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Short communication

Synthesis and some CNS activities of new benzofuranylacryloylpiperazines

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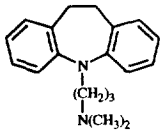
Summary — A series of novel benzofuranylacryloylpiperazines, which are structurally related to both cinnamamide derivatives and befuraline, have been prepared as their hydrochlorides. Their anticonvulsant and antidepressant activities against seizures induced by electroshock and against tetrabenazine-induced palpebral ptosis have been evaluated in mice. Some of them revealed interesting potencies since, although they are less active than the reference drugs, they exhibited a higher protective index.

CNS / benzofuran / chromene / piperazine / vinilogy / anticonvulsant activity / antidepressant activity

Introduction

Despite the widespread availability of several relatively safe and effective antiepileptic drug therapies, approximately one third of affected individuals continue to experience uncontrolled seizures. The establishment of structure–activity relationships for anticonvulsant drugs has been complicated by the chemical diversity of the molecules and by the complexity of the physiological and biochemical processes that initiate and propagate seizure activity.

There are a variety of approaches to this, including a blockade of excesses in excitatory neurotransmitters or facilitation of inhibitory mechanisms. The introduction of antidepressants like imipramine **1** and cloimipramine **2** for the treatment of refractory absence and myoclonic seizures [1] was based on their ability to depress the inhibitory pathway in the central nervous system (CNS). On the other hand, carbamazepine **3**, a prototype anticonvulsant, has been shown to possess psychotropic effects in the treatment of maniac and depressive patients [2].



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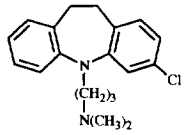

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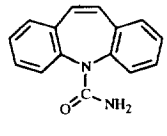

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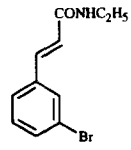
Amides of the cinnamic acid or its derivatives including cinromide **4** [3] have received considerable attention and have been reported to possess CNS (*eg*, sedative [4, 5] and anticonvulsant [6–8]) activities. The *N*-piperazinyl carbonyl structures present cardiovascular properties [9–11] and some have been claimed to be antidepressants, such as befuraline **5** [12, 13] or piberaline **6** [14].



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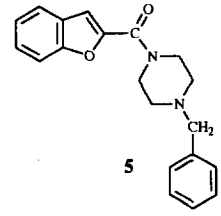

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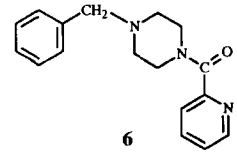

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As part of our program for new antiepileptic compounds, a combination of both chemical structures was hypothesized. This paper describes our attempts to explore the pharmacological properties related to chemical modifications carried out on a new series of (*E*)-4-[3-(2-benzofuranyl)acryloyl]piperazines (obtained as their hydrochlorides **7a–s**) substituted at N-1 and on the benzofuran ring in various ways. Our interest in this class of products was mainly based on their similarity with the biologically active compounds above. In particular, the novel acrylamide derivatives

synthesized herein are vinilogous of befuralin **5** and structurally related to cinromide **4** and piberaline **6**.

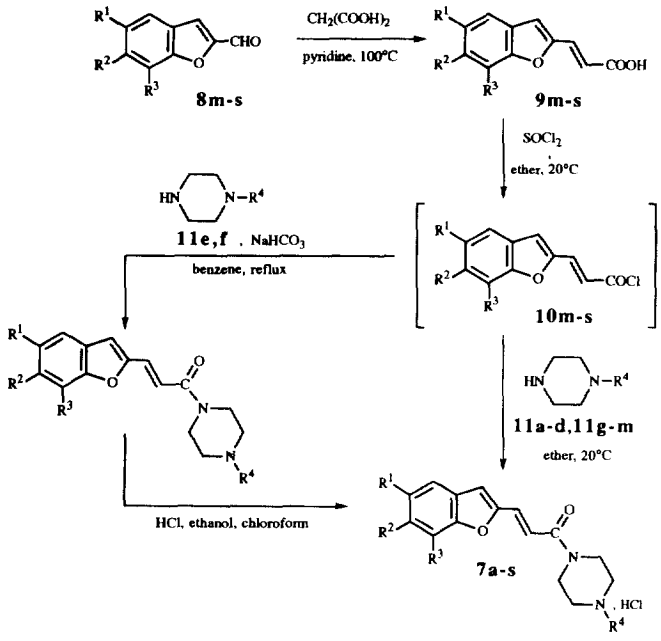
On the other hand, in order to evaluate the importance of the benzofuran ring, two analogous acryloylpiperazine hydrochlorides bearing either a benzene ring **12** or a 3-chromenyl substituent **13** were prepared.

Chemistry

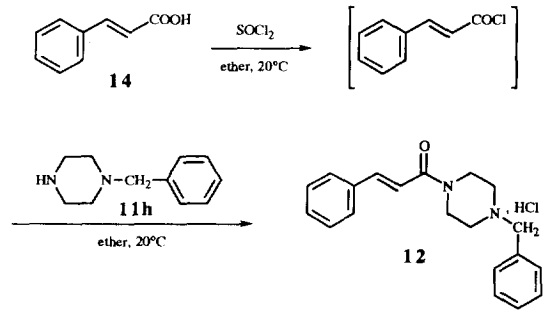
The new (*E*)-4-[3-(2-benzofuranyl)acryloyl]-1-R^4-piperazines hydrochlorides **7a–s** synthesized in the present work were obtained starting from the appropriate 2-benzofurancarboxaldehydes **8m–s** and the substituted piperazines **11a–m** according to the procedure depicted in scheme 1.

With regard to the synthesis of the salts **7e** and **7f**, the condensation in ether of the appropriate piperazine with the (*E*)-3-(2-benzofuranyl)-2-propenoyl chloride **10m** did not provide a pure product but an inseparable mixture of the desired compound with the hydrochloride of the starting piperazine **11e** or **11f**. In order to overcome this drawback, the previously isolated free base corresponding to **7e** or **7f** was further converted into its required hydrochloride.

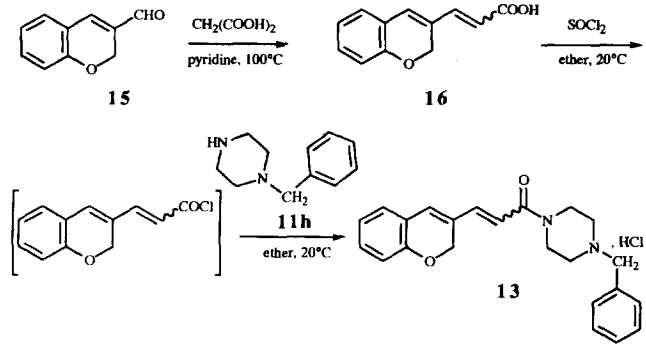
The (*E*)-4-cinnamoyl-1-benzylpiperazine hydrochloride **12** and the (*E* + *Z*)-4-[3-(3-2*H*-chromenyl)acryloyl]-1-benzylpiperazine hydrochloride **13**, required for comparison with the benzofuran derivatives **7a–s**, were prepared in a similar way starting from (*E*)-cinnamic acid **14** (scheme 2) or from 3-chromencarboxaldehyde **15** (scheme 3), respectively.



Scheme 1. For the nature of the substituents R^1, R^2, R^3 and R^4, see table I.



Scheme 2.



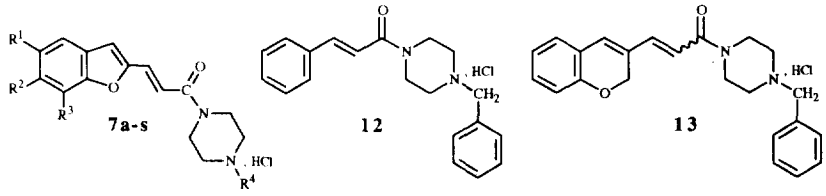
Scheme 3.

The pure *E*-configuration has been assigned to most of the compounds described herein on the basis of the large and exclusive ^3J coupling constants (16 Hz) measured between the signals of the vinylic protons. However, the smaller ^3J coupling constants (12 Hz) observed in the ^{1}H-NMR spectra of the chromene derivatives **13** and **16** are also indicative of the presence of the *Z*-form (about 40%) in these two cases.

Pharmacological results and discussion

Structures and selected properties of the synthesized compounds are summarized in table I. The Irwin screening procedure was used to evaluate the level of neurotoxocity (NET) [15] exhibited for the compounds. Anticonvulsant activity was assessed in the maximal

Table I. Structures, toxicity doses (NET) and median effective doses (ED_{50}) for maximal electroshock seizure (MES) and tetrabenazine-induced ptosis (TBZ), intraperitoneally in mice, for the synthesized (*E*)-4-[3-(2-benzofuranyl)acryloyl]-1-R^4-piperazine hydrochlorides **7a–s**, non-benzofuran derivatives **12**, **13** and reference drugs **1**, **3**, **5**.



Compounds	R^1	R^2	R^3	R^4	NET (mg/kg)	MES ED_{50} (mg/kg)	TBZ ED_{50} (mg/kg)
7a	H	H	H	phenyl	>100	>100	32 (16-62)
7b	H	H	H	2-CH_3CH_2O-phenyl	350	>35	>35
7c	H	H	H	3-CF_3-phenyl	1000	>100	>100
7d	H	H	H	2-pyridinyl	380	>38	>38
7e	H	H	H	2-pyrimidinyl	750	>75	>75
7f	H	H	H	$CH_2CONHCH(CH_3)_2$	375	>37.5	NT
7g	H	H	H	cyclohexanyl	175	>17.5	>17.5
7h	H	H	H	benzyl	1000	100	55 (45-68)
7i	H	H	H	piperonyl	800	61 (40-92)	NT
7j	H	H	H	4-Cl-benzhydryl	>1000	>100	>100
7k	H	H	H	4-OCH_3-benzyl	>1000	>100	>100
7l	H	H	H	4-Cl-benzyl	>1000	>100	NT
7m	H	H	H	phenethyl	>1000	>100	>100
7n	OCH_3	H	H	benzyl	1000	49 (42-57)	30 (11-82)
7o	H	OCH_3	H	benzyl	500	47 (40-55)	>50
7p	H	H	OCH_3	benzyl	150	>15	>15
7q	Cl	H	H	benzyl	>1000	>100	>100
7r	CH_3	H	H	benzyl	>1000	>100	100
7s	CN	H	H	benzyl	30	>20	>20
12					<100	>10	>10
13					1000	>100	>100
1	(imipramine)				<30	NT	0.5 (0.3-1.1)
3	(carbamazepine)				100	9.5 (6-14.5)	NT
5	(befuraline)				<100	>10	4 (1-11)

NT: not tested.

electroshock seizure (MES) test [16]. Antidepressant potency (TBZ) was determined by the reversion of the tetrabenazine-induced palpebral ptosis [17] at 1/10th of the neurotoxic dose or at a maximum dose of 100 mg/kg.

Study of the effect of structure on activity: influence of the benzofuran ring and functionalized side-chain

First, we decided to keep the benzofuran ring and the *N*-benzylpiperazine moieties present in befuraline **5** and started our investigations by studying the addition of a double bond (cinnamoylation) of this compound. We obtained a much less toxic compound **7h** (1000 *versus* < 100 mg/kg). The level of antidepressant activity (TBZ) was also decreased (ED_{50}: 55 *versus* 4 mg/kg), but the protective index (NET/TBZ) of both compounds remained similar. On the other hand, we observed a lower level of protection with respect to the MES test.

Next, several additional changes were achieved in the substituted acryloic part of the molecule. In this context, we prepared the cinnamoyl analogue **12**, in order to evaluate the importance of the benzofuran ring in the exhibition of the observed properties. In the same context, we also synthesized the chromene analogue **13** where the conjugated double bond system was disconnected from the intracyclic oxygen atom. The total lack of activities noted with these two compounds may suggest that the presence of the benzofuranyl ring is essential for the desired pharmacological properties.

Study of the effect of structure on activity: influence of the N-alkyl substituent (R^4)

We have further examined the influence of the substituent on the *N*-piperazine ring. We first noticed that the replacement of the benzyl group by direct fixation of an aromatic (**7a–c**), heterocyclic (**7d–e**) or saturated (**7g**) ring led to compounds devoid of activity with respect to the MES test. Furthermore, these derivatives were generally more toxic than **7h**. With respect to the TBZ test, however, only the non-substituted phenyl (**7a**) showed a relatively good antidepressant activity.

The addition of a mono-substituent in the 4-position of the benzyl group (**7k–l**) seemed unfavourable since the activity was not maintained in the two tests. Such a negative result was also noticed in the case of the 4-substituted benzhydryl derivative **7j**. The 3,4-methylenedioxy-disubstituted compound **7i** had a profile similar to that observed with the lead compound **7h**.

Finally, the separation of the phenyl ring from the nitrogen by addition of a second methylene group (**7m**) or the replacement of the benzyl group by an acetamido side-chain (**7f**) also led to an inactive compound.

Study of the effect of structure on activity: influence of the benzofuranyl substituents (R^1, R^2 and R^3)

We continued our investigations by varying the substituents on the benzofuran ring, in order to examine the effect of electron-donating and electron-withdrawing groups on the studied properties. Among the compounds substituted at the 5-position of the benzofuran ring (**7n**, **7q–s**), only the methoxy compound **7n** appeared more active than **7h** (two-fold more potent than its unsubstituted analogue with respect to the two tests) and exhibited the best overall pharmacological profile observed in the present work. The replacement of the methoxy group by other substituents at the 5-position (either with electron-withdrawing or electron-donating effects) resulted in a total loss of the desired activities. Furthermore, the 5-cyano substituent led to the very toxic derivative **7s**.

Additional compounds, bearing a methoxy group in the 6-position **7o** or in the 7-position **7p** of the benzofuran ring, were prepared. The same anticonvulsant activity with respect to the MES test was observed with the 6-methoxy derivative **7o**, which is also slightly more toxic (500 *versus* 1000 mg/kg). On the other hand, the 7-methoxy derivative **7p** was also found to be more toxic and did not reveal activity in either test.

Conclusion

As in the case of befuraline **5**, the biological results obtained with the novel compounds described in the present work confirm that the presence of both a *N*-benzyl substituent and a benzofuran ring on the same molecule are required to induce anticonvulsant and antidepressant activities. Thus, compared to the reference drug, the product **7h** (which is a vinilogue of befuraline) and some of its substituted derivatives (*eg*, **7n** or **7o**) exhibit a similar or higher protective index with respect to the MES and/or the TBZ tests. On the other hand, it is worth emphasizing that, although it is known that the 2,3-double bond of benzofuran has ethylenic rather than aromatic character [18], the cinnamoyl compound **12** (which is an 'open analogue' of befuraline) is devoid of activity.

Owing to the lack of conjugation of the intracyclic oxygen in benzofuran [18], the electronic effects of homocyclic substituents are transmitted to the 2,3-double bond through the carbon C3a. In this context, the increased activity observed with the 5-methoxy derivative **7n** (where the methoxy group induces a

weak electron-withdrawing effect on the 2,3-double bond) was not confirmed with either the 5-chloro- (**7q**) or the 5-cyano- (**7s**) substituted compounds (where the 2,3-double bond undergoes significantly stronger withdrawing effects). Furthermore, it is also noteworthy that the product **7o**, which bears a methoxy group in the 6-position, displays a biological potency similar to that of **7n** although the presence of such a substituent in such a position induces an opposite marked electron-donating effect.

These experimental facts do not allow us to infer a reliable structure–activity relationship between the electronic effects of the homocyclic substituents and the pharmacological properties in the herein studied new series. However, the role of the extension of the ethylenic conjugation in these vinilogues of befuraline **5** is probably not completely negligible.

Compound **7n** presents a similar level of activity both as anticonvulsant and antidepressant with a higher protective index that carbamazepine **3** (20 *versus* 10) or befuraline **5** (33 *versus* 25). It is efficient at 1/20th of the neurotoxic dose. It was selected and has been investigated more extensively. Unfortunately, the significant increase in the plasma triglyceride levels observed in the course of the rat toxicity study led us to stop its development.

Experimental protocols

Chemistry

Melting points were determined on a Köfler hot-stage apparatus and are uncorrected. Microanalyses were carried out by the Service de Microanalyse du CNRS, 69390 Vernaison, France. The results of elemental analysis were within ± 0.3% for C and ± 0.2% for H and N of theoretical values. ^{1}H-NMR spectra were recorded on a Varian EM 390 (90 MHz) spectrometer using tetramethylsilane (TMS) as internal standard. Splitting patterns have been designated as follows: s = singlet; bs = broad singlet; d = doublet; t = triplet; q = quartet; m = multiplet; and sh = shoulder.

Imipramine **1** and carbamazepine **3** are commercially available (Sigma Company). Befuraline **5** was synthesized following a previously reported procedure [12].

The known 2-benzofurancarboxaldehydes used as starting materials were synthesized following previously reported procedures: **8m**, **8n** and **8q** [19], **8o** [20], **8p** [21], **8r** [22], **8s** [23].

The substituted *E*-acrylic acids **9m**, **9n** and **9q** have been described previously [24]. For these compounds, physical data were found in good agreement with those of the literature. In this context, it must be pointed out that the acid **9o** has been mentioned but without data given [25].

Compound **12** was prepared starting from (*E*)-cinnamic acid **14** purchased from Aldrich Company. The synthesis of the chromene acrylic acid **16** is required for the preparation of compound **13**. Thus was carried out starting from the previously described 3-chromenecarboxaldehyde **15** [26].

The benzofuran acid chlorides **10m–s**, as well as their cinnamic and chromene analogues were prepared as crude materials and reacted without further purification.

Most of the substituted piperazines (**11a–j**) were obtained either from Aldrich or from Janssen Chimica. 4-Methoxybenzylpiperazine, 4-chlorobenzylpiperazine and 4-phenethylpiperazine (**11k–m**) were synthesized according to a known procedure [26]. If necessary, the free bases were isolated before use, starting from their hydrochlorides, by treatment with 2 N aqueous sodium hydroxide solution followed by extraction with ether or chloroform.

*Synthesis of 3-(2-benzofuranyl)-2-propenoic acids **9m–s** and 3-(3-2H-chromenyl)-2-propenoic acid **16**. General procedure*

A solution of the appropriate aldehyde (**8m–s** or **15**, 170 mmol) in anhydrous pyridine (170 ml) was placed in a 500 ml round-bottomed flask fitted with a water condenser surmounted by a drying tube. Malonic acid (19 g, 0.182 mol, 1.08 eq) was added in one portion. The reaction mixture was heated at 100°C for 1 h (**9m**, **9n** or **9p**), 3 h (**9o** or **9s**) or 8 h (**9q**, **9r** or **16**) using a boiling water bath, allowed to cool to room temperature, and then poured into ice (about 350 g). The addition of 10 N hydrochloric acid (about 200 ml, up to pH 2) gave a solid which was filtered, and then rinsed several times with distilled water until the washings were neutral. Complete drying of the precipitate in a vacuum-oven provided the satisfactorily pure acid **9m–s** (as the pure *E* isomer) or **16** (*Z* + *E* mixture as judged by NMR) which was further recrystallized.

*(E)-3-(2-Benzofuranyl)-2-propenoic acid **9m**.* Mp: 219–220°C (toluene) [lit [24] 220°C]; yield: 60%. ^{1}H-NMR (DMSO-d_6) δ: 6.46 (d, 1H, CH=C*H*-CO_2H, *J* = 16 Hz), 7.13–7.73 (m, 6H), 12.60 (sh, 1H, CO_2H).

*(E)-3-(5-Methoxy-2-benzofuranyl)-2-propenoic acid **9n**.* Mp: 224–225°C (toluene) [lit [24] 225°C]; yield: 69%. ^{1}H-NMR (DMSO-d_6) δ: 3.80 (s, 3H, OCH_3), 6.40 (d, 1H, CH=C*H*-CO_2H, *J* = 16 Hz), 6.97 (dd, 1H, H_6, J_o = 9 Hz, J_m = 2.4 Hz), 7.17 (d, 1H, H_4, J_m= 2.4 Hz), 7.23 (s, 1H, H_3), 7.48 (d, 1H, H_7, J_o = 9 Hz), 7.52 (d, 1H, C*H*=CH-CO_2H, *J* = 16 Hz), 12.50 (sh, 1H, CO_2H).

*(E)-3-(6-Methoxy-2-benzofuranyl)-2-propenoic acid **9o**.* Mp: 213–214°C (toluene); yield: 79%. ^{1}H-NMR (DMSO-d_6) δ: 3.83 (s, 3H, OCH_3), 6.33 (d, 1H, CH=C*H*-CO_2H, *J* = 16 Hz), 6.90 (dd, 1H, H_5, J_o = 9 Hz, J_m = 2.3 Hz), 7.18 (d, 1H, H_7, J_m = 2.3 Hz), 7.22 (s, 1H, H_3), 7.50 (d, 1H, C*H*=CH-CO_2H, *J* = 16 Hz), 7.53 (d, 1H, H_4, J_o = 9 Hz), 12.36 (bs, 1H, CO_2H).

*(E)-3-(7-Methoxy-2-benzofuranyl)-2-propenoic acid **9p**.* Mp: 213–215°C (toluene); yield: 72%. ^{1}H-NMR (DMSO-d_6) δ: 3.93 (s, 3H, OCH_3), 6.43 (d, 1H, CH=C*H*-CO_2H, *J* = 16 Hz), 6.88–7.30 (m, 4H), 7.53 (d, 1H, C*H*=CH-CO_2H, *J* = 16 Hz), 12.06 (sh, 1H, CO_2H).

*(E)-3-(5-Chloro-2-benzofuranyl)-2-propenoic acid **9q**.* Mp: 260–262°C (toluene/acetonitrile) [lit [23] 260°C]; yield: 90%. ^{1}H-NMR (DMSO-d_6) δ: 6.43 (d, 1H, CH=C*H*-CO_2H, *J* = 16 Hz), 7.26 (s, 1H, H_3), 7.35 (dd, 1H, H_6, J_o = 9 Hz, J_m = 1.5 Hz), 7.51 (d, 1H, C*H*=CH-CO_2H, *J* = 16 Hz), 7.58 (d, 1H, H_7, J_o = 9 Hz), 7.73 (d, 1H, H_4, J_m = 1.5 Hz), 12.60 (sh, 1H, CO_2H).

*(E)-3-(5-Methyl-2-benzofuranyl)-2-propenoic acid **9r**.* Mp: 212–215°C (toluene); yield: 74%. ^{1}H-NMR (DMSO-d_6) δ: 2.35 (bs, 3H, CH_3), 6.38 (d, 1H, CH=C*H*-CO_2H, *J* = 16 Hz), 7.05–7.66 (m, 5H), 12.45 (sh, 1H, CO_2H).

*(E)-3-(5-Cyano-2-benzofuranyl)-2-propenoic acid **9s**.* Mp: >260°C (toluene/acetonitrile); yield: 72%. ^{1}H-NMR (DMSO-

d_6) δ: 6.50 (d, 1H, CH=C*H*-CO_2H, J = 16 Hz), 7.40 (bs, 1H, H_3), 7.60 (d, 1H, C*H*=CH-CO_2H, J = 16 Hz), 7.83 (bs, 2H, H_6 and H_7), 8.23 (bs, 1H, H_4), CO_2H indistinguishable.

(E+ Z)-3-(3-2H-Chromenyl)-2-propenoic acid ***16***. Yield: 32% ^{1}H-NMR (DMSO-d_6) δ: 4.93 and 4.96 (2s, 2H, CH_2 [*Z*] and [*E*]), 5.76 (d, 0.4H, CH=C*H*-CO_2H [*Z*], J = 12 Hz), 5.85 (d, 0.6H, CH=C*H*-CO_2H [*E*], J = 16 Hz), 6.50 (d, 0.4H, C*H*=CH-CO_2H [*Z*], J = 12 Hz), 6.70–7.26 (m, 5.6H), 12.30 (sh, CO_2H).

Synthesis of 4-[3-(2-benzofuranyl)acryloyl]-1-R⁴-piperazine hydrochlorides ***7a–d*** and ***7g–s***, *4-cinnamoyl-1-benzylpiperazine hydrochloride* ***12*** *and 4-[3-(3-2H-chromenyl)acryloyl]-1-benzylpiperazine hydrochloride* ***13***. *General procedure*

A solution of the appropriate acid (**9m–s**, **14** or **16**, 80 mmol) in anhydrous diethyl ether (200 ml) was placed in a 1 l dry two-necked round-bottomed flask equipped with a septum inlet and a water condenser surmounted by a drying tube. The mixture was efficiently stirred with a magnetic bar. Thionyl chloride (84 mmol, 6.13 ml, 1.05 eq) was added with a syringe. Stirring was continued for 18 additional hours at room temperature before the volatiles were evaporated under reduced pressure. The crude acid chloride thus obtained was used without further purification and taken up with anhydrous diethyl ether (450 ml). A solution of the required substituted piperazine (**11a–d** or **11g–s**, 80 mmol) in diethyl ether (50 ml) was added. The reaction mixture was magnetically stirred for 18 h and the obtained solid was suction-filtered. This precipitate was covered with absolute ethanol, refluxed, and then allowed to cool to room temperature to give, after filtration and drying, analytically pure **7a–d**, **7g–s**, **12** or **13** in the reported yields.

(E)-4-[3-(2-Benzofuranyl)acryloyl]-1-phenylpiperazine hydrochloride ***7a***. Mp: 196–197°C; yield: 45%. ^{1}H-NMR (DMSO-d_6) δ: 3.05–3.40 (m, 6H, 3 CH_2), 3.65–3.90 (m, 2H, CH_2), 6.66–7.73 (m, 12H).

(E)-4-[3-(2-Benzofuranyl)acryloyl]-1-(2-ethoxyphenyl)piperazine hydrochloride ***7b***. Mp: 181–185°C; yield: 55%. ^{1}H-NMR (DMSO-d_6) δ: 1.40 (t, 3H, CH_2CH_3, J = 7.5 Hz), 3.28–3.63 (m, 4H, 2 CH_2), 3.88–4.30 (m, 4H, 2 CH_2), 4.17 (q, 2H, CH_2-CH_3, J = 7.5 Hz), 6.83–7.82 (m, 11H).

(E)-4-[3-(2-Benzofuranyl)acryloyl]-1-(3-trifluoromethylphenyl)piperazine hydrochloride ***7c***. Mp: 178–180°C; yield: 53%. ^{1}H-NMR (DMSO-d_6) δ: 3.20–3.46 (m, 4H, 2 CH_2), 3.73–4.00 (m, 4H, 2 CH_2), 7.05–7.75 (m, 11H).

(E)-4-[3-(2-Benzofuranyl)acryloyl]-1-(2-pyridinyl)piperazine hydrochloride ***7d***. Mp: 150–153°C; yield: 46%. ^{1}H-NMR (DMSO-d_6) δ: 3.85 (bs, 8H, 4 CH_2), 6.85–8.15 (m, 11H).

(E)-4-[3-(2-Benzofuranyl)acryloyl]-1-(cyclohexanyl)piperazine hydrochloride ***7g***. Mp: >260°C; yield: 80%. ^{1}H-NMR (DMSO-d_6) δ: 1.05–2.30 (m, 10H), 3.00–3.60 (m, 8H, 4 CH_2), 4.30–4.60 (m, 1H, CH), 7.00–7.70 (m, 7H).

(E)-4-[3-(2-Benzofuranyl)acryloyl]-1-benzylpiperazine hydrochloride ***7h***. Mp: >260°C ; yield: 89%. ^{1}H-NMR (DMSO-d_6) δ: 2.90–3.50 (m, 8H, 4 CH_2), 4.33 (bs, 2H, CH_2Ph), 7.18 (d, 1H, CH=C*H*-CO, J = 16 Hz), 7.25–7.75 (m, 11H).

(E)-4-[3-(2-Benzofuranyl)acryloyl]-1-piperonylpiperazine hydrochloride ***7i***. Mp: >260°C; yield: 80%. ^{1}H-NMR (DMSO-d_6) δ: 2.83–3.67 (m, 6H, 3 CH_2), 4.13–4.73 (m, 2H, CH_2), 4.23 (bs, 2H, CH_2Ph), 6.07 (s, 2H, OCH_2O), 6.87–7.83 (m, 10H).

(E)-4-[3-(2-benzofuranyl)acryloyl]-1-(4-chlorobenzhydryl)piperazine ***7j***. Mp: 209–210°C; yield: 57%. ^{1}H-NMR (DMSO-d_6) δ: 3.00–3.30 (m, 4H, 2 CH_2), 3.45–3.65 (m, 4H, 2 CH_2), 5.55 (bs, 1H, CH), 7.16 (d, 1H, CH=C*H*-CO, J = 16 Hz), 7.25–8.00 (m, 15H).

(E)-4-[3-(2-Benzofuranyl)acryloyl]-1-(4-methoxybenzyl)piperazine hydrochloride ***7k***. Mp: >260°C; yield: 82%. ^{1}H-NMR (DMSO-d_6) δ: 2.90–3.45 (m, 8H, 4 CH_2), 3.75 (s, 3H, OCH_3), 4.18 (bs, 2H, CH_2Ph), 6.85–7.70 (m, 11H).

(E)-4-[3-(2-Benzofuranyl)acryloyl]-1-(4-chlorobenzyl)piperazine hydrochloride ***7l***. Mp: 230–233°C; yield: 61%. ^{1}H-NMR (DMSO-d_6) δ: 2.95–3.60 (m, 8H, 4 CH_2), 4.33 (bs, 2H, CH_2Ph), 7.03–7.75 (m, 11H).

(E)-4-[3-(2-Benzofuranyl)acryloyl]-1-phenethylpiperazine hydrochloride ***7m***. Mp: 259–260°C; yield: 78%. ^{1}H-NMR (DMSO-d_6) δ: 2.90–3.75 (m, 10H, 4 CH_2 pip + N-CH_2), 4.25–4.70 (m, 2H, CH_2Ph), 7.06–7.75 (m, 12H).

(E)-4-[3-(5-Methoxy-2-benzofuranyl)acryloyl]-1-benzylpiperazine hydrochloride ***7n***. Mp: 245–247°C; yield: 60%. ^{1}H-NMR (DMSO-d_6) δ: 2.95–3.55 (m, 8H, 4 CH_2), 3.76 (s, 3H, OCH_3), 4.33 (bs, 2H, CH_2Ph), 6.96 (dd, 1H, H_6, J_o = 9 Hz, J_m = 2.5 Hz), 7.13 (d, 1H, CH=C*H*-CO, J = 16 Hz), 7.16 (d, 1H, H_4, J_m = 2.5 Hz), 7.35–7.70 (m, 8H).

(E)-4-[3-(6-Methoxy-2-benzofuranyl)acryloyl]-1-benzylpiperazine hydrochloride ***7o***. Mp: 220–222°C; yield: 66%. ^{1}H-NMR (DMSO-d_6) δ: 2.95–3.55 (m, 8H, 4 CH_2), 3.81 (s, 3H, OCH_3), 4.31 (bs, 2H, CH_2Ph), 6.90 (dd, 1H, H_5, J_o = 9 Hz , J_m = 2.5 Hz), 7.05 (d, 1H, CH=C*H*-CO, J = 16 Hz), 7.08–7.75 (m, 9H).

(E)-4-[3-(7-Methoxy-2-benzofuranyl)acryloyl]-1-benzylpiperazine hydrochloride ***7p***. Mp: 251–253°C; yield: 83%. ^{1}H-NMR (DMSO-d_6) δ: 2.97–3.50 (m, 8H, 4 CH_2), 3.95 (s, 3H, OCH_3), 4.33 (bs, 2H, CH_2Ph), 6.86–7.70 (m, 11H).

(E)-4-[3-(5-Chloro-2-benzofuranyl)acryloyl]-1-benzylpiperazine hydrochloride ***7q***. Mp: 242–245°C; yield: 69%. ^{1}H-NMR (DMSO-d_6) δ: 2.85–3.50 (m, 8H, 4 CH_2), 4.33 (bs, 2H, CH_2Ph), 7.03–7.74 (m, 11H).

(E)-4-[3-(5-Methyl-2-benzofuranyl)acryloyl]-1-benzylpiperazine hydrochloride ***7r***. Mp: >260°C; yield: 65%. ^{1}H-NMR (DMSO-d_6) δ: 2.38 (bs, 3H, CH_3), 2.95–3.50 (m, 8H, 4 CH_2), 4.30 (bs, 2H, CH_2Ph), 6.95–7.68 (m, 11H).

(E)-4-[3-(5-Cyano-2-benzofuranyl)acryloyl]-1-benzylpiperazine hydrochloride ***7s***. Mp: >260°C; yield: 62%. ^{1}H-NMR (DMSO-d_6) δ: 2.95–3.50 (m, 8H, 4 CH_2), 4.30 (bs, 2H, CH_2Ph), 7.28 (d, 1H, CH=C*H*-CO, J = 16 Hz), 7.38–7.80 (m, 9H), 8.23 (d, 1H, H_4, J_m = 1 Hz).

(E)-(4-Cinnamoyl)-1-benzylpiperazine hydrochloride ***12***. Mp: >260°C; yield: 76%. ^{1}H-NMR (DMSO-d_6) δ: 2.86–3.50 (m, 8H, 4 CH_2), 4.33 (bs, 2H, CH_2Ph), 7.23 (d, 1H, CH=C*H*-CO, J = 16 Hz), 7.33–7.78 (m, 11H).

(E +Z)-4-[3-(3-2H-Chromenyl)acryloyl]-1-benzylpiperazine hydrochloride ***13***. Yield: 46%. ^{1}H-NMR (DMSO-d_6) δ: 2.76–3.50 (m, 8H, 4 CH_2), 4.33 (bs, 2H, CH_2Ph), 5.16 (s, CH_2-O), 6.58 (d, 0.6H, CH=C*H*-CO [*E*], J = 16 Hz), 6.71–7.70 (m, 11.4H).

Synthesis of 4-[3-(2-benzofuranyl)acryloyl]-1-R^4-piperazine hydrochlorides ***7e*** and ***7f***

The crude acid chloride **10m** obtained, as described above, from the (*E*)-3-(2-benzofuranyl)-2-propenoic acid (**9m**, 80 mmol) was dissolved in anhydrous benzene (350 ml). The required substituted piperazine (**11e** or **11f**, 80 mmol) was added and then sodium hydrogen carbonate (13.4 g, 160 mmol). The reaction mixture was refluxed with stirring for 5 h and allowed to cool to room temperature. The insoluble materials were filtered out. After evaporation of the filtrate *in vacuo*, the residue was taken up with chloroform (125 ml) and a solution of 8 N hydrochloric acid in ethanol (10 ml) was added dropwise to the stirred mixture. Three hours later, removal of the solvent afforded a solid, which was treated following the previously described work-up to provide pure **7e** or **7f** in the reported yields.

(E)-4-[3-(2-Benzofuranyl)acryloyl]-1-(2-pyrimidinyl)piperazine hydrochloride ***7e***. Mp: 194–196°C; yield: 65%. ^{1}H-NMR (DMSO-d_6) δ: 3.60–4.00 (m, 8H, 4 CH_2), 6.73 (t, 1H, H_5 pyrim, J_o = 5 Hz), 7.00–7.77 (m, 7H), 8.45 (d, 2H, H_4 and H_6 pyrim, J_o = 5 Hz).

(E)-N-Isopropyl-4-[3-(2-benzofuranyl)acryloyl]-1-piperazine acetamide hydrochloride ***7f***. Mp: 248–250°C; yield: 68%. ^{1}H-NMR (DMSO-d_6) δ: 1.10 (d, 6H, 2 CH_3, J = 7.5 Hz), 3.15–3.60 (m, 8H, 4 CH_2), 3.80–4.05 (m, 3H, $COCH_2$ + CH), 7.20 (d, 1H, CH=C*H*-CO, J = 16 Hz), 7.28–7.75 (m, 6H), 8.65 (d, 1H, NH, J = 7 Hz).

Pharmacology

Animals

CD_1 male mice (Charles River, France) weighing 22–28 g were used. The animals were housed in rooms where temperature, hygrometry, air renewal and lighting duration were controlled. They had free access to food (UAR A04 feed) and water (tap water). They were allowed 48 h to get acclimatized before starting the test.

Drugs studies

Drugs were administered intraperitoneally suspended in 1% carboxymethylcellulose solutions.

Irwin test – research of the first signs of neurotoxocity (NET)

The Irwin test [15] was meant to detect any neuro-vegetative hypo- or hyperfunctioning as well as the presence (or absence) of secretions and excretions by the various organs and systems. Particular attention was devoted to locomotor apparatus and aspect of eyes. Thus, a possible reversible or irreversible agonist or antagonist interference with the autonomic nervous system or CNS was quickly detected. Symptoms were reported as a function of time for each dose administered intraperitoneally per group of five mice. Maximal dose was fixed at 1000 mg/kg. In the absence of reaction, 1/10th of the dose was used in the following tests. If the dose was too high (mortality >50%), weaker doses were selected. The following tests (MES and TBZ) were performed starting from 1/10th of the dose eliciting the symptoms.

Maximal electroshock seizure (MES) in mice

The Swinyard *et al* protocol [16] was used in order to study the anticonvulsant effect of the drugs studied. The main antiepileptics, such as phenytoin and carbamazepine, were active in this test. Maximal electroshock was obtained by means of electric current delivered through the brain using corneal electrodes applied 30 min after intraperitoneal (ip) administration of the drugs tested. Stimulation impulsion parameters were: 50 Hz (50 mA) for 0.2 s. Abolition of the maximal convulsion or tonic extention of the hind legs constituted the protection criterion. The median effective dose (ED_{50}), calculated by probit analysis based on standard methods [28], provided the 95% confidence intervals.

Palpebral ptosis induced by tetrabenazine (TBZ)

The Johnson *et al* protocol [17] was used to study the antidepressant effect of the drugs tested. The main antidepressants, *ie* imipramine compounds, were active in this test. Tetrabenazine (methanesulfonate) was injected intraperitoneally at the dose of 32 mg/kg, 30 min after the drug to be tested. The degree of palpebral ptosis for both eyes was measured 30 min afterwards. The score was 0–4: eyes completely closed: 0; 1/4 open: 1; 1/2 open: 2; 3/4 open: 3; and eyes totally open: 4. For each dose of drug tested, the number of animals with a score greater than or equal to 3 was noted, according to Bourin [29]. The median effective dose (ED_{50}) was the dose for which 50% of the mice had a score greater than or equal to 3. Calculation by computed probit analysis [28] also provided the 95% confidence intervals.

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