Synthesis of 2-(2-Imino-2,3-dihydropyrido[3,2-*e*]-1,3-thiazin-(*Z*)-4-ylidene)acetamide Derivatives

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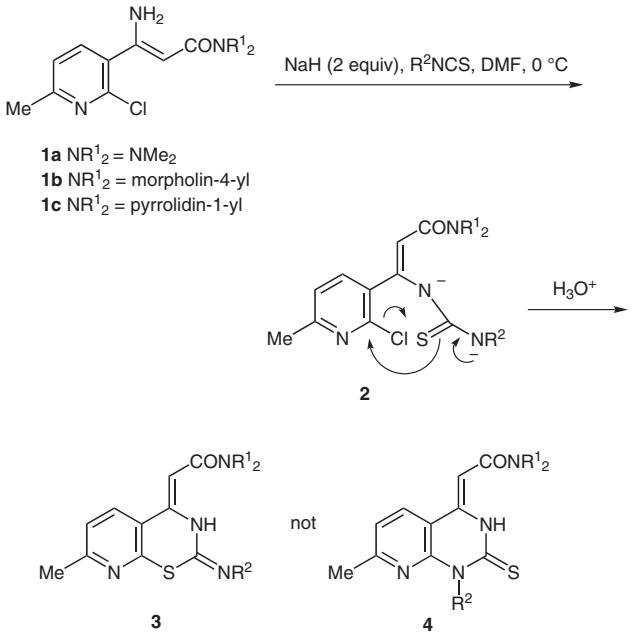
Abstract: A facile two-step preparation of the title pyridothiazine derivatives starting from commercially available 2-chloro-6-methylpyridine-3-carbonitrile is described. The reaction of this nitrile with magnesium enolates of tertiary acetamides affords (*Z*)-3-amino-3-(2-chloro-6-methylpyridin-3-yl)propenamide derivatives, which in turn are allowed to react with isothiocyanates in the presence of sodium hydride to give the desired products in satisfactory yields.

Key words: amides, cyclizations, heterocycles, imines, pyridines

We recently reported a convenient method to prepare (*Z*)-2-(2-oxo-2,3-dihydropyrido[2,3-*d*]pyrimidin-4(1*H*)-ylidene)acetamide derivatives.[1] This synthesis was based on the reaction of (*Z*)-3-amino-3-(2-chloro-6-methylpyridin-3-yl)propenamide derivatives **1** with aryl isocyanates in the presence of sodium hydride. Compounds **1** were easily prepared by the treatment of commercially available 2-chloro-6-methylpyridine-3-carbonitrile with magnesium enolates of tertiary acetamides.

In continuation of our study, we became interested in examining the reaction of the enamino amides **1** with isothiocyanates. We found that the reaction gave 2-(2-imino-2,3-dihydropyrido[3,2-*e*]-1,3-thiazin-(*Z*)-4-ylidene)acetamide derivatives **3**, as shown in Scheme 1. In this paper, we report a facile method for the preparation of these pyridothiazine derivatives.

Some compounds having the pyrido[3,2-*e*]-1,3-thiazine skeleton have been reported to exhibit biological activities.[2] However, there have been few reports on the methods for constructing this pyridothiazine system to date, though Couture et al. have described a synthesis of 2-substituted 4*H*-pyrido[3,2-*e*]-1,3-thiazin-4-ones by reactions of 2-chloropyridine-3-carboxamide with various *O*-ethyl thiolates.[3] A synthesis of 3,4-dihydro-2*H*-[1,3]thiazino[6,5-*b*]quinolines by reaction of 3-aminomethyl-2-chloroquinoline derivatives with isothiocyanates has been reported by Kombarov et al.[4] To the best of our knowledge, the present 2-(2-imino-2,3-dihydropyrido[3,2-*e*]-1,3-thiazin-4-ylidene)acetic acid skeleton, which carries a carbon substituent at the 4-position of pyrido[3,2-*e*]-1,3-thiazine ring, is unknown in the literature.



Scheme 1

Conversion of the (*Z*)-3-amino-3-(2-chloro-6-methylpyridin-3-yl)propenamide derivatives **1** into 2-(2-imino-2,3-dihydropyrido[3,2-*e*]-1,3-thiazin-(*Z*)-4-ylidene)acetamide derivatives **3** was carried out as illustrated in Scheme 1. Thus, the enamino amides **1** were treated with 2 molar amounts of sodium hydride in DMF at 0 °C. The mixture was then allowed to react with a range of isothiocyanates to give the dianionic intermediates **2**. Attack of the sulfur atom on the 2-position of the pyridine ring afforded the pyridothiazine derivatives **3**, after the usual aqueous workup followed by purification using column chromatography on silica gel, in fair to good yields (Table 1). We were unable to detect the presence any trace amounts of 2-(2-thioxopyrido[2,3-*d*]pyrimidin-4-ylidene)acetamide derivatives **4**, the products arising from the attack of nitrogen on the 2-position of the pyridine ring. The ^{13}C NMR spectra of the products **3** showed signals at about $\delta = 165$, assignable to imine carbons, and no signals at about $\delta = 200$, which would be for thiocarbonyl carbons of the compounds **4**. The stereochemistry of the 4-ylidene moiety of the products **3** was assigned to be *Z*. The *Z*-preference is ascribed to intramolecular hydrogen bonding between the H-3 of pyridothiazine ring and the amide carbonyl. NOE experiments were carried out to confirm the stereochemistry of compound **3a**. Thus, irradiation of

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Table 1 Preparation of Pyridothiazine Derivatives **3**

Entry	**1**	R^2	**3** (Yield, %)[a]
1	**1a**	Ph	**3a** (72)
2	**1a**	3-Tol	**3b** (71)
3	**1a**	4-BrC_6H_4	**3c** (65)
4	**1a**	Et	**3d** (74)
5	**1a**	*c*-Hex	**3e** (73)
6	**1a**	Bn	**3f** (73)
7	**1b**	Ph	**3g** (70)
8	**1b**	3-Tol	**3h** (68)
9	**1b**	Et	**3i** (69)
10	**1b**	*c*-Hex	**3j** (63)
11	**1c**	Ph	**3k** (73)

[a] Isolated yield.

the signal at δ = 5.68, assignable to the vinyl proton, resulted in an enhancement (9.2%) of the signal at 7.86, assignable to the H-5 of the pyridothiazine ring. Although one of the possible stereoisomers was obtained as a sole product in each reaction, the stereochemistry of the 2-imino moiety was not yet clarified.

The reactions using aliphatic isothiocyanates having δ-hydrogen(s) (entries 4–6, 9, and 10) also successfully proceeded and the desired products were obtained in the yields comparable to those using aromatic isothiocyanates (entries 1–3, 7, 8, and 11). The use of the respective enamino *tert*-butyl ester in place of the enamino amides **1** resulted in the formation of intractable mixtures of products; however, we have no explanation for this.

The use of two molar amounts of sodium hydride is essential for the satisfactory production of the desired products. For example, the reaction of **1a** with phenyl isothiocyanate using an equimolar amount of sodium hydride gave only rather decreased yield (26%) of the product **2a**, and a considerable amount of the starting material was recovered. The necessity of two molar amounts of sodium hydride can be explained by the formation of the dianionic intermediate **2** as stated for the preparation of (*Z*)-2-(2-oxo-2,3-dihydropyrido[2,3-*d*]pyrimidin-4(1*H*)-ylidene)acetamide derivatives in the previous paper.[1]

In conclusion, we have developed a simple procedure for the preparation of the novel pyridothiazine derivatives. The present method may be valuable for organic synthesis because of the ready availability of the starting materials as well as the ease of operations.

All melting points were obtained on a Laboratory Devices MEL-TEMP II melting apparatus and are uncorrected. IR spectra were determined with a Shimadzu FTIR-8300 spectrophotometer. The ^{1}H NMR spectra were determined in $CDCl_3$ using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 500 MHz or a JEOL LA400 FT NMR spectrometer operating at 400 MHz. The ^{13}C NMR spectra were determined in $CDCl_3$ using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 125 MHz. Low-resolution MS spectra were measured by a JEOL JMS AX505 HA spectrometer. TLC was carried out on a Merck Kieselgel 60 PF_{254}. Column chromatography was performed using Merck Kieselgel 60 (0.063–0.200 mm). All of the organic solvents used in this study were dried over appropriate drying agents and distilled prior to use.

3-Amino-3-(2-chloro-6-methylpyridin-3-yl)acetamide derivatives **1a** and **1b** were prepared according to the procedure previously reported by us.[1] All other chemicals used in this study were commercially available.

(*Z*)-3-Amino-3-(2-chloro-6-methylpyridin-3-yl)-1-(pyrrolidin-1-yl)propenone (1c)

This compound was prepared from 2-chloro-6-methylpyridine-3-carbonitrile and 1-acetylpyrrolidine by our previously reported procedure;[1] yield: 64%; yellow oil; R_f = 0.41 (1:2 THF–C_6H_6).

IR (neat): 3375, 3273, 3184, 1616 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.84–1.95 (m, 4 H), 2.57 (s, 3 H), 3.37–3.43 (m, 2 H), 3.49–3.56 (m, 2 H), 4.74 (s, 1 H), 6.2–6.9 (br, 2 H), 7.13 (d, *J* = 7.8 Hz, 1 H), 7.62 (d, *J* = 7.8 Hz, 1 H).

Anal. Calcd for $C_{13}H_{16}ClN$: C, 58.76; H, 6.07; N, 15.81. Found: C, 58.64; H, 6.13; N, 15.93.

***N*,*N*-Dimethyl-2-(7-methyl-2-phenylimino-2,3-dihydropyrido[3,2-*e*]-1,3-thiazin-(*Z*)-4-ylidene)acetamide (3a); Typical Procedure**

To a stirred suspension of NaH (60% in oil; 23 mg, 0.58 mmol) in DMF (2 mL) at 0 °C was added dropwise a solution of **1a** (68 mg, 0.29 mmol) in DMF (2 mL). After 15 min, PhNCS (39 mg, 0.29 mmol) was added, and the stirring was continued for an additional 1 h at the same temperature. Sat. aq NH_4Cl (10 mL) was added, and the organic materials were extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were washed with H_2O (3 × 10 mL) and brine (10 mL), and then dried (Na_2SO_4). Evaporation of solvent gave a residue, which was purified by column chromatography on silica gel (1:2 EtOAc–hexane) to afford **3a**.

Yellow solid; yield: 70 mg (72%); mp 221–223 °C (dec.) (hexane–CH_2Cl_2).

IR (KBr): 3452, 1630, 1605 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.30 (s, 3 H), 3.06 (br s, 3 H), 3.15 (br s, 3 H), 5.68 (s, 1 H), 6.93 (d, *J* = 8.2 Hz, 1 H), 7.23 (dd, *J* = 7.3, 1.4 Hz, 2 H), 7.45 (tt, *J* = 7.3, 1.4 Hz, 1 H), 7.50 (t, *J* = 7.3 Hz, 2 H), 7.86 (d, *J* = 8.2 Hz, 1 H), 14.07 (br s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.66, 82.01, 109.86, 119.38, 128.17, 128.30, 129.00, 129.46, 131.80, 139.89, 142.28, 149.16, 161.98, 168.50, 175.63.

MS (EI, 70 eV): *m*/*z* (%) = 338 (45, [M$^+$]), 292 (100).

Anal. Calcd for $C_{18}H_{18}N_4OS$: C, 63.88; H, 5.36; N, 16.56; S, 9.47. Found: C, 63.87; H, 5.40; N, 16.77; S, 9.42.

***N*,*N*-Dimethyl-2-[7-methyl-2-(3-methylphenyl)imino-2,3-dihydropyrido[3,2-*e*]-1,3-thiazin-(*Z*)-4-ylidene]acetamide (3b)**

Pale-yellow solid; mp 215 °C (dec.) (hexane–CH_2Cl_2).

IR (KBr): 3310, 1630, 1605 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.32 (s, 3 H), 2.41 (s, 3 H), 3.06 (br s, 3 H), 3.15 (br s, 3 H), 5.67 (s, 1 H), 6.92 (d, *J* = 7.9 Hz, 1 H), 7.03 (d, *J* = 7.9 Hz, 1 H), 7.04 (s, 1 H), 7.25 (d, *J* = 7.9 Hz, 1 H), 7.38 (t, *J* = 7.9 Hz, 1 H), 7.85 (d, *J* = 7.9 Hz, 1 H), 14.02 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.41, 24.72, 81.87, 109.84, 119.30, 126.41, 128.69, 128.98, 129.95, 131.75, 138.82, 139.75, 142.32, 142.32, 149.20, 161.98, 168.52, 175.65.

MS (EI, 70 eV): *m*/*z* (%) = 352 (62, [M$^+$]), 306 (100).

Anal. Calcd for $C_{19}H_{20}N_4OS$: C, 64.75; H, 5.72; N, 15.90; S, 9.10. Found: C, 64.54; H, 5.56; N, 15.70; S, 9.16.

2-[2-(4-Bromophenyl)imino-7-methyl-2,3-dihydropyrido[3,2-*e*]-1,3-thiazin-(*Z*)-4-ylidene]-*N*,*N*-dimethylacetamide (3c)
Yellow solid; mp 241–242 °C (dec.) (hexane–CH_2Cl_2).

IR (KBr): 3435, 1630, 1605 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.33 (s, 3 H), 3.06 (br s, 3 H), 3.15 (br s, 3 H), 5.69 (s, 1 H), 6.94 (d, *J* = 7.9 Hz, 1 H), 7.11 (d, *J* = 8.7 Hz, 2 H), 7.61 (d, *J* = 8.7 Hz, 2 H), 7.86 (d, *J* = 7.9 Hz, 1 H), 14.07 (br s, 1 H).

MS (EI, 70 eV): *m*/*z* (%) = 416 (52, [M$^+$]), 372 (100).

Anal. Calcd for $C_{18}H_{17}BrN_4OS$: C, 51.80; H, 4.11; N, 13.43; S, 7.68. Found: C, 51.78; H, 3.98; N, 13.33; S, 7.46.

2-(2-Ethylimino-7-methyl-2,3-dihydropyrido[3,2-*e*]-1,3-thiazin-(*Z*)-4-ylidene)-*N*,*N*-dimethylacetamide (3d)
Orange solid; mp 207 °C (dec.) (hexane–CH_2Cl_2).

IR (KBr): 3442, 1622, 1603 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.33 (t, *J* = 7.3 Hz, 3 H), 2.57 (s, 3 H), 3.04 (br s, 3 H), 3.11 (br s, 3 H), 4.81 (q, *J* = 7.3 Hz, 2 H), 5.57 (s, 1 H), 6.95 (d, *J* = 7.9 Hz, 1 H), 7.82 (d, *J* = 7.9 Hz, 1 H), 13.81 (br s, 1 H).

MS (EI, 70 eV): *m*/*z* (%) 290 (100, [M$^+$]).

Anal. Calcd for $C_{14}H_{18}N_4OS$: C, 57.91; H, 6.25; N, 19.29; S, 11.04. Found: C, 57.62; H, 5.95; N, 19.17; S, 11.27.

2-(2-Cyclohexylimino-7-methyl-2,3-dihydropyrido[3,2-*e*]-1,3-thiazin-(*Z*)-4-ylidene)-*N*,*N*-dimethylacetamide (3e)
Yellow solid; 154 °C (dec.) (hexane–CH_2Cl_2).

IR (KBr): 3435, 1630, 1605 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.87–1.87 (m, 9 H), 2.56 (s, 3 H), 2.75–2.77 (m, 1 H), 3.04 (br s, 3 H), 3.10 (br s, 3 H), 5.53 (s, 1 H), 5.93–5.98 (m, 1 H), 6.93 (d, *J* = 8.2 Hz, 1 H), 7.79 (d, *J* = 8.2 Hz, 1 H), 13.81 (br s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.37, 25.71, 26.64 (2 C), 29.21, 80.76, 111.25, 119.01, 131.94, 142.18, 147.99, 155.50, 160.59, 168.64, 175.79.

MS (EI, 70 eV): *m*/*z* (%) = 344 (51, [M$^+$]), 262 (55), 218 (100).

Anal. Calcd for $C_{18}H_{24}N_4OS$: C, 62.76; H, 7.02; N, 16.26; S, 9.31. Found: C, 62.50; H, 7.27; N, 16.06; S, 9.19.

2-(2-Benzylimino-7-methyl-2,3-dihydropyrido[3,2-*e*]-1,3-thiazin-(*Z*)-4-ylidene)-*N*,*N*-dimethylacetamide (3f)
Pale-yellow solid; mp 232–233 °C (dec.) (hexane–CH_2Cl_2).

IR (KBr): 3438, 1628, 1602 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.50 (s, 3 H), 3.05 (br s, 3 H), 3.11 (br s, 3 H), 5.59 (s, 1 H), 6.02 (s, 2 H), 6.91 (d, *J* = 7.9 Hz, 1 H), 7.21 (t, *J* = 7.3 Hz, 1 H), 7.27 (t, *J* = 7.3 Hz, 2 H), 7.54 (d, *J* = 7.3 Hz, 2 H), 7.80 (d, *J* = 7.9 Hz, 1 H), 13.91 (br s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.53, 49.58, 81.48, 110.45, 119.32, 127.03, 128.04, 128.55 (2 C), 131.94, 137.44, 141.96, 147.30, 161.70, 168.54, 175.22.

MS (EI, 70 eV): *m*/*z* (%) = 352 (100, [M$^+$]).

Anal. Calcd for $C_{19}H_{20}N_4OS$: C, 64.75; H, 5.72; N, 15.90; S, 9.10. Found: C, 64.73; H, 5.80; N, 15.66; S, 9.02.

2-(7-Methyl-2-phenylimino-2,3-dihydropyrido[3,2-*e*]-1,3-thiazin-(*Z*)-4-ylidene)-1-(morpholin-4-yl)ethanone (3g)
Pale-yellow solid; mp 273 °C (dec.) (hexane–CH_2Cl_2).

IR (KBr): 3427, 1639, 1614 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.32 (s, 3 H), 3.67–3.79 (m, 8 H), 5.65 (s, 1 H), 6.93 (d, *J* = 7.9 Hz, 1 H), 7.23 (d, *J* = 7.3 Hz, 2 H), 7.45 (t, *J* = 7.3 Hz, 1 H), 7.51 (t, *J* = 7.3 Hz, 2 H), 7.86 (d, *J* = 7.9 Hz, 1 H), 13.91 (br s, 1 H).

MS (EI, 70 eV): *m*/*z* (%) = 380 (14, [M$^+$]), 344 (50), 262 (53), 218 (100).

Anal. Calcd for $C_{20}H_{20}N_4OS$: C, 63.14; H, 5.30; N, 14.73; S, 8.43. Found: C, 62.05; H, 5.04; N, 14.62; S, 8.50.

2-[7-Methyl-2-(3-methylphenylimino)-2,3-dihydropyrido[3,2-*e*]-1,3-thiazin-(*Z*)-4-ylidene]-1-(morpholin-4-yl)ethanone (3h)
Yellow solid; mp 262–263 °C (dec.) (hexane–CH_2Cl_2).

IR (KBr): 3448, 1628, 1606 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.33 (s, 3 H), 2.41 (s, 3 H), 3.67–3.75 (m, 8 H), 5.64 (s, 1 H), 6.93 (d, *J* = 7.9 Hz, 1 H), 7.03 (d, *J* = 7.3 Hz, 1 H), 7.04 (s, 1 H), 7.26 (d, *J* = 7.3 Hz, 1 H), 7.39 (t, *J* = 7.3 Hz, 1 H), 7.85 (d, *J* = 7.9 Hz, 1 H), 13.89 (br s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.80, 20.12, 62.20, 76.31, 105.08, 114.08, 121.70, 124.12, 124.45, 125.24 (2 C), 127.17, 134.26, 135.03, 138.56, 144.57, 157.66, 162.71, 170.95.

MS (EI, 70 eV): *m*/*z* (%) = 394 (60, [M$^+$]), 306 (100).

Anal. Calcd for $C_{21}H_{22}N_4OS$: C, 63.94; H, 5.62; N, 14.20; S, 8.13. Found: C, 63.75; H, 5.52; N, 14.08; S, 8.40.

2-(2-Ethylimino-7-methyl-2,3-dihydropyrido[3,2-*e*]-1,3-thiazin-(*Z*)-4-ylidene)-1-(morpholin-4-yl)ethanone (3i)
Yellow solid; mp 240–242 °C (dec.) (hexane–CH_2Cl_2).

IR (KBr): 3431, 1629, 1611 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.33 (t, *J* = 7.0 Hz, 3 H), 2.57 (s, 3 H), 3.64–3.73 (m, 8 H), 4.80 (q, *J* = 7.0 Hz, 2 H), 5.53 (s, 1 H), 6.95 (d, *J* = 8.1 Hz, 1 H), 7.81 (d, *J* = 8.1 Hz, 1 H), 13.68 (br s, 1 H).

MS (EI, 70 eV): *m*/*z* (%) = 332 (85, [M$^+$]), 246 (100).

Anal. Calcd for $C_{16}H_{20}N_4O_2S$: C, 57.81; H, 6.06; N, 16.85; S, 9.65. Found: C, 57.45; H, 5.95; N, 16.86; S, 9.60.

2-(2-Cyclohexylimino-7-methyl-2,3-dihydropyrido[3,2-*e*]-1,3-thiazin-(*Z*)-4-ylidene)-1-(morpholin-4-yl)ethanone (3j)
Yellow solid; mp 216–218 °C (hexane–CH_2Cl_2).

IR (KBr): 3448, 1628, 1605 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87–1.87 (m, 9 H), 2.56 (s, 3 H), 2,75–2.78 (m, 1 H), 3.63–3.72 (m, 8 H), 5.50 (s, 1 H), 5.91–5.99 (m, 1 H), 6.93 (d, *J* = 8.1 Hz, 1 H), 7.77 (d, *J* = 8.1 Hz, 2 H), 13.17 (br s, 1 H).

MS (EI, 70 eV): *m*/*z* (%) = 386 (49, [M$^+$]), 304 (51), 218 (100).

Anal. Calcd for $C_{20}H_{26}N_4O_2S$: C, 62.15; H, 6.78; N, 14.50; S, 8.30. Found: C, 61.88; H, 6.91; N, 14.35; S, 8.27.

2-(7-Methyl-2-phenylimino-2,3-dihydropyrido[3,2-*e*]-1,3-thiazin-(*Z*)-4-ylidene)-1-(pyrrolidin-1-yl)ethanone (3k)
Pale-yellow solid; mp 274 °C (dec.) (hexane–CH_2Cl_2).

IR (KBr): 3417, 1634, 1604 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.90–1.94 (m, 2 H), 2.01–2.04 (m, 2 H), 2.31 (s, 3 H), 3.55–3.60 (m, 4 H), 5.52 (s, 1 H), 6.92 (d, *J* = 7.8 Hz, 1 H), 7.23 (d, *J* = 7.3 Hz, 2 H), 7.44 (t, *J* = 7.3 Hz, 1 H), 7.50 (t, *J* = 7.3 Hz, 2 H), 7.85 (d, *J* = 7.8 Hz, 1 H), 14.05 (br s, 1 H).

MS (EI, 70 eV): *m*/*z* (%) = 364 (58, [M$^+$]), 292 (12), 252 (100).

Anal. Calcd for $C_{20}H_{20}N_4OS$: C, 65.91; H, 5.53; N, 15.37; S, 8.80. Found: C, 65.65; H, 5.61; N, 15.14; S, 8.53.

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