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ABNORMAL STRECKER REACTION OF 3-FORMYLINDOLE AND ANILINE

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Abstract – Reaction of 3-formylindole, aniline, and TMSCN under conditions of the Strecker reaction yielded a Friedel-Crafts reaction product rather than the usual aminonitrile. This abnormal Strecker reaction can be applied to various aniline and 3-formylindole derivatives. DFT calculations revealed that the most thermodynamically stable product is generated in the reaction.

The Strecker reaction is a three-component coupling reaction of amine, carbonyl, and cyanide ions for synthesizing amino acid equivalents (Figure 1A).[1,2] Ammonia, alkylamines, and anilines can be used as amines, and aldehydes and ketones are used for the carbonyl group. HCN, KCN, NaCN, and TMSCN are

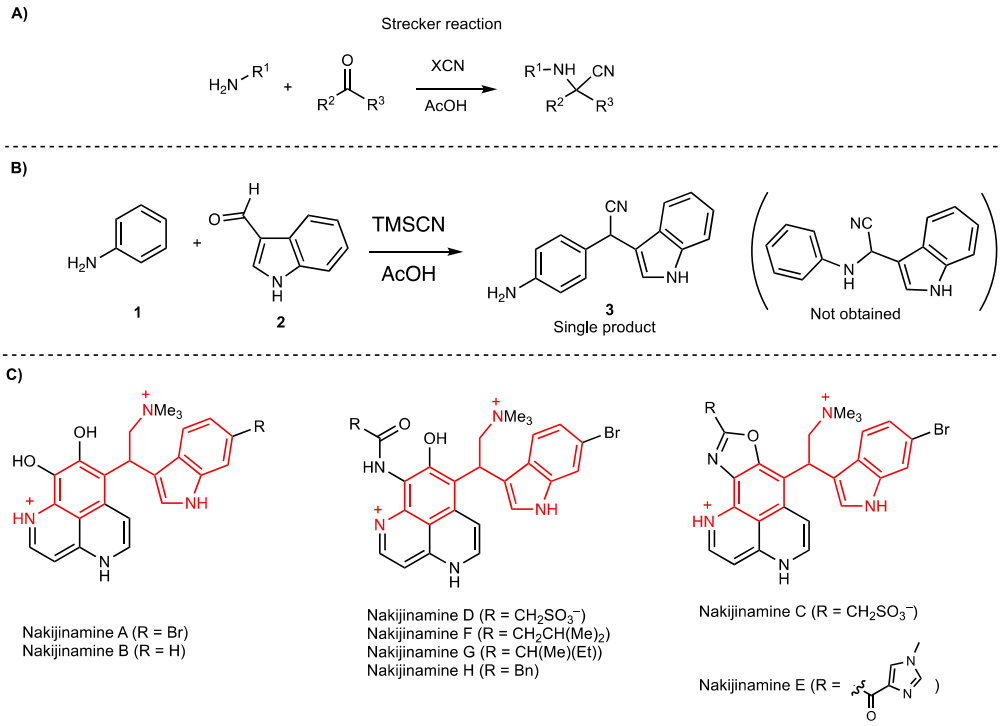
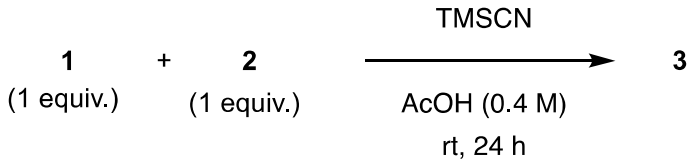


Figure 1. A) Usual Strecker reaction B) Abnormal Strecker reaction using 3-formylindole and aniline C) Structures of nakijinamines

used as cyano sources. Acetic acid is often used as the solvent and proton source for imine formation. When a Strecker reaction of 3-formylindole (**2**) was performed with aniline (**1**), **3** was obtained as a single product instead of the desired aminonitrile, indicating that a Friedel-Crafts reaction proceeded at the *p*-position of aniline (Figure 1B). The skeleton of **3** is contained in nakijinamines, which were isolated from an Okinawan marine sponge *Suberites* sp. in 2012 (Figure 1C).[3] In this short paper, we report this abnormal Strecker reaction and its mechanism.

We first investigated the reaction conditions. An equivalent of TMSCN could be reduced to 1.2 equivalents (Table 1, entry 3), and KCN could be used as a cyano source (Table 1, entry 5). Furthermore, the reaction proceeded even when using two equivalents of acetic acid (Table 1, entry 6).

Table 1. Optimization of the reaction conditions



entry	TMSCN	yield[a]
1	2.0 equiv.	79%
2	1.5 equiv.	81%
3	1.2 equiv.	82%
4	1.0 equiv.	72%
5	KCN (1.2 equiv.)	80%
6[b]	1.2 equiv.	74%

[a]Yield was determined by crude ^{1}H NMR analysis with internal references. [b]AcOH (2 equiv.) was used.

Next, the substrate scope was studied with various aniline and 3-formylindole derivatives (Figure 2). The abnormal Strecker reaction also proceeded smoothly when electron-donating substituents (**3a**-**3c**), halogens (**3g** and **3h**), phenyl (**3e**) or ester (**3f**) were substituted at the *o*-position. Interestingly, the reaction proceeded at the *p*-position of the aniline even when *o*-methoxyaniline was used (**3b** and **3i**). The structure of **3b** was confirmed by X-ray crystallographic analysis. On the other hand, reactivity was decreased for substrates with electron-withdrawing substituents (**3d**), consistent with the general trend of Friedel-Crafts reactions. In the case of *m*-substituted anilines, the reaction proceeded with *m*-Et (**3j**) and *m*-Br (**3l**) substrates, but did not proceed at all with *m*-*t*-Bu-aniline (**3k**), suggesting that the steric hindrance of the *t*-Bu group inhibited the Friedel-Crafts reaction. When using indole instead of aniline, the reaction proceeded at 3C of indole to give **3n**.[4] This reaction was also applicable to naphthalene (**3m**) and pseudoindoxyl (**3o**).

Furthermore, the reaction proceeded even with 2-Me-, 2-Ph-, N-Me- and N-*p*-methoxybenzyl (PMB)-3-formylindole (**3p**-**3s**). The reaction also proceeded with a halogen (**3t**-**3v**) and methoxy (**3w**) on the benzene ring of the indole, leading to successful synthesis of a product containing 6-Br-indole (**3v**), the main skeleton of nakijinamines.

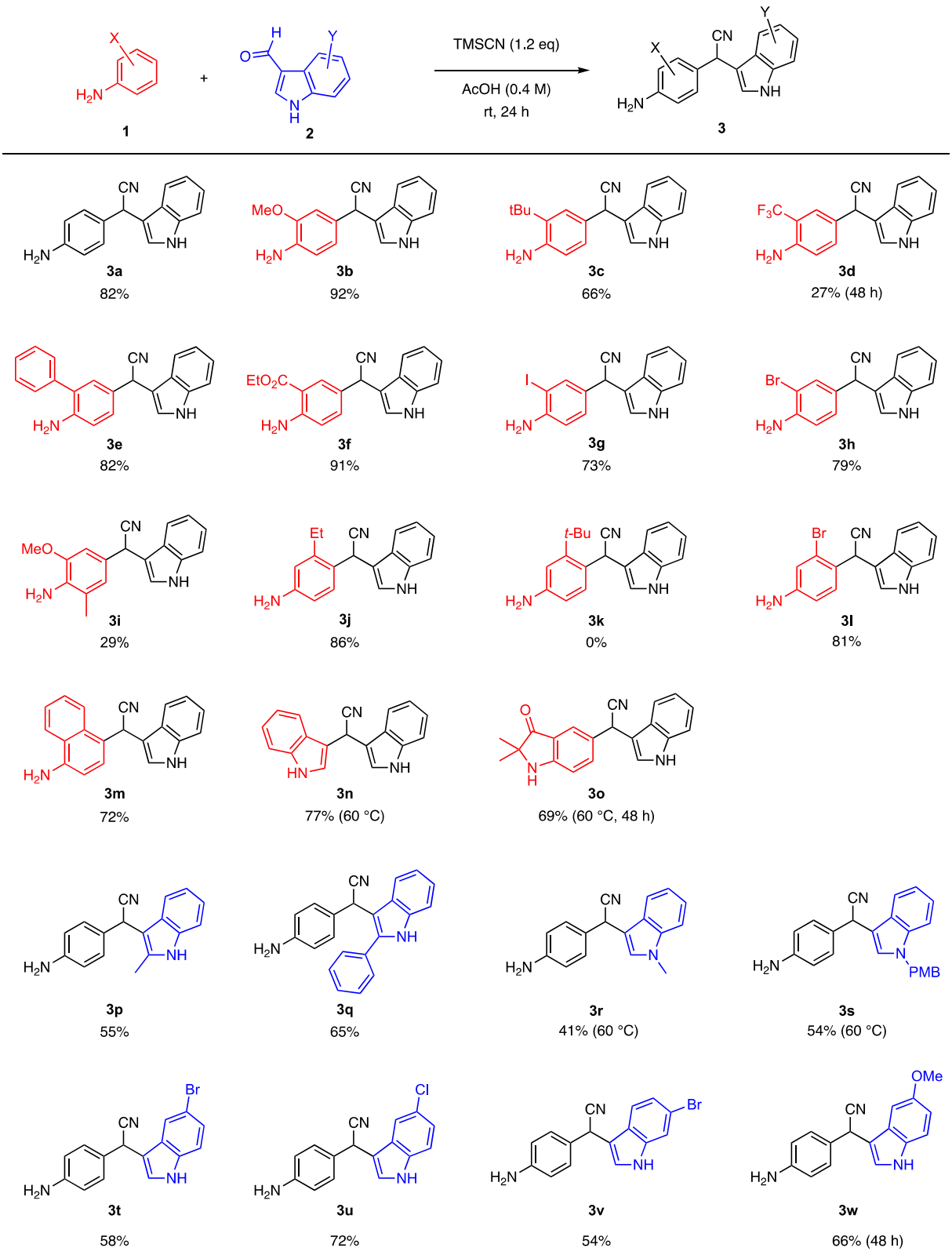


Figure 2. Substrate scope for abnormal Strecker reaction

Finally, mechanistic analysis of this reaction was carried out by DFT calculations using Gaussian16 (Figure 3). All calculations were performed at the ωB97X-D/6-31G(d,p) in AcOH (PCM) level.[5] We considered that the final step of the reaction was the Friedel-Crafts reaction, meaning that its precursor should be 3-CN-indolenium (**INT5**). Thus, we first investigated the mechanism underlying the formation of **INT5**. As a result, we found two pathways: formation of cyanohydrin followed by dehydration (Path A: **INT1** -> **INT5**) and Strecker reaction followed by the release of aniline (Path B: **INT2** -> **INT3** -> **INT4** -> **INT5**). Since **INT2** is thermodynamically unstable, the generation of **INT3** in path B is considered to be unfavorable. Therefore, the initial step of this reaction is considered to be the formation of cyanohydrin (**INT1**) in path A. The Friedel-Crafts reaction can proceed from **INT5** with small activation energy (**TS3**: ΔΔG‡ = 12.9 kcal/mol) to afford **PD** via **INT6**, indicating that the most thermodynamically stable product (**PD**: ΔG = –10.0 kcal/mol) was generated rather than the usual Strecker product (**INT3**: ΔG = –0.3 kcal/mol) or cyanohydrin (**INT1**: ΔG = 1.7 kcal/mol).

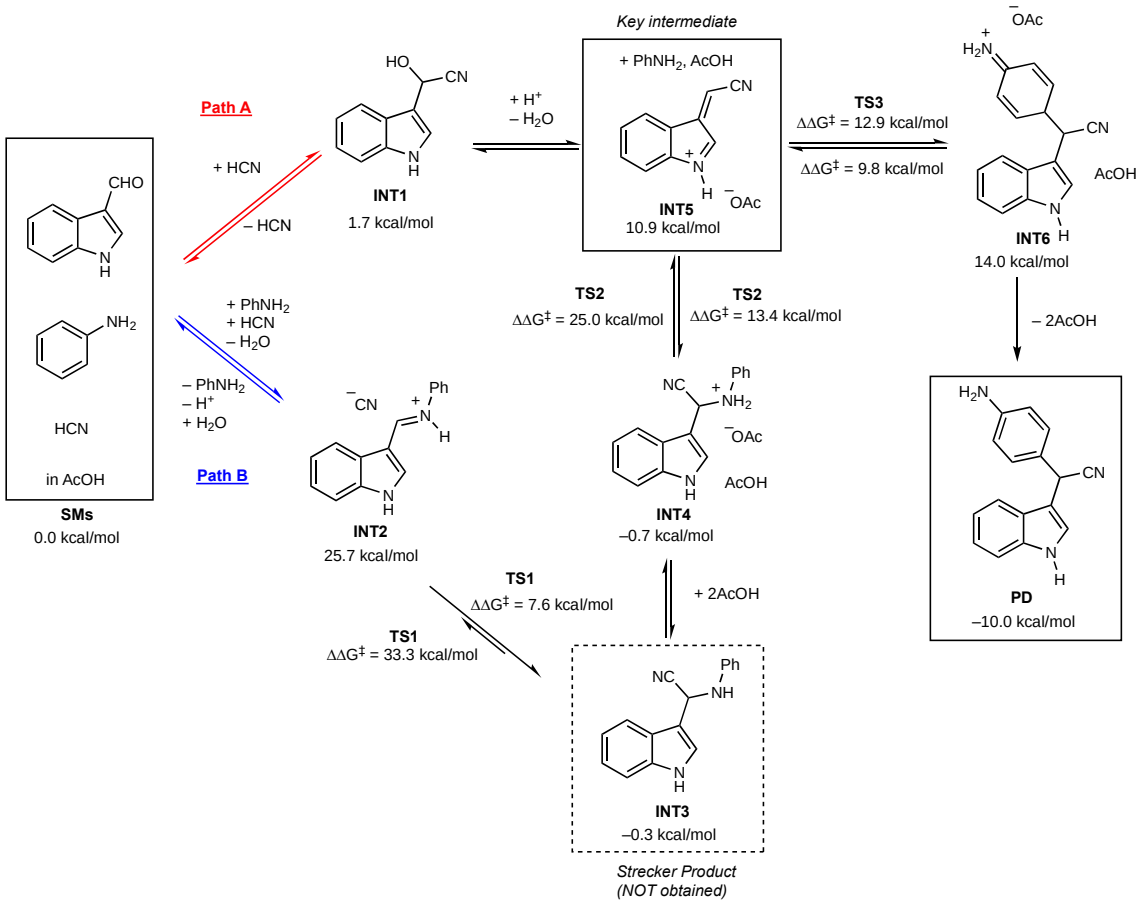


Figure 3. Reaction mechanism by DFT calculations

In summary, we found that a Strecker reaction of 3-formylindole derivatives with aniline derivatives does not give the usual amino nitriles, and an abnormal Friedel-Crafts type Strecker reaction proceeds instead. We expect that this product can be used in chemical biology research.

EXPERIMENTAL

NMR spectra were recorded on a JEOL eca 400, ecz 400, ecz 600, eca 600 spectrometer. Chemical shifts in $CDCl_3$, acetone-d_6 or DMSO-d_6 were reported downfield from TMS (= 0 ppm) or solvent signal [$CDCl_3$ (= 7.26 ppm), acetone-d_6 (= 2.04 ppm) or DMSO-d_6 (= 2.49 ppm)] for ^{1}H NMR. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, and br = broad), integration and coupling constants in Hz. For ^{13}C NMR, chemical shifts were reported in the scale relative to the solvent signal [$CHCl_3$ (77.0 ppm), acetone-d_6 (29.8 ppm) or DMSO-d_6 (39.5 ppm)] as an internal reference. ^{19}F NMR was referenced to internal hexafluorobenzene (–162.9 ppm). Data are reported as chemical shifts. ESI mass spectra were measured on JEOL AccuTOF LC-plus JMS-T100LP. Melting points were measured with a SIBATA NEL-270 melting point apparatus. Analytical thin layer chromatography was performed on Kieselgel 60F254, 0.25 mm thickness plates. Column chromatography was performed with amino-functionalized silica gel (NH-DM1020, FUJI SILYSIA). Reactions were conducted in dry solvent. Other reagents were purified by the usual methods.

All calculations were performed with Gaussian 16 program. Structure optimizations were carried out at 298.15 K, using the ωB97X-D functional with an ultrafine grid and 6-31G(d,p) basis sets. All the calculations were performed in acetic acid solvent (PCM). Harmonic vibrational frequencies were computed at the same level of theory to confirm no imaginary vibration was observed for the optimized structure, and only one imaginary vibration was observed for the transition state. The intrinsic reaction coordinate (IRC) method was used to track minimum energy paths from transition structures to the corresponding local minima.

The Crystallographic data generated in this study have been deposited in the Cambridge Crystallographic Data Centre under accession code CCDC 2120654 (compound **3b**).

General procedure for abnormal Strecker reaction.

TMSCN (0.24 mmol) was added to the solution of 3-formylindole (0.2 mmol) and aniline (0.2 mmol) in AcOH (0.5 mL) and stirred for 24 h at room temperature. The reaction was diluted with EtOAc, quenched by the addition of saturated aqueous $NaHCO_3$, and the aqueous layer was extracted with EtOAc (3 mL x 3). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated in *vacuo*. The crude residue was purified by flash column chromatography.

2-(4-Aminophenyl)-2-(1*H*-indol-3-yl)acetonitrile (3a)

EtOAc/*n*-hexane = 1/1 (eluent); off-white amorphous;

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.18 (brs, 1H), 7.45 (d, *J* = 7.4 Hz, 1H), 7.37 (d, *J* = 8.2 Hz, 1H), 7.23-7.15 (m, 4H), 7.09 (ddd, *J* = 8.2, 7.4, 1.2 Hz, 1H), 6.65 (d, *J* = 8.8 Hz, 2H), 5.28 (s, 1H), 3.69 (brs, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 146.2, 136.5, 128.5 (2C), 125.1, 124.9, 123.2, 122.5, 120.4, 120.0, 118.7, 115.3 (2C), 111.5, 111.0, 33.6.

IR (ATR) ν: 3404, 3057, 2922, 2241, 1704, 1622, 1548, 1514 cm^{-1}.

HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{16}H_{13}N_3Na$, 270.1007; found, 270.1001.

2-(4-Amino-3-methoxyphenyl)-2-(1*H*-indol-3-yl)acetonitrile (3b)

EtOAc/*n*-hexane = 1/5-1/1 (eluent); Isolated yield: 92% (51 mg); yellow amorphous;

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.21 (brs, 1H), 7.47 (d, *J* = 7.8 Hz, 1H), 7.36 (dd, *J* = 8.2, 0.9 Hz, 1H), 7.21 (ddd, *J* = 7.8, 7.6, 0.9 Hz, 1H), 7.13-7.07 (m, 2H), 6.84-6.82 (m, 2H), 6.66 (d, *J* = 8.2 Hz, 1H), 5.29 (s, 1H), 3.83-3.79 (m, 5H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 147.5, 136.6, 136.0, 125.3, 125.1, 123.1, 122.8, 120.4, 120.3, 120.2, 118.9, 114.7, 111.6, 111.4, 109.8, 55.5, 34.1.

IR (ATR) ν: 3407, 3060, 2935, 2242, 1620, 1590, 1519 cm^{-1}.

HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{16}N_3O$, 278.1293; found, 278.1285.

2-(4-Amino-3-(*tert*-butyl)phenyl)-2-(1*H*-indol-3-yl)acetonitrile (3c)

EtOAc/*n*-hexane = 1/3 (eluent); Isolated yield: 66% (40 mg); off-white amorphous;

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.15 (brs, 1H), 7.50 (d, *J* = 8.2 Hz, 1H), 7.37 (d, *J* = 8.2 Hz, 1H), 7.31 (d, *J* = 2.3 Hz, 1H), 7.21 (ddd, *J* = 8.2, 6.9, 0.9 Hz, 1H), 7.31-7.08 (m, 2H), 7.04 (dd, *J* = 8.2, 2.3 Hz, 1H), 6.60 (d, *J* = 8.2 Hz, 1H), 5.82 (s, 1H), 3.87 (brs, 2H), 1.39 (s, 9H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 144.5, 136.6, 134.1, 126.3, 126.2, 125.4, 124.9, 123.0, 122.7, 120.4, 120.1, 119.0, 118.0, 111.8, 111.4, 34.3, 34.0, 29.5 (3C).

IR (ATR) ν: 3399, 2964, 2872, 2242, 1622, 1549, 1501 cm^{-1}.

HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{22}N_3$, 304.1814; found, 304.1804.

2-(4-Amino-3-(trifluoromethyl)phenyl)-2-(1*H*-indol-3-yl)acetonitrile (3d)

The reaction was performed for 48 h.

EtOAc/*n*-hexane = 1/3 (eluent); Isolated yield: 27% (17 mg); yellow amorphous;

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.22 (brs, 1H), 7.48 (d, *J* = 1.8 Hz, 1H), 7.43-7.38 (m, 2H), 7.32 (dd, *J* = 8.2, 2.3 Hz, 1H), 7.23 (ddd, *J* = 7.3, 6.9, 0.9 Hz 1H), 7.18 (dd, *J* = 2.3, 0.9 Hz, 1H), 7.11 (ddd, *J* = 8.2, 6.9, 0.9 Hz, 1H), 6.71 (d, *J* = 8.7 Hz, 1H), 5.30 (s, 1H), 4.23 (brs, 2H).

^{13}C NMR ($CDCl_3$, 150 MHz) δ: 144.4, 136.6, 132.1, 125.9 (q, *J* = 5.8 Hz), 125.1, 124.5 (q, *J* = 273.1 Hz), 124.5, 123.2, 123.0, 120.4, 119.6, 118.7, 117.7, 113.9 (q, *J* = 30.3 Hz), 111.6, 110.8, 33.6.

^{19}F NMR ($CDCl_3$, 376 MHz) δ: –64.09.

IR (ATR) ν: 3396, 2925, 2245, 1705, 1633, 1581, 1508 cm^{-1}.

HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{17}H_{12}F_3N_3Na$, 338.0881; found, 338.0873.

2-(6-Amino-[1,1'-biphenyl]-3-yl)-2-(1*H*-indol-3-yl)acetonitrile (3e)

EtOAc/*n*-hexane = 1/5-1/1 (eluent); Isolated yield: 82% (53 mg); off-white amorphous;

^1H NMR ($CDCl_3$, 400 MHz) δ: 8.20 (brs, 1H), 7.49 (d, *J* = 7.8 Hz, 1H), 7.44-7.31 (m, 6H), 7.22-7.14 (m, 4H), 7.09 (ddd, *J* = 7.8, 7.3, 0.9 Hz, 1H), 6.70 (d, *J* = 7.8 Hz, 1H), 5.29 (s, 1H), 3.80 (brs, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 143.4, 138.7, 136.6, 129.7, 129.0 (2C), 128.9 (2C), 127.8, 127.7, 127.4, 125.3, 125.2, 123.1, 122.7, 120.3, 120.1, 118.9, 115.9, 111.5, 111.4, 33.7.

IR (ATR) ν: 3385, 3055, 2243, 1620, 1549, 1505 cm^{-1}.

HRMS (ESI) *m/z:* $[M + H]^+$ Calcd for $C_{22}H_{18}N_3$, 324.1501; found, 324.1498.

Ethyl 2-amino-5-(cyano(1*H*-indol-3-yl)methyl)benzoate (3f)

EtOAc/*n*-hexane = 1/5-1/1 (eluent); Isolated yield: 91% (58 mg); white amorphous;

^1H NMR ($CDCl_3$, 400 MHz) δ: 8.33 (brs, 1H), 7.98 (d, *J* = 2.3 Hz, 1H), 7.45 (d, *J* = 8.2 Hz, 1H), 7.34 (d, *J* = 8.2 Hz, 1H), 7.22-7.17 (m, 2H), 7.10-7.06 (m, 2H), 6.57 (d, *J* = 8.7 Hz, 1H), 5.78 (brs, 2H), 5.25 (s, 1H), 4.31 (q, *J* = 7.3 Hz, 2H), 1.34 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 167.7, 150.1, 136.6, 133.0, 130.3, 125.1, 123.2, 122.7, 122.7, 120.1, 120.0, 118.7, 117.5, 111.5, 111.0, 110.8, 60.6, 33.6, 14.2.

IR (ATR) ν: 3471, 3369, 2981, 2247, 1682, 1624, 1587, 1564 cm^{-1}.

HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{19}H_{17}N_3NaO_2$, 342.1219; found, 342.1224.

2-(4-Amino-3-iodophenyl)-2-(1*H*-indol-3-yl)acetonitrile (3g)

EtOAc/*n*-hexane = 1/3 (eluent); Isolated yield: 73% (54 mg); off-white amorphous;

^1H NMR ($CDCl_3$, 400 MHz) δ: 8.23 (brs, 1H), 7.66 (d, *J* = 2.3 Hz, 1H), 7.43 (d, *J* = 8.3 Hz, 1H), 7.35 (d, *J* = 8.3 Hz, 1H), 7.20 (ddd, *J* = 8.2, 7.8, 0.9 Hz, 1H), 7.15-7.07 (m, 3H), 6.64 (d, *J* = 8.7 Hz, 1H), 5.20 (s, 1H), 4.12 (brs, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 146.6, 137.7, 136.5, 128.6, 126.4, 125.0, 123.2, 122.8, 120.2, 119.9, 118.6, 114.7, 111.6, 110.6, 83.9, 33.0.

IR (ATR) ν: 3370, 2982, 2247, 1683, 1625, 1587, 1563 cm^{-1}.

HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{16}H_{12}IN_3Na$, 395.9974; found, 395.9973.

2-(4-Amino-3-bromophenyl)-2-(1*H*-indol-3-yl)acetonitrile (3h)

EtOAc/*n*-hexane = 1/1 (eluent); Isolated yield: 79% (52 mg); off-white amorphous;

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.23 (brs, 1H), 7.45-7.41 (m, 2H), 7.36 (d, *J* = 8.2 Hz, 1H), 7.21 (ddd, *J* = 8.2, 7.1, 1.4 Hz, 1H), 7.13-7.07 (m, 3H), 6.68 (d, *J* = 8.2 Hz, 1H), 5.23 (s, 1H), 4.12 (brs, 2H).
^{13}C NMR ($CDCl_3$, 100 MHz) δ: 144.0, 136.5, 131.6, 127.7, 126.0, 125.1, 123.2, 122.9, 120.2, 119.8, 118.7, 115.8, 111.6, 110.7, 109.2, 33.3.
IR (ATR) ν: 3376, 3055, 2925, 2244, 1619, 1549, 1500 cm^{-1}.
HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{13}BrN_3$, 326.0293; found, 326.0286.

2-(4-Amino-3-methoxy-5-methylphenyl)-2-(1*H*-indol-3-yl)acetonitrile (3i)

EtOAc/*n*-hexane = 1/3 (eluent); Isolated yield: 29% (17 mg); yellow amorphous;
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.21 (brs, 1H), 7.49 (d, *J* = 8.2 Hz, 1H), 7.36 (d, *J* = 8.2 Hz, 1H), 7.21 (ddd, *J* = 8.2, 7.3, 0.9 Hz, 1H), 7.13-7.08 (m, 2H), 6.77 (s, 1H), 6.73 (s, 1H), 5.27 (s, 1H), 3.78 (s, 5H), 2.14 (s, 3H).
^{13}C NMR ($CDCl_3$, 100 MHz) δ: 147.1, 136.6, 134.0, 125.4, 124.2, 123.1, 122.7, 122.6, 122.0, 120.4, 120.1, 118.9, 111.7, 111.4, 107.6, 55.7, 34.2, 17.2.
IR (ATR) ν: 3390, 2935, 2241, 1620, 1587, 1500 cm^{-1}.
HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{18}H_{17}N_3NaO$, 314.1269; found, 314.1259.

2-(4-Amino-2-ethylphenyl)-2-(1*H*-indol-3-yl)acetonitrile (3j)

EtOAc/*n*-hexane = 1/1 (eluent); Isolated yield: 86% (47 mg); off-white amorphous;
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.20 (brs, 1H), 7.44 (d, *J* = 7.8 Hz, 1H), 7.35 (d, *J* = 8.2 Hz, 1H), 7.23-7.16 (m, 2H), 7.09 (ddd, *J* = 8.2, 6.9, 0.9 Hz, 1H), 6.98 (s, 1H), 6.58 (d, *J* = 2.3 Hz, 1H), 6.49 (dd, *J* = 8.2, 2.3 Hz, 1H), 5.43 (s, 1H), 3.68 (brs, 2H), 2.63 (m, 2H), 1.19 (t, *J* = 7.3 Hz, 3H).
^{13}C NMR ($CDCl_3$, 100 MHz) δ: 146.4, 142.6, 136.6, 129.6, 125.3, 123.5, 122.6, 122.4, 120.5, 120.0, 118.7, 115.4, 113.2, 111.5, 111.2, 30.4, 25.4, 14.8.
IR (ATR) ν: 3377, 2240, 2965, 1705, 1621, 1501, 1457 cm^{-1}.
HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{18}H_{17}N_3Na$, 298.1320; found, 298.1314.

2-(4-Amino-2-bromophenyl)-2-(1*H*-indol-3-yl)acetonitrile (3l)

EtOAc/*n*-hexane = 1/3 (eluent); Isolated yield: 81% (53 mg); off-white amorphous;
^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.24 (brs, 1H), 7.45 (d, *J* = 7.8 Hz, 1H), 7.34 (d, *J* = 8.2 Hz, 1H), 7.20 (dd, *J* = 8.2, 6.9 Hz, 1H), 7.14-7.07 (m, 3H), 6.89 (d, *J* = 2.5 Hz, 1H), 6.49 (dd, *J* = 8.2, 2.5 Hz, 1H), 5.70 (s, 1H), 3.74 (brs, 2H).
^{13}C NMR ($CDCl_3$, 100 MHz) δ: 147.6, 136.5, 130.3, 125.1, 124.0, 123.7, 123.5, 122.8, 120.2, 119.7, 118.8, 118.7, 114.7, 111.5, 110.3, 33.6.

IR (ATR) ν: 3380, 3057, 2956, 2921, 2244, 1620, 1604, 1575, 1550 cm^{-1}.

HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{16}H_{12}BrN_3Na$, 348.0112; found, 348.0108.

2-(4-Aminonaphthalen-1-yl)-2-(1*H*-indol-3-yl)acetonitrile (3m)

EtOAc/*n*-hexane = 1/1-3/1 (eluent); Isolated yield: 72% (43 mg); white amorphous;

^1H NMR ($CDCl_3$, 600 MHz) δ: 8.12 (brs, 1H), 7.97-7.96 (m, 1H), 7.89-7.87 (m, 1H), 7.54 (d, *J* = 7.6 Hz, 1H), 7.49-7.47 (m, 2H), 7.45 (d, *J* = 7.6 Hz, 1H), 7.38 (d, *J* = 8.3 Hz, 1H), 7.23 (dd, *J* = 8.3, 6.9 Hz, 1H), 7.11 (dd, *J* = 8.3, 6.9 Hz, 1H), 6.97 (s, 1H), 6.74 (d, *J* = 7.6 Hz, 1H), 5.94 (s, 1H), 4.24 (brs, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 143.0, 136.5, 131.3, 127.3, 126.8, 125.5, 125.0, 124.1, 123.9, 123.7, 122.8, 121.7, 120.5, 120.2, 120.1, 118.9, 111.5, 111.0, 108.9, 31.4.

IR (ATR) ν: 3398, 3054, 2241, 1624, 1584, 1519 cm^{-1}.

HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{20}H_{15}N_3Na$, 320.1164; found, 320.1154.

2,2-Di(1*H*-indol-3-yl)acetonitrile (3n)

The reaction was performed at 60 °C.

EtOAc/*n*-hexane = 1/5-1/1 (eluent); Isolated yield: 77% (42 mg);

^1H NMR (DMSO-d_6, 400 MHz) δ: 11.15 (s, 2H), 7.56 (d, *J* = 8.2 Hz, 2H), 7.41-7.39 (m, 4H), 7.10 (td, *J* = 6.9, 0.9 Hz, 2H), 6.98 (ddd, *J* = 7.3, 6.9, 0.9 Hz, 2H), 6.06 (s, 1H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 136.6 (2C), 125.2 (2C), 123.7 (2C), 121.6 (2C), 120.8, 118.9 (2C), 118.6 (2C), 111.9 (2C), 109.4 (2C), 25.3.

The spectral data was identical to that reported in the literature[(4)].

2-(2,2-Dimethyl-3-oxoindolin-5-yl)-2-(1*H*-indol-3-yl)acetonitrile (3o)

The reaction was performed at 60 °C for 48 h.

EtOAc/*n*-hexane = 1/1-2/1 (eluent); Isolated yield: 69% (44 mg); orange amorphous;

^1H NMR ($CDCl_3$, 400 MHz) δ: 8.22 (brs, 1H), 7.64 (d, *J* = 1.9 Hz, 1H), 7.54 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.44-7.39 (m, 2H), 7.28 (d, *J* = 1.9 Hz, 1H), 7.23 (ddd, *J* = 8.2, 6.9, 0.9 Hz, 1H), 7.10 (ddd, *J* = 8.2, 6.9, 0.9 Hz, 1H), 6.82 (d, *J* = 8.5 Hz, 1H), 5.33 (s, 1H), 4.62 (brs, 1H), 1.33 (s, 6H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 204.7, 159.2, 136.6, 126.0, 125.0, 124.1, 123.2, 122.8, 120.2, 119.8, 119.6, 118.6, 113.1, 111.7, 110.5, 110.5, 64.6, 33.8, 24.3 (2C).

IR (ATR) ν: 3393, 2973, 2926, 2243, 1683, 1627, 1581 cm^{-1}.

HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{20}H_{17}N_3NaO$, 338.1269; found, 338.1260.

2-(4-Aminophenyl)-2-(2-methyl-1*H*-indol-3-yl)acetonitrile (3p)

EtOAc/*n*-hexane = 1/2 (eluent); Isolated yield: 55% (29 mg); off-white amorphous;

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.97 (brs, 1H), 7.45 (d, *J* = 7.8 Hz, 1H), 7.29 (d, *J* = 8.2 Hz, 1H), 7.18-7.12 (m, 3H), 7.07 (dd, *J* = 7.8, 7.3 Hz, 1H), 6.62 (d, *J* = 8.7 Hz, 2H), 5.36 (s, 1H), 3.67 (brs, 2H), 2.41 (s, 3H).

^{13}C NMR (DMSO-d_6, 100 MHz) δ: 148.0, 135.1, 133.2, 127.4 (2C), 126.3, 123.3, 120.9, 120.6, 118.8, 117.7, 113.9 (2C), 110.8, 105.4, 31.2, 11.4.

IR (ATR) ν: 3386, 2924, 2239, 1622, 1514, 1460 cm^{-1}.

HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{17}H_{15}N_3Na$, 284.1164; found, 284.1156.

2-(4-Aminophenyl)-2-(2-phenyl-1*H*-indol-3-yl)acetonitrile (3q)

EtOAc/*n*-hexane = 1/2 (eluent); Isolated yield: 65% (42 mg); yellow amorphous;

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.29 (brs, 1H), 7.52-7.39 (m, 7H), 7.22 (ddd, *J* = 8.2, 7.8, 0.9 Hz, 1H), 7.17 (d, *J* = 8.3 Hz, 2H), 7.09 (ddd, *J* = 7.8, 7.3, 0.9 Hz, 1H), 6.61 (d, *J* = 8.3 Hz, 2H), 5.49 (s, 1H), 3.67 (brs, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 145.9, 136.6, 135.9, 131.5, 129.2 (2C), 128.8, 128.3 (2C), 128.1 (2C), 126.7, 125.0, 122.9, 121.6, 120.5, 120.0, 115.3 (2C), 111.1, 106.3, 32.5.

IR (ATR) ν: 3381, 3055, 2241, 1622, 1512, 1489 cm^{-1}.

HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{22}H_{17}N_3Na$, 346.1320; found, 346.1316.

2-(4-Aminophenyl)-2-(1-methyl-1*H*-indol-3-yl)acetonitrile (3r)

The reaction was performed at 60 °C.

EtOAc/*n*-hexane = 1/3 (eluent); Isolated yield: 41% (21 mg); yellow amorphous;

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.44 (dd, *J* = 7.8, 0.9 Hz, 1H), 7.30 (d, *J* = 8.2 Hz, 1H), 7.23 (dd, *J* = 8.2, 7.3 Hz, 1H), 7.18 (d, *J* = 8.2 Hz, 2H), 7.08 (ddd, *J* = 7.8, 7.3, 0.9 Hz, 1H), 6.98 (s, 1H), 6.63 (d, *J* = 8.2 Hz, 2H), 5.25 (s, 1H), 3.73-3.69 (m, 5H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 146.2, 137.3, 128.6 (2C), 127.6, 125.7, 125.2, 122.2, 120.3, 119.6, 118.9, 115.3 (2C), 109.9, 109.6, 33.6, 32.8.

IR (ATR) ν: 3460, 3369, 3053, 2929, 2241, 1622, 1547, 1514 cm^{-1}.

HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{17}H_{15}N_3Na$, 284.1164; found, 284.1159.

2-(4-Aminophenyl)-2-(1-(4-methoxybenzyl)-1*H*-indol-3-yl)acetonitrile (3s)

The reaction was performed at 60 °C.

EtOAc/*n*-hexane = 1/3 (eluent); Isolated yield: 49% (36 mg); white amorphous;

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.43 (dd, *J* = 7.8, 0.9 Hz, 1H), 7.26 (dd, *J* = 9.2, 8.2 Hz, 1H), 7.19-7.15 (m,

3H), 7.08-7.04 (m, 4H), 6.83 (d, *J* = 8.7 Hz, 2H), 6.63 (d, *J* = 8.2 Hz, 2H), 5.26 (s, 1H), 5.19 (s, 2H), 3.76-3.69 (m, 5H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 159.1, 146.2, 137.0, 128.9, 128.7 (2C), 128.2 (2C), 126.9, 126.0, 125.1, 122.4, 120.3, 119.8, 119.1, 115.3 (2C), 114.2 (2C), 110.3, 110.1, 55.2, 49.7, 33.7.

IR (ATR) ν: 3465, 3373, 3005, 2931, 2241, 1614, 1549, 1512 cm^{-1}.

HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{24}H_{21}N_3NaO$, 390.1582; found, 390.1578.

2-(4-Aminophenyl)-2-(5-bromo-1*H*-indol-3-yl)acetonitrile (3t)

EtOAc/*n*-hexane = 1/1 (eluent); Isolated yield: 58% (39 mg); white amorphous;

^{1}H NMR (acetone-d_6, 400 MHz) δ: 10.56 (brs, 1H), 7.64 (s, 1H), 7.42-7.39 (m, 2H), 7.24 (dd, *J* = 8.7, 1.4 Hz, 1H), 7.17 (d, *J* = 8.4 Hz, 2H), 6.67 (d, *J* = 8.4 Hz, 2H), 5.55 (s, 1H), 4.75 (brs, 2H).

^{13}C NMR (acetone-d_6, 100 MHz) δ: 149.2, 136.7, 129.1 (2C), 128.1, 126.0, 125.5, 124.6, 122.0, 121.2, 115.3 (2C), 114.5, 113.0, 112.1, 33.7.

IR (ATR) ν: 3367, 2924, 2241, 1693, 1622, 1568, 1514 cm^{-1}.

HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{13}BrN_3$, 326.0293; found, 326.0293.

2-(4-Aminophenyl)-2-(5-chloro-1*H*-indol-3-yl)acetonitrile (3u)

EtOAc/*n*-hexane = 1/3-1/1 (eluent); Isolated yield: 72% (41 mg); off-white amorphous;

^{1}H NMR (acetone-d_6, 400 MHz) δ: 10.53 (brs, 1H), 7.48-7.40 (m, 3H), 7.17 (d, *J* = 8.5 Hz, 2H), 7.12 (dd, *J* = 8.7, 2.3 Hz, 1H), 6.68 (d, *J* = 8.5 Hz, 2H), 5.54 (s, 1H), 4.74 (brs, 2H).

^{13}C NMR (acetone-d_6, 100 MHz) δ: 149.2, 136.4, 129.1 (2C), 127.4, 126.2, 125.4, 124.6, 122.9, 121.2, 118.9, 115.3 (2C), 114.1, 112.2, 33.7.

IR (ATR) ν: 3363, 2924, 2241, 1693, 1622, 1572, 1514 cm^{-1}.

HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{13}ClN_3$, 282.0798; found, 282.0787.

2-(4-Aminophenyl)-2-(6-bromo-1*H*-indol-3-yl)acetonitrile (3v)

EtOAc/*n*-hexane = 1/1 (eluent); Isolated yield: 54% (35 mg); yellow solid;

^{1}H NMR (acetone-d_6, 400 MHz) δ: 10.48 (brs, 1H), 7.64 (d, *J* = 1.8 Hz, 1H), 7.41 (d, *J* = 8.7 Hz, 1H), 7.36 (dd, *J* = 2.7, 0.9 Hz, 1H), 7.18-7.14 (m, 3H), 6.67 (d, *J* = 8.7 Hz, 2H), 5.53 (s, 1H), 4.73 (brs, 2H).

^{13}C NMR (acetone-d_6, 100 MHz) δ: 149.1, 138.8, 129.1 (2C), 125.4, 125.4, 124.6, 123.2, 121.2, 121.2, 115.9, 115.4, 115.3 (2C), 112.7, 33.7.

IR (ATR) ν: 3361, 2241, 1693, 1616, 1512, 1452 cm^{-1}.

HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{13}BrN_3$, 326.0293; found, 326.0293.

Mp: 171-172 °C.

2-(4-Aminophenyl)-2-(5-methoxy-1*H*-indol-3-yl)acetonitrile (3w)

The reaction was performed for 48 h.

EtOAc/*n*-hexane = 1/1 (eluent); Isolated yield: 66% (36 mg); off-white amorphous;

^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.17 (brs, 1H), 7.22 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.17 (d, *J* = 8.7 Hz, 2H), 7.04 (d, *J* = 1.8 Hz, 1H), 6.86-6-84 (m, 2H), 6.63 (d, *J* = 8.7 Hz, 2H), 5.22 (s, 1H), 3.76-3.72 (m, 5H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ: 154.2, 146.2, 131.6, 128.7 (2C), 125.7, 124.9, 123.8, 120.3, 115.3 (2C), 112.9, 112.2, 111.0, 100.6, 55.8, 33.7.

IR (ATR) ν: 3373, 2929, 2241, 1624, 1583, 1514cm^{-1}.

HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{17}H_{15}N_3NaO$, 300.1113; found, 300.1102.

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