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Synthesis and Antimicrobial Activity of Some Novel Heterocyclic Compounds

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Abstract: ***2-Chloro–N-{4-(4-chlorophenyl)-6-[4-{dimethylamino)phenyl]pyrimidin-2-yl}acetamide were allowed to react separately with different secondary amines in presence of alkaline medium to yield the corresponding secondary amine derivatives substituted heterocycls. The compounds obtained were identified by spectral data and screened for antimicrobial activity. The result shows that all samples are more or less active agents against various micro organisms.***

Keywords: heterocyclic substituted secondary amines derivatives, spectral data, antimicrobial activities**.**

1. Introduction

The history of heterocyclic chemistry began in the 1800's, in step with the development of organic chemistry.Heterocyclic compounds have great applicability in pharmaceutics because they have specific chemical reactivity. The majority of synthetic heterocyclic compounds have found widespread use, for example as anticancer agents, antitubercular, analeptics, analgesic, hypnotics and as pesticides, insecticides and weed killers. Various synthetic procedures have been developed and considerable diversity in the ring is achieved. Heterocyclic compounds are enormous, their chemistry is complex and synthesizing them requires great skill. Important drugs, poisons and medicines (both natural and synthetic) such as sulphathiazole [1], pyrenthrin [2], rotenmone [3], alpidem [4], zolpidem [5], fluconazole [6], strychnine [7], reserpine [8], certain of the antihistamines, the ergot alkaloids caffeine[9], cocaine[10], barbiturates[11], etc. are heterocyclic compounds.

Heterocyclic compounds played a vital role in biological processes and are wide spread as natural products. They are widely found in nature particularly in nucleic acids, plant alkaloids, anthocyanins and flavones as well as in haem and chlorophyll. Additionally some vitamins, proteins,hormones contain aromatic heterocyclic system. Synthetically produced heterocycles designed by organic chemists are used for instance as agrochemicals and pharmaceuticals and play an important role in human life. Heterocycles have enormous potential as the most promising molecules as lead structures for the design of new drugs.

2. Experimental

Step-1:

Preparation of (E)-1-[(4-Chloro phenyl)-3-(4-dimethyl amino) phenyl] prop-2-en-1-one.

Chalcones were synthesized by base catalyzed Claisen-Schmidt condensation reaction of appropriately substituted acetophenone and aldehydes by known literature method. A mixture of benzaldehyde derivatives (0.01 mol) and acetophenone derivatives (0.01mol) was dissolved in 10 ml rectified spirit in a 250ml round-bottomed flask equipped with a magnetic stirrer. Then 10ml NaOH solution (1g in 10ml H_2O) was added drop wise to the reaction mixture with vigorous stirring for 30 minutes. After vigorous stirring the reaction mixture was allow to stand for twelve hours, then neutralized by 0.1-0.2N HCl where by the precipitation occurred. On filtering off, the crude chalcones were dried in air and recrystallized by rectified spirit. M.P.:-135^{0}C, Yield:-75%. IR (KBr cm-1):1648.21(C=O), 1586.13(C=C), 1190.37, 1227.03, 1341.71(C-N), 812.07(Ar-Cl).

Step-2

Preparation of 4-(4-chlorophenyl)-6-[4-(dimethylamino) phenyl] pyrimidin-2-amine.

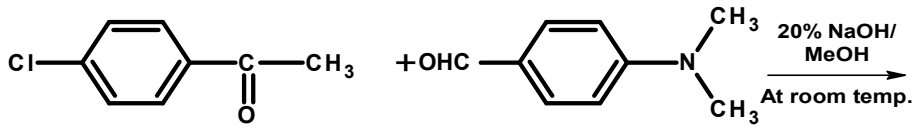
Reaction mixture of step-1 (0.01M) & Guanidine nitrate (0.015M) with Sodium methoxide in methanol was refluxed for six hours. After the completion of reaction the resultant mixture was cooled to room temperature. Separated compound was filtered, washed with water dried and crystallized from methanol to get yellow needles of the title compound. M.P.:-165^{0}C Yield:-61%. IR (KBr cm-1):3181.15, 3304.34, 3463.76(N-H), 1609.70(C=O), 1486.94(C=C), 1064.21, 1125.04, 1198.04, 1223.19(C-N), 814.47(Ar-Cl).

Step-3

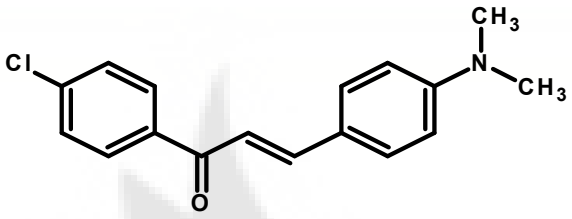
Preparation of 2-Chloro–N-{4-(4-chlorophenyl)-6-[4-{dimethylamino)phenyl] pyrimidin -2yl}acetamide.

In Benzene (30ml), chloro acetyl chloride (0.01M) and 2 drops of triethyl amine were added and the mixture was stirred in water bath. The solution of step-2 (0.01M) in benzene (28ml) was added drop wise. For cooling this solution was kept in refrigerator for 1-2 hour. Then the product was filtered and crystallized. M.P.:- 151^{0}C Yield:-60%. IR (KBr cm-1):3311.59,3434.78(N-H), 1681.12(C=O), 1541.14(C=C), 1179.83,1220.41,1353.26(C-N),814.91(Ar-Cl).

Step-1



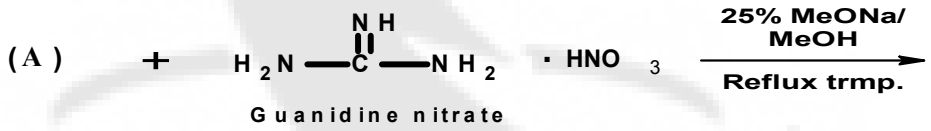
1-(4-chlorophenyl)ethanone 4-(dimethylamino)benzaldehyde



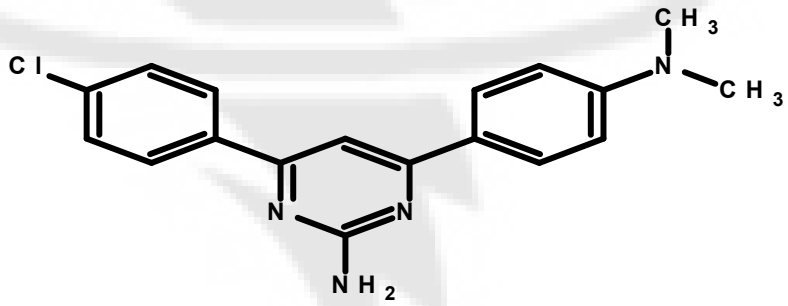
(2*E*)-1-(4-chlorophenyl)-3-[4-(dimethylamino)phenyl]prop-2-en-1-one

(A)

Step-2



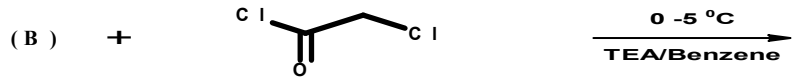
Guanidine nitrate



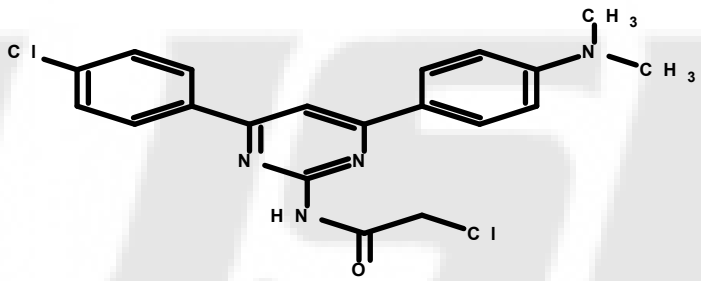
4-(4-chlorophenyl)-6-[4-(dimethylamino)phenyl]pyrimidin-2-amine

(B)

Step-3



Chloroacetyl chloride



2-chloro-*N*-{4-(4-chlorophenyl)-6-[4-(dimethylamino)phenyl]pyrimidin-2-yl}acetamide

(C)

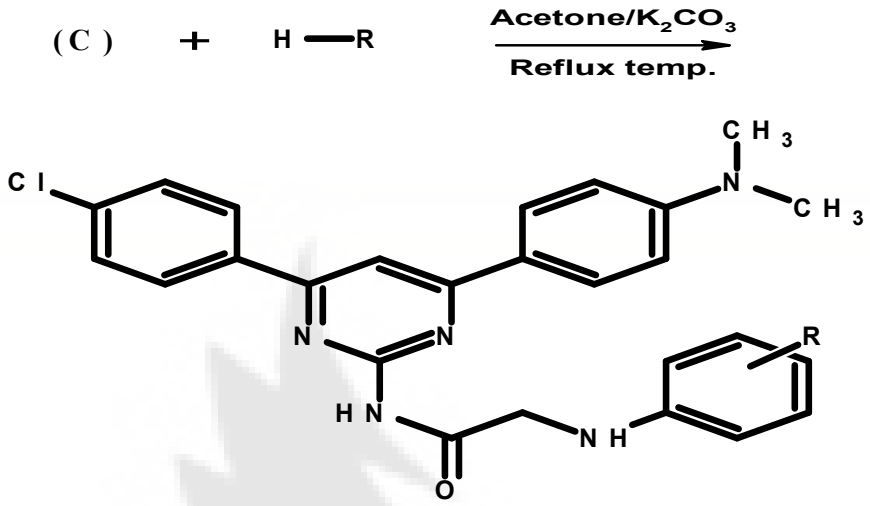
Step-4

Preparation of Secondary amine derivatives of 2-Chloro–N-{4-(4-chlorophenyl)-6-[4-{dimethylamino)phenyl]pyrimidin-2yl} acetamide.

Secondary amines were dissolved in 25ml acetone and prepare 0.0025M solution. 3.4 gm of K_2CO_3 was added. The reaction mixture was refluxed on water bath. A dropping funnel was fitted to the R.B.F. and in the dropping funnel a solution of step-3 (1.1 gm) in 20ml Chloroform or Acetone was taken. A slow addition of this solution was done. The reaction mixture was refluxed in water bath at 80^0c for 4-hours. After completion of the reaction, reaction mixture was kept at room temperature. After filtration it was washed with water and recrystalized with ethanol.

Where R = -N $(C_2H_5)_2$, -N $(C_6H_5)_2$, -N $(CH_3)_2$, -N (C_3H_3N), -N (C_8H_6), - N (C_8H_{10}), -N (C_7H_8), -N (C_4H_8), -N (C_4H_8O), 2J: -N (C_4H_6O)

Step-4



2-aryl amine-*N*-{4-(4-chlorophenyl)-6-[4-(dimethylamino)phenyl]pyrimidin-2-yl}acetamido

IR Spectral data of compound 2: 3494.81 Cm^{-1} (-NH-stretching in 2^0 amine), 3328.86 Cm^{-1} (-NH-amine), 3198.80 Cm^{-1} (Ar-H aromatic stretching), 2905.79 Cm^{-1} (-CH stretching alkane), 1598.35 Cm^{-1}(-C=C- aromatic ring), 1531.45 Cm^{-1} (-C=C- aromatic ring), 1439.51 Cm^{-1} (-CH-alkane, bending,-CH_3),1366.47 Cm^{-1} (-CH-alkane, bending, dimethyl),1201.91 Cm^{-1} (-CN- stretching, Aliphatic), 1171.89 Cm^{-1} (-CN- stretching, Aliphatic), 989.41 Cm^{-1} (-CH- bending), 848.70 Cm^{-1} (Pera substitution), 813.58 Cm^{-1} (-C-Cl stretching).

IR Spectral data of compound 5: 3324.78Cm^{-1} (-NH-stretchingin 2^0 amine), 3188.40Cm^{-1}(-NH-amine), 1647.17Cm^{-1}(>C=Ostretching), 1607.18 Cm^{-1} (Aromatic ring),1531.84 Cm^{-1}(-C=C- aromatic ring),1361.94 Cm^{-1}(-CN-aromatic, Secondary amine),1334.33 Cm^{-1}(-CN- aromatic, Secondary amine),1245.48 Cm^{-1}(-CN- amine),988.97 Cm^{-1}(-CH- bending),949.61 Cm^{-1}(-CH- bending),939.28 Cm^{-1} (-CH- bending),895.80 Cm^{-1}(Pera substitution),807.50 Cm^{-1}(-C-Cl stretching).

H ^{1} N.M.R. (CDCl3) spectral data of compound 4: 3.03 δ ppm [s,1H, -HC-Cl],5.25 δ ppm [s,1H, -HN], 9.95 δ ppm [s, 1H -NH],2.88 δ ppm [s, 1H, –CH-C=O], 6.73 to 7.99 [m,10h, Ar-H].

H ^{1} N.M.R. (CDCl3) spectral data of compound 9: 3.02 δ ppm [s,1H, -HC-Cl], 5.26 δ ppm [s,1H, -HN],7.25 to 7.99 δ ppm [m,10H, Ar-H].

3. Antibacterial activity

The antibacterial activity of all the synthesized compounds (1-10) were examined against different Gram-positive (*Bacillus cerus* and *Staphylococcus aureus)* and Gram-negative (*Escherichia coli*) organisms & anti fungal activity against (*Candida albicans*) by measuring zone of inhibition. Preparation of nutrient broth, subculture, base layer medium, agar medium and peptone water were done as per the standard procedure. Discs measuring 6.25mm in diameter were punched from Whatman No.1 filter paper. Stock solutions of synthesized compounds diluted in DMF. The antibacterial activity was performed by agar diffusion method [12, 13] at the concentration level of 50mcg/ml. Streptomycin was used as standard drug at a concentration of 50 mcg/ml. The results of the antibacterial activity are shown in Table 2.

Table 1: Physical Data of the synthesized compound

Comp. No.	R	Molecular Formula	M.P. ^0C	Yield %	Elemental Analysis	% C	% H	% N
1	$-N(CH_3)_2$	$C_{22}H_{24}ON_5Cl$	178	65	R	64.39	5.85	17.07
					F	64.34	5.8	17
2	$-N(C_2H_5)_2$	$C_{24}H_{28}ON_5Cl$	138	60	R	65.75	6.39	15.98
					F	65.72	6.35	15.95
3	$-N(C_6H_5)_2$	$C_{32}H_{28}ON_5Cl$	58	70	R	71.91	5.24	13.1
					F	71.85	5.2	13.03
4	$-N(C_3H_3N)$	$C_{23}H_{21}ON_6Cl$	144	65	R	63.74	4.84	19.39
					F	63.7	4.8	19.35
5	$-N(C_8H_6)$	$C_{28}H_{24}ON_5Cl$	138	64	R	69.71	4.98	14.52
					F	69.86	4.92	14.45
6	$-N(C_7H_8)$	$C_{27}H_{26}ON_5Cl$	40	60	R	68.64	5.5	14.83
					F	68.6	5.45	14.8
7	$-N(C_8H_{10})$	$C_{28}H_{28}ON_5Cl$	85	71	R	69.13	5.76	14.4
					F	69.1	5.7	14.35
8	$-N(C_4H_8)$	$C_{24}H_{26}ON_5Cl$	40	55	R	66.05	5.96	16.05
					F	66	5.92	16.02
9	$-N(C_4H_8O)$	$C_{24}H_{26}O_2N_5Cl$	160	72	R	63.72	5.75	15.49
					F	63.67	5.71	15.41
10	$-N(C_4H_6O)$	$C_{24}H_{24}O_2N_5Cl$	116	52	R	64	5.33	15.55
					F	63.92	5.29	15.51

Table 2: Antimicrobial data of synthesized compounds

Compd. No.	ANTIBACTERIAL ACTIVITY INHIBITION (50mcg/ml) R	% Inhibition in E.coli	% Inhibition in B.cerus	% Inhibition in S.aureus	% Inhibition in Candida al.
1	$-N(CH_3)_2$	-	-	-	-
2	$-N(C_2H_5)_2$	-	-	Moderately sensitive	-
3	$-N(C_6H_5)_2$	-	-	16	15
4	$-N(C_3H_3N)$	-	Moderately sensitive	-	-
5	$-N(C_8H_6)$	-	-	-	-
6	$-N(C_7H_8)$	-	17	19	16
7	$-N(C_8H_{10})$	-	18	18	15
8	$-N(C_4H_8)$	-	16	18	15
9	$-N(C_4H_8O)$	-	-	-	-
10	$-N(C_4H_6O)$	-	Moderately sensitive	Moderately sensitive	-

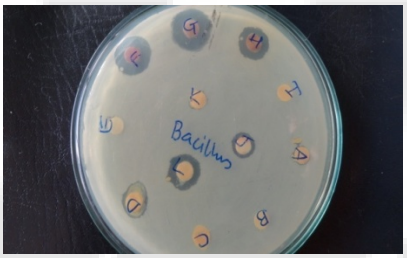


Photo 1: *B.cerus*

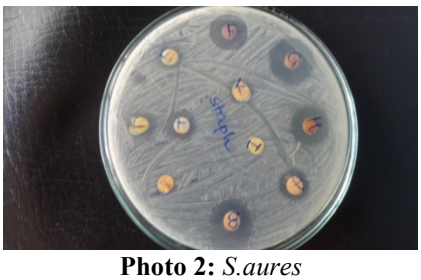


Photo 2: *S.aures*

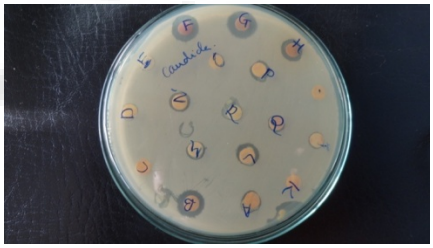


Photo 3: C.albicans

4. Results and Discussion

All the synthesized compounds (1-10) were purified by successive recrystallization using ethanol. The structures of

the synthesized compounds were determined on the basis of their FTIR data. The IR spectra of the synthesized compounds showed the presence of υC=O stretching bands at 1645cm-1 and υC=C stretching frequencies at 1527.88-1562.82 cm-1 In accordance with the data obtained from antimicrobial activity, all the synthesized Nitrogen containing chalcones have shown mild to good activity against the tested microbes. Among these Nitrogen containing chalcones, compound bearing Pyrimidine ring has shown good activity against all the tested bacteria. Standard drug was used for comparison of the synthesised compound were streptomycin & Neomycin.

5. Antimicrobial activity

In this series out of ten compounds one compounds (6 & 10) was screened against $H_{37}Rv$ strain of M. tuberculosis. Other remaining compounds of this series were inactive at 1000µg/ml against **$H_{37}Rv$** strain of ***M. tuberculosis***.

6. Acknowledgement

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