A Direct Synthesis of 3-(Pyrrolidin-3-yl)indoles for Use As Conformationally Restricted Analogs of Tryptamines

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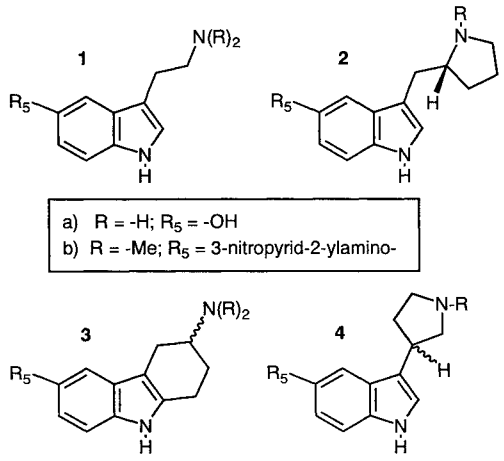
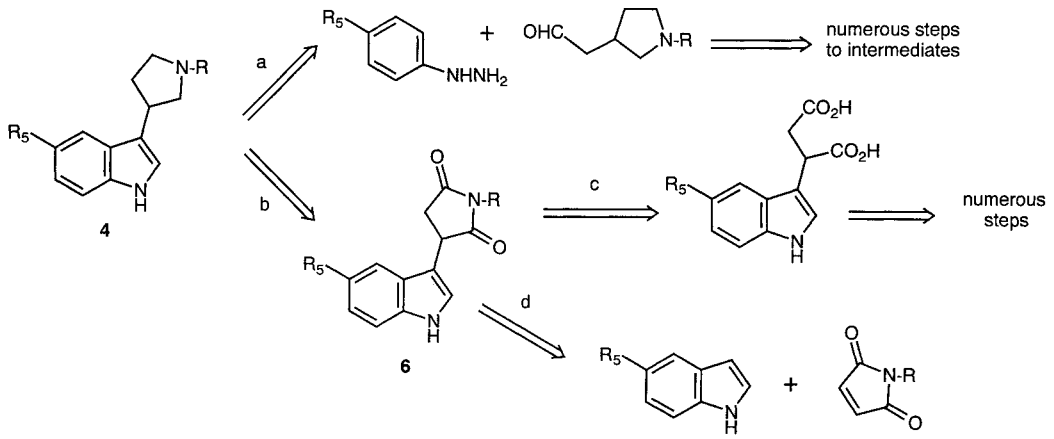
An efficient, two step synthesis of 3-(pyrrolidin-3-yl)indoles **4** is described. Indoles react with maleimides in refluxing acetic acid affording 3-(indol-3-yl)succinimides **6**. Reaction times and yields depend on the substituents on the indole **5**. Direct reduction of the succinimides **6** with LAH affords the desired conformationally restricted tryptamine derivatives **4**.

The use of conformationally restricted analogs of medicinally important molecules as a means to better understand or improve the pharmacology of those agents is a common theme in medicinal chemistry. Although often an empirical approach, the use of conformationally restricted analogs reveals positive or negative information concerning the active conformation of the biologically relevant molecule under study. In many cases, the conformationally restricted targets themselves can be synthetic challenges, and the use of new or improved methodology is often required to achieve the desired conformationally restricted target.

Tryptamines are a class of indole derivatives which have extensive medicinal utility. The best known tryptamine is serotonin (5-hydroxytryptamine, 5-HT, **1a**), which is a ubiquitous neurotransmitter in the mammalian central nervous system (CNS). Since there are a large number of receptor proteins (fourteen at the present time) which bind this small, but powerful molecule, serotonergic receptor dysfunction has been implicated in a wide array of disease states.[2] Accordingly, conformational restriction of the 3-(2-aminoethyl) sidechain of serotonin has been examined as an approach to 5-HT analogs with receptor subtype selectivity, ideally affording drugs with specific therapeutic activity and reduced side effects. Our laboratories[3-8] and others[9] have been actively pursuing such studies via the restriction of the 3-(2-aminoethyl) sidechain of serotonin (**1a**). The structure of indoles **1**–**4** denotes the various themes employed thus far in both the primary and patent literature. While compounds of generic structures **2**[3-8] and **3**[9] have been documented in the primary literature, the 3-(pyrrolidin-3-yl)indoles **4** have received almost no attention.[6,10] While there has been some reference to 3-(pyrrolidin-3-yl)indoles **4** in the serotonergic patent literature, actual synthetic details of these conformationally restricted tryptamines are often lacking. Where synthetic details are given, the universal approach to these compounds **4** is via a Fischer indolization reaction utilizing an appropriate arylhydrazine and an aliphatic aldehyde (Scheme 1, path a). The syntheses of these components are multistep, and the yields from the Fischer indole reaction are highly variable. In short, a concise and versatile synthesis of **4** has not been found in the literature.



Furthermore, in a series of indole derivatives **1b**, **2b**, and **4b** in which the C5 substituent was held constant and the C3 substituent integrated, various degrees of conformation restriction of the 2-(aminoethyl) sidechain, the



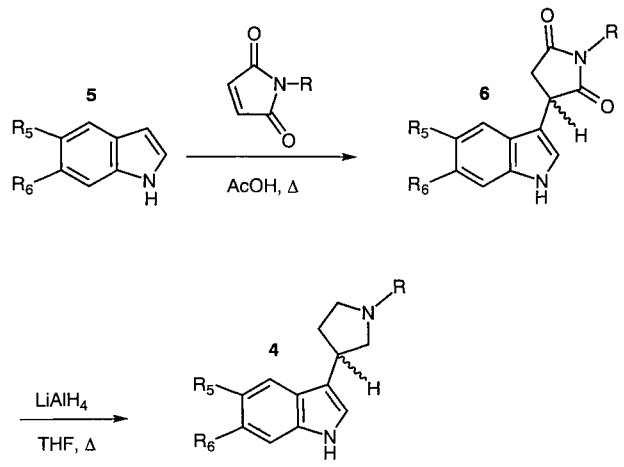
Scheme 1

3-(pyrrolidin-3-yl)indole analog **4b** was found to impart the greatest selectivity for the 5-HT_{1D} receptor,[6] a serotonin receptor subtype believed to play a role in migraine headaches.[11] Hoping to optimize this receptor subtype selectivity, we sought a rapid, general synthesis of 3-(pyrrolidin-3-yl)indoles **4** capable of allowing extensive functionalization at C5 of the indole derivative. In this report, we detail such a synthesis.

Scheme 1 (paths b and d) summarizes retrosynthetically our pathway to the desired 3-(pyrrolidin-3-yl)indoles **4**. Reduction of 3-(indol-3-yl)succinimides **6** using lithium aluminum hydride to form 3-(pyrrolidin-3-yl)indoles **4** has been previously reported by two groups in 1964 and 1966 (Scheme 1, paths b and c)[10]. They arrived at the succinimides **6** through a series of transformations which commenced with indoles and concluded with the cyclization of 2-(indol-3-yl)succinic acids with ammonia. This particular approach to **4** was limited by the cumbersome route used to obtain the 3-(indol-3-yl)succinimides **6**.

However, from a single report from 1962 on the reaction of 2-phenylindole with *N*-methylmaleimide,[12] we saw this type of Michael reaction as an ideal approach to 3-(indol-3-yl)succinimides **6**, incorporating in a single step the desired carbon framework of the 3-(pyrrolidin-3-yl)indoles **4** (Scheme 1, path d). To our knowledge, only two other examples of this indole/maleimide Michael reaction have been subsequently reported, both involving 2-(indol-2-yl)indole and *N*-methylmaleimide, and both during the pursuit of an alternative product. One group observed the reaction under $BF_3 \cdot Et_2O$ catalysis at room temperature,[13] while the other group only observed the reaction after refluxing the two components at 100 °C for 7 days.[14] Also, indole magnesium halides have been reacted with 3,4-dibromomaleimides affording 3,4-bisindol-3-ylmaleimides.[15,16] Therefore, the reaction of indoles with maleimides appeared to be a reasonable approach to the desired carbon framework of our targets, but the generality of the reaction was unexplored.

We saw the opportunity to combine the Michael reaction of indoles with maleimides forming 3-(indol-3-yl)succinimides **6** with the direct reductions of these succinimides with $LiAlH_4$ as an expeditious route to 3-(pyrrolidin-3-yl)indoles **4**, (Scheme 1, paths b and d and Scheme 2). Accordingly, Table 1 summarizes our detailed study of this general synthesis of these conformationally restricted analogs of tryptamines **4**. The Michael reaction between 5-methoxyindole **(5d)** and three equivalents of *N*-methylmaleimide *did not proceed* in refluxing dioxane (101 °C), and even after seven days at reflux *no addition product was detected.* However, use of acetic acid as the reaction solvent led to complete consumption of 5-methoxyindole after 72 hours reflux affording the desired succinimide **6f** in 80 % yield. This indicated that the Michael reaction was greatly facilitated by the acidic nature of the solvent used. This result, coupled with the ease of reaction between 2-(indol-2-yl)indole and *N*-methylmaleimide using BF_3,[13] suggests that maleimide is activated in these reactions by the presence of acid coordination to the amide oxygens which is needed for increased Michael acceptor reactivity.



Scheme 2

A wide variety of indoles successfully participated in this Michael condensation with maleimide, *N*-methylmaleimide, and *N*-benzylmaleimide (Table 1). While there appeared to be little effect on the success or rate of the reaction depending on the maleimide used, the rate and efficiency of these condensation reactions in acetic acid appeared to be related to the electronic nature of the indole used. Comparison of both the reaction times and yields of **6** using indoles with electron-donating substituents versus using indoles with electron-withdrawing substituents showed that indoles with electron-withdrawing substituents at C5 required longer reaction times and produced lower yields of the desired succinimide **6**. Electron-withdrawing substituents at C5 decrease the net contribution of the enamine-like resonance structure in the reactive character of the indole. Because of their reduced enamine-like nature, electron poor indoles participated poorly in these Michael reactions relative to electron neutral or electron rich indoles. Accordingly, 5-nitroindole, 5-cyanoindole, and indole-5-carboxylic acid afforded poor yields of **6** over the longer reaction times, and significant amounts of the starting indole were still present when these three reactions were terminated. For the other indoles, the yield of succinimide **6** for these reactions was moderate to good (Table 1), and the starting indoles were fully consumed.

Reduction of the (indol-3-yl)succinimides was accomplished using an excess of lithium aluminum hydride in refluxing THF affording the 3-(pyrrolidin-3-yl)indoles **4** in good to excellent yields. When functionality susceptible to reduction was present in the indole portion of **6** (e.g. **6k** and **6m**), reduction of that group occurred concomitantly. We found that the order of addition of reagents could have a significant effect on the efficiency of the reduction reaction. When LAH was added to a solution of **6** in THF, a greater occurrence of byproducts and reduced yields of **4** were often seen. Addition of the succinimide to a mixture of excess $LiAlH_4$ in THF at room temperature, followed by a short reflux consistently gave excellent yields of the conformationally restricted tryptamine **4** (Table 1).

Table 1. Preparation of 3-(Pyrrolidin-3-yl)indoles **4** via Succinimides **6** (see Scheme 2)

Starting Materials				Time (h)	Intermediate **6**	Yield (%)	Product **4**	Yield (%)	Overall Yield (%)
Maleimide, R	Indole, **5**	R^5	R^6						
Me	**5a**	H	H	30	**6a**	74	**4a**	88	65
Me	**5b**	F	H	24	**6b**	87	**4b**	79	69
Me	**5c**	Br	H	24	**6c**	62	**4c**	48	30
H	**5c**	Br	H	72	**6d**	61	**4d**	–	–
CH_2Ph	**5c**	Br	H	144	**6e**	23	**4e**	–	–
Me	**5d**	OMe	H	72	**6f**	80	**4f**	90	73
H	**5d**	OMe	H	69	**6g**	61	**4g**	70	42
CH_2Ph	**5d**	OMe	H	19	**6h**	57	**4h**	98	56
Me	**5e**	OCH_2O		72	**6i**	60	**4i**	76	46
Me	**5f**	$OCH_2C{\equiv}CH$	H	24	**6j**	31	**4j**	–	–
Me	**5g**	NH(C=O)Ph	H	26	**6k**	52	**4k**	76[a]	40
Me	**5h**	Me	H	24	**6l**	74	**4l**	60	44
Me	**5i**	CO_2H	H	36	**6m**	41	**4m**	73[b]	30
Me	**5j**	CN	H	96	**6n**	39	**4n**	–	–
Me	**5k**	NO_2	H	97	**6o**	2	**4o**	–	–

[a] Isolated as 5-benzylamino-(3-*N*-methylpyrrolidin-3-yl)indole.

[b] Isolated as 5-hydroxymethyl-3-(*N*-methylpyrrolidin-3-yl)indole.

In conclusion, a two step synthesis of 3-(pyrrolidin-3-yl)indoles **4** has been described (Table 1). This concise approach to these conformationally restricted analogs of tryptamine commences with the Michael reaction of a variety of indoles with a variety of maleimides in refluxing acetic acid to afford 3-(indol-3-yl)succinimides **6** (Table 1). It would appear that this reaction is general in nature, but indoles with electron-withdrawing groups at C5 appear to suffer in both reaction rate and efficiency. This is likely a result of their reduced enamine-like character in the pyrrole portion of the indole heterocycle due to increased resonance delocalization of the indole nitrogen lone pair of electrons into the benzene portion of the indole molecule. Reduction of these succinimides **6** is smoothly accomplished via the addition of the succinimide **6** to a solution/mixture of $LiAlH_4$ in THF followed by a short reflux affording the desired 3-(pyrrolidin-3-yl)indoles **4** in generally good to excellent yields (Table 1).

Melting points were determined on a Thomas-Hoover open capillary melting point apparatus and are uncorrected. IR spectra were obtained on a Nicolet 510 FT-IR Spectrometer. NMR spectra were recorded on either a Bruker AM-300 (300 MHz) or Bruker AM-250 (250 MHz) spectrometer. NMR data are reported in parts per million (δ) and are referenced to the deuterium lock signal from the sample solvent. EI mass spectra were obtained on a Kratos Profile instrument, and FAB mass spectra were obtained on a Kratos Concept IS instrument (σ = 5 ppm for HRMS). FAB mass spectrum are noted by a $[MH]^+$ or $[M \cdot NH_4]^+$ designation for molecular ions. Elemental analyses were performed at Schwarzkopf Microanalytical Laboratory in Woodside, New York. Commercial reagents (Aldrich Chemical Co.) were utilized without further purification, including Aldrich anhydrous solvents. Chromatography refers to column chromatography performed using 32–63 μm silica gel (approx 50 g silica gel per gram of material to be chromatographed) and executed under N_2 pressure (flash chromatography) conditions.

3-(Indol-3-yl)succinimides 6; General Procedure:

A solution of the indole (10.0 mmol) and the maleimide (30.0 mmol) in AcOH (50 mL) was heated at reflux under N_2 for a period of time determined by the individual components and shown in Table 1. Upon consumption of the starting indole as observed by TLC (or after the time shown in Table 1), the resulting mixture was cooled. In some cases, the desired succinimide **6** precipitated directly from the reaction mixture. Otherwise, the solution was evaporated under reduced pressure, and the residue was dissolved in EtOAc (50 mL) and a saturated solution of $NaHCO_3$ (50 mL). The EtOAc layer was removed, and the aqueous layer was extracted with EtOAc (2 × 50 mL). The organic extracts were combined, dried ($MgSO_4$), and evaporated under reduced pressure. The extraction residue was either crystallized directly or chromatographed using silica gel (ca 200 g) and eluted with an appropriate solvent system to afford the product **6**.

3-(Indol-3-yl)-N-methylsuccinimide (**6a**): Indole (**5a**) and *N*-methylmaleimide were used. Filtration of the cooled reaction mixture afforded **6a** (74%) as a yellow solid (Tables 2, 3, 6).

3-(5-Fluoroindol-3-yl)-N-methylsuccinimide (**6b**): 5-Fluoroindole (**5b**) and *N*-methylmaleimide were used. Filtration of the cooled reaction mixture afforded **6b** (87%) as a yellow solid (Tables 2, 6).

3-(5-Bromoindol-3-yl)-N-methylsuccinimide (**6c**): 5-Bromoindole (**5c**) and *N*-methylmaleimide were used. Filtration of the cooled reaction mixture afforded **6c** (62%) as a yellow solid (Tables 2, 3, 6).

3-(5-Bromoindol-3-yl)succinimide (**6d**): 5-Bromoindole (**5c**) and maleimide were used. The reaction mixture was evaporated under reduced pressure, and the residual solid was suspended in CH_2Cl_2 (75 mL). Undissolved solid was filtered to afford **6d** (61%) as a yellow powder (Tables 2, 3, 6).

N-Benzyl-3-(5-bromoindol-3-yl)succinimide (**6e**): 5-Bromoindole (**5c**) and *N*-benzylmaleimide were used. The resulting reaction mixture was evaporated under reduced pressure, and the residue was chromatographed using a 0–1% EtOAc gradient in CH_2Cl_2 to afford a gray foam. Crystallization of this foam from Et_2O/CH_2Cl_2 (9:1) afforded **6e** (23%) as a pale yellow solid (Tables 2, 3, 6).

3-(5-Methoxyindol-3-yl)-N-methylsuccinimide (**6f**): 5-Methoxyindole (**5d**) and *N*-methylmaleimide were used. The resulting reaction mixture was evaporated under reduced pressure, and the residue was chromatographed using EtOAc/hexanes (1:1) to afford a foam. Crystallization of this foam in EtOAc afforded **6f** (80%) as a pale yellow solid (Tables 2, 3, 6).

3-(5-Methoxyindol-3-yl)succinimide (**6g**): 5-Methoxyindole (**5d**) and maleimide were used. The resulting reaction mixture was evaporated under reduced pressure, and the residue was crystallized from EtOAc to afford **6g** (61%) as a yellow solid (Tables 2, 3, 6).

N-Benzyl-3-(5-methoxyindol-3-yl)succinimide (**6h**): 5-Methoxyindole (**5d**) and *N*-benzylmaleimide were used. The resulting reaction

mixture was evaporated under reduced pressure, and the residue was chromatographed using EtOAc/hexanes (1:1) to afford a pale yellow foam. Crystallization of this foam from Et_2O/CH_2Cl_2 (19:1) afforded **6h** (57%) as a white powder (Tables 2, 3, 6).

N-Methyl-3-(5,6-methylenedioxyindol-3-yl)succinimide (**6i**): 5,6-Methylenedioxyindole (**5e**) and *N*-methylmaleimide were used. Filtration of the cooled reaction mixture afforded **6i** (60%) as a tan solid (Tables 2, 3, 6).

N-Methyl-3-(5-(prop-2-ynoxy)indol-3-yl)succinimide (**6j**):[5] 5-(Prop-2-ynynloxy)indole (**5f**) and *N*-methylmaleimide were used. The resulting reaction mixture was evaporated under reduced pressure, and the residue was crystallized from EtOAc to afford **6j** (31%) as a pale yellow solid (Tables 2, 3, 6).

3-(5-Benzoylaminoindol-3-yl)-N-methylsuccinimide (**6k**): 5-Benzoylaminoindole (**5g**) and *N*-methylmaleimide were used. Chromatography of the crude product using a gradient of EtOAc/hexanes (1:3 to 1:1) afforded **6k** (52%) as a white solid (Tables 2, 3, 6).

N-Methyl-3-(5-methylindol-3-yl)succinimide (**6l**): 5-Methylindole (**5h**) and *N*-methylmaleimide were used. Filtration of the cooled mixture afforded **6l** (74%) as a tan solid (Tables 2, 3, 6).

3-(5-Carboxyindol-3-yl)-N-methylsuccinimide (**6m**): Indole-5-carboxylic acid (**5i**) and *N*-methylmaleimide were used. Filtration of the cooled reaction mixture afforded **6m** (41%) as a off-white solid (Tables 2, 3, 6).

3-(5-Cyanoindol-3-yl)-N-methylsuccinimide (**6n**): 5-Cyanoindole (**5j**) and *N*-methylmaleimide were used. The reaction mixture was evaporated under reduced pressure, and the residue was chromatographed using EtOAc to afford **6n** (39%) as a yellow solid (Tables 2, 3, 6).

N-Methyl-3-(5-nitroindol-3-yl)succinimide (**6o**): 5-Nitroindole (**5k**) and *N*-methylmaleimide were used. The solvent was evaporated under reduced pressure, and the residue was chromatographed using EtOAc to afford **6o** (2%) as a yellow foam. An analytical sample was prepared via crystallization from $CHCl_3$ to afford a pale yellow solid (Tables 2, 3, 6).

3-(Pyrrolidin-3-yl)indoles 4; General Procedure:

To a stirred solution of $LiAlH_4$ (1.00 g, 26.4 mmol, 5 eq) in anhyd THF (50 mL) at 0°C was added the succinimide **6** (5.00 mmol) as a solid portionwise. The resulting mixture was heated at reflux under N_2 for a period of time determined by the individual succinimide **6** (6–24 h). Upon consumption of **6** as determined by TLC, the resulting mixture was cooled, and $Na_2SO_4 \cdot 10\,H_2O$ (ca 15 g) was added cautiously portionwise, followed by H_2O (1 mL), and then by EtOAc (100 mL). The resulting mixture was then stirred at r.t. under N_2 for 16 h. The mixture was then filtered through Celite, and the filtrate was evaporated under reduced pressure to afford the desired 3-(pyrrolidin-3-yl)indole **4**. If necessary, column chromatography was carried out using silica gel (approx 50 g) and elution with CH_2Cl_2/MeOH/NH_4OH (9:1:0.1) or other appropriate solvent system to give **4**.

3-(N-Methylpyrrolidin-3-yl)indole (**4a**): 3-(Indol-3-yl)-*N*-methylsuccinimide (**6a**) was used, and the reaction mixture was heated at reflux for 24 h. Evaporation of the filtrate (from the workup described above) under reduced pressure afforded **4a** (88%) as a white solid (Tables 4, 5, 7).

5-Fluoro-3-(N-methylpyrrolidin-3-yl)indole (**4b**): 3-(5-Fluoroindol-3-yl)-*N*-methylsuccinimide (**6b**) was used, and the reaction mixture was heated at reflux for 4.5 h. Evaporation of the filtrate (from the

Table 2. ^{1}H NMR Spectral Data for **6**

Product	^{1}H NMR (Solvent/TMS) δ, J (Hz)
6a	(DMSO-d_6): 11.05 (br s, NH), 7.40–7.34 (m, 2H), 7.08 (ddd, J = 1.8, 7.9, 8.2, 1H), 6.97 (ddd, J = 1.0, 7.9, 8.2, 1H), 4.36 (dd, J = 5.1, 9.4, 1H), 3.23 (dd, J = 9.4, 18.0, 1H), 2.93 (s, 3H), 2.80 (dd, J = 5.1, 18.0, 1H)
6b	(DMSO-d_6): 11.2 (br s, NH), 7.43 (d, J = 2.4, 1H), 7.37 (dd, J = 4.5, 8.8, 1H), 7.21 (dd, J = 2.5, 10.0, 1H), 6.99–6.92 (m, 1H), 4.36 (dd, J = 5.3, 9.3, 1H), 3.22 (dd, J = 9.6, 17.9, 1H), 2.92 (s, 3H), 2.83 (dd, J = 5.3, 17.9, 1H)
6c	(DMSO-d_6): 11.3 (br s, NH), 7.67 (d, J = 1.8, 1H), 7.41 (d, J = 2.3, 1H), 7.35 (d, J = 8.8, 1H), 7.21 (dd, J = 1.9, 8.8, 1H), 4.39 (dd, J = 5.3, 9.3, 1H), 3.22 (dd, J = 9.3, 17.9, 1H), 2.91 (s, 3H), 2.85 (dd, J = 5.3, 17.9, 1H)
6d	(DMSO-d_6): 11.25 (br s, NH), 7.64 (d, J = 1.7, 1H), 7.42 (d, J = 2.4, 1H), 7.35 (d, J = 8.7, 1H), 7.21 (dd, J = 1.8, 8.6, 1H), 4.37 (dd, J = 5.5, 9.4, 1H), 3.37 (br s, NH), 3.17 (dd, J = 9.5, 18.0, 1H), 2.81 (dd, J = 5.5, 18.0, 1H)
6e	($CDCl_3$): 8.37 (br s, NH), 7.45–7.40 (m, 3H), 7.37–7.29 (m, 3H), 7.20 (dd, J = 1.8, 8.6, 1H), 7.06 (d, J = 8.8, 1H), 6.89 (d, J = 2.5, 1H), 4.76 (s, 2H), 4.19 (dd, J = 5.2, 9.5, 1H), 3.22 (dd, J = 9.5, 18.4, 1H), 2.84 (dd, J = 5.2, 18.4, 1H)
6f	(DMSO-d_6): 10.9 (br s, NH), 7.29 (d, J = 1.9, 1H), 7.27 (d, J = 8.4, 1H), 6.88 (d, J = 2.4, 1H), 6.77 (dd, J = 2.4, 8.8, 1H), 4.33 (dd, J = 5.0, 9.3, 1H), 3.74 (s, 3H), 3.24 (dd, J = 9.3, 17.9, 1H), 2.93 (s, 3H), 2.80 (dd, J = 5.0, 17.9, 1H)
6g	(DMSO-d_6): 11.3 (br s, NH), 10.85 (br s, NH), 7.29–7.26 (m, 2H), 6.92 (d, J = 2.3, 1H), 6.78 (dd, J = 2.4, 8.8, 1H), 4.31 (dd, J = 5.3, 9.4, 1H), 3.75 (s, 3H), 3.19 (dd, J = 9.5, 18.0, 1H), 2.77 (dd, J = 5.3, 18.0, 1H)
6h	(acetone-d_6): 10.06 (br s, NH), 7.40–7.34 (m, 2H), 7.34–7.25 (m, 5H), 6.87 (d, J = 2.4, 1H), 6.77 (dd, J = 2.4, 8.8, 1H), 4.71 (s, 2H), 4.44 (dd, J = 5.0, 9.5, 1H), 3.64 (s, 3H), 3.35 (dd, J = 9.5, 18.1, 1H), 2.88 (dd, J = 5.0, 18.1, 1H)
6i	(DMSO-d_6): 10.8 (br s, NH), 7.14 (d, J = 2.1, 1H), 6.89 (s, 1H), 6.88 (s, 1H), 5.93 (d, J = 0.7, 1H), 5.92 (d, J = 0.7, 1H), 4.27 (dd, J = 5.1, 9.3, 1H), 3.20 (dd, J = 9.3, 17.9, 1H), 2.90 (s, 3H), 2.77 (dd, J = 5.1, 17.9, 1H)
6j	(acetone-d_6): 10.15 (br s, NH), 7.35 (d, J = 8.8, 1H), 7.32 (d, J = 1.7, 1H), 7.10 (d, J = 2.4, 1H), 6.86 (dd, J = 2.4, 8.8, 1H), 4.75 (d, J = 2.4, 2H), 4.38 (dd, J = 5.0, 9.4, 1H), 3.31 (dd, J = 9.4, 18.0, 1H), 3.04 (t, J = 2.4, 1H), 2.99 (s, 3H), 2.82 (dd, J = 5.0, 18.0, 1H)
6k	(DMSO-d_6): 11.03 (br s, NH), 10.13 (s, NH), 7.95 (dd, J = 8.8, 1.7, 2H), 7.82 (d, J = 1.4, 1H), 7.59–7.45 (m, 4H), 7.33 (d, J = 8.6, 1H), 7.33 (d, J = 2.4, 1H), 4.32 (dd, J = 9.4, 5.0, 1H), 3.22 (dd, J = 17.9, 9.4, 1H), 2.94 (s, 3H), 2.74 (dd, J = 17.9, 5.0, 1H)
6l	(DMSO-d_6): 10.9 (br s, NH), 7.27 (d, J = 2.2, 1H), 7.26 (d, J = 8.3, 1H), 7.17 (s, 1H), 6.93 (dd, J = 1.2, 8.3, 1H), 4.32 (dd, J = 5.0, 9.3, 1H), 3.22 (dd, J = 9.4, 17.9, 1H), 2.93 (s, 3H), 2.78 (dd, J = 5.1, 18.0, 1H), 2.36 (s, 3H)
6m	(DMSO-d_6): 12.45 (br s, CO_2H), 11.4 (br s, NH), 8.16 (s, 1H), 7.73 (dd, J = 1.5, 8.6, 1H), 7.46 (d, J = 2.1, 1H), 7.42 (d, J = 8.6, 1H), 4.44 (dd, J = 5.1, 9.3, 1H), 3.23 (dd, J = 9.3, 17.9, 1H), 2.90 (s, 3H), 2.90–2.82 (m, 1H)
6n	(DMSO-d_6): 11.65 (br s, NH), 8.09 (s, 1H), 7.58–7.53 (m, 2H), 7.46 (d, J = 8.4, 1H), 4.46 (dd, J = 5.6, 9.2, 1H), 3.24 (dd, J = 9.2, 17.9, 1H), 2.92 (s, 3H), 2.90 (dd, J = 5.6, 17.9, 1H)
6o	(DMSO-d_6): 11.83 (br s, NH), 8.58 (d, J = 2.1, 1H), 8.02 (dd, J = 2.2, 9.0, 1H), 7.65 (d, J = 2.0, 1H), 7.55 (d, J = 9.0, 1H), 4.56 (dd, J = 5.8, 9.1, 1H), 3.26 (dd, J = 9.3, 18.0, 1H), 2.96 (dd, J = 5.4, 18.0, 1H), 2.92 (s, 3H)

Table 3. ^{13}C NMR Spectral Data of **6**

Product	^{13}C NMR (Solvent/TMS) δ, J (Hz)
6a	(DMSO-d_6): 178.5, 176.7, 136.5, 126.0, 123.5, 121.4, 118.8, 118.4, 111.7, 110.8, 37.6, 36.2, 24.6
6c	(DMSO-d_6): 178.2, 176.5, 135.1, 128.2, 124.9, 123.9, 121.0, 113.7, 111.4, 110.6, 37.3, 35.8, 24.6
6d	(DMSO-d_6): 179.7, 178.0, 135.2, 128.1, 124.8, 123.9, 121.0, 113.7, 111.4, 110.8, 38.9, 37.1
6e	($CDCl_3$): 177.9, 175.8, 135.7, 135.2, 128.9, 128.8, 128.2, 127.3, 125.6, 123.5, 121.0, 113.3, 113.1, 110.9, 42.8, 38.0, 36.3
6f	(DMSO-d_6): 178.5, 176.8, 153.2, 131.6, 126.5, 123.9, 112.4, 111.3, 110.5, 100.5, 55.4, 37.6, 36.1, 24.6
6g	(DMSO-d_6): 179.9, 178.1, 153.2, 131.6, 126.5, 123.8, 112.3, 111.3, 110.7, 100.6, 55.4, 38.9, 37.4
6h	(acetone-d_6): 178.7, 176.8, 154.9, 137.7, 133.0, 129.3, 129.1, 128.4, 127.5, 124.3, 113.2, 112.9, 112.2, 101.1, 55.8, 42.8, 39.0, 37.0
6i	(DMSO-d_6): 178.4, 176.6, 144.2, 142.0, 131.3, 121.7, 119.9, 111.1, 100.2, 97.3, 92.4, 37.6, 36.0, 24.6
6j	(acetone-d_6): 178.8, 176.9, 152.7, 133.4, 127.3, 124.5, 113.2, 113.1, 112.3, 103.5, 80.3, 76.4, 57.1, 38.7, 37.0, 24.8
6k	(DMSO-d_6): 178.5, 176.6, 165.2, 135.5, 133.6, 131.2, 131.2, 128.3, 127.6, 125.6, 124.3, 116.5, 111.5, 110.9, 110.3, 37.7, 36.3, 24.7
6l	(DMSO-d_6): 178.5, 176.7, 134.9, 127.2, 126.3, 123.5, 123.0, 118.0, 111.4, 110.2, 37.6, 36.2, 24.6, 21.3
6m	(DMSO-d_6): 178.3, 176.6, 168.3, 138.9, 134.6, 125.9, 124.9, 122.7, 121.4, 112.3, 111.4, 37.3, 35.9, 24.6
6n	(DMSO-d_6): 178.0, 176.4, 140.6, 139.6, 127.0, 125.9, 116.8, 116.4, 113.8, 112.2, 37.1, 35.5, 24.7
6o	(DMSO-d_6): 178.0, 176.4, 140.6, 139.5, 126.9, 125.9, 116.8, 116.3, 113.7, 112.1, 37.1, 35.5, 24.7

Table 5. ^{13}C NMR Spectral Data of **4**

Product	^{13}C NMR (Solvent/TMS) δ
4a	(DMSO-d_6): 136.7, 126.4, 121.1, 120.9, 118.9, 118.1, 111.5, 62.7, 55.9, 42.2, 34.8, 32.0
4c	(DMSO-d_6): 135.4, 128.2, 123.4, 122.9, 121.1, 118.3, 113.5, 110.8, 62.6, 56.0, 42.1, 34.4, 32.2
4f	(CD_3OD): 154.8, 133.8, 128.4, 122.5, 118.0, 113.1, 112.6, 101.9, 63.3, 57.0, 56.4, 42.5, 36.4, 32.8
4h	($CDCl_3$): 153.7, 139.3, 131.9, 128.9, 128.2, 127.2, 126.9, 121.0, 119.7, 112.0, 111.8, 101.7, 60.8, 56.0, 54.3, 34.6, 31.6
4i	(DMSO-d_6): 143.8, 141.5, 131.5, 120.2, 119.6, 118.6, 100.0, 97.7, 92.2, 62.6, 56.0, 42.1, 34.8, 32.1
4k	(acetone-d_6): 142.6, 141.9, 128.9, 128.2, 127.2, 121.2, 118.5, 112.3, 112.3, 101.7, 63.5, 56.9, 49.6, 42.4, 36.3, 33.7
4l	(DMSO-d_6): 135.1, 126.7, 126.4, 122.5, 121.1, 118.5, 117.5, 111.2, 62.7, 55.9, 42.2, 34.8, 32.0, 21.4
4m	($CDCl_3$): 136.3, 132.1, 127.0, 122.0, 120.6, 119.7, 118.3, 111.3, 66.2, 62.7, 56.2, 42.4, 35.0, 32.1

Table 4. ^{1}H NMR Spectral Data of **4**

Product	^{1}H NMR (Solvent/TMS) δ, J (Hz)
4a	(DMSO-d_6): 10.8 (br s, NH), 7.58 (d, J = 7.8, 1H), 7.33 (d, J = 8.1, 1H), 7.13 (d, J = 2.1, 1H), 7.08–7.03 (m, 1H), 6.98–6.93 (m, 1H), 3.59–3.48 (m, 1H), 2.95 (t, J = 8.3, 1H), 2.74–2.66 (m, 1H), 2.57–2.42 (m, 2H), 2.31 (s, 3H), 2.32–2.19 (m, 1H), 1.95–1.83 (m, 1H)
4b	($CDCl_3$): 8.36 (br s, NH), 7.30 (dd, J = 2.5, 9.8, 1H), 7.24 (dd, J = 4.3, 8.8, 1H), 7.03 (d, J = 2.1, 1H), 6.99–6.89 (m, 1H), 3.68–3.57 (m, 1H), 3.08 (t, J = 9.0, 1H), 2.89–2.81 (m, 1H), 2.71–2.64 (m, 1H), 2.60 (dd, J = 8.0, 9.0, 1H), 2.45 (s, 3H), 2.43–2.33 (m, 1H), 2.05–1.94 (m, 1H)
4c	(DMSO-d_6): 11.0 (br s, 1H), 7.74 (d, J = 2.3, 1H), 7.29 (d, J = 8.8, 1H), 7.20 (s, 1H), 7.15 (dd, J = 1.7, 8.6, 1H), 3.55–3.45 (m, 1H), 2.88 (t, J = 8.2, 1H), 2.65–2.42 (m, 3H), 2.29 (s, 3H), 2.29–2.15 (m, 1H), 1.93–1.77 (m, 1H)
4f	(CD_3OD): 7.20 (d, J = 8.8, 1H), 7.02 (s, 1H), 7.01 (d, J = 2.4, 1H), 6.74 (dd, J = 2.3, 8.8, 1H), 4.90 (s, DHO), 3.80 (s, 3H), 3.67–3.55 (m, 1H), 3.13 (dd, J = 8.0, 9.2, 1H), 2.94–2.86 (m, 1H), 2.67–2.53 (m, 2H), 2.41 (s, 3H), 2.41–2.29 (m, 1H), 2.07–1.95 (m, 1H)
4g	(CD_3OD): 7.21 (d, J = 8.8, 1H), 7.02 (d, J = 2.0, 1H), 6.75 (dd, J = 2.4, 8.8, 1H), 4.89 (s, approx 2 exchangeable H), 3.80 (s, 3H), 3.49–3.36 (m, 1H), 3.33–3.28 (m, 1H), 3.12–2.96 (m, 2H), 2.84 (dd, J = 8.2, 10.6, 1H), 2.29–2.18 (m, 1H), 2.00–1.87 (m, 1H)
4h	($CDCl_3$): 8.09 (br s, 1H), 7.39–7.23 (m, 5H), 7.19 (d, J = 9.0, 1H), 7.14 (d, J = 1.9, 1H), 6.92 (d, J = 2.4, 1H), 6.85 (dd, J = 2.3, 9.0, 1H), 3.85 (s, 3H), 3.75 (d, J = 13.1, 1H), 3.69 (d, J = 12.9, 1H), 3.70–3.59 (m, 1H), 3.14 (t, J = 8.4, 1H), 2.93–2.84 (m, 1H), 2.75–2.66 (m, 1H), 2.64 (t, J = 8.6, 1H), 2.42–2.28 (m, 1H), 2.05–1.92 (m, 1H)
4i	(DMSO-d_6): 10.55 (br s, NH), 7.05 (s, 1H), 6.95 (d, J = 2.1, 1H), 6.85 (s, 1H), 5.90 (s, 2H), 3.49–3.38 (m, 1H), 2.89 (t, J = 8.3, 1H), 2.67–2.58 (m, 1H), 2.58–2.50 (m, 1H), 2.42 (t, J = 8.1, 1H), 2.29 (s, 3H), 2.27–2.15 (m, 1H), 1.89–1.76 (m, 1H)
4k	(acetone-d_6): 9.53 (br s, NH), 7.44 (d, J = 7.4, 2H), 7.29 (t, J = 7.4, 2H), 7.19 (t, J = 7.2, 1H), 7.10 (d, J = 8.7, 1H), 6.95 (s, 1H), 6.83 (d, J = 2.1, 1H), 6.63 (dd, J = 8.6, 2.2, 1H), 3.51–3.43 (m, 1H), 2.87 (t, J = 8.7, 1H), 2.71–2.62 (m, 1H), 2.51–2.39 (m, 2H), 2.29 (s, 3H), 2.34–2.23 (m, 1H), 1.96–1.83 (m, 1H)
4l	(DMSO-d_6): 10.6 (br s, NH), 7.34 (s, 1H), 7.21 (d, J = 8.2, 1H), 7.07 (d, J = 2.1, 1H), 6.88 (dd, J = 2.1, 8.2, 1H), 3.55–3.47 (m, 1H), 2.96 (t, J = 8.2, 1H), 2.74–2.67 (m, 1H), 2.55–2.47 (m, 1H), 2.43 (t, J = 8.3, 1H), 2.37 (s, 3H), 2.30 (s, 3H), 2.30–2.17 (m, 1H), 1.93–1.82 (m, 1H)
4m	($CDCl_3$): 8.33 (br s, NH), 7.57 (s, 1H), 7.31 (d, J = 8.3, 1H), 7.19 (dd, J = 1.5, 8.3, 1H), 6.97 (d, J = 1.7, 1H), 4.74 (s, 2H), 3.68–3.57 (m, 1H), 3.06 (t, J = 8.8, 1H), 2.95 (br s, OH), 2.86–2.79 (m, 1H), 2.65–2.56 (m, 1H), 2.56 (t, J = 8.8, 1H), 2.39 (s, 3H), 2.39–2.29 (m, 1H), 2.03–1.92 (m, 1H)

Table 6. Compounds **6a–o** Prepared[a]

Product	Yield (%)	mp (°C)	IR (KBr) ν (cm^{-1})	MS m/z (%)
6a	74	235 (dec.)	1681, 1652, 1618	228 (M^+, 75), 143 (100), 83 (91)
6b	87	200 (dec.)	1769, 1683, 1582, 1486, 1459, 1454, 1440, 1418	246 (M^+, 24), 161 (100), 133 (34)
6c	62	198–199	1771, 1724, 1691, 1473, 1462, 1453, 1435, 1423	308 (M^+ with ^{81}Br, 38), 306 (M^+ with ^{79}Br, 40), 223 (93), 221 (100)
6d	61	198–200	1777, 1709, 1461, 1420	294 (M^+ with ^{81}Br, 94), 292 (M^+ with ^{79}Br, 100), 223 (97), 221 (97)
6e	23	167–170	1774, 1698, 1494, 1455, 1435, 1423, 1401	402 $([M \cdot NH_4]^+$ with ^{81}Br, 100), 400 $([M \cdot NH_4]^+$ with ^{79}Br, 88)
6f	80	146–148	1775, 1699, 1625, 1585, 1549, 1486, 1438	259 (21), 258 (M^+, 100), 243 (6), 173 (47), 158 (35), 130 (24)
6g	61	180 (dec.)	1779, 1714, 1487, 1456, 1442, 1417	245 (14), 244 (M^+, 100), 173 (91), 158 (40)
6h	57	139.5–141.5	1698, 1582, 1487, 1456, 1429, 1399	336 (22), 335 (MH^+, 100)
6i	60	260–262	1768, 1751, 1687, 1634, 1612, 1555, 1507	273 (15), 272 (M^+, 100), 240 (100), 187 (61), 137 (46), 81 (100)
6j	31	179–180	2125, 1772, 1689, 1683, 1484, 1467, 1461, 1442, 1409	283 (11), 282 (M^+, 54), 243 (100), 215 (34), 197 (34), 158 (20)
6k	52	226.5–227.5	3270 (br), 1690, 1645, 1490	348 (MH^+, 100), 332 (2), 275 (4), 263 (5)
6l	74	180–182	1767, 1745, 1688, 1583, 1488, 1440, 1415	243 (11), 242 (M^+, 71), 157 (100), 83 (91)
6m	41	290 (dec.)	1767, 1718, 1675, 1622, 1481, 1459, 1439, 1412	273 (13), 272 (M^+, 71), 187 (100), 170 (13)
6n	39	260 (dec.)	2220, 1771, 1694, 1633, 1619, 1470, 1440	254 (17), 253 (M^+, 77), 168 (100)
6o	2	242–245	1773, 1693, 1626, 1581, 1548, 1520, 1473, 1440, 1415	274 (13), 273 (M^+, 55), 188 (25), 137 (21), 81 (100)

[a] Satisfactory microanalyses (C ± 0.35, H ± 0.32, N ± 0.48) and HRMS values (± 0.0066 amu) obtained.

Table 7. Compounds **4** Prepared[a]

Product	Yield (%)	mp (°C)	IR (KBr) ν (cm^{-1})	MS m/z
4a	88	99–102	1620, 1603, 1579, 1545, 1502, 1479, 1453, 1418	201 (20), 200 (M^+, 100), 156 (55), 143 (68), 130 (54), 115 (36)
4b	79	98.5–101.5	1629, 1613, 1582, 1498, 1484, 1483, 1470, 1449, 1416	219 (14), 218 (M^+, 100), 200 (71), 169 (53)
4c	48	163–164	–	280 (M^+ with ^{81}Br, 99), 278 (M^+ with ^{79}Br, 100), 223 (17), 221 (17)
4f	90	73–74	1624, 1583, 1483, 1451	231 (13), 230 (M^+, 100), 215 (5), 173 (23), 156 (10)
4g	70	100 (dec.)	1682, 1624, 1582, 1483, 1454	217 (16), 216 (M^+, 100), 187 (52), 174 (80), 160 (36)
4h	98	foam	1630, 1481, 1460	306 (M^+, 31), 163 (32), 159 (28), 133 (69), 91 (100)
4i	76	110–112.5	1562, 1548, 1514, 1499, 1481, 1466, 1419	245 (14), 244 (M^+, 100), 187 (41), 161 (43), 57 (70)
4k	76	foam	3405–3027 (br), 1627, 1585, 1481, 1468, 1452	306 (MH^+, 100), 263 (4), 248 (4), 223 (8)
4l	60	105–107	1628, 1606, 1599, 1583, 1545, 1478, 1451, 1443, 1417	214 (M^+, 43), 171 (26), 170 (29), 157 (21), 144 (18), 57 (100)
4m	73	210 (dec.)	3231 (br), 1583, 1481, 1449	232 (67), 231 (MH^+, 100)

[a] Satisfactory microanalyses (C ± 0.46, H ± 0.27, N ± 0.36, exception: **4i**, H − 0.58) and HRMS values (± 0.0060 amu) obtained.

workup described above) under reduced pressure afforded **4b** (79%) as a crystalline, tan solid (Tables 4, 7).

5-Bromo-3-(N-methylpyrrolidin-3-yl)indole (**4c**): 3-(5-Bromoindol-3-yl)-*N*-methylsuccinimide (**6c**) was used. The reaction mixture was heated at reflux for 3 h. The filtrate (from the procedure described above) was evaporated under reduced pressure. The residue was chromatographed using elution with 1% Et_3N in MeOH to afford **4c** (48%) as an tan solid (Tables 4, 5, 7).

5-Methoxy-3-(N-methylpyrrolidin-3-yl)indole (**4f**): 3-(5-Methoxyindol-3-yl)-*N*-methylsuccinimide (**6f**) was used. The reaction mixture was heated at reflux for 7 h. The filtrate (from the procedure described above) was evaporated under reduced pressure to afford **4f** (90%) as a white solid (Tables 4, 5, 7).

5-Methoxy-3-(pyrrolidin-3-yl)indole (**4g**): 3-(5-Methoxyindol-3-yl)succinimide (**6g**) was used. The reaction mixture was heated at reflux for 6.5 h. The filtrate (from the procedure described above) was evaporated under reduced pressure to afford **4g** (70%) as a white foam (Tables 4, 5, 7).

3-(N-Benzylpyrrolidin-3-yl)-5-methoxyindole (**4h**): *N*-Benzyl-3-(5-methoxyindol-3-yl)succinimide (**6h**) was used. The reaction mixture was heated at reflux for 6 h. The filtrate (from the procedure described above) was evaporated under reduced pressure. The residue was chromatographed using elution with EtOAc to afford **4h** (98%) as a pale green foam (Tables 4, 5, 7).

5,6-Methylenedioxy-3-(N-methylpyrrolidin-3-yl)indole (**4i**): *N*-Methyl-3-(5,6-methylenedioxyindol-3-yl)succinimide (**6i**) was used. The reaction mixture was heated at reflux for 6 h. The filtrate (from the procedure described above) was evaporated under reduced pressure to afford **4i** (76%) as a pale red foam (Tables 4, 5, 7).

5-Benzylamino-3-(N-methylpyrrolidin-3-yl)indole (**4k**): 3-(5-Benzoylaminoindol-3-yl)-*N*-methylsuccinimide (**6k**) was used. The reaction mixture was heated at reflux for 6 h. Chromatography using elution with EtOAc/MeOH/Et_3N (9:0:1 to 8:1:1) afforded **4k** (76%) as a pale yellow foam (Tables 4, 5, 7).

5-Methyl-3-(N-methylpyrrolidin-3-yl)indole (**4l**): *N*-Methyl-3-(5-methylindol-3-yl)succinimide (**6l**) was used. The reaction mixture was heated at reflux for 6 h. The filtrate (from the procedure described above) was evaporated under reduced pressure to afford **4l** (60%) as a white foam (Tables 4, 5, 7).

5-Hydroxymethyl-3-(N-methylpyrrolidin-3-yl)indole (**4m**): 3-(5-Carboxyindol-3-yl)-*N*-methylsuccinimide (**6m**) was used. The reaction mixture was heated at reflux for 12 h. The filtrate (from the procedure described above) was evaporated under reduced pressure to afford **4m** (73%) as a white foam (Tables 4, 5, 7).

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