In this study, we described the properties of a thiazolylidene analog, A-716096, to elucidate biochemical neurotransmitter release, electrophysiological activity and behavioral effects *in vivo*. A-716096 was found to potentiate ACh-evoked α7 nAChR currents in oocytes expressing rat or human α7 nAChRs, but did not potentiate other nAChR subtypes (hα4β2 and hα3β4) in FLIPR-based $Ca^{2+}$ influx assays. A-716096 enhanced agonist-evoked phospho-ERK in PC12 cells as well as α7 nAChR-evoked [$^3$H] NE release in SH-SY5Y cells. Like other α7 PAMs (NS1738, TQS and PNU-120596), A-716096 did not displace the binding of either [$^3$H] MLA or [$^3$H] A-585539 to rat cortical membranes. Co- or pre-application of A-716096 amplified choline-evoked α7-like current responses in hippocampal CA1 slices and enhanced synaptic inhibitory activity in dentate gyrus in electrophysiological studies. Consistent with *in vitro* data, *in vivo* administration of A-716096 in mice increased dose-dependently phosphorylation of the downstream signaling protein, CREB. *In vivo* evoked-potential EEG recordings revealed that A-716096 improved sensory gating in DBA2 mice, a strain that exhibits natural deficits on this pre-attention measure. Taken together, these results demonstrate that A-716096 is a valuable tool compound with which to further study mechanism of action and other physiological effects of PAMs including modulation of synaptic effects and signaling mechanisms critical for learning and memory.

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**2.12**

### 2,2-Dimethylcyclopropyl-benzamides: Novel positive allosteric modulators of α7 nAChRs

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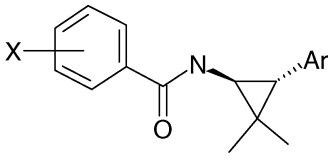
Activation of $\alpha_7$ nicotinic acetylcholine receptor (nAChR-$\alpha_7$) has been shown by pre-clinical and clinical evidence to improve cognitive function and a number of partial or full agonists are in advanced clinical trials, among them GTS-21, EVP-6124, AZD-0328 and R34787/MEM3454. Positive allosteric modulators of this ion channel offer the option of enhancing the endogenous signal of acetylcholine while avoiding the rapid desensitization and long-lasting deactivation caused by agonists. A prototypic agent in this class is PNU-120596. The identification and early optimization of a novel series of 2,2-dimethylcyclopropyl-benzamides as positive modulators of the nAChR-$\alpha_7$ channel is described.

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**2.13**

### *In vitro* and *in vivo* characterization of PheTQS, a novel α7 nAChR positive allosteric modulator

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PheTQS ((3aR, 4S, 9bS)-4-(4-methylphenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-8-sulfonamide, WO2004098600) facilitated nicotine (10 μM)-evoked responses in GH4C1 cells stably expressing human α7 nAChRs with a $pEC_{50} = 7.4 \pm 0.2$ and exhibited >30-fold selectivity vs. the 5-$HT_3$ receptor and α4β2 and α1, α3-containing nAChRs. PheTQS also facilitated ACh (300 μM)-evoked currents in rat cultured hippocampal neurons with a $pEC_{50} = 7.0 \pm 0.2$ to a maximum of 6191±955% of control response charge, but did not activate the receptor in the absence of ACh at up to 3 μM. Bath application of PheTQS (1 μM) mediated an MLA-sensitive potentiation of currents evoked by local ejection of ACh (1 mM) onto CA1 stratum radiatum interneurons in rat hippocampal slices. PheTQS exhibited good brain exposure following oral administration (Brain $C_{max}$ = 1540 ng/g, 10 mg/kg p.o.) but had no affect on activity measures up to 32 mg/kg in the rat. PheTQS (30 mg/kg, p.o.) elicited a significant increase in extracellular levels of dopamine in the prefrontal cortex and significantly increased c-Fos immunoreactivity in the central nucleus of the amygdala and the shell of the nucleus accumbens. PheTQS (10 mg/kg, i.v.) enhanced auditory gating in anaesthetised DBA2 mice and this effect was abolished by prior administration of α-bungarotoxin (1.25 nmol, i.c.v.). PheTQS (10 and 30 mg/kg, p.o.) attenuated deficits in pre-pulse inhibition in isolation-reared rats and significantly improved performance in a rat novel object recognition task. Thus, PheTQS is a selective α7 nAChR positive allosteric modulator which exhibits efficacy in rodent sensory gating and cognition models suggesting potential therapeutic utility in psychiatric disorders.

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**2.14**

### Dual allosteric modulators of neuronal nicotinic-acetylcholine and GABAA receptors

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We have designed a molecule that incorporates selective negative allosteric modulation of $GABA_A$ α5 receptors and positive modulation of α7 neuronal nicotinic receptors (nAChRs). This molecule termed 2-228 represents the first known compound with putative cognition enhancing properties derived from simultaneous modulation of both $GABA_A$ and nAChRs. The research goal is to develop a positive allosteric modulator of α7 nAChRs that