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Synthesis and Antimicrobial Screening of Novel 4-aryl-6-(4-(pyrrolidin-1-yl)phenyl)pyrimidin-2-amine

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ABSTRACT

In the present work 4-aryl-6-(4-(pyrrolidin-1-yl)phenyl)pyrimidin-2-amine were synthesized by reacting chalcones with guanidine hydrochloride. The synthesized compounds were tested for antibacterial and antifungal activity.

Keywords: Pyrrolidine, Chalcone, Pyrimidine, Antibacterial activity, Antifungal activity

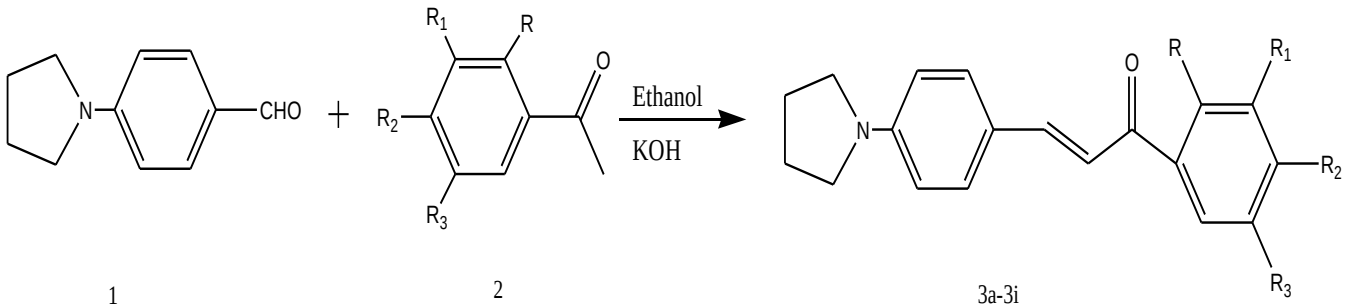
INTRODUCTION

A wide variety of heterocyclic compounds plays an important role in the pharmaceutical fields. Most of the commercially available drug molecules contains heterocyclic ring as a structural backbone. Pyrimidine ring is present in many biological compounds [1]. Pyrimidine derivatives have reported as anti-histaminic agents [2], antimicrobial agents [3], antitubercular agents [4], antifungal agents [5], anti-tumor agent [6], anticancer agent [7], analgesic, anti-inflammatory agents [8], antipyretic [9,10], antioxidant agents [11]. In the continuation of our research work to synthesis pyrrolidine containing heterocyclic compounds [12-14], we are reporting the synthesis of pyrrolidine containing pyrimidine derivatives.

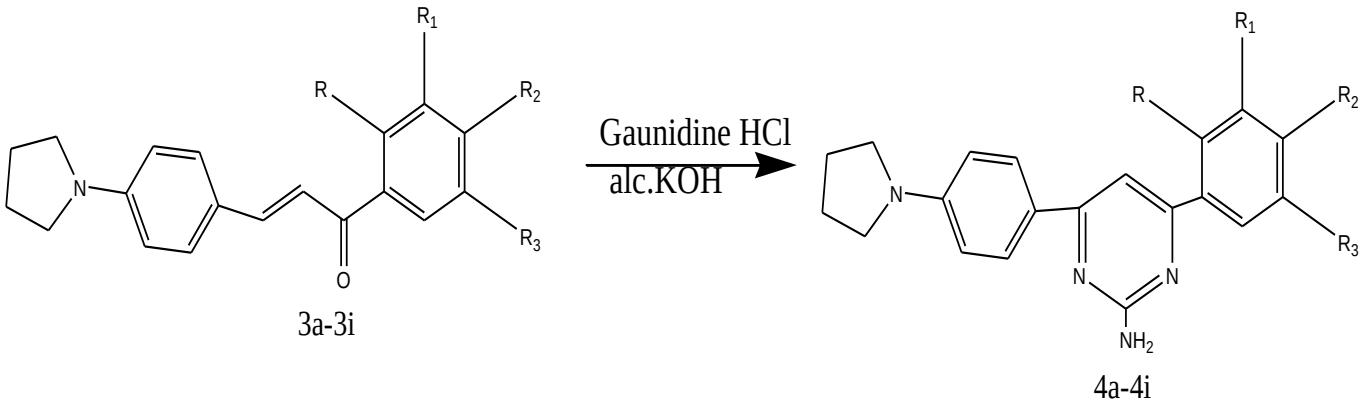
MATERIALS AND METHODS

Chemistry

The entire chemicals were purchased from Sigma-Aldrich, used without further purification. The melting points were recorded by open capillary method and are uncorrected. ^{1}H-NMR spectra were recorded on Mercury Plus Varian in DMSO-d_6 at 400 MHz using Tetramethylsilane (TMS) as an internal standard. Mass spectra were recorded on Micromass Quattro II using electronspray ionization technique. The progress of reaction was monitored by Thin Layer Chromatography (TLC) (silica, 80:20 hexane/ethyl acetate).



Scheme 1: Synthesis of (E) -1-aryl-3-(4-(pyrrolidin-1-yl)phenyl)prop-2-en-1-one (3a-3i)



Scheme 2: Synthesis of 4-(aryl)-6-(4-(pyrrolidin-1-yl) phenyl) pyrimidin-2-amine (4a-4i)

Synthesis of (E) -1-aryl-3-(4-(pyrrolidin-1-yl)phenyl)prop-2-en-1-one (3a-3i)

4-(pyrrolidin-1-yl)benzaldehyde (0.02 mol) and 4-methoxy acetophenone(0.02 mol) was taken in RB containing 50 ml ethanol. To this reaction mixture aqueous ethanolic KOH (0.04 mol) was added. The reaction mixture was stirred for 18-22 h. After completion of reaction, monitored by TLC, poured over crushed ice and solution was made acidic with 2 N HCl. The resultant crude product was filtered, washed with water and recrystallized from ethanol to afford 3a. The product 3b-3i was prepared by similar procedure (Scheme 1).

^{1}H-NMR (3a): ($CDCl_3$, δ ppm): 13.27, (s, 1H, OH), 7.96- 7.92 (m, 2H, ArH), 7.59 (d, J=8.8 Hz, 2H, ArH), 7.49-7.44 (m, 2H), 7.02 (d, J=8.4 Hz, 1H, ArH), 6.93 (t, J=8.0 Hz, 1H, ArH), 6.58 (d, J=8.8 Hz, 2H, ArH), 3.40 (m, 4H, pyrrolidine N-CH_2), 2.06 (m, 4H, Pyrrolidine CH_2); Mass (m/z) (3a): 294 (M+1); IR (3a): (cm^{-1}): 3400 (-OH), 1600 (-C=O).

^{1}H-NMR (3b): (DMSO d_6, δ ppm): 13.25 (s, 1H, -OH), 8.02 (1H, Ar-H), 7.96 (d, 1H, J=15.2 Hz, -CH=), 7.61-7.52 (3H, Ar-H), 7.34 (d, 1H, J=15.2 Hz, -CH=), 6.93-6.58 (3H, Ar-H), 3.53-3.33 (m, 4H, Pyrrolidine N-CH_2), 2.09-2.02 (m, 4H, Pyrrolidine CH_2); Mass (m/z) (3b): 374, 372; IR (3b): (cm^{-1}): 3430 (-OH), 16030 (-C=O) (Table 1).

Synthesis of 4-(aryl)-6-(4-(pyrrolidin-1-yl) phenyl) pyrimidin-2-amine (4a-4i)

To a solution of (E)-1-(4-methoxyphenyl)-3-(4-(pyrrolidin-1-yl)phenyl)prop-2-en-1-one (7a) (0.005 mol) in 10 ml ethanol, guanidine hydrochloride (0.005 mol) was added. To this reaction mixture alcoholic KOH (0.010 mol) was added. The resulting solution was refluxed for 7 h, after completion of reaction, monitored by TLC (Hexane: Ethyl acetate) (80:20), the reaction mixture was poured over crushed ice, the crude product was filtered and recrystallized from ethanol to give 9a. The compound 9b to 9i were prepared by similar procedure (Scheme 2).

^{1}H-NMR (4i): (DMSO-d_6, δ ppm): 8.25-8.05 (m, 4H, Ar-H), 7.44 (s, 1H, Ar-H), 7.03-6.51 (m, 4H, Ar-H), 5.51 (s, 2H, NH_2), 3.83 (s, 3H, OCH_3), 3.36-3.29 (m, 4H, Pyrrolidine N-CH_2), 2.09-1.91 (m, 4H, Pyrrolidine CH_2); Mass (m/z) (4i): 347 (M+1); IR (4i): (cm^{-1}): 3440 (NH_2), 1600 (C=N), 1520 (C=C) (Table 1).

Table 1. Physical data of compounds

Compound	R	R_1	R_2	R_3	Yield %	Melting point (°C)
3a	OH	H	H	H	68	108-110
3b	OH	H	H	Br	64	133-134
3c	OH	H	H	Cl	65	118-120
3d	OH	H	CH_3	Cl	67	122-124
3e	OH	Cl	H	Cl	66	102-103
3f	OH	H	H	CH_3	65	130-132
3g	H	H	Cl	H	70	125-127
3h	H	H	Br	H	62	109-110
3i	H	H	OCH_3	H	60	110-112
4a	OH	H	H	H	49	141-143
4b	OH	H	H	Br	45	145-147
4c	OH	H	H	Cl	45	155-157
4d	OH	H	CH_3	Cl	46	160-162
4e	OH	Cl	H	Cl	50	168-170
4f	OH	H	H	CH_3	40	177-178
4g	H	H	Cl	H	44	158-160
4h	H	H	Br	H	52	130-131
4i	H	H	OCH_3	H	48	138-140

RESULTS AND DISCUSSION

Chemistry

Compound 1 was prepared by reacting 4-Fluoro benzaldehyde with pyrrolidine in presence of K_2CO_3 using DMF as solvent. The resultant aldehyde [4-(pyrrolidin-1-yl)benzaldehyde] was condensed with various acetophenone to give 3a-3i. The chalcone 3a-3i was cyclized with guanidine hydrochloride in presence of KOH to give aminopyridines 4a-4i.

The structure of synthesized compounds was confirmed by IR, ^{1}H-NMR and Mass. The IR of compound 3a shows a characteristic band at 3400 cm^{-1} and 1600 cm^{-1} due to –OH and C=O group, the IR spectra of compound 4i shows characteristic band at 3440 cm^{-1} indicate presence of primary amine. The mass spectra of 3a and 4i show M+1 peak at 294 and 347 respectively. The ^{1}H-NMR spectra of 3b shows doublet at δ=7.964 ppm and δ=7.342 ppm confirm the presence of –CO-CH=CH- group. The ^{1}H-NMR of 4i shows singlet of $–NH_2$ at δ=5.51 ppm. The cluster of aromatic and aliphatic region also confirms the structure of synthesized compounds.

Antimicrobial activity

The disc diffusion method was used to study the antibacterial and antifungal activity of compounds 4a-4i. The synthesized compounds were screened for antimicrobial activity against *Pseudomonas aeruginosa* (ATCC27853), *Staphylococcus aureus* (ATCC 25923), *Escherichia coli* (ATCC 25922) and *Candida albicans.* DMSO was used as a solvent while gentamicin and nastatine were used as standard. Solution of 10 µg/ml was prepared in DMSO, Whatman filter paper 41 was used to prepared disc of 6 mm diameter. 10 µl of solution is loaded on the disc, the petri dishes was incubated for 24 h at 32°C. The zone of inhibition was measured in mm to represent the bioactivity.

The compound 4c and 4h does not show zone of inhibition against all species, while only 4f shows moderate activity against *C. albicans*. 4d shows activity against *P. aeruginosa* and 4a shows activity against all bacterial species. The results are represented in Table 2.

Table 2: Antibacterial and antifungal activities of 4-(aryl)-6-(4-(pyrrolidin-1-yl)phenyl)pyrimidin-2-amine (9a-9i)

Compound	*Pseudomonas aeruginosa* (ATCC27853)	*Staphylococcus aureus* (ATCC25923)	*Escherichia coli* (ATCC25922)	*Candida albicans*
4a	11 mm	13 mm	13 mm	--
4b	--	12 mm	14 mm	--
4c	--	--	--	--
4d	12 mm	--	--	--
4e	10 mm	10 mm	--	--
4f	--	--	--	10 mm
4g	18 mm	--	12 mm	--
4h	--	--	--	--
4i	10 mm	--	11 mm	--
Gentamicin	24 mm	21 mm	27 mm	--
Nystatin	--	--	--	23 mm

--: No inhibition

CONCLUSION

Compound 4c and 4h does not shows any activity, while compund 4f is active against *C. albicans*. 4a shows activity against all bacteria. The other synthesised compound shows moderate to low activity.

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