A CONVENIENT SYNTHESIS OF PYRIDO[3,2-b][1,4]-BENZOTHIAZINE DERIVATIVES *VIA* OXIDATIVE RING CLOSURE OF 3-SUBSTITUTED 6-[*N*-(2-MERCAPTO-PHENYL)]AMINOPYRIDINES

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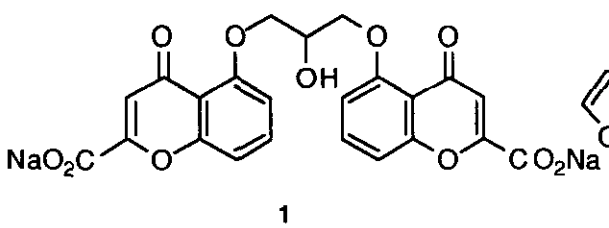
Abstract-3-Substituted pyrido[3,2-b][1,4]benzothiazines were prepared either by heating the disulfide derivatives, which were obtained by a treatment of 3-substituted 6-[*N*-(2-mercapto-phenyl)]aminopyridines with diethyl azodicarboxylate (DEAD) or NBS in DMF at room temperature under the basic conditions or directly by heating the reaction mixture 3-substituted 6-[*N*-(2-mercapto-phenyl)]aminopyridines.

The discovery of cromolyn sodium (DSCG, **1**),[1] as a clinically effective antiallergic agent, was resulted from structural variation of the naturally occurring chromone, khellin (**2**),[2-3] which possessed bronchodilatory properties. As an antiallergic agent, DSCG appears to act mainly by inhibition of the liberation of the mediators of



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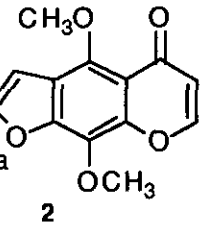

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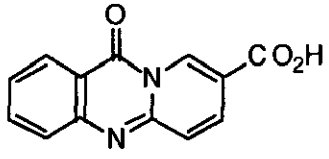

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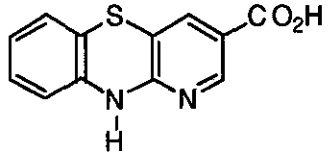


4a

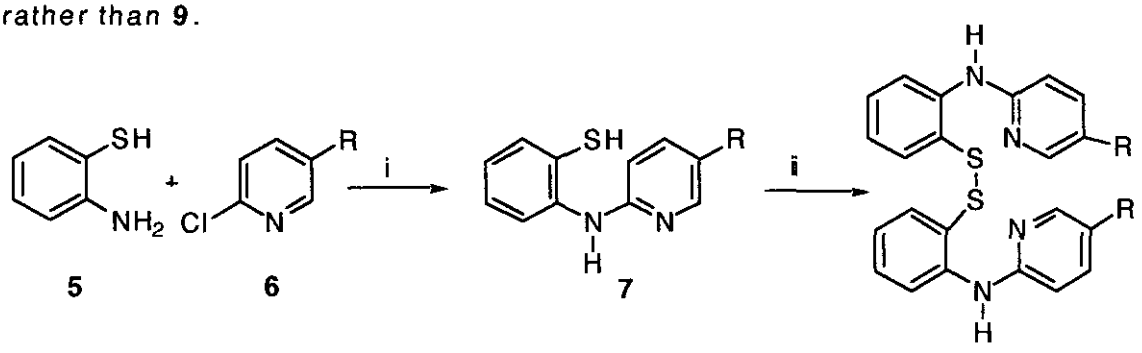
allergic reactions initiated by antigen-antibody interactions. However, due to its lack of oral absorption, which necessitates topical administration, DSCG lacks the broad efficacy of bronchodilators and as a prophylactic drug can prevent, but not alleviate, an asmatic attack.[4] Hence, an effective and orally active antiallergic agent with fewer side effects is still needed. From this point of view, compounds possessing both acidic and basic moieties in one molecule have been considered as potential antiallergic agents.[4] Compound such as pyrido[2,1-b]quinazoline-8-carboxylic acid has been found to be orally active potent antiallergic agents.[5-7] With these compounds as precendent, we are interesting in the synthesis of pyrido[3,2-b][1,4]-benzothiazine (1-azaphenothiazine) ring system containing a carboxylic group as analogous of the potent antiallergic compounds.

A perusal of literature demonstrated that there are several methods for the preparation of pyrido[3,2-b][1,4]benzothiazine derivatives, such as, direct thionation of 2-anilinopyridine with sulfur in the presence of iodine by heating at 250 °C;[8-9] treatment of 2-(3-pyridylthio)aniline derivatives with zinc at 230-240 °C;[10] through a Smiles rearrangement of 2-(*o*-aminophenylthio)-3-nitro-5-chloropyridine;[11-12] or by a thermal transformation of 3-[[2'-(2-propynylthio)phenyl]amino]-1,2,4-triazines.[13] However, these approaches need drastic conditions and the yield is low. A mild and efficient methodology toward the preparation of various pyrido[3,2-b]benzo-thiazine derivatives for biological evaluation is needed to be explored. In this paper, we report herein an alternative approach for the synthesis of this ring system by oxidative coupling reaction of 6-(*o*-mercaptophenyl)aminopyridine with certain oxidants.

To study the feasibility of this oxidative ring closure reaction, we are directed toward the synthesis of 6-(*o*-mercaptophenyl)aminopyridines (**7a-b**). First of all, 2-aminothiophenol (**5**) was reacted with 6-chloropyridine-3-carboxylic acid (**6a**) in acetic acid at reflux temperature and it gave 6-[*N*-(2-mercaptophenyl)]aminopyridine-3-carboxylic acid (**7a**) in 90% yield. The structure of this product was further confirmed by ^{1}H-nmr spectrum illustrating two deuterium oxide exchangeable peaks centered at δ 9.20 and 10.33 which are corresponding to the NH and SH, respectively. An analogous reaction by a treatment of **5** with 6-chloro-3-pyridinecarboxamide (**6b**) gave 6-[*N*-(2-mercapto-phenyl)]aminopyridine-3-carboxamide (**7b**) in 98% yield.

To affect the ring closure of **7a-b**, diethyl azodicarboxylate (DEAD) was chosen as coupling agent. When **7b** was treated with one equivalent of DEAD in CH_3CN at reflux, it afforded only 2.4% yield of pyrido[3,2-b][1,4]benzothiazine-3-carboxamide (**4b**) after column chromatography and recovered a large amount of starting

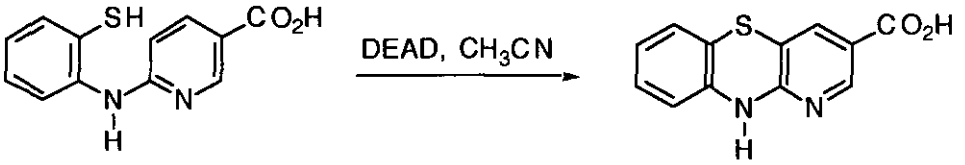
material. ^{1}H-Nmr spectrum of **4b** revealed that there are two doublets centered at δ 7.63 and 8.28, which are corresponding to the two aromatic protons on the pyridine ring, with a coupling constant 1.8 Hz through W-type interaction. This lends some support to the fact that the oxidative ring closure occurred at the carbon atom instead of the nitrogen atom. Thus, the structure of this product was assigned to be **4b** *rather than* **9**.



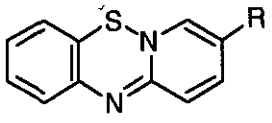
5 **6** **7** **8**

i, CH_3CO_2H, reflux, 24 h; ii, DEAD or NBS, DMF, 3-12 h.

a, R = CO_2H; b, R = $CONH_2$



7b **4b** (2.4%)



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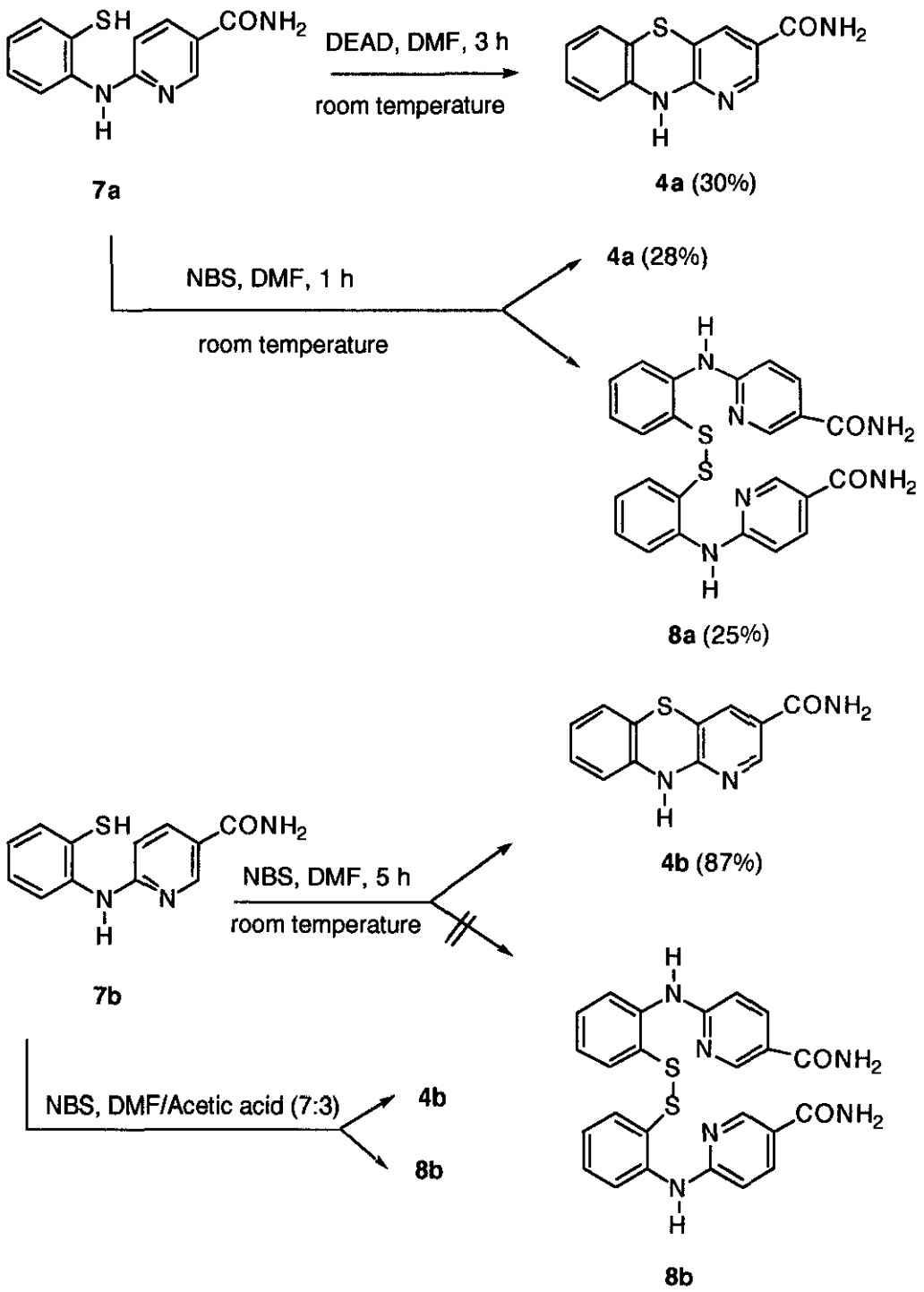
Meanwhile, ^{1}H-nmr spectrum of **4b** demonstrated that the two protons of carboxamide moiety on pyridine ring were recorded as two broad singlets at δ 7.26 and 7.78, indicative of the carboxamide exisiting in partial double bond. We reasoned that the poor yield of this reaction was probably due to the poor solubility of **7b** *in* CH_3CN. *Therefore, the solvent of the reaction was changed to* DMF.

Subsequently, repeating the same reaction at room temperature, compounds (**7a**) and (**7b**) were just oxidized to give di[2-(pyridine-3-carboxylic acid-6-yl)amino]-phenyl disulfide (**8a**) in 76% yield and di[2-(pyridine-3-carboxamide-6-



yl)amino]phenyl disulfide (**8b**) in 99% yield, respectively. No cyclized compounds were observed. On the basis of reactions described above, the formation of **4a** was probably through the initial oxidation of mercapto compound (**7a**) to disulfide (**8a**). Thus, an attempt to effect the ring closure reaction, at outset, **8a** was directly heated to reflux in DMF and the reaction did not occur at all. However, when this reaction was performed in the presence of sodium carbonate, it gave **4a** in 38% yield. Finally, compound (**4a**) was directly obtained in 30% yield by heating the reaction mixture after **7a** was treated with DEAD at room temperature for 3 h.

On the other hand, when **7a** was treated with *N*-bromosuccimide (NBS) in DMF at room temperature, it furnished disulfide (**8a**) (25%) and cyclized compound (**4a**) (28%). However, **4a** can also be prepared in 66% yield by directly heating the reaction mixture of **7a** and NBS in DMF. An analogous treatment of **7b** with NBS led to the formation of only **4b** in 87% yield. Surprisingly, there is no disulfide product observed in this reaction. This can be abscribed to the effect of carboxylic group of **7a** on the reactivity. To examine the acidic effect of the carboxylic group on the formation of disulfide, **7b** was treated with NBS in a mixture of DMF and acetic acid (7:3). It led to the formation of compounds (**4b**) and (**8b**) in the reaction mixture. This lend some support to the facts that the thiol group is readily oxidized to disulfide in acidic condition. Compound (**4a**) was evaluated for its antiallergic activity by their ability to inhibit passive cutaneous anaphylaxis (PCA) in rats. The preliminarly data showed an inhibition greater 50% at 1.0 mg/kg orally.

EXPERIMENTAL

General Methods: Melting points were obtained on an Electrothermal apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 983 G spectrophotometer. ^{1}H and ^{13}C nuclear magnetic resonance spectra were recorded on a either a JEOL JNM-EX400 or on a Bruker Model AM 300 spectrometer from National Taiwan University, Taipei, and are reported in parts per million with DMSO-d_6 as the internal standard on a δ scale. EI mass spectra was recorded on JEOL JMS-D100 mass spectrometer from National Taiwan University. Elemental analyses for C, H, and N were carried either on a Heraeus Elemental Analyzer in Cheng-Kong University, Tainan, or on a Perkin-Elmer 240 Elemental Analyzer in National Taiwan University.

6-[*N*-(2-Mercaptophenyl)]aminopyridine-3-carboxylic acid (7a)

A mixture of **6a** (2.0 g, 12.7 mmol) and **5** (1.6 ml, 14.1 mmol) in acetic acid (30 ml) was refluxed under heating mantle for 24 h. After the mixture was cooled to room temperature, the white solid was collected by filtration and recrystallized from a

mixture of DMF and water (9:1) to afford **7a** (2.92 g, 90%), mp 219 °C. Ir (KBr): 2459 (SH) cm^{-1}; ^{1}H-nmr (300 MHz, DMSO-d_6): δ 6.92 (d, 1H, *J* = 8.8 Hz , Ar-H), 7.26 (t, 1H, *J* = 7.4 Hz, Ar-H), 7.33 (t, 1H, *J* = 7.5 Hz, Ar-H), 7.42 (d, 1H, *J* = 7.6 Hz, Ar-H), 7.64 (d, 1H, *J* =7.6 Hz, Ar-H), 8.10 (d, 1H, *J* = 8.9Hz, Ar-H), 8.47 (s, 1H, Ar-H), 9.20 (br s, 1H, NH, D_2O exchangeable), 10.33 (br s, 1H, -SH, D_2O exchangeable);^{13}C -nmr (75 MHz, DMSO-d_6): δ 110.36, 117.06, 126.89, 127.48, 128.72, 129.37, 132.99, 135.94, 140.24, 146.00, 156.75, 165.34 (C=O); ms: *m/z* 246 (M^+, 30%), 230 (M^+-16), 213 (M^+-33, 100%). Anal. Calcd for $C_{12}H_{10}N_2O_2S$: C, 58.51; H, 4.09; N, 11.37. Found: C, 58.13; H, 3.87; N, 10.97.

6-[*N*-(2-Mercaptophenyl)]aminopyridine-3-carboxamide (7b) was prepared in 98 % yield by a similar approach which afforded **7a**. An analytical sample was recrystallized from DMF and water, mp 195 °C; ^{1}H-nmr (300 MHz, DMSO-d_6): δ 7.05 (d, 1H, *J* = 9.0 Hz, Ar-H), 7.22-7.46 (m, 3H), 7.63 (d, 1H, *J* = 7.4 Hz, Ar-H), 7.85 (br s, 1H, NH, D_2O exchangeable), 8.28 (d, 1H, *J* = 9.0 Hz, Ar-H), 8.52 (s, 1H, Ar-H), 10.74 (br s, 1H, -SH, D_2O exchangeable); ^{13}C-nmr (75 MHz, DMSO-d_6): δ 111.40, 120.51, 127.34, 128.27, 129.12, 129.70, 133.20, 135.08, 140.81, 141.00, 154.46, 164.56 (C=O); ms: *m/z* 245 (M^+), 229 (M^+-16), 212 (M^+-33, 100%), 199 (M^+-46). Anal. Calcd for $C_{12}H_{11}N_2OS$: C, 58.76; H, 4.52; N, 17.13. Found: C, 59.04; H, 4.20; N, 16.91.

Pyrido[3,2-b][1,4]benzothiazine-3-carboxylic acid (4a) and di[2-(pyridine-3-carboxylic acid-6-yl)amino]phenyl disulfide (8a)

Method A: A mixture of **7a** (2.0 g, 8.13 mmol) and NBS (1.45 g, 8.15 mmol) in DMF (20 ml) was stirred at room temperature. After 1 h, the solvent was removed in vacuo and then to the residue was added water and EtOH (9:1, 20 ml). The resulting yellow-green solid was collected by filtration and recrystallized from DMF and water (9:1) to give **4a** (0.56 g, 28 %), mp 325 °C; ^{1}H-nmr (300 MHz, DMSO-d_6): δ 6.82 (m, 3H, Ar-H), 6.98 (t, 1H, *J* = 6.6 Hz, Ar-H), 7.57 (d, 1H, *J* = 1.9 Hz, Ar-H), 8.28 (d, 1H, *J* = 1.9 Hz, Ar-H), 9.72 (s, 1H, -NH, D_2O exchangeable), 12.79 (br s, 1H, COOH, D_2O exchangeable); ^{13}C-nmr (75 MHz, DMSO-d_6): δ 112.02, 115.27, 115.68, 120.59, 123.40, 125.85, 127.78, 133.57, 139.09, 148.07, 155.50, 165.51(C=O); ms: *m/z* 244 (M^+, 100%), 227 (M^+-17), 212 (M^+-32), 199 (M^+-45). Anal. Calcd for $C_{12}H_8N_2O_2S$: C, 59.00; H, 3.30; N, 11.47. Found: C, 58.81; H, 3.43; N, 11.64. The filtrate was rotary evaporated to dryness in vacuo and the residue was dissolved in warm ethanol (20 ml). The solution was rotary evaporated onto 2 g of silica gel, which was then loaded onto a column of silica gel (30 g, 2.1 X 20 cm) slurry-packed in chloroform and acetic acid (200:1). Elution with this same solvent system afforded **8a** (0.5 g, 25%). An analytical sample was recrystallized from DMF and water (9:1),

mp 210 °C; ^{1}H-nmr (300 MHz, DMSO-d_6): δ 6.70 (d, 1H, J = 8.6 Hz, Ar-H), 7.17 (t, 1H, J = 7.5 Hz, Ar-H), 7.28 (t, 1H, J = 7.4 Hz, Ar-H), 7.42 (d, 1H, J = 7.7 Hz, Ar-H), 7.60 (d, 1H, J = 7.74 Hz, Ar-H), 7.97 (d, 1H, J = 8.6 Hz, Ar-H), 8.57 (s, 1H, Ar-H), 9.26 (br s, 1H, -NH, D_2O exchangeable); ^{13}C-nmr (75 MHz, DMSO-d_6): δ 108.55, 116.88, 126.17, 126.25, 128.20, 128.80, 132.50, 137.50, 138.46, 149.91, 159.02, 166.36 (C=O); ms: *m/z* 244 ($^1/_2$M$^+$-1). Anal. Calcd for $C_{24}H_{18}N_4O_4S_2 \cdot 2H_2O$: C, 54.53; H, 4.12; N, 10.25. Found: C, 54.78; H, 4.12; N, 10.25.

Method B:
A mixture of **7a** (2.0 g, 8.13 mmol) and DEAD (2.0 ml, 10.8 mmol) in DMF (30 ml) was stirred at room temperature for 3 h. The reaction mixture was rotary evaporated to dryness in vacuo and then to the residue was added water (20 ml) to get precipitate. The solid was collected by filtration and dried in oven for 12 h. The crude product was dissolved in hot DMF (10 ml) and to the mixture was added Norite (0.1 g). The mixture was then filtered through a bed of Celite. To the filtrated was added 30 ml of water to get precipitate to give **8a** (1.62 g, 76%): mp 208 °C.

Method C:
To a mixture of **8a** (0.5 g, 2.0 mmol) in DMF (30 ml) was added sodium hydrocarbonate (0.4 g, 4.8 mmol). The reaction mixture was refluxed in a heating mantle for 10 h. The solvent was rotary evaporated in vacuo to dryness. To the residue was added water (100 ml) and the solution was acidified to pH 6 with acetic acid. The mixture was then extracted with ethyl acetate (3 x 20 ml). To the solution was added 2 g of silica gel and was rotary evaporated to dryness. The resulting powder was then loaded onto a column of silica gel (20 g, 1.8 X 20 cm) slurry-packed in chloroform, methanol and acetic acid (9:0.5:0.5). Elution with this same solvent system afforded **4a** (0.19 g, 38%). mp 317 °C.

Method D:
A mixture of **7a** (0.5 g, 2.0 mmol) and DEAD (0.5 ml, 2.7 mmol) in DMF (30 ml) was stirred at room temperature for 3 h. Without further isolation, the reaction mixture was refluxed for further 12 h. The reaction mixture was rotary evaporated to dryness. To the residue was added water (30 ml) to get precipitate. This crude product was dissolved in hot DMF (10 ml) with Norite (0.2 g). The resulting solution was filtered through a bed of Celite and then to the filtrate was added distilled water to get **4a** (0.15 g, 30%). mp 320 °C.

Method E:

To a mixture of **7a** (0.5 g, 2.0 mmol) in DMF (40 ml) was added NBS (0.4 g, 2.2 mmol). The reaction mixture was refluxed in a heating mantle for 12 h. The solvent was rotary evaporated in vacuo and to the residue was added water (40 ml) to get precipitate. This crude product that was collected by filtration, was dissolved in hot DMF (10 ml). Norite (0.1 g) was added to this hot solution and the solution was passed through a bed of Celite. The filtrated was added water (30 ml) to get **4a** (0.33 g, 66%), mp 325 °C.

Pyrido[3,2-b][1,4]benzothiazine-3-carboxamide (4b)

A mixture of **7b** (2.0 g, 8.16 mmol) and NBS (2.1 g, 11.80 mmol) in DMF (40 ml) was stirred at room temperature for 5 h. The solvent was rotary evaporated in vacuo and to the residue was added ethanol and water (9:1, 20 ml) to get yellow-green solid which was collected by filtration. This crude product was dissolved in 15 ml of hot DMF and the resulting solution was treated with Norite (0.5 g). The mixture was then passed through a bed of Celite. Water (30 ml) was added to this solution to get **4b** (1.73 g, 87%). An analytical sample was dissoved in DMF and reprecipitated from water, mp 270 °C; ^{1}H-nmr (300 MHz, DMSO-d_6): δ 6.80 (m, 2H, Ar-H), 6.90-7.05 (m, 2H, Ar-H), 6.98 (t, 1H, J =7.2 Hz, Ar-H), 7.26 (br s, 1H, -NH_a, D_2O exchangeable), 7.63 (d, 1H, J = 1.9 Hz, Ar-H), 7.78 (br s, 1H, -NH_b, D_2O exchangeable), 8.28 (d, 1H, J = 1.8 Hz, Ar-H), 9.58 (s, 1H, -NH); ^{13}C-nmr (75 MHz, DMSO-d_6): δ 111.58, 115.12, 115.49, 123.13, 123.88, 125.90, 127.79, 132.41, 139.55, 146.06, 154.56, 165.53 (C=O); ms: *m/z* 243 (M^+). Anal. Calcd for $C_{12}H_9N_3OS$: C, 57.13; H, 4.00; N, 16.66. Found: C, 56.97; H, 3.63; N, 16.42.

Di[2-(pyridine-3-carboxamide-6-yl)amino]phenyl disulfide (8b)

A mixture of **7b** (1.0 g, 4.0 mmol) and DEAD (1.0 ml, 6.44 mmol) in DMF (50 ml) was stirred at room temperature for 3 h. The reaction mixture was rotary evaporated in vacuo to dryness. To the residue was added water (40 ml) to get solid which was then collected by filtration. This crude product was dissolved in hot DMF (20 ml) and then Norite (0.2 g) was added this solution. The solution was then passed through a bed of Celite. Water (40 ml) was added to the filtrate to give **8b** (1.0 g, 99%). An analytical sample was recrystallized from methanol, mp 269 °C; ^{1}H-nmr (300 MHz, DMSO-d_6): δ 6.68 (d, 1H, J = 8.8 Hz, Ar-H), 7.16 (dt, 1H, J = 1.1 Hz, J = 7.6 Hz, Ar-H), 7.21 (br s, 1H, -NH_a, D_2O exchangeable), 7.27 (dt, 1H, J = 1.1 Hz, J = 7.4 Hz, Ar-H), 7.45 (d, 1H, J = 7.7 Hz, Ar-H), 7.59 (d, 1H, J = 7.4 Hz, Ar-H), 7.82 (br s, 1H, -NH_b, D_2O exchangeable), 7.98 (dd, 1H, J = 2.3 Hz, J = 8.7 Hz, Ar-H), 8.57 (d, 1H, J = 2.2 Hz, Ar-H), 8.99 (s, 1H, -NH, D_2O exchangeable); ^{13}C-nmr (75 MHz, DMSO-d_6): δ 108.33, 120.38, 125.53, 128.17, 129.03, 131.81, 136.83, 138.17, 147.90, 158.16, 166.57(C=O); ms: *m/z* 243 ($^1/_2M^+$-1), 228 ($^1/_2M^+$-16), 211 ($^1/_2M^+$-33). Anal. Calcd for

$C_{24}H_{20}N_6O_2S_2.1/2H_2O$: C, 57.93; H, 4.25; N, 16.89. Found: C, 58.25; H, 4.35; N, 17.19.

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