JOC The Journal of Organic Chemistry

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Diastereoselective Synthesis of Dihydroisoindolo[2,1-*a*]quinolin-11-ones by Solvent-Free AMCell-SO_3H-Catalyzed Imino Diels–Alder/Intramolecular Amide Cyclization Cascade Reactions

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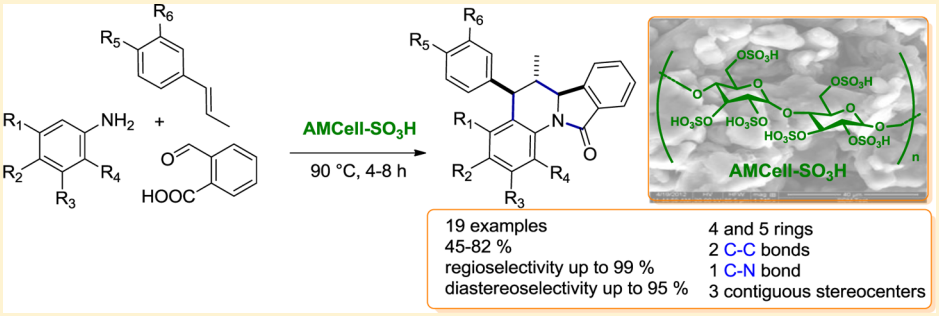
Supporting Information



ABSTRACT: Nineteen bioactive highly functionalized 6,6a-dihydroisoindolo[2,1-*a*]quinolin-11(5*H*)-one derivatives were easily prepared in good yield without solvent using catalytic amorphous milled cellulose sulfonic acid (AMCell-SO_3H), substituted anilines, propenyl-phenols, and phthaldehydic acid. The cascade reaction gave high regioselectivity and diastereoselectivity.

The search for synthetic efficiency continues to stimulate the design and development of new concepts and innovative synthetic strategies in both academic research and industrial applications.[1,2] One of the most effective approaches to improve synthetic efficiency is to implement multicomponent reactions, which have emerged as powerful tools that rapidly increase molecular complexity from simple and readily available starting materials. Such transformations reduce the consumption of solvent, catalyst, and energy, thereby minimizing waste compared to the corresponding series of individual reactions. In recent years, substantial efforts have been devoted to the development of cascade multicomponent reactions that yield small heterocyclic molecules.[3,4]

Quinoline derivatives are extremely important because of their wide spectrum of activities, which include antiparasitic,[5] antibiotic,[6] antifungal,[7] antiviral,[8] antitubercular,[9] and anticancer activities.[10,11] In particular, isoindolo[2,1-*a*]quinolines and related molecules exhibit potent activity against certain infections and tumor cell lines, acting as inhibitors of DNA gyrase and topoisomerase II.[12,13] Because of the pharmacological importance of quinoline derivatives, their synthetic development is the cornerstone of medicinal chemistry and drug discovery. Therefore, the applications of these products are important, as are the synthetic strategies and tactics used to prepare them, which include green pathways to reduce waste and energy consumption. Although several procedures to afford isoindolo[2,1-*a*]quinolines have been reported,[14−18] in most cases, these procedures are not green. The principal drawbacks are the use of toxic solvents such as toluene, acetonitrile, dichloromethane, diethyl ether, methanol and xylenes. In addition, the catalyst and reagents used in these protocols pose several risks to both the operators and the environment, and simple and flexible synthetic routes for the production of large chemical libraries of these potentially bioactive molecules have not yet been developed. To address these issues, reducing the amounts of reagents, solvents, and catalysts necessary will generate less waste and also obviate the need for tedious separation and purification protocols. This simplification is an advantage of more concise approaches involving the one-pot synthesis of such a skeleton.

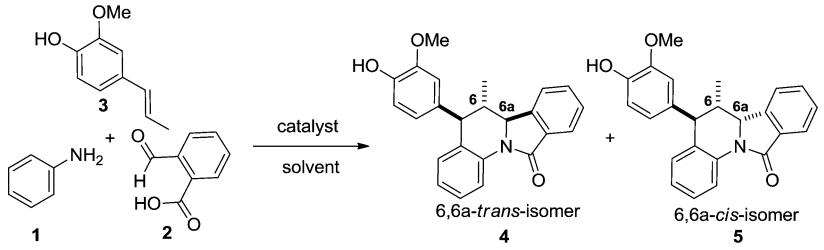
Biomass and biopolymers such as cellulose or starch, as well as some components of essential oils, such as isoeugenol, anethole, or isosafrole, have been widely used in organic synthesis because they are renewable and nontoxic. Thus, we devoted our attention to the use of renewable materials from plant sources as key components in the rapid construction of isoindolo[2,1-*a*]quinolin-11-ones. We hypothesized that these materials could be used not only as starting reagents (i.e., activated alkenes) but also as substrates for recoverable heterogeneous acid catalysts (i.e., modified cellulose-based acids).

As the most abundant renewable feedstock derived from plants, cellulose and its derivatives are attractive for the organic synthesis of new chemical entities using green processes. In

Received: March 4, 2014
Published: April 30, 2014

   dx.doi.org/10.1021/jo500516c | *J. Org. Chem.* 2014, 79, 5327−5333

Table 1. Optimization of the Cascade Reaction Conditions



entry	solvent	catalyst	time (h)	temp (°C)	yield[a] (%)	*trans*:*cis*[b,c]
1	MeCN	$AlCl_3$ (10% mol)	12	reflux	<1	–
2	MeCN	$ZnCl_2$	18	70	2	100:0
3	MeCN	$InCl_3$ (10% mol)	16	60	28	80:20
4	MeCN	$Sc(OTf)_3$ (10% mol)	10	70	34	98:2
5	MeCN	$BF_3{\cdot}OEt_2$	8	60	64	75:25
6	MeCN	$BF_3{\cdot}OEt_2$/4 Å MS	8	60	68	75:25
7	MeCN	H_2NSO_3H	14	reflux	2	83:17
8	MeOH	*o*-$C_6H_4(COOH)_2$	15	40	<1	–
9	MeCN	Mont.K10	15	reflux	nil	–
10	MeCN	Mont.K10/$HClO_4$	9	reflux	nil	–
11	MeCN	PMA (10% mol)	6	60	65	80:20
12		PEG-6000	16	180	nil	–
13	PEG-400	$BF_3{\cdot}OEt_2$	8	60	30	100:0
14		PEG_{6000}-SO_3H	15	60	9	83:17
15	MeCN	Starch-SO_3H	20	60	56	75:25
16		μCCell-SO_3H	6	90[d]	70	90:10
17		AMCell-SO_3H	6	90[d]	78	99:1

[a]Combined yield of the isolated diastereomers. [b]Determined by ^1H NMR spectroscopy. [c]*trans*/*cis* configuration refers to the 6-Me group. [d]The cascade reaction did not occur at room temperature in MeCN.

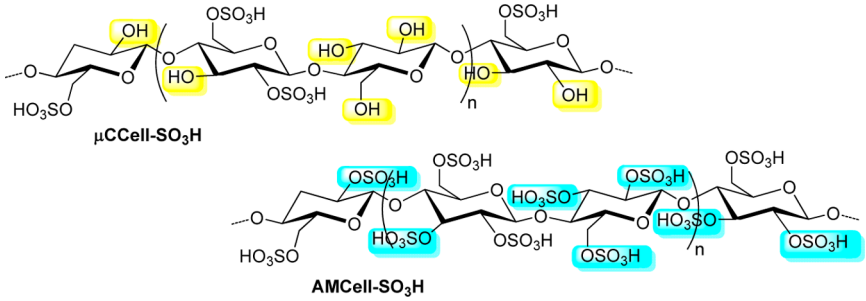


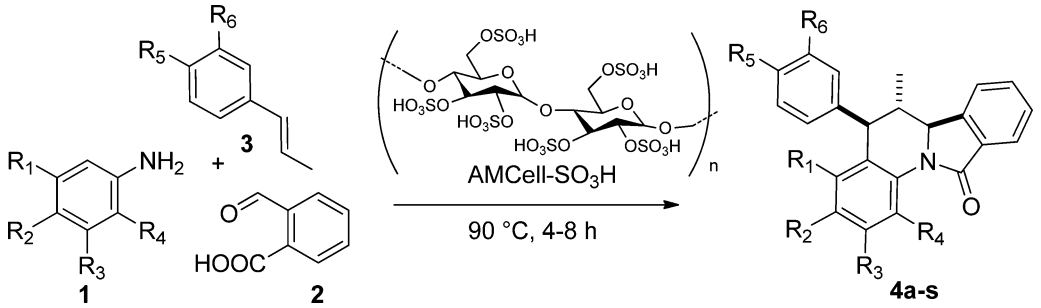
Figure 1. Structure of recoverable biopolymeric cellulose-based $ClSO_3H$ acids.

particular, chlorosulfonic acid supported on cellulose (μCell-SO_3H), obtained from commercial microcrystalline cellulose (μCCell), has been employed as a catalyst and is currently one of the best choices for the design and development of green methods for the synthesis of pharmacologically valuable heterocycles. These heterocycles include aryl-14*H*-dibenzo[*a*,*j*]-xanthenes,[19] 1,4-dihydropyridines,[20] tetrahydropyranols,[21] functionalized pyrrolidines,[22] quinoxaline derivatives,[23] tetrahydroquinolines[24] and quinolines.[25] However, phenylpropanoids, which are major components of the essential oils, have also been successfully used in the preparation of bioactive heterocycles.[26,27] These features motivated us to exploit the aforementioned catalysts and reagents in the efficient acid-catalyzed one-pot synthesis of new isoindolo[2,1-*a*]quinolin-11-ones. Notably, μCCell-SO_3H and AMCell-SO_3H, another cellulose-based $ClSO_3H$ solid acid derived from amorphous milled cellulose (AMCell), have not previously been employed as solid acids in organic synthesis. Therefore, we report herein a highly economical and effective method to prepare poly-functionalized 6,6a-dihydroisoindolo[2,1-*a*]quinolin-11(5*H*)-ones via solvent-free imino Diels–Alder/intramolecular amide cyclization cascade reactions catalyzed by AMCell-SO_3H.

Aniline **1**, phthaldehydic acid **2**, and *trans*-isoeugenol **3** were chosen as model substrates to investigate the cascade reaction leading to the dihydroisoindolo[2,1-*a*]quinolin-11(5*H*)-one scaffold **4** (Table 1). We screened several Lewis or Brønsted acids for the promotion of this transformation. In general, the use of Lewis acids in MeCN (a conventional solvent that works well for imino Diels–Alder (DA) cycloaddition processes) was unsuccessful (Table 1, entries 1–4). Some improvement was observed when catalytic $BF_3{\cdot}OEt_2$ was used, and the desired product **4** was obtained in 64–68% yield with a good *trans*/*cis* (75:25) diastereomeric ratio (the 6,6a-*trans*/6,6a-*cis* configuration refers to the 6-Me group; Table 1, entries 5 and 6). Nevertheless, despite its catalytic effectiveness, the disadvantages of $BF_3{\cdot}OEt_2$ include instability in air, incompatibility with water and environmental risks. We therefore turned to Brønsted acids, knowing that certain acids work well in three-

dx.doi.org/10.1021/jo500516c | J. Org. Chem. 2014, 79, 5327–5333

Table 2. Reaction Scope



entry	R_1	R_2	R_3	R_4	R_5	R_6	*trans:cis*[a]	product	mp[b] (°C)	yield[b] (%)	R_f[b,c]
1	H	H	H	H	OH	OMe	99:1	**4a**	238−241	78	0.55
2	H	Me	H	H	OH	OMe	87:13	**4b**	230−232	74	0.55
3	H	OMe	H	H	OH	OMe	92:8	**4c**	219−221	65	0.50
4	H	Et	H	H	OH	OMe	99:1	**4d**	245−247	72	0.50
5	H	F	H	H	OH	OMe	100:0	**4e**	252−254	75	0.45
6	H	NO_2	H	H	OH	OMe	74:26	**4f**	228−230	60	0.40
7	H	H	H	CN	OH	OMe	96:4	**4g**	242−244	70	0.50
8	H	H	H	NO_2	OH	OMe	94:6	**4h**	250−254	45	0.40
9	H	H	H	F	OH	OMe	100:0	**4i**	245−246	55	0.45
10	H	$-OCH_2O-$		H	OH	OMe	95:5	**4j**	262−264	70	0.45
11	—CH=CH—CH=CH—		H	H	OH	OMe	95:5	**4k**	224−226	68	0.50
12	H	H	H	H	OMe	H	99:1	**4l**	165−167	73	0.62
13	H	Me	H	H	OMe	H	99:1	**4m**	198−200	68	0.45
14	H	Et	H	H	OMe	H	100:0	**4n**	213-214	60	0.50
15	H	NO_2	H	H	OMe	H	99:1	**4o**	190−192	45	0.45
16	H	$-OCH_2O-$		H	OMe	H	93:7	**4p**	250−252	82	0.55
17	—CH=CH—CH=CH—		H	H	OMe	H	66:34	**4q**	>300	67	0.30
18	H	H	H	H	$-O-CH_2-O-$		94:6	**4r**	246−247	48	0.40
19	H	Me	H	H	$-O-CH_2-O-$		95:5	**4s**	187−189	45	0.50

[a]Determined by ^{1}H NMR spectroscopy. [b]Determined for pure *trans*-diastereomers. [c]Determined in *n*-hexane:ethyl acetate, 1:1/silufol UV254 TLC aluminum plates.

component imino DA reactions.[28−30] We tested H_2NSO_3H, *o*-$C_6H_4(COOH)_2$, montmorillonite K 10 (Mont.K10) and phosphomolybdic acid (PMA) (Table 1, entries 7−11). PMA was effective, promoting the cascade reaction and affording a 65% yield with satisfactory diastereoselectivity (80:20) (Table 1, entry 11); however, some difficulties in work-up were experienced. In addition, because of their innocuousness, catalysts and media based on poly(ethylene glycol)s (i.e., PEG-400/BF_3·OEt_2, PEG-6000, and PEG_{6000}-SO_3H[31]) were also screened but unfortunately were not successful (Table 1, entries 12−14). Ultimately, the imino DA/intramolecular amide cyclization cascade transformations proceeded very well. The desired product **4** was obtained in 56−78% yield in the presence of chlorosulfonic acid supported on biomass-derived biopolymers (Table 1, entries 15−17).

Notably, heterogeneous acids supported on two types of cellulose, μCCell-SO_3H[32] and AMCell-SO_3H (Figure 1), afforded the best yields (70−78% in short reaction times) and *trans*/*cis* diastereoselectivity (90:10) (Table 1, entries 16 and 17).

The efficiency of the AMCell-SO_3H catalyst may be related to the degree of substitution (DS) with OH groups. Therefore, titration was performed to determine the number of acidic sites in the solid-supported acids. μCCell-SO_3H contained 0.4 mequiv/g H^+ sites (0.6 mequiv/g maximum reported value),[32] whereas AMCell-SO_3H contained 0.9 mequiv/g H^+ sites (not previously reported), thereby providing a better DS for the pretreated cellulose.

Having optimized the conditions, we used various aniline derivatives **1**, phthaldehydic acid **2**, and three different electron-rich alkenes **3** to prepare densely functionalized isoindolo[2,1-*a*]quinolinone derivatives. The reactions were broadly applicable to a wide variety of substituted species of **1** and **3** (see Table 3). Reactions with aniline derivatives bearing either electron-withdrawing or electron-donating groups proceeded smoothly to provide good yields of the corresponding products. In general, despite some entries, electron-withdrawing groups positively affected the yield (entries 5 and 7, 75 and 70% yield, respectively), possibly through mesomeric influence. Electron-rich arylamines **1** gave high yields in most cases (Table 2, entries 2, 10, and 16); electron-deficient anilines **1** generated the heterocyclic product in a slightly lower or similar yield (Table 2, entries 5−9). The following observations were made: (i) electron-rich arylamines **1** and *trans*-isoeugenol derivative **3** (R_5 = OH, R_6 = OMe) provided the best yields of the desired products **4**; (ii) good to excellent *trans* diastereoselectivity was observed for the tested anilines, except 4-nitroaniline and 2-naphthylamine (Table 2, entries 6 and 17); (iii) very high regioselectivity was also observed for 2-naphthylamine, giving exclusively angular pentacyclic products **4** (Table 2, entries 11 and 18), whereas 3,4-(methylenedioxy)aniline gave only linear products (Table 2, entries 10 and 16).

dx.doi.org/10.1021/jo500516c | J. Org. Chem. 2014, 79, 5327−5333

These results clearly indicate that this method is superior to previously reported methods[21] with respect to eco-friendliness (lower amount of catalyst, higher yield, reduced reaction time and improved reusability). Reusability of the AMCell-SO_3H catalyst was established for up to 5 successive runs, and it showed only a marginal decrease in catalytic activity (Table 3).

Table 3. Reusability of AMCell-SO_3H in the Synthesis of 4a

run	first	second	third	fourth	fifth[a]
yield (%)	78	75	75	72	68

[a]Reaction performed at 120 °C.

The relative configurations of products **4a–s** were determined by homonuclear and inverse detection NMR experiments (see Supporting Information). The coupling constants for **4a** ($J_{5\text{-H}}$–$J_{6\text{-H}}$ = 11.1 Hz and $J_{6a\text{-H}}$–$J_{6\text{-H}}$ = 10.6 Hz) were consistent with an *axial–axial* interaction between 5-H and 6-H (an expansion of the NMR spectrum is given in the Supporting Information). Because this imino Diels–Alder/intramolecular amide cyclization cascade reaction showed excellent regioselectivity and diastereoselectivity, the following mechanism is proposed. We suggest that the preformed aldimine stabilized by an acid catalyst reacts with the activated alkene (dienophile) via a *trans-endo*-favored state in a concerted [4 + 2] cycloaddition[33,34] and that this state is stabilized by the AMCell-SO_3H catalyst and the secondary π–π interaction between the aromatic rings of the aldimine and the dienophile. The AMCell-SO_3H catalyst can also assist in the formation of the lactam ring (Scheme 1). Another possibility is that amide formation (γ-lactamization) occurs directly after aldimine formation and prior to [4 + 2] cycloaddition of the acyliminium intermediate.[35] Moreover, in a stepwise mechanism, intramolecular cyclization could occur via a diastereoselective [4 + 2] process.[36,37] To test our mechanistic hypothesis, we are currently performing additional experiments in our laboratory.

In summary, we have developed a novel solvent-free imino Diels–Alder/intramolecular amide cyclization cascade reaction catalyzed by AMCell-SO_3H (a new form of cellulose-supported sulfonic acid). We used different arylamines, the inexpensive phthaldehydic acid and alkenes with biologically relevant moieties, which are available in high quantities from essential oils. The cascade reaction used readily available starting materials, affording a 19-membered library of bioactive and highly functionalized isoindolo[2,1-*a*]quinolinone derivatives in good to excellent yields. Up to three new stereogenic centers were generated, with excellent regioselectivities and diastereoselectivities. This green AMCell-SO_3H catalyst can be easily recovered by filtration and reused several times without a significant loss in activity. In vitro antiherpetic and cytotoxicity assays are underway; the results will be published elsewhere as soon as possible.

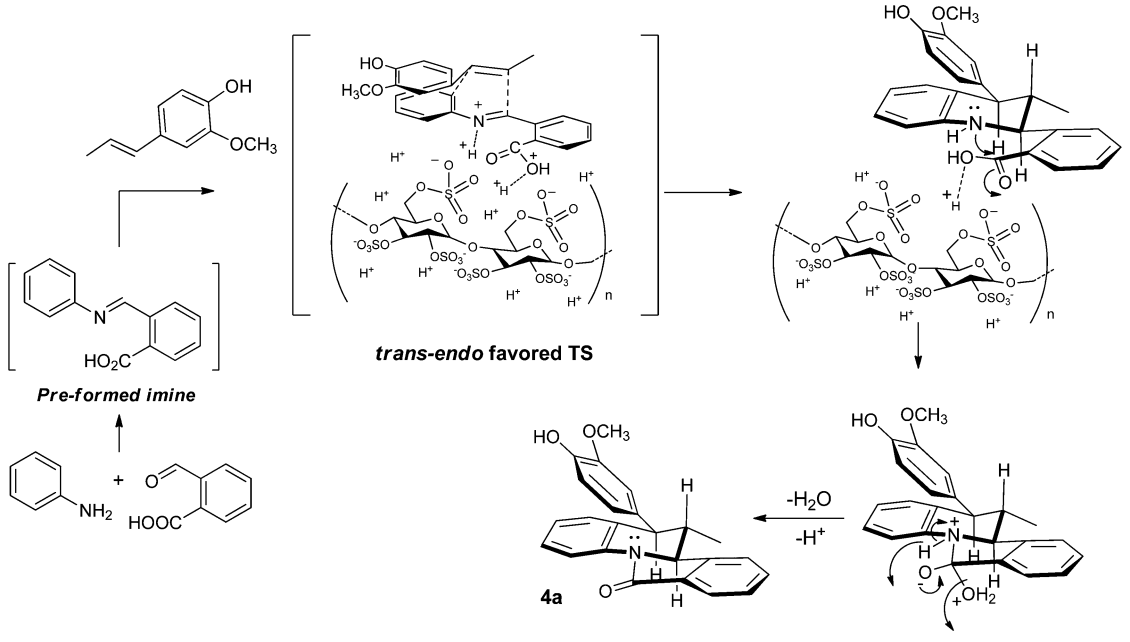
EXPERIMENTAL SECTION

A short description about general methods and explanation of descriptors An, Bd, and Gu C-5 fragment protons are provided in the Supporting Information.

Procedure for AMCell-SO_3H Preparation. Amorphous milled cellulose, AMCell was prepared from commercial microcrystalline cellulose, μCCell, using a high speed vibratory ball mill apparatus, with 60 Hz frequency, only one agate ball (d = 51.6 mm, 186.25 g), and direct shock in agate dish. The μCCell was disposed in the dish, and unique ball was put above of this; the mill was closed, and the maximum frequency was used (60 Hz) during 24 h. Then, 5 g of AMCell were dispersed in 30 mL of $CHCl_3$ at 0 °C, and the $ClSO_3H$ (0.60 mL) was slowly dropped to this reaction mixture. After 1 h of reaction the HCl was removed, and the solid was filtered, washed immediately with methanol (2 × 10 mL), dried, and used in the cascade reactions after complete characterization by IR, ED-XRF, XRD, and SEM techniques.

General Procedure for Solvent-Free AMCell-SO_3H-Catalyzed One-Pot Synthesis of 6,6a-Dihydroisoindolo[2,1-*a*]quinolin-11(5*H*)-ones. Arylamines **1** (1 mmol), phthaldehydic acid **2** (1.1 mmol), and AMCell-SO_3H (0.06 g) were mixed at room temperature. After stirring for 5 min, corresponding alkenes **3** (1.2 mmol) were added. The reaction mixture was strongly stirred to 90 °C during 4–8 h. After reaction completion, as indicated by TLC or an appropriate time, the reaction mixture was washed with acetone (3 × 20 mL). The

Scheme 1. Plausible Mechanism for the Isoindolo[2,1-*a*]quinolinone Synthesis



dx.doi.org/10.1021/jo500516c | J. Org. Chem. 2014, 79, 5327–5333

catalyst was filtered and dried for the next cycle. The acetone was evaporated to give the crude product **4**, which were purified by column chromatography on silica gel using a mixture of petroleum ether and ethyl acetate (2:1) as eluent to give the isoindolo[2,1-*a*]quinolines derivatives **4a**−**s** (Table 2).

Spectral Data for New Dihydroisoindolo[2,1-*a*]quinolin-11(*5H*)-ones 4a−s. *trans-5-(4-Hydroxy-3-methoxyphenyl)-6-methyl-6,6a-dihydroisoindolo[2,1-a]quinolin-11(5H)-one (**4a**).* Obtained 390 mg of a white solid: 78% yield; mp 238−241 °C; FTIR (KBr disk) 3271, 1682, 1126 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6), δ (ppm) 1.17 (3H, d, J = 6.5 Hz, CH_3), 1.91 (1H, td, J = 11.0, 6.5 Hz, 6-H), 3.65 (3H, s, OCH_3), 3.86 (1H, d, J = 11.1 Hz, 5-H), 4.79 (1H, d, J = 10.6 Hz, 6a-H), 6.62 (1H, d, J = 8.1 Hz, 6-H_{Gu}), 6.65 (1H, br. s, 2-H_{Gu}), 6.73 (2H, m, 4-H and 5-H_{Gu}), 6.98 (1H, t, J = 7.5 Hz, 2-H), 7.24 (1H, t, J = 7.6 Hz, 3-H), 7.60 (1H, t, J = 7.4 Hz, 8-H), 7.69 (1H, t, J = 7.1 Hz, 9-H), 7.76 (1H, d, J = 7.6 Hz, 7-H), 7.86 (1H, d, J = 7.5 Hz, 1-H), 8.36 (1H, d, J = 8.0 Hz, 10-H), 8.90 (1H, s, OH); ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm) 15.8, 40.3, 51.4, 55.6, 63.3, 112.6, 115.3, 119.5, 122.2, 123.6, 123.7, 124.8, 126.3, 128.7, 129.9, 131.2, 131.9, 132.3, 134.3, 135.5, 143.5, 145.3, 147.8, 165.0. GC−MS (70 eV), t_R = 43.43 min, m/z 371 ($M^{+\bullet}$, 80), 342 (20), 246 (22), 232 (100), 220 (50), 151 (91). Anal. Calcd for $C_{24}H_{21}NO_3$: C, 77.61; H, 5.70; N, 3.77. Found: C, 77.52; H, 5.83; N, 3.61.

*trans-5-(4-Hydroxy-3-methoxyphenyl)-3,6-dimethyl-6,6a-dihydroisoindolo[2,1-a]qui-nolin-11(5H)-one (**4b**).* Obtained 370 mg of a white solid: 74% yield; mp 230−232 °C; FTIR (KBr disk) 3394, 1666, 1126 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, δ ppm) 1.41 (3H, d, J = 6.8 Hz, 5-CH_3). 2.05 (3H, d, J = 6.4 Hz, 3-CH_3), 2.68 (1H, d, m, 6-H), 3.09 (3H, s, OCH_3), 3.39 (1H, d, J = 10.6 Hz, 5H), 5.30 (1H, d, J = 10.6 Hz, 6a-H), 7.28 (1H, s, 2-H_{Gu}), 7.32 (1H, d, J = 7.0 Hz, 6-H_{Gu}), 7.41 (2H, d, J = 9.7 Hz, 4-H and 5-H_{Gu}), 7.55 (1H, d, J = 7.1 Hz, 2-H), 8.26 (1H, t, J = 7.2 Hz, 8-H), 8.41−8.35 (1H, m, 9-H), 8.71 (1H, d, J = 7.3 Hz, 7-H), 8.79 (1H, d, J = 7.3 Hz, 10-H), 9.14 (1H, d, J = 8.2 Hz, 1-H), 9.46 (1H, s, OH); ^{13}C NMR (101 MHz, DMSO-d_6, δ ppm) 13.2, 45.3, 46.1, 50.9, 54.9, 55.1, 61.2, 110.8, 111.4, 115.4, 121.8, 122.3, 123.1, 124.7, 127.4, 128.9, 130.6, 131.9, 132.5, 134.3, 141.4, 144.3, 147.7, 150.0, 164.1; GC−MS (70 eV), t_R = 40.60 min, m/z 385 ($M^{+\bullet}$, 5), 260 (8), 246 (100). Anal. Calcd for $C_{25}H_{23}NO_3$: C, 77.90; H, 6.01; N, 3.63. Found: C, 77.78; H, 6.12; N, 3.50.

*trans-5-(4-Hydroxy-3-methoxyphenyl)-3-methoxy-6-methyl-6,6a-dihydroisoindolo-[2,1-a]quinolin-11(5H)-one (**4c**).* Obtained 325 mg of a white solid: 65% yield; mp 219−221 °C; FTIR (KBr disk) 3380, 1682, 1122 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, δ ppm) 1.16 (3H, d, J = 5.4 Hz, CH_3), 1.95−1.84 (1H, m, 6-H), 3.58 (3H, s, OCH_3), 3.66 (3H, s, OCH_3), 3.82 (1H, d, J = 10.9 Hz, 5-H), 4.72 (1H, d, J = 10.3 Hz, 6a-H), 6.23 (1H, s, 4-H), 6.61 (1H, d, J = 6.7 Hz, 6-H_{Gu}), 6.65 (1H, br. s, 2-H_{Gu}), 6.74 (1H, d, J = 7.3 Hz, 5-H_{Gu}), 6.87 (1H, d, J = 8.1 Hz, 2-H), 7.59 (1H, t, J = 7.2 Hz, 9-H), 7.66 (1H, t, J = 7.82 Hz, 8-H), 7.74 (1H, d, J = 7.1 Hz, 7-H), 7.83 (1H, d, J = 6.5 Hz, 10-H), 8.29 (1H, d, J = 8.5 Hz, 1-H), 8.90 (1H, s, OH); ^{13}C NMR (101 MHz, DMSO-d_6, δ ppm) 15.8, 40.3, 40.4, 51.6, 55.1, 55.6, 63.2, 111.4, 112.6, 115.4, 120.7, 122.1, 123.4, 124.7, 128.6, 129.1, 131.6, 132.5, 132.8, 134.0, 143.3, 145.3, 147.8, 155.3, 164.6; GC−MS (70 eV), t_R = 94.04 min, m/z 401 ($M^{+\bullet}$, 100), 262 (10), 151 (5). Anal. Calcd for $C_{25}H_{23}NO_4$: C, 74.79; H, 5.77; N, 3.49. Found: C, 74.65; H, 5.84; N, 3.20.

*trans-3-Ethyl-5-(4-hydroxy-3-methoxyphenyl)-6-methyl-6,6a-dihydroisoindolo[2,1-a]quinolin-11(5H)-one (**4d**).* Obtained 360 mg of a white solid: 72% yield; mp 245−247 °C; FTIR (KBr disk) 3410, 2962, 2961, 1666, 1034 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, δ ppm) 1.08 (6H, m, 3-CH_3 and 6-CH_3), 1.86 (1H, m, 6-H), 2.40 (1H, m, CH_2), 2.52 (1H, m, CH_2), 3.64 (3H, s, OCH_3), 3.83 (1H, d, J = 10.0 Hz, 5-H), 4.74 (1H, d, J = 10.6 Hz, 6a-H), 6.55 (1H, s, 2-H_{Gu}), 6.63 (2H, m, 4-H and 6-H_{Gu}), 6.73 (1H, d, J = 7.4 Hz, 5-H_{Gu}), 7.01 (1H, d, J = 6.97 Hz, 2-H), 7.09 (1H, d, J = 7.7 Hz, 1-H), 7.59 (1H, t, J = 7.8 Hz, 8-H), 7.66 (1H, t, J = 7.3 Hz, 9-H), 7.84 (1H, d, J = 7.2 Hz, 7-H), 8.26 (1H, d, J = 8.0 Hz, 10-H), 8.92 (1H, s, OH); ^{13}C NMR (101 MHz, DMSO-d_6, δ ppm) 15.8, 15.9, 27.6, 27.8, 40.7, 51.5, 55.6, 63.3, 112.6, 115.4, 119.6, 120.0, 122.3, 123.5, 124.8, 125.8, 128.8, 131.1, 131.8, 132.4, 133.4, 134.4, 139.1, 143.5, 147.8, 164.8; GC−MS (70 eV), t_R = 46.29 min, m/z 399 ($M^{+\bullet}$, 100), 384 (20), 260 (60), 151 (50), 115 (25). Anal. Calcd for $C_{26}H_{25}NO_3$: C, 78.17; H, 6.31; N, 3.51. Found: C, 78.25; H, 6.10; N, 3.35.

*trans-3-Fluoro-5-(4-hydroxy-3-methoxyphenyl)-6-methyl-6,6a-dihydroisoindolo[2,1-a]quinolin-11(5H)-one (**4e**).* Obtained 375 mg of a white solid: 75% yield; mp 252−254 °C; FTIR (KBr disk) 3410, 1666, 1487, 1157 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, δ ppm) 1.16 (3H, d, J = 6.5 Hz, CH_3), 1.95 (1H, td, J = 10.8, 6.4 Hz, 6-H), 3.66 (3H, s, OCH_3), 3.88 (1H, d, J = 10.9 Hz, 5-H), 4.80 (1H, d, J = 10.6 Hz, 6a-H), 6.43 (1H, dd, J = 9.9, 2.4 Hz, 4-H), 6.63 (1H, dd, J = 8.0, 1.7 Hz, 6-H_{Gu}), 6.68 (1H, d, J = 1.7 Hz, 2-H_{Gu}), 6.75 (1H, d, J = 8.0 Hz, 5-H_{Gu}), 7.11 (1H, ddd, J = 20.5, 13.2, 5.9 Hz, 2-H), 7.61 (1H, t, J = 7.3 Hz, 9-H), 7.69 (1H, t, J = 6.9 Hz, 8-H), 7.77 (1H, d, J = 7.7 Hz, 7-H), 7.87 (1H, d, J = 7.4 Hz, 10-H), 8.39 (1H, dd, J = 9.1, 5.5 Hz, 1-H), 8.97 (1H, s, OH); ^{13}C NMR (101 MHz, DMSO-d_6, δ ppm) 15.7, 39.9, 51.5, 55.6, 63.2, 112.5, 113.41 (d, $J_{C,F}$ = 22.2 Hz), 115.4, 115.8 (d, $J_{C,F}$ = 22.9 Hz), 121.4, 122.2, 123.6, 124.8, 128.8, 132.0, 132.1 (d, $J_{C,F}$ = 11.2 Hz), 133.5, 133.9 (d, $J_{C,F}$ = 6.6 Hz), 143.4, 145.5, 148.0, 158.1 (d, $J_{C,F}$ = 240.5 Hz), 164.8, 165.0; GC−MS (70 eV), t_R = 46.16 min, m/z 389 ($M^{+\bullet}$, 70), 250 (50), 151 (100). Anal. Calcd for $C_{24}H_{20}FNO_3$: C, 74.02; H, 5.18; N, 3.60. Found: C, 74.19; H, 5.31; N, 3.51.

*trans-5-(4-Hydroxy-3-methoxyphenyl)-6-methyl-3-nitro-6,6a-dihydroisoindolo[2,1-a]quinolin-11(5H)-one (**4f**).* Obtained 300 mg of a yellow solid: 60% yield; mp 228−230 °C; FTIR (KBr disk) 3425, 3332, 1759, 1512 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, δ ppm) 1.19 (3H, d, J = 6.3 Hz, CH_3), 2.10 (1H, m, 6-H), 3.65 (3H, s, OMe), 3.97 (1H, d, J = 11.0 Hz, 5-H), 4.93 (1H, d, J = 10.4 Hz, 6a-H), 6.65−6.80 (3H, m, all H_{Gu}), 7.55 (1H, s, 4-H), 7.77−7.72 (1H, 't', J = 7.26, 9-H), 7.80 (1H, d, J = 7.6 Hz, 7-H), 7.88 (1H, 't', J = 7.6 Hz, 8-H), 7.93 (1H, d, J = 7.3 Hz, 10-H), 8.17 (1H, d, J = 9.0 Hz, 2-H), 8.67 (1H, d, J = 9.3 Hz, 1-H), 9.03 (1H, s, OH); ^{13}C NMR (101 MHz, DMSO-d_6, δ ppm) 15.6, 39.0, 40.3, 55.6, 69.0, 85.6, 102.7, 103.8, 113.6, 124.0, 124.1, 124.3, 125.0, 125.1, 126.0, 126.9, 130.9, 132.8, 134.8, 139.2, 145.2, 151.9, 168.8, 176.8; GC−MS (70 eV), t_R = 46.16 min, m/z 389 ($M^{+\bullet}$, 70), 250 (50), 151 (100). Anal. Calcd for $C_{24}H_{20}N_2O_5$: C, 69.22; H, 4.84; N, 6.73. Found: C, 69.35; H, 4.98; N, 6.61.

*trans-1-Ciano-5-(4-hydroxy-3-methoxyphenyl)-6-methyl-6,6a-dihydroisoindolo[2,1-a]quinolin-11(5H)-one (**4g**).* Obtained 350 mg of a white solid: 70% yield; mp 242−244 °C; FTIR (KBr disk) 3533, 2978, 2222, 1713 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, δ ppm) 1.11 (3H, d, J = 6.4 Hz, CH_3), 1.71 (1H, td, J = 10.5, 6.4 Hz, 6-H), 3.66 (3H, s, OMe), 3.87 (1H, d, J = 10.9 Hz, 5-H), 4.78 (1H, d, J = 10.3 Hz, 6a-H), 6.59 (2H, d, J = 7.9 Hz, 4-H and 6-H_{Gu}), 6.68 (1H, d, J = 1.5 Hz, 2-H_{Gu}), 6.72 (1H, d, J = 8.0 Hz, 4-H_{Gu}), 7.09 (1H, dt, J = 13.7, 6.8 Hz, 2-H), 7.14 (1H, dd, J = 15.8, 6.0 Hz, 3-H), 7.60 (1H, t, J = 7.3 Hz, 9-H), 7.69 (1H, t, J = 7.1 Hz, 8-H), 7.75 (1H, d, J = 7.6 Hz, 7-H), 7.86 (1H, d, J = 7.6 Hz, 10-H), 8.90 (1H, s, OH); ^{13}C NMR (101 MHz, DMSO-d_6, δ ppm) 15.9, 42.4, 50.9, 55.6, 62.9, 112.6, 114.2, 115.5, 122.0, 123.2, 123.9, 124.9, 125.1, 125.7, 128.8, 131.3, 131.9, 133.8, 135.8, 145.2, 145.5, 147.8, 153.3, 155.9, 163.9; GC−MS (70 eV), t_R = 46.16 min, m/z 389 ($M^{+\bullet}$, 70), 250 (50), 151 (100). Anal. Calcd for $C_{25}H_{20}N_2O_3$: C, 75.74; H, 5.08; N, 7.07. Found: C, 75.51; H, 5.19; N, 7.14.

*trans-5-(4-Hydroxy-3-methoxyphenyl)-6-methyl-1-nitro-6,6a-dihydroisoindolo[2,1-a]quinolin-11(5H)-one (**4h**).* Obtained 200 mg of a yellow solid: 40% yield; mp 250−254 °C; FTIR (KBr disk) 3425, 3332, 1759, 1512 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, δ ppm) 1.14 (3H, d, J = 7.5 Hz, CH_3), 1.87 (1H, m, 6-H), 3.64 (3H, s, OMe), 4.02 (1H, d, J = 10.9 Hz, 5-H), 5.05 (1H, d, J = 10.1 Hz, 6a-H), 6.79−6.62 (3H, m, all H_{Gu} protons), 7.06 (1H, d, 4-H), 7.25 (1H, 't', 3-H), 7.84−7.59 (4H, m, all isondolo aromatic protons), 7.85 (1H, d, J = 7.8 Hz, 2-H), 8.99 (1H, s, OH); ^{13}C NMR (101 MHz, DMSO-d_6, δ ppm) 15.7, 40.7, 51.1, 55.6, 63.0, 64.1, 104.5, 112.4, 115.4, 123.1, 124.2, 124.6, 124.9, 129.1, 130.8, 132.5, 133.3, 134.2, 135.3, 143.0, 144.9, 145.6, 164.8, 203.6; GC−MS (70 eV), t_R = 46.16 min, m/z 389 ($M^{+\bullet}$, 70), 250 (50), 151 (100). Anal. Calcd for $C_{24}H_{20}N_2O_5$: C, 69.22; H, 4.84; N, 6.73. Found: C, 69.05; H, 4.94; N, 6.58.

*trans-1-Fluoro-5-(4-hydroxy-3-methoxyphenyl)-6-methyl-6,6a-dihydroisoindolo[2,1-a]quinolin-11(5H)-one (**4i**).* Obtained 275 mg of a white solid: 55% yield; mp 245−246 °C; FTIR (KBr disk) 3410,

dx.doi.org/10.1021/jo500516c | J. Org. Chem. 2014, 79, 5327−5333

1660, 1520, 1157 cm-1; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm) 1.11 (3H, d, J = 6.4 Hz, CH_3), 1.71 (1H, td, J = 10.5, 6.4 Hz, 6-H), 3.66 (3H, s, OMe), 3.87 (1H, d, J = 10.9 Hz, 5-H), 4.78 (1H, d, J = 10.3 Hz, 6a-H), 6.59 (2H, d, J = 7.9 Hz, 4-H and 6-H_{Gu}), 6.68 (1H, d, J = 1.5 Hz, 2-H_{Gu}), 6.72 (1H, d, J = 8.0 Hz, 4-H_{Gu}), 7.09 (1H, dt, J = 13.7, 6.8 Hz, 2-H), 7.14 (1H, dd, J = 15.8, 6.0 Hz, 3-H), 7.60 (1H, t, J = 7.3 Hz, 9-H), 7.69 (1H, t, J = 7.1 Hz, 8-H), 7.75 (1H, d, J = 7.6 Hz, 7-H), 7.86 (1H, d, J = 7.6 Hz, 10-H), 8.90 (1H, s, OH); ^{13}C NMR (101 MHz, DMSO-d_6, δ ppm) 15.9, 42.4, 50.9, 55.6, 62.9, 112.6, 114.2, 115.5, 122.0 (d, $J_{C,F}$ = 10.8 Hz), 123.2, 123.9, 124.9 (d, $J_{C,F}$ = 11.2 Hz), 125.1, 125.7, 128.8, 131.3, 131.9, 133.8, 135.8, 145.5 (d, $J_{C,F}$ = 24.2 Hz), 147.8, 153.3 (d, $J_{C,F}$ = 23.0 Hz), 155.9, 163.9 (d, $J_{C,F}$ = 245.1 Hz); GC−MS (70 eV), t_R = 37.71 min, m/z 389 ($M^{+\bullet}$, 70), 250 (50), 151 (100). Anal. Calcd for $C_{24}H_{20}FNO_3$: C, 74.02; H, 5.18; F, 4.88; N, 3.60. Found: C, 74.21; H, 5.29; N, 3.73.

trans-5-(4-Hydroxy-3-methoxyphenyl)-6-methyl-6,6a-dihydro-[1,3]dioxolo[4,5-g]isoindolo[2,1-a]quinolin-11(5H)-one (**4j**). Obtained 350 mg of a white solid: 70% yield; mp 262−264 °C; IR (KBr) 3450, 3300, 2945 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm) 1.15 (3H, d, J = 6.0 Hz, CH_3), 1.84 (1H, m, 3-H), 3.76 (1H, d, J = 10.9 Hz, 4-H), 3.67 (3H, s, OCH_3), 4.72 (1H, d, J = 10.6 Hz, 2-H), 5.96 (2H, s, CH_2), 6.17 (1H, s, 5-H), 6.59 (1H, d, J = 7.7 Hz, 6-H_{Gu}), 6.65 (1H, s, 2-H_{Gu}), 6.72 (1H, d, J = 7.7 Hz, 5-H_{Gu}), 7.50 (1H, J = 7.2 Hz, 7-H), 7.56 (1H, 't', J = 7.2 Hz, 9-H), 7.67 (1H, 't', J = 7.3 Hz, 10-H), 7.74 (1H, J = 7.2 Hz, 8-H), 7.92 (1H, s, 1-H), 8.89 (1H, s, OH); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm) 15.6, 51.4, 55.5, 63.2, 100.4, 100.9, 108.7, 109.4, 112.5, 115.2, 121.8, 123.3, 124.3, 124.5, 128.5, 129.2, 131.6, 132.1, 134.2, 143.1, 143.3, 145.1, 145.2, 147.7, 164.5, GC/MS (70 eV), t_R = 80.4 min, 415 (50, $M^{+\bullet}$), 276 (30), 149 (100). Anal. Calcd for $C_{25}H_{21}NO_5$: C, 72.28; H, 5.10; N, 3.37. Found: C, 72.37; H, 5.34; N, 3.23.

trans-7-(4-Hydroxy-3-methoxyphenyl)-8-methyl-8,8a-dihydrobenzo[h]isoindolo[2,1-a]quinolin-13(7H)-one (**4k**). Obtained 265 mg of a white solid: 68% yield; mp 224−226 °C; FTIR (KBr disk) 3332, 1682, 1512 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm) 1.18 (3H, d, J = 6.3 Hz, CH_3), 1.71 (1H, m, 8-H), 3.65 (3H, s, OCH_3), 3.94 (1H, d, J = 10.2 Hz, 7-H), 4.79 (1H, d, J = 10.3 Hz, 8a-H), 6.57 (1H, d, J = 7.8 Hz, 6-H_{Gu}), 6.69 (1H, s, 2-H_{Gu}), 6.73 (1H, d, J = 8.1 Hz, 5-H_{Gu}), 6.97 (1H, d, J = 8.6 Hz, 6-H), 7.53−7.43 (2H, m, 4-H and 5-H), 7.65−7.59 (1H, m, 11-H), 7.66 (2H, m, 3-H and 6-H), 7.73−7.68 (1H, m, 9-H), 7.75 (1H, d, J = 7.3 Hz, 2-H), 7.89−7.82 (2H, m, 12-H and 10-H), 7.91 (1H, d, J = 7.3 Hz, 1-H), 8.90 (1H, s, OH); ^{13}C NMR (101 MHz, DMSO-d_6, δ ppm) 14.2, 15.5, 39.9, 41.2, 44.4, 51.3, 53.7, 54.8, 61.8, 105.7, 112.8, 113.2, 121.2, 123.1, 124.6, 126.7, 126.9, 127.2, 127.9, 128.3, 128.9, 130.0, 130.7, 132.0, 133.6, 138.5, 145.1, 146.4; GC−MS (70 eV), tR = 46.16 min, m/z 389 ($M^{+\bullet}$, 70), 250 (50), 151 (100). Anal. Calcd for $C_{28}H_{23}NO_3$: C, 79.79; H, 5.50; N, 3.32. Found: C, 79.64; H, 5.73; N, 3.54.

trans-5-(4-Methoxyphenyl)-6-methyl-6,6a-dihydroisoindolo[2,1-a]quinolin-11(5H)-one (**4l**). Obtained 365 mg of a white solid: 73% yield; mp 165−167 °C; FTIR (KBr disk) 3220, 1660, 1100 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm) 1.16 (3H, d, J = 6.4 Hz, CH_3), 1.87−1.74 (1H, m, 6-H), 3.73 (3H, s, OCH_3), 3.94 (1H, d, J = 10.9 Hz, 5-H), 4.81 (1H, d, J = 10.6 Hz, 6a-H), 6.67 (1H, d, J = 7.9 Hz, 4-H), 6.88 (2H, d, J = 8.2 Hz, 2-H_{An} and 3-H_{An}), 6.97 (1H, t, J = 7.5 Hz, 3-H), 7.08 (2H, d, J = 8.3 Hz, 2-H_{An} and 3-H_{An}), 7.24 (1H, t, J = 7.7 Hz, 2-H), 7.59 (1H, dd, J = 14.4, 7.0 Hz, 9-H), 7.68 (1H, t, J = 7.5 Hz, 8-H), 7.76 (1H, d, J = 7.7 Hz, 7-H), 7.85 (1H, t, J = 8.2 Hz, 10-H), 8.37 (1H, d, J = 8.2 Hz, 1-H); ^{13}C NMR (101 MHz, DMSO-d_6, δ ppm) 12.5, 12.5, 15.6, 40.8, 50.9, 54.9, 55.0, 63.1, 114.0, 119.6, 123.6, 123.7, 124.8, 126.3, 128.7, 129.9, 130.4, 131.1, 131.9, 132.2, 135.6, 143.4, 157.9, 164.9; GC−MS (70 eV), t_R = 62.64 min, m/z 355 ($M^{+\bullet}$, 100), 340 (10), 326 (10), 232 (60), 135 (80). Anal. Calcd for $C_{24}H_{21}NO_2$: C, 81.10; H, 5.96; N, 3.94. Found: C, 81.23; H, 5.85; N, 3.76.

trans-3,6-Dimethyl-5-(4-methoxyphenyl)-6,6a-dihydroisoindolo-[2,1-a]quinolin-11(5H)-one (**4m**). Obtained 340 mg of a white solid: 68% yield; mp 198−200 °C; FTIR (KBr disk) 3189, 1680, 1150 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm) 1.14 (3H, d, J = 6.5 Hz, 6-CH_3), 1.78 (1H, tq, J = 12.9, 6.4 Hz, 6-H), 2.11 (3H, s, 3-CH_3), 3.74 (3H, s, OCH_3), 3.89 (1H, d, J = 11.1 Hz, 5-H), 4.75 (1H, d, J = 10.6 Hz, 6a-H), 6.48 (1H, s, 4-H), 6.88 (2H, d, J = 8.7 Hz, 2-H_{An} and 3-H_{An}), 7.07 (3H, m, 2-H, 2-H_{An} and 3-H_{An}), 7.59 (1H, t, J = 7.4 Hz, 9-H), 7.67 (1H, td, J = 7.5, 1.2 Hz, 8-H), 7.74 (1H, d, J = 7.5 Hz, 7-H), 7.85 (1H, d, J = 7.4 Hz, 10-H), 8.24 (1H, d, J = 8.3 Hz, 1-H); ^{13}C NMR (101 MHz, DMSO-d_6, δ ppm) 10.3, 15.6, 20.7, 41.1, 50.8, 54.9, 63.1, 114.0, 116.2, 119.5, 123.5, 124.7, 127.1, 128.7, 130.1, 130.4, 130.9, 131.8, 132.3, 132.6, 133.2, 135.6, 143.3, 157.9, 164.7; GC−MS (70 eV), t_R = 94.04 min, m/z 401 ($M^{+\bullet}$, 100), 262 (10), 151 (5). Anal. Calcd for $C_{25}H_{23}NO_2$: C, 81.27; H, 6.27; N, 3.79. Found: C, 81.12; H, 6.44; N, 3.61.

trans-3-Ethyl-5-(4-methoxyphenyl)-6-dimethyl-6,6a-dihydro-isoindolo[2,1-a]quinolin-11(5H)-one (**4n**). Obtained 300 mg of a beige solid: 60% yield; mp 213-214 °C; FTIR (KBr disk) 1682, 1130 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm) 1.01 (3H, t, J = 7.6 Hz, CH_3'), 1.15 (3H, d, J = 6.5 Hz, CH_3), 1.79 (1H, td, J = 11.0, 6.5 Hz, 6-H), 2.40 (2H, dt, J = 11.9, 7.3 Hz, CH_2), 3.74 (3H, s, OCH_3), 3.91 (1H, d, J = 10.7 Hz, 5-H), 4.78 (1H, d, J = 10.5 Hz, 6a-H), 6.50 (1H, s, 4-H), 6.89 (2H, d, J = 8.7 Hz, 2-H_{An} and 3-H_{An}), 7.13−7.05 (3H, m, 2-H, 2-H_{An} and 3-H_{An}), 7.60 (1H, t, J = 7.3 Hz, 9-H), 7.68 (1H, t, J = 7.0 Hz, 8-H), 7.76 (1H, d, J = 7.6 Hz, 7-H), 7.85 (1H, d, J = 7.4 Hz, 10-H), 8.27 (1H, d, J = 8.4 Hz, 1-H); ^{13}C NMR (101 MHz, DMSO-d_6, δ ppm) 15.6, 15.8, 27.7, 39.0, 40.1, 41.1, 50.9, 55.0, 63.1, 114.0, 119.6, 123.5, 124.7, 125.8, 128.7, 129.0, 130.4, 131.0, 131.8, 132.3, 133.5, 135.6, 139.0, 143.4, 157.9, 164.7; GC−MS (70 eV), t_R = 73.47 min, m/z 383 ($M^{+\bullet}$, 100), 368 (30), 260 (35). Anal. Calcd for $C_{26}H_{25}NO_2$: C, 81.43; H, 6.57; N, 3.65. Found: C, 81.27; H, 6.76; N, 3.51.

trans-3-Nitro-5-(4-methoxyphenyl)-6-dimethyl-6,6a-dihydro-isoindolo[2,1-a]quinolin-11(5H)-one (**4o**). Obtained 225 mg of a yellow solid: 45% yield; mp 190−192 °C; FTIR (KBr disk) 1682, 1150 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm) 1.17 (3H, d, J = 6.4 Hz, CH_3), 2.05−1.96 (1H, m, 6-H), 3.74 (3H, d, J = 14.5 Hz, OCH_3), 4.06 (1H, d, J = 10.9 Hz, 5-H), 4.94 (1H, d, J = 10.5 Hz, 6a-H), 6.94 (2H, d, J = 8.7 Hz, 2-H_{An} and 3-H_{An}), 7.18 (2H, d, J = 8.7 Hz, 2-H_{An} and 3-H_{An}), 7.50 (1H, d, 4-H), 7.64 (1H, t, J = 7.3 Hz, 9-H), 7.74 (1H, t, J = 7.3 Hz, 8-H), 7.82−7.78 (1H, m, 7-H), 7.93 (1H, d, J = 7.1 Hz, 10-H), 8.17 (1H, d, J = 8.0 Hz, 2-H), 8.67 (1H, d, J = 9.2 Hz, 1-H); ^{13}C NMR (101 MHz, DMSO-d_6, δ ppm) 15.5, 50.7, 55.0, 63.2, 85.5, 113.6, 114.3, 118.5, 122.3, 123.7, 124.9, 126.9, 126.9, 129.0, 130.5, 132.4, 134.2, 139.2, 142.4, 143.3, 145.1, 151.8, 158.3, 165.8; GC−MS (70 eV), t_R = 83.66 min, m/z 385 ($M^{+\bullet}$, 100), 370 (10), 262 (15). Anal. Calcd for $C_{24}H_{20}N_2O_4$: C, 71.99; H, 5.03; N, 7.00. Found: C, 71.83; H, 5.15; N, 7.17.

trans-5-(4-Methoxyphenyl)-6-methyl-6,6a-dihydro-[1,3]dioxolo-[4,5-g]isoindolo[2,1-a]quinolin-11(5H)-one (**4p**). Obtained 410 mg of a white solid: 82% yield; mp 250−252 °C; IR (KBr) 3300, 1146 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm) 1.15 (3H, d, J = 6.4 Hz, CH_3) 1.75 (1H, dd, J = 16.9, 10.6 Hz, 6-H), 3.73 (3H, s, OCH_3), 3.84 (1H, d, J = 10.8 Hz, 5-H), 4.73 (1H, d, J = 10.7 Hz, 6a-H), 5.95 (2H, d, J = 3.2 Hz, CH_2), 6.09 (1H, s, 4-H), 6.89 (2H, d, J = 8.4 Hz, 2-H_{An} and 3-H_{An}), 7.08 (2H, d, J = 8.4 Hz, 2-H_{An} and 3-H_{An}), 7.59 (1H, t, J = 7.2 Hz, 9-H), 7.67 (1H, t, J = 7.3 Hz, 8-H), 7.74 (1H, d, J = 7.6 Hz, 7-H), 7.84 (1H, d, J = 7.4 Hz, 10-H), 7.92 (1H, s, 1-H); ^{13}C NMR (101 MHz, DMSO-d_6, δ ppm) 15.6, 39.2, 40.1, 41.2, 50.9, 55.0, 63.2, 100.6, 101.2, 109.0, 114.0, 123.5, 124.3, 124.7, 128.7, 129.5, 130.2, 131.8, 132.2, 135.7, 143.1, 143.5, 145.4, 158.0, 164.6; GC−MS (70 eV), t_R = 83.66 min, m/z 415 (50, $M^{+\bullet}$), 276 (30), 149 (100). Anal. Calcd for $C_{25}H_{21}NO_4$: C, 75.17; H, 5.30; N, 3.51. Found: C, 75.37; H, 5.34; N, 3.23.

trans-7-(4-Methoxyphenyl)-8-methyl-8,8a-dihydrobenzo[h]-isoindolo[2,1-a]quinolin-13(7H)-one (**4q**). Obtained 335 mg of a white solid: 67% yield; mp > 300 °C; FTIR (KBr disk) 1682, 1212 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm) 1.22 (3H, d, J = 8.9 Hz, CH_3), 1.69−1.59 (1H, m, 8-H), 3.71 (3H, d, J = 8.9 Hz, OCH_3), 4.06 (1H, d, J = 9.9 Hz, 7-H), 4.88 (1H, d, J = 10.1 Hz, 8a-H), 6.89 (2H, d, J = 8.5 Hz, 2-H_{An} and 3-H_{An}), 6.91 (1H, d, J = 8.8 Hz, 6-H), 7.10 (2H, d, J = 8.5 Hz, 2-H_{An} and 3-H_{An}), 7.49 (2H, m, 4-H and 5-H), 7.65−7.61 (1H, m, 9-H), 7.68 (2H, d, J = 9.0 Hz, 3-H and 6-H), 7.76−7.70 (1H, m, 11-H), 7.79 (1H, d, J = 7.6 Hz, 2-H), 7.87−7.82 (1H, m, 10-H), 7.91 (1H, d, J = 7.2 Hz, 12-H), 7.95 (1H, s, 1-H); ^{13}C NMR

dx.doi.org/10.1021/jo500516c | J. Org. Chem. 2014, 79, 5327−5333

(101 MHz, DMSO-d_6, δ ppm) 13.7, 15.9, 38.9, 40.3, 45.3, 50.8, 54.9, 55.0, 63.9, 107.3, 113.9, 114.1, 122.6, 124.4, 125.8, 126.1, 126.5, 127.1, 127.6, 127.9, 128.7, 129.5, 130.1, 130.8, 132.6, 138.6, 145.8, 148.4; GC−MS (70 eV), t_R = 111.67 min, m/z 405 ($M^{+\bullet}$, 100), 376 (10), 270 (70). Anal. Calcd for $C_{28}H_{23}NO_2$: C, 82.94; H, 5.72; N, 3.45. Found: C, 82.85; H, 5.93; N, 3.29.

*trans-5-(Benzo[d][1,3]dioxol-5-yl)-6-methyl-6,6a-dihydroisoindolo[2,1-a]quinolin-11(5H)-one (**4r**).* Obtained 240 mg of a white solid: 48% yield; mp 246−247 °C; FTIR (KBr disk) 1680, 1125 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, δ ppm) 1.18 (3H, d, J = 6.5 Hz, CH_3), 1.89 (1H, tq, J = 12.8, 6.5 Hz, 6-H), 3.94 (1H, d, J = 11.1 Hz, 5-H), 4.79 (1H, d, J = 10.6 Hz, 6a-H), 5.98 (2H, s, CH_2), 6.67 (1H, d, J = 1.5 Hz, 2-H_{Bd}), 6.72 (1H, d, J = 7.6 Hz, 4-H), 6.73 (1H, dd, J = 7.9, 1.5 Hz, 6-H_{Bd}), 6.88 (1H, d, J = 7.9 Hz, 5-H_{Bd}), 7.02−6.97 (1H, m, 3-H), 7.25 (1H, t, J = 7.7 Hz, 2-H), 7.61 (1H, t, J = 7.4 Hz, 9-H), 7.71−7.66 (1H, m, 8-H), 7.77 (1H, d, J = 7.8 Hz, 7-H), 7.86 (1H, d, J = 7.5 Hz, 10-H), 8.37 (1H, d, J = 7.5 Hz, 1-H); ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm) 15.7, 51.4, 63.1, 100.9, 108.0, 108.9, 119.4, 123.1, 123.6, 124.1, 124.8, 124.9, 126.4, 129.1, 129.8, 130.8, 131.9, 132.3, 135.6, 137.4, 143.4, 146.0, 147.6, 164.9; GC−MS (70 eV), t_R = 73.141 min, m/z 369 ($M^{+\bullet}$, 100), 340 (20), 232 (40), 149 (40). Anal. Calcd for $C_{24}H_{19}NO_3$: C, 78.03; H, 5.18; N, 3.79. Found: C, 78.25; H, 5.29; N, 3.62.

*trans-5-(Benzo[d][1,3]dioxol-5-yl)-3,6-dimethyl-6,6a-dihydroisoindolo[2,1-a]quinolin-11(5H)-one (**4s**).* Obtained 200 mg of a white solid: 40% yield; mp 187−189 °C; FTIR (KBr disk) 1680, 1112 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, δ ppm) 1.16 (3H, d, J = 6.4 Hz, 6-CH_3), 1.83 (1H, d, J = 6.1 Hz, 6-H), 2.13 (3H, s, 3-CH_3), 3.88 (1H, d, J = 11.0 Hz, 5-H), 4.73 (1H, d, J = 9.4 Hz, 6a-H), 5.99 (2H, d, J = 5.0 Hz, CH_2), 6.53 (1H, s, 4-H), 6.66 (1H, s, 2-H_{Bd}), 6.72 (1H, d, J = 8.0 Hz, 6-H_{Bd}), 6.87 (1H, d, J = 7.9 Hz, 5-H_{Bd}), 7.06 (1H, d, J = 8.4 Hz, 2-H), 7.59 (1H, t, J = 7.4 Hz, 9-H), 7.67 (1H, t, J = 7.2 Hz, 8-H), 7.75 (1H, d, J = 7.5 Hz, 7-H), 7.84 (1H, d, J = 7.6 Hz, 10-H), 8.25 (1H, d, J = 8.3 Hz, 1-H); ^{13}C NMR (101 MHz, DMSO-d_6, δ ppm) 15.6, 20.7, 40.7, 51.3, 63.1, 100.9, 108., 109.0, 119.5, 123.1, 123.5, 124.7, 127.1, 128.7, 129.9, 130.6, 131.8, 132.4, 132.6, 133.2, 137.4, 143.3, 146.0, 147.6, 164.7; GC−MS (70 eV), t_R = 78.813 min, m/z 383 ($M^{+\bullet}$, 100), 354 (10), 234 (40), 149 (10). Anal. Calcd for $C_{25}H_{21}NO_3$: C, 78.31; H, 5.52; N, 3.79. Found: C, 78.52; H, 5.36; N, 3.56.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

General methods, **4a**−**s** NMR overview, Figures S1 and S2, and ^1H NMR and ^{13}C NMR spectra of all products listed in Table 2. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from Patrimonio Autónomo Fondo Nacional de Financiamiento para la Ciencia, la Tecnología y la Innovación, Francisco José de Caldas, Contract RC-0572-2012, is gratefully acknowledged. D.R.M.A. thanks COLCIENCIAS for the fellowship.

■ REFERENCES

(1) Reddy, R.; Klumpp, D. A. *Chem. Rev.* **2013**, *113*, 6905.
(2) Brenna, E.; Fuganti, C.; Gatti, F. G.; Serra, S. *Chem. Rev.* **2011**, *111*, 4036.
(3) Dömling, A.; Wang, W.; Wang, K. *Chem. Rev.* **2012**, *112*, 3083.
(4) Pellissier, H. *Chem. Rev.* **2013**, *113*, 442.
(5) Gantier, J. C.; Fournet, A.; Munos, M. H.; Hocquemiller, R. *Planta Med.* **1996**, *62*, 285.
(6) Copp, B. R. *Nat. Prod. Rep.* **2003**, *20*, 535.
(7) Meléndez, C. M.; Kouznetsov, V. V.; Sortino, M.; Alarez, S. L.; Zacchino, S. A. *Bioorg. Med. Chem.* **2008**, *16*, 7908.
(8) Bedoya, L.; Abad, M.; Calonge, E.; Saavedra, L.; Gutierrez, M.; Kouznetsov, V. V.; Alcamia, J.; Bermejo, P. *Antiviral Res.* **2010**, *87*, 338.
(9) Kumar, A.; Srivastava, S.; Gupta, G.; Chaturvedi, V.; Sinha, S.; Srivastava, R. *ACS Comb. Sci.* **2011**, *13*, 65.
(10) Nien, C.-Y.; Chen, Y.-C.; Kuo, C.-C.; Hsieh, H.-P.; Chang, C.-Y.; Wu, J.-S.; Wu, S.-Y.; Liou, J.-P.; Chang, J.-Y. *J. Med. Chem.* **2010**, *53*, 2309.
(11) Muñoz, A.; Sojo, F.; Merchan Arenas, D.; Kouznetsov, V. V.; Arvelo, F. *Chem.-Biol. Interact.* **2011**, *189*, 215.
(12) Sui, Z.; Altom, J.; Nguyen, V. N.; Fernandez, J.; Bernstein, J. I.; Hiliard, J. J.; Barrett, J. F.; Podlogar, B. L.; Ohemeng, K. A. *Bioorg. Med. Chem.* **1998**, *6*, 735.
(13) Lübbers, T.; Angehrn, P.; Gmünder, A.; Herzig, S. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4708.
(14) Pigeon, P.; Othman, M.; Netchitaïlo, P.; Decroix, B. *J. Heterocyclic Chem.* **1999**, *36*, 691.
(15) Epsztajn, J.; Jóźwiak, A.; Kołuda, P.; Sadokierska, I.; Wilkowska, I. *Tetrahedron* **2000**, *56*, 4837.
(16) Zubkov, F. I.; Boltukhina, E. V.; Turchin, K. F.; Borisova, R. S.; Varlamov, A. V. *Tetrahedron* **2005**, *61*, 4099.
(17) Khadem, S.; Udachin, K.; Enright, G.; Prakesch, M.; Arya, P. *Tetrahedron Lett.* **2009**, *50*, 6661.
(18) Merchan Arenas, D. R.; Rojas Ruiz, F. A.; Kouznetsov, V. V. *Tetrahedron Lett.* **2011**, *52*, 1388.
(19) Madhava, J. V.; Reddy, Y. T.; Reddy, P. N.; Reddy, M. N.; Kuarma, S.; Crooks, P. A.; Rajitha, B. *J. Mol. Catal. A: Chem.* **2009**, *304*, 85.
(20) Safari, J.; Banitaba, S. H.; Khalili, S. D. *J. Mol. Catal. A: Chem.* **2011**, *335*, 46.
(21) Reddy, B. V.; Venkateswarlu, A.; Kumar, G. G. K. S.; Vinu, A. *Tetrahedron Lett.* **2010**, *51*, 6511.
(22) Kumar, A.; Gupta, G.; Srivastava, S. *J. Comb. Chem.* **2010**, *12*, 458.
(23) Shaabani, A.; Rezayan, A.; Behnam, M.; Heidary, M. C. R. *Chimie* **2009**, *12*, 1249.
(24) Kumar, A.; Srivastava, S.; Gupta, G. *Tetrahedron Lett.* **2010**, *51*, 517.
(25) Shaabani, A.; Rahmati, A.; Badri, Z. *Catal. Commun.* **2008**, *9*, 13.
(26) Fonseca-Berzal, C.; Merchán Arenas, D. R.; Romero Bohórquez, A. R.; Escario, J. A.; Kouznetsov, V. V.; Gómez-Barrio, A. *Bioorg. Med. Chem. Lett.* **2013**, *17*, 4851.
(27) Kouznetsov, V. V.; Romero Bohórquez, A. R.; Stashenko, E. E. *Tetrahedron Lett.* **2007**, *48*, 8885.
(28) Kouznetsov, V. V.; Merchan Arenas, D. R.; Ortiz Areniz, C. J.; Meléndez Gómez, C. M. *Synthesis* **2011**, *24*, 411.
(29) Shena, J.; Tan, C.-H. *Org. Biomol. Chem.* **2008**, *6*, 3229.
(30) Jiang, X.; Wang, R. *Chem. Rev.* **2013**, *113*, 5515.
(31) Wang, X.; Quan, Z.; Wang, F.; Wang, M.; Zang, Z.; Li, Z. *Synth. Commun.* **2006**, *36*, 451.
(32) Safari, J.; Hossein, S.; Khalili, S. *J. Mol. Catal. A: Chem.* **2011**, *335*, 46.
(33) Smith, C. D.; Gavrilyuk, J. I.; Lough, A. J.; Batey, R. A. *J. Org. Chem.* **2010**, *75*, 702.
(34) Taylor, R. R. R.; Batey, R. A. *J. Org. Chem.* **2013**, *78*, 1404.
(35) Zhang, W.; Zheng, A.; Liu, Z.; Yang, Li.; Liu, Z. *Tetrahedron Lett.* **2005**, *46*, 5691.
(36) Sauer, J. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 16.
(37) Kouznetsov, V. V. *Tetrahedron* **2009**, *65*, 2721.