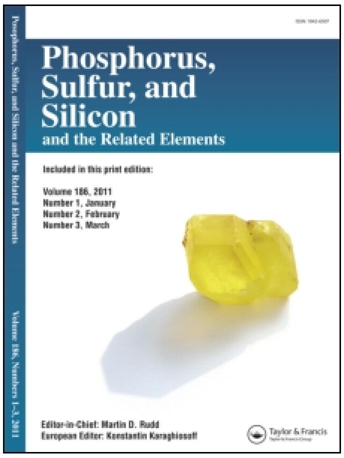

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Dimethyldithioimidocarbonates-Mediated Heterocyclizations: Synthesis of Imidazolidines and Benzheterocycles as Potent Antitubercular Agents

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A new series of thiadiazolylimidazolidines, thiadiazolylbenzimidazoles, thiadiazolylbenzoxazoles, and thiadiazolylbenzothiazoles were synthesized by heterocyclization reactions of dimethyldithioimidocarbonate of properly substituted thiadiazoles with various binucleophiles. The structures of all the newly synthesized compounds were elucidated and they were screened for antitubercular activity against Mycobacterium tuberculosis $H_{37}Rv$ using the BACTEC 460 radiometric system, where few compounds have shown more than 90% inhibition at MIC of <6.25 μg/mL in the preliminary screening level. They were also screened for their antibacterial activity against Escherichia coli *and* Bacillus cirrhosis*, and antifungal activity against* Aspergillus niger *and* Penicillium worthmanni*. Some of the compounds have shown promising in vitro antibacterial and antifungal activities.*

Keywords Antitubercular activity; antimicrobial activity; Dimethyldithioimidocarbonates; thiadiazolylimidazolidines; thiadiazolyl-benzheterocycles

INTRODUCTION

Thiadiazole derivatives are useful compounds having pharmacological and biological activities[1–6] such as antimicrobial,[1–3] anti-inflammatory,[4,5] anticonvulsant,[6] antihypertensive[7] and anticancer[8,9] activities. Furthermore, benzfused heterocycles. Particularly benzimidazoles, benzoxazoles, and benzothiazoles, are of considerable chemical and biological interest.[10–13] A combination of such two biodynamic

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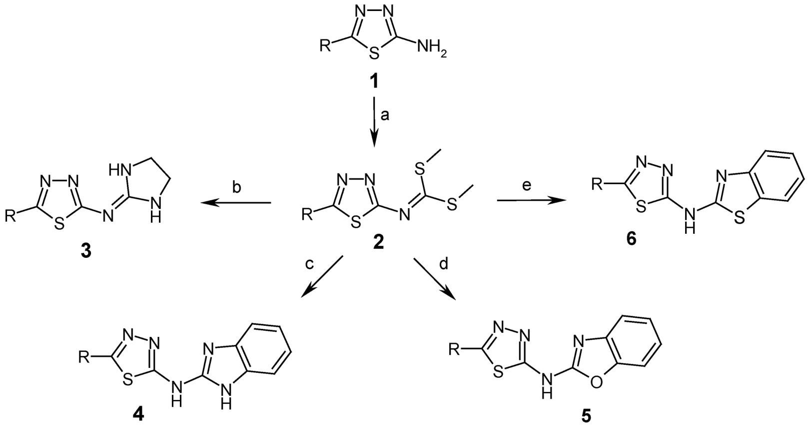
molecules is expected to increase the biological potency of the molecule in concern. In recent years much attention has been devoted to the synthesis of heterocycles as antitubercular and antimicrobial agents. The treatment of mycobacterial infections, especially tuberculosis, has become an important problem due to the emergence of monodrug and multidrug resistance.[13] It has been reported that the thiadiazole derivatives showed good activity against *Mycobacterium tuberculosis*.[15–17]

RESULTS AND DISCUSSION

The new key intermediate dimethyl 5-(benzyl/3-pyridyl)-1,3,4-thiadiazol-2-yldithioimidocarbonates (**2a**,**b**) were synthesized from corresponding 2-amino-5-(benzyl/3-pyridyl)thiadiazoles (**1a**,**b**)[18,19] by the reaction with carbon disulfide and methyl iodide in alkaline medium (Scheme 1). The products are characterized by the absence of υ_{N-H} in the IR spectra and by the presence of a singlet for six protons (at δ 2.6 for **2a** and δ 2.74 for **2b**) due to two equivalent $-SCH_3$ groups in ^1H NMR spectra. The rest of the protons resonated in the expected region. Furthermore, compound **2b** was confirmed by a ^{13}C NMR spectrum, which exhibited a characteristic signal at δ 16.4 due to carbon of two magnetically equivalent SCH_3 groups.

The intermediates dimethyldithioimidocarbonates (**2a**,**b**) were treated with ethylenediamine in DMF to yield corresponding imidazolidine derivatives (**3a**,**b**). The products obtained possessed the strong



SCHEME 1 Reagents and conditions: (a) i. aq. NaOH (20 M),CS_2, 0°C/DMF, ii. CH_3I, 0°C; (b) ethylene diamine/DMF, 120°C, 6 h; (c) 2-phenelenediamine/DMF, 120°C, 6–8 h; (d) 2-aminophenol/DMF, 120°C, 8 h; (e) 2-aminothiophenol/DMF, 120°C, 6–8 h.

υ_{N-H} around the 3330 cm^{-1} band in IR spectra, and the ^{1}H NMR spectra displayed a D_2O exchangeable broad singlet in the region δ 7.3 to 7.7 assigned for two equivalent NH protons; a singlet around δ 3.6 for 4 protons was observed indicating the fact that both hydrogens are located (Figure 1) on ring nitrogens, thus making the protons —CH_2CH_2— of imidazolidine equivalent. Furthermore the ^{13}C NMR spectrum of imidazolidine **3b** showed a characteristic signal at δ 37.5 for —CH_2-CH_2— confirming both carbons are equivalent in accordance with the ^{1}H NMR report. Compound **3b** is also confirmed by mass (ESI) spectrum.

Similarly, when intermediate dimethyldithioimidocarbonates (**2a**,**b**) were reacted with binucleophiles viz. *o*-phenylenediamine, 2-aminophenol and 2-amino thiophenol afforded corresponding benzimidazoles (**4a**,**b**), benzoxazoles (**5a**,**b**), and benzothiazoles (**6a**,**b**), respectively. From the ^{1}H NMR spectrum of benzimidazole (**4b**), it is clear that both NH protons are equivalent. This is due to the reason as described in the case of imidazolidine derivatives (**3a**,**b**). Furthermore, this is supported by the fact that, in the ^{1}H NMR spectra of benzimidazole derivatives (**4a**,**b**), C_5-H, and C_6-H of benzimidazole ring was observed as a doublet at δ 7.2 and C_4, C_7-H was observed as a doublet at δ 7.4. The ^{1}H NMR and ^{13}C NMR spectra of all benzheterocycles are in total agreement with the assigned structures. The mass spectrum of benzoxazole derivative **5a** showed a molecular ion peak at 308.1 (100%), which corresponds to its molecular weight (308.37). The new heterocyclic systems (**3–6**) were successfully constructed by the 4+1 approach, and the evolution of methanethiol (MeSH) was observed during the course of heterocyclization reactions.

BIOLOGICAL ACTIVITY

The in vitro antimycobacterial activity was assayed by Tuberculosis Antimicrobial Acquisition and Coordinating Facility (Birmingham, Alabama, USA), an antitubercular drug discovery program. Primary screening was conducted at 6.25 μg/mL against *M. tuberculosis* $H_{37}Rv$ (ATCC 27294) in BACTEC 12B[20,21] medium using a broth microdilution assay,[22]the Microplate Alamar Blue Assay (MABA). Compounds exhibiting fluorescence were tested in the BACTEC 460 radiometric

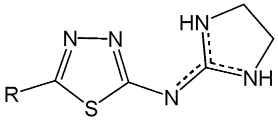


FIGURE 1 The delocalization of hydrogens over nitrogen atoms.

TABLE I The *In Vitro* Antitubercular Activity of Compounds Against *M. tuberculosis* $H_{37}Rv$

Compound no.	Assay	MIC in μg/mL	% Inhibition	Activity
2a	Alamar	>6.25	88	—
2b	Alamar	>6.25	73	—
3a	Alamar	>6.25	77	—
3b	Alamar	>6.25	37	—
4a	Alamar	>6.25	77	—
4b	Alamar	>6.25	74	—
5a	Alamar	>6.25	93	+
5b	Alamar	>6.25	95	+
6a	Alamar	>6.25	53	—
6b	Alamar	>6.25	61	—

system. Compounds affecting <90% inhibition in the primary screen were not further evaluated. Compounds demonstrating at least 90% inhibition in preliminary screening were tested at lower concentrations by serial dilution against *M. tuberculosis* $H_{37}Rv$ to determine the MIC using MABA. Compounds **5a** and **5b** exhibited excellent inhibitory activity of 93% and 95%, respectively, which were selected for further screening, where it exhibited promising inhibitory activity of 58% and 39%, respectively.

Preliminary antituberculosis activity data (Table I) reveals that intermediate dimethyl-5-alkyl/aryl-1,3,4-thiadiazol-2-yldithioimidocarbonates (**2a**,**b**) are very active, and out of all heterocyclized derivatives, only benzoxazole derivatives (**5a**,**b**) have shown very good activity against *M. tuberculosis* $H_{37}Rv$ at <6.25 μg/mL. Other compounds have shown moderate activity.

Biological significance of all the derivatives was also established by screening them against two bacterial strains *Bacillus cirrohsis* and *Escherichia coli* and two fungal species *Aspergillus niger* and *Penicillium wortmannii* by the cup plate method[19] at the concentration 25–100 μg/mL using DMF as a solvent. Norfloxacin and Greseofulvin, respectively, were used as standards. In general, antimicrobial activity data (Table II) revealed that among all the newly synthesized compounds, pyridine-substituted (at C-5 position of thiadiazole ring) compounds have shown very good antibacterial and antifungal activity at 100 μg/mL concentration and moderate activity at a lower concentration of 25 μg/mL. In particular, benzimidazole derivatives (**4a**,**b**) have shown good antibacterial activity at a higher concentration.

TABLE II The *In Vitro* Antibacterial Activity and Antifungal Activity

Compound no.	Antibacterial activity (Standard: Norfloxacin)						Antifungal activity (Standard: Greseofulvin)					
	Escherichia coli			*Bacillus cirrhosis*			*Penicillium wortmannii*			*Aspergillus niger*		
	100	50	25	100	50	25	100	50	25	100	50	25
	Relative Inhibition (%)			Relative Inhibition (%)			Relative Inhibition (%)			Relative Inhibition (%)		
2a	78	63	50	72	48	—	68	—	—	57	—	—
2b	85	68	57	76	54	42	82	65	52	78	64	58
3a	65	—	—	85	58	—	48	—	—	55	—	—
3b	86	68	62	89	68	56	76	62	55	75	52	—
4a	55	—	—	79	62	53	72	58	—	54	—	—
4b	75	64	58	84	68	56	90	72	65	74	54	48
5a	71	—	—	48	—	—	74	52	—	48	—	—
5b	85	72	67	72	52	—	72	56	42	78	64	56
6a	65	—	—	72	—	—	70	55	—	62	—	—
6b	72	64	48	82	58	45	75	68	55	72	54	—

In conclusion the preliminary *in vitro* antituberculosis, antibacterial, and antifungal screening results of novel imidazolidine and benzheterocycle derivatives of 1,3,4-thiadiazole reported in the present article reveal that many of the compounds from the series have emerged as potent antitubercular, antibacterial, and antifungal agents endowed with moderate to good activity. Possible improvements in the activity can be further achieved by slight modifications in the new heterocyclic systems reported in this article. Our findings will have an impact on chemists and pharmacists for further investigations in this field in search of potent antitubercular and antimicrobial agents.

EXPERIMENTAL

Melting points were determined using an electric melting point apparatus (Shital scientific industries, Mumbai) and are uncorrected. IR spectra (KBr) were run on a Nicolet impact 410 FT-IR spectrometer (ν_{max} in cm^{-1}). ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$, DMSO-d_6, and TFA with TMS as an internal standard (chemical shift in δ, ppm and J values in Hz) on a Brucker 300 MHz FTNMR spectrometer. Mass spectra were recorded on Thermo-Finnigan-MAT, Bremen (Model MAT8200) spectrometer. Electrospray ionization mass spectrum (ESI-MS) was recorded on a Quattro LCZ (Walters-Micromass, Manchester), and elemental analyses were carried out on a Heraus CHN rapid analyzer. Purity of the compound was checked by TLC. Nomenclature was made using Chemsketch software. All the reagents were of laboratory reagent quality and were used after purification.

Preparation of Dimethyl 5-(benzyl/3-pyridyl)-1,3,4-thiadiazol-2-yldithio imidocarbonates (2a,b): General Procedure

To a well-stirred solution of 2-amino-5-(benzyl/3-pyridyl)-1,3,4-thiadiazole **2** (10 mmol) in dimethylformamide (8 mL) were added sodium hydroxide solution (20 M, 4 mL), carbon disulfide (1.52 g, 20 mmol), and methyl iodide (3.384 g, 24 mmol) in sequence at an interval of 30 min at 0–5°C. Stirring was continued for 4 h, during which the temperature was slowly raised to r.t. The mixture was then poured into cold water, and the resulting sticky solid was extracted with chloroform, washed with water and dried over anhydrous sodium sulphate. The solvent was removed under diminished pressure, and the residual solid was recrystallized from a chloroform-hexane mixture to yield the corresponding dimethyldithioimidocarbonate (**2a**,**b**) in moderate yields as crystalline solids.

Dimethyl 5-benzyl-1,3,4-thiadiazol-2-yldithioimidocarbonate (2a)

Pale yellow needles (chloroform + hexane), yield 61%, m.p. 88–90°C; IR (KBr) υcm^{-1}: 3052, 2977, 2925, 1608, 1574; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.59 (s, 6H, SCH_3), 4.35 (s, 2H, CH_2), 7.25–7.36 (m, 5H, phenyl). Anal. calcd. for $C_{12}H_{13}N_3S_3$: C, 48.78; H, 4.44; N, 14.22. Found: C, 48.93; H, 4.50; N, 14.08%.

Dimethyl 5-pyridin-3-yl-1,3,4-thiadiazol-2-yldithioimidocarbonate (2b)

Bright yellow granules, m.p. 130–132°C; IR (KBr) υcm^{-1}: 3038, 2978, 2919, 1583, 1568; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.74 (s, 6H, SCH_3), 7.47 (dd, $J_{H5H4} = 4.8$ Hz, $J_{H5H6} = 3.1$ Hz, 1H, C_5-H, pyridine), 8.29 (d, $J = 4.8$ Hz, 1H, C_6-H, pyridine), 8.68 (d, $J = 4.4$ Hz, 1H, C_4-H, pyridine), 9.08 (s, 1H, C_2-H, pyridine); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 16.4, 124.2, 127.4, 134.6, 148.6, 151.7, 162.9, 169.0 and 177.1. Anal. calcd. for $C_{10}H_{10}N_4S_3$: C, 42.53; H, 3.57; N, 19.84. Found: C, 42.76; H, 3.61; N, 19.70%.

Preparation of 5-(benzyl/3-pyridyl)-*N*-imidazolidin-2-ylidene-1,3,4-thiadiazol-2-amine (3a,b): General Procedure

A mixture of **2** (2 mmol) and ethylenediamine (0.14 g, 2.4 mmol) in dimethylformamide (10 mL) was heated to 120°C for 6 h. The solid that separated after cooling was collected by filtration, washed with aq. ethanol, dried, and recrystallized from ethanol.

5-Benzyl-N-imidazolidin-2-ylidene-1,3,4-thiadiazol-2-amine (3a)

Colorless cubes (ethanol), yield 65%, m.p. 198–200°C; IR (KBr) υcm^{-1}: 3343, 2976, 1626, 1558; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.67 (s, 4H, imidazolidine), 4.23 (s, 2H, CH_2), 7.24–7.35 (m, 5H, phenyl), 7.72 (s, 2H, NH, D_2O exchangeable); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 37.3, 42.7, 127.4, 129.10, 129.14, 137.9, 161.5, 161.6 and 176.4. Anal. calcd. for $C_{12}H_{13}N_5S$: C, 55.58; H, 5.05; N, 27.01. Found: C, 55.74; H, 5.17; N, 26.88%.

N-Imidazolidin-2-ylidene-5-pyridin-3-yl-1,3,4-thiadiazol-2-amine (3b)

Colorless needles (ethanol), yield 61%, m.p. 254–256°C; IR (KBr) υcm^{-1}: 3335, 3046, 2962, 1618, 1572, 1527; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.58 (s, 4H, imidazolidine), 7.35 (s, 2H, NH, D_2O exchangeable), 7.47 (dd, $J_{H5H4} = 4.8$ Hz, $J_{H5H6} = 7.3$ Hz, 1H, C_5-H, pyridine), 8.29 (d, $J = 7.8$ Hz, 1H, C_6-H, pyridine), 8.68 (d, $J = 4.4$ Hz, 1H, C_4-H, pyridine), 9.08 (s, 1H, C_2-H, pyridine); MS (ESI): 247.07 (M+H), 269.05 (M+Na), 515.12 (2M+Na). Anal. calcd. for $C_{10}H_{10}N_6S$: C, 48.77; H, 4.09; N, 34.12. Found: C, 48.94; H, 4.17; N, 33.96%.

Preparation of *N*-{5-(benzyl/3-pyridyl)-1,3,4-thiadiazol-2-yl}-1*H*-benzimidazol-2-amine (4a,b): General Procedure

A mixture of **2** (2 mmol) and *o*-phenylenediamine (0.26 g, 2 mmol) was heated (120°C) in dimethylformamide (10 mL) for 8 h. The separated solid was collected by filtration, washed with aqueous alcohol, dried, and recrystallized from a suitable solvent.

N-(5-Benzyl-1,3,4-thiadiazol-2-yl)-1H-benzimidazol-2-amine (4a)

Colorless needles (DMF), yield 72%, m.p. 264–268°C; IR (KBr) υcm^{-1}: 3228, 3060, 2976, 1608, 1576, 1544; ^{1}H NMR (300 MHz, DMSO-d_6+ TFA) δ: 4.28 (s, 2H, CH_2), 7.22–7.67 (m, 9H, benzimidazole). Anal. calcd. for $C_{16}H_{13}N_5S$: C, 62.52; H, 4.26; N, 22.78. Found: C, 62.41; H, 4.31; N, 22.63%.

N-(5-Pyridin-3-yl-1,3,4-thiadiazol-2-yl)-1H-benzimidazol-2-amine (4b)

Bright yellow solid (DMF), yield 75%, m.p. >300°C; IR (KBr) υcm^{-1}: 3242, 3054, 1616, 1585, 1547; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.15 (d, $J = 3.3$ Hz, 2H, C_5, C_6-H, benzimidazole), 7.39 (d, $J = 3.3$ Hz, 2H, C_4, C_7-H, benzimidazole), 7.55 (t, $J = 7.0$ Hz, 1H, C_5-H, pyridine), 8.23 (d, $J = 6.9$ Hz, 1H, C_6-H, pyridine), 8.66 (d, $J = 6.9$ Hz, 1H, C_4-H, pyridine), 9.04 (s, 1H, C_2-H, pyridine), 12.06 (br s, 2H, NH, D_2O exchangeable); ^{13}C NMR (75 MHz, DMSO-d_6+ TFA) δ: 110.0, 113.1, 113.8, 117.6, 121.4, 124.5, 127.4, 129.2, 130.4, 141.3, 142.7, 146.0, 147.3 and 155.1. Anal. calcd. for $C_{14}H_{10}N_6S$: C, 57.13; H, 3.42; N, 28.55. Found: C, 57.25; H, 3.30; N, 28.38%.

Preparation of *N*-{5-(benzyl/3-pyridyl)-1,3,4-thiadiazol-2-yl}-1,3-benzoxazol-2-amine (5a,b): General Procedure

A mixture of dimethyldithioimidocarbonate **2** (2 mmol) and 2-aminophenol (0.26 g, 2.4 mmol) in dimethylformamide (12 mL) was heated at 120°C for 8 h. The separated solid was collected by filtration, washed with aqueous alcohol, dried and recrystallized from a methanol-dimethylformamide mixture.

N-(5-Benzyl-1,3,4-thiadiazol-2-yl)-1,3-benzoxazol-2-amine (5a)

Pale yellow prisms (methanol + DMF), yield 69%, m.p. 282–286°C; IR (KBr) υcm^{-1}: 3164, 3036, 1595, 1578, 1545; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 4.27 (s, 2H, CH_2), 7.12–7.49 (m, 9H, benzoxazole), 13.95 (s, 1H, NH, D_2O exchangeable); ^{13}C NMR (75 MHz, DMSO-d_6 + TFA): 36.3, 110.6, 113.8, 116.0, 117.6, 121.4, 123.7, 125.2, 129.5, 129.6, 137.0, 138.2, 148.0 and 163.4; MS *m/z* (%): 308.0 (100), 270.1 (2.9), 248.0 (8.6), 177.0 (19.7), 160.1 (47.7). Anal. calcd. for $C_{16}H_{12}N_4OS$: C, 62.32; H, 3.92; N, 18.17. Found: C, 62.58; H, 3.81; N, 18.05%.

N-(5-Pyridin-3-yl-1,3,4-thiadiazol-2-yl)-1,3-benzoxazol-2-amine (5b)

Pale yellow granules (methanol + DMF), yield 70%, m.p. >300°C; IR (KBr) υcm^{-1}: 3320, 3072, 1609, 1572; ^{1}H NMR (300 MHz, DMSO-d_6+ TFA) δ: 7.31–7.48 (m, 4H, benzoxazole), 7.56 (t, $J = 7.4$ Hz, 1H, C_5-H, pyridine), 8.25 (d, $J = 7.2$ Hz, 1H, C_6-H, pyridine), 8.66 (d, $J = 7.0$ Hz, 1H, C_4-H, pyridine), 9.04 (s, 1H, C_2-H, pyridine). Anal. calcd. for $C_{14}H_9N_5OS$: C, 56.94; H, 3.07; N, 23.71. Found: C, 57.18; H, 3.12; N, 23.56%.

Preparation of *N*-{5-(benzyl/3-pyridyl)-1,3,4-thiadiazol-2-yl}-1,3-benzothiazol-2-amine (6a,b): General Procedure

A mixture of dimethyldithioimidocarbonate **2** (2 mmol) and 2-aminothiophenol (0.3 g, 2.4 mmol) in dimethylformamide (12 mL) was heated at 120°C for 6–8 h. The solid that separated was collected by filtration, washed with aqueous ethanol, dried, and recrystallized from a suitable solvent.

N-(5-Benzyl-1,3,4-thiadiazol-2-yl)-1,3-benzothiazol-2-amine (6a)

Light green granules (DMF), yield 64%, m.p. 264–266°C; IR (KBr) υcm^{-1}: 3331, 3052, 1620, 1584, 1546; ^{1}H NMR (300 MHz, DMSO-d_6 + TFA) δ: 4.32 (s, 2H, CH_2), 7.15–7.52 (m, 9H, benzothiazole). Anal. calcd. for $C_{16}H_{12}N_4S_2$: C, 59.23; H, 3.73; N, 17.27. Found: C, 59.48; H, 3.80; N, 17.12%.

N-(5-Pyridin-3-yl-1,3,4-thiadiazol-2-yl)-1,3-benzothiazol-2-amine (6b)

Light green granules (DMF), yield 67%, m.p. 288–292°C; IR (KBr) υcm^{-1}: 3326, 3048, 1622, 1585, 1545; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.26 (t, $J = 7.5$ Hz, 1H, C_6-H, benzothiazole), 7.42 (t, $J = 7.5$ Hz, 1H, C_5-H, benzothiazole), 7.54–7.91 (m, 3H, C_4, C_7-H, benzothiazole;

C_5-H, pyridine), 8.31 (d, $J = 7.2$ Hz, 1H, C_4-H, pyridine), 8.70 (d, $J = 7.0$ Hz, 1H, C_6-H, pyridine), 9.10 (s, 1H, C_2-H, pyridine), 13.23 (br s, 1H, NH, D_2O exchangeable); ^{13}C NMR (75 MHz, DMSO-d_6 + TFA) δ: 109.8, 113.6, 117.5, 121.3, 122.5, 123.9, 127.1, 128.0, 130.3, 130.7, 140.5, 142.8, 143.2 and 154.8. Anal. calcd. for $C_{14}H_9N_5S_2$: C; 54.00, H, 2.91; N, 22.49. Found: C; 54.26; H, 3.02; N, 22.34%.

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