3}-alkyl-O-C_{2-4}-alkylene-O-,

$\mathbf{R^2}$ denotes H or C_{1-3}-alkyl, while each methylene group may be substituted by up to two and each methyl group may be substituted by up to three fluorine atoms, or also denotes H_3C-C(O),

$\mathbf{R^3}$ denotes a) C_{1-6}-alkylene,
b) -N($\mathbf{R^2}$),
c) an arylene group mono- or disubstituted by $\mathbf{R^{3.1}}$,
d) a heteroarylene group mono- or disubstituted by $\mathbf{R^{3.1}}$,
e) a saturated 4- to 7-membered heterocyclic ring mono- or disubstituted by $\mathbf{R^{3.1}}$,
f) an unsaturated 5- to 7-membered heterocyclic ring mono- or disubstituted by $\mathbf{R^{3.1}}$, which is fused to one or two phenyl rings via the unsaturated bonds, or
g) a saturated 8- to 10-membered aza-heterobicyclic group mono- or disubstituted by $\mathbf{R^{3.1}}$,

while the groups $\mathbf{R^{3.1}}$ may be identical or different in each case and

$\mathbf{R^{3.1}}$ denotes H, F, Cl, Br, I, C_{1-3}-alkyl, HO, C_{1-3}-alkyl-O or C_{1-3}-alkyl-O-C_{2-4}-alkylene-O-, or

$\mathbf{R^3}$ also denotes -O, if **B** does not denote the group –O-,

$\mathbf{R^4}$ denotes a) -O,
b) -C(O)O,
c) -C(O)N$\mathbf{R^2}$,
d) -N$\mathbf{R^2}$,
e) -N$\mathbf{R^2}$-N$\mathbf{R^2}$,
f) C_{3-7}-cycloalkylene,
g) C_{1-6}-alkylene,
h) an arylene group mono- or disubstituted by $\mathbf{R^{4.1}}$,

i) a heteroarylene group mono- or disubstituted by $\mathbf{R^{4.1}}$,

j) a 4- to 7-membered saturated heterocyclic ring mono- or disubstituted by $\mathbf{R^{4.1}}$,

k) a saturated 8- to 10-membered diaza-heterobicyclic group mono- or disubstituted by $\mathbf{R^{4.1}}$,

l) a 5- to 7-membered unsaturated heterocyclic ring mono- or disubstituted by $\mathbf{R^{4.1}}$, which is fused to one or two phenyl rings via the unsaturated bonds, or

m) a saturated 9- to 11-membered diaza-spirocyclic group,

while the groups $\mathbf{R^{4.1}}$ may in each case be identical or different and

$\mathbf{R^{4.1}}$ denotes H, F, Cl, Br, I, C_{1-3}-alkyl, HO, C_{1-3}-alkyl-O or C_{1-3}-alkyl-O-C_{2-4}-alkylene-O-,

$\mathbf{R^5}$ denotes H, HO, C_{1-8}-alkyl, a C_{3-7}-cycloalkyl group optionally substituted by C_{1-3}-alkyl, H_2N, C_{1-4}-alkyl-NH, (C_{3-6}-cycloalkyl)-NH, (C_{1-4}-alkyl)$_2$N, (C_{1-4}-alkyl)(C_{3-6}-cycloalkyl)N, (cyclopropylmethyl)(methyl)N, H_2N-C(O), a phenyl group mono- or disubstituted by $\mathbf{R^{5.1}}$, a heteroaryl group mono- or disubstituted by $\mathbf{R^{5.1}}$ or a 4- to 7-membered saturated heterocyclic ring mono- or disubstituted by $\mathbf{R^{5.1}}$, while the groups $\mathbf{R^{5.1}}$ may in each case be identical or different and

$\mathbf{R^{5.1}}$ denotes H, F, Cl, Br, I, C_{1-3}-alkyl, HO, C_{1-3}-alkyl-O, (C_{1-3}-alkyl)$_2$N or C_{1-3}-alkyl-O-C_{2-4}-alkylene-O-,

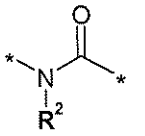
the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

2. Compounds of general formula **I** according to claim 1, wherein

A denotes a bond, C_{1-4}-alkylene or $-CH_2-C(O)$,

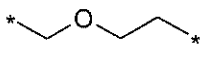
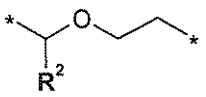
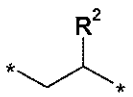
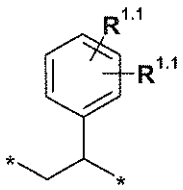
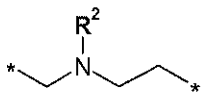
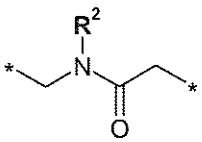
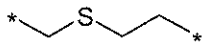
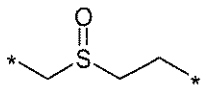
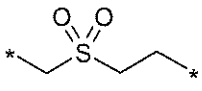
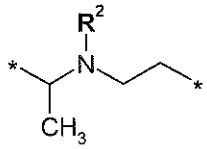
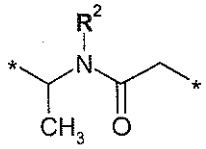
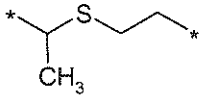
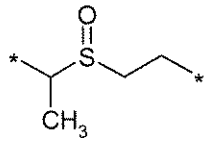
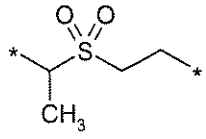
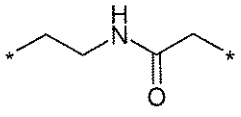
B denotes a bond, C_{1-2}-alkylene, -O or -C(O),

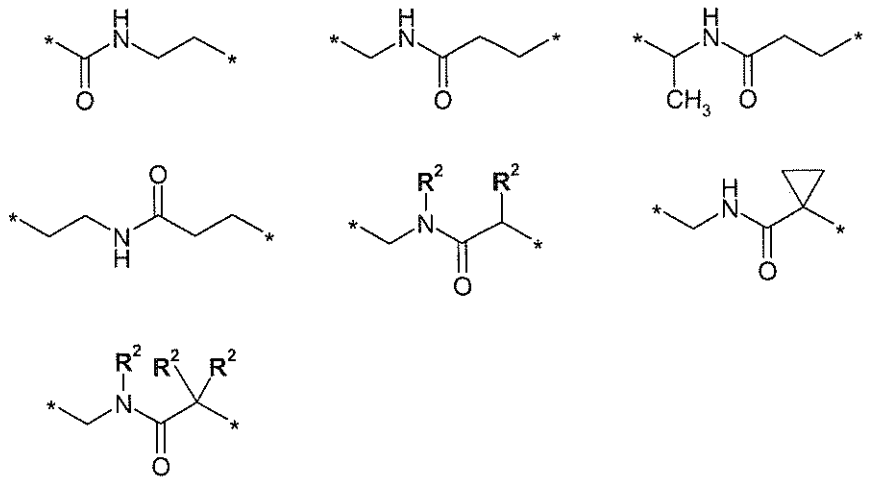
D denotes a group of general formula **II**



,

Y denotes C_{1-4}-alkylene or a group selected from

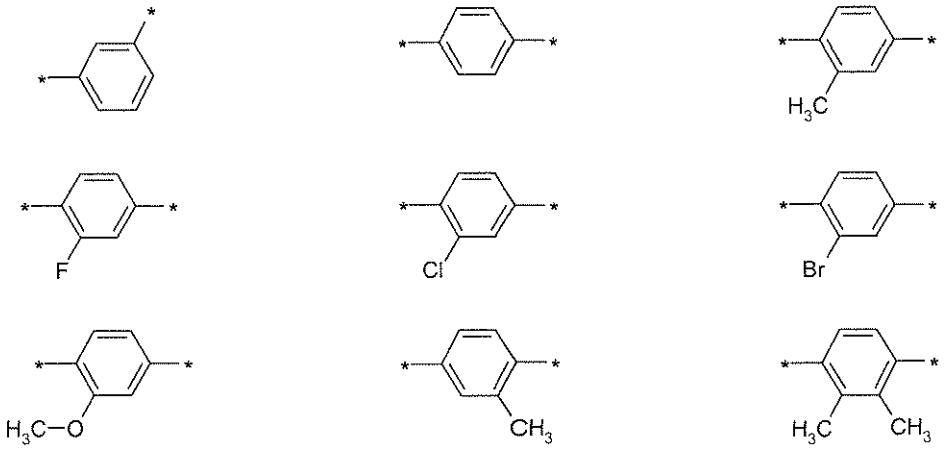


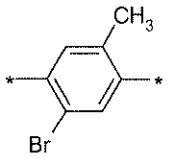
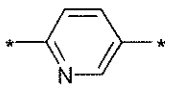
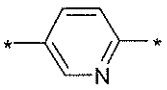
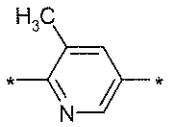
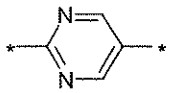
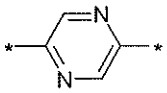
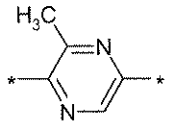
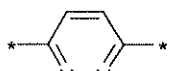
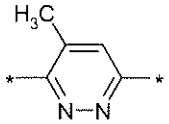
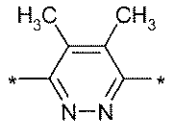
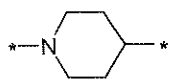
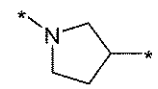
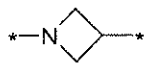
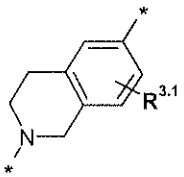
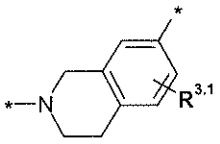
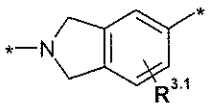
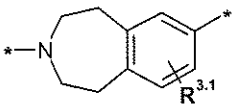
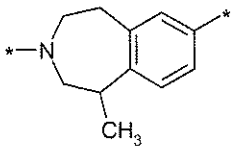
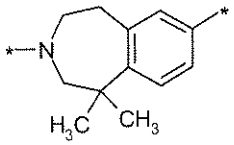
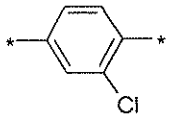
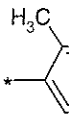
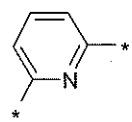
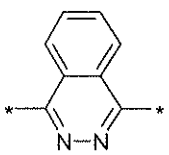
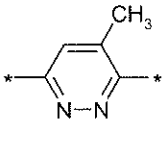
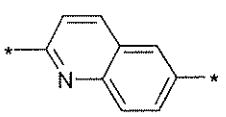
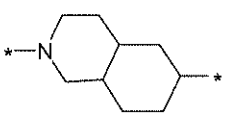
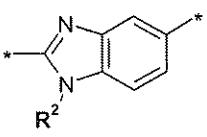
R¹ denotes aryl or heteroaryl, each of which may be substituted by one, two, three or four groups **R^1.1**, while the groups **R^1.1** may be identical or different and

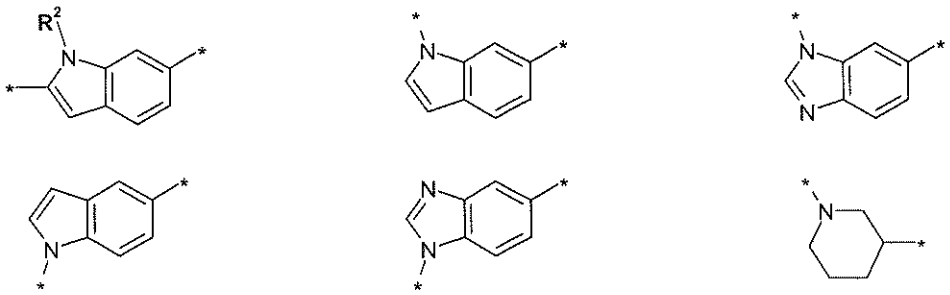
R^1.1 denotes H, F, Cl, Br, I, C_{1-3}-alkyl, F_3C, HO, C_{1-3}-alkyl-O or C_{1-3}-alkyl-O-C_{2-4}-alkylene-O-,

R² denotes H, H_3C, H_5C_2, isopropyl, F_3C-CH_2, F_2CH-CH_2 or FH_2C-H_2C,

R³ denotes C_{1-4}-alkylene, -N(**R²**) or a group selected from



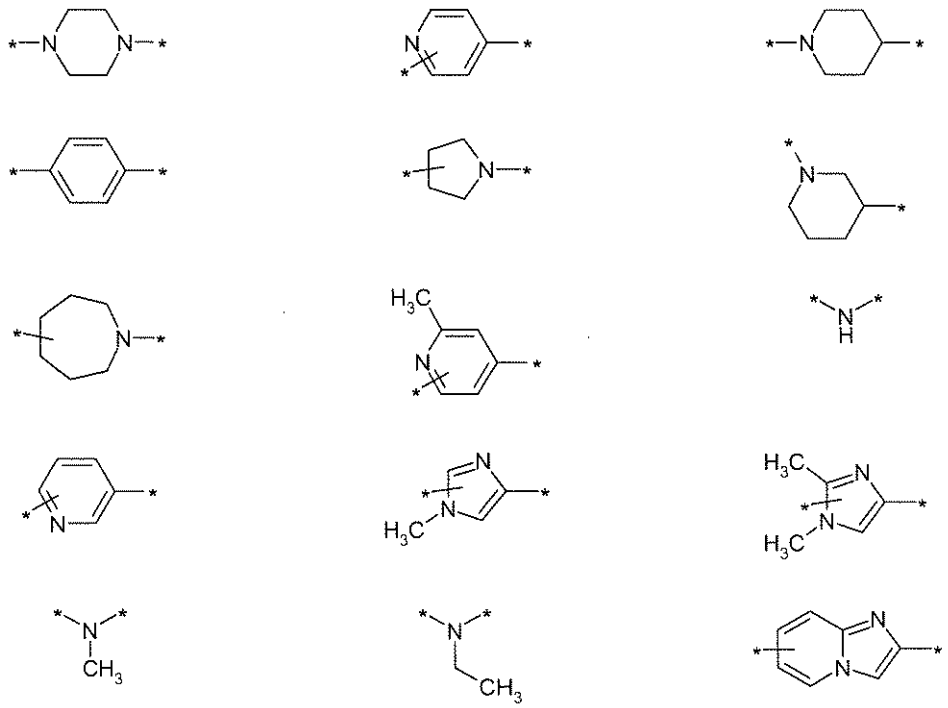


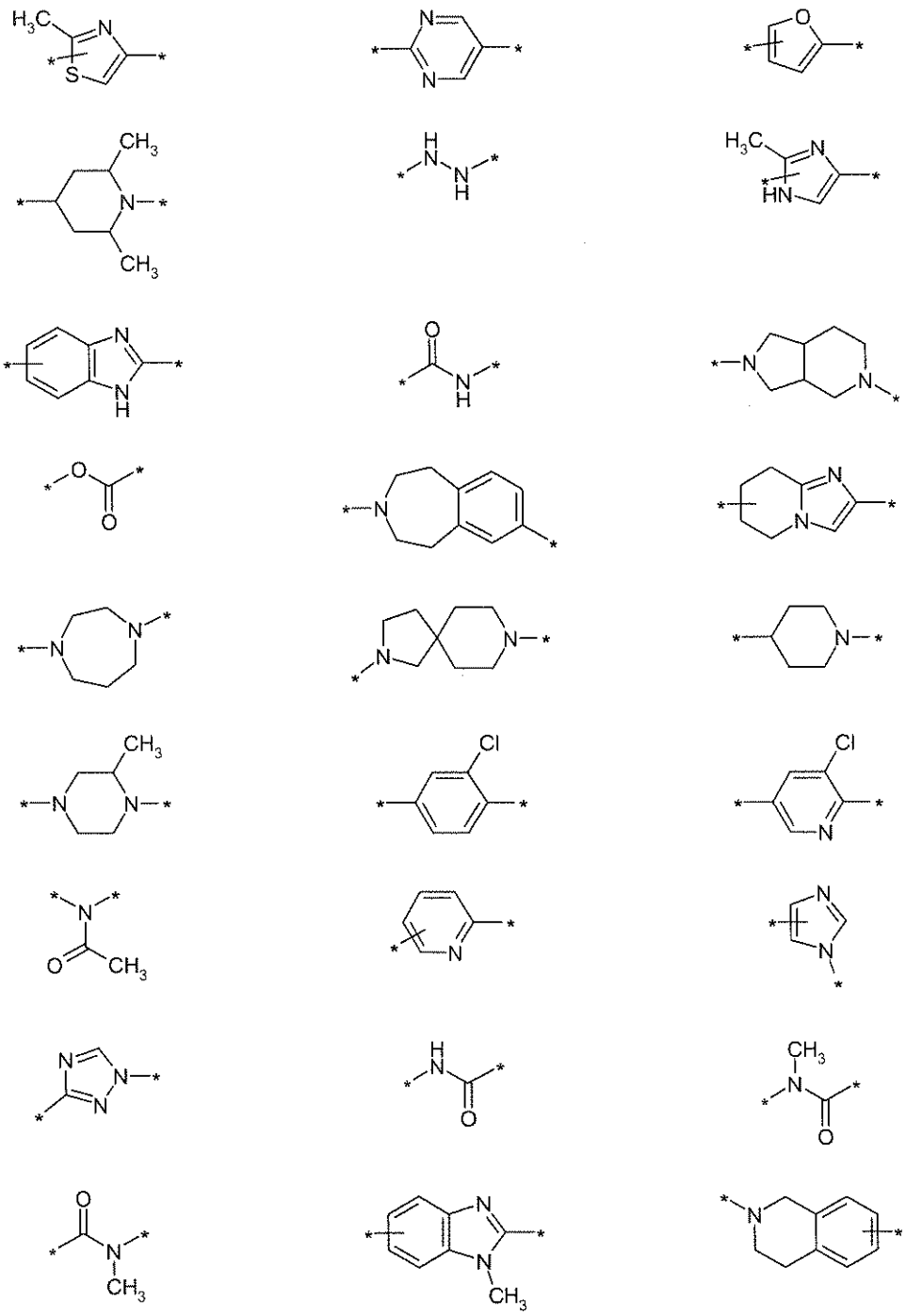
wherein

$R^{3.1}$ denotes H, F, Cl, Br, I, C_{1-3}-alkyl, HO, C_{1-3}-alkyl-O or C_{1-3}-alkyl-O-C_{2-4}-alkylene-O-, or

R^3 also denotes -O, if **B** does not denote the group –O-,

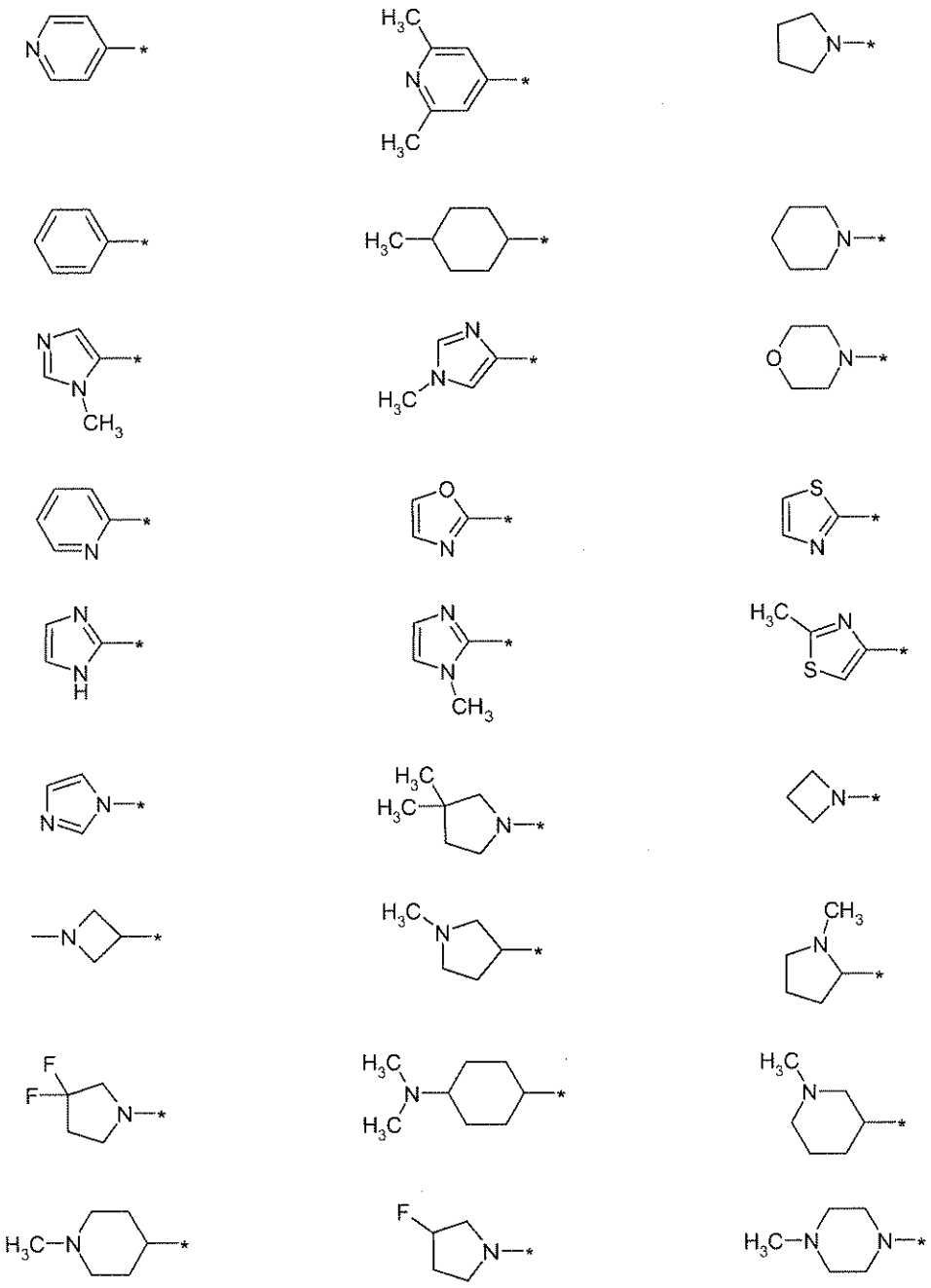
R^4 denotes C_{1-4}-alkylene, C_{3-7}-cycloalkylene, -O or a group selected from





R^5 denotes H, C_{1-8}-alkyl, C_{3-7}-cycloalkyl, HO, (C_{1-3}-alkyl)-O, (C_{1-4}-alkyl)-NH, (C_{3-6}-cycloalkyl)-NH, (C_{1-4}-alkyl)$_2$N, (C_{1-4}-alkyl)(C_{3-6}-cycloalkyl)N, (cyclopropylmethyl)(methyl)N, H_2N-C(O), or

R^5 denotes a group selected from



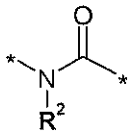
the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

3. Compounds of general formula **I** according to claim 1, wherein

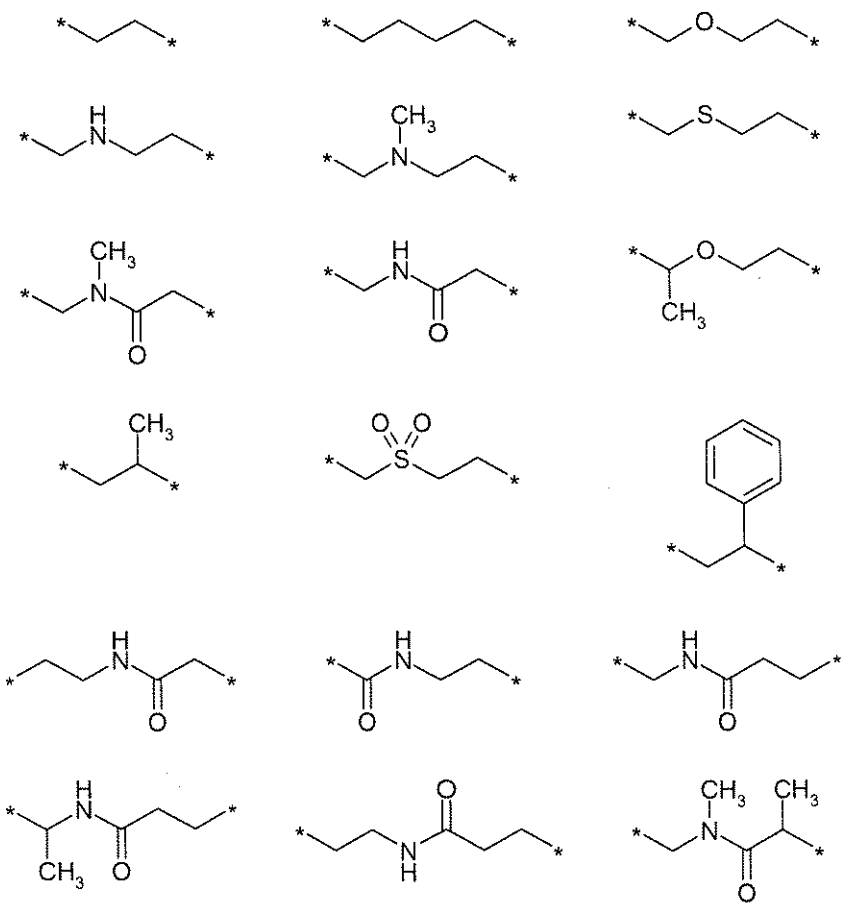
A denotes a bond, C_{1-3}-alkylene or $-CH_2-C(O)$,

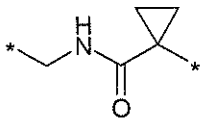
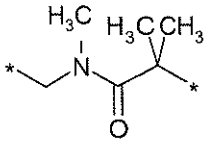
B denotes a bond, C_{1-2}-alkylene, -O or -C(O),

D denotes a group of general formula **II**


,

Y denotes a group selected from



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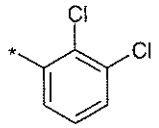
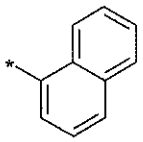
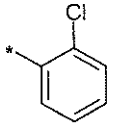
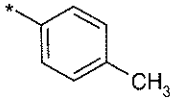
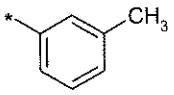
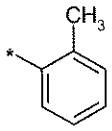
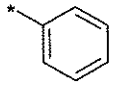
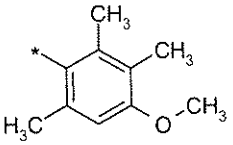
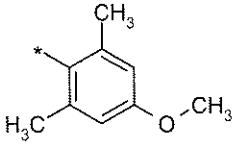
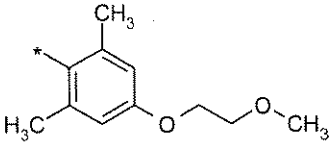
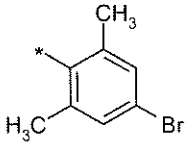
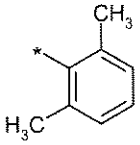
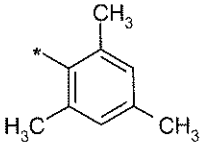
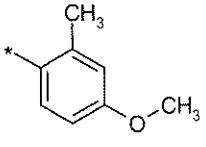
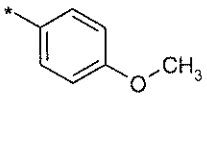
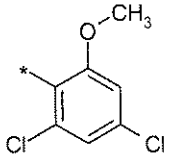
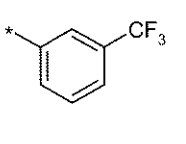
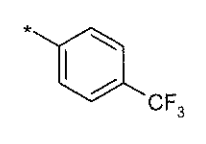
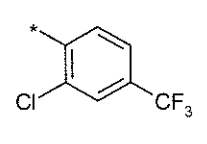
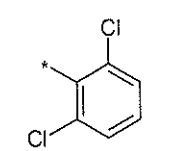
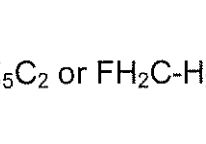
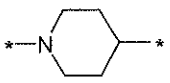
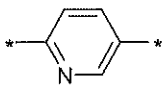
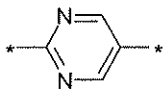
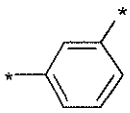
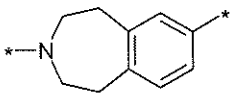
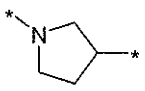
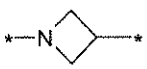
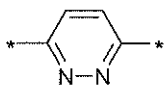
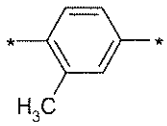
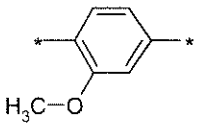
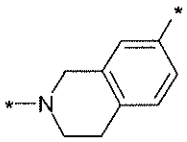
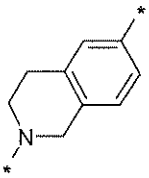
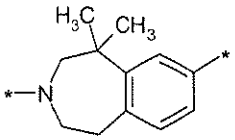
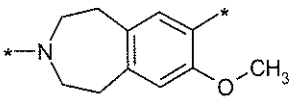
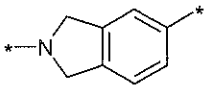
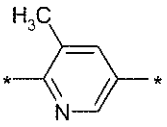
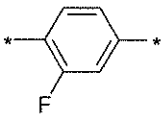
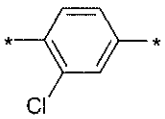
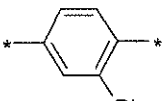
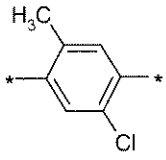
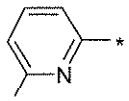
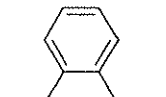
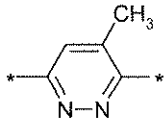
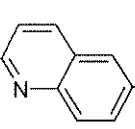
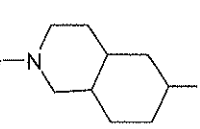
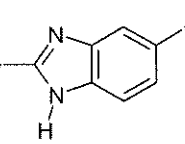
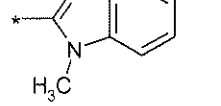
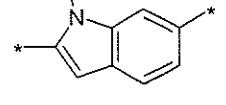
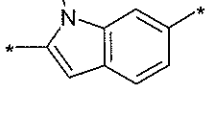
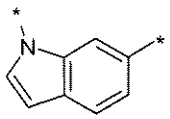
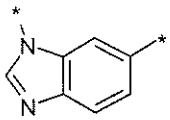
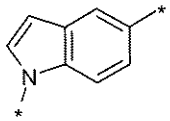
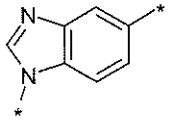
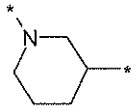























R[2] denotes H, H_3C, H_5C_2 or FH_2C-H_2C,

R[3] denotes C_{1-4}-alkylene, -NH, -N(CH_3) or a group selected from

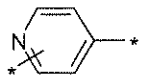
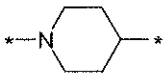
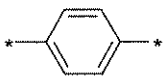
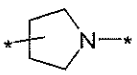
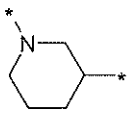
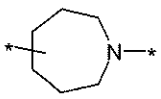
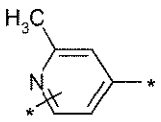






























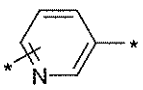
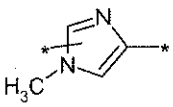
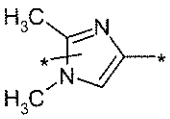






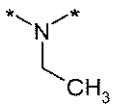
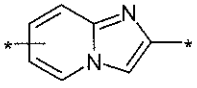
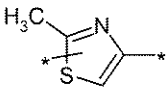
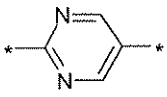
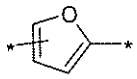
or

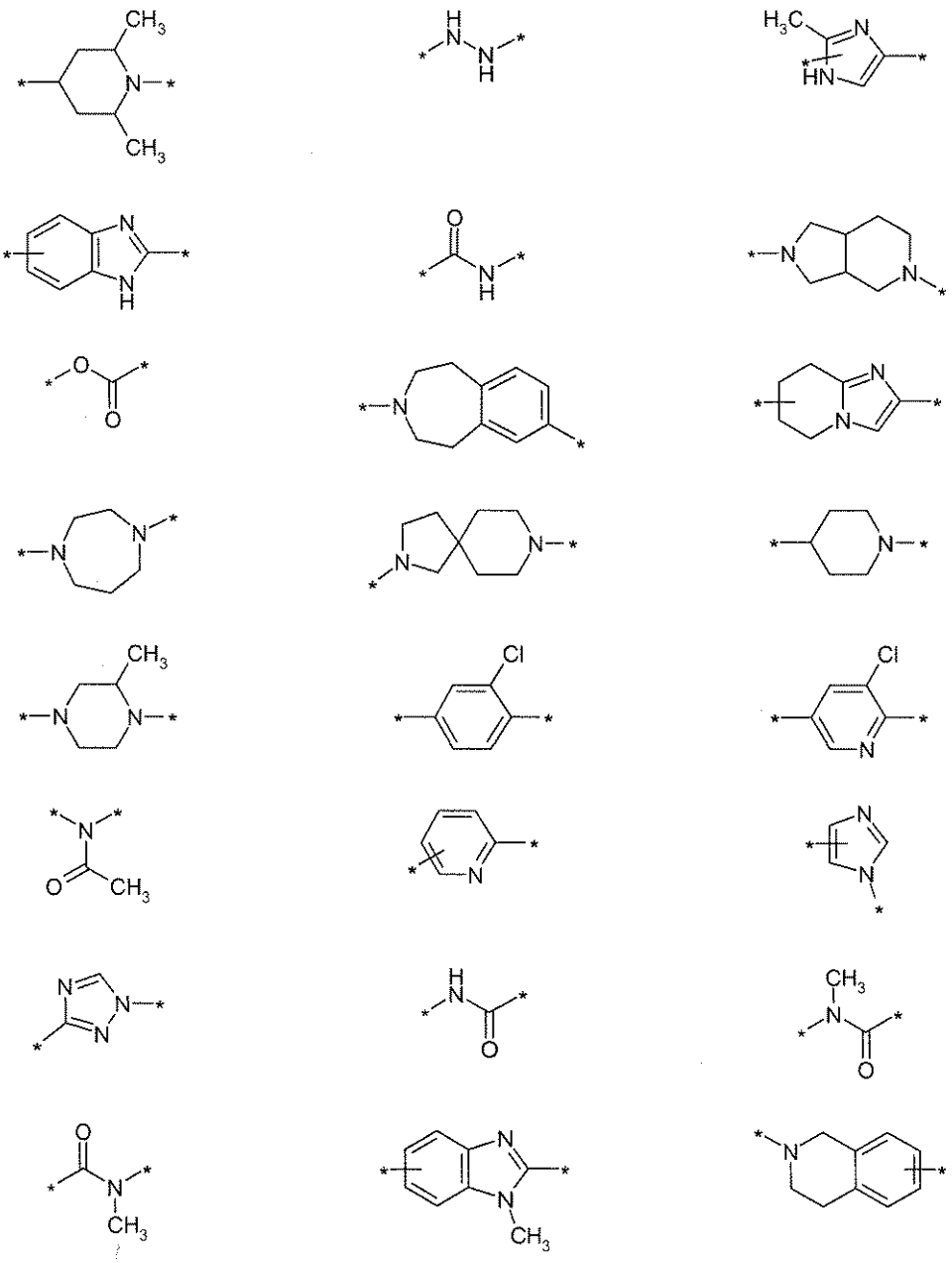
R^3 also denotes -O, if **B** does not denote the group –O-,

R^4 denotes C_{1-4}-alkylene, C_{3-7}-cycloalkylene, -O or a group selected from

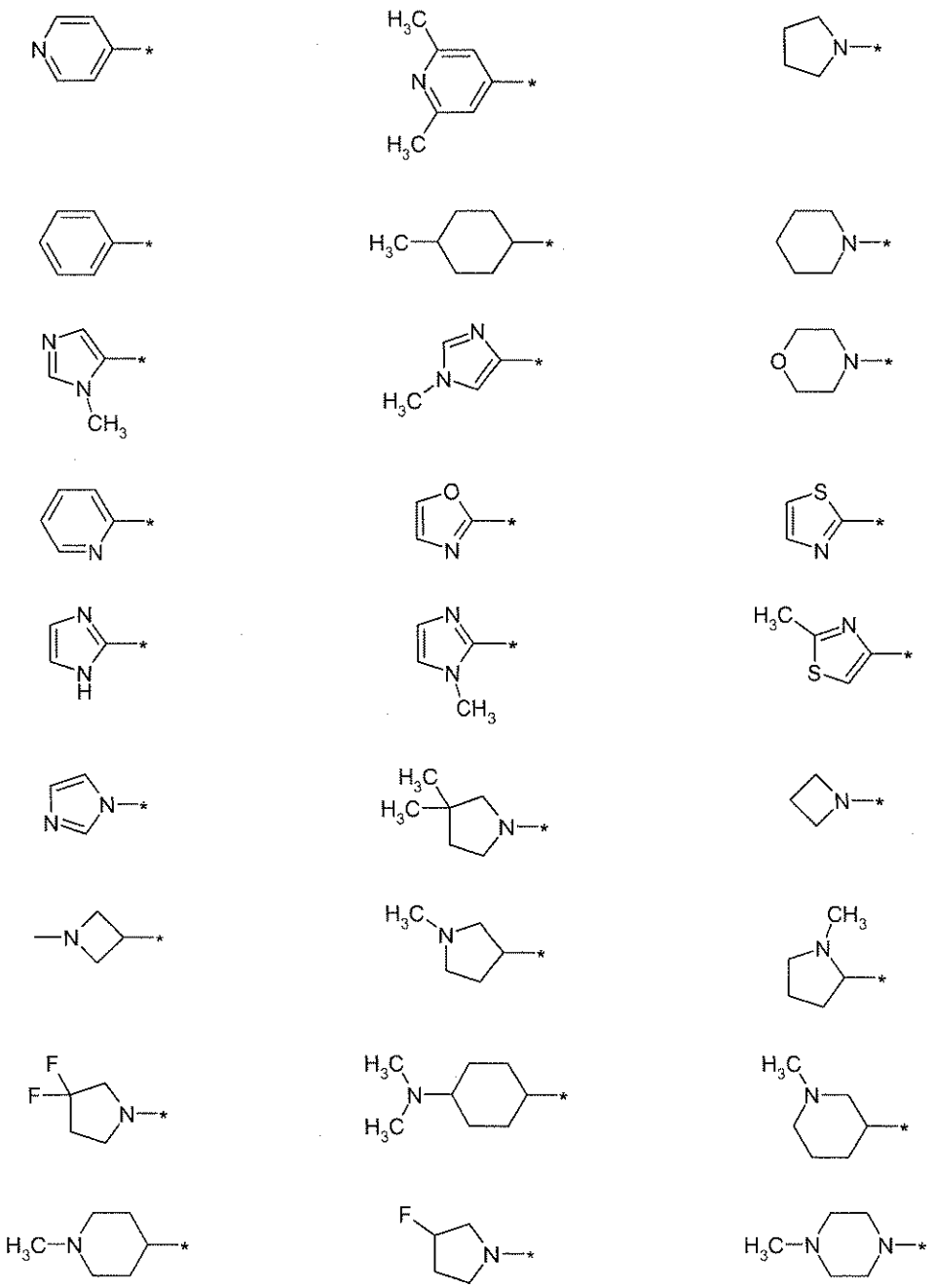






R⁵ denotes H, HO, C_{1-5}-alkyl, C_{3-5}-cycloalkyl, H_2N, (C_{1-2}-alkyl)-NH, (C_{3-6}-cycloalkyl)-NH, (C_{1-2}-alkyl)$_2$N, (C_{1-4}-alkyl)(C_{3-6}-cycloalkyl)N, (cyclopropylmethyl)(methyl)N, H_2N-C(O), or

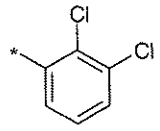
R⁵ denotes a group selected from



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

4. Compounds of general formula **I** according to claim 1, wherein

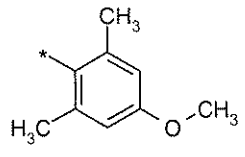
A, **B**, **D**, **Y**, R^2, R^3, R^4 and R^5 are defined as in claim 1 and

R^1 denotes the group  ,

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

5. Compounds of general formula **I** according to claim 1, wherein

A, **B**, **D**, **Y**, R^2, R^3, R^4 and R^5 are defined as in claim 1 and

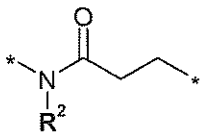
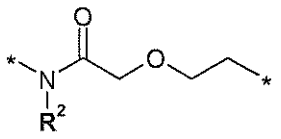
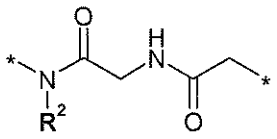
R^1 denotes the group  ,

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

6. Compounds of general formula **I** according to claim 1, wherein

A, **B**, R^1, R^3, R^4 and R^5 are defined as in claim 1 and

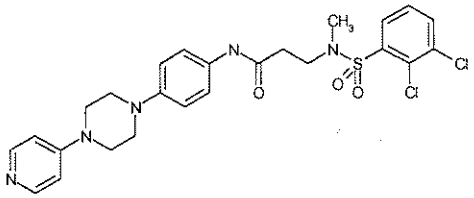
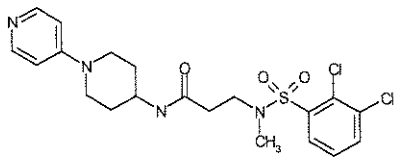
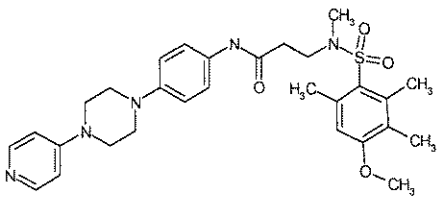
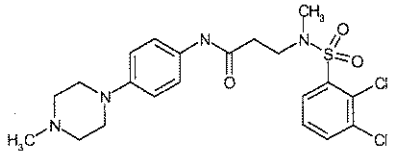
-D-Y- together denote a group selected from

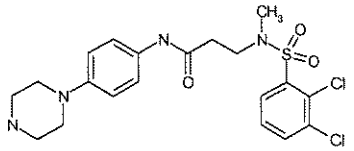
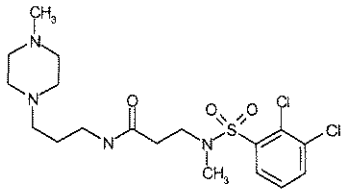
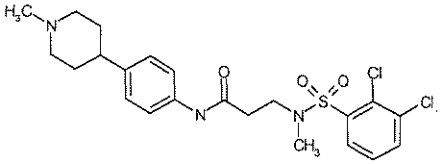
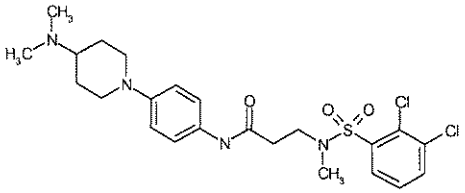
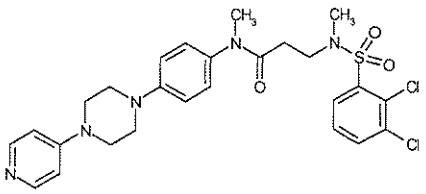
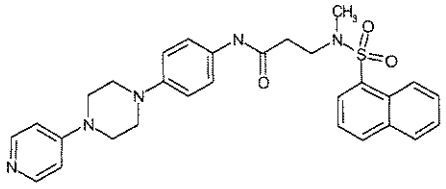
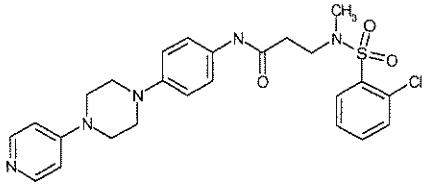
 ,  ,  , and

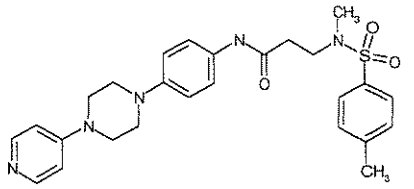
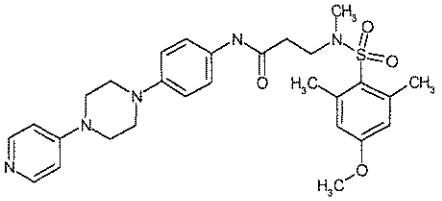
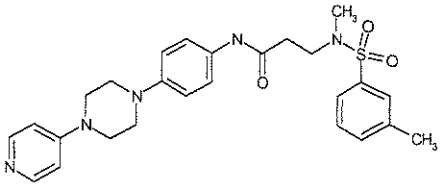
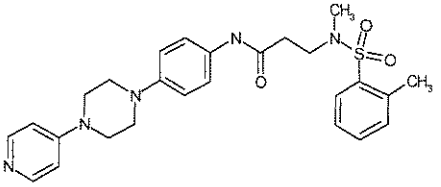
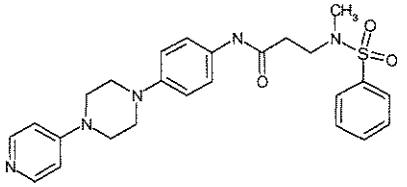
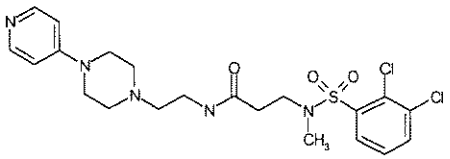
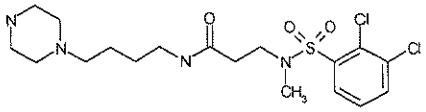
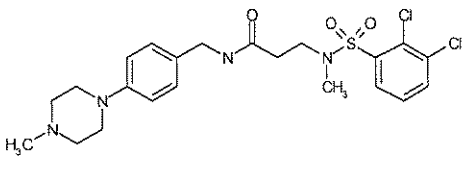
R^2 denotes H or C_{1-3}-alkyl,

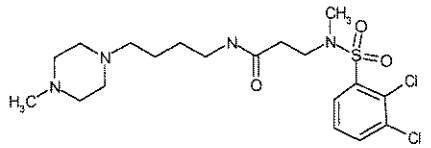
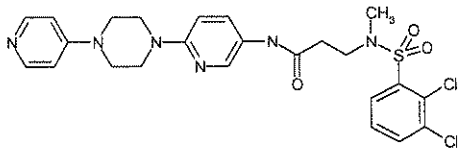
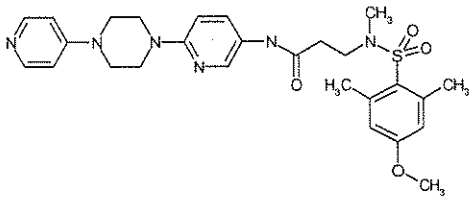
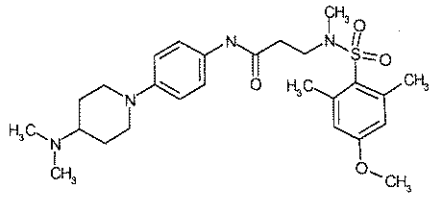
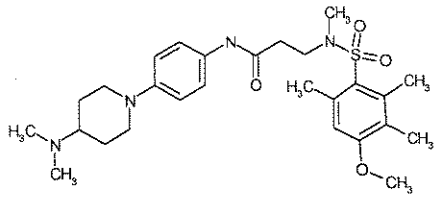
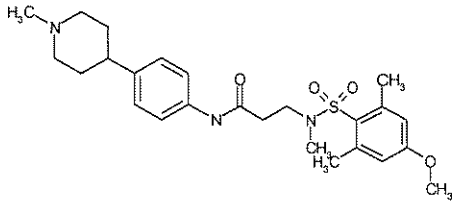
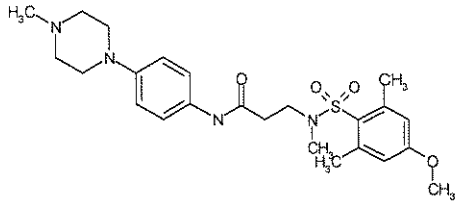
the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

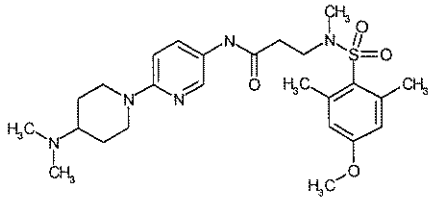
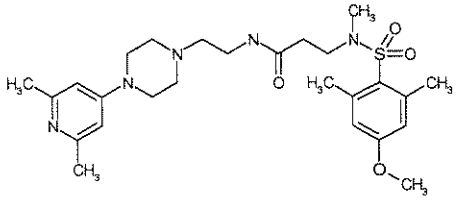
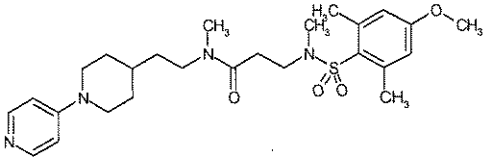
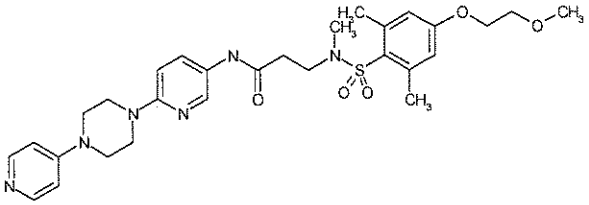
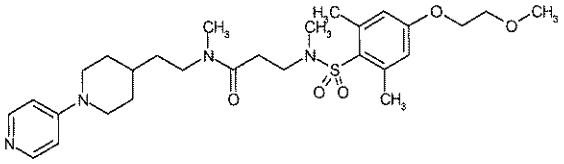
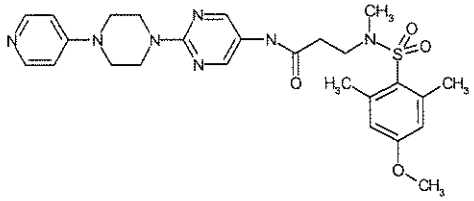
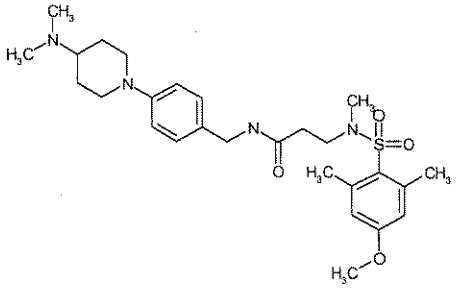
7. The following compounds of general formula **I** according to claim 1:

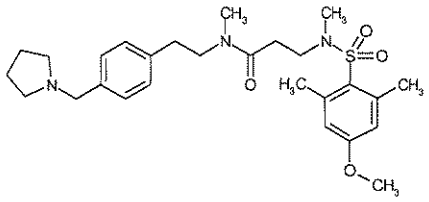
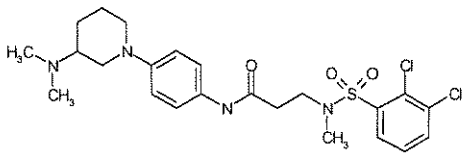
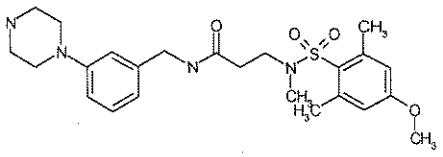
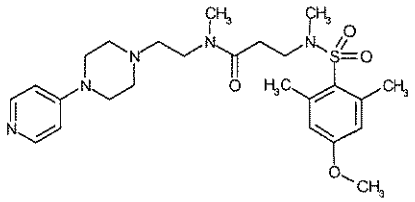
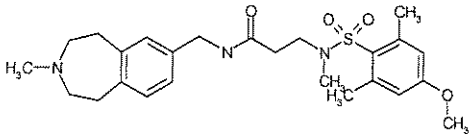
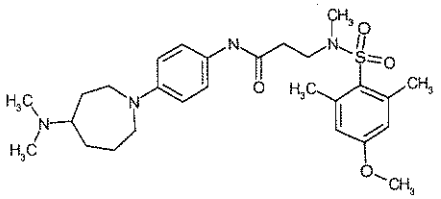
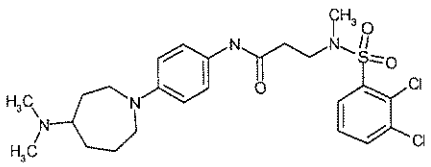
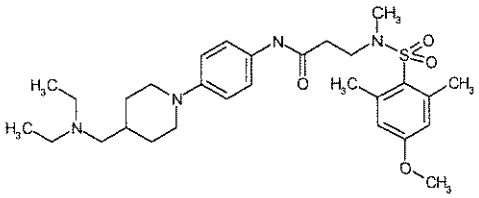
Example	Structure
(1)	
(2)	
(3)	
(4)	

Example	Structure
(5)	
(6)	
(7)	
(8)	
(9)	
(10)	
(11)	

Example	Structure
(12)	
(13)	
(14)	
(15)	
(16)	
(17)	
(18)	
(19)	

Example	Structure
(20)	
(21)	
(22)	
(23)	
(24)	
(25)	
(26)	

Example	Structure
(27)	
(28)	
(29)	
(30)	
(31)	
(32)	
(33)	

Example	Structure
(34)	
(35)	
(36)	
(37)	
(38)	
(39)	
(40)	
(41)	

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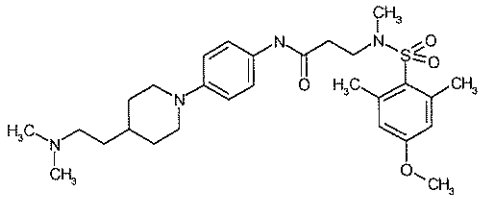
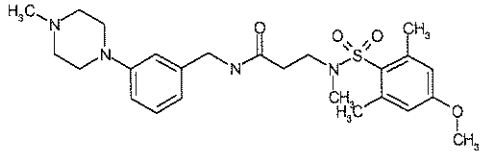
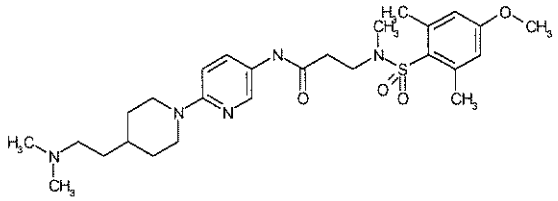
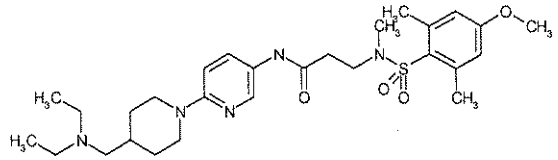
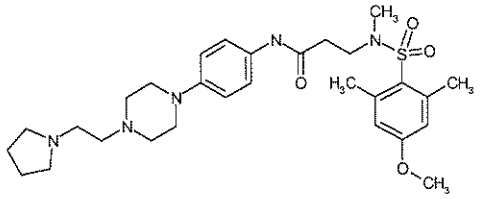
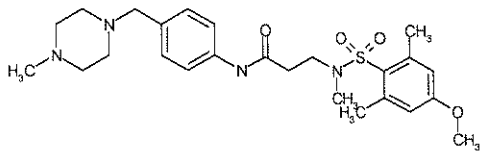
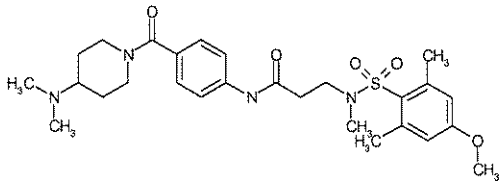
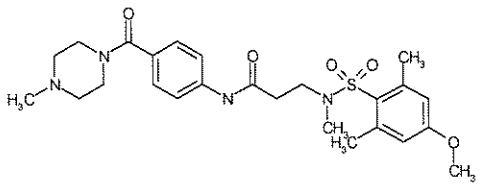
(42)	
(43)	
(44)	
(45)	
(46)	
(47)	
(48)	
(49)	

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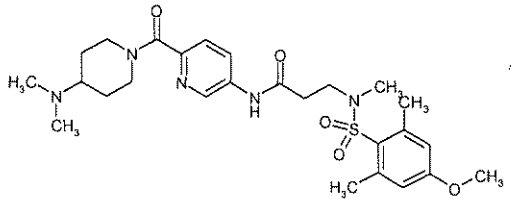
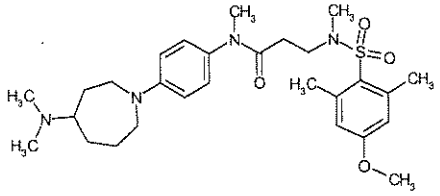
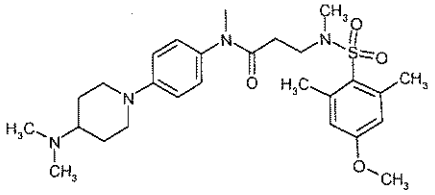
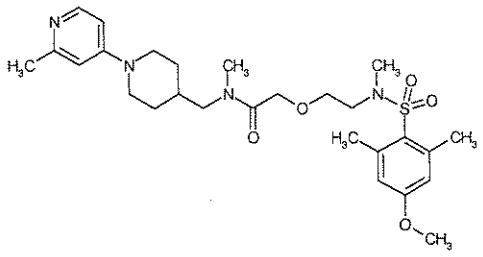
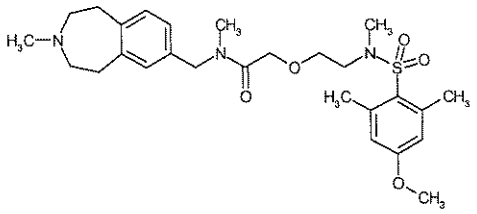
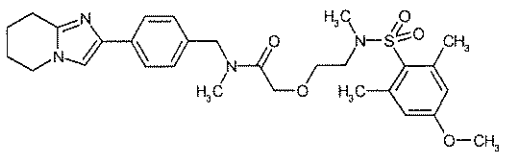
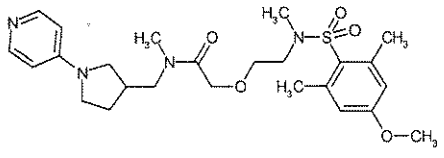
(50)	
(51)	
(52)	
(53)	
(54)	
(55)	
(56)	

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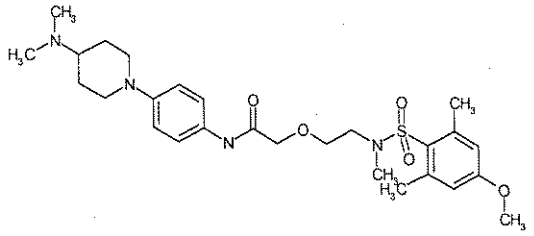
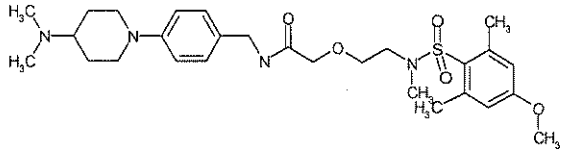
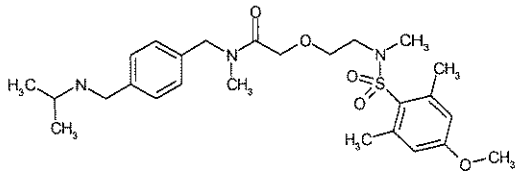
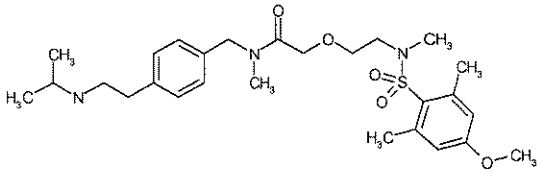
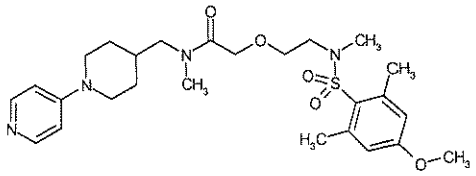
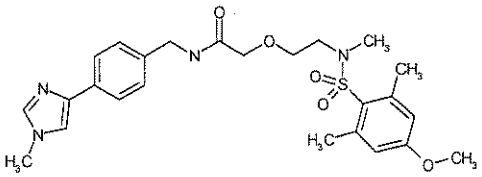
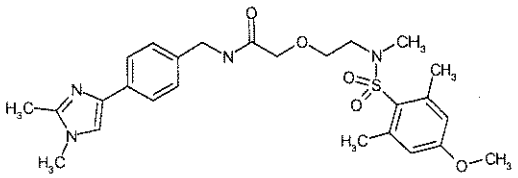
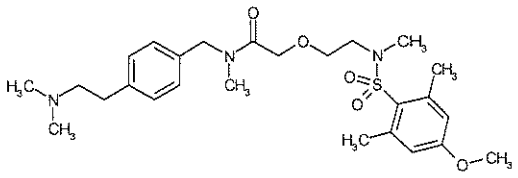
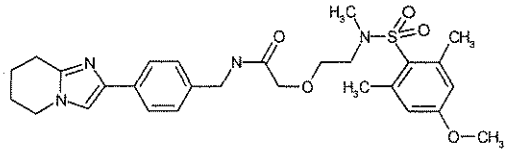
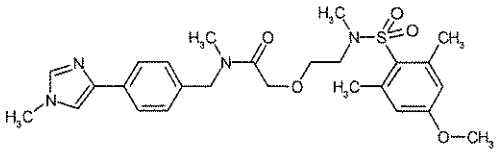
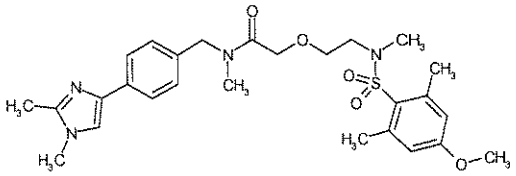
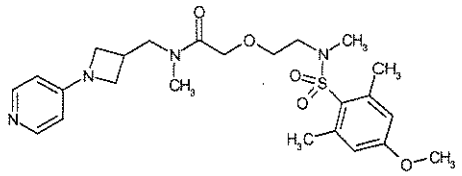
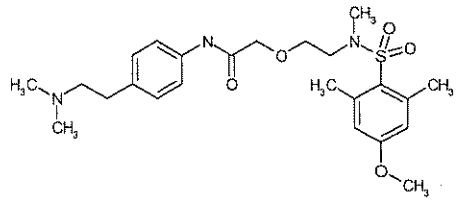
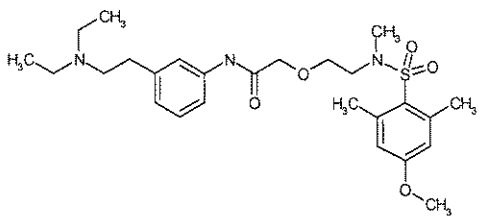
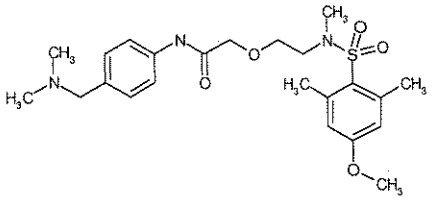
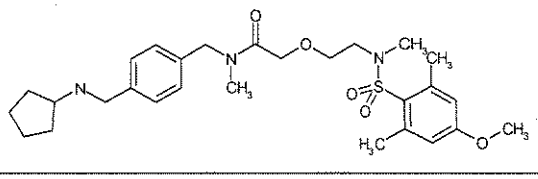
(57)	
(58)	
(59)	
(60)	
(61)	
(62)	
(63)	
(64)	

Example	Structure
(65)	
(66)	
(67)	
(68)	
(69)	
(70)	
(71)	
(72)	

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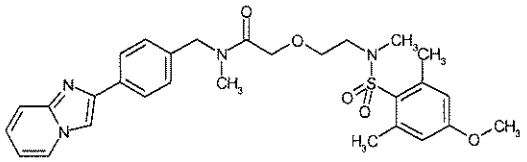
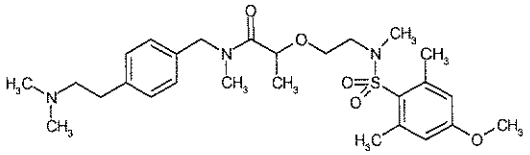
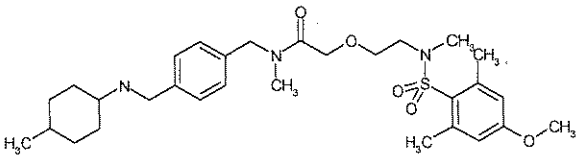
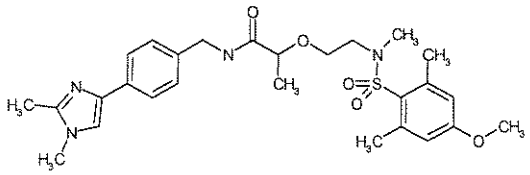
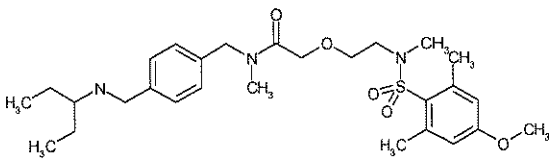
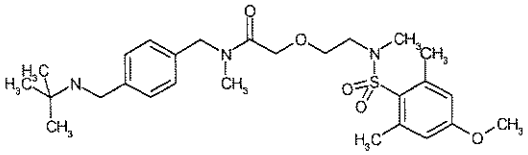
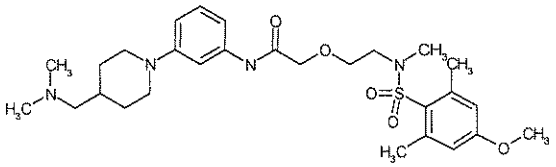
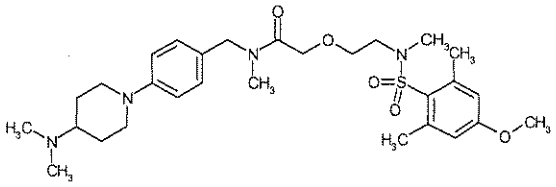
(73)	
(74)	
(75)	
(76)	
(77)	
(78)	
(79)	
(80)	

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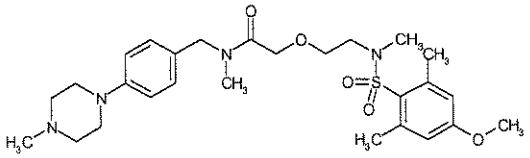
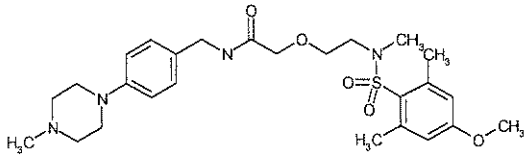
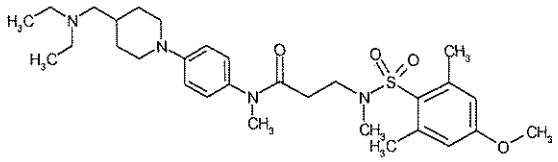
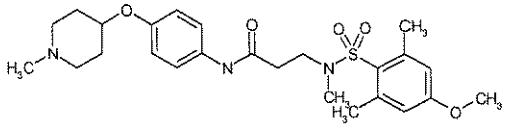
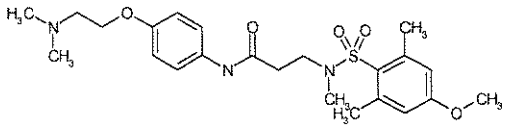
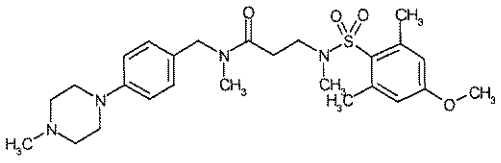
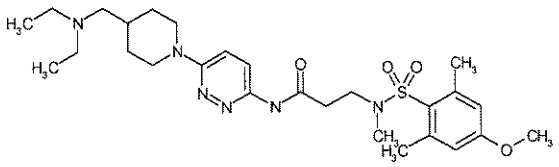
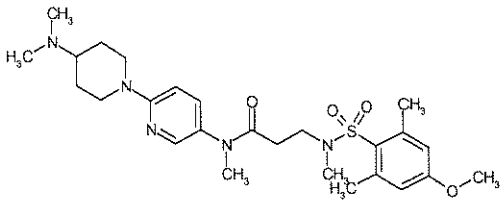
(81)	
(82)	
(83)	
(84)	
(85)	
(86)	
(87)	
(88)	

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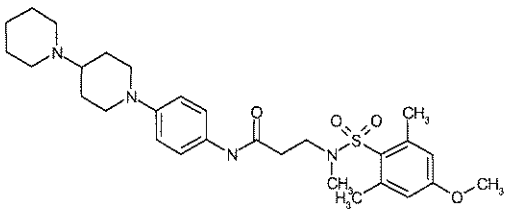
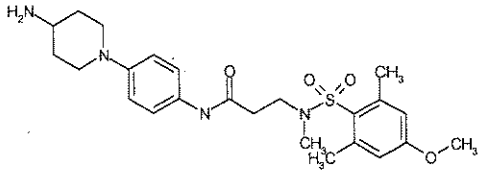
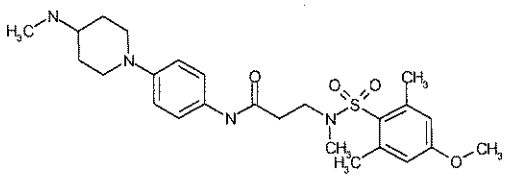
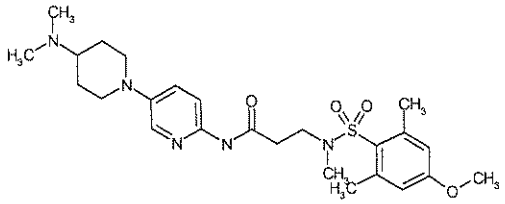
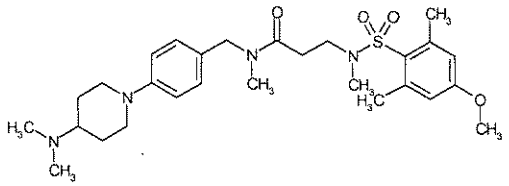
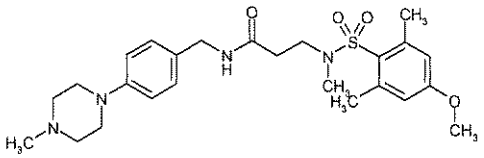
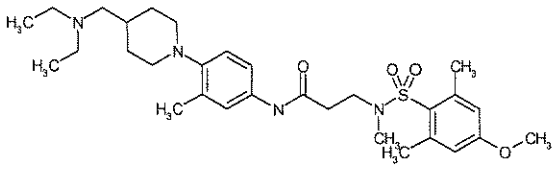
(89)	
(90)	
(91)	
(92)	
(93)	
(94)	
(95)	

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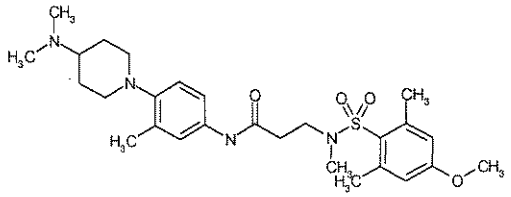
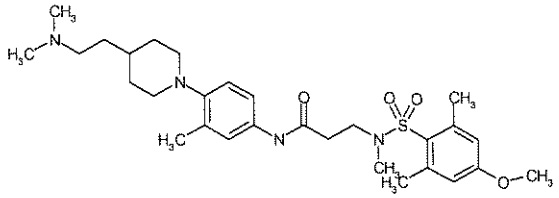
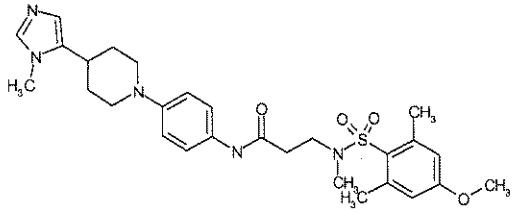
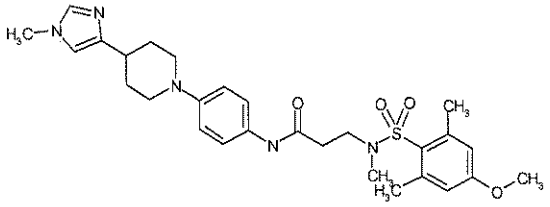
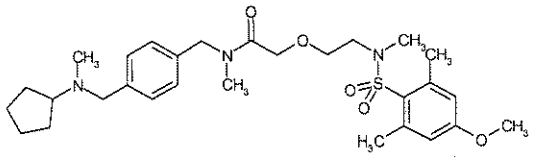
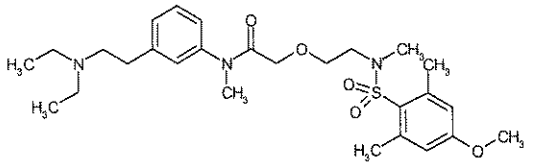
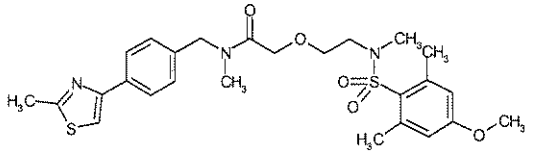
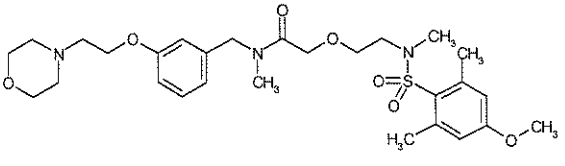
(96)	
(97)	
(98)	
(99)	
(100)	
(101)	
(102)	
(103)	

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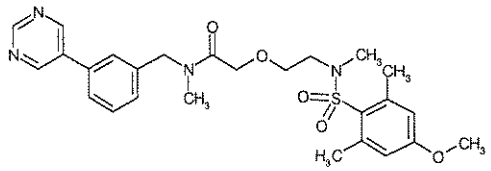
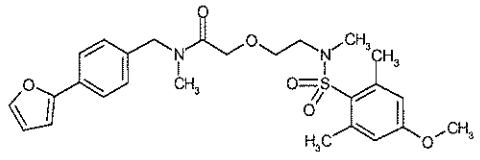
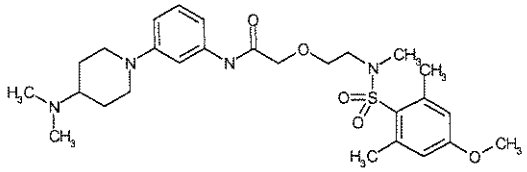
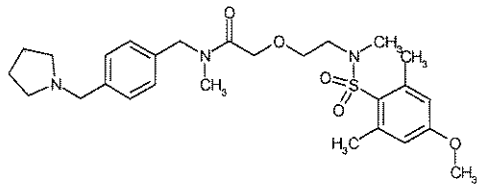
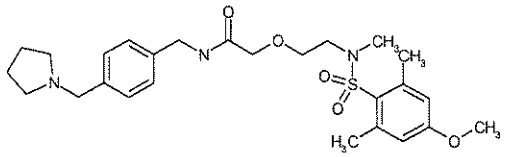
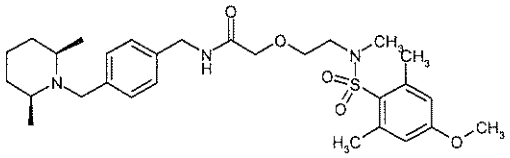
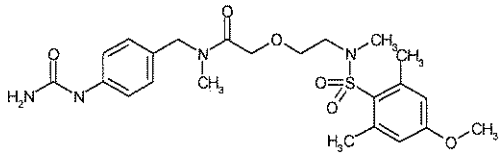
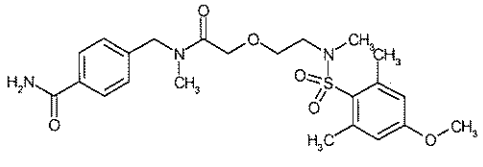
(104)	
(105)	
(106)	
(107)	
(108)	
(109)	
(110)	
(111)	

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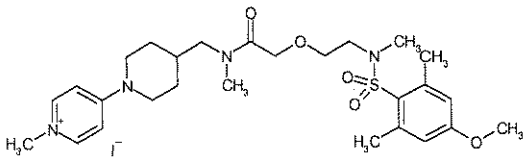
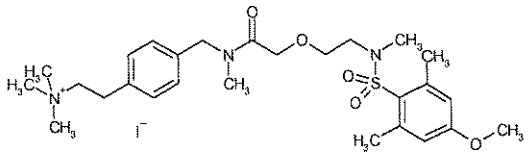
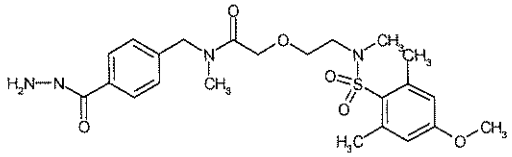
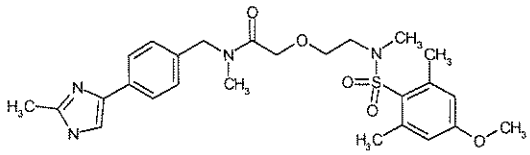
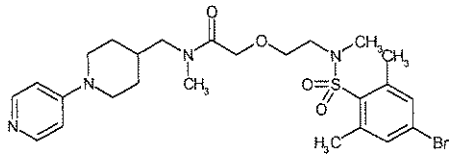
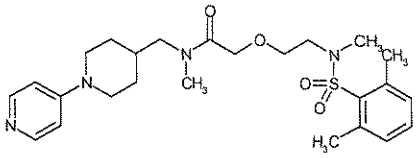
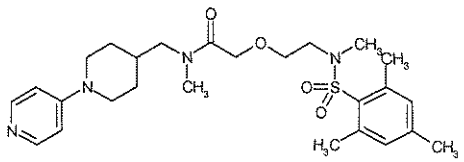
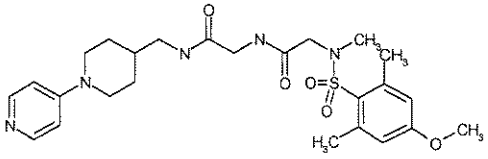
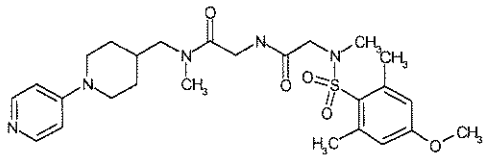
(112)	
(113)	
(114)	
(115)	
(116)	
(117)	
(118)	
(119)	
(120)	

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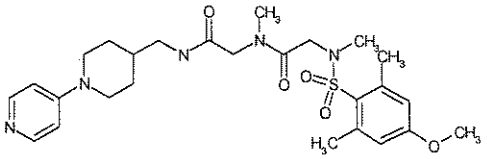
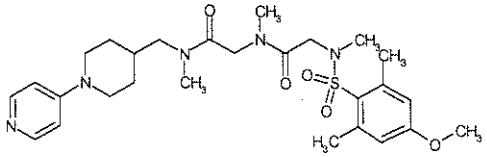
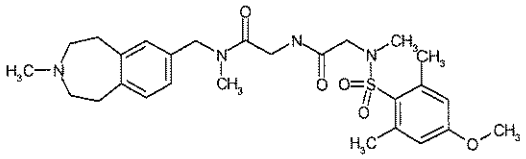
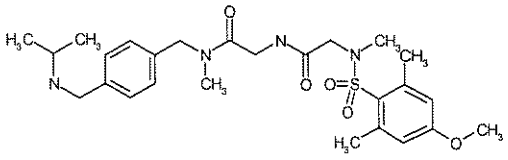
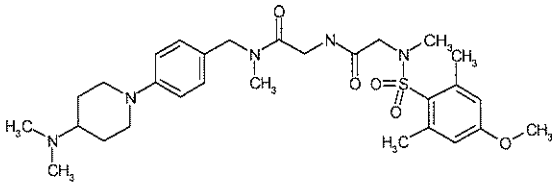
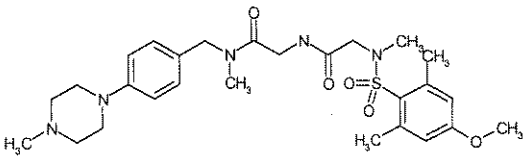
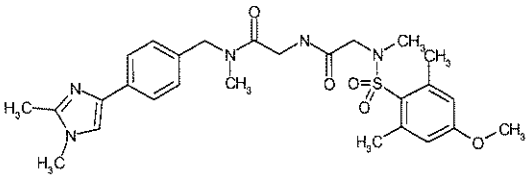
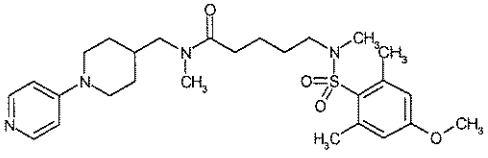
(121)	
(122)	
(123)	
(124)	
(125)	
(126)	
(127)	
(128)	

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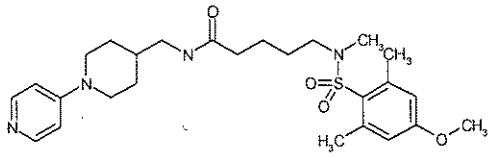
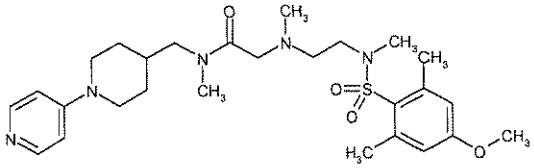
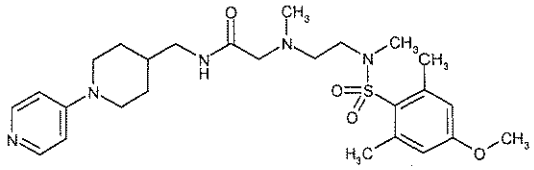
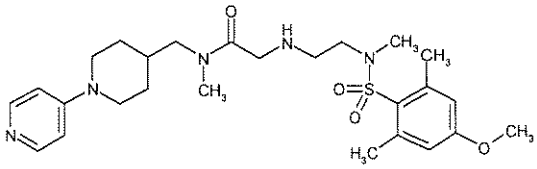
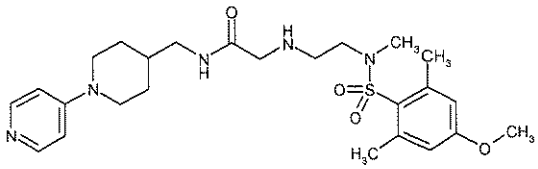
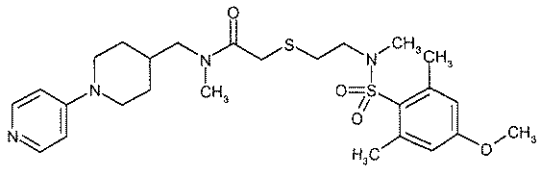
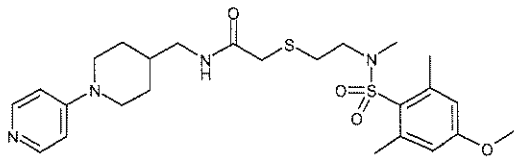
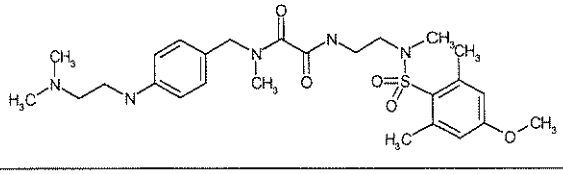
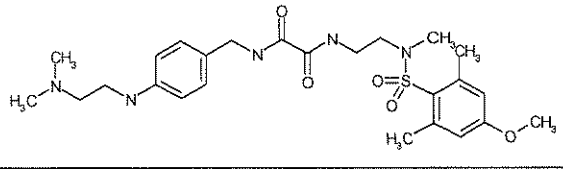
(129)	
(130)	
(131)	
(132)	
(133)	
(134)	
(135)	
(136)	
(137)	

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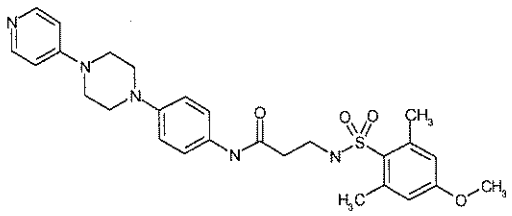
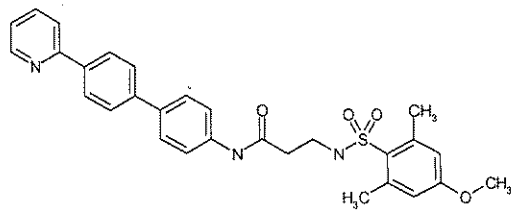
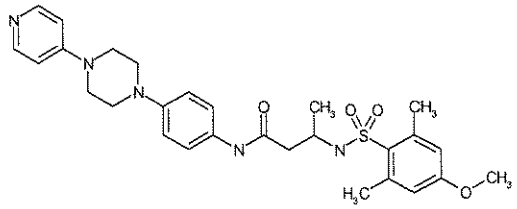
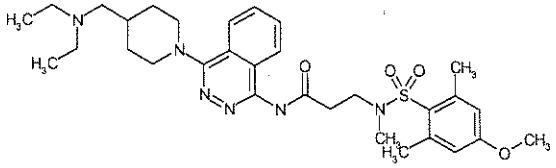
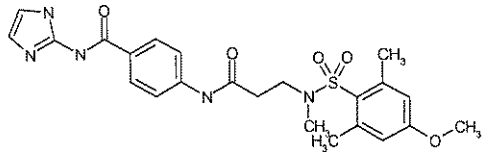
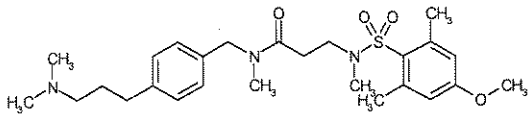
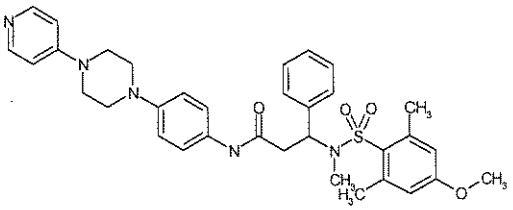
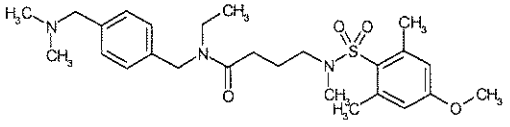
(138)	
(139)	
(140)	
(141)	
(142)	
(143)	
(144)	
(145)	

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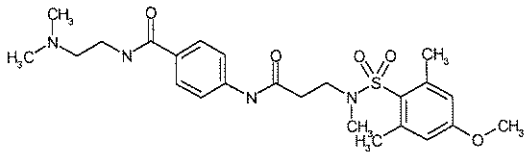
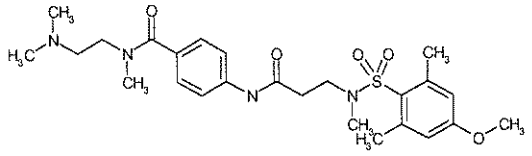
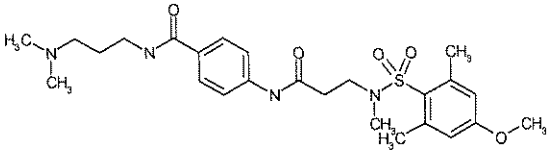
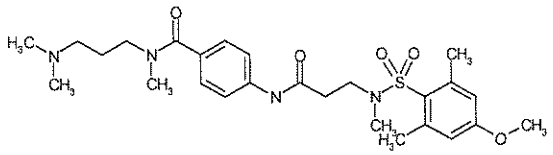
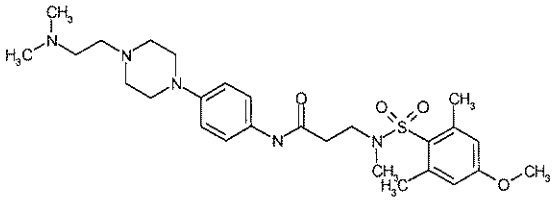
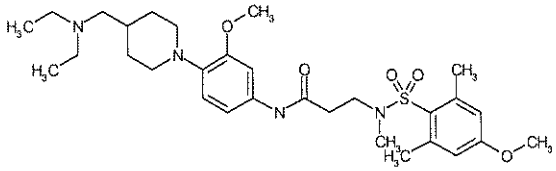
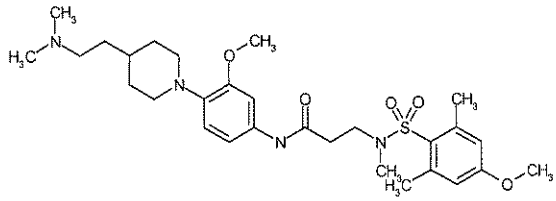
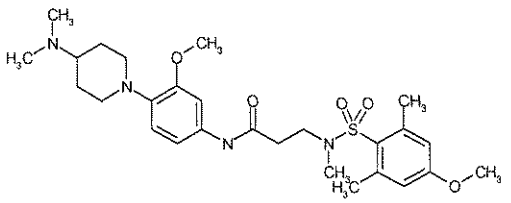
(146)	
(147)	
(148)	
(149)	
(150)	
(151)	
(152)	
(153)	

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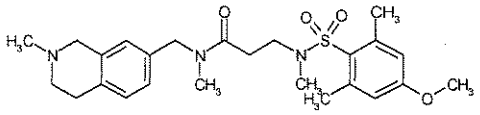
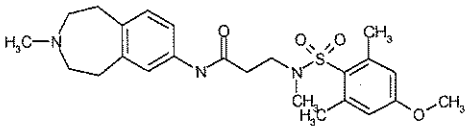
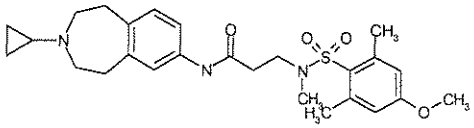
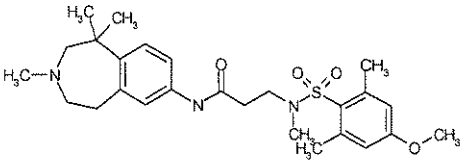
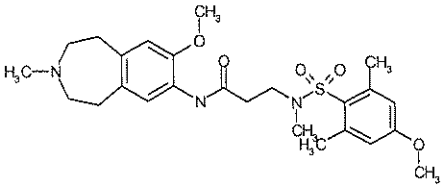
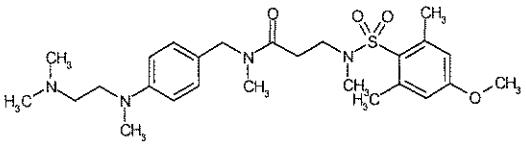
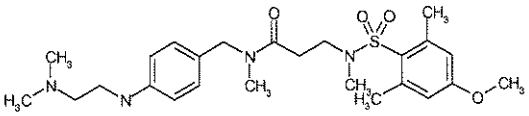
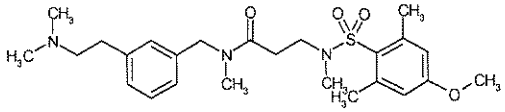
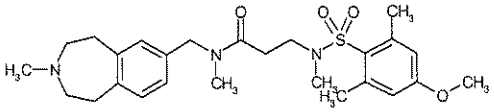
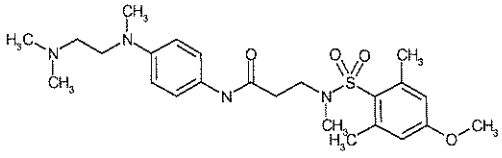
(154)	
(155)	
(156)	
(157)	
(158)	
(159)	
(160)	
(161)	
(162)	
(163)	

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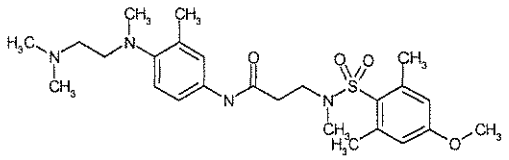
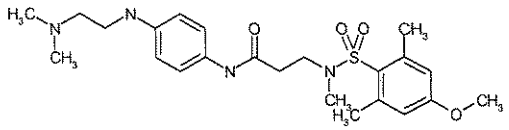
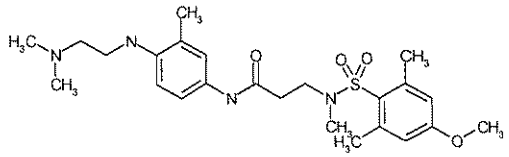
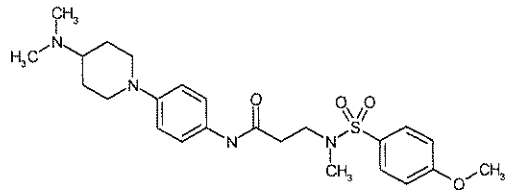
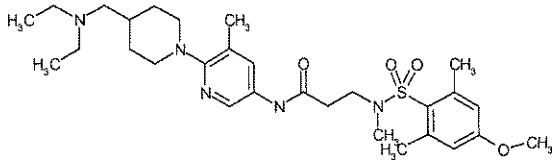
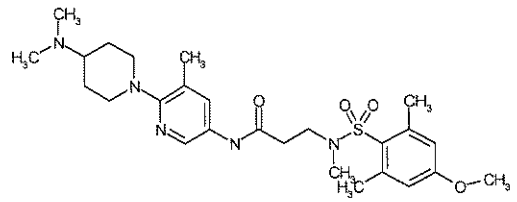
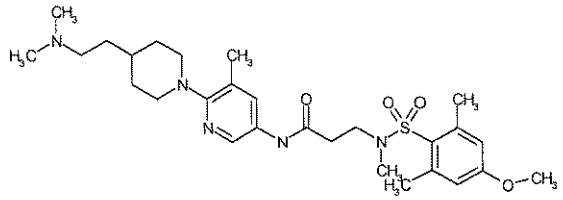
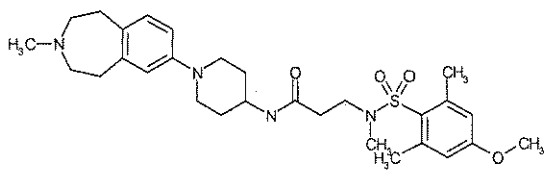
(164)	
(165)	
(166)	
(167)	
(168)	
(169)	
(170)	
(171)	

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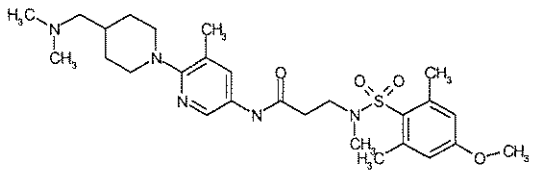
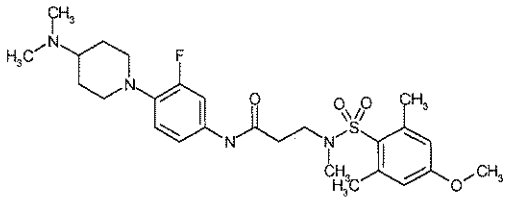
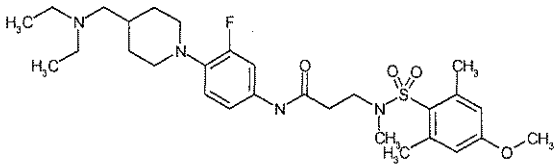
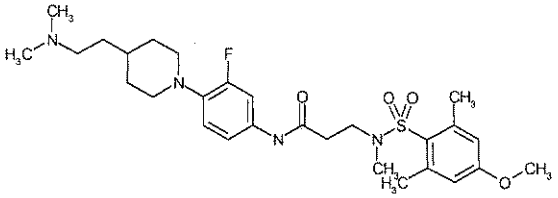
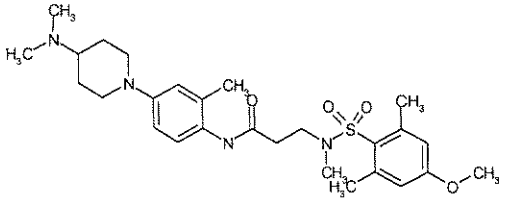
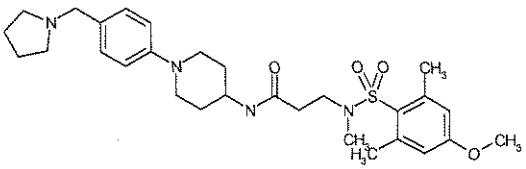
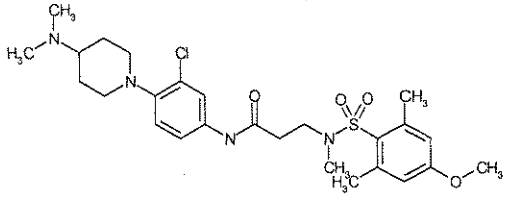
(172)	
(173)	
(174)	
(175)	
(176)	
(177)	
(178)	

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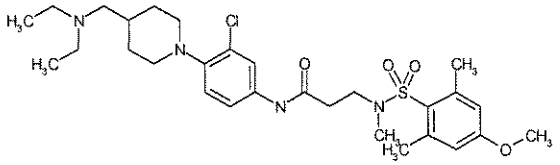
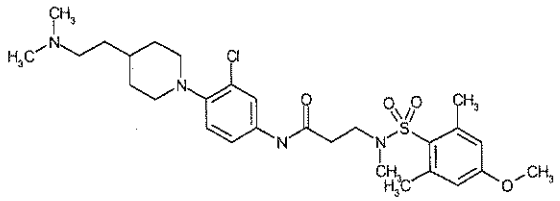
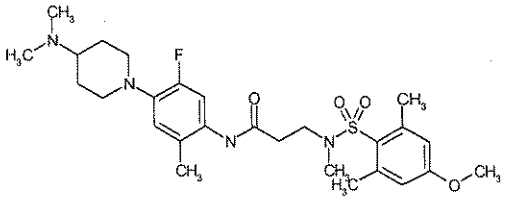
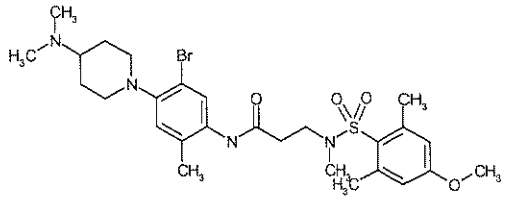
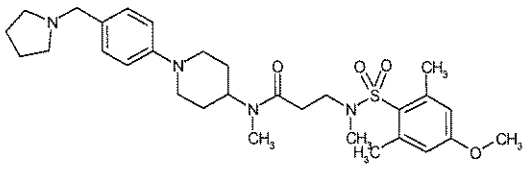
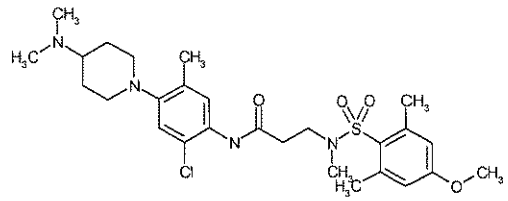
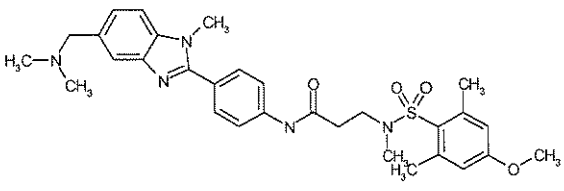
(179)	
(180)	
(181)	
(182)	
(183)	
(184)	
(185)	

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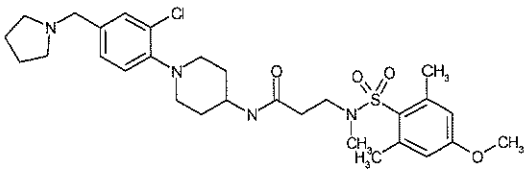
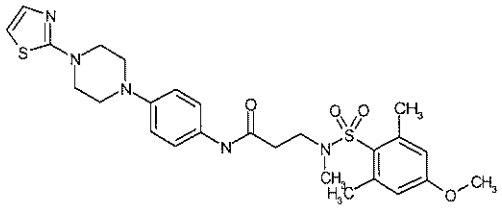
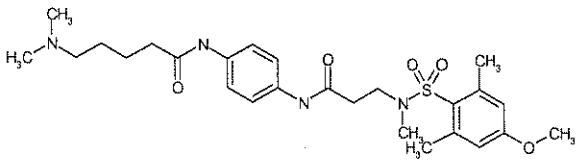
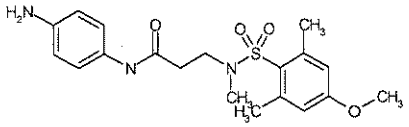
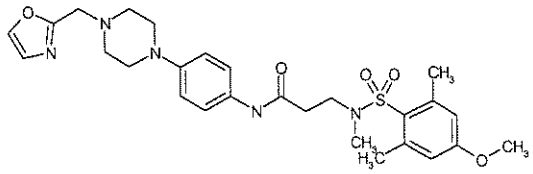
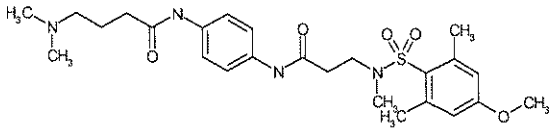
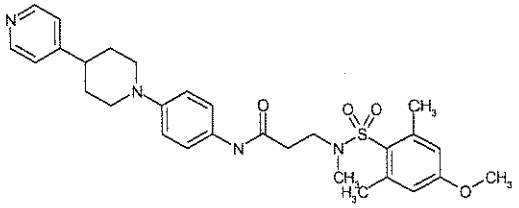
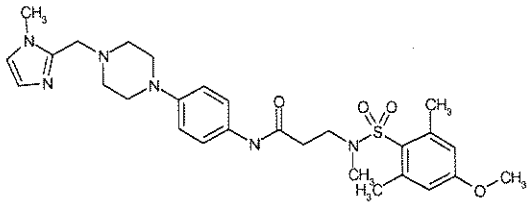
(186)	
(187)	
(188)	
(189)	
(190)	
(191)	
(192)	
(193)	

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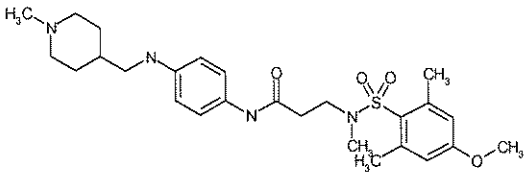
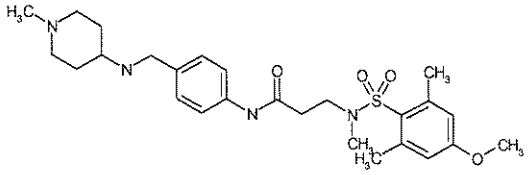
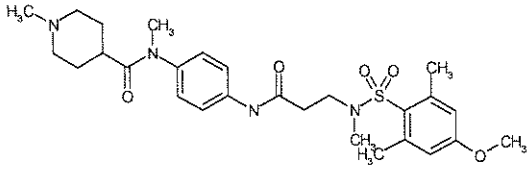
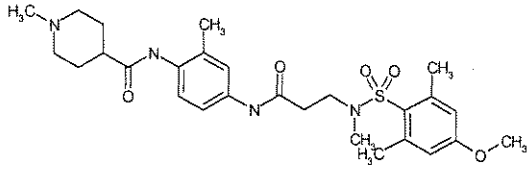
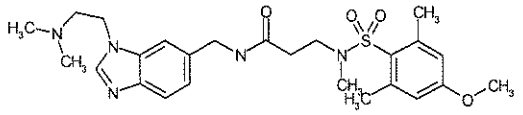
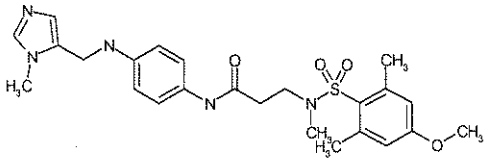
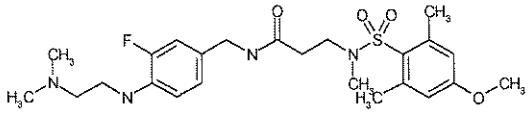
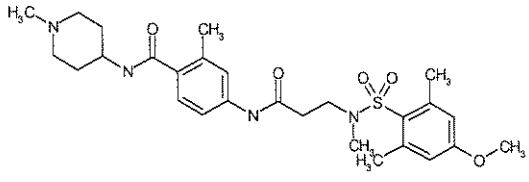
(194)	
(195)	
(196)	
(197)	
(198)	
(199)	
(200)	
(201)	

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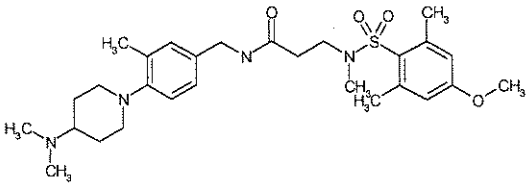
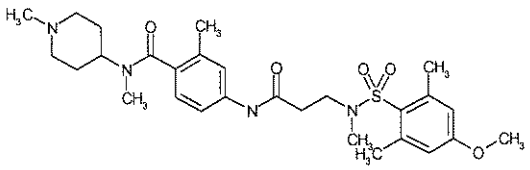
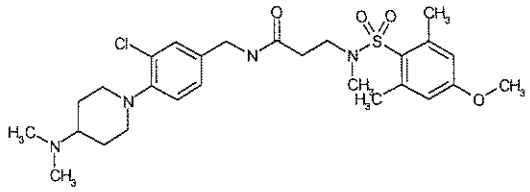
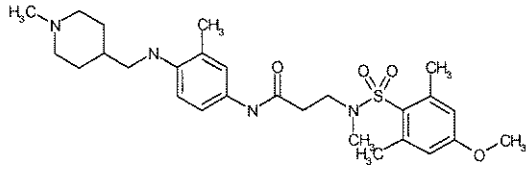
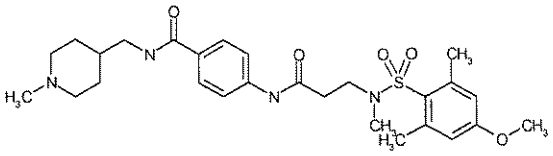
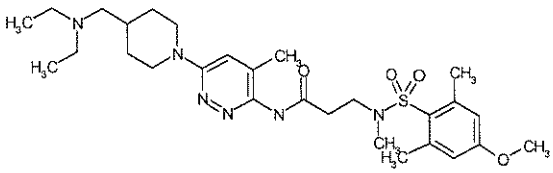
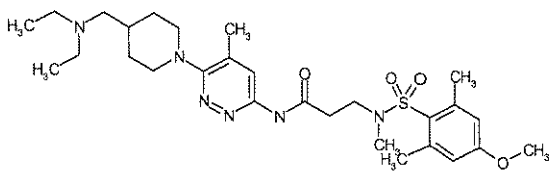
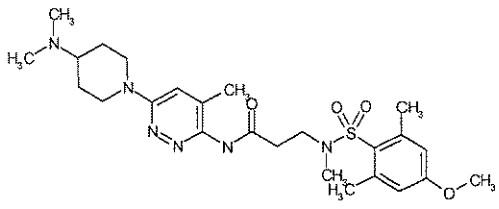
(202)	
(203)	
(204)	
(205)	
(206)	
(207)	
(208)	
(209)	

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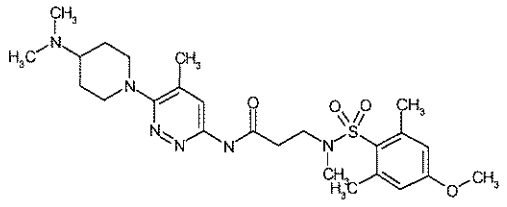
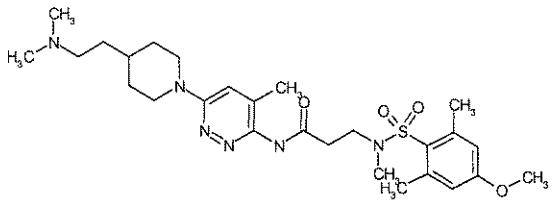
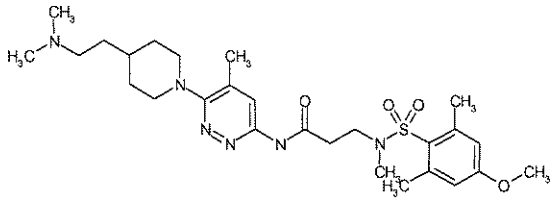
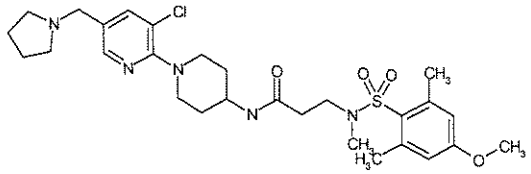
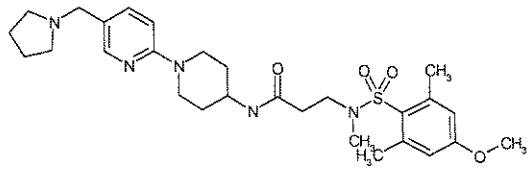
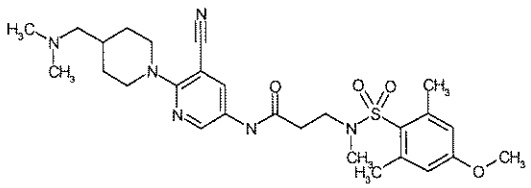
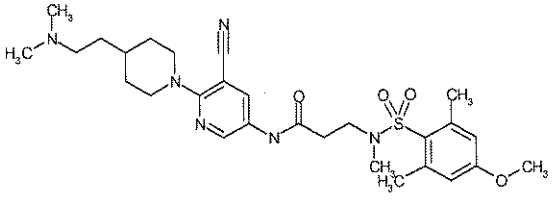
(210)	
(211)	
(212)	
(213)	
(214)	
(215)	
(216)	

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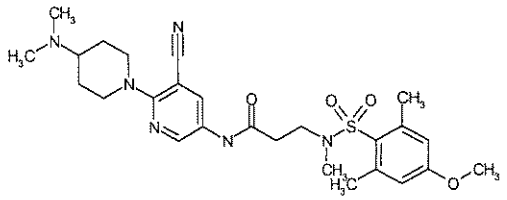
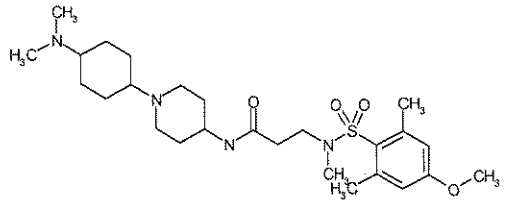
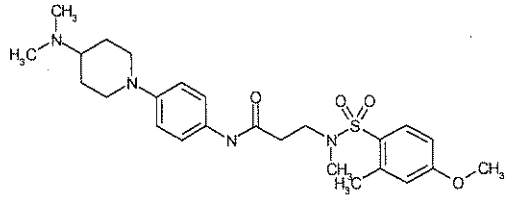
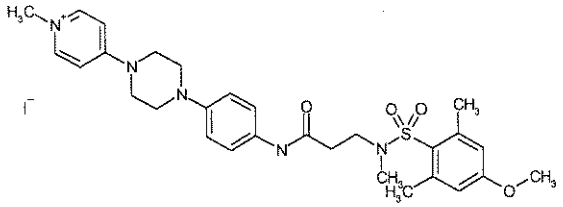
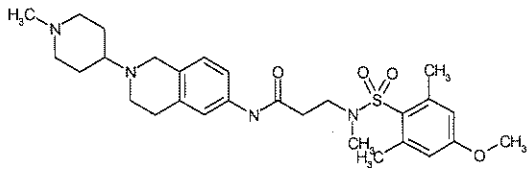
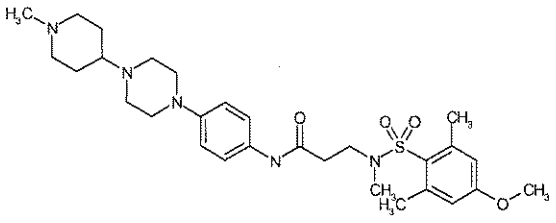
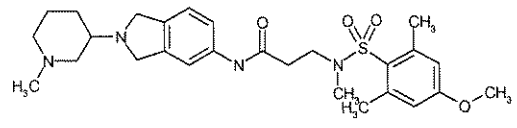
(217)	
(218)	
(219)	
(220)	
(221)	
(222)	
(223)	

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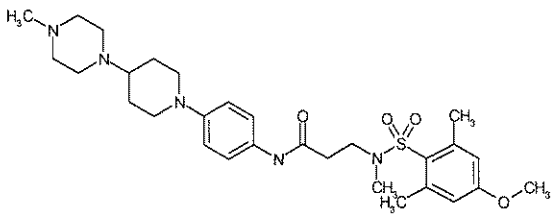
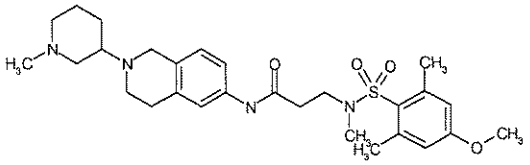
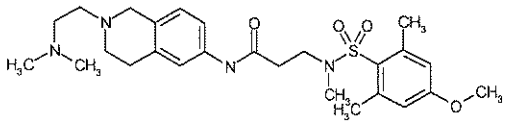
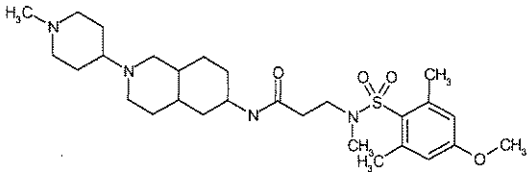
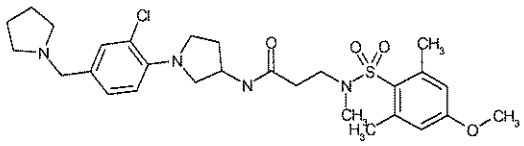
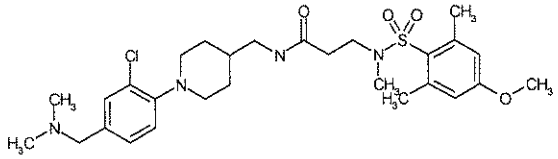
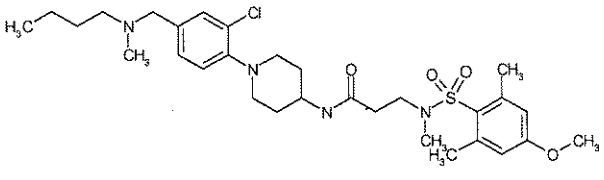
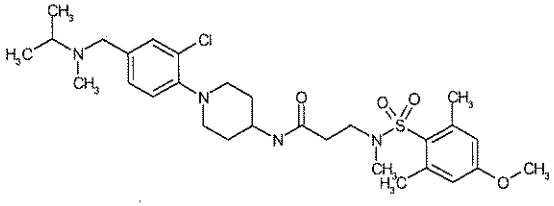
(224)	
(225)	
(226)	
(227)	
(228)	
(229)	
(230)	
(231)	

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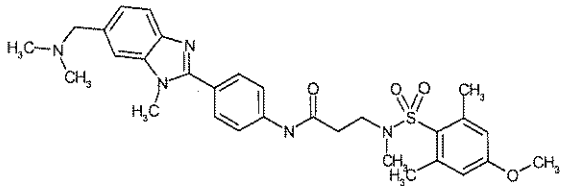
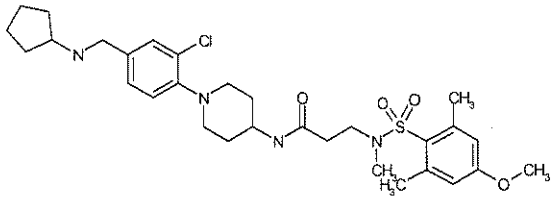
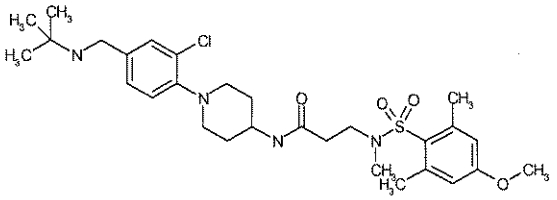
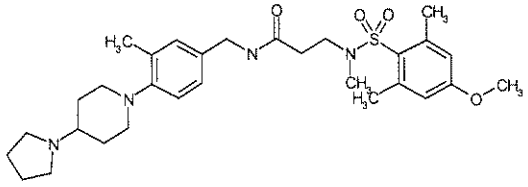
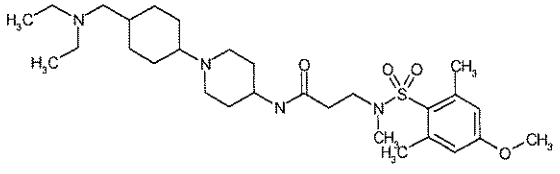
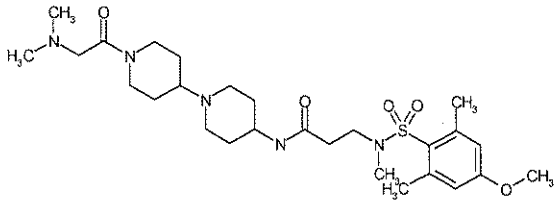
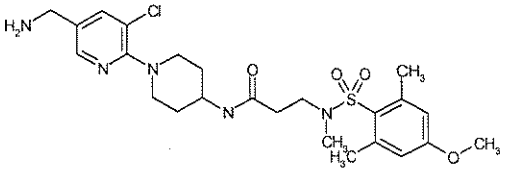
(232)	
(233)	
(234)	
(235)	
(236)	
(237)	
(238)	

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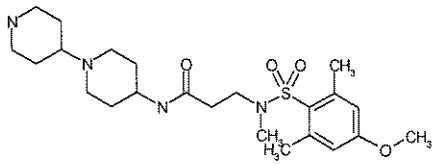
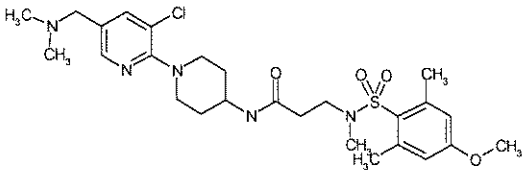
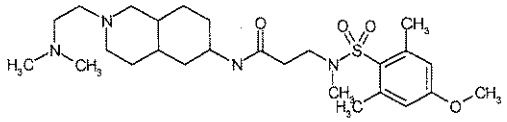
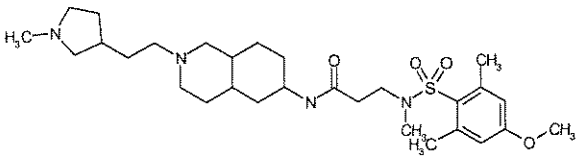
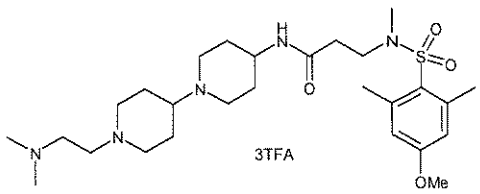
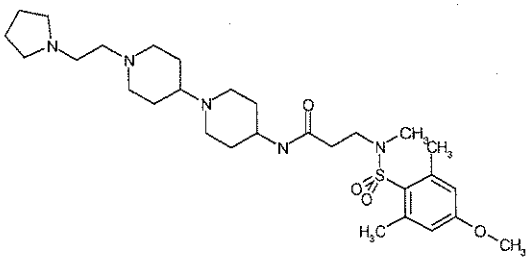
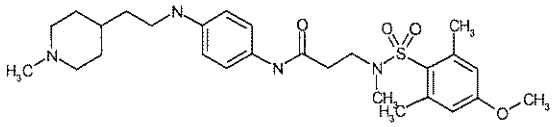
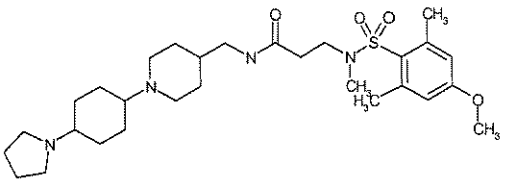
(239)	
(240)	
(241)	
(242)	
(243)	
(244)	
(245)	
(246)	

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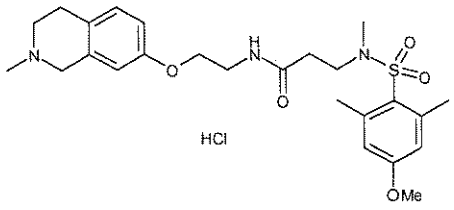
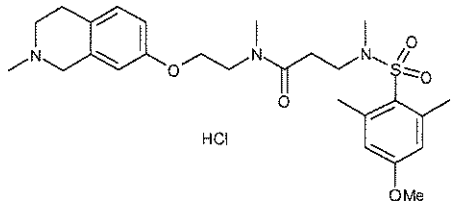
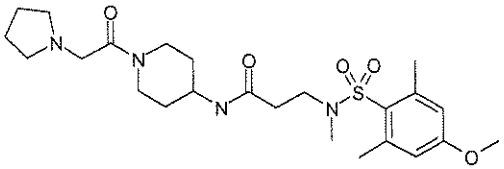
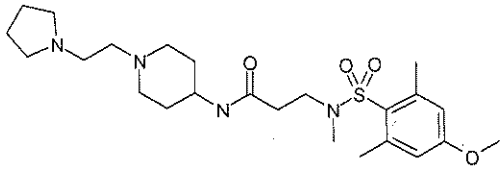
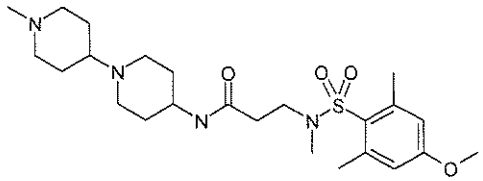
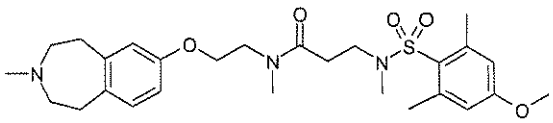
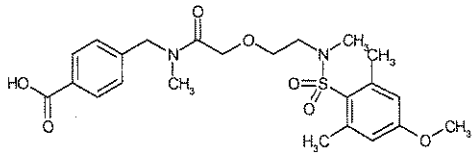
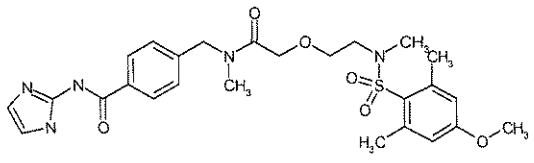
(247)	
(248)	
(249)	
(250)	
(251)	
(252)	
(253)	
(254)	

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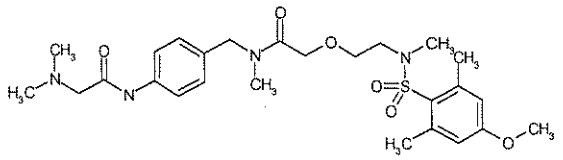
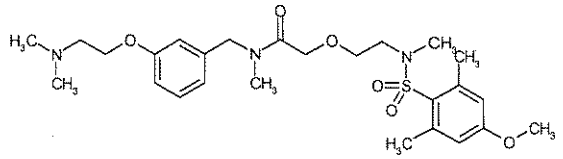
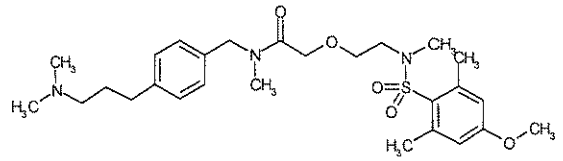
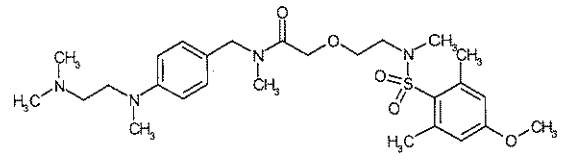
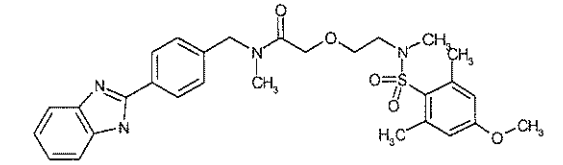
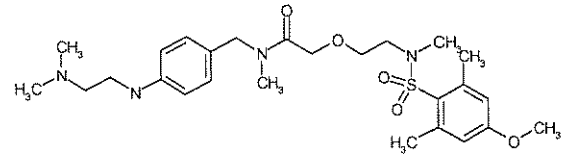
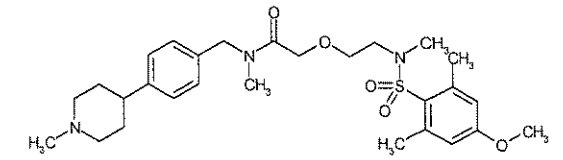
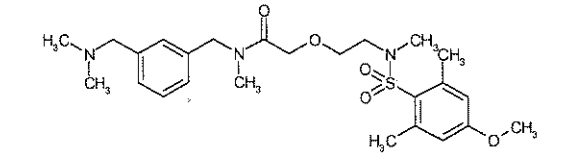
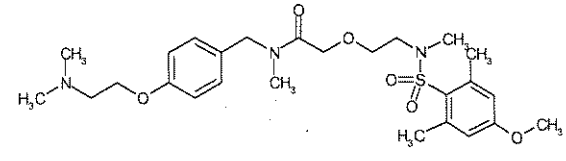
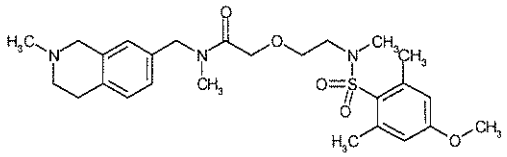
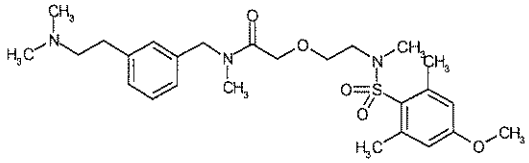
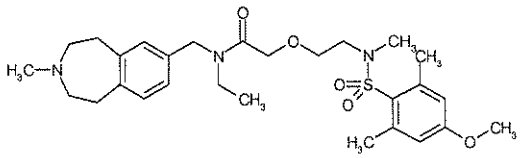
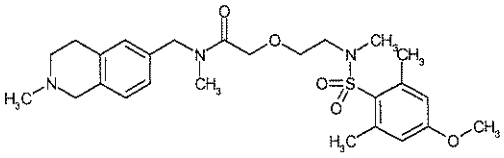
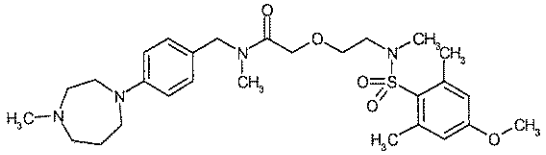
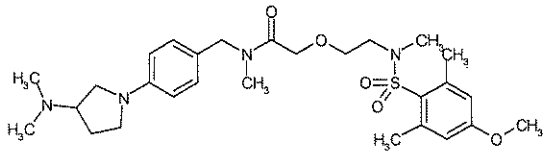
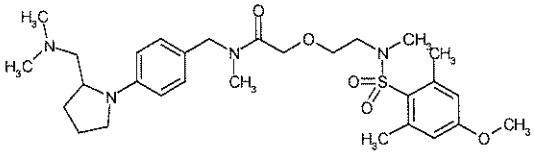
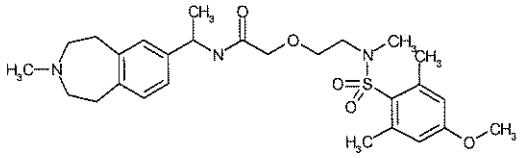
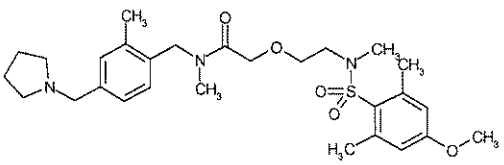
(255)	
(256)	
(257)	
(258)	
(259)	
(260)	
(261)	
(262)	
(263)	

Example	Structure
(264)	
(265)	
(266)	
(267)	
(268)	
(269)	
(270)	
(271)	
(272)	

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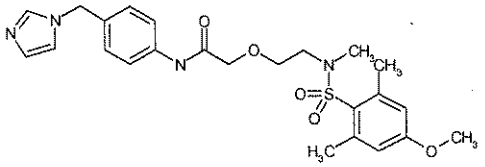
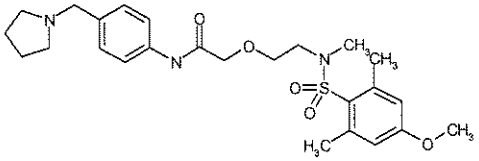
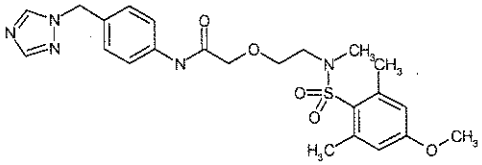
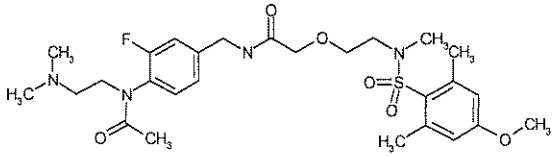
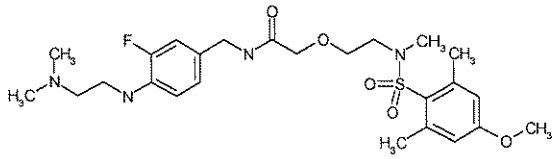
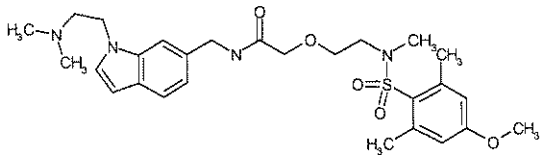
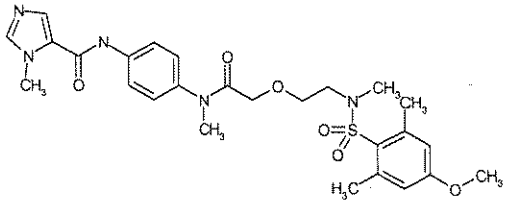
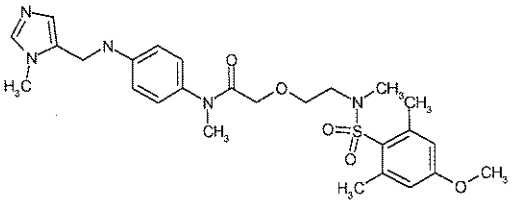
(273)	
(274)	
(275)	
(276)	
(277)	
(278)	
(279)	
(280)	

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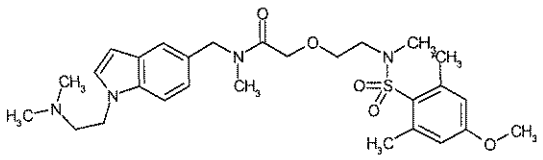
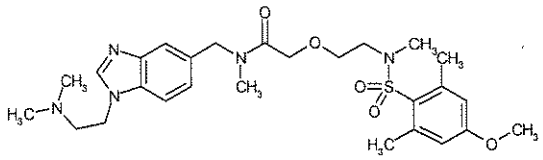
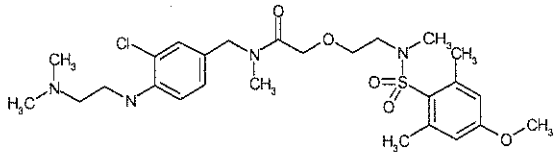
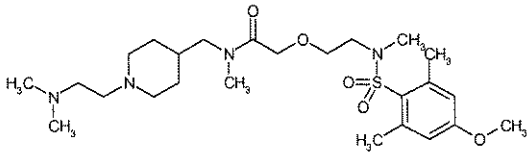
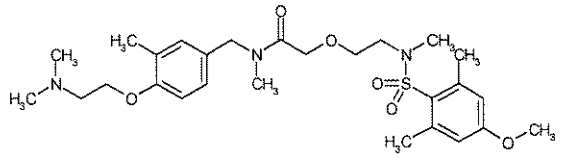
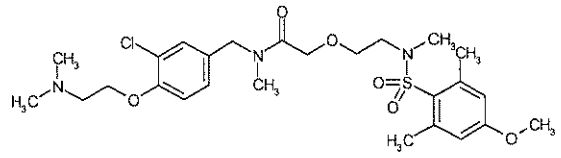
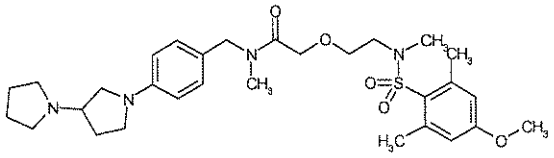
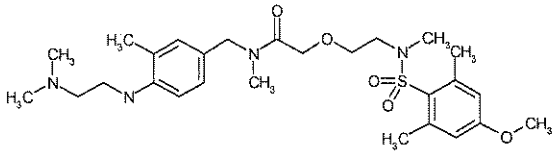
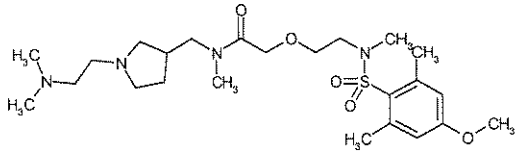
(281)	
(282)	
(283)	
(284)	
(285)	
(286)	
(287)	
(288)	
(289)	

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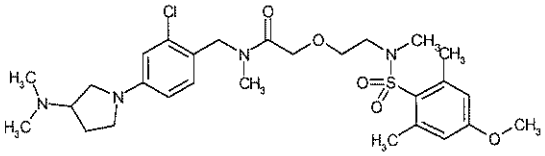
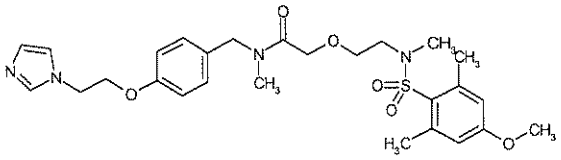
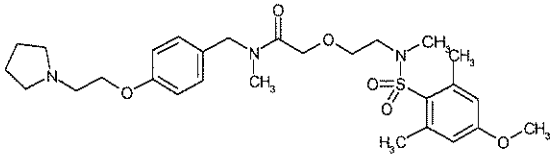
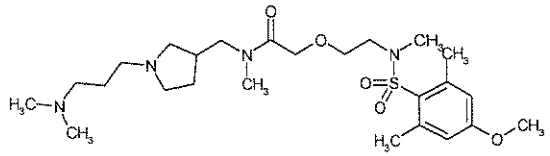
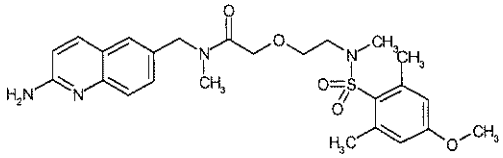
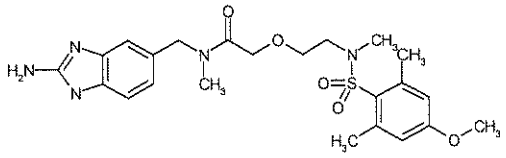
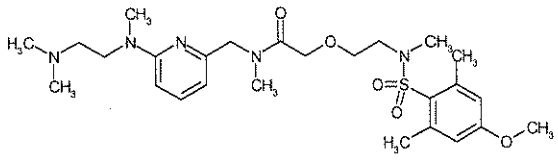
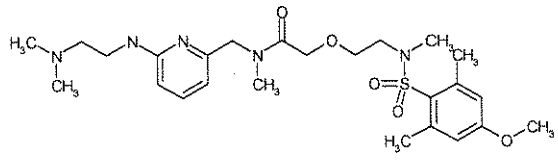
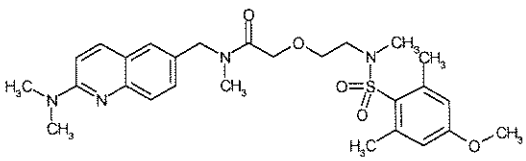
(290)	
(291)	
(292)	
(293)	
(294)	
(295)	
(296)	
(297)	
(298)	

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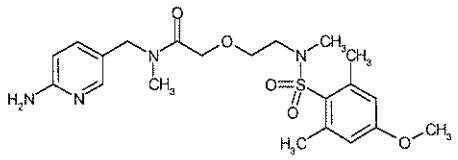
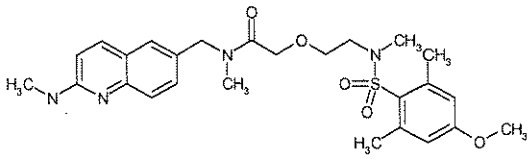
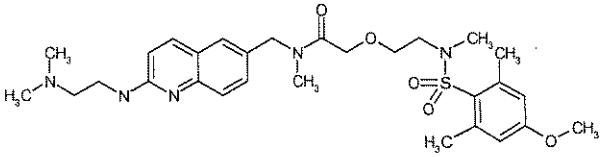
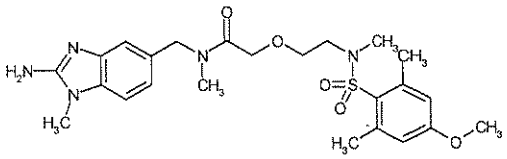
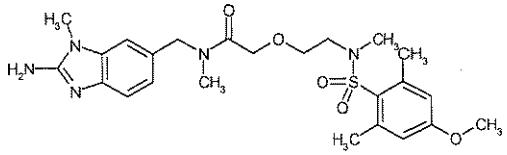
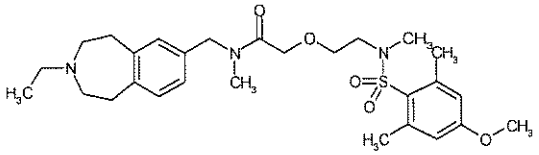
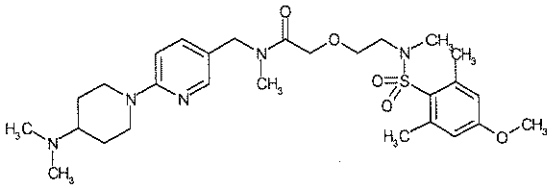
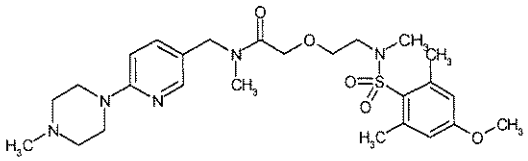
(299)	
(300)	
(301)	
(302)	
(303)	
(304)	
(305)	
(306)	

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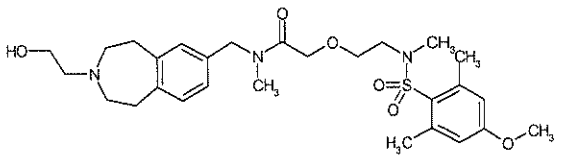
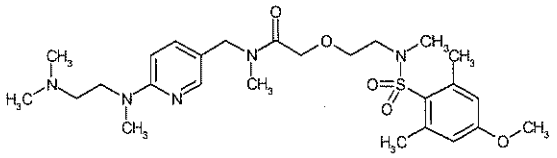
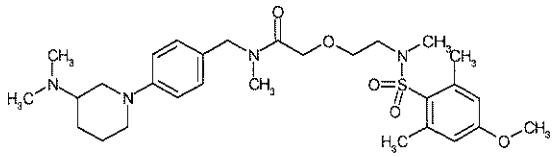
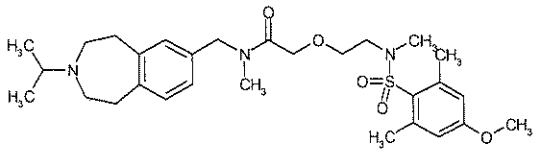
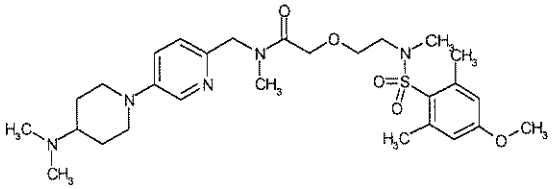
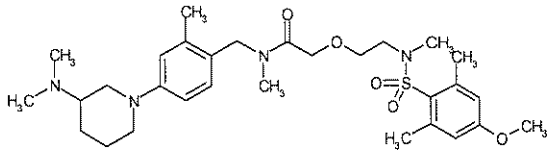
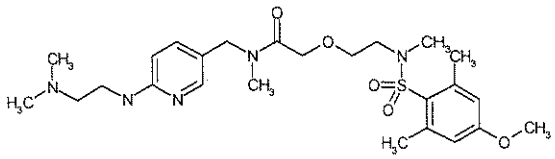
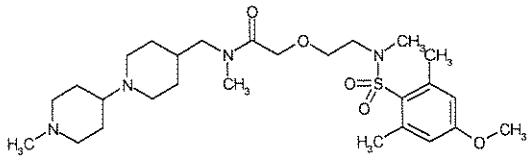
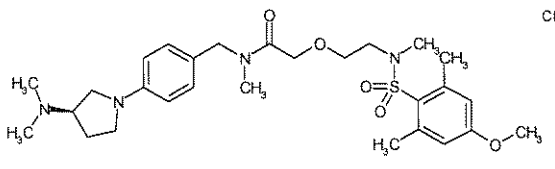
(307)	
(308)	
(309)	
(310)	
(311)	
(312)	
(313)	
(314)	
(315)	Chiral 

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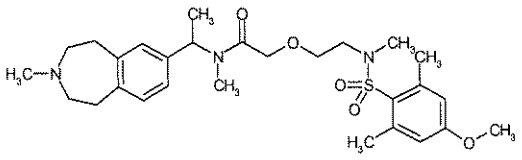
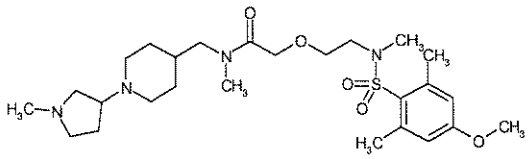
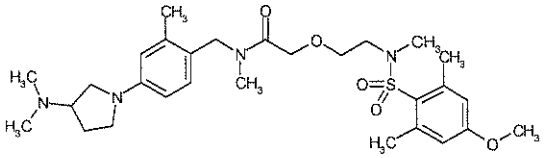
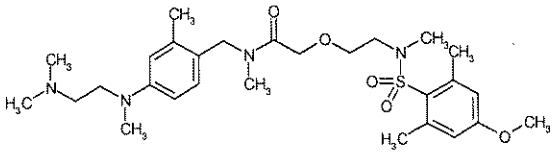
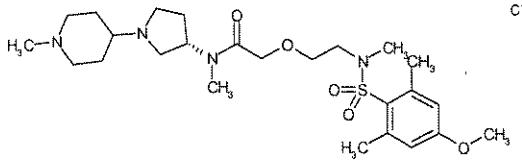
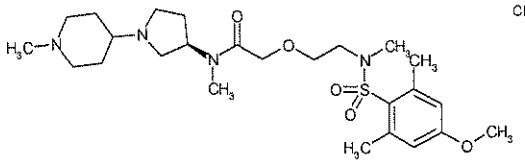
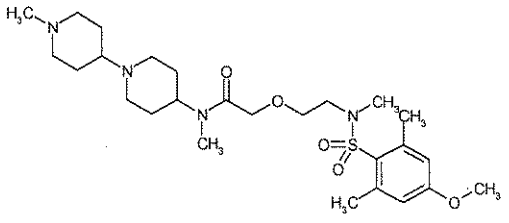
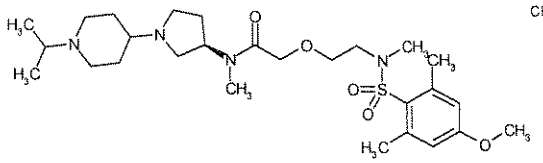
(316)	
(317)	
(318)	
(319)	
(320)	Chiral 
(321)	Chiral 
(322)	
(323)	Chiral 

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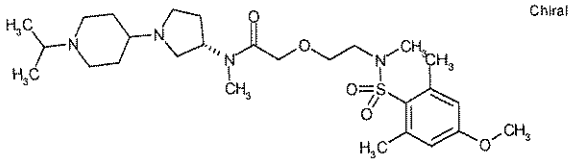
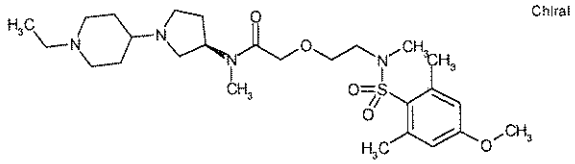
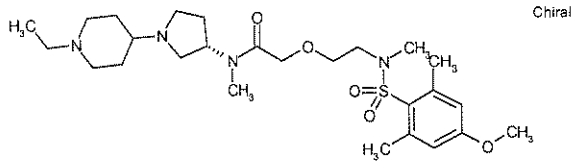
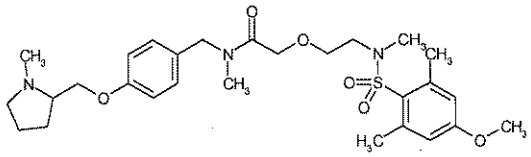
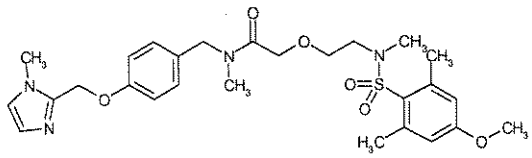
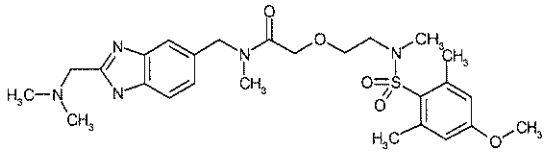
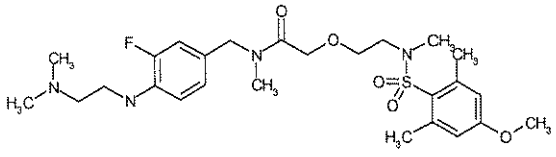
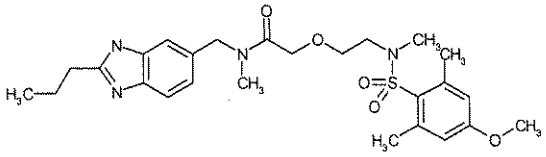
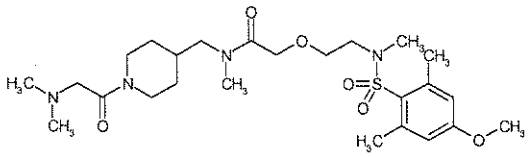
(324)	 Chiral
(325)	 Chiral
(326)	 Chiral
(327)	
(328)	
(329)	
(330)	
(331)	
(332)	

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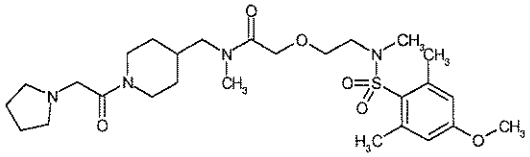
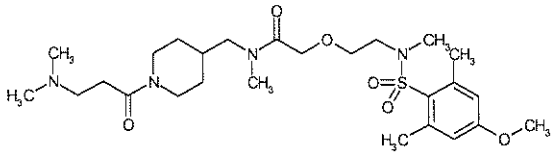
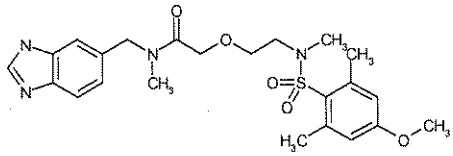
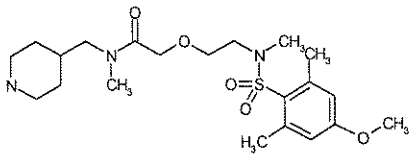
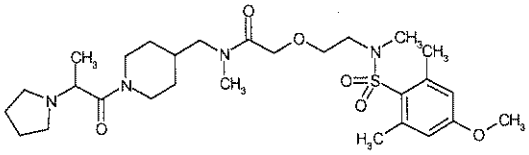
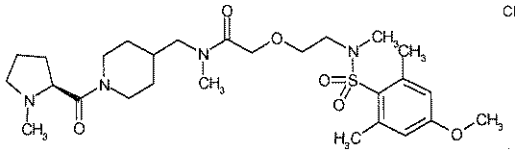
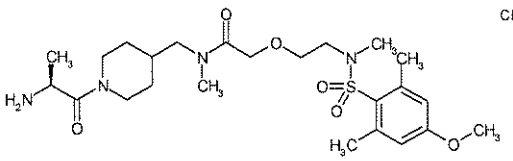
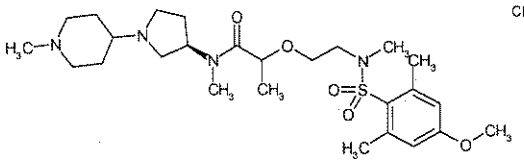
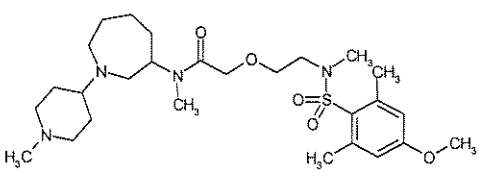
(333)	
(334)	
(335)	
(336)	
(337)	
(338)	Chiral 
(339)	Chiral 
(340)	Chiral 
(341)	

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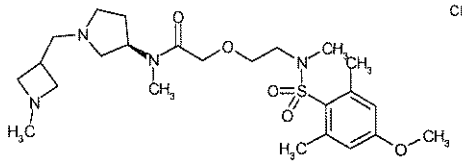
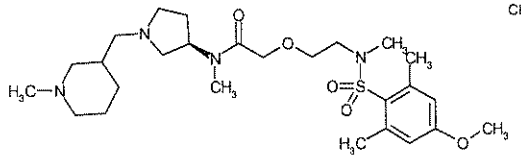
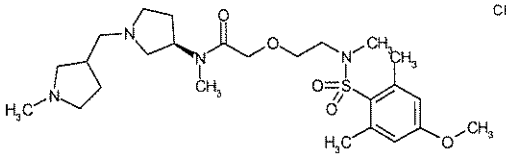
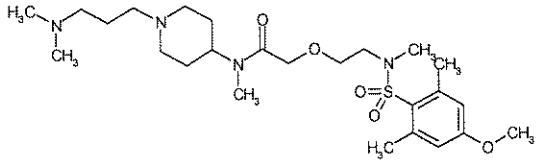
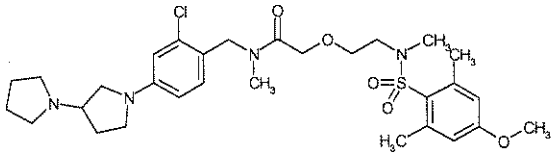
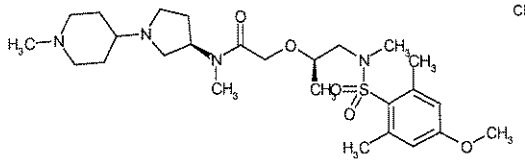
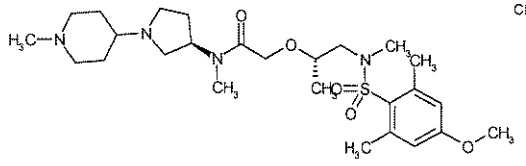
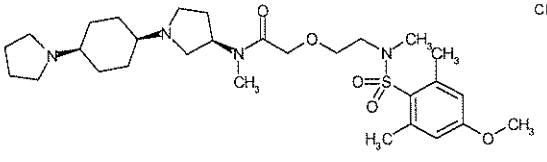
(342)	 Chiral
(343)	 Chiral
(344)	 Chiral
(345)	
(346)	
(347)	 Chiral
(348)	 Chiral
(349)	 Chiral

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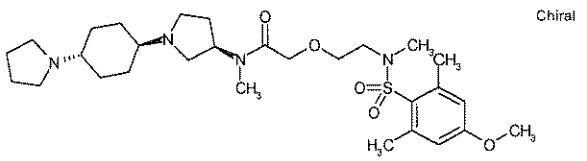
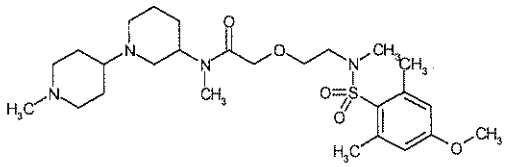
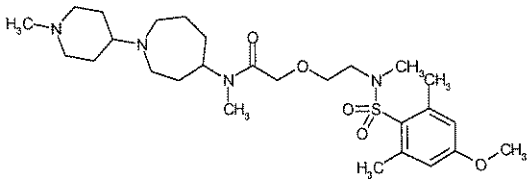
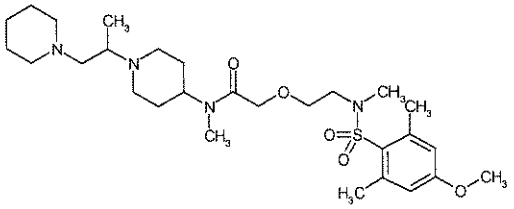
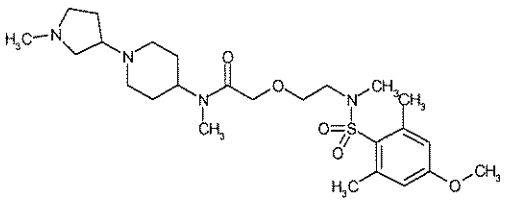
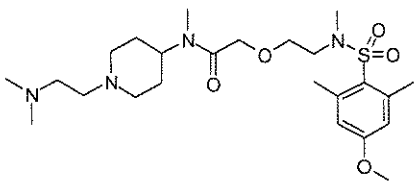
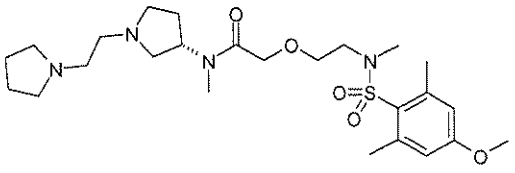
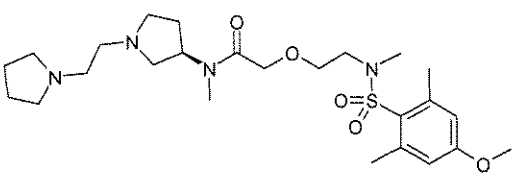
(350)	 Chiral
(351)	
(352)	
(353)	
(354)	
(355)	
(356)	
(357)	

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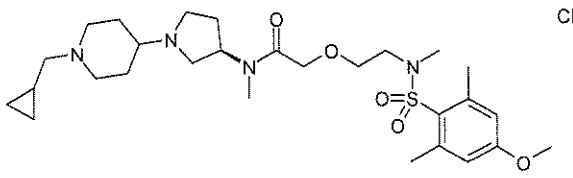
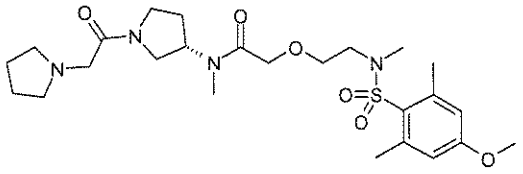
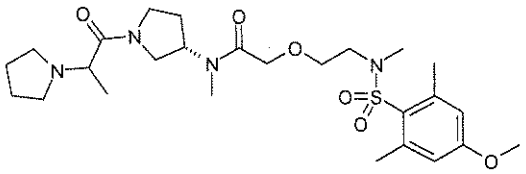
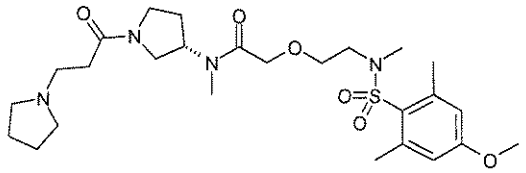
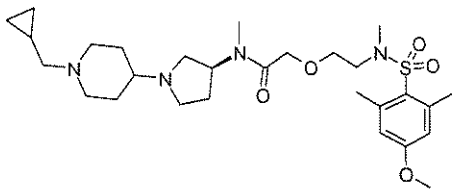
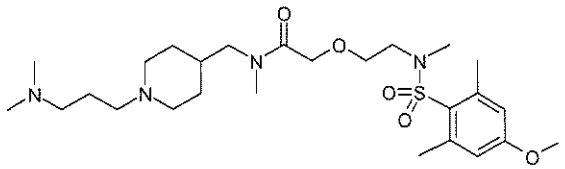
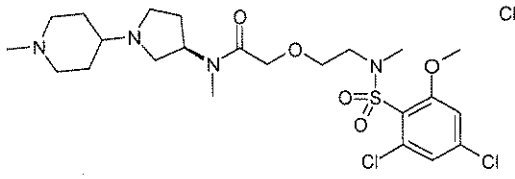
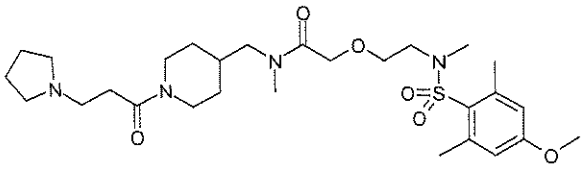
(358)	 Chiral
(359)	
(360)	
(361)	
(362)	
(363)	
(364)	 Chiral
(365)	

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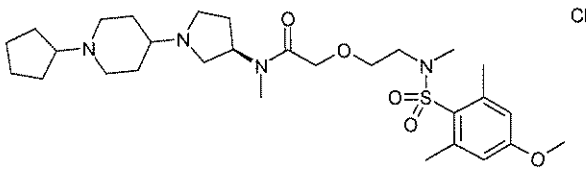
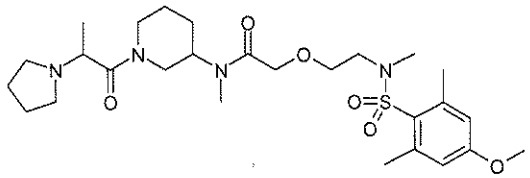
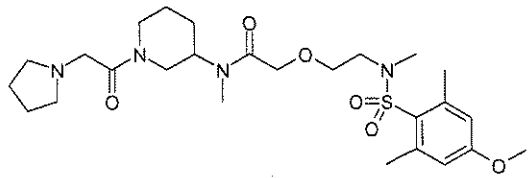
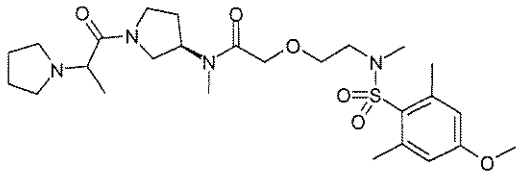
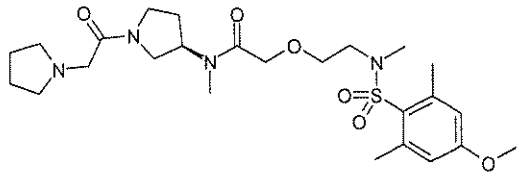
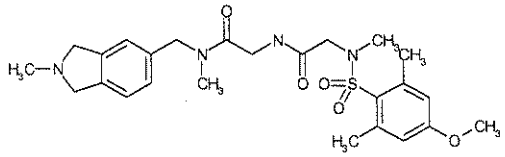
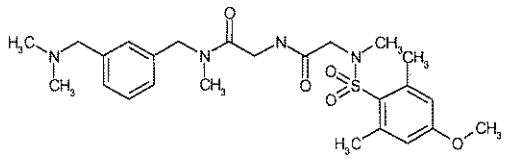
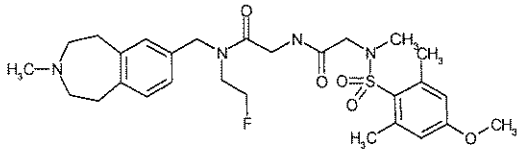
(366)	 Chiral
(367)	
(368)	
(369)	 Chiral
(370)	 Chiral
(371)	
(372)	
(373)	

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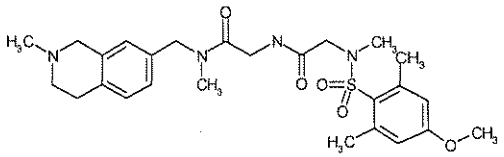
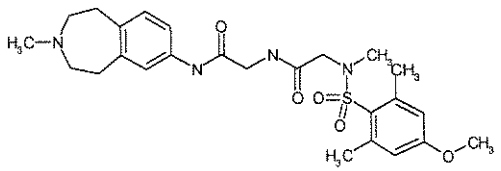
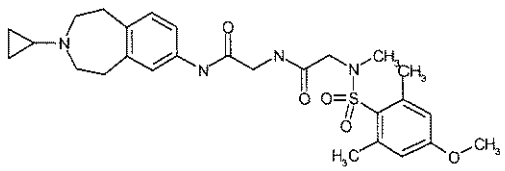
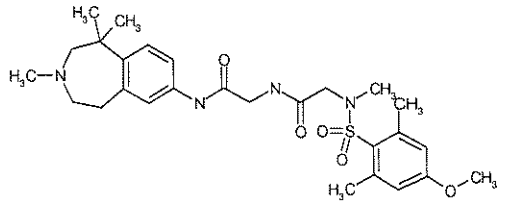
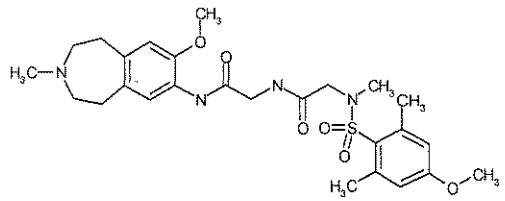
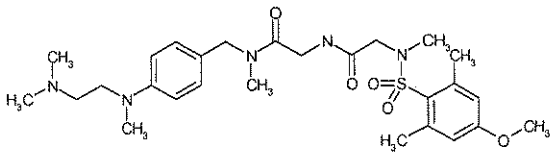
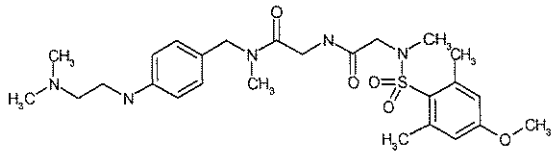
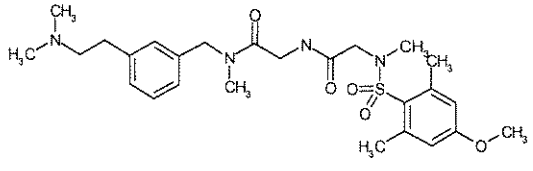
(374)	
(375)	
(376)	
(377)	
(378)	
(379)	
(380)	
(381)	

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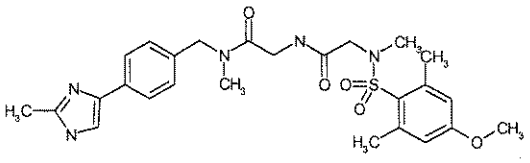
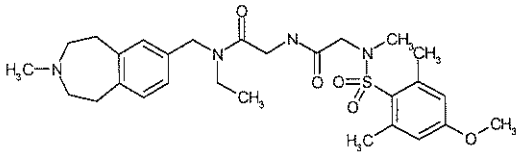
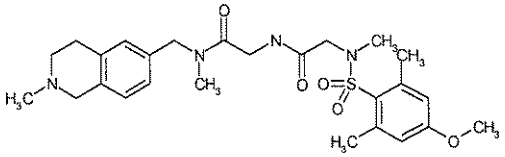
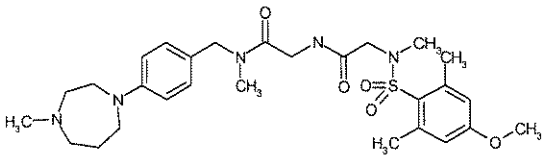
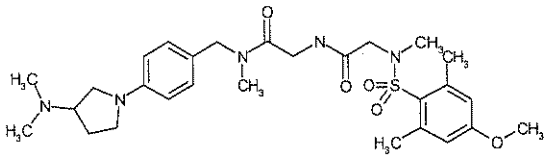
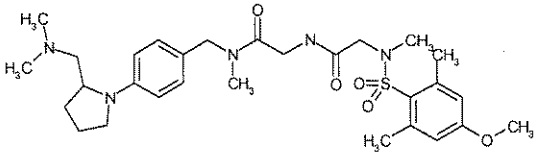
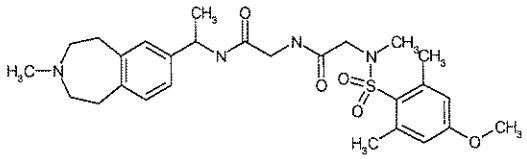
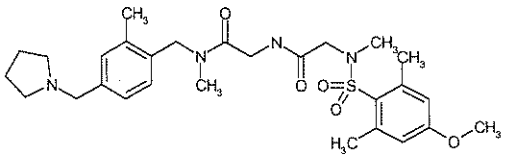
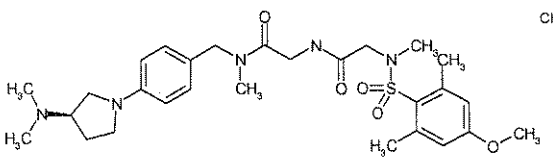
(382)	
(383)	
(384)	
(385)	
(386)	
(387)	
(388)	
(389)	
(390)	Chiral 

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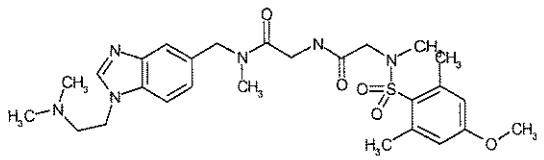
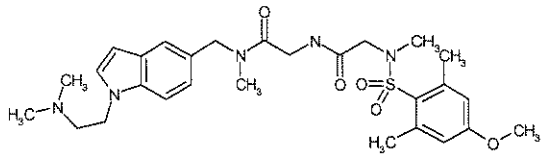
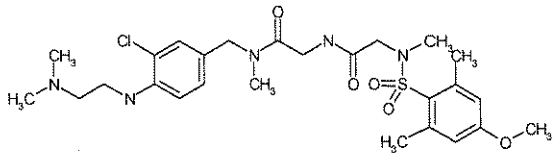
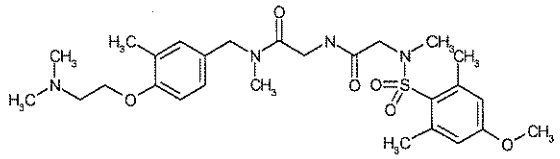
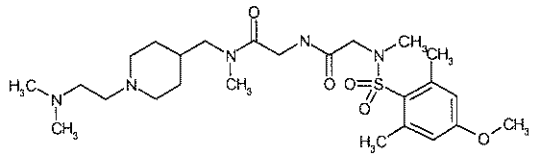
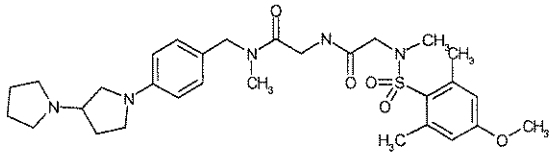
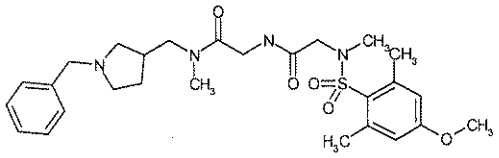
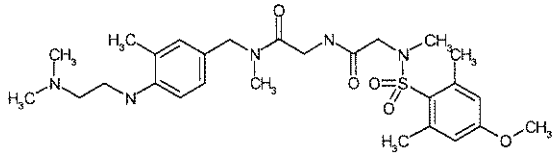
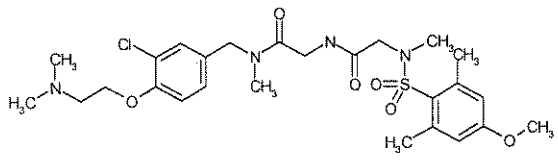
(391)	
(392)	
(393)	
(394)	
(395)	
(396)	
(397)	
(398)	
(399)	

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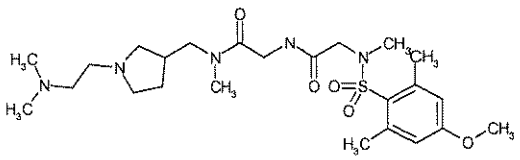
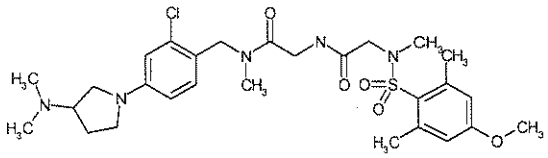
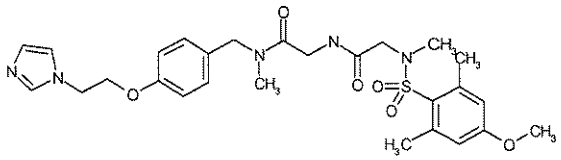
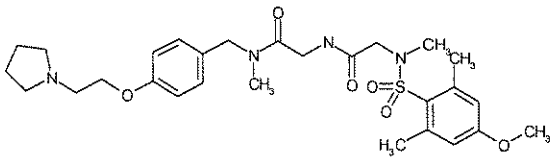
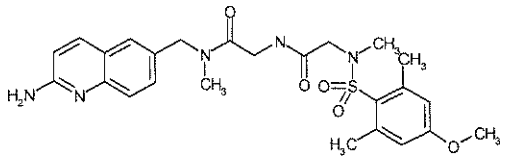
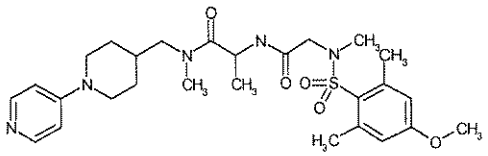
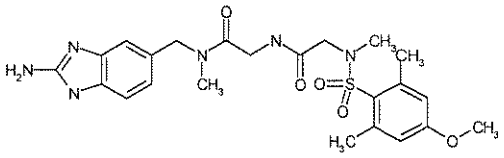
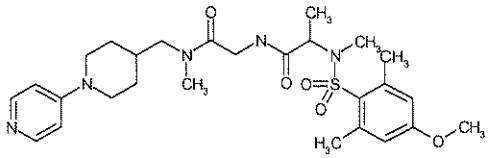
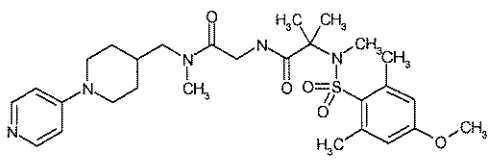
(400)	
(401)	
(402)	
(403)	
(404)	
(405)	
(406)	
(407)	
(408)	

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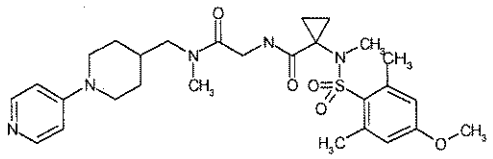
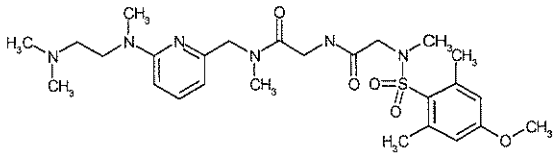
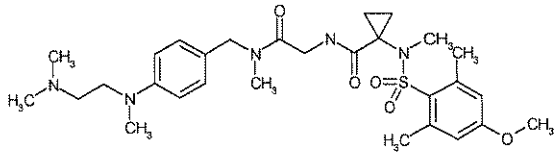
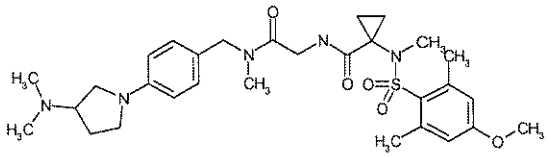
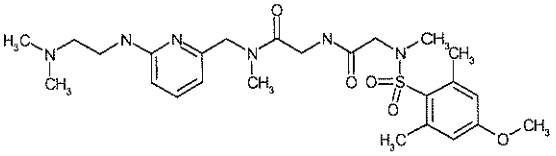
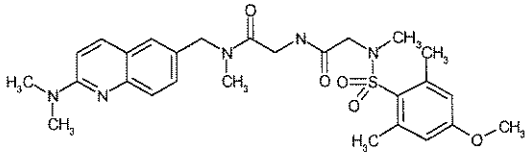
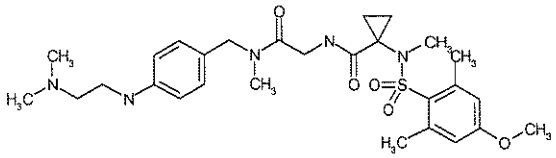
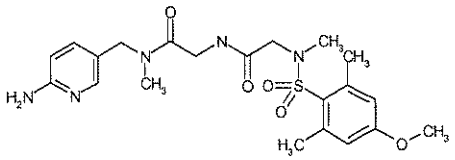
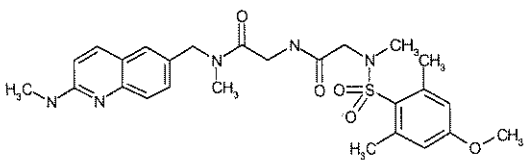
(409)	
(410)	
(411)	
(412)	
(413)	
(414)	
(415)	
(416)	
(417)	

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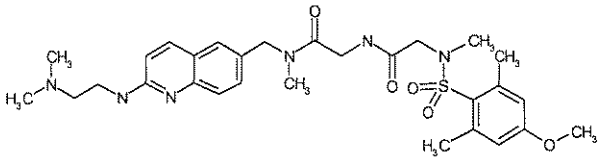
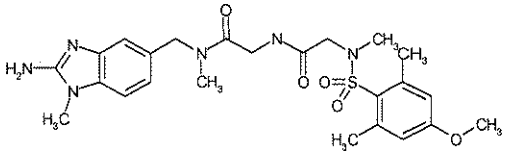
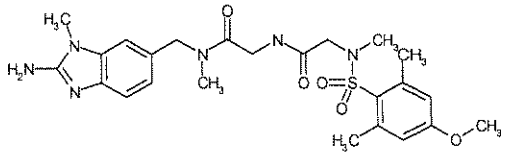
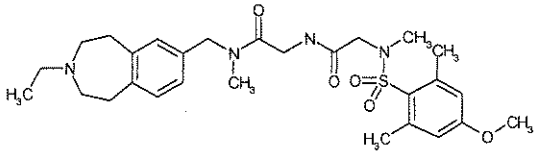
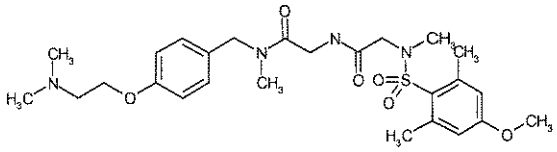
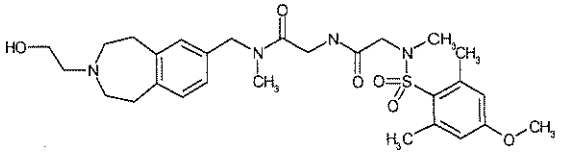
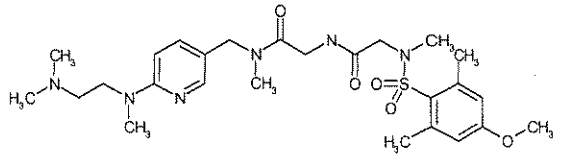
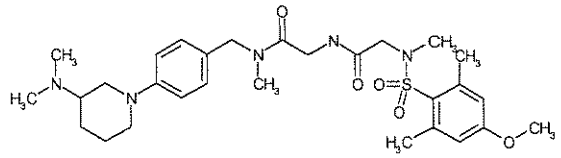
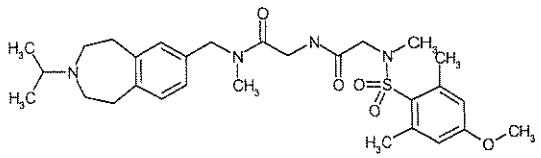
(418)	
(419)	
(420)	
(421)	
(422)	
(423)	
(424)	
(425)	
(426)	

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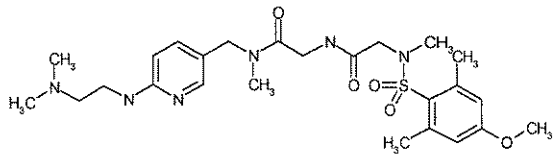
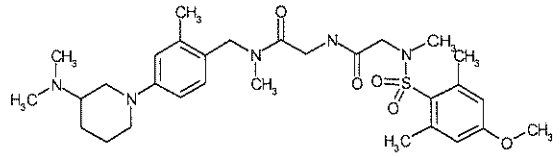
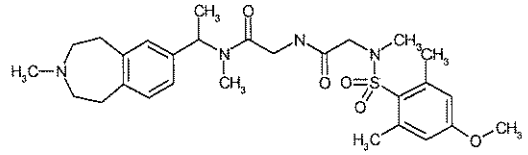
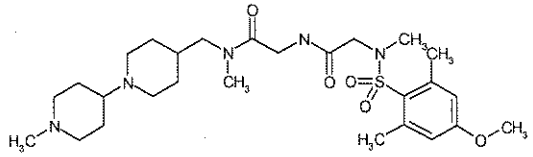
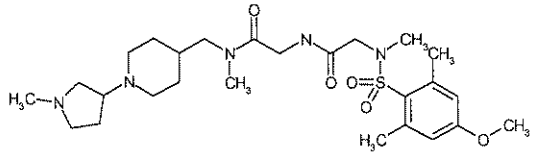
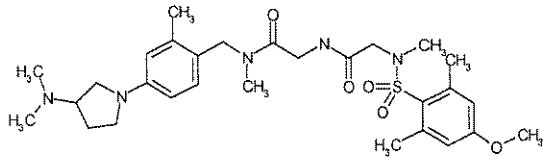
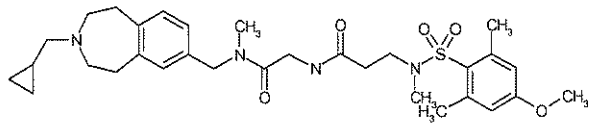
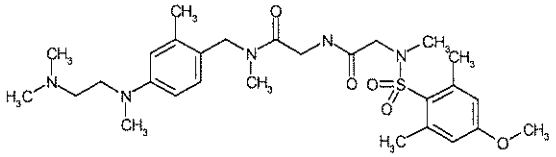
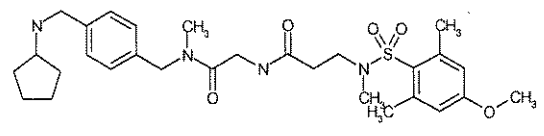
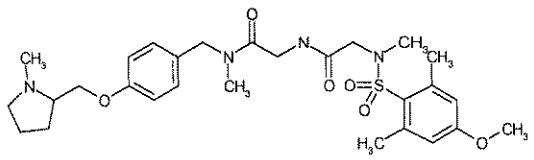
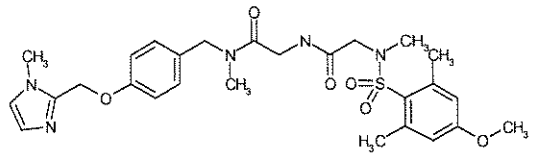
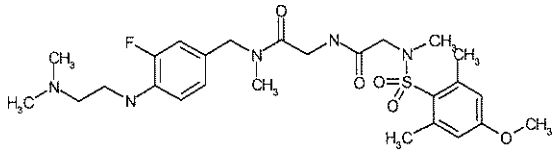
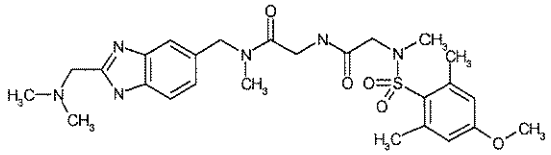
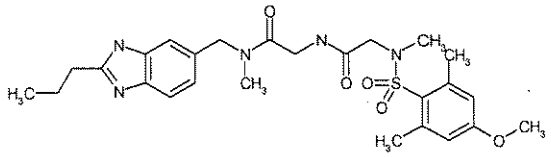
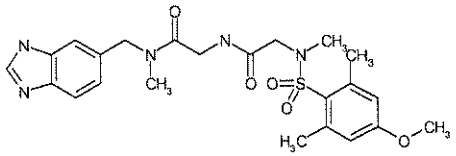
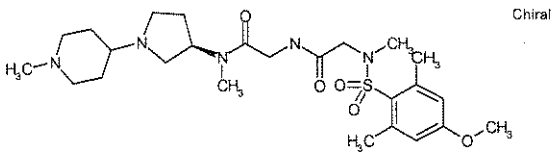
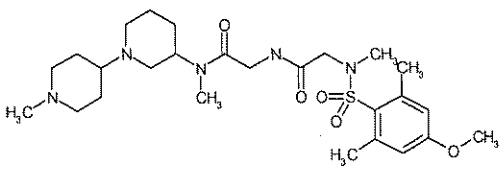
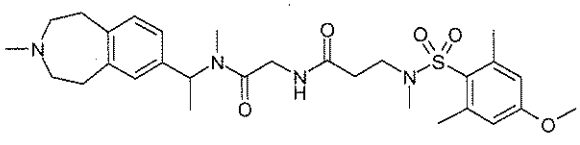
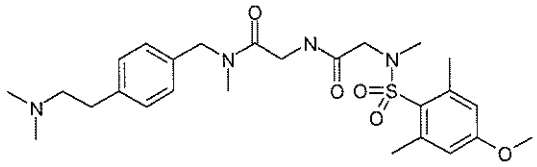
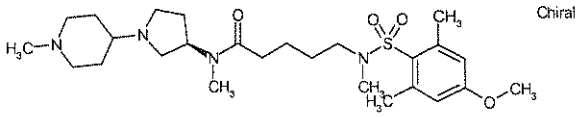
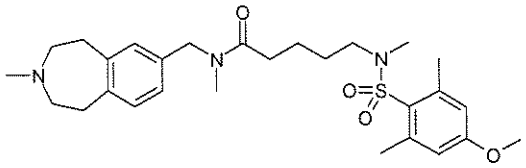
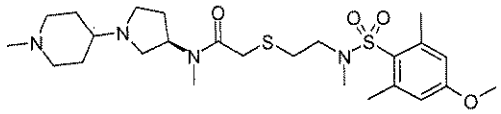
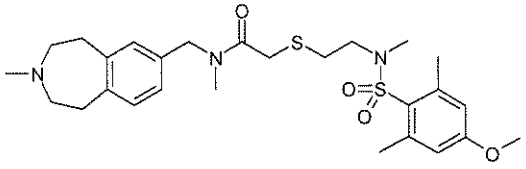
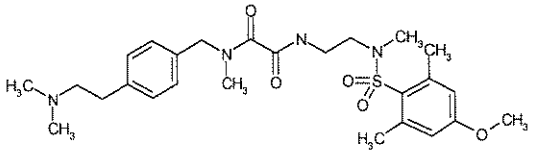
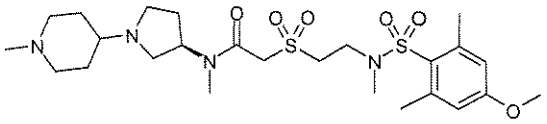
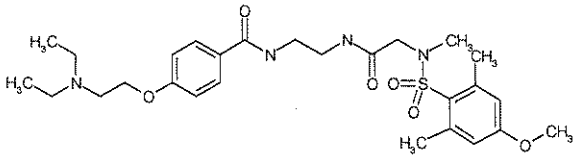
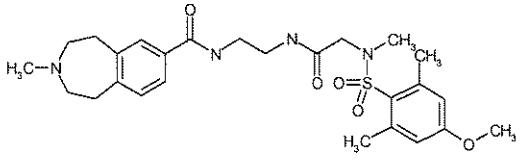
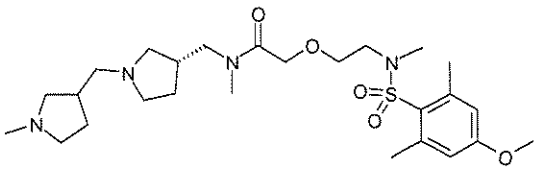
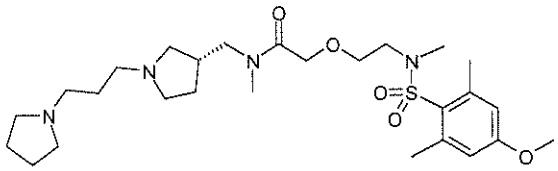
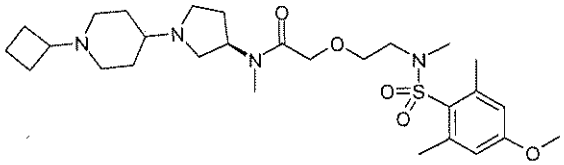
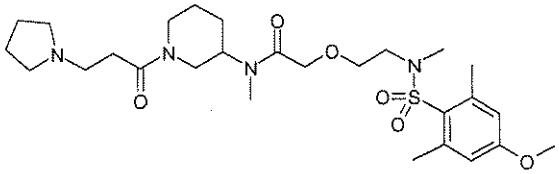
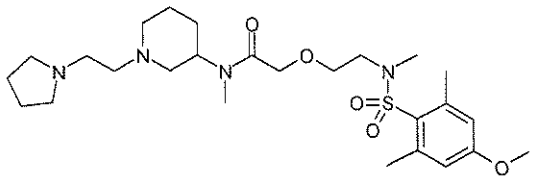
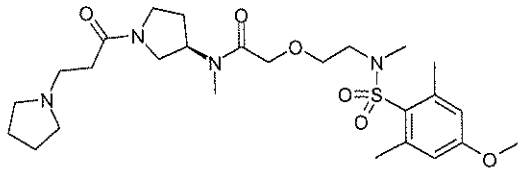
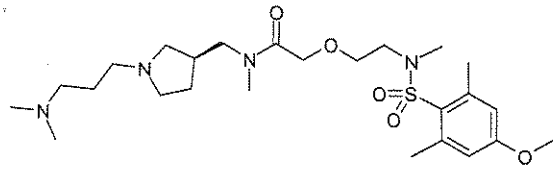
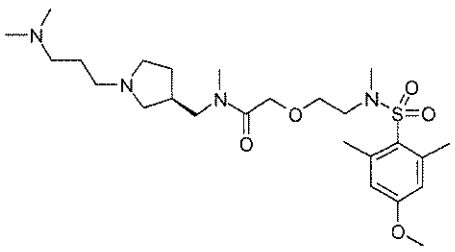
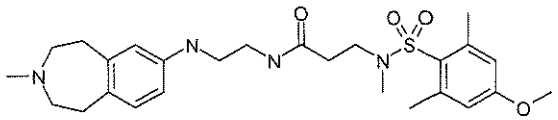
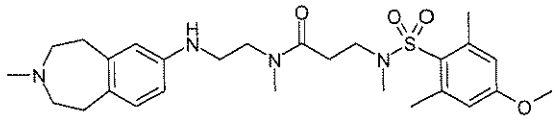
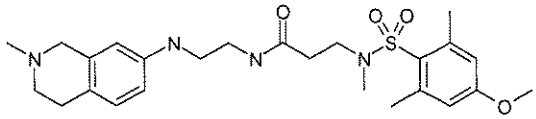
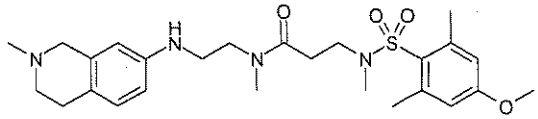
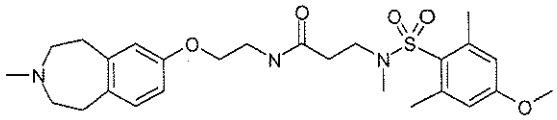
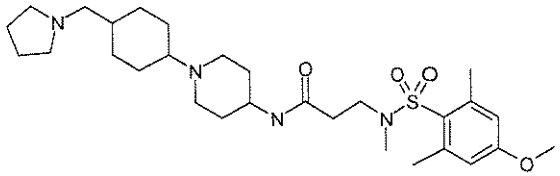
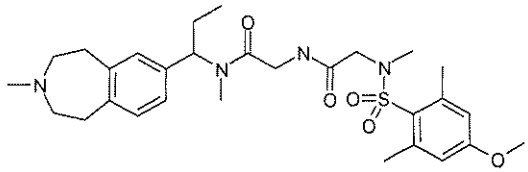
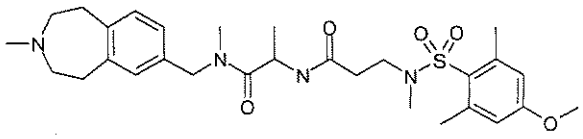
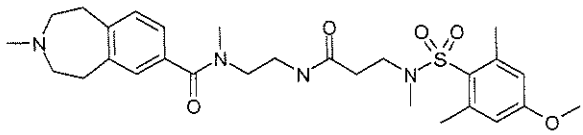
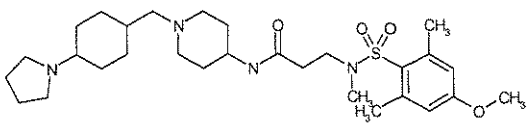
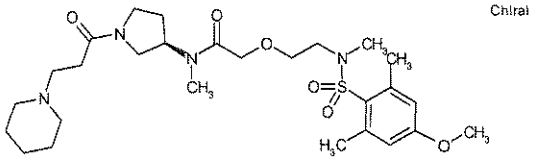
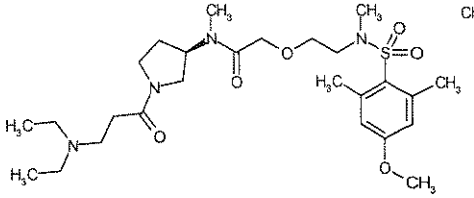
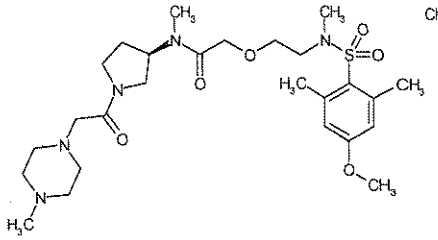
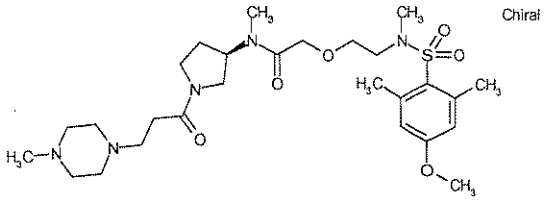
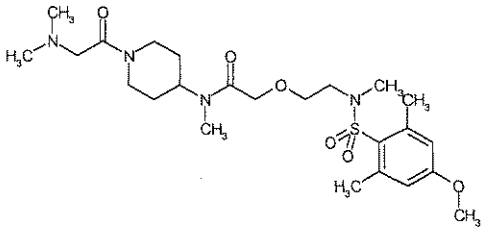
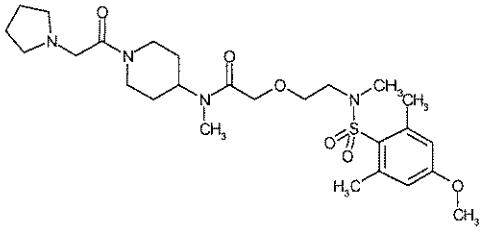
(427)	
(428)	
(429)	
(430)	
(431)	
(432)	
(433)	
(434)	
(435)	

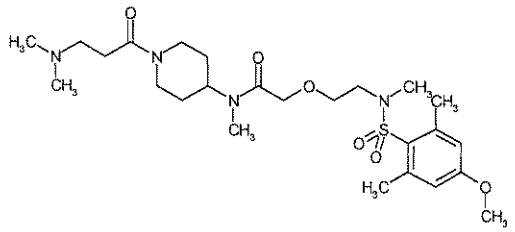
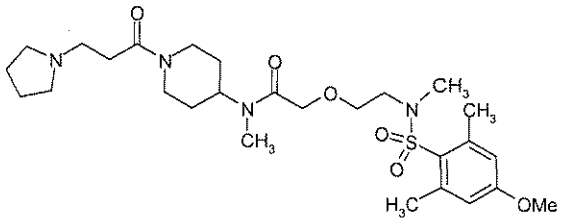
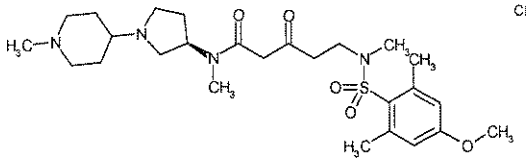
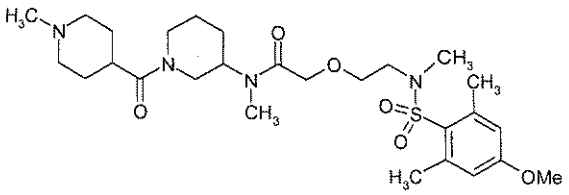
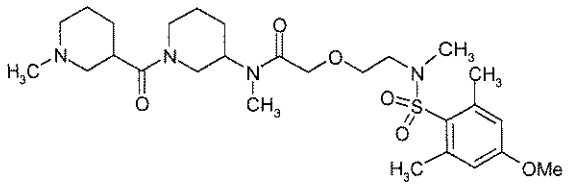
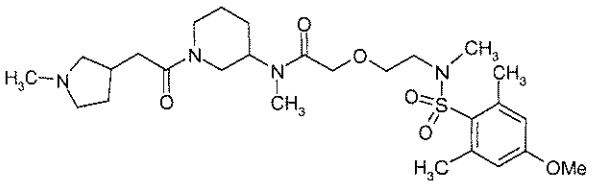
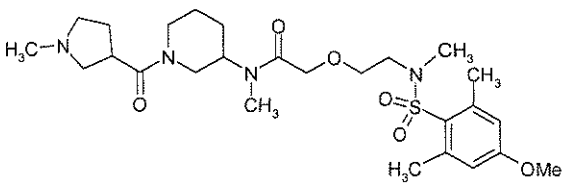
Example	Structure
(436)	
(437)	
(438)	
(439)	
(440)	
(441)	
(442)	 Chiral
(443)	
(444)	

Example	Structure
(445)	
(446)	 Chiral
(447)	
(448)	
(449)	
(450)	
(451)	
(452)	
(453)	

Example	Structure
(454)	
(455)	
(456)	
(457)	
(458)	
(459)	
(460)	
(461)	

Example	Structure
(462)	
(463)	
(464)	
(465)	
(466)	
(467)	
(468)	
(469)	
(470)	
(471)	

Example	Structure
(472)	 Chiral
(473)	 Chiral
(474)	 Chiral
(475)	 Chiral
(476)	
(477)	

Example	Structure
(478)	
(479)	
(480)	 Chiral
(481)	
(482)	
(483)	
(484)	

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

8. Physiologically acceptable salts of the compounds according to one of claims 1 to 7 with inorganic or organic acids or bases.

9. Medicament, containing a compound according to at least one of claims 1 to 7 or a physiologically acceptable salt according to claim 8 optionally together with one or more inert carriers and/or diluents.

10. Use of a compound according to at least one of claims 1 to 8 for preparing a medicament for the acute and prophylactic treatment of acute pain, visceral pain, neuropathic pain, inflammatory/pain receptor-mediated pain, tumour pain and headache diseases.

11. Process for preparing a pharmaceutical composition according to claim 9, characterised in that by a non-chemical method a compound according to at least one of claims 1 to 8 is incorporated in one or more inert carriers and/or diluents.