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Pharmcological Activities Of Some 4-Chloro Quinazolinone Derivatives

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Abstract: A series of 7-chloro-2-(3-chloropropyl)-3-[(substitutedbenzylidene) amino]quinazolin-4-(3*H*)- ones carrying different aromatic moieties were prepared and tested for their activity against certain strains of Gram negative bacteria, Gram positive bacteria and pathogenic Fungi. The results revealed that some of synthesized compounds displayed marked activity against some of the tested microorganisms. The lead compounds were characterized by melting point, TLC, calculated elemental analysis, IR and ^{1}H NMR spectral studies.
Keywords: Synthesis, Schiff base, quinazolin-4-(3H)-ones, Antimicrobial activity.

INTRODUCTION

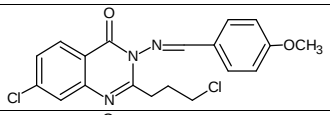
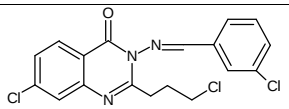
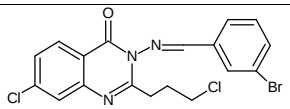
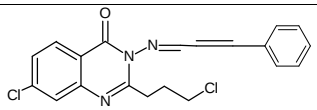
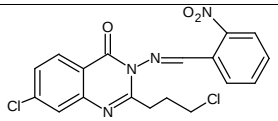
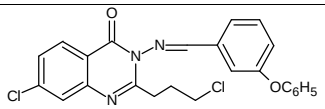
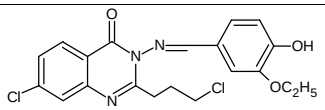
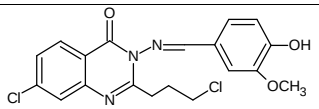
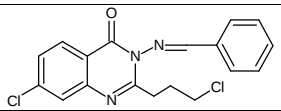
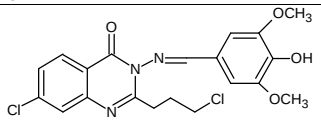
The spread of antibiotic resistance among pathogenic bacteria has become a serious problem for the clinical management of infectious diseases and has resulted in need for novel antibacterial agents other than existing antibiotics [1-5]. 4-(3H) Quinazolinones have proved to be an important class in this row owing to a wide range of biological activities such as anticancer [6], anti-inflammatory[7], anticonvulsant[8], antihypertensive [9], antimalarial [10] and anti-HIV [11]. Quinazolinones are excellent reservoir of bioactive substances. A number of biological activities [12-18] are associated with quinazolinones. The stability of the quinazoline nucleus has inspired medicinal chemists to introduce many bioactive moieties to this nucleus to synthesize new potential medicinal agents. Due to the great flexibility and diverse structural aspects of Schiff bases, a wide range of these compounds have been synthesized . Nitro and halo derivatives of Schiff bases are reported to have antimicrobial and antitumor activities [19]. Antimicrobial and antifungal activities of various Schiff bases have also been reported [20-22]. Many Schiff bases are known to be medicinally important and are used to design medicinal compounds [23]. As a continuation of previous efforts, aiming to locate new active 4-(3H) quinazolone analogs having enhanced potency as antimicrobial agents, a new series of quinazoline based Schiff base derivatives are synthesized and screened.

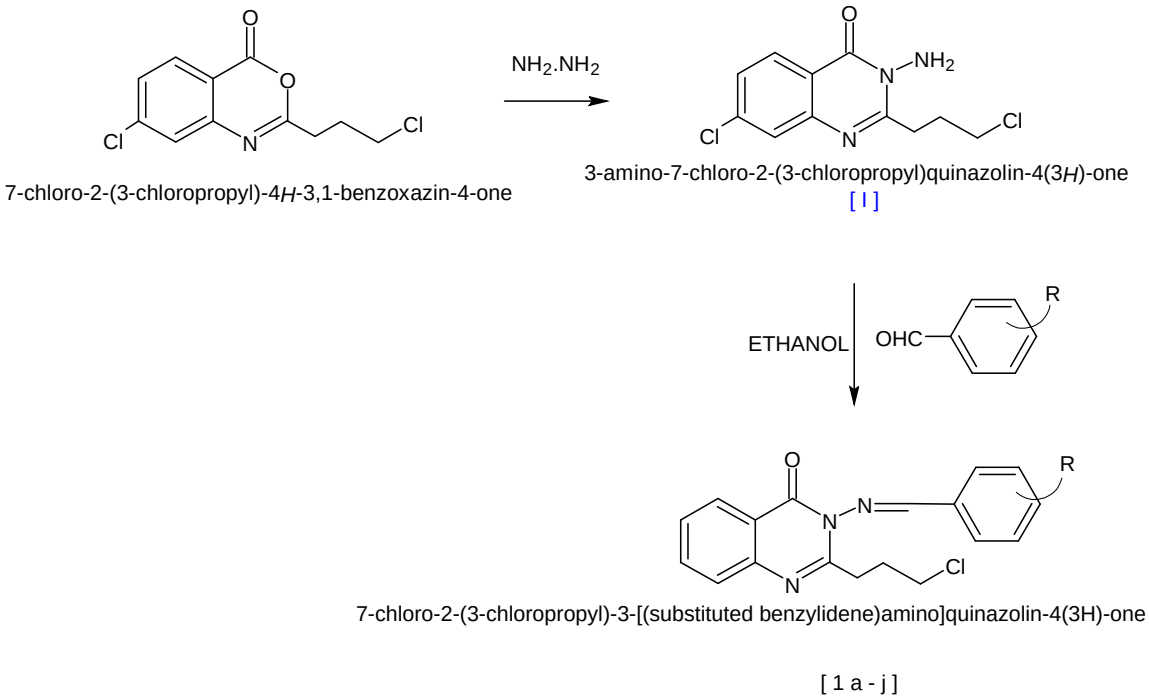
RESULTS AND DISCUSSION

7-chloro-2-(3-chloropropyl)-4*H*-3,1-benzoxazin-4-one was reacted with boiling hydrazine hydrate to give compound [I]. Reaction of above 3-amino derivative with aromatic aldehydes in glacial acetic acid afforded 3-arylidene derivatives (1a – j) (Scheme – 1). IR spectra of 3-iminoderivatives showed the disappearance of the absorption bands for NH_2 and NH while shows bands due to C=O group at 1695 cm^{-1}. All the compounds gave satisfactory elemental analysis. IR and NMR analysis were consistent with assigned structures. The compounds also shown appreciable antibacterial and antifungal activities (Table – 2).

The yields of all the synthesized compounds were found to be in the range of 76-86% (Table – 1). Thin layer chromatography was run throughout the reaction to optimize the reaction completion.

Table – 1 Synthesis of 3-substituted quinazolinones

Compound	Quinazolinone	Reaction Time	Yield (%)	M.P.(°C)
DS – 01		6 hrs	78.8	189
DS – 02		6 hrs 30 min	80.2	200
DS – 03		6 hrs	82.7	152
DS – 04		7 hrs	86.5	> 300
DS – 05		6 hrs	85.9	124
DS – 06		8 hrs	76.9	243
DS – 07		6 hrs 30 min	80.0	212
DS – 08		7 hrs	79.5	237
DS – 09		5 hrs	76.4	118
DS – 10		6 hrs	77.7	197



7-chloro-2-(3-chloropropyl)-4*H*-3,1-benzoxazin-4-one

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

[I]

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

[1 a - j]

Scheme - 1

BIOLOGICAL ACTIVITY

All the newly synthesized quinazolinone schiff base were assayed in vitro for their antibacterial activity against Staphylococcus aureus (Gram-positive bacteria) and Escherichia coli (Gram-negative bacteria) and antifungal activity against Aspergillus niger and Candida albicans. The minimum inhibitory concentration (MIC) value for antibacterial activity of compounds was determined by the cup plate method by using nutrient agar media (NAM). The minimum inhibitory concentration (MIC) values for antifungal activity were determined by using broth double dilution method (Serially diluted method) in Sabourauds dextrose broth at pH 7.4. For comparison, Ciprofloxacin was used as the reference antibacterial agents; Ketoconazole was employed as the reference antifungal agent. The antibacterial and antifungal MIC values for test compound as well as reference standard are given in Table. No. 2 and 3 respectively.

The obtained results revealed that the nature of substituent and substitution pattern on the benzene ring may have a considerable impact on the antibacterial and antifungal activities of the synthesized compounds. Of particular importance, a imine group has a considerable impact on antibacterial and antifungal activity.

ANTIBACTERIAL ACTIVITY

The minimum inhibitory concentration (MIC) was determined by the cup plate method. Ciprofloxacin was employed during the test procedures as reference. The MIC of the synthesized compounds ranges between 25-200 µg/ml. DS - 3, DS - 4, DS - 6 and DS - 8 were found moderately active, while DS – 1, DS – 2 , DS – 5 , DS – 9 AND DS – 10 were found to have an average activity compared with standard. Test compounds were found to be more sensitive towards Staphylococcus aureus (Gram-positive bacteria) and Escherichia coli (Gram-negative bacteria)

ANTIFUNGAL ACTIVITY

The minimum inhibitory concentration (MIC) was determined by the broth dilution method (Serially diluted method). Ketoconazole was employed du6d ring the test procedures as references.MIC of the synthesized compounds ranges between 12 – 23.5 µg/ml. DS – 2, DS – 3 and DS – 6 was found moderately active, while DS – 1, DS – 4, DS – 5, DS – 7, DS – 8, DS – 9 and DS – 10 were found to have an average activity compared with standard. Test compounds were found to be more sensitive towards Aspergillus niger and Candida albicans.

Table : 2 Antibacterial activity of newly synthesized compounds

Compound	MIC in µg/ml	
	E.coli	**S.Aureus**
DS – 01	10.5	11
DS – 02	13	12
DS – 03	21	22
DS – 04	19	18
DS – 05	10	11
DS – 06	22	21
DS – 07	14	11
DS – 08	24	20
DS – 09	11	10
DS – 10	9.5	12
Ciprofloxacin	25	25
Control (DMF)	--	--

T**able: 3 Antifungal activity of newly synthesized compounds**

Compound	MIC in µg/ml	
	A Niger	**C Albicans**
DS – 01	12	16.5
DS – 02	19	20
DS – 03	21.5	19
DS – 04	16	18
DS – 05	16	15
DS – 06	23.5	21
DS – 07	14	11
DS – 08	13.5	10
DS – 09	14	13
DS – 10	15	12.5
Ketoconazole	25	25
Control (DMF)	--	--

EXPERIMENTAL SECTION

General method for the synthesis of 7-chloro-2-(3-chloropropyl)-3-[(substituted benzylidene)amino] quinazolin-4-(3*H*)-ones

A mixture of 7-chloro-2-(3-chloropropyl)-4H-3,1 benzoxazin-4-one (0.3moles) and 98% hydrazine hydrate (500ml) was heated under reflux for 3 h. On cooling, the separated solid was washed with water and crystallized from ethanol. M.p. 245 c. The solid obtained was 3-amino-7-chloro-2-(3-chloropropyl)-quinazolin-4(3H)-one[I]. In an another round bottom flask a mixture of [I] (0.2 moles) and appropriate aldehyde (0.2moles) were refluxed in presence of ethanol for 3- 6 hours.On cooling the solid was washed, dried and recrystallised from ethanol.

7-chloro-2-(3-chloropropyl)-3-[(4-methoxybenzylidene)amino]quinazolin-4-(3*H*)-one

DS-01: Brown crystals, IR(KBr) : 3361, 1696,1610, 1150,712 cm^{-1}; ^1H NMR ($CdCl_3$, 500 MHz): 9.13(s,1H,benzylidenimine), 3.83(t,3H,C-OCH_3),1.54(m,2H,methylene),1.61(d,2H, methylene), 3.67(t,2H, methylene),7.1-7.9(m,7H, aromatic); Molecular Weight: 389.07; Anal. Calcd. For $C_{19}H_{17}Cl_2N_3O_2$: C = 58.47%, H = 4.39%, N = 10.77%. Found : C = 58.45%, H = 4.38%, N = 10.78%.

7-chloro-2-(3-chloropropyl)-3-[(3-chlorobenzylidene)amino]quinazolin-4-(3*H*)-one

DS-02: Yellow crystals, IR(KBr) : 3364, 1698,1611, 1140,725 cm^{-1}; ^1H NMR ($CdCl_3$, 500 MHz): 9.12(s,1H,benzylidenimine), 1.53(m,2H,methylene),1.61(d,2H, methylene), 3.67(t,2H, methylene), 7.4-7.9(m,7H, aromatic); Molecular Weight: 394.68 Anal. Calcd. For $C_{18}H_{14}Cl_3N_3O$: C = 54.78%, H = 3.58%, N = 10.65%. Found : C = 54.77%, H = 3.59%, N = 10.65%.

7-chloro-2-(3-chloropropyl)-3-[(3-bromobenzylidene)amino]quinazolin-4-(3*H*)-one

DS-03: Dark Yellow crystals, IR(KBr) : 3369, 1699,1601, 1140,725, 597 cm^{-1}; ^1H NMR ($CdCl_3$, 500 MHz): 9.15(s,1H,benzylidenimine), 1.54(m,2H,methylene),1.62(d,2H, methylene), 3.67(t,2H, methylene), 7.4-8.0(m,7H, aromatic); Molecular Weight: 436.97;Anal. Calc. For $C_{18}H_{14}BrCl_2N_3O$: C = 49.23%, H = 3.21%, N = 9.52%. Found : C = 49.24%, H = 3.20%, N = 9.54%.

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

DS-04: White crystals, IR(KBr) : 3379, 1710,1601, 1149,728 cm^{-1}; ^1H NMR ($CdCl_3$, 500 MHz): 7.5(s,1H,benzylidenimine),1.54(m,2H,methylene),1.62(d,2H, methylene), 3.67(t,2H, methylene), 5.67 (s,1H,CH=CH) ,7.4-7.9(m,8H, aromatic); Molecular Weight: 386.27;Anal. Calc. For $C_{20}H_{17}Cl_2N_3O$: C = 62.19%, H = 4.49%, N = 10.88%. Found : C = 62.20%, H = 4.48%, N = 10.89%.

7-chloro-2-(3-chloropropyl)-3-[(2-nitrobenzylidene)amino]quinazolin-4-(3*H*)-one

DS-05: Dark Yellow crystals, IR(KBr) : 3369, 1725,1621, 1530,1120,725, cm^{-1}; ^1H NMR ($CdCl_3$, 500 MHz): 8.36(s,1H,benzylidenimine), 1.54(m,2H,methylene), 1.62(d,2H, methylene), 3.67(t,2H, methylene), 7.8-8.1(m,7H, aromatic); Molecular Weight: 436.97;Anal. Calc. For $C_{18}H_{14}Cl_2N_4O_3$: C = 49.23%, H = 3.21%, N = 9.52%. Found : C = 49.24%, H = 3.20%, N = 9.54%.

7-chloro-2-(3-chloropropyl)-3-[(3-phenoxybenzylidene)amino]quinazolin-4-(3*H*)-one

DS-06: Yellow crystals, IR(KBr) : 3372, 1730,1621, 1120,735, cm^{-1}; ^1H NMR ($CdCl_3$, 500 MHz): 9.15(s,1H,benzylidenimine), 1.54(m,2H,methylene), 1.62(d,2H, methylene), 3.67(t,2H, methylene), 7.1-7.9(m,10H, aromatic); Molecular Weight: 436.97;Anal. Calc. For $C_{24}H_{19}Cl_2N_3O_2$: C = 63.73%, H = 4.23%, N = 9.29%. Found : C = 63.74%, H = 4.22%, N = 9.30%.

7-chloro-2-(3-chloropropyl)-3-[(3-ethoxy-4-hydroxybenzylidene)amino]quinazolin-4-(3*H*)-one

DS-07: Yellow crystals, IR(KBr) : 3382, 1720,1626, 1130,725, cm^{-1}; ^1H NMR ($CdCl_3$, 500 MHz): 9.15(s,1H,benzylidenimine), 1.54(m,2H,methylene), 4.09(t,3H,C-O$\underline{CH_2}CH_3$); 1.36(t,3H,C-OCH$_2\underline{CH_3}$) 5.4 (1H,s,C-OH)1.62(d,2H, methylene), 3.67(t,2H, methylene), 6.9-7.8(m,6H, aromatic); Molecular Weight:420.29 ;Anal. Calc. For $C_{20}H_{19}Cl_2N_3O_3$: C = 57.15%, H = 4.56%, N = 10.0%. Found : C = 57.13%, H = 4.57%, N = 10.01%.

7-chloro-2-(3-chloropropyl)-3-[(4-hydroxy-3-methoxy-benzylidene)amino]quinazolin-4-(3*H*)-one

DS-08: Brown crystals, IR(KBr) : 3392, 1720,1627, 1133,727, cm^{-1}; ^1H NMR ($CdCl_3$, 500 MHz): 9.15(s,1H,benzylidenimine), 1.54(m,2H,methylene),; 3.83(t,3H,C-OCH_3) 5.4(1H,s,C-OH)1.62(d,2H, methylene), 3.67(t,2H, methylene), 6.9-7.9(m,6H, aromatic); Molecular Weight:405.06;Anal. Calc. For $C_{19}H_{17}Cl_2N_3O_3$: C = 56.17%, H = 4.22%, N = 10.34%. Found : C = 56.15%, H = 4.24%, N = 10.34%.

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

DS-09: Golden brown crystals, IR(KBr) : 3382, 1725,1627, 1135,725, cm^{-1}; ^1H NMR ($CdCl_3$, 500 MHz): 9.15(s,1H,benzylidenimine), 1.54(m,2H,methylene) ; 1.62(d,2H, methylene), 3.65(t,2H, methylene), 7.5-7.9(m,8H, aromatic); Molecular Weight:360.24 ;Anal. Calc. For $C_{18}H_{15}Cl_2N_3O$: C = 60.01%, H = 4.20%, N = 11.66%. Found : C = 60.03%, H = 4.24%, N = 11.65%.

7-chloro-2-(3-chloropropyl)-3-[(4-hydroxy-3,5-dimethoxy-benzylidene)amino]quinazo- lin-4-(3*H*)-one

DS-10: Brown crystals, IR(KBr): 3392, 1720,1627, 1133,727, cm^{-1}; ^1H NMR ($CdCl_3$, 500 MHz): 9.16(s,1H,benzylidenimine), 1.54(m,2H,methylene), ; 3.83(t,3H,C-OCH_3) 5.4(1H,s,C-OH)1.62(d,2H, methylene), 3.68(t,2H, methylene), 7.1-7.9(m,5H, aromatic); Molecular Weight:436.29 ;Anal. Calc. For $C_{20}H_{19}Cl_2N_3O_4$: C = 55.06%, H = 4.39%, N = 9.63%. Found : C = 55.07%, H = 4.40%, N = 9.64%.

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