



**HAL**  
open science

## Structure simplification of the Securinine skeleton reveals the importance of BCD ring system for the cytotoxic activity on HCT116 and HL60 cell lines

Myriam Le Roch, Damien Afonso, Egor Chirkin, Xavier Guillory,  
François-Hugues Porée

### ► To cite this version:

Myriam Le Roch, Damien Afonso, Egor Chirkin, Xavier Guillory, François-Hugues Porée. Structure simplification of the Securinine skeleton reveals the importance of BCD ring system for the cytotoxic activity on HCT116 and HL60 cell lines. *Bioorganic and Medicinal Chemistry*, Elsevier, 2022, 58, pp.116658. 10.1016/j.bmc.2022.116658 . hal-03683055

**HAL Id: hal-03683055**

<https://hal-univ-rennes1.archives-ouvertes.fr/hal-03683055>

Submitted on 31 May 2022

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

## Structure simplification of the *Securinine* skeleton reveals the importance of BCD ring system for the cytotoxic activity on HCT116 and HL60 cell lines

Myriam Le Roch<sup>1</sup>, Damien Afonso<sup>1</sup>, Egor Chirkin<sup>2</sup>, Xavier Guillory<sup>1,3</sup> and François-Hugues Porée<sup>1\*</sup>

<sup>1</sup>ISCR UMR CNRS 6226, Université de Rennes 1 – Faculté de Pharmacie, Laboratoire de Chimie Thérapeutique, 2 Avenue du Pr Léon Bernard, F-35000 Rennes, France

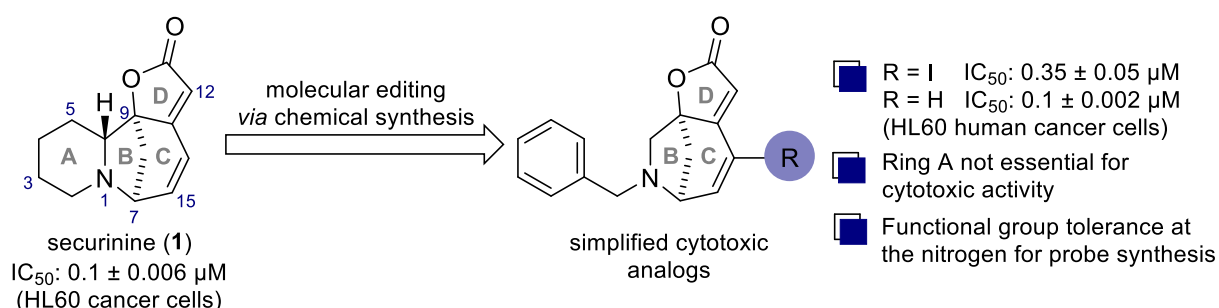
<sup>2</sup>Institut Pasteur, Collection des Cyanobactéries, Département de Microbiologie, 25-28 rue du Docteur Roux, 75015 Paris, France

<sup>3</sup>INSERM U1242, Université de Rennes 1, Rue de la Bataille Flandres Dunkerque, F-35000 Rennes, France

(ORCID: XG 0000-0001-5989-3833; EC 0000-0002-4166-7536; FHP 0000-0003-3344-5260)

Key-words: *Securinega*, simplified analogs, molecular editing, cytotoxicity, HL60, HCT116

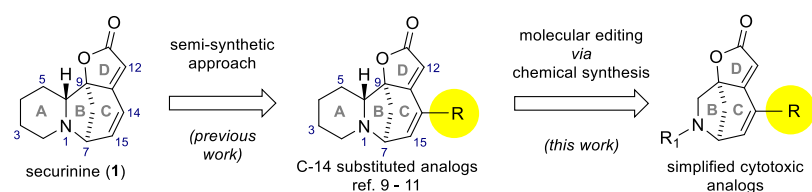
**Abstract:** Function-oriented molecular editing of the polycyclic scaffold of securinine led to the preparation of a library of simplified analogs that have been evaluated for their cytotoxicity potential against HCT116 and HL60 human cell lines. Chemical diversity at the C14 position (securinine numbering) was generated through the site-selective  $\gamma$ -iodination followed by Pd-catalyzed Sonogashira and Suzuki-Miyaura reactions. To explain the selectivity in the iodination step, a reaction mechanism has been proposed. Surprisingly, the piperidine ring (ring A) of the securinine skeleton has been found to be irrelevant for the cytotoxic activity. Based on this finding, the pharmacophoric core of securinine could be simplified to the key BCD motif. The nature of the substituent at the nitrogen can vary from a methyl or an isobutyl group to a benzyl or a carbamate moiety. Interestingly, the *N*-benzyl substituted simplified analog exhibited the same cytotoxic activity as the parent compound securinine. This functional group tolerance paves the way for the installation of reactive handles for the synthesis of molecular probes for target identification.



## 1. Introduction

*Securinega* alkaloids represent a unique class of plant metabolites whose botanical distribution is limited to *Securinega* (= *Flueggea*), *Phyllanthus*, *Margaritaria* and *Breynia* genera (Phyllanthaceae family) with the exception of *Zygogynum pauciflorum* species (Winteraceae). To date, more than 60 compounds have been isolated and characterized allowing their classification in four groups according to the unique bridged tetracyclic scaffold which includes the securinane, the norsecurinane, the neosecurinane and the norneosecurinane.<sup>1</sup> Recent phytochemical investigations led to the isolation of original minor alkaloids displaying complex and rearranged structures which in turn provided insights into some biosynthetic pathways.<sup>2</sup> In addition, extensive analytical work was conducted over the last years to assign the absolute stereochemistry of new derivatives, leading to the revision or the structure clarification of some already known alkaloids.<sup>3</sup> However, further work is still needed to elucidate the whole biosynthetic machinery for the *Securinega* alkaloids.

The original and complex architecture of the *Securinega* alkaloids prompted the chemist's community to develop versatile and efficient strategies to access these compounds.<sup>4,5</sup> Of note, most of the efforts were focused on securinine (**1**), the first isolated and most emblematic representant of this alkaloid family.<sup>6</sup> The biological potential of these compounds has also been profiled with a particular emphasis on securinine (**1**) which displays interesting properties as a central nervous system (CNS) and anticancer agent.<sup>7</sup> Because of its CNS stimulant and antispasmodic properties the nitrate salt of securinine (**1**) was clinically used in the USSR as a substitute for strychnine until the early 1990s.<sup>8</sup> In addition, antimicrobial properties of securinine and its congeners have been reported.<sup>7a</sup> Despite these compelling activities and a safe pharmacological profile, the structure-activity relationships (SAR) studies on the securinine scaffold have been to this day confined to easily accessible reactive positions. Thus far, derivatization at the C12, C14<sup>9,10</sup> and C15<sup>11,12</sup> positions has been explored and has shown to increase in some cases the overall potential of securinine (**1**) (**Scheme 1**). Because of the complexity of diverted total synthesis of **1**, all previous studies exploited the semi-synthetic approach starting from the natural alkaloid.



**Scheme 1.** C14-functionalized simplified *Securinega* analogs.

Interest for securinine (**1**) as a hit for further development as anticancer agent came mainly from Wald *et al.* who described its potential on both HCT116 and HL60 cancer cell lines.<sup>13</sup> In particular, a significant effect of securinine (**1**) in a xenograft mouse model for acute myeloid leukemia. Later, the cytotoxic activity was extended to others cancer cell lines such as MCF-7<sup>14</sup> and SW480<sup>15</sup>. Some pharmacological investigations have been carried out to elucidate the mechanism of action of securinine (**1**). Thus, securinine (**1**) was shown to downregulate in a dose- and time-dependent manner the PI3K/AKT/mTOR signaling pathway<sup>16</sup> and to activate the JNK-ERK signaling pathway<sup>17</sup> in HL60 cells line, respectively. Action on these pathways provokes the differentiation of the HL60 cells to monocytic lineage which ultimately causes cell

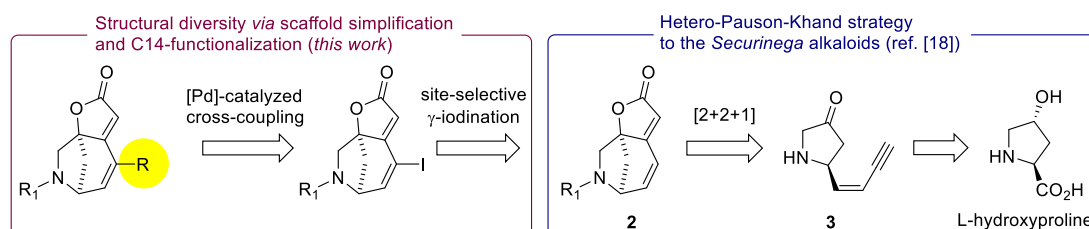
death. Other effects including ROS generation and mitochondrial dysfunction were also observed, all of these contributing to the apoptosis activation upon exposure to securinine (**1**). Furthermore, securinine (**1**) was identified to inhibit protein disulfide isomerase (PDI), a redox-dependent folding assistant whose overexpression is linked to cancer development.<sup>18</sup> The  $\alpha,\beta$  unsaturated lactone motif of securinine (**1**) was found to be crucial for the PDI inhibition by acting as a Michael acceptor. Despite its apparent risk profile due to the presence of a conjugated butenolide, securinine (**1**) was not identified as a pan-assay interference compound (PAIN) by on-line PAINS filters.<sup>19</sup> It is also worth mentioning that securinine (**1**) was used as a CNS drug for several decades and its *in vitro* metabolic stability was confirmed recently.<sup>18</sup> Therefore, securinine could be rationally considered as a good starting point for SAR exploration. Recent semi-synthetic studies on securinine (**1**) conducted separately by Wald *et al.* and Vidal *et al.* highlighted the C14 position as an interesting location for late-stage functionalization. Their strategy consisted in introducing at this position an iodine atom to subsequently carry out a Suzuki-Miyaura or a Sonogashira coupling reaction. These studies illustrated the interest in modulating the C14 position of securinine (**1**) to increase its antiproliferative properties against HL60 cell line and, to a lesser extent, HCT116 cell line. Unfortunately, as demonstrated by Vidal *et al.*, the Sonogashira adducts bearing a conjugated triple bond displayed low plasmatic stability. The C15 position was also subject to medicinal chemistry efforts. This position is synthetically advantageous as it can be directly functionalized either by Michael addition<sup>10b,11</sup> or by Heck coupling<sup>10a</sup>. Of note, in the Michael addition, the conjugated  $\alpha,\beta$ -unsaturated- $\gamma$ -lactone is lost and the C15-derivatives obtained were devoid of cytotoxic activities, thus establishing the importance of the conjugated unsaturated system in the pharmacophore model. Outside of the semi-synthetic modifications listed above, SAR studies employing the analogs resulting from the molecular editing of the securinine skeleton are critically missing. In particular, the importance of the piperidine ring (cycle A) for the cytotoxic activity of **1** is yet unknown.

## 2. Results and discussion

In order to fill this lacuna of knowledge, we sought to access the first-in-class library of simplified analogs of **1** lacking the piperidine ring and to investigate their antiproliferative potential against HCT116 and HL60 cancer cell lines. The rationale for the choice of these two cancer cell lines is linked to the previous results reported separately by the groups of Wald and Vidal, which showed a promising activity of securinine (**1**) and its C14-analogs. In our previous work, we have reported a straightforward route to the critical BCD core **2** of securinine (**1**) and related alkaloids (**Scheme 2**).<sup>20</sup> The tricyclic core **2** can be considered on its own as a simplified securinine analog which would allow to study the contribution of the cycle A to the biological activity of **1**. Moreover, BCD core **2** can be further explored as a starting point for the synthesis of analogs that are not otherwise accessible through the semi-synthetic route. Central to this approach is generating a great deal of structural complexity through the strategic application of a [2+2+1]-*hetero*-Pauson-Khand reaction. The pivotal enyne **3** could be accessed from L-hydroxyproline through a Z-selective olefination. Next, we envisaged that the C14-selective iodination of **2** should be possible as it had been demonstrated earlier by Chen *et al.* for

securinine (**1**).<sup>21</sup> Then, either a Suzuki-Miyaura or a Sonogashira Pd-catalyzed cross coupling reaction would be utilized to generate structural diversity.

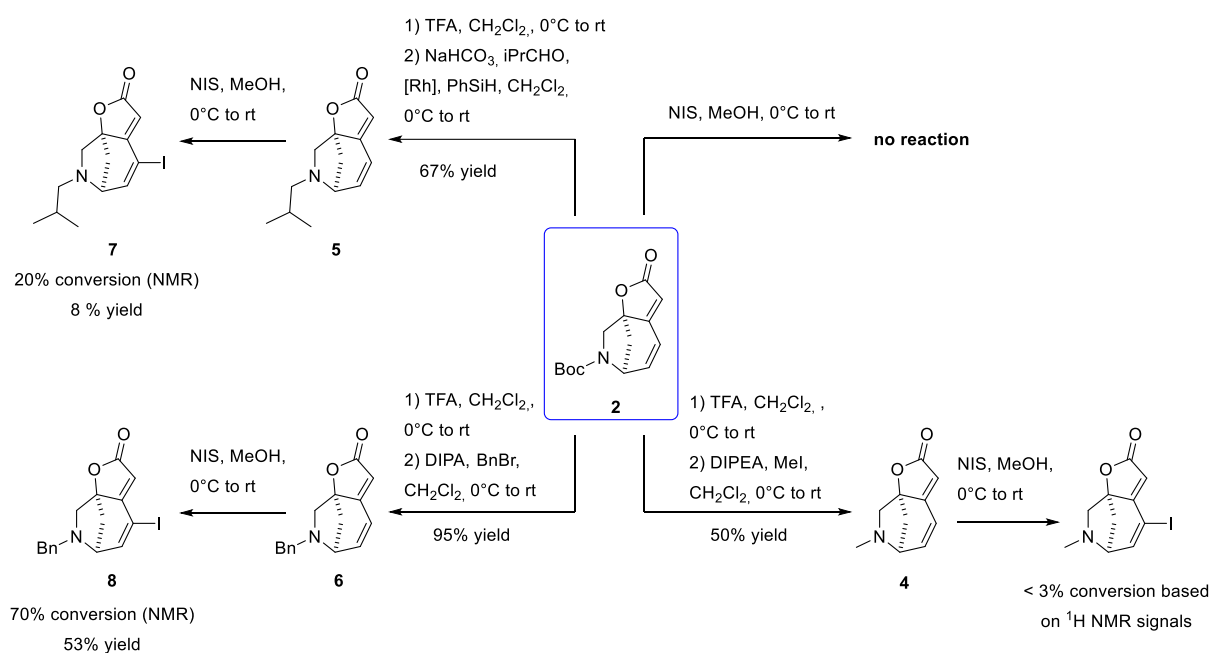
Acquiring **2** in large quantities was the major limitation for preparation of analogs through the late-stage functionalization approach. Some modifications to the previous report were made to secure the preparation of **2** in acceptable yields on a higher scale. In particular, the modified Julia olefination reaction to install the *Z*-enyne motif could be carried out on the gram scale with high reproducibility.<sup>22</sup> In this case, the premetallated conditions *i.e.* treatment of the sulfone with NaHMDS prior to the aldehyde addition, were preferred and the reaction went to completion within 1.5 h (TLC monitoring) at -55°C with a good yield (82%). Also, the conditions for the key *hetero*-Pauson-Khand cyclization were simplified: the reaction was performed at a 1.7 mmol scale in the absence of CO atmosphere. Under these conditions, the reaction was very fast (1 h), albeit the overall yields could not be improved beyond 49% despite numerous efforts. To the best of our knowledge, the use of molybdenum hexacarbonyl as a donor of CO in *hetero*-Pauson-Khand reaction is without precedent.<sup>23</sup>



**Scheme 2.** *hetero*-Pauson-Khand strategy to the BCD-core of securinine (**1**) and related alkaloids (*right*); synthetic plan for simplified analogs via scaffold simplification (*left*).

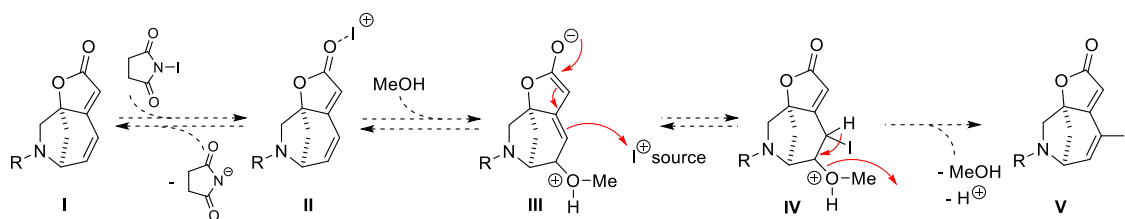
We then turned our efforts to the site-selective  $\gamma$ -iodination reaction. This reaction was serendipitously discovered by Chen *et al.* for securinine (**1**) and is known to give the C14-iodinated derivative in a modest 40% yield together with minor by-products resulting from the A-ring contraction.<sup>19</sup> We speculated that the tricyclic core **2** lacking the A-ring should exhibit even a higher level of site-selectivity. To our surprise, exposure of **2** to *N*-iodosuccinimide (NIS) in dry methanol resulted in recovery of the starting material with no trace of the iodinated derivative formed. To circumvent the unexpected lack of reactivity of **2**, we explored several other iodination conditions:  $I_2$ ,  $K_2CO_3$ ,<sup>24</sup>  $ICl_2$ ,<sup>25</sup>  $I_2$ ,  $CF_3CO_2Ag$ .<sup>26</sup> In addition, the preparation of the corresponding bromo analog was attempted either by dibromation followed by elimination of  $HBr$ ,<sup>27</sup> or *via* photocatalysis.<sup>28</sup> None of these reaction conditions furnished the expected halogenated compound. At this point, we postulated that the nature of the substituent at the nitrogen atom of **2** could play a dramatic role in the reactivity of the conjugated system. From compound **2**, *N*-methyl- (**4**), *N*-isobutyl- (**5**) and *N*-benzyl- (**6**) derivatives were prepared by acid promoted Boc removal followed by direct *N*-alkylation or reductive amination<sup>29</sup> of the amine trifluoroacetic salt. These derivatives were further treated with NIS in dry methanol according to the initial procedure (**Scheme 3**). Under these conditions, *N*-methyl substituted **4** was almost unreactive and only traces of the corresponding iodo compound were observed in the <sup>1</sup>H NMR spectrum. In the case of a *N*-isobutyl substituent (**5**), a conversion of 20% was observed by <sup>1</sup>H NMR and the iodo compound **7** was isolated in less than 10% yield by preparative TLC. The *N*-benzyl derivative **6** was the most reactive with 70% of conversion observed by <sup>1</sup>H NMR and compound **7** was isolated in 53% yield.

The energies of the highest occupied molecular orbitals (HOMO) of securinine (**1**) and compounds **2** (Boc), **4** (Me), **5** (iBu) and **6** (Bn) were calculated by DFT at the B3LYP-D3\_6-311++G(d,p) level. Among all compounds, the Boc-protected analog **2** showed the lowest HOMO level (-6.91 eV, see 4.2 Computational Details Fig 1). The electron-withdrawing substituent at the nitrogen impacted the electron density distribution in **2**, in particular at the C14 position, leading to a higher conjugation of the C14-15 double bond to the butenolide system. This observation could explain the lack of reactivity of **2** in the iodination reaction.



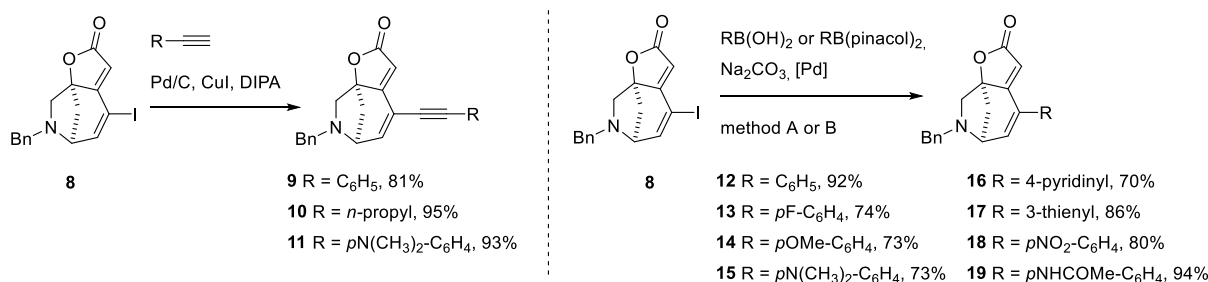
**Scheme 3.** C14-iodination of the BCD scaffold

In the report of Chen *et al.*, the mechanistic origin of the high site-selectivity in the iodination of securinine (**1**) had not been revealed. To explain the formation of the iodo adducts **7** and **8**, we put forward the mechanism outlined in **Scheme 4**. NIS is known to be a source of Lewis-acidic I<sup>+</sup> and may activate carbonyl group for nucleophilic attack (**intermediate II**).<sup>30</sup> Then, the electron-deficient tricyclic **II** undergoes conjugate addition of methanol to the reactive C15 position to form a transient zwitterion **III**. Electrophilic capture of **III** by NIS gives rise to a vicinal iodo-methoxy derivative **IV** which in turn undergoes subsequent elimination to provide iodo-derivative **V**. The similar Morita-Baylis-Hillman-type mechanistic pathways have been reported for the  $\alpha$ -iodination of  $\alpha,\beta$ -unsaturated ketones<sup>31</sup>, acrylate esters<sup>32</sup> and nitroalkenes<sup>33</sup>. It is interesting to note that NIS may play a dual role, as an electrophile and as a catalyst for the nucleophilic addition of methanol. In the case of *N*-alkyl substituted derivatives (compounds **1**, **4-6**), the observed difference of reactivity could be rationalized in terms of steric hindrance around the nitrogen atom. One could postulate that the lone pair of the nitrogen reacts with the iodonium to form a quaternary ammonium salt thus preventing the iodination step. With a small substituent such as a methyl, the iodonium sequestration is fast and the yield of the iodo derivative is poor, whereas the presence of a bulkier group such as an isobutyl or a benzyl favors the C14-selective iodination by blocking the access to the nitrogen by steric hindrance.



**Scheme 4.** Proposed mechanism for the iodination reaction.

Chemical diversity at the C14 position was introduced by Pd-mediated Suzuki-Miyaura and Sonogashira reactions (**Scheme 5**). For the Sonogashira reaction, three different partners were selected (phenyl, *n*-propyl and *p*-dimethylaminophenyl) based on the most active securinine analogs reported in the previous studies. Application of phosphine-free conditions enabled the preparation of the adducts in very good yields. However, these unstable compounds were unsuitable for storage and could not be investigated for their biological properties.<sup>34</sup> Two different reaction conditions were applied in the Suzuki-Miyaura reaction depending on the nature of the boronic acids or esters used. Phosphine-free conditions could be used with boronic acids and esters possessing an electron-donating group whereas the presence of an electro-attracting group prompted us to envisage palladium tetrakis as the Pd source.<sup>35</sup> The overall yields were good to excellent.



**Scheme 5.** C14-Functionalization by Pd coupling.

**Table 1.** Cytotoxic activity of simplified securinine analogs on colon cancer HCT116 and acute leukemia HL60 cell lines (% viability).

Compound	HCT116 (% viability)		HL60 (% viability)	
	10 μM	1 μM	10 μM	1 μM
Securinine ( <b>1</b> )	13 ± 0.5	98 ± 5	0.4 ± 0.2	8 ± 0.3
Boc-butenolide <b>2</b>	11 ± 1	94 ± 4	0.2 ± 0.1	7 ± 1
Me-butenolide <b>4</b>	92 ± 4	94 ± 5	4 ± 0.6	25 ± 7
Isobutyl-butenolide <b>5</b>	78 ± 4	83 ± 4	1 ± 0.3	15 ± 0.4
Bn-butenolide <b>6</b>	86 ± 3	100 ± 5	3 ± 0.8	11 ± 1
14-iodo Bn-butenolide <b>8</b>	1 ± 0.05	5 ± 1	0 ± 0.1 <sup>a</sup>	4 ± 1
14-phenyl Bn-butenolide <b>12</b>	89 ± 2	92 ± 2	2 ± 0.7	7 ± 0.3
14- <i>p</i> F-phenyl Bn-butenolide <b>13</b>	90 ± 5	100 ± 4	1 ± 0.2	7 ± 0.7
14- <i>p</i> OMe-phenyl Bn-butenolide <b>14</b>	100 ± 2	100 ± 1	4 ± 0.3	18 ± 1
14- <i>p</i> N(CH <sub>3</sub> ) <sub>2</sub> -phenyl Bn-butenolide <b>15</b>	84 ± 5	95 ± 4	1 ± 0.06	7 ± 3
14-pyridin-4-yl Bn-butenolide <b>16</b>	100 ± 1	100 ± 4	9 ± 1	9 ± 3

14-thiophen-3-yl Bn-butenolide <b>17</b>	90 ± 2	100 ± 1	3 ± 0.5	7 ± 1
14- <i>p</i> NO <sub>2</sub> -phenyl Bn-butenolide <b>18</b>	15 ± 0.5	93 ± 1	2 ± 0.1	3 ± 0.9
14- <i>p</i> -acetamido-phenyl Bn-butenolide <b>19</b>	89 ± 2	98 ± 6	1 ± 0.1	10 ± 2

All derivatives showed low activity levels against the HCT116 cancer cell line nearly similar to those reported previously by Vidal *et al.* for the tetracyclic *Securinega* analogs, with the exception of the iodinated compound **8** which displayed interesting properties.<sup>10</sup> It is worth mentioning that the tetracyclic securinine equivalent of iodo derivative **8** described by Vidal *et al.* also demonstrated a high percentage of growth inhibition at 1 μM (80.9%) on the same cell line. This result may serve as a compelling argument to suggest that the ring A is not important while the presence of the iodine is crucial for the antiproliferative activity. A few examples of marketed drugs containing an iodine such as levothyroxine or amiodarone are limited to aromatic compounds. The chemical stability of nontrivial vinyl iodo motif of **8** in biological media should be carefully evaluated prior to any further development. In context of this study, we urge caution on this point and consider compound **8** as an intermediate to access C14-functionalized derivatives rather than an optimizable hit. Regarding the effects on HL60 cell line, most of the analogs displayed an activity close to that of securinine at 1 μM. It is thus worth noting that the removal of the piperidine A ring and its replacement by a bulky (**2**, Boc) or a hydrophobic (**6**, benzyl) substituent didn't significantly alter the cytotoxic activity compared to securinine (**1**). Other structural modifications at the C14 position didn't improve the cytotoxicity and had a low to moderate impact on the activity. Despite being moderate, these results are interesting as they highlight the opportunity to simplify the skeleton of securinine without losing the overall effect. Of note, the *p*-nitrophenyl derivative was the most potent of this series

**Table 2.** IC<sub>50</sub> (μM) of selected compounds on HCT116 and HL60 cell lines.

Compound	IC <sub>50</sub> (μM)	
	HCT116	HL60
Securinine ( <b>1</b> )	8.6 ± 0.28	0.1 ± 0.006
Bn-butenolide <b>6</b>	ND	0.1 ± 0.002
14-iodo Bn-butenolide <b>8</b>	0.06 ± 0.002	0.35 ± 0.05
14- <i>p</i> NO <sub>2</sub> -phenyl Bn-butenolide <b>18</b>	5.8 ± 0.51	> 10
Doxorubicin (reference)	0.01 ± 0.001	0.09 ± 0.003

Taking these results into account, compounds **6**, **8** and **18** were selected for determination of their IC<sub>50</sub> and compared to securinine (**1**), the parent compound (**Table 2**). As previously observed, securinine (**1**) was more active against HL60 cell line than HCT116 cell line with an IC<sub>50</sub> of 0.1 ± 0.006 μM and 8.6 ± 0.28 μM, respectively. Interestingly, the benzyl analog **6** demonstrated on HL60 cell line an IC<sub>50</sub> value that was nearly similar to securinine (**1**). This finding highlights in a quantitative manner that the piperidine ring is not crucial for the cytotoxic activity. Moreover, presence of an aromatic substituent at the nitrogen position is well tolerated and could pave the way for the introduction of a reactive or fluorescent tag for further target



identification or biological exploration on this cell line. On the other hand, IC<sub>50</sub> determination on *p*-nitrophenyl derivative **18** was less conclusive. Despite an IC<sub>50</sub> value comparable to securinine (**1**) on HCT116 cell line, the strong effect of **18** on the viability of HL60 cell line could not be correlated with an increased IC<sub>50</sub> value (above 10 μM).

### 3. Conclusion

In conclusion, the first-in-class library of simplified securinine analogs built on the BCD core of the securinine skeleton and functionalized at the C14 position has been prepared. Molecular editing approach provided new insights into the functional dissection of the polycyclic architecture of the *Securinega* alkaloids. It has been found that the piperidine ring A of securinine (**1**) is not essential for its cytotoxic activity. The simplification of the pharmacophoric core of **1** to the key BCD motif will greatly facilitate the synthesis of analogs for further SAR exploration of the *Securinega* alkaloids. Several conclusions can be drawn from the analysis of the prepared library. The Sonogashira adducts were found to be not stable and could not be considered for further development. The substituents at the nitrogen atom ranging from a benzyl to a carbamate moiety were tolerated without impacting the overall cytotoxic activity. This functional group tolerance represents an opportunity to install reactive handles for the synthesis of molecular probes for target identification. This would open the way to a structure-based drug design approach and the rational design of novel analogs. Finally, new mechanistic details on the C14-selective  $\gamma$ -iodination were revealed. The reaction outcome was found to be influenced by the nature of the substituent at the nitrogen. We hypothesize that the presence of a Boc group prevents the nucleophilic attack through electronic effects, whereas a benzyl group furnished the best results as it closely mimics the parent alkaloid securinine (**1**). We also propose for the first time a reaction mechanism for the formation of the C14 iodo adducts that relies on a Morita-Baylis-Hillman-type reaction. Taken together, we believe that the reported results would accelerate the research on securinine (**1**) and related compounds as leads for anticancer therapy development.

## 4. Experimental

### 4.1. Chemistry

All reactions were carried out under argon atmosphere with anhydrous solvents under anhydrous conditions, unless otherwise stated. Commercially available reagents were used without further purification, unless otherwise stated. Yields refer to isolated yields, unless otherwise noted. NMR spectra were recorded on Bruker Avance 300 instrument in CDCl<sub>3</sub> or CD<sub>2</sub>Cl<sub>2</sub>. The signal of the residual non-deuterated solvent was used as the internal standard. Chemical shifts ( $\delta$ ) are reported in parts per million (ppm). The following abbreviations are used for multiplicities: s, singlet; d, doublet; t, triplet; dd, doublet of doublets; td, triplet of doublets; dt, doublet of triplets; ddd, doublet of doublets of doublets; m, multiplet. Coupling constants (*J*) are reported in Hertz (Hz) and were processed with MNova software. IR spectra were recorded on Perkin Elmer FT-IR instrument (spectrum two); only selected absorbances are reported. HRMS analyses of new compounds were performed by the "Centre Regional de Mesures Physiques de l'Ouest" (CRMPO, Rennes), and were obtained using a Bruker Maxis 4G or an Agilent 6510 Q-TOF. Optical rotations ( $\alpha$ ) were recorded on a Perkin Elmer Model

341 polarimeter at 589 nm, in a 1 dm cell and at temperature T (°C). Specific rotations  $[\alpha]_D^T$  were determined from the following formula  $[\alpha]_D^T = \alpha \times 100 / c$  (c concentration, g/100 mL).

#### 4.1.1. Boc-butenolide 2.

Part 1: modified Julia-Kocienski olefination. To a stirred solution of 2-[(3-(trimethylsilyl)prop-2-yn-1-yl)sulfonyl]benzo[d]thiazole (2.195 g, 7.09 mmol, 1.1 eq) in dry THF (200 mL) at -78°C was added dropwise NaHMDS (7.1 mL, 1M solution in THF). The reaction mixture was stirred for 15 min before addition of a solution of tert-butyl (2*S*,4*R*)-4-[(tert-butyldimethylsilyl)oxy]-2-formylpyrrolidine-1-carboxylate (2.125 g, 6.45 mmol, 1.0 eq) in dry THF (22 mL). The resulting mixture was stirred at -55°C for 1.5 h, then allowed to warm to -10°C. Brine (250 mL) and diethyl ether (250 mL) were added. After 0.5 h, the layers were separated and the aqueous phase was extracted with diethyl ether (2x200 mL). The combined organic layers were washed with brine (200 mL), dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo* to afford a brown oil. Chromatography on silica gel (cyclohexane/EtOAc, 9:1) gave the title compound as a pale-yellow oil (2.245 g, 82 % yield).

Part 2: *hetero*-Pauson-Khand cyclization. A Schlenk-tube was charged with Mo(CO)<sub>6</sub> (1.15 g, 4.35 mmol, 2.5 eq) and dry DMF (19 mL). Then, a solution of (*S*)-*tert*-Butyl 2-[(*Z*)-But-1-en-3-ynyl]-4-oxopyrrolidine-1-carboxylate (410 mg, 1.74 mmol, 1 eq) in dry toluene (33 mL) was added. The resulting mixture was stirred for 1h at 140 °C and then cooled to rt. The contents were transferred into a round bottom flask and concentrated *in vacuo*. The resulting black residue was suspended into ethyl acetate and filtered through celite then washed thoroughly with ethyl acetate. The combined organic layer was concentrated *in vacuo* to afford a black oil which was subjected to chromatography on silica gel (CH<sub>2</sub>Cl<sub>2</sub>/Et<sub>2</sub>O, 95:5) to give Boc-butenolide **2** as a pale-yellow solid (223 mg, 49 % yield). The analytical data were identical to those reported by Chirkin *et al.*

#### 4.1.2. Methyl-butenolide 4

To a solution of boc-butenolide **2** (100 mg, 0.38 mmol, 1 eq) in dry CH<sub>2</sub>Cl<sub>2</sub> (3.4 mL) at 0 °C was added trifluoroacetic acid (0.6 mL). The resulting solution was stirred allowing to warm to rt for 2 h. Volatiles were removed *in vacuo* to afford the corresponding TFA-salt as a brown solid. The residue was suspended in dry CH<sub>2</sub>Cl<sub>2</sub> (4 mL) and cooled in an ice-water bath. Then DIPEA (146 μL, 0.84 mmol, 2.2 eq) and methyl iodide (26 μL, 0.42 mmol, 1.1 eq) were successively added and the resulting mixture was stirred overnight allowing to warm to rt. EtOAc was added to reaction mixture and washed with a solution of 10% aq NaHCO<sub>3</sub> (3 mL). Aqueous phase was extracted twice with EtOAc (5 mL) and the combined organic layer was washed with brine (2 mL), dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (CH<sub>2</sub>Cl<sub>2</sub>/Acetone 2:8) to give methyl-butenolide **4** as a cream solid (34.0 mg, 50% yield).

$[\alpha]_D^{20} = -1023$  (c 0.5, CH<sub>2</sub>Cl<sub>2</sub>); m.p.: 134-135 °C

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ (ppm) 6.68 (dd, *J* = 9.1 Hz, *J* = 1.0 Hz, 1H, H<sub>4</sub>), 6.61 (dd, *J* = 9.2 Hz, *J* = 5.2 Hz, 1H, H<sub>5</sub>), 5.62 (s, 1H, H<sub>2</sub>), 3.85-3.81 (m, 1H, H<sub>6</sub>), 3.56 (d, *J* = 9.8 Hz, 1H, H<sub>8A</sub>), 2.67 (dd, *J* = 9.8 Hz, *J* = 4.4 Hz, 1H, H<sub>10A</sub>), 2.34 (s, 3H, NMe), 2.28 (d, *J* = 9.8 Hz, 1H, H<sub>8B</sub>), 1.85 (d, *J* = 9.8 Hz 1H, H<sub>10B</sub>)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>): δ (ppm) 173.0, 169.6, 144.0, 122.4, 106.6, 88.9, 60.7, 57.3, 43.2, 40.1

**HRMS** (ESI) calcd for [M+Na]<sup>+</sup> (C<sub>10</sub>H<sub>11</sub>NO<sub>2</sub>Na) 200.0682, found 200.0683

**IR** (UATR):  $\bar{\nu}$  (cm<sup>-1</sup>) 3106 (=CH), 1737 (C=O), 1625 (C=C)

#### 4.1.3. Isobutyl-butenolide 5

To a solution of Boc-butenolide **2** (65.8 mg, 0.25 mmol, 1 eq) in dry CH<sub>2</sub>Cl<sub>2</sub> (2.2 mL) at 0 °C was added trifluoroacetic acid (0.4 mL). The resulting solution was stirred allowing to warm to rt for 2 h. Volatiles were removed *in vacuo* to afford the corresponding TFA-salt as a brown solid. Then, isobutyraldehyde (23  $\mu$ L, 0.25 mmol, 1 eq) and chlorodicarbonyl rhodium (I) dimer (1 mg, 2.5  $\mu$ mol, 1 mol %) were added to the solid-salt suspended in dry CH<sub>2</sub>Cl<sub>2</sub> (2.5 mL) with NaHCO<sub>3</sub> (32 mg, 0.375 mmol, 1.5 eq). After addition of PhSiH<sub>3</sub> (62  $\mu$ L, 0.5 mmol, 2 eq) at 0 °C, the reaction mixture was slowly warmed to rt and stirred for 24 h. The reaction mixture was diluted with Et<sub>2</sub>O (8 mL) and washed with a solution of 10% aq NaHCO<sub>3</sub> (5 mL). The layers were separated and the aqueous phase was extracted with Et<sub>2</sub>O (2x8 mL). The combined organic phase was washed with a 10% aq NaHCO<sub>3</sub> solution (5 mL), brine (5 mL), dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo* to afford an orange oil. Chromatography on silica gel (petroleum ether/Et<sub>2</sub>O, 85:15) furnished isobutyl-butenolide **5** as a white solid (36.8 mg, 67% yield).

[ $\alpha$ ]<sub>D</sub><sup>20</sup> = - 974 (c 0.49, CH<sub>2</sub>Cl<sub>2</sub>); m.p.: 75-76 °C

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>): δ (ppm) 6.65 (dd, *J* = 9.2 Hz, *J* = 1.3 Hz, 1H, H<sub>4</sub>), 6.59 (dd, *J* = 9.2 Hz, *J* = 4.9 Hz, 1H, H<sub>5</sub>), 5.59 (s, 1H, H<sub>2</sub>), 3.87 - 3.84 (m, 1H, H<sub>6</sub>), 3.54 (d, *J* = 9.6 Hz, 1H, H<sub>8A</sub>), 2.65 (dd, *J* = 9.6 Hz, *J* = 4.4 Hz, 1H, H<sub>10A</sub>), 2.33 - 2.15 (m, 3H, H<sub>11A</sub>, H<sub>8B</sub>, H<sub>11B</sub>), 1.82 (d, *J* = 9.6 Hz, 1H, H<sub>10B</sub>), 1.66 - 1.53 (m, 1H, H<sub>12</sub>), 0.90 (d, *J* = 6.6 Hz, 3H, H<sub>13</sub> or H<sub>14</sub>), 0.87 (d, *J* = 6.6 Hz, 3H, H<sub>13</sub> or H<sub>14</sub>)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>): δ (ppm) 173.2, 169.8, 144.6, 121.9, 106.2, 88.8, 62.1, 59.5, 56.5, 42.9, 27.6, 21.0, 20.7

**HRMS** (ESI) calcd for [M+Na]<sup>+</sup> (C<sub>13</sub>H<sub>17</sub>NO<sub>2</sub>Na) 242.1152, found 242.1151

**IR** (UATR):  $\bar{\nu}$  (cm<sup>-1</sup>) 3065 (=CH), 1744 (C=O), 1626 (C=C)

#### 4.1.4. Bn-Butenolide 6

To a solution of Boc-butenolide **2** (400 mg, 1.52 mmol, 1 eq) in dry CH<sub>2</sub>Cl<sub>2</sub> (13.6 mL) at 0 °C was added trifluoroacetic acid (2.4 mL). The resulting solution was stirred allowing to warm to rt for 2 h. Volatiles were then removed *in vacuo* to afford the corresponding TFA-salt as a brown solid. The residue was dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (16 mL) and cooled to 0 °C. Then DIPA (685  $\mu$ L, 4.86 mmol, 3.2 eq) and benzylbromide (235  $\mu$ L, 1.98 mmol, 1.3 eq) were successively added. The mixture was stirred overnight allowing to warm to rt. A solution of 10% aq NaHCO<sub>3</sub> (20 mL) and ethyl acetate (40 mL) were added. The layers were separated and the aqueous phase was extracted with ethyl acetate (15 mL). The combined organic layer was washed with brine twice (15 mL), dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo* to afford a brown oil. Chromatography on silica gel (CH<sub>2</sub>Cl<sub>2</sub>/Et<sub>2</sub>O, 9:1) gave Bn-butenolide **6** as a cream solid (366 mg, 95% yield).

[ $\alpha$ ]<sub>D</sub><sup>20</sup> = - 843 (c 0.5, CH<sub>2</sub>Cl<sub>2</sub>); m.p.: 112-113 °C

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>): δ (ppm) 7.35-7.23 (m, 5H, H<sub>o, m, p</sub>), 6.71 (dd, *J* = 9.1 Hz, *J* = 0.8 Hz, 1H, H<sub>4</sub>), 6.58 (dd, *J* = 9.1 Hz, *J* = 5.3 Hz, 1H, H<sub>5</sub>), 5.63 (s, 1H, H<sub>2</sub>), 3.86-3.83 (m, 1H, H<sub>6</sub>), 3.70 (Syst AB, *J*<sub>AB</sub> = 13.0 Hz, 1H, H<sub>11A</sub>), 3.59 (Syst AB, *J*<sub>AB</sub> = 13.0 Hz, 1H, H<sub>11B</sub>), 3.54 (d, *J* = 9.8 Hz, 1H, H<sub>8A</sub>), 2.69 (dd, *J* = 9.7 Hz, *J* = 4.4 Hz, 1H, H<sub>10A</sub>), 2.36 (d, *J* = 9.8 Hz, 1H, H<sub>8B</sub>), 1.86 (d, *J* = 9.7 Hz, 1H, H<sub>10B</sub>)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>): δ (ppm) 173.1, 169.6, 144.1, 138.3, 128.6, 128.6, 127.5, 122.3, 106.6, 88.7, 58.6, 57.6, 56.2, 42.7

**HRMS** (ESI) calcd for [M+Na]<sup>+</sup> (C<sub>16</sub>H<sub>15</sub>NO<sub>2</sub>Na) 276.0995, found 276.0999

**IR** (UATR):  $\bar{\nu}$  (cm<sup>-1</sup>) 3137 (=CH), 1755 (C=O), 1635 (C=C)

#### 4.1.5. Iodo-butenolide (Isobutyl) **7**

According to the iodation procedure of Bn-butenolide **6** (see below), iodo-butenolide (isobutyl) **7** was obtained after preparative TLC (CH<sub>2</sub>Cl<sub>2</sub>/Et<sub>2</sub>O, 95:5).

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>): δ (ppm) 7.16 (d, *J* = 5.6 Hz, 1H, H<sub>5</sub>), 5.63 (s, 1H, H<sub>2</sub>), 3.75 - 3.72 (m, 1H, H<sub>6</sub>), 3.55 (d, *J* = 9.8 Hz, 1H, H<sub>8A</sub>), 2.68 (dd, *J* = 9.9 Hz, *J* = 4.2 Hz, 1H, H<sub>10A</sub>), 2.37 - 2.21 (m, 3H, H<sub>11A</sub>, H<sub>8B</sub>, H<sub>11B</sub>), 1.89 (d, *J* = 9.9 Hz, 1H, H<sub>10B</sub>), 1.65 - 1.60 (m, 1H, H<sub>12</sub>), 0.91 (d, *J* = 6.6 Hz, 3H, H<sub>13</sub> or H<sub>14</sub>), 0.88 (d, *J* = 6.6 Hz, 3H, H<sub>13</sub> or H<sub>14</sub>)

**HRMS** (ESI) calcd for [M+H]<sup>+</sup> (C<sub>13</sub>H<sub>17</sub>NO<sub>2</sub>I) 346.0299, found 346.0301

#### 4.1.6. Iodo-butenolide (Bn) **8**

To a suspension of Bn-butenolide **6** (366 mg, 1.44 mmol, 1 eq) in dry MeOH (9.5 mL) at 0 °C was added NIS (585 mg, 2.6 mmol, 1.8 eq). The resulting suspension was stirred overnight away of light allowing to warm to rt. Volatiles were removed *in vacuo* and the residue was dissolved in ethyl acetate (40 mL). A solution of 10% aq NaHCO<sub>3</sub> (20 mL) was added and the mixture stirred for 10 min. Layers were separated and the aqueous phase was extracted with ethyl acetate (2x20 mL). The combined organic layer was successively washed with a solution of 10% aq Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (20 mL) and brine (20 mL), dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. Chromatography on silica gel (CH<sub>2</sub>Cl<sub>2</sub>/Et<sub>2</sub>O, 95:5) furnished iodo-butenolide (Bn) **8** as a brown solid (290 mg, 53% yield).

[α]<sub>D</sub><sup>20</sup> = - 528 (c 0.58, CH<sub>2</sub>Cl<sub>2</sub>); m.p.: 92-93°C

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>): δ (ppm) 7.36-7.24 (m, 5H, H<sub>o</sub>, m, p), 7.14 (d, *J* = 5.7 Hz, 1H, H<sub>5</sub>), 5.66 (s, 1H, H<sub>2</sub>), 3.73-3.70 (m, 1H, H<sub>6</sub>), 3.74 (Syst AB, *J*<sub>AB</sub> = 13.0 Hz, 1H, H<sub>11A</sub>), 3.65 (Syst AB, *J*<sub>AB</sub> = 13.0 Hz, 1H, H<sub>11B</sub>), 3.55 (d, *J* = 10.0 Hz, 1H, H<sub>8A</sub>), 2.72 (dd, *J* = 10.0 Hz, *J* = 4.3 Hz, 1H, H<sub>10A</sub>), 2.43 (d, *J* = 10.0 Hz, 1H, H<sub>8B</sub>), 1.92 (d, *J* = 10.0 Hz, 1H, H<sub>10B</sub>)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>): δ (ppm) 171.8, 170.2, 153.6, 137.8, 128.7, 128.6, 127.7, 112.3, 87.7, 85.7, 61.1, 57.6, 56.1, 42.2

**HRMS** (ESI) calcd for [M+Na]<sup>+</sup> (C<sub>16</sub>H<sub>14</sub>NO<sub>2</sub>I) 401.9962, found 401.9966

**IR** (UATR):  $\bar{\nu}$  (cm<sup>-1</sup>) 3098 (=CH), 1760 (C=O), 1621 (C=C)

#### 4.1.7. General procedure for Sonogashira coupling reaction

In a glass Schlenk-tube, iodobutenolide **8** (50 mg, 0.13 mmol, 1 eq), palladium on activated charcoal 10% wt/Pd (7 mg, 6.59 μmol, 5 mol %) and copper iodide (2.5 mg, 0.013 mmol, 10 mol %) were successively introduced. Then, 2 mL of dry tetrahydrofuran were added. The mixture was degassed by 3 vacuum/argon cycles. DIPA (37 μL, 0.26 mmol, 2 eq) and 1.3 eq of alkyne were successively introduced and the mixture was stirred at r. t. After the iodo-butenolide has been consumed (TLC monitoring), the reaction mixture was filtered through a pad of celite eluting with EtOAc (10 mL). The organic layer was washed with a saturated aq NaHCO<sub>3</sub> solution (10 mL), brine (10 mL), dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica gel.

#### 4.1.8. (6S,8aS)-7-benzyl-4-(phenylethynyl)-7,8-dihydro-6,8a-methanofuro[2,3-c]azepin-2(6H)-one **9**

According to the general procedure, compound **9** was obtained after purification on silica gel (CH<sub>2</sub>Cl<sub>2</sub>/Et<sub>2</sub>O, 95:5) as an orange yellow gum (38.0 mg, 81%). The product decomposed upon storing even in the freezer (air and/or light sensitive).

**<sup>1</sup>H NMR** (300 MHz, CD<sub>2</sub>Cl<sub>2</sub>): δ (ppm) 7.57-7.51 (m, 2H, H<sub>o'</sub>), 7.43-7.24 (m, 8H, H<sub>o</sub>, m, m', p, p'), 6.91 (d, *J* = 5.6 Hz, 1H, H<sub>5</sub>), 5.90 (s, 1H, H<sub>2</sub>), 3.93-3.89 (m, 1H, H<sub>6</sub>), 3.81 (Syst AB, *J*<sub>AB</sub> = 13.1 Hz, 1H, H<sub>11A</sub>), 3.65 (Syst AB, *J*<sub>AB</sub> = 13.1 Hz, 1H, H<sub>11B</sub>), 3.52 (d, *J* = 9.9 Hz, 1H, H<sub>8A</sub>), 2.71 (dd, *J* = 9.9 Hz, *J* = 4.4 Hz, 1H, H<sub>10A</sub>), 2.46 (d, *J* = 9.9 Hz, 1H, H<sub>8B</sub>), 1.93 (d, *J* = 9.9 Hz 1H, H<sub>10B</sub>)

**<sup>13</sup>C NMR** (75 MHz, CD<sub>2</sub>Cl<sub>2</sub>): δ (ppm) 172.2, 169.6, 147.9, 138.8, 132.1, 129.5, 129.0, 128.8, 128.8, 127.7, 122.4, 118.5, 107.8, 92.9, 88.4, 83.3, 58.9, 57.7, 56.3, 42.3

**HRMS** (ESI) calcd for [M+Na]<sup>+</sup> (C<sub>24</sub>H<sub>19</sub>NO<sub>2</sub>Na) 376.1308, found 376.1310

**IR** (UATR):  $\bar{\nu}$  (cm<sup>-1</sup>) 2207 (C≡C), 1752 (C=O), 1627 (C=C)

#### 4.1.9. (6S,8aS)-7-benzyl-4-(pent-1-yn-1-yl)-7,8-dihydro-6,8a-methanofuro[2,3-c]azepin-2(6H)-one **10**

According to the general procedure, compound **10** was obtained after purification on silica gel (CH<sub>2</sub>Cl<sub>2</sub>/Et<sub>2</sub>O, 96:4) as a yellow oil (40.0 mg, 95%). The product decomposed upon storing even in the freezer (air and/or light sensitive).

**<sup>1</sup>H NMR** (300 MHz, CD<sub>2</sub>Cl<sub>2</sub>): δ (ppm) 7.34-7.22 (m, 5H, H<sub>o</sub>, m, p), 6.71 (d, *J* = 5.6 Hz, 1H, H<sub>5</sub>), 5.77 (s, 1H, H<sub>2</sub>), 3.85-3.81 (m, 1H, H<sub>6</sub>), 3.76 (Syst AB, *J*<sub>AB</sub> = 13.1 Hz, 1H, H<sub>11A</sub>), 3.59 (Syst AB, *J*<sub>AB</sub> = 13.1 Hz, 1H, H<sub>11B</sub>), 3.47 (d, *J* = 9.8 Hz, 1H, H<sub>8A</sub>), 2.65 (dd, *J* = 9.8 Hz, *J* = 4.4 Hz, 1H, H<sub>10A</sub>), 2.41-2.36 (m, 3H, H<sub>8B</sub>, H<sub>14</sub>), 1.86 (d, *J* = 9.8 Hz, 1H, H<sub>10B</sub>), 1.62 (h, *J* = 7.4 Hz 2H, H<sub>15</sub>), 1.04 (t, *J* = 7.4 Hz 3H, H<sub>16</sub>)

**<sup>13</sup>C NMR** (75 MHz, CD<sub>2</sub>Cl<sub>2</sub>): δ (ppm) 172.3, 170.3, 146.4, 138.9, 128.8, 128.7, 127.6, 118.9, 107.5, 94.6, 88.4, 74.9, 58.8, 57.7, 56.2, 42.4, 22.4, 21.6, 13.7

**HRMS** (ESI) calcd for [M+Na]<sup>+</sup> (C<sub>21</sub>H<sub>21</sub>NO<sub>2</sub>Na) 342.1464, found 342.1465

**IR** (UATR):  $\bar{\nu}$  (cm<sup>-1</sup>) 2227 (C≡C), 1752 (C=O), 1627 (C=C)

#### 4.1.10. (6S,8aS)-7-benzyl-4-[(4-(dimethylamino)phenyl)ethynyl]-7,8-dihydro-6,8a-methanofuro[2,3-c]azepin-2(6H)-one **11**

According to the general procedure, compound **11** was obtained after purification on silica gel (petroleum ether/EtOAc, 75:25) as an orange yellow gum (48.6 mg, 93%). The product decomposed upon storing even in the freezer (air and/or light sensitive).

**<sup>1</sup>H NMR** (300 MHz, CD<sub>2</sub>Cl<sub>2</sub>): δ (ppm) 7.40-7.23 (m, 7H, H<sub>o</sub>, o', m, p), 6.79 (d, *J* = 5.6 Hz, 1H, H<sub>5</sub>), 6.67 (d, *J* = 9.0 Hz, 1H, H<sub>m</sub>), 5.88 (s, 1H, H<sub>2</sub>), 3.90-3.87 (m, 1H, H<sub>6</sub>), 3.80 (Syst AB, *J*<sub>AB</sub> = 13.1 Hz, 1H, H<sub>11A</sub>), 3.63 (Syst AB, *J*<sub>AB</sub> = 13.1 Hz, 1H, H<sub>11B</sub>), 3.50 (d, *J* = 9.8 Hz, 1H, H<sub>8A</sub>), 3.00 (s, 6H, N(Me)<sub>2</sub>), 2.69 (dd, *J* = 9.8 Hz, *J* = 4.4 Hz, 1H, H<sub>10A</sub>), 2.44 (d, *J* = 9.8 Hz, 1H, H<sub>8B</sub>), 1.91 (d, *J* = 9.8 Hz 1H, H<sub>10B</sub>)

**<sup>13</sup>C NMR** (75 MHz, CD<sub>2</sub>Cl<sub>2</sub>): δ (ppm) 172.3, 170.2, 151.1, 145.6, 138.9, 133.2, 128.8, 128.7, 127.6, 119.0, 112.1, 108.5, 107.6, 94.7, 88.4, 81.6, 59.0, 57.7, 56.3, 42.4, 40.3

**HRMS** (ESI) calcd for [M+Na]<sup>+</sup> (C<sub>26</sub>H<sub>24</sub>N<sub>2</sub>O<sub>2</sub>Na) 419.1730, found 419.1734

**IR** (UATR):  $\bar{\nu}$  (cm<sup>-1</sup>) 2197 (C≡C), 1754 (C=O), 1627 (C=C)

#### 4.1.11. General procedure for Suzuki-Miyaura coupling reaction

**Method A:** To a Schlenk-tube charged with iodo-butenolide (Bn) **8** (50 mg, 0.13 mmol, 1 eq), boronic acid (or boronic pinacol ester) (2 eq), Na<sub>2</sub>CO<sub>3</sub> (28 mg, 0.26 mmol, 2 eq) and 10% wt Pd/C (7 mg, 6.59 μmol, 5 mol %) was added DME and water (2 mL, 1/1, v/v). The reaction mixture was stirred at 85 °C for 2.5 h, cooled to rt and then filtered through celite. The celite pad was washed with DME and ethyl acetate. The organic layer was successively washed with

1M aq NaOH, brine, dried (MgSO<sub>4</sub>), filtered and concentrated *in vacuo*. The residue was purified by chromatography on silica gel.

**Method B:** To a Schlenk-tube charged with iodo-butenolide (Bn) **8** (50 mg, 0.13 mmol, 1 eq), boronic acid (or boronic pinacol ester) (1.5 eq) and tetrakis(triphenylphosphine) palladium (7.6 mg, 6.59 μmol, 5 mol %) were added dry toluene, EtOH and 2M aq Na<sub>2</sub>CO<sub>3</sub> (2.08 mL, 62.5/12.5/25, v/v/v). The reaction mixture was stirred at 110 °C for 3 h, then diluted with water and extracted with ethyl acetate. The organic phase was washed with brine, dried (MgSO<sub>4</sub>), filtered and concentrated under reduce pressure. The residue was purified by chromatography on silica gel.

#### 4.1.12. (6S,8aS)-7-benzyl-4-phenyl-7,8-dihydro-6,8a-methanofuro[2,3-c]azepin-2(6H)-one **12**

Method A. After purification (CH<sub>2</sub>Cl<sub>2</sub>/Et<sub>2</sub>O, 95:5) compound **12** was obtained as a cream solid (40.0 mg, 92% yield).

[α]<sup>20</sup><sub>D</sub> = - 490 (c 0.49, CH<sub>2</sub>Cl<sub>2</sub>); m.p.: 120-121°C

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ (ppm) 7.49-7.24 (m, 10H, H<sub>o</sub>, o', m, m', p, p'), 6.62 (d, *J* = 5.5 Hz, 1H, H<sub>5</sub>), 5.75 (s, 1H, H<sub>2</sub>), 3.96 - 3.93 (m, 1H, H<sub>6</sub>), 3.77 (Syst AB, *J*<sub>AB</sub> = 13.0 Hz, 1H, H<sub>11A</sub>), 3.64 (Syst AB, *J*<sub>AB</sub> = 13.0 Hz, 1H, H<sub>11B</sub>), 3.63 (d, *J* = 9.9 Hz, 1H, H<sub>8A</sub>), 2.76 (dd, *J* = 9.7 Hz, *J* = 4.3 Hz, 1H, H<sub>10A</sub>), 2.50 (d, *J* = 9.9 Hz, 1H, H<sub>8B</sub>), 1.97 (d, *J* = 9.7 Hz 1H, H<sub>10B</sub>)

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ (ppm) 172.7, 169.8, 140.5, 138.3, 136.4, 136.1, 129.1, 129.0, 128.6, 128.6, 127.5, 127.5, 107.5, 89.2, 58.3, 57.7, 56.1, 42.5

HRMS (ESI) calcd for [M+Na]<sup>+</sup> (C<sub>22</sub>H<sub>19</sub>NO<sub>2</sub>Na) 352.1308, found 352.1308

IR (UATR):  $\bar{\nu}$  (cm<sup>-1</sup>) 1741 (C=O), 1618 (C=C)

#### 4.1.13. (6S,8aS)-7-benzyl-4-(4-fluorophenyl)-7,8-dihydro-6,8a-methanofuro[2,3-c]azepin-2(6H)-one **13**

Method A. After purification (CH<sub>2</sub>Cl<sub>2</sub>/EtOAc, 96:4) compound **13** was obtained as cream solid (34.0 mg, 74% yield).

[α]<sup>20</sup><sub>D</sub> = - 451 (c 0.51, CH<sub>2</sub>Cl<sub>2</sub>); m.p.: 132-133°C

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ (ppm) 7.41-7.24 (m, 7H, H<sub>o</sub>, o', m, p, p'), 7.18 - 7.10 (m, 2H, H<sub>m</sub>), 6.58 (d, *J* = 5.5 Hz, 1H, H<sub>5</sub>), 5.71 (s, 1H, H<sub>2</sub>), 3.95 - 3.92 (m, 1H, H<sub>6</sub>), 3.76 (Syst AB, *J*<sub>AB</sub> = 13.0 Hz, 1H, H<sub>11A</sub>), 3.64 (Syst AB, *J*<sub>AB</sub> = 13.0 Hz, 1H, H<sub>11B</sub>), 3.63 (d, *J* = 9.9 Hz, 1H, H<sub>8A</sub>), 2.76 (dd, *J* = 9.8 Hz, *J* = 4.3 Hz, 1H, H<sub>10A</sub>), 2.49 (d, *J* = 9.9 Hz, 1H, H<sub>8B</sub>), 1.96 (d, *J* = 9.8 Hz 1H, H<sub>10B</sub>)

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ (ppm) 172.5, 169.7, 163.1 (d, *J*<sup>1</sup><sub>C-F</sub> = 248.8 Hz), 140.5, 138.2, 135.1, 132.4 (d, *J*<sup>1</sup><sub>C-F</sub> = 3.4 Hz), 129.3 (d, *J*<sup>β</sup><sub>C-F</sub> = 8.2 Hz), 128.6, 128.6, 127.6, 116.1 (d, *J*<sup>β</sup><sub>C-F</sub> = 21.6 Hz), 107.6, 89.2, 58.3, 57.7, 56.1, 42.4

HRMS (ESI) calcd for [M+Na]<sup>+</sup> (C<sub>22</sub>H<sub>18</sub>NO<sub>2</sub>FNa) 370.1214, found 370.1215

IR (UATR):  $\bar{\nu}$  (cm<sup>-1</sup>) 3093 (=CH), 1741 (C=O), 1613 (C=C)

#### 4.1.14. (6S,8aS)-7-benzyl-4-(4-methoxyphenyl)-7,8-dihydro-6,8a-methanofuro[2,3-c]azepin-2(6H)-one **14**

Method A. After purification (CH<sub>2</sub>Cl<sub>2</sub>/EtOAc, 92:8) compound **14** was obtained as pale-yellow solid (34.7 mg, 73% yield).

[α]<sup>20</sup><sub>D</sub>: - 434 (c 0.49, CH<sub>2</sub>Cl<sub>2</sub>); m.p: 139-140°C

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ (ppm) 7.37-7.23 (m, 7H, H<sub>o</sub>, o', m, p, p'), 6.97 (d, *J* = 8.8 Hz, 1H, H<sub>m</sub>), 6.54 (d, *J* = 5.5 Hz, 1H, H<sub>5</sub>), 5.74 (s, 1H, H<sub>2</sub>), 3.93 - 3.90 (m, 1H, H<sub>6</sub>), 3.86 (s, 3H, OMe), 3.76 (Syst AB, *J*<sub>AB</sub> = 13.1 Hz, 1H, H<sub>11A</sub>), 3.63 (Syst AB, *J*<sub>AB</sub> = 13.1 Hz, 1H, H<sub>11B</sub>), 3.62 (d, *J* = 9.9 Hz, 1H, H<sub>8A</sub>), 2.75 (dd, *J* = 9.7 Hz, *J* = 4.3 Hz, 1H, H<sub>10A</sub>), 2.48 (d, *J* = 9.9 Hz, 1H, H<sub>8B</sub>), 1.95 (d, *J* = 9.7 Hz 1H, H<sub>10B</sub>)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>): δ (ppm) 172.8, 170.2, 160.2, 139.2, 138.3, 135.5, 128.8, 128.7, 128.6, 128.6, 127.5, 114.4, 107.5, 89.3, 58.3, 57.7, 56.1, 55.6, 42.6

**HRMS** (ESI) calcd for [M+H]<sup>+</sup> (C<sub>23</sub>H<sub>22</sub>NO<sub>3</sub>) 360.1594, found 360.1596

**IR** (UATR):  $\bar{\nu}$  (cm<sup>-1</sup>) 1743 (C=O), 1622 (C=C), 1249 (Ar-OMe)

#### 4.1.15. (6S,8aS)-7-benzyl-4-[4-(dimethylamino)phenyl]-7,8-dihydro-6,8a-methanofuro[2,3-c]azepin-2(6H)-one **15**

Method A. After purification (CH<sub>2</sub>Cl<sub>2</sub>/EtOAc, 9:1) compound **15** was obtained as an amorphous yellow solid (36.0 mg, 73% yield).

[α]<sup>20</sup><sub>D</sub> = - 417 (c 0.50, CH<sub>2</sub>Cl<sub>2</sub>)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>): δ (ppm) 7.34-7.23 (m, 7H, H<sub>o, o', m, p</sub>), 6.76 (d, *J* = 8.9 Hz, 1H, H<sub>m'</sub>), 6.50 (d, *J* = 5.6 Hz, 1H, H<sub>5</sub>), 5.79 (s, 1H, H<sub>2</sub>), 3.92-3.89 (m, 1H, H<sub>6</sub>), 3.75 (Syst AB, *J*<sub>AB</sub> = 13.1 Hz, 1H, H<sub>11A</sub>), 3.62 (Syst AB, *J*<sub>AB</sub> = 13.1 Hz, 1H, H<sub>11B</sub>), 3.61 (d, *J* = 9.8 Hz, 1H, H<sub>8A</sub>), 3.02 (s, 6H, N(Me)<sub>2</sub>), 2.73 (dd, *J* = 9.6 Hz, *J* = 4.3 Hz, 1H, H<sub>10A</sub>), 2.47 (d, *J* = 9.8 Hz, 1H, H<sub>8B</sub>), 1.94 (d, *J* = 9.6 Hz 1H, H<sub>10B</sub>)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>): δ (ppm) 173.0, 170.7, 150.9, 138.5, 137.4, 135.6, 128.6, 128.6, 128.3, 127.4, 124.0, 112.3, 107.3, 89.4, 58.4, 57.6, 56.0, 42.7, 40.5

**HRMS** (ESI) calcd for [M+Na]<sup>+</sup> (C<sub>24</sub>H<sub>24</sub>N<sub>2</sub>O<sub>2</sub>Na) 395.1730, found 395.1726

**IR** (UATR):  $\bar{\nu}$  (cm<sup>-1</sup>) 1748 (C=O), 1609 (C=C)

#### 4.1.16. (6S,8aS)-7-benzyl-4-(pyridin-4-yl)-7,8-dihydro-6,8a-methanofuro[2,3-c]azepin-2(6H)-one **16**

Method B. After purification (CH<sub>2</sub>Cl<sub>2</sub>/Acetone, 80:20) compound **16** was obtained as a beige solid (30.3 mg, 70% yield).

[α]<sup>20</sup><sub>D</sub>: - 529 (c 0.49, CH<sub>2</sub>Cl<sub>2</sub>); m.p.: 172-173°C

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>): δ (ppm) 8.72-8.70 (m, 2H, H<sub>m'</sub>), 7.36 - 7.24 (m, 7H, H<sub>o, o', m, p</sub>), 6.75 (d, *J* = 5.5 Hz, 1H, H<sub>5</sub>), 5.77 (s, 1H, H<sub>2</sub>), 3.98 - 3.95 (m, 1H, H<sub>6</sub>), 3.76 (Syst AB, *J*<sub>AB</sub> = 13.0 Hz, 1H, H<sub>11A</sub>), 3.65 (Syst AB, *J*<sub>AB</sub> = 13.0 Hz, 1H, H<sub>11B</sub>), 3.64 (d, *J* = 10.0 Hz, 1H, H<sub>8A</sub>), 2.79 (dd, *J* = 9.9 Hz, *J* = 4.3 Hz, 1H, H<sub>10A</sub>), 2.52 (d, *J* = 10.0 Hz, 1H, H<sub>8B</sub>), 1.97 (d, *J* = 9.9 Hz 1H, H<sub>10B</sub>)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>): δ (ppm) 172.1, 168.0, 150.7, 143.8, 143.0, 138.0, 133.9, 128.7, 128.5, 127.7, 122.1, 107.8, 89.0, 58.2, 57.7, 56.1, 42.2

**HRMS** (ESI) calcd for [M+Na]<sup>+</sup> (C<sub>21</sub>H<sub>18</sub>N<sub>2</sub>O<sub>2</sub>Na) 353.1260, found 353.1256

**IR** (UATR) :  $\bar{\nu}$  (cm<sup>-1</sup>) 3127 (=CH), 1748 (C=O), 1618 (C=C)

#### 4.1.17. (6S,8aS)-7-benzyl-4-(thiophen-3-yl)-7,8-dihydro-6,8a-methanofuro[2,3-c]azepin-2(6H)-one **17**

Method B. After purification (CH<sub>2</sub>Cl<sub>2</sub>/EtOAc, 9:1) compound **17** was obtained as amorphous pale-yellow solid (38.0 mg, 86% yield).

[α]<sup>20</sup><sub>D</sub> = - 428 (c 0.49, CH<sub>2</sub>Cl<sub>2</sub>)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>): δ (ppm) 7.43 (dd, *J* = 4.9 Hz, *J* = 2.9 Hz, 1H, H<sub>5'</sub>), 7.39 (dd, *J* = 2.9 Hz, *J* = 1.4 Hz, 1H, H<sub>2</sub>), 7.33-7.25 (m, 5H, H<sub>o, m, p</sub>), 7.19 (dd, *J* = 4.9 Hz, *J* = 1.4 Hz, 1H, H<sub>4'</sub>), 6.67 (d, *J* = 5.6 Hz, 1H, H<sub>5</sub>), 5.87 (s, 1H, H<sub>2</sub>), 3.94-3.91 (m, 1H, H<sub>6</sub>), 3.76 (Syst AB, *J*<sub>AB</sub> = 13.1 Hz, 1H, H<sub>11A</sub>), 3.63 (Syst AB, *J*<sub>AB</sub> = 13.1 Hz, 1H, H<sub>11B</sub>), 3.60 (d, *J* = 9.9 Hz, 1H, H<sub>8A</sub>), 2.75 (dd, *J* = 9.7 Hz, *J* = 4.3 Hz, 1H, H<sub>10A</sub>), 2.49 (d, *J* = 9.9 Hz, 1H, H<sub>8B</sub>), 1.95 (d, *J* = 9.7 Hz, 1H, H<sub>10B</sub>)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>): δ (ppm) 172.6, 169.7, 139.3, 138.3, 137.1, 130.4, 128.6, 128.6, 127.5, 126.9, 126.6, 123.0, 107.6, 89.3, 58.3, 57.7, 56.0, 42.6

**HRMS** (ESI) calcd for [M+Na]<sup>+</sup> (C<sub>20</sub>H<sub>17</sub>NO<sub>2</sub>NaS) 358.0872, found 358.0869

**IR** (UATR):  $\bar{\nu}$  (cm<sup>-1</sup>) 3105 (=CH), 1744 (C=O), 1615 (C=C)

#### 4.1.18. (6S,8aS)-7-benzyl-4-(4-nitrophenyl)-7,8-dihydro-6,8a-methanofuro[2,3-c]azepin-2(6H)-one **18**

Method B. After purification (CH<sub>2</sub>Cl<sub>2</sub>/EtOAc, 9:1) compound **18** was obtained as an amorphous orange solid (39.5 mg, 80% yield).

$[\alpha]^{20}_D = -474$  (c 0.51, CH<sub>2</sub>Cl<sub>2</sub>)

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ (ppm) 8.32 (d, *J* = 8.9 Hz, 1H, H<sub>m</sub>), 7.58 (d, *J* = 8.9 Hz, 1H, H<sub>o</sub>), 7.36 - 7.25 (m, 5H, H<sub>o, m, p</sub>), 6.74 (d, *J* = 5.5 Hz, 1H, H<sub>5</sub>), 5.72 (s, 1H, H<sub>2</sub>), 4.00-3.97 (m, 1H, H<sub>6</sub>), 3.77 (Syst AB, *J*<sub>AB</sub> = 13.1 Hz, 1H, H<sub>11A</sub>), 3.67 (Syst AB, *J*<sub>AB</sub> = 13.1 Hz, 1H, H<sub>11B</sub>), 3.65 (d, *J* = 10.0 Hz, 1H, H<sub>8A</sub>), 2.80 (dd, *J* = 9.9 Hz, *J* = 4.3 Hz, 1H, H<sub>10A</sub>), 2.54 (d, *J* = 10.0 Hz, 1H, H<sub>8B</sub>), 1.99 (d, *J* = 9.9 Hz 1H, H<sub>10B</sub>)

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ (ppm) 172.0, 168.3, 148.1, 143.3, 142.6, 137.9, 134.3, 128.7, 128.5, 128.5, 127.7, 124.4, 108.0, 89.1, 58.2, 57.8, 56.1, 42.2

HRMS (ESI) calcd for [M+Na]<sup>+</sup> (C<sub>22</sub>H<sub>18</sub>N<sub>2</sub>O<sub>4</sub>Na) 397.1159, found 397.1161

IR (UATR):  $\bar{\nu}$  (cm<sup>-1</sup>) 1748 (C=O), 1619 (C=C), 1515 and 1344 (NO<sub>2</sub>)

#### 4.1.19. N-[4-((6S,8aS)-7-benzyl-2-oxo-2,6,7,8-tetrahydro-6,8a-methanofuro[2,3-c]azepin-4-yl)phenyl]acetamide **19**

Method B. After purification (petroleum ether/EtOAc, 2:8) compound **19** was obtained as an amorphous cream solid (48.0 mg, 94% yield).

$[\alpha]^{20}_D = -398$  (c 0.52, CH<sub>2</sub>Cl<sub>2</sub>)

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ (ppm) 7.60 (d, *J* = 8.5 Hz, 1H, H<sub>m</sub>), 7.47 (bs, 1H, NH), 7.38-7.23 (m, 7H, H<sub>o, o', m, p</sub>), 6.58 (d, *J* = 5.5 Hz, 1H, H<sub>5</sub>), 5.73 (s, 1H, H<sub>2</sub>), 3.94-3.91 (m, 1H, H<sub>6</sub>), 3.75 (Syst AB, *J*<sub>AB</sub> = 13.1 Hz, 1H, H<sub>11A</sub>), 3.63 (Syst AB, *J*<sub>AB</sub> = 13.1 Hz, 1H, H<sub>11B</sub>), 3.62 (d, *J* = 9.9 Hz, 1H, H<sub>8A</sub>), 2.75 (dd, *J* = 9.7 Hz, *J* = 4.3 Hz, 1H, H<sub>10A</sub>), 2.49 (d, *J* = 9.9 Hz, 1H, H<sub>8B</sub>), 2.22 (s, 3H, NHCOMe), 1.95 (d, *J* = 9.7 Hz 1H, H<sub>10B</sub>)

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ (ppm) 172.8, 170.0, 168.6, 140.1, 138.7, 138.2, 135.3, 132.1, 128.6, 128.6, 128.1, 127.6, 120.2, 107.4, 89.3, 58.3, 57.7, 56.1, 42.5, 24.8

HRMS (ESI) calcd for [M+Na]<sup>+</sup> (C<sub>24</sub>H<sub>22</sub>N<sub>2</sub>O<sub>3</sub>Na) 409.1523, found 409.1526

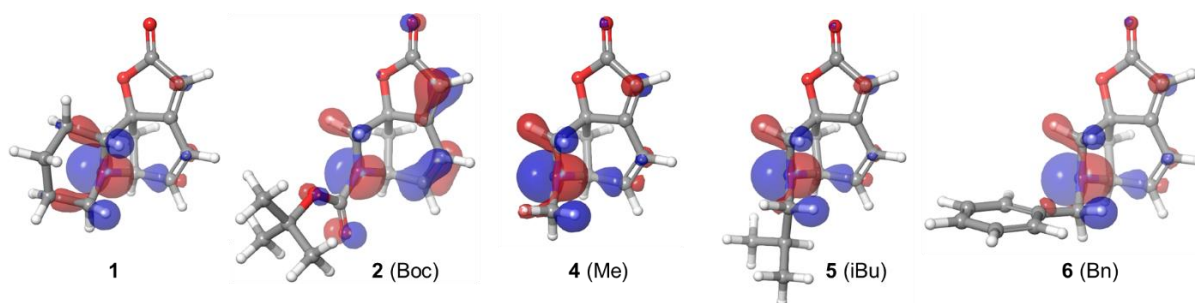
IR (UATR):  $\bar{\nu}$  (cm<sup>-1</sup>) 3313 (NH), 1735 (C=O lactone), 1693 (C=O amide), 1670 (C=C)

## 4.2. Computational Details

All calculations were carried with Gaussian 16 program. Structure optimizations of molecular structures in ground states were carried out at the B3LYP-D3 level in combination with the 6-31+G(d,p) basis set and using the PCM methanol solvent model. The vibrational frequencies were computed at the same level to check whether each optimized structure is an energy minimum (no imaginary frequency) or a transition state (single imaginary frequency). Single-point energies, molecular orbitals and Fukui indices of geometrically optimized structures were calculated using the 6-311++G(d,p) basis set.

Compounds	Lowest Frequency (cm <sup>-1</sup> )	<i>E</i> <sub>HOMO</sub> (eV)	<i>E</i> <sub>LUMO</sub> (eV)	Δ <i>G</i> <sub>298K/1atm</sub> (kcal/mol)
Securinine ( <b>1</b> )	105.77	-6.106	-2.309	-23.184
<b>2</b> (Boc)	43.27	-6.915	-2.450	-26.334
<b>4</b> (Me)	105.13	-6.321	-2.347	-21.722
<b>5</b> (iBu)	54.41	-6.144	-2.273	-24.506
<b>6</b> (Bn)	49.35	-6.232	-2.343	-25.200





**Figure 1:** DFT-generated HOMO representation of securinine (**1**) and compounds **2** (Boc), **4** (Me), **5** (iBu) and **6** (Bn)

#### 4.3. Cell Culture and Proliferation Assay

Securinine (**1**) and compounds **2**, **4**, **5**, **6**, **8**, **12-19** were evaluated by the CIBI platform (Plateforme des cibles biologiques, Institut de Chimie des Substances Naturelles, Gif/Yvette, France) on HL60 and HCT116 human cancer cell lines.

Cancer cell lines were obtained from the American Type Culture Collection (Rockville, MD, USA) and were cultured according to the supplier's instructions. Human HCT-116 colorectal carcinoma cells were grown in Gibco McCoy's 5A supplemented with 10% fetal calf serum (FCS) and 1% glutamine. HL60 myelogenous leukemia cells were grown in RPMI 1640 supplemented with 10% fetal calf serum (FCS) and 1% glutamine. Cells were maintained at 37°C in a humidified atmosphere containing 5% CO<sub>2</sub>.

Cell viability was determined by a luminescent assay according to the manufacturer's instructions (Promega, Madison, WI, USA). Briefly, the cells were seeded in 96-well plates (2.5 × 10<sup>3</sup> cells/well) containing 100 μL of growth medium. After 24 h of culture, the cells were treated with the tested compounds at two different final concentrations (10 μM and 1 μM). After 72 h of incubation, 100 μL of CellTiter Glo Reagent was added for 15 min before recording luminescence with a spectrophotometric plate reader PolarStar Omega (BMG LabTech). The dose-response curves were plotted with Graph Prism software and the IC<sub>50</sub> values were calculated using the Graph Prism software from polynomial curves (four or five-parameter logistic equations). Doxorubicin was used as an internal standard.

#### 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.

#### Acknowledgments

Université de Rennes 1 and CNRS are acknowledged for their financial support. XG is grateful to the 'Fondation ARC pour la recherche sur le cancer' for his post-doctoral fellowship (PDF20191209830).

#### Supporting Information.

Copies of the NMR data are given in the supporting information file.

#### References

- 
- [1] a) Snieckus, V. The *Securinega* Alkaloids. In *The Alkaloids: Chemistry and Physiology*; Elsevier, **1973**, Vol. 14, pp 425–506. b) Chirkin, E.; Atkalian, W.; Porée, F.-H. The *Securinega* Alkaloids. In *The Alkaloids*; Knölker, H.-J., Ed.; **2015** **74**, pp 1-120.
- [2] For recent achievements, see: a) Fan, Z.; Jaisi, A.; Chen, Y.; Shen, L.; Liu, Z.; Wu, S.; Liu, Y.; Zhang, W.; Xiao, Y. Discovery and biosynthesis of ascorbylated *Securinega* alkaloids. *ACS Catal.* **2021**, *11*, 8818-8828. b) He, Q.-F.; Wu, Z.-L.; Li, L.; Sun, W.-Y.; Wang, G.-Y.; Jiang, R.-W.; Hu, L.-J.; Shi, L.; He, R.-R.; Wang, Y.; Ye, W.-C. Discovery of neuritogenic *Securinega* alkaloids from *Flueggea suffruticosa* by a building blocks-based molecular network strategy. *Angew. Chem. Int. Ed.* **2021**, *60*, 19609-19613. c) Park, K.J.; Kim, C.S.; Khan, Z.; Oh, J.; Kim, S.Y.; Choi, S.U.; Lee, K.R. *Securinega* Alkaloids from the Twigs of *Securinega suffruticosa* and Their Biological Activities. *J. Nat. Prod.* **2019**, *82*, 1345-1353. d) Luo, X.-K.; Cai, J.; Yin, Z.-Y.; Luo, P.; Li, C.-J.; Ma, H.; Seeram, N.P.; Gu, Q.; Xu, J. Fluvirosaones A and B, Two Indolizidine Alkaloids with a Pentacyclic Skeleton from *Flueggea virosa*. *Org. Lett.*, **2018**, *20*, 991-994. e) Jeon, S.; Park, J.; Han, S. Syntheses of dimeric *Securinega* alkaloids. *Synlett*, **2017**, *28*, 2353-2359.
- [3] Wu, Z.-L.; Huang, X.-J.; Hu, L.-J.; Zhang, W.-Y.; Xie, Q.-J.; Jiang, R.-W.; Wang, Y.; Ye, W.-C. Absolute Configurations and Stereochemical Inversion Mechanism of Epimeric *Securinega* Alkaloids from *Flueggea suffruticosa*. *Org. Lett.* **2020**, *22*, 3673-3678.
- [4] Weinreb, S.M. Total synthesis of the *Securinega* alkaloids. *Nat. Prod. Rep.*, **2009**, *26*, 758-775.
- [5] Wehlauch, R.; Gademann, K. *Securinega* Alkaloids: Complex Structures, Potent Bioactivities, and Efficient Total Syntheses. *Asian J. Org. Chem.*, **2017**, *6*, 1146-1159.
- For recent syntheses, see: a) Lambert, K. M.; Cox, J. B.; Liu, L.; Jackson, A.C.; Yruegas, S.; Wiberg, K. B.; Wood, J.L. Total Synthesis of (±)-Phyllantidine: Development and Mechanistic Evaluation of a Ring Expansion for Installation of Embedded Nitrogen-Oxygen Bonds. *Angew. Chem. Int. Ed.*, **2020**, *59*, 9757-9766. b) Lee, S.; Kang, G.; Chung, G.; Kim, D.; Lee, H.-Y.; Han, S. Biosynthetically Inspiring Synthesis of Secu'amamine A, Fluvirosaones A and B. *Angew. Chem. Int. Ed.*, **2020**, *58*, 6894-6901. c) Hughes, J.M.E.; Gleason, J.L. Bio-inspired cascade and a late-stage directed sp<sup>3</sup> C-H lithiation enables a concise total synthesis of (-)-virosaine A. *Tetrahedron*, **2018**, *74*, 759-768.
- [6] Murav'eva, V.I.; Ban'kovskii, A. I. Chemical study of alkaloids of *Securinega suffruticosa*. *Dokl. Akda. Nauk. SSSR.* **1956**, *110*, 998-1000.
- [7] a) Zhang, W.; Li, J.-Y.; Lan, P.; Sun, P.-H.; Wang, Y.; Ye, W.-C.; Chen, W.M. Chemical synthesis and biological activities of *Securinega* alkaloids. *J. Chinese Pharm. Sci.*, **2011**, *20*, 203-217. b) Klochkov, S.; Neganova, M. Unique Indolizidine Alkaloid Securinine is a promising scaffold for the development of neuroprotective and antitumor drugs. *RSC Adv.*, **2021**, *11*, 19185-19195.
- [8] Russian drug compedium: Mashkovskiy, M.D. *Lekarstvennye Sredstva*. 14th edition. Moscow - Novaya Volna, 2002
- [9] Gundluru, M.K.; Agarwal, M.; Xia, Z.; Karan, G.; Wald, D.N. Small molecule securinine and norsecurinine analogs and their use in cancers inflammatory diseases and infection, **2015**, World Pat. WO2015/051284.
- [10] a) Perez, M.; Ayad, T.; Maillos, P.; Poughon, V.; Fahy, J.; Ratovelomanana-Vidal, V. Synthesis and Antiproliferative and Metabolic Evaluations of Novel Securinine Derivatives. *ACS Med. Chem. Lett.*, **2016**, *7*, 403-407. b) Perez, M.; Vidal, V.; Ayad, T.; Fahy, J.; Maillos, P. Securinine derivatives as anticancer agents, **2015**, PCT 14306944.1.

- 
- [11] a) Perez, M.; Ayad, T.; Maillos, P.; Poughon, V.; Fahy, J.; Ratovelomanana-Vidal, V. Synthesis and biological evaluation of new securinine analogues as potential anticancer agents. *Eur. J. Med. Chem.*, **2016**, *109*, 287-293. b) Perez, M.; Ayad, T.; Maillos, P.; Poughon, V.; Fahy, J.; Ratovelomanana-Vidal, V. Highly Diastereoselective 1,6-Conjugate Addition of Arylboronic Acids to Securinine. *Synlett*, **2016**, doi: 10.1055/s-0035-1561340.
- [12] a) Klochkov, S.G.; Afanas'eva, S.V.; Grigor'ev, V.V. Synthesis and biological activity of amination products of the alkaloid securinine. *Chem. Nat. Compd.*, **2008**, *44*, 197-202. b) Klochkov, S.G.; Neganova, M.E.; Afanas'eva, S.V.; Shevtsova, E.F. Synthesis and antioxidant activity of securinine derivatives. *Pharm. Chem. J.*, **2014**, *48*, 15-17.
- [13] a) Gupta, K.; Chakrabarti, A.; Rana, S.; Ramdeo, R.; Roth, B.L.; Agarwal, M.L.; Tse, W., Agarwal, M.K., Wald, D.N. Securinine, a Myeloid Differentiation Agent with Therapeutic Potential for AML. *PlosOne*, **2011**, e21203. b) Rana, S., Gupta, K., Gomez, J.; Matsuyama, S.; Chakrabarti, A.; Agarwal, M. L.; Agarwal, A.; Agarwal, M. K.; Wald, D. N. Securinine induces p73-dependent apoptosis preferentially in p53-deficient colon cancer cells. *FASEB J.*, **2010**, *24*, 2126-2134. See also: Tatematsu, H.; Mori, M.; Yang, T.-H.; Chang, J.-J.; Lee, T. T.-Y.; Lee, K.-H. Cytotoxic principles of *Securinega virosa*: virosecurinine and viroallosecurinine and related derivatives. *J. Pharm. Sci.*, **1991**, *80*, 325-327.
- [14] Li, M.; Han, S.; Zhang, G.; Ji, Z. Antiproliferative activity and apoptosis-inducing mechanism of L-securinine on human breast cancer MCF-7 cells. *Pharmazie*, **2014**, *69*, 217-223.
- [15] Chen, C.-R.; Xia, Y.-H.; Yao, S.-Y.; Zhang, Q.; Wang, Y.; Ji, Z.-N. Virosecurinine induces apoptosis by affecting Bcl-2 and Bax expression in human colon cancer SW480. *Pharmazie*, **2012**, *67*, 351-354.
- [16] Han, S.; Zhang, G.; Li, M.; Chen, D.; Wang, Y.; Ye, W.; Ji, Z. L-securinine induces apoptosis in the human promyelocytic leukemia cell line HL-60 and influences the expression of genes involved in the PI3K/AKT/mTOR signaling pathway. *Oncol. Rep.*, **2014**, *31*, 2245-2251.
- [17] Sharma, J.; Pandey, A.; Sharma, S.; Dixit, A. Securinine induces differentiation of human promyelocytic leukemia HL-60 cells through JNK-mediated signaling pathway. *Nutrition and Cancer*, **2021**, DOI: 10.1080/01635581.2021.1925710.
- [18] Kaplan, A.; Stockwell, B. Structural Elucidation of a Small Molecule Inhibitor of Protein Disulfide Isomerase. *ACS Med. Chem. Lett.* **2015**, *6*, 966-971.
- [19] Securinine is not identified as a PAINS compound by the common on-line PAINS filters (see: <https://admetmesh.scbdd.com/> or <http://www.swissadme.ch/index.php#>). For reference on PAINS filters, see: a) Baell, J. B., Holloway, G. A. New Substructure Filters for Removal of Pan Assay Interference Compounds (PAINS) from Screening Libraries and for Their Exclusion in Bioassays. *J. Med. Chem.* **2010**, *53*, 2719-2740. b) Baell, J. B., Nissink, J. W. M. Seven Year Itch: Pan-Assay Interference Compounds (PAINS) in 2017: Utility and Limitations. *ACS Chem. Biol.* **2018**, *13*, 36-44.
- [20] Chirkin, E.; Michel, S.; Porée, F.-H. Viability of a [2+2+1] *Hetero*-Pauson-Khand cycloaddition strategy toward *Securinega* alkaloids: synthesis of the BCD-ring core of securinine and related alkaloids. *J. Org. Chem.*, **2015**, *80*, 6525-6528.
- [21] Li, J.-Y.; Zhao, B.-X.; Zhang, W.; Li, C.; Huang, X.-J.; Wang, Y.; Sun, P.-H.; Ye, W.-C.; Chen, W.-M. Unexpected ring contraction and oxidation rearrangement reactions of securinine. *Tetrahedron* **2012**, *68*, 3972-3979.

- 
- [22] Initial report on this reaction: Bonini, C.; Chiummiento, L.; Videtta, V. Direct Preparation of Z-1,3-Enyne Systems with a TMS-Propargylic Sulfone: Application of a One-Pot Julia Olefination. *Synlett*, **2006**, *13*, 2079-2082.
- [23] Tao, C.; Zhang, J.; Chen, X.; Wang, X.; Li, Y.; Cheng, B.; Zhai, H. Formal synthesis of (±)-Aplykurodinone-1 through a *hetero*-Pauson-Khand cycloaddition approach. *Org. Lett.* **2017**, *19*, 1056-1059.
- [24] Lin, H., Xiao, L.-J.; Zhou, M.-J.; Yu, Xie, J.-H.; Zhou, Q.-L. Enantioselective approach to (-)-Hamigeran B and (-)-4-Bromohamigeran B via catalytic asymmetric hydrogenation of racemic ketone to assemble the chiral core framework. *Org. Lett.*, **2016**, *18*, 1434-1437.
- [25] Sha, C.K.; Shen, C.Y.; Jean, T.S.; Chiu, R.T.; Tseng, W.H. Intramolecular cyclization reactions of enone radicals. *Tetrahedron Lett.*, **1993**, *34*, 7641-7644.
- [26] Zhou, T.; Shi, Q.; Chen, C.H.; Zhu, H.; Huang, L.; Ho, P.; Lee, K.H. Anti-AIDS agents 79. Design, synthesis, molecular modeling and structure-activity relationships of novel dicamphanoyl-2',2'-dimethyldihydropyranochromone (DCP) analogs as potent anti-HIV agents. *Bioorg. Med. Chem.*, **2010**, *18*, 6678-6689.
- [27] Arican, D.; Braukmuller, S.; Brückner, R. Regioselective bromination of benzocycloheptadienones for the synthesis of substituted 3,4-benzotropolones including goupionone A. *Chem. Eur. J.*, **2017**, *23*, 4537-4541.
- [28] Wang, D.; Zhao, Y.; Yang, C.; Xia, W. Regioselective synthesis of  $\alpha$ -bromo- $\alpha,\beta$ -unsaturated carbonyl compounds via photocatalytic  $\alpha$ -bromination reactions. *Science China Chemistry*, **2016**, *59*, 190-194.
- [29] Nogues, C., Argouarch, G. Rhodium-catalyzed direct reductive amination of aldehydes and ketones with hydrosilanes. *ChemistrySelect*, **2020**, *5*, 8319-8327.
- [30] a) Kadam, S.T.; Kim, S.S. N-Iodosuccinimide (NIS) a novel and effective catalyst for the cyanosilylation of aldehydes under mild reaction conditions. *Catal. Commun.*, **2008**, *9*, 1342-1345. b) Karimi, B.; Seradj, H. N-Bromosuccinimide (NBS), a Novel and Highly Effective Catalyst for Acetylation of Alcohols under Mild Reaction Conditions. *Synlett*, **2001**, *4*, 519-520.
- [31] a) Johnson, C.R., Adams, J.P.; Braun, M.P.; Sananayake, C.B.W.; Wovkulich, P.M.; Uskoković, M.R. Direct  $\alpha$ -iodination of cycloalkenones. *Tetrahedron Lett.*, **1992**, *33*, 917-918. b) Bovonsombat, P.; Angara, G.J.; Mc Nelis, E. Concerning the formations of  $\alpha$ -iodoenones. *Tetrahedron Lett.*, **1994**, *35*, 6787-6790.
- [32] Pace, V.; Vilkauskaitė, G.; Šačkus, A.; Holzer, W. Highly efficient and chemoselective  $\alpha$ -iodination of acrylate esters through Morita-Baylis-Hillman-type chemistry. *Org. Biomol. Chem.*, **2013**, *11*, 1085-1088.
- [33] Pamarthi, R.; Kumar, R.; Sankara, C.S.; Lowe, G.J.; Zuegg, J.; Singh, S.K.; Ganesh, M.  $\alpha$ -Iodonitroalkenes as potential antifungal and antitubercular agents. *ChemistrySelect*, **2020**, *5*, 12272-12277.
- [34] These results are in accordance with the data reported by Vidal, see reference 10a.
- [35] Trost, B.; Gholami, H.; Zell, D. Palladium-catalyzed asymmetric allylic fluoroalkylation/trifluoromethylation. *J. Am. Chem. Soc.*, **2019**, *141*, 11446-11451.