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Original Article

A Convenient Synthesis of Glutarates Derivatives: Application, Theoretical DFT Calculations and Molecular Docking Study

Maha Ameur[1,*], Rania Omrani[2,*], Sonia Taktouk[2], Mohamed Amine Ben Abdallah[3], Ahmed Ridha El Ouederni[4], Rafik Gatri[2]

[1]Laboratory of Materials and Environment for Sustainable Development (LR18ES10), ISSBAT, El Manar University, Tunis, TUNISIA.
[2]Laboratory of Selective Organic and Heterocyclic Synthesis Biological Activity Evaluation (LR17ES01), Faculty of Science of Tunis, El Manar University, Tunis, TUNISIA.
[3]Laboratory of Materials Engineering and Environment (LR11ES46), National School of Engineers of Sfax (ENIS), Sfax University, TUNISIA.
[4]Research laboratory of Characterizations, Applications and Modelling of Materials (LR18ES08), Faculty of Science of Tunis, El Manar University, Tunis, TUNISIA.

ABSTRACT

Background: An easy and convenient access to a novel Gluatarate Derivatives (DCG) was successfully synthesized, using an unusual successive S_N2-S_N2 reaction of 1,4-Diazabicyclo [2.2.2] Octane (DABCO) then KCN, on the available vinyl bromide. Fukui functions, molecular electrostatic potential and HOMO-LUMO energy of the component Gluatarate Derivatives (DCG) 2b and 3b were computed using Density Functional Theory (B3LYP/6-311+G(d,p)). The technique of molecular docking was studied to predict the interaction modes between the DCG ligand selected and with different proteins. **Materials and Methods:** The objective of our experiments was to characterize the components of DCG by NMR Spectroscopy (^{1}H, ^{13}C, DEPT135 and HMBC) and by HRMS. **Results:** We developed a new approache to gluatarate derivatives involving firstly a successive S_N2-S_N2 reaction of 1,4-diazabicyclo[2.2.2]octane (DABCO) then KCN on the functional vinyl bromide. All compounds were correlated using computational DFT. The molecular docking studies revealed that glutarates derivatives 2b and 3b were as antibacterial and anti-Alzheimer activities. **Conclusion:** A new family of glutarates derivatives 2b and 3b has been described from vinyl bromide.

Keywords: Glutarates derivatives, NMR Spectroscopy characterization, DFT calculations, Molecular Docking, Anti-Alzheimer against.

Correspondence:
Dr. Maha Ameur
Laboratory of Materials and Environment for Sustainable Development (LR18ES10), El Manar University, ISSBAT, 9 Street Dr. Zoheir Safi, Tunis, TUNISIA.
Email: maha.ameur@istmt.utm.tn
ORCID: 0000-0002-5860-9519

Dr. Rania Omrani
Laboratory of Selective Organic and Heterocyclic Synthesis Biological Activity Evaluation (LR17ES01), Faculty of Science of Tunis, El Manar University, Tunis, TUNISIA.
Email: omrani.rania@gmail.com
ORCID: 0000-0002-4521-3240

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INTRODUCTION

The efficient generation of functionalized vinyl bromides is still an open challenge in organic synthesis.[1-3] In addition bromides derivative are widely used as versatile building blocks for the preparation of a large variety of biologically active compounds[4-6] and numerous natural products.[7-9] Moreover, the utility of these versatile vinyl brominated derivatives comes from their ability to react with various nucleophilic reagents. Therefore, a wide range of effective strategies have been established for the synthesis of brominated derivatives,[10-12] continues to attract the attention of organic and bioorganic chemists. Continuing with our efforts toward the functionalization of vinyl bromide, we describe herein a practical and original synthetic route to a new family of dialkyl (*E*)-2-cyanovinylglutarate 2b and 3b from functional vinylic bromide as a two-step synthesis involving, first, a successive S_N2-S_N2 reaction of 1,4-Diazabicyclo [2.2.2] Octane (DABCO), then KCN on the functional vinylic bromide.

All compounds were correlated using computational DFT. Molecular Orbitals (MO) and energies were carried out as well. Molecular docking studies were studied and explored for the anti-Alzheimer effect using different pharmacological and computational assays in order.

MATERIALS AND METHODS

Chemistry

Instruments

^{1}H and ^{13}C spectra were recorded at 300, 75 MHz respectively on a Bruker AC-300 with TMS as internal reference for ^{1}H and ^{13}C

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in $CDCl_3$. Mass spectra were accomplished with an HP 5889A quadripolar spectrometer by electronic impact EI (70 eV) or chemical ionization CI (500 eV) with NH_3 gas. High-Resolution Mass Spectrometry (HRMS) analyses were performed in Laberca Laboratory at Oniris (Nantes-Atlantic National College of Veterinary Medicine, Food *Science and Engineering*) on a mass spectrometer equipped with a door coupled to a linear Orbitrap (LTQ-Orbitrap of Thermo Fisher Scientific) in positive electrospray ionization. All reactions were purified by TLC on silica gel plates eluting with the solvents indicated.

Synthesis of Dialkyl (*E*)-2-Cyanomethylene Glutarates (DCG) 2b and 3b

Into a flask was introduced 1 g of dialkyl (E)-2-bromomethyl glutarate 1 in water distilled (10 mL). DABCO 0.9 g was added and the mixture was stirred at room temperature for 48 hr until the vinyl bromide salt was formed. To the obtained salt were added under stirring, 0.52 g of Potassium Cyanide (KCN). The mixture was then hydrolyzed by addition of a saturated solution of NaCl. After extraction with ethyl acetate, the organic layer was dried and the solvent was evaporated. The crude mixture was separated by chromatography on silica gel (petrolum ether/AcOEt: 9/1) to give the dialkyl (*E*)-2- (cyanomethylene) pentanedioate 2.

Dimethyl (*E*)-2-(cyanomethylene) pentanedioate 2b

Yield: 52%; Colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$): 6.25 (s, 1H, CH); 3.76 (s, 3H, OCH_3); 3.67 (s, 3H, OCH_3); 2.35 (t, 2H, J=6 Hz, CH_2); 2.29 (t, 2H, J=6 Hz, CH_2). ^{13}C-NMR (75 MHz, $CDCl_3$): 173.1 (C=O); 167.2 ((CH_2)C=O); 158.6 (C); 116.9 (CN); 109.5 (CH); 52.3 (OCH_3); 51.9 (OCH_3); 30.5 (CH_2); 21.1 (CH_2).

Diethyl (*E*)-2-(cyanomethylene) pentanedioate 3b

Yield: 75%; Colorless oil; ^{1}H-NMR (300 MHz, $CDCl_3$): 6.34 (s, 1H, CH); 4.26 (q, 2H, J=6 Hz, OCH_2); 4.12 (q, 2H, J=6 Hz, OCH_2); 2,91 (t, 2H, J=6 Hz, CH_2); 2,57 (t, 2H, J=6 Hz, CH_2); 1.31 (t, 3H, J=6 Hz, CH_3); 1.24 (t, 3H, J=6 Hz, CH_3). ^{13}C-NMR (75 MHz, $CDCl_3$): 171.4 (C=O); 163.9 ((CH_2)C=O); 152.1 (C); 114.9 (CN); 108.5 (CH); 62.2 (OCH_2); 60.3 (OCH_2); 32.5 (CH_2); 26.3 (CH_2); 14.1 (CH_3); 13.9 (CH_3).

Computational details

DFT calculations

DFT calculations were employed with the Gaussian 16A program with standard functional B3LYP/6-311+G(d,p) basis set.[13-16] The frontier molecular orbital surfaces were visualized by GaussView 6.1.1 software package. The optimization and the Self-Consistent Field (SCF) were described with a convergence including 10^{-6}. In addition, the band gap Energies (ΔE) was calculated of all molecules through the expression E_{HOMO}-E_{LUMO}.

Molecular docking

The docking study was performed using ezCADD[17] Smina[18] software (https://www.dxulab.org/software) to visualize 2D/3D protein-ligand interactions. Views of results were ready using the BIOVIA discovery studio 2021 client software.[19] The simulation system was assembled on the crystal structures of Protein Data Bank PDB IDs: 1AO6, 1ACJ, 1P0I and 1EVE, which were downloaded from the Royal Col laboratory for Structural Bioinformatics, RCSB database (https://www.rcsb.org). The water molecules and ligands were removed by using PyMOL[20] and polar hydrogen bonds were added.[21] Automatic cavity detection was performed using fpocket3.[22] The bonding interaction pattern (hydrogen/hydrophobic) and minimum binding affinity values (kcal/mol) were used to evaluate the resultant docked complexes.[23]

RESULTS AND DISCUSSION

Chemistry

Stereoselective synthesis of dialkyl (E)- 2-cyanovinylglutarate (DCG) 2 and 3

Glutarate have gained great attention from their numerous applications as precursors for achieving several transformations in organic chemistry.[24,25] Dialkyl (*E*)-2-bromomethylene glutarate 1 was prepared through a simple tandem-process: bromination-dehydrobromination of dialkyl-2-methylene glutarate as reported in the literature.[26] The reaction of vinylic bromide 1 with DABCO[27] (3 equiv.) in aqueous THF under stirring at room temperature furnished a quaternary ammonium salt whose reaction with KCN (3.5 equiv.) generates after workup and in moderate yield the dialkyl (*E*)-2-cyanovinylglutarate 2, 3 (Scheme 1).[28]

In order to explain the synthetic strategy for the formation of compounds 2 and 3, we specify firstly that the lower reactivity of cyanide ion as nucleophilic reagent [29] is unfavorable for the displacement of vinylic bromine of compound 1. In this regard, we propose a convenient protocol as a two-steps synthesis involving, first, a successive SN_2-SN_2 reaction of 1,4-Diazabicyclo [2.2.2]Octane (DABCO) on the β-carbon of the vinyl bromide 1 yielded a carbanion followed by the loss of bromine ion leading to the functionalized ammonium intermediate, which can react with cyanide ion to provide the corresponding functionalized vinyl nitrile 2 and 3 as the result of direct nucleophilic vinylic substitution reaction,[30] in moderate yield with *E*-configuration as the major and favored product in general.

Methodologies of comparison: Boltzmann equation

To training the relative stability of the different considered molecular species, DFT calculations were performed to calculate the electronic structure. The optimization of each structure was considered converged with a maximum gradient less than 0.0001. No frozen coordinates and no symmetry restriction were used.

One of our main goals in the present research was to focus the thermodynamically stability of adducts 2a-b and 3a-b, by using the Boltzmann equation.[31,32]

$$N_a + N_b = 1 \quad (1)$$

$$\frac{N_a}{N_b} = = exp^{\left(\frac{-\Delta G_{a-b}}{RT}\right)} \quad (2)$$

Using the Boltzann equation, the dialkyl (*E*)-2-cyanovinylglutarate derivatives 2b and 3b with (*E*)-configuration were the most products with yields equal to 91 and 99.9% respectively. The result obtained in theory of the dialkyl (*E*)-2-cyanovinylglutarate derivatives was in reasonably good agreement between experiments. The Figure 1 and the Table 1 summarized the different percentage obtained in the theory calculation with the experimental results.

Quantum chemical calculations

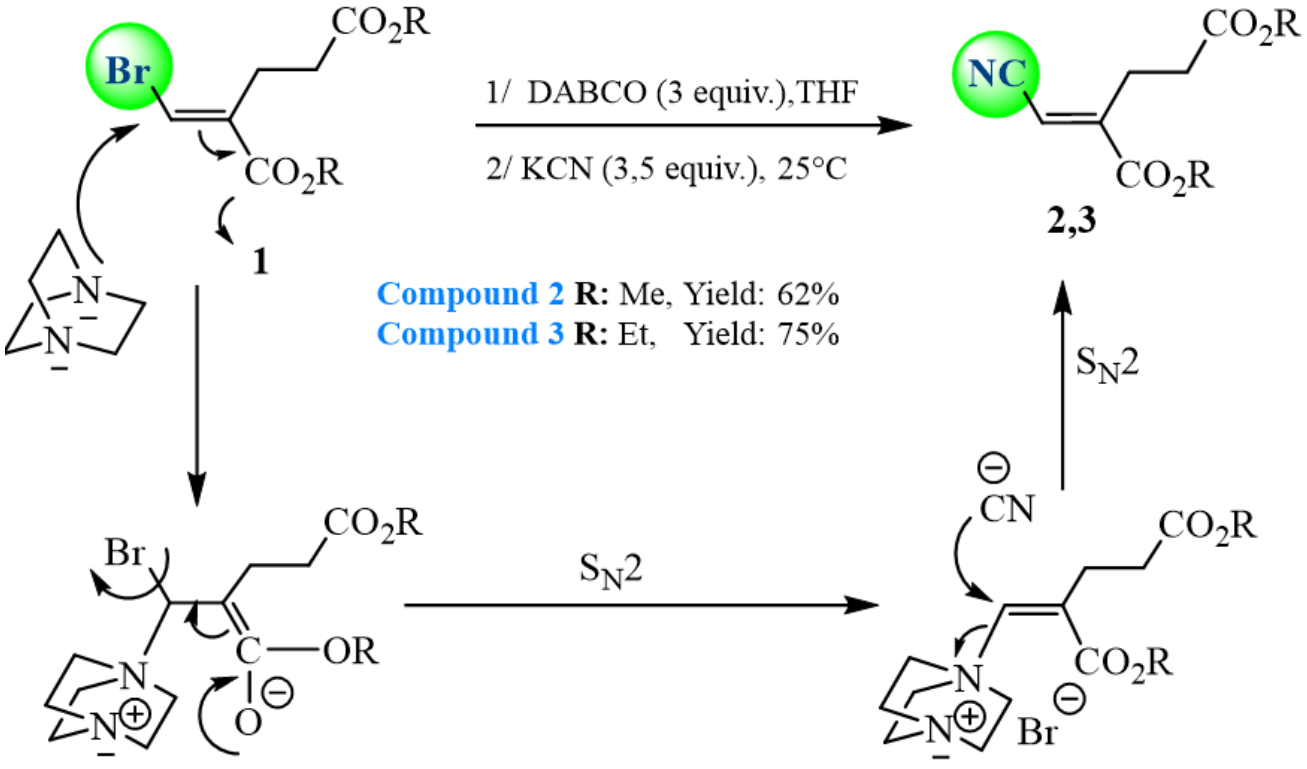
Molecular Electrostatic Potential (MEP)

The Molecular Electrostatic Potential (MEP) was derived from DFT calculations with an isodensity value of 0.002 a.u. The molecular electrostatic potential was used to identify molecular regions susceptible to most electrophilic attack that showed in blue color or the most nucleophilic attack that showed in red color, for analyzing and predicting noncovalent interactions.[33] Intermediate potentials gave in order the following color spectrum: Blue>Green>Yellow>Orange>Red.

The negative charges of the dialkyl (*E*)-2-cyanomethylene glutarates derivatives 2b and 3b colored in red in the electronic map correspond to electrophilic sites and the most negative are occupied here by the CN, C=O and C-O fragments. The positive region of the dialkyl (*E*)-2-cyanomethylene glutarates derivatives 2b and 3b, colored in blue over the electronic map correspond to nucleophilic sites and the most positive are occupied by the alkyl groups C-C (Figure 2a).

Frontier Molecular Orbital (FMO) analysis

The Frontier Molecular Orbital (FMO) theory used to describe the interaction between the Highest Occupied Molecular Orbital (HOMO) and the Lowest Unoccupied Molecular Orbital (LUMO) of the reactants and to explore chemical reactivity of all components.[16,33] The band gap energy (HOMO-LUMO) and molecular electrostatic potential map diagrams showed that the gap energies equal to 5.065, 5.022, 5.093 and 4.952 eV of the dialkyl (*E*)-2-cyanomethylene glutarates derivatives 2a (*Z*), 2b (*E*), 3a (*Z*) and 3b (*E*), respectively (Figure 2b). The Table 2 summarized the values of hardness, softness and global electrophilicity. Based on the obtained results, the lowest unoccupied molecular orbital



Scheme 1: Reaction mechanism for the synthesis of Dialkyl (*E*)-2-Cyanomethylene Glutarates (DCG) derivatives 2 and 3.

(LUMO) and the Highest Occupied Molecular Orbital (HOMO) of all compounds 2b and 3b localized on CN and C=C groups.

Global reactivity

The global electrophilicity index ω, which measure the stabilization in energy when the system acquires was expressed by the following equation.[34,35]

$$\omega=\frac{\mu^2}{2\eta} \quad (1)$$

With μ represent the electronic chemical potential and η is the global hardness. The global electrophilicity index ω can also be calculated from the frontier molecular orbital energies by following equations.[36,37]

$$\mu=\frac{\varepsilon_{HOMO}+\varepsilon_{LUMO}}{2} \quad (2)$$

$$\eta=\varepsilon_{LUMO}-\varepsilon_{HOMO} \quad (3)$$

$$\omega=\frac{(\varepsilon_{HOMO}+\varepsilon_{LUMO})^2}{2(\varepsilon_{LUMO}-\varepsilon_{HOMO})} \quad (4)$$

The global softness (S) is given[38,39]

$$S=\frac{1}{2\eta} \quad (5)$$

Molecular docking studies

Molecular docking results for Human Serum Albumin (HSA)

Molecular docking studies were accomplished to identify the binding sites on the glutarates derivatives with *Human Serum Albumin* (HSA) using ezCADD Smina software. The molecular docking of the ligands 2b and 3b formed the hydrogen bond HB and the carbon hydrogen bond between CN group with residues ARG186, LYS190 and SER192 (Table 3 and the Figure 1 in the supplementary information).

Table 1: Synthesis of dialkyl (*E*)-2-cyanomethylene glutarates derivatives 2 and 3.

Yields (%) Adducts	Experiments results	Theory results
2a	~	9
2b	100	91
3a	~	0.1
3b	100	99.9

Table 2: Global electronic properties of glutarate derivatives DCG 2b and 3b at the B3LYP/6-311+G(d,p) level of theory.

	E_{HOMO} (eV)	E_{LUMO} (eV)	S (eV)	η(eV)	μ(eV)	ω(eV)	E_{Gap} (eV)
2b	-0.290	-0.105	0.099	5.032	-5.372	2.867	5.032
3b	-0.288	-0.102	0.099	5.059	-5.304	2.780	5.059

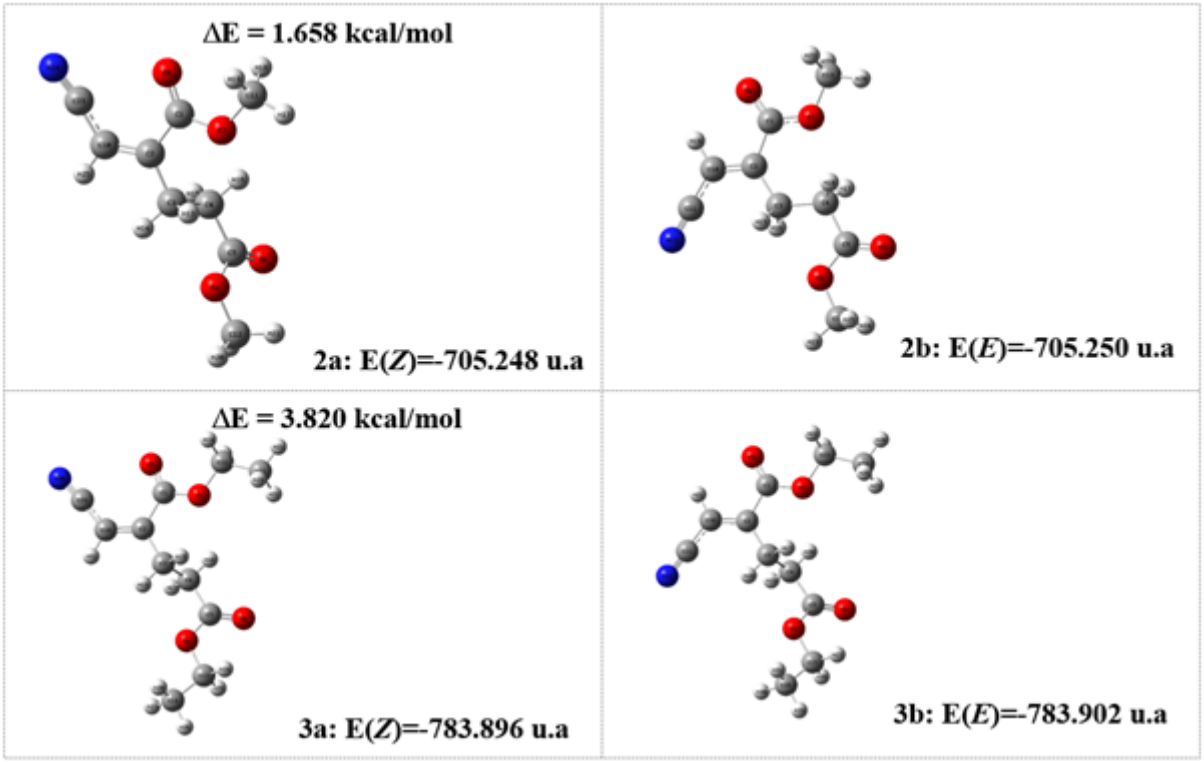
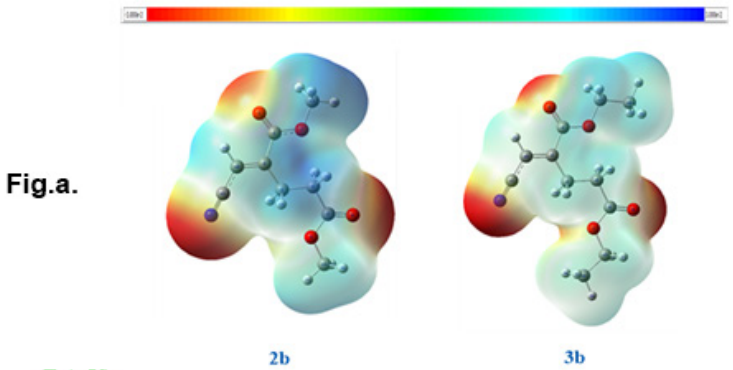


Figure 1: DFT calculations of the dialkyl (*E*)-2-cyanovinylglutarate 2a-b and 3a-b.



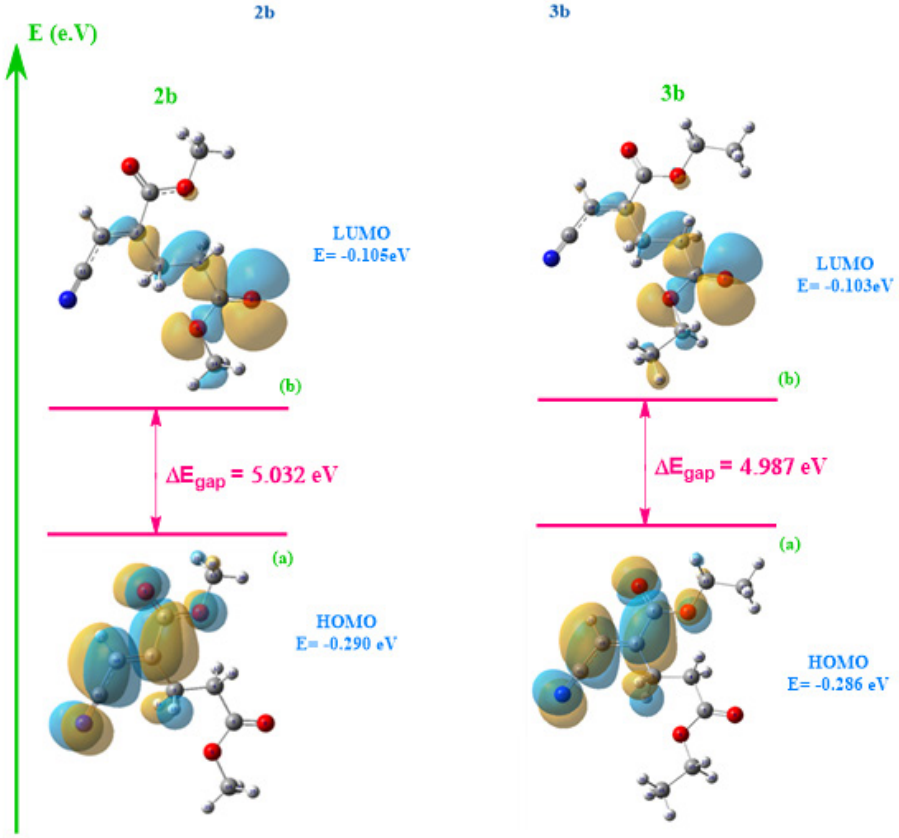


Fig.b.

Figure 2: MEP (Figure a.), HOMO (a) and LUMO (b) (Figure b.) plots of the components DCG 2b and 3b.

Table 3: Docking results of ligands 2b and 3b with the receptor PDP ID: 1AO6.

Ligand	Binding Energy (kcal/mol)	Substituent	Residues	Interactions
2b	-8.5	-CN	ARG186, LYS190	HB
		-OH	LEU182	HB
3b	-8.0	-CN	SER192	HB
		C=O	LYS199	HB
		-OEt	SER192	HB

Table 4: Binding affinity values between selected ligands DCG with different receptor IDs: 1ACJ, 1EVE and 1P0I.

Ligand	Receptor IDs	Binding Affinity (kcal/mol)	PAS	CAS
2b	1ACJ	-6.7	ASP72, TYR334, PHE288	TRP84, PHE330
	1EVE	-6.9	TYR334, ASP72, SER200	TRP84, PHE330
	1P0I	-6.0	TYR440, TRP82	HIS438
3b	1ACJ	-7.3	TYR70, TYR121, TYR334	TRP84, PHE330
	1EVE	-6.5	TYR121	GLY118
	1P0I	-7.0	TYR332, TRP82	HIS438

Molecular docking results for hydrolase (AChE and BuChE)

Our objective was to visualize the interaction between ligand and their receptors proteins as well as: Butyryl cholinesterase (BuChE, PDB ID: 1P0I) and Acetylcholine (AChE, PDB IDs: 1ACJ and 1EVE). The crystal structures of their receptors AChE and BuChE were designated from the Protein Data Bank (PDB).[35]

Inestrosa *et al*. detailed the interaction of selected ligand with the Peripheral (PAS) anionic site of AChE and the Catalytic (CAS) anionic site of BuChE in the human Acetylcholine (hAChE) and in hBuChE.[35,40] (Figure 2 in supplementary information and the Table 4) The obtained results exhibited an electrostatic interactions (Pi cation, Pi sigma and Attractive charge) between the DCG derivatives with amino acid residues PHE330, TRP84 and HIS438 and hydrophobic interactions with amino acid residues TYR70, TYR121, TYR334, TRP82, PHE288 and GLY118.

Furthermore, molecular modelling studies were performed to explore the possible interactions mode between the most active DCG derivatives 2b and 3b with BuChE (Pi Alkyl, Alkyl, Pi cation, Attractive charge, Conventional Hydrogen Bond and Carbon Hydrogen Bond). The selected ligand was observed in highest binding affinity.

All these results clearly indicated that the selected ligands glutarates derivatives could simultaneously bind to CAS and PAS of AChE and BuChE, thereby demonstrating rationality of our molecular design strategy. According to the literature,[35,40] it can be considered to reveal that the novel phosphorus derivatives were an anti-Alzheimer against.

CONCLUSION

In summary, we have developed an efficient approach for the synthesis of novel glutarates derivatives 2b and 3b from vinyl bromide 1. Theoretical studies were carried out the geometries of the components and to characterize the most nucleophilic and electrophilic centers in species using DFT method at the modest B3LYP level. Furthermore, the docking simulation between Ligand-receptors revealed that the importance of glutarate derivatives that is could provide novel anti-Alzheimer against.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

HRMS: High-Resolution Mass Spectrometry; **DABCO:** 1,4-Diazabicyclo[2.2.2]Octane; **DCG:** Dialkyl (E)-2-cyanomethylene glutarates; **THF:** Tetrahydrofuran; **DFT:** Density Functional Theory; **HOMO:** Highest Occupied Molecular Orbital; **LUMO:** Lowest Unoccupied Molecular Orbital; **PDB:** Protein Data Bank; **MEP:** Molecular Electrostatic Potential; **HAS:** Human Serum Albumin; **AChE:** Acetylcholine; **BuChE:** Butyryl cholinesterase**; hAChE:** human Acetylcholine; **PAS:** Peripheral Anionic Site; **CAS:** Catalytic Anionic Site; **SCF:** Self-Consistent Field.

AUTHOR'S CONTRIBUTIONS

Maha Ameur: Carried out the experiments, performed the synthesis of novel family. Rania Omrani: Performed the calculations, Molecular Docking Ligand-Receptor, Writing-original paper. Sonia Taktouk and Mohamed Amine Ben Abdallah: Reviewed the manuscript. Ahmed Ridha El Ouederni: Writing draft preparation. Rafik Gatri: Reviewed the manuscript. All authors discussed and reviewed the manuscript.

SUMMARY

- An easy synthesis of new glutarates derivatives 2b and 3b was successfully described.
- A DFT study was carried for all compounds using the functional (B3LYP) and the 6-311+G(d,p) basis set.
- The geometric parameters such as chemical hardness (η), chemical potential (μ),electrophilicity index (ω), chemical softness (σ) were calculated depending on the calculated HOMO-LUMO energies.
- Molecular docking was performed to evaluate the antibacterial and anti-Alzheimer activities.

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