MULTIDISCIPLINARY RESEARCH

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Synthesis, Characterization and Antimicrobial Analysis of Some New Pyrimidines Containing Pyrazole Moiety

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Abstract :

Pyrimidines are generally one of the most commonly used organic moieties. Among various heterocyclic compounds, the medicinal importance of derivatives of pyrimidine are significant, due to their antiviral, anti-neoplastic, antibiotic and anti-inflammatory including other biological activities. Herein we report novel pyrimidines containing pyrazole moiety from chromone by using thiourea. All synthesized pyrimidines were well characterized by spectral analysis and were screened for antimicrobial activity and they showed moderate activity.

Keywords: Pyrimidines, Chromones, Thiourea, antimicrobial, Gram +ve and Gram –ve microorganisms.

Introduction :

The heterocyclic compounds chemistry is as logical as that of aliphatic and aromatic compounds. Its study is great interest both from the theoretical as well as practical significance. A variety of compounds such as alkaloids, vitamins, essential amino acids, hormones, hemoglobin, large number of synthetic drugs and dyes contains heterocyclic ring systems. There are huge number of synthetic heterocyclic compounds, like furan, thiophene, pyrrole, pyrrolidine, pyridine, piperidine, pyrimidine and thiazole having significant application and many are important intermediates in the organic synthesis[1]. Among various heterocyclic compounds, the medicinal importance of derivatives of pyrimidine are significant, due to their antiviral, anti-neoplastic, antibiotic and anti-inflammatory including

other biological activities[2]. The pyrimidine ring system are present in coenzymes, uric acid, purines, nucleic acids, several vitamins and some marine microorganisms (e.g. Sponge). Numerous synthetic members of pyrimidine are also important as chemotherapeutic agents (e.g. Sulfadiazine) and synthetic drugs (e.g. Barbituric acid derivatives*).* However, these interesting biological activities attracted towards chemistry of nitrogen heterocycles[3-4]. Using the small 5-acetyl pyrimidine-2, 4, 6- (1*H*, 3*H*, 5*H*) -trione moiety as a primary building block in the preparation of many new drugs are envisioned. Direct pharmaceutical and other industrial applications are well-known of 5-acylbarbiturates[5].

Because of its great practical usefulness, fused pyrimidines go on to attract considerable attention, primarily due to exceedingly wide spectrum of biological activities. This is evident that in particularly from publications of regular reviews on the chemistry of systems where the pyrimidine ring is fused to a variety of heterocycles like quinazolines, purines, triazolo pyrimidines, pteridines, pyrazolopyrimidines, pyridopyrimidines, pyrimidoazepines, pyralopyrimidines and furopyrimidines. In 1776, fused pyrimidine chemistry began, when Scheele isolated uric acid. Though, more systematic investigations were undertaken near around 100 years later, Bischler, Niementowski, Bogert, Gabriel, and Riedel established considerable progress in this field[6]. When the discovery of the presence of a few purine and pyrimidine bases in double stranded nucleic acids then several papers on chemistry of pyrimidines and purines have been published. Numerous simple fused pyrimidines like purines and pteridines are biologically active by themselves[7-8]**,** or are essential components of incredibly important naturally occurring substances (*i.e.*, nucleic acids). Various pteridine derivatives are used as anti-leukemic drugs[9], or potassium-conserving diuretics[10]. In addition to that a number of quinazoline alkaloids shows bronchodilatory[11], hypnotic[12-13] and antimalarial activity[14-15].

Experimental :

For the synthesis of the compounds, all chemicals used were obtained especially from SD Fine chemicals and Sigma Aldrich. In liquid paraffin bath, melting points of synthesized compounds were recorded in open capillaries and which are uncorrected. The purity was checked of the synthesized compounds by using TLC, in which silica gel coated plates obtained from Merck as a stationary phase and solvent mixture of ethyl acetate and hexane as a mobile phase. Infrared spectra of synthesized compounds were recorded on Schimadzu-FT-IR Spectrophotometer using potassium bromide pellet technique and the absorption

bands are expressed in cm^{-1}. ^1H NMR spectra of synthesized compounds were recorded on Varian 400 MHz and Mercury YH 300 MHz instrument in solvents DMSO-d_6, $CDCl_3$ and TMS as an internal standard, the chemical shift data were expressed as δ values relative to TMS and in hertz (Hz) coupling constants (J) were expressed. By using electro-spray method (ES), on Macromass mass spectrophotometer (Waters), mass spectra were recorded.

General procedure :

To a mixture of Compound **1c** (0.2 gm, 0.00078 m mole) and KOH (0.05 gm, 0.05 m mole) in ethanol (10 ml), thiourea **2** (0.065 gm, 0.0025 m mole) was slowly added and this reaction mixture was refluxed for 8 hours. After completing of the reaction (monitored by TLC), this contents were cooled to the room temperature and then poured in to crushed ice, then acidified by using Conc. HCl to get yellow solid. The solid was separated by filtration and recrystallised in ethanol to afford **3c** pure solid. The compounds **3(a-h)** were prepared following by the above explained procedure. In **Table 1,** physical data of these synthesized compounds are recorded. Synthesized compounds structures have been confirmed by IR, ^1H NMR and Mass spectra.

IR (3c) (cm^{-1}): 957(C-Cl), 1213 (C-Br), 1499(C=C), 1597 (C=S), 3230(N-H), 3396(O-H).

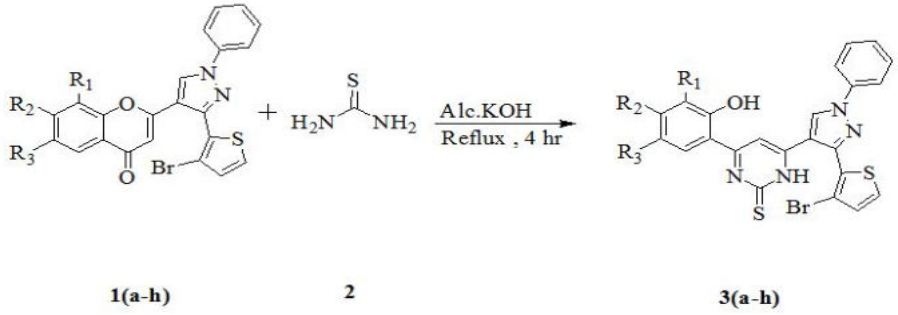
^1H NMR (3c) (DMSO) δ ppm: 6.9631 (s, 1H, N-H), 7.1863-7.2576 (m, 1H, Ar-H), 7.2999-7.4996 (m, 2H, Ar-H), 7.5123-7.6132 (m, 2H, Ar-H), 7.6298-7.6499 (m, 1H, Ar-H), 7.6548-7.7321(m, 2H, Ar-H), 7.7598-7.7681 (m, 2H, Ar-H), 7.7793-7.8289 (m, 1H, Ar-H), 8.8956(s, 1H, Pyrazole-H), 12.9125 (s, 1H, Ar-OH).

ES-MS (3c) (m/z): 541(M+1), 543(M+3).

IR (3d) (cm^{-1}): 965(C-Cl), 1196 (C-Br), 1480(C=C), 1586 (C=S), 3109(N-H), 3413(O-H).

^1H NMR (3d) (DMSO) δ ppm: 6.8741 (s, 1H, N-H), 7.3211-7.3301(m, 2H, Ar-H), 7.4125-7.4211 (m, 2H, Ar-H), 7.6087-7.6124 (m, 1H, Ar-H), 7.6412-7.6499 (m, 2H, Ar-H), 7.6715-7.6801 (m, 2H, Ar-H), 7.8214 (s, 1H, Ar-H), 8.8247(s, 1H, Pyrazole-H), 12.6548 (s, 1H, Ar-OH).

ES-MS (3d) (m/z): 575M+1), 577(M+3).



1(a-h) 2 3(a-h)

Scheme 1: Synthesis of 6-(3-(3-bromothiophen-2-yl)-1-phenyl-1H-pyrazol-4-yl)-4-(2-hydroxyphenyl) pyrimidine-2(1H)-thione

Table 1: Physical data of compounds 3(a-h)

Comp.	R_3	R_2	R_1	M.P. (^{0}C)	Yield (%)
3a	H	H	H	112-114	68
3b	CH_3	H	H	190-192	76
3c	Cl	H	H	84-86	79
3d	Cl	H	Cl	144-146	73
3e	F	H	H	186-188	82
3f	Cl	CH_3	H	122-124	81
3g	Br	H	H	160-162	72
3h	CH_3	H	CH_3	172-174	69

Result and Discussion :

Eight new pyrimidines have been synthesized successfully having good yields. The newly

synthesized compounds have been confirmed using ^{1}H NMR, melting point range, Mass, IR spectral analysis. By using disc diffusion method, all newly synthesized compounds were screened for antimicrobial activity.

Antimicrobial activity:

Compounds **3(a-h)** were screened for their antimicrobial activity against Gram positive (*Enterobacter aerogenes, Salmonella abony, Salmonella typh, Pseudomonas aerogenosa, Escherichia coli, Shigella boydii)* and Gram negative pathogens(*Staphylococcus aureus, Megaterium Bacillus, Bacillus subtilis, Bacillus cereus*) by paper disc diffusion method using tetracyclin as a reference standard

drug. By using Nystatin as standard drug, antifungal activity was screened against *Aspergillus niger, Saccharomyces cerevisiae, Candida albicans* at 100 ìg/ml concentration. Culture media was Muller Hinton agar. In mm The zone of inhibition was measured, after the 24 hr of incubation at 37^0C. Microbial data for 3(a-h) are summarized in **Table 2.**

Table 2: Antimicrobial Analysis Data of 3(a-h)

	Bacterial pathogens										Fungal pathogen		
	Gram negative pathogen						Gram positive pathogen						
Compounds	*Salmonella typhi*	*Enterobacter aerogenes*	*Escherichia coli*	*Pseudomonas aeruginosa*	*Salmonella abony*	*Shigella boydii*	*Bacillus subtilis*	*Bacillus Megaterium*	*Staphylococcus aureus*	*Bacillus cereus*	*Candida albicans*	*Saccharomyces cerevisiae*	*Aspergillus niger*
3a	-	06	12	10	14	-	-	10	18	12	-	-	11
3b	09	-	08	-	11	-	-	-	11	07	16	-	12
3c	-	-	09	-	15	-	-	09	20	06	20	09	15
3d	08	-	11	13	13	11	09	-	-	12	17	-	18
3e	-	10	11	-	15	-	-	-	-	08	09	-	13
3f	-	-	12	-	20	-	10	-	20	13	10	-	15
3g	-	-	10	19	13	-	-	10	-	08	17	-	19
3h	-	09	09	-	14	-	-	08	15	12	14	07	14
DMSO	-	-	-	-	-	-	-	-	-	-	-	-	-
STND.	22	20	20	33	21	26	25	20	30	25	24	20	25

*Standard for bacterial pathogens-tetracyclin, for fungal pathogens-nystatin

Conclusion :

In conclusion, starting from Chromones we have successfully synthesized pyrimidines and its derivatives, these newly synthesized pyrimidines compounds were screened against Gram positive as well as Gram negative bacterial strains and these compounds shows moderate activity as compared to standard drug. The obtained data through the present work shows a good agreement between the experimental and computed spectral data.

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