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NOTE

Synthesis and Antiinflammatory Activity of 3-(3-Chloro-4-fluorophenyl)-2-Substituted Phenyl-4-Thiazolidinones

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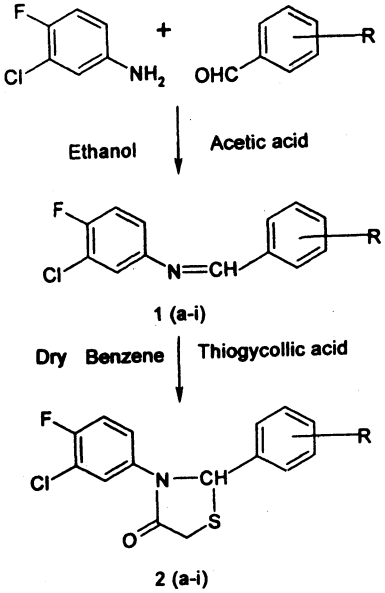
3-Chloro-4-fluoroaniline on condensation with various aromatic aldehydes afforded corresponding Schiff bases **1**. Further, these Schiff bases were converted into 3-(3-chloro-4-fluorophenyl)-2-substituted phenyl-4-thiazolidnones (**2**) by the action of thioglycollic acid. The structures of the synthesized compounds were characterized by their spectral studies. The antiinflammatory activity data of **2** was also presented.

Key Words: Synthesis, 4-Thiazolidinones, Antiinflammatory activity.

The compounds containing a thiazolidinone unit having antiinflammatory activity is well documented[1–6]. The incorporation of para fluorophenyl group in drug molecules as a means of increasing the therapeutic efficacy is reported in literature[7]. These investigations stimulated efforts for the synthesis of title compounds by **Scheme-1** with the aim to obtain new antiinflammatory agents.



Scheme-1

All melting points were determined in open capillaries in a liquid paraffin bath and are uncorrected. The UV spectra were obtained on a Hitachi 228-1050 spectrophotometer. The IR spectra were run on a Hitachi 270-117 spectrophotometer in potassium bromide pellets. The ^{1}H NMR spectra were recorded on a Varian-390, 90 MHz spectrophotometer in $CDCl_3$ solvent using tetramethyl silane as reference. Mass spectra were recorded by JEOL-JMS-300 spectrophotometer. The compounds were analyzed for C, H and N and the values were found within ± 0.4% of the calculated values.

Preparation of N-(benzylidene)-3-chloro-4-fluoroaniline[8]

A mixture of 3-chloro-4-fluoroaniline (0.01 mol) and benzaldehyde (0.01 mol) was dissolved in ethyl alcohol (30 mL). One drop of glacial acetic acid was added to it and refluxed for 3 h. The resulting clear solution was cooled and poured in ice-cold water. The separated solid was filtered and recrystallized from dimethylformamide to give **1a**. λ_{max} 209, ν_{max} (cm^{-1}) 1620 ν(C=N), 1500 ν(C=C), 1330 ν(C—F) and 600 ν(C—Cl). ^{1}H NMR: δ 6.5–7.7 (m, 8H, Ar—H) and δ 7.9 (s, 1H, N=CH). The other compounds **1(b–i)** reported in the Table-1 were prepared in the same manner.

TABLE-1
PHYSICAL AND ANTIINFLAMMATORY ACTIVITY DATA OF COMPOUNDS

Compound	R	m.p. (°C)	Yield (%)	m.f.	Inhibition (%)
1a	H	39	72	$C_{13}H_9NFCl$	NT
1b	2-NO_2	110	76	$C_{13}H_8N_2O_2FCl$	NT
1c	3-NO_2	119	85	$C_{13}H_8N_2O_2FCl$	NT
1d	4-NO_2	135	78	$C_{13}H_8N_2O_2FCl$	NT
1e	4-Cl	109	86	$C_{13}H_8NFCl_2$	NT
1f	4-Me	42	68	$C_{14}H_{11}NFCl$	NT
1g	2-OH	125	75	$C_{13}H_9NOFCl$	NT
1h	4-$N(CH_3)_2$	112	77	$C_{15}H_{14}N_2FCl$	NT
1i	3,4,5-$(OCH_3)_3$	110	83	$C_{16}H_{15}NO_3FCl$	NT
2a	H	122	58	$C_{15}H_{11}NOSFCl$	32.3
2b	2-NO_2	93	65	$C_{15}H_{10}N_2O_3SFCl$	33.8
2c	3-NO_2	132	76	$C_{15}H_{10}N_2O_3SFCl$	36.7
2d	4-NO_2	87	56	$C_{15}H_{10}NO_3SFCl$	32.3
2e	4-Cl	67	68	$C_{15}H_{10}NOSFCl_2$	39.7
2f	4-CH_3	35	59	$C_{16}H_{13}NOSFCl$	32.3
2g	2-OH	140	61	$C_{15}H_{11}NO_2SFCl$	33.8
2h	4-$N(CH_3)_2$	82	65	$C_{17}H_{16}N_2OSFCl$	29.4
2i	3,4,5-$(OCH_3)_3$	78	63	$C_{18}H_{17}NO_4SFCl$	29.0
Ibuprofen					48.5

NT: Not tested

Preparation of 3-(3-chloro-4-fluorophenyl)-2-phenyl-4-thiazolidinone[9]

A mixture of compound **1a** (0.01 mol) and thioglycollic acid (0.01 mol) was taken in dry benzene (30 mL) and then refluxed for 8 h with a Dean and Stark water separator until water had ceased to separate. The benzene was removed under reduced pressure and the residue was taken up in ether, washed successively with sodium bicarbonate solution, dilute HCl (1 : 1), 10% sodium bisulfite solution and finally with water. The residue was recrystallized from ethanol to give **2a**. λ_{max} 224 nm, (ν_{max} cm^{-1}) 1680 ν(C=O), 1330 ν(C—F), 600 ν(C—Cl), δ 6.5–7.7 (m, 8H, Ar—H), δ 5.9 (s, 1H, S—CH), δ 3.8 (s, 2H, S—CH_2), MS (m/e) 308. The other compounds **2(b–i)** reported in the Table-1 were prepared in the same manner.

The newly synthesized compounds **2(a–i)** were screened for antiinflammatory activity by carrageenan induced rate hind paw oedema method[10], using ibuprofen as standard.

The compounds **2(a–i)** exhibited potent antiinflammatory activity and this activity ranged from 29 to 40%. Among these, the compound **2e** with (4-chlorophenyl) substitution at C-2 showed the highest activity, while the others had moderate activity. However, none of these compounds had greater activity than standard reference ibuprofen, which exhibited 48.5% inhibition.

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