Microwave-Assisted Synthesis of N-*sec*- and N-*tert*-Alkylated Indoles

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Dedicated to Professor Lutz F. Tietze

Abstract: A synthesis of N-substituted indoles by means of an epoxide-opening, nucleophilic aromatic substitution, and dehydration sequence is reported, which is capable of generating even N-*tert* alkyl substituted derivatives.

Key words: indoles, cyclizations, microwave heating

Indoles are presumably the most abundant heterocycles in nature, and the synthesis of the indole framework has been a major area of focus for more than a century.[1] Despite the outstandingly long tradition of research in this field, only a single recently reported method has been shown to provide more general access to N-*tert*-alkyl-substituted indoles.[2] Herein the results of our own investigations on an indole synthesis capable to fill this gap are presented.

Apart from the well-known tritylation of indole[3] and intramolecular reactions leading to tricyclic skeletons,[4] very few reports exist on N-*tert*-alkylated indoles. The reaction of a 9*H*-carbazole with *tert*-butyl alcohol and cyanomethylenetrimethylphosphorane (CMMP) as Mitsunobu reagent belongs to these rare examples,[5] as well as the nucleophilic ring opening of 2,2-dimethylaziridines[6] and the (reversible) Michael addition of 6-methoxyindole to *tert*-butyl 3-methylcrotonate.[7] 1-Adamantyl-substituted indole has been obtained in low yield in the reaction of 1-bromoadamantane with 3-indolylmagnesium bromide.[8]

N-1,1-Dimethylprop-2-enyl ('reverse prenyl') indoles have attracted considerable interest due to their provenance in some uncommon natural products with biological activity.[9] The direct alkylation of 3-bromoindole with dimethylpropargyl chloride has been reported in the context of the synthesis of demethylasterriquinone A1.[10] The N-propargylation of *N*-methoxycarbonyltryptamine was achieved with the dicobalt hexacarbonyl complex of dimethyl propargylalcohol.[11] The more reliable pathway of access to N-reverse prenylated indoles comprises the reaction of the more nucleophilic indolines with the necessity of subsequent aromatization.[12] The reaction of indole with methyl 2-bromopropionate followed by C-alkylation is another work-around to install a tertiary carbon center adjacent to the nitrogen.[13]

During the preparation of the current publication, the palladium-catalyzed N-annulation with sterically demanding amines leading to N-functionalized indoles was disclosed by Willis.[2] N-*tert*-butylated indoles are furthermore the outcome of a few indole syntheses of limited synthetic value, for example, the boron trifluoride mediated reaction of aromatic ketones with *tert*-butyl isonitrile,[14] the [4+2] cycloaddition of *N*-*tert*-butyl vinylpyrroles with dienophiles,[15] and the addition of *tert*-butyllithium to quinone imine ketals.[16] The copper-mediated cyclization of N-*tert*-alkyl-substituted 2-alkynylanilines[17] and Doye's related indole synthesis via the titanium-catalyzed hydroamination of 2-chloro-substituted phenylacetylenes[18] yield 2-substituted indoles. Complementary to the latter, the synthesis of 3-substituted compounds is disclosed here.

Recently, a new synthesis of 7-azaindoles was reported by us.[19] By treatment of 3-epoxy substituted 2-chloro- or 2-fluoropyridines with primary amines, the bicyclic heterocycles was isolated by means of an epoxide-opening, nucleophilic aromatic substitution and dehydration sequence. The benefit of microwave-assisted heating and the broad functional group tolerance of the reaction was demonstrated.[20] Further, it was observed that the velocity of the reaction largely depends on the steric demands of the amino component, with α-trisubstituted amines reacting slowest. However, the 1-N-*tert*-substituted 7-azaindoles were prepared in up to 85% yield.

In an extension of this work, it was questioned if this method could give general access to N-*sec*- and N-*tert*-alkyl-substituted indoles. Referring back to the original indole syntheses starting from bromo- and chloroarenes and simple α-linear amines by Tambute[21] and later by Fleming,[22] it was reasoned that the fluoroarenes **2** (Scheme 1) would be best-suited to allow the pivotal ring-forming intramolecular nucleophilic aromatic substitution towards **4**. The requisite oxiranes **2** could be prepared easily in a Corey–Chaykovsky epoxide formation[23] from aryl ketones **1**.

The epoxides **2a**–**g** were obtained in 70 to 90% yield from commercially available ketones (Scheme 1). Compounds **2a** and **2b** were heated with cyclohexylamine in ethanol to 140 °C in sealed vessels to afford the amino alcohols **3a** and **3b** in 91% and 84% yield, respectively (Scheme 2).[24] The ring formation and the dehydration step were next investigated. The intramolecular reaction was performed in *n*-butanol, dimethyl sulfoxide or dimethylformamide as solvent, and microwave heating was used to reach high reaction temperatures. At 200 °C, only trace amounts of the desired indoles **5** were detected after 10 minutes reaction

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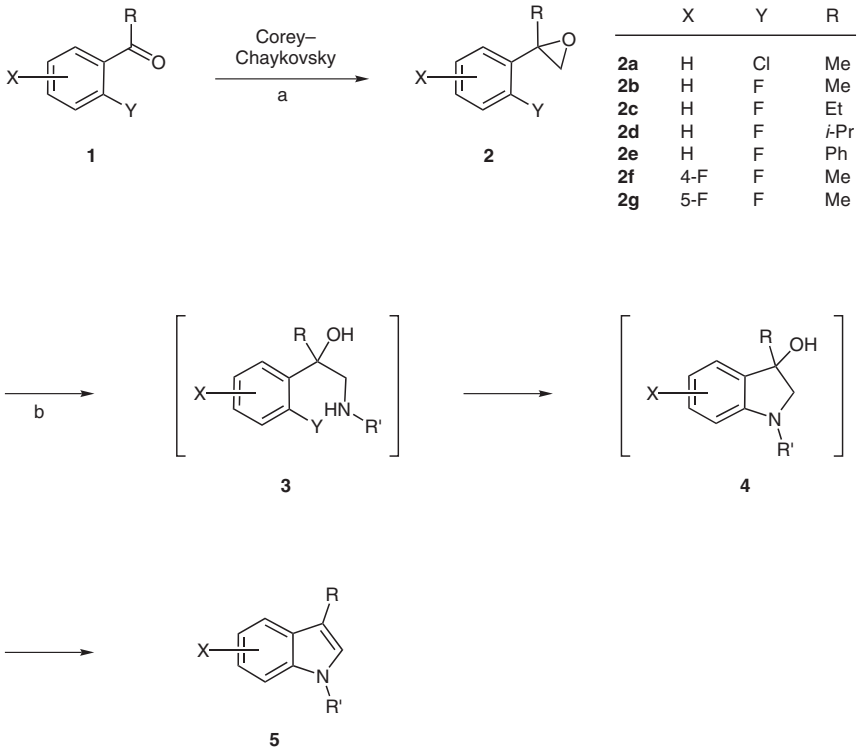


	X	Y	R
2a	H	Cl	Me
2b	H	F	Me
2c	H	F	Et
2d	H	F	*i*-Pr
2e	H	F	Ph
2f	4-F	F	Me
2g	5-F	F	Me

Scheme 1 Synthesis of indoles. Reaction mechanism. *Reagents and conditions:* (a) $Me_3S^+I^-$, *t*-BuOK, THF, r.t.; (b) R′NH_2, DMF, μW 240 °C.

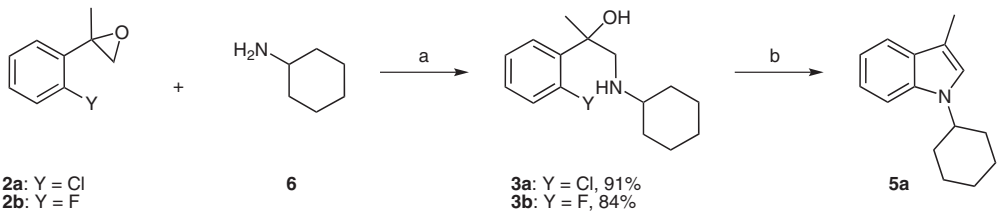
time (Table 1). Since spontaneous dehydration and aromatization occurs at this temperature as observed in the azaindole series,[20] the nucleophilic aromatic substitution must be the rate limiting step. At 240 °C, about 20% indole was formed within 10 minutes, as detected by HPLC analysis.[25] The progress of the reaction was almost independent from the nature of the solvent. However, in DMSO the isolation of the desired products became difficult after prolonged heating. Best results were obtained in DMF, even though amine smell clearly indicated the partial thermal decomposition of the solvent. The addition of diisopropylethylamine did not significantly influence the outcome of the reaction.

In the following, 30 minutes microwave heating at 240 °C in DMF was used on a routine basis for the reaction with α-secondary amines such as cyclohexylamine. When necessary, the reaction times were extended to a total of 60 or 90 minutes after intermittent HPLC analysis of the crude mixtures.

Table 1 Optimization of the Reaction Conditions for the Preparation of N-Substituted Indoles

Solvent	Temp (°C)	Y	Reaction time/Yield (%)[a]		
			10 min	30 min	60 min
n-BuOH	200	F	0	–	–
DMSO	200	F	15	–	–
DMF	200	F	<10	–	–
n-BuOH + ionic liquid	240	F	23	–	–
		Cl	<10	–	–
DMSO	240	F	–	80	–
		Cl	17	–	–
DMF	240	F	22	81	100
		Cl	18	45	80
DMF + Hünig's base	240	F	–	80	–
		Cl	25	–	82

[a] Yields determined by HPLC analysis with internal standard.



Scheme 2 Test system for the optimization of the cyclization conditions. *Reagents and conditions:* (a) EtOH, μW 140 °C, 9 h; (b) See Table 1.

Table 2 Synthesis of N-*sec*-Alkylated Indoles

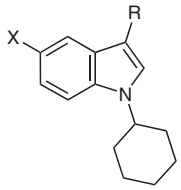
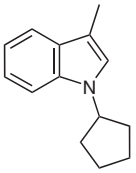
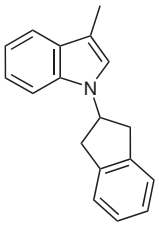
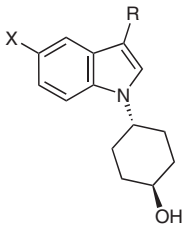
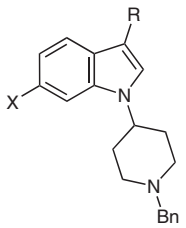
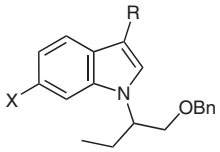
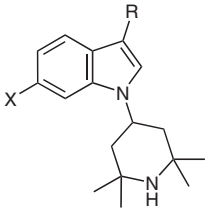
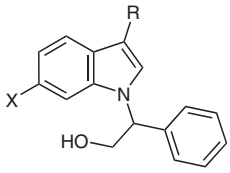
Starting Material	Product	X	R	Reaction time (h)	Yield (%)
2a	**5a** 	H	Me	0.5	40
2b	**5a**	H	Me	0.5	78
2c	**5b**	H	Et	1.0	92
2g	**5c**	F	Me	1.5	64
2b	**5d** 			0.7	64
2b	**5e** 			0.5	74
2b	**5f** 	H	Me	0.5	70
2d	**5g**	H	*i*-Pr	0.5	70
2e	**5h**	H	Ph	0.5	74
2g	**5i**	F	Me	1.0	73
2c	**5j** 	H	Et	0.5	73
2f	**5k**	F	Me	0.5	81

Table 2 Synthesis of N-*sec*-Alkylated Indoles (continued)

Starting Material	Product		X	R	Reaction time (h)	Yield (%)
2d	**5l**		H	*i*-Pr	1.5	57
2f	**5m**		F	Me	0.5	71
2f	**5n**		F	Me	0.3	74
2f	**5o**		F	Me	0.5	70

The yields of the isolated indoles varied from 60 to 90% (Table 2). Due to the elevated temperature required for the ring formation step, only a limited set of functional groups being compatible with this synthesis was expected. Primary **5o** and secondary alcohols **5f–i** proved to be sufficiently stable under the reaction conditions, and tertiary amines **5j–k** were also well tolerated, providing a basic set of functionalities suited for further derivatizations. Benzyl ethers **5l**,**m** and a sterically encumbered secondary amine **5n** did not interfere with the course of the reaction, either.

The corresponding formamides were detected as by-products from reaction of the amine components with the solvent. Anilines did not react (data not shown).

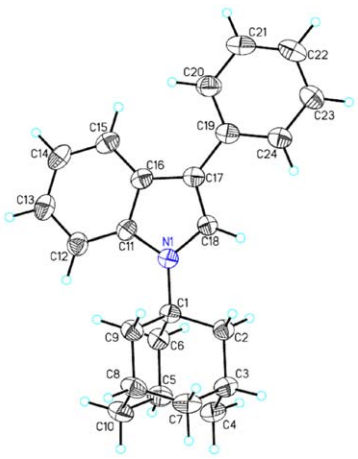


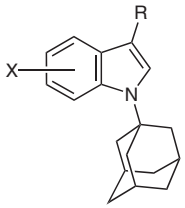
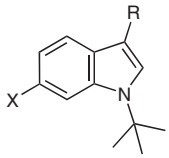
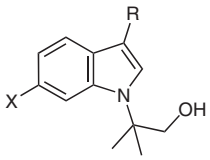
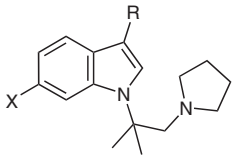
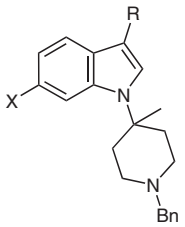
Figure 1 X-ray diffraction analysis of **5s**. ORTEP plot (50%) with labeling scheme.

As expected, α-tertiary amines such as *tert*-butylamine or adamantylamine proved to be less reactive. A two-hour heating time was required with the oxiranes **2b–e** (Table 3). Only the activated difluoro substituted substrates **2f** and **2g** reacted in shorter period. The *N*-adamantyl substituted indoles **5p–u** were isolated in 70–84% yields, and the structure of **5s** was confirmed by X-ray diffraction analysis (Figure 1). The *tert*-butyl substituted derivatives **5v–x** were obtained in 66–74% yields. Again, alcohol functionalities in **5y–aa** and tertiary amines **5bb–ee** were tolerated, and the yields reached up to 76% of the isolated product.

In summary, a reliable and easy-to-perform method to access indoles is presented here, which is valuable especially for the synthesis of the so far underexplored class of N-*tert*-alkylated indoles. One method to prepare the required oxiranes is the Corey–Chaykovsky epoxide formation. Despite the high temperatures needed for the ring-closing nucleophilic aromatic substitution, reasonable functional group compatibility was demonstrated with alcohols and amines.

^{1}H NMR and ^{13}C NMR spectra were recorded in DMSO-d_6 at r.t. on Bruker Avance spectrometers operating at 300 MHz, 400 MHz, and 500 MHz for ^{1}H NMR, and at 125 MHz for ^{13}C NMR spectra. Flash column chromatography was performed on silica gel 60 (0.063–0.200 mm) purchased from Merck KGaA, Darmstadt, Germany. Preparative HPLC chromatography was done on a 250 mm × 30 mm column packed with YMC gel ODS-AQ S-5/15 μM, with MeCN–H_2O as eluent and UV-detection. Solvents for extraction and chromatography were reagent grade and used as received. Commercial reagents were used without purification. Petroleum

Table 3 Synthesis of N-*tert*-Alkylated Indoles

Starting Material	Product		X	R	Reaction time (h)	Yield (%)
2b	**5p**		H	Me	2.0	73
2c	**5q**		H	Et	2.0	80
2d	**5r**		H	*i*-Pr	2.0	81
2e	**5s**		H	Ph	2.0	71
2f	**5t**		6-F	Me	1.0	70
2g	**5u**		5-F	Me	1.0	84
2b	**5v**		H	Me	2.0	66
2e	**5w**		H	Ph	2.0	70
2f	**5x**		F	Me	1.0	74
2b	**5y**		H	Me	2.0	57
2e	**5z**		H	Ph	2.0	40
2f	**5aa**		F	Me	1.0	76
2b	**5bb**		H	Me	2.0	32[a]
2f	**5cc**		F	Me	1.0	76
2d	**5dd**		H	*i*-Pr	2.0	68
2f	**5ee**		F	Me	1.0	69

[a] Plus 12% amino alcohol.

ether (PE) refers to the fraction boiling in the range of 40–60 °C. All microwave irradiation experiments were carried out using the Emrys optimizer microwave from Biotage. The reactions were performed in Biotage microwave vials (for 0.5–2 mL and 2–5 mL, respectively) sealed with a septum. The power range was up to 300 W at 2.45 GHz.

X-ray crystal structure determination was carried out using a diffractometer (Oxford Diffraction, Xcalibur series) equipped with a CCD area detector (model Ruby), a sealed tube with CuK_α radiation, osmic mirrors as monochromator and a Cryojet low temperature device (T = 100 K). Fullsphere data collection omega and phi scans. Programs used: Data collection and reduction Crysalis Version 1.171.29.2 (Oxford Diffraction 2005). Crystal structure solution was achieved using direct methods as implemented in SHELXTL Version 6.10,[26] and visualized using XP program. Missing atoms were subsequently located from difference Fourier synthesis and added to the atom list. Least squares refinement on F2 using all measured intensities was carried out using the program SHELXTL Version 6.10.[26] All nonhydrogen atoms were refined including anisotropic displacement parameters.

Epoxides 2 from Ketones 1; General Procedure A

Trimethylsulfonium iodide (12.2 g, 60 mmol) was suspended in THF (120 mL). The mixture was cooled to 0 °C, and *t*-BuOK (6.73 g, 60 mmol) was added. The mixture was warmed to r.t. and stirred for 5 min. Subsequently, the ketone (50 mmol) was added. The mixture was stirred at r.t. for 3 h or until complete consumption of the starting material, detected by HPLC. The precipitate was filtered off, and the filtrate was concentrated in vacuo. The product was isolated by distillation under reduced pressure.

2-(2-Chlorophenyl)-2-methyloxirane (2a)

Yield: 72%; bp 124 °C/37 mbar.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.57 (s, 3 H), 2.77 (d, J = 5.0 Hz, 1 H), 3.03 (d, J = 5.0 Hz, 1 H), 7.31–7.38 (m, 2 H), 7.42–7.48 (m, 2 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 22.5, 54.0, 57.3, 127.3, 128.5, 129.1, 129.4, 131.4, 139.3.

HRMS (EI): *m*/*z* calcd for C_9H_9ClO [M$^+$]: 168.0342; found: 168.0344.

2-(2-Fluorophenyl)-2-methyloxirane (2b)

Yield: 78%; bp 94 °C/20 mbar.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.58 (s, 3 H), 2.81 (d, J = 5.1 Hz, 1 H), 2.99 (d, J = 5.1 Hz, 1 H), 7.16–7.23 (m, 2 H), 7.34–7.41 (m, 2 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 22.9, 53.8, 54.9, 115.4 (d, $^2J_{C,F}$ = 21.0 Hz), 124.5 (d, $^4J_{C,F}$ = 3.2 Hz), 128.0 (d, $^3J_{C,F}$ = 4.4 Hz), 128.4 (d, $^2J_{C,F}$ = 14.8 Hz), 129.8 (d, $^3J_{C,F}$ = 8.1 Hz), 160.0 (d, $^1J_{C,F}$ = 245 Hz).

HRMS (EI): *m*/*z* calcd for C_9H_9FO [M$^+$]: 152.0637; found: 152.0631.

2-Ethyl-2-(2-fluorophenyl)oxirane (2c)

Yield: 92%; bp 107 °C/20 mbar.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.81 (t, J = 7.6 Hz, 3 H), 1.71–1.82 (m, 1 H), 1.88–1.99 (m, 1 H), 2.77 (d, J = 5.0 Hz, 1 H), 3.01 (d, J = 5.0 Hz, 1 H), 7.17–7.23 (m, 2 H), 7.31–7.41 (m, 2 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 8.84, 28.6 (d, $^5J_{C,F}$ = 1.8 Hz), 52.3 (d, $^4J_{C,F}$ = 0.7 Hz), 58.5, 115.3 (d, $^2J_{C,F}$ = 21.3 Hz), 124.3 (d, $^4J_{C,F}$ = 3.2 Hz), 127.0 (d, $^2J_{C,F}$ = 15.0 Hz), 129.0 (d, $^3J_{C,F}$ = 4.4 Hz), 129.8 (d, $^3J_{C,F}$ = 8.1 Hz), 159.9 (d, $^1J_{C,F}$ = 245 Hz).

HRMS (EI): *m*/*z* calcd for $C_{10}H_{11}FO$ [M$^+$]: 166.0794; found: 166.0797.

2-(2-Fluorophenyl)-2-isopropyloxirane (2d)

Yield: 78%; bp 119 °C/21 mbar.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 0.86 (d, J = 6.9 Hz, 3 H), 0.88 (d, J = 6.9 Hz, 3 H), 1.94 (sept, J = 6.9 Hz, 1 H), 2.74 (d, J = 4.7 Hz, 1 H), 3.04 (d, J = 4.7 Hz, 1H), 7.17–7.22 (m, 2 H), 7.34–7.41 (m, 2 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 17.7, 17.8 (d, $^5J_{C,F}$ = 0.9 Hz), 33.1, 51.1 (d, $^4J_{C,F}$ = 0.9 Hz), 60.9, 115.3 (d, $^2J_{C,F}$ = 21.7 Hz), 123.9 (d, $^4J_{C,F}$ = 3.2 Hz), 126.0 (d, $^2J_{C,F}$ = 15.0 Hz), 129.8 (d, $^3J_{C,F}$ = 8.3 Hz), 130.3 (d, $^3J_{C,F}$ = 4.4 Hz), 159.9 (d, $^1J_{C,F}$ = 245 Hz).

HRMS (EI): *m*/*z* calcd for $C_{11}H_{13}FO$ [M$^+$]: 180.0950; found: 180.0944.

2-(2-Fluorophenyl)-2-phenyloxirane (2e)

This compound was isolated by column chromatography on silica gel (eluent: PE–*tert*-butyl methyl ether 50:1); yield: 75%; oil.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.28 (d, J = 5.1 Hz, 1 H), 3.34 (d, J = 5.1 Hz, 1 H), 7.17–7.37 (m, 7 H), 7.47 (ddt, J = 7.8, 5.7, 1.9 Hz, 1 H), 7.57 (dt, J = 7.4, 1.6 Hz, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 55.6, 58.0 (d, $^3J_{C,F}$ = 0.9 Hz), 115.6, (d, $^2J_{C,F}$ = 20.8 Hz), 124.5 (d, $^4J_{C,F}$ = 3.5 Hz), 125.7, 126.4 (d, $^2J_{C,F}$ = 14.8 Hz), 127.9, 128.4, 130.0 (d, $^3J_{C,F}$ = 3.7 Hz), 130.6 (d, $^3J_{C,F}$ = 8.1 Hz), 139.2, 160.5 (d, $^1J_{C,F}$ = 247 Hz).

HRMS (EI): *m*/*z* calcd for $C_{14}H_{11}FO$ [M$^+$]: 214.0794; found: 214.0787.

2-(2,4-Difluorophenyl)-2-methyloxirane (2f)

Yield: 75%; bp 97 °C/22 mbar.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.81 (d, J = 5.0 Hz, 1 H), 2.98 (d, J = 5.0 Hz, 1 H), 7.07 (ddt, J = 8.6, 2.2, 0.4 Hz, 1 H), 7.26 (d, J = 11.1, 9.2, 2.2 Hz, 1 H), 7.43 (dt, J = 8.6, 6.8 Hz, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 22.8 (d, $^2J_{C,F}$ = 2.3 Hz), 53.7, 54.6, 104.0 (d, $^2J_{C,F}$ = 25.9 Hz), 111.4 (dd, $^2J_{C,F}$ = 21.2 Hz, $^4J_{C,F}$ = 3.6 Hz), 124.9 (dd, $^2J_{C,F}$ = 14.9 Hz, $^4J_{C,F}$ = 3.8 Hz), 129.3 (dd, $^3J_{C,F}$ = 9.9 Hz, $^3J_{C,F}$ = 6.0 Hz), 160.1 (dd, $^1J_{C,F}$ = 248 Hz, $^3J_{C,F}$ = 12.5 Hz), 161.8 (dd, $^1J_{C,F}$ = 246 Hz, $^3J_{C,F}$ = 12.3 Hz).

HRMS (EI): *m*/*z* calcd for $C_9H_8F_2O$ [M$^+$]: 170.0543; found: 170.0538.

2-(2,5-Difluorophenyl)-2-methyloxirane (2g)

Yield: 74%; bp 94 °C/20 mbar.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.59 (s, 3 H), 2.84 (d, J = 5.1 Hz, 1 H), 3.00 (d, J = 5.1 Hz, 1 H), 7.15–7.32 (m, 3 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 22.3 (d, $^4J_{C,F}$ = 2.8 Hz), 53.9, 54.6 (d, $^4J_{C,F}$ = 1.2 Hz), 114.4 (dd, $^2J_{C,F}$ = 25.2 Hz, $^3J_{C,F}$ = 4.9 Hz), 116.1 (dd, $^2J_{C,F}$ = 24.2 Hz, $^3J_{C,F}$ = 8.7 Hz), 117.2 (dd, $^2J_{C,F}$ = 24.5 Hz, $^3J_{C,F}$ = 8.8 Hz), 130.3 (dd, $^2J_{C,F}$ = 17.6 Hz, $^3J_{C,F}$ = 7.9 Hz), 156.1 (dd, $^1J_{C,F}$ = 241 Hz, $^4J_{C,F}$ = 2.3 Hz), 158.0 (dd, $^1J_{C,F}$ = 240 Hz, $^4J_{C,F}$ = 2.1 Hz).

HRMS (EI): *m*/*z* calcd for $C_9H_8F_2O$ [M$^+$]: 170.0543; found: 170.0539.

Amino Alcohols 3a,b from Epoxides 2a,b; General Procedure B

The oxirane (6.0 mmol) and cyclohexylamine (12.0 mmol) were dissolved in EtOH (12 mL), and the mixture was heated for 9 h to 140 °C in a microwave oven. Subsequently, the solvent was removed in vacuo, and the residue was purified by column chromatography on silica gel (eluent: CH_2Cl_2 + 2% Et_3N).

2-(2-Chlorophenyl)-1-(cyclohexylamino)propan-2-ol (3a)
^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.85–1.19 (m, 5 H), 1.45–1.52 (m, 2 H), 1.54 (s, 3 H), 1.55–1.77 (m, 4 H), 2.20 (tt, *J* = 10.0, 3.7 Hz, 1 H), 2.91 (d, *J* = 11.7 Hz, 1 H), 3.19 (d, *J* = 11.7 Hz, 1 H), 5.25 (br s, 1 H), 7.22 (dt, *J* = 7.6, 1.8 Hz, 1 H), 7.30 (dt, *J* = 7.6, 1.3 Hz, 1 H), 7.34 (dd, *J* = 7.6, 1.3 Hz, 1 H), 7.81 (dd, *J* = 7.6, 1.8 Hz, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 24.3, 24.4, 25.7, 25.8, 33.1, 33.2, 54.3, 56.2, 73.2, 126.7, 128.2, 128.7, 129.9, 130.7, 144.6.

HRMS (EI): *m*/*z* calcd for $C_{15}H_{22}ClNO$ + [H$^+$] [M$^+$ + H]: 268.1460; found: 268.1463.

1-(Cyclohexylamino)-2-(2-fluorophenyl)propan-2-ol (3b)
^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.85–0.99 (m, 2 H), 1.00–1.20 (m, 3 H), 1.34 (br s, 1 H), 1.44 (s, 3 H), 1.45–1.52 (m, 1 H), 1.55–1.64 (m, 2 H), 1.65–1.77 (m, 2 H), 2.21 (tt, *J* = 10.0, 3.7 Hz, 1 H), 2.78 (d, *J* = 10.6 Hz, 1 H), 2.89 (d, *J* = 10.6 Hz, 1 H), 5.14 (br s, 1 H), 7.07 (dd, *J* = 12.2, 8.1 Hz, 1 H), 7.14 (ddd, *J* = 7.6, 7.5, 0.9 Hz, 1 H), 7.22–7.29 (m, 1 H), 7.60 (ddd, *J* = 8.1, 7.6, 1.7 Hz, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 24.4, 25.8, 26.6 (d, $^4J_{C,F}$ = 3.9 Hz), 33.1, 55.9 (d, $^4J_{C,F}$ = 4.2 Hz), 56.3, 71.9 (d, $^3J_{C,F}$ = 4.6 Hz), 115.5 (d, $^2J_{C,F}$ = 23.8 Hz), 123.8 (d, $^4J_{C,F}$ = 3.0 Hz), 128.1 (d, $^3J_{C,F}$ = 4.9 Hz), 128.4 (d, $^3J_{C,F}$ = 8.6 Hz), 134.7 (d, $^2J_{C,F}$ = 12.9 Hz), 159.0 (d, $^1J_{C,F}$ = 243 Hz).

HRMS (EI): *m*/*z* calcd for $C_{15}H_{22}FNO$ + [H$^+$] [M$^+$ + H]: 252.1759; found: 252.1758.

Indoles 5 from Epoxides 2 and Amines; General Procedure C
An oxirane (1.0 mmol) and a primary amine (2.0 mmol) were dissolved in DMF (1.0 mL), and the mixture was heated in a microwave oven for the time indicated in Table 2 or 3 to 240 °C. Very lipophilic indoles may be extracted with pentane (5 × 5 mL) from the mixture. Otherwise, EtOAc (20 mL) was added, and the mixture was washed with H_2O (20 mL). The organic layer was dried (Na_2SO_4), the solvent was evaporated, and the residue was purified by flash column chromatography on silica gel or by preparative HPLC.

1-Cyclohexyl-3-methyl-1*H*-indole (5a)
Purified by preparative HPLC; mp 68 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.25 (qt, *J* = 12.9, 3.6 Hz, 1 H), 1.49 (qt, *J* = 12.9, 3.2 Hz, 2 H), 1.64–1.76 (m, 3 H), 1.80–1.87 (m, 2H), 1.89–1.96 (m, 2H), 2.24 (s, 3 H), 4.26 (tt, *J* = 11.7, 3.8 Hz, 1 H), 6.96–7.01 (m, 1 H), 7.09 (ddd, *J* = 7.9, 7.5, 0.6 Hz, 1 H), 7.22 (s, 1 H), 7.42–7.45 (m, 2 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 9.56, 25.1, 25.3, 33.0, 53.8, 108.8, 109.5, 118.1, 118.5, 120.7, 122.5, 128.0, 135.4.

HRMS (EI): *m*/*z* calcd for $C_{15}H_{19}N$ [M$^+$]: 213.1517; found: 213.1517.

1-Cyclohexyl-3-ethyl-1*H*-indole (5b)
Purified by flash chromatography (cyclohexane) to yield an oil.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.19–1.32 (m, 1 H), 1.25 (t, *J* = 7.5 Hz, 3 H), 1.42–1.55 (m, 2 H), 1.66–1.78 (m, 3 H), 1.80–1.88 (m, 2 H), 1.89–1.97 (m, 2 H), 2.69 (q, *J* = 7.5 Hz, 2 H), 4.26 (tt, *J* = 11.7, 3.7 Hz, 1 H), 6.97 (dd, *J* = 7.8, 7.1 Hz, 1 H), 7.09 (dd, *J* = 8.1, 7.1 Hz, 1 H), 7.21 (s, 1 H), 7.44 (d, *J* = 8.1 Hz, 1 H), 7.49 (d, *J* = 7.8 Hz, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 14.6, 17.9, 25.1, 25.4, 32.9, 53.8, 109.6, 116.0, 118.1, 118.6, 120.7, 121.3, 127.2, 135.5.

HRMS (EI): *m*/*z* calcd for $C_{16}H_{21}N$ [M$^+$]: 227.1674; found: 227.1673.

1-Cyclohexyl-5-fluoro-3-methyl-1*H*-indole (5c)
Purified by preparative HPLC to yield an oil.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.24 (qt, *J* = 12.9, 3.6 Hz, 1 H), 1.48 (qt, *J* = 12.9, 3.0 Hz, 2 H), 1.62–1.74 (m, 3 H), 1.79–1.87 (m, 2 H), 1.88–1.95 (m, 2 H), 2.21 (s, 3 H), 4.26 (tt, *J* = 11.7, 3.6 Hz, 1 H), 6.93 (ddd, *J* = 9.7, 8.9, 2.4 Hz, 1 H), 7.21 (dd, *J* = 10.0, 2.4 Hz, 1 H), 7.31 (s, 1 H), 7.47 (dd, *J* = 8.9, 4.5 Hz, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 9.48, 25.0, 25.3, 33.0, 54.0, 103.1 (d, $^2J_{C,F}$ = 22.7 Hz), 108.7 (d, $^2J_{C,F}$ = 25.9 Hz), 109.0 (d, $^4J_{C,F}$ = 4.6 Hz), 110.5 (d, $^3J_{C,F}$ = 9.7 Hz), 124.5, 128.1 (d, $^3J_{C,F}$ = 9.5 Hz), 132.1, 156.6 (d, $^1J_{C,F}$ = 231 Hz).

HRMS (EI): *m*/*z* calcd for $C_{15}H_{18}FN$ [M$^+$]: 231.1423; found: 231.1428.

1-Cyclopentyl-3-methyl-1*H*-indole (5d)
Purified by preparative HPLC to yield an oil.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.64–1.87 (m, 6 H), 2.07–2.15 (m, 2 H), 2.24 (s, 3 H), 4.82 (tt, *J* = 7.0, 7.0 Hz, 1 H), 6.97–7.01 (m, 1 H), 7.08–7.12 (m, 1 H), 7.20 (s, 1 H), 7.43 (d, *J* = 8.2 Hz, 1 H), 7.46 (d, *J* = 7.9 Hz, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 9.57, 23.7, 32.1, 55.8, 109.0, 109.8, 118.2, 118.5, 120.8, 122.7, 128.3, 136.1.

HRMS (EI): *m*/*z* calcd for $C_{14}H_{17}N$ [M$^+$]: 199.1361; found: 199.1361.

1-(2,3-Dihydro-1*H*-inden-2-yl)-3-methyl-1*H*-indole (5e)
Purified by flash chromatography (CH_2Cl_2); mp 94 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.19 (s, 3 H), 3.19 (dd, *J* = 16.1, 6.1 Hz, 2 H), 3.45 (dd, *J* = 16.1, 7.7 Hz, 2 H), 5.38 (tt, *J* = 7.7, 6.1 Hz, 1 H), 7.00–7.04 (m, 1 H), 7.07 (s, 1 H), 7.10–7.15 (m, 1 H), 7.19–7.32 (m, 4 H), 7.46–7.49 (m, 2 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 9.52, 39.1, 55.1, 109.2, 109.8, 118.5, 118.6, 121.1, 122.8, 124.5, 126.8, 128.4, 135.8, 140.8.

HRMS (EI): *m*/*z* calcd for $C_{18}H_{17}N$ [M$^+$]: 247.1361; found: 247.1361.

***trans*-4-(3-Methyl-1*H*-indol-1-yl)cyclohexanol (5f)**
Purified by preparative HPLC; mp 136 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.38–1.51 (m, 2 H), 1.73–1.84 (m, 2 H), 1.85–1.98 (m, 4 H), 2.23 (s, 3 H), 3.49–3.59 (m, 1 H), 4.26 (tt, *J* = 11.6, 3.9 Hz, 1 H), 4.67 (d, *J* = 4.4 Hz, 1 H), 6.98 (dd, *J* = 7.7, 7.4 Hz, 1 H), 7.09 (dd, *J* = 8.2, 7.7 Hz, 1 H), 7.20 (s, 1 H), 7.43–7.47 (m, 2 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 9.57, 30.8, 34.4, 53.2, 68.2, 108.9, 109.6, 118.2, 118.5, 120.8, 122.5, 128.1, 135.6.

HRMS (EI): *m*/*z* calcd for $C_{15}H_{19}NO$ [M$^+$]: 229.1467; found: 229.1467.

***trans*-4-(3-Isopropyl-1*H*-indol-1-yl)cyclohexanol (5g)**
Purified by preparative HPLC; mp 96 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.29 (d, *J* = 6.9 Hz, 6 H), 1.38–1.50 (m, 2 H), 1.75–1.98 (m, 6 H), 3.11 (sept, *J* = 6.9 Hz, 1 H), 3.55 (dtt, *J* = 10.8, 4.4, 4.2 Hz, 1 H), 4.27 (tt, *J* = 11.4, 4.2 Hz, 1 H), 4.67 (d, *J* = 4.4 Hz, 1 H), 6.97 (ddd, *J* = 7.8, 7.3, 0.3 Hz, 1 H), 7.08 (ddd, *J* = 8.1, 7.3, 0.8 Hz, 1 H), 7.17 (s, 1 H), 7.45 (dd, *J* = 8.1, 0.3 Hz, 1 H), 7.53 (dd, *J* = 7.8, 0.8 Hz, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 23.4, 25.0, 30.7, 34.4, 53.2, 68.2, 109.7, 118.1, 118.9, 119.9, 120.7, 121.3, 126.5, 135.9.

HRMS (EI): *m*/*z* calcd for $C_{17}H_{23}NO$ [M$^+$]: 257.1780; found: 257.1778.

***trans*-4-(3-Phenyl-1*H*-indol-1-yl)cyclohexanol (5h)**
Purified by flash chromatography (PE–EtOAc, 1:1); mp 129 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.43–1.55 (m, 2 H), 1.86–2.02 (m, 6 H), 3.53–3.63 (m, 1 H), 4.35–4.45 (m, 1 H), 4.71 (d, *J* = 4.2 Hz, 1 H), 7.11 (t, *J* = 7.6 Hz, 1 H), 7.19 (t, *J* = 7.9 Hz, 1 H), 7.22 (t, *J* = 7.6 Hz, 1 H), 7.42 (t, *J* = 7.9 Hz, 1 H), 7.61 (d, *J* = 8.0 Hz, 1 H), 7.67 (t, *J* = 7.9 Hz, 2 H), 7.81 (s, 1 H), 7.86 (d, *J* = 8.0 Hz, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 30.7, 34.4, 53.5, 68.1, 110.4, 115.2, 119.2, 119.8, 121.3, 123.3, 125.2, 125.3, 126.5, 128.7, 135.6, 136.3.

HRMS (EI): *m*/*z* calcd for $C_{20}H_{21}NO$ [M$^+$]: 291.1623; found: 291.1619.

***trans*-4-(5-Fluoro-3-methyl-1*H*-indol-1-yl)cyclohexanol (5i)**
Purified by preparative HPLC; mp 109 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.39–1.50 (m, 2 H), 1.71–1.83 (m, 2 H), 1.84–1.96 (m, 4 H), 2.20 (s, 3 H), 3.53 (tq, *J* = 10.7, 4.3 Hz, 1 H), 4.26 (tt, *J* = 11.6, 3.8 Hz, 1 H), 4.68 (d, *J* = 4.3 Hz, 1 H), 6.93 (ddd, *J* = 9.7, 8.8, 2.4 Hz, 1 H), 7.20 (dd, *J* = 9.8, 2.4 Hz, 1 H), 7.28 (s, 1 H), 7.48 (dd, *J* = 8.8, 4.4 Hz, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 9.5, 30.8, 34.4, 53.4, 68.2, 103.2 (d, $^2J_{C,F}$ = 22.7 Hz), 108.7 (d, $^2J_{C,F}$ = 25.9 Hz), 109.1 (d, $^4J_{C,F}$ = 4.9 Hz), 110.6 (d, $^3J_{C,F}$ = 9.7 Hz), 124.5, 128.2 (d, $^3J_{C,F}$ = 9.7 Hz), 132.3, 156.7 (d, $^1J_{C,F}$ = 231 Hz).

HRMS (EI): *m*/*z* calcd for $C_{15}H_{18}FNO$ [M$^+$]: 247.1372; found: 247.1367.

1-(1-Benzylpiperidin-4-yl)-3-ethyl-1*H*-indole (5j)
Purified by preparative HPLC to yield an oil.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.25 (t, *J* = 7.5 Hz, 3 H), 1.85–1.92 (m, 2 H), 1.92–2.01 (m, 2 H), 2.20 (dt, *J* = 11.0, 1.4 Hz, 2 H), 2.69 (q, *J* = 7.5 Hz, 2 H), 2.91–2.98 (m, 2 H), 3.54 (s, 2 H), 4.29 (tt, *J* = 11.5, 4.4 Hz, 1 H), 6.98 (t, *J* = 7.4 Hz, 1 H), 7.09 (t, *J* = 7.4 Hz, 1 H), 7.23–7.30 (m, 2 H), 7.33–7.36 (m, 4 H), 7.45 (d, *J* = 8.3 Hz, 1 H), 7.49 (d, *J* = 7.8 Hz, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 14.6, 17.9, 32.0, 52.4, 62.0, 109.6, 116.2, 118.2, 118.6, 120.8, 121.3, 126.9, 127.3, 128.2, 128.8, 135.7, 138.5.

HRMS (EI): *m*/*z* calcd for $C_{22}H_{26}N_2$ [M$^+$]: 318.2096; found: 318.2093.

1-(1-Benzylpiperidin-4-yl)-6-fluoro-3-methyl-1*H*-indole (5k)
Purified by preparative HPLC to yield an oil.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.83–1.98 (m, 4 H), 2.20 (dt, *J* = 11.6, 2.3 Hz, 2 H), 2.22 (s, 3 H), 2.90–2.96 (m, 2 H), 3.54 (s, 2 H), 4.25 (tt, *J* = 10.9, 5.0 Hz, 1 H), 6.83 (ddd, *J* = 9.6, 8.6, 1.8 Hz, 1 H), 7.23–7.29 (m, 1 H), 7.27 (s, 1 H), 7.32–7.37 (m, 5 H), 7.43 (dd, *J* = 8.6, 5.6 Hz, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 9.5, 32.0, 52.2, 52.4, 62.0, 96.0 (d, $^2J_{C,F}$ = 26.4 Hz), 106.6 (d, $^2J_{C,F}$ = 24.5), 109.5, 119.5 (d, $^3J_{C,F}$ = 10.4 Hz), 123.0 (d, $^4J_{C,F}$ = 3.5 Hz), 124.8, 126.9, 128.2, 128.8, 135.5 (d, $^3J_{C,F}$ = 12.5 Hz), 138.4, 159.0 (d, $^1J_{C,F}$ = 234.0 Hz).

HRMS (EI): *m*/*z* calcd for $C_{21}H_{23}FN_2$ [M$^+$]: 322.1845; found: 322.1845.

1-{1-[(Benzyloxy)methyl]propyl}-3-isopropyl-1*H*-indole (5l)
Purified by flash chromatography (cyclohexane–*tert*-butyl methyl ether, 4:1) to yield an oil.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.70 (t, *J* = 7.3 Hz, 3 H), 1.30 (d, *J* = 6.8 Hz, 6 H), 1.78–1.97 (m, 2 H), 3.14 (sept, *J* = 6.8 Hz, 1 H), 3.70 (dd, *J* = 10.2, 4.9 Hz, 1 H), 3.76 (dd, *J* = 10.2, 6.7 Hz, 1 H), 4.40 (d, *J* = 12.2 Hz, 1 H), 4.44 (d, *J* = 12.2 Hz, 1 H), 4.49–4.57 (m, 1 H), 6.97 (ddd, *J* = 7.8, 7.1, 0.5 Hz, 1 H), 7.07 (ddd, *J* = 8.1, 7.1, 1.0 Hz, 1 H), 7.15–7.19 (m, 3 H), 7.21–7.30 (m, 3 H), 7.45 (dd, *J* = 8.1, 0.5 Hz, 1 H), 7.55 (dd, *J* = 7.8, 1.0 Hz, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 10.5, 23.4, 24.4, 25.0, 56.2, 71.8, 71.9, 109.8, 118.0, 118.8, 120.6, 120.7, 121.6, 126.4, 127.2, 127.3, 128.1, 137.1, 138.3.

HRMS (EI): *m*/*z* calcd for $C_{22}H_{27}NO$ [M$^+$]: 321.2093; found: 321.2098.

1-{1-[(Benzyloxy)methyl]propyl}-6-fluoro-3-methyl-1*H*-indole (5m)
Purified by preparative HPLC to yield an oil.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.69 (t, *J* = 7.3 Hz, 3 H), 1.74–1.93 (m, 2 H), 2.24 (s, 3 H), 3.68 (dd, *J* = 10.2, 5.1 Hz, 1 H), 3.72 (dd, *J* = 10.2, 6.7 Hz, 1 H), 4.39 (d, *J* = 12.2 Hz, 1 H), 4.45 (d, *J* = 12.2 Hz, 1 H), 4.46–4.54 (m, 1 H), 6.83 (ddd, *J* = 9.4, 8.9, 2.0 Hz, 1 H), 7.14–7.17 (m, 2 H), 7.22 (s, 1 H), 7.22–7.31 (m, 3 H), 7.34 (dd, *J* = 11.0, 2.2 Hz, 1 H), 7.44 (dd, *J* = 8.6, 5.6 Hz, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 9.6, 10.4, 24.3, 56.3, 71.89, 71.91, 96.1 (d, $^2J_{C,F}$ = 26.6 Hz), 106.5 (d, $^2J_{C,F}$ = 24.5 Hz), 109.7, 119.3 (d, $^3J_{C,F}$ = 10.4 Hz), 123.4 (d, $^4J_{C,F}$ = 3.5 Hz), 124.7, 127.3, 127.4, 128.2, 137.0 (d, $^3J_{C,F}$ = 12.5 Hz), 138.2, 159.0 (d, $^1J_{C,F}$ = 234 Hz).

HRMS (EI): *m*/*z* calcd for $C_{20}H_{22}FNO$ [M$^+$]: 311.1685; found: 311.1685.

6-Fluoro-3-methyl-1-(2,2,6,6-tetramethylpiperidin-4-yl)-1*H*-indole (5n)
Purified by preparative HPLC; mp 58 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.11 (s, 6 H), 1.31 (s, 6 H), 1.59 (tt, *J* = 12.3 Hz, 2 H), 1.77 (dd, *J* = 12.3, 3.3 Hz, 2 H), 2.23 (s, 3H), 3.50 (br s under H_2O, 1 H), 4.67 (tt, *J* = 12.3, 3.3 Hz, 1 H), 6.85 (ddd, *J* = 9.6, 8.6, 2.0 Hz, 1 H), 7.22 (s, 1 H), 7.40 (dd, *J* = 10.8, 2.0 Hz, 1 H), 7.45 (dd, *J* = 8.6, 5.6 Hz, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 9.51, 28.3, 34.5, 44.2, 48.1, 50.8, 96.0 (d, $^2J_{C,F}$ = 26.1 Hz), 106.6 (d, $^2J_{C,F}$ = 24.5 Hz), 109.5, 119.6 (d, $^3J_{C,F}$ = 10.4 Hz), 123.0 (d, $^4J_{C,F}$ = 3.5 Hz), 124.9, 135.4 (d, $^3J_{C,F}$ = 12.5 Hz), 158.9 (d, $^1J_{C,F}$ = 234 Hz).

HRMS (EI): *m*/*z* calcd for $C_{18}H_{25}FN_2$ [M$^+$]: 288.2002; found: 288.1999.

2-(6-Fluoro-3-methyl-1*H*-indol-1-yl)-2-phenylethanol (5o)
Purified by preparative HPLC.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.26 (s, 3 H), 4.03 (ddd, *J* = 11.3, 5.2, 5.1 Hz, 1 H), 4.20 (ddd, *J* = 11.3, 8.4, 6.0 Hz, 1 H), 5.18 (dd, *J* = 6.0, 5.2 Hz, 1 H), 5.56 (dd, *J* = 8.4, 5.1 Hz, 1 H), 6.82 (ddd, *J* = 10.3, 8.0, 2.2 Hz, 1 H), 7.20–7.32 (m, 6 H), 7.44 (dd, *J* = 8.7, 5.7 Hz, 1 H), 7.46 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 9.57, 60.7, 62.9, 96.3 (d, $^2J_{C,F}$ = 26.4 Hz), 106.7 (d, $^3J_{C,F}$ = 24.3 Hz), 109.5, 119.4 (d, $^4J_{C,F}$ = 10.4 Hz), 124.2 (d, $^4J_{C,F}$ = 3.5 Hz), 125.0, 126.9, 127.5, 128.4, 136.5 (d, $^3J_{C,F}$ = 12.5 Hz), 139.4, 158.9 (d, $^1J_{C,F}$ = 234 Hz).

HRMS (EI): *m*/*z* calcd for $C_{17}H_{16}FNO$ [M$^+$]: 269.1216; found: 269.1214.

1-(Adamantan-1-yl)-3-methyl-1*H*-indole (5p)
Purified by flash chromatography (PE–CH_2Cl_2, 5:1); mp 214–217 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.71–1.85 (m, 6 H), 2.20 (br s, 3 H), 2.22 (s, 3 H), 2.28 (s, 6 H), 6.96–7.00 (m, 1 H), 7.03–7.07 (m, 1 H), 7.22 (s, 1 H), 7.47 (d, *J* = 7.7 Hz, 1 H), 7.72 (d, *J* = 8.4 Hz, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 9.5, 29.3, 35.7, 41.6, 55.8, 107.6, 113.5, 117.8, 118.8, 120.2, 122.6, 129.8, 134.2.

HRMS (EI): *m*/*z* calcd for $C_{19}H_{23}N$ [M$^+$]: 265.1830; found: 265.1824.

1-(Adamantan-1-yl)-3-ethyl-1*H*-indole (5q)
Purified by flash chromatography (PE–CH_2Cl_2, 5:1); mp 162 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.25 (t, *J* = 7.5 Hz, 3 H), 1.72–1.77 (m, 3 H), 1.79–1.85 (m, 3 H), 2.21 (s, 3 H), 2.28 (s, 6 H), 2.68 (q, *J* = 7.5 Hz, 2 H), 6.95–6.99 (m, 1 H), 7.03–7.08 (m, 1 H), 7.20 (s, 1 H), 7.51 (d, *J* = 7.9 Hz, 1 H), 7.72 (d, *J* = 8.4 Hz, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 14.6, 17.8, 29.3, 35.8, 41.6, 55.9, 113.7, 114.8, 117.9, 118.9, 120.3, 121.4, 129.0, 134.4.

HRMS (EI): *m*/*z* calcd for $C_{20}H_{25}N$ [M$^+$]: 279.1987; found: 279.1986.

1-(Adamantan-1-yl)-3-isopropyl-1*H*-indole (5r)
Purified by flash chromatography (PE–CH_2Cl_2, 5:1); mp 121 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.29 (d, *J* = 6.8 Hz, 6 H), 1.71–1.86 (m, 6 H), 2.21 (s, 3 H), 2.28 (s, 6 H), 3.11 (sept, *J* = 6.8 Hz, 1 H), 6.94–6.99 (m, 1 H), 7.02–7.07 (m, 1 H), 7.15 (s, 1 H), 7.5 (d, *J* = 7.7 Hz, 1 H), 7.72 (d, *J* = 8.5 Hz, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 23.3, 24.8, 29.3, 35.7, 41.5, 55.9, 113.7, 117.7, 119.2, 119.8, 119.9, 120.1, 128.3, 134.5.

HRMS (EI): *m*/*z* calcd for $C_{21}H_{27}N$ [M$^+$]: 293.2144; found: 293.2144.

1-(Adamantan-1-yl)-3-phenyl-1*H*-indole (5s)
Purified by trituration with MeOH; mp 170–172 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.74–1.89 (m, 6 H), 2.25 (br s, 3 H), 2.36–2.39 (m, 6 H), 7.07–7.18 (m, 2 H), 7.23 (t, *J* = 7.3 Hz, 1 H), 7.42 (t, *J* = 7.7 Hz, 2 H), 7.64–7.67 (m, 2 H), 7.71 (s, 1 H), 7.87 (t, *J* = 7.5 Hz, 2 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 29.3, 35.7, 41.4, 56.6, 114.2, 114.3, 119.4, 119.5, 120.8, 123.3, 125.3, 126.8, 127.0, 128.7, 134.9, 135.6.

HRMS (EI): *m*/*z* calcd for $C_{24}H_{25}N$ [M$^+$]: 327.1987; found: 327.1987.

1-(Adamantan-1-yl)-6-fluoro-3-methyl-1*H*-indole (5t)
Purified by trituration with EtOAc and MeOH; mp 217 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.69–1.86 (m, 6 H), 2.18–2.25 (m, 12 H), 6.85 (ddd, *J* = 9.0, 8.6, 2.0 Hz, 1 H), 7.23 (s, 1 H), 7.45 (dd, *J* = 8.6, 5.9 Hz, 1 H), 7.51 (dd, *J* = 11.7, 2.0 Hz, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 9.43, 29.3, 35.6, 41.3, 56.1, 99.7 (d, $^2J_{C,F}$ = 26.8 Hz), 106.3 (d, $^2J_{C,F}$ = 24.3 Hz), 108.1, 119.6 (d, $^3J_{C,F}$ = 10.4 Hz), 123.3 (d, $^4J_{C,F}$ = 3.5 Hz), 126.6, 133.7 (d, $^3J_{C,F}$ = 12.3 Hz), 158.0 (d, $^1J_{C,F}$ = 233 Hz).

HRMS (EI): *m*/*z* calcd for $C_{19}H_{22}FN$ [M$^+$]: 283.1736; found: 283.1732.

1-(Adamantan-1-yl)-5-fluoro-3-methyl-1*H*-indole (5u)
Purified by trituration with EtOH and MeOH; mp 168 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.70–1.85 (m, 6 H), 2.18–2.25 (m, 12 H), 6.88 (ddd, *J* = 9.3, 9.2, 2.7 Hz, 1 H), 7.21 (dd, *J* = 9.8, 2.7 Hz, 1 H), 7.30 (s, 1 H), 7.73 (dd, *J* = 9.3, 4.4 Hz, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 9.36, 29.2, 35.6, 41.6, 55.9, 103.3 (d, $^2J_{C,F}$ = 22.2 Hz), 107.9 (d, $^4J_{C,F}$ = 4.6 Hz), 108.1 (d, $^2J_{C,F}$ = 25.4 Hz), 114.4 (d, $^3J_{C,F}$ = 9.5 Hz), 124.7, 130.2 (d, $^3J_{C,F}$ = 9.5 Hz), 130.8, 156.2 (d, $^1J_{C,F}$ = 232 Hz).

HRMS (EI): *m*/*z* calcd for $C_{19}H_{22}FN$ [M$^+$]: 283.1736; found: 283.1732.

1-*tert*-Butyl-3-methyl-1*H*-indole (5v)
Purified by preparative HPLC to yield an oil.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.64 (s, 9 H), 2.23 (d, *J* = 1.0 Hz, 3 H), 6.99 (ddd, *J* = 7.6, 7.2, 0.3 Hz, 1 H), 7.08 (ddd, *J* = 8.1, 7.2, 1.0 Hz, 1 H), 7.19 (q, *J* = 1.0 Hz, 1 H), 7.47 (d, *J* = 7.6 Hz, 1 H), 7.63 (d, *J* = 8.1 Hz, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 9.42, 29.4, 55.1, 107.5, 113.0, 117.8, 118.7, 120.4, 123.6, 129.9, 134.6.

HRMS (EI): *m*/*z* calcd for $C_{13}H_{17}N$ [M$^+$]: 187.1361; found: 187.1361.

1-*tert*-Butyl-3-phenyl-1*H*-indole (5w)
Purified by trituration with EtOAc and MeOH; mp 91 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.73 (s, 9 H), 7.08–7.20 (m, 2 H), 7.23 (t, *J* = 7.3 Hz, 1 H), 7.43 (t, *J* = 7.3 Hz, 2 H), 7.67 (d, *J* = 7.3 Hz, 2 H), 7.69 (s, 1 H), 7.79 (d, *J* = 8.6 Hz, 1 H), 7.86 (d, *J* = 7.8 Hz, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 29.3, 55.9, 113.8, 114.1, 119.3, 119.4, 121.0, 124.3, 125.3, 126.8, 127.0, 128.7, 135.3, 135.5.

HRMS (EI): *m*/*z* calcd for $C_{18}H_{19}N$ [M$^+$]: 249.1517; found: 249.1517.

1-*tert*-Butyl-6-fluoro-3-methyl-1*H*-indole (5x)
Purified by preparative HPLC to yield an oil.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.62 (s, 9 H), 2.21 (d, *J* = 0.7 Hz, 3 H), 6.85 (ddd, *J* = 9.8, 8.5, 2.0 Hz, 1 H), 7.20 (q, *J* = 0.7 Hz, 1 H), 7.43 (dd, *J* = 11.6, 2.0 Hz, 1 H), 7.45 (dd, *J* = 8.5, 6.0 Hz, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 9.37, 29.2, 55.3, 99.2 (d, $^2J_{C,F}$ = 27.0 Hz), 106.2 (d, $^2J_{C,F}$ = 24.5 Hz), 108.0, 119.5 (d, $^3J_{C,F}$ = 10.4 Hz), 124.3 (d, $^4J_{C,F}$ = 3.7 Hz), 126.6, 134.2 (d, $^3J_{C,F}$ = 12.0 Hz), 158.2 (d, $^1J_{C,F}$ = 233 Hz).

HRMS (EI): *m*/*z* calcd for $C_{13}H_{16}FN$ [M$^+$]: 205.1267; found: 205.1266.

2-Methyl-2-(3-methyl-1*H*-indol-1-yl)propan-1-ol (5y)
Purified by preparative HPLC; mp 99 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.58 (s, 6 H), 2.22 (s, 3 H), 3.76 (d, *J* = 5.6 Hz, 2 H), 4.99 (t, *J* = 5.6 Hz, 1 H), 6.95–7.00 (m, 1 H), 7.02–7.07 (m, 1 H), 7.19 (s, 1 H), 7.45 (d, *J* = 7.6 Hz, 1 H), 7.58 (d, *J* = 8.3 Hz, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 9.4, 24.8, 59.2, 67.2, 107.4, 113.0, 117.8, 118.6, 120.3, 124.8, 129.8, 134.8.

HRMS (EI): *m*/*z* calcd for $C_{13}H_{17}NO$ [M$^+$]: 203.1310; found: 203.1304.

2-Methyl-2-(3-phenyl-1*H*-indol-1-yl)propan-1-ol (5z)
Purified by preparative HPLC to yield an oil.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.67 (s, 6 H), 3.86 (d, *J* = 5.6 Hz, 2 H), 5.10 (t, *J* = 5.6 Hz, 1 H), 7.08–7.17 (m, 2 H), 7.23 (t, *J* = 7.3 Hz, 1 H), 7.43 (t, *J* = 7.7 Hz, 2 H), 7.65 (d, *J* = 7.7 Hz, 2 H), 7.68 (s, 1 H), 7.75 (d, *J* = 8.3 Hz, 1 H), 7.85 (d, *J* = 7.3 Hz, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 24.7, 60.0, 67.1, 113.8, 114.0, 119.2, 119.4, 120.9, 125.3, 125.6, 126.8, 127.0, 128.8, 135.5, 135.6.

HRMS (EI): *m*/*z* calcd for $C_{18}H_{19}NO$ [M$^+$]: 265.1467; found: 265.1461.

2-(6-Fluoro-3-methyl-1*H*-indol-1-yl)-2-methylpropan-1-ol (5aa)

Purified by preparative HPLC; mp 69 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.56 (s, 6 H), 2.20 (s, 3 H), 3.73 (d, *J* = 5.6 Hz, 2 H), 5.01 (t, *J* = 5.6 Hz, 1 H), 6.84 (ddd, *J* = 9.2, 8.6, 2.2 Hz, 1 H), 7.20 (s, 1 H), 7.40 (dd, *J* = 11.5, 2.1 Hz, 1 H), 7.43 (dd, *J* = 8.6, 5.6 Hz, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 9.37, 24.6, 59.4, 67.1, 99.3 (d, $^2J_{C,F}$ = 27.0 Hz), 106.1 (d, $^2J_{C,F}$ = 24.5 Hz), 107.8, 119.3 (d, $^3J_{C,F}$ = 10.6 Hz), 125.5 (d, $^4J_{C,F}$ = 3.7 Hz), 126.5, 134.5 (d, $^3J_{C,F}$ = 12.3 Hz), 158.1 (d, $^1J_{C,F}$ = 232.3 Hz).

HRMS (EI): *m*/*z* calcd for $C_{13}H_{16}FNO$ [M$^+$]: 221.1216; found: 221.1216.

3-Methyl-1-(1,1-dimethyl-2-pyrrolidin-1-ylethyl)-1*H*-indole (5bb)

Purified by preparative HPLC.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.41–1.48 (m, 4 H), 1.65 (s, 6 H), 2.02–2.09 (m, 4 H), 2.50 (s, 3 H), 2.98 (s, 2 H), 6.95–6.99 (m, 1 H), 7.03–7.07 (m, 1 H), 7.15 (s, 1 H), 7.45 (d, *J* = 7.7 Hz, 1 H), 7.63 (d, *J* = 8.4 Hz, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 9.5, 23.3, 26.9, 54.7, 58.9, 63.2, 107.7, 113.3, 117.8, 118.6, 120.2, 124.5, 129.7, 135.0.

HRMS (EI): *m*/*z* calcd for $C_{17}H_{24}N_2$ [M$^+$]: 256.1939; found: 256.1938.

6-Fluoro-3-methyl-1-(1,1-dimethyl-2-pyrrolidin-1-ylethyl)-1*H*-indole (5cc)

Purified by preparative HPLC; mp 73 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.41–1.50 (m, 4 H), 1.63 (s, 6 H), 2.02–2.09 (m, 4 H), 2.22 (d, *J* = 0.7 Hz, 3 H), 2.95 (s, 2 H), 6.84 (ddd, *J* = 9.1, 9.0, 1.9 Hz, 1 H), 7.17 (q, *J* = 0.7 Hz, 1 H), 7.41–7.47 (m, 2 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 9.40, 23.3, 26.7, 54.6, 59.2, 63.1, 99.5 (d, $^2J_{C,F}$ = 27.0 Hz), 106.2 (d, $^2J_{C,F}$ = 24.3 Hz), 108.1, 119.4 (d, $^3J_{C,F}$ = 10.6 Hz), 125.1 (d, $^4J_{C,F}$ = 3.5 Hz), 126.5, 134.6 (d, $^3J_{C,F}$ = 12.3 Hz), 158.0 (d, $^1J_{C,F}$ = 233 Hz).

HRMS (EI): *m*/*z* calcd for $C_{17}H_{23}FN_2$ [M$^+$]: 274.1845; found: 274.1838.

1-(1-Benzyl-4-methylpiperidin-4-yl)-3-(1-methylethyl)-1*H*-indole (5dd)

Purified by flash chromatography (cyclohexane–*tert*-butyl methyl ether, 1:1) to an oil.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.29 (d, *J* = 6.8 Hz, 6 H), 1.54 (s, 3 H), 2.06–2.14 (m, 2 H), 2.35–2.50 (m, 6 H), 3.12 (sept, *J* = 6.8 Hz, 1 H), 3.47 (s, 2 H), 6.97 (dd, *J* = 8.1, 6.6 Hz, 1 H), 7.05 (dd, *J* = 8.6, 6.8, 0.6 Hz, 1 H), 7.20 (s, 1 H), 7.21–7.28 (m, 1 H), 7.29–7.34 (m, 4 H), 7.56 (d, *J* = 7.6 Hz, 1 H), 7.61 (d, *J* = 8.6 Hz, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 23.4, 24.8, 36.5, 49.5, 56.2, 62.0, 113.3, 117.9, 119.1, 120.2, 120.4, 121.0, 126.9, 128.1, 128.4, 128.7, 134.8, 138.5.

HRMS (EI): *m*/*z* calcd for $C_{24}H_{30}N_2$ + [M$^+$ + H]: 347.2482; found: 347.2484.

1-(1-Benzyl-4-methylpiperidin-4-yl)-6-fluoro-3-methyl-1*H*-indole (5ee)

Purified by preparative HPLC to yield an oil.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.49 (s, 3 H), 2.03–2.11 (m, 2 H), 2.22 (s, 3 H), 2.32–2.48 (m, 6 H), 3.45 (s, 2 H), 6.86 (ddd, *J* = 9.1, 9.0, 2.0 Hz, 1 H), 7.21–7.27 (m, 1 H), 7.28–7.34 (m, 5 H), 7.41 (dd, *J* = 11.7, 2.0 Hz, 1 H), 7.46 (dd, *J* = 9.0, 6.0 Hz, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 9.45, 24.8, 36.3, 49.5, 56.4, 62.0, 99.4 (d, $^2J_{C,F}$ = 27.0 Hz), 106.3 (d, $^2J_{C,F}$ = 24.5 Hz), 108.5, 119.5 (d, $^3J_{C,F}$ = 10.4 Hz), 124.3 (br), 126.7, 126.9, 128.1, 128.8, 134.1 (d, $^3J_{C,F}$ = 12.0 Hz), 138.5, 158.1 (d, $^1J_{C,F}$ = 233 Hz).

HRMS (EI): *m*/*z* calcd for $C_{22}H_{25}FN_2$ [M$^+$]: 336.2002; found: 336.1991.

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