

Synthesis and Biological Activity of New Donepezil-Hydrazinonicotinamide Hybrids

Authors

E. Żurek, P. Szymański, E. Mikiciuk-Olasik

Affiliation

Department of Pharmaceutical Chemistry and Drug Analyses, Medical University, Lodz, Poland

Key words

- inhibitors of acetylcholinesterase
- Alzheimer's disease
- donepezil

Abstract

Currently available treatment used in Alzheimer's disease is based on acetylcholinesterase inhibitors, e.g. donepezil, tacrine, galantamine, and rivastigmine. In the present study some derivatives of donepezil were synthesized, and their potential anticholinesterase properties were investigated using the colorimetric Ellman's method. These compounds were syn-

thesized by condensation between indanone derivatives and the hydrazine nicotinamide moiety (Hynic). For received derivatives, the selectivity and the IC_{50} values for acetylcholinesterase and butyrylcholinesterase were calculated. All the tested compounds exhibited lower affinity for AChE than donepezil and higher affinity for BChE than donepezil. Compound **33** showed the most selectivity for AChE among the obtained indanone derivatives.

Introduction

Alzheimer's disease (AD) is a slow progressive, degenerative disorder of the CNS. It is the most common form of dementia accounting for about 50–60% of all cases of dementia among persons over 65 years of age. Currently, an estimated 4.5 million older people suffer with Alzheimer's disease (AD), and researchers predict that by 2050 the number could nearly triple, to 13.5 million [1].

This disease is important not only because of the number of affected patients but also because it leads to significant physical and emotional burden on families and caregivers.

Alzheimer's disease is characterized by the loss of memory and learning ability, together with a reduced ability to perform basic activities of daily living. AD patients exhibit marked neuropsychiatric symptoms such as apathy, irritability, anxiety, depression, hallucinations and verbal and physical agitation [2].

Studies performed during the last 20 years revealed that disordered cholinergic transmission is behind cognitive impairment present in Alzheimer's disease patients. The disorders in transmission result from the reduced number of cholinergic neurons in brain regions associated with higher cognitive functions, i.e. in the neocortex and hippocampus, as well as from the

decreased level of choline acetyltransferase, leading to impaired synthesis and uptake of acetylcholine (ACh) neurotransmitter [3,4]. As ACh is degraded by cholinesterase, it stands to reason that cholinergic transmission can be improved by inhibiting the activity of this enzyme.

2 kinds of choline esterases catalyzing hydrolysis of choline esters exist in the central nervous system: acetylcholinesterase (AChE), the so-called true esterase, and butyrylcholinesterase (BChE), referred to as pseudocholinesterase or non-specific cholinesterase. AChE is bound to the membrane of cholinergic neurons, whereas BChE is present both in the neurons and in the glial cells. Both enzymes show 65% homology, and the main differences pertain to their substrate specificity.

Acetylcholinesterase selectively and rapidly hydrolyzes acetylcholine in cholinergic synapses. In turn, butyrylcholinesterase can also hydrolyze butyrylcholine and some medications and drugs, aside from acetylcholine. Moreover, it regulates cholinergic transmission in states of acetylcholinesterase deficiency. In healthy individuals, AChE accounts for 80% of esterase activity within the central nervous system, whereas the remaining 20% is provided by BChE. In Alzheimer's disease, the activity of AChE can be reduced to 67% of normal level in certain brain regions; simultaneously, an

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Correspondence

Dr. E. Żurek

Department of Pharmaceutical
Chemistry and Drug Analyses
Medical University
ul. Muszyńskiego 1
90-151 Lodz
Poland
Tel.: +48/42/677 9290
Fax: +48/42/677 9250
elzbieta.zurek@umed.lodz.pl

increase in BChE level is observed, reaching up to 165% of its normal level [5, 6].

Cholinesterase inhibitors (ChEI) constitute an important group of compounds used in the symptomatic treatment of Alzheimer's disease. They support cholinergic transmission by inhibiting acetylcholinesterase cleavage. Most commonly administered agents from this group include donepezil and galantamine, both being acetylcholinesterase inhibitors (AChEI), and rivastigmine, which inhibits both acetylcholinesterase and butyrylcholinesterase (AChEI, BChEI). Studies revealed that the administration of such double inhibitors is particularly favorable at later stages of Alzheimer's disease [7–10].

In the study, synthesis and biological evaluation of a series of new donepezil derivatives with hydrazine nicotinate moiety as potential cholinesterase inhibitors are described.

Inhibitory activity of acetylcholinesterase and butyrylcholinesterase of the obtained compounds was studied using the method of Ellman, to determine the rate of hydrolysis of acetylthiocholine (ATCh) in the presence the inhibitor [11].

Material and Methods



Chemistry

Reaction was monitored by TLC using DC-Alufolien Kieselgel 60F254 plates (Merck), with detection by UV lamp (254 nm). Melting points were measured on an Electrothermal apparatus in open capillaries and are uncorrected. Column chromatography was performed using silica gel 60 (230–400 mesh, Merc). IR spectra were recorded in KBr using a Mattson Infinity Series FT-IR spectrophotometer. ¹H NMR spectra were recorded with a Varian Mercury 300 MHz spectrometer, using tetramethylsilane as internal standard. Elemental analyses were recorded using Perkin Elmer series II, CHNSO, Analyzer 2400.

Mass spectra were performed by the Centre of Molecular and Macromolecular Studies in Lodz.

6-hydrazinopyridine-3-carboxylic acid (1)

6-chloronicotinic acid (50.8 mmol) was added to 80% hydrazine hydrate (930.0 mmol) and placed in a 100 °C oil bath for 4 h. The homogenous reaction mixture was cooled to room temperature and concentrated to dryness to give a white solid. The solid was dissolved in water and on acidification to pH 5.5 with concentrated hydrochloric acid, a precipitate was formed. The precipitate was isolated by filtration and was washed with ethanol and ether, and dried in vacuum.

Yield 85%. Mp. 295–297 °C. IR (KBr) cm^{-1} 1690, 3229, 3308. ¹H NMR (DMSO) δ : 8.5 (1H, s, COOH), 8.2 (1H, s, CHN), 7.8 (1H, d, CCHC), 6.7 (1H, d, CCHC), 3.3 (1H, s, CNH), 2.5 (2H, d, NH₂). Anal. calc. for C₆H₇N₃O₂ (%): C 47.06, H 4.61, N 27.44; Found (%): C 46.78, H 4.35, N 27.11.

6-Boc-hydrazinopyridine-3-carboxylic acid (2)

To a solution **1** (9.8 mmol) and triethyl amine (11.8 mmol) in DMF (10 mL) was added di-*tert*-butyl dicarbonate (9.8 mmol). The reaction mixture became homogenous after 1 h and stirring was continued for 16 h at room temperature. The reaction mixture was concentrated to dryness under reduced pressure to give brown solid. Recrystallization from ethyl acetate gave product **2** as a white solid.

Yield 75%. Mp. 285–287 °C. IR (KBr) cm^{-1} : 1611, 1706, 3248. ¹H NMR (DMSO) δ : 12.6 (1H, s, COOH), 8.9 (2H, d, NHC), 8.6 (1H, s,

CCHC), 8.0 (1H, d, CCHC), 6.5 (1H, d, CCHC), 3.3 (1H, d, CNH), 1.4 (9H, s, BOC). Anal. calc. for C₁₁H₁₅N₃O₄ (%): C 52.17, H 5.93, N 16.59; Found (%): C 52.08, H 5.73, N 16.67.

General procedure for the synthesis of compounds (5) and (6)

5-hydroxyindan-1-one (5.0 mmol), paraformaldehyd (5.0 mmol) and the corresponding amine were dissolved in isopropanol (20 mL). Afterwards, the pH of the suspension was adjusted to 2–3 with concentrated hydrochloric acid. The mixture was refluxed for 5 h. The solution was then evaporated to the half of the initial volume and crude precipitate was filtered off. The dry solid was recrystallized from methanol.

5-hydroxy-2-piperidin-1-ylmethylindan-1-one hydrochloride (5)

Yield 78%. Mp. 165–167 °C. IR (KBr) cm^{-1} : 1593, 1697, 2737, 2498, 3020. ¹H NMR (DMSO) δ : 10.4 (1H, b, OH), 7.5 (1H, m, Ar), 6.7–6.8 (2H, m, Ar), 3.5 (2H, d, CHCH₂), 3.4 (d, 2H, NCH₂), 3.0–3.1 (4H, m, NCH₂), 2.7–2.8 (1H, m, COCH), 1.5–1.7 (6H, m, 3·CH₂). MS (FAB) (m/z): 246 (M+1). Anal. calc. for C₁₅H₂₀ClNO₂ (%): C 63.94, H 7.17, N 4.98; Found (%): C 63.69, H 7.09, N 4.87.

2-(4-benzylpiperidin-1-ylmethyl)-5-hydroxyindan-1-one hydrochloride (6)

Yield 68%. Mp. 170–172 °C. IR (KBr) cm^{-1} : 739, 1600, 1695, 2694, 2951, 3021. ¹H NMR (DMSO) δ : 10.2 (1H, b, OH), 7.8 (1H, m, Ar), 7.2–7.4 (5H, m, Ar), 6.8–6.9 (2H, m, Ar), 3.6–3.7 (1H, m, COCH), 3.4 (2H, d, NCH₂), 3.0 (2H, d, CHCH₂), 2.7 (2H, t, ArCH₂), 2.5–2.6 (4H, m, NCH₂), 1.3–1.6 (5H, m, CH₂CHCH₂). MS (FAB) (m/z): 336 (M+1). Anal. calc. for C₂₂H₂₆ClNO₂ (%): C 71.05, H 7.05, N 3.77; Found (%): C 69.78, H 6.91, N 3.53.

General procedure for synthesis of compounds (7) and (8)

To solution of 1 M NaOH (20.1 mmol) in *tert*-butyl alcohol (6 mL) was added the corresponding *n*-bromoalkylamine hydrobromide (9.1 mmol) and di-*tert*-butyl dicarbonate (10.1 mmol). The reaction mixture was stirred for 12 h in room temperature, and then was washed with 0.1 M HCl, and 5% NaHCO₃, and brine. The organic layer was dried over Na₂SO₄ and concentrated *in vacuo* to give *N*-Boc-3-bromoalkylamine as yellow oil.

N-Boc-2-bromoethylamine (7)

Yield 84%. IR (KBr) cm^{-1} : 1692, 2968, 3280. ¹H NMR (DMSO) δ : 6.9 (1H, s, NH), 3.6 (2H, t, BrCH₂), 2.9 (2H, m, NCH₂), 1.4 (9H, s, Boc).

N-Boc-3-bromopropylamine (8)

Yield 87%. IR (KBr) cm^{-1} : 1690, 2972, 3285. ¹H NMR (DMSO) δ : 6.9 (1H, s, NH), 3.5 (2H, t, BrCH₂), 3.0 (2H, m, NCH₂), 1.8–1.9 (2H, m, CCH₂), 1.5 (9H, s, Boc).

5-Boc-aminopentanol (9)

To a mixture of 5-aminopentanol (10.0 mmol) in acetonitrile (50 mL) was dropwise added di-*tert*-butyl dicarbonate (10.0 mmol) dissolved in acetonitrile (5 mL). The mixture was stirred for 24 h at room temperature. Volatile components were evaporated. The residue was taken up in ethyl acetate. This was washed twice with 0.5 M citric acid and once with H₂O. After the mixture was dried MgSO₄, and the solvent was evaporated. The residue was vacuum desiccated overnight to yield yellow oil.

Yield 79%. IR (KBr) cm^{-1} : 1688, 2934, 3342. ^1H NMR (DMSO) δ : 6.7 (1H, s, NH), 4.4 (1H, s, OH), 3.4 (2H, t, OCH_2), 2.9 (2H, m, NCH_2), 1.4–1.6 (6H, m, CCH_2C), 1.3 (9H, s, Boc).

General procedure for synthesis of compounds (10–13)

A solution of N-Boc-3-bromoalkylamine **7**, **8** (3.5 mmol) in CH_3CN (30 mL) was added to a mixture of **5**, **6** (3.0 mmol) and K_2CO_3 (9.0 mmol) in CH_3CN (30 mL). The mixture was heated under reflux for 12 h. The inorganic material was filtered off and the solvent was evaporated *in vacuo*. The crude residue was extracted with CH_2Cl_2 , washed with H_2O and brine, dried over Na_2SO_4 , and concentrated *in vacuo* to give oil.

5-(2-Boc-aminoethoxy)-2-piperidin-1-ylmethylindan-1-one (10)

Yield 65%. IR (KBr) cm^{-1} : 1690, 1706, 2737, 2946, 3202. ^1H NMR (DMSO) δ : 7.7 (1H, m, Ar), 6.8–6.9 (2H, m, Ar), 6.7 (1H, t, NH), 4.1 (2H, t, OCH_2), 3.6 (2H, d, CH_2CH), 3.4 (2H, d, NCH_2), 3.1–3.2 (4H, m, 2· NCH_2), 3.0 (2H, m, NHCH_2), 2.6–2.7 (1H, m, COCH), 1.5–1.6 (6H, m, 3· CH_2), 1.2 (9H, s, Boc).

2-(4-benzylpiperidin-1-ylmethyl)-5-(2-Boc-aminoethoxy)-indan-1-one (11)

Yield 67%. IR (KBr) cm^{-1} : 724, 1672, 1714, 2740, 2953, 3196. ^1H NMR (DMSO) δ : 7.7 (1H, m, Ar), 7.2–7.4 (5H, m, Ar), 6.8–6.9 (2H, m, Ar), 6.7 (1H, t, NH), 4.1 (2H, t, OCH_2), 3.6 (2H, d, CH_2CH), 3.4 (2H, d, NCH_2), 3.1–3.2 (4H, m, 2· NCH_2), 3.0 (2H, m, NHCH_2), 2.8 (2H, t, ArCH_2), 2.6–2.7 (1H, m, COCH), 1.4–1.6 (5H, m, 2· CH_2 , 1·CH), 1.2 (9H, s, Boc).

5-(3-Boc-aminopropoxy)-2-piperidin-1-ylmethylindan-1-one (12)

Yield 61%. IR (KBr) cm^{-1} : 1689, 1701, 2741, 2948, 3215. ^1H NMR (DMSO) δ : 7.7 (1H, m, Ar), 6.8–6.9 (2H, m, Ar), 6.7 (1H, t, NH), 4.1 (2H, t, OCH_2), 3.6 (2H, d, CH_2CH), 3.4 (2H, d, NCH_2), 3.1–3.2 (4H, m, 2· NCH_2), 3.0 (2H, m, NHCH_2), 2.7–2.8 (1H, m, COCH), 1.7–1.8 (6H, m, 3· CH_2), 1.4–1.5 (2H, m, CCH_2C), 1.1 (9H, s, Boc).

2-(4-benzylpiperidin-1-ylmethyl)-5-(3-Boc-aminopropoxy)-indan-1-one (13)

Yield 65%. IR (KBr) cm^{-1} : 729, 1671, 1709, 2745, 2949, 3253. ^1H NMR (DMSO) δ : 7.7 (1H, m, Ar), 7.2–7.4 (5H, m, Ar), 6.8–6.9 (2H, m, Ar), 6.7 (1H, t, NH), 4.1 (2H, t, OCH_2), 3.6 (2H, d, CH_2CH), 3.4 (2H, d, NCH_2), 3.1–3.2 (4H, m, 2· NCH_2), 3.0 (2H, m, NHCH_2), 2.7–2.8 (1H, m, COCH), 2.6 (2H, t, ArCH_2), 1.6–1.8 (5H, m, 2· CH_2 , 1·CH), 1.3–1.4 (2H, m, CCH_2C), 1.2 (9H, s, Boc).

General procedure for synthesis of compounds (14) and (15)

TEA (2.0 mmol) and triphenylphosphine (Ph_3P) (2.5 mmol) were added to solution **5**, **6** (2.0 mmol) in anhydrous THF (5 mL) under argon. The mixture was stirred and cooled in an ice bath (-5°C to 0°C), while diethylazodicarboxylate (2.5 mmol) was added dropwise. After 15 min, N-Boc-aminopentanol (2.0 mmol) in DMF (1 mL) was added all at once. The reaction mixture was stirred overnight, and warmed to room temperature. The mixture was concentrated under reduced pressure. The crude product in the form of oil was purified by silica gel column chromatography, using as eluent mixtures of solvents: chloroform: methanol: NH_3 saturated 9:1:0.5.

5-(5-Boc-aminopentyloxy)-2-piperidin-1-ylmethylindan-1-one (14)

Yield 48%. IR (KBr) cm^{-1} : 1686, 1699, 2735, 2946, 3210. ^1H NMR (DMSO) δ : 7.7 (1H, m, Ar), 6.8–6.9 (2H, m, Ar), 6.7 (1H, t, NH), 3.9 (2H, t, OCH_2), 3.6 (2H, d, CH_2CH), 3.4 (2H, d, NCH_2), 3.2–3.3 (4H, m, 2· NCH_2), 3.1 (2H, m, NHCH_2), 2.8–2.9 (1H, m, COCH), 1.7–1.8 (6H, m, 3· CH_2), 1.3–1.4 (6H, m, CCH_2C), 1.1 (9H, s, Boc).

2-(4-benzylpiperidin-1-ylmethyl)-5-(Boc-aminopentyloxy)-indan-1-one (15)

Yield 45%. IR (KBr) cm^{-1} : 736, 1675, 1710, 2739, 2957, 3268. ^1H NMR (DMSO) δ : 7.6 (1H, m, Ar), 7.2–7.4 (5H, m, Ar), 6.8–6.9 (2H, m, Ar), 6.7 (1H, t, NH), 3.9 (2H, t, OCH_2), 3.6 (2H, d, CH_2CH), 3.4 (2H, d, NCH_2), 3.2–3.3 (4H, m, 2· NCH_2), 3.1 (2H, m, NHCH_2), 2.8–2.9 (1H, m, COCH), 2.7 (2H, t, ArCH_2), 1.5–1.7 (5H, m, 2· CH_2 , 1·CH), 1.3–1.4 (6H, m, CCH_2C), 1.1 (9H, s, Boc).

General procedure for preparation of compounds (16–21)

A solution of **10–15** (0.5 mmol) in anhydrous THF (5 mL) was cooled to -20°C and stirred for 30 min. Etherate HCl was added dropwise to the reaction mixture under pH=1. The precipitate was collected by suction filtration, washed with ether and dried in desiccator to give a white solid.

5-(2-aminoethoxy)-2-piperidin-1-ylmethylindan-1-one hydrochloride (16)

Yield 78%. Mp. $145\text{--}148^\circ\text{C}$. IR (KBr) cm^{-1} : 1697, 2737, 2947, 3367. ^1H NMR (DMSO) δ : 7.7 (1H, s, Ar), 6.8–6.9 (2H, m, Ar), 4.1 (2H, t, OCH_2), 3.6 (2H, d, CH_2CH), 3.4 (2H, d, NCH_2), 3.1–3.2 (4H, m, 2· NCH_2), 3.0 (2H, m, NHCH_2), 2.6–2.7 (1H, m, COCH), 2.3 (2H, s, NH_2), 1.5–1.6 (6H, m, 3· CH_2). Anal. calc. for $\text{C}_{17}\text{H}_{25}\text{ClN}_2\text{O}_2$ (%): C 62.86, H 7.76, N 8.62; Found (%): C 62.38, H 7.52, N 8.41.

5-(2-aminoethoxy)-2-(4-benzylpiperidin-1-ylmethyl)-indan-1-one hydrochloride (17)

Yield 70%. Mp. $168\text{--}171^\circ\text{C}$. IR (KBr) cm^{-1} : 738, 1695, 2694, 2944, 3370. ^1H NMR (DMSO) δ : 7.7 (1H, s, Ar), 7.2–7.4 (5H, m, Ar), 6.8–6.9 (2H, m, Ar), 4.1 (2H, t, OCH_2), 3.6 (2H, d, CH_2CH), 3.4 (2H, d, NCH_2), 3.1–3.2 (4H, m, 2· NCH_2), 3.0 (2H, m, NHCH_2), 2.8 (2H, t, ArCH_2), 2.5–2.6 (1H, m, COCH), 2.1 (2H, s, NH_2), 1.2–1.4 (5H, m, 2· CH_2 , 1·CH). Anal. calc. for $\text{C}_{24}\text{H}_{31}\text{ClN}_2\text{O}_2$ (%): C 69.46, H 7.53, N 6.75; Found (%): C 69.11, H 7.23, N 6.61.

5-(3-aminopropoxy)-2-piperidin-1-ylmethylindan-1-one hydrochloride (18)

Yield 76%. Mp. $139\text{--}142^\circ\text{C}$. IR (KBr) cm^{-1} : 1689, 2740, 2948, 3360. ^1H NMR (DMSO) δ : 7.7 (1H, s, Ar), 6.8–6.9 (2H, m, Ar), 4.1 (2H, t, OCH_2), 3.6 (2H, d, CH_2CH), 3.4 (2H, d, NCH_2), 3.1–3.2 (4H, m, 2· NCH_2), 3.0 (2H, m, NHCH_2), 2.7–2.8 (1H, m, COCH), 2.3 (2H, s, NH_2), 1.6–1.7 (6H, m, 3· CH_2), 1.2–1.4 (2H, m, CCH_2C). Anal. calc. for $\text{C}_{18}\text{H}_{27}\text{ClN}_2\text{O}_2$ (%): C 63.80, H 8.03, N 8.27; Found (%): C 63.27, H 7.85, N 8.11.

5-(3-aminopropoxy)-2-(4-benzylpiperidin-1-ylmethyl)-indan-1-one hydrochloride (19)

Yield 76%. Mp. $165\text{--}167^\circ\text{C}$. IR (KBr) cm^{-1} : 730, 1687, 2732, 2949, 3363. ^1H NMR (DMSO) δ : 7.7 (1H, s, Ar), 7.2–7.4 (5H, m, Ar), 6.8–6.9 (2H, m, Ar), 4.1 (2H, t, OCH_2), 3.6 (2H, d, CH_2CH), 3.4 (2H, d, NCH_2), 3.1–3.2 (4H, m, 2· NCH_2), 3.0 (2H, m, NHCH_2), 2.7–2.8 (1H, m, COCH), 2.6 (2H, t, ArCH_2), 2.2 (2H, s, NH_2), 1.5–1.8 (5H, m, 2· CH_2 , 1·CH), 1.2–1.3 (2H, m, CCH_2C). Anal. calc. for

$C_{25}H_{33}ClN_2O_2$ (%): C 69.99, H 7.75, N 6.53; Found (%): C 69.58, H 7.43, N 6.32.

5-(5-aminopentyloxy)-2-piperidin-1-ylmethylindan-1-one hydrochloride (20)

Yield 69%. Mp. 125–128 °C. IR (KBr) cm^{-1} : 1696, 2735, 2946, 3365. 1H NMR (DMSO) δ : 7.7 (1H, s, Ar), 6.8–6.9 (2H, m, Ar), 3.9 (2H, t, OCH_2), 3.6 (2H, d, CH_2CH), 3.4 (2H, d, NCH_2), 3.2–3.3 (4H, m, 2· NCH_2), 3.1 (2H, m, $NHCH_2$), 2.8–2.9 (1H, m, COCH), 2.2 (2H, s, NH_2), 1.6–1.7 (6H, m, 3· CH_2), 1.2–1.4 (6H, m, CCH_2C). Anal. calc. for $C_{20}H_{31}ClN_2O_2$ (%): C 65.47, H 8.52, N 7.63; Found (%): C 65.09, H 8.34, N 7.41.

5-(5-aminopentyloxy)-2-(4-benzylpiperidin-1-ylmethyl)indan-1-one hydrochloride (21)

Yield 74%. Mp. 160–163 °C. IR (KBr) cm^{-1} : 736, 1700, 2735, 2948, 3375. 1H NMR (DMSO) δ : 7.6 (1H, s, Ar), 7.2–7.4 (5H, m, Ar), 6.8–6.9 (2H, m, Ar), 3.9 (2H, t, OCH_2), 3.6 (2H, d, CH_2CH), 3.4 (2H, d, NCH_2), 3.2–3.3 (4H, m, 2· NCH_2), 3.1 (2H, m, $NHCH_2$), 2.8–2.9 (1H, m, COCH), 2.7 (2H, t, $ArCH_2$), 2.2 (2H, s, NH_2), 1.3–1.7 (5H, m, 2· CH_2 , 1·CH), 1.2–1.3 (2H, m, CCH_2C). Anal. calc. for $C_{27}H_{37}ClN_2O_2$ (%): C 70.95, H 8.16, N 6.13; Found (%): C 70.61, H 7.96, N 5.87.

General procedure for preparation of compounds (22–27)

1,1'-carbonyldiimidazole (1.0 mmol) was added to solution **2** in anhydrous THF (10 mL).

The mixture was stirred for 4 h in room temperature. Next, the corresponding amine **16–21** (1.0 mmol) and TEA (1.0 mmol) were added. The resulting amber solution was stirred for 20 h. The solvent was evaporated under reduced pressure, water was added, and the resultant mixture was extracted twice with CH_3Cl . The combined organic extracts were washed with brine and then dried with anhydrous Na_2SO_4 . The solvent was evaporated under reduce pressure and the residue was purified by crystallization from methanol.

6-Boc-hydrazino-N-[2-(1-oxo-2-piperidin-1-ylmethylindan-5-yloxy)-ethyl]-nicotinamide (22)

Yield 45%. Mp. 174–177 °C. IR (KBr) cm^{-1} : 1641, 1696, 1711, 2974, 3375. 1H NMR (DMSO) δ : 8.7 (1H, s, NHC), 8.5 (1H, s, Ar), 8.2 (1H, t, COCN), 7.9 (1H, d, Ar), 7.6 (1H, s, Ar), 6.8–6.9 (2H, m, Ar), 6.5 (1H, d, Ar), 4.1 (2H, t, OCH_2), 3.6 (2H, d, CH_2CH), 3.4 (2H, d, NCH_2), 3.3 (1H, d, CNH), 3.1–3.2 (4H, m, 2· NCH_2), 3.0 (2H, m, $NHCH_2$), 2.6–2.7 (1H, m, COCH), 1.5–1.6 (6H, m, 3· CH_2), 1.2 (9H, s, Boc). Anal. calc. for $C_{28}H_{37}N_5O_5$ (%): C 64.23, H 7.12, N 13.37; Found (%): C 63.87, H 7.23, N 13.15.

N-[-[2-(4-benzylpiperidin-1-ylmethyl)-1-oxoindan-5-yloxy]-ethyl]-6-Boc-hydrazinonicotinamide (23)

Yield 47%. Mp. 192–195 °C. IR (KBr) cm^{-1} : 742, 1601, 1695, 1702, 2989, 3278. 1H NMR (DMSO) δ : 8.8 (1H, s, NHC), 8.4 (1H, s, Ar), 8.3 (1H, s, CONH), 7.8 (1H, d, Ar), 7.7 (1H, s, Ar), 7.2–7.4 (5H, m, Ar), 6.8–6.9 (2H, m, Ar), 6.5 (1H, d, Ar), 4.1 (2H, t, OCH_2), 3.6 (2H, d, CH_2CH), 3.4 (2H, d, NCH_2), 3.3 (1H, s, CNH), 3.1–3.2 (4H, m, 2· NCH_2), 3.0 (2H, m, $NHCH_2$), 2.8 (2H, t, $ArCH_2$), 2.5–2.6 (1H, m, COCH), 1.3–1.6 (5H, m, 2· CH_2 , 1·CH), 1.2 (9H, s, Boc). Anal. calc. for $C_{35}H_{43}N_5O_5$ (%): C 68.49, H 7.06, N 11.41; Found (%): C 67.96, H 6.78, N 11.34.

6-Boc-hydrazino-N-[3-(1-oxo-2-piperidin-1-ylmethylindan-5-yloxy)-propyl]-nicotinamide (24)

Yield 50%. Mp. 176–179 °C. IR (KBr) cm^{-1} : 1640, 1694, 1710, 2985, 3315. 1H NMR (DMSO) δ : 8.7 (1H, s, NHC), 8.5 (1H, s, Ar), 8.1 (1H, t, CONH), 7.8 (1H, d, Ar), 7.6 (1H, s, Ar), 6.8–6.9 (2H, m, Ar), 6.6 (1H, d, Ar), 4.1 (2H, t, OCH_2), 3.7 (2H, d, CH_2CH), 3.4 (2H, d, NCH_2), 3.3 (1H, d, CNH), 3.1–3.2 (4H, m, 2· NCH_2), 3.0 (2H, m, $NHCH_2$), 2.6–2.7 (1H, m, COCH), 1.6–1.7 (6H, m, 3· CH_2), 1.2–1.4 (2H, m, CCH_2C), 1.0 (9H, s, Boc). Anal. calc. for $C_{29}H_{39}N_5O_5$ (%): C 64.78, H 7.31, N 13.03; Found (%): C 64.97, H 7.28, N 13.23.

N-[3-[2-(4-benzylpiperidin-1-ylmethyl)-1-oxoindan-5-yloxy]-propyl]-6-Boc-hydrazinonicotinamide (25)

Yield 49%. Mp. 194–197 °C. IR (KBr) cm^{-1} : 734, 1595, 1692, 1707, 2990, 3287. 1H NMR (DMSO) δ : 8.8 (1H, s, NHC), 8.4 (1H, s, Ar), 8.1 (1H, s, CONH), 7.9 (1H, d, Ar), 7.6 (1H, s, Ar), 7.2–7.4 (5H, m, Ar), 6.8–6.9 (2H, m, Ar), 6.5 (1H, d, Ar), 4.1 (2H, t, OCH_2), 3.6 (2H, d, CH_2CH), 3.4 (2H, d, NCH_2), 3.3 (1H, d, CNH), 3.1–3.2 (4H, m, 2· NCH_2), 3.0 (2H, k, $NHCH_2$), 2.7–2.8 (1H, m, COCH), 2.6 (2H, t, $ArCH_2$), 1.7–1.9 (5H, m, 2· CH_2 , 1·CH), 1.2–1.3 (2H, m, CCH_2C), 1.0 (9H, s, Boc). Anal. calc. for $C_{36}H_{45}N_5O_5$ (%): C 68.88, H 7.23, N 11.16; Found (%): C 68.41, H 6.91, N 10.77.

6-Boc-hydrazino-N-[5-(1-oxo-2-piperidin-1-ylmethylindan-5-yloxy)-pentyl]-nicotinamide (26)

Yield 45%. Mp. 181–183 °C. IR (KBr) cm^{-1} : 1639, 1697, 1706, 2991, 3352. 1H NMR (DMSO) δ : 8.7 (1H, s, NHC), 8.5 (1H, s, Ar), 8.2 (1H, t, CONH), 7.9 (1H, d, Ar), 7.6 (1H, s, Ar), 6.8–6.9 (2H, m, Ar), 6.5 (1H, d, Ar), 3.9 (2H, t, OCH_2), 3.6 (2H, d, CH_2CH), 3.4 (2H, d, NCH_2), 3.3 (1H, d, CNH), 3.1–3.2 (4H, m, 2· NCH_2), 3.0 (2H, m, $NHCH_2$), 2.8–2.9 (1H, m, COCH), 1.6–1.7 (6H, m, 3· CH_2), 1.1–1.3 (6H, m, CCH_2C), 1.0 (9H, s, Boc). Anal. calc. for $C_{31}H_{43}N_5O_5$ (%): C 65.82, H 7.66, N 12.38; Found (%): C 65.46, H 7.50, N 12.21.

N-[5-[2-(4-benzylpiperidin-1-ylmethyl)-1-oxoindan-5-yloxy]-pentyl]-6-Boc-hydrazinonicotinamide (27)

Yield 42%. Mp. 201–204 °C. IR (KBr) cm^{-1} : 732, 1601, 1690, 1711, 2985, 3297. 1H NMR (DMSO) δ : 8.8 (1H, s, NHC), 8.4 (1H, s, Ar), 8.1 (1H, t, CONH), 7.9 (1H, d, Ar), 7.6 (1H, s, Ar), 7.2–7.4 (5H, m, Ar), 6.8–6.9 (2H, m, Ar), 6.4 (1H, d, Ar), 3.9 (2H, t, OCH_2), 3.7 (2H, d, CH_2CH), 3.5 (2H, d, NCH_2), 3.2–3.4 (5H, m, 2· NCH_2 , CNH), 3.1 (2H, m, $NHCH_2$), 2.8–2.9 (1H, m, COCH), 2.7 (2H, t, $ArCH_2$), 1.6–1.8 (5H, m, 2· CH_2 , 1·CH), 1.2–1.3 (6H, m, CCH_2C), 1.1 (9H, s, Boc). Anal. calc. for $C_{38}H_{49}N_5O_5$ (%): C 69.59, H 7.53, N 10.68; Found (%): C 69.14, H 7.38, N 10.31.

General procedure for preparation of compounds (28–33)

0.5 mmol **22–27** was dissolved in anhydrous THF (5 mL) and ether saturated HCl was dropwise added. Mixture was stirred in room temperature and a precipitate was formed. The precipitate was isolated and the solid was washed with ether.

6-hydrazino-N-[2-(1-oxo-2-piperidin-1-ylmethylindan-5-yloxy)-ethyl]-nicotinamide hydrochloride (28)

Yield 65%. Mp. 175–178 °C. IR (KBr) cm^{-1} : 1639, 1696, 2787, 2974, 3154. 1H NMR (DMSO): 8.5 (1H, s, Ar), 8.2 (1H, t, CNHC), 7.9 (1H, d, Ar), 7.6 (1H, s, Ar), 6.8–6.9 (2H, m, Ar), 6.5 (1H, d, Ar), 4.1 (2H, t, OCH_2), 3.6 (2H, d, CH_2CH), 3.4 (2H, d, NCH_2), 3.3 (1H, d, CNH), 3.1–3.2 (4H, m, 2· NCH_2), 3.0 (2H, m, $NHCH_2$), 2.6–2.7 (1H, m, COCH), 2.2 (2H, d, NH_2), 1.5–1.6 (6H, m, 2· CH_2 , 1·CH).

MS (FAB) (m/z): 425 (M+1). Anal. calc. for $C_{23}H_{30}ClN_5O_3$ (%): C 60.06, H 6.57, N 15.23; Found (%): C 59.71, H 6.40, N 14.92.

N-[2-[2-(4-benzylpiperidin-1-ylmethyl)-1-oxoindan-5-yloxy]-ethyl]-6-hydrazinonicotinamide hydrochloride (29)

Yield 62%. Mp. 185–188°C. IR (KBr) cm^{-1} : 740, 1633, 1696, 2693, 2989, 3252. 1H NMR (DMSO) δ : 8.4 (1H, s, Ar), 8.3 (1H, s, CONH), 7.8 (1H, d, Ar), 7.7 (1H, s, Ar), 7.2–7.4 (5H, m, Ar), 6.8–6.9 (2H, m, Ar), 6.5 (1H, d, Ar), 4.1 (2H, t, OCH_2), 3.6 (2H, d, CH_2CH), 3.4 (2H, d, NCH_2), 3.3 (1H, s, CNH), 3.1–3.2 (4H, m, 2· NCH_2), 3.0 (2H, m, $NHCH_2$), 2.8 (2H, t, $ArCH_2$), 2.5–2.6 (1H, m, COCH), 2.2 (2H, d, NH_2), 1.2–1.4 (5H, m, 2· CH_2 , 1·CH). MS (FAB) (m/z): 516 (M+1). Anal. calc. for $C_{30}H_{36}ClN_5O_3$ (%): C 65.50, H 6.60, N 12.73; Found (%): C 65.28, H 6.46, N 12.59.

6-hydrazino-N-[3-(1-oxo-2-piperidin-1-ylmethylindan-5-yloxy)-propyl]-nicotinamide hydrochloride (30)

Yield 63%. Mp. 170–173°C. IR (KBr) cm^{-1} : 1642, 1690, 2698, 2985, 3159. 1H NMR (DMSO) δ : 8.5 (1H, s, Ar), 8.2 (1H, t, CNHC), 7.9 (1H, d, Ar), 7.6 (1H, s, Ar), 6.8–6.9 (2H, m, Ar), 6.5 (1H, d, Ar), 4.1 (2H, t, OCH_2), 3.6 (2H, d, CH_2CH), 3.4 (2H, d, NCH_2), 3.3 (1H, d, CNH) 3.1–3.2 (4H, m, 2· NCH_2), 3.0 (2H, m, $NHCH_2$), 2.6–2.7 (1H, m, COCH), 2.3 (2H, d, NH_2), 1.6–1.7 (6H, m, 3· CH_2), 1.2–1.4 (2H, m, CCH_2C). MS (FAB) (m/z): 439 (M+1). Anal. calc. for $C_{24}H_{32}ClN_5O_3$ (%): C 60.81, H 6.80, N 14.78; Found (%): C 60.49, H 6.64, N 14.53.

N-[3-[2-(4-benzylpiperidin-1-ylmethyl)-1-oxoindan-5-yloxy]-propyl]-6-hydrazinonicotinamide hydrochloride (31)

Yield 59%. Mp. 180–183°C. IR (KBr) cm^{-1} : 739, 1642, 1692, 2698, 2991, 3242. 1H NMR (DMSO) δ : 8.4 (1H, s, Ar), 8.3 (1H, s, CONH), 7.8 (1H, d, Ar), 7.7 (1H, s, Ar), 7.2–7.4 (5H, m, Ar), 6.8–6.9 (2H, m, Ar), 6.5 (1H, d, Ar), 4.1 (2H, t, OCH_2), 3.6 (2H, d, CH_2CH), 3.4 (2H, d, NCH_2), 3.3 (1H, s, CNH), 3.1–3.2 (4H, m, 2· NCH_2), 3.0 (2H, m, $NHCH_2$), 2.8 (2H, t, $ArCH_2$), 2.5–2.6 (1H, m, COCH), 2.1 (2H, d, NH_2), 1.3–1.7 (5H, m, 2· CH_2 , 1·CH), 1.1–1.2 (2H, m, CCH_2C). MS (FAB) (m/z): 529 (M+1). Anal. calc. for $C_{31}H_{38}ClN_5O_3$ (%): C 66.00, H 6.79, N 12.41; Found (%): C 65.56, H 6.61, N 12.27.

6-hydrazino-N-[5-(1-oxo-2-piperidin-1-ylmethylindan-5-yloxy)-pentyl]-nicotinamide hydrochloride (32)

Yield 59%. Mp. 161–164°C. IR (KBr) cm^{-1} : 1644, 1697, 2734, 2990, 3187. 1H NMR (DMSO) δ : 8.5 (1H, s, Ar), 8.2 (1H, t, CNHC), 7.9 (1H, d, Ar), 7.6 (1H, s, Ar), 6.8–6.9 (2H, m, Ar), 6.5 (1H, d, Ar), 4.0 (2H, t, OCH_2), 3.6 (2H, d, CH_2CH), 3.4 (2H, d, NCH_2), 3.3 (1H, d, CNH), 3.1–3.2 (4H, m, 2· NCH_2), 3.0 (2H, m, $NHCH_2$), 2.6–2.7 (1H, m, COCH), 2.3 (2H, d, NH_2), 1.5–1.6 (6H, m, 3· CH_2), 1.1–1.3 (6H, m, CCH_2C). MS (FAB) (m/z): 467 (M+1). Anal. calc. for $C_{26}H_{36}ClN_5O_3$ (%): C 62.60, H 7.32, N 7.06; Found (%): C 61.87, H 6.95, N 7.15.

N-[5-[2-(4-benzylpiperidin-1-ylmethyl)-1-oxoindan-5-yloxy]-pentyl]-6-hydrazinonicotinamide hydrochloride (33)

Yield 57%. Mp. 177–180°C. IR (KBr) cm^{-1} : 741, 1641, 1690, 2700, 2985, 3229. 1H NMR (DMSO) δ : 8.4 (1H, s, Ar), 8.2 (1H, s, CONH), 7.8 (1H, d, Ar), 7.7 (1H, s, Ar), 7.2–7.4 (5H, m, Ar), 6.8–6.9 (2H, m, Ar), 6.5 (1H, d, Ar), 4.1 (2H, t, OCH_2), 3.6 (2H, d, CH_2CH), 3.4 (2H, d, NCH_2), 3.3 (1H, s, CNH), 3.1–3.2 (4H, m, 2· NCH_2), 2.9 (2H, m, $NHCH_2$), 2.8 (2H, t, $ArCH_2$), 2.4–2.5 (1H, m, COCH), 2.1

(2H, d, NH_2), 1.3–1.7 (5H, m, 2· CH_2 , 1·CH), 1.2–1.3 (6H, m, CCH_2C). MS (FAB) (m/z): 558 (M+1). Anal. calc. for $C_{33}H_{42}ClN_5O_3$ (%): C 66.93, H 7.15, N 11.83; Found (%): C 66.68, H 6.96, N 11.69.

Inhibition Studies on AChE and BChE

▼

The activity of acetylcholinesterase (AChE) and butyrylcholinesterase inhibitors was measured spectrophotometrically according to the colorimetric method of Ellman (1961) with some modification. The AChE activity was determined in a mixture containing the assay solution consisting of a phosphate buffer (0.1M, pH 8.0) with the addition of a solution of 5,5'-dithiobisnitrobenzoic acid (DTNB, 0.05 mL, 0.5 M), AChE (5 U/mL) and the appropriate inhibitor (tested compounds). The final assay volume was 3 mL.

Inhibitor curves of the different derivatives were obtained using 7 concentrations of acetylthiocholine iodide as the substrate of the enzymatic reaction lasting 1 min. Enzyme activity was determined by measuring the absorbance at 412 nm after 1 min at 37°C with Perkin Elmer Lambda 25 UV/VIS Spectrophotometer. Sample without inhibitor was consistently available to provide 100% of AChE activity. The reaction rates and the percent of inhibition due to the presence of tested compounds were compared. Each reaction was independently repeated at least 3 times.

Determination of butyrylcholinesterase (BChE) inhibitory activity was carried out in a similar manner using 5 units/L of BChE instead of AChE in the final volume of 3 mL.

The IC_{50} , defined as the concentration of each compound that reduces the enzymatic activity (AChE or BChE) by 50% with respect to that without inhibitors, was calculated by non-linear and linear regression.

DTNB, enzymes (C2629 and C4290) and acetylthiocholine iodide were purchased from Sigma-Aldrich.

Results and Discussion

▼

Chemistry

In the present investigation compound **2** was synthesized following the method described by Abrams (Fig. 1) [12]. 6-chloronicotinic acid and hydrazine hydrate were refluxed at 100°C. In the next step, hydrazine N-atom was protected by di-*tert* butyl dicarbonate ((*t*-BuOCO)₂O) to give 6-Boc-hydrazinopyridine-3-carboxylic acid **2**. Condensation commercially available 5-hydroxyindan-1-one and secondary amines (piperidine **3**, 4-benzylpiperidine **4**) with paraformaldehyd gave **5**, **6** (Fig. 2) [13, 14]. In the next step, derivatives of 5-hydroxyindan-1-one **5**, **6** coupled with alkyl linker through etheric bond. Based on our study, we determined 2 methods for synthesizing compounds with a variable length of the carbon chain at C-5. N-Boc-aminoethoxy derivatives **10**, **11** were used to perform O-alkylation of **5**, **6** with N-Boc-2-bromoethylamine **7** using potassium carbonate in refluxing acetonitrile [15]. Similar reaction conditions employing N-Boc-3-bromopropylamine **8**, led to the desired **12**, **13** (Fig. 3a). Treatment of **5**, **6** under Mitsunobu conditions, using 5-aminopentanol with N-atom protected by Boc **9** provided **14**, **15** (Fig. 3b) [16–18]. N-atom of n-bromoalkylamine and N-atom of 5-aminopentanol were protected following the methods described previously [15, 19]. All the obtained N-Boc-aminoalkoxy derivatives **10–15** were deprotected in the presence of ether saturated HCl, affording **16–21** (Fig. 3c). Coupling reac-

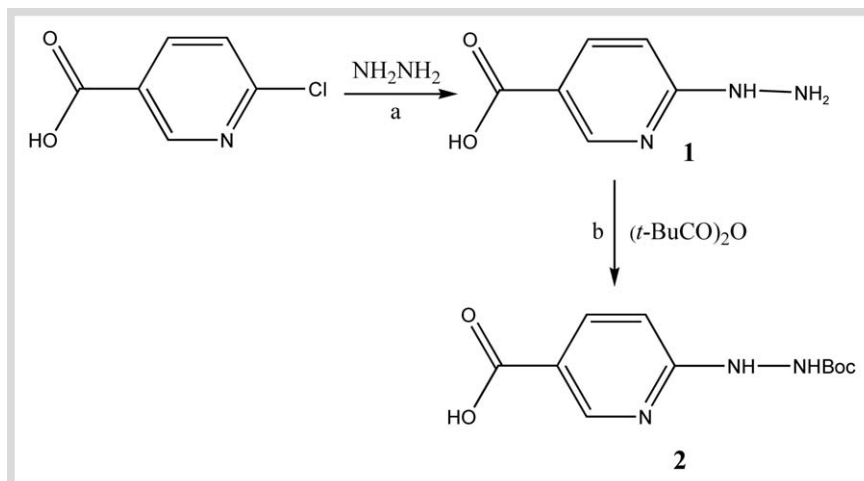


Fig. 1 Synthesis of compounds **1** and **2**. Reagents: **a** 85% NH_2NH_2 ; **b** $(t\text{-BuCO})_2\text{O}$, TEA, DMF.

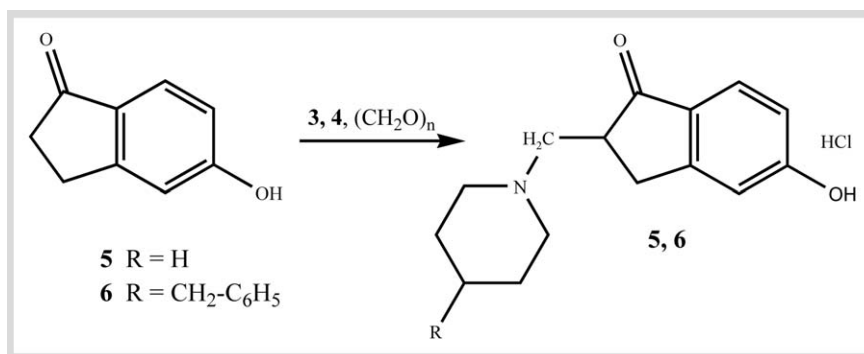


Fig. 2 Synthesis of compounds **5** and **6**. Reagents: **3, 4**, $(\text{CH}_2\text{O})_n$, isopropanol, HCl, reflux 4 h.

tion of the intermediates **16–21** with 6-Boc-hydrazinopyridine-carboxylic acid **2** in the presence carbonyldiimidazole (CDI) led to the formation of the desired compound **22–27** (► Fig. 3d) [20–22]. The final compounds **28–33** were obtained from **22–27**, which were deprotected in the presence of the ether saturated HCl (► Fig. 3e).

Biochemistry

Anticholinesterase activities of the obtained compounds **28–33** were determined by modification of Ellman's spectrophotometric method.

Parameters of the enzymatic reaction K_m and V_{max} were obtained by linear regression of the reaction rate as a function of substrate concentration (► Table 1). To determine the type of inhibition, the Michaelis-Menten equation was plotted using Lineweaver-Burk linear transformation ($1/v$ vs. $1/[S]$). K_i constants were then calculated using non linear regression [23–26].

The inhibitory activities against both AChE and BChE of the compounds **28–33** together with the reference donepezil are reported in ► Table 2, expressed as IC_{50} values [27]. All the tested compounds showed a higher inhibitory activity on AChE than BChE, and showed lower inhibition of AChE compared with donepezil. Compound **33** showed the greatest affinity for AChE, while compound **28** was found to be the least effective against this enzyme.

We also assessed the impact of the activity of the constructed derivatives obtained against AChE. After analyzing biological activity of the compounds with the same length of carbon chain, it can be concluded that replacing piperidine with benzylpiperidine substituent in compounds **28, 30**, and **32** (and obtaining compounds **29, 31**, and **33**, respectively) was reflected by a slight increase in activity against AChE. For example, the activity of

ethyl derivative of benzylpiperidine **29** increased 9-fold as compared to the ethyl derivative of piperidine **28**. Variation of the alkyl linker length between the 2 groups, indanone and Hynic, for piperidine derivatives **28, 30, 32** revealed the pentylene-linked substance to be more active than their propylene and ethylene linked counterparts. In the case of derivatives of N-benzylpiperidine **29, 31, 33**, the influence of alkylene-linker length was negligible and compounds **31** and **33** showed nearly equal potency in anti-AChE assay.

All the tested compounds showed higher inhibition of BChE than the reference (donepezil).

The selectivity toward AChE (IC_{50} ratio of BChE/AChE) and BChE (IC_{50} ratio of AChE/BChE) of the obtained compounds and reference inhibitor (donepezil) were also determined. All the tested compounds showed a higher selectivity for AChE than for BChE, while the selectivity with respect to AChE was less than in the case of the standard (donepezil), selectivity to BChE was greater than for donepezil. Compound **33** was found to be the most potent with regards to AChE activity and the most selective for AChE among the obtained indanone derivatives. The selectivity of this derivative was nearly 50-fold higher compared to the least selective derivative **28**. Concurrently, compound **28** was characterized by the highest selectivity against BChE.

Drug-modeling studies

Docking studies of donepezil-hydrazinonicotinamide hybrids on the active site of electric eel AChE inhibited by donepezil (PDB: 1EA5) revealed their mode of structural and positional requirements for potential activity. These studies elucidated the interaction between electric eel AChE and inhibitors **29–33**. The AChE-Inhibitor complex was generated using Cache software (Fujitsu). Docking analysis performed with these inhibitors

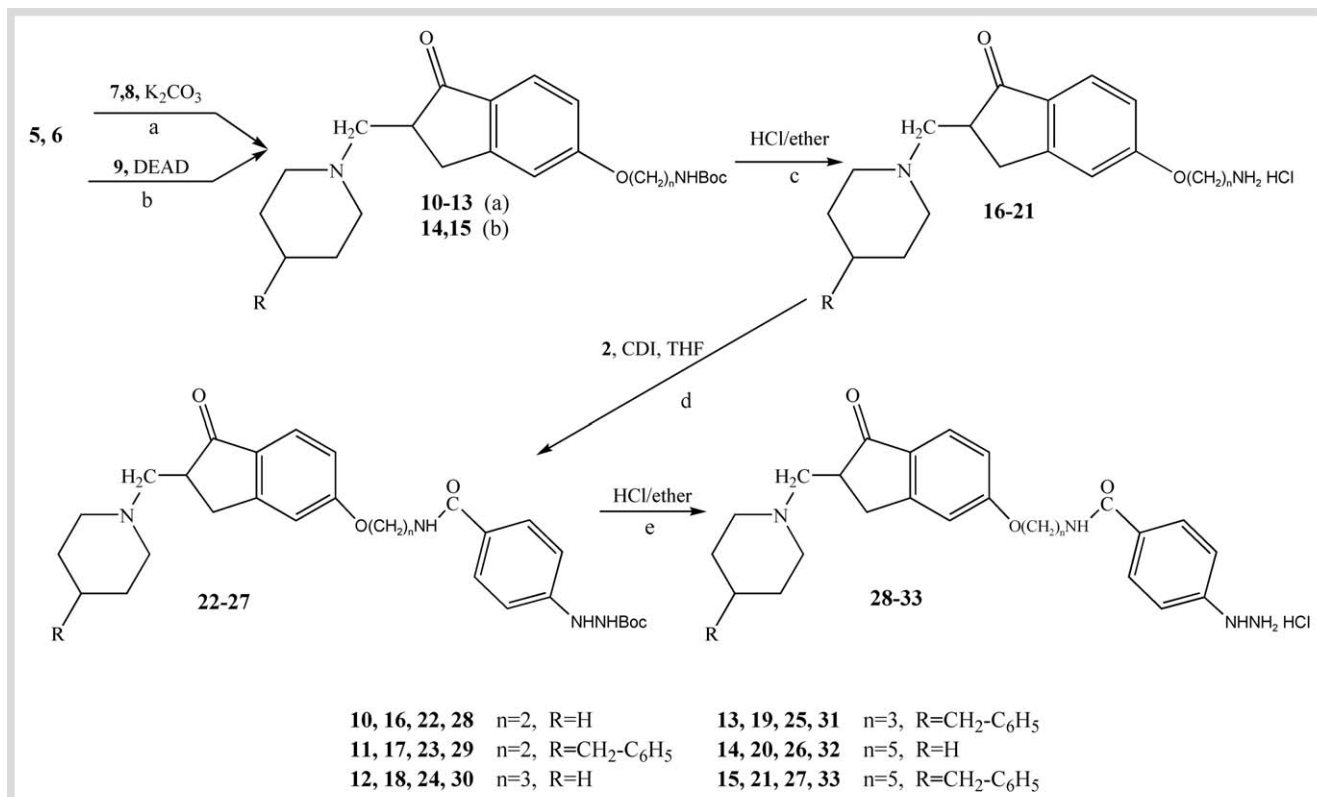


Fig. 3 Synthesis of compounds **10–33**: **a** **7, 8**, K_2CO_3 , acetonitril, reflux, 12 h; **b** **9**, Ph_3P , DEAD, TEA, THF; **c** HCl/ether; **d** CDI, TEA, THF, room temp., 20 h; **e** HCl/ether.

Table 1 Statistical parameters and values of K_m and V_{max} for AChE and BChE.

Parameters	AChE	BChE
K_m (μM)	0.096453	0.082586
V_{max} ($\mu M/mL/min$)	0.103247	0.094610
R^2	0.9895	0.9857
Standard error	0.0193	0.0017

Table 2 IC_{50} values for activities on AChE and BChE.

Com-pounds	AChE inhibition (IC_{50} , μM)	BChE inhibition (IC_{50} , μM)	Selectivity for AChE [†]	Selectivity for BChE [‡]
28	1.879×10^{-4}	1.026×10^{-3}	5.459	0.183
29	2.066×10^{-5}	1.285×10^{-3}	62.204	0.017
30	1.164×10^{-4}	8.981×10^{-4}	7.715	0.130
31	1.768×10^{-5}	2.233×10^{-3}	126.464	0.008
32	4.229×10^{-5}	1.431×10^{-3}	33.817	0.029
33	1.087×10^{-5}	2.659×10^{-3}	248.776	0.004
donepezil	0.601×10^{-5}	3.444×10^{-3}	573.096	0.002

[†] Selectivity for AChE is defined as $IC_{50}(BChE)/IC_{50}(AChE)$

[‡] Selectivity for BChE is defined as $IC_{50}(AChE)/IC_{50}(BChE)$

show that compounds **29–33** bind with the total score of -184.794 , -196.681 , -165.113 , -195.338 , -181.939 , respectively. (○ Fig. 4)

Conclusion

In summary, series of indanone derivatives with hydrazine nicotinate moiety were synthesized and their anticholinesterase

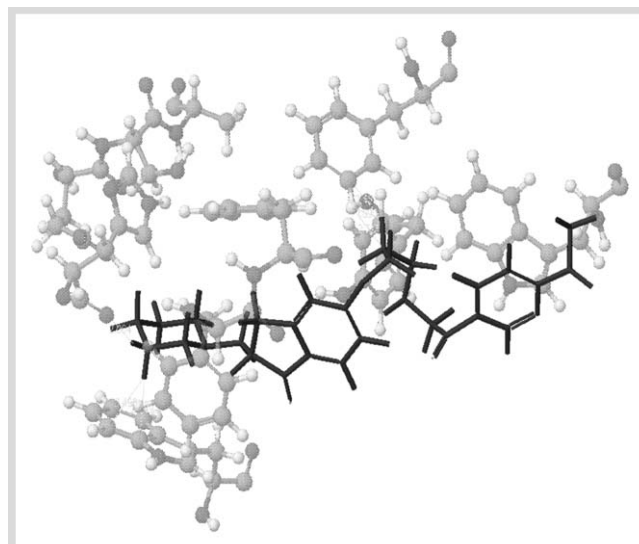


Fig. 4 The model of docking of compound **33** with main aminoacids of AChE active site.

activities were evaluated. All tested compounds exhibited a higher affinity to AChE than for BChE. Similarly, their selectivity for AChE was greater than for BChE. When compared to donepezil, all synthesized molecules were less active with regards to inhibiting AChE and slightly more active in inhibiting BChE. All tested derivatives were less selective for AChE and BChE, their selectivity is higher than the reference (donepezil). The results indicate that compound **33** (N-benzylpiperidine derivative) was the most effective inhibitor of AChE, additionally, it

had the highest selectivity for the enzyme. Compound **30** (piperidine derivative) was most active against BChE, however, compound **28** showed the highest selectivity for BChE.

Acknowledgments

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Conflict of Interest

The authors have declared no conflict of interest.

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