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Synthesis and Preliminary Pharmacological Evaluation of Thiophene Analogues of Viloxazine as Potential Antidepressant Drugs

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Abstract—A series of eight thienyloxymethylmorpholines, thiophene analogues of viloxazine, have been synthesized by three different routes. The preliminary pharmacological evaluation of this series shows antidepressant properties on the mice models used with a light sedative action. The structure–activity relationship is established in a first approximation.

Introduction

Viloxazine[1] is a known second generation antidepressant drug commercialized by ICI as Vivalan, the main inconvenience of its pharmacological profile being its short biological life which obligates the patients to a minimum of three doses per day. This fact is probably due to a fast inactivating metabolism by hydroxylation of the benzene nucleus in position 5.[2]

In this paper, we report the synthesis and a preliminary pharmacological study of a series of thiophene analogues of viloxazine **(1a–g)**. The presence of the thiophene ring instead of the benzene one can make their biological life longer, because of the difficulty of formation of the hydroxylated metabolite responsible for this undesirable effect, in the thiophene derivative, besides, the 2-thienyloxymethylmorpholine **1h**, studied and the effect of the chain position on the structure–activity relationship is compared.

Chemistry Results

We describe three different methods for the synthesis of the 2-thienyloxymethyl-morpholines **1(a–h)** (Schemes 1–3 and Table 1).

The first of them (Scheme 1) starts from alkyl 3-hydroxythiophene-2-carboxylates **2a–e**,[3–6] which due to the presence of the ester group in position 2 of the thiophene nucleus, are stable enol compounds, in contrast to other 3-hydroxythiophenes. Their potassium salts were made to react with the 4-benzyl-2-toluene-*p*-sulphonyloxymethylmorpholine[7] and the corresponding derivatives **3a–e** were obtained in reasonable yields except for the case of compound **3d** (only 31% yield). These compounds were transformed into compounds **4a–e** by removing the ester function by alkaline hydrolysis and decarboxylation of the acid group formed. The final step was reached in mild conditions using the Pearlman catalyzer[8] at reduced pressure, other attempts in more classical drastic conditions like catalytic hydrogenation at high pressure, being unsuccessful. The yields in title compounds **(1a–e)** were over 80%.

This method is not adequate for the synthesis of compound **1f**, because the starting material **2f**, can be obtained only in a low 15% yield,[9] and it cannot be used for compounds **1g** and **1h**.

The other two routes start from the epoxy derivatives **5** (Schemes 2 and 3). These compounds had been prepared by us from the corresponding methyl 3-hydroxythiophene-2-carboxylates (**5a–c**[9] and **5d,f**[10]) or from the adequate ring-brominated methylthiophenes (**5g,h**[11]). These routes are not advisable for the synthesis of compound **1e**, because the initial epoxyde **5e** can be obtained only in a very low yield.[10]

Key words: Thiophene; viloxazine; antidepressant; synthesis; pharmacology.
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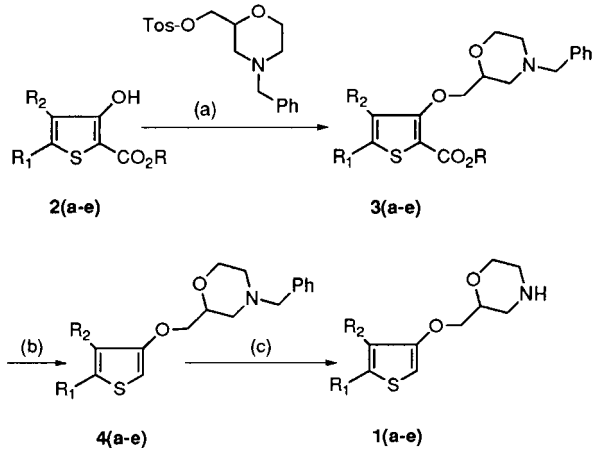
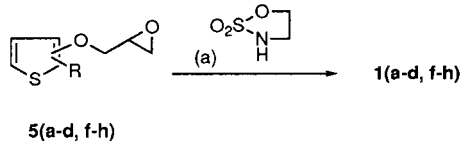
Method II (Scheme 2) is the shortest of the three and is made in a one step reaction of epoxy derivatives **5** with 1,2,3-oxathiazolidine 2,2-dioxide based in a patent for the synthesis of 2-aryloxymethylmorpholines.[12] The reaction conditions were modified by changing the patent solvent (MeOH) for a non-nucleophilic solvent (DMSO) to hinder the epoxide opening observed in the reaction conditions described, that allows the increase of the yields in the title compounds **1a–d** and **1f–h**.

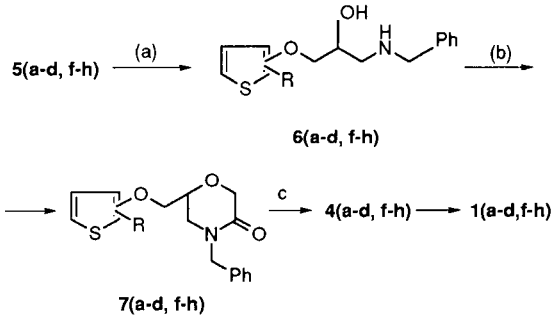
Method III (Scheme 3) consists in the epoxide opening with benzylamine to obtain in a regioselective way the aminoalcohols **6** in very good yields, which were transformed into the 4-benzyl-2-thienyloxymethyl-morpholin-5-ones (**7**) in a similar way to that described for the benzenic series[13] with chloroacetyl chloride and sodium methoxide. The oxo group of these lactams was reduced with lithium aluminium hydride and the 4-benzyl-2-thienyloxymethylmorpholines (**4**) were debenzylated to the title compounds **1a–d** and **1f–h** as described above.



Scheme 1. Route I. (a) DMF, 150°C, 17 h; (b) NaOH. Δ, 1 h; (c) (i) $PdCl_2$, C, H_2O, (ii) MeOH, [H_2], 1 atm.



Scheme 2. Route II. (a) NaOH, 50°C, 1 h.



Scheme 3. Route III. (a) Benzylamine, 100°C, 30 min; (b) (i) Et_3N, $ClCH_2COCl$, (ii) Na/MeOH, Δ , 8 h; (c) H_4LiAl, Δ, 6 h.

Biological Results and Discussion

The antidepressant properties of this series of thiophene analogues of viloxazine **1a–h** have been investigated in comparison with standard drugs. The results obtained are reported in Tables 2–10.

These compounds showed a similar acute toxicity to imipramine and viloxazine ($LD_{50} > 150$ mg/kg ip) (Table 2). The tetrabenazine test showed that title compounds

Table 1. Physical constants and method of synthesis for compounds **1a–h**

Compound	Composition[a]	mp (°C)[b]	Yield (%)	Method
1a	$C_{15}H_{17}NO_2S$	170–172[c]	43[d]	I
			47[e]	II
			47[e]	III
1b	$C_{12}H_{17}NO_2S$	164–166[c]	55[d]	I
			43[e]	II
			40[e]	III
1c	$C_{10}H_{15}NO_2S$	173–174[f]	36[d]	I
			38[e]	II
			46[e]	III
1d	$C_{12}H_{12}NO_2S$	145–147[c]	21[d]	I
			40[e]	II
			51[e]	III
1e	$C_{10}H_{15}NO_2S_2$	152–154[c]	45[d]	I
1f	$C_{11}H_{17}NO_3S$	167–168[f]	42[e]	II
			42[e]	III
1g	$C_{10}H_{15}NO_2S$	113–115[f]	48[e]	II
			53[e]	III
1h	$C_{10}H_{15}NO_2S$	118–119[f]	49[e]	II
			46[e]	III

[a] Satisfactory elemental analyses (±0.4%) for C, H, N and S were obtained for all compounds as free bases.
[b] Of the oxalates.
[c] Recrystallized from acetone.
[d] From compounds **2**.
[e] From compounds **5**.
[f] Recrystallized from acetone–MeOH.

Table 2. Determination of the acute toxicity

LD_{50} approximately	(mg/kg)	
Compound	Intraperitoneal	Oral
1a	190.33	> 500
1b	192.13	> 500
1c	208.14	> 500
1d	165.16	500
1e	206.06	> 500
1f	212.42	> 500
1g	173.48	> 500
1h	155.94	> 500
Imipramine	163.07	> 500
Viloxazine	186.57	> 500

Table 3. Effect of compounds (**1a–h**) on tetrabenazine induced ptosis, akinesia and hypothermia

Compound	Dose mg/kg ip	Ptosis mean score 30 min	Locomotor activ. (%) 30 min	Mean decrease in rectal temperature (°C) 30 min	60 min
Control	–	3.80 ± 0.13	0.00	4.05 ± 0.29	4.90 ± 0.35
1a	10	0.40 ± 0.24**	80.00*	0.86 ± 0.41**	2.06 ± 0.88**
1b	10	3.00 ± 0.45	0.00	3.56 ± 0.23	4.08 ± 0.31
1c	10	0.00 ± 0.00**	100.00*	1.72 ± 0.25**	2.00 ± 0.14**
1d	10	1.20 ± 0.58**	80.00*	2.20 ± 0.48**	3.74 ± 0.65
1e	10	0.40 ± 0.24**	100.00*	1.00 ± 0.31**	1.28 ± 0.43**
1f	10	1.00 ± 0.45**	80.00*	1.80 ± 0.48**	2.14 ± 0.33**
1g	10	1.20 ± 0.83**	20.00	1.24 ± 0.19**	1.16 ± 0.23**
1h	10	0.00 ± 0.00**	60.00*	1.14 ± 0.62**	1.76 ± 0.44**
Imipramine	10	0.00 ± 0.00**	90.00*	1.07 ± 0.29**	0.95 ± 0.32**
Viloxazine	10	0.00 ± 0.00**	100.00*	0.46 ± 0.42**	1.04 ± 0.40**
Control	–	3.20 ± 0.20	0.00	4.54 ± 0.45	5.76 ± 0.32
1a	25	0.40 ± 0.40**	60.00*	2.40 ± 0.46*	1.90 ± 0.31**
1b	25	0.80 ± 0.49**	60.00*	1.90 ± 0.21**	2.12 ± 0.22**
1c	25	0.20 ± 0.20**	20.00	3.84 ± 0.56	3.82 ± 0.77*
1d	25	0.20 ± 0.20**	60.00*	1.98 ± 0.22**	1.50 ± 0.44**
1e	25	0.40 ± 0.24**	80.00*	2.24 ± 0.31**	2.24 ± 0.31**
1f	25	0.20 ± 0.20**	60.00*	1.12 ± 0.29**	0.90 ± 0.31**
1g	25	0.20 ± 0.25**	80.00*	2.62 ± 0.34**	2.26 ± 0.26**
1h	25	0.60 ± 0.40**	60.00*	1.92 ± 0.27**	1.06 ± 0.16**
Imipramine	25	0.20 ± 0.25**	80.00*	1.65 ± 0.29**	1.85 ± 0.37**
Viloxazine	25	0.20 ± 0.25**	100.00*	2.05 ± 0.34**	1.27 ± 0.25**

*$p < 0.05$.
**$p < 0.01$.

Table 4. Effect of compounds (**1a–h**) on apomorphine induced climbing, stereotypy and hypothermia

Compound	Dose mg/kg ip	Stereotypy mean score 20 min	Climbing mean score 20 min	Mean decrease in rectal temp 30 min (°)
Control	–	2.67 ± 0.14	2.00 ± 0.00	3.62 ± 0.39
1a	10	3.00 ± 0.00	2.00 ± 0.00	1.87 ± 0.44*
1b	10	2.50 ± 0.22	2.00 ± 0.00	2.40 ± 0.55
1c	10	2.83 ± 0.17	2.00 ± 0.00	2.20 ± 0.44*
1d	10	2.50 ± 0.22	2.00 ± 0.00	2.48 ± 0.61
1e	10	2.50 ± 0.22	2.00 ± 0.00	2.73 ± 0.63
1f	10	2.67 ± 0.21	2.00 ± 0.00	1.33 ± 0.45**
1g	10	2.83 ± 0.17	2.00 ± 0.00	1.58 ± 0.42**
1h	10	2.50 ± 0.22	2.00 ± 0.00	2.31 ± 0.42
Imipramine	10	2.50 ± 0.22	2.00 ± 0.00	1.03 ± 0.57**
Viloxazine	10	2.67 ± 0.21	2.00 ± 0.00	1.17 ± 0.35**
Control	–	2.83 ± 0.11	2.00 ± 0.00	3.33 ± 0.30
1a	25	3.00 ± 0.00	2.00 ± 0.00	0.73 ± 0.57**
1b	25	2.67 ± 0.19	1.83 ± 0.17	2.38 ± 0.40
1c	25	2.75 ± 0.13	1.92 ± 0.08	1.98 ± 0.22**
1d	25	3.00 ± 0.00	2.00 ± 0.00	1.17 ± 0.38**
1e	25	2.58 ± 0.26	1.83 ± 0.17	1.65 ± 0.51**
1f	25	2.75 ± 0.13	2.00 ± 0.00	1.38 ± 0.30**
1g	25	2.67 ± 0.21	2.00 ± 0.00	1.57 ± 0.28**
1h	25	2.83 ± 0.17	2.00 ± 0.00	1.53 ± 0.63**
Imipramine	25	3.00 ± 0.00	2.00 ± 0.00	1.38 ± 0.43**
Viloxazine	25	2.83 ± 0.11	2.00 ± 0.00	−0.72 ± 0.20**

*$p < 0.05$
**$p < 0.01$.

1a–h antagonize significantly all the symptons induced by this drug (ptosis, akinesia and hypothermia) with similar or better values than the antidepressant drugs used as references (Table 3).

Table 5. Effect of compounds (**1a–h**) on 5-HTP induced behaviour

Compound	Dose mg/kg ip	Number of head twiches $x \pm$ SEM	Syndrome score $x \pm$ SEM
Control	–	0.00 ± 0.00	0.00 ± 0.00
1a	25	0.00 ± 0.00	0.00 ± 0.00
1b	10	0.00 ± 0.00	3.00 ± 0.63**
	25	6.20 ± 1.16**	15.00 ± 1.09**
1c	10	0.00 ± 0.00	5.00 ± 0.00**
	25	5.00 ± 2.77*	19.40 ± 2.67**
1d	25	0.00 ± 0.00	0.00 ± 0.00
1e	10	0.00 ± 0.00	4.00 ± 0.95**
	25	0.40 ± 0.24	10.00 ± 0.55**
1f	25	0.00 ± 0.00	0.00 ± 0.00
1g	10	0.00 ± 0.00	3.60 ± 1.43*
	25	1.60 ± 0.81	6.20 ± 1.50**
1h	10	0.00 ± 0.00	3.00 ± 1.22*
	25	4.20 ± 1.83	6.80 ± 0.80**
Fluoxetine	10	0.20 ± 0.20	6.40 ± 1.12**
	25	13.60 ± 3.28**	21.40 ± 1.17**

*$p < 0.05$.
**$p < 0.01$.

Likewise they antagonize in general terms the hypothermia induced by apomorphine in a similar way to viloxazine and imipramine (Table 4).

The study of their performance in the serotonin system was made by measuring the effects on the 5-HTP induced behaviour. Compounds **1b** and **1c** were the most similar to fluoxetine (Table 5), when we consider the total syndrome induced by 5-HTP.

Finally, to predict their antidepressant profiles without evolving pharmacological interactions, the Porsolt test

was utilized (Table 6). The majority of the compounds assayed reduced in a remarkable way, at 25 mg/kg ip dose, the duration of the immobility, with the thiophene isoster of viloxazine (**1f**), being the most active. This fact is not related with stimulant effects, because these compounds at the same dose decrease the spontaneous motor activity (Table 7).

This preliminary pharmacological study was completed with several psychopharmacological tests. So, the compounds cause, in general, hypothermia (Table 8) and potentiate pentobarbital sleeping time at a dose of 40 mg/kg ip (Table 9) and at subhypnotic dose of pentobarbital (Table 10), which rejects metabolic involvements and confirms their sedative attributes.

Table 6. Effect of compounds (**1a–h**) on the behavioural despair (forced swimming) test

Compound	Dose mg/kg ip	Duration of immobility(s) $x \pm$ SEM	Variation (%)
Control	–	172.37 ± 12.71	–
1a	10	185.10 ± 14.59	7.38
1b	10	170.20 ± 13.22	−1.26
1c	10	178.40 ± 20.44	3.50
1d	10	183.50 ± 8.54	6.46
1e	10	153.41 ± 9.52	−11.00
1f	10	149.30 ± 15.09	−13.38
1g	10	164.00 ± 12.73	−4.85
1h	10	161.10 ± 10.57	−6.54
Imipramine	10	125.70 ± 29.10	−27.07
Viloxazine	10	126.48 ± 25.50	−26.62
Control	–	163.00 ± 6.32	–
1a	25	119.40 ± 17.55**	−26.75
1b	25	133.60 ± 12.50*	−18.03
1c	25	187.80 ± 15.39	15.21
1d	25	148.60 ± 11.88	−8.83
1e	25	154.70 ± 12.00	−5.09
1f	25	93.80 ± 20.36**	−42.45
1g	25	133.30 ± 12.60*	−18.22
1h	25	125.80 ± 14.10**	−22.82
Imipramine	25	109.10 ± 7.53**	−33.07
Viloxazine	25	113.60 ± 19.92**	−30.31

*$p < 0.05$.
**$p < 0.01$.

Table 7. Effect of compounds (**1a–h**) on spontaneous locomotor activity (mean ± SEM)

Compound	Dose mg/kg ip	Number of light beam interruptions		Variation (%)	
		30 min	60 min	30 min	60 min
Control	–	204.28 ± 25.14	67.33 ± 6.98	–	–
1a	10	204.00 ± 26.25	90.75 ± 13.10	−0.14	34.78
1b	10	147.75 ± 4.50	47.75 ± 10.44	−27.67	−29.08
1c	10	70.50 ± 30.45**	55.00 ± 21.71	−65.49	−18.31
1d	10	244.00 ± 18.46	102.50 ± 11.29*	19.44	52.23
1e	10	130.25 ± 14.87	37.25 ± 3.01*	−36.24	−44.67
1f	10	122.25 ± 22.35	57.00 ± 6.12	−40.15	−15.34
1g	10	198.25 ± 24.40	80.00 ± 11.71	−2.95	18.82
1h	10	212.00 ± 13.36	88.00 ± 18.00	3.78	30.70
Viloxazine	10	221.25 ± 30.09	58.50 ± 14.54	8.31	−13.11
Control	–	225.75 ± 14.27	97.00 ± 8.05	–	–
1a	25	158.00 ± 20.48*	42.25 ± 12.79*	−30.01	−56.44
1b	25	76.00 ± 8.75**	86.00 ± 15.94	−66.33	−11.34
1c	25	39.00 ± 8.38**	40.50 ± 19.96*	−82.72	−58.25
1d	25	179.00 ± 30.75	51.00 ± 10.42*	−20.71	−47.42
1e	25	161.00 ± 33.50	117.00 ± 39.31	−28.68	20.62
1f	25	119.00 ± 18.20**	68.75 ± 14.85	−47.29	−29.12
1g	25	141.25 ± 24.52*	51.00 ± 9.80*	−37.43	−47.42
1h	25	132.00 ± 37.62	37.25 ± 7.03**	−41.53	−61.60
Viloxazine	25	130.50 ± 33.97*	82.75 ± 21.14	−42.19	−14.69

*$p < 0.05$.
**$p < 0.01$.

Table 8. Effect of compounds **1(a–h)** on body temperature (mean ± SEM)

Compound	Dose mg/kg ip	Mean decrease in rectal temperature (°C)				
		1 h	2 h	4 h	6 h	24 h
Control	–	0.42 ± 0.11	0.46 ± 0.10	0.07 ± 0.08	0.05 ± 0.06	0.26 ± 0.14
1a	10	0.46 ± 0.50	0.20 ± 0.12	0.14 ± 0.13	−0.10 ± 0.13	0.42 ± 0.14
1b	10	0.82 ± 0.33	0.26 ± 0.25	0.36 ± 0.22	−0.22 ± 0.18	−0.30 ± 0.25
1c	10	0.48 ± 0.33	0.10 ± 0.33	−0.12 ± 0.27	−0.42 ± 0.12**	0.08 ± 0.16
1d	10	0.16 ± 0.39	−0.02 ± 0.31	−0.38 ± 0.28	−0.56 ± 0.38*	−0.06 ± 0.29
1e	10	0.88 ± 0.35	0.16 ± 0.21	0.09 ± 0.27	−0.32 ± 0.40	−0.06 ± 0.77
1f	10	1.12 ± 0.24**	0.64 ± 0.15	0.00 ± 0.07	−0.20 ± 0.18	−0.44 ± 0.14*
1g	10	0.78 ± 0.09	0.16 ± 0.09	−0.24 ± 0.08	−0.26 ± 0.15*	0.02 ± 0.16
1h	10	0.74 ± 0.17	−0.06 ± 0.08*	−0.54 ± 0.10**	−0.48 ± 0.14**	−0.02 ± 0.04
Clorpromazine	5	4.36 ± 0.37**	6.44 ± 0.41**	6.42 ± 0.72**	2.84 ± 0.46**	−0.06 ± 0.22
Imipramine	10	0.74 ± 0.24	0.22 ± 0.17	−0.30 ± 0.10*	−0.60 ± 0.11**	0.24 ± 0.14
Viloxazine	10	0.74 ± 0.19	0.58 ± 0.31	0.32 ± 0.23	0.22 ± 0.22	−0.12 ± 0.73
Control	–	0.55 ± 0.33	0.50 ± 0.27	1.48 ± 0.38	2.55 ± 0.50	0.62 ± 0.23
1a	25	1.20 ± 0.33	1.54 ± 0.23*	3.62 ± 0.37**	2.68 ± 0.37	0.10 ± 0.42
1b	25	1.18 ± 0.33	0.80 ± 0.33	1.14 ± 0.18	3.08 ± 0.59	0.50 ± 0.39
1c	25	4.24 ± 0.48**	2.20 ± 0.41**	2.24 ± 0.56	4.14 ± 0.28*	1.56 ± 1.20
1d	25	1.68 ± 0.19*	2.08 ± 0.39**	3.96 ± 0.64**	2.04 ± 0.18	0.58 ± 0.63
1e	25	1.38 ± 0.24	0.62 ± 0.13	0.92 ± 0.13	3.26 ± 0.40	0.08 ± 0.29
1f	25	1.26 ± 0.35	0.64 ± 0.28	0.94 ± 0.22	3.62 ± 0.56	0.34 ± 0.15
1g	25	2.32 ± 0.24**	1.50 ± 0.28*	1.16 ± 0.19	3.26 ± 0.37	0.48 ± 0.27
1h	25	2.12 ± 0.29**	1.36 ± 0.29	1.72 ± 0.29	2.92 ± 0.39	0.58 ± 0.34
Clorpromazine	5	5.74 ± 0.90**	6.84 ± 0.53**	7.92 ± 0.81**	6.86 ± 1.21**	0.28 ± 0.32

*$p < 0.05$.
**$p < 0.01$.

Table 9. Effect of compounds **1(a–h)** on hypnotic dose of pentobarbital (40 mg/kg ip)

Compound	Dose mg/kg ip	t_1 (min)[c]	t_2 (min)[d]	Variation (%)	
		$x \pm$ SEM	$x \pm$ SEM	(t_1)	(t_2)
Control	–	5.58 ± 0.97	67.26 ± 4.06	–	–
1a	10	5.68 ± 0.65	118.38 ± 8.79**[b]	1.79	76.00
1b	10	5.02 ± 0.23	62.13 ± 10.31	−10.03	−7.63
1c	10	5.82 ± 0.49	72.34 ± 3.81	4.30	7.55
1d	10	7.39 ± 1.35	98.03 ± 8.47**[b]	32.44	45.75
1e	10	4.46 ± 0.30	91.45 ± 6.14**[b]	−20.07	35.96
1f	10	5.62 ± 0.94	77.34 ± 10.50	0.72	14.98
1g	10	4.77 ± 0.33	80.89 ± 5.18	−14.52	20.26
1h	10	6.43 ± 1.82	73.43 ± 4.22	15.23	9.17
Diazepam	2.5	2.93 ± 0.16*[a]	121.69 ± 12.85**[b]	−47.49	80.92
Control	–	5.45 ± 0.58	56.31 ± 3.12	–	–
1a	25	5.51 ± 0.45	115.51 ± 6.37**[b]	1.10	105.13
1b	25	4.27 ± 0.53	69.45 ± 7.19	−21.65	23.33
1c	25	5.85 ± 1.00	91.35 ± 7.63**[b]	7.34	62.22
1d	25	5.38 ± 0.82	128.47 ± 5.24**[b]	−1.28	128.15
1e	25	4.57 ± 0.30	83.97 ± 8.80*[a]	−16.14	49.12
1f	25	5.48 ± 0.95	80.28 ± 9.16*[a]	0.55	42.57
1g	25	5.40 ± 1.07	99.43 ± 8.39**[b]	−0.92	76.57
1h	25	6.14 ± 0.95	74.59 ± 7.52*[a]	12.66	32.46
Diazepam	2.5	3.04 ± 0.16*[a]	104.53 ± 6.73**[b]	−44.22	85.63

[a] $*p < 0.05$.
[b] $**p < 0.01$.
[c] t_1 = sleep induction time (min).
[d] t_2 = sleeping time (min).

Table 10. Effect of compounds **1(a–h)** on subhypnotic dose of pentobarbital (20 mg/kg ip)

	Dose mg/kg ip	t_1 (min)[a] N_s/N_t[b]	t_2 (min)[a] $x \pm$ SEM	$x \pm$ SEM
Control	–	0/6	–	–
1a	10	3/6	24.00 ± 0.86	21.00 ± 1.00
1b	10	2/6	6.84 ± 0.37	26.19 ± 0.12
1c	10	2/6	9.39 ± 0.60	21.15 ± 1.73
1d	10	6/6	14.82 ± 2.58	28.67 ± 2.34
1e	10	2/6	10.85 ± 2.87	26.92 ± 7.42
1f	10	1/6	5.08 ± 0.00	32.62 ± 0.00
1g	10	3/6	11.20 ± 0.34	21.83 ± 0.34
1h	10	1/6	10.70 ± 0.00	25.83 ± 0.00
Diazepam	2.5	6/6	5.97 ± 0.91	40.88 ± 0.95
Control	–	0/6	–	–
1a	25	6/6	16.22 ± 0.84	24.82 ± 2.42
1b	25	3/6	14.25 ± 1.98	22.23 ± 6.03
1c	25	6/6	14.10 ± 1.02	21.34 ± 0.99
1d	25	4/6	15.91 ± 1.60	21.58 ± 3.97
1e	25	2/6	18.04 ± 1.31	11.35 ± 7.45
1f	25	2/6	13.47 ± 0.66	11.00 ± 0.35
1g	25	5/6	15.97 ± 2.62	14.36 ± 2.37
1h	25	3/6	21.02 ± 3.87	7.81 ± 1.23
Diazepam	2.5	6/6	7.13 ± 0.79	48.29 ± 4.07

[a] t_1 = sleep induction time (min); t_2 = sleeping time (min).
[b] N_s = number of sleeping mice; N_t = total number of mice.

Conclusions

In conclusion, the title compounds are generally active ip in a series of mice models predictive of antidepressant properties, with the viloxazine thiophene isoster (**1f**) being the most active in the Porsolt test. Besides, they show a light sedative action in the same profile as other antidepressant drugs.

The initial structure–activity relationship show that the position of the morpholinomethoxy chain on the thiophene ring has no importance for the activity because compounds **1g** and **1h** have similar pharmacological results. Neither does the position of the substituents in relation to the chain seem to have a remarkable effect. This is illustrated by the fact that, in most of the pharmacological tests, compounds **1c**, **1g** and **1h**, in which the methyl group is adjacent to the side chain show similar behaviour.[14]

Experimental

Chemistry

Melting points were measured on a Büchi 510 apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR were recorded on a Bruker AM (200 MHz) spectrometer and were all consistent with molecular structures (ref. 15 and Fig. 2). Microanalyses were done on a Perkin–Elmer 240 analyzer. All the reagents used were of commercial grade and used as received.

The following compounds were prepared according to the literature: **2a**,[3] **2b**,[4] **2c**,[5] **2d**,[6] **2e**,[3] **2f**,[10] **5a–c**,[9] **5d,f**,[10] **5g,h**,[11] and 4-benzyl-2-*p*-toluenesulphonyloxymethylmorpholine.[7] Satisfactory elemental analyses (±0.4%) for C, H, N, and S were obtained for all the new described compounds.

Route 1

General procedure for the synthesis of alkyl 3-[2-(4-benzyl-morpholinyl)methoxy]thiophene-2-carboxylate (3a–e). A stirred solution of 4-benzyl-2-toluene-*p*-sul-

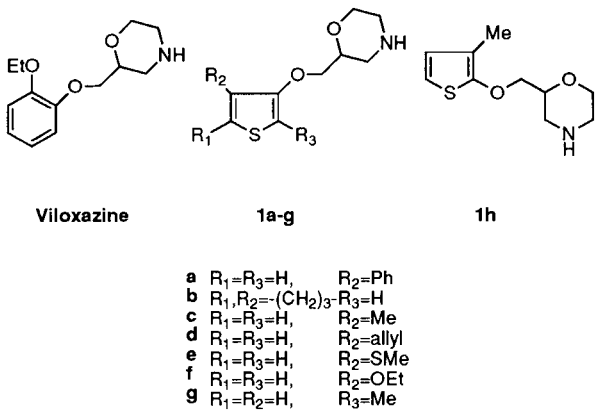


Figure 1.

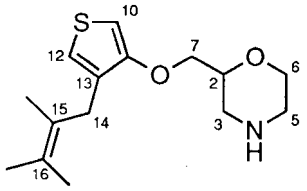


Figure 2.

phonyloxymethylmorpholine (6.83 g, 0.02 mol) and the corresponding potassium salt of the alkyl 3-hydroxythiophene-2-carboxylates (**2a–e**) (0.02 mol) in DMF (70 mL) was heated at 120–150°C for 17 h. The reaction mixture was cooled, the solvent was removed in vacuo and the residue was extracted with EtOAc and washed with water. The organic extracts were dried over anhydrous Na_2SO_4, the solvent was removed and the residue was purified by a flash chromatography column (100 g silica gel) using a mixture of *n*-hexane:EtOAc (1:1) as eluent, to yield the following oils.

Methyl 4-phenyl-3-[(4-benzyl-2-morpholinyl)methoxy]-thiophene-2-carboxylate (3a). Yield 70%. ^{1}H NMR ($CDCl_3$) δ 7.68–7.15 (m, 11H, H-12, phenyl), 3.93 (m, 1H, H-2), 3.82 (s, 3H, OMe), 3.80–3.71 (m, 4H, H-6, H-7), 3.52 (s, 2H, CH_2N), 2.87 (dd, $J_{2,3a}=12.1$, $J_{3a-3b}=1.2$ Hz, 1H, H-3a), 2.68 (dd, $J_{2,3b}=12.1$, $J_{3a,3b}=1.2$ Hz, 1H, H-3b), 2.17 (td, $J_{5,6}=11.1$, $J_{5a-5b}=4.3$ Hz, 2H, H-5). Anal. ($C_{24}H_{25}NO_4S$), C, H, N, S.

Ethyl 3-[(4-benzyl-2-morpholinyl)methoxy]-5,6-dihydro-4*H*-cyclopenta[*b*]thiophene-2-carboxylate (3b). Yield 76%. ^{1}H NMR ($CDCl_3$) δ 7.29 (m, 5H, phenyl), 4.05 (q, $J=5.9$ Hz, 2H, OCH_2), 3.92 (m, 1H, H-2), 3.90–3.67 (m, 4H, H-6, H-7), 3.50 (s, 2H, CH_2N), 2.87 (dd, $J_{2,3a}=12.0$, $J_{3a-3b}=1.4$ Hz, 1H, H-3a), 2.84–2.61 (m, 7H, $2CH_2$ cycle, H-5, H-3b), 2.48 (quint, $J=8.2$ Hz, 2H, CH_2 cycle), 1.37 (t, $J=5.9$, 3H, CH_3). Anal. ($C_{22}H_{27}NO_4S$), C, H, N, S.

Methyl 4-methyl-3-[(4-benzyl-2-morpholinyl)methoxy]-thiophene-2-carboxylate (3c). Yield 60%. ^{1}H NMR ($CDCl_3$) δ 7.27 (m, 5H, phenyl), 6.81 (q, $J=1.0$ Hz, 1H, H-12), 3.92 (m, 1H, H-2), 3.90–3.73 (m, 4H, H-6, H-7), 3.83 (s, 3H, OCH_3), 3.46 (s, 2H, CH_2N), 2.82 (dd, $J_{2,3a}=12.1$, $J_{3a-3b}=1.2$ Hz, 1H, H-3a), 2.68 (dd, $J_{2,3b}=12.1$, $J_{3a,3b}=1.2$ Hz, 1H, H-3b), 2.17 (td, $J_{5,6}=11.1$, $J_{5a-5b}=4.3$ Hz, 2H, H-5), 2.01 (s, 3H, CH_3). Anal. ($C_{19}H_{23}NO_4S$), C, H, N, S.

Methyl 4-allyl-3-[(4-benzyl-2-morpholinyl)methoxy]-thiophene-2-carboxylate (3d). Yield 31%. ^{1}H NMR ($CDCl_3$) δ 7.23 (m, 5H, phenyl), 7.04 (s, 1H, H-12), 5.87 (ddt, $J_{15-14}=5.3$, $J_{15-16}=10.4$, $J_{2-3b}=14.1$ Hz, 1H, H-15), 5.08 (d, $J=14.1$ Hz, 2H, H-16), 3.92 (m, 1H, H-2), 3.86–3.53 (m, 4H, H-6, H-7), 3.82 (s, 3H, OCH_3), 3.53 (s, 2H, CH_2N), 3.25 (d, $J_{14-15}=5.5$ Hz, 2H, H-14), 2.95 (dd, $J_{2,3a}=12.1$, $J_{3a-3b}=1.43$ Hz, 1H, H-3a), 2.66 (dd, $J_{2,3b}=12.4$, $J_{3a-3b}=1.2$ Hz, 1H, H-3b), 2.12 (td, 2H, $J_{5,6}=10.3$, $J_{5a-5b}=4.4$ Hz, 2H, H-5). Anal. ($C_{21}H_{25}NO_4S$), C, H, N, S.

Methyl 4-methylthio-3-[(4-benzyl-2-morpholinyl)methoxy]thiophene-2-carboxylate (3e). Yield 78%. ^{1}H NMR ($CDCl_3$) δ 7.29 (m, 5H, phenyl), 6.98 (s, 1H, H-12), 3.91 (m, 1H, H-2), 3.90–3.75 (m, 4H, H-6, H-7), 3.82 (s, 3H, OCH_3), 3.55 (s, 2H, CH_2N), 2.83 (dd, $J_{2,3a}=12.2$, $J_{3a-3b}=1.2$ Hz, 1H, H-3a), 2.57 (dd, $J_{2,3b}=12.2$, $J_{3a-3b}=1.2$ Hz, 1H, H-3b), 2.38 (s, 3H, SCH_3), 2.20 (td, $J_{5,6}=10.5$, $J_{5a-5b}=4.5$ Hz, 2H, H-5). Anal. ($C_{19}H_{23}NO_4S_2$), C, H, N, S.

General procedure for the synthesis of 4-benzyl-2-thienyloxymethyl morpholines (4a–e). A suspension of the respective compound **3a–e** (0.05 mol) in a 50% ethanolic 2 N NaOH solution (100 mL) was heated at reflux for 1 h. The resultant mixture was cooled to room temperature and acidified with 1 N HCl solution to pH 4. The solvent was removed in vacuo and the residue was treated with absolute EtOH (100 mL). The inorganic salts were filtered off and washed with absolute EtOH (2×25 mL). The combined filtrates were evaporated and the residue was heated at reduced pressure (0.1 mm Hg) at 200°C for 30 min. The oil obtained, once cooled, was stirred for 30 min with a 2 N NaOH solution in EtOAc (100 mL). The organic phase was separated, dried over anhydrous Na_2SO_4, and the solvent was removed. The residue was chromatographed on a silica gel column (60 g silica gel) using as eluent a mixture of *n*-hexane:EtOAc (5:2) to yield as pure oils the following compounds.

4-Benzyl-2-[3-(4-phenylthienyloxymethyl)]morpholine (4a). Yield 67%. ^{1}H NMR ($CDCl_3$) δ 7.67–7.12 (m, 11H, 10 phenyl, H-12), 6.31 (d, $J_{10-12}=3.4$ Hz, 1H,H-10), 3.92 (q, $J=5.65$ Hz, 1H, H-2), 3.90–3.71 (m, 4H H-6, H-9), 3.49 (s, 2H, CH_2N), 2.89 (dd, $J_{2,3a}=12.1$, $J_{3a-3b}=1.3$ Hz, 1H, H-3a), 2.70 (dd, $J_{2,3b}=12.1$, $J_{3a-3b}=1.31$ Hz, 1H, H-3b), 2.18 (td, $J_{5,6}=10.5$, $J_{5a-5b}=4.5$ Hz, 2H, H-5). Anal. ($C_{22}H_{23}NO_2S$), C, H, N, S.

4-Benzyl-2-[3-(5,6-dihydro-4*H*-cyclopenta[*b*]thienyloxymethyl)] morpholine (4b). Yield 88%. ^{1}H NMR ($CDCl_3$) δ 7.29 (m, 5H, phenyl), 6.01 (s, 1H, H-10), 3.91 (m, 1H, H-2), 3.85–3.69 (m, 4H, H-6, H-7), 3.51 (s, 2H, CH_2N), 2.91 (dd, $J_{2,3a}=12.0$, $J_{3a-3b}=1.3$ Hz, 1H, H-3a), 2.86–2.60 (m, 7H, $2CH_2$ cycle, H-5, H-3b), 2.44 (quint, J =8.3 Hz, 2H cycle). Anal. ($C_{19}H_{23}NO_2S$), C, H, N, S.

4-Benzyl-2-[3-(4-methylthienyloxymethyl)]morpholine (4c). Yield 68%. ^{1}H NMR ($CDCl_3$) δ 7.26 (m, 5H, phenyl), 6.81 (dq, $J_{12-10}=3.2$, $J_{12-14}=1.0$ Hz, H-12), 6.12 (d, $J=3.2$ Hz, 1H, H-10), 3.93 (m, 1H, H-2), 3.91–3.76 (m, 4H, H-6, H-7), 3.48 (s, 2H, CH_2N), 2.89 (dd, $J_{2-3a}=12.0$, $J_{3a-3b}=1.2$ Hz, 1H, H-3a), 2.63 (dd, $J_{2-3b}=12.0$, $J_{3a-3b}=1.2$ Hz, 1H, H-3b), 2.18 (td, $J_{5-6}=10.5$, $J_{5a-5b}=4.5$ Hz, 2H, H-5), 2.01 (s, 3H, CH_3). Anal. ($C_{17}H_{21}NO_2S$), C, H, N, S.

4-Benzyl-2-[3-(4-allylthienyloxymethyl)]morpholine (4d). Yield 71%. ^{1}H NMR ($CDCl_3$) δ 7.11 (m, 5H, phenyl), 6.93 (dt, $J_{12-10}=3.10$, $J_{12-14}=1.0$ Hz, 1H, H-12), 6.26 (d, $J=3.1$ Hz, 1H, H-10), 5.86 (ddt, $J_{15-14}=5.4$, $J_{15-16b}=10.2$, $J_{15-16t}=14.3$ Hz, 1H, H-15), 5.10 (d, $J_{16t-15}=13.9$ Hz, 2H, H-16), 3.90 (m, 1H, H-2), 3.86–3.62 (m, 4H, H-6, H-7), 3.52 (s, 2H, CH_2N), 3.23 (d, $J_{14-15}=5.4$ Hz, 2H, H-14), 2.93 (dd, $J_{2-3a}=12.0$, $J_{3a-3b}=1.3$ Hz, 1H, H-3a), 2.68 (dd, $J_{2,3b}=12.0$, $J_{3a-3b}=1.3$ Hz, 1H, H-3b), 2.17 (td, $J_{5-6}=10.5$, $J_{5a-5b}=4.5$ Hz, 2H, H-5). Anal. ($C_{19}H_{23}NO_2S$), C, H, N, S.

4-Benzyl-2-[3-(4-methylthiothienyloxymethyl)]morpholine (4e). Yield 76%. ^{1}H NMR ($CDCl_3$) δ 7.26 (m, 5H, phenyl), 6.82 (d, $J=3.2$, Hz, 1H, H-12), 6.21 (d, $J=3.2$ Hz, 1H, H-10), 3.90 (m, 1H, H2), 3.87-3.73 (m, 4H, H-6, H-7), 3.52 (s, 2H, CH2N), 2.80 (dd, $J_{2-3a}=12.1$, $J_{3a-3b}=1.0$ Hz, 1H, H-3a), 2.61 (dd, $J_{2,3b}=12.1$, $J_{3a-3b}=1.0$ Hz, 1H, H-3b), 2.34 (s, 3H, SCH_3), 2.20 (td, $J_{5-6}=10.3$, $J_{5a-5b}=4.2$ Hz, 2H, H-5). Anal. ($C_{17}H_{21}NO_2S_2$), C, H, N, S.

General procedure for the synthesis of 2-thienyloxymethylmorpholines (1a–e) (Table 1). $PdCl_2$ (5 g), C (12 g) and deionized water (100 mL) were mixed and rapidly stirred while being heated to 80°C and a solution of lithium hydroxide (2.5 g) in water (10 mL) was added at once and the heating was stopped. The mixture was stirred overnight, filtered, washed with a 5% aqueous solution of AcOH (100 mL) and with distilled water till the mother liquors had a neutral pH. The solid obtained was dried in vacuo at 60°C over P_2O_5 for 24 h. The catalyst so obtained (0.1 g) was added to a solution of the respective compound **4a–e** in anhydrous MeOH (10 mL) and the mixture was hydrogenated at 1 atm, until the reaction finished (control by TLC). The calalyst was filtered and washed with anhydrous MeOH (10 mL) and the filtrates were evaporated in vacuo to yield the free amine as a practically pure oil, which was transformed into the oxalic salt, by dissolving it in dry ether and adding dropwise, with stirring, a saturated ethereal solution of oxalic acid to yield a white solid, which was filtered and recrystallized from the corresponding solvent.

The following compounds were obtained according to this procedure.

2-[3-(4-Phenylthienyloxymethyl)]morpholine (1a). Yield 92%. Mp 170–172°C (acetone) (oxalic salt). ^{1}H NMR ($CDCl_3$) δ 7.52 (m, 2H phenyl), 7.35 (m, 3H, phenyl), 7.23 (d, $J_{12-10}=3.5$ Hz, 1H, H-12), 6.34 (d, $J_{10-12}=3.5$, 1H, H-10), 3.98 (m, 1H, H-2), 3.91–3.75 (m, 2H, H-7), 3.68 (td, $J_{6-5}=10.5$, $J_{6a-6b}=3.7$ Hz, 2H, H-6), 3.08 (dd, $J_{2-3a}=12.6$, $J_{3a-3b}=1.8$ Hz, 1H, H-3a), 2.83 (dd, $J_{2-3b}=10.1$, $J_{3a-3b}=1.8$ Hz, 1H, H-3b), 2.71 (m, 2H, H-5), 1.83 (s, 1H, NH); ^{13}C NMR (free amine) ($CDCl_3$) δ 152.23 (C-9), 138.24 (C-13), 132.21 (d, $J=147.0$ Hz, phenyl), 130.20 (d, $J=146.3$, phenyl), 127.71 (phenyl), 127.46 (phenyl), 127.27 (d, $J=146.2$, phenyl), 118.93 (dd, $J=182.9$, $J_{10-12}=3.9$ Hz, C-12), 98.34 (dd, $J=183.4$, $J_{10-12}=4.21$ Hz, C-10), 74.62 (d, $J=143.1$, C-2), 71.72 (t, $J=146.7$, C-7), 67.92 (t, $J=143.2$, C-6), 48.54 (t, $J=138.0$, C-3), 45.92 (t, $J=141.3$, C-5). Anal. ($C_{15}H_{17}NO_2S$), C, H, N, S.

2-[3-(5,6-Dihydro-4*H*-cyclopenta[*b*]thienyloxymethyl)]-morpholine (1b). Yield 83%. Mp 164–166°C (acetone) (oxalic salt). ^{1}H NMR (free amine) ($CDCl_3$) δ 6.04 (s, 1H, H-10), 3.92 (m, 1H, H-2), 3.94–3.78 (m, 2H, H-7), 3.70 (td, $J_{5-6}=10.5$, $J_{6a-6b}=3.6$ Hz, 2H, H-6), 3.05 (dd, $J_{2-3a}=11.0$, $J_{3a-3b}=2.1$ Hz, 1H, H-3a), 2.88–2.62 (m, 7H, H-5, H-3b, CH_2 cycle), 2.44 (quint, $J=5.3$ Hz, 2H, CH_2 cycle), 1.89 (s, 1H, NH); ^{13}C NMR (free amine) ($CDCl_3$) δ 152.12 (C-9), 141.42 (C-16), 137.44 (C-12), 99.23 (d, $J=182.0$ Hz, C-10), 74.80 (d, $J=142.5$ Hz, C-2), 71.01 (t, $J=147.7$ Hz, C-7), 67.90 (t, $J=143.1$ Hz, C-6), 48.41 (t, $J=145.4$ Hz, C-3), 45.79 (t, $J=134.8$ Hz, C-5), 29.52 (t, $J=132.3$ Hz, C-15), 29.15 (t, $J=136.4$ Hz, C-13), 27.01 (t, $J=133.0$ Hz, C-14). Anal. ($C_{12}H_{17}NO_2S$), C, H, N, S.

2-[3-(4-Methylthienyloxymethyl)]morpholine (1c). Yield 87%. Mp 173–174°C (acetone/MeOH) (oxalic salt). ^{1}H NMR (free amine) ($CDCl_3$) δ 6.81 (dq, $J_{12-10}=3.2$, $J_{12-14}=1.0$ Hz, 1H, H-12), 6.17 (d, $J=3.2$ Hz, 1H, H-10), 3.95 (m, 1H, H-2), 3.91–3.77 (m, 2H, H-7), 3.68 (td, $J_{5-6}=10.8$, $J_{6a-6b}=3.9$ Hz, 2H, H-6), 3.09 (dd, $J_{2-3a}=12.0$, $J_{3a-3b}=2.3$ Hz, 1H, H-3a), 2.87 (dd, $J_{2-3b}=11.3$, $J_{3a-3b}=2.4$ Hz, 1H, H-3b), 2.70 (m, 2H, H-5), 2.09 (s, 1H, NH), 2.08 (s, 3H, CH_3); ^{13}C NMR (free amine) ($CDCl_3$) δ 155.47 (C-9), 128.81 (C-13), 119.75 (dd, $J=184.5$, $J_{10-12}=5.8$ Hz, C-12), 96.69 (dd, $J=183.1$, $J_{10-12}=5.7$ Hz, C-10), 74.32 (d, $J=143.4$ Hz, C-2), 70.88 (t, $J=144.0$ Hz, C-7), 67.98 (t, $J=143.2$ Hz, C-6), 47.96 (t, $J=132.8$ Hz, C-3), 45.34 (t, $J=131.5$, C-5), 12.31 (qt, $J=127.8$, $J=3.0$ Hz, CH_3). Anal. ($C_{10}H_{15}NO_2S$), C, H, N, S.

2-[3-(4-Allylthienyloxymethyl)]morpholine (1d). Yield 96%. Mp 145–147°C (acetone) (oxalic salt). ^{1}H NMR (free amine) ($CDCl_3$) δ 6.92 (dt, $J_{12-10}=3.1$, $J_{12-14}=1.0$ Hz, 1H, H-12), 6.26 (d, $J_{10-12}=3.1$ Hz, 1H, H-10), 5.86 (ddt, $J_{15-14}=5.5$, $J_{15-16t}=14.2$ Hz, $J_{15-16c}=11.3$ Hz, 1H, H-15), 5.10 (d, $J_{16t-15}=14.2$ Hz, 2H, H-16), 3.95 (m, 1H, H-2), 3.91–3.79 (m, 2H, H-7), 3.70 (td, $J_{6-5}=10.5$, $J_{6a-6b}=3.7$ Hz, 2H, H-6), 3.23 (d, $J_{14-15}=5.5$, $J_{14-12}=1.0$ Hz, 2H, H-14), 3.12 (dd, $J_{2-3a}=10.6$, $J_{3a-3b}=2.8$ Hz, 1H, H-3a), 2.96 (dd, $J_{2-3b}=9.8$, $J_{3a-3b}=2.8$ Hz, 1H, H-3b), 2.73 (m, 2H, H-5), 1.82 (s, 1H, NH); ^{13}C NMR (free amine) ($CDCl_3$) δ 153.28 (C-9), 128.94 (C-13), 135.28 (d, $J=170.2$ Hz, $\underline{C}H=CH_2$), 119.45 (d, $J=184.3$ Hz, C-12), 115.38 (t, $J=169.4$ Hz, $CH=\underline{C}H_2$), 97.32 (d, $J=184.3$ Hz, C-10), 74.99 (d, $J=142.6$ Hz, C-2), 71.03 (t, $J=147.7$ Hz, C-7), 68.02 (t, $J=143.1$ Hz, C-6), 48.13 (t, $J=137.2$ Hz, C-3), 45.89 (t, $J=133.1$, C-5), 38.24 (t, $J=128.3$, CH_2). Anal. ($C_{12}H_{17}NO_2S$), C, H, N, S.

2-[3-(4-Methylthiothienyloxymethyl)]morpholine (1e). Yield 76%. Mp 152–154°C (acetone) (oxalic salt). ^{1}H NMR (free amine) ($CDCl_3$) δ 6.86 (d, $J=3.3$ Hz, 1H,

H-12), 6.28 (d, $J=3.3$ Hz, 1H, H-10), 3.97 (m, 1H, H-2), 3.92–3.74 (m, 2H, H-7), 3.65 (td, $J_{6-5}=10.7$, $J_{6a-6b}=3.6$ Hz, 2H, H-6), 3.12 (dd, $J_{2-3a}=11.0$, $J_{3a-3b}=2.0$ Hz, 1H, H-3a), 2.85 (dd, $J_{2-3b}=11.2$, $J_{3a-3b}=2.1$ Hz, 1H, H-3b), 2.67 (m, 2H, CH_2N), 2.40 (s, 3H, SCH_3) 2.19 (s, 1H, NH); ^{13}C NMR (free amine) ($CDCl_3$) δ 154.87 (C-9), 125.75 (C-13), 119.60 (dd, $J=183.2$, $J_{10-12}=4.4$ Hz, C-12), 98.22 (dd, $J=184.5$, $J_{10-12}=4.3$ Hz, C-10), 74.61 (d, $J=142.2$ Hz, C-2), 71.65 (t, $J=146.2$ Hz, C-7), 67.95 (t, $J=144.2$ Hz, C-6), 48.65 (t, $J=138.4$ Hz, C-3), 45.88 (t, $J=141.3$ Hz, C-5), 16.35 (q, $J=140.0$ Hz, CH_3). Anal. ($C_{10}H_{15}NO_2S_2$), C, H, N, S.

Route II

3-[3-(4-Allylthienyloxy)-1,2-epoxypropane (5d). This compound was synthesized in a similar way to that described for compounds **5a–c**[9] to give an oil in a 58% yield, which was purified on a silica gel column chromatography using as eluent a mixture of *n*-hexane:EtOAc (10:1). ^1H NMR ($CDCl_3$) δ 6.92 (d, $J=3.0$ Hz, 1H, H-5 thiophene), 6.21 (d, $J=3.0$ Hz, 1H, H-2 thiophene), 5.87 (m, 1H, CH), 5.13 (d, $J=14.5$ Hz, 2H, $=CH_2$), 4.35 (dd, $J_{1a-1b}=11.9$, $J_{1a-2}=2.9$ Hz, 1H, OCH_2), 3.97 (dd, $J_{1a-1b}=11.9$, $J_{1b-2}=5.9$ Hz, 1H, OCH_2), 3.31 (m, 1H, CH), 3.18 (d, $J=6.6$ Hz, 2H, CH_2), 2.96–2.72 (m, 2H, CH-C$\underline{H_2}$-O). Anal. ($C_{10}H_{12}O_2S$), C, H, S.

3-[3-(4-Ethoxythienyloxy)]-1,2-epoxypropane (5f). This compound was synthesized as above.[7] Yield 65%. ^1H NMR ($CDCl_3$) δ 6.30 (d, $J=4.0$ Hz, 1H, H-5 thiophene), 6.15 (d, $J=4.0$ Hz, 1H, H-2 thiophene), 4.25 (dd, $J_{1a-1b}=11.7$, $J_{1a-2}=2.8$ Hz, 1H, OCH_2), 4.05 (q, $J=7.1$ Hz, 2H, OC$\underline{H_2}$-CH_3), 3.95 (dd, $J_{1a-1b}=11.7$, $J_{1b-2}=5.8$ Hz, 1H, OC$\underline{H}$H), 3.40 (m, 1H, CH), 2.85 (m, 2H, CH-C$\underline{H_2}$-O), 1.41 (t, $J=7.1$ Hz, 3H, CH_3). Anal. ($C_9H_{12}O_3S$), C, H, S.

General procedure for the synthesis of 2-thienyloxymethylmorpholines (1a–d and 1f–h) (Table 1). A solution of the corresponding compound **5a–d** and **5f–h** (0.05 mol) in DMSO (25 mL) was added slowly to a stirred mixture of 1,2,3-oxathiazolidine 2,2-dioxide (17 g, 0.125 mol) in a 70% solution of NaOH (15 mL) at 50–55°C, keeping this temperature during the addition. The reaction mixture was stirred for 1 h and after a new amount of a 70% solution of NaOH (15 mL) was added and the resultant mixture was stirred for 16 h at the same temperature (50–55°C). After cooling to room temperature it was diluted with water and extracted with EtOAc (2×50 mL). The organic extracts were washed with water, dried over anhydrous Na_2SO_4 and the solvent was removed in vacuo. The residue was purified by a flash silica gel (60 g) column chromatography using MeOH as eluent to yield the free amine as a practically pure oil, which was transformed into its oxalic salt as described in the route I.

The following compounds were obtained according to this procedure:

Compounds **1a** (47% yield), **1b** (43% yield), **1c** (38% yield), **1d** (40%), which showed the same analytical spectroscopic data, than that referred in the route I.

2-[3-(4-Ethoxythienyloxymethyl)]morpholine (1f). Yield 42%. Mp 167–168°C (acetone/MeOH) (oxalic salt). ^1H NMR (free amine) ($CDCl_3$) δ 6.19 (AB system $J_{AB}=4.0$ Hz, 2H, H-12, H-10), 4.10 (q, $J=7.1$, 2H, OC$\underline{H}$2-CH_3), 3.98 (m, 1H, H-2), 3.88–3.71 (m, 2H, H-7), 3.63 (td, $J_{6-5}=11.3$, $J_{6a-6b}=3.5$ Hz, 2H, H-6), 3.10 (dd, $J_{2-3a}=12.2$, $J_{3a-3b}=1.8$, 1H, H-3a), 2.84 (dd, $J_{2-3b}=9.8$, $J_{3a-3b}=1.8$ Hz, 1H, H-3b), 2.70 (m, 2H, H-5), 1.83 (s, 1H, NH), 1.41 (t, $J=7.0$ Hz, 3H, CH_3); ^{13}C NMR (free amine) ($CDCl_3$) δ 147.97 (C-13), 147.34 (C-9), 98.18 (dd, $J=182.9$, $J_{10-12}=4.6$ Hz, C-12), 97.20 (dd, $J=184.5$, $J_{10-12}=4.3$ Hz, C-10), 74.69 (d, $J=142.7$ Hz, C-2), 71.69 (t, $J=143.8$ Hz, C-7), 67.86 (t, $J=141.1$ Hz, C-6), 65.84 (tq, $J=139.1$, $J_{15-16}=5.5$ Hz, OCH_2), 48.48 (t, $J=136.4$, C-3), 45.79 (t, $J=138.8$, C-5), 14.58 (qt, $J=126.6$, $J_{15-16}=4.7$, CH_3). Anal. ($C_{11}H_{17}NO_3S$), C, H, N, S.

2-[3-(2-Methylthienyloxymethyl)]morpholine (1g). Yield 48%. Mp 113–115°C (acetone/MeOH) (oxalic salt). ^1H NMR (free amine) ($CDCl_3$) δ 6.57 (AB system $J_{AB}=3.7$ Hz, 2H, H–12, H-13), 3.99 (m, 1H, H-2), 3.92–3.74 (m, 2H, H-7), 3.63 (td, $J_{6-5}=10.0$, $J_{6a-6b}=3.5$ Hz, 2H, H-6), 2.99 (dd, $J_{2-3a}=12.0$, $J_{3a-3b}=2.3$ Hz, 1H, H-3a), 2.82 (dd, $J_{2-3b}=10.8$, $J_{3a-3b}=2.4$ Hz, 1H, H-3b), 2.70 (m, 2H, H-5), 2.15 (s, 3H, CH_3), 1.81 (s, 1H, NH); ^{13}C NMR (free amine) ($CDCl_3$) δ 157.04 (C-9), 123.80 (dd, $J=186.4$, $J_{12-13}=4.2$ Hz, C-13), 121.45 (dd, $J=182.6$, $J_{12-13}=3.8$ Hz, C-12), 101.41 (C-10), 74.08 (d, $J=142.5$ Hz, C-2), 71.23 (t, $J=145.8$ Hz, C-7), 66.94 (t, $J=142.2$ Hz, C-6), 47.24 (t, $J=133.4$, C-3), 45.10 (t, $J=132.6$, C-5), 13.24 (qt, $J=127.3$, $J=2.8$, CH_3). Anal. ($C_{10}H_{15}NO_2S$), C, H, N, S.

2-[2-(3-Methylthienyloxymethyl)]morpholine (1h). Yield 49%. Mp 118–119°C (acetone/MeOH) (oxalic salt). ^1H NMR (free amine) ($CDCl_3$) δ 6.93 (d, $J=5.5$ Hz, 1H, H-12), 6.77 (d, $J=5.5$ Hz, 1H, H-13), 3.98 (m, 1H, H-2), 3.97–3.62 (m, 2H, H-7), 3.62 (td, $J_{6-5}=10.3$, $J_{6a-6b}=3.5$ Hz, 2H, H-6), 2.93 (dd, $J_{2-3a}=12.4$, $J_{3a-3b}=2.3$ Hz, 1H, H-3a), 2.84 (dd, $J_{2-3b}=11.8$, $J_{3a-3b}=2.3$ Hz, 1H, H-3b), 2.69 (m, 2H, H-5), 2.28 (s, 3H, CH_3), 1.79 (s, 1H, NH); ^{13}C NMR (free amine) ($CDCl_3$) δ 158.47 (C-9), 122.35 (dd, $J=188.5$, $J_{12-13}=4.2$ Hz, C-13), 118.94 (dd, $J=189.4$, $J_{12-13}=4.2$ Hz, C-12), 103.56 (C-10), 73.71 (d, $J=142.5$ Hz, C-2), 70.14 (t, $J=140.0$ Hz, C-7), 66.31 (t, $J=146.3$ Hz, C-6), 47.04 (t, $J=133.8$, C-3), 43.31 (t, $J=135.4$ Hz, C-5), 12.53 (qt, $J=128.4$, $J_{15-16}=3.4$, CH_3). Anal. ($C_{10}H_{15}NO_2S$), C, H, N, S.

Route III

General procedure for the synthesis of 1-benzylamino-3-thienyloxy-2-propanols (6a–d and 6f–h). The corresponding compound (**5a–d** and **5f–h**) (0.017 mol) was dissolved in benzylamine (5.45 g, 0.051 mol) and the reaction mixture was heated at 100°C for 30 min. Once cooled, the benzylamine was distilled at reduced pressure (0.1 mm Hg) and the resultant residue was washed with *n*-hexane and recrystallized from a mixture of *n*-hexane:EtOAc (1:1).

The following compounds were obtained according to this procedure.

1-Benzylamine-3-[3-(4-phenylthienyloxy)]-2-propanol (6a). Yield 82%. Mp 76–78°C. ^{1}H NMR ($CDCl_3$) δ 7.41 (m, 10H phenyl), 7.19 (d, J = 3.0 Hz, 1H, H-5 thiophene), 6.32 (d, J = 3.0 Hz, 1H, H-2 thiophene), 3.96 (m, 3H, OCH_2-CH), 3.73 (s, 2H, CH_2N), 3.00 (s, 1H, NH), 2.77 (d, J = 8.0 Hz, 2H, CH_2N), 2.62 (s, 1H, OH). Anal. ($C_{20}H_{21}NO_2S$), C, H, N, S.

1-Benzylamine-3-[3-(5,6-dihydro-4*H*-cyclopenta[*b*]-thienyl-oxy)]- 2-propanol (6b). Yield 72%. Mp 98–100°C. ^{1}H NMR ($CDCl_3$) δ 7.28(s, 5H phenyl), 6.01 (s, 1H, H-10), 3.98 (m, 3H, OCH_2-CH), 3.82 (s, 2H, CH_2N), 2.98 (s, 1H, NH), 2.81 (t, J = 5.90 Hz, 2H, CH2 cycle), 2.75–2.31 (m, 7H, 2CH_2 cycle, CH_2N and OH). Anal. ($C_{17}H_{21}NO_2S$), C, H, N, S.

1-Benzylamine-3-[3-(4-methylthienyloxy)]-2-propanol (6c). Yield 87%. Mp 83–85°C. ^{1}H NMR ($CDCl_3$) δ 7.33 (s, 5H, phenyl), 6.87 (d, J = 3.0 Hz, 1H, H-5 thiophene), 6.21 (d, J = 3.0 Hz, 1H, H-2 thiophene), 4.03 (m, 3H, OCH_2-CH), 3.47 (s, 2H, CH_2N), 3.08 (s, 1H, NH), 2.89 (d, J = 7.5 Hz, 2H, CH_2N), 2.63 (s, 1H, OH), 2.13 (s, 3H, CH_3). Anal. ($C_{15}H_{19}NO_2S$), C, H, N, S.

1-Benzylamine-3-[3-(4-allylthienyloxy)]-2-propanol (6d). Yield 88%. Mp 62–64°C. ^{1}H NMR ($CDCl_3$) δ 7.31 (s, 5H, phenyl), 6.90 (d, J = 3.0 Hz, 1H, H-5 thiophene), 6.19 (d, J = 3.0 Hz, 1H, H-2 thiophene), 5.88 (m, 1H, CH), 5.13 (d, J = 14.5 Hz, 2H, =CH_2), 3.92 (s, 3H, OCH_2-CH), 3.71 (s, 2H, CH_2N), 3.21 (d, J = 6.6 Hz, 2H, CH_2), 3.00 (s, 1H, NH), 2.77 (d, J = 8.0 Hz, 2H, CH_2N), 2.63 (s, 1H, OH). Anal. ($C_{17}H_{21}NO_2S$), C, H, N, S.

1-Benzylamine-3-[3-(4-ethoxythienyloxy)]-2-propanol (6f). Yield 82%. Mp 76–78°C. ^{1}H NMR ($CDCl_3$) δ 7.27 (m, 5H, phenyl), 6.19 (AB system, J_{AB} = 3.9 Hz, 2H, H-2 and H-5 thiophene), 4.00 (m, 3H, OCH_2-CH), 3.89 (q, J = 7.5 Hz, 2H, $OC\underline{H}_2$-CH_3), 3.85 (s, 2H, CH_2N), 2.83 (s, 2H, NH and OH), 2.80 (d, J = 6.5 Hz, 2H, CH_2N), 1.37 (t, J = 7.5 Hz, 3H, CH_3). Anal. ($C_{16}H_{21}NO_3S$), C, H, N, S.

1-Benzylamine-3-[3-(2-methylthienyloxy)]-2-propanol (6g). Yield 92%. Mp 78–80°C. ^{1}H NMR ($CDCl_3$) δ 7.31 (s, 5H, phenyl), 7.00 (d, J = 4.5 Hz, 1H, H-5 thiophene), 6.85 (d, J = 4.5 Hz, H-4 thiophene), 4.05 (s, 3H, OCH_2-CH), 3.82 (s, 2H, CH_2N), 2.91 (s, 2H, OH and NH), 2.67 (d, J = 7.0 Hz, 2H, CH_2N), 2.13 (s, 3H, CH_3). Anal. ($C_{15}H_{19}NO_2S$), C, H, N, S.

1-Benzylamine-3-[2-(3-methylthienyloxy)]-2-propanol (6h). Yield 80%. Mp 73–75°C. ^{1}H NMR ($CDCl_3$) δ 7.29 (s, 5H, phenyl), 6.56 (s, 2H, H-4 and H-5 thiophene), 3.99 (s, 3H, OCH_2-CH), 3.81 (s, 2H, CH_2N), 2.77 (d, J = 7.2 Hz, 2H, CH_2N), 2.53 (s, 2H, OH and NH), 2.06 (s, 3H, CH_3). Anal. ($C_{15}H_{19}NO_2S$), C, H, N, S.

General procedure for the synthesis of 4-benzyl-2-thienyloxy-methylmorpholin-5-ones (7a-d and 7f-h). A mixture of the corresponding compound **6a–d** and **6f–h** (0.03 mol) and triethylamine (4.2 mL, 0.03 mol) was dissolved in anhydrous CH_2Cl_2 (15 mL). The reaction mixture was cooled at 0°C and a solution of chloroacetyl chloride (2.28 mL, 0.03 mol) in CH_2Cl_2 (5 mL) was added dropwise with stirring and the mixture was stirred for 18 h at room temperature, was washed with a 2 N HCl solution and after with water. The organic layer was separated and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo yielding the corresponding *N*-benzylchloroacetamide as an oil.

A solution of this oil in anhydrous MeOH (5 mL) was added to a solution of sodium (0.7 g, 0.03 mol) in anhydrous MeOH (50 mL) and the mixture was heated at reflux for 8 h. The solvent was removed and the residue was treated with water and EtOAc. The aqueous layer was separated and extracted twice with EtOAc. The combined organic extracts were washed with water, dried over anhydrous Na_2SO_4 and evaporated to dryness to yield an oil, which was purified on a silica gel (150 g silica gel) column chromatography using as eluent a mixture of *n*-hexane:EtOAc (1:1). The following compounds were obtained according to this procedure:

4-Benzyl-2-[3-(4-phenylthienyloxymethyl)]morpholin-5-one (7a). Yield 84%. Mp 118–120°C (Pr^iOH). ^{1}H NMR ($CDCl_3$) δ 7.54–7.13 (m, 11H, phenyl and H-5 thiophene), 6.30 (d, J = 3.5 Hz, 1H, H-2 thiophene), 4.58 (d, J = 9.8 Hz, 2H, OCH_2CO), 4.28 (d, J = 3.5 Hz, 2H, OCH2), 4.25–3.81 (m, 1H, CH), 3.93 (s, 2H, CH_2N), 3.29 (m, 2H, CH_2N). Anal. ($C_{22}H_{21}NO_3S$), C, H, N, S.

4-Benzyl-2-[3-(5,6-dihydro-4*H*-cyclopenta[*b*]thienyloxy-methyl)]morpholin-5-one (7b). Yield 81%. Mp 93–95°C (Pr^iOH). ^{1}H NMR ($CDCl_3$) δ 7.28 (s, 5H, phenyl), 6.02 (s, 1H, H-2 thiophene), 4.63 (d, J = 4.2 Hz, 2H, OCH_2CO), 4.27 (d, J = 3.5 Hz, 2H, OCH_2), 4.24–3.80 (m, 1H, CH), 3.94 (s, 2H, CH_2N), 3.27 (m, 2H, CH_2N), 2.81 (m, 2H, CH_2 cycle), 2.73-2.32 (m, 4H, 2 CH_2 cycle). Anal. ($C_{19}H_{21}NO_3S$), C, H, N, S.

4-Benzyl-2-[3-(4-methylthienyloxymethyl)]morpholin-5-one (7c). Yield 85%. Mp 71–73°C (*n*-hexane:EtOAc). ^{1}H NMR ($CDCl_3$) δ 7.33 (s, 5H, phenyl), 6.87 (d, J = 3.0 Hz, 1H, H-5 thiophene), 6.21 (d, J = 3.0 Hz, 1H, H-2 thiophene), 4.55 (d, J = 4.3 Hz, 2H, OCH_2CO), 4.28 (d, J = 3.5 Hz, 2H, OCH_2), 4.25–3.81 (m, 1H, CH), 3.95 (s, 2H, CH_2N), 3.27 (m, 2H, CH_2N), 2.13 (s, 3H, CH_3). Anal. ($C_{17}H_{19}NO_3S$), C, H, N, S.

4-Benzyl-2-[3-(4-allylthienyloxymethyl)]morpholin-5-one (7d). Yield 80%. Oil. ^{1}H NMR ($CDCl_3$) δ 7.31 (s, 5H, phenyl), 6.92 (d, J = 3.05 Hz, 1H, H-5 thiophene), 6.28 (d, J = 3.0 Hz, 1H, H-2 thiophene), 5.88 (m, 1H, CH), 5.13 (d, J = 14,5 Hz, 2H, =CH_2), 4.65 (d, J = 4.3 Hz, 2H, OCH_2CO), 4.38 (d, J = 3.2 Hz, 2H, OCH_2), 4.21–3.83 (m, 1H, OCH), 3.94 (s, 2H, CH_2N), 3.25 (m, 2H, CH_2N), 3.12 (d, J = 6.6 Hz, 2H, CH_2). Anal. ($C_{19}H_{21}NO_3S$), C, H, N, S.

4-Benzyl-2-[3-(4-ethoxythienyloxymethyl)]morpholin-5-one (7f). Yield 83%. Mp 76–78°C (Pr^iOH). ^{1}H NMR ($CDCl_3$) δ 7.28 (m, 5H, phenyl), 6.17 (AB system, J_{AB} = 3.5 Hz, 2H, H-5 and H-2 thiophene), 4.63 (d, J = 3.3 Hz, 2H, OCH_2CO), 4.32 (d, J = 4.0 Hz, 2H, OCH_2), 4.24–3.32 (m, 3H, CH and $OC\underline{H}_2$-CH_3), 3.94 (s, 2H, CH_2N), 3.29 (m, 2H, CH_2N), 1.37 (t, J = 7.5 Hz, 3H, CH_3). Anal. ($C_{18}H_{21}NO_4S$), C, H, N, S.

4-Benzyl-2-[3-(2-methylthienyloxymethyl)]morpholin-5-one (7g). Yield 79%. Oil. ^{1}H NMR ($CDCl_3$) δ 7.31 (s, 5H, phenyl), 7.02 (d, $J=4.5$ Hz, 1H, H-5 thiophene), 6.85 (d, $J=4.5$ Hz, 1H, H-4 thiophene), 4.59 (d, $J=9.6$ Hz, 2H, OCH_2CO), 4.25 (d, $J=3.5$ Hz, 2H, OCH_2), 4.24–3.80 (m, 1H, CH), 3.92 (s, 2H, CH_2N), 3.26 (m, 2H, CH_2N), 2.12 (s, 3H, CH_3). Anal. ($C_{17}H_{19}NO_3S$), C, H, N, S.

4-Benzyl-2-[2-(3-methylthienyloxymethyl)]morpholin-5-one (7h). Yield 83%. Oil. ^{1}H NMR ($CDCl_3$) δ 7.29 (s, 5H, phenyl), 6.52 (s, 2H, H-4 and H-5 thiophene), 4.56 (d, $J=10.3$ Hz, 2H, OCH_2CO), 4.32 (d, $J=3.0$ Hz, 2H, OCH_2), 4.98–3.87 (m, 1H, CH), 3.94 (s, 2H, CH_2N), 3.25 (m, 2H, CH_2N), 1.99 (s, 3H, CH_3). Anal. ($C_{17}H_{19}NO_3S$), C, H, N, S.

General procedure for the synthesis of 4-benzyl-2-thienyl-oxymethylmorpholines (4a–d and 4f–h). A mixture of the respective compound **7a–d**, **7f–h** (0.02 mol) and 15 g of $LiAlH_4$ in 200 mL of Et_2O was heated under reflux for 6 h and then cooled. EtOAc (100 mL) was added and the mixture was heated under reflux for 10 min to decompose $LiAlH_4$. The organic phase was washed with water (two 100 mL portions) dried and evaporated to give an oil as residue, which was chromatographed in a silica gel column as described in route I.

The following compounds were obtained according to this procedure.

Compounds **4a** (79% yield), **4b** (82% yield), **4c** (72% yield), **4d** (76% yield), which showed the same analytical and spectroscopic data, as those referred in route I.

4-Benzyl-2-[3-(4-ethoxythienyloxymethyl)]morpholine (4f). Yield 74%. ^{1}H NMR ($CDCl_3$) δ 7.28 (m, 5H, phenyl), 6.12 (AB system $J_{AB}=3.25$ Hz, 2H, H-10, H-12), 4.02 (q, $J=6.8$, 2H, $OC\underline{H}_2$-CH_3), 3.96 (m, 1H, H-2), 3.92–3.69 (m, 4H, H-6, H-7), 3.50 (s, 2H, CH_2N), 2.93 (dd, $J_{2-3a}=12.0$, $J_{3a=3b}=1.3$ Hz, 1H, H-3a), 2.65 (dd, $J_{2-3}=12.0$, $J_{3a-3b}=1.3$ Hz, 1H, H-3b), 2.21 (td, $J_{5-6}=10.4$, $J_{5a-5b}=4.5$ Hz, 2H, H-5), 1.38 (t, $J=7.0$ Hz, 3H, CH_3). Anal. ($C_{18}H_{23}NO_3S$), C, H, N, S.

4-Benzyl-2-[3-(2-methylthienyloxymethyl)]morpholine (4g). Yield 80%. ^{1}H NMR ($CDCl_3$) δ 7.31 (m, 5H, phenyl), 6.57 (AB system $J_{AB}=3.8$ Hz, 2H, H-10, H-12), 3.94–3.62 (m, 5H, H-2, H-6, H-7), 3.51 (s, 2H, CH_2N), 2.86 (dd, $J_{2-3a}=12.0$, $J_{3a=3b}=1.2$ Hz, 1H, H-3a), 2.71 (dd, $J_{2-3b}=12.1$, $J_{3a-3b}=1.2$ Hz, 1H, H-3b), 2.16 (td, $J_{5-6}=10.5$, $J_{5a-5b}=4.6$ Hz, 2H, H-5), 2.09 (s, 3H, CH_3). Anal. ($C_{17}H_{21}NO_2S$), C, H, N, S.

4-Benzyl-2-[2-(3-methylthienyloxymethyl)]morpholine (4h). Yield 74%. 1H NMR ($CDCl_3$) δ 7.36 (m, 5H, phenyl), 6.93 (d, $J=5.5$ Hz, 1H, H-12) 6.77 (d, $J=5.5$ Hz, 1H, H-13), 3.97–3.61 (m, 5H, H-2, H-6, H-7), 3.50 (s, 2H, CH_2N), 2.85 (dd, $J_{2-3a}=12.0$, $J_{3a=3b}=1.3$ Hz, 1H, H-3a), 2.70 (dd, $J_{2-3b}=12.0$, $J_{3a-3b}=1.3$ Hz, 1H, H-3b), 2.19 (td, $J_{5-6}=10.5$, $J_{5a-5b}=4.5$ Hz, 2H, H-5), 2.03 (s, 3H, CH_3). Anal. ($C_{17}H_{21}NO_2S$), C, H, N, S.

General procedure for the synthesis of 2-thienyloxymethylmorpholines (1a–d and 1f–h) (Table 2). These compounds were synthesized as described in route I. The yields for compounds **1f–h**, from compounds **4f–h** are **1f** (83%), **1g** (91%) and **1h** (93%). Their analytical and spectroscopic data identical to those described in route II.

Pharmacological assays

Male and female albino Swiss mice (22–28 g) were purchased from Interfauna (Barcelona, Spain) and were housed in groups of 10/cage for a minimum of three days prior to behavioural studies with free access to standard laboratory food and tap water and maintained on a 12/12 h light–dark cycle (light from 8.00 a.m. to 8.00 p.m.). All compounds under study were dissolved in 0.9% saline and administered ip. Control animals received, under the same conditions, 0.9% saline solution. Each experimental dose group consisted of 5 animals unless otherwise stated and the ambient temperature was 22 ± 1°C, except for the potentiation of barbiturate sleeping time which were carried out in a room maintained at 30 ± 1°C.

LD_{50} in mice

The LD_{50} was calcultated from the lethality within 3 days after po and ip administration of the drugs.[16].

Effect on tetrabenazine-induced ptosis, hypothermia and suppression of locomotor activity

Mice with a rectal temperature between 36 and 38°C prior to the experiment were used. Mice received ip each test drug 30 min before the administration of tetrabenazine (32 mg/kg ip), which was dissolved in 0.1 M tartaric acid followed by adjustment to pH 6 with NaOH 10%. 30 min after the intraperitoneally injection of tetrabenazine the animals were placed at the center of a disk (20 cm in diameter) and the akinesia and the degree of ptosis exhibited by each mouse was estimated within 10 s. Mice were judged not to be akinetic if it elicited one or more of the following responses: (1) walk to the edge of the disk and look over the side, (2) mice move 180° in place, (3) mice display head movement of 90° in one direction inmediately followed by a 45° movement in the opposite direction. The degree of ptosis was rated according to the following rating scale: 0, eyes open; 1, one-quarter closed; 2, half closed, 3, three-quarters closed; and 4, completely closed.

The rectal temperature of each group was measured with a thermistor thermometer (Panlab 0331) 30 and 60 min after ip administration of tetrabenazine.

Effect on apomorphine-induced climbing, hypothermia and stereotyped behaviour in mice

According to the protocol proposed by Puech et al.[17] apomorphine (16 mg/kg) was injected subcutaneously to groups of 6 mice 30 min after ip administration of the drug. Mice were immediately placed in individual wire

mesh cages (10×10×20 cm high) and 20 min later were rated for climbing and stereotyped behaviour. Stereotypy was scored (0–3) according to their intensity. Climbing behaviour was rated according to the following scale: four paws on the bottom of the cage (no climbing) = 0; two paws on the wall = 1; four paws on the wall = 2.

Temperature was measured before and 30 min after apomorphine administration. Mice with a rectal temperature between 36 and 38°C prior to experiment were used.

Effect on 5-hydroxytryptophan (5-HTP) syndrome in mice

Test drugs were administered ip 30 min before 50 mg/kg L-5-HTP. The mice were then placed into glass bell jars and 14 min later the number of head twitches was counted in five 2-min intervals (between 14 and 16, 24 and 26, 34 and 36, 44 and 46 and 54 and 56 min).

Mice were also observed at these intervals for the presence or absence of whole body tremor, forepaw treading, hind-lamb abduction and outstretched posture with the abdomen resting on the cage floor. The total score for each mouse was calculated (maximum possible score = 25, including into the syndrome the presence or absence of head-twitches).

Effect on the forced swimming test in mice (Porsolt test)[18,19]

This test was performed according to the method described by Porsolt et al. One hour after ip administration of the test drugs, mice were individually forced to swim in a transparent glass vessel (25 cm high, 10 cm in diameter) filled with 6 cm of water at 21–24°C. The total duration of immobility (s) was measured during the last 4 min of a single 6 min test session. Mice were considered immobile when they made no further attempts to escape except the movements necessary to keep their heads above the water. Each experimental group consisted of 10 animals.

Effect on spontaneous motor activity in mice

Locomotor activity was recorded with a photocell activity meter for 15 min beginning 30 and 60 min after ip administration of each test drug.

Effect on normal body temperature

The rectal temperature of the mice was measured with a thermistor thermometer (Panlab 0331) prior to the experiment and 1, 2, 4, 6 and 24 h after ip administration of each test drug. Mice with a rectal temperature between 36 and 38°C prior to experiment were used.

Interaction with barbiturate-induced sleep in mice

Sodium pentobarbital at a subhypnotic dose of 20 mg/kg or at a hypnotic dose of 40 mg/kg was injected ip to groups of 6 mice 30 min after ip administration of the drug. The number of mice which lose righting reflex at subhypnotic dose, the latency and the duration of the sleep (loss and recovery of the righting reflex) were recorded.

Statistical analysis

Data were analysed by one-way analysis of variance (ANOVA) followed by Student's unpaired *t*-test.[20] A probability level of 0.05 or less was accepted as significant. The chi-square test was used for the percentage of locomotor activity in tetrabenazine test. Ptosis induced by tetrabenazine, stereotypy and climbing behaviour induced by apomorphine, and number of head twitches and syndrome induced by 5-HTP were analyzed using the Mann–Whitney test for non-parametric data.

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