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Research paper

Synthesis, biological evaluation and toxicity of novel tetrandrine analogues

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ABSTRACT

In this work, we present the design and synthesis of novel fully synthetic analogues of the bisbenzylisoquinoline tetrandrine, a molecule with numerous pharmacological properties and the potential to treat life-threatening diseases, such as viral infections and cancer. Its toxicity to liver and lungs and the underlying mechanisms, however, are controversially discussed. Along this line, novel tetrandrine analogues were synthesized and biologically evaluated for their hepatotoxicity, as well as their antiproliferative and chemoresistance reversing activity on cancer cells. Previous studies suggesting CYP-mediated toxification of tetrandrine prompted us to amend/replace the suspected metabolically instable 12-methoxy group. Of note, employing several *in vitro* models showed that the proposed CYP3A4-driven metabolism of tetrandrine and analogues is not the major cause of hepatotoxicity. Biological characterization revealed that some of the novel tetrandrine analogues sensitized drug-resistant leukemia cells by inhibition of the P-glycoprotein. Interestingly, direct anticancer effects improved in comparison to tetrandrine, as several compounds displayed a markedly enhanced ability to reduce proliferation of drug-resistant leukemia cells and to induce cell death of liver cancer cells. Those enhanced anticancer properties were linked to influences on activation of the kinase Akt and mitochondrial events. In sum, our study clarifies the role of CYP3A4-mediated toxicity of the bisbenzylisoquinoline alkaloid tetrandrine and provides the basis for the exploitation of novel synthetic analogues for their antitumoral potential.

1. Introduction

The natural product tetrandrine (**1**) (Fig. 1), isolated from the plant *Stephania tetrandra* [1,2], belongs to the class of bisbenzylisoquinoline alkaloids. Tetrandrine has a wide range of pharmacological activities [3,4], most interestingly antiviral [5–8], anticancer [9,10], multidrug resistance reversing [11–15] and calcium channel blocking [6,16–18] effects.

Recently, it was shown that tetrandrine (**1**) blocks endolysosomal two-pore channels (TPCs, voltage-gated calcium channels) and thereby reduces cellular entry of Ebolavirus (EBOV) [6], MERS-CoV [7], SARS-CoV-2 [5] viruses or pseudoviruses into host cells. Currently, a clinical trial (NCT04308317) is announced to investigate tetrandrine (**1**) as adjuvant treatment of COVID-19 patients in China [20]. Moreover, tetrandrine displayed strong antiproliferative and cytotoxic properties against several cancer cell lines [4,9], arrested cell cycle progression [21], induced pro-apoptotic signaling pathways [22] and reduced migration [23] of tumor cells. Additionally, tetrandrine was shown to resensitize chemoresistant tumors by inhibition of P-glycoprotein (P-gp) [11,12,14], a universal efflux pump for xenobiotics, which is a key factor of drug resistance [24] frequently causing treatment failure of tumor therapy.

All these multiple pharmacological activities make tetrandrine (**1**) an interesting lead compound and a potential drug candidate for diverse applications. Unfortunately, its clinical application as a drug is limited by its toxicity. Several toxic side effects have been reported for tetrandrine and other bisbenzylisoquinolines so far [25]. In animal models, mainly a damage of liver and lungs was observed [26–30].

The molecular mechanism of tetrandrine-induced toxicity has not been entirely elucidated yet. Li and coworkers [31] hypothesized that an interaction of tetrandrine with p38α MAPK (mitogen-activated protein kinase) led to liver injury, whereas several other

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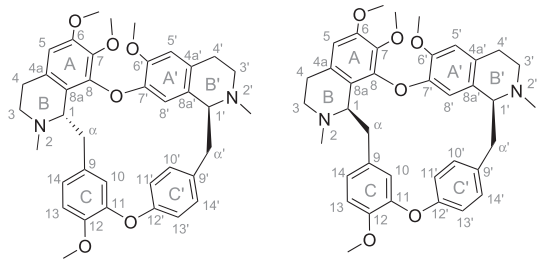


Fig. 1. Tetrandrine (**1**) (1*S*,1′*S*) and isotetrandrine (**2**) (1*R*,1′*S*) – Numbering of the skeleton according to Shamma [19].

studies suggest the involvement of cytochrome P450 (CYP) enzymes in tetrandrine-induced pulmonary [26,27] and hepatic toxicity [32]. Qi et al. [32] consider CYP2E1 as primary reason for mitochondrial dysfunction of rat hepatocytes after tetrandrine exposure, which they relate to reactive oxygen species (ROS) that were generated in the course of CYP2E1 metabolism. However, it is unknown which molecular mechanisms are connected to CYP2E1-mediated toxicity. In a metabolic study by Jin et al. [26] a CYP3A4- and CYP3A5-mediated metabolism equally leading to a potentially toxic intermediate is described. Hereby one particular structural element is suggested to be responsible for tetrandrine's toxicity. In the hypothesized metabolic pathway, the methoxy group at C-12 in *para*-position to a benzylic methylene group is first demethylated to give the corresponding phenol **3**. This phenol then undergoes enzymatic oxidation to the *para*-quinone methide **4**, which is an electrophilic intermediate prone to attack bio-nucleophiles (see Scheme 1). After incubation of tetrandrine (**1**) with human liver mircosomes in the presence of glutathione (GSH), a corresponding GSH conjugate (**5**) was detected *via* LC-MS, which provides evidence for the formation of the *para*-quinone methide **4**.

A considerable number of pharmacologically interesting bisbenzylisoquinolines and *seco* analogues such as dauricine (**6**) [33–36], berbamine (**7**) [37–39], fangchinoline (**8**) [7,15], cepharanthine (**9**) [40] and muraricine (**10**) [41,42] contain the discussed *para*-methoxybenzyl motif like the one present in tetrandrine (**1**) or the equivalent *para*-hydroxybenzyl moiety (see Fig. 2), which could potentially result in an unfavorable toxicity profile as well. So it is of great relevance to clarify if and to which extent this structural motif causes cytotoxicity after oxidation by CYP3A4/5 enzymes.

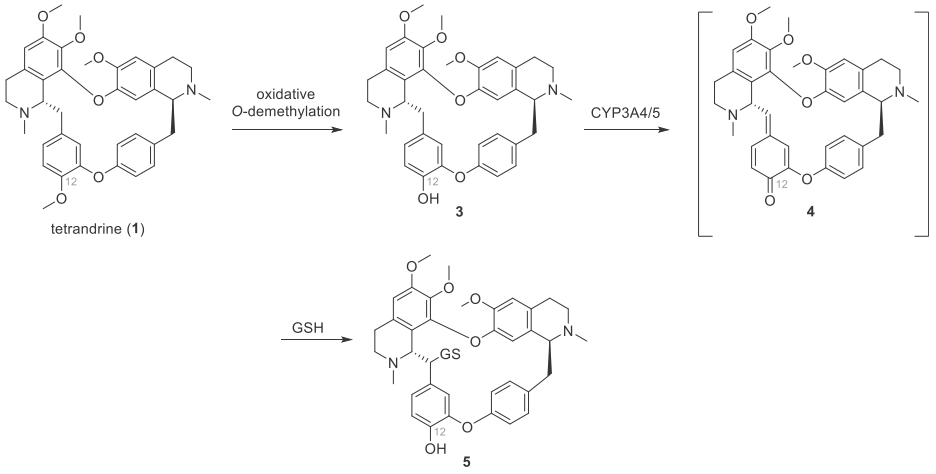
Aim of this study was to investigate if expression of CYP3A4, the most abundant CYP enzyme in human liver [43], substantially contributes to the toxicity of tetrandrine (**1**) and whether the *para*-methoxybenzyl moiety is indeed the crucial point. In a combined medicinal chemistry and cell biology approach we evaluated if a reduction of the discussed CYP3A4-mediated toxicity of tetrandrine can be achieved by replacing or eliminating the hypothesized metabolically instable 12-methoxy group. This motivated us to synthesize analogues of tetrandrine which are lacking the critical methoxy group or the entire benzyl unit. Subsequently, the toxicity of the obtained tetrandrine analogues to human hepatocyte like cells (HepaRG™) and human hepatocellular carcinoma cells (HepG2), with or without overexpression of CYP3A4, was investigated. Concurrently, we determined the impact of structural modifications on the biological activity of compounds and focused on inhibition of cancer cell proliferation and interaction with the efflux pump P-gp, as an application in tumor therapy is desired.

2. Results and discussion

2.1. Chemistry

As mentioned above, we aimed at investigating the role of the metabolically labile 12-methoxy group of tetrandrine (**1**). Thus, we designed analogues of tetrandrine, in which this methoxy group is either deleted (target compounds **RMS1**-**2**) or replaced by metabolically stabile trifluoromethoxy (**RMS3**-**4**) or chlorine substituents (**RMS7**-**8**, see Scheme 3). Further we replaced the methoxybenzyl residue by a thienylmethyl (target compound **RMS5**-**6**) and by a non-aromatic butylidene unit (**RMS9**-**10**). The synthesis of these tetrandrine analogues is based on our recently published racemic total synthesis of tetrandrine and isotetrandrine [44] following the therein described synthetic protocol of "Route 1b". The intermediate **11** (no. 19 in Ref. [44]) of the (iso)tetrandrine synthesis served as a valuable starting material, since it already comprises one tetrahydrobenzylisoquinoline unit (rings A′-C′) and ring A of the second half of the bisbenzylisoquinoline scaffold (see Fig. 1). Detailed information for the preparation of intermediate **11** is provided in the Supporting Information.

The second tetrahydroisoquinoline moiety (rings A and B) was constructed *via* trifluoromethanesulfonic acid-mediated *inter*molecular *N*-acyl Pictet-Spengler reaction of arylethylamino carbamate intermediate **11** and enol ethers **12a**-**12d** or the aliphatic aldehyde **12e**, respectively, to obtain the *seco*-



Scheme 1. Postulated CYP-enzyme mediated oxidative metabolism of tetrandrine (**1**) adopted from Jin et al. [26].

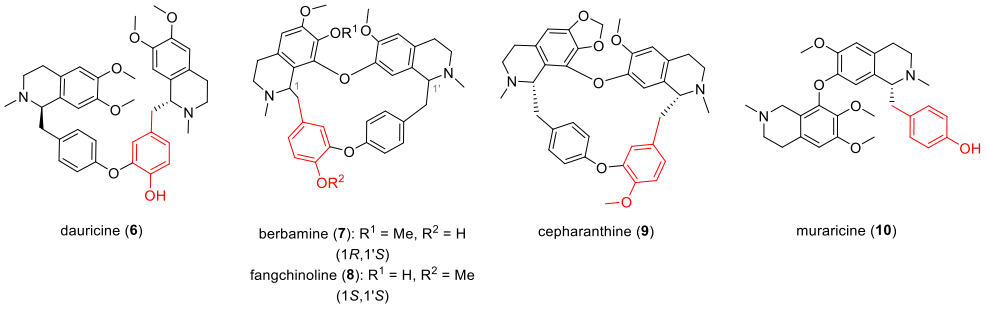
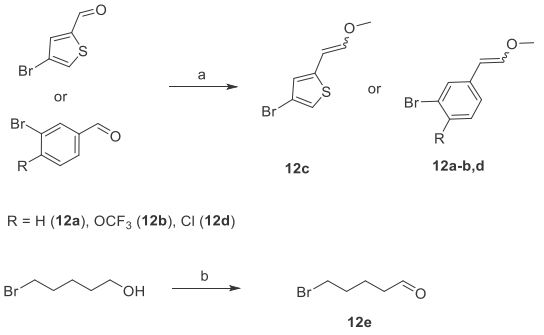


Fig. 2. Related bisbenzylisoquinolines and *seco* analogues containing the hypothesized metabolically labile *para*-methoxy(hydroxy)benzyl motif (highlighted in red). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

bisbenzylisoquinolines **13a**-**13d** and bromobutyl analogue **13e** (Scheme 3). The required enol ethers **12a-d** were conveniently prepared *via* a Wittig olefination of the corresponding commercially available aromatic aldehydes (Scheme 2), 5-bromopentanal (**12e**) was obtained by PCC oxidation of the corresponding primary alcohol [45]. The intermediates **13a**-**13e** were further processed in *intra*molecular Ullmann-type cross-coupling reactions or an S_N2 reaction (for the ω-bromobutyl intermediate **13e**) respectively to access the diaryl ether bridges (connecting rings C and C' in **14a-d**) or the aliphatic bridge in **14e**, furnishing macrocyclic bisbenzylisoquinoline analogues. Final step was the simultaneous reduction of both carbamate groups using lithium alanate to give the desired *N*-methylated compounds **RMS1**-**6** and **RMS9**-**10**. In case of the chloroarene variations **RMS7**-**8** this method led to substantial dechlorination, even when using the milder reduction reagent Red-Al® (sodium bis(2-methoxyethoxy)aluminum dihydride). To circumvent this problem, the carbamate groups were first removed by treatment with methyl lithium and the resulting secondary amino groups were subsequently N-methylated *via* reductive alkylation using formaldehyde/$NaBH_3CN$. Since the *N*-acyl Pictet-Spengler condensations expectedly proceeded with no or only rather poor diastereoselectivity [44] (with a tendency for the formation of the *R*,*R*/*S*,*S* isomers), we obtained racemic mixtures of diastereomers in every case. Luckily we were able to separate the open-chain diastereomers obtained in the *N*-acyl Pictet-Spengler reactions by flash column chromatography to provide, in the end, each tetrandrine analogue eventually as racemic compound with the relative stereoconfiguration of either tetrandrine (**1**) or isotetrandrine (**2**) (Fig. 1) in high diastereomeric ratios (d.r., determined by HPLC).

The relative stereochemistry of the final racemic compounds **RMS1**-**8** was determined by analysis of NMR data utilizing the comprehensive investigation performed by Guinaudeau et al. on



Scheme 2. Synthesis of enol ethers **12a-d** and aldehyde **12e**. Reagents and conditions: (a) $(Ph)_3P(Cl)CH_2OCH_3$, LDA, THF, 0 °C to rt (80–87%). (b) PCC, DCM, rt (64%).

more than 100 bisbenzylisoquinolines [46]. Herein the chemical shifts of distinctive protons in the NMR spectra of bisbenzylisoquinolines can be used for a reliable determination of the relative configurations at both asymmetric centers. The relative configurations of all *seco*-precursors were then assigned retrospectively. For the variations **RMS9**-**10**, which contain an alkyl bridge instead of an aromatic ring (ring C), this method is not applicable. Unfortunately, attempts of crystallization for crystallographic analysis were unsuccessful, and the determination of the stereoconfiguration in this case was therefore not possible.

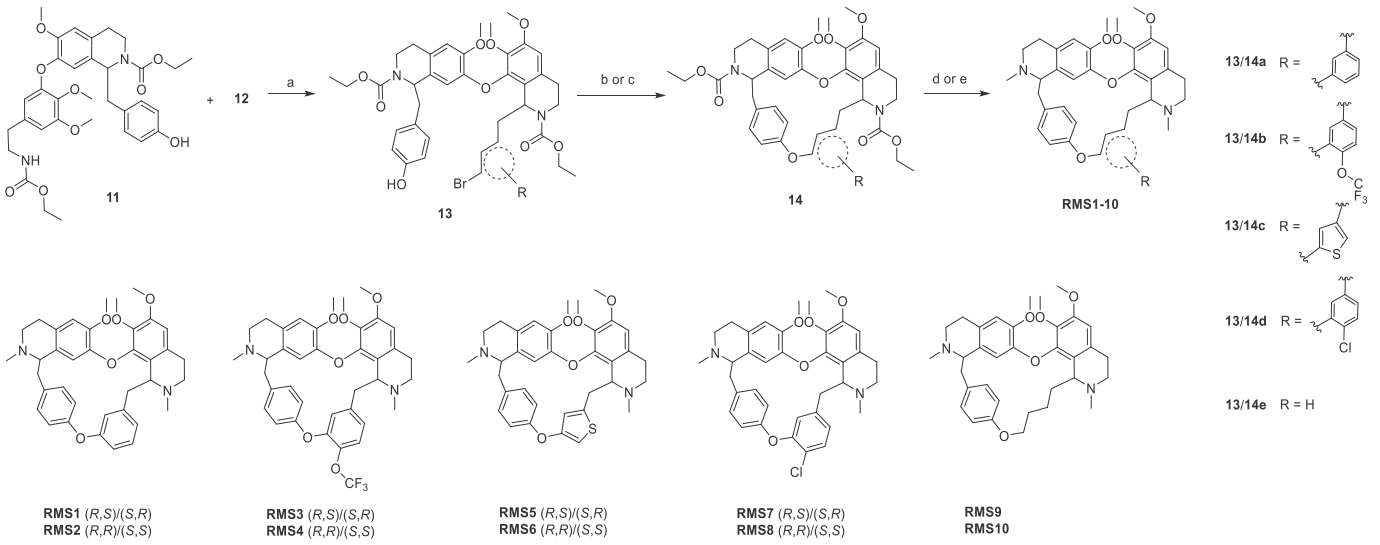
2.2. Biological evaluation

2.2.1. Assessment of CYP3A4-mediated toxicity

2.2.1.1. Evaluation of toxicity using non-malignant hepatocyte-like cells. To assess general toxicity, HepaRG™ cells, non-cancerous hepatic stem cells which possess various characteristics of healthy liver cells and which have a high activity of P450 enzymes [47,48], were treated with 10 and 20 μM of tetrandrine (**1**) and the analogues **RMS1**-**10**. Unlike expected, none of the new compounds was less toxic to HepaRG™ cells than tetrandrine (**1**) at 10 μM (Fig. 3a). In contrast, **RMS4** and **RMS8** slightly, but **RMS2** strongly decreased cell viability. Similarly, at 20 μM, **RMS2**, **RMS4** and **RMS8** were significantly more toxic to HepaRG™ cells than tetrandrine (**1**) (Fig. 3b). Of note, 20 μM of **RMS6** and **RMS9** were significantly less toxic than tetrandrine, whereas toxic effects of the other compounds did not substantially differ from those of tetrandrine (**1**). It should be noted that, depending on the substituent at C-12 of ring C, oxidation to a *para*-quinone methide cannot be excluded for 12-unsubstituted compounds **RMS1**/**RMS2** (*via* initial CYP-mediated ring hydroxylation), whereas in the trifluoromethoxy compounds **RMS3**/**RMS4** and the chloro compounds **RMS7**/**RMS8** oxidation processes are prevented by metabolically stable substituents.

To specifically determine the influence of CYP3A4 activity on toxicity *in vitro*, CYP3A4 with a C-terminal EGFP tag was cloned (CYP3A4-EGFP) and its physiological function was successfully validated by conversion of a proluminogenic CYP3A4 substrate in transiently transfected HepG2 cells, which was strongly reduced by the CYP3A4 inhibitor ketoconazole [49] (Suppl. Fig. 1a). Of note, treatment of CYP3A4 overexpressing HepaRG™ cells with respective compounds did not significantly increase cell death (Fig. 3c). As observed for the non-transfected HepaRG™ cells, **RMS2** still had the strongest effect on cell viability.

2.2.1.2. Evaluation of toxicity using HepG2 liver cancer cells. Next, transgenic HepG2 cells, a liver cancer cell line frequently used for recombinant expression of CYP enzymes and hepatotoxicity studies [49–51], were generated. Stable transfection and



Scheme 3. Synthesis of tetrandrine analogues. Reagents and conditions: (a) TfOH, DCM, 0 °C to rt (23–37% separated diastereomers). (b) for **13a-13d**: $CuBr{\cdot}Me_2S$, Cs_2CO_3, pyridine, 110 °C (17–77%). (c) for **13e**: KI, K_3PO_4, DMF, 100 °C (29–60%). (d) for **14a/b/c/e**: $LiAlH_4$, THF, 50 °C (62–94%). (e) for **14d**: 1) MeLi, THF, 0 °C, 2) aq. formaldehyde solution (37%), $NaBH_3CN$, MeOH, rt (30% over two steps).

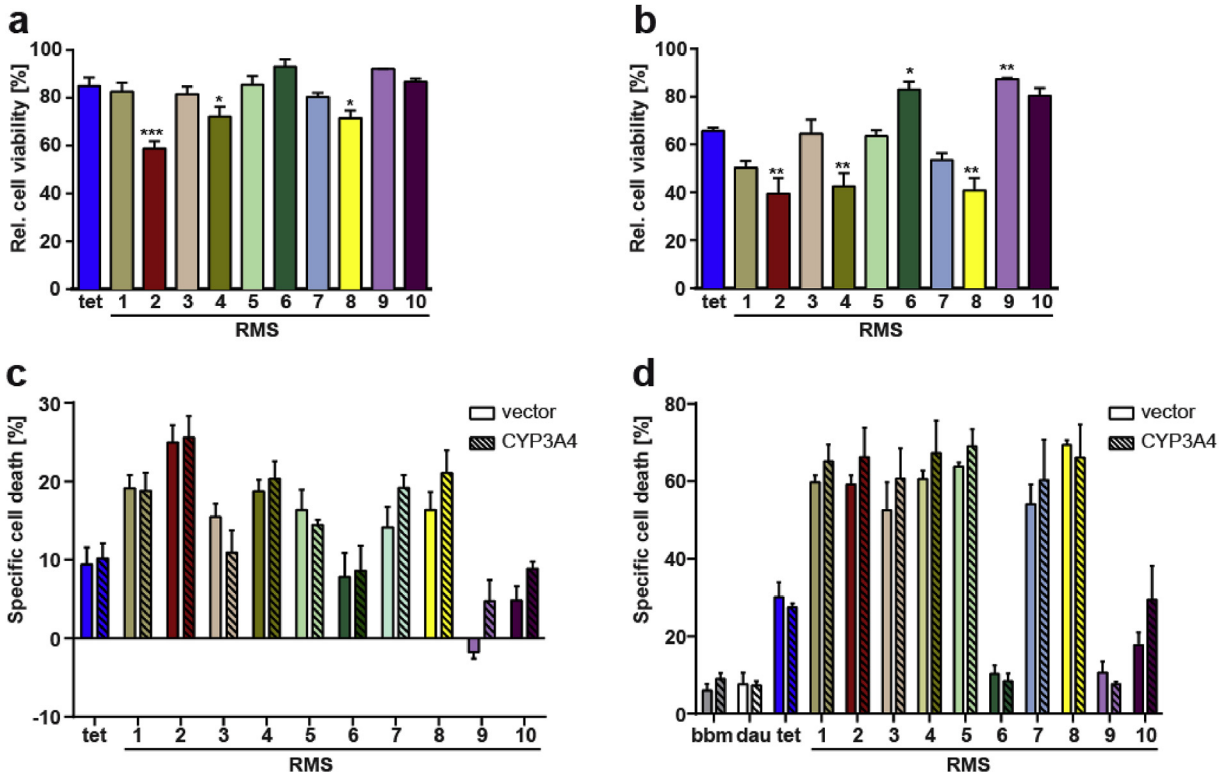


Fig. 3. Toxicity assessment using HepaRG™ and HepG2 cells. (a,b) Differentiated HepaRG™ cells were exposed to (a) 10 μM and (b) 20 μM tetrandrine (**1**) and **RMS1-RMS10** for 24 h and cell viability was determined by CellTiter-Blue® cell viability assay. Cell viability was normalized to vehicle control. Bar graphs indicate means ± SEM of three independent experiments (One-Way ANOVA followed by Dunnett's multiple comparison test, relative cell viabilites were compared with that of tetrandrine, $*P < 0.05$, $**P < 0.01$, $***P < 0.001$). (c) Differentiated HepaRG™ cells were transfected with pcDNA3-CYP3A4-EGFP or an empty vector control and treated with 10 μM of tetrandrine (**1**) and **RMS1-RMS10** for 24 h. (d) HepG2 cells stably transfected with pcDNA3-CYP3A4-EGFP or empty vector control were treated with berbamine (**7**), dauricine (**6**), tetrandrine (**1**) and **RMS1-RMS10** (15 μM) for 24 h. (c,d) Cell death was determined by propidium iodide staining and flow cytometry. Means ± SEM of three independent experiments are shown (unpaired *t*-test with Welch's correction, not significant). bbm: berbamine, dau: dauricine, Rel.: relative, tet: tetrandrine. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

overexpression of CYP3A4 were confirmed by PCR methods (Suppl. Fig. 1b and c). Again, no correlation between the level of cellular CYP3A4 expression and cytotoxicity was observed. Interestingly, most tetrandrine analogues (**RMS1**, **RMS2**, **RMS3**, **RMS4**, **RMS5**, **RMS7**, **RMS8**) exerted generally increased cytotoxicities against cancerous HepG2 cells, mostly independent of their

stereochemistry, in comparison to tetrandrine (**1**). Surprisingly, the diastereomers **RMS9** and **RMS10** slightly, while **RMS5** and **RMS6** substantially differed in their cytotoxic potencies. Of note, **RMS3** and **RMS5** influenced cell viability of HepaRG™ cells similarly to tetrandrine (**1**) (Fig. 3a–c), but they exerted strongly increased cytotoxicites to cancerous HepG2 cells (Fig. 3d).

To exclude that the observed similar cytotoxic effects on vector and CYP3A4-EGFP transfected cells were caused by insufficient initial demethylation that is required for tetrandrine (**1**) for being oxidized to a putatively toxic *para*-quinone methide, related alkaloids berbamine (**7**) and dauricine (**6**) were also tested. Both alkaloids (Fig. 2) bear a *para*-hydroxybenzyl moiety at the region of interest, which theoretically can be directly oxidized by CYP3A4 to a *para*-quinone methide with no need for previous *O*-demethylation. Similarly, for both berbamine (**7**) and dauricine (**6**), cell death was not significantly increased by cellular CYP3A4 overexpression (Fig. 3d). Taken together, the toxicity of tetrandrine (**1**) was not considerably decreased or even increased by variation of the *para*-methoxybenzyl moiety in several cellular models. However, no influence of the level of cellular CYP3A4 expression was found. Consequently, we conclude that the proposed CYP3A4-mediated generation of a *para*-quinone methide [26] does not substantially contribute to the hepatotoxicity of tetrandrine (**1**).

To decipher the correlation between the structure of quinone methides and their liver toxicity, Thompson and coworkers [52] investigated the toxicity of a series of 4-alkyl-2-methoxyphenols using an *in vitro* hepatotoxicity model. Although all tested molecules were converted into quinone methides, only little correlation between the rate of quinone methide formation in microsomes and relative toxicities of the alkylphenols was found [52]. It was suggested that primarily the reactivity of the quinone methides being formed and their stability towards solvolysis are the determining factors for their toxicity. These findings support the results of a former *in vivo* study [53] which observed differences in the toxicities of 2-methoxy-quinone methides that could be explained by their relative reactivities [54]. Thus, formation of quinone methides does not necessarily lead to toxicity *in vitro* and *in vivo*. For tetrandrine (**1**), other proposed mechanisms might play a more substantial role in toxicity, such as the generation of ROS by CYP2E1 [32] or the proposed interaction with p38α MAPK, a promotor of inflammatory processes in the liver [31], or additional effects that remain to be elucidated.

2.2.2. Evaluation of anticancer effects

2.2.2.1. Chemosensitization of drug-resistant leukemia cells by P-glycoprotein inhibition. As modification of the *para*-methoxybenzyl moiety of tetrandrine (**1**) led, depending on the kind of chemical modification and relative stereochemistry, to decreased, similar or elevated cytotoxicities to liver cells, we aimed to decipher whether and to which extent the modifications influenced known biological effects of tetrandrine on cancer cells. Firstly, their interactions with the efflux transporter P-gp [11] were investigated. Except for **RMS9** and **RMS10** (analogues lacking aromatic ring C), all tetrandrine analogues were able to prevent efflux of the model substrate calcein-AM from P-gp overexpressing, vincristine-resistant (VCR-R) CEM cells [55] equally to the parental molecule (Fig. 4a). P-gp surface expression, evaluated by flow cytometry, was not diminished by any of the compounds at the same conditions (Fig. 4b), suggesting that the observed increase in calcein fluorescence (Fig. 4a) was caused by direct interaction with P-gp. Subsequently, the compounds were used at 1 μM in combination with varying doses of vincristine (VCR). As expected, all but **RMS9** and **RMS10** were able to sensitize VCR-R CEM cells to VCR, indicated by strongly increased apoptosis rates (Fig. 4c). **RMS8** was the most potent analogue as it significantly increased apoptosis at 0.01 μM VCR (Fig. 4c). These data indicate that by replacing the *para*-methoxybenzyl moiety of tetrandrine with other substituted or unsubstituted aromatic residues, the potency to inhibit P-gp is maintained, while replacement with an alkyl chain (**RMS9** and **RMS10**) strongly reduces it. Thereby, we add new information to structure-activity relationships of bisbenzylisoquinoline alkaloids with regards to their interference with the major efflux transporter P-gp.

2.2.2.2. Studies on anticancer effects and related pathways. In a next step, we determined direct antiproliferative effects of the compounds on VCR-R CEM cells, which are cross-resistant to a variety of chemotherapeutic drugs [55]. Interestingly, most tetrandrine analogues (**RMS1**-**RMS5**, **RMS7**-**8**) displayed a markedly enhanced ability to inhibit proliferation of VCR-R leukemia cells (Fig. 5a and b). **RMS6**, **RMS9** and **RMS10** were nearly inactive. Thus, in contrast to the lead structure tetrandrine (**1**), **RMS1**-**RMS5**, **RMS7** and **RMS8** were also effective when applied as monotherapy and therefore represent potential candidates to treat multidrug resistant cancers. Notably, **RMS6** had no direct effect on proliferation (Fig. 5a and b), but successfully sensitized VCR-R CEM cells to VCR (Fig. 4c) through inhibition of P-gp (Fig. 4a).

To gain more detailed insights into the underlying mechanisms, the influence of tetrandrine (**1**) and **RMS1**-**RMS10** on pathways related to cell survival and apoptosis was investigated. Wan and coworkers [56] illustrated that tetrandrine and the multikinase inhibitor sorafenib have synergistic antitumor effects by reducing expression of anti-apoptotic proteins and activation of the kinase Akt. This prompted us to investigate how **RMS1**-**RMS10** and tetrandrine (**1**) affect the intrinsic apoptosis pathway and phosphorylation of Akt, which is a key factor for proliferation and cell survial [56]. Upon treatment with 5 μM, phosphorylation of Akt and expression levels of the anti-apoptotic proteins B-cell lymphoma-extra large (Bcl-xL) and myeloid cell leukemia sequence-1 (Mcl-1) were barely affected by any of the compounds (Fig. 5c). However, PARP cleavage, a marker for cells undergoing apoptosis [56], was detected for several RMS compounds (**RMS1**, **RMS3**, **RMS4**, **RMS8**). Mitochondrial depolarization is an indicator for early stage apoptosis [57] through the intrinsic, mitochondria-initiated pathway and mitochondrial health can be visualized with the fluorescent dye JC-1. Along this line, a shift towards green fluorescence was observed for **RMS2**, **RMS3**, **RMS4**, **RMS5** and **RMS8**, indicating disruption of the mitochondrial membrane potential ΔΨm, whereas tetrandrine (**1**), **RMS1**, **RMS6**, **RMS7**, **RMS9** and **RMS10** had no such an effect (Fig. 5d and e). Thus, these findings indicate that impaired mitochondrial functions partially account for the enhanced antiproliferative and cytotoxic effects of numerous tetrandrine analogues in comparison to tetrandrine (**1**) on VCR-R CEM cells.

In HepG2 cells, p-Akt levels were reduced by **RMS4** and **RMS5**, whereas no PARP cleavage was detected (Suppl. Fig. 2a) by any of the other tested compounds. Additionally, **RMS5** slightly diminished the expression of the anti-apoptotic Bcl-2 family proteins Bcl-XL and Mcl-1. In accordance with the absence of PARP cleavage, none of the compounds significantly disrupted ΔΨm at 5 μM (Suppl. Fig. 2b). Taken together, amendment or replacement of the 12-methoxy group of tetrandrine (**1**) by metabolically stable substituents can lead to enhanced induction of the intrinsic apoptosis pathway or activation of Akt, depending on the cancer cell line.

2.2.3. Additional toxicity studies

Considering both the antitumoral potential and the toxicity profile, **RMS3** and **RMS5** have markedly enhanced antiproliferative and cytotoxic effects on cancer cells (Figs. 3d and 5), while their toxicity to non-malignant hepatocytes is equal in comparison with

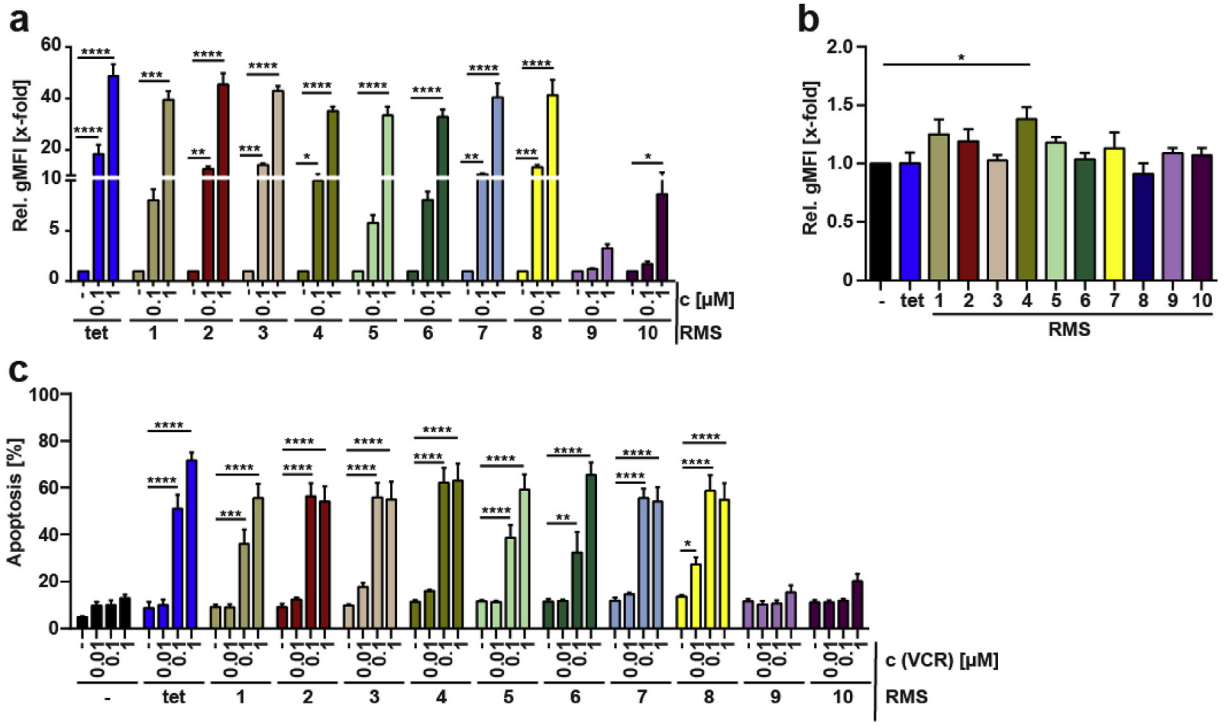


Fig. 4. P-gp inhibition and chemosensitization. (a) The influence of tetrandrine (**1**) and its analogues on the retention of the model substrate calcein-AM by the efflux transporter P-gp was assessed by flow cytometry. Cells were incubated with calcein-AM (200 nM) together with the potential P-gp inhibitors (0.1 and 1 μM) for 30 min at 37 °C. After a washing step, cells were incubated without calcein-AM for another 60 min at 37 °C before flow cytometric analysis. Geometric means of fluorescence intensities (gMFI) were normalized to the calcein-AM control. (b) No reduction of P-gp cell surface expression was observed upon exposure of VCR-R CEM cells to tetrandrine (**1**) or **RMS1**-**RMS10** (1 μM) for the conditions used in (a), as determined by flow cytometry. gMFI values were normalized to DMSO control. (c) VCR-R CEM cells were incubated in the absence or presence of tetrandrine and **RMS1**-**RMS10** (1 μM) with increasing concentrations of VCR for 48 h and apoptosis was determined by propidium iodide staining and flow cytometry. (a,c) Bar graphs indicate means ± SEM of three independent experiments (Two-Way ANOVA followed by Dunnett's multiple comparison test, $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, $^{****}P < 0.0001$). (b) Bar graphs indicate means ± SEM of three independent experiments (One-Way ANOVA followed by Dunnett's multiple comparison test, $^{*}P < 0.05$). -: solvent control, Rel.: relative, tet: tetrandrine, VCR: vincristine.

tetrandrine (Fig. 3a and b). Consequently, additional toxicity studies with primary cells were conducted to further elucidate their therapeutic potential. In line with the observations made with HepaRG™ cells (Fig. 3a and b), toxicities of **RMS3** and **RMS5** to human umbilical vein endothelial cells (HUVECs) and peripheral blood mononuclear cells (PBMCs) were similar to those caused by tetrandrine and only minor differences were found (Fig. 6a and b). While **RMS3** had a slightly stronger effect on the viability of HUVECs than tetrandrine at 10 μM (Fig. 6a), the highest percentage of dead PBMCs was detected after tetrandrine exposure at 5 and 10 μM (Fig. 6b). Taken together, the toxicity profile of the tetrandrine analogues **RMS3** and **RMS5** is largely equal to that of tetrandrine, but the improved anticancer properties theoretically enable dose reduction, providing incentive for further *in vivo* investigations.

3. Conclusion

The plant bisbenzylisoquinoline alkaloid tetrandrine (**1**) has diverse pharmacological properties [3,4], including antiviral [5–8], anticancer [9,10], multidrug resistance reversing [11–15] and calcium channel blocking [6,16–18] activities, making this alkaloid an attractive drug candidate. Unfortunately, its clinical application is limited by its toxicity, mainly affecting liver and lungs [26–30]. Five diastereomeric pairs of novel analogues of tetrandrine and its natural diastereomer isotetrandrine, respectively, were synthesized and biologically evaluated with respect to their toxicity, their antiproliferative and multidrug resistance reversing activity. The design of these new analogues was driven by the published hypothesis that one particular structural element, the methoxy group at C-12 in *para*-position to a benzylic methylene group, is responsible for toxicity due to its susceptibility to undergo enzymatic oxidation to a reactive (toxic) *para*-quinone methide, which in turn can react with bio-nucleophiles. The shape of the new compounds was intended to prevent this oxidative toxification process. Although all of the analogues lack the putative problematic structure motif, no significant decrease of toxicity could be observed without a concurrent reduction of anticancer activity. Compounds **RMS2**, **RMS4** and **RMS8** were found to be even more toxic to healthy cells than tetrandrine (**1**). Moreover, CYP3A4 overexpression in two cellular models that are established for recombinant hepatotoxicity studies suggested that the propagated mechanism of CYP3A4-mediated toxification involving the *para*-quinone methide **4** (see Scheme 1) is no primary cause for the cytotoxicity of tetrandrine and related (bis)benzylisoquinoline alkaloids. Consequently, the structure variations made in our approach are not a suitable approach in order to reduce the alkaloid's toxicity, and different strategies remain to be investigated in this respect. On the contrary, further biological characterization revealed distinct differences between tetrandrine and the synthesized analogues. While P-gp inhibitory potency was maintained by most of the performed structure variations, seven compounds exerted strongly enhanced antiproliferative potential against drug-resistant leukemia cells and increased cytotoxicities to liver cancer cells as compared with tetrandrine (**1**). Mechanistically, those compounds acted on the intrinsic, mitochondria-initiated apoptosis pathway and/or on activation of the kinase Akt. Considering both their toxicity and the pharmacological profile,

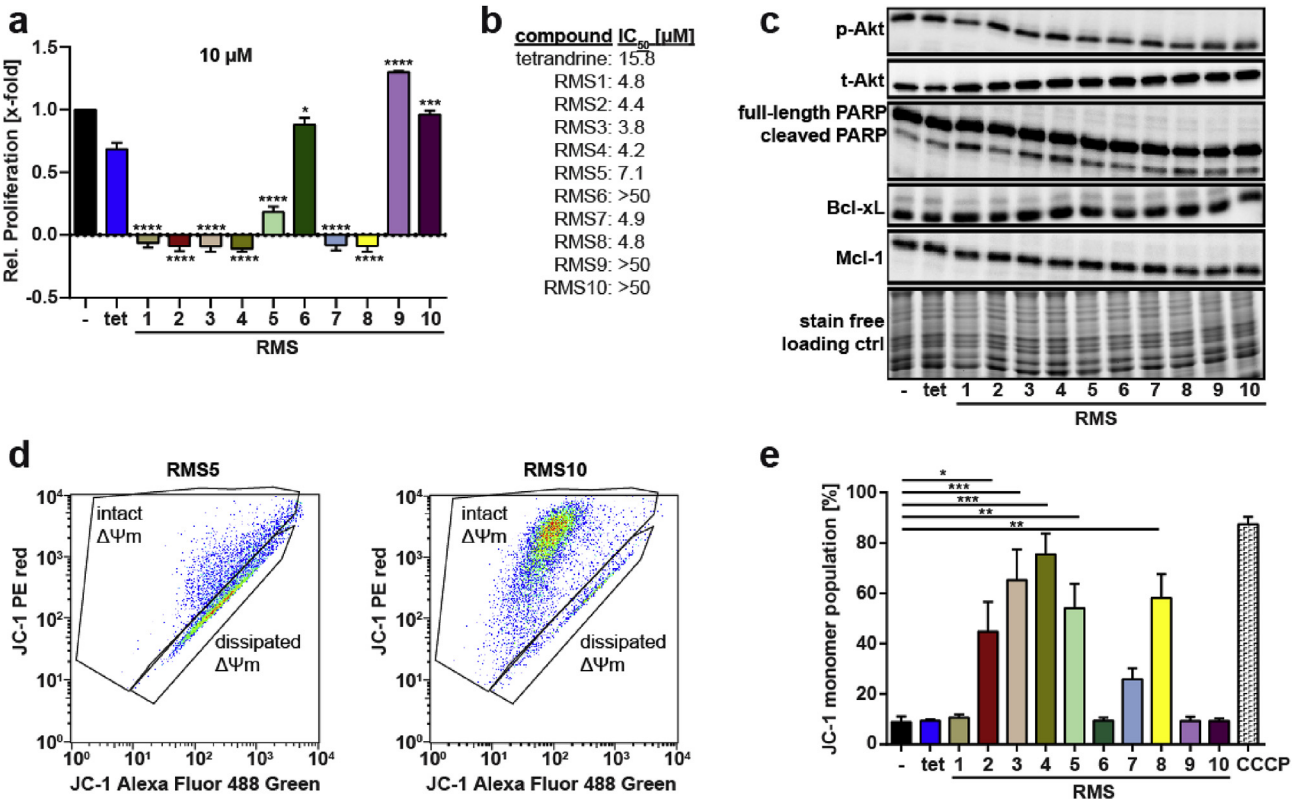


Fig. 5. RMS compounds inhibit proliferation of VCR-R CEM cells and influence the intrinsic apoptosis pathway. (a,b) Antiproliferative effects of tetrandrine (**1**) and **RMS1-RMS10** determined by CellTiter-Blue® cell viability assay after exposure of VCR-R CEM cells to the compounds for 48 h. (a) Relative proliferation at 10 µM (One-Way ANOVA followed by Dunnett's multiple comparison test, relative proliferation was compared with that of tetrandrine, $^{*}P < 0.05$, $^{***}P < 0.001$, $^{****}P < 0.0001$) and (b) IC_{50} values are shown. (c) Immunoblotting of VCR-R CEM cell lysates after exposure to tetrandrine (**1**) and **RMS1-RMS10** (5 µM, 24 h) with antibodies against p-Akt (Ser473), total Akt (t-Akt), PARP and the anti-apoptotic proteins Bcl-xL and Mcl-1. The stain-free technology was used as loading control (ctrl). (d,e) Mitochondrial membrane potential was measured with the fluorescent probe JC-1 after treatment with tetrandrine (**1**) and analogues for 24 h. A shift towards JC-1 green fluorescence serves indicator for reduction of the mitochondrial membrane potential ΔΨm. (d) Gating strategies are exemplarily shown for **RMS5** and **RMS10**. (e) Statistical evaluation of data from (d). Bar graphs indicate means ± SEM of at least three independent experiments (One-Way ANOVA followed by Dunnett's multiple comparison test, $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$). The mitochondrial uncoupler CCCP (100 µM, 1 h) served as positive control. -: solvent control, Rel.: relative, tet: tetrandrine (**1**). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

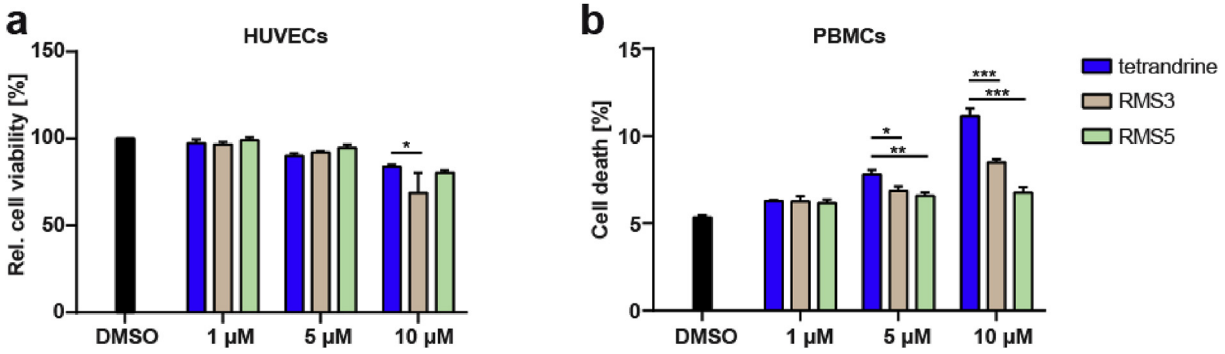


Fig. 6. Toxicity of tetrandrine (**1**), **RMS3** and **RMS5** to other primary cells. (a) Viability of human umbilical vein endothelial cells (HUVECs) after a 24 h exposure (1, 5 and 10 µM) to the compounds was assessed by CellTiter-Blue® cell viability assay. Fluorescence intensities were normalized to vehicle control. Bar graph indicates means ± SEM of three independent experiments (Two-Way ANOVA followed by Dunnett's multiple comparison test, $^{*}P < 0.05$). (b) Cell death of peripheral blood mononuclear cells (PBMCs) from a healthy donor upon treatment with tetrandrine (**1**), **RMS3** and **RMS5** was determined by propidium iodide staining and flow cytometry. Experiment was performed in triplicate (Two-Way ANOVA followed by Dunnett's multiple comparison test, $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

compounds **RMS3** and **RMS5** were found to be most promising, since they possess stronger anticancer properties, while displaying no increased toxicity to healthy liver cells. Similar toxicities to primary cells were confirmed using non-malignant blood and endothelial cells. Side effects might therefore be reduced by lowering the required therapeutic dose and, therefore, our study strongly suggests their investigation using *in vivo* models. Moreover, based on these encouraging data and facilitated by our recent work on effective total synthesis of the bisbenzylisoquinoline alkaloids tetrandrine and isotetrandrine [44], further investigations

regarding structure-activity relationships in this chemical class should be part of future medicinal chemistry projects.

4. Experimental section

4.1. Biological assays

4.1.1. Cell lines and culture

HepaRG™ cells were purchased from Life Technologies (Waltham, USA) and they were plated and maintained in Williams' medium E supplemented with GlutaMAX and HepaRG Thaw, Plate & General Purpose Medium Supplement (Thaw, Plate, & General Purpose Working Medium) (all purchased from Life Technologies). Vincristine-resistant (VCR-R) CEM cells were a kind gift from Prof. Maria Kavallaris (University of New South Wales, Australia) and cultivated with RPMI 1640 (PAN Biotech, Aidenbach, Germany), supplemented with 10% fetal calf serum (FCS) (PAA Laboratories, Toronto, Canada). HepG2 cells were obtained from German Research Centre of Biological Material (DSMZ) and cultivated with DMEM (PAN Biotech), supplemented with 10% fetal calf serum (FCS) (PAA Laboratories). Human umbilical vein endothelial cells (HUVECs) were purchased from Promocell and cultivated with ECGM Kit enhanced (PELO Biotech, Planegg, Germany) supplemented with 10% (FCS) (PAA Laboratories) and 1% penicillin/streptomycin/amphotericin B (all purchased from PAN Biotech). HUVECs were cultured for a maximum of six passages. All cells were cultured at 37 °C with 5% CO_2 with constant humidity are proven to be mycoplasma-free on a quarterly basis.

4.1.2. Molecular cloning

The cDNA template was generated by isolation of mRNA from HepaRG™ progenitor cells (QIAGEN RNeasy Mini Kit) and subsequent reverse transcription (High Capacity cDNA Reverse Transcription Kit, Applied Biosystems, Waltham, USA). cDNA was amplified by PCR (Thermo Scientific Phusion Green Hot Start II High-Fidelity Polymerase, Thermo Fisher, Waltham, USA) (CYP3A4-FW: 5′-ATATATGGTACCGCCACCATGGCTCTCATCCCA-3′, CYP3A4-RV: 5′-ATCTCGAGGGCTCCACTTACGGTGCCA-3′). The obtained PCR product was cloned into the pcDNA3-EGFP vector using FastDigest KpnI, FastDigest XhoI and T4 DNA Ligase (all purchased from Thermo Fisher) as indicated by the manufacturer. pcDNA3-EGFP was a gift from Doug Golenbock (Addgene plasmid #13031; http://n2t.net/addgene:13031; RRID:Addgene_13031). Correct insertion of the insert was confirmed by PCR, restriction digestion and Sanger sequencing. Sequencing services were provided by Eurofins Genomics (Munich, Germany). Primers were purchased from Metabion (Planegg, Germany).

4.1.3. CYP3A4 P450-Glo™ assay

Metabolic activity of CYP3A4-EGFP was confirmed using a CYP3A4 P450-Glo™ assay (Promega, Madison, USA). HepG2 cells were seeded at a density of 0.75×10^6 cells per well into a 24 well plate and allowed to adhere overnight. On the following day, cells were transfected with either pcDNA3-CYP3A4-EGFP or pcDNA3-EGFP using the Lipofectamine™ 3000 (Invitrogen, Waltham, USA) transfection reagent according to the manufacturer's instructions. On the subsequent day, cells were incubated with luciferin-IPA (3 μM) in the presence or absence of ketoconazole (Santa Cruz biotechnology, Dallas, USA) (10 μM) for 60 min. Luminescence was detected using the nonlytic method as described by the manufacturer.

4.1.4. Quantitative real-time PCR

Isolation of mRNA (RNeasy Mini Kit, QIAGEN, Venlo, Netherlands), synthesis of cDNA templates (High Capacity cDNA Reverse Transcription Kit, Applied Biosystems, Waltham, USA) and quantitative real-time PCR (ABI 7300 Real-Time PCR System, Applied Biosystems) with human actin serving as housekeeping gene were performed as described before [58]. Primers were purchased from Metabion. Primer sequences for detecting CYP3A4 mRNA expression were taken from the work of Nozaki and coworkers [59] (FW primer: 5′-GTATGGAAAAGTGTGGGGCT-3′, RV primer: 5′-GACCATCTCCTTGAGTTTTCCA-3′).

4.1.5. Toxicity assays

For assessing the toxicity of tetrandrine and the analogues, several cellular models and approaches were used: differentiated HepaRG™ cells without transfection, differentiated HepaRG™ cells with transient transfection, HepG2 cells with stable transfection, human umbilical vein endothelial cells (HUVECs) and peripheral blood mononuclear cells (PBMCs).

Differentiated HepaRG™ cells without transfection: HepaRG™ cells were differentiated in Williams' medium E supplemented with GlutaMAX and HepaRG Maintenance/Metabolism Medium Supplement (Maintenance/Metabolism Working Medium) (all purchased from Life Technologies) as indicated by the manufacturer. After 24 h treatment with the respective compound concentrations, cell viability was determined by CellTiter-Blue® cell viability assay as described by the manufacturer.

Differentiated HepaRG™ cells with transient transfection with pcDNA3-CYP3A4-EGFP: HepaRG™ cells were differentiated as described above. 16 h prior to stimulation, cells were transfected with either pcDNA3-CYP3A4-EGFP or pcDNA3-EGFP using Lipofectamine™ 3000 (Invitrogen) transfection reagent according to the manufacturer's instructions. Cells were treated as indicated for 24 h. Cell death was assessed by propidium iodide (5 μg/mL in PBS; Carl Roth, Karlsruhe, Germany) staining and flow cytometry using a BD FACS Canto II (BD Biosciences, Becton Dickinson, Franklin Lakes, USA). Data were analyzed using FlowJo 7.6 (BD Biosciences). No FSC/SSC gating was performed. Determination of the percentage of PI-A positive cells was conducted as stated below. Specific cell death was calculated as follows: $specific\ cell\ death\ (\%) = cell\ death\ (x)\ \% - cell\ death\ (control)\%$.

HepG2 cells with stable transfection with CYP3A4-EGFP: HepG2 cells were transfected with either pcDNA3-CYP3A4-EGFP or pcDNA3-EGFP using Lipofectamine™ 3000 (Invitrogen) transfection reagent according to the manufacturer's instructions. Transfected cells were constantly cultivated in the presence of 0.5 mg/mL G418 (Sigma Aldrich, St. Louis, USA) for four weeks. Presence of plasmids was confirmed by PCR (pcDNA3-forward: 5′-TACATCAATGGGCGTGGATAG-3′, pcDNA3-reverse: 5′- AGGAAGGGAAGAAAGCGAAAG-3′). Primers were purchased from metabion. HepG2 cells stably expressing either CYP3A4-EGFP or pcDNA3-EGFP were seeded at a density of 0.1×10^6 cells per well of a 24-well plate and allowed to adhere overnight. Treatment, flow cytometry and data analysis were performed as described for HepaRG™ cells. The natural product tetrandrine was kindly donated by Prof. P. Pachaly and used as free base in all assays. Berbamine (dihydrochloride) was purchased from Sigma-Aldrich (now Merck, Darmstadt, Germany) and Dauricine (free base) from Carbosynth (Compton, Berkshire, United Kingdom).

PBMCs: PBMCs were isolated from anticoagulated whole blood from healthy donors by density gradient centrifugation using Ficoll-Paque PLUS density gradient medium (GE Healthcare, Chicago, USA) as described by the manufacturer. Isolated PBMCs were cultivated in RPMI 1640 supplemented with 20% FCS and 1% penicillin/streptomycin (all purchased from PAN Biotech). 4 h after seeding, cells were treated as indicated for 48 h. Cell death was analyzed by propidium iodide (Carl Roth, Karlsruhe, Germany; 5 μg/mL in PBS) staining and flow cytometry using a BD FACS Canto II

(BD Biosciences). For evaluation, cell debris was excluded and propidium iodide positive cells were determined using FlowJo 7.6 (BD Biosciences).

HUVECs: HUVECs were seeded at a density of 0.125×10^3 cells per well of a 96-well plate and allowed to adhere overnight. After 24 h treatment with the respective compound concentrations, cell viability was determined by CellTiter-Blue® cell viability assay as described by the manufacturer.

4.1.6. Cell proliferation assays

VCR-R CEM cells were seeded at a density of 0.02×10^6 cells per well of a 96-well plate, incubated for 4 h before stimulation with the indicated concentrations of compounds for 48 h. 4 h after seeding, initial metabolic activity was determined and used as zero value. 2 h before the end of stimulation time, CellTiter-Blue® reagent (Promega) was added and fluorescence at 590 nm was detected with a Sunrise ELISA reader (Tecan, Männedorf, Switzerland). Half-maximal inhibitory concentrations (IC_{50}) values were calculated by nonlinear regression using GraphPad Prism 8.4.0 software.

4.1.7. Calcein-AM retention assay

The calcein-AM retention assay was performed as described previously [42].

4.1.8. P-gp cell surface expression

2×10^4 VCR-R CEM cells were incubated in presence of 1 μM of the respective compounds at 37 °C for 1.5 h, then cells were transferred to pre-cooled FACS tubes (BD Biosciences), centrifuged (400 g, 5 min, 4 °C) and washed with ice-cold 1% BSA in PBS. After aspiration, pelleted cells were resuspended in 20 μl of FITC Mouse Anti-Human P-gp antibody (BD Biosciences #557002), diluted with 80 μl PBS per test. Cells were incubated for 30 min at 4 °C in the dark. To determine unspecific antibody binding, FITC Mouse IgG2b κ Isotype Control (BD #58555742) was used (20 μl per test, diluted in 80 μl PBS). Thereafter, cells were washed once with ice-cold 1% BSA (Anprotec, Bruckberg, Germany) in PBS and twice with 0.5% (v/v) Tween 20 (Carl Roth, Karlsruhe, Germany) in PBS and resuspended in ice-cold PBS. Subsequently, cells were analyzed by flow cytometry on a BD FACS Canto II (BD Biosciences).

4.1.9. Apoptosis assay

VCR-R CEM cells were seeded at a density of 0.125×10^6 cells per well of a 24-well plate and incubated for 4 h. Treatment was performed with the indicated concentrations for 48 h. Apoptosis was determined by propidium iodide staining as described before [60] on a BD FACS Canto II (BD Biosciences).

4.1.10. Western blot analysis and antibodies

HepG2 were seeded at a density of 0.5×10^6 cells per well of a 6-well plate and allowed to adhere overnight. VCR-R CEM cells were seeded at a density of 2×10^6 cells per well of a 6-well plate 4 h prior to treatment. Afterwards, cells were treated with DMSO, tetrandrine or the respective RMS compounds (5 μM) for 24 or 48 h as indicated. Cell lysis was performed with RIPA (radioimmunoprecipiation) buffer as described before [58]. Separation of proteins by SDS-PAGE, transfer to Hybond PVDF (polyvinylidene difluoride) membranes (Amersham Bioscience, Little Chalfont, United Kingdom), incubation with primary and secondary antibodies and detection of chemiluminescence on a Chemidoc™ Touch Imaging System (Bio-Rad) were performed as described previously. The following antibodies were used: phospho-Akt (Ser473) (1:1000, Cell Signaling Technologies (CST), Danvers, USA, #9271), total Akt (1:1000, CST, #9272), Bcl-xL (1:1000, CST, #2762), PARP (1:1000, CST, #9542), Mcl-1 (1:1000, CST, #4572). The stain free technology (Bio-Rad, Hercules, USA) [61] was used to confirm equal protein loading using Image Lab 6.0.1 software (Bio-Rad).

4.1.11. Mitochondrial membrane potential

The cationic dye JC-1 (Thermo Fisher) was used to measure mitochondrial membrane potential ($\Delta\Psi m$). When $\Delta\Psi m$ is intact, JC-1 accumulates in mitochondria, yielding a red fluorescence. In contrast, mitochondrial depolarization is indicated by a decrease in the red/green fluorescence intensity. HepG2 cells were seeded at a density of 0.1×10^6 cells per well of a 24-well plate and allowed to adhere overnight. VCR-R CEM cells were seeded at a density of 0.125×10^6 cells per well of a 24-well plate 4 h before treatment. Subsequently, cells were treated for 24 h or 48 h with DMSO or 5 μM of the respective compounds. Cells were incubated with JC-1 (1 μg/mL) for 1 h before cells were harvested (for staining of VCR-R CEM cells, the P-gp inhibitor elacridar (5 μM; Sellekchem Chemicals, Houston, USA) was present to prevent efflux of the mitochondrial uncoupler CCCP (100 μM)), washed with PBS and resuspended in PBS for flow cytometric analysis on a BD FACS Canto II (BD Biosciences). In parallel, compensation samples were prepared using Anti-Mouse Ig, κ/Negative Control (FBS) Compensation Particles Set (BD Biosciences) and a BD PE Mouse IgG1, κ/Isotype Control (BD Biosciences #555749) and a BD Alexa Fluor® 488 Mouse IgG1 κ Isotype Control (BD Biosciences #557721) as described by the manufacturer. Prior to analysis of cellular samples, compensation of spectral overlap was performed on a BD FACS Canto II (BD Biosciences) according to the manufacturer's instructions. The percentage of Alexa-Fluor®-488-A positive populations was determined using FlowJo 7.6 (BD Biosciences).

4.2. Chemistry

4.2.1. General

All solvents and reagents were purchased from commercial suppliers and were used without further purification, unless mentioned otherwise. TLC was carried out on 0.2 mm silica gel polyester plates with a fluorescence indicator (POLYGRAM SIL G/UV254, Macherey-Nagel). NMR spectra were recorded with a 400 MHz (400 MHz for ^1H and 101 MHz for ^{13}C), 500 MHz (500 MHz for ^1H and 126 MHz for ^{13}C) or 800 MHz Bruker Biospin Avance spectrometer (800 MHz for ^1H and 201 MHz for ^{13}C). Peak assignments were based on 2D NMR experiments using standard pulse programs (COSY, HSQC/HMQC, DEPT, HMBC and NOESY). Chemical shifts were referenced to the residual solvent signal ($CDCl_3$: $\delta_H = 7.26$ ppm, $\delta_C = 77.16$ ppm). For the characterization of rotamers a temperature program was employed for recording both 1D and 2D spectra. Hereby chemical shifts were referenced to the signal of tetramethylsilane in deuterated tetrachloroethane (Tcl_2 [100 °C]: $\delta_H = 5.92$ ppm, $\delta_C = 74.0$ ppm). IR spectra were recorded using a Jasco FT/IR-4100 (type A) instrument equipped with a diamond ATR unit (Jasco PRO450-S). High resolution mass spectra (HR-MS) were recorded using a Jeol Mstation 700 or JMS GCmate II Jeol instrument for electron impact ionisation (EI). Thermo Finnigan LTQ was used for electrospray ionisation (ESI). Reaction monitoring by mass spectrometry was performed by atmospheric pressure solids analysis probe (ASAP) *via* atmospheric-pressure chemical ionisation (APCI) on an Advion expression^L CMS device. Purification by flash column chromatography (FCC) was performed using Merck silica gel 60 (0.040−0.063 mm, 230−400 mesh ASTM). For the determination of purity HPLC was performed on a HP Agilent 1100 system equipped with an Agilent 1100/1200 Diode Array Detector and an Agilent Zorbax Eclipse Plus C18-column (5.0 μm, 150 × 4.6 mm) using following method: flow 0.8 mL/min; temperature 50 °C; eluent system for compounds **RMS1**-**10**, **13c**-**d** and **14c**-**e**: 80% MeOH, 20% water, NaOH buffer pH 9; for compounds

13a and **14a**: 50% ACN, 49.9% water, 0.1% THF; for compounds **13b** and **14b**: 70% ACN, 30% water). The purity of all final compounds was >95%.

4.2.2. General procedures

General procedure 1: Wittig olefination: A suspension of (methoxymethyl)triphenylphosphonium chloride (1.2 equiv.) in anhydrous THF (2 mL per mmol aromatic aldehyde) was cooled to 0 °C under nitrogen atmosphere. A solution of lithium diisopropylamide (1.4 equiv., 2.0 M solution in THF) was added dropwise and the resulting mixture stirred for 45 min. A solution of the aromatic aldehyde (1.0 equiv.) in anhydrous THF (2 mL per mmol) was added with stirring. The mixture was allowed to warm up to ambient temperature and stirred for 4 h. The reaction was then quenched with deionized water and extracted 3x with ethyl acetate. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to afford the crude product which was purified by column chromatography.

General procedure 2: N-Acyl Pictet-Spengler condensation: A solution of carbamate (1.0 equiv.) and enol ether (1.2–2.0 equiv.) in dichloromethane (10 mL per mmol carbamate) was cooled to 0 °C under nitrogen atmosphere. Trifluoromethanesulfonic acid (TfOH, 0.1 equiv., 0.113 mol/L in acetonitrile) was added dropwise, the reaction mixture was then allowed to warm up to ambient temperature and stirred for 6–12 h. A saturated $NaHCO_3$ solution was then added for neutralization and the mixture extracted 3x with dichloromethane. The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to afford the crude product which was purified by column chromatography.

General procedure 3: Ullmann-type C–O coupling reaction: According to a modified procedure of Wang et al. [62], bromoarene (1.0–1.2 equiv.), phenol (1.0–2.0 equiv.), $CuBr \cdot Me_2S$ (1.0 equiv.) and Cs_2CO_3 (3.0 equiv.) were placed in a pressure tube or a flask closed with a screwcap with septum inlet and sealed with PTFE tape. Anhydrous pyridine (the reaction was carried out in a concentration of 0.02 mM) was added and after 5 min of pre-stirring the reaction mixture was heated to 110 °C for 2–7 days under nitrogen atmosphere. The reaction mixture was concentrated *in vacuo*, diluted with ethyl acetate and filtered over a small plug of silica gel in order to remove the catalyst and the excess base, followed by washing with ethyl acetate. The filtrate was concentrated *in vacuo* to afford a brown oil as crude product which was purified by column chromatography.

General procedure 4: Carbamate reduction: Lithium alanate (12 equiv.) was suspended in 1 mL anhydrous THF under nitrogen atmosphere. A solution of carbamate (1.0 equiv.) in anhydrous THF (1 mL per 0.02 mmol carbamate) was added dropwise and the resulting mixture was heated at 50 °C for 4–12 h. The reaction mixture was cooled to 0 °C and slowly quenched with water. After alkalizing to pH 12–14 with a 2.0 M sodium hydroxide solution, the mixture was extracted 3x with ethyl acetate. The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to afford the crude product which was purified by column chromatography.

*4.2.3. (E/Z)-3-Bromo-1-(2-methoxyvinyl)benzene (**12a**)*

Prepared from 3-bromobenzaldehyde (1.00 g, 5.41 mmol) following General Procedure 1 (Wittig olefination). Purification was accomplished by flash column chromatography (2.5% ethyl acetate in hexanes, $R_f = 0.25$) to give the title compound as a colourless oil (940 mg, 4.41 mmol, 82%, *E,Z*-isomer ratio 0.92:1, estimated by NMR integrals). NMR data of the major *Z*-isomer: ^{1}H NMR, COSY (400 MHz, $CDCl_3$): δ [ppm] = 7.77 (t, J = 1.8 Hz, 1H, 2-H), 7.43 (dt, J = 7.8, 1.4 Hz, 1H, 6-H), 7.28–7.23 (m, 1H, 4-H), 7.16–7.09 (m, 1H, 5-H), 6.17 (d, J = 7.0 Hz, 1H, 2′-H), 5.15 (d, J = 7.0 Hz, 1H, 1′-H), 3.80 (s, 3H, 2′-OCH_3). ^{13}C NMR, DEPT, HMQC, HMBC (101 MHz, $CDCl_3$): δ [ppm] = 149.2 (C-2′), 138.1 (C-1), 131.0 (C-2), 129.8 (C-5), 128.7 (C-4), 126.8 (C-6), 122.5 (C-3), 104.5 (C-1′), 61.1 (2′-OCH_3). IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3063, 2932, 2833, 1726, 1569, 1474, 1427, 1206, 1070, 782. HRMS (EI): *m/z* calcd for $[C_9H_9^{79}BrO]^{\bullet+}$ 211.9831, found: 211.9829.

*4.2.4. (E/Z)-3-Bromo-1-(2-methoxyvinyl)-4-(trifluoromethoxy) benzene (**12b**)*

Prepared from 3-bromo-4-(trifluoromethoxy)benzaldehyde (300 mg, 1.12 mmol) following General Procedure 1 (Wittig olefination). Purification was accomplished by flash column chromatography (2.5% ethyl acetate in hexanes, $R_f = 0.30$) to give the title compound as a light yellow oil (266 mg, 0.895 mmol, 80%, *E,Z*-isomer ratio 1:0.71, estimated by NMR integrals). NMR data of the major *E*-isomer: ^{1}H NMR, COSY (500 MHz, $CDCl_3$): δ [ppm] = 7.48 (d, J = 2.1 Hz, 1H, 2-H), 7.19 (dd, J = 8.4, 1.4 Hz, 1H, 5-H), 7.15 (dd, J = 8.5, 2.1 Hz, 1H, 6-H), 7.03 (d, J = 13.0 Hz, 1H, 2′-H), 5.71 (d, J = 12.9 Hz, 1H, 1′-H), 3.70 (s, 3H, 2′-OCH_3). ^{13}C NMR, DEPT, HMQC, HMBC (126 MHz, $CDCl_3$): δ [ppm] = 150.6 (C-2′), 144.2 (d, J = 2.0 Hz, C-4), 137.2 (C-1), 130.1 (C-2), 125.1 (C-6), 122.6 (C-5), 120.7 (q, J = 258.7 Hz, OCF_3), 116.5 (C-3), 102.9 (C-1′), 56.9 (2′-OCH_3). IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2940, 2838, 1641, 1492, 1247, 1156, 1096, 932, 833. HRMS (EI): *m/z* calcd for $[C_{10}H_8^{79}BrF_3O_2]^{\bullet+}$ 295.9654, found: 295.9651.

*4.2.5. (E/Z)-4-Bromo-2-(2-methoxyvinyl)thiophene (**12c**)*

Prepared from 4-bromothiophene-2-carboxaldehyde (0.500 mg, 2.62 mmol) following General Procedure 1 (Wittig olefination). Purification was accomplished by flash column chromatography (hexanes, $R_f = 0.28$) to give the title compound as a light yellow oil (471 mg, 2.15 mmol, 82%, *E,Z*-isomer ratio 1:1.13, estimated by NMR integrals). NMR data of the *E*-isomer: ^{1}H NMR, COSY (400 MHz, $CDCl_3$): δ [ppm] = 6.97 (d, J = 12.9 Hz, 1H, 2′-H), 6.89 (d, J = 1.4 Hz, 1H, 5-H), 6.70–6.68 (m, 1H, 3-H), 5.87 (d, J = 12.8 Hz, 1H, 1′-H), 3.67 (s, 3H, OCH_3). ^{13}C NMR, DEPT, HMQC, HMBC (101 MHz, $CDCl_3$): δ [ppm] = 149.9 (C-2′), 141.4 (C-2), 125.0 (C-3), 118.5 (C-5), 109.8 (C-4), 98.6 (C-1′), 57.0 (OCH_3). IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3110, 2933, 2849, 2053, 1727, 1637, 1221, 1093, 819, 722. HRMS (EI): *m/z* calcd for $[C_7H_7^{79}BrOS]^{\bullet+}$ 217.9395, found: 217.9395.

*4.2.6. (E/Z)-3-Bromo-4-chloro-1-(2-methoxyvinyl)benzene (**12d**)*

Prepared from 3-bromo-4-chlorobenzaldehyde (500 mg, 2.28 mmol) following General Procedure 1 (Wittig olefination). Purification was accomplished by flash column chromatography (2.5% ethyl acetate in hexanes, $R_f = 0.36$) to give the title compound as a light yellow oil (490 mg, 1.98 mmol, 87%, *E,Z*-isomer ratio 1.08:1, estimated by NMR integrals). NMR data of the major *E*-isomer: ^{1}H NMR, COSY (500 MHz, $CDCl_3$): δ [ppm] = 7.47 (d, J = 2.1 Hz, 1H, 2-H), 7.30 (d, J = 7.2 Hz, 1H, 5-H), 7.08 (dd, J = 8.3, 2.1 Hz, 1H, 6-H), 7.03 (d, J = 13.0 Hz, 1H, 2′-H), 5.69 (d, J = 13.0 Hz, 1H, 1′-H), 3.69 (s, 3H, OCH_3). ^{13}C NMR, DEPT, HMQC, HMBC (126 MHz, $CDCl_3$): δ [ppm] = 150.3 (C-2′), 137.0 (C-1), 131.0 (C-4), 130.4 (C-5), 130.1 (C-2), 125.1 (C-6), 122.7 (C-3) 103.1 (C-1′), 56.9 (OCH_3). IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2934, 2833, 1701, 1640, 1467, 1192, 1120, 1023, 822. HRMS (EI): *m/z* calcd for $[C_9H_8^{79}Br^{35}ClO]^{\bullet+}$ 245.9442, found: 245.9444.

*4.2.7. 5-Bromo-1-pentanal (**12e**)*

Pyridinium chlorochromate (503 mg, 2.33 mmol, 1.3 equiv.) was suspended in 10 mL anhydrous dichloromethane under nitrogen atmosphere. Then 5-bromo-1-pentanol (300 mg, 1.80 mmol) was added and the mixture was stirred for 6 h at ambient temperature. The volatiles were removed *in vacuo* and purification of the residue by flash column chromatography (25% diethyl ether in hexanes, $R_f = 0.43$) gave the product as a colourless oil (191 mg, 1.16 mmol, 64%). ^{1}H NMR, COSY (400 MHz, $CDCl_3$): δ [ppm] = 9.78 (t, J = 1.5 Hz,

1H, 1-H), 3.42 (t, J = 6.5 Hz, 2H, 5-H), 2.49 (td, J = 7.1, 1.5 Hz, 2H, 2-H), 1.95–1.86 (m, 2H, 4-H), 1.84–1.75 (m, 2H, 3-H). ^{13}C NMR, DEPT, HMQC, HMBC (126 MHz, $CDCl_3$): δ [ppm] = 201.7 (C-1), 42.9 (C-2), 33.0 (C-5), 31.9 (C-4), 20.6 (C-3). IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2954, 2865, 2840, 1725, 1437, 1358, 1122, 1058. HRMS (EI): *m/z* calcd for $[C_5H_9^{79}BrO]^{\bullet+}$ 162.9753, found: 162.9752.

4.2.8. (±)-8-((1-(4-Hydroxybenzyl)-N-(ethoxycarbonyl)-6-methoxy-1,2,3,4-tetrahydroisoquinolin-7-yl)oxy)-N-ethoxycarbonyl-6,7-dimethoxy-1-(3′-bromobenzyl)-1,2,3,4-tetrahydroisoquinoline (**13a**; separable mixture of racemic diastereomers)

Carbamate **11** (250 mg, 0.411 mmol) and enol ether **12a** (160 mg, 0.751 mmol) were condensed following General Procedure 2. The reaction was completed after 4 h. Purification by flash column chromatography (20% ethyl acetate in dichloromethane, R_f = 0.13 (1*R*,1′*R*)/(1*S*,1′*S*) isomers and 0.23 (1*R*,1′*S*)/(1*S*,1′*R*) isomers) gave the title compounds as white solids.

(1*R*,1′*R*)/(1*S*,1′*S*) isomers: yield: 111 mg, 0.141 mmol, 34%. mp: 112.0–113.0 °C. ^{1}H NMR, COSY (400 MHz, Tcl_2, 100 °C) δ [ppm] = 7.30–7.22 (m, 1H, 12-H), 7.18 (t, J = 1.8 Hz, 1H, 10-H), 7.03 (t, J = 7.7 Hz, 1H, 13-H), 6.95 (d, J = 7.6 Hz, 1H, 14-H), 6.81–6.76 (m, 2H, 10′-H, 14′-H), 6.70 (s, 1H, 5′-H), 6.58–6.51 (m, 3H, 5-H, 11′-H, 13′-H), 6.20 (s, 1H, 8′-H), 5.34 (d, J = 9.6 Hz, 1H, 1-H), 5.02 (t, J = 6.5 Hz, 1H, 1′-H), 4.68 (s, 1H, OH), 4.16–4.05 (m, 1H, 3-H), 4.00 (q, J = 7.1 Hz, 2H, ‘O*CH*$_2$CH$_3$), 3.96–3.85 (m, 1H, 3′-H), 3.90 (s, 3H, 6′-OCH_3), 3.85 (s, 3H, 6-OCH_3), 3.88–3.70 (m, 2H, O*CH*$_2$CH$_3$), 3.63 (s, 3H, 7-OCH_3), 3.33 (ddd, J = 13.2, 10.4, 5.0 Hz, 1H, 3-H), 3.18 (ddd, J = 13.3, 9.5, 4.4 Hz, 1H, 3′-H), 3.10 (dd, J = 13.9, 3.6 Hz, 1H, α-H), 2.93–2.85 (m, 1H, 4-H), 2.84 (t, J = 6.8 Hz, 2H, α′-H), 2.81–2.72 (m, 2H, α-H, 4′-H), 2.60 (d, J = 16.4 Hz, 1H, 4-H), 2.54 (dt, J = 16.0, 4.6 Hz, 1H, 4′-H), 1.14 (t, J = 7.0 Hz, 3H, ‘OCH$_2$*CH*$_3$), 0.90 (br s, 3H, OCH$_2$*CH*$_3$). ^{13}C NMR, HSQC, HMBC (101 MHz, Tcl_2, 100 °C) δ [ppm] = 155.5 (‘C=O), 155.3 (C=O), 154.2 (C-12′), 152.7 (C-6), 148.2 (C-6′), 145.9 (C-7′), 141.6 (C-9), 140.9 (C-7), 132.5 (C-10), 130.5 (C-10′, C-14′), 130.5 (C-9′), 130.0 (C-8a′), 129.4 (C-13), 129.2 (C-12), 128.5 (C-4a′), 128.2 (C-14), 123.8 (C-8a), 122.1 (C-11), 115.4 (C-11′, C-13′), 114.1 (C-8′), 113.4 (C-5′), 110.1 (C-5), 61.2 (‘O*CH*$_2$CH$_3$), 61.1 (O*CH*$_2$CH$_3$), 60.7 (7-OCH_3), 56.7 (6′-OCH_3 or 6-OCH_3), 56.6 (6′-OCH_3 or 6-OCH_3), 55.9 (C-1′), 51.9 (C-1), 42.1 (C-α′), 40.1 (C-α), 38.8 (C-3′), 37.4 (C-3), 28.3 (C-4′), 27.9 (C-4), 14.6 (‘OCH$_2$*CH*$_3$), 14.2 (OCH$_2$*CH*$_3$). The resonances of C-8 and C-4a could not be identified. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2930, 1693, 1513, 1426, 1332, 1199, 1112, 1021, 835, 765. Purity (HPLC) = 90% (λ = 210 nm). HRMS (ESI): *m/z* calcd for $[C_{41}H_{45}^{79}BrN_2O_9 + H]^+$ 789.2381, found: 789.2383.

(1*R*,1′*S*)/(1*S*,1′*R*) isomers: yield: 95.0 mg, 0.121 mmol, 29%. mp: 99.0–101.5 °C. ^{1}H NMR, COSY (400 MHz, Tcl_2, 100 °C) δ [ppm] = 7.28 (dt, J = 7.8, 1.6 Hz, 1H, 12-H), 7.24 (s, 1H, 10-H), 7.05 (t, J = 7.7 Hz, 1H, 13-H), 6.99 (d, J = 7.6 Hz, 1H, 14-H), 6.81–6.74 (m, 2H, 10′-H, 14′-H), 6.70 (s, 1H, 5′-H), 6.60–6.53 (m, 2H, 11′-H, 13′-H), 6.52 (s, 1H, 5-H), 6.11 (s, 1H, 8′-H), 5.32 (s, 1H, 1-H), 5.18 (s, 1H, OH), 4.99 (t, J = 6.5 Hz, 1H, 1′-H), 4.15–4.06 (m, 1H, 3-H), 4.01 (q, J = 7.3 Hz, 2H, ‘O*CH*$_2$CH$_3$), 3.96–3.87 (m, 1H, 3′-H), 3.89 (s, 3H, 6′-OCH_3), 3.83 (s, 3H, 6-OCH_3), 3.86–3.76 (m, 2H, O*CH*$_2$CH$_3$), 3.60 (s, 3H, 7-OCH_3), 3.36 (ddd, J = 13.1, 10.0, 4.8 Hz, 1H, 3-H), 3.23 (dd, J = 14.0, 4.1 Hz, 2H, α-H, 3′-H), 2.97–2.83 (m, 3H, α-H, α′-H, 4-H), 2.82–2.72 (m, 2H, α′-H, 4′-H), 2.57 (dt, J = 16.0, 4.5 Hz, 2H, 4′-H, 4-H), 1.15 (t, J = 7.1 Hz, 3H, ‘OCH$_2$*CH*$_3$), 0.96 (s, 3H, OCH$_2$*CH*$_3$). ^{13}C NMR, HSQC, HMBC (101 MHz, Tcl_2, 100 °C) δ [ppm] = 155.5 (C=O, ‘C=O), 154.4 (C-12′), 152.6 (C-6), 148.2 (C-6′), 145.7 (C-7′), 141.6 (C-9), 140.7 (C-7), 132.6 (C-10), 130.5 (C-10′, C-14′), 130.3 (C-9′), 129.4 (C-13), 129.2 (C-12), 129.2 (C-8a′), 128.4 (C-4a′), 128.3 (C-14), 123.4 (C-8a), 122.1 (C-11), 115.3 (C-11′, C-13′), 114.3 (C-8′), 113.3 (C-5′), 109.8 (C-5), 61.2 (O*CH*$_2$CH$_3$, ‘O*CH*$_2$CH$_3$), 60.7 (7-OCH_3), 56.6 (6′-OCH_3, 6-OCH_3), 56.1 (C-1′), 52.0 (C-1), 42.2 (C-α′), 40.2 (C-α), 38.8 (C-3′), 37.8 (C-3), 28.3 (C-4′), 28.1 (C-4), 14.6 (‘OCH$_2$*CH*$_3$), 14.3 (OCH$_2$*CH*$_3$). The resonances of C-8 and C-4a could not be identified. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2935, 1689, 1512, 1426, 1332, 1239, 1112, 1023, 769. Purity (HPLC) = 92% (λ = 210 nm). HRMS (ESI): *m/z* calcd for $[C_{41}H_{45}^{79}BrN_2O_9 + H]^+$ 789.2381, found: 789.2390.

4.2.9. (±)-8-((1-(4-Hydroxybenzyl)-N-(ethoxycarbonyl)-6-methoxy-1,2,3,4-tetrahydroisoquinolin-7-yl)oxy)-N-ethoxycarbonyl-6,7-dimethoxy-1-((3′-bromo-4′-trifluoromethoxy) benzyl)-1,2,3,4-tetrahydroisoquinoline (**13b**.; separable mixture of racemic diastereomers)

Carbamate **11** (250 mg, 0.411 mmol) and enol ether **12b** (146 mg, 0.493 mmol) were condensed following General Procedure 2. The reaction was completed after 12 h. Purification by flash column chromatography (15% ethyl acetate in dichloromethane, R_f = 0.10 (1*R*,1′*R*)/(1*S*,1′*S*) isomers and 0.15 (1*R*,1′*S*)/(1*S*,1′*R*) isomers) gave the title compounds as white solids.

(1*R*,1′*R*)/(1*S*,1′*S*) isomers: yield: 134 mg, 0.153 mmol, 37%. mp: 91.5–92.0 °C. ^{1}H NMR, COSY (400 MHz, Tcl_2, 100 °C) δ [ppm] = 7.31 (d, J = 2.0 Hz, 1H, 10-H), 7.10 (dd, J = 8.4, 1.6 Hz, 1H, 13-H), 6.99 (dd, J = 8.4, 2.1 Hz, 1H, 14-H), 6.81–6.76 (m, 2H, 10′-H, 14′-H), 6.70 (s, 1H, 5′-H), 6.57–6.51 (m, 2H, 11′-H, 13′-H), 6.54 (s, 1H, 5-H), 6.19 (s, 1H, 8′-H), 5.29 (s, 1H, 1-H), 5.02 (t, J = 6.5 Hz, 1H, 1′-H), 4.64 (s, 1H, OH), 4.15–4.03 (m, 1H, 3-H), 4.00 (q, J = 7.0 Hz, 2H, ‘O*CH*$_2$CH$_3$), 3.90 (s, 3H, 6′-OCH_3), 3.85 (s, 3H, 6-OCH_3), 3.97–3.71 (m, 3H, O*CH*$_2$CH$_3$, 3′-H), 3.62 (s, 3H, 7-OCH_3), 3.39–3.29 (m, 1H, 3-H), 3.24–3.13 (m, 1H, 3′-H), 3.11 (dd, J = 13.9, 3.7 Hz, 1H, α-H), 2.91–2.72 (m, 5H, α-H, α′-H, 4′-H, 4-H), 2.62 (d, J = 15.4 Hz, 1H, 4-H), 2.54 (dt, J = 16.0, 4.6 Hz, 1H, 4′-H), 1.14 (t, J = 6.9 Hz, 3H, ’ OCH$_2$*CH*$_3$), 0.88 (br s, 3H, OCH$_2$*CH*$_3$). ^{13}C NMR, HSQC, HMBC (101 MHz, Tcl_2, 100 °C) δ [ppm] = 155.4 (‘C=O), 155.2 (C=O), 154.2 (C-12′), 152.8 (C-6), 148.1 (C-6′), 145.8 (C-7′), 145.0 (C-12), 140.9 (C-7), 139.9 (C-9), 134.8 (C-10), 130.5 (C-10′, C-14′), 130.4 (C-9′), 129.6 (C-14), 129.3 (C-8a′), 123.5 (C-8a), 121.5 (C-13), 115.6 (C-11), 115.4 (C-11′, C-13′), 114.1 (C-8′), 113.4 (C-5′), 110.2 (C-5), 61.2 (‘O*CH*$_2$CH$_3$), 61.1 (O*CH*$_2$CH$_3$), 60.7 (7-OCH_3), 56.7, 56.6 (6′-OCH_3, 6-OCH_3), 55.9 (C-1′), 51.9 (C-1), 42.1 (C-α′), 39.6 (C-α), 38.8 (C-3′), 38.2 (C-3), 28.3 (C-4′), 27.9 (C-4), 14.6 (‘OCH$_2$*CH*$_3$), 14.1 (OCH$_2$*CH*$_3$).The resonances of C-8, C-4a, C-4a′ and OCF_3 could not be identified. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2931, 1668, 1612, 1514, 1426, 1332, 1247, 1168, 1119, 1023, 763. Purity (HPLC) = 85% (λ = 210 nm). HRMS (ESI): *m/z* calcd for $[C_{42}H_{44}^{79}BrF_3N_2O_{10} + H]^+$ 873.2204, found: 873.2217.

(1*R*,1′*S*)/(1*S*,1′*R*) isomers: yield: 91 mg, 0.104 mmol, 25%. mp: 93.5–95.0 °C. ^{1}H NMR, COSY (400 MHz, Tcl_2, 100 °C) δ [ppm] = 7.37 (d, J = 2.0 Hz, 1H, 10-H), 7.12 (dd, J = 8.4, 1.6 Hz, 1H, 13-H), 7.03 (dd, J = 8.4, 2.1 Hz, 1H, 14-H), 6.81–6.72 (m, 2H, 10′-H, 14′-H), 6.70 (s, 1H, 5′-H), 6.59–6.53 (m, 2H, 11′-H, 13′-H), 6.52 (s, 1H, 5-H), 6.09 (s, 1H, 8′-H), 5.29 (d, J = 5.6 Hz, 1H, 1-H), 4.98 (t, J = 6.4 Hz, 1H, 1′-H), 4.10–4.01 (m, 1H, 3-H), 4.02 (q, J = 7.2 Hz, 2H, ‘O*CH*$_2$CH$_3$), 3.88 (s, 3H, 6′-OCH_3), 3.96–3.76 (m, 3H, O*CH*$_2$CH$_3$, 3′-H), 3.83 (s, 3H, 6-OCH_3), 3.58 (s, 3H, 7-OCH_3), 3.37 (ddd, J = 13.3, 10.0, 4.8 Hz, 1H, 3-H), 3.23 (dd, J = 13.8, 4.0 Hz, 2H, α-H, 3′-H), 2.95–2.81 (m, 3H, α-H, α′-H, 4-H), 2.81–2.72 (m, 2H, α′-H, 4′-H), 2.64–2.54 (m, 2H, 4′-H, 4-H), 1.16 (t, J = 7.1 Hz, 3H, ‘OCH$_2$*CH*$_3$), 0.96 (br s, 3H, OCH$_2$*CH*$_3$). ^{13}C NMR, HSQC, HMBC (101 MHz, Tcl_2, 100 °C) δ [ppm] = 155.5 (C=O, ‘C=O), 154.3 (C-12′), 154.2 (C-6), 148.2 (C-6′), 145.6 (C-7′), 145.2 (C-12), 143.1 (C-7), 139.9 (C-9), 135.0 (C-10), 130.6 (C-10′, C-14′), 130.4 (C-9′), 130.0 (C-8a′), 129.7 (C-14), 123.0 (C-8a), 121.9 (C-13), 115.3 (C-11), 115.3 (C-11′, C-13′), 114.4 (C-8′), 113.3 (C-5′), 109.8 (C-5), 61.3

('OCH_2CH_3), 61.2 (OCH_2CH_3), 60.7 (7-OCH_3), 56.6, 56.5 (6′-OCH_3, 6-OCH_3), 56.5 (C-1′), 52.0 (C-1), 42.2 (C-α′), 39.7 (C-α), 38.9 (C-3′), 38.0 (C-3), 28.3 (C-4′), 28.1 (C-4), 14.6 ('OCH_2CH_3), 14.3 (OCH_2CH_3). The resonances of C-8, C-4a, C-4a′ and OCF_3 could not be identified. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2922, 1668, 1613, 1514, 1455, 1333, 1253, 1170, 1120, 1024, 764. Purity (HPLC) = 90% (λ = 210 nm). HRMS (ESI): *m/z* calcd for $[C_{42}H_{44}^{79}BrF_3N_2O_{10} + H]^+$ 873.2204, found: 873.2217.

*4.2.10. (±)-8-((1-(4-Hydroxybenzyl)-N-(ethoxycarbonyl)-6-methoxy-1,2,3,4-tetrahydroisoquinolin-7-yl)oxy)-N-ethoxycarbonyl-6,7-dimethoxy-1-((4′-bromothiophen-2′-yl) methyl)-1,2,3,4-tetrahydroisoquinoline (**13c**; separable mixture of racemic diastereomers)*

Carbamate **11** (300 mg, 0.493 mmol) and enol ether **12c** (130 mg, 0.591 mmol) were condensed following General Procedure 2. The reaction was completed after 12 h. Purification by flash column chromatography (15% ethyl acetate in dichloromethane, R_f = 0.10 (1*R*,1′*R*)/(1*S*,1′*S*) isomers and 0.15 (1*R*,1′*S*)/(1*S*,1′*R*) isomers) gave the title compounds as white solids.

(1*R*,1′*R*)/(1*S*,1′*S*) isomers: yield: 137 mg, 0.172 mmol, 35%. mp: 108.5–114.5 °C. ^{1}H NMR, COSY (400 MHz, Tcl_2, 100 °C) δ [ppm] = 6.96 (d, *J* = 1.4 Hz, 1H, 12-H), 6.81–6.77 (m, 2H, 14′-H and 10′-H), 6.68 (s, 1H, 5′-H), 6.58 (s, 1H, 10-H), 6.57–6.54 (m, 2H, 13′-H and 11′-H), 6.52 (s, 1H, 5-H), 6.22 (s, 1H, 8′-H), 5.33 (d, *J* = 9.5 Hz, 1H, 1-H), 5.02 (t, *J* = 6.4 Hz, 1H, 1′-H), 4.58 (s, 1H, OH), 4.11–4.05 (m, 1H, 3-H), 4.01 (q, *J* = 7.0 Hz, 2H, 'OCH_2CH_3), 3.94–3.81 (m, 3H, 3′-H, OCH_2CH_3), 3.87 (s, 3H, 6′-OCH_3), 3.85 (s, 3H, 6-OCH_3), 3.61 (s, 3H, 7-OCH_3), 3.31 (dd, *J* = 15.2, 3.7 Hz, 1H, α-H), 3.29–3.12 (m, 2H, 3-H, 3′-H), 3.01 (dd, *J* = 15.1, 9.3 Hz, 1H, α-H), 2.84 (dd, *J* = 9.1, 6.5 Hz, 1H, α′-H), 2.91–2.72 (m, 3H, 4-H, 4′-H, α′-H), 2.56 (ddd, *J* = 20.0, 11.4, 3.9 Hz, 2H, 4-H, 4′-H), 1.14 (t, *J* = 7.0 Hz, 3H, 'OCH_2CH_3), 1.01 (br s, 3H, OCH_2CH_3). ^{13}C NMR, HSQC, HMBC (101 MHz, Tcl_2, 100 °C) δ [ppm] = 155.5 (C=O or C=O′), 155.4 (C=O or C=O′), 154.2 (C-12′), 152.8 (C-6), 148.4 (C-6′), 146.0 (C-7′), 142.6 (C-9), 140.8 (C-7), 130.6 (C-14′ and C-10′), 130.4 (C-9′), 129.3 (C-8a′), 128.6 (C-10), 123.1 (C-8a), 121.3 (C-12), 115.4 (C-13′ and C-11′), 114.4 (C-8′), 113.5 (C-5′), 110.0 (C-5), 108.9 (C-11), 61.3 (OCH_2CH_3), 61.2 ('OCH_2CH_3), 60.7 (7-OCH_3), 56.6 (6-OCH_3 or 6′-OCH_3), 56.5 (6-OCH_3 or 6′-OCH_3), 55.9 (C-1′), 51.9 (C-1), 42.1 (C-α′), 38.7 (C-3′), 37.6 (C-3), 34.6 (C-α), 28.3 (C-4′), 27.9 (C-4), 14.6 ('OCH_2CH_3), 14.3 (OCH_2CH_3). The resonances of C-8, C-4a and C-4a′ could not be identified. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2927, 2843, 1667, 1513, 1422, 1331, 1222, 1109, 1023, 821, 764. Purity (HPLC) = 93% (λ = 210 nm). HRMS (ESI): *m/z* calcd for $[C_{39}H_{43}^{79}BrN_2O_9S-H]^-$ 793.1800, found: 793.1829.

(1*R*,1′*S*)/(1*S*,1′*R*) isomers: yield: 130 mg, 0.163 mmol, 33%. mp: 110.0–119.5 °C. ^{1}H NMR, COSY (400 MHz, Tcl_2, 100 °C) δ [ppm] = 6.98 (d, *J* = 1.4 Hz, 1H, 12-H), 6.80–6.76 (m, 2H, 14′-H, 10′-H), 6.68 (s, 1H, 5′-H), 6.62 (s, 1H, 10-H), 6.59–6.54 (m, 2H, 13′-H and 11′-H), 6.50 (s, 1H, 5-H), 6.11 (s, 1H, 8′-H), 5.29 (d, *J* = 7.0 Hz, 1H, 1-H), 4.99 (t, *J* = 6.6 Hz, 1H, 1′-H), 4.02 (q, *J* = 7.2 Hz, 3H, 3′-H, 'OCH_2CH_3), 4.00–3.88 (m, 3H, 3-H, OCH_2CH_3), 3.86 (s, 3H, 6′-OCH_3), 3.83 (s, 3H, 6-OCH_3), 3.58 (s, 3H, 7-OCH_3), 3.45 (dd, *J* = 15.2, 3.9 Hz, 1H, α-H), 3.35–3.20 (m, 2H, 3-H, 3′-H), 3.08 (dd, *J* = 15.1, 8.9 Hz, 1H, α-H), 2.93–2.81 (m, 2H, 4′-H, α′-H), 2.77 (dd, *J* = 13.9, 7.0 Hz, 2H, 4-H, α′-H), 2.63–2.51 (m, 2H, 4-H, 4′-H), 1.16 (t, *J* = 7.1 Hz, 3H, 'OCH_2CH_3), 1.07 (br s, 3H, OCH_2CH_3). ^{13}C NMR, HSQC, HMBC (101 MHz, Tcl_2, 100 °C) δ [ppm] = 155.7 (C=O or C=O′), 155.5 (C=O or C=O′), 154.3 (C-12′), 152.8 (C-6), 148.3 (C-6′), 145.7 (C-7′), 142.6 (C-9), 140.7 (C-7), 130.6 (C-14′ and C-10′), 130.4 (C-9′), 129.2 (C-8a′), 128.7 (C-10), 122.6 (C-8a), 121.3 (C-12), 115.3 (C-13′ and C-11′), 114.6 (C-8′), 113.4 (C-5′), 109.7 (C-5), 108.9 (C-11), 61.4 (OCH_2CH_3), 61.2 ('OCH_2CH_3), 60.7 (7-OCH_3), 56.5 (6-OCH_3 and 6′-OCH_3), 56.1 (C-1′), 52.0 (C-1), 42.2 (C-α′), 38.9 (C-3), 38.0 (C-3′), 34.6 (C-α), 28.3 (C-4′), 28.0 (C-4), 14.6 ('OCH_2CH_3), 14.5 (OCH_2CH_3). The resonances of C-8, C-4a and C-4a′ could not be identified. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2936, 1690, 1511, 1421, 1221, 1099, 1022, 819,764. Purity (HPLC) = 95% (λ = 210 nm). HRMS (ESI): *m/z* calcd for $[C_{39}H_{43}^{79}BrN_2O_9S-H]^-$ 793.1800, found: 793.1829.

*4.2.11. (±)-8-((1-(4-Hydroxybenzyl)-N-(ethoxycarbonyl)-6-methoxy-1,2,3,4-tetrahydroisoquinolin-7-yl)oxy)-N-ethoxycarbonyl-6,7-dimethoxy-1-(3′-bromo-4′-chlorobenzyl)-1,2,3,4-tetrahydroisoquinoline (**13d**; separable mixture of racemic diastereomers)*

Carbamate **11** (350 mg, 0.575 mmol) and enol ether **12d** (171 mg, 0.695 mmol) were condensed following General Procedure 2. The reaction was completed after 12 h. Purification by flash column chromatography (15% ethyl acetate in dichloromethane, R_f = 0.09 (1*R*,1′*R*)/(1*S*,1′*S*) isomers and 0.13 (1*R*,1′*S*)/(1*S*,1′*R*) isomers) gave the title compound as a white solid.

(1*R*,1′*R*)/(1*S*,1′*S*) isomers: yield: 128 mg, 0.155 mmol, 27%. mp: 84.0–88.0 °C. ^{1}H NMR, COSY (400 MHz, Tcl_2, 100 °C) δ [ppm] = 7.28 (d, *J* = 2.0 Hz, 1H, 10-H), 7.24 (d, *J* = 8.2 Hz, 1H, 13-H), 6.91 (dd, *J* = 8.1, 2.0 Hz, 1H, 14-H), 6.81–6.76 (m, 2H, 14′-H and 10′-H), 6.70 (s, 1H, 5′-H), 6.57–6.52 (m, 2H, 13′-H and 11′-H), 6.54 (s, 1H, 5-H), 6.19 (s, 1H, 8′-H), 5.34–5.27 (m, 1H, 1-H), 5.02 (t, *J* = 6.3 Hz, 1H, 1′-H), 4.66 (s, 1H, OH), 4.15–4.04 (m, 1H, 3-H), 4.00 (q, *J* = 6.9 Hz, 2H, 'OCH_2CH_3), 3.89 (s, 3H, 6′-OCH_3), 3.85 (s, 3H, 6-OCH_3), 3.93–3.74 (m, 3H, OCH_2CH_3, 3′-H), 3.62 (s, 3H, 7-OCH_3), 3.37–3.26 (m, 1H, 3-H), 3.24–3.13 (m, 2H, 3′-H), 3.07 (dd, *J* = 14.0, 3.8 Hz, 1H, α-H), 2.92–2.73 (m, 5H, 4-H, α-H, 4′-H, α′-H), 2.61 (d, *J* = 14.5 Hz, 1H, 4-H), 2.54 (dt, *J* = 16.1, 4.5 Hz, 1H, 4′-H), 1.14 (t, *J* = 7.0 Hz, 3H, 'OCH_2CH_3), 0.90 (br s, 3H, OCH_2CH_3). ^{13}C NMR, HSQC, HMBC (101 MHz, Tcl_2, 100 °C) δ [ppm] = 155.4 (C=O or C=O′), 155.3 (C=O or C=O′), 154.2 (C-12′), 152.7 (C-6), 148.2 (C-6′), 145.8 (C-7′), 140.9 (C-7), 139.7 (C-9), 134.6 (C-10), 132.1 (C-12), 130.5 (C-14′ and C-10′), 130.5 (C-9′), 129.7 (C-13 or C-14), 129.6 (C-13 or C-14), 129.2 (C-8a′), 128.6 (C-4a′), 123.5 (C-8a), 121.8 (C-11), 115.4 (C-13′ and C-11′), 114.1 (C-8′), 113.4 (C-5′), 110.1 (C-5), 61.2 (OCH_2CH_3 and 'OCH_2CH_3), 60.7 (7-OCH_3), 56.7 (6-OCH_3), 56.6 (6′-OCH_3), 55.9 (C-1′), 51.9 (C-1), 42.1 (C-α′), 39.6 (C-α), 38.8 (C-3′), 37.5 (C-3), 28.3 (C-4′), 27.9 (C-4), 14.6 ('OCH_2CH_3), 14.2 (OCH_2CH_3). The resonances of C-8 and C-4a could not be identified. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3174, 1689, 1509, 1419, 1201, 1097, 1021, 762. Purity (HPLC) = 89% (λ = 210 nm). HRMS (ESI): *m/z* calcd for $[C_{41}H_{44}^{79}Br^{35}ClN_2O_9 - H]^-$ 821.1846, found: 821.1851.

(1*R*,1′*S*)/(1*S*,1′*R*) isomers: yield: 122 mg, 0.150 mmol, 26%. mp: 106.5–108.5 °C. ^{1}H NMR, COSY (400 MHz, Tcl_2, 100 °C) δ [ppm] = 7.34 (d, *J* = 2.0 Hz, 1H, 10-H), 7.25 (d, *J* = 8.1 Hz, 1H, 13-H), 6.95 (dd, *J* = 8.2, 2.0 Hz, 1H, 14-H), 6.80–6.75 (m, 2H, 14′-H and 10′-H), 6.69 (s, 1H, 5′-H), 6.58–6.53 (m, 2H, 13′-H and 11′-H), 6.51 (s, 1H, 5-H), 6.08 (s, 1H, 8′-H), 5.28 (d, *J* = 8.5 Hz, 1H, 1-H), 4.98 (t, *J* = 6.7 Hz, 1H, 1′-H), 4.02 (q, *J* = 6.9 Hz, 3H, 3′-H, 'OCH_2CH_3), 3.88 (s, 3H, 6′-OCH_3), 3.87 (ddd, *J* = 25.0, 16.3, 5.2 Hz, 3H, 3-H, OCH_2CH_3), 3.83 (s, 3H, 6-OCH_3), 3.58 (s, 3H, 7-OCH_3), 3.36 (ddd, *J* = 13.2, 9.9, 4.7 Hz, 1H, 3′-H), 3.28–3.22 (m, 1H, 3-H), 3.20 (dd, *J* = 13.8, 4.1 Hz, 1H, α-H), 2.93–2.83 (m, 3H, α-H, 4′-H, α′-H), 2.82–2.73 (m, 2H, 4-H, α′-H), 2.63–2.54 (m, 2H, 4-H, 4′-H), 1.15 (t, *J* = 7.1 Hz, 3H, 'OCH_2CH_3), 0.99 (br s, 3H, OCH_2CH_3). ^{13}C NMR, HSQC, HMBC (101 MHz, Tcl_2, 100 °C) δ [ppm] = 155.5 (C=O), 155.5 (C=O′), 154.4 (C-12′), 152.7 (C-6), 148.2 (C-6′), 145.6 (C-7′), 140.7 (C-7), 139.7 (C-9), 134.7 (C-10), 132.1 (C-12), 130.6 (C-14′ and C-10′), 130.4 (C-9′), 129.7 (C-14), 129.7 (C-13), 129.2 (C-8a′), 128.5 (C-4a′), 123.1 (C-8a), 121.8 (C-11), 115.3 (C-13′ and C-11′), 114.4 (C-8′), 113.3 (C-5′), 109.8 (C-5), 61.3 (OCH_2CH_3), 61.2 ('OCH_2CH_3), 60.7 (7-OCH_3), 56.6 (6-OCH_3 and 6′-OCH_3), 56.1 (C-1′), 52.0 (C-1), 42.2 (C-α′), 39.8 (C-α), 38.8 (C-3), 38.0 (C-3′), 28.3 (C-4′), 28.1 (C-4), 14.6 ('OCH_2CH_3), 14.3 (OCH_2CH_3). The resonances of C-8 and C-4a could not be identified. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 3355, 2841, 1689, 1668, 1514, 1424, 1331, 1203, 1110, 1023, 765. Purity (HPLC) = 95% (λ = 210 nm). HRMS (ESI): *m/z* calcd for $[C_{41}H_{44}^{79}Br^{35}ClN_2O_9 - H]^-$ 821.1846, found: 821.1852.

*4.2.12. (±)-8-((1-(4-Hydroxybenzyl)-N-(ethoxycarbonyl)-6-methoxy-1,2,3,4-tetrahydroisoquinolin-7-yl)oxy)-N-ethoxycarbonyl-6,7-dimethoxy-1-(4-bromobutyl)-1,2,3,4-tetrahydroisoquinoline (**13e**; separable mixture of racemic diastereomers)*

Carbamate **11** (300 mg, 0.493 mmol) and aldehyde **12e** (98 mg, 0.591 mmol) were condensed following General Procedure 2. The reaction was completed after 12 h. Purification by flash column chromatography (15% ethyl acetate in dichloromethane, R_f = 0.10 (precursor of **RMS10**) and 0.16 (precursor of **RMS9**)) gave the title compound as a white solid.

Precursor of **RMS10**: yield: 133 mg, 0.178 mmol, 36%. mp: 77.5–78.0 °C. ^{1}H NMR, COSY (400 MHz, Tcl_2, 100 °C) δ [ppm] = 6.80–6.75 (m, 2H, 14′-H and 10′-H), 6.65 (s, 1H, 5′-H), 6.62–6.58 (m, 2H, 13′-H and 11′-H), 6.52 (s, 1H, 5-H), 6.19 (s, 1H, 8′-H), 5.12 (s, 1H, 1-H), 5.02 (t, J = 6.5 Hz, 1H, 1′-H), 4.14–3.94 (m, 6H, 3-H, 3′-H, ‘OCH_2CH$_3$, OCH_2CH$_3$), 3.86 (s, 3H, 6′-OCH$_3$), 3.82 (s, 3H, 6-OCH$_3$), 3.58 (s, 3H, 7-OCH$_3$), 3.27 (t, J = 6.9 Hz, 2H, 4″-H), 3.26–3.20 (m, 1H, 3-H), 3.16 (ddd, J = 13.5, 9.7, 4.4 Hz, 1H, 3′-H), 2.93–2.84 (m, 1H, 4-H), 2.82 (t, J = 5.5 Hz, 1H, α′-H), 2.78–2.72 (m, 1H, 4′-H), 2.68 (dt, J = 16.5, 4.5 Hz, 1H, 4-H), 2.51 (dt, J = 16.0, 4.6 Hz, 1H, 4′-H), 1.86–1.68 (m, 3H, 1″-H, 3″-H), 1.68–1.56 (m, 1H, 1″-H), 1.47–1.38 (m, 2H, 2″-H), 1.13 (t, J = 7.0 Hz, 6H, ‘OCH$_2$CH_3 and OCH$_2$CH_3). ^{13}C NMR, HSQC, HMBC (101 MHz, Tcl_2, 100 °C) δ [ppm] = 155.7 (‘C═O), 155.4 (C═O), 154.5 (C-12′), 152.4 (C-6), 148.2 (C-6′), 146.3 (C-7′), 145.1 (C-8), 140.6 (C-7), 130.4 (C-14′ and C-10′), 130.1 (C-9′), 129.6 (C-8a′), 129.3 (C-4a), 128.3 (C-4a′), 125.1 (C-8a), 115.4 (C-13′ and C-11′), 114.2 (C-8′), 113.6 (C-5′), 110.2 (C-5), 61.2 (‘OCH_2CH$_3$ or OCH_2CH$_3$), 61.1 (‘OCH_2CH$_3$ or OCH_2CH$_3$), 60.6 (7-OCH$_3$), 56.7 (6-OCH$_3$ or 6′-OCH$_3$), 56.6 (6-OCH$_3$ or 6′-OCH$_3$), 55.8 (C-1′), 50.1 (C-1), 42.1 (C-α′), 38.6 (C-3′), 37.4 (C-3), 33.7 (C-1″), 33.6 (C-4″), 32.3 (C-3″), 28.2 (C-4′), 27.8 (C-4), 24.9 (C-2″), 14.6 (‘OCH$_2$CH_3), 14.5 (OCH$_2$CH_3). IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2928, 2854, 2605, 2498, 1692, 1513, 1426, 1331, 1234, 1100, 1026, 767. Purity (HPLC) = 95% (λ = 210 nm). HRMS (ESI): *m/z* calcd for [$C_{38}H_{47}^{79}BrN_2O_9$ + H]$^+$ 755.2538, found: 755.2548.

Precursor of **RMS9**: yield: 85.5 mg, 0.113 mmol, 23%. mp: 200.5 °C. ^{1}H NMR, COSY (400 MHz, Tcl_2, 100 °C) δ [ppm] = 6.81–6.75 (m, 2H, 14′-H and 10′-H), 6.66 (s, 1H, 5′-H), 6.60–6.55 (m, 2H, 13′-H and 11′-H), 6.49 (s, 1H, 5-H), 6.10 (s, 1H, 8′-H), 5.15–5.07 (m, 1H, 1-H), 4.97 (t, J = 6.6 Hz, 1H, 1′-H), 4.16–3.97 (m, 6H, 3-H, 3′-H, ‘OCH_2CH$_3$, OCH_2CH$_3$), 3.85 (s, 3H, 6′-OCH$_3$), 3.81 (s, 3H, 6-OCH$_3$), 3.56 (s, 3H, 7-OCH$_3$), 3.33 (t, J = 6.9 Hz, 2H, 4″-H), 3.30–3.20 (m, 2H, 3-H, 3′-H), 2.96–2.85 (m, 2H, 4-H, α′-H), 2.84–2.74 (m, 2H, 4′-H, α′-H), 2.69 (dt, J = 16.2, 4.4 Hz, 1H, 4-H), 2.57 (dt, J = 15.5, 4.4 Hz, 1H, 4′-H), 1.91–1.78 (m, 3H, 1″-H, 3″-H), 1.73–1.61 (m, 1H, 1″-H), 1.51–1.40 (m, 2H, 2″-H), 1.21–1.12 (m, 6H, ‘OCH$_2$CH_3 and OCH$_2$CH_3). ^{13}C NMR, HSQC, HMBC (101 MHz, Tcl_2, 100 °C) δ [ppm] = 155.9 (C═O or C═O′), 155.5 (C═O or C═O′), 154.4 (C-12′), 152.4 (C-6), 148.4 (C-6′), 146.1 (C-7′), 145.3 (C-8), 140.5 (C-7), 130.6 (C-14′ and C-10′), 130.4 (C-9′), 129.6 (C-8a′), 124.7 (C-8a), 115.3 (C-13′ and C-11′), 114.7 (C-8′), 113.5 (C-5′), 109.8 (C-5), 61.3 (‘OCH_2CH$_3$ or OCH_2CH$_3$), 61.2 (‘OCH_2CH$_3$ or OCH_2CH$_3$), 60.6 (7-OCH$_3$), 56.7 (6-OCH$_3$ or 6′-OCH$_3$), 56.5 (6-OCH$_3$ or 6′-OCH$_3$), 56.1 (C-1′), 50.3 (C-1), 42.2 (C-α′), 38.9 (C-3′), 37.8 (C-3), 33.9 (C-1″), 33.6 (C-4″), 32.5 (C-3″), 28.3 (C-4′), 28.1 (C-4), 25.0 (C-2″), 14.6 (‘OCH$_2$CH_3 and OCH$_2$CH_3). The resonances of C-4a and C-4a′ could not be identified. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2927, 2851, 1690, 1611, 1513, 1427, 1332, 1233, 1100, 1023, 806, 761. Purity (HPLC) = 93% (λ = 210 nm). HRMS (ESI): *m/z* calcd for [$C_{38}H_{47}^{79}BrN_2O_9$ + H]$^+$ 755.2538, found: 755.2558.

*4.2.13. (±)-N,N′-Bis-(ethoxycarbonyl)-12-desmethoxy-bisnortetrandrine and −isotetrandrine (**14a**)*

Previously separated diastereomers of bisbenzylisoquinoline **13a** (50.0 mg, 0.0633 mmol of each diastereomer) were reacted following General Procedure 3. The reactions were completed after 42 h. Purification was accomplished by flash column chromatography (30% acetone in hexanes, R_f = 0.18) and the products obtained as beige solids.

(1*R*,1′*R*)/(1*S*,1′*S*) isomers: yield: 34.6 mg, 0.0488 mmol, 77%. mp: 83.0–83.5 °C. ^{1}H NMR, COSY (400 MHz, Tcl_2, 100 °C) δ [ppm] = 7.39 (d, J = 8.4 Hz, 1H, 10′-H or 14′-H), 7.14 (t, J = 7.8 Hz, 1H, 13-H), 7.10 (dd, J = 8.1, 2.5 Hz, 1H, 11′-H or 13′-H), 6.97 (dd, J = 8.1, 2.5 Hz, 1H, 12-H), 6.64 (s, 1H, 5′-H), 6.70–6.60 (m, 2H, 11′-H or 13′-H, 14-H), 6.48 (t, J = 1.9 Hz, 1H, 10-H), 6.33 (s, 1H, 5-H), 6.22–6.16 (m, 1H, 10′-H or 14′-H), 6.18 (s, 1H, 8′-H), 5.31 (dd, J = 8.1, 3.6 Hz, 1H, 1-H), 5.05 (d, J = 10.4 Hz, 1H, 1′-H), 4.36–4.21 (m, 3H, ‘OCH_2CH$_3$, 3-H), 3.99 (ddd, J = 12.2, 5.7, 3.5 Hz, 1H, 3′-H), 3.86–3.76 (m, 2H, OCH_2CH$_3$), 3.74 (s, 3H, 6-OCH$_3$), 3.49 (dd, J = 13.5, 5.0 Hz, 1H, α′-H), 3.41 (td, J = 11.7, 4.8 Hz, 2H, 3′-H, 3-H), 3.34 (s, 3H, 6′-OCH$_3$), 3.26 (s, 3H, 7-OCH$_3$), 3.19–3.08 (m, 1H, 4′-H), 2.95–2.80 (m, 2H, 4′-H, 4-H), 2.80–2.72 (m, 2H, α-H), 2.71–2.59 (m, 2H, α′-H, 4-H), 1.36 (t, J = 6.8 Hz, 3H, ‘OCH$_2$CH_3), 0.89 (br s, 3H, OCH$_2$CH_3). ^{13}C NMR, HSQC, HMBC (101 MHz, Tcl_2, 100 °C) δ [ppm] = 160.3 (C-11), 155.9 (C═O or ‘C═O), 155.6 (C═O or ‘C═O), 154.2 (C-12′), 152.1 (C-6), 149.1 (C-6′), 147.0 (C-8), 144.9 (C-7′), 142.0 (C-9), 138.9 (C-7), 134.6 (C-9′), 132.2 (C-10′ or C-14′), 130.1 (C-10′ or C-14′), 129.1 (C-13), 128.8 (C-8a′), 128.2 (C-4a′), 122.9 (C-8a), 122.2 (C-14), 122.0 (C-11′ or C-13′), 121.6 (C-11′ or C-13′), 119.7 (C-8′), 115.4 (C-10, C-12), 114.0 (C-5′), 107.3 (C-5), 61.4 (‘OCH$_2$CH$_3$), 60.7 (OCH$_2$CH$_3$), 60.3 (7-OCH$_3$), 57.7 (C-1′), 57.0 (6′-OCH$_3$), 56.3 (6-OCH$_3$), 53.5 (C-1), 42.0 (C-α′), 3′, 41.6 (C-α), 36.6 (C-3), 28.0 (C-4), 27.9 (C-4′), 14.8 (OCH$_2$CH$_3$, ‘OCH$_2$CH$_3$). The resonance of C-4a could not be identified. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2925, 2854, 1691, 1586, 1506, 1417, 1332, 1278, 1211, 1107, 1025, 839, 765. Purity (HPLC) = 100% (λ = 210 nm). HRMS (ESI): *m/z* calcd for [$C_{41}H_{44}N_2O_9$ + H]$^+$ 709.3120, found: 709.3125.

(1*R*,1′*S*)/(1*S*,1′*R*) isomers: yield: 18 mg, 0.0254 mmol, 40%. mp: 92.0–93.5 °C. ^{1}H NMR, COSY (400 MHz, Tcl_2, 100 °C) δ [ppm] = 7.36 (d, J = 8.2 Hz, 1H, 10′-H or 14′-H), 7.11 (t, J = 7.8 Hz, 1H, 13-H), 7.05 (d, J = 7.2 Hz, 1H, 11′-H or 13′-H), 6.94 (dd, J = 8.2, 2.5 Hz, 1H, 12-H), 6.64 (s, 1H, 5′-H), 6.66–6.60 (m, 2H, 11′-H or 13′-H, 14-H), 6.40–6.32 (m, 2H, 10-H, 10′-H or 14′-H), 6.28 (s, 1H, 5-H), 6.20 (s, 1H, 8′-H), 5.29 (d, J = 9.4 Hz, 1H, 1-H), 5.11 (dd, J = 9.8, 6.5 Hz, 1H, 1′-H), 4.29–4.15 (m, 3H, ‘OCH_2CH$_3$, 3-H), 3.97–3.89 (m, 1H, 3′-H), 3.88–3.76 (m, 2H, OCH_2CH$_3$), 3.73 (s, 3H, 6-OCH$_3$), 3.60 (s, 3H, 6′-OCH$_3$), 3.57–3.51 (m, 1H, α′-H), 3.49–3.41 (m, 1H, 3′-H), 3.37–3.27 (m, 1H, 3-H), 3.21–3.14 (m, 2H, α-H, 4′-H), 3.16 (s, 3H, 7-OCH_3), 2.88–2.76 (m, 2H, 4′-H, 4-H), 2.71 (dd, J = 12.8, 10.5 Hz, 1H, α′-H), 2.62 (dd, J = 13.7, 9.6 Hz, 1H, α-H), 2.53–2.42 (m, 1H, 4-H), 1.33 (t, J = 7.1 Hz, 3H, ‘OCH$_2$CH_3), 0.96 (br s, 3H, OCH$_2$CH_3). ^{13}C NMR, HSQC, HMBC (101 MHz, Tcl_2, 100 °C) δ [ppm] = 160.4 (C-11), 155.8, 155.4 (‘C═O, C═O), 154.3 (C-12′), 152.5 (C-6), 150.1 (C-6′), 144.4 (C-7′), 142.4 (C-9), 137.9 (C-7), 134.7 (C-9′), 131.5 (C-10′ or C-14′), 130.5 (C-4a′), 130.0 (C-10′ or C-14′), 128.9 (C-13), 128.3 (C-8a′), 122.4 (C-14), 122.0 (C-11′, C-13′), 120.6 (C-8a), 119.6 (C-8′), 115.8 (C-10), 115.4 (C-12), 111.8 (C-5′), 106.8 (C-5), 61.3 (‘OCH$_2$CH$_3$), 60.9 (OCH$_2$CH$_3$), 60.5 (7-OCH$_3$), 57.0 (C-1′), 56.3 (6-OCH$_3$), 56.1 (6′-OCH$_3$), 54.2 (C-1), 41.8 (C-α′), 41.5 (C-3′), 39.6 (C-α), 36.8 (C-3), 28.2 (C-4), 28.1 (C-4′), 14.8 (‘OCH$_2$CH$_3$), 14.2 (OCH$_2$CH$_3$). The resonances of C-4a and C-8 could not be identified. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2924, 1693, 1584, 1507, 1418, 1330, 1276, 1208, 1099, 1022, 837, 769. Purity (HPLC) = 88% (λ = 210 nm). HRMS (ESI): *m/z* calcd for [$C_{41}H_{44}N_2O_9$ + H]$^+$ 709.3120, found: 709.3121.

*4.2.14. (±)-N,N′-Bis-(ethoxycarbonyl)-12-desmethoxy-12-trifluoromethoxy-bisnortetrandrine and −isotetrandrine (**14b**)*

Previously separated diastereomers of bisbenzylisoquinoline **14b** (60.0 mg, 0.0687 mmol of each diastereomer) were reacted following General Procedure 3. The reactions were completed after

30 h. Purification was accomplished by flash column chromatography (25% acetone in hexanes, R_f = 0.23) and the products obtained as beige solids.

(1*R*,1′*R*)/(1*S*,1′*S*) isomers: yield: 35.0 mg, 0.0441 mmol, 64%. mp: 77.5–78.5 °C. ^{1}H NMR, COSY (400 MHz, Tcl$_2$, 100 °C) δ [ppm] = 7.41 (d, J = 8.4 Hz, 1H, 10′-H or 14′-H), 7.15–7.07 (m, 2H, 13-H and 11′-H or 13′-H), 6.68–6.64 (m, 1H, 11′-H or 13′-H), 6.65 (s, 1H, 5′-H), 6.62 (dd, J = 8.1, 2.0 Hz, 1H, 14-H), 6.59 (d, J = 1.9 Hz, 1H, 10-H), 6.33 (s, 1H, 5-H), 6.22 (dd, J = 8.3, 2.2 Hz, 1H, 10′-H or 14′-H), 6.17 (s, 1H, 8′-H), 5.29 (dd, J = 7.9, 2.8 Hz, 1H, 1-H), 5.05 (s, 1H, 1′-H), 4.37–4.27 (m, 1H, 3-H), 4.26 (q, J = 7.2 Hz, 2H, ‘OCH_2CH$_3$), 4.00 (ddd, J = 12.2, 5.7, 3.5 Hz, 1H, 3′-H), 3.87–3.76 (m, 2H, OCH_2CH$_3$), 3.74 (s, 3H, 6-OCH$_3$), 3.51 (d, J = 8.5 Hz, 1H, α′-H), 3.41 (td, J = 11.8, 4.9 Hz, 2H, 3′-H, 3-H), 3.34 (s, 3H, 6′-OCH$_3$), 3.26 (s, 3H, 7-OCH$_3$), 3.15 (td, J = 11.3, 10.8, 5.6 Hz, 1H, 4′-H), 2.94–2.84 (m, 1H, 4-H), 2.84–2.72 (m, 3H, α-H, 4′-H), 2.73–2.61 (m, 2H, α′-H, 4-H), 1.36 (t, J = 6.2 Hz, 3H, ‘OCH$_2$CH_3), 0.87 (br s, 3H, OCH$_2$CH_3). ^{13}C NMR, HSQC, HMBC (101 MHz, Tcl$_2$, 100 °C) δ [ppm] = 155.9 (‘C═O), 155.5 (C═O), 153.5 (C-12′), 152.3 (C-6), 152.2 (C-11), 149.1 (C-6′), 147.0 (C-8), 144.8 (C-7′), 140.8 (C-9), 138.9 (C-7), 136.6 (q, J = 1.8 Hz, C-12), 135.3 (C-9′), 132.3, 130.3 (C-10′, C-14′), 130.2 (C-4a′), 128.7 (C-8a′), 122.5 (C-13), 122.5 (C-8a), 122.0 (C-14), 121.9, 121.3 (C-11′, C-13′), 119.6 (C-8′), 117.4 (C-10), 113.9 (C-5′), 107.4 (C-5), 61.4 (‘OCH$_2$CH$_3$), 60.8 (OCH$_2$CH$_3$), 60.3 (7-OCH$_3$), 57.6 (C-1′), 56.9 (6′-OCH$_3$), 56.3 (6-OCH$_3$), 53.4 (C-1), 42.0 (C-α′, C-3′), 41.1 (C-α), 36.6 (C-3), 27.9 (C-4), 27.8 (C-4′), 14.8 (‘OCH$_2$CH$_3$), 14.0 (OCH$_2$CH$_3$). The resonances of C-4a and OCF$_3$ could not be identified. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 1693, 1505, 1423, 1281, 1248, 1201, 1110, 1024, 842, 767. Purity (HPLC) = 96% (λ = 210 nm). HRMS (ESI): *m/z* calcd for [$C_{42}H_{43}F_3N_2O_{10}$ + H]$^+$ 793.2943, found: 793.2955.

(1*R*,1′*S*)/(1*S*,1′*R*) isomers: yield: 15.0 mg, 0.0189 mmol, 28%. mp: 73.5–74.5 °C. ^{1}H NMR, COSY (400 MHz, Tcl$_2$, 100 °C) δ [ppm] = 7.38 (d, J = 8.0 Hz, 1H, 10′-H or 14′-H), 7.11–7.05 (m, 2H, 11′-H or 13′-H, 13-H), 6.64 (s, 1H, 5′-H), 6.62 (dt, J = 8.3, 2.6 Hz, 2H, 11′-H or 13′-H, 14-H), 6.47 (s, 1H, 10-H), 6.39 (d, J = 8.4 Hz, 1H, 10′-H or 14′-H), 6.29 (s, 1H, 5-H), 6.19 (s, 1H, 8′-H), 5.26 (d, J = 9.4 Hz, 1H, 1-H), 5.12 (q, J = 7.5 Hz, 1H, 1′-H), 4.29–4.15 (m, 3H, ‘OCH_2CH$_3$, 3-H), 3.99–3.88 (m, 1H, 3′-H), 3.88–3.76 (m, 2H, OCH_2CH$_3$), 3.73 (s, 3H, 6-OCH$_3$), 3.60 (s, 3H, 6′-OCH$_3$), 3.58–3.52 (m, 1H, α′-H), 3.45 (td, J = 11.5, 4.9 Hz, 1H, 3′-H), 3.35–3.25 (m, 1H, 3-H), 3.22–3.10 (m, 2H, α-H, 4′-H), 3.16 (s, 3H, 7-OCH$_3$), 2.86–2.73 (m, 2H, 4′-H, 4-H), 2.72 (dd, J = 12.8, 10.6 Hz, 1H, α′-H), 2.61 (dd, J = 13.8, 9.7 Hz, 1H, α-H), 2.50 (d, J = 16.3 Hz, 1H, 4-H), 1.34 (t, J = 7.1 Hz, 3H, ‘OCH$_2$CH_3), 0.98 (br s, 3H, OCH$_2$CH_3). ^{13}C NMR, HSQC, HMBC (101 MHz, Tcl$_2$, 100 °C) δ [ppm] = 155.8, 155.3 (‘C═O, C═O), 153.8 (C-12′), 152.6 (C-6), 152.3 (C-11), 150.1 (C-6′), 144.3 (C-7′), 141.1 (C-9), 138.0 (C-7), 136.7 (C-12), 135.4 (C-9′), 131.7, 130.7 (C-10′, C-14′), 128.2 (C-8a′), 122.2 (C-11′ or C-13′ or C-13, C-14), 121.7 (C-11′ or C-13′ or C-13), 120.5 (C-8a), 119.6 (C-8′), 117.9 (C-10), 111.8 (C-5′), 106.9 (C-5), 61.4 (‘OCH$_2$CH$_3$), 61.0 (OCH$_2$CH$_3$), 60.5 (7-OCH$_3$), 56.9 (C-1′), 56.3 (6-OCH$_3$), 56.0 (6′-OCH$_3$), 54.1 (C-1), 41.8 (C-α′, C-3′), 39.3 (C-α), 36.9 (C-3), 28.2 (C-4), 28.1 (C-4′), 14.8 (‘OCH$_2$CH$_3$), 14.2 (OCH$_2$CH$_3$). IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 1694, 1506, 1420, 1273, 1248, 1200, 1099, 1021, 841, 770. Purity (HPLC) = 89% (λ = 210 nm). HRMS (ESI): *m/z* calcd for [$C_{42}H_{43}F_3N_2O_{10}$ + H]$^+$ 793.2943, found: 793.2955.

*4.2.15. (±)-N,N′-Bis-(ethoxycarbonyl) ring C-thiophene analogues of bisnortetrandrine and −isotetrandrine (**14c**)*

Previously separated diastereomers of bisbenzylisoquinoline **13c** (100 mg, 0.126 mmol of each diastereomer) were reacted following General Procedure 3. The reactions were completed after 70 h. Purification was accomplished by flash column chromatography (25% acetone in hexanes, R_f = 0.17) and the products obtained as white solids.

(1*R*,1′*R*)/(1*S*,1′*S*) isomers: yield: 51.3 mg, 0.0718 mmol, 57%. mp: 74.5–76.0 °C. ^{1}H NMR, COSY (400 MHz, Tcl$_2$, 100 °C) δ [ppm] = 7.35 (d, J = 8.2 Hz, 1H, 14′-H or 10′-H), 7.13 (dd, J = 8.2, 2.5 Hz, 1H, 13′-H or 11′-H), 6.70 (d, J = 5.8 Hz, 1H, 13′-H or 11′-H), 6.60 (s, 1H, 5′-H), 6.41 (d, J = 1.7 Hz, 1H, 12-H), 6.34 (s, 1H, 5-H), 6.28 (s, 1H, 10-H), 6.19 (dd, J = 8.3, 2.2 Hz, 1H, 14′-H or 10′-H), 6.01 (s, 1H, 8′-H), 5.45 (d, J = 6.8 Hz, 1H, 1-H), 5.00 (s, 1H, 1′-H), 4.30–4.19 (m, 2H, ‘OCH_2CH$_3$), 4.11–4.02 (m, 1H, 3-H), 4.01–3.88 (m, 3H, 3′-H, OCH_2CH$_3$), 3.73 (s, 3H, 6-OCH$_3$), 3.50–3.37 (m, 3H, 3-H, 3′-H, α′-H), 3.32 (s, 3H, 6′-OCH$_3$), 3.22 (s, 3H, 7-OCH$_3$), 3.15–3.04 (m, 1H, 4′-H), 3.00 (dd, J = 15.2, 2.6 Hz, 1H, α-H), 2.91–2.75 (m, 3H, 4-H, α-H, 4′-H), 2.69 (dt, J = 16.1, 4.9 Hz, 1H, 4-H), 2.63 (d, J = 11.8 Hz, 1H, α′-H), 1.35 (t, J = 7.1 Hz, 3H, ‘OCH$_2$CH_3), 1.06 (br s, 3H, OCH$_2$CH_3). ^{13}C NMR, HSQC, HMBC (101 MHz, Tcl$_2$, 100 °C) δ [ppm] = 157.0 (C-12′), 152.3 (C-6), 149.3 (C-6′), 144.9 (C-7′), 141.5 (C-9), 139.2 (C-7), 134.4 (C-9′), 132.1 (C-14′ or C-10′), 130.3 (C-4a′), 129.8 (C-14′ or C-10′), 128.6 (C-8a′), 123.5 (C-8a), 121.0 (C-13′ and C-11′), 120.2 (C-8′), 118.2 (C-10), 113.7 (C-5′), 107.3 (C-5), 101.1 (C-12), 61.4 (‘OCH$_2$CH$_3$), 61.1 (OCH$_2$CH$_3$), 60.2 (7-OCH$_3$), 57.7 (C-1′), 56.6 (6′-OCH$_3$), 56.3 (6-OCH$_3$), 54.2 (C-1), 41.6 (C-3′ and C-α′), 38.5 (C-α), 38.2 (C-3), 28.0 (C-4), 27.9 (C-4′), 14.8 (‘OCH$_2$CH$_3$), 14.4 (OCH$_2$CH$_3$). The resonances of ‘C═O, C═O, C-8, C-4a and C-11 could not be identified. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2929, 1693, 1558, 1505, 1416, 1277, 1219, 1101, 1020, 875, 770. Purity (HPLC) = 95% (λ = 210 nm). HRMS (ESI): *m/z* calcd for [$C_{39}H_{42}N_2O_9S$ + H]$^+$ 715.2684, found: 715.2686.

(1*R*,1′*S*)/(1*S*,1′*R*) isomers: yield: 15.3 mg, 0.0214 mmol, 17%. mp: 116.0–119.0 °C. ^{1}H NMR, COSY (400 MHz, Tcl$_2$, 100 °C) δ [ppm] = 7.31 (dd, J = 8.2, 2.2 Hz, 1H, 14′-H or 10′-H), 7.08 (dd, J = 7.9, 2.2 Hz, 1H, 13′-H or 11′-H), 6.66 (dd, J = 8.3, 2.6 Hz, 1H, 13′-H or 11′-H), 6.62 (s, 1H, 5′-H), 6.40 (dd, J = 8.2, 2.2 Hz, 1H, 14′-H or 10′-H), 6.31 (d, J = 1.7 Hz, 1H, 10-H), 6.27 (s, 1H, 5-H), 6.17 (s, 1H, 8′-H), 5.97 (d, J = 1.7 Hz, 1H, 12-H), 5.32 (d, J = 8.0 Hz, 1H, 1-H), 5.11 (t, J = 8.7 Hz, 1H, 1′-H), 4.29–4.19 (m, 3H, 3-H, ‘OCH_2CH$_3$), 4.00–3.88 (m, 3H, 3′-H, OCH_2CH$_3$), 3.72 (s, 3H, 6-OCH$_3$), 3.58 (d, J = 6.6 Hz, 1H, α′-H), 3.55 (s, 3H, 6′-OCH$_3$), 3.40 (td, J = 11.4, 4.9 Hz, 1H, 3′-H), 3.32 (d, J = 15.0 Hz, 1H, α-H), 3.27–3.13 (m, 2H, 3-H, 4′-H), 3.12 (s, 3H, 7-OCH$_3$), 2.86–2.70 (m, 3H, 4-H, 4′-H, α′-H), 2.68–2.54 (m, 2H, 4-H, α-H), 1.33 (t, J = 7.0 Hz, 3H, ‘OCH$_2$CH_3), 1.09 (br s, 3H, OCH$_2$CH_3). ^{13}C NMR, HSQC, HMBC (101 MHz, Tcl$_2$, 100 °C) δ [ppm] = 156.8 (C-12′), 155.8 (C═O), 152.6 (C-6), 150.1 (C-6′), 144.0 (C-7′), 141.8 (C-9), 137.8 (C-7), 134.8 (C-9′), 131.6 (C-14′ or C-10′), 129.6 (C-14′ or C-10′), 128.3 (C-8a′), 122.1 (C-13′ or C-11′), 121.3 (C-13′ or C-11′), 120.3 (C-8a), 119.8 (C-8′), 118.0 (C-12), 111.8 (C-5′), 106.7 (C-5), 99.6 (C-10), 61.3 (‘OCH$_2$CH$_3$), 61.2 (OCH$_2$CH$_3$), 60.5 (7-OCH$_3$), 57.1 (C-1′), 56.3 (6-OCH$_3$), 56.0 (6′-OCH$_3$), 55.7 (C-1), 41.9 (C-3′), 41.2 (C-α′), 37.2 (C-3), 35.6 (C-α), 28.1 (C-4), 28.0 (C-4′), 14.8 (‘OCH$_2$CH$_3$), 14.6 (OCH$_2$CH$_3$). The resonances of ‘C═O, C-4a′, C-4a, C-8, and C-11 could not be identified. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2927, 2854, 1694, 1557, 1505, 1417, 1219, 1098, 1022, 842, 770. Purity (HPLC) = 90% (λ = 210 nm). HRMS (ESI): *m/z* calcd for [$C_{39}H_{42}N_2O_9S$ + H]$^+$ 715.2684, found: 715.2688.

*4.2.16. (±)-N,N′-Bis-(ethoxycarbonyl)-12-desmethoxy-12-chloro-bisnortetrandrine and −isotetrandrine (**14d**)*

Previously separated diastereomers of bisbenzylisoquinoline **13d** (110 mg, 0.133 mmol of each diastereomer) were reacted following General Procedure 3. The reactions were completed after 60 h. Purification was accomplished by flash column chromatography (25% acetone in hexanes, R_f = 0.15) and the products obtained as a white solid.

(1*R*,1′*R*)/(1*S*,1′*S*) isomers: yield: 48.4 mg, 0.0652 mmol, 49%. mp: 50.0–56.0 °C. ^{1}H NMR, COSY (400 MHz, Tcl$_2$, 100 °C) δ [ppm] = 7.41 (d, J = 8.2 Hz, 1H, 14′-H or 10′-H), 7.21 (d, J = 7.9 Hz, 1H, 13-H), 7.13 (dd, J = 8.2, 2.6 Hz, 1H, 13′-H or 11′-H), 6.70–6.64 (m, 1H, 13′-H or 11′-H), 6.64 (s, 1H, 5′-H), 6.58 (dd, J = 8.0, 1.9 Hz, 1H, 14-H), 6.54 (d, J = 1.8 Hz, 1H, 10-H), 6.32 (s, 1H, 5-H), 6.21 (dd, J = 8.3, 2.2 Hz, 1H,

14′-H or 10′-H), 6.16 (s, 1H, 8′-H), 5.28 (d, J = 6.1 Hz, 1H, 1-H), 5.05 (s, 1H, 1′-H), 4.35–4.22 (m, 3H, 3-H, ‘OCH_2CH$_3$), 3.99 (ddd, J = 12.7, 5.7, 3.6 Hz, 1H, 3′-H), 3.87–3.76 (m, 2H, OCH_2CH$_3$), 3.73 (s, 3H, 6-OCH$_3$), 3.50 (dd, J = 11.9, 5.2 Hz, 1H, α′-H), 3.45–3.36 (m, 2H, 3-H, 3′-H), 3.35 (s, 3H, 6′-OCH$_3$), 3.25 (s, 3H, 7-OCH$_3$), 3.14 (ddd, J = 16.5, 11.2, 5.8 Hz, 1H, 4′-H), 2.93–2.77 (m, 2H, 4-H, 4′-H), 2.76–2.72 (m, 2H, α-H), 2.69–2.61 (m, 2H, 4-H, α′-H), 1.36 (t, J = 7.0 Hz, 3H, ‘OCH$_2$CH_3), 0.88 (br s, 3H, OCH$_2$CH_3). ^{13}C NMR, HSQC, HMBC (101 MHz, Tcl$_2$, 100 °C) δ [ppm] = 155.9 (C=O or C=O′), 155.7 (C-11), 155.5 (C=O or C=O′), 153.8 (C-12′), 152.1 (C-6), 149.1 (C-6′), 147.0 (C-8), 144.8 (C-7′), 140.6 (C-9), 138.9 (C-7), 135.2 (C-9′), 132.3 (C-14′ or C-10′), 130.2 (C-14′ or C-10′), 130.2 (C-4a′), 129.7 (C-13), 128.7 (C-8a′), 128.2 (C-4a), 122.7 (C-14), 122.5 (C-8a), 121.9 (C-13′ or C-11′), 121.4 (C-13′ or C-11′), 120.3 (C-12), 119.6 (C-8′), 117.0 (C-10), 113.9 (C-5′), 107.4 (C-5), 61.4 (‘OCH_2CH$_3$), 60.8 (OCH_2CH$_3$), 60.3 (7-OCH$_3$), 57.6 (C-1′), 56.9 (6′-OCH$_3$), 56.3 (6-OCH$_3$), 53.4 (C-1), 41.9 (C-3′ and C-α′), 41.1 (C-α), 36.7 (C-3), 27.9 (C-4 and C-4′), 14.8 (‘OCH$_2$CH$_3$), 14.1 (OCH$_2$CH_3). IR (ATR): ṽ [cm^{-1}] = 2927, 2853, 1692, 1505, 1417, 1277, 1205, 1105, 1023, 840, 765. Purity (HPLC) = 95% (λ = 210 nm). HRMS (ESI): *m/z* calcd for [C$_{41}$H$_{43}^{35}$ClN$_2$O$_9$ + H]$^+$ 743.2730, found: 743.2735.

(1*R*,1′*S*)/(1*S*,1′*R*) isomers: yield: 54.3 mg, 0.0732 mmol, 55%. mp: 113.5–118.0 °C. ^{1}H NMR, COSY (400 MHz, Tcl$_2$, 100 °C) δ [ppm] = 7.39 (d, J = 8.2 Hz, 1H, 14′-H or 10′-H), 7.18 (d, J = 7.9 Hz, 1H, 13-H), 7.09 (dd, J = 8.2, 2.5 Hz, 1H, 13′-H or 11′-H), 6.65 (s, 1H, 5′-H), 6.62 (dd, J = 8.4, 2.2 Hz, 2H, 13′-H or 11′-H), 6.58 (dd, J = 8.0, 1.8 Hz, 1H, 14-H), 6.43–6.37 (m, 2H, 10-H, 14′-H or 10′-H), 6.28 (s, 1H, 5-H), 6.18 (s, 1H, 8′-H), 5.25 (d, J = 8.2 Hz, 1H, 1-H), 5.11 (dd, J = 10.4, 6.2 Hz, 1H, 1′-H), 4.31–4.11 (m, 3H, 3, ‘OCH_2CH$_3$), 3.99–3.88 (m, 1H, 3′-H), 3.87–3.77 (m, 2H, OCH_2CH$_3$), 3.73 (s, 3H, 6-OCH$_3$), 3.60 (s, 3H, 6′-OCH$_3$), 3.55 (dd, J = 11.8, 5.7 Hz, 1H, α′-H), 3.46 (td, J = 11.5, 4.9 Hz, 1H, 3′-H), 3.30 (td, J = 13.8, 12.9, 4.5 Hz, 1H, 3-H), 3.16 (s, 3H, 7-OCH$_3$), 3.19–3.08 (m, 2H, α-H, 4′-H), 2.82 (dt, J = 15.7, 4.6 Hz, 1H, 4′-H), 2.80–2.74 (m, 1H, 4-H), 2.72 (dd, J = 12.8, 10.6 Hz, 1H, α′-H), 2.63–2.54 (m, 1H, α-H), 2.47 (d, J = 16.8 Hz, 1H, 4-H), 1.33 (t, J = 7.1 Hz, 3H, ‘OCH$_2$CH_3), 0.98 (br s, 3H, OCH$_2$CH_3). ^{13}C NMR, HSQC, HMBC (101 MHz, Tcl$_2$, 100 °C) δ [ppm] = 155.8 (C-11), 155.4 (C=O and C=O′), 153.8 (C-12′), 152.6 (C-6), 150.1 (C-6′), 144.0 (C-7′), 140.8 (C-9), 137.9 (C-7), 135.3 (C-9′), 131.6 (C-14′ or C-10′), 130.6 (C-4a′), 130.2 (C-14′ or C-10′), 129.6 (C-4a), 129.4 (C-13), 128.3 (C-8a′), 123.0 (C-14), 121.9 (C-13′ and C-11′), 120.2 (C-8a and C-12), 119.6 (C-8′), 117.3 (C-10), 111.9 (C-5′), 106.9 (C-5), 61.4 (‘OCH_2CH$_3$), 61.0 (OCH_2CH$_3$), 60.5 (7-OCH$_3$), 57.0 (C-1′), 56.2 (6-OCH$_3$), 56.1 (6′-OCH$_3$), 54.1 (C-1), 41.7 (C-3′), 41.5 (C-α′), 39.2 (C-α), 37.3 (C-3), 28.2 (C-4), 28.1 (C-4′), 14.8 (‘OCH$_2$CH_3), 14.2 (OCH$_2$CH_3). The resonance of C-8 could not be identified. IR (ATR): ṽ [cm^{-1}] = 2936, 2828, 1692, 1506, 1416, 1276, 1204, 1099, 1022, 840, 768. Purity (HPLC) = 99% (λ = 210 nm). HRMS (ESI): *m/z* calcd for [C$_{41}$H$_{43}^{35}$ClN$_2$O$_9$ + Na]$^+$ 765.2549, found: 765.2550.

*4.2.17. (±)-N,N′-Bis-(ethoxycarbonyl) ring C-propylidene analogues of bisnortetrandrine and −isotetrandrine (**14e**)*

Previously separated diastereomers of bisbenzylisoquinoline **14e** (85 mg, 0.112 mmol of each diastereomer), potassium iodide (3.70 mg, 0.0225 mmol, 0.2 equiv.) and potassium carbonate (37.2 mg, 0.225 mmol, 2.0 equiv.) were dissolved in 6.0 mL of anhydrous DMF. The mixture was stirred for 48 h at 105 °C. Purification was accomplished by flash column chromatography (25% acetone in hexanes, R_f = 0.25) and the products obtained as white solids.

Precursor of **RMS10**: yield: 45.3 mg, 0.0672 mmol, 60%. mp: 103.5–104.5 °C. ^{1}H NMR, COSY (400 MHz, Tcl$_2$, 100 °C) δ [ppm] = 7.24 (br s, 1H, 14′-H or 10′-H), 6.86 (br s, 1H, 13′-H or 11′-H), 6.65 (br s, 1H, 13′-H or 11′-H), 6.60 (s, 1H, 5′-H), 6.28 (s, 1H, 5-H), 6.20 (br s, 1H, 14′-H or 10′-H), 5.66 (s, 1H, 8′-H), 5.26 (d, J = 4.5 Hz, 1H, 1-H), 4.93 (dd, J = 10.0, 4.1 Hz, 1H, 1′-H), 4.28–4.18 (m, 3H, 4″-H, OCH_2CH$_3$), 4.18–4.08 (m, 2H, ‘OCH_2CH$_3$), 4.04–3.96 (m, 2H, 3-H, 4″-H), 3.81 (dt, J = 12.4, 5.5 Hz, 1H, 3′-H), 3.70 (s, 3H, 6-OCH$_3$), 3.62–3.56 (m, 1H, 3′-H), 3.55 (s, 3H, 6′-OCH$_3$), 3.37 (dd, J = 12.2, 5.2 Hz, 1H, α′-H), 3.33–3.24 (m, 1H, 3-H), 3.13 (s, 3H, 7-OCH$_3$), 2.98 (ddd, J = 14.9, 9.0, 5.4 Hz, 1H, 4′-H), 2.88–2.75 (m, 2H, 4-H, 4′-H), 2.64 (dt, J = 16.2, 4.6 Hz, 1H, 4-H), 2.54 (t, J = 11.6 Hz, 1H, α′-H), 1.91–1.80 (m, 1H, 3″-H), 1.65–1.52 (m, 4H, 1″-H, 2″-H, 3″-H), 1.49–1.39 (m, 1H, 2″-H), 1.32 (t, J = 7.1 Hz, 3H, OCH$_2$CH_3), 1.25 (t, J = 7.1 Hz, 3H, ‘OCH$_2$CH_3). ^{13}C NMR, HSQC, HMBC (101 MHz, Tcl$_2$, 100 °C) δ [ppm] = 158.0 (C-12′), 155.8 (‘C=O), 155.7 (C=O), 152.3 (C-6), 149.6 (C-6′), 145.0 (C-7′), 138.2 (C-7), 131.7 (C-14′ or C-10′), 129.6 (C-4a′), 129.5 (C-14′ or C-10′), 128.1 (C-8a′), 123.3 (C-8a), 120.1 (C-8′), 116.9 (C-13′ and C-11′), 113.2 (C-5′), 107.2 (C-5), 68.9 (C-4″), 61.3 (OCH_2CH$_3$), 61.0 (‘OCH_2CH$_3$), 60.1 (7-OCH$_3$), 57.4 (C-1′), 56.8 (6′-OCH$_3$), 56.2 (6-OCH$_3$), 50.6 (C-1), 41.6 (C-α′), 40.9 (C-3′), 37.7 (C-3), 34.1 (C-1″), 28.6 (C-3″), 28.0 (C-4 and C-4′), 22.0 (C-2″), 14.8 (OCH$_2$CH_3), 14.7 (‘OCH$_2$CH_3). The resonances of C-9′, C-4a and C-8 could not be identified. IR (ATR): ṽ [cm^{-1}] = 2924, 2840, 1689, 1509, 1415, 1273, 1207, 1099, 1023, 879, 769. Purity (HPLC) = 99% (λ = 210 nm). HRMS (ESI): *m/z* calcd for [C$_{38}$H$_{46}$N$_2$O$_9$ + H]$^+$ 675.3276, found: 675.3288.

Precursor of **RMS9**: yield: 21.9 mg, 0.0325 mmol, 29%. mp: 178.0 °C. ^{1}H NMR, COSY (400 MHz, Tcl$_2$, 100 °C) δ [ppm] = 7.20 (d, J = 6.5 Hz, 1H, 14′-H or 10′-H), 6.96 (d, J = 6.7 Hz, 1H, 13′-H or 11′-H), 6.60 (s, 1H, 5′-H), 6.43 (d, J = 5.8 Hz, 1H, 13′-H or 11′-H), 6.28 (s, 1H, 5-H), 6.23 (d, J = 7.4 Hz, 1H, 14′-H or 10′-H), 5.90 (s, 1H, 8′-H), 5.16 (dd, J = 9.5, 2.0 Hz, 1H, 1-H), 4.98 (dd, J = 10.3, 5.6 Hz, 1H, 1′-H), 4.27–4.11 (m, 4H, ‘OCH_2CH$_3$, OCH_2CH$_3$), 4.11–4.00 (m, 3H, 3-H, 4″-H), 3.87–3.78 (m, 1H, 3′-H), 3.72 (s, 3H, 6-OCH$_3$), 3.58 (s, 3H, 6′-OCH$_3$), 3.55–3.46 (m, 1H, 3′-H), 3.43 (dd, J = 12.7, 6.0 Hz, 1H, α′-H), 3.30–3.20 (m, 1H, 3-H), 3.15 (s, 3H, 7-OCH$_3$), 3.06 (ddd, J = 15.5, 9.8, 5.5 Hz, 1H, 4′-H), 2.88–2.74 (m, 2H, 4-H, 4′-H), 2.67–2.55 (m, 2H, 4-H, α′-H), 1.81–1.70 (m, 2H, 1″-H, 3″-H), 1.69–1.59 (m, 1H, 1″-H), 1.58–1.49 (m, 1H, 3″-H), 1.48–1.38 (m, 1H, 2″-H), 1.36–1.24 (m, 7H, 2″-H, ‘OCH$_2$CH_3, OCH$_2$CH_3). ^{13}C NMR, HSQC, HMBC (101 MHz, Tcl$_2$, 100 °C) δ [ppm] = 156.4 (C-12′), 155.9 (C=O or C=O′), 155.7 (C=O or C=O′), 152.2 (C-6), 149.9 (C-6′), 144.7 (C-7′), 138.2 (C-7), 130.9 (C-14′ or C-10′), 130.1 (C-4a′), 129.4 (C-14′ or C-10′), 128.6 (C-8a′), 121.8 (C-8a), 119.7 (C-8′), 112.3 (C-5′), 107.1 (C-5), 68.7 (C-4″), 61.3 (‘OCH$_2$CH$_3$ or OCH$_2$CH$_3$), 61.2 (‘OCH$_2$CH$_3$ or OCH$_2$CH$_3$), 60.4 (7-OCH$_3$), 57.1 (C-1′), 56.4 (6′-OCH$_3$), 56.3 (6-OCH$_3$), 50.3 (C-1), 41.4 (C-α′), 41.3 (C-3′), 37.7 (C-3), 33.5 (C-1″), 28.3 (C-4), 28.1 (C-4′), 27.4 (C-3″), 21.4 (C-2″), 14.8 (OCH$_2$CH_3), 14.8 (‘OCH$_2$CH_3). The resonances of C-9′, C-4a and C-8 could not be identified. IR (ATR): ṽ [cm^{-1}] = 2927, 2860, 1690, 1508, 1414, 1275, 1203, 1098, 1023, 768. Purity (HPLC) = 83% (λ = 210 nm). HRMS (ESI): *m/z* calcd for [C$_{38}$H$_{46}$N$_2$O$_9$ + H]$^+$ 675.3276, found: 675.3274.

*4.2.18. (±)-12-Desmethoxytetrandrine and −isotetrandrine (**RMS1-2**)*

RMS1: (1*R*,1′*S*)/(1*S*,1′*R*) isomers of carbamate **14a** (17.0 mg, 0.024 mmol) were reduced following General Procedure 4. The reaction was completed after 12 h. Purification by flash column chromatography (ethyl acetate → 1.0% triethylamine and 7.5% methanol in ethyl acetate, R_f = 0.14) affording the product as a beige solid (13 mg, 0.0219 mmol, 91%). mp: 196.5–198.0 °C. ^{1}H NMR, COSY (500 MHz, CDCl$_3$): δ [ppm] = 7.28 (dd, J = 8.3, 2.1 Hz, 1H, 10′-H or 14′-H), 7.18 (t, J = 7.8 Hz, 1H, 13-H), 7.07 (dd, J = 8.1, 2.5 Hz, 1H, 11′-H or H-13′), 6.96 (dd, J = 8.1, 2.5 Hz, 1H, 12-H), 6.85 (d, J = 7.4 Hz, 1H, 14-H), 6.62 (dd, J = 8.2, 1.7 Hz, 1H, 11′-H or 13′-H), 6.53 (s, 1H, 5′-H), 6.45–6.37 (m, 2H, 10-H, 10′-H or 14′-H), 6.28 (s, 1H, 5-H), 5.99 (s, 1H, 8′-H), 3.92–3.82 (m, 2H, 1-H, 1′-H), 3.75 (s, 3H, 6-OCH$_3$), 3.60 (s, 3H, 6′-OCH$_3$), 3.45–3.36 (m, 1H, 3′-H), 3.33–3.21 (m, 2H, α′-H, 3-H), 3.12 (s, 3H, 7-OCH$_3$), 3.07 (d, J = 13.9 Hz, 1H, α-H), 2.96–2.88 (m, 2H, α′-H, 4′-H), 2.86–2.75 (m, 4H, 3-H, 3′-H, 4-H, 4′-H), 2.68–2.61 (m,

1H, α-H), 2.58 (s, 3H, 2′-NCH_3), 2.43−2.34 (m, 1H, 4-H), 2.25 (s, 3H, 2-NCH_3). ^{13}C NMR, DEPT, HMQC, HMBC (126 MHz, $CDCl_3$): δ [ppm] = 160.4 (C-11), 154.3 (C-12′), 152.0 (C-6), 150.0 (C-6′), 144.5 (C-9), 143.7 (C-7′), 137.2 (C-7), 135.4 (C-9′), 132.3 (C-10′ or 14′), 130.3 (C-10′ or 14′), 129.1 (C-13), 127.9 (C-8a′), 123.4 (C-14), 122.0 (C-11′ or 13′), 121.5 (C-11′ or 13′), 121.0 (C-8a), 120.0 (C-8′), 115.3 (C-10), 115.1 (C-12), 111.3 (C-5′), 105.6 (C-5), 63.9 (C-1′), 62.1 (C-1), 60.7 (7-OCH_3), 55.9 (6-OCH_3), 55.7 (6′-OCH_3), 46.2 (C-3′), 45.4 (C-3), 43.0 (2′-NCH_3), 42.9 (2-NCH_3), 39.4 (C-α), 37.9 (C-α′), 25.9 (C-4′), 23.7 (C-4). The resonances of C-8, C-4a and C-4a′ could not be identified. IR (ATR): ṽ [cm^{-1}] = 2923, 2853, 1740, 1606, 1506, 1462, 1255, 1114, 1018, 841, 698. Purity (HPLC) = 99%, d.r. > 99:1 (λ = 210 nm). HRMS (ESI): *m/z* calcd for $[C_{37}H_{40}N_2O_5 + H]^+$ 593.3010, found: 593.3011.

RMS2: (1*R*,1′*R*)/(1*S*,1′*S*) isomers of carbamate **14a** (47.0 mg, 0.0663 mmol) were reduced following General Procedure 4. The reaction was completed after 12 h. Purification by flash column chromatography (ethyl acetate → 1.0% triethylamine and 7.5% methanol in ethyl acetate, R_f = 0.14) affording the product as a white solid (37 mg, 0.0624 mmol, 94%). mp: 206.0−206.5 °C. ^{1}H NMR, COSY (500 MHz, $CDCl_3$): δ [ppm] = 7.35 (dd, *J* = 8.2, 2.2 Hz, 1H, 10′-H or 14′-H), 7.23 (t, *J* = 7.8 Hz, 1H, 13-H), 7.11 (dd, *J* = 8.1, 2.6 Hz, 1H, 11′-H or 13′-H), 6.99 (dd, *J* = 7.8, 2.3 Hz, 1H, 12-H), 6.97 (s, 1H, 14-H), 6.77 (dd, *J* = 8.3, 2.6 Hz, 1H, 11′H or 13′-H), 6.55 (t, *J* = 1.9 Hz, 1H, 10-H), 6.51 (s, 1H, 5′-H), 6.31 (s, 1H, 5-H), 6.30−6.28 (m, 1H, 10′-H or 14′-H), 5.99 (s, 1H, 8′-H), 3.92−3.86 (m, 1H, 1′-H), 3.78 (d, *J* = 8.7 Hz, 1H, 1-H), 3.75 (s, 3H, 6-OCH_3), 3.56−3.48 (m, 1H, 3-H), 3.49−3.42 (m, 1H, 3′-H), 3.37 (s, 3H, 6′-OCH_3), 3.32−3.25 (m, 1H, α′-H), 3.18 (s, 3H, 7-OCH_3), 2.99−2.87 (m, 4H, 3-H, 3′-H, 4-H, 4′-H), 2.80 (t, *J* = 11.7 Hz, 1H, α′-H), 2.77−2.72 (m, 2H, α-H, 4′-H), 2.63 (s, 3H, 2′-NCH_3), 2.59−2.52 (m, 1H, α-H), 2.49−2.38 (m, 1H, 4-H), 2.34 (s, 3H, 2-NCH_3). ^{13}C NMR, DEPT, HMQC, HMBC (126 MHz, $CDCl_3$): δ [ppm] = 160.2 (C-11), 154.1 (C-12′), 151.6 (C-6), 148.8 (C-6′), 144.0 (C-7′), 143.9 (C-9), 138.0 (C-7), 135.1 (C-9′), 132.8 (C-10′ or C-14′), 130.3 (C-10′ or 14′), 129.2 (C-13), 128.0 (C-8a′), 123.3 (C-14), 123.1 (C-8a), 122.0 (C-11′ or C-13′), 121.8 (C-11′ or C-13′), 120.4 (C-8′), 115.6 (C-10), 115.2 (C-12), 112.8 (C-5′), 105.9 (C-5), 64.1 (C-1′), 61.5 (C-1), 60.4 (7-OCH_3), 56.0 (6′-OCH_3 or 6-OCH_3), 55.9 (6′-OCH_3 or 6-OCH_3), 45.4 (C-3′), 44.2 (C-3), 42.8 (C-α), 42.7 (2′-NCH_3), 42.4 (2-NCH_3), 38.5 (C-α′), 25.2 (C-4′), 22.2 (C-4). The resonances of C-8, C-4a and C-4a′ could not be identified. IR (ATR): ṽ [cm^{-1}] = 2926, 2841, 1586, 1505, 1268, 1211, 1111, 1023, 841, 785. Purity (HPLC) = 99%, d.r. 95:5 (λ = 210 nm). HRMS (ESI): *m/z* calcd for $[C_{37}H_{40}N_2O_5 + H]^+$ 593.3010, found: 593.3011.

4.2.19. (±)-12-Desmethoxy-12-trifluoromethoxytetrandrine and −isotetrandrine (***RMS3*-*4***)

RMS3: (1*R*,1′*S*)/(1*S*,1′*R*) isomers of carbamate **14b** (13.0 mg, 0.0164 mmol) were reduced following General Procedure 4. The reaction was completed after 12 h. Purification by flash column chromatography (ethyl acetate → 1.5% triethylamine and 7.5% methanol in ethyl acetate, R_f = 0.11) affording the product as a white solid (9.7 mg, 0.0143 mmol, 87%). mp: 111.0−112.5 °C. ^{1}H NMR, COSY (400 MHz, $CDCl_3$): δ [ppm] = 7.30 (dd, *J* = 8.2, 2.1 Hz, 1H, 10′-H or 14′-H), 7.12 (d, *J* = 8.3 Hz, 1H, 13-H), 7.08 (d, *J* = 8.5 Hz, 1H, 11′-H or 13′-H), 6.83 (dd, *J* = 8.2, 1.5 Hz, 1H, 14-H), 6.64−6.57 (m, 2H, 10-H, 11′-H or 13′-H), 6.53 (s, 1H, 5′-H), 6.45 (br s, 1H, 10′-H or 14′-H), 6.27 (s, 1H, 5-H), 5.97 (s, 1H, 8′-H), 3.90−3.84 (m, 1H, 1′-H), 3.82 (d, *J* = 9.6 Hz, 1H, 1-H), 3.75 (s, 3H, 6-OCH_3), 3.60 (s, 3H, 6′-OCH_3), 3.45−3.35 (m, 1H, 3′-H), 3.25 (dd, *J* = 12.9, 6.3 Hz, 2H, α′-H, 3-H), 3.13 (s, 3H, 7-OCH_3), 3.05 (d, *J* = 13.8 Hz, 1H,α-H), 2.96−2.87 (m, 1H, α′-H, 4′-H), 2.87−2.75 (m, 4H, 3′-H, 3-H, 4-H, 4′-H), 2.63 (dd, *J* = 10.2, 3.6 Hz, 1H, α-H), 2.58 (s, 3H, 2′-NCH_3), 2.42−2.31 (m, 1H, 4-H), 2.26 (s, 3H, 2-NCH_3). ^{13}C NMR, DEPT, HMQC, HMBC (126 MHz, $CDCl_3$): δ [ppm] = 153.7 (C-12′), 152.3 (C-11), 152.1 (C-6), 149.9 (C-6′), 143.6 (C-7′), 143.4 (C-9), 137.2 (C-7), 136.1 (C-12), 136.0 (C-9′), 132.4 (C-10′ or C-14′), 130.5 (C-10′ or C-14′), 127.8 (C-8a′), 123.3 (C-14), 122.5 (C-13), 121.8 (C-11′ or C-13′), 121.5 (C-11′ or C-13′), 120.4 (C-8a), 119.9 (C-8′), 117.2 (C-10), 111.3 (C-5′), 105.6 (C-5), 63.8 (C-1′), 62.2 (C-1), 60.7 (7-OCH_3), 55.9 (6-OCH_3), 55.7 (6′-OCH_3), 46.1 (C-3′), 45.3 (C-3), 42.9 (2′-NCH_3), 42.7 (2-NCH_3), 39.2 (C-α), 37.7 (C-α′), 25.9 (C-4′), 22.8 (C-4). The resonances of C-8, C-4a, C-4a′ and OCF_3 could not be identified. IR (ATR): ṽ [cm^{-1}] = 2933, 2843, 1593, 1505, 1416, 1198, 1164, 1112, 1008, 838, 729. Purity (HPLC) = 98%, d.r. 95:5 (λ = 210 nm). HRMS (ESI): *m/z* calcd for $[C_{38}H_{39}F_3N_2O_6 + H]^+$ 677.2833, found: 677.2838.

RMS 4: (1*R*,1′*R*)/(1*S*,1′*S*) isomers of carbamate **14b** (32.0 mg, 0.0404 mmol) were reduced following General Procedure 4. The reaction was completed after 12 h. Purification by flash column chromatography (ethyl acetate → 1.5% triethylamine and 7.5% methanol in ethyl acetate, R_f = 0.11) affording the product as a white solid (20.2 mg, 0.0298 mmol, 74%). mp: 174.0−176.0 °C. ^{1}H NMR, COSY (400 MHz, $CDCl_3$): δ [ppm] = 7.36 (dd, *J* = 8.2, 2.2 Hz, 1H, 10′-H or 14′-H), 7.17 (d, *J* = 8.1 Hz, 1H, 13-H), 7.12 (dd, *J* = 8.2, 2.6 Hz, 1H, 11′-H or 13′-H), 6.94 (d, *J* = 8.2 Hz, 1H, 14-H), 6.76 (dd, *J* = 8.3, 2.6 Hz, 1H, 11′-H or 13′-H), 6.63 (d, *J* = 1.9 Hz, 1H, 10-H), 6.51 (s, 1H, 5′-H), 6.31 (s, 1H, 5-H), 6.32−6.28 (m, 1H, 10′-H or 14′-H), 5.98 (s, 1H, 8′-H), 3.89 (dd, *J* = 10.9, 5.7 Hz, 1H, 1′-H), 3.75 (s, 3H, 6-OCH_3), 3.72 (s, 1H, 1-H), 3.55−3.43 (m, 2H, 3-H, 3′-H), 3.38 (s, 3H, 6′-OCH_3), 3.31−3.24 (m, 1H, α′-H), 3.18 (s, 3H, 7-OCH_3), 3.00−2.85 (m, 4H, 3-H, 3′-H, 4-H, 4′-H), 2.83 (d, *J* = 11.7 Hz, 1H, α′-H), 2.79−2.70 (m, 2H, α-H, 4′-H), 2.63 (s, 3H, 2′-NCH_3), 2.54 (d, *J* = 13.6 Hz, 1H, α-H), 2.41 (dd, *J* = 11.3, 5.2 Hz, 1H, 4-H), 2.34 (s, 3H, 2-NCH_3). ^{13}C NMR, DEPT, HMQC, HMBC (126 MHz, $CDCl_3$): δ [ppm] = 153.6 (C-12′), 152.2 (C-11), 151.7 (C-6), 148.8 (C-6′), 148.6 (C-8), 143.9 (C-7′), 142.6 (C-9), 138.0 (C-7), 136.2 (C-12), 135.7 (C-9′), 133.0 (C-10′ or 14′), 130.4 (C-10′ or 14′), 128.3 (C-4a′), 128.2 (C-4a), 127.9 (C-8a′), 123.2 (C-14), 122.7 (C-8a and 13), 121.8 (C-11′ or C-13′), 121.7 (C-11′ or C-13′), 121.0 (q, *J* = 257.2 Hz, OCF_3), 120.3 (C-8′), 117.7 (C-10), 112.7 (C-5′), 106.0 (C-5), 64.1 (C-1′), 61.3 (C-1), 60.4 (7-OCH_3), 55.9 (6′-OCH_3 and 6-OCH_3), 45.4 (C-3′), 44.1 (C-3), 42.7 (2′-NCH_3), 42.3 (C-α), 42.3 (2-NCH_3), 38.3 (C-α′), 25.3 (C-4′), 21.9 (C-4). IR (ATR): ṽ [cm^{-1}] = 2926, 2846, 1596, 1504, 1250, 1200, 1163, 1113, 1020, 840. Purity (HPLC) = 99%, d.r. 94:6 (λ = 210 nm). HRMS (ESI): *m/z* calcd for $[C_{38}H_{39}F_3N_2O_6 + H]^+$ 677.2833, found: 677.2839.

4.2.20. (±)-Ring C thiophene analogues of tetrandrine and −isotetrandrine (***RMS5*-*6***)

RMS5: (1*R*,1′*S*)/(1*S*,1′*R*) isomers of carbamate **14c** (10.0 mg, 0.014 mmol) were reduced following General Procedure 4. The reaction was completed after 4 h. Purification by flash column chromatography (ethyl acetate → 2.0% trimethylamine in ethyl acetate, R_f = 0.08) affording the product as a beige solid (5.2 mg, 0.00868 mmol, 62%). mp: 149.0−151.0 °C. ^{1}H NMR, COSY (500 MHz, $CDCl_3$): δ [ppm] = 7.27−7.24 (m, 1H, 14′-H or 10′-H), 7.10 (dd, *J* = 8.1, 2.6 Hz, 1H, 13′-H or 11′-H), 6.64 (dd, *J* = 8.3, 2.6 Hz, 1H, 13′-H or 11′-H), 6.48 (s, 1H, 5′-H), 6.48−6.43 (m, 1H, 14′-H or 10′-H), 6.35 (d, *J* = 1.7 Hz, 1H, 12-H), 6.26 (s, 1H, 5-H), 6.02 (s, 2H, 10-H, 8′-H), 3.94 (d, *J* = 7.6 Hz, 1H, 1-H), 3.91−3.85 (m, 1H, 1′-H), 3.74 (s, 3H, 6-OCH_3), 3.52 (s, 3H, 6′- OCH_3), 3.50−3.43 (m, 1H, 3′-H), 3.28 (dd, *J* = 12.9, 7.0 Hz, 1H, α′-H), 3.17−3.11 (m, 2H, 3-H, α-H), 3.09 (s, 3H, 7- OCH_3), 2.96 (t, *J* = 11.0 Hz, 1H, α′-H), 2.93−2.73 (m, 6H, 3-H, 4-H, α-H, 4′-H, 3′-H), 2.56 (s, 3H, 2′-NCH_3), 2.49 (d, *J* = 19.4 Hz, 1H, 4-H), 2.37 (s, 3H, 2-NCH_3). ^{13}C NMR, DEPT, HMQC, HMBC (126 MHz, $CDCl_3$): δ [ppm] = 157.3 (C-11), 156.6 (C-12′), 152.0 (C-6), 149.8 (C-6′), 144.5 (C-9), 143.2 (C-7′), 136.8 (C-7), 135.4 (C-9′), 132.1 (C-14′ or C-10′), 130.1 (C-14′ or C-10′), 129.4 (C-4a), 129.1 (C-4a′), 127.5 (C-8a′), 121.9 (C-13′ or C-11′), 121.0 (C-13′ or C-11′), 120.7 (C-8a), 120.0 (C-8′), 117.6 (C-10), 111.3 (C-5′), 105.2 (C-5), 99.7 (C-12), 64.1 (C-1′), 63.2 (C-1), 60.7 (7-OCH_3), 55.9 (6-OCH_3), 55.6 (6′-OCH_3), 46.2 (C-3′), 44.8 (C-3), 43.1 (2′-NCH_3), 43.0 (2-NCH_3), 38.1 (C-α′), 33.8 (C-α),

25.5 (C-4′), 24.8 (C-4). The resonance of C-8 could not be identified. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2924, 2853, 1736, 1556, 1507, 1451, 1261, 1106, 1017, 798. Purity (HPLC) = 98%, d.r. >99:1 (λ = 210 nm). HRMS (ESI): *m/z* calcd for $[C_{35}H_{38}N_2O_5S + H]^+$ 599.2574, found: 599.2574.

RMS6: (1*R*,1′*R*)/(1*S*,1′*S*) isomers of carbamate **14c** (20.0 mg, 0.028 mmol) were reduced following General Procedure 4. The reaction was completed after 2 h. Purification by flash column chromatography (ethyl acetate → 2.0% trimethylamine in ethyl acetate, R_f = 0.08) affording the product as a beige solid (12.9 mg, 0.0215 mmol, 77%). mp: 251.5–252.5 °C. ^{1}H NMR, COSY (400 MHz, $CDCl_3$): δ [ppm] = 7.31 (dd, *J* = 8.2, 2.2 Hz, 1H, 14′-H or 10′-H), 7.13 (dd, *J* = 8.1, 2.6 Hz, 1H, 13′-H or 11′-H), 6.78 (dd, *J* = 8.3, 2.6 Hz, 1H, 13′-H or 11′-H), 6.50 (s, 1H, 5′-H), 6.44 (d, *J* = 1.7 Hz, 1H, 12-H), 6.29 (s, 1H, 5-H), 6.26 (dd, *J* = 8.3, 2.2 Hz, 1H, 14′-H or 10′-H), 6.24 (d, *J* = 1.7 Hz, 1H, 10-H), 5.90 (s, 1H, 8′-H), 3.93 (d, *J* = 7.2 Hz, 1H, 1-H), 3.79 (dd, *J* = 11.2, 5.5 Hz, 1H, 1′-H), 3.74 (s, 3H, 6-OCH_3), 3.52–3.43 (m, 1H, 3′-H), 3.36 (s, 3H, 6′-OCH_3), 3.31–3.21 (m, 2H, 3-H, α′-H), 3.13 (s, 3H, 7-OCH_3), 3.00–2.82 (m, 5H, 3-H, 4-H, α-H, 4′-H, 3′-H), 2.83–2.72 (m, 2H, α-H, α′-H), 2.76–2.67 (m, 1H, 4′-H), 2.58 (s, 3H, 2′-NCH_3), 2.46 (s, 3H, 2-NCH_3), 2.46–2.35 (m, 1H, 4-H). ^{13}C NMR, DEPT, HMQC, HMBC (101 MHz, $CDCl_3$): δ [ppm] = 156.9 (C-12′), 156.8 (C-11), 151.8 (C-6), 148.9 (C-6′), 148.9 (C-8), 144.3 (C-7′), 143.7 (C-9), 138.2 (C-7), 135.1 (C-9′), 132.7 (C-14′ or C-10′), 129.9 (C-14′ or C-10′), 128.5 (C-4a′), 128.0 (C-8a′), 123.7 (C-8a), 121.6 (C-13′ or C-11′), 121.0 (C-13′ or C-11′), 120.7 (C-8′), 118.5 (C-10), 112.9 (C-5′), 106.0 (C-5), 100.9 (C-12), 64.5 (C-1′), 61.8 (C-1), 60.3 (7-OCH_3), 55.9 (6-OCH_3), 55.9 (6′-OCH_3), 45.4 (C-3′), 44.5 (C-3), 42.8 (2′-NCH_3), 42.5 (2-NCH_3), 39.0 (C-α′), 37.5 (C-α), 24.9 (C-4′), 23.2 (C-4). The resonance of C-4a could not be identified. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2925, 2853, 1561, 1505, 1357, 1262, 1205, 1102, 1015, 809, 717. Purity (HPLC) = 97%, d.r. 96:4 (λ = 210 nm). HRMS (ESI): *m/z* calcd for $[C_{35}H_{38}N_2O_5S + H]^+$ 599.2574, found: 599.2580.

4.2.21. (±)-12-Desmethoxy-12-chlorotetrandrine and −isotetrandrine (***RMS7*-*8***)

RMS7: A solution of the (1*R*,1′*S*)/(1*S*,1′*R*) isomers of carbamate **14d** (40.0 mg, 0.0538 mmol) in 1.0 mL anhydrous THF was cooled to 0 °C and methyllithium (1.6 M solution in diethyl ether; 0.510 mL, 0.807 mmol, 15 equiv.) was added slowly. The mixture was stirred at 0 °C for 4 h and was then quenched with 1.0 mL deionized water. After alkalizing to pH 12–14 with 2.0 M NaOH solution, the mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to afford the secondary amine as a yellow oil. The crude amine was dissolved in 1.0 mL methanol, a solution of formaldehyde (37% in water; 20.0 μL, 0.269 mmol, 5 equiv.), one drop of acetic acid and sodium cyanoborohydride (10.7 mg, 0.161 mmol, 3 equiv.) was added. The mixture was stirred at ambient temperature for 12 h and the volatiles removed *in vacuo*. Purification by flash column chromatography (ethyl acetate → 3.0% trimethylamine in ethyl acetate, R_f = 0.16) afforded the product as a white solid (9.9 mg, 0.0159 mmol, 30%). mp: 227.5–230.0 °C. ^{1}H NMR, COSY (800 MHz, $CDCl_3$): δ [ppm] = 7.30 (d, *J* = 6.3 Hz, 1H, 14′-H or 10′-H), 7.25–7.22 (m, 1H, 13-H), 7.09 (d, *J* = 7.0 Hz, 1H, 13′-H or 11′-H), 6.79 (d, *J* = 8.2 Hz, 1H, 14-H), 6.62 (s, 1H, 13′-H or 11′-H), 6.54 (s, 2H, 10-H, 5′-H), 6.44 (s, 1H, 14′-H or 10′-H), 6.27 (s, 1H, 5-H), 5.97 (s, 1H, 8′-H), 3.87 (s, 1H, 1′-H), 3.80 (s, 1H, 1-H), 3.75 (s, 3H, 6-OCH_3), 3.61 (s, 3H, 6′-OCH_3), 3.40 (s, 1H, 3′-H), 3.26 (s, 2H, 3-H, α′-H), 3.13 (s, 3H, 7-OCH_3), 3.03 (d, *J* = 13.9 Hz, 1H, α-H), 2.92 (dt, *J* = 16.2, 6.1 Hz, 3H, 4-H, 4′-H, α′-H), 2.88–2.78 (m, 3H, 3-H, 4′-H, 3′-H), 2.66–2.54 (m, 2H, α-H), 2.58 (s, 3H, 2′-NCH_3), 2.44–2.30 (m, 1H, 4-H), 2.24 (s, 3H, 2-NCH_3). ^{13}C NMR, DEPT, HMQC, HMBC (201 MHz, $CDCl_3$): δ [ppm] = 155.7 (C-11), 153.8 (C-12′), 152.1 (C-6), 150.0 (C-6′), 143.7 (C-7′), 137.1 (C-7), 132.4 (C-14′ or C-10′), 130.5 (C-14′ or C-10′), 129.5 (C-13), 129.0 (C-4a′), 127.6 (C-8a′), 124.1 (C-14), 122.1 (C-13′ and C-11′), 120.6 (C-8a), 119.9 (C-8′), 119.5 (C-12), 116.5 (C-10), 111.4 (C-5′), 105.7 (C-5), 63.7 (C-1′), 62.1 (C-1), 60.6 (7-OCH_3), 55.9 (6-OCH_3), 55.7 (6′-OCH_3), 46.1 (C-3′), 42.8 (2-NCH_3 and 2′-NCH_3), 39.1 (C-α), 37.9 (C-α′), 25.8 (C-4′).The resonances of C-4a, C-8, C-9 and C-9′ could not be identified. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2925, 2799, 1579, 1505, 1412, 1262, 1205, 1113, 1021, 817. Purity (HPLC) = 96%, d.r. >99:1 (λ = 210 nm). HRMS (ESI): *m/z* calcd for $[C_{37}H_{39}^{35}ClN_2O_5 + H]^+$ 627.2620, found: 627.2621.

RMS8: The (1*R*,1′*R*)/(1*S*,1′*S*) isomers of carbamate **14d** (40.0 mg, 0.0538 mmol) were reacted and purified as described above for **RMS7** to afford the desired product as a white solid (10.0 mg, 0.0159 mmol, 30%). mp: 148.0–150.0 °C. ^{1}H NMR, COSY (400 MHz, $CDCl_3$): δ [ppm] = 7.36 (dd, *J* = 8.2, 2.2 Hz, 1H, 14′-H or 10′-H), 7.28 (d, *J* = 8.0 Hz, 1H, 13-H), 7.14 (dd, *J* = 8.2, 2.6 Hz, 1H, 13′-H or 11′-H), 6.90 (dd, *J* = 8.1, 1.9 Hz, 1H, 14-H), 6.76 (dd, *J* = 8.3, 2.6 Hz, 1H, 13′-H or 11′-H), 6.59 (d, *J* = 1.8 Hz, 1H, 10-H), 6.51 (s, 1H, 5′-H), 6.30 (s, 1H, 5-H), 6.30 (dd, *J* = 8.6, 2.1 Hz, 2H, 14′-H or 10′-H), 5.98 (s, 1H, 8′-H), 3.88 (dd, *J* = 10.9, 5.6 Hz, 1H, 1′-H), 3.75 (s, 3H, 6-OCH_3), 3.71 (d, *J* = 9.9 Hz, 1H, 1-H), 3.51–3.42 (m, 2H, 3-H, 3′-H), 3.37 (s, 3H, 6′-OCH_3), 3.27 (dd, *J* = 12.3, 5.7 Hz, 1H, α′-H), 3.18 (s, 3H, 7-OCH_3), 2.94 (qd, *J* = 19.6, 17.5, 7.8 Hz, 4H, 3-H, 4-H, 4′-H, 3′-H), 2.81 (t, *J* = 11.7 Hz, 1H, α′-H), 2.77–2.68 (m, 2H, α-H, 4′-H), 2.62 (s, 3H, 2′-NCH_3), 2.53 (d, *J* = 13.6 Hz, 1H, α-H), 2.44–2.37 (m, 1H, 4-H), 2.32 (s, 3H, 2-NCH_3). ^{13}C NMR, DEPT, HMQC, HMBC (101 MHz, $CDCl_3$): δ [ppm] = 155.4 (C-11), 153.5 (C-12′), 151.5 (C-6), 148.7 (C-6′), 143.8 (C-7′), 142.3 (C-9), 137.9 (C-7), 135.6 (C-9′), 132.8 (C-14′ or C-10′), 130.3 (C-14′ or C-10′), 129.5 (C-13), 128.2 (C-4a′), 127.9 (C-8a′), 123.9 (C-14), 122.6 (C-8a), 121.7 (C-13′ and C-11′), 120.2 (C-8′), 119.6 (C-12), 117.1 (C-10), 112.7 (C-5′), 105.8 (C-5), 63.9 (C-1′), 61.3 (C-1), 60.3 (7-OCH_3), 55.8 (6-OCH_3 and 6′-OCH_3), 45.2 (C-3′), 44.0 (C-3), 42.6 (2′-NCH_3), 42.2 (2-NCH_3), 42.1 (C-α), 38.2 (C-α′), 25.2 (C-4′), 21.8 (C-4). The resonances of C-8 and C-4a could not be identified. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2922, 1747, 1578, 1505, 1413, 1266, 1206, 1111, 1019, 836. Purity (HPLC) = 95%, d.r. >99:1 (λ = 210 nm). HRMS (ESI): *m/z* calcd for $[C_{37}H_{39}^{35}ClN_2O_5 + H]^+$ 627.2620, found: 627.2622.

4.2.22. (±)-Ring C propylidene analogues of tetrandrine and −isotetrandrine (***RMS9*-*10***)

RMS9: The first fraction of separated diastereomers of carbamate **14e** (20.0 mg, 0.0297 mmol) was reduced following General Procedure 4. The reaction was completed after 5 h. Purification by flash column chromatography (ethyl acetate → 3.0% trimethylamine in ethyl acetate, R_f = 0.15) afforded the product as a white solid (14.7 mg, 0.0264 mmol, 89%). mp: 92.0–94.0 °C. ^{1}H NMR, COSY (500 MHz, $CDCl_3$): δ [ppm] = 7.09 (dd, *J* = 8.3, 2.2 Hz, 1H, 14′-H or 10′-H), 6.96 (dd, *J* = 8.2, 2.6 Hz, 1H, 13′-H or 11′-H), 6.64 (s, 1H, 5′-H), 6.51 (dd, *J* = 8.4, 2.8 Hz, 1H, 13′-H or 11′-H), 6.33 (s, 1H, 5-H), 6.12 (dd, *J* = 8.4, 2.2 Hz, 1H, 14′-H or 10′-H), 5.42 (s, 1H, 8′-H), 4.27 (dt, *J* = 11.9, 4.5 Hz, 1H, 4″-H), 4.03 (ddd, *J* = 12.3, 9.2, 3.7 Hz, 1H, 4″-H), 3.84 (s, 3H, 6′-OCH_3), 3.73 (s, 3H, 6-OCH_3), 3.56 (dd, *J* = 10.6, 5.7 Hz, 1H, 1′-H), 3.41–3.33 (m, 1H, 3′-H), 3.30–3.21 (m, 2H, 1-H, 3-H), 3.15 (s, 3H, 7-OCH_3), 3.14–3.10 (m, 1H, α′-H), 2.92–2.83 (m, 2H, 4-H, 4′-H), 2.83–2.77 (m, 3H, 3-H, 4′-H, 3′-H), 2.70 (dd, *J* = 12.7, 10.6 Hz, 1H, α′-H), 2.51 (s, 3H, 2′-NCH_3), 2.45 (s, 3H, 2-NCH_3), 2.44–2.38 (m, 1H, 4-H), 1.78–1.68 (m, 2H, 3″-H, 2″-H), 1.66–1.53 (m, 2H, 3″-H, 1″-H), 1.48–1.36 (m, 2H, 2″-H, 1″-H). ^{13}C NMR, DEPT, HMQC, HMBC (126 MHz, $CDCl_3$): δ [ppm] = 155.4 (C-12′), 152.0 (C-6), 150.5 (C-6′), 145.5 (C-7′), 138.6 (C-7), 131.9 (C-14′ or C-10′), 131.1 (C-9′), 129.7 (C-14′ or C-10′), 129.2 (C-4a), 128.9 (C-4a′), 128.3 (C-8a′), 123.2 (C-8a), 120.5 (C-8′), 119.0 (C-13′ or C-11′), 115.6 (C-13′ or C-11′), 112.0 (C-5′), 107.4 (C-5), 68.1 (C-4″), 64.5 (C-1′), 60.3 (7-OCH_3), 57.9 (C-1), 56.4 (6′-OCH_3), 55.9 (6-OCH_3), 46.1 (C-3′), 44.1 (C-3), 42.8 (2′-NCH_3), 41.9 (2-NCH_3), 38.2 (C-α′), 33.9 (C-1″), 26.8 (C-3″), 25.7 (C-4′), 22.7 (C-4), 21.4 (C-2″). The resonance of C-8 could not be identified. IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2925, 2850, 1607, 1508, 1451, 1266, 1216, 1010,

832, 750. Purity (HPLC) = 96%, d.r. >99:1 (λ = 210 nm). HRMS (ESI): *m/z* calcd for $[C_{34}H_{42}N_2O_5 + H]^+$ 559.3166, found: 559.3163.

RMS10: The second fraction of separated diastereomers of carbamate **14e** (18.0 mg, 0.0267 mmol) was reduced following General Procedure 4. The reaction was completed after 5 h. Purification by flash column chromatography (ethyl acetate → 3.0% trimethylamine in ethyl acetate, R_f = 0.15) afforded the product as a white solid (10.4 mg, 0.0186 mmol, 70%). mp: 153.5 °C. ^{1}H NMR, COSY (400 MHz, $CDCl_3$): δ [ppm] = 7.22 (dd, *J* = 8.3, 2.3 Hz, 1H, 14′-H or 10′-H), 6.89 (dd, *J* = 8.3, 2.7 Hz, 1H, 13′-H or 11′-H), 6.72 (dd, *J* = 8.3, 2.7 Hz, 1H, 13′-H or 11′-H), 6.48 (s, 1H, 5′-H), 6.29 (dd, *J* = 8.3, 2.2 Hz, 1H, 14′-H or 10′-H), 6.25 (s, 1H, 5-H), 5.53 (s, 1H, 8′-H), 4.29 (dt, *J* = 9.9, 4.6 Hz, 1H, 4″-H), 4.06 (ddd, *J* = 11.7, 9.0, 3.2 Hz, 1H, 4″-H), 3.77–3.73 (m, 1H, 1′-H), 3.72 (s, 3H, 6-OCH_3), 3.66 (dd, *J* = 8.2, 3.6 Hz, 1H, 1-H), 3.51 (s, 3H, 6′-OCH_3), 3.40–3.25 (m, 2H, 3-H, 3′-H), 3.22 (dd, *J* = 12.6, 5.0 Hz, 1H, α′-H), 3.05 (s, 3H, 7-OCH_3), 3.00–2.77 (m, 4H, 3-H, 4-H, 4′-H, 3′-H), 2.71–2.61 (m, 2H, 4′-H, α′-H), 2.59 (s, 3H, 2′-NCH_3), 2.44 (s, 3H, 2-NCH_3), 2.38 (dd, *J* = 16.3, 5.7 Hz, 1H, 4-H), 1.91–1.81 (m, 1H, 3″-H), 1.73–1.56 (m, 3H, 3″-H, 2″-H), 1.55–1.45 (m, 2H, 1″-H). ^{13}C NMR, DEPT, HMQC, HMBC (101 MHz, $CDCl_3$): δ [ppm] = 158.1 (C-12′), 151.7 (C-6), 149.1 (C-6′), 148.7 (C-8), 143.6 (C-7′), 137.3 (C-7), 132.4 (C-14′ or C-10′), 131.4 (C-9′), 129.7 (C-14′ or C-10′), 128.4 (C-4a′), 128.3 (C-4a), 127.9 (C-8a′), 122.6 (C-8a), 121.0 (C-8′), 117.2 (C-13′ or C-11′), 116.0 (C-13′ or C-11′), 111.7 (C-5′), 105.8 (C-5), 68.6 (C-4″), 64.3 (C-1′), 60.2 (7-OCH_3), 58.9 (C-1), 55.9 (6-OCH_3), 55.8 (6′-OCH_3), 45.4 (C-3′), 43.9 (C-3), 42.6 (2′-NCH_3), 41.9 (2-NCH_3), 38.1 (C-α′), 34.8 (C-1″), 29.4 (C-3″), 25.8 (C-4′), 23.5 (C-2″), 22.3 (C-4). IR (ATR): $\tilde{\nu}$ [cm^{-1}] = 2926, 2854, 1656, 1578, 1507, 1352, 1262, 1203, 1114, 1012, 812. Purity (HPLC) = 98%, d.r. >99:1 (λ = 210 nm). HRMS (ESI): *m/z* calcd for $[C_{34}H_{42}N_2O_5 + H]^+$ 559.3166, found: 559.3172.

Author contributions

MM and RMS developed the concept. RMS, MM and FG conducted experiments. RMS and MM wrote the paper. AMV, FB, FG and KB substantially revised the manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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