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Synthesis and Antimicrobial Activity of some Novel Primary Amines Containing 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 primary amines in presence of alkaline medium to yield the corresponding substituted heterocyclic compounds. 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 amines, experimental, spectral data, and antimicrobial activities.

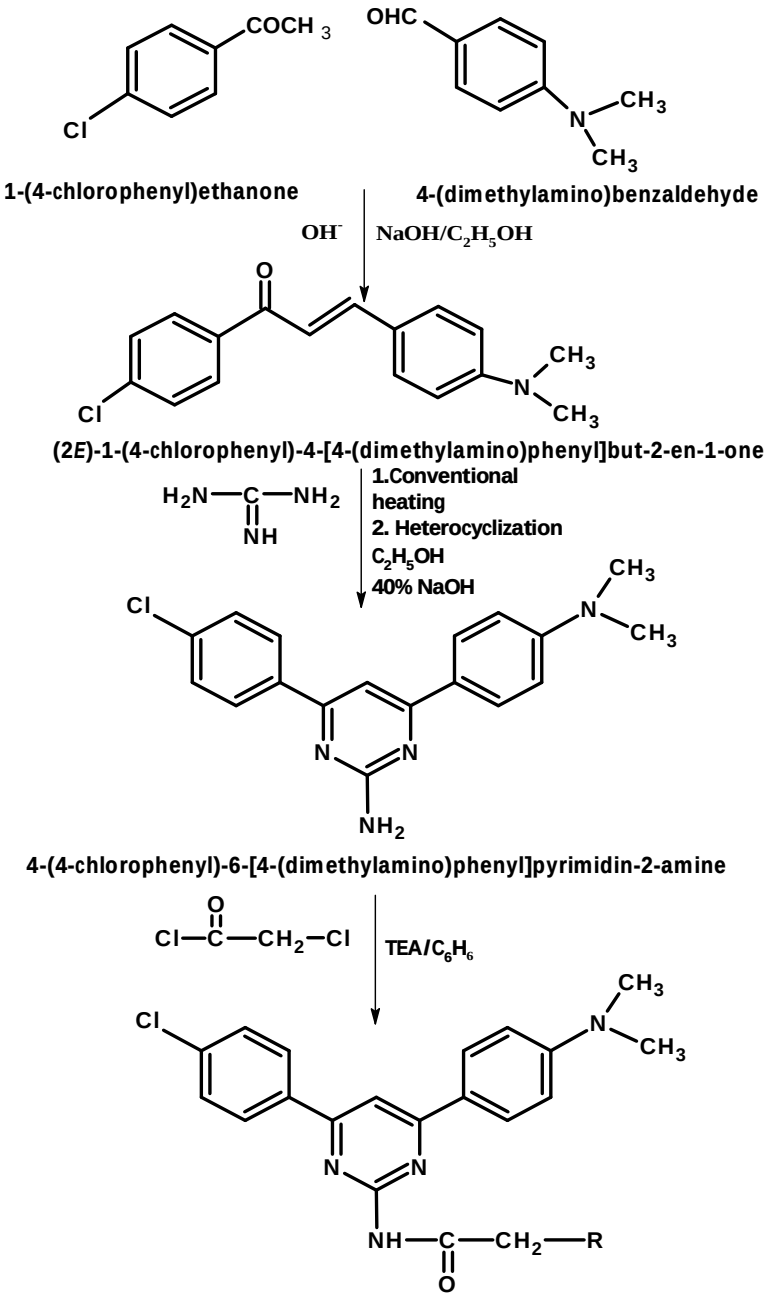
1. Introduction

The heterocyclic compounds are essential to living organisms. They play a vital role in the metabolism of all the living cells. Among large number of heterocycles found in nature, nitrogen heterocycles shows very good activity against microorganism. sulphur[1] or oxygen containing nitrogen based heterocycles are most abundant.

Yearly we found hundred of synthesized organic compound based on biological mechanism or theoretical consideration and it useful for mankind. To overcome from disease we have to continue a search. The result we find clear advantages over the existing drugs. For example good biological activity, lower toxicity, lower production cost etc. This search of heterocyclic drugs results chlordiazepoxide (tranquillizer)[2,3], imipromine (antidepressant)[4],guanethidine (antihypertensive)[5], indapamide (diuretic and antihypertensive)[6,7], are heterocyclic. Many non-steroidal drugs such as ketoprofen [8], fenoprofen and flurbiprofen [9] are also heterocyclic.Many antibiotic including penicillin [10], cephalosporin [11], norfloxacin [12], streptomycin [13, 14] etc., are well known heterocyclic compounds congaing good biological activity. We

need search of chemical inhibitors of biological function so day by day search of the biological inhibitors is increasing. We have done effort for these and result nitrogen based heterocyclic compound which containing primary amines is here.

Scheme:-



Where R = H, 2-CH_3, 4- CH_3, 2-NO_2, 3- NO_2, 4- NO_2, 4-Cl, 4-Br, 4-OCH_3, 4-$NHCOCH_3$

Experimental:

Step-1:

Preparation of (E)-1-[(4-Chloro phenyl)-3-(4-dimethyl amino) phenyl] prop-2-en-1-one.[15]

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-(dimethyl amino) 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-4

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

Primary 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 drop wise addition of this solution was done. The reaction mixture refluxed in water bath at 80^{0}c for 4-hours. After

complete the reaction cool reaction mixture at room temperature. Filter it & washed with water and recrystalized with ethanol**.**

IR Spectral data of compound 2: I.R.(KBr): 3205.75 Cm^{-1}(-NH- amine, amide), 2842.96 Cm^{-1}(-CH- alkane stretching),1645.92 Cm^{-1}(>C=O stretching),1606.17 Cm^{-1}(Amine salt),1529.39 Cm^{-1}(Amine salt &Aromatic ring),1362.69 Cm^{-1}(-CN- amine, amide),1200.84 Cm^{-1} (-CN- amine, amide),1090.68 Cm^{-1}(>C-C<alkane cis), 806.71 Cm^{-1}(-C-Cl stretching, para substitution), 569.09 Cm^{-1} (Halide stretching).

IR Spectral data of compound 4: I.R. (KBr): 3333.3Cm^{-1} (-NH- stretching amine, amide), 3288.40 Cm^{-1}(-NH-stretching), 2920.28 Cm^{-1}(-CH- alkane stretching),1606.17 Cm^{-1}(Amine salt),1602.56Cm^{-1}(-C=C-aromatic ring),1562.82 Cm^{-1}(C-NO_2, Nitro aromatic compound),1527.88 Cm^{-1}(C-NO_2,Nitro aromatic compound),1439.97 Cm^{-1}(-CH- alkane stretching),1364.45 Cm^{-1}(Me_2 –CH- bending),1201.51 Cm^{-1}(-CN amine),944.98 Cm^{-1}(>C-H alkane bending),811.70 Cm^{-1}(C-Cl stretching)

H ^{1} N.M.R. (CDCl3) spectral data of compound 4:1.34 δ ppm [d,6H, -N-(CH_3)$_2$],3.10 δ ppm [s,1H, -HC-Cl], 1.30 δ ppm [s, 1H Ar-NH],8.09 δ ppm [s, 1H, –NH], 2.17 [s,1H, -CH-C=O],6.11 to 6.82 [m,10h, Ar-H].

H ^{1} N.M.R. (CDCl3) spectral data of compound 9:3.37 δ ppm [s,3H, Ar-OCH_3], 3.03 δ ppm [s,1H, -HC-Cl], 8.00 δ ppm [s,1H, -NH], 6.61 to 6.74 δ ppm [m,10H, Ar-H].

Table 1: Physical Data of the Synthesized Compound.

Co. No.	R	Molecular Formula	M.P .^{0}C	Yield %	Elemental Analysis			
						% C	% H	% N
1	H	$C_{26}H_{26}ON_5Cl$	151	55	R F	67.90 67.79	5.66 5.60	15.23 15.12
2	2-CH_3	$C_{27}H_{28}ON_5Cl$	142	60	R F	68.43 68.40	5.91 5.85	14.78 14.70
3	4-CH_3	$C_{27}H_{28}ON_5Cl$	182	70	R F	68.43 68.40	5.91 5.85	14.78 14.70
4	2-NO_2	$C_{26}H_{26}O_3N_6Cl$	80	65	R F	61.72 61.70	5.54 5.50	16.62 16.55
5	3- NO_2	$C_{26}H_{26}O_3N_6Cl$	78	67	R F	61.72 61.70	5.54 5.50	16.62 16.55
6	4- NO_2	$C_{26}H_{26}O_3N_6Cl$	140	65	R F	61.72 61.70	5.54 5.50	16.62 16.55
7	4-Cl	$C_{26}H_{25}ON_5Cl_2$	92	70	R F	62.90 62.84	5.04 5.00	14.11 14.01
8	4-Br	$C_{26}H_{25}ON_5ClBr$	96	69	R F	57.72 57.70	4.63 4.59	12.95 12.92
9	4-OCH_3	$C_{27}H_{28}O_2N_5Cl$	62	79	R F	66.19 66.10	5.72 5.69	14.30 14.25
10	4-$NHCOCH_3$	$C_{28}H_{29}O_2N_6Cl$	150	60	R F	65.05 65.00	5.61 5.55	16.26 16.21

2. 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* and *K. neumonina*) 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 [16,17] 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 2: Antimicrobial data of Synthesized Compounds.

	I. ANTIMICROBIAL ACTIVITY INHIBITION (50mcg/ml)					
Com. No.	**1) R**	**2) % Inhibition in E.coli**	**3) % Inhibition in K.pneumonia**	**4) % Inhibition in B.cerus**	**5) % Inhibition in S.aureus**	**6) % Inhibition in C.albicans**
1_A	**H**	**-**	**-**	**-**	**-**	**-**
1_B	**2-CH_3**	**-**	**-**	**11**	**-**	**-**
1_C	**4- CH_3**	**-**	**-**	**6**	**-**	**-**
1_D	**2-NO_2**	**10**	**8**	**10**	**7**	**20**
1_E	**3- NO_2**	**11**	**10**	**15**	**10**	**21**
1_F	**4- NO_2**	**8**	**-**	**14**	**10**	**16**
1_G	**4-Cl**	**-**	**-**	**6**	**6**	**18**
1_H	**4-Br**	**10**	**-**	**10**	**8**	**-**
1_I	**4-OCH_3**	**22**	**15**	**10**	**23**	**19**
1_J	**4-$NHCOCH_3$**	**-**	**-**	**11**	**14**	**-**

3. Antimycobacterium

In this series out of ten compounds one compounds (1_H) 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**.

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