Thiophene Systems. 9. Thienopyrimidinedione Derivatives as Potential Antihypertensive Agents[1]

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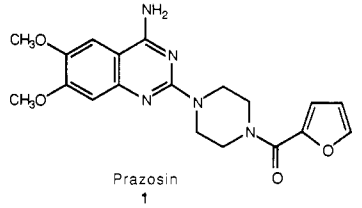
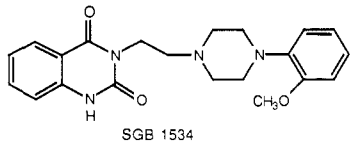
A series of thieno[3,4-*d*]-, thieno[3,2-*d*]-, and thieno[2,3-*d*]pyrimidine-2,4-diones with (phenylpiperazinyl)alkyl substitution at N-3 have been synthesized and evaluated for antihypertensive effects in spontaneously hypertensive rats (SHR). These 49 compounds were compared to the vasodilator standards prazosin (1) and the isosteric quinazoline-2,4-dione SGB 1534 (2). Substitution at the 2-, 3-, or 4-position of the phenyl ring was examined, with that at the 2-position more potent than 4-substitution while the isomeric 3-substituted compounds were least potent. Neither alkylation nor acylation at the N-1 position improved the antihypertensive effects as compared to hydrogen. The three thienopyrimidine-2,4-diones (**3**–**5**) that contain a [(2-methoxyphenyl)piperazinyl]ethyl moiety at N-3 and hydrogen at N-1 were found to be potent oral antihypertensive agents in the SHR with doses (mg/kg, po) for reducing systolic blood pressure (SBP) by 50 mmHg (ED_{-50SBP}) of 0.21, 0.19, and 1.0, respectively. The compounds **1**–**5** were further evaluated for α blocking potency by measuring the iv doses necessary to antagonize the phenylephrine pressor response by 50% (ED_{50}) in the SHR. The ED_{50} values (μg/kg) are 10.4, 3.3, 1.7, 2.1, and 15.4, respectively. These results clearly show that all three thiophene systems have potent activity as antihypertensive agents and that **3** and **4** are more potent than **1** or **2** as α_1-antagonists in vivo.

The cardiovascular disorder hypertension afflicts between 10 and 20% of the adult population and is a major risk factor in many forms of cardiovascular disease.[2] Over the past few decades several methods of treatment, e.g. diet and drug therapy, have been developed for the hypertensive patient. The use of antihypertensive drugs such as diuretics, α-agonists, α- and β-antagonists, calcium channel blockers, and ACE inhibitors has proven effective. Unfortunately, there remain problems with many of these antihypertensive drugs because of their side-effect profiles (e.g. hyperuricemia, sedation, tachycardia or postural hypertension), and lack of general activity caused by multiple blood pressure controlling compensatory mechanisms as well as poor patient compliance. The development of new and effective antihypertensive drugs to overcome these problems remains a worthwhile goal.

Of the many antihypertensive drugs, prazosin (1), an α-adrenoceptor antagonist, has proven effective in the clinic and this class of drugs has been extensively studied and recently summarized.[3] Of the variety of structural variants reported to have α-adrenoceptor antagonist effects,[4] 3-[2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl]-quinazoline-2,4-dione (SGB 1534, **2**) represents an interesting and potent α_1-antagonist.[5] Our laboratories have had an interest in preparing unique cardiovascular agents based on the quinazoline ring system[6,7] and we became interested in pursuing this area of research. Since we have also had a long-time interest in the preparation of thiophene isosteres of pharmacologically active molecules,[8,9] we decided to prepare the thieno[3,4-*d*]-, thieno-

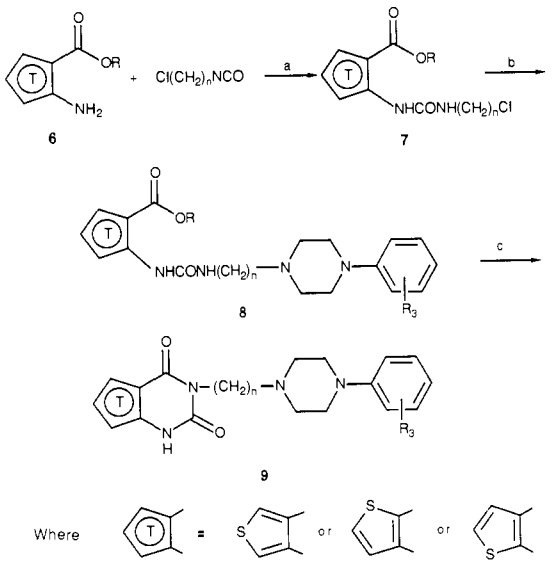


Prazosin
1



SGB 1534
2

Scheme I[a]



[a] Reagents: a, toluene/reflux; b, THF/$NaHCO_3$/NaI/reflux for days or 2-propanol/$NaHCO_3$/NaI/reflux for 18 h; c, KOH/MeOH.

(1) For the previous paper in this series, see: Olagbemvio, T. O.; Press, J. B. *J. Heterocycl. Chem.* **1982**, *19*, 391.
(2) Kaplan, N. M. *Arch. Intern. Med.* **1983**, *143*, 255.
(3) Alabaster, V. A.; Campbell, S. F.; Danilewicz, J. C.; Greengrass, C. W.; Plews, R. M. *J. Med. Chem.* **1987**, *30*, 999.
(4) For a review on α-adrenoceptor agonists and antagonists, see: Timmermans, P. B. M. W. M.; van Zwieten, P. A. *Drugs Future* **1984**, *9*, 41.
(5) Nagano, H.; et al., Eur. Pat. 89065, 1983, Chugai Pharmaceutical Co., Ltd.; *Chem. Abstr.* **1984**, *100*, 6547*p*.
(6) Press, J. B.; Bandurco, V. T.; Wong, E. M.; Hajos, Z. G.; Kanojia, R. M.; Mallory, R. A.; Deegan, E. G.; McNally, J. J.; Roberts, J. R.; Cotter, M. L.; Graden, D. W.; Lloyd, J. R. *J. Heterocycl. Chem.* **1986**, *23*, 1821.
(7) Bandurco, V. T.; Schwender, C. F.; Bell, S. C.; Combs, D. W.; Kanojia, R. M.; Levine, S. D.; Mulvey, D. M.; Appollina, M. A.; Reed, M. S.; Wong, E. M.; Falotico, R.; Moore, J. B.; Tobia, A. J. *J. Med. Chem.* **1987**, *30*, 1421.
(8) For a review of thiophene derivatives as pharmacologically active compounds, see: Press, J. B. In *Thiophene and its Derivatives*; Gronowitz, S., Ed.; Wiley: New York, 1985; Vol. 44, Part 1, pp 353–456.
(9) See, for example: Press, J. B.; Hofmann, C. M.; Wiegand, G. E.; Safir, S. R. *J. Med. Chem.* **1982**, *19*, 391 and ref 4 contained therein.

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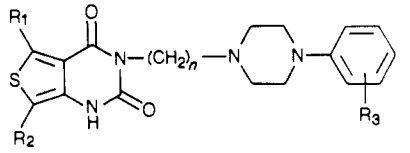
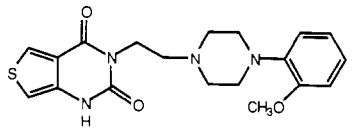
Table I. Physical Data and SHR Results for Thieno[3,4-*d*]pyrimidinediones



compd	R_1	R_2	n	R_3	synth method[a]	yield,[b] %	mp, °C	formula[c]	SHR results[d] dose, mg/kg, po	ΔSBP, mmHg	time to peak, h
3	H	H	2	2-OCH_3	C	57	274–277 dec[e]	$C_{19}H_{22}N_4O_3S$·HCl	0.5	−83 ± 10	0.5
12	H	H	2	3-OCH_3	C	18	284.5–185.5[f]	$C_{19}H_{22}N_4O_3S$	20.0	−52 ± 3	0.5
13	H	H	2	4-OCH_3	C	15	238–239[g]	$C_{19}H_{22}N_4O_3S$	10.0	−51 ± 9	0.5
14	H	H	2	H	C	21	>250[e]	$C_{18}H_{20}N_4O_2S$·HCl	10.0	−76 ± 14	0.5
15	H	H	2	2-Cl	C	39	205–207 dec[h]	$C_{18}H_{19}ClN_4O_2S$	1.25	−51 ± 5	0.5
16	H	H	2	3-Cl	C	19	207–208[i]	$C_{18}H_{19}ClN_4O_2S$	10.0	−20 ± 15	2.0
17	H	H	2	4-Cl	C	26	>250[e]	$C_{18}H_{19}ClN_4O_2S$·HCl	10.0	−56 ± 5	0.5
18	H	H	2	2-CH_3	C	38	214–216[j]	$C_{19}H_{22}N_4O_2S$	1.25	−36 ± 7	0.5
19	H	H	2	4-F	C	18	>250[e]	$C_{18}H_{19}FN_4O_2S$·HCl	10.0	−68 ± 10	0.5
20	H	H	2	2-OC_2H_5	D	19	226–228[e]	$C_{20}H_{24}N_4O_3S$·HCl	2.5	−79 ± 13	2.0
21	H	H	3	2-OCH_3	C	56	187–188.5[k]	$C_{20}H_{24}N_4O_3S$	10.0	−38 ± 7	1.0
22	H	Cl	2	2-OCH_3	D	15	188.5–189.5[l]	$C_{19}H_{21}ClN_4O_3S$	2.5	−75 ± 13	0.5
23	CH_3	H	2	2-OCH_3	C	46	265–267 dec[e]	$C_{20}H_{24}N_4O_3S$·HCl	1.25	−66 ± 15	1.0
1									1.25	−60 ± 2	0.5
2									1.25	−54 ± 7	0.5

[a] See the Experimental Section. [b] Yields are not optimized and represent the conversion of **7** to **9** (Scheme I). [c] The analyses are within ±0.4% of the theoretical values except for compound **15** (calcd/found: C, 55.30/54.87). [d] Spontaneously hypertensive rat (SHR) results from groups of four to six animals. Data are presented as the mean ± SEM. [e] Recrystallized from 2-propanol/HCl. [f] Recrystallized from EtOH/hexane. [g] Recrystallized from MeOH/ether. [h] Recrystallized from EtOH/ether. [i] Recrystallized from MeOH/EtOAc. [j] Recrystallized from EtOAc/CH_2Cl_2. [k] Recrystallized from EtOH. [l] Recrystallized from CH_2Cl_2/hexane.

[3,2-*d*]-, and thieno[2,3-*d*]pyrimidine-2,4-diones analogues of the quinazoline-2,4-dione (**2**), **3**, **4**, and **5**, respectively. This paper describes the synthesis and biological activity of these novel compounds and other substituted phenylpiperazine analogues as well as N-1 substituted compounds of **3–5**.



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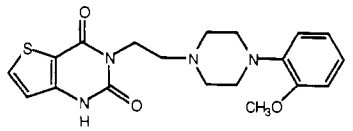

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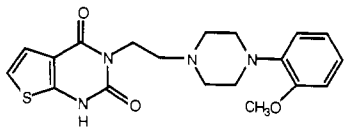

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Chemistry

The synthetic route to the thienopyrimidine-2,4-diones is summarized in Scheme I. The starting thiophene amino esters (**6**)[10] were reacted with 2-chloroethyl isocyanate in toluene to give the (2-chloroethyl)ureas (**7**, Table VIII). These ureas were then reacted with various phenyl-substituted piperazines in either THF, 2-propanol, or DMF to afford either the urea **8**, the thienopyrimidine-2,4-dione **9**, or a mixture of **8** and **9**. Although intermediate ureas **8** (which showed little interesting biological activity) were isolated and purified in some cases, in general, they were converted directly to **9** (n = 2) in methanolic sodium or potassium hydroxide. Similarly, 3-chloropropyl isocyanate was reacted with the thiophene amino esters **6** to afford compounds **9** (n = 3) with propylene separation of the thienopyrimidine-2,4-dione and the piperazine moieties. The ring-chlorinated thienopyrimidines **22** (Table I) and **35** (Table III) were prepared by reacting the corresponding urea **7** with sulfuryl chloride. A summary of compounds **9** prepared in this study is listed in Tables I–III.

To examine the effects of N-1 substitution on the antihypertensive effect of these compounds, we prepared various 1-substituted derivatives of the more potent compounds in this series (those containing the (2-methoxyphenyl)piperazine group as discussed below, i.e. **3–5**, Scheme II). These thienopyrimidine-2,4-diones in either DMF or THF were deprotonated with NaH and alkylated with various alkyl halides to afford **10**. Likewise, **3**, **4**, or **5** were reacted with either an alkyl or an aryl acid chloride in either CH_2Cl_2/TEA or DMF/NaH to cleanly produce **11**. The 1-substituted compounds **10** and **11** are summarized in Table VI.

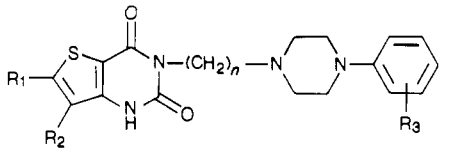
In systems such as these, both N- and O-alkylation or acylation may occur. A series of NOE experiments on the pivaloyl compounds **46** and **55** and the methyl derivative **51** revealed only enhancement of the absorption due to the thiophene proton adjacent to the 1-position. If O-alkylation or acylation had occurred, such thiophene proton enhancement in all likelihood would not have been observed and effects on the alkyl chain protons would be expected.

Results and Discussion

Tables I–III summarize the thieno[3,4-*d*]-, thieno[3,2-*d*]-, and thieno[2,3-*d*]pyrimidine-2,4-diones, respectively, prepared for this study and Table VI includes several additional compounds with various substitution at the N-1 position. These compounds were evaluated for blood pressure lowering activity in the conscious spontaneously hypertensive rat (SHR), and the results are reported in the tables as maximum change of the systolic blood pressure (SBP) at a single dose that was measured over either a 2- or a 4-h period. All of the compounds showed

(10) See the Experimental Section for the source.

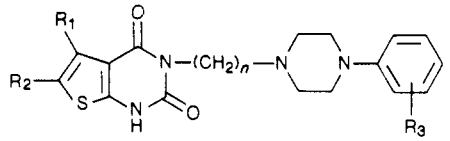
Table II. Physical Data and SHR Results for Thieno[3,2-*d*]pyrimidinediones



compd	R_1	R_2	*n*	R_3	synth method[a]	yield,[b] %	mp, °C[c]	formula[d]	SHR results[e] dose, mg/kg, po	ΔSBP, mmHg	time to peak, h
4	H	H	2	2-OCH_3	C	48	222–223	$C_{19}H_{22}N_4O_3S \cdot {}^1/_4H_2O$	1.25	−74 ± 19	0.5
24	H	H	2	3-OCH_3	C	46	212–213	$C_{19}H_{22}N_4O_3S$	2.5	−28 ± 1	1.0
25	H	H	2	4-OCH_3	C	27	130–131	$C_{19}H_{22}N_4O_3S$	10.0	−68 ± 11	1.0
26	H	H	2	H	C	35	215–217	$C_{18}H_{20}N_4O_2S$	10.0	−48 ± 5	0.5
27	H	H	2	2-Cl	C	45	193–196	$C_{18}H_{19}ClN_4O_2S$	1.25	−30 ± 6	0.5
28	H	H	2	2-CH_3	C	35	212–214	$C_{19}H_{22}N_4O_2S$	1.25	−33 ± 3	1.0
29	H	H	3	2-OCH_3	C	41	205–206	$C_{20}H_{24}N_4O_3S \cdot {}^1/_4H_2O$	10.0	−43 ± 9	0.5
1									1.25	−60 ± 2	0.5
2									1.25	−54 ± 7	0.5

[a] See the Experimental Section. [b] Yields are not optimized and represent the conversion of **7** to **9** (Scheme I). [c] These compounds were either recrystallized or triturated from ethanol. [d] The analyses are within ±0.4% of the theoretical values. [e] Spontaneously hypertensive rat (SHR) results from groups of four to six animals. Data are presented as the mean ± SEM.

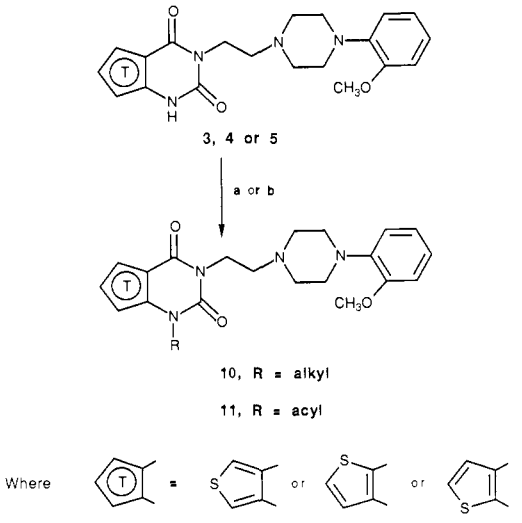
Table III. Physical Data and SHR Results for Thieno[2,3-*d*]pyrimidinediones



compd	R_1	R_2	*n*	R_3	synth method[a]	yield,[b] %	mp, °C[c]	formula[d]	SHR results[e] dose, mg/kg, po	ΔSBP, mmHg	time to peak, h
5	H	H	2	2-OCH_3	C	58	234–236	$C_{19}H_{22}N_4O_3S$	1.25	−50 ± 4	0.5
30	H	H	2	4-OCH_3	C	50	249–251 dec	$C_{19}H_{22}N_4O_3S$	10.0	−40 ± 9	0.5
31	H	H	2	H	C	76	228–230	$C_{18}H_{20}N_4O_2S$	10.0	−45 ± 4	1.0
32	H	H	2	2-Cl	C	69	216–217	$C_{18}H_{19}ClN_4O_2S$	10.0	−43 ± 18	2.0
33	H	H	2	2-CH_3	C	47	191–193	$C_{19}H_{22}N_4O_2S$	10.0	−70 ± 13	0.5
34	H	H	3	2-OCH_3	C	32	217–218	$C_{20}H_{24}N_4O_3S$	10.0	−68 ± 28	0.5
35	H	Cl	2	2-OCH_3	C	54	228–230	$C_{19}H_{21}ClN_4O_3S$	1.25	−25 ± 7	0.5
36	CH_3	H	2	2-OCH_3	C	72	209–213	$C_{20}H_{24}N_4O_3S \cdot HCl \cdot {}^1/_2H_2O$	10.0	−56 ± 4	0.5
37	CH_3	CH_3	2	2-OCH_3	C	76	196–197	$C_{21}H_{26}N_4O_3S$	20.0	−50 ± 17	1.0
1									1.25	−60 ± 2	0.5
2									1.25	−54 ± 7	0.5

[a] See the Experimental Section. [b] Yields are not optimized and represent the conversion of **7** to **9** (Scheme I). [c] These compounds were either recrystallized or triturated from ethanol. [d] The analyses are within ±0.4% of the theoretical vallus. [e] Spontaneously hypertensive rat (SHR) results from groups of four to six animals. Data are presented as the mean ± SEM.

Scheme II[a]



[a] Reagents: a, NaH/DMF or THF/alkyl halide; b, Ac_2O or acid chloride/CH_2Cl_2/TEA or acid chloride/DMF/NaH.

Table IV. Potency of Thienopyrimidinediones **3–5** and Standards in the Spontaneously Hypertensive Rat (SHR)

compd	ED_{-50SBP}[a]
3	0.21 (0.11, 0.36) (*n* = 23)
4	0.19[b] (*n* = 8)
5	1.0 (0.65, 1.67) (*n* = 12)
1	0.22 (0.14, 0.31) (*n* = 20)
2	0.54 (0.01, 5.4) (*n* = 16)

[a] The dose (mg/kg, po) of the test compound required to produce a 50 mmHg drop in systolic blood pressure (SBP) in the spontaneously hypertensive rat (*n* = number of animals tested). The fiducial limits are shown in parentheses. [b] This compound was tested at only two doses.

activity within 30 min of dosing and their respective times to peak are shown in the tables.[11] The SHR protocol

(11) The duration of blood pressure lowering activity of these compounds was not rigorously assessed since this duration should only be compared at equieffective antihypertensive doses. In general, **1** and **2** had significant antihypertensive activity for up to 4 h in this model. Compound **3** also displayed antihypertensive activity for 2–4 h while **4** and **5**, although potent antihypertensive agents, were shorter acting (<1 h).

utilized requires testing at a single dose unless the response (ΔSBP) is too small as compared to the vehicle-treated animals. Consequently, the ΔSBP for the test compounds is not reported at the same dose in all cases. The general trends in the SAR may still be summarized and the most potent compounds easily identified.

The first compounds prepared (i.e. **3–5**) were those that closely resemble the isosteric quinazoline-2,4-dione **2** and have an ethylene group (n = 2) separating the thienopyrimidine and piperazine moieties as well as a 2-methoxy substituent on the phenyl ring. These compounds have excellent antihypertensive activity in the SHR when compared to **1** or **2**. In a series of dose–response studies, the amount of drug (**3–5**) necessary to produce a 50 mmHg reduction in systolic blood pressure (ED_{-50SBP}) was measured and compared to that of **1** and **2** (Table IV). The activity of the isomeric thienopyrimidines is not equal and underscores the importance of preparing all thiophene isosteres for this type of study.[8] The [3,4-*d*] compound **3** is equipotent to the [3,2-*d*] compound **4**, and **3** is much more potent than the [2,3-*d*] isomer **5**. This trend may be seen throughout our studies with the [3,4-*d*] and [3,2-*d*] isomeric compounds in Tables I and II showing more potency than their [2,3-*d*] counterparts in Table III.

The isomeric 3- and 4-methoxyphenyl compounds were prepared in the [3,4-*d*] (**12**, **13**) and [3,2-*d*] (**24**, **25**) series whereas only the 4-methoxyphenyl (**30**) was prepared in the [2,3-*d*] series (Tables I–III). Clearly, these compounds were much less potent than their 2-methoxy counterparts; the 3-methoxy compounds were the least potent.

To further explore the effects of phenyl substitution on activity, the unsubstituted compounds **14**, **26**, and **31** were prepared. These compounds had activity similar to that of the 4-methoxyphenyl compounds (**13**, **25**, and **30**, respectively); however, they were also less potent than the 2-methoxyphenyl compounds (**3–5**). Other compounds with 2-chloro (**15**, **27**, and **32**) or 2-methyl (**18**, **28**, and **33**) substitution were prepared since these substituents have similar steric size but different electronic effects on the phenyl ring. The order of activity varies, depending on the particular thienopyrimidine system. Consider first the [3,4-*d*] series (Table I) wherein the (2-chlorophenyl)-piperazine **15** is about 1.4 times as potent as the 2-methyl compound **18**. In the [3,2-*d*] series (Table II), the 2-chloro (**27**) and 2-methyl (**28**) compounds are equipotent whereas for the [2,3-*d*] series (Table III), the 2-methylphenyl compound (**33**) is about 1.6 times as potent as the 2-chlorophenyl material (**32**). The (3- and 4-chlorophenyl)-piperazine compounds (**16** and **17**) were prepared in the [3,4-*d*] series and once again demonstrate the increased antihypertensive efficacy of 2-substituted phenyl derivatives vis-à-vis the 4-substituted phenyl, which is more potent than the 3-substituted isomer. None of these derivatives were as potent as the 2-methoxy compounds **3–5**.

The activity of the 4-substituted phenyl compounds was further explored by preparing the (4-fluorophenyl)-piperazine compound **19** (Table I). This material with its sterically smaller substituent was slightly more potent than the 4-chlorophenyl (**17**) or 4-methoxyphenyl (**13**) compounds; however, it was slightly less potent than the unsubstituted compound **14**.

It is clear that the 2-substituted phenylpiperazine compounds in this series as in another somewhat related series[12] provide the most potent compounds. However, it is unclear what physical parameter(s) contribute to this activity. Whatever the influence the 2-substituent has on activity, it would be expected to be consistent throughout the three thienopyrimidine series. Certainly these substituents must cause some steric crowding between the phenyl and piperazine rings, which may be an important factor since all the 2-methoxy compounds (Table V) are much more potent than the unsubstituted compounds (**14**, **26**, and **31**) as well as the 2-chloro or 2-methyl compounds. Additional steric bulk attenuates activity since the 2-ethoxy compound **20** is less potent than **3** (Table I). The influence of the 2-substituents is more difficult to understand when comparing the activities of the 2-chloro vs 2-methyl vs 2-H. Table V shows that the order of activity for these substituents depends on the thienopyrimidine series; vida infra. Since SHR activity is an in vivo measurement and is the net result of many other variables (e.g. drug absorption, distribution, metabolism, etc.), it is impossible to determine what additional physical parameters might cause the 2-substituted compounds to be more potent than their 3- or 4-substituted isomers.

Table V. Relative Potency of the [(2-Substituted phenyl)piperazinyl]thienopyrimidines

series	order of potency
[3,4-*d*]	OMe ≫ Cl ≈ OEt > Me ≈ H
[3,2-*d*]	OMe ≫ Cl ≈ Me > H
[2,3-*d*]	OMe ≫ Me > Cl ≈ H

The separation between the thienopyrimidine and piperazine rings was next studied with the propylene (n = 3) derivatives **21**, **29**, and **34**. All of these compounds were much less potent than their ethylene analogues (**3–5**).

The effect of substituents on the thiophene ring was explored only for the [3,4-*d*] (Table I) and [2,3-*d*] (Table III) series. The compounds in the [3,4-*d*] series (**22** and **23**) appear to be less potent than **3** but similar to the standards **1** and **2**. In the [2,3-*d*] series, the chloro (**35**) or the methyl (**36** and **37**) substituents were less potent than the parent compound **5**.

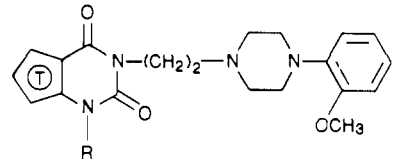
With use of **3–5** as the basis for further study, the effects of N-1 substitution on activity in the SHR were explored and are summarized in Table VI. The 1-methyl compounds (**38**, **51**, **57**), respectively, were less potent than their corresponding unsubstituted (R = H) counterparts and follow the same potency trend as noted previously. Long chain alkyl substitution (**41** and **52**) and unsaturated alkyls (**39** and **40**) as well as the alkyl carboxylic acid ester substitution (**42** and **43**) at N-1 also reduce potency.

Acylation of the [3,4-*d*] and [3,2-*d*] series (**3** or **4**) with acetic anhydride produced the less potent N-1 acetyl derivatives **44** and **54**. The dimethylacetyl (**45**) and trimethylacetyl (**46**, **55**) compounds have similar potency to that of the simple acetyl analogues **44** and **54**. Clearly, additional steric bulk at N-1 does not greatly affect the activity for this class of substituents in the SHR. N-1 pentanoyl substitution (**47**) further reduced potency while the benzoyl derivative **48** was nearly as potent as the acetyl compound **44**. The 4-chlorobenzoyl material **49** was much less potent while the 4-methoxybenzoyl derivative **50** was as potent as the unsubstituted benzamide **48**. The urethane **56** has similar potency to its corresponding acetyl derivative **54**.

To further examine their activity profile, the lead compounds **3–5** as well as the standards **1** and **2** were evaluated for α_1-antagonist activity in vivo (Table VII). These compounds were administered intravenously to the SHR and the pressor response to phenylephrine was measured before and after administration. The dose of compound required to produce 50% inhibition of the pressor response

(12) See, for example: Shiozawa, A.; et. al. *Chem. Pharm. Bull.* **1985**, *33*, 5332.

Table VI. Physical Data and SHR Results for 1-Alkyl/Acyl Derivatives of **3–5**



compd	R	synth method[a]	yield,[b] %	mp, °C	formula[c]	SHR results[d] dose, mg/kg, po	ΔSBP, mmHg	time to peak, h
thieno[3,4-*d*]								
3	H					0.5	−83 ± 10	0.5
38	CH_3	E	41	167–167.5[e]	$C_{20}H_{24}N_4O_3S \cdot {}^1/_4H_2O$	1.25	−67 ± 15	0.5
39	$CH_2CH{=}CH_2$	F	56	131–132[f]	$C_{22}H_{26}N_4O_3S$	10.0	−50 ± 7	1.0
40	$CH_2C{\equiv}CH$	F	49	142–143[g]	$C_{22}H_{24}N_4O_3S$	10.0	−52 ± 4	1.0
41	$(CH_2)_7CH_3$	F	47	82–84[g]	$C_{27}H_{38}N_4O_3S$	10.0	−54 ± 12	2.0
42	$(CH_2)_2CO_2CH_3$	F	47	140–140.5[h]	$C_{23}H_{28}N_4O_5S$	10.0	−55 ± 2	1.0
43	$(CH_2)_3CO_2C_2H_5$	F	65	108–109.5[h]	$C_{25}H_{32}N_4O_5S$	10.0	−87 ± 10	0.5
44	$COCH_3$	H	42	128–129[f]	$C_{21}H_{24}N_4O_4S$	2.5	−44 ± 10	0.5
45	$COCH(CH_3)_2$	G	59	129–130.5[h]	$C_{23}H_{28}N_4O_4S$	5.0	−53 ± 8	0.5
46	$COC(CH_3)_3$	G	64	116–117[g]	$C_{24}H_{30}N_4O_4S$	5.0	−69 ± 16	0.5
47	$CO(CH_2)_4CH_3$	G	49	81–82.5[g]	$C_{25}H_{32}N_4O_4S$	5.0	−42 ± 5	0.5
48	COC_6H_5	G	47	112–113.5[h]	$C_{26}H_{26}N_4O_4S$	5.0	−68 ± 13	1.0
49	COC_6H_4-*p*-Cl	G	31	173–174.5[e]	$C_{26}H_{25}ClN_4O_4S$	5.0	−14 ± 5	1.0
50	COC_6H_4-*p*-OCH_3	G	37	135–137[f]	$C_{27}H_{28}N_4O_5S$	2.5	−59 ± 8	2.0
thieno[3,2-*d*]								
4	H					1.25	−74 ± 19	0.5
51	CH_3	F	61	149–151[i]	$C_{20}H_{24}N_4O_3S$	1.25	−56 ± 18	0.5
52	$(CH_2)_3CH_3$	F	56	139–140[i]	$C_{23}H_{30}N_4O_3S$	1.25	−28 ± 8	0.5
53	$(CH_2)_4CO_2C_2H_5$	F	82	118–119[i]	$C_{26}H_{34}N_4O_5S$	2.5	−30 ± 9	0.5
54	$COCH_3$	H	57	156–158[i]	$C_{21}H_{24}N_4O_4S$	5.0	−58 ± 5	0.5
55	$COC(CH_3)_3$	F	40	117–120[j]	$C_{24}H_{30}N_4O_4S$	2.5	−62 ± 28	0.5
56	$CO_2C_2H_5$	F	28	121–122[j]	$C_{22}H_{26}N_4O_5S$	2.5	−30 ± 8	0.5
thieno[2,3-*d*]								
5	H					1.25	−50 ± 4	0.5
57	CH_3	F	61	174–176[i]	$C_{20}H_{24}N_4O_3S$	1.25	−28 ± 2	0.5
1						1.25	−60 ± 2	0.5
2						1.25	−54 ± 7	0.5

[a] See the Experimental Section. [b] Yields are not optimized and represent the conversion of **3**, **4**, or **5** to **10** or **11** (Scheme II). [c] The analyses are within ±0.4% of the theoretical values. [d] Spontaneously hypertensive rat (SHR) results from groups of four to six animals. Data are presents as the mean ± SEM. [e] Recrystallized from CH_2Cl_2/ether. [f] Recrystallized from CH_2Cl_2/hexane. [g] Recrystallized from ether/hexane. [h] Recrystallized from ether. [i] Recrystallized from EtOH. [j] The material was isolated analytically pure by column chromatography (SiO_2; 1–2% MeOH in CH_2Cl_2).

Table VII. Potency of Thienopyrimidinediones **3–5** and Standards as α_1-Adrenergic Antagonists

compd	ED_{50}[a]	DR_{20}[b]
3	1.7 (0.9, 3.4) (*n* = 4)	3 (*n* = 3)
4	2.1 (1.2, 3.5) (*n* = 6)	4 (*n* = 3)
5	15.4 (10.3, 23.1) (*n* = 6)	20 (*n* = 2)
1	10.4 (9.1, 11.8) (*n* = 6)	300 (*n* = 3)
2	3.3 (1.6, 10.6) (*n* = 11)	10 (*n* = 5)

[a] The dose (μg/kg, iv) of the test compound required to produce a 50% inhibition of the phenylphrine pressor response in the spontaneously hypertensive rat (*n* = number of animals tested). The fiducial limits are shown in parentheses. [b] The dose (μg/kg, iv) of the test compound required to produce a 20-fold rightward shift in the phenylephrine dose-response curve in the dog (*n* = number of animals tested).

to phenylephrine was measured and expressed as the ED_{50} (μg/kg). These compounds were also assessed for in vivo α_1-antagonist properties in an anesthetized dog model where the amount of drug needed to produce a 20-fold rightward shift in the phenylephrine dose–response curve was calculated and expressed as a DR_{20} (μg/kg). With these tests, all of these compounds are excellent α_1-antagonists with thienopyrimidines **3** and **4** more potent than prazosin and equipotent to the quinazolinedione **2**. Once again the thienopyrimidines **3–5** are *not* equipotent. While the [3,4-*d*] compound **3** is equipotent to its [3,2-*d*] isomer **4**, compound **3** is 6–9 times more potent than the [2,3-*d*] isomer **5**. These results underscore the enhanced potency of the best compounds in this study as compared to the standard prazosin suggest their potential use as antihypertensive agents.

In summary, the novel thieno[3,4-*d*]-, thieno[3,2-*d*]-, and thieno[2,3-*d*]pyrimidine ring isosteres of **2** were prepared and show good to excellent antihypertensive activity in the SHR model. Placement of various substituents at the 2-, 3-, or 4-position of the phenyl ring affected the SHR activity with the compounds containing a 2-substituted phenylpiperazine group showing the greatest activity. Steric bulk of these 2-substituents must play a role in this activity; however, complete clarification of the factors influencing activity was not within the scope of this study. Substitution at the N-1 position reduced activity. The most potent compounds were those with the 2-methoxy substituent on the phenyl piperazine moiety and hydrogen at the N-1 position (**3–5**). Our study shows the utility of replacing the quinazoline ring of **2** with a thienopyrimidine moiety to produce two compounds **3** and **4** that are more potent as α_1-antagonists than prazosin and equipotent to the quinazoline-2,4-dione **2**. Also, the isomeric thienopyrimidines **3–5** are not equipotent and point to the necessity of preparing and testing all three thiophene isostere replacements for benzene. Evaluation of the side-effect profile and selectivity of these compounds is necessary for further development.

Experimental Section

Materials. Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra

were recorded on a Perkin-Elmer 283 or 1430 instrument. ^1H NMR spectra were recorded on a Varian T-60 or EM 390 instrument with the chemical shifts reported in δ downfield from tetramethylsilane as internal standard. All spectra were in agreement with the structures cited. The elemental analyses were run on a Perkin-Elmer 240C instrument. Standard flash column techniques were employed to purify crude reaction mixtures with 230–400-mesh E. Merck silica gel under positive nitrogen pressure.

General procedures for the synthetic steps shown in Schemes I and II are given below along with details for a representative compound. Methyl 4-aminothiophene-3-carboxylate,[13] methyl 4-amino-2-methylthiophene-3-carboxylate,[14] and ethyl 2-aminothiophene-3-carboxylate[15] were prepared by literature procedures whereas all the other aminothiophenecarboxylates were available commercially.

Method A. General Procedure for the Preparation of (Chloroalkyl)ureas 7 of Scheme I (Table VIII). A solution of methyl 4-aminothiophene-3-carboxylate (9.65 g, 50 mmol) in toluene (100 mL) was treated with 2-chloroethyl isocyanate (4.7 mL, 55 mmol). After this solution had been refluxed for 3 h, it was cooled to afford 7.9 g of white solid. A second crop afforded another 4.3 g (12.2 g total, 93%). A portion of this material was recrystallized from CH_2Cl_2/ether/hexane to produce **58** as a white solid: mp 110–112 °C; ^1H NMR ($CDCl_3$) δ 3.55–3.70 (m, 4, CH_2), 3.87 (s, 3, OCH_3), 5.40 (m, 1, $NHCH_2$), 7.73 (d, J = 4 Hz, 1, thiophene 5-H), 8.03 (d, J = 4 Hz, 1, thiophene 2-H), and 9.20 (br s, 1, NH). Anal. ($C_9H_{11}ClN_2O_3S$) C, H, N.

Method B. General Procedure for the Preparation of (Chloroalkyl)ureas 60 and 66 (Table VIII). A solution of (chloroethyl)urea **64** (5.0 g, 18.1 mmol) in ice-cold CH_2Cl_2 (100 mL) was treated with sulfuryl chloride (1.52 mL, 19 mmol). After the mixture had been stirred at room temperature for 18 h, it was washed with a saturated $NaHCO_3$ solution and dried over $MgSO_4$. The solvent was condensed to 20 mL and then mixed with hexane to afford the chlorinated product **66** (4.74 g, 84%) as a pink solid: mp 122–128 °C; ^1H NMR ($CDCl_3$) δ 1.33 (t, J = 7 Hz, 3, CH_3), 3.53–3.77 (m, 4, CH_2), 4.27 (q, J = 7 Hz, 2, CH_2CH_3), 5.63 (br s, 1, $NHCH_2$), 6.95 (s, 1, thiophene 3-H), and 10.30 (br s, 1 NH). Anal. ($C_{10}H_{12}Cl_2N_2O_3S$) C, H, N.

Method C. General Procedure for the Preparation of (Phenylpiperazinyl)ureas 8 of Scheme I (Table IX) and Conversion to Thienopyrimidine-2,4-diones 9 (Tables I–III). A mixture of (chloroethyl)urea **62** (8.44 g, 32.1 mmol), 4-(2-methoxyphenyl)piperazine hydrochloride (14.68 g, 64.2 mmol), $NaHCO_3$ (8.12 g, 96.6 mmol), and NaI (1.7 g, 11.3 mmol) in THF (200 mL) was refluxed for 2.5 days. After this mixture was concentrated, the residue was treated with water (100 mL) and extracted with CH_2Cl_2 (2 × 100 mL). The organic extract was dried over $MgSO_4$ and evaporated to produce a crude material, which was purified by flash silica gel chromatography with 2% MeOH in CH_2Cl_2. There was obtained the (phenylpiperazinyl)urea **70** (9.0 g, 67%) as a colorless solid: mp 149–151 °C; ^1H NMR ($CDCl_3$) δ 2.50–3.63 (m, 12, CH_2), 3.87 (s, 6, $ArOCH_3$ and CO_2CH_3), 5.48 (br s, 1, $NHCH_2$), 6.95 (m, 4, Ar), 7.42 (d, J = 5 Hz, 1, thiophene 4-H), 8.02 (d, J = 5 Hz, 1, thiophene 5-H), and 9.43 (br s, 1, NH). Anal. ($C_{20}H_{26}N_4O_4S$) C, H, N.

A solution of urea **70** (7.0 g, 16.7 mmol) in methanolic KOH (1 N, 50 mL) was refluxed for 1 h, poured into ice water (200 mL), acidified with glacial AcOH (5 mL), and neutralized with solid $NaHCO_3$. There was isolated a white precipitate, which was triturated in refluxing EtOH to afford **4** (4.65 g, 72%): mp 222–223 °C; ^1H NMR (DMSO-d_6) δ 2.43–3.27 (m, 10, CH_2), 3.83 (s, 3, OCH_3), 4.10 (t, J = 7 Hz, 2, $CONCH_2$), 6.80–7.00 (m, 5, Ar and thiophene), and 8.08 (d, J = 5 Hz, 1, thiophene). The NH was not detected. Anal. ($C_{19}H_{22}N_4O_3S \cdot {}^1/_4H_2O$) C, H, N, S.

Method D. General Procedure for the Preparation of Thienopyrimidine-2,4-diones 20 and 22 (Table I). A mixture of (chloroethyl)urea **58** (5.24 g, 20 mmol), 4-(2-ethoxyphenyl)-piperazine hydrochloride (9.71 g, 40 mmol), $NaHCO_3$ (5.04 g, 60 mmol), and NaI (1.9 g, 12 mmol) in 2-propanol (40 mL) was refluxed for 18 h. After this mixture had been concentrated to one-half its original volume, water was added and the brown oily precipitate was extracted into CH_2Cl_2. The organic extract was washed with water and brine and dried over $MgSO_4$. Solvent removal produced a viscous brown oil, which was purified by flash silica gel chromatography with 2% MeOH in CH_2Cl_2. There was obtained a cream-colored solid, which was converted to its white hydrochloride salt (**20**) in 2-propanol/HCl (1.55 g, 19%): mp 226–228 °C; ^1H NMR (DMSO-d_6) δ 1.30 (t, J = 7 Hz, 3, CH_3), 3.00–3.60 (m, 10, CH_2), 3.95 (q, J = 7 Hz, 2, OCH_2CH_3), 4.20 (m, 2, $CONCH_2$), 6.80 (m, 5, Ar and thiophene), 8.35 (d, J = 2.8 Hz, 1, thiophene), and 10.9 (s, 1, NH). Anal. ($C_{20}H_{24}N_4O_3S \cdot HCl$) C, H, N.

Method E. Alkylation of Thienopyrimidine-2,4-dione 3 (Table VI). A solution of **3** (1.5 g, 3.88 mmol) in THF (50 mL) was treated with 60% NaH (0.2 g, 5.82 mmol) under nitrogen. After stirring for 30 min, the orange solution was quenched with MeI (0.24 mL, 3.88 mmol) and stirred at room temperature for 16 h. The reaction was diluted with water and then concentrated to afford a tan precipitate, which was crystallized from CH_2Cl_2/ether to produce **38** (0.64 g, 41%): mp 167–167.5 °C; ^1H NMR ($CDCl_3$) δ 2.60–2.90 (br m, 6, CH_2), 3.00–3.20 (m, 4, CH_2NAr), 3.50 (s, 3, NCH_3), 3.83 (s, 3, OCH_3), 4.20 (t, J = 7.5 Hz, 2, $CONCH_2$), 6.53 (d, J = 4 Hz, 1, thiophene), 6.87 (br s, 4, Ar), and 8.20 (d, J = 4 Hz, 1, thiophene). Anal. ($C_{20}H_{24}N_4O_3S \cdot {}^1/_4H_2O$) C, H, N.

Method F. General Procedure for the Alkylation/Acetylation of Thienopyrimidine-2,4-diones 3–5 (Table VI). An ice-cold solution of **3** (1.69 g, 4 mmol) in DMF (20 mL) was treated with 60% NaH (0.24 g, 6 mmol) under nitrogen. After stirring at room temperature for 30 min, the solution was quenched with allyl bromide (0.532 g, 4.4 mmol) and stirred at room temperature for 16 h. The reaction was poured into ice water and extracted with CH_2Cl_2. The extracts were washed with brine and dried over $MgSO_4$. Solvent removal produced the crude product which was purified by flash silica gel chromatography with 40% EtOAc in hexane. The material from the column was recrystallized from CH_2Cl_2/hexane to produce **39** (0.96 g, 56%): mp 131–132 °C; ^1H NMR ($CDCl_3$) δ 2.65 (m, 6, CH_2), 2.94 (m, 4, CH_2NAr), 3.70 (s, 3, OCH_3), 4.10 (t, J = 6 Hz, 2, $CONCH_2$), 4.50 (m, 2, $CH_2CH{=}CH_2$), 5.15 (m, 2, $CH{=}CH_2$), 5.60–6.00 (m, 1, $CH{=}CH_2$), 6.45 (d, J = 3 Hz, 1, thiophene), 6.80 (m, 4, Ar), and 8.10 (d, J = 3 Hz, 1, thiophene). Anal. ($C_{22}H_{26}N_4O_3S$) C, H, N.

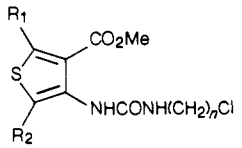
Method G. General Procedure for the Acetylation of Thienopyrimidine-2,4-diones 3 (Table VI). A suspension of **3** (2.0 g, 5.2 mmol) in CH_2Cl_2 (50 mL) was treated sequentially with triethylamine (0.86 mL, 6.2 mmol) and isobutyryl chloride (0.662 g, 6.2 mmol) under nitrogen. After stirring at room temperature for 2.5 h, the clear golden-yellow solution was condensed and the residue was purified by flash silica gel chromatography with 1% MeOH in CH_2Cl_2. There was obtained a pale-yellow oil, which was crystallized from ether to afford **45** as a white solid (1.4 g, 59%): mp 129–130.5 °C; ^1H NMR ($CDCl_3$) δ 1.30 (d, J = 7.1 Hz, 6, $CH(CH_3)_2$), 2.83 (m, 6, CH_2), 3.00 (m, 4, CH_2NAr), 3.70 (septet, J = 7.1 Hz, 1, $CH(CH_3)_2$), 3.82 (s, 3, OCH_3), 4.20 (t, J = 6.3 Hz, 2, $CONCH_2$), 6.90 (br s, 4, Ar), 7.60 (d, J = 3.2 Hz, 1, thiophene), and 8.20 (d, J = 3.2 Hz, 1, thiophene). Anal. ($C_{23}H_{28}N_4O_4S$) C, H, N.

Method H. General Procedure for the Acetylation of Thienopyrimidine-2,4-diones 3 and 4 with Acetic Anhydride (Table VI). A solution of **3** (2.0 g, 5.2 mmol) in acetic anhydride (10 mL) as heated to reflux for 5 h under nitrogen. Solvent removal produced the crude product which was crystallized from CH_2Cl_2/hexane at −30 °C. There was obtained **44** as a light brown solid (0.943 g, 42%): mp 128–129 °C; ^1H NMR ($CDCl_3$) δ 2.62 (s, 3, $COCH_3$), 2.69 (m, 6, CH_2), 2.95 (m, 4, CH_2NAr), 3.71 (s, 3, OCH_3), 4.12 (t, J = 6 Hz, 2, $CONCH_2$), 6.80–7.00 (m, 4, Ar), 7.90 (d, J = 3.5 Hz, 1, thiophene), and 8.15 (d, J = 3.5 Hz, 1, thiophene). Anal. ($C_{21}H_{24}N_4O_4S$) C, H, N.

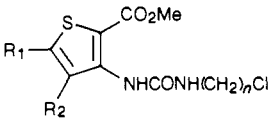
***N*-(3-Carbomethoxythien-4-yl)-*N*-[2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl]urea (69).** A solution of **58** (5.2 g, 20 mmol) in DMF (60 mL) was treated with 4-(2-methoxyphenyl)piperazine hydrochloride (5.89 g, 30 mmol) and was heated to 80 °C for 16 h under nitrogen. The cooled solution produced 2.3 g of unreacted 4-(2-methoxyphenyl)piperazine hydrochloride.

(13) (a) Baker, B. R.; Schaub, R. E.; Joseph, J. P.; McEvoy, F. J.; Williams, J. H. *J. Org. Chem.* **1953**, *18*, 138. (b) Hromatka, O.; Binder, D.; Eichinger, K. *Monatsh. Chem.* **1973**, *104*, 1520.
(14) Binder, D.; Noe, C. R.; Zahora, M. *Arch. Pharm. (Weinheim, Ger.)* **1981**, *314*, 557.
(15) Gewald, K. *Chem. Ber.* **1965**, *98*, 3571.

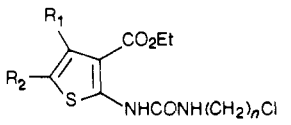
Table VIII. Physical Data of (Chloroalkyl)urea Intermediates



[3,4-*d*] series



[3,2-*d*] series

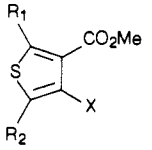


[2,3-*d*] series

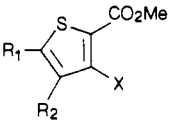
compd	R_1	R_2	n	synth method[a]	yield,[b] %	mp, °C	recryst solvent	formula[c]
[3,4-*d*] series								
58	H	H	2	A	93	110–112	CH_2Cl_2/ether/hexane	$C_9H_{11}ClN_2O_3S$
59	H	H	3	A	61	80–83	ether/hexane	$C_{10}H_{13}ClN_2O_3S$
60	H	Cl	2	B	61			*d*
61	CH_3	H	2	A	55	112–116	CH_2Cl_2/ether	$C_{10}H_{13}ClN_2O_3S$
[3,2-*d*] series								
62	H	H	2	A	56	139–142	toluene	$C_9H_{11}ClN_2O_3S$
63	H	H	3	A	61	78–84	hexane	$C_{10}H_{13}ClN_2O_3S$
[2,3-*d*] series								
64	H	H	2	A	44	85–87	*e*	$C_{10}H_{13}ClN_2O_3S$
65	H	H	3	A	51	92–95	*e*	$C_{11}H_{15}ClN_2O_3S$
66	H	Cl	2	B	84	122–128	hexane	$C_{10}H_{12}Cl_2N_2O_3S$
67	CH_3	H	2	A	77	126.5–130	CH_2Cl_2/ether	$C_{11}H_{15}ClN_2O_3S$
68	CH_3	CH_3	2	A	61	115–116	*e*	$C_{12}H_{17}ClN_2O_3S$

[a] See the Experimental Section. [b] Yields are not optimized and represent the conversion of **6** to **7** (Scheme I). [c] The analyses are within ±0.4% of the theoretical values except where noted. [d] This material was not purified. [e] The material was isolated analytically pure by column chromatography (SiO_2; 10–15% EtOAc in hexane).

Table IX. Physical Data of (Phenylpiperazinyl)urea Intermediates



[3,4-*d*] series



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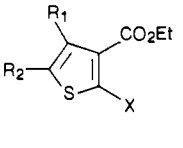
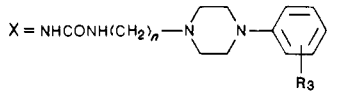


[2,3-*d*] series



compd	R_1	R_2	n	R_3	synth method[a]	yield,[b] %	mp, °C[c]	formula[d]
[3,4-*d*] series								
69	H	H	2	2-OCH_3	DMF/80 °C	11	195–199	$C_{20}H_{26}N_4O_4S{\cdot}2HCl$
[3,2-*d*] series								
70	H	H	2	2-OCH_3	C	67	149–151	$C_{20}H_{26}N_4O_4S$
71	H	H	2	3-OCH_3	C	58	120–122	$C_{20}H_{26}N_4O_4S$
72	H	H	2	4-OCH_3	C	34	158–160	$C_{20}H_{26}N_4O_4S$
73	H	H	2	H	C	57	162–164	$C_{19}H_{24}N_4O_3S$[e]
74	H	H	2	2-Cl	C	59	61–65	$C_{19}H_{23}ClN_4O_3S{\cdot}{}^1/_2H_2O$
75	H	H	2	2-CH_3	C	48	118–123	$C_{20}H_{26}N_4O_3S$[f]
76	H	H	3	2-OCH_3	C	79	149–151	$C_{21}H_{28}N_4O_4S$
[2,3-*d*] series								
77	H	H	2	2-OCH_3	C	74	129–132	$C_{21}H_{28}N_4O_4S$
78	H	H	2	4-OCH_3	C	51	103–106	$C_{21}H_{28}N_4O_4S$
79	H	H	2	H	C	85	117–120	$C_{20}H_{26}N_4O_3S$
80	H	H	2	2-Cl	C	81	141–143	$C_{20}H_{25}ClN_4O_3S$
81	H	H	2	2-CH_3	C	53	118–123	$C_{21}H_{28}N_4O_3S$
82	H	H	3	2-OCH_3	C	64	43–50	$C_{22}H_{30}N_4O_4S$[g]
83	H	Cl	2	2-OCH_3	C	86	53–58	$C_{21}H_{27}ClN_4O_4S$
84	CH_3	CH_3	2	2-OCH_3	C	89	56–62	$C_{23}H_{32}N_4O_4S$

[a] See the Experimental Section. [b] Yields are not optimized and represent the conversion of **7** to **8** (Scheme I). [c] All of the materials were isolated analytically pure by column chromatography (SiO_2; 2% MeOH in CH_2Cl_2) except for compound **69**, which was recrystallized from 2-propanol/HCl. [d] The analyses are within ±0.4% of the theoretical values except where noted. [e] Calcd/found: C, 58.74/58.31. [f] Calcd/found: C, 59.68/57.15; H, 6.51/6.15; N, 13.92/13.51. [g] Calcd/found: C, 59.17/58.75.

After the filtrate had been concentrated, the residue was purified by flash silica gel chromatography with 1–3% EtOH in CH_2Cl_2. The urea **69** was obtained as a gummy solid and was converted to its white crystalline dihydrochloride salt (1.1 g, 11%): mp 195–199 °C; ^1H NMR (DMSO-d_6) δ 3.00–3.80 (m, 12, CH_2), 3.77 (s, 3, OCH_3), 3.80 (s, 3, OCH_3), 5.80–6.00 (m, 2, HCl and HDO), 6.80–7.10 (m, 4, Ar), 7.70 (d, J = 3 Hz, 1, thiophene), 7.87 (m, 1, CON*H*CH_2), 8.30 (d, J = 3 Hz, 1, thiophene), and 9.00 (s, 1, NHCO). Anal. ($C_{20}H_{26}N_4O_4S{\cdot}2HCl$) C, H, N.

Antihypertensive Activity. The antihypertensive activity was assessed by using the following procedure: adult male spontaneously hypertensive rats (SHR) were placed in restrainers in a chamber warmed to 32 °C. A standard indirect method employing a pneumatic pulse transducer and inflatable tail cuff was used to measure systolic blood pressure (SBP) in the conscious state. After baseline SBP's were recorded, groups of four to six SHR received a single oral dose of drug or vehicle (0.5% methylcellulose) administered by gavage at doses of 0.5–20 mg/kg. SBP's were obtained at 0.5, 1, 2, 3, and 4 hours posttreatment: the data reported in Tables I–III and VI are the maximum changes in SBP ± SEM observed. These changes in SBP were compared to the vehicle effect, which was on the average 15 ± 5 mmHg.

The oral dose of drug required to produce a 50 mmHg reduction in systolic blood pressure (ED_{-50SBP}) was calculated by regression analysis. The data in Table IV are presented as ED_{-50SBP} (mg/kg, po) with 95% fiducial limits.

α_1-Adrenergic Antagonist Activity. The potency of these compounds as α_1-adrenergic antagonists was determined by using the following procedure: adult male SHR or mongrel dogs were anesthetized and bilaterally vagotomized. A carotid artery and jugular vein were cannulated for monitoring mean arterial blood pressure and drug administration, respectively. The percent inhibition of α_1-adrenergic receptor activation was quantified by measuring pressor responses to phenylephrine before and after antagonist treatment. The dose of antagonist required to produce a 50% inhibition of the phenylephrine pressor response (ED_{50}; rats) or a 20-fold rightward shift in the dose–response curve (DR_{20}; dogs) was calculated by regression analysis. The data in Table VII are presented as ED_{50} or DR_{20} values (μg/kg, iv) with 95% fiducial limits.

Acknowledgment. We thank Dr. M. L. Cotter and staff for spectral measurements and elemental analyses and Dr. David Graden for NOE experiments and useful discussions.

Registry No. **3**, 110164-48-2; **3** (free base), 110164-06-2; **4**, 110164-15-3; **5**, 110164-21-1; **12**, 110164-10-8; **13**, 110164-09-5; **14**, 110164-53-9; **14** (free base), 110187-04-7; **15**, 110164-08-4; **16**, 111308-59-9; **17**, 110164-51-7; **17** (free base), 110164-11-9; **18**, 110164-07-3; **19**, 110164-52-8; **19** (free base), 110164-12-0; **20**, 114942-96-0; **20** (free base), 114942-97-1; **21**, 110164-13-1; **22**, 114942-98-2; **23**, 110164-56-2; **23** (free base), 110164-14-2; **24**, 114942-99-3; **25**, 110164-18-6; **26**, 110164-19-7; **27**, 110164-17-5; **28**, 110164-16-4; **29**, 110164-20-0; **30**, 110164-25-5; **31**, 110164-24-4; **32**, 110164-23-3; **33**, 110164-22-2; **34**, 110164-26-6; **35**, 110164-28-8; **36**, 114943-00-9; **37**, 110164-29-9; **38**, 110164-30-2; **39**, 110164-31-3; **40**, 110164-32-4; **41**, 110164-33-5; **42**, 110164-36-8; **43**, 110164-37-9; **44**, 110164-39-1; **45**, 110164-40-4; **46**, 110164-42-6; **47**, 110164-41-5; **48**, 110164-43-7; **49**, 110164-44-8; **50**, 114943-01-0; **51**, 110164-34-6; **52**, 110187-05-8; **53**, 110197-52-9; **54**, 110187-06-9; **55**, 110164-46-0; **56**, 110164-38-0; **57**, 110164-35-7; **58**, 110164-47-1; **59**, 110164-54-0; **60**, 114943-02-1; **61**, 110164-55-1; **62**, 110164-57-3; **63**, 110164-63-1; **64**, 110164-65-3; **65**, 110164-71-1; **66**, 110164-74-4; **67**, 110164-73-3; **68**, 110164-76-6; **69**, 110164-50-6; **69** (free base), 110164-49-3; **70**, 110164-58-4; **71**, 114943-03-2; **72**, 110164-61-9; **73**, 110164-62-0; **74**, 110164-60-8; **75**, 110164-59-5; **76**, 110164-64-2; **77**, 110164-66-4; **78**, 110164-70-0; **79**, 110164-69-7; **80**, 114943-04-3; **81**, 110164-67-5; **82**, 110164-72-2; **83**, 110164-75-5; **84**, 110164-77-7; $BrCH_2CH{=}CH_2$, 106-95-6; $BrCH_2C{\equiv}CH$, 106-96-7; $Br(CH_2)_7CH_3$, 111-83-1; $Br(CH_2)_2CO_2Me$, 3395-91-3; $Br(CH_2)_3CO_2Et$, 2969-81-5; $Br(CH_2)_3CH_3$, 109-65-9; $Br(CH_2)_4CO_2Et$, 14660-52-7; $ClCOC(CH_3)_3$, 3282-30-2; $ClCO(CH_2)_4CH_3$, 142-61-0; ClCOPh, 98-88-4; p-$ClCOC_6H_4Cl$, 122-01-0; p-$ClCOC_6H_4OMe$, 100-07-2; $ClCO_2Et$, 541-41-3; methyl 4-aminothiophene-3-carboxylate, 69363-85-5; methyl 4-amino-2-methylthiophene-3-carboxylate, 114943-05-4; methyl 3-aminothiophene-2-carboxylate, 22288-78-4; ethyl 2-aminothiophene-3-carboxylate, 31891-06-2; ethyl 2-amino-4-methylthiophene-3-carboxylate, 43088-42-2; ethyl 2-amino-4,5-dimethylthiophene-3-carboxylate, 4815-24-1; 2-chloroethyl isocyanate, 1943-83-5; 3-chloropropyl isocyanate, 13010-19-0; 4-(2-methoxyphenyl)piperazine hydrochloride, 5464-78-8; 4-(3-methoxyphenyl)piperazine hydrochloride, 16015-70-6; 4-(4-methoxyphenyl)piperazine hydrochloride, 84145-43-7; 4-phenylpiperazine hydrochloride, 2210-93-7; 4-(2-chlorophenyl)piperazine hydrochloride, 41202-32-8; 4-(2-tolyl)piperazine hydrochloride, 95356-15-3; 4-(3-chlorophenyl)piperazine hydrochloride, 13078-15-4; 4-(4-chlorophenyl)piperazine hydrochloride, 13078-12-1; 4-(4-fluorophenyl)piperazine hydrochloride, 16141-90-5; 4-(2-ethoxyphenyl)piperazine hydrochloride, 83081-75-8; isobutyryl chloride, 79-30-1.

Nucleoside Conjugates. 10. Synthesis and Antitumor Activity of 1-β-D-Arabinofuranosylcytosine 5′-Diphosphate–1,2-Dipalmitins[1]

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Three 1-β-D-arabinofuranosylcytosine 5′-diphosphate–1,2-dipalmitins from L-, D-, and DL-α-dipalmitoylphosphatidic acids have been synthesized and their antitumor activity against two ara-C^2 resistant L1210 lymphoid leukemia sublines in mice were evaluated. These new prodrugs of ara-C include ara-CDP-L-dipalmitin (**1**), ara-CDP-D-dipalmitin (**2**), and ara-CDP-DL-dipalmitin (**3**). The L and DL isomers produced significant increase in life span (>400%) and four to five long-term survivors (>45 days) out of six animals bearing ip implanted partially ara-C resistant L1210 subline [L1210/ara-C (I)], while the D isomer displayed a marginal activity (ILS 100–121%). In contrast, the L isomer was completely ineffective against deoxycytidine kinase deficient ara-C resistant L1210 subline [L1210/ara-C (II)]. However, the results demonstrate that the L and DL isomers of ara-CDP-dipalmitin are promising new prodrugs of ara-C with improved efficacy.

1-β-D-Arabinofuranosylcytosine 5′-diphosphate–L-1,2-dipalmitin (ara-CDP-L-dipalmitin, **1**)[2] (Figure 1) is an ara-C conjugate of phospholipid that has demonstrated a superior antitumor activity over ara-C independent of the treatment schedules.[3-6] The DL racemic mixture, ara-CDP-DL-diplamitin (**3**), has also shown promising therapeutic results.[7-9] To determine stereochemical significance

(1) Presented, in part, at the National Meeting of the American Chemical Society, Washington, DC, September 1983, MEDI 59.

(2) The abbreviations used are: ara-C, 1-β-D-arabinofuranosylcytosine; ara-CMP, 1-β-D-arabinofuranosylcytosine 5′-monophosphate; ara-CDP-L-(D or DL)-dipalmitin; 1-β-D-arabinofuranosylcytosine 5′-diphosphate–L-(D or DL)-1,2-dipalmitin; ribo-CDP-L-dipalmitin, cytidine 5′-diphosphate-L-1,2-dipalmitin; ara-CMP-morpholidate, 1-β-D-arabinofuranosylcytosine 5′-monophosphoromorpholidate 4-morpholine-*N*,*N*′-dicyclohexylcarboxamidinium salt.

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