An Efficient and Highly Selective Method for the Synthesis of Cryptotackiene Derivatives Catalyzed by Iodine

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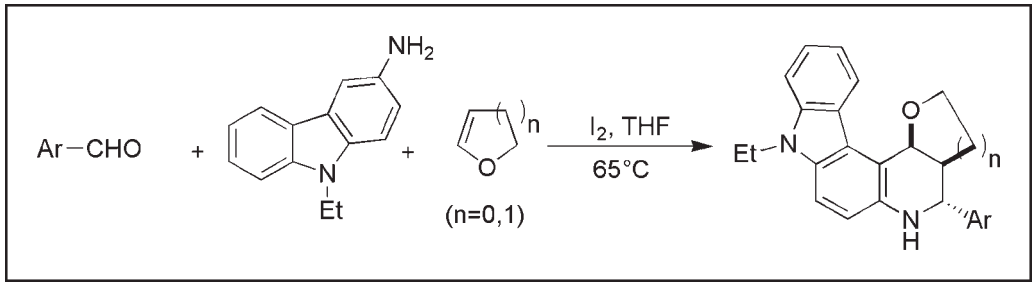

A mild, efficient and highly selective approach to the synthesis of cryptotackiene derivatives via three-component reactions of 3-amino-9-ethylcarbazole and aromatic aldehydes with electron-rich alkenes, such as 2,3-dihydrofuran, or 3,4-dihydro-2*H*-pyran catalyzed by iodine in THF is reported. It is worth to note that only *trans*-products were obtained with high selectivity in good to high yields, which confirmed by X-ray diffraction analysis.

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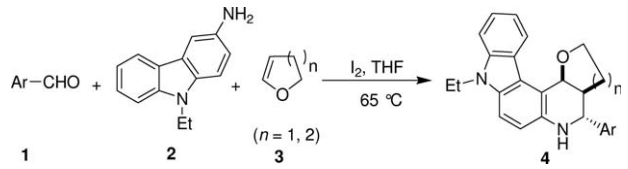
INTRODUCTION

Cryptotackiene, a linear 5-*N*-methyl-5*H*-indolo[2,3-*b*]quinoline alkaloid isolated from the West African shrub *Cryptolepis sanguinolenta*, has been reported to exhibit strong antiplasmodial activity [1]. A few of cryptotackiene derivatives are found to display strong antimicrobial and cytotoxic activities *in vitro* and significant antitumor properties *in vivo* [2]. In addition, its isomeric moiety, named ellipticine (5,11-dimethyl-6*H*-indolo[2,3-*g*]isoquinoline), also exhibits promising results in the treatment of osteolytic breast cancer metastases, brain tumors, kidney sarcoma, and myeloblastic leukemia [3]. More recent studies have also indicated that they possessed a good activity against HIV [4]. Accordingly, a wide variety of strategies [5–7] have been reported to construct these aforementioned active moieties for their important biological activities.

The imino Diels–Alder [4+2] cyclo-addition reaction presents a powerful synthetic tool to the construction of the polycyclic cryptotackiene ring systems. Of which the imines derived from aromatic amines and aldehyde, act as heterodienes and undergo Diels–Alder reaction with various dienophiles in the presence of acidic catalysts [8–11]. The multicomponent reactions (MCRs) involving 3-amino-9-ethylcarbazole, which reported by Gaddam and Nagarajan, represent an effective synthetic pathway toward cryptotackiene derivatives [12]. However, the known methods suffer from some disadvantages. For instance, these procedures often require harsh reaction conditions, multistep reaction, metal catalysts, expensive reagents or no stereo-selectivity. Especially for the stereo-selectivity, they always give *cis*- and *trans*-isomers using 2,3-dihydrofuran, 3,4-dihydro-2*H*-pyran as starting materials.

As an inexpensive, efficient, and environmentally benign catalyst, iodine has been used extensively in organic synthesis. More and more organic transformations [13] promoted by molecular iodine have been documented in recent years. In our previous paper, we have synthesized series of benzo[*f*]quinoline derivatives via three-component reactions of aromatic aldehyde, naphthalen-2-amine, and various ketones [14] induced by iodine. As a continuation of our research devoted to this iodine-catalyzed reaction, 3-amino-9-ethylcarbazole was selected as similar amine to react with aromatic aldehyde, and 2,3-dihydrofuran or 3,4-dihydro-2*H*-pyran for the challenge of its stereo-selectivity. It was noteworthy that only *trans*-4-aryl-8-ethyl-3,3*a*,4,5,8,12*d*-hexahydro-2*H*-furo[3,2-*c*]indolo[3,2-*f*]quinoline or *trans*-5-aryl- 9-

Scheme 1. Reaction of **1**, **2**, and **3**.



ethyl-2,3,4,4*a*,5,6,9,13*d*-hexahydropyrano[3,2-*c*]indolo [3,2-*f*]quinoline derivatives were obtained with high selectivity in good to high yields.

RESULTS AND DISCUSSION

Treatment of aromatic aldehyde **1**, 3-amino-9-ethylcarbazole **2**, and 2,3-dihydrofuran **3** in THF in the presence of 5 mol % iodine at reflux condition afforded the corresponding *trans*-4-aryl-8-ethyl-3,3*a*,4,5,8,12*d*-hexahydro-2*H*-furo[3,2-*c*]indolo[3,2-*f*]quinoline derivatives **4** in good to high yields with high stereo-selectivity (Scheme 1). Obviously, these results were different from *trans*- to *cis*-isomers catalyzed by $InCl_3$ in ionic liquid [12].

In our initial study, the reaction of 4-nitrobenzaldehyde **1d**, 3-amino-9-ethylcarbazole **2**, and 2,3-dihydrofuran **3** was used as a model reaction to optimize the reaction conditions. The reaction was first carried out in THF in the absence of I_2. It was found that no reaction occurred at room temperature or reflux condition (Table 1, entries 1 and 2). Similar reactions were attempted in the presence of 5, 10, and 20 mol % of I_2. The results from Table 1 (entries 5-7) show that 5 mol % I_2 at reflux in THF is sufficient to initiate the reaction. Higher loading of the catalyst had no significant influence on the reaction yield. To find the optimum reaction temperature, the reaction was carried out with 5 mol % of I_2 at room temperature, 50°C and reflux temperature, resulting in the isolation of **4d** in trace amount, 68% and 88% yields (Table 1, entries 3-5), respectively. Thus, 5 mol % of I_2 and a reaction temperature at reflux were optimal conditions. In addition, CH_3CN, benzene, DMF, and $CHCl_3$ (Table 1, entries 8-11) were also tested as the solvents. In these cases, product **4d** was formed in slightly lower yields (Table 1, entries 8-11).

According to the optimized conditions, various aromatic aldehydes **1** were then subjected to react with 3-amino-9-ethylcarbazole **2** and **3** to generate a library of **4** (Table 2, entries 1 to 8). For aldehyde **1**, the yields of **4** were not sensitive to the electronic properties of the aromatic ring in the presence of electron-withdrawing groups (such as halide and nitro) or electron-donating groups (such as alkoxyl group) (Table 2). The *trans*-structure of **4g** was further confirmed by X-ray diffraction analysis, and the crystal structure was shown in Figure 1. The 2,3-dihydrofuran could be expended to other electron-rich alkenes, such as 3,4-dihydro-2*H*-pyran was also chosen as reactant to react with **1** and **2**, giving corresponding *trans*-5-aryl-9-ethyl-2,3,4,4*a*,5,6,9,13*d*-hexahydropyrano[3,2-*c*]indolo[3,2-*f*]quinoline with good yields and stereo-selectivity (Table 2, entries 9 to 12).

According to the literatures [15], we think that iodine catalyzes the reaction as a mild Lewis acid. The mechanism was tentatively proposed as shown in Scheme 2. The Schiff base **I** may be formed first by the reaction of aromatic aldehyde and 3-amino-9-ethylcarbazole. Then imino-Diels–Alder reaction between the iodine-activated Schiff base **II** and 2,3-dihydrofuran takes place

Table 1

Synthetic results of **4d** under different reaction conditions.[a]

Entry	Temp. (°C)	Amount (mol %)	Solvent	Time (h)	Yields (%)[b]
1	r.t.	0	THF	24	0
2	Reflux	0	THF	24	0
3	r.t.	5	THF	24	trace
4	50	5	THF	24	68
5	Reflux	5	THF	19	88
6	Reflux	10	THF	19	88
7	Reflux	20	THF	19	83
8	Reflux	5	CH_3CN	20	72
9	Reflux	5	Benzene	24	82
10	80	5	DMF	15	75
11	Reflux	5	$CHCl_3$	19	76

[a] Reagents and conditions: 4-Nitrobenzaldehyde **1d** (0.302 g, 2 mmol), **2** (0.420 g, 2 mmol), **3** 2,3-dihydrofuran (0.210 g, 3 mmol), solvent (10 mL).
[b] Isolated yields.

Table 2

Synthetic results of **4** catalyzed by iodine in THF.[a]

Entry	Ar	*n*	Products	Time (h)	Isolated yields (%)
1	4-ClC_6H_4	1	**4a**	19	85
2	4-BrC_6H_4	1	**4b**	18	85
3	4-$MeOC_6H_4$	1	**4c**	12	80
4	4-$NO_2C_6H_4$	1	**4d**	20	88
5	3-ClC_6H_4	1	**4e**	20	80
6	2,4-$Cl_2C_6H_3$	1	**4f**	19	78
7	3,4-$Cl_2C_6H_3$	1	**4g**	20	70
8	3,5-$(MeO)_2C_6H_3$	1	**4h**	18	82
9	4-FC_6H_4	2	**4i**	20	78
10	4-$CH_3C_6H_4$	2	**4j**	19	75
11	3,4-$Cl_2C_6H_3$	2	**4k**	20	82
12	4-$MeOC_6H_4$	2	**4l**	19	80

[a] Reagents and conditions: **1** (2 mmol), **2** (0.420 g, 2 mmol), **3** (3 mmol), I_2 (0.026 g, 0.1 mmol), THF (10 mL).

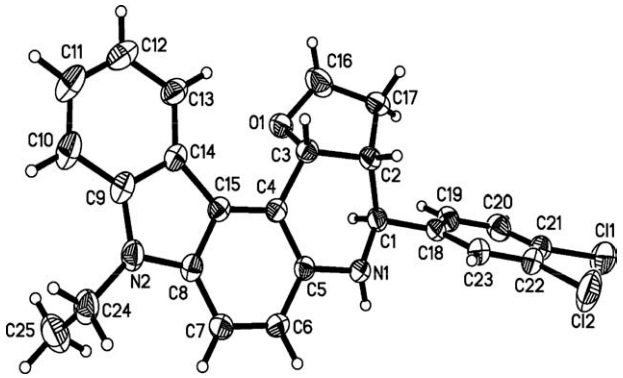


Figure 1. Crystal structure of product **4g** indicating the *trans*-structure.

selectively to form intermediate **III** for its stability, followed by isomerization to give the final product **4**.

CONCLUSIONS

In conclusion, we found a mild and efficient method for the synthesis of *trans*-cryptotackiene derivatives via three-component reactions of aromatic aldehyde, 3-amino-9-ethylcarbazole, and 2,3-dihydrofuran or 3,4-dihydro-2*H*-pyran catalyzed by iodine. The features of this procedure are mild reaction conditions, good to high yields, operational simplicity, and high stereoselectivity.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on a TENSOR 27 spectrometer in KBr pellet. ^{1}H NMR spectra were obtained from solution in DMSO-d_6 with Me_4Si as internal standard using a Bruker-400 spectrometer. HRMS analyses were carried out using Bruker-micro TOF-Q-MS analyzer.

General procedure for the syntheses of *trans*-4-aryl-8-ethyl-3,3*a*,4,5,8,12*d*-hexahydro-2*H*-furo[3,2-*c*]indolo[3,2-*f*]quinoline or *trans*-5-aryl-9-ethyl-2,3,4,4*a*,5,6,9,13*d*-hexahydropyrano[3,2-*c*]indolo[3,2-*f*]quinoline derivatives 4. A dry 50 mL flask was charged with aromatic aldehyde (2.0 mmol), 2,3-dihydrofuran or 3,4-dihydro-2*H*-pyran (3.0 mmol), 3-amino-9-ethylcarbazole (0.420 g, 2.0 mmol), I_2 (0.026 g, 0.1 mmol), and THF (10 mL). The reaction mixture was stirred at reflux condition for 12–20 h, and then cooled to room temperature. The generated yellow solid was filtered off. The crude yellow products were washed with ethanol and purified by recrystallization from DMF and water, followed by being dried at 50°C several hours at vacuum to give **4**.

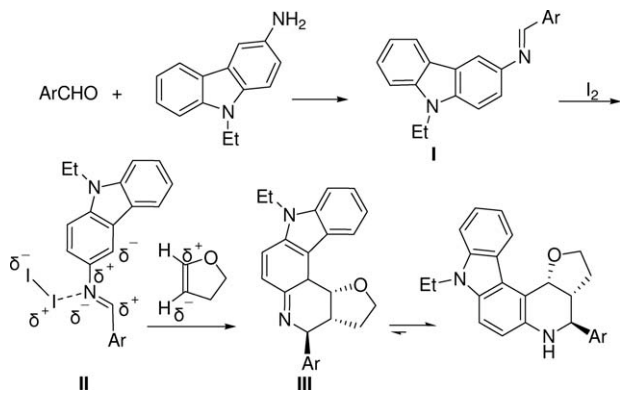
***trans*-4-(4-Chlorophenyl)-8-ethyl-3,3a,4,5,8,12d-hexahydro-2H-furo[3,2-c]indolo[3,2-f]quinoline (4a).** This compound was obtained as yellow crystals (0.683 g, 85%), m.p.: 223–225°C; IR (KBr) ν_{max}/cm^{-1} 3371, 3047, 2974, 2871, 1593, 1504, 1487, 1455, 1410, 1380, 1327, 1285, 1266, 1209, 1186, 1154, 1090, 1045, 1012, 926, 828, 802, 751. ^{1}H NMR (DMSO-d_6): δ_H 1.27 (t, J = 7.2 Hz, 3H, CH_3), 1.56–1.62 (m, 1H, CH), 1.98–2.09 (m, 1H, CH), 2.37–2.43 (m, 1H, CH), 3.72 (d, J = 11.2 Hz, 1H, CH), 3.85–3.91 (m, 1H, CH), 4.00 (q, J = 4.0 Hz, 1H, CH), 4.39 (q, J = 7.2 Hz, 2H, NCH_2), 5.03 (d, J = 5.2 Hz, 1H, CH), 6.01 (s, 1H, NH), 6.98 (d, J = 8.8 Hz, 1H, ArH), 7.11–7.14 (m, 1H, ArH), 7.37–7.41 (m, 2H, ArH), 7.47 (d, J = 8.4 Hz, 2H, ArH), 7.52 (d, J = 8.4 Hz, 1H, ArH), 7.56 (d, J = 8.4 Hz, 2H, ArH), 8.15 (d, J = 8.0 Hz, 1H, ArH). HRMS (ESI, *m*/*z*): Calcd. for $C_{25}H_{23}ClON_2Na$ (M + Na^+) 425.1397, found 425.1381.

***trans*-4-(4-Bromophenyl)-8-ethyl-3,3a,4,5,8,12d-hexahydro-2H-furo[3,2-c]indolo[3,2-f]quinoline (4b).** This compound was obtained as yellow crystals (0.758 g, 85%), m.p.: 227–230°C; IR (KBr) ν_{max}/cm^{-1} 3349, 2972, 2858, 1623, 1590, 1502, 1457,1406, 1382, 1327, 1285, 1266, 1210, 1184, 1152, 1092, 1069, 1041, 1010, 925, 828, 802, 743. ^{1}H NMR (DMSO-d_6): δ_H 1.27 (t, J = 6.80 Hz, 3H, CH_3), 1.56–1.63 (m, 1H, CH), 1.99–2.06 (m, 1H, CH), 2.37–2.43 (m, 1H, CH), 3.71 (d, J = 11.2 Hz, 1H, CH), 3.86–4.03 (m, 1H, CH), 4.01 (q, J = 4.0 Hz, 1H, CH), 4.39 (q, J = 14.0 Hz, 2H, NCH_2), 5.03 (d, J = 5.2 Hz, 1H, CH), 6.01 (s, 1H, NH), 6.98 (d, J = 8.8 Hz, 1H, ArH), 7.10–7.14 (m, 1H, ArH), 7.37–7.42 (m, 2H, ArH), 7.50–7.53 (m, 3H, ArH), 7.61 (d, J = 8.4 Hz, 2H, ArH), 8.14 (d, J = 7.6 Hz, 1H, ArH). HRMS (ESI, *m*/*z*): Calcd. for $C_{25}H_{23}BrN_2ONa$ (M + Na^+) 469.0891, found 469.0888.

***trans*-8-Ethyl-4-(4-methoxyphenyl)-3,3a,4,5,8,12d-hexahydro-2H-furo[3,2-c]indolo[3,2-f]quinoline (4c).** This compound was obtained as yellow crystals (0.611 g, 80%), m.p.: 166–167°C; IR (KBr) ν_{max}/cm^{-1} 3350, 3042, 2929, 2836, 1604, 1509, 1380, 1351, 1325, 1302, 1285, 1267, 1248, 1171, 1153, 1109, 1093, 1046, 1025, 972, 924, 887, 834, 806, 782, 742. ^{1}H NMR (DMSO-d_6): δ_H 1.26 (t, J = 7.2 Hz, 3H, CH_3), 1.59–1.62 (m, 1H, CH), 1.98–2.07 (m, 1H, CH), 2.37–2.42 (m, 1H, CH), 3.78 (d, J = 3.2 Hz 1H, CH), 3.86 (m, 3H, CH_3O), 3.98–3.99 (m, 1H, CH), 4.38 (q, 2H, NCH_2), 5.02 (d, J = 4.8 Hz, 1H, CH), 5.90 (s, 1H, NH), 6.96–7.00 (m, 3H, ArH), 7.10–7.14 (m, 1H, ArH), 7.36–7.40 (m, 2H, ArH), 7.44 (d, J = 8.4 Hz, 2H, ArH), 7.51 (d, J = 8.4 Hz, 1H, ArH), 8.14 (d, J = 8.0 Hz, 1H, ArH). HRMS (ESI, *m*/*z*): Calcd. for $C_{26}H_{27}N_2O_2$ (M + H^+) 399.2067, found 399.2073.

***trans*-8-Ethyl-4-(4-nitrophenyl)-3,3a,4,5,8,12d-hexahydro-2H-furo[3,2-c]indolo[3,2-f]quinoline (4d).** This compound was obtained as yellow crystals (0.727 g, 88%), m.p.: 253–254°C; IR (KBr) ν_{max}/cm^{-1} 3367, 2976, 2932, 2845, 1668, 1624, 1600, 1515, 1459, 1382, 1344, 1287, 1267, 1209, 1185,

Scheme 2. Possible mechanism for the formation of products **4**.



1154, 1092, 1047, 1012, 930, 860, 796, 741. ^{1}H NMR (DMSO-d_6): δ_H 1.27 (t, J = 7.2 Hz, 3H, CH_3), 1.57–1.63 (m, 1H, CH), 2.01–2.06 (m, 1H, CH), 2.43–2.46 (m, 1H, CH), 3.87–3.93 (m, 2H, CH_2), 4.04 (q, 1H, CH), 4.40(q, J = 7.2 Hz, 2H, NCH_2), 5.06 (d, J = 5.2 Hz, 1H, CH), 6.17 (s, 1H, NH), 6.99 (d, J = 8.8 Hz, 1H, ArH), 7.11–7.15 (m, 1H, ArH), 7.37–7.44 (m, 2H, ArH), 7.53 (d, J = 8.4 Hz, 1H, ArH), 7.84 (d, J = 8.8 Hz, 2H, ArH), 8.15 (d, J = 7.6 Hz, 1H, ArH), 8.27 (d, J = 8.8 Hz, 2H, ArH). HRMS (ESI, *m/z*): Calcd. for $C_{25}H_{23}BrN_2ONa$ (M + Na^+) 436.1637, found 4636.1634.

trans-4-(3-Chlorophenyl)-ethyl-3,3a,4,5,8,12d-hexahydro-2H-furo[3,2-c]indolo[3,2-f]quinoline (4e). This compound was obtained as yellow crystals (0.643 g, 80%), m.p.: 194–196°C; IR (KBr) ν_{max}/cm^{-1} 3375, 3048, 2968, 2929, 2856, 1597, 1503, 1471, 1381, 1329, 1269, 1206, 1152, 1091, 1041, 890, 798, 742. ^{1}H NMR (DMSO-d_6): δ_H 1.27 (t, J = 7.2 Hz, 3H, CH_3), 1.60–1.65 (m, 1H, CH), 2.03–2.08 (m, 1H, CH), 2.41–2.47 (m, 1H, CH), 3.74 (d, J = 11.2 Hz, 1H, CH), 3.88–3.90 (m, 1H, CH), 4.02 (q, 1H, CH), 4.39 (q, J = 7.2 Hz, 2H, NCH_2), 5.03 (d, J = 5.2 Hz, 1H, CH), 6.08 (s, 1H, NH), 6.98 (d, J = 8.8 Hz, 1H, ArH), 7.10–7.14 (m, 1H, ArH), 7.37–7.47 (m, 5H, ArH), 7.52 (d, J = 8.0 Hz, 2H, ArH), 7.62 (s, 1H, ArH), 8.14 (d, J = 8.0 Hz, 1H, ArH). HRMS (ESI, *m/z*): Calcd. for $C_{25}H_{24}ClN_2O$ (M + H^+) 403.1572, found 403.1582.

trans-4-(2,4-Dichlorophenyl)-8-ethyl-3,3a,4,5,8,12d-hexahydro-2H-furo[3,2-c]indolo[3,2-f]quinoline (4f). This compound was obtained as yellow crystals (0.680 g, 78%), m.p.: 213–215°C; IR (KBr) ν_{max}/cm^{-1} 3053, 2970, 2885, 1588, 1503, 1470, 1452, 1383, 1325, 1285, 1266, 1209, 1152, 1095, 1046, 925, 867, 823, 793, 735. ^{1}H NMR (DMSO-d_6): δ_H 1.27 (t, J = 6.80 Hz, 3H, CH_3), 1.55–1.61 (m, 1H, CH), 2.09–2.14 (m, 1H, CH), 3.94–4.00 (m, 2H, CH_2), 4.29 (d, J = 11.2 Hz, 1H, CH), 4.39 (q, J = 7.2 Hz, 2H, NCH_2), 5.07 (d, J = 8.8 Hz, 1H, CH), 6.06 (s, 1H, NH), 6.96 (d, J = 8.8 Hz, 1H, ArH), 7.11–7.14 (m, 1H, ArH), 7.37–7.44 (m, 2H, ArH), 7.52–7.55 (m, 2H, ArH), 7.70 (d, J = 2.0 Hz, 1H, ArH), 7.76 (d, J = 8.4 Hz, 1H, ArH), 8.15 (d, J = 8.0 Hz, 1H, ArH). HRMS (ESI, *m/z*): Calcd. for $C_{25}H_{23}Cl_2N_2O$ (M + H^+) 437.1182, found 437.1180.

trans-4-(3,4-Dichlorophenyl)-8-ethyl-3,3a,4,5,8,12d-hexahydro-2H-furo[3,2-c]indolo[3,2-f]quinoline (4g). This compound was obtained as yellow crystals (0.611 g, 70%), m.p.: 227–229°C; IR (KBr) ν_{max}/cm^{-1} 3053, 2970, 2885, 1588, 1503, 1470, 1452, 1383, 1325, 1285, 1266, 1209, 1152, 1095, 1046, 925, 867, 823, 793, 735. ^{1}H NMR (DMSO-d_6): δ_H 1.27 (t, J = 7.2 Hz, 3H, CH_3), 1.59–1.63 (m, 1H, CH), 2.04–2.09 (m, 1H, CH), 2.41–2.47 (m, 1H, CH), 3.75 (d, J = 11.2 Hz, 1H, CH), 3.89–3.92 (m, 1H, CH), 4.01 (q, 1H, CH), 4.39 (q, J = 14.0 Hz, 2H, NCH_2), 5.03 (d, J = 4.8 Hz, 1H, CH), 6.09 (s, 1H, NH), 6.96 (d, J = 8.4 Hz, 1H, ArH), 7.12 (t, J = 7.6 Hz, 1H, ArH), 7.37–7.43 (m, 2H, ArH), 7.52–7.57 (m, 2H, ArH), 7.68 (d, J = 8.4 Hz, 1H, ArH), 7.84 (d, J = 2.0 Hz, 1H, ArH), 8.14 (d, J = 8.0 Hz, 1H, ArH). HRMS (ESI, *m/z*): Calcd. for $C_{25}H_{23}Cl_2N_2O$ (M + H^+) 437.1182, found 437.1190.

trans-4-(3,5-Dimethoxyphenyl)-8-ethyl-3,3a,4,5,8,12d-hexahydro-2H-furo[3,2-c]indolo[3,2-f]quinoline (4h). This compound was obtained as yellow crystals (0.702 g, 82%), m.p.: 229–231°C; IR (KBr) ν_{max}/cm^{-1} 3352, 3056, 2973, 2875, 1592, 1506, 1461, 1402, 1384, 1335, 1269, 1213, 1153, 1095, 1043, 1028, 946, 893, 835, 793, 740. ^{1}H NMR (DMSO-d_6): δ_H 1.27 (t, J = 6.80 Hz, 3H, CH_3), 1.68–1.74 (m, 1H, CH), 2.02–2.11 (m, 1H, CH), 2.41–2.47 (m, 1H, CH), 3.65 (d, J = 11.2 Hz, 1H, CH), 3.78 (s, 6H, $2CH_3O$), 3.88–3.92 (m, 1H, CH), 3.99–4.04 (m, 1H, CH), 4.39 (q, J = 6.8 Hz, 2H, NCH_2), 5.02 (d, J = 5.2 Hz, 1H, CH), 5.97 (s, 1H, NH), 6.49 (s, 1H, ArH), 6.72 (d, J = 1.6 Hz, 2H, ArH), 7.00 (d, J = 8.8 Hz, 1H, ArH), 7.10–7.14 (m,1H, ArH), 7.36–7.41 (m, 2H, ArH), 7.52 (d, J = 8.4 Hz, 1H, ArH), 8.14 (d, J = 8.0 Hz, 1H, ArH). HRMS (ESI, *m/z*): Calcd. for $C_{27}H_{29}N_2O_3$ (M + H^+) 429.2173, found 429.2175.

trans-9-Ethyl-5-(4-fulorophenyl)-2,3,4,4a,5,6,9,13d-hexahydropyrano[3,2-c]indolo[3,2-f]quinoline (4i). This compound was obtained as yellow crystals (0.624g, 78%), m.p.: 217–218°C; IR (KBr) ν_{max}/cm^{-1} 3374, 3049, 2951, 2928, 2894,2851, 2832, 1623, 1601, 1505, 1469, 1454, 1379, 1365, 1348, 1326, 1285, 1274, 1254, 1215, 1153, 1076, 1058,1042, 1011, 903, 849, 801, 748. ^{1}H NMR (DMSO-d_6): δ_H 1.25 (t, J = 6.80 Hz, 3H, CH_3), 1.32 (d, J = 10.8 Hz, 2H, CH_2), 1.75–1.87 (m, 2H, CH_2), 2.01 (d, J = 11.2 Hz, 1H, CH), 3.87–3.93 (m, 1H, CH), 4.05–4.07 (m, 1H, CH), 4.36 (q, J = 6.8 Hz, 2H, NCH_2), 4.64 (d, J = 11.6 Hz, 1H, CH), 5.06 (d, J = 3.2 Hz, 1H, CH), 5.85 (s, 1H, NH), 6.86 (d, J = 8.8 Hz, 1H, ArH), 7.11–7.15 (m, 1H, ArH), 7.21–7.26 (m, 2H, ArH), 7.35–7.40 (m,2H, ArH), 7.50–7.58 (m, 3H, ArH), 7.92 (d, J = 7.6 Hz, 1H, ArH). HRMS (ESI, *m/z*): Calcd. for $C_{26}H_{26}FN_2O$ (M + H^+) 401.2029, found 401.2035.

trans-9-Ethyl-5-(4-methylphenyl)-2,3,4,4a,5,6,9,13d-hexahydropyrano[3,2-c]indolo[3,2-f]quinoline (4j). This compound was obtained as yellow crystals (0.594 g, 75%), m.p.: 206–207°C; IR (KBr) ν_{max}/cm^{-1} 3369, 3044, 3019, 2976, 2956, 2928, 2893, 2829, 2851, 1600, 1503, 1457, 1379, 1365, 1346, 1326, 1284, 1272, 1255, 1213, 1194, 1152, 1077, 1056, 1042, 1020, 902, 830, 800, 749. ^{1}H NMR (DMSO-d_6): δ_H 1.25 (t, J = 6.80 Hz, 3H, CH_3), 1.35 (d, J = 14 Hz, 2H, CH_2), 1.74–1.85 (m, 2H, CH_2), 2.00–2.03 (m, 1H, CH), 2.34 (s, 3H, CH_3), 3.87–3.92 (m, 1H, CH), 4.04–4.07 (m, 1H, CH), 4.35–4.41 (m, 2H, NCH_2), 4.58 (d, J = 11.6 Hz, 1H, CH), 5.05 (s, 1H, CH), 5.77 (s, 1H, NH), 6.86 (d, J = 8.8 Hz, 1H, ArH), 7.11–7.14 (m, 1H, ArH), 7.22 (d, J = 7.6 Hz, 2H, ArH), 7.34–7.43 (m,1H, ArH), 7.50 (d, J = 8.0 Hz, 1H, ArH), 7.92 (d, J = 8.0 Hz, 1H, ArH). HRMS (ESI, *m/z*): Calcd. for $C_{27}H_{29}N_2O$ (M + H^+) 397.2280, found 397.2287.

trans-5-(3,4-Dichlorophenyl)-9-ethyl-2,3,4,4a,5,6,9,13d-hexahydropyrano[3,2-c]indolo[3,2-f]quinoline (4k). This compound was obtained as yellow crystals (0.738 g, 82%), m.p.: 216–217°C; IR (KBr) ν_{max}/cm^{-1} 3344, 3066, 2970, 2932, 2893, 2843, 1592, 1503, 1460, 1404, 1380, 1365, 1328, 1287, 1273, 1252, 1233, 1216, 1195, 1128, 1082, 1057, 1042, 1026, 1011, 894, 835, 794, 740, 634. ^{1}H NMR (DMSO-d_6): δ_H 1.28 (t, J = 6.80 Hz, 3H, CH_3), 1.33–1.35 (m, 2H, CH_2), 1.75–1.89 (m, 2H, CH_2), 2.04–2.09 (m, 1H, CH), 3.90 (t, J = 11.2 Hz, 1H, CH), 4.04–4.07 (m, 1H, CH), 4.36–4.39 (m, 2H, CH), 4.66 (d, J = 10.8 Hz, 1H, CH), 5.06 (s, 1H, CH), 5.94 (s, 1H, NH), 6.85 (d, J = 8.4 Hz, 1H, ArH), 7.11–7.15 (m,1H, ArH), 7.36–7.40 (m, 2H, ArH), 7.52–7.54 (m, 2H, ArH), 7.67 (d, J = 8.0 Hz, 1H, ArH), 7.80 (s,1H, ArH), 7.92 (d, J = 8.0 Hz, 1H, ArH). HRMS (ESI, *m/z*): Calcd. for $C_{26}H_{25}Cl_2N_2O$ (M + H^+) 451.1344, found 451.1346.

trans-9-Ethyl-5-(4-methoxyphenyl)-2,3,4,4a,5,6,9,13d-hexahydropyrano[3,2-c]indolo[3,2-f]quinoline (4l). This compound was obtained as yellow crystals (0.659 g, 80%), m.p.: 190–191°C; IR (KBr) ν_{max}/cm^{-1} 3371, 3044, 2954, 2928, 2899, 2829, 1606, 1587, 1509, 1456, 1364, 1326, 1284, 1239, 1212,

1174, 1152, 1076, 1056, 1036, 1009, 901, 835, 802, 745. ^{1}H NMR (DMSO-d_6): δ_H 1.25 (t, J = 6.80 Hz, 3H, CH_3), 1.36 (d, J = 16.4 Hz, 2H, CH_2), 1.74–1.85 (m, 2H, CH_2), 1.98–2.01 (m, 1H, CH), 3.78 (s, 3H, CH_3O), 3.87–3.92 (m, 1H, CH), 4.04–4.07 (m, 1H, CH), 4.35–4.39 (m, 2H, NCH_2), 4.56–4.59 (m, 1H, CH), 5.05 (s, 1H, CH), 5.75 (s, 1H, NH), 6.86 (d, J = 8.0 Hz, 1H, ArH), 6.97 (d, J = 8.4 Hz, 2H, ArH), 7.12 (t, J = 7.6 Hz, 1H, ArH), 7.34–7.44 (m, 4H, ArH), 7.50 (d, J = 8.0 Hz, 1H, ArH), 7.92 (d, J = 8.0 Hz, 1H, ArH). HRMS (ESI, m/z): Calcd. for $C_{27}H_{29}N_2O_2$ ($M + H^+$) 413.2229, found 413.2223.

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