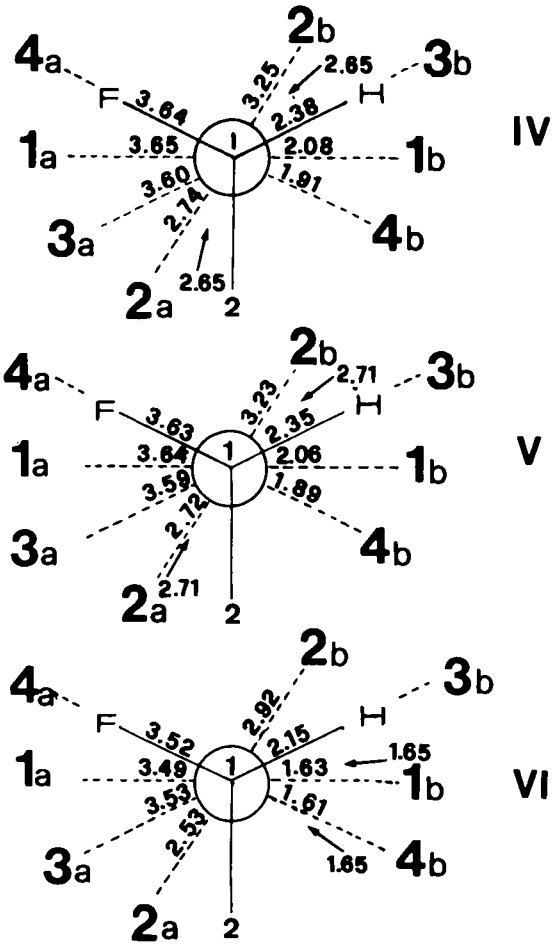

Figure 4—*Experimental dipole moments (values with arrows) and theoretical moments calculated for each ring orientation for IV, V, and VI.*

steric hindrances between halogens in the 2a structure. Conversely, structures 1b and 4b would have to be equally possible for VI, because the C_1—F and the C_2—X bonds are practically *anti* in each case. However, as steric hindrances between the halogen bonded to C-2 and the phenyl ring are minimized in position 1b, the latter will be more stable. These results are in close agreement with ^{13}C-NMR data (18).

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Synthesis and Biological Evaluation of New 2,3-Dihydrothiazole Derivatives for Antimicrobial, Antihypertensive, and Anticonvulsant Activities

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Received December 2, 1982, from the *Pharmaceutical Chemistry Department, Faculty of Pharmacy, University of Alexandria, Egypt.* Accepted for publication August 2, 1983.

Abstract □ A novel series of 2-arylimino-2,3-dihydrothiazole derivatives, substituted in the 3-position with a β-phenethyl moiety and the 4-position with substituted aryl functions, was synthesized as potential antimicrobial, antihypertensive and anticonvulsive agents. While no antimicrobial or significant antihypertensive activity was observed for the products, XII, XIII, and XXI displayed potent anticonvulsant activity.

Keyphrases □ 2,3-Dihydrothiazole derivatives—synthesis antimicrobial, antihypertensive, and anticonvulsant properties □ Antimicrobial activity—2,3-dihydrothiazole derivatives, antihypertensive and anticonvulsant properties

The synthesis and pharmacological properties of a variety of thioureas (1-3), thiosemicarbazones (4-6), thiosemicarbazides (1, 7, 8), thiazoles (2, 6, 7), and thiadiazines (9) derived from various biologically active nuclei (1-5, 8), aromatic (6), and heterocyclic compounds (7, 9) have been recently described in connection with our studies on the structure-activity relationships of certain thio compounds. The high bactericidal activity displayed by some 3,4-diarylthiazolin-2-oxo-(3-substituted 4-oxoquinazolin-2-yl)hydrazones (7) prompted the investigation of a novel series of 2-arylimino-2,3-dihydrothiazoles (VIII-XXXIII) which bear a structural similarity to such active thiazolines with respect to the substituents in the 4-position. This paper reports the synthesis and evaluation of these materials for antimicrobial, antihypertensive, and anticonvulsant activities.

RESULTS AND DISCUSSION

Chemistry—The *N*-substituted *N'*-(2-phenethyl)thiourea derivatives (II-VII), Scheme I, were synthesized (Table I) by treating 2-phenethylamine (I) with the appropriate aryl- or aralkylisothiocyanate in refluxing ethanol

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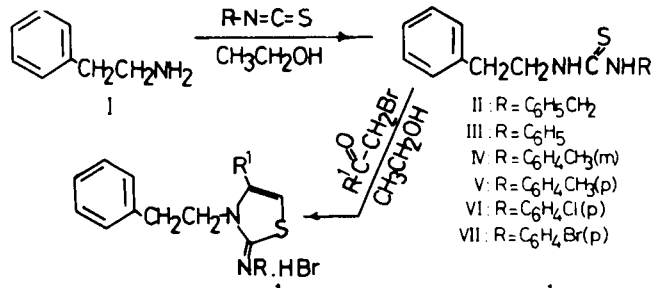
Table I—Synthesized *N,N'*-Disubstituted Thiourea (II-VII) and 4-Thiazoline Derivatives (VIII-XXXIII), and Their Anticonvulsant Activities [a]

Compound	Yield, %	mp, °C	Molecular Formula	Anticonvulsant Activity, % Protection [b]
II	82	118-120	$C_{16}H_{18}N_2S$	—
III	85	106-107 [c]	$C_{15}H_{16}N_2S$	—
IV	79	101-102	$C_{16}H_{18}N_2S$	—
V	85	124-126	$C_{16}H_{18}N_2S$	—
VI	80	135-137	$C_{15}H_{15}ClN_2S$	—
VII	83	130-132	$C_{15}H_{15}BrN_2S$	—
VIII	84	166-167	$C_{24}H_{23}BrN_2S$	+13
IX	89	207-208	$C_{24}H_{22}Br_2N_2S$	−20
X	87	230-231	$C_{24}H_{22}BrN_3O_2S$	+12
XI	81	180-181	$C_{25}H_{25}BrN_2S$	+53
XII	86	226-227	$C_{24}H_{22}BrClN_2S$	+91 [d]
XIII	88	229-230	$C_{23}H_{21}BrN_2S$	+162
XIV	88	230-231	$C_{23}H_{20}Br_2N_2S$	+25
IV	93	266-267	$C_{23}H_{20}BrN_3O_2S$	+12
XVI	100	209-210	$C_{24}H_{23}BrN_2S$	+23
XVII	82	219-220	$C_{24}H_{23}BrN_2S$	+5
XVIII	86	240-241	$C_{24}H_{22}Br_2N_2S$	+37
XIX	85	266-267	$C_{24}H_{22}BrN_3O_2S$	+1
XX	79	204-205	$C_{25}H_{25}BrN_2S$	−17
XXI	93	235-236	$C_{24}H_{23}BrN_2S$	+94
XXII	96	266-267	$C_{24}H_{22}Br_2N_2S$	−22
XXIII	95	274-275	$C_{24}H_{22}BrN_3O_2S$	+24
XXIV	91	233-234	$C_{25}H_{25}BrN_2S$	−5
XXV	94	269-270	$C_{23}H_{20}BrClN_2S$	+1
XXVI	98	270-271	$C_{23}H_{19}Br_2ClN_2S$	−8
XXVII	94	279-280	$C_{23}H_{19}BrClN_3O_2S$	−5
XXVIII	92	269-270	$C_{24}H_{22}BrClN_2S$	−15
XXIX	100	264-265	$C_{23}H_{19}BrCl_2N_2S$	+19
XXX	91	265-266	$C_{23}H_{20}Br_2N_2S$	+17
XXXI	98	267-268	$C_{23}H_{19}Br_3N_2S$	+6
XXXII	94	275-276	$C_{23}H_{19}Br_2N_3O_2S$	+25
XXXIII	91	263-264	$C_{24}H_{22}Br_2N_2S$	−7

[a] All compounds underwent elemental analyses for C and H. Compounds II VIII, XI, XIV-XVI, XXII, XXIII, XXVII, and XXIX-XXXI were also analyzed for N; II, V, VIII, X, XIII, XV-XVII, XX, XXI, XXIII-XXV, XXVIII, and XXX-XXXIII were analyzed for S; and IX, XIV, XXII, XXXI, and XXXII were analyzed for Br. All values were within ±0.4% of the theoretical values. [b] Percentages of protection for diazepam (5 mg/kg po) and chlordiazepoxide (10 mg/kg po) were +174 and +185, respectively. [c] Reported (13) mp 111 °C, without confirmation of elemental analysis. [d] Associated with symptoms of toxicity.

(10). The products were treated with either phenacyl bromide or the properly substituted phenacyl bromide in boiling ethanol to give the required 2,3-dihydrothiazole derivatives (VIII-XXXIII) as hydrobromide salts (see Table I).

Biological Screening[1]—*Antimicrobial Activity*—Using the serial dilution method in Mueller Hinton agar (6), VIII-XXXIII did not show antimicrobial effect against *Escherichia coli* NCTC 10418, *Klebsiella aerogene* A, *Pseudomonas aeroginosa* NCTC 10662, *Serratia marcescens* US32, *Staphylococcus aureus* Oxford, *Candida albicans* W97, and *Bacteroides fragilis* BC4, NCTC 8560, and B3.



	R	R'		R	R'
VIII:	$C_6H_5CH_2$	C_6H_5	IX:	$C_6H_5CH_2$	$C_6H_4Br(p)$
X:	$C_6H_5CH_2$	$C_6H_4NO_2(p)$	XI:	$C_6H_5CH_2$	$C_6H_4CH_3(p)$
XII:	$C_6H_5CH_2$	$C_6H_4Cl(p)$	XIII:	C_6H_5	C_6H_5
XIV:	C_6H_5	$C_6H_4Br(p)$	XV:	C_6H_5	$C_6H_4NO_2(p)$
XVI:	C_6H_5	$C_6H_4CH_3(p)$	XVII:	$C_6H_4CH_3(m)$	C_6H_5
XVIII:	$C_6H_4CH_3(m)$	$C_6H_4Br(p)$	XIX:	$C_6H_4CH_3(m)$	$C_6H_4NO_2(p)$
XX:	$C_6H_4CH_3(m)$	$C_6H_4CH_3(p)$	XXI:	$C_6H_4CH_3(p)$	C_6H_5
XXII:	$C_6H_4CH_3(p)$	$C_6H_4Br(p)$	XXIII:	$C_6H_4CH_3(p)$	$C_6H_4NO_2(p)$
XXIV:	$C_6H_4CH_3(p)$	$C_6H_4CH_3(p)$	XXV:	$C_6H_4Cl(p)$	C_6H_5
XXVI:	$C_6H_4Cl(p)$	$C_6H_4Br(p)$	XXVII:	$C_6H_4Cl(p)$	$C_6H_4NO_2(p)$
XXVIII:	$C_6H_4Cl(p)$	$C_6H_4CH_3(p)$	XXIX:	$C_6H_4Cl(p)$	$C_6H_4Cl(p)$
XXX:	$C_6H_4Br(p)$	C_6H_5	XXXI:	$C_6H_4Br(p)$	$C_6H_4Br(p)$
XXXII:	$C_6H_4Br(p)$	$C_6H_4NO_2(p)$	XXXIII:	$C_6H_4Br(p)$	$C_6H_4CH_3(p)$

Scheme I

Antihypertensive Activity—The 2-phenylimino-3-phenyl-4-phenyl-2,3-dihydrothiazole (XIII) caused a slight fall in blood pressure 6 h after administration of a dose of 100 mg/kg in spontaneously hypertensive rats. The 2,3-dihydrothiazoles XI and XX (at a dose of 5 mg/kg) and XXI (at a dose of 100 mg/kg), as the other selected examples of the series, did not exhibit antihypertensive activity.

Anticonvulsant Activity—The oral administration of VIII-XXXIII in doses of 100 mg/kg in mice 60 min prior to induction of convulsions by pentylenetetrazol[2] (8 mg/mL in saline), gave variable anticonvulsant activities ranging from +162 to −22% protection (Table I). The 2,3-dihydrothiazoles XIII and XXI were the most potent, causing +162 and +94% protection, respectively. The +91% protection exhibited by XII was accompanied by symptoms of toxicity.

Such results, as compared with those recently reported for the thiazoline-2-hydrazonoquinazolones (7), are indicative of the effect of the bulky phenethyl group, which is a constant substituent, on the supression of the antimicrobial activity of all products (12). The insignificant antihypertensive effect displayed by XIII as well as the general lack of anticonvulsant activity, despite the observed potency of XII, XIII, and XXI, could not lead to reliable structure-activity relationships in these 2,3-dihydrothiazoles.

EXPERIMENTAL SECTION[3]

N-Aryl-N'-(2-phenethyl)thiourea Derivatives (II-VII)—A mixture of 2-phenethylamine (I) (1.2 g, 0.01 mol) and the appropriate aryl- or aralkylisothiocyanate (0.01 mol) in ethanol (20 mL) was heated at reflux for 1 h. The mixture was concentrated under reduced pressure, and the material which separated on cooling was removed by filtration, washed with 10% HCl, dried, and recrystallized from ethanol. The yields and physical constants of the products (II-VII) are presented in Table I. IR (mineral oil) ν: 3370 and

[1] Performed in accordance with the protocol of the biological screening of the Chemotherapeutic Research Centre, Beecham Pharmaceuticals, Brockham Park, Betchworth, Surrey, RH3 7AJ, U.K.

[2] Metrazol; Sigma, U.K.

[3] All melting points are uncorrected. IR spectra were measured on a Beckman 4210 IR Spectrophotometer. ^{1}H-NMR spectra were measured on a Varian A-90, and mass spectra on a Finnigan 3200.

3250-3160 (NH), 1550-1525, 1345, 1320-1305, and 945-910 cm^{-1} (NCS I, II, III, and IV amide bands, respectively) (11); ^{1}H-NMR of II ($CDCl_3$): δ 2.82 (t, 2, J = 7.5 Hz, $C_6H_5CH_2CH_2$—), 3.68 (q, 2, J = 7.5 Hz, $C_6H_5CH_2CH_2$—), 4.41 (d, 2, J = 5 Hz, $C_6H_5CH_2$—), 5.64 (s, distorted, 1, 2-phenethyl-NH, exchangeable), 6.07 (s, distorted, 1, benzyl-NH, exchangeable), and 7.13 ppm (m, 10, ArH).

2-Arylimino-4-aryl-3-(2-phenethyl)-2,3-dihydrothiazole Hydrobromides (VIII–XXXIII)—A mixture of *N*-aryl-*N'*-(2-phenethyl)thioureas (II–VII) (0.001 mol) and phenacyl bromide or the appropriately substituted phenacyl bromide (0.0011 mol) in absolute ethanol (10 mL) was heated at reflux for 4 h. Some of the products separated during the heating, while others crystallized after cooling the mixture. The products were removed by filtration, dried, and recrystallized from benzene containing a few drops of absolute ethanol. The yields and physical constants of the products (VIII–XXXIII) are listed in Table I. IR (mineral oil) ν: 2780–2670 (—NH) and 1610–1590 cm^{-1} (C=N); ^{1}H-NMR of XXIII (Me_2SO-d_6): δ 2.41 (s, 3, CH_3), 2.94 (t, 2, J = 7.5 Hz, $C_6H_5CH_2CH_2$—), 4.46 (t, 2, J = 7.5 Hz, $C_6H_5CH_2CH_2$—), 7.26 (m, 10, ArH and C_5—H of the thiazoline ring), 7.70 (d, 2, J = 9 Hz, ArH, *meta* to nitro group), and 8.44 ppm (d, 2, J = 9 Hz, ArH, *ortho* to nitro group); ^{1}H-NMR for XXVIII: δ 2.41 (s, 3, CH_3), 2.87 (t, 2, J = 7.5 Hz, $C_6H_5CH_2CH_2$—), 4.34 (t, 2, J = 7.5 Hz, $C_6H_5CH_2CH_2$—), 6.87 (s, 1, C_5-thiazoline proton), and 7.25 ppm (m, 13, ArH); ^{1}H-NMR for XXX: δ 2.81 (t, 2, J = 7.5 Hz, $C_6H_5CH_2CH_2$—), 4.27 (t, 2, J = 7.5 Hz, $C_6H_5CH_2CH_2$—), 6.80 (s, 1, C_5-thiazoline proton), and 7.29 ppm (m, 14, ArH). MS, *m/z* (relative abundance %) for XXIII: M^+ at 415(7), 312(22), 311(100), 310(20), 134(19), 105(47), 104(22), 103(26), 91(49), and 89(28). For XXVIII: M^+ at 404 and M + 2 at 406(8), 302(36), 301(22), 300(100), 299(15), 149(27), 148(51), 147(74), 134(27), 118(31), 115(28), 105(52), 104(21), 103(29), and 91(48). For XXX: M^+ at 435 and M + 2 at 437(0.9), 332(57), 331(17), 330(50), 139(22), 135(31), 134(100), 105(41), 104(49), 103(32), 102(23), 91(86), 90(24), 89(20), and 82(16).

Antihypertensive Testing—Rats, maintained in an incubator (32–35°C) for 20–40 min, were restrained to measure systolic blood pressure and heart rate indirectly by the tail cuff method[4]. Each determination was the mean of at least six recordings. Groups of four animals were used, and measurements were made predose (time zero) 1, 2, 4, and 6 h after administration of the products, with occasional readings at 24 h.

Anticonvulsant Testing—The compounds suspended in 1% methylcellulose were administered orally (1 mL/100 g) to CD-1 male mice (18–25 g), 10 per group, 1 h before intravenous infusion of 8 mg/mL of pentylenetetrazol in saline at a rate of 0.5 mL/min. The time of infusion required to elicit a tonic extensor spasm was noted, and the dose of pentylenetetrazol administered was calculated. The results (Table I) are expressed as the percentage change compared with controls treated with vehicle only. Statistical significance was determined using the Student's t test.

[4] W, W8005 B.P. recorder.

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Synthesis of *N*,*N'*-Disubstituted *N''*-2-(2-Quinolinylmethylthio)ethylguanidines as Potential Anticancer Agents

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Abstract □ A simple method for obtaining the title compounds was found in the alkaline rearrangement of *S*-2-aminoethylisothiouronium salts, which were obtained from the condensation of thiourea or substituted thioureas with 2-bromoethylamine hydrobromide. No activity was found for the substituted guanidines against P388 lymphocytic leukemia in mice, or as H_2-receptor antagonists.

Keyphrases □ *N,N'*-Disubstituted *N''*-2-(2-quinolinylmethylthio)ethylguanidines—anticancer activity, potential H_2-receptor antagonist □ Anticancer agents—potential, *N,N'*-disubstituted *N''*-2-(2-quinolinylmethylthio)ethylguanidines, H_2-receptor antagonist activity

A number of strongly basic compounds have shown appreciable anticancer activity. Bis(guanidines) and guanylhydrazones are active in leukemia systems (1, 2), and bis(guanylhydrazones) of anthracene-9,10-dicarboxaldehydes (3) have a particularly broad spectrum of anticancer activity. Recently, synthesized bis(*S*-alkyl) (4), and *S*-alkyl cycloalkylamino (5) derivatives of *N*-methylquinolinium dithioacetic acid showed reproducible activity against P388 lymphocytic leukemia in mice, the best activity being shown by one of the basic (morpholino) derivatives. It appeared that further increase in basicity of this series was warranted. The basic side chain of the cimetidine molecule was selected for inclusion in the quinoline-2-methyl structure because of the reported cytostatic and immunosuppressive activities of some guanidine derivatives (6). Modification of the basicity by inclusion of electron-attracting or -releasing functions on the guanidine moiety was

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