

IN VITRO ANTIMICROBIAL STUDIES OF NEWLY SYNTHESIZED 1, 3-OXAZOLYL- QUINAZOLIN-4(3H) ONES

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Abstract

Synthesis of 2-[2-(2,6-dichloro-phenylamino)-phenylmethyl]-3-{4-[(substituted phenyl) amino]-1,3-oxazol-2-yl-}quinazolin-4(3H)ones (**5a-o**) has been achieved from 2-[(2,6-Dichlorophenylamino)-phenyl]-acetic acid (**1**) with thionyl chloride, gave acid chloride (**2**), from nucleophilic interaction of 2-[2-(2,6-dichloro-phenylamino)-methyl-3,1-benzoxazin-4(H)one (**3**), with urea nucleophile. The formation of the final compounds (**5a-o**) have been established by elemental analysis, IR, ¹H NMR and ¹³C NMR spectral data. All compounds have been screened for their antibacterial and antifungal activities.

Rezumat

Au fost sintetizați 5 compuși din clasa 2-[2-(2,6-diclor-fenilamino)-fenilmetil]-3-{4-[(substituitfenil)amino]-1,3-oxazol-2-il-}quinazolin-4(3H)onelor.

Aceștia au fost analizați spectral prin metode IR, 1H RMN și 13C RMN. Toți compușii au fost testați pentru evaluarea potențialului lor antibacterian și antifungic.

Keywords: Antibacterial, Antifungal, Benzoxazinone, 1,3-Oxazole, Quinazolinone

Introduction

Quinazolines are important derivatives and play a vital role in the biological processes and synthetic drugs. These derivatives are fused heterocycles that show many biological activities as anticonvulsant [1], antitubercular [2], anticancer [3] and antimicrobial [4] activities in anesthetized rabbits and in conscious spontaneously hypertensive rats.

2-(2,6-Dichlorophenylamino)-phenyl acetic acid has a wide range of therapeutic activities, mainly anti-inflammatory and anti-platelet aggregation [5]. Oxazole plays a vital role in the manufacturing of various biologically active drugs as antidiabetic, antihyperglycemic, antirheumatic, anticancer, antiviral activities [6-8]. Oxazole containing compounds proved to be very useful in the pharmaceutical field and henceforth we have expanded our previous work on quinazolinones by substituted acetylacetamides and substituted aryl amines [9,10].

Materials and methods

Melting points of all compounds were determined in an open capillary and are uncorrected. The purity of the studied compounds was checked by TLC (Thin Layer Chromatography), IR spectra were recorded on a Perkin–Elmer RX-1 FTIR spectrophotometer using KBr pellets. ^1H NMR (400MHz) and ^{13}C NMR (100MHz) spectra were recorded on a Bruker Avance II system in CDCl_3 (deuterated chloroform). Elemental analyses of the newly synthesized compounds were performed on a Carlo Erba 1108 analyzer. Elemental analyses of all the compounds were in agreement with the calculated values.

2-[(2,6-Dichloro-phenyl amino)phenyl]acetyl chloride (2) was prepared by the reported method and directly used in the next step [11].

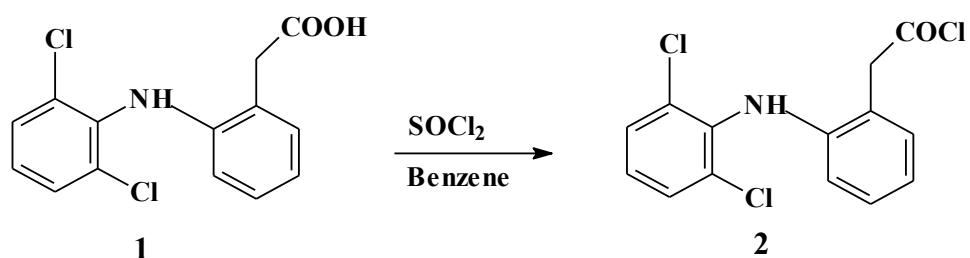


Figure 1

Synthesis of 2-[(2,6-dichloro-phenyl amino)phenyl]acetyl chloride

2-[2-(2,6-Dichloro-phenylamino)phenyl]methyl-3,1-benzoxazin-4(H)ones (3) was Prepared by the reported method and directly used in the next step [12].

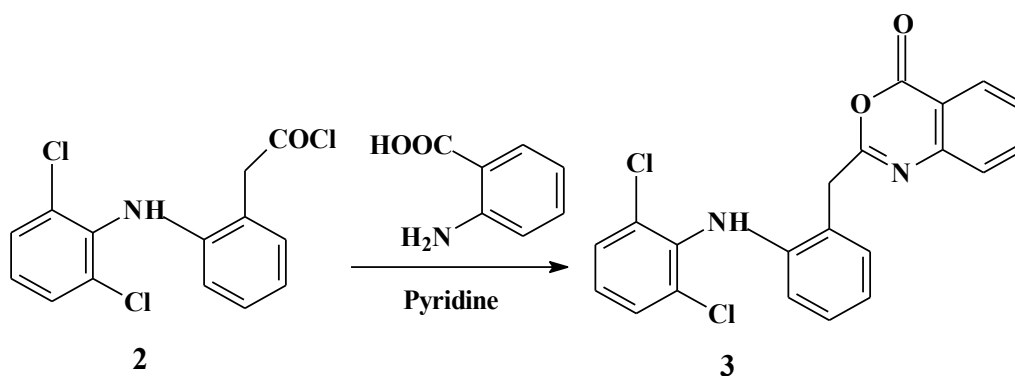


Figure 2

Synthesis of benzoxazin-4(*H*)ones

2-[2-(2,6-Dichloro-phenylamino)phenyl]methyl-3-carboxamide-quinazolin-4(3H)ones (4). 2-[2-(2,6-Dichlorophenylamino)phenyl]-methyl-3,1-benzoxazin-4(H)ones (3.97g, 0.01mol) and urea (0.60g, 0.01mol) in 20 mL of pyridine was refluxed on an oil bath at 180-200 °C for 6 hr. After completion, the reaction mixture was poured into ice cold water containing conc. HCl, the separated solid was filtered, washed and recrystallised from ethanol. (60% yield, m.p.-180 °C) (Figure 3)

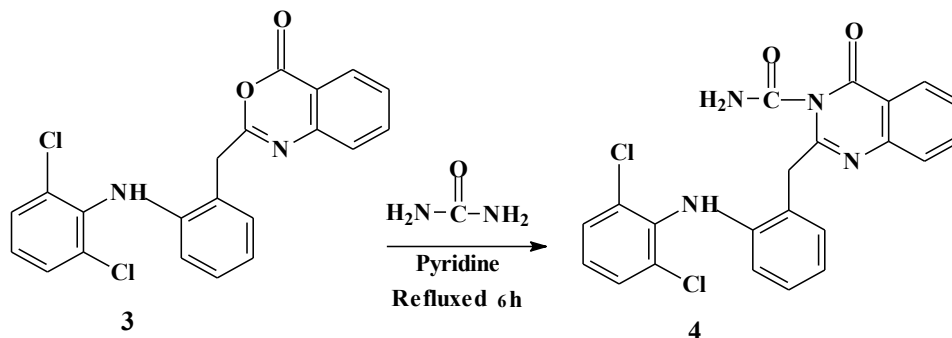


Figure 3
Synthesis of quinazolin-4(3H)ones

General procedure for the preparation of 5a-o

2-Chloro-N-(2-substituted)acetamides (0.01mol) and 2-[2-(2,6-dichlorophenylamino)-phenyl]-methyl-3-carboxamide quinazoline-4(3H)ones **4** (0.01mol) in ethanol were refluxed for 6 hr and allowed to rest overnight. The solid, which separated on cooling was filtered and recrystallised from a mixture of DMF (N,N-dimethyl formamide) and ethanol (5-10% of DMF in ethanol). The reaction time and purity of the compound were checked by TLC using acetone: ethanol (1:1) mixture as mobile phase.

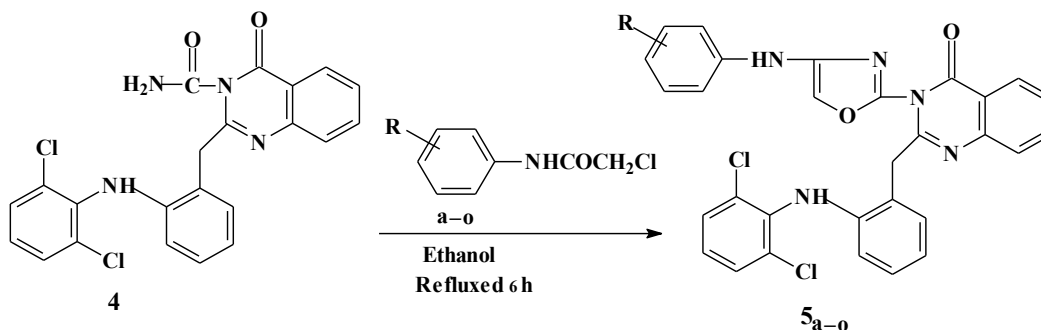


Figure 4
Synthesis of the new compounds 5a-o

$R=5(a = 2\text{-Cl}, b = 3\text{-Cl}, c = 4\text{-Cl}, d = 2\text{-CH}_3, e = 3\text{-CH}_3, f = 4\text{-CH}_3, g = 2\text{-NO}_2, h = 3\text{-NO}_2, i = 4\text{-NO}_2, j = 4\text{-OCH}_3, k = 2,5\text{-(Cl)}_2, l = 3,4\text{-(Cl)}_2, m = 2\text{-Cl}, 4\text{-NO}_2, n = 4\text{-Cl}, 2\text{-NO}_2, o = H)$

Results and Discussion

All the new synthesized compounds were tested for their antibacterial activities Minimum Inhibitory Concentration (MIC) against Gram positive (*S. aureus* and *S. pyogenes*), Gram negative (*P. aeruginosa* and *E. coli*) bacteria and fungal species (*C. albicans*, *A. niger* and *A. clavatus*) by Broth dilution method [13].

Antibacterial activity

1,3-Oxazol-2-yl-quinazolin-4(3*H*)ones **5_a** and **5_o** ($R=2\text{-Cl}$ and $-H$ respectively) demonstrated good activity against *E. coli*. **5_a** ($R=2\text{-Cl}$) showed good activity against *P. aeruginosa*. **5_a**, **5_h**, **5_l** and **5_n** ($R=2\text{-Cl}$, 3-NO_2 , $3,4\text{-(Cl)}_2$, and $\{2\text{-NO}_2, 4\text{-Cl}\}$ respectively) demonstrated excellent activity against *S. aureus*. **5_a** and **5_l** ($R=2\text{-Cl}$ and 4-NO_2) demonstrated good activity and **5_d**, **5_k** ($R=2\text{-CH}_3$, $2,5\text{-(Cl)}_2$) excellent activity against *S. pyogenes* compared with ampicillin. **5_h** ($R=3\text{-NO}_2$) demonstrated good activity against *S. aureus*. **5_d** ($R=2\text{-CH}_3$) showed excellent activity and **5_k** ($R=2,5\text{-(Cl)}_2$) showed good activity against *S. pyogenes* compared with chloramphenicol and ciprofloxacin.

Antifungal activity

1,3-Oxazol-2-yl-quinazolin-4(3*H*)ones **5_o** ($R=H$) showed excellent activity and **5_a**, **5_b**, **5_c**, **5_d**, **5_h**, **5_l**, **5_n** ($R=2\text{-Cl}$, 3-Cl , 4-Cl , 2-CH_3 , 3-NO_2 , 4-NO_2 and 2-NO_2 , 4-Cl) good activity against *C. albicans* with griseofulvin. **5_o** ($R=H$) demonstrated good activity against *A. niger* and *A. clavatus* with griseofulvin and nystatin. **5_o** ($R=H$) demonstrated good activity against *C. albicans* compared with nystatin.

Table I

Physical and analytical data of synthesized compounds (5a-o)

Compd.	R	Molecular Formula	M.P. (°C)	Yield (%)	Elemental analysis Calculated (found)		
					%C	%H	%N
5 _a	2-Cl	C ₃₀ H ₂₀ O ₂ N ₅ Cl ₃	90-92	58	61.17 (61.15)	03.39 (03.37)	11.89 (11.87)
5 _b	3-Cl	C ₃₀ H ₂₀ O ₂ N ₅ Cl ₃	93-95	60	61.17 (61.19)	03.39 (03.42)	11.89 (11.92)
5 _c	4-Cl	C ₃₀ H ₂₀ O ₂ N ₅ Cl ₃	112-115	53	61.17 (61.22)	03.39 (03.46)	11.89 (11.95)
5 _d	2-CH ₃	C ₃₁ H ₂₃ O ₂ N ₅ Cl ₂	97-99	55	65.49 (65.45)	04.04 (04.02)	12.32 (12.29)
5 _e	3-CH ₃	C ₃₁ H ₂₃ O ₂ N ₅ Cl ₂	101-03	57	65.49 (65.53)	04.04 (04.09)	12.32 (12.36)
5 _f	4-CH ₃	C ₃₁ H ₂₃ O ₂ N ₅ Cl ₂	115-117	55	65.49 (65.57)	04.04 (04.11)	12.32 (12.39)
5 _g	2-NO ₂	C ₃₀ H ₂₀ O ₄ N ₆ Cl ₂	88-90	58	60.10 (60.05)	03.33 (03.30)	14.02 (14.00)
5 _h	3-NO ₂	C ₃₀ H ₂₀ O ₄ N ₆ Cl ₂	96-98	59	60.10 (60.10)	03.33 (03.34)	14.02 (14.07)
5 _i	4-NO ₂	C ₃₀ H ₂₀ O ₄ N ₆ Cl ₂	89-91	52	60.10 (60.05)	03.33 (03.30)	14.02 (14.12)
5 _j	4-OCH ₃	C ₃₁ H ₂₃ O ₃ N ₅ Cl ₂	113-115	51	63.69 (63.66)	03.93 (03.90)	11.98 (11.95)
5 _k	2,5-(Cl) ₂	C ₃₀ H ₁₉ O ₂ N ₅ Cl ₄	94-96	53	57.78 (57.75)	03.04 (03.01)	11.23 (11.19)
5 _l	3,4-(Cl) ₂	C ₃₀ H ₁₉ O ₂ N ₅ Cl ₄	98-100	54	57.78 (57.77)	03.04 (03.09)	11.23 (11.25)
5 _m	2-Cl,4-NO ₂	C ₃₀ H ₁₉ O ₄ N ₆ Cl ₃	102-104	56	56.82 (56.79)	02.99 (02.94)	13.25 (13.21)
5 _n	4-Cl,2-NO ₂	C ₃₀ H ₁₉ O ₄ N ₆ Cl ₃	116-118	58	56.82 (56.85)	02.99 (02.99)	13.25 (13.29)
5 _o	H	C ₃₀ H ₂₁ O ₂ N ₅ Cl ₂	91-93	57	64.98 (64.96)	03.79 (03.74)	12.63 (12.60)

Table II. IR, ^1H -NMR and ^{13}C -NMR spectral data of compounds (5a-o)

Com	IR(KBr)	^1H NMR (δ ppm)	^{13}C NMR (δ ppm)
5 _a	3445 (NH), 2920, 2845 (C-H), 1675 (C=O), 1610 (C=N), 1320 (C-N), 785 (C-Cl);	-NH- (1H,s,9.35) Ar-H (16H,m,6.50-7.80), -CH ₂ -(2H,s,3.74), 6.60 (1H,s, CH of oxazole ring)	163.1(C ₂),160.6(C ₄),131.5(C ₅), 124.2(C ₆),139.5(C ₇),118.1 (C ₈), 132.6 (C ₉), 150.8 (C ₁₀)
5 _b	3438 (NH), 2925, 2840 (C-H), 1679 (C=O), 1614 (C=N), 316 (C-N), 781 (C-Cl);	NH- (1H,s,9.45) Ar-H (16H,m,6.56-7.87), -CH ₂ -(2H,s,3.74) 6.61 (1H,s, CH of oxazole ring)	163.5(C ₂),161.7(C ₄),130.4 (C ₅), 123.3(C ₆),137.8(C ₇),119.1(C ₈), 133.2 (C ₉), 149.5 (C ₁₀)
5 _c	3422 (NH), 2949, 2844 (C-H), 1671 (C=O), 1608 (C=N), 1309 (C-N), 779 (C-Cl);	NH- (1H,s,9.42)Ar-H (16H,m,6.51-7.83), -CH ₂ -(2H,s,3.69) 6.62 (1H,s, CH of oxazole ring)	162.4(C ₂),61.2 (C ₄), 130.2 (C ₅), 124.3 (C ₆), 142.3 (C ₇), 120.4 (C ₈), 132.5 (C ₉), 150.5 (C ₁₀)
5 _d	3445 (NH), 2921, 2841 (C-H), 1681 (C=O), 1611 (C=N), 1325 (C-N), 787 (C-Cl);	NH- (1H,s,9.31) Ar-H (16 H,m,6.55-7.83), -CH ₂ -(2H,s,3.75), 2.31 (s, 3H, CH ₃) 6.58 (1H,s, CH of oxazole ring)	165.3(C ₂),161.4(C ₄),131.3 (C ₅), 126.4(C ₆),136.8(C ₇),117.5(C ₈),133.3 (C ₉),150.2 (C ₁₀)
5 _e	3448 (NH), 2924, 2853 (C-H), 1673 (C=O), 1618 (C=N), 1319 (C-N), 791 (C-Cl);	NH- (1H,s,9.42) Ar-H 16H,m,6.51-7.90), -CH ₂ -(2H,s,3.78), 2.34 (s, 3H, CH ₃) 6.59 (1H,s,CH of oxazole ring)	164.4(C ₂),159.5(C ₄),130.6 (C ₅), 127.1(C ₆),136.9(C ₇),119.3 (C ₈), 133.5(C ₉),151.3(C ₁₀)
5 _f	3422 (NH), 2933, 2851 (C-H), 1683 (C=O), 1609 (C=N), 1329 (C-N), 780 (C-Cl);	NH- (1H,s,9.39) Ar-H 16H,m,6.55-7.88), -CH ₂ -(2H,s,3.65), 2.36 (s, 3H, CH ₃) 6.57 (1H,s, CH of oxazole ring)	162.1(C ₂),161.8(C ₄),132.8 (C ₅), 124.3 (C ₆), 141.2 (C ₇), 122.4 (C ₈), 134.6(C ₉),151.9 (C ₁₀)
5 _g	3425 (NH), 2920, 2845 (C-H), 1681 (C=O), 1610 (C=N), 1320 (C-N), 785 (C-Cl) 1364, 1546 (-NO ₂ sym, asym);	NH- (1H,s,9.35) Ar-H (16H,m,6.50-7.80), -CH ₂ -(2H,s,3.74) 6.58 (1H,s, CH of oxazole ring)	162.3 (C ₂), 160.7 (C ₄), 131.6 (C ₅),123.1(C ₆),141.2(C ₇), 119.6 (C ₈), 135.2(C ₉),151.6 (C ₁₀)
5 _h	3448 (NH), 2929, 2850 (C-H), 1679 (C=O), 1614 (C=N), 1316 (C-N), 781 (C-Cl), 1367, 1556 (-NO ₂ sym, asym);	NH- (1H,s,9.48) Ar-H(16H,m,6.50-7.81), -CH ₂ -(2H,s,3.78) 6.60 (1H,s, CH of oxazole ring)	163.7 (C ₂), 160.2 (C ₄), 134.3 (C ₅), 125.5 (C ₆), 141.6 (C ₇), 120.3(C ₈),136.3(C ₉),150.7(C ₁₀)
5 _i	3422 (NH), 2919, 2844 (C-H), 1671 (C=O), 1608 (C=N), 1309 (C-N), 789 (C-Cl), 1364, 1546 (-NO ₂ sym, asym);	NH- (1H,s,9.41) Ar-H 16H,m,6.55-7.87), -CH ₂ -(2H,s,3.66) 6.59 (1H,s, CH of oxazole ring)	164.5(C ₂),161.5(C ₄),133.5 (C ₅), 126.3 (C ₆), 142.1 (C ₇), 122.5 (C ₈), 136.3(C ₉), 151.1 (C ₁₀)
5 _j	3423 (NH), 2934, 2852 (C-H), 1685 (C=O), 1611 (C=N), 1328 (C-N), 782 (C-Cl);	NH- (1H,s,9.42) Ar-H (16 H,m,6.59-7.88), -CH ₂ -(2H,s,3.66), -OCH ₃ (3H, s, 3.59) 6.58 (1H,s, CH of oxazole ring)	164.3(C ₂),162.5(C ₄),133.7 (C ₅), 124.1(C ₆),141.2(C ₇),12531(C ₈), 135.4 (C ₉), 151.3 (C ₁₀)
5 _k	3425 (NH), 2933, 2851 (C-H), 1683 (C=O), 1609 (C=N), 1329 (C-N), 780 (C-Cl);	NH- (1H,s,9.43) Ar-H (15H,m,6.56-7.83), -CH ₂ -(2H,s,3.68) 6.57 (1H,s, CH of oxazole ring)	164.7(C ₂),160.5(C ₄),133.5 (C ₅), 123.8 (C ₆), 140.3 (C ₇), 123.3 (C ₈), 133.5(C ₉), 150.3 (C ₁₀)
5 _l	3421 (NH), 2933, 2851 (C-H), 1683 (C=O), 1609 (C=N), 1329 (C-N), 780 (C-Cl);	NH- (1H,s,9.44) Ar-H (15H,m,6.58-7.85), -CH ₂ -(2H,s,3.65) 6.58 (1H,s, CH of oxazole ring)	163.2(C ₂),162.5(C ₄),134.6 (C ₅), 125.5 (C ₆), 141.2 (C ₇), 124.3 (C ₈), 134.6(C ₉), 152.8 (C ₁₀)
5 _m	3448 (NH), 2929, 2850 (C-H), 1679 (C=O), 1614 (C=N), 1316 (C-N), 781 (C-Cl), 1367, 1556 (-NO ₂ sym, asym);	NH- (1H,s,9.35) Ar-H (15H,m,6.50-7.80), -CH ₂ -(2H,s,3.75) 6.60 (1H,s, CH of oxazole ring)	162.9(C ₂),162.8(C ₄),132.5 (C ₅), 125.9 (C ₆), 140.2 (C ₇), 124.2 (C ₈), 134.3 (C ₉), 152.5 (C ₁₀)
5 _n	3439 (NH), 2918, 2849 (C-H), 1673 (C=O), 1620 (C=N), 1320 (C-N),782 (C-Cl), 1361,1555 (-NO ₂ sym, asym);	NH- (1H,s,9.42) Ar-H 15H,m,6.64-7.85), -CH ₂ -(2H,s,3.71) 6.59 (1H,s, CH of oxazole ring)	163.8(C ₂),161.5(C ₄),132.7 (C ₅), 125.1(C ₆),140.3(C ₇),123.1 (C ₈), 133.9 (C ₉), 151.4 (C ₁₀)
5 _o	3448 (NH), 2929, 2850 (C-H), 1679 (C=O), 1614 (C=N), 1316 (C-N), 781 (C-Cl);	NH- (1H,s,9.49)Ar-H (17H,m,6.59-7.86), -CH ₂ -(2H,s,3.69) 6.60 (1H,s, CH of oxazole ring);	163.7(C ₂),163.7(C ₄),132.1 (C ₅), 123.5 (C ₆), 141.2 (C ₇), 122.3 (C ₈), 134.4 (C ₉), 151.7 (C ₁₀)

Table III
Antibacterial and antifungal activities of (5a-o) compounds

Compounds	Minimal Inhibition Concentration in µg/mL						
	Gram Negative		Gram Positive		Fungal species		
	<i>E. coli</i> MTCC - 443	<i>P. aeruginosa</i> MTCC - 2488	<i>S. aureus</i> MTCC - 96	<i>S. pyogenes</i> MTCC - 442	<i>C. albicans</i> MTCC - 227	<i>A. niger</i> MTCC- 282	<i>A. clavatus</i> MTCC - 1323
1	200	100	200	25	1000	>1000	>1000
3	200	500	12.5	500	1000	1000	1000
4	62.5	100	200	250	250	1000	1000
5_a	100	100	100	100	500	1000	500
5_b	500	500	1000	1000	500	500	1000
5_c	200	500	500	1000	500	1000	1000
5_d	500	1000	500	25	500	1000	500
5_e	500	500	1000	500	1000	500	1000
5_f	1000	200	500	1000	1000	500	500
5_g	1000	500	1000	1000	1000	500	500
5_h	200	500	50	500	500	1000	500
5_i	500	1000	500	100	500	1000	1000
5_j	500	500	1000	500	1000	1000	1000
5_k	250	200	500	50	1000	500	1000
5_l	150	200	200	250	1000	1000	1000
5_m	1000	1000	500	500	1000	1000	1000
5_n	1000	200	200	200	500	500	500
5_o	100	1000	1000	500	100	100	100
Gentamycin	0.05	1	0.25	0.5	-	-	-
Ampicilin	100	100	250	100	-	-	-
Chloramphenicol	50	50	50	50	-	-	-
Ciprofloxacin	25	25	50	50	-	-	-
Norfloxacin	10	10	10	10	-	-	-
Nystatin	-	-	-	-	100	100	100
Greiseofulvin	-	-	-	-	500	100	100

Conclusions

Results showed that most of the synthesized compounds were active against *C. albicans* but they had poor activity against other fungal species. Carboxamide of urea **4** gave good activity against *E. coli*, *S. aureus* with ampicilin and *C. albicans* with griseofulvin. Compound **5_o**(R= H), showed

good activity against fungal species of *A. niger* and *A. clavatus*. From the above results of antibacterial and antifungal activity, it can be concluded that the compounds bearing -Cl, -CH₃ and -NO₂ groups are more potent than the other compounds. They showed comparatively good antibacterial as well as antifungal activity. Modification in the **lead** molecule *via* different stages, changes the biological activities that were observed by the above results. Thus, the present work provides new outlines on the study of structure-activity relationships of oxazolyl derivatives, putting special emphasis on incorporation with quinazoline moiety.

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