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Synthesis and molecular docking studies of 4*H*-chromene derivatives as a calcium channel blocking agent

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Abstract

Voltage-gated Ca^{2+} channels play a vital role in the transmission of electrical signals by temporarily increasing intracellular Ca^{2+} levels and exerting an action potential on the cell surface membrane. As a blocker of calcium channels, nimodipine specifically blocks L-type calcium channels, which are present in smooth muscle cells in blood vessels. By blocking these channels, nimodipine prevents calcium from entering the cells, resulting in relaxation and dilation of the blood vessels. In this way, several 4H-chromene derivatives were obtained through electro synthesis in propanol, using electrons as a catalyst to generate propanol anion as a base. This process involved obtaining malononitrile anion, which readily underwent Knovenagel condensation with aromatic aldehydes, followed by the reaction of the active methylene of dimedione with the electrophile C=C of the intermediate. Finally, the expected product was o−btained through cyclisation and tautomerization. The effect of current, solvent, and anode type were studied, and it was observed that the optimized current, solvent, and anode for the synthesis of nanoparticles of 4*H*-chromene were 50 mA/cm^2, propanol, and a magnesium anode in an undivided cell at room temperature. The proposed method produces

4*H*-chromene directly from initial compounds in a mild and safe condition. All synthesized compounds were screened through molecular docking studies, which utilized the crystal structure of CavAb. Compound 8f exhibited the minimum binding energy and good affinity toward the active pocket of CavAb compared to nimodipine as a calcium channel blocking agent.

Keywords: Electrosynthesis; Knoevenagel; Calcium channel blocking agents**;** Nimodipine; Molecular docking studies.

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Introduction

A considerable number of methods have been already reported to synthesize pyran-annulated heterocyclic scaffolds, which within the last several years have drawn a significant amount of attention in medicinal chemistry. Mainly, the synthetic chemists are of the idea to develop applicable synthetic routes in order to obtain these potentially interesting heterocycles. The presence of a variety of homo- and/or heterogeneous catalysts is a particular feature of these presented methods, involving a three-component tandem reaction of 1,3-diketones, aldehydes, and malononitrile/ethyl cyanoacetate [1].

Moreover, since they can offer biological properties of a wide range such as antimicrobial [2], antifungal [3], antibacterial [4], antioxidant [5], antileishmanial [6], anticancer [7], and hypotensive [8], functionalized 4*H*-chromene derivatives have attracted great interest because. Some of these compounds were also used as inhibitors [9].

Amongst natural products only a few examples have been isolated which contain 4*H*-chromene compounds and that is why this structure is rather an unusual one. As an example of naturally occurring 4*H*-chromene, 7-hydroxy-6-methoxy-4*H*-chromene with organoleptic property can be named which is extracted from Wisteria sinensis flowers [10].

Isolated from the stems of Uvaria ufieliiwhich, uvafzlelin is another naturally occurring 4*H*-chromene with a broad range of antimicrobial activity against gram-positive and acid-fast bacteria Figure 1 [11].

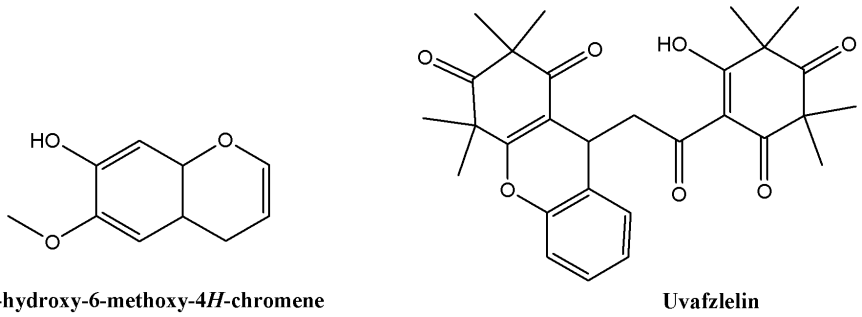


Figure1. Natural 4*H*-chromenes with biological activities.

Moreover, as an encouraging and desirable scaffold to develop powerful antitumor agents, the fused chromene nuclei have arisen. β-enaminonitrile (A) (LY290181) is an effective example of an antiproliferative vehicle for different cell lines, which can cause a hindrance to the microtubules and mitosis phase [12, 13]. The 2-N-succinimido derivatives (B) as another

example exhibit an anti-rheumatic property [14], while β-enaminonitriles (C) show an effective cytotoxic [15] and apoptotic behavior against MCF-7, MDA-MB-231, HepG-2, T-47D, SK-N-MC, KB, PC3, and different cell lines as such. Furthermore, it has been reported that β-enaminonitriles/esters (D) [16-21] are one of the most antiproliferative agents, all shown in Figure 2.

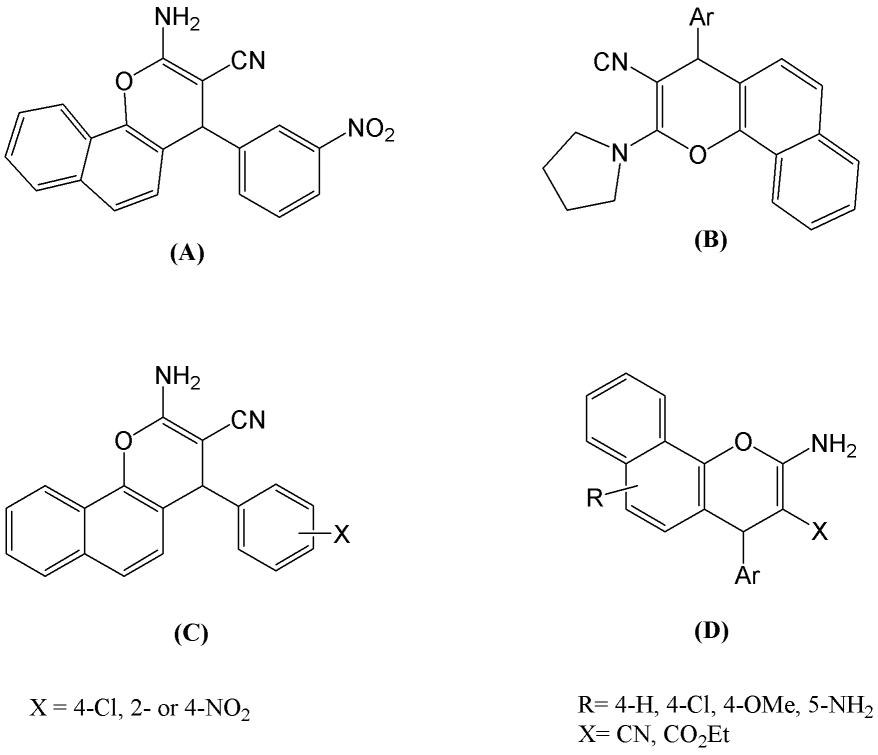
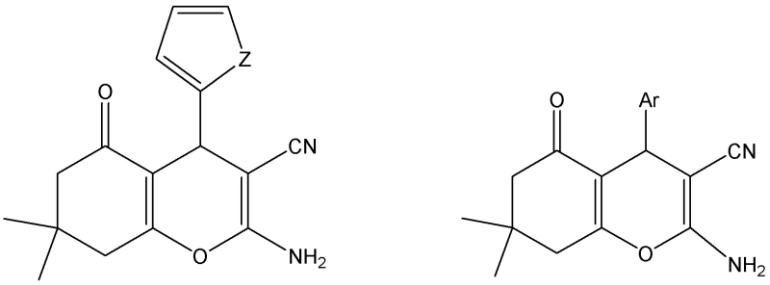


Figure 2. Structures of some fused chromene derivatives with specific biological properties.

It has been evaluated recently that a series of synthetic 4*H*-chromene with dimedone- annulated possess potent anticancer and also antibacterial properties Figure 3 [4, 7, 22].



1b: Z= O; 1c: Z= S; 1d: Z= NH

(anticancer and antibacterial)

1l: Ar = 4-$NO_2C_6H_4$
1m: Ar = 3-OHC_6H_4
(antibacterial)

Figure 3. Representative examples of synthetic 4*H*-chromene with dimedone- annulated which are pharmacologically active.

Channels are the cellular structures, which are involved in many metabolic regulations and can check the entry of many nutrients and minerals into the cell [23]. By the way, ion channels are not only important to regulate the vital physiologic events of the body as muscle contraction, neuronal and cardiac excitability, fluid movement, immune cell activation, and hormone secretion, but also, they are remarkable targets for drug development [24]. In this regard, in many different cell types, voltage-gated Ca^{2+} channels act as the route for Ca^{2+} to enter into the cytosol [25]. Therefore, as major keys in signal transduction of electrical excitability, voltage-gated Ca^{2+} channels convert the electrical signal of the action potential in the cell surface membrane to an intracellular Ca^{2+} transient [25].

Accordingly, there are diverse molecular subtypes of voltage-gated Ca^{2+} channels, mediating the voltage-gated Ca^{2+} currents with various regulatory, physiological, and pharmacological properties in different cell types [25]. Therefore, voltage-gated calcium channels are known as important drug targets [26]. Nimodipine is a medication that belongs to the dihydropyridine class of calcium channel blockers. It specifically targets L-type calcium channels. L-type channels are a type of voltage-gated calcium channel that plays a crucial role in controlling the influx of calcium ions into cells. In the context of nimodipine, its interaction with L-type calcium channels is relevant to its therapeutic effects, particularly in the treatment of certain conditions like subarachnoid hemorrhage. The drug's mechanism of action involves blocking these channels, thereby affecting calcium ion flow and exerting its beneficial effects in specific medical contexts [27]. In continuation of our work on electro synthesis of organic compounds, the 4*H*-chromenes synthesized in this study will be compared with nimodipine, a calcium channel blocker, through molecular docking studies[28-33].

Experimental

Apparatus and Reagents

A SAMA potentiostate/galvanostate (Isfahan, Iran) was used to perform the controlled-current coulometry and preparative electrolysis. An iron cathode (5 cm^2) and a magnesium anode (5 cm^2) were applied as working electrodes. An Electrothermal 9200 apparatus was used to measure melting points which are uncorrected. Bomen FT-IR-MB 100 spectrometer measured IR spectra. ^1H and ^{13}C NMR spectra were obtained using a Bruker DRX-300 Avance spectrometer at 300 and 75 MHz (TMS as internal standard). Chemical shifts are reported (δ) relative to TMS and coupling constant (J) is reported in hertz (Hz). Elemental analysis for C, H and N were performed using a Heraus CHN rapid analyzer.

Molecular docking study

Using the Auto Dock Tools (version 1.5.6), docking studies were carried out. For this purpose, the calcium channel crystallographic structure as a complex bound with antagonist nimodipine (pdb ID: 5KMF) was extracted from the brookhavenprotein database (http://www.rcsb.org) [34]. Then, the channel structure was modified by removing the additional molecules. The 3D structure of nimodipine (as the standard) and compounds **8a-h** were provided using MarvineSketch 5.8.3, 2012, ChemAxon (http://www.chemaxon.com) and through Auto Dock Tools converted to pdbqt files. Also, using the same software, the protein pdbqt file was prepared. As inputs for the AUTOGRID program the obtained pdbqt files of the mentioned compounds and protein were introduced. Using the latter program all maps were calculated with 0.375 Å spacing between grid points in the center of nimodipine with x = -7.308, y = 135.275, and z = 13.6665. 40 × 40 × 40 Å was set as the dimensions of the binding site box. Flexible ligand docking was applied for studied compounds. 50 runs of AUTODOCK program search by Lamarckian genetic algorithm was applied for each docked system. Finally, in order to analyze the interactions, the lowest energy conformation of ligand-channel complex was considered. The visualization of the results was carried out by BIOVIA Discovery Studio v.3.5.

The synthesis of nanoparticles of 4H-chromene through electro-synthesis procedure

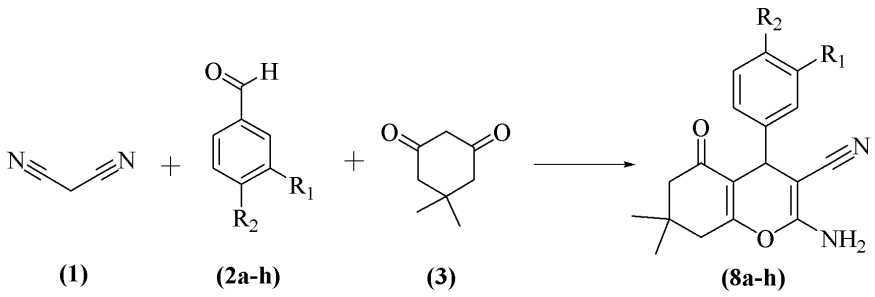
An undivided cell equipped with an iron cathode (5 cm^2) and a magnesium anode (5 cm^2) at room temperature, was used to electrolyze a stirring mixture of 1 mmol malononitrile (**1**), 3-fluoro benzaldehyde (**2b**), dimedone (**3**) and NaBr (0.05 gr, 0.5 mmol) in anhydrous propanol (25 mL) applying a constant current density of 50 mA/cm^2 (I = 10 mA). Monitoring by thin-layer chromatography (ethyl acetate/*n*-hexane 1/1) the completion of the reaction was assured

and then the evaporation of the solvent was carried out under reduced pressure. Subsequently, 20 mL ethanol (80%) was added to the reaction mixture. Centrifugation separated the resulting solid. Finally, the nanoparticles of product (**8b**) were collected for further analysis.

Results and Discussion

Electro synthesis of 4H-chromene

As the electrochemical reduction proceeds in the presented method, a mixture of 1 mmol malononitrile (**1**), benzaldehyde (**2a-h**), dimedone (**3**) and NaBr (0.05 gr, 0.5 mmol) in anhydrous propanol converts to 4*H*-chromene (**8a-h**) as shown in Scheme 1.



Scheme 1. The formation of nanoparticles of 4*H*-chromene.

The reaction was optimized against current, solvent, and anode. The obtained results are all summarized and reported in (Table 1).

Table 1. [a]Comparing the effect of different currents, concentrations, anodes and solvents on the reaction of malononitrile (**1**), benzaldehyde (**2a**) and dimedone (**3**) to afford 2-amino-7,7-dimethyl-5-oxo-4-phenyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**8a**).

Entry	Current (mA)	Time (min)	Anode	Electricity passed (F/mol)	Solvent	Yield [b] (%)
1	50	60	Mg	1.9	*n*-PrOH	98
2	100	80	Mg	5	*n*-PrOH	90
3	50	85	C	2.6	*n*-PrOH	43
4	50	25	Mg	0.8	EtOH	52

[a]In all reactions, 0.5 mmol of NaBr and an iron cathode (5 cm^2) were used. [b]Isolated yields based on dimedone.

As can be seen from Table 2, using 1 mmol of each reagent and a magnesium anode, under a constant current of 50 mA at room temperature, obtained 2-amino-7,7-dimethyl-5-oxo-4-

phenyl-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile (**8a**) with 98% yield after 60 min (Entry1). Increasing the current amount up to 100 mA decrease the yield (Entry 2). When graphite was used as the anode, the yield decreased while time of the reaction increased (Entry 3) compared to the reactions performed in the presence of a magnesium anode (Entries 1-4). Using ethanol as the solvent decreased the yield and improved the reaction time. Therefore, eight compounds were synthesized in the optimum conditions (Scheme 1, Table 2) providing considerable yields (60%-90%) within 60 min.

Table 2. [a] Results obtained using a series of representative aldehydes, malononitrile and dimedone in the presented reaction.

Compounds	R_1	R_2	Yield [b] (٪)	M.p (°C)	Lit. M.p (°C)	Time (min)
8a	H	H	98	218-220	225-226[35]	98
8b	F	H	60	211-212	210-212[36]	70
8c	Cl	H	97	221-223	235-236[35]	85
8d	OMe	H	68	198-200	195-197[37]	65
8e	NO_2	H	81	208-210	215-216[35]	84
8f	H	NO_2	67	177-179	185-186[35]	80
8g	H	F	85	180-182	188-189[37]	80
8h	H	Cl	76	208-210	215-216[35]	90

[a]In all reactions, 0.5 mmol of NaBr, an iron cathode (5 cm^2), a magnesium anode (5 cm^2), and room temperature were used. [b]Isolated yields based on dimedone.

The reaction with aldehydes carrying electron-donating groups such as methoxy group obtained relatively lower yields; however, those carrying aromatic electron-withdrawing groups mostly did quite well and gave almost quantitative yields. The identities of substances **8a-h** were verified through IR and NMR spectroscopy. In the IR spectrum, the carbonyl groups were attributed to the band which was observed at about ~1600 cm^{-1}. The characteristic signals of the protons of C (4) H at ~4.00 ppm is observed in the ^1H NMR spectra. While synthesizing these compounds, some interesting properties were observed, for instance the products could not be sintered using a normal sinter or sinter glass.

Instead, centrifuge was needed for separating the products from propanol medium; then SEM micrographs obtained from the powder of template-synthesized nanoparticles showed that the products are nanoparticles and their average size, DSEM, is < 100 nm (Figure 4).

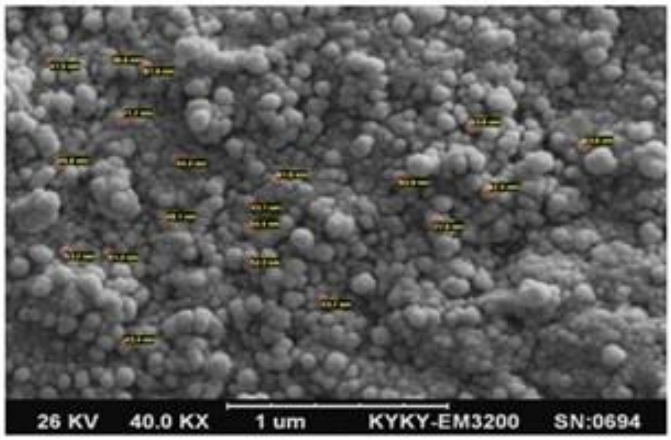
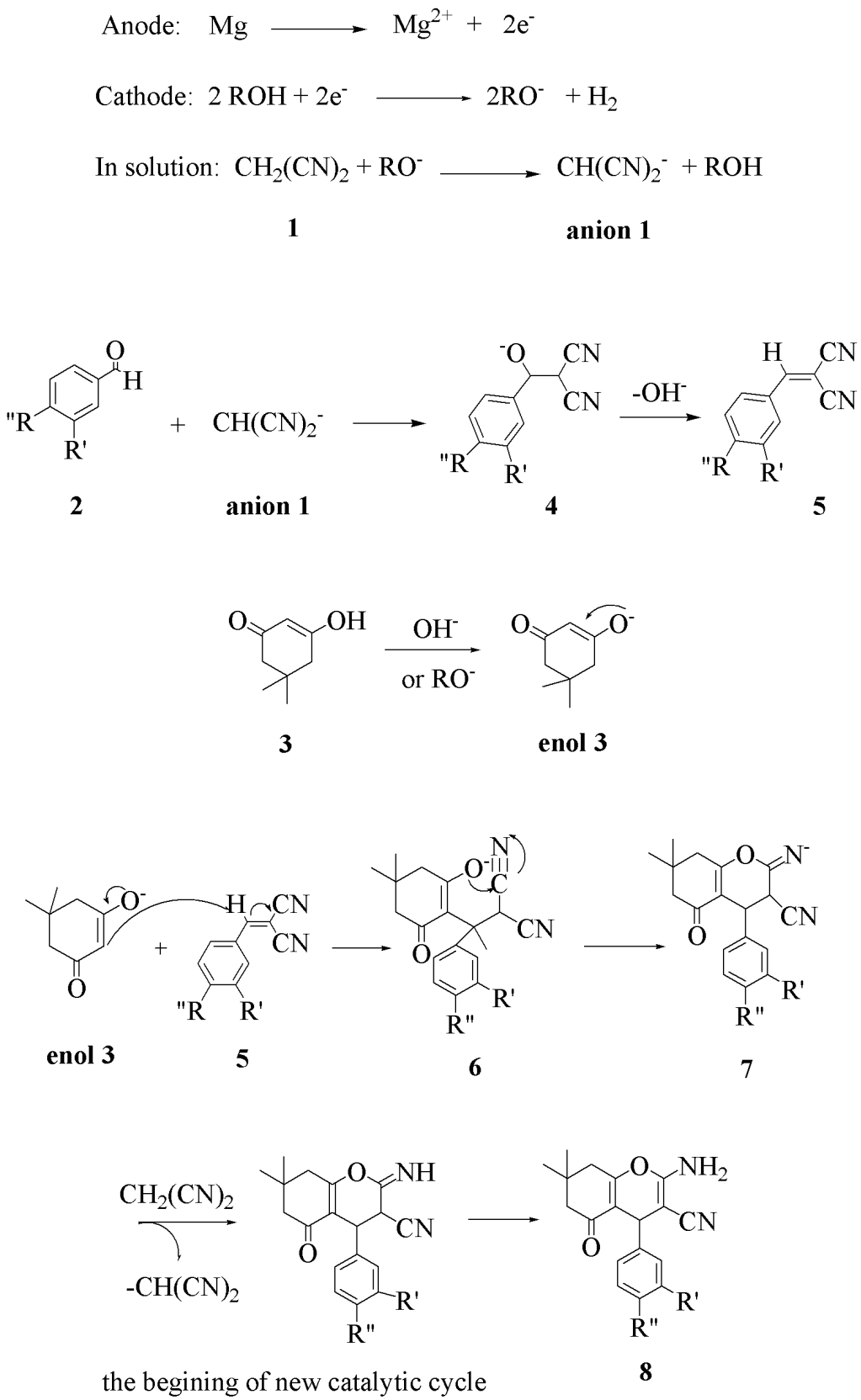


Figure 4. SEM image of nanoparticles of 2-amino-4-(4-fluorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile.

Both Knoevenagel condensation and Michael addition are involved in the three-component reaction of malononitrile, aromatic aldehydes and dimedone. Scheme 2 shows the possible mechanism for the formation of 4*H*-chromene. Deprotonating an alcohol at the cathode produces an alkoxide anion. The subsequent reaction between the alkoxide anion and malononitrile (**1**) results in the malononitrile anion (**anion 1**). Then via the initial formation of 2-benzylidene-malonitrile (**5**) Knoevenagel reaction occurs, from the condensation of aromatic aldehyde (**2**) and malononitrile anion. Intermediate (**6**) is then obtained through the reaction of the active methylene of dimedione with the electrophile C=C of intermediate (**5**). Through the nuclephilic attack of–OH group on the cyano (CN) moiety, the latter intermediate is then cyclized, giving intermediate (**7**). Finally, tautomerization the yields the expected product (**8**).



Scheme 2. The plausible mechanism for the synthesis of 4*H*-chromene.

Molecular docking study

To evaluate the interaction modes and binding energies of compounds **8a-h**, by Auto Dock Tools docking study was performed into calcium channel. 3D structure of the standard antagonist nimodipine in calcium channel is showed in Fig. 5a. As can be seen in Fig. 5b, nimodipine formed hydrophobic interactions with Ile1199, Met1188, Tyr1195, and Tyr1168. This drug also formed carbon hydrogen bonds with Tyr1168, and Gly1164. Furthermore, weak van der Waals interactions between nimodipine and residues Phe1167, Phe1171, Trp1179, Glu1165, and Arg1185 were observed in calcium channel. The value of the binding energy of nimodipine is −6.21 kcal/mol.

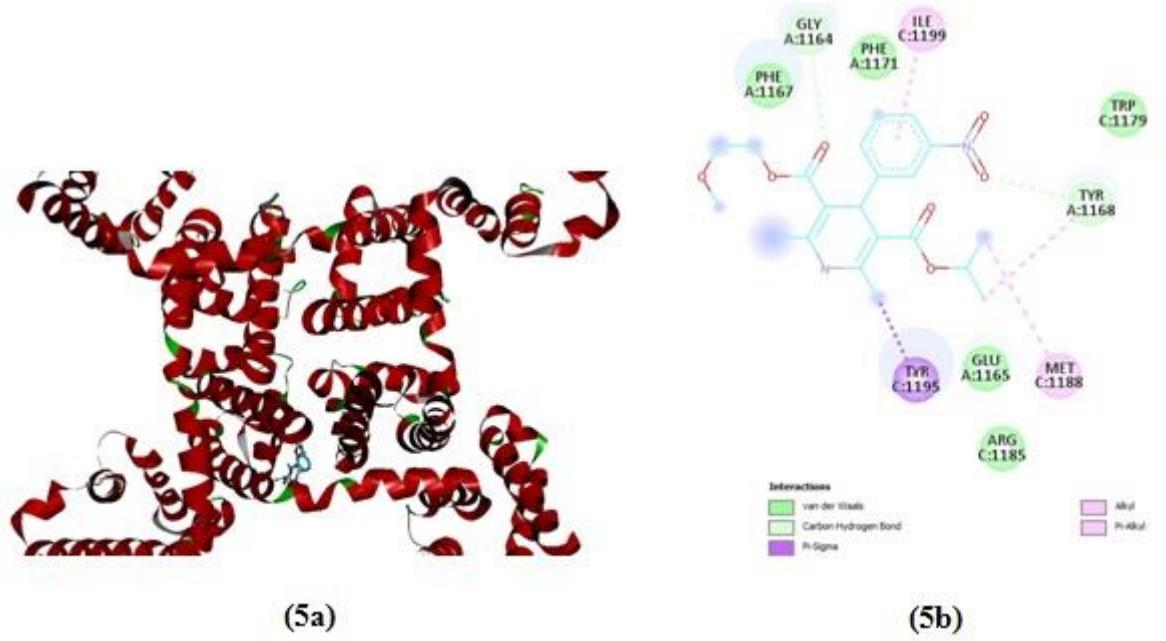
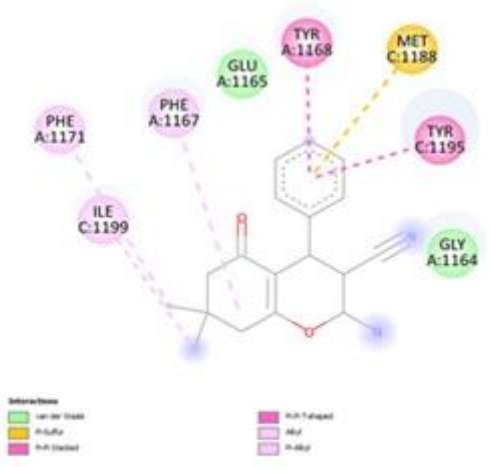
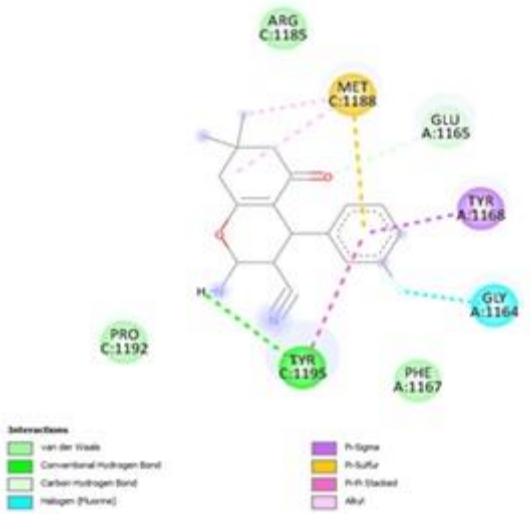


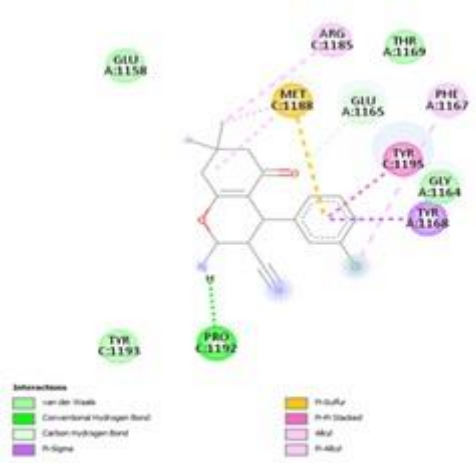
Figure 5. (a) Nimodipine in calcium channel; (b) interaction mode of nimodipine with calcium channel.


TYR A:1168
MET C:1188
GLU A:1165
PHE A:1167
PHE A:1171
TYR C:1195
ILE C:1199
GLY A:1164

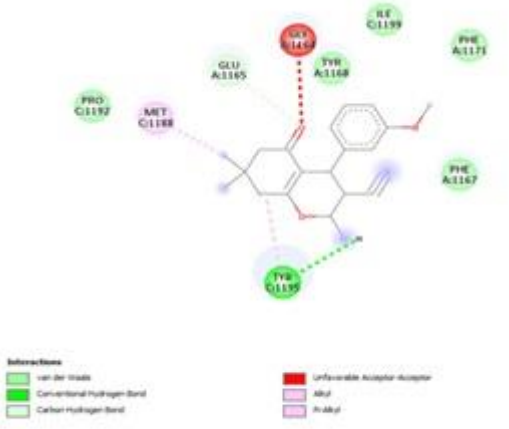
(8a)


ARG C:1185
MET C:1188
GLU A:1165
TYR A:1168
GLY A:1164
PRO C:1192
TYR C:1195
PHE A:1167

(8b)


ARG C:1185
THR A:1169
GLU A:1158
MET C:1188
GLU A:1165
PHE A:1167
TYR C:1195
GLY A:1164
TYR A:1168
TYR C:1191
PRO C:1192

(8c)


ILE C:1199
PHE A:1171
GLU A:1165
TYR A:1168
PRO C:1192
MET C:1188
PHE A:1167

(8d)

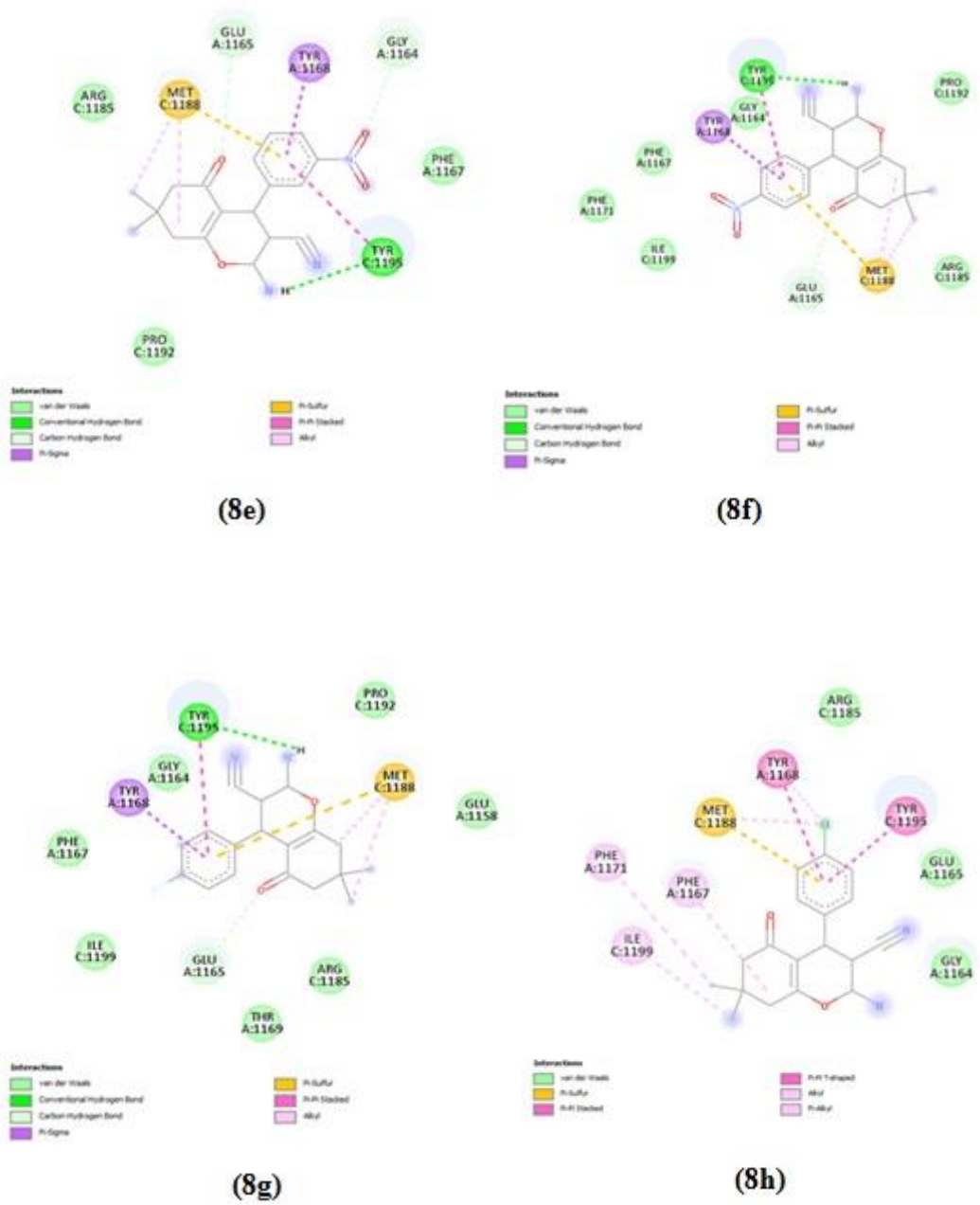


Figure 6. Interaction modes of compounds **8a-h** with calcium channel.

Interaction modes of compounds **8a-h** in calcium channel were showed in the Figure 6. Furthermore, binding energy values and interacting residues related to these interaction modes were listed in Table 3.

Table 3. Binding energies and interacting residues in interaction modes of compounds **8a-h** in calcium channel.

Entry	B.E.	Interacting residues
8a	−7.48	Phe1167, Gly1164, Phe1171, Ile1199, Tyr1168, Met1188, Glu1165, and Tyr1195
8b	−7.46	Pro1192, Phe1167, Gly1164, Tyr1168, Met1188, Glu1165, Arg1185, and Tyr1195
8c	−7.93	Glu1158, Arg1185, Met1188, Thr1169, Glu1165, Phe1167, Tyr1195, Gly1164, Tyr1168, Pro1192, and Tyr1193
8d	−7.58	Pro1192, Met1188, Glu1158, Gly1164, Tyr1168, Ile1199, Phe1171, Phe1167, and Tyr1195
8e	−7.59	Pro1192, Phe1167, Gly1164, Tyr1168, Met1188, Glu1165, Arg1185, and Tyr1195
8f	−7.61	Phe1167, Gly1164, Phe1171, Ile1199, Pro1192, Tyr1168, Met1188, Glu1165, Arg1185, and Tyr1195
8g	−7.42	Pro1192, Phe1167, Gly1164, Ile1199, Tyr1168, Met1188, Glu1165, Thr1169, Arg1185, Glu1158, and Tyr1195
8h	−8.02	Phe1167, Gly1164, Phe1171, Ile1199, Tyr1168, Met1188, Glu1165, and Tyr1195

As can be seen in this table, all compounds **8a-h** have lower binding energies (B.E. values = -8.02 to -7.42 kcal/mol) than nimodipine (−6.21 kcal/mol) and thus can bind more easily to calcium channel than nimodipine can. Among the studied compounds, chloro derivatives **8h** and **8c** with 4-chloro and 3-chloro substituents, respectively, have the lowest binding energies.

Conclusion

There is no doubt that electro synthesis is general practical alternative to existing procedure for the synthesis of nanoparticles of various derivatives of 4*H*-chromene. Electron used as a catalyst shows environmentally friendly character, highly efficient and inexpensive. Moreover, the experimental procedure for this reaction is remarkably simple and without the use of hazardous or expensive organic solvent. The entire feature makes this protocol to be an attractive method for synthesis of nanoparticles of organic compounds. Molecular docking studies showed compound **8h** and **8c** with 4-chloro and 3-chloro substituents obtain minimum binding energy and good affinity toward the active pocket of CavAb compared to nimodipine as a calcium channel blocking agent.

Acknowledgements

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