Quinazolin-2-ones Having a Spirohydantoin Ring. III.[1] A General and Efficient Synthesis of 3′-Substituted Spiro[imidazolidine-4,4′(1′*H*)-quinazoline]-2,2′,5(3′*H*)-triones[2]

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The reaction of 1-carbamoylisatins 2 with 2-ethyl-2-isothiourea hydrobromide in the presence of triethylamine followed by acid-catalyzed cyclization of the resulting 4-(2-ethyl-2-isothioureido)carbonyl-3,4-dihydro-4-hydroxy-2(1*H*)-quinazolinones 7 provides a general and high-yielding route to 3′-substituted spiro[imidazolidine-4,4′(1′*H*)-quinazoline]-2,2′,5(3′*H*)-triones 8.

Keywords aldose reductase inhibitor; spirohydantoin; 1-carbamoylisatin; thiourea; 2-ethyl-2-isothiourea hydrobromide; spiroquinazolin-2-one; spiro[imidazolidine-4,4′(1′*H*)-quinazoline]-2,2′,5(3′*H*)-trione

Aldose reductase inhibitors are of therapeutic interest for the chronic complications of diabetes such as retinopathy, neuropathy, nephropathy, and cataracts.[3] Recently, much attention has been paid to the aldose reductase inhibitory activity of several spirohydantoins and related cyclic amides.[4] In the course of our studies on quinazolines,[5] we have focussed on the syntheses and the biological activities of quinazolin-2-ones having such a spirohydantoin ring in the hope of finding potent and effective aldose reductase inhibitors.

A reported approach to such a ring system involves the reaction of either 3-iminoisatin or 1-carbamoylisatins with isocyanates followed by base treatment.[6,7] However, this method is not applicable for the synthesis of the desired quinazolin-2-one derivatives having an unsubstituted spirohydantoin ring. Recently we described a modification of this synthetic sequence using urea instead of isocyanates; it reacts with 1-methylcarbamoylisatin (**2a**) (method A)[8]or 1-ethoxycarbonylisatin (**9**) (method B),[1] yielding ultimately spiro[imidazolidine-4,4′(1′*H*)-quinazoline]-2,2′,5(3′*H*)-triones (**8**) (Chart 1). Unfortunately, method A suffers from low overall yield owing to the low solubility and poor nucleophilicity of urea, while method B cannot be applied to the synthesis of spiroquinazolin-2-ones having a bulky group such as benzyl at the 3-position for steric reasons. In this paper, we describe a new modification of the method using either thiourea or isothiourea.

Treatment of **2a** with thiourea in the presence of triethylamine in tetrahydrofuran (THF) at room temperature gave 3,4-dihydro-4-hydroxy-3-methyl-4-thioureidocarbonyl-2(1*H*)-quinazolinone (**3**) in 48% yield. When the resulting thioureido derivative **3** was refluxed in 1,2-dichlorobenzene, two spiro products **4** and **5** were obtained in 50% and 42% yields, respectively. The structure of **4** was determined by an X-ray analysis (Fig. 1). The spirothiohydantoin derivative **5** was assigned on the basis of spectroscopic and elemental analyses. The infrared (IR) spectrum of **5** showed absorption bands at 1780 and 1680 cm^{-1} due to two carbonyl groups.[9] The proton nuclear magnetic resonance (^{1}H-NMR) spectrum of **5** exhibited three singlet signals due to three NH protons at δ 10.00, 10.90 and 12.40, respectively. Interestingly, the spirothiazolinone **4** was converted into the spirothiohydantoin **5** upon heating with 10% HCl. This transformation would involve ring opening accompanied with the cleavage of the S–C bond of the spirothiazolinone ring, followed by recyclization by the attack of the amino group to the carbon at the 4-position of the quinazoline ring. In practice, **3** was heated with 10% HCl to give exclusively the spirothiohydantoin **5** in 83% yield. The spirothiohydantoin **5** was then converted into the desired spiroquinazolin-2-one **8a** by oxidation with 30% hydrogen peroxide (H_2O_2) in 10% sodium hydroxide (NaOH)[10] in a good yield.

Although the reaction of **2a** with thiourea, as we expected, proceeded smoothly, the yield of this step was still unsatisfactory. We then examined the reaction of **2a** with 2-

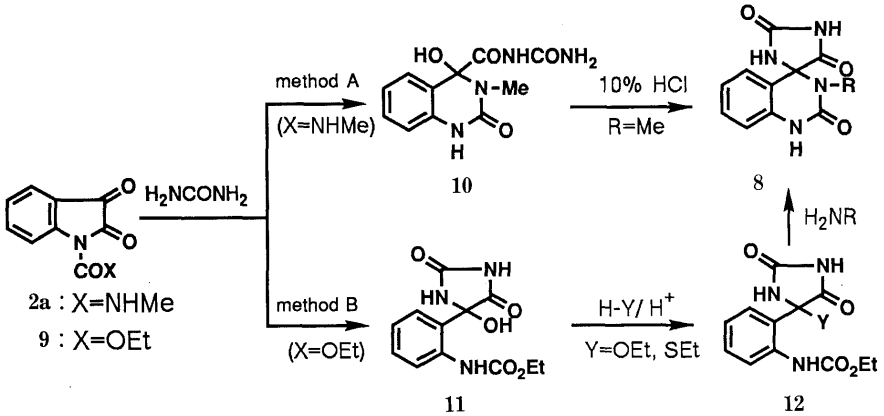


Chart 1

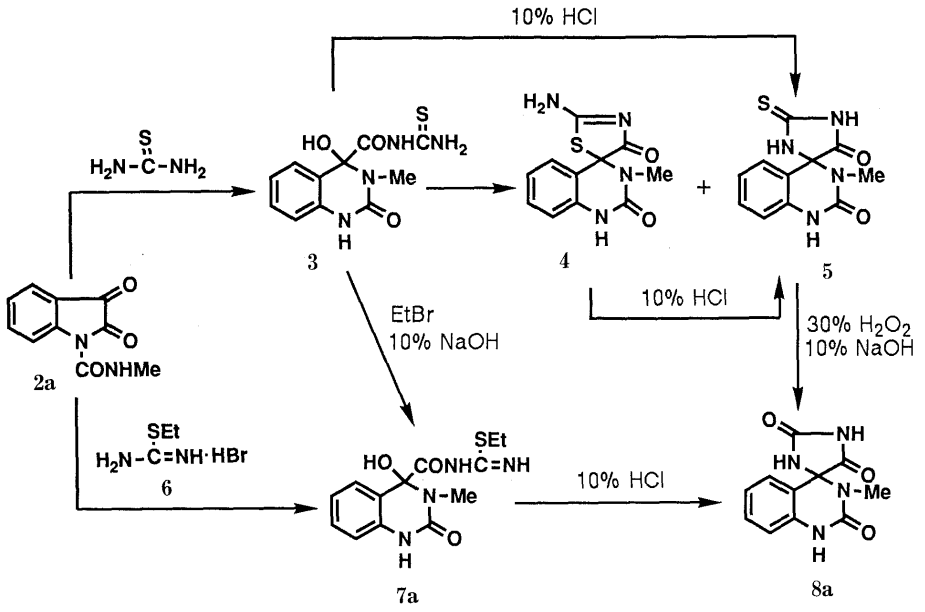


Chart 2

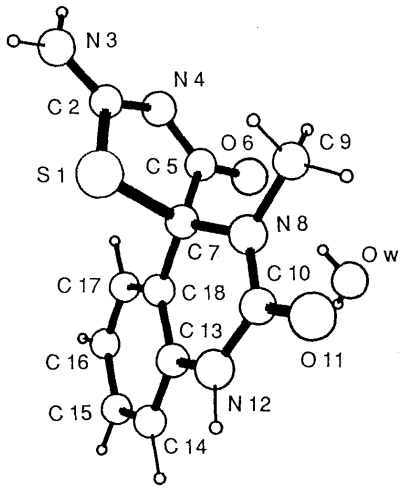
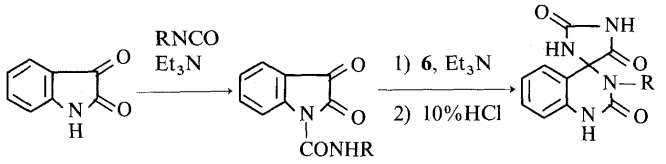


Fig. 1. Perspective View of Compound **4**

TABLE I. Synthesis of 3-Substituted Spiroquinazolin-2-ones (**8**)



Entry	R	2 Yield (%)	8 Yield (%)
a	Me	96	85
b	Et	—[a]	75[b]
c	iso-Pr	—[a]	69[b]
d	*n*-Bu	64	53
e	CH_2Ph	78	69
f	Ph	93	70

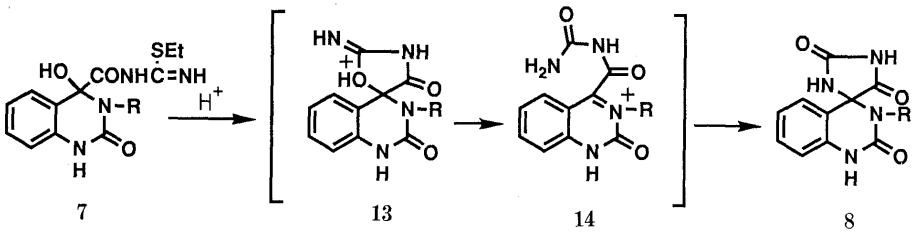
a) Not isolated. *b*) Yield from isatin (**1**).

ethyl-2-isothiourea hydrobomide (**6**). When **2a** was allowed to react with **6** in the presence of triethylamine in THF at room temperature, the reaction proceeded more smoothly to afford **7a** in 65% yield. The product **7a** was identical with an authentic sample prepared by treatment of **3** with ethyl bromide in 10% NaOH. Compound **7a** was then treated with 10% HCl at 80 °C to give **8a** in 75% yield. It was found that these two step reactions can be done in one pot without isolation of relatively unstable **7a**. Thus, in the reaction of **2a** with **6**, the reaction mixture was concentrated under reduced pressure and treated with 10% HCl to give the desired spiroquinazolin-2-one **8a** in 85% overall yield. Apparently, this synthetic route for **8a** is superior to any previously reported method in terms of overall yield and ease of manipulation. We then applied this method to the synthesis of various 3-substituted spiroquinazolin-2-ones **8**.

A series of 1-carbamoylisatins **2** were firstly synthesized by the reaction of isatin (**1**) and isocyanates. The resulting products **2** were treated with **6** to afford the corresponding 3-substituted 4-hydroxyquinazolin-2-one derivatives **7**, which were directly converted into the target compounds **8** by heating with 10% HCl. The results are summarized in Table I. We could synthesize in good yields the spiroquinazolin-2-ones **8** having bulky substituents such as isopropyl and phenyl groups at the 3-position, which could not be obtained by the previously reported methods.

A possible mechanism for the formation of **8** from **7** is depicted in Chart 3. The acid-catalyzed cyclization of **7** would give the imino oxazolidinium derivative **13** with the elimination of ethanethiol.[11] Subsequent ring opening of **13** would result in the formation of the acyl iminium cation intermediate **14**, which undergoes spontaneous recyclization by nucleophilic attack of the $-CONH_2$ group to give compound **8**.

In summary, we found a new, practical and versatile synthetic procedure for various 3-substituted spiroquinazolin-2-ones having a hydantoin ring which involves the reactions of 1-carbamoylisatins with 2-ethyl-2-isothiourea followed by acid treatment. The assay of the biological activities of the derivatives thus obtained is in progress.



7 13 14 8

Chart 3

Experimental

All melting points were measured by the use of a Yamato MP-21 melting point apparatus and are uncorrected. IR spectra were recorded on a Shimadzu IR-420 spectrophotometer. Ultraviolet (UV) spectra were recorded on a Shimadzu UV-250 spectrophotometer. ^{1}H-NMR spectra were obtained using a Hitachi R-40 (90 MHz) spectrometer with tetramethylsilane (TMS) as an internal standard. Mass spectra (MS) were taken with a Hitachi M-60 mass spectrometer at an ionizing potential of 30 eV. All the data for X-ray structural analysis were collected with a Rigaku AFC/5 FOS four-circle diffractometer. Column chromatography was carried out with Kieselgel 60 (230—400 mesh, E. Merck) and analytical thin layer chromatography (TLC) was performed with precoated Kieselgel $60F_{254}$ plates (0.25 mm thickness, E. Merck).

Materials 1-Methylcarbamoylisatin (**2a**) and 1-phenylcarbamoylisatin (**2f**) were prepared from **1** according to the reported procedure.[12]

1-Butylcarbamoylisatin (2d) Butyl isocyanate (9.91 g, 0.1 mol) was added dropwise to a solution of **1** (14.71 g, 0.1 mol) and triethylamine (10.12 g, 0.1 mol) in *N*,*N*-dimethylformamide (DMF) (80 ml) at 0 °C and the mixture was stirred at the same temperature for 1 h. Then, the resulting crystals were collected, washed with diisopropyl ether (IPE), and recrystallized from ethyl acetate (AcOEt)–IPE to give **2d** (15.76 g, 64%), mp 97—99 °C. IR (Nujol): 3360, 1755, 1743, 1700 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 0.7—1.1 (3H, m, CH_3), 1.1—1.9 [4H, m, $(CH_2)_2$], 3.1—4.6 (2H, m, $NHCH_2$), 7.1—7.4 (1H, m, NH), 7.5—7.8 (2H, m, ArH × 2), 8.0—8.4 (2H, m, ArH × 2). MS *m/z*: 246 (M^+). *Anal.* Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73: N, 11.38. Found: C, 63.08; H, 5.72; N, 11.41.

1-Benzylcarbamoylisatin (2e) This compound was synthesized from **1** (14.71 g, 0.1 mol) and benzyl isocyanate (13.32 g, 0.1 mol) in the same way as described for the preparation of **2d**. Yield 21.85 g (78%), mp 165—167 °C (from AcOEt). IR (Nujol): 3360, 1755, 1743, 1700 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 4.53 (2H, d, J=6 Hz, CH_2Ph), 7.16—7.83 (8H, m, ArH × 8), 8.28 (1H, d, J=8 Hz, ArH), 8.70 (1H, t, J=6 Hz, NH), MS *m/z*: 280 (M^+). *Anal.* Calcd for $C_{16}H_{12}N_2O_3$: C, 68.56; H, 4.32; N, 10.00. Found: C, 68.58; H, 4.38; N, 10.24.

3,4-Dihydro-4-hydroxy-3-methyl-4-thioureidocarbonyl-2(1*H*)-quinazolinone (3) Thiourea (1.7 g, 22 mmol) was added to a solution of **2a** (4.08 g, 20 mmol) and triethylamine (2.22 g, 22 mmol) in THF (50 ml) and the mixture was stirred at room temperature for 3 h. The resulting crystals were collected, washed with water, and recrystallized from DMSO–water to give **3** (2.7 g, 48%), mp >280 °C. IR (Nujol): 3350, 3300, 3150, 1705, 1650, 1605 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.80 (3H, s, CH_3), 6.70—7.50 (4H, m, ArH × 4), 8.25 (1H, s), 9.31 (1H, s), 9.72 (1H, s), 9.82 (2H, s), *Anal.* Calcd for $C_{11}H_{12}N_4O_3S$: C, 47.13; H, 4.32; N, 19.99; S, 11.44. Found: C, 47.05; H, 4.21; N, 19.89; S, 11.10.

2′-Amino-3-methylspiro[quinazoline-4(1*H*),5′-thiazoline]-2,4′-(3*H*)-dione (4) A suspension of **3** (2.24 g, 8 mmol) in 1,2-dichlorobenzene (20 ml) was refluxed of 2 h. After work-up, the crude product was charomatographed on silica gel using $CHCl_3$–ethanol (95 : 5) as an eluent. The first fraction gave **5** (0.91 g, 42%), mp >280 °C (from DMF–water). IR (Nujol): 3450, 3200, 1780, 1760 (sh), 1675, 1615 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.74 (3H, s, CH_3), 6.90—7.40 (4H, m, ArH × 4), 10.00 (1H, s, NH), 10.90 (1H, s, NH), 12.40 (1H, br, NH). UV λ_{max}^{MeOH} (log ε): 270 (4.30), 250 (4.23). MS *m/z*: 262 (M^+). *Anal.* Calcd for $C_{11}H_{10}N_4O_2S \cdot 1/2H_2O$: C, 48.70; H, 4.09; N, 20.65; S, 11.82. Found: C, 48.96; H, 3.91; N, 20.35; S, 12.07.

The second fraction gave **4** (1.09 g, 50%), mp >280 °C (from MeOH–water). IR (Nujol): 3400, 3200, 1680 (br), 1600 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.80 (3H, s, CH_3), 6.80—7.30 (4H, m, ArH × 4), 9.20 (1H, s, NH), 9.51 (1H, s, NH), 10.01 (1H, s, NH). UV λ_{max}^{MeOH} (log ε): 294 (sh) (4.29), 252 (sh) (3.93), 225 (3.33). MS *m/z*: 262 (M^+). *Anal.* Calcd for $C_{11}H_{10}N_4O_2S \cdot 3/5H_2O$: C, 48.38; H, 4.13; N, 20.52; S, 11.74. Found: C, 48.34; H, 4.28; N, 20.58; S, 11.58.

X-Ray Structure Analysis The diffraction experiment on **4**, $C_{11}H_{10}N_4O_2S \cdot H_2O$, was carried out using a colorless transparent prism with dimensions of 0.40 × 0.25 × 0.15 mm^3 obtained from MeOH solution with water by the vapor diffusion method. The four-circle diffractometer (AFC/5, RIGAKU) was used with graphite-monochromated Cu $K\alpha$ radiation (λ=1.5418 Å). The unit cell dimensions were determined from the angular setting of 25 reflections (2θ values in the range of 30—60°), and refined by the least-squares method. The crystal data are as follows: a=17.137(1), b=13.341(1), c=6.406(1) Å, α=90.00, β=116.43(1), γ=90.00°, U=1311.5 (2) Å^3, monoclinic, space group $P2_1/a$, Z=4, D_x=1.328 g/cm^3, $F(000)$=544, μ(Cu $K\alpha$)=21.564 cm^{-1}. Three dimensional intensity data were measured by the ω–2θ scan technique (2$\theta \leqq$120°); 1951 unique reflections were measured, of which 1729 with $|F_o| \geqq 2.67 \times \sigma(F)$ were considered as observed. No absorption corrections were applied. The structure was solved by the direct method using MULTAN80[13] and the difference Fourier method. The refinement of atomic parameters was carried out using the block-diagonal matrix least-squares method with anisotropic temperature factors for the non-hydrogen atoms. Of 12 hydrogen atoms, 4 atoms were located on the difference Fourier maps and refined with isotropic temperature factors. The positions of other hydrogen atoms were assumed geometrically and fixed. Throughout the refinement, the function $\Sigma w(|F_o|-|F_c|)^2$ was minimized. During the final refinement stage, the weighting scheme of $\sqrt{w} = 1/\sigma(F_o)$ was used. The final R value was 0.045 (R_w=0.058) and the maximum residual electron density was 0.3e/Å^3 on the final Fourier synthesis. The atomic scattering factors were taken from "International Tables for X-ray Crystallography".[14] The molecular structure is shown in Fig. 1. The fractional atomic coordinates, bond lengths and bond angles are listed in Tables II—IV, respectively.

Table II. Final Atomic Coordinates and Equivalent Isotropic or Isotropic Thermal Parameters with e.s.d. in Parentheses

Atom	x	y	z	B_{eq}
S1	0.24751 (4)	0.14756 (6)	0.61462 (11)	3.61 (3)
C2	0.1456 (2)	0.1501 (2)	0.3684 (4)	3.15 (10)
N3	0.0846 (1)	0.0903 (2)	0.3603 (4)	3.98 (10)
N4	0.1353 (1)	0.2129 (2)	0.1968 (3)	3.26 (8)
C5	0.2065 (2)	0.2688 (2)	0.2443 (4)	3.08 (10)
O6	0.2116 (1)	0.3366 (2)	0.1221 (3)	4.14 (8)
C7	0.2893 (2)	0.2425 (2)	0.4774 (4)	3.05 (10)
N8	0.3192 (1)	0.3314 (2)	0.6222 (3)	3.11 (8)
C9	0.2535 (2)	0.3917 (3)	0.6519 (5)	4.16 (12)
C10	0.4033 (2)	0.3381 (2)	0.7942 (4)	3.25 (10)
O11	0.4238 (1)	0.3984 (2)	0.9555 (3)	4.09 (8)
N12	0.4633 (1)	0.2774 (2)	0.7766 (4)	3.74 (9)
C13	0.4459 (2)	0.2162 (2)	0.5839 (4)	3.44 (10)
C14	0.5133 (2)	0.1737 (3)	0.5507 (6)	4.59 (13)
C15	0.4944 (2)	0.1135 (3)	0.3599 (6)	5.30 (15)
C16	0.4084 (2)	0.0948 (3)	0.2004 (5)	5.24 (15)
C17	0.3416 (2)	0.1372 (3)	0.2344 (5)	4.10 (12)
C18	0.3595 (2)	0.1986 (2)	0.4260 (4)	3.11 (10)
Ow	0.3521 (2)	0.4750 (2)	0.2364 (4)	5.86 (11)

$B_{eq}=4/3(B_{11}a^2+B_{22}b^2+B_{33}c^2+B_{13}ac)$.

3′-Methyl-2-thioxospiro[imidazolidine-4,4′-(1′*H*)-quinazoline]-2′,5(3′*H*)-dione (5) (a) From **3**: A suspension of **3** (0.5 g, 1.8 mmol) in 10% HCl solution (10 ml) was stirred at 80 °C for 3 h. After cooling, the resulting crystals were collected, washed with water, and recrystallized from DMF–water to give **5** (0.40 g, 83%), mp >280 °C.

(b) From **4**: A suspension of **4** (2.1 g, 8 mmol) in 10% HCl solution (10 ml) was stirred at 80 °C for 3 h. After cooling, the resulting crystals were collected, washed with water, and recrystallized from DMF–water

TABLE III. Bond Lengths with e.s.d. in Parentheses

Atom 1–atom 2	Distance (Å)
S1–C2	1.757 (2)
S1–C7	1.857 (3)
C2–N3	1.297 (4)
C2–N4	1.330 (4)
N4–C5	1.345 (4)
C5–O6	1.224 (4)
C5–C7	1.575 (3)
C7–N8	1.451 (3)
C7–C18	1.501 (4)
N8–C9	1.463 (4)
N8–C10	1.372 (3)
C10–O11	1.231 (3)
C10–N12	1.353 (4)
N12–C13	1.397 (4)
C13–C14	1.386 (5)
C13–C18	1.391 (3)
C14–C15	1.375 (5)
C15–C16	1.392 (4)
C16–C17	1.379 (5)
C17–C18	1.391 (4)

TABLE IV. Bond Angles with e.s.d. in Parentheses

Atom 1–atom 2–atom 3	Angle (°)
C2–S1–C7	90.0 (1)
S1–C2–N3	119.0 (2)
S1–C2–N4	117.9 (2)
N3–C2–N4	123.1 (2)
C2–N4–C5	112.9 (2)
N4–C5–O6	125.5 (2)
N4–C5–C7	115.7 (2)
O6–C5–C7	118.7 (2)
S1–C7–C5	103.1 (2)
S1–C7–N8	110.8 (2)
S1–C7–C18	110.7 (2)
C5–C7–N8	109.7 (2)
C5–C7–C18	110.5 (2)
N8–C7–C18	111.7 (2)
C7–N8–C9	117.3 (2)
C7–N8–C10	120.8 (2)
C9–N8–C10	116.9 (2)
N8–C10–O11	121.5 (3)
N8–C10–N12	117.3 (2)
O11–C10–N12	121.2 (2)
C10–N12–C13	123.5 (2)
N12–C13–C14	120.6 (2)
N12–C13–C18	118.7 (3)
C14–C13–C18	120.6 (3)
C13–C14–C15	119.5 (3)
C14–C15–C16	120.7 (4)
C15–C16–C17	119.5 (3)
C16–C17–C18	120.6 (2)
C7–C18–C13	118.2 (2)
C7–C18–C17	122.7 (2)
C13–C18–C17	119.1 (3)

to give **5** (1.95 g, 93%), mp >280 °C.

4-(2-Ethyl-2-isothioureido)carbonyl-3,4-dihydro-4-hydroxy-3-methyl-2(1*H*)-quinazolinone (7a) (a) From **2a**: Triethylamine (4.5 g, 44 mmol) and **6**[15] (7.4 g, 40 mmol) were added to a solution of **2a** (8.16 g, 40 mmol) in THF (100 ml), and the mixture was stirred at room temperature for 3 h. The resulting crystals were collected, washed with water, and recrystallized from DMF–water to give **7a** (8.0 g, 65%), mp >280 °C. IR (Nujol): 3410, 3200, 3120, 1720, 1658, 1605 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 0.96 (3H, t, J=7 Hz, CH_2CH_3), 2.81 (3H, s, 3-CH_3), 3.05—3.72 (2H, m, SCH_2), 6.60—7.75 (6H, m), 9.72 (1H, br), 9.30—10.70 (1H, br). *Anal.* Calcd for $C_{13}H_{16}N_4O_3S$: C, 50.63; H, 5.23; N, 18.17; S, 10.40. Found: C, 50.56; H, 4.99; N, 18.12; S, 10.46.

(b) From **3**: A 10% NaOH solution (0.12 g, 3 mmol) was added to a solution of **3** (0.84 g, 3 mmol) in DMF (10 ml), and the mixture was stirred at room temperature for 30 min. Then, ethyl bromide (0.33 g, 3 mmol) was added dropwise to the mixture. After being stirred at room temperature for an additional 30 min, the resulting mixture was concentrated under reduced pressure and crystallized from water. The product was recrystallized from DMF–water to give **7a** (0.65 g, 70%), mp >280 °C.

3′-Methylspiro[imidazolidine-4,4′(1′*H*)-quinazoline]-2,2′,5(3′*H*)-trione (8a)[8] (a) From **2a**: Triethylamine (4.45 g, 44 mmol) and **6** (7.4 g, 40 mmol) were added to a solution of **2a** (8.16 g, 40 mmol) in THF (100 ml), and the mixture was stirred at room temperature for 3 h. Then, the reaction mixture was concentrated under reduced pressure. A 10% HCl solution (50 ml) was added to the residue, and the mixture was heated at 80 °C for 3 h. After cooling, the resulting crystals were collected, washed with water and recrystallized from DMSO to give **8a** (8.36 g, 85%), mp >280 °C.

(b) From **5**: A 30% hydrogen peroxide solution (2 ml) was added to a solution of **5** (1.0 g, 3.7 mmol) in 10% NaOH solution (10 ml), and the mixture was stirred at room temperature for 1 h. After being acidified with 10% HCl solution, the resulting crystals were collected, washed with water, and recrystallized from DMSO to give **8a** (0.85 g, 91%), mp >280 °C.

(c) From **7a**: A suspension of **7a** (2.0 g, 6.5 mmol) in 10% HCl solution (20 ml) was heated at 80 °C for 3 h. After cooling, the resulting crystals were collected, and recrystallized from DMSO to give **8a** (1.2 g, 75%), mp >280 °C.

3′-Ethylspiro[imidazolidine-4,4′(1′*H*)-quinazoline]-2,2′,5(3′*H*)-trione (8b)[1] Triethylamine (5.06 g, 50 mmol) and ethyl isocyanate (3.91 g, 55 mmol) were added to a solution of **1** (7.36 g, 50 mmol) in THF (75 ml) at 0°C, and the mixture was stirred at the same temperature for 1 h. Then, triethylamine (1.01 g, 10 mmol) and **6** (11.11 g, 60 mmol) were added to the reaction mixture, and the mixture was stirred at room temperature for 3 h. The resulting mixture was concentrated under reduced pressure. A 10% HCl solution (35 ml) was added to the residue and the mixture was heated at 80 °C for 3 h. After cooling, the resulting crystals were collected, washed with water, and recrystallized from DMF–water to give **8b** (9.76 g, 75%), mp >280 °C.

3′-Isopropylspiro[imidazolidine-4,4′(1′*H*)-quinazoline]-2,2′,5(3′*H*)-trione (8c) This compound was synthesized from **1** (7.36 g, 50 mmol) in the same way as described for the preparation of **8b**. Yield, 9.47 g, (69%), mp >280 °C (from DMF–water). IR (Nujol): 3330, 3210, 1790, 1740, 1672 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.40 [6H, d, J=6 Hz, $CH(CH_3)_2$], 3.0—3.4 (1H, sept., J=6 Hz, NCH), 6.6—7.4 (4H, m, ArH×4), 9.15 (1H, s, NH), 9.66 (1H, s, NH), 11.16 (1H, s, NH). MS m/z: 274 (M^+). *Anal.* Calcd for $C_{13}H_{14}N_4O_3$: C, 56.93; H, 5.15; N, 20.43. Found: C, 56.85; H, 5.22; N, 20.69.

3′-Butylspiro[imidazolidine-4,4′(1′*H*)-quinazoline]-2,2′,5(3′*H*)-trione (8d) This compound was synthesized from **2d** (2.46 g, 10 mmol) in the same way as described for the preparation of **8a**. Yield, 1.53 g, (53%), mp 263—266 °C (DMF–water). IR (Nujol): 3240, 1782, 1725, 1665 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 0.7—1.9 [7H, m, $(CH_2)_2CH_3$], 2.7—3.8 (2H, m, NCH_2), 6.7—7.4 (4H, m, ArH×4), 9.05 (1H, s, NH), 9.77 (1H, s, NH), 11.14 (1H, s, NH). MS m/z: 288 (M^+). *Anal.* Calcd for $C_{14}H_{16}N_4O_3$: C, 58.33; H, 5.59; N, 19.43. Found: C, 58.24; H, 5.64; N, 19.04.

3′-Benzylspiro[imidazolidine-4,4′(1′*H*)-quinazoline]-2,2′,5(3′*H*)-trione (8e) This compound was synthesized from **2e** (2.80 g, 10 mmol) in the same way as described for the preparation of **8a**. Yield, 2.22 g (69%), mp >280 °C (DMF–water). IR (Nujol): 3240, 3050, 1782, 1738, 1720 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 4.33, 4.66 (1H each, ABq, J=16 Hz, CH_2Ph), 6.87—7.50 (9H, m, ArH×9), 9.13 (1H, s, NH), 9.97 (1H, s, NH), 11.18 (1H, s, NH). MS m/z: 322 (M^+). *Anal.* Calcd for $C_{17}H_{14}N_4O_3$: C, 63.35; H, 4.38; N, 17.38. Found: C, 63.22; H, 4.29; N, 17.58.

3′-Phenylspiro[imidazolidine-4,4′(1′*H*)-quinazoline]-2,2′,5(3′*H*)-trione (8f) This compound was synthesized from **2f** (10.64 g, 40 mmol) in the same way as described for the preparation of **8a**. Yield, 8.87 g, (72%), mp >280 °C (DMF–water). IR (Nujol): 3400, 3050, 1785, 1738, 1660 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 6.64—7.50 (9H, m, ArH×9), 9.10 (1H, s, NH), 10.05 (1H, s, NH), 10.80 (1H, br, NH). MS m/z: 308 (M^+). *Anal.* Calcd for $C_{16}H_{12}N_4O_3 \cdot 1/2H_2O$: C, 60.56; H, 4.13; N, 17.66. Found: C, 60.63; H, 4.10; N, 17.54.

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