Synthesis and Antiplatelet Activity of 1-*tert*-Butylamino-3-(3-thienyloxy)-2-propanols

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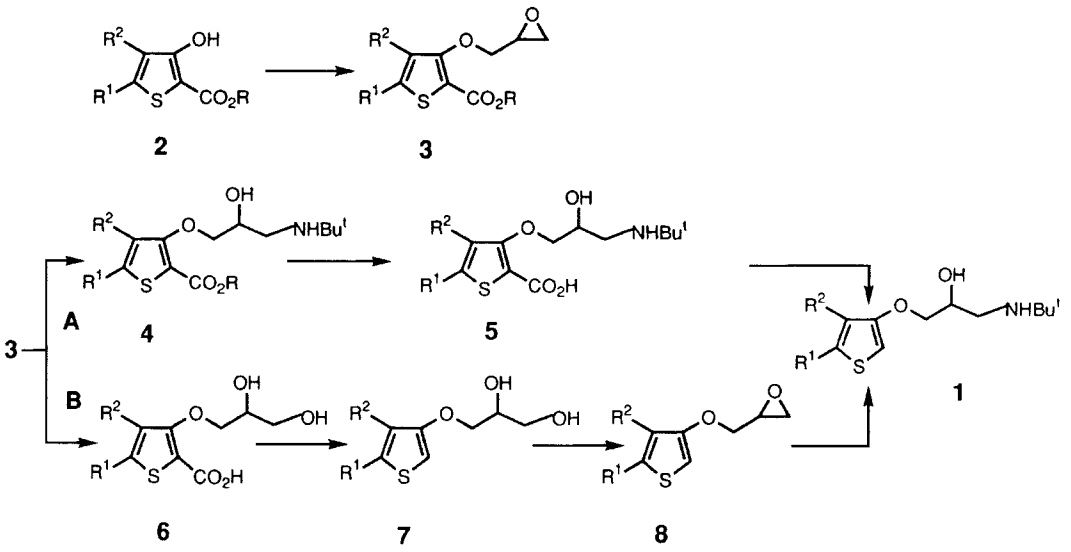
Summary

The synthesis of new 1-*tert*-butylamino-3-(3-thienyloxy)-2-propanols by two alternative methods is described. Their initial antiplatelet activity evaluation against ADP, adrenaline, and collagen is reported, and the preliminary structure-activity relationships are established. The appropriateness of further pharmacological investigations, especially for the best compound of the series **1f**, is indicated.

Introduction

We have described the pharmacological profile of diverse thienyloxypropanolamines[1–7] synthesized in our laboratories. One feature observed in some of them and in related compounds is their ability to inhibit platelet aggregation[5–7]. This fact encouraged us to design a new series of thienyloxypropanolamines (**1**) to complete the study of this activity and to establish the structure-activity relationships.

The choice of the *tert*-butylamine group was made on the basis of the results obtained in other series of related com-



1–8	R^1	R^2	R	1–8	R^1	R^2	R
a	H	H	Me	**m**	$-(CH_2)_5-$		Et
b	H	Me	Me	**n**	$-(CH_2)_6-$		Et
c	H	Ph	Me	**o**	$-CH(Me)(CH_2)_2-$		Me
d	H	Cl	Me	**p**	$-CH(Me)(CH_2)_3-$		Me
e	Me	H	Me	**q**	$-(CH_2)_2CH(Me)CH_2-$		Me
f	Ph	H	Me	**r**	$-(CH_2)_2S-$		Me
g	Me	Me	Me	**s**	$-CH_2SCH_2-$		Me
h	Ph	Me	Me	**t**	$-(CH_2)_3S-$		Et
i	Cl	Me	Me	**u**	$-(CH_2)_2SCH_2-$		Me
j	Cl	Cl	Me	**v**	-SCH=CMe-		Me
k	$-(CH_2)_3-$		Et	**w**	-CH=CH-S-		Me
l	$-(CH_2)_4-$		Et				

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pounds in which it had proved to be the most active of the amino rests studied[5]. One or two lipophilic substituents on the thiophene nucleus or a lipophilic homocycle or heterocycle in the 4,5 thiophene positions were incorporated to the structures, because lipophilicity is directly related to the antiaggregant activity[8].

In this paper, we report the synthesis and the preliminary *in vitro* antiplatelet aggregation action of compounds **1(a–w)**.

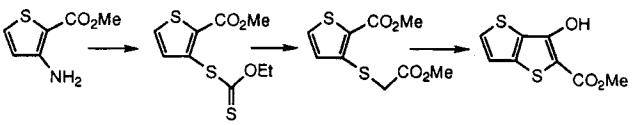
Results and Discussion

Chemistry

The synthesis of these compounds was achieved by two alternative methods (A, B) starting from the epoxy derivatives **3**, which can be obtained by a selective *O*-alkylation of the hydroxy compounds **2**, as depicted in the Scheme.

The starting materials were the alkyl 3-hydroxythiophene-2-carboxylates **2**, which are enol compounds and stable to air, in contrast to 3-hydroxythiophenes without electron-withdrawing groups. This allowed their *O*-alkylation to yield compounds **3**.

Compounds **2(a–v)** were obtained in our laboratory by various methods (see Experimental) and the unknown compound **2w** was synthesized by transformation of methyl 3-aminothiophene-2-carboxylate, through the xanthate derivative into the diester **9** and its cyclization in basic medium to compound **2w**.



9 **2w**

Table 1. New compounds **3** prepared.

Product[a]	Method	Yield (%)	mp °C[b]	Molecular Formula	IR ν (cm^{-1}) CO	^{1}H NMR ($CDCl_3$/TMS)[c] δ, *J* (Hz)
3e	1	79	44–46	$C_{10}H_{12}O_4S$	1710	2.42 (s, 3H, CH_3); 6.57 (s, 1H, H-4 thiophene)
3f	1	37	82–83	$C_{11}H_{14}O_4S$	1720	7.02 (s, 1H, H-4 thiophene), 7.30–7.60 (m, 5H, phenyl)
	2	82				
3h	1	80	94–96	$C_{16}H_{16}O_4S$	1705	2.17 (s, 3H, CH_3); 7.35 (s, 5H, phenyl)
3s	1	55	88–90	$C_{11}H_{12}O_4S_2$	1705	–
	2	40				
3w	2	45	69–70	$C_{11}H_{10}O_4S_2$	1705	7.05 (d, 1H, *J* = 5.9, H-4 thiophene); 7.42 (d, 1H, *J* = 5.9, H-5 thiophene)

[a] All the other compounds **3** are described in a recent paper[9].
[b] Recrystallized from *i*PrOH.
[c] The compounds showed the expected ^{1}H NMR data for the methyne, oxymethylene, thiomethylene, methoxycarbonyl, and epoxy group protons.

Table 2. Compounds **4**·HCl prepared

Product	Yield	mp °C (solvent)	Molecular Formula or Lit. mp (°C)	IR ν (cm^{-1}) NH	OH	CO	[D_6]DMSO or $CDCl_3$, TMS)[a] δ, *J* (Hz)
4a	80	189–191[b]	$C_{13}H_{22}ClNO_4S$	3250	3125	1685	7.17 (d, 1H, *J* = 5.56, H-4 thiophene), 7.84 (d, 1H, *J* = 5.56, H-5 thiophene)[c]
4e	40	136–138[d]	$C_{14}H_{24}ClNO_4S$	3190	3120	1680	6.60 (s, 1H, H-4, thiophene)[c]
4f	74	178–180[d]	$C_{19}H_{26}ClNO_4S$	3350	3200	1690	7.30–7.52 (m, 4H, phenyl); 7.67–7.80 (m, 2H, H-4 thiophene and 1H phenyl)[c]
4g	76	152–154[b]	$C_{15}H_{26}ClNO_4S$	3300	3200	1670	1.95 (s, 3H, CH_3); 2.25 (s, 3H, CH_3)[c]
4h	75	146–148[b]	$C_{20}H_{28}ClNO_4S$	3300	3225	1675	2.10 (s, 3H, CH_3); 7.35 (s, 5H, phenyl)[c]
4k	81	129–130[b]	129–130[2]	3300	3120	1690	–[e]
4l	82	131–133[b]	131–133[2]	3200	3100	1690	–[e]
4m	47	147–149[b]	$C_{19}H_{32}ClNO_4S$	3210	3090	1670	–[e]
4s	54	150–152[b]	$C_{15}H_{24}ClNO_4S_2$	3240	3160	1690	–[e]
4t	47	160–162[b]	$C_{17}H_{28}ClNO_4S_2$	3400	3220	1655	–[e]

[a] All these compounds showed the following common NMR spectroscopic data 1.15–1.55 (s, 9H, $3CH_3$, *t*-Bu); 2.85–3.70 (m, 2H, CH_2N); 3.95–4.67 (m, 3H, OCH_2-CH); 8.65–9.95 (m, 2H, NH_2^+). Besides they show the characteristic signals of methoxycarbonyl, ethoxycarbonyl, and methylene ring protons.
[b] Recrystallized from EtOH/Et_2O.
[c] Recorded on ([D_6]DMSO).
[d] Recrystallized from *i*PrOH.
[e] Recorded on $CDCl_3$ as free amine; the signal corresponding to the NH group was observed in the random 2.37–3.15.

Table 3. Compounds **5**·HCl prepared.

Product	Yield	mp (°C)[a]	Molecular Formula	IR ν (cm^{-1}) NH	OH	CO	^{1}H NMR ([D$_6$]DMSO, TMS)[b] δ, *J* (Hz)
5a	34	182–184	$C_{12}H_{20}ClNO_4S$	3280	3100	1645	7.12 (d, 1H, *J* = 5.47, H-4 thiophene); 7.75 (d, 1H, *J* = 5.47, H-5, thiophene)
5e	62	190–192	$C_{13}H_{22}ClNO_4S$	3300	3090	1650	2.90 (s, 3H, CH_3); 6.90 (s, 1H, H-4 thiophene)
5f	63	216–218	$C_{18}H_{24}ClNO_4S$	3300	3090	1690	7.40–7.50 (m, 3H, H-4 thiophene and 2H phenyl); 7.65–7.82 (m, 3H, phenyl)
5g	98	158–160	$C_{14}H_{24}ClNO_4S$	3375	3100	1675	1.95 (s, 3H, CH_3); 2.25 (s, 3H, CH_3)
5h	46[c]	166–168	$C_{19}H_{26}ClNO_4S$	3400	3200	1670	2.10 (s, 3H, CH_3); 7.35 (s, 5H, phenyl)
5k	82	167–168	$C_{15}H_{24}ClNO_4S$	3340	3090	1650	–
5l	72	158–159	$C_{16}H_{26}ClNO_4S$	3380	3140	1680	–
5m	52	174–176	$C_{17}H_{28}ClNO_4S$	3410	3180	1680	–
5s	56	170–172	$C_{14}H_{22}ClNO_4S_2$	3350	31001	1670	–
5t	58	182–184	$C_{15}H_{24}ClNO_4S_2$	3390	3160	1695	–

[a] Recrystallized from EtOH/Et_2O.
[b] All these compounds showed the following common NMR spectroscopic data: 1.27–1.45 (s, 9H, 3CH_3*t*Bu); 2.85–3.50 (m, 2H, CH_2N); 3.95–4.47 (m, 3H, OCH_2CH); 8.60–9.42 (m, 1H, NH_2^+). They also show the characteristic signals of methoxy and methylene ring protons.
[c] 84% Yield as internal salt.

The selective *O*-alkylation of compounds **2** was carried out by two alternative methods[9] and led to compounds **3(a–w)** (see Experimental and Table 1). These compounds were transformed into the final products **1** via two different routes.

The first route (route A) is the classical pathway and consists in the expoxide opening with *tert*-butylamine to yield compounds **4** followed by removal of the ester group by hydrolysis to obtain compounds **5**, which were thermally decarboxylated to the title compounds **1** (Tables 2–4).

In the second one (route B) the hydrolysis reaction is the first step to yield compounds **6**, which were decarboxylated to the dihydroxy compounds **7** and transformed into the oily epoxy derivatives **8**. Treatment of the latter with *tert*-butylamine yielded the desired compounds **1**.

This route B, which involves more steps than route A, does however have some advantages. First, the fact that the alkoxycarbonyl group is hydrolyzed at the beginning of the reaction sequence in route B avoids the possibility of formation of secondary products by internal cyclization of the amino group and the adjacent ester, as observed in the route A.

Secondly, the isolation of compounds **4** resulting from the hydrolysis reaction in pathway A is difficult and tedious because of their amphoteric nature, while in route B this cannot happen. Besides, the decarboxylation reaction is more efficient in this way because the stability of compounds **6** is generally greater than that of compounds **5**.

The final compounds **1** obtained by these two methods are listed in Table 4 and in the experimental section.

Pharmacology

The results of a preliminary *in vitro* antiplatelet aggregation activity of compounds **1(a–w)** are shown in Table 5. The IC_{50} was calculated for all the compounds against ADP, adrenaline, and collagen.

Most of these compounds show remarkable inhibitory effect against human platelet aggregation *in vitro*. Compound **1f** was most active against the three inducers of platelet aggregation whilst the least active compound was unsubstituted derivative **1a**. This result shows the importance of the substituents on the thiophene nucleus: The presence of a phenyl group in position 5 (**1f**) or the homocycles in positions 4,5 (**1k–q**) gives the highest activity. Moreover, the presence of a chlorine atom seems to have a very positive influence on inhibitory activity, in agreement with previous data[7].

Nevertheless, the presence of methyl groups (**1b**, **1e**, **1g**) or a sulfur atom in the homocyclic (**1r–u**) or heterocyclic derivatives (**1v**, **1w**) are less significant for the activity although they are still more active than the parent compound **1a**.

In homocyclic derivatives the activity increases with the number of methylene links (**1n** > **1m** > **1l** > **1k**), whilst methyl substitution on the homocycle decreases the activity (**1o–q**). Substitution in position 5 of the thiophene nucleus exerts a greater effect than the substitution in the position 4 (**1f** > **1c** or **1e** > **1b**).

The majority of these compounds **1** showed slightly more activity against the aggregation induced by adrenaline than that induced by collagen except for compounds **1c**, **1h**, **1s**, and **1t**. Compounds **1d**, **1f**, **1h**, **1i**, **1j**, **1l**, **1m**, **1n**, **1p**, or **1q** show IC_{50} values even lower than those obtained for acetylsalicylic acid, ticlopidine, and sulfinpyrazone.

Table 4. Compounds **1** prepared.

Product	Method	Yield (%)	Mp (°C)	Molecular formula	IR (ν) (cm^{-1}) NH	OH	CO	^{1}H NMR ([D$_6$]DMSO, TMS) δ, *J* (Hz)
1a	A	57	116–117	$C_{15}H_{23}NO_6S$[a]	3500		1625	6.60 (d, 1H, $J_{2,5}$ = 3.09; $J_{2,4}$ = 1.5, H-2 thiophene); 6.80 (dd, 1H, $J_{4,5}$ = 5.20; $J_{4,2}$ = 1.51, H-4 thiophene); 7.43 (dd, 1H, $J_{5,4}$ = 5.20; $J_{5,2}$ = 3.09, H-5 thiophene)
	B	50	136–238					
1b	B	67	144–146	$C_{16}H_{25}NO_6S$[a]	3375		1640	2.05 (s, 3H, CH_3); 6.02 (d, 1H, *J* = 2.9, H-2 thiophene); 7.15 (d, 1H, *J* = 2.9, H-5 thiophene)
1c	B	79	121–123	$C_{21}H_{27}NO_6S$[a]	3350		1635	6.75–6.80 (m, 1H, H-2 thiophene); 7.32–7.75 (m, 6H, H-5 thiophene and 5H phenyl)
1d	B	53	147–149	$C_{15}H_{22}ClNO_6S$[a]	3475		1630	6.85 (d, 1H, *J* = 2.7, H-2 thiophene); 7.55 (d, 1H, *J* = 2.7, H-5 thiophene)
1e	A	40	124–126	$C_{12}H_{22}ClNO_2S$[b]	3340	3280	1605	6.25–6.37 (m, 1H, H-2 thiophene); 6.47–6.50 (m, 1H, H-4 thiophene)
1f	A	54	150–152	$C_{17}H_{24}ClNO_2S$[b]	3220	3170	1575	6.60 (d, 1H, *J* = 1.5, H-2 thiophene); 7.20 (d, 1H, *J* = 1.5, H-4 thiophene); 7.50–7.65 (m, 5H, phenyl)
1g	A	50	160–162	$C_{13}H_{24}ClNO_2S$[b]	3400	3200	1580	1.87 (s, 3H, CH_3); 2.22 (s, 3H, CH_3); 6.27 (s, 1H, H-2 thiophene)
1h	A	62	148–150	$C_{18}H_{26}ClNO_2S$[b]	3360	3320	1575	2.10 (s, 3H, CH_3); 6.65 (s, 1H, H-2 thiophene); 7.42 (s, 5H, phenyl)
1i	B	53	142–144	$C_{16}H_{24}ClNO_6S$[a]	3650		1630	1.95 (s, 3H, CH_3); 6.47 (s, 1H, H-2 thiophene)
1j	B	61	122–123	$C_{15}H_{21}Cl_2NO_6S$[b]	3350		1625	6.82 (s, 1H, H-2 thiophene)
1k	A	65	164–165	164–165[2]	3350		1570	6.15 (s, 1H, H-2 thiophene)
1l	A	77	159–160	159–160[2]	3340		1590	6.07 (s, 1H, H-2 thiophene)
1m	A	47	147–149	$C_{16}H_{28}ClNO_2S$[b]	3380		1575	6.22 (s, 1H, H-2 thiophene)
	B	67	156–158					
1n	B	43	146–148	$C_{21}H_{33}NO_6S$[a]	3350		1625	6.27 (s, 1H, H-2 thiophene)
1o	B	80	130–132	$C_{19}H_{29}NO_6S$[a]	3350	3250	1560	6.12 (s, 1H, H-2 thiophene)
1p	B	70	136–138	$C_{20}H_{31}NO_6S$[a]	3350		1580	6.35 (s, 1H, H-2 thiophene)
1q	B	75	150–152	$C_{20}H_{31}NO_6S$[a]	3300		1570	6.27 (s, 1H, H-2 thiophene)
1r	B	61	116–118	$C_{17}H_{25}NO_6S_2$[a]	3375	3250	1575	6.50 (s, 1H, H-2 thiophene)
1s	A	21	124–126	$C_{13}H_{22}ClNO_2S_2$[b]	3270		1575	6.57 (s, 1H, H-2 thiophene)
1t	A	74	160–162	$C_{14}H_{24}ClNO_2S_2$[b]	3280		1580	6.47 (s, 1H, H-2 thiophene)
	B	66	118–120					
1u	B	87	176–178	$C_{18}H_{27}NO_6S_2$[a]	3340		1580	6.17 (s, 1H, H-2 thiophene)
1v	B	46	134–136	$C_{18}H_{25}NO_6S_2$[a]	3200		1585	6.17 (s, 1H, H-2 thiophene); 7.70 (s, 1H, H-4 thiophene)
1w	B	73	138–140	$C_{17}H_{23}NO_6S_2$[a]	3350	3275	1625	6.72–6.77 (m, 1H, H-2 thiophene); 7.47 (d, 1H, *J* = 5.4, H-4 thiophene); 7.67 (d, 1H, *J* = 5.4, H-5 thiophene)

[a] Maleate (recrystallized from anhydrous Et_2O).
[b] Hydrochloride (recrystallized from EtOH/Et_2O).

None of the compounds of this series showed better results than acetylsalycilic acid (ASA) in the inhibition of the aggregation induced by collagen but compounds **1f**, **1i**, **1m**, **1n** and **1q** in particular give IC_{50} values in the same range as ASA.

In general, inhibition of the ADP action is smaller than the other two but compounds **1f**, **1h**, **1i**, **1l**, **1m**, and **1h** give better results than ticlopidine, which is a specific inhibitor of ADP aggregation.

In summary, the lipophilic substituents (π values in parentheses)[10] are favourable for the activity in the order Ph (π = 1.80) > Cl (π = 0.68) > homocycles or heterocycles with a sulfur atom > methyl (π = 0.50) > H (π = 0); substitution in position 5 of the thiophenic nucleus seems to be more important than in position 4 and the order in the inhibition power of the series is adrenaline > collagen >> ADP.

All these date suggest the appropriateness of further pharmacological investigation as antithrombotic agents for compounds **1f**, **1h**, **1i**, **1j**, **1l**, **1m**, **1n**, **1p**, and **1q**, and especially for compound **1f**, the best of the series.

Table 5. Inhibition of platelet aggregation.

Product	R^1	R^2	IC_{50} (μg/mL) (95% confid. limits)		
			Adrenaline	Collagen	ADP
1a	H	H	>250	>250	>250
1b	H	Me	68 (62–76)	>250	>250
1c	H	Ph	210 (188–239)	128 (116–142)	232 (211–258)
1d	H	Cl	51 (46–58)	74 (65–85)	186 (166–211)
1e	Me	H	136 (126–148)	225 (188–266)	>250
1f	Ph	H	33 (27–40)	38 (31–49)	52 (46–60)
1g	Me	Me	52 (43–67)	121 (107–139)	>250
1h	Ph	Me	132 (120–145)	64 (57–72)	62 (53–74)
1i	Cl	Me	43 (37–51)	39 (33–45)	83 (76–93)
1j	Cl	Cl	57 (50–65)	68 (61–77)	110 (92–133)
1k	$-(CH_2)_3-$		47 (41–55)	82 (75–90)	75 (66–88)
1l	$-(CH_2)_4-$		43 (38–50)	58 (50–71)	98 (90–108)
1m	$-(CH_2)_5-$		40 (35–47)	47 (41–55)	59 (53–67)
1n	$-(CH_2)_6-$		36 (29–46)	46 (41–53)	63 (50–78)
1o	$-CH(Me)(CH_2)_2-$		77 (71–86)	106 (96–118)	219 (193–251)
1p	$-CH(Me)(CH_2)_3-$		51 (44–60)	94 (83–104)	167 (142–193)
1q	$-(CH_2)_2CH(Me)CH_2-$		47 (42–55)	46 (39–55)	193 (179–199)
1r	$-(CH_2)_2S-$		187 (171–205)	230 (108–255)	>250
1s	$-CH_2SCH_2-$		141 (129–155)	129 (110–151)	185 (159–217)
1t	$-(CH_2)_3S-$		182 (166–199)	132 (119–147)	>250
1u	$-(CH_2)_2SCH_2-$		169 (154–187)	>250	>250
1v	–SCH=CMe–		128 (116–143	>250	209 (181–233)
1w	–CH=CH–S–		82 (73–93)	233 (216–256)	>250
Acetylsalicylic acid (ASA)			64 (58–71)	19 (15–25)	>250
Ticlopidine			106 (99–116)	>250	89 (81–99)
Sulfinpirazone			223 (204–246)	168 (113–185)	>250

Experimental

Chemistry

Microanalyses were performed on a Perkin Elmer 240 analyzer and satisfactory results ±0.4% of calculated values were obtained for the new compounds. Melting points were measured in a Bchi 510 apparatus and are uncorrected. IR spectra were recorded on a Shimadzu-435 IR spectrophotometer and ^1H NMR on a Bruker AM (200 MHz) spectrometer. All the reagents used were of commercial grade and used as such.

The starting compounds **2(a–v)** were prepared according to the literature: **2a**[11], **2b,i**[12], **2c**[13], **2d**[14], **2e**[15], **2g,k,l**[16], **2j**[17], **2m–u**[18], **2v**[19] The unknown compound **2h** was synthesized according to the classical Fiesselmann procedure[20] starting from methyl 2-benzoylpropionate in a 34% yield, m.p. 102–104 °C (MeOH).

*Methyl 3-methoxycarbonylmethylthiophene-2-carboxylate (**9**)*

Methyl 3-aminothiophene-2-carboxylate[11] (9.4 g, 0.06 mol) was added to a vigorously stirred 50% solution of HCl (24 mL). The reaction mixture was stirred at room temp. for 30 min and once cooled below 0 °C (ice-salt bath) and then diazotised with sodium nitrite (4.2 g, 0.06 mol) in water (8.4 mL) keeping the temperature below 0 °C. The resulting diazonium salt was stirred for 1 h at this temperature and a stirred solution of K_2CO_3 (8.25 g, 0.071 mol) and potassium ethylxantate (9.6 g, 0.06 mol) in water (100 mL) heated at 60 °C was added. The reaction mixture was kept at 60–70 °C, until the N_2 release ceased, was cooled and extracted with ether. The organic phase was washed with a 10% NaOH solution and after with water, dried over Na_2SO_4 and the solvent was evaporated at reduced pressure. The red oily residue obtained was used in nex reaction without further purification.

To a solution of this oil (3.20 g, 0.013 mol) in dry THF (35 mL) and in ethylendiamine (3.0 mL), ethyl chloroacetate (3.0 mL) was added with external cooling. The reaction mixture was left at room temperature for 1 h with stirring, whereupon iced water was added to the reaction mass and after was acidified with a 17% HCl solution. The oil formed was extracted with EtOAc, dried over Na_2SO_4, the solvent was evaporated and the residue was crystallized from methanol: yield 6.19 g (42%); mp 62–64 °C (MeOH). Anal. ($C_9H_{10}S_2O_4$); IR (nujol, ν): 1760, 1745 (C=O); ^1H NMR ($CDCl_3$, δ): 3.70 (s, 3H, OCH_3); 3.80 (s, 2H, SCH_2); 3.85 (s, 3H, OCH_3); 7.12 (d, 1H, J = 5.9 Hz, H-4 thiophene); 7.52 (d, 1H, J = 5.9, H-5 thiophene).

*Methyl 3-Hydroxythieno[3,2-b]thiophene-2-carboxylate (**2w**)*

Compound **9** (24.6 g, 0.1 mol) was added to a 2N solution of NaOMe in MeOH (175 mL) under a N_2 atmosphere. The reaction mixture was left for 1 day under these conditions and the solvent was then evaporated. Iced water

(175 mL) was added and the mixture was acidified with a 2N solution of HCl until pH 1, with external cooling. The product obtained was extracted with ether, washed with water and dried over Na_2SO_4. The solvent was evaporated to dryness and the residue was purified by crystallization to yield 13.7 g (64%) of a colorless solid. mp 80–81 °C (MeOH); Anal. ($C_8H_6S_2O_3$). IR (nujol, ν) 3275 (OH); 1660 (CO); ^{1}H NMR ($CDCl_3$, δ): 3.90 (s, 3H, OCH_3); 7.17 (d, 1H, J = 6.0 Hz, H-6 thiophene); 7.60 (d, 1H, J = 6.0 Hz, H-5 thiophene), 10.05 (s, 1H, OH).

*Alkyl 3-(2,3-Epoxy)propoxythiophene-2-carboxylates (**3**)*

Compounds **3a-d**, **3g**, **3i–r**, and **3t–u** were synthesized by these methods and are described in the literature[9].

Method 1

Epichlorohydrin (2.3 g, 0.024 mol) was added dropwise to a stirred solution of the corresponding 3-hydroxythiophene-2-carboxylate (**2e**, **2f**, **2h** and **2s**; 0.01 mol), *tert*-BuOK (1.4 g, 0.012 mol) in DMSO (17 mL). The reaction mixture was heated at 100 °C for 2–3 h and after cooling at room temperature the solvent was distilled off at 0.1 Torr. The residue was extracted with hot *n*-hexane, the solvent evaporated and the epoxy derivatives **3**, formed were purified by crystallization from *i*PrOH (Table 1).

Method 2

Anhydrous K_2CO_3 (1.4 g, 0.01 mol) was added to a stirred solution of the corresponding 3-hydroxythiophene-2-carboxylate (**2f**, **2s** and **2w;** 0.01 mol). in ethyl methyl ketone (30 mL) and the stirring was continued for 10 min until the potassium salts of the hydroxy compounds **2** were formed. Then epibromhydrin (1.9 g, 0.013 mol) was added and the mixture was heated at reflux temp. for 2 d. The solvent was evaporated, cold water (20 mL) was added and the mixture was extracted with EtOAc (25 mL) and dried over Na_2SO_4. The solvent was distilled off and the epoxy derivatives **3** formed were crystallized from *i*PrOH (Table 1).

*Alkyl 3-(3-tert-Butylamino-2-hydroxy)propoxythiophene-2-carboxylates (**4**)*

tert-Butylamine (10 mL) and a little amount of *i*PrOH (1 mL) was added to the corresponding epoxy derivative **3** (**3a**, **3e–h**, **3k–m**, **3s–t**; 0.01 mol). The reaction mixture was left at room temperature until the reaction advance finished (followed by TLC) and then evaporated to dryness at reduced pressure. The residue was dissolved in absolute EtOH and treated with ethereal hydrogen chloride to yield compounds **4**, which were isolated as hydrochlorides (Table 2).

*3-(3-tert-Butylamino-2-hydroxy)propoxythiophene-2-carboxylic Acids (**5**)*

A suspension of the adequate compounds **4**·HCl (**4a**, **4e–h**, **4k–m**, **4s–t**; 0.01 mol) in a 1N NaOH aqueous solution was heated under reflux until total dissolution had occurred. After cooling to room temp. the alkaline hydrolysis solution was acidified with a 1N aqueous solution of HCl to the isoelectric point. The product formed was extracted with $CHCl_3$, the organic phase was dried over Na_2SO_4 and the solvent evaporated to dryness. The residue was identified as the internal salt and converted in the hydrochloride, by its solution in absolute EtOH and treatment with the exact stoichiometric volume of standard 1N HCl solution. The solvent was removed and the residue was crystallized from EtOH/Et_2O (Table 3).

*3-(2,3-Dihydroxy)propoxythiophene-2-carboxylic Acids (**6**)*

Compounds **6a–d**, **6g**, **6i–r**, and **6t–v** are described in the literature[9] and were synthesized by the same method than that used for the synthesis of **6w**.

*3-(2,3-Dihydroxy)propoxythieno[3,2-b]thiophene-2-carboxylic acids (**6w**)*

A suspension of the epoxy derivative **3w** (2.14 g; 0.01 mol) in aqueous 1N NaOH (15 mL) was refluxed until total disolution. The mixture was then cooled and acidified with an aqueous 5% HCl solution with external cooling until acid pH and was extracted with EtOAc (25 mL). The organic layer was dried (Na_2SO_4), the solvent was evaporated and the residue was purified by crystallization from EtOAc to yield 2.57 g (94%) of a colorless solid. m.p. 136–137 °C. Anal. ($C_{10}H_{10}S_2O_5$). IR (nujol, ν) 3400-3200 (OH); 1540 (CO). ^{1}H NMR ([D_6]DMSO, δ): 3.45 (d, 2H, J = 4.5 Hz, CH_2OH); 3.70–3.72 (m, 1H, $CHOH$); 4.27–4.40 (m, 2H, OCH_2); 7.40 (d, 1H, J = 5.7 Hz, H-4 thiophene); 7.90 (d, 1H, J = 5.1 Hz, H-5 thiophene).

*3-(3-Thienyloxy)-1,2-propanediols (**7**)*

Compounds **7a–d**, **7g**, **7i–4r**, and **7t** are described in the literature[9] and were synthesized by the same method than that used for the synthesis of **7w**.

*3-(3-Thieno[3,2-b]thienyloxy)-1,2-propanediol (**7w**)*

Compound **6w** (2.74 g, 0.01 mol) was heated at 165 °C under reduced pressure (0.1 Torr.) in a Kugelrohr apparatus for 20 min, to yield 1.38 g (60%) of a colorless solid. m.p. 81–83 °C (EtOAc). Anal. ($C_9H_{10}S_2O_3$). IR (nujol, ν); 3350–3100 (OH). ^{1}H NMR ([D_6]DMSO, δ): 3.25–3.42 (m, 2H, CH_2OH), 3.77–4.07 (m, 3H, OCH_2-CH-OH); 4.62 (t, 1H, J = 5.9 Hz, OH-3); 4.95 (d, 1H, J = 4.5 Hz, OH-2); 6.65 (d, 1H, J = 1.5 Hz, H-2 thiophene); 7.30 (d, 1H, J = 4.5 Hz, H-4 thiophene); 7.60 (dd, 1H, J = 4.5 Hz; J = 1.5 Hz, H-5 thiophene).

*3-(3-Thienyloxy)-1,2-epoxypropanes (**8**)*

Compounds **8a–d**, **8g**, **8i–r**, and **8t–v** are described in the literature[9] and were synthesized by the same method than that used for the synthesis of **8w**.

*3-(3-Thieno[3,2-b]thienyloxy)-1,2-epoxypropane (**8w**)*

p-Toluenesulfonyl chloride (1.9 g, 0.01 mol) was added at 0 °C to a stirred solution of 3-(3-thieno[3,2-b]thienyloxy)-1,2-propanediol (**7w**, 2.30 g, 0.01 mol) in anhydrous py (22.5 mL). The reaction mixture was left for 1 d. at room temp. and then a solution of H_2SO_4 (8.7 mL) in water (50 mL) was added cooling with an ice-bath. The organic layer was separated and the aqueous one was extracted with EtOAc (30 mL). The organic extracts were dried (Na_2SO_4) and evaporated at reduced pruessure to afford the two possible monotosyl derivatives (two spots in TLC) as an oil that was not purified.

This oil was dissolved in DMSO (7.6 mL) and a 20% aqueous solution of NaOH (3.8 mL) was added. The reaction mixture was stirred for 30 min, whereupon water (7.6 mL) was added. The resulting solution was extracted with EtOAc (30 mL), and the organic extract was dried (Na_2SO_4) and evaporated to dryness to yield compound **8w** as an oil that was purified by chromatography on a silica gel column using (hexane/EtOAc) (10/1) as eluent. Anal. ($C_9H_8S_2O_2$). ^{1}H NMR ($CDCl_3$, δ): 2.70–2.97 (m, 2H, CH-CH_2), 3.27–3.47 (m, 1H, CH); 4.02 (dd, 1H, J = 11.9 Hz, 5.9 Hz, OCH_2); 4.30 (dd, 1H, J = 11.9 Hz; 4.5 Hz, OCH_2); 6.37 (d, 1H, J = 2.25 Hz, H-2 thiophene); 7.15 (dd, 1H, J = 4.5 Hz; 2.25 Hz, H-4 thiophene); 7.27 (dd, 1H, J = 4.5 Hz; 1.5 Hz, H-5 thiophene).

*1-tert-Butylamino-3-(3-thienyloxy)-2-propanols (**1**)*

Method A

The hydrochlorides of compounds **5a**, **5e–h**, **5k–m**, and **5s–t** were decarboxylated by treating at 220 °C for approximately 30 min under reduced pressure (0.1 Torr) until CO_2 evolution had ceased. The residue was purified by crystallization from EtOH/Et_2O to yield in the corresponding compound **1**·HCl (Table 4).

Method B

tert-Butylamine (10 mL) and a little amount of *i*PrOH (1 mL) was added to the corresponding epoxyderivative **8** (**8a–d**, **8i**, **j**, **8m–r**, and **8t–w**, 0.01 mol). The reaction mixture was left at room temp. until the reaction advance finished (followed by TLC) and then evaporated to dryness at reduced pressure to yield oils. Maleic acid (0.01 mol) dissolved in EtOH was added and the corresponding maleates crystallized by dilution with anhydrous Et_2O (Table 4).

Pharmacology

Platelet Preparation

Blood was obtained from fasted healthy human male donors, 20–40 years of age, not exposed to any drug for a period of at least three weeks. Blood samples were withdrawn from the anticubital vein and rapidly mixed with trisodium citrate 3.8%, one part of citrate to nine parts of blood.

Platelet rich plasma (PRP) and platelet poor plasma (PPP) were obtained by centrifugation of the anticoagulated blood at room temp. and mixed to obtain a final platelet count of 250.000 platelet/mm^3.

Platelet Aggregation

The aggregation studies were performed between 1 h and 2 h after venipuncture.

Aggregations were performed at 37 °C on a dual channel aggregometer (Labor) and recorded, following the photometric Born method[21]. Stirring speed was 600 rpm and velocity of paper 2 cm/min In order to test inhibition of platelet aggregation the compounds were added to the cuvette 2 min before addition of ADP, adrenaline or collagen at the lowest concentration necessary to produce irreversible aggregation. An initial and final control of platelet aggregation was performed. The aggregation tracings were compared to those of controls incubated with equivalent amounts of the same vehicle in which the drug was dissolved.

The compounds were tested at increasing doses from 1 mg/mL to 250 µg/mL during 10 experiences. The dose-response curves were constructed and the IC_{50} (concentration inhibiting 50% of aggregation) calculated[22].

Drugs

The drugs used were ADP, adrenaline, collagen, acetylsalicylic acid, ticlopidine and sulfinpyrazone.

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