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Short communication

Synthesis and inhibitory effects on platelet aggregation of 3-(2-thienyl)- and 3-(1-imidazolyl)-1,2-benzisoxazole derivatives

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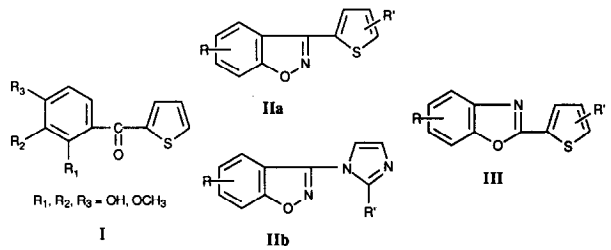
Summary — A series of 3-(2-thienyl)- and 3-(1-imidazolyl)-1,2-benzisoxazoles as well as some isomeric benzoxazoles were synthesized and tested *in vitro* for their inhibitory effect on arachidonic acid-induced human platelet aggregation. The most active compound (7-methoxy-3-(2-thienyl)-1,2-benzisoxazole **5c**) was nearly 20–30-fold more potent than acetylsalicylic acid in inhibiting platelet aggregation. Structure–activity relationships within the series are briefly discussed.

1,2-benzisoxazole / platelet aggregation inhibitor

Introduction

The preventive treatment of many cardiovascular diseases requires research on effective antithrombotic agents. In this perspective, we reported the synthesis of a series of aryl thienyl ketones **I** which showed potent inhibitory effects *in vitro* on human platelet aggregation [1, 2].



The biological activity of **I** has been associated with the competitive inhibition of prostaglandin synthetase (cyclooxygenase) [3]. The molecular structure of the most active compound (R_1 = OH; $R_2 = R_3$ = OCH_3), analysed by X-ray diffraction [3], revealed a weak torsion angle between the thienyl and phenyl rings. Furthermore, this conformation is favoured by a strong hydrogen bond involving the phenolic group and the carbonyl oxygen atom. Therefore, it was of interest to examine the introduction of further rigidity into the system. In order to investigate the relationship between the similarity of molecular shapes and biological activities, we decided to replace the aroyl moiety of **I** by a benzisoxazolic system. We report here the synthesis of a series of 3-(2-thienyl)-1,2-benzisoxazoles **IIa**, 3-(1-imidazolyl)-1,2-benzisoxazoles **IIb**, and the evaluation of their inhibitory effects on human arachidonic acid-induced platelet aggregation. For completeness, we also describe the biological activity of some isomeric 2-(2-thienyl) benzoxazoles **III**, the side products issued from the synthesis of **IIa**.

Chemistry

The synthesis of the compounds **5a–e** in table I was carried out by the general methodology outlined in scheme 1. Except where otherwise stated, the aryl thienyl ketones **2** were prepared by Friedel-Crafts acylation of a suitably substituted thiophene with 2,3-dimethoxybenzoyl chloride. Use of mild reaction conditions (*ie* a slight excess of Lewis acid) in these acylations led directly to the monophenolic products, with selective demethylation of the *ortho*-methoxy group. Treatment of **2** with hydroxylamine hydrochloride in refluxing sodium hydroxide aqueous ethanolic medium gave the corresponding oxime **3** as a mixture of *E* and *Z* isomers that was not purified further. The oxime isomer mixtures were then treated according to

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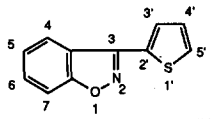
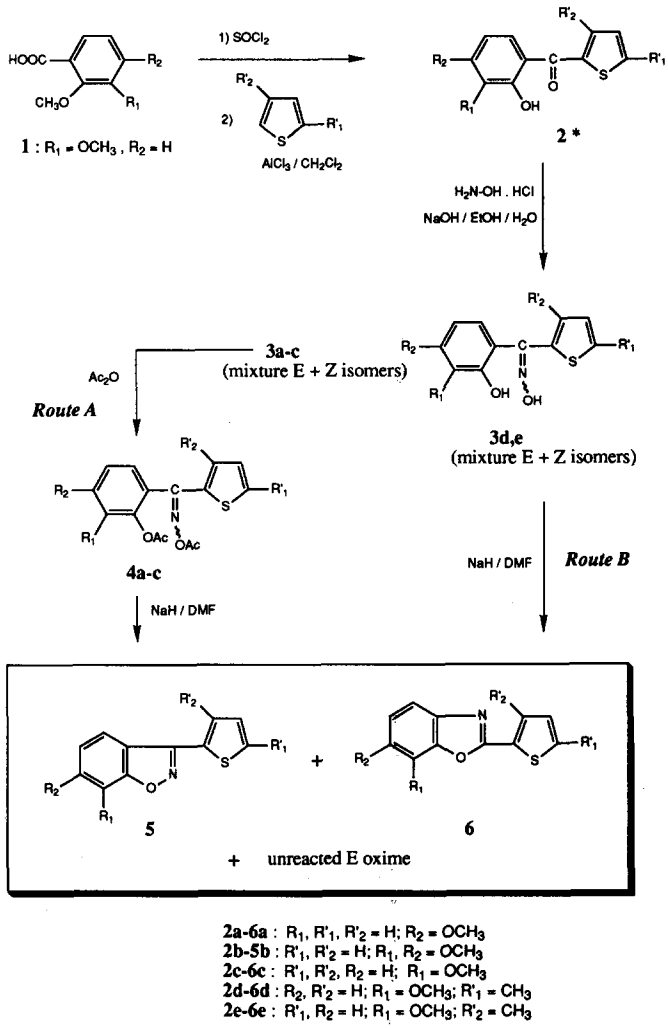
Table I. Physical data and *in vitro* platelet anti-aggregating activity of 3-(2-thienyl)-1,2-benzisoxazoles.



Compd	Substituents	Formula (mw)	mp °C	Inhibition of AA-induced platelet aggregation (a)	
				ED_{50} (μM) (b) (c)	Rel. potency to ASA
5a	6-OCH_3	$C_{12}H_9NO_2S$ (231.27)	97	120 - 180	1.5
5b	6-OCH_3, 7-OCH_3	$C_{13}H_{11}NO_3S$ (261.30)	86-7(d)	180 - 270	1
5c	7-OCH_3	$C_{12}H_9NO_2S$ (231.27)	108-10	6 - 9	20-30
5d	7-OCH_3, 5'-CH_3	$C_{13}H_{11}NO_2S$ (245.30)	73	180 - 270	1
5e	7-OCH_3, 3'-CH_3	$C_{13}H_{11}NO_2S$ (245.30)	115	36 - 90	3-5
5f	7-OCH_3, 5'-Br	$C_{12}H_8BrNO_2S$ (310.18)	105	(e)	0
5g	7-OCH_3, 5-Br	$C_{12}H_8BrNO_2S$ (310.18)	137	120 - 180	1.5
5h	7-OCH_3, 5'-COOH	$C_{13}H_9NO_4S$ (275.29)	275	(e)	0
5i	7-OCH_3, 5-COOH	$C_{13}H_9NO_4S$ (275.29)	262	(e)	0
7	7-OH	$C_{11}H_7NO_2S$ (217.25)	129	(e)	0
8	7-OCH_2-COOEt	$C_{15}H_{13}NO_4S$ (303.34)	68	9 - 22	12-20
9	7-OCH_2-COOH	$C_{13}H_9NO_4S$ (275.29)	196	270 - 540	0.50-0.66
10	7 -OCH_2-CO-N⟨⟩N-CH_3	$C_{18}H_{19}N_3O_3S$ (357.43)	145	(e)	0
11	7 -OCH_2-⟨epoxide⟩	$C_{14}H_{11}NO_3S$ (273.31)	116-8	45 - 90	3-4
12	7-OCH_2-CHOH-CH_2OH	$C_{14}H_{13}NO_4S$ (291.32)	105-7	(e)	0
13	7-OCH_2-CH_2OH	$C_{13}H_{11}NO_3S$ (261.30)	105	60 - 120	2.25-3
14	7-O-CO-CH_3	$C_{13}H_9NO_3S$ (259.29)	120	(e)	0
Acetyl Salicylic Acid (ASA)				180 - 270	1

(a) Values mentioned are the mean of 3 experiments; (b) ED_{50}: highest dose without effect; (c) ED_{100}: lowest dose which causes complete inhibition; (d) lit [9]: 86–87°C; (e) no activity observed at highest concentration.

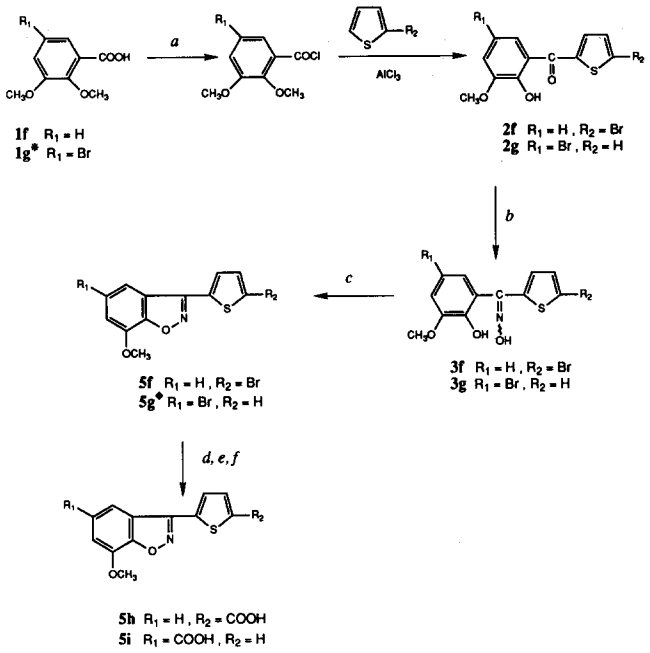


Scheme 1. Synthesis of compounds **5** and **6**. *__2a__ and **2b** were prepared by acylation of 1,3-dimethoxybenzene and 1,2,3-trimethoxybenzene, respectively, with 2-thiophenecarbonyl chloride (see [1]).

Route A or *Route B*, depending on the nature of the thiophene substituents. The methylthienyl derivatives **3d** and **3e** were directly cyclized with sodium hydride in *N,N*-dimethylformamide *(Route B)* to give a mixture of 1,2-benzisoxazoles **5**, benzoxazoles **6** and unreacted *E* oximes, separable by preparative HPLC. For unsubstituted thienyl oximes **3a–c**, it was convenient to accomplish cyclization after acetylation *(Route A)*. The concomitant formation of the isomeric benzoxazole was demonstrated in the course of cyclization of compound **4a**, from mass spectroscopy and ^{13}C-NMR data and was discussed in a previous communication [4]. For other compounds of the series, the benzoxazole isomer was readily identified by HPLC analysis and from its fluorescence properties [5, 6].

Scheme 2 outlines the preparation of carboxylic acid derivatives. Bromo compounds **5f** and **5g** were obtained from 2,3-dimethoxybenzoic acid **1f** or its 5-bromo derivative **1g**, respectively, according to the same sequence as described for scheme 1. The halogen-containing benzisoxazoles were subjected to a metallation reaction using *n*-butyllithium at low temperature, in diethyl ether. The target carboxylic acid derivatives **5h** and **5i** were prepared by treatment of the lithio-intermediates with CO_2, followed by hydrolysis with aqueous hydrochloric acid.

The 1,2-benzisoxazoles **8–14** were synthesized as indicated in scheme 3. Preparation of the required

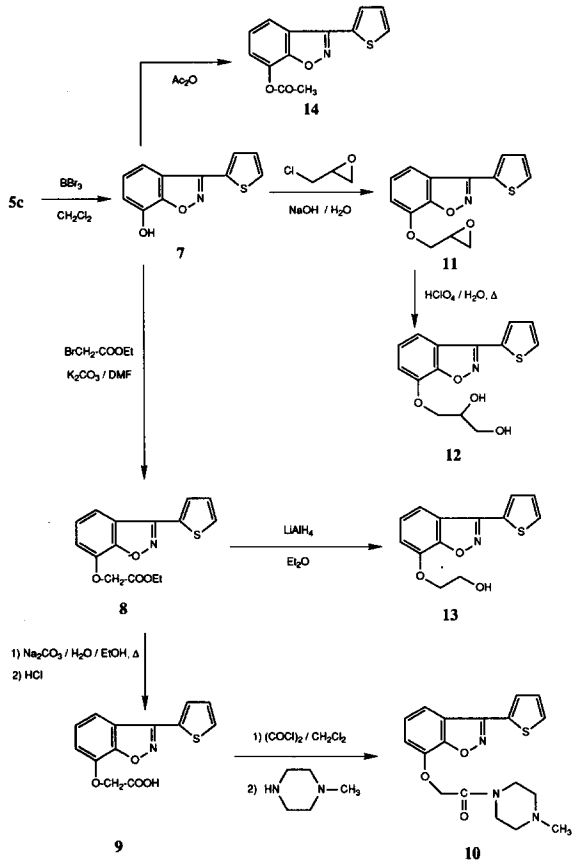


Scheme 2. Preparation of carboxylic derivatives **5h** and **5i**. Reagents (a) $(COCl)_2/CH_2Cl_2$; (b) $H_2NOH{\cdot}HCl/NaOH/EtOH/H_2O$; (c) NaH/DMF; (d) *n*-BuLi/Et_2O, – 35°C; (e) CO_2; (f) H_2O/HCl. *See [7, 8]. ◆ NaH/DMF cyclization of the oxime **3g** yielded a mixture of **5g** and 5-bromo-7-methoxy-2-(2-thienyl) benzoxazole **6g** (see table III) which were isolated by chromatographic workup.

3-(2-thienyl)-1,2-benzisoxazol-7-ol intermediate **7** was achieved by demethylation of the methoxy compound **5c** with refluxing boron tribromide in dichloromethane. Alkylation of **7** with ethyl bromoacetate followed either by reduction with lithium aluminium hydride, or by base hydrolytic workup gave the hydroxyethylether **13** or the benzisoxazolyloxyacetic acid **9**, respectively. Conversion of **9** to the acid chloride, followed by reaction with *N*-methylpiperazine afforded the amide **10**.

Alternatively, alkylation of **7** with epichlorohydrin yielded the glycidyl ether **11**, which, upon dilute perchloric acid treatment, provided the dihydroxypropylether **12**. Acetylation of **7** afforded the ester **14**.

The sequence to the 3-(1-imidazolyl)-1,2-benzisoxazoles **19** (table II) is depicted in scheme 4. Compounds **19a, b, e** were prepared by reaction of a suitably substituted 3-chloro-1,2-benzisoxazole **18a, b** (obtained according to literature methods) either with imidazole or with ethyl imidazole-4-carboxylate, in the presence of sodium hydride in *N,N*-dimethylformamide *(Route C)*. The synthesis of compounds **19c** and **19d** *(Route D)* followed a related strategy to that described for **8** and **9** in scheme 3.



Scheme 3. Synthesis of the 1,2-benzisoxazoles **8–14**.

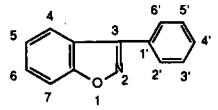
Pharmacology

The inhibitory activities on platelet aggregation were assessed by the turbidometric method of Born [10], using human platelet-rich plasma (PRP). Aggregation was induced by arachidonic acid (AA). In many test compounds, the dose–inhibition curves showed a steep pattern because the dose ranges between ED_0 (the highest dose without effect) and ED_{100} (the lowest dose which causes complete inhibition) were relatively narrow. This phenomenon has been reported in earlier papers [11, 12]. Therefore, the antiplatelet activities are expressed in terms of the ED_{50} range. Acetylsalicylic acid (ASA) was included in the tests as a reference substance. For each compound, the results are given in the form of relative potency to this substance.

Biological results and discussion

From the pharmacological data summarized in tables I–III, it appears that the most active compound

Table II. Physical data and *in vitro* platelet anti-aggregating activity of 3-aryl- and 3-(1-imidazolyl)-1,2-benzisoxazoles.



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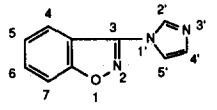

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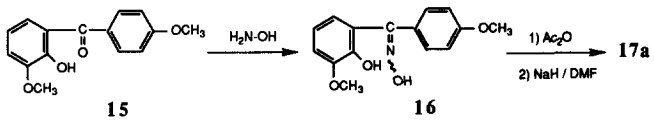
Compd	Substituents	Formula (mw)	mp °C	Inhibition of AA-induced platelet aggregation (a) ED50 (μM) (b) (c)	Rel. potency to ASA
17a(d)	4'-OCH_3, 7-OCH_3	$C_{15}H_{13}NO_3$ (255.28)	102	30 - 38	6-7
19a	–	$C_{10}H_7N_3O$ (185.19)	118	360 - 900	0.3-0.5
19b	7-OCH_3	$C_{11}H_9N_3O_2$ (215.21)	140	60 - 270	1-3
19c	7-OCH_2-COOEt	$C_{14}H_{13}N_3O_4$ (287.28)	100	30 - 135	2-6
19d	7-OCH_2-COOH	$C_{12}H_9N_3O_4$ (259.22)	240	(e)	0
19e	7-OCH_3, 4'-COOEt	$C_{14}H_{13}N_3O_4$ (287.28)	137	(e)	0
Acetyl Salicylic Acid (ASA)				180 - 270	1

(a, b, c, e) See corresponding footnotes in table I; (d) this compound was prepared according to the following sequence (see *Experimental protocols*):



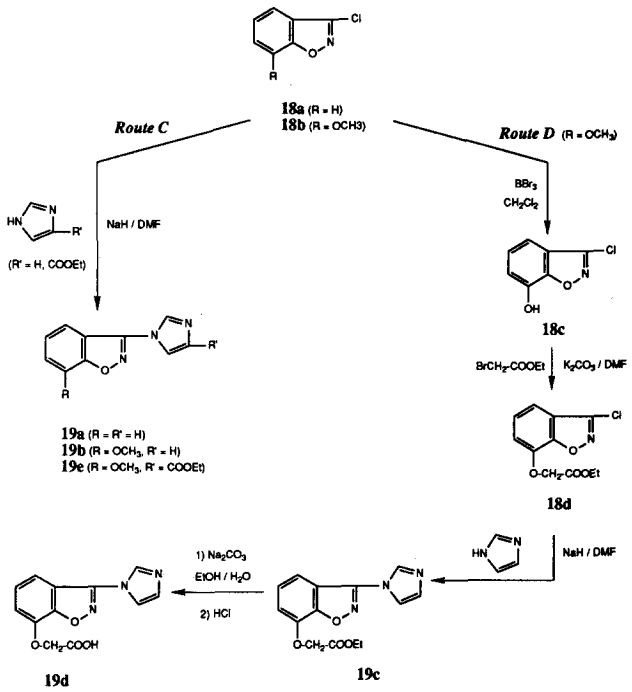
was the 7-methoxy-3-(2-thienyl)-1,2-benzisoxazole **5c**; its ability to inhibit platelet aggregation was 20–30 times that of ASA, under our experimental conditions.

Benzisoxazole ring modifications

Referring to compound **5c**, of all the 7-methoxy group variations (table I), only the ethyl ester derivative **8** displayed a high level of anti-aggregating activity. However, no clear structure–activity pattern emerged since the oxy-acetic acid **9** was weakly active. The amide **10** and the acetylated derivative **14**, were devoid of antiplatelet properties. The oxirane methyl compound **11** retained relatively good activity whereas its 'open' dihydroxy derivative **12** was completely inactive. This observation shows that increasing the hydrophilic character around the 7-substituent was found to be an unsuitable modification.

Furthermore, the prominent role taken by the 7-methoxy group in the antiplatelet effect was clearly indicated by the total inactivity of the desmethyl derivative **7**.

Variants at positions 5 and 6 of the benzisoxazole system led either to inactive derivative (**5i**) or moderately active compounds (**5a**, **5b**, **5g**).



Scheme 4. Reaction sequence leading to the 3-(1-imidazolyl)-1,2-benzisoxazoles **19**.

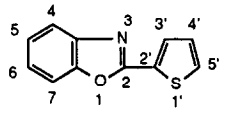
Table III summarizes the results obtained for some benzoxazole derivatives. Even though the aromaticity of benzoxazoles is comparable to that of 1,2-benzisoxazoles, the introduction of this isomeric structure was unfavourable: compound **6c** was nearly 20–30-fold less potent than **5c** in inhibiting platelet aggregation. The other benzoxazoles were weakly active (**6a**, **6g**) or completely inactive (**6d**, **6e**).

Thiophene ring modifications

As indicated in table I, introduction of a bromine substituent (compound **5f**) or a carboxylic acid group (compound **5h**) in the thienyl ring of **5c**, resulted in a loss of biological properties. However, comparing compounds **5d** and **5e** suggests that position 3 of the thiophene is more tolerant to substitution than position 5, at least for methyl group.

In an attempt to understand the contribution of the cyclic structure at position 3 of the benzisoxazole nucleus on biological activity, we synthesized some non-thiophenic derivatives differing in the degree of aromaticity (table II). Permutation of the thiophene nucleus by a nitrogen ring such as imidazole resulted in a marked decrease in anti-aggregating activity (compounds **19a–e**). On the other hand, the introduction of a π electron-rich group such as the *para*-

Table III. Physical data and *in vitro* platelet anti-aggregating activity of 2-(2-thienyl) benzoxazoles.



Compd	Substituents	Formula (mw)	mp °C	Inhibition of AA-induced platelet aggregation (a)	
				ED_{50} (μM) (b) (c)	Rel. potency to ASA
6a	6-OCH_3	$C_{12}H_9NO_2S$ (231.27)	74	120 - 180	1.5
6c	7-OCH_3	$C_{12}H_9NO_2S$ (231.27)	116	180 - 270	1
6d	7-OCH_3, 5'-CH_3	$C_{13}H_{11}NO_2S$ (245.30)	110	(e)	0
6e	7-OCH_3, 3'-CH_3	$C_{13}H_{11}NO_2S$ (245.30)	127	(e)	0
6g	7-OCH_3, 5-Br	$C_{12}H_8BrNO_2S$ (310.18)	146	360 - 900	0.3-0.5
Acetyl Salicylic Acid (ASA)				180 - 270	1

(a, b, c, e): See corresponding footnotes in table I.

methoxyphenyl moiety (compound **17a**) retained, to a large extent, the pharmacological activity. It has long been accepted that one of the most widely employed criteria for the quantitative assessment of aromaticity is the resonance energy [20]. Available values [20, 21] for benzene, thiophene and imidazole are respectively 152, 121 and 59 kJ mol^{-1}, indicating that imidazole has a lower degree of aromaticity than the other 2. However, the marked increase in activity exhibited by the thiophene derivative **5c**, compared to the *para*-methoxyphenyl analogue **17a** seems to indicate that aromaticity is not the only factor involved in the biological response. The thiophenic sulfur atom might be important for activity; this observation is in agreement with our previous findings [2].

Conclusion

To our knowledge, the literature does not report 1,2-benzisoxazoles as antithrombotic drugs. In comparison with the previously investigated aryl thienyl ketones [1], the compounds studied in the present paper may be considered as resulting from incorporation of the 2-hydroxyarylketone moiety into an isoxazolic linkage, through a nitrogen atom. The similarity in the biological profile between the aroyl system and the 1,2-benzisoxazole nucleus has been described previously for various classes of pharmacological agents such as neuroleptics [13], diuretics [14] and uricosurics [9, 15]. Therefore, our results provide a novel example of bioisosterism for these molecular components. On account of the high level of inhibitory activity on platelet aggregation observed *in vitro* for compound **5c**, this was selected for further study in order to establish the mode of action of this new class of antiplatelet drugs.

Experimental protocols

Chemistry

The structures of all compounds were supported by the IR spectra (KBr pellets, Shimadzu IR 470 spectrometer) and ^{1}H-NMR data (the 60 MHz spectra were recorded on a Varian EM 360 L spectrometer and the 200 MHz spectra were obtained from a Bruker AC 200 spectrometer; tetramethylsilane was used as internal reference). Preparative HPLC was performed on a Waters Associates Prep LC system 500 using silica-gel columns. Melting points were determined with an Electrothermal digital capillary melting point apparatus and are uncorrected. Elemental analyses were performed by the Service central d'analyse du CNRS (Vernaison, France) and were within ± 0.4% of the calculated values except where otherwise stated.

*Preparation of aryl (2-thienyl) ketones **2a–g***

(2-Hydroxy-4-methoxyphenyl)(2-thienyl)methanone **2a**, (2-hydroxy-3,4-dimethoxyphenyl)(2-thienyl)methanone **2b** [1] and (2-hydroxy-3-methoxyphenyl)(2-thienyl)methanone **2c** [2] were prepared as previously described.

*(2-Hydroxy-3-methoxyphenyl)(5-methyl-2-thienyl)methanone **2d**.* This was obtained in the same manner as **2c**, from 2,3-dimethoxybenzoyl chloride and 2-methylthiophene as a yellow oil which was chromatographed over silica-gel column eluting with dichloromethane/hexane (75:25), in 55% yield. ^{1}H-NMR (60 MHz, CCl_4) δ 2.50 (s, 3H, CH_3); 3.85 (s, 3H, OCH_3); 6.67–7.02 (AB system, 2H, J_{AB} = 4 Hz, thiophene); 6.73–7.18 (m, 2H, ArH); 7.43–7.60 (m, 1H, ArH); 11.05 (s, 1H, OH). Anal $C_{13}H_{12}O_3S$ (C, H, S).

*(2-Hydroxy-3-methoxyphenyl)(3-methyl-2-thienyl)methanone **2e**.* This was obtained from 3-methylthiophene in the same manner as **2c**. The crude product was slightly contaminated with (2-hydroxy-3-methoxyphenyl)(4-methyl-2-thienyl)methanone. Chromatography over a silica-gel column eluting with dichloromethane/hexane (75:25) afforded pure **2e** in 42% yield. ^{1}H-NMR (60 MHz, CCl_4) δ 2.35 (s, 3H, CH_3); 3.80 (s, 3H, OCH_3); 6.54–7.08 (m, 2H, ArH); 6.82–7.47 (AB system, 2H, J_{AB} = 5 Hz, thiophene); 7.21–7.41 (m, 1H, ArH); 11.20 (s, 1H, OH). Anal $C_{13}H_{12}O_3S$ (C, H, S).

*(5-Bromo-2-thienyl)(2-hydroxy-3-methoxyphenyl)methanone **2f**.* This was obtained from 2-bromothiophene in the same manner as **2c**, in 70% yield; mp 84°C after recrystallization from hexane. ^{1}H-NMR (60 MHz, $CDCl_3$) δ 3.85 (s, 3H, OCH_3); 6.60–7.50 (m, 5H, ArH and thiophene); 11.10 (s, 1H, OH). Anal $C_{12}H_9BrO_3S$ (C, H, Br, S).

*(5-Bromo-2-hydroxy-3-methoxyphenyl)(2-thienyl)methanone **2g**.* This was obtained from 5-bromo-2,3-dimethoxybenzoyl chloride and thiophene, in 36% yield; mp 90°C after recrystallization from heptane. ^{1}H-NMR (60 MHz, $CDCl_3$) δ 3.90 (s, 3H, OCH_3); 7.25 (s, 1H, ArH); 7.75 (s, 1H, ArH); 7.10–7.35 (m, 1H, thiophene); 7.65–7.90 (m, 2H, thiophene); 11.20 (s, 1H, OH). Anal $C_{12}H_9BrO_3S$ (C, H, Br, S).

*Preparation of aryl (2-thienyl) ketone oximes **3***

(2-Hydroxy-4-methoxyphenyl)(2-thienyl)methanone oxime **3a** was obtained as described in [4] and (2-hydroxy-3,4-dimethoxyphenyl)(2-thienyl)methanone oxime **3b** as described in [2].

(2-Hydroxy-3-methoxyphenyl)(2-thienyl)methanone oxime ***3c***. This was obtained from **2c**, in the same manner as **3a**, in 55% yield, mp 145–150°C (mixture of *E* and *Z* isomers) after recrystallization from toluene/acetone (90:10). IR(KBr): 3400 cm^{-1} (ν_{O-H}, oxime). ^{1}H-NMR (60 MHz, CD_3-CO-CD_3) δ 3.85 (s, 3H, OCH_3); 6.90 (s, 1H, OH); 7.10 (s, 1H, OH); 6.70–7.20 (m, 5H, ArH and thiophene); 7.55–7.80 (m, 1H, thiophene). Calc for $C_{12}H_{11}NO_3S$: C, 57.78; H, 4.45; N, 5.62; S, 12.86; Found: C, 57.75; H, 4.50; N, 5.09; S, 12.74.

(2-Hydroxy-3-methoxyphenyl)(5-methyl-2-thienyl)methanone oxime ***3d***. This was obtained from **2d**, in the same manner as **3a**, in 46% yield, mp 116–118°C (mixture of *E* and *Z* isomers) after recrystallization from toluene. IR (KBr): 3300 cm^{-1} (ν_{O-H}, oxime). ^{1}H-NMR (200 MHz, $CDCl_3$) δ 2.51 (s, 3H, CH_3); 3.89 (s, 3H, OCH_3); 6.70–6.76 (m, 1H, ArH); 6.80–6.95 (m, 2H, 1 ArH + 1 OH); 6.85–6.93 (AB system, 2H, J_{AB} = 5 Hz, thiophene); 6.97–7.02 (m, 1H, ArH); 7.25 (s, 1H, OH). Anal $C_{13}H_{13}NO_3S$ (C, H, N, S).

(2-Hydroxy-3-methoxyphenyl)(3-methyl-2-thienyl)methanone oxime ***3e***. This was obtained from **2e**, in the same manner as **3a**, in 52% yield, mp 196–197°C (mixture of *E* and *Z* isomers) after recrystallization from toluene. IR (KBr): 3360 cm^{-1} (ν_{O-H}, oxime). ^{1}H-NMR (200 MHz, $CDCl_3$) δ 2.10 (s, 3H, CH_3); 3.89 (s, 3H, OCH_3); 6.54–6.61 (m, 1H, ArH); 6.69–6.79 (m, 1H, ArH); 6.87–6.94 (m, 1H, ArH); 6.97–7.47 (AB system, 2H, J_{AB} = 4.5 Hz, thiophene); 7.24 (s, 1H, OH); 8.35 (br, s, 1H, OH). Anal $C_{13}H_{13}NO_3S$ (C, H, N, S).

(2-Hydroxy-3-methoxyphenyl)(5-bromo-2-thienyl)methanone oxime ***3f***. This was obtained from **2f**, in the same manner as **3a**, in 63% yield, mp 135–140°C (mixture of *E* and *Z* isomers) after recrystallization from cyclohexane/ethyl acetate. IR (KBr): 3300 cm^{-1} (ν_{O-H}, oxime). ^{1}H-NMR (60 MHz, $CDCl_3$) δ 3.90 (s, 3H, OCH_3); 6.80–7.40 (m, 4H, 3 ArH + 1 OH); 7.10–7.50 (AB system, 2H, J_{AB} = 4 Hz, thiophene); 10.50 (br, s, 1H, OH). Anal $C_{12}H_{10}BrNO_3S$ (C, H, Br, N, S).

(5-Bromo-2-hydroxy-3-methoxyphenyl)(2-thienyl)methanone oxime ***3g***. This was obtained from **2g**, in the same manner as **3a**, in 47% yield, mp 202–205°C (mixture of *E* and *Z* isomers) after recrystallization from heptane. IR (KBr): 3350 cm^{-1} (ν_{O-H}, oxime). ^{1}H-NMR (60 MHz, $CDCl_3$) δ 3.90 (s, 3H, OCH_3); 6.65–7.55 (m, 5H, ArH + thiophene); 10.30 (br, s, 2H, 2 OH). Anal $C_{12}H_{10}BrNO_3S$ (C, H, Br, N, S).

General procedure for the preparation of oxime acetates ***4***

A stirred solution of 25 mmol **3** in acetic anhydride (200 ml) was heated at 90°C for 1 h. The reaction mixture was allowed to stir at room temperature for 18 h, and then poured into 200 g ice. After 1 h hydrolysis, the resulting precipitate was filtered, washed with water, dried at 20°C *in vacuo* providing **4** which was recrystallized from heptane.

(2-Acetoxy-4-methoxyphenyl)(2-thienyl)methanone *O*-acetyl oxime **4a** was prepared according to [4].

(2-Acetoxy-3,4-dimethoxyphenyl)(2-thienyl)methanone O-acetyl oxime ***4b***. This was obtained from **3b** in 38% yield, mp 117°C. IR (KBr): 1775 cm^{-1} ($\nu_{C=O}$). ^{1}H-NMR (60 MHz, $CDCl_3$) δ 1.95 (s, 3H, O-CO-CH_3); 2.30 (s, 3H, N-O-CO-CH_3); 3.80 (s, 3H, OCH_3); 3.85 (s, 3H, OCH_3); 6.75–7.20 (AB system, 2H, J_{AB} = 9 Hz, 2 ArH); 6.85–7.25 (m, 2H, thiophene); 7.55–7.70 (m, 1H, thiophene). Anal $C_{17}H_{17}NO_6S$ (C, H, N, S).

(2-Acetoxy-3-methoxyphenyl)(2-thienyl)methanone O-acetyl oxime ***4c***. This was obtained from **3c**, in 61% yield, mp 105–106°C. IR (KBr): 1770 cm^{-1} ($\nu_{C=O}$). ^{1}H-NMR (60 MHz, $CDCl_3$) δ 2.00 (s, 3H, O-CO-CH_3); 2.35 (s, 3H, N-O-CO-CH_3); 3.85 (s, 3H, OCH_3); 6.90–7.40 (m, 5H, ArH and thiophene); 7.60–7.80 (m, 1H, thiophene). Anal $C_{16}H_{15}NO_5S$ (C, H, N, S).

Preparation of 3-(2-thienyl)-1,2-benzisoxazoles ***5*** *and 2-(2-thienyl)benzoxazoles* ***6***

Route A. Cyclization of the (2-acetoxyaryl)(2-thienyl)methanone O-acetyl oximes ***4***. To a stirred suspension of 27 mmol sodium hydride (60% dispersion in mineral oil) in anhydrous *N,N*-dimethylformamide (20 ml) at 0°C, under a nitrogen atmosphere, was added dropwise 25 mmol **4** in 50 ml dimethylformamide, over 10 min. The reaction mixture was stirred at room temperature for 4 h and poured into cold brine (300 ml). After extraction with ethyl acetate, the organic layer was washed with brine and dried (Na_2SO_4). After the solvents had been removed by distillation, the residue was chromatographed through a silica-gel column eluting with hexane/dichloromethane (60:40), to give first the 1,2-benzisoxazole **5**. The isomeric benzoxazole **6** was eluted later. From the final fraction was obtained the unreacted (*E*) oxime.

6-Methoxy-3-(2-thienyl)-1,2-benzisoxazole ***5a*** *and 6-methoxy-2-(2-thienyl) benzoxazole* ***6a***. These were obtained from **4a**. The experimental procedure and spectral data (^{1}H- and ^{13}C-NMR, MS) for these compounds were given in a previous communication [4].

6,7-Dimethoxy-3-(2-thienyl)-1,2-benzisoxazole ***5b***. This was obtained from **4b**, as the sole product in 39% yield, mp 86–87°C after recrystallization from hexane. ^{1}H-NMR (60 MHz, $CDCl_3$) δ 3.85 (s, 3H, OCH_3); 4.10 (s, 3H, OCH_3); 6.85–7.65 (AB system, 2H, J_{AB} = 9 Hz, 2 ArH); 7.05–7.25 (m, 1H, thiophene); 7.35–7.50 (m, 1H, thiophene); 7.55–7.70 (m, 1H, thiophene). Anal $C_{13}H_{11}NO_3S$ (C, H, N, S).

7-Methoxy-3-(-2-thienyl)-1,2-benzisoxazole ***5c*** *and 7-methoxy-2-(2-thienyl) benzoxazole* ***6c***. These were obtained from **4c** in 24 and 18% yields respectively.

Selected data for **5c**: mp 108–110°C after recrystallization from cyclohexane. ^{1}H-NMR (60 MHz, $CDCl_3$) δ 4.00 (s, 3H, OCH_3); 6.85–7.55 (m, 5H, ArH and thiophene); 7.65–7.85 (m, 1H, thiophene). Anal $C_{12}H_9NO_2S$ (C, H, N, S).

Selected data for **6c**: mp 116°C after recrystallization from cyclohexane. ^{1}H-NMR (60 MHz, $CDCl_3$) δ 4.00 (s, 3H, OCH_3); 6.75–7.60 (m, 5H, ArH and thiophene); 7.85–8.05 (m, 1H, thiophene). Anal $C_{12}H_9NO_2s$ (C, H, N, S).

Route B. Cyclization of the (2-hydroxyaryl)(2-thienyl)methanone oximes ***3***. In some cases, direct treatment of the oximes **3** with sodium hydride in DMF afforded the desired cyclized products.

7-Methoxy-3-(5-methyl-2-thienyl)-1,2-benzisoxazole ***5d*** *and 7-methoxy-2-(5-methyl-2-thienyl) benzoxazole* ***6d***. These were obtained from **3d** in 25 and 17% yield, respectively.

Selected data for **5d**: mp 73°C after recrystallization from hexane. ^{1}H-NMR (200 MHz, $CDCl_3$) δ 2.48 (s, 3H, CH_3); 3.95 (s, 3H, OCH_3); 6.73–6.78 (m, 1H, ArH); 6.87–7.41 (AB system, 2H, J_{AB} = 6.3 Hz, thiophene); 7.13–7.22 (m, 1H, ArH); 7.45–7.50 (m, 1H, ArH). Anal $C_{13}H_{11}NO_2S$ (C, H, N, S).

Selected data for **6d**: mp 110°C after recrystallization from cyclohexane. ^{1}H-NMR (60 MHz, $CDCl_3$) δ 2.50 (s, 3H, CH_3);

4.00 (s, 3H, OCH_3); 6.73–6.95 (m, 2H, ArH); 7.15–7.36 (m, 1H, ArH); 7.20–7.76 (AB system, 2H, J_{AB} = 4 Hz, thiophene). Anal $C_{13}H_{11}NO_2S$ (C, H, N, S).

7-Methoxy-3-(3-methyl-2-thienyl)-1,2-benzisoxazole ***5e*** *and 7-methoxy-2-(3-methyl-2-thienyl) benzoxazole* ***6e***. These were obtained from **3e** in 24 and 32% yields, respectively.

Selected data for **5e**: mp 115°C after recrystallization from cyclohexane. ^{1}H-NMR (60 MHz, $CDCl_3$) δ 2.55 (s, 3H, CH_3); 4.00 (s, 3H, OCH_3); 6.85–7.60 (m, 3H, ArH); 6.96–7.46 (AB system, 2H, J_{AB} = 5 Hz, thiophene). Anal $C_{13}H_{11}NO_2S$ (C, H, N, S).

Selected data for **6e**: mp 127°C after recrystallization from cyclohexane. ^{1}H-NMR (60 MHz, $CDCl_3$) δ 2.75 (s, 3H, CH_3); 4.05 (s, 3H, OCH_3); 6.70–7.35 (m, 3H, ArH); 6.85–7.45 (AB system, 2H, J_{AB} = 6 Hz, thiophene). Anal $C_{13}H_{11}NO_2S$ (C, H, N, S).

7-Methoxy-3-(5-bromo-2-thienyl)-1,2-benzisoxazole ***5f***. This was obtained from **3f**, as sole product in 37% yield, mp 105°C after recrystallization from cyclohexane. ^{1}H-NMR (60 MHz, $CDCl_3$) δ 4.00 (s, 3H, OCH_3); 6.85–7.45 (m, 3H, ArH); 7.05–7.50 (AB system, 2H, J_{AB} = 4 Hz, thiophene). Anal $C_{12}H_8BrNO_2S$ (C, H, Br, N, S).

5-Bromo-7-methoxy-3-(2-thienyl)-1,2-benzisoxazole ***5g*** *and 5-bromo-7-methoxy-2-(2-thienyl) benzoxazole* ***6g***. These were obtained from **3g** in 27 and 7% yields respectively.

Selected data for **5g**: mp 137°C after recrystallization from hexane. ^{1}H-NMR (60 MHz, $CDCl_3$) δ 4.05 (s, 3H, OCH_3); 7.08 (s, 1H, ArH); 7.60 (s, 1H, ArH); 7.05–7.85 (m, 3H, thiophene). Anal $C_{12}H_8BrNO_2S$ (C, H, Br, N, S).

Selected data for **6g**: mp 146°C after recrystallization from cyclohexane. ^{1}H-NMR (60 MHz, $CDCl_3$) δ 4.00 (s, 3H, OCH_3); 6.96 (s, 1H, ArH); 7.06–7.26 (m, 1H, thiophene); 7.40–7.66 (m, 1H, thiophene); 7.46 (s, 1H, ArH); 7.85–8.03 (m, 1H, thiophene). Anal $C_{12}H_8BrNO_2S$ (C, H, Br, N, S).

Preparation of carboxylic acid derivatives ***5h, i***

5-(7-Methoxy-1,2-benzisoxazol-3-yl)thiophene-2-carboxylic acid ***5h***. To a stirred solution of 1.55 g (5 mmol) of **5f** in anhydrous diethyl ether (20 ml) maintained at –35°C under nitrogen, was added dropwise *via* a syringe 3.15 ml a 1.6 M *n*-butyllithium solution in hexane (5.04 mmol). The mixture was stirred for 15 min and was then poured upon a large excess of solid carbon dioxide (100 g) in the form of a Cardice-ether slurry contained in a large beaker. After complete evolution of excess carbon dioxide, the crude mixture was hydrolysed by cautious addition of water (50 ml). The organic layer was treated with 2M sodium hydroxide (50 ml). The combined aqueous solutions were washed with diethyl ether (2 x 15 ml), then acidified (pH ≈ 1) with hydrochloric acid. The white precipitate was collected, washed with cold water and dried. Recrystallization from heptane/acetone (90:10) afforded 0.79 g of **5h** (58%), mp 275°C. IR (KBr): 1689 cm^{-1} ($\nu_{C=O}$); 2500–3300 cm^{-1} (ν_{O-H}). ^{1}H-NMR (60 MHz, DMSO–d_6), δ 4.05 (s, 3H, OCH_3); 7.17–7.80 (m, 3H, ArH); 7.82–8.03 (AB system, 2H, J_{AB} = 4 Hz, thiophene), 12.20 (br, s, 1H, COOH). Anal $C_{13}H_9NO_4S$ (C, H, N, S).

7-Methoxy-3-(2-thienyl)-1,2-benzisoxazole-5-carboxylic acid ***5i***. This was obtained from **5g**, in the same manner as **5h**, in 16% yield, mp 262°C after recrystallization from cyclohexane. IR (KBr): 1670 cm^{-1} ($\nu_{C=O}$); 2500–3400 (ν_{O-H}). ^{1}H-NMR (60 MHz, DMSO–d_6) δ 4.10 (s, 3H, OCH_3); 7.40 (s, 1H, ArH); 7.85 (s, 1H, ArH); 7.35–8.10 (m, 3H, thiophene); 10.60 (s, 1H, COOH). Anal $C_{13}H_9NO_4S$ (C, H, N, S).

Preparation of 7-alkyloxy-3-(2-thienyl)-1,2-benzisoxazoles ***8–13***

3-(2-Thienyl)-1,2-benzisoxazol-7-ol ***7***. To a stirred solution of 1.15 g (5 mmol) of **5c** in dichloromethane (25 ml) at 0°C under nitrogen, was added dropwise 2.50 g (10 mmol) of boron tribromide. After the addition was complete, the reaction mixture was warmed at reflux for 18 h under stirring, and was then poured into 100 ml ice water. Following 15 min hydrolysis, the resulting mixture was extracted with diethyl ether (3 x 50 ml). The organic layer was washed with brine, dried (Na_2SO_4) and evaporated to give 0.84 g of **7** (78%), mp 129°C after recrystallization from heptane/acetone (90:10). IR (KBr): 3200 cm^{-1} (br, band, ν_{O-H}). ^{1}H-NMR (60 MHz, CD_3-CO-CD_3) δ 7.00–7.75 (m, 5H, ArH and thiophene); 7.85–8.05 (m, 1H, thiophene); 9.30 (br, s, 1H, OH). Anal $C_{11}H_7NO_2S$ (C, H, N, S).

{[3-(2-Thienyl)-1,2-benzisoxazol-7-yl]oxy}-acetic acid, ethyl ester ***8***. A mixture of **7** (2.17 g, 10 mmol), potassium carbonate (3.45 g, 25 mmol) and ethyl bromoacetate (2.50 g, 15 mmol) in 30 ml anhydrous *N,N*- dimethylformamide was warmed at 60°C for 2 h, under vigorous stirring. After cooling, the reaction mixture was poured into water (100 ml) and extracted with dichloromethane. The organic phase was well washed with 4M hydrochloric acid and water. Evaporation of the solvents gave an oily residue which solidified on cooling. Recrystallization from hexane/acetone (95:5) afforded 2.60 g (85%) of **8**, mp 68°C. IR (KBr): 1770 cm^{-1} ($\nu_{C=O}$). ^{1}H-NMR (60 MHz, $CDCl_3$) δ 1.25 (t, J = 7.5 Hz, 3H, CH_3); 4.20 (q, J = 7.5 Hz, 2H, -CH_2-CH_3); 4.85 (s, 2H, -O-CH_2); 6.85–7.62 (m, 5H, ArH and thiophene); 7.67–7.82 (m, 1H, thiophene). Anal $C_{15}H_{13}NO_4S$ (C, H, N, S).

{[3-(2-Thienyl)-1,2-benzisoxazol-7-yl]oxy}-acetic acid ***9***. The ethyl ester **8** (1.52 g, 5 mmol) was hydrolysed at reflux for 2 h in 50 ml of ethanol/water mixture (1:1) with sodium carbonate (1.06 g, 10 mmol). After cooling, the mixture was acidified with 4 M hydrochloric acid. The obtained precipitate was collected by filtration, well washed with water and recrystallized from 75% ethanol to give 1.05 g (76%) of **9**, mp 196°C. IR (KBr): 1730 cm^{-1} ($\nu_{C=O}$); 2500–3200 (ν_{O-H}). ^{1}H-NMR (60 MHz, DMSO–d_6) δ 5.00 (s, 2H, -OCH_2); 7.10–8.05 (m, 6H, ArH and thiophene); 13.10 (br, s, 1H, COOH). Anal $C_{13}H_9NO_4S$ (C, H, N, S).

4-Methyl-1-{[3-(2-thienyl)-1,2-benzisoxazol-7-yl] oxyacetyl} piperazine ***10***. Oxalyl chloride (1.27 g, 10 mmol) was added portionwise *via* a syringe to a stirred solution of **9** (1.37 g, 5 mmol) in dichloromethane (30 ml) under nitrogen. The resulting mixture was stirred to room temperature over a 6-h period. After cooling in an ice bath, a solution of freshly distilled *N*-methylpiperazine (1.00 g, 10 mmol) in dichloromethane (10 ml) was added. The reaction mixture was stirred for 12 h at room temperature and evaporated. The resulting residue was recrystallized from water to give 1.30 g **10** (66%) as the hydrochloride salt, mp 266–267°C. The salt was dissolved in water at 60°C, and the solution made basic with dilute aqueous sodium hydroxide, to yield the free base which was collected. After washing (H_2O) and drying *in vacuo*, recrystallization from hexane/acetone (90:10) afforded pure **10**, mp 145°C. IR (KBr): 1665 cm^{-1} ($\nu_{C=O}$). ^{1}H-NMR (60 MHz, $CDCl_3$) δ 2.25 (s, 3H, N-CH_3); 2.30–2.50 (m, 4H, piperazine); 3.50–3.75 (m, 4H, piperazine); 5.00 (s, 2H, -OCH_2); 7.00–7.90 (m, 6H, ArH and thiophene). Anal $C_{18}H_{19}N_3O_3S$ (C, H, N, S).

7-(Oxiranylmethoxy)-3-(2-thienyl)-1,2-benzisoxazole ***11***. A stirred mixture of **7** (1.08 g, 5 mmol) and epichlorohydrin (1.85 g, 20 mmol) was heated to *ca* 80°C and treated with a solution of sodium hydroxide (0.21 g, 5.25 mmol) in water (0.5 ml). The resulting mixture was heated at 80°C under stirring for 2 h. After cooling, water (20 ml) was added and the reaction mixture extracted with dichloromethane. The combined organic phases were washed with water until neutral, dried (Na_2SO_4) and concentrated to give an oil which was purified by chromatography on a silica-gel column eluting with dichloromethane/ethyl acetate (98:2). The first fraction afforded 0.61 g of **11** (45%), mp 116–118°C after recrystallization from heptane. ^{1}H-NMR (60 MHz, $CDCl_3$) δ 2.55–2.95 (m, 2H, CH_2 oxirane); 3.15–3.50 (m, 1H, CH oxirane); 3.90–4.60 (m, 2H, -OCH_2); 6.80–7.80 (m, 6H, ArH and thiophene). Anal $C_{14}H_{11}NO_3S$ (C, H, N, S).

3-{[3-(2-Thienyl)-1,2-benzisoxazol-7-yl]oxy}-1,2-propanediol ***12***. A slurry of **11** (1.37 g, 5 mmol) and 72% perchloric acid (2 ml) in water (20 ml) was heated at 80°C for 12 h with vigorous stirring. After cooling, the mixture was basified with aqueous sodium carbonate, and extracted with dichloromethane. The dried extract (Na_2SO_4) was concentrated *in vacuo* and chromatographed on a silica-gel column eluting with dichloromethane/methanol (97:3) to give 0.20 g of **12** (14%), mp 105–107°C. IR (KBr): 3300 cm^{-1} (ν_{O-H}). ^{1}H-NMR (200 MHz, DMSO–d_6) δ 3.35–3.60 (m, 2H, CH_2OH); 3.86–4.02 (m,1H, -CHOH); 4.10–4.36 (m, 2H, -OCH_2); 4.80 (t, 1H, -CH_2-*OH*); 5.15 (d, 1H, CH*OH*); 7.26–7.49 (m, 3H, ArH); 7.74–7.81 (m, 1H, thiophene); 7.89–7.97 (m, 1H, thiophene); 8.06–8.13 (m, 1H, thiophene). Anal $C_{14}H_{13}NO_4S$ (C, H, N, S).

2-{[3-(2-Thienyl)-1,2-benzisoxazol-7-yl] oxy}-1-ethanol ***13***. To a stirred suspension of lithium aluminium hydride (0.14 g, 3.75 mmol) in anhydrous diethyl ether (50 ml) was added dropwise **8** (1.52 g, 5 mmol) dissolved in diethyl ether (20 ml), under nitrogen atmosphere. The mixture was stirred at ambient temperature for 24 h, then hydrolysed with a saturated aqueous solution of sodium sulfate. The residual alumina precipitate was removed by filtration and washed with diethyl ether (2 x 20 ml). The combined organic layers, dried (Na_2SO_4) and evaporated to give a residue which was recrystallized from cyclohexane/acetone (80:20) to afford 0.30 g **13** (23%), mp 105°C. IR(KBr): 3250 cm^{-1} (ν_{O-H}). ^{1}H-NMR (60 MHz, $CDCl_3$) δ 2.75 (t, 1H, OH); 3.85–4.15 (m, 2H, CH_2OH); 4.15–4.45 (m, 2H, OCH_2); 6.85–7.80 (m, 6H, ArH and thiophene). Anal $C_{13}H_{11}NO_3S$ (C, H, N, S).

Preparation of 7-acetoxy-3-(2-thienyl)-1,2-benzisoxazole ***14***
A stirred solution of 2.17 g (10 mmol) **7** in acetic anhydride (20 ml) was heated under reflux for 1 h. After acetic acid and excess acetic anhydride had been distilled off under reduced pressure, the reaction mixture was allowed to cool and treated with 200 ml cold water. The resulting precipitate was washed with water until neutral and dried *in vacuo*. After chromatography on silica-gel column eluting with dichloromethane, a recrystallization from heptane afforded 1.4 g of **14** (54%), mp 120°C. IR(KBr): 1760 cm^{-1} ($\nu_{C=O}$). ^{1}H-NMR (60 MHz, $CDCl_3$) δ 2.45 (s, 3H, CH_3); 7.05–7.95 (m, 6H, ArH and thiophene). Anal $C_{13}H_9NO_3S$ (C, H, N, S).

Preparation of 7-methoxy-3-(4-methoxyphenyl)-1,2-benzisoxazole ***17a***

2-Hydroxy-3,4'-dimethoxybenzophenone ***15***. This was obtained from 2,3-dimethoxybenzoylchloride and anisole according to the protocol indicated in reference [2], in 74% yield, mp 96°C after recrystallization from heptane.

2-Hydroxy-3,4'-dimethoxybenzophenone oxime ***16***. This was obtained from **15**, in the same manner as **3a**, in 67% yield, mp 231°C (mixture of *E* and *Z* isomers) after recrystallization from ethanol. IR(KBr): 3420 cm^{-1} (ν_{O-H} oxime). ^{1}H-NMR (60 MHz, DMSO–d_6) δ 3.80 (s, 3H, OCH_3); 3.85 (s, 3H, OCH_3); 6.30–7.40 (m, 7H, ArH); 11.25 (br, s, 2H, OH).

7-Methoxy-3-(4-methoxyphenyl)-1,2-benzisoxazole ***17a***. A solution of **16** (2.73 g, 10 mmol) in acetic anhydride (100 ml) was stirred at 90°C for 1 h and then kept at room temperature for 18 h. The reaction mixture was concentrated *in vacuo* and the residue triturated with cyclohexane to give 2.26 g (64%) of crude 2-acetoxy-3,4'-dimethoxybenzophenone-*O*-acetyloxime, mp 126°C. ^{1}H-NMR (60 MHz, $CDCl_3$) δ 1.90 (s, 3H, CO-CH_3); 2.10 (s, 3H, CO-CH_3); 3.80 (s, 3H, OCH_3); 3.85 (s, 3H, OCH_3); 6.50–7.50 (m, 7H, ArH).

To a solution of this intermediate (1.79 g, 5 mmol) in anhydrous *N,N*-dimethylformamide (30 ml) was added 0.24 g (6 mmol) of sodium hydride (60% dispersion in mineral oil). After stirring for 4 h at ambient temperature, the reaction mixture was poured into cold water and extracted with ethyl acetate. Upon normal workup, the extract gave a residue which was chromatographed through a silica-gel column eluting with dichloromethane/ethyl acetate (95:5) to afford 0.38 g (30%) of **17a**, mp 102°C after recrystallization from cyclohexane. ^{1}H-NMR (60 MHz, $CDCl_3$) δ 3.80 (s, 3H, OCH_3); 4.00 (s, 3H, OCH_3); 6.80–7.50 (m, 3H, ArH); 6.90–7.90 (AA'BB' system, 4H, ArH). Anal $C_{15}H_{13}NO_3$ (C, H, N).

Preparation of 3-(1-imidazolyl)-1,2-benzisoxazoles ***19a–e***
3-Chloro-1,2-benzisoxazole **18a** and 3-chloro-7-methoxy-1,2-benzisoxazole **18b** were synthesized according to the Böshagen method [16] *via* the corresponding 3-hydroxy derivatives [17, 18].

3-(1-Imidazolyl)-1,2-benzisoxazole ***19a***. To a stirred suspension of 2.30 g (55 mmol) sodium hydride (60% dispersion in mineral oil) in anhydrous *N,N*-dimethylformamide (50 ml) was added a mixture of **18a** (7.68 g, 50 mmol) and imidazole (3.75 g, 55 mmol) in dimethylformamide (30 ml). The reaction mixture was heated at 80°C for 24 h, and after cooling, poured into ice water (100 ml). The resulting precipitate was collected by filtration, and recrystallized from water to give 5.09 g of **19a** (55%), mp 118°C. ^{1}H-NMR (60 MHz, DMSO–d_6) δ 7.35–8.35 (m, 6H, ArH and imidazole); 8.70 (s, 1H, imidazole). Calc for $C_{10}H_7N_3O$: C, 64.86; H, 3.81; N, 22.69. Found: C, 65.46; H, 3.79; N, 22.85.

3-(1-Imidazolyl)-7-methoxy-1,2-benzisoxazole ***19b***. This was obtained from **18b** and imidazole, in the same manner as **19a**, in 70% yield, mp 140°C after recrystallization from heptane/acetone (90:10). ^{1}H-NMR (60 MHz, DMSO–d_6) δ 4.05 (s, 3H, OCH_3); 7.15–8.05 (m, 5H, ArH and imidazole); 8.55 (s, 1H, imidazole). Anal $C_{11}H_9N_3O_2$ (C, H, N).

1-(7-Methoxy-1,2-benzisoxazol-3-yl)imidazole-4-carboxylic acid, ethyl ester ***19e***. This was obtained from **18b** and ethyl imidazole-4-carboxylate [19] in the same manner as **19a**, in 10% yield, mp 137°C after chromatography on a silica-gel column eluting with dichloromethane/ethyl acetate (60:40). IR (KBr): 1740 cm^{-1} ($\nu_{C=O}$). ^{1}H-NMR (60 MHz, $CDCl_3$) δ 1.40 (t, J = 7.5 Hz, 3H, -CH_2-CH_3); 4.10 (s, 3H, -O-CH_3); 4.45 (q, J = 7.5 Hz; 2H, -CH_2-CH_3); 6.95–7.55 (m, 3H, ArH); 8.35 (s, 2H, imidazole). Anal $C_{14}H_{13}N_3O_4$ (C, H, N).

3-Chloro-1,2-benzisoxazol-7-ol ***18c***. This was obtained from **18b** and boron tribromide in dichloromethane, in the same manner as **7**, in 72% yield, mp 116°C, after chromatography on silica-gel column eluting with dichloromethane/ethyl acetate (50:50). IR(KBr): 3300 cm^{-1} (ν_{OH}). ^{1}H-NMR (60 MHz, $CDCl_3$) δ 6.80–7.35 (m, 3H, ArH); 9.50 (br, s, 1H, OH).

[(3-Chloro-1,2-benzisoxazol-7-yl)oxy]-acetic acid, ethyl ester ***18d***. This was obtained from **18c** and ethyl bromoacetate, in the same manner as **8**, in 94% yield, mp 60°C after recrystallization from heptane/acetone (95:5). IR (KBr): 1760 cm^{-1} ($\nu_{C=O}$). ^{1}H-NMR (60 MHz, $CDCl_3$) δ 1.40 (t, J = 7.5 Hz, 3H, $-CH_2-CH_3$); 4.40 (q, J = 7.5 Hz; 2H, $-CH_2-CH_3$); 4.95 (s, 2H, $-O-CH_2$); 7.00–7.80 (m, 3H, ArH).

{[3-(1-Imidazolyl)-1,2-benzisoxazol-7-yl]oxy}-acetic acid,ethyl ester ***19c***. This was obtained from **18d** and imidazole, in the same manner as **19a**, in 34% yield after chromatography through a silica-gel column (dichloromethane/ethyl acetate, 50:50) followed by recrystallization from heptane, mp 100°C. IR(KBr): 1760 cm^{-1} ($\nu_{C=O}$). ^{1}H-NMR (60 MHz, $CDCl_3$) δ 1.35 (t, J = 7.5 Hz, 3H, $-CH_2-CH_3$); 4.35 (q, J = 7.5 Hz; 2H, $-CH_2-CH_3$); 5.00 (s, 2H, $-O-CH_2$); 7.05–7.85 (m, 5H, ArH and imidazole); 8.35 (s, 1H, imidazole). Anal $C_{14}H_{13}N_3O_4$ (C, H, N).

{[3-(1-Imidazolyl)-1,2-benzisoxazol-7-yl]oxy}-acetic acid ***19d***. A stirred mixture of **19c** (1.44 g, 5 mmol) and sodium carbonate (2.65 g, 25 mmol) in 50% ethanol (60 ml) was heated at reflux for 2 h. The reaction mixture was concentrated *in vacuo* to about one-third the initial volume, and neutralized with 20% aqueous acetic acid. The filtered crude product was washed with water and recrystallized from ethanol to afford 0.56 *g* **19d** (43%), mp 240°C. IR(KBr): 1680 cm^{-1} ($\nu_{C=O}$); 2500– 3400 cm^{-1} (ν_{O-H}). ^{1}H-NMR (60 MHz, DMSO–d_6) δ 4.55 (s, 2H, OCH_2); 7.05–8.10 (m, 5H, ArH and imidazole); 8.60 (s, 1H, imidazole); 12.50 (br, s, 1H, COOH). Anal $C_{12}H_9N_3O_4$ (C, H, N).

Pharmacological evaluation: inhibitory effect on arachidonic acid-induced platelet aggregation

The experimental protocol was described in our previous communication [1].

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