Synthesis of new 4-(phenylamino)thieno[2,3-*b*]pyridines and derivatives of the novel benzo[*b*]thieno[3,2-*h*]-1,6-naphthyridine tetracyclic system

Luiz C. S. Pinheiro,[a] Júlio C. Borges,[a] César D. Oliveira,[a] Vitor F. Ferreira,[a] Gilberto A. Romeiro,[a] Isakelly P. Marques,[a] Paula A. Abreu,[b] Izabel C. P. P. Frugulheti,[b] Carlos R. Rodrigues,[a,d] Magaly G. Albuquerque,[c] Helena C. Castro,[b]* and Alice M. R. Bernardino[a]*

[a]Universidade Federal Fluminense, Instituto de Química, Departamento de Química Orgânica, Programa de Pós-Graduação em Química Orgânica, Campus do Valonguinho, CEP 24210-150, Niterói, RJ, Brazil

[b]Universidade Federal Fluminense, Instituto de Biologia, Departamento de Biologia Celular e Molecular, CEP 24020-150, Niterói, RJ, Brazil

[c]Universidade Federal do Rio de Janeiro, Instituto de Química, Departamento de Química Orgânica, 21949-900, Rio de Janeiro, RJ, Brazil.

[d]Universidade Federal do Rio de Janeiro, Faculdade de Farmácia, ModMolQSAR, 24020-150, Rio de Janeiro, RJ, Brazil

E-mail: gqolice@vm.uff.br, hcastro@vm.uff.br

Abstract

Recently 1-hydroxyacridone derivatives were described as a new class of non-nucleoside inhibitors of Herpes Simplex Virus-1 (HSV-1), the agent of the most common human diseases. Based on these molecules, we applied rigid analogue and isosteric replacement approaches to design and synthesize five new benzo[*b*]thieno[3,2-*h*]-1,6-naphthyridines derivatives **8a-e** as feasible anti-HSV prototypes. Herein we described the synthesis of this series of compounds and a theoretical evaluation of the drug score and drug likeness of these compounds by using an *in silico* ADMET screening.

Keywords: Benzothienonaphthyridine, HSV-1, *in silico* ADMET screening

Introduction

Herpes simplex Virus 1 and 2 (HSV-1 and HSV-2) are agents of the most common humans diseases that include keratoconjutivicts, encephalitis, oral and genital infections. [1-4] Current clinical anti-herpes virus compounds used for the treatment of the HSV symptomatic recurrent

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infections are nucleoside (*i.e.* acyclovir) and non-nucleoside analogues (*i.e.* foscarnet).[1-9] However there are HSV drug-resistant strains that may also show cross-resistance with other anti-HSV agents (*i.e.* pencyclovir, and gancyclovir).[10-19] Therefore HSV resistance against current treatments requires the synthesis of new antiviral agents.[6, 18, 19]

Literature has described citrusinine-I **I** (Figure 1), an acridone alkaloid[20] and a series of 1-hydroxyacridones **II**[22-24] as being active against HSV-1. These compounds include 5-chloro-1,3-dihydroxyacridone ($ED_{50} = 4\pm1$ μM) possessing remarkable activity against *Herpes simplex* virus type 1 (HSV-1).[22-24] Recently our group described the synthesis of new derivatives of ethyl 4-(phenylamino)thieno[2,3-*b*]pyridine-5-carboxylate **III** and their activity against HSV-1.[25]

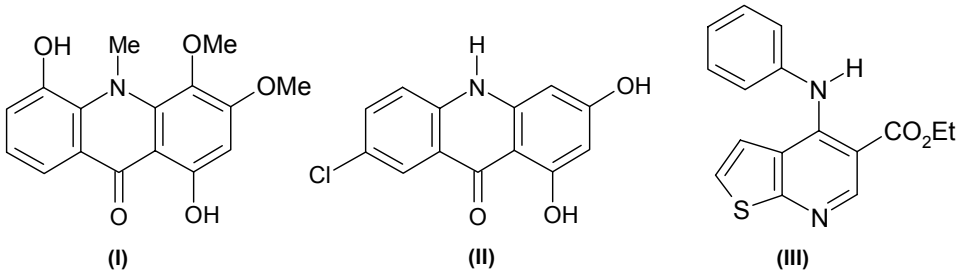


Figure 1. Citrusinine-I **(I)**, acridone **(II)** and ethyl 4-(phenylamino)thieno[2,3-*b*]pyridine-5-carboxylate **(III)**.

In this work, we used traditional medicinal chemistry principles, such as isosteric replacement and rigid analogue approaches, to design a new potentially antiviral benzo[*b*]thieno[3,2-*h*]-1,6-naphthyridine scaffold (Figure 2). The designing of this scaffold was based on two heterocycles, ethyl 4-(phenylamino)thieno[2,3-*b*]pyridine-5-carboxylate **III**, presenting anti-HSV-1 activity among a diverse antiviral profile,[25] and synthetic 1-hydroxyacridone derivatives **IV** with anti-HSV-1 activity.[25-30] Figure 2 shows that the acridone motif is a classical isoster of the benzo[*b*]-1,6-naphthyridine aromatic system, while the ring closure jointing the *N*-aryl rings of the 4-(phenylamino)thieno[2,3-*b*]pyridine-5-carboxylic acid system **V** leads to the benzo[*b*]thieno[3,2-*h*]-1,6-naphthyridine **VI** motif corresponding to the rigid analogue approach.

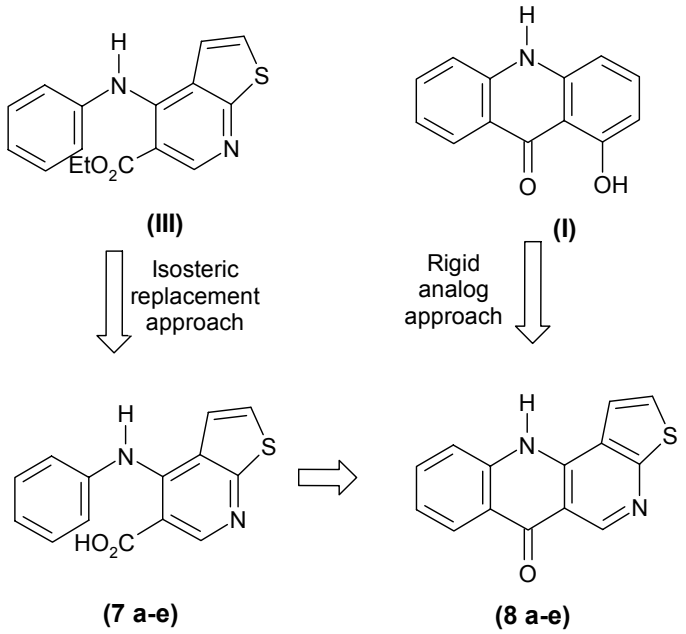


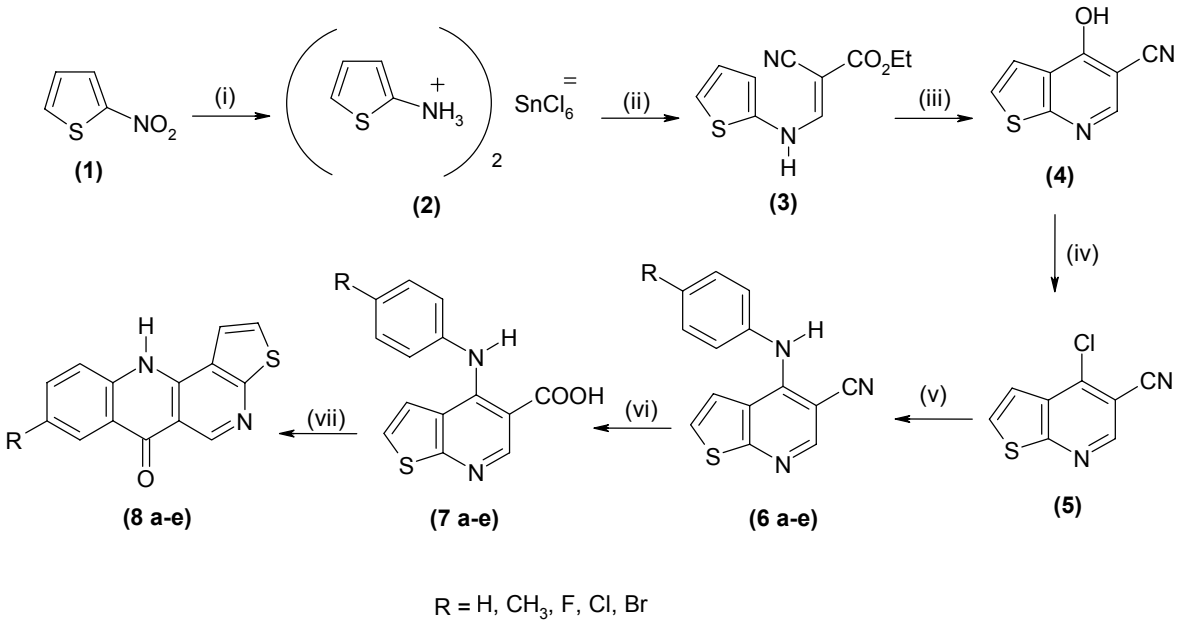
Figure 2

To investigate the impact of replacing the isosteric aromatic ring and the influence of the restricted flexibility imposed by the new benzo[*b*]thieno[3,2-*h*]-1,6-naphthyridine system, the compounds were submitted to an *in silico* ADMET screening to theoretically evaluate the drug score and drug likeness compared to acyclovir, a commercial antiviral drug, and 5-chloro-1,3-dihydroxyacridone.

Results and Discussion

Initially, 2-nitrothiophene **1** (Scheme 1) was reduced with tin and hydrochloric acid, leading to bis-(2-thienylammonium)hexachlorostannate **2**. This compound was immediately condensed with ethyl (ethoxymethylene)cyanoacetate in pyridine at 40-50^{o} C over a period of 24 hours to produce ethyl α-cyano-β-(*N*-2-thienylammonium)acrylate **3** in 88% yield. The cyclization of the acrylate was carried out by refluxing in Dowtherm for 40 minutes, after which 4-hydroxythieno[2,3-*b*]pyridine-5-carbonitrile **4** was isolated in 78% yield, by precipitating from petroleum ether. Compound **4** was easily chlorinated in refluxing phosphorus oxychloride at 110^{o} C over a period of 6 hours to afford 4-chlorothieno[2,3-*b*]pyridine-5-carbonitrile **5** in 76% yield. Nucleophilic displacement of the chlorine atom in compound **5** by aromatic amines was described in our previous report [26] to give 4-amino derivatives **6a-e.** This was achieved by heating at 140^{o} C without solvents for 4 hours an equimolar mixture of the appropriate aniline and compound **(5)**. The cyano group of 4-amino derivatives **6a-e** was hydrolysed to the new 4-(phenylamino)thieno[2,3-*b*]pyridine-5-carboxylic acids **7a-e** in moderate yields (40-50%), by

heating in a solution of ethylene glycol containing potassium hydroxide. Carboxylic acids **7a-e** were obtained in better yields (65-75%) upon acid hydrolysis of the corresponding 4-amino derivatives **6a-e** with 6 N hydrochloric acid. The cyclization of carboxylic acids **7a-e** into the respective benzo[*b*]thieno[3,2-*h*]-1,6-naphthyridine derivatives **8a-e** proceeded smoothly by refluxing in phosphorus oxychloride.



Scheme 1. Reagents and conditions: (i) Sn, 35% HCl, 45° C, (ii) ethyl (ethoxymethylene)cyanoacetate, pyridine, 40-50° C, 24 h, (iii) Dowtherm, 250° C, 30 min, (iv) $POCl_3$, 110° C, 6 h, (v) anilines, 140° C, 4 h, (vi) KOH, ethyleneglycol, reflux, 24 h, or 6 N HCl, reflux, 24 h, (vii) $POCl_3$, 110° C, 24 h.

To summarize, five new 4-(phenylamino)thieno[2,3-*b*]pyridine-5-carboxylic acids **7a-e**, and five derivatives of a new tetracyclic heteroaromatic system benzo[*b*]thieno[3,2-*h*]-1,6-naphthyridines **8a-e** were synthesized in good yields (65-78%).

In silico ADMET screening

The five benzo[*b*]thieno[3,2-*h*]-1,6-naphthyridine derivatives **8a-e** were submitted to an *in silico* ADMET screening (http://www.organic-chemistry.org/prog/peo/ and http://www.molinspiration.com/cgi-bin/properties) to analyze their overall potential drug likeness and drug score compared to the 5-chloro-1,3-dihydroxyacridone and the commercial antiviral drug, acyclovir. Therefore, we evaluated some parameters such as: a) the cLogP value, which refers to the molecular hydrophobicity and that affects drug absorption, bioavailability, hydrophobic drug-receptor interactions, metabolism of molecules, as well as their toxicity, b) the Lipinski "Rule of 5", which states that most "drug-like" molecules have logP <= 5, molecular

weight <= 500, number of hydrogen bond acceptors <= 10, and number of hydrogen bond donors <= 5; c) the toxicity risks (mutagenic, tumorigenic, and reproductive effects), d) the drug likeness value determined within the Fluka traded drugs collection, and e) the drug score that combines drug likeness, c log *P*, log *S*, molecular weight, and toxicity risks, and theoretically may be used to evaluate the drug potential of a compound [29] (Figure 4).

Our results revealed that the benzo[*b*]thieno[3,2-*h*]-1,6-naphthyridines lipophilicity (3.0>cLogP<3.8) is similar to that observed for acridone (cLogP=3.2) and is not greater than 5.0, feature important for drug good absorption and permeation according to Lipinski [29, 30] (Figure 4). The molecular volume and weight of benzo[*b*]thieno[3,2-*h*]-1,6-naphthyridines (213Å>MV<231Å and 265Da>MW<330Da) are greater than acyclovir (MV = 188Å, MW= 225Da) and the acridone (MV = 206Å, MW= 261Da) but similar to more than 80% of all Fluka traded drugs (MW<450Da) and to that determined by Lipinski "Rule of 5" [29]. According to our research, the benzo[*b*]thieno[3,2-*h*]-1,6-naphthyridines structure described herein fulfilled all Lipinski rules (2.6>LogP<3.5, 265Da>MW<330Da, hydrogen bond acceptors =3 and donors=1), which may suggest their potentiality for displaying some biological activity.

Two of the benzo[*b*]thieno[3,2-*h*]-1,6-naphthyridines **8a** and **8d** show positive drug likeness values even higher than acyclovir and acridone, which suggests the presence of active fragments frequently present in the commercial drugs. Interestingly, the 8-chlorobenzo[*b*]thieno[3,2-*h*]-1,6-naphthyridin-6(11*H*)-one **8d** derivative is analogous to 5-chloro-1,3-dihydroxyacridone, a point that could be well is favour of finding antiviral activity in this compound. In addition, naphthyridine derivatives show equivalent values in the drug score compared with the antiviral acyclovir and acridone, which reinforces their overall drug-like structure.

According to our theoretical study, the naphthyridine derivatives **8a-e** show low tumorgenicity, mutagenicity and reproductive effects profiles (green scale) similar to acyclovir and the 5-chloro-1,3-dihydroxyacridone (not shown). It is important to notice that the toxicity predicted herein neither is a fully reliable toxicity prediction, nor guarantees that these compounds are completely free of any toxic effect. However, it reinforces the promising profile of these compounds for further experimental investigation [27, 28].

Conclusions

In acridones, the variation of the functional groups has impact on the activity as described in the literature. Due to the isosteric replacement and rigid analogue structure, the new series of benzo[*b*]thieno[3,4-*h*]-1,6-naphthyridines reported herein may have the potential to display an anti-HSV-1 profile. Although the Osiris risk alerts are not a fully reliable toxicity prediction, the theoretical low-toxicity profile of these compounds and their analogous drug likeness and drug score values compared to acyclovir and 5-chloro-1,3-dihydroxyacridone may suggest the potentiality of these compounds as new antiviral prototypes to be further investigated.

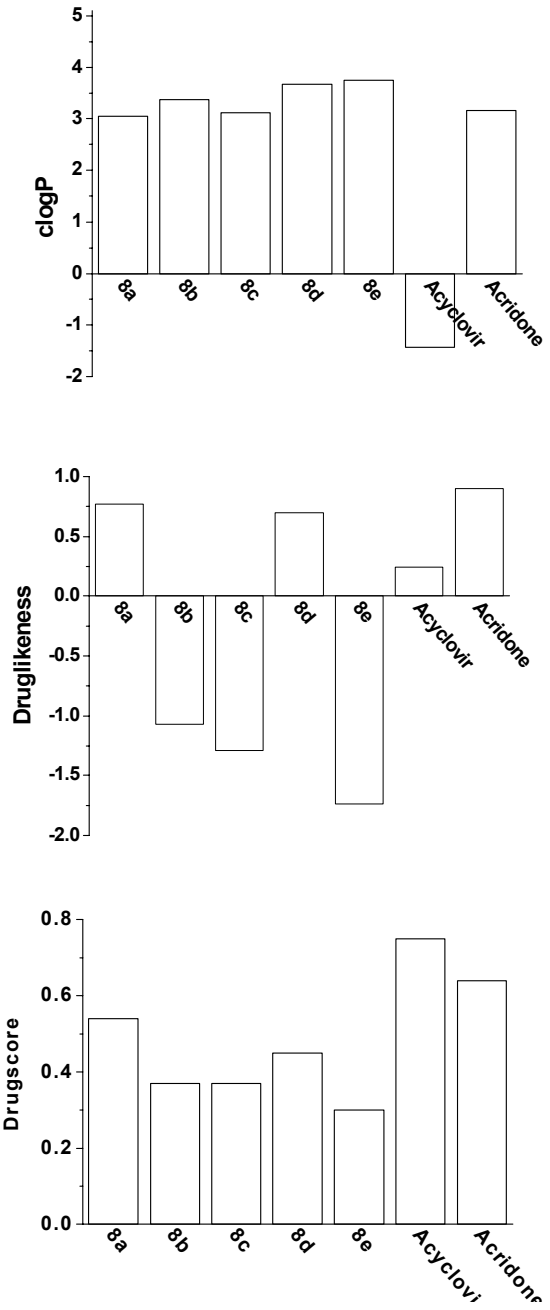


Figure 3. Calculated Log P, drug likeness and drug score values for the new benzo[*b*]thieno[3,2-*h*]-1,6-naphthyridine derivatives **(8a-e)** compared to acyclovir, the commercial antiviral drug, and 5-chloro-1,3-dihydroxyacridone using Osiris program (http://www.organic-chemistry.org/prog/peo/druglikeness.html).

Experimental Section

General Procedures. The ^{1}H Nuclear Magnetic Resonance (NMR) spectra obtained from Varian model Unity Plus spectrometer operating at 300.00 MHz, using tetramethylsilane as internal standard. The chemical shifts (δ) reported in ppm and the coupling constants (J) in Hertz. Fourier transform infrared (FT-IR) absorption spectra were recorded in a Perkin-Elmer mode Spectrum One FT-IR spectrophotometer. The solid samples were measured using potassium bromide pellets. Melting points (m.p.) were determined with a Fisher-Johns apparatus. TLC was carried out using silica gel F-254 Glass Plate (20 x 20 cm). All other reagents and solvents used were analytical grade. The EIMS spectra were recorded using a Finingan MAT 711 A instrument. The ionization energy was 70 eV with the source 200^o C and an accelerative voltage of 8 KV. The standard direct insertion probe introduced the samples. High-resolution data were obtained with the instrument using 10 000 resolution.

General procedure for synthesis of 4-(phenylamino)thieno[2,3-b]pyridine-5-carbonitriles (6 a-e)[26]

An equimolar (5 mmol) amounts of 4-chlorothieno[2,3-*b*]pyridine-5-carbonitrile and the appropriate aniline were heated in a silicone oil bath at 140° C for 2 hours. The mixture was diluted with CH_2Cl_2 and purified by preparative silica gel plates (Glass Backed TLC Silica Gel, Hard Layer 250μm, F-254), eluent CH_2Cl_2.

General procedure for synthesis of 4-(phenylamino)thieno[2,3-b]pyridine-5-carboxylic acids (7 a-e)

(a) Acid hydrolysis. A solution of 4-(phenylamino)thieno[2,3-*b*]pyridine-5-carbonitriles **(6 a-e)** (2 mmol) in 6 N HCl (5 mL) was heated under reflux for 24 h. On cooling, the mixture was alkalinized with 10 % aq. NaOH solution and the precipitated was filtered and recrystallized from a mixture of ethanol and water. Yield **(7 a-e)** 75, 70, 67, 75, 70%, respectively.

(b) Alkaline hydrolysis. A solution of 4-(phenylamino)thieno[2,3-*b*]pyridine-5-carbonitriles **(6 a-e)** (2 mmol), 2 g of potassium hydroxide pellets, 4 mL of ethyleneglycol, was heated under reflux for 24 h. On cooling mixture was acidified with diluted HCl (1:3), and the precipitated was filtered and recrystallized from a mixture of ethanol and water. Yield **(7 a-e)** 48, 40, 40, 50, 45%, respectively.

4-(Phenylamino)thieno[2,3-*b*]pyridine-5-carboxylic acid (7a). Yield: 75%, m.p.: > 300° C; IR (KBr, cm-1): (ν OH 3200-2800, ν C=O 1670); ^{1}H NMR (DMSO, δ in ppm) 7.54; (d, 6.0 Hz, 1H, H2), 6.40; (d, 6.0 Hz, 1H, H3), 8.98; (s, 1H, H6), 7.58-7.36; (m, 5Ar-H), 10.55; (s, 1H, COOH); ^{13}C NMR (75 MHz, DMSO-d_6, δ in ppm) 123.6; 121.9; 120.2; 147.4; 96.8; 153.4; 164.8; 129.5; 126.4; 139.2; 120.2; 170.2; EI (70 eV) m/z (%): $M^{+\cdot}$ 271.0593 (100).

4-(4'-Methylphenylamino)thieno[2,3-*b*]pyridine-5-carboxylic acid (7b). Yield: 70%, m.p.: > 300° C; IR (KBr, cm-1): (ν OH 3200-2800, ν C=O 1672); ^{1}H NMR (300 MHz, DMSO-d_6, TMS, δ in ppm) 7.52 (d, 6.00 Hz, 1H, H2); 6.33 (d, 6.0 Hz, 1H, H3); 8.94 (s, 1H, H6); 7.37 (d, 9.0 Hz,

2Ar-H); 7.29 (d, 9.0 Hz, 2Ar-H); 2.39 (s, 3H, CH_3); 10.58 (s, 1H, COOH); ^{13}C NMR (75 MHz, DMSO-d_6, δ in ppm) 124.5; 123.0; 119.7; 148.7; 97.8; 149.7; 165.4; 124.5; 133.1; 135.3; 136.3; 21.8; 170.3; EI (70 eV) m/z (%): $M^{+\cdot}$ 285.0854 (100).

4-(4'-Fluorophenylamino)thieno[2,3-*b*]pyridine-5-carboxylic acid (7c). Yield: 67%, m.p.: > 300° C; IR (KBr, cm-1): (ν OH 3200-2800, ν C=O 1670); ^{1}H NMR (300 MHz, DMSO-d_6, TMS, δ in ppm) 7.46 (d, 6.0 Hz, 1H, H2), 6.23 (d, 6.0 Hz, 1H, H3), 8.91 (s, 1H, H6), 7.24 (ddd, 8.7; 6.6; 2.1 Hz, 2Ar-H); 6.95 (ddd 8.7; 6.6; 2.1 Hz, 2Ar-H), 10.55; (s, 1H, COOH); ^{13}C NMR (75 MHz, DMSO-d_6, δ in ppm) 123.4; 121.5; 119.4; 148.0; 97.1; 147.5; 165.1; 127.3; 116.3; 134.4; 160.1; 170.5; EI (70 eV) m/z (%): $M^{+\cdot}$ 287.0424 (100).

4-(4'-Chlorophenylamino)thieno[2,3-*b*]pyridine-5-carboxylic acid (7d). Yield: 75%, m.p.: > 300° C; IR (KBr, cm-1): (ν OH 3200-2800, ν C=O 1671); ^{1}H NMR (300 MHz, DMSO-d_6, TMS, δ in ppm) 7.57; (d, 6.0 Hz, 1H, H2), 6.46; (d, 6.0 Hz, 1H, H3), 8.93; (s, 1H, H6), 7.54; (d, 8.7 Hz, 2Ar-H), 7.34; (d, 8.7 Hz, 2Ar-H), 10.50; (s, 1H, COOH); ^{13}C NMR (75 MHz, DMSO-d_6, δ in ppm) 127.2; 125.4; 119.8; 146.7; 98.7; 149.2; 126.9; 130.7; 133.2; 138.8; 169.6; EI (70 eV) m/z (%): $M^{+\cdot}$ 305.0112 (100).

4-(4'-Bromophenylamino)thieno[2,3-*b*]pyridine-5-carboxylic acid (7e). Yield: 70%, m.p.: > 300° C; IR (KBr, cm-1): (ν OH 3200-2800, ν C=O 1670); ^{1}H NMR (300 MHz, DMSO-d_6, TMS, δ in ppm) 7.62; (d, 6.0 Hz, 1H, H2), 6.55; (d, 6.0 Hz, 1H, H3), 8.98; (s, 1H, H6), 7.68; (d, 8.4 Hz, 2Ar-H), 7.30; (d, 8.4 Hz, 2Ar-H) 10.54; (s, 1H, COOH); ^{13}C NMR (75 MHz, DMSO-d_6, δ in ppm) 125.2; 121.5; 119.5; 146.3; 97.4; 149.4; 166.5; 120.4; 123.2; 126.8; 133.1; 121.5; 138.7; 169.7; EI (70 eV) m/z (%): $M^{+\cdot}$ 350.9538 (100).

General procedure for synthesis of bnzo[*b*]thieno[3,2-*h*]-1,6-naphthyridines (8 a-e)[31]

A mixture of the acids derivatives **(7 a-e)** (2 mmol) and phosphorus oxychloride (5 mL) was heated under reflux for 3 hours. The reaction mixture was poured over crushed ice. In some cases the excess of phosphorus oxychloride was removed under reduced pressure before invert crushed ice and neutralized with water. The resulting precipitate was collected and purified by flash column chromatography

Benzo[*b*]thieno[3,2-*h*]-1,6-naphthyridin-6(11*H*)-one (8a). Yield: 70%, m.p.: > 300° C; IR (FC, silica gel). (KBr, cm^{-1}); (ν NH 3422 - 3037, ν C=O 1629) ^{1}H NMR (300 MHz, DMSO-d_6, TMS, δ in ppm) 8.09 (d, 6.0 Hz, 1H, H1); 8.31 (d, 6.0 Hz, 1H, H2); 9.36 (s, 1H, H5); 8.42-7.50 (m, 4 Ar-H); ^{13}C NMR (75 MHz, DMSO-d_6, δ in ppm) 125.7; 120.3; 121.9; 145.8; 162.3; 124.1; 133.8; 126.5; 112.2; 140.9; 138.7; 128.2; 123.6; 120.5; EI (70 eV) m/z (%): M+. 252.0354 (100).

8-Methylbenzo[*b*]thieno[3,2-*h*]-1,6-naphthyridin-6(11*H*)-one (8b). Yield: 78%, m.p.: > 300° C; IR (KBr, cm^{-1}); (ν NH 3424 - 3094, ν C=O 1632) ^{1}H NMR (300 MHz, DMSO-d_6, TMS, δ in ppm) 8.03 (d, 6.0 Hz, 1H, H1); 8.28 (d, 6.0 Hz, 1H, H2); 9.31 (s, 1H, H5); 8.13;(s, 1H, H7); 7.84 (d, 8.7 Hz, 1H, H9); 7.75 (d, 8.7 Hz, 1H, H10); 12.33 (s, NH); 2.53 (s, 3H, CH_3); ^{13}C NMR (75 MHz, DMSO-d_6, δ in ppm) 126.4; 120.8; 121.5; 146.3; 163.2; 124.5; 134.5; 125.8; 112.3; 141.8; 139.1; 127.9; 123.1; 120.7; 21.90 ESI-(+)-MS [M+H]+ 267.1012 (100).

8-Fluorobenzo[*b*]thieno[3,2-*h*]-1,6-naphthyridin-6(11*H*)-one (8c). Yield: 65%, m.p.: > 300° C; IR (KBr, cm^{-1}); (ν NH 3400 - 3111, ν C=O 1622) ^{1}H NMR (300 MHz, DMSO-d_6, TMS, δ in ppm) 8.09 (d, 6.0 Hz, 1H, H1); 8.23 (d, 6.0 Hz, 1H, H2); 9.33 (s, 1H, H5); 8.05-7.86 (m, 3 Ar-H); 12.30 (s, NH); ^{13}C NMR (75 MHz, DMSO-d_6, δ in ppm) 126.5; 121.2; 122.2; 146.8; 162.7; 125.7; 135.1; 127.2; 112.5; 142.0; 139.5; 128.8; 123.9; 121.1; ESI-(+)-MS [M+H]+ 271.0797 (100).

8-Chlorobenzo[*b*]thieno[3,2-*h*]-1,6-naphthyridin-6(11*H*)-one (d). Yield: 72%, m.p.: > 300° C; IR (KBr, cm-1); (ν NH 3400 - 3105, ν C=O 1630) ^{1}H NMR (300 MHz, DMSO-d_6, TMS, δ in ppm) 8.08 (d, 6.0 Hz, 1H, H1); 8.34 (d, 6.0 Hz, 1H, H2); 9.31 (s, 1H, H5); 8.26 (d, 2.4 HZ 1H, H7); 7.96 (dd, 9.0; 2.4 HZ 1H, H9); 8.02 (d, 9.0 HZ 1H, H10); 12.59 (s, NH); ^{13}C NMR (75 MHz, DMSO-d_6, δ in ppm) 126.8; 120.4; 121.2; 146.6; 162.8; 124.7; 134.1; 126.8; 112.1; 141.0; 139.3; 127.6; 123.7; 120.1; EI (70 eV) m/z (%): M+. 285.9971 (100)

8-Bromobenzo[*b*]thieno[3,2-*h*]-1,6-naphthyridin-6(11*H*)-one (8e). Yield: 70%, m.p.: > 300° C; IR (KBr, cm-1); (ν NH 3420 - 2500, ν C=O 1627) ^{1}H NMR (300 MHz, DMSO-d_6, TMS, δ in ppm) 8.09 (d, 6.0 Hz, 1H, H1); 8.38 (d, 6.0 Hz, 1H, H2); 9.33 (s, 1H, H5); 8.44 (d, 2.4 HZ 1H, H7); 8.00 (d, 8.7 HZ 1H, H9); 8.09 (d, 8.7 HZ 1H, H10); 12.66 (s, NH); ^{13}C NMR (75 MHz, DMSO-d_6, δ in ppm) 126.7; 120.9; 121.7; 146.5; 162.6; 125.1; 134.8; 127.5; 112.9; 141.3; 139.7; 128.2; 123.4; 120.5; ESI-(+)-MS [M+H]+ 330.9849 (100)

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