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Mesolimbic selective antipsychotic arylcarbamates

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Abstract – 4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidine has been linked to various arylcarbamates to obtain compounds having affinity for dopamine-D_1 and -D_2, serotonin $5HT_{2A}$ and α_1-adrenoceptors. When linkers with restricted flexibility are used, the biological activity is reduced indicating that a bended conformation is needed in this series of bioactive molecules. Compounds with a relatively low $D_2/5HT_{2A}$ affinity ratio in receptor binding experiments and high affinity for the α_1-adrenoceptors exhibit a pharmacological profile which suggests a preferential effect on the mesocorticolimbic dopaminergic system and an 'atypical' antipsychotic activity. © Elsevier, Paris

antipsychotic activity / mesolimbic selectivity / arylcarbamates / dopamine / serotonin

1. Introduction

Antipsychotic drugs antagonizing central dopaminergic receptors have been used for several decades in the treatment of psychiatric disorders, e.g. schizophrenia [1]. Although these drugs can reduce the positive symptoms of schizophrenia, they unfortunately often induce extrapyramidal motoric side effects and are furthermore often not able to ameliorate the negative symptoms of schizophrenia. The antipsychotic action has been suggested to be due to a blockade of the mesocorticolimbic dopaminergic system, while the motoric side effects are believed to be due to antagonism of dopaminergic receptors in the nonlimbic nigro-striatal dopamine system of the brain [2].

In order to achieve mesolimbic selective antipsychotic activity, compounds with affinity for the dopamine D_1- and D_2-receptors, the serotonin 5-HT_{1A} and 5-HT_{2A}-receptors as well as the α_1-adrenergic receptors have been investigated. Clozapine, a mesolimbic selective antipsychotic drug to which all other neuroleptics are compared, has been found to antagonise several subtypes of dopamine, serotonin, adrenergic, muscarinic and histaminergic receptors [3, 4]. In addition, compounds like sertindole, risperidone, and olanzapine (*figure 1*) which exhibit effective antagonistic properties at dopaminergic, serotonergic $5HT_{2A}$- and α-adrenergic receptors have been found to have antipsychotic properties with reduced extrapyramidal side effects [5, 6].

We have recently described that NNC 19-1228 (1-(3-(6-benzothiazolylcarbamoyloxyl)propyl)-4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidine) (**7**) and its congener NNC 22-0031 (4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-(3-(3,4-methylenedioxyphenylcarbamoyloxy)propyl)piperidine) (**8**) have potent antipsychotic activity with little or no motoric side effects in animal models [7]. The behavioural selectivity of NNC 22-0031 has been substantiated by studies confirming its anatomical selectivity. In contrast to the 'typical' neuroleptic haloperidol, 'atypical' neuroleptics like clozapine, risperidone, sertindole and NNC 22-0031 exhibit an apparent cortical selectivity in awake rats by preferentially elevating interstitial levels of the dopamine metabolite 3,4-dihydroxyphenylacetic acid (DOPAC) in the medial prefrontal cortex but not in the dorsolateral striatum [8]. Furthermore, NNC 22-0031

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like other 'atypical' neuroleptics are able to selectively induce synthesis of the transcription factor protein Fos in the medial prefrontal cortex (PFC) in rats. By comparison, the prototypical neuroleptic haloperidol induces Fos expression equally in both the medial PFC and in the dosolateral striatum (DlSt) [9].

The common structural feature of NNC 19-1228 (**7**) and NNC 22-0031 (**8**) is the 3-(4-piperidinyl)-1,2-benzisoxazol moiety, which combined through a flexible polymethylene linker with an aromatic (pi-electron rich) system, in several reports [10–13] has been shown to confer compounds with antipsychotic properties. In this paper we describe the synthesis and biological properties of a series of derivatives of NNC 22-0031 (**8**) in which the linker and the terminal arylcarbamoyloxy group has been varied. We then determined the activity of each compound in an in vitro and an in vivo profile of biological tests in order to evaluate the effect of space filling modifications and reduced flexibility.

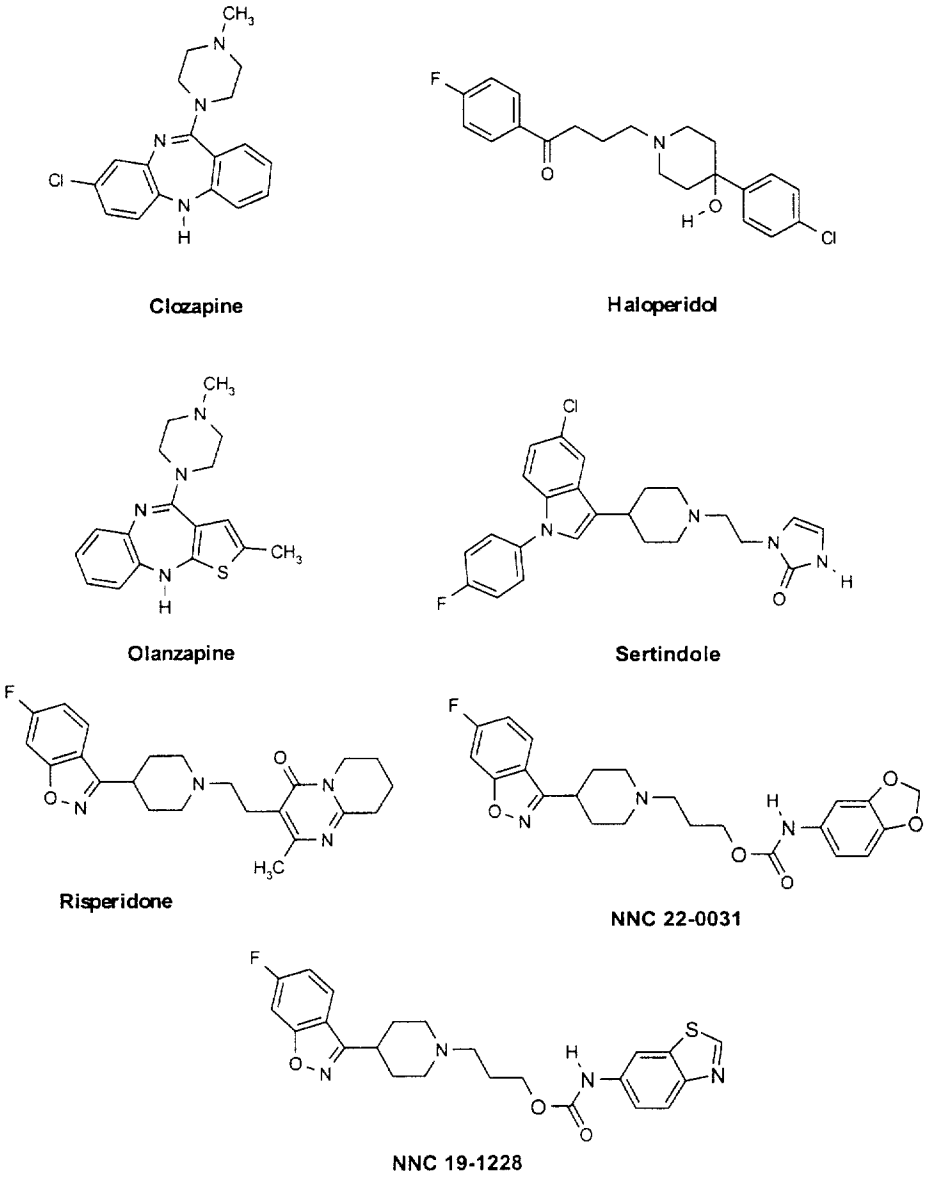


Figure 1. Antipsychotic reference compounds.

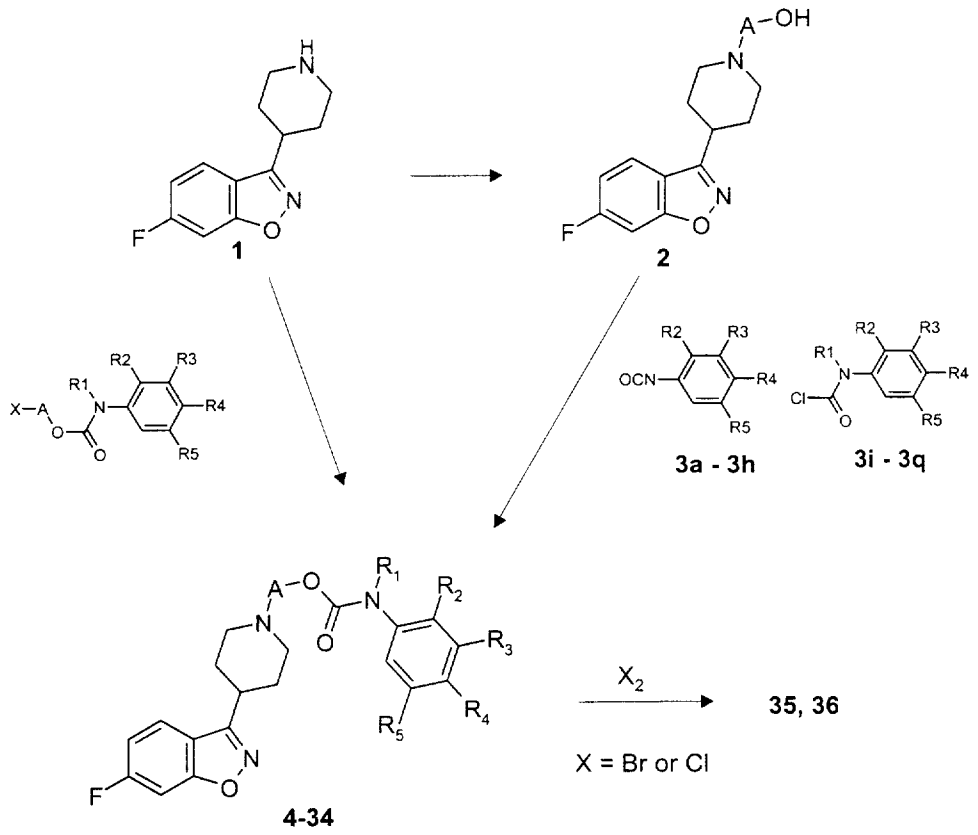


Figure 2.

2. Chemistry

The general synthetic strategy (*figure 2*) involved modification of 4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidine (**1**) [10] through either the key hydroxy alkyl intermediates **2** by reacting with arylisocyanates **3a–3h** or arylcarbamoyl chlorides **3i–3q**, or by direct alkylating to get compounds **4–34**. Halogenation of compound **8** gave the chloro and bromo derivatives **35** and **36**.

The ω-hydroxyalkyl derivatives **2a–2j** were prepared according to *figure 3*.

Commercially available ω-hydroxyalkylhalides were used for making the derivatives having the unbranched linkers (**2a–2d**). In several other cases, however, alternative methods for making the hydroxyalkyl piperidines were necessary.

Addition of **1** to 2-phenylacrylic acid, prepared from 3-hydroxy-2-phenylpropanoic acid, gave 3-(4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidino)-2-phenylpropanoic acid which by reduction with $LiAlH_4$ in toluene containing 20% (v/v) tetrahydrofuran gave **2e**. When the $LiAlH_4$ reduction was attempted using tetrahydrofuran as solvent, ring opening of the 1,2-benzisoxazol reduced yield considerably.

2,2-(1,2-Ethylene)-1,3-dihydroxypropane, prepared by $LiAlH_4$ reduction from diethyl 2,2-ethylenemalonate, was treated with n-butyl lithium and p-toluenesulfonyl chloride to give 3-chloro-2-(1,2-ethylene)propanol which under Finkelstein conditions was reacted with **1** to give **2f**.

1 was reacted with 3,3-pentamethyleneglutaric acid anhydride to give 4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-(4-carboxy-3,3-pentamethylene-1-oxo-but-1-yl)piperidine. This compound was reduced using sodium borohydride and borontrifluoride in tetrahydrofuran to give **2g**.

A similar approach was used when reacting **1** with cyclohexyl-1,2-dicarboxylic acid anhydride. Subsequent re-

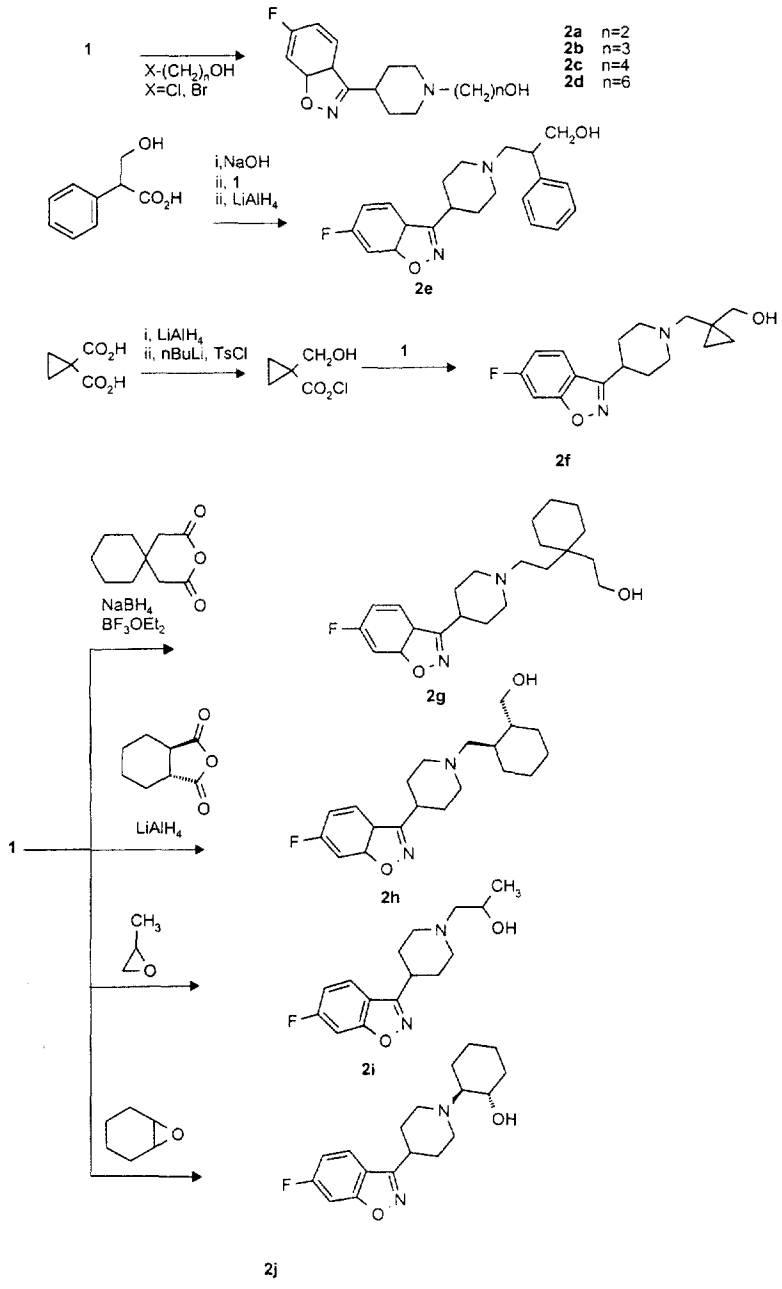
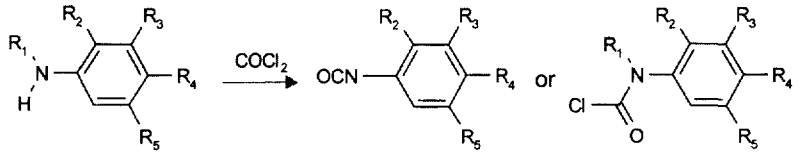


Figure 3.

duction using $LiAlH_4$ gave the 1-(2-hydroxymethylcyclohexylmethyl)piperidine **2h**.

By reacting with either propylene oxide or with 7-oxabicyclo[4.1.0]heptane at elevated temperature in an autoclave for several days **2i** and **2j** were prepared in moderate yield.

The aryl isocyanates **3a–3h** and the arylcarbamoyl chlorides **3i–3q** were prepared according to *figure 4* and



No.	R_1	R_2	R_3	R_4	R_5
3a	H	H	H	H	H
3b	H	OCH_3	H	H	H
3c	H	H	Cl	OCH_3	H
3d	H	H	OCH_3	OCH_3	OCH_3
3e	H	H	–S–CH=N–		H
3f	H	H	$-O-CH_2-O-$		H
3g	H	H	$-O-(CH_2)_2-O-$		H
3h	H	Br	$-O-CH_2-O-$		H
3i	CH_3	H	H	H	H
3j *	CH_3	H	–S–CH=N–		H
3k *	CH_3	H	$-O-CH_2-O-$		H
3l	C_2H_5	H	$-O-CH_2-O-$		H
3m	$-(CH_2)_2-$		H	H	H
3n *	$-(CH_2)_2-$		$-O-CH_2-O-$		H
3o *	$-(CH_2)_2O-$		H	H	H
3p	$-(CH_2)_3-$		H	H	H
3q *	$-(CH_2)_3-$		$-O-CH_2-O-$		H

Figure 4. * Compounds synthesised according to *figure 5*.

figure 5 if not commercially available (**3a, 3b, 3d**). Commercially available anilines were used to prepare compounds **3c, 3e–3i, 3l, 3m,** and **3p** (*figure 4*).

In some cases the amine starting materials for the desired carbamoyl chlorides had to be prepared (*figure 5*). 6-Aminobenzothiazole, or 3,4-methyldioxyaniline, was treated with trifluoroacetic acid anhydride and methyl iodide to give the N-methylanilines which by phosgene treatment gave the carbamoyl chlorides (**3j** and **3k**). Using the general procedure of Sundberg and Laurino [14], 3,4-methylenedioxyaniline was transformed into 5,6-methylenedioxyindole, which was reduced catalytically and reacted with phosgene to give **3n**. 2-Hydroxyaniline was benzoylated, treated with 1,2-dibromoethane under phase transfer conditions and hydrolysed to give the benzoxazine which by phosgene treatment gave the 4-carbamoyl chloride **3o**. 1-(6,7-Methylenedioxy-1,2,3,4-tetrahydroquinoline)carbonyl chloride **3q** was prepared starting from 3-(4,5-methylenedioxy-2-nitrophenyl)acrylic acid, which upon catalytically reduction and concomitant ring closing gave 6,7-methylenedioxy-1,2,3,4-tetrahydro-2-oxoquinoline. Reduction using sodium borohydride acetate and phosgene treatment gave **3q**.

Treatment of the ω-hydroxyalkyl derivatives **2a–2j** with the appropriate activated aniline derivatives **3a–3q** gave the desired products **4–31** (*figure 6*).

In several cases alternative procedures were needed (*figure 7*). *Trans*-2,3-methylene-1,4-butandiol prepared by $LiAlH_4$ reduction of *trans*-diethyl cyclopropyl-1,2-dicarboxylate, was treated with nBuLi and the isocyanate **3f** or **3m**. The resulting alcohol was tosylated and subsequently treated with **1** to give **32** or **33** relatively. By a similar procedure the indolinyl derivative **34**, having the 2,2-(1,2-ethylene)propyl linker were prepared. Finally, halogenation of **8** gave the chloro and bromo derivatives (**35** and **36**) (*figure 8*).

3. Results and discussion

The affinity of the compounds for the dopamine D_1- and D_2-, serotonin-$5HT_{2A}$ and α_1-adrenergic receptors was measured in in vitro radioligand binding assays (*table I*). Most of the compounds had a mixed profile with high affinity for several or all of the above mentioned receptors. The aryl carbamates, with flexible unbranched linkers (**4–12, 14–24**), all had high affinity for the

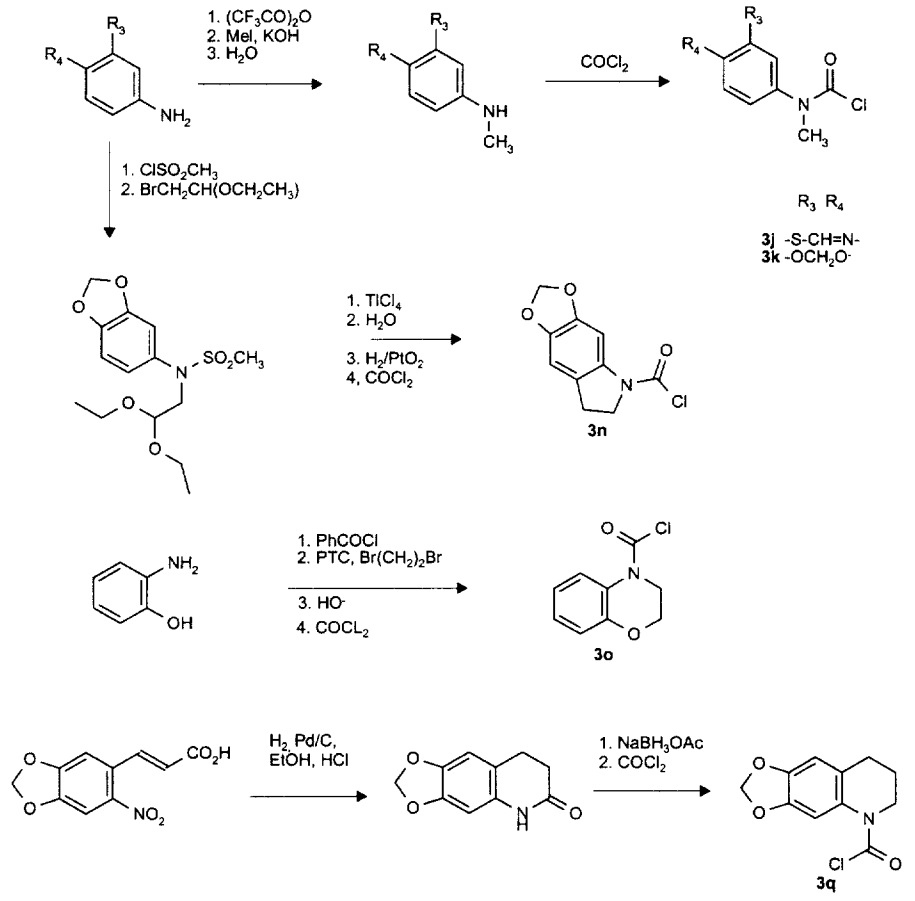
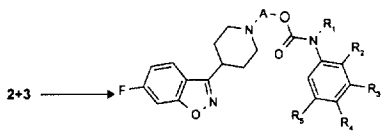


Figure 5.

dopamine D_1 and D_2, the serotonin $5HT_{2A}$ and the α_1-adrenoceptors. For these compounds the substituents on the aryl group and the length of the linker had only a minor importance. Large substituents such as $-OCH_3$ (**5**) or -Br (**36**) in the o-position of the aryl group, however, reduced the affinity for the $5HT_{2A}$ receptor when compared to compounds **4** and **8**. Alkyl (CH_3- or C_2H_5-) substituents on the carbamoyl nitrogen (**14–17**) had only minor effects on binding, although a decrease in affinity of the N-ethyl-derivative (**17**) for the D_2-receptor was observed. Restricting rotation of the carbamate group as in compounds **18–24** gave only small changes in receptor binding affinities. By adding large substituents like the phenyl group of **25** and **26** and the spiro-cyclohexyl of **28** to the linker and/or by introducing reduced flexibility as in compounds **29**, **30**, **32** and **33**, a reduction in affinity could be observed. This effect was most significant for compound **30** which had a moderate to large loss in affinity for the receptors tested. Small substituents on the linker as for compounds **13**, **27**, **31**, and **34,** had only minor effects on receptor binding.

In several studies it has been suggested that combined blockade of dopaminergic, serotonergic and α_1-adrenergic receptors can mediate mesolimbic antipsychotic potential [7, 13, 15]. The ratio of affinities for the dopamine D_2- and the serotonin $5HT_{2A}$-receptors has furthermore been implied as an indicator which differentiates 'typical' (haloperidol like, D_2-/$5HT_{2A}$ < 1) from 'atypical' (clozapine-like, D_2-/$5HT_{2A}$ > 1) antipsychotics [16, 17]. This is supported by PET studies with clozapine showing a high $5HT_{2A}$ occupancy in humans compared to D_2 occupancy [18, 19]. The importance of $5HT_{2A}$ receptors is furthermore supported by electrophysiological studies in rats showing that selective $5HT_{2A}$ antagonists can induce a partial inhibition of neuronal firing in the ventral tegmental area (VTA) while neurones in the substantia nigra pars compacta (SNC) are not affected [20] and lately by a report which suggests that the gene



4–31

No.	A	R_1	R_2	R_3		R_4	R_5
4	$-(CH_2)_3-$	H	H	H		H	H
5	$-(CH_2)_3-$	H	OCH_3	H		H	H
6	$-(CH_2)_3-$	H	H	Cl		OCH_3	H
7	$-(CH_2)_3-$	H	H		–S–CH=N–		H
8	$-(CH_2)_3-$	H	H		$-O-CH_2-O-$		H
9	$-(CH_2)_3-$	H	H	OCH_3		OCH_3	OCH_3
10	$-(CH_2)_3-$	H	H		$-O-(CH_2)_2-O-$		H
11	$-(CH_2)_2-$	H	H		$-O-CH_2-O-$		H
12	$-(CH_2)_6-$	H	H		$-O-CH_2-O-$		H
13	$-CH_2CH(CH_3)-$	H	H		$-O-CH_2-O-$		H
14	$-(CH_2)_3-$	CH_3	H	H		H	H
15	$-(CH_2)_3-$	CH_3	H		–S–CH=N–		H
16	$-(CH_2)_3-$	CH_3	H		$-O-CH_2-O-$		H
17	$-(CH_2)_3-$	C_2H_5	H		$-O-CH_2-O-$		H
18	$-(CH_2)_3-$	$-(CH_2)_2-$		H		H	H
19	$-(CH_2)_3-$	$-(CH_2)_3-$		H		H	H
20	$-(CH_2)_3-$	$-(CH_2)_2-$			$-O-CH_2-O-$		H
21	$-(CH_2)_2-$	$-(CH_2)_3-$			$-O-CH_2-O-$		H
22	$-(CH_2)_3-$	$-(CH_2)_3-$			$-O-CH_2-O-$		H
23	$-(CH_2)_4-$	$-(CH_2)_3-$			$-O-CH_2-O-$		H
24	$-(CH_2)_3-$	$-(CH_2)_2O-$		H		H	H
25	$-CH_2CH(Ph)CH_2-$	$-(CH_2)_2-$			$-O-CH_2-O-$		H
26	$-CH_2CH(Ph)CH_2-$	$-(CH_2)_3-$			$-O-CH_2-O-$		H
27	$-CH_2C(CH_2)_2CH_2-$	$-(CH_2)_2-$			$-O-CH_2-O-$		H
28	$-(CH_2)_2C(CH_2)_5(CH_2)_2-$	H	H	OCH_3		OCH_3	OCH_3
29		H	H		$-O-CH_2-O-$		H
30		H	H		$-O-CH_2-O-$		H
31	$-CH(CH_3)CH-$	$-(CH_2)_3-$		H		H	H

Figure 6.

for the $5HT_{2A}$ receptor confers susceptibility to schizophrenia [21]. However, the $5HT_{2A}$-antagonist ritanserin does not induce Fos protein immuno reactivity in the medial prefrontal cortex and the combination of haloperidol and ritanserin does not mimic the effect of clozapine [8].

The α_1-adrenoceptor component of receptor binding may also be of importance for the action of 'atypical' neuroleptics [7]. By combining the 'typical' antipsychotic haloperidol with the α_1 antagonist prazosine a selective reversal of the blockade of the firing of SNC neurones but not the VTA neurones can be seen [22]. However, the addition of prazosine to haloperidol does not mimic the effect of clozapine on Fos protein immuno reactivity in the rat forebrain [23]. In the rat paw model of antipsychotic activity it has been shown that a combination of D_1-, $5HT_{2A}$and α_1-antagonists yields, a behavioral profile similar to that of the 'atypical' clozapine, can be obtained [24].

By looking for compounds which potently bind to both dopamine D_1 and D_2, serotonin $5HT_{2A}$ and α_1-adrenoceptors and for which the ratio D_2-/$5HT_{2A}$ (IC_{50}'s)

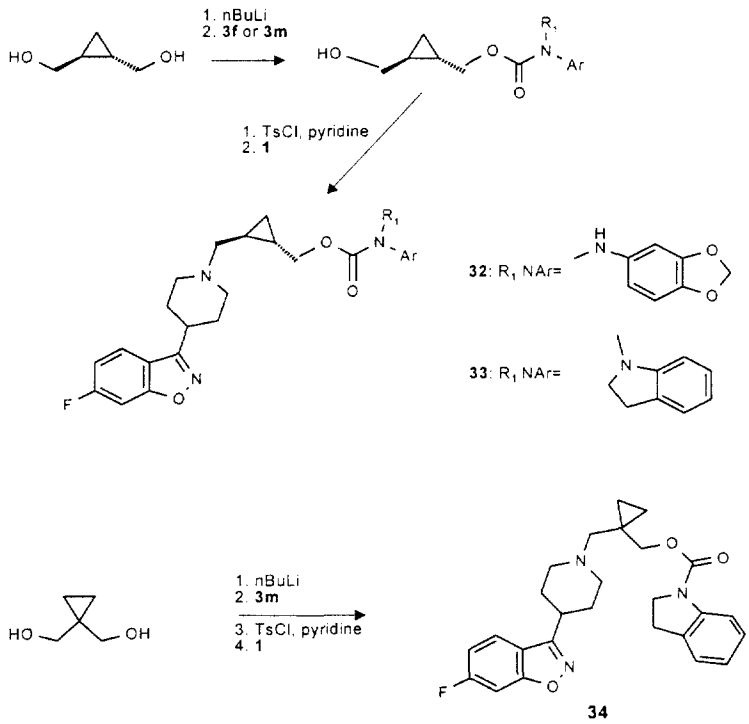


Figure 7.

were relative high (approximately 1 or more), several compounds could be selected as candidates for further testing in in vivo behavioural models (*table II*).

Tests measuring the reversal of methylphenidate (MPD)-induced hypermotility and stereotyped gnawing behaviour have previously been used to screen for the identification of mesolimbic, selective, antipsychotic activity [7]. Whereas MPD-induced motility is believed to predict mesolimbic selectivity [25], MPD-induced gnawing is considered a 'classical' stimulant-induced behaviour involving the nigrostriatal DA pathway [26].

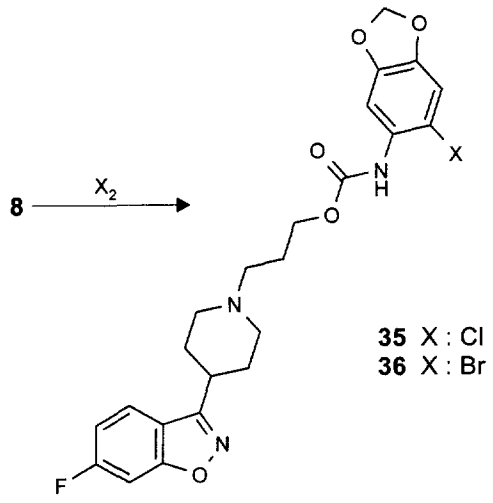


Figure 8.

Several compounds were potent inhibitors of MPD-induced motility with little or no effect in the gnawing test. Among the most potent and selective were compounds **4**, **7**, **8**, **15**, **16**, **18**, **19**, **20**, **22**, **23**, **35**, and **36**. Compounds **12** and **29** were potent but non-selective while compounds, **25**, **26**, **27**, **28**, **29**, **30**, **31**, and **34** were considerably less active in the motility test. Interestingly, all the potent and selective compounds have linkers with a 3 carbon chain while the inactive all have substituted linkers.

Condition avoidance responding (CAR) in rats is a classical test for antipsychotic activity in which both haloperidol, risperidone, clozapine and sertindole are active. In the catalepsy test for extrapyrimidal syndrome (EPS)-inducing potential, haloperidol is very active whereas the 'atypical' antipsychotics clozapine, risperidone and sertindole are inactive at doses of up to more than 64 mg/kg.

Table I. In vitro binding affinities IC_{50} (in nM) of test compounds and selected antipsychotic reference substances.

Compound	D_1	D_2	$5HT_{2A}$	α_1-
4	61.56 ± 3.03	14.40 ± 1.63	5.17 ± 0.233	4.17 ± 0.267
5	64	22.20 ± 2.4	10.23 ± 0.39	3.67 ± 0.68
6	57.9 ± 3.78	5.97 ± 1.33	7.33 ± 0.12	3.7
7	26	4.57 ± 0.422	0.64	3.3
8	14.9 ± 1.20	7.18 ± 0.598	4	3.2
9	100	10	0.79	3.9
10	21	1.9	1.4	2.6
11	69	14.63 ± 1.68	5.10 ± 0.29	6.97 ± 0.78
12	45.87 ± 1.36	3.2	6.37 ± 0.55	–
13	198.33 ± 7.13	13.20 ± 1.41	6.90 ± 0.66	–
14	40.97 ± 1.85	8.93 ± 0.285	7.17 ± 0.88	6.13 ± 0.22
15	45.33 ± 1.67	4.55 ± 0.45	4.8	6.47 ± 0.59
16	25.83 ± 0.98	4.83 ± 0.22	4.07 ± 0.09	4 ± 0.20
17	28.42 ± 1.41	18	6.70 ± 0.92	3.67 ± 0.12
18	58.8 ± 3.67	7.40 ± 1.04	9.2	3.80 ± 0.31
19	65.23 ± 1.59	3.5	6.10 ± 0.32	3.20 ± 0.36
20	34	3.93 ± 0.18	2.43 ± 0.09	3.27 ± 0.09
21	125 ± 67	4.90 ± 0.10	7.07 ± 0.39	35.70 ± 3.99
22	35	9.10 ± 1.20	6.40 ± 0.74	12.07 ± 0.78
23	43 ± 5.35	4.9	32	9.93 ± 0.59
24	–	–	6.5 ± 0.79	5.3 ± 1.48
25	–	–	49.33 ± 6.54	56.23 ± 12.03
26	121	–	69.5 ± 3.98	20.37 ± 3.17
27	152.3 ± 5.20	4.03 ± 0.23	7.7 ± 1	30
28	69.46 ± 7.67	33.03 ± 3.5	13.5 ± 0.76	–
29	219.70 ± 15.84	4.23 ± 0.72	4	–
30	> 1000	184.17 ± 17.51	> 1000	–
31	236.33 ± 1.76	29	4.3 ± 0.42	–
32	–	–	2.7 ± 0.49	3.87 ± 0.43
33	72	18.47 ± 0.91	11.63 ± 0.19	2.83 ± 0.09
34	429	13.63 ± 1.40	8.60 ± 0.21	31.57 ± 0.32
35	60.45 ± 0.75	3.2	4.13 ± 0.43	8.33 ± 1.08
36	64.40 ± 1.91	3.6	16.95 ± 3.15	3.5 ± 0.30
Clozapine	173	134	25	32
Haloperidol	127	4.3	128	50

IC_{50} values for inhibition of [^{3}H]ketanserin ($5HT_{2A}$) or [^{3}H]prazocine (α_1-) to rat frontal cortical membranes and of [^{3}H]spiperone (D_2-) or [^{3}H]SCH23390 to rat striatal membranes. Results are means ± SEM of 3–14 experiments. SEM not given for results based on 2 experiments.

The selected test compounds were moderately to weakly active in CAR while considerably less potent in the catalepsy test. The most potent and selective compounds were **7, 8, 10, 11**, and **18**.

Overall comparison of the in vivo screening data suggested that the compounds **7**, **8**, **10**, **11**, and **18** had a possible mesolimbic, selective, antipsychotic potential.

Limbic selectivity, as indicated by the pharmacological profile, was accompanied by an anatomical selectivity: Microdialysis assessment in vivo of the dopamine metabolite dihydroxyphenyl acetic acid (DOPAC) was obtained in limbic (i.e. medial prefrontal cortex) and nonlimbic (i.e. dorsolateral striatum) areas of freely moving rats (*figure 9*). At doses of 0.3, 1 and 3 mg/kg of compound **7** (NNC 19-1228), 1 and 3 mg/kg of compound **8** (NNC 22-0031) and 2 and 4 mg/kg of compound **10** (NNC 19-1225) there was a clear separation between the increase in interstitial DOPAC in medial prefrontal cortex and dorsolateral striatum. This result was in accordance with the earlier reported limbic preference of

Table II. In vivo pharmacological profile ED_{50} (in mg/kg) of test compounds and selected antipsychotic reference compounds.

Compound	MPD motility	MPD gnawing	CAR	Catalepsy
4	3.8	> 100	29	> 100
5	10.8	> 100	> 30	–
6	–	–	> 30	–
7	1.7	94	16	> 100
8	1.7	> 100	5.9	> 100
9	10.8	> 100	24	> 100
10	15.3	> 100	11	> 100
11	8.3	54	12	> 100
12	8.6	4.5	> 5.0	> 10
13	10.4	36.4	–	–
14	10.3	81	30	–
15	5.6	75	–	–
16	3.2	32	15	27.4
17	11.4	> 100	20.5	–
18	3.8	54.3	12.4	> 100
19	1.2	> 100	> 30	67
20	2.0	35.9	12	30
21	11.2	> 100	–	–
22	2.8	32	–	> 100
23	6.3	> 100	–	–
24	10.2	> 100	–	–
25	32.2	–	–	–
26	39.9	–	–	–
27	48.6	–	–	–
28	43.7	–	–	–
29	12.7	8.3	–	–
30	70	–	–	–
31	40	–	> 5	–
32	11.4	–	–	–
33	39.3	> 100	–	–
34	85	–	–	–
35	6.0	32.8	–	–
36	8.0	25	7.5	6.8
Clozapine	40	122	11	> 64
Haloperidol	0.3	0.9	0.2	0.8

clozapine, risperidone, and sertindole [8, 13]. In contrast the 'typical' neuroleptic haloperidol effects DOPAC levels equally in both areas [8, 13].

It has been demonstrated that acute administration of antipsychotic drugs excites DA neurones of the rat midbrain, causing elevation of baseline firing rates. In addition, due to their ability to antagonise DA receptors, such drugs also reverse the inhibition of DA neurone firing produced by DA agonists such as apomorphine ad amphetamine. 'atypical' antipsychotic drugs appear to produce somewhat selective effects on A10 DA cells, which is witnessed during acute experiments as an ability to reverse DA agonist-induced firing of A10 DA cells to supra-threshold rates, while reversing A9 DA cells to only baseline rates or below. In contrast, 'typical' antipsychotic drugs produce similar effects on both populations of neurones [22].

Using standard extracelluar single-cell recording from identified A9 and A10 DA neurones in chloral anaesthetised rats [27] it has been shown that compound **7** (NNC 19-1228) and **8** (NNC 22-0031) reverse apomorphine-induced inhibition of firing of A10 DA cells to above basal levels while reversing that of A9 DA cells to near basal levels (*figure 10*). By this method, compound **7** was more potent than **8**, but perhaps not quite as selective. Both compounds are selective for the A10 neurones and more potent than clozapine. Reference results with clozapine indicate that it is most selective, whereas the 'typical' antipsychotic haloperidol did not produce any difference between A9 and A10 DA cells (*figure 10*).

4. Conclusion

A generally adopted medicinal chemistry strategy for producing 'atypical' antipsychotic agents has been to modify dopamine or serotonin mimicking arylpiperazine or -piperidine derivatives. By combining such entities through a linker with a system rich in pi-electrons, compounds can be made which antagonise dopaminergic, serotonin and adrenergic receptor binding.

In this study we have linked a 3-(6-fluoro-1,2-benzisoxazol-3-yl)piperidine with an arylcarbamate to get compounds which bind to dopamine-D_1 and -D_2, serotonin $5HT_{2A}$ and α_1-adrenergic receptors and which have higher affinity for $5HT_{2A}$ than D_2-receptors. This strategy has yielded compounds which in behavioural and anatomical studies have properties suggesting an 'atypical' antipsychotic profile.

Two compounds (**12** and **29**) both have a haloperidol-like 'typical'-behavioral profile in mice, which cannot be explained by their receptor binding profile. Both examples have high affinities for the dopamine-D_2 receptor and $D_2/5HT_{2A}$-ratio > 1.

It is recognised that the in vivo potency and selectivity might be influenced by modulation of receptors different from those investigated in this study. Compounds **7** and **8** have been screened for binding to several different receptors in vitro [7]. It was found that the two compounds failed to bind significantly to most neurotransmitter receptor or uptake sites. An exception is a moderate affinity of **8** for ^{3}H-pyrilamine-labelled histamine receptors (IC_{50} = 330 nM) and ^{3}H-mesurlergine-labelled $5HT_{2c}$ receptors (IC_{50} = 108 nM). None of the

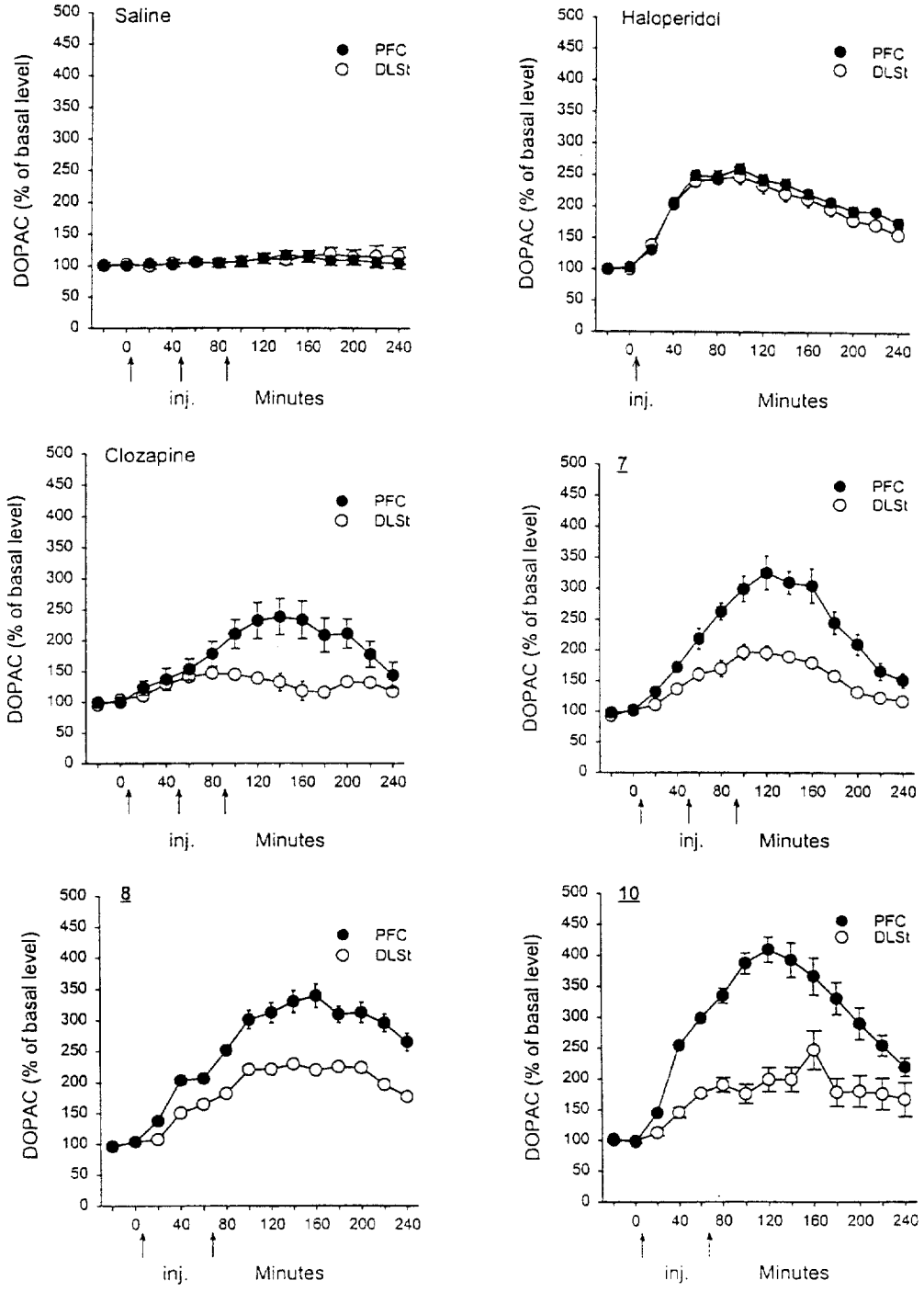


Figure 9. Effect of saline, NNC 19-1225 (**10**) (accumulative doses of 2 and 4 mg/kg), NNC 19-1228 (**7**) (accumulative doses of 0.3, 1 and 3 mg/kg), NNC 22-0031 (**8**) (accumulative doses of 1 and 3 mg/kg), haloperidol (0.1 mg/kg), and clozapine (accumulative doses of 1.2 and 4 mg/kg) on extracellular levels of DOPAC in prefrontal cortex (solid circles) and in the dorsolateral striatum (open circles) of awake rats. Each curve shows the mean value for three to six animals with individual points calculated as percentage of the last two basal values before drug administration.

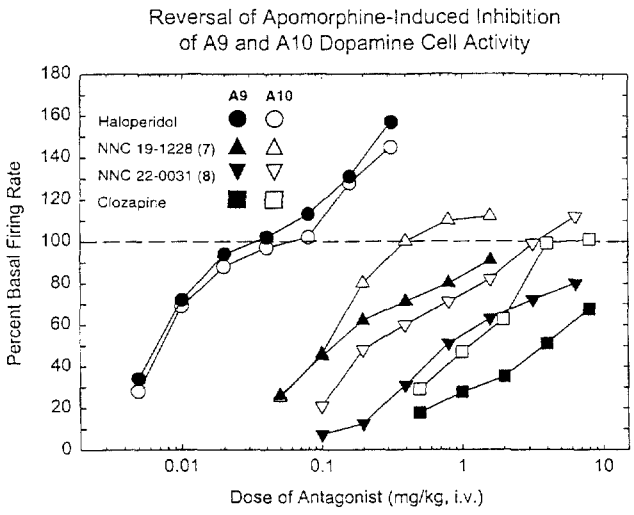


Figure 10. Dose–response curves illustrating the relative potency and efficacy of NNC 19-1228 (**7**) and NNC 22-0031 (**8**) to reverse the complete inhibition of dopamine cell activity produced by intravenous administration of apomorphine. The sample size for each curve is 12. Error bars are not shown to improve the clarity of the figure; standard errors were never over 12%. NNC 19-1228 (**7**) was significantly more effective at reversing the inhibition of A10 cells as compared to A9 dopamine cells ($F_{1,22} = 11.27$, $p < 0.01$), albeit primarily at higher doses. NNC 22-0031 (**8**) was also significantly more effective at reversing A10 as compared to A9 dopamine neurones ($F_{1,22} = 16.59$, $p < 0.001$), across the entire dose range evaluated. For comparative purposes, previous results obtained in identical experiments with haloperidol and clozapine are also plotted. It is clear that both NNC 19-1228 (**7**) and NNC 22-0031 (**8**) fall somewhere between these 2 prototypes with respect both to potency and selectivity for A10 dopamine cells.

two compounds had any affinity for muscarinic receptors ($IC_{50} > 1000$ nM).

The most potent and selective compounds in vitro and in vivo, compounds **7** (NNC 19-1228), **8** (NNC 22-0031), and **10** (NNC 19-1225) all have a flexible, unsubstituted polymethylene chain linking the arylpiperidine and the arylcarbamate entities. This result suggests that coincident binding of both structural elements might be a necessity in order to obtain the optimal pharmacological profile. An analogous study [28] published during the preparation of this manuscript also suggests that in a series of 4-(1,2-benzisothiazol-3-yl)-1-piperazinyl derivatives a folded conformation might be optimal. Although neither this study nor the present data proves a bended biactive conformation, they do suggest that conformational flexibility is important for antipsychotics prepared as a consequence of the above strategy.

5. Experimental protocols

5.1. Chemistry

Melting points (uncorrected) were determined using a Buchi capillar melting point apparatus. ^{1}H-NMR were recorded at 200 MHz, on a Bruker AC-200 MHz FT-NMR instrument unless otherwise indicated, and mass spectra with a Finnigan 5100 mass spectrophotometer. Column chromatography was performed on silica gel 60 (70–230 mesh, ASTM, Merck). Elemental analysis was performed by Novo Nordisk, Microanalytical Laboratory, Denmark, and was within ±0.4% of the calculated values unless otherwise noticed. For all compounds purity was checked by thin-layer chromatography on Merck silica gel 60 F_{254} pre-coated aluminium sheets, and by high performance liquid chromatography. No particular attempts were made to optimise reaction conditions for most of the reactions described.

*5.1.1. 4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-(3-phenylcarbamoyloxy)propyl)-piperidine, hydrochloride **4***

a: 4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidine (**1**), hydrochloride (5.0 g, 20 mmol), 3-bromopropanol (2.0 mL, 21.6 mmol) and potassium carbonate (6.5 g, 47 mmol) in 300 mL dry acetone were refluxed for 16 h. The mixture was cooled to room temperature, filtered and concentrated in vacuo. Recrystallisation from ethanol/water gave 4.3 g of 3-(4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidino)propanol (**2b**). M.p. 139–141 °C.

b: Phenylisocyanate (**3a**) (0.36 g, 3 mmol) and **2b** (0.3 g, 1.1 mmol) was refluxed in toluene (25 mL) for 6 h. The mixture was cooled to room temperature and hydrochloric acid in ether was added. The resulting precipitate was recrystallised from ethanol/ether and isopropanol/ether to give 180 mg of the title compound as white crystals. M.p. 204.5–205.5 °C. MS (70 eV): *m/z* 397 (39%, M^+), 278 (4), 259 (26), 233 (50), 178 (28), 96 (100). ^{1}H-NMR (DMSO-d_6): 2.25 (broad, d, 4H), 2.48 (broad, d, 2H), 3.23 (m, 5H), 3.69 (d, 2H), 4.23 (m, 2H), 6.99 (t, 1H), 7.3 (m, 3H), 7.45 (d, 2H), 7.72 (d, 1H), 8.25 (m, 1H), 9.7 (s, 1H), 11.1 (s, 1H). Anal. ($C_{24}H_{26}FN_3O_7$, 0.25 H_2O) CHN.

*5.1.2. 4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-(3-(2-methoxyphenylcarbamoyloxy)propyl)piperidine, hydrochloride **5***

2-Methoxyphenylisocyanate (**3b**) (270 mg, 2 mmol) and 3-(4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidino)propanol (**2b**) (280 mg, 1 mmol) was dissolved in 100 mL dry toluene and refluxed for 16 h. 50 mL ethyl acetate was added to the cooled mixture, which was then washed with water and saturated sodium chloride. 2.5 mL (1.9 M) HCl in ethanol was added and the solution was concentrated to about 30 mL crystallising 310 mg (66.8%) of the desired product. M.p. 174–175 °C. MS (70 eV): *m/z* 427 (30%, M^+), 289 (19), 233 (33), 96 (100). ^{1}H-NMR (DMSO-d_6): 2.18 (broad, 4H), 2.45 (m, 2H), 3.17 (broad, 4H), 3.65 (m, 3H), 3.83 (s, 3H), 4.20 (t, 2H), 6.98 (m, 4H), 7.3 (dt, 1H), 7.72 (m, 2H), 8.25 (m, 1H), 8.45 (s, 1H), 11.0 (s, 1H). Anal. ($C_{23}H_{27}N_3O_4ClF$, 0.5 H_2O) CHNCl.

*5.1.3. 4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-(3-(3-chloro-4-methoxyphenyl-carbamoyloxy)propyl)piperidine, hydrochloride **6***

To a solution of phosgene (7.5 mmol) in 9 mL dry toluene was added 3-chloro-4-methoxyaniline (470 mg, 3 mmol) dissolved in 25 mL of dry toluene. The mixture was refluxed for 4 h and at 60 °C for 16 h. After cooling and concentration in vacuo the crude

3-chloro-4-methoxyphenylisocyanate (**3c**) was used without further purification to react with 3-(4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidino)propanol (**2b**) (560 mg, 2 mmol) using the procedure for compound **4** to prepare 500 mg (50.2%) of the desired product. M.p. 212–215 °C. ^{1}H-NMR (DMSO-d_6): 2.15 (m, 4H), 2.38 (broad, 2H), 3.15 (broad, m, 4H), 3.48 (m, 1H), 3.65 (d, 2H), 3.8 (s, 3H), 4.22 (t, 2H), 7.05 (d, 1H), 7.32 (m, 2H), 7.63 (broad, 1H), 7.7 (dd, 1H), 8.35 (m, 1H), 9.70 (s, 1H), 11.1 (broad, 1H). Anal. ($C_{23}H_{26}N_3O_4FCl_2$, 0.5 H_2O) CHNCl.

5.1.4. 1-(3-(6-Benzothiazolylcarbamoyloxy)propyl)-4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidine, oxalate ***7***

A mixture of 6-aminobenzothiazole (300 mg, 2 mmol) in toluene (20 mL) and phosgene (10 mL 20% in toluene, 19 mmol) was refluxed for 6 h. The solvent was removed under reduced pressure to give crude 6-benzothiazolylisocyanate (**3e**). Using the procedure for compound **4** the crude (**3e**) was combined with 3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-piperidino]propanol (**2b**) (410 mg, 1.5 mmol) in 10 mL DMF to give the 0.7 g (85.7%) of the title compound. M.p. 176–177 °C. MS (70 eV): *m/z* 454 (3%, M^+), 27 (25), 233 (30), 190 (17), 176 (55), 150 (37), 140 (53), 96 (100). ^{1}H-NMR (DMSO-d_6): 2.05–2.25 (m, 6H), 2.90–3.15 (m, 4H), 3.5 (broad, 3H), 4.21 (t, 2H), 7.32 (dt, 1H), 7.55 (dd, 1H), 7.72 (dd, 1H), 7.92 (d, 2H), 8.12 (dt, 1H), 8.35 (s, 1H), 9.25 (s, 1H), 10.0 (s, 1H). A small sample was for microanalysis converted to the dihydrochloride by standard procedures. Anal. ($C_{23}H_{25}FN_4OSCl_2$, 0.25 H_2O) CHNCl.

5.1.5. 4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-(3-(3,4-methylenedioxyphenyl-carbamoyloxy)propyl)piperidine, oxalate ***8***

Using the procedure described for compound **4** starting from 3-(4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidino)propanol (**2b**) (140 mg, 0.5 mmol) and 3,4-methylenedioxyphenylisocyanate (**3f**) (240 mg, 1.5 mmol), prepared from 3,4-methylenedioxyaniline and phosgene, was prepared 210 mg (79%) of the title compound. M.p. 133–136 °C. MS (70 eV): *m/z* 441 (20%, M^+), 303 (15), 278 (16), 233 (53), 163 (52),140 (37), 96 (100). ^{1}H-NMR (DMSO-d_6): 2.10 (m, 4H), 2.25 (broad d, 2H), 3.05 (m, 4H), 3.50 (broad, 3H), 4.15 (t, 2H), 6.00 (s, 2H), 6.85 (m, 2H), 7.13 (broad s, 1H), 7.35 (dt, 1H), 7.75 (dd, 1H), 8.10 (dt, 1H), 9.65 (s, 1H). Anal. ($C_{23}H_{24}FN_3O_5$, 1.4 $C_4H_6O_6$) CHN.

5.1.6 4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-(3-(3,4,5-trimethoxyphenylcarbamoyloxy)propyl)piperidine, oxalate ***9***

A mixture of 3,4,5-trimethoxyaniline (365 mg, 2.0 mmol) in toluene (20 mL) and phosgene (6 mL 20% in toluene; 12 mmol) was refluxed for 6 h. The solvent was removed under reduced pressure to give crude 3,4,5-trimethoxyphenylisocyanate (**3d**) to which was added 3(4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidino)-propanol (**2b**) (420 mg, 1.5 mmol) in DMF (10 mL). The mixture was stirred at 100 °C for 2 h and then at room temperature for 16 h, whereupon it was taken up in ethyl acetate and water. The organic phase was washed with water and saturated sodium chloride and concentrated in vacuo. The resulting oil was taken up in acetone/ethanol (4:1, v/v) and oxalic acid (150 mg) in 2 mL acetone added to precipitate the desired product. The product was washed with ice cold ethanol giving 550 mg (63.5%) of the title compound. M.p. 77–80 °C. MS (70 eV): *m/z* 487 (9%, M^+), 287 (31), 233 (40), 209 (56), 194 (45), 140 (67), 96 (100). ^{1}H-NMR ($CDCL_3$): 2.05 (m, 4H), 2.22 (broad d, 2H), 2.95–3.15 (m, 4H), 3.5 (broad, 3H), 3.6 (s, 3H), 3.71 (s, 6H), 4.15 (t, 2H), 6.82 (s, 2H), 7.32 (dt, 1H), 7.75 (dd, 1H), 8.09 (dt, 1H), 9.6 (s, 1H). Anal. ($C_{17}H_{32}N_3O_6F$) CHN.

5.1.7. 1-(3-(3,4-Ethylenedioxyphenyl-carbamoyloxy)propyl)-4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidine, oxalate ***10***

A mixture of 1,4-benzodioxan-6-amine (300 mg, 2.0 mmol) in toluene (20 mL) and phosgene (10 mL 20% in toluene; 19 mmol) was refluxed for 6 h. The solvent was removed under reduced pressure to give crude 3,4-ethylenedioxyphenylisocyanate (**3g**). To the crude product was added 3-[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidino]propanol (**2b**) (420 mg, 1.5 mmol) in DMF (10 mL). The mixture was stirred at 100 °C for 2 h and then at room temperature for 16 h, whereupon it was taken up in ethyl acetate and water. The organic phase was washed with water and saturated sodium chloride and concentrated in vacuo. The resulting oil was taken up in acetone/ethanol (4:1, v/v) and oxalic acid (150 mg) in 2 mL acetone added to precipitate the desired product. The product was washed with ice cold ethanol to give 600 mg (73.3%) of the title compound. M.p. 109–110 °C. MS (70 eV): *m/z* 455 (32%, M^+), 278 (23), 233 (49), 177 (89), 140 (48), 121 (42), 96 (100). ^{1}H-NMR ($CDCl_3$): 2.05 (m, 5H), 3.10 (broad, 4H), 3.50 (broad, 3H), 4.15 (t, 2H), 4.30 (m, 3H), 6.75 (d, 1H), 6.87 (d, 1H), 7.05 (broad s, 1H), 7.35 (dt, 1H), 7.75 (dd, 1H), 8.10 (dt, 1H), 9.5 (s, 1H). Anal. ($C_{24}H_{27}N_3O_5FCl$) CHN.

5.1.8. 4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-(2-(3,4-methylenedioxyphenyl-carbamoyloxy)ethyl)piperidine, hydrochloride ***11***

Starting from 3,4-methylenedioxyphenylisocyanate (**3f**) (320 mg, 2 mmol) and 2-(4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidino)ethanol (**2a**) (270 mg, 1 mmol) in 5 mL dry DMF using the procedure described for compound **4** was prepared 210 mg of the title compound as free base. This product was dissolved in 5 mL ethanol/acetone (50%, v/v) and ethanolic hydrochloric acid added to precipitate 180 mg (40%) of the desired product as white crystals. M.p. 226–229 °C. MS (70 eV): *m/z* 428 (47%, M^+), 246 (42), 233 (100), 208 (21), 190 (47), 163 (70). ^{1}H-NMR (DMSO-d_6): 2.22 (m, 2H), 2.40 (m, 2H), 3.25 (m, 2H), 3.5 (broad, 3H), 3.7 (broad, d, 2H), 4.52 (broad, 2H), 5.98 (s, 2H), 6.85 (m, 2H), 7.15 (s, 1H), 7.35 (dt, 1H), 7.72 (dd, 1H), 8.25 (m, 1H), 9.85 (s, 1H), 11.0 (s, 1H). Anal.($C_{22}H_{23}FN_3O_5Cl$) CHNCl.

5.1.9. 4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-(6-(3,4-methylenedioxyphenylcarbamoyloxy)hexyl)piperidine ***12***

a: A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazole (**1**) hydrochloride (1 g, 3.9 mmol), lithium carbonate (865 mg, 1.7 mmol) and 6-chloro-1-hexanol (534 mg, 3.9 mmol) in 5 mL dry DMF was heated at 100 °C for 48 h. The reaction was poured into water and the aqueous mixture was extracted with ethyl acetate. The ethyl acetate phase was washed with water, brine, dried with sodium sulphate and concentrated in vacuo. The crude product was purified by column chromatography on silica gel 60 eluting with ethyl acetate: methanol (9:1, v/v). Concentration of the appropriate fractions afforded 310 mg (25.6%) of 6-fluoro-3-(1-(1-hydroxyhex-6-yl)-4-piperidinyl)-1,2-benzisoxazole (**2d**) as an oil. MS (70 eV): *m/z* 320 (M^+, 28%), 233 (47), 190 (15), 182 (50), 96 (100), 82 (100), 82 (21), 55 (23). ^{1}H-NMR ($CDCl_3$): 1.39 (m, 4H), 1.58 (m, 4H), 2.10(m, 6H), 2.41 (t, 2H), 3.09 (broad d, 3H), 3.65 (t, 2H), 7.04 (dt, 1H), 7.23 (dd, 1H), 7.75 (q, 1H).

b: Starting from 6-fluoro-3-(1-(1-hydroxyhex-6-yl)-4-piperidinyl)-1,2-benzisoxazole (**2d**) (270 mg, 0.84 mmol) and 3,4-methylenedioxyphenylisocyanate (**3f**) (297 mg, 1.69 mmol) using the procedure described for compound **4** was prepared 210 mg (51.8%) of the title compound as an amorphous solid. MS (70 eV): *m/z* 483 (M^+, 1.5%), 320 (22), 233 (45), 182 (32), 163 (100), 130 (75), 96 (70), 77 (35). ^{1}H-NMR ($CDCl_3$): 1.4 (m, 4H), 1.6 (m, 4H), 2.11 (m, 6H), 2.42 (t, 2H), 3.09 (broad d, 3H), 4.15 (t, 2H), 5.95 (s, 2H), 6.70 (m, 2H), 7.05 (m, 2H), 7.24 (m, 2H), 7.72 (q, 1H).

*5.1.10. 4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-(2-(3,4-methylenedioxyphenylcarbamoyloxy)propyl)piperidine, oxalate **13***

a: A mixture of 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazol (**1**) (1.5 g, 6.8 mmol) and propylene oxide (2 g, 34.4 mmol) in 25 mL acetonitrile was heated to 50 °C in an autoclave for 3 days. The cooled reaction was concentrated in vacuo and purified by column chromatography on silica gel 60 eluting with ethyl acetate: methanol (9:1, v/v). Concentration of the appropriate fraction afforded 1.3 g (68.4%) of 6-fluoro-3-(1-(2-hydroxyprop-1-yl)-4-piperidinyl)-1,2-benzisoxazole (**2i**). M.p. 45–47 °C. MS (70 eV): *m/z* 278 (M^+, 18%), 233 (100), 190 (28), 109 (12), 96 (70), 82 (25), 68 (14), 55 (22).

b: Starting from 3-(1-(2-hydroxyprop-1-yl)-4-piperidinyl)-6-fluoro-1,2-benzisoxazole (**2i**) (500 mg, 1.1 mmol) and 3,4-methylenedioxyphenylisocyanate (**3f**) (500 mg, 2.2 mmol) using the procedure described for compound **4** was prepared 100 mg (17%) of the title compound. M.p. 163–164 °C. MS (70 eV): *m/z* 441 (M^+, 11%), 260 (32), 233 (100), 190 (25), 163 (17), 136 (33), 96 (58). ^{1}H-NMR (DMSO-d_6): 1.25 (d, 3H), 1.92–2.18 (m, 5H), 2.80 (broad, 1H), 3.00 (broad, 2H), 3.42 (broad, 3H), 5.11 (m, 1H), 5.94 (s, 2H), 6.85 (dd, 2H), 7.15 (s, 1H), 7.28 (dt, 1H), 7.71 (dd, 1H), 8.0 (q, 1H), 9.75 (s, 1H). Anal. ($C_{25}H_{26}N_3FO_9$, 0.5 H_2O) CHN.

*5.1.11. 4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-(3-(N-methyl-N-phenylcarbamoyloxy) propyl)piperidine, oxalate **14***

To a solution of phosgene (11.6 mmol) in 6 mL of dry toluene and 10 mL methylene chloride was added a solution of N-methylaniline (1.07 g, 10 mmol) and triethylamine (1.4 g, 14 mmol) in 10 mL methylene chloride over 20 min at 0 °C. After being stirred at 30 °C for 2 h the mixture was diluted with 200 mL heptane and washed with 5 N H_2SO_4, water, brine, dried over Na_2SO_4 and concentrated in vacuo. The crude product was taken up in heptane and 1.2 g (71%) of N-methyl-N-phenylcarbamoyl chloride (**3i**) was collected by filtration. M.p. 85–87 °C.

To a solution of 3-(4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidino)propanol (**2b**) (289 mg, 1 mmol) in 30 mL THF was added n-butyllithium in hexane (0.7 mL, 1.12 mmol) and allowed standing for 30 min. A solution of N-methyl-N-phenylcarbamoylchloride (**3i**) (190 mg, 1.12 mmol) in 5 mL THF was added over 25 min and stirred for 16 h. The reaction mixture was diluted with 100 mL of diethyl ether and washed with water, brine, dried over Na_2SO_4 and concentrated in vacuo. The crude product was taken up in acetone and oxalic acid added to give 330 mg (66%) of the title compound upon recrystallisation from 2-propanol. M.p. 174–176 °C. MS (70 eV): 411 (M^+, 46%), 273 (27), 233 (100). ^{1}H-NMR (DMSO-d_6): 2.25 (broad, 2H), 1.95 (broad, 2H), 2.1 (broad, 2H), 2.95 (broad, 4H), 3.25 (s, 3H), 3.45 (broad, 3H), 4.11 (dd, 2H), 7.22 (dd, 1H), 7.35 (m, 5H), 7.74 (dd, 1H), 8.13 (ddd, 1H). Anal. ($C_{25}H_{28}N_3FO_7$) CHN.

*5.1.12. 4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-(3-(N-(6-benzothiazolyl)-N-methylcarbamoyloxy)propyl)piperidine, oxalate **15***

a: 6-Aminobenzothiazole (1.5 g, 10 mmol) and triethylamine (1.4 g, 14 mmol) was suspended in 30 mL dry toluene at 10 °C. Trifluoroacetic acid anhydride (2.5 g, 12 mmol) in 5 mL dry toluene was added under stirring at 10–15 °C during 30 min, whereupon the mixture was gradually solubilised. The mixture was poured into 100 mL ether, and then washed five times, each time with 15 mL H_2O. The organic phase was dried over Na_2SO_4 and concentrated to a volume of 10 mL. Addition of petroleum ether precipitated 2.05 g (83.3%) 6-trifluoroacetamidobenzothiazole as white crystals. M.p. 155–156 °C. ^{1}H-NMR ($CDCl_3$): 7.45 (dd, 1H), 8.08 (d, 1H), 8.38 (broad s, 1H), 8.61 (d, 1H), 9.01 (s, 1H).

b: To 6-Trifluoroacetamidobenzothiazole (1.97 g, 8 mmol) in 40 mL dry acetone was added methyl iodide (4.54 g, 32 mmol) and then KOH (2.1 g, 32 mmol). The mixture was refluxed for 40 min and concentrated in vacuo. The product was taken up in 40 mL H_2O, refluxed for 40 min and extracted with methylene chloride. The organic phase was washed with water, dried over Na_2SO_4 and concentrated in vacuo. The product was purified by flash chromatography (silica gel, methylene chloride) to give 550 mg (42%) 6-methylaminobenzothiazole. ^{1}H-NMR ($CDCl_3$): 2.89 (s, 3H), 3.95 (broad, 1H), 6.78 (dd, 1H), 7.01 (d, 1H), 7.90 (d, 1H), 8.72 (s, 1H).

c: By following the procedure described for compound **14**, 3-(4-(6-fluoro-1,2-benzoisoxazol-3-yl)piperidino)propanol (**2b**) (680 mg, 3 mmol) was reacted with N-methyl-N-(benzothiazol-6-yl)carbamoylchlorid (**3j**) (560 mg, 2 mmol) giving 180 mg (18%) of the title compound. M.p. 156–162 °C. MS (70 eV): 468 (M^+, 25%) 330 (13), 249 (22), 233 (48), 96 (100). ^{1}H-NMR (DMSO-d_6): 1.9–2.2 (broad, 6H), 2.95 (broad, 4H), 3.22 (s, 3H), 3.45 (broad, 3H), 4.15 (t, 2H), 7.32 (ddd, 1H), 7.45 (dd, 1H), 7.75 (dd, 1H), 8.05 (m, 2H), 8.15 (d, 1H), 9.35 (s, 1H). Anal. ($C_{26}H_{27}FN_4O_7S$, 0.5 H_2O) CHNS.

*5.1.13. 4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-(3-(N-methyl-N-(3,4-methylenedioxy-phenyl)carbamoyloxy)propyl)piperidine, hydrochloride **16***

a: By following the procedure described for compound **14**, N-methyl-3,4-methylenedioxyaniline [29] (3.02 g, 20 mmol) was reacted with phosgene to give 3.0 g (69.8%) N-methyl-N-(3,4-methylenedioxyphenyl)carbamoylchloride (**3k**). M.p. 71–73 °C. ^{1}H-NMR ($CDCl_3$): 3.32 (s, 3H), 6.04 (s, 2H), 6.70 (m, 2H), 6.87 (d, 1H).

b: By following the procedure described for compound **14**, 3-(4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidino)propanol (**2b**) (278 mg, 1 mmol) was reacted with **3k** (240 mg, 1.12 mmol) to give 170 mg (34.5%) of the title compound. M.p. 126–129 °C. MS (70 eV): 455 (M^+, 64%), 317 (22), 237 (36), 233 (50), 96 (100). ^{1}H-NMR (DMSO-d_6): 2.25 (broad, 6H), 3.10 (broad, 4H), 3.22 (s, 3H), 3.55 (broad, 3H), 4.12 (t, 2H), 6.05 (s, 2H), 6.75 (dd, 1H), 6.90 (d, 1H), 6.95 (d, 1H), 7.32 (ddd, 1H), 7.75 (dd, 1H), 8.22 (broad, 1H), 10.75 (s, 1H). Anal. ($C_{24}H_{26}FN_3O_5$, H_2O) CHN.

*5.1.14. 1-(3-(N-Ethyl-N-(3,4-methylenedioxyphenyl)-4-(6-fluoro-1,2-benzisoxazol-3-yl)carbamoyloxy)propyl)piperidine, oxalate **17***

a: By following the procedure described for compound **14**, N-ethyl-3,4-methylenedioxyaniline (1.65 g, 10 mmol) was reacted with phosgene to give 1.5 g (66.4%) N-ethyl-N-(3,4-methylene-

dioxyphenyl)carbamoylchloride (**3l**). M.p. 68–69 °C. ^{1}H-NMR ($CDCl_3$): 1.22 (t, 3H), 3.70 (q, 2H), 6.05 (s, 2H), 6.68 (m, 2H), 6.85 (d, 1H).

b: To 3-(4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidino)propanol (**2b**) (280 mg, 1 mmol) in 15 mL dry THF stirred under nitrogen atmosphere, was added n-butyl lithium (0.9 mL 1.6 M in hexane, 1.5 mmol). The mixture was stirred at room temperature for 1.5 h, whereupon N-ethyl-N-(3,4-methylenedioxyphenyl)carbamoyl-chloride (**3l**) (340 mg, 1.5 mmol) in 15 mL dry THF was added. The mixture was stirred at room temperature for 16 h and then separated between water and ethyl acetate. The organic phase was washed with H_2O and saturated NaCl, dried over Na_2SO_4 and concentrated in vacuo. The product was purified by column chromatography (silica gel, ethyl acetate, methanol (4:1, v/v)) and dissolved in 2 mL acetone. Addition of oxalic acid precipitated the title compound which was recrystallised from ethanol, methanol (20:1) to give 250 mg (42%). M.p. 180–182 °C. MS (70 eV): 469 (M^+, 82%), 331 (31), 250 (45), 233 (100). ^{1}H-NMR (DMSO-d_6): 1.02 (t, 3H), 1.8–2.3 (m, 6H), 3.05 (m, 4H), 3.45–3.60 (m, 5H), 4.1 (s, 2H), 6.09 (s, 2H), 6.75 (d, 1H), 6.95 (m, 2H), 7.38 (t, 1H), 7.74 (d, 1H), 8.29 (m, 1H), 10.75 (broad, 1H). Anal. $C_{25}H_{29}N_3FO_5Cl$, 1.75 H_2O) CHNCl.

5.1.15. 4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-(3-((indolin-1-yl)-carbonyloxy)propyl)piperidine hydrochloride ***18***

By following the same procedure described for compound **14**, 3-(4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidino)propanol (**2b**) (280 mg, 1 mmol) was reacted with 1-indolinecarbonyl chloride (**3m**) (270 mg, 1.5 mmol) to give 120 mg (25%) of the title compound. M.p. 218–219 °C. MS (70 eV): 423 (M^+, 30%), 285 (21), 233 (60), 204 (52), 96 (100). ^{1}H-NMR (DMSO-d_6): 2.20 (broad, d, 4H), 2.4 (m, 2H), 3.2 (m, 6H), 3.45 (m, 1H), 3.65 (d, 2H), 4.0 (broad, 2H), 4.25 (broad, 2H), 6.95 (ddd, 1H), 7.2 (m, 2H), 7.35 (ddd, 1H), 7.7 (dd, 1H), 8.22 (ddd, 1H), 11.0 (s, 1H). Anal. ($C_{24}H_{26}N_3FO_3$) CHN.

5.1.16. 4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-(3-((1,2,3,4-tetra-hydroquinolin-1-yl) carbonyloxy)propyl)piperidine, hydrochloride ***19***

a: To phosgene (58 mmol, 30 mL 1.93 M in toluene) and methylene chloride (50 mL) stirred at 0 °C was added during 40 min 1,2,3,4-tetrahydroquinoline (6.66 g, 50 mmol) and triethylamine (7.08 g, 70 mmol) in 50 mL methylene chloride. The mixture was then stirred at 0 °C for 1 h and poured into 800 mL petroleum ether. This mixture was washed three times with 50 mL 5 N H_2SO_4 and once with saturated NaCl. The organic phase was dried over Na_2SO_4 and concentrated in vacuo giving 8.6 g of 1-(1,2,3,4-tetrahydro)quinolinecarbonyl chloride (**3p**) as an oil. ^{1}H-NMR ($CDCl_3$): 2.05 (dt, 2H), 2.80 (t, 2H), 3.94 (t, 2H), 7.15 (m, 3H), 7.72 (d, 1H).

b: 3-(4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidino)propanol (**2b**) (280 mg, 1 mmol) was added to NaH (100 mg 50% in mineral oil, 1.5 mmol) in 5 mL dry DMF at 0 °C under nitrogen atmosphere. The mixture was stirred at 0 °C for 30 min and for 90 min at room temperature, whereupon 1-(1,2,3,4-tetrahydro)quinoline-carbonyl chloride (**3p**) (300 mg, 1.5 mmol) in 2 mL dry DMF was added during 5 min. The mixture was stirred consecutively at room temperature for 16 h and at 60 °C for 1 h, and was then separated between water and ether. The organic phase was evaporated, and the resulting oil was purified by column chromatography (silica gel; ethyl acetate; methanol (4:1, v/v) and then dissolved in absolute ethanol (2 mL). Addition of ethereal hydrochloric acid precipitated the title compound (300 mg) which was recrystallised in ethanol and acetone, methanol (9:1 v/v) to give 200 mg (42%) of white crystals. M.p. 188–190 °C. MS (70 eV): 437 (M^+, 7.5), 278 (6), 233 (23), 140 (33), 96 (100). ^{1}H-NMR (DMSO-d_6): 1.9 (m, 2H), 2.25 (broad, 6H), 2.72 (t, 2H), 3.15 (m, 4H), 3.45 (m, 1H), 3.70 (m, 4H), 4.22 (t, 2H), 7.00 (d, 1H), 7.15 (m, 2H), 7.35 (dt, 1H), 7.61 (d, 1H), 7.73 (dd, 1H), 8.20 (dd, 1H), 10.70 (s, 1H). Anal. ($C_{25}H_{29}N_3FO_3Cl$, 0.3 H_2O) CHN.

5.1.17. 4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-(3-((5,6-methylene-dioxyindoline-1-yl)carbonyloxy)propyl)piperidine, hydrochloride ***20***

a: Using the general procedure described by Sundberg and Laurino [14] 3,4-methylenedioxyaniline was transformed into 5,6-methylenedioxyindole.

b: 5,6-methylenedioxyindole (1.3 g, 8 mmol) dissolved in 25 mL glacial acetic acid was then reduced catalytically (1 atm., 22 °C) using 370 mg PtO_2 hydrate to give 570 mg of crude 2,3-dihydro-5,6-methylenedioxyindole which was used without further purification.

c: As described above 2,3-dihydro-5,6-methylenedioxyindole (570 mg, 3.5 mmol) was reacted with phosgene to give 530 mg (77%) of 1-(2,3-dihydro-5,6-methylenedioxyindole)carbonyl chloride (**3n**) as a semicrystalline oil. MS (70 eV): *m/z* 255 (M^+, 100%), 162 (80), 132 (100). ^{1}H-NMR ($CDCl_3$): 3.05 (t, 2H), 4.20 (t, 2H), 5.95 (s, 2H), 6.59 (s, 1H), 7.42 (s, 1H).

d: By following the procedure described for compound **14**, 3-(4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidine)propanol (**2b**) (410 mg, 1.5 mmol) was reacted with 1-(2,3-dihydro-5,6-methylenedioxyindole)carbonyl chloride **3n** (450 mg, 2 mmol) to give 200 mg (28%) of the title compound. M.p. 208–210 °C. MS (70 eV): *m/z* 467 (M^+, 50%), 261 (80), 233 (50), 162 (56), 132 (80), 96 (100). ^{1}H-NMR (DMSO-d_6): 2.25 (broad m, 6H), 3.05 (t, 3H), 3.25 (broad m, 4H), 3.52 (m, 1H), 3.70 (broad d, 2H)), 4.04 (broad t, 2H), 4.25 (broad s, 2H), 5.98 (s, 2H), 6.85 (s, 1H), 7.38 (m, 2H), 7.75 (dd, 1H), 8.24 (dd, 1H), 10.8 (broad, 1H). Anal. ($C_{25}H_{27}N_3FO_5$, HCl) CHNCl.

5.1.18. 4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-(2-((6,7-methylene-dioxy-1,2,3,4-tetrahydroquinolin-1-yl)carbonyloxy)ethyl)piperi-dine, oxalate ***21***

a: 3-(4,5-Methylenedioxy-2-nitrophenyl)acrylic acid (10 g, 42 mmol) in 50 mL dry DMF, 450 mL absolute ethanol and 1.5 mL conc. HCl were reduced catalytically at 1 atm., 22 °C, using 1.5 g 5% palladium on carbon to give 6.5 g (81%) 6,7-mehylenedioxy-1,2,3,4-tetrahydro-2-oxoquinoline as light brown crystals, which were used without further purification.

b: To 6,7-methylenedioxy-1,2,3,4-tetrahydro-2-oxoquinoline (1.0 g, 5 mmol) suspended in 20 mL dioxane at 0 °C was added $NaBH_4$ (1.0 g, 25 mmol) whereupon a mixture of glacial acetic acid (1.4 mL, 25 mmol) in 25 mL dioxane was added dropwise over 10 min. After addition was completed, the mixture was refluxed for 1.5 h, concentrated in vacuo and taken up in H_2O and methylene chloride. The organic phase was dried over Na_2SO_4 and evaporated to give 700 mg 6,7-methylenedioxy-1,2,3,4-tetra-hydroquinoline as an oil. The oil was taken up in acetone and treated with 1 mL 5.5 M HCl in methanol to give 550 mg (68%) of the hydrochloride. M.p. 238–240 °C. ^{1}H-NMR (DMSO-d_6): 1.73

(dt, 2H), 2.55 (t, 2H), 3.08 (t, 2H), 5.25 (broad s, 1H), 5.76 (s, 2H), 6.09 (s, 1H), 6.42 (s, 1H), 11.7 (s, 1H).

c: Using the same procedure as described for compound **14**, 6,7-methylene-dioxy-1,2,3,4-tetrahydroquinoline (1.8 g, 10 mmol) was reacted with phosgene to prepare 2.2 g (97%) 1-(6,6-methylenedioxy-1,2,3,4-tetrahydroquinoline)carbonyl chloride (**3q**). M.p. 86–87 °C. ^{1}H-NMR ($CDCl_3$): 2.01 (dt, 2H), 2.69 (t, 2H), 3.89 (t, 2H), 5.95 (s, 2 H), 6.55 (s, 1H), 7.30 (s, 1H).

d: By following the procedure described for compound **14**, 2-(4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidino)ethanol (**2a**) (260 mg, 1 mmol) was reacted with **3q** (234 mg, 1 mmol) to give 350 mg (63%) of the title compound. M.p. 167–171 °C. MS: (70 eV): 467 (M^+, 100%), 27 (22), 247 (67), 190 (40), 177 (100). ^{1}H-NMR (DMSO-d_6): 1.8 (broad t, 2H), 2.1 (broad, 2H), 2.2 (broad. 2H), 2.62 (t, 2H), 2.9 (broad s, 2H), 3.18 (broad s, 2H), 3.4 (broad s, 3H), 3.55 (broad t, 2H), 4.35 (s, 2H), 5.9 (s, 2H), 6.68 (s, 1H), 7.15 (s, 1H), 7.25 (dt, 1H), 7.70 (dd, 1H), 8.05 (broad t, 1H). Anal. ($C_{25}H_{26}N_3FO_5$, 0.25 H_2O) CHN.

5.1.19. 4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-(3-((6,7-methylenedioxy-1,2,3,4-tetrahydroquinolin-1-yl)carbonyloxy)propyl)piperidine, hydrochloride ***22***

By following the procedure described for compound **14**, 3-(4-(fluoro-1,2-benzisoxazol-3-yl)piperidine)propanol (**2b**) (1.5 g, 5.5 mmol) was reacted with 1-(6,7-methylenedioxy-1,2,3,4-tetrahydroquinoline)carbonyl chloride (**3q**) (1,3 g, 5.5 mmol) to give 1.0 g (77%) of the title compound. M.p. 165–166 °C. MS: (70 eV): 481 (M^+, 42%), 291 (20), 233 (22), 176 (70), 118 (73), 96 (100). ^{1}H-NMR (DMSO-d_6): 1.82 (m, 2H), 2.21 (broad m, 4H), 2.35 (m, 2H), 2.63 (t, 2H), 3.18 (m, 3H), 3.5 (m, 1H), 3.68 (t, 4H), 4.21 (t, 2H), 5.98 (s, 2H), 6.72 (s, 1H), 7.17 (s, 1H), 7.45 (dt, 1H), 7.75 (dd, 1H), 8.22 (dd, 1H), 10.90 (s, H). Anal. ($C_{26}H_{29}N_3FO_5Cl$) CHNCl.

5.1.20. 4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-(4-((6,7-methylenedioxy-1,2,3,4-tetrahydroquinolin-1-yl)carbonyloxy)butyl)piperidine, oxalate ***23***

By following the procedure described for compound **14**, 4-(4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidino)butanol (**2c**) (290 mg, 1 mmol) was reacted with 1-(6,6-methylenedioxy-1,2,3,4-tetrahydroquinoline)carbonyl chloride (**3q**) (235 mg, 1 mmol) to give 350 mg (72%) of the title compound. M.p. 106–108 °C. MS: (70 eV): *m/z* 495 (M^+, 100%), 275 (75), 233 (20), 177 (100). ^{1}H-NMR ($CDCl_3$): 1.70 (m, 4H), 1.95 (dt, 2H), 2.10 (m, 6H), 2.40 (t, 2H), 2.65 (t, 2H), 3.05 (m, 3H), 3.65 (t, 2H), 4.20 (t, 2H), 5.90 (s, 2H), 6.5 (s, 4H), 7.05 (dt, 1H), 7.15 (s, 1H), 7.22 (dd, 1H), 7.7 (dd, 1H). Anal. ($C_{27}H_{30}N_3FO_5$, 0.25 H_2O) CHN.

5.1.21. 1-(3-(Dihydro-1,4-benzoxazin-1-yl-carbonyloxy)propyl)-4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidine, hydrochloride ***24***

By following the procedure described for compound **14**, 3-(4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidene)propanol (**2b**) (420 mg, 1.5 mmol) was reacted with 1-(dihydro-1,4-benzoxazine) carbonyl chloride (**3o**) (400 mg, 2 mmol) to give 550 mg (76%) of the title compound. M.p. 190–193 °C, MS (70 eV) *m/z* 439 (M^+, 100%), 301 (32), 233 (57), 220 (40), 96 (95). ^{1}H-NMR (DMSO-d_6): 2.22 (broad, 6H), 2.44 (m, 2H), 3.2 (m, 4H) 3.4–3.55 (m, 3H), 3.65 (d, 2H), 3.91 (t, 2H), 4.3 (m, 4H), 6.9 (m, 2H), 7.02 (dd, 1H), 7.35 (dt, 1H), 7.71 (dd, 1H), 7.80 (broad d, 1H), 8.28 (dd, 1H), 11.2 (s, 1H). Anal. ($C_{29}H_{27}N_3O_4FCl$) CHNCl.

5.1.22. 4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-(3-((5,6-methylenedioxyindoline-1-yl)carbonyloxy)-2-phenylpropyl)piperidine, oxalate ***25***

a: 2-Phenylacrylic acid (1.8 g, 12 mmol) and 4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidine (2.4 g, 11 mmol) in 100 mL dry isopropanol was refluxed for 3 h. The mixture was concentrated in vacuo and taken up in water whereupon $NaHCO_3$ was added until pH 8–9. The formed crystals were isolated, washed with ethyl acetate and dried over to give 2.0 g (50%) 3-(4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidino-2-phenylpropanoic acid. M.p. 194–200 °C. ^{1}H-NMR (DMSO-d_6): 1.78 (m, 2H), 2.05 (broad d, 2H), 2.21 (m, 2H), 2.58 (broad, 1H), 3.08 (m, 3H), 3.84 (m, 2H), 7.26 (m, 6H), 7.68 (dd, 1H), 8.02 (dd, 1H).

b: To 3-(4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidino)-2-phenylpropanoic acid (1.8 g, 4.9 mmol) in 25 mL dry toluene, stirred at 0 °C, a solution of $LiAlH_4$ in THF (5 mL, 1 M, 5 mmol) was added dropwise. 20 min after addition was completed the mixture was allowed to warm to room temperature for 15 min whereupon H_2O was added dropwise to precipitate aluminium hydroxide. To the organic phase was added 50 mL ether, and the mixture was washed with water and concentrated in vacuo to get 1.6 g (94%) of 3-(4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidino)-2-phenylpropanol(**2e**) as an oil. MS (70 eV): *m/z* 35 (M^+ 1, 4%), 233 (100), 190 (30), 96 (35).

c: By following the procedure described for compound **14**, 3-(4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidino)propanol (**2e**) (350 mg, 1 mmol) was reacted with 1-(2,3-dihydro-5,6-methylenedioxyindole)carbonyl chloride (**3n**) (150 mg, 0.7 mmol) to give 300 mg (49%) of the title compound. M.p. 163–164 °C. MS (70 eV): *m/z* 543 (M^+, 6%), 353 (25), 233 (100), 204 (30), 163 (37). ^{1}H-NMR (DMSO-d_6): 2.04 (broad m, 4H), 2.96 (broad t, 4H), 3.41 (broad m, 5H), 3.62 (broad m, 1H), 3.87 (t, 2H), 4.31 (broad, 2H), 5.95 (s, 2H), 6.81 (s, 1H), 7.35 (m, 7H), 7.75 (dd, 1H), 8.03 (dd, 1H). Anal. ($C_{31}H_{30}N_3FO_5$, 1.5 $C_2H_2O_4$, 0.5 H_2O) CHN.

5.1.23. 4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-(3-((6,7-methylenedioxy-1,2,3,4-tetrahydroquinolin-1-yl)carbonyloxy)-2-phenylpropyl)piperidine, oxalate ***26***

Following the procedure described for compound **14** 3-(4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidino)-2-phenylpropanol (**2e**) (350 mg, 1 mmol) was reacted with 1-(6,7-methylenedioxy-1,2,3,4-tetrahydroquinolin)carbonyl chloride (**3q**) (200 mg, 0.8 mmol) to give 280 mg (50%) of the title compound. M.p. 157–159 °C. MS (70 eV): *m/z* 557 (M^+, 10%), 367 (37), 233 (100), 204 (30), 96 (60). ^{1}H-NMR (DMSO-d_6): 1.72 (m, 2H), 1.95 (broad, 2H), 2.11 (broad, 2H), 2.58 (t, 2H), 2.8 (broad, 2H), 3.25 (broad, 5H), 3.52 (m, 4H), 4.25 (dd, 1H), 4.4 (dd, 1H), 5.95 (s, 2H), 6.62 (s, 1H), 6.85 (broad, 1H), 7.35 (m, 6H), 7.7 (dd, 1H), 8.0 (m, 1H). Anal. ($C_{34}H_{34}N_3O_9F$, 0.25 H_2O) CHN.

5.1.24. 4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-(2,2-(1,2-ethylene)-3-((6,7-methylenedioxy-1,2,3,4-tetrahydroquinolin-1-yl)carbonyloxy)-propyl)piperidine, oxalate ***27***

a: To 2,2-(1,2-ethylene)-1,3-dihydroxypropane (1.0 g, 10 mmol) in 20 mL dry THF, stirred under nitrogen at 0 °C, was added n-butyllithium (5 mL, 16 M in hexane, 8 mmol). A solution of p-toluenesulfonyl chloride (1.5 g, 8 mmol) in 5 mL dry THF was added dropwise, whereupon the mixture was stirred at room temperature for 4 h. The mixture was concentrated in vacuo and taken up in H_2O and CH_2Cl_2. The organic phase was washed with

saturated sodium chloride, dried over $MgSO_4$ and evaporated to give 900 mg (50%) 3-chloro-2-(1,2-ethylene)propanol as an oil. ^{1}H-NMR ($CDCl_3$): 0.68 (d, 4H), 3.60 (s, 2H), 3.63 (s, 2H).

b: 4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidine, hydrochloride (1.3 g, 5.4 mmol) and K_2CO_3 (740 mg, 5.4 mmol) was added to a mixture of 3-chloro-2,2-(1,2-ethylene)propanol (700 mg, 2.7 mmol) and NaI (410 mg, 2.7 mmol) in 10 mL dry acetone. The mixture was refluxed for 10 min, stirred at 50 °C for 16 h and concentrated in vacuo. The product was taken up in H_2O and ethyl acetate. The organic phase was dried over $MgSO_4$ and evaporated to give an oil, which was purified by column chromatography (CH_2Cl_2, CH_3OH (9:1, v/v)). Trituration with petroleum ether gave 430 mg (52%) of 2-(1,2-ethylene)-3-(4-(6-fluoro-1,2-benziso-xazol-3-yl)piperidino)propanol (**2f**). M.p. 95–96 °C. ^{1}H-NMR ($CDCl_3$): 0.38 (t, 2H), 0.57 (t, 2H), 2.11 (m, 6H), 2.55 (s, 2H), 3.10 (dt, 1H), 3.35 (brd, 2H), 3.58 (s, 2H), 7.07 (dt, 1H), 7.31 (dd, 1H), 7.68 (dd, 1H).

c: To 2,2-(1,2-ethylene)-3-(4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidino)-propanol (**2f**) (210 mg, 0.7 mmol) stirred under N_2 in 20 mL dry THF at 0 °C was added n-butyllithium (0.7 mL, 1.6 M in hexane, 1.1 mmol). The mixture was then stirred at room temperature for 1 h, cooled to 0 °C whereupon 1-(6,7-methylenedioxy-1,2,3,4-tetrahydroquinoline)carbonyl chloride (**3q**) (240 mg, 1.0 mmol) was added. The mixture was stirred at room temperature for 70 h, concentrated in vacuo and separated between H_2O and methylene chloride. The organic fraction was purified by column chromatography (CH_2Cl_2, CH_3OH (9:1, v/v)). The title compound was isolated by addition of oxalic acid to give 70 mg white crystals. M.p. 190–197 °C. MS (70 eV): *m/z* 507 (M^+, 60%), 287 (65), 259 (50), 233 (25), 177 (100). ^{1}H-NMR: ($CDCl_3$): 0.4 (broad t, 2H), 0.65 (broad t, 2H), 2.0 (m, 8H), 2.35 (s, 2H), 2.70 (t, 2H), 3.15 (m, 3H), 3.75 (t, 3H), 4.15 (s, 2H), 5.90 (s, 2H), 6.60 (s, 1H), 7.05 (dt, 1H), 7.2 (m, 2H), 7.65 (dd, 1H). Anal. ($C_{28}H_{30}N_3FO_5$, 1.5 $C_2H_2O_4$, 0.5 H_2O) CHN.

5.1.25. 4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-(5-(3,4,5-trimethoxyphenyl-carbamoyloxy)-3,3-pentamethylenepent-1-yl)piperidine ***28***

a: To a solution of 4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidine hydrochloride (1.03 g, 4 mmol) and triethylamine (1.2 g, 12 mmol) in 20 mL dry THF was added 3,3-pentamethylenglutaric acid anhydride (728 mg, 4 mmol). The reaction mixture was heated to 60 °C for 16 h and then cooled at room temperature. Water (100 mL) was added and the mixture acidified with 1 N hydrochloride acid to pH 3 and extracted with ethyl acetate (200 mL) washed with water, brine and dried with sodium sulphate and concentrated in vacuo. The crude product was recrystallised from methanol to give 1.1 g (64%) of 4-((6-fluoro-1,2-benzisoxazol-3-yl)piperidino)-4-oxo-3,3-pentamethylenebutanoic acid. M.p. 174–176 °C.

b: A solution of 4-((6-fluoro-1,2-benzisoxazol-3-yl)piperidino)-4-oxo-3,3-pentamethylenebutanoic acid (1 g, 2.5 mmol) in THF (25 mL) was added sodium borohydride (0.27 g, 7.5 mmol) and cooled to 5 °C, boron trifluoride etherate (1.44 mg, 10.2 mmol) was added dropwise at 5 °C. The temperature was maintained at 5 °C for 4 h and then at room temperature for 16 h. To the reaction mixture was added methanol (20 mL) and after 20 min water (50 mL) was added and extracted with ethyl acetate (200 mL) washed with water, brine, dried with sodium sulphate and concentrated in vacuo. The crude product was purified by chromatography on silica gel 60 with ethyl acetate as eluent. Concentration of appropriate fractions gave 390 mg (41%) of 4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-(5-hydroxy-3,3-pentamethylenpent-1-yl)piperidine (**2g**). MS/EI (70 eV): *m/z* 374 (55%, M^+), 344, 233 (100%), 190, 109, 96, 82. ^{1}H-NMR ($CDCl_3$): 1.3 (broad, 3H), 1.45–1.65 (broad, 7H), 1.9 (m, 1H), 2.08 (m, 1H), 2.2 (broad, 2H), 2.55 (broad, 4H), 3.11 (dt, 1H), 3.4 (m, 2H), 4.2 (d, 1H), 4.65 (d, 1H), 7.1 (dt, 1H), 7.26 (dd, 1H), 7.6 (q, 1H).

c: Starting from 4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-(5-hydroxy-3,3-pentamethylenpent-1-yl)piperidine (**2g**) (300 mg, 0.80 mmol) and 3,4,5-trimethoxyphenylisocyanate (**3d**) (200 mg, 0.96 mmol), 110 mg (23%) of the title compound was prepared. MS/FAB (8 KV, 2mA): 584 (M^+), 375, 233, 178, 166, 138. Anal. ($C_{32}H_{42}FN_3O_6$, 0.5 H_2O) CHN.

5.1.26. ±-trans-4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-(4-(3,4-methylendioxophenyl carbamoyloxy)-2,3-tetramethylene-but-1-yl)piperidine, oxalate ***29***

A mixture of 4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidine, hydrochloride (2.5 g, 9.8 mmol) and triethylamine (3 g, 29.7 mmol) in THF (100 mL) was heated to 60 °C and a solution of *trans*-1,2-cyclohexanedicarboxylic anhydride (1.54 g, 10 mmol) was added. The mixture was refluxed for 24 h. The cooled mixture was added 0.1 N HCl (50 mL) and extracted with ethylacetate (200 mL). The organic phase was washed with water, brine, dried with sodium sulphate and concentrated in vacuo to yield 2.9 g (79%) of ±-*trans*-4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-(2-carboxy-cyclohexyl-carbonyl)piperidine. ^{1}H-NMR (DMSO-d_6): 1.26 (m, 4H), 1.71 (m, 4H), 2.01 (broad d, 4H), 2.74 (broad t, 1H), 2.85 (m, 2H), 3.27 (t, 1H), 3.48 (m, 1H), 4.15 (broad d, 1H), 4.45 (broad t, 1H), 7.28 (dt, 1H), 7.67 (dd, 1H), 8.02 (dd, 1H), 11.78 (broad s, 1H).

A solution of ±-*trans*-4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-(2-carboxy-cyclohexylcarbonyl)-piperidine (2 g, 5.3 mmol) in toluene (100 mL) and THF (10 mL) was added $LiAlH_4$ in THF (13 mL, 13 mmol) over 10 min. After being stirred for 2.5 h at room temperature, water (10 mL) was added dropwise followed by filtration and concentration in vacuo to yield 1.5 g (81%) of ±-*trans*-4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-(2-hydroxymethyl-cyclohexylmethyl)piperidine (**2h**). ^{1}H-NMR (DMSO-d_6): 1.1 (m, 6H), 1.41 (broad dd, 1H), 1.71 (m, 6H), 2.05 (m, 5H), 2.42 (dd, 1H), 2.91 (d, 1H), 3.05 (d, 1H), 3.15 (m, 1H), 3.34 (m, 2H), 5.57 (broad s, 1H), 7.40 (dt, 1H), 7.70 (dd, 1H), 8.06 (dd, 1H).

A solution of ±-*trans*-4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-(2-hydroxymethyl-cyclohexylmethyl)piperidine (**2h**) (350 mg, 1 mmol) in DMF (5 mL) was added 3,4-methylendioxo-phenylisocyanate (**3f**) (360 mg, 2 mmol) and stirred for 16 h at room temperature. After concentration in vacuo the crude product was purified by column chromatography using methylenchloride: methanol (9.5:0.5, v/v) the appropriate fractions were concentrated in vacuo, taken up in acetone and added a solution of oxalic acid the precipitate was collected and dried yielding 90 mg (15%) of the title compound. M.p. ^{1}H-NMR (DMSO-d_6): 1.05 (broad dd, 1H), 1.22 (broad, 4H), 1.49 (broad, 1H), 1.68 (broad s, 2H), 1.79 (m, 2H), 1.95 (broad d, 1H), 2.15 (broad, 4H), 2.85 (broad m, 2H), 3.01 (m, 1H), 3.20 (broad d, 1H), 3.46 (m, 3H), 4.03 (dd, 1H), 4.13 (dd, 1H), 5.95 (s, 2H), 6.81 (dd, 2H), 7.11 (broad s, 1H), 7.20 (dt, 1H), 7.72 (dd, 1H), 8.05 (dd, 1H), 9.6 (s, 1H). Anal. ($C_{32}H_{34}N_3FO_9$, 0.5 H_2O) CHN.

5.1.27. 4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-(1-(3,4-methylenedioxyphenylcarbamoyloxy)cyclohex-2-yl)piperidine ***30***

a: A mixture of 4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidine (1 g, 4.5 mmol) and 7-oxabicyclo[4.1.0]heptane (5 g, 51 mmol) was refluxed for 48 h. The mixture was cooled to room temperature, concentrated in vacuo and purified by column chromatography with ethyl acetate; methanol (9:1, v/v) as eluent to give 1.1 g (76%) of 4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-(1-hydroxycyclohex-2-yl)piperidine (**2j**). M.p. 116–118 °C. MS/EI (70 eV): *m/z* 318 (57%, M^+), 259, 180 (100%), 122, 108, 82, 55. ^{1}H-NMR ($CDCl_3$): 1.26 (broad d, 4H), 1.7 (m, 3H), 2.08 (m, 5H), 2.31 (m, 2H), 2.80 (t, 2H), 3.11 (m, 2H), 3.48 (m, 1H), 7.05 (dt, 1H), 7.31 (dd, 1H), 7.71 (dd, 1H).

b: Starting from 4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-(1-hydroxycyclohex-2-yl)-piperidine (**2j**) (500 mg, 1.57 mmol) and 3,4-methylenedioxyphenylisocyanate (**3f**) (500 mg, 3.06 mmol) using the procedure described for compound **4** was prepared 100 mg (13%) of the title compound. M.p. 121–122 °C. ^{1}H-NMR (DMSO-d_6): 1.11–1.41 (broad, 4H), 1.7 (broad, 4H), 1.82–2.03 (broad, 4H), 2.33 (t, 1H), 2.48 (t, 1H), 2.67 (t, 1H), 2.78 (broad, 1H), 3.05 (broad, 2H), 4.78 (m, 1H), 5.98 (d, 2H), 6.82 (d, 1H), 6.9–7.0 (broad, 2H), 7.2 (d, 1H), 7.65 (broad, 2H), 9.5 (s, 1H).

5.1.28. 4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-(2-((1,2,3,4-tetrahydroquinolin-1-yl)carbonyloxy)-1-propyl)piperidine, hydrochloride ***31***

A solution 4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-(2-hydroxyprop-1-yl)-piperidine (**2i**) (278 mg, 1 mmol) in 20 mL dry THF was cooled to –70 °C, under nitrogen atmosphere was added n-butyllithium (3 M in hexane, 0.4 mL, 1.2 mmol). After 0.5 h a solution of 1,2,3,4-tetrahydroquinolin-1-carbonylchloride (**3p**) (235 mg, 1.2 mmol) in 10 mL dry THF was added dropwise. The reaction was stirred at –70 °C for 1 h and then 16 h at room temperature, concentrated in vacuo and purified by chromatography with ethyl acetate:methanol (9:1, v/v) as eluent.

The appropriate fractions were collected. The solvent was evaporated in vacuo to give an oily residue which was dissolved in acetone (5 mL). A 2 M solution of hydrogen chloride in diethylether (1 mL) was added at room temperature whereby a white precipitate was formed. The solid was collected and air dried to give 200 mg (42%) of the title compound. M.p. 76–79 °C. ^{1}H-NMR ($CDCl_3$): 1.3 (d, 3H), 2.0 (m, 6H), 2.1–2.5 (m, 3H), 2.69 (dd, 1H), 2.8 (t, 2H), 3.08 (m, 3H), 3.71 (m, 1H), 3.88 (m, 1H), 5.15 (m, 1H), 6.95 (m, 5H), 7.52 (q, 1H), 7.78 (dd, 1H). Anal. ($C_{25}H_{28}N_3FO_3$, 0.5 H_2O) CHN.

5.1.29. ±-trans-4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-(2,3-methylene-4-(3,4-methylenedioxyphenylcarbamoyloxy)butyl) piperidine, oxalate ***32***

a: Using the same procedure as described for compound **4**, *trans*-2,3-methylene-1,4-butanol (800 mg, 8 mmol) was reacted with 3,4-methylenedioxyphenylisocyanate (**3f**) (1.3 g, 8 mmol) to get (±)-*trans*-2,3-methylene-4-(3,4-methylenedioxyphenylcarbamoyloxy)butanol (750 mg, 28 mmol). The product was treated with p-toluenesulfonyl chloride (570 mg, 3.0 mmol) in 2 mL pyridine and 10 mL dry CH_2Cl_2 which upon work up afforded 650 mg (55.4%) (±)-*trans*-2,3-methylene-1-(3,4-methylenedioxyphenylcarbamoyloxy)-4-tosyloxybutane as an oil. M.p. 58–60 °C. ^{1}H-NMR ($CDCl_3$): 0.6 (m, 2H), 1.15 (m, 2H), 3.90 (m, 4H), 5.9 (s, 2H), 6.65 (d, 2H), 6.88 (s, 1H), 7.05 (s, 1H), 7.33 (d, 2H), 7.75 (d, 2H).

b: (±)-*trans*-2,3-Methylene-1-(3,4-methylenedioxyphenylcarbamoyloxy)-4-tosyloxybutane (420 mg, 1 mmol), 4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidine (440 mg, 1 mmol) and K_2CO_3 (280 mg, 2 mmol) was stirred in 20 mL DMF at 100 °C for 3 h and at room temperature. The mixture was separated between water and ether. The organic fraction was purified by column chromatography (CH_2Cl_2, CH_3OH (25:1), v/v) and treated with oxalic acid to get 25 mg (5%) of the desired product. M.p. 174–179 °C. ^{1}H-NMR (DMSO-d_6) as HCl: 0.72 (m, 2H), 1.21 (broad, 1H), 1.35 (broad, 1H), 2.18 (broad, d, 2H), 2.35 (m, 2H), 3.0 (m, 1H), 3.15 (m, 3H), 3.45 (t, 1H), 3.65 (t, 2H), 4.02 (d, 2H), 5.91 (s, 2H), 6.75 (d, 1H), 6.80 (d, 1H), 7.10 (s, 1H), 7.35 (dt, 1H), 7.7 (dd, 1H), 8.2 (dd, 1H), 9.6 (s, 1H), 10.9 (s, 1H).

5.1.30. ±-trans-4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-((2,3-methylene)-4-((indolin-1-yl)carbonyloxy)butyl)piperidine, hydrochloride ***33***

a: Indoline (4.8 g, 40 mmol) and triethylamine (6 mL, 40 mmol) in 50 mL dry methylene chloride was added to a solution of phosgene (32 mL of a 1.9 M solution in toluene) in ice cold methylene chloride (50 mL). After 1 h at 0 °C the mixture was concentrated in vacuo, redissolved in dry ether and filtered through a short path of silica gel. By addition of petroleum ether, 6.7 g (93%) of indolin-1-carbonyl chloride (**3m**) crystallised out. M.p. 68 °C. ^{1}H-NMR ($CDCl_3$): 3.20 (t, 2H), 4.25 (t, 2H), 7.12 (dd, 1H), 7.25 (m, 2H), 7.9 (dd, 1H).

b: By the same procedure described for compound **14**, indolin-1-carbonyl chloride (**3m**) (1.4 g, 7.8 mmol) was reacted with *trans*-2,3-methylene-1,4-butanediol (0.8 g, 7.8 mmol) to give ±-*trans* 4-(1-indolinecarbonyloxy)-2,3-methylene-butanol (1.0 g) (53%) as an oil. MS (70 eV): *m/z* 247 (M^+, 75%) 163 (58, 119 (100)). ^{1}H-NMR ($CDCl_3$): 0.55 (d, 2H), 1.1 (broad m, 2H), 3.10 (t, 2H), 3.49 (m, 2H), 3.95 (t, 2H), 4.1 (m, 2H), 6.9 (t, 1H), 7.1 (d, 2H), 7.8 (broad d, 1H).

c: By the procedure described above, ±-*trans*-4-(1-indolinecarbonyloxy)-2,3-methylenebutanol (900 mg, 3.6 mmol) was reacted with p-toluenesulfonylchloride (1.3 g, 6.8 mmol) to give 0.9 g (94.2%) ±-*trans*-1-chloro-4-(1-indoline-carbonyloxy)-2,3-metylenebutane as an oil. MS (70 eV): *m/z* 265 (M^+, 43%), 132 (90), 118 (100). ^{1}H-NMR ($CDCl_3$): 0.70 (m, 2H), 1.32 (broad d, 2H), 3.12 (t, 2H), 3.38 (dd, 1H), 3.6 (dd, 1H), 4.01 (br, 1H), 4.1 (t, 2H), 4.25 (broad, 1H), 6.95 (t, 1H), 7.18 (d, 2H), 7.9 (broad, 1H).

±-*trans*-1-Chloro-4-(1-indoline-carbonyloxy)-2,3-methylenebutane (900 mg, 3 mmol) 4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidine (550 mg, 2.5 mmol) NaI (480 mg, 3.3 mmol) and K_2CO_3 (450 mg, 3.5 mmol) was stirred in 50 mL methyl isopropyl ketone (MIPK) at 75 °C for 20 h and refluxed for 8 h to give 550 mg (55%) of the title compound. M.p. 213–214 °C. MS (70 eV): *m/z* 449 (M^+, 100%), 311 (25), 233 (20), 146 (40), 128 (42). ^{1}H-NMR (DMSO-d_6): 0.75 (m, 2H), 1.3 (broad, 1H), 1.45 (broad, 1H), 2.2 (broad, 2H), 2.35 (broad, 2H), 2.9 (m, 1H), 3.11 (m, 4H), 3.25 (broad, 1H). 3.5 (broad, m, 3H), 3.7 (t, 2H), 4.0 (broad, 1H), 4.2 (m, 1H), 6.9 (t, 1H), 7.15 (d, 1H), 7.3 (dt, 1H), 7.75 (dd, 1H), 8.2 (dt, 1H), 10.9 (s, 1H). Anal. ($C_{26}H_{28}N_3FO_3$, 0.25 H_2O) CHN.

5.1.31. 4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-(2,2-(1,2-ethylene)-3-(indolin-1-yl-carbonyloxy)propyl)piperidine, oxalate ***34***

a: To 2,2-(1,2-ethylene)propanediol (1.8 g, 17 mmol) in 20 mL dry THF, stirred at 0 °C under N_2, was added n-butyllithium

(12.5 mL, 1.6 M in hexane, 20 mmol). After 10 min at 0 °C, the mixture was stirred at room temperature for 45 min and cooled on ice, whereupon indolin-1-carbonyl chloride (**3m**) (3.6 g, 20 mmol) in 10 mL dry THF was added. The reaction mixture was stirred for 1 h, concentrated in vacuo and separated between water and ethyl acetate. The organic fraction was purified by column chromatography (methylene chloride, ethyl acetate 1:1, v/v) to give 0.8 g (20%) of 2,2-(1,2-ethylene)-3-(1-indolincarbonyloxy)propanol. MS (70 eV): *m/z* 247 (M^+, 35%), 163 (45), 132 (55), 119 (100). ^{1}H-NMR ($CDCl_3$): 0.65 (d, 4H), 3.31 (t, 2H), 3.48 (s, 2H), 4.03 (t, 2H), 4.21 (broad s, 2H), 6.98 (t, 1H), 7.18 (d, 2H), 7.90 (broad d, 1H).

b: 2,2-(1,2-Ethylene)-3-(1-indolincarbonyloxy)propanol (460 mg, 1.8 mmol), p-toluenesulfonyl chloride (510 mg, 2.7 mmol) and pyridine (250 µL, 2.7 mmol) in 25 mL methylene chloride, was stirred for 4 h at 0 °C at room temperature for 16 h and at reflux for 4 h. The mixture was extracted with water and 1 N HCl, dried over Na_2SO_4 and concentrated in vacuo. The resulting oil was purified by column chromatography (methylene chloride, ethyl acetate 1:1, v/v) to get 1-chloro-2,2-(1,2-ethylene)-3-(1-indolinecarbonyloxy)propane (180 mg) (24%) as an oil. ^{1}H-NMR ($CDCl_3$): 0.7 (d, 4H), 3.1 (t, 2H), 3.58 (s, 2H), 4.0 (t, 2H), 4.22 (s, 2H), 6.95 (t, 1H), 7.20 (m, 2H), 7.75 (broad d, 1H).

c: 1-Chloro-2,2-(1,2-ethylene)-3-(1-indolinecarbonyloxy)propane (180 mg, 0.7 mmol), and 4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidine (**1**) (240 mg, 1.1 mmol) was reacted as described for compound **33**. The mixture was concentrated in vacuo and separated between water and ethyl acetate. The organic fraction was evaporated and redissolved in acetone. Addition of oxalic acid (100 mg) in 2 mL acetone precipitated the desired product, which was recrystallised from ethanol to give 240 mg (64%). M.p. 203–205 °C. MS (70 eV): *m/z* 449 (M^+, 100%), 287 (42), 233 (30), 219 (35), 146 (50), 82 (98). ^{1}H-NMR (DMSO-d_6): 0.76 (d, 4H), 2.15 (m, 4H), 2.99 (broad, 3H), 3.11 (t, 2H), 3.49 (broad, 3H), 4.02 (t, 2H), 4.13 (s, 2H), 6.95 (d, 1H), 7.26 (m, 3H), 7.74 (m, 2H), 8.05 (dd, 1H). Anal. ($C_{26}H_{28}N_3FO_3$) CHN.

5.1.32 1-(3-(2-Chloro-4,5-methylenedioxyphenylcarbamoyloxy)propyl)-4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidine, hydrochloride ***35***

To a solution of 4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-(3-(3,4-methylenedioxyphenylcarbamoyloxy)propyl)piperidine (**8**) (470 mg, 1.1 mmol) in methylene chloride (10 mL) was dropwise added a solution of chlorine in tetrachloromethane (1 mL, 1.1 mmol). After being stirred over night the reaction was washed with sodium bicarbonate, water, and brine, dried over Na_2SO_4 and concentrated in vacuo. The crude product was dissolved in acetone and addition hydrochloride in diethylether precipitated the title compound (210 mg, 38%). MS (70 eV): *m/z* 475 (35%, M^+), 337 (18), 233 (38), 197 (44), 96 (100). ^{1}H-NMR ($CDCl_3$): 1.91 (m,2H), 2.1 (m, 6H), 2.52 (t, 2H), 3.1 (broad, 3H), 4.29 (t, 2H), 5.98 (s, 2H), 6.78 (s, 1H), 6.92 (s, 1H), 7.03 (dt, 1H), 7.24 (dd, 1H), 7.7 (m, 2H). Anal. ($C_{23}H_{24}N_3FO_5Cl_2$) CHNCl.

5.1.33. 1-(3-(2-Bromo-4,5-methylenedioxyphenylcarbamoyloxy)propyl)4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidine, hydrochloride ***36***

4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-(3-(3,4-methylenedioxyphenylcarbamoyloxy)propyl)piperidine (**8**) (220 mg, 0.5 mmol) was dissolved in 2 mL glacial acetic acid and the mixture stirred at room temperature under N_2. Br_2 (0.25 µL, 0.5 mmol) dissolved in 1.0 mL glacial acetic acid was added. The mixture was stirred for 2 h whereupon aqueous K_2CO_3 was added to neutralise the solution, which was then extracted with ethyl acetate. The organic phase was dried over magnesium sulphate and concentrated in vacuo. The product was taken up in acetone and HCl in ether added to crystallise the desired product as 40 mg (15%) white crystals. M.p. 215–218 °C. MS (70 eV): *m/z* 521 (17%, M^+), 519 (17%, M^+), 278 (20), 243 (35), 241 (34), 233 (56), 96 (100) ^{1}H-NMR (DMSO-d_6): 2.1–2.38 (m, 7H), 3.2 (m, 4H), 3.68 (d, 2H), 4.15 (t, 2H), 6.12 (s, 2H), 7.05 (s, 1H), 7.25 (s, 1H), 7.38 (dt, 1H), 7.72 (dd, 1H), 8.12 (dd, 1H), 8.99 (s, 1H), 9.70 (s, 1H). Anal. ($C_{23}H_{23}N_3FBrO_5Cl$, 0.75 H_2O) CHNCl.

5.2. Receptor binding

Assays were performed essentially as described previously [13]. The affinity of a test substance for a receptor was briefly determined by measuring its ability to compete in vitro for radioligand binding at receptor sites expressed on rat striatal membranes (dopamine-D_1, -D_2), rat frontal cortex membranes (serotonin-5-HT_{2A}, adrenergic-α_1). Radioligands employed in each assay, obtained from New England Nuclear (USA), were as follows: [^{3}H]SCH23390 (80.4 Ci/mmol), 0.2 nM final concentration (dopamine-D_1); [^{3}H]Spiperone (18.5 Ci/mmol), 0.05 nM final concentration (dopamine-D_2); [^{3}H]Ketanserin (75.9 Ci/mmol), 0.4 nM final concentration (serotonin-5-HT_{2A}); [^{3}H]Prazocine (74.4 Ci/mmol), 0.5 nM final concentration (adrenergic-α_1). Specific binding was defined as the total binding present in membranes after incubation with radioligand minus the non-specific binding remaining after including 2 µM cis-Flupenthixol (dopamine-D_1), 0.2 µM Domperidone (dopamine-D_2), 2 µM Cyproheptadine (serotonin-5-HT_{2A}) or 10 µM Phentolamine (adrenergic-α_1). Free and bound ligand were separated by vacuum filtration through Whatman GF/B filters. Test substances were tested using 3 or more concentrations in order to obtain IC_{50} values described in *table I*. Each assay was performed 2–14 times and the results averaged. SEM is calculated when the results are based on more than 2 individual experiments.

5.3. Pharmacology

All the test drugs were given as a suspension in 5% duphasole-x. Log-probit methods were used to calculate ED_{50} values. For the pharmacological screening tests the number of doses defining the inhibition curves were frequently only two which were sufficient to estimate ED_{50} but which did not give enough data points to calculate confidence intervals.

5.3.1. (MPD)-induced stereotyped gnawing in mice

The method previously described in [13] was used. Three to five doses of each test drug were then administered per orally (10 mice in 5 pairs per dose of test drug). The effect of methyl phenidate (MPD) (60 mg/kg s.c.) induced stereotyped gnawing was observed 60 min after treatment.

5.3.2. MPD-induced motility in mice

The method described in [13] was used. Three to five doses of test drug were administered (p.o.). Each dose was administered to 4 mice; these 4 mice were placed in the same chamber (above). The

effect on methyl phenidate (MPD) (30 mg/kg s.c.) induced motility was observed 60 min after treatment. The data are expressed as percent inhibition of control MPD values (saline pre-treatment, 30 mg/kg MPD).

5.3.3. Conditioned avoidance responding in rats

The method described in [13] was used. Briefly rats were trained to perform a shuttle response in a two-way shuttle box in order to avoid an electric shock through the grid floor. The shock was signalled by a tone generator. Avoidance response was determined 120 min upon (i.p.) injection of compound.

5.3.4. Induction of catalepsy in rats

The method described in [13] was used. Briefly, rats were injected (i.p. 120 min pre-treatment) with the test compound and placed individually on an inclined wire mesh screen. The extremities of the animals were gently abducted. The latency to move any extremity was used to define the intensity of catalepsy.

5.3.5. Microdialysis procedure

The method described in [13] was used. The interstitial level of the dopamine metabolite dihydroxyphenyl acetic acid $[DOPAC]_e$ was measured in two brain areas by use of microdialysis. The microdialysis probes were inserted through a guided cannula into the medial prefrontal cortex, or in the dorsolateral striatum. At least 20 min perfusate samples were collected prior to administration of drugs which were injected intravenously over 1 min. Measurements were continued over 4 h whereafter the animals were killed. The concentration of DOPAC in the microdialysis samples were determined using HPLC.

5.3.6. Electrophysiology

Standard methods of extracellular single-cell recording from identified A9 and A10 dopamine neurones were used, as previously detailed [27]. All recordings were obtained from choral hydrate anaesthetised rats (400 mg/kg i.p.). Dopamine neurones were identified and recorded for 5 min to establish the baseline firing rate of the cell. At this time, the dopamine receptor agonist apomorphine was administered intravenously in a cumulative dose procedure to a total dose of 128 μg/kg (1, 1, 2, 4, 8, 16, 32, 64 μg/kg). This procedure resulted in a complete cessation of activity for every dopamine cell tested. Following a 2–3 min wait, NNC 19-1228 (**7**) or NNC 22-0031 (**8**) were injected intravenously using a cumulative dose regimen culminating in a total dose of 1.6 mg/kg for NNC 19-1228 and 6.4 mg/kg NNC 22-0031. For comparative purposes, similar experiments were conducted with the 'typical' antipsychotic agent haloperidol and the 'atypical' antipsychotic drug clozapine. All inter-injection intervals were 1 min in duration. A total of 12 cells was recorded from both the A9 and A10 cell groups. Histological examinations of recording sites was performed to verify location of each cell within the two regions.

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