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Analgesic activity of 3-alkyl (aryl)-4-(nitrophenylmetheleneamino) -4,5-dihydro-1H-1,2,4-triazol-5-ones

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ABSTRACT

Six new 3-alkyl (aryl)-4-(arylmetheleneamino)-4, 5-dihydro-1H-1, 2, 4-triazol-5-ones were prepared by refluxing 4, 5-dihydro-1H-1, 2, 4-triazol-5-ones with substituted benzaldehyde. Compounds obtained were characterized and screened for analgesic activity by acetic acid induced writhing. These compounds were found to be active analgesic activity. Compound **(3c, 3d** and **3f)** were shown highly potent analgesic activity.

KEYWORDS

Synthetic;
Ttriazolone;
Analgesic activity;
Acetic acid.

INTRODUCTION

Triazole has been associated with diverse pharmacological activities[1-5]. In this correlation, the antibacterial antifungal and especially anti-tumor properties were exhibited by various 1,2,4-triazol-5-ones which made them to be as an important class[5-7].

Various 1,2,4-triazoles and 4,5-dihydro-1H-1,2,4-triazol-5-ones were found to be associated with diverse pharmacological activities[1-5]. 3-Alkyl(aryl)-4-amino-4,5-dihydro-1H-1,2,4-triazol-5-ones and its derivatives play vital role in heterocyclic chemistry because of its broad spectrum of activities such as analgesic, anti-inflammatory, antimicrobial, hypoglycemic, antihypertensive, anti-HIV, and especially anti-tumor properties[4-8]. In the present communication 4,5-dihydro-1H-1,2,4-triazol-5-ones were reacted with substituted aromatic aldehyde. Structures of various synthesized compounds were characterized on the basis of IR, NMR spectral data. These compounds were also screened for antimicrobial and analgesic activity.

MATERIAL AND METHOD

Analytical parameters

Melting points were determined by open tube capillary method and are uncorrected. Completion of reaction was determined by single spotted TLC. Structures of compounds were determined by infrared spectroscopy (IR) and proton nuclear magnetic resonance (^{1}H-NMR). IR spectra were recorded using KBr disc on FTIR. ^{1}H-NMR was recorded using $CDCl_3$ solution on FT-NMR Varian Mercury 300 MHz and proton chemical shifts were relative to tetramethylsilane as internal solvent. Column chromatography was performed using glass column with glass wool at the bottom and silica gel (60-120 mesh). Visualization of compounds on chromatographic plates was done by expo-

sure to iodine vapors.

(a) Synthesis of alkyl imidates

To an ice-cold solution of 1 mole of the appropriate nitrile in 1:1 moles of absolute alcohol, dry hydrogen chloride was added until 1:1 moles had been absorbed. The resulting solution was allowed to stand at 0^0C in the refrigerator for 12 hours, thereafter cold absolute ether was added to this solution and the crystals obtained were filtered off immediately, washed with cold absolute ether and dried in dessicator[9].

(b) Synthesis of 4,5-dihydro-1H-1,2,4-triazol-5-ones

Ethyl imido carboxylate hydrochloride (0.01 mol) dissolved in 30 ml of absolute ethanol was treated with an ethanolic sodium ethoxide solution prepared by dissolving sodium (0.01mol) in 20 ml of absolute ethanol. After stirring for 10 minutes sodium chloride precipitate was filtered and solution of carbohydrazide (0.01mol) in 70 ml of 95% ethanol was added to the filtrate. Then the mixture was refluxed for 10 hrs and evaporated at 35-45^{0}C under reduced pressure. The solid formed was recrystalized several times from an appropriate solvent to afford pure compound 4,5-dihydro-1H-1,2,4-triazol-5-one[10].

(c) Synthesis of 3-alkyl(aryl)-4-(arylmethelene amino)-4,5-dihydro-1H-1,2,4-triazol-5-ones

3-Alkyl (aryl)-4-amino-4, 5-dihydro-1H-1,2,4-triazol-5-ones (0.01mol) was refluxed with substituted benzaldehyde (0.01mol) at 175-180^{0}C for 3 hrs and cooled. Several recrystalization of residue from an appropriate solvent gives pure compound[11].

IR and NMR spectral data of compounds (IIIa-IIIf)

IIIa: 3-Methyl-4-[(4-nitrophenylmethelene amino)]-4,5-dihydro-1H-1,2,4-triazol-5-one:

IR: NH-3188, NH - 3074, C=O-1710, C=N - 1596, N=O - 1346, Di-substituted benzene - 850; **^{1}H NMR:** NH - 11.8-12.0, CH - 9.8-10.0, CH_2 (s) - 3.4-3.6, Ar-H (m) -8.0-8.2, Ar-H (m) - 8.2-8.4;

IIIb: 3-Methyl-4-[(3-nitrophenylmetheleneamino)] -4,5-dihydro-1H-1,2,4-triazol-5-one

IR: NH-3184, NH-3060, C=O-1703, C = N-1606, N = O -1344 (1300-1600), Di-substituted benzene-850; **^{1}H NMR:** NH - 11.8-12.0, CH-10.0-10.2, CH_2 (s) - 3.2-3.4, Ar-H (m) - 7.6-7.8, Ar-H (m) - 8.2-8.4.

(3c): 3-Phenyl-4-[(4-nitrophenylmetheleneamino)]-4,5-dihydro-1H-1,2,4-triazol-5-one

IR: NH-3354, NH - 3178, C=O-1705, C=N-1643, N=O-1519, Mono-substituted benzene-85; **^{1}H NMR:** CH-10.0-10.2, CH2 (s) - 3.2-3.4, Ar-H (m) - 7.2-7.6, Ar-H (m) - 7.6-8.2;

(3d): 3-Phenyl-4-[(3nitrophenylmetheleneamino)]-4,5-dihydro-1H-1,2,4-triazol-5-one

IR: NH-3064, C=O-1705, C=N-1644, N=O-1521, Mono-substituted benzene-852; **^{1}H NMR:** CH-10.0-10.2, CH2 (s)-3.2-3.4, Ar-H (m)-7.2-7.6, Ar-H (m)-7.6-8.2.

(3e): 3-Benzyl-4-[(4-nitrophenylmetheleneamino)]-4, 5-dihydro-1H-1,2,4-triazol-5-one

IR: NH-3066, C=O-1708, C=N-1596, N=O-1346, OH (Enolic)-2923, Mono-substituted benzene-690, Di-substituted benzene-848; **^{1}H NMR:** NH-12.4-12.6, CH-9.8-10.0, CH_2 (s)-3.0-3.4, Ar-H (m)-7.2-7.6, Ar-H (m)-7.6-8.4.

IIIf: 3-Benzyl-4-[(3-nitrobenzenemethelene amino)] -4,5-dihydro-1H-1,2,4-triazol-5-one

IR: NH-3174, C=O-1708, C=N-1645, N=O-1527, OH (Enolic)-3354, Mono-substituted enzene-690, Di-substituted benzene-848; **^{1}H NMR:** NH-12.4-12.6, CH-9.8-10.0, CH_2 (s)-3.0-3.4, Ar-H (m)-7.2-7.6, Ar-H (m)-7.6-8.4

Pharmacological activity

Analgesic activity by using 1% acetic acid induced writhings

Male Swiss mice (20-25 g), in a group of six, were used through out the experiments. Mice were housed in plastic cages and controlled with 12 hour light/dark cycle, and at constant temperature (22 ± 2^{0}C). As drug is completely soluble in DMSO, it is taken as a control vehicle. All the compounds were screened using the method of Ghosh[12]. Percentage protection exhibited by the test compounds, administered at a dose of 20 mg/kg in DMSO solution intraperitonially, against the acetic acid induced writhing or stretching syndrome were recorded. Indomethacin (10 mg/kg) was employed as

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TABLE 3: Analgesic activity of synthesized compounds

Sample no.	Dose (in mg/kg)	Writhing movement (±)	Percent decrease in writhing
3a	20	3.00 ± 0.31	81.25 %
3b	20	9.8 ± 0.48	37.50 %
3c	20	2.2 ± 0.37	100.00 %
3d	20	1.8 ± 0.37	100.00 %
3e	20	10.00 ± 0.37	37.50 %
3f	20	1.2 ± 0.20	93.75 %
Control	20	16 ± 0.37	0 %
Standard	10	1 ± 0.00	100.00 %

n=6 # P< 0.01 as compared with control

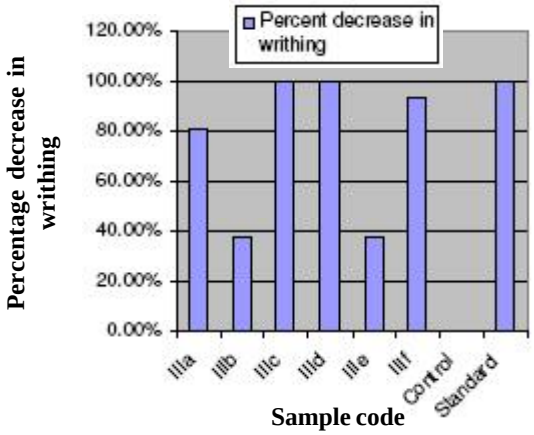
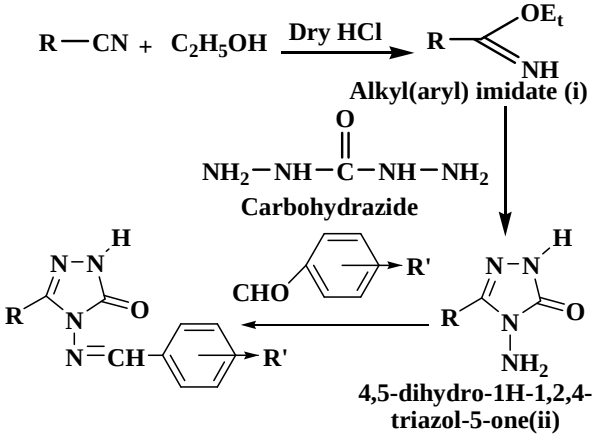


Figure 1 : Analgesic activity of synthesized compounds



Compounds	R	R'
3a	CH_3	p-NO_2
3b	CH_3	m-NO_2
3c	C_6H_5	p-NO_2
3d	C_6H_5	m-NO_2
3e	$C_6H_5CH_2$	p-NO_2
3f	$C_6H_5CH_2$	m-NO_2

Scheme of synthesis

reference standard under similar conditions and results are recorded in TABLE 1.

RESULT AND DISCUSSION

Compound **(2c)** and **(2d)** were found to be better analgesic agents. It can be concluded that substitution at 3rd - position of triazolone by phenyl ring is responsible for analgesic activity. All compound shows analgesic activity but compound IIIb, IIIf and IIIe has less activity as compared to others. The present investigation shown that the synthesized compounds are better analgesic agents.

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