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Manel Hassine, Hichem Ben Jannet, Noureddine Ghermani, Mouad Alami, Samir Messaoudi. Synthesis of N-(Hetero)arylconvolvine Derivatives through a Palladium-Catalyzed Buchwald–Hartwig Cross-Coupling. *Synthesis: Journal of Synthetic Organic Chemistry*, 2019, 10.1055/s-0039-1690238. hal-02396680

HAL Id: hal-02396680

<https://hal.science/hal-02396680>

Submitted on 6 Dec 2019

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Synthesis of N-(hetero)aryl-Convulvine Derivatives Through a Palladium-Catalyzed Buchwald-Hartwig Cross-Coupling

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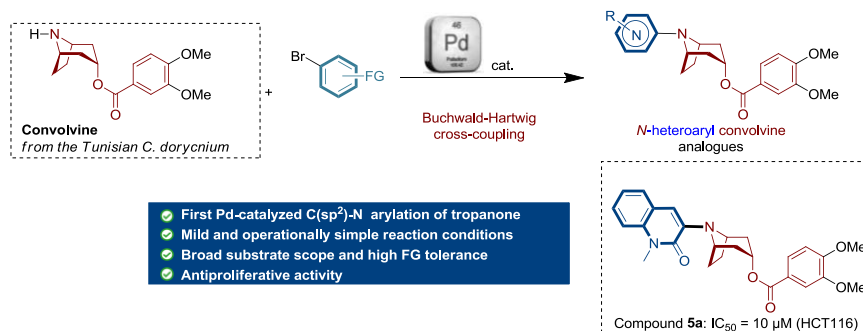
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Received:
 Accepted:
 Published online:
 DOI:

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

Key words convulvine, Buchwald-Hartwig reaction, Palladium catalysis, tropane

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, antiemetics and bronchodilators.³

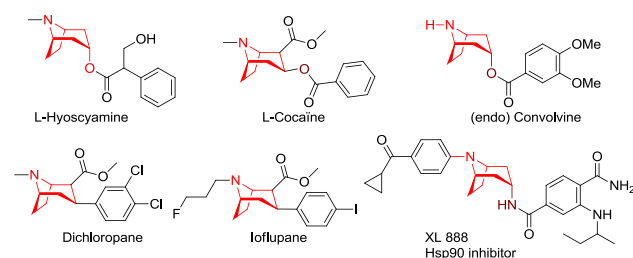


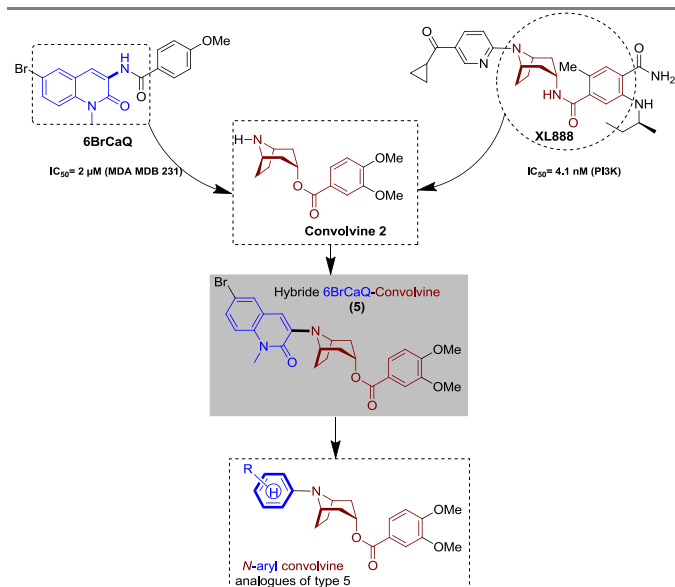
Figure 1. Tropane natural products and some semi-synthetic analogues.

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 affording an interesting tropane natural compound Convulvine (**Figure 1**) that was isolated for the first time from this plant.

One of the interesting tropane-compound currently under clinical investigation is the tropane-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 down regulation of several hsp90 client proteins (HER2, Raf-1 and cdk-4).

Because of the exciting activities of XL888 and 6BrCaQ, we were interested whether the combination of the tropane core of XL888 and the quinoline nucleus of 6BrCaQ in a one molecule may lead to more efficacious antiproliferative compounds. Herein, we planned to prepare a new series of N-(hetero)aryl convulvine analogues (**Figure 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 convulvine analogues **1-10** are described. Preliminary *in vitro* efficacy of these compounds in terms of antiproliferative activity is reported.

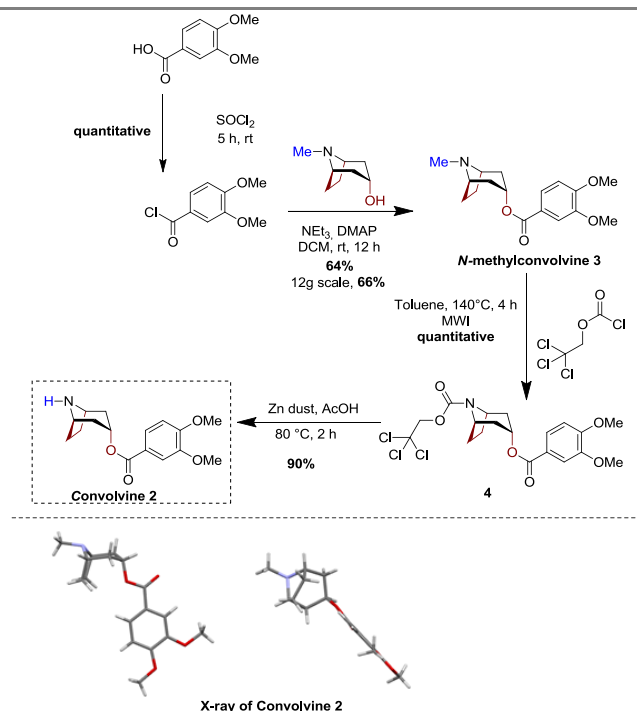


Scheme 1. General strategy to N-(hetero)aryl convolvine analogues

Convolvine (**Figure 1**) was isolated as a white solid from the *n*-BuOH extract from the roots of *C. from the Tunisian C. dorycnium*. Its structure was evidenced through the ¹H and ¹³C spectroscopy examination and by comparison with literature data.⁷ We note that this same compound has been also isolated from *Convolvulus subhirsutus*⁸ and *Convolvulus 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 pre-formed 2,3-dimethoxybenzoyl chloride. Our first attempt was performed according to the protocol of Maksay *et al.*¹⁰ using NEt₃ as a base in refluxing toluene. Under these conditions, the desired *N*-methylconvolvine **3** was isolated in yield never exceed 20%. This result is in concordance with the observation of Maksay *et al.*¹⁰ who's 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 dichloromethane was stirred at room temperature overnight in the presence of a trimethylamine 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 tropane 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**).



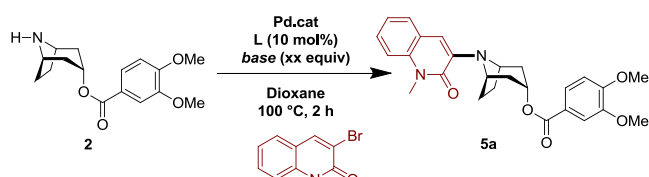
Scheme 2. Synthesis of convolvine **2**.

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 derivatives¹² 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 any affecting the ester group. This sequence allows us obtaining the convolvine **2** in 56% overall yield even when achieving the synthesis in 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-bromoquinoline **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 The reaction of **1a** (1 equiv) with **2** (2 equiv) was first investigated under our previously reported procedure [Pd(OAc)₂ (5mol%), XantPhos (5 mol%), Cs₂CO₃, 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 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 result 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).

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 ₂ CO ₃	XantPho	0
2	Pd(OAc) ₂	Cs ₂ CO ₃	XPhos	0
3	Pd(OAc) ₂	<i>t</i> BuONa	XPhos	12
4	PdG2XPhos	<i>t</i> BuONa	-	10
5	Pd(OAc) ₂	<i>t</i> BuONa	XPhos	66
6	Pd(OAc) ₂	<i>t</i> BuONa	XPhos	95

^a3-bromoquinolinone **1a** (1 equiv), convolvine **2** (2 equiv), [Pd(OAc)₂] (5 mol %), Ligand (5 mol%), base (1.5 equiv), 2 h, 100, [0.5M]. ^bYield of isolated **5a**.^c

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, –CF₃, –Cl, –NO₂, –NC) or electron-donating (–OMe) substituents to give aryl *N*-convolvine **5b–f**, **5j**, **6l** and **5m** in good yields. In addition, the sterically demanding *ortho* substitution pattern engaged in the coupling reaction of **2**, furnishing compounds **5g** and **5j** having an *ortho* substituent group. Interestingly, heteroarene such as 3-bromoquinolinone, 5-bromoindole and 3-bromopyridin were good substrates in this reaction (compounds **5a**, **5n–o**). Of note, in the case of coupling with di-bromoquinolinone, only dicoupling product **6o** 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 h exposure (Table 2), and GI₅₀ values were determined at the concentration required to produce 50% inhibition. Taxotere® was used as a positive control (IC₅₀ = 1 nM).

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 survival 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 GI₅₀ for compound **5a** (GI₅₀ = 10 μM) was measured and was found to be approximately the same that the reference 6BrCaQ (GI₅₀ = 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 compound that inhibit cell growth more effectively than the **5a** (survival = 57%, GI₅₀ = 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. One can be noted that convolvine **2** with free-NH is less cytotoxic since 60% of cells survive when incubated with convolvine **2**.

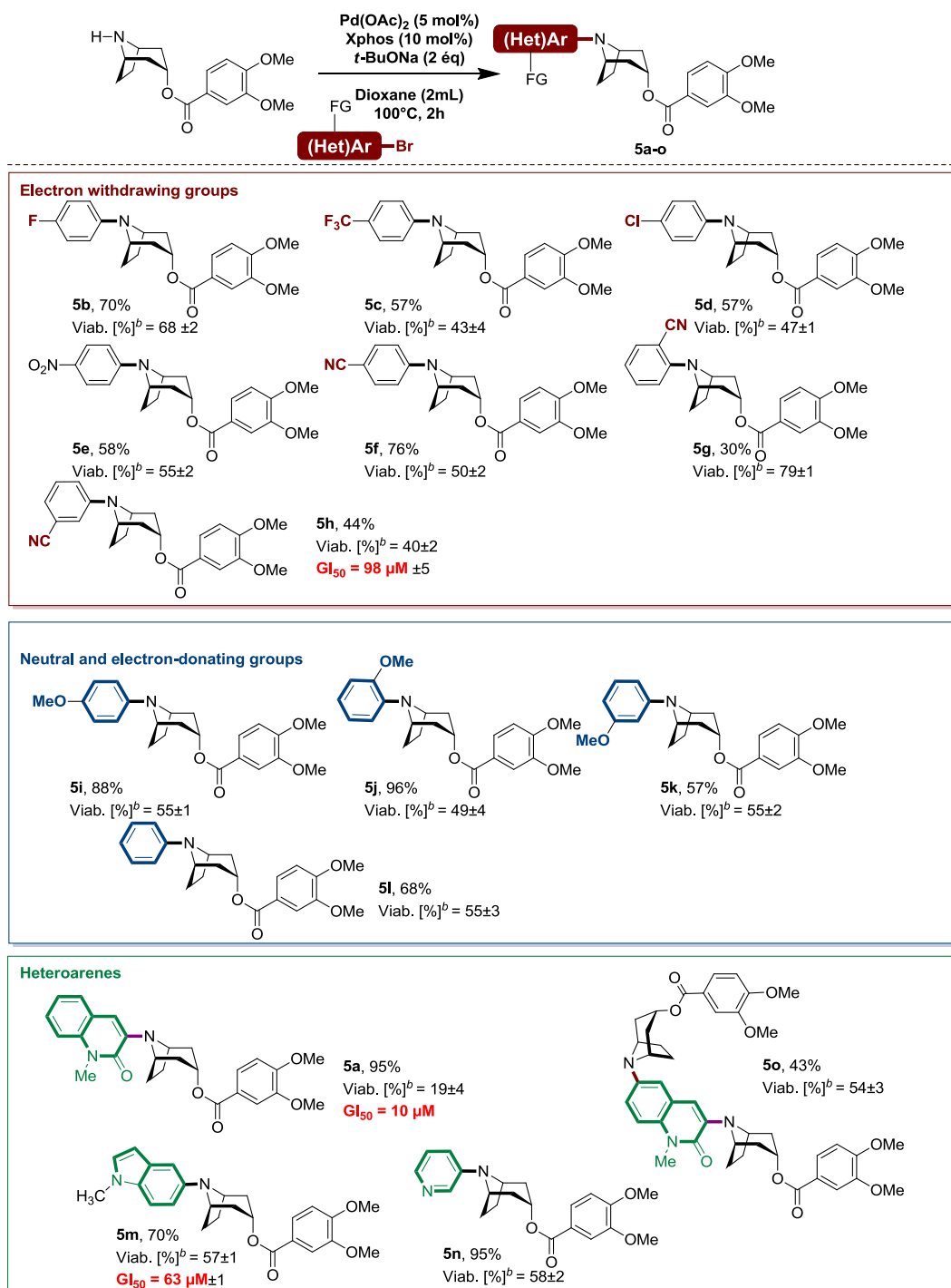
In conclusion, we developed an efficient and practical protocol for the *N*-arylation of the tropane nucleus of convolvine without affecting the benzoic ester part. This transformation exhibited broad substrate scope with respect to the aryl bromide partners. Through this methodology, we designed and synthesized a series of *N*-(hetero)aryl-convolvines, and we 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 pharmacomodulations of this compound may increase its biological activity.

Experimental section

General experimental methods:

The compounds were all identified by usual physical methods, e.g., ¹H NMR, ¹³C NMR, IR, MS (ESI). ¹H and ¹³C NMR spectra were measured in CDCl₃, DMSO-*d*₆ with a Bruker Avance-300. ¹H chemical shifts are reported in ppm from an internal standard TMS or of residual solvent peak. ¹³C chemical shifts are reported in ppm from the residual solvent peak. IR spectra were measured on a Bruker Vector 22

Table 2. Scope of the coupling reaction of convolvine **2** with various (hetero)aryl bromides and cytotoxic activity against HCT-116 cells.



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

spectrophotometer. 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 methanol 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 Bioresources: 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 Methanol-Water mixture (7:3) for three days at room temperature. Then the aqueous solution obtained after evaporation of solvent under vacuum, was partitioned with *n*-BuOH to yield 100g (6.7%) of the correspond extract. The *n*-BuOH extract was subjected to RP-18 flash column chromatography with gradient elution (H₂O; H₂O/MeOH, 90:10 to 30:70), yielding twelve fractions (F₁–F₁₂) of which the fraction 9 appears a pure convolvine(300 mg) according to TLC analysis.

General information:

All reactions were conducted under an argon atmosphere. Solvents: cyclohexane, pentane, ethyl acetate (EtOAc), methylene chloride (CH₂Cl₂) and methanol (MeOH) for extraction and chromatography were of technical grade. The compounds were all identified by usual physical methods, i.e., 1D and 2D NMR (COSY, HSQC, HMBC and NOESY), IR, ES-HRMS. ¹H and ¹³C NMR spectra were measured in CDCl₃ or Acetone-*d*₆ on a 300 and 400 MHz spectrometer. ¹H chemical shifts are reported in parts per million from an internal standard TMS or of residual chloroform (7.27 ppm). The following abbreviations are used: m (multiplet), s (singlet), br s (broad singlet), d (doublet), t (triplet) dd (doublet of doublet). ¹³C chemical shifts are reported in parts per million from the central peak of deuteriochloroform (77.14). IR spectra were acquired on a FTIR 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). Melting points (mp) were determined on a capillary melting point apparatus and were uncorrected.

Synthetic details for compounds 2-4:

Compound 3: *8-methyl-8-azabicyclo [3.2.1] octan-3-yl 3,4-dimethoxybenzoate (3)* To a solution of commercial *endo*-tropine (1g, 7.08 mmol, 1 eq) in dry DCM were added 2,3-dimethoxybenzoyl chloride (1.562 g, 7.78 mmol, 1.1 eq), triethylamine (2.961 mL, 21.2 mmol, 3 eq) and 4-dimethylaminopyridine (0.951 g, 7.78 mmol, 1.1 eq) under argon atmosphere. The reaction mixture was stirred at room temperature overnight before being cooled in 0°C and quenched with a saturated NH₄Cl aqueous solution. The aqueous layer extracted with DCM (3 times). The combined organic layers were dried (MgSO₄), 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%; white solid; TLC: R_f = 0.58 (85:15 CH₂Cl₂ / MeOH), m.p.: 223–224°C. IR (neat): 2939, 2361, 1703, 1600, 1514, 1467, 1449, 1417, 1345, 1272, 1220, 1175, 1133, 1025, 877, 764, 632 cm⁻¹. ¹H NMR (300 MHz, CDCl₃) δ 7.56 (dd, 1H, J_1 = 8.4, J_2 = 1.9 Hz, H₆), 7.51 (d, 1H, J = 1.9 Hz, H₂), 6.90 (d, 1H, J = 8.4 Hz, H₅), 5.37 (m, 1H, H₃), 3.94 (s, 3H, H₇), 3.92 (s, 3H, H₈), 3.78 (br s, 2H, H_{1,5}), 2.77 (s, 3H, H₉), 2.55–2.25 (m, 6H, H_{2,4,6α,7α}), 2.20–2.05 (m, 2H, H_{6β,7β}). ¹³C NMR (75 MHz, CDCl₃) δ 165.19 (C₈), 153.53 (C₄), 149.06 (C₃), 123.14 (C₆), 122.38 (C₁), 112.10 (C₂), 110.53 (C₅), 65.19 (C₃), 61.91 (C_{1,5}), 56.22 (C₇), 56.15 (C₈), 40.21 (C₉), 34.49 (C_{2,4}), 24.95 (C_{6,7}). MS (m/z): 306.1705 ([M+H]⁺).

Compound 4: *2,2,2-trichloroethyl 3-((3,4-dimethoxybenzoyl)oxy)-8-azabicyclo[3.2.1]octane-8-carboxylate (4)* The Schlenk tube containing the *N*-Meconvolvine (0.1 g, 0.327 mmol, 1 eq) was capped with a rubber septum, evacuated and backfilled with argon. This evacuation/backfill sequence was repeated one additional time. Dry toluene (2 mL) was added with 2,2,2-trichloroéthylechloroformate (0.135 mL, 0.982 mmol, 3 eq). The septum was replaced with a Teflon screwcap. The Schlenk tube was sealed, and the mixture was stirred at 140°C for 4 hours under microwave irradiations. The resulting suspension was cooled to room temperature and concentrated. The desired product is obtained as a white solid with a quantitative yield (0.32 mmol).

White solid; TLC: R_f = 0.62 (6:4 cyclohexane/EtOAc), m.p.: 135–136°C, 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, CDCl₃) δ 7.61 (dd, 1H, J_1 = 8.4, J_2 = 1.8 Hz, H₆), 7.52 (d, 1H, J = 1.8 Hz, H₂), 6.89 (d, 1H, J = 8.4 Hz, H₅), 5.33 (m, 1H, H₃), 4.84 (d, 1H, J = 12.0 Hz, H_{10a}), 4.66 (d, 1H, J = 12.0 Hz, H_{10b}), 4.41 (br s, 2H, H_{1,5}), 3.91 (s, 3H, H₇), 3.90 (s, 3H, H₈), 2.37–2.03 (m, 6H, H_{2,4,6α,7α}), 1.93 (m, 2H, H_{6β,7β}). ¹³C NMR (75 MHz, CDCl₃) δ 165.45 (C₈), 153.15 (C₉), 151.40 (C₄), 148.81 (C₃), 123.24 (C₆), 122.96 (C₁), 111.98 (C₂), 110.45 (C₅), 95.92 (C₁₁), 74.60 (C₁₀), 67.84 (C₃), 56.10 (C₇), 56.00 (C₈), 53.03 (C₁), 52.90 (C₅), 36.38 (C₂), 35.61 (C₄), 28.55 (C₆), 27.70 (C₇). MS (m/z): 466.0526 ([M+H]⁺).

Compound 2 (endo-convolvine): *8-azabicyclo[3.2.1]octan-3-yl 3,4-dimethoxybenzoate (endo-convolvine 2)*

The Schlenk tube was charged with the carbamate (0.1 g, 0.214 mmol, 1 eq) and Zinc dust (0.042 g, 0.642 mmol, 3 eq) in acid acetic (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 during 2 hours. The resulting suspension was cooled to room temperature and quenched with ammonia water concentrated and extracts three times with DCM. The aqueous layer extracted with DCM (3 times). The combined organic layers were dried (MgSO₄), filtered and concentrated *in vacuo*. Purification by flash column chromatography on silica gel yielded the desired product (0.192 mmol) as a white solid.

Yield 90%; white solid; TLC: R_f = 0.36 (8:2 CH₂Cl₂ / MeOH), m.p.: 101–102°C, IR (neat): 2939, 2837, 1702, 1601, 1514, 1465, 1416, 1357, 1270, 1224, 1177, 1132, 1076, 1023, 875, 849, 765, 629 cm⁻¹. ¹H and ¹³C NMR (75 MHz, CDCl₃) δ 165.6, 152.9, 148.6, 123.3, 123.2, 111.9, 110.3, 68.5, 55.9, 53.4 (2C), 37.6, 37.6, 29.4 (2C). MS (m/z): 292.1541 ([M+H]⁺).

1. General procedure for Pd-Catalyzed coupling of convolvine with various aryls and heteroaryles:

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 bromoquinolin-2(1H)-one/aryl/heteroaryle bromides, 2 mmol of the convolvine) 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 liquid reactant 1,4-dioxane (2 mL) were 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 room temperature and filtered through Celite eluting with ethyl acetate, and the inorganic salts were removed. The filtrate was concentrated and purification of the residue by silica gel column chromatography gave the desired product.

Compound 5a: *8-(6-bromo-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-8azabicyclo [3.2.1] octan-3-yl 3,4-dimethoxybenzoate*

Yield 97% (0.97 mmol), yellow solid; m.p.: 146–147°C; TLC: R_f 0.38 (Chloroforme/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, 1H, J_1 = 8.4, J_2 = 2.0 Hz, H₆), 7.58 (d, 1H, J = 1.9 Hz, H₂), 7.53 (dd, 1H, J_1 = 7.7, J_2 = 1.3 Hz, H₇), 7.40 (d, 1H, J = 8.3 Hz, H₅), 7.35–7.29 (m, 1H, H₅), 7.19–7.13 (m, 1H, H₃), 7.10 (d, 1H, J = 8.4 Hz, H₅), 7.05 (s, 1H, H₄), 5.26 (m, 1H, H₃),

Yield 96% (0.96 mmol), white solid; m.p.: 129–130°C; TLC: 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, 1H, $J_1 = 8.4$, $J_2 = 1.8$ Hz, H_6), 7.59 (d, 1H, $J = 1.8$ Hz, H_2), 6.92 (d, 1H, $J = 8.4$ Hz, H_5), 6.86–6.83 (m, 4H, $\text{H}_{3',4',5',6'}$), 5.34 (m, 1H, H_3), 4.21 (br s, 2H, $\text{H}_{1,5}$), 3.94 (s, 6H, $\text{H}_{7,8}$), 3.86 (s, 3H, H_7), 2.52–2.35 (m, 2H, $\text{H}_{2\alpha,4\alpha}$), 2.28–2.02 (m, 4H, $\text{H}_{2\beta,4\beta,6\alpha,7\alpha}$), 1.91 (d, 2H, $J = 14.8$ Hz, $\text{H}_{6\beta,7\beta}$). ^{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 ($\text{C}_{1,5}$), 36.36 ($\text{C}_{2,4}$), 27.65 ($\text{C}_{6,7}$). MS (m/z): 398.1968 ($[\text{M}+\text{H}]^+$).

Compound 5k: 8-(4-methoxyphenyl)-8-azabicyclo[3.2.1]octan-3-yl 3,4-dimethoxybenzoate

Yield 57% (0.57 mmol), white solid; m.p.: 123–124°C; TLC: 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, 1H, $J_1 = 8.4$, $J_2 = 1.8$ Hz, H_6), 7.58 (d, 1H, $J = 1.8$ Hz, H_2), 7.17 (t, 1H, $J = 8.1$ Hz, H_5), 6.93 (d, 1H, $J = 8.4$ Hz, H_5), 6.42 (dd, 1H, $J_1 = 8.1$, $J_2 = 1.7$ Hz, H_6), 6.38–6.19 (m, 2H, $\text{H}_{2',4'}$), 5.22 (m, 1H, H_3), 4.23 (br s, 2H, $\text{H}_{1,5}$), 3.94 (s, 3H, H_7), 3.93 (s, 3H, H_8), 3.80 (s, 3H, H_7), 2.44–2.05 (m, 6H, $\text{H}_{2,4,6\alpha,7\alpha}$), 1.76 (d, 2H, $J = 15.2$ Hz, $\text{H}_{6\beta,7\beta}$). ^{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 ($\text{C}_{1,5}$), 31.68 ($\text{C}_{2,4}$), 28.36 ($\text{C}_{6,7}$). MS (m/z): 398.1968 ($[\text{M}+\text{H}]^+$).

Compound 5l: 8-phenyl-8-azabicyclo[3.2.1]octan-3-yl 3,4-dimethoxybenzoate

Yield 68% (0.68 mmol), white solid; m.p.: 183–184°C; TLC: 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, 1H, $J_1 = 8.4$, $J_2 = 1.8$ Hz, H_6), 7.59 (d, 1H, $J = 1.8$ Hz, H_2), 7.29 (s, 1H, H_3), 7.23 (s, 1H, H_5), 6.94 (d, 1H, $J = 8.4$ Hz, H_5), 6.80 (d, 2H, $J = 8.5$ Hz, $\text{H}_{2',6'}$), 6.72 (t, 1H, $J = 7.3$ Hz, H_4), 5.22 (m, 1H, H_3), 4.27 (br s, 2H, $\text{H}_{1,5}$), 3.96 (s, 3H, H_7), 3.95 (s, 3H, H_8), 2.48–2.04 (m, 6H, $\text{H}_{2,4,6\alpha,7\alpha}$), 1.77 (d, 2H, $J = 15.1$ Hz, $\text{H}_{6\beta,7\beta}$). ^{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 ($\text{C}_{3',5'}$), 123.42 (C_6), 123.36 (C_1), 117.25 (C_4), 115.07 ($\text{C}_{2',6'}$), 112.08 (C_2), 110.53 (C_5), 68.96 (C_3), 56.17 (C_7), 56.07 (C_8), 52.94 ($\text{C}_{1,5}$), 31.53 ($\text{C}_{2,4}$), 28.33 ($\text{C}_{6,7}$). MS (m/z): 368.1870 ($[\text{M}+\text{H}]^+$).

Compound 5m: 8-(1-methyl-1H-indol-5-yl)-8-azabicyclo[3.2.1]octan-3-yl 3,4-dimethoxybenzoate

Yield 70% (0.70 mmol), white solid; m.p.: 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, 1H, $J_1 = 8.4$, $J_2 = 1.8$ Hz, H_6), 7.65 (d, 1H, $J = 1.6$ Hz, H_2), 7.30 (d, 1H, $J = 4.1$ Hz, H_5), 7.06 (d, 1H, $J = 1.7$ Hz, H_4), 7.02 (d, 1H, $J = 3.0$ Hz, H_3), 6.98 (d, 1H, $J = 8.4$ Hz, H_6), 6.93 (dd, 1H, $J_1 = 8.9$, $J_2 = 1.9$ Hz, H_7), 6.39 (d, 1H, $J = 2.9$ Hz, H_2), 5.25 (m, 1H, H_3), 4.33 (br s, 2H, $\text{H}_{1,5}$), 4.00 (s, 6H, $\text{H}_{7,8}$), 3.79 (s, 3H, H_9), 2.54–2.49 (m, 2H, $\text{H}_{2\alpha,4\alpha}$), 2.39–2.21 (m, 4H, $\text{H}_{2\beta,4\beta,6\alpha,7\alpha}$), 1.82 (d, 2H, $J = 15.1$ Hz, $\text{H}_{6\beta,7\beta}$). ^{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 ($\text{C}_{4'a}$), 129.69 ($\text{C}_{6'b}$), 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 ($\text{C}_{1,5}$), 32.97 (C_9), 31.82 ($\text{C}_{2,4}$), 28.28 ($\text{C}_{6,7}$). MS (m/z): 421.2122 ($[\text{M}+\text{H}]^+$).

Compound 5n: 8-(pyridin-3-yl)-8-azabicyclo[3.2.1]octan-3-yl 3,4-dimethoxybenzoate

Yield 95% (0.95 mmol), white solid; m.p.: 140–141°C; TLC: R_f 0.45 ($\text{CH}_2\text{Cl}_2/\text{EtOAc}$: 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, 1H, H_2), 7.98 (br s, 1H, H_4), 7.67 (dd, 1H, $J_1 = 8.4$, $J_2 = 1.4$ Hz, H_6), 7.56 (d, 1H, $J = 1.4$ Hz, H_2), 7.12–7.16 (m, 1H, H_5), 7.04 (d, 1H, $J = 8.4$ Hz, H_6), 6.92 (d, 1H, $J = 8.4$ Hz, H_5), 5.20 (m, 1H, H_3), 4.26 (br s, 2H, $\text{H}_{1,5}$), 3.93 (s, 3H, H_7), 3.92 (s, 3H, H_8), 2.42–2.07 (m, 6H, $\text{H}_{2,4,6\alpha,7\alpha}$), 1.80 (d, 2H, $J = 15.2$ Hz, $\text{H}_{6\beta,7\beta}$). ^{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 ($\text{C}_{1,5}$), 31.58 ($\text{C}_{2,4}$), 28.18 ($\text{C}_{6,7}$). MS (m/z): 369.1811 ($[\text{M}+\text{H}]^+$).

Compound 5o: 8-(6-((1R,3R,5S)-3-(3,4-dimethoxybenzoyloxy)-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-dimethoxy benzoate

Yield 43% (0.43 mmol), white solid; m.p.: 118–119°C; TLC: R_f 0.51 ($\text{CH}_2\text{Cl}_2/\text{EtOAc}$: 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, 2H, $J_1 = 8.4$, $J_2 = 1.9$ Hz, H_6 , $6''$), 7.58 (br s, 2H, H_2 , $2''$), 7.31 (d, 1H, $J = 8.8$ Hz, H_8), 7.16–6.92 (m, 5H, $\text{H}_{5',4',5'',7',5''}$), 5.26 (m, 1H, H_3), 5.18 (m, 1H, H_3''), 4.83 (br s, 2H, $\text{H}_{1,5}$), 4.35 (br s, 2H, $\text{H}_{1'',5''}$), 3.91 (s, 6H, $\text{H}_{7,8}$), 3.89 (s, 6H, $\text{H}_{7'',8''}$), 3.69 (s, 3H, H_9), 2.80 (br s, 2H, $\text{H}_{2\alpha,4\alpha}$), 2.44–2.22 (m, 6H, $\text{H}_{2\beta,4\beta,6,7}$), 1.87–1.76 (m, 8H, $\text{H}_{2',4',6',7'}$). ^{13}C NMR (75 MHz, Acetone- d_6) δ 165.87 ($\text{C}_{8,8''}$), 154.46 (C_2), 150.05 ($\text{C}_{4,4''}$), 138.16 ($\text{C}_{3,3''}$), 136.66 (C_6), 134.57 (C_1), 130.92 ($\text{C}_{4'a}$), 130.35 ($\text{C}_{8'a}$), 124.13 ($\text{C}_{1,1''}$), 124.00 ($\text{C}_{6,6''}$), 115.60 ($\text{C}_{2,2''}$), 114.72 (C_7), 112.98 ($\text{C}_{5,5''}$), 111.90 ($\text{C}_{4',5'}$), 69.27 ($\text{C}_{3,3''}$), 56.24 ($\text{C}_{7,8}$), 56.12 ($\text{C}_{7'',8''}$), 55.00 ($\text{C}_{1,5,1'',5''}$), 34.68 ($\text{C}_{2,4,2'',4''}$), 32.26 (C_9), 28.27 ($\text{C}_{6,7,6'',7''}$). MS (m/z): 738.3414 ($[\text{M}+\text{H}]^+$).

Protocol for Cell Culture and Proliferation Assay: Cancer cell lines were obtained from the American type Culture Collection (Rockville, MD) 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 ($\lambda_{\text{ex}} = 560$ nm, $\lambda_{\text{em}} = 590$ nm) using a Victor microtiter plate fluorimeter (Perkin-Elmer, 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

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Acknowledgment

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 also grateful to Prof. Fethia Harzallah-Skhiri, High Institute of Biotechnology of Monastir, Tunisia, for botanical identification of the plant material and 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).

Supporting Information

Supporting information for this article (^1H , ^{13}C , COSY, HSQC, HMBC and NOESY NMR spectra) is available online at

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- (11) Crystallographic data (excluding structure factors) for the structure of N-methylconvolvine 3 have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 1535462. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).
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