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Original article

Structure–activity studies with ring E analogues of methyllycaconitine. Synthesis and evaluation of enantiopure isomers of selective antagonist at the α3 nicotinic receptor

K.A. Ismail [a,*], S.C. Bergmeier [b]

[a] *Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Alexandria, Alexandria, Egypt*
[b] *Department of Chemistry and Biochemistry, Ohio University, Athens, OH 45701, USA*

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Abstract

The four diastereomers **4a**–**d** of methyllycaconitine (MLA) analogue **3** ($R = (CH_2)_3Ph$, $R' = CH_3$) have been synthesized in enantiomerically pure form by coupling both (*S*)- and (*R*)-2-(methylsuccinimido)benzoic acid (**5a** and **5b**) with both (*S*)- and (*R*)-3-hydroxymethyl-*N*-(3-phenyl) propylpiperidine (**6a** and **6b**) using TBTU. These compounds were assayed for potency as nicotinic acetylcholine receptor (nAChRs) antagonist. All the four diastereomers showed the same potency at both the α3 and α7 receptors as racemic compound **3**. This indicates that the binding at nicotine acetylcholine receptors (nAchRs) is probably non-stereospecific.

Keywords: methyllycaconitine; diastereomers; enantiomers; 2-(methyl-succinimido)benzoic acid; nicotine acetylcholine receptors

1. Introduction

It is becoming increasingly evident that different nicotinic acetylcholine receptor (nAChR) subtypes mediate a variety of important physiological functions. Furthermore, nAChRs have been linked to a variety of disease states [1,2]. The involvement of specific nAChR subtypes in the disease states remains to be elucidated. The development of subtype-specific nAChR ligands should not only facilitate our under-standing of these disease states, but may lead to novel treatment strategies for these diseases as well.

Methyllycaconitine (MLA) is a norditerpenoid alkaloid that has seen extensive use as an antagonist at the α7-nAChR [3,4]. We had reported previously on the synthesis and evaluation of a series of racemic simple analogues **3** of MLA [5,6] (Fig. 1) that act as micromolar inhibitors at nAChRs. Our previous reports produced two significant findings about our ring E analogues **3**. First, optimal potency is observed when the piperidine ring nitrogen is substituted with a 3-phenylpropyl chain (**3**, $R = (CH_2)_3Ph$, $R' = CH_3$). A second significant finding was that unlike MLA, analogues such as **3** show moderate selectivity for the heteromeric α3-nAChR as compared to the α7-nAChR (α3: IC_{50} 11.4 μM, α7: IC_{50} 111 μM). A few other examples of simpler analogues of MLA have been reported as well [7–15]. ^{13}C NMR and optical rotation have been used to characterize the absolute configuration of the methylsuccinimide moiety in MLA as *S* [16,17].

Our previous preparation of MLA analogue **3** produced completely racemic products. If **3** was a direct analogue of MLA we would need the C_3-(*S*), $C_{3'}$-(*S*) enantiomer [18]. It was quite possible that other binding modalities may be operative in our analogue **3** relative to MLA. Thus it would seen appropriate that all four diastereomers be prepared and evaluated rather than only the C_3-(*S*), $C_{3'}$-(*S*) enantiomer.

In this paper we report the synthesis and characterization of all four diastereomers of our MLA analogue **4** ($R = (CH_2)_3Ph$, $R' = CH_3$) in enantiomerically pure form. These compounds have been assayed for potency by determining their ability to displace ^{125}I-α-(BGT) binding from a rat brain membrane preparation.

* Correspondence and reprints
E-mail address: kadiga99@yahoo.com (K.A. Ismail).

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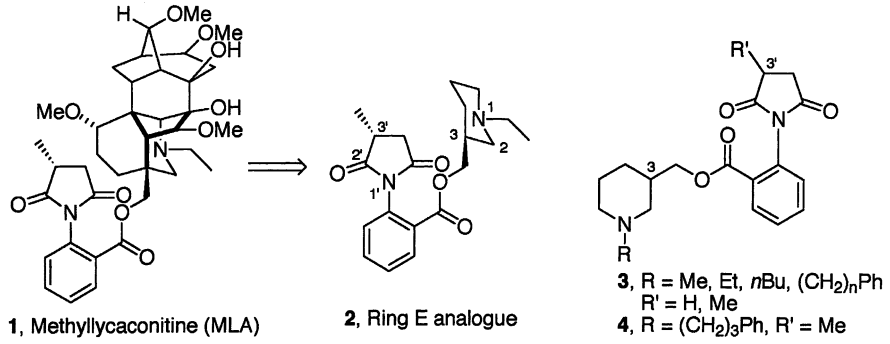

Fig. 1. Methyllycaconitine and ring E analogue.

2. Chemistry

In order to prepare the four diastereomers in enantiomerically pure form we will need both enantiomers of 2-(methylsuccinimido)benzoic acid **5** and 3-hydroxymethyl-*N*-(3-phenyl)propylpiperidine **6** (Fig. 2).

The synthesis of the acid derivative **5** involves the condensation of methylsuccinic anhydride with anthranilic acid [5,9]. The needed optically pure anhydrides **8a** and **8b** were prepared by dehydration of the corresponding commercially available acids **7a** and **7b**, respectively, using acetyl chloride [19] (Fig. 3). The synthesis of (*S*)- and (*R*)-2-(methylsuccinimido) benzoic acid **5a** and **5b** has been accomplished in excellent yield by the fusion of anthranilic acid with (*S*)- and (*R*)-methylsuccinic anhydride [5,9] (Fig. 3).

The synthesis of enantiomerically pure alcohol **6** was a bit more challenging. The availability of optically pure nipecotic acid **9** via resolution provided us with an obvious starting material. Resolution of nipecotic acid was achieved via fractional crystallization of the camphorsulfonic acid (CSA) salt [20]. Pure (*S*)-nipecotic acid **10a** was obtained using (*S*)-CSA and pure (*S*)-nipecotic acid **10b** was obtained using (*R*)-CSA. Acylation of either **10a** or **10b** with hydrocinnamoyl chloride provide amides **11a** or **11b** in 70 and 75% yield respectively. The carboxylic acid and amide of **11a** and **11b** were concurrently reduced with $LiAlH_4$ [21] to produce (*S*)- and (*R*)-3-hydroxymethyl-*N*-(3-phenyl) propylpiperidine **6a** and **6b** in good yield (Fig. 4).

Determination of the optical purity of **6a** and **6b** was achieved by ^1H NMR spectroscopic analysis of the (*R*)-α-methoxy-α-trifluoromethyl phenylacetate esters.

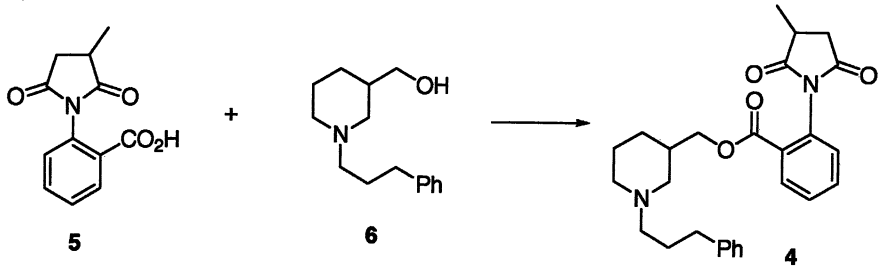

Fig. 2. Synthesis of ring E analogue.

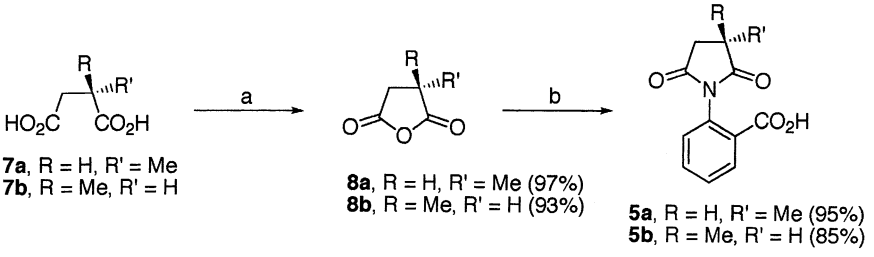

Fig. 3. (a) CH_3COCl, reflux, 3 h, (b) anthranilic acid, neat, 145 °C, 0.1 mmHg, 3 h.

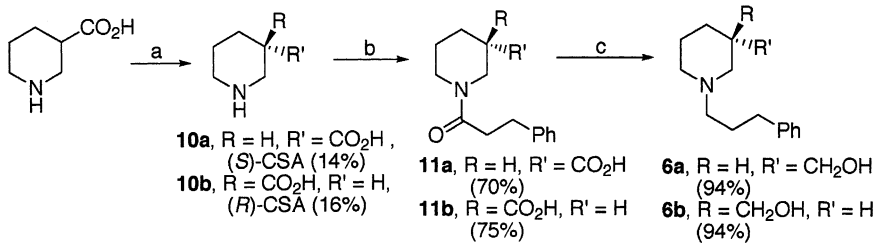

Fig. 4. (a) (*S*)- or (*R*)-10-camphorsulphonic acid (CSA), acetone:water recrystallize. (b) Hydrocinnamoyl chloride, Et_3N, DMAP. $(LiAlH)_4$, reflux, 24 h.

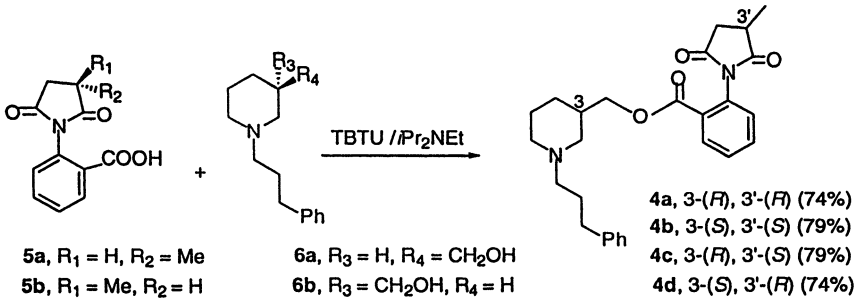

Fig. 5. Coupling conditions for ring E analogue.

Based on the ^1H NMR we can conclude that both amino alcohols are $>98\%$ enantiomerically pure.

Coupling of the 2-(methylsuccinimido)benzoic acid **5a** and **5b** to the amino alcohols **6a** and **6b** using 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) produced our target compounds **4a-d** (Fig. 5). Our target compounds **4a–d** were converted to their water-soluble hydrochloride salts prior to biological evaluation.

3. Biological activity

The four prepared diastereomers **4a–d** were assayed for potency by determining their ability to displace ^{125}I-α-bungarotoxin ([^{125}I] α-BGT) [22] and [^{3}H] nicotine [23] binding from a rat brain membrane preparation. We have also assayed these analogues using adrenal chromaffin cells (primarily α3 receptors) as functional assay [24].

Our results to date indicate that all of the four diastereomers showed the same potency at both the α3 and α7 receptors. This indicated that the binding at nAChRs is non-stereospecific. Further pharmacological evaluation is being carried out to determine the type of binding (competitive versus non-competitive).

4. Experimental

General. Thin layer chromatography (TLC) was performed on Whatman coated silica gel F_{254} aluminum foils. Visualization was accomplished with UV light/or phosphomolybdic acid solution followed by heating. Purification of the reaction products was carried out by flash column chromatography using glass column dry packed with silica gel (230–400 mesh) according to the method of Still [25]. Organic solutions were dried over $MgSO_4$; evaporated refers to removal of solvent on a rotary evaporator under reduced pressure. Melting points were determined using a Thomas Hoover capillary melting point apparatus and are uncorrected. IR spectra were obtained on salt plates in KBr pellet or in CCl_4, using a Nicolet Protege 460 model spectrometer. Peaks are reported in cm^{-1}. ^1H and ^{13}C NMR spectra were recorded on a Bruker 250 MHz spectrometer with TMS as internal standard in $CDCl_3$ unless otherwise noted. Mass spectral data were determined at the Ohio State University Chemical Instrument center with a Kratos MS-30 mass spectrometer. Optical rotations were recorded on a Perkin–Elmer 241 Polarimeter using mercury or sodium spectral lines at 435 or 589 nm, respectively. Solvents were dried and purified according to the recommended procedures. All reactions were carried out under an argon atmosphere, unless otherwise noted.

*4.1. (S)-Methylsuccinic anhydride (**8a**)*

A solution of (*S*)-methylsuccinic acid **7a** (0.5 g, 3.8 mmol) in acetyl hloride (0.8 ml, 11.3 mmol) was refluxed for 3 h. The mixture was evaporated to give white crystals which were washed twice with cold Et_2O and dried under vacuum to give 0.42 g (97%) of **8a**,

m.p. 45–47 °C; IR (KBr) 1795, 1790, 1210. $[\alpha]_D$ −33.9° (*c* 1.0, $CHCl_3$) and −37.2° (*c* 3.5, dioxane), ($[\alpha]_D$ − 36.5°, (*c* 3.5, dioxane)) [16]. ^{1}H NMR (DMSO-d_6) δ 3.27 (m, 1H), 3.06 (dd, 1H, $J = 19.5$, 10 Hz), 2.69 (dd, 1H, $J = 19.5$, 7.8 Hz), 1.23 (d, 3H, $J = 7.8$ Hz).

4.2. (R)-Methylsuccinic anhydride (**8b**)

This compound was prepared by the same procedure as for the *S*-enantiomer, starting with (*R*)-methylsuccinic acid **7b** on a 0.5 g scale to give 0.4 g (93%) of **8b**. All analytical data were identical except for $[\alpha]_D$ +34.4 (*c* 1.0, $CHCl_3$).

4.3. (S)-2-(Methylsuccinimido)benzoic acid (**5a**)

(*S*)-Methylsuccinic anhydride **8a** (0.1 g, 0.9 mmol) was stirred at 40 °C, then anthranilic acid (0.12 g, 0.9 mmol) was added and the mixture was heated at 145 °C under reduced pressure (0.1 mmHg) for 3 h. The residue was chromatographed (toluene: EtOAc: HOAc (9: 0.5: 0.5) to give 0.19 g (95%) of **5a** as hygroscopic yellowish white crystals. $[\alpha]_D$ −12.5° (*c* 1.0, $CHCl_3$); IR (neat) 3501, 1769, 1620. ^{1}H NMR ($CDCl_3$) δ 10.5 (bs, 1H), 8.2 (d, 1H, $J = 7.5$ Hz), 7.72 (t, 1H), 7.52 (t, 1H), 7.22 (d, 1H, $J = 7.5$ Hz), 3.1 (m, 2H), 2.5 (d, 1H, $J = 15$ Hz), 1.4 (d, 3H, $J = 7.5$ Hz). ^{13}C NMR ($CDCl_3$) 180.2, 176.4, 169.7, 134.7, 133.3, 132.9, 130.2, 129.8, 128.6, 123.7, 35.8, 16.9. HRMS Calc. for $C_{12}H_{11}NO_4$ was 233.244. Found: 233.068.

4.4. (R)-2-(Methylsuccinimido)benzoic acid (**5b**)

This compound was prepared by the same procedure as for the (*S*)-enantiomer **5a**, starting with (*R*)-methylsuccinic anhydride **8b** (0.1 g, 0.9 mmol) to produce 0.17 g (85%) of **5b**. All analytical data were identical except for $[\alpha]_D$ +14.1 (*c* 1.0, $CHCl_3$).

4.5. (S)-Nipecotic acid salt (**10a**) [20]

(*S*)-10-camphorsulfonic acid (9 g, 38.7 mmol) was added to a stirred hot solution of racemic nipecotic acid **9** (5 g, 38.7 mmol) in acetone (70 ml), water was added to dissolve. The solution was cooled to r.t. and allowed to stand overnight. The precipitate was filtered and recrystallized three times with acetone/water (6/1, v/v) to afford 2 g of **10a** as white needles (14%); m.p. 222–224 °C; $[\alpha]_D$ +25.78° (*c* 1.0, MeOH).

4.6. (R)-Nipecotic acid salt (**10b**)

The same procedure was used as for the *S*-enantiomer starting with (*R*)-10-camphorsulfonic acid (9 g, 38.7 mmol) to afford 2.2 g of **10b** (16%); m.p. 222–224 °C; $[\alpha]_D$ −26.36° (*c* 1.0, MeOH).

4.7. (S)-N-Hydrocinnamoylpiperidine-3-carboxylic acid (**11a**)

To a 0 °C solution of (*S*)-nipecotic acid salt **10a** (0.5 g, 1.4 mmol) in CH_2Cl_2 (10 ml), Et_2N (10 ml, 6.9 mmol) and DMAP (0.2 g, 0.14 mmol), hydrocinnamoyl chloride (0.24 ml, 1.6 mmol) was added dropwise. The mixture was stirred overnight at r.t. The solution was acidified with 1 N HCl, the organic layer was separated, dried over $MgSO_4$, filtered and concentrated. The residue was chromatographed (50% EtOAc in hexanes + 0.5% HOAc) to give 0.25 g (69.4%) of **11a** as white crystals; m.p. 141–143 °C; $[\alpha]_D$ + 51.58° (*c*, 1.0, $CHCl_3$). IR (KBr) 3452, 3022, 1725, 1613, 1597. ^{1}H NMR ($CHCl_3$) δ 9.85 (bs, 1H), 7.4–7.09 (m, 5H), 4.6 (bd, 1H, $J = 1.5$ Hz), 4.05 (bd, 1H, $J = 1.5$ Hz), 3.7 (t, 1H), 3.4 (t, 1H), 3.12 (m, 2H), 2.7 (m, 2H), 2.51 (m, 1H), 2.32 (m, 1H), 2.1 (m, 1H), 1.8 (m, 1H), 1.4 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 171.7, 141.4, 128.9, 126.5, 47.6, 46.5, 44.1, 42.5, 35.5, 35.2, 31.9, 27.5, 27.4, 25.2, 24.1. HRMS Calc. for $C_{15}H_{19}NO_3$ was 261.316. Found: 261.135.

4.8. (R)-N-Hydrocinnamoylpiperidine-3-carboxylic acid (**11b**)

This compound was prepared by using the same procedure as for the (*S*)-enantiomer, starting with (*R*)-nipecotic acid salt **10b** (0.5 g, 1.4 mmol) to give 0.27 g (75%) of **11b** as white crystals. All analytical data were identical except for m.p. 146–148 °C and $[\alpha]_D$ −52° (*c*, 1.0, $CHCl_3$).

4.9. (S)-3-Hydroxymethyl-N-(3-phenyl)propylpiperidine (**6a**)

A solution of the (*S*)-acid derivative **11a** (0.2 g, 0.76 mmol) in THF (2 ml) was added via cannula to a refluxing suspension of $LiAlH_4$ (90 mg, 2.3 mmol) in THF (1 ml). The mixture was refluxed for 24 h. After the reaction was complete, it was cooled, diluted with Et_2O (3 mL), and water (90 μl) was added dropwise, then stirred 5 min, 15% aqueous NaOH (90 μl) was then added and stirred for another 5 min, then water (0.2 ml) was again added. This gave a white precipitate, which was filtered. The filtrate was concentrated and dried under vacuum to give 0.16 g (94%) of **6a** as a yellow oil. $[\alpha]_{435}$ −9.4° (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.38–7.2 (m, 5H), 5.13 (s, 1H) 3.55 (m, 2H), 2.72 (bd, 1H, $J = 10.5$ Hz), 2.6 (t, 3H), 2.31 (t, 2H), 2.11 (t, 1H), 2.01 (t, 1H), 1.9–1.48 (m, 6H), 1.27–1.04 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 142, 127, 125, 66.5, 57, 56, 38, 35, 28, 27, 24. HRMS Calc. for $C_{15}H_{23}NO$ was 233.326. Found: 233.176.

4.10. (R)-3-Hydroxymethyl-N-(3-phenyl)propyl-piperidine (**6b**)

This compound was prepared by the same procedure as for the (*S*)-enantiomer **6a**, starting with the (*R*)-acid derivative **11b** (0.2 g, 0.76 mmol) to give 0.17 g (94%) of the desired pure (*R*)-amino alcohol **6b** as a yellow oil. All analytical data were identical except for $[\alpha]_{435}$ + 9.2° (*c* 1.0, $CHCl_3$).

4.11. General procedure for the condensation of the succinimido derivative (**5a** or **5b**) with the amino alcohol (**6a** or **6b**)

The succinimido derivative (0.34 g, 1.5 mmol) and TBTU (0.48 g, 1.5 mmol) in CH_3CN (5 ml) was stirred at r.t. In a second flask, the amino alcohol derivative (0.6 g, 1.5 mmol) in CH_3CN (5 ml) was cooled to 0 °C and diisopropylethylamine (0.52 ml, 3 mmol) was added. This solution was added via cannula to the succinimido solution. The mixture was stirred at r.t. for 24 h. The solution was evaporated to produce a brownish residue which was chromatographed (EtOAc, toluene, Et_3N; 7: 2.8: 0.2) to give the products.

4.12. 3-(R)-3′-(R)-ester (**4a**)

0.14 g (73.6%). $[\alpha]_{435}$ + 22.87° (*c* 1.0, $CHCl_3$). IR (neat) 2951, 1782, 1598. ^{1}H NMR ($CHCl_3$) δ 8.1 (d, 1H, $J = 7.5$ Hz), 7.6 (t, 1H), 7.45 (t, 1H), 7.3–7.05 (m, 6H), 4.1 (d, 2H, $J = 6.25$ Hz), 3.1 (bd, 2H, $J = 15$ Hz), 2.9 (bd, 2H, $J = 15$ Hz), 2.6 (m, 2H), 2.32 (m, 2H), 2.15–1.58 (m, 7H), 1.5–1.45 (m, 3H), 1.38 (d, 3H, $J = 7.5$ Hz). ^{13}C NMR ($CHCl_3$) δ 180.3, 176.4, 164.7, 142.5, 133.8, 133.1, 131.9, 130.2, 129.7, 128.8, 128.7, 127.7, 126.1, 68.3, 58.5, 57.4, 54.3, 39.0, 37.4, 36.1, 35.7, 34.1, 28.8, 27.6, 24.9, 16.7. HRMS Calc. for $C_{27}H_{32}N_2O_4$ was 448.553. Found 448.234.

4.13. 3-(S)-3′-(S)-ester (**4b**)

0.15 g (78.9%). $[\alpha]_{435}$ − 25.6° (*c* 1.0, $CHCl_3$). All other analytical data were identical to the 3-(*R*)-3′-(*R*) diastereomer **4a**.

4.14. 3-(R)-3′-(S)-ester (**4c**)

0.15 g (78.9%). $[\alpha]_{435}$ − 19.7° (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CHCl_3$) δ 8.09 (d, 1H, $J = 7.5$ Hz), 7.61 (t, 1H), 7.5 (t, 1H), 7.31–7.02 (m, 6H), 4.2–4.0 (m, 2H), 3.18 (bd, 2H, $J = 15$ Hz), 3.1 (bd, 2H, $J = 15$ Hz), 2.5 (m, 2H), 2.34 (m, 2H), 2.2–1.6 (m, 7H), 1.55 –1.45 (m, 3H), 1.4 (d, 3H, J = 7.5Hz). All other data were identical to the 3-(*R*)-3′-(*R*)- and 3-(*S*)-3′-(*S*)-diastereomers **4a** and **4b**, respectively.

4.15. 3-(S)-3′-(R)-ester (**4d**)

0.14 g (73.6%). $[\alpha]_{435}$ + 20.6° (*c* 1.0, $CHCl_3$). All other data were identical to the 3-(*R*)-3′-(*S*) ester **4c**. HRMS Calc. for $C_{27}H_{32}N_2O_4$ was 448.553. Found: 448.237.

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