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An efficient and convenient synthesis of heterocycle-fused indazoles via the N–N bond forming reaction of nitroarenes induced by low-valent titanium reagent

Wei Lin, Ming-Hua Hu, Xian Feng, Cheng-Pao Cao, Zhi-Bin Huang *, Da-Qing Shi *

Key Laboratory of Organic Synthesis of Jiangsu Province, College of Chemistry, Chemical Engineering and Materials Science, Soochow University, Suzhou 215123, PR China

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ABSTRACT

A mild and efficient one-pot protocol for the preparation of 8,13-dihydro-7*H*-indolo[2′,3′:3,4]pyrido[1,2-*b*]indazole and 5,6-dihydroindazolo[3,2-*a*]isoquinoline via the reductive cyclization of nitro-aryl substrates mediated by a low-valent titanium reagent has been developed. The attractive features of the current method include an N–N bond formation and the selective reduction of the C=N bond and nitro group, both of which were easily achieved in one-pot by controlling the pH of the reaction mixture.

1. Introduction

Indazole derivatives are an important class of heterocyclic pharmaceuticals because of their significant and broad spectrum of biological properties, including antitumor,[1] anti-HIV,[2] antidepressant,[3] antimicrobial,[4] anti-inflammatory,[5] and contraceptive activities.[6] Compared to 1*H*-indazoles, 2*H*-indazoles have been shown to possess potent levels of affinity for 5-HT_{1A} receptors,[7] estrogen receptor â,[8] and the imidazoline I_2 receptor.[9] Several different synthetic methods have been developed for the construction of this intriguing 2*H*-indazole scaffold involving the use of several different starting materials, including (1) the direct N-arylation[10] or N-alkylation[11] of an indazole; (2) the reductive cyclization of *o*-nitrobenzylamines using Sn, Zn, Fe, $SnCl_2$, low-valent titanium, or an electrochemical method;[12] (3) the Pd-catalyzed domino reaction of 2-halophenyl acetylenes with hydrazines;[13] (4) the Fe-catalyzed N–N bond formation of 2-azidophenyl ketoximes;[14] (5) the reaction of 2-chloromethylarylzinc reagents and aryldiazonium salts;[15] (6) the [3+2] cycloaddition of arynes and sydnones;[16] (7) the copper-catalyzed three-component reaction of 2-bromobenzaldehydes, primary amines, and sodium azide;[17] and (8) the treatment of (*o*-nitrobenzylidene)amines with either $P(OEt)_3$, $PdCl_2(PPh_3)_2/SnCl_2/CO(g)$, or $SnCl_2/Et_3N/PhSH$ followed by treatment with tosyl chloride.[18] Unfortunately, however, there are several drawbacks associated with the use of each of these existing methods that have severely limited their application, including poor levels of regioselectivity, low yields, the use of expensive ligands or reagents, the requirement for forcing reaction conditions or specialized equipment. With these issues in mind, there is clearly an urgent need for the development of a simple and efficient method for the synthesis of 2*H*-indazoles using readily available starting materials under mild reaction conditions.

Low-valent titanium reagents have attracted increasing levels of interest in organic synthesis because of their pronounced ability to promote the reductive coupling reactions of carbonyl compounds.[19] In a recent publication, we described our work toward the synthesis of heterocycles using low-valent titanium reagents.[20] To the best of our knowledge, there have been few reports about the synthesis of heterocycle-fused indazoles.[18d] Herein, we will report the efficient and convenient synthesis of heterocycle-fused indazole derivatives via the reductive cyclization of nitro-aryl substrates mediated by a low-valent titanium reagent.

2. Results and discussion

For our preliminary evaluation of the transformation, the reductive cyclization of 1-(2-nitrophenyl)-4,9-dihydro-3*H*-pyrido

* Corresponding authors. Tel.: +86 512 65880049; fax: +86 512 65880095; e-mail addresses: zbhuang@suda.edu.cn (Z.-B. Huang), dqshi@suda.edu.cn, dqshi@263.net (D.-Q. Shi).

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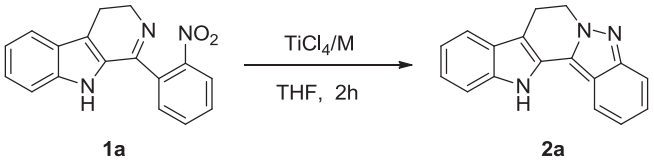
[3,4-*b*]indole (**1a**), which were synthesized according to procedures reported in the literature involving the conventional Bischler–Napieralski reaction[21] from 2-nitrobenzoic acids and tryptamine, was selected as a model reaction (Scheme 1). The reductive cyclization reaction of **1a** was then evaluated under a variety of different conditions in the presence of several different low-valent titanium reagents. The results are summarized in Table 1.



Scheme 1. Model reaction.

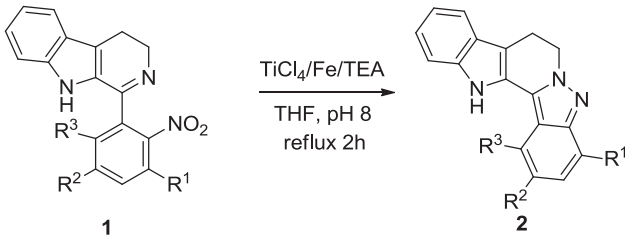
Table 1
Optimization of reaction conditions for the synthesis of **2a**

Entry	$TiCl_4$/metal (M)	Ratio	Temp (°C)	Base/pH value	Yield[a]/%
1	$TiCl_4$/Zn	1:4	Reflux	No base/2	10
2	$TiCl_4$/Zn	1:4	Reflux	TEA/8	78
3	$TiCl_4$/Fe	1:4	Reflux	TEA/8	90
4	$TiCl_4$/Mg	1:4	Reflux	TEA/8	89
5	$TiCl_4$/Sm	1:4	Reflux	TEA/8	87
6	$TiCl_4$/Fe	1:4	Reflux	TEA/4	75
7	$TiCl_4$/Fe	1:4	Reflux	TEA/5	78
8	$TiCl_4$/Fe	1:4	Reflux	TEA/6	86
9	$TiCl_4$/Fe	1:4	Reflux	TEA/7	87
10	$TiCl_4$/Fe	1:4	Reflux	TEA/9	89
11	$TiCl_4$/Fe	1:4	Reflux	TEA/10	87
12	$TiCl_4$/Fe	1:2	Reflux	TEA/8	70
13	$TiCl_4$/Fe	1:3	Reflux	TEA/8	87
14	$TiCl_4$/Fe	1:5	Reflux	TEA/8	87
15	$TiCl_4$/Fe	1:4	rt	TEA/8	37
16	$TiCl_4$/Fe	1:4	40	TEA/8	45
17	$TiCl_4$/Fe	1:4	60	TEA/8	80

[a] Yield was determined by HPLC-MS.

As shown in Table 1, we examined the effect of different low-valent titanium systems and pH values on the success of the cyclization step. When substrate **1a** was reduced by $TiCl_4$/Zn and no base was added, only 10% desired product **2a** was obtained (Table 1, entry 1). When substrate **1a** was reduced with different low-valent titanium reagents in TEA and pH=8 (Table 1, entries 2–5), $TiCl_4$/Fe, $TiCl_4$/Mg, and $TiCl_4$/Sm gave similar result of synthesis of **2a** (90%, 89%, 87%, respectively) (Table 1, entries 3–5). Considering Fe is cheaper, we used $TiCl_4$/Fe to further research optimize conditions. Similar test was carried out at pH value ranging from 4 to 10 with an increment of 1 each time. The yield of product **2a** was increased as pH value was increased from 4 to 8 (Table 1, entries 6–9 and 3). However, a further increase of pH value to 9 and 10 failed to improve the yield of product **2a** (Table 1, entries 10 and 11). To further optimize reaction conditions, a similar test was carried out with different ratio of **1a** with low-valent titanium reagent from 1:2 to 1:4. The yield of product **2a** was increased as ratio was increased from 1:2 to 1:4 (Table 1, entries 3, 12, 13). However, a further increase of ratio to 1:5 failed to improve the yield of product **2a** (Table 1, entry 14). Moreover, we also try examined the effect of different temperatures (Table 1, entries 3, 15–17), to our delight at refluxed the reaction proceeded smoothly in high yield. Therefore, TEA and pH=8 was chosen as the reaction condition for all further synthesis of 8,13-dihydro-7*H*-indolo[2′,3′:3,4]pyrido[1,2-*b*]indazole.

In order to apply this reaction to a library synthesis of 8,13-dihydro-7*H*-indolo[2′,3′:3,4]-pyrido[1,2-*b*]indazole **2**, various 1-(2-nitrophenyl)-4,9-dihydro-3*H*-pyrido[3,4-*b*]indoles **1** were subjected to the reaction conditions (Scheme 2) and the results are summarized in Table 2.

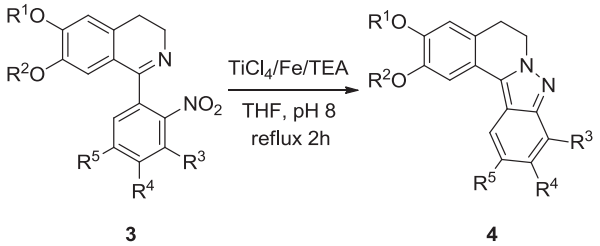


Scheme 2. The synthesis of 8,13-dihydro-7*H*-indolo[2′,3′:3,4]pyrido[1,2-*b*]indazoles **2**.

Table 2
Synthesis of 8,13-dihydro-7*H*-indolo[2′,3′:3,4]pyrido[1,2-*b*]indazoles **2**

Entry	R^1	R^2	R^3	Compound	Isolated yield (%)
1	H	H	H	**2a**	88
2	Cl	H	H	**2b**	86
3	CH_3	H	H	**2c**	92
4	H	H	Cl	**2d**	85
5	H	CH_3	H	**2e**	90
6	H	H	CH_3	**2f**	91

To expand the scope of the current method, 1-(2-nitrophenyl)-3,4-dihydroisoquinoline (**3**) was examined as a replacement for the 1-(2-nitrophenyl)-4,9-dihydro-3*H*-pyrido[3,4-*b*]indoles (**1**) (Scheme 3). The reductive cyclization products 5,6-dihydroindazolo[3,2-*a*]isoquinoline (**4**) was obtained in isolated yields in excess of 90%. Furthermore, the substituents on the phenethylamine and 2-nitrobenzoic acid moieties had no effect on the outcome of the reaction. The results are summarized in Table 3.



Scheme 3. The synthesis of 5,6-dihydroindazolo[3,2-*a*]isoquinoline **4**.

Table 3
Synthesis of 5,6-dihydroindazolo[3,2-*a*]isoquinoline **4**

Entry	R^1	R^2	R^3	R^4	R^5	Compound	Isolated yield (%)
1	CH_3	CH_3	H	H	CH_3	**4a**	92
2	CH_3	CH_3	H	H	Cl	**4b**	94
3	CH_3	CH_3	H	H	H	**4c**	95
4	CH_3	CH_3	H	H	CH_3O	**4d**	90
5	CH_3	CH_3	H	CH_3O	CH_3O	**4e**	95
6	CH_3	CH_3	Cl	H	H	**4f**	91
7	CH_3	CH_3	CH_3	H	H	**4g**	92
8	CH_2		H	H	H	**4h**	94
9	CH_2		H	Cl	H	**4i**	93

The structures of all products **2** and **4** were characterized by IR, ^{1}H NMR, ^{13}C NMR spectral data as well as HRMS analysis. The structure of **4h** was further confirmed by X-ray diffraction analysis.[22] The molecular structure of **4h** is shown in Fig. 1.

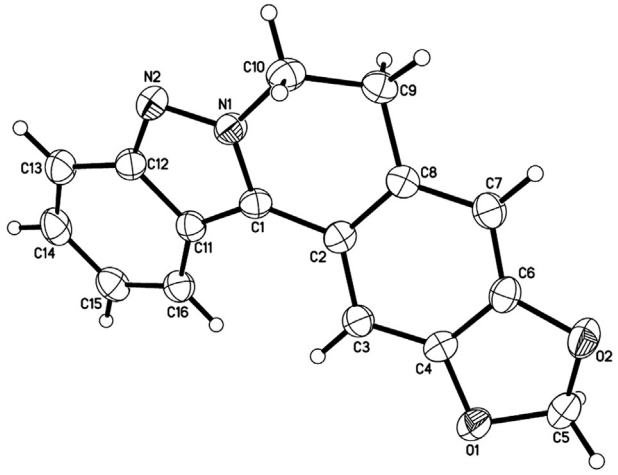


Fig. 1. The crystal structure of compound **4h**.

A plausible mechanistic pathway to products in Scheme 4, although the details are still unclear. $TiCl_4$ is reduced by iron dust to give low-valent titanium species. In the initial step, 1-(2-nitrophenyl)-4,9-dihydro-3*H*-pyrido[3,4-*b*]indole (**1**) was reduced by low-valent titanium species to **I**. The nitroso compound **I** then cyclized by the nucleophilic attack of the NH group onto the nitroso group giving intermediate **II**. Finally, the expected product **2** was produced by elimination of water promoted by ETA and low-valent titanium species.

synthesized via the reductive cyclization of nitro-aryl substrates induced by low-valent titanium reagent in the presence of TEA. This method has several distinct advantages, in that the starting materials are readily available, the handling procedures required of the reaction are relatively straightforward, and the substrate scope is particularly broad.

4. Experimental section

4.1. General

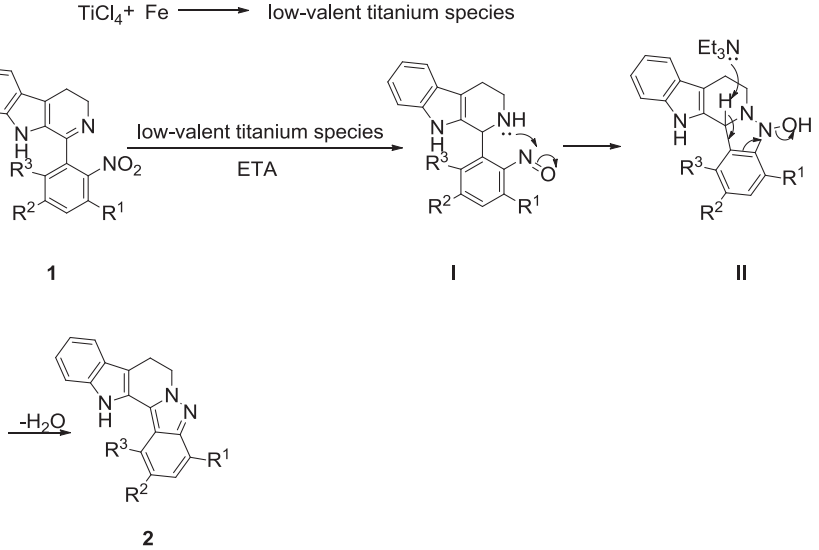
Tetrahydrofuran (THF) was distilled from sodium-benzophenone immediately prior to use. All the reactions were conducted under N_2 atmosphere. Melting points are uncorrected. IR spectra were recorded on Varian F-1000 spectrometer in KBr with absorptions in cm^{-1}. ^{1}H NMR and ^{13}C NMR were determined on Varian Invoa-300 MHz or Invoa-400 MHz spectrometer in DMSO-d_6 or $CDCl_3$ solution. *J* values are in Hertz. Chemical shifts are expressed in parts per million downfield from internal standard TMS. HRMS analyses were carried out using TOF-MS or GCT-TOF instrument.

4.2. Characterization data of 1 and 3 are represented as follows

The synthesis of compounds **1** and **3** was according to the literature.[21e]

*4.2.1. 1-(2-Nitrophenyl)-4,9-dihydro-3H-pyrido[3,4-b]indole (**1a**).* Mp: 144–146 °C (lit.[18d] 145–147 °C). IR (KBr) *ν*: 3397, 3025, 2984, 2874, 1621, 1525, 1445, 1345, 1319, 1291, 1172, 1082 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): *δ* (ppm) 3.00 (t, *J*=8.4 Hz, 2H, CH_2), 4.02 (t, *J*=8.4 Hz, 2H, CH_2), 7.13–7.17 (m, 1H, ArH), 7.24 (s, 2H, ArH), 7.55 (t, *J*=7.5 Hz, 1H, ArH), 7.61 (d, *J*=7.8 Hz, 2H, ArH), 7.71 (t, *J*=7.5 Hz, 1H, ArH), 7.90 (s, 1H, NH), 8.07 (d, *J*=8.1 Hz, 1H, ArH).

*4.2.2. 1-(3-Chloro-2-nitrophenyl)-4,9-dihydro-3H-pyrido[3,4-b]indole (**1b**).* Mp: 149–150 °C. IR (KBr) *ν*: 3067, 2942, 2837, 1593, 1528,



Scheme 4. Proposed mechanism for the synthesis of compound **2**.

3. Conclusion

In summary, a series of 8,13-dihydro-7*H*-indolo[2′,3′:3,4]pyrido[1,2-*b*]indazoles and 5,6-dihydroindazolo[3,2-*a*]isoquinolines were

1341, 1320, 1307, 1279, 1174, 1155, 1080, 1042 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): *δ* (ppm) 2.84–2.94 (m, 2H, CH_2), 3.62–3.64 (m, 1H, CH–H), 4.06–4.11 (m, 1H, CH–H), 7.06 (t, *J*=6.9 Hz, 1H, ArH), 7.19 (t, *J*=7.5 Hz, 1H, ArH), 7.30 (d, *J*=7.8 Hz, 1H, ArH), 7.60 (d,

J=7.5 Hz, 1H, ArH), 7.77 (t, *J*=7.8 Hz, 1H, ArH), 7.98 (d, *J*=7.8 Hz, 1H, ArH), 8.19 (t, *J*=8.1 Hz, 1H, ArH), 11.17 (s, 1H, NH).

*4.2.3. 1-(3-Methyl-2-nitrophenyl)-4,9-dihydro-3H-pyrido[3,4-b]indole (**1c**).* Mp: 138–140 °C. IR (KBr) *ν*: 3423, 3103, 2933, 2840, 1592, 1517, 1342, 1315, 1305, 1281, 1173, 1154, 1073, 1037 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): *δ* (ppm) 2.40 (s, 3H, CH_3), 2.92 (t, *J*=8.4 Hz, 2H, CH_2), 3.93 (t, *J*=8.4 Hz, 2H, CH_2), 7.11–7.15 (m, 1H, ArH), 7.23 (t, *J*=6.6 Hz, 2H, ArH), 7.36 (d, *J*=7.2 Hz, 2H, ArH), 7.42–7.47 (m, 1H, ArH), 7.59 (d, *J*=8.1 Hz, 1H, ArH), 8.10 (s, 1H, NH).

*4.2.4. 1-(2-Chloro-6-nitrophenyl)-4,9-dihydro-3H-pyrido[3,4-b]indole (**1d**).* Mp: 218–220 °C. IR (KBr) *ν*: 3067, 2943, 2835, 1594, 1528, 1341, 1321, 1307, 1278, 1175, 1153, 1081, 1044 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): *δ* (ppm) 2.81–3.00 (m, 2H, CH_2), 3.58–3.70 (m, 1H, CH–H), 4.05–4.13 (m, 1H, CH–H), 7.07 (t, *J*=7.2 Hz, 1H, ArH), 7.20 (t, *J*=7.5 Hz, 1H, ArH), 7.31 (d, *J*=8.1 Hz, 1H, ArH), 7.62 (d, *J*=7.8 Hz, 1H, ArH), 7.79 (t, *J*=8.1 Hz, 1H, ArH), 8.01 (d, *J*=8.1 Hz, 1H, ArH), 8.20 (t, *J*=8.1 Hz, 1H, ArH), 11.18 (s, 1H, NH).

*4.2.5. 1-(5-Methyl-2-nitrophenyl)-4,9-dihydro-3H-pyrido[3,4-b]indole (**1e**).* Mp: 190–192 °C (lit.[18d] 189–191 °C). IR (KBr) *ν*: 3424, 3102, 2935, 2841, 1590, 1516, 1342, 1315, 1305, 1281, 1171, 1152, 1072, 1035 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): *δ* (ppm) 2.45 (s, 3H, CH_3), 2.86–2.92 (m, 2H, CH_2), 3.86 (t, *J*=7.5 Hz, 2H, CH_2), 7.03–7.08 (m, 1H, ArH), 7.16–7.20 (m, 1H, ArH), 7.31 (d, *J*=8.1 Hz, 1H, ArH), 7.41 (s, 1H, ArH), 7.53–7.61 (m, 2H, ArH), 8.08 (d, *J*=7.8 Hz, 1H, ArH), 11.02 (s, 1H, NH).

*4.2.6. 1-(2-Methyl-6-nitrophenyl)-4,9-dihydro-3H-pyrido[3,4-b]indole (**1f**).* Mp: 206–208 °C. IR (KBr) *ν*: 3425, 3107, 2933, 2840, 1592, 1517, 1342, 1316, 1304, 1286, 1174, 1151, 1077, 1038 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): *δ* (ppm) 2.35 (s, 3H, CH_3), 2.83 (t, *J*=8.4 Hz, 2H, CH_2), 3.77 (t, *J*=8.4 Hz, 2H, CH_2), 7.05 (t, *J*=7.5 Hz, 1H, ArH), 7.19 (t, *J*=8.1 Hz, 1H, ArH), 7.35 (d, *J*=8.4 Hz, 1H, ArH), 7.46 (d, *J*=6.6 Hz, 1H, ArH), 7.60 (t, *J*=7.2 Hz, 3H, ArH), 11.09 (s, 1H, NH).

*4.2.7. 6,7-Dimethoxy-1-(5-methyl-2-nitrophenyl)-3,4-dihydroisoquinoline (**3a**).* Mp: 138–140 °C (lit.[18d] 137–139 °C). IR (KBr) *ν*: 3585, 3564, 3477, 3409, 1614, 1601, 1569, 1539, 1525, 1504, 1464, 1455, 1356, 1322, 1277, 1236, 1215, 1124, 1025, 884, 874, 835, 809, 754 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): *δ* (ppm) 2.45 (s, 3H, CH_3), 2.71 (t, *J*=7.5 Hz, 2H, CH_2), 3.50 (s, 3H, OCH_3), 3.66 (t, *J*=7.2 Hz, 2H, CH_2), 3.82 (s, 3H, OCH_3), 6.31 (s, 1H, ArH), 6.98 (s, 1H, ArH), 7.39 (s, 1H, ArH), 7.51 (d, *J*=8.1 Hz, 1H, ArH), 8.01 (d, *J*=8.4 Hz, 1H, ArH).

*4.2.8. 1-(5-Chloro-2-nitrophenyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (**3b**).* Mp: 164–165 °C. IR (KBr) *ν*: 3552, 3475, 3415, 2932, 2836, 1605, 1561, 1525, 1465, 1455, 1388, 1354, 1334, 1318, 1320, 1291, 1268, 1233, 1213, 1175, 1123, 1101, 1078, 1025, 887, 874, 836, 809, 754 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): *δ* (ppm) 2.73 (t, *J*=6.8 Hz, 2H, CH_2), 3.56 (s, 3H, OCH_3), 3.70 (t, *J*=6.8 Hz, 2H, CH_2), 3.84 (s, 3H, OCH_3), 6.40 (s, 1H, ArH), 7.01 (s, 1H, ArH), 7.70 (s, 1H, ArH), 7.83 (d, *J*=8.8 Hz, 1H, ArH), 8.15 (dd, J_1=2.4 Hz, J_2=8.8 Hz, 1H, ArH).

*4.2.9. 6,7-Dimethoxy-1-(2-nitrophenyl)-3,4-dihydroisoquinoline (**3c**).* Mp: 114–116 °C (lit.[18d] 113–115 °C). IR (KBr) *ν*: 3551, 3474, 3414, 1637, 1616, 1567, 1526, 1471, 1457, 1442, 1352, 1323, 1307, 1283, 1268, 1235, 1215, 1192, 1177, 1122, 1024, 948, 883, 808, 720, 618 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): *δ* (ppm) 2.72 (t, *J*=7.6 Hz, 2H, CH_2), 3.52 (s, 3H, OCH_3), 3.68 (t, *J*=7.6 Hz, 2H, CH_2), 3.83 (s, 3H, OCH_3), 6.37 (s, 1H, ArH), 6.99 (s, 1H, ArH), 7.59 (d, *J*=7.6 Hz, 1H, ArH), 7.71 (t, *J*=7.6 Hz, 1H, ArH), 7.82 (t, *J*=7.2 Hz, 1H, ArH), 8.08 (d, *J*=8.0 Hz, 1H, ArH).

*4.2.10. 6,7-Dimethoxy-1-(5-methoxy-2-nitrophenyl)-3,4-dihydroisoquinoline (**3d**).* Mp: 126–128 °C. IR (KBr) *ν*: 3552, 3480, 3414, 2937, 2834, 1602, 1584, 1567, 1512, 1482, 1460, 1406, 1353, 1334, 1297, 1282, 1265, 1243, 1210, 1161, 1122, 1079, 1048, 1025, 882, 861, 835, 789 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): *δ* (ppm) 2.77 (t, *J*=7.6 Hz, 2H, CH_2), 3.55 (s, 3H, OCH_3), 3.73 (t, *J*=7.2 Hz, 2H, CH_2), 3.86 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 6.36 (s, 1H, ArH), 7.03 (s, 1H, ArH), 7.07 (d, *J*=2.8 Hz, 1H, ArH), 7.26 (dd, J_1=2.8 Hz, J_2=9.2 Hz, 1H, ArH), 8.19 (d, *J*=9.2 Hz, 1H, ArH).

*4.2.11. 1-(4,5-Dimethoxy-2-nitrophenyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (**3e**).* Mp: 176–178 °C. IR (KBr) *ν*: 3650, 3630, 3621, 1577, 1560, 1541, 1522, 1508, 1473, 1458, 1353, 1336, 1296, 1257, 1216, 1072, 875, 731, 669, 650 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): *δ* (ppm) 2.77 (t, *J*=6.0 Hz, 2H, CH_2), 3.56 (s, 3H, CH_3O), 3.72 (t, *J*=5.4 Hz, 2H, CH_2), 3.87 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 6.39 (s, 1H, ArH), 7.02 (s, 1H, ArH), 7.08 (s, 1H, ArH), 7.72 (s, 1H, ArH).

*4.2.12. 1-(3-Chloro-2-nitrophenyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (**3f**).* Mp: 142–143 °C. IR (KBr) *ν*: 3630, 3555, 3477, 3414, 2963, 1637, 1597, 1559, 1534, 123, 1508, 1474, 1458, 1375, 1358, 1333, 1262, 1099, 1022, 802, 669 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): *δ* (ppm) 2.99–3.00 (m, 2H, CH_2), 3.65 (s, 3H, OCH_3), 3.93–3.95 (m, 5H, OCH_3+CH_2), 6.67 (s, 1H, ArH), 7.24 (s, 1H, ArH), 7.93–7.94 (m, 2H, ArH), 8.11–8.12 (m, 1H, ArH).

*4.2.13. 6,7-Dimethoxy-1-(3-methyl-2-nitrophenyl)-3,4-dihydroisoquinoline (**3g**).* Mp: 138–140 °C. IR (KBr) *ν*: 3584, 3563, 3479, 3415, 1615, 1602, 1568, 1538, 1524, 1505, 1463, 1454, 1357, 1321, 1275, 1235, 1214, 1123, 1024, 885, 875, 834, 808, 753 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): *δ* (ppm) 2.45 (s, 3H, CH_3), 2.76 (t, *J*=7.6 Hz, 2H, CH_2), 3.71 (s, 3H, OCH_3), 3.80 (t, *J*=7.6 Hz, 2H, CH_2), 3.94 (s, 3H, OCH_3), 6.56 (s, 1H, ArH), 6.76 (s, 1H, ArH), 7.35–7.40 (m, 2H, ArH), 7.47 (t, *J*=7.6 Hz, 1H, ArH).

*4.2.14. 5-(2-Nitrophenyl)-7,8-dihydro-[1,3]dioxolo[4,5-g]isoquinoline (**3h**).* Mp: 100–101 °C. IR (KBr) *ν*: 3585, 3562, 2931, 2835, 1589, 1519, 1468, 1456, 1441, 1342, 1321, 1305, 1265, 1224, 1193, 1175, 1025, 950, 885, 719 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): *δ* (ppm) 2.80–2.81 (m, 2H, CH_2), 3.80–3.81 (m, 2H, CH_2), 5.93 (s, 2H, CH_2), 6.28 (s, 1H, ArH), 6.74 (s, 1H, ArH), 7.52–7.53 (m, 1H, ArH), 7.60–7.61 (m, 1H, ArH), 7.70–7.71 (m, 1H, ArH), 8.11 (d, *J*=7.6 Hz, 1H, ArH).

*4.2.15. 5-(4-Chloro-2-nitrophenyl)-7,8-dihydro-[1,3]dioxolo[4,5-g]isoquinoline (**3i**).* Mp: 220–222 °C. IR (KBr) *ν*: 2959, 2941, 2898, 2857, 1610, 1594, 1585, 1510, 1483, 1446, 1427, 1401, 1373, 1339, 1313, 100, 1266, 1240, 1213, 1166, 1076, 1037, 932, 874, 845, 828, 801, 756. ^1H NMR (300 MHz, DMSO-d_6): *δ* (ppm) 3.13–3.14 (m, 2H, CH_2), 3.92–3.93 (m, 2H, CH_2), 6.17 (s, 2H, CH_2), 6.82 (s, 1H, ArH), 7.22 (s, 1H, ArH), 7.87 (d, *J*=7.8 Hz, 1H, ArH), 8.15 (d, *J*=7.5 Hz, 1H, ArH), 8.49 (s, 1H, ArH).

4.3. General procedure for the synthesis of triazaindeno[1,2-*a*]fluorene 2 and 5,6-dihydro-indazolo[3,2-*a*]isoquinoline 4

$TiCl_4$ (0.44 mL, 4 mmol) was added a stirred suspension of iron powder (0.23 g, 4 mmol) in freshly distilled anhydrous THF (10 mL) at room temperature (rt) under a dry N_2 atmosphere. After completion of the addition, the mixture was refluxed for 2 h. The suspension of the low-valent titanium reagent formed was cooled to rt, and then, 8 mL TEA was added; the pH was about 8. A solution of nitro-aryl substrates (**1** or **3**) 1 mmol in THF (3 mL) was added dropwise. The reaction mixture was then refluxed for 2 h under N_2. After this period, the thin layer chromatography (TLC) analysis of the mixture showed the reaction to be complete. The reaction mixture was quenched with 18% HCl (15 mL) and extracted with $CHCl_3$ (3×40 mL). The combined extracts were washed with water

(3×40 mL) and dried over anhydrous Na_2SO_4. After evaporation of the solvent under reduced pressure, the crude product was purified by recrystallization from 95% ethanol to give the pure products **2** or **4**.

*4.3.1. 8,13-Dihydro-7H-indolo[2′,3′:3,4]pyrido[1,2-b]indazole (**2a**).* Mp: 257–259 °C (lit.[18d] 256–258 °C). IR (KBr) ν: 3191, 3060, 2927, 1624, 1505, 1436, 1394, 1345, 1311, 1295, 1230, 1175, 1145, 1116, 1090, 1005 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 3.37 (t, J=7.5 Hz, 2H, CH_2), 4.76 (t, J=7.5 Hz, 2H, CH_2), 7.13–7.22 (m, 3H, ArH), 7.32 (t, J=7.2 Hz, 1H, ArH), 7.47 (d, J=7.8 Hz, 1H, ArH), 7.59 (d, J=7.5 Hz, 1H, ArH), 7.74 (d, J=9.0 Hz, 1H, ArH), 7.86 (d, J=8.4 Hz, 1H, ArH), 8.72 (s, 1H, NH).

*4.3.2. 4-Chloro-8,13-dihydro-7H-indolo[2′,3′:3,4]pyrido[1,2-b]indazole (**2b**).* Mp: 175–177 °C. IR (KBr) ν: 3186, 3105, 2905, 1645, 1475, 1445, 1365, 1335, 1316, 1233, 1169, 1148, 1115, 1092, 1057 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 3.37 (t, J=7.5 Hz, 2H, CH_2), 4.75 (t, J=7.5 Hz, 2H, CH_2), 7.09–7.22 (m, 4H, ArH), 7.47 (d, J=8.1 Hz, 1H, ArH), 7.59 (d, J=7.5 Hz, 1H, ArH), 7.64 (d, J=8.4 Hz, 1H, ArH), 9.43 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 25.5, 55.2, 115.2, 118.6, 121.0, 122.4, 124.1, 125.5, 127.4, 128.1, 129.2, 130.3, 131.0, 131.9, 132.1, 143.1, 153.9. HRMS: m/z (M^+) calcd for $C_{17}H_{12}{}^{35}ClN_3$: 293.0720; found: 293.0718.

*4.3.3. 4-Methyl-8,13-dihydro-7H-indolo[2′,3′:3,4]pyrido[1,2-b]indazole (**2c**).* Mp: 160–162 °C. IR (KBr) ν: 3192, 2932, 1632, 1590, 1512, 1444, 1395, 1345, 1310, 1292, 1229, 1174, 1142, 1119, 1082, 1007 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.65 (s, 3H, CH_3), 3.32 (t, J=7.5 Hz, 2H, CH_2), 4.74 (t, J=7.5 Hz, 2H, CH_2), 7.04–7.07 (m, 2H, ArH), 7.18–7.23 (m, 2H, ArH), 7.42 (d, J=8.4 Hz, 1H, ArH), 7.57 (d, J=6.9 Hz, 1H, ArH), 7.72 (d, J=7.8 Hz, 1H, ArH), 9.14 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 17.5, 21.2, 49.3, 108.5, 111.8, 116.4, 116.9, 118.8, 120.9, 122.8, 123.1, 125.8, 126.4, 126.8, 127.3, 128.1, 137.8, 148.7. HRMS: m/z (M^+) calcd for $C_{18}H_{15}N_3$: 273.1266; found: 273.1264.

*4.3.4. 1-Chloro-8,13-dihydro-7H-indolo[2′,3′:3,4]pyrido[1,2-b]indazole (**2d**).* Mp: 266–268 °C. IR (KBr) ν: 3187, 3105, 2911, 1635, 1509, 1465, 1385, 1340, 1310, 1290, 1231, 1171, 1142, 1115, 1092, 1002 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ (ppm) 3.28 (t, J=7.2 Hz, 2H, CH_2), 4.68 (t, J=7.5 Hz, 2H, CH_2), 7.07–7.27 (m, 4H, ArH), 7.56–7.68 (m, 3H, ArH), 10.59 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 25.6, 55.2, 115.2, 118.6, 121.1, 122.4, 124.1, 125.6, 127.4, 128.2, 129.3, 130.4, 131.1, 131.9, 132.1, 143.2, 154.0. HRMS: m/z (M^+) calcd for $C_{17}H_{12}{}^{35}ClN_3$: 293.0720; found: 293.0712.

*4.3.5. 2-Methyl-8,13-dihydro-7H-indolo[2′,3′:3,4]pyrido[1,2-b]indazole (**2e**).* Mp: 255–257 °C (lit.[18d] 254–257 °C). IR (KBr) ν: 3185, 3105, 2925, 1630, 1594, 1515, 1445, 1398, 1350, 1309, 1290, 1235, 1175, 1143, 1110, 1083, 1002 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ (ppm) 2.44 (s, 3H, CH_3), 3.27 (t, J=7.2 Hz, 2H, CH_2), 4.65 (t, J=6.9 Hz, 2H, CH_2), 7.06–7.16 (m, 3H, ArH), 7.48–7.55 (m, 3H, ArH), 8.09 (s, 1H, ArH), 11.74 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 20.3, 21.5, 48.7, 106.9, 111.9, 116.3, 117.1, 118.4, 118.6, 119.7, 122.0, 125.7, 125.8, 126.1, 128.6, 130.5, 137.7, 146.4.

*4.3.6. 1-Methyl-8,13-dihydro-7H-indolo[2′,3′:3,4]pyrido[1,2-b]indazole (**2f**).* Mp: 261–263 °C. IR (KBr) ν: 3195, 2935, 1647, 1572, 1473, 1442, 1362, 1332, 1312, 1232, 1165, 1143, 1117, 1094, 1055 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ (ppm) 2.51 (s, 3H, CH_3), 3.29–3.30 (m, 2H, CH_2), 4.70 (t, J=6.0 Hz, 2H, CH_2), 7.04–7.05 (m, 3H, ArH), 7.11–7.17 (m, 1H, ArH), 7.48 (d, J=6.9 Hz, 1H, ArH), 7.56 (d, J=6.6 Hz, 1H, ArH), 8.11 (s, 1H, ArH), 11.73 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 22.3, 25.7, 54.1, 112.6, 117.3, 121.2, 123.3, 123.9, 125.1, 127.2, 127.5, 130.3, 131.2, 131.4, 132.1, 132.2, 143.1, 153.1. HRMS: m/z (M^+) calcd for $C_{18}H_{15}N_3$: 273.1266; found: 273.1266.

*4.3.7. 2,3-Dimethoxy-11-methyl-5,6-dihydroindroindazolo[3,2-a]isoquinoline (**4a**).* Mp: 150–152 °C (lit.[18d] 152–154 °C). IR (KBr) ν: 3686, 3646, 2928, 2855, 2356, 2328, 1915, 1866, 1823, 1790, 1747, 1731, 1714, 1538, 1496, 1463, 1452, 1347, 1269, 1253, 1219, 1207, 807 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 2.44 (s, 3H, CH_3), 3.16 (t, J=7.2 Hz, 2H, CH_2), 3.82 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 4.51 (t, J=6.8 Hz, 2H, CH_2), 7.08 (s, 1H, ArH), 7.12 (d, J=8.8 Hz, 1H, ArH), 7.43 (s, 1H, ArH), 7.52 (d, J=8.8 Hz, 1H, ArH), 7.84 (s, 1H, ArH). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 27.2, 33.7, 53.1, 61.4, 61.7, 113.1, 118.1, 122.9, 122.9, 124.4, 125.7, 130.8, 133.9, 134.7, 136.3, 152.2, 153.8, 154.1.

*4.3.8. 11-Chloro-2,3-dimethoxy-5,6-dihydroindroindazolo[3,2-a]isoquinoline (**4b**).* Mp: 162–164 °C. IR (KBr) ν: 3677, 36,430, 3589, 2938, 2366, 2328, 1905, 1876, 1813, 17,905, 1748, 1737, 1560, 1542, 1508, 1489, 1458, 1347, 1264, 1243, 1210, 1203, 802, 669 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 3.18 (t, J=6.8 Hz, 2H, CH_2), 3.82 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 4.55 (t, J=6.4 Hz, 2H, CH_2), 7.10 (s, 1H, ArH), 7.27 (d, J=9.2 Hz, 1H, ArH), 7.40 (s, 1H, ArH), 7.67 (d, J=9.2 Hz, 1H, ArH), 8.18 (s, 1H, ArH). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 33.5, 53.3, 61.4, 61.7, 113.3, 117.9, 122.9, 124.8, 125.0, 125.2, 131.1, 131.7, 132.2, 135.8, 151.6, 153.9, 154.6. HRMS: m/z $[M+H]^+$ calcd for $C_{17}H_{16}{}^{35}ClN_2O_2$: 315.0900; found: 315.0890.

*4.3.9. 2,3-Dimethoxy-5,6-dihydroindroindazolo[3,2-a]isoquinoline (**4c**).* Mp: 181–182 °C (lit.[18d] 180–182 °C). IR (KBr) ν: 3060, 2934, 2832, 1608, 1530, 1496, 1456, 1404, 1341, 1288, 1216, 1112, 1035, 1000, 858, 796, 741, 685, 645, 597, 577 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 3.18 (t, J=6.4 Hz, 2H, CH_2), 3.82 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 4.55 (t, J=6.8 Hz, 2H, CH_2), 7.08 (s, 1H, ArH), 7.14 (t, J=8.0 Hz, 1H, ArH), 7.29 (t, J=7.6 Hz, 1H, ArH), 7.45 (s, 1H, ArH), 7.63 (d, J=8.4 Hz, 1H, ArH), 8.13 (d, J=8.4 Hz, 1H, ArH). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 33.6, 53.2, 61.4, 61.6, 113.0, 118.0, 122.7, 123.0, 125.4, 126.4, 127.3, 130.9, 131.3, 135.6, 153.3, 153.8, 154.3.

*4.3.10. 2,3,11-Trimethoxy-5,6-dihydroindroindazolo[3,2-a]isoquinoline (**4d**).* Mp: 154–156 °C. IR (KBr) ν: 3552, 3480, 3414, 2890, 2829, 1637, 1618, 1585, 1540, 1499, 1465, 1438, 1362, 1351, 1322, 1297, 1285, 1253, 1223, 1203, 1179, 816, 622 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 3.17 (t, J=6.8 Hz, 2H, CH_2), 3.83 (s, 3H, CH_3O), 3.88 (s, 3H, CH_3O), 3.93 (s, 3H, CH_3O), 4.51 (t, J=7.2 Hz, 2H, CH_2), 6.98 (dd, J_1=2.0 Hz, J_2=9.2 Hz, 1H, ArH), 7.08 (s, 1H, ArH), 7.29 (d, J=4.0 Hz, 1H, ArH), 7.42 (s, 1H, ArH), 7.56 (d, J=9.6 Hz, 1H, ArH). HRMS: m/z $[M+H]^+$ calcd for $C_{18}H_{19}N_2O_3$: 311.1396; found: 311.1401.

*4.3.11. 2,3,10,11-Tetramethoxy-5,6-dihydroindroindazolo[3,2-a]isoquinoline (**4e**).* Mp: 182–184 °C. IR (KBr) ν: 2937, 2922, 1611, 1551, 1499, 1458, 1449, 1436, 1398, 1371, 1320, 1303, 1290, 1260, 1229, 1191, 1169, 1156, 1112, 1028, 1011, 977, 860, 814, 784 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ (ppm) 3.12 (t, J=6.8 Hz, 2H, CH_2), 3.80 (s, 6H, 2× CH_3O), 3.86 (s, 3H, CH_3O), 3.90 (s, 3H, CH_3O), 4.42 (d, J=6.8 Hz, 2H, CH_2), 6.97 (s, 1H, ArH), 7.05 (s, 1H, ArH), 7.24 (s, 1H, ArH), 7.37 (s, 1H, ArH). ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 28.9, 47.8, 56.0, 56.2, 56.3, 56.6, 96.9, 99.0, 107.9, 111.6, 113.0, 120.7, 125.6, 129.6, 144.7, 148.1, 148.6, 148.8, 151.2. HRMS: m/z (M^+) calcd for $C_{19}H_{20}N_2O_4$: 340.1423; found: 304.1431.

*4.3.12. 9-Chloro-2,3-dimethoxy-5,6-dihydroindroindazolo[3,2-a]isoquinoline (**4f**).* Mp: 174–176 °C. IR (KBr) ν: 3435, 3062, 1723, 1635, 1610, 1538, 1500, 1486, 1466, 1424, 1374, 1332, 1292, 1261, 1239, 1198, 1120, 1075, 1058, 1025, 800, 754, 681, 566 cm^{-1}. ^1H NMR

(400 MHz, $CDCl_3$): δ (ppm) 3.19 (t, J=7.2 Hz, 2H, CH_2), 3.94 (s, 3H, CH_3O), 4.00 (s, 3H, CH_3O), 4.65 (t, J=6.8 Hz, 2H, CH_2), 6.84 (s, 1H, ArH), 7.06 (t, J=8.0 Hz, 1H, ArH), 7.33 (d, J=7.2 Hz, 1H, ArH), 7.40 (s, 1H, ArH), 7.84 (d, J=8.4 Hz, 1H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 23.5, 42.9, 50.9, 51.1, 102.1, 106.3, 113.6, 113.9, 114.9, 117.0, 117.8, 119.9, 120.2, 126.9, 140.8, 143.3, 143.9. HRMS: m/z (M^+) calcd for $C_{17}H_{15}{}^{35}ClN_2O_2$: 314.0822; found: 314.0822.

*4.3.13. 2,3-Dimethoxy-9-methyl-5,6-dihydroindroindazolo[3,2-a]isoquinoline (**4g**).* Mp: 125–126 °C. IR (KBr) ν: 3850, 3646, 1841, 1789, 1769, 1731, 1694, 1681, 1667, 1660, 1650, 1639, 1614, 1582, 1574, 1550, 1538, 1519, 1505, 1455, 1359, 1308, 1264, 1236, 1195, 1160, 1065, 1059, 1029, 815, 734, 681, 576 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.65 (s, 3H, CH_3), 3.19 (t, J=6.8 Hz, 2H, CH_2), 3.93 (s, 3H, CH_3O), 4.01 (s, 3H, CH_3O), 4.63 (t, J=6.8 Hz, 2H, CH_2), 6.83 (s, 1H, ArH), 7.05–7.09 (m, 2H, ArH), 7.46 (s, 1H, ArH), 7.77–7.81 (m, 1H, ArH). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 22.6, 33.6, 53.1, 61.3, 61.5, 112.8, 118.0, 122.4, 123.7, 125.6, 127.6, 130.3, 130.8, 132.6, 135.8, 153.6, 153.8, 154.2. HRMS: m/z $[M+Na]^+$ calcd for $C_{18}H_{18}N_2NaO_2$: 317.1266; found: 317.0227.

*4.3.14. 5,6-Dihydro-[1,3]dioxolo[4,5-g]indazolo[3,2-a]isoquinoline (**4h**).* Mp: 158–160 °C. IR (KBr) ν: 3855, 3822, 3775, 3745, 3726, 3691, 3650, 3620, 2912, 1560, 1542, 1523, 1508, 1499, 1478, 1458, 1293, 1230, 1031, 958, 924, 909, 859, 841, 749, 669 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 3.16 (t, J=6.4 Hz, 2H, CH_2), 4.55 (t, J=6.8 Hz, 2H, CH_2), 6.09 (s, 2H, CH_2), 7.07 (s, 1H, ArH), 7.13 (t, J=7.2 Hz, 1H, ArH), 7.30 (t, J=8.0 Hz, 1H, ArH), 7.57 (s, 1H, ArH), 7.62 (d, J=8.4 Hz, 1H, ArH), 8.12 (d, J=8.4 Hz, 1H, ArH). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 33.6, 52.6, 106.8, 109.7, 114.6, 122.2, 122.4, 125.8, 126.2, 127.3, 131.6, 132.5, 135.7, 152.2, 152.3, 152.5. HRMS: m/z $[M+H]^+$ calcd for $C_{16}H_{13}N_2O_2$: 265.0977; found: 265.1127.

*4.3.15. 10-Chloro-5,6-dihydro[1,3]dioxolo[4,5-g]indazolo[3,2-a]isoquinoline (**4i**).* Mp: 174–176 °C. IR (KBr) ν: 3215, 2905, 1619, 1516, 1502, 1491, 1477, 1445, 1417, 1402, 1377, 1336, 1299, 1279, 1257, 1241, 1204, 1160, 1051, 1038, 942, 929, 904, 848, 840, 796, 748, 695 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 3.12 (t, J=6.8 Hz, 2H, CH_2), 4.49 (t, J=6.8 Hz, 2H, CH_2), 6.07 (s, 2H, CH_2), 7.01–7.05 (m, 2H, ArH), 7.49 (s, 1H, ArH), 7.66 (s, 1H, ArH), 8.10 (d, J=9.2 Hz, 1H, ArH). ^{13}C NMR (75 MHz, DMSO-d_6): δ (ppm) 28.8, 48.0, 102.1, 104.9, 109.7, 116.2, 116.7, 120.7, 122.9, 123.3, 127.7, 131.1, 131.3, 147.5, 147.8, 148.3. HRMS: m/z $[M]^+$, Calcd for $C_{16}H_{11}{}^{35}ClN_2O_2$: M 298.0509; found: 298.0507.

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22. The single-crystal growth was carried out in ethanol solutions at rt. Intensity data were collected on a Rigaku Mercury diffractometer with graphite monochromated M_oK_α radiation (λ=0.71070 Å) using the ω scan mode with 3.08°<θ<25.35°. Crystal data for 4 h: empirical formula $C_{14}H_{12}N_2O_2$, crystal dimension 0.65×0.58×0.55 mm, monoclinic, space group P-1, a=8.057(3) Å, b=15.736(5) Å, c=10.149(4) Å, α=90°, β=110.414(6)°, γ=90°. V=1206.1(7) Å^3, Mr=264.28, Z=4, Dc=1.455 Mg/m^3, $\mu(M_oK_\alpha)$=0.098 mm^{-1}, $F(000)$=552, S=1.047, R_1=0.0623, wR_2=0.1555.