

# Synthesis, in vitro evaluation and molecular docking of a new class of indolylpropyl benzamidopiperazines as dual AChE and SERT ligands for Alzheimer's disease

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During the last decade, the one drug-one target strategy has resulted to be inefficient in facing diseases with complex ethiology like Alzheimer's disease and many others. In this context, the multitarget paradigm has emerged as a promising strategy. Based on this consideration, we aim to develop novel molecules as promiscuous ligands acting in two or more targets at the same time. For such purpose, a new series of indolylpropyl-piperazinyl oxoethyl-benzamido piperazines were synthesized and evaluated as multitarget-directed drugs for the serotonin transporter (SERT) and acetylcholinesterase (AChE). The ability to decrease  $\beta$ -amyloid levels as well as cell toxicity of all

compounds were also measured. In vitro results showed that at least four compounds displayed promising activity against SERT and AChE. Compounds 18 and 19 ( $IC_{50} = 3.4$  and  $3.6 \mu M$  respectively) exhibited AChE inhibition profile in the same order of magnitude as donepezil (DPZ,  $IC_{50} = 2.17 \mu M$ ), also displaying nanomolar affinity in SERT. Moreover, compounds 17 and 24 displayed high SERT affinities ( $IC_{50} = 9.2$  and  $1.9$  nM respectively) similar to the antidepressant citalopram, and significant micromolar AChE activity at the same time. All the bioactive compounds showed a low toxicity profile in the range of concentrations studied. Molecular docking allowed us to rationalize the binding mode of the synthesized compounds in both targets. In addition, we also show that compounds 11 and 25 exhibit significant  $\beta$ -amyloid lowering activity in a cell-based assay, 11 (50% inhibition,  $10 \mu M$ ) and 25 (35% inhibition,  $10 \mu M$ ). These results suggest that indolylpropyl benzamidopiperazines based compounds constitute promising leads for a multitargeted approach for Alzheimer's disease. © 2020 Elsevier Masson SAS

AChE

Alzheimer's disease

Dual-active compounds

Indole derivatives

Multitarget

SERT

1 [4 [3 (1h indol 3 yl)propyl]piperazin 1 yl] 2 (4 benzoylpiperazin 1 yl)ethan 1 one

1 [4 [3 (1h indol 3 yl)propyl]piperazin 1 yl] 2 [4 (2 bromobenzoyl)piperazin 1 yl]ethan 1 one

1 [4 [3 (1h indol 3 yl)propyl]piperazin 1 yl] 2 [4 (3 bromobenzoyl)piperazin 1 yl]ethan 1 one

1 [4 [3 (1h indol 3 yl)propyl]piperazin 1 yl] 2 [4 (3 chlorobenzoyl)piperazin 1 yl]ethan 1 one

1 [4 [3 (1h indol 3 yl)propyl]piperazin 1 yl] 2 [4 (3 fluorobenzoyl)piperazin 1 yl]ethan 1 one

1 [4 [3 (1h indol 3 yl)propyl]piperazin 1 yl] 2 [4 (3methoxybenzoyl)piperazin 1 yl]ethan 1 one

1 [4 [3 (1h indol 3 yl)propyl]piperazin 1 yl] 2 [4 (4 chlorobenzoyl)piperazin 1 yl]ethan 1 one

1 [4 [3 (1h indol 3 yl)propyl]piperazin 1 yl] 2 [4 (4 fluorobenzoyl)piperazin 1 yl]ethan 1 one

1 [4 [3 (1h indol 3 yl)propyl]piperazin 1 yl] 2 [4 (4 methoxybenzoyl)piperazin 1 yl]ethan 1 one

1 [4 [3 (1h indol 3 yl)propyl]piperazin 1 yl] 2 [4 (4bromobenzoyl)piperazin 1 yl]ethan 1 one

1 [4 [3 (1h indol 3 yl)propyl]piperazin 1 yl] 2 [4 (4methylbenzoyl)piperazin 1 yl]ethan 1 one

1 [4 [3 (5 fluoro 1h indol 3 yl)propyl]piperazin 1 yl] 2 [4 (4 methylbenzoyl)piperazin 1 yl]ethan 1 one

1 [4 [3 (5 fluoro 1h indol 3 yl)propyl]piperazin 1 yl] 2 [4 (4 fluorobenzoyl)piperazin 1 yl]ethan 1 one

1 [4 [3 (5 fluoro 1h indol 3 yl)propyl]piperazin 1 yl] 2 [4 (4 methoxybenzoyl)piperazin 1 yl]ethan 1 one

2 (4 benzoylpiperazin 1 yl) 1 [4 [3 (5 fluoro 1h indol 3 yl)propyl]piperazin 1 yl]ethan 1 one

2 [4 (4 bromobenzoyl)piperazin 1 yl] 1 [4 [3 (5 fluoro 1h indol 3 yl)propyl]piperazin 1 yl]ethan 1 one

2 [4 (4 chlorobenzoyl)piperazin 1 yl] 1 [4 [3 (5 fluoro 1h indol 3 yl)propyl]piperazin 1 yl]ethan 1 one

cholinesterase inhibitor

piperazine derivative

tert butyl 4 [2 (4 benzoylpiperazin 1 yl)acetyl]piperazine 1 carboxylate

tert butyl 4 [2 [4 (2 bromobenzoyl)piperazin 1 yl]acetyl]piperazine 1 carboxylate

tert butyl 4 [2 [4 (3 bromobenzoyl)piperazin 1 yl]acetyl]piperazine 1 carboxylate

tert butyl 4 [2 [4 (3 chlorobenzoyl)piperazin 1 yl]acetyl]piperazine 1 carboxylate

tert butyl 4 [2 [4 (3 fluorobenzoyl)piperazin 1 yl]acetyl]piperazine 1 carboxylate

tert butyl 4 [2 [4 (4 bromobenzoyl)piperazin 1 yl]acetyl]piperazine 1 carboxylate

tert butyl 4 [2 [4 (4 chlorobenzoyl)piperazin 1 yl]acetyl]piperazine 1 carboxylate

tert butyl 4 [2 [4 (4 fluorobenzoyl)piperazin 1 yl]acetyl]piperazine 1 carboxylate

tert butyl 4 [2 [4 (4 methoxybenzoyl)piperazin 1 yl]acetyl]piperazine 1 carboxylate

tert butyl 4 [2 [4 (4 methylbenzoyl)piperazin 1 yl]acetyl]piperazine 1 carboxylate

unclassified drug

unindexed drug

Alzheimer disease

animal cell

Article

carbon nuclear magnetic resonance

cell viability

cholinesterase inhibition

controlled study

drug synthesis

HEK293 cell line

human

human cell

hydrogen bond

IC50

in vitro study

molecular docking

mouse

Neuro-2a cell line

nonhuman

proton nuclear magnetic resonance

SH-SY5Y cell line