Novel Arylpyrazino[2,3-*c*][1,2,6]thiadiazine 2,2-Dioxides as Inhibitors of Platelet Aggregation. 1. Synthesis and Pharmacological Evaluation

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A series of N-1-substituted derivatives of pyrazino[2,3-*c*][1,2,6]thiadiazine 2,2-dioxides bearing aryl groups at the pyrazino moiety have been prepared. The synthesis involves ring formation between the diaminothiadiazine and suitable dicarbonyl compounds and subsequent introduction of the substituent at N-1. The compounds have been tested in vitro, as inhibitors of rabbit and human platelet aggregation, and ex vivo against rat platelet aggregation induced by arachidonic acid, ADP, collagen, U46619, and I-BOP. The results obtained indicate that some pyrazino[2,3-*c*][1,2,6]thiadiazine derivatives show significant platelet aggregation inhibition similar to other antithrombotic agents and that the antiplatelet properties may be mediated by interference with the arachidonic acid pathway.

Introduction

The basic molecular mechanisms involved in the formation and dissolution of thrombus are the subject of continuous research. Platelet aggregation is an important part of the process, and so, special attention is given to agents capable of interfering with platelet recruitment into forming thrombus and which can, therefore, play an important role in the treatment of atherosclerosis, thrombosis, and acute coronary syndromes.[1]

One approach for the development of novel agents to antiplatelet therapy via the arachidonic acid cascade consists of the inhibition of the biological effects of thromboxane A_2 (TxA_2).[2−4] Different lines of research are currently under investigation in this area including the development of thromboxane receptor antagonists as well as compounds interfering with the biosynthesis of TxA_2 through inhibition of cyclooxygenase or thomboxane synthase. However, this last approach has not yet demonstrated efficacy in the clinic[2] due probably to PGH_2 accumulation. Therefore, compounds with TxA_2/endoperoxide receptor blocking activity or compounds displaying dual properties such as TxA_2 synthase inhibition and TxA_2/endoperoxide receptor blockage could be useful in thrombotic disease.[2,5]

Within this context, we describe here a new class of platelet aggregation inhibitors with no structural relation to other antiplatelet agents known and which are aryl derivatives of the pyrazino[2,3-*c*][1,2,6]thiadiazine 2,2-dioxide system. This heterocyclic structure, which was first synthesized in our group,[6] has been the subject of our research, and we have previously reported on its particular structural characteristics[7−9] and, also, on the biological properties of some of its derivatives bearing alkyl groups at positions 6 and 7.[10] We now wish to report the synthesis and effect on the platelet aggregation, induced by different agonists, both in vitro and ex vivo of a new series of N-1-substituted derivatives of pyrazino[2,3-*c*][1,2,6]thiadiazine 2,2-dioxide derivatives with one or two aryl rests at the pyrazino moiety.

Chemistry

The compounds prepared for this work are gathered in Table 1. Their synthetic route is a two-step procedure involving, first, the preparation of the parent NH-pyrazino[2,3-*c*][1,2,6]thiadiazines with the desired aryl substituents at positions 6 and 7 and then introduction of the substituent at position N-1 using different alkylating agents.

Thus, the first step is the condensation between 3,4,5-triamino-2*H*-1,2,6-thiadiazine 1,1-dioxide (**1**)[11] and adequately functionalized dicarbonyl compounds. So, reaction of **1** with symmetric 1,2-dicarbonyl compounds such as benzil, 2,2′-thenil, 2,2′-furil, and 2,2′-pyridil afforded the corresponding 6,7-diphenyl, 6,7-di(2-thienyl), 6,7-di(2-furyl), and 6,7-di(2-pyridyl) compounds **2**,[6] **3**, **4**, and **5**, respectively (Scheme 1).

When the dicarbonyl compound used to build the pyrazino moiety is not symmetrical, then, in principle, the two possible isomers at positions 6 and 7 can be obtained. We had already reported one case in which by replacing one of the two carbonyl compounds with hydroxyimino function it was possible to obtain only the isomer bearing at position 7 the substituent linked to it.[12] Thus, by reaction of **1** with α-hydroxyiminoacetophenone and 1-phenyl-2-hydroxyimino-1-propanone, it was possible to obtain, exclusively, the 6-phenyl-7*H*- and 6-phenyl-7-methylpyrazinothiadiazines **6**[12] and **7**. However, when the keto aldehyde compounds phenylglyoxal and 1-phenyl-1,2-propanedione were used, the corresponding 7-phenyl-6*H* and 7-phenyl-6-methyl derivatives **8**[12] and **9** were obtained. The 6-bromo- and 6-chloropyrazinothiadiazines **10**[12] and **11** were prepared from the unsubstituted at position 6 derivative **8** by reaction with NBS in methanol and with NCS in DMF, respectively (Scheme 1).

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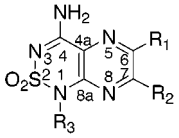
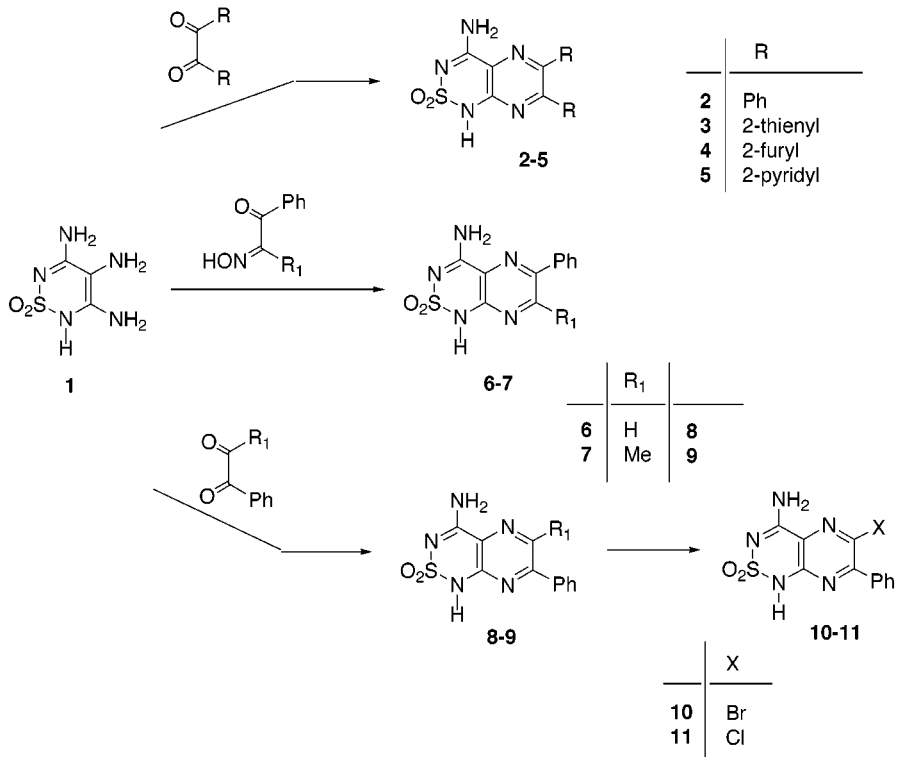
Table 1. Physicochemical Data for 4-Aminopyrazino[2,3-*c*][1,2,6]thiadiazine 2,2-Dioxides **3**−**5**, **7**, **9**, and **11**−**24**



compd	R_1	R_2	R_3	mp (°C)	recryst solv	formula	anal.[a]
3	2-thienyl	2-thienyl	H	268−9	EtOH/H_2O	$C_{13}H_9N_5O_2S_3$	C,H,N,S
4	2-furyl	2-furyl	H	310−12	H_2O/E_tOH	$C_{13}H_9N_5O_4S$	C,H,N,S
5	2-pyridyl	2-pyridyl	H	>350	AcOH/H_2O	$C_{15}H_{11}N_7O_2S\cdot1.5H_2O$	C,H,N,S
7	Ph	Me	H	274−6	EtOH/H_2O	$C_{12}H_{11}N_5O_2S$	C,H,N,S
9	Me	Ph	H	274−6	H_2O	$C_{12}H_{11}N_5O_2S$	C,H,N,S
11	Cl	Ph	H	263−5	MeOH/H_2O	$C_{11}H_8ClN_5O_2S$	C,H,Cl,N,S
12	Ph	Ph	Et	260−1	EtOH	$C_{19}H_{17}N_5O_2S$	C,H,N
13	Ph	Ph	CH_2Ph	258	EtOH	$C_{24}H_{19}N_5O_2S$	C,H,N,S
14	Ph	Ph	CH_2CO_2Et	234	EtOH	$C_{21}H_{19}N_5O_4S$	C,H,N,S
15	Ph	Ph	$CH_2CO_2{}^tBu$	204−5		$C_{23}H_{23}N_5O_4S$	C,H,N,S
16	Ph	Ph	CH_2CONH_2	293−5		$C_{19}H_{16}N_6O_3S$	C,H,N,S
17	2-thienyl	2-thienyl	Et	244−5	Acetone/H_2O	$C_{15}H_{13}N_5O_2S_3$	C,H,N,S
18	2-furyl	2-furyl	Me	232−4	^{i}PrOH	$C_{14}H_{11}N_5O_4S$	C,H,N,S
19	2-pyridyl	2-pyridyl	Me	255−6	EtOH/Acetone	$C_{16}H_{13}N_7O_2S$	C,H,N,S
20	Ph	Me	Et	161−3	EtOH/H_2O	$C_{14}H_{15}N_5O_2S$	C,H,N,S
21	Me	Ph	Et	206−7	H_2O/E_tOH	$C_{14}H_{15}N_5O_2S$	C,H,N,S
22	Cl	Ph	Et	214−6	EtOH	$C_{13}H_{12}ClN_5O_2S$	C,H,Cl,N,S
23	Ph	H	Me	295	CH_2Cl_2/MeOH	$C_{12}H_{11}N_5O_2S$	C,H,N,S
24	Br	Ph	CH_2CO_2Et	182−4	EtOH/H_2O	$C_{15}H_{14}B_rN_5O_4S$	C,H,N,S

[a] Elemental analyses were within ±0.4% of the calculated values for the formulas given.

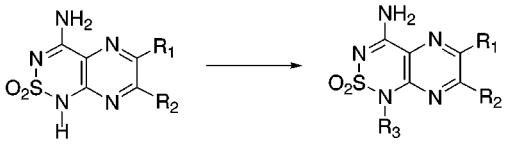
Scheme 1



Different alkyl derivatives of the pyrazino[2,3-*c*][1,2,6]-thiadiazines were prepared using the corresponding halides in acetone and with either potassium carbonate or triethylamine as base (Table 1, Scheme 2). Thus, 6,7-diphenylpyrazinothiadiazine **2** with ethyl iodide, benzyl bromide, and ethyl and *tert*-butyl bromoacetate in acetone and potassium carbonate yielded the corresponding N-1 ethyl, benzyl, ethoxycarbonylmethyl, and *tert*-butoxycarbonylmethyl derivatives **12**, **13**, **14**, and **15**, respectively. The carbamoylmethyl compound **16** was prepared from the 1-ethoxycarbonylmethyl derivative **14** by treatment with ammonia in methanol at room temperature.

Treatment with ethyl iodide of 6,7-di(2-thienyl)-1*H*-pyrazinothiadiazine **3**, in the presence of triethylamine, afforded the corresponding 1-ethyl derivative **17**, while reaction of the 6,7-di(2-furyl) derivative **4** with methyl iodide was performed using potassium carbonate to give the 1-methyl derivative **18**. In the case of the 6,7-di(2-pyridyl)pyrazinothiadiazine **5** with methyl iodide and triethylamine, it was possible to obtain the N-1 methyl derivative **19** in a very major proportion in relation to

Scheme 2



2- 7, 9 - 11 **12- 24**

	R_1	R_2
2	Ph	Ph
3	2-thienyl	2-thienyl
4	2-furyl	2-furyl
5	2-pyridyl	2-pyridyl
6	Ph	H
7	Ph	Me
9	Me	Ph
10	Br	Ph
11	Cl	H

	R_1	R_2	R_3
12	Ph	Ph	Et
13	Ph	Ph	CH_2Ph
14	Ph	Ph	CH_2CO_2Et
15	Ph	Ph	$CH_2CO_2{}^tBu$
16	Ph	Ph	CH_2CONH_2
17	2-thienyl	2-thienyl	Et
18	2-furyl	2-furyl	Me
19	2-pyridyl	2-pyridyl	Me
20	Ph	Me	Et
21	Me	Ph	Et
22	Cl	Ph	Et
23	Ph	H	Me
24	Br	Ph	CH_2CO_2Et

Table 2. ^{13}C NMR Data (δ, DMSO-d_6) for Pyrazino[2,3-*c*][1,2,6]thiadiazine 2,2-Dioxides **3**−**5**, **7**, **9**, and **11**−**24**

compd	R_1	R_2	R_3	C-4	C-7	C-8a	C-6	C-4a	other signals
3	2-thienyl	2-thienyl	H	157.9	149.5	146.9	138.2	119.2	139.5, 138.6, 132.0, 130.6, 129.4, 128, 8, 128.2
4	2-furyl	2-furyl	H	157.9	147.1	144.4	134.1	119.4	149.6, 149.1, 146.5, 143.9, 115.5, 112.7, 112.0
5	2-pyridyl	2-pyridyl	H	158.3	155.5	147.4	144.5	120.1	155.7, 148.3, 147.8, 136.7, 124.0, 123.8, 123.1
7	Ph	Me	H	158.8	156.9	147.1	146.5	119.4	137.0, 129.2, 128.6, 128.1, 23.2
9	Me	Ph	H	158.5	157.1	146.9	144.6	119.8	136.9, 129.5, 128.9, 128.2, 22.2
11	Cl	Ph	H	157.4	156.5	147.5	135.1	119.9	137.3, 130. 4, 129.5, 128.5
12	Ph	Ph	Et	158.5	155.3	146.5	144.4	120.8	137.4, 137.1, 129.8, 128.6, 128.3, 128.1, 37.9, 14.0
13	Ph	Ph	CH_2Ph	158.6	155.1	146.6	144.9	121.0	137.1, 137.0, 136.9, 129.8, 128.6, 128.2, 128.2, 128.1, 127.3, 37.9, 14.0
14	Ph	Ph	CH_2CO_2Et	158.3	155.0	146.1	145.3	120.8	158.9, 158.8, 138.5, 138.3, 129.3, 129.0, 121.9, 121.9, 115.2, 114.2, 55.0, 28.1
15	Ph	Ph	$CH_2CO_2{}^tBu$	158.5	155.0	146.2	145.2	120.8	137.0, 136.9, 129.9, 129.8, 129.7, 128.8, 128.2, 167.6, 61.1, 43.5, 14.1
16	Ph	Ph	CH_2CONH_2	158.3	154.7	146.6	144.7	121.2	137.0, 129.7, 129.6, 128.6, 128.2, 128.1, 168.2, 43.9
17	2-thienyl	2-thienyl	Et	157.8	148.9	146.4	136.7	119.9	140.2, 138.6, 132.6, 130.6, 129.4, 128.8, 128.4, 127.5, 38.1, 13.6
18	2-furyl	2-furyl	Me	157.7	146.9	143.6	132.8	120.4	149.5, 149.3, 146.6, 143.9, 115.9, 112.7, 112.1, 111.9, 28.3
19	2-pyridyl	2-pyridyl	Me	158.6	155.5	147.8	143.3	121.1	137.0, 136.9, 129.9, 129.8, 129.7, 128.8, 128.2, 167.6, 61.1, 43.5, 14.1
20	Ph	Me	Et	158.8	156.4	146.6	145.6	120.3	136.9, 129.4, 128.7, 128.2, 23.9, 37.7, 14.0
21	Me	Ph	Et	158.6	156.7	147.1	145.6	120.4	136.8, 129.3, 128.7, 128.2, 23.6, 28.0
22	Cl	Ph	Et	157.1	155.5	147.5	136.5	120.9	135.1, 130.5, 129.6, 128.2, 28.4
23	Ph	H	Me	158.4	145.5	147.9	143.7	122.3	134.4, 129.6, 128.8, 126.6, 28.3
24	Br	Ph	CH_2CO_2Et	157.3	157.0	146.6	130.6	121.8	167.2, 136.3, 130.4, 129.6, 128.7, 61.1, 43.6, 13.7

the1-methyl-7-(*N*-methylpyridinio)pyrazino[2,3-*c*][1,2,6]-thiadiazine iodide, all other alkylating conditions used giving rise also to the dimethyl compound as a result of methylation at the pyridine nitrogen.

The 1-ethyl derivatives **20**, **21**, and **22** were obtained by reaction of compounds **7**, **9**, and **11** with ethyl iodide, in acetone, with potassium carbonate in the first two cases and with triethylamine in the last. Treatment of the 6-phenyl derivative **6** with methyl iodide and potassium carbonate yielded **23,** and finally, the reaction of the 6-bromo derivative **10** with ethyl bromoacetate and triethylamine afforded **24.**

The structures of the newly synthesized compounds have been established by analytical and spectroscopic data (Table 2). The assignments of all compounds by ^{13}C NMR spectra have been carried out according to the chemical shifts and from the long-range coupling constants.

Platelet Aggregation Studies

The new arylpyrazinothiadiazines obtained were screened for their platelet aggregation inhibitory activity in vitro on citrated rabbit platelet-rich plasma in which aggregation was induced with arachidonic acid (AA) and adenosine diphosphate (ADP). Selected compounds were further evaluated for their in vitro effect on human platelet aggregation induced by arachidonic acid (AA), collagen (COLL), or the TxA_2 mimetics U46619 and I-BOP. Finally, ex vivo activity of the most promising compounds was evaluated in rats measuring the platelet aggregation induced by the above-men-

Table 3. Effect of Pyrazinothiadiazine 2,2-Dioxides **12**−**28** on in Vitro Rabbit Platelet Aggregation Induced by Arachidonic Acid (AA) and Adenosine Diphosphate (ADP)

				platelet aggregation inhibition	
compd	R_1	R_2	R_3	AA[a]	ADP[b]
12	Ph	Ph	Et	0.3	46
13	Ph	Ph	CH_2Ph	3	30
14	Ph	Ph	CH_2CO_2Et	0.1	30
15	Ph	Ph	$CH_2CO_2{}^tBu$	1	32
16	Ph	Ph	CH_2CONH_2	3	47
17	2-thienyl	2-thienyl	Et	3	43
18	2-furyl	2-furyl	Me	1.0	63[c]
19	2-pyridyl	2-pyridyl	Me	3	43
20	Ph	Me	Et	1	47
21	Me	Ph	Et	1	59[c]
22	Cl	Ph	Et	10	23
23	Ph	H	Me	0.3	43
24	Br	Ph	CH_2CO_2Et	10	36
25[d]	Ph	H	Et	1	33
26[d]	Br	Ph	Et	1	31
27[d]	H	Ph	Et	>10	
28[d]	H	Ph	CH_2CO_2Et	>10	
ASA				2.5	
adenosine					64

[a] Several concentrations of 0.1 and 1.0 mg/mL have been assayed in triplicate for each compound against AA (1 mM)-induced platelet aggregation. Activity is expressed as the EC_{100} (mg/mL), effective concentration which produced a 100% inhibitory response. [b] Test compounds have been assayed at the fixed concentration of 100 mg/mL against ADP (1−2 μM)-induced platelet aggregation. Activity is expressed as the percentage of the inhibitory response when compared to controls. [c] Test compound inhibition by more than 50% of maximum platelet aggregation induced by ADP was considered of pharmacological significance. [d] These compounds had previously been reported in ref 10.

tioned agonists at scheduled times after oral administration of test compounds.

Discussion

All the final N-1-substituted pyrazino[2,3-*c*][1,2,6]-thiadiazine 2,2-dioxides **12**−**28** were primarily screened for their in vitro antiplatelet properties on rabbit platelet rich-plasma,[13] and the results are shown in Table 3. Significant inhibition of arachidonic acid-induced rabbit platelet aggregation was observed for most of the compounds with EC_{100} values ranging from 0.1 to 10 μg/mL. The most active derivative in this series was compound **14** (EC_{100}, 0.1 μg/mL) while the 6*H*-7-phenyl derivatives **27** and **28** were devoid of significant activity. On the other hand, only derivatives **18** and **21** showed an inhibitory activity greater than 50% at much higher concentrations (100 μg/mL) against ADP-induced aggregation.[14]

Compounds **12**, **14**, **20**, **25**, and **26** were further evaluated in vitro at different concentrations for their effects on platelet aggregation in human plasma induced by collagen, arachidonic acid, U46619, and I-BOP (Table 4). All the compounds inhibited both collagen- and arachidonic acid-induced human platelet aggregation being more potent against collagen than arachidonic acid. With the exception of compound **26**, all derivatives were also active against U46619- and I-BOP-induced platelet aggregation. In addition, they were devoid of significant activity when ADP was used as platelet aggregation-inducing agent (results not shown). As a whole, the results obtained in both in vitro tests support the view that the antiplatelet activity observed in this series of derivatives could be mediated by interference with the platelet arachidonic acid pathway. Confirming the findings obtained in rabbit platelets, compound **14** was very potent against human platelet aggregation induced by collagen and arachidonic acid but less active when U46619 was used as aggregating agent. According to this pharmacological profile, derivative **14** seems to act selectively in the arachidonic acid cascade by inhibiting platelet cyclooxygenase with a potency greater than ASA (acetylsalicylic acid). On the other hand, compounds **12**, **20**, and **25** behave as antagonists of the endoperoxide/TxA_2 receptor, although derivative **25** has a somewhat more selective action against I-BOP-induced platelet aggregation than derivative **12** which is more selective against U46619. The in vitro potency of these compounds when compared with that of BAY-U varies according to different agonists used, but it is always lower.

Once the in vitro antiaggregating effect on rabbit and human platelets was confirmed, the active derivatives **12**, **14, 20, 25**, and **26** were subjected to ex vivo evaluation (Table 5) to assess their in vivo potency. Derivatives **12**, **20**, and **25** demonstrated potent ex vivo activity against rat platelet aggregation induced by collagen and I-BOP after 30 min of their oral administration which declined 120 min thereafter. The inhibitory activity of these compounds against collagen-induced aggregation at 30 min postdosing was equipotent to that of reference compounds at 120 min and better than that of ASA and ticlopidine when I-BOP was used as aggregation inducer. Compound **26** showed weaker but long-lasting antiplatelet activity, with about 70% inhibition of collagen-induced aggregation after 2 h

Table 4. Effect of Selected Pyrazinothiadiazine 2,2-Dioxides on in Vitro Human Platelet Aggregation Induced by Arachidonic Acid (AA), Collagen (COLL), U-46619, and I-BOP[a]

	AA[b]		COLL[b]		U-46619[b]		I-BOP[b]	
compd	concn	inhib (%)	concn	inhib (%)	concn	inhib (%)	concn	inhib (%)
BAY-U	0.2	96.0 ± 0.7	0.2	97.0 ± 1.8	0.2	98.0 ± 2.5	0.1	93.0 ± 0.7
ASA	25	96.0 ± 1.1	12.5	94.0 ± 0.8	50	28.0 ± 11.5[c]	50	43.0 ± 15.6[c]
12	30	94.0 ± 0.5	1	95.0 ± 0.4	1	82.0 ± 8.9	10	80.0 ± 1.4
14	1	82.9 ± 11.8	3	88.6 ± 3.6	30	75.7 ± 6.6		ND[d]
20	30	93.0 ± 2.2	1	97.0 ± 0.4	3	81.0 ± 0.4	3	99.0 ± 0.8
25	30	95.0 ± 2.0	1	97.0 ± 0.2	10	100 ± 0	1	84.0 ± 6.7
26	30	34.8 ± 25.9[c]	0.6	95.4 ± 0.6	*e*		3	43.1 ± 22.1[c]

[a] The evaluation method is described in the Experimental Section. The concentrations of the aggregating agents for inducing submaximal platelet aggregation were as follows: AA, 1 mM; COLL, 1−2 μg/mL; U-46619, 1.4 μM; I-BOP, 225−250 nM. [b] Results expressed as the lowest concentration (μM) required to obtain a submaximal (80−90%) inhibitory response. Each value is the mean ± SEM of 3−4 determinations. [c] Concentration which produced the greatest response observed. [d] ND, not determined. [e] No effect up to 30 μM.

Table 5. Inhibitory Effects of Selected Pyrazino[2,3-*c*][1,2,6]thiadiazine 2,2-Dioxides 30 and 120 min after Oral Administration on Platelet Aggregation Induced by Arachidonic Acid (AA), Collagen (COLL), and I-BOP in Rats ex Vivo[a]

compd	dose (mg/kg)	time (min) after administration	platelet aggregation inhibitory activity[b]		
			AA	COLL	I-BOP
BAY-U	25	120	74.2 ± 14.6	95.3 ± 1.7	72.5 ± 16.6
ASA	100	120	93.8 ± 4.4	84.6 ± 10.1	0.9 ± 0.6
ticlopidine	100	120	0.9 ± 0.7	98.7 ± 0.4	57.1 ± 18.7
12	100	30	6.5 ± 2.4	82.6 ± 12.8	100 ± 0
		120	1.0 ± 0.9	26.3 ± 21.3	30.0 ± 20.3
20	100	30	20.0 ± 17.9	93.5 ± 2.3	59.6 ± 21.8
		120	48.8 ± 24.4	47.2 ± 23.7	50.3 ± 24.9
25	100	30	11.3 ± 7.6	95.5 ± 0.7	100.0 ± 0
		120	50.9 ± 23.8	59.6 ± 19.6	51.2 ± 24.4
26	100	30	9.0 ± 4.3	53.9 ± 21.2	9.1 ± 3.7
		120	0	69.5 ± 13.6	25.2 ± 21.7

[a] The evaluation method is described in the Experimental Section. The concentrations of the aggregating agents for inducing submaximal platelet aggregation were as follows: AA, 0.4 mM; COLL, 1−2 μg/mL; I-BOP, 225−250 nM. [b] Activity expressed as percentage of inhibition; values are the mean ± SEM of 3−5 determinations.

postdosing. All compounds tested were less potent ex vivo against arachidonic acid-induced platelet aggregation.

Compound **14** which had shown potent activity in both in vitro tests was devoid of significant antiplatelet effects when administered orally to rats. On the other hand, none of the compounds tested were able to induce any biologically significant activity against rat platelet ADP-induced aggregation ex vivo (results not shown).

Conclusions

Arylpyrazinothiadiazines have been synthesized and identified as a new class of platelet aggregation inhibitors. Preliminary structural requirements for activity are the presence of one phenyl group in the 6,7-disubstituted derivatives or one phenyl group at position 6 in monosubstituted derivatives (previous results indicated that compounds unsubstituted at position 1 and N-1-substituted 6,7-alkyl derivatives were devoid of antiplatelet activity). In relation to position 1, the results obtained indicate that only the 1-ethyl derivatives show in vivo activity. Also, the pharmacological results obtained from platelet aggregation studies support the view that the antiplatelet activity observed in this series of derivatives may be mediated by interference with the platelet arachidonic acid pathway.

On the basis of these findings, studies to establish quantitative structure−activity relationships in order to optimize the antiplatelet activity observed in compounds **12**, **25**, and **26** will be reported in part 2 of this research.

Experimental Section

General. Melting points were determined with a Reichert-Jung Thermovar micro melting point apparatus and are uncorrected. ^{1}H NMR spectra (300 MHz) and ^{13}C NMR spectra (75 MHz) were recorded on a Varian XL-300 spectrometer and are reported in ppm on the δ scale. The signals of the solvent were used as reference. Mass spectra (electron impact, 70 eV) were obtained on a VG 12-250 (VG Masslab). Elemental analyses were performed on a Heraeus CHN-O-Rapid analyzer. Column chromatography was carried out on silica gel (Merck, particle size 70−230 mesh).

General Procedure for the Synthesis of Compounds 3−5, 7, and 9. To a suspension of **1** (1.0 mmol) in methanol and either concentrated hydrochloric acid or acetic acid was added the corresponding carbonyl compound (1.1 mmol) and the mixture was refluxed. The reaction mixture was evaporated to dryness, and water was added to the residue. The precipitate was filtered, washed with dichloromethane, and recrystallized from the appropriate solvent (Table 1).

4-Amino-6,7-di(2-thienyl)-1*H*-pyrazino[2,3-*c*][1,2,6]-thiadiazine 2,2-Dioxide (3). From **1** (1.00 g, 5.6 mmol), methanol (40 mL), concentrated hydrochloric acid (0.6 mL), and 2,2′-thenil (1.40 g, 6.2 mmol). Reaction time 15 h. Recrystallization from ethanol/water yielded **3** (0.52 g, 54%). ^{1}H NMR (DMSO-d_6): δ 12.38 (br s, 1H, NH), 8.66 (br s, 1H, NH_2), 8.32 (br s, 1H, NH_2), 7.82 (dd, 1H, $H_{thienyl}$), 7.76 (dd, 1H, $H_{thienyl}$), 7.39 (dd, 1H, $H_{thienyl}$), 7.15 (dd, 1H, $H_{thienyl}$), 7.15 (dd, 1H, $H_{thienyl}$), 7.07 (dd, 1H, $H_{thienyl}$). This compound had previously been reported from compound **1** and thiophene-2-carboxaldehyde.[15]

4-Amino-6,7-di(2-furyl)-1*H*-pyrazino[2,3-*c*][1,2,6]-thiadiazine 2,2-Dioxide (4). From **1** (3.00 g, 16.8 mmol), methanol (100 mL), concentrated hydrochloric acid (2.0 mL), and 2,2′-furil (3.60 g, 18.5 mmol). Reaction time 2 h. Recrystallization from water/ethanol yielded **4** (3.85 g, 69%). ^{1}H NMR (DMSO-d_6): δ 12.45 (br s, 1H, NH), 8.69 (br s, 1H, NH_2), 8.50 (br s, 1H, NH_2), 7.93 (m, 1H, H_{furyl}), 7.81−7.80 (m, 2H, H_{furyl}), 7.03 (d, 2H, H_{furyl}), 6.71−6.68 (m, 1H, H_{furyl}).

4-Amino-6,7-di(2-pyridyl)-1*H*-pyrazino[2,3-*c*][1,2,6]-thiadiazine 2,2-Dioxide (5). From **1** (3.80 g, 20.0 mmol), acetic acid (130 mL), and 2,2′-pyridil (5.00 g, 18.5 mmol). Reaction time 2 h. Recrystallization from acetic acid/water yielded **5** (1.69 g, 45%). ^{1}H NMR (DMSO-d_6): δ 11.94 (br s, 1H, NH), 8.73 (br s, 1H, NH_2), 8.67 (br s, 1H, NH_2), 8.33 (dd, 1H, $H_{pyridyl}$), 8.19 (m, 2H, $H_{pyridyl}$), 7.90 (t, 2H, $H_{pyridyl}$), 7.77 (dd, 1H, $H_{pyridyl}$), 7.40−7.20 (m, 2H, $H_{pyridyl}$).

4-Amino-7-methyl-6-phenyl-1*H*-pyrazino[2,3-*c*][1,2,6]-thiadiazine 2,2-Dioxide (7). From **1** (5.00 g, 28.0 mmol), 1-phenyl-2-hydroxyimino-1-propanone (5.45 g, 33.6 mmol), and methanol (60 mL). Reaction time 24 h. Recrystallization from acetic acid/water yielded **7** (3.75 g, 46%). ^{1}H NMR (DMSO-d_6): δ 12.29 (br s, 1H, NH),8.60 (br s, 1H, NH_2), 8.48 (br s, 1H, NH_2), 7.67−7.53 (m, 5H, Ph), 2.54 (s, 3H, CH_3).

4-Amino-6-methyl-7-phenyl-1*H*-pyrazino[2,3-*c*]1,2,6-thiadiazine 2,2-Dioxide (9). From **1** (5.00 g, 28.2 mmol), 1-phenyl-1,2-propanedione (5.00 g, 33.7 mmol), and acetic acid (100 mL). Reaction time 7 h. Recrystallization from ethanol/water yielded **9** (5.80 g, 71%). ^{1}H NMR (DMSO-d_6): δ 12.24 (br s, 1H, NH), 8.58 (br s, 1H, NH_2), 8.42 (br s, 1H, NH_2), 7.74 (m, 3H, Ph), 7.50 (m, 2H, Ph), 2.53 (s, 3H, CH_3).

4-Amino-6-chloro-7-phenyl-1*H*-pyrazino[2,3-*c*][1,2,6]-thiadiazine 2,2-Dioxide (11). To a solution of **8** (4.00 g, 14.5 mmol) in DMF (20 mL) was added *N*-chlorosuccinimide (1.97 g, 14.5 mmol). The reaction mixture was stirred at room temperature for 24 h. Then, the solution was evaporated to dryness, and water was added to the residue. The precipitate was filtered and recrystallized from methanol/water to yield **11** (3.73 g, 73%). ^{1}H NMR (DMSO-d_6): δ12.45 (br s, 1H, NH), 8.74 (br s, 1H, NH_2), 8.63 (br s, 1H, NH_2), 7.79−7.74 (m, 2H, Ph), 7.75−7.52 (m, 3H, Ph).

General Procedure for the Alkylation of Pyrazino[2,3-*c*][1,2,6]thiadiazine 2,2-Dioxides. To the corresponding 4-amino-1*H*-pyrazino[2,3-*c*][1,2,6]thiadiazine 2,2-dioxide derivative in acetone and either potassium carbonate or triethylamine was added the alkyl halide. The reaction mixture was refluxed and evaporated to dryness, and water was added to the residue. The precipitate was filtered and recrystallized from the appropriate solvent (Table 1).

4-Amino-1-ethyl-6,7-diphenylpyrazino[2,3-*c*][1,2,6]-thiadiazine 2,2-Dioxide (12). From **2** (1.00 g, 2.8 mmol), acetone (80 mL), potassium carbonate (0.18 g, 1.3 mmol), and ethyl iodide (0.3 mL, 3.5 mmol). Reaction time 24 h. Recrystallization from ethanol yielded **12** (0.83 g, 78%). ^{1}H NMR (DMSO-d_6): δ 8.89 (br s, 1H, NH_2), 8.76 (br s, 1H, NH_2), 7.53−7.30 (m, 10H, Ph), 4.12 (q, 2H, CH_2), 1.37 (t, 3H, CH_3).

4-Amino-1-benzyl-6,7-diphenylpyrazino[2,3-*c*][1,2,6]-thiadiazine 2,2-Dioxide (13). From **2** (1.00 g, 2.8 mmol), acetone (130 mL), potassium carbonate (0.19 g, 1.4 mmol), potassium iodide (250 mg, 1.5 mmol), and benzyl bromide (3.8 mL, 3.5 mmol). Reaction time 30 h. Recrystallization from ethanol yielded **13** (0.98 g, 79%). ^{1}H NMR (DMSO-d_6): δ 8.99 (br s, 1H, NH_2), 8.84 (br s, 1H, NH_2), 7.51−7.27 (m, 15H, Ph), 5.23 (s, 2H, CH_2).

4-Amino-1-[(ethoxycarbonyl)methyl]-6,7-diphenyl-pyrazino[2,3-*c*][1,2,6]thiadiazine 2,2-Dioxide (14). From **2** (2.25 g, 6.4 mmol), acetone (475 mL), potassium carbonate (0.19 g, 1.4 mmol), potassium iodide (250 mg, 1.5 mmol), and ethyl bromoacetate (2.7 mL, 9.5 mmol). Reaction time 40 h. Recrystallization from ethanol yielded **14** (2.36 g, 85%). ^{1}H NMR (DMSO-d_6): δ 9.05 (br s, 1H, NH_2), 8.93 (br s, 1H, NH_2), 7.55−7.31 (m, 10H, Ph), 4.76 (s, 2H, N−CH_2), 4.13 (q, 2H, O−CH_2), 1.21 (t, 3H, CH_3).

4-Amino-1-[(*tert*-butoxycarbonyl)methyl]-6,7-diphenylpyrazino[2,3-*c*][1,2,6]thiadiazine 2,2-Dioxide (15). From **2** (1.50 g, 4.2 mmol), acetone (60 mL), potassium carbonate (0.29 g, 2.1 mmol), potassium iodide (0.25 g, 1.5 mmol), and *tert*-buthyl bromoacetate (0.65 mL, 4.6 mmol). Reaction time 90 h. The residue was purified by column chromatography using as eluent dichloromethane/methanol (50/1) to give **15** (1.24 g, 58%). ^{1}H NMR (DMSO-d_6): δ 9.05 (br s, 1H, NH_2), 8.90 (br s, 1H, NH_2), 7.54−7.29 (m, 10H, Ph), 4.64 (s, 2H, CH_2), 1.31 (s, 9H, CH_3).

4-Amino-1-ethyl-6,7-di(2-thienyl)pyrazino[2,3-*c*][1,2,6]-thiadiazine 2,2-Dioxide (17). From **3** (1,50 g, 4.1 mmol), acetone (150 mL), triethylamine (0.6 mL, 8.2 mmol), and ethyl iodide (0.6 mL (8.2 mmol). Reaction time 72 h. Recrystallization from acetone/water yielded **17** (1.10 g, 69%). ^{1}H NMR (DMSO-d_6): δ 8.85 (br s, 1H, NH_2), 8.58 (br s, 1H, NH_2), 7.85−7.78 (m, 2H, $H_{thienyl}$), 7.43 (dd, 1H, $H_{thienyl}$), 7.22 (dd, 1H, $H_{thienyl}$), 7.20−7.09 (m, 2H, $H_{thienyl}$), 4.08 (c, 2H, CH_2) 1.38 (t, 3H, CH_3).

4-Amino-6,7-di(2-furyl)-1-methylpyrazino[2,3-*c*][1,2,6]-thiadiazine 2,2-Dioxide (18). From **4** (1.70 g, 5.3 mmol), acetone (475 mL), potassium carbonate (0.40 g, 5.3 mmol), and methyl iodide (0.7 mL, 10.6 mmol). Reaction time 96 h. Recrystallization from ethanol yielded **18** (1.30 g, 72%). ^{1}H NMR (DMSO-d_6): δ 8.88 (br s, 1H, NH_2), 7.93 (br s, 1H, NH_2), 7.93−7.80 (m, 2H, H_{furyl}), 7.06−6.80 (m, 2H, H_{furyl}), 6.70 (s, 2H, H_{furyl}), 3.44 (s, 3H, CH_3).

4-Amino-1-methyl-6,7-di(2-pyridyl)pyrazino[2,3-*c*][1,2,6]-thiadiazine 2,2-Dioxide (19). From **5** (1.50 g, 4.6 mmol), acetone (150 mL), triethylamine (0.6 mL, 4.6 mmol), and methyl iodide (0.9 mL, 13.8 mmol). Reaction time 72 h. The precipitated was filtered and washed several times with dichloromethane to give 0.3 g (20%) of 4-amino-1-methyl-6-(2-pyridyl)-7-(*N*-methylpyridinio)pyrazino[2,3-*c*][1,2,6]thiadiazine 2,2-dioxide iodide. ^{1}H NMR (DMSO-d_6): δ 9.04 (br s, 1H, NH_2), 8.95 (br s, 1H, NH_2), 9.31 (d, 1H, $H_{pyridyl}$), 8.60 (t, 1H, $H_{pyridyl}$), 8.49 (d, 1H, $H_{pyridyl}$), 8.26−8.01 (m, 4H, $H_{pyridyl}$), 7.99−7.46 (d, 1H, $H_{pyridyl}$), 4.24 (s, 3H, CH_3), 3.61 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6): δ 158.1, 155.5, 147.2, 143.9, 121.1, 137.0, 136.9, 129.9, 129.8, 129.7, 128.8, 128.2, 166.4, 81.6, 44.1, 27.5. MS (*m*/*e*) 382 ($M^+ - 127$), 127 (I^-). The filtrate was evaporated to dryness and recrystallized from ethanol−acetone to yield **19** (0.89 g, 60%). ^{1}H NMR (DMSO-d_6): δ 9.01 (br s, 1H, NH_2), 8.94 (br s, 1H, NH_2), 8.30 (d, 1H, $H_{pyridyl}$), 8.28−8.21 (m, 2H, $H_{pyridyl}$), 8.19−7.87 (m, 3H, $H_{pyridyl}$), 7.39−7.29 (m, 2H,$H_{pyridyl}$), 3.48 (s, 3H, CH_3).

4-Amino-1-ethyl-7-methyl-6-phenylpyrazino[2,3-*c*][1,2,6]-thiadiazine 2,2-Dioxide (20). From **7** (0.35 g, 1.2 mmol), acetone (150 mL), potassium carbonate (0.09 g, 0.6 mmol), and ethyl iodide (0.2 mL, 2.4 mmol). Reaction time 10 h. Recrystallization from methanol/water yielded **20** (0.37 g, 75%). ^{1}H NMR (DMSO-d_6): δ 8.77 (br s, 2H, NH_2), 8.59 (br s, 2H, NH_2), 7.74 (m, 2H, Ph), 7.49 (m, 3H, Ph), 4.07 (q, 2H, CH_2), 2.63 (s, 3H, CH_3), 1.33 (t, 3H, CH_3).

4-Amino-1-ethyl-6-methyl-7-phenylpyrazino[2,3-*c*][1,2,6]-thiadiazine 2,2-Dioxide (21). From **9** (1.11 g, 3.8 mmol), acetone (120 mL), potassium carbonate (0.26 g, 1.9 mmol), and ethyl iodide (0.63 mL, 7.6 mmol). Reaction time 24 h. Recrystallization from ethanol/water yielded **21** (0.82 g, 67%). ^{1}H NMR (DMSO-d_6): δ 8.78 (br s, 1H, NH_2), 8.67 (br s, 1H, NH_2), 7.75−7.55 (m, 5H, Ph), 4.04 (q, 2H, CH_2), 2.61 (s, 3H, CH_3), 1.30 (t, 3H, CH_3).

4-Amino-6-chloro-1-ethyl-7-phenylpyrazino[2,3-*c*][1,2,6]-thiadiazine 2,2-Dioxide (22). From **11** (2.00 g, 6.4 mmol), acetone (80 mL), triethylamine (0.9 mL, 6.5 mmol), and ethyl iodide (0.8 mL, 9.7 mmol). Reaction time 96 h. Recrystallization from ethanol yielded **22** (1.56 g, 74%). ^{1}H NMR (DMSO-d_6): δ 8.93 (br s, 1H, NH_2), 8.83 (br s, 1H, NH_2), 7.87−7.83 (m, 2H, Ph), 7.56−7.55 (m, 3H, Ph), 4.04 (q, 2H, N-CH_2), 1.30 (t, 3H, CH_3).

4-Amino-1-methyl-6-phenylpyrazino[2,3-*c*][1,2,6]-thiadiazine 2,2-Dioxide (23). From **6** (3.00 g, 11.0 mmol), acetone (300 mL), potassium carbonate (0.71 g, 5.1 mmol), and methyl iodide (3.4 mL, 5.5 mmol). Reaction time 24 h. Recrystallization from ethanol/water yielded **23** (1.10 g, 38%). ^{1}H NMR (DMSO-d_6): δ 9.36 (s, 1H, CH), 9.03 (s.a., 2H, NH_2), 8.36−7.50 (m, 5H, Ph), 3.43 (s, 3H, CH_3).

4-Amino-6-bromo-1-[(ethoxycarbonyl)methyl]-7-phenylpyrazino[2,3-*c*][1,2,6]thiadiazine 2,2-Dioxide (24). From **10** (2.94 g, 8.3 mmol), acetone (250 mL), triethylamine (1.2 mL, 8.3 mmol), and ethyl bromoacetate (3.3 mL, 11.4 mmol). Reaction time 96 h. Recrystallization from ethanol/water yielded **24** (2.62 g, 74%). ^{1}H NMR (DMSO-d_6): δ 9.11 (br s, 1H, NH_2), 9.10 (br s, 1H, NH_2), 7.79−7.74 (m, 2H, Ph), 7.56−7.53 (m, 3H, Ph), 4.67 (s, 2H, CH_2), 4.10 (q, 2H, O−CH_2), 1.09 (t, 3H, CH_3).

4-Amino-1-(carbamoylmethyl)-6,7-diphenylpyrazino-[2,3-*c*][1,2,6]thiadiazine 2,2-Dioxide (16). A solution of **14** (0.90 g, 2,5 mmol) in methanol (80 mL) at 0 °C was saturated with a slow stream of ammonia for 1 h and stirred at room temperature for 3 h. Then the solution was evaporated to dryness, and water was added to the residue. The precipitate was filtered to give **16** (0.79 g, 77%). ^{1}H NMR (DMSO-d_6): δ 8.98 (br s, 1H, NH_2), 8.87 (br s, 1H, NH_2), 7.52−7.22 (m, 10 H, Ph and 2H, $CONH_2$), 4.53 (s, 2H, CH_2).

In Vitro Platelet Aggregation Studies. Blood was collected from male New Zealand white rabbits (2.5−3.5 kg) by cardiac puncture or from healthy volunteers who gave informed consent (Blood Bank, Hospital Sant Pau, Barcelona, Spain). The blood was anticoagulated with 3.8% trisodium citrate (9:1, v/v). Platelet-rich plasma (PRP) and platelet-poor plasma (PPP) were prepared by sequential centrifugation of citrated blood at room temperature, at 250*g* for 10 min and at 2000*g* for 20 min, respectively. The platelet counts of the PRP were adjusted to 5×10^5 cells/μL (rabbits) or 3×10^5 cells/μL (humans) by dilution with PPP. Platelet aggregation was monitored according to Born's method[14] using a four-channel aggregometer (Aggrecorder, Menarini, Italy). Test compounds (0.1−30 μM) dissolved in DMSO (2.5 μL) were preincubated at 37 °C for 10 min with PRP (500 μL). After this time platelet aggregation was induced by addition of arachidonic acid (AA; 1 mM), adenosine diphosphate (ADP; 1−2 μM), collagen (COLL; 1−2 μg/mL) or the TxA_2 mimetics U46619 (1.4 μM) and I-BOP (225−250 nM). These concentrations of the agonists have been chosen in order to produce 80−90% of maximal aggregation upon addition of PRP and therefore to minimize

the individual variability of response. Acetylsalicylic acid (ASA; 12.5−50 μM), BAY-U (0.1−0.3 μM), and adenosine (100 μM) were used as reference compounds.

The percent inhibition of platelet aggregation produced by test compounds was calculated 5 min after the addition of the aggregating agents, from the reduction of the maximal amplitude of the aggregation compared to the values obtained in the paired vehicle-treated experiments. The lowest concentration required to obtain a maximal (80−100% inhibition) response was determined for each compound from the corresponding concentration−response curves.

Ex Vivo Platelet Aggregation Studies. Male Wistar rats weighing 200−250 g were used after an overnight fasting. Test compounds suspended in carboxymethylcellulose 0.25% (w/v) in Tween 80 (10%) were administered orally by gavage at the dose of 100 mg/kg in a volume of 10 mL/kg of body weight. Blood was obtained by cardiac puncture under ether anesthesia at 30 and 120 min after administration. BAY-U (25 mg/kg), ASA (100 mg/kg), and ticlopidine (100 mg/kg) administered orally were used as reference compounds, and their effect was determined at 120 min postdosing. Sodium heparin at a final concentration of 1 U/mL was used as anticoagulant. Platelet aggregation was determined as described above for in vitro study in PRP diluted to (4−5) $\times$ 10^5 cells/μL in PPP. The aggregation inducers employed were arachidonic acid (0.4 mM), collagen (1−2 μg/mL), or I-BOP (225−250 nM). Drug activity was expressed as percent inhibition of platelet aggregation at 5 min after challenge with agonists.

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