İsmail Okan Ateş, Asaf Evrim Evren, Begüm Nurpelin Sağlik and Leyla Yurttaş*

New indane derivatives containing 2-hydrazinothiazole as potential acetylcholinesterase and monoamine oxidase-B inhibitors

https://doi.org/10.1515/znc-2021-0058
Received February 26, 2021; accepted May 8, 2021;
published online May 28, 2021

Abstract: Although radical treatment of Alzheimer's and Parkinson's disease is not possible yet, it is aimed to slow the course of the disease and increase the life quality of individuals with the drugs used in the clinic at the present time. Successful results have been achieved in the use of cholinesterase inhibitors and monoamine oxidase inhibitors together in these neurodegenerative diseases. In this study, indane ring which are in the structure of anticholinesterase effective molecules and 2-hydrazinothiazole structure whose inhibitory activities reported on monoamine oxidase-B (MAO-B) were combined; 4-(substituted phenyl)-2-[2-(3-phenyl-2,3-dihydro-1*H*-inden-1-ylidene) hyd razinyl]thiazole derivatives (**3a–3i**) were synthesized as dual inhibitors. The structures of the compounds were verified by IR, ^{1}H-NMR, ^{13}C-NMR, and HRMS spectroscopy. When enzyme inhibition activities were evaluated, it was determined that the compounds **3a** (42.33%) and **3d** (42.39%) on acetylcholinesterase (AChE) enzyme; compounds **3g** (75.42%) and **3h** (60.33%) showed inhibition on MAO-B enzyme at most, at 10^{-3} M concentration.

Keywords: ADME prediction; anticholinesterase activity; indane; monoamine oxidase inhibition; thiazole.

***Corresponding author: Leyla Yurttaş**, Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Anadolu University, Eskişehir, Turkey, E-mail: lyurttas@anadolu.edu.tr
İsmail Okan Ateş and Begüm Nurpelin Sağlik, Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Anadolu University, Eskişehir, Turkey
Asaf Evrim Evren, Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Anadolu University, Eskişehir, Turkey; and Vocational School of Health Services, Bilecik Seyh Edebali University, Bilecik, Turkey. https://orcid.org/0000-0002-8651-826X

1 Introduction

The degeneration that occurs in the neuron and synapse structures of the central nervous system and increased levels of neurofibrillary tangles, neuritic plaques, and granulovacuolar degeneration cause loss of function and causes loss of cognitive activities described as Alzheimer's disease and dementia. Extracellular depositions of amyloid protein (β-AP), hyperphosphorylation of tau proteins, oxidative damage, apoptotic cell death, and cholinergic dysfunction are etiologic reasons of the disease [1–3]. As the accumulation of amyloid beta peptide (AP) in senile plaques is a consequence of the disease, recent researches have shown that tau protein plays a central role in the pathogenesis of AD, and therefore this protein becomes a diagnostic and therapeutic target for this disease [4]. Although there are many new target therapy approaches, the cholinergic hypothesis is still up-to-date and the drugs used in treatment mostly act on this target. In humans, there are two types of cholinesterases, acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE). Both of these enzymes catalyze the hydrolysis of acetylcholine. The point where the two enzymes differ from each other is their substrate selectivity, tissue localization and sensitivity. Acetylcholinesterase is found at the neuromuscular junction and chemical synapses which breaks down acetylcholine into choline esters. Its primary physiological function is the rapid hydrolysis of acetylcholine at the synapse and at the neuromuscular junction, thus terminating neural conduction. Considering the relationship of the disease with cholinergic deficiency in the brain, increasing the decreased cholinergic activity by preventing acetylcholine hydrolysis is targeted in the treatment. For this purpose, cholinesterase inhibitor drugs such as donepezil, galantamine, rivastigmine, and memantine are used clinically nowadays. In addition to Alzheimer's disease, various synthetic AChE inhibitors are used to alleviate the symptoms of neurological disorders such as myasthenia gravis, Lewy bodies, Parkinson's disease, and prophylactically in poisoning [5–7].

Monoaminoxidases are mitochondrial enzymes mostly found in gastrointestinal, hepatic, and neuronal tissues. They have important roles in the metabolism of released neurotransmitters that they catalyze the oxidative deamination of both endogenous and exogenous monoamines for detoxification. Two isoenzymes MAO-A and MAO-B are encoded in the human X-chromosomal Xp1 123 gene, and these two forms have homogeneity over 70%. Biochemically, the two forms can be distinguished by their substrates and inhibitor specificity; while MAO-A shows greater affinity for hydroxylated amines such as noradrenaline (NA) and serotonin (5-hydroxytryptamine, 5-HT); MAO-B shows greater affinity for nonhydroxylated amines such as benzylamine and β-phenylethylamine. Dopamine (DA) and tyramine show similar affinity for each form of enzyme. Selegiline (1-deprenyl) and rasagiline are selective inhibitors of MAO-B, while chlorgillin is a selective inhibitor of MAO-A. Monoamine oxidase A and B inhibitor drugs are mainly used in psychiatric (depression) and neurological diseases (Parkinson's) [8, 9]. In recent studies, it has been reported that the combination of cholinesterase and monoaminoxidase inhibitor drugs gives positive results in the treatment of Alzheimer's disease, in fact some anti Alzheimer drugs are successfully used in both Alzheimer's and Parkinson's diseases [10–12].

Indane ring was started to be searched after bacteriostatic effect of indan-1,3-dione derivatives was discovered in the 1930s. Indane ring exists in the structure of many natural compounds and drugs such as indinavir (HIV-1 protease inhibitor); indantadol (MAO-inhibitor), indatralin (amine uptake inhibitor), clidanac (anti inflammatory), indecainide (antiarrhythmic), indacrinone (diuretic), donepezil (anti Alzheimer's), rasagiline, ladostigil (neuroprotective), and hedulin (anticoagulant) (Figure 1) [13, 14]. Among its derivatives, 1-indanones are one of the most studied structures in terms of both synthetic chemistry and biological activity [15–17].

Since thiazole ring was first obtained in 1887, it has been reported in many studies due to the synthetic feasibility, wide range of applications in medicinal and industrial chemistry, and possessing frequently seen molecular skeleton in natural compounds. Thiazole and its ring analogs are found in the structure of biological active compounds such as penicillins and thiamine (vitamin B1) and drugs such as antibacterial sulfatiazole; anticancer bleomycin, dasatinib, thiazofurine; antibiotics such as cefdinir, cefepime, ceftriaxone, cefixime, ceftazimide; antifungal abafungin, ravuconazole, thiabendazole; antiviral ritonavir; anti inflammatory simeprevir; meloxicam, fanetizol, sudoksikam; antiparkinsonian pramipexole; antihistaminic famotidine, nizatidine, ebrotidine; and antiparasitic nitazoxanide [18, 19].

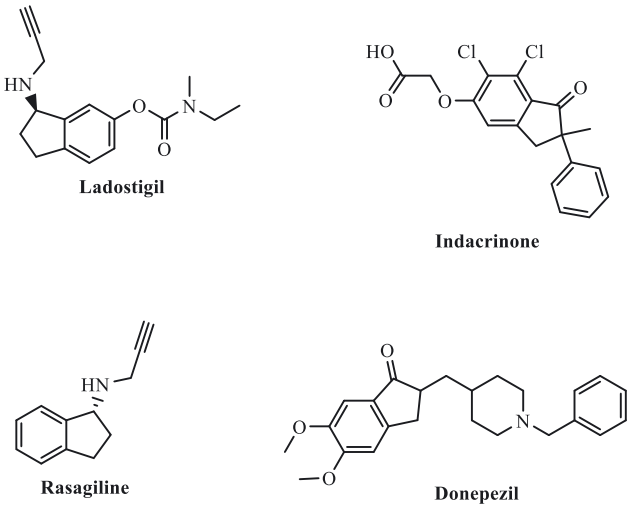
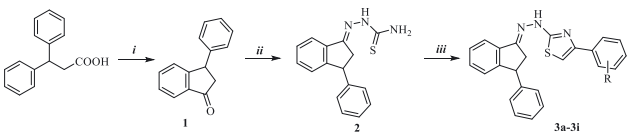


Figure 1: Some of the drugs containing indane ring.

Based on the obtained data, new indane derivatives bearing 2-hydrazinothiazole moiety were synthesized within the scope of this work and the inhibitory activities of the compounds on AChE and MAO-B enzymes were investigated.

2 Results and discussion

The final compounds in the study were obtained by a three-step synthesis procedure as shown Scheme 1. In the first step, 3,3-diphenylpropionic acid was heated with polyphosphoric acid under Friedel–Crafts reaction conditions to procure intramolecular cyclization. The Schiff base was formed with thiosemicarbazide from the obtained compound, 3-phenyl-1-indanone (**1**). In last step, the intermediate product containing thioamide residue (**2**) obtained in the last step and 2′-bromoacetophenones in α-haloketone structure were reacted according to the synthesis of Hantzsch thiazole synthesis to gain final compounds (**3a–3i**). The structure of the 4-(substituted phenyl)-2-[2-(3-phenyl-2,3-dihydro-1*H*-inden-1-ylidene)hydrazinyl]thiazole (**3a–3i**) derivatives were confirmed by using IR, ^{1}H-NMR, ^{13}C-NMR, and HRMS spectral methods.



Scheme 1: Synthesis of the compounds (**3a–3i**) Reagents and conditions ***i***: PPA, 90 °C, 7–8 h; ***ii***: TSC, EtOH, reflux, 2 h; and ***iii***: Phenylacetyl bromide derivatives, EtOH, rt, 2 h.

When the IR spectra of the titled compounds (**3a–3i**) were examined, common bonds belonging N–H, C=C and C=N, C–N bands and benzene ring were observed in all compounds. The stretching bands for N–H, C=C, and C=N bond were detected between the range of 3344–3190 cm^{-1} and 1641–1456 cm^{-1}. The band of C–O bond seen in methoxy-containing derivatives (**3b, 3c,** and **3h**) was determined in the range of 1284–1010 cm^{-1} together with the bands showing the C–N bond in all compounds, and the out-of-plane deformation bands of the substituted benzene ring were established between 837 and 696 cm^{-1}. Medium intensity bands were assigned at 1504 and 1308 cm^{-1} belonging to NO_2 substituent in the spectrum of the compound **3g**. The data obtained was compatible with the IR spectra of similar compounds [20].

The main structure of the 4-(substituted phenyl)-2-[2-(3-phenyl-2,3-dihydro-1*H*-inden-1-ylidene) hydrazinyl]thiazole (**3a–3i**) derivatives constitutes indane and thiazole rings. Besides these versatile rings, two phenyl rings and hydrazine functional group are also part of the skeleton seen in all compounds. When the ^{1}H-NMR spectra of the compounds are examined, C_3 proton of the indane ring was observed as double doublet ($J_{1,2}$: 4 and 8 Hz) at around 4.64 ppm, C_2 protons of the ring have been detected at two separate regions at 2.85–2.88 ppm ($J_{1,2}$: 4 and 18 Hz) and at 3.44–3.50 ppm ($J_{1,2}$: 8 and 18 Hz). This cleavage pattern was in full agreement with the ^{1}H-NMR spectra reported literature for similar compounds [21]. The common amino proton of the compounds was observed at the range of 11.15–11.38 ppm, and the signals belonging to aromatic protons were found at 6.85–8.13 ppm. When NMR spectra of the synthesized compounds were evaluated, it was seen that they had the same chemical shift and cleavage patterns with similar compounds in the literature [22].

E/Z isomerism can be seen in the compounds due to the imine (–C=N–) structure. When the NMR spectrum of the compounds was evaluated, it was determined that the only one type of isomer of the compounds was obtained, not as a mixture [23].

When the ^{13}C-NMR spectra of the compounds were examined, the C_2 carbon belonging to the indane ring resonated at 38.36–38.40 ppm and the C_3 carbon at 46.85–46.87 ppm. The peak at the range of 168.29–170.30 ppm was assigned to the 2nd carbon atom of the thiazole ring and the peaks of many aromatic carbon atoms were observed at the range of 102.40–163.63 ppm. In the spectra of 1,4-disubstituted phenyl containing derivatives, signals originating from equivalent carbons in the aromatic region were determined. Signals belonging to methoxy and methyl substituents were detected at around 55.60 ppm for compounds **3b, 3c,** and **3h** and at 21.29 ppm for compound **3d**. The findings are in agreement with the literature data [24].

HRMS results were showed that molecular weights of the compounds were compatible with the calculated values and the difference was started in the third decimal. Elemental analysis were also satisfying that were in accordance with molecular weights of the compounds at the range of ±0.4%.

2.1 Evaluation of physicochemical parameters of synthesized compounds

In silico prediction of physicochemical properties of newly synthesized compounds by computing enables predetermination of absorption, distribution, metabolization, and elimination (ADME) properties of them, thus determination of the pharmacokinetics of the molecules. The physicochemical, pharmacokinetic, and druglikeness properties of the final compounds were estimated using SwissADME software [25] and represented in Table 1. Molecular weight (MA), hydrogen bond acceptor (HBA), number of H bond donors (HBD), topological polar surface area (TPSA), absorption from the gastrointestinal tract (GIA), partition coefficient (log *P*), and skin absorption coefficient (log K_p) values were calculated and also the drug likeness scores of the molecules were determined according to five different filters. All of the compounds have a hydrogen bond donor due to the hydrazine group and hydrogen bond acceptor between 2 and 4 depending on the substituents they contain. It was determined that TPSA was between 65.52 and 111.34 and log *P* was between 4.17 and 6.39. It has been determined that the absorption of the compounds from the gastrointestinal system is high and the absorption through the skin is moderate. When drug likeness was evaluated through Lipinski, Ghose, Veber, Egan, and Muegge filters, it was seen that the compounds passed through 2, 3, and 5 of them. However, it was determined that there is no violation on Lipinski's rule of five for all compounds, and this showed that the compounds were suitable in terms of the parameters to be able to an oral drug [26].

2.2 Evaluation of enzyme inhibition activity of compounds

The inhibition potential of the synthesized 4-(substituted phenyl)-2-[2-(3-phenyl-2,3-dihydro-1*H*-inden-1-ylidene) hyd razinyl]thiazole (**3a–3i**) derivatives on acetylcholinesterase and monoamine oxidase B enzymes were investigated and the results were presented in Table 2. Compounds were

Table 1: Some physicochemical properties of the compounds (**3a–3i**).

	MW	HBA	HBD	TPSA	Log *P*	GI abs.	Log K_p	DL
3a	381.50	2	1	65.52	4.17	High	−4.72	5/5
3b	411.52	3	1	74.75	5.35	High	−4.36	2/5
3c	411.52	3	1	74.75	5.34	High	−4.36	2/5
3d	395.52	2	1	65.52	5.68	High	−3.98	2/5
3e	415.94	2	1	65.52	5.89	High	−3.92	2/5
3f	399.48	3	1	65.52	5.67	High	−4.19	2/5
3g	426.49	4	1	111.34	4.78	High	−4.82	3/5
3h	441.54	4	1	83.98	5.28	High	−4.56	2/5
3i	450.38	2	1	65.62	6.39	Low	−3.69	2/5

MW, molecular weight; HBA, hydrogen bond acceptor; HBD, hydrogen bond donor; TPSA, topological polar surface area; Log *P*, partition coefficient (average of five predictions); GI abs, gastrointestinal absorption; DL, druglikeness (including Lipinski, Ghose, Veber, Egan, Muegge rules).

studied against both enzymes at concentrations of 10^{-3} and 10^{-4} M and results were given as percent inhibition. Donepezil and selegiline were used as standard drugs for AChE inhibition and MAO-B inhibition, respectively.

Compounds caused inhibition on AChE between 32.82 and 42.39% at 10^{-3} M concentration and 20.36–31.15% at 10^{-4} M concentration. Donepezil induced 99.16% inhibition at 10^{-3} M dose and none of the compounds could provide 50% or more inhibition thus, IC_{50} could not be calculated for the compounds. In addition, compounds containing nonsubstituted (**3a**), 4-methyl (**3d**), and 4-chloro (**3e**) phenyl residues were provoked over 40% inhibition at 10^{-3} M concentration. In a recent study [27], similar molecules titled 2-[2-(6-methoxy-2,3-dihydro-1*H*-inden-1-ylidene)hydrazinyl]-4-(substituted phenyl)thiazole were reported to exhibit significant cholinesterase inhibitory activity on AChE. In especial, nonsubstituted, 4-nitro, 2,4-dimethyl, and 2,4-dichloro phenyl substituted derivatives were identified to show obvious activity. Although high activity was not observed in our compounds, the best inhibition percentages were observed in derivatives containing similar substituents. The reason for the weak activity may be that the compounds do not span the entire length of the active site gorge of the enzyme like donepezil due to phenyl moiety at third position of indane ring, so they cannot fit the enzyme properly. When we examined in terms of MAO-B inhibition, the compounds caused 45.12–75.42% inhibition at 10^{-3} M concentration and 30.24–42.31% at 10^{-4} M concentration, while selegiline inhibited 98.59% at 10^{-3} M concentration. The compounds bearing 4-methoxy (**3c**), 4-methyl (**3d**), 4-chloro (**3e**), 4-nitro (**3g**), 2,5-dimethoxy (**3h**), and 3,4-dichloro (**3i**) phenyl residues provided over 50% inhibition. None of these compounds could rise above 42.31% at the lower concentration. In a previous study [28], 1-(4-arylthiazol-2-yl)-2-(3-methylcyclohexylidene)hydrazine derivatives were evaluated for their MAO-B inhibitory activity and reported selective activity against hMAO-B with IC_{50} ranging between 21.90 and 0.018 μM. Nonsubstituted, 4-Cl, 4-CH_3, and 4-OCH_3 substituted phenyl containing compounds on C4 position of thiazole ring were determined MAO-B inhibitory activity in micromolar range, that similarly, same substituted derivatives were defined more better than the others, in our study.

3 Materials and methods

3.1 Chemistry

All chemicals were purchased from Sigma-Aldrich Chemical Co (Sigma-Aldrich Corp., St. Louis, MO, USA) and Merck Chemicals (Merck KGaA, Darmstadt, Germany). All melting points (m.p.) were determined by MP90 digital melting point apparatus (Mettler Toledo, Ohio, USA) and were uncorrected. All reactions were monitored by

Table 2: % Inhibition rates of the obtained compounds against AChE and MAO-B enzymes at 10^{-3} and 10^{-4} M concentrations.

Compounds	AChE inhibition %		MAO-B inhibition %	
	10^{-3} M	10^{-4} M	10^{-3} M	10^{-4} M
3a	42.33 ± 0.93	25.79 ± 0.81	48.13 ± 0.99	27.10 ± 0.88
3b	39.12 ± 0.72	21.37 ± 0.69	45.12 ± 0.81	31.08 ± 0.87
3c	35.34 ± 0.72	22.10 ± 0.60	53.03 ± 1.03	32.12 ± 0.86
3d	42.39 ± 1.00	25.10 ± 0.73	55.32 ± 0.91	35.71 ± 0.81
3e	40.95 ± 0.71	20.36 ± 0.63	52.12 ± 0.92	30.04 ± 0.62
3f	37.75 ± 0.69	31.15 ± 0.81	48.57 ± 0.87	29.17 ± 0.80
3g	33.36 ± 0.89	24.74 ± 0.72	75.42 ± 1.10	42.31 ± 0.95
3h	38.64 ± 0.64	30.11 ± 0.87	60.33 ± 1.01	35.99 ± 0.84
3i	32.82 ± 0.75	22.20 ± 0.57	56.13 ± 0.84	30.24 ± 0.63
Donepezil	99.16 ± 1.30	97.40 ± 1.26	–	–
Selegiline	–	–	98.59 ± 2.06	94.85 ± 1.11

thin-layer chromatography (TLC) using Silica Gel 60 F254 TLC plates (Merck KGaA, Darmstadt, Germany). In TLC, petroleum ether–ethyl acetate (3:1) was used as mobile phase. Spectroscopic data were recorded with the following instruments: IR, Shimadzu Affinity 1S spectrophotometer (Shimadzu, Tokyo, Japan); NMR, Agilent 300 MHz NMR spectrometer (Agilent technologies, California, USA), in DMSO-d_6, using TMS as internal standard; M + 1 peaks were determined by Shimadzu 8040 LC/MS/MS system (Shimadzu, Tokyo, Japan). Elemental analyses were performed on a Leco 932 CHNS analyzer (Leco, Michigan, USA).

3.2 3-Phenyl-2,3-dihydro-1*H*-inden-1-one (1)

Yield: 65%. Empirical M.p. 69–76 °C. Literature M.p. 75–78 [29]. 3,3-diphenylpropionic acid (0.065 mol; 14.69 g) and polyphosphoric acid 10 times more by weight in a flask was placed in water bath and the mixture was heated for 7–8 h after melting. The completion of the reaction was checked by thin layer chromatography by taking some of the liquefied reaction mixture. The solution that was then poured into ice water without cooling and the pH was achieved to be neutral with careful addition of sodium hydroxide solution to it. After drying, the product was crystallized from ethanol [30].

3.3 2-(3-Phenyl-2,3-dihydro-1*H*-inden-1-ylidene) hydrazin-1-carbothioamide (2)

Yield: 74%. Empirical M.p. 156–160 °C. 2-Phenyl-1-indanone **(1)** (0.06 mol; 12.48 g) and thiosemicarbazide (0.08 mol; 7.28 g) were boiled in ethanol for 2 h. The end of the reaction was checked by TLC, the reaction mixture was allowed to cool. The crystals formed in the flask were filtered by washing with alcohol, then it was crystallized from ethanol [31,32].

3.4 Synthesis of 4-(substituted phenyl)-2-[2-(3-phenyl-2,3-dihydro-1*H*-inden-1-ylidene)hydrazinyl] thiazole derivatives (3a–3i)

2-(3-Phenyl-2,3-dihydro-1*H*-inden-1-ylidene) hydrazine-1-carbothioamide **(2)** (0.002 mol; 0.56 g) and appropriate α-bromoacetophenone derivatives (0.002 mol) in ethanol were stirred for 6 h at room temperature, the reaction was terminated by the control of TLC. The precipitated crude product was then filtered off from the cooled reaction mixture, and it was crystallized from ethanol after drying [32].

3.5 4-Phenyl-2-[2-(3-phenyl-2,3-dihydro-1*H*-inden-1-ylidene)hidrazinyl]thiazole (3a)

Yield: 63%. M.p. 246–247 °C. IR (ATR) ν_{max} (cm^{-1}): 3211 (N–H stretching band), 3030 (Aromatic C–H stretching band), 1641–1489 (C=C and C=N stretching band), 1105 (C–N stretching band), 758, 748 and 700 (monosubstituted and 1,2-disubstituted benzene out-of-plane bending bands). ^{1}H-NMR (300 MHz, DMSO-d_6, ppm) δ: 2.86 (1H, dd, J: 3.95, 18.91 Hz, indane C_2–H), 3.48 (1H, dd, J: 8.88, 18.82 Hz, indane C_2–H), 4.64 (1H, dd, J: 3.57, 8.49 Hz, indane C_3–H), 7.04–7.06 (1H, m, Ar–H), 7.16 (2H, d, J: 7.47 Hz, Ar–H), 7.23–7.25 (1H, m, Ar–H), 7.30–7.35 (5H, m, Ar–H), 7.38–7.43 (2H, m, Ar–H), 7.68–7.70 (1H, m, Ar–H), 7.87 (2H, d, J: 7.91 Hz, Ar–H), 11.33 (1H, brs, N–H). ^{13}C-NMR (75 MHz, DMSO-d_6, ppm) δ: 38.39, 46.86, 104.37, 121.09, 126.03, 127.07, 127.95, 128.03, 128.11, 128.34, 128.79, 129.09, 129.24, 130.83, 135.0, 137.86, 145.39, 151.39, 155.01, 169.87. For $C_{13}H_{13}N_3OS$ calculated: 75.56% C, 5.02% H, 11.01% N; found: 75.58% C, 5.03% H, 11.03% N. HRMS (m/z): $[M + H]^+$ calcd for $C_{24}H_{19}N_3S$: 382.1372, found: 382.1382.

3.6 4-(3-Methoxyphenyl)-2-[2-(3-phenyl-2,3-dihydro-1*H*-inden-1-ylidene)hidrazinyl]thiazole (3b)

Yield: 67%. M.p. 233–235 °C. IR (ATR) ν_{max} (cm^{-1}): 3219 (N–H stretching band), 3045 (Aromatic C–H stretching band), 1618–1489 (C=C and C=N stretching band), 1240–1024 (C–N and C–O stretching band), 765, 756, 748, and 700 (monosubstituted, 1,2-disubstituted, and 1,3-disubstituted benzene out-of-plane bending bands). ^{1}H-NMR (300 MHz, DMSO-d_6, ppm) δ: 2.86 (1H, dd, J: 3.69, 18.43 Hz, indane C_2–H), 3.48 (1H, dd, J: 8.75, 18.89 Hz, indane C_2–H), 3.79 (3H, s, OCH_3), 4.64 (1H, dd, J: 3.64, 8.60 Hz, indane C_3–H), 6.85–6.89 (1H, m, Ar–H), 7.04–7.06 (1H, m, Ar–H), 7.15–7.18 (2H, m, Ar–H), 7.20–7.26 (1H, m, Ar–H), 7.30–7.35 (5H, m, Ar–H), 7.28–7.37 (2H, m, Ar–H), 7.67–7.70 (1H, m, Ar–H), 7.87 (1H, d, J: 7.91 Hz, Ar–H), and 11.34 (1H, brs, N–H). ^{13}C-NMR (75 MHz, DMSO-d_6, ppm) δ: 38.39, 46.86, 55.54, 55.57, 104.83, 111.22, 113.62, 113.96, 114.46, 118.43, 120.67, 121.12, 126.27, 127.07, 127.94, 128.11, 129.24, 130.15, 130.87, 136.26, 137.82, 145.25, 145.37, 151.43, 151.57, 155.23, 159.48, 159.97, 168.59, and 169.75. For $C_{25}H_{21}N_3OS$ calculated: 72.97% C, 5.14% H, 10.21% N; found: 72.99% C, 5.14% H, 10.21% N. HRMS (m/z): $[M + H]^+$ calcd for $C_{25}H_{21}N_3OS$: 412.1478; found: 412.1496.

3.7 4-(4-Methoxyphenyl)-2-[2-(3-phenyl-2,3-dihydro-1*H*-inden-1-ylidene)hidrazinyl]thiazole (3c)

Yield: 69%. M.p. 247–249 °C. IR (ATR) ν_{max} (cm^{-1}): 3217 (N–H stretching band), 3067 (Aromatic C–H stretching band), 1610–1456 (C=C and C=N stretching band), 1240–1024 (C–N and C–O stretching band), 831, 718, and 698 (monosubstituted, 1,2-disubstituted and 1,4-disubstituted benzene out-of-plane bending bands). ^{1}H-NMR (300 MHz, DMSO-d_6, ppm) δ: 2.86 (1H, dd, J: 3.85, 18.98 Hz, indane C_2–H), 3.48 (1H, dd, J: 8.75, 18.89 Hz, indane C_2–H), 3.72 ve 3.79 (3H, 2s, OCH_3), 4.64 (1H, dd, J: 3.43, 9.05 Hz, indane C_3–H), 6.92 (1H, d, J: 9.0 Hz, Ar–H), 6.97 (1H, d, J: 8.89 Hz, Ar–H), 7.02–7.06 (1H, m, Ar–H), 7.11–7.18 (3H, m, Ar–H), 7.23–7.25 (1H, m, Ar–H), 7.30–7.38 (4H, m, Ar–H), 7.62–7.66 (1H, m, Ar–H), 7.69–7.72 (1H, m, Ar–H), 7.78 (1H, d, J: 8.55 Hz, Ar–H), and 11.29 (1H, brs, N–H). ^{13}C-NMR (75 MHz, DMSO-d_6, ppm) δ: 38.45, 46.85, 55.60, 102.40, 114.27, 114.48, 121.23, 126.28, 127.08, 127.50, 127.94, 128.12, 128.31, 129.24, 129.37, 129.70, 130.98, 131.42, 137.67, 137.73, 145.32, 151.53, 155.79, 159.41, 168.50, and 169.66. For $C_{25}H_{21}N_3OS$ calculated: 72.97% C, 5.14% H, 10.21% N; found: 72.94% C, 5.13% H, 10.20% N. HRMS (m/z): $[M + H]^+$ calcd for $C_{25}H_{21}N_3OS$: 412.1478; found: 412.1492.

3.8 4-(4-Methylphenyl)-2-[2-(3-phenyl-2,3-dihydro-1*H*-inden-1-ylidene)hidrazinyl]thiazole (3d)

Yield: 72%. M.p. 216–217 °C. IR (ATR) ν_{max} (cm^{-1}): 3230 (N–H stretching band), 3032 (Aromatic C–H stretching band), 1558–1456 (C=C and C=N stretching band), 1111 (C-N stretching band), 819, 750, and 700 (monosubstituted, 1,2-disubstituted and 1,4-disubstituted benzene

out-of-plane bending bands). ^{1}H-NMR (300 MHz, DMSO-d_6, ppm) δ: 2.31 (3H, s, CH_3), 2.86 (1H, dd, J: 3.98, 18.91 Hz, indane C_2–H), 3.47 (1H, dd, J: 8.80, 19.60 Hz, indane C_2–H), 4.64 (1H, dd, J: 3.58, 8.79 Hz, indane C_3–H), 7.03–7.06 (1H, m, Ar–H), 7.14–7.17 (2H, m, Ar–H), 7.20–7.26 (4H, m, Ar–H), 7.28–7.36 (4H, m, Ar–H), 7.67–7.70 (1H, m, Ar–H), 7.75 (2H, d, J: 8.05 Hz, Ar–H), and 11.21 (1H, brs, N–H). ^{13}C-NMR (75 MHz, DMSO-d_6, ppm) δ: 21.29, 38.37, 46.85, 103.46, 121.10, 126.0, 126.27, 127.07, 127.94, 128.11, 129.24, 129.66, 130.83, 132.28, 137.32, 137.85, 145.39, 151.39, 155.05, and 169.75. For $C_{25}H_{21}N_3S$ calculated: 75.92% C, 5.35% H, 10.62% N; found: 75.94% C, 5.34% H, 10.60% N. HRMS (m/z): $[M + H]^+$ calcd for $C_{25}H_{21}N_3S$: 396.1529; found: 396.1545.

3.9 4-(4-Chlorophenyl)-2-[2-(3-phenyl-2,3-dihydro-1*H*-inden-1-ylidene)hidrazinyl]thiazole (3e)

Yield: 75%. M.p. 155–157 °C. IR (ATR) ν_{max} (cm^{-1}): 3341 (N–H stretching band), 3064 and 3032 (Aromatic C–H stretching band), 1516–1456 (C=C and C=N stretching band), 1132–1010 (C–N stretching band), 759, 725, and 698 (monosubstituted, 1,2-disubstituted, and 1,4-disubstituted benzene out-of-plane bending bands). ^{1}H-NMR (300 MHz, DMSO-d_6, ppm) δ: 2.85 (1H, dd, J: 4.03, 18.78 Hz, indane C_2–H), 3.47 (1H, dd, J: 9.06, 18.01 Hz, indane C_2–H), 4.64 (1H, dd, J: 3.80, 8.62 Hz, indane C_3–H), 7.03–7.06 (1H, m, Ar–H), 7.15–7.17 (2H, m, Ar–H), 7.23–7.26 (1H, m, Ar–H), 7.30–7.36 (4H, m, Ar–H), 7.40 (1H, s, Ar–H), 7.46 (2H, d, J: 8.64 Hz, Ar–H), 7.66–7.70 (1H, m, Ar–H), 7.88 (2H, d, J:8.64 Hz, Ar–H), and 11.25 (1H, brs, N–H). ^{13}C-NMR (75 MHz, DMSO-d_6, ppm) δ: 38.36, 46.87, 105.13, 121.05, 126.26, 127.06, 127.70, 128.11, 129.09, 129.23, 130.80, 132.30, 134.14, 137.88, 145.39, 151.35, 154.83, and 170.02. For $C_{24}H_{18}ClN_3S$ calculated: 69.30% C, 4.36% H, 10.10% N; found: 69.32% C, 4.37% H, 10.12% N. HRMS (m/z): $[M + H]^+$ calcd for $C_{24}H_{18}ClN_3S$: 416.0983; found: 416.0999.

3.10 4-(4-Florophenyl)-2-[2-(3-phenyl-2,3-dihydro-1*H*-inden-1-ylidene)hidrazinyl]thiazole (3f)

Yield: 65%. M.p. 117–120 °C. IR (ATR) ν_{max} (cm^{-1}): 3332 (N–H stretching band), 3022 (Aromatic C–H stretching band), 1558–1456 (C=C and C=N stretching band), 1234–1095 (C–N stretching band), 840, 759, 752, 732, and 696 (monosubstituted, 1,2-disubstituted and 1,4-disubstituted benzene out-of-plane bending bands). ^{1}H-NMR (300 MHz, DMSO-d_6, ppm) δ: 2.85 (1H, dd, J: 4.09, 18.58 Hz, indane C_2–H), 3.44 (1H, d, J: 9.06 Hz, indane C_2–H), 4.64 (1H, dd, J: 3.74, 9.09 Hz, indane C_3–H), 7.03–7.06 (1H, m, Ar–H), 7.15–7.38 (10H, m, Ar–H), 7.67–7.69 (1H, m, Ar–H), 7.88–7.92 (2H, m, Ar–H), and 11.15 (1H, brs, N–H). ^{13}C-NMR (75 MHz, DMSO-d_6, ppm) δ: 38.36, 46.87, 104.05, 115.75, 116.03, 121.04, 126.26, 127.06, 127.94, 128.10, 129.22, 130.77, 137.91, 145.41, 151.32, 154.72, 163.63, and 169.99. For $C_{24}H_{18}FN_3S$ calculated: 72.16% C, 4.54% H, 10.52% N; found: 72.18% C, 4.55% H, 10.53% N. HRMS (m/z): $[M + H]^+$ calcd for $C_{24}H_{18}FN_3S$: 400.1290; found: 400.1278.

3.11 4-(4-Nitrophenyl)-2-[2-(3-phenyl-2,3-dihydro-1*H*-inden-1-ylidene)hidrazinyl]thiazole (3g)

Yield: 64%. M.p. 243–248 °C. IR (ATR) ν_{max} (cm^{-1}): 3332 (N–H stretching band), 3062 and 3022 (Aromatic C–H stretching band), 1595–1338 (C=C and C=N stretching band), 1504, and 1338 (NO_2 stretching band), 1234–1055 (C–N stretching band), 860, 754, and 700 (monosubstituted, 1,2-disubstituted and 1,4-disubstituted benzene out-of-plane bending bands). ^{1}H-NMR (300 MHz, DMSO-d_6, ppm) δ: 2.85 (1H, dd, J: 3.98, 19.01 Hz, indane C_2–H), 3.48 (1H, dd, J: 8.84, 19.01 Hz, indane C_2–H), 4.64 (1H, dd, J: 3.69, 8.64 Hz, indane C_3–H), 7.04–7.07 (1H, m, Ar–H), 7.15–7.18 (2H, m, Ar–H), 7.24–7.26 (1H, m, Ar–H), 7.30 (1H, s, Ar–H), 7.32–7.37 (3H, m, Ar–H), 7.68–7.71 (1H, m, Ar–H), 7.74 (1H, s, Ar–H), 8.13 (2H, d, J: 9.07 Hz, Ar–H), 8.29 (2H, d, J: 9.07 Hz, Ar–H), and 11.38 (1H, brs, N–H). ^{13}C-NMR (75 MHz, DMSO-d_6, ppm) δ: 38.42, 46.87, 109.25, 121.09, 124.62, 126.78, 127.96, 128.13, 129.24, 130.90, 137.78, 141.29, 145.35, 146.59, 149.08, 151.44, 155.16, and 170.30. For $C_{24}H_{18}N_4O_2S$ calculated: 67.59% C, 4.25% H, 13.14% N; found: 67.57% C, 4.26% H, and 13.15% N. HRMS (m/z): $[M + H]^+$ calcd for $C_{24}H_{18}N_4O_2S$: 427.1223; found: 427.1240.

3.12 4-(2,5-Dimethoxyphenyl)-2-[2-(3-phenyl-2,3-dihydro-1*H*-inden-1-ylidene)hidrazinyl]thiazole (3h)

Yield: 67%. M.p. 227–229 °C. IR (ATR) ν_{max} (cm^{-1}): 3190 (N–H stretching band), 3064, and 3032 (Aromatic C–H stretching band), 1606–1456 (C=C and C=N stretching band), 1280–1012 (C–N stretching band), 783, 759, 750, and 700 (monosubstituted, 1,2-disubstituted and 1,2,4-trisubstituted benzene out-of-plane bending bands). ^{1}H-NMR (300 MHz, DMSO-d_6, ppm) δ: 2.88 (1H, dd, J: 3.93, 19.03 Hz, indane C_2–H), 3.50 (1H, dd, J: 8.08, 18.58 Hz, indane C_2–H), 3.73 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 4.65 (1H, dd, J: 3.57, 8.56 Hz, indane C_3–H), 6.86–6.91 (1H, m, Ar–H), 7.02–7.07 (2H, m, Ar–H), 7.13–7.18 (2H, m, Ar–H), 7.22–7.26 (1H, m, Ar–H), 7.30–7.37 (4H, m, Ar–H), 7.44 (1H, s, Ar–H), 7.58–7.59 (1H, m, Ar–H), 7.70–7.73 (1H, m, Ar–H), and 11.32 (1H, brs, N–H). ^{13}C-NMR (75 MHz, DMSO-d_6, ppm) δ: 38.49, 46.85, 55.91, 55.95, 56.37, 56.41, 108.65, 113.29, 114.53, 116.70, 121.27, 126.31, 127.09, 127.93, 128.14, 129.23, 131.08, 137.65, 145.27, 151.27, 151.60, 153.46, 168.18, and 168.29. For $C_{26}H_{23}N_3O_2S$ calculated: 70.73% C, 5.25% H, 9.52% N; found: 70.75% C, 5.24% H, and 9.54% N. HRMS (m/z): $[M + H]^+$ calcd for $C_{26}H_{23}N_3O_2S$: 442.1594; found: 442.1584.

3.13 4-(3,4-Dichlorophenyl)-2-[2-(3-phenyl-2,3-dihydro-1*H*-inden-1-ylidene)hidrazinyl]thiazole (3i)

Yield: 67%. M.p. 185–188 °C. IR (ATR) ν_{max} (cm^{-1}): 3344 (N–H stretching band), 3024 (Aromatic C–H stretching band), 1568–1340 (C=C and C=N stretching band), 1296–1128 (C–N stretching band), 837, 756, 719, and 700 (monosubstituted, 1,2-disubstituted and 1,4-disubstituted benzene out-of-plane bending bands). ^{1}H-NMR (300 MHz, DMSO-d_6, ppm) δ: 2.85 (1H, dd, J: 3.86, 19.12 Hz, indane C_2–H), 3.46 (1H, dd, J: 9.04, 17.72 Hz, indane C_2–H), 4.64 (1H, dd, J: 3.76, 9.04 Hz, indane C_3–H), 7.03–7.06 (1H, m, Ar–H), 7.14–7.17 (2H, m, Ar–H), 7.20–7.25 (1H, m, Ar–H), 7.30–7.36 (4H, m, Ar–H), 7.56 (1H, s, Ar–H), 7.65–7.70 (1H, m, Ar–H), 7.85 (2H, dd, J:2.12, 8.20 Hz, Ar–H), 8.10 (1H, s, Ar–H), and 11.27 (1H, brs, N–H). ^{13}C-NMR (75 MHz, DMSO-d_6, ppm) δ:: 38.36, 46.86, 106.57, 121.07, 126.0, 126.27, 127.07, 127.65, 127.93, 128.11, 129.23, 130.05, 131.33, 131.88, 135.83, 137.82, 145.36, 138.44, 151.38, 155.02, and 170.10. For $C_{24}H_{17}Cl_2N_3S$ calculated: 64.00% C, 3.80% H, 9.33% N; found: 63.98% C, 3.81% H, 9.35% N. HRMS (m/z): $[M + H]^+$ calcd for $C_{24}H_{17}Cl_2N_3S$: 450.0593; found: 450.0604.

3.14 Biochemistry

3.14.1 AChE inhibition: The anticholinesterase activities of the compounds to be synthesized within the scope of the thesis were carried out on the AChE enzyme according to the modified Ellman method [33]. The AChE enzyme (E.C.3.1.1.7, electric eel) was dissolved in a 1% gelatin solution at a concentration of 500 U/mL, then diluted to 5 U/mL. This stock solution prepared was used by being diluted to the method concentration of 2.5 U/mL just before the experiment. Acetylthiocholine iodide (ATC) 0.075 M used as substrate was prepared and 0.217 g was dissolved in water and the volume was completed to 10 mL. In the preparation of 0.01 M 5-5-dithiobis (2-nitrobenzoic acid) (DTNB) solution, 0.396 g of substance was weighed and dissolved in water. By adding 0.15 g sodium bicarbonate to this solution, the volume is completed to 100 mL with water. While preparing the phosphate buffer, 13.61 g of potassium dihydrogen phosphate was dissolved in 1 L water, the pH of the prepared solution was adjusted to 8.0 + 0.1 of 0.1 N potassium hydroxide solution. All the solutions used in the studies were stored at –20 °C and brought to room temperature before the experiment. In the inhibition study, 140 µL phosphate buffer, 20 µL enzyme solution, 20 µL inhibitor solution, 20 µL DTNB solution, and 10 µL ATC solution were prepared in 96-well plates for each cell. After the solutions on the plates were mixed, they were incubated in the oven for 15 min and the absorbance reading was made at 412 nm. The inhibitor compounds were applied at a concentration of 10^{-3} and 10^{-4} M, and all experiments were run in four replicates.

3.15 MAO-B inhibition

MAO-B enzyme inhibitory activities of the synthesized compounds were investigated by the fluorometric method [34]. Recombinant hMAO-B (0.64 U/mL) enzyme, Horseradish Peroxidase (200 U/mL, 100 µL), Ampliflu™ Red (20 mM, 200 µL) and tyramine (100 mM, 200 µL) solutions phosphate buffer required for the study. It was prepared by dissolving and diluting in it. All solutions were prepared daily. Test compounds (20 µL) and hMAO-B (100 µL) enzyme were placed in a black flat bottom 96-well micro test plate and incubated at 37 °C for 30 min. Then, 100 µL of working solutions were added to this mixture and the mixture was incubated again at 37 °C for 30 min. Fluorescence (E_x/E_m = 535/587 nm) was measured every 5 min. Experiments were run in four replicates.

4 Conclusion

In this work, new 4-(substituted phenyl)-2-[2-(3-phenyl-2,3-dihydro-1*H*-inden-1-ylidene) hydrazinyl]thiazole (**3a–3i**) derivatives were synthesized and they were investigated on AChE and MAO-B enzymes. The structures of the titled compounds were illuminated IR by ^{1}H-NMR, ^{13}C-NMR and mass spectroscopy methods.

It was determined that the compounds showed higher effect on MAO-B enzyme than AChE enzyme. It was determined that **3a** and **3d** against AChE, **3g** and **3h** against MAO-B were the most active compounds, which were evaluated as percent inhibition at 10^{-3} and 10^{-4} M concentrations. However, none of the compounds were as effective as donepezil and selegiline, and the inhibition concentration could not be calculated due to the low effect levels. When the physicochemical properties of the compounds were evaluated as *in silico*, it was determined that they adapt to the oral drug properties.

When the potential enzyme inhibition effects of the compounds were evaluated in terms of both existing drugs and molecules reported in the literature, it was expected that the activity potential would be higher. It is planned to synthesize new derivatives containing indane ring and 2-hydrazinothiazole skeleton with different substituents and evaluate their enzyme inhibition potentials in future studies in line including molecular docking program.

Acknowledgments: We gratefully thank Anadolu University DOPNA Laboratory for analyzing the synthesized compounds.
Author contributions: All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.
Research funding: None declared.
Conflict of interest statement: The authors confirm that this article content has no conflict of interest.

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Supplementary material: The online version of this article offers supplementary material (https://doi.org/10.1515/znc-2021-0058).