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Design and Synthesis of Novel Quinazolin-4(3*H*)-One Appended 1,2,4-Oxadiazoles as Antimicrobial Agents

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A novel series of hybrid heterocycles having quinazolinone based 1,2,4-oxadiazoles scaffold with methylamino linkage were obtained in two synthetic pathways. In method I, quinazolinone based ester reacted with amidoximes and gave the corresponding hybrid products in poor yields. To reduce the duration of reaction time and increase the yields of the products, dehydrochlorination reaction of 6-aminoquinazolinone was carried out with 5-chloromethyl-1,2,4-oxadiazoles in other synthetic method, which furnished the products in good to excellent yields. The synthesized 1,2,4-oxadiazole hybrids were characterized using spectroscopic techniques and also screened for their antimicrobial activity against bacteria and fungi, among which chloro-substituted analogues **6d** and **6e** presented potent activity against all strains whereas other analogues proven to have moderate activities.

Keywords: Aminoquinazolinone, Quinazolinonylglycinate, Amidoximes, 1,2,4-Oxadiazoles, Antimicrobial activity.

INTRODUCTION

Scaffolds comprising nitrogen and oxygen are highly adaptable tools in the drug research field, and their synthesis has been expedited [1]. 1,2,4-Oxadiazoles contain two nitrogen and one oxygen atom in a five-membered ring, referred to as azoxime [2]. The scaffolds of azoxime have been extensively investigated due to their significant biological implications such as antiviral [3], antidepressant [4], anticancer [5], antioxidant [6], anti-inflammatory [7] and antiparasitic [8] activities. Oxalamine is one of the pioneering pharmaceutical drug to incorporate 1,2,4-oxadiazole and it was released as a cough suppressant in the commercial market [9]. Several marketed drugs feature a 1,2,4-oxadiazole ring in their structure, for instance, butalamine is utilized as a vasodilator [10], pleconaril serves as an antiviral drug [11], ataluren acts before or during the hydrolysis stage and acts as a competitive inhibitor of productive RFC binding [12] and proxazole is employed for functional gastrointestinal disorders [13].

1,2,4-Oxadiazole compounds have been proven to exhibit inhibitory activity against several enzymes and receptors, including human deacetylase sirtuin 2 (HDSirt2), histone deacetylase (HDAC), penicillin-binding protein (PBP2a), carbonic anhydrase (CA), rearranged during transfection (RET) kinase, efflux pump, cyclooxygenases (COX-1 and COX-2) and butyrylcholinesterase (BChE). They also demonstrate affinity for σ1, σ2, kappa opioid (KOR), orexin and estradiol (ER) receptors [14,15].

Molecular hybridization is a method of designing new ligands or prototypes by identifying pharmacophoric subunits in the molecular structure of known bioactive derivatives. By combining these subunits, new hybrid architectures can be developed that retain the specific characteristics of the original templates [16,17]. Hybridization of quinazolinones with various heterocycles could led to a novel potent molecule with diverse biological significance. There were few reports available on quinazolin-4(3*H*)-one based 1,2,4-oxadiazole hybrids [18]. Inspired by significant biological applications quinazolin-4-(3*H*)-one and 1,2,4-oxadiazole, availability of limited literature and in extension to our previous work [16], we have aimed to synthesize a new series of hybrids having quinazolinone as well as 1,2,4-oxadiazole scaffolds with methylamino linker (Fig. 1) and evaluate their antimicrobial activity potentiality.

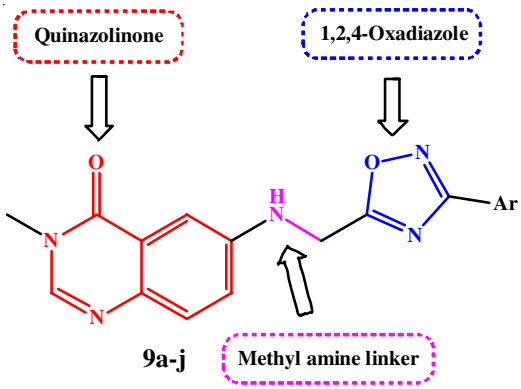


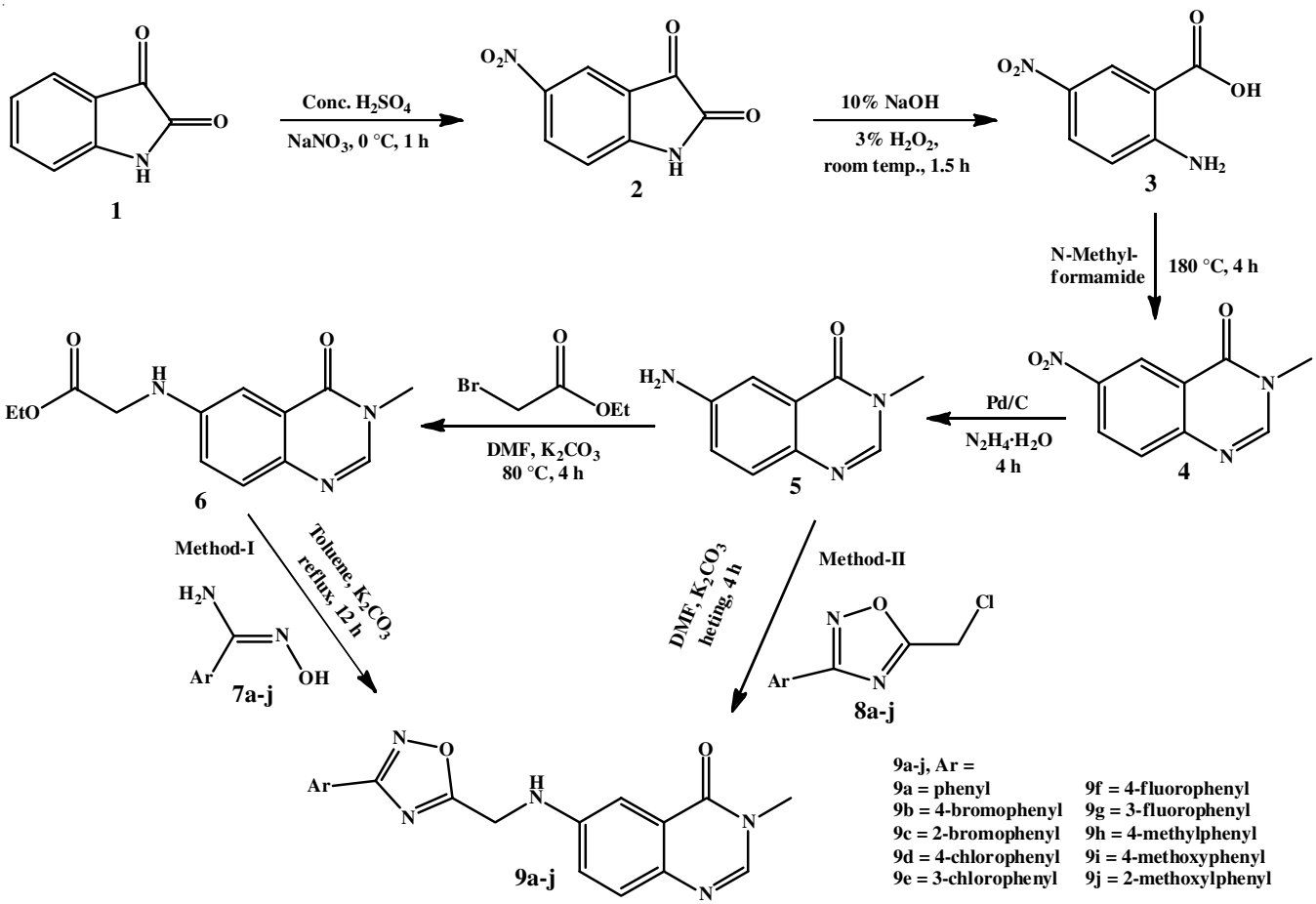
Fig. 1. Design rationale of quinazolinone-1,2,4-oxadiazole hybrids

EXPERIMENTAL

Without additional purification, all the synthetic reagents, catalysts and solvents were acquired from industrial sources such as Merck, Sigma-Aldrich, and Avra chemicals. Using penetrating silica gel Merck $60F_{254}$ plates, TLC was employed to check the progress of the reaction. To determine the melting points of the synthesized compounds, the Stuart SMP3 liquefying point mechanical assembly was used. The recrystallization and a section chromatography approach with a silica gel 60-120 lattice to purify the products. The IR spectra were recorded on a Shimadzu FTIR 8400 S spectrometer with KBr pallets, while ^{1}H & ^{13}C NMR were measured on a Bruker 400 spectrometer at 400 and 100 MHz, respectively, using $CDCl_3$ and DMSO as solvents and TMS as an internal standard. A Shimadzu GC-MS QP 1000 spectrometer was used to record the mass spectra.

Synthesis of ethyl (3-methyl-4-oxo-3,4-dihydroquinazolin-6-yl)glycinate (6): 6-Aminoquinazolin-4-(3*H*)-one (**5**, 0.01 mmol) was dissolved in 25 mL of dry DMF, added K_2CO_3 (0.02 mmol), stirred for few minutes then ethyl bromoacetate (0.01 mmol) was added to the reaction mixture and heated at 80 ºC. After 4 h, the reaction mixture was poured into ice cold water and filtered the separated solid, purified using column chromatography with EtOAc:hexane (60:40) to afford the pure white solid product. Yield: 81%; m.p.: 158-161 ºC. IR (KBr, ν_{max}, cm^{-1}): 1730, 1650; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.08 (s, 1H), 7.45 (d, *J* = 8.8 Hz, 1H), 7.18 (dd, *J* = 8.8, 2.8 Hz, 1H), 7.03 (d, *J* = 2.7 Hz, 1H), 6.63 (t, *J* = 6.4 Hz, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 4.00 (d, *J* = 6.3 Hz, 2H), 3.46 (s, 3H), 1.21 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm: 170.06, 160.65, 149.22, 144.01, 141.13, 125.61, 124.39, 123.01, 113.87, 61.18, 45.51, 33.16, 14.70; $[M+H]^+$ peak at *m/z* 262.32.

Synthesis of 3-methyl-6-(((3-aryl-1,2,4-oxadiazol-5-yl)-methyl)amino)quinazolin-4(3*H*)-ones (9a-j): The synthesis of titled compounds **9a-j** was carried out in two different methods (**Scheme-I**).



Scheme-I: Synthesis of 3-methyl-6-(((3-aryl-1,2,4-oxadiazol-5-yl)methyl)amino)quinazolin-4(3*H*)-one analogues (**9a-j**)

Method-I: To a stirred solution of aminoquinazolinone ester **6** (0.01 mmol) in 10 mL of toluene an appropriate aryl amidoximes **7a-j** (0.01mmol) and K_2CO_3 (0.02 mmol) were added and refluxed for 12 h. After completion of the reaction excess toluene was removed by vacuum then workup procedure with water and EtOAc. The resultant compound was purified by column chromatography to yield the corresponding pure oxadiazole product **9a-j**. The yields were in the range of only 32-38%.

Method-II: In method-I, the reaction proceeds with more time and yield was less. To improve the product yield and decrease the reaction time compared to method-I, 6-aminoquinazolinone (**5**) and chloromethyl 1,2,4-oxadiazoles **8a-j** were used as precursors in obtaining the target quinazolinone based disubstituted 1,2,4-oxadiazoles with methylamino linker **9a-j**.

To 6-aminoquinazolinone (**5**) (0.01mmol) in 10 mL of DMF taken in a sealed tube added anhydrous K_2CO_3 (0.02 mmol) and appropriate 5-(chloromethyl)-3-phenyl-1,2,4-oxadiazole (**8a-j**) (0.01mmol), heated at 80 ºC for 4 h. The progress of the reaction was monitored by TLC, then the reaction mixture was poured into ice cold water, filtrated the solid and purified by column chromatography using (60-120 silica gel) hexane: EtOAc (3:7) to afford the corresponding pure compounds **9a-j**. The yields were in the range of 72-75%.

3-Methyl-6-(((3-phenyl-1,2,4-oxadiazol-5-yl)methyl)-amino)quinazolin-4(3*H*)-one (9a): Brown colour solid; yield: 75%; m.p.: 169-173 ºC. IR (KBr, ν_{max}, cm^{-1}): 1650 (C=O): ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.14 (s, 1H), 8.03 (dd, *J* = 7.9, 2.6 Hz, 2H), 7.63-7.60 (m, 3H), 7.54 (d, *J* = 8.8 Hz, 1H), 7.32 (dd, *J* = 8.8, 2.8 Hz, 1H), 7.26 (d, *J* = 2.7 Hz, 1H), 7.15 (t, *J* = 6.4 Hz, 1H), 4.90 (d, *J* = 6.4 Hz, 2H), 3.48 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm: 179.00, 168.11, 161.06, 147.09, 144.90, 140.49, 132.19, 129.80, 128.66, 128.43, 128.24, 127.46, 126.36, 122.82, 122.27, 104.05, 40.58, 33.95. ESI-MS: $[M+H]^+$ peak at *m/z* 334.12.

6-(((3-(4-Bromophenyl)-1,2,4-oxadiazol-5-yl)methyl)-amino)-3-methylquinazolin-4(3*H*)-one (9b): Brown colour solid; yield: 73%; m.p.: 170-175 ºC. IR (KBr, ν_{max}, cm^{-1}): 1652 (C=O): ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.00 (s, 1H), 7.85 (d, *J* = 8.1 Hz, 2H), 7.67 (d, *J* = 8.0 Hz, 2H), 7.35 (d, *J* = 4.6 Hz, 1H), 7.06-6.98 (m, 1H), 6.95 (t, *J* = 6.4 Hz, 1H), 6.57 (dd, *J* = 8.1, 4.6 Hz, 1H), 4.74 (d, *J* = 6.5 Hz, 2H), 3.36 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm: 171.34, 162.29, 161.01, 147.38, 144.66, 140.38, 134.01, 132.15, 131.77, 130.39, 128.60, 122.94, 122.04, 121.91, 104.41, 104.00, 40.80, 33.87. ESI-MS: $[M+H]^+$ peak at *m/z* 412.24.

6-(((3-(2-Bromophenyl)-1,2,4-oxadiazol-5-yl)methyl)-amino)-3-methylquinazolin-4(3*H*)-one (**9c**): Light brown colour solid; yield: 73%; m.p.: 172-176 ºC, IR (KBr, ν_{max}, cm^{-1}): 1652 (C=O): ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.04 (s, 1H), 7.78 (dd, *J* = 8.7, 2.7 Hz, 1H), 7.71 (d, *J* = 7.2 Hz, 2H), 7.68-7.59 (m, 1H), 7.43 (d, *J* = 8.7 Hz, 1H), 7.17 (dd, *J* = 8.8, 2.1 Hz, 1H), 7.05 (d, *J* = 2.3 Hz, 1H), 6.54 (t, *J* = 5.4 Hz, 1H), 4.83 (d, *J* = 5.1 Hz, 2H), 3.48 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm: 179.07, 168.41, 161.14, 147.09, 144.90, 140.49, 134.19, 132.20, 129.80, 128.66, 128.43, 127.46, 126.36, 122.82, 122.27, 103.83, 40.71, 33.83. ESI-MS: $[M+H]^+$ peak at *m/z* 412.58.

6-(((3-(4-Chlorophenyl)-1,2,4-oxadiazol-5-yl)methyl)-amino)-3-methylquinazolin-4(3*H*)-one (9d): Light yellow solid; yield: 73%; m.p.: 169-174 ºC. IR (KBr, ν_{max}, cm^{-1}): 1652 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.14 (d, *J* = 5.9 Hz, 1H), 8.06 (d, *J* = 7.6 Hz, 2H), 7.68 (d, *J* = 7.5 Hz, 2H), 7.33-7.23 (m, 1H), 7.16 (dd, *J* = 6.8 Hz, 2.7 Hz, 1H), 7.09 (d, *J* = 2.7 Hz, 1H), 6.71 (t, *J* = 6.4 Hz, 1H), 4.91 (d, *J* = 6.4 Hz, 2H), 3.51 (d, *J* = 5.8 Hz 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm: 178.84, 171.47, 160.99, 147.12, 144.85, 144.51, 142.13, 140.56, 140.16, 130.32, 128.70, 127.42, 123.66, 122.61, 122.16, 103.63, 45.43, 33.89. ESI-MS: $[M+H]^+$ peak at *m/z* 368.67.

6-(((3-(3-Chlorophenyl)-1,2,4-oxadiazol-5-yl)methyl)-amino)-3-methylquinazolin-4(3*H*)-one (9e): Light white colour solid; yield: 72%; m.p.: 168-172 ºC, IR (KBr, ν_{max}, cm^{-1}): 1651 (C=O): ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.08 (s, 1H), 7.95 (d, *J* = 7.2 Hz, 2H), 7.67-7.58 (m, 2H), 7.46 (d, *J* = 7.1 Hz, 1H), 7.31-7.16 (m, 2H), 6.72 (t, *J* = 5.3 Hz, 1H), 4.83 (d, *J* = 5.4 Hz, 2H), 3.46 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm: 176.55, 167.08, 161.01, 147.69, 144.48, 140.21, 137.68, 134.42, 131.99, 128.49, 126.96, 126.23, 122.93, 121.95, 103.69, 38.93, 33.87. ESI-MS: $[M+H]^+$ peak at *m/z* 368.40.

6-(((3-(4-Fluorophenyl)-1,2,4-oxadiazol-5-yl)methyl)-amino)-3-methylquinazolin-4(3*H*)-one (9f): Light green colour solid; yield: 72%; m.p.: 168-172 ºC. IR (KBr, ν_{max}, cm^{-1}): 1650 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.16 (s, 1H), 8.07 (d, *J* = 8.7 Hz, 2H), 7.54 (d, *J* = 8.8 Hz, 2H), 7.32 (d, *J* = 7.8 Hz, 1H), 7.27 (d, *J* = 2.7 Hz, 1H), 7.15 (dd, *J* = 7.8, 2.7 Hz, 1H) 6.7 (t, *J* = 6.2 Hz, 1H), 4.90 (d, *J* = 6.0 Hz, 2H), 3.49 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm: 179.20, 167.32, 165.69, 160.96, 147.56, 147.11, 144.87, 140.56, 130.10, 130.01, 128.70, 123.03, 122.91, 122.13, 117.08, 116.86, 104.15, 39.07, 33.90. ESI-MS: $[M+H]^+$ peak at *m/z* 352.48.

6-(((3-(3-Fluorophenyl)-1,2,4-oxadiazol-5-yl)methyl)-amino)-3-methylquinazolin-4(3*H*)-one (9g): Green colour solid; yield: 72%; m.p.: 171-175 ºC, IR (KBr, ν_{max}, cm^{-1}): 1650 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.02 (s, 1H), 7.77 (dd, *J* = 8.3, 5.1 Hz, 1H), 7.62-7.35 (m, 2H), 7.21-7.16 (m, 2H), 7.09 (s, 1H), 6.73-6.19 (m, 2H), 4.80 (d, *J* = 5.4 Hz, 2H), 3.50 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm: 179.46, 167.08, 160.95, 147.69, 147.07, 144.85, 140.64, 134.42, 131.85, 128.73, 128.49, 126.96, 126.13, 122.93, 122.09, 104.21, 40.86, 33.87. ESI-MS: $[M+H]^+$ peak at *m/z* 352.58.

3-Methyl-6-(((3-(*p*-tolyl)-1,2,4-oxadiazol-5-yl)methyl)-amino)quinazolin-4(3*H*)-one (**9h**): White colour solid; yield; yield: 73%; m.p.: 170-174 ºC. IR (KBr, ν_{max}, cm^{-1}): 1651 (C=O): ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.08 (d, *J* = 5.9 Hz, 1H), 7.87 (d, *J* = 8.1 Hz, 2H), 7.49-7.44 (m, 1H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.28-7.16 (m, 2H), 6.65 (t, *J* = 6.3 Hz, 1H), 4.83 (d, *J* = 6.5 Hz, 1H), 3.45 (d, *J* = 5.8 Hz, 3H), 2.39 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm: 171.47, 168.07, 161.06, 147.70, 147.12, 144.51, 142.13, 140.16, 130.32, 128.70, 128.47, 127.42, 123.66, 122.84, 122.01, 103.63, 40.81, 33.89, 29.06. ESI-MS: $[M+H]^+$ peak at *m/z* 348.27.

6-(((3-(4-Methoxyphenyl)-1,2,4-oxadiazol-5-yl)methyl)-amino)-3-methylquinazolin-4(3*H*)-one (**9i**): White colour

solid; yield: 74%; m.p.: 170-174 ºC, IR (KBr, ν_{max}, cm^{-1}): 1652 (C=O): ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.18 (s, 1H), 7.92 (d, *J* = 7.8 Hz, 2H), 7.48 (d, *J* = 7.9 Hz, 2H), 7.23 (m, 2H), 7.16 (dd, *J* = 6.4, 2.1 Hz, 1H), 6.71 (t, *J* = 6.4 Hz, 1H), 4.91 (d, *J* = 6.4 Hz, 2H), 4.03 (s, 1H) 3.51 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm: 172.46, 171.25, 163.49, 160.39, 148.34, 146.50, 145.34, 136.06, 135.59, 129.16, 125.95, 125.07, 122.39, 122.30, 115.07, 103.92, 60.43, 45.36, 34.62. ESI-MS: $[M+H]^+$ peak at *m/z* 364.40.

6-(((3-(2-Methoxyphenyl)-1,2,4-oxadiazol-5-yl)methyl)-amino)-3-methylquinazolin-4(3*H*)-one (**9j**): Light white solid; yield: 73%; m.p.: 170-174 ºC, IR (KBr, ν_{max}, cm^{-1}): 1652 (C=O): ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.04 (s, 1H), 7.78 (dd, *J* = 7.6, 5.9 Hz, 1H), 7.43 (dd, *J* = 8.7, 5.6 Hz, 1H), 7.28 (m, 3H), 7.18 (dd, *J* = 8.8, 2.1 Hz, 1H), 7.07 (d, *J* = 2.0 Hz, 1H), 6.54 (t, *J* = 4.9 Hz, 1H), 4.01 (d, *J* = 5.1 Hz, 2H), 3.95 (s, 3H), 3.49 (s, 3H).^{13}C NMR (101 MHz, DMSO-d_6) δ ppm: 171.35, 160.77, 160.63, 156.49, 147.94, 145.30, 144.83, 138.53, 136.44, 128.12, 157.45, 123.87, 122.93, 122.65, 122.13, 103.77, 64.16, 45.37, 34.14. ESI-MS: $[M+H]^+$ peak at *m/z* 364.87.

RESULTS AND DISCUSSION

Synthesis of 3-methyl-6-(((3-aryl-1,2,4-oxadiazol-5-yl)-methyl)amino)quinazolin-4(3H)-ones (**9a-j**) described in **Scheme-I** using 6-aminoquinazolin-4(3*H*)-one (**5**) as a starting material. Initially, the nitration of isatin (**1**) gave nitro compound **2**, which was hydrolyzed in the presence of $NaOH/H_2O_2$ to obtain 2-amino-5-nitrobenzoic acid (**3**) [19]. The intermolecular cyclization of compound **3** with *N*-methylformamide produced 3-methyl-6-nitroquinazolin-4-(3*H*)-one (**4**) [20]. The nitro group of compound **4** was reduced in the presence of Pd/C with hydrazine hydrate in methanol under reflux for 4 h to furnish 6-aminoquinazolin-4(3*H*)-one (**5**). On the other hand, following the reported procedure [21] diversely substituted benzonitriles converted to the corresponding amidoximes **7a-j**, which further in the next step reacted with chloroacetyl chloride in THF under reflux to obtain 5-chloromethyl-3-aryl-1,2,4-oxadiazoles **8a-j**. Amidoximes **7a-j** and chloromethyl 1,2,4-oxadiazoles **8a-j** were used as precursors in synthesizing the target compounds in method I and method II, respectively.

The synthesis of the target hybrid compounds having quinazolinone and 1,2,4-oxadiazoles scaffolds with methylamino linker **9a-j** was carried out in two different methods. In method-I, 6-aminoquinazolinone (**5**) was reacted with ethyl bromoacetate in presence of K_2CO_3 in 15 mL DMF heating at 80 ºC for 6 h to give ethyl-(3-methyl-4-oxo-3,4-dihydroquinazolin-6-yl)-glycinate (**6**). Formation of compound **6** was demonstrated by the appearance of quartet and triplet peaks at δ 4.13 ppm and δ 1.21 ppm, which is attributed due to the ethyl group of ester group and the triplet and doublet peaks at δ 6.59 and 4.00 ppm due to N-H and methylene protons mutual coupling interaction. The singlet signals appeared at δ 8.10 and 3.46 ppm are due to the C-2 proton of quinazolinone ring and N-CH_3 protons, respectively. In ^{13}C NMR spectrum, the ester and amide carbonyl carbon peaks were observed at δ 170.06 and 160.65 ppm.

Intermediate **6** which further reacted individually with various aromatic amidoximes **7a-j** in toluene in presence of K_2CO_3 under reflux for 12 h to furnish the desired products **9a-j** with low yield (35-38%). To overcome this problem in method-II, we directly used 6-aminoquinazolinone (**5**) in DMF to react with 5-chloromethyl-3-aryl-1,2,4-oxadiazoles (**8a-j**) at 80 ºC for 4 h to furnish the titled compounds quinazolinone-1,2,4-oxadiazoles (**9a-j**) with good yields (72-75%). In compound **9a** ^{1}H NMR spectrum, the N-CH_3 protons signal is appeared at δ 3.48 ppm, methylene and N-H protons planked together appeared as a doublet and triplet signals at δ 4.90 and 7.15 ppm. In ^{13}C NMR spectrum, the characteristic oxadiazole carbons with high δ value are observed at δ 179.00 ppm and δ 168.11 ppm, amide carbonyl carbon resonated at δ 161.06 ppm. The peak at *m/z* 334 for $[M+H]^+$ ion is indicated in its ESI-MS spectrum.

Antimicrobial activity: The newly synthesized quinazolinone appended 1,2,4-oxadiazoles were evaluated for their *in vitro* antimicrobial activity against two Gram-positive (*S. aureus*, *B. substilis*), two Gram negative (*E. coli*, *P. aeruginosa*) and two fungal strains (*C. albicans*, *A. niger*) *via* agar disc fusion method [22] using ampicillin and itraconazole as standard reference drugs. All of these compounds had shown moderate to potent activity against all microbes which reflected in the zone of inhibition (Table-1). The 4-chloro and 3-chloro substituted analogues **9d**, **9e** displayed an outstanding inhibition

TABLE-1
ZONE OF INHIBITION (DIAMETER IN mm) OF QUINAZOLINONE APPENDED 1,2,4-OXADIAZOLES (**9a-j**) AGAINST BACTERIAL AND FUNGAL STRAINS

Compd.	Inhibition zone dia in mm, concentration (50 µg/mL)					
	Gram-negative bacteria		Gram-positive bacteria		Fungal strains	
	E. coli	*P. aeruginosa*	*S. aureus*	*B. subtilis*	*C. albicans*	*A. niger*
9a	13	12	12	14	16	14
9b	12	13	13	15	14	15
9c	11	10	12	13	13	15
9d	20	21	20	19	21	19
9e	21	19	20	22	19	20
9f	12	12	13	14	13	14
9g	11	10	12	14	15	14
9h	14	13	13	12	16	13
9i	11	12	13	13	15	15
9j	12	13	12	13	13	12
Ampicillin	20	21	19	19	–	–
Itraconazole	–	–	–	–	18	18

against both bacterial and fungal strains in comparison to reference drugs ampicillin and itraconazole. All of these molecules showed more activity on fungal strains compared to bacteria.

Conclusion

A novel series of quinazolinone appended 1,2,4-oxadiazole hybrid compounds (**9a-j**) were synthesised successfully in two different synthetic pathways. In method I, using the quinazolinone based ester compound **6** with amidoximes **7a-j** yielded the target compounds in poor yields. To decrease the reaction time and increase yields of the products, method II was performed by reacting 6-aminoquinazolinone (**5**) with 5-chloromethyl-3-aryl-1,2,4-oxadiazoles (**8a-j**), which furnished the products in good to excellent yields. Further, the title compounds were screened for their antimicrobial activity against Gram-positive (*S. aureus*, *B. substilis*), Gram-negative (*E. coli*, *P. aeruginosa*) and fungal strains (*C. albicans*, *A. niger*), among which chloro substituted analogues **6d** and **6e** presented potent activity against all strains where as other analogues proven to have moderate activities. Hence, novel quinazolinone-1,2,4-oxadiazoles could be potent antimicrobials, they can be investigated further in the process of drug discovery.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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