15, 94670-46-9; 16, 6542-76-3; 17R, 94670-47-0; 17S, 94730-87-7; 18R, 94670-48-1; 18S, 94730-88-8; 19R, 84799-92-8; 19S, 84759-76-2; 20R, 94730-89-9; 20S, 94730-90-2; 21R, 94706-12-4; 21S, 94798-96-6; 22, 60398-41-6; 23, 60398-42-7; 24, 94706-13-5; 25R, 94670-49-2; 25S, 94730-91-3; 26, 94670-50-5; 27, 94670-51-6; 28, 94670-52-7; 29, 94670-53-8; 30, 94670-54-9; 31, 94670-55-0; 32, 94670-56-1; 33, 94670-57-2; 34, 94670-58-3; 35, 94670-59-4; 36, 94670-60-7; 37, 94670-61-8; 38, 94706-14-6; 39, 94670-62-9; 40, 94670-63-0; 41, 94670-64-1; 42, 94670-65-2; 43, 94670-66-3; 44, 94670-67-4; aminoacetaldehyde diethyl acetal, 645-36-3; benzoyl chloride, 98-88-4; (*N*-benzoylamino)acetaldehyde diethyl acetal, 56459-72-4; di-*tert*-butyl dicarbonate, 24424-99-5; benzoic anhydride, 93-97-0; *N*-Boc-phenylalanine, 13734-34-4; diazomethane, 334-88-3; *N*-((3-benzamido-1-carboxamido-4-phenyl)butyl)-Ala-Pro-OCH_3, 94670-68-5; *N*-((3-benzamido-1-carbomethoxy-4-phenyl)butyl)-Ala-Pro-OCH_3, 94670-69-6; 3-[(*tert*-butoxycarbonyl)amino]-4-phenyl-1-butanol, 94670-70-9; 3-benzamido-4-phenyl-1-butanol, 94706-15-7; Boc-glycine *N*-hydroxysuccinimide, 3392-07-2; (L)-Boc-phenylalanine *N*-hydroxysuccinimide, 3674-06-4; pyroglutamic acid, 98-79-3; phosgene, 75-44-5; angiotensin converting enzyme, 9015-82-1; (*R*)-*N*-((3-benzamido-1-carbomethoxy-4-phenyl)butyl)-Ala-Pro-OCH_3, 94730-92-4; (*S*)-*N*-((3-benzamido-1-carbomethoxy-4-phenyl)butyl)-Ala-Pro-OCH_3, 94730-93-5; Ala-Pro, 13485-59-1; *N*-*t*-Boc-Pro-OCH_3, 59936-29-7; N^{ϵ}-Cbz-Lys-O-*t*-Bu·HCl, 5978-22-3; N^{α}-pyroglutamyl-N^{ϵ}-Cbz-Lys, 94670-71-0.

Synthesis and Platelet Aggregation Inhibitory Activity of 4,5-Bis(substituted)-1,2,3-thiadiazoles

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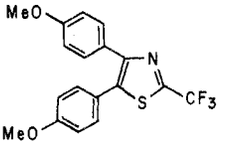
Atherosclerosis and Thrombosis, The Upjohn Company, Kalamazoo, Michigan 49001. *Received March 29, 1984*

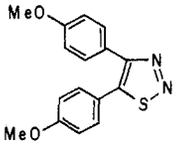
Routine screening of compounds for inhibition of collagen-induced platelet aggregation in vitro revealed 4,5-bis-(4-methoxyphenyl)-1,2,3-thiadiazole (**2**) was active and it represents the first example of a 1,2,3-thiadiazole with possible antithrombotic activity. In order to devleop a structure–activity relationship for this heterocycle, a number of new 4(5)-mono- and -disubstituted 1,2,3-thiadiazoles were synthesized. These were tested in our screen and a number of additional active compounds were found. The most active compounds (**2**, **5a**, **5b**, and **6c**) were those in which the heterocycle was substituted with benzene rings possessing para electron-donating groups.

A direct correlation has been drawn between platelet function and the development of cardiovascular disease states such as atherosclerosis[1] and its complications of myocardial infarction, transient ischemic attacks, and stroke.[2-4] Cyclooxygenase inhibitors, which inhibit platelet aggregation induced by collagen and arachidonic acids, have been explored to alter these disease states.[5,6] Yet, none of the platelet drugs has been overwhelmingly successful.[7] Since platelets may form a thrombus when exposed to collagen as a result of an arterial injury, we feel compounds that inhibit collagen-induced platelet aggregation would be of therapeutic interest.

Recently one of us and others have reported a very interesting platelet-inhibitory compound **1**[8] that has been shown to be active in vivo in humans.[9] During the course of study with this compound, another antithrombotic compound was synthesized, thiadiazole **2**. No one had previously shown that this heterocyclic system possessed platelet inhibitory activity.



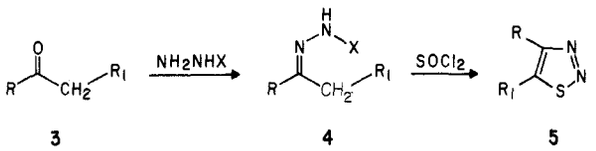
1



2

In order to understand the structure–activity relationship of this heterocycle, we planned to make a series of analogues and test them in vitro by the method of Born and Cross.[10] By synthesizing a number of 4- and 5-substituted 1,2,3-thiadiazoles, we discovered additional active drugs and the results are reported herein.

Scheme I



3 4 5

X = C(O)OEt or $SO_2C_6H_4Me$

We became interested in making analogues of the lead 1,2,3-thiadiazole due to its high biological activity, the stability of this heterocycle, the ease of its synthesis, and the novelty of these compounds. 1,2,3-Thiadiazoles are thermally stable below 200 °C, they are stable in strong acid (HCl), and 4,5-disubstituted thiadiazoles are stable to reducing conditions.[11] Although there are several methods available for the synthesis of this heterocyclic system, there are not many examples in the literature of structurally complex 1,2,3-thiadiazoles. We chose the method of Hurd and Mori[12] to synthesize 1,2,3-thiadiazoles in which α-methylene ketones or aldehydes are starting substrates (Scheme I).

Many of the ketones and aldehydes used in this report were commercially available and some of those not commercially available were synthesized by standard Friedel–Crafts reaction conditions[13] (Table I).

Appropriate acid chlorides reacted with electron-rich phenyl groups, in the presence of aluminum chloride, to afford the corresponding ketones. Stannic chloride was

(1) Woolf, N. *Br. Med. Bull.* **1978**, *34*, 137.
(2) Mitchell, J. R. A. *Br. Med. Bull.* **1978**, *34*, 103.
(3) Bouchier-Hayes, D. *Ir. Med. J.* **1983**, *76*, 101.
(4) Koch-Weser, J. *N. Eng. J. Med.* **1978**, *298*, 1403.
(5) Genton, E.; Gent, M.; Hirsh, J.; Harker, L. A. *N. Eng. J. Med.* **1975**, *293*, 1174.
(6) Koch-Weser, J. *N. Eng. J. Med.* **1978**, *298*, 1403.
(7) Verstraete, M. *Louvain Med.* **1981**, *100*, 453.
(8) Rynbrandt, R. H.; Nishizawa, E. E.; Balogoyen, D. P.; Mendoza, A. R.; Annis, K. A. *J. Med. Chem.* **1981**, *24*, 1507.
(9) Linet, O. I.; Eckert, S. M.; Gruber, C. A.; Huang, D. C. *Circulation* **1982**, *66*, II-323.
(10) Born, G. V. R.; Cross, M. J. *J. Physiol.* **1963**, *168*, 178.
(11) Thomas, E. W. "Comprehensive Heterocyclic Chemistry"; Potts, K. T., Ed.; Pergamon Press Ltd.: Oxford, 1984; Vol. 6, Chapter 4.24.
(12) Hurd, C. D.; Mori, R. I. *J. Am. Chem. Soc.* **1955**, *77*, 5359.
(13) Olah, G. A. "Friedel–Crafts and Related Reactions"; Interscience Publishers: New York, 1963; Vol. 1.

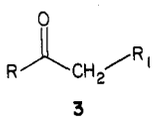
0022-2623/85/1828-0442$01.50/0

Table I. Synthesis of Ketones via the Friedel–Crafts Reaction

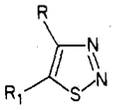
compd	catalyst	solvent	temp, °C	time, h	ketone	yield, %
3a	$AlCl_3$	CH_2Cl_2	25	4	$4\text{-}MeOC_6H_4C(O)CH_2C_6H_5$	63.7[a]
3b	$AlCl_3$	C_6H_6	80	4	$C_6H_5C(O)CH_2(4\text{-}MeOC_6H_4)$	63.3[b]
3c	$AlCl_3$	CH_2Cl_2	25	1	$2,4\text{-}(MeO)_2C_6H_3C(O)CH_2(4\text{-}MeOC_6H_4)$	74.8
3d	$AlCl_3$	CH_2Cl_2	25	3	$4\text{-}MeSC_6H_4C(O)CH_2(4\text{-}MeOC_6H_4)$	38.0[c] 29.0 (ortho)
3e	$AlCl_3$	CH_2Cl_2	25	2	$4\text{-}MeOC_6H_4C(O)CH_2(2\text{-}C_4H_3S)$	52.4 12.0 (ortho)
3f	$SnCl_4$	CH_2Cl_2	0	3	$2\text{-}(C_4H_2S)C(O)CH_2(4\text{-}MeOC_6H_4)$	68.9[d]
3g	$SnCl_4$	CH_2Cl_2	25	2	$2\text{-}(C_4H_3S)C(O)CH_2(2\text{-}C_4H_3S)$	40.5[d]
3h	CF_3SO_3H	CH_2Cl_2	40	3	$2\text{-}(C_4H_3O)C(O)CH_2(4\text{-}MeOC_6H_4)$	35.3[e]

[a] See ref 23. [b] See ref 24. [c] See ref 25. [d] See ref 26. [e] See ref 27.

Table II. Synthesis of 1,2,3-Thiadiazoles via Acylhydrazones



3

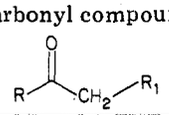
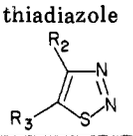


5

carbonyl compd **3**				thiadiazole **5**	
compd	R	R_1	yield of acylhydrazone, %		yield of thiadiazole, %
3a	$4\text{-}MeOC_6H_4$	C_6H_5	54.2	**5a**	64.6
3b	C_6H_5	$4\text{-}MeOC_6H_4$	76.9	**5b**	82.3
3c	$2,4(MeO)_2C_6H_3$	$4\text{-}MeOC_6H_4$	47.9	**5c**	44.7
3d	$4\text{-}MeSC_6H_4$	$4\text{-}MeOC_6H_4$	97.0	**5d**	63.3
3e	$4\text{-}MeOC_6H_4$	$2\text{-}(C_4H_3S)$	96.2	**5e**	38.5
3f	$2\text{-}(C_4H_3S)$	$4\text{-}MeOC_6H_4$	35.2	**5f**	33.4
3g	$2\text{-}(C_4H_3S)$	$2\text{-}(C_4H_3S)$	73.3	**5g**	66.0
3h	$2\text{-}(C_4H_3O)$	$4\text{-}MeOC_6H_4$	43.9	**5h**	31.4
3i	$4\text{-}NO_2C_6H_4$	$4\text{-}NO_2C_6H_4$	77.6	**5i**	60.2
3j	C_6H_5	$3,4\text{-}(\text{-}OCH_2O\text{-})C_6H_3$	95.0	**5j**	65.0
3k	$4\text{-}MeC_6H_4$	H	75.0	**5k**	51.0[a]
3l	$3,4,5\text{-}(MeO)_3C_6H_2$	H	82.0	**5l**	16.0
				5m[b]	38.0
3n	$3,4\text{-}Cl_2C_6H_3$	H	83.0	**5n**	92.0
3o	$4\text{-}ClC_6H_4$	H	75.0	**5o**	91.0[c]
3p	$4\text{-}MeOC_6H_4$	H	78.0	**5p**	76.0[c]
3	$4\text{-}MeOC_6H_4$	$4\text{-}MeOC_6H_4$	50.0	**2**	60.0

[a] See ref 28. [b] See text for structure. [c] See ref 29.

Table III. Synthesis of 1,2,3-Thiadiazoles via Tosylhydrazones

carbonyl compound 			thiadiazole 		
R	R_1	yield of tosylhydrazone, %	R_2	R_3	yield of thiadiazole, %
Me	C_5H_{11} (**3q**)	60.0	Me	C_5H_{11} (**5q**)	36.0
			C_6H_{13}	H (**5r**)	27.0
Me	Me (**3s**)	76.0	Me	Me (**5s**)	38.0
			C_2H_5	H (**5t**)	4.0
H	C_6H_5 (**3u**)	57.0	H	C_6H_5 (**5u**)	43.0[a]
C_6H_5	C_6H_5 (**3v**)	85.0	C_6H_5	C_6H_5 (**5v**)	55.0[a]
C_6H_5	H (**3w**)	82.0	C_6H_5	H (**5w**)	77.0[a]
$-(CH_2)_{10}-$ (**3x**)		75.0	$-(CH_2)_{10}-$ (**5x**)		71.0

[a] See ref 29.

employed to catalyze the reaction of thiophene with acid chlorides.

Acylation of furan with acid chlorides, catalyzed by stannic chloride, led to polymer formation. By varying the catalyst we were able to obtain the desired furan adduct **3h** in 18% yield with boron triflurodie etherate and in 36% yield with a 1% solution of trifluoromethanesulfonic acid in methylene chloride.

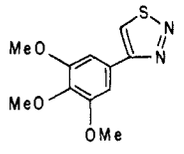
Although ketone **3i** was not available by Friedel–Crafts chemistry, we deemed it an important starting material for amine-substituted aromatic derivatives of 1,2,3-thiadiazoles. We felt free amines would not survive the conditions we employed to form thiadiazoles ($SOCl_2$), but the nitro groups would serve as masked amines.

Following a literature procedure, ketone **3i** was synthesized.[14] Due to the poor yield (22%) of this reaction in our hands, we explored an alternate route. Another literature procedure proved superior and afforded **3i** in much higher yield.[15]

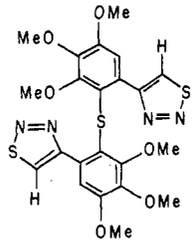
(14) Krohnke, F.; Meyer-Delius, M. *Chem. Ber.* **1951**, *84*, 411.
(15) Zimmer, H.; Bercy, J. P. *Justus Liebigs Ann. Chem.* **1965**, 107.

Following the general method of Hurd and Mori,[12] aldehydes and ketones were treated with (*p*-tolylsulfonyl)-hydrazide or ethyl carbazate to form acylhydrazones. These hydrazones in most experiments were treated with neat thionyl chloride to produce the corresponding 1,2,3-thiadiazoles (Tables II and Table III).

All the 1,2,3-thiadiazoles in Table II and III were the predicted reaction products except compound **5m**. Although the expected product **5l** was formed, compound **5m** was the major product isolated. There is literature precedence for the reaction of thionyl chloride with aromatic compounds to afford sulfides.[16] Compound **5m** could also be synthesized by treating thiadiazole **5l** with thionyl chloride. As no other diaryl sulfides were detected in this series, we presume the electron-rich trimethoxyphenyl moiety must have facilitated this reaction.



5l

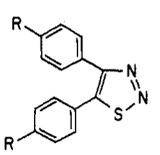


5m

Regioselectivity in ring closure plays a role in the formation of the first four thiadiazoles in Table III. The tosylhydrazone derived from 2-octanone (**3q**) exists as a 4:1 mixture of isomers in solution (NMR, $CDCl_3$). Treatment of this mixture with thionyl chloride afforded thiadiazoles **5q** and **5r** in which cyclization to the methylene group predominated. Likewise a 4:1 mixture of tosylhydrazones derived from 2-butanone (**3s**) afforded thiadiazoles **5s** and **5t**. Zimmer and Meier have studied the regioselectivity of ring-closure reactions to 1,2,3-thiadiazoles and they found methylene hydrogens are more reactive than methyl hydrogens.[17]

Hurd and Mori's method of 1,2,3-thiadiazole synthesis is quite general, yet we were unable to prepare 4-phenyl-5-methyl-1,2,3-thiadiazole from the corresponding acylhydrazone. This compound is so similar to other analogues that we have synthesized, that we are puzzled by its reluctance to form.

The (aminophenyl)-1,2,3-thiadiazole analogues were derived from 4,5-bis(4-nitrophenyl)-1,2,3-thiadiazole (**5i**). Hydrogenation of **5i** by 5% palladium on carbon at 50 psi of hydrogen, for 16 h, afforded diamine **6a** in 95% yield. Others have also noted the rate of hydrogenation of a nitro group was sluggish when sulfur was present in the molecule.[18]



6a, R = NH_2
b, R = NHEt
c, R = NMe_2

Reductive alkylation of **6a** provided the remaining aminophenyl analogues. Treatment of **6a** with sodium borohydride and acetic acid at 20 °C afforded chemoselectively 4,5-bis[4-(*N*-ethylamino)phenyl]-1,2,3-thiadiazole (**6b**).[19] A recently published procedure's conditions for the methylation of analine were employed to convert **6a** to **6c**.[20]

An additional analogue was synthesized by boron tribromide cleavage of the methoxy groups in **2** to afford **7** in 77% yield.

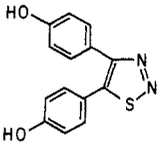


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Table IV. In Vitro Collagen-Induced Platelet Inhibitory Activity of 1,2,3-Thiaiazoles

compd	IC_{50}[a]	rel potency[b]	compd	IC_{50}[a]	rel potency[b]
2	1[c]	100.0	**5j**	3.2[d]	0.03
5b	3[c]	31.3	**5p**	3.2[d]	0.03
5a	10[c]	10.0	**5u**	3.2[d]	0.03
6c	10[c]	10.0	**5v**	3.2[d]	0.03
5d	32[c]	3.1	**5w**	3.2[d]	0.03
5c	32[c]	3.1	**6a**·2HCl	3.2[d]	0.03
5h	32[c]	3.1	**6b**	3.2[d]	0.03
5e	1.0[d]	0.1	**7**	3.2[d]	0.03
5g	3.2[d]	0.03	aspirin	10.0[d]	0.01

[a] Concentration of 1,2,3-thiadiazole required to inhibit, by 50% (IC_{50}), collagen-induced platelet aggregation in human PRP. [b] Relative to flurbiprofen. [c] Nanograms/milliliter. [d] Micrograms/milliliter.

Biological Results

Our primary screen identifies compounds that are inhibitors of collagen-induced platelet aggregation of human platelet-rich plasma (PRP).[8,21,22] The advantage of this screen is the ability to easily test a large number of compounds and thereby develop a large data base to formulate a structure–activity relationship. All of the 1,2,3-thiadiazole analogues were screened for activity and only those with activity greater than aspirin are listed in Table IV in decreasing order of activity.

From the data in Table IV a general picture of structure–activity relationships emerges. Compounds without aromatic substitution at the 4- and 5-position of the 1,2,3-thiadiazole were only active at a concentration of 3.2 $\mu g\ mL^{-1}$ or higher. Substitution of 1,2,3-thiadiazoles with any aromatic group in the 4- or 5-position did not guarantee significant activity. For example, compounds **5k**, **5l**, **5m**, **5n**, and **5o** were only active at a concentration of 10.0 $\mu g\ mL^{-1}$ or higher. The pattern becomes clearer when we see the most active compounds were 1,2,3-thiadiazoles substituted in the 4- and/or 5-position with benzene rings possessing para electron-donating groups: **2**, **5b**, **5a**, **6c**, and **5d**. Potent but less active analogues were thiadiazoles substituted with electron-rich heterocycles: **5h** and **5e**. In comparison to compounds **5u**, **5v**, and **5w**, the substitution on the aromatic moiety of compounds **5g**, **5j**, **5p**, **6a**·2HCl, **6b**, and **7** neither enhances nor detracts from the activity. An analogue **5i**, with the least amount of activity (100 $\mu g\ mL^{-1}$), possessed electron-withdrawing nitro groups on the

(16) Oae, S.; Zalut, C. *J. Am. Chem. Soc.* **1960**, *82*, 5359.
(17) Zimmer, O.; Meier, H. *Chem. Ber.* **1981**, *114*, 2938.
(18) Entwistle, I. D.; Johnstone, R. A. W.; Povall, T. J. *J. Chem. Soc., Perkin Trans 1* **1975**, 1300.
(19) Gribble, G. W.; Lord, P. D.; Skotnicki, J.; Dietz, S. E.; Eaton, J. T.; Johnson, J. L. *J. Am. Chem. Soc.* **1974**, *96*, 7812.
(20) Guimanini, A. G.; Chiavari, G.; Musiani, M. M.; Rossi, P. *Synthesis* **1980**, 743.
(21) Nishizawa, E. E.; Mendoza, A. R.; Honohan, T.; Annis, K. A. *Thromb. Haemostasis* **1982**, *47*, 173.
(22) Nishizawa, E. E.; Wynalda, D. J.; Suydam, D. E.; Malony, B. A. *Throm. Res.* **1973**, *3*, 577.

Table V. Physical and Analytical Data for 1,2,3-Thiadiazoles

no.	formula	NMR ($CDCl_3$), δ	anal.	mp, °C/bp, °C (mm)	isolation[a,b]
5a	$C_{15}H_{12}N_2OS$	3.80 (s, 3 H), 6.91 (d, 2 H), 7.40 (s, 5 H), 7.60 (d, 2 H)	CHNS	81.5–82.5	A
5b	$C_{15}H_{12}N_2OS$	3.75 (s, 3 H), 6.75–7.71 (m, 9 H)	CHNS	56.5–58.0	F
5c	$C_{17}H_{16}N_2O_3S$	3.47 (s, 3 H), 3.76 (s, 3 H), 3.83 (s, 3 H), 6.54 (s, 1 H), 6.78 (d, 1 H), 6.87 (d, 2 H), 7.28 (d, 2 H), 7.49 (d, 1 H)	CHNS	90.0–91.5	F + G
5d	$C_{16}H_{14}N_2OS_2$	2.48 (s, 3 H), 3.80 (s, 3 H), 6.89 (d, 2 H), 7.22 (d, 2 H), 7.27 (d, 2 H), 7.57 (d, 2 H)	CHNS	117.1–118.9	AB
5e	$C_{13}H_{10}N_2OS_2$	3.85 (s, 3 H), 6.98 (d, 2 H), 7.16 (m, 2 H), 7.43 (m, 1 H), 7.64 (d, 2 H)	CHNS	72.2–73.3	F + G, A
5f	$C_{13}H_{10}N_2OS_2$	3.82 (s, 3 H), 6.96 (d, 2 H), 6.98 (m, 2 H), 7.26 (m, 1 H), 7.36 (d, 2 H)	CHNS	81.0–82.0	F + G, A
5g	$C_{10}H_8N_2S$	6.93–7.60 (m)	CHNS	150 (0.2)	F, distilled
5h	$C_{13}H_{10}N_2O_2S$	3.82 (s, 3 H), 6.47 (m, 1 H), 6.80 (m, 1 H), 6.94 (d, 2 H), 7.38 (d, 2 H), 7.44 (m, 1 H)	CHNS	80.6–82.0	G + H
5i	$C_{14}H_8N_4O_4S$	7.68 (d, 2 H), 7.82 (d, 2 H), 8.35 (d, 2 h), 8.39 (d, 2 H)	CHNS	185.0–186.5	B + C
5j	$C_{15}H_{10}N_2O_2S$	5.98 (s, 2 H), 6.66–6.98 (m, 3 H), 7.22–7.85 (m, 5 H)	CHNS	107.0–109.0	F, A
5k	$C_9H_8N_2S$	2.35 (s, 3 H), 7.32 (d, 2 H), 7.96 (d, 2 H), 8.0 (s, 1 H)	CHN	74.0–76.0	A
5l	$C_{11}H_{12}N_2O_2S$	3.92 (s, 9 H), 7.29 (s, 2 H), 8.69 (s, 1 H)	CHNS	91.0–93.0	F + G + H,A + D
5m	$C_{22}H_{22}N_4O_6S_3$	3.44 (s, 6 H), 3.80 (s, 6 H), 3.88 (s, 6 H), 7.17 (s, 2 H), 9.11 (s, 2 H)	CHNS	196.0–197.0 dec	F + G + H,A + C
5n	$C_8H_4Cl_2N_2S$	7.40–8.21 (m, 3 H), 8.75 (s, 1 H)	CHClNS	87.0–89.0	A
5o	$C_8H_5ClN_2S$	7.49 (d, 2 H), 8.00 (d, 2 H), 8.68 (s, 1 H)	CHClNS	136.0–137.5	A
5p	$C_9H_8N_2OS$	3.84 (s, 3 H), 7.00 (d, 2 H), 7.95 (d, 2 H), 8.52 (s, 1 H)	CHNS	91.0–93.5	A
5q	$C_8H_{14}N_2S$	0.75–1.00 (m, 3 H), 1.02–1.90 (m, 6 H), 2.62 (s, 3 H), 2.87 (t, 2 H)	CHN	oil	F + H
5r	$C_8H_{14}N_2S$	0.75–1.01 (m, 3 H), 1.02–2.15 (m, 8 H), 3.16 (t, 2 H), 8.14 (s, 1 H)	CHN	oil	F + H
5s	$C_4H_6N_2S$	2.54 (s, 3 H), 2.60 (s, 3 H)	CHN	oil	F + H
5t	$C_4H_6N_2S$	1.44 (t, 3 H), 3.20 (q, 3 H), 8.30 (s, 1 H)		oil	F + H
5u	$C_8H_6N_2S$	7.30–7.80 (m, 5 H), 8.84 (s, 1 H)	CHNS	46–48 90–100 (0.2)	distilled
5v	$C_{14}H_{10}N_2S$	7.26–7.82 (m)	CHNS	92–94	E
5w	$C_8H_6N_2S$	7.30–7.71 (m, 3 H), 7.82–8.23 (m, 2 H), 8.61 (s, 1 H)	CHNS	75–77	A
5x	$C_{12}H_{20}N_2S$	1.10–1.55 (m, 2 H), 1.55–2.24 (m, 4 H), 2.80–3.16 (m, 4 H)	CHNS	29–32	E
7	$C_{14}H_{10}N_2O_2S$	4.82 (br s, 2 H), 6.82 (d, 2 H, J = 9.0 Hz), 6.86 (d, 2 H, J = 9.0 Hz), 7.23 (d, 2 H, J = 9.0 Hz), 7.48 (d, 2 H, J = 9.0 Hz)	CHNS	221–222	C, H_2O

[a] Recrystallized from: A = Et_2O, B = EtOAc, C = MeOH, D = CH_2Cl_2, E = hexane. [b] Chromatographed on SiO_2 and eluted with: F = CH_2Cl_2, G = Hexane, H = EtOAc.

aromatic rings. Interchange of aromatic substituents attached at the 4- or 5-position of 1,2,3-thiadiazole does not have a large effect on the compound's biological activity, for example, **5a** vs. **5b** or **5u** vs. **5w**. However, one set of compounds that does not follow this rule is **5e** and **5f**. Compound **5e** is active at 1.0 μg mL^{-1} and **5f** is only active at 100 μg mL^{-1}. This is one aspect of the structure–activity relationship we do not understand.

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer 297 spectrometer. ^{1}H NMR spectra were recorded on a Varian Associates EM-390 (90 MHz) spectrometer and are reported in δ units from internal tetramethylsilane. ^{13}C NMR were recorded on a Varian CFT-20 spectrometer and are reported in parts per million from tetramethylsilane on the δ scale. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are reported uncorrected. Mass spectra were recorded on a Varian MAT-CH5 spectrometer. Combustion analyses were performed by the Upjohn Physical and Analytical Chemistry Laboratory and by the Spang Microanalytical Laboratory. Unless specified, all solvents and reagents were used without further purification.

Synthesis of Ketones by the Friedel–Crafts Reaction. Ketones **3a–g** were synthesized with use of the conditions illustrated in Table I. The structures of these ketones were supported by NMR and IR spectra.

Reaction To Form Hydrazones. One equivalent of a ketone was treated with a slight excess of ethyl carbazate and a spatula tip of TsOH in refluxing toluene, with azeotropic removal of H_2O. After 2 h the reaction was complete, the solvent was removed, and the acylhydrazone was pure enough for further reactions. Alternatively, 1 equiv of ketone was treated with 1 equiv of (*p*-tolylsulfonyl)hydrazide in hot aqueous MeOH or EtOH. Upon completion of the reaction, a solid usually precipitated, which was recrystallized from MeOH.

Synthesis of 1,2,3-Thiadiazole. All the thiadiazoles in Tables II and III were synthesized under essentially identical conditions. One specific experimental procedure for the formation of a 1,2,3-thiadiazole follows. For the remaining compounds, only isolation and characterization data are summarized in Table V.

4,5-Bis(*p*-methoxyphenyl)-1,2,3-thiadiazole (2). Neat thionyl chloride (20 mL) was cooled with an ice bath and ethyl [1,2-bis(4-methoxyphenyl)ethylidene]hydrazinecarboxylate (7.0 g, 20 mmol) was added in one portion. After initial evolution of HCl gas, the reaction was warmed to 60 °C for 1 h. The thionyl chloride was removed under vacuum and the residue was triturated with Et_2O to afford a solid (7.5 g, 125%), mp 80–82 °C. This was recrystallized from Et_2O to afford red crystals (3.59 g, 60%), mp 84–86 °C. To remove the red color and obtain an analytical sample, the solid was dissolved in Et_2O and filtered through silica gel to afford white crystals: mp 84–86 °C; ^{1}H NMR ($CDCl_3$) δ 3.78 (s, 6 H), 6.89 (d, 4 H, J = 8 Hz), 7.24 (d, 2 H, J = 8 Hz), 7.59 (d, 2 H, J = 8 Hz). Anal. Calcd for $C_{16}H_{14}N_2O_2S$: C, 64.41; H, 4.73; N, 9.39; S, 10.75. Found: C, 64.04; H, 4.72; N, 9.52; S, 10.91.

4,5-Bis(4-aminophenyl)-1,2,3-thiadiazole (6a). Thiadiazole **5i** (11.8 g, 36.1 mmol) was hydrogenated in EtOH (200 mL) over 5% Pd–C (3.6 g) at 50 psi for 16 h. The solution was filtered through a Celite pad and washed with EtOH. Solvent was removed under reduced pressure and the crude solid was recrystallized from EtOAc–MeOH to afford 9.2 g (95.1%) of **6a**: mp 236 °C dec; ^{1}H NMR (Me_2SO) δ 5.42 (brs, 2 H), 5.66 (brs, 2 H), 6.62 (d, 2 H, J = 9 Hz), 6.76 (d, 2 H, J = 9 Hz), 7.13 (d, 2 h, J = 9 Hz), 7.34 (d, 2 H, J = 9 Hz); IR ($CHCl_3$) 3330, 3210, 2950, 1600, 1020, 820 cm^{-1}. The dihydrochloride salt was made with HCl gas in MeOH. Addition of Et_2O precipitated 2.23 g (87.8%) of the salt: mp 243 °C dec. Anal. Calcd for $C_{14}H_{14}Cl_2N_2S$: C, 49.27; H, 4.13; N, 16.42; S, 9.39. Found: C, 48.94; H, 3.73; N, 16.40; S, 9.36.

4,5-Bis[4-(*N*-ethylamino)phenyl]-1,2,3-thiadiazole (6b). Pellets of $NaBH_4$ (2.55 g, 67.1 mmol) were slowly added to thiadiazole **6a** (1.8 g, 6.71 mmol) in acetic acid (25 mL). The reaction temperature was kept constant at 15 °C during the addition. The reaction was stirred for 0.5 h and cooled to 0 °C. The solution was brought to pH 10 by the addition of NaOH pellets. The aqueous solution was extracted with EtOAc (3X). The organic layers were combined and dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude solid was chromatographed on SiO_2 (100 g; hexane/EtOAc, 4/1). The isolated solid was recrystallized from Et_2O/EtOAc to afford 950 mg (44.0%) of **6b**: mp 96.5–98.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.26 (t, 6 H, J = 7 Hz), 3.22 (q, 4 H, J = 7 Hz), 3.90 (brs, 2 H), 6.52 (d,

Table VI. Percent Inhibition of Collagen-Induced Platelet Aggregation Data for Compounds **2** and **5b**

	experiment I		experiment II	
concn of compd, $\mu g\ mL^{-1}$	flurbiprofen,[a] % inhibn	compd **2**, % inhibn	flurbiprofen,[a] % inhibn	compd **5b**, % inhibn
0.001		32.4		32.4
0.032		55.4		50.0
0.010		90.0		56.8
0.10			27.0	
0.32	36.5		56.8	
1.00	82.4		90.5	

[a] Standard.

2 H, J = 9 Hz), 6.69 (d, 2 H, J = 9 Hz), 7.20 (d, 2 H, J = 9 Hz), 7.52 (d, 2 H, J = 9 Hz); IR ($CHCl_3$) 3420, 2950, 1610, 1520, 1320, 820 cm^{-1}. Anal. Calcd for $C_{18}H_{20}N_4S$: C, 66.64; H, 6.21; N, 17.27; S, 9.88. Found: C, 66.94; H, 6.19; N, 16.75; S, 9.62.

4,5-Bis[4-(*N*,*N*-dimethylamino)phenyl]-1,2,3-thiadiazole (6c). A slurry of thiadiazole **6a** (1.26 g, 4.7 mmol) and $NaBH_4$ (2.06 g, 54 mmol) in THF (40 mL) was added to a solution of THF (60 mL), 3 M H_2SO_4, and formalin (3.34 mL, 39 mmol) at 15 °C. The reaction was kept at pH 4 by adding 3 M H_2SO_4. The reaction was stirred for 1 h and then quenched with 25% aqueous NaOH at 0 °C. The aqueous layer was extracted twice with EtOAc. The organic layers were combined and dried over $MgSO_4$, and the solvent was removed under reduced pressure. The solid was recrystallized from Et_2O to afford 1.06 g of **6c** (72.1%): mp 152.5–154.0 °C; ^1H NMR ($CDCl_3$) δ 2.95 (s, 12 H), 6.62 (d, 2 H, J = 8 Hz), 6.70 (d, 2 H, J = 8 Hz), 7.20 (d, 2 H, J = 8 Hz), 7.56 (d, 2 H, J = 8 Hz); IR ($CHCl_3$) 2810, 1610, 1520, 1360, 820 cm^{-1}. Anal. Calcd for $C_{18}H_{20}N_4S$: C, 66.64; H, 6.21; N, 17.27; S, 9.88. Found: C, 66.89; H, 6.15; N, 16.98; S, 9.78.

In Vitro Assay. Human blood was obtained from the antecubital vein and was treated with 3.8% sodium citrate (1 part citrate to 9 parts of blood). Platelet-rich plasma (PRP) was prepared by centrifuging the citrated blood at 200*g* for 10 min at 10 °C and then separated. The remaining blood was centrifuged at 2000*g* for 10 min at 10 °C to obtain the platelet-poor plasma (PPP). The platelet count was adjusted with autologous PPP to 3×10^5 platelets/mm^3. A collagen concentration required to give sightly less than maximal aggregation was used to test compounds for inhibition of aggregation with use of Payton aggregation module coupled with an Omniscribe recorder. The concentrations of compounds in Table IV represents those that gave approximately 50% inhibition (IC_{50}). The approximate IC_{50} of these compounds on collagen-induced platelet aggregation was obtained at $^1/_2$ log intervals of drug concentration. Flurbiprofen was used as internal standard to monitor the day-to-day variation in platelet sensitivity.[22]

Table VI shows typical studies on different days for the first two compounds in Table IV. Generally, no correction for platelet sensitivity was necessary; thus, no correction was applied, e.g., compound **5b** (the IC_{50} of flurbiprofen was previously established to be between 0.1 and 0.32 $\mu g/mL$). However, in experiment I, it can be seen that the platelets were less responsive to the inhibitor (required more flurbiprofen to obtain 50% inhibition); consequently the activity (IC_{50}) of compound **2** was increased by $^1/_2$ log (from 3.2 to 1.0 ng/mL).

Acknowledgment. Compound **2** was first synthesized by R. H. Rynbrandt, The Upjohn Co. We thank the Physical and Analytical Department of The Upjohn Co. for MS, IR, and elemental analyses and T. M. Vidmar, in the Biostatistics Department of the Upjohn Co., for helpful discussions.

Registry No. **2**, 94843-16-0; **3**, 120-44-5; **3a**, 1023-17-2; **3b**, 24845-40-7; **3c**, 67804-60-8; **3d**, 33420-82-5; **3e**, 94843-38-6; **3f**, 67947-62-0; **3g**, 53119-26-9; **3h**, 81474-54-6; **3i**, 3769-83-3; **3j**, 40804-81-7; **3k**, 122-00-9; **3l**, 1136-86-3; **3n**, 2642-63-9; **3o**, 99-91-2; **3p**, 100-06-1; **3q**, 111-13-7; **3s**, 78-93-3; **3u**, 122-78-1; **3v**, 451-40-1; **3w**, 98-86-2; **3x**, 830-13-7; **4** (R = 4-$MeOC_6H_4$, R_1 = C_6H_5, X = C(O)OEt), 94843-40-0; **4** (R = C_6H_5, R^1 = 4-$MeOC_6H_4$, X = C(O)OEt), 94843-41-1; **4** (R = 2,4$(MeO)_2C_6H_3$, R_1 = 4-$MeOC_6H_4$, X = C(O)OEt), 94843-42-2; **4** (R = 4-$MeSC_6H_4$, R_1 = 4-$MeOC_6H_4$, X = C(O)OEt), 94843-43-3; **4** (R = 4-$MeOC_6H_4$, R_1 = 2-(C_4H_3S), X = C(O)OEt), 94859-20-8; **4** (R = 2-(C_4H_3S), R_1 = 4-$MeOC_6H_4$, X = C(O)OEt), 94843-44-4; **4** (R = 2-(C_4H_3S), R_1 = 2-(C_4H_3S), X = C(O)OEt), 94843-45-5; **4** (R = 2-(C_4H_3O), R_1 = 4-$MeOC_6H_4$, X = C(O)OEt), 94843-46-6; **4** (R = 4-$NO_2C_6H_4$, R_1 = 4-$NO_2C_6H_4$, X = C(O)OEt), 94843-47-7; **4** (R = C_6H_5, R_1 = 3,4-(-OCH_2O-)C_6H_3, X = C(O)OEt), 94843-48-8; **4** (R = 4-MeC_6H_4, R_1 = H, X = C(O)OEt), 55508-85-5; **4** (R = 3,4,5-$(MeO)_3C_6H_2$, R^1 = H, X = C(O)OEt), 94843-49-9; **4** (R = 3,4-$Cl_2C_6H_3$, R_1 = H, X = C(O)OEt), 55538-08-4; **4** (R = 4-ClC_6H_4, R_1 = H, X = C(O)OEt), 25445-82-3; **4** (R = 4-$MeOC_6H_4$, R_1 = H, X = C(O)OEt), 25445-81-2; **4** (R = 4-$MeOC_6H_4$, R_1 = 4-$MeOC_6H_4$, X = C(O)OEt), 94843-39-7; **4** (R = Me, R_1 = C_5H_{11}, X = Ts), 54798-76-4; **4** (R = Me, R_1 = Me, X = Ts), 4031-16-7; **4** (R = H, R_1 = C_6H_5, X = Ts), 17336-58-2; **4** (R = C_6H_5, R^1 = C_6H_5, X = Ts), 19816-85-4; **4** (R = C_6H_5, R_1 = H, X = Ts), 4545-21-5; **4** (R = R_1 = $(CH_2)_{10}$, X = Ts), 3552-02-1; **5a**, 94843-18-2; **5b**, 94843-19-3; **5c**, 94843-20-6; **5d**, 94843-21-7; **5e**, 94843-22-8; **5f**, 94843-23-9; **5g**, 94843-24-0; **5h**, 94843-25-1; **5i**, 94843-26-2; **5j**, 94843-27-3; **5k**, 40753-14-8; **5l**, 94843-28-4; **5m**, 94843-29-5; **5n**, 94843-30-8; **5o**, 18212-23-2; **5p**, 18212-22-1; **5q**, 94843-31-9; **5r**, 94843-32-0; **5s**, 65923-96-8; **5t**, 94843-33-1; **5u**, 18212-29-8; **5v**, 5393-99-7; **5w**, 25445-77-6; **5x**, 72730-31-5; **6a**, 94843-34-2; **6a**·2HCl, 94843-35-3; **6b**, 94843-36-4; **6c**, 94843-37-5; **7**, 94843-17-1; (*p*-tolylsulfonyl)hydrazide, 1576-35-8; ethyl carbazate, 4114-31-2.

(23) Arnold, D. R.; Leigh, R. W.; Palmer, G. E. *J. Am. Chem. Soc.* **1976**, *98*, 6225.
(24) Schaumann, E.; Grabley, F. *Justus Liebigs Ann. Chem.* **1977**, 88.
(25) Fitzi, K.; Pfister, R. Swiss Patent 554 867, 1974; *Chem. Abstr.* **1975**, *82*, 57697.
(26) Cherkofsky, S. C.; Sharpe, T. R. German Patent 2 805 167, 1978; *Chem. Abstr.* **1978**, *89*, 180002.
(27) Effenberger, F.; Epple, G. German Patent 2 139 994, 1973; *Chem. Abstr.* **1973**, *78*, 135881.
(28) Shafiee, A.; Lalezari, I. *J. Heterocycl. Chem.* **1973**, *10*, 11.
(29) Raap, R.; Micetich, R. G. *Can. J. Chem.* **1968**, *46*, 1057.