Synthesis of 2-[Mercapto(cyano)methylene]-1,2,3,4-tetrahydroquinazolin-4-ones and 2-Amino-4-methylpyrazolo-[1,5-*a*]quinazolin-5(4*H*)-one

Judit Fleischer, Kálmán Takács, and István Hermecz*

CHINOIN Pharmaceutical and Chemical Works Co. Ltd., H-1045 Budapest, Tó u. 1-5, Hungary

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A series of 2-[mercapto(cyano)methylene]-1,2,3,4-tetrahydroquinazolin-4-ones and 2-amino-4-methylpyrazolo[1,5-*a*]quinazolin-5(4*H*)-one were prepared from 2-cyanomethylquinazolin-4(3*H*)-ones *via* α-bromo derivatives **4** and amide oxime **8**, respectively. The new compounds have been characterized by elemental analyses and ^{1}H-nmr, in some cases by ir and ^{13}C-nmr investigations.

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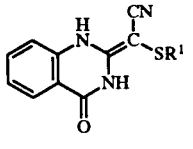
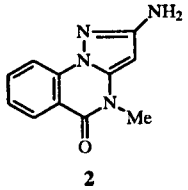
Recently quinazolin-4-ones have received considerable attention in the literature of pharmaceutical chemistry [1]. Heterocyclic fused quinazolinones have been reported to demonstrate affinity for the glycine site on the *N*-methyl-D-aspartic acid receptor complex [2]. As part of our program aimed at the development of potent *N*-methyl-D-aspartic acid antagonists, we synthesized a series of substituted 2-[mercapto(cyano)methylene]-1,2,3,4-tetrahydroquinazolin-4-ones **1** and pyrazolo[1,5-*a*]quinazolin-5(4*H*)-one **2**. Now we report their syntheses.



1



2

Preparation of Sulphur Containing Quinazolinones **1**.

As illustrated in Scheme 1, the synthesis of **5** was achieved in two steps from readily available quinazolinones **3** [3]. The key intermediates **4** were prepared in the reaction of **3** and *N*-bromosuccinimide in acetonitrile at room temperature. The reaction of **4** with thiourea in methanol afforded isothiuronium salts **7**. Isothiuronium salts are well known to undergo alkaline hydrolysis to yield thiols [4]. However, instead of thiol formation, isothioureas **5** generated by the action of base on compounds **7**. Isothioureas **5** was found to be highly stable.

In order to obtain substituted thiol derivatives, **4a** (R = H) was reacted with alkyl or aralkyl thiols in methanol to give mercaptoquinazolinone derivatives **1** (Table 1, Table 2). It is interesting that *N*-substituted derivative **4b** (R = Me) reacted only with 4-chlorobenzothiol and the expected **6** was obtained. The treatment of **4b** with other thiols lead to the starting material **3b**.

Preparation of 2-Amino-4-methylpyrazolo[1,5-*a*]quinazolin-5(4*H*)-one **2**.

The cyano group of **3** reacted with hydroxylamine in ethanol to give amidoxime **8** (Scheme 2). Treating **8** with acetic anhydride *O*-acyl derivatives **9** were obtained. Heating of **9b** (R = Me) in ethanol afforded 2-amino-4-methylpyrazolo[1,5-*a*]quinazolin-5(4*H*)-one **2** in good yield. The cyclization of **9a** (R = H) was failed.

Scheme 1

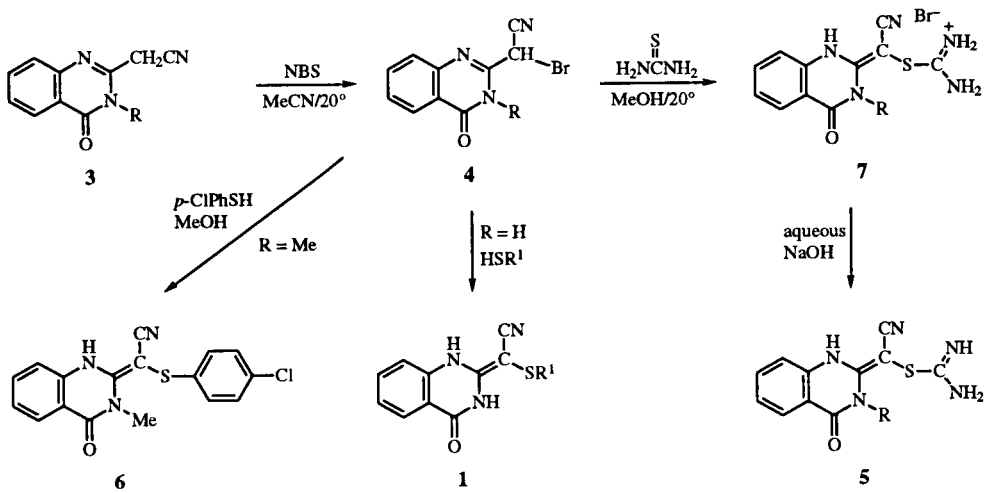


Table 1
Physical and Analytical Data on Compounds 1

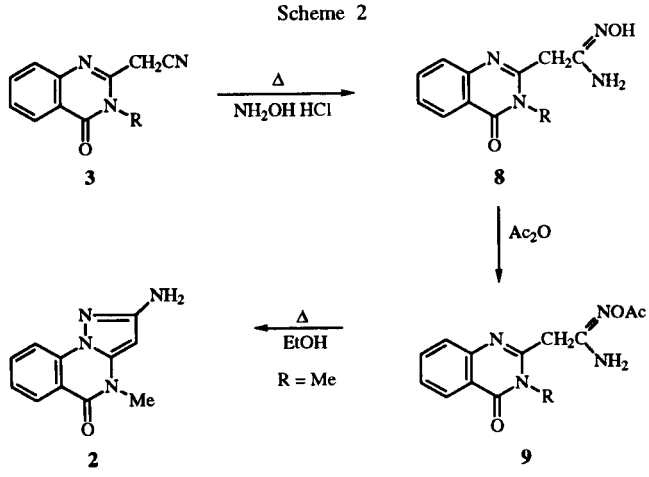
Compound No.	R^1	Yield (%)	Mp (°C)	Formula	Analysis (%) Calcd./Found			
					C	H	N	S
1a	$-COCH_3$	10	248-250	$C_{12}H_9N_3O_2S$	55.59	3.49	16.21	
			acetonitrile		55.19	3.16	15.81	
1b	$-CH_2CH_2OH$	30	231-233	$C_{12}H_{11}N_3O_2S$	55.15	4.24	16.08	12.27
			2-propanol		55.12	4.10	16.48	12.10
1c	$-CH_2CH(OH)CH_3$	32	196-198	$C_{13}H_{13}N_3O_2S$	56.71	4.76	15.26	
			2-propanol		56.26	4.64	15.27	
1d	$-CH_2CH_2CH_2Cl$	48	208-210	$C_{13}H_{12}ClN_3OS$	53.15	4.12	14.30	
			ethanol		52.96	3.84	14.37	
1e	$-CH_2COOCH_3$	45	220-221	$C_{13}H_{11}N_3O_3S$	53.97	3.83	14.52	
			ethanol		53.50	3.70	14.40	
1f	$-CH_2CH_2COOCH_3$	21	229-230	$C_{14}H_{13}N_3O_3S$	55.43	4.31	13.85	10.57
			acetone		55.87	4.21	13.92	10.71
1g	$-CH(CH_3)COOH$	18	219-220	$C_{13}H_{11}N_3O_3S$	53.98	3.83	14.53	
			ethanol		53.61	3.97	14.33	
1h	$-CH(CH_3)COOCH_3$	10	206-208 [a]	$C_{14}H_{13}N_3O_3S$	55.44	4.32	13.85	
					55.62	4.45	14.25	
1i	$4\text{-}ClC_6H_4$	52	285-287	$C_{16}H_{10}ClN_3OS$	58.63	3.07	12.82	
			ethanol		58.40	3.23	12.94	
1j		32	215-217	$C_{15}H_{11}N_3O_2S$	60.60	3.81	14.13	
			ethanol		60.63	3.81	14.24	

[a] Flash chromatography on silicagel, eluent: 5:1 = toluene and methanol.

Table 2
Spectroscopic Data on Compounds 1

Compound No.	*E:Z* ratio (ppm of minor NH)	ir cm^{-1}	^{1}H-nmr δ (ppm)
1a	3:1 (11.13)	3190, 2183, 1683, 1585, 1304, 1156	2.58 (s, 3H, CH_3), 7.29-7.90 (m, 3H, aromatic), 8.0 (d, 1H, 5H), 10.91 (br, NH), 11.71 (br, NH)
1b	1:0	3410, 3200, 2200, 1680, 1630, 1580, 1300	2.68 (m, 2H, CH_2), 3.54 (m, 2H, CH_2), 5.29 (s, 1H, OH), 7.18-7.67 (m, 3H, aromatic), 7.88 (d, 1H, 5H), 10.53 (br, 1H, NH), 11.18 (br, 1H, NH)
1c	2:1 (10.72, 11.19)	3500, 3180, 2200, 1680, 1630, 1460, 1320	1.19 (m, 3H, CH_3), 2.67 (m, 2H, CH_2), 3.76 (m, 2H, CH, OH), 7.23-7.89 (m, 3H, aromatic), 7.90 (d, 1H, 5H), 10.64 (br, 1H, NH), 11.23 (br, 1H, NH)
1d	4:3 (10.56, 11.09)	3200, 2200, 1700, 1650, 1600, 1430, 1320	2.01 (m, 2H, CH_2), 2.66 (m, 2H, CH_2), 3.75 (m, 2H, CH_2), 7.18-7.71 (m, 3H, aromatic), 7.88 (d, 1H, 5H), 10.31 (br, 1H, NH), 11.16 (br, 1H, NH)
1e	2:1 (10.67, 11.22)	3264, 3197, 3029, 2173, 1729, 1665, 1591, 1482, 1285, 1048	3.45 (d, 2H, CH_2), 3.63 (d, 3H, CH_3), 7.20-7.88 (m, 3H, aromatic), 7.90 (d, 1H, 5H), 10.40 (s, 1H, NH), 11.28 (s, 1H, NH)
1f	3:2 (10.51)	3180, 2170, 1730, 1700, 1620, 1580, 1310	2.64 (m, 2H, CH_2), 2.79 (m, 2H, CH_2), 3.60 (d, 3H, CH_3), 7.18-7.86 (m, 3H, aromatic), 7.89 (d, 1H, 5H), 10.15 (br, 1H, NH), 11.16 (br, 1H, NH)
1g	7:2 (10.60, 11.18)	3200, 2170, 1680, 1630, 1580, 1310	1.37 (m, 3H, CH_3), 3.52 (m, 1H, CH), 7.20-7.70 (m, 3H, aromatic), 7.90 (d, 1H, 5H), 10.20 (s, 1H, NH), 11.32 (s, NH), 12.84 (br, OH)
1h	2:1 (10.64)	3200, 2170, 1720, 1680, 1620, 1580, 1300	1.37 (m, 3H, CH_3), 3.59 (s, 1H, CH), 3.62 (s, 3H, CH_3), 7.25-7.70 (m, 3H, aromatic), 7.90 (d, 1H, 5H), 10.29 (br, 1H, NH), 11.32 (br, 1H, NH)
1i	1:1 (10.90, 11.42)	3230, 3180, 2180, 1670, 1630, 1580, 1420, 1300	7.22-7.89 (m, 7H, aromatic), 7.90 (d, 1H, 5H), 10.76 (br, 1H, NH), 11.47 (br, 1H, NH)
1j	7:3 (10.36, 11.05)	3180, 2170, 1700, 1630, 1570, 1300	3.83 (s, 2H, CH_2), 6.28 (m, 2H, furane), 7.18-7.81 (m, 4H, aromatic + furane), 7.85 (d, 1H, 5-H), 9.63 (br, NH), 11.22 (d, 1H, NH)

Scheme 2



EXPERIMENTAL

Melting points were determined on a Büchi 535 apparatus and are uncorrected. The yields were not maximized. The ^1H and ^{13}C nmr spectra were recorded in dimethyl sulphoxide-d_6 with tetramethylsilane as the internal standard on Bruker AC 400 instrument at 400.132 and 100.614 Mhz, respectively. The ir spectra were obtained in potassium bromide pellets with a Perkin Elmer 1600 spectrophotometer. Microanalysis were performed on Carlo Erba CHNOS 1106 apparatus.

General Procedure for the Bromination of 2-Cyanomethylquinazolin-4(3*H*)-ones **3**.

To a solution of quinazolinone **3** (32 mmoles) in acetonitrile (250 ml) *N*-bromosuccinimide (5.7 g, 32 mmoles) was added. The mixture was stirred for 3 hours at room temperature. The precipitated compounds **4** were filtered.

2-[Bromo(cyano)methyl]quinazolin-4(3*H*)-one (**4a**).

This compound was obtained from **3a** as yellow crystals in a yield of 73%, mp 213-215°; ^1H-nmr: δ 5.99 (s, 1H, CH), 7.60-7.97 (m, 3H, Ar-H), 8.13 (d, 1H, 5-H), 12.85 ppm (br, 1H, NH); ^{13}C-nmr: δ 26.6, 115.1, 121.6, 126.3, 127.9, 128.4, 135.3, 147.8, 149.6, 161.4 ppm; ir: ν 2900, 1680, 1610, 1250, 780 cm^{-1}.

Anal. Calcd. for $C_{10}H_6BrN_3O$: C, 45.48; H, 2.29; N, 15.91; Br, 30.21. Found: C, 45.66; H, 2.11; N, 16.10; Br, 29.91.

2-[Bromo(cyano)methyl]-3-methylquinazolin-4(3*H*)-one (**4b**).

This compound was obtained from **3b** as yellow crystals in a yield of 65%, mp 170-173°; ^1H-nmr: δ 3.56 (s, 3H, CH_3), 6.69 (s, 1H, CH), 7.60-7.91 (m, 3H, Ar-H), 8.13 ppm (d, 1H, 5-H); ir: ν 2900, 1680, 1580, 770 cm^{-1}.

Anal. Calcd. for $C_{11}H_8N_3BrO$: C, 47.50; H, 2.89; N, 15.11; Br, 28.73. Found: C, 47.93; H, 2.84; N, 15.30; Br, 28.25.

General Procedure for Sulphur Containing Quinazoldinones **1a-1j**.

To a solution of **4a** (0.5 g, 1.9 mmoles) in methanol (10 ml) alkyl and aralkyl mercaptan (2 mmoles) were added and the mixture was stirred at room temperature for 2 hours. The precipitated sulphur containing quinazolinone **1a-1j** was filtered off, washed with methanol and dried (see Tables 1 and 2).

General Procedure for Isothiouronium Salts **7** and Isothioureas **5**.

To a suspension of **4** (10 mmoles) in methanol (50 ml) thiourea (0.80 g, 10 mmoles) was added and a yellow clean solution was obtained. After two-hour stirring at room temperature yellow crystals were precipitated. The isolated solid **7** was washed with methanol and dried.

To a suspension of isothiuronium salt **7** (0.3 mmole) in methanol (5 ml) sodium hydroxide (40 mg, 1 mmole) was added and the solution was stirred for 2 hours at room temperature. The precipitated base **5** was filtered, washed with methanol.

S-[(1,2,3,4-Tetrahydro-4-oxoquinazolin-2-ylidene)(cyano)-methyl]isothiouronium Bromide (**7a**).

This compound was obtained as white crystals in a yield of 58%, mp 197° dec; ^1H-nmr: δ 7.32-7.95 (m, 4H, Ar-H), 8.94-9.15 (t, 4H, 2 x NH_2), 11.12 (bs, 1H, NH), 11.68 ppm (s, 1H, NH); ^{13}C-nmr: 115.6, 117.2, 120.1, 124.6, 126.9 (2C), 136.0, 140.3, 156.9, 160.0, 171.0 ppm; ir: ν 3100, 2200, 1700, 1650, 1580, 1420, 1310, 740 cm^{-1}.

Anal. Calcd. for $C_{11}H_{10}N_5OSBr$: C, 38.84; H, 2.95; N, 20.59; S, 9.41. Found: C, 38.47; H, 2.81; N, 20.16; S, 9.42.

S-[(1,2,3,4-Tetrahydro-4-oxoquinazolin-2-ylidene)(cyano)-methyl]isothiourea (**5a**).

This compound was obtained as white crystals in a yield of 64%, mp 270° dec; ^1H-nmr: δ 7.11 (t, 1H, Ar-H), 7.38 (d, 1H, Ar-H), 7.57 (t, 1H, Ar-H), 7.76 (br, 3H, NH_2 and NH), 7.91 (d, 1H, Ar-H), 11.0 (br, 1H, NH); ir: ν 3300, 3030, 1610, 1540, 1460, 1420, 1330 cm^{-1}.

Anal. Calcd. for $C_{11}H_9N_5OS$: C, 50.95; H, 3.49; N, 27.07; S, 12.36. Found: C, 50.75; H, 3.26; N, 26.97; S, 12.74.

S-[(3-Methyl-4-oxo-1,2,3,4-tetrahydroquinazolin-2-ylidene)-(cyano)methyl]isothiouronium Bromide (**7b**).

This compound was obtained as yellow crystals in a yield of 63%, mp 163-164°; ^1H-nmr: δ 3.74 (s, 3H, CH_3), 7.3-8.05 (m, 4H, Ar-H), 9.1 (s, 2H, NH_2), 10.97 ppm (s, 1H, NH); ir: ν 3480, 3460, 3250, 3100, 2200, 1700, 1550, 1290 cm^{-1}.

Anal. Calcd. for $C_{12}H_{12}BrN_5OS$: C, 40.68; H, 3.42; N, 19.77; Br, 22.56. Found: C, 40.49; H, 3.49; N, 19.61; Br, 22.65.

S-[(3-Methyl-4-oxo-1,2,3,4-tetrahydroquinazolin-2-ylidene)-(cyano)methyl]isothiourea (**5b**).

This compound was obtained as white crystals in a yield of 78%, mp 257-258°; ^1H-nmr: δ 3.69 (s, 3H, CH_3), 7.24 (t, 1H, Ar-H), 7.48 (d, 1H, Ar-H), 7.69 (t, 1H, ArH), 7.76 (s, 2H, NH_2), 7.96-8.00 (m, 3H, Ar-H and 2 x NH); ir: ν 3410, 3150, 1650, 1610, 1530, cm^{-1}.

Anal. Calcd. for $C_{12}H_{11}N_5OS$: C, 52.73; H, 4.06; N, 25.63. Found: C, 52.91; H, 4.21; N, 25.80.

2-[(4-Chlorophenylthio)cyanomethylene]-3-methyl-1,2,3,4-tetrahydroquinazolin-4-one (**6**).

To a solution of **4b** (0.4 g, 1.4 mmoles) in methanol (6 ml), 4-chlorobenzothiol (0.2 g, 1.38 mmoles) was added and the mixture was stirred at room temperature for 1.5 hours. The precipitated crystals were filtered, washed with methanol, recrystallized from methanol to give compound **6** as white crystals in a yield of 53%, mp 199-200°; ^1H-nmr: δ 3.73 (s, 3H, CH_3), 7.21-7.93 (m, 7H, aromatic), 8.10 (d, 1H, aromatic), 10.70 (br, 1H, NH); ir: ν 3220, 2200, 1680, 1620, 1560, cm^{-1}.

Anal. Calcd. for $C_{17}H_{12}N_3OSCl$: C, 59.73; H, 3.54; N, 12.29. Found: C, 59.83; H, 3.56; N, 12.40.

General Procedure for the Synthesis of 2-[4-Oxo-3,4-dihydroquinazolin-2-yl]acetamide Oximes **8**.

To a solution of hydroxylamine hydrochloride (1.39 g, 20 mmoles) in water (10 ml) potassium bicarbonate (2.0 g, 20 mmoles) was added. The clear aqueous solution was added to a solution of 2-cyanomethylquinazolin-4(3*H*)-one (**3**) (1 mmole) in ethanol (20 ml). The solution was refluxed for 4 hours, it was cooled to 0° and the precipitated crystals of **8** were filtered.

2-[4-Oxo-3,4-dihydroquinazolin-2-yl]acetamide Oxime (**8a**).

This compound was obtained as white crystals in a yield of 87%, mp 231-232°; ^{1}H-nmr: δ 3.35 (s, 2H, CH_2), 5.58 (s, 2H, NH_2), 7.43-7.73 (m, 3H, Ar-H), 8.07 (d, 1H, 5-H), 9.10 (s, 1H, OH), 12.16 ppm (s, 1H, NH); ir: ν 3436, 3401, 3280, 3161, 3035, 2910, 1650, 1620, 1607, 1562 cm^{-1}.

Anal. Calcd. for $C_{10}H_{10}N_4O_2$: C, 55.04; H, 4.62; N, 25.69. Found: C, 55.26; H, 4.77; N, 25.45.

2-[3-Methyl-4-oxo-3,4-dihydroquinazolin-2-yl]acetamide Oxime (**8b**).

This compound was obtained as white crystals in a yield of 64%, mp 168-169°; ^{1}H-nmr: δ 3.52 (s, 3H, CH_3), 3.67 (s, 2H, CH_2), 5.64 (s, 2H, NH_2), 7.47-7.80 (m, 3H, Ar-H), 8.11 (d, 1H, 5-H), 9.10 (s, 1H, OH); ir: ν 3496, 3388, 3300, 3179, 1598, 1570 cm^{-1}.

Anal. Calcd. for $C_{11}H_{12}N_4O_2$ H_2O: C, 52.79; H, 5.64; N, 22.39. Found: C, 52.53; H, 5.74; N, 22.39.

O-Acetyl-2-[4-oxo-3,4-dihydroquinazolin-2-yl]acetamide Oxime (**9a**).

A mixture of **8a** (1.0 g, 4.6 mmoles) in acetic anhydride (30 ml) was heated at 100° until a solution was obtained, then it was cooled to room temperature and stirred for 2 hours. The precipitated **9a** was collected as white crystals. The yield was 80%, mp 165° dec; ^{1}H-nmr: δ 2.05 (s, 3H, CH_3), 3.48 (s, 2H, CH_2), 6.60 (s, 2H, NH_2), 7.47-7.81 (m, 3H, Ar-H), 8.10 (d, 1H, 5-H), 12.22 ppm (s, 1H, NH); ir: ν 3460, 3200, 2934, 1696, 1612, 1291 cm^{-1}.

Anal. Calcd. for $C_{12}H_{12}N_4O_3$: C, 55.37; H, 4.65; N, 21.53. Found: C, 55.34; H, 4.46; N, 21.28.

O-Acetyl-2-[3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl]-acetamide Oxime (**9b**).

The solution of **8b** (4 mmoles) in acetic anhydride (10 ml) were stirred at room temperature for 2 hours, then the precipitated **9b** was collected as white crystals. The yield was 72%, mp 232- 233°; ^{1}H-nmr: δ 2.02 (s, 3H, CH_3), 3.56 (s, 3H, CH_3), 3.79 (s, 2H, CH_2), 6.63 (s, 2H, NH_2), 7.49-7.82 (m, 3H, Ar-H), 8.11 (d, 1H, 5-H); ir: ν 3383, 3307, 3198, 3060, 2940, 1728, 1687, 1653, 1636, 1600, 1570, 1235 cm^{-1}.

Anal. Calcd. for $C_{13}H_{14}N_4O_3$: C, 56.93; H, 5.15; N, 20.43. Found: C, 56.50; H, 5.30; N, 19.98.

2-Amino-4-methylpyrazolo[1,5-*a*]quinazolin-5(4*H*)-one (**2**).

A suspension of **9b** (400 mmoles) in ethanol (10 ml) was refluxed for 1 hour, then it was cooled to room temperature. The precipitated crystals were filtered off, washed and dried to give **2** as yellow crystals. The yield was 70%, mp 247-249°; ^{1}H-nmr: δ 3.40 (s, 3H, CH_3), 5.77 (s, 2H, NH_2), 6.45 (s, 1H, CH), 7.47-8.40 ppm (m, 4H, Ar-H); ^{13}C-nmr: δ 29.6, 102.9, 116.1, 116.7, 124.9, 127.9, 128.7, 134.0, 135.6, 143.4, 156.6 ppm; ir: ν 3315, 3102, 1649, 1438, 1407, 1281, 1049 cm^{-1}.

Anal. Calcd. for $C_{11}H_{10}N_4O$: C, 61.67; H, 4.71; N, 26.15. Found: C, 61.69; H, 4.57; N, 26.22.

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