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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis, characterization, acetylcholinesterase inhibition, and molecular docking studies of new piperazine substituted dihydrofuran compounds

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Abstract

Novel unsaturated piperazine and homopiperazine derivatives **(3a–h)** were synthesized in medium to good yields by acylation reactions of piperazine and homopiperazine with methacrylic anhydride **(2a)** and benzoyl chloride **(2b)**. Piperazine containing dihydrofuran compounds **(5a–l)** were obtained from radical addition and cyclizations of **3a–h** with 1,3-dicarbonyl compounds such as dimedone **(4a)**, ethyl acetoacetate **(4b)** and acetylacetone **(4c)** mediated by $Mn(OAc)_3$ for the first time. While the reaction of **3b** (1-methacryloylpiperazine) with **4a** and **4b** gave bis-dihydrofurans (**5b** and **5d**) beside mono-dihydrofurans (**5a** and **5c**), the reaction of **3b–e**, **3g**, **3h**, and **3e** with 1,3-dicarbonyl compounds gave mono dihydrofuran compounds (**5f–l**) in medium to high yields. Structures of all novel compounds were determined by melting point analysis, ^{1}H NMR, ^{13}C NMR, HRMS, and FTIR methods. All piperazine containing dihydrofuran compounds were evaluated for their inhibitory activities toward acetylcholinesterase (AChE) by Ellman method and IC_{50} values were presented. Compounds **5c**, **5d**, **5e**, **5i**, and **5l** show highest inhibitory activities with IC_{50} values of 5.79, 3.89, 5.07, 4.30, and 2.24 μM, respectively. In addition, molecular docking studies were performed on selected structures **5d**, **5i**, and **5l** to investigate ligand–protein interactions. Binding energies were calculated and compared with standart drug donepezil.

Keywords Piperazine · Dihydrofuran · Radical cyclization · Acetylcholinesterase inhibition

Introduction

Alzheimer's disease (AD) is a progressive and chronic neurodegenerative disorder which is one of the main causes of dementia that effects elder people (Anand et al. 2014; Gao et al. 2018). Among the various proposed pathogenesis hyphotesis of AD, cholinergic hyphothesis is the most commonly accepted and the decrease of neurotransmitter acetylcholine levels in the brain is considered the most prominent cause of AD (Akasofu et al. 2008; Dumas and Newhouse 2011; Molinuevo and Gauthier 2013).

Acetylcholinesterase (AChE) is an enzyme belongs to cholinesterase family and the main biological function of AChE is to terminate impulse transmission at cholinergic synapses by catalyzing the rapid hydrolysis of the neurotransmitter acetylcholine (Tougu 2001; Berwaldt et al. 2019). Inhibiting AChE is the most effective and promising way and AChE inhibitors such as donepezil (Sugimoto et al. 1995), rivastigmine (Weintraub et al. 2011) and galantamine (Giacobini 2004) are frequently used for the treatment of AD.

Nitrogen bearing heterocycles have drawn much attention due to their biological properties (Yang et al. 2007; Khan et al. 2014). Piperazine structure is considered as a "privileged structure" in medicinal chemistry owing to their capabilities of binding to multiple receptors with high affinity (Szabo et al. 2014). There are many biological activity studies such as, anticonvulsant (Harish et al. 2013), antibacterial (Chaudhary et al. 2006), antituberculosis (Patel and Telvekar 2014), antiviral (Wang et al. 2009), anticancer (Duan et al. 2013), and antimalarial (Pretorius et al. 2013). Also there are many reports of piperazine derivatives showing acetylcholinesterase inhibition in literature (Meena et al. 2015; Piemontese et al. 2018; Demirayak et al. 2019) which make piperazine containing compounds suitable and potential candidates for AD treatment drugs.

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Dihydrofurans gathered much attention due to their biological activities. They have much potential to be used as building blocks for drugs. Sarcophytoxide (Chen et al. 2012), Clerodin (Lallemand et al. 2002), Fercoprolone (Appendino et al. 1998), and Austocystin (Kornsakulkarn et al. 2012) are some natural biologically active compounds that contain dihydrofuran moieties. It is known that dihydrofurans can be synthesized from transition metal salts (Mn^{3+}, Ce^{4+}, Co^{3+}, etc.) capable of transferring single electrons that form α-carbon radicals with enolizable active methylene compounds and the addition of this radical to unsaturated systems are widely used to generate new C–C bonds (Melikyan 1993; Snider 1996; Mondal and Bora 2013). Among these metal salts, cerium(IV) ammonium nitrate (Kobayashi et al. 2003; Chuang and Wu 2004; Nair et al. 2006) and manganese(III) acetate and are widely used in these reaction. There are many works in literature about syntheses mediated by $Mn(OAc)_3$ such as synthesis of spirodiones (Hyunh et al. 2017), azofulvene derivatives from indoles (Lofstrand et al. 2016), ferrocene substituted dihydrofurans (Aslan et al. 2017), spirobenzofurans (Ergüntürk et al. 2017), polysubstituted α-naphtols (He et al. 2020), bicyclic tetrahydrofurans (Chany et al. 2015), macrocyclic compounds with dihydrofuran rings (Ito et al. 2011), and spirodihydrofurans (Yokote et al. 2020). Also there are works about alkene cyanophosphinoylation (Zhang et al. 2017), C–H alkylation of arenes (Castro et al. 2016) and radical alkoxycarbonylation of indoles (Li et al. 2018).

Our research group has reported the radical addition and cyclization of 1,3-dicarbonyl compounds with various unsaturated systems such as aromatic and heteroaromatic conjugated alkenes (Yılmaz et al. 2005, 2008; Yilmaz 2011a, b; Yılmaz and Pekel 2011; Yilmaz et al. 2014; Ustalar and Yilmaz 2017; Özgür et al. 2019), dienes (Hocaoglu, Yilmaz 2019; Yılmaz et al. 2011a, b; Ustalar et al. 2017; Yilmaz and Ustalar 2016) and conjugated amide derivatives (Yılmaz and Pekel, 2001a, b; Burgaz et al. 2007; Yılmaz et al. 2011a, b; Yilmaz et al. 2016) using manganese(III) acetate and cerium (IV) ammonium nitrate (CAN), obtaining functionalized dihydrofuran containing compounds.

In this work we synthesized new piperazine substituted dihydrofuran compounds **(5a–l)** obtained by the $Mn(OAc)_3$ mediated radical cyclization of enolizable 1,3-dicarbonyls **(4a–c)** with unsaturated piperazine and homopiperazine derivatives **(3a–h)** in medium to high yields. There are no detailed works in literature about AChE inhibiton studies of dihydrofuran derivatives. Thus, we evaluated AChE inhibitions of piperazine substituted dihydrofuran compounds in detail. Evaluation of AChE inhibition capabilities of synthesized compounds were performed according to in vitro Ellman method (Ellman et al. 1961). Also in silico docking studies were performed on compounds (**5d**, **5i**, and **5l**) to explore ligand–protein interaction and binding affinities with the active site of AChE.

Materials and methods

Experimental

Melting points were determined on a Gallenkamp capillary melting point apparatus. IR spectra (ATR) were obtained with a Bruker Tensor27 spectrophotometer in the 400–4000 cm^{-1} range with 2 cm^{-1} resolutions. ^1H NMR and ^{13}C NMR spectra were recorded on a Varian Mercury-400 High performance Digital FT-NMR and Varian Oxford NMR300 spectrometers. High resolution mass time-of-flight spectra were measured on an Agilent 1200/6210 LC/MS spectrophotometer. UV absorbance was measured by Rigol Ultra-3000 UV–Vis spectrophotometer. Thin layer chromatography (TLC) was performed on Merck aluminum-packed silica gel plates. Purification of products was performed by column chromatography on silica gel (Merck silica gel 60, 40–60 µm) or preparative TLC on silica gel of Merck (PF254-366 nm). All reagents and solvents were highest purity and were used without further purification. Radical oxidant $Mn(OAc)_3$ was synthesized by electrochemical method (Yılmaz et al. 2011a, b).

General synthesis procedure and spectroscopic data of unsaturated piperazine compounds (3a–h)

The unsaturated piperazine and homopiperazine derivatives **(3a–h)** were synthesized by acylation reactions of piperazine and homopiperazine with methacrylic anhydride (**2a**) and benzoyl chloride (**2b**). Compounds **3a** (Korhonen 1995), **3b** (Shea et al. 1990), and **3g** (Kazuo 1984) were synthesized by modifying the literature method. Corresponding starting piperazine derivative (**1a–d**) was dissolved in 20 mL chloroform and the solution was stirred in ice bath for 15 min. Then a dilute solution of suitable acylation reagent (**2a** and **2b**) in chloroform was added dropwise. After instillation, reaction was removed from ice bath and allowed to stir overnight. Water (20 mL) was added and crude product was extracted three times with chloroform (3 × 20 mL). Combined organic phases were dried over anhydrous Na_2SO_4 and evaporated. The crude product **(3a–h)** was purified by column chromatography on silica using n-hexane/EtOAc (1:1) as eluent.

2-Methyl-1-(piperazin-1-yl)prop-2-en-1-one (3a)

It was obtained as a yellow oil; yield: 72% (16.5 g, 100 mmol); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.16

(1H, s, –C=CH), 5.00 (1H, s, –C=CH), 3.55 (4H, s, $–CH_2–$), 2.84 (4H, s, $–CH_2–$), 1.93 (3H, s, $–CH_3$) (Korhonen 1995).

1,1′-(Piperazine-1,4-diyl)bis(2-methylprop-2-en-1-one) (3b)

It was obtained as a colorless solid; yield 75% (3.82 g, 10 mmol); mp: 113–115 °C (114–115 °C, Shea et al. 1990); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.24 (2H, s, –C=CH), 5.05 (2H, s, –C=CH) 3.58 (8H, s, $–CH_2–$) 1.96 (6H, s, $–CH_3$) (Shea et al. 1990).

1-(4-Benzoylpiperazin-1-yl)-2-methylprop-2-en-1-one (3c)

It was obtained as a colorless solid; yield 72% (1.36 g, 5 mmol); mp: 101–103 °C; IR (ATR) υ_{max} 3050 (aromatic C–H), 2972 (aliphatic C–H), 2915 (aliphatic C–H), 1635 (amide C=O), 1603 (C=C), 1194 (C–N), 750, 700 (aromatic C–H) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.43–7.37 (5H, m, Ar–H), 5.22 (1H, s, –C=CH), 5.04 (1H, s, –C=CH), 3.60 (8H, s, $–CH_2–$), 1.95 (3H, s, $–CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 171.3 (C=O), 170.6 (C=O), 139.9 (C=C), 135.1 (aromatic C), 130.0 (aromatic C), 128.6 (aromatic C), 127.0 (aromatic C), 116.1 (–C=C–), 46.6 ($–CH_2$), 41.6 ($–CH_2$), 20.4 ($–CH_3$); HRMS (ESI) (*m/z*): Calcd for $C_{15}H_{18}N_2O_2$ 258.136, found: 258.447 $(M + H)^+$.

2-Methyl-1-(4-(tetrahydrofuran-2-carbonyl) piperazin-1-yl)prop-2-en-1-one (3d)

It was obtained as a yellow oil; yield 82% (1.13 g, 4 mmol); IR (ATR) υ_{max} 2976 (aliphatic C–H), 2918 (aliphatic C–H), 2871 (aliphatic C–H), 1641 (C=C), 1630 (amide C=O), 1611 (C=C), 1195 (C–N), 1080 (C–O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.24 (1H, s, –C=CH), 5.05 (1H, s, –C=CH), 4.60 (1H, t, J = 6.0 Hz, –CH), 3.94–3.82 (2H, m, $–CH_2$), 3.76–3.44 (8H, m, $–CH_2$), 2.06–1.99 (2H, m, $–CH_2–$), 1.92 (3H, s, $–CH_3$), 1.90–1.88 (2H, m, $–CH_2–$); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 171.3 (C=O), 169.9 (C=O), 139.9 (C=C), 116.0 (C=C), 75.9 (O–C–), 69.0 ($–CH_2–$), 45.4 ($–CH_2–$), 42.2 ($–CH_2–$), 28.0 ($–CH_2–$), 25.7 ($–CH_2–$), 20.4 ($–CH_3$); HRMS (ESI) (*m/z*) Calcd for $C_{13}H_{20}N_2O_3$ 253.15467, found: 253.15552 $(M + H)^+$.

1-(4-(Furan-2-carbonyl)piperazin-1-yl)-2-methylprop-2-en-1-one (3e)

It was obtained as a yellow oil; yield 88% (1.21 g, 4.8 mmol); IR (ATR) υ_{max} 3117 (aromatic C–H), 2978 (aliphatic C–H), 2917 (aliphatic C–H), 2862 (aliphatic C–H), 1638 (amide C=O) 1608 (C=C), 1180 (C–N), 1092 (C–O), 750, 700 (aromatic C–H) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.51 (1H, s, Ar–H), 7.06 (1H, d, J = 3.2 Hz, Ar–H), 6.51 (1H, dd, J = 3.6, 2.0 Hz, Ar–H), 5.26 (1H, s, –C=CH), 5.08 (1H, s, –C=CH), 3.81 (4H, s, $–CH_2–$), 3.68 (4H, s, $–CH_2–$), 1.98 (3H, s, $–CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 171.3 (C=O), 159.1 (C=O), 147.5 (aromatic C), 143.9 (aromatic C), 139.9 (C=C), 117.1 (aromatic C), 116.1 (C=C), 111.4 (aromatic C), 46.8 ($–CH_2–$), 41.7 ($–CH_2–$), 20.4 ($–CH_3$); HRMS (ESI) (*m/z*) Calcd for $C_{13}H_{16}N_2O_3$ 249.12337, found: 249.12382 $(M + H)^+$.

1-(1,4-Diazepan-1-yl)-2-methylprop-2-en-1-one (3f)

It was obtained as a yellow oil; yield 70% (2.53 g, 15 mmol); IR (ATR) υ_{max} 3367 (N–H), 2972 (aliphatic C–H), 1644 (amide C=O) 1615 (C=C), 1201 (C–N) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 5.16 (1H, s, –C=CH), 5.02 (1H, s, –C=CH), 3.64–3.44 (2H, m, $–CH_2–$), 3.50 (1H, s, –NH), 3.00–2.88 (2H, m, $–CH_2–$), 2.60 (4H, s, $–CH_2–$), 1.97 (3H, s, $–CH_3$), 1.86 (2H, m, $–CH_2–$); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 172.7 (C=O), 141.0 (C=C), 114.9 (C=C), 58.0 ($–CH_2–$), 50.3 ($–CH_2–$), 47.3 ($–CH_2–$), 31.3 ($–CH_2–$), 18.2 ($–CH_3$); HRMS (ESI) (*m/z*) Calcd for $C_9H_{16}N_2O$ 168.125 found: 168.434 $(M+H)^+$.

1,1′-(1,4-Diazepane-1,4-diyl)bis(2-methylprop-2-en-1-one) (3g)

It was obtained as a yellow oil; yield 70% (3.3 g, 12 mmol) ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.13 (2H, s, –C=CH), 4.96 (2H, s, –C=CH), 3.68–3.50 (8H, m, $–CH_2–$), 1.92 (6H, s, $–CH_3$), 1.82 (2H, s, $–CH_2–$) (Kazuo 1984).

1-(4-Benzoyl-1,4-diazepan-1-yl)-2-methylprop-2-en-1-one (3h)

It was obtained as a yellow oil; yield 60% (1.95 g, 7 mmol); IR (ATR) 3079 (aromatic C–H), 2948 (aliphatic C–H), 2919 (aliphatic C–H), 2872 (aliphatic C–H), 1630 (amide C=O), 1613 (C=C), 1299 (C–N), 731, 703 (aromatic C–H) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.33–7.25 (5H, m, Ar–H), 5.10 (1H, s, –C=CH), 4.96 (1H, s, –C=CH), 3.75–3.33 (8H, m, $–CH_2–$), 2.25 (1H, s, $–CH_2–$), 1.90 (3H, s, $–CH_3$), 1.67 (1H, s, $–CH_2–$); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 172.8 (C=O), 171.5 (C=O), 140.6 (C=C), 136.0 (aromatic C), 129.5 (aromatic C), 128.5 (aromatic C), 126.5 (aromatic C), 115.4 (C=C), 50.2 ($–CH_2–$), 49.4 ($–CH_2–$), 48.7 ($–CH_2–$), 47.7 ($–CH_2–$), 27.9

(–CH_2–), 20.5 (–CH_3); HRMS (ESI) (*m/z*) Calcd for $C_{16}H_{20}N_2O_2$ 273.15975 found: 273.16014 $(M + H)^+$.

General synthesis procedure and spectroscopic data of piperazine-dihydrofuran compounds (5a–k)

A solution of $Mn(OAc)_3$ (2 mmol, 530 mg) in 15 mL glacial acetic acid was heated to 80 °C until dissolved. After that the solution temperature was set to 65 °C. A solution of corresponding 1,3-dicarbonyl (**4a–c**) (1 mmol) and related unsaturated piperazine compound (1.2 mmol) in 3 mL of AcOH was added to $Mn(OAc)_3$ solution. The mixture was stirred and disappearance of dark brown color indicated that the reaction was finished. Water (20 mL) was added and crude product was extracted with chloroform (3 × 20 mL). Combined organic phases were neutralized with saturated $NaHCO_3$ solution, dried over anhydrous Na_2SO_4 and evaporated. The residue was purified with column chromatography using chloroforom–acetone (85:15) as eluent.

2-(4-Methacryloylpiperazine-1-carbonyl)-2,6,6-trimethyl-2,3,6,7-tetrahydrobenzofuran-4(5H)-one (5a)

It was obtained as a colorless solid; yield 77% (277 mg, 0.76 mmol); mp: 139–141 °C; IR (ATR) υ_{max} 2955 (aliphatic C–H), 2922 (aliphatic C–H), 2875 (aliphatic C–H), 1636 (amide C=O), 1620 (C=C), 1194 (C–N), 1016 (C–O); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.23 (1H, s, –C=CH), 5.04 (1H, s, –C=CH), 3.57 (8H, s, –CH_2–), 3.47 (1H, d, $J = 15.2$ Hz, –CH_2–), 2.69 (1H, d, $J = 15.2$ Hz, –CH_2–), 2.27 (2H, d, $J = 7.2$ Hz, –CH_2–), 2.23 (2H, s, –CH_2–), 1.94 (3H, s, –CH_3), 1.60 (3H, s, -CH_3), 1.10 (3H, s –CH_3), 1.08 (3H, s, –CH_3); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 194.6 (C=O), 172.9 (C=C–O), 171.3 (C=O), 169.7 (C=O), 139.9 (C=C), 116.1 (C=C), 111.4 (C=C–O), 91.9 (O–C–), 50.8 (–CH_2–), 46.1 (–CH_2–), 43.5 (–CH_2–), 37.7 (–CH_2–), 37.5 (–CH_2–), 32.2 (–CH_2–), 28.6 (–CH_2–), 26.2 (–CH_2–), 20.4 (-CH_3), 20.4 (–CH_3); HRMS (ESI) (*m/z*) Calcd for $C_{20}H_{28}N_2O_4$ 361.21346 found: 361.21282 $(M + H)^+$.

2,2′-(Piperazine-1,4-dicarbonyl)bis(2,6,6-trimethyl-2,3,6,7-tetrahydrobenzofuran-4(5H)-one) (5b)

It was obtained as a colorless solid; yield 40% (192 mg, 0.38 mmol); mp: 205–207 °C; IR (ATR) 2955 (aliphatic C–H), 2904 (aliphatic C–H), 2874 (aliphatic C–H), 2850 (aliphatic C–H), 1628 (amide C=O), 1610 (C=C), 1180 (C–N), 1012 (C–O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.58 (8H, s, –CH_2–), 3.46 (2H, d, $J = 15.2$ Hz, –CH_2–), 2.68 (2H, d, $J = 15.2$ Hz, –CH_2–), 2.31 (4H, d, $J = 16.0$ Hz, –CH_2–), 2.24 (4H, d, $J = 16.0$ Hz, –CH_2–), 1.59 (6H, s, –CH_3), 1.10 (6H, s, –CH_3), 1.07 (6H, s, –CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 194.7 (C=O), 173.0 (C=C–O–), 169.8 (C=O), 111.4 (C=C–O), 91.9 (O–C–), 50.9 (–CH_2–), 46.1 (–CH_2–), 43.6 (–CH_2–), 37.8 (–CH_2–), 37.6 (–CH_2–), 34.3 (–CH_2–), 28.7 (–CH_3–), 26.3 (–CH_3); HRMS (ESI) (*m/z*) Calcd for $C_{28}H_{38}N_2O_6$ 499.28026 found: 499.28260 $(M + H)^+$.

Ethyl 5-(4-methacryloylpiperazine-1-carbonyl)-2,5-dimethyl-4,5-dihydrofuran-3-carboxylate (5c)

It was obtained as a colorless solid; yield 40% (122 mg, 0.38 mmol); mp: 74–76 °C; IR (ATR) 2974 (aliphatic CH), 2901 (aliphatic CH), 1702 (ester C=O), 1628 (amide C=O), 1610 (C=C), 1246 (C–N), 1195 (C–O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 5.22 (1H, s, –C=CH), 5.03 (1H, s, –C=CH), 4.15 (2H, q, $J = 7.2$ Hz, –O–CH_2CH_3), 3.58 (1H, d, $J = 15.6$ Hz, –CH_2–), 3.56 (8H, s, –CH_2–), 2.71 (1H, d, $J = 15.6$ Hz, –CH_2–), 2.17 (3H, s, –CH_3), 1.94 (3H, s, –CH_3), 1.56 (3H, s, –CH_3), 1.25 (3H, t, $J = 7.2$ Hz, –O–CH_2CH_3) ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 171.4 (C=C–O), 170.5 (C=O), 165.5 (C=O), 164.5 (C=O), 139.9 (C=C), 116.1 (C=C), 102.3 (C=C–O), 88.3 (O–C), 59.7 (–CH_2), 46.4 (–CH_2), 43.6 (–CH_2), 41.2 (–CH_2), 26.0 (CH_3), 20.4 (CH_3), 14.3 (CH_3), 14.0 (CH_3); HRMS (ESI) (*m/z*) Calcd for $C_{17}H_{24}N_2O_4$ 321.18088 found: 321.18203 $(M + H)^+$.

Diethyl 5,5′-(piperazine-1,4-dicarbonyl)bis(2,5-dimethyl-4,5-dihydrofuran-3-carboxylate) (5d)

It was obtained as a colorless solid; yield 12% (60 mg, 0.12 mmol); mp: 123–125 °C; IR (ATR) 2982 (aliphatic C–H), 2930 (aliphatic C–H), 1794 (ester C=O), 1698 (amide C=O), 1620 (C=C), 1197 (C–N), 1056 (C–O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 4.16 (4H, q, $J =$ 7.2 Hz, –O–CH_2CH_3), 3.61 (2H, d, $J = 15.2$ Hz, –CH_2–), 3.60 (8H, s, –CH_2–), 2.73 (2H, d, $J = 15.2$ Hz, –CH_2–), 2.19 (6H, s, –CH_3), 1.57 (6H, s, –CH_3), 1.27 (6H, t, $J = 7.2$ Hz, –O–CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 176.4 (C=C–O), 165.6 (C=O), 164.5 (C=O), 102.3 (C=C–O), 88.3 (O–C), 59.7 (–CH_2–), 46.4 (–CH_2–), 43.6 (–CH_2–), 41.2 (–CH_2–), 26.03 (–CH_3), 14.3 (–CH_3), 14.1 (–CH_3); HRMS (ESI) (*m/z*) Calcd for $C_{24}H_{34}N_2O_8$ 501.2274 found: 501.22171 $(M + Na)^+$.

Ethyl 2,5-dimethyl-5-(4-(2,6,6-trimethyl-4-oxo-2,3,4,5,6,7-hexahydrobenzofuran-2-carbonyl) piperazine-1-carbonyl)-4,5-dihydrofuran-3-carboxylate (5e)

It was obtained as a yellow oil; yield 36% (175 mg, 0.35 mmol) mp: 143–145 °C IR (ATR) 2956 (aliphatic

C–H), 2916 (aliphatic C–H), 2850 (aliphatic C–H), 1703 (ester C=O), 1627 (amide C=O), 1615 (C=C), 1141 (C–N), 1014 (C–O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 4.16 (2H, q, $J = 7.2$ Hz, –O–C$\underline{H}_2$CH$_3$), 3.72 (8H, s, –CH_2–), 3.59 (1H, dd, $J = 15.2$, 2.0 Hz, –CH_2–), 3.47 (1H, dd, $J = 15.2$, 2.0 Hz, –CH_2–), 2.73 (1H, dd, $J = 15.2$, 2.0 Hz, –CH_2–) 2.70 (1H, dd, $J = 15.2$, 2.0 Hz, –CH_2–), 2.30 (2H, dd, $J = 14.0$, 1.2 Hz, –CH_2–), 2.25 (2H, dd, $J = 14.0$, 1.2 Hz, –CH_2–), 2.18 (3H, d, $J = 2.0$ Hz, –CH_3), 1.60 (3H, s, –CH_3), 1.57 (3H, s, –CH_3), 1.25 (3H, t, $J = 7.2$ Hz, –CH_3), 1.11 (3H, s, –CH_3) 1.08 (3H, s, –CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 194.5 (C=O), 172.9 (C=C–O), 165.5 (C=O), 164.5 (C=O), 111.42 (C=C–O), 91.8 (O–C), 88.3 (O–C), 59.7 (–CH_2–), 50.9 (–CH_2–), 46.2 (–CH_2–), 43.4 (–CH_2–), 41.2 (–CH_2–), 37.8 (–CH–), 37.5 (–CH_2–), 34.2 (–CH_2–), 28.7 (–CH_2–), 28.69 (–C–), 28.6 (–CH_3), 26.2 (–CH_3), 26.0 (–CH_3), 14.3 (–CH_3), 14.0 (–CH_3); HRMS (ESI) (*m/z*) Calcd for $C_{26}H_{36}N_2O_7$ 489.25953 found: 489.25956 $(M + H)^+$.

1-(4-(4-Acetyl-2,5-dimethyl-2,3-dihydrofuran-2-carbonyl)piperazin-1-yl)-2-methylprop-2-en-1-one (5f)

It was obtained as a yellow oil; yield 65% (208 mg, 0.64 mmol) IR (ATR) 2982 (aliphatic C–H), 2920 (aliphatic C–H), 2864 (aliphatic C–H), 1630 (amide C=O), 1613 (C=C), 1192 (C–N), 1017 (C–O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.23 (1H, s, –C=CH), 5.03 (1H, s, –C=CH), 3.74 (1H, d, $J = 15.2$ Hz, –CH_2–), 3.56 (8H, s, –CH_2–), 2.76 (1H, d, $J = 15.2$ Hz, –CH_2–), 2.19 (3H, s, –CH_3), 2.17 (3H, s, –CH_3), 1.94 (3H, s, –CH_3), 1.57 (3H, s, –CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 194.8 (C=O), 171.4 (C=C–O), 170.3 (C=O), 164.1 (C=O), 139.8 (C=C), 116.1 (C=C), 111.5 (C=C–O), 88.6 (O–C), 46.4 (–CH_2–), 43.5 (–CH_2–), 41.9 (–CH_2–), 29.6 (–CH_3), 26.0 (–CH_3), 20.4 (–CH_3), 14.8 (-CH_3); HRMS (ESI) (*m/z*) Calcd for $C_{17}H_{24}N_2O_4$ 321.18088 found: 321.18203 $(M + H)^+$.

2-(4-Benzoylpiperazine-1-carbonyl)-2,6,6-trimethyl-2,3,6,7-tetrahydrobenzofuran-4(5H)-one (5g)

It was obtained as a yellow solid; yield 60% (238 mg, 0.60 mmol); mp:142–144 °C; IR (ATR) 2961 (aliphatic C–H), 2916 (aliphatic C–H) 2869 (aliphatic C–H), 2850 (aliphatic C–H), 1640 (amide C=O), 1627 (C=C), 1230 (C–N), 1008 (C–O), 749, 705 (aromatic C–H) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.44–7.38 (5H, m, Ar–H), 3.67 (8H, s, –CH_2–), 3.48 (1H, d, $J = 15.2$ Hz, –CH_2–), 2.69 (1H, d, $J = 15.2$ Hz, –CH_2–), 2.27 (2H, s, –CH_2–), 2.23 (2H, s, –CH_2–) 1.60 (3H, s, –CH_3), 1.10 (3H, s, –CH_3), 1.08 (3H, s, –CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 194.6 (C=O), 173 (–C=C–O), 170.7 (C=O), 169.8 (C=O), 135.1 (aromatic C), 130.2 (aromatic C), 128.7 (aromatic C), 127.1 (aromatic C), 111.5 (C=C), 92 (O–C), 50.9 (–CH_2–), 46.3 (–CH_2–), 43.6 (–CH_2–), 37.8 (–CH_2–), 37.6 (–C–), 34.3 (–CH_2), 28.7 (–CH_3), 28.7 (–CH_3), 26.3 (–CH_3); HRMS (ESI) (*m/z*) Calcd for $C_{23}H_{28}N_2O_4$ 397.21218 found: 397.21301 $(M + H)^+$.

2,6,6-Trimethyl-2-(4-(tetrahydrofuran-2-carbonyl) piperazine-1-carbonyl)-2,3,6,7-tetrahydrobenzofuran-4(5H)-one (5h)

It was obtained as a yellow solid; yield 43% (167 mg, 0.42 mmol); mp: 76–78 °C; IR (ATR) 2957 (aliphatic C–H), 2930 (aliphatic C–H) 2872 (aliphatic C–H), 1711 (C=O) 1631 (amide C=O), 1610 (C=C), 1232 (C–N), 1028 (C–O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 4.56 (1H, t, $J = 5.2$ Hz, O–CH–), 3.86 (2H, m, –CH_2–), 3.66 (8H, s, –CH_2–), 3.46 (1H, d, $J = 15.2$ Hz, –CH_2–), 2.68 (1H, d, $J = 15.2$ Hz, –CH_2–), 2.27 (2H, d, $J = 6.0$ Hz, –CH_2–), 2.22 (2H, s, –CH_2–), 2.03–1.87 (4H, m, –CH_2–), 1.59 (3H, s, –CH_3), 1.10 (3H, s, –CH_3), 1.08 (3H, s, –CH_3); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 194.5 (C=O), 173 (C=C–O), 171.2 (C=O), 169.6 (C=O), 111.4 (C=C–O), 91.9 (O–C), 75.9 (–C–), 69.0 (–CH_2–), 50.8 (–CH_2–), 45.3 (–CH_2–), 42.1 (–CH_2–), 37.7 (–CH_2–), 37.5 (–CH_2–), 34.2 (–C–), 29.6 (–CH_2–), 28.6 (–CH_2–), 28.0 (–CH_3), 26.2 (–CH_3), 25.7 (–CH_3); HRMS (ESI) (*m/z*) Calcd for $C_{21}H_{30}N_2O_5$ 391.22275 found: 391.22301 $(M + H)^+$.

2-(4-(Furan-2-carbonyl)piperazine-1-carbonyl)-2,6,6-trimethyl-2,3,6,7-tetrahydrobenzofuran-4(5H)-one (5i)

It was obtained as a yellow oil; yield 40% (154 mg, 0.40 mmol) IR (ATR) 3115 (aromatic C–H), 2955 (aliphatic C–H), 2926 (aliphatic C–H), 2870 (aliphatic C–H), 1626 (amide C=O), 1610 (C=C), 1232 (C–N), 1026 (C–O), 746, 700 (aromatic C–H) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.50 (1H, d, $J = 0.8$ Hz, Ar–H), 7.06 (1H, d, $J = 3.6$ Hz, Ar–H), 6.50 (1H, dd, $J = 3.6$, 0.8 Hz, Ar–H), 3.71 (8H, s, –CH_2–), 3.50 (1H, d, $J = 15.2$, –CH_2–), 2.71 (1H, d, $J = 15.2$, –CH_2–), 2.30 (2H, d, $J = 3.2$ Hz, –CH_2–), 2.25 (2H, s, –CH_2–), 1.62 (3H, s, –CH_3), 1.12 (3H, s, –CH_3), 1.10 (3H, s, –CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 194.6 (–C=O), 172.9 (C=C–O), 169.7 (C=O), 159.2 (C=O), 147.5 (aromatic C), 143.9 (aromatic C), 117.2 (aromatic C), 111.5 (aromatic C), 111.4 (C=C–O), 91.9 (–C–), 50.9 (–CH_2), 46.3 (–CH_2–), 43.6 (–CH_2–), 37.8 (–CH_2–), 37.5 (–C–), 34.2 (–CH_2–), 28.7 (–CH_3), 28.6 (–CH_3), 26.2 (–CH_3); HRMS (ESI) (*m/z*) Calcd for $C_{21}H_{26}N_2O_5$ 387.19145 found: 387.19210 $(M + H)^+$.

2-(4-Methacryloyl-1,4-diazepane-1-carbonyl)-2,6,6-trimethyl-2,3,6,7-tetrahydrobenzofuran-4(5H)-one (5j)

It was obtained as a colorless oil; yield 41% (153 mg, 0.40 mmol); IR (ATR) 2955 (aliphatic C–H), 2872 (aliphatic C–H), 1630 (amide C=O), 1615 (C=C), 1232 (C–N), 1028 (C–O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 5.14 (1H, s, –C=CH), 4.96 (1H, d, $J = 15.2$ Hz, $–CH_2–$), 3.92–3.36 (8H, m, $–CH_2–$), 3.43 (1H, d, $J = 15.6$ Hz, $–CH_2–$), 2.68 (1H, d, $J = 15.2$ Hz, $–CH_2–$), 2.29 (2H, s, $–CH_2–$), 2.22 (2H, s, $–CH_2$), 1.93 (3H, s, $–CH_3$), 1.82 (2H, s, $–CH_2–$), 1.58 (3H, d, $J = 8.4$ Hz, $–CH_3$), 1.08 (6H, d, $J = 8.8$ Hz, $–CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 194.6 (C=O), 173.3 (C=C–O), 172.3 (C=O), 170.6 (C=O), 140.5 (C=C), 115.4 (C=C), 111.3 (C=C–O), 92.1 (–C–), 50.9 ($–CH_2–$), 49.7 ($–CH_2–$), 49.9 ($–CH_2–$), 47.5 ($–CH_2–$), 47.0 ($–CH_2–$), 37.7 ($–CH_2–$), 34.2 (–C–), 29.6 ($–CH_2–$), 28.7 ($–CH_3$), 28.5 ($–CH_3$), 28.15 ($–CH_2–$), 26.3 ($–CH_3$), 20.5 ($–CH_3$); HRMS (ESI) (*m/z*) Calcd for $C_{21}H_{30}N_2O_4$ 375.22783 found: 375.22850 $(M + H)^+$.

2-(4-Benzoyl-1,4-diazepane-1-carbonyl)-2,6,6-trimethyl-2,3,6,7-tetrahydrobenzofuran-4(5H)-one (5k)

It was obtained as a colorless oil; yield 50% (205 mg, 0.50 mmol); IR (ATR) 3079 (aromatic C–H), 2956 (aliphatic C–H), 2926 (aliphatic C–H), 2870 (aliphatic C–H), 1626 (amide C=O), 1610 (C=C), 1230 (C–N), 1006 (C–O), 746, 704 (aromatic C–H) cm^{-1}; ^1H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.37v7.19 (5H, m, Ar–H), 4.00–3.26 (8H, m, $–CH_2–$), 3.46 (1H, d, $J = 15.2$ Hz, $–CH_2–$), 2.68 (1H, d, $J = 15.2$ Hz, $–CH_2–$), 2.29 (2H, s, $–CH_2–$), 2.21 (2H, s, $–CH_2–$) 1.97 (1H, s, $–CH_2–$), 1.71 (1H, s, $–CH_2–$), 1.60 (3H, s, $–CH_3$), 1.08 (6H, d, $J = 15.2$ Hz, $–CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 194.7 (C=O), 173.3 (C=C–O), 171.5 (C=O), 171.0 (C=O), 136.0 (aromatic C), 129.6 (aromatic C), 128.5 (aromatic C), 126.4 (aromatic C), 111.4 (C=C–O), 92.1 (–C–), 50.9 ($–CH_2–$), 50 ($–CH_2–$), 48.0 ($–CH_2–$), 47.4 ($–CH_2–$), 45.8 ($–CH_2–$), 37.8 ($–CH_2–$), 29.6 (–C–), 28.7 ($–CH_2–$), 28.5 ($–CH_3–$) 28.4 ($–CH_3$), 27.3 ($–CH_3$), 26.3 ($–CH_2–$); HRMS (ESI) (*m/z*) Calcd for $C_{24}H_{30}N_2O_4$ 411.22783 found: 411.22854 $(M + H)^+$.

Ethyl 5-(4-(furan-2-carbonyl)piperazine-1-carbonyl)-2,5-dimethyl-4,5-dihydrofuran-3-carboxylate (5l)

It was obtained as yellow oil; yield 20% (75 mg, 0.20 mmol); IR (ATR) 3100 (aromatic C–H), 2960 (aliphatic C–H), 2920 (aliphatic C–H), 1710 (ester C=O), 1630 (amide C=O), 1615 (C=C), 1230 (C–N), 1100 (C–O), 750, 700 (aromatic C–H) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.48 (1H, d, $J = 1.2$ Hz, Ar–H), 7.03 (1H, d, $J = 3.2$ Hz, Ar–H), 6.48 (1H, dd, $J = 3.2$, 1.2 Hz, Ar–H), 4.14 (2H, q, $J = 7.6$ Hz, $–O–CH_2CH_3$), 3.81 (8H, s, $–CH_2–$), 3.59 (1H, dd, $J = 15.6$, 1.6 Hz, $–CH_2–$), 2.72 (1H, dd, $J = 15.6$, 1.6 Hz, $–CH_2–$), 2.18 (3H, s, $–CH_3$), 1.57 (3H, s, $–CH_3$), 1.25 (3H, t, $J = 7.6$ Hz, $O–CH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 170.6 (C=C–O), 165.6 (C=O), 164.6 (C=O), 159.2 (C=O), 147.6 (aromatic C), 143.9 (aromatic C), 117.1 (aromatic C), 111.5 (aromatic C), 102.3 (C=C–O), 88.3 (–C–), 59.7 ($–CH_2–$), 46.3 ($–CH_2–$), 43.5 ($–CH_2–$), 41.2 ($–CH_2–$), 26.0 ($–CH_3$), 14.3 ($–CH_2–$), 14.0 ($–CH_3$); HRMS (ESI) (*m/z*) Calcd for $C_{19}H_{24}N_2O_6$ 377.17071 found: 377.17199 $(M + H)^+$.

Results and discussion

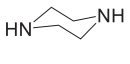
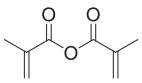
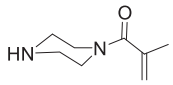
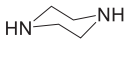
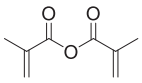
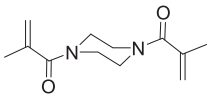
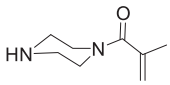
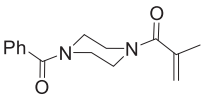
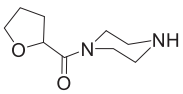
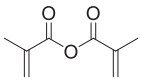
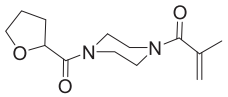
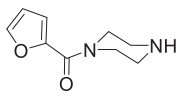
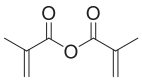
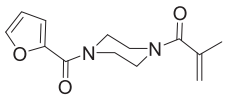
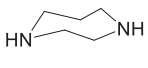
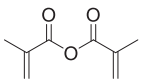
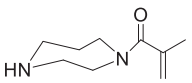
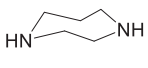
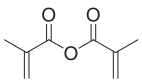
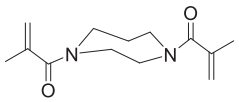
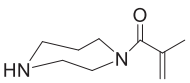
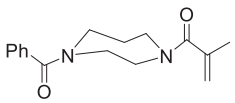
Chemistry

The starting reagents (**3a–h**), unsaturated piperazines and homo piperazines, were obtained from the reaction of piperazine (**1a**), piperazine derivatives (**1c**, **1d**, and **3a**) and homo piperazines (**1b** and **3f**), with acylation reagents (methacrylic anhydride (**2a**) and benzoyl chloride (**2b**)) in medium to high yields (Table 1). All acylated products bear methacryloyl moeities and their FTIR spectra show amide stretchings between 1672–1620 cm^{-1} and alkene stretchings at 1620–1600. Also, ^1H NMR spectra of **3a–h** show two terminal alkene protons between 5.3–5.0 ppm as singlet for each proton and also aromatic protons of **3c**, **3e**, and **3h** are observed between 7.43–6.50 ppm. Moreover, ^{13}C NMR spectra of novel unsaturated piperazine derivatives show C=O carbon peaks between 172–169 ppm and C=C peaks belonging to methacryl moeity between 141–139 ppm and 116–114 ppm. All HRMS analysis of novel unsaturated piperazine derivatives were performed with a ±5 ppm maximum margin or error.

Radical cyclization of dimethacryloyl piperazine (**3b**) with dimedone (**4a**) mediated by $Mn(OAc)_3$ gave mono dihydrofuran (**5a**, 77%) and bis-dihydrofuran (**5b**, 10%). These compounds were diferentiated by their ^1H NMR spectra. Although terminal alkene protons of **5a** resonated at 5.23 ppm and 5.04 ppm, absence of these peaks in spectrum of **5b** indicates that product **5b** is bis-dihydrofuran. In addition, geminal proton peaks of these dihydrofuran ring are observed between 3.50–3.46 and 2.73–2.68 ppm as doublets ($J = 15.2$ Hz) for each proton. Also, the treatment of **3b** with ethyl acetoacetate (**4b**) formed dihydrofurans **5c** (40%) and **5d** (12%) and these compounds were differentiated by ^1H NMR similarly to **5a** and **5b**.

To further increase the formation yield of bis-dihydrofuran compound (**5b**), reaction of mono dihydrofuran (**5a**) with

Table 1 Acylation reactions of piperazines to give unsaturated piperazine compounds

Entry	Piperazines	Acylation reagents	Products	Yield (%)[a]
1	 **1a**	 **2a**		**3a**, 72[b]
2	 **1a**	 **2a**		**3b**, 75[c]
3	 **3a**	 **2b**		**3c**, 72[d]
4	 **1c**	 **2a**		**3d**, 82[e]
5	 **1d**	 **2a**		**3e**, 88[e]
6	 **1b**	 **2a**		**3f**, 70[b]
7	 **1b**	 **2a**		**3g**, 70[c]
8	 **3f**	 **2b**		**3h**, 60[d]

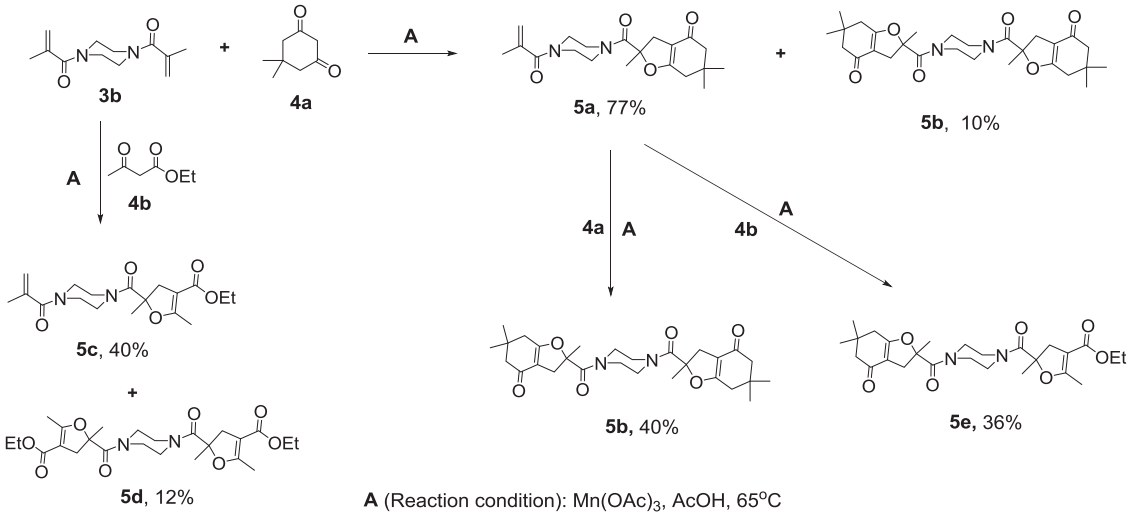
[a]Isolated yield based on the piperazine derivatives

[b](Molar ratio: **1a** or **1b**: **2a** = 1: 0.5), −10 °C; c) (**1a** or **1b**: **2a** = 1:2), 0 °C; d) (**3a** or **3f**: **2b** = 1:1), triethylamine, 0 °C) e) (**1c** or **1d**: **2a** = 1:1), 0 °C

dimedone (**4a**) was performed and compound **5b** was obtained in 40% yield. In addition, bis-dihydrofuran compound (**5e**) was obtained from the radical cyclization of **5a** with ethyl acetoacetate (**4b**) in 36% yield (Scheme 1).

As can be seen on Table 2, radical cyclization of **3b** with acetylacetone (**4c**) gave **5f** in 65% yield. In addition, piperazine-dihydrofuran compounds **5g** (60%), **5h** (43%), and **5i** (40%) were obtained by the reactions of **3c–e** with dimedone (**4a**), in medium yields, respectively. Radical cyclizations of homopiperazine derivatives (**3g** and **3h**) were also performed with dimedone (**4a**) and as a result **5j** (41%) and **5k** (50%) were obtained in medium yields. Also compound **5l** (20%) was obtained from the reaction of **3e** with **4b** in low yield.

The proposed mechanism for the formation of dihydrofurans is explained in Scheme 2. According to this mechanism, the enol form of dimedone (**A**) reacts with $Mn(OAc)_3$ and an alpha carbon radical **B** is formed, while



Scheme 1 Synthesis of compounds **5a–e**

Mn^{3+} reduces to Mn^{2+}. An electron from alkene is added to this α-carbon radical and produces the radical carbon intermediate **C**. Intermediate C oxidizes to carbocation **D** with $Mn(OAc)_3$ and intramolecular cyclization of **D** forms the product **E (5a)**.

Biological activity

In vitro inhibition experiments of AChE

In vitro AChE inhibitory activities of test compounds were determined by slightly modified Ellman method (Ellman et al. 1961). AChE (from electric eel, type V-S), acetylthiocholine iodide (ATCI), 5,5′-Dithiobis(2-nitrobenzoic acid) (DTNB) were obtained from Sigma Aldrich.

The assay solution contained 1480 µL of phosphate buffer (pH = 8.0, 0.1 M), 50 µL of DTNB solution (prepared with pH 7 phosphate buffer), 20 µL of different concentrations of test compounds in ethanol-deionized water (1:1), 10 µL of substrate solution (ATCI, prepared with deionized water), and 25 µL of AChE solution (prepared with deionized water and 1% gelatin). All test compounds were incubated for 10 min at 30 °C and absorbances at 412 nm were determined. A control reaction containing all ingredients except inhibitory test compounds was performed same as above and the absorbance at 412 nm was considered 100% enzyme activity. The percentage activity of AChE for any tested compound was calculated with the formula:

$$\%\,\text{Enzyme activity} = (A_s/A_0) \times 100,$$

A_s: Absorbance of assay solution with inhibitor.

A_0: Absorbance of control.

The concentration of each test compound was tested in triplicate and IC_{50} values were calculated graphically using GraphPad Prism 8.0.3 software. IC_{50} value is defined as the concentration of sample which performs 50% inhibition towards AChE.

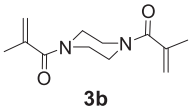
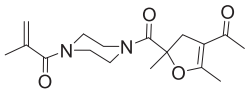
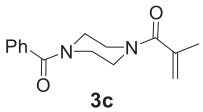
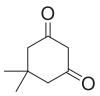
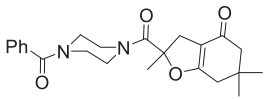
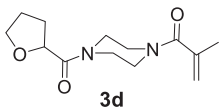
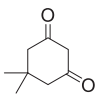
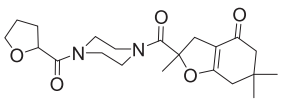
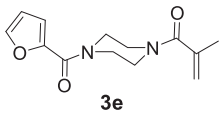
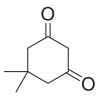
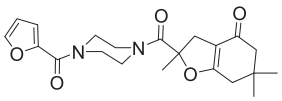
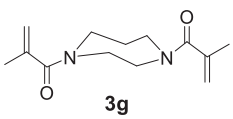
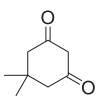
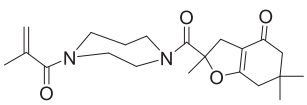
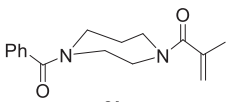
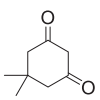
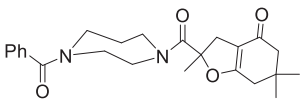
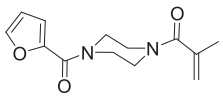
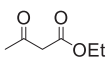
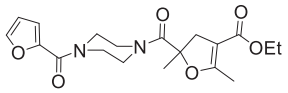
In vitro evaluation of inhibitory activities of piperazine-dihydrofuran compounds (5a–k) towards AChE

Over recent years there are some works in literature about AChE inhibition of piperazine containing compounds. Aliabadi et al. (2017) described the synthesis of benzamide-piperazine derivatives and evaluate their inhibition capabilities against AChE and reported IC_{50} values between 0.44–27 µM (Aliabadi et al. 2017). In addition, Chaves and coworkers developed hydroxybenzimidazole-donepezil hybrids and evaluated them for AChE inhibition. They reported IC_{50} values between 1.67–21 µM (Chaves et al. 2020). Moreover, benzothiazole-piperazine hybrids were developed by Mishra et al. and evaluated for their AChE inhibition. They reported IC_{50} values between 2.31 and 26.43 µM (Mishra et al. 2020).

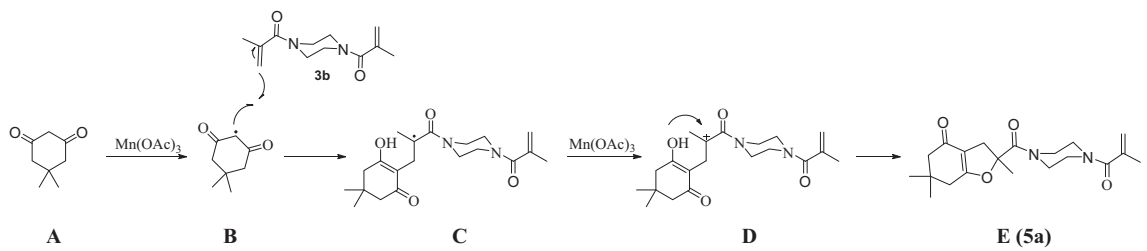
Although AChE inhibition of many piperazine derivatives were reported in the literature, acylated piperazine derivatives (**3b–h**) were tested against AChE and it was found that they have almost no inhibition effect (IC_{50} > 100 µM). However, piperazine substituted dihydrofuran compounds (**5a–l**) were tested against AChE and it was confirmed that they show significantly higher inhibitions. All results were compared to standard drugs Donepezil and Galanthamine (Table 3).

IC_{50} values of piperazine containing dihydrofurans (**5a**–**5d**) formed by the reaction of dimethacryloyl piperazine (**3b**) with dimedone (**4a**) and ethyl acetoacetate

Table 2 Radical cyclizations of piperazine derivatives

Entry	Piperazines	1,3-Dicarbonyls	Products	Yield (%)[a]
1	 **3b**	 **4c**		**5f**, 65
2	 **3c**	 **4a**		**5g**, 60
3	 **3d**	 **4a**		**5h**, 43
4	 **3e**	 **4a**		**5i**, 40
5	 **3g**	 **4a**		**5j**, 41
6	 **3h**	 **4a**		**5k**, 50
7	 **3e**	 **4b**		**5l**, 20

[a]Isolated yield based on 1,3-dicarbonyl compounds



Scheme 2 Proposed mechanism of $Mn(OAc)_3$ mediated radical cyclization

(**4b**) were calculated as 17.93, 11.17, 5.79, and 3.89 μM, respectively. Also, compound (**5e**) has AChE inhibition effect with an IC_{50} value of 5.07 μM. In addition compound **5f** shows medium inhibition ($IC_{50} = 11.87$ μM). It can be seen that carbethoxy carrying compound (**5d**) show best inhibition effect ($IC_{50} = 3.89$ μM) against AChE among

Table 3 IC_{50} values of piperazine-dihydrofuran compounds (5a–l) toward AChE

Compound	IC50 ± SD (μM)[a]
5a	17.93 ± 2
5b	11.17 ± 1
5c	5.79 ± 0.8
5d	3.89 ± 0.3
5e	5.07 ± 0.4
5f	11.87 ± 0.7
5g	14.34 ± 2
5h	8.55 ± 0.3
5i	4.30 ± 0.3
5j	>100
5k	>100
5l	2.24 ± 0.4
Donepezil[b]	0.041
Galanthamine[b]	1.65

[a]The values are mean of three independent experiments ± SD

[b]Ref. (Fu et al. 2020)

them. These results show that bis-dihydrofurans (**5b**, **5d**, and **5e**) possess higher inhibiton power than mono-dihydrofurans and carbethoxy carrying piperazine-dihydrofuran compounds (**5c**, **5d**, and **5e**) are much more potent than the other dihydrofuran compounds (**5a** and **5b**).

By comparing piperazine substituted dihydrofuran (**5a**) with homopiperazine-dihydrofuran (**5k**), it can be seen that, while **5a** has inhibition effect on AChE with an IC_{50} value of 17.93 μM, compound **5k** has almost no inhibiton effect ($IC_{50} > 100$ μM). Similar result was achieved from the comparison of compounds **5g** and **5k**. On the other hand, the IC_{50} values of piperazine substituted dihydrofuran (**5g–i)** were calculated as 14.34 μM for benzoyl substituted compound **5g**, 8.55 μM for tetrahydrofuroyl substituted compound **5h** and 4.30 μM for furoyl substituted compound **5i**. According to these results, it can be seen that tetrahydrofuroyl and furoyl substituted piperazine-dihydrofuran compounds have significantly more inhibiton effect.

Summarily, in the light of these results, it can be concluded that both carbethoxy and furoyl substitutions have significant positive effect on AChE inhibiton capabilities of piperazine-dihydrofuran compounds. For this reason, compound **5l** was designed and it's inhibition effect was tested and show much higher inhibiton than other piperazine-dihydrofuran compounds ($IC_{50} = 2.24$ μM), as expected.

In silico molecular docking experiments

Three dimensional structure of recombinant human AChE complexed with donepezil was obtained from Protein Data Bank (PDB code: 4EY7) (Cheung et al. 2012). All water molecules, detergents and B-chain of enzyme were removed. Conformational analysis was performed with Avogadro software and most stable conformations were optimized with semiempirical PM6 method in Gaussian 09 Software. All ligand–protein docking calculations were performed as flexible ligand in rigid protein using AutoDock Vina software (Trott and Olson 2010). Best docking mod of ligand in terms of binding energy (kcal/mol) was selected and used. Docking results of ligands were compared with standart drug donepezil.

Molecular docking results of selected piperazine-dihydrofuran compounds (5d, 5i, and 5l)

To investigate the ligand–protein interactions, molecular docking studies were performed on the three most potent inhibitor compounds **5d**, **5i**, **5l** and standart drug donepezil. Firstly, to validate the docking procedure, co-crystallized ligand donepezil was re-docked to target AChE enzyme. Validation result shows near perfect alignment with original ligand with RMSD of 0.340 and −12.2 kcal/mol binding score. Overlapping of native ligand donepezil and re-docked donepezil was given at Fig. 1.

Top docking poses of ligands in terms of free energy were used to evaluate interactions with protein. Binding energies for donepezil, **5d**, **5i**, and **5l** are −12.2, −8.9, −8.7, and −9.6 kcal/mol, respectively. AChE active site cavity with docked donepezil and ligand **5l** were given at Fig. 2 to compare binding poses of donepezil and **5l**.

As can be seen on Fig. 3 donepezil N-benzyl moeity interacts with aromatic groups of HIS447 and TRP86 through π–π interactions. Also, piperidine ring forms π–alkyl and π–π interactions with aromatic moeities of TYR341, TYR337, and PHE338. In addition carbonyl oxygen forms a conventional C–H interaction with PHE295. TRP286 interacts with benzene and methoxy group through π–π and π–σ bonds, respectively. Similarly TYR341 forms π–π and π–σ interactions with benzene and CH_2 group, respectively. Ligand–protein interactions of top binding poses of ligands **5d**, **5i**, and **5l** were given in Fig. 4.

By investigating the interactions between top docking mod of **5i** and AChE it can be seen that, dimedone methyls form interactions like donepezil with aromatic groups of HIS447 at catalytic triad and TRP86 at anionic site through π–alkyl bonds. In addition dihydrofuran methyl and piperazine ring interacts with TYR341 and TYR 124 at peripheral anionic site of AChE through π–alkyl interactions. Lastly, aromatic furan ring forms a π–π interaction with TYR341.

By investigating the interactions of bis carbethoxy bearing piperazine-dihydrofuran compound **5d**, it can be seen that amide carbonyl forms a conventional C–H interaction with PHE295, similar to donepezil carbonyl moeity.

In addition, methyl on the dihydrofuran ring interacts through π–alkyl bonds with peripheral anionic site residues TRP286, TYR124, and TYR341. The other methyl on the dihydrofuran forms π–alkyl interactions with PHE297 and PHE338 at acyl pocket. In addition ester group of **5d** interacts with HIS287 with conventional C–H interaction.

By looking at ligand–protein interactions of **5l**, the most potent inhibitor in this work, it can be seen that both methyl moeities interacts with TRP286 with π–σ and π–alkyl interactions. Also, two dihydrofuran methyls form π–alkyl interactions with TYR341, TYR124, PHE297, and PHE338. In addition, piperazine ring forms π–alkyl interactions with PHE338 and TYR337 similar to piperidine ring of donepezil. Moreover, furan ring interacts with TRP86 through a π–π interaction.

By considering the ligand–protein interactions of the most potent inhibitors (**5d**, **5i**, and **5l**) on this work, it can be seen that they show similar mode of actions like standart drug donepezil and docking results support in vitro experimental results.

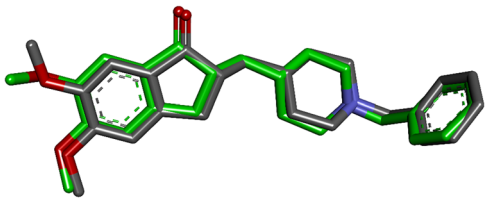


Fig. 1 Overlapping of native donepezil (gray) and re-docked donepezil (green)

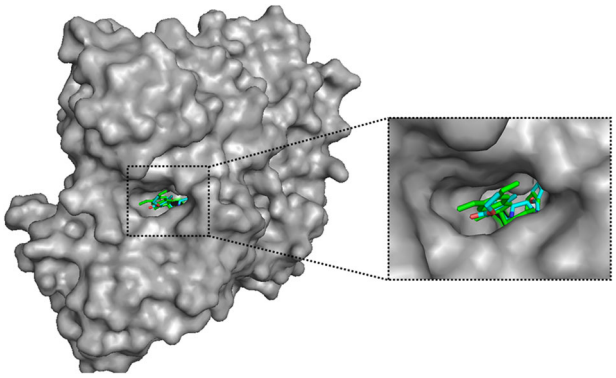


Fig. 2 AChE active site cavity with donepezil (green) and **5l** (cyan) inside

Conclusion

In the presented work, potential AChE inhibitors, new piperazin, and homopiperazine containing dihydrofurans **(5a–l)**, were synthesized by $Mn(OAc)_3$ mediated radical cyclization and their AChE inhibition capabilities were tested. Although, all piperazine-dihydrofuran compounds (except **5j** and **5k**) showed high inhibitory activities (IC_{50} values of ranging from 2.24 to 17.93 μM), all starting unsaturated piperazine derivatives (**3a–h**) show weak inhibitions ($IC_{50} > 100$ μM). These results indicated that dihydrofuran moeity has positive effect on inhibitions. Carbethoxy and furoyl carrying dihydrofuran compounds show high inhibition than other dihydrofuran compounds. For this reason, compound **5l**, which contains both furoyl and carbethoxy moieties was synthesized and show highest inhibition of all ($IC_{50} = 2.24$ μM).

In addition molecular docking studies were performed on three most potent inhibitors (**5d**, **5i**, and **5l**), to investigate ligand–protein interactions and binding energies. Ligand–protein interactions show similar mode of actions to standart drug donepezil. Binding energies are −12.2 kcal/mol for donepezil and −8.9, −8.7, and −9.6 kcal/mol for

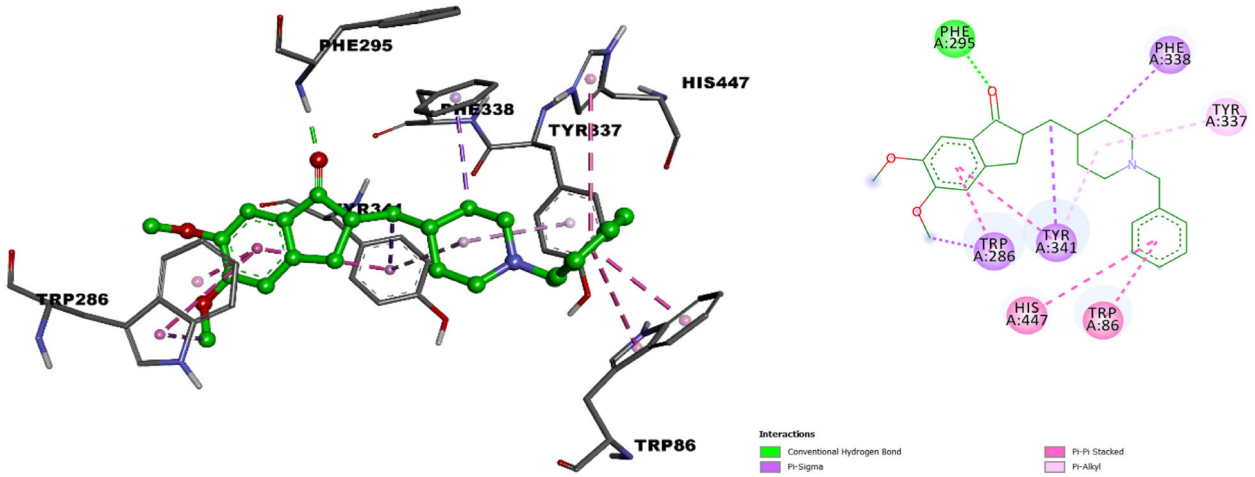


Fig. 3 3D and 2D ligand–protein interactions of donepezil with AChE

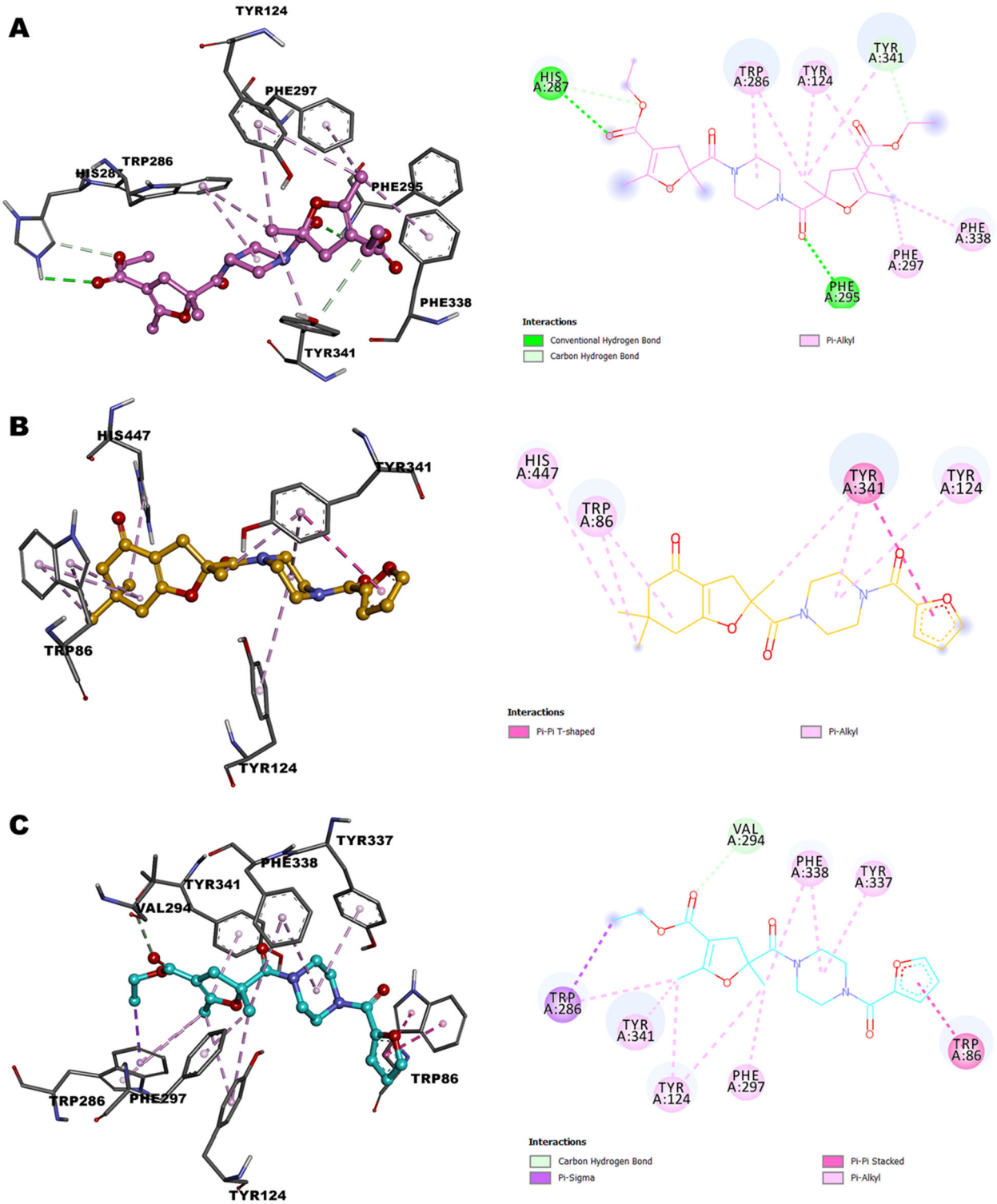


Fig. 4 3D and 2D ligand–protein interactions of **5d** (**a**), **5i** (**b**), and **5l** (**c**) with AchE

5d, **5i**, and **5l**, respectively. All these results are promising and obtained piperazine-dihydrofuran compounds may be potential AChE inhibitors.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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