Solution-Phase Parallel Synthesis of *N*,6-Disubstituted Isoquinuclidines as Ibogaine Analogs

M.S. Levi, M.O.F. Khan and R.F. Borne*

Department of Medicinal Chemistry and Laboratory for Applied Drug Design and Synthesis, School of Pharmacy, University of Mississippi, University, MS 38677, USA

Received April 13, 2004: Accepted August 27, 2004

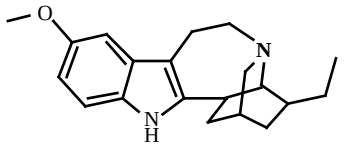
Abstract: The naturally-occurring alkaloid ibogaine, found in the West African shrub *Tabernanthe iboga*, possesses the ability to diminish self-administration of substances of abuse, such as cocaine, heroin and alcohol. This was the lead structure for the design of a 75-member library of *N*,6-disubstituted isoquinuclidines. A solution-phase method for their synthesis is described.

Keywords: Addiction, ibogaine, isoquinuclidine, parallel synthesis, anti-addictive.

In a previous study [1], we developed solution-phase small-molecule libraries containing structural analogs of ibogaine (**1,** NIH 10567, Endabuse™), a natural product isolated from the African shrub *Tabernanthe iboga.* Ibogaine has been widely studied as a treatment of stimulant dependence [2]. Reviews of the history, chemistry, mechanisms of action, pharmacokinetic properties, metabolism, neurochemical and anti-addictive properties have appeared [2, 3, 4]. Ibogaine possesses the ability to diminish self-administration of cocaine [5] as well as morphine [6] and alcohol [7]. These studies suggest that it may possess therapeutically useful anti-addiction and anti-craving properties, however its use has been restricted because of reports of neurotoxicity [8]. We have attempted to separate the beneficial anti-addictive properties from the neurotoxic effects by preparing various structural analogs of the parent alkaloid.

To date, few totally synthetic analogs of ibogaine have been synthesized and pharmacologically evaluated. Repke *et al*. [9] reported the synthesis and evaluation of indolotropane analogs of ibogaine. Among these indolotropanes, the most potent inhibitor of MK-801 binding was 15-fold less potent than ibogaine. Efange *et al*. [10] synthesized a group of phenyl-substituted analogs of 1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole, a major ibogaine fragment and while five analogs showed 8-10-fold higher affinity for the dopamine transporter (DAT) than ibogaine and noribogaine, all displayed poor affinity for the dopamine D1 and D2, mu and kappa opioid receptors and the NMDA receptor-coupled cation channel. During our studies the synthesis and preliminary pharmacological evaluation of several heteroaryl isoquinuclidines was reported [11]. The absence of the azepine ring did not drastically limit considerable affinity for the DAT, serotonin transporter (SERT), kappa and NMDA receptor systems.

The library of *N*,6-disubstituted isoquinuclidines reported here represents ibogaine analogs in which the ethylene bridge between the isoquinuclidine nitrogen and the 3-position of the indole has been eliminated while maintaining the *N*,6-disubstitution pattern present in ibogaine.



1. (Ibogaine)

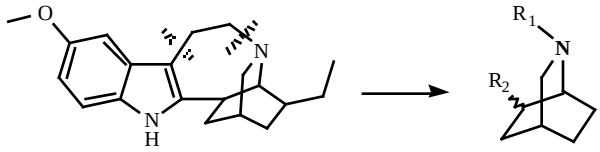


Fig. (1).

In our study, R_1 (Fig. 2) and R_2 (Fig. 3) represents arylalkyl, aryl and alkyl substituents. Additionally, the 7-ethyl group was replaced with H to simplify stereochemical requirements.

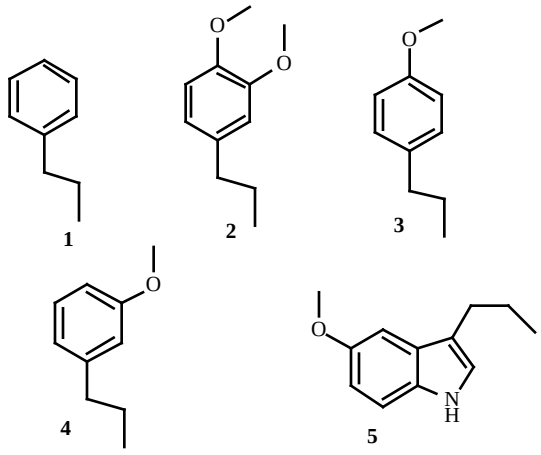


Fig. (2). R1 substituents {1-5}.

The phenyl, anisole and veratrole rings should indicate the necessity of the methoxy group of ibogaine, while the methyl group will provide insight as to the size and nature of the substituent. By combining the different *N*- and 6-

*Address correspondence to this author at the Department of Medicinal Chemistry and Laboratory for Applied Drug Design and Synthesis, School of Pharmacy, University of Mississippi, University, MS 38677, USA; Tel: +1-662-915-5881; Fax: +1-662-915-5638; E-mail: rborne@olemiss.edu

1570-1808/05 $50.00+.00

substituents, we hoped to gain insight into the structural requirements of the various receptor systems that may be targets in the treatment of addiction.

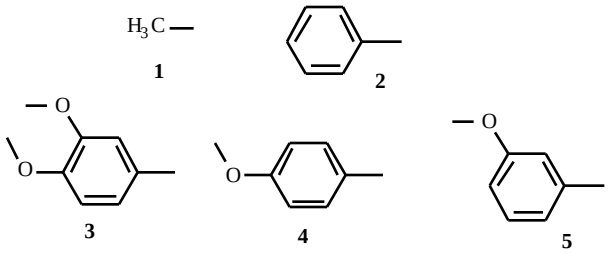
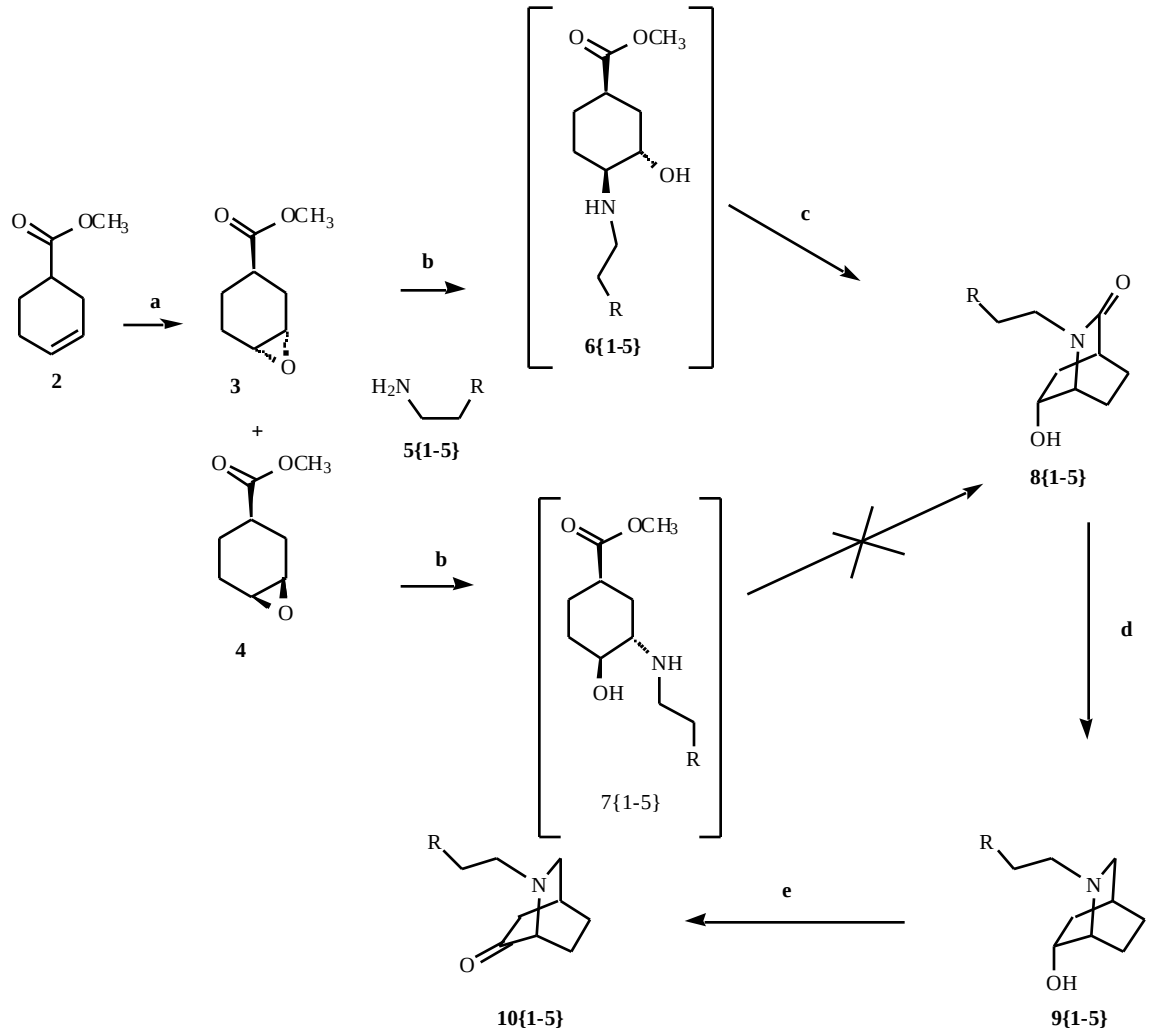


Fig. (3). R2 substituents {1-5}.

FORMATION OF THE *N*,6-DISUBSTITUTED ISOQUINUCLIDINES

The approach leading to the *N*,6-disubstituted isoquinuclidines is illustrated in Scheme 1. The key starting materials were the *N*-substituted-6-isoquinuclidones **10**{1-5}.

Synthesis of the *N*,6-disubstituted isoquinuclidines began with the epoxidation of commercially available methyl 3-cyclohexene-1-carboxylate (**2**) using 3-chloroperoxybenzoic acid (*m*-CPBA) in ethyl ether to give a mixture of epoxides **3** and **4**. Henbest [12] determined that a *trans* relationship of the epoxide to the carbomethoxy group is produced and results from the peracid's approach from the least hindered side of the olefin. Huffman [13] later performed the reaction in chloroform rather than ethyl ether and obtained a mixture of *cis*- and *trans*-epoxides with the latter predominating, obviously indicating that solvent has a direct effect on stereochemistry of the resulting epoxide. Since the required epoxide is *trans* to the ester, a normal *trans*-diaxial opening by the amine produces the 4-amino substituent *cis* to the carbomethoxy group. Also, Law *et al*. [14] found that Henbest's epoxidation using ethyl ether, if carried out at 10°C instead of 0°C, will produce a mixture of epoxides. Thus, the *cis* epoxide, upon *trans*-diaxial opening, produces the 3-amino substituent *trans* to the carbomethoxy group. Separation of the two isomers was not attempted because subsequent ring opening with an amine and thermal cyclization results in molecules of widely differing



(a) *m*-CPBA, ether; (b) RNH_2, EtOH, reflux; (c) Δ, N_2; (d) Red-Al®, C_6H_6, reflux; (e) KO*t*Bu, $C_6H_5C(O)C_6H_5$, C_6H_6, 40°C.

Scheme 1.

physiochemical properties (**6** and **7**) greatly easing the isolation of the desired lactams **8**{1-5}.

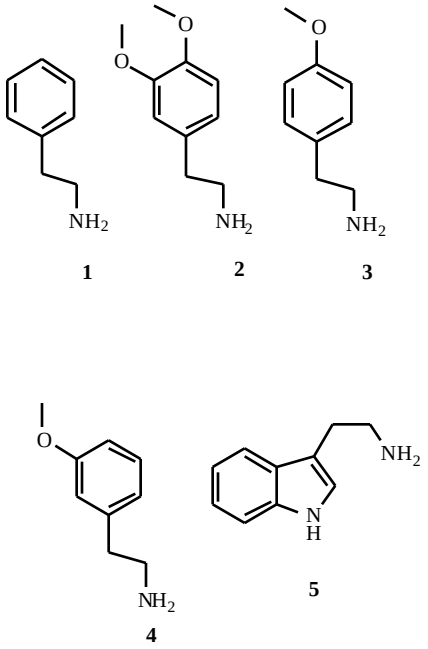


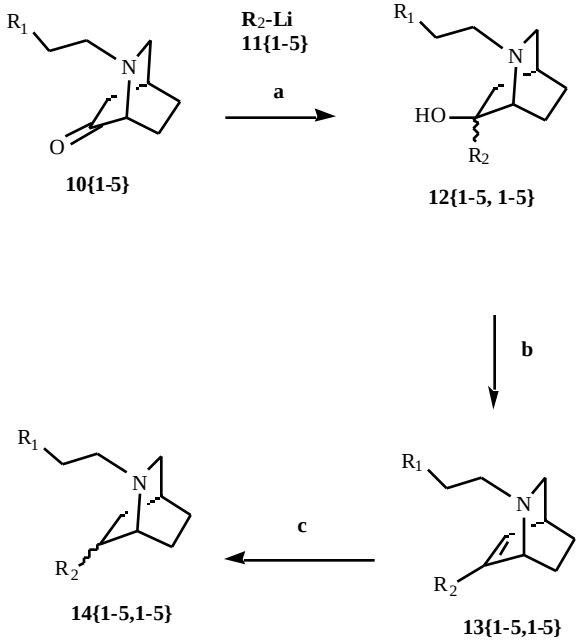
Fig. (4). First Diversity Reagent 5 {1-5}.

Upon opening the epoxide with various arylethylamines **5**{1-5}, the first element of diversity is introduced into the molecules (Fig. (**4**)). The required lactams **8**{1-5} were formed by heating **6**{1-5} at 160°C neat under an inert atmosphere [15] Carrying out the entire cyclization with air present resulted in polymerization and, thus, low yields. Purification was achieved by refluxing the crude reaction mixture in 10% aq NaOH solution with an equal amount of methanol, hydrolyzing any ester to its water-soluble acid. This cyclization yields the isoquinuclidine functionalized exclusively at the 6-position. The lactams were reduced cleanly using Red-Al® in benzene at 80°C to afford the tertiary amines **9**{1-5} in good yields. Oxidation of the hydroxyl groups to ketones **10**{1-5} was achieved *via* a modified Oppenauer procedure [16] using benzophenone and potassium *t*-butoxide and was accomplished in 90 minutes and in fair yields.

Once the ketones were obtained, they were further functionalized at the 6-position using a modified Grignard procedure [14] where lithium replaced the traditional magnesium halide to introduce the second element of diversity (Fig. (**5**)). The bromoanisoles and bromoveratrole in ether were added to a solution of *n*-butyllithium at –78ºC under argon and allowed to stir for 2 hours while the temperature was slowly warmed to –50ºC. Solutions of methyl and phenyl lithium were commercially obtained and added to their reaction vessels at this point. Upon addition of the ketone **10**{1-5} to each of the vessels, the reactor was allowed to warm to room temperature and stirring continued all night. Workup was by acid/base extraction with subsequent HPLC purification. Dehydration of the Grignard products **12**{1-5,1-5} was accomplished using benzene with a catalytic amount of *p*-tosic acid by refluxing using a Dean-Stark trap. Dehydration products **13**{1-5,1-5} were then hydrogenated overnight at 40 psi in ethanol over Pd/C to give the reduced isoquinuclidines **14**{1-5,1-5}.

PURIFICATION

Purification was achieved by analytical and preparative gradient HPLC using 30% CH_3CN / 70% H_2O progressing to 100% CH_3CN over 12 minutes. All structures were



(a) ether, -78° C to rt; (b) C_6H_6, *p*-TsOH, reflux,; (c) H_2, Pd/C

Scheme 2.

confirmed using ^{1}H NMR analysis and mass spectrometry (MS).

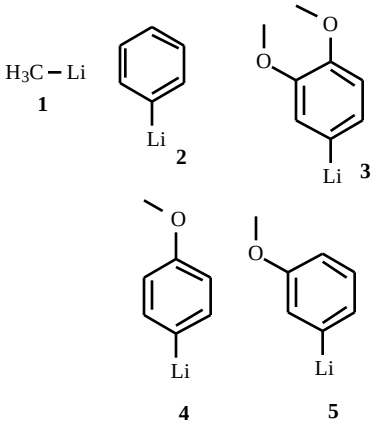


Fig. (5). Second Diversity Reagents **12**{1-5}.

Future studies include separating isomers of **14**{1-5,1-5} and evaluating them at the kappa, mu, delta, NMDA, sigma-1, sigma-2, and nicotinic receptors as well as the dopamine and serotonin transporters. These agents will hopefully provide insight into the unknown mechanisms of action of ibogaine and anti-addictive agents.

REFERENCES

[1] Levi, M.S.; Khan, M.O.F.; Borne, R.F. *Lett. Drug Design Disc*., **2004**, *1*, 384.
[2] Popik, P.; Layer, R.T.; Skolnick, P. *Pharmacol. Rev*., **1995**, *47*, 235.
[3] Popik, P.; Glick, S.D. *Drugs Future*, **1996**, *21*, 1109.
[4] Levi, M.S.; Borne, R.F. *Current Med. Chem*., **2002**, *9*, 1807.
[5] Cappendijk, S.L.T.; Dzoljic, M.R. *Eur. J. Pharmacol*., **1993**, *241*, 261.
[6] Pearl, S.M.; Johnson, D.W.; Glick, S.D. *Psychopharmacol*., **1995**, *121*, 470.
[7] Sershen, H.; Hashim, A.; Lajtha, A. *Pharmacol. Biochem. Behav*., **1996**, *53*, 863.
[8] O'Hearn, E.; Molliver, M.E. *J. Neurosci*., **1997**, *17*, 8828.
[9] Repke, D. B.; Artis, D. R.; Nelson, J. T.; Wong, E. H. F. *J. Org. Chem*., **1994**, *59*, 2164.
[10] Efange, S.M.N.; Mash, D.C.; Khare, A.B.; Ouyang, Q. *J. Med. Chem*., **1998**, *41*, 4486.
[11] Passarella, D.; Favia, R.; Giardini, A.; Lesma, G.; Martinelli, M.; Silvani, A.; Danieli, B.; Efange, S.M.N.; Mash, D.C. *Bioorg. Med. Chem*., **2003**, *11*, 1007.
[12] Henbest, H.B.; Nicholls, B. *J. Chem. Soc*., **1959**, 221.
[13] Huffman, J.W.; Rao, C.B.S.; Kamiya, T. *J. Org. Chem*., **1967**, *32*, 697.
[14] Law, S.J.; Borne, R.F. *Eur. J. Med. Chem*., **1980**, *15*, 229.
[15] Nelson, W.L.; Wilson, R.S. Muscarinic agents. *J. Pharm. Sci*., **1970**, *59*, 98-100.
[16] Borne, R.F.; Clark, C.R.; Peden, R.L. *J. Heterocyclic Chem*., **1973**, *10*, 241.