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# Solvent-free multi-component synthesis of unsymmetrical bis(indolyl)alkanes with Lewis acid-surfactant-SiO<sub>2</sub> as nanocatalyst

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#### ABSTRACT

Herein we report the multicomponent synthesis of the bis(indolyl)methane derivatives in a ball mill. The reaction was carried out under solvent-free conditions using only the Lewis acid-surfactant-SiO<sub>2</sub> composite nanocatalyst (LASSC) prepared in situ. The unsymmetrical bis(indolyl) methane derivatives containing nitro or fluorine substitution with a yield of 72%–92% were obtained in a short reaction time. Within we verified that under the action of the combined catalyst of  $AICI_3 \cdot 6H_2O + SDS + SiO_2$ , the method of preparing unsymmetrical bis(indolyl)methane by mechanical grinding without solvent has obvious advantages. Finally, we inspected that the catalysis system can be used eight times without a significant decrease in activity.

#### **ARTICLE HISTORY** Received 8 September 2020

#### **KEYWORDS**

Mechanochemistry; LASSC catalyst; Unsymmetrical bis(indolyl)methane; solvent-free; Ball mill

#### **GRAPHICAL ABSTRACT**



• Supplemental data for this article can be accessed on the publisher's website.

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# Introduction

With the emergence of the energy crisis and the development of green chemistry, researchers seek to minimize the use of hazardous reagents in the industry, eliminate waste and recycle as much as possible, and obtain excellent products in a more green and environmentally friendly way.<sup>[1-3]</sup> Currently, mechanochemistry is considered to be an effective way to replace traditional solution chemistry.<sup>[4-6]</sup> Due to mechanochemistry has the characteristics of reducing the use of toxic solvents, improving catalyst utilization and reducing energy consumption, it is very consistent with the concept of green chemistry.<sup>[7,8]</sup> Since F. Toda et al.<sup>[9,10]</sup> demonstrated for the first time that many organic reactions in solution chemistry can also be achieved in a solid state, solvent-free methods has developed rapidly,<sup>[11,12]</sup> especially in the field of unsymmetric organic synthesis.<sup>[13,14]</sup> Similarly, Liquid assisted grinding (LAG) has been used as a continuation of the traditional solvent-free mechanochemical method, which uses a small amount of liquid as an aid to increase the chemical reaction rate or control the selectivity of the reaction.<sup>[15]</sup> It has a certain role in inorganic and organic synthesis. However, its mechanism of action is more complicated or even unclear, and its product yield has not been significantly improved. Current research shows that the mechanism of LAG may be related to molecular migration<sup>[16]</sup> or liquid polarity.<sup>[17]</sup> Therefore, it is still challenging to develop solvent-free mechanical milling with high selectivity and yield.

Indole derivatives are known to have a variety of biochemical properties including antibacterial, anticancer, and antiinflammatory, are used as antibiotics in pharmaceuticals.<sup>[18-20]</sup> The symmetrical bis(indolyl)methane (BIM) are usually available by coupling reactions involving an aldehyde and indole in the presence of acid catalysts or promoters.<sup>[21-24]</sup> However, the unsymmetrical bis(indolyl)methane is still remains challenging in organic synthesis.<sup>[25,26]</sup> At present, the main catalyst used in synthesis includes TsOH,<sup>[27]</sup> Ga(OTf)<sub>3</sub>,<sup>[26]</sup> silica gel,<sup>[28]</sup> Zn(OTf)<sub>2</sub>,<sup>[29]</sup> NaOH,<sup>[30]</sup> etc. However, there are some disadvantages in the above catalytic synthesis methods, such as expensive or difficult to recycle of catalysts; use of large amounts of toxic reagents or solvents (toluene, chloroform, etc.); the longer reaction time (more than several hours), etc. In addition, most methods use 3-indole aromatic alcohols as reaction substrates to condense with nucleophiles to prepare unsymmetrical bis(indolyl)alkanes.<sup>[31-33]</sup>

To our knowledge, the synthesis of unsymmetrical bis(indolyl)methane by Friedel-Crafts alkylation and solvent-free mechanical ball milling at room temperature is unknown. The Lewis acid-surfactant-SiO<sub>2</sub> combined catalyst (LASSC) has proven to have special catalytic properties in organic synthesis.<sup>[34]</sup> It is advantageous to use LASSC to catalyze organic reactions, due to its composition is readily available, requires no solvent, nontoxic, and can be reused multiple times. Here, we disclose the details of the three-component Friedel-Crafts alkylation reaction of indoles and aldehydes catalyzed by LASSC. The unsymmetrical bis(indolyl)methane derivatives with higher yields were obtained in a short time (Scheme 1).

# **Experimental section**

# **Equipment and materials**

All chemicals were of analytical grade and obtained from Beijing Innochem Technology Co., Ltd., and used without further purification. The equipment uses the tissue grinder



#### Scheme 1.

provided by Wuhan Saiweier Technology Co., Ltd. (China). The power of the device in actual work is 60 watts.

# **Experimental condition optimization**

The Lewis metal salt: (mainly including AlCl<sub>3</sub>; AlCl<sub>3</sub>· $6H_2O$ ; FeCl<sub>3</sub>· $6H_2O$ ; SnCl<sub>4</sub>· $5H_2O$ ; Cu(NO<sub>3</sub>)<sub>2</sub>· $3H_2O$ , etc., 0.05 mmol); sodium dodecyl sulfate (SDS, 0.15 mmol); column chromatography silica gel (300 mg) was mixed in a 5 mL sample tube and placed in a ball mill. The ball mill has a power of 60 Hz and is prereacted for ten min. Then, the reaction starting material p-nitrobenzaldehyde **1** (0.5 mmol), indole **2** (0.5 mmol), 6-bromoindole **3** (0.5 mmol) was added, and the reaction was continued at a power of 60 Hz for a specific time. After the reaction was completed, the reaction mixture was dissolved in ethyl acetate (10 mL) and filtered. The filtrate was concentrated, and the residue was purified with silica gel chromatography (Petroleumether/EtOAc =3:1) to give product **5a**. The filtered solid mixture was dried and then used in the next reaction.

#### **Experimental procedure for compounds 5a–51**

The AlCl<sub>3</sub>·6H<sub>2</sub>O (0.05 mmol); sodium dodecyl sulfate (SDS, 0.15 mmol); column chromatography silica gel (300 mg) was mixed in a 5 mL sample tube and placed in a ball mill. The ball mill has a power of 60 Hz and is pre-reacted for ten min. Then, the reaction starting material aromatic aldehyde 1 (0.5 mmol), different substituents indoles 2 (0.5 mmol) and 3 (0.5 mmol) was added, and the reaction was continued at a power of 60 Hz for a specific time. After the reaction was completed, the reaction mixture was dissolved in ethyl acetate (10 mL) and filtered. The filtrate was concentrated, and the residue was purified with silica gel chromatography (Petroleumether/EtOAc = 2:1-5:1) to give product 5a-51.

ŅO2

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81

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CHO NO <sub>2</sub> + 1	+ B.T. ball milling A.T. ball milling A.T. ball milling HN HN 4a	К + () NH + ()	Br + Br	HN Ab
Entry <sup>a</sup>	Catalysts	Time (min)	Ratio (4a: 5a: 4b)	Yield <sup>b</sup> (%)
1 <sup>c</sup>	NaOH/ EtOH-H <sub>2</sub> O	120	47: 10: 43	35
2	NaOH	120	::	No reaction
3	AICI <sub>3</sub>	23	49:: 51	79
4	AICI <sub>3</sub> .6H <sub>2</sub> O+SiO <sub>2</sub>	15	37: 28: 35	81
5	LASSC (AICI <sub>3</sub> .6H <sub>2</sub> O +SiO <sub>2</sub> +SDS)	8	1: 97: 2	93
6	LASSC (FeCl <sub>3</sub> .6H <sub>2</sub> O +SiO <sub>2</sub> +SDS)	18	7: 89: 4	89
7	LASSC (SnCl <sub>4</sub> .5H <sub>2</sub> O +SiO <sub>2</sub> +SDS)	19	11: 86: 3	87
8	LASSC (BaCl <sub>2</sub> .2H <sub>2</sub> O +SiO <sub>2</sub> +SDS)	30 / >120	49: 3: 48	No reaction / 71
9	LASSC (MgCl <sub>2</sub> .6H <sub>2</sub> O +SiO <sub>2</sub> +SDS)	30 / >90	34: 43: 23	No reaction / 74

ŅO2

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#### Table 1. Optimization of the catalyst system.

LASSC (Cu(NO<sub>3</sub>)<sub>2</sub>.3H<sub>2</sub>O +SiO<sub>2</sub>+SDS)

LASSC (Ce(NO<sub>3</sub>)<sub>3</sub>.6H<sub>2</sub>O +SiO<sub>2</sub>+SDS)

LASSC (Zn(NO<sub>3</sub>)<sub>2</sub>.6H<sub>2</sub>O +SiO<sub>2</sub>+SDS)

<sup>a</sup> Reaction conditions: **1** (0.5 mmol); **2** (0.5 mmol); **3** (0.5 mmol). SDS (0.15 mmol);SiO<sub>2</sub> (column chromatography silica gel, 300 mg); Lewis metal salt (0.05 mmol). NaOH (0.1mmol); Entries 2-12 were ball milling. The power was 60Hz. <sup>b</sup> Isolated yields. R.T; solvent-free. <sup>c</sup>  $V_{(EtOH)}$ : $V_{(H2O)}$  =1:1 (2ml).

19

21

23

9.81.10

6:86:8

9:81:10

# **Results and discussion**

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Initially, we chose *p*-nitrobenzaldehyde, indole, and 6-bromoindole as models to investigate the conditions for the Friedel-Crafts alkylation reaction. As shown in Table 1, different catalysts show different selectivity. M. L. Deb et al.<sup>[30,35]</sup> reported that unsymmetrical bis(indolyl)methane can be obtained by using NaOH in a mixed solvent of ethanol and water, and it is generally difficult to obtain unsymmetrical bis(indolyl) methane in the presence of a Lewis acid catalyst. But, we obtained under the same conditions using the base catalyst NaOH was not satisfactory, and the yield was only 35% (Table 1, entry 1).

Nextly, we changed the reaction strategy and used a ball mill for solvent-free reaction. The result is very unsatisfactory and no products appear (entry 2). Similarly, the use of Lewis metal salts such as  $AlCl_3$  tends to symmetric coupling products, and unsymmetrical coupling product is almost non-existent (entry 3). Interestingly, the combination of  $AlCl_3 \cdot 6H_2O$  and  $SiO_2$  can make the reaction part tend to be coupled unsymmetrically (entry 4), indicating that this combined catalyst can produce special compound configurations under the action of mechanical ball milling. Because the LASSC catalyst system has shown excellent catalytic performance in the synthesis of symmetric

CHO NO <sub>2</sub>	$R_2 \qquad N \\ 2 \\ + \\ R_3 \xrightarrow{\qquad N \\ 3 \\ 3 \\ 3 \\ 3 \\ 3 \\ 3 \\ 3 \\ 3 \\ 3 \\$	LASSC R.T. ball milling	R <sub>2</sub> HN		+ R <sub>2</sub> + NO2 + NH	$\sum_{HN}^{NO2} + R_3 + R$
Entry <sup>a</sup>	R <sub>2</sub>	R <sub>3</sub>	Time/ min	Product	Ratio (4: 5: 6)	Yield <sup>b</sup> /%
1	6-H	6-Br	8	5a	1: 97: 2	93
2	6-CN	6-Br	10	5b	30: 38: 32	94
3	6-NO <sub>2</sub>	6-Br	5	5c	19: 55: 26	93
4	6-OMe	6-Br	10	5d	32: 45: 23	92
5	5-OMe	6-Br	15	5e	30: 38: 32	89
6	6-COOMe	6-Br	15	5f	17: 41: 32	73
7	6-F	6-Br	5	5g	: 100:	95
8	6-NH <sub>2</sub>	6-Br	30	5h	9: 3: 88	53
9	6-OH	6-Br	32	5i	14: 2: 84	48
10	6-F	6-CI	8	5j	: 100:	96(96,94,94,93,91,90,90,88) <sup>d</sup>
11	6-F	7-Br	11	5k	23: 48: 29	88
12 <sup>c</sup>	6-F	1-Me	15	51	27: 39: 34	93

Table 2. Synthesis of unsymmetrical nitro-substituted bis(indolyl)methane compounds by LASSC ball milling.

<sup>*a*</sup> Reaction condition: **1** (0.5 mmol); **2** (0.5 mmol); **3** (0.5 mmol). LASSC catalyst (including AlCl<sub>3</sub>.6H<sub>2</sub>O (0.05 mmol); SDS (0.15 mmol); SiO<sub>2</sub> (300 mg).); Room temperature. <sup>*b*</sup> Isolated yield. <sup>*c*</sup> The R<sub>3</sub> is N-Methylindole. <sup>*d*</sup> The product yield of LASSC catalyst repeated 8 times.

bis(indolyl)methanes, we have studied different combin- ations of Lewis metal salts with SDS and  $SiO_2$  catalysts (entries 5–12). Fortunately, these combinations are excellent in the catalytic synthesis of unsymmetrical bis(indolyl) methane, with yields ranging from 81% to 93%, except BaCl<sub>2</sub>·2H<sub>2</sub>O and MgCl<sub>2</sub>·6H<sub>2</sub>O. After prolonging the reaction time, the product yields of the two were 71% and 74%, respectively (entries 8-9). It is worth noting that the combination of LASSC ( $AlCl_3 \cdot 6H_2O + SDS + SiO_2$ ) also exhibits excellent catalytic performance in the synthesis of unsymmetrical bis(indolyl) methane, both in terms of reaction time and product yield (Table 1, entry 5). This is due to the fact that the three components of  $AlCl_3$ ·6H<sub>2</sub>O, SDS and SiO<sub>2</sub> can form a nano-network fiber structure with specific catalytic activity through intermolecular forces and coordination, which provides conditions for the formation of unsymmetrical indole methane compounds.

We tried to synthesize a series of unsymmetrical bis(indolyl)methanes with nitro groups under optimal conditions, and the results are shown in Table 2. The combination of different indole substituents shows different selectivity under the same catalyst. Among them, entry 1, entry 7 and entry 10 showed good selectivity, and all substrates were converted into unsymmetrical coupling products, and almost no symmetric products were produced. This result is exciting. All indole of the electron-withdrawing group



Table 3. Expansion of unsymmetrical fluorine-substituted bis(indolyl) methane derivatives under ball milling.

<sup>a</sup> Reaction condition: **1** (0.5 mmol); **2** (0.5 mmol); **3** (0.5 mmol); LASSC catalyst (including: AlCl<sub>3</sub>.6H<sub>2</sub>O(0.05mmol);SDS (0.15mmol); SiO<sub>2</sub>(300 mg)). Room temperature and solvent-free. Isolated yield.

can react with aromatic aldehyde and generate corresponding unsymmetrical products. Also, the ratio of unsymmetrical coupling products is always higher than that of symmetric coupling products. However, for the electron-donating group reaction, almost no uncoupled products appear, and only symmetrical products (entries 8–9). But the conversion of all reaction substrates is thorough, and the total yield remains above 70%. The reaction involving *N*-methylindole produced both symmetric and unsymmetrical products in a short period of time, and the total yield of the three coupling products



Scheme 2. A mechanism of speculation.

remained around 93% (entry 12). In addition, the structure of compound 5j was confirmed by X-ray single-crystal diffraction (as shown in Table 3).

Recycling and reuse of catalysts is an important indicator for evaluating catalysts and is one of the green chemistry guidelines. We selected the model reaction to be evaluated (Table 2, entry 10). The recovery of the catalyst is simple and easy to operate, and only a small amount of ethyl acetate is required for washing to obtain a fresh catalyst. The results show that the catalyst LASSC has a product yield of 88% after being recycled for eight times in the model reaction, indicating excellent reproducibility of the LASSC catalyst. The reason is that the LASSC catalysts are combined in a cross-linking manner, and the Lewis metal salt is well combined with the surfactant and the silica through hydrogen bonding and coordination, and the active catalytic center is always present in the system.

Organofluorine compounds are widely used in a variety of fields, ranging from pharmaceuticals and agrochemicals to advanced materials and polymers etc.<sup>[36]</sup> In view of this, we expanded the preparation of a series of fluorine-containing unsymmetrical bis(indolyl)derivatives, as shown in Table 3. Fortunately, both aromatic aldehydes with electron-withdrawing or electron-donating groups can synthesize unsymmetrical bis(indolyl)methane derivatives at room temperature through LASSC catalysts, with yields ranging from 72% to 92% (Table 3, 5'a-5'o). The corresponding yield of the aromatic aldehyde containing an electron-donating group such as -CH<sub>3</sub>, -OH, etc. is lower than



Scheme 3. The gram-scale preparation of compound 5'a.

the yield corresponding to the electron-withdrawing group. In addition, we have found that these reactions have very high selectivity, and all produce unsymmetrical coupling products without symmetric products. Meanwhile, we used some aliphatic aldehydes such as butyraldehyde, furfural, etc. and fluorine-containing substituted indole to carry out a three-component solvent-free grinding reaction (Table 3, 5'p-5's). The product yields has all lower than the corresponding yields of aromatic aldehydes, and 2-pyridine carboxaldehyde does not participate in any reaction; the reaction time was also longer than aromatic aldehydes, generally more than 45 minutes and the raw material part were left. Similarly, these unsymmetrical bis(indolyl)methane derivatives may have potential medicinal value in terms of antiviral, antibacterial, and the like.

Based on our experimental observations and our understanding of the known literature, we proposed a speculative mechanism for the reaction shown in Scheme 2. It is believed that the Lewis acid composite catalyst first reacts with the aldehyde to generate carbonyl radicals, and the free radicals interact with the relatively more active fluorinecontaining indole to produce the intermediate 3-indolyl methanol compound. Then, the relatively low-activity chloroindole attacks the intermediate through nucleophilic attack and loses a molecule of water, forming a complete target compound. In this work, the catalyst used is a nano-cage structure with spatial crosslinking. Its diameter may depend on the double-layer and long-chain structure of SDS and the three-dimensional spatial junction of crystalline aluminum chloride. To a certain extent, it inhibits and selectively allows some small molecules to participate in the reaction. This is also the possible reason why most of the unsymmetrical bis(indolyl)alkanes appear in the reaction system, while the symmetric compounds are only a small amount. Through mechanism experiments, we first observed the formation of fluorine-containing 3-indolyl methanol compounds. After increasing the reaction time, most of the fluorescent spots of the target product were gradually observed, and a slight amount of symmetric compounds were also observed in it.

Under the optimal reaction conditions, we have achieved the synthesis of unsymmetrically coupled products at the gram level through the catalyst (Scheme 3). The catalyst LASSC was added in proportion, the power of the ball mill was 60 Hz, and the reaction was for 60 min. After the reaction was completed, ethyl acetate was used to dissolve and purify the product. The target product, 1.96 g, was successfully obtained with a 5'a yield of more than 90%. The above data shows that the LASSC catalyst we developed can achieve the quantification of the target product, and its yield is ideal.

# Conclusion

We have demonstrated a novel and efficient protocol for the synthesis of unsymmetrical bis(indolyl)methanes by using a Lewis salt composite catalyst (LASSC) mediated Friedel-Crafts alkylation of different substituents indole and aldehydes with the one-step method. This catalytic process has a certain selectivity for the indole of different groups. Moreover, the operational simplicity, mild reaction conditions, and multiple recycling of this protocol provide a potential strategy to scale up the preparation of unsymmetrical bis(indolyl)methanes, as demonstrated by the excellent yield obtained from the gram-scale synthesis. To the best of our knowledge, an unsymmetrical bis(indolyl) methanes compound was synthesized in this protocol, for the first time through a micro-nano chiral environment constructed using achiral catalysts.

# The data of some unknown compounds are as follows

# 3-((1h-indol-3-yl)(4-nitrophenyl)methyl)-6-bromo-1H-indole (5a)

Yellow solid (93%); M.p = 120.1–121.5 °C;<sup>1</sup>H NMR (400 MHz, DMSO- $d_6$ )  $\delta$  11.22 – 10.93 (m, 2H), 8.18 – 8.12 (m, 2H), 7.65 – 7.54 (m, 3H), 7.39 (d, J=8.1 Hz, 1H), 7.31 (d, J=7.8 Hz, 1H), 7.22 (dd, J=8.5, 5.8 Hz, 1H), 7.10 – 7.01 (m, 2H), 6.96 – 6.86 (m, 3H), 6.04 (s, 1H). <sup>13</sup>C NMR (101 MHz, DMSO)  $\delta$  158.95 (d, J=233 Hz), 152.67, 152.54, 145.91 (d, J=2 Hz), 137.56, 136.53 (d, J=13 Hz), 129.46, 125.43 (d, J=3 Hz), 125.06, 124.61, 123.54, 123.26 (d, J=3 Hz), 121.47, 121.45, 120.70, 119.92 (d, J=10 Hz), 116.91 (d, J=9 Hz), 116.83, 116.74, 114.21 (d, J=14 Hz), 107.07 (d, J=25 Hz), 97.64 (d, J=25 Hz), 39.05. IR (thin film)  $\nu_{max}$  3436; 2987; 1714; 1515; 1423; 1332; 810; 749. HRMS (ESI) m/z=445.0426, Called for C<sub>23</sub>H<sub>16</sub>BrN<sub>3</sub>O<sub>2</sub> [M-H]<sup>-</sup> 445.0408.

# 6-Chloro-3-((6-fluoro-1H-indol-3-yl)(4-nitrophenyl)methyl)-1H-indole (5j)

Yellow solid (96%); M.p = 186.6–188.0 °C;<sup>1</sup>H NMR (400 MHz, DMSO-d6)  $\delta$ 11.18 – 11.02 (m, 2H), 8.15 (d, J = 8.5 Hz, 2H), 7.63 – 7.55 (m, 2H), 7.42 (d, J = 1.9 Hz, 1H), 7.25 (dt, J = 9.1, 4.5 Hz, 2H), 7.15 (dd, J = 10.1, 2.4 Hz, 1H), 6.96 – 6.86 (m, 3H), 6.76 (td, J = 9.3, 2.4 Hz, 1H), 6.06 – 6.00 (m, 1H). <sup>13</sup>C NMR (101 MHz, DMSO)  $\delta$ 158.91 (d, J = 233 Hz), 152.68, 152.57, 145.88, 137.03, 136.49 (d, J = 13 Hz), 129.45, 126.03 (d, J = 2 Hz), 125.15 (d, J = 3 Hz), 125.10, 124.58, 123.54, 123.24, 120.28, 119.90 (d, J = 10 Hz), 118.89, 116.89, 116.80, 116.72, 111.30, 107.03 (d, J = 24 Hz), 97.61 (d, J = 25 Hz), 39.07. IR (thin film)  $\nu_{max}$  3431; 2959; 2878; 1716; 1515; 1433; 1341; 810; 749. HRMS (ESI) m/z = 419.0837, Called for C<sub>23</sub>H<sub>15</sub>ClFN<sub>3</sub>O<sub>2</sub> [M-H]<sup>-</sup> 409.0755.

# 6-Chloro-3-((4-chlorophenyl)(6-fluoro-1H-indol-3-yl)methyl)-1H-indole (5'a)

Light pink solid (92%); M.p = 157.3-157.8 °C; <sup>1</sup>H NMR (400 MHz, DMSO-d6)  $\delta$  11.02 (t, J = 2.7 Hz, 1H), 10.94 (d, J = 2.8 Hz, 1H), 7.40 (d, J = 1.9 Hz, 1H), 7.33 (d, J = 2.1 Hz, 4H), 7.22 (ddd, J = 10.0, 7.0, 4.1 Hz, 2H), 7.12 (dd, J = 10.1, 2.4 Hz, 1H), 6.92 - 6.85 (m, 2H), 6.82 (d, J = 2.6 Hz, 1H), 6.74 (ddd, J = 10.9, 8.9, 2.4 Hz, 1H), 5.84 (t, J = 3.1 Hz, 2H), 7.12 (dd, J = 10.9, 8.9, 2.4 Hz, 1H), 5.84 (t, J = 3.1 Hz, 2H), 7.12 (dd, J = 10.9, 8.9, 2.4 Hz, 1H), 5.84 (t, J = 3.1 Hz, 2H), 7.83 (t, J = 3.1 Hz), 7.83 (t,

1H). <sup>13</sup>C NMR (101 MHz, DMSO)  $\delta$  158.74 (d, J=232 Hz), 143.55, 143.40 (d, J=10 Hz), 136.92, 136.36 (d, J=14 Hz), 130.43, 130.02, 128.09 (d, J=4 Hz), 125.77 (d, J=3 Hz), 125.18 (d, J=3 Hz), 124.76, 124.19, 123.25 (d, J=3 Hz), 120.28, 119.88 (d, J=12 Hz), 118.65, 117.68, 117.54 (d, J=10 Hz), 111.10, 106.89, 106.66 (d, J=3 Hz), 97.39 (d, J=26 Hz), 38.66. IR (thin film)  $\nu_{max}$  3421; 2926; 2852; 1708; 1623; 1515; 1458; 1345; 807; 744. HRMS (ESI) m/z=408.0596, Called for C<sub>23</sub>H<sub>15</sub>Cl<sub>2</sub>FN<sub>2</sub> [M + H]<sup>+</sup> 408.0539.

## 6-Chloro-3-((6-fluoro-1H-indol-3-yl)(4-fluorophenyl)methyl)-1H-indole (5'i)

Light pink solid (89%); M.p = 96.1–96.7 °C;<sup>1</sup>H NMR (400 MHz, DMSO- $d_6$ )  $\delta$  11.01 (t, J = 2.8 Hz, 1H), 10.93 (t, J = 2.8 Hz, 1H), 7.40 (d, J = 1.9 Hz, 1H), 7.34 (ddd, J = 8.0, 5.2, 2.2 Hz, 2H), 7.23 (dd, J = 8.7, 4.3 Hz, 2H), 7.15 – 7.04 (m, 3H), 6.89 (dd, J = 8.5, 1.9 Hz, 1H), 6.85 (d, J = 2.4 Hz, 1H), 6.81 (d, J = 2.5 Hz, 1H), 6.74 (td, J = 9.3, 2.4 Hz, 1H), 5.84 (t, J = 2.9 Hz, 1H). <sup>13</sup>C NMR (101 MHz, DMSO)  $\delta$  160.82 (d, J = 183 Hz), 159.33, 157.57, 140.53, 136.94, 136.38 (d, J = 13 Hz), 129.94, 129.85, 125.76, 125.20, 124.70, 124.14, 123.31, 120.31, 119.91 (d, J = 11 Hz), 118.61, 118.02 (d, J = 8 Hz), 114.87 (d, J = 6 Hz), 114.67 (d, J = 7 Hz), 111.08, 106.74 (d, J = 27 Hz), 97.37 (d, J = 26 Hz), 38.55. IR (thin film)  $\nu_{\text{max}}$  3342; 2974; 2889; 1619; 1515; 1429; 1348; 810; 742. HRMS (ESI) m/z = 392.0892, Called for  $C_{23}H_{15}ClF_2N_2$  [M + Na]<sup>+</sup> 392.0842.

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