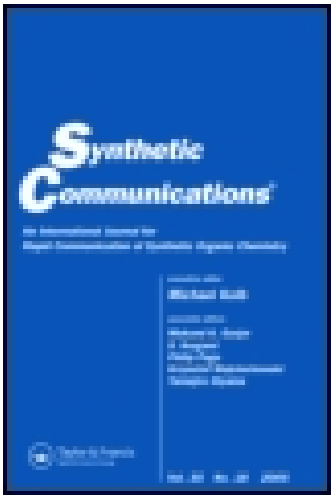

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Heteroannulated Quinazoline and Quinazolinone Derivatives from (Z)-2-[1-Benzamido-2-(3,4,5-trimethoxyphenyl)]vinyl-3,1-benzoxazin-4(3H)-one

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HETEROANNULATED QUINAZOLINE AND QUINAZOLINONE DERIVATIVES FROM (Z)-2-[1-BENZAMIDO-2-(3,4,5-TRIMETHOXYPHENYL)] VINYL-3,1-BENZOXAZIN-4(3H)-ONE

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The title compound 1 was prepared and allowed to react with a series of nitrogen nucleophiles to afford the quinazoline and quinazolinone derivatives 2–12 and tetrazole derivative 13. The IR, ^{1}H NMR, ^{13}C NMR, and mass spectra of all the synthesized compounds were discussed.

Keywords: Benzoxazin-4(3H)-one; imidazo-[1,5-*b*]-quinazolin-4(3H)-one derivatives; [1,2,5]-oxadiazino-[3,2-*b*]-quinazolin-4(3H)-one derivatives; [1,2,4]-triazino-[6,1-*b*]-quinazolin-4(3H)-one derivatives; [1,2,4]-triazolo-[1,5-*c*]-quinazolin-4(3H)-one derivatives

INTRODUCTION

One of the most important features of 4(3H)-3,1-benzoxazin-4(3H)-ones is their use as key starting materials for synthesizing new heterocyclic ring systems, including quinazoline and quinazolinone derivatives, which possess various synthetic applications[1–15] and potential biological activity.[16–24] Of these compounds, for example, allenic quinazolines are cell-growth inhibitors of Tarceva, 4-anilinoquinazolines are orally active inhibitors of erbB2 receptor tyrosine kinase, and 6,7,8-substituted quinazolines are potent and highly selective PDE5 inhibitors, which have potential therapeutic uses for male erectile dysfunction.[23–25] Futhermore, several quinazolinones were synthesized as potential antimicrobial,[26] anticancer,[16] and antimalarial[27] agents. Moreover, 4(3H)-quinazolinone is a frequently encountered unit in natural products; however, pyrido-[3,2-*h*]-quinazolines have been recently discovered to have organic semiconductor properties.[28,29] These aforementioned findings prompted us to synthesize quinazoline and quinazolinone derivatives via the interaction of the benzoxazinone **1** with different nitrogen nucleophiles, which could be more precise and interesting pharmaceutical compounds.

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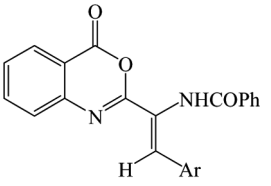
RESULTS AND DISCUSSION



1

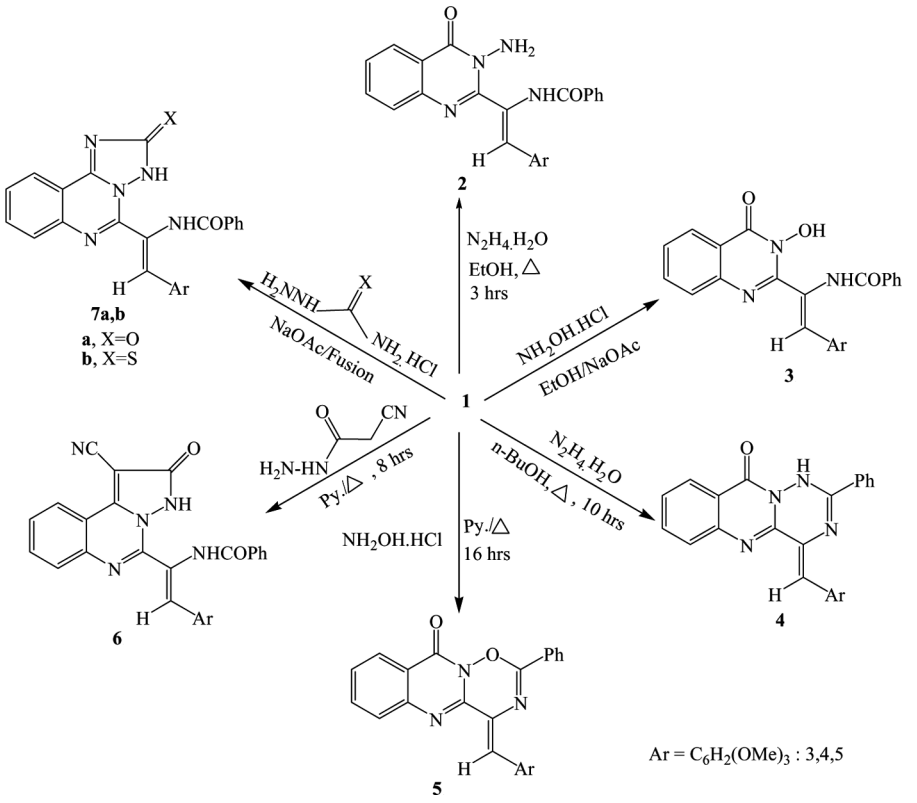
Ar = $C_6H_2(OMe)_3$: 3,4,5

Compound **1** was prepared in a fairly good yield by treating 2-aminobenzoic acid with 4-arylidene-5(4H)-oxazolone in boiling pyridine. Compelling evidence for the structure of **1** was inferred from the infrared (IR) spectrum, which revealed strong absorption bands at 3276, 1760, and 1676 cm^{-1}, attributable to NH, CO (δ-lactone), and CO (α,β-unsat. amide), respectively. ^1H NMR and ^{13}C NMR were consistent with the assigned structure (see the Experimental section). Electron-impact (EI) fragmentation of compound **1** showed the molecular ion peak at m/z 458 (30.74%) together with the base peak at m/z 105 (100%), corresponding to the highly stable cation $PhC{\equiv}O^+$.

When compound **1** was reacted with hydrazine hydrate (80%) or hydroxylamine hydrochloride in the presence of fused sodium acetate in refluxing ethanol for 3 h, it afforded (Z)-3-amino-, or (Z)-3-hydroxy-, 2-substituted quinazolin-4(3H)-ones **2** and **3**, respectively. It was obvious that the reaction proceeded via hetero-ring-opening followed by cyclization in situ. The IR spectra of compounds **2** and **3** showed the carbonyl absorption frequencies of the six-membered lactam rings at 1688 and 1676 cm^{-1}, respectively, along with the absorption bands (CO, α,β-unsat. amide) at 1661 cm^{-1}(**2**) and 1656 cm^{-1}(**3**). In addition, ^1H NMR spectra of compound **2** revealed a broad singlet at δ 5.32 ppm (NH_2, 2H); however, compound **3** showed a singlet at δ 10.37 ppm (1H, OH). Both bands were exchangeable with D_2O.[30–34]

Prolonged heating of the former reaction mixture in n-butanol for 10 h and the latter one in pyridine for 16 h yielded (Z)-2-phenyl-4(3,4,5-trimethoxybenzylidene)-1H-[1,2,4]-triazino-[6,1-*b*]-, and [1,2,5]-oxdiazino-[3,2-*b*]-, quinazolin-10(4H)-ones **4** and **5**, respectively (Scheme 1). The IR spectra of compounds **4** and **5** lack the absorption frequencies of the open amide carbonyl groups; however, the carbonyl absorptions of cyclic lactam rings were exhibited at 1681 and 1702 cm^{-1}, respectively. ^1H NMR spectrum of **4** displayed a singlet at δ 8.93 ppm (1H, NH, triazine ring, exchangeable with D_2O); however, a similar spectrum of compound **5** lacks the latter peak. Morever, the mass spectra of the former compound **4** showed the molecular ion peak at m/z 454 (17.66%), and the latter one **5** showed the base peak at m/z 455 (M^+, 100%).

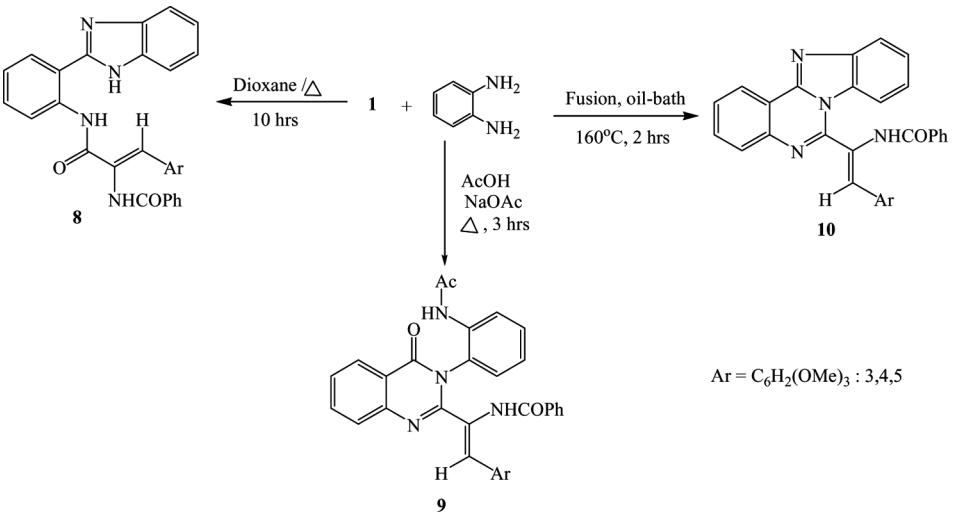
Treatment of compound **1** with cyanoacetic acid hydrazide in refluxing pyridine resulted in the formation of annelated pyrazolo-[1,5-*c*]quinazoline derivative (**6**) (Scheme 1). Furthermore, when compound **1** was reacted with semi- or thiosemicarbazide hydrochloride in the presence of anhydrous sodium acetate in the absence of solvents at 160–170 °C, it yielded the triazolo-[1,5-*c*]-quinazoline derivatives (**7a**) and (**7b**), respectively.[35,36] The IR spectrum of **6** displayed the carbonyl absorption



Scheme 1. Reactions of compound **1** with hydrazine hydrate, hydroxylamine hydrochloride, cyanoacetic acid hydrazide, and semi- and thiosemicarbazide at different reaction conditions.

bands at 1692 cm^{-1}(CO, pyrazolone ring) and at 1652 cm^{-1}(CO, open amide), along with the absorption at 2220 cm^{-1}(C≡N). Compound **7a** showed similar absorptions at 1698 cm^{-1} (pyraz. ring) and 1647 cm^{-1}(open amide). In turn, **7b** lacks the carbonyl absorption (pyraz. ring); however, it showed the frequencies 1672 cm^{-1} (CO, open amide) and 1286 cm^{-1}(C=S). The EI fragmentation showed the molecular ion peaks of compound **6** at m/z 416 ($M^{+\cdot}$ – PhCO, 23.94%), **7a** at m/z 497 ($M^{+\cdot}$, 12.28%), and **7b** at m/z 513 ($M^{+\cdot}$, 23.26%).

With the aim of expanding the synthetic potential of the 4(3H)-benzoxazinone **1**, it was allowed to react with o-phenylenediamine under different reaction conditions. Thus, when conducted with the latter reagent in boiling dioxane, it afforded Z-N-[1-(2-(1H-benzoimidazol-2-yl)phenylamino)-1-oxo-3-(3,4,5-trimethoxyphenyl)-prop-2-en-yl]benzamide (**8**). The reaction took place via hetero-ring-opening followed by 1,5-exo-trig cyclization in situ. The IR spectrum showed the disappearance of the carbonyl absorption band of δ-lactone, whereas two absorptions were displayed at 1671 (br.) and 1662 cm^{-1}(two CO, open amides). The mass spectrum showed m/z 548 (17.22%; $M^{+\cdot}$). However, when the reaction was carried out in boiling acetic acid, it yielded Z-3-(2′-acetamidophenyl)-2-[1′-benzamido-2′-(3,4,5-trimethoxyphenyl)vinyl]quinazolin-4(3H)-one (**9**). The IR spectrum revealed three

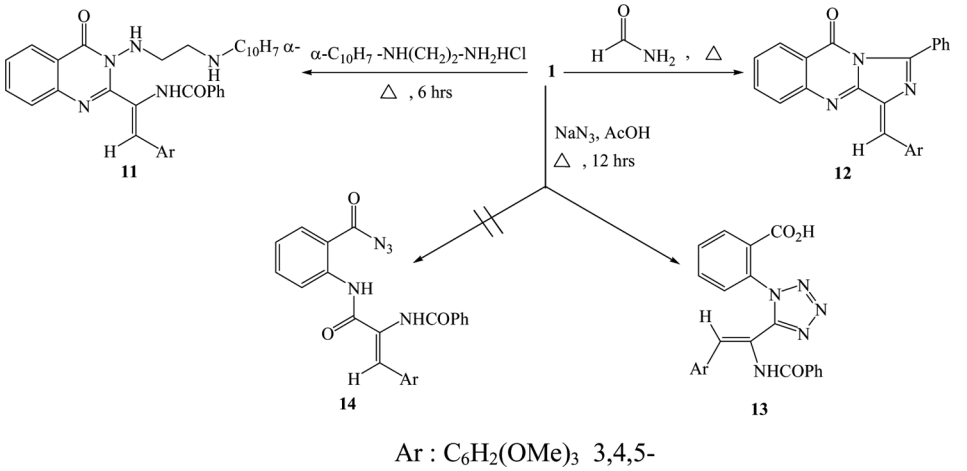


Scheme 2. Reactions of **1** with o-phenylenediamine under different reaction conditions. Formation of compounds **8–10**.

carbonyl absorptions at 1702 (CO, quinazolone ring), 1673, and 1661 cm^{-1} (2 CO, open amides). Upon treatment of **1** with the same diamine reagent in the absence of solvents at 160 °C in an oil bath, Z-3H,4H-2-[1′-benzamido-2′-(3,4,5-trimethoxyphenyl)vinyl]benzimidazo-[1,2-*c*]-quinazoline (**10**) was formed (Scheme 2). The recorded peak in the mass spectrum of compound **10** at m/z 530 (14.75%) indicates the removal of two molecules of water under the reaction conditions via ring opening followed by double cyclizations in situ. The structure of compound **10** was confirmed from the microanalytical and spectroscopic data. Thus, the IR spectrum was devoid of carbonyl absorption bands for the quinazolone ring and retained strong absorption bands at 1665 (amide CO) and1632 cm^{-1} (2C=N) (see the Experimental section).

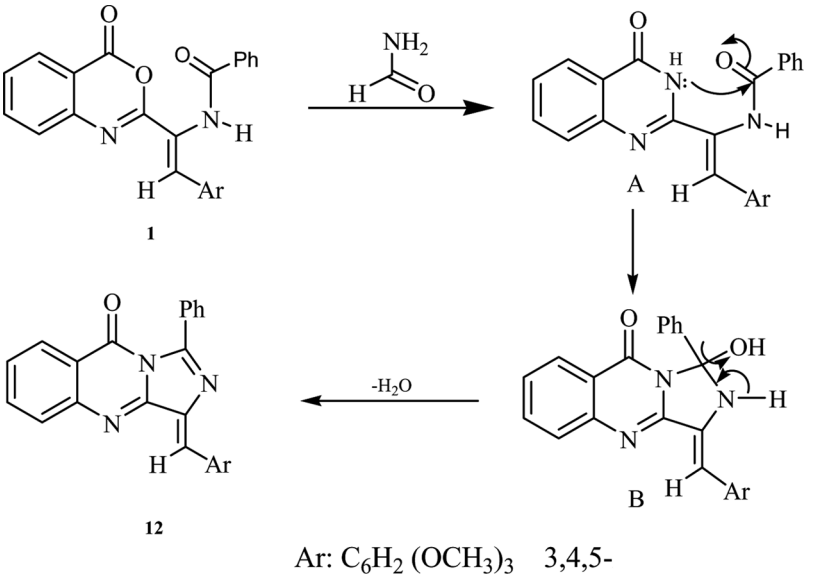
Interaction of the benzoxazinone **1** with N-(1-naphthyl)ethylenediamine hydrochloride in refluxing pyridine for 6 h yielded 3-(N-1-naphthylamino)ethyl-2-substituted quinazolin-4(3H)-one **11** (Scheme 3). The IR spectrum of the latter compound displayed two broad absorptions at 3290 and 3178 cm^{-1} (3NH) and two absorption bands at 1683 (CO, quinazolone) and 1667 cm^{-1}(CO, open amide); in addition, the mass spectrum showed a fragmentation peak at m/z 473 ($M^{+\cdot}$ – C_2H_2, HN-$C_{10}H_7$) (see the Experimental section).

Refluxing the benzoxazinone **1** with excess formamide in an oil bath at 170 °C for 10 h afforded Z-3-(3′,4′,5′-trimethoxybenzylidene)-1-phenylimidazo-[5,1-*b*]-quinazolin-9(3H)-one, **12**. The reaction presumably involved first the decomposition of formamide under the influence of the employed temperature to produce ammonia, which reacts with **1** to give the quinazolinone intermediate A. Afterwards, the reaction went throuough internal nucleophilic addition followed by a loss of a water molecule in situ from the intermediate B to yield the thermodynamically more stable product **12**.[37,38] The IR spectrum of **12** lacks the open amide carbonyl absorption band; however, its quinazolone carbonyl absorption was displayed at 1684 cm^{-1}.

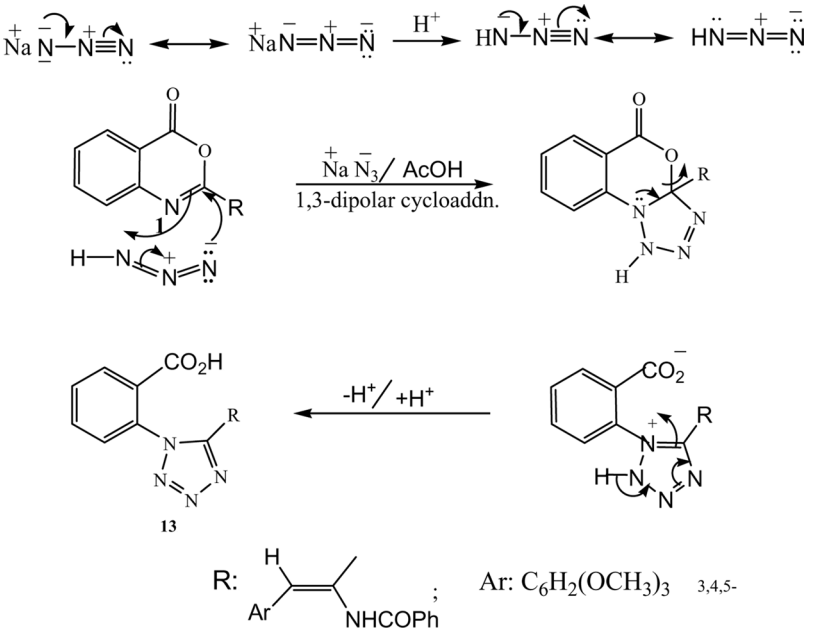


Scheme 3. Reactions of **1** with N-(1-naphthyl)ethylenediamine hydrochloride, formamide, and sodium azide. Formation of compounds **11–13**.

The EI fragmentation of compound **12** showed m/z 530 (22.3%), corresponding to the molecular ion peak. Furthermore, ^{1}H NMR and ^{13}C NMR were consistent with the proposed structure. This reaction is considered as a successful attempt to annulate a fused quinazolinone. It takes place via hetero-ring opening followed by cyclization to give the quinazolinone derivative, which was further cyclized via a condensation reaction to create the imidazole nucleus.[39]



Scheme 4. Mechanistic pathway for the formation of compound **12**.



Scheme 5. Mechanistic pathway for the formation of compound **13**.

Recently, treatment of the oxazinone **1** with sodium azide in refluxing AcOH for 12 h afforded Z-2-[5-(1′-benzamido-2′-(3,4,5-trimethoxyphenyl)vinyl)-1H-tetrazolo-1-yl]-benzoic acid **13**. Adequate evidence for the structure **13** is forthcoming from the study of its spectral data. The IR (υ cm^{-1}) spectrum exhibited the absorption bands at 3319 (br. NH, OH), 1708 (CO, acid), 1671 (CO, amide). ^{1}H NMR spectrum revealed a singlet at δ 11.07 ppm (1H, COOH). In addition, the EI fragmentation showed the molecular ion peak at m/z 501 (8.93%). Nevertheless, no evidence was detected for the formation of the aroyl azide **14**.[40–42]

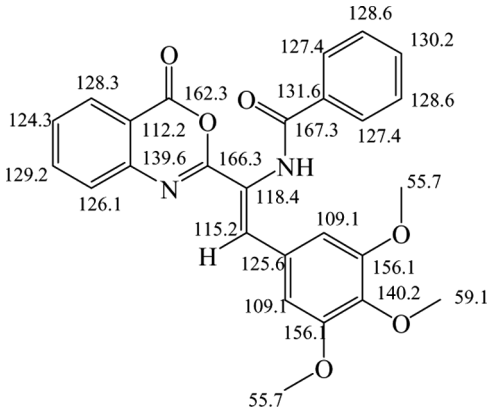
Plausible mechanisms for the formation of compounds **12** and **13** are outlined in Schemes **4** and **5**, respectively.

EXPERIMENTAL

All melting points were taken on a Gallen Kamp electric melting-point apparatus. IR spectra were recorded in KBr and were determined on a Perkin-Elmer 2000 Fourier transform (FT)–IR system. NMR spectra were determined on Varian Gemini instruments (200 MHz for ^{1}H NMR and 50 MHz for ^{13}C NMR) in $CDCl_3$ or dimethylsulfoxide (DMSO-d_6) as solvent and tetramethylsilane (TMS) as internal standard; chemical shifts are reported in δ (ppm). Mass spectra were measured on VG Autospec QMS 30 and MS 9 (AEI) spectrometers with EI 70 eV. Elemental analyses were measured using a Perkin-Elmer 2400 CHN Elemental Analyzer. The monitoring of the progress of all reactions and the homogeneity of the synthesized compounds were carried out by thin-layer chromatography (TLC).

Z-2-[1′-Benzamido-2′-(3,4,5-trimethoxyphenyl)]vinyl-3,1-benzoxazin-4(3H)-one (1)

A mixture of 2-aminobenzoic acid (1.4 g, 0.01 mol) and (3,4,5-trimethoxybenzylidene)-5(4H)-oxazolone (3.4 g, 0.01 mol) in pyridine (30 ml) was heated under reflux for 6 h (TLC). After cooling, the reaction mixture was poured into ice-cold hydrochloric acid. The solid separated was filtered off, stirred for 30 min with 50 ml sodium bicarbonate solution (10%), filtered, washed with water (4×50 ml), and recrystallized from light petroleum ether (bp 100–120 °C) to give **1** as yellow crystals (3.19 g, yield 69.6%), mp 96–98 °C. IR (ν cm^{-1}): 3276 (NH), 1760 ($CO_{oxaz.}$), 1676 (CO_{amide}). ^{1}H NMR ($CDCl_3$, δ ppm) 9.3 (s, 1H, NH, exchangeable with D_2O), 8.26–7.74 (m, 9$H_{arom.}$), 6.73 (s, 2H_{arom}), 6.14 (s, 1H, olefinic proton), 3.85 (s, 6H, 2OMe), 3.82 (s, 3H, OMe). Ms m/z (%): 458 (30.74), 353 (60.27), 181 (22.34), 147 (32.92), 105 (100.0), 77 (67.86). Anal. calcd. $C_{26}H_{22}N_2O_6$ (458.44): C, 68.11; H, 4.83; N, 6.11. Found: C, 68.31; H, 5.09; N, 5.98. ^{13}C NMR ($CDCl_3$) is shown here:



Synthesis of Z-2-[1′-Benzamido-2′-(3,4,5-trimethoxyphenyl)]-vinyl-3-amino-quinazolin-4 (3H)-one (2)

A solution of the benzoxazinone **1** (1.84 g, 0.004 mol) and hydrazine hydrate (80%) (1.28 g, 0.025 mol) in ethanol (30 ml) was refluxed for 3 h (TLC). Evaporation of the solvent in vacuo left an oily product, which triturated with methanol to give a solid product recrystallized from dioxane as yellow crystals; mp 207–209 °C (1.7 g, yield, 82.5%). IR (ν cm^{-1}): 3416, 3321, 3279 (NH_2), 1688 ($CO_{quinaz.}$), 1661 (CO_{amide}). ^{1}H NMR (DMSO-d_6, δ ppm) 8.8 (s, 1H, NH, exchangeable with D_2O), 8.42–7.26 (m, 9$H_{arom.}$), 6.96 (s, 2H_{arom}), 6.17 (s, 1H, CH=), 5.32 (br.s, 2H, NH_2, exchangeable with D_2O), 3.92 (s, 6H, 2OMe), 3.81 (s, 3H, OMe). Ms m/z (%): 472 (9.35), 367 (15.0), 181 (23.79), 161 (72.32), 105 (100.0), 77 (66.36). Anal. calcd. for $C_{26}H_{24}N_4O_5$ (472.49): C, 66.09; H, 5.13; N, 11.86. Found: C, 66.26; H, 4.96; N, 11.57.

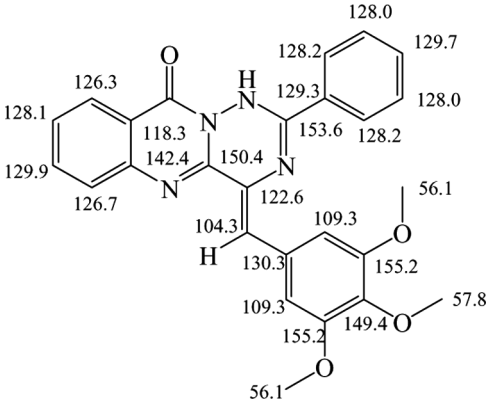
Z-2-[1-Benzamido-2-(3,4,5-trimethoxyphenyl)vinyl]-3-hydroxyquinazolin-4(3H)-one (3)

A mixture of **1** (1.84 g, 0.004 mol), hydroxylamine hydrochloride (1.04 g, 0.015 mol), and anhydrous sodium acetate (1.5 g) in absolute ethanol (50 ml) was

refluxed for 6 h. The reaction mixture was poured onto water, stirred for 30 min, and then filtered off. The deposited product was dried and recrystallized from ethanol to give **3** as pale yellow crystals (1.2 g, yield, 60.6%); mp 236–238 °C. IR (ν cm^{-1}): centered at 3432 (NH, OH), 1676 (CO), 1656 (CO_{amide}). ^1H NMR (DMSO-d_6, δ ppm) 10.37 (s, 1H, OH, exchangeable with D_2O), 8.79 (s, 1H, NH, exchangeable with D_2O), 8.3–7.4 (m, $9H_{arom.}$), 7.27 (s, $2H_{arom}$), 6.22 (s, 1H, CH=), 3.93 (s, 6H, 2OMe), 3.82 (s, 3H, OMe). Ms *m/z* (%): 473 (11.36), 456 (17.88), 351 (30.38), 181 (8.31), 167 (17.62), 105 (100.0). Anal. calcd. for $C_{26}H_{23}N_3O_6$ (473.46): C, 65.95; H, 4.91; N, 8.88. Found: C, 66.13; H, 4.62; N, 8.60.

(Z)-2-Phenyl-4-(3,4,5-trimethoxybenzylidene)-1H-[1,2,4]-triazino-[6,1-*b*]-quinazolin-10(4H)-one (4)

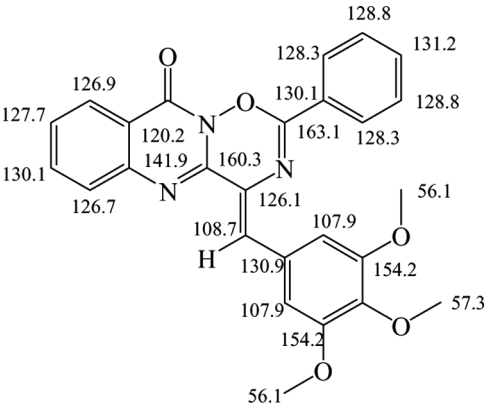
A solution of the benzoxazinone **1** (1.84 g, 0.004 mol) and hydrazine hydrate (80%) (1.0 g, 0.02 mol) in n-butanol (30 ml) was heated under reflux for 10 h. Evaporation of the solvent in vacuo left a solid product, which when treated with water. A pale-yellow solid was deposited, filtered off, dried, and recrystallized from dimethylformamide (DMF) to give the quinazolin-10(4H)-one derivative **3** as yellowish-white crystals; mp 183–185 °C (1.2 g, yield, 60.6%). IR (ν cm^{-1}): 3310 (NH), 1681 (CO), 1632 (C=N). ^1H NMR (DMSO-d_6, δ ppm) 8.93 (s, 1H, NH, exchangeable with D_2O), 8.11–7.24 (m, $9H_{arom.}$), 6.81 (s, $2H_{arom}$), 6.34 (s, 1H, CH =), 3.92 (s, 6H, 2OMe), 3.81 (s, 3H, OMe). Ms *m/z* (%): 454 (17.66), 377 (24.95), 276 (40.36), 181 (38.28), 91 (27.64), 77 (56.68). Anal. calcd. for $C_{26}H_{22}N_4O_4$ (454.48): C, 68.71; H, 4.89; N, 12.33. Found: C, 68.82; H, 4.63; N, 12.08. ^{13}C NMR (DMSO-d_6) is shown as follows:



(Z)-2-Phenyl-4-(3,4,5-trimethoxybenzylidene)-1H-[1,2,5]-oxadiazino[3,2-*b*]quinazolin-10(4H)-one (5)

A solution of **1** (1.84 g, 0.004 mol) and hydroxylamine hydrochloride (1.04 g, 0.015 mol) in pyridine (30 ml) was refluxed for 16 h. The reaction mixture was cooled and poured onto a crushed ice/HCl mixture. The solid that separated was filtered off, washed with water, dried, and then recrystallized from dioxane to give **5** as yellowish-white crystals; mp 177–179 °C (0.8 g, yield 40%). IR (νc m^{-1}): 1702

(CO), 1642 (C=N). ^{1}H NMR (DMSO-d_6, δ ppm) 8.61–7.25 (m, 9$H_{arom.}$), 6.93 (s, 2H_{arom}), 6.14 (s, 1H, CH=), 3.92 (s, 6H, 2OMe), 3.84 (s, 3H, OMe). Ms m/z (%): 455 (100.0), 378 (12.68), 276 (70.29), 181 (18.24), 91 (24.67), 65 (33.71). Anal. calcd. for $C_{26}H_{21}N_3O_5$(455.47): C, 68.56; H, 4.66; N, 9.23. Found: C, 68.39; H, 4.41; N, 9.02. ^{13}C NMR (DMSO-d_6) is shown as follows:



Z-2H,3H-5-[1′-Benzamido-2′-(3,4,5-trimethoxyphenyl)]vinyl-2-oxo-pyrazolo-[1,5-*c*]-quinazolin-1-carbonitrile (6)

Cyanoacetic acid hydrazide was added to a solution of **1** (4.58 g, 0.01 mol) in pyridine (15 ml) and the solution mixture was stirred for 8 h (TLC). Evaporation of solvent in vacuo left a semisolid product, which was neutralized using ice-cold 0.1 N HCl (25 ml). The deposit was filtered off, dried, and recrystallized from dioxane to give **6** as pale-yellow crystals; mp 256–258 °C (3.6 g, yield 69.1%). IR (ν cm^{-1}): 3312 (NH), 2220 (C≡N), 1692 (CO), 1652 (CO). ^{1}H NMR (DMSO-d_6, δ ppm) 9.1 (s, 1H, NH, exchangeable with D_2O), 8.76 (s, 1H, NH, exchangeable with D_2O), 8.40–7.32 (m, 9$H_{arom.}$), 7.03 (s, 2H_{arom}), 6.18 (s, 1H, CH=), 3.74 (s, 6H, 2OMe), 2.85 (s, 3H, OMe). Ms m/z (%): 416 (M-PhCO, 23.94), 209 (34.16), 181 (17.25), 105 (100.0), 91 (8.46). Anal. calcd. for $C_{29}H_{23}N_5O_5$(521.53): C, 66.78; H, 4.45; N, 13.43. Found: C, 66.92; H, 4.58; N, 13.08.

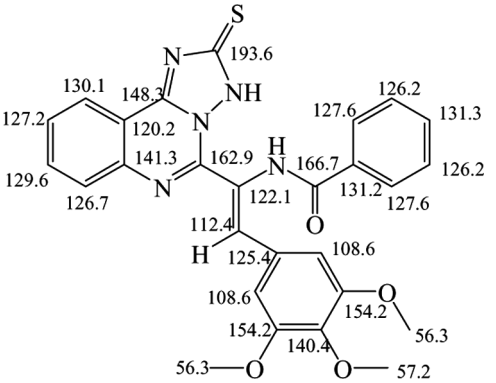
Z-2H,3H-5-[1′-Benzamido-2′-(3,4,5-trimethoxyphenyl)vinyl]-2-oxo-[1,2,4]-triazolo-[1,5-*c*]-quinazoline (7a) and 2-thioxo-[1,2,4]-triazolo-[1,5-*c*]-quinazoline (7b)

General procedure. A mixture of benzoxazinone **1** (1.38 g, 0.003 mol), semi- or thiosemicarbazide hydrochloride (0.005 mol), and anhydrous sodium acetate (0.8 g, 0.01 mol) was heated on an oil bath at 160–170 °C for 1 h. The cooled mixture was poured onto water (50 ml) and stirred for 15 min. The solid product was collected by filteration, dried, and recrystallized from the proper solvent to give **7a** and **7b**.

Compound 7a. Recrystallized from benzene as light brown crystals; mp 312–314 °C (0.7 g, yield 46.08%). IR (ν cm^{-1}): 3317, 3212 (NH), 1698 (CO), 1647 (CO). ^{1}H NMR ($CDCl_3$, δ ppm) 8.7 (br.s, 2H, exchangeable with D_2O), 8.23–7.1

(m, $9H_{arom.}$), 6.81 (s, $2H_{arom}$), 6.27 (s, 1H, CH=), 3.94 (s, 6H, 2OMe), 3.84 (s, 3H, OMe). Ms m/z (%): 497 ($M^{+\cdot}$, 12.28), 312 (18.74), 186 (37.62), 181 (22.35), 105 (100.0), 91 (7.86), 77 (73.45). Anal. calcd. for $C_{27}H_{23}N_5O_5$(497.51): C, 65.18; H, 4.67; N, 14.08. Found: C, 65.51; H, 4.38; N, 13.97.

Compound 7b. Recrystallized from dioxane as brownish-red crystals; mp > 300 °C (0.9 g, yield 57.3%). IR (ν cm^{-1}): 3304, 3250 (NH), 1672 (CO), 1286 (C=S). ^{1}H NMR (DMSO-d_6, δ ppm) 8.84 (br.s, 2H, NH, exchangeable with D_2O), 8.3–7.0 (m, $9H_{arom.}$), 6.93 (s, $2H_{arom}$), 6.48 (s, 1H, CH=), 3.92 (s, 6H, 2OMe), 3.82 (s, 3H, OMe). Ms m/z (%): 513 ($M^{+\cdot}$, 23.26), 105 (100.0), 77 (40.43). Anal. calcd. for $C_{27}H_{23}N_5O_4S$ (513.57): C, 63.14; H, 4.52; N, 13.64; S, 6.24. Found: C, 63.37; H, 4.42; N, 13.28; S, 6.36. ^{13}C NMR (DMSO-d_6) is shown as follows:



Z-N-[1-(2-(1H-Benzo[*d*]imidazol-2-yl)phenylamino)-1-oxo-3-(3,4,5-trimethoxyphenyl)prop-2-en-yl]-benzamide (8)

Equimolar mixture of **1** (1.84 g, 0.004 mol) and o-phenylenediamine (0.54 g, 0.005 mol) in dioxane (30 ml) was heated under reflux for 10 h. The excess solvent was removed in vacuo. The solid was filtered off, dried, and recrystallized from ethanol to give the benzimidazole derivative **8** as pale-yellow crystals; mp 280–283 °C (1.2 g, yield 50.2%). IR (ν cm^{-1}): 3342, 3280, 3162 (NH), 1671 (CO), 1662 (CO). ^{1}H NMR (DMSO-d_6, δ ppm) 8.93 (br.s, 2H, NH, exchangeable with D_2O), 8.4 (s, 1H, NH, exchangeable with D_2O), 8.0–7 (m, $13H_{arom.}$), 6.94 (s, $2H_{arom}$), 6.06 (s, 1H, CH=), 3.92 (s, 6H, 2OMe), 3.85 (s, 3H, OMe). Ms m/z (%): 548 ($M^{+\cdot}$, 17.22), 236 (32.76), 188 (12.38), 105 (100.0), 77 (70.69). Anal. calcd. for $C_{32}H_{28}N_4O_5$(548.59): C, 70.06; H, 5.16; N, 10.21. Found: C, 70.24; H, 5.42; N, 10.07.

(Z)-3-(2′-Acetamidophenyl)-2-[1′-benzamido-2′-(3,4,5-trimethoxyphenyl)vinyl]quinazolin-4(3H)-one (9)

A mixture of compound **1** (1.84 g, 0.004 mol), o-phenylenediamine (0.5 g, 0.005 mol), and freshly fused sodium acetate (0.8 g, 0.01 mol) in glacial acetic acid (20 ml) was refluxed for 3 h. After cooling, the reaction mixture was poured onto water. The deposited was collected by filtration, dried, and recrystallized from toluene to give **9** as yellow crystals; mp > 300 °C (1.6 g, yield 62.2%). IR (ν cm^{-1}): 3317, 3241

(NH), 1702, 1673, 1661. ^{1}H NMR (DMSO-d_6, δ ppm) 9.04 (br.s, 2H, exchangeable with D_2O), 8.2–7.2 (m, 13$H_{arom.}$), 7.08 (s, 2H_{arom}), 6.54 (s, 1H, CH=), 3.85 (s, 9H, 2OMe), 2.35 (s, 3H, COMe). Ms *m/z* (%): 457 (11.44), 351 (27.67), 181 (18.82), 135 (39.68), 105 (100.0), 77 (32.41). Anal. calcd. for $C_{34}H_{30}N_4O_6$(590.63): C, 69.14; H, 5.13; N, 9.48. Found: C, 69.32; H, 5.37; N, 9.18.

(Z)-3H,4H-2-[1′-Benzamido-2′-(3,4,5-trimethoxyphenyl)-vinyl]benzimidazo-[1,2-*c*]-quinazoline (10)

A mixture of the benzoxazinone **1** (1.84 g, 0.004 mol) and o-phenylenediamine (0.5 g, 0.005 mol) was stirred in an oil bath at 150 °C for 2 h. After cooling, the reaction mixture was poured onto sodium bicarbonate solution 10% (15 ml) and stirred for 10 min. The residue was collected by filtration, washed several times with water, dried, and recrystallized from methanol to give **10** as yellow crystals; mp 166–168 °C (0.86 g, yield 37.2%). IR (ν cm^{-1}): 3215 (NH), 1665 (CO), 1632 (C=N). ^{1}H NMR (DMSO-d_6, δ ppm) 8.7 (s, 1H, NH, exchangeable with D_2O), 8.4–7.3 (m, 13$H_{arom.}$), 7.07 (s, 1H, CH=), 3.85 (s, 9H, 2OMe). Ms *m/z* (%): 530 (14.75), 313 (46.28), 171 (100.0), 105 (97.36), 77 (48.29). Anal. calcd. for $C_{32}H_{26}N_4O_4$(530.58): C, 72.44; H, 4.95; N, 10.56. Found: C, 72.75; H, 5.22; N, 10.46.

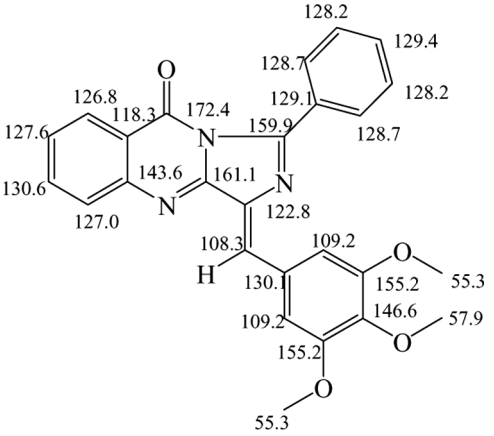
3-(N-1-Naphthyl)aminoethyl-2-[1′-benzamido-2′-(3,4,5-trimethoxyphenyl)vinyl] quinazolin-4(3H)-one (11)

N-(1-Naphthyl)ethan-1,2-diamine hydrochloride (1.5 g, 0.006 mol) was added to a solution of **1** (1.84 g, 0.004 mol) in dry pyridine (30 ml) with stirring for 15 min. The whole mixture was heated under reflux for 6 h. After cooling, the reaction mixture was poured onto crushed ice/HCl. The solid was collected by filtration, dried, and recrystallized from dioxane as light-brown crystals; mp 273–275 °C (1.4 g, yield 51.8%). IR (ν cm^{-1}): 3290, 3178 (NH), 1683, 1667 (CO). ^{1}H NMR (DMSO-d_6, δ ppm) 8.9 (s, 1H, NH, exchangeable with D_2O), 8.6–7.3 (m, 16$H_{arom.}$), 6.86 (s, 2H_{arom}), 6.15 (s, 1H, CH=), 3.93 (s, 9H, 2OMe), 3.35 (t, 4H). Ms *m/z* (%): 473 [($M^{+\cdot}$ – C_2H_2, HN-$C_{10}H_7$), 29.36], 312 (22.37), 105 (100.0), 77 (62.40). Anal. calcd. for $C_{38}H_{35}N_4O_5$(641.73): C, 71.12; H, 5.51; N, 10.92. Found: C, 71.40; H, 5.28; N, 11.08.

(Z)-1-Phenyl-3-(3′,4′,5′-trimethoxybenzylidene)imidazo-[5,1-*b*]-quinazolin-9(3H)-one (12)

A mixture of compound **1** (1.84 g, 0.004 mol) and formamide (10 ml) was stirred under reflux for 10 h (TLC). Evaporation of solvent in vacuo left a semisolid product, which was stirred with water for 10 min. The solid deposited was filtered off, dried, and recrystallized from methanol to give the imidazoquinazolinone derivative **12** as yellowish-white crystals; mp 243–245 °C (1.1 g, yield 47.8%). IR (ν cm^{-1}): 1684 ($CO_{quinaz.}$), 1632 (C=N). ^{1}H NMR ($CDCl_3$, δ ppm) 8.37–7.62 (m, 9$H_{arom.}$), 7.28 (s, 2H_{arom}), 6.19 (s, 1H, CH=), 3.87 (s, 9H, 2OMe). Ms *m/z* (%): 530 (22.32), 352 (17.73), 181 (42.23), 91 (100.0), 77 (70.92), 65 (30.95). Anal. calcd. for

$C_{26}H_{21}N_3O_4$(439.46): C, 71.06; H, 4.83; N, 9.56. Found: C, 70.81; H, 5.12; N, 9.44. ^{13}C NMR ($CDCl_3$) is shown as follows:



(Z)-2-[5-(1′-benzamido-2′-(3,4,5-trimethoxyphenyl)vinyl)-1H-tetrazol-1-yl]benzoic Acid (13)

Sodium azide (0.65 g, 0.01 mol) was added to a solution of compound **1** (1.84 g, 0.004 mol) in acetic acid (20 ml), and the mixture was heated under reflux for 12 h (TLC). The reaction mixture after concentration was poured onto crushed ice. The solid separated was filtered off, dried, and recrystallized from dioxane to give the tetrazole derivative **13** as colorless crystals; mp 180–182 °C (0.9 g, yield 42.8%). IR (ν cm^{-1}): br. centered at 3319 (NH, OH), 1708 (CO_{acid}), 1671 (CO_{amide}). ^1H NMR ($CDCl_3$, δ ppm) 11.07 (s, 1H, COOH, exchangeable with D_2O), 8.86 (s, 1H, NH, exchangeable with D_2O), 8.63–7.14 (m, $9H_{arom.}$), 7.09 (s, $2H_{arom}$), 6.24 (s, 1H, CH=), 3.94 (s, 9H, 2OMe). Ms m/z (%): 501 [$M^{+\cdot}$; 8.93], 457 (13.95), 381 (22.11), 181 (30.37), 105 (100.0), 91 (17.39), 77 (62.65). Anal. calcd. for $C_{26}H_{23}N_5O_6$(501.48): C, 62.27; H, 4.63; N, 13.96. Found: C, 62.36; H, 4.36; N, 13.71.

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