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Versatile Synthesis of 2-(Substituted phenyl)-6,7-dihydro-1*H*-indol-4(5*H*)-ones from Morita–Baylis–Hillman Acetates of 2-Oxo-2-(substituted phenyl)acetaldehyde[‡]

Harikrishna Batchu[a] and Sanjay Batra*[a]

Keywords: Nitrogen heterocycles / Synthetic methods / Indole Derivatives / Morita–Baylis–Hillman

A versatile synthesis of 2-(substituted phenyl)-6,7-dihydro-1*H*-indol-4(5*H*)-ones from adducts of the Morita–Baylis–Hillman reaction between 2-oxo-2-(substituted phenyl)acetaldehydes and cyclohex-2-enone under mild conditions is described.

Introduction

6,7-Dihydro-1*H*-indole-4(5*H*)-one is an important structural motif because it serves as the starting material for construction of several indole-based compounds.[1] In addition, derivatives bearing this core are of considerable pharmacological interest and possess an array of biological activities including HSP90 inhibition,[2] soluble guanylate cyclase inhibition,[3] kv 1.5 blocking,[4] *anti*-psychotic,[5] GABAA-α5 receptor ligands,[6] antiproliferation and aurora kinase inhibition.[7] Furthermore 4-oxo-4,5,6,7-tetrahydroindole is a sub-structural unit of the biologically important alkaloids, mitomycins,[8] and several elegant syntheses of this structural unit have been reported. The first synthesis, reported in 1962 by Stetter and Lauterbach, involved treatment of 1,3-cyclohexadiones with α-haloketones leading to triones that upon reaction with ammonia or primary amines afforded substituted 4-oxo-4,5,6,7-tetrahydroindoles.[9] A variant to the procedure included alkylation of cyclohexa-1,3-dione with ethyl bromopyruvate to generate 4-oxotetrahydrobenzofuran-3-carboxylic acid that reacted with ammonia at high temperature to give the product.[10] In another strategy electro-oxidative coupling of cyclohexa-1,3-dione with ethyl vinyl ether followed by aminolysis was reported.[11] Heravi et al. disclosed that a potassium hydrogen sulfate catalyzed Ugi reaction between cyclohexylisocyanide, an aldehyde, a cyclic 1,3-dicarbonyl compound and ammonium acetate in acetonitrile produced 2,3-disubstituted 6,7-dihydro-1*H*-indole-4(5*H*)-ones.[12] Aoyagi et al. generated the same core through Pd-catalyzed oxidation of hydroxy-enamines.[13] Recently, during studies towards development of new anticancer agents, Huang's group synthesized this scaffold from 1,3-cyclohexanedione and 5-aminolevulinic acid hydrochloride.[14] More recently, Li's group reported a multi-component approach for this moiety through a microwave-promoted reaction between differently substituted enamines, phenylglyoxal monohydrate and acetic acid.[15,16]

The Morita–Baylis–Hillman (MBH) reaction has been used extensively in heterocyclic synthesis during the last decade.[17] In one of our research programs we have been exploring the synthetic potential of MBH derivatives for realizing aza-heterocycles.[18] We envisaged the synthesis of 6,7-dihydro-1*H*-indole-4(5*H*)-ones from the adduct of the MBH reaction between 2-oxo-2-phenylacetaldehyde and cyclohex-2-enone (Figure 1). A S_N2' reaction of a primary amine on the double bond of the cycloalkene unit of the MBH acetate followed by intramolecular cyclization involving the keto group is anticipated to afford the desired product. Here, we have developed a facile synthesis of substituted 6,7-dihydro-1*H*-indole-4(5*H*)-ones. The advantage of this method is that it is versatile and a wide range of primary amines can be used to give the N-substituted 6,7-dihydro-1*H*-indole-4(5*H*)-one unit.

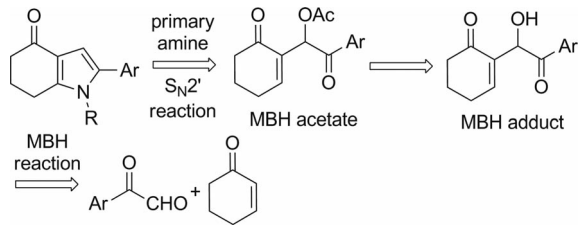

Figure 1. Retrosynthetic plan for the formation of 6,7-dihydro-1*H*-indole-4(5*H*)-one from the MBH adduct of 2-oxo-2-phenylacetaldehyde.

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[a] Medicinal and Process Chemistry Division, CSIR-Central Drug Research Institute, PO Box 173, Lucknow 226 001, India
Fax: +91-522-2623405, 2623938
E-mail: batra_san@yahoo.co.uk
s_batra@cdri.res.in

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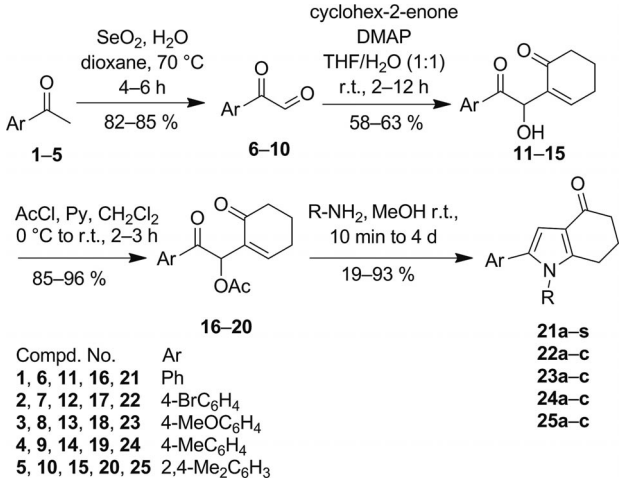
Results and Discussion

The initial step of this study was to investigate the MBH reaction of 2-oxo-2-phenylacetaldehyde with cyclohex-2-enone (Scheme 1). 2-Oxo-2-phenylacetaldehyde monohydrate (**6**) was treated with cyclohex-2-enone in the presence of 4-dimethylaminopyridine (DMAP) or imidazole in THF/water or dioxane/water as solvent. Following optimization, we found that performing the reaction in the presence of 0.4 equiv. of DMAP in THF/H_2O (1:1, v/v) gave MBH adduct **11** in 58% yield. Although the use of imidazole as catalyst also afforded **11**, the yield was relatively low. Adduct **11** was then efficiently transformed into the corresponding MBH acetate **16** through reaction with acetyl chloride in the presence of pyridine in dichloromethane for 3 h at room temperature. Subsequently **16** was treated with saturated methanolic ammonia at room temperature. The reaction was complete in 10 min to give the required 2-phenyl-6,7-dihydro-1*H*-indole-4(5*H*)-one (**21a**) as a solid product in 89% yield. Encouraged by this result we performed MBH reactions on 2-oxo-2-(substituted phenyl)-acetaldehydes[19] **7**–**10** with cyclohex-2-enone in the presence of DMAP in aqueous medium affording the respective adducts **12**–**15** in 58–63% yields. Treating compounds **12**–**15** with acetyl chloride under the optimized conditions afforded acetates **17**–**20** in 85–96% yields, respectively. Reactions of **17**–**20** with methanolic ammonia produced the desired 2-(substituted phenyl)-6,7-dihydro-1*H*-indole-4(5*H*)-ones **22a**–**25a** as solids in excellent yields without the need for purification.

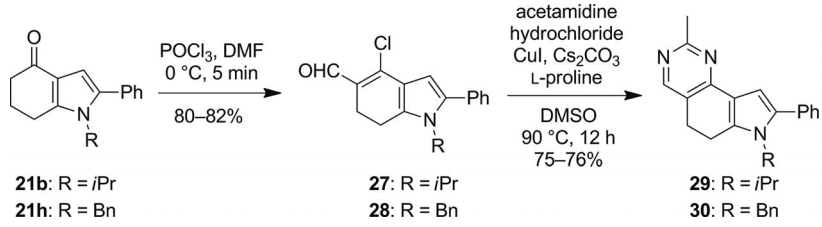


Scheme 1. Synthesis of substituted 6,7-dihydro-1*H*-indole-4(5*H*)-ones.

At this stage we proposed that the reaction sequence could be accomplished in a one-pot protocol. In order to investigate this possibility, 2-oxo-2-phenylacetaldehyde monohydrate (**6**) was added to a solution of cyclohex-2-enone and DMAP in dichloromethane and stirred at room temperature for 2 d. Thereafter, triethylamine and acetic anhydride were added and the reaction mixture was stirred for 15 min. Further methanolic ammonia was added, and the reaction was continued for a another 15 min before workup. Interestingly, this protocol resulted in the isolation of **21a** in 27% yield. Based on this result, it was considered best to isolate the MBH acetate before reaction with the primary amine.

Having optimized the conditions with ammonia, we set out to investigate the scope of this methodology for a variety of primary amines and MBH acetates. The results of the study are summarized in Table 1. The reactions of ammonia with MBH acetates **16**–**20** were complete in 10 min (Table 1, Entries 1–5), whereas those with isopropylamine (Table 1, Entries 6–10) or with *N*-(2-aminoethyl)morpholine took 30 min or 4 h, respectively, for completion (Table 1, Entries 11–15). The reactions of amino acids were also fast and complete within 30 min (Table 1, Entries 16–17). Similarly, the reaction with phenyl hydrazine was complete in 4 h to provide the product in 61% yield (Table 1, Entry 25). Due to our interest in development of new antimalarials, three quinoline derivatives were also prepared in good yields (Table 1, Entries 22–24).[20] In contrast to the previous results obtained, the reactions of anilines and hydrophobic amines were sluggish and the products were isolated in moderate to low yields only (Table 1, Entries 21, 26 and 28). In addition, 2-nitroaniline failed to react to furnish the expected product **21o** (Table 1, Entry 27). 1,3-Propanediamine gave mono- (**21r**) and di-indolone (**21s**) derivatives in almost equal quantities (Table 1, Entry 30). Amongst the MBH acetates, it was observed that the presence of an electron donating substitution on the aromatic ring (from the α-ketobenzaldehyde) significantly enhances the yields of the corresponding indolone derivatives (Table 1, Entries 3, 8, 13).

The chloroformylation of such indolones is already reported in the literature.[21] It was envisaged that the formation of the chloroformyl derivative of these indolones fol-



Scheme 2. Synthesis of 6,7-dihydro-5*H*-pyrrolo[2,3-*h*]quinazolines.

Table 1. Scope of the protocol with different primary amines.

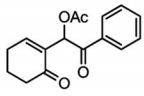
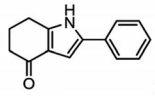
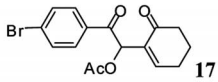
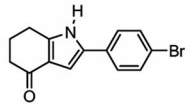
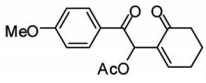
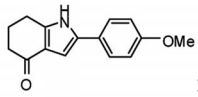
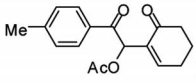
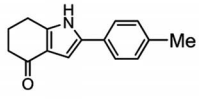
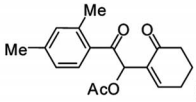
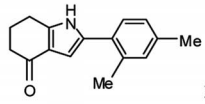
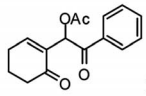
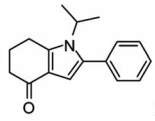
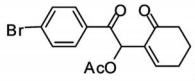
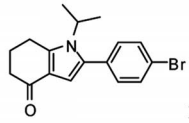
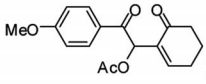
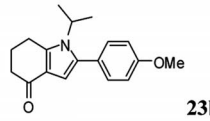
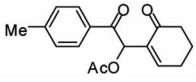
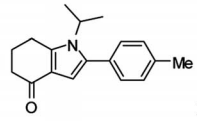
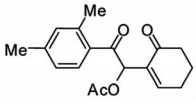
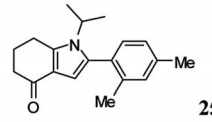
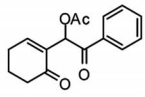
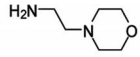
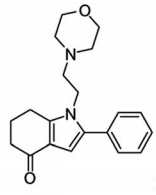
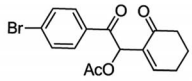
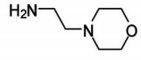
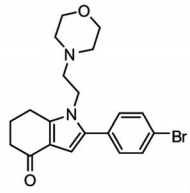
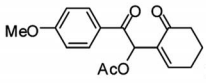
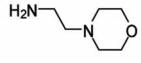
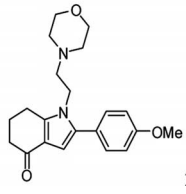
Entry	MBH acetate	Amine	Time	Product	Yield [%][a]
1	 **16**	NH_3	10 min	 **21a**	89[b]
2	 **17**	NH_3	10 min	 **22a**	74[b]
3	 **18**	NH_3	10 min	 **23a**	92[b]
4	 **19**	NH_3	10 min	 **24a**	76[b]
5	 **20**	NH_3	10 min	 **25a**	93[b]
6	 **16**		30 min	 **21b**	88
7	 **17**		30 min	 **22b**	85
8	 **18**		30 min	 **23b**	86
9	 **19**		30 min	 **24b**	73
10	 **20**		30 min	 **25b**	91
11	 **16**		4 h	 **21c**	73
12	 **17**		4 h	 **22c**	73
13	 **18**		4 h	 **23c**	90

Table 1. *(continued)*

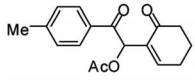
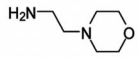
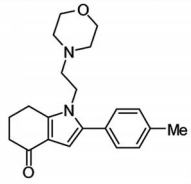
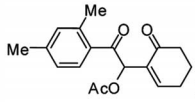
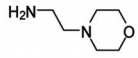
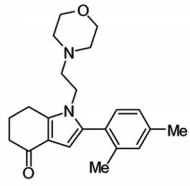
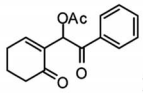
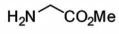
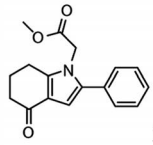
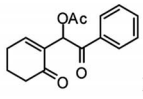
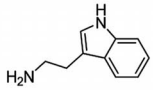
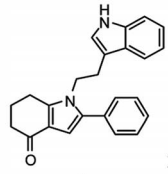
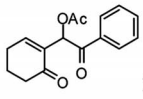
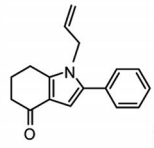
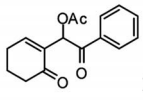
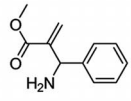
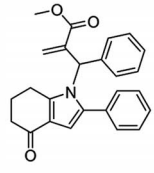
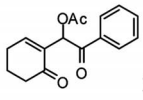
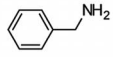
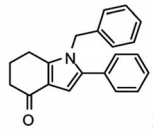
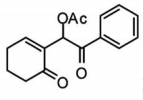
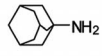
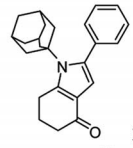
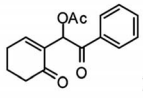
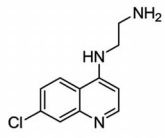
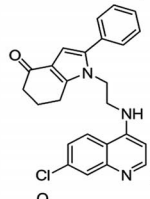
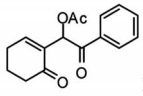
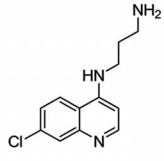
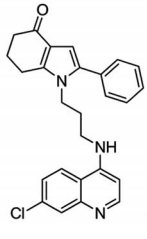
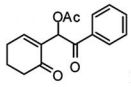
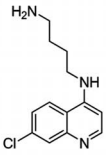
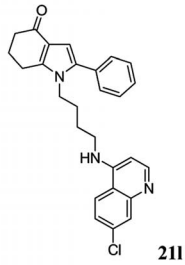
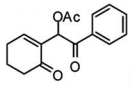
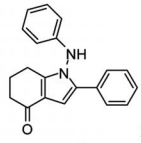
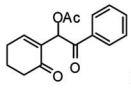
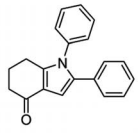
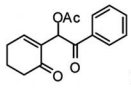
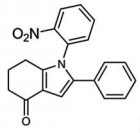
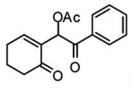
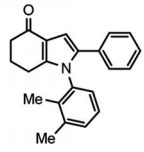
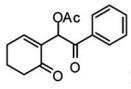
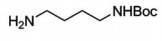
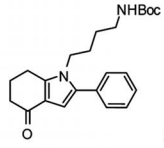
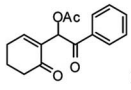
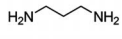
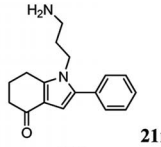
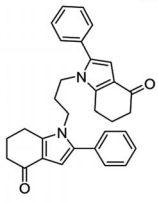
Entry	MBH acetate	Amine	Time	Product	Yield [%][a]
14	 **19**		4 h	 **24c**	70
15	 **20**		4 h	 **25c**	92
16	 **16**		30 min	 **21d**	80
17	 **16**		30 min	 **21e**	74
18	 **16**		1 d	 **21f**	71
19	 **16**		2 h	 **21g**	52
20	 **16**		12 h	 **21h**	90
21	 **16**		4 d	 **21i**	48
22	 **16**		12 h	 **21j**	75
23	 **16**		12 h	 **21k**	76

Table 1. *(continued)*

Entry	MBH acetate	Amine	Time	Product	Yield [%][a]
24	 **16**		12 h	 **21l**	75
25	 **16**		4 h	 **21m**	61
26	 **16**		1 d	 **21n**	35
27	 **16**		4 d	 **21o**	–
28	 **16**		4 d	 **21p**	22
29	 **16**		30 min	 **21q**	88
30	 **16**		30 min	 **21r** +  **21s**	20 + 19

[a] Isolated yield after column chromatography. [b] No column chromatography was required.

lowed by copper-mediated coupling reaction with amidines would furnish new pyrroloquinazolines (Scheme 2). In a representative study tetrahydroindolones **21b** and **21h** were subjected to Vilsmeier Haack reactions in the presence of DMF/$POCl_3$ resulting in the isolation of chloroformyl derivatives **27** and **28**, respectively. Treating compounds **27** and **28** with acetamidine hydrochloride in the presence of CuI, L-proline and Cs_2CO_3 at 90 °C in DMSO for 12 h produced the expected 6,7-dihydro-5*H*-pyrrolo[2,3-*h*]quinazolines **29** and **30** in good yields.

Conclusions

In summary, we have developed a new synthesis of tetrahydroindolones from MBH adducts in good yields. This

protocol is attractive because it employs readily-available starting materials and allows diverse functionality to be installed on the nitrogen atom of the indole.

Experimental Section

Melting points were determined in capillary tubes with a Precision melting point apparatus containing silicon oil. IR spectra were recorded by using a Perkin–Elmer RX I FTIR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded with either a Bruker DPX-200 or a Bruker Avance DRX-300 spectrometer with tetramethylsilane as an internal standard. MS (ESI) were recorded with a Thermo Finnigan LCQ Advantage, Ion Trap Mass spectrometer. HRMS spectra were recorded in the EI mode with an Agilent 6520 Q-TOF, LC-MS–MS mass spectrometer.

General Procedure for the Preparation of 6–10 as Exemplified for 2-Oxo-2-phenylacetaldehyde (6): Water (2.5 mL) was added to a stirred solution of SeO_2 (16.64 g, 150 mmol) in dioxane (40 mL) and heated to reflux until the SeO_2 dissolved. Compound **1** (10.0 g, 83.3 mmol) was added to the solution and the reaction was maintained at reflux temperatures. After the reaction was complete, as monitored by TLC, the mixture was filtered through a filter paper and then filtered through a pad of Celite. The filtrate was evaporated to afford a crude product that was purified by distillation under reduced pressure. The fraction separated at 95–97 °C/25 Torr yielded the product as a yellow liquid. This liquid was dissolved in hot water (40 mL) and allowed to crystallize to afford **6** as a white solid (10.39 g, 82%).

General Procedure for the Preparation of 11–15 with Cyclohex-2-enone as Exemplified for 11: 4-Dimethylaminopyridine (36 mg, 0.30 mmol) was added to a stirred solution of cyclohex-2-enone (87 mg, 0.905 mmol) in THF/water (2 mL, 1:1, v/v) at room temperature and stirred for 20 min. Compound **6** (100 mg, 0.66 mmol) was added to the mixture and the reaction was stirred for 12 h. The reaction mixture was diluted with water (5 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (6 mL), dried with anhydrous Na_2SO_4 and concentrated under reduced pressure to afford the crude product. Purification of the crude material by column chromatography (EtOAc/hexanes, 20:80, v/v) gave pure product **11** as brown oil (88 mg, 58%).

General Procedure for the Preparation of 16–20 as Exemplified for 16: Pyridine (1.5 mL, 18.42 mmol) was added to a stirred solution of **11** (1.82 g, 7.91 mmol) in dichloromethane (30 mL) at 0 °C and stirred for 10 min. Acetyl chloride (1.4 mL, 19.74 mmol) was added and the reaction mixture was stirred at room temperature for 3 h. After completion of the reaction, as monitored by TLC, water (25 mL) was added and the reaction was extracted with dichloromethane (3 × 25 mL). The combined organic layers were washed with brine (25 mL), dried with anhydrous Na_2SO_4 and concentrated under reduced pressure to afford the crude product. Purification of the crude material by column chromatography (EtOAc/hexanes, 10:90, v/v) gave pure product **16** as an off-white solid (1.83 g, 85%).

General Procedure for the Preparation of 21a–s and 22–25a–c as Exemplified for 2-Phenyl-1,5,6,7-tetrahydro-4*H*-indol-4-one (21a): Methanolic ammonia (1 mL) was added to a stirred solution of **16** (50 mg, 0.18 mmol) in methanol (10 mL) and allowed to stir at room temperature for 10 min. After completion of reaction, as monitored by TLC, the solvent was evaporated under reduced pressure to afford the crude product that was purified by triturating with an EtOAc/hexanes mixture to give pure product **16a** as a white solid (35 mg, 89%). M.p. 245–246 °C. R_f = 0.30 (hexanes/EtOAc, 3:2, v/v). IR (KBr): $\tilde{\nu}$ = 1630 (CO), 3441 (NH) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.18–2.24 (m, 2 H, CH_2), 2.52 (t, J = 6.3 Hz, 2 H, CH_2), 2.88 (t, J = 6.1 Hz, 2 H, CH_2), 6.82 (d, J = 1.5 Hz, 1 H, ArH), 7.26 (s, 1 H, ArH), 7.36–7.48 (m, 4 H, ArH), 8.65 (s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.0, 24.0, 38.0, 102.5, 121.9, 124.3, 127.2, 129.1, 131.9, 133.3, 145.1, 195.1 ppm. MS (ESI+): m/z = 212.2. HRMS: calcd. for $C_{14}H_{14}NO$ $[M + H]^+$ 212.1075; found 212.1083.

1-Isopropyl-2-phenyl-1,5,6,7-tetrahydro-4*H*-indol-4-one (21b): 88% as brown oil (45 mg from 55 mg). R_f = 0.32 (hexanes/EtOAc, 3:2, v/v). IR (neat): $\tilde{\nu}$ = 1648 (CO) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.46 (d, J = 7.0 Hz, 6 H, 2 CH_3), 2.20 (t, J = 6.1 Hz, 2 H, CH_2), 2.50 (t, J = 6.4 Hz, 2 H, CH_2), 3.00 (t, J = 6.0 Hz, 2 H, CH_2), 4.44–4.53 (m, 1 H, CH), 6.49 (s, 1 H, ArH), 7.31–7.41 (m, 5 H, ArH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.4, 24.4, 24.6, 38.0, 48.5, 105.7, 121.5, 128.0, 128.6, 130.0, 133.3, 136.4, 143.5, 194.5 ppm. MS (ESI+): m/z = 254.1. HRMS: calcd. for $C_{17}H_{20}NO$ $[M + H]^+$ 254.1545; found 254.1549.

1-(2-Morpholin-4-ylethyl)-2-phenyl-1,5,6,7-tetrahydro-4*H*-indol-4-one (21c): 73% as a brown solid (217 mg from 250 mg). M.p. 93–95 °C. R_f = 0.26 ($CHCl_3$/MeOH, 9:1, v/v). IR (KBr): $\tilde{\nu}$ = 1642 (CO) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.20–2.26 (m, 6 H, 3 × CH_2), 2.41 (t, J = 7.0 Hz, 2 H, CH_2), 2.52 (t, J = 6.4 Hz, 2 H, CH_2), 2.86 (t, J = 5.8 Hz, 2 H, CH_2), 3.58 (t, J = 4.2 Hz, 4 H, 2 × CH_2), 4.00 (t, J = 7.0 Hz, 2 H, CH_2), 6.55 (s, 1 H, ArH), 7.39–7.42 (m, 5 H, ArH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.6, 23.9, 38.0, 42.1, 53.9, 58.5, 66.8, 105.9, 120.7, 128.1, 128.7, 129.5, 132.5, 136.0, 144.8, 194.5 ppm. MS (ESI+): m/z = 325.2. HRMS: calcd. for $C_{20}H_{25}N_2O_2$ $[M + H]^+$ 325.1916; found 325.1920.

Methyl 2-(4-Oxo-2-phenyl-4,5,6,7-tetrahydro-1*H*-indol-1-yl)acetate (21d): 80% as an off-white solid (166 mg from 200 mg). M.p. 103–105 °C. R_f = 0.26 (hexanes/EtOAc, 3:2, v/v). IR (KBr): $\tilde{\nu}$ = 1647 (CO) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.20–2.26 (m, 2 H, CH_2), 2.53 (t, J = 6.2 Hz, 2 H, CH_2), 2.72 (t, J = 5.9 Hz, 2 H, CH_2), 3.79 (s, 3 H, CH_3), 4.58 (s, 2 H, CH_2), 6.60 (s, 1 H, ArH), 7.26 (s, 1 H, ArH), 7.30 (d, J = 1.7 Hz, 1 H, ArH), 7.37–7.41 (m, 3 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.2, 23.7, 37.9, 46.2, 53.0, 105.7, 121.2, 128.4, 128.9, 129.4, 131.8, 136.5, 145.3, 168.8, 194.3 ppm. MS (ESI+): m/z = 284.2. HRMS: calcd. for $C_{17}H_{18}NO_3$ $[M + H]^+$ 284.1287; found 284.1280.

1-[2-(1*H*-Indol-3-yl)ethyl]-2-phenyl-1,5,6,7-tetrahydro-4*H*-indol-4-one (21e): 74% as an off-white solid (192 mg from 200 mg). M.p. 197–198 °C. R_f = 0.15 ($CHCl_3$/MeOH, 9:1, v/v). IR (KBr): $\tilde{\nu}$ = 1633 (CO). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.46 (s, 6 H, CH_2), 2.86 (t, J = 6.9 Hz, 2 H, CH_2), 4.17 (t, J = 7.0 Hz, 2 H, CH_2), 6.62 (s, 1 H, ArH), 6.69 (s, 1 H, ArH), 7.00–7.06 (m, 1 H, ArH), 7.11–7.19 (m, 2 H, ArH), 7.34 (d, J = 8.2 Hz, 1 H, ArH), 7.41 (d, J = 2.7 Hz, 5 H, ArH), 8.11 (s, 1 H, NH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.4, 23.7, 26.7, 37.9, 45.5, 106.1, 111.5, 118.2, 119.6, 120.3, 122.2, 122.5, 127.1, 128.1, 128.8, 129.5, 132.8, 135.9, 136.3, 145.5, 194.8 ppm. MS (ESI+): m/z = 355.1. HRMS: calcd. for $C_{24}H_{23}N_2O$ $[M + H]^+$ 355.1810; found 355.1804.

1-Allyl-2-phenyl-1,5,6,7-tetrahydro-4*H*-indol-4-one (21f): 71% as a white solid (164 mg from 250 mg). M.p. 167–169 °C. R_f = 0.28 (hexanes/EtOAc, 3:2, v/v). IR (KBr): $\tilde{\nu}$ = 1650 (CO) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.19–2.20 (m, 2 H, CH_2), 2.52 (t, J = 5.8 Hz, 2 H, CH_2), 2.77 (t, J = 5.6 Hz, 2 H, CH_2), 4.48 (d, J = 1.7 Hz, 2 H, CH_2), 4.89 (d, J = 17.0 Hz, 1 H, CH), 5.24 (d, J = 10.4 Hz, 1 H, C*H*H), 5.85–5.97 (m, 1 H, CH*H*), 6.61 (s, 1 H, ArH), 7.38 (s, 5 H, ArH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.2, 23.9, 38.0, 46.9, 105.3, 116.8, 120.7, 128.0, 128.7, 129.1, 132.2,

133.5, 136.3, 145.1, 194.4 ppm. MS (ESI+): *m/z* = 252.1. HRMS: calcd. for $C_{17}H_{18}NO$ [M + H]$^+$ 252.1388; found 252.1383.

Methyl 2-[(4-Oxo-2-phenyl-4,5,6,7-tetrahydro-1*H*-indol-1-yl)(phenyl)methyl]acrylate (21g): 52% as a brown oil (147 mg from 200 mg). R_f = 0.27 (hexanes/EtOAc, 3:2, v/v). IR (neat): $\tilde{\nu}$ = 1653 (CO). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.98–2.04 (m, 2 H, CH_2), 2.14–2.16 (m, 2 H, CH_2), 2.39–2.43 (m, 2 H, CH_2), 3.66 (s, 3 H, OCH_3), 6.50 (s, 1 H, ArH), 6.57 (d, *J* = 1.2 Hz, 1 H, ArH), 6.63 (s, 1 H, ArH), 7.02–7.04 (m, 2 H, ArH) 7.27 (d, *J* = 5.0 Hz, 1 H, ArH), 7.32–7.33 (m, 1 H, ArH) 7.34–7.36 (m, 7 H, ArH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 24.4, 25.1, 37.8, 52.5, 60.0, 106.1, 124.3, 127.7, 128.2, 128.4, 128.6, 128.8, 128.9, 129.1, 129.7, 137.4, 139.6, 145.1, 194.9 ppm. MS (ESI+): *m/z* = 386.1. HRMS: calcd. for $C_{25}H_{24}NO_3$ [M + H]$^+$ 386.1756; found 386.1750.

1-Benzyl-2-phenyl-1,5,6,7-tetrahydro-4*H*-indol-4-one (21h): 90% as an off-white solid (996 mg from 1.00 g). M.p. 104–106 °C. R_f = 0.31 (hexanes/EtOAc, 3:2, v/v). IR (KBr): $\tilde{\nu}$ = 1650 (CO), 3441 (NH) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.11–2.15 (m, 2 H, CH_2), 2.51 (t, *J* = 6.2 Hz, 2 H, CH_2), 2.62 (t, *J* = 5.8 Hz, 2 H, CH_2), 5.13 (s, 2 H, CH_2), 6.68 (s, 1 H, ArH), 6.93 (d, *J* = 6.7 Hz, 2 H, ArH), 7.26 (s, 1 H, ArH), 7.27–7.34 (m, 7 H, ArH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.5, 23.8, 38.0, 48.1, 105.6, 121.0, 125.7, 127.7, 128.0, 128.7, 129.1, 136.8, 137.3, 145.2, 194.5 ppm. MS (ESI+): *m/z* = 302.1. HRMS: calcd. for $C_{21}H_{20}NO$ [M + H]$^+$ 302.1545; found 302.1439.

1-Adamantyl-2-phenyl-1,5,6,7-tetrahydro-4*H*-indol-4-one (21i): 48% as a white solid (122 mg from 200 mg). M.p. 217–219 °C. R_f = 0.32 (hexanes/EtOAc, 3:2, v/v). IR (KBr): $\tilde{\nu}$ = 1651 (CO), 3410 (NH) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.60 (s, 6 H, 3× CH_2), 2.05 (s, 3 H, 3× CH), 2.13–2.18 (m, 8 H, CH_2), 2.48 (t, *J* = 6.1 Hz, 2 H, CH_2), 3.21 (t, *J* = 5.8 Hz, 2 H, CH_2), 6.33 (s, 1 H, ArH), 7.30 (s, 5 H, ArH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 25.3, 29.2, 30.3, 35.9, 37.8, 43.8, 62.5, 109.6, 121.7, 127.5, 127.6, 130.6, 136.8, 138.5, 144.9, 194.8 ppm. MS (ESI+): *m/z* = 346.3. HRMS: calcd. for $C_{24}H_{28}NO$ [M + H]$^+$ 346.2171; found 346.2168.

1-[2-(7-Chloroquinolin-4-ylamino)ethyl]-2-phenyl-6,7-dihydro-1*H*-indol-4(5*H*)-one (21j): 75% as an off-white solid (343 mg from 300 mg). M.p. 52–54 °C. R_f = 0.40 ($CHCl_3$/MeOH, 9:1, v/v). IR (KBr): $\tilde{\nu}$ = 1636 (CO), 3247 (NH) cm^{-1}. ^{1}H NMR (300 MHz, [D$_6$]-DMSO): δ = 1.94–1.99 (m, 2 H, CH_2), 2.28–2.31 (m, 2 H, CH_2), 2.49 (s, 2 H, CH_2), 2.82 (t, *J* = 5.5 Hz, 2 H, CH_2), 4.17–4.19 (m, 2 H, CH_2), 5.92 (d, *J* = 5.3 Hz, 1 H, ArH), 6.32 (s, 1 H, CH_2), 7.35–7.36 (m, 5 H, ArH), 7.43–7.47 (m, 1 H, ArH), 7.76 (d, *J* = 2.1 Hz, 1 H, ArH), 8.05 (d, *J* = 9.2 Hz, 1 H, ArH), 8.19 (d, *J* = 5.3 Hz, 1 H, ArH) ppm. ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ = 21.1, 21.6, 23.3, 37.6, 42.2, 98.1, 105.0, 119.9, 123.8, 124.3, 127.3, 127.8, 128.5, 129.3, 131.9, 132.8, 133.6, 135.2, 145.0, 148.7, 149.5, 151.4, 192.6 ppm. MS (ESI+): *m/z* = 416.2. HRMS: calcd. for $C_{25}H_{23}ClN_3O$ [M + H]$^+$ 416.1530; found 416.1536.

1-[3-(7-Chloroquinolin-4-ylamino)propyl]-2-phenyl-6,7-dihydro-1*H*-indol-4(5*H*)-one (21k): 76% as a brown solid (359 mg from 300 mg). M.p. 62–64 °C. R_f = 0. 42 ($CHCl_3$/MeOH, 9:1, v/v). IR (KBr): $\tilde{\nu}$ = 1639 (CO), 3242 (NH) cm^{-1}. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 1.84–1.89 (m, 2 H, CH_2), 1.99–2.04 (m, 2 H, CH_2), 2.31–2.35 (m, 2 H, CH_2), 2.50 (t, *J* = 1.7 Hz, 2 H, CH_2), 2.85 (t, *J* = 5.5 Hz, 2 H, CH_2), 4.08–4.13 (m, 2 H, CH_2), 6.26 (d, *J* = 5.3 Hz, 1 H, ArH), 6.33 (s, 1 H, CH_2), 7.20–7.23 (m, 3 H, ArH), 7.33–7.36 (m, 2 H, ArH), 7.42–7.45 (m, 1 H, ArH), 7.78–7.82 (m, 1 H, ArH), 8.12 (d, *J* = 9.0 Hz, 1 H, ArH), 8.32–8.36 (m, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 21.7, 23.4, 28.5, 31.6, 37.6, 41.9, 98.7, 105.0, 119.8, 124.2, 124.4, 126.7, 127.6, 128.5, 128.6, 129.3, 132.1, 133.9, 135.2, 145.2, 150.4, 151.1, 192.9 ppm. MS (ESI+): *m/z* = 430.3. HRMS: calcd. for $C_{26}H_{25}ClN_3O$ [M + H]$^+$ 430.1686; found 430.1685.

1-[4-(7-Chloroquinolin-4-ylamino)butyl]-2-phenyl-6,7-dihydro-1*H*-indol-4(5*H*)-one (21l): 75% as a brown solid (366 mg from 300 mg). R_f = 0.48 ($CHCl_3$/MeOH, 9:1, v/v). M.p. 73–75 °C. IR (KBr): $\tilde{\nu}$ = 1639 (CO), 3241 (NH) cm^{-1}. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 1.47–1.49 (m, 2 H, CH_2), 1.56–1.58 (m, 2 H, CH_2), 2.03–2.07 (m, 2 H, CH_2), 2.31–2.36 (m, 2 H, CH_2), 2.82–2.86 (m, 2 H, CH_2), 3.12 (d, *J* = 5.1 Hz, 2 H, CH_2), 3.95–3.99 (m, 2 H, CH_2), 6.31 (s, 1 H, CH_2), 6.36 (d, *J* = 5.5 Hz, 1 H, ArH), 7.28–7.34 (m, 5 H, ArH), 7.43–7.47 (m, 1 H, ArH), 7.78 (d, *J* = 1.8 Hz, 1 H, ArH), 8.21 (d, *J* = 9.0 Hz, 1 H, ArH), 8.37 (d, *J* = 4.6 Hz, 1 H, ArH) ppm. ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ = 21.7, 23.4, 24.5, 27.4, 37.6, 41.7, 43.7, 98.7, 104.8, 117.1, 119.7, 124.3, 124.5, 126.2, 127.7, 128.6, 128.7, 132.3, 134.1, 135.1, 144.9, 150.4, 150.8, 192.7 ppm. MS (ESI+): *m/z* = 444.2. HRMS: calcd. for $C_{27}H_{27}ClN_3O$ [M + H]$^+$ 444.1843; found 444.1849.

1-Anilino-2-phenyl-1,5,6,7-tetrahydro-4*H*-indol-4-one (21m): 61% as dark brown oil (20 mg from 30 mg). R_f = 0.30 (hexanes/EtOAc, 3:2, v/v). IR (neat): $\tilde{\nu}$ = 1642 (CO), 3453 (NH) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.08–2.16 (m, 2 H, CH_2), 2.50–2.54 (m, *J* = 6.0 Hz, 2 H, CH_2), 2.70 (t, *J* = 6.1 Hz, 2 H, CH_2), 6.50 (d, *J* = 7.7 Hz, 2 H, ArH), 6.62 (s, 1 H, NH), 6.73 (s, 1 H, ArH), 6.92 (t, *J* = 7.3 Hz, 1 H, ArH), 7.20–7.30 (m, 5 H, ArH), 7.36–7.40 (m, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.5, 23.6, 29.9, 38.2, 103.7, 112.6, 118.8, 121.6, 127.9, 128.2, 128.6, 129.8, 130.8, 136.0, 146.2, 146.8, 194.4 ppm. MS (ESI+): *m/z* = 303.1. HRMS: calcd. for $C_{20}H_{19}N_2O$ [M + H]$^+$ 303.1497; found 303.1492.

1,2-Diphenyl-1,5,6,7-tetrahydro-4*H*-indol-4-one (21n): 35% as a white solid (74 mg from 200 mg). M.p. 232–234 °C. R_f = 0.27 (hexanes/EtOAc, 3:2, v/v). IR (KBr): $\tilde{\nu}$ = 1652 (CO). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.14 (s, 2 H, CH_2), 2.54–2.55 (m, 2 H, CH_2), 2.67 (t, *J* = 5.5 Hz, 2 H, CH_2), 6.80 (s, 1 H, ArH), 7.05–7.08 (m, 2 H, ArH) 7.16–7.17 (m, 5 H, ArH), 7.39–7.40 (m, 3 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.2, 23.9, 38.2, 105.9, 121.2, 127.1, 127.8, 128.3, 128.3, 128.4, 129.4, 131.9, 136.3, 137.7, 146.1, 194.8 ppm. MS (ESI+): *m/z* = 288.2. HRMS: calcd. for $C_{20}H_{18}NO$ [M + H]$^+$ 288.1388; found 288.1382.

1-(2,3-Dimethylphenyl)-2-phenyl-1,5,6,7-tetrahydro-4*H*-indol-4-one (21p): 22% as a brown solid (51 mg from 200 mg). M.p. 132–134 °C. R_f = 0.37 (hexanes/EtOAc, 3:2, v/v). IR (KBr): $\tilde{\nu}$ = 1651 (CO) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.76 (s, 3 H, CH_3), 2.07–2.15 (m, 2 H, CH_2), 2.26 (s, 3 H, CH_3), 2.32–2.41 (m, 2 H, CH_2), 2.52–2.59 (m, 2 H, CH_2), 6.83 (s, 1 H, ArH), 7.06–7.23 (m, 8 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 20.4, 22.7, 24.0, 38.2, 105.2, 121.0, 126.3, 127.1, 127.7, 128.3, 128.8, 128.9, 130.6, 132.2, 133.9, 134.9, 136.7, 138.8, 152.5, 194.8 ppm. MS (ESI+): *m/z* = 316.2 [M + H]$^+$. HRMS: calcd. for $C_{22}H_{22}NO$ [M + H]$^+$ 316.1701; found 316.1705.

Phenyl *tert*-Butyl 4-(4-Oxo-2-phenyl-4,5,6,7-tetrahydro-1*H*-indol-1-yl)butylcarbamate (21q): 88% as a brown oil (308 mg from 250 m g). R_f = 0.28 (hexanes/EtOAc, 3:2, v/v). IR (neat): $\tilde{\nu}$ = 1643 (CO), 3378 (NH) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26–1.35 (m, 2 H, CH_2), 1.42 (s, 9 H, 3 CH_3), 1.48–1.56 (m, 2 H, CH_2), 2.18–2.24 (m, 2 H, CH_2), 2.49–2.53 (m, 2 H, CH_2), 2.81 (t, *J* = 6.1 Hz, 2 H, CH_2), 2.97 (d, *J* = 5.9 Hz, 2 H, CH_2), 3.90 (t, *J* = 7.6 Hz, 2 H, CH_2), 4.36 (s, 1 H, NH), 6.54 (s, 1 H, ArH), 7.35–7.42 (m, 5 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.6, 23.9, 27.2, 27.8, 28.5, 38.0, 39.8, 44.1, 66.1, 79.4, 105.8, 120.6, 128.0, 128.8, 129.3, 132.7, 135.9, 144.5, 156.1, 194.4 ppm. MS (ESI+): *m/z* = 383.2. HRMS: calcd. for $C_{23}H_{31}N_2O_3$ [M + H]$^+$ 383.2335; found 383.2340.

1-(3-Aminopropyl)-2-phenyl-1,5,6,7-tetrahydro-4*H*-indol-4-one (21r): 20% as brown oil (48 mg from 250 mg). R_f = 0.24 ($CHCl_3$/MeOH, 9:1, v/v). IR (neat): $\tilde{\nu}$ = 1631 (CO), 3434 (NH) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.19–2.25 (m, 2 H, CH_2), 2.50–2.53 (m, 4 H, 2× CH_2), 2.83–2.88 (m, 3 H, 2 H of one CH_2 and 1 H of other CH_2), 2.96 (s, 1 H, 1 H of other CH_2), 3.98–4.02 (m, 2 H, CH_2), 6.55 (s, 1 H, ArH), 7.38–7.42 (m, 5 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.6, 24.0, 34.2, 38.0, 39.0, 42.3, 76.8, 105.8, 120.7, 128.1, 128.8, 129.4, 132.7, 136.0, 194.4 ppm. MS (ESI+): *m*/*z* = 269.2. HRMS: calcd. for $C_{17}H_{20}N_2O[M + H]^+$ 269.1654; found 269.1650.

1,1′-(Propane-1,3-diyl)bis[2-phenyl-6,7-dihydro-1*H*-indol-4(5*H*)-one] (21s): 19% as brown oil (39 mg from 250 mg). R_f = 0.84 ($CHCl_3$/MeOH, 9:1, v/v). IR (neat): $\tilde{\nu}$ = 1647 (CO). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.41 (s, 2 H, CH_2), 2.12 (s, 4 H, CH_2), 2.47 (s, 4 H, 2× CH_2), 2.54 (s, 4 H, 2× CH_2), 3.71 (s, 4 H, 2× CH_2), 6.55 (s, 2 H, ArH), 7.20 (s, 3 H, ArH), 7.37 (s, 7 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.3, 22.3, 22.8, 23.8, 29.1, 29.3, 29.5, 29.7, 29.8, 31.5, 31.8, 32.1, 34.0, 37.9, 41.4, 76.8, 106.2, 114.2, 121.0, 128.2, 129.0, 129.1, 132.2, 135.6, 139.4, 144.0, 194.2 ppm. MS (ESI+): *m*/*z* = 463.2. HRMS: calcd. for $C_{31}H_{31}N_2O_2$ $[M + H]^+$ 463.2386; found 463.2380.

2-(4-Bromophenyl)-1,5,6,7-tetrahydro-4*H*-indol-4-one (22a): 74% as a brown solid (55 mg from 90 mg). M.p. >250 °C. R_f = 0.28 (hexanes/EtOAc, 3:2, v/v). IR (KBr): $\tilde{\nu}$ = 1638 (CO), 3259 (NH) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.19 (t, *J* = 6.2 Hz, 2 H, CH_2), 2.49–2.53 (m, 2 H, CH_2), 2.87 (t, *J* = 6.1 Hz, 2 H, CH_2), 6.81 (d, *J* = 2.0 Hz, 1 H, ArH), 7.33 (d, *J* = 8.5 Hz, 2 H, ArH), 7.50 (d, *J* = 8.4 Hz, 2 H, ArH), 8.68 (s, 1 H, NH) ppm. ^{13}C NMR (50 MHz, $[D_6]$DMSO): δ = 22.2, 23.4, 37.4, 101.7, 119.3, 120.7, 125.2, 130.7, 131.2, 131.4, 145.2, 193.8 ppm. MS (ESI+): *m*/*z* = 290.1. HRMS: calcd. for $C_{14}H_{13}BrNO$ $[M + H]^+$ 290.0181; found 290.0185.

2-(4-Bromophenyl)-1-isopropyl-1,5,6,7-tetrahydro-4*H*-indol-4-one (22b): 85% as brown oil (48 mg from 60 mg). R_f = 0.32 (hexanes/EtOAc, 3:2, v/v). IR (neat): $\tilde{\nu}$ = 1630 (CO) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.45 (d, *J* = 7.1 Hz, 6 H, 2 CH_3), 2.17–2.24 (m, 2 H, CH_2), 2.48–2.52 (m, 2 H, CH_2), 2.99 (t, *J* = 6.2 Hz, 2 H, CH_2), 4.39–4.50 (m, 1 H, CH), 6.49 (s, 1 H, ArH), 7.18 (d, *J* = 8.3 Hz, 2 H, ArH), 7.54 (d, *J* = 8.3 Hz, 2 H, ArH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.4, 24.3, 24.5, 37.7, 48.6, 106.3, 116.0, 121.5, 122.4, 131.5, 131.8, 132.1, 132.8, 133.0, 135.2, 144.1, 195.0 ppm. MS (ESI+): *m*/*z* = 332.1. HRMS: calcd. for $C_{17}H_{19}BrNO$ $[M + H]^+$ 332.0650; found 332.0647.

2-(4-Bromophenyl)-1-(2-morpholin-4-ylethyl)-1,5,6,7-tetrahydro-4*H*-indol-4-one (22c): 73% as a white solid (104 mg from 124 mg). M.p. 125–128 °C. R_f = 0.26 ($CHCl_3$/MeOH, 9:1, v/v). IR (KBr): $\tilde{\nu}$ = 1628 (CO) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.19–2.22 (m, 2 H, CH_2), 2.29 (t, *J* = 4.5 Hz, 4 H, 2× CH_2), 2.42 (t, *J* = 6.9 Hz, 2 H, CH_2), 2.49–2.54 (m, 2 H, CH_2), 2.86 (t, *J* = 6.1 Hz, 2 H, CH_2), 3.58–3.61 (m, 4 H, 2× CH_2), 3.99 (t, *J* = 7.0 Hz, 2 H, CH_2), 6.55 (s, 1 H, ArH), 7.26 (d, *J* = 8.3 Hz, 2 H, ArH), 7.55 (d, *J* = 8.4 Hz, 2 H, ArH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.6, 22.6, 23.8, 24.9, 37.9, 42.3, 50.0, 54.0, 58.5, 66.8, 106.3, 120.8, 130.9, 131.5, 132.0, 134.7, 145.2, 194.4 ppm. MS (ESI+): *m*/*z* = 403.1. HRMS: calcd. for $C_{20}H_{24}BrN_2O_2$ $[M + H]^+$ 403.1021; found 403.1018.

2-(4-Methoxyphenyl)-1,5,6,7-tetrahydro-4*H*-indol-4-one (23a): 92% as a brown solid (44 mg from 60 mg). M.p. 247–248 °C. R_f = 0.28 (hexanes/EtOAc, 3:2, v/v). IR (KBr): $\tilde{\nu}$ = 1634 (CO), 3257 (NH) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.16–2.22 (m, 2 H, CH_2), 2.50 (t, *J* = 6.3 Hz, 2 H, CH_2), 2.86 (t, *J* = 6.0 Hz, 2 H, CH_2), 3.82 (s, 3 H, CH_3), 6.68 (d, *J* = 2.2 Hz, 1 H, ArH), 6.92 (d, *J* = 8.7 Hz, 2 H, ArH), 7.40 (d, *J* = 8.7 Hz, 2 H, ArH), 8.62 (s, 1 H, NH) ppm. ^{13}C NMR (50 MHz, $[D_6]$DMSO): δ = 22.2, 23.6, 37.7, 55.1, 100.2, 114.3, 120.7, 124.7, 125.2, 132.3, 144.7, 158.1, 192.8 ppm. MS (ESI+): *m*/*z* = 242.2. HRMS: calcd. for $C_{15}H_{16}NO_2$ $[M + H]^+$ 242.1181; found 242.1176.

1-Isopropyl-2-(4-methoxyphenyl)-1,5,6,7-tetrahydro-4*H*-indol-4-one (23b): 86% as a brown solid (161 mg from 200 mg). M.p. 103–108 °C. R_f = 0.32 (hexanes/EtOAc, 3:2, v/v). IR (KBr): $\tilde{\nu}$ = 1645 (CO) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.44 (d, *J* = 6.6 Hz, 6 H, 2 CH_3), 2.20 (s, 2 H, CH_2), 2.52 (s, 2 H, CH_2), 2.99 (s, *J* = 6.0 Hz, 2 H, CH_2), 3.85 (s, 3 H, CH_3), 4.43–4.54 (m, 1 H, CH), 6.45 (s, 1 H, ArH), 6.94 (d, *J* = 7.8 Hz, 2 H, ArH), 7.22–7.26 (m, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.4, 24.4, 24.5, 37.9, 48.3, 55.4, 105.3, 114.0, 121.3, 125.6, 131.3, 136.1, 143.1, 159.5, 194.4 ppm. MS (ESI+): *m*/*z* = 284.2. HRMS: calcd. for $C_{18}H_{22}NO_2$ $[M + H]^+$ 284.1651; found 284.1648.

2-(4-Methoxyphenyl)-1-(2-morpholinoethyl)-6,7-dihydro-1*H*-indol-4(5*H*)-one (23c): 90% as brown oil (53 mg from 50 mg). R_f = 0.28 ($CHCl_3$/MeOH, 9:1, v/v). IR (neat): $\tilde{\nu}$ = 1647 (CO) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.18–2.24 (m, 4 H, 2× CH_2), 2.33 (s, 2 H, CH_2), 2.49–2.53 (m, 4 H, 2× CH_2), 2.90 (s, 2 H, CH_2), 3.66 (s, 4 H, 2× CH_2), 3.85 (s, 5 H, CH_3 and CH_2), 6.50 (s, 1 H, ArH), 6.96 (d, *J* = 8.4 Hz, 2 H, ArH), 7.29 (d, *J* = 8.7 Hz, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.7, 23.9, 29.8, 38.0, 53.8, 55.5, 66.6, 105.7, 114.2, 120.7, 124.8, 130.9, 144.4, 159.7, 194.3 ppm. MS (ESI+): *m*/*z* = 355.2. HRMS: calcd. for $C_{21}H_{27}N_2O_3$ $[M + H]^+$ 355.1810; found 355.1804.

2-(4-Methylphenyl)-1,5,6,7-tetrahydro-4*H*-indol-4-one (24a): 76% as a white solid (120 mg from 200 mg). M.p. >250 °C. R_f = 0.29 (hexanes/EtOAc, 3:2, v/v). IR (KBr): $\tilde{\nu}$ = 1631 (CO), 3257 (NH) cm^{-1}. ^1H NMR (300 MHz, $[D_6]$DMSO): δ = 2.01–2.05 (m, 2 H, CH_2), 2.30 (s, 3 H, CH_3), 2.31 (s, 2 H, CH_2), 2.80 (t, *J* = 5.7 Hz, 2 H, CH_2), 6.6 (d, *J* = 1.7 Hz, 1 H, ArH), 7.17 (d, *J* = 7.8 Hz, 2 H, ArH), 7.53 (d, *J* = 7.9 Hz, 2 H, ArH), 11.7 (s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, $[D_6]$DMSO): δ = 20.7, 22.2, 23.6, 37.7, 65.4, 100.9, 120.7, 123.8, 129.2, 129.4, 132.3, 135.7, 144.9, 192.8 ppm. MS (ESI+): *m*/*z* = 226.1. HRMS: calcd. for $C_{15}H_{16}NO$ $[M + H]^+$ 226.1232; found 226.1226.

1-Isopropyl-2-(4-methylphenyl)-1,5,6,7-tetrahydro-4*H*-indol-4-one (24b): 73% as a white solid (170 mg from 250 mg). R_f = 0.32 (hexanes/EtOAc, 3:2, v/v). IR (KBr): $\tilde{\nu}$ = 1657 (CO) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.45 (d, *J* = 7.1 Hz, 6 H, 2 CH_3), 2.17–2.21 (m, 2 H, CH_2), 2.40 (s, 3 H, CH_3), 2.51 (t, *J* = 6.4 Hz, 2 H, CH_2), 3.00 (t, *J* = 6.1 Hz, 2 H, CH_2), 4.46–4.50 (m, 1 H, CH), 6.46 (s, 1 H, ArH), 7.21 (s, 4 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.4, 22.4, 24.4, 24.6, 38.0, 48.4, 105.5, 121.5, 129.3, 130.0, 130.4, 136.4, 138.0, 143.2, 194.4 ppm. MS (ESI+): *m*/*z* = 268.1. HRMS: calcd. for $C_{18}H_{22}NO$ $[M + H]^+$ 268.1701; found 268.17011.

1-(2-Morpholinoethyl)-2-*p*-tolyl-6,7-dihydro-1*H*-indol-4(5*H*)-one (24c): 70% as an off-white solid (207 mg from 250 mg). M.p. 122–124 °C. R_f = 0.28 ($CHCl_3$/MeOH, 9:1, v/v). IR (KBr): $\tilde{\nu}$ = 1643 (CO) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.47–2.51 (m, 2 H, CH_2), 2.55 (s, 4 H, 2× CH_2), 2.68 (s, 3 H, CH_3), 2.71–2.74 (m, 2 H, CH_2), 2.77–2.82 (m, 2 H, CH_2), 3.14 (t, *J* = 6.1 Hz, 2 H, CH_2), 3.89 (s, 4 H, 2× CH_2), 4.29 (s, 2 H, CH_2), 6.80 (s, 1 H, ArH), 7.51–7.54 (m, 4 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.4, 22.6, 23.9, 30.4, 34.3, 38.0, 42.2, 53.9, 58.6, 66.9, 105.6, 120.6, 125.6, 129.4, 135.9, 136.0, 138.0, 144.6, 194.3 ppm. MS (ESI+): *m*/*z* = 339.2. HRMS: calcd. for $C_{21}H_{27}N_2O_2$ 339.2073; found 339.2078.

2-(2,4-Dimethylphenyl)-1,5,6,7-tetrahydro-4*H*-indol-4-one (25a): 93% as an off white solid (148 mg from 200 mg). M.p. 242–244 °C.

R_f = 0.29 (hexanes/EtOAc, 3:2, v/v). IR (KBr): $\tilde{\nu}$ = 1629 (CO), 3414 (NH) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.16–2.24 (m, 2 H, CH_2), 2.34 (s, 3 H, CH_3), 2.40 (s, 3 H, CH_3), 2.52 (t, J = 6.3 Hz, 2 H, CH_2), 2.87 (t, J = 6.1 Hz, 2 H, CH_2), 6.59 (d, J = 2.4 Hz, 1 H, ArH), 7.03–7.09 (m, 2 H, ArH), 7.20 (d, J = 7.7 Hz, 1 H, ArH), 8.31 (s, 1 H, NH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$/[D_6]DMSO): δ = 20.4, 20.6, 22.0, 23.4, 37.4, 69.4, 70.0, 103.8, 120.0, 125.9, 127.7, 128.7, 131.0, 131.5, 134.6, 136.0, 144.0, 193.8 ppm. MS (ESI+): m/z = 240.2. HRMS: calcd. for $C_{16}H_{18}NO$ $[M + H]^+$ 240.1338; found 240.1442.

2-(2,4-Dimethylphenyl)-1-isopropyl-1,5,6,7-tetrahydro-4*H*-indol-4-one (25b): 91% as a brown solid (170 mg from 200 mg). M.p. 178–179 °C. R_f = 0.29 (hexanes/EtOAc, 3:2, v/v). IR (KBr): $\tilde{\nu}$ = 1651 (CO) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.33–1.43 (m, 6 H, 2 CH_3), 2.13 (s, 3 H, CH_3), 2.21 (s, 2 H, CH_2), 2.36 (s, 3 H, CH_3), 2.52 (s, 2 H, CH_2), 2.98 (s, 2 H, CH_2), 4.07–4.08 (m, 1 H, CH_2), 6.37 (s, 1 H, ArH), 7.01–7.09 (m, 3 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.3, 21.3, 22.3, 24.4, 24.5, 29.8, 37.9, 48.4, 105.5, 121.4, 126.4, 130.0, 130.9, 131.6, 134.7, 138.5, 138.6, 142.5, 194.5 ppm. MS (ESI+): m/z = 282.2. HRMS: calcd. for $C_{19}H_{24}NO$ $[M + H]^+$ 282.1858; found 282.1864.

2-(2,4-Dimethylphenyl)-1-(2-morpholinoethyl)-6,7-dihydro-1*H*-indol-4(5*H*)-one (25c): 92% as brown oil (216 mg from 200 mg). R_f = 0.28 ($CHCl_3$/MeOH, 9:1, v/v). IR (neat): $\tilde{\nu}$ = 1648 (CO) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.14 (s, 3 H, CH_3), 2.19–2.27 (m, 7 H, 2× CH_2 and CH_3), 2.36 (s, 4 H, 2× CH_2), 2.52 (t, J = 6.3 Hz, 2 H, CH_2), 2.86 (t, J = 6.1 Hz, 2 H, CH_2), 3.60 (s, 4 H, CH_2), 3.80 (s, 2 H, CH_2), 6.42 (s, 1 H, ArH), 7.02–7.05 (m, 1 H, ArH), 7.08–7.10 (m, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.2, 21.4, 22.6, 23.9, 30.5, 38.0, 53.8, 58.5, 66.7, 105.9, 120.5, 125.7, 126.5, 128.9, 131.2, 131.4, 134.2, 138.2, 138.8, 143.8, 194.4 ppm. MS (ESI+): m/z = 353.1. HRMS: calcd. for $C_{22}H_{29}N_2O_2$ $[M + H]^+$ 353.2229; found 353.2235.

General Procedure for the Preparation of Compounds 27–28 as Exemplified for 4-Chloro-1-isopropyl-2-phenyl-6,7-dihydro-1*H*-indole-5-carbaldehyde (27): $POCl_3$ (0.5 mL, 5.36 mmol) was added to a stirred solution of **21b** (500 mg, 1.98 mmol) in DMF (5 mL) at 0 °C and stirred for 10 min. The reaction mixture was then poured onto crushed ice and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (30 mL), dried with anhydrous Na_2SO_4 and concentrated under reduced pressure to afford the crude product. Purification of the crude material by column chromatography (EtOAc/hexanes, 10:90, v/v) furnished the pure product **27** (485 mg, 82%) as a yellow solid. M.p. 129–131 °C. R_f = 0.76 (hexanes/EtOAc, 3:2, v/v). IR (KBr): $\tilde{\nu}$ = 1644 (CO) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.46 (d, J = 7.0 Hz, 6 H, CH_3), 2.80–2.86 (m, 2 H, CH_2), 2.95–3.01 (m, 2 H, CH_2), 4.43–4.53 (m, 1 H, CH), 6.37 (s, 1 H, ArH), 7.32–7.45 (m, 5 H, ArH), 10.15 (s, 1 H, CHO) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.6, 22.9, 23.0, 27.5, 29.8, 48.6, 106.4, 119.8, 122.7, 128.1, 128.7, 129.8, 132.9, 135.6, 136.4, 145.6, 189.3 ppm. MS (ESI+): m/z = 300.2. HRMS: calcd. for $C_{18}H_{19}ClNO$ $[M + H]^+$ 300.1155; found 300.1159.

1-Benzyl-4-chloro-2-phenyl-6,7-dihydro-1*H*-indole-5-carbaldehyde (28): 80% as a yellow solid (1.44 g from 1.56 g). M.p. 163–165 °C. R_f = 0.73 (hexanes/EtOAc, 3:2, v/v). IR (KBr): $\tilde{\nu}$ = 1645 (CO) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.58–2.64 (m, 2 H, CH_2), 2.75–2.81 (m, 2 H, CH_2), 5.13 (s, 2 H, CH_2), 6.53 (s, 1 H, ArH), 6.94 (d, J = 6.6 Hz, 2 H, ArH), 7.28–7.34 (m, 8 H, ArH), 10.15 (s, 1 H, CHO) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.6, 22.6, 48.3, 106.4, 119.2, 123.1, 125.8, 127.8, 128.0, 128.8, 129.1, 129.2, 132.0, 136.9, 137.2, 137.4, 145.4, 189.2 ppm. MS (ESI+): m/z = 348.2. HRMS: calcd. for $C_{22}H_{19}ClNO$ $[M + H]^+$ 348.1155; found 348.1160.

General Procedure for the Preparation of Compounds 29–30 as Exemplified for 7-Isopropyl-2-methyl-8-phenyl-6,7-dihydro-5*H*-pyrrolo[2,3-*h*]quinazoline (29): Acetamidine hydrochloride (76 mg, 0.80 mmol) and Cs_2CO_3 (436 mg, 1.34 mmol) were added to a stirred solution of **27** (200 mg, 0.67 mmol) in DMSO (5 mL), and the mixture was purged with nitrogen for 10 min. CuI (13 mg, 0.068 mmol) and L-proline (15 mg, 0.13 mmol) were then added and the reaction was stirred at 90 °C for 12 h under a nitrogen atmosphere. After completion of the reaction, water (15 mL) was added to the reaction mixture and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried with anhydrous Na_2SO_4 and concentrated under reduced pressure to afford the crude product. Purification of the crude material by column chromatography (EtOAc/hexanes, 20:80, v/v) furnished the pure **29** (154 mg, 76%) as an off-white solid. M.p. 72–74 °C. R_f = 0.27 (hexanes/EtOAc, 3:2, v/v). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.48 (d, J = 7.0 Hz, 6 H, CH_3), 2.66 (s, 3 H, CH_3), 2.94–3.00 (m, 2 H, CH_2), 3.05–3.09 (m, 2 H, CH_2), 4.48–4.58 (m,1 H, CH), 6.70 (s, 1 H, ArH), 7.37–7.42 (m, 5 H, ArH) 8.24 (s, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.6, 23.0, 25.4, 26.1, 48.2, 104.9, 119.2, 121.2, 127.6, 128.5, 129.7, 133.7, 136.2, 136.7, 153.1, 159.2, 166.6 ppm. MS (ESI+): m/z = 304.2. HRMS: calcd. for $C_{20}H_{22}N_3$ $[M + H]^+$ 304.1814; found 304.1819.

7-Benzyl-2-methyl-8-phenyl-6,7-dihydro-5*H*-pyrrolo[2,3-*h*]quinazoline (30): 75% as an off-white solid (151 mg from 200 mg). M.p. 73–75 °C. R_f = 0.17 (hexanes/EtOAc, 3:2, v/v). ^1H NMR (300 MHz, $CDCl_3$): δ = 2.68 (s, 5 H, CH_2 & CH_3), 2.91 (s, 2 H, CH_2), 5.17 (s, 2 H, CH_2), 6.89 (s, 1 H, ArH), 6.96 (s, 2 H, ArH), 7.27–7.34 (m, 8 H, ArH), 8.21 (s, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.8, 25.1, 26.0, 48.0, 105.0, 118.6, 121.5, 125.8, 127.6, 127.7, 128.7, 129.1, 132.6, 137.2, 137.8, 138.1, 153.2, 159.2, 166.5 ppm. MS (ESI+): m/z = 352.2. HRMS: calcd. for $C_{24}H_{22}N_3$ $[M + H]^+$ 352.1814; found 352.1819.

Supporting Information (see footnote on the first page of this article): Spectroscopic data of remaining compounds and ^1H and ^{13}C NMR spectra of all compounds are included.

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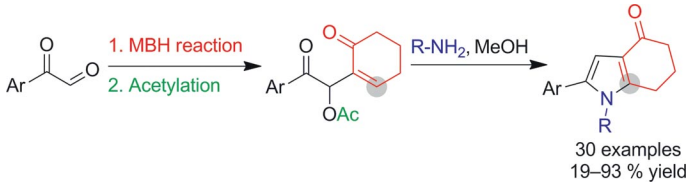

Application of adducts prepared by the Morita–Baylis–Hillman reaction between 2-oxo-2-(substituted phenyl)acetaldehydes and cyclohex-2-enone for the synthesis of 2-(substituted phenyl)-6,7-dihydro-1*H*-indol-4(5*H*)-ones has been described.

Keywords: Nitrogen heterocycles / Synthetic methods / Indole Derivatives / Morita–Baylis–Hillman

