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Synthesis of the Metabolites of Afloqualone and Related Compounds

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Seven main metabolites (**3**—**9**) of afloqualone (**1**, 6-amino-2-fluoromethyl-3-(*o*-tolyl)-4(3*H*)-quinazolinone and related 4(3*H*)-quinazolinone derivatives were synthesized. The metabolites **4** and **5** containing a sulfur atom were prepared by the reaction of 6-acetamido-2-chloromethyl-3-(*o*-tolyl)-4(3*H*)-quinazolinone (**11**) with $NaSCH_3$ followed by oxidation with H_2O_2. Reaction of **11** and *N*-acetyl-L-cysteine gave the mercapturic acid-conjugated metabolite **6**. Condensation of 2-fluoroacetamido-5-nitrobenzoic acid (**19**) and 2-aminobenzyl alcohol (**20**) with dicyclohexylcarbodiimide (DCC) in the presence of 1-hydroxybenzotriazole afforded 2-fluoromethyl-3-(*o*-hydroxymethylphenyl)-6-nitro-4(3*H*)-quinazolinone (**21**), which was converted to the metabolites **7** and **8**. Treatment of the 2-bromomethyl-4(3*H*)-quinazolinone (**24**) with $AgBF_4 \cdot H_2O$ in dimethylsulfoxide (DMSO) gave the 2-hydroxymethyl metabolite **9**. None of the main metabolites (**2**—**9**) showed significant central nervous system depressant activity.

Keywords——afloqualone; 6-amino-2-fluoromethyl-3-(*o*-tolyl)-4(3*H*)-quinazolinone; metabolite of afloqualone; 4(3*H*)-quinazolinone; oxidation of sulfide; CNS depressant activity

In the course of our studies on biologically active halogenated compounds, afloqualone (**1**, 6-amino-2-fluoromethyl-3-(*o*-tolyl)-4(3*H*)-quinazolinone) has been found to be a new centrally acting muscle relaxant,[1] and it is now undergoing clinical testing. A study on its biological fate using radioactive afloqualone showed that afloqualone was absorbed readily from the gastrointestinal tract and excreted relatively rapidly after oral administration to various animals.[2] In a metabolic study,[3] some new sulfur-containing 4(3*H*)-quinazolinone derivatives were isolated from the urine of rats, monkeys, and dogs as metabolites of afloqualone. The main metabolites, which were tentatively assigned[3a] from their nuclear magnetic resonance

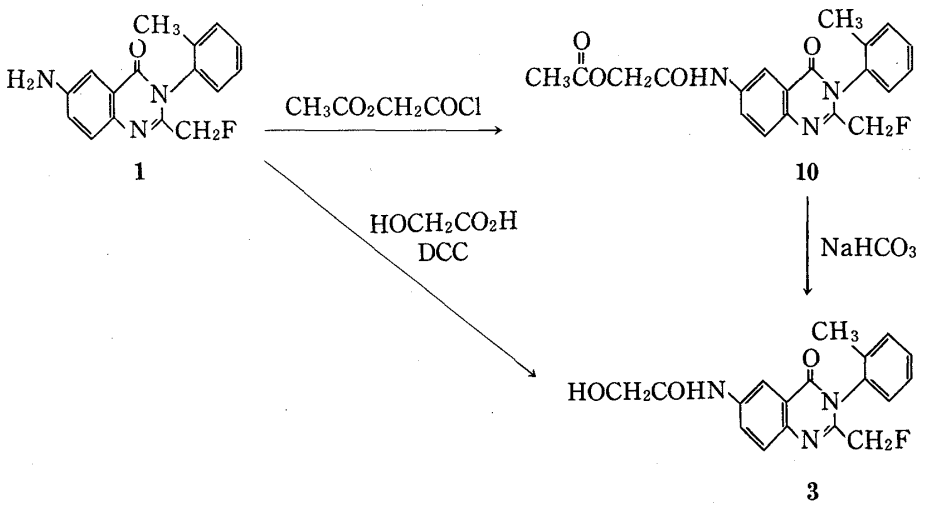
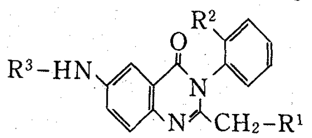


Chart 1

(NMR) spectra and mass spectra (MS), are shown in Table I. Most of the metabolites in rats and monkeys were acylated at the 6-amino group of the 4(3*H*)-quinazolinone skeleton. This paper describes the synthesis of the metabolites and related compounds which were prepared for the purpose of structural elucidation and investigation of the pharmacological properties.

Synthesis of *N*-hydroxyacetyl afloqualone (**3**) was carried out by two methods as shown in Chart 1. Acylation of **1** with acetoxyacetyl chloride, followed by basic hydrolysis with $NaHCO_3$ in aqueous MeOH, gave **3** in good yield. An alternative route to **3** is one-pot synthesis from **1**. Condensation of **1** with glycolic acid using *N*,*N'*-dicyclohexylcarbodiimide (DCC) afforded **3** in 35% yield.

TABLE I. Main Metabolites of Afloqualone (**1**) in Rats



Compound No.	R^1	R^2	R^3	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N	S
2	F	CH_3	CH_3CO	239—242[a]					
3	F	CH_3	$HOCH_2CO$	213—215	$C_{18}H_{16}FN_3O_3$	63.33	4.72	12.31	
						(63.43	4.79	12.32)	
4	SO_2CH_3	CH_3	CH_3CO	222—224[b]	$C_{19}H_{19}N_3O_4S$	59.21	4.97	10.90	8.30
						(59.03	5.20	10.77	8.21)
5	$SOCH_3$	CH_3	CH_3CO	216—217[b]	$C_{19}H_{19}N_3O_3S$	61.78	5.19	11.38	8.66
						(61.57	5.33	11.20	8.65)
6	SCH_2CHCO_2H $NHCOCH_3$	CH_3	CH_3CO	[c]	$C_{24}H_{26}N_4O_5S$	59.74	5.43	11.61	6.64
						(59.50	5.44	11.51	6.64)
7	F	CH_2OH	CH_3CO	245—247	$C_{18}H_{16}FN_3O_3$	63.33	4.72	12.31	
						(63.20	4.81	12.40)	
8	F	CH_2OH	$HOCH_2CO$	241—243	$C_{18}H_{16}FN_3O_4$	60.50	4.51	11.76	
						(60.34	4.53	11.85)	
9	OH	CH_3	CH_3CO	223—225	$C_{18}H_{17}N_3O_3$	66.86	5.30	13.00	
						(66.73	5.26	13.11)	

a) J. Tani, Y. Yamada, T. Ochiai, I. Inoue, and T. Oine, *Chem. Pharm. Bull.*, **27**, 2675 (1979).
b) Decomposition. *c*) Because the acid was not crystallized, the analysis was done with the methyl (**18**, mp 155—156 °C).

The metabolites **4**, **5**, and **6**, in which a sulfur atom is incorporated into the parent molecule, were prepared by the routes shown in Chart 2. The 2-chloromethyl compound **11** was converted into the 2-methylthiomethyl derivative **12** by reaction with $NaSCH_3$. Oxidation of **12** with H_2O_2 provided the sulfoxide **5** and/or the sulfone **4** depending on the reaction conditions. The sulfoxide **5** was synthesized in 91% yield by oxidation of **12** with 35% H_2O_2 (4.0 eq mol) in AcOH at room temperature for 1 h. For the preparation of the sulfone **4**, a large excess of H_2O_2 and a longer reaction time were required (see Experimental).

Solvolytic deacetylation of **4** and **12** in MeOH containing HCl proceeded smoothly to afford **14** and **13**, respectively. However, under similar conditions, synthesis of **17** from **5** could not be accomplished because the Pummerer-type reaction of the sulfoxide group took place simultaneously. Therefore, we attempted the following alternative route for the preparation of **17**. Trifluoroacetylation of **13** gave **15**, which was oxidized with H_2O_2 to give the sulfoxide **16**. Treatment of **16** with piperidine in MeOH at 50—60°C afforded **17** in 75% yield. Compounds **13** and **17** were detected in the urine of dogs after oral administration of radioactive afloqualone.[3b)]

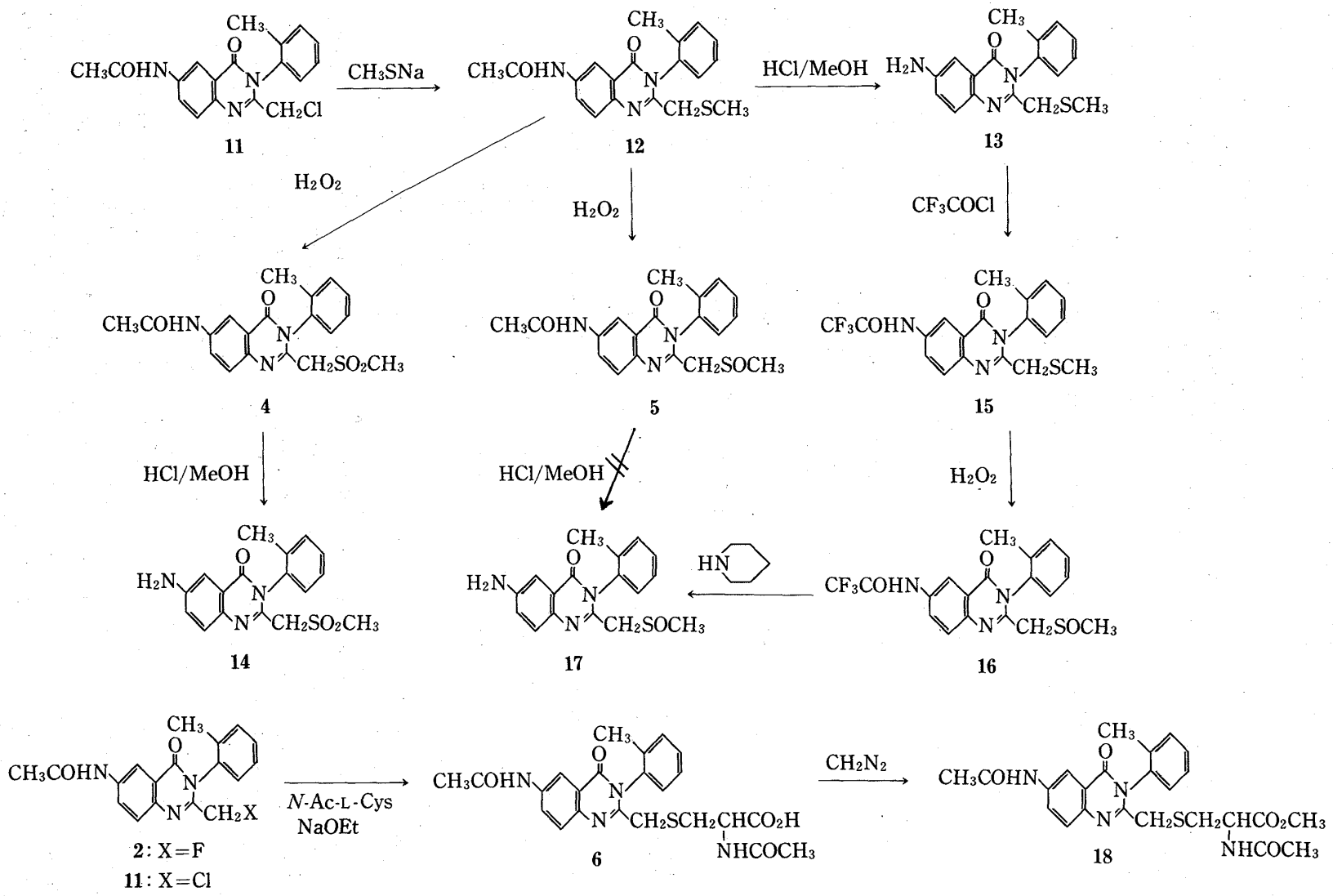


Chart 2

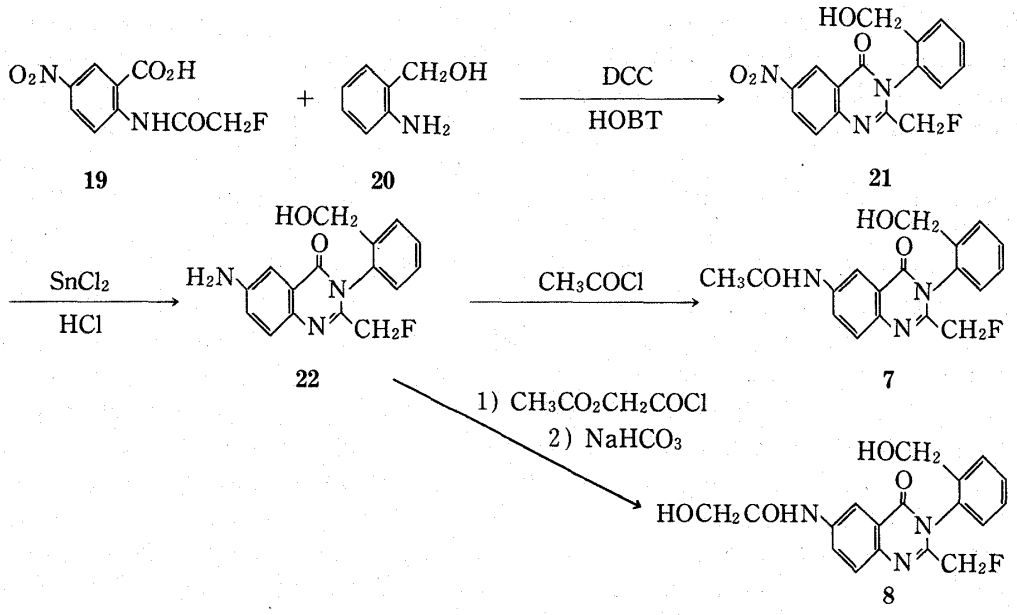


Chart 3

The acidic metabolite **6**, which was considered to be one of the precursors of the sulfur-containing metabolites **4** and **5**, was prepared by the reaction of **2** or **11** with *N*-acetyl-L-cysteine in the presence of NaOEt and converted into the methyl ester **18** by treatment with diazomethane.

The metabolites **7** and **8** were synthesized *via* the hydroxylated afloqualone **22** as the common intermediate. The quinazolinone (**21**) was prepared in moderate yield by condensation–cyclization of **19** and **20** with DCC in the presence of 1-hydroxybenzotriazole (HOBT). Reduction of **21** with stannous chloride afforded **22** in 64% yield. Selective *N*-acetylation of **22** with acetyl chloride proceeded without difficulty to give **7**. Treatment of **22** with acetoxyacetyl chloride, followed by basic hydrolysis, afforded **8** in 70% yield. An attempt to prepare the 2-hydroxymethyl metabolite **9** by hydrolytic hydroxylation of the halomethyl

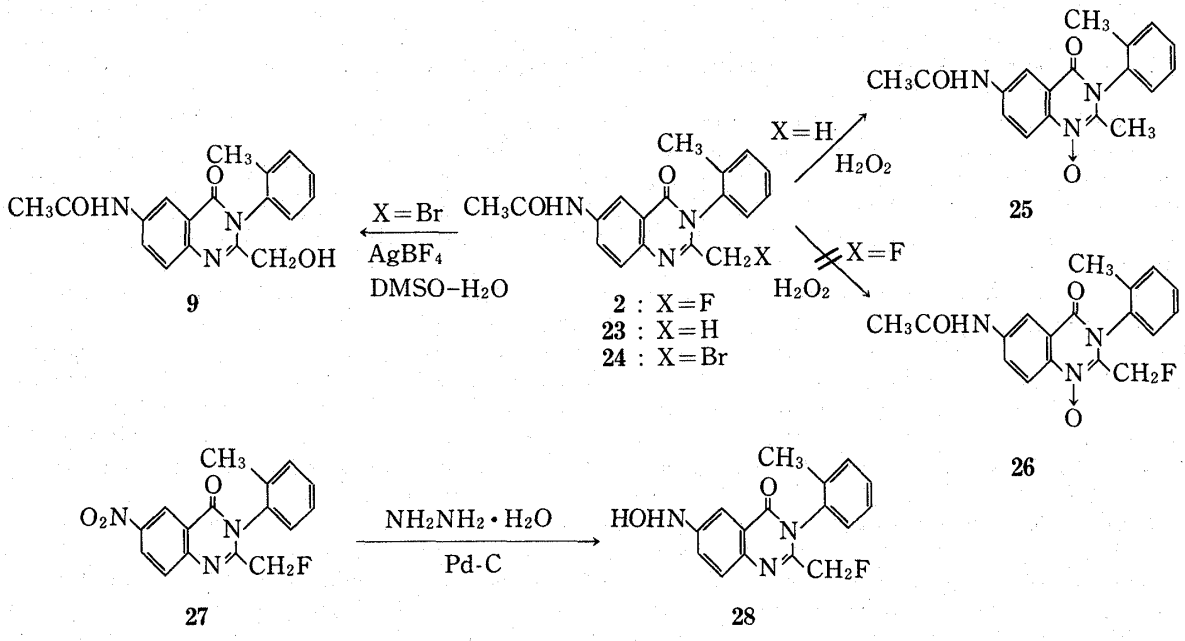


Chart 4

group of **11** or **24** under basic conditions was unsuccessful. Then, the metabolite **9** was synthesized by treatment of **24** with $AgBF_4 \cdot H_2O$ in DMSO containing a small amount of H_2O.

In the metabolic study, the *N*-oxide **26** was assumed to be one possible metabolite of afloqualone by analogy with the metabolism of methaqualone,[4] but it was not detected in the urine of any species of animals used in spite of extensive studies. To confirm the absence of **26**, we tried to prepare an authentic sample of **26**. All our attempts to synthesize **26** were unsuccessful. In the case of the 2-methyl analog, however, the *N*-oxide **25** was prepared in 12.7% yield by oxidation of **23** with H_2O_2. *N*-Hydroxylation is known to be one of the metabolic pathways of some aromatic amines. Reduction of the 6-nitro compound **27** with $NH_2NH_2 \cdot H_2O$ in the presence of 5% Pd-C gave the 6-hydroxyamino compound **28**, which was not found among the metabolites of afloqualone.

All of the main metabolites (**2**—**9**) isolated from the urine of rats were identified by comparison with the corresponding authentic samples prepared as described above. None of the main metabolities of afloqualone exhibited significant central nervous system (CNS) depressant activity even at 100 mg/kg (*p.o.*) in mice, and LD_{50} values of the metabolites were all greater than 1000 mg/kg in mice on oral administration. The 6-amino compounds **13**, **14**, **17**, and **22** showed weak CNS depressant activity. Among them, the most active compound **22** was about 3 times less active than afloqualone in the rotating rod test.[1,5] These results are in accord with our previous finding that the nonprotected 6-amino group and the size of the 2-substituent are very important for the CNS depressant activity.[1b]

Experimental

All melting points were determined on a Yamato MP-21 apparatus and are uncorrected. NMR spectra were recorded on a Hitachi Perkin-Elmer R-20A instrument with Me_4Si as an internal standard. Mass spectra (MS) were measured with a Hitachi M-60 mass spectrometer.

6-Acetoxyacetamido-2-fluoromethyl-3-(*o*-tolyl)-4(3*H*)-quinazolinone (10)——Acetoxyacetyl chloride[6] (16 g, 0.117 mol) was added dropwise to a stirred solution of afloqualone (**1**, 28.3 g, 0.1 mol) in tetrahydrofuran (THF) (300 ml) at room temperature, and stirring was continued overnight. After removal of the solvent *in vacuo*, the residue was triturated with H_2O and neutralized with aqueous $NaHCO_3$. The resultant precipitate was collected by filtration to give crude **10** (38 g, 99.2%); mp 220—223°C. Recrystallization from *N*,*N*-dimethylformamide (DMF)–2-propanol gave 35 g (93.8%) of pure **10** as colorless prisms; mp 221—223°C. NMR (DMSO-d_6) δ: 2.07 (3H, s), 2.17 (3H, s), 4.73 (2H, s), 4.99 (2H, d, J=45 Hz), 7.43 (4H, s), 7.78 (1H, d, J=9 Hz), 8.09 (1H, dd, J=9 Hz, J=3 Hz), 8.51 (1H, d, J=3 Hz), 10.50 (1H, br s). *Anal.* Calcd for $C_{20}H_{18}FN_3O_4$: C, 62.66; H, 4.73; N, 10.96; F, 4.96. Found: C, 62.73; H, 4.69; N, 10.90; F, 4.82.

2-Fluoromethyl-6-hydroxyacetamido-3-(*o*-tolyl)-4(3*H*)-quinazolinone (3)——Method A: A mixture of **10** (35 g, 0.092 mol), $NaHCO_3$ (10 g, 0.119 mol), MeOH (700 ml), and H_2O (400 ml) was refluxed for 1 h. The reaction mixture became a clear solution. After cooling of the mixture, most of the MeOH was removed by evaporation *in vacuo*. H_2O was added to the residue and the resultant crystalline precipitate was collected by filtration. Recrystallization of the crystals from EtOH gave pure **3** (25.2 g, 80.9%) as colorless prisms; mp 213—215°C. NMR (DMSO-d_6) δ: 2.07 (3H, s), 4.07 (2H, d, J=6 Hz), 4.98 (2H, d, J=46 Hz), 5.69 (1H, t, J=6 Hz), 7.41 (4H, s), 7.75 (1H, d, J=9 Hz), 8.17 (1H, dd, J=9 Hz, J=3 Hz), 8.65 (1H, d, J=3 Hz), 10.13 (1H, br s).

Method B: *N*,*N*′-Dicyclohexylcarbodiimide (3.1 g, 0.015 mol) was added to a stirred solution of **1** (2.83 g, 0.01 mol), glycolic acid (0.85 g, 0.011 mol), and 1-hydroxybenzotriazole (2.0 g, 0.011 mol) in THF (50 ml) at room temperature. Stirring was continued for 6 h at the same temperature. The precipitate which had formed was filtered off and the filtrate was concentrated to dryness *in vacuo*. The residue was dissolved in $CHCl_3$, then the solution was washed with aqueous $NaHCO_3$, and dried ($MgSO_4$). Removal of the solvent gave a crystalline mass, which was purified by column chromatography on silica gel (150 g, solvent: C_6H_6: THF=7: 3) to give crude **3** (1.2 g, 35.2%). Recrystallization from EtOH gave an analytically pure sample of **3**. This sample was identical with that obtained by method A.

6-Acetamido-2-methylthiomethyl-3-(*o*-tolyl)-4(3*H*)-quinazolinone (12)——An aqueous solution of CH_3SNa (20%, 155 g, 0.443 mol) was added to a solution of 6-acetamido-2-chloromethyl-3-(*o*-tolyl)-4(3*H*)-quinazolinone (**11**, 102.3 g, 0.3 mol) in THF (1.5 l) at room temperature. The mixture was stirred for 7 h at room temperature and the solvent was removed by evaporation *in vacuo*. The residue was crystallized by trituration with H_2O. The crystals were collected by filtration and washed with 2-propanol to give almost pure **12** (98 g, 92.5%); mp 175—177°C. Recrystallization from 2-propanol gave a pure sample of **12** as colorless prisms; mp 176—178°C. NMR ($CDCl_3$) δ: 1.61 (3H, s), 2.14 (6H, s), 3.18 (1H, d, J=14 Hz), 3.47 (1H, d,

J=14 Hz), 7.2—7.5 (4H, m), 7.70 (1H, d, J=9 Hz), 8.12 (1H, d, J=3 Hz), 8.57 (1H, dd, J=9 Hz, J=3 Hz), 9.14 (1H, br s). *Anal.* Calcd for $C_{19}H_{19}N_3O_2S$: C, 64.58; H, 5.42; N, 11.89; S, 9.06. Found: C, 64.48; H, 5.73; N, 11.62; S, 8.97.

6-Acetamido-2-methylsulfonylmethyl-3-(*o*-tolyl)-4(3*H*)-quinazolinone (**4**)——A mixture of **12** (40 g, 0.113 mol), 35% H_2O_2 (100 ml, 1.13 mol), and AcOH (400 ml) was stirred for 48 h at room temperature. The reaction mixture was poured into H_2O (1.5 l) and the mixture was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with aqueous $NaHCO_3$, dried ($MgSO_4$), and evaporated to dryness *in vacuo*. The residue was crystallized by trituration with a mixture of 2-propanol and C_6H_6. The crystals were collected and recrystallized from EtOH to give **4** (20.5 g, 48.4%) as pale yellow prisms; mp 222—224°C. NMR ($CDCl_3$) δ: 1.69 (3H, s), 2.09 (3H, s), 3.17 (3H, s), 4.04 (2H, s), 7.2—7.6 (4H, m), 7.66 (1H, d, J=9 Hz), 8.07 (1H, d, J=3 Hz), 8.60 (1H, dd, J=9 Hz, J=3 Hz), 8.80 (1H, br s).

6-Acetamido-2-methylsulfinylmethyl-3-(*o*-tolyl)-4(3*H*)-quinazolinone (**5**)——A mixture of **12** (40 g, 0.113 mol), 35% H_2O_2 (40 ml, 0.45 mol), and AcOH (400 ml) was stirred for 1 h at room temperature. The reaction mixture was poured into H_2O (1.5 l) and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with aqueous $NaHCO_3$ and H_2O, dried ($MgSO_4$), and concentrated to dryness. Trituration of the residue with EtOH gave crude **5** (38 g, 91%); mp 215—216°C (dec.). Recrystallization of the crude product from EtOH (1.2 l) gave pure **5** (30.2 g) as colorless prisms; mp 216—217°C (dec.). NMR ($CDCl_3$–DMSO-d_6) δ: 2.13 (6H, s), 2.74 (3H, s), 3.4—4.1 (2H, m), 7.1—7.5 (4H, m), 7.61 (1H, d, J=9 Hz), 8.22 (1H, dd, J=9 Hz, J=3 Hz), 8.31 (1H, d, J=3 Hz), 9.94 (1H, br s).

6-Amino-2-methylthiomethyl-3-(*o*-tolyl)-4(3*H*)-quinazolinone (**13**)——Compound **12** (4.0 g, 0.011 mol) was added to 20% methanolic hydrogen chloride (40 ml) and the mixture was stirred overnight at room temperature. The reaction mixture was diluted with H_2O (200 ml), neutralized with $NaHCO_3$, and extracted with $CHCl_3$. The $CHCl_3$ layer was dried ($MgSO_4$) and evaporated to dryness. The residue was crystallized by trituration with Et_2O to give crude **13** (3.2 g, 90.8%); mp 135—137°C. Recrystallization from 2-propanol–diisopropyl ether gave **13** as pale yellow prisms; mp 140—142°C. NMR ($CDCl_3$) δ: 2.10 (3H, s), 2.13 (3H, s), 3.18 (1H, d, J=14 Hz), 3.46 (1H, d, J=14 Hz), 4.14 (2H, br s), 6.8—7.6 (7H, m). *Anal.* Calcd for $C_{17}H_{17}N_3OS$: C, 65.58; H, 5.50; N, 13.50; S, 10.28. Found: C, 65.79; H, 5.74; N, 13.33; S, 10.31.

6-Amino-2-methylsulfonylmethyl-3-(*o*-tolyl)-4(3*H*)-quinazolinone (**14**)——Deacetylation of **4** (2.75 g, 7 mmol) was carried out in the same manner as described for the preparation of **13**. The crude product was purified by column chromatography on silica gel (100 g) using $CHCl_3$ as a solvent to give **14** (1.7 g, 69.4%) as a syrup; NMR ($CDCl_3$) δ: 2.08 (3H, s), 3.23 (3H, s), 3.83 (2H, br s), 4.03 (2H, s), 6.7—7.6 (7H, m). An ethanolic solution (20 ml) of **14** (1.6 g) was treated with dry hydrogen chloride to give **14**•2HCl (1.5 g, 56%); mp 217—220°C (dec.). Recrystallization from EtOH gave analytically pure **14**•2HCl as colorless needles: mp 217—220°C (dec.). *Anal.* Calcd for $C_{17}H_{17}N_3O_3S$·2HCl: C, 49.05; H, 4.60; N, 10.10; Cl, 17.03; S, 7.69. Found: C, 49.36; H, 4.99; N, 9.96; Cl, 16.62; S, 7.40.

2-Methylthiomethyl-3-(*o*-tolyl)-6-trifluoroacetamido-4(3*H*)-quinazolinone (**15**)——Trifluoroacetic anhydride (3.3 g, 0.016 mol) was added to a stirred mixture of **13** (4.3 g, 0.014 mol), pyridine (1.3 g, 0.016 mol), and THF (20 ml) at room temperature. Stirring was continued for 2 h at the same temperature and the solvent was removed *in vacuo*. The residue was dissolved in $CHCl_3$, then the solution was washed with H_2O, and dried ($MgSO_4$). Evaporation of $CHCl_3$, followed by trituration with diisopropyl ether, gave **15** (5.3 g, 95%) as colorless prisms; mp 165—168°C. This sample was used in the next step without further purification. NMR ($CDCl_3$) δ: 2.10 (3H, s), 2.14 (3H, s), 3.18 (1H, d, J=14 Hz), 3.49 (1H, d, J=14 Hz), 7.2—7.5 (4H, m), 7.78 (1H, d, J=10 Hz), 8.15 (1H, d, J=3 Hz), 8.56 (1H, dd, J=10 Hz, J=3 Hz), 11.0 (1H, br s).

2-Methylsulfinylmethyl-3-(*o*-tolyl)-6-trifluoroacetamido-4(3*H*)-quinazolinone (**16**)——A mixture of **15** (5.3 g, 0.013 mol), 35% H_2O_2 (5 ml), and AcOH (30 ml) was stirred for 30 min at room temperature. The mixture was poured into H_2O (300 ml), and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O and aqueous $NaHCO_3$. After removal of the solvent, the residue was crystallized by trituration with 2-propanol–diisopropyl ether to give almost pure **16** (4.3 g, 77.3%) as pale yellow prisms; mp 168—170°C. NMR (DMSO-d_6) δ: 2.10 (3H, s), 2.67 (3H, s), 3.3—4.3 (2H, m), 7.3—7.7 (4H, m), 7.79 (1H, d, J=10 Hz), 8.18 (1H, dd, J=10 Hz, J=3 Hz), 8.57 (1H, d, J=3 Hz), 11.55 (1H, br s). *Anal.* Calcd for $C_{19}H_{16}F_3N_3O_3S$: C, 53.89; H, 3.81; N, 9.92; F, 13.46. Found: C, 53.63; H, 3.92; N, 9.85; F, 13.70.

6-Amino-2-methylsulfinylmethyl-3-(*o*-tolyl)-4(3*H*)-quinazolinone (**17**)——A mixture of **16** (4.0 g, 9.5 mmol), piperidine (1.0 g, 0.011 mol), and MeOH (80 ml) was heated with stirring at 50—60°C for 3 h. Evaporation of the solvent yielded a crystalline product (2.3 g, 74%) which was recrystallized from 2-propanol to give pure **17** as pale yellow prisms; mp 194—195°C (dec.). NMR ($CDCl_3$) δ: 2.13 (3H, s), 2.77 (3H, s), 3.73 (2H, s), 3.95 (2H, br s), 6.9—7.8 (7H, m). MS m/e: 327 (M^+). *Anal.* Calcd for $C_{17}H_{17}N_3O_2S$: C; 62.37; H, 5.24; N, 12.84; S, 9.78. Found: C, 61.95; H, 5.38; N, 12.60; S, 9.36.

***N*-Acetyl-*S*-[6-acetamido-3,4-dihydro-4-oxo-3-(*o*-tolyl)quinazolin-2-yl]methyl-L-cysteine Methyl Ester** (**18**)——*N*-Acetyl-L-cysteine (245 mg, 1.5 mmol) was added to a freshly prepared ethanolic solution of NaOEt (58 mg of Na and 10 ml of EtOH) at room temperature. A solution of **2** (325 mg, 1 mmol) in EtOH (30 ml) was added to the above mixture. The reaction mixture was stirred for 1 h at room temperature and then for an additional 1 h at 70°C. After removal of the solvent *in vacuo*, the residue was dissolved in H_2O (10 ml) and the solution was washed with AcOEt (20 ml). The aqueous layer was acidified with dil. HCl and extracted

with AcOEt. The AcOEt extract was dried ($MgSO_4$) and concentrated to dryness to give crude *N*-acetyl-*S*-[6-acetamido-3,4-dihydro-4-oxo-3-(*o*-tolyl)quinazolin-2-yl]methyl-L-cysteine (**6**, 430 mg, 92%) as a syrup. An ethereal solution of diazomethane (large excess) was added to an ice-cold solution of the crude **6** (430 mg) in EtOH (30 ml). The mixture was allowed to stand overnight at room temperature. After removal of the solvent, the oily residue was purified by flash chromatography on silica gel with C_6H_6–THF (1: 1) as a solvent to give crude **18** (384 mg, 87%). Recrystallization from EtOH–Et_2O gave a pure sample of **18**; mp 155—156°C. NMR ($CDCl_3$) δ: 1.76 (3H, s), 2.05 (3H, s), 2.11 (3H, s), 2.9—3.2 (2H, m), 3.45 (2H, t, J=5 Hz), 3.68 (3H, s), 4.7—5.1 (1H, m), 7.10 (1H, br), 7.2—7.45 (4H, m), 7.69 (1H, d, J=8 Hz), 8.05 (1H, d, J=3 Hz), 8.50 (1H, dd, J=8 Hz, J=3 Hz), 8.85 (1H, s). MS *m/e*: 482 (M^+).

2-Fluoromethyl-3-(*o*-hydroxymethylphenyl)-6-nitro-4(3*H*)-quinazolinone (**21**)——*N*,*N*′-Dicyclohexylcarbodiimide (62 g, 0.3 mol) was added portionwise with good stirring at 10—15°C to a solution of 2-fluoroacetamido-5-nitrobenzoic acid (**19**, 47.5 g, 0.2 mol), 2-aminobenzyl alcohol (**20**, 24.6 g, 0.2 mol), and 1-hydroxybenzotriazole (40 g, 0.3 mol) in THF (1.0 l). Stirring was continued for 3 h at room temperature. The precipitate which had formed was collected by filtration and the filtrate was concentrated to dryness *in vacuo*. The residue was crystallized by trituration with C_6H_6–THF (7: 3). The crystals were collected and washed with aqueous $NaHCO_3$ and 2-propanol to afford 16.5 g (25.2%) of crude **21**; mp 157—165°C. Recrystallization from EtOH gave a pure sample of **21** (14.1 g) as pale yellow prisms; mp 178—180°C. NMR (DMSO-d_6) δ: 4.32 (2H, s), 5.08 (2H, d, J=46 Hz), 4.5—5.2 (1H, br s), 7.3—7.8 (4H, m), 8.10 (1H, d, J=10 Hz), 8.64 (1H, dd, J=10 Hz, J=3 Hz), 8.85 (1H, d, J=3 Hz). *Anal.* Calcd for $C_{16}H_{12}FN_3O_4$: C, 58.36; H, 3.67; N, 12.76; F, 5.77. Found: C, 58.28; H, 3.71; N, 12.76; F, 5.80.

6-Amino-2-fluoromethyl-3-(*o*-hydroxymethylphenyl)-4(3*H*)-quinazolinone (**22**)——A solution of $SnCl_2 \cdot 2H_2O$ (80 g, 0.35 mol) in conc. HCl (72 ml) was added to a stirred suspension of **21** (29 g, 0.088 mol) in MeOH (450 ml) at 0—5°C over a period of 15 min. The mixture was stirred at room temperature for 3 h and then poured into H_2O (2.0 l). This solution was neutralized with $NaHCO_3$. The resultant precipitate was collected by filtration and extracted twice with a mixture (1.0 l) of $CHCl_3$ and MeOH (1: 1). The combined extracts were concentrated to dryness *in vacuo*. The residue was triturated with $CHCl_3$–H_2O. The crystals were collected by filtration, dried, and dissolved in 1.5 l of $CHCl_3$–MeOH (1: 1). The solution was treated with charcoal (5 g) and concentrated to dryness *in vacuo*. The residue was triturated with 2-propanol to give almost pure **22** (17 g, 64%); mp 169—172°C. Recrystallization from THF gave pure **22**; mp 170—172°C (lit., mp 170—172°C).[1b]

6-Acetamido-2-fluoromethyl-3-(*o*-hydroxymethylphenyl)-4(3*H*)-quinazolinone (**7**)——Acetyl chloride (1.3 g, 0.023 mol) was added to a stirred suspension of **22** (6.0 g, 0.02 mol) in THF (200 ml) at room temperature and stirring was continued for 3 h. The solvent was removed *in vacuo*. The residue was triturated with aqueous $NaHCO_3$ to give crude **7** (6.3 g, 92%); mp 241—245°C. Recrystallization from DMF–EtOH (1: 1) gave pure **7** as colorless prisms; mp 245—247°C. NMR (DMSO-d_6) δ: 2.12 (3H, s), 4.38 (2H, s), 4.98 (2H, d, J=46 Hz), 5.20 (1H, br s), 7.3—7.6 (4H, m), 7.71 (1H, d, J=9 Hz), 8.03 (1H, dd, J=9 Hz, J=3 Hz), 8.45 (1H, d, J=3 Hz), 10.31 (1H, s).

2-Fluoromethyl-6-hydroxyacetamido-3-(*o*-hydroxymethylphenyl)-4(3*H*)-quinazolinone (**8**)——Acetoxyacetyl chloride (9.6 g, 0.07 mol) was added dropwise to a stirred suspension of **22** (17.5 g, 0.0585 mol) in THF (600 ml) at room temperature. The reaction mixture was stirred for 4 h at the same temperature and then concentrated *in vacuo*. The residue was triturated with aqueous $NaHCO_3$ to afford a crystalline product. The wet product was treated with a boiling mixture of MeOH (200 ml) and 5% aqueous $NaHCO_3$ (20 ml). The mixture first became clear and soon new crystals precipitated out. After the solution had cooled, the crystals were collected by filtration to yield crude **8** (16.7 g, 80%); mp 226—229°C. Recrystallization from DMF–EtOH (1: 2) gave pure **8** (14.6 g, 70%) as colorless prisms; mp 241—243°C. NMR ($CDCl_3$–DMSO-d_6) δ: 4.06 (2H, d, J=6 Hz), 4.27 (2H, d, J=6 Hz), 4.99 (2H, d, J=45 Hz), 5.17 (1H, t, J=6 Hz), 5.64 (1H, t, J=6 Hz), 7.3—7.7 (4H, m), 7.78 (1H, d, J=9 Hz), 8.16 (1H, dd, J=9 Hz, J=3 Hz), 8.61 (1H, d, J=3 Hz), 10.06 (1H, s). MS *m/e*: 357 (M^+).

6-Acetamido-2-hydroxymethyl-3-(*o*-tolyl)-4(3*H*)-quinazolinone (**9**)——A mixture of **24** (5.8 g, 0.015 mol), $AgBF_4 \cdot H_2O$ (3.85 g) DMSO (20 ml), and H_2O (0.18 ml) was stirred for 3 h at room temperature. The precipitate which had formed was removed by filtration and the filtrate was concentrated to cryness *in vacuo*. The residue was dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with aqueous $NaHCO_3$ and dried ($MgSO_4$). After removal of the solvent by evaporation, the residue was triturated with 2-propanol to give crude **9** (3.6 g, 70%); mp 217—220°C. Recrystallization from 2-propanol gave an analytically pure sample of **9**; mp 223—224°C. NMR ($CDCl_3$–DMSO-d_6) δ: 2.09 (6H, s), 3.6—4.6 (3H, m),[7] 7.0—7.5 (4H, m), 7.66 (1H, d, J=9 Hz), 8.2—8.5 (2H, m), 9.65 (1H, br s).

6-Acetamido-2-methyl-3-(*o*-tolyl)-4(3*H*)-quinazolinone 1-Oxide (**25**)——A mixture of 6-acetamido-2-methyl-3-(*o*-tolyl)-4(3*H*)-quinazolinone (**23**, 3.0 g, 0.01 mol),[8] 35% H_2O_2 (1 ml), and AcOH (15 ml) was heated at 50—60°C for 10 h. The reaction mixture was poured into H_2O (100 ml) and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with aqueous $NaHCO_3$ and H_2O, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed on a silica gel column (150 g). The starting material **23** (700 mg) was recovered from the fraction eluted with $CHCl_3$–MeOH (95: 5). From the fraction eluted with $CHCl_3$–MeOH–AcOH (95: 5: 5), a crude crystalline product (400 mg, 12.7%) was obtained. Recrystallization from EtOH (20 ml)

gave analytically pure **25** as colorless prisms; mp 248—250°C. NMR (DMSO-d_6) δ: 2.13 (6H, s), 2.28 (3H, s), 7.47 (4H, s), 8.11 (1H, dd, $J=9$ Hz, $J=3$ Hz), 8.39 (1H, d, $J=9$ Hz), 8.53 (1H, d, $J=3$ Hz), 10.50 (1H, br s). MS *m/e*: 323 (M^+). *Anal.* Calcd for $C_{18}H_{17}N_3O_3$: C, 66.86; H, 5.30; N, 13.00. Found: C, 66.60; H, 5.43; N, 12.92.

2-Fluoromethyl-6-hydroxyamino-3-(*o*-tolyl)-4(3*H*)-quinazolinone (28)——A mixture of 80% $NH_2NH_2 \cdot H_2O$ (0.8 g), THF (10 ml), and EtOH (10 ml) was added dropwise to a stirred mixture of **27** (6.5 g, 0.021 mol), 5% Pd-C (0.4 g), THF (50 ml), and EtOH (50 ml) at 45—55°C over a period of 30 min. The mixture was stirred for 1.5 h at the same temperature. After removal of Pd-C by filtration, the solvent was evaporated off *in vacuo*. The residue was triturated with $CHCl_3$ to give almost pure **28** (1.5 g, 25%) as a colorless powder; mp >260°C. NMR (DMSO-d_6)δ: 2.04 (3H, s), 4.95 (2H, d, $J=47$ Hz), 7.1—7.9 (7H, m), 8.70 (1H, s), 8.85 (1H, br s). MS *m/e*: 299 (M^+). *Anal.* Calcd for $C_{16}H_{14}FN_3O_2$: C, 64.20; H, 4.72; N, 14.04; F, 6.35. Found: C, 63.99; H, 4.65; N, 14.28; F, 6.30.

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