Synthesis and radioactive labeling of galanthamine derivatives for examination of nicotinic acetylcholine receptor system

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The most commonly applied therapeutic approach to balance nicotinic cholinergic deficits in Alzheimer's disease (AD) patients is the administration of acetylcholinesterase inhibitors (AChE-I) although they have been proven to be of limited therapeutic value. A novel approach to drug treatment in AD is the application of allosterically potentiating ligands (APL) acting on nicotinic acetylcholine receptors (nAChR). APLs interact with the receptor via binding sites that are distinct from those for nicotinic agonists and antagonists. They also up-modulate the channel activity of nAChRs in response to acetylcholine and other nicotinic agonists [1]. Representative members of this class of ligands are the plant alkaloids physostigmine, codeine and galanthamine.

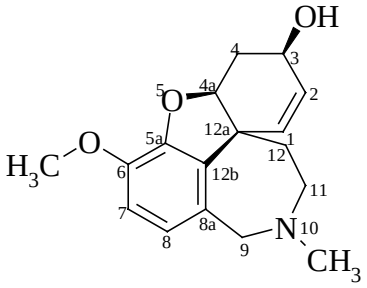

Fig.1: Structure of galanthamine (1)

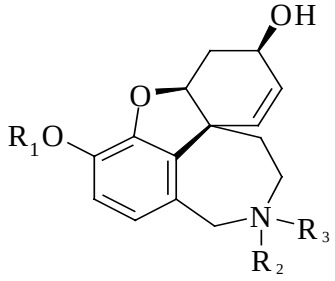

Fig.2: Structures of the galanthamine derivatives:
6-O-demethyl-6-O-fluoroethyl-galanthamine (3):
R_1=CH_2CH_2F, R_2=CH_3;
10-N-demethyl-10-N-fluoroethyl-galanthamine (6):
R_1=CH_3, R_2=CH_2CH_2F;
N-methylgalanthaminium (7):
R_1=R_2=R_3=CH_3

Galanthamine (Fig.1) acts as either an AChE-I or an APL (it also enforces receptor dependent neurotransmitter release on account of an unknown mechanism). The primary object of this work was to synthesise a galanthamine derivative which possesses only one of these properties, preferably acting as APL. These derivatives might be employed in PET studies and psychopharmacological examinations. Fig.2 shows the derivatives that have been synthesised and tested *in vitro* up to now.

Radioactive labelling of precursors 2 and 5 could easily be achieved by fluoroalkylation with 2-[^{18}F]fluoroethyltosylate in DMF (2: 5 mg, 0.95 eq. 1 N NaOH, 20 min, 100°C; 5: 5 mg, 30 min, 140°C) in average radiochemical yields of 92% ([^{18}F]3) and 31% ([^{18}F]6) (referred to 2-[^{18}F]fluoroethyltosylate, decay corrected). [^{3}H]7 was synthesised by reaction of 1 with [^{3}H]CH_3I (10 mCi, s.a. 80 Ci/mmol) in toluene (reaction conditions: r.t., 1 day) with a radiochemical yield of 62% (s.a. 54 Ci/mmol).

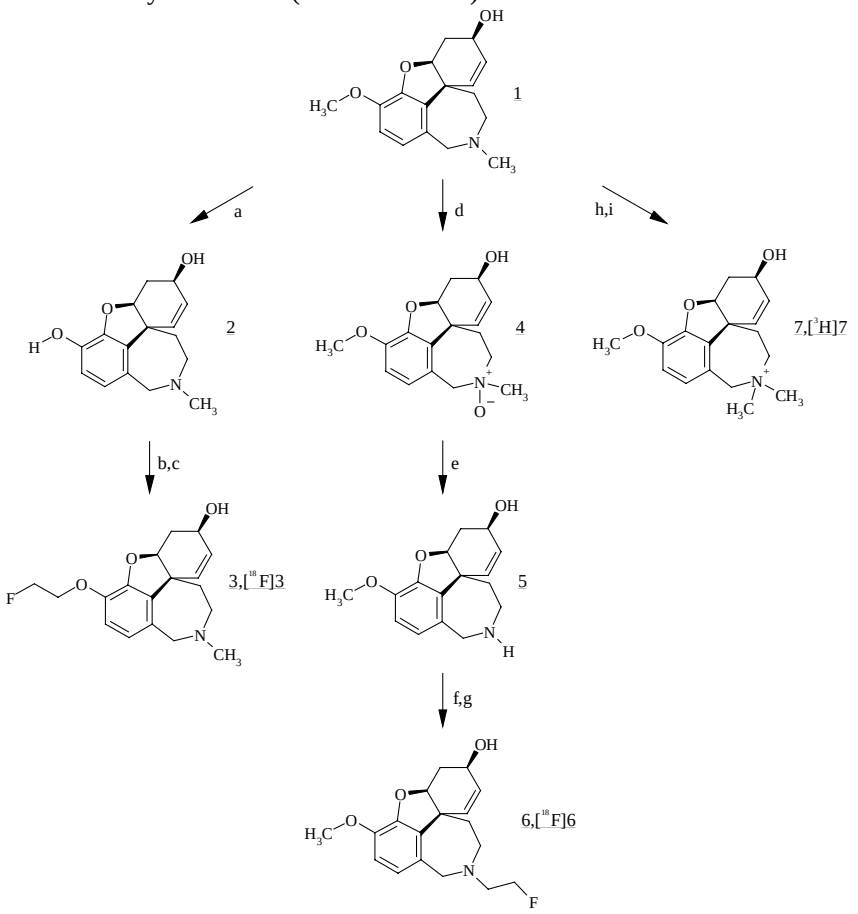

Fig. 3: Reaction conditions: a) L-Selectride, THF [2]; b) FCH_2CH_2Br, Cs_2CO_3, DMF [2]; c) [^{18}F]FCH_2CH_2OTos, NaOH, DMF; d) MCPBA, $CHCl_3$ [3]; e) $FeSO_4 \cdot 7\ H_2O$, CH_3OH [3]; f) FCH_2CH_2Br, NEt_3, CH_3CN [2]; g) [^{18}F]FCH_2CH_2OTos, DMF; h) CH_3I; Et_2O [4]; i) [^{3}H]CH_3I, toluene (for more details see also [5])

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[5] Schildan A. et al. Annual review 1999, Article B8: 37