Synthesis of 2-(Substituted Anilino) 4-(Substituted Phenyl)thiazoles

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Abstract □ 2-(Substituted anilino) 4-(substituted phenyl)thiazoles were synthesized by condensing 2-haloketones with substituted thioureas. The biological screening of some compounds indicated hypoglycemic and hyperglycemic activity.

Keyphrases □ Thiazoles, various substituted—synthesized, evaluated for hypoglycemic and hyperglycemic activity □ Hypoglycemic activity—various substituted thiazoles evaluated □ Hyperglycemic activity—various substituted thiazoles evaluated □ Structure–activity relationships—various substituted thiazoles evaluated for hypoglycemic and hyperglycemic activity

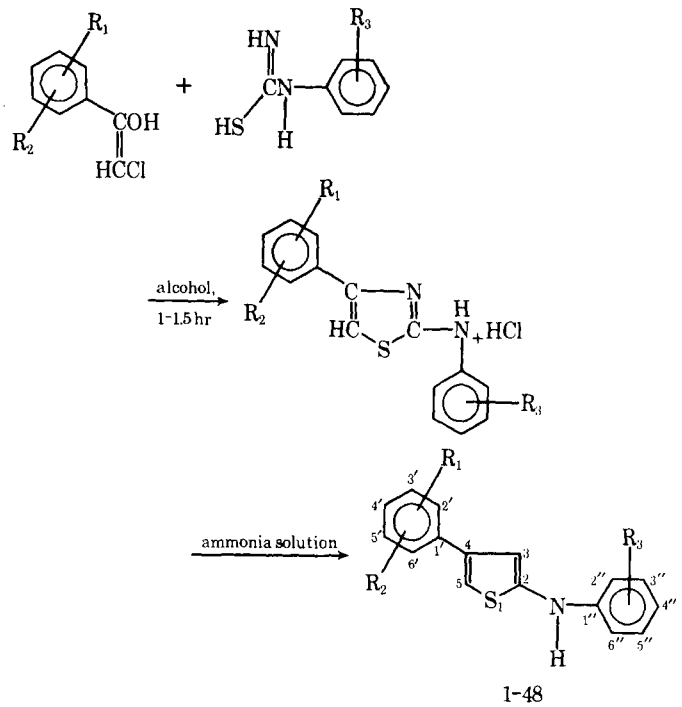
Five-membered heterocyclic compounds with two or three similar or dissimilar hetero atoms are established hypoglycemic and hyperglycemic agents. A literature survey revealed that sulfur-containing compounds are relatively better hypo/hyperglycemic agents (1, 2), but no definite correlation was observed between the nature of sulfur-containing functional groups and hypo/hyperglycemic activity. Important hypoglycemic agents contain *N*-substituted urea and thiourea residues. Thiazoles contain a thiourea moiety, and 2-anilinothiazoles contain an *N*-substituted thiourea moiety. Therefore, it was thought that 2-anilinothiazoles might have hypo/hyperglycemic activity. Therefore, variously substituted 2-anilinothiazoles were synthesized, and some were tested for hypo/hyperglycemic activity.

EXPERIMENTAL

A mixture of a haloketone (0.01 mole), substituted thiourea (0.01 mole), and alcohol (10 ml) was refluxed on a water bath for 1.5 hr. The crystalline hydrochloride obtained was filtered and washed with ether to remove the unreacted ketone. It was then crystallized from aqueous alcohol. The hydrochloride was boiled with excess dilute ammonium hydroxide. The solid thus obtained was filtered, washed with water, and crystallized from 95% alcohol; the yield was 60–70%.

RESULTS AND DISCUSSION

Chemistry—Thiazole synthesis, as described by Hantzsch and Weber (3), was followed for the synthesis of Compounds 1–48 (Scheme I); it involved the condensation of 2-haloketones with thioureas. 2-Haloketones were readily available through the Friedel–Crafts reaction. All thioureas required were previously reported and were synthesized from commercially available substituted anilines by Kurzer's (4) procedure. The 2-haloketones and thioureas condensed smoothly in ethanol to form 2-(substituted anilino) 4-(substituted phenyl)thiazole hydrochlorides which, when made basic with ammonia, yielded Compounds 1–48.



1-48

Scheme I

The formation of thiazole derivatives was determined by their sharp melting points, elemental analyses, and IR spectra (Table I).

Secondary amines show only a single NH-stretching band in the 3500–3200-cm^{-1} range (5). Russell and Thompson (6) extensively studied the IR spectra of secondary amines and examined both the intensity and frequency of the NH band in a wide range of compounds. They reported

Table I—Physical Constants, Elemental Analyses, and IR Spectral Data of 2-(Substituted Anilino) 4-(Substituted Phenyl)thiazoles

Compound	R_1 and R_2	R_3	Melting Point[a]	Carbon, % Calc.	Carbon, % Found	Hydrogen, % Calc.	Hydrogen, % Found	IR Frequencies, cm^{-1} Amino Group	IR Frequencies, cm^{-1} Thiazole Ring
1	3′,4′-Dichloro	H	158° (175°)	56.08	56.23	3.11	3.27	3590, 1620	1570, 1425, 1370, 1030, 820
2	3′,4′-Dichloro	2″-Chloro	115° (206°)	50.64	51.01	2.53	2.99	3230, 1590	1500, 1425, 1385, 1030, 830
3	3′,4′-Dichloro	3″-Chloro	105° (200°)	50.64	49.95	2.53	2.75	—	—
4	3′,4′-Dichloro	4″-Chloro	144° (203°)	50.64	50.80	2.53	2.35	3320, 1610	1560, 1440, 1400, 1026, 840
5	3′,4′-Dichloro	3″-Bromo	103° (198°)	45.00	44.85	2.25	2.52	—	—
6	3′,4′-Dichloro	4″-Bromo	150° (205°)	45.00	44.34	2.25	2.41	3380, 1590	1550, 1435, 1390, 1030, 800
7	3′,4′-Dichloro	2″-Hydroxy	219° (254°)	53.42	53.01	2.96	2.27	3320, 1620	1560, 1430, 1370, 1020, 820
8	3′,4′-Dichloro	3″-Hydroxy	185° (220°)	53.42	52.92	2.96	2.52	3200, 1600	1560, 1425, 1390, 1030, 800

(*continued*)

Table I—*Continued*

Compound	R_1 and R_2	R_3	Melting Point[a]	Carbon, %		Hydrogen, %		IR Frequencies, cm^{-1}	
				Calc.	Found	Calc.	Found	Amino Group	Thiazole Ring
9	3′,4′-Dichloro	4″-Hydroxy	114° (232°)	53.42	53.90	2.96	3.06	3500, 1610	1570, 1420, 1395, 1030, 820
10	3′,4′-Dichloro	2″-Methoxy	132° (180°)	54.70	54.51	3.47	3.85	3370, 1600	1540, 1440, 1380, 1020, 830
11	3′,4′-Dichloro	2″-Pyridyl	175° (243°)	52.57	52.85	2.79	2.32	3400, 1610	1540, 1470, 1380, 1020, 820
12	2′,5′-Dichloro	H	120° (190°)	56.08	56.15	3.11	3.58	3571, 1610	1567, 1430, 1370, 1040, 815
13	2′,5′-Dichloro	2″-Chloro	120° (206°)	50.64	50.82	2.53	3.11	1595	1555, 1464, 1380, 1045, 815
14	2′,5′-Dichloro	3″-Chloro	161° (202°)	50.64	50.99	2.53	2.82	3485, 1600	1560, 1430, 1370, 1006, 815
15	2′,5′-Dichloro	4″-Chloro	141° (195°)	50.64	50.41	2.53	3.06	3545, 1618	1580, 1450, 1370, 1042, 820
16	2′,5′-Dichloro	3″-Bromo	158° (205°)	45.00	44.94	2.25	2.52	1600	1560, 1455, 1380, 1045, 820
17	2′,5′-Dichloro	4″-Bromo	141° (188°)	45.00	45.26	2.25	3.02	1616	1576, 1450, 1370, 1040, 815
18	2′,5′-Dichloro	3″-Iodo	157° (210°)	40.27	40.71	2.01	2.24	1590	1540, 1450, 1370, 1040, 815
19	2′,5′-Dichloro	2″-Hydroxy	210° (236°)	53.42	53.54	2.96	3.34	3340, 1620	1570, 1450, 1370, 1040, 820
20	2′,5′-Dichloro	3″-Hydroxy	158° (230°)	53.42	53.58	2.96	2.84	3450, 1618	1570, 1425, 1370, 1035, 802
21	2′,5′-Dichloro	4″-Hydroxy	130° (225°)	53.42	52.57	2.96	2.96	3200, 1600	1570, 1420, 1370, 1030, 820
22	2′,5′-Dichloro	2″-Methoxy	96° (185°)	54.70	54.40	3.47	3.70	3260, 1600	1570, 1420, 1370, 1030, 820
23	2′,5′-Dichloro	3″-Methoxy	141° (144°)	54.70	54.33	3.47	4.14	3320, 1630	1570, 1420, 1370, 1040, 825
24	2′,5′-Dichloro	2″-Methyl	142° (208°)	59.07	59.01	3.69	3.72	3345, 1590	1560, 1430, 1375, 1040, 810
25	2′,5′-Dichloro	2″-Pyridyl	155° (258°)	52.57	52.25	2.79	4.56	3360, 1615	1550, 1460, 1380, 1040, 810
26	2′-Chloro-5′-methyl	H	194° (195°)	63.90	63.72	4.32	4.15	1590	1580, 1450, 1380, 1040, 800
27	2′-Chloro-5′-methyl	2″-Chloro	80° (198°)	57.32	57.52	3.58	3.28	—	—
28	2′-Chloro-5′-methyl	3″-Chloro	110° (205°)	57.32	57.01	3.58	3.72	3200, 1590	1550, 1415, 1370, 1040, 800
29	2′-Chloro-5′-methyl	4″-Chloro	176° (201°)	57.32	56.79	3.58	4.20	3200, 1590	1560, 1440, 1400, 1020, 820
30	2′-Chloro-5′-methyl	3″-Bromo	137° (206°)	48.98	48.57	3.26	3.03	—	—
31	2′-Chloro-5′-methyl	4″-Bromo	183° (202°)	48.98	48.70	3.26	2.80	3050, 1613	1570, 1445, 1340, 1100, 815
32	2′-Chloro-5′-methyl	2″-Hydroxy	168° (200°)	60.66	59.95	4.10	4.25	3350, 1625	1575, 1475, 1385, 1040, 815
33	2′-Chloro-5′-methyl	3″-Hydroxy	165° (210°)	60.66	60.43	4.10	3.89	3340, 1620	1565, 1440, 1380, 1030, 810
34	2′-Chloro-5′-methyl	4″-Hydroxy	135° (248°)	60.66	59.87	4.10	3.76	3500, 1650	1550, 1424, 1380, 1042, 815
35	2′-Chloro-5′-methyl	2″-Methoxy	70° (190°)	60.29	60.01	4.71	4.52	—	—
36	2′-Chloro-5′-methyl	4″-Methoxy	96° (163°)	60.29	59.95	4.71	5.03	—	—
37	2′-Chloro-5′-methyl	2″-Methyl	133° (198°)	64.86	64.92	4.77	4.23	3360, 1600	1560, 1440, 1380, 1030, 820
38	2′-Chloro-5′-methyl	4″-Methyl	187° (210°)	64.86	64.63	4.77	4.90	1590	1560, 1440, 1395, 1060, 815
39	2′-Chloro-5′-methyl	2″-Pyridyl	142° (220°)	59.70	59.93	3.98	4.23	—	—
40	2′-Bromo-5′-methyl	H	140° (195°)	55.65	55.46	3.75	4.50	3400, 1618	1570, 1450, 1380, 1060, 815
41	2′-Bromo-5′-methyl	2″-Chloro	142° (196°)	50.87	50.52	3.16	3.57	—	—
42	2′-Bromo-5′-methyl	4″-Chloro	189° (184°)	50.87	51.29	3.16	3.46	1600	1570, 1450, 1385, 1060
43	2′-Bromo-5′-methyl	3″-Bromo	137° (210°)	45.28	45.00	2.83	2.62	3540, 1580	1550, 1440, 1360, 1040, 810
44	2′-Bromo-5′-methyl	2″-Hydroxy	158° (185°)	53.19	53.47	3.60	3.32	3420, 1605	1570, 1465, 1380, 1065, 805
45	2′-Bromo-5′-methyl	4″-Hydroxy	205° (220°)	53.19	52.95	3.60	4.10	3500, 1640	1565, 1410, 1380, 1065, 810
46	2′-Bromo-5′-methyl	2″-Methoxy	80° (211°)	54.41	53.69	4.00	5.01	1590	1560, 1420, 1380, 1045, 820
47	2′-Bromo-5′-methyl	2″-Methyl	145° (192°)	56.82	57.55	4.17	3.87	3160, 1600	1550, 1420, 1380, 1030, 820
48	2′-Bromo-5′-methyl	2″-Pyridyl	143° (205°)	52.02	52.60	3.46	4.08	1615	1550, 1420, 1380, 810

[a] Figures in parentheses represent the melting points of the hydrochlorides.

Table II—Data of Hypo/Hyperglycemic Activity of 2-(Substituted Anilino) 4-(Substituted Phenyl)thiazoles

Compound	Increase (+) or Decrease (−) of Blood Glucose Affected by Compounds[a], %			Results
	1 hr	2 hr	4 hr	
2	−4	−4	+2	Inactive
3	−5	−17	−21	Hypoglycemic
4	+15	−4	−7	Inactive
6	−9	−14	−14	Hypoglycemic
7	−11	−9	−11	Inactive
9	+15	+5	+3	Hyperglycemic
12	+11	−3	−4	Hyperglycemic
14	+4	−7	−12	Hypoglycemic
15	+4	−16	−12	Hypoglycemic
17	+4	−12	−14	Hypoglycemic
19	−2	0	−5	Inactive
20	+11	+4	+2	Hyperglycemic
21	−3	−2	−2	Hypoglycemic
28	−10	−17	−12	Hypoglycemic
29	+2	−5	−2	Inactive
31	−2	+2	+2	Inactive
32	+5	−2	+3	Inactive
34	−13	−13	−9	Inactive
42	−3	−12	−9	Hypoglycemic

[a] Results are expressed as the percentage difference in milligrams between the mean change in control and treated groups after a drug dose of 150 mg/kg.

that the frequency falls in the 3350–3310-cm^{-1} range with low intensity in aliphatic secondary amines. In alkylaryl amines, the frequency rises to nearly 3450 cm^{-1} with a higher intensity. The absorption frequencies of diaryl secondary amines do not seem to have been studied in detail. Substituted 2-anilinothiazoles are secondary amines of this type. The NH-stretching frequencies in these compounds lie in the 3550–3320-cm^{-1} range.

The bands due to the NH deformation in secondary aromatic amines are confused to some extent because of C=C ring stretching absorption in the same region. The strong band in the 1640–1600-cm^{-1} region showed the characteristics of anilino structures in general.

The characteristic thiazole ring vibrations have been assigned as 1570-1540, 1470-1420, 1400-1370, and 1035-1025 cm^{-1} (7-9). The bands in the 800–700-cm^{-1} region at the low frequency region are associated with out-of-plane bending vibrations of the CH-stretching of the thiazole ring. The presence of these bands in the IR spectra of the compounds under study confirmed the presence of the thiazole ring.

Hypo/Hyperglycemic Activity—The activity was tested in normal rats (average weight of 200 g). They were divided into groups of seven and fed orally with test compounds (150 mg/kg) as solution in 5% gum tragacanth. Seven rats were kept as controls. Blood samples were drawn each hour from tail veins for glucose measurements. Changes in blood glucose content of the tested rats were compared with those of the controls at 1, 2, 4, and 48 hr in each case. The data of the *in vivo* activity tests are given in Table II.

A compound is considered hypoglycemically active if it produces a 30% decrease in blood glucose and hyperglycemically active if it produces a 10% increase in blood glucose:

$$\% \text{ change} = \frac{\Delta T - \Delta C}{\text{control glucose value at that hour}} \qquad \text{(Eq. 1)}$$

where ΔT is the change of blood glucose from zero time for treated groups and ΔC is the change of blood glucose from zero time for control groups.

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