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A Novel Series of Biologically Active Quinazolinones through Ring Transformation of 2-(5-Nitrofuran-2-yl)-4H-benzo[d][1,3]oxazin-4-one

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Abstract: 2-(5-nitrofuran-2-yl)-4H-benzo[d][1,3]oxazin-4-one(2) was subjected to reaction with $NH_2NH_2.H_2O$, formamide, $NH_2OH.HCl$ to give the quinazolinones **3-5**, respectively. When benzoxazinone **2** was subjected to the reaction with1, 2-phenylene diamine or thiosemicarbazide under different conditions ,it produced the quinazolinone derivatives **6-9**, respectively. Reaction of the aminoquinazolinone **3** with acetyl chloride, benzoyl chloride, benzenesulphonyl chloride , ethyl chloroacetate or ethyl anthranilate, furnished the quinazolinone derivatives **10a,b-13**, respectively. On the other hand, reaction of **3** with CS_2 / NaOH gave the salt **14**, which upon treatment with dimethyl sulphate furnished the thioester **15**, which underwent reactions with primary and secondry amines to give the thioamides **16a-c**. Finally, the hydroxyquinazolinone **4** was treated with Ac_2O or ethyl chloroacetate to afford the acetoxy compound **17** and the ester **18**, respectively.The later reacted with $NH_2NH_2.H_2O$ to produce the hydrazide**19**.

Keywords: Quinazolinone, methyldithioate, benzimidazoloquinazoline, triazolo[1,5-c]quinazoline, hydrazinecarbothioamide.

Introduction: quinazolinones belong to the most frequently reported heterocyclic compounds in medicinal chemistry, which possess diverse biological activities like antineoplastic [1]-[3], anti-inflammatory, analgesic [4]-[8], antihistaminic [9], anti-hypertensive [10], cardiac stimulant activity [11], antimalarial [12], anticonvulsant [13]-[15], antimicrobial [16]-[18], etc.Based on the aforementioned facts and as a continuation of our previous efforts [19]-[24] aiming to establish heterocyclic compounds with antimicrobial activity, we prepared 2-(5-nitrofuran-2-yl)-4H-benzo[d][1,3]oxazin-4-one(2),which underwent different reaction to producebiologically active quinazolinone derivativesthrough hetercyclic ring transformation.The synthesized compounds were screened for their activity against Gram negative Escherichiacoli, Gram positive bacteria (Staphylococcus aureus, Bacillus subtilis) and pathogenic fungi (Saccharomyces cerevisiae, Candida albicans).The structures of the new synthesized compounds were confirmed by IR, ^{1}H-NMR, mass spectra and elemental analyses.

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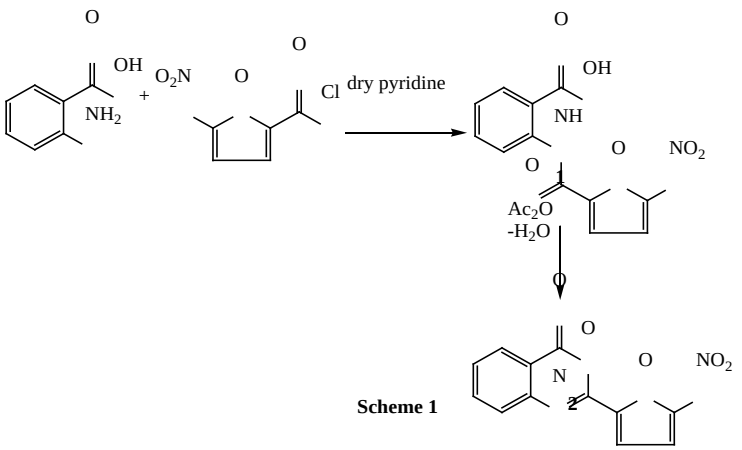
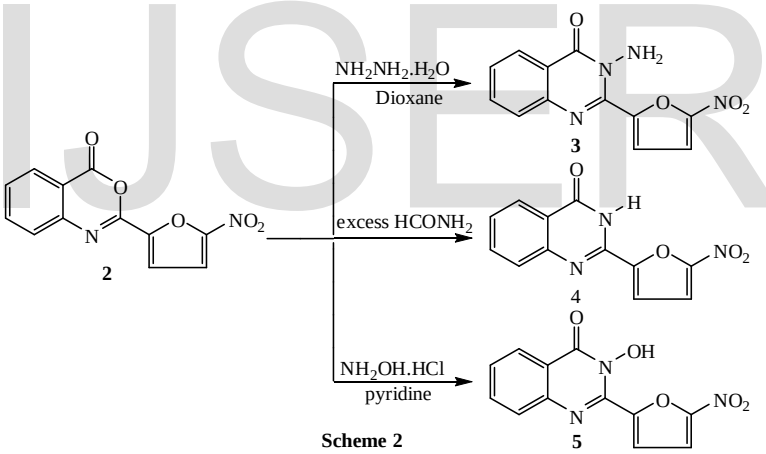
Results and Discusion:

The key starting material, 2-(5-nitrofuran-2-yl)-4H-benzo[d][1,3]oxazin-4-one(**2**), was synthesized (Scheme 1) from 5-nitrofuroyl chloride and anthranilic acid in the presence of dry pyridine *via* N-acylantharanilic acid derivative **1**, which underwent ring closure upon heating with Ac_2O to afford the title compound **2** [25].

Refluxing benzoxazinone **2** with $NH_2NH_2.H_2O$ in dioxane afforded the N-aminoquinazolinone **3**, while heating **2** in excess of formamide produced the quinazolinone derivative **4** [26]. When **2** was heated with hydroxylamine hydrochloride in pyridine, hydroxylquinazolinone derivative **5** [27] was obtained (Scheme 2).



Scheme 1

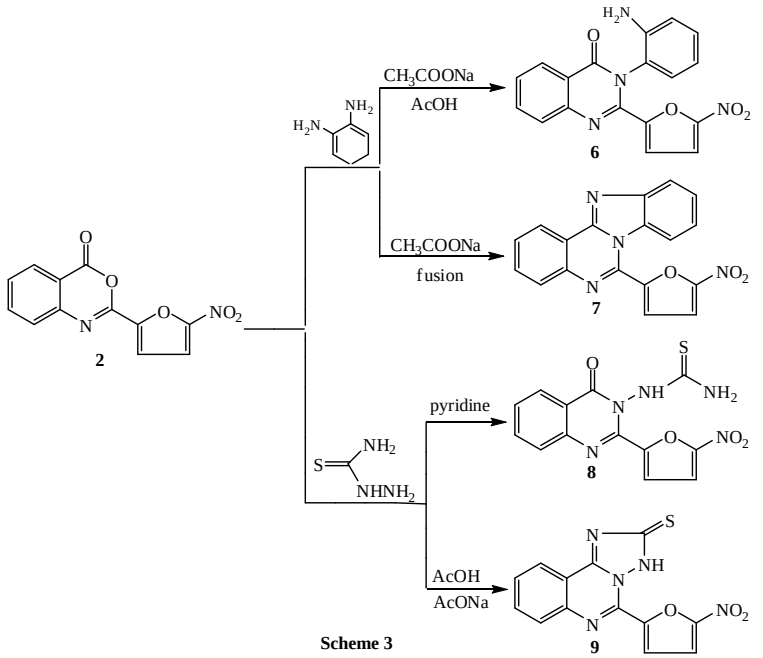


Scheme 2

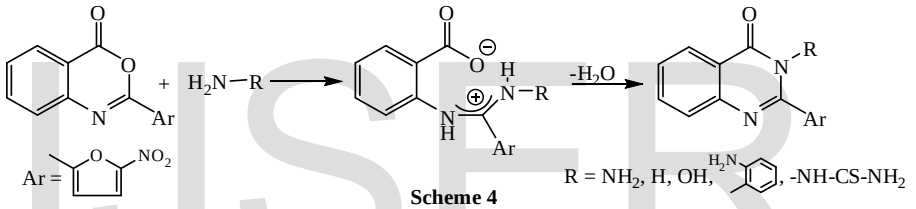
With the aim of expanding the synthetic potential of benzoxazinone **2** , we have studied its reaction with o-phenylenediamine and thiosemicarbazide under different conditions. Thus, refluxing **2** with 1,2-phenylenediamine in AcOH in the presence of fused NaOAc furnished the corresponding aninophenylquinazolinone **6**, while the benzimidazoloquinazoline derivative **7** was obtained when the same reaction was performed under fusion conditions.

Similarly, reaction of thiosemicarbazide with benzoxazinone **2** in pyridine produces the thiourea derivative **8**, but when the reaction was carried out in AcOH, the triazoloquinazoline derivative **9** was obtained (Scheme 3).

According to our speculation, these results can be interpreted as follows: The N-nucleophiles attack the benzoxazinone **2** in a fashion in which the amino group first undergoes H-bonding to the N-atom of the heterocycle. Then, the amino group reacts by nucleophilic addition at the azavinylic C(2) to form an inner amidinium salt, which subsequently is dehydrated to the quinazolinone derivative (Scheme 4).In case of compounds **7** and **9**, after the quinazolinone derivative was formed , a heterocyclic ring closure took place through a condensation reaction between NH_2 and C=O groups.



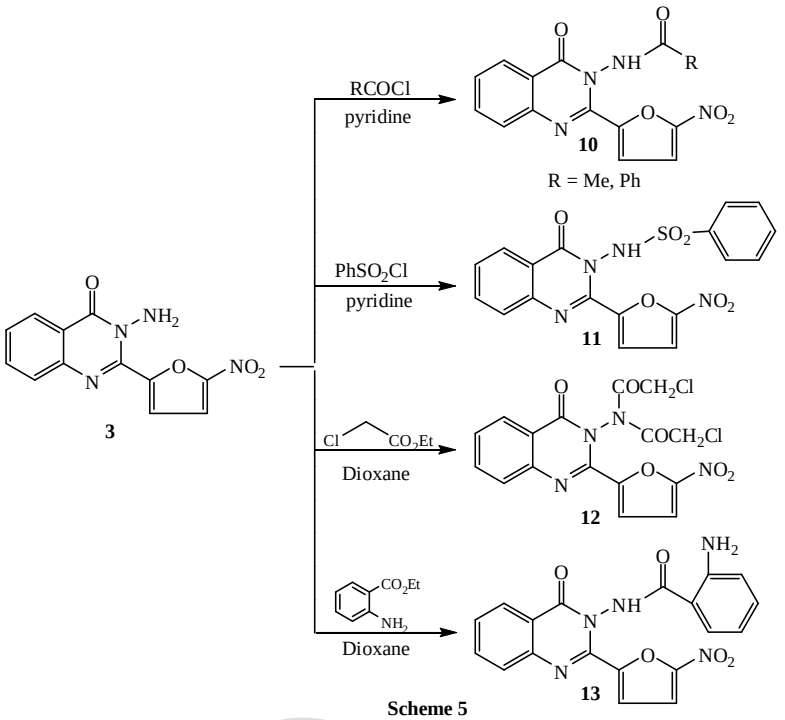
Scheme 3



Scheme 4

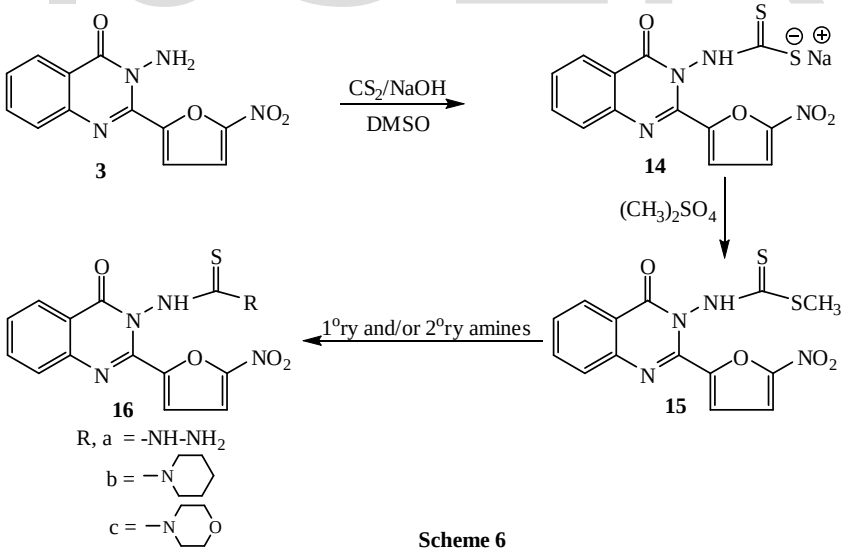
Compound **3** is considered as key starting material for a diversity of heterocyclic compounds; because it has hydrogen atoms of amino group which can be easily changed. In this context compound **3** was converted to the corresponding amides **10a, b** and **11** on treatment with acetyl chloride, benzoyl chloride or benzene sulphonyl chloride in pyridine. Furthermore, N-aminoquinazolinone **3** was converted to more interesting diamide derivative **12** *via* reaction with ethyl chloroacetate in boiling dioxane. The reaction takes place *via* nucleophilic displacement at acyl moiety and not at the alkyl halide moiety. This seems to be logic because the energy barrier required for the tetrahedral mechanism is less than SN^2 mechanism and consequently the reaction proceeds through the first mechanism rather than the second one. The energy barrier that hampers SN^2 can be understood from the fact that in case of tetrahedral mechanism, the system receives much of its "energy payment" from the formation of the new bond (N-CO) before having to pay its" energy dept" for the breaking of (C-OR) bond.

On the other hand, refluxing **3** with ethyl anthranilate under the same conditions furnished only the mono amide derivative **13** (Scheme 5). The formation of mono amide rather than the di-amide may be attributed to the steric hinderance caused by the first aniline moiety.



Scheme 5

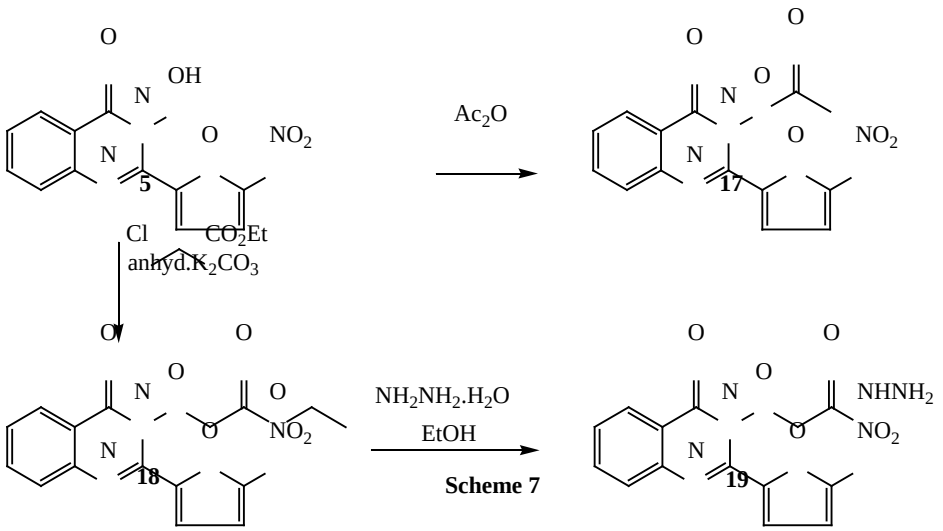
The point of interest in this investigation is study of the behavior of the aninoquinazolinone **3** towards CS_2. Thus, when quinazolinone **3** in DMSO was added to CS_2 and NaOH, it afforded the sodium salt of carbamodithioate **14** which reacted with Me_2SO_4 to give dithioate ester **15** which upon treatment with $NH_2NH_2.H_2O$ and secondary amines (namely, piperidine or morpholine) in DMF yielded thioamide derivatives **16a-c** were produced (Scheme 6).



Scheme 6

Finally, the structure of the 3-hydroxyquinazolinone derivative **5** was inferred chemically by studying its behavior towards C-electrophiles. In the presemt work, treatment of 5 with boiling Ac_2O afforded 3-acetyloxyquinazolinone derivative **17**. On the other hand, the conversion of **5** into ethyl acetate derivative **18** was achieved *via* the interaction with ethyl chloroacetate in the presence of anhydrous K_2CO_3 in boiling dry acetone. Compound **18**

was chemically confirmed by the reaction with hydrazine hydrate in boiling ethanol to afford the acetohydrazide derivative **19** (Scheme 7).



Scheme 7

Biological activities. Antibacterial Activity

All of the new synthesized compounds were screened for in vitro antibacterial activity against gram negative bacteria Serratiamarcesens, and proteusmerabitis and gram positive bacteria, Staphylococcus, Aureus and Bacillus cereus. The standard drug used was Ampicilin. The investigation of antibacterial screening reported in table 1 revealed that some of the newly synthesized compounds showed moderate to good inhibition at 100 µg/ml in DMF.Compounds **3,4,8,9,18** and **19** exhibited high activity.

Antifungal Activity

Most of the new synthesized compounds were screened for in vitro antifungal activity against Aspergillus ochraceus Wilhelm and penicillium chrysogenumthom by agar diffusion technique. The standard drug used was Mycostatine. The investigation of antifungal screening reported in table1 revealed that some of the newly synthesized compounds showed moderate to good inhibition at 100 µg/ml in DMF. Compounds **3,4,7,8,15,16,17,18** and **19** showed good activity.

Table 1 : Antimicrobial activity of the synthesized compounds.

Compd No	Antibacterial Activity				Antifungal Activity	
	Gram positive		Gram negative		Aspergillus ochraceus Wilhelm	Penicillium chrysogenum Thom
	Staphylococcus aureus	Bacillus cereus	Serrati amarce sens	proteusmerabitis		
2	++	++	++	++	+	+
3	+++	+++	+++	+++	++	++
4	+++	+++	+++	++	++	++
5	++	++	++	++	+	+
6	+	+	+	+	+	+
7	++	++	+	+	+	++
8	+++	+++	++	+++	++	++
9	+++	++	+++	+++	++	+
10	+	+	+	+	+	+
11	+	+	+	+	+	+
12	+	+	+	+	+	+
13	+	+	+	+	+	+
15	++	++	++	++	+	++
16	++	++	++	++	+	++
17	++	++	++	++	+	++
18	+++	+++	+++	+++	++	++
19	+++	+++	+++	+++	++	++
Standard	++++	++++	++++	++++	++++	++++

The width of the zone of inhibition indicates the potency of antibacterial activity; (-) no antibacterial activity; (+) less activity with the diameter of the zones equal to 0.2 – 0.5 cm, (++) moderate activity with the diameter of the zones equal to 0.6-1.4 cm; (+++) marked high activity with the diameter of the zones equal to 1.5 – 3.0 cm; (++++) very high activity with the diameter of the zones (over 3.0 cm).

Experimental:

All melting points are uncorrected and were determined on Gallen Kamp electric melting point apparatus. The microanalyses were within the acceptable limits (±0.4%) of the theoretical values and were carried out in theMicroanalytical Center, Cairo University, Egypt. IR spectra (in KBr, cm-1/ν) on Shimadzu FTIR 8101 PC.1H-NMR spectra were recorded on a Varian 300 MHz with residual proton signal of the deuterated solvent as the internal reference (δ_H = 7.26 ppm for $CDCl_3$ and δ_H = 2.51 ppm for DMSO-d_6). The chemical shifts were reported as parts per million (δ ppm) and coupling constant (J)values are given in Hz using tetramethylsilane (TMS) as internal standard from downfield to upfield.The mass spectra were recorded on Shimadzu GCMS-QP-1000EX mass spectrometer at 70 e.v. Homogeneity of the synthesized compounds was checked by Merk Thin-layer chromatography (TLC) aluminium sheet silica gel 60 F254 with detection by UV quenching at 254 nm.Reagents and solvents were used as obtained from the supplier without further purification.

2-(5-nitrofuran-2-yl)-4H-benzo[d][1,3]oxazin-4-one (2).

To a solution of anthranilic acid (1.37 g, 0.01 mol) in pyridine (30 ml) 5-nitrofuran-2-carbonyl chloride (3.51 g, 0.02 mol) was added during 0.5 hr. Then, the reaction mixture was stirred for additional 1 hr at room temperature. The reaction mixture was poured on ice/HCl and left overnight. The precipitate obtained was filtered off, washed by water (3x 100) and dried to give the anthranil1. A suspension of 2-(5-nitrofuran-2-carboxamido)benzoic acid (1) (2.76g, 0.01 mol) in freshly distilled acetic anhydride (40 ml) was heated under reflux for 4 h and then concentrated under vacuum. The residue was crystallized from benzene to afford compound **2**.

Compound 2: Yield: 81% (2.1g), m.p.152-154°C, IR :1619 (C=N), 1752 (C=O of δ-lactone). ^{1}H-NMR ($CDCl_3$): 6.78-8.33 (m, 6H, Ar-H, and furan-H). MS: 258 (M^{+}). Anal.calc. for $C_{12}H_6N_2O_5$ (258): C: 55.81, H:2.33, N:10.85; found: C: 56.09, H:2.53, N:11.08.

3-Amino-2-(5-nitrofuran-2-yl)quinazolin-4(3H)-one (3).

A mixture of benzoxazinone **2** (2.58, 0.01 mol) and hydrazine hydrate (1.0 g, 0.02 mol) was heated under reflux in dioxin (30 ml) for 3 hr. After concentration, the solid that separated out, was filtered off, dried and then recrystallized from dioxan to produce the aminoquinazolinone **3**.

Compound 3: Yield 77% (2.1g), m.p.222-224°C, IR :1608 (C=N), 1663 (C=O), 3224, 3317 (NH_2). ^{1}H-NMR (DMSO-d_6): 6.89- 8.39 (m, 6H, Ar-H, and furan-H), 9.25 (br., 2H, NH_2, D_2O exchangeable). MS: 272 (M^{+}). Anal.calc. for $C_{12}H_8N_4O_4$ (272): C: 52.94, H: 2.94, N: 20.59; found: C: 53.18, H: 3.19, N: 20.38.

2-(5-nitrofuran-2-yl)quinazolin-4(3H)-one (4).

A solution of benzoxazinone2 (2.58 g, 0.01 mol) in formamide (15 ml) was refluxed for 2 hr. The reaction mixture was left to cool and was then poured onto ice/H2O. The solid deposited was separated by filtered, dried and recrystallized from ethanol to give the quinazoline4.

Compound 4: Yield 75% (1.93g), m.p.245-247°C, IR: 1612 (C=N), 1668 (C=O), 3194 (NH). ^{1}H-NMR ($CDCl_3$): 6.81-8.31 (m, 6H, Ar-H, and furan-H), 11.1 (br., H, NH, D_2O exchangeable). MS: 257 (M^{+}). Anal. calc. for $C_{12}H_7N_3O_4$ (257): C: 56.03, H: 2.72, N: 16.34; found: C: 55.87, H: 3.00, N: 16.66.

3-Hydroxy-2-(5-nitrofuran-2-yl)quinazolin-4(3H)-one (5).

A mixture of benzoxazinone **2** (2.58 g, 0.01 mol) and hydroxylamine hydrochloride (2.09 g, 0.03 mol) in pyridine (30 ml) was heated under reflux for 3hr. After cooling, the reaction mixture was poured into ice/HCl. The solid that obtained was filtered off and crystallized from ethanol affording the hydroxyl quinazolinone derivative **5**.

Compound 5: Yield 69% (1.89g), m.p.231-233°C, IR :1623 (C=N), 1671 (C=O), 3374 (OH). ^{1}H-NMR ($CDCl_3$): 6.84-8.42 (m, 6H, Ar-H, and furan-H), 10.83 (br., H, OH, D_2O exchangeable). MS : 273 (M^{+}). Anal. calc. for $C_{12}H_7N_3O_5$ (273): C: 52.75, H: 2.56, N: 15.38; found: C: 53.00, H: 2.44, N: 15.67.

3-(2-aminophenyl)-2-(5-nitrofuran-2-yl)quinazolin-4(3H)-one (6).

A solution of compound **2** (2.58g, 0.01 mol) and o-phenylenediamine (1.08g, 0.01 mol) in acetic acid (30 ml), in presence of fused sodium acetate (0.6g), was heated under reflux for 2hr. The reaction mixture was left to cool and then poured into water (100 ml) with continuous stirring. The solid the separated out was filtered off and crystallized from benzene producing compound6.

Compound 6: Yield 72% (2.51g), m.p.256-258°C, IR :1615 (C=N), 1665 (C=O), 3187, 3339 (NH_2). ^{1}H-NMR ($CDCl_3$): 6.77- 8.35 (m, 10H, Ar-H, and furan-H), 9.11 (br., 2H, NH_2, D_2O exchangeable). MS: 348 (M^{+}). Anal. calc. for $C_{18}H_{12}N_4O_4$ (348): C: 62.07, H: 3.45, N: 16.09; found: C: 61.77, H: 3.68, N: 15.78.

2-(5-nitrofuran-2-yl)benzimidazolo[1,2-c]quinazoline (7).

A mixture of benzoxazinone **2** (2.58g, 0.01 mol) and o-

phenylenediamine (1.08g, 0.01 mol) and fused sodium acetate (0.6g), was heated in an oil bath at 170°C for 2 hr. The reaction mixture was left to cool and then poured into hot water (100 ml) with continuous stirring. The solid the separated out was filtered off and crystallized from dioxne to give compound **7**.

Compound 7: Yield 60% (1.98g), m.p.287-289°C, IR : 1620 (C=N). ^{1}H-NMR (DMSO-d_6): 6.72- 8.40 (m, 10H, Ar-H, and furan-H). MS: 330 (M^{+}). Anal. calc. for $C_{18}H_{10}N_4O_3$ (330) : C: 65.45, H: 3.03, N: 16.97; found: C: 65.76, H: 2.88, N: 17.22.

1-(2-(5-nitrofuran-2-yl)-4-oxoquinazolin-3(4H)-yl)thiourea (8).

Thiosemicarbazide (0.91 g, 0.01 mol) was added to a solution of benzoxazinone2 (2.58 g, 0.01 mol) in pyridine (20 ml) and refluxed for 4 hr. After cooling the reaction mixture was poured into ice/HCl. The solid that was separated out filtered off, dried and then crystallized from ethanol to produce8.

Compound 8: Yield 71% (2.35g), m.p.266-269°C, IR :1630(C=N), 1679 (C=O), 3198, 3275 and 3371 (NH, NH_2). ^{1}H-NMR (DMSO-d_6): 6.81- 8.37 (m, 6H, Ar-H, and furan-H) 9.44 (br., 2H, NH_2, D_2O exchangeable), 10.74 (br., H, NH, D_2O exchangeable). MS: 331 (M^{+}). Anal. calc. for $C_{13}H_9N_5O_4S$ (331): C: 47.13, H: 2.72, N: 21.15, S: 9.67; found: C: 46.87, H: 2.55, N: 20.88, S: 9.36.

5-(5-nitrofuran-2-yl)-[1,2,4]triazolo[1,5-c]quinazoline-2(3H)-thione (9).

To a solution of compound 2(2.58 g, 0.01 mol) in glacial acetic acid (30 ml), thiosemicarbazide (0.91 g, 0.01 mol) was added, in the presence of sodium acetate , and heated under reflux for 4 h. The mixture was allowed to stand overnight, and the separated solid was crystallized from ethanol to afford the triazolo derivative 9.

Compound 9: Yield 71% (2.35g), m.p.237-239°C, IR :1153 (C=S), 1610(C=N), 3275(NH). ^{1}H-NMR (DMSO-d_6): 6.70-8.21 (m, 6H, Ar-H, and furan-H) 10.54 (br., H, NH, D_2O exchangeable). MS: 313 (M+). Anal. calc. for $C_{13}H_7N_5O_3S$ (313): C: 49.84, H: 2.24, N: 22.36, S: 10.22; found: C: 50.16, H: 2.66, N: 22.63, S: 9.88.

N-(2-(5-nitrofuran-2-yl)-4-oxoquinazolin-3(4H)-yl)acetamide (10a) and N-(2-(5-nitrofuran-2-yl)-4-oxoquinazolin-3(4H)-yl)benzamide (10b)

A mixture of quinazolinone **3** (2.72 g,0.01 mol) and acetyl chloride and/or benzoyl chloride (0.79 g, 1.77 g, 0.01 mol) in pyridine (20 ml) was refluxed for 3 hr. The cold mixture was poured into ice/HCl. The separated solid was filtered off, dried and crystallized from toluene to give 10a and benzene to afford 10b, respectively.

Compound 10a: Yield 81% (2.55g), m.p.201-203°C, IR :1618(C=N), 1651,1686(C=O),3289(NH). ^{1}H-NMR ($CDCl_3$): 2.29 (s, 3H, $COCH_3$), 6.88- 8.39 (m, 6H, Ar-H, and furan-H) 10.61 (br., H, NH, D_2O exchangeable). MS: 314 (M+). Anal. calc. for C14H10N4O5 (314): C: 53.50, H: 3.18, N: 17.83; found: C: 53.77, H: 3.47, N: 18.14.

Compound 10b: Yield 71% (2.67g), m.p.189-191°C, IR :1621(C=N), 1656,1690(C=O),3278(NH). ^{1}H-NMR ($CDCl_3$): 6.79- 8.36 (m, 11H, Ar-H, and furan-H) 10.89 (br., H, NH, D_2O exchangeable). MS: 376 (M^{+}). Anal. calc. for $C_{19}H_{12}N_4O_5$ (376): C: 60.64, H: 3.19, N: 14.89; found: C: 60.30, H: 3.50, N: 15.16.

N-(2-(5-nitrofuran-2-yl)-4-oxoquinazolin-3(4H)-yl)benzensulphonamide (11)

To a solution of the quinazolinone **3** (2.72 g, 0.01 mol) in pyridine (20 ml), benzene sulphonyl chloride (1.76 g, 0.01 mol) was added. The reaction mixture was allowed to heat under refluxed for 3 hr. After cooling, the mixture was poured into ice/HCl. The separated solid was filtered off, dried and crystallized from toluene affording the sulphonamide derivative 11.

Compound 11: Yield 76% (3.13g), m.p.228-230°C, IR :1612(C=N), 1685(C=O),3249(NH). ^{1}H-NMR ($CDCl_3$): 6.81- 8.29 (m, 11H, Ar-H, and furan-H) 10.62 (br., H, NH, D_2O exchangeable). MS: 412 (M^{+}). Anal. calc. for $C_{18}H_{12}N_4O_6S$ (412): C: 52.43, H: 2.91, N: 13.59, S: 7.77; found: C: 52.11, H: 3.23, N: 13.91, S: 8.06.

2-Chloro-N-(2-chloroacetyl)-N-(2-(5-nitrofuran-2-yl)-4-oxoquinazolin-3(4H)-yl)acetamide (12).

A mixture of quinazolinone **3** (2.72 g, 0.01 mol) and ethyl chloroacetate (1.23 g, 0.01 mol) in dioxan was refluxed for 4 hr. The solid that was separated after cooling, filtered off and crystallized from ethanolproducing the acetamide derivative 12.

Compound 12: Yield 45% (1.91 g), m.p.256-258°C, IR : 761 (C-Cl), 1616 (C=N) , 1655, 1674 (C=O). ^{1}H-NMR (CDCl3): 4.39 (s, 4H, $2CH_2Cl$), 6.78- 8.25 (m, 6H, Ar-H, and furan-H). MS: 424 (M^{+}). Anal. calc. for $C_{16}H_{10}C_{l2}N_4O_6$ (424): C: 45.28, H: 2.36, N: 13.21, Cl: 16.51; found: C: 45.00, H: 2.65, N: 12.93, Cl: 16.36.

2-Amino-N-(2-(5-nitrofuran-2-yl)-4-oxoquinazolin-3(4H)-yl)benzamide (13)

A solution of the quinazolinone **3** (2.72 g, 0.01 mol) and aminoethylbenzoate (1.65 g, 0.01 mol) in dioxan (30 ml) was heated under reflux for 3 hr. The reaction mixture was concentrated and left to cool. The residue obtained was filtered off, dried and recrytallized from toluene to give compound 13.

Compound 13: Yield 59% (2.31 g), m.p.193-195°C, IR: 1611(C=N), 1668(C=O), 3188, 3282 and 3379 (NH, NH2).

^{1}H-NMR ($CDCl_3$): 6.86- 8.28 (m, 10H, Ar-H, and furan-H), 9.41 (br., 2H, NH_2, D_2O exchangeable), 10.66 (br., H, NH, D_2O exchangeable). MS: 391 (M^+). Anal. calc. for $C_{19}H_{13}N_5O_5$ (391): C: 58.31, H: 3.32, N: 17.90; found: C: 58.60, H: 3.66, N: 19.23.

Methyl 2-(5-nitrofuran-2-yl)-4-oxoquinazolin-3(4H)-ylcarbamodithioate (15).

To a vigorously stirred solution of quinazolinone 3 (5.44 g, 0.02 mol) in DMSO (10 ml) at room temperature, carbon disulphide (1.6 ml, 0.026 mol) and sodium hydroxide (1.2 ml, 0.02 mol) were added dropwise during 30 min, stirring was continued for further 30 min, the sodium salt **14** was precipitated. Dimethylsulphate (2.5 g, 0.02 mol) was then added to the reaction mixture at 5-10°C and stirring was continued for additional 3 h. The reaction mixture was filtered off, washed with H2O (3x100 ml), dried and crystallized from toluene affordingthe methyl dithioate derivative 15.

Compound 15: Yield 69% (5.00 g), m.p.179-182$_o$C, IR :1323 (C=S), 1624(C=N), 1673(C=O), 2901 (C-H aliph), 3223(NH). ^{1}H-NMR ($CDCl_3$): 2.38 (s, 3H, S-CH_3), 6.69-8.22 (m, 6H, Ar-H, and furan-H), 9.19 (br., H, NH, D_2O exchangeable). MS: 362 (M^+). (M+). Anal. calc. for $C_{14}H_{10}N_4O_4S_2$ (362): C: 46.41, H: 2.76, N: 15.47, S: 17.68; found: C: 46.10, H: 3.03, N: 15.21, S:18.02.

N-(2-(5-nitrofuran-2-yl)-4-oxoquinazolin-3(4H)-yl)hydrazinecarbothioamide (16a), N-(2-(5-nitrofuran-2-yl)-4-oxoquinazolin-3(4H)-yl)piperidine-1-carbothioamide (16b) and N-(2-(5-nitrofuran-2-yl)-4-oxoquinazolin-3(4H)-yl)morpholine-4-carbothioamide (16c).

A mixture of the methyl dithioate ester derivative **15** (3.62 g, 0.01 mol) and hydrazine hydrate, piperidine and/or morpholine (1.0 g, 1.7 g, 1.74 g, 0.02 mol respectively) in DMF (20 ml) was refluxed for 22 h, then cooled and poured into ice/H2O, the residue obtained was filtered off, dried and crystallized from dioxan, benzene, respectively to give 16a-c.

Compound 16a: Yield 79% (2.73 g), m.p.247-249°C, IR :1328 (C=S), 1618(C=N), 1669(C=O), 3182, 3263, 3311(NH, NH2). 1H-NMR (DMSO-d6): 6.73- 8.33 (m, 6H, Ar-H, and furan-H), 9.09 (br., 2H, NH_2, D_2O exchangeable), 9.38 (br., H, NH, D_2O exchangeable), 10.78 (br., H, NH, D_2O exchangeable). MS: 346 (M^+). Anal. calc. for $C_{13}H_{10}N_6O_4S$ (346): C: 45.09, H: 2.89, N: 24.28, S: 9.25; found: C: 44.80, H: 3.18, N: 24.01, S: 8.94.

Compound 16b: Yield 70% (2.79 g), m.p.208-210°C, IR :1324 (C=S), 1613(C=N), 1678(C=O), 3244(NH). ^{1}H-NMR ($CDCl_3$): 1.34 (m, 6H piperidine ring), 2.91 (t, *J* = 7.2, 4H, CH_2-N-CH_2), 6.77- 8.40 (m, 6H, Ar-H, and furan-H), 10.53 (br., H, NH, D_2O exchangeable). MS: 399 (M^+). (M+). Anal. calc. for $C_{18}H_{17}N_5O_4S$ (399): C: 54.14, H: 4.26, N: 17.54, S: 8.02; found: C: 54.39, H: 4.57, N: 17.88, 8.33.

Compound 16c: Yield 69% (2.76 g), m.p.231-233°C, IR : 1321 (C=S), 1622(C=N), 1676(C=O), 3252(NH). ^{1}H-NMR ($CDCl_3$): 2.93 (t, *J* = 7.2, 4H, CH_2-N-CH_2), 3.22 (t, *J* = 7.4, 4H, CH_2-O-CH_2), 6.71- 8.31 (m, 6H, Ar-H, and furan-H), 10.39 (br., H, NH, D_2O exchangeable). MS: 401 (M^+). Anal. calc. for $C_{17}H_{15}N_5O_5S$ (401): C: 50.87, H: 3.74, N: 17.46, S: 7.98; found: C: 51.18, H: 4.03, N: 17.77, 8.31.

2-(5-nitrofuran-2-yl)-4-oxoquinazolin-3(4H)-yl acetate (17).

A solution of the hydroxyl quinazolinone derivative 5 (2.73 g, 0.1 mol) in freshly distilled acetic anhydride (15 ml) was reflxed for 4 h. The mixture was concentrated and the residue cooled recrystallized from benzene to produce the ester derivative 17.

Compound 17: Yield 76% (2.39 g), m.p.180-182°C, IR :1609(C=N), 1667, 1701(C=O), 3254 (NH). ^{1}H-NMR ($CDCl_3$): 2.39(s, 3H, $COCH_3$), 6.85- 8.40 (m, 6H, Ar-H, and furan-H). MS: 315 (M^+). Anal. calc. for $C_{14}H_9N_3O_6$ (315): C: 53.33, H: 2.86, N: 13.33; found: C: 53.04, H: 3.15, N: 13.02.

Ethyl 2-(2-(5-nitrofuran-2-yl)-4-oxoquinazolin-3(4H)-yloxy)acetate (18).

A mixture of compound **5** (2.73 g, 0.1 mol), ethyl chloroacetate (2.72g, 0.02 mol) and anhydrous potassium carbonate (0.04 mol) in dry acetone (60 ml) was reflxed for 22 h on water bath. The excess solvent was removed by rotator evaporator, and the residue was poured on to cold water. The obtained solid was filtered off and crystallized from toluene affording the ethyl acetate derivative **18**.

Compound 18: Yield 84% (3.02 g), m.p.208-210°C, IR :1613(C=N), 1670, 1722(C=O), 3254 (NH). ^{1}H-NMR ($CDCl_3$):1.35 (t, *J* = 6.7, 3H, COCH2CH3), 3.89 (q, *J* = 7.3, 2H, $COCH_2CH_3$), 4.58 (s, 2H, OCH_2CO), 6.80- 8.36 (m, 6H, Ar-H, and furan-H). MS: 359 (M^+). Anal. calc. for $C_{16}H_{13}N_3O_7$ (359): C: 53.48, H: 3.62, N: 11.70; found: C: 53.19, H: 3.90, N: 12.00.

2-(2-(5-nitrofuran-2-yl)-4-oxoquinazolin-3(4H)-yloxy)acetohydrazide (19).

A solution of compound **18** (3.59g, 0.01 mol) and hydrazine hydrate (0.75 g, 0.015 mol) in ethanol (60 ml) was refluxed for 4h. The reaction mixture was concentrated and then allowed to cool and the obtained solid was filtered of and crystallized from dioxane to form the hydrazide19.

Compound 19: Yield 71% (2.45 g), m.p.246-248°C, IR

:1607(C=N), 1658, 1681(C=O), 3189, 3274, 3332(NH, NH2). ^{1}H-NMR ($CDCl_3$): 4.66 (s, 2H, OCH_2CO), 6.88-8.44 (m, 6H, Ar-H, and furan-H), 9.23 (br, 2H, NH_2, D_2O exchangeable), 10.14 (br., H, NH, D_2O exchangeable). MS: 345 (M^{+}). Anal. calc. for $C_{14}H_{11}N_5O_6$ (345): C: 48.70, H: 3.19, N: 20.29; found: C: 49.01, H: 2.92, N: 19.98.

Conclusion:

In this paper, the synthesized 2-(5-nitrofuran-2-yl)-4H-benzo[d][1,3]oxazin-4-one **2** was successfully converted into the more stable and the higher functionalized substituted quinazolinone derivatives through heterocyclic ring transformation. Also the plethora of research described in this manuscript indicates a wide spectrum of biological activities exhibited by the newly synthesized quinazolinone derivatives as antimicrobial agents.

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