The Syntheses of 3-Substituted 4-(Pyridin-2-ylthio)indoles *via* Leimgruber-Batcho Indole Synthesis

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We have designed a new family of radioligands, 3-(amino- and hydroxymethyl)-4-(5-iodopyridin-2-ylthio)indoles, combining characteristically distinct moieties proven to impart successful binding ability in a variety of structurally diverse selective serotonin reuptake inhibitors recently published. Described in this article are the syntheses of 3-substituted 4-(5-iodopyridin-2-ylthio)-indoles, featuring successful adaptation of the modified Leimgruber-Batcho indole synthesis onto the key intermediate 1-(5-iodopyridin-2-ylthio)-2-methyl-3-nitrobenzene (**6**) prepared from the nucleophilic aromatic substitution of chloropyridine **7** with thiophenol **8**.

Key Words : 4-(Pyridin-2-ylthio)indole, Heterocyclic sulfide, Indole synthesis, Serotonin transporter, Sulfide synthesis

Introduction

Serotonin (**1**, 5-hydroxytryptamine, 5-HT; Chart 1) is a prominent neurotransmitter with diverse physiological actions in both the central and peripheral nervous systems. Recent reviews have summarized on the important associations between serotonergic functions and depression.[1-5] Selective serotonin reuptake inhibitors (SSRIs) are second-generation antidepressants designed for the preferential increase of 5-HT transmission by inhibiting the serotonin transporter (SERT).

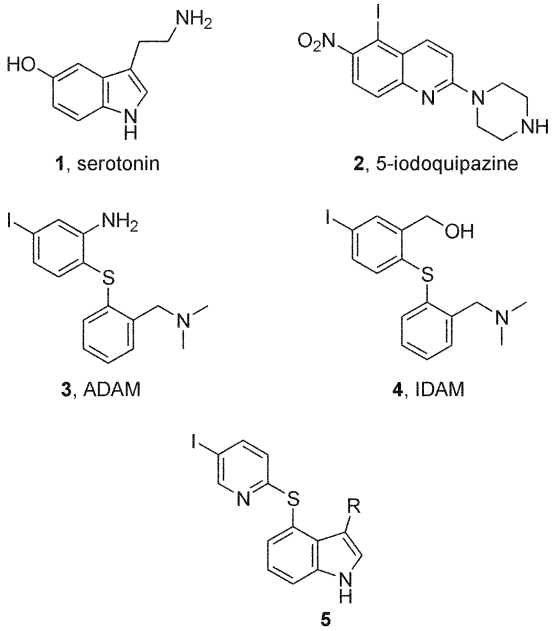

Chart 1

Imaging of SERT and serotonin receptor[6] in the human brain would provide a useful tool in understanding how alterations of this system relate to depressive illness and other psychiatric disorders. Radioligands like [^{11}C]McN5652[7] and 5-[^{123}I]iodo-6-nitroquipazine (**2**)[8-11] (Chart 1) have shown somewhat encouraging results in this regard, while the recently-reported ligands [^{123}I]-ADAM **3** and [^{123}I]-IDAM **4** have displayed significant improvements in single photon emission computed tomography (SPECT) measurements.[12-14] Although these radioligands all serve as potent selective ligands of SERT, they bear significant structural differences from one another. In light of their successes, and in an effort to optimize structural contributions for better SERT binding,[15-19] we have designed a new type of radioligand, 4-(pyridin-2-ylthio)indole **5** (Chart 1), as a hybrid combining various structural moieties characteristic of these potent inhibitors.

The designed target compound **5** is synthetically challenging due to the lack of available methodology for the formation of heterodiaryl sulfides, specifically the 4-

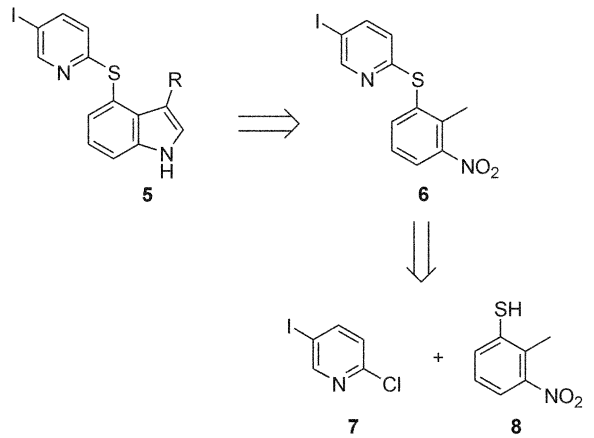

Figure 1. The retrosynthesis of 3-substituted 4-(5-iodopyridin-2-ylthio)indoles.

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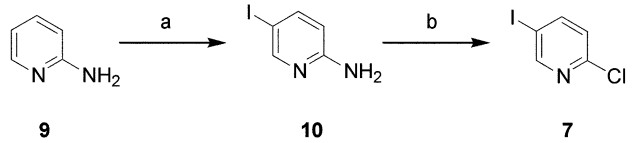
thioindole units. We selected the Leimgruber-Batcho indole synthesis[20,21] as the key step in converting precursor **6** to indole **5** for its mild reaction conditions and potential regiochemical control in the synthesis of 4-substituted indoles (see Figure 1 for retrosynthetic analysis). The key intermediate **6** was prepared by the nucleophilic aromatic substitution of chloropyridine **7** with thiophenol **8**. Subsequent Vilsmeier formylation, followed by reductive-amination and/or reduction gave rise to an array of 4-(pyridin-2-ylthio)indoles.

Results and Discussion

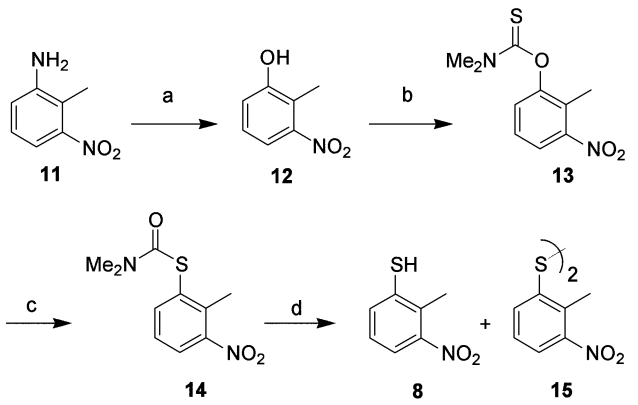
2-Chloro-5-iodopyridine (**7**) (Scheme 1) was prepared as previously reported, converting commercially available 2-aminopyridine (**9**) to 2-amino-5-iodopyridine (**10**[22]) with periodic acid and iodine, followed by halogenation, upon formation of the diazonium salt, to give **7**[23] in 41% yield.

Preparation of 2-methyl-3-nitrothiophenol was successfully achieved by the process outlined in Scheme 2. Diazotization and subsequent hydrolysis of aniline **11** afforded phenol **12** in excellent yield. Treatment of **12** with dimethylthiocarbamoyl chloride in the presence of KOH provided thionocarbamate **13**, which was then thermally converted to thiocarbamate **14** under the Newman and Karnes conditions.[24] Hydrolysis of **14** afforded thiol **8** with a trace of disulfide byproduct **15**.

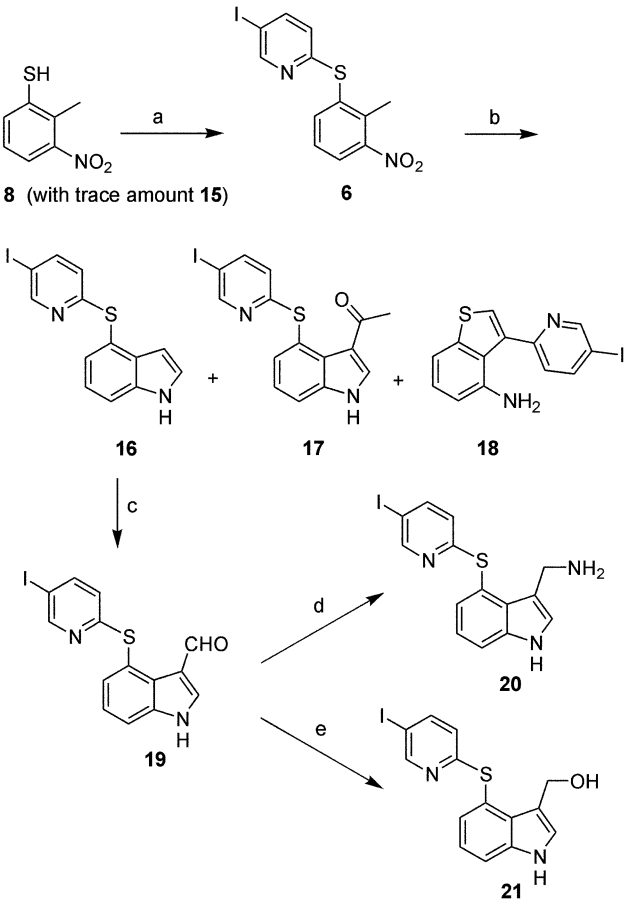
Chloropyridine **7** and thiol **8** were subsequently used as starting materials in the preparation of 4-(pyridin-2-ylthio)-indole analogues as shown in Scheme 3. The iodo moiety of **7** precluded the use of metal catalysts for the coupling of **7**



Scheme 1. (a) I_2, H_5IO_6, AcOH, H_2SO_4, 80 °C, 1 h, 65%; (b) $NaNO_2$, HCl, CuCl, 0 °C-rt, overnight, 41%.



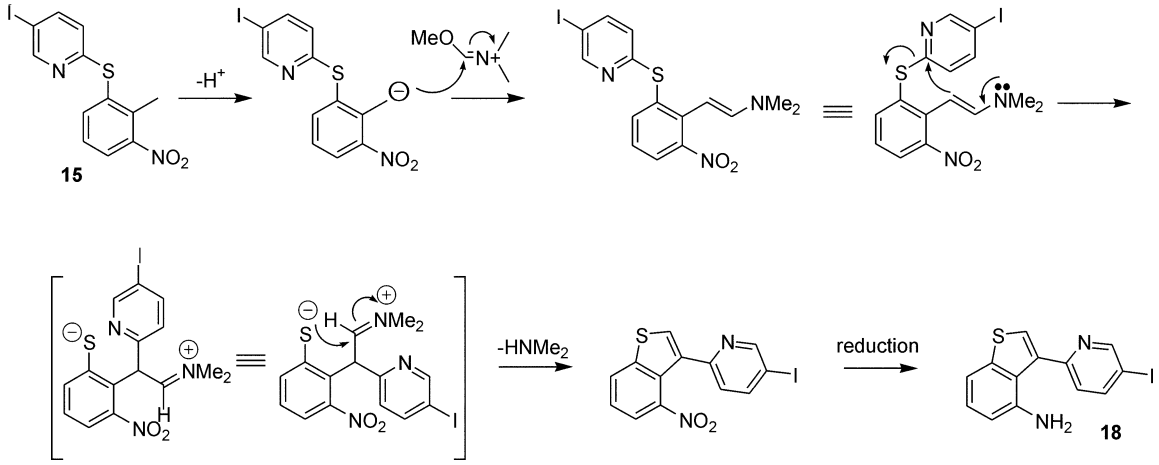
Scheme 2. (a) $NaNO_2$, H_2SO_4, H_2O, 0-5 °C, 10 min, 120 °C, 5 min, 94%; (b) *N,N*-dimethylthiocarbamoyl chloride, KOH, THF, H_2O, 0 °C-rt, 30 min, 76%; (c) 220 °C in a sealed tube, 3 h, 80%; (d) KOH, H_2O, MeOH, 80 °C, 1 h, (**8**, 95%) (**15**, trace).



Scheme 3. (a) 7, PPh_3, Et_3N, DMF, 110 °C, 20 h, 71%; (b) (i) dimethylformamide dimethyl acetal (DMF-DMA), pyrrolidine, DMF, 110 °C, 2 h, (ii) Fe, AcOH, 100 °C, 3 h, (**16**, 28%, **17**, 11%, **18**, 13%); (c) $POCl_3$, DMF, 40 °C, 1 h, 40%; (d) $NaCNBH_3$, NH_4OAc, MeOH, rt, 3 days, 20%; (e) $NaBH_4$, EtOH, rt, 4 h, 52%.

with **8**, but the coupling reaction proceeded to give the desired sulfide **6** quite nicely when heated in a sealed tube under N_2 in the absence of a metal catalyst. Unfortunately, under these conditions we also obtained disulfide byproduct **15**, which turned out to be extremely difficult to be separated from the product **6**. In the coupling reaction of of **7** with **8**, interestingly, the addition of triphenylphosphine not only prevented thiol **8** from the formation of disulfide **15**, but also permitted to use the mixture of thiophenol **8** and disulfide **15** as a suitable starting material under these conditions.

The modified Leimgruber-Batcho indole synthesis (Scheme 3) was attempted under a variety of conditions. Our first effort, which utilized acetic acid as solvent in the reduction step, afforded the desired indole **16** as well as acetyl derivative **17** and thiophene **18** as by-products. The structure of **18** was confirmed by spectroscopic data, including 2D-HETCOR NMR and mass spectrometry (a possible reaction mechanism for the formation of thiophene is shown in Scheme 4). A subsequent attempt using HCl/EtOH as solvent gave only trace amounts of the target product **16** and some unidentified residues. After a considerable number of trials, an 1 : 1 mixture of AcOH/EtOH was found to be



Scheme 4. A Plausible Mechanism for the Formation of Thiophene **18**.

optimal solvent system, which dramatically suppressed the formation of byproducts, provided the desired product **16**. Formylation of **16** *via* the Vilsmeier reaction yielded aldehyde **19**, which was subsequently taken for either reductive-amination or reduction to give 3-aminomethylindole **20** or 3-hydroxymethylindole **21**.

Conclusion

In conclusion, we have successfully synthesized a series of 4-(pyridin-2-ylthio)indole derivatives for serotonin transporter imaging agent evaluation. Addition of triphenylphosphine in the coupling reaction of **7** with **8** effectively prevented disulfide formation. A modified Leimgruber-Batcho indole synthesis was successfully conducted with the key intermediate 1-(5-iodopyridin-2-ylthio)-2-methyl-3-nitrobenzene (**6**). The heterodiaryl sulfide chemistry utilized in this synthesis could be useful for the preparation of other novel bioactive compounds. The biological evaluation of these sulfide analogues will be reported in due course.

Experimental Section

2-Amino-5-iodopyridine (10). A mixture of 2-aminopyridine (2.06 g, 21.9 mmol), acetic acid (14 mL), water (3 mL), sulfuric acid (0.42 mL), and H_5IO_6 (1.05 g, 4.6 mmol) was allowed to stir at 80 °C for 15 min. Iodine crystals (2.28 g, 9.0 mmol) were added in portions. After it was stirred for 1 h, the reaction mixture was poured into saturated sodium thiosulfate solution and extracted with ethyl acetate. The organic layer was separated, dried (Na_2SO_4), and evaporated to give **10** (3.13 g, 65%) as an orange solid: ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.85 (br, 2H), 6.36 (dd, J = 8.8, 0.8 Hz, 1H), 7.64 (dd, J = 8.8, 2.2 Hz, 1H), 8.18 (d, J = 2.0 Hz, 1H). CAS No. 20511-12-0.

2-Chloro-5-iodopyridine (7). A mixture of aminopyridine **10** (1.05 g, 4.74 mmol) and concentrated HCl (10 mL) was stirred at 0 °C for 10 min. Sodium nitrite (1.38 g, 20.0 mmol) was slowly added, then followed by CuCl (0.50 g, 5.1 mmol) with stirring continued overnight. The mixture was poured into 1 : 1 NH_4OH : H_2O, extracted with ethyl acetate, dried (Na_2SO_4), and concentrated. The crude residue was purified by flash column chromatography on silica gel using dichloromethane as an eluant to yield **7** (0.47 g, 41%) as a colorless solid: ^{1}H NMR (200 MHz, DMSO-d_6) δ 7.36 (d, J = 8.4 Hz, 1H), 8.18 (dd, J = 8.2, 2.2 Hz, 1H), 8.64 (d, J = 1.6 Hz, 1H); ^{13}C NMR (50 MHz, DMSO-d_6) δ 93.1, 126.8, 148.0, 150.2, 155.9; CAS No. 69045-79-0.

2-Methyl-3-nitrophenol (12). To a mixture of **11** (3.8 g, 25.0 mmol), concentrated sulfuric acid (5.5 mL) and water (7.5 mL), 20 g of ice was added and the solution was cooled to 0-5 °C. A solution of sodium nitrite (1.8 g, 26 mmol) in 1.5 mL of water was added. After stirred for 10 min, the mixture was allowed to stand at 0-5 °C for 5 min. To a boiling solution of concentrated sulfuric acid (16.5 mL) and water (15 mL), the diazotized solution was slowly added. After adding, the mixture was boiled for 5 min and then poured to a beaker containing ice-water. The precipitate was collected by suction filtration, washed with cold water and dried. The solid was purified by flash column chromatography (EtOAc : hexanes, 1 : 9) to yield 3.63 g (94%) of **12** as a yellow solid: ^{1}H NMR (200 MHz, DMSO-d_6) δ 2.23 (s, 3H), 7.12 (dd, J = 8.2, 1.8 Hz, 1H), 7.19 (dd, J = 8.2, 7.8 Hz, 1H), 7.44 (dd, J = 7.8, 1.8 Hz, 1H); ^{13}C NMR (50 MHz, DMSO-d_6) δ 11.8, 114.7, 119.3, 127.4, 151.5, 157.2; CAS No. 5460-31-1.

2-Methyl-3-nitrophenyl *N,N*-Dimethylthionocarbamate (13). To a powder of **12** (3.06 g, 20.0 mmol) was added a solution of potassium hydroxide (1.12 g, 20.0 mmol) in 15 mL of H_2O at rt. The mixture was cooled below 5 °C in ice-water bath. A solution of *N,N*-dimethylthiocarbamyl chloride (0.185 g, 1.5 mmol) in 5 mL of dry THF was added with cooling. After the addition, the reaction mixture was allowed to stir at rt for 30 min. The mixture made alkaline with 10% potassium hydroxide and extracted with dichloromethane. The organic layers are combined, washed with brine, and dried over. The residue was purified by flash column chromatography (CH_2Cl_2 : hexanes, 8 : 2) to give **13** (3.67 g, 76%) as an yellow solid: ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.36 (s, 3H), 3.40 (s, 3H), 3.48 (s, 3H), 7.26 (dd, J = 8.0, 1.4 Hz,

1H), 7.36 (t, J = 8.0 Hz, 1H), 7.83 (dd, J = 8.0, 1.4 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.0, 39.0, 43.7, 122.3, 126.6, 127.5, 128.5, 150.7, 153.5, 186.4. MS (EI) 240 (M^-), 225, 223, 194, 179, 151, 121, 88, 72 (100), 63, 51. HRMS (EI) Calc. for $C_{10}H_{12}N_2O_3S$ (M^-) 240.0569. Found 240.0564.

2-Methyl-3-nitrophenyl *N,N*-Dimethylthiocarbamate (14). A powder of **13** (1.57 g, 6.5 mmol) was added into a sealed tube and purged with N_2. The tube was capped and heated at 215-220 °C for 3 h. The reaction was cooled to rt. The residue was purified by flash column chromatography (CH_2Cl_2) to provide **14** (1.24 g, 80%) as an orange solid: ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.59 (s, 3H), 3.03 (br, 3H), 3.14 (br, 3H), 7.33 (dd, J = 7.8, 7.6 Hz, 1H), 7.75 (dd, J = 7.6, 1.4 Hz, 1H), 7.85 (dd, J = 8.0, 1.4 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.7, 37.3, 125.9, 126.7, 132.5, 137.7, 141.7, 151.5, 165.2; MS (EI) 240 (M^-), 210, 168, 149, 121, 110, 72 (100), 56. HRMS (EI) Calc. for $C_{10}H_{12}N_2O_3S$ (M^-) 240.0569. Found 240.0570.

2-Methyl-3-nitrothiophenol (8). A solution of **14** (1.24 g, 5.2 mmol) and KOH (0.60 g, 10.7 mmol) in H_2O (2 mL) and MeOH (10 mL) was heated at 80 °C for 1 h under N_2 atmosphere. The reaction mixture was cooled and poured to 5 g of ice. The solution was washed with CH_2Cl_2 (20 mL × 2). The organic layer was discarded. The aqueous layer was acidified by 4 M HCl solution and extracted with CH_2Cl_2 (20 mL × 2). The organic layers were combined, dried (Na_2SO_4) to give a mixture of **8** (0.84 g, 95%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.44 (s, 3H), 3.58 (s, 1H), 7.17 (t, J = 8.0 Hz, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.55 (dd, J = 8.0, 0.8 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.2, 121.6, 126.9, 130.0, 133.7, 135.8, 151.6; MS (EI) 169 (M^+), 152 (100), 124, 121, 110, 97, 77, 63, 45, 39; HRMS (EI) Calc. for $C_7H_7NO_2S$ (M^+) 169.0198. Found 169.0195.

Di(2-methyl-3-nitrophenyl) Disulfide (15). (trace amount) ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.60 (s, 6H), 7.29 (dd, J = 8.2, 8.0 Hz, 1H), 7.69 (d, J = 8.0 Hz, 1H), 7.71 (dd, J = 8.2, 8.0 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.3, 123.6, 127.3, 131.7, 132.3, 138.4, 151.5; MS (EI) 336 (M^-, 100), 320, 306, 259, 241, 168, 129, 121, 110, 77, 57. HRMS (EI) Calc. for $C_{14}H_{12}O_4N_2S_2$ (M^+) 336.0239. Found 336.0242.

1-(5-Iodopyridin-2-ylthio)-2-methyl-3-nitrobenzene (6). A mixture of **8** and **15** (0.84 g, 4.97 mmol), **7** (1.19 g, 4.97 mmol), PPh_3 (0.13 g, 0.5 mmol) and Et_3N (0.72 mL) in DMF (5 mL) was added into a sealed tube and purged with N_2. The reaction was heated at 110 °C for 20 h. The mixture was cooled, added CH_2Cl_2 (20 mL) and washed with H_2O and brine. The organic layer was dried (Na_2SO_4) and evaporated. The residue was purified by flash column chromatography (EtOAc : hexanes, 8 : 2) to give **6** (1.32 g, 71%) of as a yellow solid: ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.56 (s, 3H), 6.77 (d, J = 8.4 Hz, 1H), 7.37 (dd, J = 8.0, 7.8 Hz, 1H), 7.76-7.82 (m, 2H), 7.87 (d, J = 8.0 Hz, 1H), 8.59 (d, J = 2.2 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.5, 89.1, 123.5, 125.8, 127.4, 133.8, 137.1, 140.5, 145.2, 151.9, 156.1, 158.3; MS (EI) 372 (M^-), 357, 353, 327, 311, 227, 197, 154, 121, 89, 77, 63, 51, 39. HRMS (EI) Calc. for $C_{12}H_9N_2O_2SI$ (M^+) 371.9430. Found 371.9426.

4-(5-Iodopyridin-2-ylthio)indole (16). A mixture of **6** (1.72 g, 4.6 mmol), dimethylformamide dimethyl acetal (1.4 mL, 10 mmol) and pyrrolidine (0.4 mL, 5 mmol) in 8 mL of DMF was allowed to heat at 110 °C for 2 h under N_2 atmosphere. The reaction was cooled, added ether (20 mL) and washed with H_2O (20 mL × 2). The organic layer was dried over, and evaporated. The red residue was dissolved in the mixture of AcOH (15 mL) and EtOH (15 mL) and added iron powder (2 g). The suspension was heated at 100 °C for 3 h. The reaction was cooled, filtered and washed by water. The filtrate was basified by 1 M NaOH solution and extracted with ether, washed with H_2O and brine. The extract was dried over and was purified by flash column chromatography (ethyl acetate : hexanes, 1 : 4) to provide **16** (0.62 g, 36%) as a off-white solid: ^{1}H NMR (200 MHz, DMSO-d_6) δ 6.27-6.29 (m, 1H), 6.43 (d, J = 8.4 Hz, 1H), 7.19 (dd, J = 7.6, 7.4 Hz, 1H), 7.32 (dd, J = 7.2, 1.0 Hz, 1H), 7.44 (dd, J = 3.0, 2.4 Hz, 1H), 7.59 (dd, J = 8.0, 1.0 Hz, 1H), 7.83 (dd, J = 8.4, 2.2 Hz, 1H), 8.60 (d, J = 2.2 Hz, 1H) 11.49 (br, 1H); ^{13}C NMR (50 MHz, DMSO-d_6) δ 88.7, 100.4, 113.9, 119.0, 121.8, 122.3, 126.7, 127.0, 130.5, 136.3, 144.8, 154.7, 160.2; MS (EI) 352 (M^+), 224 (100), 207, 147, 104, 77, 73, 50. HRMS (EI) Calc. for $C_{13}H_9N_2SI$ (M^-) 351.9531. Found 351.9529.

3-Acetyl-4-(5-iodopyridin-2-ylthio)indole (17) and 3-(4-Iodopyridin-2yl)-4-aminothiophene (18). Same procedure used as **16**, pure AcOH (30 mL) was used instead of the mixture of AcOH and EtOH in the reduction step to provide **16** (0.48 g, 28%), **17**, and **18**. **17** (0.20 g, 11%) as a white solid: ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.05 (s, 3H), 7.40 (dd, J = 8.2, 7.6 Hz, 1H), 7.52 (d, J = 8.4 Hz, 1H), 7.63 (dd, J = 8.0, 1.0 Hz, 1H), 7.62 (s, 1H), 8.12 (dd, J = 8.4, 2.2 Hz, 1H), 8.27 (d(br), J = 7.4 Hz, 1H), 8.88 (d, J = 2.2 Hz, 1H) 11.45 (br, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 25.0, 91.4, 118.5, 118.9, 126.0, 126.6, 127.2, 130.2, 135.2, 135.7, 142.6, 146.6, 153.6, 155.0, 168.4; MS (EI) 394 (100, M^+), 379, 352, 281, 224, 209, 197, 121, 73, 50; HRMS (EI) Calc. for $C_{15}H_{11}N_2OSI$ (M^-) 393.9637. Found 393.9636. **18** (0.23 g, 13%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$)[25] δ 5.11 (br, 2H), 6.64 (dd, J = 7.6, 1.2 Hz, 1H), 7.18 (dd, J = 8.0, 7.6 Hz, 1H), 7.28 (dd, J = 8.0, 1.2 Hz, 1H), 7.40 (s, 1H), 7.46 (dd, J = 8.2, 0.8 Hz, 1H), 8.05 (dd, J = 8.2, 2.4 Hz, 1H), 8.86 (dd, J = 2.4, 0.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$)[25] δ 91.3, 111.0, 112.5, 124.0, 126.0, 127.0 136.5, 142.9, 144.2, 145.3, 154.3, 155.2; MS (EI) 352 (M^+, 100), 336, 281, 225, 224, 198, 121, 113, 99, 77, 57. HRMS (EI) Calc. for $C_{13}H_9N_2SI$ (M^-) 351.9531. Found 351.9532.

3-Formyl-4-(5-iodopyridin-2-ylthio)indole (19). Phosphorus oxychloride (0.05 mL, 0.27 mmol) was added dropwise with stirring to DMF (0.5 mL) at 0-5 °C. A solution of **16** (0.10 g, 0.28 mmol) in DMF (1 mL) was then added dropwise. After addition, the mixture was stirred at 40 °C for 1 h. The mixture was poured to 1 g of crushed ice and then made alkaline by 1 M NaOH solution. The resulting suspension was heated to the boiling point and cooled to rt. The precipitate was filtered, washed by water, air-dried. The solid was purified by flash column chromatography (CH_2Cl_2 : hexanes, 6 : 4) to give **19** (42 mg, 40%) as a off-white solid:

^{1}H NMR (400 MHz, DMSO-d_6) δ 6.56 (dd, J = 8.4, 0.8 Hz, 1H), 7.33 (dd, J = 8.0, 7.6 Hz, 1H), 7.53 (dd, J = 7.6, 0.8 Hz, 1H), 7.72 (dd, J = 8.0, 0.8 Hz, 1H), 7.88 (dd, J = 8.4, 2.0 Hz, 1H), 8.25 (d, J = 3.2 Hz, 1H), 8.59 (dd, J = 2.0, 0.8 Hz, 1H) 10.32 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 89.9, 116.0, 118.9, 120.1, 123.0, 124.0, 128.2, 131.7, 134.2, 138.4, 145.8, 155.8, 160.0, 186.0; MS (EI) 380 (M^+), 351, 347 (100), 320, 224, 176, 148, 129, 104, 88, 72, 57. HRMS (EI) Calc. for $C_{14}H_9N_2OSI$ (M^+) 379.9480. Found 379.9477.

3-(Aminomethyl)-4-(5-iodopyridin-2-ylthio)indole (20). To a solution of **19** (0.10 g, 0.26 mmol), ammonium acetate (0.20 g, 2.6 mmol) in 4 mL of MeOH was added a solution of 1.0 M $NaCNBH_3$ in THF (0.26 mL, 0.26 mmol) with stirring. The reaction was stirred at rt for 3 days. The reaction was acidified by 2 M HCl solution until pH <2, then extracted with ether (20 mL × 2). The organic layers were combined, washed by 1 M NaOH, dried over. The residue was purified by flash column chromatography (CH_2Cl_2 : MeOH, 10 : 1) to give **20** (20 mg, 20%) of as a white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.27 (br, 2H), 6.37 (d, J = 8.4 Hz, 1H), 7.22 (dd, J = 8.0, 7.6 Hz, 1H), 7.28 (d, J = 7.2 Hz, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.74 (d, J = 2.8 Hz, 1H), 7.81 (dd, J = 7.6, 2.4 Hz, 1H), 8.43 (d, J = 2.4 Hz, 1H), 9.22 (br, 1H), 12.04 (br, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 42.0, 90.2, 105.8, 115.3, 119.6, 122.9, 123.1, 128.3, 130.2, 130.7, 137.8, 145.7,155.5, 161.0 MS (FAB) 382 (M^+), 380, 365 (100), 332, 239, 207, 115. HRMS (FAB) Calc. for $C_{14}H_{13}N_3SI$ ($M+H^-$) 381.9875. Found 3819871.

3-(Hydroxymethyl)-4-(5-iodopyridin-2-ylthio)indole (21). A suspension of **19** (38 mg, 0.10 mmol), $NaBH_4$ (4.0 mg, 0.1 mmol) in 0.6 mL of 95% EtOH was stirred at rt for 4 h. The reaction mixture was added with water and extracted with ethyl acetate. The organic layers were combined, then washed by water and brine, and dried (Na_2SO_4). The crude was purified by flash column chromatography (EtOAc : hexanes, 3 : 7) to provide **21** (20 mg, 52%) as an off-white-off solid: ^{1}H NMR (400, DMSO-d_6) δ 4.63-4.67 (m, 3H), 6.35 (dd, J = 8.8, 0.4 Hz, 1H), 7.17 (dd, J = 8.0, 7.2 Hz, 1H), 7.25 (dd, J = 7.2, 1.2 Hz, 1H), 7.34 (dd, J = 1.6, 1.2 Hz, 1H), 7.55 (dd, J = 8.0, 2.0 Hz, 1H), 7.85 (dd, J = 8.8, 2.4 Hz, 1H), 8.59 (dd, J = 2.2, 0.4 Hz, 1H), 11.31 (d, J = 2.0 Hz, 1H); ^{13}C NMR (50 MHz, DMSO-d_6) δ 57.2, 89.1, 114.8, 117.6, 119.4, 122.4, 122.5, 126.0, 128.1, 129.0, 138.3, 145.6, 155.3, 162.6; MS (FAB) 383 (M^-), 365 (100), 332, 239, 160, 117. HRMS (FAB) Calc. for $C_{14}H_{12}N_2OSI$ ($M+H^-$) 382.9715. Found 382.9713.

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