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Research Article

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Synthesis Characterization and Antibacterial Activity of (5- Amino 1,3,4 Thia Diazol-2yl) -3,4 - Dihydro-2h -Pyrido[1,2-A]Pyrimidin-2-Ones

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ABSTRACT

Thiadiazole derivatives of 2H –pyrido[1,2-a]pyrimidin-2-ones were synthesized, characterized by IR and NMR and were screened for their antibacterial activity against Escherichia coli and Staphylococcus aureus and compared with standard drug ciproflaxin. The ClogP, solubility drug likeliness and the mutagen city properties were computed using chem. draw, molinspiration and OSIRIS software's. the compounds possessed a positive value for drug likeliness properties.

Keywords: Pyrido [1,2-a]pyrimidine-2-ones; Thiadiazole synthesis; Antibacterial activity; Clogpvalues

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INTRODUCTION

Pyridopyrimidines are bioactive nitrogen heterocyclic compounds and several of their substituted derivatives have been associated with diverse immune pharmacological activities such as analgesic, anti-inflammatory, anti-allergic, antiplatelet aggregator and anti-histaminic[1]. Many derivatives of pyridopyrimidine like Risperidone, was explored and used in a wide range as potent antipsychotic agent[2].Novel pyrido[1,2-a]pyrimidin-4-ones possessed antimalarial activity[3]. The synthesis of compounds incorporating 1,3,4 thia diazole ring have attracted wide spread attention due to their diverse pharmacological properties such as antimicrobial, anti-inflammatory analgesic and anti tumoral activities. Several 1,3,4 thiadiazole have been found to be biologically active e.g they showed the anticancer, antiviral anti-inflammatory and anticonvulsant activity[4]**.** Schiff bases of imidazo-[2, 1b]-1, 3, 4-thiadiazole derivatives were found to possess antimicrobial properties[5]. 2-(5-phenyl-1,3,4- thiadiazol-2-ylamino)-N-p-tolylacetamide (TD7) was reported to be a potent antidiabetic agent[6].1,3,4 thiadiazole are antimicrobial agents[7], atinociceptive agents[8] and an anticancer agent[9]. The exposure 2-(substituted phenyl)-amino-5-(4-pyridyl)-4H-1,3,4- Thiadiazole caused decreased activity of glutamic oxaloacetic acid transaminase (GOT), glutamic pyruvic acid transaaminase (GPT), and urea[10]. Hence a trial to incorporate 1,3,4 thia diazole moiety into the pyrido[1,2-a] pyrimidone nucleus was attempted and antibacterial activity of the compound was also carried out.

EXPERIMENTAL SECTION

The infrared (IR) spectra were recorded in KBr pellet technique on a Perkin-Elmer spectrophotometer. Absorption frequencies are quoted in reciprocal centimeter.Nuclear Magnetic Resonance (^{1}HNMR) spectra were determined by Bruker modern 400MHz and Bruker Avance 500MHz NMR instrument in DMSO-d_6, with tetra methyl silane as internal reference. Chemical shift are quoted in parts per million (ppm) (s = singlet; d = doublet; t = triplet and m = multiplet).Mass experiments were performed on GC (T 8000 TOP CE) and combined with mass spectrometer (Md 800 FIS ONS).

Preparation of (5-amino-1,3,4-thiadiazol-2-yl)methylene)-3,4-dihydro-2h-pyrido[1,2-a]pyrimidin-2-ones
A mixture of 2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene acetic acid[11], thiosemicarbazide and phosphorous oxy chloride (5ml) was refluxed gently in a steam bath for 3hours under exclusion of moisture.

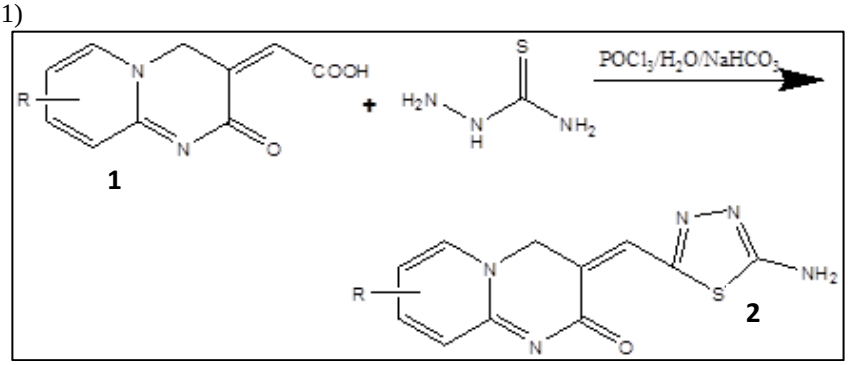
After cooling, water was added (50ml). The mixture was refluxed for 3hours and filtered. The filtrate was neutralized with sodium bicarbonate. The precipitate was filtered and washed with ice cold water and crystallized from alcohol.

Antibacterial activity

The standardized inoculums was inoculated in the plates prepared earlier (aseptically) by dipping a sterile in the inoculums removing the excess of inoculums by passing by pressing and rotating the swab firmly against the side of the culture tube above the level of the liquid and finally streaking the swab all over the surface of the medium 3 times rotating the plate through an angle of 60^0C after each application. Finally passed the swab round the edge of the agar surface. Left the inoculums to dry at room temperature with the lid closed.Each Petri dish was divided into 4 quadrants, in 3 quadrants extract discs such as I (25µg), II (50µg), III (100µg) discs (discs are soaked overnight in extract solution) and one quadrant for Standard Ciprofloxacin 5µg, were placed in each quadrant with the help of sterile forceps. Then petri dishes were placed in the refrigerator at 4^0C or at room temperature for 1 hour for diffusion. Incubate at 37^0C for 24 hours. Observed the zone of inhibition produced by different Antibiotics. Measured it using a scale or divider or verneir callipers and recorded the average of two diameters of each zone of inhibition.

RESULTS AND DISCUSSION

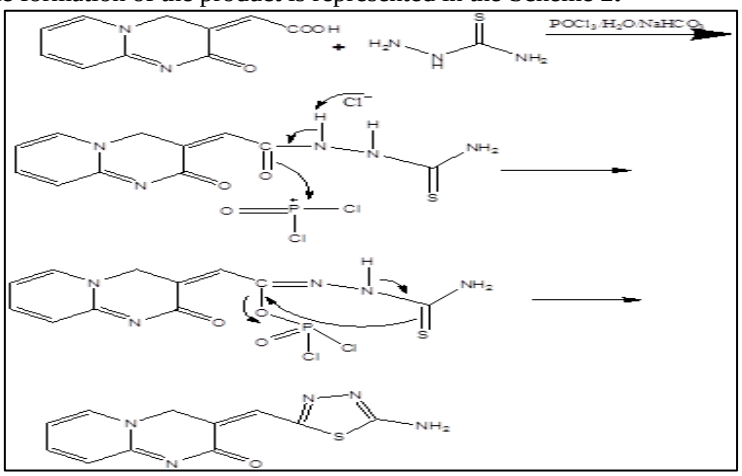
The compounds 5-amino-(1,3,4-thia diazol-2yl)-3,4-dihydro-2H-pyrido [1,2-a]pyrimidine-2-ones were prepared by the reaction of the 2-oxo-2H pyrido[1,2-a]-pyrimidin-ylidine-2-one acetic acid [11] with thio-semicarbazide in $POCl_3$, followed by the neutralization with sodium bicarbonate. The compounds were obtained in good yields. (Scheme 1)



R= H, 9-Me,8-Me,7-Me,6-Me

Scheme 1

The spectral data agreed with the proposed chemical structures. Characteristic absorption bands in IR spectra for the title compounds were observed at 3290-3100 cm-1, 1615 cm^{-1},1499 cm^{-1} and at 700cm^{-1} respectively corresponding to the $–NH_2$ stretching vibrations, –C=O,–C=N and C-S-C group respectively in the product. In the ^{1}HNMR spectra signals, for the pyrido pyrimidine nucleus appeared at δ 7.0, δ7.2, δ7.7, δ8.2, δ8.3 ανδ δ5.0. Τηε NH2 proton was observed at □□7.4. In the ^{13}CNMR 11 signals corresponding to eleven carbon atoms were observed and in the mass spectrum M^+ ion was seen at m/z=270. The mechanism for the formation of the product is represented in the Scheme 2**.**



Scheme 2

All the synthesized compounds were screened for antibacterial activity against *Escherichia coli* and *Staphylococcus aureus* according to the agar disc diffusion method with standard drug ciproflaxin. The results of the antibacterial activity of the compounds are presented in the Table 1. All the compounds showed moderate inhibitory activity against both the strains at 100 µg. The ClogP, solubility drug likeliness and the mutagen city properties were computed using chem. draw, molinspiration and OSIRIS software's. The Clogp values which is the partition function between octanol and water was found to be lesser indicating more permeable nature of the compounds. The higher negative values for the solubility prediction indicated the more soluble nature of the compounds. The compounds showed low risk against mutagenecity and the drug likeliness score is also good.

Table 1: Antibacterial activity of the synthesized compounds

Compound	*R*	Zone of inhibition(mm)	
		***Escherichia coli* (100 µg)**	***Staphylococcus aureus* (100 µg)**
2a	H	13	14
2b	9Me	14	14
2c	8Me	14	15
2d	7Me	15	17
2e	6Me	15	17
Ciproflaxin		27	27

CONCLUSION

The title compounds (5- amino 1,3,4 thia diazol-2yl) -3,4 – dihydro-2H –pyrido[1,2-a]pyrimidin-2-ones were prepared and screened for their antibacterial activity. The compounds show moderate activity against *Escherichia coli* and *Staphylococcus aureus.* The ClogP values and druglikeliness properties were also calculated using Chem draw, Molinspiration and OSIRIS software's which were all in good agreement with the results. The activity of the compounds can be increased by changing the substituents and a insight into the mechanism of action must be carried out to improve the pharmacological properties.

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