RESEARCH PAPER

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Synthesis and Anti-Inflammatory and Analgesic Activities of 2-Arylamino 4-(4-Chlorophenyl)Thiazole-5-Acetic Acids/Esters

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New substituted 2-amino-4-(4-chlorophenyl) thiazole-5-acetic acids (6a-k) and esters (7a-l) were prepared by condensaton of thioureas with methyl 3-bromo-3-(4-chlorobenzoyl) propionate. The compounds showed good anti-inflammatory (55-80%, ibuprofen 85%) and analgesic (40-58%, aspirin 57%) activities.

Arylacetic acids[1] are well known clinically as anti-inflammatory and analgesic drugs. It has been observed that ethyl 4-(4-bromophenyl) thiazole-2-acetate[2] reduced inflammation and that 2(4-chlorophenyl) thiazole-4-acetic acid[2] (fenclozic acid) had superior anti-inflammatory action and was in clinical use till it was withdrawn due to hepatotoxic side effects.[3] Several other 2- and 4-thiazoleacetic acids[2,4,6] have been reported to possess anti-inflammatory and analgesic activities.

Many thiazole-5-acetic acids with an aryl substitution at position C-2 have been reported to have anti-inflammatory and analgesic properties. Most of these compounds generally carry aryl[6-12], alkyl[6,13] or carboxyl[14] group at C-4 position. Hirai and Sugimoto[15] have patented a series of 2-amino substituted thiazole-5-acetic, propionic esters and acids as potential agents for anti-inflammatory and analgesic activities. Kowalczyk-Bronisz *et al.*[16-18], have studied the immunosuppressant action of a number of 2-N-acyl, 2-N-aralkylidene and 2-N-aralkyl derivatives of 2-amino-4-(4-chlorophenyl)thiazole-5-acetic acid along with anti-inflammatory activity. Sawhney *et al.*[19] reported anti-inflammatory activity in a series of imidazo(2,1-b)thiazole acetic acids, a cyclized product of 2-aminothiazole-5-acetic acid.

A compound with substituted arylamino moiety at position C-2 in such a system has not been reported. An arylamino group in these compounds is suitably situated with respect to the acetic acid unit, biosterically similar to indomethacin, and fits appropriately in the NSAIDs receptor site[20,21]. Therefore, novel title compounds were synthesised and their anti-inflammatory and analgesic activities studied.

The acylation of chlorobenzene with succinic anhydride in the presence of anhydrous aluminium chloride gave 3-(4-chlorobenzoyl)propionic acid **(1)** which was esterfied with methanol to give methyl 3-(4-chlorobenzoyl)propionate **(2)** and then brominated to methyl 3-bromo-3- (4-chlorobenzoyl)propionate **(4)**. The bromoester was condensed with thiourea, phenylthiourea and substituted phenylthioureas (2-Cl, 3-Cl, 4-Cl, 2-CH_3, 4-CH_3, 4-Br and 4-F, prepared from respective amine and ammonium thiocyanate with benzoyl chloride)[22] to get the substituted methyl 2-amino-4-(4-chlorophenyl) thiazole-5-acetate **(7)**. The thiazole acetates were saponified to respective thiazoleacetic acids **(6)** (Scheme I).

EXPERIMENTAL

IR spectra were taken on a Phillips Pye Unicam SP-3200 IR spectrometer using the KBr disc method. PMR spectra were obtained using a EM390 CW-NMR 90 MHz in $CDCl_3$ as solvent.

*For Correspodence

3-(4-Chlorobenzoyl)propionic acid **(1)** prepared by Friedel Craft's acylation[23] was esterfied usng sulphuric acid method to get methyl 3-(4-chlorobenzoyl)propionate **(2)**.

Methyl 3-bromo-3-(4-chlorobenzoyl)propionate (4)

Bromine (1.7 g, 11 mmol) was added dropwise to a soluton of methyl 3-(4-chlorobenzoyl)propionate (2.2 g, 10 mmol) in 20 ml hot chloroform, with stirring. The reaction mixture was stirred for an additional 2h. The reaction mixture was washed with water, dried over anhydrous sodium sulphate and then the solvent removed, to get the bromoester **(4)** as a viscous oil which was used as such for the next step. Yield : 95%.

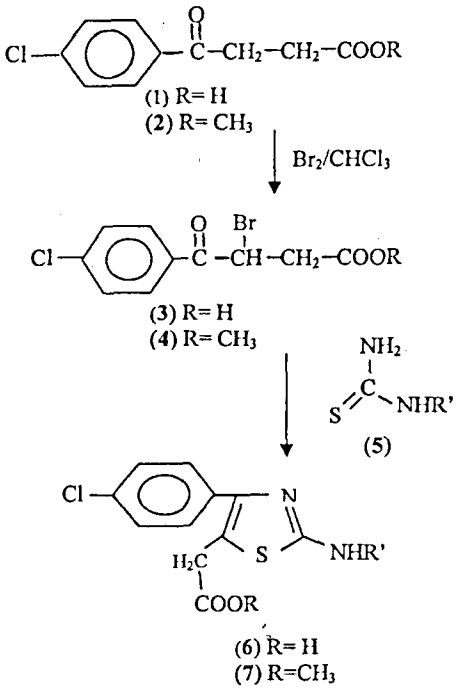
Methyl 4-(4-chlorophenyl)-2-phenylamino)thiazole-5-acetate(7b)

The bromoester **(4)** (1.4 g, 5 mmol), pheylthiourea (0.76 g, 5 mmol) and ethanol 20 ml were heated for 15 min. Anhydrous sodium carbonate (0.25 g) was added and heating continued for 1h. The precipitation of the base thiazole acetate **(7b)** occurred with addition of water, this was filtered, dried and crystallized from aqueous alcohol. Yield : 1.3 g, 73%; m.p. : 122°; Found : C, 60.30; H, 4.19; N, 7.81; S, 8.76; Cl, 9.82; $C_{18}H_{15}O_2N_2SCl$ requires C, 60.25, H, 4.20; N, 7.80; S, 8.93; Cl, 9.88%. IR (KBr) cm^{-1} : 3400 (m, N-H; 3025 (w, Ar-H); 1720 (m, C = O ester); 1600, 1540, 1495 (m,Ar C=C); 730 (m, Ar-Cl). PMR ($CDCl_3$) : 3.62, s, 3H, $COOC\underline{H}_3$; 3.75, s, 2H, $C\underline{H}_2$; 7.0-7.6, m, 10H, N<u>H</u> and Ar-<u>H</u>.

4-(4-Chlorophenyl)-2-(phenylamino)thiazole-5-acetic acid (6b)

The above thiazole ester **7b** (2 g) was added to a 10% NaOH (10 ml) solution. It was refluxed for 2 h, cooled and filtered, acidification precipitated the acid **(6b)** which was filtered, dried and crystallized from ethanol. Yield : 1.5 g, 80%; m.p. 240-42°, Found : C, 59.24; H, 3.81; N, 8.02; S, 9.21; Cl, 10.16, $C_{17}H_{13}O_2N_2SCl$ requires C, 59.23; H, 3.79; N, 8.12; S, 9.30; Cl, 10.28. IR (KBr) cm^{-1} : 3400-3500 (br, COO-H); 3360 (m, N-H); 1700 (m, C=O acid); 1600 (s, Ar C=C); 740 (m, Ar-Cl).

Ethyl 4-(4-chlorophenyl)-2-(phenylamino)thiazole-5-acetate (7c) : Starting with ethyl 3-bromo-3-(4-chlorobenzoyl)propionate and phenylthiourea and adopting the same procedure as described in the synthesis of methyl thiazoleacetate **(7b)**, ethyl thiazole-5-acetate **(7c)** was obtained. Yield : (55%); m.p. : 119-120°; Found; C, 61.23; H, 4.64; N, 7.52; S, 8.56; Cl, 9.62; $C_{19}H_{17}O_2N_2SCl$, requires C, 61.20; H, 4.59; N, 7.51; S, 8.59; Cl, 9.50%. IR (KBr) cm^{-1} : 3380 (m, N-H) : 3010 (w, Ar-H); 1715 (s, C=0 ester); 735 (m, Ar-Cl). PMR ($CDCl_3$) : 1.32, t, 3H, $CH_2C\underline{H}_3$; 3.73, s. 2H, $C\underline{H}_2$; 4.21, q, 2H, $C\underline{H}_2C\underline{H}_3$; 7.0-7.7, m, 10H, N<u>H</u> and Ar<u>H</u>.



SCHEME I

The same compound **(6b)** was also obtained by condensation of 3-bromo-3-(4-chlorobenzoyl)propionic acid **(3)** with phenylthiourea **(5)**. Similarly other compounds **6a-k** and **7a-l** were prepared.

PHARMACOLOGICAL STUDIES

Suspensions of the test compounds were prepared in 10% v/v Tween 80 solution. In all the cases, controls received the same quantity of Tween 80 solutions. The standard error and the statistical significance (t-test) were computed by usual methods.

Anti-inflammatory activity was evaluated by carrageenan-induced rat hind paw oedema mehod of Winter *et al.*[24,25] Albino rats were distributed into control, standard, and test (6- animals each) groups. The test compounds and ibuprofen were administered orally at the dose of 100 mg/kg. Thirty minutes after compound administra-

Table I - Melting points, yields and pharmacological activity of test compounds

Compd. No.	R'	R	M.P.	% Yield	%A.A.*	%analgesic activity*
6a	H	H	221-23	68	NS	NS
b	C_6H_5	H	240-42	80	80.2	NS
c	2-Cl C_6H_4	H	208-10	81	78.9	NS
d	3-Cl C_6H_4	H	230-31	79	67.7	NS
e	4-Cl C_6H_4	H	210-12	82	70.5	NS
f	2-CH_3 C_6H_4	H	235-37	86	63.4	NS
g	3-CH_3 C_6H_4	H	242-43	76	67.7	NS
h	4-CH_3 C_6H_4	H	248-50	74	73.3	NS
j	4-F C_6H_4	H	261-62	81	69.1	NS
k	4-Br C_6H_4	H	238-40	80	71.9	NS
7a	H	CH_3	157	70	52.2	44.0
b	C_6H_5	CH_3	122	73	77.5	57.8
c	C_6H_5	C_2H_5	119-20	55	78.9	58.2
d	2-Cl C_6H_4	CH_3	94-95	58	NS	NS
e	3-Cl C_6H_4	CH_3	103-04	71	60.6	26.6
f	4-Cl C_6H_4	CH_3	124-25	85	64.8	32.4
g	2-CH_3 C_6H_4	CH_3	123-24	80	59.2	NS
h	3-CH_3 C_6H_4	CH_3	176-77	74	66.2	36.5
j	4-CH_3 C_6H_4	CH_3	139-40	59	69.1	41.9
k	4-F C_6H_4	CH_3	171	68	62.0	40.9
l	4-Br C_6H_4	CH_3	155-56	64	69.1	38.4
	Ibuprofen				84.6	
	Aspirin				—	57.2

Test compounds were administered orally at 100 mg/kg dose level. NS denotes that compound was not screened. Asterisk indicates statistical significance at $P \leq 0.05$. AA stands for anti-inflammatory activity.

tion, oedema was induced in the hind paw by injection of 0.05ml of 1% carrageenan. Paw volumes were measured before and 4 h after injecton of carrageenan by a plethysmometer. The per cent inhibition was calculated using the formula: = (1- Vt/Vc) 100, where Vt and Vc are the mean relative changes in the paw volume in test and control respectively.

Analgesic activity was determined using the acetic acid-induced writhing method.[25,26] Albino mice weighing between 20-30 g in groups of six each were used. Test compounds and aspirin were administered orally at the dose of 100 mg/kg. After 30 min of the administration of compounds and drug, the mice were given 0.5% acetic acid at a dose of 0.1 ml/10 g intraperitoneally to induce writhing. The writhing episodes produced in these animals were counted for 20 min and compared with those in the control group. Percent protection for each compound was calculated.

The LD_{50} values were also determined for the compounds **6c** (>3000 mg/kg oral, 850 mg/kg i.p.) and **7b** (>3000 mg/kg oral, 1000 mg/kg i.p.) in mice using both oral and i.p. routes of administration.[27]

RESULTS AND DISCUSSION

Table 1 presents the melting points, yields and pharmacological activities of compounds. Anti-inflammatory activities of compounds **6b**, **7b** and **7c** are equivalent to ibuprofen (standard). Methyl and ethyl esters do not show much difference. Among the halogenated compounds, the 2-chloro is most active while 3-chloro and 4-chloro derivatives showed lesser activity. In the methyl series the 3-methyl and 4-methyl compounds are more active than the 2-methyl compound. The thiazole acetic acids **(6)** were found to be more active then the methyl thiazole acetates **(7)**. Except for the ethyl 4-(4-chlorphenyl)-2-(2-methyl phenylamino)thiazole-5-acetate **(7g)** all the other aryl substituted compounds possessed significant anti-inflammatory activity as compared to that of ibuprofen. The high LD_{50} value (>3000mg/kg oral, 800-1000mg/kg, i/p) of these compounds clearly indicate that they are safe.

It is found that satisfactory correlation was obtained, in regresson analysis, as the thiazole acetic acid series of **6b, 6d, 6e, 6g, 6h, 6j, 6k** analysed for the equation log $A=0.302\,\pi^2 - 0.266\,\pi - 0.083\,\sigma + 1.893$ with n=7, R=0.859. The thiazole acetates **7b, 7e, 7f, 7h, 7j, 7k** and **7l** analysed for the equation log $A = 0.440\,\pi^2 - 0.348\,\pi - 0.191\,\sigma + 1.871$ with n=7, R=0.889. The analgesic activity of the N-phenyl system **7b** and **7c** were as good as standard aspirin. The others compounds showed lesser analgesic activity.

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