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# Facile synthetic approach towards vasorelaxant active 4-hydroxyquinazoline-4-carboxamides†

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A Facile synthetic approach is reported towards 4-hydroxyquinazoline-4-carboxamides **13a–i** through ring expansion of 2,3-dioxoindoline-1-carboxamides **10a–c** during secondary amine **11a–d** nucleophilic reaction. Single crystal X-ray studies of **10c** and **13d** support the structures. Some of the synthesized quinazolinecarboxamides **13** show promising vasorelaxant properties with potency higher than that of Doxazosin through the pre-contracted (norepinephrine hydrochloride) rat aorta standard bioassay. Good molecular models (2D-QSAR, pharmacophore) describe the biological observations.



## Introduction

Quinazoline is an important heterocyclic system that occupies a striking position in medicinal chemistry due to the diverse biological and/or pharmacological properties associated with its derivatives.[1–6] For example, Gefitinib (Iressa) **1** is a drug clinically approved by the FDA for treatment of non-small cell lung cancer (NSCLC, on May 5, 2003) (Fig. 1). It is a tyrosine kinase inhibitor accessible for patients with metastatic NSCLC.[7,8] Erlotinib (Tarceva) **2** is also a kinase inhibitor approved by the FDA (Nov. 18, 2004) for locally advanced or metastatic NSCLC and pancreatic cancers.[9,10] Lapatinib (Tykerb) **3** is approved by the FDA (Mar. 13, 2007) for treatment of advanced or metastatic breast cancer.[11,12] However, due to the drug resistance observed by the targeted first generation reversible EGFR (epidermal growth factor receptor) drugs **1–3**, by many patients, the second generation irreversible EGFR inhibitors were developed.[13] Of which, Afatinib (Gilotrif) **4** and Dacomitinib (Vizimpro) **5** were approved for treatment of metastatic NSCLC (FDA on July 12, 2013 and Sept. 27, 2018, respectively).[14–17]

Additionally, Doxazosin **6** and Terazosin **7** are well known drugs for hypertension.[18] Hypertension is one of the cardiovascular diseases which are the first cause of human death globally (approximately 17.9 millions representing 31% of global deaths in 2016 according to WHO "World Health Organization"[19,20]). Heart attack and stroke are usually associated with hypertension.[21] Many $\alpha_1$-adrenergic receptor ($\alpha_1$-AR) antagonists are clinically useful drugs for vascular smooth muscle relaxation (vasodilator) such as Doxazosin **6** and Terazosin **7** but associate with severe side effects.[22] The high mortality factor of hypertension and serious side effects of the clinically known drugs dimensioned their applications, directed the research efforts for developing novel effective hits/leads. The recent publications describing diverse biological properties of quinazoline containing-compounds as antibacterial,[23] antiviral,[24] antifungal,[25] antiplasmodial,[26] anti-inflammatory,[27] cholinesterase,[28,29] and monoamine oxidase inhibitors[30] also prompted the present work.

The present study is directed towards construction of novel quinazoline-based analogues and investigation their vasorelaxant properties. The amino group located at the 4-position of the antihypertensive active drugs **6** and **7** were replaced by a hydroxy group due to the common chemical properties of the two functions. The alicyclic-amino ring is also attached to the quinazolinyl C-4 forming an amidic linkage (Scheme 1). Many synthetic pathways were developed for construction of quinazoline-containing compounds including *m*-chloroperbenzoic acid oxidative rearrangement of 4-imino-(1*H*,4*H*)-3,1-benzoxazin-2-ones and reaction of isatins with arylamines in the presence of hydrogen peroxide as an oxidant.[31] Previous publications described the ring opening of isatins under the effect of water, alcohols, amines,[32,33] urea,[34] hydrazines[33,35] and guanidine.[34,36] The present study describes a facile synthetic approach *via* ring expansion of isatin-1-carboxamides during secondary amine nucleophilic attack.

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† Electronic supplementary information (ESI) available: Copy of IR, $^1$H- and $^{13}$C-NMR spectra, biological curves, computational tables/figures. CCDC 1913146 and 1913147. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9ra04321g

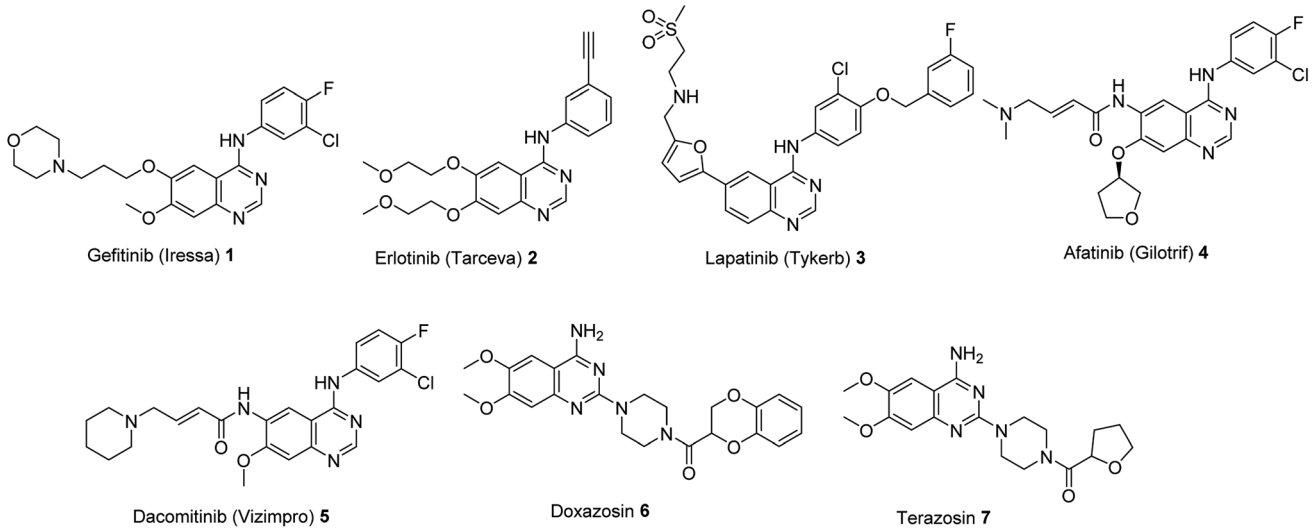


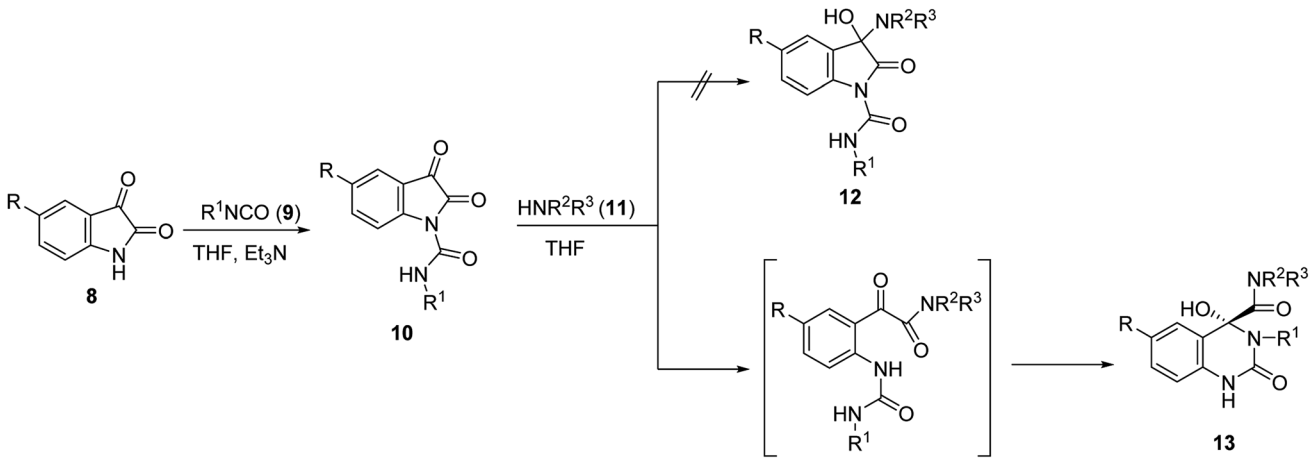

Fig. 1 Quinazoline-based antitumor and antihypertensive drugs.

## Results and discussion

### Chemistry

Isocyanates **9a,b** were subjected to reaction with isatins **8a,b** in dry tetrahydrofuran (THF) in the presence of sufficient amount of triethylamine at 0 °C affording the corresponding 2,3-dioxoindoline-1-carboxamides **10a–c** in good yields which were used in the next reaction without any further purification. *N*-Ethyl-2,3-dioxoindoline-1-carboxamide (**10c**) could be isolated in good microcrystallized form accessible for single crystal X-ray studies, which add good support for the structure (Fig. 2).

Reaction of **10a–c** with secondary amines **11a–d** in dry THF led to ring expansion affording directly the 4-hydroxyquinazoline-4-carboxamides **13a–i** and not the expected 3-hydroxy-2-oxoindoline-1-carboxamides **12**. IR




**8a**, R = H
**8b**, R = Cl

**9a**, $R^1$ = Ph
**9b**, $R^1$ = Et

**10a**; R = H, $R^1$ = Ph
**10b**; R = Cl, $R^1$ = Ph
**10c**; R = H, $R^1$ = Et

**11a**; $NR^2R^3$ = Diethylamine
**11b**; $NR^2R^3$ = Pyrrolidine
**11c**; $NR^2R^3$ = Piperidine
**11d**; $NR^2R^3$ = Morpholine

**13a**; R = H, $R^1$ = Ph, $NR^2R^3$ = Diethylamino ((71% yield)
**13b**; R = H, $R^1$ = Ph, $NR^2R^3$ = Pyrrolidinyl (74% yield)
**13c**; R = Cl, $R^1$ = Ph, $NR^2R^3$ = Pyrrolidinyl (85% yield)
**13d**; R = H, $R^1$ = Ph, $NR^2R^3$ = Piperidinyl (77% yield)
**13e**; R = Cl, $R^1$ = Ph, $NR^2R^3$ = Piperidinyl (68% yield)
**13f**; R = H, $R^1$ = Et, $NR^2R^3$ = Piperidinyl 73% yield)
**13g**; R = H, $R^1$ = Ph, $NR^2R^3$ = Morpholinyl (71% yield)
**13h**; R = Cl, $R^1$ = Ph, $NR^2R^3$ = Morpholinyl (75% yield)
**13i**; R = H, $R^1$ = Et, $NR^2R^3$ = Morpholinyl (77% yield)

Scheme 1 Synthetic route towards 4-hydroxyquinazoline-4-carboxamides **13a–i**.

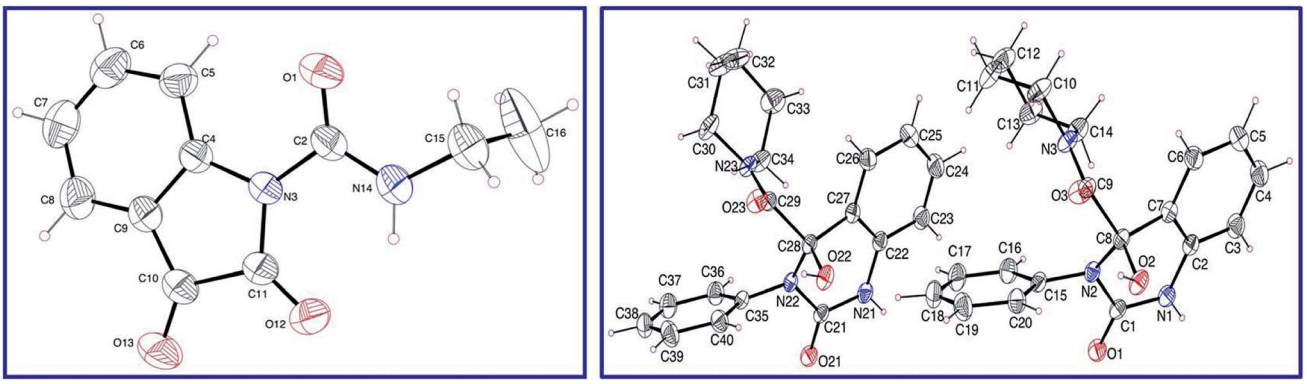



Fig. 2 ORTEP views of compounds **10c** (left) and **13d** (right) with the atom-numbering scheme. H atoms are shown as small spheres of arbitrary radii.

spectrum of **13a** (an example of the synthesized analogues) reveals the carbonyl groups as a broad signal at $\nu$ = 1670 $cm^{-1}$. $^1$H-NMR spectrum of **13a** reveals the triplet and quartet signals of the ethyl groups at $\delta_H$ = 1.03 and 2.74 ppm, respectively, which are also well observed at $\delta_C$ = 10.8, 18.5; 41.1, 56.0, respectively in the $^{13}$C-NMR spectrum. The quinazolinyl C-2 and amidic carbonyls are shown at $\delta_C$ = 151.9, 172.4 ppm, respectively. Meanwhile, the characteristic quinazolinyl C-4 is exhibited at $\delta_C$ = 87.1 ppm (spectral charts are exhibited in ESI Fig. S1–S30,† overlapping of few carbon signals in the $^{13}$C-NMR spectral data of compounds **13g,h** is observed). Single crystal X-ray studies of **13d** support the chemical/stereochemical structure assigned (Fig. 2). The reaction is assumed to take place through amine **11** nucleophilic attack at the indolyl C-2 giving rise to five-membered ring opening followed by re-cyclization with ring expansion to the six-membered quinazoline heterocycle (Scheme 1).

## X-ray studies

ORTEP views of compounds **10c** and **13d** are revealed in Fig. 2. Compound **10c** is crystallized in the monoclinic space group *C*2/*c* while, compound **13d** is crystallized in the monoclinic space group $P2_1/n$ (ESI Table S1†). The main constituent of **10c** is the indolyl heterocycle and the main constituents of **13d** are quinazolinyl, piperidinyl and phenyl rings. Compound **10c** exhibits one molecule per asymmetric unit cell and four molecules per unit cell. However, compound **13d** shows two molecules per asymmetric unit cell and eight molecules per unit cell. In **10c**, the ethyl group is nearly perpendicular to the plane containing the main constituent. Meanwhile, the piperidinyl ring of compound **13d** exhibits a chair conformation and the phenyl as well as quinazolinyl heterocycle are nearly planar. Generally, the geometrical parameters of compounds **10c** and **13d** (ESI Tables S2 and S3†) are comparable to structures having similar constituents.[37] Different sets of intermolecular hydrogen-bonding interactions stabilize the crystal structure of the studied compounds and led to the formation of supramolecular assemblies (ESI Table S4, Fig. S31 and S32†).

## Vasodilation studies

The standard pre-contracted (norepinephrine hydrochloride) rat aorta technique was utilized for determination the vasodilation properties of the synthesized compounds **10c**, **13a–i** and compared with Doxazosin ($\alpha_1$-AR antagonist).[38] From the exhibited data (Table 1, ESI Fig. S33 and S34†) it can be concluded that, many of the synthesized quinazolines are vasorelaxant active agents with efficacy comparable to that of Doxazosin. Compound **13h** seems superior among all the tested analogues with 2.2 folds potency relative to the standard reference ($IC_{50}$ = 158, 348 μM for **13h** and Doxazosin, respectively). Compounds **13e** also shows remarkable vasorelaxant properties (about 139% potency of Doxazosin with $IC_{50}$ = 250 μM). Promising smooth muscle relaxation is also shown by compounds **13a,d,f,g** ($IC_{50}$ = 298–332 μM). *N*-Ethyl-2,3-dioxoindoline-1-carboxamide (**10c**) is also a promising vasorelaxant active agent (1.47 folds efficacy relative to the standard drug).

Based on the observed vasodilation properties few SAR (structure–activity relationship) rules can be stated. The chlorine substituent attached at the quinazolinyl C-6 is an important factor for enhancing the biological properties observed as exhibited in pairs **13b**/**13c**, **13d**/**13e** and **13g**/**13h**. The alicyclic-amino ring of the amidic function is also a controlling parameter for biological activity. The importance of the amino ring for

Table 1 Vasorelaxant properties of **10c**, **13a–i** and Doxazosin

| Entry | Compd. | R | $R^1$ | $NR^2/R^3$ | $IC_{50}$, μM |
|---|---|---|---|---|---|
| 1 | **10c** | H | Et | — | 236 |
| 2 | **13a** | H | Ph | $NEt_2$ | 302 |
| 3 | **13b** | H | Ph | Pyrrolidinyl | 415 |
| 4 | **13c** | Cl | Ph | Pyrrolidinyl | 392 |
| 5 | **13d** | H | Ph | Piperidinyl | 332 |
| 6 | **13e** | Cl | Ph | Piperidinyl | 250 |
| 7 | **13f** | H | Et | Piperidinyl | 305 |
| 8 | **13g** | H | Ph | Morpholinyl | 298 |
| 9 | **13h** | Cl | Ph | Morpholinyl | 158 |
| 10 | **13i** | H | Et | Morpholinyl | 416 |
| 11 | Doxazosin | — | — | — | 348 |

vasodilation properties enhancement can be arranged in the following order morpholinyl > piperidinyl > pyrrolidinyl (compound **13f** is an exception).

### Molecular modeling studies

**2D-QSAR study.** QSAR (quantitative structure–activity relationship) study is a widely used computational technique for explaining the biological observations and better understanding the parameters optimizing properties.[39] Two descriptor QSAR model was obtained by CODESSA-Pro for the vasorelaxant quinazoline-4-carboxamides **13a–i** ($R^2 = 0.970$, ESI Table S5†). Explanation/calculation of the QSAR descriptors was mentioned in the ESI.† Goodness of the QSAR model is supported by the leave one-out and leave many-out (up to 20% of the compounds used in the study) coefficient values relative to the original QSAR coefficient value ($R^2 = 0.970$, $R^2$cvOO = 0.905, $R^2$cvMO = 0.937). The predicted $IC_{50}$ values relative to the experimental are also supporting evidence for the robust of computational model (Fig. 3).

**3D-Pharmacophore study.** Three chemical features (two hydrophobics "H-1, H-2" and one hydrogen bonding donor "HBD", ESI Fig. S35 and S36†) are shown by the 3D-pharmacophoric model (Discovery Studio 2.5 software) for the vasorelaxant active quinazoline-4-carboxamides **13a–i**.[40] All the synthesized compounds reveal alignment of the hydroxyl group with the HBD and the amino residue/ring of the amidic linkage with one of the hydrophobic in variable fitness affording diverse estimated biological properties (ESI Table S8†). These observations support the elements of design for the present study and also the assigned SAR mentioned. The high correlations between the estimated and experimental biological properties support the goodness of the 3D-pharmacophoric model.

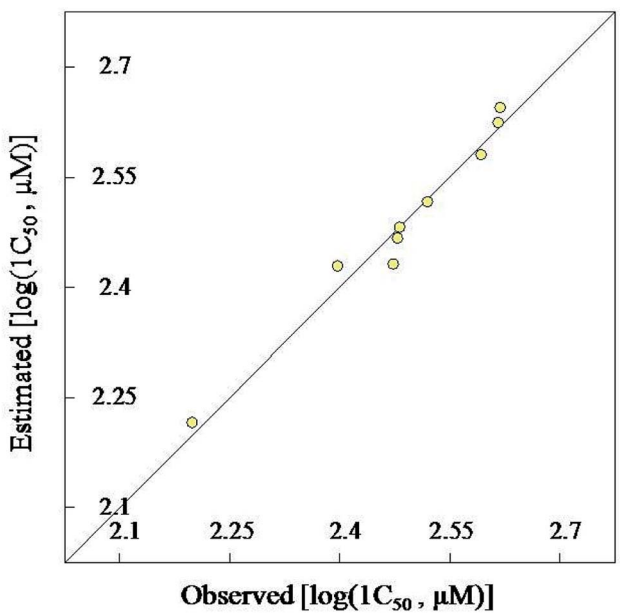



Fig. 3 BMLR-QSAR model plot of correlation representing the observed *versus* predicted [log($IC_{50}$, μM)] values for the synthesized vasorelaxant quinazoline (**13a–i**).

## Conclusions

4-Hydroxyquinazoline-4-carboxamides **13a–i** are synthesized in a facile synthetic approach (yield 68–85%) *via* reaction of 2,3-dioxoindoline-1-carboxamides **10a–c** with secondary amines **11a–d** in dry THF. Single crystal X-ray studies of **10c** and **13d** support the chemical structures. Some of the synthesized quinazolines reveal vasorelaxant properties with efficacy comparable to that of Doxazosin especially, compound **13h** that exhibits 2.2 folds potency relative to the standard reference. 2D-QSAR model describes the biological observations ($N = 9$, $n = 2$, $R^2 = 0.970$). Also, the 3D-pharmacophoric model supports the elements of design for the present study.

## Experimental

### Chemistry

Melting points were determined on a capillary point apparatus (Stuart SMP3) equipped with a digital thermometer. IR spectra (KBr) were recorded on a Shimadzu FT-IR 8400S spectrophotometer. Reactions were monitored using thin layer chromatography (TLC) on 0.2 mm silica gel F254 plates (Merck) utilizing various solvents for elution. The chemical structures of the synthesized compounds were characterized by nuclear magnetic resonance spectra ($^1$H-NMR, $^{13}$C-NMR) and determined on a Bruker NMR spectrometer (500 MHz, 125 MHz). $^{13}$C-NMR spectra are fully decoupled. Chemical shifts were reported in parts per million (ppm) using the deuterated solvent peak or tetramethylsilane as an internal standard.

### Reaction of 8a,b with isocyanates 9a,b

A solution of the corresponding isocyanate **9a,b** (5 mmol) in dry THF (5 ml) was added dropwise to a mixture of the appropriate **8a,b** (5 mmol) in dry THF (20 ml) containing triethylamine (5.5 mmol), at 0 °C. The reaction was magnetically stirred at the same temperature for 10 h then, stored in the fridge overnight. The separated solid was collected and washed with benzene affording **10a,b** which was used without any more purifications. In case of the reaction of **8a** and **9b**, the separated solid was crystallized from benzene affording **10c** as orange microcrystals.

***N*-Ethyl-2,3-dioxoindoline-1-carboxamide (10c).** It was obtained from the reaction of **8a** and **9b** (reaction time 10 h) as orange microcrystals from benzene with mp 159–161 °C and yield 73% (0.80 g). IR: $\nu_{max}$/cm$^{-1}$ 3337, 1756, 1740, 1701, 1612. $^1$H-NMR (DMSO-$d_6$) $\delta$ (ppm): 1.15 (t, $J = 7.2$ Hz, 3H, C$H_3$CH$_2$), 3.30–3.35 (m, 2H, CH$_3$C$H_2$), 7.28 (t, $J = 7.5$ Hz, 1H, arom. H), 7.67 (d, $J = 7.5$ Hz, 1H, arom. H), 7.71 (t, $J = 7.9$ Hz, 1H, arom. H), 8.17 (d, $J = 8.2$ Hz, 1H, arom. H), 8.22 (t, $J = 5.3$ Hz, 1H, NH). $^{13}$C-NMR (DMSO-$d_6$) $\delta$ (ppm): 14.7 (CH$_2$*C*H$_3$), 34.4 (N*C*H$_2$CH$_3$), 116.5, 118.9, 124.3, 124.6, 137.5, 148.2 (arom. C), 150.4 (urea CO), 158.9 (indolyl C-2), 180.4 (indolyl C-3). Anal. calcd for

$C_{11}H_{10}N_2O_3$ (218.21): C, 60.55; H, 4.62; N, 12.84. Found: C, 60.76; H, 4.77; N, 12.93.

### Reaction of 10a–c with secondary amines 11a–d

The appropriate secondary amine **11a–d** (5.5 mmol) was added dropwise to the magnetically stirred solution of **10a–c** (5 mmol) in dry THF (20 ml) at room temperature (20–25 °C) for the appropriate time. The separated solid was collected and crystallized from a suitable solvent affording the corresponding **13a,c,d,g–i**. In case of **13b**, **13e**, and **13f** the reaction mixture was evaporated till dryness under reduced pressure. The remaining material was triturated with methanol (5 ml). The separated solid was collected and crystallized from a suitable solvent.

***N,N*-Diethyl-4-hydroxy-2-oxo-3-phenyl-1,2,3,4-tetrahydroquinazoline-4-carboxamide (13a).** It was obtained from the reaction of **10a** and **11a** (reaction time 8 h) as colorless microcrystals from methanol with mp 145–147 °C and yield 71% (1.20 g). IR: $\nu_{max}/cm^{-1}$ 3202, 3059, 1670, 1609, 1497, 1412. $^1$H-NMR (DMSO-$d_6$) $\delta$ (ppm): 1.03 (t, $J = 6.9$ Hz, 6H, 2 $CH_2CH_3$), 2.74 (q, $J = 6.4$ Hz, 4H, 2 $CH_2CH_3$), 6.41 (br s, 1H, NH), 6.80–6.85 (m, 2H, arom. H), 7.05 (d, $J = 7.4$ Hz, 1H, arom. H), 7.14 (t, $J = 7.3$ Hz, 1H, arom. H), 7.22–7.27 (m, 5H, arom. H), 9.62 (br s, 1H, OH). $^{13}$C-NMR (DMSO-$d_6$) $\delta$ (ppm): 10.8 ($CH_2CH_3$), 18.5 ($CH_2CH_3$), 41.1 ($NCH_2CH_3$), 56.0 ($NCH_2CH_3$), 87.1 (quinazolinyl C-4), 113.0, 120.5, 124.0, 125.7, 126.5, 127.6, 128.1, 130.7, 136.0, 139.3 (arom. C), 151.9 (quinazolinyl C-2), 172.4 (carboxamide CO). Anal. calcd for $C_{19}H_{21}N_3O_3$ (339.40): C, 67.24; H, 6.24; N, 12.38. Found: C, 67.38; H, 6.30; N, 12.42.

**4-Hydroxy-3-phenyl-4-(pyrrolidine-1-carbonyl)-3,4-dihydroquinazolin-2(1*H*)-one (13b).** It was obtained from the reaction of **10a** and **11b** (reaction time 10 h) as colorless microcrystals from methanol with mp 184–186 °C and yield 74% (1.25 g). IR: $\nu_{max}/cm^{-1}$ 3503, 3402, 1678, 1636, 1605, 1504. $^1$H-NMR (DMSO-$d_6$) $\delta$ (ppm): 1.59–1.76 (m, 3H, pyrrolidinyl H), 2.53–2.56 (m, 1H, pyrrolidinyl H), 3.01 (quintet, $J = 7.0$ Hz, 1H, pyrrolidinyl H), 3.18 (d, $J = 4.8$ Hz, 1H, pyrrolidinyl H), 3.35–3.38 (m, 1H, pyrrolidinyl H), 3.48–3.53 (m, 1H, pyrrolidinyl H), 6.70 (s, 1H, NH), 6.93–7.00 (m, 3H, arom. H), 7.24 (d, $J = 7.4$ Hz, 2H, arom. H), 7.30–7.38 (m, 4H, arom. H), 10.22 (s, 1H, OH). $^{13}$C-NMR (DMSO-$d_6$) $\delta$ (ppm): 22.7, 25.8 (pyrrolidinyl C-3/4), 46.5, 47.5 (pyrrolidinyl C-2/5), 85.9 (quinazolinyl C-4), 113.8, 119.8, 121.7, 125.5, 127.3, 128.2, 129.4, 129.5, 135.8, 137.6 (arom. C), 150.9 (quinazolinyl C-2), 166.2 (carboxamide CO). Anal. calcd for $C_{19}H_{19}N_3O_3$ (337.38): C, 67.64; H, 5.68; N, 12.46. Found: C, 67.81; H, 5.59; N, 12.57.

**6-Chloro-4-hydroxy-3-phenyl-4-(pyrrolidine-1-carbonyl)-3,4-dihydroquinazolin-2(1*H*)-one (13c).** It was obtained from the reaction of **10b** and **11b** (reaction time 6 h) as colorless microcrystals from *n*-butanol with mp 208–210 °C and yield 85% (1.58 g). IR: $\nu_{max}/cm^{-1}$ 3564, 3345, 3210, 1682, 1643, 1605, 1489. $^1$H-NMR (DMSO-$d_6$) $\delta$ (ppm): 1.59–1.74 (m, 4H, pyrrolidinyl H), 2.57–2.62 (m, 1H, pyrrolidinyl H), 3.01 (quintet, $J = 6.7$ Hz, 1H, pyrrolidinyl H), 3.33–3.52 (m, 2H, pyrrolidinyl H), 6.91 (s, 1H, NH), 6.92 (d, $J = 2.1$ Hz, 1H, arom. H), 6.98 (d, $J = 8.7$ Hz, 1H, arom. H), 7.22 (d, $J = 7.4$ Hz, 2H, arom. H), 7.31–7.39 (m, 4H, arom. H), 10.25 (s, 1H, OH). $^{13}$C-NMR (DMSO-$d_6$) $\delta$ (ppm): 22.6, 25.9 (pyrrolidinyl C-3/4), 46.6, 47.6 (pyrrolidinyl C-2/5), 86.0 (quinazolinyl C-4), 115.8, 122.0, 124.9, 125.1, 127.4, 128.2, 129.5, 129.6, 134.8, 137.4 (arom. C), 150.6 (quinazolinyl C-2), 165.8 (carboxamide CO). Anal. calcd for $C_{19}H_{18}ClN_3O_3$ (371.82): C, 61.38; H, 4.88; N, 11.30. Found: C, 61.57; H, 5.00; N, 11.38.

**4-Hydroxy-3-phenyl-4-(piperidine-1-carbonyl)-3,4-dihydroquinazolin-2(1*H*)-one (13d).** It was obtained from the reaction of **10a** and **11c** (reaction time 6 h) as colorless microcrystals from ethanol with mp 176–178 °C and yield 77% (1.35 g). IR: $\nu_{max}/cm^{-1}$ 3387, 1682, 1636, 1605, 1501. $^1$H-NMR (DMSO-$d_6$) $\delta$ (ppm): 0.62 (br s, 1H, piperidinyl H), 1.12–1.46 (m, 5H, piperidinyl H), 2.64 (t, $J = 10.9$ Hz, 1H, piperidinyl H), 3.12 (t, $J = 11.8$ Hz, 1H, piperidinyl H), 3.49 (d, $J = 12.8$ Hz, 1H, piperidinyl H), 3.94 (d, $J = 12.3$ Hz, 1H, piperidinyl H), 6.75 (s, 1H, NH), 6.93–7.00 (m, 3H, arom. H), 7.30–7.34 (m, 6H, arom. H), 10.22 (s, 1H, OH). $^{13}$C-NMR (DMSO-$d_6$) $\delta$ (ppm): 23.3, 24.0, 25.1 (piperidinyl C-3/4/5), 44.3, 46.9 (piperidinyl C-2/6), 85.4 (quinazolinyl C-4), 114.2, 120.6, 121.7, 125.6, 127.5, 128.3, 129.5, 129.7, 135.0, 137.8 (arom. C), 150.7 (quinazolinyl C-2), 166.2 (carboxamide CO). Anal. calcd for $C_{20}H_{21}N_3O_3$ (351.41): C, 68.36; H, 6.02; N, 11.96. Found: C, 68.14; H, 5.84; N, 12.16.

**6-Chloro-4-hydroxy-3-phenyl-4-(piperidine-1-carbonyl)-3,4-dihydroquinazolin-2(1*H*)-one (13e).** It was obtained from the reaction of **10b** and **11c** (reaction time 12 h) as colorless microcrystals from *n*-butanol of mp 180–182 °C and yield 68% (1.30 g). IR: $\nu_{max}/cm^{-1}$ 3314, 3210, 1682, 1643, 1605, 1493. $^1$H-NMR (DMSO-$d_6$) $\delta$ (ppm): 0.65–0.77 (m, 1H, piperidinyl H), 1.22–1.53 (m, 5H, piperidinyl H), 2.69 (t, $J = 11.0$ Hz, 1H, piperidinyl H), 3.16 (t, $J = 11.4$ Hz, 1H, piperidinyl H), 3.48 (d, $J = 13.4$ Hz, 1H, piperidinyl H), 3.93 (d, $J = 12.5$ Hz, 1H, piperidinyl H), 6.90 (br s, 2H, NH + arom. H), 7.01 (d, $J = 8.6$ Hz, 1H, arom. H), 7.30–7.42 (m, 6H, arom. H), 10.45 (s, 1H, OH). $^{13}$C-NMR (DMSO-$d_6$) $\delta$ (ppm): 23.2, 24.1, 25.1 (piperidinyl C-3/4/5), 44.1, 46.7 (piperidinyl C-2/6), 85.1 (quinazolinyl C-4), 116.0, 122.3, 124.86, 124.94, 127.4, 128.2, 129.3, 129.6, 134.0, 137.5 (arom. C), 150.4 (quinazolinyl C-2), 165.5 (carboxamide CO). Anal. calcd for $C_{20}H_{20}ClN_3O_3$ (385.85): C, 62.26; H, 5.22; N, 10.89. Found: C, 62.44; H, 5.03; N, 10.73.

**3-Ethyl-4-hydroxy-4-(piperidine-1-carbonyl)-3,4-dihydroquinazolin-2(1*H*)-one (13f).** It was obtained from the reaction of **10c** and **11c** (reaction time 24 h) as colorless microcrystals from benzene with mp 165–167 °C and yield 73% (1.10 g). IR: $\nu_{max}/cm^{-1}$ 3318, 3198, 3121, 1667, 1636, 1609, 1504. $^1$H-NMR (DMSO-$d_6$) $\delta$ (ppm): 0.61 (br s, 1H, piperidinyl H), 1.10 (t, $J = 7.0$ Hz, 4H, $CH_3CH_2$ + piperidinyl H), 1.37–1.53 (m, 4H, piperidinyl H), 3.00–3.33 (m, 5H, $CH_3CH_2$ + 3 piperidinyl H), 3.96 (br s, 1H, piperidinyl H), 6.75 (s, 1H, NH), 6.86 (d, $J = 8.1$ Hz, 1H, arom. H), 6.90–6.96 (m, 2H, arom. H), 7.25 (t, $J = 7.6$ Hz, 1H, arom. H), 9.96 (s, 1H, OH). $^{13}$C-NMR (DMSO-$d_6$) $\delta$ (ppm): 14.3 ($CH_3CH_2$), 23.2, 24.1, 25.1 (piperidinyl C-3/4/5), 37.8 ($CH_3CH_2$), 44.5, 46.5 (piperidinyl C-2/6), 84.6 (quinazolinyl C-4), 113.6, 119.6, 121.3, 125.7, 129.5, 135.0 (arom. C), 150.3 (quinazolinyl C-2), 167.5 (carboxamide CO). Anal. calcd for $C_{16}H_{21}N_3O_3$ (303.36): C, 63.35; H, 6.98; N, 13.85. Found: C, 63.22; H, 6.87; N, 13.79.

**4-Hydroxy-4-(morpholine-4-carbonyl)-3-phenyl-3,4-dihydroquinazolin-2(1*H*)-one (13g).** It was obtained from the reaction of **10a** and **11d** (reaction time 20 h) as colorless microcrystals from

ethanol with mp 173–175 °C and yield 71% (1.25 g). IR: $\nu_{max}/cm^{-1}$ 3618, 3526, 3345, 3198, 1682, 1639, 1609. $^1$H-NMR (DMSO-$d_6$) $\delta$ (ppm): 2.83 (t, $J$ = 8.9 Hz, 1H, morpholinyl H), 2.96 (t, $J$ = 9.5 Hz, 1H, morpholinyl H), 3.20–3.45 (m, 5H, morpholinyl H), 3.65–3.72 (m, 1H, morpholinyl H), 6.79 (s, 1H, NH), 6.96–7.03 (m, 3H, arom. H), 7.29–7.35 (m, 6H, arom. H), 10.28 (s, 1H, OH). $^{13}$C-NMR (DMSO-$d_6$) $\delta$ (ppm): 43.4, 46.7 (morpholinyl $NCH_2$), 64.6, 65.7 (morpholinyl $OCH_2$), 85.8 (quinazolinyl C-4), 114.2, 118.7, 120.7, 121.6, 125.3, 127.2, 128.1, 128.7, 129.2, 129.6, 135.0, 137.9 (arom. C), 150.8 (quinazolinyl C-2), 166.5 (carboxamide CO). Anal. calcd for $C_{19}H_{19}N_3O_4$ (353.38): C, 64.58; H, 5.42; N, 11.89. Found: C, 64.64; H, 5.56; N, 11.76.

**6-Chloro-4-hydroxy-4-(morpholine-4-carbonyl)-3-phenyl-3,4-dihydroquinazolin-2(1*H*)-one (13h).** It was obtained from the reaction of **10b** and **11d** (reaction time 6 h) as colorless microcrystals from *n*-butanol with mp 189–191 °C and yield 75% (1.45 g). IR: $\nu_{max}/cm^{-1}$ 3352, 3213, 1686, 1643, 1609. $^1$H-NMR (DMSO-$d_6$) $\delta$ (ppm): 2.82–2.86 (m, 1H, morpholinyl H), 2.99 (t, $J$ = 9.1 Hz, 1H, morpholinyl H), 3.23–3.43 (m, 5H, morpholinyl H), 3.64 (br d, $J$ = 10.1 Hz, 1H, morpholinyl H), 6.95–7.02 (m, 3H, NH + 2 arom. H), 7.31–7.41 (m, 6H, arom. H), 10.42 (s, 1H, OH). $^{13}$C-NMR (DMSO-$d_6$) $\delta$ (ppm): 43.4, 46.7 (morpholinyl $NCH_2$), 64.8, 65.8 (morpholinyl $OCH_2$), 85.8 (quinazolinyl C-4), 116.1, 124.6, 125.0, 127.3, 128.2, 129.2, 129.6, 134.1, 137.7 (arom. C), 150.5 (quinazolinyl C-2), 166.0 (carboxamide CO). Anal. calcd for $C_{19}H_{18}ClN_3O_4$ (387.82): C, 58.84; H, 4.68; N, 10.84. Found: C, 58.96; H, 4.78; N, 11.04.

**3-Ethyl-4-hydroxy-4-(morpholine-4-carbonyl)-3,4-dihydroquinazolin-2(1*H*)-one (13i).** It was obtained from the reaction of **10c** and **11d** (reaction time 10 h) as colorless microcrystals from benzene with mp 161–163 °C and yield 77% (1.17 g). IR: $\nu_{max}/cm^{-1}$ 3310, 3267, 3210, 1748, 1655, 1609. $^1$H-NMR ($CDCl_3$) $\delta$ (ppm): 1.33 (t, $J$ = 7.0 Hz, 3H, $CH_3CH_2$), 2.94 (br t, $J$ = 9.8 Hz, 1H, morpholinyl H), 3.11 (br d, $J$ = 13.7 Hz, 1H, morpholinyl H), 3.23–3.27 (m, 1H, morpholinyl H), 3.34–3.55 (m, 4H, $CH_3CH_2$ + 2 morpholinyl H), 3.61 (t, $J$ = 9.8 Hz, 1H, morpholinyl H), 3.78 (br d, $J$ = 11.9 Hz, 1H, morpholinyl H), 4.01 (br d, $J$ = 13.3 Hz, 1H, morpholinyl H), 6.65 (s, 1H, NH), 6.87 (d, $J$ = 8.1 Hz, 1H, arom. H), 7.03 (t, $J$ = 7.4 Hz, 1H, arom. H), 7.06 (t, $J$ = 6.5 Hz, 1H, arom. H), 7.31 (d, $J$ = 8.3 Hz, 1H, arom. H), 9.57 (s, 1H, OH). $^{13}$C-NMR ($CDCl_3$) $\delta$ (ppm): 14.7 ($CH_3CH_2$), 38.8 ($CH_3CH_2$), 44.6, 46.9 (morpholinyl $NCH_2$), 65.3, 66.4 (morpholinyl $OCH_2$), 85.0 (quinazolinyl C-4), 114.4, 119.1, 122.6, 125.9, 130.3, 134.5 (arom. C), 152.0 (quinazolinyl C-2), 169.1 (carboxamide CO). Anal. calcd for $C_{15}H_{19}N_3O_4$ (305.33): C, 59.01; H, 6.27; N, 13.76. Found: C, 59.08; H, 6.36; N, 13.89.

### Single crystal X-ray studies

Experimental procedure for the single X-ray studies of compounds **10c** and **13d** is mentioned in the ESI.†

### Vasodilation studies

Experimental procedure utilized for vasodilation studies is mentioned in the ESI.†

### Molecular modeling studies

Experimental procedures for the molecular modeling studies are mentioned in the ESI.†

## Conflicts of interest

The authors have declared no conflict of interest.

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