Novel and Potent Adenosine 3′,5′-Cyclic Phosphate Phosphodiesterase III Inhibitors: Thiazolo[4,5-*b*][1,6]naphthyridin-2-ones

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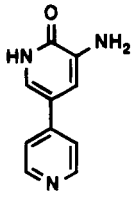
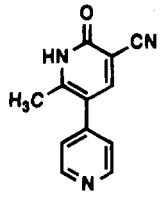
The transformation of 3-bromo-1,6-naphthyridin-2(1*H*)-ones **8** to thiazolo[4,5-*b*][1,6]naphthyridin-2(1*H*)-ones **12** resulted in a 2–9-fold increase in cAMP phosphodiesterase (PDE) III inhibitory potency. Unlike the secondary binding sites on the cAMP PDE III isozyme which interact with the methyl group of milrinone (**2**) and CI-930 (**4**), the site which interacts with the 5-substituents of 1,6-naphthyridin-2(1*H*)-ones and the 8-substituents of thiazolo[4,5-*b*][1,6]-naphthyridin-2(1*H*)-ones **12** is able to accommodate a diverse group of substituents which have different steric and electronic requirements.

Introduction

Congestive heart failure (CHF) is a widespread, highly malignant, and ultimately fatal disease[1] with an estimated 3–4 million cases in the United States alone. It is well-known that impairment of myocardial contractility is involved in the development of CHF; however, the molecular mechanisms for the initiation and progression of the disease are poorly understood.[2] Traditional therapies including a combination of diuretics and digitalis,[3] and more recently, angiotensin converting enzyme (ACE) inhibitors,[4] have attempted to correct the cardiac and circulatory deficiencies of CHF rather than intervene in the disease process. The discovery of the novel nonglycosidic, clinically useful, cardiotonic agents amrinone (**1**)[5] and milrinone (**2**)[6] in our laboratory stimulated intensive research in this area resulting in the synthesis of about a dozen diverse heterocycles[7] which have received considerable attention in the last 15 years. The positive inotropic and vasodilatory action of these agents are directly related to the inhibition of guanosine 3′,5′-cyclic phosphate-inhibitable adenosine 3′,5′-cyclic phosphate phosphodiesterase (cAMP PDE III).[8]



1
amrinone



2
milrinone

Bristol et al.[9] proposed a hypothetical five-point model for the positive ionotropic activity due to cAMP PDE III inhibition. However, later work showed that there are only two common features of the cAMP PDE III inhibitors synthesized thus far, an amide (-NHCO-) functionality and overall planar topography of the molecule.[7] Addtionally, in some compounds the introduction of a small lipophilic moiety, the size of a methyl group, has been shown to dramatically increase the in vitro cAMP PDE III inhibitory potency,[10] and this group has been proposed to interact at a secondary binding site occupied by a portion of the sugar moiety of cAMP. However, in milrionone (**2**) and CI-930 (**4**), the methyl groups are on opposite sides with respect to the -NHCO- functional group. Furthermore, for both of these compounds, the size of the alkyl group is very critical for cAMP PDE III activity. Homologation to ethyl and propyl groups resulted in a dramatic loss of in vitro potency.[10] It has been pointed out[10] that the presence of a single small lipophilic pocket on the cAMP PDE III isozyme which can accommodate only a small methyl group cannot explain similar results when this group is located on the opposite sides as in the case of milrione (**2**) and CI-930 (**4**). Either two identical pockets must be involved or the effects on potency are attributable to some other phenomenon that is common to both positions.[10] We recently reported the synthesis[11] and cAMP PDE III inhibitory activity[12] of a series of novel 1,6-naphthyridin-2-ones. Medorinone (**3**), the optimum compound of the series, was selected for advanced evaluation.[13] Like **2** and **4**, the presence of a substituent at the 5-position of medorinone (**3**) is essential for in vitro cAMP PDE III activity. For example, the replacement of methyl by hydrogen in **3** resulted in a 34-fold drop in potency[12] which is similar to that observed for **4**.[10] In comparison, the loss in potency for **2** is 100-fold.[10] This is not a coincidence; the methyl substituents in **3** and **4** are on the same side with respect to the -NHCO- functional group. Unlike the pockets on the cAMP PDE III isozyme which interact with the methyl group of **4** and **2**, the pocket which interacts with the 5-substituted of **3** is able to accommodate not only higher alkyl homologs but also groups such as phenyl, 4-substituted phenyl, heteroaryl, and alkylamino,[14] giving increased potency in some cases.[12] These groups differ greatly from the methyl group in terms of polarity and electronic and steric requirements. These results suggest that either subpockets exists within this pocket which accommodate these diverse groups or this pocket is very flexible and undergoes conformational and electronic changes to accommodate a diverse group of substituents. To explore this phenomenon further, we converted **3** and some of its active analogs to thiazolo-[4,5-*b*][1,6]naphthyridin-2(3*H*)-ones **12** hoping that this

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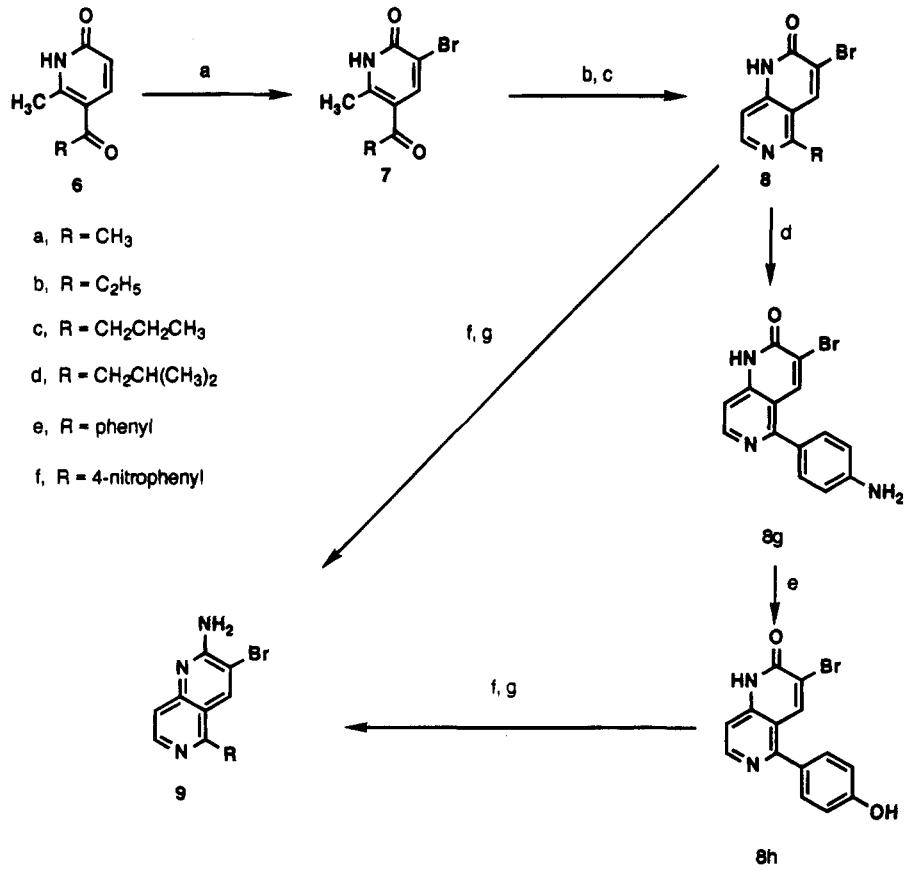
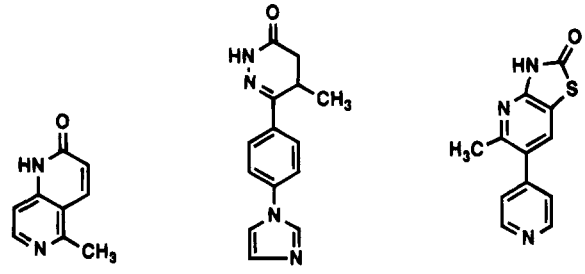
Scheme 1[a]



[a] (a) NBS/CCl_4; (b) $[(CH_3)_2N]_2CHOC(CH_3)_3$/*p*-dioxane; (c) NH_4OAc/DMF; (d) $SnCl_2$/HCl; (e) $NaNO_2/H_2SO_4$; (f) $POCl_3$; (g) NH_3/EtOH. When R = 4-nitrophenyl, reaction path d will convert **8f** to **8g**.

transformation would result in enhancement of the in vitro cAMP PDE III activity as was the case with the conversion of **2** to thiazolo[4,5-*b*]pyridin-2(3*H*)-one **5** which resulted in a 15-fold improvement of in vitro potency.[15]



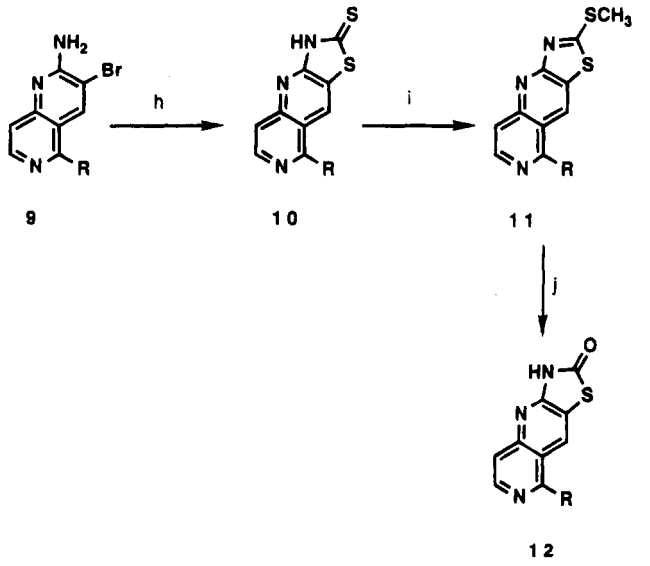
Chemistry

The synthesis of compounds **12a,e** was reported recently.[16] The other compounds were prepared by following the same procedure outline in Scheme 1. Bromination od pyridinone **6** with NBS provided bromopyridone **7** which was reacted with Bredereck's reagent, and the resulting intermediate upon treatment with ammononium acetate gave bromonaphthyridinone **8**. Reaction of **8** with phosphorus oxychloride followed by ammonia in an autoclave gave 2-amino-3-bromonaphthyridine **9** which was subsequently converted to thiazolo[4,5-*b*][1,6]naphthyridinone **12** in three steps (Scheme 2). The preparation of **12g** (R = 4 aminophenyl) from 5-(4-nitrophenyl)naphthyridinone **8f** or 5-(4-aminophenyl)naphthyridinone **8g** was unsuccessful due to complications arising from the reaction of ethyl potassium xanthate with the amino and nitro groups. In order to prepare 8-(4-hydroxyphenyl)thiazolonaphthyridinone **12h**, **8f** was reduced with stannous chloride and the resulting amino derivative **8g** was converted to 5-(4-hydroxyphenyl)naphthyridinone **8h** by diazotization. Nitration of **12h** gave **13**. The diazotization of anilino derivative **14** unexpectedly resulted in nitrophenol **15**. The structure of **15** was confirmed by ^{1}H-NMR and MS spectra and elemental analyses (Scheme 3).

Biology

Thiazolonaphthyridinones **12** showed improved cAMP PDE III in vitro activity over the corresponding naphthyridinones with the exception of compound **12c**. The maximum increase in potency (9-fold) was observed for **12a** derived from medorinone (**3**). The other four compounds (**12b,d,e,h**) showed a 2–3-fold increase of in vitro potency. Compound **13** was found to be 3 times as active as **12h**. This may be due to increased acidity of the phenolic group or increased polarity of the nitrophenol. The greater potency of thiazolonaphthyridinones **12** over naphthyridinones[12] is probably due to the presence of a basic nitrogen, N(4), adjacent to the amide group. The amide group (-NHCO-) which is a common feature of all the cAMP PDE III inhibitors has been proposed[10] to occupy the same binding site (known as the primary site) on the cAMP PDE III isozyme as the phosphate moiety of cAMP. The basic nitrogen N(4) may strengthen the binding at the primary site via H-bonding or ionic interaction. The secondary binding

Scheme 2[a]



[a] (h) $H_5C_2OC(=S)SK$.NMP; (i) CH_3I/K_2CO_3/DMF; (j) CH_3ONa/DMF.

site for the interaction of 5-substituents of naphthyridinones and 8-substituents of thiazolonaphthyridinones **12** is able to accommodate a diverse group of substituents which have very different steric requirements and marked differences in polarity. Further synthesis in conjunction with modeling studies and X-ray crystallography of active compounds in both series would be helpful in developing a clear understanding of the pharmacophore for these compounds and will be the subject of a future publication.

Conclusion

Transformation of naphthyridinones[11] to thiazolonaphthyridinones resulted in more potent cAMP PDE III inhibitors with in vitro activity in the nanomolar range. Unlike the secondary binding sites on the cAMP PDE III isozyme which interact with the methyl groups of milrinone (**2**) and CI-930 (**4**), the site where the 5-substituents of naphthyridinones[11] and the 8-substituents of thiazolonaphthyridinones **12** bind is able to accommodate a diverse group of substituents with different steric and electronic requirements.

Experimental Section

General. Melting points were determined in open capillaries in an oil bath and are uncorrected. The ^{1}H-NMR spectra were obtained on a General Electric QE-300 spectrometer in deuterated trifluoroacetic acid unless otherwise noted. All ^{1}H-NMR spectra used tetramethylsilane as an internal standard, and chemical shifts are reported in parts per million in δ units. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. Each compound gave elemental analysis within ±0.45% of the theoretical values for C, H, N.

General Procedure for the Preparation of 5-Alkanoyl-(or aroyl)-3-bromo-6-methylpyridin-2(1*H*)-ones 7. A stirred mixture of 5-alkanoyl(or aroyl)-6-methylpyridin-2(1*H*)-one **6**[11,12] (0.1 mol), *N*-bromosuccinimide (0.11 mol), benzoyl peroxide (0.4 mmol), and CCl_4 (250 mL) was heated under reflux for 8 h and then concentrated on a rotary evaporator. The residual light orange solid was slurried in water (300 mL), collected, and recrystallized.

3-Bromo-5-propanoyl-6-methylpyridin-2(1*H*)-one (7b): yield 82%; mp 202–205 °C (EtOH); ^{1}H-NMR ($CDCl_3$) δ 13.01 (s, 1H), 8.31 (s, 1H), 2.86 (q, 2H), 2.75 (s, 3H), 1.21 (t, 3H). Anal. ($C_9H_{10}BrNO_2$) C, H, N.

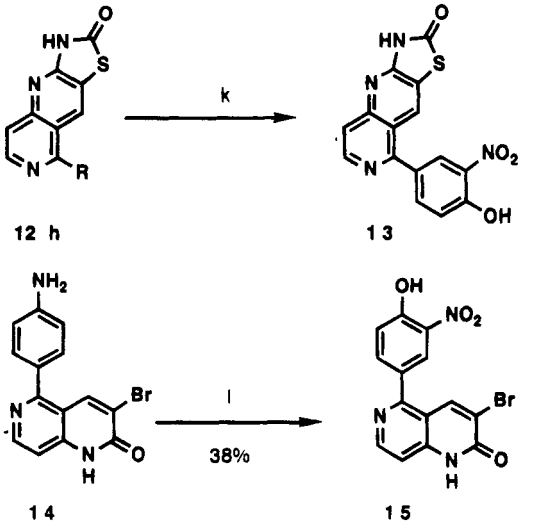
3-Bromo-5-butanoyl-6-methylpyridin-2(1*H*)-one (7c): yield 87%; mp 184–186 °C (2-PrOH); ^{1}H-NMR ($CDCl_3$) δ 13.00 (s, 1H), 8.30 (s, 1H), 2.98 (t, 2H), 2.81 (s, 3H), 1.81 (hextet, 2H), 1.08 (t, 3H). Anal. ($C_{10}H_{12}BrNO_2$) C, H, N.

3-Bromo-6-methyl-5-(3-methylbutanoyl)pyridin-2(1*H*)-one (7d): yield 58%; mp 177–178 °C (2-PrOH); ^{1}H-NMR ($CDCl_3$) δ 13.02 (s, 1H), 8.25 (s, 1H), 2.70 (s, 3H), 2.65 (d, 2H), 2.31 (m, 1H), 1.01 (d, 6H). Anal. ($C_{11}H_{14}BrNO_2$) C, H, N.

3-Bromo-6-methyl-5-(4-nitrobenzoyl)pyridin-2(1*H*)-one (7f): yield 75%; mp 292–294 °C (DMF); ^{1}H-NMR δ 8.51 (d, 2H), 8.25 (s, 1H), 8.04 (d, 2H), 2.71 (s, 3H). Anal. ($C_{13}H_9BrN_2O_4$) C, H, N.

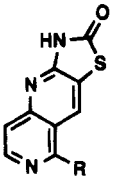
General Procedure for the Preparation of 5-Alkyl(or aryl)-3-bromo-1,6-naphthyridin-2(1*H*)-ones 8. To a stirred mixture of **7** (0.1 mol) and *p*-dioxane (200 mL) was added Bredereck's reagent (0.11 mol). The resulting mixture was heated under reflux for 5 h, and the resulting yellow insoluble product was collected, dried (95–98% crude yield), and added to a stirred mixture of ammonium acetate (0.2 mol) and DMF

Scheme 3



[a] (k) KNO_3/CF_3CO_2H; (l) $NaNO_2/H_2SO_4$.

Table 1. In Vitro cAMP PDE III Activity[a]



compd	R	cAMP PDE III IC_{50} (μM)[b]
12a	CH_3	0.062 (0.057–0.066) [0.55]
12b	C_2H_5	0.022 (0.020–0.025) [0.048]
12c	$CH_2CH_2CH_3$	0.067 (0.062–0.072) [0.048]
12d	$CH_2CH(CH_3)_2$	0.33 (0.30–0.35) [0.57]
12e	phenyl	0.43 (0.36–0.52) [1.40]
12h	4-hydroxyphenyl	0.24 (0.23–0.25) [0.60]
13	4-hydroxy-3-nitrophenyl	0.083 (0.078–0.087) [0.34]

[a] The preparation of cAMP PDE III and the assay for measuring the in vitro activity were published in refs 12 and 15. [b] Mean of three determinations (95% confidence interval) [IC_{50} values for the corresponding 1,6-naphthyridin-2(1*H*)-ones].[12]

(150 mL). The reaction mixture was heated at 95–100 °C for 5 h and concentrated under reduced pressure; the tan solid residue was slurried in water (200 mL), collected, and recrystallized to provide **8**.

3-Bromo-5-ethyl-1,6-naphthyridin-2(1*H*)-one (8b): yield 86%; mp 215–216 °C (EtOH); ^{1}H-NMR δ 8.79 (s, 1H), 7.83 (d, 1H), 3.50 (q, 2H), 1.60 (t, 3H). Anal. ($C_{10}H_9BrN_2O$) C, H, N.

3-Bromo-5-propyl-1,6-naphthyridin-2(1*H*)-one (8c): yield 85%; mp 218–219 °C (MeOH); ^{1}H-NMR δ 8.86 (s, 1H), 8.61 (d, 1H), 7.88 (d, 1H), 3.48 (t, 2H), 2.00 (hextet, 2H), 1.20 (t, 3H). Anal. ($C_{11}H_{11}BrN_2O$) C, H, N.

3-Bromo-5-(2-methylpropyl)-1,6-naphthyridin-2(1*H*)-one (8d): yield 83%; mp 222–224 °C (MeOH); ^{1}H-NMR δ 8.85 (s, 1H), 8.66 (d, 1H), 7.77 (d, 1H), 3.36 (d, 2H), 2.25 (m, 1H), 1.24 (d, 6H). Anal. ($C_{12}H_{13}BrN_2O$) C, H, N.

3-Bromo-5-(4-nitrophenyl)-1,6-naphthyridin-2(1*H*)-one (8f): yield 92%; mp >300 °C (DMF); ^{1}H-NMR δ 8.86 (d, 1H), 8.72 (d, 2H), 8.49 (s, 1H), 8.18 (d, 2H), 8.01 (d, 1H). Anal. ($C_{14}H_8BrN_3O_3$) C, H, N.

General Procedure for the Preparation of 5-Alkyl(or aryl)-3-bromo-1,6-naphthyridin-2-amines 9. A mixture of **8** (0.1 mol) and $POCl_3$ (250 mL) was heated under reflux with stirring for 16 h and then concentrated under reduced pressure. The viscous oily residue was dissolved in $CHCl_3$ (150 mL) and poured into a vigorously stirred mixture of ice and concentrate aqueous ammonia. The resulting mixture was extracted with $CHCl_3$ (2 × 250 mL). Removal of $CHCl_3$ gave a solid residue which was added to ethanol saturated with ammonia (250 mL) cooled in an ice bath. The resulting mixture was heated in an autoclave at 100–105 °C for the 16 h and then cooled to room temperature. The mixture thus obtained was concentrated under reduced pressure. The solid residue was slurried in water (100 mL), collected, and recrystallized to yield **9**.

3-Bromo-5-ethyl-1,6-naphthyridin-2amine (9b): yield 92%; mp 194–195 °C (EtOH); ^{1}H-NMR ($CDCl_3$) δ 8.50 (d, 1H), 8.45 (s, 1H), 7.32 (d, 1H), 5.70 (br s, 2H), 3.17 (q, 2H), 0.93 (t, 3H). Anal. ($C_{10}H_{10}BrN_3$) C, H, N.

3-Bromo-5-propyl-1,6-naphthyridin-2-amine (9c): yield 71%; mp 178–180 °C (MeOH); ^{1}H-NMR δ 9.10 (s, 1H), 8.81 (d, 1H), 8.20 (d, 1H), 3.50 (t, 2H), 2.01 (m, 2H), 1.23 (t, 3H). Anal. ($C_{11}H_{12}BrN_3$) C, H, N.

3-Bromo-5-(2-methylpropyl)-1,6-naphthyridin-2-amine (9d): yield 52%; mp 203–204 °C (MeOH); ^{1}H-NMR δ 9.08 (s, 1H), 8.80 (d, 1H), 8.23 (d, 1H), 3.40 (d, 2H), 2.25 (m, 1H), 1.24 (d, 6H). Anal. ($C_{12}H_{14}BrN_3$) C, H, N.

3-Bromo-5-(4-hydroxyphenyl)-1,6-naphthyridin-2-amine (9h): yield 65%; mp 280–283 °C (MeOH); ^{1}H-NMR δ 8.93 (s, 1H), 8.87 (d, 1H), 8.24 (d, 1H), 7.75 (d, 2H), 7.35 (d, 2H). Anal. ($C_{14}H_{10}BrN_{30}$) C, H, N.

General Procedure for the Preparation of 8-Alkyl(or aryl)thiazolo[4,5-*b*][1,6]naphthyridine-2(3*H*)-thiones 10. A stirred mixture of **9** (0.1 mol), EtOC(=S)SK (0.2 mol), and NMP (200 mL) was heated in an oil bath at 165–170 °C for 7 h and then dissolved in hot water and filtered. The filtrate was acidified with acetic acid, and the resulting crystalline product was collected and dried to afford **10**.

8-Ethylthiazolo[4,5-*b*][1,6]naphthyridine-2(3*H*)-thione (10b): yield 98%; mp 304–305 °C; ^{1}H-NMR δ 9.10 (s, 1H), 8.67 (d, 1H), 8.30 (d, 1H), 3.75 (q, 2H), 1.70 (t, 3H). Anal. ($C_{11}H_9N_3S_2$) C, H, N.

8-Propylthiazolo[4,5-*b*][1,6]naphthyridine-2(3*H*)-thione (10c): yield 85%; mp ≥300 °C; ^{1}H-NMR δ 8.88 (s, 1H), 8.64 (d, 1H), 8.26 (d, 1h), 3.63 (t, 2H), 2.18 (m, 2H), 1.24 (t, 3H). Anal. ($C_{12}H_{11}N_3S_2$) C, H, N.

8-(2-Methylpropyl)thiazolo[4,5-*b*][1,6]naphthyridine-2(3*H*)-thione (10d): yield 88%; mp 285–289 °C; ^{1}H-NMR δ 8.98 (s, 1H), 8.65 (d, 1H), 8.23 (d, 1H), 3.50 (d, 2H), 2.31 (m, 2H), 1.21 (d, 6H). Anal. ($C_{13}H_{13}N_3S_2$) C, H, N.

8-(4-Hydroxyphenyl)thiazolo[4,5-*b*][1,6]naphthyridine-2(3*H*)-thione (10h): yield 95%; mp >300 °C; ^{1}H-NMR δ 8.79 (s, 1H), 8.71 (d, 1H), 8.31 (d, 1H), 7.74 (d, 2H), 7.33 (d, 2H). Anal. ($C_{15}H_9N_3OS_2$) C, H, N.

General Procedure for the Preparation of 8-Alkyl(or aryl)-2-(methylthio)thiazolo[4,5-*b*][1,6]naphthyridines 11. A mixture of **10** (0.1 mol), anhydrous milled K_2CO_3 (0.12 mol), and DMF (200 mL) was stirred at room temperature for 30 min and then treated with methyl iodide (0.1 mol) over a period of 20 min. After further stirring for 30 min, most of the DMF was removed under reduced pressure. The residue was washed with water and recrystallized to give **11**.

8-Ethyl-2(methylthio)thiazolo[4,5-*b*][1,6]naphthyridine (11b): yield 94%; mp 171–173 °C (2-PrOH); ^{1}H-NMR δ 8.78 (s, 1H), 8.61 (d, 1H), 7.79 (d, 1H), 3.30 (q, 2H), 2.91 (s, 3H), 1.44 (t, 3H). Anal. ($C_{12}H_{11}N_3S_2$) C, H, N.

2-(Methylthio)-8-propylthiazolo[4,5-*b*][1,6]naphthyridine (11c): yield 65%; mp 180–181 °C (2-PrOH); ^{1}H-NMR δ 9.08 (s, 1H), 8.70 (d, 1H), 8.26 (d, 1H), 3.64 (t, 2H), 2.08 (m, 2H), 1.22 (t, 3H). Anal. ($C_{13}H_{13}N_3S_2$) C, H, N.

8-(2-Methylpropyl)-2-(methylthio)thiazolo[4,5-*b*][1,6]-naphthyridine (11d): yield 66%; mp 132–134 °C (EtOH); ^{1}H-NMR δ 9.18 (s, 1H), 9.04 (d, 1H), 8.65 (d, 1H), 3.73 (d, 1H), 3.15 (s, 3H), 2.40 (m, 2H), 1.26 (d, 6H). Anal. ($C_{14}H_{15}N_3S_2$) C, H, N.

8-(4-Hydroxyphenyl)-2-(methylthio)thiazolo[4,5-*b*][1,6]-naphthyridine (11h): yield 78%; mp 245–248 °C (MeOH/$CDCl_3$); ^{1}H-NMR (DMSO-d_6) δ 9.85 (br s, 1H), 9.19 (s, 1H), 8.72 (d, 1H), 7.85 (d, 1H), 7.63 (d, 2H), 6.99 (d, 2H). Anal. ($C_{16}H_{11}N_3OS_2$) C, H, N.

General Procedure for the Preparation of 8-Alkyl(or aryl)thiazolo[4,5-*b*][1,6]naphthyridin-2(3*H*)-ones 12. A mixture of **11** (**0**.1 mol), sodium methoxide (0.2 mol), and DMF (100 mL) was stirred at ambient temperature for 7 h and then concentrated under reduced pressure. The residue was dissolved in water and acidified with acetic acid. The resulting precipitate was collected and recrystallized to provide **12**.

8-Ethylthiazolo[4,5-*b*][1,6]naphthyridin-2(3*H*)-one (12b): yield 75%; mp 295–300 °C (MeOH); ^{1}H-NMR δ 9.12 (s, 1H), 8.61 (d, 1H), 8.31 (d, 1H), 3.76 (q, 2H), 1.72 (t, 3H). Anal. ($C_{11}H_9N_3OS$) C, H, N.

8-Propylthiazolo[4,5-*b*][1,6]naphthyridin-2(3*H*)-one (12c): yield 57%; mp 262–263 °C (MeOH); ^{1}H-NMR δ 9.08 (s, 1H), 8.65 (d, 1H), 8.26 (d, 1H), 3.16 (t, 2H), 2.05 (hextet, 2H), 1.14 (t, 3H). Anal. ($C_{12}H_{11}N_3OS$) C, H, N.

8-(2-Methylpropyl)thiazolo[4,5-*b*][1,6]naphthyridin-2(3*H*)-one (12d): yield 63%; mp 228–229 °C (EtOH); ^{1}H-NMR δ 9.14 (s, 1H), 8.73 (d, 1H), 8.29 (d, 1H), 3.55 (d, 2H), 3.35 (m, 2H), 1.18 (d, 6H). Anal. ($C_{13}H_{13}N_3OS$) C, H, N.

8-(4-Hydroxyphenyl)thiazolo[4,5-*b*][1,6]naphthyridin-2(3*H*)-one (12h): yield 75%; mp >300 °C (MeOH); ^{1}H-NMR δ 8.97 (s, 1H), 8.79 (d, 1H), 8.38 (d, 1H), 7.81 (d, 2H), 7.42 (d, 2H). Anal. ($C_{15}H_9N_3O_2S$) C, H, N.

3-Bromo-5-(4-aminophenyl)-1,6-naphthyridin-2(1*H*)-one (8g). Compound **8f** (120 g, 0.33 mol) was add to a stirred solution of $SnCl_2{\cdot}2H_2O$ (226 g, 1 mol), H_2O (200 mL), and concentrated HCl (800 mL). The resulting mixture was heated at 90–95 °C for 5 h and then left at room temperature overnight. The dull yellow, solid product was collected, washed with cold 6 N HCl, and then suspended in water (400 mL). The resulting stirred slurry was made neutral (pH ≈ 7) by treating with concentrated aqeuous ammonia. The yellow precipitate was collected, washed with water, dried, and recrystallized from DMF to afford 81.7 g (78%) of **8g**, mp >300 °C. Anal. ($C_{14}H_{10}BrN_3O$) C, H, N.

5-(4-Hydroxyphenyl)-3-bromo-1,6-naphthyridin-2(1*H*)-one (8h). To a vigorously stirred solution of **8g** (72 g, 0.23 mol) and 50% aqueous sulfuric acid (500 mL) cooled in an ice bath was added a solution of sodium nitrite (16.89 g, 0.24 mol) in water (50 mL) over a period of 1 h at 0–5 °C. The resulting thick orange mixture was further stirred in an ice bath for 3 h, left at room temperature overnight, and then heated at 60–65 °C. After the evolution of nitrogen stopped (3 h), the mixture was cooled and the crystalline product was collected, washed with water, and recrystallized from DMF to afford 65.2 g (91%) of **8h**: mp >300 °C; ^{1}H-NMR δ 8.70 (d, 1H), 8.65 (s, 1H), 7.90 (d, 1H), 7.70 (d, 2H), 7.32 (d, 2H). Anal. ($C_{14}H_9BrN_2O_2$) C, H, N.

8-(4-Hydroxy-3-nitrophenyl)thiazolo[4,5-*b*][1,6]naphthyridin-2(3*H*)-one (13). To a stirred solution of **12h** (0.4 g, 1.36 mmol) in trifluoroacetic acid (10 mL) cooled in an ice bath was added potassium nitrate (0.14 g, 1.38 mmol). The resulting solution was allowed to come to room temperature,

maintained under these conditions overnight, and concentrated to dryness under reduced pressure. The light orange, solid residue was treated with 5% aqueous sodium acetate (10 mL) and collected. Recrystallization from DMF/EtOH gave 0.42 g (91%) of **13**: mp >300 °C; ^{1}H-NMR δ 8.96 (d, 1H), 8.74 (s, 1H), 8.25 (s, 1H), 7.92 (d, 1H), 7.71 (d, 1H), 7.34 (d, 1H). Anal. ($C_{15}H_8BrN_4O_4S$) C, H, N.

5-(4-Hydroxy-3-nitrophenyl)-1,6-naphthyridin-2(*H*)-one (15). To a stirred solution of naphthyridinone **14**[12] (5.0 g, 21.1 mmol) dissolved in 50% aqueous H_2SO_4 (50 mL) cooled in an ice/MeOH bath at −5 °C was added a solution of $NaNO_2$ in water (10 mL) over a period of 30 min. The resulting solution was allowed to come to room temperature and stirred overnight. The brown, gummy precipitate was collected and recrystallized from DMF to give 2.26 g (38%) of **15**: mp >300 °C; MS *m/z* 283 (M^+, 80); ^{1}H-NMR δ 8.55 (d, 1H), 8.14 (d, 1H), 7.95 (d, 1H), 7.81 (dd, 1H), 7.29 (d, 1H), 7.25 (d, 1H), 6.55 (d, 1H). Anal. ($C_{14}H_9N_3O_4$) C, H, N.

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