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DESIGN, SYNTHESIS AND MICROBIAL ACTIVITY OF SOME NOVEL 4,6-DIPHENYL-2-AMINE PYRIMIDINE DERIVATIVES

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ABSTRACT:
A series of some newer 2-aminepyrimidine derivatives were synthesized viareacting betweensubstituted acetophenones **(1a-g)**with 6-methoxybenzaldehyde **(2)**in ethanolic solution of sodium hydroxide to yield substituted 3-(6-methoxy naphthalen-1-yl)-1-phenylprop-2-en-1-one **(3a-g)** (chalcones), these chalcones were further reacted with guanidinium carbonate in the presence of DMF, which led to the formation of substituted 4-(6-methoxynaphthalen-1-yl)-6-phenylpyrimidin-2-amine derivatives **(4a-g).** The structures of newly synthesized compounds were confirmed by IR, ^{1}H NMR, mass and elemental analysis. These pharmacological active molecule 2-aminepyrimidine derivatives were evaluated *in vitro* for Antibacterial activity against *Escherichia coli*, *Pseudomonas aeruginosa*, *Bacillus subtilis,* and *Staphylococcus aureus*and Antifungal activity against *Asp. Niger, Asp. Flavus, Pen. Chrysogenum, FusariumMoneliforme.* The biological activity results revealed that the synthesized derivative possesses promising to moderate antibacterial and antifungal activity

KEYWORDS: Chalcones, 2-aminepyrimidine derivatives, antibacterial, antifungal activity.

INRTODUCTION

Infectious diseases caused by bacteria, fungi and other parasite are major threat for health of mankind. With availability of number of drugs in market, the problem is not solved, because of longer duration of therapy, different unwanted side effect of drugs and high cost factor; there is need of new chemical entity having more potency and fewer side effects. To tackle the current situation, scientific community all over the world is trying to discover the new affordable and more active compounds which may cross all barriers. Nowadays, it is possible to make modifications of active chemical structures, in order to synthesize compounds with improved therapeutic activity and to reduced toxicity and easily affordable.

In the present days the heterocyclic ring system continues attract considerable interest due to a wide variety of biological activities like, antibacterial, antifungal, anti-tubercular, anticancer, analgesic, anti-inflammatory, anticonvulsant antidepressant and anti-arrhythmic activities [I, II]. Also in the family of heterocyclic compounds nitrogen containing heterocycles are an important class of compounds in the medicinal chemistry and also contributed to the society from biological and industrial point which helps to understand life processes [III].

Pyrimidines are biologically very important heterocycles and represent by far the most ubiquitous members of the diazine family with uracil and thymine being constituents of ribonucleic acid (RNA) and deoxyribonucleic acid (DNA) and with cytosine. During the last two decades several pyrimidine derivatives have been developed which are found to have wide clinical and pharmacological applications[IV].

Pyrimidine derivatives generally studied are 2-hydroxy pyrimidine, 2-mercapto pyrimidine and 2-amino pyrimidine [V], Pyrimidine heterocycles possessing amino group has a unique place in medicinal chemistry [VI]. Some of amino pyrimidine derivatives have been found to possess antiulcer [VII], anti-inflammatory [VIII], anticancer [IX] activity. Drugs which are included 2-amino pyrimidine are antifolates (2-Amino-4-hydroxy pyrimidines) [X] possessing antagonistic activity against folic acid and sulfa drugs (Sulfadiazine) which are sulphur containing pyrimidine derivative drugs.

A great deal of research is being carried out to synthesize new heterocyclic compounds having biological importance. The increasing interest in this field and in continuation of our ongoing study on heterocyclic compounds [XI] promoted us to synthesize some 2-amino pyrimidine derivatives.In this present study, a series of some new 2-aminepyrimidine derivatives were synthesized viareacting betweensubstituted acetophenones **(1a-g)**with 6-methoxybenzaldehyde **(2)**in ethanolic solution of sodium hydroxide to yield substituted 3-(6-methoxy naphthalen-1-yl)-1-phenylprop-2-en-1-one **(3a-g)** (chalcones), these chalcones were further reacted with guanidinium carbonate in the presence of DMF, which led to the formation of substituted 4-(6-methoxynaphthalen-1-yl)-6-phenylpyrimidin-2-amine derivatives **(4a-g)(Scheme-I).**The structures of newly synthesized compounds were confirmed by IR, ^{1}H NMR, mass and elemental analysis. All the synthesized compounds were evaluated for antimicrobial activity.

MATERIALS AND METHODS

Experimental

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded using Perkin –Elmer spectrometer.^{1}H NMR spectra were recorded on Brucker Advance II 400 spectrometer in DMSO by using TMS as internal standard. Thin layer chromatography was performed with E. Merk precoated TLC plates, silica gel $60F_{254}$ with thickness of 0.25mm and spots were visualized by irradiation with ultraviolet light (254 nm). Physical constants and analytical data of all the compoundsreported in this paper.

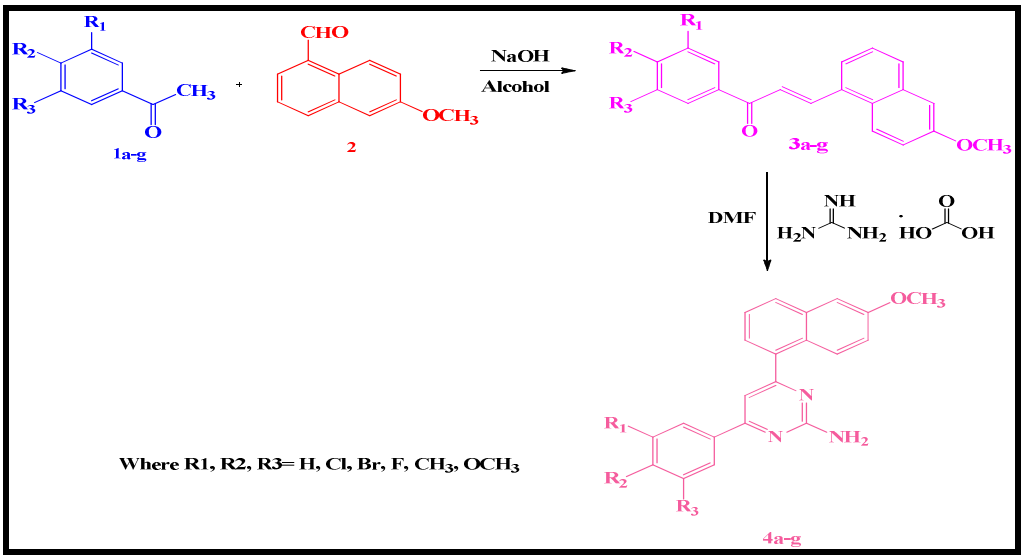
General procedure for the synthesis of 1-(substituted phenyl)-3-(6-methoxynaphthalen-1-yl)prop-2-en-1-one(Chalcone) (3a-g).

A mixture of substituted acetophenone**(1a-g)**(0.01mol) and6-methoxy-1-naphthaldehyde (**2)**(0.01mol) was stirred in ethanol (30 ml) and thensodium hydroxide solution (15 ml, 0.02 mol) was added to it. The reaction mixture was kept overnight at room temperature and then it was poured on crushed ice and acidified with dilute hydrochloric acid. The Chalcone i.e. [1-(substituted phenyl)-3-(6-methoxynaphthalen-1-yl)prop-2-en-1-one] **(3a-g)** precipitate out as solid. Then it was filtered, dried and purified by crystallization from acetic acid. Percentage yield and physical constants were recorded.

General procedure for the synthesis of 4-(substituted phenyl)-6-(6-methoxynaphthalen-1-yl)pyrimidin-2-amine (4a-g)

To a mixture of Chalcone i.e. [1-(substituted phenyl)-3-(6-methoxynaphthalen-1-yl)prop-2-en-1-one] **(3d)** and guanidinium carbonate (1:1 molar ratio) in DMF was refluxedfor 3 hours. The reaction mixture was poured in cold water. The solid thus separated was filtered, washed with water and dried at 80^{o}C. The product was crystallized from ethanol to afford light yellow crystals. Percentage yield and physical constants were recorded

Scheme-I



RESULT AND DISCUSSION

Considering the synthetic and biological significance of pyrimidin-2-amine, chemists have directed more efforts to synthesized new 4,6-diphenylpyrimidin-2-amine, hopping to obtained new molecule with pharmacological significance. Therefore in the present work it was thought worthwhile to construct new 4,6-diphenylpyrimidin-2-amine.

The structures of the synthesized compounds (**4a-g**) were confirmed on the basis of spectral and elemental analysis.Literature survey reveals that the synthesized pharmacological active molecule i.e. substituted 4-(6-methoxynaphthalen-1-yl)-6-phenylpyrimidin-2-amine derivatives **(4a-g)** was not reported. The antimicrobial results revealed that the synthesized derivative possesses promising to moderate antibacterial and antifungal activity which helpful to modern chemist for development of pyrimidine molecule.

Depend upon substitution on ketone it give good yield. It was found that electron withdrawing groups substitution gives higher yield, while electron donating gives lesser yield.

Spectral data of compounds

(4a): 4-(6-methoxynaphthalen-1-yl)-6-phenylpyrimidin-2-amine

Yield 85%; m.p. 145^{o}C: Elemental analysis Cal. for $C_{21}H_{17}N_3O$; C, 77.04; H, 5.23; found: C, 76.94; H, 5.16 %; IR (KBr pellets Cm^{-1}): 3440 (N-H), 1604.66 (C=N), 1483.37 (C=N), 1190 (-OCH_3); ^{1}H NMR (DMSO, 400 MHz) δ 7.30-8.65 (m, 12H, Ar-H), 6.65 (s, 2H, -NH_2), 3.90 (s, 3H, -OCH_3); Mass (m/z): 328.22 (M+1).

(4b): 4-(4-chlorophenyl)-6-(6-methoxynaphthalen-1-yl)pyrimidin-2-amine

Yield 90%; m.p. 169^{o}C: Elemental analysis Cal. for $C_{21}H_{16}ClN_3O$; C, 69.71; H, 4.46;N, 11.61;found: C, 69.64; H, 4.36; N, 11.50; %; IR (KBr pellets Cm^{-1}):3430 (N-H), 1602.66 (C=N), 1473.37 (C=N), 1180 (-OCH_3); ^{1}H NMR (DMSO, 400 MHz) δ 7.25-8.55 (m, 11H, Ar-H), 6.55 (s, 2H, -NH_2),3.80 (s, 3H, -OCH_3); Mass (m/z): 362.12, 363.16 (M+1).

(4c): 4-(4-bromophenyl)-6-(6-methoxynaphthalen-1-yl)pyrimidin-2-amine

Yield 87%; m.p. 175^{o}C: Elemental analysis Cal. for $C_{21}H_{16}BrN_3O$; C, 62.08; H, 3.97; N, 10.34; found: C, 62.00; H, 9.90; N, 10.30; %;IR (KBr pellets Cm^{-1}): 3432 (N-H), 1600.23 (C=N), 1470.32 (C=N), 1185 (-OCH_3); ^{1}H NMR (DMSO, 400 MHz) δ 7.35-8.56 (m, 11H, Ar-H), 6.56 (s, 2H, -NH_2), 3.85 (s, 3H, -OCH_3); Mass (m/z): 405.12, 406.23, 407.11 (M+1).

(4d): 4-(4-fluorophenyl)-6-(6-methoxynaphthalen-1-yl)pyrimidin-2-amine
Yield 92%; m.p. 140°C: Elemental analysis Anal. Cal. for $C_{21}H_{16}FN_3O$; C, 73.03; H, 4.67;N, 12.17;found: C, 72.94; H, 4.60;N, 12.10; %; IR (KBr pellets Cm^{-1}): 3443 (N-H), 1600.22 (C=N), 1483.37 (C=N), 1194 (-OCH_3); ^{1}H NMR (DMSO, 400 MHz)δ 7.20-8.75 (m, 11H, Ar-H), 6.69 (s, 2H, -NH_2),3.94 (s, 3H, -OCH_3); Mass (m/z):346.25, 347.12 (M+1).
(4e): 4**-(6-methoxynaphthalen-1-yl)-6--(4-methyphenyl)pyrimidin-2-amine**
Yield 90%; m.p. 150°C: Elemental analysis Anal. Cal. for $C_{22}H_{19}N_3O$; C, 77.40; H, 5.61; N, 12.31; found: C, 77.34; H, 5.50;N, 12.20; %; IR (KBr pellets Cm^{-1}):3434 (N-H), 1610.32 (C=N), 1480.20 (C=N), 1190 (-OCH_3); ^{1}H NMR (DMSO, 400 MHz) δ 7.20-8.72 (m, 11H, Ar-H), 6.63 (s, 2H, -NH_2), 3.85 (s, 3H, -OCH_3), 2.33 (s, 3H, Ar-CH_3); Mass (m/z): 342.16 (M+1).
(4f): 4-(6-methoxynaphthalen-1-yl)-6-(4-methoxyphenyl)pyrimidin-2-amine
Yield 80%; m.p. 170 °C: Elemental analysis Anal. Cal. for $C_{22}H_{19}N_3O_2$; C, 73.93; H, 5.36; N, 11.76; found: C, 73.84; H, 5.30;N, 11.70; %; IR (KBr pellets Cm^{-1}): 3440 (N-H), 1600.22 (C=N), 1485.27 (C=N), 1190 (-OCH_3); ^{1}H NMR (DMSO, 400 MHz) δ 7.22-8.70 (m, 11H, Ar-H), 6.65 (s, 2H, -NH_2), 3.90 (s, 6H, 2 x -OCH_3); Mass (m/z): 358.23 (M+1).
(4g): 4-(2,4-dichlorophenyl)-6-(6-methoxynaphthalen-1-yl)pyrimidin-2-amine
Yield 60%; m.p. 135°C: Elemental analysis Anal. Cal. for $C_{21}H_{15}Cl_2N_3O$; C, 63.65; H, 3.82; N, 10.60; found: C, 63.54; H, 3.76;N, 10.57; %; IR (KBr pellets Cm^{-1}): 3440 (N-H), 1600.22 (C=N), 1480.12 (C=N), 1175 (-OCH_3); ^{1}H NMR (DMSO, 400 MHz)δ 7.18-8.60 (m, 10H, Ar-H), 6.60 (s, 2H, -NH_2), 3.80 (s, 3H, -OCH_3); Mass (m/z):397.12 (M+1).

Biological activity:
The newly synthesized compounds were screened for their antibacterial activity against*E.coli, Salmonella typhi, Staphylococcusaureus* and *Bacillus subtilis* by disc diffusion method[XII], using penicillin as standard and antifungal activity against *Aspergillus niger, Aspergillus flavus penicillium chrysogenum, Fusarium moneliforme,* by poison plate method[XIII]using Griseofulvin as reference standard and DMSO as control solvent.The investigation of antibacterial screening results indicates that few of the compounds shows significant property and some of the compounds are moderately active. The investigation of antifungal activity data revealed that some compounds have promising and some showed no antifungal activity. The results are shown in **Table 1 and 2** respectively.

TABLE1-ANTIBACTERIAL SCREENING RESULTS OF THE COMPOUNDS**4(a-g).**

Sr. No.	**Entry**	Diameter of growth inhibition zone (mm)			
		E. coli	***Salmonella typhi***	***Staphylococcus aureus***	***Bacillus subtilis***
1	**4a**	09	11	12	15
2	**4b**	19	17	20	24
3	**4c**	12	14	16	20
4	**4d**	14	17	24	22
5	**4e**	13	14	10	09
6	**4f**	17	18	16	19
7	**4g**	10	13	13	16
8	**DMSO**	-ve	-ve	-ve	-ve
9	**Penicillin**	22	25	35	38
-ve no antibacterial activity					

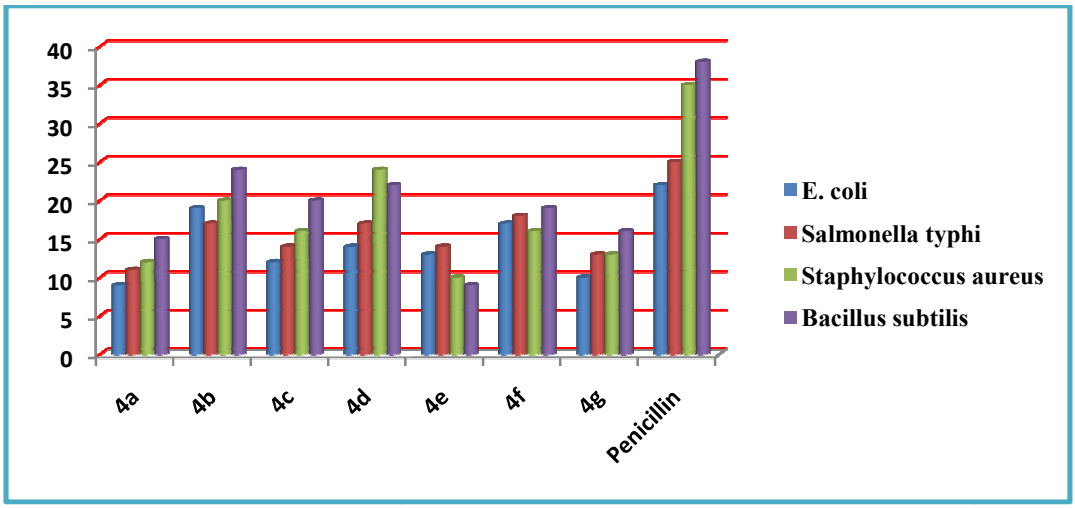


Fig-1 Flow Chart for Antibacterial screening

TABLE2-ANTIFUNGAL SCREENING RESULTS OF THE COMPOUNDS**4(a-g).**

Sr. No.	**Entry**	Diameter of growth inhibition zone (mm)			
		Asp. Niger	***Asp. flavus***	***Pen. chrysogenum***	***Fusarium Moneliforme***
1	**4a**	+ve	-ve	RG	-ve
2	**4b**	-ve	-ve	-ve	+ve
3	**4c**	-ve	-ve	RG	-ve
4	**4d**	-ve	+ve	-ve	-ve
5	**4e**	+ve	RG	+ve	-ve
6	**4f**	-ve	-ve	-ve	-ve
7	**4g**	-ve	-ve	-ve	-ve
8	**DMSO**	+ve	+ve	+ve	+ve
9	**Griseofulvin**	-ve	-ve	-ve	-ve
-ve -No growth Antifungal activity present , +ve -Growth Antifungal activity absent RG -Reduced growth					

CONCLUSION

In the above paper we have synthesized some novel 4,6-diphenyl-2-amine pyrimidine by condensing Chalcone i.e. [1-(substituted phenyl)-3-(6-methoxynaphthalen-1-yl)prop-2-en-1-one] and guanidinium carbonate (1:1 molar ratio) in DMF to obtained an pharmacological active molecule which possesses very good to moderate antibacterial and antifungal activity which helpful to modern chemist for development of pyrimidine molecule.

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CONFLICT OF INTEREST

The author(s) declare that there is no conflict of interests regarding the publication of this article.

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