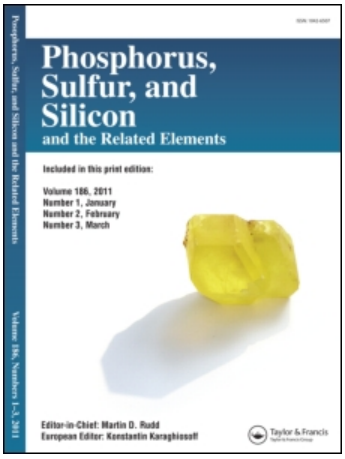

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SOME ASPECTS ON ACYCLO- 4-[QUINAZOLIN-3-YL]BENZENESULFONAMIDE NON-NUCLEOSIDES SYNTHESIS

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SOME ASPECTS ON ACYCLO-4-[QUINAZOLIN-3-YL]BENZENESULFONAMIDE NON-NUCLEOSIDES SYNTHESIS

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*The reaction of 4-[1,2,3,4-tetrahydroquinazolin-2,4-dion-3-yl]benzenesulfonamide **4** and 4-[2-thioxo-1,2,3,4 tetrahydroquniazolin-4-on-3-yl]benznesulfonamide **5** with chloromethylethyl ether, chloromethylbenzyl ether, and (2-acetoxyethoxy)methyl bromide afforded compounds **7a–c**, **8a,b**, and **13** which are analogues to MKC-442, TNK 561, and HEPT.*

Keywords: Benzenesulfonamide; MKC-442; quinazolines; non-nucleosides; TNK 561

A wide spectrum of biological activities associated with quinazolines and their condensed derivatives, some derivatives show antiviral, CNS-depressant, anticonvulsant, antimalaric, and anticancer activity.[1–5] HIV is known as the causative agent for AIDS,[6] enormous efforts have been made to understand the life cycle of this retrovirus, in order to define biochemical targets for its selective inhibition by chemotherapeutic agent. Reverse transcriptase (RT), the polymerase specifically coded by HIV, was in this respect one of the first targets to be identified for the development of anti-AIDS drugs. These drugs acting as inhibitors of the reverse transcriptase enzyme, through interaction with reverse transcriptase (RT) at an "allosteric" binding pocket[7] which is proximal to the catalytic site for DNA synthesis.[8] Structure activity studies in the 1-[(2-hydroxyethoxymethyl)-6-phenylthio]thymine or HEPT[9,10] have resulted in the identification of several new promising clinical candidates,

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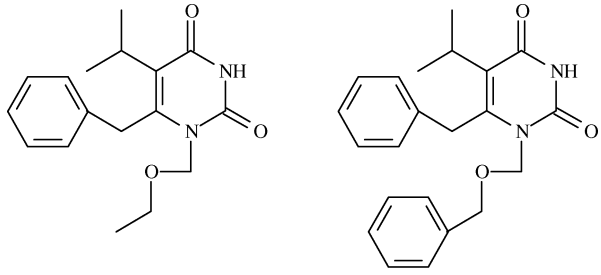
including MKC-442 and TNK 561.[11,*] As a part of our program of research on the synthesis of new glycosides with considerable biological activity.[12–14]

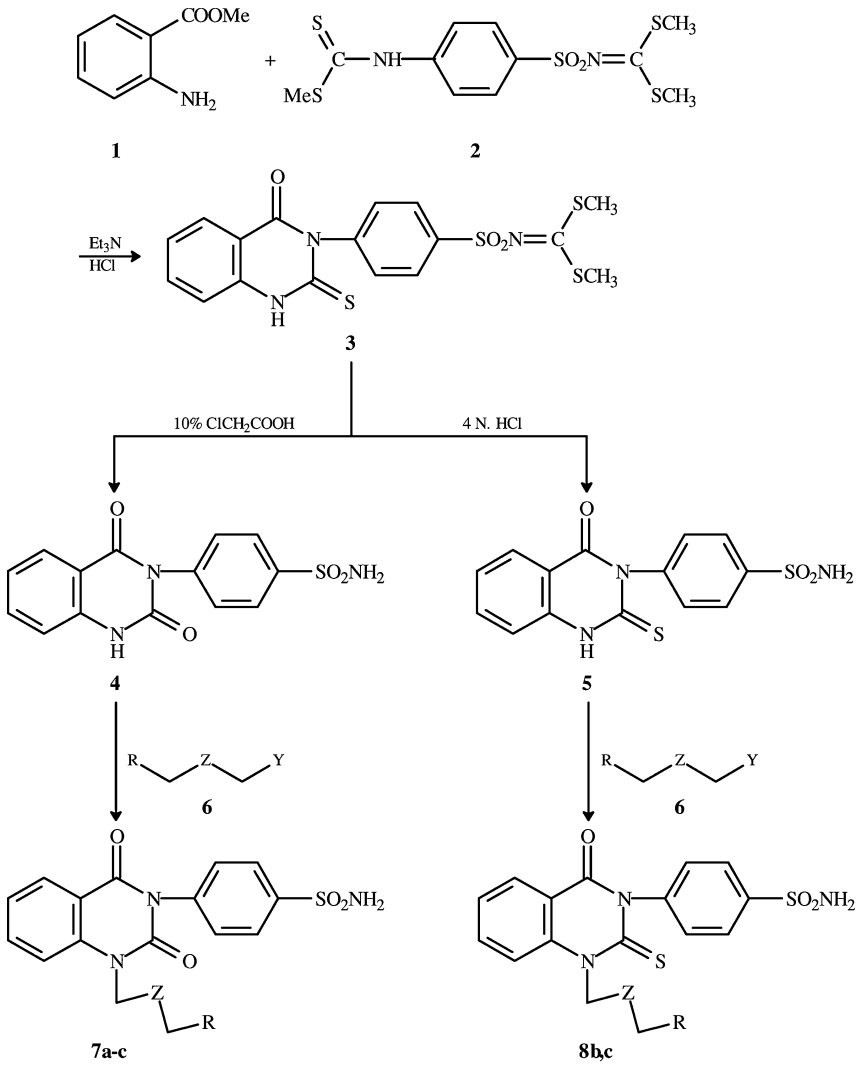


MKC -442 **TNK 561**

RESULTS AND DISCUSSION

The aim of the work mentioned in this article, synthesis of analogues MKC-442, TNK 561, and HEPT Which bearing benzensulfonamide **7b**,**c**, **8b**,**c**, and **13**. It is expected that the benzenesulfonamide will exhibit high biologically activity.[15] The treatment of dimethyl N-(4-oxo-2-thioxo-1,2,3,4-tetrahydro-3-quinazolinylsulfonyl)] dithiocarbonoimidate **3**[16] with 10% $ClCH_2COOH$ yielded 4-[1,2,3,4-tetrahydroquina-zolin-2,4-dion-3-yl]benzenesulfonamide **4**. While the treatment of compound **3** with 4N HCl afforded 4-[2-thioxo-1,2,3,4-tetrahydroquinazolin-4-on-3-yl]benzenesulfonamide **5**. 4-(Quinazolin-3-yl)benzenesulfonamide derivatives **4** or **5** were further reacted with chloromethylethyl ether, chloromethylbenzyl ether or chloromethyl methylsulphide in dry DMF and sodium hydride to produce compounds **7a**,**c** and **8a**,**b** which are analogues to MKC-442 and TNK 561. It is expected that the benzenesulfonamide strong electron withdrawing group will directed the electrophilic reaction in 4-[2-thioxo-1,2,3,4-tetrahydroquinozolin-4-on-3-yl]benzenesulfonamide **5** towards the nitrogen and not the sulfur atoms to form N^1- Nucleosides **8a**,**b**. On the other hand when the benzenesulfonamide was replaced by an aryl group, the electrophilic reaction was directed towards the sulfur atom to produce S^2-nucleosides.[17]

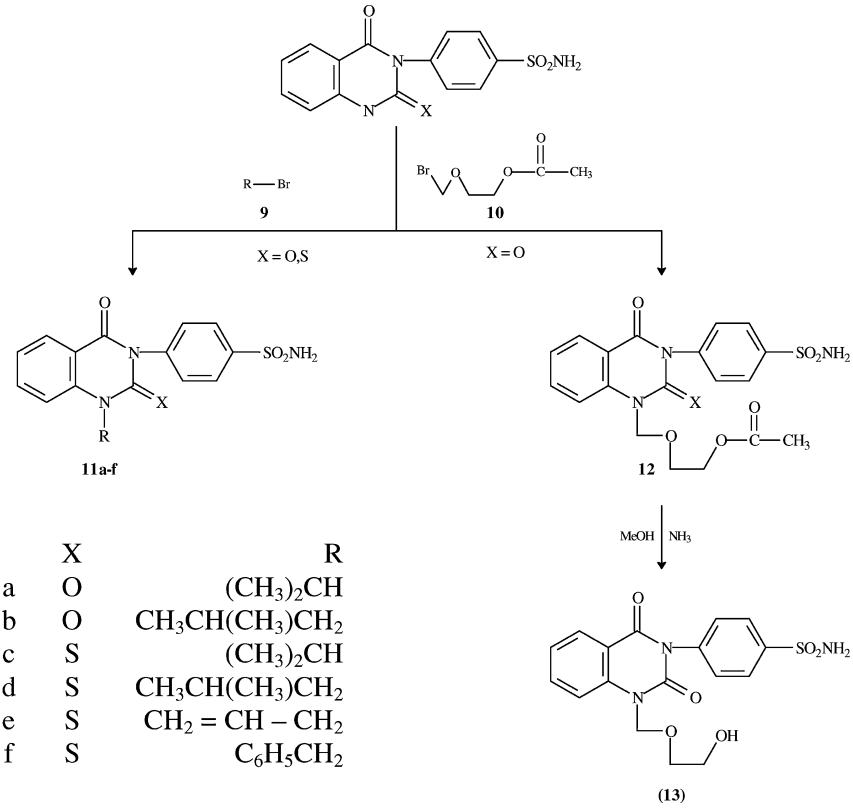
*MKC-442 demonstrating higher synthestic anti-HIV activity with AZT than neuirapine will soon enter clinical studies.



7	R	Z	8	R	Z
a	H	S	a	CH_3	S
b	CH_3	O	b	C_6H_5	O
c	C_6H_5	O			

SCHEME 1

4-[Quinazolin-3-yl]benzenesulfonamide derivatives **4** or **5** were reacted with isopropyl bromide, secondary butyl bromide, allyl bromide, or benzyl bromide to form non-nucleoside compounds **11a–f**. 4-[1,2,3,4-Tetrahydroquinazolin-2,4-dion-3-yl]benzenesufonamide **4** was reacted with (2-acetoxyethoxy)methyl bromide **10** to furnish **12**. Deacetylation of **12** was done by methanolic ammonia to give 4-[2-(2-hydroxyethoxy)methyl-1,2,3,4-tetrahydroquinazolin-2,4-dion-3-yl] benzenesulfonamide **13** which is analogue to HEPT.



	X	R
a	O	$(CH_3)_2CH$
b	O	$CH_3CH(CH_3)CH_2$
c	S	$(CH_3)_2CH$
d	S	$CH_3CH(CH_3)CH_2$
e	S	$CH_2 = CH - CH_2$
f	S	$C_6H_5CH_2$

SCHEME 2

EXPERIMENTAL

NMR spectra were recorded on a Bruker 250 FT NMR spectrometer, TMS as internal standard. MS were recorded on a varian MAT. 311A spectrometer. The silica gel (0.040–0.63 nm) was used for CC

purchased from Merck. Results of elemental analysis were in acceptable range.

4-[1,2,3,4-Tetrahydroquinazolin-2,4-dion-3-yl]-benenesulfonamide (4)

Compound 3 (450 mg, 1 mmol) in 10 ml of 10% $ClCH_2COOH$ was stirred at room temperature for 24 h. The precipitate was formed, filtered off, washed by 50 ml H_2O. The crude product was purified by crystallization from ethanol. Yield 82% as white solid; m.p. > 300°C. ^{1}H-NMR: 11.55 (s, 1H, NH); 8.01–7.75 (m, 10H, Ar—H and NH_2). ^{13}C-NMR: 166.53 (C-2); 154.37(C-4); 148.21, 144.27, 143.16, 139.79, 134.31, 131.99, 130.71, 127.05, 119.75, 118.69(C arom.). MS(EI). m/z 317(M+). (Found C, 53.24; H, 3.33; N, 13.01 Calc. for $C_{14}H_{11}N_3O_4S$ (MW = 317.07) C, 53.00; H, 3.50; N, 13.50).

4-[2-Thioxo-1,2,3,4-tetrahydroquinazolin-4-on-3-yl]-benzenesulfonamide (5)

Compounds **3** (450 mg, 1 mmol) in 20 ml of 4N HCl was refluxed for 2 h. After cooling the white precipitate was formed, filtered off, washed by 50 ml H_2O, and crystallization from ethanol. Yield 76% as white solid; m.p. > 300°C. ^{1}H-NMR: 7.92–7.33 (m, 8 H, Ar—H); 4.43(br, 2 H, NH_2). ^{13}C-NMR: 175.60(C=S); 159.75(C-4); 143.66, 142.15, 139.58, 135.71, 129.85, 127.35, 126.48, 124.54, 116.11, 115.76(C arom.); MS(EI): m/z 333(M^+). (Found: C, 50.31; H, 3.49; N, 12.70. Calc for $C_{14}H_{11}N_3O_3S_2$ (MW = 333.63) C, 50.41; H, 3.33; N, 12.60).

General Procedure for Compounds 7, 8, 11, and 12

Quinazoline derivatives **4** or **5** (5 mmol) and NaH (6 mmol) in 10 ml of dry DMF were stirred at room temperature for 1 h, then compounds **6**, **9**, or **10** (6 mmol) were added and the reaction mixture was stirred 8-24 h at room temperature (monitored by TLC analysis). The solvent was evaporated under vacuum, the residue was dissolved in 20 ml ethyl acetate and 30 ml H_2O. The organic layer was extracted and dried over anhydrous $MgSO_4$. The product was purified by silica gel column chromatography (10% ethyl acetate/cyclohexane, v:v).

4-[1-Ethoxymethyl-1,2,3,4-tetrahydroquinazolin-2,4-dion-3-yl]benzenesulfonamide (7a)

Yield 73% as a white solid; m.p. 189–190°C. ^{1}H-NMR: 8.06–7.55 (m, 8H, Ar—H); 5.63 (s, 2H,H-1′); 3.67 (m, 2H, OCH_2—CH_3); 1.20 (t, 3H,

OCH_2—CH_3). ^{13}C-NMR: 161.25 (C-4); 150.67(C-2); 143.86, 139.08, 138.99, 135.48 129.69, 127.84, 126.31, 123.39, 115.46, 115.08 (C-arom.); 73.00(C-1′) 63.59(O-CH_2CH_3);14.81(O—CH_2CH_3). MS(EI): m/z 375(M^+). (Found: C, 54.33; H, 4.50; N, 11.39 Calc. for $C_{17}H_{17}N_3O_5S$ (MW = 375.35) C, 54.39; H, 4.56; N, 11.21).

4-[1-Benzyloxymethyl-1,2,3,4-tetrahydroquinazolin-2,4-dion-3-yl]benzenesulfonamide (7b)

Yield 63% as a white solid; m.p. 188–170°C. ^{1}H-NMR: 8.25–7.53 (m, 13H, Ar—H); 4.46 (s, 2H, H-1′); 4.71 (s, 2H, O-CH_2Ph). MS(EI): m/z 437(M^+). (Found: C, 60.13; H, 4.55; N, 9.37 Calc. for $C_{22}H_{19}N_3O_5S$ (MW = 437.41) C, 60.36; H, 4.37; N, 9.60).

4-[1-(Methylsulphide)methyl-1,2,3,4-tetrahydroquinazolin-2,4-dion-3-yl]benzenesulfonamide (7c)

Yield 78% as a white solid; m.p. 159-160°C. ^{1}H-NMR: 8.14–7.51(m, 8H, Ar—H); 4.04(s, 2H, H-1′); 2.60(s, 3H, S-CH_3). ^{13}C-NMR: 180–57(C-2); 155(C-4); 146.92 141.77, 139.80, 135.05, 130.57, 127.89, 126.49, 126.17, 126.08, 119.46 (C arom.); 67.87 (C-1′); 39.77(—S—CH_3). (Found: C, 50.97; H, 4.28; N, 11.01 Calc. for $C_{16}H_{15}N_3O_4S_2$ (MW = 377.41) C, 51.06; H, 4.02; N, 11.16).

4-[1-Ethoxymethyl-2-thioxo-1,2,3,4-tetrahydroquinazolin-4-on-3-yl]benzenesulfonamide (8a)

Yield 69% a white solid; m.p. 189–170°C.; ^{1}H-NMR: 7.06–6.70 (m, 8H, Ar—H); 4.37 (s, 2H, 2H-1′); 3.61(m, 2H, OC$H_2$$CH_3$); 1.56 (t, 3H, OCH_2CH_3). ^{13}C-NMR: 187.34 (C=S); 162.22 (C-4); 180.78, 155.01, 148.89, 146.84, 141.63 140.02, 135.05, 130.54, 127.86, 128.23, 128.10 (C arom.); 72.45 (C-1′); 64.69 (OCH_2CH_3), 16.21 (O—CH_2–CH_3). Found C, 52.39 H, 4.01 N, 10.86 Calc. for $C_{17}H_{17}N_3O_4S_2$(MW = 391.42) C, 52.17 H, 4.38 N, 10.73).

4-[1-Benzyloxymethyl-2-thioxo-1,2,3,4-tetrahydroquinazolin-4-on-3-yl]benzenesulfonamide (8b)

Yield 61%; m.p. 173–175°C. ^{1}H-NMR: 8.15–7.29 (m, 13H, Ar—H); 5.53 (s, 2H, H-1′); 4.49(s, 2H, OCH_2Ph). ^{13}C-NMR: 187.37(C=S); 180.79 (C-4); 154.81 148.88, 141.65, 139.99, 137.27, 135.07 128.18, 127.79, 127.83, 119.54 (C arom.); 72.127 (C-1′); 70.91 (O—CH_2Ph). (Found: C, 58.03; H,

4.52; N, 8.99 Calc. for $C_{22}H_{19}N_3O_4S_2$ (MW = 453.50) C, 58.27 H, 4.22 N, 9.27).

4-[1-Isopropyl-1,2,3,4-tetrahydroquinzolin-2,4-dion-3-yl]-benzenesulfonamide (11a)

Yield 82% as a white solid, m.p. 170–172°C. ^{1}H-NMR: 8.12–7.49 (m, 8H, ArH); 3.99 (m, 1H, C*H*$(CH_3)_2$) 1.35 (d, $J = 6.78$ Hz, 6H, CH (C*H*$_3)_2$) ^{13}C-NMR: 180.51 (C=S); 155.87 (C-4); 147.21, 141.49, 139.87, 134.91, 130.49, 127.78, 128.39, 125.92, 125.87, 119.35 (Ar-C); 37.70 (*C*H$(CH_3)_2$), 22.20, 16.15 (CH(*C*H$_3)_2$); MS: m/z 359(M^+) (Found: C, 56.62; H, 4.56; N, 11.55 Calc. for $C_{17}H_{17}N_3O_4S$ (MW = 359.36) C, 56.31 H, 4.77 N, 11.63).

4-[1-(2-Butyl)-1,2,3,4-tetrahydroquinazolin-2,4-dion-3-yl]benzenesulfonamide (11b)

Yield 85% as a white solid, m.p. 187–188°C. ^{1}H-NMR: 8.13–7.47(m, 8H, Ar—H) 3.93 (m, 1H, H-1′); 1.88 (m, 2H, C*H*$_2$-CH$_3$); 1.26 (d, $J = 6.95$ Hz, 1H, C*H*$_2$); 0.95 (m, 3H, CH$_2$-C*H*$_3$) ^{13}C-NMR: 181.30 (C=S), 158.65 (C-4); 147.83, 142.15, 140.62, 135.59, 131.09, 128.45, 127.08, 128.62, 126.54, 120.03, (C arom.); 44.58 (C-1′); 29.08 (*C*H$_2$-CH$_3$); 20.48 (*C*H$_3$) 11.85 (CH2-CH$_3$). (Found: C, 57.63 H, 5.42 N, 11.08 Calc. for $C_{18}H_{19}N_3O_4S$ (MW = 373.40) C, 57.90 H, 5.13 N, 11.25).

4-[1-Isopropyl-2-thioxo-1,2,3,4-tetrahydroquinazolin-4-on-3-yl]benzenesulfonamide (11c)

Yield 78% as a white solid; m.p. 173–178°C. ^{1}H-NMR: 8.17–7.54 (m, 8H, Ar—H) 4.05 (m, 1H, H-1′); 1.38 (d, $J = 6.79$ Hz, 6H, CH(C*H*$_3)_2$.^{13}C-NMR: 187.28 (C=S); 180.62 (C-4); 155.89, 147.23, 141.52, 139.89, 134.94, 130.51, 127.81, (m126.41, 125.96, 119.36 (C arom.); 37.73 (*C*H$(CH_3)_2$; 16.18 CH(*C*H$_3)_2$. (Found: C, 54.50 H, 4.22 N, 11.43 Calc for $C_{17}H_{17}N_3O_3S_2$ (MW = 375.47) C, 54.39 H, 4.56 N, 11.19).

4-[1-(2-Butyl)-2-thioxo-1,2,3,4-tetrahydroquinazolin-4-on-3-yl]benzenesulfonamide (11d)

Yield 79% as a white solid; 163–165°C. ^{1}H-NMR: 8.15–7.51, 8H, ArH), 3.95 (m, 1H, H-1′); 1.72 (m, 2H, C*H*$_2$CH$_3$); 1.35(d, $J = 6.85$ Hz, C*H*$_3$); 0.98(m, 3H, CH$_2$-C*H*$_3$). ^{13}C-NMR: 187.23(C=S); 180.62 (C-4);155.98 147.12, 141.48, 139.94, 134.89, 130.51, 130.51, 130.48, 127.78, 126.38, 119.35 (C arom.); 43.89 (C-1′); 28.39 (*C*H$_2$CH$_3$); 19.81 (*C*H3); 11.17

(CH_2CH_3). (Found: C, 55.61 H, 5.20 N, 10.82 Calc. for $C_{18}H_{19}N_3O_3S_2$ (MW = 389.45) C, 55.48; H, 4.92; N, 10.79).

4-[1-Allyl-2-thioxo-1,2,3,4-tetrahydroquinaolin-4-on-3-yl]benzenesulfonamide (11e)

Yield 61% as a white solid, m.p. 168–170°C. ^{1}H-NMR: 8.13–7.50 (m, 8H, Ar—H); 5.81 (m, H, C*H*=CH_2), 5.32 (dd, 2H, H-1′); 3.87 (d, J = 6.56 Hz, 2H, CH=CH_2). ^{13}C-NMR: 187.97 (C=S); 161.25 (C-4); 158.18, 147.71, 140.42, 135.63, 131.19, 128.49, 127.09, 128.68, 120.04, 119.52 (C arom.). (Found: C, 54.72 H, 3.97 N, 11.48. (Calc. for $C_{17}H_{15}N_3O_3S_2$ (MW = 373.45) C, 54.68 H, 4.05 N, 11.25).

4-[1-Benzyl-2-thiox-1,2,3,4-tetrahydroquinazolin-4-on-3-yl]benzenesulfonamide (11f)

Yield 83% as a white solid; m.p. 195–197°C. ^{1}H-NMR: 8.12–7.20 (m, 3 H, Ar—H); 4.46 (s, 2H, CH_2Ph). ^{13}C-NMR: 187.96 (C=S); 161.22 (C-4); 156.40, 147.67, 142.28, 127.86, 127.77, 127.12, 126.87, 126.55, 120.07 (C arom.); 36.42 (CH_2Ph). (Found: C, 59.33; H, 4.10; N, 10.14, calc. for $C_{21}H_{17}N_3O_3S_2$ (MW = 423.47) C, 59.56; H, 4.05, N, 9.92).

4-[2-(2-Acetoxyethoxy)methyl-1,2,3,4-tetrahydroquinazolin-2,4-dion-3-yl]benzenesulfonamide (12)

Yield 62% as a white solid; m.p. 160–162°C. ^{1}H-NMR: 8.42–7.63 (m, 8H, Ar—H); 5.49 (s, 2H, H-1′); 4.32 (m, 2H, O—CH_2—CH_2) 4.13 (m, 2H, OCH_2-CH_2), 2.18 (s, 3H, COCH_3). ^{13}C-NMR: 174.31 (*CO*CH_3), 170.40 (C-2), 163.01 (C-4), 161.06, 147.52, 146.30, 144.03, 134.62, 127.38, 127.20, 127.09, 126.70, 126.26 (C arom.). (Found: C, 52.47; H, 4.55; N, 9.80. (Calc. for $C_{19}H_{19}N_3O_7S$ (MW = 433.73) C, 52.61; H, 4.50,N 9.69).

4-[2-(2-Hydroxyethoxy)methyl-1,2,3,4-tetrahydroquinazolin-2,4-dion-3-yl]benzenesulfonamid (13)

Compound **12** (434.7 mg, 1 mmol) was dissolved in 10 ml methanol /NH_3 and the reaction mixture was stirred at room temperature for 24 h until TLC showed no starting material left. The solvent was evaporated under vacuum and the residue was purified by silica gel column chromatography (50% ethyl acetate/cyclohexane, v:v) affords white solid (370 mg, 86%); m.p. 150–152°C. ^{1}H-NMR: 8.12–7.43 (m, 8H, Ar—H) 5.43 (s, 2H, H-1′), 3.71 (t, 2H, O—CH_2—CH_2) 3.60 (t, 2H, OCH_2CH_2). ^{13}C-NMR: 180.30 (C=S); 147.49 (C-2); 145.10, 136.20, 134.82, 134.19,

132.82, 127.91, 127.01, 128.64, 126.30, 125.71 (C arom.); 75.11 (C-1′), 70.13 (O-CH_2-CH_2), 59.43 (O-CH_2 – CH_2). (Found: C, 52.00; H, 4.66; N, 10.91 Calc. for $C_{17}H_{17}N_3O_6S$ (MW = 391.35) C, 52.17; H, 4.38; N, 10.86.

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