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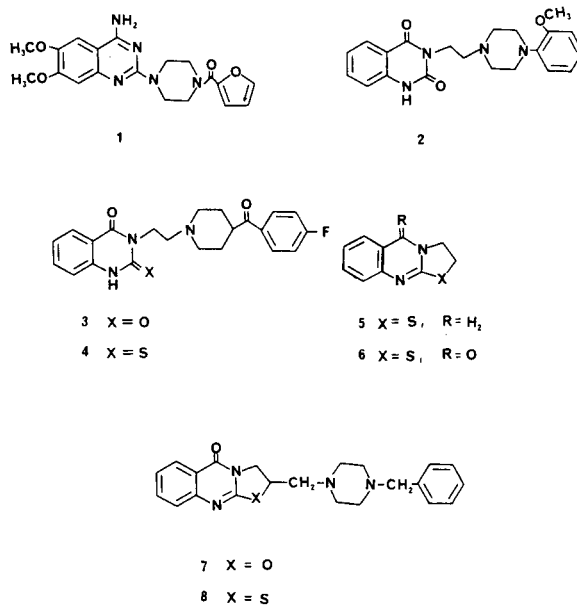
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To search for novel antihypertensive heterocycles in the condensed quinazoline series, two representative compounds were synthesized *via* a suitable reaction sequences. Treating anthranilonitrile with allyl isocyanate gave 2-(allylureido)benzotrile (10) in a quantitative yield. Compound 10 was cyclized to 3-allylquinazoline-2(1H), 4(3H)-dione (11). Bromination of 11 in carbon tetrachloride converted it into the corresponding 3-(2,3-dibromopropyl) derivative (12) in 92% yield. Ring closure of 12 was effected by the action of alkali to afford 2-bromomethyl-2,3-dihydro-5H-oxazolo[2,3-b]quinazolin-5-one (13). The title compound, 2-(4-benzylpiperazin-1-ylmethyl)-2,3-dihydro-5H-oxazolo[2,3-b]quinazolin-5-one (7) could be obtained by a reaction of either 12 or 13 with 1-benzylpiperazine respectively. Starting from the readily available 3-allyl-2H-thioxoquinazolin-4(3H)-one (16) *via* the analogous reactions gave the 2-bromomethyl-2,3-dihydro-5H-thiazolo[2,3-b]quinazolin-5-one (19) in good yield. However, the reaction of 19 with 1-benzylpiperazine provided another target compound, 2-(4-benzylpiperazin-1-ylmethyl)-2,3-dihydro-5H-thiazolo[2,3-b]quinazolin-5-one (8) only in poor yield (8%). As major product, the dehydrobrominated compound, 2-methylene-2,3-dihydro-5H-thiazolo[2,3-b]quinazolin-5-one (22) was isolated. A preliminary pharmacological evaluation revealed that both compounds 7 and 8 are devoid of the antihypertensive activity.

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A variety of antihypertensive agents are known for compounds containing quinazoline and quinazolinone ring systems [2]. For example, pyrazosin (1) [3], a 2-substituted quinazoline derivative, has been proven effective in the clinic acting as a α -adrenoceptor antagonist. Other 3-substituted quinazolinones such as SGB-1534 (2) [4], ketanserine (3) [5] and thioketanserine (4) [6] have been found to have antihypertensive activities by a α_1 -antagonist and serotonin- S_2 antagonist respectively. However, a recent report from our laboratory described some condensed quinazoline and quinazolinone heterocycles, such as 2,3-dihydro-5H-thiazolo[2,3-b]quinazolin-5-one (5) [7], 2,3-dihydro-5H-thiazolo[2,3-b]quinazolin-5-one (6) [8] derivatives, as antihypertensive agents. The mode of action of these condensed heterocyclic compounds remains to be clarified. With these compounds as a precedent, we felt that tricyclic quinazoline derivatives of the general structures 5 and 6 would possess a rigid structural feature necessary to elicit the biological activities of both 2 and 4. Thus, we became interested in pursuing this area of research.

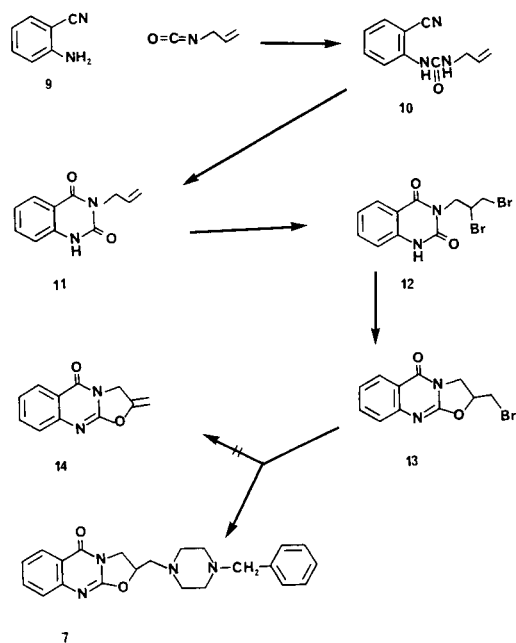
This paper describes the synthesis of antihypertensive activity of 2-(4-benzylpiperazin-1-ylmethyl)-2,3-dihydro-5H-oxazolo[2,3-b]quinazolin-5-one (7) and 2-(4-benzylpiperazin-1-ylmethyl)-2,3-dihydro-5H-thiazolo[2,3-b]quinazolin-5-one (8).



At the outset, we reasoned that 2-bromomethyl-2,3-dihydro-5H-oxazolo[2,3-b]quinazolin-5-one (13) is considered as a key intermediate for the synthesis of compound 7 (Scheme 1). To synthesize 13, anthranilonitrile (9) was reacted with allyl isocyanate leading to the formation of 2-(allylureido)benzotrile (10), subsequently a ring closure of compound 10 was effected in ethanolic

hydrogen hydrochloride to form 3-allylquinazoline-2(1*H*),4(3*H*)-dione (**11**). Bromination of compound **11** was conducted in carbon tetrachloride with bromine instead of using pyridinium bromide perbromide as the reported procedure [9] furnished 3-(2',3'-dibromopropyl)quinazoline-2(1*H*),4(3*H*)-dione (**12**) in 92% yield. Compound **13** obtained by a simple treatment of compound **12** with potassium carbonate in DMF at room temperature, was treated with two equivalents of 1-benzylpiperazine in DMF at 50° and then neutralized with 10% sodium hydroxide solution affording 2-(4-benzylpiperazin-1-ylmethyl)-2,3-dihydro-5*H*-oxazolo[2,3-*b*]quinazolin-5-one (**7**) in 86% yield. Alternatively, a treatment of **12** with 1-benzylpiperazine in the presence of potassium carbonate could also provide **7** in 23% yield.

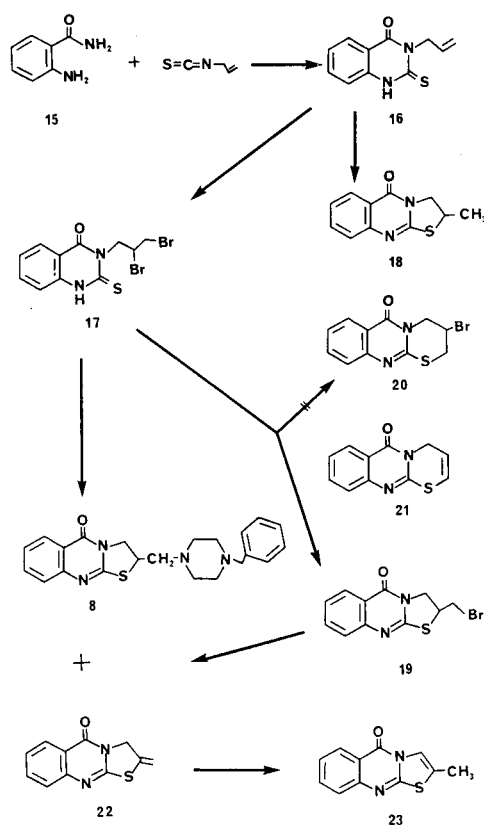
Scheme 1



To synthesize compound **8**, we used readily available 3-allyl-2(*H*)-thioxoquinazolin-4(3*H*)-one (**16**) as the starting material. Compound **16** was obtained according to our recently described procedure [1] by treatment of anthranilamide and allyl isothiocyanate as outlined in Scheme 2. On the other hand, in order to study the effect of the basic nucleus of **8** on the biological activity, 2,3-dihydro-2-methylthiazolo[2,3-*b*]quinazolin-5-one (**18**) [10] was prepared in 64% yield by a ring closure of **16** in a mixture of hydrochloric acid and acetic acid. 3-(2',3'-Dibromopropyl)-2-thioxo-1*H*,3*H*-quinazolin-4-one (**17**) obtained in 94% yield by a treatment of compound **16** with bromine in carbon tetrachloride in ice-salt bath, was treated with potassium carbonate in DMF at room temperature and only one major product was isolated. On the basis of the

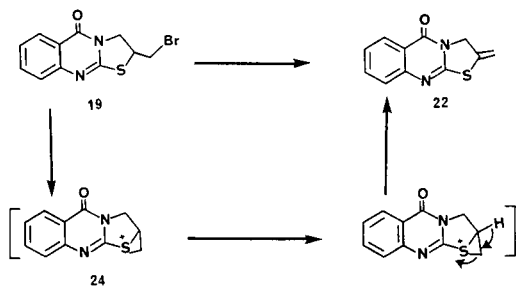
elemental analysis alone, we reasoned that the product could not only be 2-bromomethyl-2,3-dihydro-5*H*-thiazolo[2,3-*b*]quinazolin-5-one (**19**) but could also be 3,4-dihydro-3-bromo-2*H*,6*H*-1,3-thiazino[2,3-*b*]quinazolin-6-one (**20**). It was difficult to differentiate the structure of the product between **19** and **20** from ¹H nmr and ¹³C nmr spectral data in our hands. Thus the product obtained from the reaction

Scheme 2



of **17** with base was treated with 1-benzylpiperazine in DMF at room temperature and only one product was isolated. Surprisingly, the ¹H nmr and ¹³C nmr spectra of the product revealed that not any peaks for the 1-benzylpiperazine were observed and illustrated that the product obtained could be either 4*H*,6*H*-[1,3]thiazino[2,3-*b*]quinazolin-6-one (**21**) or 2-methylen-2,3-dihydro-5*H*-thiazolo[2,3-*b*]quinazolin-5-one (**22**). In order to distinguish the structure of the product between **21** and **22**, the product was subsequently treated with concentrated sulfuric acid and the ¹H nmr spectrum of the isolated product showed one doublet at δ 2.37 (J = 1.37 Hz) for the methyl group. Therefore, on the basis of ¹H nmr, ¹³C nmr spectrum and elemental analysis data as well as by analogy with the formation of 2-methyl-5*H*-thiazolo[3,2-*a*]thieno[2,3-*d*]pyrimidin-5-one from 2-methylen-2,3-dihydro-5*H*-thiazolo[3,2-*a*]thieno[2,3-*d*]pyrimidin-5-one [11] under similar experimen-

Scheme 3

Table 1
Crystal Data

Compound 22

Formula	C ₁₁ H ₈ N ₂ S ₁ O ₁	$\mu(\text{mm}^{-1})$	0.29
Crystal size (mm)	0.4 x 0.4 x 0.5	Transmission	0.96-1.00
Lattice	Monoclinic	$2\theta_{\text{max}}$	50
Sp. Gr.	P 2 ₁ /c	h, k, l	$\pm 16, 6, 16$
a (Å)	14.082(7)	$\lambda(\text{Å})$	0.7093
b (Å)	5.175(1)	No. of reflections	1688
c (Å)	13.759(5)	No. of observed reflections	1469 (>1.5 σ)
β (°)	106.72(4)	No. of Variables	137
Volume (Å ³)	960.1(6)	R(F)	0.035
Z	4	Rw(F)	0.033
F(000)	444	S	1.34
Temperature	300 K		

tal condition, we have assigned the structure of latter product as 2-methyl-5*H*-thiazolo[2,3-*b*]quinazolin-5-one (**23**). In retrospect of the reaction sequences, we confirmed that the structure of the product obtained by simple treatment of **17** with base was assigned to be compound **19** instead of **20**, subsequent treatment of **19** with base caused an

Table 2
Atomic Parameters x, y, z and Beq. $\text{Beq} = 8\pi^2/3 \sum U_{ij} a_i^* a_j^* a_i a_j$

	x	y	a	Beq
C1	0.30833(17)	0.0277(5)	0.92662(17)	3.00(9)
C2	0.21958(16)	0.1858(5)	0.90127(17)	3.01(10)
C3	0.20460(18)	0.3720 (5)	0.82498(18)	3.78(11)
C4	0.12099(20)	0.5221 (6)	0.80138(20)	4.33(12)
C5	0.05101(20)	0.4883 (5)	0.85364(22)	4.35(12)
C6	0.06384(18)	0.3050 (5)	0.92833(20)	3.92(12)
C7	0.14923(17)	0.1527 (5)	0.95421(17)	3.12(10)
N8	0.16184(14)	-0.0244 (4)	1.03314(15)	3.47(9)
C9	0.24107(17)	-0.1600 (5)	1.05240(17)	3.03(10)
S10	0.27109(5)	-0.38131(14)	1.15233(5)	4.17(3)
C11	0.37750(17)	-0.4873 (5)	1.12104(17)	3.30(10)
C12	0.39648(17)	-0.3260 (5)	1.03777(19)	3.56(11)
N13	0.31200(13)	-0.1501 (4)	1.00249(14)	2.92(8)
C14	0.43164(20)	-0.6837 (6)	1.16605(20)	4.38(13)
O15	0.37597(12)	0.0409 (4)	0.88796(13)	4.21(8)
H3	0.257	0.396	0.787	4.3
H4	0.111	0.655	0.745	5.0
H5	-0.010	0.605	0.837	4.9
H6	0.011	0.280	0.965	4.5
H12A	0.457	0.771	0.065	4.3
H12B	0.594	0.413	0.019	4.3
H14A	0.496	0.284	0.150	4.9
H14B	0.413	0.225	0.221	4.9

elimination of hydrogen bromide leading to the formation of **22** and then the proton-catalyzed isomerization of **22** to form **23**. The exocyclic double bond character of **22** was confirmed by the X-ray spectral data as well.

EXPERIMENTAL

Melting points were obtained on an Electrothermal apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 983 G spectrophotometer. The ¹H and ¹³C nuclear magnetic resonance spectra were recorded on a Bruker Model

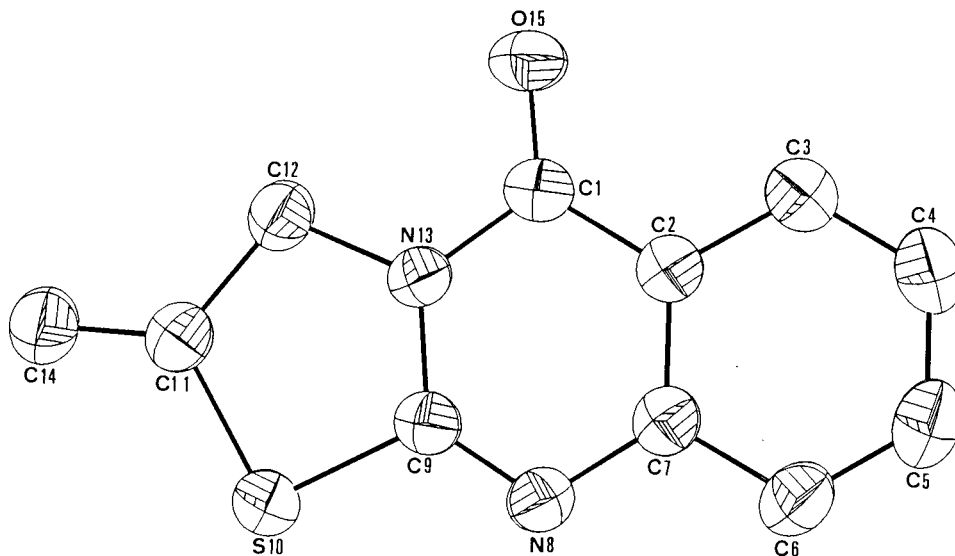


Figure 1. X-ray crystallography of compound 22

Table 3
Bond Distances (Å) and Angles (°)

Distances

C(1)-C(2)	1.450(3)	C(6)-C(7)	1.395(3)
C(1)-N(13)	1.381(3)	C(6)-H(6)	1.03
C(1)-O(15)	1.219(3)	C(7)-N(8)	1.393(3)
C(2)-C(3)	1.395(3)	N(8)-C(9)	1.280(3)
C(2)-C(7)	1.399(3)	C(9)-S(10)	1.7452(25)
C(3)-C(4)	1.369(4)	C(9)-N(13)	1.366(3)
C(3)-H(3)	1.03	S(10)-C(11)	1.761(3)
C(4)-C(5)	1.388(4)	C(11)-C(12)	1.502(4)
C(4)-H(4)	1.02	C(11)-C(14)	1.314(4)
C(5)-C(6)	1.372(4)	C(12)-N(13)	1.465(3)
C(5)-H(5)	1.02		

Angles

C(2)-C(1)-N(13)	113.58(19)	C(7)-N(8)-C(9)	115.50(19)
C(2)-C(1)-O(15)	126.21(22)	N(8)-C(9)-S(10)	121.49(17)
N(13)-C(1)-O(15)	120.21(22)	N(8)-C(9)-N(13)	126.53(22)
C(1)-C(2)-C(3)	120.26(21)	S(10)-C(9)-N(13)	111.97(17)
C(1)-C(2)-C(7)	119.76(21)	C(9)-S(10)-C(11)	92.41(12)
C(3)-C(2)-C(7)	119.99(22)	S(10)-C(11)-C(12)	111.33(17)
C(2)-C(3)-C(4)	120.23(23)	S(10)-C(11)-C(14)	123.01(20)
C(3)-C(4)-C(5)	119.74(25)	C(12)-C(11)-C(14)	125.66(23)
C(4)-C(5)-C(6)	120.99(24)	C(11)-C(12)-N(13)	106.99(19)
C(5)-C(6)-C(7)	119.99(24)	C(1)-N(13)-C(9)	122.08(19)
C(2)-C(7)-C(6)	119.04(22)	C(1)-N(13)-C(12)	120.95(18)
C(2)-C(7)-N(8)	122.41(21)	C(9)-N(13)-C(12)	116.84(19)
C(6)-C(7)-N(8)	118.54(21)		

Unfortunately, 2-(4-benzylpiperazin-1-ylmethyl)-2,3-dihydro-5H-thiazolo[2,3-b]quinazolin-5-one (**8**) was obtained only in low yield (8%) when compound **19** was reacted with 1-benzylpiperazine in methyl isobutyl ketone in the presence of potassium carbonate, the major product was found to be **22** in 85% yield as well. Alternatively, a treatment of compound **17** with 1-benzylpiperazine in methyl isobutyl ketone in the presence of potassium carbonate and potassium iodide also furnished predominately compound **22** in 79% yield accompanied with compound **8** as a minor product in 5.8% yield.

There is essentially no 2-methylen-2,3-dihydro-5H-oxazolo[2,3-b]quinazolin-5-one (**14**) observed when compound **13** was reacted with 1-benzylpiperazine. However, under similar reaction conditions, a conversion of **19** into **22** *via* a base catalyzed elimination of hydrogen bromide was probably due to the d-orbital character of the sulfur atom promoting the nucleophilic attack of the sulfur atom to form the sulfonium ion **24** [12] following by a ring opening of **24** through loss of a proton to give an exocyclic double bond. The formation of **13** from the reaction of **12** with base was deduced on the basis of the analytical data and in analogy with the formation of **19** from **17**. The intramolecular displacement occurred either *via* the amide or thioamide to the secondary bromide instead of the primary bromide in compound **12** and **17**, the propinquity may

play an important role.

A preliminary pharmacological evaluation revealed that compounds **7** and **8** were inactive in anesthetized spontaneous hypertensive rat at i.v. doses of 8 mg/kg.

AM-300 spectrometer from National Taiwan University, Taipei, using DMSO- d_6 or deuteriochloroform as the solvent and as the internal standard. Mass spectra were obtained on a Finnigan MAT TSQ-46C GC/MS spectrometer at National Taiwan University. Elemental analysis was carried out on a Perkin-Elmer 240 Elemental Analyzer in National Taiwan University.

Crystal Structure Determination.

Compound **22** was recrystallized from tetrahydrofuran as rod crystals. Intensity data were measured at room temperature on an Enraf-Nonius CAD4 diffractometer with monochromated Mo-K α radiation in $\theta/2\theta$ scan mode. Three standard reflections were monitored every two hours throughout the measurements, the variation are less than 1%. The other experimental details are given in Table 1. The structure was solved by direct method and refined by full-matrix least squares process. The final atomic parameters are given in Table 2. The atomic scattering factors were calculated according to the analytical equation, the coefficients were taken from references [13]. All the calculations were made on a microvax computer with NRCVax programs [14].

The molecular structure with the thermal ellipsoids are shown in Figure 1. Bond distances and angles are given in Table 3. The double bond character on C₁₁-C₁₄, C₉-N₈ and C₁-O₁₅ are confirmed.

2-(Allylureido)benzoxonitrile (**10**).

A mixture of anthranilonitrile (10 g, 85 mmoles) and allyl isocyanate (7.49 ml, 85 mmoles) was heated slightly to dissolve and was allowed to stand at room temperature for 48 hours to give 17 g (100%) of **10**; ir (potassium bromide): 3331, 3263, 2226 (CN), 1639, 1562, 1449, 1298, 1247 cm⁻¹; ¹H nmr (DMSO- d_6): 300 MHz, δ 3.74 (p, 2H, CH₂), 5.09 (q, 1H, =CH), 5.17 (q, 1H, =CH), 5.86 (m, 1H, CH), 7.09 (t, 2H, Ar-H), 7.56 (t, 1H, Ar-H), 7.67 (d, 1H, Ar-H), 8.43 (d, 1H, Ar-H), 7.65 (d, 1H, NH), 8.54 (s, 1H, NH); ¹³C nmr (DMSO- d_6): 75 MHz, δ 41.47, 101.00, 114.97, 116.99, 120.61, 120.73, 122.22, 132.96, 133.83, 135.69, 142.66, 154.32.

Anal. Calcd. for C₁₁H₁₁N₃O (201.23): C, 65.66; H, 5.51; N, 20.89. Found: C, 65.38; H, 5.51; N, 21.05.

3-Allyl-quinazoline-2(1H),4(3H)-dione (**11**).

A mixture of **10** (17 g, 85 mmoles) in ethanol (105 ml) and concentrated hydrochloric acid (105 ml) was refluxed for 30 minutes. After the mixture was cooled to room temperature, the solid was collected by filtration and combined with the solid that was collected from the filtrate by neutralizing with sodium bicarbonate to give 16.81 g (96%) of **11**. An analytical sample was recrystallized from methanol; ¹H nmr (DMSO- d_6): 300 MHz, δ 4.48 (d, J = 5.1 Hz, 2H, CH₂), 5.07 (d, J = 5.3 Hz, 1H, =CH), 5.10 (s, 1H, =CH), 5.05 (m, 1H, =CH), 7.19 (t, 2H, Ar-H), 7.64 (t, 1H, Ar-H), 7.91 (d, J = 7.8 Hz, 1H, Ar-H), 11.44 (s, 1H, NH); ¹³C nmr (DMSO- d_6): 75 MHz, δ 41.92, 113.64, 115.12, 116.26, 122.49, 127.34, 132.74, 134.98, 139.40, 149.82, 161.57.

3-(2',3'-Dibromopropyl)-quinazoline-2(1H),4(3H)-dione (**12**).

Bromine (2.0 ml) was added dropwise to a solution, cooled to -5°, of **11** (7.5 g, 37.5 mmoles) in carbon tetrachloride (50 ml) over

the course of 60 minutes. The resulting mixture was then stirred for a further 2 hours at 0°, and the temperature was subsequently allowed to rise to room temperature within 60 minutes. The precipitate was collected by filtration and recrystallized from acetic acid affording 12.5 g (92%) of **12**, mp 219-221° [lit [9] 217-218°]; ¹H nmr (DMSO-d₆): 300 MHz, δ 3.94 (q, 1H, CH), 4.04 (q, 1H, CH), 4.25 (m, 1H, CH), 4.47 (m, 1H, CH), 4.78 (m, 1H, CH), 7.16-7.33 (m, 2H, Ar-H), 7.64-7.66 (p, 1H, Ar-H), 7.92-7.94 (d, J = 7.8 Hz, 1H, Ar-H), 11.50 (s, 1H, NH); ¹³C nmr (DMSO-d₆): 75 MHz, δ 36.48, 44.78, 49.94, 113.66, 115.14, 122.57, 127.44, 135.15, 139.42, 150.06, 162.02; ms: m/z: 362 (M⁺), 281, 201, 146.

2-Bromomethyl-2,3-dihydro-5H-oxazolo[2,3-b]quinazolin-5-one (13).

A mixture of **12** (10 g, 0.028 mole) and potassium carbonate (3.81 g, 0.028 mole) in DMF (20 ml) and water (5 ml) was stirred at room temperature for 2 hours. To the mixture was then added water (600 ml) to get precipitate. The solid was collected by filtration and was purified by column chromatography [silica gel: 280 g, solvent system: ethyl acetate-toluene (2:5), column diameter: 4.5 cm] to give 4.97 g (64%) of **13** and 820 mg (15%) of **11**, mp 154° [lit [9] 170-174°]; ¹H nmr (deuteriochloroform): 300 MHz, δ 3.66 (m, 2H, CH₂), 4.25 (q, 1H, CH), 4.46 (q, 1H, CH), 5.19 (m, 1H, CH), 7.31-8.18 (m, 4H, Ar-H); ¹³C nmr (deuteriochloroform): 75 MHz, δ 31.9, 46.43, 75.62, 77.21, 118.57, 125.05, 126.36, 126.67, 128.14, 129.16, 134.95, 148.76; ms: m/z 282 (M⁺ + 1), 224, 201, 146, 90.

Anal. Calcd. for C₁₁H₉N₂O₂Br (281.11): C, 47.00; H, 3.22; N, 9.96. Found: C, 47.09; H, 3.30; N, 9.85.

2-(4-Benzylpiperazin-1-ylmethyl)-2,3-dihydro-5H-oxazolo[2,3-b]quinazolin-5-one (7).

Method A.

A mixture of **13** (500 mg, 1.8 mmoles), 1-benzylpiperazine (0.31 ml, 1.8 mmoles), sodium carbonate (198 mg, 1.8 mmoles) and potassium iodide (50 mg) in methyl isobutyl ketone (10 ml) was refluxed for 2 hours. The solid was collected by filtration and washed with toluene. The crude product was recrystallized from acetonitrile to give 180 mg (27%) of **7**, mp 127°C; ¹H nmr (DMSO-d₆): 300 MHz, δ 2.33 (br s, 4H, CH₂NCH₂), 2.49 (br s, 4H, CH₂NCH₂), 2.74 (d, J = 5.5 Hz, 2H, CH₂), 3.41 (s, 2H, CH₂), 3.93 (q, 1H, CH), 4.31 (q, 1H, CH), 5.13 (p, 1H, CH), 7.19-7.42 (m, 7H, Ar-H), 7.68 (p, 1H, Ar-H), 8.03 (t, 1H, Ar-H); ¹³C nmr (DMSO-d₆): 75 MHz, δ 45.40, 52.61, 53.31, 59.72, 61.99, 76.82, 118.35, 124.14, 125.68, 125.94, 126.85, 128.11, 128.76, 134.48, 138.12, 149.09, 155.63, 160.00; ms: m/z: 376 (M⁺), 285, 258, 246, 203, 189, 146, 91.

Anal. Calcd. for C₂₂H₂₄N₄O₂ (376.46): C, 70.19; H, 6.42; N, 14.88. Found: C, 70.27; H, 6.40; N, 14.67.

Method B.

A mixture of **13** (500 mg, 1.8 mmoles) and 1-benzylpiperazine (0.62 ml, 3.6 mmoles) in DMF (2 ml) was heated at 50°. After 3 hours, the solid was filtrated and washed with water (20 ml) to give 290 mg of **7** in 86% yield. The ¹H nmr and ¹³C nmr spectrum are similar to those obtained from method A.

Method C.

A mixture of **12** (5.0 g, 0.014 mole), 1-benzylpiperazine (2.60 ml, 0.015 mole), sodium carbonate (1.5 g, 0.014 mole) and potassium iodide (2 g) in methyl isobutyl ketone (180 ml) was

refluxed for 3 hours. The solid was filtered off and the filtrate was concentrated to dryness. The residue was purified by column chromatography [silica gel: 150 g, solvent system: chloroform-ethanol (10:1), column diameter: 3 cm] to give 1.21 g (23%) of **7**.

3-Allyl-2H-thioxoquinazolin-4(3H)-one (16).

To a solution of anthranilamide (10 g, 73 mmoles) in acetonitrile (60 ml) was added allyl isothiocyanate (8.6 ml, 88 mmoles) and was stirred at room temperature for 24 hours. The white precipitated solid was collected by filtration and recrystallized from a mixture of ethanol and tetrahydrofuran (v:v, 1:1) to give 11.85 g (74%) of **16**, mp 201°; ir (potassium bromide): 3260, 1651, 1620, 1526, 1487, 1414, 1323, 1190, 1124 cm⁻¹; ¹H nmr (DMSO-d₆): 300 MHz, δ 5.02 (q, 2H, CH₂), 5.11 (m, 1H, =CH), 5.16 (m, 1H, =CH), 5.90 (m, 1H, =CH), 7.29-7.39 (m, 1H, Ar-H), 7.70-7.75 (m, 1H, Ar-H), 7.93 (m, 1H, Ar-H), 12.95 (s, 1H, NH); ¹³C nmr (DMSO-d₆): 75 MHz, δ 47.54, 115.38, 115.60, 117.07, 124.49, 127.25, 131.75, 135.48, 139.07, 159.98, 175.04; ms: m/z 218 (M⁺).

Anal. Calcd. for C₁₁H₁₀N₂OS (218.28): C, 60.53; H, 4.61; N, 12.83. Found: C, 60.48; H, 4.33; N, 12.84.

3-(2',3'-Dibromopropyl)-2-thioxo-1H,3H-quinazolin-4-one (17).

Bromine (2.5 ml) was added dropwise to a solution, cooled to -5°, of **16** (10 g, 0.46 mole) in carbon tetrachloride (100 ml) over the course of 60 minutes. The resulting mixture was then stirred for a further 2 hours at 0° and the temperature is subsequently allowed to rise to room temperature within 60 minutes. The precipitated solid was collected by filtration and recrystallized from methanol affording 16.2 g (94%) of **17**, mp 303°; ¹H nmr (DMSO-d₆): 300 MHz, δ 3.92 (m, 2H, CH₂), 4.40 (m, 2H, CH₂), 4.48 (m, 1H, CH), 7.40-7.50 (m, 2H, Ar-H), 7.75 (m, 1H, Ar-H), 8.45 (q, 1H, Ar-H); ¹³C nmr (DMSO-d₆): 75 MHz, δ 36.26, 43.39, 51.65, 118.90, 125.11, 126.06, 126.13, 134.78, 147.59, 159.36, 159.43.

Anal. Calcd. for C₁₁H₁₀N₂Br₂SO (378.09): C, 34.94; H, 2.66; N, 7.40. Found: C, 35.16; H, 2.65; N, 7.42.

2-Methyl-2,3-dihydro-5H-thiazolo[2,3-b]quinazolin-5-one (18).

A mixture of **16** (0.5 g, 2.3 mmoles) in acetic acid (1 ml) and concentrated hydrochloric acid (2 ml) was refluxed for 2 hours. After the mixture was cooled to room temperature, the solid that was formed by neutralizing the mixture with 10% sodium hydroxide solution, was collected by filtration and washed with water (20 ml) affording 420 mg of crude product. The residue was recrystallized from 15% of aqueous ethanol to give 320 mg (64%) of **18**, mp 109°C; ¹H nmr (deuteriochloroform): 300 MHz, δ 1.56 (d, 3H, CH₃), 4.02 (m, 1H, CH), 4.15 (q, 1H, CH), 4.56 (q, 1H, CH), 7.37 (m, 1H, Ar-H), 7.53 (d, 1H, Ar-H), 7.67 (t, 1H, Ar-H), 8.17 (d, 1H, Ar-H); ¹³C nmr (deuteriochloroform): 75 MHz, δ 20.63, 38.56, 55.07, 119.13, 125.93, 125.97, 126.62, 134.65, 148.69, 159.65, 160.54; ms: m/z 218 (M⁺), 203, 162.

Anal. Calcd. for C₁₁H₁₀N₂OS (218.28): C, 60.49; H, 4.61; N, 12.88. Found: C, 60.72; H, 4.61; N, 13.03.

2-Bromomethyl-2,3-dihydro-5H-thiazolo[2,3-b]quinazolin-5-one (19).

Compound **17** (28 g, 7.4 mmoles) in DMF (40 ml) was added to a mixture of potassium carbonate (11.25 g, 8.1 mmoles) and water (15 ml) and the mixture was stirred at room temperature for 1.5 hour. The mixture was then diluted with water (300 ml). The solid was collected by filtration and washed with water (50 ml) to give

19.42 g of crude product. The residue was purified by column chromatography [silica gel: 110 g, solvent system: chloroform-ethyl acetate (95:5), column diameter: 3 cm], to afford 16.2 g (74%) of **19** and 60 mg (3.7%) of **16**, mp 117-119°; ¹H nmr (deuteriochloroform): 300 MHz, δ 3.55 (q, 1H, CH), 3.68 (q, 1H, CH), 4.09 (m, 1H, CH), 4.42 (q, 1H, CH), 4.76 (q, 1H, CH), 7.38 (m, 1H, Ar-H), 7.52 (m, 1H, Ar-H), 7.68 (m, 1H, Ar-H), 8.17 (m, 1H, Ar-H); ¹³C nmr (deuteriochloroform): 75 MHz, δ 33.23, 43.17, 51.88, 119.08, 125.96, 126.33, 126.65, 134.80, 148.45, 157.77, 160.39; ms: m/z 298 (M+1), 217, 203, 162.

Anal. Calcd. for C₁₁H₈N₂BrSO (297.18): C, 44.45; H, 3.05; N, 9.42. Found: C, 44.69; H, 3.10; N, 9.30.

2-(4-Benzylpiperazin-1-ylmethyl)-2,3-dihydro-5H-thiazolo[2,3-b]quinazolin-5-one (**8**) and 2-Methylen-2,3-dihydro-5H-thiazolo[2,3-b]quinazolin-5-one (**22**).

Method A.

A mixture of **19** (0.8 g, 2.7 mmoles), 1-benzylpiperazine (0.47 ml, 2.7 mmoles) and sodium carbonate (285 mg, 2.69 mmoles) in methyl isobutyl ketone (15 ml) was refluxed for 2 hours. The solvent was then concentrated to 5 ml. The solid was collected by filtration to give 310 mg of **22**. The filtrate was then evaporated to an oily residue and subsequently the residue was absorbed in tetrahydrofuran (20 ml). The solid that was formed, was collected as **22** (60 mg). The total yield of **22** was 370 mg (85%). An analytical sample as needle crystals was prepared from acetonitrile, mp 197-199°C; ¹H nmr (deuteriochloroform): 300 MHz, δ 5.08 (t, 2H, CH₂), 5.33 (q, 1H, CH), 5.47 (q, 1H, =CH), 7.38 (t, 1H, Ar-H), 7.52 (d, J = 8.1 Hz, 1H, Ar-H), 7.68 (q, 1H, Ar-H), 8.18 (d, 1H, J = 7.2 Hz, Ar-H); ¹³C nmr (deuteriochloroform): 75 MHz, δ 54.17, 108.33, 119.29, 126.14, 126.26, 126.57, 133.04, 134.75, 148.71, 158.135, 159.82; ms: m/z 216 (M⁺), 183, 162.

Anal. Calcd. for C₁₁H₈N₂SO (216.26): C, 61.09; H, 3.72; N, 12.95. Found: C, 60.90; H, 3.73; N, 12.98.

The filtrate was again evaporated *in vacuo* to an oily residue and the residue was diluted with ethanol. The solid was collected by filtration to obtain 80 mg (8%) of **8**. An analytical sample was prepared from acetonitrile, mp 179-181°; ¹H nmr (deuteriochloroform): 300 MHz, δ 2.56 (m, 8H, CH₂), 2.73 (m, 2H, CH₂), 3.58 (s, 2H, CH₂), 4.02 (m, 1H, CH), 4.36 (q, 1H, CH), 4.43 (q, 1H, CH), 7.37-8.20 (m, 9H, Ar-H); ¹³C nmr (deuteriochloroform): 75 MHz, δ 41.05, 51.24, 52.68, 61.54, 62.62, 119.10, 125.90, 126.12, 126.57, 127.59, 128.42, 129.53, 134.61, 149.00, 160.70; ms: m/z 392 (M⁺), 189, 91.

Anal. Calcd. for C₂₂H₂₄N₄OS (392.53): C, 67.31; H, 6.16; N, 14.27. Found: C, 67.17; H, 6.31; N, 13.96.

Method B.

A mixture of **17** (2.0 g, 5.3 mmoles), 1-benzylpiperazine (1.2 ml, 7.0 mmoles), sodium carbonate (0.56 g, 5.3 mmoles) and potassium iodide (200 mg) in methyl isobutyl ketone (6 ml) was refluxed for two and half hours. The solid was collected by filtration and washed with methyl isobutyl ketone (2 ml) and water (5

ml) to give 700 mg of **22**. The filtrate was then evaporated *in vacuo* to oil residue. The residue was purified by column chromatography [silica gel: 80 g, solvent system: chloroform-acetonitrile (5:2), column diameter: 2.5 cm] to obtain 200 mg of **22** and 60 mg of **8** (2.9%). The total yield for **22** was 900 mg (79%). The ¹H nmr and ¹³C nmr spectrum are similar to those obtained from method A.

2-Methyl-5H-thiazolo[2,3-b]quinazolin-5-one (**23**).

A mixture of compound **22** (1.22 g, 5.6 mmoles) in concentrated sulfuric acid (5 ml) was heated at 40° for 15 minutes and was then poured into 10% sodium hydroxide solution (120 ml) to get precipitate 1.15 g. The solid was collected by filtration and recrystallized from ethanol affording 0.98 g (82%) of compound **23**, mp 183°; ¹H nmr (DMSO-d₆): 300 MHz, δ 2.37 (d, 3H, J = 1.37 Hz, CH₃), 7.45 (q, 1H, =C-H), 7.58 (d, 1H, J = 8.3 Hz, Ar-H), 7.79 (m, 2H, Ar-H), 8.18 (d, 1H, J = 8.3 Hz, Ar-H); ¹³C nmr (DMSO-d₆): 75 MHz, δ 12.75, 116.33, 117.38, 122.83, 124.90, 125.72, 126.24, 134.41, 147.60, 157.17, 157.92; ms: m/z 216 (M⁺), 187, 162, 149.

Anal. Calcd. for C₁₁H₈N₂SO (216.26): C, 61.09; H, 3.72; N, 12.95. Found: C, 60.88; H, 3.73; N, 12.87.

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