HETEROCYCLES, Vol. 57, No. 8, 2002, pp. 1471 - 1485, Received, 7th May, 2002

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

Pramod K. Mohanta and Kyongtae Kim*

School of Chemistry and Molecular Engineering, Seoul National University, Seoul 151-742, South Korea

**Abstract -** Reactions of dithiazoles (**1a-e**) and (**9a-b**) with 3,4-dimethoxy-phenethylamine (**2**) in $CH_2Cl_2$ 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 $P_2O_5/POCl_3$ 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.

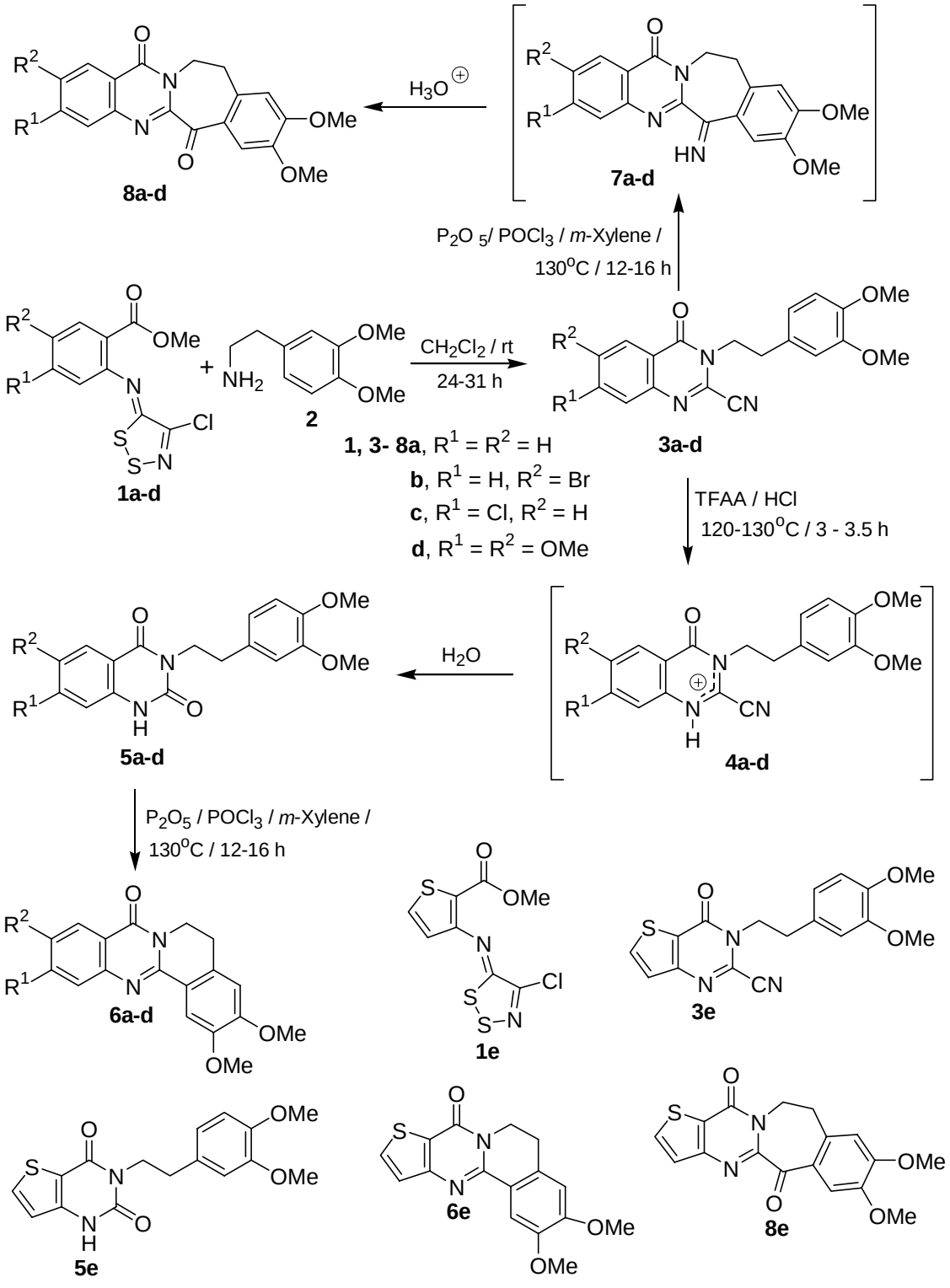
Tetracyclic quinazolin-4(3*H*)-one ring systems form the characteristic framework of numerous heterocyclic physiologically active compounds. For instance, a number of alkaloids such as tryptanthrin (also known as couroptitine),[1] alantrypinone,[2] asperlicin C,[3] circumdatin F,[3] and sclerotigenin[3] 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*)-one[4] skeleton exhibit a multitude of interesting pharmacological properties such as cardiotonic,[5] analgesic,[6] cytotoxic[7] and neurokinin NK1 receptor activities.[8] Similarly, quinazolinedione template appears in a wide rage 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 $\alpha_{1A}$- adrenoceptor antagoniststst.[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-dithiazoles[12] 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 aliphatic[13] 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 $P_2O_5$/$POCl_3$.

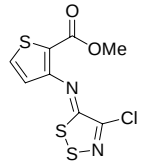
Dithiazoles (**1a-d**), used as starting materials for the synthesis of **3** are prepared according to the reported procedure[13] by condensation of methyl anthranilates with 4,5-dichloro-1,2-3-dithiazolium chloride (Appel's salt)[15] in pyridine/$CH_2Cl_2$ at room temperature. Reaction of **1a** with **2** in $CH_2Cl_2$ at room temparature 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 quinazolinocarboline 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 $P_2O_5$/$POCl_3$ 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 $P_2O_5/POCl_3$ in refluxing xylene to form (**6b-d** and **6e)**, respectively. On the other hand, when **3a** was treated with $POCl_3/P_2O_5$ directly in *m*-xylene, the linearly fused quinazolinone (**8a**) was obtained presumably *via* **7a** (Scheme 1).

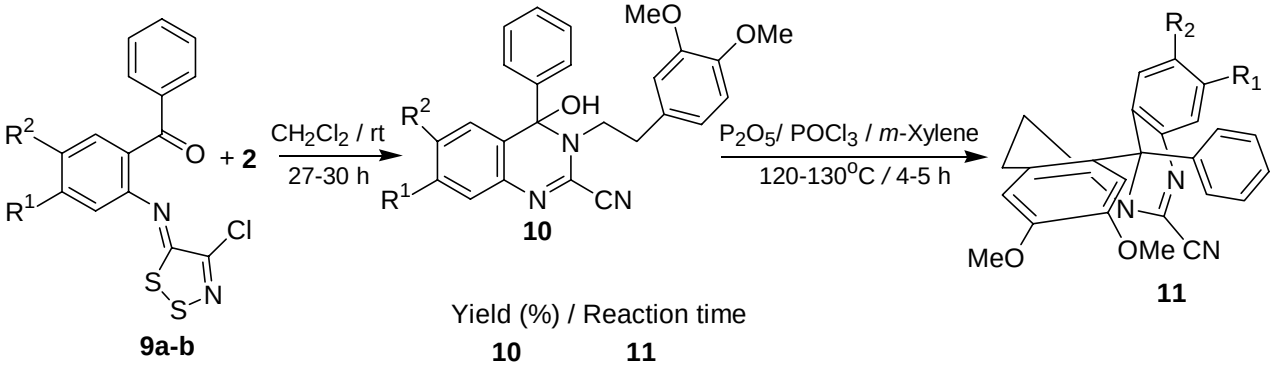



**Scheme 1**

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

| **1, 3-8** | Yield (%) / Time **3** | Yield (%) / Time **5** | Yield (%) / Time **6** | Yield (%) / Time **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 $CH_2Cl_2$ at room



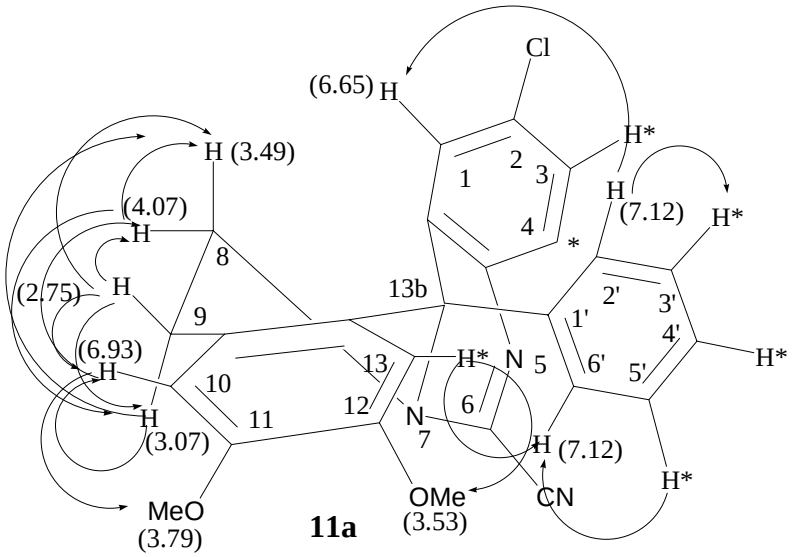

Yield (%) / Reaction time

| | **10** | **11** |
|---|---|---|
| **a**, $R^1 = H$, $R^2 = Cl$ | 60 (30 h) | 78 (5 h) |
| **b**, $R^1 = Me$, $R^2 = H$ | 62 (27 h) | 72 (4 h) |

**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 $P_2O_5/POCl_3$ 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 protons[19] in the $^1$H 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 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 $CH_2Cl_2$ (25 –35 mL), a solution of **2** (140 - 974 mg, 0.77 – 5.37 mmol) in $CH_2Cl_2$ (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 shaked with $CH_2Cl_2$ (2 × 20 mL) to extract the product [compounds (**10a-b**) were extracted with $CHCl_3$ (3 × 20 mL)]. The combined organic extract was washed with water (30 mL), dried ($MgSO_4$) 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 ($CH_2Cl_2$-*n*-hexane), mp 159-160˚C; IR (KBr) (ν, $cm^{-1}$) 1686, 1584, 1510; $^1$H NMR ($CDCl_3$, 300 MHz, δ) 3.08 (2H, t, *J* = 7.6 Hz, $CH_2$), 3.79 (3H, s, OMe), 3.86 (3H, s, OMe), 4.48 (2H, t, *J* = 7.6 Hz, $NCH_2$ ), 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); $^{13}$C NMR ($CDCl_3$, 75 MHz, δ ) 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 $C_{19}H_{17}N_3O_3$: 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 ($CHCl_3$-*n*-hexane), mp 193-194ºC; IR (KBr) (ν, $cm^{-1}$) 1686, 1571, 1507, 1459 ; $^1$H NMR ($CDCl_3$, 300 MHz, δ) 3.08 (2H, t, *J* = 7.5 Hz, $CH_2$), 3.81 (3H, s, OMe), 3.86 (3H, s, OMe), 4.48 (2H, t, *J* = 7.6 Hz, $NCH_2$), 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); $^{13}$C NMR ($CDCl_3$, 75 MHz, δ ) 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 $C_{19}H_{16}N_3O_3Br$: 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, δ ) 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 $C_{19}H_{16}N_3O_3Cl$: 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, δ ) 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 $C_{21}H_{21}N_3O_5$: 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, δ ) 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 $C_{17}H_{15}N_3O_3S$: 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 ($M^+$+1, 11.94), 447 ($M^+$, 7.18), 267 (13.34), 165 (100), 154 (60.82). *Anal*. Calcd for $C_{25}H_{22}N_3O_3Cl$: 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; $^1$H 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 ($M^+$+1, 25.98), 427 ($M^+$, 12.22), 307 (13.10), 247 (12.50), 165 (43.18), 154 (100), 136 (81.07). *Anal*. Calcd for $C_{26}H_{25}N_3O_3$: 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(1*H*,3*H*)-diones (5a-d) and 3-(3,4-dimethoxyphenethyl)thieno[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-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(1*H*,3*H*)-dione (5a):** colorless crystals, mp 199-200˚C

(lit.,[17] 202-203˚C); IR (KBr) (ν, $cm^{-1}$) 3456, 1702, 1648, 1510; $^1$H 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 ($M^+$+ 1, 50.5), 326 ($M^+$, 40.2), 164 (89.8), 154 (100). *Anal*. Calcd for $C_{18}H_{18}N_2O_4$: 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(1*H*,3*H*)-dione (5b):** colorless solid, mp 231-233ºC; IR (KBr) (ν, $cm^{-1}$) 3340, 1708, 1648, 1507; $^1$H NMR (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 (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 $C_{18}H_{17}N_2O_4Br$: 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(1*H*,3*H*)-dione (5c):** colorless solid, mp 226-228˚C; IR (KBr) (ν, $cm^{-1}$) 3292, 1715, 1644, 1587; $^1$H NMR (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 (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 $C_{18}H_{17}N_2O_4Cl$: 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(1*H*,3*H*)-dione (5d):** colorless solid, mp 233-234˚C; IR (KBr) (ν, $cm^{-1}$) 3392, 1702, 1644, 1612, 1504; $^1$H 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);

$^{13}$C NMR ($CDCl_3$, 75 MHz, δ) 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 $C_{20}H_{22}N_2O_6$: 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 207-208ºC; IR (KBr) (υ, $cm^{-1}$) 3291, 1702, 1638, 1510, 1436; $^1$H NMR ($CDCl_3$, 300 MHz, δ) 2.96 (2H, t, *J* = 7.9 Hz, $CH_2$), 3.85 (3H, s, OMe), 3.87 (3H, s, OMe), 4.27 (2H, t, *J* = 7.9 Hz, $NCH_2$), 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); $^{13}$C NMR ($CDCl_3$, 75 MHz, δ) 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 $C_{16}H_{16}N_2O_4S$: 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 $P_2O_5$ (640 – 1036 mg, 5.5 – 7.3 mmol) in *m*-xylene (20 - 25 mL), $POCl_3$ (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 $CHCl_3$ (3 × 20 mL). The combined organic extract was washed with water (20 mL), dried ($MgSO_4$) 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 ($CH_2Cl_2$-*n*-hexane), mp 248-249˚C (lit.,[18a] 249-250 ˚C); IR, $^1$H and $^{13}$C 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 ($CHCl_3$-

*n*-hexane), mp 238-240ºC; IR (KBr) (υ, $cm^{-1}$) 1657, 1587, 1548; $^1$H 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, δ) 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 $C_{18}H_{15}N_2O_3Br$: 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; $^1$H 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, δ) 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 $C_{18}H_{15}N_2O_3Cl$ : 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; $^1$H 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, δ) 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 ($M^+$+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 $C_{20}H_{20}N_2O_5$ : 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 º C (decomp); IR (KBr) (ν, $cm^{-1}$) 1657, 1536, 1500; $^1$H 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, δ) 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 $C_{16}H_{14}N_2O_3S$ : 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 ($CH_2Cl_2$-*n*- hexane), mp 269-271˚C (decomp); IR (KBr) (ν, $cm^{-1}$) 1664, 1587, 1507; $^1$H NMR ($CDCl_3$, 300 MHz, δ) 3.38 (2H, t, *J* = 5.3 Hz, $CH_2$), 3.94 (6H, br s, 2 x OMe), 4.64 (2H, t, *J* = 5.0 Hz, $NCH_2$), 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); $^{13}$C NMR ($CDCl_3$, 75 MHz, δ) 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 $C_{19}H_{16}N_2O_4$: 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 ($CHCl_3$-*n*-hexane), mp 261-263ºC; IR (KBr) (ν, $cm^{-1}$) 1676, 1593, 1507; $^1$H NMR ($CDCl_3$, 300 MHz, δ) 3.37 (2H, t, *J* = 5.3 Hz, $CH_2$), 3.94 (6H, s, 2 x OMe ), 4.63 (2H, t, *J* = 4.9, $CH_2$), 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); $^{13}$C NMR ($CDCl_3$, 75 MHz, δ) 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 $C_{19}H_{15}N_2O_4Br$: 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 ($CHCl_3$-*n*-hexane), mp 254-255˚C; IR (KBr) (ν, $cm^{-1}$) 1676, 1648, 1587; $^1$H NMR ($CDCl_3$, 300 MHz, δ) 3.37 (2H, t, *J* = 5.6 Hz, $CH_2$), 3.94 (6H, s, 2 x OMe), 4.61 (2H, t, *J* = 4.9 Hz, $CH_2$), 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); $^{13}$C NMR ($CDCl_3$, 75 MHz, δ) 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 $C_{19}H_{15}N_2O_4Cl$: 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 ($CHCl_3$-*n*-hexane), mp 277-278 ºC; IR (KBr) (ν, $cm^{-1}$) 1660, 1651, 1596, 1497, 1449; $^1H$ NMR ($CDCl_3$, 300 MHz, δ) 3.36 (2H, t, *J* = 5.6 Hz, $CH_2$), 3.93 (6H, s, 2 × OMe), 3.97 (3H, s, OMe), 4.02 (3H, s, OMe), 4.64 (2H, t, *J* = 3.8 Hz, $NCH_2$), 6.68 (1H, s, ArH), 7.24 (1H, s, ArH), 7.48 (1H, s, ArH), 7.63 (1H, s, ArH); $^{13}C$ NMR ($CDCl_3$, 75 MHz, δ) 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 $C_{21}H_{20}N_2O_6$: 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 ($CH_2Cl_2$-*n*-hexane), mp 257-258˚C; IR (KBr) (ν, $cm^{-1}$) 1664, 1590, 1507; $^1H$ NMR ($CDCl_3$, 300 MHz, δ) 3.37 (2H, t, *J* = 4.8 Hz, $CH_2$), 3.94 (6H, br s, 2 x OMe), 4.67 (2H, t, *J* = 5.0 Hz, $NCH_2$), 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); $^{13}C$ NMR ($CDCl_3$, 75 MHz, δ) 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 $C_{17}H_{14}N_2O_4S$: 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-9,13*b*-dihydro-11,12-dimethoxy-13*b*-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, δ) 2.75 (1H, dd, *J* = 4.0, 16.9 Hz, $CH_2$); 3.07 (1H, ddd, *J* = 5.0, 9.1, 16.8 Hz, $CH_2$), 3.49 (1H, ddd, *J* = 2.8, 5.4, 12.5 Hz, $NCH_2$), 3.53 (3H, s, OMe), 3.79 (3H, s, OMe), 4.07 (1H, dd, *J* = 5.4, 13.9 Hz, $NCH_2$), 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);$^{13}C$ NMR (DMSO-$d_6$, 125 MHz, δ) 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 $C_{25}H_{20}N_3O_2Cl$: C, 69.85; H, 4.69; N, 9.77. Found: C, 69.73; H, 4.53; N, 9.51.

**9,13*b*-Dihydro-11,12-dimethoxy-3-methyl-13*b*-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; $^{1}$H NMR (DMSO-$d_6$, 300 MHz, $\delta$) 2.31(3H, s, $CH_3$), 2.68 (1H, dd, $J$ = 4.7, 16.3 Hz, $CH_2$), 3.26 (1H, ddd, $J$ = 3.4, 7.2, 16.5 Hz, $CH_2$), 3.42 (1H, ddd, $J$ = 2.8, 4.9, 14.0 Hz, $NCH_2$), 3.64 (3H, s, OMe), 3.89 (3H, s, OMe), 4.06 (1H, ddd, $J$ = 1.5, 6.9, 14.2 Hz, $NCH_2$), 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); $^{13}$C NMR (DMSO-$d_6$, 75 MHz, $\delta$) 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 $C_{26}H_{23}N_3O_2$: C, 76.26; H, 5.66; N, 10.26. Found: C, 76.42; H, 5.82; N, 9.98.

**ACKNOWLEDGEMENTS**

The authors thank Brain Korea-21 Research Foundation for financial support.

**REFERENCES**

1. J. P. Michael, *Natural Product Reports*, 1997, **17**, 605.
2. D. J. Hart and N.A. Magomedov, *J. Am. Chem. Soc.*, 2001, **123**, 5829.
3. B. B Snider and M.V. Busuyek, *Tetrahedron*, 2001, **57**, 3301.
4. (a) J. Bergman, 'The Alkaloids: The Quinazolinocarboline Alkaloids,' Vol. 21**,** ed. by A. R. Brossi, Academic Press, Inc. New York, 1983, pp. 29-54. (b) J. D. Freed, D. J. Hart, and N. A. Magomedov, *J. Org. Chem*., 2001, **66**, 839. (c) M.J. Deetz, J. P. Malerich, A. M. Beatty, and B. D. Smith, *Tetrahedron Lett*., 2001, **42**, 1851. (d) A. Witt and J. Bergman, *J. Org. Chem*., 2001, **66**, 2784. (e) K. C. Liu, M. H. Yen, J. W. Chern, and Y. O. Lin, *Arch. Pharm.*, 1983, **316**, 379.
5. (a) N. Shoji, A. Umeyama, T. Takemoto, A. Kajiwara, and Y. Ohizumi, *J. Pharm. Sci.*, 1986, **75**, 612. (b) Y. C. Kong, *Adv. Pharm. Ther*., 1982, **6**, 239.
6. Y. C. Kong, S. Y. Hu, F. K. Lau, C. T. Che, H. W. Yeung, S. Cheung, and C. C. Hwang, *Am. J. Chin. Med*., 1976, **4**, 105.
7. L.-M.Yang, C.-F. Chen, and K.-H. Lee, *Bioorg. and Med. Chem. Lett.*, 1995, **5**, 465. (b) Z.-Ze Ma, Y. Hano, T. Nomura, and Y.-J. Chen, *Heterocycles*, 1997, **46**, 541.
8. H. H. Sun, C. J. Barrow, D. M. Sedlock, A. M. Gillum, and R. Cooper, *J. Antibiotics*, 1994, **47**, 515.

9. (a) J. Russo, *J. Med. Chem.*, 1991, **34**, 1850. (b) D. W. Fry, A. J. Kraker, A. McMichael, L. A. Ambroso, J. M. Nelson, W. R. Leopold, R. W. Conners, and A. J. Bridges, *Science*, 1994, **265**, 1093.(c) T. Kotani, Y. Nagaki, A. Ishii, and Y. Konishi, *J. Med. Chem.*, 1997, **40**, 684. (d) N. J. Liverton, D. J. Armstrong, D. A. Claremon, D. C. Remy, J. J. Baldwin, R. J. Lynch, G. Zhang, and R. Gould, *Bioorg. and Med. Chem. Lett*., 1998, **8**, 483.

10. M. D. Meyer, R. J. Altenbach, H. Bai, F. Z. Basha, W. A. Carroll, J. F. Kerwin, S. A. J. Lebold, E. Lee, K. J. Patt, K. B. Sippy, K.Tietje, M. D.Wendt, M. E. Brune, S. A. Buckner, A. A. Hancok, and I. Drizin, *J. Med. Chem.*, 2001, **44**, 1971.(b) J. J. McNally and J. B. Press, *J. Org. Chem.*, 1991, **56**, 245.

11. M.-K. Jeon, K. Kim, and Y**.** Park, *Chem. Commun.*, 2001, 1412**.** (b) Y.- G. Chang and K. Kim, *Heterocycles*, 1999, **51**, 2653.

12. (a) T. Besson, G. Guillaumet, C. Lamazzi, and C. W. Rees, *Synlett*, 1997, 704. (b) K. Kim, *Sulfur Reports*, 1998, **21**, 147 and references cited therein.

13. H.-S. Lee, Y. G. Chang, and K. Kim, *J. Heterocycl. Chem.*, 1998, **35**, 659.

14. Y. G. Chang and K. Kim, *J. Chem. Soc., Perkin Trans.1*, submitted.

15. R. Appel, H. Janssen, M. Siray, and F. Knoch, *Chem. Ber.*, 1985, **118**, 1632.

16. P. K. Mohanta and K. Kim, *Tetrahedron Lett.*, 2002, **43**, 3993.

17. S. Hayao, H. J. Havera, W.G. Strycker, T. J. Leipzig, R. A. Kulp, and H. E. Hartzler, *J. Med. Chem.*,1965, **8**, 807.

18. (a) T. Kametani, T. Higa, C. V. Loc, M. Ihara, M. Koizumi, and K. Fukumoto, *J. Am. Chem. Soc.*, 1976, **98**, 6186. (b) I. Kanmacher, J.-F. Stambach, and L. Jung, *Heterocycles*, 1990, **31**, 2131.

19. D. R. Dalton, K. C. Ramey, H. J. Gisler, Jr., L. J. Lendvay, and A. Abraham, *J. Am. Chem. Soc.*, 1969, **91**, 9367.