Cyclocondensation of 3-Amino-2-iminonaphtho[1,2-*d*]-thiazole with α-Ketocarboxylic Acid Derivatives: Synthesis of 2-Substituted 3-Oxo-3*H*-naphtho[1′,2′:4,5]thiazolo-[3,2-*b*][1,2,4]triazines as Potential Anti-HIV Agents [1]

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The cyclocondensation of 3-amino-2-iminonaphtho[1,2-*d*]thiazole (**1**) with a series of α-keto mono- and dicarboxylic acid derivatives **5a-i** under different conditions was investigated. When the experiments were performed by refluxing in glacial acetic acid, the corresponding cyclized products, 2-substituted 3-oxo-3*H*-naphtho[1′,2′:4,5]thiazolo[3,2-*b*][1,2,4]triazines **4** were obtained in fair to good yields. On the other hand, when the reaction was conducted in boiling ethanol, it gave only the open chain condensates **6**, or in rare cases, together with minor amount of **4**. Since the intermediates **6** exist as mixture of both *E*- and *Z*-isomers, cyclization through heating was found insufficient. In any event representative compounds **4b,g,i** have been evaluated for anti-HIV activity, but none of them were active.

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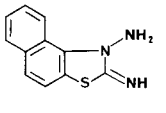
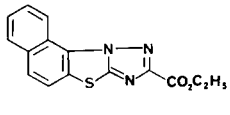
In a previous communication [2], we reported the cyclocondensation of 3-amino-2-iminonaphtho[1,2-*d*]thiazole (**1**) with diethyl oxalate and oxalic acid. The reaction was found to proceed *via* different routes leading to the formation of a monocondensation product, ethyl naphtho[1′,2′:4,5]thiazolo[3,2-*b*][1,2,4]triazole-2-carboxylate (**2**), or dicondensation product, 2,2′-binaphtho[1′,2′:4,5]thiazolo[3,2-*b*]-[1,2,4]triazole (**3**), or an acylative condensation product, 2-hydroxy-3*H*-naphtho[1′,2′:4,5]thiazolo[3,2-*b*][1,2,4]triazin-3-one (**4a**) each depending on the reaction conditions. A preliminary *in vitro* evaluation of compound **4a** (NSC-624494) revealed that this novel ring system seems to be a very interesting pharmacophore and possesses pronounced activity to inhibit the cytopathic effects of human immunodeficiency virus with the EC_{50} 1.41-1.80 x 10^{-6} *M* in CEM-Z and 2.69-5.38 x 10^{-6} *M* in CEM-V cell lines [3]. It thus prompted us to describe our subsequent research results, the cyclocondensation of compound **1** with a series of representative α-ketocarboxylic acid derivatives.



1



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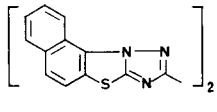

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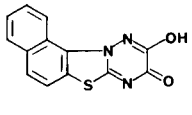
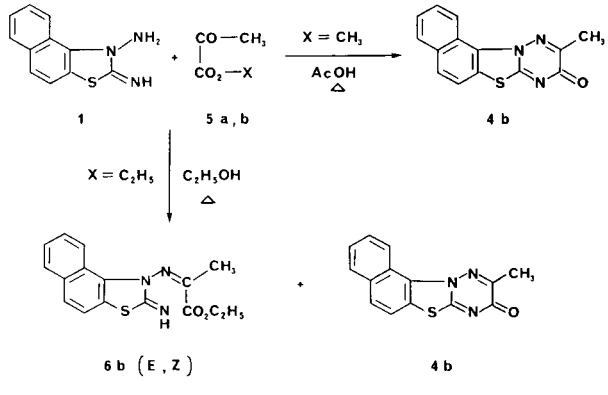


4 a

The starting compound **1** was prepared in good yield by selective *N*-amination of the readily available 2-aminonaphtho[1,2-*d*]thiazole [4] with *O*-mesitylenesulfonylhydroxylamine according to a reported procedure [5]. The subsequent condensation reaction was first performed by heating **1** with excess amount of methyl pyruvate (**5a**) in glacial acetic acid under reflux. It then afforded the expected cyclocondensation product, 2-methyl-3*H*-naphtho-[1′,2′:4,5]thiazolo[3,2-*b*][1,2,4]triazin-3-one (**4b**) in 80% yield. However, when ethyl pyruvate (**5b**) was used in place of **5a** and the reaction was carried out in boiling ethanol, compound **4b** could be isolated only in 23% yield. As the major product, the corresponding open-chain condensate, ethyl 2-(2-imino-3-naphtho[1,2-*d*]thiazolylimino)pyruvate (**6b**) was obtained in 60% yield. Since **6b** existed as a mixture of both *E*- and *Z*-isomers, as indicated in the ^{1}H nmr spectrum, an attempt to cyclize this intermediate by prolonged heating turned out to be inappropriate and **4b** could be produced in lower yield.

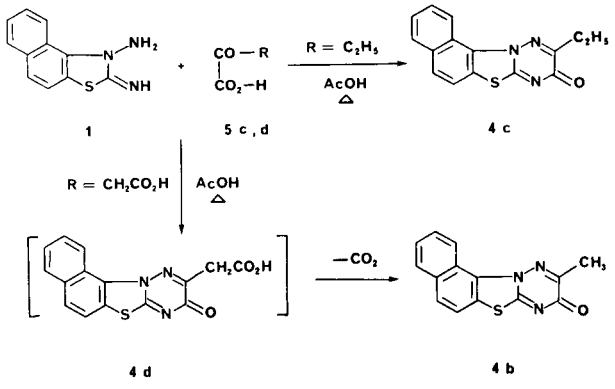
Scheme 1



As an alternation, the reaction of **1** with free acids was also studied. For example, refluxing **1** with 2-oxobutyric acid (**5c**) in glacial acetic acid gave the cyclized product, 2-ethyl-3*H*-naphtho[1′,2′:4,5]thiazolo[3,2-*b*][1,2,4]triazin-3-one (**4c**) in 31% yield. Similar treatment of **1** with oxalacetic acid (**5d**) provided 3-oxo-3*H*-naphtho[1′,2′:4,5]thiazolo-

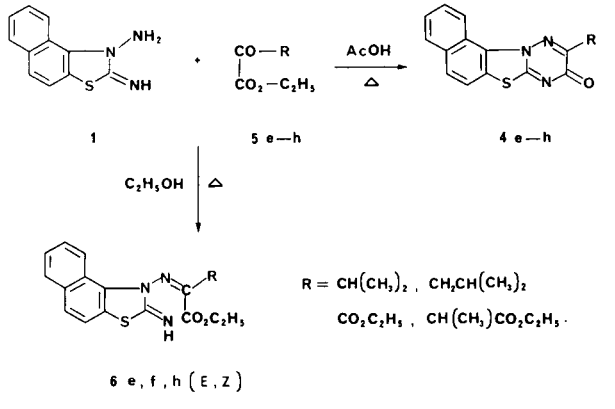
[3,2-*b*][1,2,4]triazin-2-acetic acid (**4d**) as expected. Unfortunately, this compound could not be isolated and it was soon decarboxylated in the reaction mixture to produce **4b** in 26% yield. In any event, no open-chain intermediate was found in either cases, and the corresponding methyl and ethyl ester of **4d** could be synthesized in another way, by treating **1** with dimethyl and diethyl acetylenedicarboxylate in good yield. The procedure has been described in a recent report [6].

Scheme 2



The reaction of **1** with other α-keto esters, namely, ethyl 3-methyl-2-oxobutyrate (**5e**), ethyl 4-methyl-2-oxovalerate (**5f**), diethyl ketomalonate (**5g**), and diethyl oxalpropionate (**5h**) was also performed by heating in glacial acetic acid. It then furnished the cyclized target compounds, 2-isopropyl-, 2-isobutyl-3*H*-naphtho[1′,2′:4,5]thiazolo[3,2-*b*]-[1,2,4]triazin-3-ones **4e,f**, ethyl 3-oxo-3*H*-naphtho[1′,2′:4,5]-thiazolo[3,2-*b*][1,2,4]triazine-2-carboxylate (**4g**) and ethyl α-methyl-3-oxo-3*H*-naphtho[1′,2′:4,5]thiazolo[3,2-*b*][1,2,4]-triazin-2-acetate (**4h**) in 34, 39, 77 and 23% yields respectively. Because compounds **4e**, **4f** and **4h** were isolated in relatively lower yields, the reactions of **1** with **5e**, **5f** and **5h** were then repeated, but by boiling in ethanol for 24 hours. It is surprising that unlike the reaction of **1** and **5b**, no cyclized compounds were obtained in any of the cases.

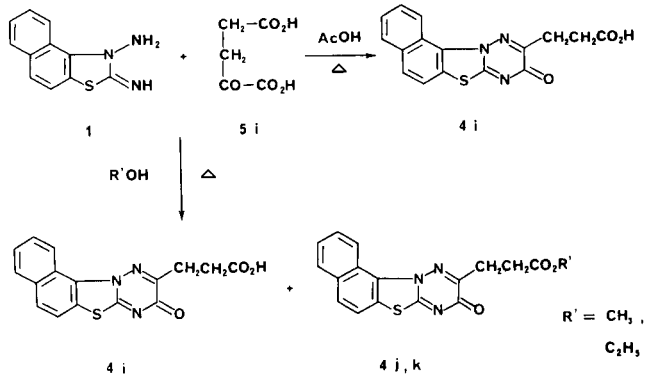
Scheme 3



Instead of these, the corresponding open-chain intermediates, ethyl 2-(2-imino-3-naphtho[1,2-*d*]thiazolylimino)isovalerate (**6e**), -isocaproate (**6f**) and diethyl 2-(2-imino-3-naphtho[1,2-*d*]thiazolylimino)-3-methylsuccinate (**6h**) were isolated in 75, 37 and 76% yields, respectively. Since these intermediated were found also to exist in a mixture of *E*- and *Z*-isomers, no attempt was made to conduct the ring-closure reaction.

Finally, compound **1** was brought into reaction with another free acid, α-keto glutaric acid (**5i**) by refluxing either in glacial acetic acid or in methanol and ethanol, respectively. After working up in the usual manner, the expected cyclocondensation product, 3-oxo-3*H*-naphtho-[1′,2′:4,5]thiazolo-[3,2-*b*][1,2,4]triazine-2-propionic acid (**4i**) was obtained in satisfactory yields (68-78%). However, in the latter two cases, minor amounts of **4i** reacted further with the reaction media to give the corresponding methyl and ethyl esters **4j,k** in 23-25% yields. Thus it should be pointed out that under such conditions, no open-chain intermediate or decarboxylation product was isolated from the reaction mixture.

Scheme 4



In conclusion, it must be noted that the reaction of 3-amino-2-iminonaphtho[1,2-*d*]thiazole (**1**) with α-ketocarboxylic esters occurred preferentially between the *N*-amino and α-keto functions to form a hydrazone intermediate, which underwent an acylative cyclization to afford the title compounds. However, when the reaction was performed under more vigorous conditions, or appropriate carboxylic acids were used in place of the esters, the corresponding cyclocondensation products could be obtained directly, though some side-reactions might occur eventually. In all cases, the title compounds could be isolated conveniently in fair to good yields.

Three representative memebers of the title compounds, namely compound **4b** (R = CH_3), **4g** (R = $CO_2C_2H_5$) and **4i** (R = $CH_2CH_2CO_2H$) were evaluated for *in vitro* activity to inhibit the cytopathic effects of human immunodeficiency virus (HIV) on T4 lymphocytes (CEM cell line) at the National Cancer Institute, USA, using the microculture

formazan assay procedure [7]. These compounds showed their cyctotoxicity on uninfected cells with $IC_{50} > 3.36 \times 10^{-5}$, 6.86×10^{-5} and 4.99×10^{-5} *M*, respectively, but unlike compound **4a** (R = OH), no protective activity on infected cells was observed. Since compounds that degenerate or are rapidly metabolized under the culture conditions may not show activity in this screening, it seems that more derivatives of this ring system, whose functional groups are characterized to cover a greater range of activity and stability-related physico-chemical parameters should be synthesized for further evaluation.

EXPERIMENTAL

All melting points were determined with Tottoli apparatus and are uncorrected. The ultraviolet and infrared spectra were measured with Perkin Elmer M 555 and Perkin Elmer 983 G spectrophotometers, respectively. The ^1H nuclear magnetic resonance spectra were recorded either on JEOL FX 100 or Bruker AM 300 WB spectrometers. The mass spectra were conducted on JEOL JMS 400 spectrometer. The elemental analyses were performed in the Instrument Center of National Science Council at National Taiwan University, Taipei, Republic of China.

2-Methyl-3*H*-naphtho[1',2':4,5]thiazolo[3,2-*b*][1,2,4]triazin-3-one (**4b**).

A mixture of 1.08 g (0.005 mole) of **1** and 1.03 g (0.01 mole) of **5a** in 5 ml of glacial acetic acid was heated under reflux for 8 hours. After cooling, the crystalline product was collected on a filter, washed with ethanol and recrystallized from a mixture of dimethylformamide and ethanol (1:1) to give 1.08 g (80%) of dark brown crystals, mp 276-277°, Rf 0.63, silica gel G, ethyl acetate + *n*-hexane (6:1); uv (ethanol): λ max (log ε) 236 (4.67), 318 ((4.01), 342 (4.04) nm; λ min (log ε) 313 (3.95), 327 (3.89) nm; ir (potassium bromide): 3061 (=C-H), 1640 (C=O), 1578, 1563, (C=N/C=C), 1220 (C-N), 700 (C-S) cm^{-1}; ^1H nmr (DMSO-d_6): δ (ppm) 2.47 (s, 3H, CH_3), 7.69-8.17 (m, 5H, ArH), 9.48 (d, 1H, H-6, J = 8.8 Hz); ms: (70 eV) m/z (%) 267 (M^+, 46), 226 (M-CH_3CN, 100), 198 ($C_{11}H_6N_2S$, 23), 172 ($C_{10}H_6NS$, 12).

Anal. Calcd. for $C_{14}H_9N_3OS$: C, 62.91; H, 3.39; N, 15.72; S, 11.99. Found: C, 63.20; H, 3.37; N, 15.92; S, 11.98.

Ethyl (*E,Z*)-2-(2-Imino-3-naphtho[1,2-*d*]thiazolylimino)pyruvate (**6b**).

A solution of 1.08 g (0.005 mole) of **1** and 1.2 g (0.01 mole) of compound **5b** in 100 ml of ethanol was heated under reflux for 12 hours. After cooling, a dark brown crystalline substance was formed and separated by filtration. The filtrate was evaporated under reduced pressure to dryness and the residue was recrystallized from ethanol to afford 1.0 g (60%) of yellow crystals, mp 194-195°, Rf 0.67, silica gel G, ethyl acetate + *n*-hexane (6:1); uv (ethanol): λ max (log ε) 223 (4.39), 255 (4.51) nm; λ min (log ε) 236 (4.35) nm; ir (potassium bromide): 3450 (O-H), 3295, 3126 (N-H), 3060 (=C-H), 1725, 1688 (C=O), 1589 (C=N/C=C), 1260, 1125 (C-O), 740 (C-S) cm^{-1}; ^1H nmr (DMSO-d_6): δ (ppm) 1.23 (t, 3H, CH_3, J = 7.0 Hz), 1.71 (s, 3H, CH_3, *Z*-form), 1.92 (s, 3H, CH_3, *E*-form), 420 (q, 2H, CH_2, J = 7.0 Hz), 6.20 (s, 1H, NH, *E*-form), 6.36 (1H, NH, *Z*-form), 6.64 (s, 2H, H_2O. hydrate), 7.28-7.68 (m, 6H, ArH); ms: (70 eV) m/z (%) 331 (M^+, 21), 286 (M-OC_2H_5, 10), 198 ($C_{11}H_6N_2S$, 14), 172 ($C_{10}H_6NS$, 100).

Anal Calcd. for $C_{16}H_{15}N_3O_2S \cdot H_2O$: C, 57.99; H, 5.17; N, 12.68. Found: C, 57.89; H, 5.16; N, 12.69.

The dark brown crystalline substance obtained from the above reaction mixture was recrystallized from a mixture of dimethylformamide and ethanol (1:1) to give 0.3 g (23%) of **4b**, mp 276-277°.

2-Ethyl-3*H*-naphtho[1',2':4,5]triazolo[3,2-*b*][1,2,4]triazin-3-one (**4c**).

A mixture of 1.08 g (0.005 mole) of **1** and 1.02 g (0.01 mole) of **5c** in 5 ml of glacial acetic acid was heated under reflux for 8 hours. The solvent was then eliminated under reduced pressure and the residue was triturated with 5 ml of dimethylformamide. The crystalline product was recrystallized from ethanol to give 0.43 g (31%) of dark brown scales, mp 263-264°; uv (ethanol): λ max (log ε) 236 (4.69), 317 (4.07), 343 (4.10) nm; λ min (log ε) 312 (4.02), 327 (3.95) nm; ir (potassium bromide): 3059 (=C-H), 1643 (C=O), 1565, 1498 (C=N/C=C), 1340 (C-N), 670 (C-S) cm^{-1}; ^1H nmr (DMSO-d_6): δ (ppm) 1.37 (t, 3H, CH_3, J = 7.2 Hz), 2.89 (q, 2H, CH_2, J = 7.2 Hz), 7.70-8.18 (m, 5H, ArH), 9.50 (d, 1H, H-6, J = 8.4 Hz); ms: (70 eV) m/z (%) 281 (M^+, 100), 226 (M-C_2H_5CN, 82), 198 ($C_{11}H_6N_2S$, 16), 172 ($C_{10}H_6NS$, 10).

Anal. Calcd. for $C_{15}H_{11}N_3OS$: C, 64.04; H, 3.94; N, 14.94; S, 11.40. Found: C, 63.96; H, 3.92; N, 15.01; S, 11.40.

Attempted Synthesis of 3-Oxo-3*H*-naphtho[1',2':4,5]thiazolo[3,2-*b*][1,2,4]triazin-2-acetic Acid (**4d**).

A mixture of 1.08 g (0.005 mole) of **1** and 1.32 g (0.01 mole) of **5d** in 5 ml of glacial acetic acid was heated under reflux for 8 hours and concentrated under reduced pressure. The residue was collected and recrystallized from dimethylformamide to afford 0.35 g (26%) of **4b** as dark brown crystals, mp 276-277°. The uv, ir, ^1H nmr and ms spectra are fully consistent with those described above.

2-Isopropyl-3*H*-naphtho[1',2':4,5]triazolo[3,2-*b*][1,2,4]triazin-3-one (**4e**).

A mixture of 1.08 g (0.005 mole) of **1** and 1.5 g (0.01 mole) of **5e** in 5 ml of glacial acetic acid was heated under reflux for 8 hours. The solvent was then eliminated under reduced pressure and the crystalline residue was recrystallized from dimethylformamide to produce 0.5 g (34%) of yellow crystals, mp 240-241°, Rf 0.14, silica gel G, ethyl acetate + *n*-hexane (1:2); uv (ethanol): λ max (log ε) 237 (4.68), 318 (4.05), 344 (4.08) nm; λ min (log ε) 313 (4.00), 327 (3.94) nm; ir (potassium bromide): 3065 (=C-H), 1645 (C=O), 1560, 1490 (C=N/C=C), 1340 (C-N), 670 (C-S) cm^{-1}; ^1H nmr (DMSO-d_6): 1.37 (d, 6H, $2CH_3$, J = 6.8 Hz), 3.36 (m, 1H, CH), 7.67-8.17 (m, 5H, ArH), 9.45 (d, 1H, H-6, J = 8.4 Hz); ms: (70 eV) m/z (%) 295 (M^+, 32), 226 (M-C_3H_7CN, 100), 198 ($C_{11}H_6N_2S$, 16), 172 ($C_{10}H_6NS$, 12).

Anal. Calcd. for $C_{16}H_{13}N_3OS$: C, 65.07; H, 4.44; N, 14.23. Found: C, 65.01; H, 4.44; N, 14.40.

Ethyl (*E,Z*)-2-(2-Imino-3-naphtho[1,2-*d*]thiazolylimino)isovalerate (**6e**).

A solution of 1.08 g (0.005 mole) of **1** and 1.05 g (0.007 mole) of **5e** in 100 ml of ethanol was heated under reflux for 24 hours. After cooling the precipitate was collected and recrystallized

from ehtanol to yield 1.35 g (75%) of white crystals, mp 204-205°, Rf 0.09, silica gel G, ethyl acetate + *n*-hexane (1:2); uv (ethanol): λ max (log ε) 224 (4.42), 256 (4.46) nm; λ min (log ε) 239 (4.35) nm; ir (potassium bromide): 3453 (O-H), 3329, 3207 (N-H), 3058 (=C-H), 1722, 1685 (C=O), 1585, 1513 (C=N/C=C), 1257, 1117 (C-O), 630 (C-S) cm^{-1}; ^1H nmr (DMSO-d_6): δ (ppm) 0.95 (m, 6H, $2CH_3$), 2.29 (m, 1H, CH), 4.26 (m, 2H, CH_2), 6.06 (s, 1H, NH, *E*-form), 6.17 (s, 1H, NH, *Z*-form), 6.68 (s, 2H, H_2O, hydrate), 7.42-7.90 (m, 6H, ArH); ms: (70 eV) m/z (%) 359 (M^+, 57), 316 (M-C_3H_7, 41), 286 (M-$CO_2C_2H_5$, 11), 198 ($C_{11}H_6N_2S$, 12), 172 ($C_{10}H_6NS$, 100).

Anal. Calcd. for $C_{18}H_{19}N_3O_2S\cdot H_2O$: C, 60.15; H, 5.89; N, 11.69; S, 8.92. Found: C, 60.16; H, 5.91; N, 11.77; S, 8.98.

2-Isobutyl-3*H*-naphtho[1′,2′:4,5]triazolo[3,2-*b*][1,2,4]triazin-3-one (**4f**).

A mixture of 1.08 g (0.005 mole) of **1** and 1.6 g (0.01 mole) of **5f** in 5 ml of glacial acetic acid was heated under reflux for 8 hours and then allowed to stand at room temperature for 2 days. The precipitate formed was collected and recrystallized from dimethylformamide to give 0.6 g (39%) of crystals, mp 226-227°; uv (ethanol): λ max (log ε) 237 (4.70), 318 (4.04), 3.44 (4.08) nm: λ min (log ε) 311 (3.99), 327 (3.93) nm; ir (potassium bromide): 3065 (=C-H), 1643 (C=O), 1575, 1564 (C=N/C=C), 1350 (C-N), 680 (C-S) cm^{-1}; ^1H nmr (DMSO-d_6): δ (ppm) 1.05 (d, 6H, $2CH_3$, J = 6.6 Hz), 2.29 (m, 1H, CH), 2.71 (d, 2H, CH_2, J = 6.6 Hz), 7.68-8.17 (m, 5H, ArH), 9.42 (d, 1H, H-6, J = 8.4 Hz); ms: (70 eV) m/z (%) 309 (M^+, 86), 294 (M-CH_3, 26), 266 (M-C_3H_7, 18), 226 (M-C_4H_9CN, 100), 198 ($C_{11}H_6N_2S$, 31).

Anal. Calcd. for $C_{17}H_{15}N_3OS$: C, 66.00; H, 4.87; N, 13.58; S, 10.36. Found: C, 65.92; H, 4.86; N, 13.70; S, 10.19.

Ethyl (*E,Z*)-2-(2-Imino-3-naphtho[1,2-*d*]thiazolylimino)isocaproate (**6f**).

A solution of 1.08 g (0.005 mole) of **1** in 100 ml of ethanol was treated with 1.6 g (0.01 mole) of **5f** and heated under reflux for 24 hours. The reaction mixture was concentrated under reduced pressure and the residue was recrystallized from ethanol to yield 0.7 g (37%) of white scales, mp 167-168°; uv (ethanol): λ max (log ε) 225 (4.40), 256 (4.49) nm; λ min (log ε) 239 (4.35) nm; ir (potassium bromide): 3488 (O-H), 3287, 3206 (N-H), 3050 (=C-H), 1721, 1688 (C=O), 1585, 1500 (C=N/C=C), 1380 (C-N), 1230 (C-O), 635 (C-S) cm^{-1}; ^1H nmr (DMSO-d_6): δ (ppm) 0.90 (d, 6H, $2CH_3$, J = 6.6 Hz), 1.27 (t, 3H, CH_3, J = 6.8 Hz), 1.75 (m, 1H, CH), 1.99 (d, 2H, CH_2, J = 6.6 Hz), 4.22 (q, 2H, CH_2, J = 6.8 Hz), 6.05 (s, 1H, NH, *E*-form), 6.25 (s, 1H, NH, *Z*-form), 6.65 (s, 2H, H_2), hydrate), 7.35-7.89 (m, 6H, ArH); ms: (70 eV) m/z (%) 373 (M^+, 58), 330 (M-C_3H_7, 38), 300 (M-$CO_2C_2H_5$, 19), 198 ($C_{11}H_6N_2S$, 54), 172 ($C_{10}H_6NS$, 100).

Anal. Calcd. for $C_{19}H_{21}N_3O_2S\cdot H_2O$: C, 61.11; H, 6.21; N, 11.25. Found: C, 61.14; H, 6.23; N, 11.30.

Ethyl 3-Oxo-3*H*-naphtho[1′,2′:4,5]thiazolo[3,2-*b*][1,2,4]triazine-2-carboxylate (**4g**).

A mixture of 1.08 g (0.005 mole) of **1** and 1.8 g (0.01 mole) of **5i** in 5 ml of glacial acetic acid was heated under reflux for 8 hours. After cooling, the precipitate was collected, washed with ethanol and recrystallized from dimethylformamide to afford 1.25 g (77%) of yellow needles, mp 231-232°, Rf 0.16, silica gel G, ethyl acetate + *n*-hexane (1:1); uv (ethanol): λ max (log ε) 237 (4.77), 361 (3.80) nm; λ min (log ε) 347 (3.65) nm; ir (potassium bromide): 3064 (=C-H), 1740, 1656 (C=O), 1565, 1485 (C=N/C=C), 1164 (C-O), 640 (C-S) cm^{-1}; ^1H nmr (DMSO-d_6): δ (ppm) 1.39 (t, 3H, CH_3, J = 7.2 Hz), 4.48 (q, 2H, CH_2, J = 7.2 Hz), 7.70-8.19 (m, 5H, ArH), 9.20 (d, 1H, H-6, J = 8.6 Hz); ms: (70 eV) m/z (%) 325 (M^+, 26), 280 (M-C_2H_5O, 12), 252 (M-$CO_2C_2H_5$, 10), 226 ($C_{12}H_6N_2OS$, 100), 198 ($C_{11}H_6N_2S$, 16).

Anal. Calcd. for $C_{16}H_{11}N_3O_3S$: C, 59.07; H, 3.41; N, 12.92. Found: C, 58.99; H, 3.30; N, 13.22.

Ethyl α-Methyl-3-oxo-3*H*-naphtho[1′,2′:4,5]thiazolo[3,2-*b*][1,2,4]-triazine-2-acetate (**4h**).

A mixture of 1.08 g (0.005 mole) of **1** and 2.0 g (0.01 mole) of **5h** in 5 ml of glacial acetic acid was heated under reflux for 8 hours and then concentrated under reduced pressure to dryness. The residue was triturated with dimethylformamide and the crystalline substance was collected, washed with ethanol and recrystallized from dimethylformamide to give 0.4 g (23%) of yellow platelet, mp 209-210°, Rf 0.21, silica gel G, ethyl acetate + *n*-hexane (1:1); uv (ethanol): λ max (log ε) 237 (4.72), 342 (4.02) nm; λ min (log ε) 328 (3.86) nm; ir (potassium bromide): 3055 (=C-H), 1722, 1646 (C=O), 1576, 1563 (C=N/C=C), 1320 (C-N), 1175 (C-O), 680 (C-S) cm^{-1}; ^1H nmr (DMSO-d_6): δ (ppm) 1.18 (t, 3H, CH_3, J = 7.0 Hz), 1.60 (d, 3H, CH_3, J = 7.0 Hz), 4.17 (m, 3H, CH_2, CH), 7.69-8.18 (m, 5H, ArH), 9.35 (d, 1H, H-6, J = 8.8 Hz); ms: (70 eV) m/z (%) 353 (M^+, 31), 308 (M-C_2H_5O, 10), 280 (M-$CO_2C_2H_5$, 18), 226 ($C_{12}H_6N_2OS$, 100), 198 ($C_{11}H_6N_2S$, 48), 172 ($C_{10}H_6NS$, 21).

Anal. Calcd. for $C_{18}H_{15}N_3O_3S$: C, 61.18; H, 4.28; N, 11.89. Found: C, 61.13; H, 4.25; N, 12.26.

Diethyl 2-(2-Imino-3-naphtho[1,2-*d*]thiazolylimino)-3-methylsuccinate (**6h**).

A solution of 1.08 g (0.005 mole) of **1** and 2.0 g (0.01 mole) of **5h** in 100 ml of ethanol was heated under reflux for 24 hours. The solvent was eliminated under reduced pressure and the residue was recrystallized from ethanol to produce 1.6 g (76%) of white crystals, mp 184-185°, Rf 0.17, silica gel G, ethyl acetate + *n*-hexane (1:1); uv (ethanol): λ max (log ε) 225 (4.43), 255 (4.47) nm; λ min (log ε) 241 (4.36) nm; ir (potassium bromide): 3450 (O-H), 3298, 3221 (N-H), 3072 (=C-H), 1725, 1678 (C=O), 1584, 1570 (C=N/C=C), 1250, 1190 (C-O), 680 (C-S) cm^{-1}; ^1H nmr (DMSO-d_6): δ (ppm) 1.20 (m, 6H, $2CH_3$), 1.30 (d, 3H, CH_3, J = 6.8 Hz), 1.58 (q, 1H, CH, J = 6.8 Hz), 4.10 (m, 4H, $2CH_2$), 6.17 (s, 1H, NH), 6.16 (d, 2H, H_2O), 7.32-7.86 (m, 6H, ArH); ms: (70 eV) m/z (%) 417 (M^+, 39), 344 (M-$CO_2C_2H_5$, 14), 271 (M-$2CO_2C_2H_5$, 20), 198 ($C_{11}H_6N_2S$, 100), 172 ($C_{10}H_6NS$, 52).

Anal. Calcd. for $C_{20}H_{21}N_3O_4S\cdot H_2O$: C, 57.54; H, 5.55; N, 10.07. Found: C, 57.54; H, 5.52; N, 10.04.

3-Oxo-3*H*-naphtho[1′,2′:4,5]thiazolo[3,2-*b*][1,2,4]triazine-2-propionic Acid (**4i**).

A mixture of 1.08 g (0.005 mole) of **1** and 1.1 g (0.0075 mole) of **5i** in 5 ml of glacial acetic acid was heated under reflux for 8 hours. After cooling, the solid substance was collected, washed with ethanol and recrystallized from a mixture of benzene and dimethylformamide to produce 1.27 g (78%) of crystals, mp 292-294°; uv (ethanol): λ max (log ε) 236 (4.58), 317 (3.93), 343 (3.97) nm; λ min (log ε) 312 (3.89), 327 (3.83) nm; ir (potassium bromide): 3070 (=C-H), 2645 (O-H), 1740, 1645 (C=O), 1593, 1560 (C=N/C=C), 1220 (C-O), 680 (C-S) cm^{-1}; ^1H nmr

(DMSO-d_6): δ (ppm) 2.87 (t, 3H, CH_2, J = 6.7 Hz), 3.09 (t, 2H, CH_2, J = 6.7 Hz), 7.70-7.79 (m, 2H, H-9, 10), 8.08-8.18 (m, 3H, H-7, 8, 11), 9.42 (d, 1H, H-6, J = 8.9 Hz), 12.43 (s, 1H, CO_2H); ms: (70 eV) m/z (%) 325 (M^+, 39), 280 (M-CO_2H, 10), 226 ($C_{12}H_6N_2OS$, 100), 198 ($C_{11}H_6N_2S$, 16), 172 ($C_{10}H_6NS$, 10), 154 ($C_{10}H_6N_2$, 16).

Anal. Calcd. for $C_{16}H_{11}N_3O_3S$: C, 59.07; H, 3.41; N, 12.92. Found: C, 58.62; H, 3.48; N, 12.74.

Methyl 3-Oxo-3*H*-naphtho[1′,2′:4,5]thiazolo[3,2-*b*][1,2,4]triazine-2-propionate (**4j**).

A solution of 1.08 g (0.005 mole) of **1** and 1.1 g (0.0075 mole) of **5i** in 100 ml of methanol was heated under reflux for 24 hours. After cooling, the precipitate was collected and recrystallized from a mixture of benzene and *n*-hexane to give 1.1 g (68%) of **4i**, mp 293-294°.

The filtrate was evaporated to dryness and the residue was triturate with *n*-hexane, allowed to stand at room temperature for 48 hours. The solid product was collected and recrystallized from a mixture of dimethylformamide and ethanol to produce 0.4 g (25%) of white crystals, mp 247-248°; uv (ethanol): λ max (log ε) 236 (4.64), 317 (3.99), 344 (4.03) nm; λ min (log ε) 313 (3.95) 327 (3.88) nm; ir (potassium bromide): 3060 (=C-H), 1737, 1644 (C=O), 1596, 1575 (C=N/C=C), 1168, 1139 (C-O), 680 (C-S) cm^{-1}; ^1H nmr (DMSO-d_6): δ (ppm) 2.93 (m, 2H, CH_2) 3.10 (m, 2H, CH_2), 3.64 (s, 3H, CH_3), 7.71-7.76 (m, 2H, H-9, 10), 8.06-8.17 (m, 3H, H-7, 8, 11), 9.31-9.40 (m, 1H, H-6); ms: (70 eV) m/z (%) 339 (M^+, 49), 308 (M-CH_3O, 13), 280 (M-CO_2CH_3, 14), 226 ($C_{12}H_6N_2OS$, 100), 198 ($C_{11}H_6N_2S$, 18), 172 ($C_{10}H_6NS$, 10). 154 ($C_{10}H_6N_2$, 21).

Anal. Calcd. for $C_{17}H_{13}N_3O_3S$: C, 60.17; H, 3.86; N, 12.38. Found: C, 59.95; H, 3.67; N, 12.42.

Ethyl 3-Oxo-3*H*-naphtho[1′,2′:4,5]thiazolo[3,2-*b*][1,2,4]triazine-2-propionate (**4k**).

Repeating the above reaction but using ethanol as reaction medium gave 1.2 g (70%) of **4i**, mp 293-294° after recrystallized from a mixture of benzene and *n*-hexane.

The filtrate was evaporated to dryness and the residue was treated as described above. The solid product was recrystallized from a mixture of dimethylformamide and ethanol to afford 0.4 g (24%) of white crystals, mp 218-219°; uv (ethanol): λ max (log ε) 237 (4.69), 318 (4.04), 344 (4.07) nm; λ min (log ε) 313 (4.00), 328 (3.93) nm; ir (potassium bromide): 3060 (=C-H), 1728, 1641 (C=O), 1575, 1564 (C=N/C=C), 1173, 1027 (C-O), 680 (C-S) cm^{-1}; ^1H nmr (DMSO-d_6): δ (ppm) 1.17 (t, 3H, CH_3, J = 7.1 Hz), 2.92 (m, 2H, CH_2), 4.08 (q, 2H, CH_2, J = 7.1 Hz), 7.70-7.79 (m, 2H, H-9, 10), 8.07-8.18 (m, 3H, H-7, 8, 11), 9.34-9.42 (m, 1H, H-6); ms: (70 eV) m/z (%) 353 (M^+, 37), 308 (M-OC_2H_5, 14), 280 (M-$CO_2C_2H_5$, 15), 226 ($C_{12}H_6N_2OS$, 100), 198 ($C_{11}H_6N_2S$, 15), 172 ($C_{10}H_6NS$, 11), 154 ($C_{10}H_6N_2$, 14).

Anal. Calcd. for $C_{18}H_{15}N_3O_3S$: C, 61.18; H, 4.28; N, 11.89. Found: C, 61.09; H, 4.07; N, 11.85.

In vitro Anti-HIV Evaluation.

Compound **4b**, **4g** and **4i** were selected for *in vitro* anti-HIV evaluation. The evaluation was operated in the Antiviral Evaluation Branch, National Cancer Institute, Bethesda, Maryland, USA, using the microculture formazan assay procedure [7]. These compounds showed the cytotoxicity on uninfected cells with IC_{50} $>3.36 \times 10^{-5}$ and 4.99×10^{-5} *M*, respectively, but no protective activity on infected cells.

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