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PAPER

Regiospecific epoxide opening: a facile approach for the synthesis of 3-hydroxy-3-aminomethylindolin-2-one derivatives

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A mild and eco-friendly method has been developed for aminolysis of 3-oxirane-indolin-2-ones with aliphatic and aromatic amines to afford 3-hydroxy-3-aminomethylindolin-2-ones. An enhancement in reaction rate was observed when water was used as the reaction medium. The reactions proceed regiospecifically to open the epoxide ring from the less-substituted end.

Introduction

Controls on the safe use and disposal of hazardous chemicals has forced the scientific community to adopt environmentally benign reactions and conditions. The largest contributor to the magnitude of the *E* factor[1] for a reaction is an organic solvent, many of which are ecologically harmful and require additional expense for their proper disposal. Modern approaches to reduce the environmental hazards of organic solvents are either to run reactions in solvent free conditions or to use solvents which have lesser or no detrimental effects on ecosystems.[2] Thus, organic reactions in water[3] have drawn the attention of researchers due to its unique characteristics like non-flammability, high dielectric constant, high boiling point, hydrogen bond donor/acceptor properties and above all economic benefits. Greener reactions are therefore of prime importance in organic chemistry.

β-Amino alcohols are important precursors in several synthetic drugs and natural products,[4] and are also employed for preparation of amino acids[5] and chiral auxiliaries.[6] One of the most straightforward methods to synthesize these templates would be the direct aminolysis of epoxides (oxiranes). However, the strategy is limited by sluggish reactions with weakly nucleophilic amines, poor regioselectivity and difficulties in handling sensitive epoxides. The electrophilic activation of epoxides is often carried out as a viable strategy to facilitate nucleophilic attack. Thus, the use of alumina,[7] alkali metal perchlorates and tetrafluoroborate,[8] silica gel in solvent free conditions,[9] metal triflates,[10] metal alkoxides,[11] metal halides,[12] zirconium sulfophenyl phosphonate,[13] microwave irradiation,[14] ultrasonification in water,[15] refluxing with hexafluoro-2-propanol,[16] ionic liquids,[17] iron(III) trifluoroacetate,[18] $Yb(OTf)_3$/supercritical carbon dioxide,[19] metal amides and triflamide[20] have been successfully tried, although these methodologies suffer from one or more reaction constraints, such as longer reaction times, high temperatures, high pressure, moderate yields, poor regioselectivity, the use of air- and moisture-sensitive catalysts, stoichiometric amounts of catalyst, costly reagents/catalysts and the fact that they mostly use organic halogenated solvents. Recent reports have indicated the use of water as a solvent for epoxide opening, providing much cleaner reaction conditions.

One-carbon higher homologues, γ-amino alcohols are found in various natural products like arundaphine, donaxaridine and paratunamide D, denoted as 3-substituted-3-hydroxyindolin-2-one alkaloids (Fig. 1).[21] 3-Substituted-3-hydroxyindolin-2-ones are known to possess antibacterial, antiprotozoal and anti-inflammatory activities, and have also demonstrated agonistic activity with progesterone receptors, their activity being influenced by the substituent at the C-3 position as well as the absolute configuration at the stereogenic centre.[22]

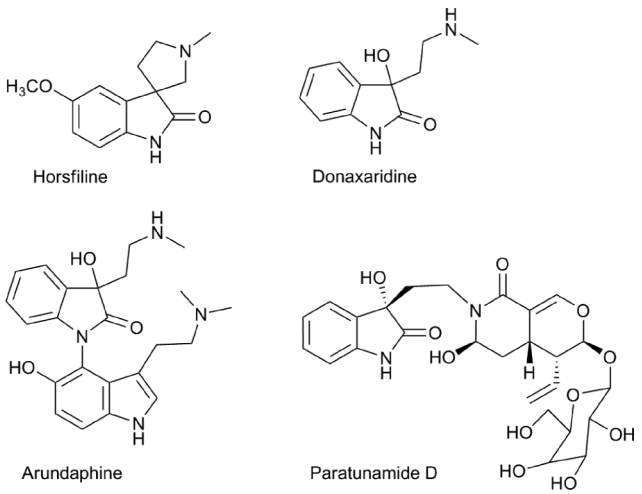

Fig. 1 Natural products containing the indolin-2-one scaffold.

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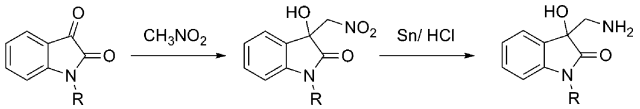
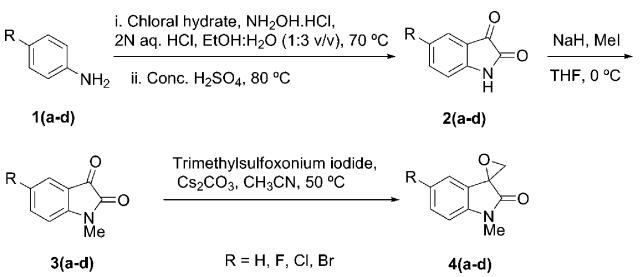
In continuation of our work on bioactive heterocycles,[23] the current investigations are mainly focused on 3-substituted-3-hydroxyindolin-2-one derivatives.[23e] The previously available report for the preparation of 3-hydroxy-3-aminomethylindolin-2-one employed hazardous conditions involving nitromethane and tin or palladium, and also needed a high temperature and a long reaction time (Scheme 1).[24] This prompted us to employ water as the reaction medium for the aminolysis of 3-oxirane-indolin-2-ones to obtain 3-hydroxy-3-aminomethylindolin-2-ones under very mild conditions. The reactions proceeded with high yields and regiospecificities, opening the oxirane ring from the less-substituted end.



Scheme 1 Reported method for the preparation of 3-hydroxy-3-aminomethylindolin-2-one.

Results and discussion

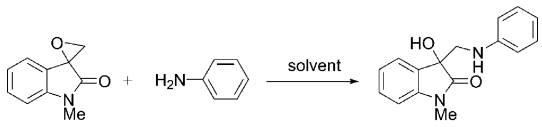
The oxirane derivatives of isatin were prepared as illustrated in Scheme 2. Isatins were synthesised from aniline by the Sandmeyer[25a] reaction using chloral hydrate under acidic conditions in a polar medium. Furthermore, it was *N*-methylated[25b] using NaH and methyl iodide in dry THF. Formation of the oxirane ring at the 3-position using trimethylsulfoxonium iodide and cesium carbonate at 50 °C in acetonitrile afforded the spiro[indolin3,2′-oxiran]-2-ones, which were subjected to aminolysis.



Scheme 2 Synthesis of 1-methylspiro(indolin3,2′-oxiran)-2-one.

To standardise the reaction conditions, a model reaction of 3-oxirane-indolin-2-one and aniline in different solvents was performed at room temperature (30 °C), and the results are summarized in Table 1. Non-polar solvents like toluene afforded poor yields, while an improvement was observed with polar solvents. Moderate yields were obtained with polar aprotic solvents, while the polar protic solvent EtOH indicated an enhancement in the reaction rate. The best result was obtained in an aqueous medium. Furthermore, the thermal dependency of the reaction in water was analyzed by carrying it out at five different temperatures from 0 to 50 °C at intervals of 10 °C. At low temperatures (0 and 10 °C), the reactions were sluggish, affording poor conversion to the desired product. The course of the reaction demonstrated a drastic change at 50 °C, attaining completion in 2 h.

Table 1 Effect of solvents[a]

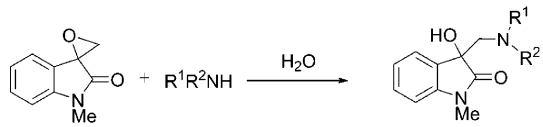


4a 7(i) 8(a)(i)

Entry	Solvent	Conversion[b] (%)
1	Toluene	10
2	CH_3CN	25
3	EtOAc	35
4	THF	30
5	DCM	20
6	EtOH	60
7	EtOH : H_2O (7 : 3)	76
8	H_2O	85

[a] Oxirane (1.0 mmol), amine (1.0 mmol), distilled water (5 mL), time 2 h, temp. 30 °C; [b] Determined by ^1H NMR.

Table 2 Reactions with various aliphatic amines[a]



4(a) 5(i-xi) R^1 = aryl/alkyl, R^2 = alkyl/H 6(a)(i-xi)

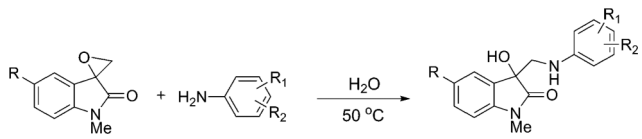
Entry	R_1	R_2	Product	Yield[b] (%)
1	CH_3	H	**6(a)(i)**	95
2	*i*-C_3H_7	H	**6(a)(ii)**	95
3	*t*-C_4H_9	H	**6(a)(iii)**	97
4	$C_6H_5CH_2$	H	**6(a)(iv)**	97
5	*cy*-C_6H_{11}	H	**6(a)(v)**	94
6	CH_3	CH_3	**6(a)(vi)**	98
7	C_6H_5	CH_3	**6(a)(vii)**	97
8	$C_6H_5CH_2$	$C_6H_5CH_2$	**6(a)(viii)**	98
9		$(-CH_2-)_4$	**6(a)(ix)**	98
10		$(-CH_2-)_5$	**6(a)(x)**	99
11		$(-CH_2CH_2OCH_2CH_2-)$	**6(a)(xi)**	99

[a] Oxirane (1.0 mmol), amine (1.0 mmol), distilled water (5 mL), time 30 min, temp. 30 °C. [b] Isolated yield.

The optimized conditions were further extended to different aliphatic and aromatic amines to generalise the scope of the reaction. The oxirane ring was opened from the less-hindered side, affording the products regiospecifically. In the case of aliphatic amines (Table 2), an acceleration in the course of the reaction was observed. The reaction was complete in 30 min at room temperature (30 °C). For aromatic amines, the reactions tolerated both electron withdrawing and electron donating groups alike, affording high yields of the desired products (Table 3).

Due to its hydrogen bond donor and acceptor properties, water is expected to activate both the reactants as they come into close proximity and to assist in overcoming the transition state barrier for bonding to occur.[3j] It can be speculated that water enhances the electrophilicity of the oxirane ring through hydrogen bonding, facilitating the nucleophilic attack of the amine. The hydrogen bonding between the amine hydrogen and oxygen of the amide carbonyl may provide additional stabilization to the transition state, allowing the epoxide to be

Table 3 Reactions with various aromatic amines[a]



Entry	R	R_1	R_2	Product	Yield[b] (%)
1	H	H	H	**8(a)(i)**	95
2	H	4-CH_3	H	**8(a)(ii)**	97
3	H	4-F	H	**8(a)(iii)**	98
4	H	4-Cl	H	**8(a)(iv)**	98
5	H	4-Br	H	**8(a)(v)**	97
6	H	2-Cl	4-F	**8(a)(vi)**	95
7	H	2-OH	5-NO_2	**8(a)(vii)**	98
8	H	3-NO_2	H	**8(a)(viii)**	96
9	F	H	H	**8(b)(i)**	96
10	F	4-CH_3	H	**8(b)(ii)**	95
11	F	4-F	H	**8(b)(iii)**	98
12	F	4-Cl	H	**8(b)(iv)**	97
13	F	4-Br	H	**8(b)(v)**	96
14	F	2-Cl	4-F	**8(b)(vi)**	97
15	F	2-OH	5-NO_2	**8(b)(vii)**	96
16	F	3-NO_2	H	**8(b)(viii)**	98
17	Cl	H	H	**8(c)(i)**	98
18	Cl	4-CH_3	H	**8(c)(ii)**	96
19	Cl	4-F	H	**8(c)(iii)**	97
20	Cl	4-Cl	H	**8(c)(iv)**	99
21	Cl	4-Br	H	**8(c)(v)**	98
22	Cl	2-Cl	4-F	**8(c)(vi)**	96
23	Cl	2-OH	5-NO_2	**8(c)(vii)**	98
24	Cl	3-NO_2	H	**8(c)(viii)**	97
25	Br	H	H	**8(d)(i)**	96
26	Br	4-CH_3	H	**8(d)(ii)**	95
27	Br	4-F	H	**8(d)(iii)**	98
28	Br	4-Cl	H	**8(d)(iv)**	97
29	Br	4-Br	H	**8(d)(v)**	98
30	Br	2-Cl	4-F	**8(d)(vi)**	98
31	Br	2-OH	5-NO_2	**8(d)(vii)**	96
32	Br	3-NO_2	H	**8(d)(viii)**	96

[a] Oxirane (1.0 mmol), amine (1.0 mmol), distilled water (5 mL), time 2 h, temp. 50 °C. [b] Isolated yield.

opened specifically from the less-hindered side. Based on these assumptions, a plausible mechanism is proposed in Fig. 2.

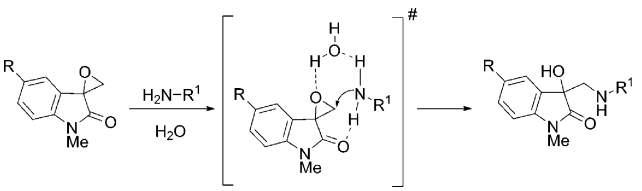


Fig. 2 A plausible mechanism for the reaction.

Experimental section

All reagents required for this study were purchased from commercial sources and used as such without further purification. Solvents were distilled and dried before use. ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, on a Bruker Avance DPX 400 (400 MHz) spectrometer in $CDCl_3/CD_3OD$ using TMS as an internal standard. The chemical shifts (δ) for ^{1}H and ^{13}C spectra are given in ppm relative to residual signals of the solvent. Coupling constants are given in Hz. The following abbreviations are used to indicate multiplicity: s, singlet; d, doublet; t, triplet; td, triple doublet; dt, double triplet; q, quartet; m, multiplet; brs, broad signal. HRMS were recorded on a Bruker Maxix TOF mass spectrometer. Melting points are uncorrected.

Typical procedure for oxirane formation

A mixture of trimethylsulfoxonium iodide (1.0 mmol) and cesium carbonate (2.0 mmol) in dry CH_3CN was stirred at 50 °C for 1 h under a nitrogen atmosphere to generate the sulfur ylide. To this, a solution of *N*-methylisatin (1.0 mmol) in dry CH_3CN (5 mL) was added dropwise over 10 min. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was filtered through a Celite® bed and the filtrate evaporated to dryness. The crude product thus obtained was purified by column chromatography on silica gel (60–120 mesh) using EtOAc : hexane (20 : 80) mixture as the eluent to afford the pure product.

1-Methylspiro[indoline-3,2′-oxiran]-2-one (4a). Pale yellow solid; m.p. = 84–86 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.28 (s, 3H), 3.44 (d, 1H, J = 6.6 Hz), 3.59 (d, 1H, J = 6.7 Hz), 6.93 (d, 1H, J = 7.8 Hz), 7.07–7.13 (m, 2H), 7.37–7.41 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.7, 54.1, 56.4, 108.9, 122.1, 122.7, 122.9, 130.4, 145.1, 172.8; ESI-HRMS(m/z): [M + Na]$^+$ calc. for $C_{10}H_9NO_2Na$, 198.0531, found 198.0525.

5-Fluoro-1-methylspiro[indoline-3,2′-oxiran]-2-one (4b). White solid; m.p. = 159–161 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.27 (s, 3H), 3.42 (d, 1H, J = 6.6 Hz), 3.60 (d, 1H, J = 6.7 Hz), 6.83–6.88 (m, 2H), 7.09 (dt, 1H, J = 2.6, 9.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.8, 54.3, 56.4, 109.5, 109.6, 110.2, 110.5, 116.6, 116.8, 124.4, 124.5, 141.0, 171.5; ESI-HRMS(m/z): [M + Na]$^+$ calc. for $C_{10}H_8FNO_2Na$, 216.0437, found 216.0431.

5-Chloro-1-methylspiro[indoline-3,2′-oxiran]-2-one (4c). Pale yellow solid, m.p. = 163–165 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.28 (s, 3H), 3.43 (d, 1H, J = 6.6 Hz), 3.59 (d, 1H, J = 6.7 Hz), 6.85 (d, 1H, J = 8.3 Hz), 7.09 (d, 1H, J = 2.1 Hz), 7.36 (dd, 1H, J = 2.2, 8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.8, 54.2, 56.1, 109.8, 122.6, 124.5, 128.5, 130.3, 143.6, 171.3; ESI-HRMS(m/z): [M + Na]$^+$ calc. for $C_{10}H_8ClNO_2Na$, 232.0141, found 232.0136.

5-Bromo-1-methylspiro[indoline-3,2′-oxiran]-2-one (4d). Pale brown solid, m.p. = 167–169 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.27 (s, 3H), 3.43 (d, 1H, J = 6.7 Hz), 3.59 (d, 1H, J = 6.6 Hz), 6.80 (d, 1H, J = 8.3 Hz), 7.23 (d, 1H, J = 1.9 Hz), 7.51 (dd, 1H, J = 2.0, 8.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.8, 54.3, 56.1, 108.5, 115.6, 124.8, 125.4, 133.2, 144.0, 171.2; ESI-HRMS(m/z): [M + Na]$^+$ calc. for $C_{10}H_8BrNO_2Na$, 275.9636, found 275.9631.

General procedure for epoxide aminolysis in water

A mixture of oxirane (1.0 mmol), amine (1.0 mmol) and distilled water (5 mL) was stirred at 50 °C until complete conversion of the epoxide was observed by TLC. The reaction mixture was extracted into Et_2O (10 mL), dried over anhydrous sodium sulfate and concentrated to obtain the crude product. The crude

products were either washed with cold hexane or eluted through a column of neutral alumina using EtOAc : hexane mixture as the eluent to afford the pure products.

3-Hydroxy-1-methyl-3-((methylamino)methyl)indolin-2-one [6(a)(i)]. Colourless semisolid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.49 (s, 3H), 2.91 (s, 2H), 3.17 (s, 3H), 3.70 (brs, 2H), 6.82 (d, 1H, J = 7.7 Hz), 7.09 (t, 1H, J = 7.6 Hz), 7.30–7.38 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.1, 36.5, 57.4, 73.9, 108.4, 123.1, 123.9, 129.2, 129.8, 143.7, 178.1; ESI-HRMS(m/z): [M + Na]$^+$ calc. for $C_{11}H_{14}N_2O_2Na$, 229.0953, found 229.0947.

3-Hydroxy-3-((isopropylamino)methyl)-1-methylindolin-2-one [6(a)(ii)]. Colourless liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.12 (dd, 6H, J = 6.3, 8.3 Hz), 2.84–2.94 (m, 3H), 3.16 (s, 3H), 3.85 (brs, 2H), 6.82 (d, 1H, J = 7.8 Hz), 7.09 (dt, 1H, J = 0.9, 7.6 Hz), 7.31–7.34 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.7, 23.0, 26.1, 49.3, 52.6, 73.2, 108.4, 123.1, 123.8, 129.4, 129.9, 143.7, 178.4; ESI-HRMS(m/z): [M + Na]$^+$ calc. for $C_{13}H_{18}N_2O_2Na$, 257.1266, found 257.1260.

3-((*tert*-Butylamino)methyl)-3-hydroxy-1-methylindolin-2-one [6(a)(iii)]. Pale yellow solid, m.p. = 94–95 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.29 (s, 9H), 2.81 (d, 1H, J = 12.4 Hz), 3.20 (s, 3H), 3.51 (t, 1H, J = 12.2 Hz), 6.86 (d, 1H, J = 7.8 Hz), 7.14 (t, 1H, J = 7.5 Hz), 7.36 (t, 1H, J = 7.7 Hz), 7.52 (d, 1H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.1, 27.0, 46.7, 53.9, 71.7, 108.7, 123.7, 124.2, 129.4, 130.1, 143.0, 177.5; ESI-HRMS(m/z): [M + Na]$^+$ calc. for $C_{14}H_{20}N_2O_2Na$, 271.1422, found 271.1417.

3-((Benzylamino)methyl)-3-hydroxy-1-methylindolin-2-one [6(a)(iv)]. Colourless liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.91 (q, 2H, J = 12.2, 24.8 Hz), 3.17 (s, 3H), 3.89 (dd, 2H, J = 13.0, 18.0 Hz), 6.82 (d, 1H, J = 7.6 Hz), 7.09 (t, 1H, J = 7.5 Hz), 7.27–7.38 (m, 7H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.1, 53.7, 54.5, 73.8, 108.4, 123.1, 123.9, 127.2, 128.1, 128.5, 129.0, 129.9, 139.6, 143.8, 178.2; ESI-HRMS(m/z): [M + Na]$^+$ calc. for $C_{17}H_{18}N_2O_2Na$, 305.1266, found 305.1260.

3-((Cyclohexylamino)methyl)-3-hydroxy-1-methylindolin-2-one [6(a)(v)]. Colourless semisolid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.06–1.27 (m, 6H), 1.57–1.61 (m, 1H), 1.69–1.76 (m, 2H), 1.85–1.88 (m, 1H), 1.92–1.95 (m, 1H), 2.42–2.47 (m, 1H), 2.81 (d, 1H, J = 12.1 Hz), 2.98 (d, 1H, J = 12.2 Hz), 3.15 (s, 3H), 6.80 (d, 1H, J = 7.8 Hz), 7.06–7.09 (m, 1H), 7.29–7.34 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.9, 25.0, 26.0, 33.7, 33.9, 73.4, 108.3, 123.0, 123.8, 129.5, 129.7, 143.8, 178.5; ESI-HRMS(m/z): [M + Na]$^+$ calc. for $C_{16}H_{22}N_2O_2Na$, 297.1579, found 297.1573.

3-((Dimethylamino)methyl)-3-hydroxy-1-methylindolin-2-one [6(a)(vi)]. Off white solid, m.p. = 134–136 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.43 (s, 6H), 2.76 (s, 2H), 3.18 (s, 3H), 4.55 (brs, 1H), 6.81 (d, 1H, J = 7.8 Hz), 7.08 (dt, 1H, J = 0.8, 7.6 Hz), 7.30–7.36 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.2, 47.8, 65.2, 74.2, 108.2, 122.9, 124.0, 129.7, 130.3, 143.9, 178.5; ESI-HRMS(m/z): [M + Na]$^+$ calc. for $C_{12}H_{16}N_2O_2Na$, 243.1109, found 243.1104.

3-Hydroxy-1-methyl-3-((methyl(phenyl)amino)methyl) indolin-2-one [6(a)(vii)]. White solid, m.p. = 118–120 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.91 (s, 3H), 3.16 (s, 3H), 3.27 (brs, 1H), 3.64 (d, 1H, J = 15.2 Hz), 3.82 (d, 1H, J = 15.2 Hz), 6.72–6.84 (m, 4H), 7.06 (t, 1H, J = 7.5 Hz), 7.19 (t, 2H, J = 8.2 Hz), 7.33 (t, 1H, J = 7.6 Hz), 7.44 (d, 1H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.3, 40.4, 61.0, 76.4, 108.4, 113.3, 117.8, 123.1, 124.8, 128.9, 130.0, 137.0, 143.6, 150.5, 177.8; ESI-HRMS(m/z): [M + Na]$^+$ calc. for $C_{17}H_{18}N_2O_2Na$, 305.1266, found 305.1260.

3-((Dibenzylamino)methyl)-3-hydroxy-1-methylindolin-2-one [6(a)(viii)]. Colourless liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.05 (d, 2H, J = 2.0 Hz), 3.08 (s, 3H), 3.52 (d, 2H, J = 13.6 Hz), 3.75 (brs, 1H), 3.82 (d, 2H, J = 13.6 Hz), 6.74 (d, 1H, J = 7.8 Hz), 6.83 (d, 1H, J = 7.3 Hz), 6.92 (t, 1H, J = 7.4 Hz), 7.17–7.19 (m, 4H), 7.21–7.31 (m, 7H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.2, 52.9, 59.2, 59.5, 74.8, 108.1, 123.1, 124.1, 127.0, 127.2, 128.3, 128.4, 128.5, 129.2, 129.5, 130.5, 138.6, 140.2, 143.9, 178.8; ESI-HRMS(m/z): [M + Na]$^+$ calc. for $C_{24}H_{24}N_2O_2Na$, 395.1735, found 395.1730.

3-Hydroxy-1-methyl-3-(pyrrolidin-1-ylmethyl)indolin-2-one [6(a)(ix)]. Pale brown solid, m.p. = 134–135 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.74–1.79 (m, 4H), 2.65–2.71 (m, 2H), 2.84–2.90 (m, 3H), 2.99 (d, 1H, J = 13.4 Hz), 3.17 (s, 3H), 3.85 (brs, 1H), 6.80 (d, 1H, J = 7.8 Hz), 7.07 (dt, 1H, J = 0.9, 7.6 Hz), 7.29–7.36 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.3, 26.2, 56.2, 62.2, 74.2, 108.1, 122.9, 124.0, 129.6, 130.5, 143.8, 178.5; ESI-HRMS(m/z): [M + Na]$^+$ calc. for $C_{14}H_{18}N_2O_2Na$, 269.1266, found 269.1260.

3-Hydroxy-1-methyl-3-(piperidin-1-ylmethyl)indolin-2-one [6(a)(x)]. Pale yellow solid, m.p. = 112–114 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.42–1.45 (m, 2H), 1.57–1.63 (m, 4H), 2.54–2.59 (m, 3H), 2.76–2.81 (m, 3H), 3.16 (s, 3H), 5.33 (brs, 1H), 6.79 (d, 1H, J = 7.5 Hz), 7.07 (dt, 1H, J = 0.9, 7.7 Hz), 7.26–7.32 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.8, 26.1, 26.4, 56.4, 64.3, 73.6, 108.1, 122.9, 123.9, 129.5, 130.8, 143.8, 174.4; ESI-HRMS(m/z): [M + Na]$^+$ calc. for $C_{15}H_{20}N_2O_2Na$, 283.1422, found 283.1417.

3-Hydroxy-1-methyl-3-(morpholinomethyl)indolin-2-one [6(a)(xi)]. White solid, m.p. = 163–164 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.52–2.57 (m, 2H), 2.73–2.84 (m, 4H), 3.17 (s, 3H), 3.65 (t, 4H, J = 4.3 Hz), 4.60 (brs, 1H), 6.81 (d, 1H, J = 7.7 Hz), 7.08 (t, 1H, J = 7.4 Hz), 7.30–7.35 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.2, 55.1, 64.2, 67.3, 74.3, 108.3, 123.0, 124.0, 129.8, 129.9, 143.9, 178.3; ESI-HRMS(m/z): [M + Na]$^+$ calc. for $C_{14}H_{18}N_2O_3Na$, 285.1215, found 285.1210.

3-Hydroxy-1-methyl-3-((phenylamino)methyl)indolin-2-one [8(a)(i)]. Pale yellow solid, m.p. = 125–126 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.18 (s, 3H), 3.34 (dd, 1H, J = 1.7, 12.8 Hz), 3.70 (dd, 1H, J = 10.0, 12.8 Hz), 3.77 (brs, 1H), 4.45 (d, 1H, J = 8.3 Hz), 6.70 (dd, 2H, J = 0.8, 8.4 Hz), 6.76 (t, 1H, J = 7.4 Hz), 6.86 (d, 1H, J = 7.8 Hz), 7.11–7.19 (m, 3H), 7.37 (dt, 1H, J = 1.2, 7.8 Hz), 7.47 (dd, 1H, J = 0.8, 7.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.2, 50.9, 74.5, 108.7, 114.0, 118.7, 123.4, 124.2, 128.4, 129.3, 130.3, 143.6, 147.7, 177.5; ESI-HRMS(m/z): [M + Na]$^+$ calc. for $C_{16}H_{16}N_2O_2Na$, 291.1109, found 291.1104.

3-Hydroxy-1-methyl-3-((*p*-tolylamino)methyl)indolin-2-one [8(a)(ii)]. White solid, m.p. = 99–101 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.24 (s, 3H), 3.19 (s, 3H), 3.31 (d, 1H, J = 12.8 Hz),

3.66 (t, 1H, J = 9.6 Hz), 3.78 (brs, 1H), 4.34 (brs, 1H), 6.64 (d, 2H, J = 7.2 Hz), 6.86 (d, 1H, J = 7.8 Hz), 6.99 (d, 2H, J = 7.7 Hz), 7.13 (t, 1H, J = 7.5 Hz), 7.37 (t, 1H, J = 7.7 Hz), 7.47 (d, 1H, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.4, 26.2, 51.3, 74.3, 108.6, 114.3, 123.3, 124.1, 128.1, 128.4, 129.7, 130.2, 143.7, 145.3, 177.6; ESI-HRMS(m/z): [M + Na]$^+$ calc. for $C_{17}H_{18}N_2O_2Na$, 305.1266, found 305.1260.

3-((4-Fluorophenylamino)methyl)-3-hydroxy-1-methylindolin-2-one [8(a)(iii)]. Pale yellow solid, m.p. = 127–129 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.17 (s, 3H), 3.34 (d, 1H, J = 12.8 Hz), 3.63 (d, 1H, J = 12.8 Hz), 3.87 (brs, 2H), 6.62–6.66 (m, 2H), 6.85–6.90 (m, 3H), 7.14 (dt, 1H, J = 0.8, 8.2 Hz), 7.38 (dt, 1H, J = 1.2, 7.8 Hz), 7.47 (dd, 1H, J = 0.7, 7.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.2, 51.7, 74.6, 108.7, 115.0, 115.1, 115.5, 115.7, 123.4, 124.2, 128.4, 130.3, 143.5, 143.9, 155.3, 157.6, 177.5; ESI-HRMS(m/z): [M + Na]$^+$ calc. for $C_{16}H_{15}FN_2O_2Na$, 309.1015, found 309.1010.

3-((4-Chlorophenylamino)methyl)-3-hydroxy-1-methylindolin-2-one [8(a)(iv)]. White solid, m.p. = 144–147 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.14 (s, 3H), 3.36 (d, 1H, J = 13.0 Hz), 3.63 (d, 1H, J = 13.0 Hz), 4.29 (brs, 2H), 6.56 (d, 2H, J = 8.6 Hz), 6.85 (d, 1H, J = 7.8 Hz), 7.07 (d, 2H, J = 8.6 Hz), 7.12 (t, 1H, J = 7.6 Hz), 7.37 (dt, 1H, J = 1.0, 7.8 Hz), 7.46 (dd, 1H, J = 0.8, 7.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.2, 50.9, 74.8, 108.7, 114.8, 122.9, 123.4, 124.2, 128.5, 129.0, 130.2, 143.4, 146.4, 177.5; ESI-HRMS(m/z): [M + Na]$^+$ calc. for $C_{16}H_{15}ClN_2O_2Na$, 325.0720, found 325.0714.

3-((4-Bromophenylamino)methyl)-3-hydroxy-1-methylindolin-2-one [8(a)(v)]. White solid, m.p. = 153–154 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.19 (s, 3H), 3.32 (d, 1H, J = 12.9 Hz), 3.54 (brs, 1H), 3.65 (t, 1H, J = 11.8 Hz), 4.52 (d, 1H, J = 9.6 Hz), 6.57 (d, 2H, J = 7.8 Hz), 6.88 (d, 1H, J = 7.8 Hz), 7.14 (t, 1H, J = 7.6 Hz), 7.25 (d, 2H, J = 9.3 Hz), 7.39 (t, 1H, J = 7.7 Hz), 7.46 (d, 1H, J = 7.3 Hz); ^{13}C NMR($CDCl_3$, 100 MHz) δ 26.3, 50.8, 74.6, 108.8, 110.2, 115.4, 123.4, 124.2, 128.3, 130.3, 131.9, 143.5, 146.7, 177.4; ESI-HRMS(m/z): [M + Na]$^+$ calc. for $C_{16}H_{15}BrN_2O_2Na$, 369.0215, found 369.0209.

3-((2-Chloro-4-fluorophenylamino)methyl)-3-hydroxy-1-methylindolin-2-one [8(a)(vi)]. White solid, m.p. = 131–133 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.20 (s, 3H), 3.46 (dd, 1H, J = 3.5, 12.8 Hz), 3.58 (brs, 1H), 3.66 (dd, 1H, J = 9.4, 12.8 Hz), 4.82 (dd, 1H, J = 2.8, 9.2 Hz), 6.66 (dd, 1H, J = 5.0, 9.0 Hz), 6.82–6.89 (m, 2H), 7.03 (dd, 1H, J = 2.9, 8.2 Hz), 7.14 (dt, 1H, J = 0.8, 7.7 Hz), 7.37–7.41 (m, 1H), 7.48 (dd, 1H, J = 0.8, 7.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.3, 50.9, 74.9, 108.8, 112.5, 112.6, 114.1, 114.4, 116.3, 116.6, 120.0, 120.1, 123.4, 124.2, 128.2, 130.4, 140.3, 143.5, 153.7, 156.1, 177.1; ESI-HRMS(m/z): [M + Na]$^+$ calc. for $C_{16}H_{14}ClFN_2O_2Na$, 343.0626, found 343.0620.

3-Hydroxy-3-((2-hydroxy-5-nitrophenylamino)methyl)-1-methylindolin-2-one [8(a)(vii)]. Brick red solid, m.p. = 177–180 °C; ^{1}H NMR (CD_3OD, 400 MHz) δ 3.16 (s, 3H), 3.64 (d, 1H, J = 13.2 Hz), 3.71 (d, 1H, J = 13.0 Hz), 5.48 (brs, 1H), 6.67 (d, 1H, J = 8.5 Hz), 6.98 (d, 1H, J = 7.6 Hz), 7.10 (t, 1H, J = 6.8 Hz), 7.31–7.35 (m, 2H), 7.44–7.49 (m, 2H); ^{13}C NMR (CD_3OD, 100 MHz) δ 26.4, 50.9, 77.0, 106.1, 109.9, 113.1, 115.1, 124.2, 125.3, 131.0, 138.9, 142.0, 144.9, 152.8, 166.0, 179.3; ESI-HRMS(m/z): [M + Na]$^+$ calc. for $C_{16}H_{15}N_3O_5Na$, 352.0909, found 352.0904.

3-Hydroxy-1-methyl-3-((3-nitrophenylamino)methyl)indolin-2-one [8(a)(viii)]. Yellow solid, m.p. = 142–144 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.19 (s, 3H), 3.43 (dd, 1H, J = 3.4, 13.0 Hz), 3.72–3.77 (m, 2H), 4.88 (dd, 1H, J = 2.8, 8.8 Hz), 6.88 (d, 1H, J = 7.8 Hz), 6.93–6.96 (m, 1H), 7.14 (dt, 1H, J = 0.8, 7.7 Hz), 7.25 (t, 1H, J = 8.1 Hz), 7.38 (dt, 1H, J = 1.2, 7.8 Hz), 7.42 (t, 1H, J = 2.3 Hz), 7.48 (dd, 1H, J = 0.7, 7.4 Hz), 7.52–7.54 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.3, 50.4, 74.7, 107.1, 108.9, 112.9, 119.6, 123.6, 124.2, 128.2, 129.7, 130.5, 143.3, 148.7, 149.3, 177.2; ESI-HRMS(m/z): [M + Na]$^+$ calc. for $C_{16}H_{15}N_3O_4Na$, 336.0960, found 336.0955.

5-Fluoro-3-hydroxy-1-methyl-3-((phenylamino)methyl)indolin-2-one [8(b)(i)]. Pale yellow solid, m.p. = 104–106 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.18 (s, 3H), 3.35 (d, 1H, J = 13.0 Hz), 3.66 (t, 1H, J = 12.1 Hz), 3.84 (brs, 1H), 4.45 (d, 1H, J = 9.2 Hz), 6.71 (d, 2H, J = 8.0 Hz), 6.76-6.81 (m, 2H), 7.08 (t, 1H, J = 8.8 Hz), 7.17–7.26 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.4, 50.9, 74.8, 109.2, 109.3, 112.5, 112.7, 114.0, 116.3, 116.5, 118.9, 129.3, 130.0, 130.1, 139.4, 147.5, 158.4, 160.8, 177.3; ESI-HRMS(m/z): [M + Na]$^+$ calc. for $C_{16}H_{15}FN_2O_2Na$, 309.1015, found 309.1010.

5-Fluoro-3-hydroxy-1-methyl-3-((*p*-tolylamino)methyl)indolin-2-one [8(b)(ii)]. White solid, m.p. = 148–149 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.24 (s, 3H), 3.17 (s, 3H), 3.32 (d, 1H, J = 12.8 Hz), 3.61 (t, 1H, J = 11.5 Hz), 3.86 (brs, 1H), 4.31 (d, 1H, J = 9.3 Hz), 6.64 (d, 2H, J = 7.3 Hz), 6.77–6.80 (m, 1H), 7.00 (d, 2H, J = 7.6 Hz), 7.07 (t, 1H, J = 8.9 Hz), 7.23 (d, 1H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.4, 26.4, 51.3, 74.6, 109.2, 109.3, 112.4, 112.7, 114.3, 116.3, 116.5, 128.4, 129.8, 130.0, 130.0, 139.5, 145.1, 158.4, 160.8, 177.3; ESI-HRMS(m/z): [M + Na]$^+$ calc. for $C_{17}H_{17}FN_2O_2Na$, 323.1172, found 323.1166.

5-Fluoro-3-((4-fluorophenylamino)methyl)-3-hydroxy-1-methylindolin-2-one [8(b)(iii)]. Pale brown solid, m.p. = 149–151 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.18 (s, 3H), 3.33 (d, 1H, J = 12.8 Hz), 3.58 (t, 1H, J = 11.6 Hz), 3.82 (brs, 1H), 4.36 (d, 1H, J = 8.9 Hz), 6.63–6.67 (m, 2H), 6.78–6.82 (m, 1H), 6.89 (t, 2H, J = 8.6 Hz), 7.08 (t, 1H, J = 8.8 Hz), 7.23 (d, 1H, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.4, 51.7, 74.6, 109.3, 109.4, 112.4, 112.7, 115.1, 115.2, 115.6, 115.8, 116.4, 116.6, 129.9, 129.9, 139.5, 143.7, 155.4, 157.8, 158.4, 160.8, 177.2; ESI-HRMS(m/z): [M + Na]$^+$ calc. for $C_{16}H_{14}F_2N_2O_2Na$, 327.0921, found 327.0916.

3-((4-Chlorophenylamino)methyl)-5-fluoro-3-hydroxy-1-methylindolin-2-one [8(b)(iv)]. White solid, m.p. = 155–156 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.17 (s, 3H), 3.33 (d, 1H, J = 13.0 Hz), 3.58–3.66 (m, 2H), 4.45 (d, 1H, J = 9.1 Hz), 6.60–6.62 (m, 2H), 6.78–6.80 (m, 1H), 7.05–7.13 (m, 3H), 7.20–7.26 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.4, 51.0, 74.8, 109.3, 109.4, 112.4, 112.7, 115.0, 116.4, 116.6, 123.4, 129.1, 129.9, 139.4, 146.1, 158.4, 160.8, 177.2; ESI-HRMS(m/z): [M + Na]$^+$ calc. for $C_{16}H_{14}ClFN_2O_2Na$, 343.0626, found 343.0620.

3-((4-Bromophenylamino)methyl)-5-fluoro-3-hydroxy-1-methylindolin-2-one [8(b)(v)]. White solid, m.p. = 159–162 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.16 (s, 3H), 3.34 (d, 1H, J =

13.0 Hz), 3.61 (t, 1H, J = 11.7 Hz), 3.83 (d, 1H, J = 4.9 Hz), 4.46 (d, 1H, J = 8.9 Hz), 6.56 (d, 2H, 7.4 Hz), 6.79–6.81 (m, 1H), 7.08 (t, 1H, J = 8.8 Hz), 7.21–7.25 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.4, 50.8, 74.8, 109.4, 110.4, 112.5, 112.7, 115.4, 116.4, 116.6, 132.0, 139.3, 146.6, 177.1; ESI-HRMS(m/z): [M + Na]$^+$ calc. for $C_{16}H_{14}BrFN_2O_2Na$, 387.0120, found 387.0115.

3-((2-Chloro-4-fluorophenylamino)methyl)-5-fluoro-3-hydroxy-1-methylindolin-2-one [8(b)(vi)]. White solid, m.p. = 110–112 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.18 (s, 3H), 3.47 (dd, 1H, J = 3.3, 13.3 Hz), 3.64 (dd, 1H, J = 9.5, 12.7 Hz), 3.83 (brs, 1H), 4.76 (d, 1H, J = 6.6 Hz), 6.65 (dd, 1H, J = 5.0, 8.9 Hz), 6.79–6.87 (m, 2H), 7.02–7.10 (m, 2H), 7.25 (dd, 1H, J = 2.2, 7.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.4, 50.9, 75.2, 109.4, 109.4, 112.5, 112.6, 112.7, 112.8, 114.2, 114.4, 116.4, 116.4, 116.6, 120.1, 120.2, 129.8, 129.9, 139.4, 140.1, 153.8, 156.2, 158.4, 160.8, 177.0; ESI-HRMS(m/z): [M + Na]$^+$ calc. for $C_{16}H_{13}ClF_2N_2O_2Na$, 361.0531, found 361.0526.

5-Fluoro-3-hydroxy-3-((2-hydroxy-5-nitrophenylamino)methyl)-1-methylindolin-2-one [8(b)(vii)]. Yellow solid, m.p. = 199–201 °C; ^{1}H NMR (CD_3OD, 400 MHz) δ 3.14 (s, 3H), 3.66 (dd, 2H, J = 13.9, 19.4 Hz), 4.59 (brs, 1H), 6.68 (d, 1H, J = 8.4 Hz), 6.93–6.95 (m, 1H), 7.04–7.08 (m, 1H), 7.25 (d, 1H, J = 7.4 Hz), 7.39 (s, 1H), 7.44 (d, 1H, J = 8.5 Hz); ^{13}C NMR (CD_3OD, 100 MHz) δ 25.2, 49.4, 75.9, 104.9, 109.2, 109.3, 111.7, 111.9, 112.1, 113.4, 115.4, 115.6, 131.6, 137.1, 139.5, 141.0, 150.5, 160.8, 177.5; ESI-HRMS(m/z): [M + Na]$^+$ calc. for $C_{16}H_{14}FN_3O_5Na$, 370.0815, found 370.0810.

5-Fluoro-3-hydroxy-1-methyl-3-((3-nitrophenylamino)methyl)indolin-2-one [8(b)(viii)]. Yellow solid, m.p. = 137–139 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.20 (s, 3H), 3.45 (dd, 1H, J = 3.4, 13.1 Hz), 3.73 (dd, 1H, J = 9.3, 13.1 Hz), 3.77 (brs, 1H), 4.86 (dd, 1H, J = 2.8, 9.1 Hz), 6.83 (dd, 1H, J = 4.0, 8.5 Hz), 6.97 (dd, 1H, J = 1.9, 7.8 Hz), 7.10 (dt, 1H, J = 2.6, 8.8 Hz), 7.24–7.29 (m, 2H), 7.44 (t, 1H, J = 2.2 Hz), 7.56–7.58 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.5, 50.5, 74.8, 107.2, 109.5, 109.6, 112.5, 112.8, 113.1, 116.6, 116.8, 119.7, 129.8, 139.2, 148.5, 149.3, 158.4, 160.9, 176.9; ESI-HRMS(m/z): [M + Na]$^+$ calc. for $C_{16}H_{14}FN_3O_4Na$, 354.0866, found 354.0861.

5-Chloro-3-hydroxy-1-methyl-3-((phenylamino)methyl)indolin-2-one [8(c)(i)]. Pale yellow solid, m.p. = 132–133 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.16 (s, 3H), 3.35 (d, 1H, J = 12.8 Hz), 3.67 (t, 1H, J = 11.4 Hz), 3.97 (brs, 1H), 4.39 (d, 1H, J = 9.2 Hz), 6.69–6.79 (m, 4H), 7.18 (t, 2H, J = 7.2 Hz), 7.34 (d, 1H, J = 8.2 Hz), 7.45 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.4, 50.9, 74.6, 109.6, 114.0, 119.0, 124.9, 128.8, 129.3, 130.1, 130.1, 142.1, 147.5, 177.1; ESI-HRMS(m/z): [M + Na]$^+$ calc. for $C_{16}H_{15}ClN_2O_2Na$, 325.0720, found 325.0714.

5-Chloro-3-hydroxy-1-methyl-3-((*p*-tolylamino)methyl)indolin-2-one [8(c)(ii)]. White solid, m.p. = 167–168 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.24 (s, 3H), 3.17 (s, 3H), 3.31 (d, 1H, J = 12.5 Hz), 3.63 (t, 1H, J = 8.5 Hz), 3.87 (brs, 1H), 4.29 (brs, 1H), 6.65 (d, 2H, J = 6.5 Hz), 6.78 (d, 1H, J = 6.8 Hz), 7.00 (d, 2H, J = 6.6 Hz), 7.34 (d, 1H, J = 8.1 Hz), 7.44 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.4, 26.3, 51.3, 74.4, 109.6, 114.4, 124.8, 128.4, 128.8, 129.8, 130.0, 130.1, 142.2, 145.1, 177.2; ESI-HRMS(m/z): [M + Na]$^+$ calc. for $C_{17}H_{17}ClN_2O_2Na$, 339.0876, found 339.0871.

5-Chloro-3-((4-fluorophenylamino)methyl)-3-hydroxy-1-methylindolin-2-one [8(c)(iii)]. White solid, m.p. = 88–90 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.15 (s, 3H), 3.33 (d, 1H, J = 12.9 Hz), 3.60 (d, 1H, J = 12.9 Hz), 3.96 (brs, 2H), 6.64 (m, 2H), 6.78 (d, 1H, J = 8.3 Hz), 6.88 (t, 2H, J = 8.6 Hz), 7.34 (dd, 1H, J = 1.8, 8.3 Hz), 7.44 (d, 1H, J = 1.9 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.4, 51.7, 74.6, 109.7, 115.2, 115.3, 115.6, 115.8, 124.9, 128.9, 130.0, 130.1, 142.0, 143.5, 155.5, 157.8, 177.1; ESI-HRMS(m/z): [M + Na]$^+$ calc. for $C_{16}H_{14}ClFN_2O_2Na$, 343.0626, found 343.0620.

5-Chloro-3-((4-chlorophenylamino)methyl)-3-hydroxy-1-methylindolin-2-one [8(c)(iv)]. Pale brown solid, m.p. = 171–173 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.18 (s, 3H), 3.32 (dd, 1H, J = 2.6, 13.0 Hz), 3.60–3.66 (m, 1H), 4.45 (d, 1H, J = 8.2 Hz), 6.63 (d, 2H, J = 8.4 Hz), 6.80 (d, 1H, J = 8.3 Hz), 7.13 (d, 2H, J = 8.4 Hz), 7.36 (d, 1H, J = 8.3 Hz), 7.44 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.4, 50.9, 74.6, 109.7, 115.0, 123.5, 124.8, 128.9, 129.1, 129.9, 130.2, 142.0, 146.1, 177.0; ESI-HRMS(m/z): [M + Na]$^+$ calc. for $C_{16}H_{14}Cl_2N_2O_2Na$, 359.0330, found 359.0325.

3-((4-Bromophenylamino)methyl)-5-chloro-3-hydroxy-1-methylindolin-2-one [8(c)(v)]. White solid, m.p. = 153–155 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.15 (s, 3H), 3.32 (dd, 1H, J = 3.3, 13.0 Hz), 3.61 (dd, 1H, J = 10.0, 13.0 Hz), 3.91 (brs, 1H), 4.41 (d, 1H, J = 9.7 Hz), 6.55 (d, 2H, J = 8.8 Hz), 6.78 (d, 1H, J = 8.3 Hz), 7.24 (d, 2H, J = 8.8 Hz), 7.33–7.36 (m, 1H), 7.43 (d, 1H, J = 1.9 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.4, 50.8, 74.7, 109.7, 110.5, 115.5, 124.8, 128.9, 130.0, 130.2, 132.0, 142.0, 146.5, 177.0; ESI-HRMS(m/z): [M + Na]$^+$ calc. for $C_{16}H_{14}BrClN_2O_2Na$, 402.9825, found 402.9819.

5-Chloro-3-((2-chloro-4-fluorophenylamino)methyl)-3-hydroxy-1-methylindolin-2-one [8(c)(vi)]. Off-white solid, m.p. = 99–101 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.17 (s, 3H), 3.44 (dd, 1H, J = 3.5, 13.0 Hz), 3.59 (brs, 1H), 3.64 (dd, 1H, J = 9.6, 13.0 Hz), 4.80 (dd, 1H, J = 3.1, 9.4 Hz), 6.67 (dd, 1H, J = 5.0, 9.0 Hz), 6.80 (d, 1H, J = 8.3 Hz), 6.86 (dt, 1H, J = 2.9, 8.2 Hz), 7.03 (dd, 1H, J = 2.9, 8.2 Hz), 7.35 (dd, 1H, J = 2.1, 8.3 Hz), 7.46 (d, 1H, J = 2.1 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.4, 50.9, 74.8, 109.8, 112.7, 112.7, 114.2, 114.5, 116.4, 116.7, 120.2, 120.3, 124.9, 128.9, 129.7, 130.3, 140.1, 142.1, 153.9, 156.3, 176.7; ESI-HRMS(m/z): [M + Na]$^+$ calc. for $C_{16}H_{13}Cl_2FN_2O_2Na$, 377.0236, found 377.0230.

5-Chloro-3-hydroxy-3-((2-hydroxy-5-nitrophenylamino)methyl)-1-methylindolin-2-one [8(c)(vii)]. Brick red solid, m.p. = 165–167 °C; ^{1}H NMR (CD_3OD, 400 MHz) δ 3.15 (s, 3H), 3.64 (dd, 2H, J = 13.0, 14.7 Hz), 6.64 (d, 1H, J = 8.2 Hz), 6.94 (d, 1H, J = 7.7 Hz), 7.31 (d, 1H, J = 8.1 Hz), 7.37 (s, 1H), 7.46 (s, 2H); ^{13}C NMR (CD_3OD, 100 MHz) δ 25.1, 49.4, 75.8, 101.8, 102.9, 104.8, 109.6, 112.0, 114.1, 124.5, 129.3, 131.6, 140.1, 144.8, 155.6, 177.8; ESI-HRMS(m/z): [M + Na]$^+$ calc. for $C_{16}H_{14}ClN_3O_5Na$, 386.0520, found 386.0514.

5-Chloro-3-hydroxy-1-methyl-3-((3-nitrophenylamino)methyl)indolin-2-one [8(c)(viii)]. Yellow solid, m.p. = 156–158 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.20 (s, 3H), 3.44 (dd, 1H, J = 3.2, 13.1 Hz), 3.46 (brs, 1H), 3.74 (dd, 1H, J = 9.4, 13.0 Hz),

4.83 (d, 1H, J = 6.9 Hz), 6.83 (d, 1H, J = 8.3 Hz), 6.99 (dd, 1H, J = 1.5, 8.2 Hz), 7.28–7.32 (m, 1H), 7.38 (dd, 1H, J = 2.0, 8.3 Hz), 7.46–7.48 (m, 2H), 7.59 (d, 1H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.4, 50.4, 74.6, 107.3, 109.8, 113.3, 119.8, 124.9, 129.1, 129.7, 129.8, 130.4, 141.9, 148.4, 149.2, 176.7; ESI-HRMS(m/z): [M + Na]$^+$ calc. for $C_{16}H_{14}ClN_3O_4Na$, 370.0571, found 370.0565.

5-Bromo-3-hydroxy-1-methyl-3-((phenylamino)methyl)indolin-2-one [8(d)(i)]. Pale brown solid, m.p. = 143–144 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.15 (s, 3H), 3.35 (d, 1H, J = 13.0 Hz), 3.67 (d, 1H, J = 13.0 Hz), 4.72 (brs, 2H), 6.69–6.79 (m, 4H), 7.18 (dt, 2H, J = 1.8, 7.4 Hz), 7.49 (dd, 1H, J = 2.0, 8.3 Hz), 7.58 (d, 1H, J = 2.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.3, 50.9, 74.6, 110.1, 114.0, 116.0, 118.9, 127.6, 129.3, 130.5, 133.0, 142.6, 147.5, 177.1; ESI-HRMS(m/z): [M + Na]$^+$ calc. for $C_{16}H_{15}BrN_2O_2Na$, 369.0215, found 369.0209.

5-Bromo-3-hydroxy-1-methyl-3-((*p*-tolylamino)methyl)indolin-2-one [8(d)(ii)]. White solid, m.p. = 161–163 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.26 (s, 3H), 3.18 (s, 3H), 3.33 (d, 1H, J = 12.9 Hz), 3.64 (t, 1H, J = 9.6 Hz), 3.87 (brs, 1H), 4.30 (d, 1H, J = 7.6 Hz), 6.66 (d, 2H, J = 8.1 Hz), 6.75 (d, 1H, J = 8.2 Hz), 7.02 (d, 2H, J = 8.2 Hz), 7.51 (td, 1H, J = 1.0, 1.9 Hz), 7.59 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.4, 26.3, 51.3, 74.4, 110.1, 114.4, 116.0, 127.6, 128.4, 129.8, 130.4, 133.0, 142.7, 145.1, 177.1; ESI-HRMS(m/z): [M + Na]$^+$ calc. for $C_{17}H_{17}BrN_2O_2Na$, 383.0371, found 383.0366.

5-Bromo-3-((4-fluorophenylamino)methyl)-3-hydroxy-1-methylindolin-2-one [8(d)(iii)]. White solid, m.p. = 175–177 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.15 (s, 3H), 3.32 (d, 1H, J = 12.8 Hz), 3.59 (t, 1H, J = 10.0 Hz), 4.03 (brs, 1H), 4.29 (d, 1H, J = 9.2 Hz), 6.61–6.65 (m, 2H), 6.73 (d, 1H, J = 8.2 Hz), 6.86–6.90 (m, 2H), 7.48–7.50 (m, 1H), 7.57 (d, 1H, J = 1.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.3, 51.6, 74.5, 110.2, 115.1, 115.2, 115.6, 115.8, 116.1, 127.6, 130.3, 133.1, 142.6, 143.7, 155.4, 157.8, 177.0; ESI-HRMS(m/z): [M + Na]$^+$ calc. for $C_{16}H_{14}BrFN_2O_2Na$, 387.0120, found 387.0115.

5-Bromo-3-((4-chlorophenylamino)methyl)-3-hydroxy-1-methylindolin-2-one [8(d)(iv)]. White solid, m.p. = 179–181 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.15 (s, 3H), 3.32 (dd, 1H, J = 3.0, 13.0 Hz), 3.62 (dd, 1H, J = 10.1, 13.0 Hz), 3.79 (brs, 1H), 4.42 (d, 1H, J = 7.5 Hz), 6.59–6.63 (m, 2H), 6.74 (d, 1H, J = 8.3 Hz), 7.10–7.13 (m, 2H), 7.50 (dd, 1H, J = 2.0, 8.3 Hz), 7.57 (d, 1H, J = 1.9 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.4, 50.9, 74.5, 110.2, 115.0, 116.1, 123.5, 127.6, 129.1, 130.2, 133.1, 142.5, 146.0, 176.9; ESI-HRMS(m/z): [M + Na]$^+$ calc. for $C_{16}H_{14}BrClN_2O_2Na$, 402.9825, found 402.9819.

5-Bromo-3-((4-bromophenylamino)methyl)-3-hydroxy-1-methylindolin-2-one [8(d)(v)]. Pale brown solid, m.p. = 157–159 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.16 (s, 3H), 3.32 (d, 1H, J = 12.9 Hz), 3.62 (t, 1H, J = 11.0 Hz), 3.76 (brs, 1H), 4.43 (d, 1H, J = 9.0 Hz), 6.57 (d, 2H, J = 7.5 Hz), 6.74 (d, 1H, J = 8.0 Hz), 7.25 (d, 2H, J = 7.9 Hz), 7.50 (d, 1H, J = 8.1 Hz), 7.57 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.4, 50.8, 74.4, 106.0, 110.2, 112.7, 115.6, 116.1, 127.6, 132.0, 133.2, 146.5, 161.8, 176.8; ESI-HRMS(m/z): [M + Na]$^+$ calc. for $C_{16}H_{14}Br_2N_2O_2Na$, 446.9320, found 446.9314.

5-Bromo-3-((2-chloro-4-fluorophenylamino)methyl)-3-hydroxy-1-methylindolin-2-one [8(d)(vi)]. White solid, m.p. = 107–109 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.17 (s, 3H), 3.44 (dd, 1H, J = 2.8, 12.9 Hz), 3.51 (d, 1H, J = 1.1 Hz), 3.64 (dd, 1H, J = 9.7, 12.4 Hz), 4.78 (d, 1H, J = 8.6 Hz), 6.67 (dd, 1H, J = 5.0, 8.9 Hz), 6.74 (d, 1H, J = 8.2 Hz), 6.83–6.88 (m, 1H), 7.02–7.05 (m, 1H), 7.49–7.51 (m, 1H), 7.59 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.3, 51.0, 74.7, 110.2, 112.7, 112.8, 114.2, 114.4, 116.1, 116.4, 116.7, 120.3, 127.6, 130.1, 133.2, 140.1, 142.6, 154.5, 156.3, 176.6; ESI-HRMS(m/z): [M + Na]$^+$ calc. for $C_{16}H_{13}BrClFN_2O_2Na$, 420.9731, found 420.9725.

5-Bromo-3-hydroxy-3-((2-hydroxy-5-nitrophenylamino)methyl)-1-methylindolin-2-one [8(d)(vii)]. Yellow solid, m.p. = 152–154 °C; ^{1}H NMR (CD_3OD, 400 MHz) δ 3.15 (s, 3H), 3.68 (dd, 2H, J = 13.6, 15.2 Hz), 4.61 (brs, 2H), 6.69 (d, 1H, J = 8.6 Hz), 6.89 (d, 1H, J = 8.3 Hz), 7.38 (d, 1H, J = 2.6 Hz), 7.44–7.47 (m, 2H), 7.58 (d, 1H, J = 2.0 Hz); ^{13}C NMR (CD_3OD, 100 MHz) δ 26.5, 50.7, 77.2, 106.4, 111.5, 113.1, 114.9, 116.7, 128.8, 133.3, 133.7, 138.5, 142.3, 144.0, 151.9, 178.8; ESI-HRMS(m/z): [M + Na]$^+$ calc. for $C_{16}H_{14}BrN_3O_5Na$, 430.0015, found 430.0009.

5-Bromo-3-hydroxy-1-methyl-3-((3-nitrophenylamino)methyl)indolin-2-one [8(d)(viii)]. Yellow solid, m.p. = 166–168 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.20 (s, 3H), 3.40–3.44 (m, 2H), 3.73 (dd, 1H, J = 9.6, 13.1 Hz), 4.81 (dd, 1H, J = 2.8, 9.3 Hz), 6.77 (d, 1H, J = 8.3 Hz), 6.97–7.00 (m, 1H), 7.29 (t, 1H, J = 8.1 Hz), 7.45 (t, 1H, J = 2.2 Hz), 7.52 (dd, 1H, J = 2.0, 8.1 Hz), 7.57–7.60 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.4, 50.4, 74.5, 107.2, 110.3, 113.3, 116.3, 119.8, 127.7, 129.8, 129.9, 133.3, 142.4, 148.4, 149.3, 176.6; ESI-HRMS(m/z): [M + Na]$^+$ calc. for $C_{16}H_{14}BrN_3O_4Na$, 414.0065, found 414.0060.

Conclusions

An eco-friendly process in water has been developed for the aminolysis of 3-oxirane-indolin-2-one derivatives with aliphatic and aromatic amines. The reactions afford high yields of 3-hydroxy-3-aminomethylindolin-2-ones with regiospecificity by opening the oxirane ring from the less-hindered side. The use of a green solvent, the simplicity of the reaction and the ease of product isolation make this a suitable method for the synthesis of these scaffolds.

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