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New thieno and pyrazolo[2,1]benzothiazepine derivatives with antidepressant activity

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As a part of a research project directed to the discovery of novel psychotropic agents, we have already described the synthesis of a number of hetero[2,1]benzothiazepines which displayed a noticeable antidepressant activity in several classical screening tests [1]. In an attempt to improve the activity of such compounds, we have prepared and evaluated a series of new derivatives of these ring systems in which different aminoethoxy side chains were included. The synthesis of compounds **1**–**12** will be published elsewhere.

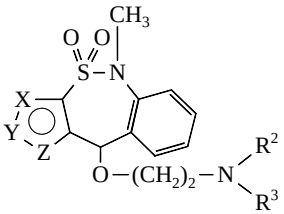
The pharmacological assessment of these compounds indicated that, in general, they did not modify the parameters evaluated in the Irwin test [2] and they were shown to have low values of acute lethal toxicity ($LD_{50} > 300$ mg/kg p. o.).

As it was observed (data not shown), the majority of the screened compounds statistically decreased, at the highest dose assayed (100 mg/kg p. o.), the spontaneous locomotor activity, but without reaching the low value elicited by diazepam. On the contrary, compounds **4**, **9** and **10** showed a psychostimulating effect at 25 mg/kg p. o. by about 37.9, 34.7, 40.3 and 50.3%, respectively. Nevertheless, this increase in mice activity was not observed at a dose four times higher (100 mg/kg p. o.).

As regards the effects of these aminoalkylethers on the rectal temperature, it was found that compounds **1**, **5** and **8** at 100 mg/kg p. o., and compound **7** at both doses assayed, produced a slight but significant ($p < 0.01$) hypothermia at the first hour. In contrast, compound **9**, at the dose of 25 mg/kg p. o., significantly increased ($p < 0.05$) the normal body temperature of mice by approximately 1.08 ± 0.20 °C with respect to the initial value. This effect was apparent at the first hour after administration of the product, and still observed up to 4 h after administration. Some of them (**4**, **5**, **6** and **7**) significantly increased ($p < 0.01$) at 100 mg/kg p. o. the sleep induced in mice by a hypnotic dose of sodium pentobarbital. Besides, these compounds did not show any peripheric or central anticholinergic activity in the oxotremorine assay (data not shown).

In the Porsolt forced swim test [3], which is a conductual assay generally used for the prediction of antidepressant activity without involving pharmacological interaction,

Table 1: Effect of compounds 1–11 on forced swim test as a function of dose



1–4 X = CH, Y = S, Z = CH
5–7 X = CH, Y = CH, Z = S
8–12 X = N, Y = NCH_3, Z = CH

Compd.			Dose	Duration of immobility (s) (x ± SEM)		Variation
	R^1	R^2	mg/kg p.o.	Control	Test drug	(%)
1	H	CH_3	25	182.10 ± 4.77	173.26 ± 6.47	− 4.85
			100	184.12 ± 3.48	154.13 ± 16.38*	−16.29
2	CH_3	CH_3	25	182.10 ± 4.77	171.89 ± 6.14	− 5.00
			100	184.12 ± 3.48	100.92 ± 10.85**	−45.19
3	$(CH_2)_4$		25	182.10 ± 4.77	177.93 ± 3.92	− 2.28
			100	184.12 ± 3.48	166.40 ± 7.87*	− 9.62
4	$(CH_2)_2–NH–(CH_2)_2$		25	182.10 ± 4.77	156.75 ± 7.92**	−13.92
			100	184.12 ± 3.48	164.79 ± 4.82**	−10.50
5	H	CH_3	25	182.10 ± 4.77	176.63 ± 7.05	− 3.00
			100	184.12 ± 3.48	148.80 ± 21.09*	−19.18
6	CH_3	CH_3	25	182.10 ± 4.77	145.07 ± 9.24**	−20.33
			100	184.12 ± 3.48	148.91 ± 8.10**	−19.12
7	$(CH_2)_2–NH–(CH_2)_2$		25	182.10 ± 4.77	158.02 ± 9.24*	−13.22
			100	184.12 ± 3.48	175.19 ± 9.94	− 4.85
8	H	CH_3	25	182.10 ± 4.77	151.25 ± 11.14**	−16.94
			100	184.12 ± 3.48	184.13 ± 7.59	0.00
9	CH_3	CH_3	25	182.10 ± 4.77	164.92 ± 6.59	− 9.43
			100	184.12 ± 3.48	160.66 ± 5.60**	−12.74
10	$(CH_2)_4$		25	182.10 ± 4.77	155.56 ± 9.45*	−14.57
			100	184.12 ± 3.48	159.55 ± 4.55**	−13.34
11	$(CH_2)_5$		25	182.10 ± 4.77	174.72 ± 7.09	− 4.05
			100	184.12 ± 3.48	151.47 ± 8.32**	−17.73
Imipramine			25	182.10 ± 4.77	141.22 ± 5.19**	−22.45
			100	184.12 ± 3.48	112.11 ± 6.76**	−39.11
Tianeptine			25	182.10 ± 4.77	147.56 ± 15.27**	−18.97
			100	184.12 ± 3.48	134.66 ± 10.77**	−26.86

* $p < 0.05$; ** $p < 0.01$

most of the tested products significantly shortened the immobility period of mice (Table 1). Compounds **2** at a dose of 100 mg/kg p. o. and **6** at the two doses assayed were the most effective, with activity values better or similar than those found for imipramine and tianeptine, the drugs used as reference standards. It must be pointed out that the antidepressant activity detected in these products is not due to their stimulant properties, because they have no significant effects or reduce the motor activity in the rank of doses active in the Porsolt test.

In the tetrabenazine test, compounds **1**, **6**, **9** and **10**, and to a lesser extent **5**, **7**, **11**, and **12**, were found to significantly antagonize the ptosis induced by the drug in the experimental animals (Table 2), which suggests a certain α-adrenergic or serotonergic activity for them. Only compound **11** antagonized in a significant manner ($p < 0.05$) (60%) the motor depression, which indicates a dopaminergic acitivity that had already been detected in antidepressant drugs with an added psychostimulating action.

Likewise, only **2** at 100 mg/kg p.o. significantly antagonized the hypothermia induced by tetrabenazine 30 min after its administration (**2**: 1.74 ± 0.19, $p < 0{,}05$; imipramine: 1.78 ± 0.30 $p < 0.05$; control: 2.71 ± 0.22; results are mean decrease in rectal temperature ± SEM), which seems to evidence a direct or indirect β-mimetic activity [4].

Since compounds **1**–**12** were designed as heterocyclic bioisosteres of tianeptine [5] and this drug interferes in a selective mode with the 5-HT-reuptake system, we also investigated the ability of **2** and **6**, the most active compounds in the animal assays, to interact *in vitro* with 5-HT_{1A} and 5-HT_2 receptors from rat brain membrane preparations. Both compounds were found to have low affinities for the two receptors assayed (5-HT_{1A}: **2**, $Ki = > 10^{-4}$ M; **6**, $Ki = > 10^{-4}$ M. 5-HT_2: **2**, $Ki = 8618$ nM; **6**, $Ki = 5432$ nM), as it happens in the case of tianeptine ($IC_{50} > 10$ mM) [6, 7].

From these results, it can be concluded that several components of the series under study were effective p.o. in different animal models predictive of antidepressant activity like the Porsolt test and the antagonism to tetrabenazine-induced effects. The dimethyl thieno[3,4-*c*] and thieno[3,2-*c*] derivatives **2** and **6**, were in this order, the most effective, with activities similar or better than those of the reference drugs. The pyrazolo[3,4-c] derivatives, however, showed a lower degree of activity in these tests.

Experimental

According to the method of Irwin [2], the behaviour of the mice was observed at 1 and 2 h after p.o. injection of test drugs. The LD_{50} was calculated from lethality within 3 days after p.o. administration of the drugs by the method of Litchfield and Wilcoxon [8]. Potentiation of pentobarbital sleeping time, effects on spontaneous motility and body temperature as well as antagonism to oxotremorine-induced effects [9] by these compounds were performed in mice as described earlier [1]. The potential antidepressant activity of these compounds was evaluated by the antagonism of tetrabenazine-induced effects [10, 11] and the behavioural despair test in mice [1, 3, 12]. Data were analyzed by one-way analysis of variance (ANOVA) followed by Student's unpaired t-test [13]. The chi-square test was used for the percentage of locomotor activity in the tetrabenazine test. Tremor and salivation induced by oxotremorine and ptosis induced by tetrabenazine were analyzed using the Mann-Whitney test for non-parametric data.

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Table 2: Effect of some benzothiazepines on tetrabenazine induced ptosis as a function of dose

Compd.			Dose	Ptosis (x ± SEM)	
	R^1	R^2	mg/kg p.o.	Control	Test drug
1	H	CH_3	25	3.40 ± 0.16	2.70 ± 0.15**
			100	3.11 ± 0.20	2.00 ± 0.00**
5	H	CH_3	25	3.40 ± 0.16	2.60 ± 0.22**
			100	3.11 ± 0.20	3.00 ± 0.31
6	CH_3	CH_3	25	3.40 ± 0.16	3.40 ± 0.22
			100	3.11 ± 0.20	2.00 ± 0.00**
7	$(CH_2)_2-NH-(CH_2)_2$		25	3.40 ± 0.16	3.10 ± 0.18
			100	3.11 ± 0.20	2.20 ± 0.20*
9	CH_3	CH_3	25	3.40 ± 0.16	3.00 ± 0.21
			100	3.11 ± 0.20	2.00 ± 0.00**
10	$(CH_2)_4$		25	3.40 ± 0.16	3.33 ± 0.16
			100	3.11 ± 0.20	2.00 ± 2.00**
11	$(CH_2)_5$		25	3.40 ± 0.16	2.40 ± 0.35**
			100	3.11 ± 0.20	2.80 ± 0.37
12	$(CH_2)_2-NH-(CH_2)_2$		25	3.40 ± 0.16	2.60 ± 0.26*
			100	3.11 ± 0.20	3.00 ± 0.31
Imipramine			25	3.40 ± 0.16	0.00 ± 0.00**
			100	3.11 ± 0.20	0.30 ± 0.21**

* $p < 0.05$; ** $p < 0.01$