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Synthesis and Antiinflammatory Activity of Some 2-(Substituted phenyl)-3-(4,5-diphenyl-1*H*-imidazol-2-yl)-1,3-thiazolidin-4-one Derivatives

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4,5-Diphenylimidazoline-2-amine (**I**) was treated with different aryl aldehydes in ethanol to yield the corresponding Schiff bases (**IIa-e**). The Schiff bases (**IIa-e**) on refluxing with thioglycolic acid in 1,4-dioxane yielded 2-(substituted phenyl)-3-(4,5-diphenyl-1*H*-imidazol-2-yl)-1,3-thiazolidin-4-one (**IIIa-e**). The compounds were characterized by elemental analysis, ^{1}H NMR, mass and IR spectral studies. All the title compounds were screened for antiinflammatory activity. Compounds **IIIa**, **IIIb** and **IIId** have exhibited good anti-inflammatory activity.

Key Words: Antiinflammatory activity, Thiazolidin-4-one.

INTRODUCTION

Imidazole derivatives are found to posses various biological activities *viz.*, antibacterial[1,2], antifungal[3], antiinflammatory[4], antihistaminic[5] and antihypertensive[6]. 4-Thiazolidinines have gained unique important due to broad spectrum of pharmacological activities which are reflected by their use as anti tubercular[7], anticonvulsant[8], antifungal[9], antibacterial[10,11] and antitumour agents[12]. Therefore, it was thought to combine imidazole and 4-thiazolodinenone rings together in a molecular framework to see the additive effects of these rings towards the biological activities.

EXPERIMENTAL

The melting points of the compounds were determined in open capillaries and are uncorrected. Purity of the compounds were checked by micro TLC using silica gel G coated glass plates using benzene-methanol (9:1; v/v) as irrigant and iodine vapour as detecting agent. The IR spectra (cm^{-1}) were recorded in KBr discs on a Jasco FT/IR-5300 spectrometer. ^{1}H NMR spectra ($CDCl_3$) were recorded on Bruker DPX (400 MHz) using TMS as internal standard (chemical shift in ppm). Elemental analysis was within ± 0.4 % of their calculated values.

Synthesis of 4,5-diphenylimidazoline-2-amine (I): An appropriate benzoin (1.98 g, 0.01 mol) and guanidine (0.97 g, 0.01 mol) were intimately mixed in 95 % of ethanol were refluxed for 3-4 h. The reaction mixture was cooled and triturated with crushed ice (≈ 150 g). The crude product separated was filtered, washed thoroughly with small portions of cold water and dried. The product was recrystallized from ethanol to get a white crystalline compound. Yield 87 %; IR (KBr, ν_{max}, cm^{-1}): 3470, 3398 (NH *str.* 1°-amine), 1594 (C=N) and 1262 (C-N); ^1H NMR ($CDCl_3$, δ ppm): 10.6 (s, IH, NH exchangable with D_2O), 7.3-7.8 (m, 10H, Ar-H), 5.2 (s, 2H, NH_2 exchangable with D_2O); m/z: 398 (M+1); Elem. anal. ($C_{24}H_{19}N_3OS$) Found %: C, 72.32; H, 4.92; N, 10.75; Calculated %: C, 72.52; H, 4.82; N, 10.57.

Synthesis of 2-(substituted phenyl)methylene]-4,5-diphenyl-1*H*-imidazol-amine (IIa-e): A mixture of 4,5-diphenylimidazoline-2-amine (**I**) (2.35 g, 0.01 mol) and aryl aldehydes (0.01 mol) in 95 % of ethanol were refluxed for 3-4 h. The contents were cooled and poured on to crushed ice. The crude product thus separated was filtered, dried and recrystallized from appropriate solvent.

IIa: Yield 77 %; m.p. 110-111 ºC; IR (KBr, ν_{max}, cm^{-1}): 3415 (N-H), 1584 (C=N); ^1H NMR ($CDCl_3$, δ ppm): 8.0 (1H, s, NH), 7.3-7.8 (15H, m, Ar-H), 5.4 (1H, s, Ar-CH); m/z: 324 (M+1); Elem. anal. ($C_{22}H_{17}N_3$) Found %: C, 81.52; H, 5.65; N, 12.76; Calculated %: C, 81.71; H, 5.30; N, 12.99.

IIb: Yield 65 %; m.p. 93-94 ºC; IR (KBr, ν_{max}, cm^{-1}): 3379 (N-H), 1594 (C=N); ^1H NMR ($CDCl_3$, δ ppm): 8.2 (1H, s, NH), 7.3-7.5 (14H, m, Ar-H), 5.2 (1H, s, Ar-CH); m/z: 340 (M+1); Elem. anal. ($C_{22}H_{17}N_3O$) Found %: C, 77.98; H, 5.26; N, 12.65; Calculated %: C, 77.86; H, 5.05; N, 12.38.

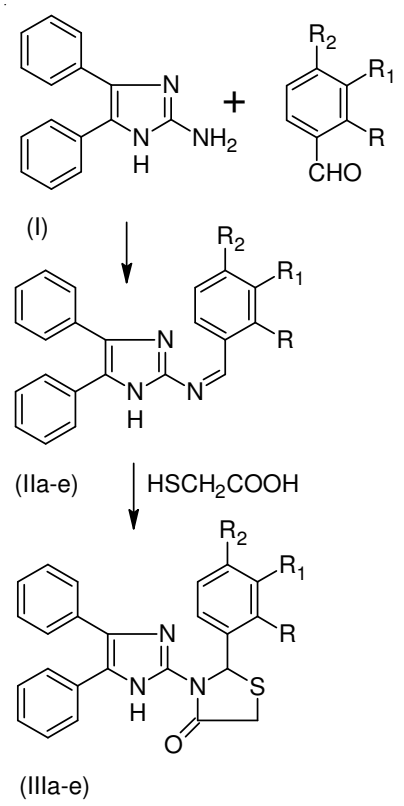
IIc: Yield 75 %; m.p. 91-92 ºC; IR (KBr, ν_{max}, cm^{-1}): 3494 (OH, N-H), 1594 (C=N); ^1H NMR ($CDCl_3$, δ ppm): 8.6 (1H, s, NH), 7.3-7.9 (13H, m, Ar-H), 5.2 (1H, s, Ar-CH), 3.2 (3H, s, OCH_3); m/z: 370 (M+1); Elem. anal. ($C_{23}H_{19}N_3O_2$) Found %: C, 74.86; H, 5.48; N, 11.05; Calculated %: C, 74.78; H, 5.18; N, 11.37.

IId: Yield 90 %; m.p. 78-79 ºC; IR (KBr, ν_{max}, cm^{-1}): 3365 (N-H), 1600 (C=N); ^1H NMR ($CDCl_3$, δ ppm): 8.4 (1H, s, NH), 7.3-7.9 (14H, m, Ar-H), 5.0 (1H, s, Ar-CH); m/z: 358 (M+1); Anal. ($C_{22}H_{16}ClN_3$) Found %: C, 73.65; H, 4.54; N, 11.94; Calculated %: C, 73.84; H, 4.51; N, 11.74.

IIe: Yield 78 %; m.p. 70-71 ºC; IR (KBr, ν_{max}, cm^{-1}): 3416 (N-H), 1590 (C=N); ^1H NMR ($CDCl_3$, δ ppm): 8.6 (1H, s, NH), 7.3-7.8 (13H, m, Ar-H), 5.2 (1H, s, Ar-CH); m/z: 393 (M+1); Elem. anal. ($C_{22}H_{15}Cl_2N_3$) Found %: C, 67.55; H, 3.45; N, 10.56; Calculated %: C, 67.36; H, 3.85; N, 10.71.

Synthesis of 2-(substituted phenyl)-3-(4,5-diphenyl-1*H*-imidazol-2-yl)-1,3-thiazolidin-4-one (IIIa-e): To 2-(substituted phenyl)methylene-4,5-diphenyl-1*H*-imidazol-amine (**IIa-e**) (1.61 g; 0.005 mol) in 50 mL of 1,4-dioxane, thioglycollic acid (0.92 g; 0.01 mol) were added and refluxed

on a steam bath for 8 h. The contents were then cooled and poured into sodium bicarbonate solution (4N). The crude product thus separated was filtered, washed with water, dried and recrystallized from mixture of glacial acetic acid and water (1:3) (**Scheme-I**). The physical properties of the synthesized compounds given in Table-1.



Scheme-I

TABLE-1
PHYSICAL DATA OF THE COMPOUNDS (**IIIa-e**)

Compd.	R	R_1	R_2	Yield (%)	m.p. (ºC)	m.f.	m.w.	R_f value*
IIIa	H	H	H	87	90-91	$C_{24}H_{19}N_3OS$	398	0.56
IIIb	OH	H	H	73	110-111	$C_{24}H_{19}N_3O_2S$	414	0.62
IIIc	H	OH	OCH_3	71	99-100	$C_{25}H_{21}N_3O_3S$	444	0.48
IIId	Cl	H	H	88	83-84	$C_{24}H_{18}ClN_3OS$	432	0.64
IIIe	Cl	H	Cl	73	80-81	$C_{24}H_{17}Cl_2N_3OS$	466	0.52

*R_f value was determined in benzene:methanol (9:1). Recrystallization solvent-acetic acid:water (1:3).

IIIa: Yield 87 %; m.p. 90-91 ºC; IR (KBr, ν_{max}, cm^{-1}): 3378 (N-H), 1679 (C=O), 1262 (C-N); ^1H NMR ($CDCl_3$, δ ppm): 8.0 (1H, s, NH), 7.3-7.8 (15H, m, Ar-H), 6.0 (1H, s, S-CH-Ar), 4.6 (2H, s, S-CH_2); m/z: 398 (M+1); Elem. anal. ($C_{24}H_{19}N_3OS$) Found %: C, 72.32; H, 4.92; N, 10.75; Calculated %: C, 72.52; H, 4.82; N, 10.57.

IIIb: Yield 73 %; m.p. 110-111 ºC; IR (KBr, ν_{max}, cm^{-1}): 3379 (N-H), 1678 (C=O), 1262 (C-N); ^1H NMR ($CDCl_3$, δ ppm): 8.2 (1H, s, NH), 7.3-7.5 (14H, m, Ar-H), 5.9 (1H, s, S-CH-Ar), 4.62 (2H, s, S-CH_2); m/z: 414 (M+1); Elem. anal. ($C_{24}H_{19}N_3O_2S$) Found %: C, 69.42; H, 4.99; N, 10.05; Calculated %: C, 69.71; H, 4.63; N, 10.16.

IIIc: Yield 71 %; m.p. 99-100 ºC; IR (KBr, ν_{max}, cm^{-1}): 3420 (OH, N-H), 1680 (C=O), 1262 (C-N); ^1H NMR ($CDCl_3$, δ ppm): 8.6 (1H, s, NH), 7.3-7.9 (13H, m, Ar-H), 5.9 (1H, s, S-CH-Ar), 4.6 (2H, s, S-CH_2), 3.2 (3H, s, OCH_3); m/z: 444 (M+1); Elem. anal. ($C_{25}H_{21}N_3O_3S$) Found %: C, 67.89; H, 4.45; N, 9.88; Calculated %: C, 67.70; H, 4.77; N, 9.47.

IIId: Yield 88 %; m.p. 83-84 ºC; IR (KBr, ν_{max}, cm^{-1}): 3379 (N-H), 1679 (C=O), 1262 (C-N); ^1H NMR ($CDCl_3$, δ ppm): 8.6 (1H, s, NH), 7.3-7.9 (14H, m, Ar-H), 6.3 (1H, s, S-CH-Ar), 4.6 (2H, s, S-CH_2); m/z: 432 (M+1); Elem. anal. ($C_{24}H_{18}ClN_3OS$) Found %: C, 66.54; H, 4.54; N, 9.69; Calculated %: C, 66.74; H, 4.20; N, 9.73.

IIIe: Yield 73 %; m.p. 80-81 ºC; IR (KBr, ν_{max}, cm^{-1}): 3379 (N-H), 1679 (C=O), 1262 (C-N); ^1H NMR ($CDCl_3$, δ ppm): 8.6 (1H, s, NH), 7.3-7.8 (13H, m, Ar-H), 6.0 (1H, s, S-CH-Ar), 4.34 (2H, s, S-CH2); m/z: 467 (M+1); Elem. anal. ($C_{24}H_{17}Cl_2N_3OS$) Found %: C, 61.52; H, 3.35; N, 9.38; Calculated %: C, 61.81; H, 3.67; N, 9.01.

Antiinflammatory activity: The acute toxicity study, before anti-inflammatory activity, was carried out by the Karber's method[13] and the LD_{50} values were read by, (Highest dose of drug)-(Total product/no of animals), where total product is the product of dose difference and mean mortality. The LD_{50} values of the compounds were 1450, 1400, 1350, 1400 and 1400, respectively.

The antiinflammatory activity of the synthesized compounds was studied by carrageenan induced rat paw oedema method[14]. Six groups of rats were pre-treated with test compounds **IIIa-e** and ibuprofen by per oral route in doses of 145, 140, 135, 140, 140 and 20 mg/kg body weight, respectively, after 0.5 h prior to carrageenan injection. One group received only carboxymethyl cellulose as control. After 0.5 h, 0.1 mL of carrageenan (1 % w/v) was injected into planter region of hind paw of rats. Measurement of paw volume (mL) was made by mercury displacement technique using plethysmometer at 1 and 3 h, after carrageenan injection. The % inhibition (reduced paw volume) was calculated by, 100-T/C × 100, where T is increase paw volume after test compounds was administered and C is increase paw volume of control group.

RESULTS AND DISCUSSION

The antiinflammatory activity with respect to the chemical structure reveals that compound **IIIa**, **IIIb** and **IIId** bearing phenyl, 2-hydroxyphenyl and 2-chlorophenyl moieties, respectively, exhibited good antiinflammatory activity with percentage of inhibition within 39-44, when compared with standard, ibuprofen (47 %) (Table-2).

TABLE-2
ANTIINFLAMMATORY ACTIVITY OF THE COMPOUNDS (**IIIa-e**)

Design of treatment	Dose (mg/kg)	Paw volume (mL)		Inhibition (%)	
		1 h	2 h	1 h	2 h
Control	0.1 mL of 1 % w/v CMC	0.80 ± 0.02	0.99 ± 0.03	-	-
Ibuprofen	20	0.62 ± 0.04	0.52 ± 0.08	23	47
IIIa	145	0.64 ± 0.02	0.55 ± 0.09*	20	44
IIIb	140	0.68 ± 0.04	0.60 ± 0.10*	15	39
IIIc	135	0.71 ± 0.02	0.63 ± 0.06	11	21
IIId	140	0.74 ± 0.02	0.60 ± 0.04*	8	39
IIIe	140	0.69 ± 0.04	0.63 ± 0.02	14	36

Values are expressed as mean ± SEM for six animals.
*$p < 0.001$ compared to respective control group.

Conclusion

Schiff bases of 4,5-diphenyl imidazoline-2-amine have been prepared. These Schiff bases converted in to 4-thiazolidinenone derivatives with thioglycolic acid. All the compounds have been screened for antiinflammatory activity. Compounds **IIIa**, **IIIb** and **IIId** have exhibited promising antiinflammatory activity. Therefore, the compounds **IIIa**, **IIIb** and **IIId** can be recommended for further studies.

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