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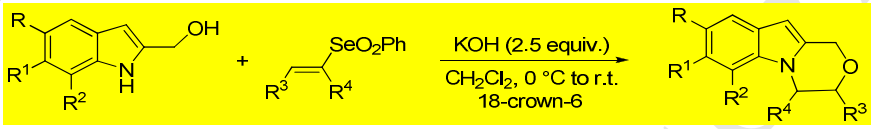
Martina Palomba, Elisa Vinti, Francesca Marini, Claudio Santi, Luana Bagnoli*
Department of Pharmaceutical Sciences, Group of Catalysis and Organic Green Chemistry, University of Perugia, Via del Liceo 1, 06123 Perugia, Italy



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*Department of Pharmaceutical Sciences, , Group of Catalysis and Organic Green Chemistry, Università di Perugia, Via del Liceo 1, 06123 Perugia, Italy

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ABSTRACT

Herein we report the synthesis of biologically relevant oxazino[4,3-*a*]indoles by an environmentally friendly Michael addition-cyclization cascade using potassium hydroxide in dichloromethane employing variously substituted vinyl selenones and (1*H*-indol-2yl)methanols. The addition of 18-crown-6, as a complexing agent, is crucial to achieve high chemo- and regio-selectivity.

1. Introduction

Heterocycle-fused indoles play an important role as biologically active compounds and pharmaceuticals.[1] For example, etodolac and pemedolac are anti-infiammatory and analgesic agents and other pyrano[3,4-*b*]indoles have been reported as potent inhibitors of hepatitis C virus (HCV) NS5B polymerase.[2] Also, oxazino[4,3-*a*]indoles have attracted attention for their potential antidepressant and antitumor properties (Figure 1).[3]

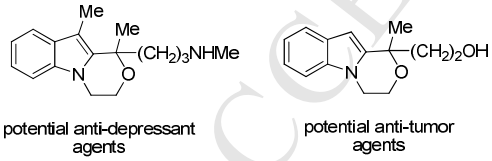


Figure 1 Biologically active oxazine[4,3-*a*]indoles

Very recently, a few examples of the preparation of oxazino[4,3-*a*]indoles appeared in literature.[4] Bandini[4a] and Gharpure[4b] have reported the synthesis of densely functionalized oxazino[4,3-*a*]indoles respectively through a gold catalyzed cascade sequence and through an intramolecular oxa-Pictet-Spengler reaction of an indole moiety with an N-tethered vinylogous carbonate. Also, Chen, Xiao *et al.* have synthesized unsubstitued or mono-substituted oxazino[4,3-*a*]indoles by the domino addition-cyclization reactions of (1*H*-indol-2-yl)methanols and vinyl sulfonium salts.[4c]

In recent years we have studied several domino processes using vinyl selenones as substrates for Michael addition-initiated ring closure reactions with carbon as well as heteroatom-centred nucleophiles.[5] Complex molecules can be easily obtained through a domino approach that allows the sequential formation of a number of bonds without the need for isolation of intermediates. This increases the overall sustainability of the protocol, minimizing the production of waste and reducing the formation of side products. Using vinyl selenones in domino procedures, biologically relevant heterocycles, like enantiopure 1,4-dioxanes, morpholines and piperazines,[5b] and six-membered benzo-1,4-heterocyclic compounds[5a] have been successfully prepared. In continuation of these studies we now report a novel application of vinyl selenones in a Michael-addition-initiated -ring closure reaction (MIRC) using (1*H*-indol-2-yl)methanols as bis-nucleophiles evidencing the effect of 18-crown-6 in the control of the selectivity.

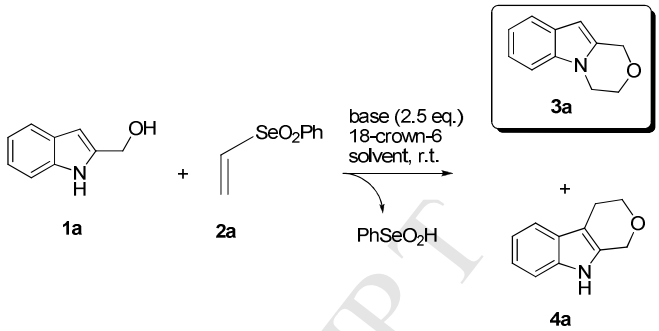
2. Results and discussion

The (1*H*-indol-2yl)methanols were easily prepared by reduction of the corresponding ester derivates according to the procedure described in the literature.[4c] In the first

* Corresponding author. Tel.: +39-075-585-5105; fax: +39-075-585-5116; e-mail: luana.bagnoli@unipg.it (L. Bagnoli)

experiments the (1*H*-indol-2yl)methanol **1a,** as Michael donor, and vinyl selenone **2a**, as the Michael acceptor, were used (Table 1). The phenylselenonyl group plays a dual role in the domino reaction: it activates the olefin during the β-addition and, subsequently, represents a good leaving group making the cyclization possible. Firstly, we evaluated the effect of different bases and solvents (entries 1-12, Table 1). The choice of the base resulted to be crucial for the success of the synthesis. The reaction did not occurred in the absence of a base or using an excess of organic bases (entries 1-3). Scarce yields of the cyclic products were obtained using cesium carbonate or sodium hydride (entries 4-5). On the contrary using potassium hydroxide in dichloromethane an 80% combined yield can be achieved and 3,4-dihydro-1*H*-oxazino[4,3-*a*]indoles **3a**[4c] and the tetrahydropyrano[3,4-*b*]indoles **4a**[6] are formed in a ~ 2:1 ratio (entry 6). A reaction carried out using a lower amount of base led to a lower yield (entry 7). Moreover a survey of the solvents revealed that the substitution of the dichloromethane with polar or apolar solvents gave poorer results (entries 8-12). However the addition of the complexing agent 18-crown-6 was crucial to achieve successful selective processes (entries 13-18). In fact, independently from the solvents, the exclusive formation of 3,4-dihydro-1*H*-oxazino[4,3-*a*]indole **3a** was observed. As shown in entry 14, Table 1, the best result was obtained using an excess of potassium hydroxide, 18-crown-6 and starting alcohol **1a** in dicloromethane. (81% yield of **3a**). With the optimized conditions we evaluated the versatility of the methodology using variously commercially substituted (1*H*-indol-2yl)methanols bearing electron donating group and electron withdrawing groups **1b-h**. The results summarized in Table 2 confirm that in the presence of 18-crown-6, in all cases, **3a-h** were formed as single products in good to excellent yields and the C-3 alkylated products **4a-f** were not formed (entries 1-8, Table 2). The pyrano derivatives **4a-b** obtained in the absence of 18-crown-6 are also characterized. (entries 1a-2a, Table 2).

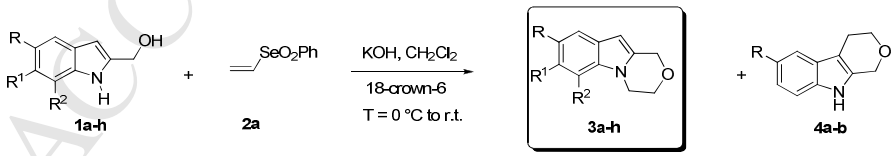
Table 1. Domino Michael addition/cyclization: optimization of the reaction conditions.



Entry	Eq. **1a**	Base 2.5 eq.	Solvent	18 Crown-6	Time (h)	Yield (%) **3a**	Yield (%) **4a**
1	1	-	CH_2Cl_2	-	48	-	-
2	1	DBU	CH_2Cl_2	-	48	-	-
3	1	Et_3N	CH_2Cl_2	-	48	-	-
4	1	Cs_2CO_3	CH_2Cl_2	-	48	15	trace
5	1	NaH	CH_2Cl_2	-	24	30	trace
6	1	KOH	CH_2Cl_2	-	24	50	30
7	1	KOH (1 eq.)	CH_2Cl_2	-	24	25	30
8	1	KOH	toluene	-	24	19	28
9	1	KOH	THF	-	24	15	7
10	1	KOH	CH_3CN[a]	-	24	21	-
11	1	KOH	DMF[a]	-	24	45	-
12	1	KOH	EtOH	-	24	-	-
13	1	KOH	CH_2Cl_2	2.5 eq.	12	71	-
14	2	KOH	CH_2Cl_2	2.5 eq.	12	81	-
15	2	KOH	CH_2Cl_2	1 eq.	12	66	-
16	2	KOH	toluene	2.5 eq.	12	58	-
17	2	KOH	DMF	2.5 eq.	12	55	-
18	2	KOH	THF	2.5 eq.	12	57	-

[a] Using DMF and CH_3CN as solvents, 10% and 9% yields of N-addition-elimination products were also formed respectively.

Table 2. Selective formation of oxazino[4,3-*a*]indoles **3a-h** with 18-crown-6 from vinyl selenone **2a**. Tetrahydropyrano[3,4-*b*]indoles **4a-b** were isolated only in the absence of 18-crown-6.

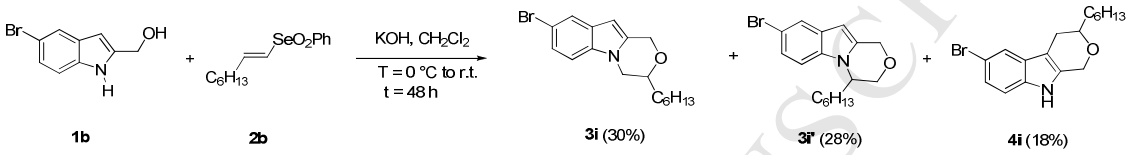


Entry	**1a-h**	Additive	Time reaction	**3a-h** (Yields)	**4a-b** (Yields)
1	**1a:** R = H, R^1 = H, R^2 = H	18-crown-6	12 h	**3a:** 81%	
1a		-	24 h	**3a:** 50%	**4a:** 30%
2	**1b:** R = Br, R^1 = H,= R^2 = H	18-crown-6	12 h	**3b:** 72%	
2a		-	24 h	**3b:** 35%	**4b:** 34%
3	**1c:** R = Me, R^1 = H, R^2= H	18-crown-6	12 h	**3c:** 78%	
4	**1d:** R = OMe, R^1 = H, R^2 = H	18-crown-6	12 h	**3d:** 91%	
5	**1e:** R = Cl, R^1 = H, R^2 = H	18-crown-6	12 h	**3e:** 74%	

6	**1f:** R = F, R^1 = H, R^2 = H	18-crown-6	12 h	**3f:** 98%
7	**1g:** R = H, R^1 = NO_2 R^2 = H	18-crown-6	12 h	**3g:** 86%
8	**1h:** R = OMe, R^1 = OMe R^2 = H	18-crown-6	12 h	**3h:** 61%

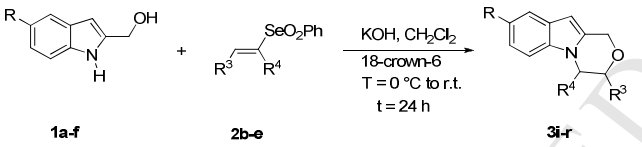
In order to extend the applicability of the process and better clarify the mechanism we carried out the reaction using substituted selenones. As highlighted in Scheme 1 using (5-bromo-1*H*-indol-2yl)methanol **1b** and selenone **2b** in the absence of 18-crown-6 the reaction was poorly selective and oxazino[4,3-*a*]indoles **3i** and **3i´** and the pyrano[3,4-*b*]indole **4i** were formed. Several typical trends in NMR and IR spectroscopy have been considered for the structural determination.[7] The position of the alkyl substituent (C_6H_{13}) was assigned by ^{13}C NMR on the basis of the CHO chemical shift at ~75ppm in **3i** and **4i**, and the chemical shift of the CHN signal at 52.1 ppm in the case of **3i´**. Once again we observed that the presence of 18-crown-6 is crucial for achieving high selectivities leading to the formation of exclusively the oxazine derivative **3i**[8] (Table 3, entry 1). Various indol-2-yl methanols **1a-f** and beta and alpha selenones **2b-e** were employed in order to expand the scope of application and in all cases we observed high selectivity. As highlighted in Table 3 only oxazino[4,3-*a*]indoles **3i-r** were formed in satisfactory to good yields (entries 1-10).

Scheme 1. Results obtained using vinyl selenone **2b** in the absence of 18-crown-6.



1b **2b**

Table 3. Selective formation of the oxazino[4,3-*a*]indoles **3i-r** with 18-crown-6.



1a-f **2b-e** **3i–r**

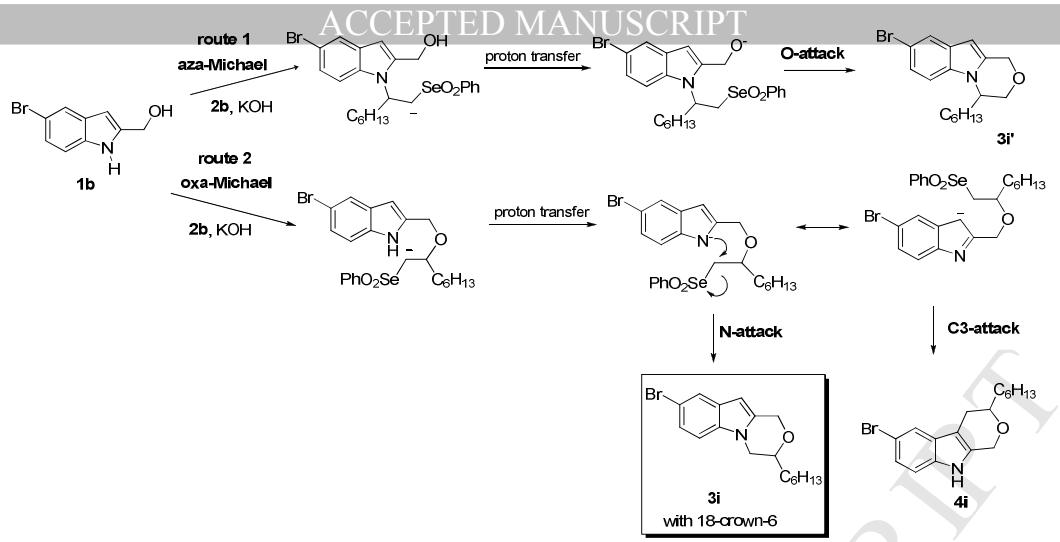
Entry	1a-f	2b-e	3i–r (Yields)
1	**1b:** R = Br	**2b:** R^3 =C_6H_{13}, R^4 = H	**3i:** 77%
2	**1a:** R = H	**2b:** R^3 = C_6H_{13},R^4 = H	**3j:** 60%
3	**1d:** R = OMe	**2b:** R^3 = C_6H_{13},R^4 = H	**3k:** 63%
4	**1a:** R = H	**2c:** R^3 = C_4H_9,R^4 = H	**3l:** 61%
5	**1f:** R = F	**2c:** R^3 = C_4H_9, R^4 = H	**3m:** 66%
6	**1d:** R = OMe	**2c:** R^3 = C_4H_9, R^4 = H	**3n:** 71%
7	**1a:** R = H	**2d**[a]**:** R^3 =CH_3, R^4= H	**3o:** 60%
8	**1e:** R = Cl	**2d**[a]**:** R^3 =CH_3, R^4 = H	**3p:** 50%
9	**1c:** R = CH_3	**2d**[a]**:** R^3 = CH_3, R^4 = H	**3q:** 45%
10	**1a:** R = H	**2e:** R^3 = H, R^4 = CH_3	**3r:** 40 %

[a] Selenone **2d** is a mixture of *E*/*Z* (1:1) isomers.

Based on the results obtained with substituted selenones **2b-e** (Scheme 1, Table 3) we can propose a plausible mechanism.

In Scheme 2 we exemplify the process by using **1b** and β–substituted selenone **2b**. The (1*H*-indol-2-yl)methanol has two nucleophilic sites for the initial Michael addition: the indolic N-H and the hydroxyl group. The formation of compounds such as **3i´**, with the alkyl chain in the α position of the nitrogen atom, is initiated by an aza-Michael addition. The subsequent proton transfer forms the oxygen anion that promotes the intramolecular displacement of the phenylselenonyl group (route 1, Scheme 2). On the contrary the compounds **3i** and **4i**, with the alkyl chain in α position of the oxygen atom, are obtained when the oxa-Michael addition takes place (route 2, scheme 2). The subsequent proton transfer generates a bidentate anion which reacts by N-cyclization or C3-cyclization affording the 3-hexyl-3,4-dihydro-1*H*-[1,4]oxazino[4,3-*a*]indole, **3i** or the 3-hexyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indole, **4i**, respectively. A similar competition in the presence of a bidentate nucleophile has been observed by Aggarwal in the formation of morpholines *via* Michael addition initiated cyclizations of vinyl sulfonium salts.[9] In this work a high level of oxa-Michael selectivity was obtained trough a careful choice of base and solvent, despite the pKa values of the nitrogen or oxygen nucleophiles involved (TsNH, pKa 17, DMSO vs OH, pKa 30, DMSO). In our case the presence of 18-crown-6 is crucial for achieving the exclusive formation of the 3-substituted oxazines **3i-r**, derived by oxa-Michael attack followed by N-cyclization. (Table 3, Scheme 2). The crown ether, by suppressing the tight ion pairing,[10] not only accelerates the reaction of the more nucleophilic "naked" oxygen during the formation of the Michael adduct, but also promotes the subsequent N-cyclization, preventing the C3-attack. Crown ethers have already been employed to promote nucleophilic substitution exclusively at the nitrogen atom of indoles in the presence of base in aprotic solvents.[11]

Scheme 2. Proposed mechanism



3. Conclusion

In summary we have carried out a new approach to synthesize biologically relevant oxazino[4,3-*a*]indoles through a Michael addition/cyclization reaction cascade of vinyl selenones with (1*H*-indole-2-yl)methanols as *bis*-nucleophiles. An extensive study for fine-tuning of reaction conditions has been performed, identifying the crucial role of 18-crown-6 for achieving high selectivity. Starting material availability, functional group tolerance and mild reaction conditions are relevant aspects of this simple procedure. Further applications of this strategy for the synthesis of other important indole derivatives are currently underway in our laboratory.

4.1. General

^{1}H and ^{13}C-NMR spectra were recorded in $CDCl_3$ at 400 and 100.62 MHz, respectively, on a Bruker Avance-DRX 400 instrument. Chemical shifts (δ) are reported in parts per million relative to residual solvent signals ($CHCl_3$, 7.26 ppm for ^{1}H NMR, $CDCl_3$ 77.0 ppm for ^{13}C NMR). Coupling constants are given in Hertz (Hz). The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad signal. FT-IR spectra were recorded with a Jasco model 410 spectrometer equipped with a diffuse reflectance accessory. High resolution mass spectra (HRMS) were recorded on an Agilent 6540-UHD Accurate Mass Q-TOF LC/MS instrument. The melting points are uncorrected. Thin layer chromatography (TLC) was performed on silica gel 60 F_{254} (Merck) on aluminum sheets. Reaction products were purified by column chromatography performed on Merck silica gel 60 (70-230 mesh).

4.2. Starting material

Starting vinyl selenones **2a-e** were prepared from the corresponding vinyl selenides by oxidation with an excess of *m*-chloroperbenzoic acid.[5c-d,12] The (1*H*-indol-2-yl)methanols **1a-h** were prepared according to literature procedures.[4c,13,14]

4.3. General procedure for the synthesis of 3,4-dihydro-1*H*-[1,4]oxazino[4,3-*a*]indole 3a-r.

A stirred solution of (1*H*-indol-2-yl)methanol compounds **1a-h** (0.24 mmol) in dichloromethane (3 mL) was treated with potassium hydroxide (16.8 mg, 0.30 mmol and 18-crown-6 (79.30 mg, 0.30 mmol) at 0 °C under argon. After 10 min a solution of vinyl selenones **2a-e** (0.12 mmol) in dichloromethane (3 mL) was added at 0°C and the reaction mixtures were allowed to warm to r.t.. The progress of the reactions were monitored by TLC. After 12 h the solvent was evaporated under vacuum. The products were purified using column chromatography on silica gel (EtOAc/ PE 5:95 as eluant) afford the oxazine derivates **3a-r**. The physical and spectral data of the 3,4-dihydro-1*H*-[1,4]oxazino[4,3-*a*]indoles **3a-f** are identical to those reported in the literature.[4c] The physical and spectral data of 3,4-dihydro-1*H*-[1,4]oxazino[4,3-*a*]indoles **3g-r** are reported below.

4.3.1. *3,4-Dihydro-1H-[1,4]oxazino[4,3-a]indole* (**3a**).[4c]: (16.8 mg, 81%), ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.60 (d, 1H, *J* = 7.6 Hz, CH) 7.32 (d, 1H, *J* = 8.0 Hz CH), 7.21 (t, 1H, *J* = 7.0 Hz, CH), 7.15 (t, 1H, *J* = 7.8 Hz, CH), 5.02 (s, 2H, CH_2O), 4.22-4.19 (m, 2H, CH_2O), 4.14-4.11 (m, 2H, CH_2N).

4.3.2. *8-Bromo-3,4-dihydro-1H-[1,4]oxazino[4,3-a]indole* (**3b**).[4c] (21.8 mg, 72%),. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.70 (d, 1H, *J* = 1.8 Hz, CH) 7.27 (dd, 1H, *J* = 1.8, 8.6 Hz CH), 7.15 (d, 1H, *J* = 8.6 Hz, CH), 6.17 (s, 1H, CH), 4.97 (s, 2H, CH_2O), 4.21-4.15 (m, 2H, CH_2O), 4.08-4.02 (m, 2H, CH_2N).

4.3.3. *8-Methyl-3,4-dihydro-1H-[1,4]oxazino[4,3-a]indole* (**3c**).[4c] (17.5 mg, 78%), ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.38 (s, 1H, CH) 7.24 (d, 1H, *J* = 8.8 Hz, CH), 7.03 (d, 1H, *J* = 8.4 Hz, CH), 6.16 (s, 1H, CH), 4.99 (s, 2H, CH_2O), 4.20-4.14 (m, 2H, CH_2O), 4.08-4.01 (m, 2H, CH_2N), 2.47 (s, 3H, CH_3).

4.3.4. *8-Methoxy-3,4-dihydro-1H-[1,4]oxazino[4,3-a]indole* (**3d**).[4c] (22.1 mg, 91%), ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.18 (d, 1H, *J* = .8.8 Hz, CH), 7.06 (d, 1H, *J* = 2.4 Hz, CH), 6.84 (dd, 1H, *J* = 2.4, 8.8. Hz, CH), 6.15 (s, 1H, CH), 4.97 (s, 2H, CH_2O), 4.20-4.12 (m, 2H, CH_2O), 4.08-4.01 (m, 2H, CH_2N), 3.83 (s, 3H, OCH_3).

4.3.5. *8-Chloro-3,4-dihydro-1H-[1,4]oxazino[4,3-a]indole* (**3e**).[4c] (18.2 mg, 74%), ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.53 (d, 1H, *J* = .1.8 Hz, CH), 7.26-7.11 (m, 2H, 2CH), 6.16 (s, 1H, CH), 4.97 (s, 2H, CH_2O), 4.20-4.14 (m, 2H, CH_2O), 4.08-4.02 (m, 2H, CH_2N).

4.3.6. *8-Fluoro-3,4-dihydro-1H-[1,4]oxazino[4,3-a]indole* (**3f**).[4c] (22.5 mg, 98%), ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.27-7.15 (m, 2H, 2CH), 6.93 (dt, 1H, *J* = 2.5, 8.9 Hz), 6.19 (s, 1H, CH), 4.98 (s, 2H, CH_2O), 4.20-4.13 (m, 2H, CH_2O), 4.09-4.02 (m, 2H, CH_2N).

4.3.7. *6-Nitro-3,4-dihydro-1H-[1,4]oxazino[4,3-a]indole* (**3g**). (24.1 mg, 86%), yellow solid. mp 91-94 °C; R_f (EtOAc/PE 20:80) 0.48. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.83 (d, 1H, *J* = 7.8 Hz, CH,) 7.80 (d, 1H, *J* = 8.4 Hz CH), 7.17 (t, 1H, *J* = 7.9 Hz, CH), 6.42 (s, 1H, CH), 5.05 (s, 2H, CH_2O), 4.24-4.20 (m, 2H, CH_2O), 4.14-4.09 (m, 2H, CH_2N). ^{13}C NMR (100.62 MHz, $CDCl_3$, 25 °C): δ = 136.4 (C*ipso*), 136.2 (C*ipso*), 132.5 (C*ipso*), 127.5 (C*ipso*), 126.4 (CH, Ar), 119.2 (CH, Ar), 119.1 (CH, Ar), 98.1 (CH, Ar), 64.9 (CH_2O), 64.7 (CH_2O), 45.4 (CH_2N). HRMS (ESI): m/z calcd for $C_{11}H_{11}N_2O_3$ $(M+H)^+$ 219.0770, found 219.0767. FT-IR (KBr) ν_{max} 3093, 2922, 2851, 1514, 1344, 1294, 1108, 806, 728 cm^{-1}.

4.3.8. *7,8-Dimethoxy-3,4-dihydro-1H-[1,4]oxazino[4,3-a]indole* **(3h).** (17.1 mg, 61%), yellow solid. mp 137-140 °C; R_f (EtOAc/PE 20:80) 0.15. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.06 (s, 1H, CH), 6.08 (s, 1H, CH), 6.13 (s, 1H, CH), 4.97 (s, 2H, CH_2O), 4.20-4.15 (m, 2H, CH_2O), 4.06-4.02 (m, 2H, CH_2N), 3.97 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3). ^{13}C NMR (100.62 MHz, $CDCl_3$, 25 °C): δ = 146.3 (C*ipso*), 145.2 (C*ipso*), 131.4 (C*ipso*), 130.5 (C*ipso*), 120.5 (C*ipso*), 102.2 (CH, Ar), 95.5 (CH, Ar), 92.3 (CH, Ar), 65.1 (CH_2O), 64.6 (CH_2O), 56.3 (CH_3O), 56.2 (CH_3O), 41.9 (CH_2N). HRMS (ESI): m/z calcd for $C_{13}H_{16}NO_3$ $(M+H)^+$ 234.1130, found 234.1125. FT-IR (KBr) ν_{max} 2929, 1653, 1489, 1340, 1206, 1164, 1090, 912, 851, 761 cm^{-1}

4.3.9 *8-Bromo-3-hexyl-3,4-dihydro-1H-[1,4]oxazino[4,3-a] indole* (**3i**). (31.1 mg, 77%), yellow solid, mp 68-73 °C; R_f (EtOAc/PE 20:80) 0.87. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.72 (d, 1H, *J* = 1.8 Hz, CH), 7.27 (dd, 1H, *J* = 1.8, 8.6 Hz, CH), 7.16 (d, 1H, *J* = 8.6 Hz, CH), 6.17 (s, 1H, CH), 5.11 (d, 1H, *J* = 15.0 Hz, CH_2O), 4.92 (d, 1H, *J* = 15.0 Hz, CH_2O), 4.09 (dd, 1H, *J* = 3.3, 11.3 Hz, CH_2N), 3.94-3.87 (m, 1H, CHO), 3.68 (t, 1H, *J* = 11.0 Hz, CH_2N), 1.80-1.29 (m, 10H, $5CH_2$), 0.93 (t, 3H, *J* = 6.8 Hz, CH_3). ^{13}C NMR (100.62 MHz, $CDCl_3$, 25 °C): δ = 134.6 (C*ipso*), 134.2 (C*ipso*), 129.8 (C*ipso*), 123.6 (CH, Ar), 122.7 (CH, Ar), 113.1 (C*ipso*), 109.8 (CH, Ar), 94.9 (CH, Ar), 74.3 (CHO), 64.5 (CH_2O), 46.5 (CH_2N), 33.5 (CH_2), 31.7 (CH_2), 29.2 (CH_2), 25.3 (CH_2), 22.6 (CH_2), 14.0 (CH_3). HRMS (ESI): m/z calcd for $C_{17}H_{23}{}^{79}BrNO$ $(M+H)^+$ 336.0963, found 336.0963. FT-IR (KBr) ν_{max} 3100, 2928, 2854, 1459, 1365, 1335, 1097, 1052, 866, 789 cm^{-1}.

4.3.10. *3-Hexyl-3,4-dihydro-1H-[1,4]oxazino[4,3-a]indole* (**3j**). (18.5 mg, 60%), yellow solid, mp 48-52 °C; R_f (EtOAc/PE 20:80) 0.82. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.61 (d, 1H, *J* = 7.7 Hz, CH), 7.31 (d, 1H, *J* = 8.1 Hz, CH), 7.23-7.13 (m, 2H, CH), 6.25 (s, 1H, CH), 5.14 (d, 1H, *J* = 14.8 Hz, CH_2O), 4.95 (d, 1H, *J* = 14.8 Hz, CH_2O), 4.14 (dd, 1H, *J* = 3.2, 11.3 Hz, CH_2N), 3.96-3.87 (m, 1H, CHO), 3.71 (t, 1H, *J* = 11.0 Hz, CH_2N), 1.83-1.38 (m, 10H, $5CH_2$), 0.94 (t, 3H, *J* = 6.8 Hz, CH_3). ^{13}C NMR (100.62 MHz, $CDCl_3$, 25 °C): δ = 135.9 (C*ipso*), 133.0 (C*ipso*), 128.2 (C*ipso*), 120.8 (CH, Ar), 120.2 (CH, Ar), 119.9 (CH, Ar), 108.4 (CH, Ar), 95.3 (CH, Ar), 74.4 (CHO), 64.7 (CH_2O), 46.6 (CH_2N), 33.6 (CH_2), 31.7 (CH_2), 29.2 (CH_2), 25.3 (CH_2), 22.6 (CH_2), 14.1 (CH_3). HRMS (ESI): m/z calcd for $C_{17}H_{24}NO$ $(M+H)^+$ 258.1858, found 258.1855. FT-IR (KBr) ν_{max} 3046, 2926, 2857, 1542, 1457, 1368, 1337, 1095, 1066, 783, 741 cm^{-1}.

4.3.11. *3-Hexyl-8-methoxy-3,4-dihydro-1H-[1,4]oxazino[4,3-a] indole* (**3k**). (21.7 mg, 63%), orange solid, mp 52-56 °C; R_f (EtOAc/PE 20:80) 0.76. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.19 (d, 1H, *J* = 8.8 Hz), 7.07 (d, 1H, *J* = 2.3 Hz, CH), 6.86 (dd, 1H, *J* = 2.3, 8.8 Hz, CH), 6.17 (s, 1H, CH), 5.10 (d, 1H, *J* = 14.8 Hz, CH_2O), 4.92 (d, 1H, *J* = 14.8 Hz, CH_2O), 4.09 (dd, 1H, *J* = 3.3, 11.3 Hz, CH_2N), 3.94-3.87 (m, 1H, CHO), 3.88 (s, 3H, CH_3O), 3.67 (t, 1H, *J* = 11.0 Hz, CH_2N), 1.80-1.32 (m, 10H, $5CH_2$), 0.92 (t, 3H, *J* = 6.8 Hz, CH_3). ^{13}C NMR (100.62 MHz, $CDCl_3$, 25 °C): δ = 154.4 (C*ipso*), 133.6 (C*ipso*), 131.3 (C*ipso*), 128.6 (C*ipso*), 110.7 (CH, Ar), 109.1 (CH, Ar), 102.2 (CH, Ar), 95.0 (CH, Ar), 74.4 (CHO), 64.7 (CH_2O), 55.8 (CH_3O), 46.6 (CH_2), 33.6 (CH_2), 31.7 (CH_2), 29.2 (CH_2), 25.3 (CH_2), 22.6 (CH_2), 14.1 (CH_3). HRMS (ESI): m/z calcd for $C_{18}H_{26}NO_2$ $(M+H)^+$ 288.1964 found 288.1964. FT-IR (KBr) ν_{max} 3260, 2923, 2853, 1481, 1457, 1232, 1184, 1034, 800, 739 cm^{-1}.

4.3.12. *3-Butyl-3,4-dihydro-1H-[1,4]oxazino[4,3-a]indole* (**3l**). (16.8 mg, 61%), yellow solid, mp 75-79 °C; R_f (EtOAc/PE 20:80) 0.83. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.60 (d, 1H, *J* = 7.8 Hz, CH), 7.31 (d, 1H, *J* = 8.0 Hz, CH), 7.20 (t, 1H, *J* = 7.0 Hz, CH), 7.13 (t, 1H, *J* = 7.1 Hz, CH), 6.24 (s, 1H, CH), 5.13 (d, 1H, *J* = 14.8 Hz, CH_2O), 4.95 (d, 1H, *J* = 14.8 Hz, CH_2O), 4.15 (dd, 1H, *J* = 3.1, 11.3 Hz, CH_2N), 3.96-3.87 (m, 1H, CHO), 3.70 (t, 1H, *J* = 11.1 Hz, CH_2N), 1.80-1.40 (m, 6H, $3CH_2$), 0.99 (t, 3H, *J* = 7.0 Hz, CH_3). ^{13}C NMR (100.62 MHz, $CDCl_3$, 25 °C): δ = 135.9 (C*ipso*), 132.9 (C*ipso*), 128.2 (C*ipso*), 120.8 (CH, Ar), 120.2 (CH, Ar), 119.9 (CH, Ar), 108.5 (CH, Ar), 95.3 (CH, Ar), 74.4 (CHO), 64.7 (CH_2O), 46.5 (CH_2N), 33.3 (CH_2), 27.5 (CH_2), 22.7 (CH_2), 13.9 (CH_3). HRMS (ESI): m/z calcd for $C_{15}H_{20}NO$ $(M+H)^+$ 230.1545, found 230.1542. FT-IR (KBr) ν_{max} 3045, 2956, 2858, 1549, 1471, 1458, 1370, 1339, 1223, 1092, 1003, 780, 741 cm^{-1}.

4.3.13. *3-Butyl-8-fluoro-3,4-dihydro-1H-[1,4]oxazino[4,3-a] indole* (**3m**). (19.6 mg, 66%), yellow solid, mp 75-79 °C; R_f (EtOAc/PE 20:80) 0.79. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.23 (dd, 1H, *J* = 2.3 Hz, *J* = 9.8 Hz, CH), 7.20 (dd, 1H, *J* = 4.4 Hz, *J* = 8.8 Hz, CH), 6.94 (dt, 1H, *J* = 2.3 Hz, *J* = 9.1 Hz, CH), 6.19 (s, 1H, CH), 5.11 (d, 1H, *J* = 14.9 Hz, CH_2O), 4.92 (d, 1H, *J* = 14.9 Hz, CH_2O), 4.10 (dd, 1H, *J* = 3.2, 11.3 Hz, CH_2N), 3.95-3.86 (m, 1H, CHO), 3.69 (t, 1H, *J* = 11.0 Hz, CH_2N), 1.80-1.40 (m, 6H, $3CH_2$), 0.99 (t, 3H, *J* = 7.0 Hz, CH_3). ^{13}C NMR (100.62 MHz, $CDCl_3$, 25°C): δ = 158.1 (C*ipso*, d, *J* = 232 Hz,), 134.7 (C*ipso*), 132.6 (C*ipso*), 128.4 (CH, Ar, d, *J*= 10.0 Hz), 109.0 (CH, Ar, d, *J* = 26.0 Hz), 108.9 (CH, Ar, d, *J* = 10.0 Hz), 105.1 (CH, Ar, d, *J* = 23.5 Hz), 95.4 (CH, Ar, d, *J* = 4.5 Hz), 74.3 (CH_2O), 64.6 (CH_2O), 46.6 (CH_2N), 33.2 (CH_2), 27.5 (CH_2), 22.6 (CH_2), 13.9 (CH_3). HRMS (ESI): m/z calcd for $C_{15}H_{19}FNO$ $(M+H)^+$ 248.1451, found 248.1448. FT-IR (KBr) ν_{max} 3059, 2954, 2849, 1577, 1480, 1180, 1157, 1092, 872, 770 cm^{-1}.

4.3.14. *3-Butyl-8-methoxy-3,4-dihydro-1H-[1,4]oxazino[4,3-a] indole* (**3n**). (22.1 mg, 71%), white solid, mp 86-89 °C; R_f (EtOAc/PE 20:80) 0.73. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.18 (d, 1H, *J* = 8.8 Hz, CH), 7.05 (d, 1H, *J* = 2.3 Hz CH), 6.84 (dd, 1H, *J* = 2.3, 8.8 Hz, CH), 6.15 (s, 1H, CH), 5.08 (d, 1H, *J* = 14.8 Hz, CH_2O), 4.59 (d, 1H, *J* = 14.8 Hz, CH_2O), 4.08 (dd, 1H, *J* = 3.2, 11.3 Hz, CH_2N), 3.90-3.82 (m, 1H, CHO), 3.86 (s, 3H, CH_3O), 3.66 (t, 1H, *J* = 11.0 Hz, CH_2N), 1.84-1.35 (m, 6H, $3CH_2$), 0.97 (t, 3H, *J* = 7.1 Hz, CH_3). ^{13}C NMR (100.62 MHz, $CDCl_3$, 25 °C): δ = 154.4 (C*ipso*), 133.6 (C*ipso*), 131.2 (C*ipso*), 128.5 (*Cipso*), 110.7 (CH, Ar), 109.2 (CH, Ar), 102.2 (CH, Ar), 94.9 (CH, Ar), 74.4 (CHO), 64.6 (CH_2O), 55.8 (OCH_3), 46.5 (CH_2N), 33.2 (CH_2), 27.4 (CH_2), 22.6 (CH_2), 13.9 (CH_3). HRMS (ESI): m/z calcd for $C_{16}H_{22}NO_2$ $(M+H)^+$ 260.1651,

found 260.1646. FT-IR (KBr) ν_{max} 3103, 2998, 2957, 2864, 2856, 1547, 1483, 1367, 1329, 1250, 1084, 1086, 978, 852, 701 1619, 1579, 1480, 1203, 1092, 843, 781 cm^{-1}.

4.3.15. *3-Methyl-3,4-dihydro-1H-[1,4]oxazino[4,3-a]indole* (**3o**). (13.5 mg, 60%), yellow solid, mp 113-119 °C; R_f (EtOAc/PE 20:80) 0.64. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.59 (d, 1H, *J* = 7.7 Hz, CH), 7.30 (d, 1H, *J* = 8.0 Hz, CH), 7.20 (t, 1H, *J* = 7.6 Hz, CH), 7.14 (t, 1H, *J* = 7.1 Hz, CH), 6.24 (s, 1H, CH), 5.12 (d, 1H, *J* = 14.8 Hz, CH_2O), 4.97 (d, 1H, *J* = 14.8 Hz, CH_2O), 4.13 (dd, 1H, *J* = 3.1, 11.2 Hz, CH_2N), 4.11-4.03 (m, 1H, CHO), 3.68 (t, 1H, *J* = 10.8 Hz, CH_2N), 1.47 (d, 3H, *J* = 6.4 Hz, CH_3). ^{13}C NMR (100.62 MHz, $CDCl_3$, 25°C): δ = 135.9 (C*ipso*), 132.6 (C*ipso*), 128.2 (C*ipso*), 120.8 (CH, Ar), 120.2 (CH, Ar), 120.0 (CH, Ar), 108.5 (CH, Ar), 95.4 (CH, Ar), 70.4 (CHO), 65.0 (CH_2O), 47.6 (CH_2N), 19.1 (CH_3). HRMS (ESI): m/z calcd for $C_{12}H_{14}NO_2$ $(M+H)^+$ 188.1075, found 188.1071. FT-IR (KBr) ν_{max} 3058, 2973, 2895, 1545, 1471, 1339, 1255, 1091, 1050, 784, 740 cm^{-1}.

4.3.16. *8-Chloro-3-methyl-3,4-dihydro-1H-[1,4]oxazino[4,3-a]indole* **(3p)**.(13.3 mg, 50%), white solid, mp 125-130 °C; R_f (EtOAc/PE 20:80) 0.53. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.55 (d, 1H, *J* = 1.4 Hz, CH), 7.19 (d, 1H, *J* = 8.6 Hz, CH), 7.14 (dd, 1H, *J* = 1.4, 8.6 Hz, CH), 6.18 (s, 1H, CH), 5.11 (d, 1H, *J* = 15.0 Hz, CH_2O), 4.95 (d, 1H, *J* = 15.0 Hz, CH_2O), 4.12-4.04 (m, 1H, CHO), 4.10 (dd, 1H, *J* = 3.3, 11.6 Hz, CH_2N), 3.68 (t, 1H, *J* = 11.1 Hz, CH_2N), 1.47 (d, 3H, *J* = 6.0 Hz, CH_3). ^{13}C NMR (100.62 MHz, $CDCl_3$, 25 °C) δ = 134.3 (C*ipso*), 134.0 (C*ipso*), 129.2 (C*ipso*), 125.6 (C*ipso*), 121.0 (CH, Ar), 119.6 (CH, Ar), 109.3 (CH, Ar), 95.1 (CH, Ar), 70.3 (CHO), 64.4 (CH_2O), 47.8 (CH_2N), 18.9 (CH_3). HRMS (ESI): m/z calcd for $C_{12}H_{13}{}^{35}ClNO$ $(M+H)^+$ 222.0686, found 222.0684. FT-IR (KBr) ν_{max} 3113, 2979, 2868, 1563, 1452, 1422, 1308, 1254, 1140, 1092, 1068, 879, 784 cm^{-1}.

4.3.17. *3,8-Dimethyl-3,4-dihydro-1H-[1,4]oxazino[4,3-a] indole* **(3q)**. Yield: (10.9 mg, 45%), yellow solid, mp 103-107 °C; R_f (EtOAc/PE 20:80) 0.64. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.36 (s, 1H, CH), 7.17 (d, 1H, *J* = 8.3 Hz, CH), 7.01 (d, 1H, *J* = 8.2 Hz, CH), 6.14 (s, 1H, CH), 5.08 (d, 1H, *J* = 14.7 Hz, CH_2O), 4.94 (d, 1H, *J* =14.7 Hz, CH_2O), 4.09 (dd, 1H, *J* = 2.9, 12.8 Hz, CH_2N), 4.07-4.00 (m, 1H, CHO), 3.63 (t, 1H, *J* = 11.0 Hz, CH_2N), 2.45 (s, 3H, CH_3), 1.45 (d, 3H, *J* = 5.6 Hz, CH_3). ^{13}C NMR (100.62 MHz), $CDCl_3$, 25 °C): δ = 134.4 (C*ipso*), 132.7 (C*ipso*), 129.2 (C*ipso*), 128.5 (C*ipso*), 122.4 (CH), 119.9 (CH), 108.1 (CH), 94.9 (CH), 70.4 (CHO), 64.6 (CH_2O), 47.8 (CH_2N), 21.4 (CH_3), 19.1 (CH_3). HRMS (ESI): m/z calcd for $C_{13}H_{16}NO$ $(M+H)^+$ 202.1232, found 202.1227. FT-IR (KBr) ν_{max} 3021, 2978, 2842, 1573, 1483, 1422, 1364, 1260, 1144, 1091, 1061, 899, 761 cm^{-1}.

4.3.18. *4-Methyl-3,4-dihydro-1H-[1,4]oxazino[4,3-a]indole* **(3r).** (9.0 mg, 40%), yellow solid, mp 110-114 °C; R_f (EtOAc/PE 20:80) 0.69. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.59 (d, 1H, *J* = 7.6 Hz, CH), 7.34 (d, 1H, *J* = 7.9 Hz, CH), 7.22 (t, 1H, *J* = 7.2 Hz, CH), 7.13 (t, 1H, *J* = 7.2 Hz, CH), 6.21 (s, 1H, CH), 5.09 (d, 1H, *J* = 14.7 Hz, CH_2O), 4.94 (d, 1H, *J* = 14.7 Hz, CH_2O), 4.48-4.44 (m, 1H, CHN), 4.09 (dd, 1H, *J* = 3.2, 11.6 Hz, CH_2O), 4.03 (t, 1H, *J* = 11.6 Hz, CH_2O), 1.52 (d, 3H, *J* = 6.5 Hz, CH_3). ^{13}C NMR (50.31 MHz, $CDCl_3$, 25 °C): δ = 135.1 (C*ipso*), 132.3 (C*ipso*), 128.2 (C*ipso*), 120.7 (CH), 120.4 (CH), 119.8 (CH), 109.1 (CH), 95.4 (CH), 70.1 (CH_2O), 65.0 (CH_2O), 47.6 (CHN), 18.1 (CH_3). HRMS (ESI): m/z calcd for $C_{12}H_{14}NO$ $(M+H)^+$ 188.1075, found 188.1072. FT-IR (KBr) ν_{max} 3109, 2856, 1547, 1483, 1367, 1329, 1250, 1084, 1086, 978, 852, 701 cm^{-1}.

The formation of 8-bromo-4-hexyl-3,4-dihydro-1*H*-[1,4]oxazino[4,3-*a*]indole **3i´** and the 1,3,4,9-tetrahydropyrano[3,4-*b*]indoles **4a-b,** and **4i** were observed when the reactions were carried out in the absence of 18-crown-6 and employing 1 equivalent of the compounds **1a-b**. The products were purified using column chromatography on silica gel (EtOAc/PE from 5:95 to 20:80).The physical and spectral data of 1,3,4,9-tetrahydropyrano[3,4-*b*]indole **4a** are identical to that reported in the literature.[6] The physical and spectral data of 3,4-dihydro-1*H*-[1,4]oxazino[4,3-*a*]indole **3i´** and the 1,3,4,9-tetrahydropyrano[3,4-b]indole **4b** and **4i** are reported below.

4.3.19. *8-Bromo-4-hexyl-3,4-dihydro-1H-[1,4]oxazino[4,3-a] indole* (**3i´**). (11.3 mg, 28%), brown oil; R_f (EtOAc/PE 20:80) 0.79. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.70 (d, 1H, *J* = 1.5 Hz, CH), 7.26 (dd, 1H, *J* = 1.5, 8.5 Hz, CH), 7.15 (d, 1H, *J* = 8.5 Hz, CH), 6.14 (s, 1H, CH), 5.09 (d, 1H, *J* = 15.0 Hz, CH_2O), 4.91 (d, 1H, *J* = 15.0 Hz, CH_2O), 4.18 (t, 1H, *J* = 11.0 Hz, CH_2O), 4.18-4.07 (m, 1H, CHN), 3.95 (dd, 1H, *J* = 2.9, 11.8 Hz, CH_2O), 2.05-1.27 (m, 10H, $5CH_2$), 0.89 (t, 3H, *J* = 6.8 Hz, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 133.8 (2C*ipso*), 129.9 (C*ipso*), 123.4 (CH, Ar), 122.8 (CH, Ar), 112.9 (C*ipso*), 110.4 (CH, Ar), 94.8 (CH, Ar), 66.8 (CH_2O), 64.7 (CH_2O), 52.1 (CHN), 31.7 (CH_2), 31.6 (CH_2), 29.1 (CH_2), 26.0 (CH_2), 22.5 (CH_2), 14.0 (CH_3). HRMS (ESI): m/z calcd for $C_{17}H_{23}{}^{81}BrNO$ $(M+H)^+$ 338.0943, found 338.0932. FT-IR (KBr): ν_{max} 2928, 2855, 1456, 1359, 1337, 1263, 1099, 1051, 790 cm^{-1}.

4.3.20. *1,3,4,9-Tetrahydropyrano[3,4-b]indole* (**4a**).[6] (6.2 mg, 30%), ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ =7.82 (brs, 1H), 7.52 (d, 1H, *J* = 7.6 Hz, Ar), 7.34 (d, 1H, *J* = 7.6 Hz, Ar), 7.22-7.08 (m, 2H, Ar), 4.84 (t, 2H, *J* = 1.5 Hz, CH_2O), 4.05 (t, 2H, *J* = 5.4 Hz, CH_2O), 2.87 (tt, 2H, *J* = 1,5, 5.4 Hz, CH_2).

4.3.21. *6-Bromo-1,3,4,9-tetrahydropyrano[3,4-b]indole* (**4b**). (10.3 mg, 34%), brown solid, mp 139-142 °C; R_f (20% EtOAc/PE) 0.25. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.87 (brs, 1H, NH), 7.63 (d, 1H, *J* = 1.7 Hz, CH), 7.26 (dd, 1H, *J* = 1.7, 8.5 Hz, CH), 7.20 (d, 1H, *J* = 8.5 Hz, CH), 4.83 (s, 2H, CH_2O), 4.04 (t, 2H, *J* = 5.5 Hz, CH_2O), 2.81 (t, 2H, *J* = 5.5 Hz, CH_2). ^{13}C NMR (100.62 MHz, $CDCl_3$, 25 °C): δ = 134.5 (C*ipso*), 132.8 (C*ipso*), 128.9 (C*ipso*), 124.4 (CH, Ar), 120.7 (CH, Ar), 112.8 (C*ipso*), 112.2 (CH, Ar), 107.3 (C*ipso*), 65.6 (CH_2O), 63.5 (CH_2O), 21.9 (CH_2). HRMS (ESI): m/z calcd for $C_{11}H_{11}{}^{79}BrNO$ $(M+H)^+$ 252.0024, found 252.0024. FT-IR (KBr) ν_{max} 3304, 2964, 1716, 1453, 1023, 794 cm^{-1}.

4.3.22 *6-Bromo-3-hexyl-1,3,4,9-tetrahydropyrano[3,4-b]indole* (**4i**). (7.3 mg, 18%), brown oil; R_f (EtOAc/PE 20:80) 0.49. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.75 (brs, 1H), 7.60 (s, 1H, CH), 7.23 (d, 1H, *J* = 8.6 Hz, CH), 7.18 (d, 1H, *J* = 8.6 Hz, CH), 4.84 (s, 2H, CH_2O), 3.73-3.64 (m, 1H, CHO), 2.73 (dd, 1H, *J* = 2.0, 15.1 Hz, CH_2), 2.57 (dd, 1H, *J* = 10.1, 15.1 Hz, CH_2), 1.76-1.26 (m, 10H, $5CH_2$), 0.89 (t, 3H, *J* = 6.8 Hz, CH_3). ^{13}C NMR (100.62 MHz, $CDCl_3$, 25 °C) δ = 134.8 (C*ipso*), 133.1 (C*ipso*), 128.9 (C*ipso*), 124.3 (CH, Ar), 120.6 (CH, Ar), 112.7 (C*ipso*), 112.2 (CH, Ar), 108.0 (C*ipso*), 75.8 (CHO), 63.4 (CH_2O), 35.8 (CH_2), 31.8 (CH_2), 29.3 (CH_2), 27.5 (CH_2), 25.7 (CH_2), 22.6 (CH_2), 14.1 (CH_3). HRMS (ESI): m/z calcd for $C_{17}H_{23}{}^{79}BrNO$ $(M+H)^+$ 336.0963, found 336.0932. FT-IR (KBr): ν_{max} 3402, 2925, 2856, 1465, 1306, 1051, 792 cm^{-1}.

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References and notes

1. a) Lombardo, V. M.; Thomas, C. D.; Scheidt, K. A. *Angew. Chem. Int. Ed.* **2013**, *52*, 12910-12914. b) Bandini, M. Eichholzer, A. Tragni, M.; Umani-Ronchi, A. *Angew. Chem. Int. Ed*. **2008**, *120*, 3282-3285; *Angew. Chem. Int. Ed.* **2008**, *47*, 3238-3241. c) Crich, D.; Banerjee A. *Acc. Chem. Res.* **2007**, *40*, 151-161. d) Somei, M.; Yamada, F. *Nat. Prod. Rep.* **2005**, *22*, 73-103. e) Leboho, T. C.; Michael, J. P.; van Otterlo, W. A. L.; van Vuuren, S. F.; de Koning, C. B. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4948-4951.
2. a) Ascic, E.; Ohm, R. G.; Petersen, R.; Hansen, M. R.; Hansen, C. L.; Madsen, D.; Tanner, D.; Nielsen, T. E. *Chem. Eur. J*. **2014**, *20*, 3297-3300. b) Medeiros, M. R.; Schaus, S. E.; Porco Jr., J. A. *Org. Lett*. **2011**, *13*, 4012-4015. c) Zhang, X.; Li, X.; Lanter, J. C.; Sui, Z. *Org. Lett*. **2005**, *7*, 2043-2046. d) Agnusdei, M.; Bandini, M.; Melloni, A.; Umani-Ronchi, A. *J. Org. Chem.* **2003**, *68*, 7126-7129. e) Gopalsamy, A.; Lim, K.; Ciszewski, G.; Park, K.; Ellingboe, J. W.; Bloom, J.; Insaf, S.; Upeslacis, J.; Mansour, T. S.; Krishnamurthy, G.; Damarla, M.; Pyatski, Y.; Ho, D.; Howe, A. Y. M.; Orlowski, M.; Feld, B.; O' Connell, J. *J. Med. Chem.* **2004**, *47*, 6603-6608.
3. a) Demerson, C. A.; Santroch, G.; Humber, L. G. *J. Med. Chem.* **1975**, *18*, 577-580. b) Farina, C.; Gagliardi, S.; Misiano, P.; Celestini, P.; Zunino, F. PCT Int. Appl. (2005) WO 2005105213 A2. 2005110.
4. a) Chiarucci, M.; Mocci, R.; Syntrivanis, L.-D.; Cera, G.; Mazzanti, A.; Bandini, M. *Angew. Chem. Int. Ed*. **2013**, *52*, 10850-10853. b) Gharpure, S. J.; Sathiyanarayanan, A. M. *Chem. Commun*. **2011**, *47*, 3625-3627. c) An, J.; Chang, N.-J.; Song, L.-D.; Jin, Y.-Q.; Ma, Y.; Chen, J.-R.; Xiao, W.-J. *Chem. Commun.* **2011**, *47*, 1869-1871. d) Chiarucci, M.; Matteucci, E.; Cera, G.; Fabrizi, G.; Bandini M. *Chem. Asian J*. **2013**, *8*, 1776-1779.
5. a) Bagnoli, L.; Casini, S.; Marini, F.; Santi, C. Testaferri, L. *Tetrahedron*, **2013**, *69*, *2*, 481-486. b) Bagnoli, L.; Scarponi, C.; Rossi, M. G.; Testaferri, L.; Tiecco, M. *Chem. Eur. J.* **2011**, *17*, 993-999. c) Bagnoli, L.; Scarponi, C.; Testaferri, L.; Tiecco, M. *Tetrahedron: Asymmetry* **2009**, *20*, 1506-1514. d) Sternativo, S.; Marini, F.; Del Verme, F.; Calandriello, A.; Testaferri, L; Tiecco, M. *Tetrahedron* **2010**, *66*, 6851-6857. e) Sternativo, S.; Calandriello A.; Costantino, F.; Testaferri, L.; Tiecco, M.; Marini F. *Angew. Chem. Int. Ed.* **2011**, *50*, 9382-9385. f) Sternativo, S.; Battistelli, B.; Bagnoli, L.; Santi, C.; Testaferri, L.; Marini, F. *Tetrahedron Lett.* **2013**, *54*, 6755-6757. g) Palomba, M.; Rossi, L.; Sancineto, L.; Tramontano, E.; Corona, A., Bagnoli, L.; Santi, C.; Pannecouque, C.; Tabarrini, O.; Marini, F. *Org. Biomol. Chem.* **2016**, *14*, 2015-2024.
6. a) Jana, N.; Nguyen, Q.; Driver, T. G. *J. Org. Chem.* **2014**, *79*, 2781-2791. b) Cheng, M. J; Wu, M. D.; Chen, I –S.; Yuan, G.-F. *Chem. Pharm. Bull*. **2008**, *56*, 394-397.
7. The oxazino[4,3-*a*]indoles **3i** and **3i´** present a characteristic signal in the ^{1}H NMR spectra at ~ 6.1 ppm (H_{10} proton), in analogy with other oxazino[4,3-*a*]indoles **3a-f**.[4c] The pyrano[3,4-*b*]indoles **4i** are identified by the signal of NH in the ^{1}HNMR (brs, 7.75 ppm) and IR spectra (brs, 3402 cm^{-1}).
8. The COSY and NOESY experiment confirmed the structure indicated for compound **3i** with the alkyl chain in the three position (see supporting information). Moreover, the proton coupling constants indicate that the alkyl chain (R^2 = C_6H_{13}) occupies an equatorial position.
9. Matlock, V. J.; Svejstrup, T. D.; Songara, P.; Overington, S.; McGarrigle, E. M., Aggarwal, V. K. *Org. Lett.* **2015**, *17*, 5044-5047.
10. a) Xiong, X.; Ovens, C.; Pilling, A. W.; Ward, J. W.; Dixon, D. J. *Org. Lett*. **2008**, *10*, 565-567. b) Nising, C. F.; Brase, S. *Chem. Soc. Rev.* **2008**, *37*, 1218-1228.
11. a) Santaniello, E.; Farachi, C.; Ponti, F. *Synthesis*, **1979**, 617-618. b) Yim, E. S.; Park, M. K.; Han, B. H. *Ultrasonic Sonochemistry*, **1997**, *4*, 95-98.
12. Buyck, T.; Wang, Q.; Zhu, J. *J. Am. Chem. Soc*. **2014**, *136*, 11524-11528.
13. Narayana, B.; Ashalatha, B. V.; Raj, K. K. V. *J. Chem. Res.* **2006**, 309-311.
14. Bingul, M.; Kumar, N.; Black, D. StC. *Tetrahedron* **2016**, *72*, 234-239.