171. New Alkoxypyridine-sulfonamides: Synthesis, Biological Evaluation, and Physicochemical Properties

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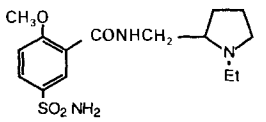
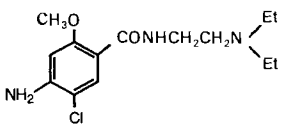
As a further pharmacomodulation of benzamide derivatives, two structural modifications were introduced by synthesizing pyridinesulfonamides **5** and **6** (*Scheme*). The pharmacological profile of substituted benzamides such as metoclopramide (**2**) is not retained in the pyridine-sulfonamides **6**: the latter have very low toxicity but do not exhibit any affinity for D2 and 5-HT2 receptors, and gastrointestinal prokinetic activity is weak (*Table 3*). Lipophilicity does not seem to be a determining factor for this lack of activity. A conformational analysis shows that the sulfonamide group in **6** is rather unfavorable for an intramolecular H-bond formation when compared to the carboxamide group of, *e.g.*, **2**. Nevertheless, the interaction remains possible and leads to a stable conformation (*Fig. 1*, *Table 5*). Moreover, the sp^3 character of the sulfonamide N-atom of **6** modifies the relative spatial orientation of one substituent in relation to each of the others. This feature seems to be more important for the observed very low activity than the H-bond formation itself.

Introduction. – Substituted benzamides are often used in therapeutics for their antiemetic and antipsychotic properties. In the pharmacological profile of the first synthesized orthopramides, both activities are usually retained. It is now generally suspected that different mechanisms are involved. Compounds like sulpiride (**1**), metoclopramide (**2**), raclopride or tropapride seem to be mainly Na^+-dependent antidopaminergic drugs with a predominant neuroleptic profile [1]. This approach has been continuously investigated in the development of antipsychotic drugs with low incidence of extrapyramidal side effects. The recent identification of a 'D3' receptor [2] should offer a new potential target for atypical neuroleptics. More specifically gastrokinetic compounds like cisapride, renzapride, or zacopride act *via* other non-dopaminergic mechanisms which could be related to serotonergic receptors [3–8]. The gastrokinetic effects of cisapride are largely due to an enhanced release of acetylcholine in the myenteric plexus, a mechanism not completely understood and already found with metoclopramide (**2**) [9]. Modulating the substitution at position 2 of the benzamide also gave access to compounds with interesting gastrointestinal prokinetic activity without D2 dopaminergic receptor affinity [10] [11].



1 Sulpiride



2 Metoclopramide

Since the discovery of the first orthopramides [12], a lot of similar compounds with structural modifications in the amide side chain [13–16], in the benzene-ring substitution [10] [11] [17] [18], and at the carboxamide group itself were synthesized. In some cases, the nonclassical 'bioisosteric' replacement of the carboxamide group by a sulfonamide group produced antiemetic and psychotropic compounds [19–21]. However, the introduction of a sulfonamide group in the clebopride [22] or tropapride series [23] caused a dramatic decrease in antidopaminergic potential. Moreover, the replacement of the benzene ring by a heterocycle like pyridine [24], pyrimidine [25], or pyrazine [26] yielded more active compounds.

In the present study, two structural modifications were made at the same time by synthesizing pyridinesulfonamide derivatives. In this preliminary approach, the classical *N*-side chains of sulpiride (**1**) or metoclopramide (**2**) were selected, as these two molecules exhibit both types of activity. A biological evaluation was conducted to determine the gastrointestinal prokinetic activity and to evaluate the D2 and 5-HT2 binding affinity.

Chemistry. – The pyridinesulfonamide derivatives were synthesized starting from 4-hydroxypyridine-3-sulfonic acid (**3**) which was prepared as described in [29] (see

Scheme

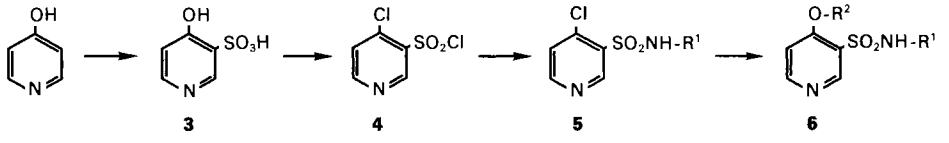


Table 1. *Physical Data and Yield of 4-Chloropyridine-3-sulfonamides* **5**

	R^1	Formula	M.p. [°][a])	Yield [%]
5a	$Me_2N(CH_2)_2$	$C_9H_{14}ClN_3O_2S$	96	80
b	$Et_2N(CH_2)_2$	$C_{11}H_{18}ClN_3O_2S$	94	85
c	$Me_2N(CH_2)_3$	$C_{10}H_{16}ClN_3O_2S$	92	85
d	$Et_2N(CH_2)_3$	$C_{12}H_{20}ClN_3O_2S$	oil	80
e	1-ethylpyrrolidin-2-methyl	$C_{12}H_{18}ClN_3O_2$	121	85

[a]) Crystallization from petroleum ether (100–140°).

Table 2. *Physical Data and Yield of 4-Alkoxypyridine-3-sulfonamides* **6**

	R^1	R^2	Formula	M.p. [°][a])	Yield [%]
6a	$Me_2N(CH_2)_2$	Me	$C_{10}H_{17}N_3O_3S$	78	85
b	$Me_2N(CH_2)_2$	Et	$C_{11}H_{19}N_3O_3S$	75	75
c	$Et_2N(CH_2)_2$	Me	$C_{12}H_{21}N_3O_3S$	96	85
d	$Et_2N(CH_2)_2$	Et	$C_{13}H_{23}N_3O_3S$	46	80
e	$Me_2N(CH_2)_3$	Me	$C_{11}H_{19}N_3O_3S$	91	80
f	$Me_2N(CH_2)_3$	Et	$C_{12}H_{21}N_3O_3S$	48	75
g	$Et_2N(CH_2)_3$	Me	$C_{13}H_{23}N_3O_3S$	62	70
h	$Et_2N(CH_2)_3$	Et	$C_{14}H_{25}N_3O_3S$	62	65
i	1-ethylpyrrolidin-2-methyl	Me	$C_{13}H_{21}N_3O_3S$	112	85
j	1-ethylpyrrolidin-2-methyl	Et	$C_{14}H_{23}N_3O_3S$	80	80

[a]) Crystallization from petroleum ether (100–140°)/toluene 8:2.

Scheme). Reaction of **3** with $POCl_3/PCl_5$ (→**4**) and then with the appropriate amine yielded 4-chloropyridine-3-sulfonamides **5**, from which 4-alkoxypyridine-3-sulfonamides **6** were easily prepared by treatment with an excess of sodium alkoxide in refluxing alcohol. Some data of sulfonamides **5a–e** and **6a–j** are listed in *Tables 1* and *2*, respectively. The structure of **6a** and **6c** were determined by X-ray analysis [27] [28].

Results and Discussion. – Taking into account the literature data, we could expect that the new compounds would behave as antiemetics or psychotropes. Representative sulfonamides **6** were tested in pharmacological experiments aimed at measuring the acute toxicity *per os* in mice, the prokinetic activity of mouth-to-caecum transit with barium meal in mice, and the neuroleptic potential by radioligand binding studies (deplacement of [^{3}H]ketanserine and [^{3}H]spiroperidol for serotonergic and dopaminergic receptors, resp.; *Table 3*). All compounds **6** have very low toxicity (LD_{50} > 1000 mg/kg) but are devoid of any significant activity in the *in vivo* test. The receptor affinities are not significant (IC_{50} > 10^{-5} M). How can that inactivity be explained?

Table 3. *Acute Toxicity and Intestinal Prokinetic Activity*

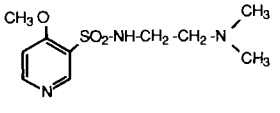
	LD_{50}, *p.o.* [mg/kg]	Dose, *p.o.* [mg/kg]	Number *n* of animals with barium in caecum (total number *T* of animals)			
			60 min after meal		90 min after meal	
			n (*T*)	%	*n* (*T*)	%
6c	> 1000	0	0 (7)	0	1 (7)	14
		10	0 (7)	0	1 (7)	14
		30	0 (7)	0	2 (7)	28
		90	0 (7)	0	0 (7)	0
d	> 1000	0	1 (7)	14	1 (14)	7
		10	0 (7)	0	1 (7)	14
		30	0 (7)	0	0 (7)	0
		90	0 (7)	0	1 (7)	14
e	> 1000	0	0 (7)	0	1 (7)	14
		10	0 (7)	0	0 (7)	0
		30	0 (7)	0	0 (7)	0
		90	0 (7)	0	0 (7)	0
f	> 1000	0	0 (7)	0	0 (7)	0
		10	0 (7)	0	1 (7)	14
		30	0 (7)	0	1 (7)	14
		90	1 (7)	14	1 (7)	14
		180	1 (7)	14		
h	1000	0	1 (14)	7	9 (14)	64
		10	3 (7)	42	2 (7)	28
		30	1 (7)	14	1 (7)	14
		90	0 (7)	0	0 (7)	0
i	1000	0	1 (14)	7	1 (7)	14
		10	0 (7)	0	0 (7)	0
		30	2 (8)	25	0 (7)	0
		90	1 (7)	14	1 (7)	14
Vehicle	–	–	2 (7)	28	1 (7)	14
Metoclopramide (**2**)	250	5	4 (7)	57	7 (7)	100
Cisapride	> 2000	10	7 (7)	100	7 (7)	100

According to *El Tayar et al.* [30], there is no clear relationship in the orthopramide series between lipophilicity and dopaminergic affinity (D2). In a series of tropapride analogues, however, *Collin et al.* [31] established a strong correlation between lipophilicity and dopaminergic affinity. Thus, the lipophilicity of some compounds, active or not, were measured in an octanol/H_2O partition system at pH 7.4. But the data do not provide any additional information, log*P* of **6i** (−0.76) and **6c** (−0.84) being just between those of metoclopramide (**2**; 0.53) and sulpiride (**1**; −1.12). It seems, therefore, that lipophilicity is not a major parameter.

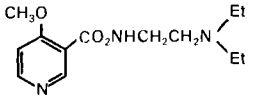
Moreover, it was suggested [32–36] that the activity of orthopramide compounds is conditioned by the formation of a H-bond between the carboxamide NH and the O-atom of the MeO group. In these cases, this H-bond generates a pseudocyclic structure which is considered as essential in the interaction with the receptor. The presence of a similar though much less favorable situation in sulfonamides **6** was suggested by a conformational analysis (see below).

We also compared the X-ray structures of compounds **6a** [28] and **6c** [27] with those of metoclopramide (**2**) [32] [35] and sulpiride (**1**) [37–39] (see *Table 4*). The most interesting geometric parameters (ϕ_1, ϕ_2, d_1, and d_2) of **6a** and **6c** are very different from those observed in the crystal structures of **1** and **2**. Thus, the introduction of a sulfonamide group considerably modifies the relative spatial orientation of the side chain and aromatic ring. These results fully confirm the conclusions of *Collin et al.* about a sulfobenzamide analogue of tropapride [23].

Conformational Analysis. To establish if a stable conformation of **6** with an intramolecular H-bond is likely to exist, a conformational analysis of **6a**, the pyridinecarboxamide analogue **7**, and a sulfonamide analogue **8** of metoclopramide was performed and compared with that of sulpiride (**1**) and metoclopramide (**2**).



6a



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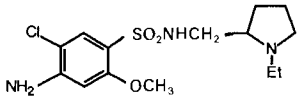

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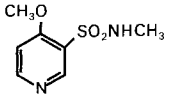

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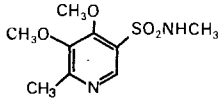

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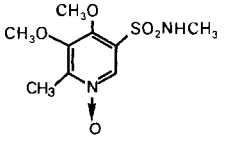

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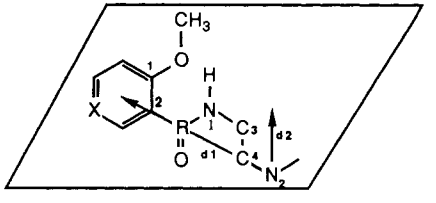
The geometry of the molecules was fully optimized at the MNDO quantum-chemistry level [40]. This method has been shown to provide good estimates of equilibrium geometries for neutral heterocyclic compounds. At the MNDO equilibrium geometry, the energy calculations of the conformers defined by a stepwise 10° rotation around C(2)–R (ϕ_1) were carried out at the STO-3G *ab initio* level, keeping all other degrees of freedom unchanged. Moreover, the 120 parameters of **2** itself were also fully optimized at the STO-3G level in order to evaluate the consistency of the STO-3G and MNDO results; thus the ϕ_1 value of **2** is −26.9 and −30.0°, and the O···HN distance 1.83 and 1.81 Å, respectively (*Table 5*).

For the three carboxamides **1**, **2**, and **7**, the conformational analysis shows the relative stability of two endocyclic structures at both sides of the O lone pairs of the MeO substituent (data of *Table 5* for the most stable conformation). In the sulfonamides **6a**

Table 4. *Crystallographic Parameters of* **6a** *and* **6c** *as Compared to Those of Sulpiride* (**1**) *and Metoclopramide* (**2**). Torsion angles in degrees and distances in Å with e.s.d. values in brackets.



		X	R	C(1)–C(2)–R–N(1) ϕ_1	C(2)–R–N(1)–C(3) ϕ_2	R–N(1)–C(3)–C(4) ϕ_3	N(1)–C(3)–C(4)–N(2) ϕ_4	d_1[a]	d_2[b]
6a	[28]	N	SO	61.1 (4)	69.9 (3)	–125.6 (5)	65.7 (5)	3.68 (5)	3.22 (5)
6c	[27]	N	SO	66.4 (2)	74.3 (2)	91.5 (2)	71.8 (2)	6.80 (4)	3.16 (4)
(*S*)-Sulpiride A	[37]	C	C	14.0 (5)	171.4 (5)	111.3 (5)	–171.2 (5)	7.32 (1)	1.08 (2)
(*S*)-Sulpiride B	[37]	C	C	11.1 (5)	–174.9 (5)	114.5 (5)	166.3 (5)	7.46 (1)	0.71 (2)
rac-Sulpiride	[37]	C	C	8.7 (9)	179.5 (9)	131.1 (9)	–169.3 (9)	7.41 (1)	0.89 (2)
Sulpiride	[38]	C	C	13.0 (9)	–178.8 (9)	123.7 (9)	–170.9 (9)	7.42 (1)	0.84 (2)
Sulpiride HCl	[39]	C	C	4.7 (9)	–178.8 (9)	–84.3 (9)	–59.1 (9)	6.15 (1)	2.33 (2)
Metoclopramide	[32]	C	C	4.8 (9)	179.1 (9)	173.7 (9)	69.4 (9)	6.34 (1)	1.56 (1)
Metoclopramide 0.1	[35]	C	C	2.8 (9)	177.7 (9)	175.3 (9)	71.1 (9)	6.36 (1)	1.56 (1)

[a]) d_1 = distance between the center of the aromatic ring and the N(2)-atom.

[b]) d_2 = distance between the plane of the aromatic ring and the N(2)-atom.

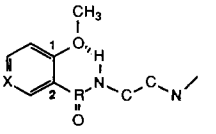


Table 5. *Electronic and Geometric Parameters for the Most Stable Conformation of* **1**, **2**, **6a**, *and* **7**–**11**

	H-Bond [Å]	C(1)–C(2)–R–N ϕ_1 [°]	Net neg. charge on CH_3O	C(1)–O–H–N ϕ (H-bond) [°]
Sulpiride (**1**; X = C, R = C)	1.918	40	0.264	54.87
Metoclopramide (**2**; X=C, R=C) MNDO	1.815	–30	0.270	–41.46
STO-3G	1.828	–26.9	0.243	–13.59
6a (X = N, R = SO)	2.833	–60	0.258	10.15
7 (X = N, R = C)	1.810	–30	0.265	–42.23
8 (X = C, R = SO)	3.100	70	0.262	–6.88
9 (X = N, R = SO)	2.568	–59.7	0.228	7.19
10 (X = N, R = SO)	2.478	–61.6	0.239	4.55
11 (X = N→O, R = SO)	2.464	–60.6	0.241	4.84

and **8**, the H-bond length is significantly greater due to the ϕ_1 value but also to the sp^3 character of the sulfonamide N-atom. Nevertheless, the torsion angle of the H-bond (ϕ(H-bond)) indicates a quasi coplanar geometry in **6a** (10.15°) and in **8** (–6.88°). It is thus possible to form a bond between the O-atom of the MeO group and the sulfonamide N*H*. This feature is clearly illustrated by the superimposition of the stereoscopic drawings of metoclopramide (**2**) and **6a** at their STO-3G-optimized geometry (*Fig. 1*).

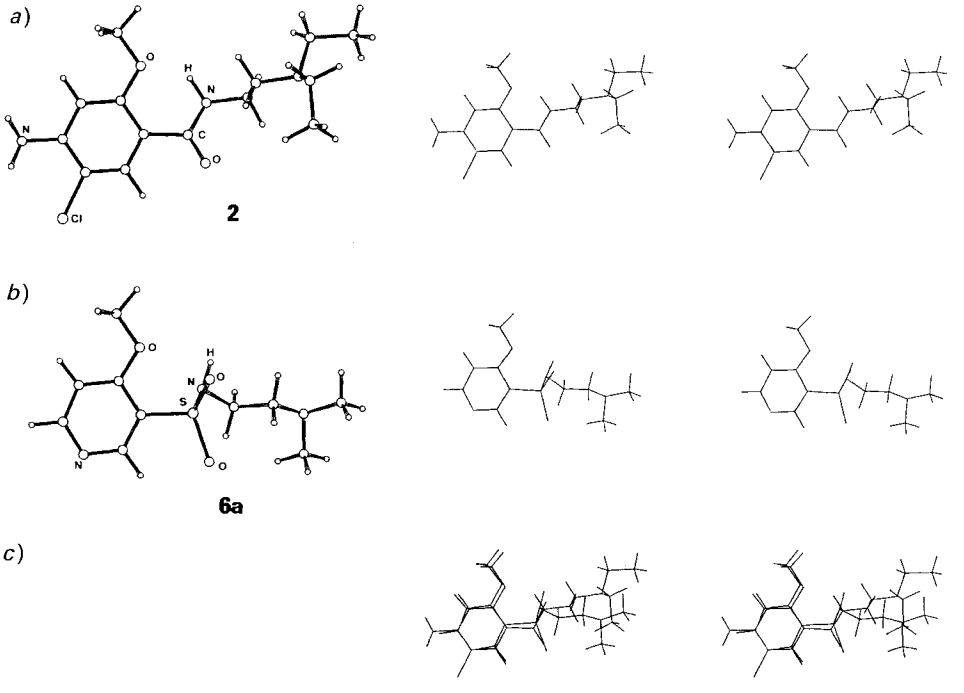


Fig. 1. *Stereoscopic drawings of* a) *metoclopramide* (**2**), b) *sulfonamide* **6a**, *and* c) *superimposed* **2** *and* **6a**

Electronic Properties. To analyze the influence of the substitution at the aromatic ring on H-bond formation, the geometry of the three model compounds **9**–**11** was fully optimized at the STO-3G level. The results show that the H-bond length decreases when the electronic charge of the MeO O-atom is enhanced (**10** and **11**, *Table 5*). The major influence of the sulfonamide is shown by the negative charge on the substituted C-atom (*Fig. 2*). The bulkiness of the substituents destroys the near planarity of the MeO group involved in the H-bond formation and thus reduces the torsional angle.

Collin et al. [31] attempted to define some guidelines in the intracyclic H-bond formation calculating the total atomic charges with the widely used *Mulliken* population analysis; in that study, the atomic coordinates of the heavy atoms were derived from the crystallographic data. However, it is well known that the geometry has a very strong incidence on the *Mulliken* population results. In the present study, some calculations were performed at STO-3G level, using the MNDO fully optimized geometries. The comparison between **6a** at the MNDO geometry and the model compound **9** at the STO-3G level clearly emphasizes this geometry incidence on the *Mulliken* results, particularly in the environment of the S-atom. Therefore, **6a** itself has been re-optimized in order to analyze the differences in charge distributions at both levels of geometry calculation (*Fig. 2*).

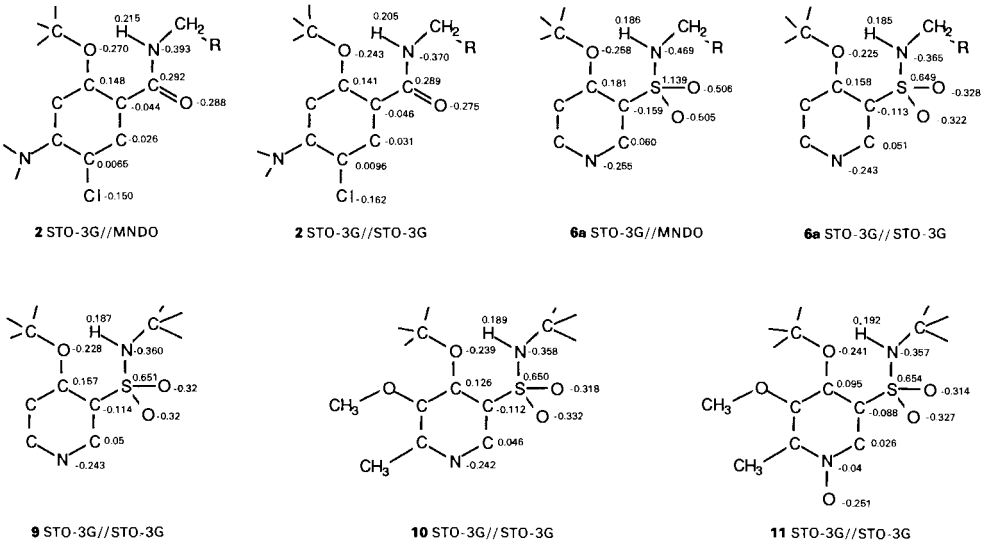


Fig. 2. *Net atomic charges derived from* Mulliken *population analysis*

Conclusion. – According to the literature, it seemed possible to maintain the activity of orthopramides, when their benzene ring is replaced by a pyridine ring [24], or when their carboxamide group is replaced by a sulfonamide group [19–21]. It appears, however, that the pyridinesulfonamide derivatives are totally inactive. Several parameters, like lipophilicity, geometric properties, and electronic distribution, involved in the intramolecular H-bond, have, therefore, been examined to explain this inactivity. It is clear that the log *P* values are not significant enough to distinguish active compounds from inactive ones.

Although the introduction of a sulfonamide group is rather unfavorable to the formation of an intramolecular H-bond, such an interaction remains possible and leads to a stable conformation found in the optimized geometry. However, the sp^3 character of the sulfonamide N-atom induces a different spatial orientation of the amide side chain. In the model pyridine compounds **9–11**, the electronic-density increase in the vicinity of the MeO group improves the formation of the H-bond. This feature, often presented as the prerequisite for pharmacological activity, is not the only feature conditioning the side-chain orientation, a feature shown to be preponderant in the present study.

Experimental Part

General. TLC: *Merck* silica gel *60 F254* plates. M.p.: open capillary tubes; *Tottoli* (*Büchi*) melting-point apparatus; uncorrected. IR spectra: *Perkin-Elmer-297* spectrophotometer. ^{1}H-NMR spectra: *Bruker-AW-80* spectrometer with Me_4Si as internal standard; assignments consistent with spectra. Elemental analyses (C, H, N, S): *Carlo-Erba-CHNS-O-EA1108* elemental analyzer; they were performed in house and are within ±0.4% of the theoretical values.

4-Chloropyridine-3-sulfonyl Chloride (**4**). See [29].

*4-Chloro-*N*-[2-(dimethylamino)ethyl]pyridine-3-sulfonamide* (**5a**). A little excess of 2-(dimethylamino)-ethylamine is added dropwise to a well stirred soln. of **4** (0.037 mol) in $CHCl_3$ (300 ml). After completion of the reaction, (TLC monitoring (AcOEt/petroleum ether 7:3)), the soln. is washed twice with 30% NH_3 soln. (100 ml) and then with H_2O (200 ml) and dried ($MgSO_4$). Petroleum ether (100–140°); (150 ml) is added and the soln. concentrated at r.t. *in vacuo* until crystallization. After 2 h at 0°, the product is collected by filtration, washed with petroleum ether (40–60°), and dried at r.t. *in vacuo*. IR (KBr): 1565, 1335, 1165, 765. ^{1}H-NMR ($CDCl_3$): 9.15 (*s*, H–C(2)); 8.68 (*d*, H–C(5)); 7.46 (*d*, H–C(6)); 5.8 (*s*, NH); 3.00 (*t*, CH_2CH_2); 2.35 (*t*, CH_2CH_2); 2.08 (*s*, 2 CH_3).

The 4-chloropyridine-3-sulfonamides **5b–e** were prepared analogously: see *Table 1*.

N*-[2-(Dimethylamino)ethyl]-4-methoxypyridine-3-sulfonamide* (**6a**). To a soln. of **5a** (0.05 mol) in MeOH (300 ml), a large excess of NaOMe (5 times) is added and the mixture refluxed. After completion of the reaction (TLC monitoring (AcOEt/$CHCl_3$ 1:1)) and evaporation, the residue is dissolved in H_2O (250 ml) and the resulting soln. acidified with HCl and filtrated. After neutralization with NH_3 soln., the filtrate is extracted 4–5 times with $CHCl_3$ (500–600 ml), the $CHCl_3$ extract dried ($MgSO_4$) and evaporated, and the residue recrystallized from petroleum ether (100–140°) toluene 8:2. The crystals are collected by filtration, washed with petroleum ether (40–60°), and dried at r.t. *in vacuo*. IR (KBr): 2830, 2780, 1580, 1330, 1155. ^{1}H-NMR ($CDCl_3$): 8.93 (*s*, H–C(2)); 8.65 (*d*, H–C(5)); 6.92 (*d*, H–C(6)); 3.98 (*s*, MeO); 2.98 (*t*, CH_2CH_2); 2.35 (*t*, CH_2CH_2); 2.08 (*s*, 2 CH_3).

The 4-alkoxypyridine-3-sulfonamides **6b–j** were prepared analogously: see *Table 2*.

Radioligand Binding Study. Experiments on receptor preparations are performed following classical methods previously described [41–43].

Gastrointestinal Prokinetic Activity. The barium meal mouth-to-caecum transit is an application of the radiologic method used in rat [44] and man [45]. The prokinetic activity of substances is determined by their capacity to increase the percentage of animals which present barium meal in the caecum comparatively to a control group: Female mice (22–24 g) are used for the test. The substances, which are dissolved or suspended in 0.5% carboxymethylcellulose, are administered orally to different groups of mice (n=7). The doses are chosen equal or superior to the standard dose of metoclopramide (5 mg/kg) or cisapride (10 mg/kg). The control group receives the vehicle. The volume administered, which is identical at each dose, is 0.1 ml/10 g of corpus weight. The barium meal (*Prontobario-esophage-Bracco*) is given (0.2 ml/mouse) immediately after the compounds. The presence of barium in caecum is examined after 60 and 90 min. The number of animals which present the barium meal in caecum is compared with the total number of animals.

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REFERENCES

[1] E. Stephanini, A. Marchisio, P. Devoto, F. Vernaleone, R. Collu, P.F. Spano, *Brain Res.* **1980,** *198,* 229.
[2] P. Sokoloff, B. Giros, M.-P. Martres, M.-L. Bouthenet, J.-C. Schwartz, *Nature (London)* **1990,** *347,* 146.
[3] D.H. Staniforth, M. Pennick, *Eur. J. Clin. Pharmacol.* **1990,** *38,* 161.
[4] F.D. King, G.J. Sanger, *Ann. Rep. Med. Chem.* **1988,** *23,* 201.
[5] W.L. Smith, C.B. Jackson, A.G. Proakis, C.A. Leonard, M.R. Munson, R.S. Alphin, *Proc. Am. Soc. Clin. Oncol.* **1986,** *5,* 260.
[6] B. Costall, A.M. Domeney, S.J. Gunning, M.E. Kelly, R.J. Naylor, V. Nohria, J.B. Owera-Atepo, K.M. Simpson, C.C.W. Tan, D. Tattersall, *Neuropharmacology* **1987,** *26,* 669.
[7] A. Schiavone, M. Volonté, R. Micheletti, *Eur. J. Pharmacol.* **1990,** *187,* 323.
[8] A. Dumuis, M. Sebben, J. Bockaert, *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1989,** *340,* 403.
[9] I. Pfeuffer-Friederich, H. Kilbinder, in 'Gastrointestinal Motility', Ed. C. Roman, MTP Press Ltd., Lancaster–Boston–The Hague–Dordrecht, 1984, pp. 527–534.
[10] I. Monkovic, D. Willner, M.A. Adam, M. Brown, R.R. Crenshaw, C.E. Fuller, P.F. Juby, G.M. Luke, J.A. Matiskella, T.A. Montzka, *J. Med. Chem.* **1988,** *31,* 1548.
[11] I. Monkovic, M. Brown, G.M. Luke, R.T. Standridge, D. Willner, A.R. Crosswell, A. Algieri, J.P. Buyniski, R.R. Crenshaw, P.F. Juby, *Eur. J. Med. Chem.* **1989,** *24,* 233.
[12] L. Justin Besancon, C. Laville, M. Thominet, *C. R. Séances Acad. Sci. (Paris)* **1964,** *258,* 4384.
[13] J. Prieto, J. Moragues, R.G. Spickett, A. Vega, M. Colombo, W. Salazar, D.J. Roberts, *J. Pharm. Pharmacol.* **1977,** *29,* 147.
[14] M. Jalfre, B. Bucher, N. Dorme, G. Mocquet, R.D. Porsolt, *Arch. Int. Pharmacodyn.* **1983,** *264,* 232.
[15] P.G.H. Van Daele, M.F.L. De Bruyn, F.M. Sommen, M. Janssen, J.M. Van Nueten, J.A.J. Schuurkes, C.J.E. Niemegeers, J.E. Leysen, *Drug Dev. Res.* **1986,** *8,* 225.
[16] T. Imbert, N. Dorme, M. Langlois, E.P. 0,099,789, 1984.
[17] T. Tahara, K. Hayano, S. Murakami, T. Fukuda, M. Setoguchi, K. Ikeda, N. Marubayashi, *Chem. Pharm. Bull.* **1990,** *38,* 1609.
[18] T. Högberg, P. Ström, T. de Paulis, B. Stensland, I. Csöregh, K. Lundin, H. Hall, S.O. Ögren, *J. Med. Chem.* **1991,** *34,* 948.
[19] J.-P. Fournier, P. Choay, EP 0,088,849, 1983.
[20] R.C. Moreau, J.-P. Fournier, G. Narcisse, F. Hubert, P. Choay, *Eur. J. Med. Chem.* **1977,** *12,* 421.
[21] R. Boudet-Dalbin, S. Durand, Y. Adam, R.C. Moreau, O. Foussart-Blanpin, *Eur. J. Med. Chem.* **1986,** *21,* 131.
[22] T. de Paulis, H. Hall, Y. Kumar, S. Rämsby, S.O. Ögren, T. Högberg, *Eur. J. Med. Chem.* **1990,** *25,* 507.
[23] S. Collin, D.P. Vercauteren, G. Evrard, F. Durant, *J. Chem. Soc., Perkin Trans. 2* **1989,** 407.
[24] J. Gosteli, A. Stomi, A. Zust, CH 624,681, 1981.
[25] P. Dostert, T. Imbert, J.-F. Ancher, M. Langlois, B. Bucher, G. Mocquet, *Eur. J. Med. Chem.* **1982,** *17,* 437.
[26] M. Takashima, M. Murakomi, K. Takahashi, Y. Mirato, M. Takeda, Japan Kokay 77,83,679, 1977.
[27] M. Sbit, L. Dupont, O. Dideberg, J.-F. Liégeois, J. Delarge, *Acta Crystallogr., Sect. C* **1988,** *44,* 907.
[28] L. Dupont, O. Dideberg, J.-F. Liégeois, J. Delarge, *Acta Crystallogr., Sect. C* **1990,** *46,* 1863.
[29] J. Delarge, *Ann. Pharm. Fr.* **1973,** *31,* 467.
[30] N. El Tayar, G.J. Kilpatrick, H. Van de Waterbeemd, B. Testa, P. Jenner, *Eur. J. Med. Chem.* **1988,** *23,* 173.
[31] S. Collin, N. El Tayar, H. Van de Waterbeemd, F. Moureau, D.P. Vercauteren, F. Durant, M. Langlois, B. Testa, *Eur. J. Med. Chem.* **1989,** *24,* 163.
[32] M. Cesario, C. Pascard, M. El Moukhtari, L. Jung, *Eur. J. Med. Chem.* **1981,** *16,* 13.
[33] T. Furaya, S. Iwanami, A. Takenata, Y. Sasada, *Bull. Chem. Soc. Jpn.* **1982,** *55,* 2321.
[34] H. Van de Waterbeemd, B. Testa, *Helv. Chim. Acta* **1981,** *64,* 2183.
[35] W. Shin, T.S. Chang, C.H. Koo, *Bull. Korean Chem. Soc.* **1983,** *4,* 123.
[36] H. Van de Waterbeemd, B. Testa, *J. Med. Chem.* **1983,** *26,* 203.
[37] L.Y.Y. Ma, N. Camerman, A. Camerman, *Acta Crystallogr., Sect. B* **1982,** *38,* 2861.
[38] C. Houttemane, J.-C. Boivin, G. Nowogrocki, D.J. Thomas, J.-P. Bonte, *Acta Crystallogr., Sect. B* **1981,** *37,* 981.
[39] N.M. Blaton, O.M. Peeters, C.J. de Ranter, O. Denisoff, L. Molle, *Cryst. Struct. Commun.* **1981,** *10,* 833.
[40] M.J.S. Dewar, W. Thiel, *J. Am. Chem. Soc.* **1977,** *99,* 4899.
[41] B. Ilien, A. Schotte, P.M. Laduron, *FEBS Lett.* **1982,** *138,* 311.
[42] B. Ilien, H. Gorissen, P.M. Laduron, *Biochem. Pharmacol.* **1980,** *29,* 3341.
[43] J.E. Leysen, C.J.E. Niemegeers, J.P. Tollenaere, P.M. Laduron, *Nature (London)* **1978,** *272,* 168.
[44] G. Loiseau, R. Millisher, A.M. Donadieu, J.P. Marquet, *Arzneim.-Forsch., Drug Res.* **1977,** *27,* 606.
[45] K. Schulze-Delrieu, *Gastroenterology* **1979,** *77,* 768.