SYNTHESIS AND EVALUATION OF POSSIBLE SUBTYPE-SELECTIVE ANTAGONISTS OF NICOTINIC ACETYLCHOLINE RECEPTORS

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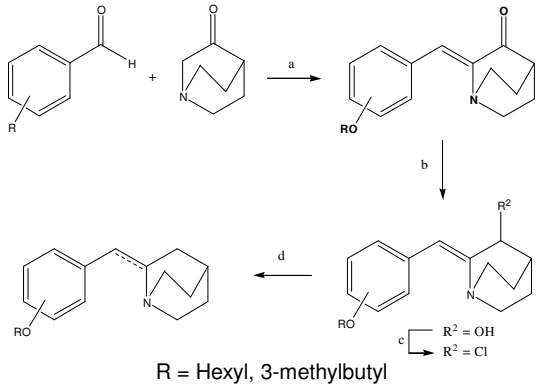
INTRODUCTION

Development of selective agonists or antagonists for the Nicotinic acetylcholine receptors (nAChR) may result in new and potentially useful therapeutic agents. It has been reported in the literature that potent and selective nAChR antagonists could be used for the treatment of nicotine dependence and may be an efficacious adjuvant therapy in many different oncologic protocols.[1,2] nAChr antagonists studied previously by us having an indole ring core, *N*[1]-alkyl groups and a quaternized moiety showed potency but little selectivity.[3]

RESULTS AND DISCUSSION

The synthesis of quinuclidines **1a-e** was achieved as ilustred in Scheme 1. Quinuclidine-3-one hydrochloride and powdered anhydrous potassium hydroxide were dissolved in methanol and stirred for 15 mins, the corresponding aldehyde was then added in portions and the mixture was stirred for an additional 16 h. The reaction mixture was then diluted with water and cooled to 0 ºC yielding the corresponding vinylquinuclidinones as yellow precipitates. The vinylclinuclidinones were dissolved separately in methanol and $NABH_4$ was added in portions with vigorous stirrer. After 1 h, acetone was slowly added, the mixture was evaporated to dryness and the resulting residue suspended in water and extracted with chloroform and the organic phase was dried over anhydrous Na_2SO_4.to give the alcohol. The latter compound was converted to the chloro intermediate hydrochloride upon treatment with thionyl chloride. Dechlorination by hydrogenation with Raney nickel and carbon-carbon double bond reduction by hydrogenation over 10% palladium on charcoal was effected to yield the desired products.

The structure of one intermediate (R = 3-methylbutyl) was confirmed by X ray study, figure 1.



R = Hexyl, 3-methylbutyl

Scheme 1. Reagents and conditions: a. KOH, MeOH, rt., 16 h.b. $NaBH_4$, MeOH, rt, 1 h. c. $SOCl_2$, rt, 1h. d. Raney -Ni, H_2, 50 psi, EtOH, 16h.

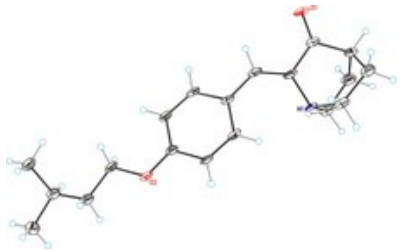


Figure 1. X ray structure for R = 3-methylbutyl.

CONCLUSION

Quinuclidine based new compounds were designed and synthesized using reported methodologies. X-ray structure of one of them was determinate and the results of biological assays will be presented during the congress.

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