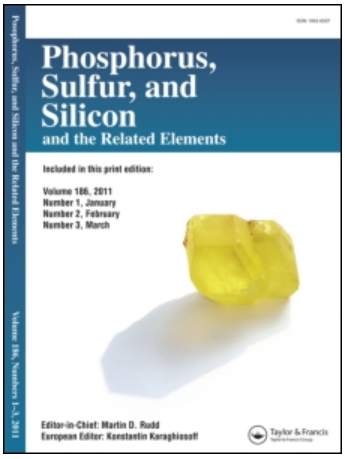


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# Synthesis of New Thiadiazoles, 1,2,4-Triazolo[3,4-*b*]-1,3,4-thiadiazoles, and 1,2,4-Triazolo[2,3-*c*]quinazoline Derivatives from 3,1-Benzoxazin(4*H*)-one Derivative

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# Synthesis of New Thiadiazoles, 1,2,4-Triazolo[3,4-*b*]-1,3,4-thiadiazoles, and 1,2,4-Triazolo[2,3-*c*]quinazoline Derivatives from 3,1-Benzoxazin(4*H*)-one Derivative

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*3,1-benzoxazin-4H-one derivative was reacted with Grignard reagents, primary and secondary amines, glycine, hydrazine hydrate, azines, and Schiff's base. The acid hydrazide derivative was the key starting material for the synthesis of triazole, triazolo[3,4-b]thiadiazole, thiadiazole, and triazolo[2,3-c]quinazoline.*

**Keywords** Azines; benzoxazinone; quinazoline; Schiff's bases; thiadiazoles; triazole

## INTRODUCTION

A literature survey revealed that benzoxazinones and their derivatives possess a broad spectrum of therapeutic activity.[1–5] With respect to this and also as a part of our program dealing with the synthesis of polyfused heterocyclic systems,[6–11] benzoxazinone **1** was prepared[12] and used as the key intermediate for further chemical transformation.

## RESULTS AND DISCUSION

2-substituted-3,1-benzoxazin-4(H)-one derivatives reacted with aryl magnesium halide to give triaryl carbinol derivatives, while benzyl magnesium chloride afforded the deoxybenzoin derivative and not the corresponding carbinol.[13] Herein, title compound **1** was refluxed with excess phenyl-, p-tolyl-, p-anisyl magnesium bromide, and/or benzyl magnesium chloride, in dry diethylether/benzene mixture, producing triaryl carbinol derivatives **2a**–**d** representing only one mode of addition at C=O in all cases (Scheme 1).

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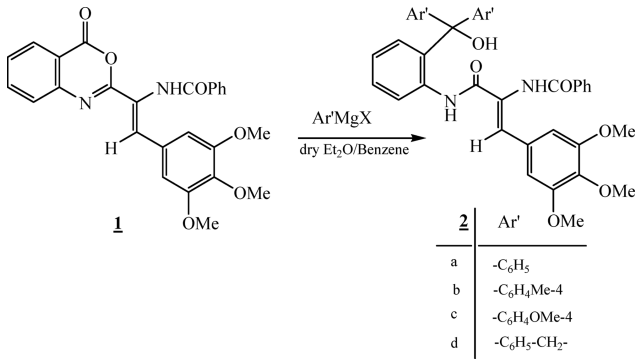



**SCHEME 1**

The structure of **2** was supported by analytical data, IR, and $^1$H NMR spectra, which indicate that two moles of Grignard reagent were involved in the reaction (Table I).

Treatment of **1** with primary and secondary amines such as cyclohexylamine, benzylamine, piperidine, morpholine, and/or

**TABLE I Characterization Data for Compounds 2a–d**

| | IR (KBr) cm$^{-1}$ | | | | |
|---|---|---|---|---|---|
| | $\nu_{NH,OH}$ | $\nu_{C-H}$ | $\nu_{CO}$ | $^1$H-NMR ($CDCl_3$)$\delta$ ppm | MS (% Abundance) |
| **2a** | 3504<br>3330<br>3125 | 2934<br>2850 | 1686<br>1680 | 3.67 (s, 3H, $OCH_3$), 3.9 (s, 6H, $2OCH_3$), 4.1 (s, 1H, OH), 6.5 (s, 1H, CH=), 7.9–6.8 (m, 21 H, arom.), 8.6, 8.2 (2s, 2H, NH) | $M^{\pm}$ 614 (76), [M-$H_2O$], 596 (40), [M-OH] 597 (41.2), Ph-C$\equiv O^+$, 105 (100), $Ph^{\oplus}$ 77(57.2) |
| **2b** | 3560<br>3321<br>3117 | 2941<br>863 | 1682<br>1671 | 1.3 (br.s, 6H, $2CH_3$), 3.7, 3.9 (two s, 9H, 3 $OCH_3$), 4.3 (s, 1H, OH), 6.4 (s, 1H, CH=), 6.8–7.8 (m, 19H, Ar-H), 8.3, 8.7 (2s, 2H, NH) | 642 (0.7), 624 (43.6), 623 (12), 105 (100), 91 (26.6), 77 (56.3), 65 (41.2) |
| **2c** | 3548<br>3320<br>3118 | 2941<br>2872 | 1678<br>1667 | 3.7–3.9 (two s, 15 H, 5 $OCH_3$), 4.2 (s, 1H, OH), 6.6 (s, 1H, CH=), 6.6–7.8 (m, 19H, arom.), 8.4, 8.5 (1s, 2H, NH) | $M^{\pm}$674 (12), 657 (M-OH) (13.6), 656 [M-$H_2O$ (9.7)], 624 (26.6), 105 (100), 77 (47.7) |
| **2d** | 3556<br>3311<br>3120 | 2920<br>2844 | 1684<br>1669 | 3.7–3.9 (two s, 9H, 3 $OCH_3$), 4.1 (s, 1H, OH), 5.1 (two s, 4H, 2 $CH_2Ph$), 6.0 (s, 1H, CH=), 6.7–7.9 (m, 21H, Ar-H), 8.4, 8.6 (2s, 2H, NH) | 642 (16), 624 (0.3), 339 (20.9), 91 (100), 105 (66.4), 77 (40.6), 65 (19.6) |

**TABLE II Spectral Data of Compounds 3a–e**

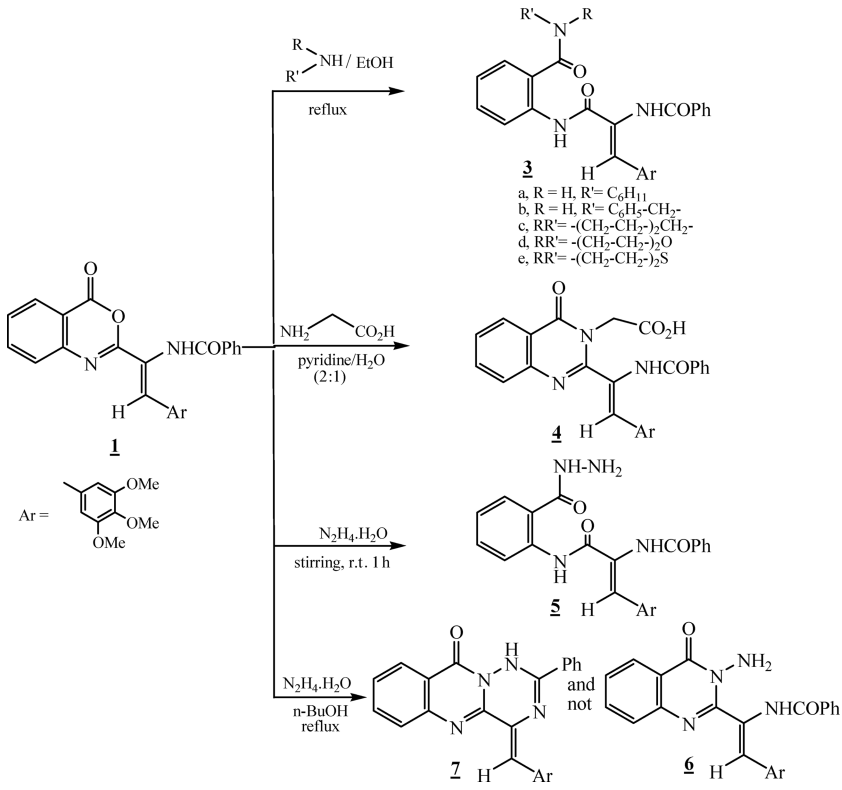
| | IR (KBr) $cm^{-1}$ | | $^1$H-NMR ($CDCl_3$ or DMSO-$d_6$) ($\delta$ ppm) | MS (Abundance %) |
|---|---|---|---|---|
| | $\nu_{NH}$ | $\nu_{CO}$ | | |
| **3a** | 3312<br>3180 | 1686, 1672,<br>1666 | 1.3–2 (br.s, 11H, $C_6H_{11}$), 3.65–3.9 (two s, 9H, 3 $OCH_3$), 6.6 (s, 1H, CH=), 7.1–7.6 (m, 11H, arom.H's), 7.7–8.9 (two s, 3H, NH) | 557 (16.1), 459 (45.1), 105 (100), 77 (66.7) |
| **3b** | 3360<br>3204 | 1682, 1676<br>1669 | 3.75–3.9 (two s, 9H), 5.2 (br. s, 2H), 5.8 (s, 1H), 7.1–7.8 (m, 16H), 8.0 (br. s, 2H), 9.2 (br. s, 1H) | 565 (20.7), 459 (16.3), 458 (21.3), 105 (100), 77 (12.7) |
| **3c** | 3356<br>3200 | 1689, 1680<br>1670 | 3.75–3.9 (s, 9H), 6.0 (s, 1H), 7–8.1 (m, 12H), 8.9 (br. s, 2H), 10.2 (s, 1H) | 459 (7.8), 397 (18.2), 339 (40.1), 105 (100), 85 (90.2), 77 (42.6) |
| **3d** | 3300<br>3180 | 1684, 1678<br>1668 | 1.1–1.3 (br.s, 8H), 3.6–3.9 (br. s, 9H), 6.1 (s, 1H), 7–8.4 (m, 11H), 8.8 (s, 1H), 9.8 (s, 1H) | 545 (6.8), 454 (17.3), 339 (28.2), 207 (20.1), 105 (100), 87 (30.4), 77 (38.6) |
| **3e** | 3435<br>3318 | 1686, 1676<br>1670 | 1.3 (br.s, 4H), 2.8 (br.s, 4H), 3.45 (s, 6H), 3.8 (s, 3H), 6.1 (s, 1H), 7.2–7.8 (m, 11H), 8.4–8.5 (two s, 2H) | 561 (40.3), 458 (6), 250 (18.1), 193 (60.1), 119 (80), 105 (100), 103 (40.9), 77 (62.8) |



thiomorpholine in refluxing ethanol yielded, in all cases, the cinnamoyl anthranilamide derivatives **3a**–**e**, respectively. The structure of **3** was substantiated from the correct elemental analysis as well as spectroscopic data (Table II).

Quinazolines have been found to be CNS depressants anticonvulsants,[14] hypnotics, and muscle relaxants[15] and to possess a monoamine oxidase inhibitor activity.[16] Also, some aminoacid derivatives were reported to be used in treating high blood pressure.[17] This promoted the authors to synthesize some new molecules containing quinazoline nucleus and aminoacid moiety, hopping that they may show biological activity. Thus, reaction of **1** with glycine in a refluxing pyridine-water mixture (2:1) gave compound **4**. Stirring **1** with hydrazine hydrate at r.t. (1:1), in absolute ethanol, afforded the acid hydrazide derivative **5** whose structure was substantiated from IR and mass spectra and correct elemental analysis.

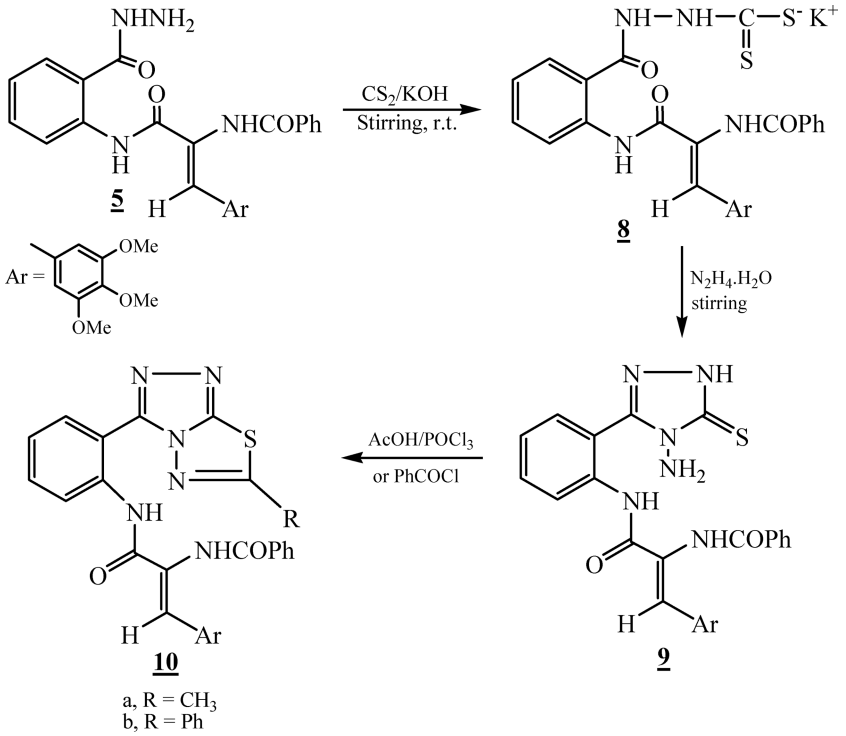
On the other hand, reaction of **1** with hydrazine hydrate in boiling n-butanol afforded a product with the molecular formula $C_{26}H_{22}N_4O_4$ [$M^+ = 454$ (27.3%)] as the sole product (one spot in TLC). All the data indicated that the product was trazine **7** and not the expected aminoquinazolinone **6** (Scheme 2).




**SCHEME 2**

The authors extended their investigation by using compound **5** as a starting material for the synthesis of some heterocyclic compounds.[18] Thus, the acid hydrazide **5** was stirred at r.t. with carbon disulfide in the presence of potassium hydroxide to give the corresponding potassium dithiocarbazate derivative **8,** which readily cyclized with hydrazine hydrate to afford the triazole-5-thione **9**. The reaction of **9** with acetic acid in the presence of phosphorous oxychloride and/or benzoyl chloride yielded the corresponding 1,3,4-thiadiazole derivatives **10a**,**b** (Scheme 3).

On the other hand, treatment of **5** with carbon disulphide in the presence of potassium hydroxide resulted in the formation of a product with the molecular formula $C_{27}H_{24}N_4O_5S_2$, which was identified, by $^1H$ NMR and mass spectra, as 1,3,4-thiadiazole **11**. Reacting **5** with phenyl isothiocyanate, in boiling THF, furnished 1,2,4-triazole **12**, which was obtained in a good yield. Compound **5** was fused in an oil bath at 170°C with ammonium thiocyanate producing the quinazoline derivative **13**

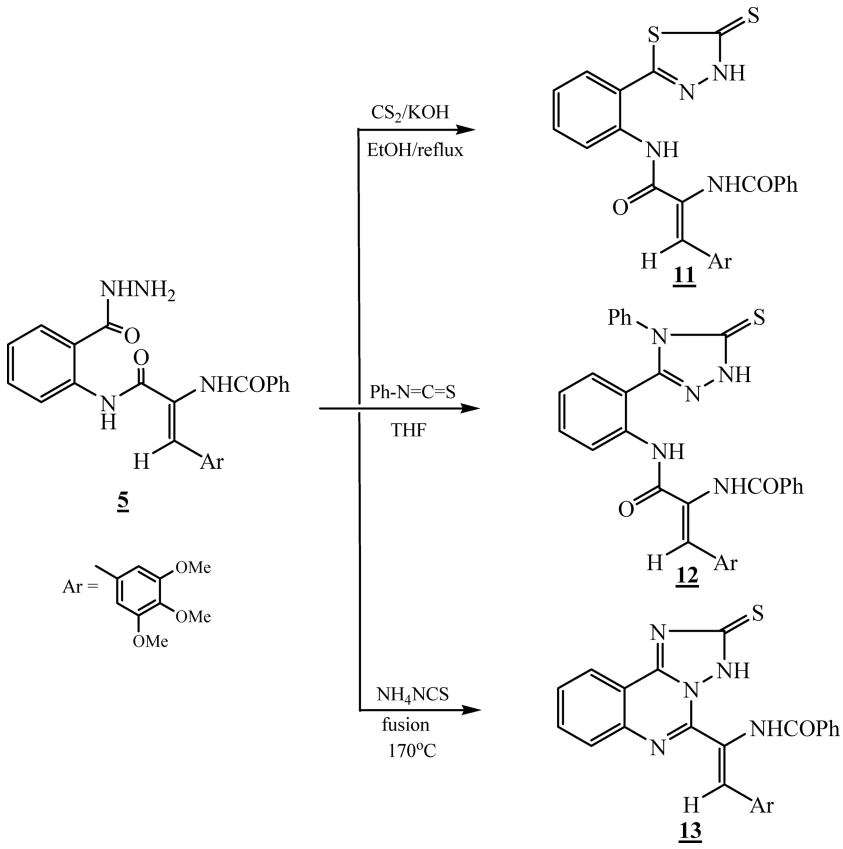



**SCHEME 3**

(Scheme 4). The molecular ion peak ($M^+ = 513$) in the mass spectrum of **13** was completely in accord with the proposed structure.

Benzoxazin-4-ones can be considered as semiacid anhydrides, and they undergo many reactions of true acid anhydrides.[19] Acid anhydrides react with Schiff bases and azines to give products depending upon reaction conditions.[20] The reaction, in many cases, involved the displacement of arylidene groups of the imines molecule. Thus, refluxing **1** with 4-methylaniline and/or 4-chlorobenzylidene-4-methylaniline in dry benzene yielded **14**. However, when the reaction was conducted in glacial acetic acid containing catalytic amounts of fused sodium acetate, quinazolin-4(H)one **15** was obtained in a quantitative yield (Scheme 5).

Structures **14** and **15** were rigidly established by their identity with an authentic sample prepared by the reaction of **1** with p-toluidine in refluxing ethanol and/or n-butanol and by heating **14** above its melting point. The displacement of the arylidene group of the Schiff's base took place during the reaction. This was further indicated by the detection of the aromatic aldehyde in the reaction media.

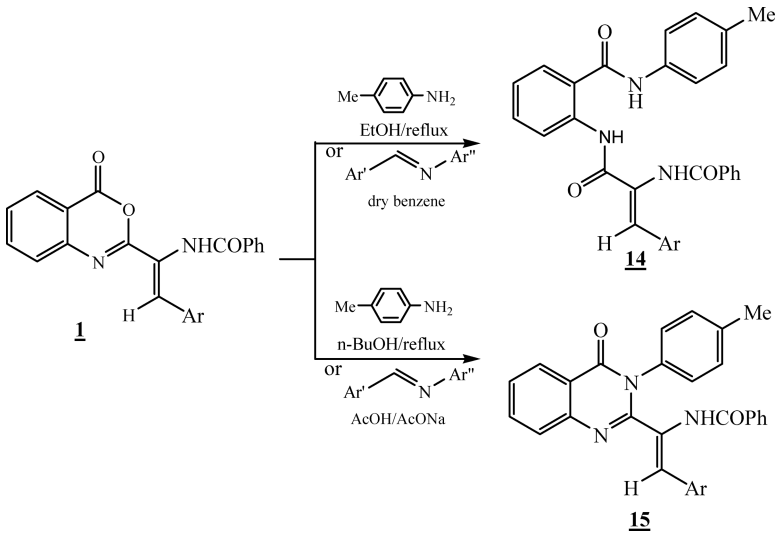



**SCHEME 4**

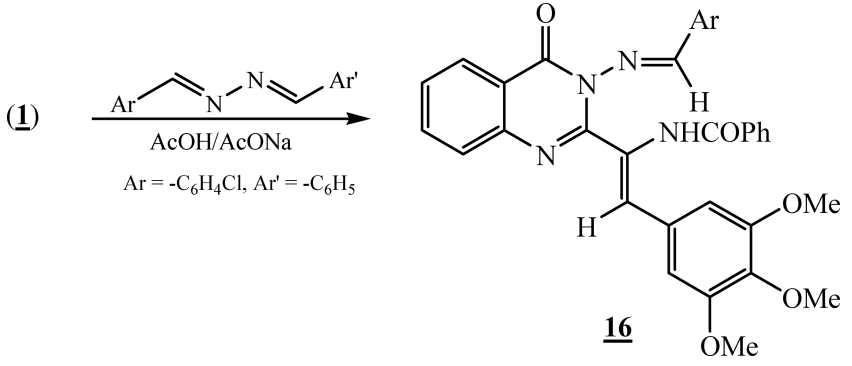
The reaction of **1** with azines involves the displacement of one arylidene group during the reaction. Thus, reacting **1** with p-chlorobenzalazine, in the presence of a catalytic amount of fused sodium acetate, yielded quinazolin-4(H)one **16** (Scheme 6).

## EXPERIMENTAL

All melting points were taken on a Griffin and Geory melting point apparatus and are uncorrected. IR spectra were recorded on Pye Unicam SP 1200 spectrophotometer using KBr Wafer technique. $^{1}$H NMR spectra were determined on a Varian Gemini 200 MHz, Bruker AC-200 MHz using TMS as an internal standard (chemical shifts in $\delta$-scale). EI-MS were measured on a Schimadzu-GC-MS instrument operating at 70 eV. $^{13}$C NMR spectra were measured in $CDCl_3$ solution on Jool




**SCHEME 5**




**SCHEME 6**

75 MHz. Microanalysis measurements were carried out at Ain Shams University laboratories, and satisfactory analytical data (±0.4) were obtained for all compounds. The homogeneity of the synthesized compounds was controlled by TLC.

## N-(2-(3,4,5-trimethoxypheny)-1-(4-oxo-4H-benzo[d][1,3]oxazin-2-yl)vinyl)benzamide (1)

A mixture of 4-(3′,4′,5′-trimethoxybenzylidene)-2-phenylisooxazol-5-one (10 mmol, 3.40 g) and anthranilic acid (10 mmol, 1.37 g) in acetic acid (100 mL) was refluxed for 6 h. The reaction mixture was

concentrated, and the yellow solid that separated after cooling was filtered off, washed with water several times, dried, and recrystallized from ethanol. The crystalline anthranilide product was treated with freshly distilled acetic anhydride (15 mL) and heated gently on water-bath for one hour. The reaction mixture was left for slow evaporation in a porcelain dish. The separated solid product was washed with cold 5% sodium carbonate solution to remove the unreacted acid, then washed with water several times, and filtered off, dried, and recrystallized from ethanol to give **1**, m.p. 126–128°C; yield 55%. IR: $\nu$ 1765, 1722 (CO, $\delta$-lactone), 1675 $cm^{-1}$ (amide). $^1H$ NMR ($CDCl_3$): $\delta$ 3.82, 3.96, (two singlet, 9H, 3 $OCH_3$), 6.7 (s, 1H, olefinic proton), 7–8.3 (m, 11H, arom. protons), 8.4 (s, 1H, NH). $^{13}C$ NMR ($CDCl_3$): 173.1 (CO—O), 172 (CO—NH), 159.1, 154.1, 152.3 (3C-$OCH_3$), 145 (C=N), 138.3, 137, 130.1, 128.5, 128.1, 127.6, 127.2, (arom. carbons), 109 (HC=), 108 (C=), 60.1, 58.8, 57.1 (3 $OCH_3$). MS: m/z: 458 [$M^{\pm}$], 105 (100%, Ph-C$\equiv O^+$), 146 (25.2%) 90 (16.1%), 77 (47.3%), 64 (3.1%). Anal. calcd. for $C_{26}H_{22}N_2O_6$ (458): C, 68.12; H, 4.80; N, 6.11; found: C, 67.83; H, 5.01; N, 5.59.



## Reaction of 1 with Grignard reagents: Formation of 2a–d

A solution of aryl magnesium halide such as phenyl magnesium bromide, 4-methoxy phenyl magnesium bromide, 4-methylphenyl magnesium bromide, or benzyl magnesium chloride (15 mmol) in anhydrous diethyl ether (100 mL) was added dropwise to a warm solution of the appropriate benzoxazinone **1** (5 mmol, 2.29 g) in anhydrous diethyl ether (100 mL) with continuous stirring, and then the mixture was refluxed on a water bath for 10 h and left at r.t. for 24 h. The Grignard complex was decomposed with a saturated solution of ammonium chloride (200 mL) and extracts with diethyl ether (4 × 50 mL). The combined diethyl ether layers were washed thoroughly with water, dried over anhydrous sodium sulphate, and evaporated. The remaining viscous oil was triturated several times with light petroleum ether (60–80°C), then dissolved in methanol, treated with charcool, filtered, concentrated, and left to stand in the refrigerator for 24 h. The solid product obtained was recrystallized from a suitable solvent to give **2a–d** (Table I).

### *N-(1-(2-(Hydroxydiphenylmethyl)phenylcarbamoyl)-2-(3,4,5-trimethoxyphenyl)vinyl)-benzamide (2a)*

Recrystallized from benzene as brown crystals; m.p: 173–175°C; yield 37%; anal. calcd. for $C_{38}H_{34}N_2O_6$ (614): C, 74.27; H, 5.54; N, 4.56; found: C, 74.36; H, 5.60; N, 4.75.

### *N-(1-(2-(Hydroxybis(4-methylphenyl)methyl) phenylcarbamoyl)-2-(3,4,5-trimethoxyphenyl)-vinyl)benzamide (2b)*

Recrystallized from ethanol as pale brown crystals; m.p: 167–169°C; yield 32%; anal. calcd. for $C_{40}H_{38}N_2O_6$ (642): C, 74.77; H, 5.92; N, 4.36; found: C, 74.48; H, 5.97; N, 4.59.

### *N-(1-(2-(Hydroxybis(4-methoxyphenyl)methyl)phenylcarbamoyl)-2-(3,4,5-trimethoxy-phenyl)vinyl)benzamide (2c)*

Recrystallized from L. P. (60–80°C) as pale brown crystals; m.p: >300°C; yield 46.6%; anal. calcd. for $C_{40}H_{38}N_2O_8$ (674): C, 71.22; H, 5.64; N, 4.15; found: C, 70.86; H, 5.32; N, 4.45.

### *N-(1-(2-(2-(Hydroxy-1,3-diphenylpropan-2-yl)phenylcarbamoyl)-2-(3,4,5-trimethoxy-phenyl)vinyl-benzamide (2d)*

Recrystallized from L. P. (80–100°C) as pale brown crystals; m.p. 191–193°C; yield 46.7%; anal. calcd. for $C_{40}H_{38}N_2O_6$ (642): C. 74.77; H, 5.92; N, 4.36; found: C, 75.28; H, 5.3; N, 4.62.



## Benzamide Derivatives 3a–e

A mixture of **1** (10 mmol, 4.58 g) and appropriate amines such as cyclohexylamine, benzylamine, piperidine, morpholine, and thiomorpholine (10 mmol) in ethanol (30 mL) was heated on a water bath for 2 h. The solid that deposited after concentration and cooling was filtered off, dried, and recrystallized from a suitable solvent to give **3a–e** (Table II).

### *N-(1-(2-(Cyclohexylcarbamoyl)phenylcarbamoyl)-2-(3,4,5-trimethoxyphenyl)vinyl)-benzamide (3a)*

Recrystallized from benzene as pale brown crystals; m.p: 226–228°C; yield 86.4%; anal. calcd. for $C_{32}H_{35}N_3O_6$ (557): C, 68.94; H, 6.28; N, 7.54; found: C, 69.31; H, 6.02; N, 7.88.

### *N-(1-(2-(Benzylcarbamoyl)phenylcarbamoyl)-2-(3,4,5-trimethoxyphenyl)vinyl)benzamide (3b)*

Recrystallized from a mixture of benzene drops of ethanol as colorless crystals; m.p: 216–218°C; yield 77.3%; anal. calcd. for $C_{33}H_{31}N_3O_6$ (565): C, 70.09; H, 5.49; N, 7.43; found: C, 70.38; H, 5.2; N, 7.35.

### *N-(1-(2-(Oxopiperidino)phenylcarbamoyl)-2-(3,4,5-trimethoxyphenyl)vinyl)benzamide (3c)*

Recrystallized from benzene as light yellow crystals, m.p. 205–206°C; yield 92.3%; anal. calcd. for $C_{31}H_{33}N_3O_6$ (543): C, 68.51; H, 6.08; N, 7.73; found: C, 68.06; H, 6.31; N, 7.93.

### *N-(1-(2-(Oxomorpholino)phenylcarbamoyl)-2-(3,4,5-trimethoxyphenyl)vinyl)benzamide (3d)*

Recrystallized form a mixture of L. P. (80–100°C)/benzene, as yellow crystals, m.p: 140–142°C; yield 73.9%; anal. calcd. for $C_{30}H_{31}N_3O_7$ (545): C, 66.06; H, 5.69; N, 7.71; found: C, 65.92; H, 5.37; N, 7.75.

### *N-(1-(2-(Oxothiomorpholino)phenylcarbamoyl)-2-(3,4,5-trimethoxyphenyl)vinyl)benzamide (3e)*

Recrystallized from ethanol as colorless crystals, m.p: 234–236°C; yield 31.1%; anal. calcd. for $C_{30}H_{31}N_3SO_6$, (561): C, 64.17; H, 5.53; N, 7.49; S, 5.70; found: C, 64.22; H, 5.38; N, 7.30; S, 5.18.



### 2-(2-(1-(N-Benzamido)-2-(3,4,5-trimethoxyphenyl)vinyl)-4-oxoquinazolin-3(4H)-yl) Acetic Acid (4)

Compound **1** (5 mmol, 2.29 g) and glycine (6 mmol, 0.45 g) were heated in 30 mL pyridine/water mixture (ratio 2:1) for 6 h at 160°C. After evaporation of the solvent, the residue was poured into 4N HCl (100 mL) affording the required compound **4**, which was recrystallized from benzene as yellow crystals, m.p: 198–199°C; yield 34.1%. IR: $\nu$ br. 3520 (NH, OH), 1710 (CO acid), 1678 $cm^{-1}$ (CO). MS: m/e: 471 (10.8), $[M^+-CO_2]$, 414 (9.6), 338 (22.92), 168 (20.1), 105 (100), 77 (73.2). Anal. calcd. for $C_{28}H_{25}N_3O_7$ (515): C, 65.24; H, 4.85; N, 8.16; found: C, 65.03; H, 4.46; N, 7.87.

## Hydrazinolysis of 1

### *In Ethanol: N-(1-(2-Hydrazido)carbamoyl)-2-(3,4,5-trimethoxyphenyl)vinyl)-benzamide 5*

A mixture of **1** (10 mmol, 4.58 g) and hydrazine hydrate 80% (0.03 mol, 1.5 mL) in absolute ethanol (30 mL) was stirred at r.t. for 2 h. The solid product deposited was filtered off, dried, and recrystallized from a mixture of benzene-ethanol to give hydrazide **5** as colourless crystals, m.p: 161–163°C; yield 86%. IR: $\nu$ br. 3250 (NH), 1660, 1648(CO). MS: m/e: 490 (32), 472 $[M^+-H_2O]$, 181 (100%). Anal. calcd. for $C_{26}H_{26}N_4O_6$, (490): C, 63.67; H, 5.31; N, 11.43; found: C, 63.90; H, 5.09; N, 11.09.

### *In n-Butanol: 4-(3,4,5-Trimethoxybenzylidene)-2-phenyl-1H-1,2,4-triazino[6,1-b]-quinazolin-10(4H)-one (7)*

A mixture of **1** (10 mmol, 4.58 g) and hydrazine hydrate 80% (0.03 mol, 1.5 mL) in n-butanol (30 mL) was refluxed for 20 h (TLC). The excess solvent was removed by distillation, and the solid that separated after cooling was triturated with ethanol, filtered off, and recrystallized from a mixture of benzene-ethanol as brown crystals, m.p: 116–167°C (yield 21.4%). IR: $\nu$ 3210 (NH), 1705 (CO), 1641 (C=N), 1595 (C=C). MS: 454 (100%), 288 (M-Ar) (33.3), no peak characteristic for Ph-C≡$O^+$ at m/e 105. Anal. calcd. for $C_{26}H_{22}N_4O_4$ (454), C, 68.72; H, 4.85; N, 12.33; found: C, 68.38; H, 4.61; N, 12.67.

## Potassium Dithiocarbazate Derivative 8

To a cold stirred solution of acid hydrazide **5** (10 mmol, 4.9 g) and potassium hydroxide (0.84 g) in absolute ethanol (100 mL), carbon disulphide (5 mL) was gradually added, and the solution formed was diluted with absolute ethanol (75 mL). The reaction mixture was agitated for 16 h at r.t. A white precipitate of potassium dithiocarbazate was separated out, which filtered off, dried, and recrystallized from benzene as white crystals, m.p: 196–198°C; yield 73.6%. IR: $\nu$ br. centered at 3258 (NH), 1686, 1670 (CO), 1350 (C=S). $^1$H NMR ($CDCl_3$): 12.1 (s, 2H, 2NH), 10.4 (s, 2H, 2NH) exchangeable with $D_2O$, 8.8–7.0 (m, 12H, Ar-H + C=CH), 3.78 (two s, 9H, 3$OCH_3$). $^{13}$CNMR 179.1, 170.4, 169.2 (3 CO), 160.1, 160.3, 163.1 (3 C—OMe), 164 (C=S), 120, 120 (C=C) 133 → 125.3 (aromatic carbons).

## N-(1-(2-(4-Amino-5-thioxo-1H-1,2,4-triazol-3-yl) phenylcarbamoyl)-2-(3,4,5-trimethoxy-phenyl)vinyl)benzamide (9)

A mixture of **8** (10 mmol, 6.04 g), hydrazine hydrate (10 mmol, 0.5 mL), and water (2 mL) was stirred and heated under reflux for 2 h; the color of the reaction mixture changed to green, hydrogen sulphide was evolved, and a homogenous solution was obtained. The reaction mixture was cooled, diluted with cold water (50 mL), and acidified with conc. HCl. The resulting precipitate was filtered off, washed with cold water, and recrystallized from ethanol as light brown crystals; m.p: 124–126°C; yield 18.6%. IR: $\nu$ br, 3442 (NH), 1680, 1677 (CO) 1632 (C=N), 1595 (C=C), 1325, 1248, 1005 $cm^{-1}$ (NCS). MS: m/e: ($M^+$) 546 (0.13), 518 (M-$N_2$) (10.1), 459 (13.8), 77 (53.2). Anal. calcd. for $C_{27}H_{26}N_6O_5S$ (546): C, 59.34; H, 4.76; N, 15.38; S, 5.86; found: C, 59.4; H, 4.46; N, 15.07; S, 6.23.

### N-(1-(2-(6-Methyl[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-3-yl)phenylcarbamoyl)-2-(3,4,5-trimethoxyphenyl)-vinyl)benzamide (10a)

A mixture of **9** (10 mmol, 5.46 g), acetic acid (10 mmol, 0.6 mL), and phosphorous oxychoride (4 mL) was gently heated under reflex for half hour. The reaction mixture was cooled and poured gradually into 10% $NaHCO_3$ (50 mL) with stirring. The separated solid was filtered off, wash with water, dried, and recrystalized from L. P. (100–120°C) to give **10a** as brown crystals, m.p: 106–108°C; yield 29.8%. IR: $\nu$ br.3431 (NH), 1688, 1672 (CO), 1632 (C=N); MS: m/e: [$M^{\pm}$] 570 (11.6), 494 (M-$CS_2$, 13.6); anal. calcd. for $C_{29}H_{26}N_6O_5S$ (570): C, 61.05; H, 4.56; N, 14.74; S, 5.61; found: C,60.89; H,4.50; N,15.01; S,5.30.

### N-(1-(2-(6-Phenyl[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-3-yl)phenylcarbamoyl)-2-(3,4,5-trimethoxyphenyl)-vinyl)benzamide (10b)

Benzoyl chloride (5 mL) was added gradually to a stirred solution of **9** (10 mmol, 5.46 g), in acetic acid (20 mL), with gentle heating on a water bath for half an hour. The solvent was evaporated, and the reaction mixture was poured into ice-cold water. The crude residue was triturated with light petrol, and the solid deposited was recrystallized from L.P. (b.p. 80–100°C) to give **10b** as light brown crystals; m.p: 147–148°C; yield 32%. IR: $\nu$ br 3460 (NH), 1672, 1660 (CO), 1630 (C=N); MS: m/e: [$M^+$] (17.6), 340(9.6), 105 (100), 77(46.6); anal. calcd. for $C_{34}M_{28}N_6O_5S$ (632): C, 64.56; H, 4.43; N, 13.29; S, 5.06; found: C, 64.72; H, 4.12, N, 12.97; S, 4.71.

### N-(1-(2-(4,5-Dihydro-5-thioxo-1,3,4-thiadiazol-2-yl)phenylcarbamoyl)-2-(3,4,5-trimethoxy-phenyl)vinyl)-benzamide (11)

To a stirred mixture of **5** (10 mmol, 4.9 g) and potassium hydroxide (1 g) in absolute ethanol (50 mL), carbon disulphide (2.5 mL) was added gradually for 1 h, and the reaction mixture was refluxed on a water bath for 12 h. The solid formed after cooling was filtered off, dissolved in water, and acidified with HCl. The solid that separated out was filtered off, dried, and recrystallized from ethanol affording **11** as brown crystals, m.p: 188–190°C; yield 33%. IR: $\nu$ br 3446 (NH), 1672 (CO), 1272 (C=S), 1610 $cm^{-1}$ (C=C). $^1$H-NMR (DMSO-$d_6$): $\delta$ 3.8 (two s, 9H), 7.0–8.4 (m, 12H), 10.4 (d, 2H). MS: m/e: [$M^+$] 548 (0.25), 472 (33) (M-$CS_2$), 340 (6.12), 105 (100), 77 (36.7). Anal. calcd. for $C_{27}H_{24}N_4O_5S_2$ (548): C, 59.12; H, 4.38; N, 10.22; S, 11.68; found: C, 59.44; H, 4.21; N, 10.63; S, 11.29.

### N-(1-(2-(4,5-Dihydro-4-phenyl-5-thioxo-1H-1,2,4-triazol-3-yl)phenylcarbamoyl)-2-(3,4,5-trimethoxyphenyl)vinyl)-benzamide (12)

A mixture of **5** (10 mmol, 4.9 g) and phenylisothiocyanate (10 mmol, 1.35 g) in tetrahydrofuran (30 mL) was refluxed for 6 h. The excess solvent was evaporated under reduced pressure, and the reaction mixture was poured into $H_2O$ and extracted with diethylether (2 × 100). Evaporation of diethylether left a semisolid product, which triturated with diluted methanol to give **12** as a light brown crystals, m.p: 171–172°C; yield 41.2%. IR($\nu$): br. 3285 (NH), 1685, 1676 (CO), 1280 (C=S).$^1$H-NMR ($CDCl_3$): $\delta$ 3.80–3.85 (two s, 9H), 7.0 (S, 1H), 7.1–8.3 (m, 16H), 9.8 (s, 1H), 10.8 (S, 1H). MS: m/e: [$M^+$] 593 (10.2) 430 (7.9) 105 ($PhC{\equiv}O^+$, 100), 93 (32.7), 77 (47.9). Anal. calcd. for $C_{33}H_{29}N_5O_5S$ (607): C, 65.24; H, 4.78; N, 11.53; S, 5.27; found C, 65.61; H, 5.02; N, 11.19; S, 5.20.



### N-(1-(2,3-Dihydro-2-thioxo-[1,2,4]triazolo[1,5-c]quinazolin-5-yl)-2-(3,4,5-trimethoxy-phenyl)vinyl)benzamide (13)

A mixture of **5** (1.5 g), and ammonium thiocyanate (2.1 g) was fused on an oil bath at 180°C for half an hour. The crude mixture was dissolved in hot water (30 mL), cooled, and acidified with concentrated hydrochloric acid. The solid deposited was recrystallized from ethanol producing **13** as brown crystals, m.p: 186–188°C; yield 36.6%. IR: $\nu$ br. 3320 (NH), 2072 (C=S), 1678 (CO), 1622 (C=N). MS: m/e: $M^+ = 513$ (6.3), 168 (17.2), 105 (100), 77 (56.8). Anal. calcd. for $C_{27}H_{23}N_5O_4S$ (513): C, 63.16; H, 4.48; N, 13.65; S, 6.24; found: C, 62.82; H, 4.31; N, 14.1; S, 5.97.

### N-(1-(2-(4-Methylphenylcarbamoyl)phenylcarbamoyl)2-(3,4,5-trimethoxyphenyl)-vinyl)benzamide (14)

To a solution of **1** (10 mmol, 4.58 g) in dry benzene (20 mL), 4-chlorobenzylidine-4-methylaniline (10 mmol, 2.29 g) was added, and the whole mixture was heated under reflex for 6 h. The solid formed after cooling was filtered off and recrystallized from benzene to give **14** as light brown crystals, m.p: 173–175°C (yield 55%). IR: 3360, 3250, 3180 (NH), 1670, 1653, 1641 $cm^{-1}$ (CO); Anal. calcd. for $C_{33}H_{31}N_3O_6$ (565): C, 70.09; H, 5.49; N, 7.43; found: C, 69.87; H, 5.11; N, 7.40.

### Synthesis of an Authentic Sample

The mixture of **1** (10 mmol, 4.58 g) and p-toluidine (10 mmol, 1.07 g) in ethanol (20 mL) was heated under reflux for 10 h. The solid formed

after cooling was filtered off and crystallized from benzene to give **14** (m.p., mixed m.p., TLC, and IR comparison).

### N-(1-(3,4-Dihydro-4-oxo-3-p-tolylquinazolin-2-yl)-2-(3,4,5-trimethoxyphenyl)vinyl)-benzamide (15) and N-(1-(3-(4-chlorobenzylideneamino)-3,4-dihydro-4-oxoquinazolin-2-yl)-2-(3,4,5-trimethoxyphenyl)-vinyl)benzamide (16): General Procedure

A mixture of **1** (10 mmol, 4.58 g), a Schiff base and/or azine (10 mmol), and fused sodium acetate (0.3 g) in glacial acetic acid (30 mL) was heated under reflux for 6 h and then poured into cold water. The solid that formed was filtered off, washed with hot water several times, and recrystallized from a suitable solvent to produce **15** and **16**, respectively.

**15**, recrystallized from ethanol as orange crystals, m.p: 110–112°C; yield 51%. IR: $\nu$ 3370, 3260 (NH), 1722, 1650 (CO); anal. calcd. for $C_{33}H_{29}N_3O_5$(547): C, 72.39; H, 5.30; N, 7.68. Found: C, 72.51; H, 5.00; N, 7.37.

**16**, recrystallized from ethanol as pale yellow crystals, m.p: 190–192°C; yield 32.3%. IR: 3216 (NH), 1711, 1652 (C=O), 1626 $cm^{-1}$ (C=N); MS: m/e: 595 (11.8); Anal. calcd. for $C_{33}H_{27}ClN_4O_5$ (595): C, 66.55; H, 4.54; N, 9.41; Cl, 5.97; found: C, 66.21; H, 4.27; N, 9.57; Cl, 6.21.



### Synthesis of An Authentic Sample of 15

1. Compound **14** (1.5 g) was heated at 200°C for 1 h and left to cool. The resulting melt was triturated with boiling ethanol and concentrated. The solid that formed after cooling crystallized from ethanol to give **15** as orange crystals (yield 70%) m.p. 110–112°C.
2. Compound **1** (10 mmol, 4.58 g) was heated with p-toluidine in refluxing n-butunol (20 mL) for 10 h. The solid separated after concentration and cooling was found to be identical with **15** (m.p., mixed m.p., TLC, and IR comparison).

### Preparation of An Authentic Sample of 16

A mixture of the hydrazide **5** (10 mmol, 4.9 g), 4-chlorobenzaldehyde (10 mmol, 1.4 g), fused sodium acetate (3.0 g), and glacial acetic acid (30 mL) was heated under reflux for 3 h. The reaction mixture was filtered while hot and poured into water; the solid deposited was filtered off and recrystallized from ethanol to give **16** as pale yellow crystals, m.p: 190–192°C (m.p., mixed m.p., TLC, and IR comparison).

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