Synthesis of Novel Quinazoline Non-nucleosides Analogues of The HIV Drug Emivirine

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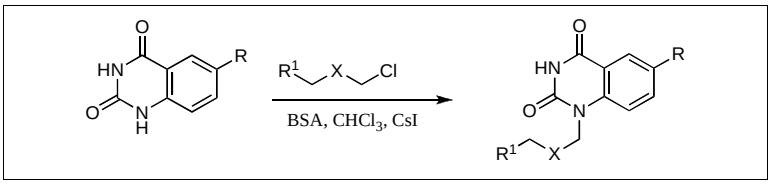

Novel quinazoline non-nucleosides analogues of Emivirine were described. Compounds **1a-c** were silylated and reacted with the appropriate chloroethers (**2a-c**) in the presence of CsI to give the corresponding non-nucleosides **3a-h** and **4a-h**. Silylation of **1a-c** and treatment with bis(allyloxy)methanes (**5a,b**) afforded the corresponding 1-(allyloxymethyl)quinazolines **6a-f**. 1-(Propargyloxymethyl)-quinazolines **8a,b** were obtained by treatment of the silylated **1a,b** with bis(propargyloxy)methane (**7**) in the presence of TMS triflate.

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Reverse transcriptase (RT) being essential in the replication process of human immunodeficiency virus (HIV) can still be considered as one of the most attractive targets for the development of new antiretroviral drugs [1,2]. In recent years, much effort has been put into the design and synthesis of HIV-1 non-nucleoside RT inhibitors (NNRTIs) [3,4]. NNRTIs bind to a specific allosteric site on HIV-1 RT, approximately 10 Å away from the catalytic site. Unlike the nucleoside reverse transcriptase inhibitors (NRTIs) which require anabolism to the triphosphate to become chain-terminating substrate, NNRTIs bind directly to the enzyme and inhibit catalytic function by distorting the three-dimensional structure of the HIV-1 RT [5].

Among the representatives of the NNRTIs, 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine (HEPT) has been extensively studied for many years [6]. Although HEPT did not show very high activity against HIV-1, it was considered an interesting lead compound for the synthesis of analogues, among them the 6-benzyl-1-(ethoxymethyl)-5-isopropyluracil (Emivirine, formerly MKC-442) [7], which showed high activity against HIV-1, and was chosen as a candidate for clinical trials with AIDS patients [8].

Three NNRTIs, namely, nevirapine (Viramune) [9], delavirdine (Rescriptor) [10] and efavirenz (Sustiva, Stocrin) [11], have so far been formally licensed for clinical use in the treatment of HIV-1 infections [12]. Emivirine should have been the fourth one, but its development has, in the meantime, been halted as it was found to activate the liver enzyme Cytochrome P450, which metabolizes protease inhibitors [13].

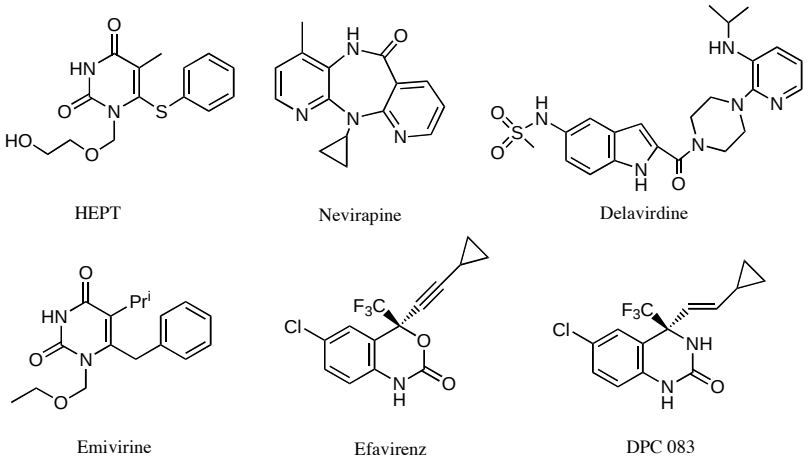


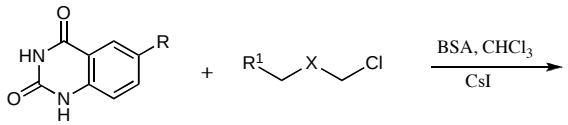
Figure 1

The quinazoline compound DPC 083, a derivative of efavirenz, has marked activity against HIV-1 strains with various mutations in their reverse transcriptase (L100I, K103N, Y181C, Y188L, K103N + L100I and K103N + Y181C) [14]. This fact promoted me to synthesize other new quinazoline non-nucleoside derivatives.

Recently, Emivirine analogues with a 1-allyloxymethyl substituent showed activity against HIV-1 in the picomolar range were reported [15]. As a part of my continuing interest in the chemistry of NNRTIs [15-20], and in an effort to find a new generation of HIV inhibitors, the present work describes a series of novel quinazoline non-nucleosides analogues of Emivirine, which also regarded as DPC 083 derivatives, with ethoxymethyl, allyloxymethyl and propargyloxymethyl substituents at N-1 position.

Quinazoline-2,4-diones **1a-c** were prepared according to the method described by Dunkel *et al* [21], and silylated with *N,O*- bis-(trimethylsilyl)acetamide (BSA) [22] in anhydrous chloroform. Alkylation of the silylated quinazolines with chloromethyl methyl ether (**2a**), chloromethyl ethyl ether (**2b**) and/or chloromethyl methyl sulfide (**2c**) in the presence of cesium iodide afforded the corresponding Emivirine analogues **3a-h** in 44-80 % yields. 1,3-Bis-alkylated quinazolines **4a-d** were also obtained as minor products of alkylation reaction on unsubstituted quinazoline-2,4-dione (**1a**) and its 6-methyl derivative (**1b**), but not in case of the chloro derivative **1c**. This may be attributed to the electron withdrawing effect of the chloro substituent that deactivates the nucleophilic reaction at *N*-3 position of the quinazoline ring (Scheme 1).

Scheme 1

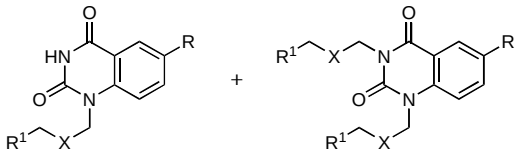


1a-c

	R
a	H
b	CH_3
c	Cl

2a-c

	R^1	X
a	H	O
b	CH_3	O
c	H	S



3a-h

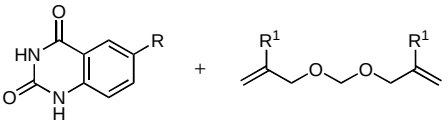
	R	R^1	X
a	H	H	O
b	H	CH_3	O
c	H	H	S
d	CH_3	H	O
e	CH_3	CH_3	O
f	Cl	H	O
g	Cl	CH_3	O
h	Cl	H	S

4a-d

	R	R^1	X
a	H	H	O
b	H	CH_3	O
c	CH_3	H	O
d	CH_3	CH_3	O

Compounds **1a-c** were silylated with BSA in anhydrous acetonitrile followed by alkylation with bis(allyloxy)-methane (**5a**) and/or bis(2-methylallyloxy)methane (**5b**) under the Vorbrüggen conditions [23] using trimethylsilyl trifluoromethane sulfonate (TMS triflate) to give the corresponding 1-allyloxymethylquinazolines (**6a-c**) and 1-(2-methylallyloxymethyl)quinazolines (**6d-f**) in 78-82 % and 76-81 % yields, respectively (Scheme 2).

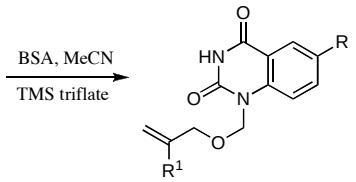
Scheme 2



1a-c

5a,b

	R^1
a	H
b	CH_3

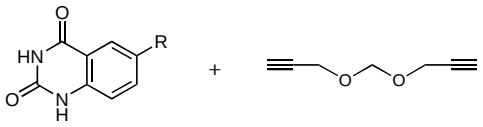


6a-f

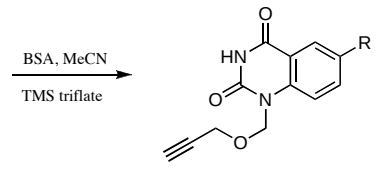
	R	R^1
a	H	H
b	CH_3	H
c	Cl	H
d	H	CH_3
e	CH_3	CH_3
f	Cl	CH_3

On the other hand, *N*-1 propargyloxymethylquinazoline-2,4-diones **8a,b** were prepared in good yields by silylation of **1a,b** in acetonitrile using BSA, followed by treatment with bis(propargyloxy)methane (**7**) in the presence of TMS triflate (Scheme 3).

Scheme 3



1a,b **7**



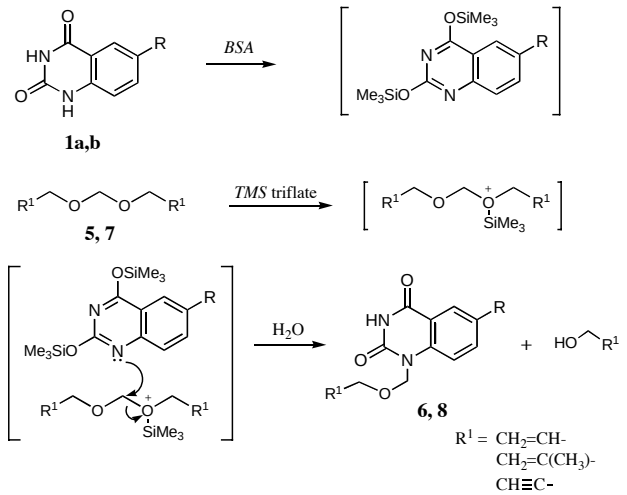
8a,b

	R
a	H
b	CH_3

Only N-1 alkylated products were obtained on reaction of compounds **1a-c** with the acetals **5a,b** and **7** in the

presence of TMS trifilate. This may be due the steric factor. Treatment of the appropriate acetal with trimethylsilyl trifluoromethane sulfonate (TMS triflate) afforded the bulky oxonium ion that undergo a nucleophilic attack by the silylated quinazoline – at *N*-1 position- on the electron-deficient carbon followed by a cleavage of CH_2-O bond to give **6a-f** and **8a,b** after hydrolysis (Scheme 4).

Scheme 4



The acetals **5a,b** and **7** were prepared in a previous work [15] by refluxing the appropriate alcohol, dibromomethane and tetrabutylammonium bromide in anhydrous benzene according to the method of Nazaretyan *et al* [24].

N-1 Alkylation products were proved by NOE enhancement in the aromatic proton 8-H when N-1 CH_2 was irradiated. Mass spectra of all compounds containing chlorine atom showed fragments corresponding to the typical pattern of chlorine isotopes (^{35}Cl and ^{37}Cl).

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). Mass (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 H. C. Orsted 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.

Quinazoline Non-nucleoside Derivatives **3a-h** and **4a-d**.

General Procedure.

N,O-Bis(trimethylsilyl)acetamide (BSA) (0.87 ml, 0.0035 mol) was added to a suspension of quinazoline-2,4-dione (**1a-c**, 0.001 mol) 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), the appropriate chloroethers **2a-c** (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 mixture was extracted with CH_2Cl_2 (3 x 50 ml). The organic phase was collected, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed on silica gel column using 0-1 % MeOH/$CHCl_3$ to give **3a-h** and **4a-d**.

1-(Methyloxymethyl)quinazoline-2,4(1*H*,3*H*)-dione (**3a**).

This compound was obtained as white crystals; yield 1.41 g (68 %); mp 208-209 °C. ^1H nmr (DMSO-d_6): δ 3.32 (s, 3H, CH_3), 5.47 (s, 2H, CH_2), 7.28-8.03 (m, 4H, H_{arom}), 11.64 (s, 1H, NH); ^{13}C nmr (DMSO-d_6): δ 55.60 (CH_3), 73.31 (CH_2), 115.35, 115.73, 123.06, 127.23, 135.04, 140.37 (C_{arom}), 150.57 (C-2), 161.71 (C-4); ms: (EI) m/z (%) = 206 (M^+, 28).

Anal. Calcd. for $C_{10}H_{10}N_2O_3$ (206.198): C 58.25, H 4.89, N 13.59. Found C 58.22, H 4.83, N 13.48.

1-(Ethyloxymethyl)quinazoline-2,4(1*H*,3*H*)-dione (**3b**).

This compound was obtained as white crystals; yield 1.58 g (72 %); mp 174-175 °C. ^1H nmr (DMSO-d_6): δ 1.09 (t, *J* = 7.0 Hz, 3H, CH_3), 3.55 (q, *J* = 7.0 Hz, 2H, CH_2), 5.51 (s, 2H, CH_2), 7.28-8.03 (m, 4H, H_{arom}), 11.64 (s, 1H, NH); ^{13}C nmr (DMSO-d_6): δ 14.81 (CH_3), 63.36 (CH_2), 71.81 (CH_2), 115.37, 115.71, 123.03, 127.22, 135.05, 140.45 (C_{arom}), 150.51 (C-2), 161.72 (C-4); ms: (EI) m/z (%) = 220 (M^+, 54).

Anal. Calcd. for $C_{11}H_{12}N_2O_3$ (220.23): C 59.99, H 5.49, N 12.72. Found C 59.63, H 5.44, N 12.57.

1-(Methylthiomethyl)quinazoline-2,4(1*H*,3*H*)-dione (**3c**).

This compound was obtained as white crystals; yield 1.42 g (64 %); mp 204-205 °C. ^1H nmr (DMSO-d_6): δ 2.17 (s, 3H, CH_3), 5.28 (s, 2H, CH_2), 7.28-8.05 (m, 4H, H_{arom}), 11.68 (s, 1H, NH); ^{13}C nmr (DMSO-d_6): δ 14.07 (CH_3), 45.02 (CH_2), 115.66, 116.06, 122.83, 127.51, 134.84, 139.63 (C_{arom}), 150.33 (C-2), 161.47 (C-4); ms: (EI) m/z (%) = 222 (M^+, 29).

Anal. Calcd. for $C_{10}H_{10}N_2O_2S$•0.25 H_2O (226.77): C 52.97, H 4.67, N 12.35. Found C 52.67, H 4.29, N 12.17.

6-Methyl-1-(methyloxymethyl)quinazoline-2,4(1*H*,3*H*)-dione (**3d**).

This compound was obtained as white crystals; yield 0.97 g (44 %); mp 207-209 °C. ^1H nmr (DMSO-d_6): δ 2.36 (s, 3H, CH_3), 3.30 (s, 3H, CH_3), 5.44 (s, 2H, CH_2), 7.32-7.80 (m, 3H, H_{arom}), 11.57 (s, 1H, NH); ^{13}C nmr (DMSO-d_6): δ 19.91 (CH_3), 55.52 (CH_3), 73.26 (CH_2), 115.29, 115.53, 126.83, 132.40, 135.88, 138.21 (C_{arom}), 150.53 (C-2), 161.70 (C-4); ms: (EI) m/z (%) = 220 (M^+, 53).

Anal. Calcd. for $C_{11}H_{12}N_2O_3$•0.125 H_2O (222.48): C 59.39, H 5.55, N 12.59. Found: C 59.27, H 5.36, N 12.28.

1-(Ethyloxymethyl)-6-methylquinazoline-2,4(1*H*,3*H*)-dione (**3e**).

This compound was obtained as white crystals; yield 1.11 g (47 %); mp 178-180 °C. ^1H nmr (DMSO-d_6): δ 1.08 (t, *J* = 7.0 Hz, 3H, CH_3), 2.36 (s, 3H, CH_3), 3.52 (q, *J* = 7.0 Hz, 2H, CH_3), 5.48 (s, 2H, CH_2), 7.35-7.80 (m, 3H, H_{arom}), 11.56 (s, 1H, NH); ^{13}C nmr (DMSO-d_6): δ 14.81 (CH_3), 19.91 (CH_3), 63.27 (CH_2), 71.74 (CH_2), 115.33, 115.50, 126.80, 132.36, 135.91, 138.27 (C_{arom}), 150.45 (C-2), 161.69 (C-4); ms: (EI) m/z (%) = 234 (M^+, 74).

Anal. Calcd. for $C_{12}H_{14}N_2O_3$•0.125 H_2O (236.51): C 60.95, H 6.07, N 11.84. Found C 60.90, H 5.93, N 11.72.

6-Chloro-1-(methyloxymethyl)quinazoline-2,4(1*H*,3*H*)-dione (**3f**).

This compound was obtained as white crystals; yield 1.61 g (67 %); mp 230-232 °C. ^{1}H nmr (DMSO-d_6): δ 3.32 (s, 3H, CH_3), 5.45 (s, 2H, CH_2), 7.49-7.92 (m, 3H, H_{arom}), 11.80 (s, 1H, NH); ^{13}C nmr (DMSO-d_6): δ 55.66 (CH_3), 73.51 (CH_2), 117.35, 117.70, 126.13, 127.36, 134.66, 139.26 (C_{arom}), 150.32 (C-2), 160.70 (C-4); ms: (EI) m/z (%) = 240 (M^+, 42).

Anal. Calcd. For $C_{10}H_9ClN_2O_3$ (240.64): C 49.91, H 3.77, N 11.64. Found C 49.97, H 3.60, N 11.59.

6-Chloro-1-(ethyloxymethyl)quinazoline-2,4(1*H*,3*H*)-dione (**3g**).

This compound was obtained as white crystals; yield 2.03 g (80 %); mp 194-196 °C. ^{1}H nmr (DMSO-d_6): δ 1.09 (t, *J* = 7.0 Hz, 3H, CH_3), 3.54 (q, *J* = 7.0 Hz, 2H, CH_2), 5.49 (s, 2H, CH_2), 7.47-7.91 (m, 3H, H_{arom}), 11.79 (s, 1H, NH); ^{13}C nmr (DMSO-d_6): δ 14.77 (CH_3), 63.40 (CH_2), 71.99 (CH_2), 117.30, 117.72, 126.10, 127.32, 134.67, 139.31 (C_{arom}), 150.25 (C-2), 160.69 (C-4); ms: (EI) m/z (%) = 254 (M^+, 48).

Anal. Calcd. for $C_{11}H_{11}ClN_2O_3$ (254.67): C 51.88, H 4.35, N 11.00. Found C 51.89, H 4.26, N 10.92.

6-Chloro-1-(methylthiomethyl)quinazoline-2,4(1*H*,3*H*)-dione (**3h**).

This compound was obtained as white crystals; yield 1.56 g (61 %); mp 229-231 °C. ^{1}H nmr (DMSO-d_6): δ 2.15 (s, 3H, CH_3), 5.27 (s, 2H, CH_2), 7.50-7.94 (m, 3H, H_{arom}), 11.83 (s, 1H, NH); ^{13}C nmr (DMSO-d_6): δ 13.94 (CH_3), 45.21 (CH_2), 117.68, 118.04, 126.38, 127.20, 134.40, 138.54 (C_{arom}), 150.10 (C-2), 160.45 (C-4); ms: (EI) m/z (%) = 256 (M^+, 54).

Anal. Calcd. for $C_{10}H_9ClN_2O_2S$•0.5H_2O (265.72): C 45.20, H 3.79, N 10.54. Found C 45.53, H 3.32, N 10.46.

1,3-Bis(methyloxymethyl)quinazoline-2,4(1*H*,3*H*)-dione (**4a**).

This compound was obtained as white crystals; yield 0.175 g (7 %); mp 158-159 °C. ^{1}H nmr (deuteriochloroform): δ 3.42 (s, 3H, CH_3), 3.46 (s, 3H, CH_3), 5.51 (s, 2H, CH_2), 5.54 (s, 2H, CH_2), 7.29-8.04 (m, 4H, H_{arom}); ^{13}C nmr (deuteriochloroform): δ 56.47 (CH_3), 57.63 (CH_3), 72.81 (CH_2), 75.28 (CH_2), 115.33, 115.72, 123.11, 127.25, 135.01, 140.46 (C_{arom}), 151.34 (C-2), 161.82 (C-4); ms: (MALDI,) m/z = 273 (M + Na^+).

Anal. Calcd. for $C_{12}H_{14}N_2NaO_4$: 273.0845. Found 273.0834.

1,3-Bis(ethyloxymethyl)quinazoline-2,4(1*H*,3*H*)-dione (**4b**).

This compound was obtained as white crystals; yield 0.176 g (6 %); mp 114-115 °C. ^{1}H nmr (deuteriochloroform): δ 1.20 (t, *J* = 6.9 Hz, CH_3), 1.22 (t, *J* = 7.1 Hz, 3H CH_3), 3.68 (q, *J* = 6.9 Hz, 2H, CH_2), 3.70 (q, *J* = 7.1 Hz, CH_2), 5.51 (s, 2H, CH_2), 5.59 (s, 2H, CH_2), 7.29-8.02 (m, 4H, H_{arom}); ^{13}C nmr (deuteriochloroform): δ 14.93 (CH_3), 15.16 (CH_3), 64.52 (CH_2), 65.69 (CH_2), 71.13 (CH_2), 73.62 (CH_2), 115.29, 115.68, 123.17, 127.34, 135.07, 140.52 (C_{arom}), 151.42 (C-2), 161.77 (C-4); ms: (MALDI) m/z = 301 (M + Na^+).

Anal. Calcd. for $C_{14}H_{18}N_2NaO_4$: 301.1158. Found 301.1153.

1,3-Bis(methyloxymethyl)-6-methylquinazoline-2,4(1*H*,3*H*)-dione (**4c**)

This compound was obtained as white crystals; yield 0.51 g (19 %); mp 142-143 °C. ^{1}H nmr (deuteriochloroform): δ 2.41 (s, 3H, CH_3), 3.45 (s, 3H, CH_3), 3.48 (s, 3H, CH_3), 5.54 (s, 2H, CH_2), 5.57 (s, 2H, CH_2), 7.30-7.51 (m, 2H, H_{arom}), 8.02 (s, 1H, H_{arom}); ^{13}C nmr (deuteriochloroform): δ 20.50 (CH_3), 56.60 (CH_3), 57.82 (CH_3), 72.54 (CH_2), 75.12 (CH_2), 114.87, 115.31, 128.63, 133.63, 136.52, 137.43 (C_{arom}), 151.50 (C-2), 161.99 (C-4); ms: (MALDI) m/z = 287 (M + Na^+).

Anal. Calcd. for $C_{13}H_{16}N_2NaO_4$: 287.1002. Found 287.0998.

1,3-Bis(ethyloxymethyl)-6-methylquinazoline-2,4(1*H*,3*H*)-dione (**4d**)

This compound was obtained as white crystals; yield 0.62 g (21 %); mp 127-128 °C. ^{1}H nmr (deuteriochloroform): δ 1.18 (t, *J* = 6.9 Hz, 3H, CH_3), 1.21 (t, *J* = 7.1 Hz, 3H, CH_3), 2.17 (s, 3H, CH_3), 3.69 (q, *J* = 6.9 Hz, 2H, CH_2), 3.71 (q, *J* = 7.1 Hz, 2H, CH_2), 5.57 (s, 2H, CH_2), 5.63 (s, 2H, CH_2), 7.34-7.50 (m, 2H, H_{arom}), 8.01 (s, 1H, H_{arom}); ^{13}C nmr (deuteriochloroform): δ 14.96 (CH_3), 15.18 (CH_3), 20.49 (CH_3), 64.58 (CH_2), 65.79 (CH_2), 71.03 (CH_2), 73.68 (CH_2), 114.96, 115.35, 128.56, 133.47, 136.43, 137.57 (C_{arom}), 151.41 (C-2), 162.01 (C-4); ms: (MALDI) m/z = 315 (M + Na^+).

Anal. Calcd. for $C_{15}H_{20}N_2NaO_4$: 315.1315. Found 315.1302.

General Procedure for Preparation of Compounds **6a-f**.

Compound **1a-c** (0.001 mol) was stirred in anhydrous CH_3CN (15 ml) under nitrogen and *BSA* (0.87 ml, 0.0035 mol) was added. After a clear solution was obtained (10 min), the reaction mixture was cooled to -50 °C and TMS triflate (0.18 ml, 0.001 mol) was added followed by dropwise addition of the appropriate acetal **5a,b** (0.002 mol). The mixture was stirred at room temperature for 3 h. The reaction was quenched with sat. aq. $NaHCO_3$ solution (5 ml) and evaporated under reduced pressure. The residue was extracted with ether (3 x 50 ml), the combined organic fractions were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed on silica gel column with 0-1 % MeOH/$CHCl_3$ to afford the desired compounds **6a-f**

1-(Allyloxymethyl)quinazoline-2,4(1*H*,3*H*)-dione (**6a**).

This compound was obtained as white crystals; yield 1.9 g (82 %); mp 144-145 °C. ^{1}H nmr (deuteriochloroform): δ 4.17 (bs, 2H, CH_2), 5.17-5.35 (m, 2H, CH_2=), 5.64 (s, 2H, CH_2), 5.82-5.91 (m, 1H, CH), 7.27-8.23 (m, 4H, H_{arom}), 9.75 (s, 1H, NH); ^{13}C nmr (deuteriochloroform): δ 70.07 (CH_2), 72.59 (CH_2), 117.82 (CH_2=), 133.51 (=CH-), 115.34, 116.02, 123.75, 128.46, 135.52, 140.63 (C_{arom}), 150.94 (C-2), 162.19 (C-4); ms: (EI) m/z (%) = 232 (M^+, 18).

Anal. Calcd. for $C_{12}H_{12}N_2O_3$•0.125H_2O (234.49): C 61.47, H 5.26, N 11.94. Found C 61.57, H 5.13, N 11.83.

1-(Allyloxymethyl)-6-methylquinazoline-2,4(1*H*,3*H*)-dione (**6b**)

This compound was obtained as white crystals; yield 1.96 g (80 %); mp 147-148 °C. ^{1}H nmr (DMSO-d_6): δ 2.36 (s, 3H, CH_3), 4.07 (dd, *J* = 1.3, 4.0 Hz, 2H, CH_2), 5.11-5.28 (m, 2H, CH_2=), 5.51 (s, 2H, CH_2), 5.82-5.91 (m, 1H, CH), 7.36-7.80 (m, 3H, H_{arom}), 11.57 (s, 1H, NH); ^{13}C nmr (DMSO-d_6): δ 19.90 (CH_3), 68.77 (CH_2), 71.71 (CH_2), 116.64 (CH_2=), 134.34 (=CH-), 115.30, 115.52, 126.83, 132.40, 135.90, 138.25 (C_{arom}), 150.46 (C-2), 161.68 (C-4); ms: (EI) m/z (%) = 246 (M^+, 35).

Anal. Calcd. for $C_{13}H_{14}N_2O_3$ (246.26): C 63.40, H 5.73, N 11.38. Found C 63.32, H 5.64, N 11.33.

1-(Allyloxymethyl)-6-chloroquinazoline-2,4(1*H*,3*H*)-dione (**6c**).

This compound was obtained as white crystals; yield 2.09 g (78 %); mp 154-155 °C. ^{1}H nmr (DMSO-d_6): δ 4.08 (dd, *J* = 1.3, 4.1 Hz, 2H, CH_2), 5.11-5.29 (m, 2H, CH_2=), 5.52 (s, 2H, CH_2), 5.80-5.93 (m, 1H, CH), 7.49-7.92 (m, 3H, H_{arom}), 11.80 (s, 1H, NH); ^{13}C nmr (DMSO-d_6): δ 68.85 (CH_2), 71.92 (CH_2), 117.72 (CH_2=), 134.25 (=CH-), 116.78, 117.33, 126.12, 127.36, 134.68, 139.30 (C_{arom}), 150.24 (C-2), 160.69 (C-4); ms (EI) m/z (%) = 266 (M^+, 18).

Anal. Calcd. for $C_{12}H_{11}ClN_2O_3$ (266.68): C 54.05, H 4.16, N 10.50. Found C 53.83, H 4.04, N 10.33.

1-[(2-Methylallyl)oxymethyl]quinazoline-2,4(1*H*,3*H*)-dione (**6d**).

This compound was obtained as white crystals; yield 2.0 g (81 %); mp 134-135 °C. ^{1}H nmr (deuteriochloroform): δ 1.69 (s, 3H, CH_3), 4.08 (s, 2H, CH_2), 4.89, 5.00 (2 x s, 2H, CH_2=), 5.64 (s, 2H, CH_2), 7.27-8.21 (m, 4H, H_{arom}), 9.80 (s, 1H, NH); ^{13}C nmr (deuteriochloroform): δ 19.43 (CH_3), 72.67 (CH_2), 73.00 (CH_2), 112.66 (CH_2=), 115.30, 115.99, 123.70, 128.42, 135.47, 140.65 (C_{arom}), 141.11 (=*C*(Me)-), 150.91 (C-2), 162.21 (C-4); ms: (EI) m/z (%) = 246 (M^+, 6).

Anal. Calcd. for $C_{13}H_{14}N_2O_3$ (246.26): C 63.40, H 5.73, N 11.38. Found C 63.31, H 5.70, N 11.29.

6-Methyl-1-[(2-methylallyl)oxymethyl]quinazoline-2,4(1*H*,3*H*)-dione (**6e**).

This compound was obtained as white crystals; yield 1.97 g (76 %); mp 156-158 °C. ^{1}H nmr (DMSO-d_6): δ 1.62 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 3.98 (s, 2H, CH_2), 4.82, 4.92 (2 x s, 2H, CH_2=), 5.51 (s, 2H, CH_2), 7.37-7.80 (m, 3H, H_{arom}), 11.57 (s, 1H, NH); ^{13}C nmr (DMSO-d_6): δ 19.19 (CH_3), 19.92 (CH_3), 71.65 (CH_2), 71.83 (CH_2), 111.55 (CH_2=), 115.30, 115.53, 126.85, 132.40, 135.89, 138.29 (C_{arom}), 141.53 (=*C*(Me)-), 150.47 (C-2), 161.71 (C-4); ms: (EI) m/z (%) = 260 (M^+, 12).

Anal. Calcd. for $C_{14}H_{16}N_2O_3$ (260.29): C 64.60, H 6.20, N 10.76. Found C 64.60, H 6.16, N 10.73.

6-Chloro-1-[(2-methylallyl)oxymethyl]quinazoline-2,4(1*H*,3*H*)-dione (**6f**).

This compound was obtained as white crystals; yield 2.25 g (80 %); mp 174-175 °C. ^{1}H nmr (DMSO-d_6): δ 1.62 (s, 3H, CH_3), 3.98 (s, 2H, CH_2), 4.83, 4.92 (2 x s, 2H, CH_2=), 5.52 (s, 2H, CH_2), 7.50-7.92 (m, 3H, H_{arom}), 11.79 (s, 1H, NH); ^{13}C nmr (DMSO-d_6): δ 19.19 (CH_3), 71.70 (CH_2), 72.02 (CH_2), 111.66 (CH_2=), 117.33, 117.74, 126.14, 127.37, 134.69, 139.34 (C_{arom}), 141.45 (=*C*(Me)-), 150.26 (C-2), 160.71 (C-4); ms: (EI) m/z (%) = 280 (M^+, 20).

Anal. Calcd. for $C_{13}H_{13}ClN_2O_3$ (280.71): C 55.62, H 4.67, N 9.98. Found C 55.47, H 4.52, N 9.85.

1-(Propargyloxymethyl)quinazoline-2,4(1*H*,3*H*)-diones (**8a,b**).

BSA (0.87 ml, 0.0035 mol) was added to a suspension of compound **1a,b** (0.001 mol) in anhydrous CH_3CN (15 ml) and the reaction mixture was stirred under nitrogen at room temperature. After a clear solution was obtained (10 min), the mixture was cooled to -50 °C and TMS triflate (0.64 ml, 0.004 mol) was added followed by dropewise addition of bis(propargyloxy)methane (**7**, 0.248 g, 0.002 mol). The reaction mixture was stirred at room temperature for 4 h, then sat. aq. $NaHCO_3$ solution (5 ml) was added. The solvent was evaporated under reduced pressure and the residue was extracted with ether (3 x 50 ml). The ether phase was collected, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed on silica gel column using 0-1 % MeOH/$CHCl_3$ to give **8a,b**.

1-(Propargyloxymethyl)quinazoline-2,4(1*H*,3*H*)-dione (**8a**).

This compound was obtained as white crystals; yield 1.5 g (65 %); mp 181-182 °C. ^{1}H nmr (DMSO-d_6): δ 3.42 (t, *J* = 2.4 Hz, 1H, CH), 4.28 (d, *J* = 2.4 Hz, CH_2), 5.58 (s, 2H, CH_2), 7.31-8.02 (m, 4H, H_{arom}), 11.64 (s, 1H, NH); ^{13}C nmr (DMSO-d_6): δ 55.78 (CH_2), 71.46 (CH_2), 77.05 (CH), 79.85 (≡C-), 115.31, 115.78, 123.11, 127.26, 136.03, 140.38 (C_{arom}), 150.54 (C-2), 161.73 (C-4); ms (EI) m/z (%) = 230 (M^+, 26).

Anal. Calcd. for $C_{12}H_{10}N_2O_3$•0.25H_2O (234.73): C 61.40, H 4.51, N 11.93. Found C 61.67, H 4.29, N 11.83.

6-Methyl-1-(propargyloxymethyl)quinazoline-2,4(1*H*,3*H*)-dione (**8b**).

This compound was obtained as white crystals; yield 1.49 g (61 %); mp 195-196 °C. ^{1}H nmr (DMSO-d_6): δ 2.36 (s, 3H, CH_3), 3.41 (t, *J* = 2.3 Hz, 1H, CH), 4.25 (d, *J* = 2.3 Hz, 2H, CH_2), 5.55 (s, 2H, CH_2), 7.34-7.80 (m, 3H, H_{arom}), 11.57 (s, 1H, NH); ^{13}C nmr (DMSO-d_6): δ 19.91 (CH_3), 55.71 (CH_2), 71.42 (CH_2), 77.00 (CH), 79.83 (≡C-), 115.26, 115.57, 126.85, 132.42, 135.86, 138.22 (C_{arom}), 150.48 (C-2), 161.69 (C-4); ms (EI) m/z (%) = 244 (M^+, 45).

Anal. Calcd. for $C_{13}H_{12}N_2O_3$ (244.25): C 63.93, H 4.95, N 11.47. Found C 63.89, H. 4.96, N 11.42.

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