Synthesis M. Hassine et al. Paper

Synthesis of *N*-(Hetero)arylconvolvine Derivatives through a Palladium-Catalyzed Buchwald–Hartwig Cross-Coupling

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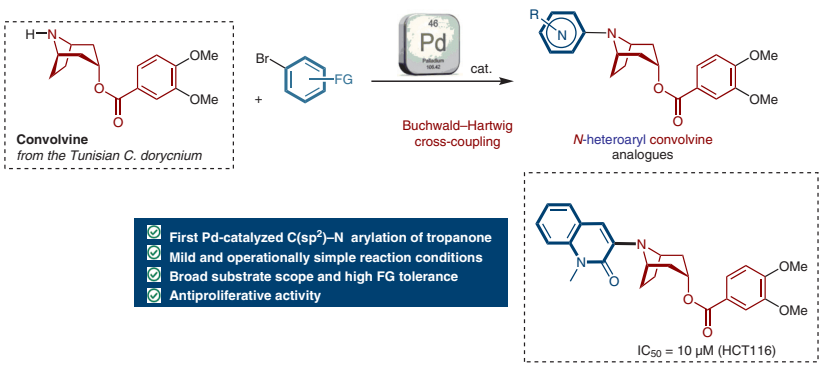

Received: 02.10.2019
Accepted after revision: 14.10.2019
Published online: 05.11.2019
DOI: 10.1055/s-0039-1690238; Art ID: ss-2019-z0536-op

Abstract The present study describes the isolation of convolvine from the roots of the Tunisian plant *Convolvulus dorycnium* L. and its synthesis through a four-step sequence starting from tropine. Then, an efficient synthesis of *N*-(het)aryltropanes derivatives by a sequence of a palladium-catalyzed N-arylationof convolvine has been established. This strategy enabled access to unknown tropane scaffolds of biological interests.

Key words convolvine, Buchwald–Hartwig reaction, palladium catalysis, tropane

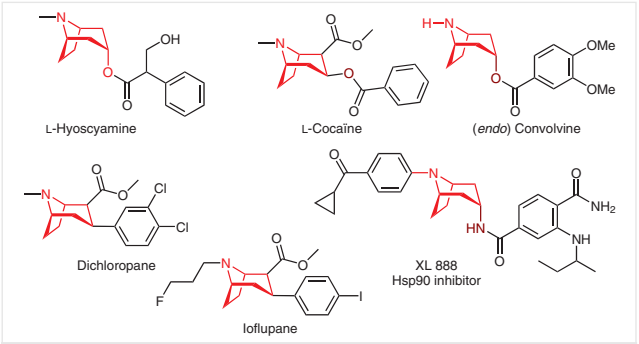

Figure 1 Tropane natural products and some semi-synthetic analogues

Tropane is an important nitrogen bicyclic motif found in many natural and synthetic compounds.[1] Tropane derivatives are among the economically most important pharmaceuticals.[2] More than twenty active pharmaceutical ingredients (APIs) containing the tropane moiety are manufactured by pharmaceutical industries as antispasmodics, anesthetics, antiemetrics, and bronchodilators.[3]

The biological importance of some *Convolvulus* species and the high biological activity of the tropane alkaloids encouraged us to undertake a phytochemical study of *Convolvulus dorycnium* L. whose *n*-BuOH extract of the roots afforded an interesting tropane natural compound convolvine (Figure 1), which was isolated for the first time from this plant.

One of the interesting tropane compound currently under clinical investigation is the tropanone-based inhibitor XL888, which is reported as a potent and selective ATP-competitive inhibitor of Hsp90.[4] In preclinical studies, XL888 inhibits the proliferation of a broad panel of human tumor cell lines and induces marked degradation of HSP90 client proteins. In addition, XL888 is highly active in multiple human tumor xenograft models in mice.

In the context of the development of new Hsp90 inhibitors, we reported in a previous study that the 3-amidoquinolinone compound 6BrCaQ (Scheme 1)[5,6] is a highly potent Hsp90 inhibitor. This derivative displayed antiproliferative activities ranging from 2 to 8 µM against various cancer cell lines (MCF7, MDA MB231, Caco2, IGROV-1, and ISHIKAWA). Moreover, this lead compound is able to induce a significant downregulation of several Hsp90 client proteins (HER2, Raf-1, and cdk-4).

Because of the exciting activities of XL888 and 6BrCaQ, we were interested to find out whether the combination of the tropane core of XL888 and the quinoline nucleus of 6BrCaQ in one molecule may lead to more efficacious antiproliferative compounds of the type **5** (Scheme 1). Herein, we planned to prepare a new series of N-(hetero)arylconvolvine analogues (Table 2), in which various chemical modifications at the heteroaromatic nucleus were performed in the aim to better understand the SAR in this novel series. In this article, the synthesis and the biological evaluation of novel (hetero)aryl convolvine analogues **5a–o**

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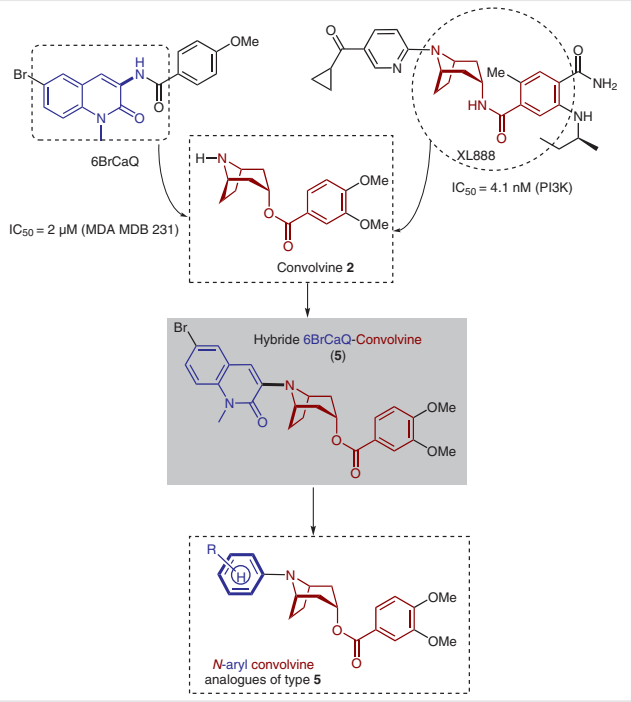


Scheme 1 General strategy to N-(hetero)aryl convolvine analogues

are described. Preliminary in vitro efficacy of these compounds in terms of antiproliferative activity is reported.

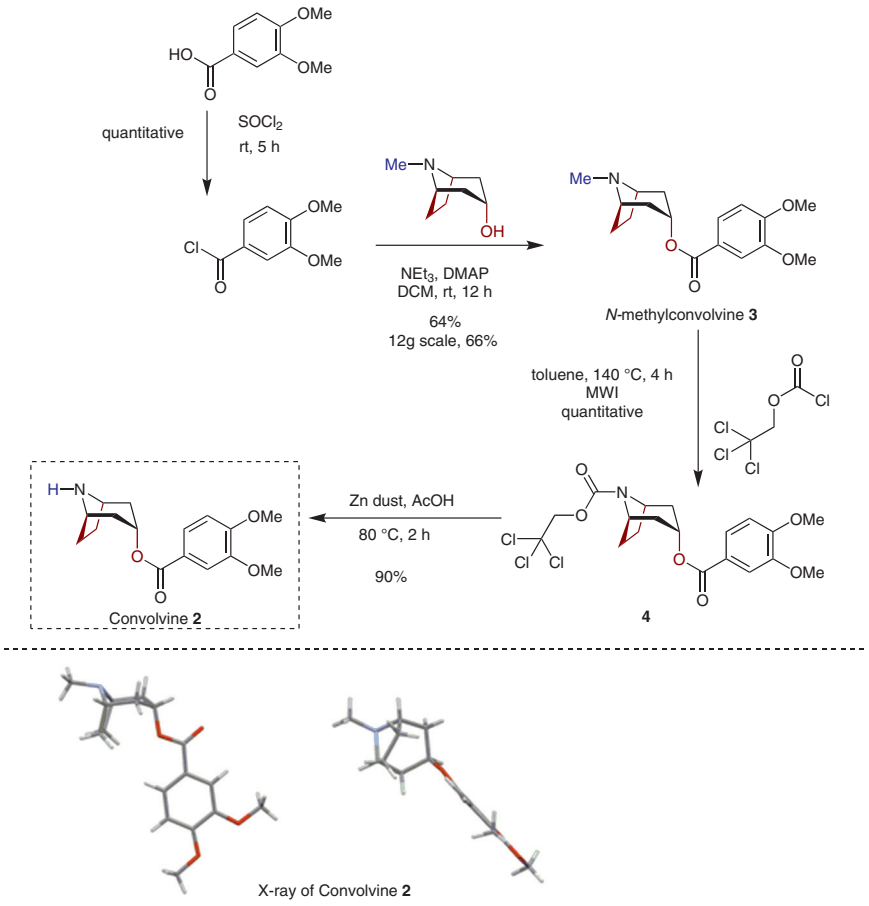
Convolvine (Figure 1) was isolated as a white solid from the *n*-BuOH extract from the roots of the Tunisian *Convolvulus dorycnium*. Its structure was evidenced through the ^{1}H and ^{13}C spectroscopy examination and by comparison with literature data.[7] We note that this same compound has been also isolated from *C. subhirsutus*[8] and *C. krauseanus*[9] without specifying the corresponding stereochemistry.

To have at our disposal a sufficient quantity of convolvine as a starting material for the further modifications, we envisioned to perform its synthesis in a gram scale rather than its isolation from plant. Accordingly, the synthesis commenced from *O*-acylation of tropine with the preformed 2,3-dimethoxybenzoyl chloride (Scheme 2). Our first attempt was performed according to the protocol of Maksay et al.[10] using NEt_3 as a base in refluxing toluene. Under these conditions, the desired *N*-methylconvolvine (**3**) was isolated in yield, which never exceeded 20%. This result is in concordance with the observation of Maksay et al.[10] who has suggested that the acylation of tropine is usually difficult because of the sterically hindered hydroxyl group. To increase the yield of the *O*-acylation various reaction parameters were explored. Thus, when a solution of the tropine and the freshly pre-formed 2,3-dimethoxybenzoyl chloride in DCM was stirred at room temperature overnight in the presence of triethylamine as a base and a catalytic amount of DMAP, the *N*-methylconvolvine (**3**) was isolated after purification in good 64% yield (Scheme 2). It is important to note that the acylation reaction was also performed in a gram scale (84 mmol, 12 g), and the product **3** was isolated in a similar yield (66%).

The X-ray crystal structure of *N*-methylconvolvine (**3**)[11] depicted in Scheme 2 shows that the conformation of the tropane scaffold and the aryl nucleus are not planar with an dihedral angle around 90°. Moreover, the *endo*-stereochemistry of the tropine nucleus, which is corroborated with the NMR data, was conserved during the acylation process as confirmed by the X-crystal structure analysis of compound **3** (Scheme 2).

With the *N*-methylconvolvine in our hand, we next turned our attention to the deprotection of the nitrogen atom in the intermediate **3**. The challenge of this transformation is to achieve the demethylation while keeping intact the ester function. Several methods are known for the demethylation of tropane derivatives[12] such the use of ethyl chloroformate or 2,2,2-trichloroethyl chloroformate as demethylating agents. These methods proceed through two concomitant steps; (i) acylation/demethylation of the nitrogen and (ii) deacylation of the carbamate function. All our attempts to synthesis the *endo*-convolvine (**2**) using these two demethylating reagents, under several reported conditions failed. At this stage, we decided to perform step by step the protocol of the demethylation when 2,2,2-trichloroethyl chloroformate was used. In the first step, the carbamate **4** resulting from acylation of the *N*-methylconvolvine under microwave conditions followed by *N*-demethylation of the ammonium intermediate, was obtained in a quantitative yield (Scheme 2). Removal of the trichloroethoxycarbonyl group was then achieved using zinc dust in acetic acid solution. Under these conditions the *endo*-convolvine (**2**) was isolated in a 90% yield as a pure *endo*-conformer without affecting the ester group. This sequence allows us to obtain the convolvine (**2**) in 56% overall yield even when achieving the synthesis on a gram scale (2 g).

Upon completion of the synthesis of the convolvine, we turned our attention to functionalization of the nitrogen atom of convolvine through Pd-catalyzed cross coupling. The main issue of this coupling is to maintain the benzoic ester group intact during the cross coupling under basic conditions. To this end, we examined the coupling of 3-bromo-1-methylquinolinone (**1a** with convolvine (**2**) as a model study under various source of palladium/ligand catalysts, bases, and solvents. Representative results from this study are summarized in Table 1. The reaction of **1a** (1 equiv) with **2** (2 equiv) was first investigated under our previously reported procedure [$Pd(OAc)_2$ (5 mol%), XantPhos (5 mol%), Cs_2CO_3, 1,4-dioxane, at 110 °C][13] (Table 1, entry 1). Unfortunately, this coupling reaction failed and only the starting materials were recovered unchanged. Using the monodentate ligand XPhos instead of the bidentate XantPhos was also unsuccessful (entry 2). Interestingly, switching from Cs_2CO_3 as the base to the more basic *t*-BuONa, the coupling reaction furnished **5a** in a 12% yield (entry 3). This first re-

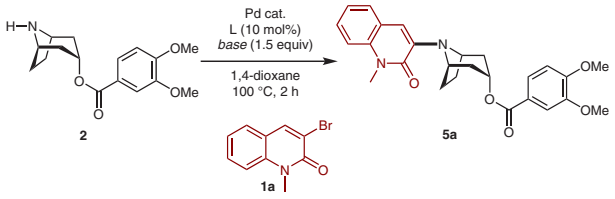


Scheme 2 Synthesis of convolvine (**2**)

sult indicates clearly that the reactivity of the amine of convolvine is far to be trivial. To increase the yield of **5a**, we examined the influence of other reaction parameters. Pleasantly, when the coupling reaction was performed by using the ratio of Pd/L = 1:2 [5 mol% $Pd(OAc)_2$ and 10 mol% of XPhos], the yield was improved up to 66% and the benzoic ester was maintained intact (entry 5). By increasing the amount of the base (from 1.5 equiv to 2 equiv), we managed to isolate 95% of the desired product **5a** (entry 6).

Motivated by these results, we next explored the scope of the coupling reaction of convolvine (**2**) with various (hetero)aryl bromides. Gratifyingly, all the N-arylations proceeded cleanly to give the substituted aryl *N*-convolvine analogues **5a–o** in good to excellent yields. As depicted in Table 2, convolvine (**2**) was readily coupled with aryl bromides having *para* and *meta* electron-withdrawing (F, CF_3, Cl, NO_2, NC) or electron-donating (OMe) substituents to give *N*-arylconvolvines **5b–f**, **5j**, **5l**, and **5m** in good yields. In addition, the sterically demanding *ortho* substitution pattern engaged in the coupling reaction of **2**, furnished compounds **5g** and **5j** having an *ortho* substituent group. Interestingly, heteroarene such as 3-bromoquinolinone,

Table 1 Survey of Reaction Conditions for the *N*-Arylation of Convolvine (**2**) with 3-Bromoquinolinone **1a**[a]



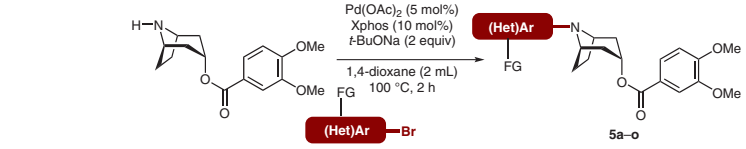
Entry	[Cu]	Base	Ligand	Yield (%)[b]
1	$Pd(OAc)_2$	Cs_2CO_3	XantPhos	0
2	$Pd(OAc)_2$	Cs_2CO_3	XPhos	0
3	$Pd(OAc)_2$	*t*-BuONa	XPhos	12
4	PdG2XPhos	*t*-BuONa	–	10
5	$Pd(OAc)_2$	*t*-BuONa	XPhos	66
6[c]	**$Pd(OAc)_2$**	***t*-BuONa**	**XPhos**	**95**

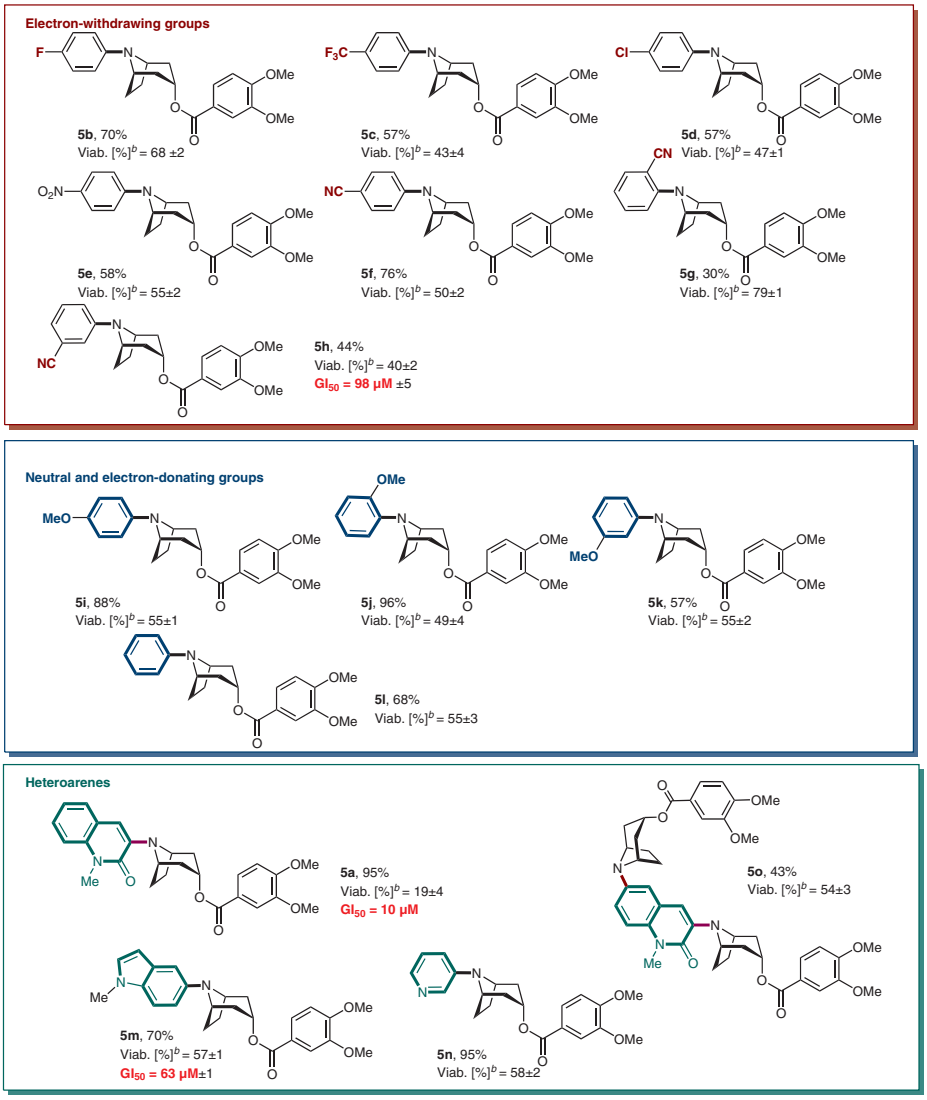
[a] Reaction conditions: 3-Bromoquinolinone **1a** (1 equiv), convolvine (**2**; 2 equiv), [$Pd(OAc)_2$] (5 mol%), ligand (5 mol%), base (1.5 equiv), 2 h, 100 °C, [0.5 M].
[b] Yield of isolated **5a**.
[c] Two equiv of the base were used.

5-bromoindole, and 3-bromopyridine were good substrates in this reaction (compounds **5a**, **5n**,**o**). Of note, in the case of coupling with dibromoquinolinone, only the bis-coupled product **5o** was isolated as the single product in 43% yield.

Upon completion of their syntheses, the in vitro activity of convolvine derivatives **5a–o** was evaluated by their growth-inhibitory potency against a human colon carcinoma HCT-116 cells at the concentrations of 10^{-5} M. The quantification of cell survival in this cell line was established by using MTT assays after 72 hours exposure (Table 2), and GI_{50} values were determined at the concentration required to produce 50% inhibition. Taxotere® was used as a positive control (IC_{50} = 1 nM).

Table 2 Scope of the Coupling Reaction of Convolvine (**2**) with Various (Hetero)aryl Bromides and Cytotoxic Activity against HCT-116 Cells[a]





[a] Reaction conditions: Convolvine (1 equiv), aryl bromide (2 equiv), $Pd(OAc)_2$ (5 mol%), Xphos (10 mol%), *t*-BuONa (2 equiv), 1,4-dioxane at 100 °C, 2 h.
[b] Value of the anti-proliferative effect (% of viable cells compared to 100% untreated cells) of convolvine analogues in HCT-116 cell line at a concentration of 10^{-5} M (MTT method).

The results of this study, summarized in Table 2, demonstrated that all tested compounds were able to decrease the cell viability in HCT-116 cells until 19–79% survivals compared to the reference compound 6BrCaQ (10% survival) indicating the biological potential of convolvine pharmacophore in this series. Interestingly, the combination of the quinolinone nucleus with convolvine moiety **5a** induced a significant decrease of the cell viability in HCT-116 cells (19% survival) when compared with the reference 6BrCaQ (10% survival). Pleasantly, the growth inhibition value GI_{50} for compound **5a** (GI_{50} = 10 μM) was measured and was found to be approximatively the same that of the reference 6BrCaQ (GI_{50} = 8 μM). This result clearly validates our initial strategy. Substitution of the nitrogen of the convolvine by an indole nucleus (compound **5m**) did not produce a compound that inhibit cell growth more effectively than the **5a** (survival = 57%, GI_{50} = 63 μM). Another important observation is that the disubstituted convolvine **5o** affects slightly the growth of HCT-116 cells (54% survival) when compared with the *monosubstituted* convolvine **5a** (19% survival). These results clearly suggest that the presence of a bulky substituent at the C-7 position of the quinolinone nucleus affect cell viability. It can be noted that convolvine (**2**) with free-NH is less cytotoxic since 60% of cells survive when incubated with convolvine (**2**).

In conclusion, we have developed an efficient and practical protocol for the *N*-arylation of the tropane nucleus of convolvine without affecting the benzoic ester part. This transformation exhibited broad substrate scope with respect to the aryl bromide partners. Through this methodology, we designed and synthesized a series of *N*-(hetero)arylconvolvines, and identified compound **5a** displaying the most stronger antiproliferative activity against HCT-116 cell lines. These preliminary results show the biological potential of convolvine pharmacophore and suggest that pharmaco-modulations of this compound may increase its biological activity.

All reactions were conducted under an argon atmosphere. Solvents: cyclohexane, pentane, EtOAc, DCM, and MeOH for extraction and chromatography were of technical grade. The compounds were all identified by usual physical methods, for example, 1D and 2D NMR (COSY, HSQC, HMBC, and NOESY), IR, ES-HRMS. ^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$ or acetone-d_6 on a Bruker Avance 300 and 400 MHz spectrometers. ^{1}H chemical shifts are reported in parts per million from an internal standard TMS or of residual $CHCl_3$ (7.27 ppm). Standard abbreviations are used to denote spin multiplicities. ^{13}C chemical shifts are reported in parts per million from the central peak of $CDCl_3$ (77.14 ppm). IR spectra were recorded on a Bruker Vector 22 spectrophotometer and are reported in wave numbers (cm^{-1}). R_f values refer to TLC on 0.25 mm silica gel plates (60-F254). Flash chromatography was performed on silica gel 60 (0.040–0.063 mm).

Analytical TLC was performed on Merck precoated silica gel 60F plates. Merck silica gel 60 (0.015–0.040 mm) was used for column chromatography. Melting points were recorded on a Büchi B-450 apparatus and are uncorrected. High-resolution mass spectra (HR-MS) were recorded on a Bruker MicroTOF spectrometer, using ESI with MeOH as the carrier solvent. Nominal and exact *m*/*z* values are reported in Daltons.

Plant Material

The roots of *Convolvulus dorycnium* L. were collected from the region of Sidi Khelifa, Sousse (Tunisia) on June 2012. The plant was identified by Prof. Fethia Harzallah-Skhiri in the Laboratory of Bioressources: Integrative Biology and Valorization at Higher Institute of Biotechnology of Monastir (Tunisia). A voucher specimen (CD-12) was deposited in the herbarium of the above laboratory.

Extraction and Isolation

Dry roots of *C. dorycnium* (1.473 kg) were extracted twice with MeOH/H_2O mixture (7:3) for 2 days at rt. Then the aqueous solution obtained after evaporation of solvent under vacuum was partitioned with *n*-BuOH to yield 100 g (6.7%) of the corresponding extract. The *n*-BuOH extract was subjected to RP-18 flash column chromatography with gradient elution (H_2O; H_2O/MeOH, 90:10 to 30:70), yielding twelve fractions (F_1–F_{12}) of which the fraction F_9 appears to be of pure convolvine (300 mg) according to TLC analysis.

8-Methyl-8-azabicyclo[3.2.1]octan-3-yl 3,4-Dimethoxybenzoate (3)

To a solution of commercial *endo*-tropine (1 g, 7.08 mmol, 1 equiv) in anhyd DCM were added 2,3-dimethoxybenzoyl chloride (1.562 g, 7.78 mmol, 1.1 equiv), NEt_3 (2.961 mL, 21.2 mmol, 3 equiv), and 4-dimethylaminopyridine (0.951 g, 7.78 mmol, 1.1 equiv) under argon atmosphere. The reaction mixture was stirred at rt overnight before being cooled at 0 °C and quenched with sat. aq NH_4Cl. The aqueous layer was extracted with DCM (3 ×). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by flash column chromatography on silica gel yielded the desired product (4.53 mmol) as a white solid; yield: 64% (4.53 mmol); mp 223–224 °C; R_f = 0.58 (85:15 DCM/MeOH).

IR (neat): 2939, 2361, 1703, 1600, 1514, 1467, 1449, 1417, 1345, 1272, 1220, 1175, 1133, 1025, 877, 764, 632 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.56 (dd, J_1 = 8.4 Hz, J_2 = 1.9 Hz, 1 H, $H_{6'}$), 7.51 (d, J = 1.9 Hz, 1 H, $H_{2'}$), 6.90 (d, J = 8.4 Hz, 1 H, $H_{5'}$), 5.37 (m, 1 H, H_3), 3.94 (s, 3 H, $H_{7'}$), 3.92 (s, 3 H, $H_{8'}$), 3.78 (br s, 2 H, $H_{1,5}$), 2.77 (s, 3 H, H_9), 2.55–2.25 (m, 6 H, $H_{2,4,6\alpha,7\alpha}$), 2.20–2.05 (m, 2 H, $H_{6\beta,7\beta}$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.19 (C_8), 153.53 ($C_{4'}$), 149.06 ($C_{3'}$), 123.14 ($C_{6'}$), 122.38 ($C_{1'}$), 112.10 ($C_{2'}$), 110.53 ($C_{5'}$), 65.19 (C_3), 61.91 ($C_{1,5}$), 56.22 ($C_{7'}$), 56.15 ($C_{8'}$), 40.21 (C_9), 34.49 ($C_{2,4}$), 24.95 ($C_{6,7}$).

MS: *m*/*z* = 306.1705 ($[M + H]^+$).

2,2,2-Trichloroethyl 3-[(3,4-Dimethoxybenzoyl)oxy]-8-azabicyclo[3.2.1]octane-8-carboxylate (4)

A Schlenk tube containing the *N*-Me convolvine (**3**; 0.1 g, 0.327 mmol, 1 equiv) was capped with a rubber septum, evacuated, and backfilled with argon. This evacuation/backfill sequence was repeated one additional time. Anhyd toluene (2 mL) was added along with 2,2,2-trichloroethyl chloroformate (0.135 mL, 0.982 mmol, 3 equiv). The septum was replaced with a Teflon screwcap. The Schlenk tube was sealed, and the mixture was stirred at 140 °C for 4 h under microwave irradiation. The resulting suspension was cooled to rt and concentrated. The desired product was obtained as a white solid; yield: quantitative (0.32 mmol); mp 135–136 °C; R_f = 0.62 (6:4 cyclohexane/EtOAc).

IR (neat): 2937, 2361, 1713, 1702, 1601, 1514, 1465, 1414, 1313, 1289, 1270, 1248, 1221, 1178, 1102, 1078, 1023, 961, 942, 834, 762, 713, 632 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.61 (dd, J_1 = 8.4 Hz, J_2 = 1.8 Hz, 1 H, $H_{6'}$), 7.52 (d, J = 1.8 Hz, 1 H, $H_{2'}$), 6.89 (d, J = 8.4 Hz, 1 H, $H_{5'}$), 5.33 (m, 1 H, H_3), 4.84 (d, J = 12.0 Hz, 1 H, H_{10a}), 4.66 (d, J = 12.0 Hz, 1 H, H_{10b}), 4.41 (br s, 2 H, $H_{1,5}$), 3.91 (s, 3 H, $H_{7'}$), 3.90 (s, 3 H, $H_{8'}$), 2.37–2.03 (m, 6 H, $H_{2,4,6\alpha,7\alpha}$), 1.93 (m, 2 H, $H_{6\beta,7\beta}$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.45 (C_8), 153.15 (C_9), 151.40 ($C_{4'}$), 148.81 ($C_{3'}$), 123.24 ($C_{6'}$), 122.96 ($C_{1'}$), 111.98 ($C_{2'}$), 110.45 ($C_{5'}$), 95.92 (C_{11}), 74.60 (C_{10}), 67.84 (C_3), 56.10 ($C_{7'}$), 56.00 ($C_{8'}$), 53.03 (C_1), 52.90 (C_5), 36.38 (C_2), 35.61 (C_4), 28.55 (C_6), 27.70 (C_7).

MS: m/z = 466.0526 ($[M + H]^+$).

8-Azabicyclo[3.2.1]octan-3-yl 3,4-Dimethoxybenzoate [*endo*-Convolvine (2)]

A Schlenk tube was charged with the carbamate **4** (0.1 g, 0.214 mmol, 1 equiv) and Zc dust (0.042 g, 0.642 mmol, 3 equiv) in AcOH (2 mL). The tube was capped with a rubber septum, evacuated, and backfilled with argon. This evacuation/backfill sequence was repeated one additional time. The septum was replaced with a Teflon screwcap. The Schlenk tube was sealed, and the mixture was stirred at 80 °C for 2 h. The resulting suspension was cooled to rt and quenched with concd aq NH_4OH. The aqueous layer was extracted with DCM (3 ×). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by flash column chromatography on silica gel afforded the desired product as a white solid; yield: 90% (0.192 mmol); mp 101–102 °C; R_f = 0.36 (8:2 CH_2Cl_2/MeOH).

IR (neat): 2939, 2837, 1702, 1601, 1514, 1465, 1416, 1357, 1270, 1224, 1177, 1132, 1076, 1023, 875, 849, 765, 629 cm^{-1}.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 65.6, 152.9, 148.6, 123.3, 123.2, 111.9, 110.3, 68.5, 55.9, 53.4 (2 C), 37.6, 37.6, 29.4 (2 C).

MS: m/z = 292.1541 ($[M + H]^+$).

Pd-Catalyzed Coupling of Convolvine (2) with Various Aryls and Heteroaryls; General Procedure

A flame-dried resealable Schlenk tube was charged with $Pd(OAc)_2$ (2 mg, 0.05 mmol, 5 mol%), Xphos (8 mg, 0.10 mmol, 10 mol%), the solid reactant(s) [1.0 mmol of the 3-bromoquinolin-2(1*H*)-one/aryl/heteroaryl bromides, 2 mmol of convolvine (**2**)], and *t*-BuONa (33 mg, 2 mmol). The Schlenk tube was capped with a rubber septum, evacuated, and backfilled with argon; this evacuation/backfill sequence was repeated one additional time. The solvent 1,4-dioxane (2 mL) was added through the septum. The septum was replaced with a Teflon screwcap. The Schlenk tube was sealed, and the mixture was stirred at 100 °C for 2 h. The resulting suspension was cooled to rt and filtered through Celite eluting with EtOAc, and the inorganic salts were removed. The filtrate was concentrated and purification of the residue by silica gel column chromatography gave the desired product.

8-(1-Methyl-2-oxo-1,2-dihydroquinolin-3-yl)-8-azabicyclo-[3.2.1]octan-3-yl 3,4-Dimethoxybenzoate (5a)

Yield: 95% (0.97 mmol); yellow solid; mp 146–147 °C; R_f = 0.38 ($CHCl_3$/EtOAc 95:5).

IR (neat): 2958, 1702, 1632, 1592, 1563, 1514, 1463, 1416, 1379, 1359, 1342, 1309, 1289, 1270, 1248, 1219, 1177, 1167, 1132, 1107, 1084, 1026, 979, 943, 872, 825, 764, 731, 701, 682, 647, 631 cm^{-1}.

^1H NMR (400 MHz, acetone-d_6): δ = 7.69 (dd, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 1 H, $H_{6'}$), 7.58 (d, J = 1.9 Hz, 1 H, $H_{8''}$), 7.53 (dd, J_1 = 7.7 Hz, J_2 = 1.3 Hz, 1 H, $H_{7''}$), 7.40 (d, J = 8.3 Hz, 1 H, $H_{2'}$), 7.35–7.29 (m, 1 H, $H_{5''}$), 7.19–7.13 (m, 1 H, $H_{3''}$), 7.10 (d, J = 8.4 Hz, 1 H, $H_{5'}$), 7.05 (s, 1 H, $H_{4''}$), 5.26 (m, 1 H, H_3), 4.84 (br s, 2 H, $H_{1,5}$), 3.91 (s, 3 H, $H_{7'}$), 3.89 (s, 3 H, $H_{8'}$), 3.73 (s, 3 H, $H_{9''}$), 2.40–2.34 (m, 2 H, $H_{2\alpha,4\alpha}$), 2.32–2.27 (m, 2 H, $H_{2\beta,4\beta}$), 2.15–2.11 (m, 2 H, $H_{6\alpha,7\alpha}$), 1.84 (d, J = 14.4 Hz, 2 H, $H_{6\beta,7\beta}$).

^{13}C NMR (400 MHz, acetone-d_6): δ = 165.89 (C_8), 159.55 ($C_{2''}$, 154.45 ($C_{4'}$), 150.06 ($C_{3'}$), 146.66 ($C_{1''}$), 137.94 ($C_{8''a}$), 136.19 ($C_{4''a}$), 127.07 ($C_{5''}$), 126.56 ($C_{7''}$), 124.00 ($C_{6''}$), 123.07 ($C_{1'}$), 122.79 ($C_{6'}$), 114.71 ($C_{8''}$), 114.46 ($C_{2'}$), 113.00 ($C_{5'}$), 111.92 ($C_{4''}$), 69.24 (C_3), 56.23 ($C_{7'}$), 56.12 ($C_{8'}$), 55.01 ($C_{1,5}$), 34.70 ($C_{2,4}$), 31.58 ($C_{9''}$), 28.26 ($C_{6,7}$).

MS: m/z = 449.1559 ($[M + H]^+$).

8-(4-Fluorophenyl)-8-azabicyclo[3.2.1]octan-3-yl 3,4-Dimethoxybenzoate (5b)

Yield: 70% (0.70 mmol); yellow solid; mp 180–181 °C; R_f = 0.44 (cyclohexane/EtOAc 8:2).

IR (neat): 3050, 2956, 2937, 2915, 2838, 1702, 1601, 1589, 1517, 1504, 1465, 1442, 1416, 1377, 1358, 1345, 1328, 1291, 1270, 1249, 1227, 1211, 1175, 1132, 1107, 1085, 1033, 987, 948, 929, 880, 871, 819, 802, 764, 734, 707, 632 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.68 (dd, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1 H, $H_{6'}$), 7.58 (d, J = 1.6 Hz, 1 H, $H_{2'}$), 7.02–6.81 (m, 3 H, $H_{5',5'',3''}$), 6.72 (m, 2 H, $H_{2'',6''}$), 5.21 (m, 1 H, H_3), 4.17 (br s, 2 H, $H_{1,5}$), 3.95 (s, 3 H, $H_{7'}$), 3.94 (s, 3 H, $H_{8'}$), 2.46–2.09 (m, 6 H, $H_{2,4,6\alpha,7\alpha}$), 1.76 (d, J = 15.2 Hz, 2 H, $H_{6\beta,7\beta}$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.73 (C_8), 157.15 ($C_{4''}$), 153.17 ($C_{4'}$), 148.90 ($C_{3'}$), 142.92 ($C_{1''}$), 123.37 ($C_{6'}$), 116.29 ($C_{1'}$), 116.05 ($C_{3'',5''}$), 116.00 ($C_{2'',6''}$), 112.09 ($C_{2'}$), 110.54 ($C_{5'}$), 68.73 (C_3), 56.17 ($C_{7'}$), 56.08 ($C_{8'}$), 53.63 ($C_{1,5}$), 31.41 ($C_{2,4}$), 28.32 ($C_{6,7}$).

MS: m/z = 386.1770 ($[M + H]^+$).

8-[4-(Trifluoromethyl)phenyl]-8-azabicyclo[3.2.1]octan-3-yl 3,4-Dimethoxybenzoate (5c)

Yield: 57% (0.57 mmol); white solid; mp 179–180 °C; R_f = 0.50 (cyclohexane/EtOAc 7:3).

IR (neat): 2956, 2937, 2915, 2838, 1702, 1601, 1589, 1517, 1504, 1465, 1442, 1416, 1377, 1358, 1345, 1328, 1291, 1270, 1249, 1227, 1211, 1175, 1132, 1107, 1085, 1033, 987, 948, 929, 880, 871, 819, 802, 764, 734, 707, 632 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.69 (dd, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1 H, $H_{6'}$), 7.58 (d, J = 1.6 Hz, 1 H, $H_{2'}$), 7.47 (d, J = 8.6 Hz, 2 H, $H_{3'',5''}$), 6.94 (d, J = 8.4 Hz, 1 H, $H_{5'}$), 6.78 (d, J = 8.6 Hz, 2 H, $H_{2'',6''}$), 5.22 (m, 1 H, H_3), 4.30 (br s, 2 H, $H_{1,5}$), 3.95 (s, 3 H, $H_{7'}$), 3.94 (s, 3 H, $H_{8'}$), 2.44–2.09 (m, 6 H, $H_{2,4,6\alpha,7\alpha}$), 1.82 (d, J = 15.2 Hz, 2 H, $H_{6\beta,7\beta}$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.69 (C_8), 153.24 ($C_{1''}$), 148.94 ($C_{4'}$), 148.57 ($C_{3'}$), 127.07 ($C_{3''}$), 127.02 ($C_{5''}$), 123.38 ($C_{6'}$), 123.25 ($C_{1'}$), 118.69 ($C_{4''}$), 118.26 ($C_{7''}$), 114.05 ($C_{2'',6''}$), 112.11 ($C_{2'}$), 110.56 ($C_{5'}$), 68.59 (C_3), 56.20 ($C_{7'}$), 56.10 ($C_{8'}$), 53.07 ($C_{1,5}$), 31.94 ($C_{2,4}$), 28.30 ($C_{6,7}$).

MS: m/z = 436.1736 ($[M + H]^+$).

8-(4-Chlorophenyl)-8-azabicyclo[3.2.1]octan-3-yl 3,4-Dimethoxybenzoate (5d)

Yield: 57% (0.58 mmol); white solid; mp 170–171 °C; R_f = 0.61 (cyclohexane/EtOAc 7:3).

IR (neat): 2957, 2935, 2916, 2837, 1710, 1703, 1596, 1514, 1494, 1464, 1443, 1416, 1379, 1358, 1345, 1329, 1296, 1270, 1248, 1225, 1216, 1176, 1133, 1098, 1082, 1032, 987, 948, 930, 881, 871, 814, 765, 736, 700, 682, 632 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.68 (dd, J_1 = 8.4 Hz, J_2 = 1.8 Hz, 1 H, $H_{6'}$), 7.58 (d, J = 1.8 Hz, 1 H, $H_{2'}$), 7.19 (d, J = 8.8 Hz, 2 H, $H_{3'',5''}$), 6.93 (d, J = 8.4 Hz, 1 H, $H_{5'}$), 6.70 (d, J = 8.9 Hz, 2 H, $H_{2'',6''}$), 5.20 (m, 1 H, H_3), 4.20 (br s, 2 H, $H_{1,5}$), 3.95 (s, 3 H, $H_{7'}$), 3.94 (s, 3 H, $H_{8'}$), 2.42–2.06 (m, 6 H, $H_{2,4,6\alpha,7\alpha}$), 1.76 (d, J = 15.2 Hz, 2 H, $H_{6\beta,7\beta}$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.71 (C_8), 153.19 ($C_{4'}$), 148.91 ($C_{3'}$), 144.95 ($C_{1''}$), 129.55 ($C_{3'',5''}$), 123.37 ($C_{6'}$), 123.33 ($C_{4''}$), 121.88 ($C_{1'}$), 116.21 ($C_{2'',6''}$), 112.09 ($C_{2'}$), 110.55 ($C_{5'}$), 68.70 (C_3), 56.18 ($C_{7'}$), 56.09 ($C_{8'}$), 53.26 ($C_{1,5}$), 31.46 ($C_{2,4}$), 28.33 ($C_{6,7}$).

MS: m/z = 402.1468 ($[M + H]^+$).

8-(4-Nitrophenyl)-8-azabicyclo[3.2.1]octan-3-yl 3,4-Dimethoxybenzoate (5e)

Yield: 58% (0.58 mmol); yellow solid; mp 202–203 °C; R_f = 0.59 (cyclohexane/EtOAc 7:3).

IR (neat): 2960, 2917, 2850, 2214, 1710, 1705, 1605, 1514, 1494, 1465, 1446, 1417, 1383, 1348, 1306, 1290, 1272, 1249, 1223, 1178, 1168, 1134, 1107, 1086, 1031, 988, 945, 930, 883, 871, 822, 766, 736, 699, 632 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.15 (d, J = 9.2 Hz, 2 H, $H_{3'',5''}$), 7.67 (dd, J_1 = 8.4 Hz, J_2 = 1.8 Hz, 1 H, $H_{6'}$), 7.57 (d, J = 1.8 Hz, 1 H, $H_{2'}$), 6.94 (d, J = 8.4 Hz, 1 H, $H_{5'}$), 6.70 (d, J = 9.2 Hz, 2 H, $H_{2'',6''}$), 5.26 (m, 1 H, H_3), 4.39 (br s, 2 H, $H_{1,5}$), 3.96 (s, 3 H, $H_{7'}$), 3.95 (s, 3 H, $H_{8'}$), 2.47–2.10 (m, 6 H, $H_{2,4,6\alpha,7\alpha}$), 1.92 (d, J = 15.2 Hz, 2 H, $H_{6\beta,7\beta}$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.63 (C_8), 153.38 ($C_{1'}$), 150.67 ($C_{4'}$), 149.01 ($C_{3'}$), 137.51 ($C_{4''}$), 126.86 ($C_{3''}$), 126.77 ($C_{5''}$), 123.40 ($C_{6'}$), 123.04 ($C_{1'}$), 112.82 ($C_{2'',6''}$), 112.14 ($C_{2'}$), 110.60 ($C_{5'}$), 68.17 (C_3), 56.24 ($C_{7'}$), 56.15 ($C_{8'}$), 53.61 ($C_{1,5}$), 33.25 ($C_{2,4}$), 28.20 ($C_{6,7}$).

MS (APCI positive): m/z = 413.1705 ($[M + H]^+$).

8-(4-Cyanophenyl)-8-azabicyclo[3.2.1]octan-3-yl 3,4-Dimethoxybenzoate (5f)

Yield: 76% (0.76 mmol); white solid; mp 206–207 °C; R_f = 0.40 (cyclohexane/EtOAc 7:3).

IR (neat): 3055, 2961, 2927, 2854, 1704, 1605, 1588, 1513, 1464, 1444, 1420, 1383, 1350, 1292, 1266, 1223, 1179, 1168, 1134, 1104, 1080, 1032, 986, 943, 870, 842, 822, 796, 766, 733, 702, 664, 630 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.67 (dd, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1 H, $H_{6'}$), 7.57 (d, J = 1.6 Hz, 1 H, $H_{2'}$), 7.49 (d, J = 8.8 Hz, 2 H, $H_{3'',5''}$), 6.93 (d, J = 8.4 Hz, 1 H, $H_{5'}$), 6.74 (d, J = 8.8 Hz, 2 H, $H_{2'',6''}$), 5.23 (m, 1 H, H_3), 4.31 (br s, 2 H, $H_{1,5}$), 3.95 (s, 3 H, $H_{7'}$), 3.94 (s, 3 H, $H_{8'}$), 2.42–2.09 (m, 6 H, $H_{2,4,6\alpha,7\alpha}$), 1.86 (d, J = 15.3 Hz, 2 H, $H_{6\beta,7\beta}$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.65 (C_8), 153.31 ($C_{1'}$), 148.93 ($C_{4',3'}$), 134.13 ($C_{3'',5''}$), 123.38 ($C_{6'}$), 123.11 ($C_{1'}$), 120.49 ($C_{7''}$), 114.21 ($C_{2'}$), 112.11 ($C_{5'}$), 110.58 ($C_{2'',6''}$), 98.47 ($C_{4''}$), 68.33 (C_3), 56.22 ($C_{7'}$), 56.12 ($C_{8'}$), 53.11 ($C_{1,5}$), 32.52 ($C_{2,4}$), 28.23 ($C_{6,7}$).

MS: m/z = 393.1815 ($[M + H]^+$).

8-(2-Cyanophenyl)-8-azabicyclo[3.2.1]octan-3-yl 3,4-Dimethoxybenzoate (5g)

Yield: 30% (0.30 mmol); white solid; mp 138–139 °C; R_f = 0.35 (cyclohexane/EtOAc 7:3).

IR (neat): 2959, 2214, 1703, 1598, 1514, 1486, 1465, 1446, 1417, 1380, 1358, 1290, 1269, 1247, 1222, 1177, 1133, 1107, 1072, 1029, 935, 882, 814, 765, 733, 708, 631 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.67 (dd, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1 H, $H_{6'}$), 7.57 (d, J = 1.6 Hz, 1 H, $H_{2'}$), 7.52 (d, J = 7.7 Hz, 1 H, $H_{3''}$), 7.39 (t, J = 7.2 Hz, 1 H, $H_{5''}$), 6.98–6.77 (m, 3 H, $H_{5',4'',6''}$), 5.35 (m, 1 H, H_3), 4.43 (br s, 2 H, $H_{1,5}$), 3.95 (s, 3 H, $H_{7'}$), 3.94 (s, 3 H, $H_{8'}$), 2.51–2.38 (m, 2 H, $H_{2\alpha,4\alpha}$), 2.28–2.24 (m, 2 H, $H_{2\beta,4\beta}$), 2.12–2.06 (m, 2 H, $H_{6\alpha,7\alpha}$), 2.00 (d, J = 16.4 Hz, 2 H, $H_{6\beta,7\beta}$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.68 (C_8), 153.18 ($C_{4'}$), 152.14 ($C_{1''}$), 148.90 ($C_{3'}$), 135.29 ($C_{5''}$), 133.84 ($C_{3''}$), 123.37 ($C_{6'}$), 123.29 ($C_{1'}$), 119.79 ($C_{7''}$), 119.37 ($C_{4''}$), 116.61 ($C_{6''}$), 112.13 ($C_{2'}$), 110.54 ($C_{5'}$), 101.59 ($C_{2''}$), 68.23 (C_3), 57.28 ($C_{1,5}$), 56.18 ($C_{7'}$), 56.10 ($C_{8'}$), 36.15 ($C_{2,4}$), 27.73 ($C_{6,7}$).

MS: m/z = 393.1811 ($[M + H]^+$).

8-(3-Cyanophenyl)-8-azabicyclo[3.2.1]octan-3-yl 3,4-Dimethoxybenzoate (5h)

Yield: 44% (0.44 mmol); white solid; mp 149–150 °C; R_f = 0.35 (cyclohexane/EtOAc 7:3).

IR (neat): 2958, 2838, 2359, 2227, 1705, 1598, 1571, 1515, 1492, 1466, 1438, 1417, 1379, 1338, 1305, 1290, 1272, 1218, 1177, 1133, 1109, 1083, 1033, 982, 942, 873, 765, 733, 682, 632 cm^{-1}.

H NMR (300 MHz, $CDCl_3$): δ = 7.68 (dd, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1 H, $H_{6'}$), 7.57 (d, J = 1.6 Hz, 1 H, $H_{2'}$), 7.30 (t, J = 7.9 Hz, 1 H, $H_{5''}$), 7.06–6.82 (m, 4 H, $H_{4'',6'',2'',5'}$), 5.22 (m, 1 H, H_3), 4.24 (br s, 2 H, $H_{1,5}$), 3.95 (s, 3 H, $H_{7'}$), 3.94 (s, 3 H, $H_{8'}$), 2.43–2.11 (m, 6 H, $H_{2,4,6\alpha,7\alpha}$), 1.82 (d, J = 15.3 Hz, 2 H, $H_{6\beta,7\beta}$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.66 (C_8), 153.25 ($C_{4'}$), 148.93 ($C_{1''}$), 146.47 ($C_{3'}$), 130.48 ($C_{5''}$), 123.38 ($C_{6'}$), 123.17 ($C_{1'}$), 120.37 ($C_{4''}$), 119.63 ($C_{7''}$), 119.02 ($C_{6''}$), 117.64 ($C_{2''}$), 113.55 ($C_{3''}$), 112.09 ($C_{2'}$), 110.56 ($C_{5'}$), 68.40 (C_3), 56.20 ($C_{7'}$), 56.10 ($C_{8'}$), 53.16 ($C_{1,5}$), 31.74 ($C_{2,4}$), 28.27 ($C_{6,7}$).

MS: m/z = 393.1811 ($[M + H]^+$).

8-(4-Methoxyphenyl)-8-azabicyclo[3.2.1]octan-3-yl 3,4-Dimethoxybenzoate (5i)

Yield: 88% (0.88 mmol); white solid; mp 136–137 °C; R_f = 0.54 (cyclohexane/EtOAc 7:3).

IR (neat): 3051, 2960, 2933, 2854, 1710, 1707, 1603, 1510, 1465, 1445, 1418, 1381, 1360, 1291, 1266, 1242, 1224, 1215, 1179, 1132, 1108, 1086, 1034, 1004, 930, 879, 853, 821, 791, 767, 733, 702, 632 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.69 (dd, J_1 = 8.4 Hz, J_2 = 1.5 Hz, 1 H, $H_{6'}$), 7.59 (d, J = 1.5 Hz, 1 H, $H_{2'}$), 6.93 (d, J = 8.4 Hz, 1 H, $H_{5'}$), 6.86 (d, J = 8.9 Hz, 2 H, $H_{2'',6''}$), 6.76 (d, J = 9.0 Hz, 2 H, $H_{3'',5''}$), 5.22 (m, 1 H, H_3), 4.18 (br s, 2 H, $H_{1,5}$), 3.95 (s, 3 H, $H_{7'}$), 3.94 (s, 3 H, $H_{8'}$), 3.77 (s, 3 H, $H_{7''}$), 2.48–2.09 (m, 6 H, $H_{2,4,6\alpha,7\alpha}$), 1.75 (d, J = 15.1 Hz, 2 H, $H_{6\beta,7\beta}$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.71 (C_8), 153.09 ($C_{4'}$), 151.89 ($C_{4''}$), 148.85 ($C_{3'}$), 140.74 ($C_{1''}$), 123.41 ($C_{6'}$), 123.33 ($C_{1'}$), 116.35 ($C_{2'',6''}$), 115.24 ($C_{3'',5''}$), 112.06 ($C_{2'}$), 110.51 ($C_{5'}$), 68.86 (C_3), 56.13 ($C_{7'}$), 56.03 ($C_{8'}$), 55.77 ($C_{7''}$), 53.71 ($C_{1,5}$), 31.50 ($C_{2,4}$), 28.25 ($C_{6,7}$).

MS: m/z = 398.1968 ($[M + H]^+$).

8-(2-Methoxyphenyl)-8-azabicyclo[3.2.1]octan-3-yl 3,4-Dimethoxybenzoate (5j)

Yield: 96% (0.96 mmol); white solid; mp 129–130 °C; R_f = 0.42 (cyclohexane/EtOAc 7:3).

IR (neat): 2956, 2836, 2255, 1704, 1601, 1516, 1498, 1466, 1453, 1417, 1378, 1356, 1291, 1271, 1221, 1177, 1130, 1108, 1069, 1030, 933, 910, 881, 813, 766, 728, 648, 631 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.69 (dd, J_1 = 8.4 Hz, J_2 = 1.8 Hz, 1 H, $H_{6'}$), 7.59 (d, J = 1.8 Hz, 1 H, $H_{2'}$), 6.92 (d, J = 8.4 Hz, 1 H, $H_{5'}$), 6.86–6.83 (m, 4 H, $H_{3'',4'',5'',6''}$), 5.34 (m, 1 H, H_3), 4.21 (br s, 2 H, $H_{1,5}$), 3.94 (s, 6 H, $H_{7',8'}$), 3.86 (s, 3 H, $H_{7''}$), 2.52–2.35 (m, 2 H, $H_{2\alpha,4\alpha}$), 2.28–2.02 (m, 4 H, $H_{2\beta,4\beta,6\alpha,7\alpha}$), 1.91 (d, J = 14.8 Hz, 2 H, $H_{6\beta,7\beta}$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.75 (C_8), 153.01 ($C_{4'}$), 151.22 ($C_{2''}$), 148.80 ($C_{3'}$), 138.72 ($C_{1''}$), 123.55 ($C_{1'}$), 123.35 ($C_{6'}$), 121.14 ($C_{4''}$), 120.92 ($C_{3''}$), 116.85 ($C_{6''}$), 112.09 ($C_{2'}$), 111.94 ($C_{5''}$), 110.49 ($C_{5'}$), 68.77 (C_3), 56.44 ($C_{7'}$), 56.12 ($C_{8'}$), 56.04 ($C_{7''}$), 55.61 ($C_{1,5}$), 36.36 ($C_{2,4}$), 27.65 ($C_{6,7}$).

MS: m/z = 398.1968 ($[M + H]^+$).

8-(3-Methoxyphenyl)-8-azabicyclo[3.2.1]octan-3-yl 3,4-Dimethoxybenzoate (5k)

Yield: 57% (0.57 mmol); white solid; mp 123–124 °C; R_f = 0.44 (cyclohexane/EtOAc 7:3).

IR (neat): 2958, 2836, 2253, 1710, 1610, 1600, 1573, 1515, 1494, 1465, 1417, 1359, 1290, 1271, 1222, 1178, 1164, 1133, 1108, 1081, 1032, 983, 941, 909, 872, 765, 727, 688, 648 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.69 (dd, J_1 = 8.4 Hz, J_2 = 1.8 Hz, 1 H, $H_{6'}$), 7.58 (d, J = 1.8 Hz, 1 H, $H_{2'}$), 7.17 (t, J = 8.1 Hz, 1 H, $H_{5''}$), 6.93 (d, J = 8.4 Hz, 1 H, $H_{5'}$), 6.42 (dd, J_1 = 8.1 Hz, J_2 = 1.7 Hz, 1 H, $H_{6''}$), 6.38–6.19 (m, 2 H, $H_{2'',4''}$), 5.22 (m, 1 H, H_3), 4.23 (br s, 2 H, $H_{1,5}$), 3.94 (s, 3 H, $H_{7'}$), 3.93 (s, 3 H, $H_{8'}$), 3.80 (s, 3 H, $H_{7''}$), 2.44–2.05 (m, 6 H, $H_{2,4,6\alpha,7\alpha}$), 1.76 (d, J = 15.2 Hz, 2 H, $H_{6\beta,7\beta}$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.78 (C_8), 161.21 ($C_{3''}$), 153.16 ($C_{4'}$), 148.91 ($C_{3'}$), 147.65 ($C_{1''}$), 130.49 ($C_{5''}$), 123.39 ($C_{6'}$), 112.12 (C_2), 111.19 ($C_{1'}$), 110.56 ($C_{5'}$), 108.15 ($C_{4''}$), 101.99 ($C_{6''}$), 101.72 ($C_{2''}$), 68.98 (C_3), 56.21 ($C_{7'}$), 56.11 ($C_{8'}$), 55.32 ($C_{7''}$), 53.16 ($C_{1,5}$), 31.68 ($C_{2,4}$), 28.36 ($C_{6,7}$).

MS: m/z = 398.1968 ($[M + H]^+$).

8-Phenyl-8-azabicyclo[3.2.1]octan-3-yl 3,4-Dimethoxybenzoate (5l)

Yield: 68% (0.68 mmol); white solid; mp 183–184 °C; R_f = 0.48 (cyclohexane/EtOAc 7:3).

IR (neat): 2360, 2341, 2330, 1704, 1597, 1511, 1460, 1418, 1387, 1321, 1303, 1271, 1226, 1193, 1174, 1140, 1114, 1086, 1029, 872, 831, 766, 752, 724 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.70 (dd, J_1 = 8.4 Hz, J_2 = 1.8 Hz, 1 H, $H_{6'}$), 7.59 (d, J = 1.8 Hz, 1 H, $H_{2'}$), 7.29 (s, 1 H, $H_{3''}$), 7.23 (s, 1 H, $H_{5''}$), 6.94 (d, J = 8.4 Hz, 1 H, $H_{5'}$), 6.80 (d, J = 8.5 Hz, 2 H, $H_{2'',6''}$), 6.72 (t, 1 H, J = 7.3 Hz, $H_{4''}$), 5.22 (m, 1 H, H_3), 4.27 (br s, 2 H, $H_{1,5}$), 3.96 (s, 3 H, $H_{7'}$), 3.95 (s, 3 H, $H_{8'}$), 2.48–2.04 (m, 6 H, $H_{2,4,6\alpha,7\alpha}$), 1.77 (d, J = 15.1 Hz, 2 H, $H_{6\beta,7\beta}$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.74 (C_8), 153.13 ($C_{4'}$), 148.88 ($C_{3'}$), 146.30 ($C_{1''}$), 129.72 ($C_{3'',5''}$), 123.42 ($C_{6'}$), 123.36 ($C_{1'}$), 117.25 ($C_{4''}$), 115.07 ($C_{2'',6''}$), 112.08 ($C_{2'}$), 110.53 ($C_{5'}$), 68.96 (C_3), 56.17($C_{7'}$), 56.07 ($C_{8'}$), 52.94 ($C_{1,5}$), 31.53 ($C_{2,4}$), 28.33 ($C_{6,7}$).

MS: m/z = 368.1870 ($[M + H]^+$).

8-(1-Methyl-1*H*-indol-5-yl)-8-azabicyclo[3.2.1]octan-3-yl 3,4-Dimethoxybenzoate (5m)

Yield: 70% (0.70 mmol); white solid; mp 188–189 °C; R_f = 0.31 (cyclohexane/EtOAc 7:3).

IR (neat): 2957, 1702, 1624, 1601, 1570, 1514, 1491, 1464, 1448, 1418, 1379, 1353, 1291, 1270, 1247, 1218, 1177, 1163, 1132, 1107, 1083, 1033, 941, 877, 822, 765, 728, 648, 631 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.76 (dd, J_1 = 8.4 Hz, J_2 = 1.8 Hz, 1 H, $H_{6'}$), 7.65 (d, J = 1.6 Hz, 1 H, $H_{2'}$), 7.30 (d, J = 4.1 Hz, 1 H, $H_{5''}$), 7.06 (d, J = 1.7 Hz, 1 H, $H_{4''}$), 7.02 (d, J = 3.0 Hz, 1 H, $H_{3''}$), 6.98 (d, J = 8.4 Hz, 1 H, $H_{6''}$), 6.93 (dd, J_1 = 8.9 Hz, J_2 = 1.9 Hz, 1 H, $H_{7''}$), 6.39 (d, J = 2.9 Hz, 1 H, $H_{2''}$), 5.25 (m, 1 H, H_3), 4.33 (br s, 2 H, $H_{1,5}$), 4.00 (s, 6 H, $H_{7',8'}$), 3.79 (s, 3 H, $H_{9''}$), 2.54–2.49 (m, 2 H, $H_{2\alpha,4\alpha}$), 2.39–2.21 (m, 4 H, $H_{2\beta,4\beta,6\alpha,7\alpha}$), 1.82 (d, 2 H, J = 15.1 Hz, $H_{6\beta,7\beta}$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.80 (C_8), 153.06 ($C_{4'}$), 148.84 ($C_{3'}$), 140.52 ($C_{1''}$), 131.15 ($C_{4''a}$), 129.69 ($C_{4''b}$), 129.16 ($C_{6''}$), 123.56 ($C_{1'}$), 123.38 ($C_{6'}$), 112.61 ($C_{2'}$), 112.09 ($C_{5'}$), 110.53 ($C_{3''}$), 110.20 ($C_{2''}$), 105.92 ($C_{8''}$), 99.96 ($C_{7''}$), 69.17 (C_3), 56.17 ($C_{7'}$), 56.07 ($C_{8'}$), 54.17 ($C_{1,5}$), 32.97 ($C_{9''}$), 31.82 ($C_{2,4}$), 28.28 ($C_{6,7}$).

MS: m/z = 421.2122 ($[M + H]^+$).

8-(Pyridin-3-yl)-8-azabicyclo[3.2.1]octan-3-yl 3,4-Dimethoxybenzoate (5n)

Yield: 95% (0.95 mmol); white solid; mp 140–141 °C; R_f = 0.45 (CH_2Cl_2/EtOAc 4:6).

IR (neat): 2957, 2838, 2360, 1703, 1601, 1580, 1515, 1487, 1465, 1418, 1378, 1349, 1302, 1290, 1272, 1248, 1218, 1177, 1133, 1108, 1087, 1032, 986, 948, 930, 823, 798, 765, 730, 707, 632, 614 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.19 (br s, 1 H, $H_{2''}$), 7.98 (br s, 1 H, $H_{4''}$), 7.67 (dd, J_1 = 8.4 Hz, J_2 = 1.4 Hz, 1 H, $H_{6'}$), 7.56 (d, J = 1.4 Hz, 1 H, $H_{2'}$), 7.12–7.16 (m, 1 H, $H_{5''}$), 7.04 (d, J = 8.4 Hz, 1 H, $H_{6''}$), 6.92 (d, J = 8.4 Hz, 1 H, $H_{5'}$), 5.20 (m, 1 H, H_3), 4.26 (br s, 2 H, $H_{1,5}$), 3.93 (s, 3 H, $H_{7'}$), 3.92 (s, 3 H, $H_{8'}$), 2.42–2.07 (m, 6 H, $H_{2,4,6\alpha,7\alpha}$), 1.80 (d, J = 15.2 Hz, 2 H, $H_{6\beta,7\beta}$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.62 (C_8), 153.18 ($C_{4'}$), 148.87 ($C_{3'}$), 142.29 ($C_{1''}$), 138.48 ($C_{4''}$), 137.57 ($C_{2''}$), 124.06 ($C_{1'}$), 123.33 ($C_{6'}$), 123.19 ($C_{5''}$), 121.49 ($C_{6''}$), 112.05 ($C_{2'}$), 110.52 ($C_{5'}$), 68.44 (C_3), 56.15 ($C_{7'}$), 56.05 ($C_{8'}$), 52.83 ($C_{1,5}$), 31.58 ($C_{2,4}$), 28.18 ($C_{6,7}$).

MS: m/z = 369.1811 ($[M + H]^+$).

8-(6-{(1*R*,3*R*,5*S*)-3-[(3,4-dimethoxybenzoyl)oxy]-8-azabicyclo-[3.2.1]octan-8-yl}-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-8-azabicyclo[3.2.1]octan-3-yl 3,4-Dimethoxybenzoate (5o)

Yield: 43% (0.43 mmol); white solid; mp 118–119 °C; R_f = 0.51 (CH_2Cl_2/EtOAc 9:1).

IR (neat): 2958, 2917, 2851, 1703, 1633, 1604, 1589, 1514, 1465, 1439, 1417, 1380, 1346, 1290, 1271, 1249, 1222, 1178, 1168, 1133, 1107, 1085, 1031, 987, 944, 931, 880, 872, 821, 798, 765, 734, 701, 632 cm^{-1}.

^1H NMR (300 MHz, acetone-d_6): δ = 7.69 (dd, J_1 = 8.4 Hz, J_2 = 1.9 Hz, 2 H, $H_{6',6''''}$), 7.58 (br s, 2 H, $H_{2',2''''}$), 7.31 (d, J = 8.8 Hz, 1 H, $H_{8''}$), 7.16–6.92 (m, 5 H, $H_{5',4'',5'',7'',5''''}$), 5.26 (m, 1 H, H_3), 5.18 (m, 1 H, $H_{3''''}$), 4.83 (br s, 2 H, $H_{1,5}$), 4.35 (br s, 2 H, $H_{1''',5''''}$), 3.91 (s, 6 H, $H_{7',8'}$), 3.89 (s, 6 H, $H_{7'''',8''''}$), 3.69 (s, 3 H, $H_{9''}$), 2.80 (br s, 2 H, $H_{2\alpha,4\alpha}$), 2.44–2.22 (m, 6 H, $H_{2\beta,4\beta,6,7}$), 1.87–1.76 (m, 8 H, $H_{2'',4'',6'',7''}$).

^{13}C NMR (75 MHz, acetone-d_6): δ = 165.87 ($C_{8,8''''}$), 154.46 ($C_{2''}$), 150.05 ($C_{4',4''''}$), 138.16 ($C_{3',3''''}$), 136.66 ($C_{6''}$), 134.57 ($C_{1''}$), 130.92 ($C_{4''a}$), 130.35 ($C_{8''a}$), 124.13 ($C_{1',1''''}$), 124.00 ($C_{6',6''''}$), 115.60 ($C_{2',2''''}$), 114.72 ($C_{7''}$), 112.98 ($C_{5',5''''}$), 111.90 ($C_{4'',5''}$), 69.27 ($C_{3,3''''}$), 56.24 ($C_{7',8'}$), 56.12 ($C_{7'''',8''''}$), 55.00 ($C_{1,5,1''',5''''}$), 34.68 ($C_{2,4,2''',4'''}$), 32.26 ($C_{9''}$), 28.27 ($C_{6,7,6''',7'''}$).

MS: m/z = 738.3414 ($[M + H]^+$).

Protocol for Cell Culture and Proliferation Assay

Cancer cell lines were obtained from the American type Culture Collection (Rockville, MD, USA) and were cultured according to the supplier's instructions. Briefly, HCT116 cells were grown in RPMI 1640 containing 10% FCS and 1% glutamine. All cell lines were maintained at 37 °C in a humidified atmosphere containing 5% CO_2. Cell viability was assessed using Promega CellTiter-Blue TM reagent according to the manufacturer's instructions. Cells were seeded in 96-well plates (5 × 103 cells/well) containing 50 µL growth medium. After 24 h of culture, the cells were supplemented with 50 µL of the tested compound dissolved in DMSO (less than 0.1% in each preparation). After 72 h of incubation, 20 µL of resazurin was added for 2 h before recording fluorescence (λ_{ex} = 560 nm, λ_{em} = 590 nm) using a Victor microtiter plate fluorimeter (PerkinElmer, USA). The IC_{50} corresponds to the concentration of the tested compound that caused a decrease of 50% in fluorescence of drug treated cells compared with untreated cells. Experiments were performed in triplicate.

Funding Information

Authors acknowledge support of this project by CNRS, University Paris Sud, and by La Ligue Nationale Contre le Cancer throughout an Equipe Labellisée 2014 grant. The authors are grateful to the Ministry of Higher Education and Scientific Research of Tunisia for financial support. Our laboratory (BioCIS UMR 8076) is a member of the laboratory of excellence LERMIT supported by a grant from ANR (ANR-10-LABX-33).

Acknowledgment

The authors are grateful to Prof. Fethia Harzallah-Skhiri, High Institute of Biotechnology of Monastir, Tunisia, for botanical identification of the plant material.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690238.

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