DESIGN AND SYNTHESIS OF SELECTIVE LIGANDS TARGETING DIFFERENT nAChR SUBTYPES

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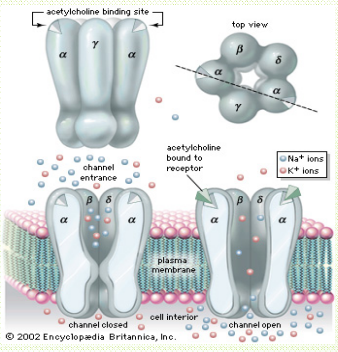
BACKGROUND AND AIMS OF THE STUDY

NICOTINIC ACETYLCHOLINE RECEPTORS

Differences in the pharmacological and functional properties of the nicotinic acetylcholine receptors (nAChRs) largely depend on their subunit composition. Recent studies indicate that receptor subtypes are selectively implicated in some diseases in which nAChRs have been found to be modified.

Four transmembrane domain neurotransmitter-gated ion channels, composed of pentameric combinations with a high degree of complexity conferred by 10 different α and non-α subunits.



DESIGN AND SYNTHESIS OF SUBTYPE-SELECTIVE nAChR LIGANDS

In order to control different nicotinic brain functions pharmacologically, it is very important to have drugs (agonists or antagonists) that selectively affect the different receptor subtypes in such a way as to maximize the desired effect and minimize the unwanted effects. To achieve these goals, I designed and synthesized different series of compounds potentially able to selectively activate a nAChR subtype:

- **α3β4 nAChR subtype**

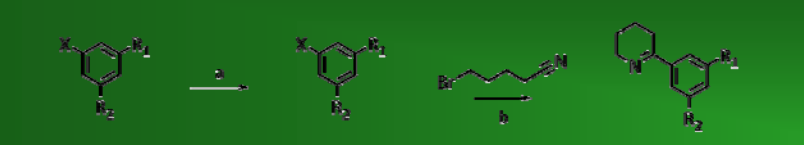
Involved in: nicotine addiction
Reference agonist: anabaseine (non-selective)
Design and synthetic approaches: ligand-based and target-based drug design
Aims: to improve anabaseine's activity and selectivity at the a3b4 nAChR subtype

- **α7 nAChR subtype**

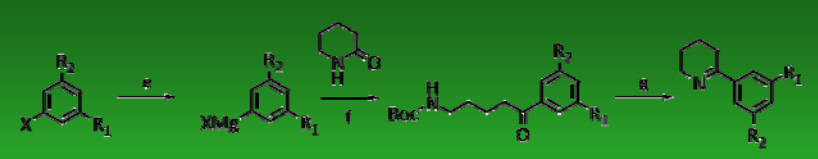
Involved in: AD (Alzheimer's disease), memory, learning, attention, inflammatory diseases (diabetes, obesity, arthritis...)
Reference compounds: PAMs type I (Genistein, 5-hydroxyindole)
Design and synthetic approaches: ligand-based and target-based drug design
Aims: to improve PAMs' activity and selectivity at the a7 nAChR subtype

CHEMISTRY

ANABASEINE DERIVATIVES

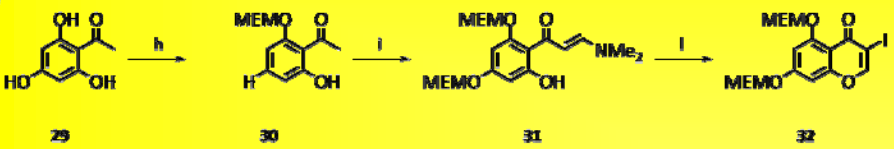


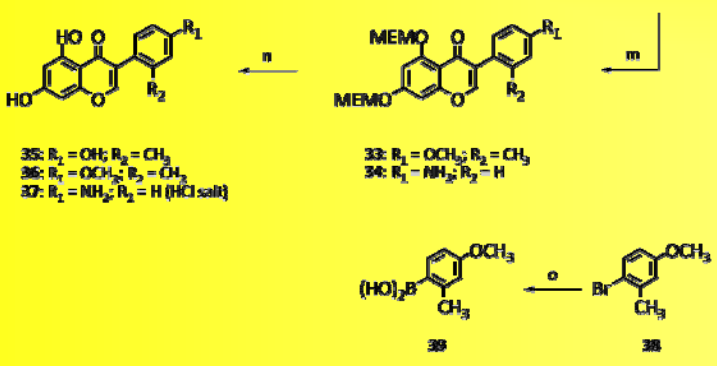
(a) Mg turnings, THF dry, r.t. or 2.5M n-BuLi/hexane, THF dry, -78°C, 2h; (b) THF dry, r.t., 1h → 12h; (c) $Ni(CO)_4$, 10% Pd/C, DMAP, DIPEA, MeOH, dioxane, MW, 50 W, 130°C, 2h; (d) 65% Red-Al/toluene, THF, r.t., 12h.



(e) Mg turnings, THF dry, r.t.; (f) 2.5 M BuLi/hexane, $(Boc)_2O$, THF, -78°C, 2h; (g) CF_3COOH, r.t., 4h.

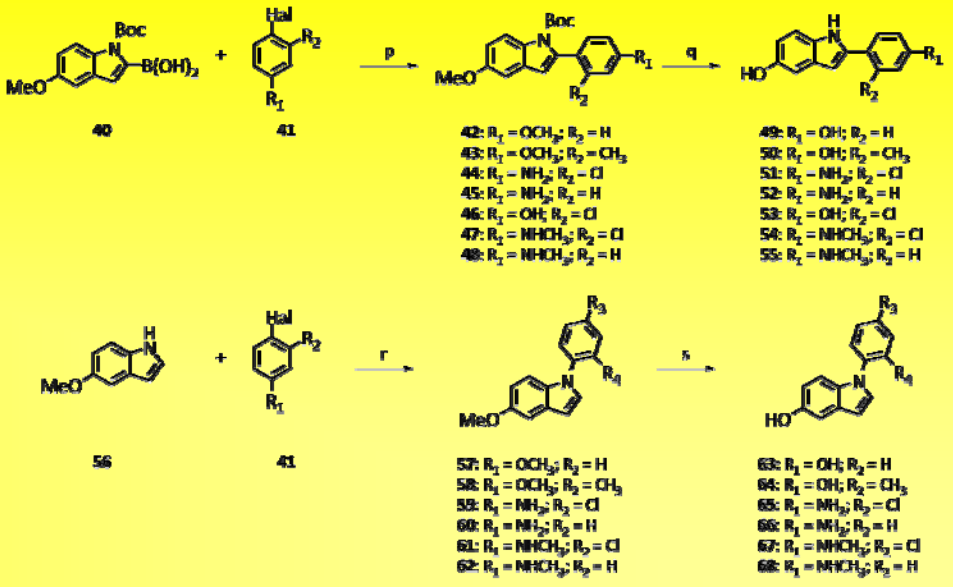
GENISTEIN DERIVATIVES





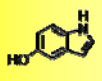
(h) 1) DIPEA, CH_2Cl_2, 0°C, 30 min; 2) MEMCl, 0°C, 30 min; (i) DMF/DMA, MW, 85°C, 1h; (l) I_2, $CHCl_3$, Pyridine; (m) phenylboronic acid, Na_2CO_3, Pd/C 10%, DME - H_2O 1:1; (n) 1M BBr_3, CH_2Cl_2 dry (35), 12N HCl, $CHCl_3$ - MeOH 1:1 (36) or 4N HCl in dioxane (37); (o) 2.5M n-BuLi, $B(OiPr)_3$, THF dry.

5-HYDROXYINDOLE DERIVATIVES



(p) 2M Na_2CO_3, tetrakis $Pd(PPh_3)_4$, DME, H_2O, 95-100°C, 2-5h; (q) 1M BBr_3, CH_2Cl_2 dry, -78°C (1h)→r.t. (12h); (r) K_2CO_3, CuI, *D*-proline, DMSO, 100-120°C, 24-72h (57-60) or K_3PO_4, CuI, *N,N'*-dimethylethylenediamine, toluene dry, 110-120°C (61, 62); (s) 1M BBr_3, CH_2Cl_2 dry, -78°C (1h)→ r.t. (12h).

ALLOSTERIC MODULATORS



COMPOUND												
	NICOTINE	ANABASEINE	ANABASEINE HCl	10 HCl	11 HCl	12 HCl	13 HCl	14 HCl	16 HCl	26 HCl	27 HCl	28 HCl
α3β4 [^{3}H]Epi - K_i (nM)	481	1760 (33)	107 (33)	155 (20)	108 (20)	48 (17)	29.8 (32)	194 (35)	80 (24)	70.8 (30)	77.2 (33)	4.74 (37)
α4β2 [^{3}H]Epi - K_i (nM)	11.1	182 (16)	66.8 (15)	1450 (37)	2040 (23)	1770 (21)	5020 (43)	32700 (137)	744 (38)	18800 (91)	11500 (62)	3790 (44)
α7 [^{125}I]α-BgTx - K_i (nM)	1600	137 (47)	31.5 (43)	384 (53)	2370 (57)	204 (44)	43.2 (37)	2560 (30)	821 (73)	343 (47)	394 (38)	11.3 (29)
Selectivity α3β4 *vs* α4β2	0.02	0.10	0.62	9.35	18.89	36.88	168.46	168.56	9.3	265.54	148.96	799.58
Selectivity α3β4 *vs* α7	3.33	0.08	0.29	2.48	21.94	4.25	1.45	13.20	10.26	4.84	5.10	2.38

PHARMACOLOGICAL RESULTS OF ANABASEINE DERIVATIVES

Binding affinities of compounds **10-14**, **16**, **26-28** for nAChR subtypes: α3β4 (HEK 293 cell), α4β2 (rat cortical membrane) and α7 (rat hippocampal membrane). Receptors were labeled with [^{3}H]Epibatidine (α3β4, α4β2) or with [^{125}I]α-bungarotoxin.