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A new approach to isoindoloisoquinolinones. A simple synthesis of nuevamine

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Abstract—A convenient and versatile short step synthesis of isoindoloisoquinolinones, illustrated by the total synthesis of the alkaloid nuevamine **1a**, is described. The tetracyclic lactam compounds were obtained by a tactical combination of the Parham procedure for the elaboration of the isoindolinone template and an aryne-mediated cyclization giving rise to the nitrogen containing six-membered heteroring unit.
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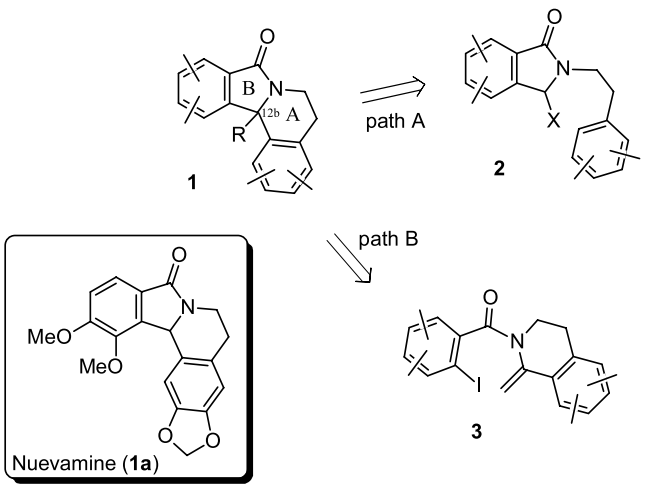
1. Introduction

Members of the plant family *Berberidaceae* are known to produce an array of unusual isoquinoline alkaloids. Their study is facilitated by the fact that relatively large amounts of these plants can be collected. This therefore makes conceivable the study of minor alkaloids present, that is, those available only in small amounts, which often afford an insight into the catabolic pathways for the principal alkaloids. This is notably the case of isoindolo[1,2-*a*]-isoquinolinones **1**, a class of tetracyclic lactams which are interesting due to the real and potential biological activities of many of their derivatives.[1] The eminent example nuevamine **1a** has been isolated from *Berberis darwinii* Hook, gathered in southern Chile, in the vicinity of Cuidad Osorno.[2] This alkaloid occupies a special place since it was the first recognized isoindoloisoquinolinone reported from natural sources. Initially, its structure was erroneously assigned but later revision led unambiguously to structure **1a**.[3] Two main general approaches to the synthesis of isoindolo[1,2-*a*]isoquinolinones have been reported so far. They differ in the type of the annulation process and in the heteroring unit embedded in the alkaloid skeleton, formed in the last step. Thus, creation of ring A has been generally achieved by intramolecular cyclization of *N*-acyliminium ions derived from α-substituted isoindolinone derivatives **2** (Retrosynthetic Scheme 1, path A) and a closer analysis of the literature reveals that improvement and modification of this synthetic approach has been confined to the development of new precursors of the acyliminium species.



Scheme 1.

Thus, intramolecular amidoarylation as the key ring-forming step has been ensured from α-hydroxy (X=OH)[4] and α-alkoxy (X=OMe)[5] lactamic precursors by treatment with a wide variety of Lewis acid catalysts such as scandium and copper triflates,[5c,d] $SnCl_4$,[5e] TMSOTf,[5c] $BF_3{\cdot}OEt_2$,[5e,f] $TiCl_4$,[5b] and trifluoroacetic acid.[4,5a] An original structural modification recently developed by Katritzky led to the generation of the *N*-acyliminium cation by loss of a benzotriazolyl anion upon treatment of **2** (X=benzotriazolyl) with $TiCl_4$.[6] An alternative synthetic tactic has been also proposed by Sotomayor in which the intermediate *N*-acyliminium species was generated from a preformed

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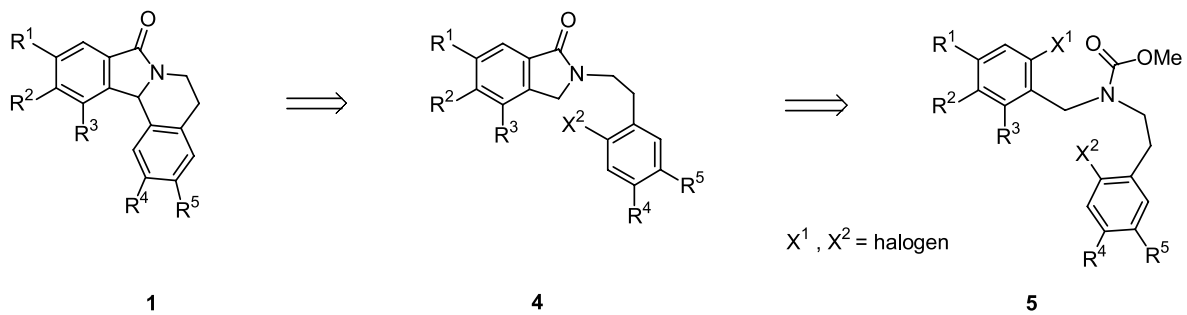
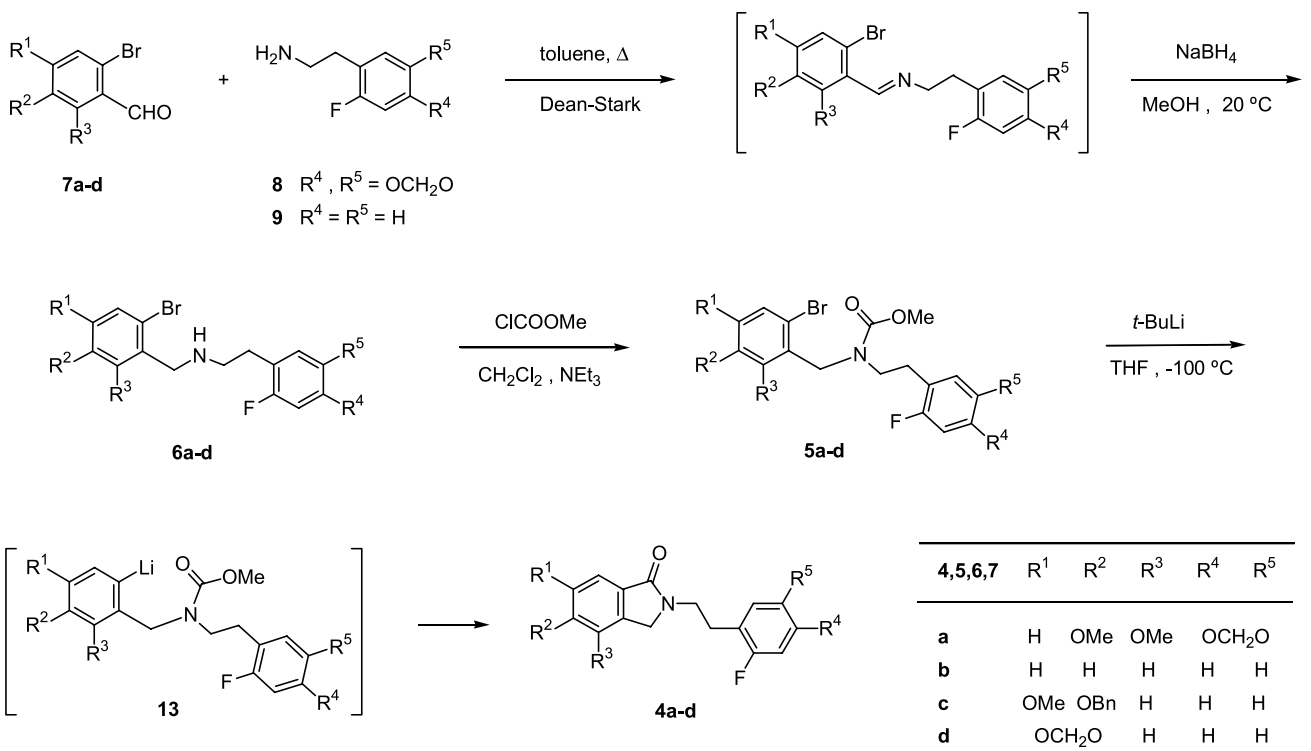
annulated model **1** (R=OH).[7] This skilful approach allowed intermolecular α-amidoalkylation, giving access to a wide variety of C-12b substituted nuevamine-type alkaloids. However, probably due to difficulties associated with the elaboration of the starting compounds and particularly the absolute necessity of having an unsymmetrically disubstituted isoindolinone parent compound available, most of these syntheses have only been claimed to give access to the nuevamine skeleton. Isoindoloisoquinolinones have been also accessed by ring B formation performed by intramolecular Heck cyclization of aromatic enamides **3** (Scheme 1, path B). In this annulation process the 6-*endo-trig* cyclization often competes with the 5-*exo-trig* cyclization but this problem has been circumvented by the addition of a hydride source which favors the regio-controlled formation of the five-membered ring product.[8] Unfortunately, all models elaborated by this technique are inevitably alkylated at the C-12b position and this precludes the synthesis of unsubstituted models such as the alkaloid nuevamine. Some more confidential methods based upon the phosphoric acid cyclization of β-phenylethylaminophthalide[9] or by a combination of the Pictet–Spengler reaction with Pd-catalyzed carbonylation applied to (2-iodobenzylidene)-phenethylamine derivatives[10] have been also used occasionally for the assemblage of the isoindoloisoquinolinone framework. Consequently, the elegant synthetic approach reported by Castedo et al.[3] which allowed the unambiguous assignment of the structure of the alkaloid nuevamine can arguably be deemed to be the sole total synthesis to date of this natural product.

2. Results and discussion

In continuation of our investigation into the synthesis of alkaloids with an isoindolinone ring system as the main structural subunit[11] we herein wish to disclose an alternative, efficient and tactically new approach to isoindoloisoquinolinones illustrated by the total synthesis of the alkaloid nuevamine isolated as a racemate from Chilean barberries. Our strategy, which is depicted in retrosynthetic Scheme 2, is based on the use of 2-arylethylisoindolinones **4** as key



Scheme 2.

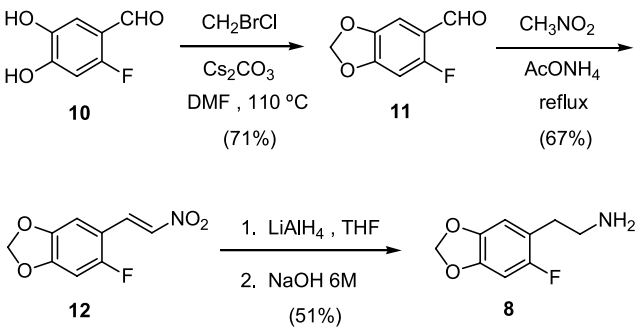


4,5,6,7	R^1	R^2	R^3	R^4	R^5
a	H	OMe	OMe	OCH_2O	
b	H	H	H	H	H
c	OMe	OBn	H	H	H
d	OCH_2O		H	H	H

Scheme 3.

intermediates. These lactams were obtained by Parham-type cyclization induced by aromatic lithiation of the halogenodiarylalkylamine **5** with a carbamate function acting as the internal electrophile.[12] Aryne-mediated cyclization induced by basic treatment of the primarily annulated compounds **4** then should complete the synthesis of the target isoindoloisoquinolinones **1**. A contentious issue in the elaboration of the starting compounds was judging the proper choice for the halogen atoms X^1, X^2 connected to the environmentally different aromatic units of **5**. Critical to the success of the strategy was the incorporation of a halogen atom X^1 liable to cause the aromatic metallation–cyclization sequence leading to **4** by a metal–halogen exchange, while sparing the second halogen atom X^2. In contrast X^2 should allow and, if feasible, facilitate the mandatory aryne formation for the ultimate annulation step. Since it has been clearly established that metal–halogen exchange occurs preferentially with aryl bromides and iodides, whereas arylfluorides and chlorides do not normally react with organolithium compounds but undergo instead *ortho*-metallation and aryne formation afterwards[13] we embarked on the synthesis of the diversely halogenated carbamates **5a–d** (Scheme 3).

The first facet of the synthesis was the elaboration of the halogenated diarylalkylamines **6a–d**. These compounds were readily obtained by a reductive amination process involving the bromobenzaldehyde derivatives **7a–d** and the appropriate fluorinated arylethylamines **8**, **9**. Initially, the aromatic fluorinated amine **8** was obtained by the three step sequence depicted in Scheme 4 which involves the double reduction of the nitrostyrene derivative **12** deriving from the fluorocarboxaldehyde derivative **11**.



Scheme 4.

The compound **11** was readily accessible by linking the vicinal hydrophenolic functions of the parent compound **10** (Scheme 4).

Treatment of amines **6a–d** with methyl chloroformate delivered the carbamates **5a–d** in excellent yields (73–91%). To ensure the formation of the lithiated intermediate **13** a THF solution of the appropriate arylbromide was treated with 1.1 equiv. of *t*-BuLi at −100 °C in THF. The intramolecular ring closure was instantaneous as demonstrated by the isolation solely of the annulated compounds **4a–d** upon aqueous work-up (Table 1).

Table 1. Yields for compounds **6a–d**, **5a–d** and **4a–d** produced via Scheme 3

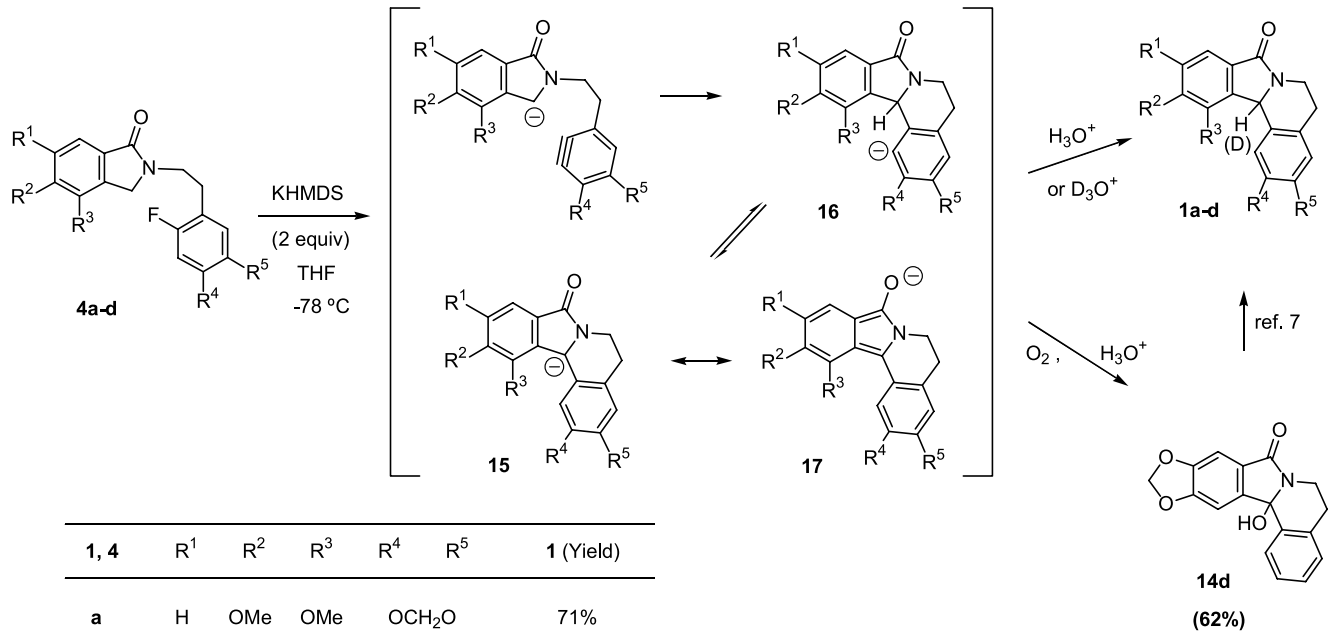
	6 (%)	**5** (%)	**4** (%)
a	94	78	68
b	86	91	72
c	97	76	64
d	95	73	62

The concept of the subsequent generation of the six-membered heteroring unit embedded in the isoindoloisoquinolinone skeleton originated from the following premises: (i) isoindolinones have been easily metalated at the benzylic position of the lactam unit thus allowing the connection of a range of electrophiles at the 3-position of the heteroring system;[14] (ii) arylfluorides are good candidates for the generation of arynes[13,15a] and the anion–aryne cyclization processes, particularly those involving nitrogen-bearing nucleophiles and carbanions, occupy a place of choice in the arsenal of alkaloid synthesis tactics.[15b] Compounds **4b–d** were then treated with KHMDS [potassium bis(trimethylsilyl)amide] (2.2 equiv.) in the presence of 18-crown-6 at −78 °C in THF and gratifyingly classical work-up delivered single compounds which were unambiguously identified as the annulated isoindolinones **1b–d**. Performing this reaction sequence with the appropriate open model **4a** led straightforwardly to the target natural product nuevamine **1a** with a very satisfactory yield (38% over last three steps).

It is worth noting that reactions must be preferably carried out after careful degassing of the solution since quite significant amounts of products which were hydroxylated at C-12b, as exemplified by the formation of **14d**, were obtained in reactions performed in non-deoxygenated solutions (Scheme 5). The formation of this α-hydroxylactam may tentatively be explained by capture of the carbanionic species **15** by oxygen. Intermediate **15** would be formed by a prototropy of **16**, attributable to a greater stabilization of the bibenzylic carbanionic species which can further adopt the *o*-quinodimethane structure **17**. The fact that acidic work-up with D_3O^+ led to the exclusive incorporation of deuterium on the bibenzylic C-12b position as exemplified by the formation of **1a**(D) corroborates this hypothesis. However, this reaction was not really detrimental to the elaboration of the desired compounds **1a–d** since the hemiaminal compounds (e.g., **14d**) can be almost quantitatively converted into the dehydroxylated models (e.g., **1d**)[7] and can also serve for the introduction of substituents at C-12b.[7]

3. Conclusion

In summary, we have identified a novel and flexible synthetic approach to isoindoloisoquinolinones. In only two key synthetic steps from easily accessible precursors we have prepared the isoindolinone template by reliance on the Parham procedure and the creation of the isoquinoline ring system by an aryne-mediated cyclization process. The total synthesis of the alkaloid nuevamine emphasizes the versatility and regiospecificity of this new conceptual approach and we believe that this work demonstrates a general new methodology for the preparation of similar structurally modified isoindoloisoquinolinone alkaloids.



1, 4	R^1	R^2	R^3	R^4	R^5	1 (Yield)
a	H	OMe	OMe	OCH_2O		71%
b	H	H	H	H	H	73%
c	OMe	OBn	H	H	H	77%
d	OCH_2O		H	H	H	69%

Scheme 5.

4. Experimental

4.1. General

Tetrahydrofuran (THF) was pre-dried with anhydrous Na_2SO_4 and distilled over sodium benzophenone ketyl under Ar before use. DMF, CH_2Cl_2, NEt_3, and toluene were distilled from CaH_2. Dry glassware was obtained by oven-drying and assembly under dry Ar. The glassware was equipped with rubber septa and reagent transfer was performed by syringe techniques. For flash chromatography, Merck silica gel 60 (40–63 μ; 230–400 mesh ASTM) was used. The melting points were obtained on a Reichert–Thermopan apparatus and are not corrected. NMR spectra: Bruker AM 300 (300 and 75 MHz, for ^1H and ^{13}C respectively). For ^1H, ^{13}C NMR, $CDCl_3$ was used as solvent, TMS as internal standard. Microanalyses were performed by the CNRS microanalysis center.

The bromobenzaldehyde derivatives **7a**[16,17] and **7c**[18,19] were synthesized according to literature methods.

4.2. Synthesis of 2-(6-fluorobenzo[1,3]dioxol-5-yl)-ethylamine (8)

2-Fluoro-4,5-dihydroxybenzaldehyde **10** was obtained from 4-fluoroveratrole by sequential formylation[20] and demethylation.[21]

4.2.1. 6-Fluorobenzo[1,3]dioxole-5-carbaldehyde (6-fluoropiperonal, 11). Bromochloromethane (2.61 g, 20.2 mmol) was added, under Ar, to a stirred suspension of 2-fluoro-4,5-dihydroxybenzaldehyde **10** (2.10 g, 13.4 mmol) and cesium carbonate (6.57 g, 20.2 mmol) in anhydrous DMF (20 mL) and the resulting mixture was heated at 110 °C for 3 h. After cooling to room temperature the mixture was filtered through a pad of Celite® which was subsequently washed with EtOAc (50 mL). Water (50 mL) was added, the organic layer was separated and the aqueous layer was extracted with EtOAc (3×50 mL). The organic layers were combined, washed with water, brine and dried ($MgSO_4$). Evaporation of the solvent left a residue, which was purified by flash column chromatography with hexanes/AcOEt (50:50) as eluent. Yield 1.60 g (71%); mp 72–73 °C; ^1H NMR (δ) 6.05 (s, 2H, OCH_2O), 6.61 (d, J_{HF}=9.8 Hz, 1H, aromatic H), 7.19 (d, J_{HF}=5.4 Hz, 1H, aromatic H), 10.15 (s, 1H, CHO); ^{13}C NMR (δ) 97.9 (d, J_{CF}=29 Hz), 102.9, 104.9 (d, J_{CF}=3 Hz), 117.9 (d, J_{CF}=8 Hz), 144.8 (d, J_{CF}=1 Hz), 154.0 (d, J_{CF}=15 Hz), 162.5 (d, J_{CF}=252 Hz), 185.4 (d, J_{CF}=8 Hz). Anal. Calcd for $C_8H_5O_3F$ (168.1): C, 57.15; H, 3.00%. Found: C, 57.35; H, 2.94%.

4.2.2. 5-Fluoro-6-(2-nitrovinyl)-benzo[1,3]dioxole (12). A solution of 6-fluorobenzo[1,3]dioxole-5-carbaldehyde (1.45 g, 8.6 mmol), $AcONH_4$ (0.15 g, mmol) in nitromethane (CH_3NO_2, 6.5 mL) was refluxed for 5 h. After cooling, the yellow precipitate was filtered and washed with MeOH (20 mL) to afford yellow crystals. Yield 1.12 g, (67%); mp 143–144 °C; ^1H NMR (δ) 6.07 (s, 2H, OCH_2O), 6.68 (d, J_{HF}=9.8 Hz, 1H, aromatic H), 6.87 (d, J_{HF}=5.9 Hz, 1H, aromatic H), 7.55 (d, J=13.7 Hz, 1H, CH=), 8.03 (d, J=13.7 Hz, 1H, CH=); ^{13}C NMR (δ) 98.7 (d, J_{CF}=30 Hz), 102.9, 106.8 (d, J_{CF}=4 Hz), 110.6 (d, J_{CF}=13 Hz), 132.2 (d, J_{CF}=3 Hz), 137.0 (d, J_{CF}=9 Hz), 144.9, 152.1 (d, J_{CF}=15 Hz), 158.5 (d, J_{CF}=250 Hz). Anal. Calcd for $C_9H_6FNO_4$ (211.1): C, 51.20; H, 2.86; N, 6.63%. Found: C, 51.02; H, 3.01; N, 6.55%.

4.2.3. 2-(6-Fluorobenzo[1,3]dioxol-5-yl)ethylamine (8). A solution of the nitro derivative **12** (2.00 g, 10.3 mmol) in dry THF (15 mL) was added dropwise, under Ar, to an ice cooled suspension of lithium aluminum hydride ($LiAlH_4$, 3.89 g, 102.6 mmol) in dry THF (50 mL). The mixture was stirred at 0 °C for 2 h and then refluxed overnight. The suspension was cooled to 0 °C and the excess of $LiAlH_4$ was quenched with 6 M aqueous sodium hydroxide (50 mL). The precipitate was filtered off and extracted with boiling THF for 1 h, then filtered and washed with Et_2O (50 mL). The combined organic layers were washed with brine and dried (Na_2SO_4). After evaporation of the solvent the residue was purified by flash column chromatography with AcOEt/Et_3N (90:10) as eluent. Yield 0.96 g (51%); oil; ^1H NMR (δ_H) 1.76 (br s, 2H, NH_2), 2.73 (t, J=7.1 Hz, 2H, CH_2), 3.23 (t, J=7.1 Hz, 2H, CH_2), 5.79 (s, 2H, OCH_2O), 6.43 (d, J_{HF}=8.8 Hz, 1H, aromatic H), 6.54 (d, J_{HF}=5.6 Hz, 1H, aromatic H); ^{13}C NMR (δ_C) 29.2, 51.9, 97.7 (d, J_{CF}= 31 Hz), 101.5, 109.6 (d, J_{CF}=6 Hz), 119.0 (d, J_{CF}=14 Hz), 143.3 (d, J_{CF}=2 Hz), 146.2 (d, J_{CF}=14 Hz), 155.6 (d, J_{CF}=237 Hz). Anal. Calcd for $C_9H_{10}FNO_2$ (183.2): C, 59.01; H, 5.50; N, 7.65%. Found: C, 59.23; H, 5.40; N, 7.77%.

4.3. General procedure for the synthesis of the amines 6a–d

A solution of the [2-(2-fluorophenyl)ethyl]amine derivative **8** or **9** (10 mmol) and the appropriate bromobenzaldehyde derivative **7a–d** (10 mmol) in toluene (40 mL) was refluxed for 3 h in a Dean–Stark apparatus. After removal of toluene in vacuo the *N*-benzylidene-[2-(2-fluorophenyl)ethyl]-amine derivative was used directly in the next step without further purification. $NaBH_4$ (20 mmol, 0.76 g) was added portionwise to a solution of the previously obtained Schiff base in MeOH (50 mL) at room temperature. The mixture was stirred at room temperature for 1 h and the solvent was removed under vacuo. The crude mixture was dissolved in dichloromethane (50 mL), washed with saturated aqueous NH_4Cl solution (30 mL) and then brine (30 mL). The organic solution was dried (Na_2SO_4), filtered and concentrated in vacuo. The crude oily amines **6a–d** were purified by flash column chromatography with AcOEt/hexanes/NEt_3 (80:10:10) as eluent.

4.3.1. (6-Bromo-2,3-dimethoxybenzyl)-[2-(6-fluorobenzo[1,3]dioxol-5-yl)ethyl]amine (6a). Yield 3.78 g, (94%), oil; ^1H NMR (δ) 1.70 (br s, 1H, NH), 2.68–2.77 (m, 4H, 2×CH_2), 3.79 (s, 6H, 2×CH_3), 3.92 (s, 2H, CH_2), 5.86 (s, 2H, OCH_2O), 6.50 (d, J_{HF}=9.0 Hz, 1H, aromatic H), 6.60 (d, J_{HF}=6.1 Hz, 1H, aromatic H), 6.67 (d, J= 8.8 Hz, 1H, aromatic H), 7.19 (d, J=8.8 Hz, 1H, aromatic H); ^{13}C NMR (δ) 29.4 (d, J_{CF}=2 Hz), 47.6, 48.7, 55.8, 61.1, 97.8 (d, J_{CF}=31 Hz), 101.5, 112.5 (d, J_{CF}=6 Hz), 112.5, 115.4, 118.7 (d, J_{CF}=19 Hz), 127.8, 133.6, 143.4 (d, J_{CF}= 2 Hz), 146.2 (d, J_{CF}=14 Hz), 148.6, 152.2, 155.6 (d, J_{CF}=236 Hz). Anal. Calcd for $C_{18}H_{19}BrFNO_4$ (412.3): C, 52.44; H, 4.65; N, 3.40%. Found: C, 52.56; H, 4.78; N, 3.17%.

4.3.2. (2-Bromobenzyl)-[2-(2-fluorophenyl)ethyl]amine (6b). Yield 2.65 g (86%); oil; ^1H NMR (δ) 1.57 (br s, 1H, NH), 2.91 (s, 4H, 2×CH_2), 3.90 (s, 2H, CH_2), 6.99–7.13 (m, 3H, aromatic H), 7.15–7.29 (m, 3H, aromatic H), 7.37 (d, J=7.6 Hz, 1H, aromatic H), 7.53 (d, J=7.8 Hz, 1H, aromatic H); ^{13}C NMR (δ) 29.8 (d, J_{CF}=2 Hz), 49.1 (d, J_{CF}=1 Hz), 53.5, 115.3 (d, J_{CF}=22 Hz), 124.0 (d, J_{CF}= 4 Hz), 124.0, 126.9 (d, J_{CF}=16 Hz), 127.4, 127.9 (d, J_{CF}= 8 Hz), 128.5, 130.2, 131.0 (d, J_{CF}=5 Hz), 132.8, 139.3, 161.3 (d, J_{CF}=243 Hz). Anal. Calcd for $C_{15}H_{15}BrFN$ (308.2): C, 58.46; H, 4.91; N, 4.54%. Found: C, 58.21; H, 5.14; N, 4.41%.

4.3.3. (5-Benzyloxy-2-bromo-4-methoxybenzyl)-[2-(2-fluorophenyl)ethyl]amine (6c). Yield 4.31 g (97%); oil; ^1H NMR (δ) 1.56 (br s, 1H, NH), 2.81 (s, 4H, 2×CH_2), 3.76 (s, 2H, CH_2), 3.85 (s, 3H, CH_3), 5.10 (s, 2H, CH_2), 6.93 (s, 1H, aromatic H), 6.98–7.07 (m, 3H, aromatic H), 7.16–7.21 (m, 2H, aromatic H), 7.25–7.36 (m, 3H, aromatic H), 7.42 (d, J=7.1 Hz, 2H, aromatic H); ^{13}C NMR (δ) 29.7 (d, J_{CF}= 2 Hz), 48.8, 53.0, 56.3, 71.1, 114.2, 115.3 (d, J_{CF}=22 Hz), 115.6, 116.1, 124.0 (d, J_{CF}=4 Hz), 126.9 (d, J_{CF}=16 Hz), 127.4, 127.9 (d, J_{CF}=8 Hz), 128.0, 128.6, 130.9 (d, J_{CF}= 5 Hz), 131.3, 136.8, 147.4, 149.2, 161.3 (d, J_{CF}=243 Hz). Anal. Calcd for $C_{23}H_{23}BrFNO_2$ (444.35): C, 62.17; H, 5.22; N, 3.15%. Found: C, 62.23; H, 5.30; N, 3.29%.

4.3.4. (6-Bromobenzo[1,3]dioxol-5-ylmethyl)-[2-(2-fluorophenyl)ethyl]amine (6d). Yield 3.34 g (95%); oil; ^1H NMR (δ) 1.54 (br s, 1H, NH), 2.86 (s, 4H, 2×CH_2), 3.77 (s, 2H, CH_2), 5.94 (s, 2H, CH_2), 6.86 (s, 1H, aromatic H), 6.96 (s, 1H, aromatic H), 7.02–7.08 (m, 2H, aromatic H), 7.14–7.25 (m, 2H, aromatic H); ^{13}C NMR (δ_C) 29.8 (d, J_{CF}=2 Hz), 48.9 (d, J_{CF}=1 Hz), 53.4, 101.6, 110.0, 112.7, 114.0, 115.3 (d, J_{CF}=22 Hz), 124.0 (d, J_{CF}=4 Hz), 126.8 (d, J_{CF}=16 Hz), 127.9 (d, J_{C-F}=8 Hz), 131.0 (d, J_{CF}=5 Hz), 132.5, 147.3, 147.4, 161.3 (d, J_{CF}=243 Hz). Anal. Calcd for $C_{16}H_{15}BrFNO_2$ (352.2): C, 54.56; H, 4.29; N, 3.98%. Found: C, 54.23; H, 4.51; N, 4.19%.

4.4. General procedure for the synthesis of the carbamic acid methyl esters 5a–d

Methyl chloroformate (0.99 g, 10.5 mmol) was added dropwise at 0 °C to a stirred solution of the secondary amine **6a–d** (7.0 mmol) and NEt_3 (1.42 g, 14.0 mmol) in CH_2Cl_2 (40 mL). The mixture was allowed to warm to room temperature and then stirred for an additional 3 h. The mixture was washed with water (30 mL) and brine (30 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo to left an oily residue which was purified by flash column chromatography with AcOEt/hexanes (40:60) as eluent.

4.4.1. (6-Bromo-2,3-dimethoxybenzyl)-[2-(6-fluorobenzo-[1,3]dioxol-5-yl)ethyl]carbamic acid methyl ester (5a). Yield 2.57 g (78%); oil; ^1H NMR (δ, mixture of two rotational isomers 2:3) 2.52–2.64 (m, 2H, CH_2), 3.12–3.23 (m, 2H, CH_2), 3.74 (s, 3H, CH_3), 3.76 (s, 6H, 2×CH_3), 4.61 and 4.68 (2×s, together 2H, CH_2), 5.81 (s, 2H, OCH_2O), 6.41 (d, J_{HF}=8.6 Hz, 1H, aromatic H), 6.59 (d, J_{HF}=7.3 Hz, 1H, aromatic H), 6.70 (d, J=8.8 Hz, 1H, aromatic H), 7.18 (d, J=8.8 Hz, 1H, aromatic H); ^{13}C NMR (δ, mixture of two rotational isomers) 28.0 (d, J_{CF}=2 Hz), 45.0, 45.4, 52.5, 55.9, 60.8, 97.6 (d, J_{CF}=30 Hz), 101.5, 109.4 (d, J_{CF}= 5 Hz), 113.4, 115.8, 117.6 (d, J_{CF}=15 Hz), 127.9, 130.1,

143.3 (d, J_{CF}=2 Hz), 146.3 (d, J_{CF}=14 Hz), 149.5, 152.3, 155.6 (d, J_{CF}=237 Hz), 156.6. Anal. Calcd for $C_{20}H_{21}BrFNO_6$ (470.3): C, 51.08; H, 4.50; N, 2.98%. Found: C, 51.27; H, 4.32; N, 2.84%.

4.4.2. (2-Bromobenzyl)-[2-(2-fluorophenyl)ethyl]carbamic acid methyl ester (5b). Yield 2.33 g (91%); oil; ^{1}H NMR (δ) (δ, mixture of two rotational isomers 4:5) 2.86–2.94 (m, 2H, CH_2), 3.44–3.50 (m, 2H, CH_2), 3.68 (s, 3H, CH_3), 4.46 and 4.57 (2×s, together 2H, CH_2), 6.96–7.25 (m, 7H, aromatic H), 7.51 (d, J=7.8 Hz, 1H, aromatic H); ^{13}C NMR (δ_C), (δ, mixture of two rotational isomers A and B) 27.7 (A), 28.3 (B), 46.9 (B), 47.9 (A), 50.6 (B), 50.9 (A), 52.8, 115.3 (d, J_{CF}=22 Hz), 122.9 (A), 123.4 (B), 124.1 (d, J_{CF}=4 Hz), 125.7 (d, J_{C-F}=16 Hz), 127.6 (B), 127.9 (A), 128.3 (d, J_{CF}=8 Hz), 128.8 (two peaks overlapping), 129.1, 131.2 (d, J_{CF}=5 Hz), 132.8, 136.8, 156.8 (A), 157.2 (B), 161.3 (d, J_{CF}=244 Hz). Anal. Calcd for $C_{17}H_{17}BrFNO_2$ (366.2): C, 55.75; H, 4.68; N, 3.82%. Found: C, 55.65; H, 4.49; N, 4.13%.

4.4.3. (5-Benzyloxy-2-bromo-4-methoxybenzyl)-[2-(2-fluorophenyl)ethyl]carbamic acid methyl ester (5c). Yield 2.67 g (76%); mp 54–55 °C (from hexane–toluene); ^{1}H NMR (δ, mixture of two rotational isomers 4:5) 2.70–2.85 (m, 2H, CH_2), 3.22–3.34 (m, 2H, CH_2), 3.66 (s, 3H, CH_3), 3.85 (s, 3H, CH_3), 4.33 and 4.46 (2×s, together 2H, CH_2), 5.10 (s, 2H, OCH_2O), 6.62 and 6.84 (2×s, together 1H, s, aromatic H), 6.96–7.25 (m, 6H, aromatic H), 7.29–7.37 (m, 4H, aromatic H); ^{13}C NMR (δ_C, mixture of two rotational isomers) 29.7, 46.4, 49.8, 52.7, 56.3, 71.1, 113.9, 115.2 (d, J_{CF}=22 Hz), 115.8, 116.1, 124.0 (d, J_{CF}=4 Hz), 125.8 (d, J_{CF}=16 Hz), 127.4, 127.9, 128.2 (d, J_{CF}=8 Hz), 128.6, 128.9, 131.2 (d, J_{CF}=5 Hz), 136.6, 147.6, 149.5, 157.2, 161.3 (d, J_{CF}=244 Hz). Anal. Calcd for $C_{25}H_{25}BrFNO_4$ (502.4): C, 59.77; H, 5.02; N, 2.79%. Found: C, 59.92; H, 5.11; N, 3.02%.

4.4.4. (6-Bromobenzo[1,3]dioxol-5-ylmethyl)-[2-(2-fluorophenyl)ethyl]carbamic acid methyl ester (5d). Yield 2.09 g (73%); mp 76–78 °C (from hexane–toluene); ^{1}H NMR (δ_H, mixture of two rotational isomers 2:3) 2.80–2.89 (m, 2H, CH_2), 3.36–3.44 (m, 2H, CH_2), 3.64 (s, 3H, CH_3), 4.34 and 4.44 (2×s, together 2H, CH_2), 5.91 (s, 2H, OCH_2O), 6.60 and 6.75 (2×s, together 1H, aromatic H), 6.93 (s, 1H, aromatic H), 6.96–7.09 (m, 2H, aromatic H), 7.18–7.25 (m, 2H, aromatic H); ^{13}C NMR (δ_C, mixture of two rotational isomers A and B) 27.6 (A), 28.2 (B), 46.7 (B), 47.6 (A), 50.2 (B), 50.5 (A), 52.8, 101.8, 108.1 (A), 109.0 (B), 112.5 (B), 112.7 (A), 113.3 (A), 113.6 (B), 115.2 (d, J_{CF}=22 Hz), 124.1 (d, J_{CF}=4 Hz), 125.7 (d, J_{CF}=16 Hz), 128.2 (d, J_{CF}=8 Hz), 130.0 (A), 130.1 (B), 131.2 (d, J_{CF}=5 Hz), 147.7, 156.6 (A), 157.2 (B), 161.3 (d, J_{CF}=244 Hz). Anal. Calcd for $C_{18}H_{17}BrFNO_4$ (410.2): C, 52.70; H, 4.18; N, 3.41%. Found: C, 52.61; H, 4.04; N, 3.31%.

4.5. General procedure for the synthesis of the isoindolinones 4a–d

A solution of *t*-BuLi (2.5 mL, 1.7 M in pentane, 4.25 mmol) was added dropwise by syringe at −100 °C under Ar to a solution of carbamate **5a–d** (3.86 mmol) in dry THF (50 mL). The reaction mixture was allowed to warm to 0 °C over a period of 30 min followed by addition of saturated aqueous NH_4Cl (5 mL). The mixture was diluted with water (30 mL), extracted with Et_2O (2×25 mL) and the combined organic layers were dried (Na_2SO_4). Evaporation of solvent in vacuo left a solid residue which was purified by flash column chromatography with AcOEt/hexanes (60:40) as eluent. Isoindolinones **4a–d** were finally purified by recrystallization from hexane–toluene.

4.5.1. 2-[2-(6-Fluorobenzo[1,3]dioxol-5-yl)ethyl]-4,5-dimethoxy-2,3-dihydro-isoindol-1-one (4a). Yield 942 mg (68%); mp 161–162 °C; ^{1}H NMR (δ) 2.89 (t, J=6.8 Hz, 2H, CH_2), 3.76 (t, J=6.8 Hz, 2H, CH_2), 3.90 (s, 3H, CH_3), 3.92 (s, 3H, CH_3), 4.30 (s, 2H, CH_2), 5.91 (s, 2H, OCH_2O), 6.55 (d, J_{HF}=9.0 Hz, 1H, aromatic H), 6.65 (d, J_{HF}=6.4 Hz, 1H, aromatic H), 6.99 (d, J=8.3 Hz, 1H, aromatic H), 7.52 (d, J=8.3 Hz, 1H, aromatic H); ^{13}C NMR (δ) 28.0, 42.9, 48.1, 56.2, 60.3, 97.9 (d, J_{CF}=31 Hz), 101.7, 109.3 (d, J_{CF}=5 Hz), 112.7, 117.2 (d, J_{CF}=18 Hz), 119.5, 126.3, 133.2, 143.4, 143.7, 146.7 (d, J_{CF}=14 Hz), 154.6, 155.7 (d, J_{CF}=236 Hz), 168.1. Anal. Calcd for $C_{19}H_{18}FNO_5$ (359.4): C, 63.51; H, 5.05; N, 3.90%. Found: C, 63.44; H, 4.84; N, 4.17%.

4.5.2. 2-[2-(2-Fluorophenyl)ethyl]-2,3-dihydro-isoindol-1-one (4b). Yield 707 mg (72%); mp 116–118 °C; ^{1}H NMR (δ) 3.02 (t, J=7.3 Hz, 2H, CH_2), 3.86 (d, J=7.3 Hz, 2H, CH_2), 4.25 (s, 2H, CH_2), 6.98–7.05 (m, 2H, aromatic H), 7.15–7.25 (m, 2H, aromatic H), 7.36–7.52 (m, 3H, aromatic H), 7.82 (d, J=7.3 Hz, 1H, aromatic H); ^{13}C NMR (δ) 28.3 (d, J_{CF}=2 Hz), 42.73 (d, J_{CF}=1 Hz), 50.5, 115.3 (d, J_{CF}=22 Hz), 122.6 123.6, 124.3 (d, J_{CF}=4 Hz), 125.6 (d, J_{CF}=16 Hz), 128.0, 128.4 (d, J_{CF}=8 Hz), 131.1 (d, J_{CF}=5 Hz), 131.2, 132.8, 141.2, 161.3 (d, J_{CF}=244 Hz), 168.5. Anal. Calcd for $C_{16}H_{14}FNO$ (255.3): C, 75.28; H, 5.53; N, 5.49%. Found: C, 75.48; H, 5.79; N, 5.27%.

4.5.3. 5-Benzyloxy-2-[2-(2-fluorophenyl)ethyl]-6-methoxy-2,3-dihydro-isoindol-1-one (4c). Yield 966 mg (64%); mp 123–124 °C; ^{1}H NMR (δ) 2.97 (t, J=7.1 Hz, 2H, CH_2), 3.80 (t, J=7.1 Hz, 2H, CH_2), 3.89 (s, 3H, CH_3), 4.08 (s, 2H, CH_2), 5.15 (s, 2H, OCH_2O), 6.84 (s, 1H, aromatic H), 6.95–7.03 (m, 2H, aromatic H), 7.13–7.22 (m, 2H, aromatic H), 7.28–7.37 (m, 6H, aromatic H); ^{13}C NMR (δ) 28.3 (d, J_{CF}=2 Hz), 42.7, 50.0, 56.2, 71.1, 105.7, 107.3, 115.3 (d, J_{CF}=22 Hz), 124.2 (d, J_{CF}=4 Hz), 125.5, 125.7 (d, J_{CF}=16 Hz), 127.2, 1281, 128.3 (d, J_{CF}=8 Hz), 128.7, 131.0 (d, J_{CF}=5 Hz), 134.4, 136.4, 150.2, 151.5, 161.2 (d, J_{CF}=243 Hz), 168.7. Anal. Calcd for $C_{24}H_{22}FNO_3$ (377.4): C, 73.64; H, 5.66; N, 3.58%. Found: C, 73.51; H, 5.75; N, 3.84%.

4.5.4. 6-[2-(2-Fluorophenyl)ethyl]-6,7-dihydro-[1,3]dioxolo[4,5-*f*]-isoindol-5-one (4d). Yield 716 mg (62%); mp 104–105 °C; ^{1}H NMR (δ) 3.00 (t, J=7.1 Hz, 2H, CH_2), 3.81 (t, J=7.1 Hz, 2H, CH_2), 4.12 (s, 2H, CH_2), 6.02 (s, 2H, OCH_2O), 6.77 (s, 1H, aromatic H), 6.98–7.05 (m, 2H, aromatic H), 7.16–7.26 (m, 3H, aromatic H); ^{13}C NMR (δ) 28.4 (d, J_{CF}=2 Hz), 42.8, 50.2, 101.8, 103.0, 103.4, 115.3 (d, J_{CF}=2 Hz), 124.3 (d, J_{CF}=4 Hz), 125.7 (d, J_{CF}=16 Hz), 126.7, 128.4 (d, J_{CF}=8 Hz), 131.1 (d, J_{CF}=5 Hz), 136.5, 148.2, 151.1, 161.3 (d, J_{CF}=243 Hz), 168.1. Anal. Calcd for $C_{17}H_{14}FNO_3$ (299.3): C, 68.22; H, 4.71; N, 4.68%. Found: C, 68.03; H, 4.94; N, 4.65%.

4.6. General procedure for the generation of isoquinoline skeleton of the compounds 1a–d by intramolecular ring closure

A solution of isoindolinone **4a–d** (1.04 mmol) and 18-crown-6 (600 mg, 2.28 mmol) in dry THF (50 mL) was carefully degassed by three freeze–thaw cycles and stirred at −78 °C under dry deoxygenated Ar. Then a solution of KHMDS (4.6 mL, 0.5 M in toluene, 2.28 mmol) was added dropwise. The mixture was stirred for 15 min at −78 °C and then allowed to warm to room temperature within 2 h. Aqueous NH_4Cl solution (10%, 5 mL) was added and after dilution with water (30 mL) the mixture was extracted with Et_2O (2×25 mL). The combined organic layers were dried (Na_2SO_4) and the solvents were evaporated in vacuo to left **1a–d** as solids which were purified by flash column chromatography with Et_2O as eluent.

4.6.1. 5,12b-Dihydro-6*H*-11,12-dimethoxy-1,3-dioxolo-[4,5-*g*]isoindolo[1,2a]isoquinolin-8-one (Nuevamine, 1a). Yield 250 mg (71%); mp 210–211 °C (lit.[2] 212 °C); ^{1}H NMR (δ) 2.85 (dt, J_{gem}=15.4 Hz, J=6.1 Hz, 1H, CH_2), 3.00 (dt, J_{gem}=15.4 Hz, J=6.1 Hz, 1H, CH_2), 3.57 (dt, J_{gem}=12.5 Hz, J=6.1 Hz, 1H, CH_2), 3.96 (s, 3H, CH_3), 3.98 (s, 3H, CH_3), 3.94–4.02 (m, 1H, CH_2), 5.61 (s, 1H, NCH), 5.87 (d, J_{gem}=17.9 Hz, 1H, OCH_2O), 5.88 (d, J_{gem}=17.9 Hz, 1H, OCH_2O), 6.65 (s, 1H, aromatic H), 7.05 (d, J=8.3 Hz, 1H, aromatic H), 7.28 (s, 1H, aromatic H), 7.57 (d, J=8.3 Hz, 1H, aromatic H); ^{13}C NMR (δ) 28.9, 38.9, 56.3, 58.5, 60.5, 101.0, 107.5, 108.4, 113.3, 119.8, 126.4, 128.2, 128.8, 136.0, 144.4, 146.5, 146.8, 155.6, 167.9.

4.6.2. 5,12b-Dihydro-6*H*-isoindolo[1,2-*a*]isoquinolin-8-one (1b). Yield 178 mg (73%); mp 114–116 °C (lit.[6] 114–116 °C).

4.6.3. 11-Benzyloxy-10-methoxy-5,12b-dihydro-6*H*-isoindolo[1,2-*a*]isoquinolin-8-one (1c). Yield 297 mg (77%); mp 147–149 °C; ^{1}H NMR (δ) 2.78 (ddd, J_{gem}=15.6 Hz, J=4.6, 4.9 Hz, 1H, CH_2), 2.94 (ddd, J_{gem}=15.7 Hz, J=6.4, 9.0 Hz, 1H, CH_2), 3.36–3.48 (m, 1H, CH_2), 3.87 (s, 3H, CH_3), 4.25 (ddd, J_{gem}=12.9 Hz, ^3J=4.9, 6.4 Hz, 1H, CH_2), 5.23 (d, J_{gem}=12.4 Hz, 1H, OCH_2), 5.33 (d, J_{gem}=12.4 Hz, 1H, OCH_2), 5.40 (s, 1H, NCH), 7.10–7.46 (m, 11H, aromatic H); ^{13}C NMR (δ) 29.3, 34.8, 56.2, 58.6, 71.3, 105.7, 109.0, 124.8, 125.6 (two peaks overlapping), 126.6, 127.3, 128.1, 128.7, 129.1, 134.6, 134.8, 136.5, 137.3, 150.6, 151.2, 168.3. Anal. Calcd for $C_{24}H_{21}NO_3$ (371.4): C, 77.61; H, 5.70; N, 3.77%. Found: C, 77.77; H, 5.83; N, 3.97%.

4.6.4. 5,6,8,13b-Tetrahydro[1,3]dioxolo[4′,5′:5,6]isoindolo[1,2-*a*]isoquinolin-8-one (1d). Yield 200 mg (69%); mp 170–172 °C; ^{1}H NMR (δ) 2.82 (ddd, J_{gem}=15.7 Hz, J=4.5, 4.9 Hz, 1H, CH_2), 3.01 (ddd, J_{gem}=15.7 Hz, J=5.7, 9.3 Hz, 1H, CH_2), 3.41 (ddd, J_{gem}=12.9 Hz, J=4.5, 9.3 Hz, 1H, CH_2), 4.35 (ddd, J_{gem}=12.9 Hz, J=4.9, 5.7 Hz, 1H, CH_2), 5.51 (s, 1H, NCH), 6.03 (d, J_{gem}=11.8 Hz, 1H, OCH_2O), 6.035 (d, J_{gem}=11.8 Hz, 1H, OCH_2O), 7.15–7.28 (m, 5H, aromatic H), 7.51 (d, J=7.3 Hz, 1H, aromatic H); ^{13}C NMR (δ) 29.4, 38.4, 58.8, 102.1, 103.4, 103.9, 125.1, 126.7, 126.9, 127.4, 129.3, 134.4, 134.8, 139.8, 148.5, 151.4, 167.8. Anal. Calcd for $C_{17}H_{13}NO_3$ (279.3): C, 73.11; H, 4.69; N, 5.01%. Found: C, 73.08; H, 4.80; N, 4.87%.

4.6.5. 13b-Hydroxy-5,6,8,13b-tetrahydro[1,3]dioxolo[4′,5′:5,6]isoindolo[1,2-*a*]isoquinolin-8-one (14d). Yield 190 mg (62%); mp 189–190 °C; ^{1}H NMR (δ_H, DMSO d_6) 2.77–2.83 (m, 2H, CH_2), 3.36 (dt, J_{gem}=12.7 Hz, J=8.1 Hz, 1H, CH_2), 4.12–4.19 (m, 1H, CH_2), 6.10 (s, 1H, OCH_2O), 6.16 (s, 1H, OCH_2O), 6.95 (br s, 1H, OH), 7.05 (s, 1H, aromatic H), 7.11–7.27 (m, 3H, aromatic H), 7.73 (s, 1H, aromatic H), 8.00 (d, J=7.8 Hz, 1H, aromatic H); ^{13}C NMR (δ_C, DMSO d_6) 28.8, 34.6, 85.1, 101.9, 102.2, 104.5, 124.3, 126.4, 127.7, 128.1, 128.9, 134.2, 137.6, 144.4, 148.5, 151.4, 165.9. Anal. Calcd for $C_{17}H_{13}NO_4$ (295.3): C, 69.15, 4.44; N, 4.74%. Found: C, 69.22; H, 4.25; N, 4.89%.

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