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Research Article

Synthesis, and Antibacterial activities of Newer 6-(3-(1,2-dihydro-6-phenyl-2-aminopyrimidin-4-yl) phenyl amino) pyridazin-3(2H)-one

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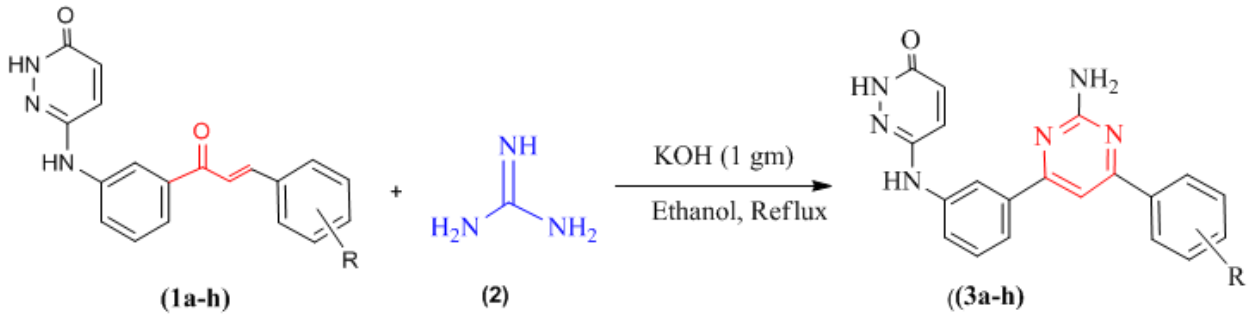
ABSTRACT
Several substituted pyridazone derivative of Acetophenone are condensed with aromatic aldehydes, and resulting Chalcones are used for the synthesis of diarylpyrimidines. Organic compounds containing pyrimidines, thiopyrimidines as a core unit are known to exhibit various biological activities and pharmaceutical activities. So, all newly synthesized compounds were screened for their antibacterial activity. Most of the compounds showed significant antibacterial activities.

GRAPHICAL ABSTRACT



KEYWORDS
Pyrimidines, Guanidine, Antibacterial, Reflux.

1. INTRODUCTION

Organic compounds containing pyrimidines as a core unit are known to exhibit various biological and pharmaceutical activities [1]. Over the past decades, many procedures have been reported for the preparation of pyrimidines and thiopyrimidines,[2-4] however, after a detailed literature survey, we found that there were no any publications devoted to synthesis of pyridazolone derivatives containing pyrimidines and thiopyrimidines. Pyrimidines have a long and distinguished history extending from the days of their discovery as an important constituent of nucleic acids to their current use in the chemotherapy of AIDS. During the last two decades, several pyrimidines derivatives have been developed as chemotherapeutic agents and have found wide clinical applications. Many pyrimidines and related heterocyclic compounds are found to possess a wide important pharmacophore and privileged structure in medicinal chemistry. Pyrimidines and thiopyrimidines showed pharmacological activities like antihypertensive [5], analgesic [6], tuberculosis [7], neuroleptic[8], and antimicrobial activity [9]. On the other side pyrimidines and its derivatives have been received much attention due to their interesting pharmacological Properties [10-15]. Some pyrimidines derivative also studied for their leishmanial chemotherapeutic properties [16]. These interesting microbial properties of thiopyrimidines have been prompted the synthesis of some new series of compounds of this class.

2. MATERIALS AND METHODS

All chemicals used were AR grade. Chemicals such as 3-aminoacetophenone, 2, 6-dichloropyradizine, substituted aromatic benzaldehyde, DMSO, Ethanol, Pet ether, Guanidine thiourea, urea etc. were used. For purification column chromatography were used.

2.1. General Procedure

Melting points were determined in open capillary tubes and are uncorrected. The purities of the compounds were checked on silica-gel-coated Al plates. IR spectra were recorded in KBr on a Perkin Elmer Spectrum BX series FT-IR spectrometer. ^{1}HNMR spectra were recorded on Bruker DRX 300 MHz NMR spectrometer using TMS as internal standard and mass spectra on a Joel D-300 spectrometer.

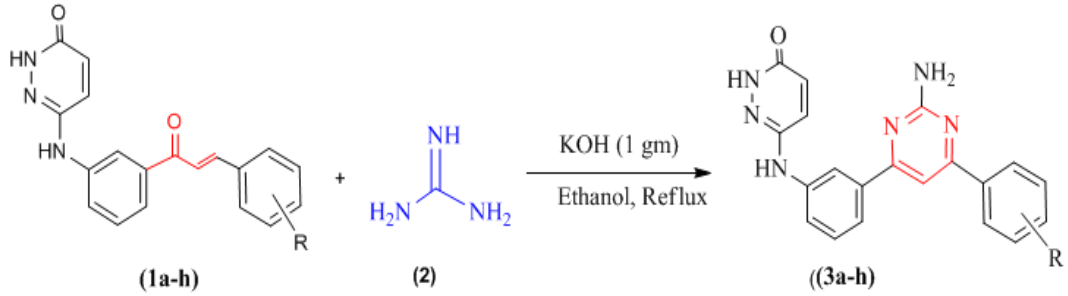
2.2. Experimental Procedure for 6- (3- ((E) -4- (3, 4 dimethoxy phenyl) but- 3-enoyl)phenylamino) pyridazin -3 (2H)one:(preparation of chalcone)

The 6-(3-acetylphenylamino) pyridazin-3(2H)-one (0.02 mol) and 3,4- dimethoxy benzaldehyde (0.02 mol) were dissolved in ethanol (15 ml), under stirring. Aqueous KOH (50%, 12 ml) was added drop wise. The reaction mixture was stirred at room temperature and kept overnight in a bulb oven at 55-60°C. After 18 hr, the reaction mixture was diluted with H_2O and acidified with HCl (10%). The separated solid was filtered and crystallized from glacial acetic acid to give.

Similarly, other compounds of series were also prepared by same procedure. The melting points, yields, elemental analyses of different chalcones. We synthesized novel Chalcones using conventional method in the literature [17-18] and that novel Chalcones used in this research work.

2.3. Experimental Procedure for Pyridazin-3(2H)-one (3a-3h)

A mixture of Chalcone (6-(3-((E)-4-Nitro phenyl)but-3-enoyl)phenyl amino)pyridazin-3(2H)-one) (0.01mol) and guanidine (0.01mol.) was dissolved in ethanol (20 mL) and solid potassium hydroxide (1g) in water (5ml) and contents were refluxed for 6.5 hrs. Completion of the reaction was monitored by thin layer chromatography (TLC). The crude product obtained was purified by silica gel column chromatography with ethyl acetate/n-hexane (1:1) as eluent (Scheme-1). All other 2-amino pyrimidines were synthesized similarly.



Scheme 1. Synthesis of pyrimidine derivatives.

2.4.Spectral Data Analysis

6-(3-(1,2-dihydro-6-(3,4-dimethoxyphenyl)-2-aminopyrimidin-4-yl)phenyl amino) pyridazin-3(2H)-one (3c):

Molecular Formula; $C_{20}H_{16}N_6O_2$; Yield; 65%, m. p.; 176-178^{0}C; FT-IR (KBr): 1610 cm^{-1} (Ar. C=C Str.), 3100-3350 cm^{-1} (Broad peaks for 3 N-H Str.), 1648 cm^{-1}, (C=O), 1500 cm^{-1} (C-N str.); ^{1}H NMR (DMSO-d_6) (δ ppm) 3.7 (s 6H), 2.4 (s, 1H), 5.8 (s, 1H, Ar-H), 4.3 (s, 1H), δ 7. 3 (s, 1H, Ar-H), 6.65-6.80 (m, 5H, Ar-H), 6.7-7.8 (m, 3H, Ar-H), Mass; (m/z), Calculated; 372; Found 371(M^+).

6-(3-(1,2-dihydro-6-(,4-chlorophenyl)-2-aminopyrimidin-4yl)phenylamino) pyridazin-3(2H)-one (3e):

Molecular Formula=$C_{20}H_{15}ClN_6O$; Yield= 58%, m. p. = 177^{0}C; FT-IR (KBr): 1600 cm^{-1} (Ar. C=C Str.), 3000-3250 cm^{-1} (Broad peaks for 3 N-H Str.), 1673.1 cm^{-1}, (C=O), 1458 cm^{-1} (C-N str.); ^{1}H NMR (DMSO-d_6) (δ ppm) 1.3 (s, 1H), 2.2 (s, 1H), 2.6 (s, 1H), 2.00 (d, 1H), 2.7 (d, 1H), δ 7. 3 (s, 1H, Ar-H), 7.6-7.70 (m, 4, Ar-H), δ7.4-7.5 (m, 4H, Ar-H), Mass; (m/z), Calculated 391; Found 390(M^+).

6-(3-(1,2-dihydro-6-(4-methoxyphenyl)-2-aminopyrimidin-4-yl)phenyl amino) pyridazin-3(2H)-one (3g):

Molecular Formula; $C_{21}H_{18}N_6O_2$, Yield; 72%, m. p.; 169^{0}C; FT-IR(KBr): 3250 cm^{-1}(Ar C=C Str.), 3101- 3221 cm^{-1}, (Broad peaks for 2 N-H Str.), 1806 cm^{-1} (C=O), 1680 cm^{-1} (C=O); ^{1}H NMR (DMSO-d_6): (δ ppm); 3.9 (s, 3H) , 5.1 (s, 1H), 7.1 (s,1H), 6.5 (s, 1H), 6.72-7.6 (d, 4H, Ar-H), 6.4-6.5(m, 4H, Ar-H), 7.00-7.30 (m, 2H, Ar-H); 6.4 (s, 1H), Mass; (m/z) , Calculated 386. Found 385 (M^+)

6-(3-(1,2-dihydro-6-(3,4,5-trimethoxyphenyl)-2-aminopyrimidin-4-yl) phenyl amino) pyridazin-3(2H)-one (3h.):

Molecular Formula; $C_{23}H_{22}N_6O_4$, Yield; 56%, m. p.; 186^0C; FT-IR(KBr): 3240 cm^{-1}(Ar C=C Str.), 3001- 3121 cm^{-1}, (Broad peaks for 2 N-H Str.), 1800 cm^{-1} (C=O), 1655 cm^{-1} (C=O); ^{1}H NMR (DMSO-d_6): (δ ppm); 3.9 (s, 9H,), 5.1 (s, 1H), 2.1 (s,1H), 6.5 (s, 2H), 7.6 (d, 2H, Ar-H), 6.4-6.5(m, 3H, Ar-H), 7.00-7.30 (s, 1H, Ar-H); 6.4 (s, 1H)Mass;(m/z), Calculated 446 Found 445 (M^+).

2.5. Spectral Interpretation

The IR spectra of the 2-amino pyrimidines showed characteristic absorption band at 3101- 3221 cm^{-1} due to NH_2. Beside this the disappearance of band at 1630-1640 cm^{-1} or 1650-1670 cm^{-1} suggest that C=O stretching due to $COCH_3$ group is not present. The ^{1}H NMR spectra of the compounds synthesized showed characteristic singlet peaks at 2.30-2.45 due to Ar-CH_3. A singlet is observed near at 6.2-7.2 due to one hydrogen at C-3 position of the pyrimidines (when it is unsubstituted) and aromatic proton peak at 7.4-7.5 is observed for C-5 proton.

These characteristic peaks observed for the IR and ^{1}H NMR of the pyrimidines are in agreement with those observed earlier. Mass spectra of the representative pyrimidines confirm the molecular formula weight of the compound.

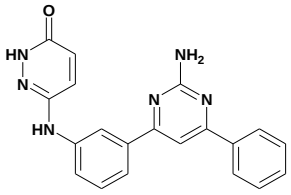
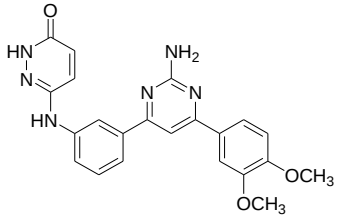
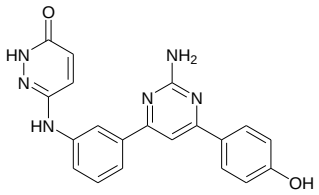
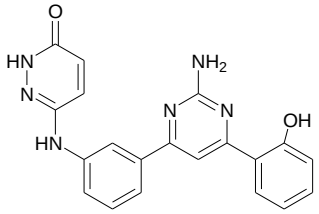
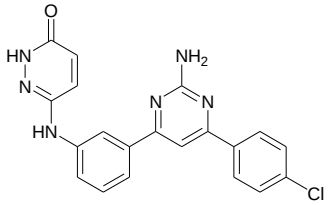
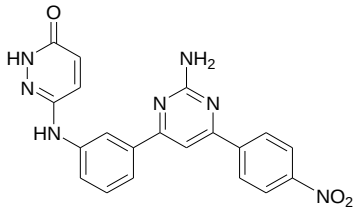
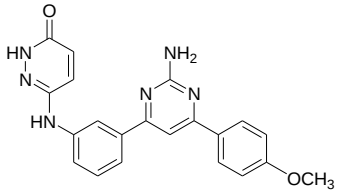
2.6. Anti-Bacterial Activity

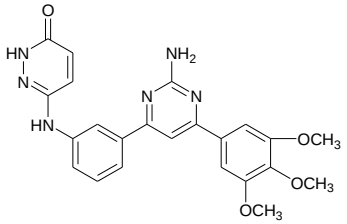
All of the novel synthesized compounds were screened for their antimicrobial activity against the Gram –ve bacteria *Escherichia coli* (ATCC 8739) and Gram +ve bacteria *Staphylococcus aureus (ATCC6538*), *in-vitro* using ager diffusion method [19-20], at a concentration 20mg/mL. DMSO used as a solvent.

3. RESULTS AND DISCUSSION

Many synthetic methods of pyrimidine have been reported from urea, thiourea and Guanidine Chalcones. But synthesis of pyrimidines from Guanidine gives very good yield as compared to urea & thiourea. In the present work, we describe the synthesis of 2-amino pyrimidines which have biological important in chemistry by using 6-(3-((*E*)-3-phenylacryloyl)phenyl amino) pyridazin-3(*2H*)-one to give 6-(-3-(-2 amino-6-phenyl pyrimidin-4yl)pyridazin-3(*2H*)-one.(3a-l) by conventional method. The product obtained in 55 to 72 % yield within around seven hours by refluxing. Best result in terms of yield and reaction time was obtained with small amount of alkali (Aqueous KOH). The structures of the compounds were established on the basis of spectroscopic data and elemental analysis. (Table 1)

Table 1. Physical data of Substituted 2-amino Pyrimidine.

Entry	R	Compound	Yield (%)	Time (Hrs)	M.P. (°C)
3a	-H		65	7	187-189
3b	3,4-OCH_3		69	7.5	173-175
3c	4-OH		59	7	189-191
3d	2-OH		70	6.5	165-167
3e	4-Cl		72	7	193-195
3f	4-NO_2		50	7.5	156-158
3g	4-OCH_3		75	7	160-162

3h	3, 4, 5-OCH_3		71	6.5	178-180

(*Reaction condition*- chalcone (6-(3-((e)-4-nitro phenyl)but-3-enoyl)phenyl amino)pyridazin-3(2h)-one) (0.01mol) and guanidine (0.01mol.) was dissolved in ethanol (20 ml) and solid potassium hydroxide (1g) in water (5ml) reflux).

3.1. Antibacterial activity

Compound (3a, 3c & 3g) showed highly efficient antibacterial activity against *S. aureus* (*ATCC* 6538) (gram positive bacteria) more than Penicillin standard. In case of *E. Coli (ATCC8739)*(gram positive bacteria), compounds (3a, 3c, 3f & 3g) showed highly efficient antibacterial activity, compound 3c showed more activity than penicillin as standard sample activity. Many synthesized compounds were also found to be efficient equivalent to standard. (Table 2, Fig. 1)

Table 2. In-*vitro* Antibacterial activity of 2- amino pyrimidine derivatives.

Entry	**R**	**Antibacterial Activity**	
		G^+ S. aureus (ATCC6538)	***G^- E. Coli* (ATCC 8739)**
3a	-H	**10mm**	**11mm**
3b	3,4-OCH_3	8mm	7mm
3c	4-OH	**11mm**	**15mm**
3d	2-OH	-ve	8mm
3e	4-Cl	9mm	8mm
3f	4-NO_2	7mm	**11mm**
3g	4-OCH_3	8.5mm	**11.5mm**
3h	3, 4, 5-OCH_3	**11mm**	**-ve**
STD	**Penicillin**	**8.5mm**	**11.5mm**

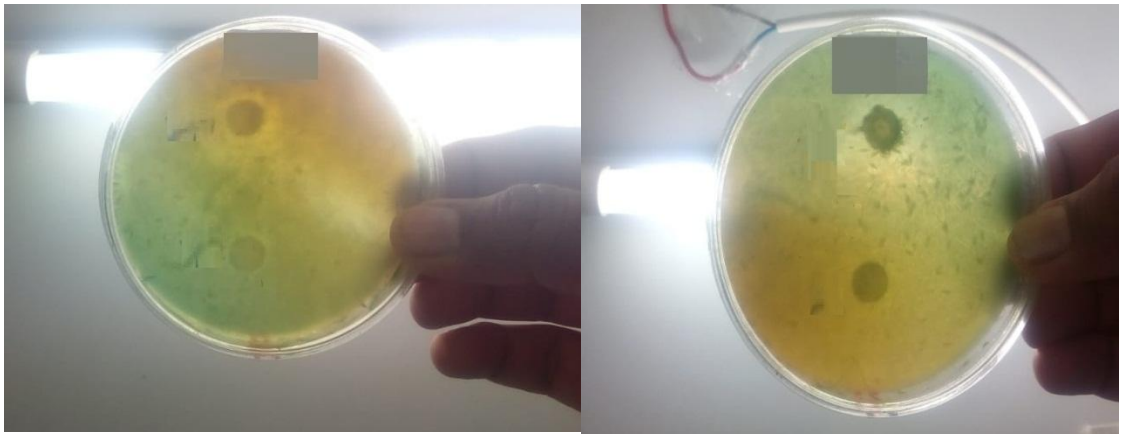


Fig. 1. Antibacterial activity plate.

4. CONCLUSION

Pyrimidines occupy a distinct and unique place in our life. This hetero cyclic moiety has great biological and medicinal significance. A large array of pyrimidine drugs possesses a variety of medicinal properties. 2-amino pyrimidines have been shown more importance properties in the field of synthetic organic chemistry. The method used in the synthesis of newer pyrimidines was found good because all products obtained have moderate to good percentage yield. Many of newer pyrimidines showed antibacterial activities. The advantage of this synthesis was good to moderate yield by using small amount of alkali.

5. ACKNOWLEDGEMENTS

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6. REFERENCES

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