Synthesis of new quinazoline-2,4(1*H*,3*H*)-dione non-nucleoside analogues of the reverse transcriptase inhibitor TNK-651

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The synthesis is described of a series of new non-nucleoside analogues of the reverse transcriptase inhibitor TNK-651 from quinazoline-2,4(1*H*,3*H*)-diones. Compounds **2a–c** were silylated and treated with benzyl chloromethyl ether in the presence of CsI to give 1-benzyloxymethylquinazoline derivatives **3a–c**. Treatment of the silylated quinazolinediones **2a–c** with the appropriate acetals **5a–e** in the presence of *TMS* triflate afforded the corresponding TNK-651 analogues **6–10**.

Keywords: reverse transcriptase inhibitors, anti-HIV drugs, quinazoline-2,4-diones, TNK-651 analogues

Effective treatment regimens for the human immunodefiãency virus (HIV-1) infection have included three main classes: those that prevent the fusion of the viral envelope with the cellular plasma membrane (fusion inhibitors), those that prevent infection of target cells (reverse transcriptase inhibitors), and those that prevent HIV-1-infected cells from yielding infectious viruses (protease inhibitors).[1]

In recent years, much effort has been put into the design and synthesis of HIV-1 non-nucleoside reverse transcriptase inhibitors (NNRTIs). More than 30 structurally different classes of compound have been identified as NNRTIs.[2-4] The NNTRIs are highly speãfic, as their binding site is a hydrophobic pocket located approximately 10 Å from the polymerase active site. They bind allosterically, forãng the RT-subunit into an inactive conformation.[5,6] One of the first NNRTIs was 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine (HEPT).[7,8] HEPT was considered a lead compound for NNRTIs synthesis, even though it was not very active itself. Among the many HEPT analogues synthesised are 6-benzyl-1-(ethoxymethyl)-5-isopropyluraãl (Emivirine)[9-11] and the corresponding 1-benzyloxymethyl analogue (TNK-651)[6] which showed high activity against HIV-1.

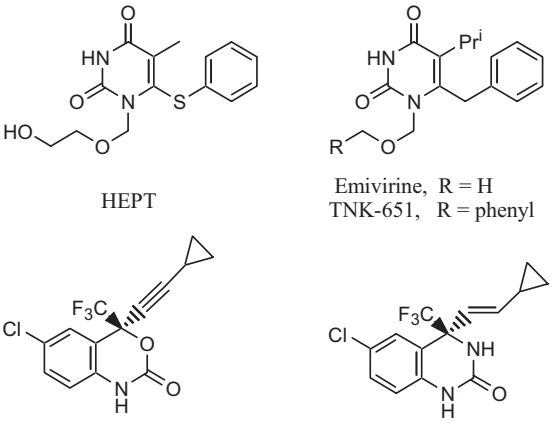
Three NNRTIs have so far been formally licensed for clinical use in the treatment of HIV infections, namely, nevirapine (Viramune)[12], delavirdine (Rescriptor)[13] and efavirenz (Sustiva, Stocrin)[14]. The quinazoline compound DPC-083, a derivative of efavirenz, has marked activity against HIV-1 strains with various mutations (L100I, K103N, Y181C, Y188L, K103N + L100I and K103N + Y181C).[15]

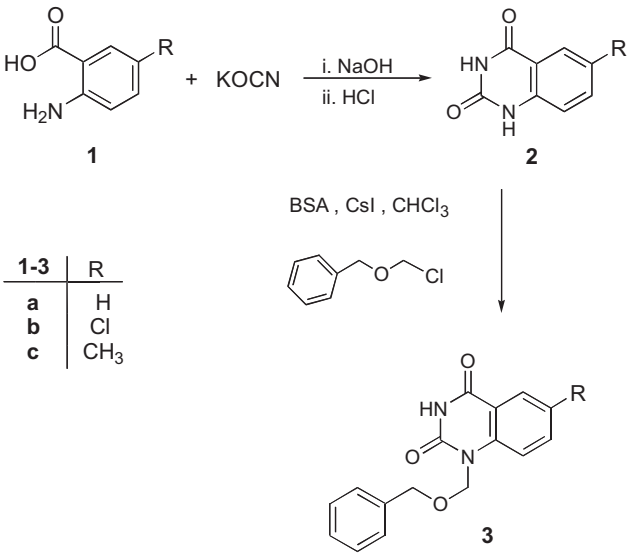
Recently, I synthesised a series of quinazoline-2,4(1*H*,3*H*)-dione non-nucleoside analogues of Emivirine,[16] in an effort to find new HIV inhibitors and as a part of my interest in the chemistry of NNRTIs.[17-23] The present study describes the synthesis of novel quinazoline-2,4(1*H*,3*H*)-dione non-nucleoside analogues of TNK-651.

Results and discussion

Quinazoline-2,4(1*H*,3*H*)-diones **2a–c** were prepared by treatment of the corresponding substituted anthranilic aãd **1a–c** with potassium cyanate according to the method described by Dunkel *et al*.[24] Silylation of compounds **2a–c** with *N,O*-bis(trimethylsilyl)acetamide (BSA) in anhydrous chloroform followed by alkylation with benzyl chloromethyl ether in the presence of caesium iodide afforded the corresponding TNK-651 analogues **3a–c** in 74–78% yields (Scheme 1).

Bis(indan-1-yloxy)methane (**5a**),[22] bis(indan-2-yloxy) methane (**5b**),[22] bis-(3-cyclohexen-1-ylmethoxy)methane





Scheme 1

(**5c**),[18] bis-((*E*)-ãnnamyloxy)methane (**5d**, R^2 = H),[18] bis-((*E*)-2-methyl-3-phenylallyloxy)methane (**5d**, R^2 = CH_3)[18] and bis(2-phenylethyloxy)methane (**5e**) were prepared from the corresponding alcohols 1-indanol, 2-indanol, 3-cyclohexene-1-methanol, (*E*)-ãnnamyl alcohol, (*E*)-2-methyl-3-phenyl-2-propen-1-ol and 2-phenylethanol, respectively, by reaction with dibromomethane using potassium hydroxide in anhydrous benzene in the presence of tetrabutylammonium bromide according to the method of Nazaretyan *et al*.[25] (Scheme 2)

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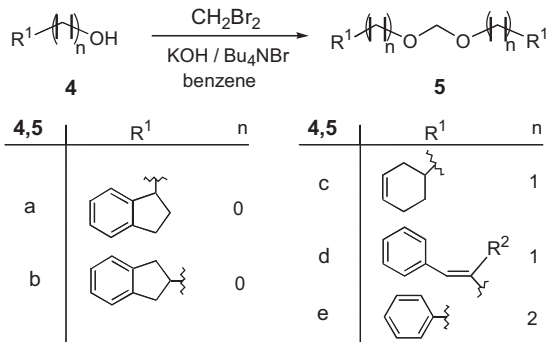


Scheme 2

Compounds **2a–c** were silylated with BSA in anhydrous acetonitrile and reacted with **5a** and/or **5b** using trimethylsilyl trifluoromethanesulfonate (TMS triflate) as a Lewis aãd catalyst[26] to give the corresponding *N*(1)-indan-1-yloxymethylquinazolines (**6a,b**) and indan-2-yloxymethylquinazolines (**7a–c**) in 73, 75 and 68–71% yields, respectively. 1-(Cyclohex-3-en-1-ylmethyloxy)methyl-6-substituted-quinazoline-2,4(1*H*,3*H*)-diones (**8a–c**) were obtained in 71–73% yields by silylation of **2a–c** followed by treatment with the acetal **5c** in the presence of TMS triflate (Scheme 3).

Treatment of bis-((*E*)-ãnnamyloxy)methane (**5d**, $R^2 = H$) and/or bis-((*E*)-2-methyl-3-phenylallyloxy)methane (**5d**, $R^2 = CH_3$) with the silylated quinazolines **2a–c** in anhydrous acetonitrile in the presence of TMS triflate afforded 1-((*E*)-ãnnamyloxymethyl)quinazoline-2,4(1*H*,3*H*)-dione(**9a**)and1-((*E*)-2-methyl-3-phenylallyloxymethyl)quinazolines **9b–d** in 79 and 78–81% yields, respectively. Further, quinazoline-2,4(*1H*,3*H*)-dione (**2a**) and its 6-methyl derivative **2c** were silylated and reacted with bis(2-phenylethyloxy)methane (**5e**) to furnish 1-(2-phenylethyloxymethyl)quinazoline-2,4(1*H*,3*H*)-dione (**10a**) and 6-methyl-1-(2-phenylethyloxymethyl)quinazoline-2,4(1*H*,3*H*)-dione (**10b**) in 71 and 73% yields, respectively (Scheme 3).

The fact that the *N*-alkylation furnished 1-alkylated products was proved by the NOE enhancement of the aromatic proton 8-H when *N*-1 CH_2 was irradiated.

The mass spectra of all compounds containing chlorine showed fragments corresponding to the typical pattern of chlorine isotopes (^{35}Cl and ^{37}Cl).

Compounds **3b,c**, **6a,b**, **7a,b**, **8a–c** and **9a–d** were tested against wild-type HIV-1. No compounds exhibited significant activity at 100 μM against HIV-1 in MT-4 cells.

Experimental

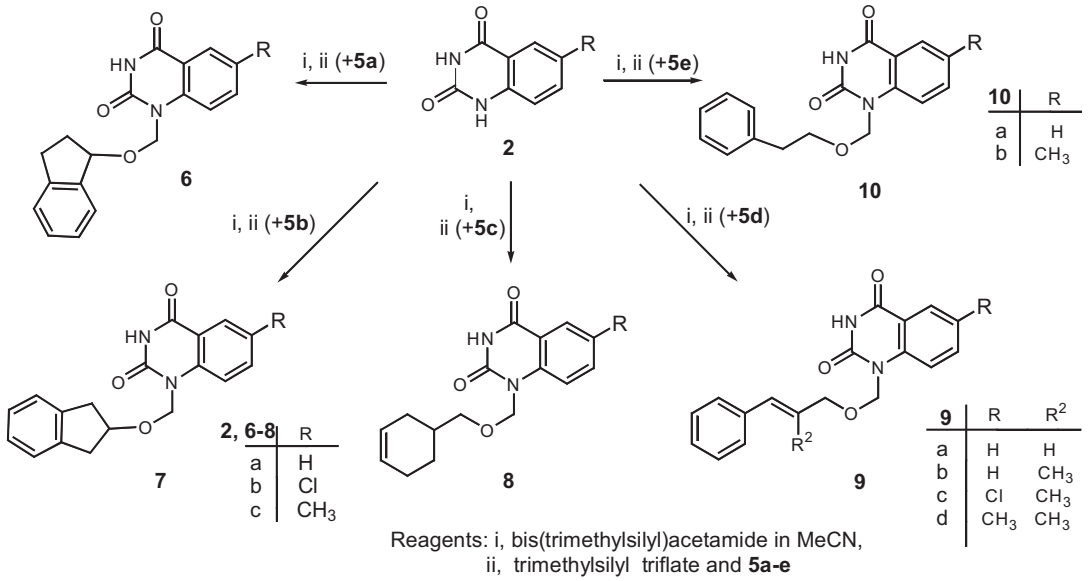
NMR spectra were recorded on a Varian Gemini 2000 NMR spectrometer at 300 MHz for ^1H and 75 MHz for ^{13}C with TMS as an internal standard. Chemical shifts are reported in ppm (δ), and signals are expressed as s (singlet), d (doublet), t (triplet), q (quartet) or m (multiplet). MALDI spectra were recorded on an IonSpec Fourier Transform Ion Cyclotron Resonance Mass Spectrometer. Melting points were determined on a Büchi melting point apparatus. Elemental analyses were performed at the H.C. Ørsted Institute, University of Copenhagen. The progress of reactions was monitored by TLC (DC-alufolio 60 F_{254}) from Merck. For column chromatography Merck silica gel (0.040–0.063 mm) was used.

1-Benzyloxymethylquinazoline-2,4(1H,3H)-diones (**3a–c**)
N,O-Bis(trimethylsilyl)acetamide (BSA) (0.87 ml, 0.035 mol) was added to a suspension of quinazoline-2,4(1*H*,3*H*)-dione **2a–c** (1 mmol) in anhydrous $CHCl_3$ (20 ml) and the mixture was stirred at room temperature under nitrogen. After a clear solution was obtained (20-30 min), benzyl chloromethyl ether (0.21 ml, 0.015 mol) and CsI (0.26 g, 0.001 mol) were added. The reaction mixture was stirred at room temperature under nitrogen for 3–4 h. Sat. aq. $NaHCO_3$ (20 ml) was added and the mixture was extracted with CH_2Cl_2 (3 × 50 ml). The organic phase was collected, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed on silica gel column using $CHCl_3$ to give **3a–c**.

1-(Benzyloxymethyl)quinazoline-2,4(1H,3H)-dione (**3a**): White solid (215 mg, 76%); m.p. 169–171°C. ^1H NMR (DMSO-d_6, 300 MHz): δ 4.62 (s, 2H, CH_2), 5.61 (s, 2H, CH_2), 7.25–8.02 (m, 9H, H_{arom}), 11.63 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6, 75 MHz): δ 69.8 (CH_2), 71.9 (CH_2), 115.4, 115.8, 123.0, 127.2, 127.5, 128.1, 135.0, 137.6, 140.4 (C_{arom}); 150.5 (C-2), 161.7 (C-4) ppm. MS (MALDI): *m/z* 305 (M^+ + Na, 37%). Anal. Calcd. for $C_{16}H_{14}N_2O_3$ (282.29): C 68.07, H 5.00, N 9.92. Found: C 68.00, H 4.93, N 9.80%.

1-(Benzyloxymethyl)-6-chloroquinazoline-2,4(1H,3H)-dione (**3b**): White solid (247 mg, 78%), m.p. 200–202°C. ^1H NMR (DMSO-d_6, 300 MHz): δ 4.61 (s, 2H, CH_2), 5.60 (s, 2H, CH_2), 7.25–7.91 (m, 8H, H_{arom}), 11.78 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6, 75 MHz): δ 69.8 (CH_2), 72.1 (CH_2), 117.6, 117.8, 126.1, 127.3, 127.35, 127.5, 128.1, 134.6, 137.5, 139.3 (C_{arom}), 150.3 (C-2), 160.7 (C-4) ppm. MS (MALDI): *m/z* 339 (M^+ + Na, 29%). Calcd for $C_{16}H_{13}ClN_2NaO_3$: 339.0506. Found: 339.0505.

1-(Benzyloxymethyl)-6-methylquinazoline-2,4(1H,3H)-dione (**3c**): White solid (220 mg, 74%), m.p. 194–196°C. ^1H NMR (DMSO-d_6, 300 MHz): δ 2.36 (s, 3H, CH_3), 4.60 (s, 2H, CH_2), 5.59 (s, 2H, CH_2), 7.26–7.79 (m, 8H, H_{arom}), 11.56 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6, 75 MHz): δ 19.9 (CH_3), 69.7 (CH_2), 71.9 (CH_2), 115.55,



Scheme 3

115.3, 126.8, 127.5, 128.1, 132.4, 135.9, 137.6, 138.25 (C_{arom}), 150.5 (C-2), 161.7 (C-4) ppm. MS (MALDI): *m/z* 319 (M^+ + Na, 44%). Calcd for $C_{17}H_{16}N_2NaO_3$: 319.1053. Found: 319.1049.

Bis-(2-phenylethyloxy)methane (**5e**).
2-Phenylethanol (12.2 g, 0.1 mol), dibromomethane (8.79 g, 0.0505 mol), and tetrabutylammonium bromide (1.74 g, 0.00535 mol) were added to potassium hydroxide (5.66 g, 0.101 mol) in anhydrous benzene (30 ml), and the suspension was heated under reflux for 5 hours. After cooling, H_2O (50 ml) was added and the resulting solution was extracted with ether (3 × 50 ml). The ether phase was dried with anhydrous $MgSO_4$ and evaporated. The residue was chromatographed on silica gel column using $CHCl_3$ to afford **5e** as a colourless oil (8.1 g, 63%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.91 (t, 4H, *J* = 7.0 Hz, 2 × CH_2), 3.76 (t, 4H, *J* = 7.0 Hz, 2 × CH_2), 4.73 (s, 2H, CH_2), 7.26–7.37 (m, 10 H, H_{arom}) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ 36.3 (CH_2), 68.5 (CH_2), 95.2 (CH_2), 126.2, 128.1, 128.9, 139.0 (C_{arom}) ppm. MS (EI): *m/z* (%) 256 (M^+, 3), 229 (5), 154 (3), 136 (11), 119 (16), 105 (100), 92 (49), 77 (13).

1-(Indanyloxymethyl)quinazolines (**6a,b**, **7a–c**): *general procedure*
Quinazoline-2,4(1*H*,3*H*)-dione (**2a–c**, 1 mmol) was stirred in dry acetonitrile (15 ml) under nitrogen and *N,O*-bis(trimethylsilyl) acetamide (BSA) (0.87 ml, 3.5 mmol) was added. After a clear solution was obtained (10 min), the mixture was cooled to –50°C and *TMS* triflate (0.18 ml, 1 mmol) was added followed by the dropwise addition of bis(indan-1-yloxy)methane (**5a**) or bis(indan-2-yloxy)methane (**5b**) (0.56 g, 2 mmol). The reaction mixture was stirred at room temperature for 5 h, and the reaction was quenched by addition of sat. aq. $NaHCO_3$ solution (5 ml). The mixture was evaporated under reduced pressure and the residue was extracted with ether (3 × 50 ml). The combined ether fractions were collected, dried ($MgSO_4$) and evaporated under reduced pressure. The products were purified by silica gel column chromatography (20% ether in petroleum ether (40–60°C)) to afford **6a,b** and 7**a–c**.

1-(Indan-1-yloxymethyl)quinazoline-2,4(1H,3H)-dione (**6a**): White solid (225 mg, 73%), m.p. 174–176°C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.90–1.95, 2.29–2.36 (2 × m, 2H, 2'-H), 2.76–2.80, 2.91–2.97 (2 × m, 2H, 3'-H); 5.13 (dd, *J* = 4.4, 6.4 Hz, 1H, 1'-H), 5.63, 5.70 (2 × s, 2H, CH_2), 7.09–8.04 (m, 8H, H_{arom}), 11.70 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6, 75 MHz): δ 29.5 (CH_2), 32.3 (CH_2), 71.0 (CH), 80.6 (CH_2), 115.5, 115.8, 123.1, 124.3, 126.2, 127.2, 127.8, 128.3, 135.1, 140.5, 142.2, 143.4 (C_{arom}), 150.6 (C-2), 161.75 (C-4) ppm. MS (MALDI): *m/z* (%) 331 (M^+ + Na, 32). Calcd for $C_{18}H_{16}N_2NaO_3$: 331.1053. Found: 331.1049.

6-Chloro-1-(indan-1-yloxymethyl)quinazoline-2,4(1H,3H)-dione (**6b**): White solid (256 mg, 75%), m.p. 171–172°C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.89–1.93, 2.28–2.33 (2 × m, 2H, 2'-H), 2.74–2.79, 2.91–2.95 (2 × m, 3'-H), 5.12 (dd, *J* = 4.4, 6.4 Hz, 1H, 1'-H), 5.62, 5.68 (2 × s, 2H, CH_2), 7.08–7.94 (m, 7H, H_{arom}), 11.86 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6, 75 MHz): δ 29.5 (CH_2), 32.2 (CH_2), 71.1 (CH), 80.5 (CH_2), 117.4, 117.9, 124.1, 124.6, 126.1, 126.2, 127.4, 128.3, 134.7, 139.4, 142.1, 143.4 (C_{arom}), 150.3 (C-2), 160.7 (C-4) ppm. MS (EI): *m/z* (%) 342 (M^+, 11), 312 (6), 227 (25), 210 (34), 196 (31), 166 (67), 153 (38), 133 (97), 117 (100). Anal. Calcd. for $C_{18}H_{15}ClN_2O_3$ (342.78): C 63.07, H 4.41, N 8.17. Found: C 62.93, H 4.38, N 8.06.

1-(Indan-2-yloxymethyl)quinazoline-2,4(1H,3H)-dione (**7a**): White solid (218 mg, 71%), m.p. 193–194°C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.85–2.92, 3.09-3.16 (2 × m, 4H, 1'-H, 3'-H), 4.54 (quint, *J* = 3.7 Hz, 1H, 2'-H), 5.61 (s, 2H, CH_2), 7.10–8.03 (m, 8H, H_{arom}), 11.68 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6, 75 MHz): δ 38.95 (C-1', C-3'), 70.65 (C-2'), 77.7 (CH_2), 115.4, 115.7, 123.1, 124.4, 126.3, 127.2, 135.1, 140.45, 140.5 (C_{arom}), 150.55 (C-2), 161.7 (C-4) ppm. MS (EI): *m/z* (%) 308 (M^+, 9), 277 (4), 240 (7), 206 (3), 172 (6), 162 (4), 132 (19), 116 (100). Anal. Calcd. for $C_{18}H_{16}N_2O_3$ (308.33): C 70.12, H 5.23, N 9.09. Found: C 70.10, H 5.19, N 8.99%.

6-Chloro-1-(indan-2-yloxymethyl)quinazoline-2,4(1H,3H)-dione (**7b**): White solid (231 mg, 68%), m.p. 214–216°C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.84–2.91, 3.08–3.15 (2 × m, 4H, 1'-H, 3'-H), 4.53 (quint, *J* = 3.7 Hz, 1H, 2'-H), 5.56 (s, 2H, CH_2), 7.10–7.93 (m, 7H, H_{arom}), 11.83 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6, 75 MHz): δ 38.9 (C-1', C-3'), 70.8 (C-2'), 77.7 CH_2), 117.4 117.8 124.4, 126.1, 126.3, 127.4 134.7, 139.4 140.5 (C_{arom}), 150.3 (C-2), 160.7 (C-4) ppm. MS (MALDI): *m/z* (%) 365 (M^+ + Na, 89). Calcd for $C_{18}H_{15}ClN_2NaO_3$: 365.0663. Found: 365.0660.

1-(Indan-2-yloxymethyl)-6-methylquinazoline-2,4(1H,3H)-dione (**7c**): White solid (221 mg, 69%), m.p. 187–189°C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.35 (s, 3H, CH_3), 2.84–2.90, 3.10-3.16 (2 × m, 4H, 1'-H, 3'-H), 4.52 (quint, *J* = 3.7 Hz, 1H, 2'-H), 5.55 (s, 2H, CH_2), 7.10–7.81 (m, 7H, H_{arom}), 11.61 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6, 75 MHz): δ 19.9 (CH_3), 39.0 (C-1', C-3'), 70.6 (C-2'), 77.6 (CH_2), 115.4, 115.5, 124.4, 126.3, 126.8, 132.4, 136.0, 138.3, 140.5 (C_{arom}), 150.5 (C-2), 161.7 (C-4) ppm. MS (MALDI): *m/z* (%) 345 (M^+ + Na, 100). Anal. Calcd. for $C_{19}H_{18}N_2O_3$ (322.36): C 70.79, H 5.63, N 8.69. Found: C 70.74, H 5.60, N 8.65%.

1-(3-Cyclohexen-1-ylmethoxymethyl)-quinazolines (**8a–c**): *general procedure*
Quinazoline-2,4(1*H*,3*H*)-dione (**2a–c**, 1 mmol) was stirred in dry acetonitrile (15 ml) under nitrogen and BSA (0.87 ml, 3.5 mmol) was added. After a clear solution was obtained (10 min), the mixture was cooled to –50°C and TMS triflate (0.18 ml, 1 mmol) was added followed by the dropwise addition of bis-(3-cyclohexen-1-ylmethoxy)methane (**5c**) (0.472 g, 2 mmol). The reaction mixture was stirred at room temperature for 6 h, and the mixture was worked up as for the preparation of compounds **6** and **7** to give the title compounds.

1-(Cyclohex-3-en-1-ylmethoxymethyl)quinazoline-2,4(1H,3H)-dione (**8a**): White solid (204 mg, 71%), m.p. 155–156°C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.57–2.01 (m, 7H, 2 × CH_2, CH), 3.41 (d, *J* = 6.4 Hz, 2H, CH_2), 5.53 (s, 2H, CH_2), 5.53–5.63 (m, 2H, 2 × CH), 7.28–8.03 (m, 4H, H_{arom}), 11.64 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6, 75 MHz): δ = 23.8 (CH_2), 24.8 (CH_2), 27.7 (CH_2), 33.1 (CH), 72.3 (CH_2), 72.35 (CH_2), 115.4, 115.7, 123.0, 126.7, 135.0, 140.4 (C_{arom}), 125.7 (CH=), 127.2 (CH=), 150.5 (C-2), 161.7 (C-4) ppm. MS (MALDI): *m/z* 309 (M^+ + Na, 49%). Anal. Calcd. for $C_{16}H_{18}N_2O_3$ (286.33): C 67.12, H 6.34, N 9.78. Found: C 67.06, H 6.34, N 9.57%.

6-Chloro-1-(cyclohex-3-en-1-ylmethoxymethyl)quinazoline-2,4(1H,3H)-dione (**8b**): White solid (235 mg, 73%), m.p. 162–164°C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.57–2.01 (m, 7H, 3 × CH_2, CH), 3.40 (d, *J* = 6.4 Hz, 2H, CH_2), 5.48 (s, 2H, CH_2), 5.51–5.63 (m, 2H, 2 × CH), 7.48–7.92 (m, 3H, H_{arom}), 11.79 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6, 75 MHz): δ 23.6 (CH_2), 24.8 (CH_2), 27.7 (CH_2), 33.1 (CH), 72.38 (CH_2), 72.44 (CH_2), 117.3, 117.7, 126.1, 126.6, 134.7, 139.3 (C_{arom}), 125.7 (CH=), 127.3 (CH=), 150.25 (C-2), 160.7 (C-4) ppm. MS (MALDI): *m/z* 343 (M^+ + Na, 37%). Calcd for $C_{16}H_{17}ClN_2NaO_3$: 343.0820. Found: 343.0822.

1-(Cyclohex-3-en-1-ylmethoxymethyl)-6-methylquinazoline-2,4(1H,3H)-dione (**8c**): White solid (212 mg, 71%), m.p. 173–175°C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.56–2.00 (m, 7H, 3 × CH_2, CH), 2.36 (s, 3H, CH_3), 3.39 (d, *J* = 6.4 Hz, 2H, CH_2), 5.49 (s, 2H, CH_2), 5.53–5.63 (m, 2H, 2 × CH), 7.35–7.80 (m, 3H, H_{arom}), 11.56 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6, 75 MHz): δ 19.9 (CH_3), 23.8 (CH_2), 24.8 (CH_2), 27.7 (CH_2), 33.1 (CH), 72.2 (CH_2), 72.3 (CH_2), 115.3, 115.5, 126.7, 132.4, 135.9, 138.3 (C_{arom}), 125.7 (CH=), 126.8 (CH=), 150.5 (C-2), 161.7 (C-4) ppm. MS (MALDI) *m/z* 323 (M^+ + Na, 54%). Calcd for $C_{17}H_{20}N_2NaO_3$: 323.1366. Found: 323.1367.

1-(2-Alkenyloxymethyl)quinazolines (**9a–d**): *general procedure*
Quinazoline-2,4(1*H*,3*H*)-dione (**2a–c**, 1 mmol) was stirred in dry acetonitrile (15 ml) under nitrogen and BSA (0.87 ml, 3.5 mmol) was added. After a clear solution was obtained (10 min), the mixture was cooled to –50°C and TMS triflate (0.18 ml, 1 mmol) was added followed by the dropwise addition of bis((*E*)-ãnnamyloxy)methane (**5d**, R^2 = H) (0.56 g, 2 mmol) or bis((*E*)-2-methyl-3-phenylallyloxy)methane (**5d**, R^2 = CH_3) (0.616 g, 2 mmol). The reaction mixture was stirred at room temperature for 5 h, and the mixture was worked up as for the preparation of compounds **6** and **7** to give compounds **9a** and **9b–d**, respectively.

1-((E)-Cinnamyloxymethyl)quinazoline-2,4(1H,3H)-dione (**9a**): White solid (243 mg, 79%), m.p. 160–161°C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 4.25 (d, *J* = 5.8 Hz, 2H, CH_2), 5.59 (s, 2H, CH_2), 6.28 (td, *J* = 5.8, 16.1 Hz, 1H, CH), 6.59 (d, *J* = 16.1 Hz, 1H, CH), 7.23–8.03 (m, 9H, H_{arom}), 11.66 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6, 75 MHz): δ 68.55 (CH_2), 71.7 (CH_2), 123.1 (CH=), 115.4, 115.75, 125.6, 126.2, 127.2, 127.6, 128.5, 135.1, 136.2, 140.45 (C_{arom}), 131.7 (CH=), 150.5 (C-2), 161.7 (C-4) ppm. MS (MALDI) *m/z* 331 (M^+ + Na, 41%). Anal. Calcd. for $C_{18}H_{16}N_2O_3$ (308.33): C 70.12, H 5.23, N 9.09. Found: C 70.16, H 5.22, N 9.08%.

1-((E)-2-Methyl-3-phenylallyloxymethyl)quinazoline-2,4(1H,3H)-dione (**9b**): White solid (257 mg, 80%), m.p. 165–166°C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.75 (s, 3H, CH_3), 4.16 (s, 2H, CH_2), 5.61 (s, 2H, CH_2), 6.49 (s, 1H, CH), 7.20–8.03 (m, 9H, H_{arom}), 11.66 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6, 75 MHz): δ 15.2 (CH_3), 71.9 (CH_2), 74.1 (CH_2), 123.1 (CH=), 115.4, 115.7, 126.1, 126.4, 127.2, 128.1, 128.5, 134.4, 135.0, 140.5 (C_{arom}), 136.8 (*C*(Me)=), 150.5 (C-2), 161.7 (C-4) ppm. MS (MALDI) *m/z* 345 (M^+ + Na, 89%). Anal. Calcd. for $C_{19}H_{18}N_2O_3$ (322.36): C 70.79, H 5.63, N 8.69. Found: C 70.79, H 5.60, N 8.62%.

6-Chloro-1-((E)-2-methyl-3-phenylallyloxymethyl)quinazoline-2,4(1H,3H)-dione (**9c**): White solid (288 mg (81%), m.p. 157–158°C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.75 (s, 3H, CH_3), 4.15 (s, 2H, CH_2), 5.59 (s, 2H, CH_2), 6.48 (s, 1H, CH), 7.21–7.93 (m, 8H, H_{arom}), 11.82 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6, 75 MHz): δ 15.3 (CH_3), 72.0 (CH_2), 74.1 (CH_2), 126.3 (CH=), 117.3, 117.8, 126.4, 126.5, 127.4, 128.1, 128.5, 134.3, 134.7, 139.3 (C_{arom}), 136.7 (*C*(Me)=), 150.2 (C-2), 160.7 (C-4) ppm. MS (MALDI): *m/z* 379 (M^+ + Na, 34%). Calcd for $C_{19}H_{17}ClN_2NaO_3$: 379.0820. Found: 379.0824.

6-Methyl-1((E)-2-methyl-3-phenylallyloxymethyl)quinazoline-2,4(1H,3H)-dione (**9d**): White solid (262 mg, 78%, m.p. 158–160°C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.74 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 4.14 (s, 2H, CH_2), 5.58 (s, 2H, CH_2), 6.48 (s, 1H, CH), 7.20–7.81 (m, 8H, H_{arom}), 11.59 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6, 75 MHz): δ 15.2 (CH_3), 19.9 (CH_3), 71.8 (CH_2), 74.0 (CH_2), 126.1 (CH=), 115.4, 115.55, 126.45, 126.9, 128.1, 128.5, 132.4, 134.4, 135.9, 138.3 (C_{arom}), 136.8 (*C*(Me)=), 150.45 (C-2), 161.7 (C-4) ppm. MS (MALDI): *m/z* 359 (M^+ + Na, 88%). Anal. Calcd. for $C_{20}H_{20}N_2O_3$ (336.38): C 71.41, H 5.99, N 8.33. Found: C 71.40, H 5.98, N 8.28%.

1-(2-Phenylethyloxymethyl)quinazoline-2,4(1H,3H)-diones (**10a,b**) Quinazoline-2,4(1*H*,3*H*)-dione (**2a,b**, 1 mmol) was stirred in dry acetonitrile (15 ml) under nitrogen and BSA (0.87 ml, 3.5 mmol) was added. After a clear solution was obtained (10 min), the mixture was cooled to –50°C and TMS triflate (0.18 ml, 1 mmol) was added followed by the dropwise addition of bis-(2-phenylethyloxy)methane (**5e**) (0.512 g, 2 mmol). The reaction mixture was stirred at room temperature for 4 h, and the mixture was worked up as described in preparation of **6** and **7** to give the title compounds.

1-(2-Phenylethyloxymethyl)quinazoline-2,4(1H,3H)-dione (**10a**): White solid (211 mg, 71%), m.p. 136–137°C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 2.79 (t, *J* = 6.5 Hz, 2H, CH_2), 3.75 (t, *J* = 6.5 Hz, 2H, CH_2), 5.51 (s, 2H, CH_2), 7.13–7.99 (m, 9H, H_{arom}), 11.61 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6, 125 MHz): δ 35.7 (CH_2), 69.35 (CH_2), 72.6 (CH_2), 115.9, 116.3, 123.5, 126.5, 127.7, 128.5, 129.3, 135.5, 139.0, 140.95 (C_{arom}), 151.1 (C-2), 162.2 (C-4) ppm. MS (EI): *m/z* (%) 296 (M^+, 31), 219 (54), 205 (13), 191 (7), 175 (11), 161 (8), 119 (18), 105 (100). Anal. Calcd. for $C_{17}H_{16}N_2O_3$ (296.32): C 68.91, H 5.44, N 9.45. Found: C 68.89, H 5.41, N 9.32%.

6-Methyl-1-(2-phenylethyloxymethyl)quinazoline-2,4(1H,3H)-dione (**10b**): white solid (227 mg, 73%), m.p. 145–146°C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 2.35 (s, 3H, CH_3), 2.78 (t, *J* = 6.5 Hz, 2H, CH_2), 3.73 (t, *J* = 6.5 Hz, 2H, CH_2), 5.49 (s, 2H, CH_2), 7.14–7.78 (m, 8H, H_{arom}), 11.54 (s, 1H, NH) ppm; ^{13}C NMR (DMSO-d_6, 125 MHz): δ 20.45 (CH_3), 35.7 (CH_2), 69.3 (CH_2), 72.5 (CH_2), 115.9, 116.1, 126.5, 127.3, 128.55, 129.2, 132.9, 136.3, 138.8, 139.0 (C_{arom}), 151.1 (C-2), 162.2 (C-4) ppm. MS (EI): *m/z* (%) 310 (M^+, 23), 295 (17), 233 (42), 219 (31), 205 (12), 191 (7), 135 (9), 91 (100). Anal. Calcd. for $C_{18}H_{18}N_2O_3$ (310.35): C 69.66, H 5.85, N 9.03. Found: C 69.58, H 5.84, N 8.99%.

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