

NEW SYNTHETIC ROUTE TO TETRACYCLIC QUINAZOLIN-4(3*H*)-ONE RING SYSTEM

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Abstract - Reactions of dithiazoles (**1a-e**) and (**9a-b**) with 3,4-dimethoxyphenethylamine (**2**) in CH₂Cl₂ at room temperature produce 3,4-dihydro-3-(3,4-dimethoxyphenethyl)-4-oxoquinazoline-2-carbonitriles (**3a-d**) and 4-hydroxy-4-phenyl-3,4-dihydroquinazoline-2-carbonitriles (**10a-b**), respectively. Compounds (**3a-d**) on treatment with TFAA/HCl at 120-130°C gave 3-(3,4-dimethoxy-phenethyl)quinazoline-2,4(1*H*,3*H*)-diones (**5a-d**) in excellent yields. Quinazolin-4(3*H*)-ones (**3a-d**), quinazoline-2,4(1*H*,3*H*)-diones (**5a-d**) and their thieno analogs (**3e** and **5e**) as well as 4-hydroxy-3-(3,4-dimethoxyphenethyl)-4-phenyl-3,4-dihydroquinazoline-2-carbonitriles (**10a-b**) are cyclized in the presence of P₂O₅/POCl₃ in xylene at 130°C to tetracyclic benzazepino[2,3-*b*]quinazolinones (**8a-d**), isoquino[1,2-*b*]quinazolinones (**6a-d**), thienopyrimidinones (**6e** and **8e**) as well as isoquino[1,2-*c*]quinazoline-6-carbonitriles (**11a-b**), respectively, in good yields.

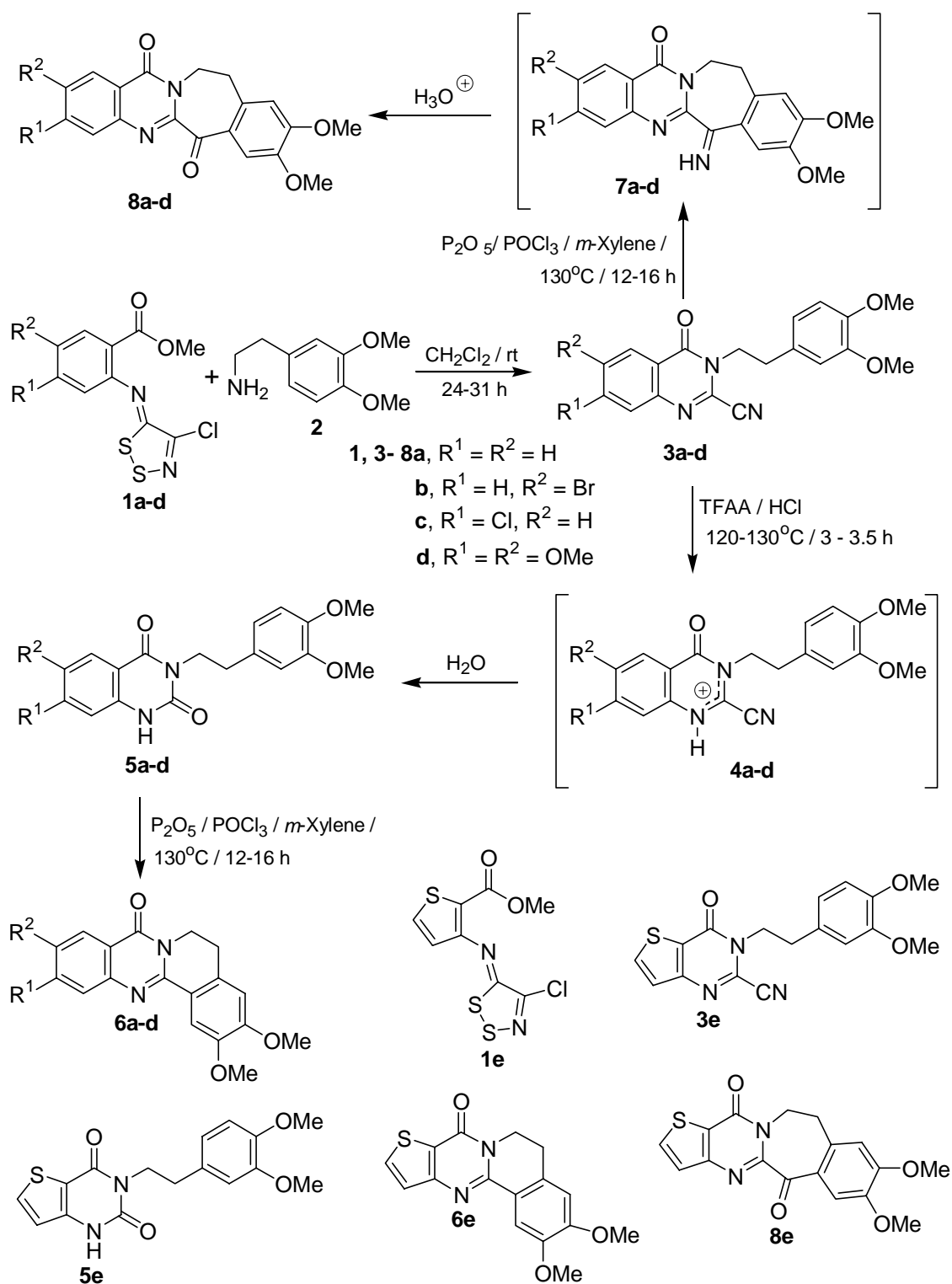
Tetracyclic quinazolin-4(3*H*)-one ring systems form the characteristic framework of numerous heterocyclic physiologically active compounds. For instance, a number of alkaloids such as tryptanthrin (also known as couroptitine),¹ alantrypinone,² asperlicin C,³ circumdatin F,³ and sclerotigenin³ comprised of quinazolin-4(3*H*)-one template in which a bicyclic ring system is fused to the pyrimidine ring of quinazolin-4(3*H*)-one. In addition, molecules based on polycyclic quinazolin-4(3*H*)-one⁴ skeleton exhibit a multitude of interesting pharmacological properties such as cardiogenic,⁵ analgesic,⁶ cytotoxic⁷ and neurokinin NK1 receptor activities.⁸ Similarly, quinazolinone template appears in a wide range of bioactive molecules that interact with G-protein coupled receptors (GPCRs, adrenergic, serotonergic, dopaminergic, endothelin ET_A), and enzymes (cyclooxygenase, collagenase, aldose reductase and

carbonic anhydrase).⁹ Recently, structure activity relationship study reveals that quinazoline-2,4(1*H*, 3*H*)-diones having *N*-3 side chain (two carbon tether) are essential for good reactivity, and SGB-1534 and its analogs in that series are found to be α_{1A} -adrenoceptor antagonist.¹⁰

Over the past few years, we have been working on the development of new synthetic strategies for nitrogen and sulfur heterocycles,¹¹ which are based on the use of 5-arylimino-4-chloro-5*H*-1,2,3-dithiazoles¹² as key intermediates. At present, we are interested in devising new synthetic route for tetracyclic quinazolin-4(3*H*)-one derivatives from methyl *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)anthranilates (**1**). The synthesis of a novel series of 2-cyanoquinazolin-4(3*H*)-ones have been reported in our earlier papers by describing the reaction of **1** with various aliphatic¹³ and aromatic primary amines.¹⁴ We have supposed that treatment of **1** with 3,4-dimethoxyphenethylamine (**2**) gives 3,4-dihydro-3-(3,4-dimethoxyphenethyl)-4-oxoquinazoline-2-carbonitrile (**3**), which cyclizes into tetracyclic quinazoline derivatives. In this paper, we discuss the results obtained from the reactions of **3** with TFAA/HCl and P₂O₅/POCl₃.

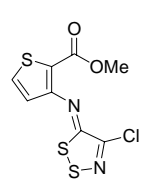
Dithiazoles (**1a-d**), used as starting materials for the synthesis of **3** are prepared according to the reported procedure¹³ by condensation of methyl anthranilates with 4,5-dichloro-1,2,3-dithiazolium chloride (Appel's salt)¹⁵ in pyridine/CH₂Cl₂ at room temperature. Reaction of **1a** with **2** in CH₂Cl₂ at room temperature gave 2-cyanoquinazolinone (**3a**) in 63% yield with extrusion of sulfur (Scheme 1). A number of tri and tetrasubstituted quinazolinones (**3b-d**) and thienopyrimidinone (**3e**) were synthesized from the reactions of dithiazoles (**1b-e**) with **2** under similar conditions, respectively. Taking our earlier experiences into account for the synthesis of quinazolinocarbolone natural products,¹⁶ **3a** was treated with TFAA/HCl at 120°C with a view to obtain quinazolinone derivative (**6a**). On heating this reaction mixture for 3.5 h, quinazoline-2,4(1*H*, 3*H*)-dione (**5a**) (lit.,¹⁷ 202-203°C) (Scheme 1) was obtained exclusively. The formation of **5a** may be due to the hydrolytic elimination of cyano group from carbocation (**4a**). Compound (**5a**) was reported to exhibit sedative and hypertensive properties.¹⁷ When compound (**5a**) was heated (130°C) with P₂O₅/POCl₃ in *m*-xylene under Bischler-Napieralski conditions, isoquino[1,2-*b*]quinazolin-8-one (**6a**)¹⁸ was obtained in 62 % yield. Similarly compound (**3b-d**) and the

thieno analog (**3e**) on treatment with TFAA/HCl at 120-130°C yielded **5a-d** and thienopyrimidine-2,4-dione (**5e**), which underwent cyclodehydration with P₂O₅/POCl₃ in refluxing xylene to form (**6b-d** and **6e**), respectively. On the other hand, when **3a** was treated with POCl₃/P₂O₅ directly in *m*-xylene, the linearly fused quinazolinone (**8a**) was obtained presumably via **7a** (Scheme 1).

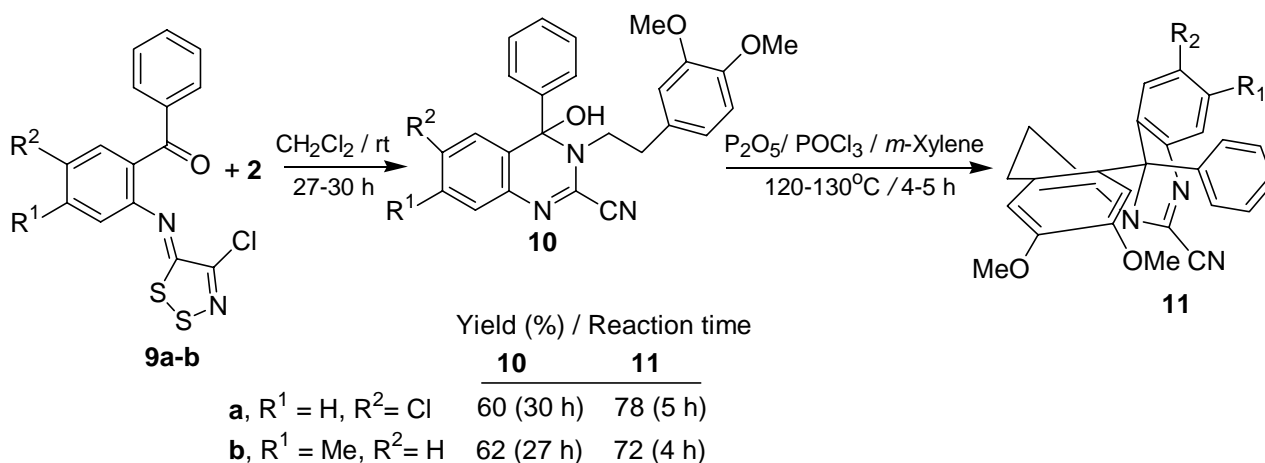


Scheme 1

Table 1. Yield and Reaction Times for the Synthesis of Compounds (**3**, **5**, **6** and **8**)

| 1, 3-8 | Yield (%) / Time | Yield (%) / Time | Yield (%) / Time | Yield (%) / Time |
|--|------------------|------------------|------------------|------------------|
| | 3 | 5 | 6 | 8 |
| a , R ¹ = R ² = H | 63 (24 h) | 93 (3 h) | 62 (12 h) | 69 (16 h) |
| b , R ¹ = H, R ² = Br | 74 (31 h) | 94 (3 h) | 68 (14 h) | 67 (15 h) |
| c , R ¹ = Cl, R ² = H | 78 (31 h) | 97 (3 h) | 64 (13 h) | 65 (14 h) |
| d , R ¹ = R ² = OMe | 71 (29 h) | 96 (3.5 h) | 68 (16 h) | 66 (16 h) |
| e ,  | 76 (30 h) | 96 (3.5 h) | 49 (12 h) | 51 (12 h) |

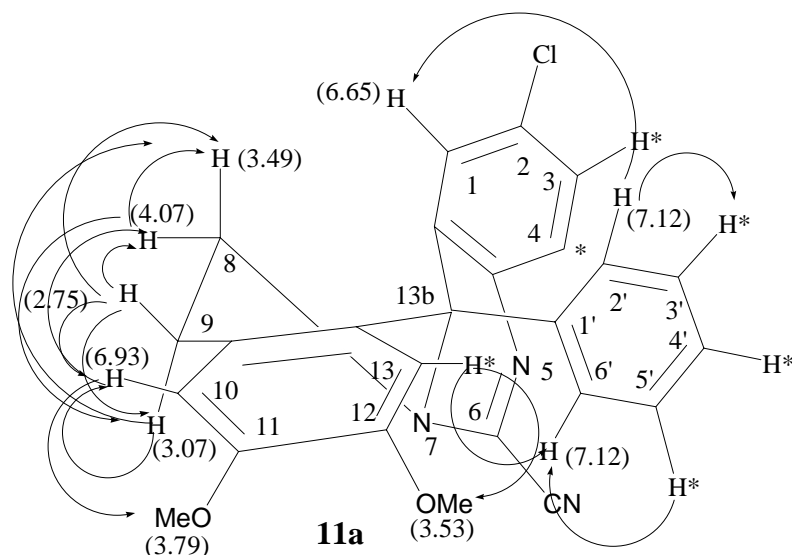
The other substituted benzazepino[2,3-*b*]quinazolinones (**8b-d**) and their thieno analog (**8e**) were also obtained from **3b-d** and **3e** respectively under similar conditions (Table 1). Dithiazoles (**9a** and **9b**), prepared from the respective 2-aminobenzophenones, were reacted with **2** in CH₂Cl₂ at room



Scheme 2

temperature to yield respective 3,4-dihydro-4-hydroxy-4-phenylquinazoline-2-carbonitriles (**10a**) and (**10b**), which underwent cyclodehydration in the presence of P₂O₅/POCl₃ to form isoquino[2,1-*c*]quinoline-6-carbonitriles (**11a**) and (**11b**) having phenyl group at C-13*b* position (Scheme 2). The formation of **11a** was evidenced by the appearance of two singlets at δ 6.36 and δ 6.93 due to the respective H-13 and H-10 aromatic protons¹⁹ in the ¹H NMR spectrum, while the C-13*b* carbon of **11a** in

the ^{13}C NMR spectrum appeared at δ 66.9. In addition, the N-CH_2 - proton signals (δ 3.49, 4.07) of isoquino[2,1-*c*]quinoline (**11a**) appeared in downfield with respect to the proton signals (δ 3.25, 3.59) of N-CH_2 - of the corresponding 3,4-dihydroquinazoline-2-carbonitrile (**10a**). The NOE experimental results of **11a** in ^1H NMR spectrum are shown in Figure 1.



* H-3, H-3', H-4, H-5' = δ 7.34-7.43

* H-4 = δ 7.21; H-13 = δ 6.36

Figure 1

To sum up, quinazolin-4(3*H*)-ones, quinazoline-2,4(1*H*, 3*H*)-diones, tetracyclic quinazolinones and their thieno analogs were synthesized from methyl *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)anthranilates in good yields.

EXPERIMENTAL

All melting points were recorded on a Fisher-Johns melting point apparatus and are uncorrected. IR spectra were obtained on a Shimadzu IR-470 spectrophotometer in KBr. ^1H NMR (300 MHz, 500 MHz) and ^{13}C NMR (75 MHz, 125 MHz) spectra were recorded in CDCl_3 or $\text{DMSO-}d_6$ using TMS as internal standard. MS spectra were obtained by electron impact at 70 eV. Elemental analyses were determined by the National Center for Inter-University Research Facilities, Seoul National University. Dichloromethane was distilled over P_2O_5 prior to use. Column chromatography was performed on silica gel (Merck, 70-230 mesh, ASTM). Starting materials methyl *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)anthranilates (**1a-e**) and 2-(benzoyl)arylimino-4-chloro-5*H*-1,2,3-dithiazoles (**9a-b**) were prepared according to reported

method.¹³

3,4-Dihydro-3-(3,4-dimethoxyphenethyl)-4-oxoquinazoline-2-carbonitriles (3a-d), 3,4-Dihydro-3-(3,4-dimethoxyphenethyl)thieno[3,2-*d*]-4-oxopyrimidine-2-carbonitrile (3e) and 6-Chloro- (or 7-Methyl-) 3,4-dihydro-3-(3,4-dimethoxyphenethyl)-4-hydroxy-4-phenylquinazoline-2-carbonitriles (10a-b); General Procedure: To a stirred solution of dithiazole (**1a-e/9a-b**) (0.70 – 4.89 mmol) in CH₂Cl₂ (25 –35 mL), a solution of **2** (140 - 974 mg, 0.77 – 5.37 mmol) in CH₂Cl₂ (10 -20 mL) was added and the reaction mixture was stirred (monitored by TLC) at rt for 24-31 h. The mixture was poured into water (30 mL) and the organic layer was separated out. The aqueous layer was shaken with CH₂Cl₂ (2 × 20 mL) to extract the product [compounds (**10a-b**) were extracted with CHCl₃ (3 × 20 mL)]. The combined organic extract was washed with water (30 mL), dried (MgSO₄) and the solvent was evaporated under reduced pressure to afford crude **3a-e/10a-b**, which was purified by passing through silica gel column using *n*-hexane-EtOAc [**3a-e** (17:3)/ **10a-b** (3:2)] as eluent.

3,4-Dihydro-3-(3,4-dimethoxyphenethyl)-4-oxoquinazoline-2-carbonitrile (3a): colorless crystals (CH₂Cl₂-*n*-hexane), mp 159-160°C; IR (KBr) (ν, cm⁻¹) 1686, 1584, 1510; ¹H NMR (CDCl₃, 300 MHz, δ) 3.08 (2H, t, *J* = 7.6 Hz, CH₂), 3.79 (3H, s, OMe), 3.86 (3H, s, OMe), 4.48 (2H, t, *J* = 7.6 Hz, NCH₂), 6.75-6.79 (3H, m, ArH), 7.58 (1H, td, *J* = 1.3, 7.5 Hz, ArH), 7.77 (1H, dd, *J* = 1.1, 7.7 Hz, ArH), 7.84 (1H, td, *J* = 1.3, 7.5 Hz, ArH), 8.36 (1H, dd, *J* = 1.6, 8.0 Hz, ArH); ¹³C NMR (CDCl₃, 75 MHz,) 34.3, 48.4, 55.7, 55.8, 111.3, 111.4, 112.0, 121.2, 122.6, 127.0, 128.4, 128.7, 130.0, 131.4, 135.1, 146.3, 148.1, 149.1, 159.8; MS (EI) *m/z* 335 (M⁺, 46), 164 (100), 149 (42). *Anal.* Calcd for C₁₉H₁₇N₃O₃: C, 68.05; H, 5.11; N, 12.53. Found: C, 68.01; H, 5.09; N, 12.54.

6-Bromo-3,4-dihydro-3-(3,4-dimethoxyphenethyl)-4-oxoquinazoline-2-carbonitrile (3b): colorless crystals (CHCl₃-*n*-hexane), mp 193-194°C; IR (KBr) (ν, cm⁻¹) 1686, 1571, 1507, 1459; ¹H NMR (CDCl₃, 300 MHz, δ) 3.08 (2H, t, *J* = 7.5 Hz, CH₂), 3.81 (3H, s, OMe), 3.86 (3H, s, OMe), 4.48 (2H, t, *J* = 7.6 Hz, NCH₂), 6.73-6.81 (3H, m, ArH), 7.64 (1H, d, *J* = 8.6 Hz, ArH), 7.93 (1H, dd, *J* = 2.6, 8.7 Hz, ArH), 8.47 (1H, d, *J* = 2.3 Hz, ArH); ¹³C NMR (CDCl₃, 75 MHz,) 34.2, 48.6, 55.8, 55.9, 111.3, 111.5, 112.1, 121.23, 123.9, 124.2, 125.9, 129.7, 131.0, 131.7, 138.4, 145.1, 148.3, 149.2, 158.7; MS (EI) *m/z* 413 (M⁺, 4.03), 164 (100), 151 (16. 57). *Anal.* Calcd for C₁₉H₁₆N₃O₃Br: C, 55.09; H, 3.89; N, 10.14. Found: C,

55.35; H, 3.64; N, 10.34.

7-Chloro-3,4-dihydro-3-(3,4-dimethoxyphenethyl)-4-oxoquinazoline-2-carbonitrile (3c): colorless crystals (CHCl_3 -*n*-hexane), mp 180-181°C; IR (KBr) (ν , cm^{-1}) 1689, 1577, 1510 ; ^1H NMR (CDCl_3 , 300 MHz, δ) 3.08 (2H, t, $J = 7.3$ Hz, CH_2), 3.81 (3H, s, OMe), 3.86 (3H, s, OMe), 4.47 (2H, t, $J = 7.6$ Hz, NCH_2), 6.73-6.89 (3H, m, ArH), 7.58 (1H, dd, $J = 1.4, 8.5$ Hz, ArH), 7.75 (1H, s, ArH), 8.26 (1H, d, $J = 8.5$ Hz, ArH); ^{13}C NMR (CDCl_3 , 75 MHz,) 34.2, 48.5, 55.8, 55.8, 111.1, 111.4, 112.1, 121.0, 121.2, 127.9, 128.4, 128.5, 130.5, 132.6, 142.0, 147.1, 148.3, 149.2, 159.2; MS (EI) m/z 369 (M^+ , 7.36), 164 (100), 151 (14.55), 149 (13.95). *Anal.* Calcd for $\text{C}_{19}\text{H}_{16}\text{N}_3\text{O}_3\text{Cl}$: C, 61.71; H, 4.36; N, 11.36. Found: C, 61.87; H, 4.59; N, 11.42.

3,4-Dihydro-6,7-dimethoxy-3-(3,4-dimethoxyphenethyl)-4-oxoquinazoline-2-carbonitrile (3d): colorless crystals (CHCl_3 -*n*-hexane), mp 196-197°C; IR (KBr) (ν , cm^{-1}) 1664, 1600, 1580, 1452 ; ^1H NMR (CDCl_3 , 300 MHz, δ) 3.08 (2H, t, $J = 7.5$ Hz, CH_2), 3.80 (3H, s, OMe), 3.86 (3H, s, OMe), 4.01 (3H, s, OMe), 4.04 (3H, s, OMe), 4.48 (2H, t, $J = 7.5$ Hz, NCH_2), 6.75-6.79 (3H, m, ArH), 7.14 (1H, s, ArH), 7.64 (1H, s, ArH); ^{13}C NMR (CDCl_3 , 75 MHz,) 34.4, 48.4, 55.7, 55.8, 56.5 (2C), 105.6, 108.4, 111.3, 111.6, 112.0, 116.7, 121.2, 128.8, 129.8, 142.5, 148.1, 149.1, 151.4, 155.3, 159.2; MS (EI) m/z 395 (M^+ , 4.12); (164, 100), 149 (12.32). *Anal.* Calcd for $\text{C}_{21}\text{H}_{21}\text{N}_3\text{O}_5$: C, 63.79; H, 5.35; N, 10.63. Found: C, 63.41; H, 5.37; N, 10.55.

3,4-Dihydro-3-(3,4-dimethoxyphenethyl)thieno[3,2-*d*]-4-oxopyrimidine-2-carbonitrile (3e): colorless crystals (CH_2Cl_2 -*n*-hexane), mp 184-185°C; IR (KBr) (ν , cm^{-1}) 1673, 1548, 1507; ^1H NMR (CDCl_3 , 300 MHz, δ) 3.10 (2H, t, $J = 7.3$ Hz, CH_2), 3.80 (3H, s, OMe), 3.86 (3H, s, OMe), 4.52 (2H, t, $J = 7.6$ Hz, NCH_2), 6.76-6.82 (3H, m, ArH), 7.39 (1H, d, $J = 5.1$ Hz, ArH), 7.89 (1H, d, $J = 5.3$ Hz, ArH); ^{13}C NMR (CDCl_3 , 75 MHz,) 34.4, 48.4, 55.8, 55.9, 111.5, 112.1, 112.2, 125.4, 125.8, 126.5, 128.5, 132.5, 135.6, 148.3, 149.2, 154.9, 155.9; MS (EI) m/z 341 (M^+ , 5.4), 164 (100), 149 (16.6). *Anal.* Calcd for $\text{C}_{17}\text{H}_{15}\text{N}_3\text{O}_3\text{S}$: C, 59.81; H, 4.43; N, 12.31; S, 9.39. Found: C, 59.52; H, 4.41; N, 12.16; S, 9.48.

6-Chloro-3,4-dihydro-4-hydroxy-3-(3,4-dimethoxyphenethyl)-4-phenylquinazoline-2-carbonitrile (10a): colorless needles (EtOH-benzene), mp 193-194°C; IR (KBr) (ν , cm^{-1}) 3216, 1584, 1507; ^1H NMR

(DMSO- d_6 , 300 MHz, δ) 2.41 (1H, td, $J = 5.1, 12.3$ Hz, CH_2), 2.88 (1H, td, $J = 5.3, 12.1$ Hz, CH_2), 3.25 (1H, td, $J = 5.4, 12.4$ Hz, NCH_2), 3.59 (1H, td, $J = 5.1, 11.9$ Hz, NCH_2), 3.72 (3H, s, OMe), 3.74 (3H, s, OMe), 6.47 (1H, d, $J = 1.5$ Hz, ArH), 6.52 (1H, dd, $J = 1.6, 9.7$ Hz, ArH), 6.77 (1H, d, $J = 8.1$ Hz, ArH), 6.85 (1H, d, $J = 2.0$ Hz, ArH), 7.24-7.32 (1H, m, ArH), 7.35-7.42 (2H, m, ArH), 7.46 (1H, d, $J = 6.8$ Hz, ArH), 7.53 (2H, d, $J = 7.7$ Hz, ArH), 7.85 (1H, s, ArH); ^{13}C NMR (DMSO- d_6 , 75 MHz, δ) 37.0, 48.9, 55.5, 55.7, 85.7, 112.2 (2 C), 113.2, 120.5, 126.9, 127.1 (2 C), 127.4, 128.6 (2 C), 128.8, 129.4, 130.2, 130.5, 130.7, 133.2, 138.1, 144.3, 147.8, 150.0; FAB-MS m/z 448 ($\text{M}^+ + 1$, 11.94), 447 (M^+ , 7.18), 267 (13.34), 165 (100), 154 (60.82). *Anal.* Calcd for $\text{C}_{25}\text{H}_{22}\text{N}_3\text{O}_3\text{Cl}$: C, 67.04; H, 4.95; N, 9.38. Found: C, 67.27, H, 4.71; N, 9.14.

3,4-Dihydro-4-hydroxy-3-(3,4-Dimethoxyphenethyl)-7-methyl-4-phenylquinazoline-2-carbonitrile

(10b): colorless needles (EtOH-benzene), mp 182-183°C; IR (KBr) (ν , cm^{-1}) 3168, 1584, 1548, 1507; ^1H NMR (DMSO- d_6 , 300 MHz, δ) 2.23 (3H, s, CH_3), 2.44 (1H, td, $J = 5.0, 11.9$ Hz, CH_2), 2.84 (1H, td, $J = 5.3, 12.3$ Hz, CH_2), 3.45 (1H, td, $J = 5.1, 11.4$ Hz, NCH_2), 3.67 (1H, td, $J = 4.9, 11.7$ Hz, NCH_2), 3.73 (3H, s, OMe), 3.78 (3H, s, OMe), 6.34 (1H, d, $J = 1.5$ Hz, ArH), 6.45 (1H, dd, $J = 7.6, 1.5$ Hz, ArH), 6.70 (1H, d, $J = 7.9$ Hz, ArH), 6.81 (1H, d, $J = 6.8$ Hz, ArH), 6.89 (1H, s, ArH), 6.94 (1H, dd, $J = 1.2, 7.9$ Hz, ArH), 7.36-7.45 (3H, m, ArH), 7.52 (2H, d, $J = 7.1$ Hz, ArH); ^{13}C NMR (DMSO- d_6 , 75 MHz, δ) 20.9, 36.6, 49.6, 56.7, 56.9, 86.2, 111.4, 111.8, 112.3, 120.6, 124.1, 125.4, 128.0 (2 C), 128.1 (2 C), 128.5, 128.5, 128.9, 130.2, 133.5, 138.8, 139.3, 143.4, 147.7, 149.0; FAB-MS m/z 428 ($\text{M}^+ + 1$, 25.98), 427 (M^+ , 12.22), 307 (13.10), 247 (12.50), 165 (43.18), 154 (100), 136 (81.07). *Anal.* Calcd for $\text{C}_{26}\text{H}_{25}\text{N}_3\text{O}_3$: C, 73.05; H, 5.89; N, 9.83. Found: C, 73.32, H, 5.65; N, 9.74.

3-(3,4-Dimethoxyphenethyl)quinazoline-2,4(1H,3H)-diones (5a-d) and 3-(3,4-dimethoxyphenethyl)thieno[3,2-*d*]pyrimidine-2,4(1H,3H)-dione (5e); General Procedure

A mixture of **3** (0.48 – 0.81 mmol), HCl (37%) (1.6 - 2.8 mL) and TFAA (11.32 – 19.11 mmol, 1.6 – 2.7 mL) was heated at 120-130°C for 3.0-3.5 h (monitored by TLC). The reaction mixture was cooled to rt and was poured onto crushed ice. The solid precipitated out was filtered, washed with water repeatedly till the residue become free from acid. The residue was recrystallized from CHCl_3 -*n*-hexane.

3-(3,4-Dimethoxyphenethyl)quinazoline-2,4(1H,3H)-dione (5a): colorless crystals, mp 199-200°C

(lit.,¹⁷ 202-203°C); IR (KBr) (ν , cm^{-1}) 3456, 1702, 1648, 1510; ^1H NMR (CDCl_3 , 300 MHz, δ) 2.98 (2H, t, $J = 7.9$ Hz, CH_2), 3.83 (3H, s, OMe), 3.86 (3H, s, OMe), 4.32 (2H, t, $J = 7.9$ Hz, NCH_2), 6.79-6.95 (3H, m, ArH), 7.16 (1H, d, $J = 8.1$ Hz, ArH), 7.26 (1H, t, $J = 7.4$ Hz, ArH), 7.50 (1H, t, $J = 7.5$ Hz, ArH), 8.15 (1H, d, $J = 8.8$ Hz, ArH), 10.84 (1H, br s, NH, D_2O -exchangeable); ^{13}C NMR (CDCl_3 , 75 MHz, δ) 34.1, 42.9, 56.2, 56.7, 111.6, 112.5, 115.0, 115.6, 121.3, 123.9, 128.7, 131.5, 135.5, 139.1, 148.1, 149.2, 152.7, 162.7; FAB-MS m/z 327 ($\text{M}^{++} + 1$, 50.5), 326 (M^+ , 40.2), 164 (89.8), 154 (100). *Anal.* Calcd for $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_4$: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.51; H, 5.51; N, 8.52.

6-Bromo-3-(3,4-dimethoxyphenethyl)quinazoline-2,4(1H,3H)-dione (5b): colorless solid, mp 231-233°C; IR (KBr) (ν , cm^{-1}) 3340, 1708, 1648, 1507; ^1H NMR ($\text{DMSO-}d_6$, 300 MHz, δ) 2.83 (2H, t, $J = 6.7$ Hz, CH_2), 3.75 (6H, s, 2 x OMe), 4.01 (2H, t, $J = 6.4$ Hz, NCH_2), 6.76 (1H, d, $J = 8.5$ Hz, ArH), 6.82 (1H, s, ArH), 6.91 (1H, dd, $J = 8.2, 2.9$ Hz, ArH), 7.16 (1H, dd, $J = 8.7, 3.8$ Hz, ArH), 7.83 (1H, m, ArH), 8.0 (1H, dd, $J = 4.4, 2.2$ Hz, ArH), 11.60 (1H, br s, NH); ^{13}C NMR ($\text{DMSO-}d_6$, 75 MHz, δ) 32.9, 41.7, 55.5, 55.6, 112.1, 112.5, 114.1, 115.7, 117.7, 120.7, 129.4, 131.8, 137.7, 138.8, 147.6, 148.8, 149.9, 160.9; MS (EI) m/z 404 (M^+ , 8.5), 226 (4.04), 164 (100), 151 (14.19). *Anal.* Calcd for $\text{C}_{18}\text{H}_{17}\text{N}_2\text{O}_4\text{Br}$: C, 53.35; H, 4.23; N, 6.91. Found: C, 53.47; H, 4.55; N, 6.72.

7-Chloro-3-(3,4-dimethoxyphenethyl)quinazoline-2,4(1H,3H)-dione (5c): colorless solid, mp 226-228°C; IR (KBr) (ν , cm^{-1}) 3292, 1715, 1644, 1587; ^1H NMR ($\text{DMSO-}d_6$, 300 MHz, δ) 2.80 (2H, t, $J = 7.1$ Hz, CH_2), 3.40 (3H, s, OMe), 3.73 (3H, s, OMe), 4.08 (2H, t, $J = 7.4$ Hz, NCH_2), 6.70 (1H, dd, $J = 1.7, 8.0$ Hz, ArH), 6.78 (1H, s, ArH), 6.85 (1H, d, $J = 8.1$ Hz, ArH), 7.15 (1H, d, $J = 1.8$ Hz, ArH), 7.20 (1H, dd, $J = 1.9, 8.4$ Hz, ArH), 7.89 (1H, dd, $J = 1.9, 8.4$ Hz, ArH), 11.52 (1H, br s, NH); ^{13}C NMR ($\text{DMSO-}d_6$, 75 MHz, δ) 33.0, 41.7, 55.5, 55.7, 112.1, 112.5, 112.9, 114.6, 120.7, 122.9, 129.6, 131.1, 139.5, 140.6, 147.6, 148.8, 150.1, 161.3; MS (EI) m/z 360 (M^+ , 9.5), 310 (4.67), 180 (7.44), 164 (100), 151 (14.19). *Anal.* Calcd for $\text{C}_{18}\text{H}_{17}\text{N}_2\text{O}_4\text{Cl}$: C, 59.92; H, 4.75; N, 7.76. Found: C, 59.81; H, 4.64; N, 7.97.

6,7-Dimethoxy-3-(3,4-dimethoxyphenethyl)quinazoline-2,4(1H,3H)-dione (5d): colorless solid, mp 233-234°C; IR (KBr) (ν , cm^{-1}) 3392, 1702, 1644, 1612, 1504; ^1H NMR (CDCl_3 , 300 MHz, δ) 2.95 (2H, t, $J = 8.0$ Hz, CH_2), 3.80 (3H, s, OMe), 3.81 (3H, s, OMe), 3.84 (3H, s, OMe), 3.85 (3H, s, OMe), 4.23 (2H, t, $J = 7.9$ Hz, NCH_2), 6.50 (1H, s, ArH), 6.78-6.91 (3H, m, ArH), 7.61 (1H, s, ArH), 9.60 (1H, br s, NH);

¹³C NMR (CDCl₃, 75 MHz,) 33.7, 42.4, 55.9 (2 C), 56.3 (2 C), 107.0, 108.23, 111.4, 112.3, 120.9, 125.9, 131.2, 134.2, 146.3, 147.8, 149.0, 151.7, 155.6, 161.8; MS (EI) m/z 386 (M⁺, 4.52), 207 (4.03), 164 (100), 149 (9.90). *Anal.* Calcd for C₂₀H₂₂N₂O₆: C, 62.17; H, 5.74; N, 7.25. Found: C, 62.11; H, 5.52; N, 7.47.

3-(3,4-Dimethoxyphenethyl)thieno[3,2-*b*]pyrimidine-2,4(1*H*, 3*H*)-dione (5e): colorless solid, mp 207-208°C; IR (KBr) (ν, cm⁻¹) 3291, 1702, 1638, 1510, 1436; ¹H NMR (CDCl₃, 300 MHz, δ) 2.96 (2H, t, *J* = 7.9 Hz, CH₂), 3.85 (3H, s, OMe), 3.87 (3H, s, OMe), 4.27 (2H, t, *J* = 7.9 Hz, NCH₂), 6.79-6.88 (3H, m, ArH), 6.92 (1H, d, *J* = 5.1 Hz, ArH), 7.85 (1H, d, *J* = 5.1 Hz, ArH), 10.82 (1H, br s, NH); ¹³C NMR (CDCl₃, 75 MHz,) 33.6, 42.5, 55.8, 55.8, 111.2, 112.1, 113.1, 116.5, 120.9, 131.0, 135.3, 143.5, 147.62, 148.8, 153.0, 158.4; MS (EI) m/z 332 (M⁺, 10.68), 318 (96), 164 (100), 149 (13.86). *Anal.* Calcd for C₁₆H₁₆N₂O₄S: C, 57.82; H, 4.85; N, 8.43; S, 9.65. Found: C, 58.03; H, 4.98; N, 8.23; S, 9.48.

5,6-Dihydro-2,3-dimethoxyisoquino[1,2-*b*]quinazolin-8-ones (6a-d); 5,6-Dihydro-2,3-dimethoxythieno[3',2':4,5]pyrimido[2,1-*a*]isoquinolin-8-one (6e); 5,6-Dihydro-2,3-dimethoxy[3]benzazepino[2,3-*b*]quinazoline-8,14-dione (8a-e) and 9,13*b*-Dihydro-11,12-dimethoxy-13*b*-phenyl-8(*H*)-isoquino[2,1-*c*]quinazoline-6-carbonitriles (11a-b); General Procedure

To a suspension of **3a-e/5a-e/10a-b** (0.45 – 0.73 mmol) and P₂O₅ (640 – 1036 mg, 5.5 – 7.3 mmol) in *m*-xylene (20 - 25 mL), POCl₃ (1.23 – 1.97 mL, 13.17 – 21.37 mmol) was added at rt and the reaction mixture was heated at 130°C for 12-16 h [4-5 h in case of **10a-b**] (monitored by TLC). The mixture was cooled down to rt, poured slowly into saturated potassium bicarbonate solution. The upper xylene layer was separated out. Aqueous layer was extracted with CHCl₃ (3 × 20 mL). The combined organic extract was washed with water (20 mL), dried (MgSO₄) and the solvent was evaporated under reduced pressure to afford crude **8a-e/6a-e/11a-b**, which was purified by passing through silica gel column using *n*-hexane-EtOAc [**8a-e** (3:2)/**6a-e** (3:1)/**11a-b** (4:1)] as eluent.

5,6-Dihydro-2,3-dimethoxyisoquino[1,2-*b*]quinazolin-8-one (6a): colorless crystals (CH₂Cl₂-*n*-hexane), mp 248-249°C (lit.,^{18a} 249-250 °C); IR, ¹H and ¹³C NMR and MS spectroscopic data are reported in the literature.¹⁸

10-Bromo-5,6-dihydro-2,3-dimethoxyisoquino[1,2-*b*]quinazolin-8-one (6b): colorless needles (CHCl₃-

n-hexane), mp 238-240°C; IR (KBr) (ν , cm^{-1}) 1657, 1587, 1548; ^1H NMR (CDCl_3 , 300 MHz, δ) 3.04 (2H, t, $J = 6.5$ Hz, CH_2), 3.97 (3H, s, OMe), 4.03 (3H, s, OMe), 4.39 (2H, t, $J = 6.5$ Hz, CH_2), 6.74 (1H, s, ArH), 7.63 (1H, d, $J = 8.7$ Hz, ArH), 7.81 (1H, dd, $J = 8.7, 2.7$ Hz, ArH), 7.94 (1H, s, ArH), 8.42 (1H, d, $J = 1.9$ Hz, ArH); ^{13}C NMR (CDCl_3 , 75 MHz,) 26.9, 39.9, 56.1, 56.2, 109.7, 109.9, 119.4, 121.5, 121.8, 129.1, 129.4, 131.0, 137.3, 146.8, 148.6, 149.7, 152.4, 160.7. MS (EI) m/z 386 (M^+ , 100), 371 (27.30), 355 (14.02). *Anal.* Calcd for $\text{C}_{18}\text{H}_{15}\text{N}_2\text{O}_3\text{Br}$: C, 55.83; H, 3.90; N, 7.23. Found: C, 55.59; H, 3.78; N, 7.36.

11-Chloro-5,6-dihydro-2,3-dimethoxyisoquino[1,2-*b*]quinazolin-8-one (6c): colorless needles (CHCl_3 -*n*-hexane), mp 240-242°C; IR (KBr) (ν , cm^{-1}) 1664, 1584, 1545; ^1H NMR (CDCl_3 , 300 MHz, δ) 2.99 (2H, t, $J = 6.5$ Hz, CH_2), 3.81 (3H, s, OMe), 3.99 (3H, s, OMe), 4.35 (2H, t, $J = 6.4$ Hz, NCH_2), 6.69 (1H, s, ArH), 7.33 (1H, dd, $J = 1.7, 8.6$ Hz, ArH), 7.71 (1H, d, $J = 2.0$ Hz, ArH), 7.90 (1H, s, ArH), 8.19 (1H, d, $J = 8.5$ Hz, ArH); ^{13}C NMR (CDCl_3 , 75 MHz,) 26.9, 39.7, 56.1, 56.2, 109.6, 110.0, 118.8, 121.4, 125.9, 126.7, 128.3, 131.1, 140.3, 148.6, 148.9, 150.4, 152.5, 161.3; MS (EI) m/z 342 (M^+ , 100), 327 (31.31), 311 (22.31). *Anal.* Calcd for $\text{C}_{18}\text{H}_{15}\text{N}_2\text{O}_3\text{Cl}$: C, 63.07; H, 4.41; N, 8.17. Found: C, 62.96; H, 4.59; N, 8.31.

5,6-Dihydro-2,3,10,11-tetramethoxyisoquino[1,2-*b*]quinazolin-8-one (6d): colorless solid (CHCl_3 -*n*-hexane), mp 259-261°C; IR (KBr) (ν , cm^{-1}) 1668, 1587, 1541; ^1H NMR (CDCl_3 , 300 MHz, δ) 3.02 (2H, t, $J = 6.5$ Hz, CH_2), 3.96 (3H, s, OMe), 4.01 (3H, s, OMe), 4.04 (6H, s, 2 x OMe), 4.40 (2H, t, $J = 6.5$ Hz, NCH_2), 6.73 (1H, s, ArH), 7.18 (1H, s, ArH), 7.60 (1H, s, ArH), 7.95 (1H, s, ArH); ^{13}C NMR (CDCl_3 , 75 MHz,) 28.9, 39.6, 56.1, 56.2, 56.3, 56.4, 108.6, 109.7, 111.2, 112.1, 120.9, 127.8, 134.1, 143.3, 146.2, 147.6, 148.9, 152.3, 155.4, 161.7; MS (EI) m/z 369 ($\text{M}^+ + 1$, 7.14), 355 (38.13), 341 (8.99), 281 (67.64), 221 (33.24), 207 (100), 191 (10.64), 147 (29.89). *Anal.* Calcd for $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_5$: C, 65.21; H, 5.47; N, 7.60. Found: C, 65.46; H, 5.68; N, 7.41.

5,6-Dihydro-2,3-dimethoxythieno[3',2':4,5]pyrimido[2,1-*a*]isoquinolin-8-one (6e): colorless solid (CHCl_3 -*n*-hexane), mp 257-258 ° C (decomp); IR (KBr) (ν , cm^{-1}) 1657, 1536, 1500; ^1H NMR (CDCl_3 , 300 MHz, δ) 3.04 (2H, t, $J = 6.1$ Hz, CH_2), 3.97 (3H, s, OMe), 4.03 (3H, s, OMe), 4.43 (2H, t, $J = 6.1$ Hz, NCH_2), 6.75 (1H, s, ArH), 7.36 (1H, d, $J = 5.3$ Hz, ArH), 7.77 (1H, d, $J = 5.3$ Hz, ArH), 7.92 (1H, s, ArH); ^{13}C NMR (CDCl_3 , 75 MHz,) 27.1, 39.6, 56.1, 56.2, 109.6, 109.9, 121.7, 125.2, 125.9, 130.7, 134.1, 148.6, 151.2, 152.2, 156.6, 158.0; MS (EI) m/z 314 (M^+ , 100), 299 (21.28), 283 (9.7). *Anal.*

Calcd for C₁₆H₁₄N₂O₃S : C, 61.13; H, 4.49; N, 8.91; S, 10.20. Found: C, 60.93; H, 4.61; N, 8.74; S, 10.36.

5,6-Dihydro-2,3-dimethoxy[3]benzazepino[2,3-*b*]quinazoline-8,14-dione (8a): colorless solid (CH₂Cl₂-*n*-hexane), mp 269-271°C (decomp); IR (KBr) (ν, cm⁻¹) 1664, 1587, 1507; ¹H NMR (CDCl₃, 300 MHz, δ) 3.38 (2H, t, *J* = 5.3 Hz, CH₂), 3.94 (6H, br s, 2 x OMe), 4.64 (2H, t, *J* = 5.0 Hz, NCH₂), 6.69 (1H, s, ArH), 7.47 (1H, s, ArH), 7.55 (1H, t, *J* = 6.7 Hz, ArH), 7.76-7.84 (2H, m, ArH), 8.33 (1H, d, *J* = 7.9 Hz, ArH); ¹³C NMR (CDCl₃, 75 MHz,) 34.5, 41.8, 56.0, 56.2, 111.9, 112.50, 121.9, 125.9, 126.9, 127.4, 128.1, 128.7, 134.7, 134.8, 147.5, 148.1, 153.7, 160.0, 187.8; FAB-MS *m/z* 336 (M⁺, 100), 321 (40.55), 308 (23.83), 293 (12.24), 191 (15.06), 168 (10.72). *Anal.* Calcd for C₁₉H₁₆N₂O₄: C, 67.85; H, 4.79; N, 8.33. Found: C, 67.74; H, 4.63; N, 8.54.

10-Bromo--5,6-dihydro-2,3-dimethoxy[3]benzazepino[2,3-*b*]quinazoline-8,14-dione (8b): colorless needles (CHCl₃-*n*-hexane), mp 261-263°C; IR (KBr) (ν, cm⁻¹) 1676, 1593, 1507; ¹H NMR (CDCl₃, 300 MHz, δ) 3.37 (2H, t, *J* = 5.3 Hz, CH₂), 3.94 (6H, s, 2 x OMe), 4.63 (2H, t, *J* = 4.9 Hz, CH₂), 6.16 (1H, s, ArH), 7.46 (1H, s, ArH), 7.69 (1H, d, *J* = 8.7 Hz, ArH), 7.86 (1H, dd, *J* = 8.6, 2.0 Hz, ArH), 8.46 (1H, d, *J* = 2.0 Hz, ArH); ¹³C NMR (CDCl₃, 75 MHz,) 34.4, 42.0, 56.1, 56.3, 111.9, 112.5, 122.0, 123.2, 127.2, 129.5, 130.4, 134.8, 138.0, 146.4, 148.2, 153.8, 154.0, 158.9, 187.5; MS (EI) *m/z* 416 (M⁺+2, 95.64), 415 (M⁺+1, 38.47), 414 (M⁺, 100), 399 (40.06), 385 (27.03), 207 (10.28), 191 (19.70). *Anal.* Calcd for C₁₉H₁₅N₂O₄Br: C, 54.96; H, 3.64; N, 6.75. Found: C, 55.07; H, 3.55; N, 6.67.

11-Chloro-5,6-dihydro-2,3-dimethoxy[3]benzazepino[2,3-*b*]quinazoline-8,14-dione (8c): colorless needles (CHCl₃-*n*-hexane), mp 254-255°C; IR (KBr) (ν, cm⁻¹) 1676, 1648, 1587; ¹H NMR (CDCl₃, 300 MHz, δ) 3.37 (2H, t, *J* = 5.6 Hz, CH₂), 3.94 (6H, s, 2 x OMe), 4.61 (2H, t, *J* = 4.9 Hz, CH₂), 6.69 (1H, s, ArH), 7.45 (1H, s, ArH), 7.49 (1H, dd, *J* = 2.0, 8.6 Hz, ArH), 7.78 (1H, d, *J* = 2.6 Hz, ArH), 8.25 (1H, d, *J* = 8.5 Hz, ArH); ¹³C NMR (CDCl₃, 75 MHz,) 34.4, 41.3, 56.07, 55.3, 111.9, 112.5, 120.3, 127.2, 128.1, 128.4, 128.7, 134.8, 141.0, 148.2, 148.5, 153.9, 154.8, 159.4, 187.5; MS (EI) *m/z* 372 (M⁺+2, 37.61), 371 (M⁺+1, 33.25), 370 (M⁺, 100), 355 (46.12), 341 (26.22), 327 (12.79), 311 (11.78), 299 (12.34), 191 (16.53). *Anal.* Calcd for C₁₉H₁₅N₂O₄Cl: C, 61.55; H, 4.08; N, 7.56. Found: C, 61.37; H, 3.85; N, 7.66.

5,6-Dihydro-2,3,10,11-tetramethoxy[3]benzazepino[2,3-*b*]quinazoline-8,14-dione (8d): colorless

solid (CHCl₃-*n*-hexane), mp 277-278 °C; IR (KBr) (ν, cm⁻¹) 1660, 1651, 1596, 1497, 1449; ¹H NMR (CDCl₃, 300 MHz, δ) 3.36 (2H, t, *J* = 5.6 Hz, CH₂), 3.93 (6H, s, 2 × OMe), 3.97 (3H, s, OMe), 4.02 (3H, s, OMe), 4.64 (2H, t, *J* = 3.8 Hz, NCH₂), 6.68 (1H, s, ArH), 7.24 (1H, s, ArH), 7.48 (1H, s, ArH), 7.63 (1H, s, ArH); ¹³C NMR (CDCl₃, 75 MHz,) 34.1, 41.8, 56.1, 56.2, 56.3, 56.4, 105.9, 109.1, 112.1, 112.7, 115.5, 127.6, 134.9, 143.8, 148.2, 150.2, 153.7, 155.2, 159.2, 187.7; FAB-MS *m/z* 397 (M⁺, 100), 381 (15.13), 257 (11.47), 164 (39.75), 154 (43.57), 149 (63.35), 136 (60.42). *Anal.* Calcd for C₂₁H₂₀N₂O₆: C, 63.63; H, 5.09; N, 7.07. Found: C, 63.71; H, 5.13; N, 7.41.

5,6-Dihydro-2,3-dimethoxythieno[2',3':4,5]pyrimido[2,1-*b*][3]benzazepine-3,13-dione (8e) light yellow solid (CH₂Cl₂-*n*-hexane), mp 257-258 °C; IR (KBr) (ν, cm⁻¹) 1664, 1590, 1507; ¹H NMR (CDCl₃, 300 MHz, δ) 3.37 (2H, t, *J* = 4.8 Hz, CH₂), 3.94 (6H, br s, 2 x OMe), 4.67 (2H, t, *J* = 5.0 Hz, NCH₂), 6.68 (1H, s, ArH), 7.41 (1H, d, *J* = 5.3 Hz, ArH), 7.46 (1H, s, ArH), 7.82 (1H, d, *J* = 5.5 Hz, ArH); ¹³C NMR (CDCl₃, 75 MHz,) 34.4, 41.5, 56.1, 56.3, 111.9, 112.5, 123.9, 125.9, 126.1, 127.3, 134.8, 135.0, 148.2, 153.9, 156.0, 156.4, 187.6; MS (EI) *m/z* 342 (M⁺, 100), 327 (45.59), 312 (25.53). *Anal.* Calcd for C₁₇H₁₄N₂O₄S: C, 59.64; H, 4.12; N, 8.18, S, 9.37. Found: C, 59.42; H, 4.25; N, 8.21; S, 9.16.

2-Chloro-9,13b-dihydro-11,12-dimethoxy-13b-phenyl-8(*H*)-isoquino[2,1-*c*]quinazoline-6-carbonitrile (11a): colorless needles (EtOH-benzene), mp: 222-223 °C; IR (KBr) (ν, cm⁻¹) 1593, 1571, 1539; ¹H NMR (DMSO-*d*₆, 500 MHz,) 2.75 (1H, dd, *J* = 4.0, 16.9 Hz, CH₂); 3.07 (1H, ddd, *J* = 5.0, 9.1, 16.8 Hz, CH₂), 3.49 (1H, ddd, *J* = 2.8, 5.4, 12.5 Hz, NCH₂), 3.53 (3H, s, OMe), 3.79 (3H, s, OMe), 4.07 (1H, dd, *J* = 5.4, 13.9 Hz, NCH₂), 6.36 (1H, s, ArH), 6.65 (1H, d, *J* = 2.2 Hz, ArH), 6.93 (1H, s, ArH), 7.12 (2H, d, *J* = 6.9 Hz, ArH), 7.21 (1H, d, *J* = 8.4 Hz, ArH), 7.34-7.43 (4H, m, ArH); ¹³C NMR (DMSO-*d*₆, 125 MHz,) 28.3, 45.5, 56.4, 56.4, 66.9, 112.2, 113.4, 113.9, 127.2, 127.4, 128.4, 128.6, 129.0 (2C), 129.1, 129.4 (2C), 129.7, 130.0, 131.8, 136.2, 140.0, 145.4, 147.6, 149.5; FAB-MS *m/z* 430 (M⁺+1, 53.93), 429 (M⁺, 12.13), 352 (61.56), 321 (40.55), 308 (23.83), 289 (9.54), 154 (100), 136 (84.14). *Anal.* Calcd for C₂₅H₂₀N₃O₂Cl: C, 69.85; H, 4.69; N, 9.77. Found: C, 69.73; H, 4.53; N, 9.51.

9,13b-Dihydro-11,12-dimethoxy-3-methyl-13b-phenyl-8(*H*)-isoquino[2,1-*c*]quinazoline-6-carbonitrile (11b): colorless needles (EtOH-benzene), mp 216-217 °C, IR (KBr) (ν, cm⁻¹) 1584, 1548, 1509,

1456; ¹H NMR (DMSO-*d*₆, 300 MHz,) 2.31(3H, s, CH₃), 2.68 (1H, dd, *J* = 4.7, 16.3 Hz, CH₂), 3.26 (1H, ddd, *J* = 3.4, 7.2, 16.5 Hz, CH₂), 3.42 (1H, ddd, *J* = 2.8, 4.9, 14.0 Hz, NCH₂), 3.64 (3H, s, OMe), 3.89 (3H, s, OMe), 4.06 (1H, ddd, *J* = 1.5, 6.9, 14.2 Hz, NCH₂), 6.51 (1H, s, ArH), 6.54 (1H, s, ArH), 6.66 (1H, s, ArH), 6.92 (1H, dd, *J* = 0.9, 7.9 Hz, ArH), 7.04 (1H, s, ArH), 7.15 (2H, br t, *J* = 3.8 Hz, ArH), 7.30 (3H, m, ArH); ¹³C NMR (DMSO-*d*₆, 75 MHz,) 20.9, 27.5, 44.0, 55.9, 55.9, 67.0, 111.0, 112.1, 112.7, 124.4, 125.4, 125.9, 127.7, 127.9, 128.2, 128.9, 129.0 (2C), 129.9, 135.6, 138.9, 139.7, 145.7, 147.0, 148.6; FAB-MS *m/z* 410 (M⁺+1, 72.55 %), 409 (M⁺, 5.15), 383 (3.0), 332 (100), 165 (9.65), 91 (8.84), 77 (8.68). *Anal.* Calcd for C₂₆H₂₃N₃O₂: C, 76.26; H, 5.66; N, 10.26. Found: C, 76.42; H, 5.82; N, 9.98.

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