Synthesis of Representative 10-Aryl-, 10-Aralkyl- and 10-Heteraryl-9*H*-naphtho[1′,2′:4,5]thiazolo[3,2-*b*]-[1,2,4]triazin-9-ones as Potential Anti-HIV Agents

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Dedicated to the memory of Professor Roland K. Robins

To prepare the title compounds, cyclocondensation of 1-amino-2-iminonaphtho[1,2-*d*]thiazole (**2**) with some representative glyoxylic acid derivatives was investigated. Heating **2** with methyl phenylglyoxylate (**3a**) in methanol afforded only the open chain intermediates **4a,b**. However, when this reaction was performed in refluxing glacial acetic acid, the expected compound, 10-phenyl-9*H*-naphtho[1′,2′:4,5]thiazolo[3,2-*b*][1,2,4]-triazin-9-one (**5a**) was produced in 27% yield. Similar treatment of **2** with benzyl-, 2-furyl- and 2-thienylglyoxylic acids **3b-d** gave the corresponding 10-benzyl-, 10-(2-furyl)- and 10-(2-thienyl)-9*H*-naphtho[1′,2′:4,5]thiazolo[3,2-*b*][1,2,4]triazin-9-ones **5b-d** in 48-67% yields. As by-products, 9-benzoyl- and 9-(2-thenoyl)naphtho-[1′,2′:4,5]thiazolo[3,2-*b*][1,2,4]triazoles **6a,d** were also isolated. Compound **5a** was selected for *in vitro* anti-HIV evaluation but found to be inactive.

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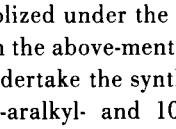
Introduction.

In an earlier paper [1], we described the synthesis of 10-hydroxy-9*H*-naphtho[1′,2′:4,5]thiazolo[3,2-*b*][1,2,4]triazin-9-one (**1a**, NSC-624494), a new compound which showed pronounced activity to inhibit the cytopathic effects of human immunodeficiency virus (HIV). The medium effective concentration, ED_{50} of **1a** was found to be 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 [2]. As a progressive continuation, we also synthesized a number of analogs of this compound, namely, 9*H*-naph[1′,2′:4,5]thiazolo[3,2-*b*][1,2,4]triazin-9-one (**1b**) and its 10-substituted derivatives **1c-o** [3-5]. It is surprising that a preliminary evaluation of some representative members of these compounds, for example **1b** (R = H, NSC-631905), **1c** (R = CH_3, NSC-631906), **1g** (R = $CO_2C_2H_5$, NSC-631908), **1i** (R = $CH_2CH_2CO_2CH_3$, NSC-631909) and **1l** (R = $CH_2CH_2CO_2H$, NSC-631910) using the same assay procedure revealed that none of them was active [3-5]. Since compounds that degenerate or are rapidly metabolized under the culture conditions may not show activity in the above-mentioned screening, it thus prompted us to undertake the synthesis of some representative 10-aryl-, 10-aralkyl- and 10-heteraryl-9*H*-naphtho-[1′,2′:4,5]thiazolo[3,2-*b*][1,2,4]triazin-9-one derivatives for further evaluation.



1 a - o

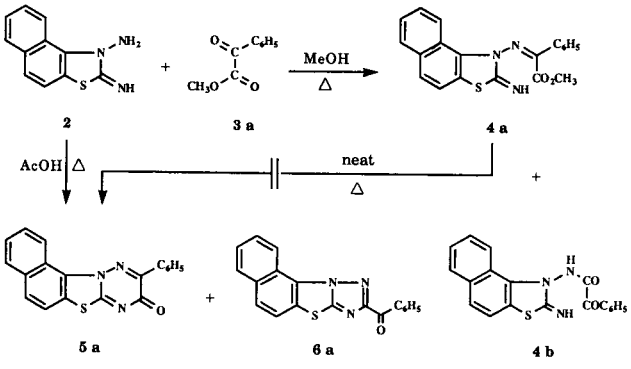
R = OH	$CH_2CH(CH_3)_2$	$CH(CH_3)CO_2C_2H_5$
H	$CO_2C_2H_5$	$CH_2CH_2CO_2H$
CH_3	CH_2CO_2H	$CH_2CH_2CO_2CH_3$
C_2H_5	$CH_2CO_2CH_3$	$CH_2CH_2CO_2C_2H_5$
$CH(CH_3)_2$	$CH_2CO_2C_2H_5$	$COCH(OC_2H_5)_2$

Results and Discussion.

The synthetic experiments were performed starting from 1-amino-2-iminonaphtho[1,2-*d*]thiazole (**2**), which was obtained by selective *N*-amination of the readily available 2-aminonaphtho[1,2-*d*]thiazole [7] with *O*-mesitylenesulfonylhydroxylamine according to a procedure described previously [8]. The subsequent synthesis was tried at first by heating compound **2** with excess amount of methyl phenylglyoxylate (**3a**) under reflux in methanol. The reaction was found to take place *via* two pathways and to stop in both cases in the open-chain intermediate step. The first one proceeded through dehydrative condensation to afford a Schiff's base, methyl (*E,Z*)-2-(2-imino-1-naphtho-[1,2-*d*]thiazolylimino)phenylglyoxylate (**4a**) in 69% yield. The second one proceeded through acylative condensation to furnish an amide derivative, 2-imino-1-(phenylglyoxylylamino)naphtho[1,2-*d*]thiazole (**4b**) in 16% yield. An attempt to cyclize compound **4a** by heating neatly to melting at 125° turned out only a mixture of decomposition products which were very difficult to be separated. On the other hand, when the above reaction was brought by heating in glacial acetic acid at refluxing temperature for 8 hours (Procedure A), the expected cyclized product, 10-phenyl-9*H*-naphtho[1′,2′:4,5]thiazolo[3,2-*b*][1,2,4]triazin-9-one (**5a**) was obtained in 27% yield. This compound gave satisfactory analytical and spectral data to support its structure and these data were also consistent with those of its other analogs reported previously [3-5]. However, a minor amount of a by-product, 9-benzoylnaphtho[1′,2′:4,5]thiazolo[3,2-*b*][1,2,4]triazole (**6a**) was isolated from the mother liquid in 18% yield. Differentiation of compound **5a** and **6a** was made mainly on the basis of spectral analyses. For example, both compounds showed the prom-

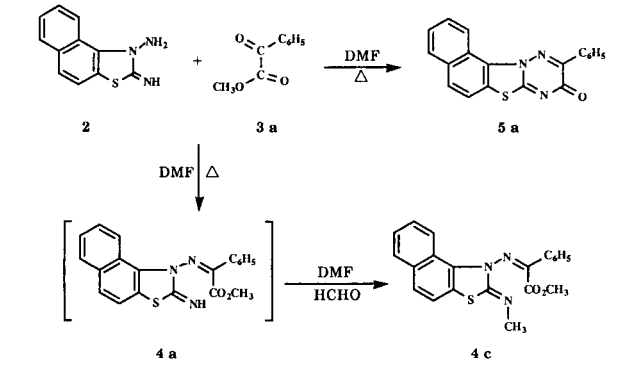
inent molecular ion peak at m/z 329 as expected. However, compound **5a** was cleaved to give the M-C_6H_5CN fragment at m/z 226 as base ion peak, while compound **6a** exhibited the base ion peak at m/z 224 due to the cleavage M-C_6H_5CO; and such a cleavage could never occur in compound **5a**.

Scheme 1



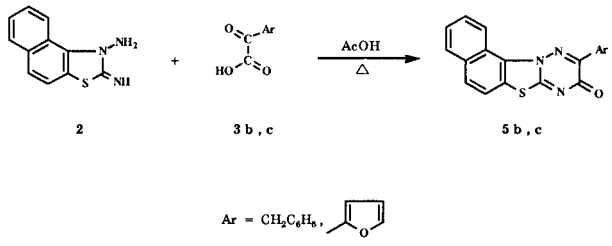
As an alteration, compound **5a** was also prepared by refluxing **2** with excess amount of **3a** in dimethylformamide (Procedure B). Unfortunately, it was obtained only in 12% yield, while a by-product, *N*-methylated derivative of **4a**, namely methyl 2-(2-methylimino-1-naphtho[1,2-d]-thiazolylimino)phenylglyoxylate (**4c**) was isolated in 32% yield. The formation of compound **4c** from the above reaction was quite surprising because *N*-methylation of **2** or the open-chain intermediate **4a** could never occur with the reaction partner **3a**. Since the reaction solvent, dimethylformamide is known to decompose easily to formaldehyde under the action of heat and light, a reductive methylation of the imino nitrogen of **2** or **4a** by the freshly formed formaldehyde thus took place in the presence of dimethylformamide as the reducing agent - Leuckart reaction [9]. It thus blocked the acylative cyclization of the open-chain intermediate.

Scheme 2



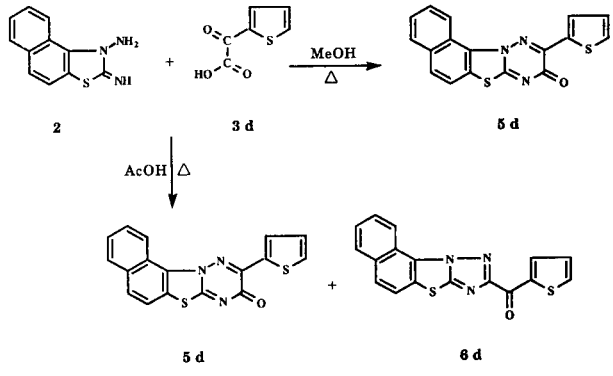
Furthermore, treatment of compound **2** with an excess amount of benzylglyoxylic acid (**3b**) or 2-furylglyoxylic acid (**3c**) similarly in glacial acetic acid by heating provided the corresponding target compounds, 10-benzyl-9*H*-naphtho[1′,2′:4,5]thiazolo[3,2-*b*][1,2,4]triazin-9-one (**5b**) and 10-(2-furyl)-9*H*-naphtho[1′,2′:4,5]thiazolo[3,2-*b*][1,2,4]-triazin-9-one (**5c**) in 23 and 67% yield, respectively. Though compounds **5b** and **5c** were obtained in not very good yields, no open-chain intermediate or by-product was found in the reaction mixture.

Scheme 3



Finally, compound **2** was brought into reaction with 2-thienylglyoxylic acid (**3d**) by refluxing in ethanol. After 24 hours, it gave the expected compound, 10-(2-thienyl)-9*H*-naphtho[1′,2′:4,5]thiazolo[3,2-*b*][1,2,4]triazin-9-one (**5d**) in 48% yield, while no by-product was found from the reaction mixture. However, when this reaction was performed also in refluxing glacial acetic acid, compound **5d** could be isolated in same yield as expected but was accompanied by a minor amount (12%) of 9-(2-thenoyl)naphtho[1′,2′:4,5]thiazolo[3,2-*b*][1,2,4]triazole (**6d**). Structures of compound **5d** and **6d** were assigned also on the basis of mass spectra, where **5d** showed the base ion peak at m/z 226 due to the M-C_4H_3SCN cleavage pattern while **6d** gave the base ion peak at m/z 224 arised from M-C_4H_3SCO fragmentation. The formation of **6d** suggested that the reaction between **2** and **3d** took place also *via* two pathways just like case involving the reaction of **2** and **3a** indicated above.

Scheme 4



In conclusion, it should be mentioned that in performing the cyclocondensation of **2** with glyoxylic acid derivatives, the reaction medium must be carefully selected to avoid the formation of some open-chain intermediates and cyclized by-products. In all cases, the title compounds could be generated conveniently in fair yields. Leuckart

reaction was only a rare special case so far found.

Compound **5a** (NSC-631907) was selected for *in vitro* evaluation of its activity to inhibit the cyctopathic effects of human immunodeficiency virus (HIV) on T4 lymphocytes (CEM cell line) using the microculture formazan assay procedure [6]. It showed the cytotoxicity on uninfected celles with $IC_{50} > 4.9 \times 10^{-5}$ *M*, but no protective activity on infected cells.

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 ^{1}H nuclear magnetic resonance spectra were recorded either on JEOL FX 100 or Bruker AM 300WB spectrometers. The mass spectra were conducted on JEOL JMS 400 spectrometer. The elemental analyses were performed on Perkin Elmer 240 C elemental analyser in the Instrument Center of National Science Council at National Taiwan University, Taipei, Republic of China.

1-Amino-2-iminonaphtho[1,2-*d*]thiazole (**2**).

Compound **2** was prepared from 20.1 g (0.1 mole) of 2-aminonaphtho[1,2-*d*]thiazole by *N*-amination with *O*-mesitylenesulfonylhydroxylamine in dichloromethane according to a procedure described previously [8], yield 17.6 g (82%), mp 190-191°.

Methyl (*E,Z*)-2-(2-Imino-1-naphtho[1,2-*d*]thiazolylimino)phenylglyoxylate (**4a**).

A solution of 1.08 g (0.005 mole) of **2** and 1.64 g (0.01 mole) of methyl phenylglyoxylate (**3a**) in 100 ml of methanol was heated under reflux for 12 hours and then concentrated under reduced pressure to about 20 ml. After cooling, the dark brown crystalline product was collected by filtration and recrystallized from methanol to afford 1.3 g (69%) of light yellow needle crystals, mp 120-121°, Rf 0.82, silica gel G, ethyl acetate/*n*-hexane (6:1); uv (ethanol): λ max (log ε) 218 (4.43), 255 (4.53) nm; λ min (log ε) 236 (4.35) nm; ir (potassium bromide): 3640, 3450 (O-H), 3320, 3230 (N-H), 3060 (=C-H), 1735, 1645 (C=O), 1586, 1545, 1487 (C=N/C=C), 1255, 1040 (C-O), 700 (C-S) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ (ppm) 3.74 (s, 3H, CH_3), 5.97 (s, 1H, NH, *E*-form), 6.60 (s, 1H, NH, *Z*-form), 6.76 (s, 2H, H_2O hydrate), 7.37-7.42 (m, 5H, ArH), 7.52 (m, 2H, H-7, 8), 7.68 (m, 2H, H-5, 6), 7.80 (m, 1H, H-9), 7.90 (d, 1H, H-4, J = 8.0 Hz); ms: (70 eV) m/z (%) 361 (M^+, 24), 302 (M-CO_2CH_3, 16), 213 ($C_{11}H_7N_3S$, 22), 199 ($C_{11}H_7N_2S$, 82), 172 ($C_{10}H_6NS$, 100), 140 ($C_{10}H_6N$, 20).

Anal. Calcd. for $C_{20}H_{15}N_3O_2S \cdot H_2O$: C, 63.31; H, 4.52; N, 11.07. Found: C, 63.19; H, 5.00; N, 10.75.

2-Imino-1-(phenylglyoxylylamino)naphtho[1,2-*d*]thiazole (**4b**).

The filtrate from the above reaction was allowed to stand at 4° overnight and the greenish yellow crystalline product was collected and recrystallized from a mixture of dimethylformamide and methanol to give 0.27 g (16%) of light yellow needle crystals, mp >300°, Rf 0.71, silica gel G, ethyl acetate/*n*-hexane (6:1); uv (ethanol): λ max (log ε) 230 (4.62), 301 (4.25) nm; λ min (log ε) 273 (4.16) nm; ir (potassium bromide): 3259 (N-H), 3055 (=C-H), 1720, 1695 (C=O), 1560, 1500 (C=N/C=C), 1283 (C-N), 695 (C-S) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ (ppm) 7.36-7.51 (m, 4H, NH and ArH), 7.53-7.68 (m, 2H, ArH), 7.70-7.89 (m, 4H, H-5, 6, 7, 8), 7.90 (m, 1H, H-9), 8.05 (d, 1H, H-4, J = 8.0 Hz); ms: (70 eV) m/z (%) 347 (M^+, 52), 242 (M-COC_6H_5, 18), 214 ($C_{11}H_7N_2S$, 16), 199 ($C_{11}H_7NS$, 37), 172 ($C_{10}H_6NS$, 100), 140 ($C_{10}H_6N$, 20).

Anal. Calcd. for $C_{19}H_{13}N_3O_2S$: C, 65.69; H, 3.77; N, 12.10. Found: C, 65.39; H, 3.63; N, 12.02.

10-Phenyl-9*H*-naphtho[1′,2′:4,5]thiazolo[3,2-*b*][1,2,4]triazin-9-one (**5a**).

Procedure A.

A solution of 1.08 g (0.005 mole) of **2** in 10 ml of glacial acetic acid was treated with 1.64 g (0.01 mole) of **3a** and the reaction mixture was heated under reflux for 8 hours. After cooling, the precipitate was collected through filtration and recrystallized from dimethylformamide to produce 0.4 g (27%) of light yellow scales, mp 275-276°, Rf 0.58, silica gel G, ethyl acetate/*n*-hexane (6:1); uv (ethanol): λ max (log ε) 205 (4.49), 239 (4.75), 282 (4.27), 361 (4.05) nm; λ min (log ε) 217 (4.41), 267 (4.24), 334 (3.91) nm; ir (potassium bromide): 3056 (=C-H), 1642 (C=O), 1536, 1480 (C=N/C=C), 1262, 1225 (C-N), 695 (C-S) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ (ppm) 7.61 (m, 3H, H-3′, 4′, 5′), 7.70-7.85 (m, 2H, H-2, 3), 8.11-8.26 (m, 5H, H-1, 4, 5, H-2′, 6′), 9.47 (d, 1H, H-6, J = 8.7 Hz); ms: (70 eV) m/z (%) 329 (M^+, 40), 226 (M-C_6H_5CN, 100), 198 ($C_{11}H_6N_2S$, 14), 172 ($C_{10}H_6NS$, 10), 154 ($C_{10}H_6N_2$, 12).

Anal. Calcd. for $C_{19}H_{11}N_3OS$: C, 69.29; H, 3.37; N, 12.76. Found: C, 69.28; H, 3.29; N, 12.82.

Procedure B.

A solution of 1.08 g (0.005 mole) of **2** and 1.64 g (0.01 mole) of **3a** in 50 ml of dimethylformamide was heated under reflux for 12 hours. After cooling, the precipitate was collected through filtration and recrystallized from dimethylformamide to provide 0.2 g (12%) of compound **5a** as light yellow scales, mp 275-276°.

9-Benzoylnaphtho[1′,2′:4,5]thiazolo[3,2-*b*][1,2,4]triazole (**6a**).

The filtrate from procedure A was concentrated under reduced pressure and the residue was dissolved in a suitable amount of methanol and allowed to stand at 4° overnight. The precipitate formed was collected and recrystallized from a mixture of benzene and dimethylformamide to afford 0.3 g (18%) of orange needle crystals, mp >300°, Rf 0.53, silica gel G, ethyl acetate/*n*-hexane (6:1); uv (ethanol): λ max (log ε) 209 (4.56), 226 (4.60), 264 (4.36), 314 (4.13), 418 (4.32) nm; λ min (log ε) 215 (4.54), 251 (4.34), 293 (3.91), 333 (3.76) nm; ir (potassium bromide): 3065 (=C-H), 1596 (C=O), 1485 (C=N/C=C), 1226 (C-N), 695 (C-S) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ (ppm) 7.57-7.67 (m, 3H, H-3′, 4′, 5′), 7.83-8.00 (m, 2H, H-2, 3), 8.27-8.41 (m, 3H, H-1, 4, 5), 8.81-8.84 (m, 2H, H-2′, 6′), 10.11 (d, 1H, H-6, J = 8.6 Hz); ms: (70 eV) m/z (%) 329 (M^+, 45), 224 (M-C_6H_5CO, 100), 184 ($C_{11}H_6NS$, 19), 140 ($C_{10}H_6N$, 64).

Anal. Calcd. for $C_{19}H_{11}N_3OS$: C, 69.29; H, 3.37; N, 12.76. Found: C, 69.28; H, 3.26; N, 12.78.

Methyl 2-(2-Methylimino-1-naphtho[1,2-*d*]thiazolylimino)phenylglyoxylate (**4c**).

The filtrate from procedure B was also concentrated under reduced pressure and the residue was dissolved in a suitable amount of ethanol and allowed to stand at 4° overnight. The precipitate formed was collected and recrystallized from a mix-

ture of dimethylformamide and ethanol to afford 0.6 g (32%) of light yellow needle crystals, mp 160-161°, Rf 0.91, silica gel G, ethyl acetate/*n*-hexane (6:1); uv (ethanol): λ max (log ε) 218 (4.71), 255 (4.52), 290 (4.30) nm; λ min (log ε) 242 (4.40), 271 (4.15) nm; ir (potassium bromide): 3059 (=C-H), 1710 (C=O), 1617, 1584 (C=N/C=C), 1320, 1295 (C-N), 1180 (C-O), 695 (C-S) cm^{-1}; ^1H nmr (DMSO-d_6): δ (ppm) 2.56 (s, 3H, NCH_3), 3.38 (s, 3H, OCH_3), 7.40-7.49 (m, 3H, ArH), 7.51-7.60 (m, 2H, ArH), 7.68-7.75 (m, 2H, H-7, 8), 7.82-7.89 (m, 2H, H-5, 6), 8.05 (m, 1H, H-9), 8.13 (d, 1H, H-4, J = 8.0 Hz); ms: (70 eV) m/z (%) 375 (M^+, 48), 328 (M-CH_3O, 100), 316 (M-CH_3OCO, 30), 198 ($C_{11}H_6N_2S$, 34), 186 ($C_{10}H_6N_2S$, 20), 172 ($C_{10}H_6NS$, 24).

Anal. Calcd. for $C_{21}H_{17}N_3O_2S$: C, 67.18; H, 4.56; N, 11.19; S, 8.54. Found: C, 67.24; H, 4.58; N, 11.27; S, 8.46.

10-Benzyl-9*H*-naphtho[1′,2′:4,5]thiazolo[3,2-*b*][1,2,4]triazin-9-one (**5b**).

A solution of 1.08 g (0.005 mole) of **2** and 1.64 g (0.01 mole) of benzylglyoxylic acid (**3b**) in 10 ml of glacial acetic acid was heated under reflux for 8 hours. Then, the solvent was evaporated under reduced pressure and the residue was dissolved in 10 ml of dimethylformamide. After cooling, the precipitate formed was collected on a filter and the filtrate was dilute with 50 ml of ethanol and a second crop of precipitate was formed. The product was collected and recrystallized from dimethylformamide to give 0.2 g (12%) of light yellow needles, mp 239-240°, Rf 0.19, silica gel G, ethyl acetate/*n*-hexane (1:1); uv (ethanol): λ max (log ε) 208 (4.49), 236 (4.70), 318 (4.04), 344 (4.08) nm; λ min (log ε) 218 (4.43), 314 (3.99), 329 (3.94) nm; ir (potassium bromide): 3025 (=C-H), 1640 (C=O), 1563, 1484 (C=N/C=C), 1106 (C-N), 700 (C-S) cm^{-1}; ^1H nmr (DMSO-d_6): δ (ppm) 4.19 (s, 2H, CH_2), 7.38-7.65 (m, 7H, ArH), 8.01-8.12 (m, 3H, H-1, 4, 5), 8.70 (d, 1H, H-6, J = 8.8 Hz); ms: (70 eV) m/z (%) 343 (M^+, 88), 226 (M-C_6H_5CN, 100), 198 ($C_{11}H_6N_2S$, 62), 172 ($C_{10}H_6NS$, 31), 154 ($C_{10}H_6N_2$, 55).

Anal. Calcd. for $C_{20}H_{13}N_3OS$: C, 69.95; H, 3.82; N, 12.24. Found: C, 69.90; H, 3.75; N, 12.31.

10-(2-Furyl)-9*H*-naphtho[1′,2′:4,5]thiazolo[3,2-*b*][1,2,4]triazin-9-one (**5c**).

A solution of 1.08 g (0.005 mole) of **2** in 10 ml of glacial acetic acid was treated with a 1.4 g (0.01 mole) of 2-furylglyoxylic acid (**3c**) and the reaction mixture was heated under reflux for 8 hours. After cooling, the precipitate was collected on a filter, washed with ethanol and recrystallized from dimethylformamide to produce 1.1 g (67%) of dark brown needles, mp 282-283°, Rf 0.23, silica gel G, ethyl acetate/*n*-hexane (1:1); uv (ethanol): λ max (log ε) 209 (4.44), 240 (4.67), 306 (4.28), 339 (4.09), 375 (4.19) nm; λ min (log ε) 218 (4.41), 284 (4.18), 331 (4.04), 345 (4.05) nm; ir (potassium bromide): 3079 (=C-H), 1644 (C=O), 1585, 1535 (C=N/C=C), 1323 (C-N), 1017 (C-O), 754 (C-S) cm^{-1}; ^1H nmr (DMSO-d_6): δ (ppm) 6.84 (m, 1H, H-3′), 7.70-7.85 (m, 2H, H-2, 3), 7.90 (m, 1H, H-4′), 8.09-8.17 (m, 3H, H-1, 4, 5), 8.18 (m, 1H, H-2′), 9.64 (d, 1H, H-6, J = 8.7 Hz); ms: (70 eV) m/z (%) 319 (M^+, 96), 226 (M-C_4H_3OCN, 100), 198 ($C_{11}H_6N_2S$, 86), 172 ($C_{10}H_6NS$, 32), 154 ($C_{10}H_6N_2$, 34), 140 ($C_{10}H_6N$, 20).

Anal. Calcd. for $C_{17}H_9N_3O_2S$: C, 63.94; H, 2.84; N, 13.16. Found: C, 64.04; H, 2.71; N, 13.11.

10-(2-Thienyl)-9*H*-naphtho[1′,2′:4,5]thiazolo[3,2-*b*][1,2,4]triazin-9-one (**5d**).

Procedure A.

A solution of 1.08 g (0.005 mole) of **2** in 100 ml of ethanol was treated with 1.6 g (0.01 mole) of 2-thienylglyoxylic acid (**3c**) and the reaction mixture was heated under reflux for 24 hours. After cooling, the precipitate was collected and recrystallized from dimethylformamide to produce 0.8 g (48%) of yellow needle crystals, mp 246-247°, Rf 0.60, silica gel G, ethyl acetate/*n*-hexane (1:2); uv (ethanol): λ max (log ε) 209 (4.45), 240 (4.65), 309 (2.24), 382 (4.18) nm; λ min (log ε) 218 (4.43), 287 (4.19), 334 (3.98) nm; ir (potassium bromide): 3091, 3080 (=C-H), 1652 (C=O), 1529, 1476 (C=N/C=C), 1320 (C-N), 740 (C-S) cm^{-1}; ^1H nmr (DMSO-d_6): δ (ppm) 7.35 (m, 1H, H-4′), 7.71-7.90 (m, 2H, H-2, 3), 7.98 (m, 1H, H-3′), 8.10-8.19 (m, 3H, H-1, 4, 5), 8.47 (m, 1H, H-5′), 9.54 (d, 1H, H-6, J = 8.7 Hz); ms: (70 eV) m/z (%) 335 (M^+, 67), 226 (M-C_4H_3SCN, 100), 198 ($C_{11}H_6N_2S$, 21), 172 ($C_{10}H_6NS$, 11), 154 ($C_{10}H_6N_2$, 25).

Anal. Calcd. for $C_{17}H_9N_3OS_2$: C, 60.88; H, 2.70; N, 12.53. Found: C, 60.41; H, 2.50; N, 12.70.

Procedure B.

A solution of 1.08 g (0.005 mole) of **2** and 1.6 g (0.01 mole) of **3d** in 10 ml of glacial acetic acid was heated under reflux for 8 hours. After cooling, the precipitate was collected through filtration. The filtrate was concentrated under reduced pressure and the residue was suspended in 25 ml of ethanol and then filtered. The combined solid product was recrystallized from dimethylformamide to afford 0.8 g (48%) of compound **5a** as yellow needle crystals, mp 246-247°.

9-(2-Thenoyl)naphtho[1′,2′:4,5]thiazolo[3,2-*b*][1,2,4]triazole (**6d**).

The ethanolic mother liquid from the above reaction was further concentrated and the crude product was purified by passing through silica gel column using ethyl acetate/*n*-hexane (1:3) as eluent. The separated product was recrystallized from benzene to give 1.0 g (12%) of yellow crystals, mp 294-295°, Rf 0.34, silica gel G, ethyl acetate/*n*-hexane (1:2); ir (potassium bromide): 3060 (=C-H), 1595 (C=O), 1490, 1482 (C=N/C=C), 1225 (C-N), 698 (C-S) cm^{-1}; ^1H nmr (DMSO-d_6): δ (ppm) 7.42 (m, 1H, H-4′), 7.84 (m, 1H, H-3′), 7.95 (m, 1H, H-5′), 8.21-8.31 (m, 2H, H-2, 3), 8.35-8.41 (m, 2H, H-4, 5), 8.70 (m, 1H, H-1), 11.0 (d, 1H, H-6, J = 8.2 Hz); ms: (70 eV) m/z (%) 335 (M^+, 66), 224 (M-C_4H_3SCO, 100), 198 ($C_{11}H_6N_2S$, 11), 184 ($C_{11}H_6NS$, 45), 172 ($C_{10}H_6NS$, 10), 140 ($C_{10}H_6N$, 72).

Anal. Calcd. for $C_{17}H_9N_3OS_2$: C, 60.88; H, 2.70; N, 12.53. Found: C, 60.57; H, 2.41; N, 12.84.

In Vitro Anti-HIV Evaluation.

Compound **5a** (NSC-631907) was selected for *in vitro* anti-HIV evaluation. The experiment was performed in the Antiviral Evaluation Branch, National Cancer Institute, Bethesda, Maryland, USA, using the microculture formazan assay procedure [6]. It showed the cytotoxicity on uninfected cells with $IC_{50} > 4.9 \times 10^{-5}$ *M*, but no protective activity on infected cells was observed.

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