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SYNTHESIS AND EVALUATION OF HETEROCYCLIC COMPOUNDS AS ANTIBACTERIAL SENSITIVITY

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Several 6-amino-2-thioxo-2, 3-dihydropyrimidin-4(1H)-one (1), Ethyl-2-(6-amino-2-thioxo-1, 2-dihydropyrimidin-4-yloxy) acetate (2), 2-(6-amino-2-thioxo-1, 2-dihydropyrimidin-4-yloxy) acetohydrazide (3) and 6-amino-4-((5-mercapto-1,3,4-oxadiazol-2-yl) methoxy) pyrimidin-2(1H)-thione (4) have been synthesized and tested for their antibacterial activity. The structure of the synthesized compounds have been elucidated on the basis of their elemental analyses and spectral data.

Key words : Pyrimidine, Oxadiazole, Antibacterial activity, Ciprofloxacin.

INTRODUCTION

Pyrimidine nucleus exhibited remarkable pharmacological activities. Literature indicates that compounds having pyrimidine nucleus have wide range of therapeutic uses that include antibacterial [1], antimicrobial [2], anti-inflammatory [3], and anticonvulsant [4] etc. Oxadiazole derivatives also possess a variety of therapeutic activities such as antimicrobial [5], antibacterial [6], anti-inflammatory [7], anticonvulsant [8] and analgesic [9] etc. The incorporation of oxadiazole moiety in pyrimidine fram work has been found to enhance the activity. Hence, in the present study the position-4 in pyrimidine nucleus was used as the target for chemical modification. The compounds have evaluated for their antibacterial activity against some selected pathogens.

EXPERIMENTAL

The melting point of the compounds was determined in open glass capillaries with the help of thermionic melting point apparatus. The homogeneity of all newly synthesized compounds was routinely checked by thin layer chromatography. Elemental analysis of all the synthesized compounds were determined by perkin-Elmer 2400 elemental analyzer and IR spectra were recorded on a Beckman Acculab-10 spectrometer (ν_{max} in cm^{-1}).

RESULT AND DISCUSION

All the synthesized compounds were evaluated for antibacterial activity. For antibacterial screening various bacteria, S. aureus, P. vulgaris and E. coli were used and compared with standard drug ciprofloxacin. The antibacterial activity was assayed by cup

plate method [10]. The results of such studies are given in table 1. Almost all the compounds showed moderate to good activity against all microorganisms employed in the screening studies. Compound 4 showed better antibacterial activity among the compounds tested.

Table 1. Antibacterial activity of pyrimidine derivatives

Compounds	Bacterial inhibition zone/mm		
	S. aureus	P. vulgaris	E. coli
1	10	12	9
2	15	13	12
3	18	15	17
4	22	20	23
Ciprofloxacin	20	20	22

Preparation of 6-amino-2-thioxo-2, 3-dihydropyrimidin-4(1H)-one (1)

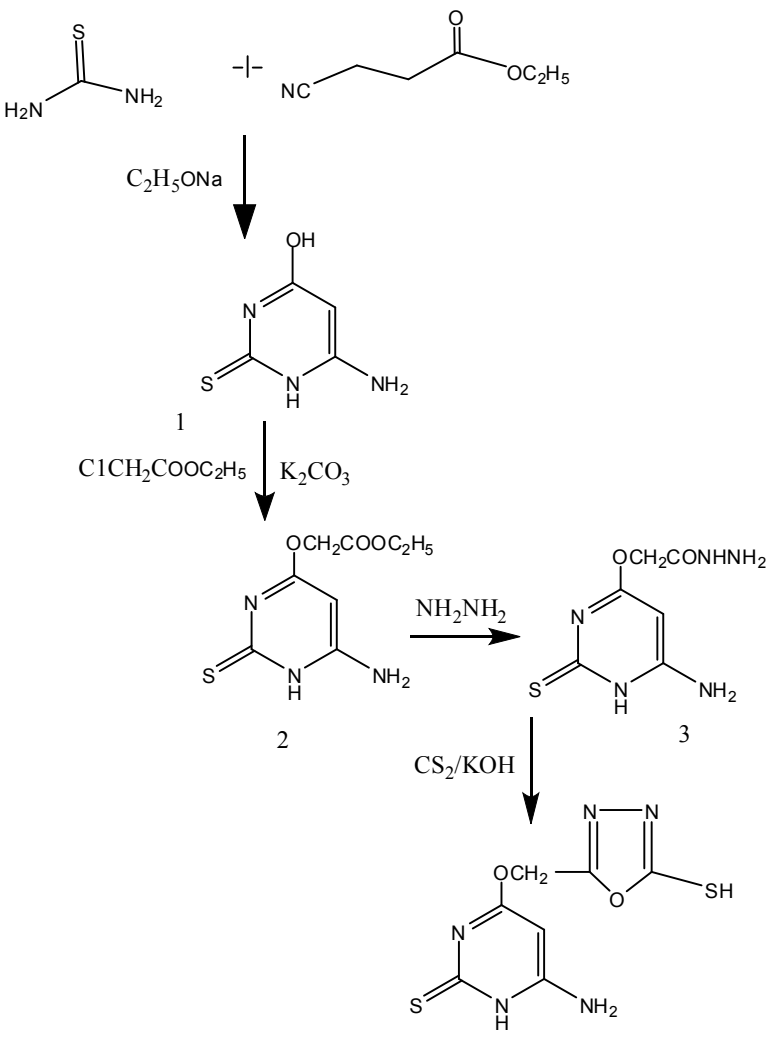
Ethyl cyanoacetate (0.01 mol) and thiourea (0.01 mol) in the presence of sodium ethoxide reflux for 8 h. The reaction mixture was poured onto ice. The product was filtered, washed, dried and recrystallized with appropriate solvent to give compound 1. Yield 65%; m.p. > 145°C; IR (KBr) ν_{max} in cm^{-1} 1622 (C=C of aromating ring), 3022 (C-H aromatic), 3090 (N-H), 3320 (NH_2), 3400 (OH); ^{1}HNMR ($CDCl_3$ + DMSO d_6) δ in ppm : 6.5 (s, 1H, CH-Ar), 7.2 (s, 1H, NH exchangeable with D_2O), 8.9 (s, 2H, NH_2 exchangeable with D_2O), 12.0 (s, 1H, OH exchangeable with D_2O) Anal. Calcd. for $C_4H_5N_3OS$: C, 33.56; H, 3.52; N, 29.35%. Found: C, 33.58; H, 3.55; N, 29.32%.

Preparation of Ethyl-2-(6-amino-2-thioxo-1,2-dihydropyrimidin-4-yloxyl)acetate (2)

A mixture of compound 1 (0.1 mol) and 0.15 mol of anhyd. K_2CO_3 in an excess of acetone (300 ml) was stirred at reflux temperature for 3 hr. To the stirred suspension ethyl chloroacetate in dry acetone (50 ml) was added dropwise during 1 hr at reflux temperature for 7 hr. After keeping the reaction mixture overnight, the excess of solvent was removed and the residue poured onto crushed ice. The separated solid was filtered, washed with water and recrystallized from ethanol. . Yield 60%; m.p.>145^{0}C; IR (KBr) ν_{max} in cm^{-1} 1545 (C-N), 1632 (C=C of aromating ring), 1653 (C=O), 3030 (C-H aromatic), 3094 (N-H) 3318 (NH_2); ^{1}HNMR ($CDCl_3$ + DMSO d_6) δ in ppm: 3.5 (s, 2H, O-CH_2), 6.7 (s, 1H, CH-Ar), 7.26 (s, 1H, NH exchangeable with D_2O), 3.4 (s, 2H, CH_2), 4.1 (s, 3H, CH3), 8.6 (s, 2H, NH_2 exchangeable with D_2O) Anal. Calcd. for $C_4H_{11}N_3O_3S$: C, 41.91; H, 4.84; N, 18.33%. Found: C, 41.93; H, 4.85; N, 18.30%.

Preparation of Ethyl-2-(6-amino-2-thioxo-1,2-dihydropyrimidin-4-yloxyl)acetohydrazide (3)

To the suspension of compound 2 in ethanol (150 ml) hydrazine hydrate (0.05 mol) was added and the reaction mixture refluxed for 4 hr. The resulting mixture was then added to crushed ice and water and the solid that separated was filtered, washed with cold water, dried and recrystallized from an appropriate solvent. . Yield 54%; m.p.>170^{0}C; IR (KBr) ν_{max} in cm^{-1} 1565 (C-N), 1625 (C=C of aromating ring), 1657 (C=O), 3035 (C-H aromatic), 3095 (N-H), 3324 (NH_2); ^{1}HNMR ($CDCl_3$ + DMSO d_6) δ in ppm: 3.8 (s, 2H, O-CH_2), 6.5 (s, 1H, CH-Ar), 7.26 (s, 2x1H, NH exchangeable with D_2O), 9.00 (s, 2x2H, NH_2 exchangeable with D_2O); Anal.Calcd. for $C_6H_9N_5O_2S$: C, 33.48; H, 4.21; N, 32.54%. Found: C, 33.46; H, 4.25; N, 32.51%.



SCHEME 1

Preparation of 6-amino-4-((5-mercapto-1,3,4-oxadiazol-2-yl)methoxy)pyrimidin-2(1H)-thione(4)

A mixture of compound 3 (0.1 mol), 0.5 N KOH solution (2 ml) and carbon disulphide (1 ml) in ethanol (50 ml) was refluxed on a water bath for 6 hr. The solvent was evaporated and the residue dissolved in cold water. The resulting mixture was acidified with dil. Acetic acid to precipitate then filtered, washed with water, dried and recrystallized from ethanol. Yield 43%; m.p. > 215°C; IR (KBr) ν_{max} in cm^{-1} 1286 (N-N), 1560 (C-N), 1620 (C=C of aromating ring), 3033 (C-H aromatic), 3098 (N-H), 3315 (NH_2); ^{1}HNMR ($CDCl_3$ + DMSO d_6) δ in ppm: 3.8 (s, 2H, O-CH_2), 6.5 (s, 1H, CH-Ar), 7.26 (s, 1H, NH exchangeable with D_2O), 9.00 (s, 2H, NH_2 exchangeable with D_2O), 13.0 (s, H, SH; Anal. Calcd. for $C_7H_7N_5O_2S_2$: C, 32.68; H, 2.74; N, 27.22%. Found: C, 32.66; H, 2.75; N, 27.24%.

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