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Synthesis of pyrimido[4′,5′:2,3][1,4]thiazepino-[7,6-*b*]quinolines, derivatives of a novel ring system

Abstract: Several derivatives of the novel pyrimido[4′,5′:2,3][1,4]thiazepino[7,6-*b*]quinoline ring system have been synthesized through cyclocondensation of 5-amino-6-methylpyrimidine-4-thiols **5a,b** and 2-chloroquinoline-3-carbaldehydes **6a–c** in the presence of K_2CO_3 in DMF.

Keywords: heterocyclization; pyrimidothiazepinoquinoline; quinoline; thiazepine.

DOI 10.1515/hc-2014-0095
Received June 2, 2014; accepted August 28, 2014; previously published online September 24, 2014

Dedication: In memory of Professor Mohammad Rahimizadeh.

Introduction

Heterocycles containing a 1,4-thiazepine moiety are important targets in synthetic and medicinal chemistry because of their presence in a wide range of natural and synthetic active agents [1–4]. Among them, fused derivatives represent interesting pharmaceutical properties. For example, different alkyl derivatives of dihydro-1,4-benzothiazepine are HIV-1 enzyme integrase inhibitor [5] and antitumor agents [6]. Several heteroannulated analogues of this core fragment are also potent inhibitors of herpes simplex virus type 1 replication [7], show antihistamine activity [8], and are vasoconstrictor agents [9]. Various methods for the synthesis of fused 1,4-thiazepine derivatives have been reported in recent years with respect to their different structures [10–18]. Synthetic approaches to these compounds involve addition [19], condensation [20], coupling [21], rearrangement [22], and thermolysis [23] reactions in multistep syntheses. These compounds have also been prepared through the treatment of thioxanthen-9-ol with *o*-mesitylene sulfonyl hydroxylamine [4] or cyclization of *o*-nitrobenzene halides with *o*-thiosalicylic acid esters as well as reduction and dehydration of the resulting products [5].

As part of our ongoing studies dealing with the synthesis of new biologically active heterocyclic compounds [24–27], herein, we wish to report on the synthesis and structural elucidations of various pyrimido-[4′,5′:2,3][1,4]thiazepino[7,6-*b*]quinoline derivatives as a novel heterocyclic system.

Results and discussion

2,4-Dichloro-6-methyl-5-nitropyrimidine (**1**) was conveniently synthesized according to the published procedure [28]. The nitro group of this compound was reduced by treatment with iron powder in acetic acid at room temperature to give 2,4-dichloro-6-methylpyrimidin-5-amine (**2**). Further treatment of compound **2** with KSCN in boiling dimethyl formamide (DMF) gave 5-chloro-7-methylthiazolo[5,4-*d*]pyrimidin-2-amine (**3**). Nucleophilic displacement of chlorine atom in 2-position of the pyrimidine ring in compound **3** with morpholine and piperidine as typical secondary amines furnished the respective substituted derivatives 7-methyl-5-morpholinothiazolo[5,4-d]pyrimidin-2-amine (**4a**) and 7-methyl-5-piperidinothiazolo[5,4-d]pyrimidin-2-amine (**4b**). The synthesized compounds **4a,b** were hydrolyzed in aqueous KOH solution to produce the respective 5-amino-6-methylpyrimidine-4-thiols **5a,b**. Meanwhile, chloroquinoline-3-carbaldehydes **6a–c** were conveniently prepared according to the reported procedure [29]. Potassium carbonate catalyzed cyclocondensation reaction of compounds **6a–c** with compounds **5a,b** in DMF under reflux proceeded smoothly and gave the first members of the hitherto unknown 4-methylpyrimido[4′,5′:2,3][1,4]thiazepino[7,6-*b*] quinolines **7a–f**. The progress of these reactions was monitored by thin layer chromatography (TLC) using *n*-hexane/ethyl acetate (EtOAc) (8:1) as eluent (Scheme 1).

All synthesized products were characterized by spectroscopic and microanalytical data. For instance, the IR spectrum of compound **7a** did not show the stretching vibration bands of compounds **5a** and **6a** at 3336 and 3248 cm^{-1} for the amino group, 2666 cm^{-1} for the thiol, and at 1690 cm^{-1}

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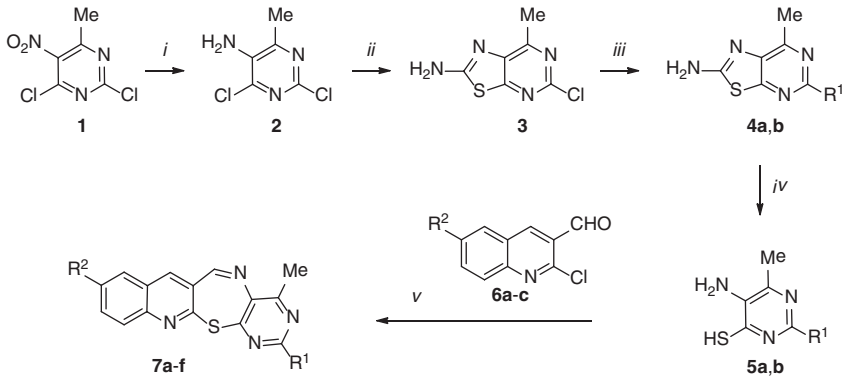


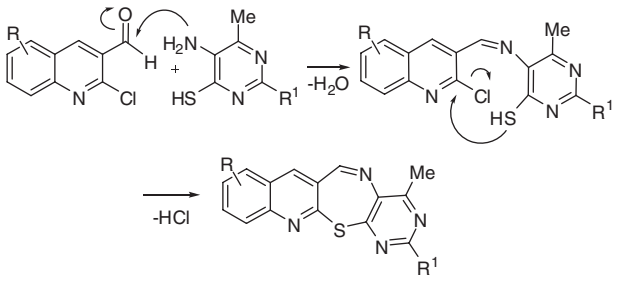
7a: R^1 = morpholino; R^2 = H
7b: R^1 = morpholino; R^2 = Cl
7c: R^1 = morpholino; R_2 = Me
7d: R^1 = piperidino; R^2 = H
7e: R^1 = piperidino; R^2 = Cl
7f: R^1 = piperidino; R^2 = Me
4a, **5a**: R^1 = morpholino
4b, **5b**: R^1 = piperidino

Scheme 1 Reagents and conditions: (i) Fe powder, HOAc, rt, 2 h; (ii) KSCN, DMF, reflux, 3 h; (iii) morpholine or piperidine, EtOH, reflux, 6 h; (iv) $KOH_{(aq)}$, reflux, 10 h; (v) K_2CO_3, DMF, reflux, 8–12 h.

belonging to a carbonyl group. The ^{1}H NMR spectrum of **7a** does not show the signal for an aldehydic proton found in the spectrum of compound **6a** at 9.20 ppm. There are no D_2O exchangeable signals, which indicates the absence of SH and NH_2 groups present in the starting material **5a**. The spectrum shows a new sharp singlet signal at 8.71 ppm corresponding to the imino proton of the thiazepine ring of **7a**. Elimination of HCl is observed in the mass spectrum of **7a**. The molecular ion peak of **7a** is observed at *m/z* 363 (M^+), which, together with the results of elemental analysis, fully support the molecular formula of $C_{19}H_{17}N_5OS$. Analogous results were obtained for the remaining products **7b–f**. A self-explanatory mechanism for the synthesis of 4-methylpyrimido[4′,5′:2,3][1,4]thiazepino[7,6-*b*]quinoline derivatives **7a–f** is proposed in Scheme 2.

Conclusion

Compounds **7a–f** containing the previously unknown pyrimido[4′,5′:2,3][1,4]thiazepino[7,6-*b*]quinoline ring system were synthesized for the first time by cyclocondensation of 2-chloroquinoline-3-carbaldehydes and 5-amino-6-methylpyrimidine-4-thiols in the presence of K_2CO_3 in boiling DMF. Products **7a–f** were obtained in high yields.



Scheme 2

Experimental

Melting points were recorded on an Electrothermal 9100 melting point apparatus. The IR spectra were obtained in KBr pellets on an Avatar 370 FT-IR Thermo Nicolet spectrometer. The ^{1}H NMR (400 MHz) and the ^{13}C NMR (100 MHz) spectra were recorded on a Bruker Avance DRX-400 spectrometer. The mass spectra were scanned on a Varian Mat CH-7 instrument operating at 70 eV. Elemental analyses were performed on a Thermo Finnigan Flash EA microanalyzer.

2,4-Dichloro-6-methylpyrimidin-5-amine (2)

A mixture of 2,4-dichloro-6-methyl-5-nitropyrimidine (**1**, 10 mmol, 2.1 g) and iron powder (2.5 g) in acetic acid (50 mL) was stirred at room temperature for 2 h. After completion of the reaction, the mixture was filtered off and the filtrate was concentrated in *vacuo*. The resulting solid was crystallized from ethyl acetate: yield 70% of a red powder; mp 101–103°C; ^{1}H NMR ($CDCl_3$): δ 2.32 (s, 3H, CH_3), 6.08 (s, 2H, NH_2, D_2O exchangeable); ^{13}C NMR ($CDCl_3$): δ 22.6, 115.2, 155.6, 159.6, 168.2; IR: ν 3472, 3371, 1621, 1555 cm^{-1}; MS (*m/z*) 178 (M^+), 180 (M^++2). Anal. Calcd for $C_5H_5Cl_2N_3$: C, 33.73; H, 2.83; N, 23.60. Found: C, 33.70; H, 2.81; N, 23.57.

5-Chloro-7-methylthiazolo[5,4-*d*]pyrimidin-2-amine (3)

A mixture of 2,4-dichloro-6-methylpyrimidin-5-amine (**2**, 10 mmol, 1.7 g) and KSCN (10 mmol, 0.97 g) in DMF (15 mL) was heated under

reflux for 3 h. After completion of the reaction, the mixture was cooled and the resulting precipitate was collected by filtration and crystallized from ethanol: yield 85% of a brown powder; mp 255–257°C; ^{1}H NMR (DMSO-d_6): δ 2.56 (s, 3H, CH_3), 6.88 (s, 2H, NH_2, D_2O exchangeable); ^{13}C NMR (DMSO-d_6): δ 22.6, 115.2, 145.6, 159.6, 166.5 167.2; IR: ν 3195, 3288, 2961, 1618 cm^{-1}; MS (*m/z*) 200 (M^+), 202 (M^++2), 170 (M^+-S), 126 (M^+-thiourea). Anal. Calcd for $C_6H_5ClN_4S$: C, 35.92; H, 2.51; N, 27.92; S, 15.98. Found: C, 35.85; H, 2.47; N, 27.88; S, 15.93.

General procedure for the preparation of compounds 4a,b

A mixture of 5-chloro-7-methylthiazolo[5,4-*d*]pyrimidin-2-amine (**3**, 10 mmol, 2.0 g) and the appropriate secondary amine (30 mmol) in ethanol (20 mL) was heated under reflux for 6 h. The progress of the reaction was monitored by TLC using *n*-hexane/EtOAc (6:1) as eluent. Then, the solvent was removed under reduced pressure using rotary evaporator. The crude residue was washed with ethanol (2×20 mL) and dried.

7-Methyl-5-morpholinothiazolo[5,4-d]pyrimidin-2-amine (4a) This compound was obtained in 90% yield as a gray powder; mp 235–237°C; ^{1}H NMR (DMSO-d_6): δ 2.36 (s, 3H, CH_3), 3.65 (t, 4H, CH_2N, J = 5.2 Hz), 3.76 (t, 4H, CH_2O, J = 5.2 Hz), 6.9 (br s, 2H, NH_2, D_2O exchangeable); ^{13}C NMR (DMSO-d_6): δ 22.6, 44.5, 62.3, 115.1, 145.4, 159.6, 166.8 167.1; IR: ν 3145, 3230, 2953, 2859, 1654 cm^{-1}; MS (*m/z*) 251 (M^+), 221 (M^+-S), 177 (M^+-thiourea), 166 (M^+-morpholine). Anal. Calcd for $C_{10}H_{13}N_5OS$: C, 47.79; H, 5.21; N, 27.87; S, 12.76. Found: C, 47.74; H, 5.18; N, 27.84; S, 12.72.

7-Methyl-5-piperidinothiazolo[5,4-*d*]pyrimidin-2-amine (4b) This compound was obtained in 90% yield as a gray powder; mp 207–210°C; ^{1}H NMR (DMSO-d_6): δ 1.50–1.56 (m, 6H, $3CH_2$), 2.44 (s, 3H, CH_3), 3.73–3.75 (m, 4H, 2-CH_2N), 6.92 (br s, 2H, NH_2, D_2O exchangeable); ^{13}C NMR (DMSO-d_6): δ 22.6, 24.3, 26.4, 54.8, 125.1, 143.4, 160.5, 165.8, 168.1; IR: ν 3135, 3245, 2940, 2865, 1615 cm^{-1}; MS (*m/z*) 249 (M^+) 219 (M^+-S), 166 (M^+-piperidine). Anal. Calcd for $C_{11}H_{15}N_5S$: C, 52.99; H, 6.06; N, 28.09; S, 12.86. Found: C, 52.90; H, 6.04; N, 27.99; S, 12.82.

General procedure for the preparation of compounds 5a,b

A mixture of **4a** or **4b** (10 mmol) in aqueous 15% KOH solution (20 mL) was heated in a water bath for 10 h. The reaction mixture was then neutralized with acetic acid, and the separated solid was collected by filtration and crystallized from water.

5-Amino-6-methyl-2-morpholinopyrimidine-4-thiol (5a) This compound was obtained in 86% yield as yellow solid; mp 215–217°C; ^{1}H NMR (DMSO-d_6): δ 2.33 (s, 3H, CH_3), 3.65 (t, 4H, CH_2N, J = 4.8 Hz), 3.75 (t, 4H, CH_2O, J = 4.8 Hz), 6.56 (br s, 2H, NH_2, D_2O exchangeable), 5.50 (br s, 1H, SH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6): δ 23.6, 46.5, 66.3, 115.8, 133.0, 147.9, 167.2; IR: ν 3336, 3248, 2940, 2865, 2666, 1610 cm^{-1}; MS (*m/z*) 226 (M^+), 194 (M^+-SH), 141 (M^+-morpholine). Anal. Calcd for $C_9H_{14}N_4OS$: C, 47.77; H, 6.24; N, 24.76; S, 14.17. Found: C, 47.70; H, 6.21; N, 24.72; S, 14.14.

5-Amino-6-methyl-2-piperidinopyrimidine-4-thiol (5b) This compound was obtained in 80% yield as yellow solid; mp 187–190°C; ^{1}H NMR (DMSO-d_6): δ 1.51–1.56 (m, 6H, $3CH_2$), 2.45 (s, 3H, CH_3), 3.75–3.77 (m, 4H, $2CH_2N$), 6.81 (br s, 2H, NH_2, D_2O exchangeable), 6.40 (br s, 1H, SH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6): δ 22.6, 24.3, 25.4, 56.8, 128.1, 162.5, 168.8, 170.1; IR: ν 3348, 3256, 2924, 2853, 2668, 1615 cm^{-1}; MS (*m/z*) 224 (M^+), 192 (M^+-SH), 141 (M^+-piperidine). Anal. Calcd for $C_{10}H_{16}N_4S$: C, 53.54; H, 7.19; N, 24.98; S, 14.29. Found: C, 53.51; H, 7.14; N, 24.92; S, 14.25.

General procedure for the preparation of 4-methylpyrimido[4′,5′:2,3][1,4]thiazepino[7,6-*b*]quinolines 7a-f

To a mixture of 2-chloroquinoline-3-carbaldehyde (**6a–c**, 1 mmol) and K_2CO_3 (2 mmol, 0.13 g) in DMF (50 mL), the appropriate 5-amino-6-methylpyrimidine-4-thiol (**5a,b**, 1 mmol) was added, and the mixture was heated under reflux for 8–12 h according to the TLC monitoring using *n*-hexane/EtOAc (8:1) as eluent. After the completion of the reaction, water was added and the resulting solid was filtered off and purified by column chromatography using *n*-hexane/EtOAc (8:1) as mobile phase.

4-(4-Methylpyrimido[4′,5′:2,3][1,4]thiazepino[7,6-*b*]quinolin-2-yl)morpholine (7a) This compound was obtained in 65% yield as a pale yellow powder; mp 245–247°C; ^{1}H NMR ($CDCl_3$): δ 2.53 (s, 3H, CH_3), 3.75 (t, 4H, CH_2N, J = 5.2 Hz), 3.86 (t, 4H, CH_2O, J = 5.2 Hz), 7.61 (t, 1H, ArH, J = 8 Hz), 7.79 (t, 1H, ArH, J = 8 Hz), 7.88 (d, 1H, ArH, J = 8 Hz), 8.12 (d, 1H, ArH, J = 8 Hz), 8.22 (s, 1H, ArH), 8.71 (s, 1H, HC=N); ^{13}C NMR ($CDCl_3$): δ 22.0, 44.8, 66.8, 117.3, 127.0, 127.9, 128.1, 129.2, 130.2, 131.7, 138.2, 148.6, 149.0, 154.0, 155.1, 159.5, 166.1; IR: ν 3047, 3023, 2961, 2864, 1605, 1561, 1447 cm^{-1}; MS (*m/z*) 363 (M^+), 365 (M^++2), 333 (M^+-S), 277 (M^+-morpholine). Anal. Calcd for $C_{19}H_{17}N_5OS$: C, 62.79; H, 4.71; N, 19.27; S, 8.82. Found: C, 62.75; H, 4.67; N, 19.24; S, 8.85.

4-(10-Chloro-4-methylpyrimido[4′,5′:2,3][1,4]thiazepino[7,6-*b*]quinolin-2-yl)morpholine (7b) This compound was obtained in 70% yield as a yellow powder; mp 305–307°C; ^{1}H NMR ($CDCl_3$): δ 2.51 (s, 3H, CH_3), 3.74 (t, 4H, $2CH_2N$, J = 5.2 Hz), 3.85 (t, 4H, $2CH_2O$, J = 5.2 Hz), 7.71 (dd, 1H, ArH, J = 8 Hz, J = 2.0 Hz), 7.85 (d, 1H, J = 2.0 Hz, ArH), 8.04 (d, 1H, ArH, J = 8 Hz), 8.12 (s, 1H, ArH), 8.71 (s, 1H, HC=N); ^{13}C NMR ($CDCl_3$): δ 22.0, 44.4, 66.8, 126.6, 127.0, 130.7, 131.0, 132.5, 133.8, 137.0, 147.3, 151.7, 152.0, 153.6, 154.5, 159.6, 166.4; IR: ν 3076, 3019, 2953, 2868, 2839, 1607, 1555, 1491, 1449, 1311 cm^{-1}; MS (*m/z*) 397 (M^+), 362 (M^+-Cl), 367 (M^+-S), 311 (M^+-morpholine). Anal. Calcd for $C_{19}H_{16}ClN_5OS$: C, 57.35; H, 4.05; N, 17.60; S, 8.06. Found: C, 57.31; H, 4.02; N, 17.56; S, 8.01.

4-(4,10-Dimethylpyrimido[4′,5′:2,3][1,4]thiazepino[7,6-*b*]quinolin-2-yl)morpholine (7c) This compound was obtained in 55% yield as a yellow powder; mp 256–258°C; ^{1}H NMR ($CDCl_3$): δ 2.45 (s, 3H, CH_3), 2.61 (s, 3H, CH_3), 3.66 (t, 4H, $2CH_2N$, J = 4.4 Hz), 3.73 (t, 4H, $2CH_2O$, J = 4.4 Hz), 7.47 (d, 1H, ArH, J = 8Hz), 7.84 (s, 1H, ArH), 7.88 (d, 1H, ArH, J = 8 Hz), 8.29 (s, 1H, ArH), 8.92 (s, 1H, HC=N); ^{13}C NMR ($CDCl_3$): δ 21.3, 22.8, 45.1, 66.3, 117.4, 127.0, 127.5, 128.9, 129.2, 130.2, 131.2, 137.3, 148.9, 150.7, 154.0, 155.2, 160.3, 165.4; IR: ν 3030, 2962, 2904, 2855, 1617, 1579, 1538, 1507, 1494, 1444 cm^{-1}; MS (*m/z*) 377 (M^+), 347 (M^+-S), 291 (M^+-morpholine). Anal. Calcd for $C_{20}H_{19}N_5OS$: C, 63.64; H, 5.07; N, 18.55; S, 8.49. Found: C, 63.61; H, 5.01; N, 18.51; S, 8.45.

4-Methyl-2-piperidinopyrimido[4′,5′:2,3][1,4]thiazepino[7,6-*b*]quinoline (7d) This compound was obtained in 65% yield as an orange powder; mp 305–307°C; ^{1}H NMR ($CDCl_3$): δ 1.52–1.59 (m, 6H, $3CH_2$), 2.44 (s, 3H, CH_3), 3.71–3.73 (m, 4H, 2-CH_2N), 7.61 (t, 1H, ArH, *J* = 7.8 Hz), 7.80 (t, 1H, ArH, *J* = 7.8 Hz), 7.9 (d, 1H, ArH, *J* = 8.0 Hz), 8.14 (d, 1H, ArH, *J* = 8.0 Hz), 8.23 (s, 1H, ArH), 8.74 (s, 1H, HC=N); ^{13}C NMR ($CDCl_3$): δ 23.5, 24.7, 26.4, 54.8, 118.6, 126.3, 127.3, 127.8, 128.5, 129.1, 130.2, 137.1, 148.5, 160.8, 160.9, 161.4, 163.1, 163.6; IR: ν 3007, 2937, 2855, 1620, 1569, 1506, 1445 cm^{-1}; MS (m/z) 361 (M^+), 331 (M^+-S), 377 (M^+-piperidine). Anal. Calcd for $C_{20}H_{19}N_5S$: C, 66.46; H, 5.30; N, 19.37; S, 8.87. Found: C, 66.50; H, 5.12; N, 19.4; S, 8.9.

10-Chloro-4-methyl-2-piperidinopyrimido[4′,5′:2,3][1,4]thiazepino[7,6-*b*]quinoline (7e) This compound was obtained in 72% yield as a yellow powder; mp 272–274°C; ^{1}H NMR ($CDCl_3$): δ 1.56–1.61 (m, 6H, $3CH_2$), 2.50 (s, 3H, CH_3), 3.79–3.82 (m, 4H, $2CH_2$N), 7.16–7.21 (m, 1H, ArH), 7.83 (d, 1H, ArH, *J* = 4 Hz), 8.1 (d, 1H, ArH, *J* = 4 Hz), 8.23 (s, 1H, ArH), 8.74 (s, 1H, HC=N); ^{13}C NMR ($CDCl_3$): δ 25.8, 27.3, 27.6, 37.2, 125.6, 127.3, 131.1, 131.8, 132.5, 135.2, 137.0, 147.5, 150.3, 152.1, 153.6, 155.5, 159.4, 166.0; IR: ν 3024, 2990, 2926, 2831, 1629, 1611, 1593, 1500, 1395, 1337 cm^{-1}; MS (*m/z*) 395 (M^+), 397 (M^++2), 360 (M^+-Cl), 365 (M^+-S), 311 (M^+-piperidine). Anal. Calcd for $C_{20}H_{18}ClN_5S$: C, 60.67; H, 4.58; N, 17.69; S, 8.10. Found: C, 60.65; H, 4.45; N, 17.50; S, 8.16.

4,10-Dimethyl-2-piperidinopyrimido[4′,5′:2,3][1,4]thiazepino[7,6-*b*]quinoline (7f) This compound was obtained in 70% yield as a yellow powder; mp 294–295°C; ^{1}H NMR ($CDCl_3$): δ 1.55–1.61 (m, 6H, $3CH_2$), 2.35 (s, 3H, CH_3), 2.47 (s, 3H, CH_3), 3.63–3.67 (m, 4H, $2CH_2$N), 7.40 (d, 1H, ArH, *J* = 8 Hz), 7.84 (s, 1H, ArH), 7.92 (d, 1H, ArH, *J* = 8 Hz), 8.3 (s, 1H, ArH), 8.81 (s, 1H, HC=N); ^{13}C NMR ($CDCl_3$): δ 21.9, 23.7, 28.4, 33.9, 66.1, 117.1, 124.2, 125.9, 127.3, 128.3, 129.2, 130.8, 131.2, 136.3, 148.7, 150.7, 154.1, 162.3, 165.2; IR: ν 3020, 2940, 2835, 1616, 1562, 1501, 1445, 1363 cm^{-1}; MS (*m/z*) 375 (M^+), 377 (M^++2), (M^+-Cl), 345 (M^+-S), 391 (M^+-piperidine). Anal. Calcd for $C_{21}H_{21}N_5S$: C, 67.17; H, 5.64; N, 18.65; S, 8.54. Found: C, 67.20; H, 5.70; N, 18.63; S, 8.78.

Acknowledgments: The authors gratefully acknowledge the Research Council of Ferdowsi University of Mashhad for financial support of this project 25422/3.

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