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NOTE

Antiinflammatory Activity of Some New 3-(2H-1-benzopyran-2′-one-3′-yl)-5-Substituted Aryl Isoxazolines

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Newer isoxazoline derivatives were synthesized by condensing novel chalcones with hydroxylamine hydrochloride in neutral medium. All the compounds were characterized on the basis of IR and ^{1}H NMR spectral data. The compounds were evaluated for antiinflammatory activity against carrageenan induced rat paw edema and all the compounds showed significant antiinflammatory activity.

Key Words: Isoxazolines, Antiinflammatory activity.

INTRODUCTION

Isoxazoline is a five-membered heterocyclic ring system containing oxygen and nitrogen atoms. Three classes are theoretically possible for isoxazoline ring system. These are 2-isoxazoline, 3-isoxazoline and 4-isoxazoline. Of these only 2-isoxazolines have been investigated in detail and are generally prepared by condensation of α,β-unsaturated ketones[1] with hydroxylamine hydrochloride in neutral or basic medium. A number of isoxazoline derivatives are reported to possess different biological activities like antiinflammatory[2], antibacterial[3], antifungal[4], anti-HIV[5], antidepressant[6], antimuscarinic[7] and anticancer[8] activities. These observations stimulated us with a presumption that new isoxazoline derivatives would produce better antiinflammatory activity. Hence an attempt was made by us to synthesize some isoxazoline derivatives for antiinflammatory activity.

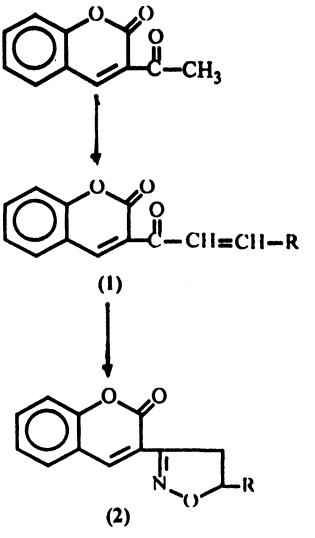
EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. The purity of the compounds was checked by running TLC on silica gel-G plates. IR (KBr) and ^{1}H NMR (DMSO) spectra were recorded on Perkin-Elmer 783 spectrophotometer and Bruker model DRX-3000 NMR spectrophotometer respectively.

Synthesis of (2H-1-benzopyran-2′-one-3′-yl)styryl ketones[9] (1): Equimolar quantities of 3-acetyl coumarin and respective aromatic adehydes were refluxed in absolute ethanol using piperidine as catalyst for 5 h; then the product was concentrated. The solid was filtered, dried and recrystallized from ethanol.

Synthesis of Isoxazolines[10] (2): A mixture of compound (1) (0.01 mol) in 50 mL of ethanol and NH_2OH·HCl (0.02 mol) was refluxed for 8 h. The solution was evaporated and solid collected and recrystallized from ethanol **(Scheme-1).**

Antiinflammatory activity: A freshly prepared 1% (w/v) suspension of car-



Scheme 1

rageenan in normal saline was injected underneath planter region of the right paw of the Wistar albino rat by the method described by Winter *et al.*[11] One group of six rats was kept as control and the animals of other groups of six each were pretreated with test compounds intraperitoneally (25 mg/kg) 30 min earlier to the carrageenan injection. One group received standard drug, Indomethacin, intraperitoneally (25 mg/kg). The volume of foot was measured before and after 4 h after carrageenan injection employing plethysmometer and per cent antiinflammatory activity was calculated. The results of antiinflammatory activity of synthesized compounds along with their physical data are given in Table-1.

TABLE-1
PHYSICAL DATA OF COMPOUNDS SYNTHESIZED AND THEIR ANTIINFLAMMATORY ACTIVITY

Compd.	R	m.f.	m.p. (°C)	% Inhibition in edema
1a	3,4,5-Trimethoxyphenyl	$C_{21}H_{19}NO_6$	175	60.27
1b	2-Hydroxyphenyl	$C_{18}H_{13}NO_4$	122	67.12
1c	2-Chlorophenyl	$C_{18}H_{12}NO_3Cl$	135	68.03
1d	4-Chlorophenyl	$C_{18}H_{12}NO_3Cl$	125	64.84
1e	4-Hydroxyphenyl	$C_{18}H_{13}NO_4$	185	63.01
1f	3-Hydroxyphenyl	$C_{18}H_{13}NO_4$	120	63.90
1g	4-Dimethylaminophenyl	$C_{20}H_{18}N_2O_3$	132	55.70
1h	4-methoxyphenyl	$C_{19}H_{15}NO_4$	130	57.07
1i	3,4-Dimethoxyphenyl	$C_{20}H_{17}NO_5$	178	58.44
1j	2,4-Dihydroxyphenyl	$C_{18}H_{13}NO_5$	192	66.21

Standard drug = Indomethacin (% inhibition in edema = 73.85).

RESULTS AND DISCUSSION

The entire synthesized compounds showed characteristic IR absorption bands at 1660–1640 cm^{-1} due to ν(C=N), 1225–1215 cm^{-1} due to ν(C—O—N) and 1730-1710 cm^{-1} due to ν(C=O) bonds. ^1H NMR spectra of all compounds showed two characteristic signals at δ 3.9–5.00 (1H, m, —CH—) and δ 5.4–6.5 (2H, m, $—CH_2—$).

The compound having hydroxyl group at position-2 of phenyl ring showed better antiinflammatory activity than the corresponding position-4 or when it is 2,4-disubstituted hydroxyl group. Presence of chlorine atom at position-2 gave most potent compound of this series, but presence of *p*-dimethylamino and methoxy groups in the phenyl ring showed decrease in antiinflammatory activity. Presence of coumaryl moiety at C-3 of isoxazoline ring favours antiinflammatory activity.

Finally, out of 10 compounds screened for antiinflammatory activity, 4 compounds showed very good activity and rest of the 6 compounds showed significant antiinflammatory activity when compared to standard drug.

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