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In vitro microbial studies of some newly synthesized azetidinones derivatives

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ABSTRACT

Various substituted 3-chloro-4-(substitutedphenyl)-1-{4-[7-chloro-2-(3-chloropropyl)-4-oxoquinazolin-3(4H)-yl}azetidin-2-ones (2a-j) containing different functional groups have been synthesized by treating 7-chloro-2-(3-chloropropyl)-3-{4-[(substitutedbenz- ylidene)amino]phenyl}quinazolin-4-(3H)-ones (1a-j) with chloroacetyl chloride in presence of triethyl amine at reflux temperature. The lead compounds were characterized by melting point, TLC, calculated elemental analysis, IR and ^{1}H NMR spectral studies. The compounds were tested for antimicrobial studies and showed significant activity at low and high concentration as compared to standard.

Keywords: Quinazolinone, azetidinone, antimicrobial activity, spectral analysis

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INTRODUCTION

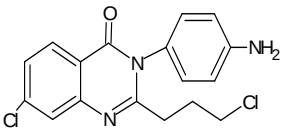
2-Azetidinones, commonly known as β-lactams, are well-known heterocyclic compounds among the organic and medicinal chemists [1]. the activity of the famous antibiotics such as penicillins, cephalosporins and carbapenems are attributed to the presence of 2-azetidinone ring in them. Recently, some other types of biological activity besides the antibacterial activity have been reported in compounds containing 2-azetidinone ring [2,3]. such biological activities include antimicrobial [4], anti-tuburcular [5], carbonic anhydrase inhibitors [6], local anaesthatics [7], anti-inflammatory [8], anthelmintic [9], anticonvulsant [10], hypoglycemic agents activity [11]. The β-lactams also serve as synthons for many biologically important classes of organic compounds [12]. Due to this, the investigation of chemistry and biology of these compounds continue to appeal the synthetic and medicinal organic chemists.
In search for new biodynamic potent molecule, it was thought worthwhile to incorporate some additional heterocyclic moieties in the β-lactam nucleus and study their biological and pharmacological activity [13]. The review of literature reveal prompted us to synthesize substituted quinazolones and targeted azetidinones and those will be screened for antimicrobial activities.

MATERIALS AND METHODS

Melting points were determined using an open-ended capillary method and are uncorrected. The purity of synthesized compounds was checked by TLC. IR spectra were recorded in KBr using Perkin Elmer Spectrum BX series spectrophotometer. ^{1}H NMR spectra were carried out on Bruker DRX – 300 MHz (^{1}H). NMR spectrophotometer using TMS as internal standard in $CDCl_3$-DMSO solvent. Micro analytical data were obtained from Central Drug Research Institute, Lucknow, India.

General synthesis of 3-chloro-1-(10-hydroxy-10-oxo-5,10-dihydro-phenophosphazin-2-yl)-4-(substituted phenyl)-azetidin-2-one (3a-j)
7-chloro-2-(3-chloropropyl)-4*H*-3,1-benzoxazin-4-one (1) was allowed to react with different aromatic aldehydes in presence of ethanol and acid catalyst to get the corresponding Schiff bases (2a-j). The above synthesized Schiff bases and triethyl amine (1:3) was dissolved in DMF in a RBF and chloroacetyl chloride was added slowly with constant stirring. The reaction mixture was stirred at RT for an hour and then refluxed for 8-10 hours. Excess of

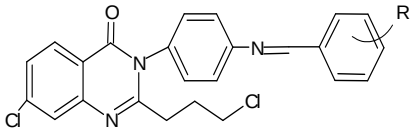
solvent was then removed by distillation. The solid thus separated was filtered, washed and dried. The crude product was then recrystallised with glacial acetic acid. The physical characteristics of synthesized compounds (3a-j) are listed in Table – 1.



3-(4-aminophenyl)-7-chloro-2-(3-chloropropyl)quinazolin-4(3*H*)-one

[I]

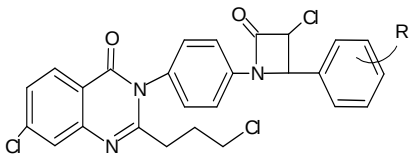
ArCHO ethanol



3-[4-(substituted benzylidene amino)phenyl] -7-chloro-2-(3-chloropropyl)quinazolin-4(3H)-one

[1a - j]

$ClCH_2COCl$ TEA



3-chloro-4-(substituted phenyl)-1-{4-[7-chloro-2-(3-chloropropyl)-4-oxoquinazolin-3-(4H)-

[2a - j]

Scheme - 1

Table – 1 The Physical constants of the synthesized compounds

Compound	R	Yield (%)	M.P. (°c)	Molecular formula	Elemental analysis Found/ calculated (%)		
					C	H	N
DP - 01	4-OCH_3	82.3	264	$C_{27}H_{23}Cl_2N_3O_3$	63.79 (63.80)	4.56 (4.54)	8.27 (8.28)
DP – 02	3-Cl	85.5	> 300	$C_{26}H_{20}Cl_3N_3O_2$	60.89 (60.88)	3.93 (3.91)	7.54 (7.55)
DP – 03	3-Br	72.6	289	$C_{26}H_{20}BrCl_2N_3O_2$	56.04 (56.53)	3.62 (3.63)	7.54 (7.52)
DP – 04	1 CH=CH	70.2	170	$C_{28}H_{23}Cl_2N_3O_2$	66.67 (66.66)	4.60 (4.62)	8.33 (8.31)
DP – 05	2-NO_2	60.6	256	$C_{26}H_{20}Cl_2N_4O_4$	59.67 (59.68)	3.85 (3.86)	10.7 (10.71)
DP – 06	3-OC_6H_5	72.9	279	$C_{32}H_{25}Cl_2N_3O_3$	67.37 (67.39)	4.42 (4.41)	7.37 (7.38)
DP – 07	3-OC_6H_5 4-OH	83.5	290	$C_{28}H_{25}Cl_2N_3O_4$	62.46 (62.47)	4.68 (4.67)	7.80 (7.82)
DP - 08	3-OCH_3 4-OH	68.9	272	$C_{27}H_{23}Cl_2N_3O_4$	61.84 (61.86)	4.42 (4.44)	8.01 (8.03)
DP – 09	- H	78.2	>300	$C_{26}H_{21}Cl_2N_3O_2$	65.28 (65.30)	4.42 (4.43)	8.78 (8.80)
DP – 10	3,5-OCH_3 4-OH	65.6	260	$C_{28}H_{25}Cl_2N_3O_5$	60.66 (60.67)	4.55 (4.54)	7.58 (7.57)

Table – 2 Antimicrobial activities

Sr. No.	Name of the Compound	Mean Zone of inhibition (in mm)					
		S aureus		*E coli*		*C Albicans*	
		50 µg	100 µg	50 µg	100 µg	50 µg	100 µg
1.	Procaine Penicillin	19	22	-	-	-	-
2.	Streptomycin	-	-	19	24	-	-
3.	Griseofalvin	-	-	-	-	20	25
4.	DP – 01	12 (0.63)	18 (0.81)	11 (0.58)	20 (0.83)	11 (0.55)	16 (0.69)
5.	DP – 02	11 (0.58)	14 (0.63)	8 (0.42)	15 (0.63)	13 (0.65)	17 (0.68)
6.	DP – 03	10 (0.53)	17 (0.77)	12 (0.63)	16 (0.67)	12 (0.60)	19 (0.76)
7.	DP – 04	9 (0.47)	16 (0.72)	13 (0.68)	13 (0.54)	11 (0.55)	16 (0.69)
8.	DP – 05	14 (0.74)	15 (0.68)	15(0.79)	11 (0.45)	10 (0.50)	20 (0.80)
9.	DP – 06	12 (0.63)	17 (0.77)	17 (0.89)	18 (0.75)	13 (0.60)	21 (0.84)
10.	DP – 07	11 (0.58)	19 (0.86)	9 (0.47)	14 (0.58)	16 (0.80)	17 (0.68)
11.	DP – 08	17 (0.89)	20 (0.91)	10 (0.53)	13 (0.54)	14 (0.70)	21 (0.84)
12.	DP – 09	12 (0.63)	11 (0.50)	11 (0.58)	12 (0.50)	13 (0.60)	20 (0.79)
13.	DP – 10	10 (0.53)	16 (0.72)	12 (0.63)	16 (0.67)	17 (0.85)	18 (0.72)

Activity Index = Test compound / Standard compound

Table – 3 Assignments of main IR bands (cm^{-1}) for the synthesized compounds

Comp. No.	(C=O) str.	(C-Cl) str.	(C-N) str.	(CH=CH) str.	(N-H) str.	(C=N) str.	(N=O) str.	(C-Br) str.
DP – 01	1696	722	1153	1411	3352	1607	--	--
DP – 02	1680	726	1156	1416	3354	1609	--	--
DP – 03	1691	730	1162	1419	3352	1630	--	589
DP – 04	1700	735	1151	1420	3361	1625	--	--
DP – 05	1697	728	1146	1421	3319	1622	1525	--
DP – 06	1692	722	1159	1413	3325	1628	--	--
DP – 07	1679	715	1153	1414	3359	1630	--	--
DP – 08	1698	725	1151	1411	3360	1618	--	--
DP – 09	1685	712	1152	1415	3371	1622	--	--
DP – 10	1693	736	1158	1426	3324	1625	--	--

Table-4 ^{1}H NMR data for the synthesized compounds

Compound No.	Assignments
DP – 01	5.5(s, 1H, CH-Cl); 3.74(t, 3H, C-OCH_3); 1.54(m, 2H, methylene), 1.61(d, 2H, methylene), 3.67(t, 2H, methylene); 6.4-7.7(m, 11H, aromatic)
DP – 02	5.1(s, 1H, CH-Cl); 1.54(m, 2H, methylene), 1.61(d, 2H, methylene), 3.67(t, 2H, methylene), 6.5-7.7(m, 11H, aromatic)
DP – 03	5.5(s, 1H, CH-Cl); 1.54(m, 2H, methylene), 1.61(d, 2H, methylene), 3.67(t, 2H, methylene), 6.4-7.7(m, 11H, aromatic)
DP – 04	4.9(s, 1H, CH-Cl); 5.5(s, 1H, C-H); 6.7(s, 1H, C-H); 1.54 (m, 2H, methylene), 1.61(d, 2H, methylene), 3.67(t, 2H, methylene), 6.5-7.3(m, 11H, aromatic)
DP – 05	5.3(s, 1H, CH-Cl); 1.54(m, 2H, methylene), 1.61(d, 2H, methylene), 3.67(t, 2H, methylene), 6.4-8.2(m, 11H, aromatic)
DP – 06	5.4(s, 1H, CH-Cl); 1.54(m, 2H, methylene), 1.61(d, 2H, methylene), 3.67(t, 2H, methylene), 6.4-7.3(m, 16H, aromatic)
DP – 07	5.4(s, 1H, CH-Cl); 1.34(t, 3H, C-OCH_3); 5.1(1H, s, C-OH); 1.53(m, 2H, methylene), 1.60(d, 2H, methylene), 3.67(t, 2H, methylene); 6.5-7.1(m, 10H, aromatic)
DP – 08	5.1(s, 1H, CH-Cl); 3.75(t, 3H, C-OCH_3); 3.99(d, 2H, C-CH_2); 5.0(1H, s, C-OH); 1.52(m, 2H, methylene), 1.6(d, 2H, methylene), 3.66(t, 2H, methylene), 6.4-7.0(m, 10H, aromatic)
DP – 09	5.5(s, 1H, CH-Cl); 1.54(m, 2H, methylene), 1.61(d, 2H, methylene), 3.67(t, 2H, methylene), 6.4-7.6(m, 12H, aromatic)
DP – 10	5.4(s, 1H, CH-Cl); 3.72(t, 3H, C-OCH_3); 5.0(1H, s, C-OH); 1.54(m, 2H, methylene), 1.60(d, 2H, methylene), 3.65(t, 2H, methylene), 6.5-7.0(m, 9H, aromatic)

***Invitro* antimicrobial activity:**

All the synthesized compounds were screened for invitro and antimicrobial activities. The antibacterial activity was tested using Cup plate method against S aureus and E coli Whereas antifungal activity was tested using Sabourard Dextrose medium against C Albicans. The impregnated dose of the drug for both the analysis was 50 µg/ml and 100 µg/ml. The plates were incubated at 35°c and examined for zone of inhibition around each disc after 24hrs. Results were compared with the activity of standard drugs like Procaine Penicillin, Streptomycin and Griseoflavin. All the compounds exhibited moderated antibacterial and antifungal activities.

Anti-bacterial activity

Synthesis and pharmacological screening of 3-chloro-1-(10-hydroxy-10-oxo-5,10-dihydro-phenophosphazin-2-yl)-4-(substituted phenyl)-azetidin-2-one were tested for the antibacterial activity against bacteria *S.aureus*, and *E.coli*. The test compounds DP-1, DP-3, DP-4, DP-6, DP-7 and D-8 showed moderate antibacterial activity against *S.aureus* (gram +ve) compare to standard drug procaine penicillin. Compounds DP-1 and DP-6 showed promising antibacterial activity against, *E.coli* (gram –ve) compared to standard drugs and streptomycin.

Anti-fungal activity
Synthesized compounds were tested for antifungal activity against *Candida albicans*. Among the compounds tested; DP-5, DP-6, DP-8 and DP-9 showed good activity against *Candida albicans* at both concentration compare to standard Griseofulvin.

RESULTS AND DISCUSSION

In the present study Schiff bases (1a-j) of 3-(4-aminophenyl)-7-chloro-2-(3-chloropropyl) quinazolin-4(3*H*)-one were synthesized by condensation of its amino group with different substituted aromatic aldehydes. The Azetidinone derivatives (2a-j) of above synthesized Schiff bases were synthesized by reaction of imino with chloroacetyl chloride in presence of triethyl amine (Scheme – 1) . Here we have synthesized several azetidinone derivatives having a spiro structure. All the compounds gave satisfactory elemental analysis (Table - 1). IR (Table – 3) and NMR (Table – 4) analysis were consistent with assigned structures. The compounds also shown appreciable antimicrobial activities (Table – 2)

CONCLUSION

Result of present study demonstrate that, a new class of different aromatic 4(H)-quinazolinones encompassing azetidinone derivatives were synthesized and evaluated as antibacterial agents. The newly synthesized heterocyclics exhibited promising antimicrobial activity against *Staphylococcus aureus*, and *Escherichia coli*. The antifungal studies against *Candida albicans* showed significant activity at low and high concentration compared to standard. It can be concluded that this class of compounds certainly holds great promise towards good active leads in medicinal chemistry. A further study to acquire more information concerning pharmacological activity is in progress.

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