Notes

Tetrahydropyrido[2,1-*b*]quinazolin-11-ones and Tetrahydropyrido[1,2-*a*]quinazolin-6-ones via Thermal Cyclization of 2-Substituted 4(3*H*)-Quinazolinones

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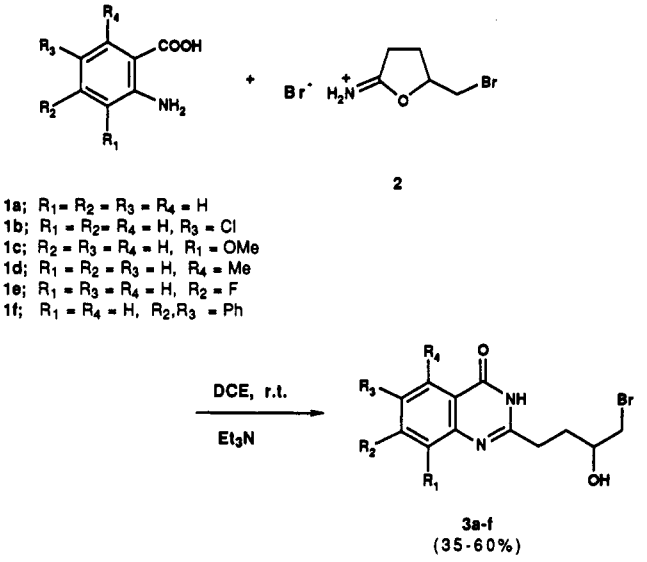
Received July 21, 1992

4-Quinazolinones are an important class of biologically active compounds. In particular 2-styryl-4(3*H*)-quinazolinones are interesting as antimitotic anticancer agents,[1] 4(1*H*)-quinazolinones show a potent antiinflammatory and antiallergic activity,[2] a series of 3-aryl-4(3*H*)-quinazolinones, structurally related to methaqualone, have anticonvulsant activity,[3] and the sedative–hypnotic properties of 4(3*H*)-quinazolinones are widely documented.[4] Owing to the importance of this class of heterocycles, the construction of the quinazolinone ring has been extensively studied.[5]

Analogous to our recent work[6] in which we described the synthesis of benzazole heterocycles through intramolecular condensation reactions[7] of *o*-phenylene dinucleophiles with a cyclic imidate, we applied this methodology here to the synthesis of 2-substituted quinazolinones.

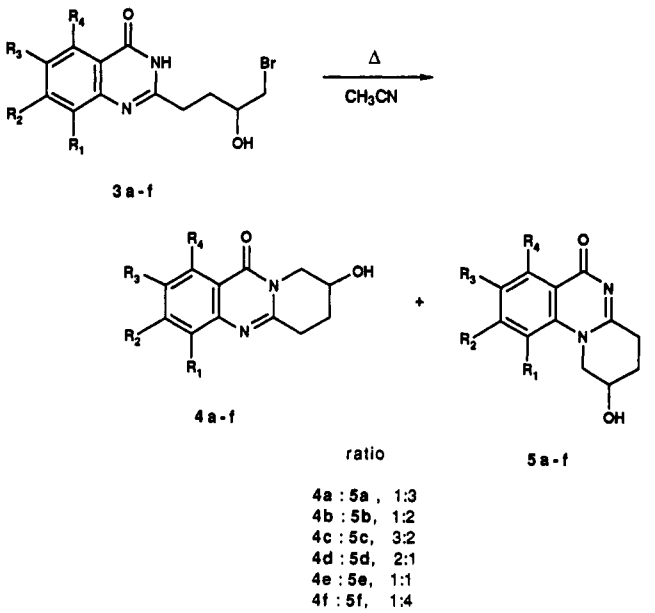
The reaction of 5-(bromomethyl)-2-iminotetrahydrofuran hydrobromide (**2**), generated in situ from 4-pentenamide and bromine, with substituted anthranilic acids **1**[8] afforded the 2-substituted 4(3*H*)-quinazolinones **3** in satisfactory yields using mild conditions (Scheme I). This reaction can be viewed as a transformation of a cyclic imidate with an exocyclic imino nitrogen into a compound in which the imidate function lies completely within the ring. Compounds **3a–f** are interesting both as new 2-substituted quinazolinones and because the bromomethyl moiety at the δ-position is suitable for the synthesis of annulated products through a intramolecular cyclization as observed for substituted benzimidazole.[6] It is well documented that quinazoline alkaloids are nitrogen-bridgehead compounds with interesting biological activities as antiallergic, i.e. pyrido[2,1-*b*]quinazolines,[9] and as bronchodilatory agents, e.g. vasiscine.[10]

Scheme I



1a; $R_1 = R_2 = R_3 = R_4 = H$
1b; $R_1 = R_2 = R_4 = H$, $R_3 = Cl$
1c; $R_2 = R_3 = R_4 = H$, $R_1 = OMe$
1d; $R_1 = R_2 = R_3 = H$, $R_4 = Me$
1e; $R_1 = R_3 = R_4 = H$, $R_2 = F$
1f; $R_1 = R_4 = H$, $R_2,R_3 = Ph$

Scheme II



4a : 5a , 1:3
4b : 5b, 1:2
4c : 5c, 3:2
4d : 5d, 2:1
4e : 5e, 1:1
4f : 5f, 1:4

Refluxing 1-bromo-4-[3,4-dihydro-4-oxoquinazolin-2-yl]-2-butanols **3a–f** in acetonitrile for 3–10 h afforded practically quantitative yields with variable ratios of the regioisomeric tetrahydropyrido[2,1-*b*]quinazolinones **4** and tetrahydropyrido[1,2-*a*]quinazolinones **5** (Scheme II). The different ratios of the compounds **4** and **5** are probably due to the influence of the aromatic substituents on the equilibrium between the amide (3-H) and the vinylogous amide (1-H) forms.[11]

(1) Jiang, J. B.; Hesson, D. P.; Dusak, B. A.; Dexter, D. L.; Kang, G. J.; Hamel, E. *J. Med. Chem.* **1990**, *33*, 1721.
(2) Ozaki, K.-I.; Yamada, Y.; Oine, T. *Chem. Pharm. Bull.* **1983**, *31*, 2234.
(3) Wolfe, J. F.; Rathmann, T. L.; Sleevi, M. C.; Campbell, J. A.; Greenwood, T. D. *J. Med. Chem.* **1990**, *33*, 161.
(4) Buyuktimkin, S. *Arch. Pharmacol.* **1986**, *319*, 933; Kornet, M. J. *Eur. J. Med. Chem.-Chim. Ther.* **1986**, *21*, 529. Vaidya, N. A.; Panos, C. H.; Kite, A.; Iturrian, W. B.; Blanton, C. D. Jr. *J. Med. Chem.* **1983**, *26*, 1422.
(5) Armarego, W. L. F. *Adv. Heterocycl. Chem.* **1979**, *24*, 16.
(6) Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P.; Gleria, M. *Heterocycles* **1991**, *32*, 1055.
(7) (a) Roger, R.; Neilson, D. G. *Chem. Rev.* **1961**, *61*, 169. (b) Neilson, D. G. *The Chemistry of Amidines and Imidates*; Patai, S., Ed.; Wiley Interscience: London, 1975; Chapter 9.
(8) The choice of the acids has been made on the basis of their cheapness and to check the applicability of this method to various substituted anthranilic acids.
(9) Schwender, C. F.; Sunday, B. R.; Decker, V. L. *J. Med. Chem.* **1982**, *25*, 742. Tilley, J. W.; Levitan, P.; Welton, A. F.; Crowley, H. J. *J. Med. Chem.* **1983**, *26*, 1638.
(10) Nakagawa, Y.; Stevens, R. V. *J. Org. Chem.* **1988**, *53*, 1873.
(11) Katritzky, A. R.; Karelson, M.; Harris, P. A. *Heterocycles* **1991**, *32*, 329.

0022-3263/93/1958-0741$04.00/0

The reaction can be viewed as an easy intramolecular N-alkylation. The separation of the two regioisomers was achieved easily because of the insolubility of quinazolinones **5** in various organic solvents. Owing to this feature, compound **5f** had to be characterized as the (*tert*-butyldimethylsilyl)oxy derivative **6f**. The structure of the series of tetrahydropyrido[2,1-*b*]quinazolinones **4** and of tetrahydropyrido[1,2-*a*]quinazolinones **5** was assigned on the basis of the spectroscopic data obtained for **4d** and **5d** by comparison to 2-substituted quinazolinones **3d**. The IR spectrum of compound **4d** showed an amidic carbonyl stretching band at 1670 cm^{-1}, identical to that of the open product **3d**, while the carbonyl compound **5d** showed a band at 1635 cm^{-1} due to the effect of the conjugated carbon–nitrogen double bond.[12] The ^{13}C NMR spectra of **3d** and **4d** allowed assignment of the peaks at δ 163.36 (C_4 of **3d**) and δ 162.30 (C_{11} of **4d**) as the carbonyl groups and δ 157.72 (C_2 of **3d**) and δ 155.07 (C_{5a} of **4d**) as the carbon–nitrogen double bond, respectively. On the other hand, the ^{13}C NMR spectrum of **5d** showed the carbonyl group (C_6) at δ 171.07 while the carbon–nitrogen double bond (C_{4a}) shifted downfield at δ 160.17 due to conjugation with the carbonyl group.[13] This conjugation aided total H–D exchange of the C_4-protons of **5d** after 4 days in D_2O. The exchange was confirmed by the ^{13}C NMR spectrum where the triplet of the C_4 at δ 27.91 became a multiplet because of the coupling with deuterium. On the other hand, compound **4d** was recovered unaltered after 4 days in D_2O. Such a difference of acidity between the α-CH_2 of **5d** and **4d** confirmed further their structures, but in the literature there are no comparative data of acidity on related compounds as 1,2-dimethyl-4(1*H*)- and 2,3-dimethyl-4(3*H*)-quinazolinones.

In conclusion, cyclic imidate **2** is a useful reagent for the synthesis of various heterocyclic rings, i.e. benzazoles and quinazolinones, both because it gives condensation reactions under very mild conditions and because the imidate opening affords an alkyl chain suitable to various elaborations, i.e. annulation reactions.

Experimental Section

All melting points are uncorrected. ^1H and ^{13}C NMR spectra were obtained on a 300-MHz Varian Gemini 300 and on a 200-MHz Bruker AC-200 spectrometers. Chemical shifts are given in parts per million from Me_4Si as internal standard. Infrared spectra were recorded on a Perkin-Elmer Model 297 grating spectrometer. Elemental analyses were performed on a 1106 Microanalyzer (Carlo Erba).

Preparation of 4(3*H*)-Quinazolinones 3. General Procedure. To a stirred solution of 4-pentenamide (0.5 g, 5 mmol) in 1,2-dichloroethane (DCE) (10 mL) was added a solution of bromine (5.5 mmol) in 2 mL of DCE at 0 °C. Stirring was continued for 20 min whereupon a suspension of the cyclic imidate **2** formed. After the reaction mixture was allowed to warm to rt, the appropriate anthranilic acid (6.5 mmol) was added in one portion, and then triethylamine (5 mmol) in DCE (3 mL) was added dropwise with vigorous stirring. After 30 min the quinazolinone **3** precipitated. A saturated solution of $NaHCO_3$ (10 mL) was added and the reaction mixture was stirred for 20 min. The crude quinazolinone was filtered off, washed with diethyl ether, and crystallized from methanol–acetone.

1-Bromo-4-[3,4-dihydro-4-oxoquinazolin-2-yl]-2-butanol (3a): 55% yield; mp 147–150 °C; IR (Nujol) 3300, 1670, 1610 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.80 (m, 1 H) 2.03 (m, 1 H), 2.60–2.83 (m, 2 H), 3.50 (m, 2 H), 3.72 (m, 1 H), 5.25 (br, 1 H, exchange with D_2O), 7.45 (pseudo t, 1 H, J = 7.7 Hz), 7.60 (d, 1 H, J = 7.0 Hz), 7.76 (pseudo t, 1 H, J = 7.7 Hz), 8.08 (d, 1 H, J = 7.0 Hz), 12.3 (br s, 1 H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 23.82, 24.52, 53.55, 60.60, 118.03, 120.48, 127.89, 129.70, 137.13, 140.02, 158.90, 162.47. Anal. Calcd for $C_{12}H_{13}BrN_2O_2$: C, 48.50; H, 4.41; N, 9.43. Found: C, 48.66; H, 4.35; N, 9.48.

1-Bromo-4-[3,4-dihydro-4-oxo-6-chloroquinazolin-2-yl]-2-butanol (3b): 48% yield; mp 155–158 °C; IR (Nujol) 3300, 1665, 1600 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.80 (m, 1 H), 2.0 (m, 1 H), 2.72 (m, 2 H), 3.47 (m, 2 H), 3.73 (br s, 1 H), 5.20 (br, 1 H, exchange with D_2O), 7.60 (d, 1 H, J = 8.2 Hz), 7.75 (d, 1 H, J = 8.2 Hz), 7.98 (s, 1 H), 12.5 (br s, 1 H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 30.61, 31.75, 39.70, 69.17, 122.46, 125.12, 129.26, 130.64, 134.74, 147.95, 158.60, 161.40. Anal. Calcd for $C_{12}H_{12}BrClN_2O_2$: C, 43.46; H, 3.65; N, 8.45. Found: C, 43.60; H, 3.57; N, 8.52.

1-Bromo-4-[3,4-dihydro-4-oxo-8-methoxyquinazolin-2-yl]-2-butanol (3c): 35% yield; mp 146–149 °C; IR (Nujol) 3400, 1670, 1600 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.80 (m, 1 H), 2.0 (m, 1 H), 2.62–2.83 (m, 2 H), 3.47 (m, 2 H), 3.71 (m, 1 H), 3.87 (s, 3 H), 5.34 (br, 1 H, exchange with D_2O), 7.36 (m, 2 H), 7.62 (d, 1 H, J = 7.8 Hz), 12.2 (br s, 1 H). Anal. Calcd for $C_{13}H_{15}BrN_2O_3$: C, 47.72; H, 4.62; N, 8.56. Found: C, 47.88; H, 4.54; N, 8.48.

1-Bromo-4-[3,4-dihydro-4-oxo-5-methylquinazolin-2-yl]-2-butanol (3d): 60% yield; mp 132–135 °C; IR (Nujol) 3400, 3190, 1670, 1620, 1600 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.80 (m, 1 H), 2.10 (m, 1 H), 2.67 (m, 2 H), 2.75 (s, 3 H), 3.46 (dd, 1 H, J = 5.8 and 10.1 Hz), 3.52 (dd, 1 H, J = 4.8 and 10.1 Hz), 3.70 (m, 1 H), 5.20 (br, 1 H, exchange with D_2O), 7.18 (d, 1 H, J = 7.1 Hz), 7.38 (d, 1 H, J = 7.8 Hz), 7.68 (pseudo t, 1 H, J = 7.7 Hz), 11.5 (s, 1 H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 22.45, 30.34, 31.92, 39.97, 69.29, 119.59, 125.23, 128.79, 133.82, 140.46, 150.80, 157.72, 163.36. Anal. Calcd for $C_{13}H_{15}BrN_2O_2$: C, 50.18; H, 4.86; N, 9.00. Found: C, 50.26; H, 4.79; N, 9.11.

1-Bromo-4-[3,4-dihydro-4-oxo-7-fluoroquinazolin-2-yl]-2-butanol (3e): 35% yield; mp 124–128 °C; IR (Nujol) 3200, 1670, 1605 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.80 (m, 1 H), 2.0 (m, 1 H), 2.56–2.82 (m, 2 H), 3.47 (m, 2 H), 3.70 (br s, 1 H), 5.23 (br, 1 H, exchange with D_2O), 7.32 (m, 2 H), 8.12 (m, 1 H), 12.4 (br s, 1 H). Anal. Calcd for $C_{12}H_{12}BrFN_2O_2$: C, 45.73; H, 3.84; N, 8.89. Found: C, 45.88; H, 3.78; N, 8.95.

1-Bromo-4-[3,4-dihydro-4-oxobenzo[*g*]quinazolin-2-yl]-2-butanol (3f): 42% yield; mp 168–170 °C; IR (Nujol) 3200, 1670, 1610 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.86 (m, 1 H), 2.08 (m, 1 H), 2.72 (m, 2 H), 3.51 (m, 2 H), 3.75 (br s, 1 H), 5.30 (br, 1 H, exchange with D_2O), 7.54 (pseudo t, 1 H, J = 7.4 Hz), 7.63 (pseudo t, 1 H, J = 7.4 Hz), 8.06 (d, 1 H J = 8.5 Hz), 8.15 (s, 1 H), 8.17 (d, 1 H, J = 8.5 Hz), 8.76 (s, 1 H), 12.0 (br s, 1 H). Anal. Calcd for $C_{16}H_{15}BrN_2O_2$: C, 55.35; H, 4.35; N, 8.07. Found: C, 55.48; H, 4.27; N, 8.16.

Thermal Cyclization of Quinazolinones 3. General Procedure. The selected quinazolinone **3** (1 mmol) was suspended in acetonitrile (15 mL) and refluxed for 3–10 h until the its total disappearance (by TLC). The solvent was evaporated under reduced pressure, and the residue was diluted with chloroform and washed with a saturated solution of $NaHCO_3$. Filtration of the chloroform suspension afforded the crude pyrido[1,2-*a*]-quinazolinones **5** and subsequent evaporation of chloroform solution gave the crude pyrido[2,1-*b*]quinazolinones **4** in variable molar ratio and quantitative yield. Compounds **4a–f** were crystallized from chloroform–methanol. Compounds **5a** and **5f** were rinsed with methanol and dried to yield a white solid. Compounds **5b–e** were purified by chromatography (silica gel, ethyl acetate–methanol 9:1).

8-Hydroxy-6,7,8,9-tetrahydropyrido[2,1-*b*]quinazolin-11-one (4a): 23% yield; mp 187–190 °C; IR (Nujol) 3200, 1650, 1580 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 1.80 (m, 1 H), 2.05 (m, 1 H), 2.92 (m, 2 H), 3.83 (dd, 1 H, J = 4 and 14 Hz), 4.05 (dd, 1 H, J = 4 and 14 Hz), 4.22 (m, 1 H), 5.20 (d, 1 H, J = 4 Hz, exchange with D_2O), 7.45 (pseudo t, 1 H, J = 8 Hz), 7.56 (d, 1 H, J = 8 Hz), 7.77 (pseudo t, 1 H, J = 8 Hz), 8.10 (d, 1 H, J = 8 Hz). Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.77; H, 5.51; N, 12.85.

(12) Hagiwara, Y.; Kurihara, M.; Yoda, N. *Tetrahedron* **1969**, *25*, 783.
(13) Similar behavior has been detected in ^{13}C NMR spectra of 1,2-dimethyl-4(1*H*)- and 2,3-dimethyl-4(3*H*)-quinazolinones: Bhattacharyya, J. *Heterocycles* **1980**, *14*, 1469.

2-Hydroxy-1,2,3,4-tetrahydropyrido[1,2-*a*]quinazolin-6-one (5a): 71% yield; mp > 240 °C; IR (Nujol) 3200, 1630, 1600, 1520 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.88 (m, 1 H), 2.02 (m, 1 H), 2.82 (dt, 1 H, J = 6.3 and 18.3 Hz), 3.0 (m, 1 H), 3.98 (dd, 1 H, J = 4.4 and 12.6 Hz), 4.13 (dd, 1 H, J = 4.0 and 12.6 Hz), 4.3 (m, 1 H), 5.38 (br s, 1 H), 7.51 (pseudo t, 1 H, J = 7.7 Hz), 7.72 (d, 1 H, J = 8.4 Hz), 7.82 (pseudo t, 1 H, J = 7.7 Hz), 8.07 (d, 1 H, J = 8.4 Hz). Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.44; H, 5.68; N, 13.06.

2-Chloro-8-hydroxy-6,7,8,9-tetrahydropyrido[2,1-*b*]quinazolin-11-one (4b): 31% yield; mp 173–175 °C; IR (Nujol) 3400, 1655, 1590 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.92–2.18 (m, 3 H), 2.87 (dt, 1 H, J = 6.3 and 17.5 Hz), 3.17 (ddd, 1 H, J = 6.9, 8.7, and 17.5 Hz), 3.90 (dd, 1 H, J = 3.5 and 14.3 Hz), 4.24 (dd, 1 H, J = 3.9 and 14.3 Hz), 4.43 (m, 1 H), 7.47 (d, 1 H, J = 8.6 Hz), 7.58 (dd, 1 H, J = 2.1 and 8.6 Hz), 8.11 (d, 1 H, J = 2.1 Hz). Anal. Calcd for $C_{12}H_{11}ClN_2O_2$: C, 57.49; H, 4.42; N, 11.17. Found: C, 57.61; H, 4.35; N, 11.23.

8-Chloro-2-hydroxy-1,2,3,4-tetrahydropyrido[1,2-*a*]quinazolin-6-one (5b): 63% yield; mp > 240 °C; IR (Nujol) 3400, 1635, 1590, 1510 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.89 (m, 1 H), 2.03 (m, 1 H), 2.84 (m, 1 H), 3.0 (m, 1 H), 3.98 (dd, 1 H, J = 2.6 and 12.3 Hz), 4.11 (dd, 1 H, J = 2.1 and 12.3 Hz), 4.30 (br s, 1 H), 5.34 (br s, 1 H, exchange with D_2O), 7.80 (m, 2 H), 7.98 (s, 1 H). Anal. Calcd for $C_{12}H_{11}ClN_2O_2$: C, 57.49; H, 4.42; N, 11.17. Found: C, 57.38; H, 4.45; N, 11.11.

8-Hydroxy-4-methoxy-6,7,8,9-tetrahydropyrido[2,1-*b*]quinazolin-11-one (4c): 57% yield; mp 190–192 °Cl; IR (Nujol) 3360, 1660, 1590 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 1.80 (m, 1 H), 2.05 (m, 1 H), 2.95 (m, 2 H), 3.5 (br, 1 H), 3.83 (dd, 1 H, J = 3 and 14 Hz), 3.90 (s, 3 H), 4.05 (dd, 1 H, J = 5 and 14 Hz), 7.35 (m, 2 H), 7.64 (d, 1 H, J = 7.5 Hz). Anal. Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.55; H, 5.66; N, 11.25.

2-Hydroxy-10-methoxy-1,2,3,4-tetrahydropyrido[1,2-*a*]quinazolin-6-one (5c): 38% yield; mp 215–220 °C dec; IR (Nujol) 3360, 1630, 1600, 1585 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 1.78 (m, 1 H), 2.08 (m, 1 H), 2.85 (m, 2 H), 3.90 (s, 3 H), 4.15 (m, 1 H), 4.42 (m, 2 H), 5.12 (d, 1 H, J = 3.2 Hz, exchange with D_2O), 7.43 (m, 2 H), 7.65 (m, 1 H). Anal. Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.49; H, 5.81; N, 11.44.

8-Hydroxy-1-methyl-6,7,8,9-tetrahydropyrido[2,1-*b*]quinazolin-11-one (4d): 64% yield; mp 147–149 °C; IR (Nujol) 3350, 1670, 1590, 1560 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 1.79 (m, 1 H), 2.04 (m, 1 H), 2.76 (s, 3 H), 2.80–3.10 (m, 2 H), 3.78 (dd, 1 H, J = 4 and 14 Hz), 3.98 (dd, 1 H, J = 4.4 and 14 Hz), 4.22 (m, 1 H), 5.22 (br s, 1 H, exchange with D_2O), 7.20 (d, 1 H, J = 7.2 Hz), 7.38 (d, 1 H, J = 8 Hz), 7.60 (pseudo t, 1 H, J = 7.6 Hz); ^{13}C NMR (50.1 MHz, DMSO-d_6) δ 22.70, 26.91, 27.67, 48.01, 62.24, 118.59, 124.74, 128.38, 133.49, 140.06, 149.05, 155.07, 162.30. Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.93; H, 6.03; N, 12.24.

2-Hydroxy-1-methyl-1,2,3,4-tetrahydropyrido[1,2-*a*]quinazolin-6-one (5d): 32% yield; mp 235–238 °C; IR (Nujol) 3350, 1635, 1620, 1595 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 1.80–2.10 (m, 2 H), 2.75 (s, 3 H), 2.82 (m, 1 H), 2.98 (m, 1 H), 3.92 (dd, 1 H, J = 4.4 and 12.8 Hz), 4.05 (dd, 1 H, J = 4.1 and 12.8 Hz), 4.32 (m, 1 H), 5.37 (d, 1 H, J = 3.4 Hz, exchange with D_2O), 7.27 (d, 1 H, J = 7.2 Hz), 7.50 (d, 1 H, J = 8 Hz), 7.63 (pseudo t, 1 H, J = 7.6 Hz); ^{13}C NMR (50.1 MHz, DMSO-d_6) δ 22.78, 26.03, 27.91, 52.85, 61.95, 113.13, 119.22, 128.49, 132.67, 140.97, 142.95, 160.17, 171.07. Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.87; H, 6.17; N, 12.25.

3-Fluoro-8-hydroxy-6,7,8,9-tetrahydropyrido[2,1-*b*]quinazolin-11-one (4e): 46% yield; mp 176–179 °C; IR (Nujol) 3400, 1660, 1595 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.78 (m, 1 H), 2.05 (m, 1 H), 2.84 (dt, 1 H, J = 6.6 and 17.4 Hz), 3.0 (m, 1 H), 3.82 (dd, 1 H, J = 3.6 and 13.8 Hz), 4.04 (dd, 1 H, J = 4.2 and 13.8 Hz), 4.22 (m, 1 H), 5.20 (d, 1 H, J = 3.5 Hz, exchange with D_2O), 7.33 (m, 2 H), 8.16 (dd, 1 H, J = 6.7 and 8.9 Hz). Anal. Calcd for $C_{12}H_{11}FN_2O_2$: C, 61.53; H, 4.73; N, 11.96. Found: C, 61.71; H, 4.66; N, 12.10.

9-Fluoro-2-hydroxy-1,2,3,4-tetrahydropyrido[1,2-*a*]quinazolin-6-one (5e): 47% yield; mp > 240 °C; IR (Nujol) 3400, 1630, 1585, 1510 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.85 (m, 1 H), 1.98 (m, 1 H), 2.80 (dt, 1 H, J = 5.4 and 17.2 Hz), 2.98 (m, 1 H), 3.93 (dd, 1 H, J = 3.7 and 12.1 Hz), 4.05 (dd, 1 H, J = 3.6 and 12.1 Hz), 4.28 (m, 1 H), 5.43 (br s, 1 H, exchange with D_2O), 7.34 (pseudo t, 1 H, J = 2.3 and 9 Hz), 7.61 (dd, 1 H, J = 2.4 and 12.1 Hz), 8.12 (dd, 1 H, J = 7 and 9.3 Hz). Anal. Calcd for $C_{12}H_{11}FN_2O_2$: C, 61.53; H, 4.73; N, 11.96. Found: C, 61.69; H, 4.77; N, 11.85.

1,2,3,4-Tetrahydro-2-hydroxy-12*H*-benzo[*g*]pyrido[2,1-*b*]quinazolin-12-one (4f): 17% yield; mp 230 °C dec; IR (Nujol) 3200, 1670, 1600 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 1.80 (m, 1 H), 2.10 (m, 1 H), 2.88 (dt, 1 H, J = 6.9 and 16.8 Hz), 3.03 (ddd, 1 H, J = 6.5, 7.6 and 16.8 Hz), 3.88 (dd, 1 H, J = 3.7 and 13.8 Hz), 4.09 (dd, 1 H, J = 4.6 and 13.8 Hz), 4.23 (m, 1 H), 5.22 (br s, 1 H, exchange with D_2O), 7.54 (m, 1 H), 7.63 (m, 1 H), 8.06 (d, 1 H, J = 8.3 Hz), 8.12 (s, 1 H), 8.20 (d, 1 H, J = 8.3 Hz), 8.82 (s, 1 H). Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.26; H, 5.22; N, 10.61

Compound **5f** (76%) was characterized as (*tert*-butyldimethylsilyl)oxy derivative **6f**. To a suspension of **5f** (0.26 g, 1 mmol) in DMF (1 mL) were added *tert*-butyldimethylsilyl chloride (0.22 g, 1.5 mmol) and imidazole (0.2 g, 3 mmol). The suspension was vigorously stirred at rt for 48 h. A saturated solution of $NaHCO_3$ (5 mL) was added and the pale yellow precipitate was filtered off. The crude silyloxy derivative **6f** was dissolved in methanol, and water was added to achieve the crystallization (0.29 g, 78%).

1,2,3,4-Tetrahydro-2-[(*tert*-butyldimethylsilyl)oxy]-6*H*-benzo[*g*]pyrido[1,2-*a*]quinazolin-6-one (6f): mp > 240 °C; IR (Nujol) 1635, 1610, 1590 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 0.1 (s, 3 H), 0.15 (s, 3 H), 0.84 (s, 9 H), 1.94 (m, 1 H), 2.09 (m, 1 H), 2.93 (m, 1 H), 3.05 (m, 1 H), 4.08 (dd, 1 H, J = 3.6 and 12.8 Hz), 4.25 (dd, 1 H, J = 3.4 and 12.8 Hz), 4.58 (br s, 1 H), 7.58 (pseudo t, 1 H, J = 7.2 Hz), 7.68 (pseudo t, 1 H, J = 7.2 Hz), 8.14 (d, 1 H, J = 8.2 Hz), 8.20 (d, 1 H, J = 8.2 Hz), 8.28 (s, 1 H), 8.78 (s, 1 H). Anal. Calcd for $C_{22}H_{28}N_2O_2Si$: C, 68.95; H, 7.42; N, 7.36. Found: C, 68.71; H, 7.35; N, 7.29.