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Novel 4-[5-(Substituted-1,2,4-oxadiazol-3-yl)phenylamine] Derivatives of 6,7-Dimethoxy-quinazolines as Potent Inhibitors of VEGF Receptors I and II

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A series of novel 4-[5-(substituted-1,2,4-oxadiazol-3-yl)phenylamine] derivatives at C-4 position of 6,7-dimethoxy-quinazolines were synthesized through multistep synthesis. The new compounds were tested for inhibition of vascular endothelial growth factor receptor II (VEGFR-2). Many compounds display VEGFR-2 inhibitory activity with an IC_{50} as low as 0.017 μM in an HTRF enzymatic assay. Compound **8j** exhibited good antibacterial activity by inhibiting the growth of methicillin-sensitive *Staphylococcus aureus* (MSSA), methicillin-resistant *Staphylococcus aureus* (MRSA) and ATCC 35218 *Escherichia coli* (MIC: 0.25-16.00 μg/mL).

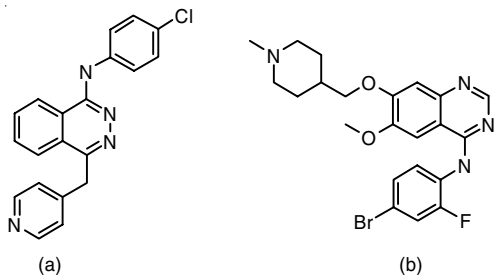
Keywords: Quinazolines, Carboxamidamide, Angiogenesis, VEGFR-2, VEGFR-1.

INTRODUCTION

Angiogenesis, the formation of new blood vessels from preexisting vessels, is a complex process that normally occurs in adults only under specific conditions such as wound healing, inflammation and in menstrual cycle [1,2]. Angiogenesis is an essential step in tumor growth and metastasis [3]. Angiogenic processes have been implicated in a number of disease states such as rheumatoid arthritis, inflammation, cancer and degenerative eye conditions and modulators of angiogenesis are emerging as powerful clinical tools in oncology and ophthalmology [4,5].

A promising strategy in the fight against cancer is to inhibit the angiogenesis process of a solid tumor, therefore limiting a tumor cell's access to nutrient [6]. Significant advances have occurred with the development of novel antiangiogenic treatments that target growth factor receptor signaling pathways. One such pathway involves the vascular endothelial growth factor (VEGF) signal transduction, which is critical for the process of neovascularization, otherwise known as angiogenesis [7,8]. Vascular endothelial growth factor (VEGF) has been considered to play a major role in angiogenesis, the formation of new vasculature from an existing vascular network [9].

A number of small-molecule inhibitors affect VEGF/VEGFR signaling by directly competing with the ATP-binding site of the respective intracellular kinase domain. This event leads to the blockade of a VEGFR phosphorylation and ultimately to the apoptotic death of the aberrant endothelial cells. Perhaps, the most successful marketed agent reportedly working *via* this mechanism is Avastin™ [4,5]. Other drug candidates that exhibit this mechanism of action include Novartis'PTK 787 (Vatalanib™, A) and Astra-Zeneca's ZD6474 (Vandetanib™, B) (Fig. 1).



(a) (b)

Fig. 1. Chemical structures of PTK 787 (a) and ZD 6474 (b)

We envisioned that one of the essential pharmacophore of ZD6474 and their analogues include the quinazoline ring. There has been a continued interest in the quinazoline skeleton in medicinal chemistry and drug development. Quinazoline derivatives have demonstrated significant anticancer activities. The enzymes and receptor agonist or antagonist action of these derivatives further increase their biological importance. A number of drugs based on quinazolines are marketed, thereby

proving it be an excellent template for a lead generation library [10]. Quinazoline derivatives have also demonstrated significant antibacterial activity [11].

Also, 1,2,4-oxadiazoles are well known compounds with promising physiological activities [12,13]. 1,2,4-Oxadiazole rings occur widely in biologically active synthetic compounds and are often used in drug discovery as good bioisosters of amide and esters [14]. Furthermore, they have been reported to have agonist for cortical muscarinic receptors [15], benzodiazepine [16], 5-HT_{1D} (5-hydroxytryptamine) receptors [17] and as antagonists for 5-HT_3 [18] or histamine H3 receptors [19]. Furthermore, they show activity against several breast and colorectal cancer cell lines [20,21].

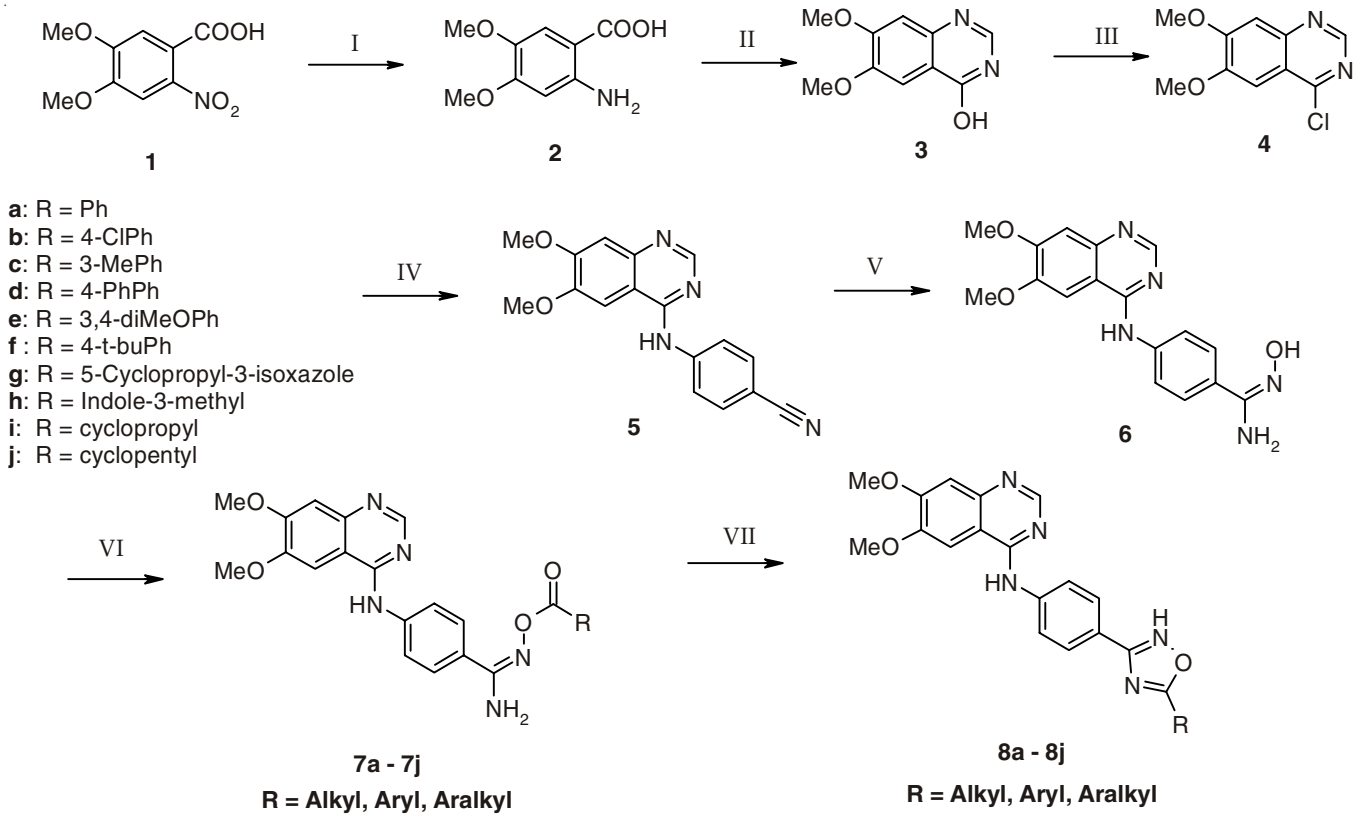
We envisaged the synthesis of novel molecules based on the two lead pharmacophores realized *viz.,* quinazolines and 1,2,4-oxadiazoles. In this communication, we disclose a series of novel 4-[5-(substituted-1, 2,4-oxadiazol-3-yl)]phenylamine derivatives of 6,7-dimethoxy-quinazolines as potent inhibitors of VEGFR-2.

EXPERIMENTAL

Chemicals were obtained from Sigma-Aldrich Co. TLC experiments were performed on alumina-backed silica gel 40 F254 plates (Merck, Darmstadt, Germany). The plates were illuminated under UV (254 nm) and $KMnO_4$. Melting points were determined using Buchi B-540 and are uncorrected. All ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-300 MHz NMR and Bruker Avance III HD 400 MHz NMR, Bruker BioSpin Corp., Germany. Molecular weights of unknown compounds were checked by LC-MS 6200 series Agilent Technology. Chemical shifts are reported in ppm (δ) with reference to internal standard TMS. IR spectra were recorded using a Bruker Alpha FTIR spectrometer using a diamond ATR single reflectance module (24 scans). Elemental analysis was carried out with a Perkin-Elmer model 240C apparatus. The results of elemental analysis (C, H and N) were within ± 0.4 % of the calculated amounts.

The new quinazoline derivatives described herein were synthesized as shown in **Scheme-I**. Previously described methods were used for synthesis of 6,7-dimethoxyquinazoline derivatives **2** [22], **3** [23], **4** [24] and **5** [25]. Reaction of known compound **5** with hydroxylamine and potassium hydroxide in ethanol at 80 °C yielded the corresponding carboximidamide derivative (**6**).

4-(6,7-Dimethoxyquinazolin-4-ylamino)-N′-hydroxybenzenecarboximidamide (6): To a solution of 4-(6,7-dimethoxyquinazolin-4-ylamino)benzonitrile (**5**) (5.0 g, 16.3 mmol) in ethanol (50 mL) was added potassium hydroxide (2.74 g, 49 mmol), followed by portion-wise addition of hydroxylamine hydrochloride (3.4 g, 49 mmol) at 0 °C. The reaction mixture was then allowed to stir at 80 °C for 12 h. Completion of the reaction was monitored by TLC. After completion of reaction, water (50 mL) was added to the reaction mixture and the volatiles were evaporated under reduced pressure. Aqueous layer was extracted with ethylacetate (2 × 50 mL). Organic layer was washed with water



Scheme-I: Conditions and reagents: (I) 10 % Pd/C, H_2 gas, MeOH, 25 °C, 5 h; (II) Formamidine acetate, 2-methoxyethanol, 120 °C, 12 h; (III) $POCl_3$, 100 °C, 2 h; (IV) 4-cyanoaniline, 2-propanol, 80 °C, 4 h; (V) $NH_2OH·HCl$, KOH, EtOH, 80 °C, 12 h; (VI) R-COOH, EDC·HCl, HOBt, DMPA, 25 °C, 1 h; (VII) DBU, DMF, 80 °C, 12 h

(1 × 50 mL), saturated brine solution (1 × 50 mL) and dried over anhydrous sodium sulfate. Solvents were evaporated under reduced pressure and the residue was recrystallized using 2-propanol to get product **6**.

Beige solid; Yield 76 %; m.p.: 152-153 °C; IR (ATR, ν_{max}, cm^{-1}): 3619.80 (O-H); 3053.55 (Ar-CH); 1633.12 (Ar-C=C); 1246.25 (C-O) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 3.92 (s, 3H, -OCH_3); 3.97 (s, 3H, -OCH_3), 5.79 (bs, 2H, -NH_2), 7.18 (s, 1H, ArH), 7.66 (d, *J* = 7.5 Hz, 2H, ArH), 7.87 (d, J = 7.8 Hz, 2H, ArH), 7.98 (s, 1H, ArH), 8.47 (s, 1H, -N=CH), 9.55 (bs, 1H, OH), 9.73 (bs, 1H, NH). ^{13}C NMR (DMSO-d_6 75 MHz) δ: 56.20 (CH_3, -OCH_3), 56.81 (CH_3, -OCH_3), 102.67 (quinazoline C), 107.51 (quinazoline C), 109.44 (quinazoline C), 121.87 (Ar C), 125.87 (Ar C), 128.25 (ArC), 140.71 (quinazoline C), 147.37 (ArC), 149.31 (quinazoline C), 151.19 (quinazoline C), 153.15 (quinazoline, N=CHN), 154.66 (quinazoline, N-C=N), 156.64 (C=NOH). LC-MS (ESI, *m/z*): 341 $(M + 1)^+$. Anal. calcd. for $C_{17}H_{17}N_5O_3$: C, 60.17; H, 5.05; N, 20.64. Found: C, 60.20; H, 5.10; N, 20.57.

General procedure for the synthesis of N-[4-(6,7-dimethoxy-quinazolin-4-ylamino)]phenyl)-[(E)-hydroxy-iminomethyl]amides (7a-7j): To a solution of compound **6** (500 mg, 1.4 mmol) in N,N-dimethylformamide (2.5 mL) were added N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide·HCl (EDC·HCl) (421 mg, 2.2 mmol), 1-hydroxybenzotriazole (HOBt) (297 mg, 2.2 mmol) and 4-dimethylaminopyridine (DMAP) (36 mg, 0.3 mmol) at 0 °C under nitrogen atmosphere. After 5 min, corresponding acid (1.4 mmol) was added to the reaction mixture at 0 °C and reaction mixture was slowly allowed to reach room temperature (25 °C) and continued stirring at room temperature over a period of 1 h. The resulting reaction mass was poured into crushed ice to precipitate the product. The precipitated solid was filtered and dried under reduced pressure and was recrystallized with hot 2-propanol to yield the title compounds (**7a-7j**).

N-[4-(6,7-Dimethoxy-quinazolin-4-ylamino)phenyl]-[(E)-hydroxyiminomethyl]benzamide (7a): Starting from 0.17 g benzoic acid (**a**), the title compound **7a** was obtained. Yellow solid; Yield: 0.48 g (74 %); m.p.: 139-140 °C; IR (ATR, ν_{max}, cm^{-1}): 3315.46 (amide N-H), 3064.85 (Ar-CH), 1624.85 (C=O), 1581.37 (Ar-C=C), 1236.27 (C-O). ^{1}H NMR (DMSO-d_6 300 MHz) δ (ppm): 3.95 (s, 3H, -OCH_3), 3.98 (s, 3H, -OCH_3), 6.94 (bs, 2H, -NH_2), 7.22 (s, 1H, ArH), 7.53-7.57 (m, 2H, ArH), 7.65-7.71 (m, 2H, ArH), 7.81 (d, *J* = 6.6 Hz, 2H, ArH),7.89 (s, 1H, ArH), 7.96 (d, *J* = 6.6 Hz, 2H, ArH), 8.2 (d, *J* = 6.3 Hz, 2H, ArH), 8.54 (s, 1H, -N=CH), 9.67 (bs, 1H, NH). ^{13}C NMR (DMSO-d_6 100 MHz) δ: 56.28 (CH_3, -OCH_3), 56.68 (CH_3, -OCH_3), 102.28 (quinazoline C), 107.67 (quinazoline C), 109.54 (quinazoline C), 121 (ArC), 122.5 (ArC), 128.2 (ArC), 128.9 (ArC), 129.9 (ArC), 130.5 (ArC), 132 (ArC), 139.5 (ArC), 143.2 (quinazoline C), 146.8 (quinazoline C), 152.8 (quinazoline C), 153.8 (quinazoline, N=CHN), 156.3 (quinazoline, N=C-NH), 167.5 (NH_2-C=NO), 170 (C=O). LC-MS (ESI, *m/z*): 444.6 $(M + 1)^+$. Anal. calcd. for $C_{24}H_{21}N_5O_4$: C, 65.00; H, 4.77; N, 15.79. Found: C, 65.22; H, 4.65; N, 15.89.

4-Chloro-N-[4-(6,7-dimethoxy-quinazolin-4-ylamino)-phenyl]-[(E)-hydroxyiminomethyl]benzamide (7b): Starting from 0.219 g of 4-chlorobenzoic acid (**b**) the title compound **7b** was obtained. Light brown solid; Yield: 0.42 g (60 %); m.p.: 141-142 °C; IR (ATR, ν_{max}, cm^{-1}): 3298.13 (N-H), 3134.89 (Ar-CH), 1720.45 (C=O), 1583.02 (Ar-C=C), 1236.03 (C-O). ^{1}H NMR (DMSO-d_6 300 MHz) δ (ppm): 3.95 (s, 3H, -OCH_3), 3.98 (s, 3H, -OCH_3), 6.99 (bs, 2H, -NH_2), 7.22 (s, 1H, ArH), 7.62 (d, *J* = 6.6 Hz, 2H, ArH), 7.82 (d, *J* = 5.7 Hz, 2H, ArH), 7.89 (s, 1H, ArH), 7.96 (d, *J* = 6.9 Hz, 2H, ArH), 8.22 (d, *J* = 6.6 Hz, 2H, ArH), 8.53 (s, 1H, -N=CH), 9.66 (bs, 1H, NH). ^{13}C NMR (DMSO-d_6 100 MHz) δ: 56.28 (CH_3, -OCH_3), 56.68 (CH_3, -OCH_3), 102.28 (quinazoline C), 107.67 (quinazoline C), 109.54 (quinazoline C), 120.92 (ArC), 122 (ArC), 127.82 (ArC), 128.8 (ArC), 130.6 (ArC), 131.5 (ArC), 139 (ArC), 143 (quinazoline C), 147 (quinazoline C), 149 (ArC), 153 (quinazoline C), 154.87 (quinazoline, N=CHN), 156.4 (quinazoline, N=C-NH), 167.62 (NH_2-C=NOH), 172 (C=O). LC-MS (ESI, *m/z*): 478.9 $(M + 1)^+$. Anal. calcd. for $C_{24}H_{20}N_5O_4Cl$: C, 60.32; H, 4.22; N, 14.65. Found: C, 60.44; H, 4.48; N, 14.68.

N-[4-(6,7-Dimethoxy-quinazolin-4-ylamino)phenyl]-[(E)-hydroxyiminomethyl]-3-methyl-benzamide (7c): Starting from 0.19 g of *m*-toluic acid (**c**) the title compound **7c** was obtained. Light brown solid; Yield: 0.4 g (60 %); m.p.: 145-146 °C; IR (ATR, ν_{max}, cm^{-1}): 3363.37 (N-H), 3067.19 (Ar-CH), 1724.80 (C=O), 1515.52 (Ar-C=C), 1241.94 (C-O). ^{1}H NMR (DMSO-d_6 300 MHz) δ (ppm): 2.41 (s, 3H, -CH_3), 3.95 (s, 3H, -OCH_3), 3.98 (s, 3H, -OCH_3), 6.93 (bs, 2H, -NH_2), 7.22 (s, 1H, ArH), 7.41-7.47 (m, 2H, ArH), 7.81 (d, *J* = 6.6 Hz, 2H, ArH), 7.9 (s, 1H, ArH), 7.95-8.0 (m, 4H, ArH), 8.54 (s, 1H, -N=CH), 9.69 (bs, 1H, NH). ^{13}C NMR (DMSO-d_6 100 MHz) δ: 20.9 (CH_3-Ph), 56.28 (CH_3, -OCH_3), 56.68 (CH_3, -OCH_3), 102.28 (quinazoline C), 107.67 (quinazoline C), 109.54 (quinazoline C), 120.92 (ArC), 122 (ArC), 127.82 (ArC), 128.7 (ArC), 129.9 (ArC), 132.2 (ArC), 133 (ArC), 135 (ArC), 136.1 (ArC), 139.8 (ArC), 143.6 (quinazoline C), 146.9 (quinazoline C), 152.9 (quinazoline C), 153.8 (quinazoline, N=CHN), 156.8 (quinazoline, N=C-NH), 167.9 (NH_2-C=NO), 170.2 (C=O). LC-MS (ESI, *m/z*): 458.6 $(M + 1)^+$. Anal. calcd. for $C_{25}H_{23}N_5O_4$: C, 65.64; H, 5.07; N, 15.31. Found: C, 65.67; H, 5.24; N, 15.46.

Biphenyl-3-carboxylic acid [4-(6,7-dimethoxy-quinazolin-4-ylamino)phenyl]-[(E)-hydroxyiminomethyl]amide (7d): Starting from 0.27 g of 4-biphenylcarboxylic acid (**d**) the title compound **7d** was obtained. Off-white solid; Yield: 0.6 g (80 %); m.p.: 165-166 °C; IR (ATR, ν_{max}, cm^{-1}): 3346.72 (N-H), 1714.89 (C=O), 1507.81 (Ar-C=C), 1369.27 (Ar-C=C), 1237.62 (C-O). ^{1}H NMR (DMSO-d_6 300 MHz) δ (ppm): 3.95 (s, 3H, -OCH_3), 3.99 (s, 3H, -OCH_3), 6.97 (bs, 2H, -NH_2), 7.22 (s, 1H, ArH), 7.45-7.51 (m, 1H, ArH), 7.78 (d, *J* = 6.6 Hz, 2H, ArH), 7.9 (s, 1H, ArH), 7.85-7.81 (m, 4H, ArH), 8.28 (d, *J* = 6.6 Hz, 2H, ArH), 8.53 (s, 1H, -N=CH), 9.65 (bs, 1H, NH). ^{13}C NMR (DMSO-d_6 100 MHz) δ: 56.3 (CH_3, -OCH_3), 56.66 (CH_3, -OCH_3), 102.3 (quinazoline C), 107.69 (quinazoline C), 109.71 (quinazoline C), 121.5 (ArC), 122.8 (ArC), 125.3 (ArC), 128.8 (ArC), 129.2 (ArC), 129.6 (ArC), 129.9 (ArC), 130.2 (ArC), 136.4 (ArC), 139.8 (ArC), 141.6 (ArC), 143.6 (quinazoline C), 146.9 (quinazoline C), 153.8 (quinazoline C), 154.9 (quinazoline, N=CHN), 156.8 (quinazoline, N=C-NH),

168.15 (NH_2-C=NO), 172 (C=O). LC-MS (ESI, *m/z*): 520.7 $(M + 1)^+$. Anal. calcd. for $C_{30}H_{25}N_5O_4$: C, 69.35; H, 4.85; N, 13.48. Found: C, 69.42; H, 4.98; N, 13.71.

N-[4-(6,7-Dimethoxy-quinazolin-4-ylamino)phenyl]-[(E)-hydroxyiminomethyl]-3,4-dimethoxy-benzamide (7e): Starting from 0.24 g of 3,4-dimethoxybenzoic acid (**e**) the title compound **7e** was obtained. Brown solid; Yield: 0.33 g (45 %); m.p.: 145-146 °C; IR (ATR, ν_{max}, cm^{-1}): 3307.26 (N-H), 3077.40 (Ar-CH), 1712.69 (C=O), 1583.62 (Ar-C=C), 1246.25 (C-O). ^{1}H NMR (DMSO-d_6 300 MHz) δ (ppm): 3.86 (s, 3H, -OCH_3), 3.95 (s, 3H, -OCH_3), 3.98 (s, 3H, -OCH_3), 6.90 (bs, 2H, -NH_2), 7.08 (d, *J* = 6.6 Hz, 2H, ArH), 7.22 (s, 1H, ArH), 7.6 (s, 1H, ArH),7.79-7.89 (m, 4H, ArH), 7.95 (d, *J* = 6.3 Hz, 2H, ArH), 8.53 (s, 1H, -N=CH), 9.65 (bs, 1H, NH). ^{13}C NMR (DMSO-d_6 100 MHz) δ: 56.27 (CH_3, -OCH_3), 56.56 (CH_3, -OCH_3), 56.65 (CH_3, -OCH_3), 56.75 (CH_3, -OCH_3), 102.26 (quinazoline C), 107.3 (quinazoline C), 109.6 (quinazoline C), 116.5 (ArC), 117 (ArC), 120.5 (ArC), 122.5 (ArC), 123.5 (ArC), 124 (ArC), 127.4 (ArC), 139.5 (ArC), 143.4 (quinazoline C), 146.9 (quinazoline C), 148.2 (ArC), 153.2 (ArC), 153.7 (quinazoline, N=CHN), 153.9 (quinazoline C), 156.4 (quinazoline, N=C-NH), 166.7 (NH_2-C=NO), 174 (C=O). LC-MS (ESI, *m/z*): 504.7 $(M + 1)^+$. Anal. calcd. for $C_{26}H_{25}N_5O_6$: C, 62.02; H, 5.00; N, 13.91. Found: C, 62.15; H, 5.17; N, 13.98.

4-*tert*-Butyl-N-[4-(6,7-dimethoxy-quinazolin-4-ylamino)phenyl]-[(E)-hydroxyiminomethyl]benzamide (7f): Starting from 0.25 g of 4-*tert*-butylbenzoic acid (**f**) the title compound **7f** was obtained. Off-white solid; Yield: 0.59 g (81 %); m.p.: 190-191 °C; IR (ATR, ν_{max}, cm^{-1}): 3440.62 (N-H), 3009.65 (Ar-CH), 1720.18 (C=O), 1509.34 (Ar-C=C), 1237.62 (C-O). ^{1}H NMR (DMSO-d_6 300 MHz) δ (ppm): 1.33 (s, 9H, -$(CH_3)_3$), 3.94 (s, 3H, -OCH_3), 3.98 (s, 3H, -OCH_3), 6.89 (bs, 2H, -NH_2), 7.22 (s, 1H, ArH), 7.50 (d, *J* = 6.3 Hz, 2H, ArH), 7.81 (d, *J* = 6.6 Hz, 2H, ArH), 7.88 (s, 1H, ArH), 7.96 (d, *J* = 6.6 Hz, 2H, ArH), 8.53 (s, 1H, -N=CH), 9.64 (bs, 1H, NH). ^{13}C NMR (DMSO-d_6 100 MHz) δ: 31.7 (CH_3, -$(CH_3)_3$), 35.1 (C, -$C(CH_3)_3$) 56.28 (CH_3, -OCH_3), 56.68 (CH_3, -OCH_3), 102.28 (quinazoline C), 107.69 (quinazoline C), 109.58 (quinazoline C), 121.3 (ArC), 122.8 (ArC), 125.2 (ArC), 128.8 (ArC), 129.1 (ArC), 129.9 (ArC), 139.8 (ArC), 143.6 (quinazoline C), 146.9 (quinazoline C), 151.1 (ArC), 153.1 (quinazoline C), 154.3 (quinazoline, N=CHN), 156.3 (quinazoline, N=C-NH), 167.5 (NH_2-C=NO), 170 (C=O). LC-MS (ESI, *m/z*): 500.7 $(M + 1)^+$. Anal. calcd. for $C_{28}H_{29}N_5O_4$: C, 67.32; H, 5.85; N, 14.02. Found: C, 67.47; H, 5.64; N, 14.14.

5-Cyclopropyl-isoxazole-3-carboxylic acid [4-(6,7-dimethoxy-quinazolin-4-ylamino)phenyl]-[(E)-hydroxyiminomethyl]amide (7g): Starting from 0.214 g of 5-cyclopropyl-3-isoxazolecarboxylic acid (**g**) the title compound **7g** was obtained. Light brown solid; Yield: 0.36 g (52 %); m.p.: 151-152 °C; IR (ATR, ν_{max}, cm^{-1}): 3257.90 (N-H), 3010.4 (Ar-CH), 1743.01 (C=O), 1507.88 (Ar-C=C), 1580.82 (Ar-C=C), 1233.21 (C-O). ^{1}H NMR (DMSO-d_6 300 MHz) δ (ppm): 3.95 (s, 3H, -OCH_3), 3.98 (s, 3H, -OCH_3), 6.97 (bs, 2H, -NH_2), 7.23 (s, 1H, ArH), 7.79 (d, *J* = 8.4 Hz, 2H, ArH), 7.89 (s, 1H, ArH), 7.97 (d, *J* = 8.1 Hz, 2H, ArH), 8.53 (s, 1H, -N=CH), 9.66 (bs, 1H, NH). ^{13}C NMR (DMSO-d_6 100 MHz) δ: 6.5 (cyclopropane C), 9.2 (cyclopropane C), 56.65 (CH_3, -OCH_3), 98.66 (isoxazole C), 102.7 (quinazoline C), 107.5 (quinazoline C), 110.11 (quinazoline C), 117.25 (ArC), 125.62 (ArC), 128.13 (ArC), 139.6 (ArC), 143.4 (quinazoline C), 147.2 (quinazoline C), 150.2 (isoxazole C), 153.5 (quinazoline C), 154 (quinazoline, N=CHN), 156.5 (quinazoline, N=C-NH), 158.9 (isoxazole C), 167 (NH_2-C=NO), 173 (C=O). LC-MS (ESI, *m/z*): 475.6 $(M + 1)^+$. Anal. calcd. for $C_{24}H_{22}N_6O_5$: C, 60.75; H, 4.67; N, 17.71. Found: C, 60.94; H, 4.52; N, 17.73.

N-[4-(6,7-Dimethoxy-quinazolin-4-ylamino)phenyl]-[(E)-hydroxyiminomethyl]-2-(1H-indol-3-yl)acetamide (7h): Starting from 0.245 g of indole-3-aceticacid (**h**) the title compound **7h** was obtained. Brown solid; Yield: 0.25 g (35 %); m.p.: 162-163 °C; IR (ATR, ν_{max}, cm^{-1}): 3343.76 (N-H), 3011.66 (Ar-CH), 1734.96 (C=O), 1582.98 (Ar-C=C), 1241.22 (C-O). ^{1}H NMR (DMSO-d_6 300 MHz) δ (ppm): 3.34 (s, 2H, -$OCOCH_2$), 3.94 (s, 3H, -OCH_3), 3.97 (s, 3H, -OCH_3), 6.77 (bs, 2H, -NH_2), 6.98-7.17 (m, 2H, ArH), 7.21 (s, 1H, ArH), 7.30 (s, 1H, indole-H), 7.36 (d, *J* = 8.1 Hz, 1H, ArH), 7.6 (d, *J* = 7.5 Hz, 1H, ArH),7.71-7.74 (m, 2H, ArH), 7.87 (s, 1H, ArH), 7.91 (d, *J* = 8.8 Hz, 2H, ArH), 8.51 (s, 1H, -N=CH), 9.62 (bs, 1H, NH), 10.98 (bs, 1H, indole-NH); ^{13}C NMR (DMSO-d_6 75 MHz) δ: 30.12 (CH_2, indole-CH_2), 56.23 (CH_3, -OCH_3), 56.65 (CH_3, -OCH_3), 102.28 (quinazoline C), 107.63 (quinazoline C), 109.43 (indole C), 111.83 (quinazoline C), 115.47 (indole C), 118.90 (Ar C), 119.01 (indole C), 121.48 (indole C) 121.65 (indole C), 124.57 (indole C), 126.24 (ArC), 127.34 (Ar C), 127.6 (indole C), 136.52 (indole C), 142.07 (quinazoline C), 147.54 (Ar C), 149.42 (quinazoline C), 153.11 (quinazoline C), 154.77 (quinazoline, N=CHN), 156.50 (quinazoline, N=C-NH), 156.82 (NH_2-C=NO), 169.68 (C=O). LC-MS (ESI, *m/z*): 497.7 $(M + 1)^+$. Anal. calcd. for $C_{27}H_{24}N_6O_4$: C, 65.31; H, 4.87; N, 16.93. Found: C, 65.48; H, 4.80; N, 17.09.

Cyclopropanecarboxylic acid [4-(6,7-dimethoxy-quinazolin-4-ylamino)phenyl]-[(E)-hydroxyiminomethyl]-amide (7i): Starting from 0.12 g of cyclopropane carboxylic acid (**i**) the title compound **7i** was obtained. Off-white solid; Yield: 0.36 g (60 %); m.p.: 195-196 °C; IR (ATR, ν_{max}, cm^{-1}): 3313.14 (N-H), 3312.86 (O-H), 3012.95 (Ar-CH), 1650.12 (C=O), 1592.29 (Ar C=C), 1190.82 (C-O). ^{1}H NMR (DMSO-d_6 300 MHz) δ (ppm): 0.87-0.92 (m, 4H), 1.89-1.93 (m, 1H), 3.94 (s, 3H, -OCH_3), 3.97 (s, 3H, -OCH_3), 6.8 (bs, 2H, -NH_2), 7.21 (s, 1H, ArH), 7.74 (d, *J* = 6.6 Hz, 2H, ArH), 7.87 (s, 1H, ArH), 7.92 (d, *J* = 6.6 Hz, 2H, ArH), 8.51 (s, 1H, -N=CH), 9.61 (bs, 1H, NH). ^{13}C NMR (DMSO-d_6 100 MHz) δ: 8.6 (cyclopropane C), 13.4 (cyclopropane C), 56.31 (CH_3, -OCH_3), 56.63 (CH_3, -OCH_3), 102.32 (quinazoline C), 107.71 (quinazoline C), 109.58 (quinazoline C), 121.4 (ArC), 122.81 (ArC), 125.2 (ArC), 140.1 (ArC), 143.58 (quinazoline C), 146.8 (quinazoline C), 153.3 (quinazoline C), 154.7 (quinazoline, N=CHN), 158.1 (quinazoline, N=C-NH), 167.6 (NH_2-C=NO), 182 (C=O). LC-MS (ESI, *m/z*): 408.6 $(M + 1)^+$. Anal. calcd. for $C_{21}H_{21}N_5O_4$: C, 61.91; H, 5.20; N, 17.19. Found: C, 61.98; H, 5.28; N, 17.37.

Cyclopentanecarboxylic acid [4-(6,7-dimethoxy-quinazolin-4-ylamino)phenyl]-[(E)-hydroxyiminomethyl]-amide (7j): Starting from 0.16 g of cyclopentane carboxylic acid (**j**) the title compound **7j** was obtained Yellow solid; Yield: 0.46 g (73 %); m.p.: 185-186 °C; IR (ATR, ν_{max}, cm^{-1}): 3213.98

(N-H), 3382.14 (O-H), 3110.95 (Ar-CH), 1670.72 (C=O), 1540.42 (Ar C=C), 1174.82 (C-O). ^{13}C NMR (DMSO-d_6 100 MHz) δ: 22.8 (cyclopentane C), 25.3 (cyclopentane C), 38.9 (cyclopentane C), 56.38 (CH_3, -OCH_3), 56.69 (CH_3, -OCH_3), 102.44 (quinazoline C), 107.91 (quinazoline C), 109.71 (quinazoline C), 121.6 (ArC), 122.92 (ArC), 125.3 (ArC), 140.6 (ArC), 143.62 (quinazoline C), 147.2 (quinazoline C), 153.4 (quinazoline C), 154.8 (quinazoline, N=CHN), 158.6 (quinazoline, N=C-NH), 167.9 (NH_2-C=NO), 182.9 (C=O). LC-MS (ESI, *m/z*): 436.6 $(M + 1)^+$. Anal. calcd. for $C_{23}H_{25}N_5O_4$: C, 63.44; H, 5.79; N, 16.08. Found: C, 63.63; H, 5.92; N, 16.31.

General procedure for the synthesis of 6,7-dimethoxy-quinazolin- 4-[5-(substituted-1,2,4-oxadiazol-3-yl)-phenylamine]s (8a-8j): To a solution of compounds **7a**-**7j** (1 mmol) in N,N-dimethylformamide (2.5 volumes) was added 1,8-diazabicylco(5.4.0)undec-7-ene-2,3,4,6,7,8,9,10-octahydropyrimido(1,2-a)azepine (DBU) (2.9 mmol) at room temperature (25 °C). Reaction mixture was allowed to stir at 80 °C over a period of 12 h. The resulting reaction mass was poured into crushed ice to precipitate the product. The precipitated solid was filtered and dried under reduced pressure. Recrystallization using hot 2-propanol yielded the title compounds (**8a**-**8j**).

(6,7-Dimethoxy-quinazolin-4-yl)-[4-(5-phenyl-1,2,4-oxadiazol-3-yl)phenyl]amine (8a): Starting from 0.3 g of **7a** the title compound **8a** was obtained. Beige solid; Yield: 0.23 g (80 %); m.p.: 138-139 °C; IR (ATR, ν_{max}, cm^{-1}): 3406.79 (NH), 3068.30 (Ar-CH), 1582.13 (Ar-C=C), 1243.92 (C-O).^{1}H NMR (DMSO-d_6 300 MHz) δ (ppm): 3.94 (s, 3H, -OCH_3), 3.98 (s, 3H, -OCH_3), 7.22 (s, 1H, ArH), 7.64-7.74 (m, 3H, ArH), 7.89 (s, 1H, ArH), 8.09-8.15 (m, 4H, ArH), 8.2 (d, *J* = 6.9 Hz, 2H, ArH), 8.56 (s, 1H, -N=CH), 9.72 (s, 1H, NH). ^{13}C NMR (DMSO-d_6 100 MHz) δ: 56.33 (CH_3, -OCH_3), 56.71 (CH_3, -OCH_3), 102.3 (quinazoline C), 107.9 (quinazoline C), 109.6 (quinazoline C), 120.93 (ArC), 122.2 (ArC), 127.01 (ArC), 127.86 (ArC), 128.06 (ArC), 129.05 (ArC), 136.58 (ArC), 147.7 (ArC), 147.93 (quinazoline C), 152.91 (quinazoline C), 156.21 (quinazoline C), 156.51 (quinazoline, N=CHN), 167.87 (quinazoline, N=C-NH), 170.2 (oxadiazole C), 177.8 (oxadiazole C). LC-MS (ESI, *m/z*): 426.5 $(M + 1)^+$. Anal. calcd. for $C_{24}H_{19}N_5O_3$: C, 67.76; H, 4.50; N, 16.46. Found: C, 67.67; H, 4.35; N, 16.48.

(6,7-Dimethoxy-quinazolin-4-yl)-[4-{5-(4-chlorophenyl)-1,2,4-oxadiazol-3-yl}phenyl]amine (8b): Starting from 0.3 g of **7b** the title compound **8b** was obtained. Beige solid; Yield: 0.21 g (73 %); m.p.: 134-135 °C; IR (ATR, ν_{max}, cm^{-1}): 3509.16 (NH), 3060.94 (Ar-CH), 1516.67 (Ar-C=C), 1240.46 (C-O).^{1}H NMR (DMSO-d_6 300 MHz) δ (ppm): 3.94 (s, 1H, -OCH_3), 3.98 (s, 1H, -OCH_3), 7.22 (s, 1H, ArH), 7.75 (d, *J* = 7.2 Hz, 2H, ArH), 7.88 (s, 1H, ArH), 8.0-8.19 (m, 4H, ArH), 8.21 (d, 2H, *J* = 7.5 Hz, ArH), 8.56 (s, 1H, -N=CH), 9.72 (s, 1H, NH). ^{13}C NMR (DMSO-d_6 100 MHz) δ: 56.38 (CH_3, -OCH_3), 56.74 (CH_3, -OCH_3), 102.23 (quinazoline C), 107.6 (quinazoline C), 109.58 (quinazoline C), 120.8 (ArC), 122.15 (ArC), 127.84 (ArC), 128.5 (ArC), 129.6 (ArC), 133.5 (ArC), 134.8 (ArC) 147.68 (ArC), 147.95 (quinazoline C), 152.86 (quinazoline C), 156.2 (quinazoline C), 156.42 (quinazoline, N=CHN), 167.87 (quinazoline, N=C-NH), 170.2 (oxadiazole C), 177.8 (oxadiazole C). LC-MS (ESI, *m/z*): 460.8 $(M + 1)^+$. Anal. calcd. for $C_{24}H_{18}N_5O_3Cl$: C, 62.68; H, 3.95; N, 15.23. Found: C, 62.55; H, 3.72; N, 15.26.

(6,7-Dimethoxy-quinazolin-4-yl)-[4-{5-(3-methyl-phenyl)-1,2,4-oxadiazol-3-yl}phenyl]amine (8c): Starting from 0.3 g of **7c** the title compound **8c** was obtained. Light brown solid; Yield: 0.174 g (60 %); m.p.: 139-140 °C; IR (ATR, ν_{max}, cm^{-1}): 3255.34 (NH), 3084.02 (Ar-CH), 1585.49 (Ar-C=C), 1512.72 (Ar-C=C), 1243.83 (C-O).^{1}H NMR (DMSO-d_6 300 MHz) δ (ppm): 2.45 (s, 3H), 3.94 (s, 1H, -OCH_3), 3.98 (s, 1H, -OCH_3), 7.22 (s, 1H, ArH), 7.55 (d, *J* = 4.2 Hz, 2H, ArH), 7.89 (s, 1H, ArH), 8.01 (d, *J* = 9.0 Hz, 2H, ArH), 8.12-8.20 (m, 4H, ArH), 8.56 (s, 1H, -N=CH), 9.72 (s, 1H, NH). ^{13}C NMR (DMSO-d_6 100 MHz) δ: 22.5 (CH_3,-PhCH_3),56.35 (CH_3, -OCH_3), 56.73 (CH_3, -OCH_3), 102.25 (quinazoline C), 107.5 (quinazoline C), 109.54 (quinazoline C), 120.8 (ArC), 122.17 (ArC), 123.2 (ArC), 127.6 (ArC), 127.7 (ArC), 128.8 (ArC), 129.5 (ArC), 136.5 (ArC), 138.3 (ArC) 147.68 (ArC), 147.92 (quinazoline C), 152.86 (quinazoline C), 156.4 (quinazoline C), 156.44 (quinazoline, N=CHN), 167.4 (quinazoline, N=C-NH), 170.6 (oxadiazole C), 177.7 (oxadiazole C). LC-MS (ESI, *m/z*): 440.5 $(M + 1)^+$. Anal. calcd. for $C_{25}H_{21}N_5O_3$: C, 68.33; H, 4.82; N, 15.94. Found: C, 68.45; H, 4.91; N, 15.79.

(6,7-Dimethoxy-quinazolin-4-yl)-[4-{5-(4-biphenyl)-1,2,4-oxadiazol-3-yl}phenyl]amine (8d): Starting from 0.3 g of **7d** the title compound **8d** was obtained. Beige solid; Yield: 0.25 g (86 %); m.p.: 152-153 °C;IR (ATR, ν_{max}, cm^{-1}): 3329.34 (NH), 3061.49 (Ar-CH), 1513.01 (Ar-C=C), 1241.10 (C-O).^{1}H NMR (DMSO-d_6 300 MHz) δ (ppm): 3.94 (s, 3H, -OCH_3), 3.98 (s, 3H, -OCH_3), 7.22 (s, 1H, ArH), 7.45-7.56 (m, 3H, ArH), 7.8 (d, *J* = 7.2 Hz, 2H, ArH), 7.89 (s, 1H, ArH), 7.97 (d, *J* = 7.2 Hz, 2H, ArH), 8.11-8.24 (m, 4H, ArH), 8.27 (d, *J* = 8.1 Hz, 2H, ArH), 8.56 (s, 1H, -N=CH), 9.73 (s, 1H, NH); ^{13}C NMR (DMSO-d_6 75 MHz) δ: 56.30 (CH_3, -OCH_3), 56.73 (CH_3, -OCH_3), 102.24 (quinazoline C), 107.5 (quinazoline C), 109.55 (quinazoline C), 120.5 (ArC), 122.16 (ArC), 127.02 (biphenyl C), 127.41 (biphenyl C), 127.65 (ArC), 128.00 (biphenyl C), 129.63 (biphenyl C), 136.7 (biphenyl C), 147.69 (ArC), 147.92 (quinazoline C), 152.87 (quinazoline C), 156.19 (quinazoline C), 156.45 (quinazoline, N=CHN), 167.93 (quinazoline, N=C-NH), 170.14 (oxadiazole C), 177.68 (oxadiazole C). LC-MS (ESI, *m/z*): 502.5 $(M + 1)^+$. Anal. calcd. for $C_{30}H_{23}N_5O_3$: C, 71.84; H, 4.62; N, 13.96. Found: C, 71.68; H, 4.76; N, 13.75.

(6,7-Dimethoxy-quinazolin-4-yl)-[4-{5-(3,4-dimethoxy-phenyl)-1,2,4-oxadiazol-3-yl}phenyl]amine (8e): Starting from 0.3 g of **7e** the title compound **8e** was obtained. Beige solid; Yield: 0.152 g (52 %); m.p.: 136-137 °C; IR (ATR, ν_{max}, cm^{-1}): 3333.61 (NH), 3082.43 (Ar-CH), 1578.22 (Ar-C=C), 1240.55 (C-O). ^{1}H NMR (DMSO-d_6 300 MHz) δ (ppm): 3.88 (s, 3H, -OCH_3), 3.90 (s, 3H, -OCH_3), 3.94 (s, 3H, -OCH_3), 3.98 (s, 1H, -OCH_3), 7.21-7.24 (m, 2H, ArH), 7.65 (s, 1H, ArH), 7.8 (d, *J* = 9.9 Hz, 2H, ArH), 7.89 (s, 1H, ArH), 8.07-8.16 (m, 4H, ArH), 8.56 (s, 1H, -N=CH), 9.7 (s, 1H, NH). ^{13}C NMR (DMSO-d_6 100 MHz) δ: 56.39 (CH_3, -OCH_3), 56.79 (CH_3, -OCH_3), 102.22 (quinazoline C), 107.9 (quinazoline C), 109.6 (quinazoline C), 118.6 (ArC), 120.8 (ArC), 121.8 (ArC), 122.18 (ArC), 127.84 (ArC), 136.1 (ArC), 147.58 (ArC), 147.93 (quinazoline C), 148.1 (ArC), 148.6 (ArC), 152.81

(quinazoline C), 156.31 (quinazoline C), 156.48 (quinazoline, N=CHN), 167.96 (quinazoline, N=C-NH), 170.2 (oxadiazole C), 177.8 (oxadiazole C). LC-MS (ESI, *m/z*): 486.5 $(M + 1)^+$. Anal. calcd. for $C_{26}H_{23}N_5O_5$: C, 64.32; H, 4.78; N, 14.42. Found: C, 64.29; H, 4.73; N, 14.20.

(6,7-Dimethoxy-quinazolin-4-yl)-[4-{5-(4-*tert*-butyl-phenyl)-1,2,4-oxadiazol-3-yl}phenyl]amine (8f): Starting from 0.3 g of **7f** the title compound **8f** was obtained. Beige solid; Yield 0.238 g (82 %); m.p.: 136-138 °C; IR (ATR, ν_{max}, cm^{-1}): 3330.67 (NH), 3047.79 (Ar-CH), 1510.62 (Ar-C=C), 1241.20 (C-O).^{1}H NMR (DMSO-d_6 300 MHz) δ (ppm): 1.34 (s, 9H,- $(CH_3)_3$), 3.94 (s, 3H, -OCH_3), 3.98 (s, 3H, -OCH_3), 7.23 (s, 1H, ArH), 7.69 (d, *J* = 6.9 Hz, 2H, ArH), 7.9 (s, 1H, ArH), 8.08-8.22 (m, 6H, ArH), 8.56 (s, 1H, -N=CH), 9.7 (s, 1H, NH). ^{13}C NMR (DMSO-d_6 100 MHz) δ: 31.6 (CH_3), 34.9 (C-$(CH_3)_3$), 56.39 (CH_3, -OCH_3), 56.78 (CH_3, -OCH_3), 102.24 (quinazoline C), 107.9 (quinazoline C), 109.62 (quinazoline C), 120.98 (ArC), 122.19 (ArC), 125.7 (ArC), 126.6 (ArC), 127.83 (ArC), 133.4 (ArC), 147.69 (ArC), 147.98 (ArC), 148.2 (quinazoline C), 152.89 (quinazoline C), 156.13 (quinazoline C), 156.50 (quinazoline, N=CHN), 167.81 (quinazoline, N=C-NH), 170.4 (oxadiazole C), 177.65 (oxadiazole C). LC-MS (ESI, *m/z*): 482.6 $(M + 1)^+$. Anal. calcd. for $C_{28}H_{27}N_5O_3$: C, 69.84; H, 5.65; N, 14.54. Found: C, 69.93; H, 5.52; N, 14.69.

(6,7-Dimethoxy-quinazolin-4-yl)-[4-{5-(5-cyclopropyl-isoxazole-3-yl)-1,2,4-oxadiazol-3-yl}phenyl]amine (8g): Starting from 0.3 g of **7g** the title compound **8g** was obtained. Light brown solid; Yield: 0.16 g (55 %); m.p.: 132-133 °C; IR (ATR, ν_{max}, cm^{-1}): 3514.16 (NH), 3019.15 (Ar-CH), 1592.28 (Ar-C=C), 1220.64 (C-O).^{1}H NMR (DMSO-d_6 300 MHz) δ (ppm): 1.02-1.21 (m, 4H, cyclopropyl -CH_2), 2.29-2.40 (m, 1H, cyclopropyl -CH), 3.94 (s, 3H, -OCH_3), 3.98 (s, 1H, -OCH_3), 7.22 (s, 1H, ArH), 7.89 (s, 1H, ArH), 8.09 (d, *J* = 8.4 Hz, 2H, ArH), 8.13 (d, *J* = 9.3 Hz, 2H, ArH), 8.56 (s, 1H, -N=CH), 9.73 (bs, 1H, NH). ^{13}C NMR (DMSO-d_6 100 MHz) δ: 6.2 (cyclopropyl C), 9.5 (cyclopropyl C), 56.34 (CH_3, -OCH_3), 56.7 (CH_3, -OCH_3), 99.4 (quinazoline C), 102.28 (isoxazole C), 107.71 (quinazoline C), 109.61 (quinazoline C), 121.2 (ArC), 128.16 (ArC), 143.61 (ArC), 147.73 (quinazoline C), 149.59 (isoxazole C), 153.07 (quinazoline C), 156.40 (quinazoline C), 156.9 (isoxazole C), 157.8 (quinazoline, N=CHN), 168.2 (quinazoline, N=C-NH), 170 (oxadiazole C), 177 (oxadiazole C). LC-MS (ESI, *m/z*): 457.4 $(M + 1)^+$. Anal. calcd. for $C_{24}H_{20}N_6O_4$: C, 63.15; H, 4.42; N, 18.41. Found: C, 63.02; H, 4.34; N, 18.49.

(6,7-Dimethoxy-quinazolin-4-yl)-[4-{5-(1H-indol-3-ylmethyl)-1,2,4-oxadiazol-3-yl}phenyl]amine (8h): Starting from 0.3 g of **7h** the title compound **8h** was obtained. Brown solid; Yield: 0.12 g (41 %); m.p.: 138-140 °C; IR (ATR, ν_{max}, cm^{-1}): 3317.43(NH), 3008.96 (Ar-CH), 1599.63 (Ar-C=C), 1239.85 (C-O).^{1}H NMR (DMSO-d_6 300 MHz) δ (ppm): 3.37 (s, 2H, indole-CH_2), 3.97 (s, 3H, -OCH_3), 3.99 (s, 3H, -OCH_3), 7.01-7.14 (m, 2H, ArH), 7.21 (s, 1H, ArH), 7.36 (s, 1H, indole-H), 7.38 (d, *J* = 8.4 Hz, 1H, ArH), 7.56 (d, *J* = 7.8 Hz, 1H, ArH), 7.87 (s, 1H, ArH), 8.01-8.18 (m, 4H, ArH), 8.54 (s, 1H, -N=CH), 9.68 (bs, 1H, NH), 11.12 (bs, 1H, indole-NH); ^{13}C NMR (DMSO-d_6 100 MHz) δ: 31.2 (-CH_2, indole), 56.3 (CH_3, -OCH_3), 56.71 (CH_3, -OCH_3), 102.21 (quinazoline C), 103.4 (indole C), 107.8 (quinazoline C), 108.9 (indole C), 109.63 (indole C), 120.9 (ArC), 121.1 (indole C),121.9 (indole C), 122.1 (indole C), 122.6 (ArC), 127.5 (indole C), 127.84 (ArC), 135.1 ((indole C), 136.7 (indole C), 147.68 (ArC), 147.99 (quinazoline C), 152.89 (quinazoline C), 156.30 (quinazoline C), 156.60 (quinazoline, N=CHN), 167.91 (quinazoline, N=C-NH), 170.8 (oxadiazole C), 177.91 (oxadiazole C). LC-MS (ESI, *m/z*): 479.6 $(M + 1)^+$. Anal. calcd. for $C_{27}H_{22}N_6O_3$: C, 67.77; H, 4.63; N, 17.56. Found: C, 67.82; H, 4.56; N, 17.61.

(6,7-Dimethoxy-quinazolin-4-yl)- [4-(5-cyclopropyl-1, 2,4-oxadiazol-3-yl)phenyl]amine (8i): Starting from 0.3 g of **7i** the title compound **8i** was obtained. White solid; Yield: 0.18 g (57 %); m.p.: 164-163 °C; IR (ATR, ν_{max}, cm^{-1}): 3316.62 (NH), 3009.22 (Ar-CH), 1516.99 (Ar-C=C), 1544.29 (Ar-C=C), 1239.85 (C-O).^{1}H NMR (DMSO-d_6 300 MHz) δ (ppm): 1.19-1.29 (m, 4H, cyclopropyl -CH_2), 2.3-2.36 (m, 1H, cyclopropyl -CH), 3.94 (s, 3H, -OCH_3), 3.97 (s, 3H, -OCH_3), 7.22 (s, 1H, ArH), 7.87 (s, 1H, ArH), 7.97 (d, *J* = 8.7 Hz, 2H, ArH), 8.06 (d, *J* = 8.7 Hz, 2H, ArH), 8.54 (s, 1H, -N=CH), 9.68 (s, 1H, NH). ^{13}C NMR (DMSO-d_6 75 MHz) δ: 6.3 (cyclopropyl C), 9.8 (cyclopropyl C), 56.39 (CH_3, -OCH_3), 56.80 (CH_3, -OCH_3), 102.3 (quinazoline C), 107.9 (quinazoline C), 109.61 (quinazoline C), 120.91 (ArC), 122.15 (ArC), 127.81 (ArC), 147.69 (ArC), 147.91 (quinazoline C), 152.88 (quinazoline C), 156.20 (quinazoline C), 156.48 (quinazoline, N=CHN), 167.91 (quinazoline, N=C-NH), 170.13 (oxadiazole C), 177.63 (oxadiazole C). LC-MS (ESI, *m/z*): 390.5 $(M + 1)^+$. Anal. calcd. for $C_{21}H_{19}N_5O_3$: C, 64.77; H, 4.92; N, 17.98. Found: C, 64.96; H, 5.13; N, 17.85.

(6,7-Dimethoxy-quinazolin-4-yl)-[4-(5-cyclopentyl-1, 2,4-oxadiazol-3-yl)phenyl]amine (8j): Starting from 0.3 g of **7j** the title compound **8j** was obtained. White solid; Yield: 0.225 g (78 %); m.p.: 155-156 °C; IR (ATR, ν_{max}, cm^{-1}): 3468.47 (NH), 3205.08 (Ar-CH), 1478.65 (Ar-C=C), 1242.78 (C-O).^{1}H NMR (DMSO-d_6 300 MHz) δ (ppm): 1.7-1.79 (m, 4H, cyclopentyl CH_2), 1.84-1.89 (m, 2H, cyclopentyl –CH_2), 2.12-2.2 (m, 2H, cyclopentyl –CH_2), 3.43-3.51 (m, 1H, cyclopentyl –CH), 3.93 (s, 3H, -OCH_3), 3.97 (s, 3H, -OCH_3), 7.22 (s, 1H, ArH), 7.87 (s, 1H, ArH), 8.0 (d, *J* = 8.7 Hz, 2H, ArH), 8.06 (d, *J* = 8.7 Hz, 2H, ArH), 8.54 (s, 1H, -N=CH), 9.68 (s, 1H, NH). ^{13}C NMR (DMSO-d_6 75 MHz) δ: 25.60 (cyclopentyl C), 31.38 (cyclopentyl C), 36.7 (cyclopentyl C), 56.28 (CH_3, -OCH_3), 56.68 (CH_3, -OCH_3), 102.28 (quinazoline C), 107.67 (quinazoline C), 109.54 (quinazoline C), 120.92 (ArC), 122.07 (ArC), 127.82 (ArC), 147.64 (ArC), 149.50 (quinazoline C), 153.06 (quinazoline C), 154.87 (quinazoline C), 156.40 (quinazoline, N=CHN), 167.62 (quinazoline, N=C-NH), 170.3 (oxadiazole C), 183 (oxadiazole C). LC-MS (ESI, *m/z*): 418.5 $(M + 1)^+$. Anal. calcd. for $C_{23}H_{23}N_5O_3$: C, 66.17; H, 5.55; N, 16.78. Found: C, 66.29; H, 5.46; N, 16.66.

HTRF assay: VEGFR tyrosine kinase inhibition is determined by measuring the phosphorylation level of poly-Glu-Ala-Tyr-biotin (pGAT-biotin) peptide in a homogeneous time resolved fluorescence (HTRF) assay. Into a black 96-well Costar plate is added 2 µL/well of 25x compound in 100 % DMSO (final concentration in the 50 µL kinase reaction is typically 1 nM to 10 µM). Next, 38 µL of reaction buffer (25

mM Hepes, pH 7.5, 5 mM $MgCl_2$, 5 mM $MnCl_2$, 2 mM DTT and 1 mg/mL BSA) containing 0.5 mmol pGAT-biotin and 3-4 ng KDR enzyme is added to each well. After 5-10 min preincubation, the kinase reaction is initiated by the addition of 10 µL of 10 µM ATP in reaction buffer, after which the plate is incubated at room temperature for 45 min. The reaction is stopped by addition of 50 µL KF buffer (50 mM Hepes, pH 7.5, 0.5 M KF and 1 mg/mL BSA) containing 100 mM EDTA and 0.36 µg/mL PY20K (Eu-cryptate labeled antiphosphotyrosine antibody, CIS Bio International). After 30 min, 100 µL of 10 nM SV-XL (modified APC-labeled streptavidin, CIS Bio International) in KF buffer is added and after additional 2 h incubation at room temperature, the plate is read in a RUBYstar HTRF Reader.

Antibacterial assay: All the compounds were screened for their *in vitro* antibacterial activity against representative Gram-positive and Gram-negative strains, by means of standard twofold serial dilution method using agar media. Minimum inhibitory concentration (MIC) is defined as the minimum concentration of the compound required to give complete inhibition of bacterial growth after incubation at 35 °C for 24 h. After incubation, readings are taken manually and the optical density is measured at 600 nm. The lowest concentration of the test item/s which prevents visible growth of a microorganism is considered as minimal inhibitory concentration.

RESULTS AND DISCUSSION

The synthesis of compound **7a** was first attempted by reaction of compound **6** with benzoic acid **a** in the presence of N-ethyl-N'-(3-dimethylaminopropyl)carbodiimideHCl (EDC·HCl), 1-hydroxybenzotriazole (HOBt) and 4-dimethylaminopyridine (DMAP) at room temperature. Compound **7a** was isolated in 74 % yield after recrystallization using hot 2-propanol. Utilizing the similar conditions, compounds **7a-7j** was synthesized in good yields. The reactions were complete within 1 h and the products were precipitated in 35-80 % yield by adding water to the reaction mixture. Purification was done by recrystallization using hot 2-propanol.

Cyclization of the amidoxime derivative compound **7a** was initially tried by heating compound **7a** with N,N″-dicylohexylcarbodimide (DCC) in ethanol at 80 °C. But the isolation and purification involved column chromatography due to the formation of dicyclohexylurea (DCU) from the coupling agent owing to lower yields. We then employed 1,8-diazabicycloundec-7-ene (DBU) as the dehydrating agent. The 1,2,4-oxadiazole derivatives **8a-8j** were efficiently synthesized by reacting compound **7a-7j** with DBU in N,N-dimethylformamide (DMF) solvent at 80 °C. Cyclization was complete in 12 h and the products were precipitated in 40-85 % yield by adding water to the reaction mixture. Purification of all the compounds was done by recrystallization using hot 2-propanol.

The structures of all the newly synthesized compounds were confirmed by IR, ^1H and ^{13}C NMR and LC mass spectral studies. The structure of compound **5** was interpreted by its IR spectrum which showed the presence of –CN group due to the appearance of strong band at 2225.56 cm^{-1}.

The structure of compound **6** was interpreted by IR, ^1H NMR and LCMS analysis. The IR spectrum of compound **6** showed the presence of –OH group due to the appearance of strong band at 3619.65 cm^{-1}. In its ^1H NMR spectrum, the appearance of broad singlets at δ 9.55 and 9.73 confirmed the presence of newly introduced carboximidamide group. Further, the LCMS showed its molecular ion peak at 340.1 (M + H) which is in accordance with its molecular formula $C_{17}H_{17}N_5O_3$. The structure of compounds **7a-7j** was confirmed by IR, ^1H and ^{13}C NMR and LC-MS analysis. The ^1H NMR of **7a** showed broad singlet at δ 6.94 for two protons which corresponds to $–NH_2$ group of carboximidamide in the molecule. The IR spectrum showed the presence of –C=O group of amide at 1721.59 cm^{-1} which again was confirmed by the appearance of signal at 170 in the ^{13}C NMR. The structure of **7a** was again confirmed by LCMS which showed the molecular ion peak at *m/z* 444.6 (M + H) which correspond to the molecular formula $C_{24}H_{21}N_5O_4$.

The structure of compounds **8a-8j** was confirmed by IR, ^1H and ^{13}C NMR and LC-MS analysis. The ^1H NMR of **8a** didn't show the peak for $–NH_2$ group of carboximidamide, thereby confirming the oxadizole ring formation. The ^{13}C NMR showed a signal at 177.8 confirming the presence of oxadiazole ring in the molecule. Further, the LCMS showed its molecular peak at *m/z* 426.5 (M + H), which is in accordance with its molecular formula $C_{24}H_{20}N_5O_3$.

Activity of compounds 8a-8j against VEGFR-2: All compounds **8a-8j** were tested against isolated VEGRF-2 by measuring the ability to inhibit phosphorylation of a biotinylated-polypeptide substrate (p-GAT, CIS Bio International) in a homogeneous time-resolved fluorescence (HTRF) assay at an ATP concentration of 2 µM. The results were reported as a 50 % inhibition concentration value (IC_{50}), a literature VEGFR-2 inhibitor also being included as an internal standard for quality control (ZD 6474; IC_{50} = 45 ± 15 nM).

The results generated from this study Table-1 showed that substituted oxadiazolequinazolines exhibited good to excellent inhibitory activity against VEGRF-2 (compounds **8d**, **8g-8h**). Compounds with introduction of heterocylic substituents in the 1,2,4-oxadiazole ring **8g-8h** were highly active with IC_{50} values of 75 and 17 nM respectively. Interestingly, the biphenyl group was also beneficial for VEGFR-2 inhibition (**8d**; IC_{50} =

TABLE-1
ACTIVITY OF 4-[5-(SUBSTITUTED-1,2,4-OXADIAZOL-3-YL)-PHENYLAMINE] DERIVATIVES OF 6,7-DIMETHOXY-QUINAZOLINES (**8a –8j**) AGAINST VEGFR-2

Compound	R	Enzymatic, IC_{50} (µM)*
8a	Ph	> 10
8b	4-Cl Ph	0.27 ± 0.03
8c	3-Me Ph	> 10
8d	4-Ph Ph	0.048 ± 0.06
8e	3,4-diMeO Ph	> 10
8f	4-*t*-Bu Ph	0.23 ± 0.07
8g	5-Cyclopropyl-3-isoxazole	0.075 ± 0.007
8h	Indole-3-methyl	0.017 ± 0.03
8i	Cyclopropyl	> 10
8j	Cyclopentyl	> 10

*IC_{50} values were determined from logarithmic concentration-inhibition curves (at least eight points) and are given as means of at least two separate experiments

48 nM). Acceptable enzymatic inhibition was observed with *para*-chloro and *tert*-butyl phenyl substituents (**8b**; IC_{50} = 0.27 μM, **8f**; IC_{50} = 0.23 μM). Other analogues showed a dramatic decrease in the enzymatic acitivity.

Activity of compounds 8a-8j against VEGFR-1: All the compounds **8a-8j** were also tested in an HTRF format against VEGFR-1, a receptor tyrosine kinase related to VEGFR-2. The results in Table-2 indicate that the compounds inhibit VEGFR-1 at a compound screening concentration of 10 μM. The data generated shows that VEGFR-2 active compounds display good activity against VEGFR-1 as well. A percentage inhibition of < 40 % at 10 μM is considered to be inactive.

TABLE-2
ACTIVITY OF 4-[5-(SUBSTITUTED-1,2,4-OXADIAZOL-3-YL)PHENYLAMINE] DERIVATIVES OF 6,7-DIMETHOXY-QUINAZOLINES (**8a-8j**) AGAINST VEGFR-1

Compound	% Inhibition of VEGFR-1 at 10 μM*	% Inhibition of VEGFR-2 at 10 μM*
8a	40	35
8b	89	90
8c	60	59
8d	91	95
8e	40	35
8f	57	92
8g	86	100
8h	91	97
8i	43	38
8j	58	57

*Average of n = 3

***in vitro* Antibacterial activity:** All the newly synthesized compounds **8a-8j** were evaluated for their *in vitro* antibacterial activities against human pathogens by means of standard twofold serial dilution method using agar media. The *in vitro* antibacterial activity was performed against three Gram-positive bacterial strains including methicillin-sensitive *Staphylococcus aureus*, vancomycin-resistant *Enterococcus faecalis*, methicillin-resistant *Staphylococcus aureus* and three Gram-negative strains including *Klebsiella pneumoniae* (clinical). Ciprofloxacin and linezolid were used as reference standards.

The data generated from this study (Table-3) showed that some of the target compounds exhibit good potency in inhibiting the growth of Gram-positive bacteria such as *Staphylococci aureu*s including MRSA and VRE. faecalis (0.25-8.00 μg/mL). The *in vitro* activity of compound **8j** against Gram-positive bacteria such as methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecalis* are comparable to the marketed drugs linezolid and ciprofloxacin. The *in vitro* activity of compound **8j** against Gram-negative bacteria such as *Klebsiella pneumonia*, *Acinetobacter baumannii* and *Moraxella catarrhalis* are superior to the marketed drug linezolid and slightly less active when compared to ciprofloxacin.

The antibacterial activity of compounds (**8a-8j**) suggested that introduction of 4-(5-(cycloalkyl substituted-1,2,4-oxadiazol-3-yl)-phenylamine derivatives of 6,7-dimethoxy-quinazolines improved the antibacterial activity against Gram-positive strains with retention of activity against Gram-negative strains. However, 4-(5-(aryl substituted-1, 2,4-oxadiazol-3-yl)-phenylamine derivatives (**8a-8j**) are less potent than the reference compounds linezolid and ciprofloxacin.

Conclusion

A series of novel 4-(5-(substituted-1,2,4-oxadiazol-3-yl)-phenylamine derivatives are synthesized at C-4 position of 6,7-dimethoxy-quinazolines as high potent inhibitors of the VEGFR-2 receptor. These compounds are also inhibitors of the VEGFR-1 receptor. The compounds also provide an opportunity of laying the foundation for development of more promising molecules of anticancer potency. Compound **8j** exhibited good antibacterial activity by inhibiting the growth of methicillin-sensitive *Staphylococcus aureus* (MSSA), methicillin-resistant *Staphylococcus aureus* (MRSA) and ATCC 35218 *Escherichia coli* (MIC: 0.25-16.00 μg/mL).

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TABLE-3
ANTIBACTERIAL ACTIVITY OF 4-[5-(SUBSTITUTED-1,2,4-OXADIAZOL-3-YL)-PHENYLAMINE] DERIVATIVES OF 6,7-DIMETHOXY-QUINAZOLINES (**8a-8j**)

Compound	Gram-positive panel MIC (μg/mL)			Gram-negative panel MIC (μg/mL)		
	ATCC 29213 *Staphylococcus aureus* (MSSA)	ATCC 29212 *Enterococcus faecalis*	ATCC 33591 *Staphylococcus aureus* (MRSA)	ATCC 35218 *Escherichia coli*	ATCC 35657 *Klebsiella pneumoniae*	ATCC 25238 *Moraxella catarrhalis*
8a	16	32	32	4	4	2
8b	16	32	32	8	8	2
8c	32	64	>64	4	2	1
8d	16	32	32	4	4	2
8e	16	32	32	4	4	2
8f	32	64	>64	4	2	2
8g	34	64	>64	4	2	2
8h	16	64	64	4	4	2
8i	16	32	64	2	2	0.5
8j	4	16	4	0.25	0.5	0.25
Linezolid	4	16	2	>64	>64	8
Ciprofloxacin	0.5	1	0.5	0.015	0.007	0.03

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