45. Potential Antipsychotic Agents

Part 8[1])

Antidopaminergic Properties of a Potent Series of 5-Substituted (−)-(*S*)-*N*-[(1-ethylpyrrolidin-2-yl)methyl]-2,3-dimethoxybenzamides. Synthesis *via* Common Lithio Intermediates

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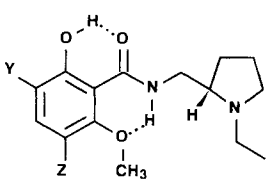
A series of 5-substituted (−)-(*S*)-*N*-[(1-ethylpyrrolidin-2-yl)methyl]-2,3-dimethoxybenzamides were made by reaction of the corresponding benzoyl chlorides with (*S*)-1-ethylpyrrolidine-2-methylamine (→ **14–16**, **18–21**). The acids required were prepared in a regiospecific manner from 5-bromo-2,3-dimethoxybenzoic acid which was protected as dihydrooxazole (→ **4–8**), metalated, reacted with various electrophiles (MeI, EtI, BuBr, CCl_3CCl_3 or MeSSMe), and hydrolyzed (→ **9–13**). Alternatively, (−)-(*S*)-5-bromo-*N*-[(1-ethylpyrrolidin-2-yl)methyl]-2,3-dimethoxybenzamide was treated with KH followed by BuLi and an electrophile (I_2 or Me_3SiCl) to give the 5-iodo and 5-(trimethylsilyl) derivatives **17** and **22**, respectively. All 5-substituted amides were highly potent inhibitors of [^{3}H]spiperone binding in rat striatal membranes with IC_{50} values of 0.5 to 5 nM *(Table 3)*. Thus, a relatively large steric bulk can be accomodated in the position *para* to the 2-MeO group. This work also supports the notion that a positive as well as negative electrostatic potential can be located in this position. A selected number of derivatives were also investigated *in vivo* and found to inhibit apomorphine-induced behavioural responses in the same dose range as haloperidol and raclopride *(Table 4)*. This new group of benzamides is suitable for investigations of dopamine D-2 receptors in labelled or unlabelled form.

Introduction. – In our laboratories, a number of salicylamides with selective dopamine D-2 antagonistic effects have been developed *(Table 1)* [2–8]. The suitable receptor-binding properties obtained have been utilized in the design of various types of radioligands, *e.g.* ^{3}H-, ^{11}C-, ^{18}F-, ^{123}I-, and ^{125}I-labelled salicylamides which successfully

Table 1. *Inhibition of [^{3}H]Spiperone Binding* in vitro *by Representative Dopamine D-2 Antagonists of the Salicylamide Type*



	Y	Z	IC_{50} [nM]
FLA 797	Br	H	12
raclopride	Cl	Cl	32
FLB 463	Br	CH_3O	1.4

[1]) Part 7: [1].

have been used for *in vitro* and *in vivo* investigations of the dopamine D-2 receptor [7–12]. Furthermore, animal studies showed that several of the salicylamides were more potent in inhibiting apomorphine-induced hyperactivity than in inhibiting stereotypies [2–6], which might indicate a preferential blockade of limbic over striatal dopamine receptors or a blockade of a subclass of D-2 receptors in the striatum [4] [8] [13]. These compounds have a potential to be effective drugs in the treatment of schizophrenia with a low tendency to induce extrapyramidal side-effects (EPS) since the acute and chronic motor disturbancies are believed to result from blockade of dopamine receptors in striatum [8] [13]. Raclopride, one of these compounds, is currently investigated in clinical trials [14].

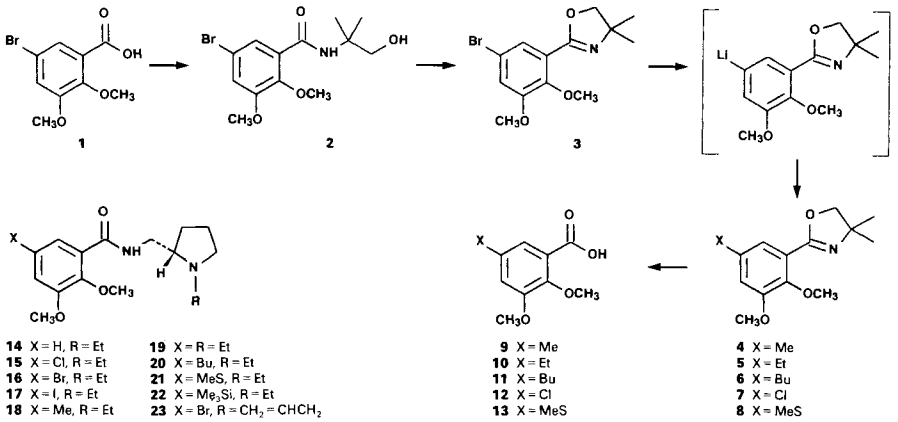
The recently described 5,6-dimethoxysalicylamides, *e.g.* FLB 463, were found to be a class of derivatives which were extremely potent to block dopamine D-2 receptors *in vitro* as well as *in vivo* [5] [7]. These salicylamides possessed slightly different requirements on the aromatic substituents in relation to the substituted 6-methoxysalicylamides lacking a 5-MeO group [5] [8]. Thus, the affinity for the dopamine D-2 receptor was only marginally affected by the nature of the 3-substituent (Y substituent *p* to the *o*-MeO group) in the 5,6-dimethoxysalicylamide series, although the lipophilicity of the 3-substituent is of major importance for the activity of the monomethoxysalicylamides [8] [15]. This underlines the favourable properties inherent to the 5,6-dimethoxysalicylamide system.

The salicylamides are conformationally restricted by two intramolecular H-bonds (OH to CO and NH to OMe; see *Table 1*), *i.e.* one bond more than the non-phenolic 2-methoxybenzamides or orthopramides [16] [17]. The molecular electrostatic-potential characteristics are highly variable for the salicylamides in contrast to what has been reported for other types of benzamides [18]. In an investigation on the importance of the 2,3-dimethoxybenzamide moiety in compounds with (pyrrolidin-2-yl)methyl side chains, we recently described the benzamide **16** (see below, *Scheme 1*), the dehydroxy analogue of FLB 463, which displayed a stereoselective inhibition of the dopamine D-2 receptor [1]. The benzamide **16** was about equipotent with the corresponding salicylamide (FLB 463), despite the absence of the phenolic OH group, and the (*S*)-enantiomer **16** was a 100-fold more active than its (*R*)-enantiomer. The 2,3-dimethoxybenzamide substitution pattern has been used primarily in dopamine antagonists having lipophilic N-substituents [6] [19], even if other examples such as veralipride, *N*-[(1-allylpyrrolidin-2-yl)methyl]-2,3-dimethoxy-5-sulfamoylbenzamide [20], are known.

It is of importance to further determine the relationships between the salicylamides and benzamides lacking the 2-OH group in order to see if any structural requirements are uniquely associated with one of the series or whether they can be treated simultaneously in QSAR and MEP studies. Thus, the high potency of **16** prompted the syntheses of additional analogues in order to learn more about the influence of the aromatic substituents in this series in relation to the 5,6-dimethoxysalicylamides [5] [7]. This paper describes the regiospecific syntheses of various 5-substituted 2,3-dimethoxybenzamides *via* common lithio intermediates. The compounds were investigated *in vitro* for their ability to inhibit the binding of [^{3}H]spiperone in rat striatal membranes. A selected number of compounds were also subjected to a limited *in vivo* investigation.

The highly potent antagonists described in this work should provide valuable tools for the investigation of dopamine D-2 receptor functions, and they are suitable for the development into radioligands for studies *in vitro* and *in vivo*. These results will be reported shortly [21].

Scheme 1



Chemistry. – In order to ascertain regiospecific and flexible syntheses of the 5-substituted 2,3-dimethoxybenzamides, we adopted two synthetic strategies which both imply common lithio intermediates. One method utilizes the known 5-bromo-2,3-dimethoxybenzoic acid [1] [22] (**1**) which was converted to a number of 5-substituted acids as shown in *Scheme 1*. The 5-bromo acid **1** was first protected in high yield as dihydrooxazole **3** by a two-step procedure *via* **2** according to *Meyers* and coworkers [23]. Dihydrooxazole **3** was treated with 1.1 equiv. of BuLi in THF at −78° to form the lithio intermediate which was reacted with various electrophiles to give the corresponding 5-substituted dihydrooxazoles **4**–**8** according to *Table 2*. Hydrolysis in aqueous hydrochloric acid gave the benzoic acids **9**–**13** in good overall yields from the 5-bromo acid **1** *(Table 2)*.

Benzoic acids **1** and **9**–**13** were converted to acyl chlorides and reacted with (*S*)-1-ethylpyrrolidine-2-methylamine (obtained by a stereoconservative process from L-pro-

Table 2. *Transformation of Dihydrooxazole* **3** *to the 5-Substituted 2,3-Dimethoxybenzoic Acids* **9**–**13** via **4**–**8** (see *Scheme 1*)

Electrophile (equiv.)[b]	Intermediate[a]	Yield [%]	Product[a]	Yield [%]	M.p. [°]	Solvent	Formula	Anal.[c]
MeI (2.2)	**4**	76	**9**	63	92–93	i-Pr_2O	$C_{10}H_{12}O_4$	C,H,O
EtI (2.1)	**5**	67	**10**[d]	70	oil			–
BuBr (1.5)	**6**	81	**11**	52	oil			–
Cl_3CCCl_3 (1.6)	**7**	49	**12**[e]	83	124–126	i-Pr_2O/hexane	$C_9H_9ClO_4$	C,H,Cl,O
MeSSMe (1.6)	**8**	44	**13**[f]	76	90–92	i-Pr_2O/hexane	$C_{10}H_{12}O_4S$	C,H,O,S

[a] All dihydrooxazoles **4**–**8** and benzoic acids **9**–**13** had the expected ^{1}H-NMR and/or MS.

[b] The intermediate dihydrooxazoles **4**–**8** were prepared by reaction of 2-(2,3-dimethoxy-5-lithiophenyl)-4,5-dihydro-4,4-dimethyloxazole with the indicated electrophile (see *Exper. Part*).

[c] Microanalysis values correct within ± 0.4%.

[d] Previously prepared by hydrogenation of 2,3-dimethoxy-5-ethenylbenzoic acid [26].

[e] Previously prepared by chlorination of 3-methoxysalicylic acid followed by methylation [19e].

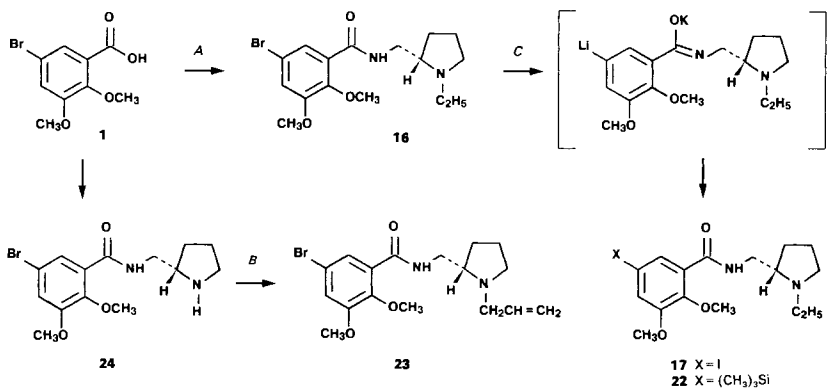
[f] [19b]: M.p. 92°. Synthesized by reduction of 5-(chlorosulfonyl)-2,3-dimethoxybenzoic acid followed by methylation.

Table 3. *Synthesis, Physical Data, and Inhibition of [^{3}H]Spiperone Binding (IC_{50}, [nM]) of 5-Substituted 2,3-Dimethoxybenzamides*

	X	R	*Method*	Yield [%]	$[\alpha]_D$ (*c*)[a]	M.p. [°]	Mass spectra [*m/z* (rel. int.)][b]	Formula	Anal.[c]	IC_{50} [nM][d]
14	H	Et	*A*[e]	100	−73 (0.60)	104–106	292 (0.11), 165 (3.1)	$C_{16}H_{24}N_2O_3 \cdot C_2H_2O_4$	–	52
15	Cl	Et	*A*	91	−72 (7.5)	50–52[f]	201, 199 (1.4, 4.1)	$C_{16}H_{23}ClN_2O_3$	C,H,N	0.4
16	Br	Et	*A*[e]	93	−59 (1.15)	135–136	372, 370 (0.07, 0.08); 245, 243 (1.0, 1.0)	$C_{16}H_{23}BrN_2O_3 \cdot HBr$	–	1.2
17	I	Et	*C*	25	−48 (1.40)	oil	418 (0.05), 291 (1.8)	$C_{16}H_{23}IN_2O_3$	C,H,N	0.7
18	Me	Et	*A*	90	−73 (1.9)	oil	179 (4.2)	$C_{17}H_{26}N_2O_3$	C,H,N[g]	5.2
19	Et	Et	*A*	55	−64 (0.59)	oil	193 (5.1)	$C_{18}H_{28}N_2O_3$	C,H,N[h]	1.3
20	Bu	Et	*A*	96	−57 (0.47)	oil	348 (0.08), 221 (2.5)	$C_{20}H_{32}N_2O_3$	–	2.7
21	MeS	Et	*A*	94	−80 (4.1)	oil	211 (5.1)	$C_{17}H_{26}N_2O_3S$	C,H,N	1.1
22	Me_3Si	Et	*C*	33	−52 (0.60)	oil	364 (0.08), 237 (1.8)	$C_{19}H_{32}N_2O_3Si$	C,H,N[i]	3.5
23	Br	CH_2 = $CHCH_2$	*B*	83	−57 (1.06)	116	384, 382 (0.28, 0.28); 245, 243 (1.3, 1.4)	$C_{17}H_{23}BrN_2O_3 \cdot HBr$	C,H,N	1.5

[a]) [α] of the basic form in acetone with *c* at 20–25°.
[b]) EI-MS (70 eV); base peak at *m/z* 98 in all cases, except for **23** (*m/z* 110); M^+ and/or $ArCO^+$ are shown.
[c]) Microanalysis values correct within ± 0.4% when not stated otherwise.
[d]) Correlation coefficients $r > 0.96$, except for **23** ($r = 0.81$).
[e]) According to [1].
[f]) Solidified upon standing.
[g]) N: calc., 9.14; found, 8.52.
[h]) C: calc., 67.47; found, 66.43.
[i]) N: calc., 7.68; found, 7.19.

Scheme 2



line [24]) to give the benzamides **14–16** and **18–21** in excellent yields *(Schemes 1* and *2, Table 3, Method A)*. Alternatively, the 5-bromo-2,3-dimethoxybenzamide **16** obtained from **1** was first treated with KH to suppress hydrogen-metal exchange in the following halogen-metal exchange step *(Method C)*. The potassium salt was then reacted with BuLi at −78° (→ lithio intermediate) and I_2 or (chloro)trimethylsilane to give the 5-iodo- and 5-(trimethylsilyl)benzamides **17** and **22**, respectively, in reasonable overall yields, even if a substantial amount of the reduced benzamide **14** was formed as side product *(Scheme 2)*. The two methods offer short and flexible ways of introducing different types of aromatic substituents with full regiocontrol.

The *N*-allyl analogue **23** of **16** was prepared to allow for comparisons with the corresponding salicylamide [5]. The secondary amine **24** was obtained from the acyl chloride of **1** by reaction with (*S*)-1-tritylpyrrolidine-2-methylamine [25] *(Scheme 2)*, and subsequent alkylation with allyl bromide in dimethylformamide furnished amide **23** in high overall yield from **1** *(Method B)*.

Results and Discussion. – The affinity of the compounds for the dopamine D-2 receptor was assessed by the inhibition of [^{3}H]spiperone binding in rat striatal membranes *in vitro (Table 3)* [27]. The incubations were done at +37° and (+)-butaclamol was used for determination of nonspecific binding. The IC_{50} values were calculated by log-logit regression analysis.

Compound **14** lacking a 5-substituent is considerably less active than the other benzamides. Halogen substitution at C(5) leads to the highly active derivatives **15–17** having IC_{50} values of 1 nM or less. Alkyl substitution at C(5) gives compounds **18–20** with somewhat higher IC_{50} values (1–5 nM). However, the 5-Br and 5-Et derivatives are equipotent. The 5-CH_3S derivative **21** is as active as the halogeno-substituted compounds. Introduction of the bulky Me_3Si group at C(5) gives the surprisingly active benzamide **22**. The *N*-allyl derivative **23** is as potent as the *N*-ethyl analogue **16** and the corresponding salicylamide described earlier [5].

No easily detectable trend in the influence of the 5-substituents on the activity can be seen. Apparently, a relatively large bulk can be tolerated at C(5) as shown by the I and CH_3S derivatives **17** and **21**. Also the even bulkier Bu and Me_3Si derivatives **20** and **22**

Table 4. In vivo *Activities of 2,3-Dimethoxybenzamides in Relation to Some Representative Antipsychotics in the Rat* (ED_{50} [μmol/kg *i.p.*])

	Blockade of apomorphine-induced responses[a])	
	Hyperactivity	Stereotypies
15	0.16 (0.06–0.26)	0.21 (0.15–0.28)
16[b])	0.002 (0.0002–0.006)	0.14 (0.12–0.17)
19	0.52[c])	0.64 (0.45–0.88)
23	0.019 (0.004–0.030)	0.10 (0.08–0.12)
Haloperidol	0.23 (0.08–0.32)	0.28 (0.25–0.31)
Raclopride	0.13 (0.05–0.23)	1.80 (1.57–2.13)

[a]) The compounds were injected *i.p.* 60 min prior to apomorphine (1 mg/kg *s.c.*). The hyperactivity and stereotypies were scored and calculated as described previously [4] [5]. The ED_{50} values were calculated by regression analysis using *Fieller*'s theorem for estimates of the 95% confidence limits.

[b]) Data taken from [1].

[c]) Interpolated from log dose-response curves.

are considerably active. The electronic influence of the 5-substituent is of minor importance, in the range of investigated substituents, which is in line with the behaviour of the corresponding salicylamides [5]. Furthermore, these 3-halogenated (Cl, Br, I) and 3-alkylated (Et, Pr) 5,6-dimethoxysalicylamides are equipotent (IC_{50} 0.3–2.4 nM [5] [7]) with the herein described 2,3-dimethoxybenzamides **15**–**20** lacking the *o*-OH group.

The structure-activity data obtained in this series of highly potent dopamine D-2 antagonists do not confirm the molecular electrostatic-potential pharmacophore [28] or the QSAR support of the same model [29] for substituted benzamides (*cf.* Discussion in [18]). This work rather supports the notion that a positive as well as negative electrostatic potential can be located in the position *p* (C(5)) to the 2-MeO group [18].

Some compounds were also studied *in vivo* for their ability to block apomorphine-induced oral stereotypies and hyperactivity in the rat *(Table 4)* according to previously described procedures [4] [5]. The 5-Br compounds **16** and **23** are equally active in inhibiting stereotypies, but the *N*-Et derivative **16** displays a somewhat higher functional separation between the inhibition of hyperactivity and stereotypies than the *N*-allyl compound **23**. Also the 5-chloro- and 5-ethylbenzamides **15** and **19**, respectively, inhibit the apomorphine-induced oral stereotypies in the same dose range, but they are considerably less prone, albeit equipotent with raclopride and haloperidol, to block the hyperactivity component of the behavioural syndrome. Thus, only **16** and **23** display a functional separation between the two apomorphine-induced behaviours, which is regarded to reflect preferential inhibition of limbic dopaminergic transmission and hence a lower tendency to induce extrapyramidal side-effects in man at antipsychotically effective doses [8] [13]. Further studies are required to determine whether the observed behavioural effects stem from selective regional binding or, as proposed in the case of raclopride [4], from binding to a dopamine D-2 subclass.

It can be concluded that several possibilities of making different types of radioligands for PET (positron-emission tomography) and SPECT (single photon emission computed tomography) with considerable activity and selectivity for the dopamine D-2 receptor can be envisioned among this type of 2,3-dimethoxybenzamides, *e.g.* ^{123}I, ^{75}Br, $^{11}CH_3$, and $^{11}CH_3CH_2$ substituents at C(5), which will be reported in due course. An interesting

approach to potential ^{18}F labelling by the introduction of $F(CH_2)_{2-3}$ has been communicated recently [30]. Furthermore, the $(CH_3)_3Si$ derivative **22** allows for *ipso*-directing control in the introduction of radioactive halogeno atoms by milder methods than described herein.

Experimental Part

General. FC = flash chromatography. Prep., centrifugally accelerated TLC: *Chromatotron* from *Harrison Research*. GLC: *SE 30* capillary column, *Hewlett-Packard 3390A* integrator. M.p.: in open capillary tubes on a *Mettler-FP61* apparatus; uncorrected. $[\alpha]_D$: *Optical-Activity-AA-100 polarimeter*. ^{1}H-NMR and ^{13}C-NMR spectra: *Jeol FX 200* spectrometer with Me_4Si as internal standard; δ in ppm. Mass spectra (*m/z* (rel. int.)): *LKB-2091* instrument. Elemental analyses were performed by Analytische Laboratorium, Elbach, FRG, and are within ±0.4% of the theoretical values unless otherwise indicated.

*(−)-(S)-*N*-[(1-Ethylpyrrolidin-2-yl)methyl]-2,3-dimethoxy-5-methylbenzamide* (**18**; *Method A*). A mixture of 2,3-dimethoxy-5-methylbenzoic acid (0.30 g, 1.5 mmol), $SOCl_2$ (0.20 ml, 2.8 mmol), and 3 drops of DMF as catalyst was stirred in 10 ml of toluene at 60° under N_2 for 1 h. After cooling, the solvent was evaporated and the residue dissolved in CH_2Cl_2 and evaporated again. The residue consisting of 2,3-dimethoxy-5-methylbenzoyl chloride was dissolved in 10 ml of CH_2Cl_2. A soln. of (*S*)-1-ethylpyrrolidine-2-methylamine [24] (0.78 g, 1.83 mmol) in 5 ml of CH_2Cl_2 was added and the mixture stirred overnight at r.t. The solvent was evaporated and the residue dissolved in 2M HCl and washed with Et_2O. The aq. layer was made alkaline and extracted twice with Et_2O. Drying ($MgSO_4$) and evaporation gave 420 mg (90%) of pure **18** as an oil. $[\alpha]_D^{22} = -73$ (*c* = 1.9, acetone). ^{1}H-NMR ($CDCl_3$): 7.51 (*d*, H–C(6)); 6.85 (*d*, H–C(4)); 3.88 (*s*, 2 MeO). ^{13}C-NMR ($CDCl_3$): 165.5, 152.2, 145.5, 133.9, 126.3, 122.8, 116.1, 62.5, 61.1, 56.9, 53.4, 47.9, 41.1, 28.3, 22.5, 21.1, 13.6. EI-MS (70 eV): 179 (4.2, $Me(MeO)_2C_6H_2CO^+$), 98 (100).

The 5-substituted (*S*)-*N*-[(1-ethylpyrrolidin-2-yl)methyl]-2,3-dimethoxybenzamides **14**–**16** and **19**–**21** were prepared analogously: see *Table 3* for details.

*(+)-(S)-5-Bromo-2,3-dimethoxy-*N*-[pyrrolidin-2-yl)methyl]benzamide* (**24**). For 1 h, 5-bromo-2,3-dimethoxybenzoyl chloride [1] (3.8 mmol) was reacted with (*S*)-1-tritylpyrrolidine-2-methylamine [25] (1.35 g, 3.9 mmol) in 10 ml of CH_2Cl_2 at r.t. The solvent was evaporated and the residue treated with 10 ml of EtOH and 0.1 ml of conc. HCl soln. for 1 h at r.t. After evaporation, the residue was partitioned between 0.5M HCl and Et_2O. The aq. phase was made alkaline, extracted with CH_2Cl_2, dried (Na_2SO_4), and evaporated: 1.10 g (84%) of **24** as an oil. $[\alpha]_D^{22} = +3.4$ (*c* = 0.42, acetone). ^{1}H-NMR ($CDCl_3$): 7.93 (*d*, H–C(6)); 7.23 (*d*, H–C(4)); 3.94 (*s*, 2 MeO). EI-MS (70 eV): 342, 340 (0.20, 0.19, $[M-H]^+$), 245, 243 (4.5, 4.8, $Br(MeO)_2C_6H_2CO^+$), 70 (100).

*(−)-(S)-*N*-[(1-Allylpyrrolidin-2-yl)methyl]-5-bromo-2,3-dimethoxybenzamide* (**23**; *Method B*). Allyl bromide (105 µl, 1.25 mmol) was added to a mixture of **24** (400 mg, 1.17 mmol), K_2CO_3 (200 mg, 1.45 mmol), and DMF (10 ml). After stirring for 1.5 h at r.t., the mixture was partitioned between 100 ml of 0.2M HCl/Et_2O 1:1. The aq. phase was made alkaline and extracted twice with Et_2O. Drying (Na_2SO_4) and evaporation gave a residue which was purified by FC (SiO_2, i-Pr_2O/MeOH/NH_3 100:10:1): 370 mg (83%) of pure **23**. $[\alpha]_D^{22} = -57$ (*c* = 1.06, acetone). ^{1}H-NMR ($CDCl_3$): 7.91 (*d*, H–C(6)); 7.18 (*d*, H–C(4)); 5.0–6.05 (*m*, $CH{=}CH_2$); 3.91 (*s*, 2 MeO); EI-MS (70 eV): 384, 382 (0.28, 0.28 M^+), 245, 243 (1.3, 1.4, $Br(MeO)_2C_6H_2CO^+$), 110 (100).

*(−)-(S)-*N*-[(1-Ethylpyrrolidin-2-yl)methyl]-5-iodo-2,3-dimethoxybenzamide* (**17**; *Method C*). A soln. of (*S*)-5-bromo-*N*-[(1-ethylpyrrolidin-2-yl)methyl]-2,3-dimethoxybenzamide (**16**; 245 mg, 0.68 mmol) in 5 ml of THF was added to a mixture of KH (39 mg, 0.97 mmol; oil dispersion washed with hexane and evaporated under N_2) and THF (5 ml) at −20° under N_2. The temp. was allowed to gradually reach r.t. and after 1 h, the mixture was cooled to −78° and BuLi (0.63 ml of 1.5M hexane soln., 0.95 mmol) added dropwise. After stirring for 1.5 h at −78°, a soln. of I_2 (500 mg, 2.0 mmol) in THF (3 ml) was added rapidly and the temp. raised to r.t. within 0.5 h. After 0.5 h, 0.5M HCl (50 ml) was added and the mixture extracted 3 times with Et_2O. The aq. layer was made alkaline and extracted with CH_2Cl_2, dried (Na_2SO_4), and evaporated: crude oil containing 34% of **17** and 45% of the reduced product **14**. Repeated radial disc chromatography on SiO_2 with i-Pr_2O/MeOH/NH_3 100:5:1 gave 70 mg (25%) of pure **17**. $[\alpha]_D^{22} = -48$ (*c* = 1.40, acetone). ^{1}H-NMR ($CDCl_3$): 8.12 (*d*, H–C(6)); 7.37 (*d*, H–C(4)); 3.91 (*s*, 2 MeO). EI-MS (70 eV): 418 (0.05, M^+), 291 (1.8, $I(MeO)_2C_6H_2CO^+$), 165 (0.28), 164 (0.22), 111 (2.0), 98 (100).

*(−)-(S)-*N*-[(1-Ethylpyrrolidin-2-yl)methyl]-2,3-dimethoxy-5-(trimethylsilyl)benzamide* (**22**) was prepared by *Method C* using chloro(trimethyl)silane as electrophilic reagent. Yield 33% after purification by repeated radial chromatography as above. $[\alpha]_D^{22} = -52$ (*c* = 0.60, acetone). ^{1}H-NMR ($CDCl_3$): 7.96 (*d*, H–C(6)); 7.21 (*d*, H–C(4));

3.94 (*s*, 2 MeO); 0.27 (*s*, Me_3Si). EI-MS (70 eV): 364 (0.08, M^+), 349 (1.1, $[M-CH_3]^+$), 237 (1.8, $Me_3Si(MeO)_2C_6H_2CO^+$), 223 (0.65), 98 (100), 73 (Me_3Si^+, 2.6).

*5-Bromo-*N*-(2-hydroxy-1,1-dimethylethyl)-2,3-dimethoxybenzamide* (**2**). A mixture of 5-bromo-2,3-dimethoxybenzoic acid (**1**; 15.0 g, 57 mmol), $SOCl_2$ (12.8 ml, 172 mmol), and toluene (100 ml) was heated at 50° for 2 h. The solvent was evaporated and CH_2Cl_2 added to the residue and then evaporated. To the acyl chloride in 50 ml of CH_2Cl_2, a soln. of 2-amino-2-methylpropan-1-ol (10.3 g, 115 mmol) in 50 ml of CH_2Cl_2 was added at +10° within 10 min. After stirring at r.t. for 2 h, another 200 ml of CH_2Cl_2 were added, and the mixture was washed with H_2O, dried (Na_2SO_4), and evaporated: 19.0 g. FC (SiO_2, i-Pr_2O) afforded 14.7 g (77%) of pure **2**. ^{1}H-NMR ($CDCl_3$): 8.26 (br. NH); 7.86 (*d*, H–C(6)); 7.22 (*d*, H–C(4)); 4.76 (*t*, OH), 3.92 (*s*, 2 MeO); 3.72 (*d*, CH_2O); 1.40 (*s*, $(CH_3)_2C$).

2-(5-Bromo-2,3-dimethoxyphenyl)-4,5-dihydro-4,4-dimethyloxazole (**3**). At r.t., **2** (13.0 g, 39 mmol) was cyclized by dropwise addition of $SOCl_2$ (6.6 g, 55 mmol). After stirring for 0.5 h, the mixture was poured into Et_2O, and 1M NaOH was added. The Et_2O layer was separated, dried (Na_2SO_4), and evaporated: 10.0 g (82%) of pure **3**. ^{1}H-NMR ($CDCl_3$): 7.54 (*d*, H–C(6)); 7.15 (*d*, H–C(4)); 4.12 (*s*, CH_2); 3.86, 3.85 (2 *s*, 2 MeO); 1.37 (*s*, $(CH_3)_2C$).

2-(2,3-Dimethoxy-5-methylphenyl)-4,5-dihydro-4,4-dimethyloxazole (**4**). To a soln. of **3** (2.0 g, 6.4 mmol) in 20 ml of anh. THF were injected 4.38 ml of 1.6M BuLi in hexane (7.0 mmol) at −78° under N_2. After stirring for 1 h, MeI (1.99 g, 14 mmol) was injected and the temp. raised to −45°. After stirring for another 1.5 h, the mixture was poured into 100 ml of 1M NaOH and extracted twice with Et_2O. The Et_2O layer was dried (Na_2SO_4), evaporated, and separated on a SiO_2 column with i-Pr_2O: 1.2 g (76%) of pure **4** as an oil. ^{1}H-NMR ($CDCl_3$): 7.19 (*d*, H–C(6)); 6.86 (*d*, H–C(4)); 4.13 (*s*, CH_2); 3.86 (*s*, 2 MeO); 2.30 (*s*, CH_3); 1.37 (*s*, $(CH_3)_2C$).

The compounds **5**–**8** were prepared analogously by reaction of 2-(2,3-dimethoxy-5-lithiophenyl)-4,5-dihydro-4,4-dimethyloxazole and the electrophile indicated in *Table 2*.

2,3-Dimethoxy-5-methylbenzoic Acid (**9**). For 1 h, **4** (1.1 g, 4.4 mmol) was heated to reflux in 10 ml of 2M HCl. The mixture was extracted with Et_2O. Drying (Na_2SO_4) and evaporation gave 0.55 g (63%) of crystals which were recrystallized from i-Pr_2O: 0.40 g of pure **9**. M.p. 92–93°. ^{1}H-NMR ($CDCl_3$): 7.48 (*d*, H–C(6)); 6.97 (*d*, H–C(4)); 4.03 (*s*, 2-MeO); 3.90 (*s*, 3-MeO); 2.34 (*s*, CH_3). ^{13}C-NMR ($CDCl_3$): 165.9, 151.9, 146.3, 134.9, 123.8, 121.7, 118.6, 62.1, 56.2, 21.1.

The benzoic acids **10**–**13** were prepared analogously from the dihydrooxazoles **5**–**8**, resp. *(Table 2)*.

[^{3}H]Spiperone Binding [4] [27]. Male *Sprague-Dawley* rats were killed by decapitation. The striata were rapidly dissected out on ice and homogenized in *Tris*-HCl buffer (0.05M, pH 7.6). The homogenate was centrifuged for 10 min at 48000 *g*, resuspended, and recentrifuged. The final pellet was resuspended in *Tris*-HCl buffer containing 0.1% of ascorbic acid and various salts to a final concentration of 5 mg/ml. The incubations were performed at 37° for 10 min in plastic trays and were terminated, and bound ligand was separated from free by filtration and subsequent washing on glass fiber paper. (+)-Butaclamol (1 μM) was used for the determination of nonspecific binding. The radioactivity of the filters was determined by a liquid scintillation counter. The IC_{50} values were calculated using log-logit regression analysis.

Blockade of Apomorphine-Induced Stereotypies and Hyperactivity [4] [5]. Male *Sprague-Dawley* rats (275–325 g) were used. The behaviour was scored 5, 20, 40, and 60 min after injection of apomorphine hydrochloride (1 mg/kg) given subcutaneously into the neck. The scoring was performed as described previously [4] [5]. The test compounds were dissolved in saline or AcOH and dist. H_2O and injected *i.p.* 60 min prior to apomorphine. After the injection of apomorphine, the animals were placed in individual cages. The ED_{50} values refer to the calculated doses that reduce the scores by 50% over the total observation period of 60 min of that of the apomorphine control. The ED_{50} values for stereotypies and hyperactivity have been calculated by regression analysis using *Fieller*'s theorem for calculation of the 95% confidence limit [5]. The ED_{50} value of the response has been defined as the midpoint between the mean of the apomorphine control group and the mean of the saline control group.

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