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SYNTHESIS OF NEW 1,3-OXAZOLYL-7-CHLOROQUINAZOLIN-4(*3H*)ONES AND EVALUATION OF THEIR ANTIMICROBIAL ACTIVITIES

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Abstract: 2-[2-(2,6-Dichlorophenyl)amino]phenylmethyl-3-{4-[(substituted phenyl)amino]-1,3-oxazol-2-yl}-7-chloroquinazolin-4(3*H*)ones **5a-o** have been prepared from 2-[(2,6-dichloro phenyl)amino]phenyl acetic acid **1**, which was converted to acid chloride **2** and cyclized with anthranilic acid afforded benzoxazin-4(*H*)ones **3**. Further reaction with urea gave carboxamide-7-chloroquinazolin-4(3*H*)ones **4** cyclized with substituted phenyl acetamide **a-o**. All the compounds have been confirmed by elemental analysis, IR**,** NMR spectral data and evaluated for antimicrobial activity. Compounds **5o, 5k**, and **5m** (**R = 1-H, 2,5-(Cl)**$_2$, and **2-Cl, 4-NO**$_2$) showed good activity, compared with the standard drugs.

Keywords: antibacterial, antifungal, benzoxazinone, 1, 3-oxazole, quinazolinone

Quinazolinones are versatile nitrogen containing heterocycles, possessing various biological and pharmacological activities such as anti-inflammatory (1), anticonvulsant (2), antitubercular (3), antibacterial (4), anti-HIV, antibacterial and antifungal (5, 6), antimitotic and anticancer (7). In pharmacological studies, diclofenac sodium has shown anti-inflammatory, analgesic and antipyretic properties. It reveals many therapeutic activities like antispasmodic (8), antimycobacterial (9), anti-inflammatory and anti-platelet aggregation activity (10) and anti-inflammatory and analgesic activities (11).

Oxazole plays very vital role for biological activities viz. antidiabetic (12), antihyperglycemic (13), antirheumatic (14), anticancer (15) and antiviral (16). Combination of two or more biologically active moieties increases or decreases their activities. With these aspects in mind, we have enhanced our previous work on quinazolinones by substitution of various acetyl acetamide and substituted aryl amines searching for antimicrobial activity (17–20); we have synthesized and studied antimicrobial activity of newly 1,3-oxazolyl derivatives.

EXPERIMENTAL

All the chemicals and solvents of Rankem, Sisco, Qualigens and Spectrochem were used for this work. Compound **1** was purchased from Arjun exports, Surat. Melting points were determined in open capillaries and are uncorrected; the purity of the compounds was checked by TLC. The IR absorption spectra were recorded on Perkin–Elmer RX-1 FTIR spectrophotometer using KBr pellet and the proton magnetic resonance spectra (^{1}H-NMR at 400 MHz and ^{13}C-NMR at 100 MHz) were recorded on Bruker Avance II in $CDCl_3$ using tetramethylsilane (TMS) as internal reference. Elemental analysis was performed on Carlo Erba 1108 analyzer.

The bands of C-H stretching of methyl and methylene were observed near 2926 and 2853 cm^{-1}, N-H stretching band at 3450–3350 cm^{-1}, C=O stretching band of quinazolinone were observed at 1700–1660 cm^{-1}. ^{1}*H*-NMR spectra of all compounds showed a singlet of -NH- at 9.30. The multiplets of aromatic protons were observed in the range of δ 7.83–6.59 ppm.

2-[(2,6-Dichlorophenyl)amino]phenyl acetyl chloride (**2**)

Prepared by reported method and directly used in the next step (21, 22).

2-[2-(2,6-Dichlorophenyl)amino]phenylmethyl-7-chloro-3,1-benzoxazin-4(*H*)one (**3**)

A mixture of 2-[2-(2,6**-**dichlorophenyl)amino] phenyl acetyl chloride **2** (3.14 g, 0.01 mol) and 4-chloroanthranilic acid (2.92 g, 0.01 mol) in pyridine

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(60 mL) were stirred at 0–5°C for 1 h, then further stirred for 1 h at room temperature. A pasty mass obtained was neutralized with sodium carbonate (5%) and washed with distilled water. A solid separated was filtered, dried and recrystalized from methanol. M.p.: 187°C, yield 53%. IR (KBr, cm^{-1}): 3448 (NH), 2922, 2848 (C-H), 1668 (>C=O), 1610 (C=N), 1308 (C-N), 783 (C-Cl), 750 (NH). ^{1}H-NMR (400 MHz, $CDCl_3$, δ, ppm): 9.27 (s, 1H, -NH-), 7.58–6.40 (m, 10H, Ar-H), 3.79 (s, 2H, $-CH_2$).

2-[2-(2,6-Dichlorophenyl)amino]phenylmethyl-3-carboxamide-7-chloroquinazoline-4(3*H*)one (**4**)

2-[2-(2,6-Dichlorophenyl)amino]phenylmethyl-7-chloro-3,1-benzoxazin-4(*H*)ones **3** (4.30 g, 0.01 mol) and urea (0.60 g, 0.01 mol) in pyridine (40 mL) were refluxed on oil bath for 6 h. After completion, the reaction mixture was poured into ice cold water and neutralized with 50% HCl solution. The separated solid was filtered, washed and recrystallized from ethanol. M.p.: 190°C, yield 58%. IR (KBr, cm^{-1}): 3438 (NH), 2930, 2855 (C-H), 1679 (>C=O), 1614 (C=N), 1308 (C-N), 783 (C-Cl), 750 (NH). ^{1}H-NMR (400 MHz, $CDCl_3$, δ, ppm): 9.25 (s, 1H,-NH-), 7.56–6.39 (m, 4H, Ar-H), 5.80 (s, 2H, $-NH_2$), 3.78 (s, 2H, $–CH_2$).

2-[2-(2,6-Dichlorophenyl)amino]phenylmethyl-3-{4-[(2-chlorophenyl)amino]-1,3-oxazol-2-yl}-7-chloroquinazolin-4-(3*H*)one (**5a**)

2-Chloro-N-(2-chlorophenyl)acetamide (2.04 g, 0.01 mol) and 2-[2-(2,6-dichlorophenyl) amino]phenylmethyl-3-carboxamide-7-chloroquinazoline-4(3*H*)one (4.72 g, 0.01 mol) in ethanol were refluxed for 6 h and allowed to stand undisturbed overnight. The solid which separated on cooling was filtered and recrystallized from a mixture of ethanol and DMF (5–10% of DMF in ethanol). IR (KBr, cm^{-1}): 3448 (NH), 2922, 2848 (C-H), 1668 (>C=O), 1610 (C=N), 1308 (C-N), 783 (C-Cl). ^{1}H-NMR (400 MHz, $CDCl_3$, δ, ppm): 9.27 (s, 1H, -NH-), 7.62–6.32 (m, 16H, Ar-H), 6.58 (s, 1H, CH of oxazole ring), 3.96 (s, 2H, $-CH_2$). ^{13}C-NMR (100 MHz, $CDCl_3$, δ, ppm): 163.1 (C_2), 160.6 (C_4), 150.8 (C_{10}), 139.5 (C_7), 132.6 (C_9), 131.5 (C_5), 124.2 (C_6), 118.1 (C_8).

2-[2-(2,6-Dichlorophenyl)amino]phenylmethyl-3-{4-[(3-chlorophenyl)amino]-1,3-oxazol-2-yl}-7-chloroquinazolin -4(*3H*)one (**5b**)

IR (KBr, cm^{-1}): 3438 (NH), 2840, 2925 (C-H), 1679 (>C=O), 1614 (C=N), 1316 (C-N), 781 (C-Cl). ^{1}H-NMR (400 MHz, $CDCl_3$, δ, ppm): 9.25 (s, 1H, -NH-), 7.69–6.36 (m, 16H, Ar-H), 6.61 (s, 1H, CH of oxazole ring), 3.92 (s, 2H, $-CH_2$). ^{13}C-NMR (100 MHz, $CDCl_3$, δ, ppm): 163.5 (C_2), 161.7 (C_4), 149.5 (C_{10}), 137.8 (C_7), 133.2 (C_9), 130.4 (C_5), 123.3 (C_6), 119.1 (C_8).

2-[2-(2,6-Dichlorophenyl)amino]phenylmethyl-3-{4-[(4-chlorophenyl)amino]-1,3-oxazol-2-yl}-7-chloroquinazolin 4(*3H*)one (**5c**)

IR (KBr, cm^{-1}): 3442 (NH), 2844, 2927 (C-H), 1671 (>C=O), 1608 (C=N), 1309 (C-N), 779 (C-Cl). ^{1}H-NMR (400 MHz, $CDCl_3$, δ, ppm): 9.40 (s, 1H, -NH-), 7.66–6.33 (m, 16H, Ar-H), 6.52 (s, 1H, CH of oxazole ring), 3.86 (s, 2H, $-CH_2$). ^{13}C-NMR (100 MHz, $CDCl_3$, δ, ppm): 162.4 (C_2), 161.2 (C_4), 150.5 (C_{10}), 142.3 (C_7), 132.5 (C_9), 130.2 (C_5), 124.3 (C_6), 120.4 (C_8).

2-[2-(2,6-Dichlorophenyl)amino]phenylmethyl-3-{4-[(2-methylphenyl)amino]-1,3-oxazol-2-yl}-7-chloroquinazolin-4(*3H*)one (**5d**)

IR (KBr, cm^{-1}): 3445 (NH), 2941, 2921 (C-H), 1681(>C=O), 1611 (C=N), 1325 (C-N), 787 (C-Cl). ^{1}H-NMR (400 MHz, $CDCl_3$, δ, ppm): 9.31 (s, 1H, -NH-), 7.67–6.32 (m, 16H, Ar-H), 6.58 (s, 1H, CH of oxazole ring), 3.85 (s, 2H, $-CH_2$), 2.21 (s, 3H, CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$, δ, ppm): 165.3 (C_2), 161.4 (C_4), 150.2 (C_{10}), 136.8 (C_7), 133.3 (C_9), 131.3 (C_5), 126.4 (C_6), 117.5 (C_8).

2-[2-(2,6-Dichlorophenyl)amino]phenylmethyl-3-{4-[(3-methylphenyl)amino]-1,3-oxazol-2-yl}-7-chloroquinazolin-4(*3H*)one (**5e**)

IR (KBr, cm^{-1}): 3448 (NH), 2953, 2924 (C-H), 1673 (>C=O), 1618 (C=N), 1319 (C-N), 791 (C-Cl). ^{1}H-NMR (400 MHz, $CDCl_3$, δ, ppm): 9.33 (s, 1H, -NH-), 7.65–6.32 (m, 16H, Ar-H), 6.58 (s, 1H, CH of oxazole ring), 3.77 (s, 2H, $-CH_2$), 2.23 (s, 3H, $-CH_3$). ^{13}C-NMR (100 MHz, $CDCl_3$, δ, ppm): 164.4 (C_2), 159.5 (C_4), 151.3(C_{10}), 136.9 (C_7), 133.5 (C_9), 130.6 (C_5), 127.1 (C_6), 119.3 (C_8),

2-[2-(2,6-Dichlorophenyl)amino]phenylmethyl-3-{4-[(4-methylphenyl)amino]-1,3-oxazol-2-yl}-7-chloroquinazolin-4(*3H*)one (**5f**)

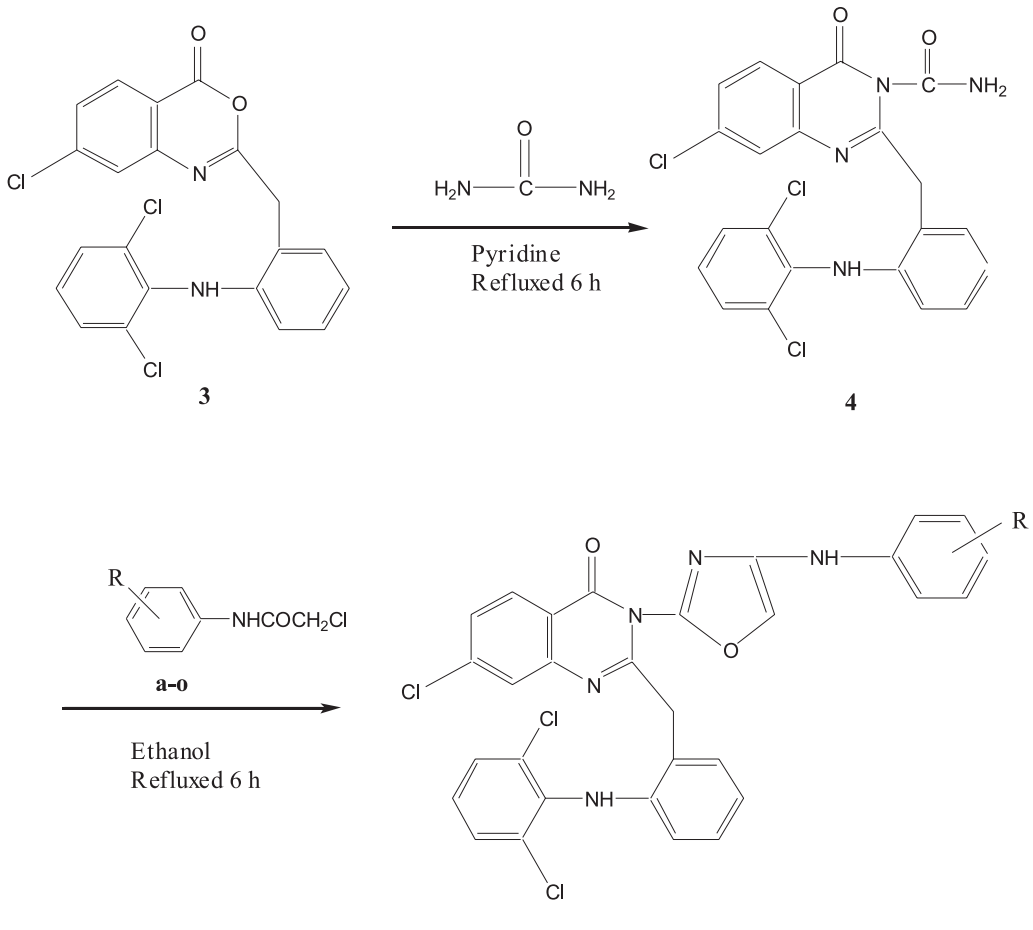
IR (KBr, cm^{-1}): 3442 (NH), 2951, 2933 (C-H), 1683 (>C=O), 1609 (C=N), 1329 (C-N), 780 (C-Cl). ^{1}H-NMR (400 MHz, $CDCl_3$, δ, ppm): 9.35 (s, 1H, -NH-), 7.66–6.32 (m, 16H, Ar-H), 6.60 (s, 1H, CH of oxazole ring), 3.92 (s, 2H, $-CH_2$), 2.26 (s, 3H, $-CH_3$). ^{13}C-NMR (100 MHz, $CDCl_3$, δ, ppm): 162.1 (C_2), 161.8 (C_4), 151.9 (C_{10}), 141.2 (C_7), 134.6 (C_9), 132.8 (C_5), 124.3 (C_6), 122.4 (C_8).

2-[2-(2,6-Dichlorophenyl)amino]phenylmethyl-3-{4-[(2-nitrophenyl)amino]-1,3-oxazol-2-yl}-7-chloroquinazolin-4(*3H*)one (**5g**)

IR (KBr, cm^{-1}): 3445 (NH), 2945, 2920 (C-H), 1681 (>C=O), 1610 (C=N), 1548, 1366, (-NO_2 asym, sym), 1320 (C-N), 785 (C-Cl). ^{1}H-NMR (400 MHz, $CDCl_3$, δ, ppm): 9.36 (s, 1H, -NH-), 6.36–7.69 (m, 16H, Ar-H), 6.58 (s, 1H, CH of oxazole ring), 3.82 (s, 2H, -CH_2). ^{13}C-NMR(100 MHz, $CDCl_3$, δ, ppm): 162.3 (C_2), 160.7 (C_4), 151.6 (C_{10}), 141.2 (C_7), 135.2 (C_9), 131.6 (C_5), 123.1 (C_6), 119.6 (C_8).

2-[2-(2,6-Dichlorophenyl)amino]phenylmethyl-3-{4-[(3-nitrophenyl)amino]-1,3-oxazol-2-yl}-7-chloroquinazolin-4(*3H*)one (**5h**)

IR (KBr, cm^{-1}): 3446 (NH), 2951, 2929 (C-H), 1679 (>C=O), 1617 (C=N), 1559, 1362 (-NO_2 asym, sym), 1316 (C-N), 781 (C-Cl). ^{1}H-NMR (400 MHz,



R=5

a = 2-Cl	f = 4-CH_3	k = 2,5-$(Cl)_2$
b = 3-Cl	g = 2-NO_2	l = 3,4-$(Cl)_2$
c = 4-Cl	h = 3-NO_2	m = 2- Cl, 4-NO_2
d = 2-CH_3	i = 4-NO_2	n = 4- Cl, 2 -NO_2
e = 3-CH_3	j = 4-OCH_3	o = H

Scheme 1.

Table 1. Physical properties of compounds **a-o** and **5a-o.**

Compound	R	Molecular formula	M.p. °C	Yield (%)	Analysis Calculated (found)		
					%C	%H	%N
a	2-Cl	$C_8H_7NOCl_2$	76–77	53	47.09 (47.02)	3.46 (3.42)	6.86 (6.81)
b	3-Cl	$C_8H_7NOCl_2$	83–84	52	47.09 (47.02)	3.46 (3.42)	6.86 (6.81)
c	4-Cl	$C_8H_7NOCl_2$	73–74	48	47.09 (47.02)	3.46 (3.42)	6.86 (6.81)
d	2-CH_3	$C_9H_{10}NOCl$	68–69	56	58.86 (58.81)	5.49 (5.46)	7.63 (7.59)
e	3-CH_3	$C_9H_{10}NOCl$	80–81	54	58.86 (58.81)	5.49 (5.46)	7.63 (7.59)
f	4-CH_3	$C_9H_{10}NOCl$	78–79	60	58.86 (58.81)	5.49 (5.46)	7.63 (7.59)
g	2-NO_2	$C_8H_7N_2O_3Cl$	64–65	51	44.77 (44.71)	3.29 (3.27)	13.05 (13.01)
h	3-NO_2	$C_8H_7N_2O_3Cl$	69–70	58	44.77 (44.71)	3.29 (3.27)	13.05 (13.01)
i	4-NO_2	$C_8H_7N_2O_3Cl$	73–74	53	44.77 (44.71)	3.29 (3.27)	13.05 (13.01)
j	4-OCH_3	$C_9H_{10}NO_2Cl$	84–85	57	54.15 (54.07)	5.05 (5.02)	7.02 (6.08)
k	2,5-$(Cl)_2$	$C_8H_6NOCl_3$	70–71	61	40.29 (40.23)	2.54 (2.52)	5.87 (5.82)
l	3,4-$(Cl)_2$	$C_8H_6NOCl_3$	72–73	63	40.29 (40.23)	2.54 (2.52)	5.87 (5.82)
m	2-Cl,4-NO_2	$C_8H_6N_2O_3Cl_2$	67–68	54	38.58 (38.52)	2.43 (2.41)	11.25 (11.21)
n	4-Cl,2-NO_2	$C_8H_6N_2O_3Cl_2$	77–78	59	38.58 (38.52)	2.43 (2.41)	11.25 (11.21)
o	H	C_8H_8NOCl	74–75	52	56.65 (56.57)	4.75 (4.72)	8.26 (8.20)
5a	2-Cl	$C_{30}H_{19}O_2N_5Cl_4$	109–111	52	57.78 (57.75)	03.04 (03.02)	11.23 (11.20)
5b	3-Cl	$C_{30}H_{19}O_2N_5Cl_4$	100–102	56	57.78 (57.75)	03.04 (03.02)	11.23 (11.20)
5c	4-Cl	$C_{30}H_{19}O_2N_5Cl_4$	104–106	54	57.78 (57.75)	03.04 (03.02)	11.23 (11.20)
5d	2-CH_3	$C_{31}H_{22}O_2N_5Cl_3$	101–102	53	61.74 (61.70)	03.65 (03.61)	11.61 (11.57)
5e	3-CH_3	$C_{31}H_{22}O_2N_5Cl_3$	98-100	59	61.74 (61.70)	03.65 (03.61)	11.61 (11.57)
5f	4-CH_3	$C_{31}H_{22}O_2N_5Cl_3$	103–105	55	61.74 (61.70)	03.65 (03.61)	11.61 (11.57)
5g	2-NO_2	$C_{30}H_{19}O_4N_6Cl_3$	104–106	61	56.82 (56.77)	02.99 (02.95)	13.25 (13.23)
5h	3-NO_2	$C_{30}H_{19}O_4N_6Cl_3$	108–110	57	56.82 (56.77)	02.99 (02.95)	13.25 (13.23)
5i	4-NO_2	$C_{30}H_{19}O_4N_6Cl_3$	111–113	53	56.82 (56.77)	02.99 (02.95)	13.25 (13.23)

Table 1. Continued.

Compound	R	Molecular formula	M.p.	Yield (%)	Analysis Calculated (found)		
					%C	%H	%N
5j	4-OCH_3	$C_{31}H_{22}O_3N_5Cl_3$	106–108	60	60.14 (60.10)	03.55 (03.50)	11.31 (11.28)
5k	2,5-$(Cl)_2$	$C_{30}H_{18}O_2N_5Cl_5$	102–104	59	54.75 (54.73)	02.73 (02.69)	10.64 (10.60)
5l	3,4-$(Cl)_2$	$C_{30}H_{18}O_2N_5Cl_5$	101–103	55	54.75 (54.73)	02.73 (02.69)	10.64 (10.60)
5m	2-Cl,4-NO_2	$C_{30}H_{18}O_4N_6Cl_4$	115–117	57	53.89 (53.85)	02.69 (02.65)	12.57 (12.55)
5n	4-Cl,2-NO_2	$C_{30}H_{18}O_4N_6Cl_4$	105–107	60	53.89 (53.85)	02.69 (02.65)	12.57 (12.55)
5o	H	$C_{30}H_{20}O_2N_5Cl_3$	97–99	53	61.17 (61.15)	03.39 (03.35)	11.89 (11.85)

$CDCl_3$, δ, ppm): 9.40 (s, 1H, -NH-), 7.65–6.36 (m, 16H, Ar-H), 6.56 (s, 1H, CH of oxazole ring), 3.83 (s, 2H, $-CH_2$). ^{13}C-NMR (100 MHz, $CDCl_3$, δ, ppm): 163.7 (C_2), 160.2 (C_4), 150.7 (C_{10}), 141.6 (C_7), 136.3 (C_9), 134.3 (C_5), 125.5 (C_6), 120.3 (C_8).

2-[2-(2,6-Dichlorophenyl)amino]phenylmethyl-3-{4-[(4-nitrophenyl)amino]-1,3-oxazol-2-yl}-7-chloroquinazolin-4(*3H*)one (**5i**)

IR (KBr, cm^{-1}): 3447 (NH), 2944, 2919 (C-H), 1671 (>C=O), 1618 (C=N), 1309 (C-N), 789 (C-Cl), 1542, 1368 ($-NO_2$, asym, sym). ^{1}H-NMR (400 MHz, $CDCl_3$, δ, ppm): 9.41 (s, 1H, -NH-), 7.69–6.37 (m, 16H, Ar-H), 6.55 (s, 1H, CH of oxazole ring), 3.88 (s, 2H, $-CH_2$). ^{13}C-NMR (100 MHz, $CDCl_3$, δ, ppm): 164.5 (C_2), 161.5 (C_4), 151.1 (C_{10}), 142.1 (C_7), 136.3 (C_9), 133.5 (C_5), 126.3 (C_6), 122.5 (C_8).

2-[2-(2,6-Dichlorophenyl)amino]phenylmethyl-3-{4-[(4-methoxyphenyl)amino]-1,3-oxazol-2-yl}-7-chloroquinazolin-4(*3H*)one (**5j**)

IR (KBr, cm^{-1}): 3325 (NH), 2958, 2934 (C-H), 1684 (>C=O), 1610 (C=N), 1335 (C-N), 786 (C-Cl). ^{1}H-NMR (400 MHz, $CDCl_3$, δ, ppm): 9.38 (s, 1H, -NH-), 7.67–6.37 (m, 16H, Ar-H), 6.62 (s, 1H, CH of oxazole ring), 3.94 (s, 3H, OCH_3), 3.86 (s, 2H, $-CH_2$). ^{13}C-NMR (100 MHz, $CDCl_3$, δ, ppm): 164.3 (C_2), 162.5 (C_4), 151.3 (C_{10}), 141.2 (C_7), 135.4 (C_9), 133.7 (C_5), 125.3 (C_8), 124.1 (C_6).

2-[2-(2,6-Dichlorophenyl)amino]phenylmethyl-3-{4[(2,5-dichlorophenyl)amino]-1,3-oxazol-2-yl}-7-chloroquinazolin-4(*3H*)one (**5k**)

IR (KBr, cm^{-1}): 3332 (NH), 2951, 2933 (C-H), 1686 (>C=O), 1605 (C=N), 1338 (C-N), 781 (C-Cl). ^{1}H-NMR (400 MHz, $CDCl_3$, δ, ppm): 9.34 (s, 1H, -NH-), 7.70–6.39 (m, 15H, Ar-H), 6.56 (s, 1H, CH of oxazole ring), 3.77 (s, 2H, $-CH_2$). ^{13}C-NMR (100 MHz, $CDCl_3$, δ, ppm): 164.7 (C_2), 160.5 (C_4), 150.3 (C_{10}), 140.3 (C_7), 133.5 (C_5), 132.5(C_9), 123.8 (C_6), 123.3 (C_8).

2-[2-(2,6-Dichlorophenyl)amino]phenylmethyl-3{-4[(3,4-dichlorophenyl)amino]-1,3-oxazol-2-yl}-7-chloroquinazolin-4(*3H*)one (**5l**)

IR (KBr, cm^{-1}): 3324 (NH), 2952, 2933 (C-H), 1681 (>C=O), 1606 (C=N), 1339 (C-N), 782 (C-Cl). ^{1}H-NMR (400 MHz, $CDCl_3$, δ, ppm): 9.42 (s, 1H, -NH-), 7.65–6.39 (m, 15H, Ar-H), 6.55 (s, 1H, CH of oxazole ring), 3.86 (s, 2H, $-CH_2$). ^{13}C-NMR (100 MHz, $CDCl_3$, δ, ppm): 163.2 (C_2), 162.5(C_4), 152.8 (C_{10}), 141.2 (C_7), 134.6 (C_9), 133.6 (C_5), 125.5 (C_6), 124.3 (C_8).

2-[2(2,6-Dichlorophenyl)amino]phenylmethyl-3-{4-[(2-chloro,4-nitrophenyl)amino]-1,3-oxazol-2-yl}-7-chloroquinazolin-4(*3H*)one (**5m**)

IR (KBr, cm^{-1}): 3329 (NH), 2954, 2929 (C-H), 1678 (>C=O), 1616 (C=N), 1346 (C-N), 784 (C-Cl), 1551, 1362, ($-NO_2$ asym, sym). ^{1}H-NMR (400 MHz, $CDCl_3$, δ, ppm): 9.31 (s, 1H, -NH-), 7.62–6.34 (m, 15H, Ar-H), 6.55 (s, 1H, CH of oxazole ring), 3.72 (s, 2H, $-CH_2$). ^{13}C-NMR (100 MHz, $CDCl_3$, δ, ppm): 162.9 (C_2), 162.8 (C_4), 152.5 (C_{10}), 140.2 (C_7), 134.3 (C_9), 132.5 (C_5), 125.9 (C_6), 124.2 (C_8).

2-[2(2,6-Dichlorophenyl)amino]phenylmethyl-3-{4-[(4-chloro-2-nitrophenyl)amino]-1,3-oxazol-2-yl}-7-chloroquinazolin-4(*3H*)one (**5n**)

IR (KBr, cm^{-1}): 3323 (NH), 2948, 2918 (C-H), 1674 (>C=O), 1625 (C=N), 1343 (C-N), 782 (C-Cl),

Table 2. Antimicrobial activity of compounds **4a-o** and **5a-o.**

Compd. no.	R	Minimum inhibitory concentration in µg/mL						
		Gram negative		Gram positive		Fungal species		
		E. coli	*P. aeruginosa*	*S. aureus*	*S. pyogenes*	*C. albicans*	*A. niger*	*A. clavatus*
1		200	100	200	25	1000	>1000	>1000
3		500	200	50	200	500	1000	1000
4		150	250	500	500	500	1000	1000
a	2-Cl	500	1000	250	250	1000	1000	>1000
b	3-Cl	250	500	500	1000	1000	1000	>1000
c	4-Cl	250	1000	250	250	>1000	>1000	>1000
d	2-CH_3	100	200	250	250	>1000	>1000	>1000
e	3-CH_3	100	250	500	500	500	500	>1000
f	4-CH_3	500	500	100	100	1000	500	>1000
g	2-NO_2	500	1000	500	250	>1000	>1000	>1000
h	3-NO_2	50	100	200	200	500	500	500
i	4-NO_2	250	500	1000	1000	500	>1000	>1000
j	4-OCH_3	500	500	1000	1000	500	>1000	>1000
k	2,5-$(Cl)_2$	500	1000	250	500	1000	1000	>1000
l	3,4-$(Cl)_2$	500	500	500	1000	1000	1000	>1000
m	2-Cl, 4-NO_2	250	500	500	1000	>1000	>1000	500
n	4-Cl, 2-NO_2	125	250	100	250	500	>1000	>1000
o	H	250	500	250	250	500	>1000	>1000
5a	2-Cl	500	200	500	1000	500	1000	1000
5b	3-Cl	100	250	100	150	1000	1000	1000
5c	4-Cl	500	500	500	500	1000	500	1000
5d	2-CH_3	500	200	100	50	500	500	500
5e	3-CH_3	100	500	100	500	1000	1000	500
5f	4-CH_3	500	100	200	500	1000	500	500
5g	2-NO_2	250	500	200	100	500	1000	1000
5h	3-NO_2	100	100	500	100	500	1000	1000
5i	4-NO_2	62.5	100	250	500	500	1000	1000
5j	4-OCH_3	1000	500	500	100	1000	1000	1000
5k	2,5-$(Cl)_2$	50	100	200	100	1000	1000	1000
5l	3,4-$(Cl)_2$	100	250	250	250	200	100	100
5m	2-Cl, 4-NO_2	500	500	500	500	1000	500	500
5n	4-Cl, 2-NO_2	500	500	500	1000	500	1000	1000
5o	H	500	500	500	500	500	500	500
Gentamycin		0.05	1	0.25	0.5	-	-	-
Ampicillin		100	100	250	100	-	-	-
Chloramphenicol		50	50	50	50	-	-	-
Ciprofloxacin		25	25	50	50	-	-	-
Norfloxacin		10	10	10	10	-	-	-
Nystatin		-	-	-	-	100	100	100
Griseofulvin		-	-	-	-	500	100	100

1552, 1360 (-NO_2 asym, sym). ^{1}H-NMR (400 MHz, $CDCl_3$, δ, ppm): 9.32 (s, 1H, -NH-), 7.69–6.35 (m, 15H, Ar-H), 6.52 (s, 1H, CH of oxazole ring), 3.92 (s, 2H, -CH_2). ^{13}C-NMR (100 MHz, $CDCl_3$, δ, ppm): 163.8 (C_2), 161.5(C_4), 151.4 (C_{10}), 140.3 (C_7), 133.9 (C_9), 132.7 (C_5), 125.1 (C_6), 123.1 (C_8).

2-[2-(2,6-Dichlorophenyl)amino]phenylmethyl-3-{4-[(phenyl)amino]-1,3-oxazol-2-yl}-7-chloroquinazolin-4(*3H*)one (**5o**)

IR (KBr, cm^{-1}): 3327 (NH), 2950, 2929 (C-H), 1679 (>C=O), 1617 (C=N), 1344 (C-N), 785 (C-Cl). ^{1}H-NMR (400 MHz, $CDCl_3$, δ, ppm): 9.33 (s, 1H, -NH-), 7.72–6.35 (m, 17H, Ar-H), 6.52 (s, 1H, CH of oxazole ring), 3.95 (s, 2H, -CH_2). ^{13}C-NMR (100 MHz, $CDCl_3$, δ, ppm): 164.7 (C_2), 163.7 (C_4), 151.7 (C_{10}), 141.2 (C_7), 134.4 (C_9), 132.1 (C_5), 123.5 (C_6), 122.3 (C_8).

Antimicrobial activity

All the synthesized compounds were tested for antibacterial and antifungal activity (MIC) *in vitro* by broth dilution method (23) with two Gram positive bacteria: *S. aureus* MTCC-96, *S. pyogenes* MTCC-442 and two Gram negative bacteria: *E. coli* MTCC-443, *P. aeruginosa* MTCC-2488 and fungi: *C. albicans* MTCC-227, *A. niger* MTCC-282 and *A. clavatus* MTCC-1323 taking gentamycin, ampicillin, chloramphenicol, ciprofloxacin, norfloxacin, nystatin and griseofulvin as standard drugs.

RESULTS

2-[2-(2,6-Dichlorophenyl)amino]phenylmethyl-3-{4-[(substitutedphenyl) amino]-1,3-oxazol-2-yl}-7-chloroquinazolin-4-(3*H*)ones **5a-o** have been prepared from 2-[(2,6-dichloro phenyl) amino]phenyl acetic acid **1**; the conversion of compounds from **1** to **5a-o** is shown in Scheme 1. Physical properties of **5a-o** are given in Table 1. The structures of synthesized **5a-o** were confirmed by IR and NMR spectral data. The MIC values in µg/mL of compounds are reported in Table 2.

DISCUSSION AND CONCLUSION

The 2-[(2,6-dichlorophenyl)amino]phenyl acetic acid **1** demonstrated good activity against *P. aeruginosa* and comparable activity against *S. aureus* with ampicillin and *S. pyogenes* with ampicillin, chloramphenicol and ciprofloxacin, respectively; while it showed mild to moderate activity against *E. coli*. The synthesized compound – 4-benzoxazinone **3** possessed excellent activity against *S. aureus* as compared to ampicillin, chloramphenicol and ciprofloxacin; addition of urea with **3** gave carboxamide quinazolinone, which showed comparable with ampicillin activity against *E. coli* and good against *P. aeruginosa* and *S. aureus*.

Antibacterial and antifungal activity of 15 amides of substituted primary aromatic amines as an intermediate were tested for antibacterial activity and compared with final products. Amide **h** (R = 3-NO_2) demonstrated maximum whereas **d** and **e** (R = 2-CH_3 and 3-CH_3, respectively) showed good activity against *E. coli*; **h** (R = 3-NO_2) showed good against *P. aeruginosa*. **f**, **h**, **k** (R = 4-CH_3, 3-NO_2, 2,5-$(Cl)_2$, respectively) showed comparable activity and **a**, **c**, **d**, **n** and **o** (R = 2-Cl,4-Cl, 2-CH_3,2-NO_2, 4-Cl, H, respectively) against *S. aureus*, **f** (R = 4-CH_3) against *S. pyogenes* with ampicillin and **h** (R = 3-NO_2) demonstrated good activity against *E. coli* with chloramphenicol. 1,3-Oxazol-2-yl-7-chloroquinazolin-4-(*3H*)ones **5i** and **5k** (R = 4-NO_2 and 2,5-$(Cl)_2$, respectively) showed maximum activity and **5b**, **5e**, **5h** and **5l** (R = 3-Cl, 3-CH_3, 3-NO_2 and 3,4-$(Cl)_2$, respectively) against *E. coli*, **5f**, **5h**, **5i**, and **5k** (R = 4-CH_3, 3-NO_2, 4-NO_2 and 2,5-$(Cl)_2$) demonstrated good activity against *P. aeruginosa*. **5b**, **5d**, **5e**, **5f**, **5g**, **5k** (R = 3-Cl, 2-CH_3,3-CH_3,4-CH_3,2-NO_2 and 2,5-$(Cl)_2$, respectively) showed maximum activity and **5i**, **5l** (R = 4-NO_2 and 3,4-$(Cl)_2$, respectively) good activity against *S. aureus*. **5d** (R = 2-CH_3) showed comparable and **5g**, **5h**, **5i** and **5k** (R = 2-NO_2, 3-NO_2, 4-NO_2 and 2,5-$(Cl)_2$, respectively) good activity against *S. pyogenes* with ampicillin. **5k** (R = 2,5-$(Cl)_2$) demonstrated good activity against *E. coli* with chloramphenicol and **5d** (R = 2-CH_3) showed good activity against *S. pyogenes* with chloramphenicol and ciprofloxacin.

Amides **e, h, i, j, k** and **o** (R = 3-CH_3, 3-NO_2, 4-NO_2, 4-OCH_3, 2,5-$(Cl)_2$ and H, respectively) demonstrated good activity against *C. albicans* with greseofulvin. 1,3-Oxazol-2-yl-7-chloroquinazolin-4-(*3H*)ones **5l** (R = 3,4-$(Cl)_2$) showed maximum and **5a, 5d, 5g, 5h, 5i**, **5n**, **5o** (R = 2-Cl, 2-CH_3, 2-NO_2, 3-NO_2, 4-NO_2, 2-NO_2, 4-Cl and H, respectively) good activity against *C. albicans* with greseofulvin. **5l** (R = 3,4-$(Cl)_2$) showed good activity against *A. niger* and *A. clavatus* with nystatin and greseofulvin.

We concluded that the compounds bearing -Cl, -CH_3 and -NO_2 groups are more active. The structural variation gave the new ideas for the further investigation on oxazolyl derivatives. Thus, present work provides good outlines on the study of structure activity relationships of oxazolyl derivatives putting special emphasis on incorporation of quinazoline moiety.

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