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Nature-inspired indolyl-2-azabicyclo[2.2.2]oct-7-ene derivatives as promising agents for the attenuation of withdrawal symptoms: synthesis of 20-desethyl-20-hydroxymethyl-11-demethoxyibogaine

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Microwave assisted Diels–Alder cycloaddition of 5-Br-*N*-benzylpyridinone (**2**) with methyl acrylate is described to gain an easy access to 7-bromo-2-benzyl-3-oxo-2-aza-5 or 6-carbomethoxy bicyclo[2.2.2]oct-7-enes (**3**)–(**6**). The preparation of the ibogaine analogue 20-desethyl-(20-*endo*)-hydroxymethyl-11-demethoxyibogaine (**17**) is described by stereoselective hydrogenation of the C(7)–C(8) double bond. Biological evaluation showed an interesting *in vitro* binding profile toward dopamine transporter, serotonin transporter and opioid receptor systems accompanied by an antiwithdrawal effect in mice for hydroxymethyl 7-indolyl-2-aza-bicyclo[2.2.2]oct-2-ene (**14**). The simplification of the ibogaine structure appears as a promising approach toward the design of compounds that could reduce the withdrawal symptoms.

Keywords: Ibogaine; Ibogaine analogs; Microwave-assisted reactions; Antiwithdrawal effect

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1. Introduction

The iboga alkaloids [1] not only present a challenge to synthetic chemists but are also the starting point for intriguing pharmacological adventures. In particular this was the case of ibogaine (**1**, figure 1), a compound used by African natives for its hunger-combating effects, as well as to generate a euphoric state in ritual ceremonies. Anecdotal and clinical reports suggest that a single dose of ibogaine given to subjects dependent on opioids or cocaine has the capacity to abolish or minimize withdrawal symptoms, as well as to decrease or revoke drug craving for extended periods [2]. Since the pharmacological profile of ibogaine is not related to a specific receptor, the synthesis of structures resembling the indoloazepine–isoquinuclidine ring system is desirable.

We have recently shown that a quality collection of 7-heteroaryl-2-azabicyclo [2.2.2]oct-7-ene derivatives [3] can be obtained in a two-step procedure by cycloaddition of 5-Br-*N*-benzylpyridinone (**2**) with methyl acrylate and subsequent cross-coupling with an activated heteroaromatic derivative. The radioligand binding assays demonstrated the possibility to approach the receptorial affinity of ibogaine even with some of these structurally simplified analogues containing the substituted isoquinuclidyl nucleus.

In continuing our efforts to synthesize analogues of iboga alkaloids, we report here on the synthesis of 20-desethyl-(20-*endo*)-hydroxymethyl-11-demethoxybogaine (**17**) whose crucial step is the stereoselective hydrogenation of the C(7)–C(8) double bond of the 2-benzyl-7-[1-indol-2-yl]-(6-*endo*)-hydroxymethyl-2-aza-bicyclo[2.2.2] oct-7-ene (**11**) followed by bridging of the N(2) to position 3 of the indole moiety to form the azepine ring. Biological tests revealed a binding profile for compound **14**, very similar to that of ibogaine, and an interesting *in vivo* activity.

2. Results and discussion

The first step of our work was to develop an improved procedure for the preparation of the 7-bromo-2-benzyl-3-oxo-2-aza-5 or 6-carbomethoxy bicyclo [2.2.2]oct-7-enes (**3**)–(**6**) by cycloaddition of 5-Br-*N*-benzylpyridinone (**2**) (scheme 1) with methyl acrylate. This cycloaddition has been previously [3] performed by heating a solution of **2** and methyl acrylate (in 1 : 22 ratio) in a closed vessel at 120°C for 10 days, resulting in the formation of a mixture of **3**–**6** with an 84% yield. This procedure was not satisfactory due to the long reaction time and the troubles with purification caused by the polymerization of methyl acrylate. To overcome these difficulties we thought that the application of microwave (MW) assisted organic chemistry could be of help [4]. We started to study the MW assisted reaction by irradiation at 150°C of the same mixture as in the thermal procedure, but after 6 h (table 1) only a low conversion to

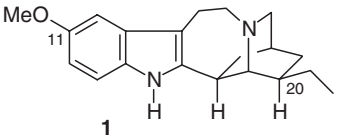

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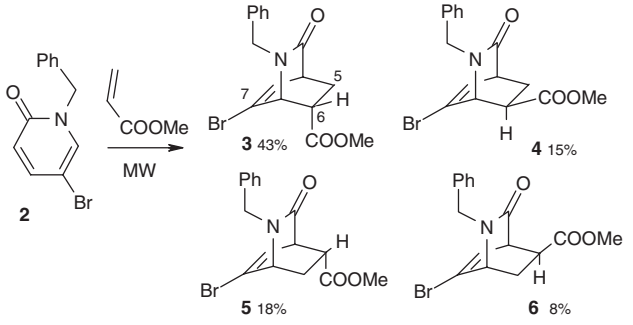
Figure 1. Ibogaine.



Scheme 1. Composition of the mixture obtained by MW assisted Diels–Alder reaction.

Table 1. MW assisted Diels–Alder reaction (150°C) of **2** and methyl acrylate.

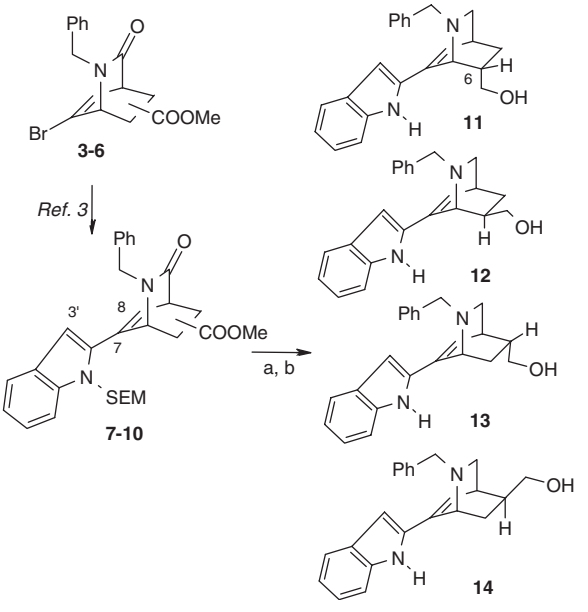
	Conversion (%)		
Reaction medium	90 min	6 h	14 h
CH_2Cl_2	–	11	–
$BMIMPF_6$[a]	10.5	45	–
Montmorr.	20	polym	–
$MgSO_4$	20	polym	–
SiO_2	20.5	21	–
Al_2O_3 bas	18.9	17	–
Al_2O_3 aci.	20	polym	–
Al_2O_3 ne	10	45	60
No MW 120°C sealed tube [3]			
CH_2Cl_2		84 (after 10 days)	

[a] 10% in toluene.

3–**6** (11%) was obtained. This result could not be improved by prolonging the irradiation or changing the substrate/acrylate ratio, or the solvent. Only in the case of the use of toluene containing 10% of the ionic liquid [5] (1-butyl-3-methylimidazolium hexafluorophosphate, $BMIMPF_6$), a more acceptable transformation (45%) was detected after 6 h [6].

A substantial improvement in the conversion was obtained by carrying out the reaction under solvent-free conditions, by impregnating reagents on solid mineral supports in "dry media" [7]. Using montmorrilonite and $MgSO_4$ as solid supports methyl acrylate polymerization was the predominant result. Also unsatisfactory was the use of SiO_2. The solid support of choice was neutral Al_2O_3, which gave a 45% total yield after 6 h that could be increased to 60% by prolonging the irradiation to 14 h [8]. No appreciable polymerization of methyl acrylate was observed, thus allowing an easy manipulation of the products' mixture. No differences in the regio- and diastereoselectivity of the reaction products was observed as compared with conventional heating (scheme 1). Compounds **3**–**6** could be obtained as pure products only in small amounts, whereas in preparative scale they were obtained as a mixture of **3**, **6** and **5**, **4**. The four isomers were easily distinguishable by NMR spectroscopy [3].

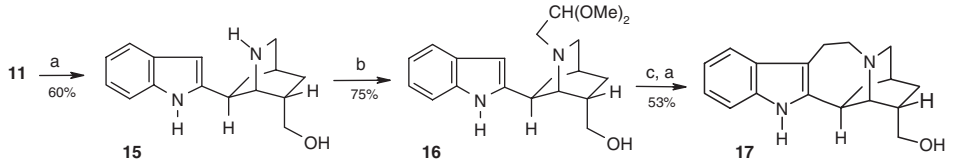
Having produced the carbomethoxy azabicyclo octenes **3**–**6**, the next step was the construction of the pentacyclic skeleton of iboga alkaloids. This could be achieved



Scheme 2. (a) $LiAlH_4$, (b) TBAF, $NH_2(CH_2)_2NH_2$.

by coupling of **3**–**6** with *in situ* generated 2-indolylzinc chloride, as previously described by us [3], followed by stereoselective hydrogenation of the double bond between positions 7 and 8 and incorporation of the azepine ring. Although considerable efforts have been devoted to the total synthesis of iboga alkaloids over the past decades [9], the stereocontrolled construction of this characteristic skeleton still represents a significant and difficult challenge.

We had first studied the hydrogenation reaction of compounds **7**–**10** (scheme 2), but in all cases we obtained a 1 : 1 mixture of the compounds derived from the attack over both the diastereotopic faces [10] as judged by NMR analysis. We then decided to separately convert amides **7**–**10** into the aminoalcohols **11**–**14** [11] by $LiAlH_4$ reduction and cleavage of the SEM group (TBAF, $NH_2(CH_2)_2NH_2$, DMF 90°C) [12] (scheme 2). So we had the possibility to study the influence of the hydroxymethyl appendage to guide stereoselective hydrogenation of C(7)–C(8) double bond from the *endo* face. In principle this could be maximized by exploiting the favorable orientation of the hydroxymethyl group of the *endo* adducts to enforce addition of hydrogen from its own face of the molecule [13]. This was in fact the case. Catalytic hydrogenation of the *exo* adducts **12** and **14** proved to be completely non-stereoselective, affording a mixture of C(7) epimers that was difficult to obtain as pure compounds. Hydrogenation of **13** gave a 2 : 1 preferential addition on the *endo* face. The composition of the mixture was determined on the base of the integration of the signals due to the protons at C(17) position that appear as multiplets at δ 2.56–2.38 (H-16 *endo*) and at 2.37–2.26 (H-16 *eso*). The hydrogenation of **11**, on the contrary, proved to be completely stereoselective probably due to the close proximity of the hydroxymethyl group to the newly created stereocentre. The concomitant removal of the benzyl group afforded a 75% yield of compound **15** [14] (scheme 3), which was nicely characterized by the usual spectroscopic methods.



Scheme 3. (a) H_2, Pd/C, (b) $BrCH_2CH(OMe)_2$, K_2CO_3, (c) $BF_3 \cdot Et_2O$.

Table 2. Relative affinities (IC_{50}, μM) of ibogaine (**1**) and **14**.

Target	DAT (WIN35,428)	SERT (RTI-55)	K (U69593)	NMDA (MK801)
Ibogaine (**1**)	4.11	0.59	25	5.2
14	4.4	0.5	19.5	31.5
Reference	Mazindol	Citalopram	Naloxone	MK801
Drug	1.13 nM	0.9 nM	6.1 nM	4.1 nM

The introduction of the two carbon chains, that are necessary for the completion of the synthesis, was realized by reaction of compound **15** with the dimethylacetal of bromoacetaldehyde in MeOH in the presence of K_2CO_3 to give derivative **16** that presents all the carbons necessary to elaborate the pentacyclic skeleton of iboga alkaloids. The compound **16** was directly treated with $BF_3 \cdot Et_2O$ to induce cyclization of the generated aldehyde at C(3) of the indole nucleus with the formation of a styrenic double bond. The subsequent catalytic hydrogenation proved to be sluggish but the 20-desethyl-20-hydroxymethyl-11-demethoxyibogaine (**17**) [15] could be isolated and fully characterized.

3. Biological evaluation

The *in vitro* binding profile [16] of compounds **11**–**14**, **17** gave reproducible results only for compound **14** (table 2). Ibogaine **1** and compound **14** showed very similar binding affinity for dopamine transporter (DAT), serotonin transporter (SERT) and K (opioid) receptor systems, although differing with regard to NMDA.

We then elected to study the effect of compound **14** in morphine withdrawal in mice [17]. Results (figure 2) indicate that the compound significantly (*T*-Test, $T_{(2.396,16)}$, $p < 0.05$) reduced the signs of morphine withdrawal (number of jumps) [18]. No signs of toxicity were apparent; in particular it is noteworthy that there were no tremors as observed with ibogaine [19].

4. Conclusions

We have described the use of a MW assisted Diels–Alder reaction on neutral Al_2O_3 to optimize the preparation of the diastereoisomeric mixture of 7-bromo-2-benzyl-(5 or 6)-carbomethoxy-3-oxo-2-azabicyclo[2.2.2]oct-7-enes. The most abundant adduct **3** was converted into the ibogaine analogue **17** by cross-coupling reaction with 2-indolylzinc chloride followed by reduction of the methoxycarbonyl to a hydroxymethyl group, which was crucial to address the correct stereoselective catalytic hydrogenation of the

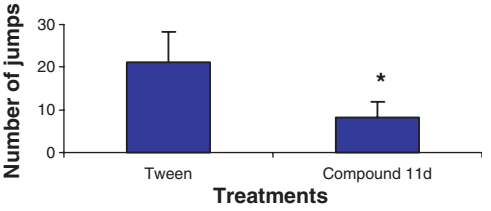


Figure 2. Effects of compound **14** on naloxone-induced withdrawal in morphine-dependent mice. Data are expressed as mean ± SEM ($n = 9$). Compound **14** = 80 mg kg^{-1}. * $p < 0.05$; independent *T*-test.

C(7)–C(8) double bond. The construction of the azepine ring gave the final compound **17**. The *in vitro* evaluation demonstrated that only compound **14**, which is unfortunately derived from the less abundant bicyclo adduct **6**, possesses an antiwithdrawal effect, a reduced toxicity and in particular a reduced tremorgenic effect, in comparison with ibogaine. The position and orientation of the hydroxymethyl group seems to be crucial for the beneficial effect on the binding affinity [20]. As a final remark, these results highlight once again that nature continues to be a source of inspiration in the design of simplified new pharmacologically active compounds. This kind of approach permits us to overcome the troubles connected with the use of combinatorial chemistry in drug discovery.

Acknowledgement

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[8] Microwave-assisted reactions were carried out using a CEM Discover microwave apparatus, equipped with an internal probe that monitors reaction temperature and pressure, and maintains the desired temperature. 5-Bromo-*N*-benzylpyridin-2-one (75 mg, 0.29 mmol), methyl acrylate (1.3 mL, 58.5 mmol) were dispersed on Al_2O_3, (4 g). The initial power supplied was 150 W; once the temperature reached 150°C, the instrument adjusted the power to maintain a constant temperature. After completion of the reaction, a mixture of CH_2Cl_2/MeOH 1 : 1 was added to the reaction mixture, inorganic support was filtered and the final reaction mixture was recovered after evaporation. For purification see [3].

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[11] **11**: ^{1}H-NMR ($CDCl_3$) δ 8.13 (1H, bs), 7.54 (1H, d, $J=8$ Hz), 7.35–7.23 (6H, m), 7.18 (1H, t, $J=8$ Hz), 7.08 (1H, t, $J=8$ Hz), 6.71 (1H, d, $J=7$ Hz), 6.38 (1H, s), 3.83 (1H, m), 3.71 (1H, A portion of AB system), 3.40 (1H, B portion of AB system), 3.38 (1H, dd, $J=10$, 6 Hz), 3.13 (1H, dd, $J=10$, 2 Hz), 3.11 (1H, t, $J=10$ Hz), 2.72–2.62 (1H, m), 2.61–2.51 (1H, m), 2.06 (1H, ddd, $J=10$, 2, <2 Hz), 1.81 (1H, ddd, $J=12$, 10, 3 Hz), 0.75 (1H, dddd, $J=12$, 5, 2, <2 Hz); ^{13}C-NMR ($CDCl_3$) δ 139.4, 138.7, 137.4, 133.1, 129.3, 129.0, 128.2 (2C), 126.9 (2C), 125.4, 122.3, 120.6, 120.0, 110.8, 99.1, 65.3, 61.9, 56.0, 54.6, 41.1, 31.1, 26.8; Anal. Calcd $C_{23}H_{24}N_2O$: C 80.19, H 7.03, N 8.13. Found: C 80.17, H 7.15, N 8.21; **12** ^{1}H-NMR ($CDCl_3$) (selected signals) δ 8.30 (1H, bs), 7.55–7.11 (9H, m), 3.91 (1H, bs), 6.71 (1H, d, $J=7$ Hz); Anal. Calcd $C_{23}H_{24}N_2O$: C 80.19, H 7.03, N 8.13. Found: C 80.22, H 7.05, N 8.18; **13**: ^{1}H-NMR ($CDCl_3$) (selected signals) δ 8.40 (1H, bs), 7.53 (1H, d, $J=8$ Hz), 7.35–7.23 (6H, m), 7.18 (1H, t, $J=8$ Hz), 7.08 (1H, t, $J=8$ Hz), 6.71 (1H, d, $J=7$ Hz), 6.38 (1H, s), 3.93 (1H, m); Anal. Calcd $C_{23}H_{24}N_2O$: C 80.19, H 7.03, N 8.13. Found: C 80.21, H 7.06, N 8.16; **14**: ^{1}H-NMR ($CDCl_3$) δ 8.12 (1H, bs), 7.54 (1H, d, $J=8$ Hz), 7.35–7.24 (6H, m), 7.18 (1H, t, $J=8$ Hz), 7.07 (1H, t, $J=8$ Hz), 6.51 (1H, d, $J=7$ Hz), 6.38 (1H, s), 3.83 (1H, m), 3.80 (1H, dd, $J=10$, 2 Hz), 3.72 (1H, t, $J=10$ Hz), 3.61 (1H, A portion of AB system), 3.38 (1H, B portion of AB system), 3.36 (1H, dd, $J=10$, 6 Hz), 2.76–2.70 (1H, m), 2.12–2.04 (1H, m), 2.06 (1H, m), 1.81 (1H, m), 0.83 (1H, m); ^{13}C-NMR ($CDCl_3$) δ 141.1, 138.2, 137.9, 135.6, 129.5, 129.3, 128.8 (2C), 127.4 (2C), 126.7, 122.6, 120.9, 120.3, 111.5, 99.9, 65.3, 62.7, 55.3, 50.9, 36.7, 32.9, 32.6. Anal. Calcd $C_{23}H_{24}N_2O$: C 80.19, H 7.03, N 8.13. Found: C 80.21, H 7.06, N 8.16.
[12] When the deprotection reaction was performed using **3**–**6** as substrates, the obtained product was indolylpyridin-2-one resulting from retro Diels–Alder reaction of the azabicyclo[2.2.2]octane ring system.
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[14] **15**: Amorphous solid, ^{1}H-NMR ($CDCl_3$) δ 8.35 (1H, bs), 7.52 (1H, d, $J=7$ Hz), 7.29 (1H, d, $J=7$ Hz), 7.15–7.00 (2H, m), 6.29 (1H, s), 3.51 (1H, m), 3.49 (1H, bs), 3.15 (1H, dd, $J=12$, 7 Hz), 2.90 (1H, t, $J=12$ Hz), 2.89–1.50 (10H, m); ^{13}C-NMR ($CDCl_3$) δ 141.3, 135.4, 128.3, 121.2, 119.8, 119.6, 110.9, 98.9, 64.1, 53.5, 51.2, 37.1, 33.0, 29.2, 28.2, 26.2; HRMS: 256.1576 [($C_{16}H_{20}N_2O$); Calcd 256.1570].
[15] **17**: Amorphous solid, ^{1}H-NMR ($CDCl_3$) δ 7.67 (1H, bs), 7.48 (1H, d, $J=7$ Hz), 7.20 (1H, d, $J=7$ Hz), 7.05–6.98 (2H, m), 3.42–1.10 (17H, m); ^{13}C-NMR ($CDCl_3$) δ 141.6, 135.2, 128.8, 121.4, 119.6, 117.8, 110.2, 108.8 64.1, 55.2, 53.2, 51.1, 39.2, 37.1, 29.2, 28.2, 26.2, 20.6; HRMS: 282.1721 [($C_{18}H_{22}N_2O$); Calcd 282.1732].
[16] Although the molecular mechanisms underlying the antiaddictive activity of **1** are not known, the compound displays moderate affinity for dopamine and serotonin transporters, K opioid receptor and the MK-801 site on the NMDA receptor. Ligand binding assays. Radioligands were purchased from NEN/DuPont (Boston, MA) or Amersham Corp. (Arlington Heights, IL). All binding assays were conducted as described previously (see [2]). The ability of modified ibogaine fragments to inhibit binding to neuroreceptors or transporters was first assessed at doses of 100 nM and 10 μM. Positive controls were routinely assayed in parallel using specific reference drugs with known affinities. Assay tubes were incubated under the specified conditions and filtered through Whatman 934AH filters on Millipore manifolds. Nonspecific binding was defined as the cpm bound in the presence of a saturating concentration of an established competing ligand. To accurately determine potency values, full competition curves were obtained at relevant binding sites using 10–15 concentrations of ibogaine (**1**). Ligand competition data were analysed using the DRUG program of EBDA/LIGAND (Biosoft, Elsevier).
[17] *In vivo* assay. Methods: Animals: Male albino adult (25–35 g) mice (CF-1 strain), bred at the Fundação Estadual de Produção e Pesquisa em Saúde (Porto Alegre, RS, Brazil), were used in all the experiments. Mice were kept on a 12 light/dark cycle, at a room temperature of 22°C, with free access to food and water in our own facilities for at least 2 weeks before the experiments. Drugs: Morphine sulfate and Naloxone were purchased from Sigma Chemicals (St. Louis, MO, USA), and Tween 80 from Dellaware (USA). Compound **14** was dissolved in a drop of Tween and the adequate volume obtained with water; the final concentration of Tween in the solution did not exceed 10%. Naloxone-induced jumping in morphine-dependent mice. The method first described in 1995 (see [18]) was adapted as previously described by us (see [19]). Morphine sulfate was injected intraperitonially (i.p.) three times daily (09:30, 13:30 and 17:30 h) with the following dosage schedule: the first three administrations were of 50, 50 and 75 mg kg^{-1} (a higher dose is used for the last daily injection in order to minimize potential overnight withdrawal); all administrations were increased daily by 25 mg kg^{-1}. Morphine administration was carried out over three consecutive days, with an additional dose (50 mg kg^{-1}) administered on the morning (09:30 h) of the test (day 4). Two hours after the last dose of morphine, mice were injected (i.p.) with: saline, Tween or compound **14** (80 mg kg^{-1}). Forty-five minutes after these treatments, mice were given naloxone (5 mg kg^{-1}, i.p.) and immediately placed in transparent acrylic cylinders (19 cm diameter,

42 cm high). The number of jumps (at least 1 cm above the floor) during the subsequent 15 min was recorded. A control group (run in parallel with experimental groups) consisted of the same schedule of drug and treatments administration, except that all injections were of saline (NaCl 0.9%). None of the mice in the control group jumped at any time, and there was no difference between saline and Tween treated groups (data not shown). Statistical analysis: The results were analysed with independent *T*-test.

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