# 2-Substituted 2,3-Dihydro-5*H*-thiazolo[2,3-*b*]quinazoline Derivatives



Vassil St. Georgiev*, Grace A. Bennett, Lesley A. Radov,
Dietgard K. Kamp, and Laura A. Trusso

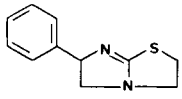
Departments of Organic Chemistry and Pharmacology, Pennwalt Corporation, Pharmaceutical Division,
Rochester, New York 14623, U. S. A.

Received March 31, 1986

The synthesis of a series of 2-substituted 2,3-dihydro-5*H*-thiazolo[2,3-*b*]quinazoline derivatives is described. Some of the title compounds exerted antiinflammatory and immunomodulating activities in laboratory animal models.

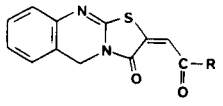
*J. Heterocyclic Chem.*, **23**, 1359 (1986).

Over the years the immunomodulating activity of levamisole (**1**) has been well documented [1]. Structurally, levamisole represents an imidazo[2,1-*b*]thiazole system substituted at C-6 with a phenyl group.



1

Recognizing that fact, we have prepared a number of structurally related 2-substituted 2,3-dihydro-5*H*-thiazolo-[2,3-*b*]quinazoline derivatives depicted by structure **2**.



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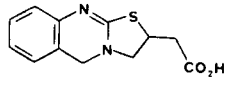
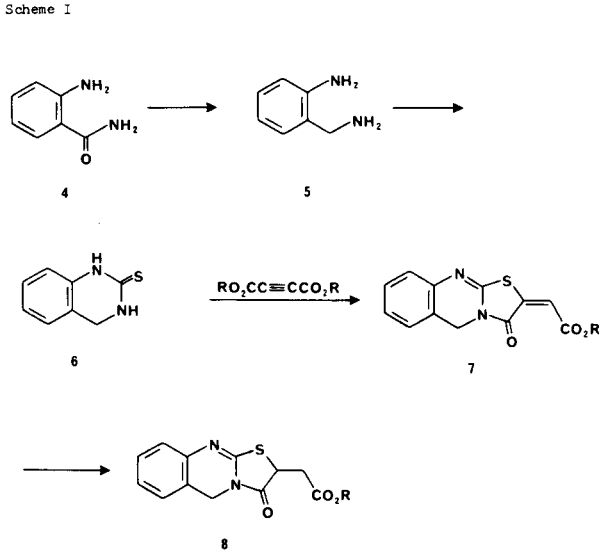


3

As one can see from structures **1** and **2**, while the three heteroatoms in compounds **2** are arranged similarly to those of levamisole (**1**), the phenyl ring in the molecule of derivatives **2** is fused to the heterocyclic moiety providing a rigid tricyclic system. Furthermore, the ketone group and the exomethylene double bond of compounds **2** may be reduced simultaneously, or in a selective manner to furnish the corresponding saturated analogs **3**. The carboxylic group of the side chain of derivatives **2** may also undergo chemical modifications [2].

The synthesis of compounds **2** was short and straightforward. Thus, reduction of 2-aminobenzamide (**4**) with lithium aluminum hydride gave 2-aminobenzylamine (**5**) [3]. The latter was treated with thiophosgene to yield the 3,4-dihydro-2(1*H*)-quinazolinethione (**6**) [3]. Condensation of derivative **6** with an appropriate dialkyl acetylenedicarboxylate provided the corresponding (3-oxo-2*H*,5*H*-thiazolo[2,3-*b*]quinazolin-2-ylidene)acetic acid alkyl ester **7**. Reduction of the exomethylene double bond of compound **7** with sodium tellurium hydride afforded the dihydro analog **8** (Scheme I).

Scheme I



Reaction of (3-oxo-2*H*,5*H*-thiazolo[2,3-*b*]quinazolin-2-ylidene)acetic acid (**7a**) with phenol in the presence of *N*,*N*-bis(2-oxo-3-oxazolidinyl)phosphorodiamidic chloride gave rise to the (3-oxo-2*H*,5*H*-thiazolo[2,3-*b*]quinazolin-2-ylidene)acetic acid phenyl ester (**7d**). Alternatively, treatment of compound **7a** with benzylamine in the presence of diethylphosphoryl cyanide, yielded the *N*-benzyl-(3-oxo-2*H*,5*H*-thiazolo[2,3-*b*]quinazolin-2-ylidene)acetamide (**9a**) (Scheme II).

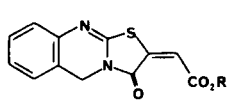
The *N*-*t*-butyl-*N*-benzyl-(3-oxo-2*H*,5*H*-thiazolo[2,3-*b*]-quinazolin-2-ylidene)acetamide (**9e**) was obtained following the treatment of (3-oxo-2*H*,5*H*-thiazolo[2,3-*b*]quinazolin-2-ylidene)acetic acid (**7a**) with *N*-(*t*-butyl)benzylamine in the presence of *N*,*N*-bis(2-oxo-3-oxazolidinyl)phosphorodiamidic chloride (Scheme II).

All compounds that were prepared during the present study are listed in Table I.

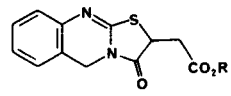
When tested for biological activity, a number of the title 2-substituted 2,3-dihydro-5*H*-thiazolo[2,3-*b*]quinazoline derivatives demonstrated anti-inflammatory activity in the

Table I

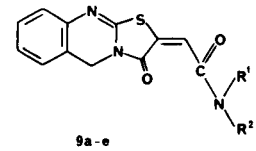
(3-Oxo-2*H*,5*H*-thiazolo[2,3-*b*]quinazolin-2-ylidene)acetic Acid and Its Esters **7a-d**, 2,3-Dihydro-3-oxo-5*H*-thiazolo[2,3-*b*]quinazolin-2-acetic Acid Esters **8a,b**, and (3-Oxo-2*H*,5*H*-thiazolo[2,3-*b*]quinazolin-2-ylidine)acetamides **9a-e**



**7a-d**



**8a,b**



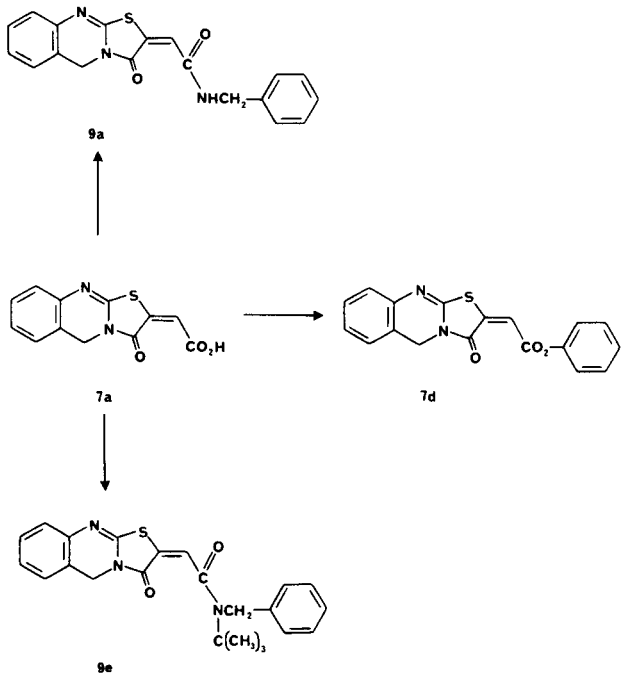
**9a-e**

| Compound | R |
|---|---|
| **7a** | H |
| **7b** | $CH_3$ |
| **7c** | $C_2H_5$ |
| **7d** | $C_6H_5$ |

| Compound | R |
|---|---|
| **8a** | $CH_3$ |
| **8b** | $C_2H_5$ |

| Compound | $R^1$ | $R^2$ |
|---|---|---|
| **9a** | H | $CH_2C_6H_5$ |
| **9b** | H | cyclohexyl |
| **9c** | H | $CH_2CH=CH_2$ |
| **9d** | H | 1-adamantanemethyl |
| **9e** | $C(CH_3)_3$ | $CH_2C_6H_5$ |

Scheme II




carrageenin-induced rat paw edema assay. In addition, some compounds were also found to display immunomodulating activity in the Kennedy plaque test. Thus, derivatives **8a** and **9a** markedly suppressed the humoral immunocompetence at doses of 1.56, 6.25 and 25.0 mg/kg. Derivative **9d** showed immunosuppressive activity only at the highest dose level (25.0 mg/kg), whereas analog **9e** demonstrated a significant immunopotentiation at a dose of 1.56 mg/kg and a significant immunosuppression at the

Table II

Immunomodulating Activity [a] of Compounds **7-9** on the IgM Production in Female C3H Mice Sensitized with Sheep Erythrocytes

| Compound | Route of Administration [b] | Daily Dose (mg/kg) 1.56 | 3.125 | 6.25 | 12.5 | 25.0 |
|---|---|---|---|---|---|---|
| **7c** [c] | oral | | 125 | 104 | 89 | 81 |
| **8a** [d] | ip | 62 [e] | | 75 [e] | | 88 [e] |
| **9a** [f] | ip | 54 [e] | | 58 [e] | | 65 [e] |
| **9c** [d] | ip | 84 | | 87 | | 79 |
| **9d** [f] | ip | 109 | | 97 | | 53 [e] |
| **9e** [f] | ip | 151 [g] | | 112 | | 78 |

[a] Expressed as a percentage of control response. [b] Drug administered for 3 consecutive days starting 24 hours postsensitization *via* intraperitoneal (ip) or oral routes. [c] Control response value = 71.1 plaques/$10^5$ spleen cells; 6-mercaptopurine (6-MP) response value = 27.4 plaques/$10^5$ spleen cells [h]. [d] Control response value = 70.7 plaques/$10^5$ spleen cells; 6-MP response value = 29.4 plaques/$10^5$ spleen cells [h]. [e] Statistically significant decrease when compared to control values ($p < 0.05$ using analysis of variance). [f] Control response value = 70.7 plaques/$10^5$ spleen cells; 6-MP response value = 29.4 plaques/$10^5$ spleen cells [h]. [g] Statistically significant increase when compared to control values ($p < 0.05$ using analysis of variance). [h] 6-MP was administered ip.

25.0 mg/kg dose level. While no statistically significant immunomodulating activity (based on several experiments) was evident following treatment with analogs **7c** and **9c**, a tendency toward immunosuppression was observed with both compounds at a dose of 25.0 mg/kg (Table II). From the experimental data presented in Table II it becomes evident that changing the 6-phenylimidazo[2,1-*b*]thiazole ring system of levamisole to the rigid tricyclic 2-substituted 2,3-dihydro-5*H*-thiazolo[2,3-*b*]quinazoline system led, in general, to a change in the nature of the immunomodulating activity - from immunopotentiating (in the case of levamisole) to the predominantly immunosuppressive

activity of compounds **7-9** [4]. As seen from Table II, the majority of compounds **7-9** when tested in the Kennedy plaque assay exerted immunosuppressive activity equipotent to that of the standard drug 6-mercaptopurine [5].

## EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The ir spectra were obtained on a Nicolet MX-1 FT spectrometer as potassium bromide discs. The $^1$H nmr spectra were obtained on a Varian EM-360A (60 MHz) spectrometer using tetramethylsilane as an internal standard. All spectra were consistent with the assigned structures.

2-Aminobenzylamine (**5**).

To a stirring suspension of 4.56 g (0.12 mole) of lithium aluminum hydride in 30 ml of anhydrous tetrahydrofuran were added dropwise 4.0 g (0.03 mole) of 2-aminobenzamide (**4**) dissolved in 15 ml of anhydrous tetrahydrofuran. The reaction mixture was refluxed for 26 hours. After completion, the excess lithium aluminum hydride was decomposed by dropwise addition of aqueous sodium hydroxide. An additional 15 ml of tetrahydrofuran were added in order to aid in the dispersion of the aluminum salts. The suspension was filtered using suction. The residual solid was stirred in 120 ml of hot chloroform and filtered. The filtrate was evaporated under reduced pressure, and the resulting 2-aminobenzylamine (**5**) as a brown oil solidified while drying at 25° under high vacuum, mp 59-59.5°. Compound **5** was used in the next step without further purification.

3,4-Dihydro-2(1*H*)-quinazolinethione (**6**).

A solution of 6.35 g (0.052 mole) of 2-aminobenzylamine (**5**) and 12.24 g (0.12 mole) of triethylamine in 150 ml of anhydrous ether was cooled to −78° (acetone-dry ice). To this mixture was added dropwise over a period of 1 hour, a solution of 7.2 g (0.06 mole) of thiophosgene in 40 ml of anhydrous ether, while maintaining the temperature at −78°. After allowing the heterogeneous reaction mixture to warm up to room temperature, it was filtered using suction. The filter cake was suspended in 100 ml of anhydrous ether, then filtered and washed on the filter with 50 ml of anhydrous ether. The solid residue was dissolved in 150 ml of methanol and 6.72 g (0.12 mole) of potassium hydroxide were added and stirred into the solution. The potassium chloride that precipitated was filtered off and the filtrate was evaporated to dryness under reduced pressure. The resulting compound **6** was recrystallized from aqueous ethanol, mp 210-212°. It was used in the next step without further purification.

Both derivatives **5** and **6** were prepared according to the procedures of Grosso *et al.* [3].

(3-Oxo-2*H*,5*H*-thiazolo[2,3-*b*]quinazolin-2-ylidene)acetic Acid Methyl Ester (**7b**).

A solution of 3.34 g (0.02 mole) 3,4-dihydro-2(1*H*)-quinazolinethione (**6**) and 3.55 g (0.025 mole) dimethyl acetylenedicarboxylate in 150 ml of toluene was refluxed for 2 hours. After cooling, the reaction mixture was filtered and the resulting solid was recrystallized from ethyl acetate to yield 1.32 g of the title compound as fine yellow crystals, mp 252-253°; ir (potassium bromide): 1572 and 1485 cm$^{-1}$ (C=C), 765 cm$^{-1}$ (=CH, aromatic 1,2-substitution), 1713 and 1693 cm$^{-1}$ (ester C=O), 1591 cm$^{-1}$ (phenyl), 1205 and 1186 cm$^{-1}$ (C-O-C), 1713 cm$^{-1}$ (thiazole ring carbonyl), 1610 cm$^{-1}$ (C=N); nmr (deuteriochloroform): ppm 3.88 (s, $OCH_3$, 3H), 4.99 (s, quinazoline $CH_2$, 2H), 6.98 (s, C=CH, 1H), 7.10-7.32 (cm, aromatic, 4H).

*Anal.* Calcd. for $C_{13}H_{10}N_2O_3S$: C, 56.93; H, 3.67; N, 10.21; S, 11.69. Found: C, 56.95; H, 3.74; N, 10.14; S, 11.69.

(3-Oxo-2*H*,5*H*-thiazolo[2,3-*b*]quinazolin-2-ylidene)acetic Acid Ethyl Ester (**7c**).

Derivative **7c** was prepared by a procedure similar to that described for compound **7b**, mp 222-224° (ethyl acetate); ir (potassium bromide): 1573 and 1490 cm$^{-1}$ (C=C), 3080 cm$^{-1}$ (=CH), 770 cm$^{-1}$ (=CH, aromatic 1,2-substitution), 1595 cm$^{-1}$ (phenyl), 1714 cm$^{-1}$ (ester C=O), 1191 cm$^{-1}$ (C-O-C), 1696 cm$^{-1}$ (thiazole ring carbonyl), 1620 cm$^{-1}$ (C=N); nmr (deuteriochloroform-dimethyl sulfoxide-$d_6$): ppm 1.32-1.39 (t, $CH_3$, 3H), 4.30-4.37 (cm, $CH_2$, 2H), 4.99 (s, quinazoline $CH_2$, 2H), 6.95 (s, exomethylene CH, 1H), 7.11-7.35 (cm, aromatic, 4H).

*Anal.* Calcd. for $C_{14}H_{12}N_2O_3S$: C, 58.32; H, 4.19; N, 9.72; S, 11.12. Found: C, 58.36; H, 4.29; N, 9.70; S, 11.20.

(3-Oxo-2*H*,5*H*-thiazolo[2,3-*b*]quinazolin-2-ylidene)acetic Acid (**7a**).

Derivative **7a** was prepared by a procedure similar to that described for compound **7b**, mp 263-264° (2-propanol); ir (potassium bromide): 1575 and 1495 cm$^{-1}$ (C=C), 3065 cm$^{-1}$ (=CH), 775 cm$^{-1}$ (=CH, aromatic 1,2-substitution), 3500 cm$^{-1}$ (OH), 1747 cm$^{-1}$ (carboxyl), 1635 cm$^{-1}$ (thiazole ring carbonyl), 1604 cm$^{-1}$ (C=N); nmr (deuteriochloroform-dimethyl sulfoxide-$d_6$): ppm 4.94 (s, quinazoline $CH_2$, 2H), 5.00-6.50 (bs, OH, 1H labile), 6.84 (s, =CH, 1H), 7.00-7.29 (cm, aromatic, 4H).

*Anal.* Calcd. for $C_{12}H_8N_2O_3S$: C, 55.38; H, 3.10; N, 10.76; S, 12.32. Found: C, 55.21; H, 3.36; N, 10.64; S, 12.56.

2,3-Dihydro-3-oxo-5*H*-thiazolo[2,3-*b*]quinazolin-2-acetic Acid Methyl Ester (**8a**).

A suspension of sodium borohydride (3.03 g, 0.08 mole) and 4.38 g (0.034 mole) of tellurium powder in 135 ml of anhydrous ethanol was heated under nitrogen atmosphere for 15 minutes. After cooling to −20°, 8.08 ml of glacial acetic acid in 33.65 ml of anhydrous ethanol were added dropwise and the reaction mixture was stirred at that temperature for 5 minutes, followed by the addition of 3.50 g (0.013 mole) of (3-oxo-2*H*,5*H*-thiazolo[2,3-*b*]quinazolin-2-ylidene)acetic acid methyl ester in 13.5 ml of anhydrous ethanol. The reaction mixture was allowed to warm to ambient temperature and then was stirred overnight. Following filtration through celite the solvent was evaporated under reduced pressure. The residue was taken up in water and extracted with chloroform. The organic extract was dried over anhydrous magnesium sulfate and evaporated under reduced pressure yielding 1.16 g of the 2,3-dihydro analog **8a**, mp 143-144° (ethyl acetate); ir (potassium bromide): 1592 and 1574 cm$^{-1}$ (C=C), 768 cm$^{-1}$ (=CH, aromatic 1,2-substitution), 1727 cm$^{-1}$ (ester C=O), 1640 cm$^{-1}$ (thiazole ring carbonyl), 1618 cm$^{-1}$ (C=N); nmr (deuteriochloroform): ppm (s, quinazoline $CH_2$, 2H), 3.70 (s, $OCH_3$, 3H), 4.40-4.50 (cm, S-CH, 1H), 4.35 (d, $CH_2$-$CO_2Me$, 2H), 7.00-7.35 (cm, aromatic, 4H).

*Anal.* Calcd. for $C_{13}H_{12}N_2O_3S$: C, 56.51; H, 4.38; N, 10.14; S, 11.60. Found: C, 56.61; H, 4.43; N, 10.17; S, 11.50.

2,3-Dihydro-3-oxo-5*H*-thiazolo[2,3-*b*]quinazolin-2-acetic Acid Ethyl Ester (**8b**).

Derivative **8b** was prepared by a procedure similar to that described for compound **8a**, mp 139-142° (ether); ir (potassium bromide): 1572 and 1489 cm$^{-1}$ (C=C), 774 cm$^{-1}$ (=CH, aromatic 1,2-substitution), 1187 cm$^{-1}$ (C-O-C), 1721 cm$^{-1}$ (ester C=O), 1720 cm$^{-1}$ (thiazole ring carbonyl), 1613 cm$^{-1}$ (C=N); nmr (deuteriochloroform): ppm 4.85 (s, quinazoline $CH_2$, 2H), 4.31-4.50 (cm, S-CH, 1H), 4.15-4.30 (q, $CH_2Me$, 2H), 2.90-3.35 (cm, $CH_2CO_2Et$, 2H), 1.75-1.85 (t, $CH_2CH_3$, 3H), 7.00-7.35 (cm, aromatic, 4H).

*Anal.* Calcd. for $C_{14}H_{14}N_2O_3S$: C, 57.92; H, 4.86; N, 9.65; S, 11.04. Found: C, 57.73; H, 4.96; N, 9.58; S, 10.80.

*N*-Benzyl-(3-oxo-2*H*,5*H*-thiazolo[2,3-*b*]quinazolin-2-ylidene)acetamide (**9a**).

To a stirred mixture of (3-oxo-2*H*,5*H*-thiazolo[2,3-*b*]quinazolin-2-ylidene)acetic acid (**7a**) (10.5 g, 1.9 mmoles) and benzylamine (0.23 g, 2.1 mmoles) in 25 ml of *N*,*N*-dimethylformamide, at 0°, was added diethylphosphoryl cyanide (0.28 g, 2.1 mmoles) (in *N*,*N*-dimethylformamide solution), followed by triethylamine (0.41 g, 4.0 mmoles). The reaction

mixture was stirred for 4 hours at 0° and at room temperature overnight. Then, the mixture was diluted with benzene-ethyl acetate and washed sequentially with 5% hydrochloric acid, water, saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride. The organic solution was dried over anhydrous magnesium sulfate and evaporated to dryness under reduced pressure to give compound **9a** (10.09 g), mp 258-259° (ethyl acetate); ir (potassium bromide): 1593 and 1572 $cm^{-1}$ (C=C), 772 and 760 $cm^{-1}$ (=CH, aromatic), 3558 $cm^{-1}$ (NH), 1693 $cm^{-1}$ (quinazoline ring carbonyl), 1655, 1542 and 1221 $cm^{-1}$ (amide), 1617 $cm^{-1}$ (aromatic); nmr (dimethyl sulfoxide-$d_6$): ppm 4.42 (d, N-$CH_2$-Ph, 2H), 4.92 (s, quinazoline $CH_2$, 2H), 7.10 (s, =CHC=O, 1H), 7.13 (cm, aromatic, 9H), 9.23 (t, NH, 1H).

*Anal.* Calcd. for $C_{19}H_{15}N_3O_2S$: C, 65.31; H, 4.33; N, 12.03; S, 9.18. Found: C, 64.94; H, 4.48; N, 11.85; S, 9.15.

*N*-Cyclohexyl-(3-oxo-2*H*,5*H*-thiazolo[2,3-*b*]quinazolin-2-ylidene)acetamide (**9b**).

Derivative **9b** was prepared by a procedure similar to that described for compound **9a**, mp 287-288° (anhydrous ethanol); ir (potassium bromide): 3058, 3040, 1594, 1574, 1532 and 760 $cm^{-1}$ (phenyl ring and ring substitution pattern), 1710 $cm^{-1}$ (thiazole ring carbonyl), 1652, 1396 and 1222 $cm^{-1}$ (amide); nmr (dimethyl sulfoxide-$d_6$): ppm 1.00-2.00 (cm, 5 x $CH_2$, cyclohexyl, 10H), 3.70 (bm, N-CH, 1H), 4.92 (s, quinazoline $CH_2$, 2H), 7.05 (s, =CHC=O, 1H), 7.13-7.28 (cm, aromatic, 4H), 8.63 (d, NH, 1H).

*Anal.* Calcd. for $C_{18}H_{19}N_3O_2S$: C, 63.32; H, 5.61; N, 12.31; S, 9.39. Found: C, 63.16; H, 5.59; N, 12.25; S, 9.48.

*N*-Allyl-(3-oxo-2*H*,5*H*-thiazolo[2,3-*b*]quinazolin-2-ylidene)acetamide (**9c**).

Derivative **9c** was prepared by a procedure similar to that described for compound **9a**, mp 275-276° (anhydrous ethanol); ir (potassium bromide): 3058, 1592, 1571 and 750 $cm^{-1}$ (phenyl ring and ring substitution pattern), 1704 $cm^{-1}$ (thiazole ring carbonyl), 3361 $cm^{-1}$ (NH), 1658, 1535 and 1226 $cm^{-1}$ (amide), 1617 $cm^{-1}$ (C=N); nmr (deuteriochloroform-dimethyl sulfoxide-$d_6$): ppm 3.87 (t, $CH_2$-CH, 2H), 4.94 (s, quinazoline $CH_2$, 2H), 5.15 (dd, d, $=CH_2$, 2H), 5.78-5.90 (cm, =CH, 1H), 7.12-7.25 (cm, aromatic, 4H), 8.81 (t, NH, 1H).

*Anal.* Calcd. $C_{15}H_{13}N_3O_2S$: C, 60.19; H, 4.38; N, 14.04; S, 10.71. Found: C, 59.93; H, 4.45; N, 13.94; S, 10.50.

*N*-(1-Adamantanemethyl)-(3-oxo-2*H*,5*H*-thiazolo[2,3-*b*]quinazolin-2-ylidene)acetamide (**9d**).

Derivative **9d** was prepared by a procedure similar to that described for compound **9a**, mp 294-295° (chloroform); ir (potassium bromide): 3065, 3058, 3020, 1592, 1573, 1545 and 758 $cm^{-1}$ (phenyl ring and ring substitution pattern), 3383 $cm^{-1}$ (NH), 1704, 1667, 1545 and 1219 $cm^{-1}$ (amide), 1614 $cm^{-1}$ (C=N); nmr (dimethyl sulfoxide-$d_6$): ppm 1.40-2.00 (three bs, 6 x $CH_2$, 3 x CH, adamantane, 15H), 2.94 (bs, N-$CH_2$, 2H), 4.95 (bs, quinazoline $CH_2$, 2H), 7.21 (bm, aromatic and =CHC=O, 5H), 8.30 and 8.50 (two bm, NH, 1H).

*Anal.* Calcd. $C_{23}H_{25}N_3O_2S$: C, 67.79; H, 6.18; N, 10.31; S, 7.87. Found: C, 67.16; H, 6.13; N, 10.21; S, 7.81.

*N*-*t*-Butyl-*N*-benzyl-(3-oxo-2*H*,5*H*-thiazolo[2,3-*b*]quinazolin-2-ylidene)-acetamide (**9e**).

A solution of (3-oxo-2*H*,5*H*-thiazolo[2,3-*b*]quinazolin-2-ylidene)acetic acid (**7a**) (1.3 g, 5 mmoles), triethylamine (1.5 ml, 0.01 mole) and *N*-(*t*-butyl)benzylamine (0.93 ml, 5 mmoles) in 10 ml of methylene chloride was cooled to 10°. Then, 1.27 g (5 mmoles) of *N,N*-bis(2-oxo-3-oxazolidinyl)phosphorodiamidic chloride was added and the reaction mixture was stirred at room temperature for 20 hours. Following acidification with diluted hydrochloric acid, the reaction mixture was filtered and the organic layer was washed with water, then dried over anhydrous magnesium sulfate, and evaporated to dryness under reduced pressure leaving an orange-yellow solid residue which was recrystallized from anhydrous ethanol (0.71 g), mp 195-197°; ir (potassium bromide): 3070, 3038, 1595, 1574 and 710 $cm^{-1}$ (phenyl ring and ring substitution pattern), 1712 and 1633 $cm^{-1}$ (amide), 1616 $cm^{-1}$ (C=N); nmr (dimethyl sulfoxide-$d_6$): ppm 1.42 (s, *t*-butyl, 9H), 4.84 and 4.87 (two s, quinazoline $CH_2$, $CH_2$-Ph, 4H), 7.04 (s, =CHC=O, 1H), 7.15-7.45 (cm, aromatic, 9H).

*Anal.* Calcd. for $C_{25}H_{23}N_3O_2S$: C, 68.12; H, 5.72; N, 10.36; S, 7.91. Found: C, 67.85; H, 5.79; N, 10.34; S, 8.04.

(3-Oxo-2*H*,5*H*-thiazolo[2,3-*b*]quinazolin-2-ylidene)acetic Acid Phenyl Ester (**7d**).

A solution of 1.30 g (5 mmoles) of (3-oxo-2*H*,5*H*-thiazolo[2,3-*b*]quinazolin-2-ylidene)acetic acid (**7a**), 1.27 g (5 mmoles) of *N,N*-bis(2-oxo-3-oxazolidinyl)phosphorodiamidic chloride, 0.49 g (5.2 mmoles) of phenol and 1.01 g (10 mmoles) of triethylamine, in 10 ml of methylene chloride was stirred at room temperature under nitrogen atmosphere for 18 hours. Then, 10 ml of saturated aqueous sodium bicarbonate were added in order to make the reaction medium slightly basic. A precipitate was formed and then filtered off leaving a filtrate that was dried over anhydrous magnesium carbonate and evaporated under reduced pressure. The residual orange-yellow solid was recrystallized from anhydrous ethanol (0.62 g), mp 194-195°; ir (potassium bromide): 3085, 3065, 1593, 1570, 1490, 1485, 771 and 690 $cm^{-1}$ (phenyl ring and ring substitution pattern), 1723 $cm^{-1}$ (ester C=O), 1197, 1172 and 1160 $cm^{-1}$ (C-O-C), 1703 $cm^{-1}$ (thiazole ring carbonyl), 1612 $cm^{-1}$ (C=N); nmr (deuteriochloroform-dimethyl sulfoxide-$d_6$): ppm 4.99 (s, quinazoline $CH_2$, 2H), 7.00-7.50 (cm, aromatic, 9H).

*Anal.* Calcd. for $C_{18}H_{12}N_2O_3S$: C, 64.27; H, 3.60; N, 8.33; S, 9.53. Found: C, 64.48; H, 3.64; N, 8.38; S, 9.96.

## REFERENCES AND NOTES

[1] H. Schneiden, *Int. J. Immunopharmacol.*, **3**, 9 (1981).

[2] In an independent study, Liu *et al. Arch. Pharm., Weinheim,* **316**, 569 (1983) reported the preparation of a number of 2,3-dihydro-5*H*-thiazolo[2,3-*b*]quinazoline derivatives that included some of the compounds **2** also prepared by us.

[3] J. A. Grosso, D. E. Nichols, M. B. Nichols and G. K. W. Yim, *J. Med. Chem.*, **23**, 1261 (1980).

[4] This report represents Part 7 of the series "Drug-Induced Modifications of the Immune Response".

[5] H. Froberg and M. S. Schencking, *Arch. Toxicol.*, **32**, 1 (1974).