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Research Article

Synthesis, Characterization, and Anti-inflammatory activity of Some Novel Oxazole Derivatives

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Abstract

A series of novel oxazole derivatives (A, A₁, A₂) were synthesized starting from acetone and urea. The compound (A) was obtained by heating it with acetophenone and urea in iodine. Compound (A) on treatment with 4-amino benzaldehyde (Z)-N-(4-amino benzylidene)-4-((E)-Penta-2, 4-diene-2) oxazole-2-amine afforded (A₁). Acylation of compound (A) with 4-amino benzoyl chloride to obtain the corresponding N-(4 phenyl oxazole-2-yl)- benzamide (A₂). The structures of compounds were established employing FTIR and ¹H-NMR spectral analysis. All oxazole derivatives were evaluated for anti-inflammatory activity by the carrageenan-induced Rat hind paw method. Derivative A₁ shows maximum anti-inflammatory activity.

Keywords: Oxazoles, anti-inflammatory, Benzamide, acetophenone, indomethacin.

INTRODUCTION

Numerous medications and physiologically significant compounds have heterocyclic systems. One such moiety that has received attention recently is oxazole because of its growing significance in the field of medicinal chemistry¹. Oxazole-containing secondary metabolites and oxazoline skeletons, which are frequently generated from amino acids, are widely distributed in nature². Oxazoles are characterized by having oxygen and nitrogen atoms in a 1,3 connection on a five-membered ring³. Exhibiting extensive biological activities such as antibacterial, antifungal, antiviral, antitubercular, anticancer, anti-inflammatory, and so on, oxazole compounds in medicinal chemistry could easily connect with a range of enzymes and receptors in biological systems⁴. The local reaction of living mammalian tissues to harm caused by any substance is known as inflammation. In particular, it is a set of molecular and cellular reactions that have evolved to eradicate invading agents and promote tissue restoration⁵. Benzoxazole is the name given to benzo derivatives of oxazole. Oxazolines are the names for partially reduced oxazoles and include 2-oxazoline, 3-oxazoline, and 4-oxazoline respectively. Oxazolidine is the name for the fully saturated equivalent³.

MATERIALS AND METHODS

Chemistry⁶

The melting point of the compound synthesized was uncorrected and recorded by open glass capillary method on the "Janki implex melting point apparatus" and compared with the reported melting point wherever applicable ¹H-NMR spectra and ¹³CNMR spectra were reported on GEOLAR -300 shifts were expressed in parts per million (ppm). IR spectra were recorded using "BRUKER ALFA-E infrared spectrophotometer. Analytical thin layer chromatography (TLC) was carried out on pre-coated plates (silica gel G254).

Synthesis of (Z)-N-(4-aminobenzylidene)-4-((E)-penta-2,4-diene-2)oxazole-2-amine (A₁).

A mixture of compound (A) (Scheme.1) and 4-amino benzaldehyde was dissolved in ethyl acetate: n-hexane, 1:5, v/v), and the solvent was evaporated under reduced pressure. The obtained solid mass recrystallized from ethyl acetate and n-hexane solvent mixture.

Yield: 52.0%, mp: 178°C, RF 0.50, Silica gel G, Hexane, Ethylacetate (1:5)

IR (KBr, cm⁻¹): 3169 (C-H, aromatic), 1581 (C=N), 1555 (C-O) stretching ¹H-NMR (CDCl₃) σ (ppm): 8.22 (d, 2H, aromatic), 7.62 (s, 1H, =CH), 7.69 (s, 1H, -CH oxazole), 7.4-7.6 (m, 5H, ph), 4.25

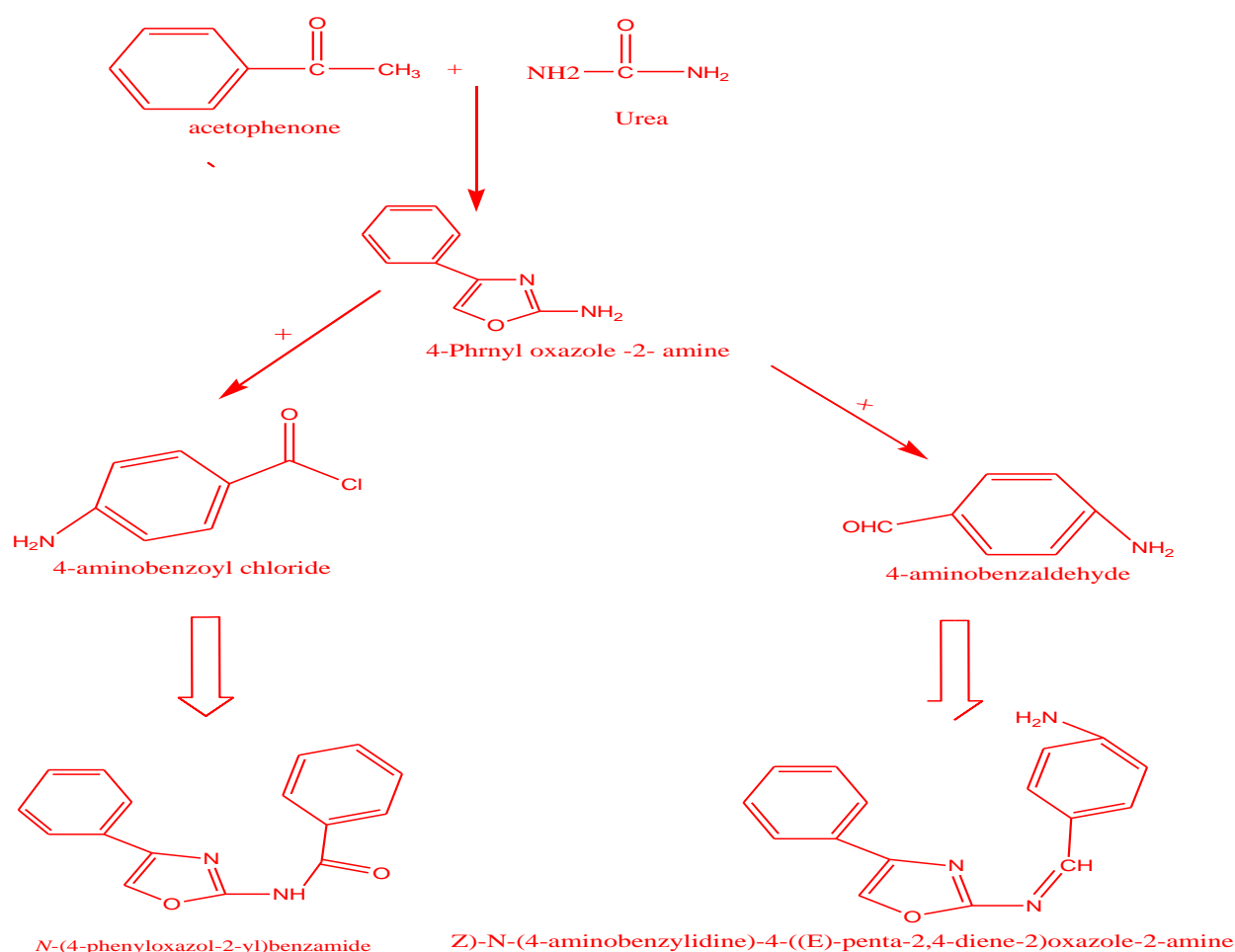
Synthesis of N-(4 phenyloxazole-2-yl)- benzamide (A₂)

A mixture of 4-Phenyl oxazole -2- amine (A) (2m mol) with 4-amino benzoyl chloride (2.1m mol) was dissolved in dry pyridine (5 ml). The reaction mixture was kept in an ice bath for 6 hours with continuous stirring. After completion of the reaction, the mixture was poured into ice water and extracted with CHCl₃. The organic layer was washed with Dil. NaHCO₃

and the solvent were evaporated under reduced pressure. The obtained solid mass was recrystallized from an ethyl acetate and n-hexane solvent mixture. The product was checked for purity on TLC.

Yield: 48.0%, mp: more than 250°C, RF 0.50, Silicagel G, Hexane, Ethyl acetate (1:5)

IR (KBr, cm⁻¹): 3165 (N-H), 3023 (C-H, aromatic), 3065 (C=C), 1580 (C=N) for oxazole ring, 1620 (C=O), 3072 (C-N). ¹H-NMR (CDCl₃) σ (ppm): 7.32 (d, 2H, aromatic), 7.63 (s, 1H, -CH, oxazole), 7.35-7.21 (m, 5H, ph), 8.00 (s, 1H, NH), 7.95 (CO).



Scheme 1. Synthetic Pathways for the Preparation of (Z)-N-(4-aminobenzylidene)-4-((E)-penta-2,4-diene-2)oxazole-2-amine (A₁) and N-(4 phenyloxazole-2-yl)- benzamide.(A₂)

Carrageenan Induced Rat hind Paw Edema

The anti-Inflammation activity was determined by the carrageenan-induced Rat hind edema method of Rats (120-140g) used for the experiment. The drugs were prepared as a suspension by triturating with water and 0.5% sodium CMC. The standard group received 40 mg/Kg body weight of indometacin, the test group received 100 mg/Kg body weight of synthesized compounds and the control group received 2% w/v of CMC. The difference between the (zero hours) reading and one of the subsequent readings provides the actual edema volume at that time. The mean paw volume at different times was calculated and compared with the control of percentage inhibition of inflammation after 3 hours.

RESULTS AND DISCUSSION

Chemistry

The synthetic route of the oxazole derivatives is outlined in (scheme. 1). acetophenone was heated with urea in presence of iodine to obtain 4-phenyl)oxazole-2-amine (A). Refluxing of compound (A) with 4-aminobenzaldehyde in ethanol afforded (Z)-N-(4-aminobenzylidene)-4-((E)-penta-2,4-diene-2)oxazole-2-amine (A₁) in good yields. Acylation of compound (A) with 4-amino benzoyl chloride in dry pyridine gave N-(4 phenyloxazole-2-yl)- benzamide. (A₂). The structure of the synthesized compounds was confirmed by IR and ¹H-NMR spectral analysis.

Anti-Inflammation Activity

The compounds were subjected to anti-inflammation activities by paw edema method using indomethacin drug as standard. All the oxazole derivatives (A, A₁, A₂) have shown promising anti-inflammation activities, as shown in Table 1.

Table 1: Anti-inflammatory activity of thiazole derivatives (A, A₁, and A₂)

CompoundNo.	Mean Paw Edema Volume					
	0 hour	0.5 hour	1 hour	2 hour	3 hour	% inhibition after 3 rd hour
Control	0.2±0.03	0.44±0.02	0.58±0.02	1.76±0.02	1.82±0.02	-----
Indomethacin	1.22±0.03	1.34±0.02**	1.32±0.02**	1.46±0.02**	1.44±0.02**	45.86
A	0.14±0.04	0.24±0.02*	1.30±0.04**	1.52±0.04**	1.34±0.02**	35.38
A₁	1.20±0.05	1.24±0.03*	1.42±0.04**	1.50±0.03**	1.28±0.03**	28.67
A₂	1.46±0.02	1.50±0.03*	1.46±0.02**	1.46±0.05**	1.34±0.02**	25.46

*P < 0.05, and **P < 0.01 – significant.

The differences between (0 hours) reading and one of the subsequent readings (1, 2, 3, and 4th hour), respectively, provide the actual edema volume at that time. The mean paw volume at different times was calculated and compared with the control⁷ Derivatives (A, A₁, and A₂) showed the percentage inhibition at the 4th hour (35.38,28.67,), respectively, and the percentage inhibition of **Indomethacin** drug as (standard drug) at 4th hour (45.86%). In comparison with **Indomethacin** as (a standard drug) to anti-inflammatory activity, compounds A, A₁, and A₂ have shown significant anti-inflammatory activity. Compounds A₁ show excellent anti-inflammatory activity than A and A₂ compounds, compared with standard drugs.

CONCLUSION

All the oxazole derivatives have shown promising anti-inflammatory activities. Compounds A₁ has shown excellent anti-inflammatory. The results of this study show that the thiazole derivatives (A₁ and A₂) can be used as an easily accessible source of anti-inflammation in the pharmaceutical industry.

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