Platelet Antiaggregant Methoxyphenylthienyl Ketoxime Ethers: Synthesis and Structure–Activity Relationships

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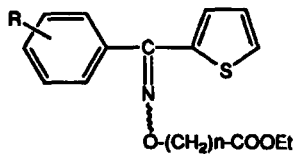
Some new oximinoalkanoic (n = 2,3,4) esters and acids derived from methoxyphenylthienyl ketones have been synthesized and evaluated *in vitro* for their inhibitory effects on arachidonic acid-induced human platelet aggregation. Of the eighteen oximinoethers tested the most active derivatives, which were four times more active as aspirin, belonged to the *para* methoxy series with Z configuration and n = 2 or 3.

Thrombocyten-aggregationshemmende Methoxyphenylthienyl-Ketoxim-Ether: Synthese und Strukutur-Wirkungs-Beziehungen

Eine Reihe von neuen Oximinocarbonnsäureestern (n = 2, 3, 4) und -säuren, strukturverwandt mit Methoxyphenylthienyl-Ketonen wurde synthetisiert und deren Hemmwirkung *in vitro* auf die Arachidonsäure-induzierte menschliche Blutplättchenaggregation bewertet. Im Vergleich zu der Hemmwirkung von Aspirin, wird gezeigt, daß unter den achtzehn geprüften Oximinoethern, die wirksamsten Verbindungen 4 mal so wirksam wie Aspirin waren. Sie weisen eine Methoxygruppe in *para*-Stellung mit *Z*-Konfiguration und n = 2 oder 3 auf.

In recent years, some oximinoethers have received attention as potential platelet aggregation inhibitors [1–4]. A series of reports from our laboratory has documented the *in vitro* human platelet antiaggregant potential in aryl thienyl ketones [5–7]. In continuing endeavors to obtain this biological effect, we present in this work results on the synthesis, pharmacological activity, and structure-activity relationships of some new methoxyphenylthienyl ketoxime ethers according to the general formula presented in Fig. 1.



R = OCH_3 (ortho, meta, para)
n = 2,3,4

Figure 1

Chemistry

The synthesis of title compounds is outlined in Fig. 2. Reaction of the thienyl methanone **1** with hydroxylamine hydrochloride and sodium hydroxide in aqueous ethanolic solution afforded a mixture of the *E* and *Z* oxime isomers (**2** and **3**) which have been isolated by preparative HPLC. Each *E* or *Z* oxime isomer was treated with appropriate ethyl bromoalkanoate and potassium carbonate in *N,N*-dimethylformamide solution to afford the corresponding ethyl oximinoalkanoates (*E*: **4–6**; *Z*: **7–9**). Subsequent saponification with potassium hydroxide, at room temp. in ethanolic solution, gave the expected acids (*E*: **10–12**; *Z*: **13–15**).

Structure Determination

The structures of the two series of prepared compounds were ascertained by ^1H- and ^{13}C NMR spectroscopy. Chemical shift assignments of the nuclei of oximes **2a–c** and **3a–c** and acids **11a–c** and **14a–c** (n = 3) [8] are securely attributed by extensive use of heteronuclear 2D correlation experiments HMQC [9] and HMBC [10] (Bruker AMX 500 spectrometer). The ^1H- and ^{13}C NMR chemical shifts and coupling constant values for the derivatives depicted in Fig. 3 are listed in Tables 1 and 2.

It is worthy of note that, in the oxime series **2a–c** and **3a–c**, carbon 1 in the *E* isomers appears 3.2–4.6 ppm upfield to that of the corresponding *Z* isomers, and carbon 8 in the *E* isomers appears 8.1– 8.9 ppm downfield to that of the corresponding *Z* isomers (Table 2). The ability to distinguish between *E* and *Z* isomer series lies in the shielding effect of the oxime oxygen on the α carbon when this oxygen is *syn* to the said carbon [11,12]. The configurations of the ethers **11a–c** and **14a–c** were deduced from their isolated parents *E* or *Z* starting oximes under our experimental conditions, and were confirmed for each separated ether using similar ^{13}C shifts (Table 2).

Additionally, carbon 9 and carbon 11 of *Z* isomers appear 1.5–4.3 and 3.0–3.4 ppm, respectively, further downfield with respect to the *E* series whereas carbon 10 is 1.3–2.2 ppm further upfield. These values agree well with those described for other thienyl oxime derivatives [13]. As previously observed [14], the configurations of starting oximes **2a–c** and **3a–c**, under basic conditions for alkylation (**2** → **4–6** and **3** → **7–9**) and under conditions for alkaline hydrolysis (**4–6** → **10–12** and **7–9** → **13–15**), are stable (no isomerization).

Results and Discussion

The compounds were evaluated *in vitro* for their inhibitory effects on arachidonic acid (AA) induced human platelet aggregation. The results, expressed as the concentration required to inhibit by 50 % the threshold aggregating concentration of AA, are reported in Table 3. Each compound was studied by comparison with acetylsalicylic acid (ASA).

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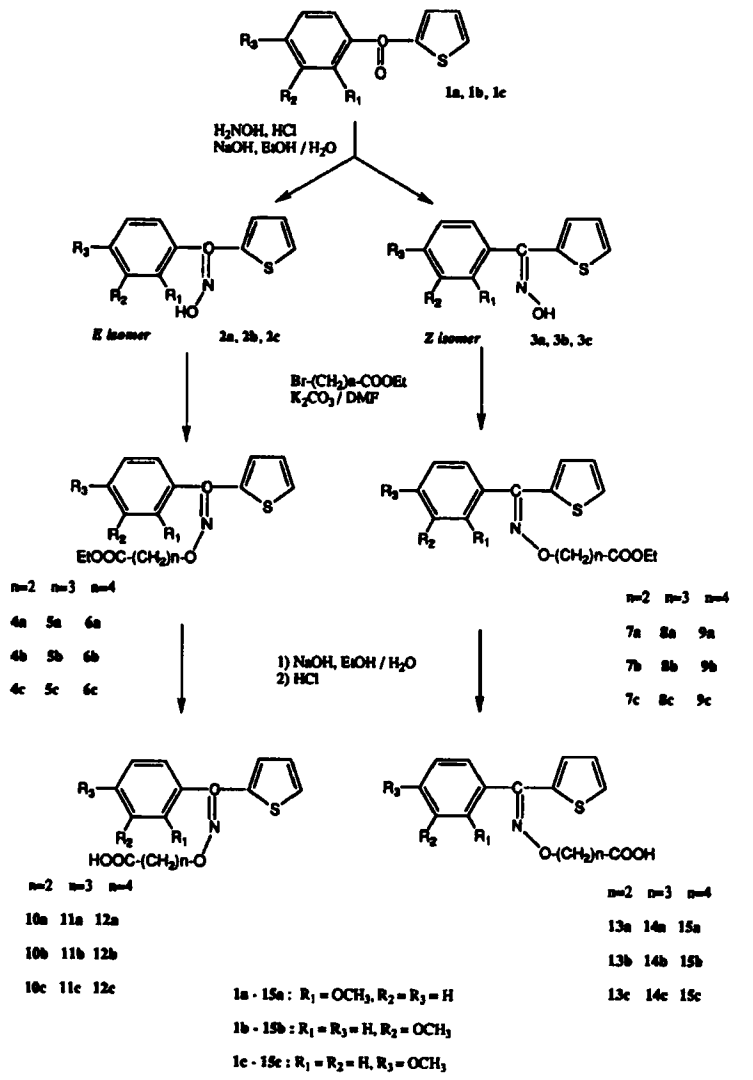

Figure 2

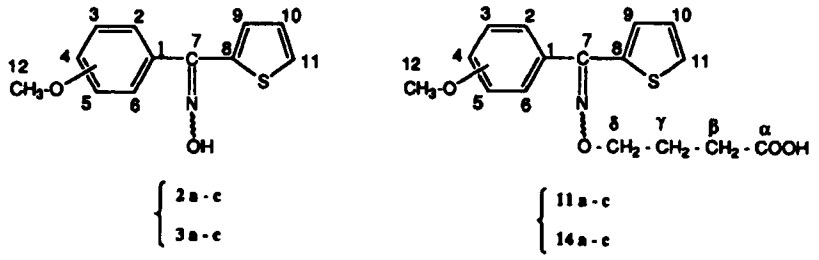

Figure 3

We concentrated on examining structure–activity relationships on modifications of three structural features (refer to Fig. 1):

- position of the methoxy substituent on the aromatic ring;
- influence of *E* or *Z* configuration of oxime group;
- length of the polymethylene linkage between the carboxylic group and the ether-oxygen.

As shown in Table 3, derivative **3b** demonstrated a very weak inhibitory effect and compounds **2a**, **3a**, **2b**, **2c**, and **3c** were inactive. This finding showed that the free oxime group was ineffective, irrespective of conformation. Thus, transformation of ketone **1c** (four-fold more active than ASA [5]) to oxime **2c** cancelled the inhibitory effect. The antiaggregant activity of the other ketones **1a** and **1b** could not be evaluated because of their complete insolubility either in dimethyl sulfoxide or other solvents suitable for human platelet aggregation assay.

Table 1. 500 MHz ^{1}H NMR chemical shifts [a] and coupling constants (Hz) [b] for compounds **2a–c**, **3a–c**, **11a–c**, and **14a–c** in [D$_6$]DMSO.

Proton	2	3	4	5	6	9	10	11	12
2a	–	7.10 d (7.7)	7.41 br t (7.7)	7.02 t (7.7)	7.12 d (7.7)	7.46 d (5.0)	6.95 dd (5.0–3.6)	6.61 d (3.6)	3.70 *s*
3a	–	7.12 d (7.6)	7.45 ddd (7.6-7.6-1.8)	7.02 t (7.6)	7.24 dd (7.6–1.8)	7.70 d (5.1)	7.01 dd (5.1–3.8)	6.81 d (3.8)	3.67 *s*
2b	6.91 br s	–	7.01 dd (7.8-2.6)	7.39 t (7.8)	6.92 m	7.49 d (5.1)	6.99 dd (5.1–3.7)	6.75 d (3.7)	3.76 *s*
3b	7.01 br s	–	7.03 m	7.36 t (7.8)	7.03 m	7.78 d (5.1)	7.09 dd (5.1–3.8)	7.13 d (3.8)	3.81 *s*
2c	7.36 m[c] (11.8)[d]	7.01 m[c] (11.8)[d]	–	7.01 m[c]	7.36 m[c]	7.47 d (5.0)	6.99 dd (5.0–3.5)	6.78 d (3.5)	3.79 *s*
3c	7.42 m[c] (10.7)[d]	6.98 m[c] (10.7)[d]	–	6.98 m[c]	7.42 m[c]	7.74 d (5.1)	7.07 dd (5.1–3.4)	7.14 d (3.4)	3.78 *s*
11a	–	7.13 d (7.7)	7.43 br t (7.7)	7.03 t (7.7)	7.13 d (7.7)	7.53 d (5.0)	6.98 dd (5.0–3.4)	6.68 d (3.4)	3.71 *s*
14a	–	7.13 d (7.9)	7.47 br t (7.9)	7.03 t (7.9)	7.25 d (7.9)	7.78 d (5.1)	7.04 dd (5.1–3.9)	6.86 d (3.9)	3.68 *s*
11b	6.90 br s	–	7.03 d (7.8)	7.40 t (7.8)	6.91 m	7.59 d (5.0)	7.01 dd (5.0–3.5)	6.80 d (3.5)	3.78 *s*
14b	7.01 br s	–	7.02 m	7.38 t (7.8)	7.03 m	7.88 d (5.0)	7.13 dd (5.0–3.9)	7.15 d (3.9)	3.78 *s*
11c	7.34 m[c] (10.8)[d]	7.02 m[c] (10.8)[d]	–	7.02 m[c]	7.34 m[c]	7.55 d (5.0)	7.01 dd (5.0–3.6)	6.83 d (3.6)	3.80 *s*
14c	7.41 m[c] (10.7)[d]	7.00 m[c] (10.7)[d]	–	7.00 m[c]	7.41 m[c]	7.85 d (5.1)	7.11 dd (5.1–3.8)	7.14 d (3.8)	3.80 *s*

Proton:	N-OH	Proton:	COOH	Hβ	Hγ	Hδ
2a	11.10, s	**11a**	12.04, br s	2.23, t, (7.2)	1.79, quint, (7.0)	4.04, t, (6.3)
3a	12.02, s	**14a**	12.10, br s	2.44, t, (7.4)	1.97, quint, (7.0)	4.27, t, (6.3)
2b	11.30, s	**11b**	12.05, br s	2.25, t, (7.4)	1.83, quint, (7.0)	4.08, t, (6.3)
3b	12.20, s	**14b**	12.11, br s	2.41, t, (7.4)	1.96, quint, (7.0)	4.28, t, (6.3)
2c	11.20, s	**11c**	12.05, br s	2.27, t, (7.4)	1.88, quint, (7.0)	4.08, t, (6.4)
3c	12.09, s	**14c**	12.12, br s	2.41, t, (7.4)	1.97, quint, (7.0)	4.27, t, (6.4)

[a] Assigned by HMQC, HMBC, and COSY experiments. [b] Values in brackets. [c] AA'BB' system. [d] w ½

Table 2. 125 MHz ^{13}C NMR data [a] for compounds **2a–c**, **3a–c**, **11a–c**, and **14a–c** in [D_6]DMSO.

Carbon	2a	3a	2b	3b	2c	3c	11a	14a	11b	14b	11c	14c
1	122.3	125.5	133.9	137.9	124.4	129.0	121.8	124.6	133.6	137.0	124.1	128.0
2	156.1	157.5	114.1	114.3	130.2	130.2	155.4	157.4	113.8	114.6	130.2	130.3
3	111.6	111.6	158.9	158.9	113.4	113.6	111.5	111.6	158.9	159.0	113.5	113.6
4	130.1	130.2	114.2	114.4	159.4	159.3	130.3	130.5	114.6	114.7	159.7	159.9
5	120.2	120.2	129.3	129.2	113.4	113.6	120.2	120.2	129.4	129.3	113.5	113.6
6	129.2	130.8	120.7	121.2	130.2	130.2	128.8	130.8	120.4	121.4	130.2	130.3
7	149.4	147.4	151.2	149.4	150.4	149.3	149.5	148.0	152.0	150.1	151.8	146.9
8	140.6	132.5	140.5	131.8	141.2	132.3	139.3	132.1	139.2	131.6	139.9	131.9
9	127.0	130.2	127.2	130.9	127.1	130.2	127.2	131.5	129.0	132.3	128.8	130.3
10	127.0	125.5	127.2	125.6	127.7	125.5	127.2	125.9	127.3	125.9	127.2	125.9
11	127.0	130.2	127.9	130.9	127.7	130.9	128.2	131.5	129.4	132.4	128.8	132.2
12	55.4	55.3	55.1	55.1	55.1	55.1	55.4	55.4	55.1	55.1	55.1	55.1
α	–	–	–	–	–	–	174.1	174.0	173.9	174.0	174.0	173.9
β	–	–	–	–	–	–	29.7	30.2	29.9	30.3	30.1	30.2
γ	–	–	–	–	–	–	24.4	24.3	24.2	24.3	24.3	24.3
δ	–	–	–	–	–	–	72.6	73.3	72.9	73.6	72.9	73.4

[a] Assignments based on the HMQC and HMBC experiments.

Table 3. *In vitro* platelet anti-aggregating activity [5].

Compounds	Inhibition of AA induced platelet aggregation (a) IC_{50} (μM)	Potency relative to ASA
ortho methoxy series		
E isomers		
2a	(b)	0
10a	(b)	0
11a	(b)	0
12a	(b)	0
Z isomers		
3a	(b)	0
13a	(b)	0
14a	(b)	0
15a	(b)	0
meta methoxy series		
E isomers		
2b	(b)	0
10b	720	0.30
11b	1500	0.15
12b	(b)	0
Z isomers		
3b	720	0.30
13b	375	0.60
14b	560	0.40
15b	720	0.30
para methoxy series		
E isomers		
2c	(b)	0
10c	(b)	0
11c	(b)	0
12c	(b)	0
Z isomers		
3c	(b)	0
13c	55	4
14c	55	4
15c	110	2
Acetylsalicylic acid (ASA)	225	1

(a) Values mentioned are the mean of three experiments. (b) No activity.

The oximinoethers, in the *ortho* series, *i.e.* compounds **10a–12a** and **13a–15a** were all inactive.

In the *meta* series, *Z* isomers **13b** and **14b** were more active than oxime **3b**, whereas **15b** showed the same inhibition as starting oxime **3b**. The *E* isomers **10b** and **11b** were, however, slightly inhibiting and **12b** was as inactive as the oxime **2b**. These results indicated that *Z* isomers were more potent platelet anti-aggregating than *E* isomers. On the other hand, it was interesting to note that extension of the polymethylene chain by one carbon atom (**10b** to **11b** and **13b** to **14b**) resulted in a slight lowering of potency. A further lengthening of the chain by incorporating two methylene groups (**10b** to **12b** and **13b** to **15b**) resulted in still lower activity.

In the *para* series, the *E* isomers **10c–12c** were completely inactive. In contrast, the *Z* isomer **15c** (4 methylene groups) showed good potency in inhibiting platelet aggregation: it is about twice as active as ASA. The presence of two or three methylene groups in the oximinoether chain led to a marked increase in antiaggregant activity. So, compounds **14c** and **13c** are about four times more potent than ASA itself.

Conclusion

The *E* isomers were inactive in the *ortho* and *para* methoxy series and gave only a very weak inhibition of platelet aggregation in the *meta* series.

By comparing the inhibitory activities in the *Z* series of the positional isomers on the benzene ring, the potency decreased in order para > meta > ortho. So, among the eighteen tested oximinoethers, the most active derivatives belonged to the *para* methoxy series with *Z* configuration. Interestingly, in this series of compounds, the distance n between the carboxylic group and the ether-oxygen appears to have a significant influence: compounds **13c** (n = 2) and **14c** (n = 3) are two times more active than compound **15c** (n = 4). To the best of our knowledge, this work is the first example of configuration-dependent platelet antiaggregant activity of oxime ethers.

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Experimental Part

Chemistry

Mp: open capillary tubes on an electrothermal digital melting point apparatus (uncorr.) Separation of isomers by preparative HPLC, Waters Associates Prep LC system 500, silica gel. IR spectra: Shimadzu IR 470 (KBr).– ^{1}H NMR spectra: Varian EM 360 L, 60 MHz, Bruker AMX 500, 500 MHz. ^{13}C NMR spectra: Bruker AMX 500, 125 MHz; δ = (ppm), TMS as internal standard. Elemental analyses were carried out by the Service central de microanalyse du CNRS (Vernaison, France) and were within ± 0.4 % of the calculated values except where otherwise stated (oily compounds).

(2-Methoxyphenyl)(2-thienyl) methanone (**1a**)

(2-Hydroxyphenyl)(2-thienyl) methanone: To a stirred solution of 2-methoxybenzoic acid (15.2 g, 100 mmol) in dry dichloromethane (100 mL) at room temp. under nitrogen, was added dropwise a solution of oxalyl chloride (16.2 mL, 200 mmol) in dry dichloromethane (50 mL) over a 30 min period. After the addition was complete, the reaction mixture was stirred for 12 h. To this solution cooled at 0 °C was added slowly thiophene (10 mL, 120 mmol), then anhydrous aluminum chloride (20 g, 150 mmol) in small portions, with vigorous stirring. The reaction mixture was refluxed for 2 h and cooled, then poured into ice– hydrochloric acid. Hydrolysis was continued for an hour and the reaction mixture was extracted with dichloromethane. The dried extract (Na_2SO_4) was concentrated *in vacuo* and purified by silica gel column chromatography (CC) (diethyl ether–hexane, 60:40). The resulting residue treated with boiling hexane gave an orange-colored oil (18.7 g, 92 %), which was used without further purification. IR (KBr): ν = 1620 cm^{-1} (C=O), 3150 (OH).– ^{1}H NMR ([D$_6$]DMSO): δ = 11.65 (s, 1H, exchangeable with D_2O), 8.15–6.65 (m, 7H).

Methylation of (2-hydroxyphenyl)(2-thienyl) methanone: To a stirred solution of (2-hydroxyphenyl)(2-thienyl) methanone (16.4 g, 80 mmol) in 50 % aqueous ethanol (300 mL), heated at 60 °C, was added sequentially sodium hydroxide (6.4 g, 160 mmol) in water (30 mL) and dimethyl sulfate (15.2 mL, 160 mmol). The reaction mixture was heated to reflux for 30 min. After distillation of ethanol, cooling in ice water, the residue was extracted three times with diethyl ether. The combined org. layers were washed with water, dried over sodium sulfate, and concentrated *in vacuo*. The residue was chromatographed using dichloromethane as eluent to give **1a** (20 g, 92 %) as a colorless oil. IR (KBr): ν = 1640 cm^{-1} (C=O).– ^{1}H NMR ([D$_6$]DMSO): δ = 7.65–6.75 (m, 7H), 3.65 (s, 3H).

(3-Methoxyphenyl)(2-thienyl) methanone (**1b**). Following the procedure described for the synthesis of (2-hydroxyphenyl)(2-thienyl) methanone, reaction of 3-methoxybenzoic acid (15.2 g, 100 mmol) with oxalyl chloride (16.2 mL, 200 mmol) and thiophene (10 mL, 120 mmol), followed by chromatography (hexane–diethyl ether, 50:50) produced **1b** (19.8 g, 91 %) as a light yellow oil. IR (KBr): ν = 1630 cm^{-1} (C=O).– ^{1}H NMR ([D$_6$]DMSO): δ = 8.05–6.85 (m, 7H), 3.80 (s, 3H).– Anal. ($C_{12}H_{10}O_2S$) C, H, S.

(4-Methoxyphenyl)(2-thienyl) methanone (**1c**) was prepared as previously described [5].

Synthesis of aryl (2-thienyl) ketone oximes (**2** *and* **3**)

(2-Methoxyphenyl)(2-thienyl) methanone oxime (**2a** + **3a**) was prepared as previously described [15] in 94 % yield (mixture of *E* and *Z* isomers). The mixture was purified by silica gel CC (hexane–diethyl ether, 90:10) to give the *E* isomer **2a**; yield 20 %, mp 152 °C (hexane).– ^{1}H NMR: see Tables 1 and 2, and the *Z* isomer **3a**; yield 80 %, mp 173 °C (hexane).– NMR: see Tables 1 and 2.– Anal. ($C_{12}H_{11}NO_2S$) C, H, N, S.

(4-Methoxyphenyl)(2-thienyl) methanone oxime (**2c** + **3c**) was prepared as previously described [16] in 83 % yield (mixture of *E* and *Z* isomers). The mixture was purified by preparative HPLC using hexane–diethyl ether (80:20) as eluent to give the *E* isomer **2c**; yield 33 %, mp 144 °C (hexane).– NMR: see Tables 1 and 2, and the *Z* isomer **3c**; yield 67 %, mp 128 °C (hexane).– NMR: see Tables 1 and 2.– Anal. ($C_{12}H_{11}NO_2S$) C, H, N, S.

(3-Methoxyphenyl)(2-thienyl) methanone oxime (**2b** + **3b**) was obtained from **1b** in the same manner as (**2c** + **3c**) in 91 % yield (mixture of *E* and *Z* isomers). The mixture was separated by HPLC using hexane– diethyl ether (80:20) as eluent to give the *E* isomer **2b**; yield 25 %, mp 122 °C (hexane).– NMR: see Tables 1 and 2, and the *Z* isomer **3b**; yield 75 %, mp 79°C (hexane).– NMR: see Tables 1 and 2.– Anal. ($C_{12}H_{11}NO_2S$) C, H, N, S.

Synthesis of aryl (2-thienyl) ketoxime ethers

Compounds with an ester group (**4–9**)

Each ketoxime ester (**4–9**) was used without further purification to obtain the carboxylic derivatives (**10–15**).

Elemental Analyses

Compounds	Theoretical values (%)				Experimental values (%)			
	C	H	N	S	C	H	N	S
2a	61.78	4.75	6.01	13.74	61.68	4.74	5.96	13.69
10a	59.00	4.95	4.59	10.50	58.60	4.90	4.64	10.05
11a	60.17	5.36	4.38	10.04	60.17	5.42	4.29	9.89
12a	61.24	5.74	4.20	9.62	60.93	5.71	4.28	9.55
3a	61.78	4.75	6.01	13.74	61.75	4.77	5.97	13.65
13a	59.00	4.95	4.59	10.50	59.10	4.92	4.63	10.42
14a	60.17	5.36	4.38	10.04	59.75	5.40	4.68	10.17
15a	61.24	5.74	4.20	9.62	61.21	5.75	4.17	9.56
2b	61.78	4.75	6.01	13.74	61.77	4.76	5.99	13.72
10b	59.00	4.95	4.59	10.50	58.94	4.92	4.65	10.45
11b	60.17	5.36	4.38	10.04	60.47	5.59	4.02	9.77
12b	61.24	5.74	4.20	9.62	60.89	5.85	4.13	9.41
3b	61.78	4.75	6.01	13.74	61.82	4.71	6.04	13.69
13b	59.00	4.95	4.59	10.50	58.79	4.82	4.48	10.31
14b	60.17	5.36	4.38	10.04	59.73	5.38	4.15	10.00
15b	61.24	5.74	4.20	9.62	60.91	5.82	4.15	9.44
2c	61.78	4.75	6.01	13.74	61.80	4.74	6.03	13.71
10c	59.00	4.95	4.59	10.50	58.92	4.89	4.63	10.40
11c	60.17	5.36	4.38	10.04	60.09	5.33	4.41	9.98
12c	61.24	5.74	4.20	9.62	61.51	5.75	4.27	9.61
3c	61.78	4.75	6.01	13.74	61.75	4.72	6.00	13.68
13c	59.00	4.95	4.59	10.50	58.73	5.03	4.44	10.40
14c	60.17	5.36	4.38	10.04	60.15	5.32	4.33	9.96
15c	61.24	5.74	4.20	9.62	61.19	5.77	4.25	9.54

E isomers

(E)-3-[[[[(2-Methoxyphenyl)(2-thienyl)]methylene]amino]oxy]propanoic acid, ethyl ester (**4a**). To a stirred mixture of **2a** (2.33 g, 10 mmol) in anhydrous *N,N*-dimethylformamide (30 mL) and potassium carbonate (3.45 g, 25 mmol) under nitrogen, heated at 60 °C, was added dropwise ethyl 3-bromopropionate (2.05 mL, 17.5 mmol). After addition was complete, the reaction mixture was warmed at 60 °C for 12 h, with stirring, and then poured into 100 mL of ice water. After extraction with diethyl ether, the org. layer was washed with brine, dried (Na_2SO_4) and evaporated to give 1.06 g of a colorless oil (32 %) after purification by silica gel CC (hexane–diethyl ether, 80:20).– ^{1}H NMR (CCl_4): δ = 7.45–6.55 (m, 7H), 4.35 (t, 2H), 4.05 (q, 2H), 3.65 (s, 3H), 2.55 (t, 2H), 1.15 (t, 3H).

(E)-4-[[[[(2-Methoxyphenyl)(2-thienyl)]methylene]amino]oxy]butanoic acid, ethyl ester (**5a**) was obtained in the same manner as **4a** from **2a** and ethyl 4-bromobutyrate as a colorless oil which was purified by silica gel CC (hexane–diethyl ether, 80:20), in 65 % yield.– ^{1}H NMR (CCl_4): δ = 7.55–6.65 (m, 7H), 4.15 (t, 2H) 4.00 (q, 2H), 3.75 (s, 3H), 2.45–1.70 (m, 4H), 1.20 (t, 3H).

(E)-5-[[[[(2-Methoxyphenyl)(2-thienyl)]methylene]amino]oxy]pentanoic acid, ethyl ester (**6a**) was obtained in the same manner as **4a** from **2a** and ethyl 5-bromovalerate and purified by silica gel CC (hexane– diethyl ether, 80:20); yield 39 %, mp 76 °C (hexane).– ^{1}H NMR (CCl_4): δ = 7.45–6.65 (m, 7H), 4.15 (t, 2H), 4.05 (q, 2H), 3.75 (s, 3H), 2.45–2.05 (m, 2H), 1.85–1.45 (m, 4H), 1.20 (t, 3H).

(E)-3-[[[[(3-Methoxyphenyl)(2-thienyl)]methylene]amino]oxy]propanoic acid, ethyl ester (**4b**) was obtained in the same manner as **4a** from **2b** and ethyl 3-bromopropionate and purified by silica gel CC (hexane– diethyl ether, 80:20) to give a colorless oil in 30 % yield.– ^{1}H NMR (CCl_4): δ = 7.50–6.75 (m, 7H), 4.40 (t, 2H), 4.15 (q, 2H), 3.80 (s, 3H), 2.65 (t, 2H), 1.20 (t, 3H).

(E)-4-[[[[(3-Methoxyphenyl)(2-thienyl)]methylene]amino]oxy]butanoic acid, ethyl ester (**5b**) was obtained in the same manner as **4a** from **2b** and ethyl 4-bromobutyrate and purified by silica gel CC (hexane– chloroform, 95:5) to give a colorless oil in 76 % yield.– ^{1}H NMR (CCl_4): δ = 7.55–6.75 (m, 7H), 4.15 (t, 2H), 4.05 (q, 2H), 3.75 (s, 3H), 2.50–1.75 (m, 4H), 1.15 (t, 3H).

(E)-5-[[[[(3-Methoxyphenyl)(2-thienyl)]methylene]amino]oxy]pentanoic acid, ethyl ester (**6b**) was obtained in the same manner as **4a** from **2b** and ethyl 5-bromovalerate and purified by silica gel CC (hexane– chloroform, 95:5) to give a pale yellow oil in 55 % yield.– ^{1}H NMR (CCl_4): δ = 7.40–6.75 (m, 7H), 4.10 (t, 2H), 4.05 (q, 2H), 3.75 (s, 3H), 2.45–2.15 (m, 2H), 1.90–1.50 (m, 4H), 1.15 (t, 3H).

(E)-3-[[[[(4-Methoxyphenyl)(2-thienyl)]methylene]amino]oxy]propanoic acid, ethyl ester (**4c**) was obtained in the same manner as **4a** from **2c** and ethyl 3-bromopropionate and purified by silica gel CC (hexane– diethyl ether, 80:20) to give a pale yellow oil in 46 % yield.– ^{1}H NMR ($CDCl_3$): δ = 7.55–6.65 (m, 7H), 4.35 (t, 2H), 4.10 (q, 2H), 3.75 (s, 3H), 2.65 (t, 2H), 1.15 (t, 3H).

(E)-4-[[[[(4-Methoxyphenyl)(2-thienyl)]methylene]amino]oxy]butanoic acid, ethyl ester (**5c**) was obtained in the same manner as **4a** from **2c** and ethyl 4-bromobutyrate and purified by silica gel CC (hexane– diethyl ether, 80:20); yield 65 %, mp 56 °C (hexane).– ^{1}H NMR ($CDCl_3$): δ = 7.60–6.85 (m, 7H), 4.20 (t, 2H), 4.15 (q, 2H), 3.85 (s, 3H), 2.60–1.85 (m, 4H), 1.25 (t, 3H).

(E)-5-[[[[(4-Methoxyphenyl)(2-thienyl)]methylene]amino]oxy]pentanoic acid, ethyl ester (**6c**) was obtained in the same manner as **4a** from **2c** and ethyl 5-bromovalerate and purified by silica gel CC (hexane– diethyl ether, 80:20); yield 38 %, mp 76 °C (hexane).– ^{1}H NMR ($CDCl_3$): δ = 7.60–6.80 (m, 7H), 4.20 (t, 2H), 4.15 (q, 2H), 3.80 (s, 3H), 2.50–2.15 (m, 2H), 2.00–1.55 (m, 4H), 1.20 (t, 3H).

Z isomers

(Z)-3-[[[[(2-Methoxyphenyl)(2-thienyl)]methylene]amino]oxy]propanoic acid, ethyl ester (**7a**) was obtained in the same manner as **4a** from **3a** and ethyl 3-bromopropionate and purified by silica gel CC (dichloromethane), yield 51 %, mp 102 °C (hexane–acetone, 80:20).– ^{1}H NMR ([D$_6$]DMSO): δ = 7.75–6.70 (m, 7H), 4.35–3.85 (m, 2H), 4.15 (q, 2H), 3.80 (s, 3H), 3.20–2.70 (m, 2H), 1.25 (t, 3H).

(Z)-4-[[[[(2-Methoxyphenyl)(2-thienyl)]methylene]amino]oxy]butanoic acid, ethyl ester (**8a**) was obtained in the same manner as **4a** from **3a** and ethyl 4-bromobutyrate as a brown oil which was purified by silica gel CC (diethyl ether–hexane, 70:30); yield 72 % .– ^{1}H NMR ([D$_6$]DMSO) δ = 7.55–6.75 (m, 7H), 4.35 (t, 2H), 4.10 (q, 2H), 3.65 (s, 3H), 2.65– 1.95 (m, 4H), 1.25 (t, 3H).

(Z)-5-[[[[(2-Methoxyphenyl)(2-thienyl)]methylene]amino]oxy]pentanoic acid, ethyl ester (**9a**) was obtained in the same manner as **4a** from **3a** and ethyl 5-bromovalerate and purified by silica gel CC (diethyl ether) to give a colorless oil in 30 % yield.– ^{1}H NMR ([D$_6$]DMSO): δ = 7.75–6.75 (m, 7H), 4.15 (q, 2H), 3.85 (t, 2H), 3.75 (s, 3H), 2.45–1.45 (m, 6H), 1.20 (t, 3H).

(Z)-3-[[[[(3-Methoxyphenyl)(2-thienyl)]methylene]amino]oxy]propanoic acid, ethyl ester (**7b**) was obtained in the same manner as **4a** from **3b** and ethyl 3-bromopropionate and purified by silica gel CC (hexane–diethyl ether, 80:20) to give a pale yellow oil in 25 % yield.– ^{1}H NMR ([D$_6$]DMSO): δ = 7.60–6.80 (m, 7H), 4.55 (t, 2H), 4.10 (q, 2H), 3.75 (s, 3H), 2.75 (t, 2H), 1.25 (t, 3H).

(Z)-4-[[[[(3-Methoxyphenyl)(2-thienyl)]methylene]amino]oxy]butanoic acid, ethyl ester (**8b**) was obtained in the same manner as **4a** from **3b** and ethyl 4-bromobutyrate and purified by silica gel CC (hexane– diethyl ether, 80:20) to give a yellow oil in 40 % yield.– ^{1}H NMR ([D$_6$]DMSO) δ = 7.60–6.80 (m, 7H), 4.35 (t, 2H), 4.05 (q, 2H), 3.75 (s, 3H), 2.65–1.90 (m, 4H), 1.15 (t, 3H).

(Z)-5-[[[[(3-Methoxyphenyl)(2-thienyl)]methylene]amino]oxy]pentanoic acid, ethyl ester (**9b**) was obtained in the same manner as **4a** from **3b** and ethyl 5-bromovalerate and purified by silica gel CC (hexane– chloroform, 98:2) to give a colorless oil in 80 % yield.– ^{1}H NMR ([D$_6$]DMSO): δ = 7.60–6.80 (m, 7H), 4.15 (t, 2H), 4.05 (q, 2H), 3.75 (s, 3H), 2.45–2.15 (m, 2H), 1.95–1.60 (m, 4H), 1.15 (t, 3H).

(Z)-3-[[[[(4-Methoxyphenyl)(2-thienyl)]methylene]amino]oxy]propanoic acid, ethyl ester (**7c**) was obtained in the same manner as **4a** from **3c** and ethyl 3-bromopropionate and purified by silica gel CC (hexane– diethyl ether, 80:20) in 50 % yield, mp 54°C (hexane).– ^{1}H NMR (CCl_4): δ = 7.60–6.75 (m, 7H), 4.55 (t, 2H), 4.05 (q, 2H), 3.75 (s, 3H), 2.75 (t, 2H), 1.15 (t, 3H).

(Z)-4-[[[[(4-Methoxyphenyl)(2-thienyl)]methylene]amino]oxy]butanoic acid, ethyl ester (**8c**) was obtained in the same manner as **4a** from **3c** and ethyl 4-bromobutyrate and purified by silica gel CC (hexane–diethyl ether, 80:20) to give a colorless oil in 60 % yield.– ^{1}H NMR ($CDCl_3$): δ = 7.65–6.85 (m, 7H), 4.40 (t, 2H), 4.10 (q, 2H), 3.75 (s, 3H), 2.70–1.95 (m, 4H), 1.20 (t, 3H).

(Z)-5-[[[[(4-Methoxyphenyl)(2-thienyl)]methylene]amino]oxy]pentanoic acid, ethyl ester (**9c**) was obtained in the same manner as **4a** from **3c** and ethyl 5-bromovalerate and purified by silica gel CC (hexane–diethyl ether, 80:20); yield 59 %, mp 50 °C (hexane).– ^{1}H NMR (CCl_4): δ = 7.55–6.75 (m, 7H), 4.25 (t, 2H), 4.05 (q, 2H), 3.75 (s, 3H), 2.50–2.15 (m, 2H), 1.95–1.65 (m, 4H), 1.20 (t, 3H).

*Compounds with a carboxylic group (**10–15**)*

E isomers

(E)-3-[[[[(2-Methoxyphenyl)(2-thienyl)]methylene]amino]oxy]propanoic acid (**10a**). A mixture of **4a** (3.33 g, 10 mmol) in ethanol (60 mL) and sodium hydroxide, 2N solution in water, (60 mL) was stirred at room temp. for 24 h. After evaporation of ethanol, the aqueous layer was slowly acidified to pH ≈ 3 by adding 2N HCl. The white emulsion was extracted with diethyl ether, washed until neutral, and dried (Na_2SO_4). The solvent was evaporated *in vacuo* to give 2.50 g of a pale brown oil **10a** (83 %). IR (KBr): ν = 3300–2350 cm^{-1} (OH), 1705 (C=O).– ^{1}H NMR ([D$_6$]DMSO): δ = 11.60 (s, 1H, exchangeable with D_2O), 7.70–6.75 (m, 7H), 4.35 (t, 2H), 3.80 (s, 3H), 2.65 (t, 2H).– Anal. ($C_{15}H_{15}NO_4S$) C, H, N, S,

(E)-4-[[[[(2-Methoxyphenyl)(2-thienyl)]methylene]amino]oxy]butanoic acid (**11a**) was obtained from **5a** in the same manner as **10a**, in 80 % yield, mp 103 °C (ethanol). IR (KBr): ν = 3350–2450 cm^{-1} (OH), 1705 (C=O).– NMR: see Tables 1 and 2.– Anal. ($C_{16}H_{17}NO_4S$) C, H, N, S.

(E)-5-[[[[(2-Methoxyphenyl)(2-thienyl)]methylene]amino]oxy]pentanoic acid (**12a**) was obtained from **6a** in the same manner as **10a** in 87 % yield as a pale brown oil. IR (KBr): ν = 3200–2350 cm^{-1} (OH), 1700 (C=O).– ^{1}H NMR ([D$_6$]DMSO): δ = 11.60 (s, 1H, exchangeable with D_2O), 7.65–6.65

(m, 7H), 4.10 (t, 2H), 3.75 (s, 3H), 2.20 (t, 2H), 1.75–1.35 (m, 4H).– Anal. ($C_{17}H_{19}NO_4S$) C, H, N, S.

(E)-3-[[[[(3-Methoxyphenyl)(2-thienyl)]methylene]amino]oxy]propanoic acid (**10b**) was obtained from **4b** in the same manner as **10a**, in 75 % yield, mp 120–121 °C (ethanol). IR (KBr): ν = 3250–2500 cm^{-1} (OH), 1700 (C=O).– ^1H NMR ([D6]DMSO): δ = 12.00 (s, 1H, exchangeable with D_2O), 7.75–6.85 (m, 7H), 4.35 (t, 2H), 3.85 (s, 3H), 2.65 (t, 2H).– Anal. ($C_{15}H_{15}NO_4S$) C, H, N, S.

(E)-4-[[[[(3-Methoxyphenyl)(2-thienyl)]methylene]amino]oxy]butanoic acid (**11b**) was obtained from **5b** in the same manner as **10a**, in 67 % yield, mp 103 °C (heptane). IR (KBr): ν = 3400–2500 cm^{-1} (OH), 1700 (C=O).– NMR: see Tables 1 and 2.– Anal. ($C_{16}H_{17}NO_4S$) C, H, N, S.

(E)-5-[[[[(3-Methoxyphenyl)(2-thienyl)]methylene]amino]oxy]pentanoic acid (**12b**) was obtained from **6b** in the same manner as **10a** in 63 % yield as a pale brown oil. IR (KBr): ν = 3300–2350 cm^{-1} (OH), 1700 (C=O).– ^1H NMR ([D6]DMSO): δ = 10.60 (s, 1H, exchangeable with D_2O), 7.75–6.80 (m, 7H), 4.15 (t, 2H), 3.85 (s, 3H), 2.25 (t, 2H), 1.80–1.45 (m, 4H).– Anal. ($C_{17}H_{19}NO_4S$) C, H, N, S.

(E)-3-[[[[(4-Methoxyphenyl)(2-thienyl)]methylene]amino]oxy]propanoic acid (**10c**) was obtained from **4c** in the same manner as **10a**, in 60 % yield, mp 174 °C (heptane–acetone, 80:20). IR (KBr): ν = 3150– 2450 cm^{-1} (OH), 1720 (C=O).– ^1H NMR ([D6]DMSO): δ = 12.00 (s, 1H, exchangeable with D_2O), 7.75–6.65 (m, 7H), 3.95 (t, 2H), 3.85 (s, 3H), 2.80 (t, 2H).– Anal. ($C_{15}H_{15}NO_4S$) C, H, N, S.

(E)-4-[[[[(4-Methoxyphenyl)(2-thienyl)]methylene]amino]oxy]butanoic acid (**11c**) was obtained from **5c** in the same manner as **10a**, in 69 % yield, mp 109 °C (heptane–acetone, 80:20). IR (KBr): ν = 3250– 2500 cm^{-1} (OH), 1700 (C=O).– NMR: see Tables 1 and 2.– Anal. ($C_{16}H_{17}NO_4S$) C, H, N, S.

(E)-5-[[[[(4-Methoxyphenyl)(2-thienyl)]methylene]amino]oxy]pentanoic acid (**12c**) was obtained from **6c** in the same manner as **10a** in 70 % yield as a pale brown oil. IR (KBr): ν = 3500–2600 cm^{-1} (OH), 1700 (C=O).– ^1H NMR ($CDCl_3$): δ = 9.30 (s, 1H, exchangeable with D_2O), 7.60–6.85 (m, 7H), 4.15 (t, 2H), 3.85 (s, 3H), 2.35 (t, 2H), 1.95–1.55 (m, 4H).– Anal. ($C_{17}H_{19}NO_4S$) C, H, N, S.

Z isomers

(Z)-3-[[[[(2-Methoxyphenyl)(2-thienyl)]methylene]amino]oxy]propanoic acid (**13a**) was obtained from **7a** in the same manner as **10a**, in 60 % yield, mp 180 °C (heptane–acetone, 90:10). IR (KBr): ν = 3200– 2500 cm^{-1} (OH), 1710 (C=O).– ^1H NMR ([D6]DMSO): δ = 12.00 (s, 1H, exchangeable with D_2O), 7.75–6.65 (m, 7H), 3.95 (t, 2H), 3.85 (s, 3H), 2.80 (t, 2H).– Anal. ($C_{15}H_{15}NO_4S$) C, H, N, S.

(Z)-4-[[[[(2-Methoxyphenyl)(2-thienyl)]methylene]amino]oxy]butanoic acid (**14a**) was obtained from **8a** in the same manner as **10a**, in 72 % yield, mp 137 °C (heptane–acetone, 90:10). IR (KBr): ν = 3300– 2400 cm^{-1} (OH), 1700 (C=O).– NMR: see Tables 1 and 2.– Anal. ($C_{16}H_{17}NO_4S$) C, H, N, S.

(Z)-5-[[[[(2-Methoxyphenyl)(2-thienyl)]methylene]amino]oxy]pentanoic acid (**15a**) was obtained from **9a** in the same manner as **10a**, in 44 % yield, mp 150–152 °C (hexane–ether, 80:20). IR (KBr): ν = 3200– 2550 cm^{-1} (OH), 1705 (C=O).– ^1H NMR ([D6]DMSO): δ = 9.90 (s, 1H, exchangeable with D_2O), 7.75–6.65 (m, 7H), 3.80 (s, 3H), 3.75 (t, 2H), 2.15 (t, 2H), 1.95–1.25 (m, 4H).– Anal. ($C_{17}H_{19}NO_4S$) C, H, N, S.

(Z)-3-[[[[(3-Methoxyphenyl)(2-thienyl)]methylene]amino]oxy]propanoic acid (**13b**) was obtained from **7b** in the same manner as **10a**, in 66 % yield, as a pale yellow oil. IR (KBr): ν = 3200–2400 cm^{-1} (OH), 1705 (C=O).– ^1H NMR ([D6]DMSO): δ = 11.20 (s, 1H, exchangeable with D_2O) 8.05–6.80 (m, 7H), 4.50 (t, 2H), 3.80 (s, 3H), 2.75 (t, 2H).– Anal. ($C_{15}H_{15}NO_4S$) C, H, N, S.

(Z)-4-[[[[(3-Methoxyphenyl)(2-thienyl)]methylene]amino]oxy]butanoic acid (**14b**) was obtained from **8b** in the same manner as **10a**, in 65 % yield, mp 62 °C (hexane–ether, 90:10). IR (KBr): ν = 3300–2500 cm^{-1} (OH), 1700 (C=O).– NMR: see Tables 1 and 2.– Anal. ($C_{16}H_{17}NO_4S$) C, H, N, S.

(Z)-5-[[[[(3-Methoxyphenyl)(2-thienyl)]methylene]amino]oxy]pentanoic acid (**15b**) was obtained from **9b** in the same manner as **10a**, in 65 % yield, as a pale yellow oil. IR (KBr): ν = 3350–2350 cm^{-1} (OH), 1700 (C=O).– ^1H NMR ([D6]DMSO): δ = 11.50 (s, 1H, exchangeable with D_2O), 8.35–7.00 (m, 7H), 4.35 (t, 2H), 3.85 (s, 3H), 2.35 (t, 2H), 2.00–1.55 (m, 4H).– Anal. ($C_{17}H_{19}NO_4S$) C, H, N, S.

(Z)-3-[[[[(4-Methoxyphenyl)(2-thienyl)]methylene]amino]oxy]propanoic acid (**13c**) was obtained from **7c** in the same manner as **10a**, in 52 % yield, mp 94 °C (heptane–acetone, 90:10). IR (KBr): ν = 3200– 2500 cm^{-1} (OH), 1722 (C=O).– ^1H NMR ([D6]DMSO) δ = 11.20 (s, 1H, exchangeable with D_2O), 8.00–6.90 (m, 7H), 4.50 (t, 2H), 3.85 (s, 3H), 2.75 (t, 2H).– Anal. ($C_{15}H_{15}NO_4S$) C, H, N, S.

(Z)-4-[[[[(4-Methoxyphenyl)(2-thienyl)]methylene]amino]oxy]butanoic acid (**14c**) was obtained from **8c** in the same manner as **10a**, in 66 % yield, mp 75 °C (heptane–acetone, 70:30). IR (KBr): ν = 3300– 2500 cm^{-1} (OH), 1695 (C=O).– NMR: see Tables 1 and 2.– Anal. ($C_{16}H_{17}NO_4S$) C, H, N, S.

(Z)-5-[[[[(4-Methoxyphenyl)(2-thienyl)]methylene]amino]oxy]pentanoic acid (**15c**) was obtained from **9c** in the same manner as **10a**, in 60 % yield, mp 70 °C (cyclohexane–diethyl ether, 70:30). IR (KBr): ν = 3400–2500 cm^{-1} (OH), 1700 (C=O).– ^1H NMR ([D6]DMSO): δ = 10.20 (s, 1H, exchangeable with D_2O), 7.70–6.85 (m, 7H), 4.55–4.20 (m, 2H), 3.85 (s, 3H), 2.60–2.25 (m, 2H), 2.15–1.65 (m, 4H).– Anal. ($C_{17}H_{19}NO_4S$) C, H, N, S.

Pharmacology

The inhibitory effect on arachidonic acid-induced human platelet aggregation was studied *in vitro* according to modified previously described procedures [5].

Platelet preparations

Whole blood was drawn from the cubital vein of healthy volunteers who were selected on the basis of abstention from any medication for 7 days prior to phlebotomy into 0.1 vol. of 3.8 % sodium citrate. Platelet rich plasma (PRP: platelet counts between 2.5 and 3 × 10^8/mL) was prepared by centrifugation of whole blood at 90 g for 20 min. These procedures were performed at room temp.

Aggregation test

The aggregatory response of the platelets was assessed in an optical aggregometer (Platelet aggregation profiler model PAP 4 Bio Data Corporation) following the addition of arachidonic acid (AA) at 37 °C.

Typically, a mixture of 225 µL PRP and 20 µL physiological serum and 1.5 µL of tested compound (60 mM and dilution, dissolved in dimethylsulfoxide) was preincubated at 37 °C for 3 min, with magnetic stirring (1100 rpm). Aggregation was then initiated by 3 µL or less of AA (0.1 M–Sigma purity 99 %).

During all our tests, we confirmed that the 1.5 µL DMSO introduced into the plasmatic midst had no influence on the platelet aggregation intensity, in agreement with several authors [17–19].

Results

The anti-platelet effects of these compounds were expressed as IC_{50} values and as potency relative to acetylsalicylic acid, according to *Lévy-Toledano* [20].

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