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Synthesis of 2-alkyl-3-aryl-substituted quinuclidines as novel dopamine transporter inhibitors

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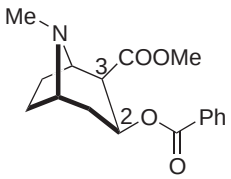
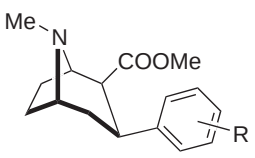
Abstract

The synthesis of 2-alkyl-3-aryl-substituted quinuclidines was accomplished in a simple synthetic sequence. The separation of enantiomers was carried out using chiral HPLC.

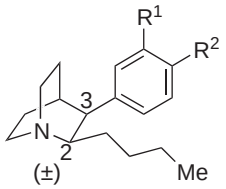
Cocaine abuse remains a serious health and social problem in the United States and worldwide, with an estimated 1.5 million cocaine users in the United States alone. As a consequence, it is obvious that immediate strategies are needed for the treatment of cocaine addiction to combat the destructive effects of this reinforcing drug on individuals and on society at large. The reinforcing and stimulant properties of cocaine have been associated with its ability to bind to monoamine transporter systems, particularly the dopamine transporter (DAT).[1] To date, most structure–activity studies of DAT inhibitors have been focused on a limited number of compounds, including cocaine/tropane analogs, GBR compounds, methylphenidate analogs, mazindol analogs, and piperidine analogs.[2] In view of the urgency and complexity of the development of an effective cocaine therapy, we believe that the discovery of DAT inhibitors that have truly novel chemical scaffolds may have considerable value. Lead compounds with novel chemical scaffolds will provide new chemical insights into DAT inhibitor design. DAT inhibitors with novel chemical scaffolds may also have pharmacological and behavioral profiles different from known DAT inhibitors.



(*R*)-(-)-Cocaine (**1**)



WIN series (**2**)



Quinuclidine (**3**)

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Previously, we have reported the discovery of 4-hydroxy-1-methyl-4-(4-methylphenyl)-3-piperidyl 4-methylphenyl ketones as a novel class of dopamine transporter inhibitors through 3D-database pharmacophore searching.[3] In continuation of our efforts to identify ligands of possible use in the treatment of cocaine abuse, we discovered quinuclidines as another novel class of dopamine transporter inhibitors employing the same method.[4] With the aid of molecular modeling based on the structure activity relationships (SAR) of the 'WIN series', we predicted that alkyl substitution at C2 and aryl substitution at C3 of such quinuclidines should yield new analogs as potent DAT inhibitors (Fig. 1). An extensive literature search revealed that no synthetic method has been reported to prepare compounds of general structure **3**, i.e. C2-alkyl- and C3-aryl-substituted quinuclidines. Herein, we report a simple route for the synthesis of compound **3**.

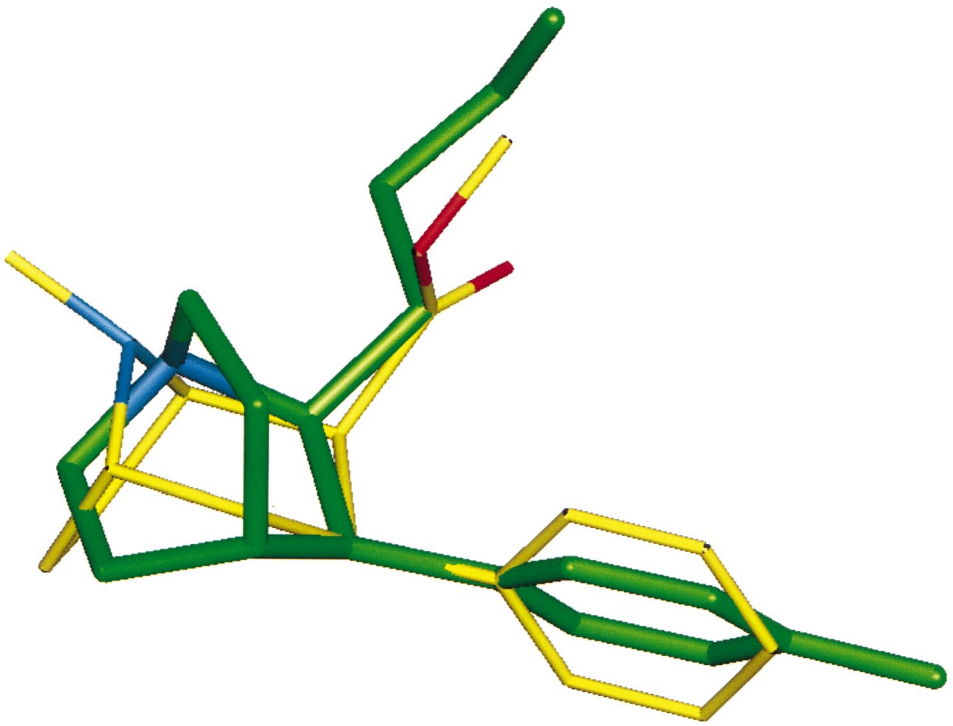
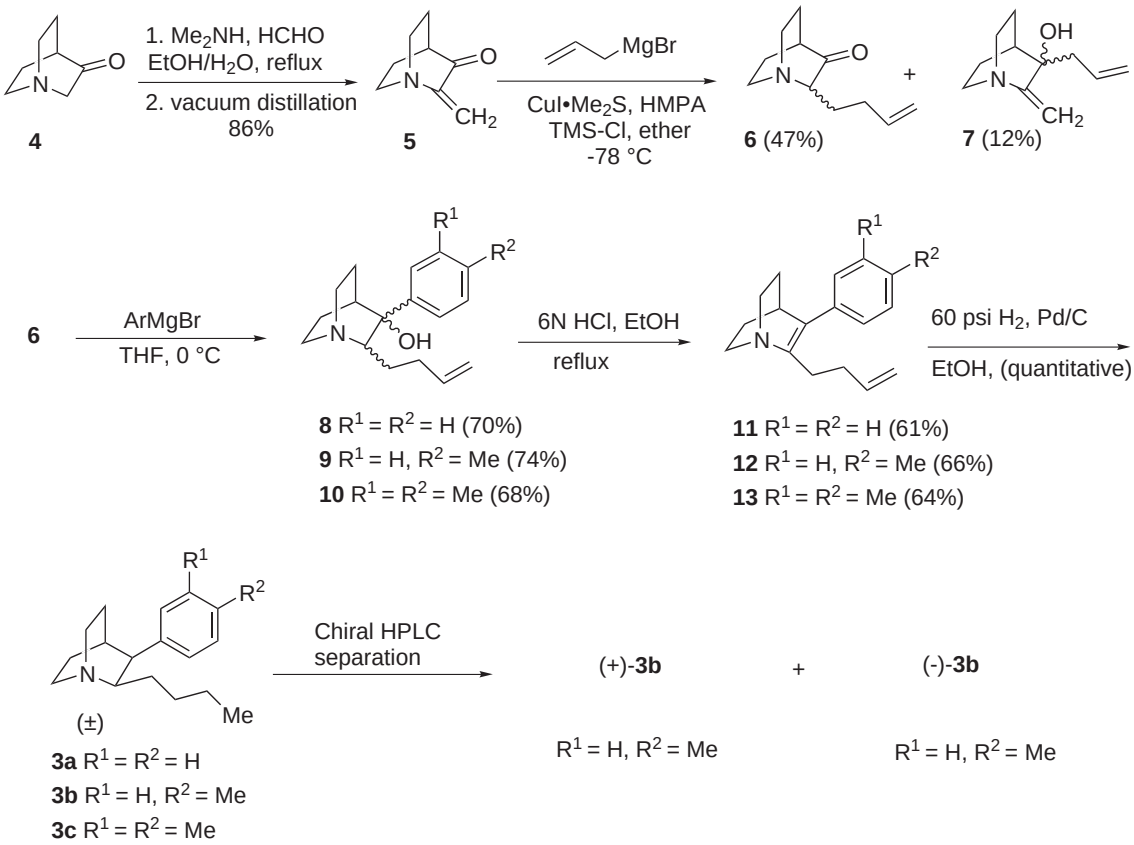


Figure 1. Superposition of the lowest energy conformations of compound **2** (yellow) and quinuclidine (±)-**3b** (green)

Thus, starting from 3-quinuclidinone (**4**), 2-methylene-3-quinuclidinone (**5**) was prepared by a Mannich reaction (Scheme 1).[5] Our earlier attempts to directly alkylate 3-quinuclidinone (**4**) under various reaction conditions using different bases like LDA, NaHMDS and $NaNH_2$ with 1-iodopropane or allyl bromide proved unsuccessful. Reaction of **4** with aq. dimethylamine and aq. formaldehyde in an ethanol/water mixture at 70°C gave the Mannich base, which on distillation gave compound **5** in 86% yield. Reaction of **5** with allylmagnesium bromide in the presence of $CuI{\cdot}Me_2S$ and Me_3SiCl at −78°C furnished the conjugate addition product **6** in 47% yield along with the 1,2-addition product **7** in 12% yield, which were isolated by column chromatography. Addition of arylmagnesium bromide to compound **6** was carried out in THF at 0°C to give compounds **8**, **9** or **10**, which were subsequently treated with a 1:1 mixture of

EtOH and 6N HCl under reflux conditions to give the dehydrated compounds **11**, **12** or **13**, respectively. Reduction of the double bonds was carried out using standard hydrogenation conditions (60 psi H_2, Pd/C, EtOH) to provide compounds **3a**, **3b** and **3c** in near quantitative yields.[6]



Scheme 1.

The hydrogen addition took place with *syn* stereochemistry as expected, and the structure of compound (±)-**3b** was confirmed by X-ray crystallography. The enantiomers (+)-**3b** and (−)-**3b** were separated on a 250×10 mm Chirex 3018 HPLC column, in which the chiral stationary phase (CPS) consists of (*S*)-proline covalently bound to γ-aminopropyl silinized silica gel (5 μm particle size) and derivatized via an urea linkage with (*R*)-1-(α-naphthyl)ethylamine.[7] The optical rotation of (+)-**3b** ($t_R = 19.5$ min) was found to be $[\alpha]_D = +104$ (*c* 0.5, acetone) and that of (−)-**3b** ($t_R = 23.0$ min) was $[\alpha]_D = -104$ (*c* 0.5, acetone).

In summary, the synthesis and chiral separation of a novel class of 2-alkyl-3-aryl-substituted quinuclidines has been accomplished in a five step sequence. This synthesis will provide access to a new class of dopamine transporter inhibitors which may be useful in the development of medications for the treatment of cocaine abuse. Preliminary biological testing showed that some of these compounds are potent DAT inhibitors, thus confirming our design strategy. The details of this work will be reported elsewhere.[4]

Acknowledgements

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6. (a) Compound **3a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.79 (3H, t, $J=6.8$ Hz), 1.07–1.36 (6H, m), 1.45–1.56 (1H, m), 1.70–1.76 (2H, m), 2.01–2.12 (2H, m), 2.67–2.78 (1H, m), 2.96–3.29 (5H, m), 7.19–7.34 (5H, m); ^{13}C NMR ($CDCl_3$) δ 14.0, 22.3, 22.7, 26.8, 29.7, 30.2, 30.3, 40.7, 45.4, 49.4, 60.2, 125.5, 127.8, 128.9, 142.9; MS m/z (%) 243 (25), 42 (100); compound **3b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.77 (3H, t, $J=6.8$ Hz), 1.02–1.32 (6H, m), 1.40–1.49 (1H, m), 1.65–1.72 (2H, m), 1.96–2.06 (2H, m), 2.32 (3H, s), 2.64–2.74 (1H, m), 2.89–3.00 (1H, m), 3.05–3.23 (4H, m), 7.06–7.14 (4H, m); ^{13}C NMR ($CDCl_3$) δ 14.2, 21.1, 22.5, 22.9, 27.2, 29.9, 30.4, 30.6, 40.9, 45.3, 49.7, 60.4, 128.8, 129.0, 135.1, 140.0; MS m/z (%) 257 (29), 42 (100); compound **3c**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.78 (3H, t, $J=6.9$ Hz), 1.07–1.33 (6H, m), 1.41–1.49 (1H, m), 1.64–1.70 (2H, m), 2.00–2.08 (2H, m), 2.24 (3H, s), 2.52 (3H, s), 2.64–2.74 (1H, m), 2.90–3.23 (5H, m), 6.99–7.06 (3H, m); ^{13}C NMR ($CDCl_3$) δ 14.3, 19.4, 20.1, 22.5, 22.9, 27.3, 29.9, 30.4, 30.6, 41.0, 45.4, 49.7, 60.4, 126.4, 129.3, 130.7, 133.8, 136.1, 140.5; MS m/z (%) 271 (36), 42 (100). (b) All new compounds have shown satisfactory elemental analyses.
7. (a) The chiral HPLC separation was performed at a flow rate of 5.0 mL/min at room temperature using hexane/CH_2Cl_2/ethanol/trifluoroacetic acid as a mobile phase in a 83:15:2:0.1 ratio and UV detection at 254 and 280 nm. The sample was prepared by dissolving racemic compound (5 g/L) in the mobile phase, and 30 μL of this solution was injected per run. (b) Cleveland, T. *J. Liq. Chromatogr*. **1995**, *18*, 649–671.