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Original Article

Synthesis of 3-pyridyl [1, 2, 4] triazolo [3, 4-b] [1, 3, 4] thiadiazepines and evaluation of their antibacterial and antifungal activities

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ABSTRACT

Some novel 3-pyridyl [1, 2, 4] triazolo [3, 4-b] [1, 3, 4] thiadiazepines derivatives were synthesized from substituted 4-amino 5-pyridine- 3-yl-1, 2, 4 triazole 3-thiol and substituted chalcones in the presence of glacial acetic acid and ethanol. Identification of the new compounds was established by Infra Red spectral data. All the synthesized compounds were tested for their *in-vitro* antibacterial and antifungal activities. The best activity was observed with compounds 3b, 3d, 3e.

Key words: 1, 2, 4- triazole, Triazolo thiadiazepine, Anti-bacterial activity, Anti-fungal activity

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INTRODUCTION

Triazole derivatives are well known for their significant biological activities. Various 1, 4 – benzodiazepine derivatives were found to exhibit various pharmacological activities. The activity is enhanced by the attachment of a heterocyclic ring system to the parent benzodiazepine. Triazole derivatives such as estazolam, triazolam, alprazolam are successfully used as tranquillizers, hypnotics and depressants respectively in clinical practices. Furthermore 1, 5 – benzothiazepine derivatives like Diltiazem, Nictiazem and Triazesim have been found to posses coronary vasodilating and antidepressant activity. 1,2,4-Triazole nucleus has been incorporated into a wide variety of therapeutically interesting compounds including H1/H2 histamine receptor molecules, cholinesterase active agents, anti-anxiety agents and sedatives. Thus our interest in the chemistry of 1, 2, 4– triazoles and their biological activity prompted us to synthesize triazolo thiadiazepines by the reaction of substituted chalcones with 4-amino 5-pyridine- 3-yl-1, 2, 4 triazole 3-thiol. In this study, we describe the synthesis and biological evaluation of a new series of 3-pyridyl-1, 2, 4-triazolo (3, 4-b) 1, 3, 4-thiadiazepines [(1)].

The objective of the present study is to synthesize some novel derivatives of 3-pyridyl [1, 2, 4] triazolo [3, 4-b] [1, 3, 4] thiadiazepines which have been found to possess an interesting profile of anti-bacterial and anti-fungal activities.

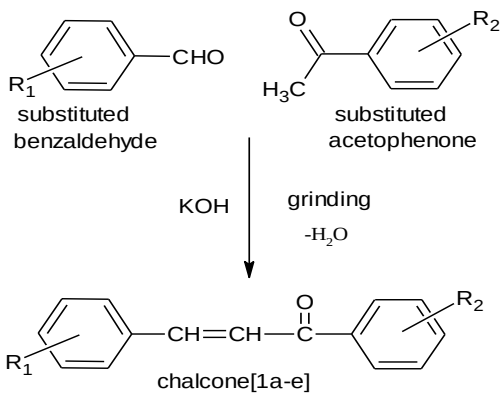
MATERIALS AND METHODS

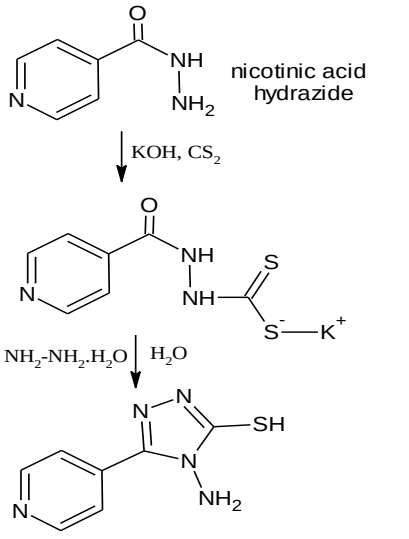
Synthetic methods for preparation of 3-pyridyl [1, 2, 4] triazolo [3, 4-b] [1, 3, 4] thiadiazepines was summarized in scheme.

Step-1: Synthesis of substituted chalcones [(2) (7)]: Substituted acetophenone (0.01 mol), substituted benzaldehyde (0.01 mol) and solid pellets of KOH (0.02mol) were taken in a mortar and grind for several minutes. The obtained solid mixture was diluted with cold ethanol, neutralized by dil. HCl and recrystallized from acetic acid.

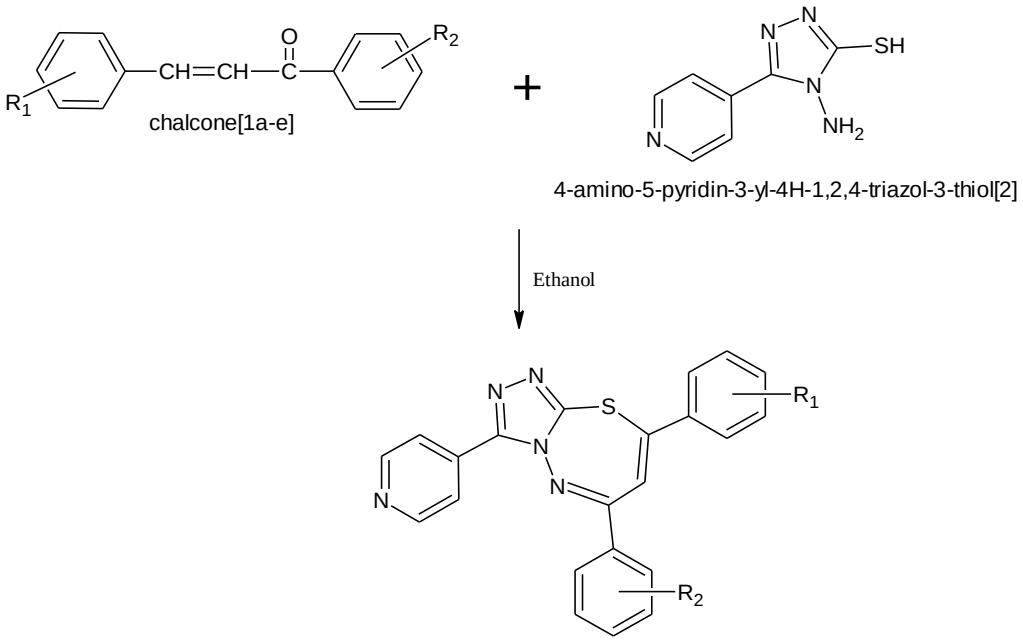
Step-2: Synthesis of 4-amino 5-pyridine- 3-yl-1, 2, 4-triazole 3-thiol [(1) (3) (4)]: KOH (0.15mol) was dissolved in absolute ethanol (200 ml). To the above solution, isoniazid (0.1 mol) was added and the solution was cooled in ice. To this CS_2 (0.15 mol) was added in small portion with constant stirring. The reaction mixture was agitated continuously for 16 hrs. It was then diluted with diethyl ether (100 ml) and dried under vacuum. The potassium salt thus obtained (0.05mol) was suspended in water (100ml); hydrazine hydrate (0.15mol) was added and refluxed for 10hrs with occasional shaking. The colour of the reaction mixture changed to green with evolution of H_2S gas. After the complete evolution of H_2S gas, the solution was cooled to room temperature and diluted with water (100ml). On acidification with conc.HCl, the required 4-amino 5-pyridine- 3-yl-1, 2, 4 triazole 3-thiol was precipitated. It was filtered, washed thoroughly with cold water and dried. It was recrystallized form ethanol.

Step-3: Synthesis of 3-pyridyl [1,2,4] triazolo [3,4-b] [1,3,4] thiadiazepines [(5) (6) (9)]: To a solution of chalcone (2, 0.01 mol) in ethanol (20ml) was added a few drops of piperidine and 4-amino-5-substituted 1,2,4- triazole 3-thiol (0.01 mol). The mixture was heated under reflux for 3-4 hrs and then added 1 ml acetic acid. The refluxing was continued for another 3-4 hrs. About half of the solvent was distilled off and the refluxing mixture was allowed to stand at room temperature. The solid product thus separated was filtered, dried and recrystallized from ethanol [(10)].





4-amino-5-pyridin-3-yl-4H-1,2,4-triazol-3-thiol[2]



6-(4-substituted phenyl)-8-(N-substituted phenyl)-3-(pyridin-yl) [1,2,4] triazolo [3,4-b][1,3,4] thiadiazepine [3a-e]

Anti-microbial activity (anti-bacterial [1] [5] **and anti-fungal** [1]**):** Cylinder bore method was employed to study in-vitro anti-microbial activity of (3a-3e) against E.coli, S.aureus and C.albicans. The preparation of the nutrient broth, subculture, nutrient agar medium and Sabouraud Dextrose Agar medium was done as per the standard procedure. Each test compounds (5mg) were dissolved in 5ml of dimethyl sulfoxide (1000µg/ml). Nutrient agar medium was used for anti-bacterial activity where Gentamycin (GM) was used as reference drug and dimethyl sulfoxide (DMSO) as a control which did not reveal any inhibition. Sabouraud Dextrose Agar medium was employed to test anti-fungal activity where Griseofulvin (GF) was used as reference drug and DMSO as a control which revealed no inhibition.

RESULTS AND DISCUSSION

IR spectral data: IR spectra were recorded using KBr pellets in the range of 4000- 500 cm^{-1} on Jasco FTIR model 4100 type A to elucidate the structure of the compounds. The presence of characteristic peak of functional groups in the IR spectra of the synthesized analogues substantiates the formation of the designed compounds

(KBr cm-1) 3082, 3037 (Ar C-H str), 1603 (C=N str), 1590, 1540, 1490, 1450 (C=C ring str), 1035 (C-S str), 1240 (N-N=C)

Anti-microbial activity: Cylinder bore method was employed to study in-vitro anti-microbial activity of (3a-3e) against E.coli, S.aureus and C.albicans. The preparation of the nutrient broth, subculture, nutrient agar medium and Sabouraud Dextrose Agar medium was done as per the standard procedure. Each test compounds (5mg) was dissolved in 5ml of dimethyl sulfoxide (1000µg/ml). Nutrient agar medium was used for anti-bacterial activity where Gentamycin (GM) was used as reference drug and dimethyl sulfoxide (DMSO) as a control which did not reveal any inhibition. Sabouraud Dextrose Agar medium was employed to test anti-fungal activity where Griseofulvin (GF) was used as reference drug and DMSO as a control which revealed no inhibition.

	R_1	R_2	Zone of inhibition (mm)		
			E.coli	S.aureus	C.albicans
3a	-H	-H	09	10	10
3b	-4-NH_2	-Cl	19	18	19
3c	-4-NO_2	-OCH_3	09	10	08
3d	-4-F	-NO_2	17	15	15

3e	-2-OH	$-CH_3$	20	18	18
Gentamycin	-------	-------	21	25	Not done
Griseofulvin	-------	-------	Not done	Not done	23
Dimethyl sulfoxide	-------	-------	00	00	00

CONCLUSION

A novel series of 3-pyridyl [1, 2, 4] triazolo [3, 4-b] [1, 3, 4] thiadiazepines derivatives were synthesized from substituted 4-amino 5-pyridine-3-yl-1, 2, 4 triazole 3-thiol and substituted chalcones in the presence of glacial acetic acid and ethanol and were identified by Infra Red spectral data. The compounds were screened for anti-microbial activity. The best activity was observed with compounds 3b, 3d, 3e.

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