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Theoretical Study On Nonlinear Optical Response And Molecular Docking Of Triazole Derivative

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Abstract: A biologically and optically active triazole derivative (E)-1-(2,3,6,7-tetrahydro-1H,5H-pyrido[3,2,1-ij]quinolin-9-yl)-N-(4H-1,2,4-triazol-4-yl)methanimine (QTM) has been designed and its structural characterization was accomplished theoretically. Optical properties such as nonlinear optical response have been investigated. Frontier molecular orbital (FMO) analysis, Molecular Electrostatic Potential (MEP) study, drug-likeness evaluation, and molecular docking were executed against the AChE and BChE receptors.

Keywords: optically, triazole, nonlinear, structural

1. Introduction

The development of photonics and optoelectronics is associated with advancing nonlinear optics (NLO) [1-4]. The organic material that possesses a high NLO response greatly influences the electro-optic conversion performance. Consequently, developing an organic compound with a high NLO response has become more crucial in recent eras. The second-order NLO response is more important for several practical applications of NLO materials. Therefore, the need for non-centrosymmetric electronic geometry is slaked from material with a second-order NLO response. The organic molecule containing an extended conjugated π-bond could become a non-centrosymmetric electronic skeleton by adding an electron-accepting or electron-donating group with these compounds [1-5]. Julolidine-based triazole derivative has good electron transfer capability, excellent chemical stability, easy structure modification, and high thermal stability, making it a considerable agent for developing NLO active material [6, 7]. The electron-donating nation of triazole excellently influences the electron transition function.

In Alzheimer's disease, **acetylcholinesterase (AChE)** and **butyrylcholinesterase (BChE)** are enzymes that play a key role in the breakdown of acetylcholine, a neurotransmitter essential for memory and cognitive function [1, 8, 11, 13]. As Alzheimer's progresses, the brain's acetylcholine levels decrease,

contributing to cognitive decline. AChE is primarily responsible for breaking down acetylcholine, and inhibiting this enzyme can help increase acetylcholine levels, temporarily improving cognitive function. BChE also breaks down acetylcholine, particularly in the later stages of Alzheimer's, as its activity increases while AChE activity decreases [9-11, 13]. This shift exacerbates cognitive decline. Inhibitors targeting both AChE and BChE are used in Alzheimer's treatments to prevent acetylcholine breakdown and improve memory and cognition. Drugs like donepezil and rivastigmine work by inhibiting these enzymes, helping to slow the progression of the disease [1, 11, 13]. In the present paper, a novel Julolidine-based triazole derivative has been designed, and its frontier molecular analysis, NLO response, and molecular docking against the AChE and BChE receptor have been studied.

2. Computational details

DFT (Density functional theory) calculations were accomplished using the Gaussian 09 software [12]. B3LYP functional and 6–311++G (d,p) basis set were used to compute all the properties of the designed molecule (Figure 1) (E)-1-(2,3,6,7-tetrahydro-1H,5H-pyrido[3,2,1-ij]quinolin-9-yl)-N-(4H-1,2,4-triazol-4-yl) methenamine (QTM).

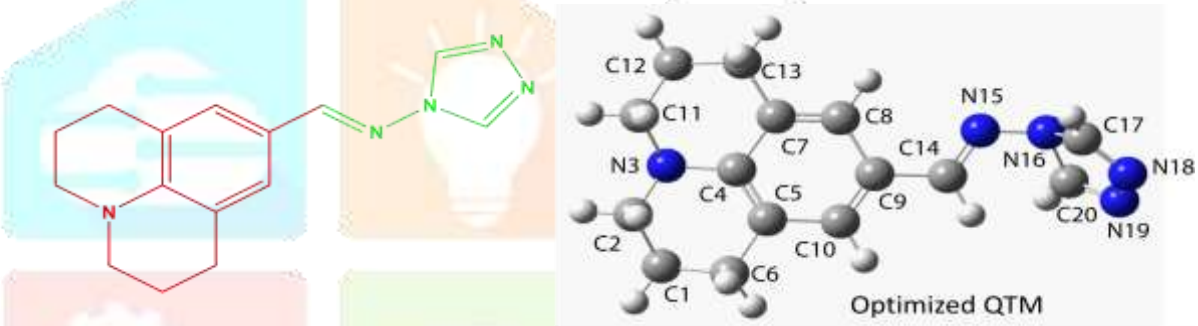

Figure 1 designed molecule (E)-1-(2,3,6,7-tetrahydro-1H,5H-pyrido[3,2,1-ij]quinolin-9-yl)-N-(4H-1,2,4-triazol-4-yl)methanimine (QTM).

The molecular docking was performed using auto dock vina software [1], and drug-likeness was evaluated by the online server Swiss ADMET (http://www.swissadme.ch/).

3. Results and discussion

3.1 Molecular structure

The structure of the title compound QTM has been optimized, and the energy of the optimized structure is minimal, which is confirmed by the absence of a negative wave number in frequency analysis. We observed that the torsional angle of the molecule is 1.74 degrees (°) between atoms C9-C14-N15-N16, whereas the distance between the C14=N15 bond is 1.0949 Å, whereas N15-N16, C9-C14 are 2.4909 Å, and 1.4602 Å as well as the bond angles C14-N15-N16, and C9-C14-N15 are 88.1141 and 122.5016 degrees (°). The rest of the structural parameters (bond angle and bond length) are given in Table 1, which matches well with previously reported analogs and confirms the structure of the molecule QTM [1].

Table 1. Optimized structural parameters (bond angle and bond length)

bond distance		bond angle	
R(1,2)	1.5321	A(2,1,6)	109.6069
R(1,6)	1.5355	A(1,2,3)	111.1655
R(2,3)	1.4674	A(2,3,4)	120.8944
R(3,4)	1.3983	A(2,3,11)	116.6585
R(3,11)	1.4675	A(4,3,11)	120.9728
R(11,12)	1.5318	A(3,4,5)	120.5102
R(12,13)	1.5354	A(3,4,7)	120.4637
R(7,13)	1.519	A(5,4,7)	119.016
R(7,8)	1.3902	A(4,5,6)	120.4006
R(8,9)	1.407	A(4,5,10)	119.3321
R(9,10)	1.4045	A(6,5,10)	120.2666
R(5,10)	1.3939	A(1,6,5)	111.2623
R(5,6)	1.5187	A(4,7,8)	119.6302
R(9,14)	1.4602	A(4,7,13)	120.2275
R(14,15)	1.2923	A(8,7,13)	120.141
R(15,16)	2.4909	A(7,8,9)	121.9296
R(16,17)	1.2945	A(8,9,10)	117.8635
R(17,18)	1.3957	A(8,9,14)	122.0915
R(18,19)	1.4599	A(10,9,14)	120.0434
R(19,20)	1.5116	A(5,10,9)	122.2234
R(16,20)	1.5056	A(3,11,12)	111.1535
		A(11,12,13)	109.614
		A(7,13,12)	111.3778
		A(14,15,16)	88.1141
		A(9,14,15)	122.5016
		A(18,19,20)	104.6287
		D(9,14,15,16)	-174.4042

3.2 Frontier molecular orbital analysis

HOMO and LUMO are collectively known as frontier molecular orbital; HOMO is associated with the electron-donating capacity of the molecule, whereas LUMO indicates the electron-accepting capability of the molecule [1, 13]. In the case of our molecule, the HOMO is localized over some atoms of Julolidine moiety and on pi-spacer (C14=N15) as well as fully spread over the triazole molecule. LUMO of QTM is located over only triazole moiety; this type of observation reveals that the electron gets transferred from Julolidine to triazole moiety of QTM through pi-space (C14=N15); the calculated energy for HOMO is 1.7627 eV which is associated with the molecular orbital number 72. The energy of LUMO is found to be -

0.4802 eV and is the energy of orbital number 73. Finally, the HOMO-LUMO energy gap (E_{H-L}) of the molecule QTM is 1.2825 eV, which confirms the biologically active character of the molecule and suggests its capacity to become an NLO active agent.

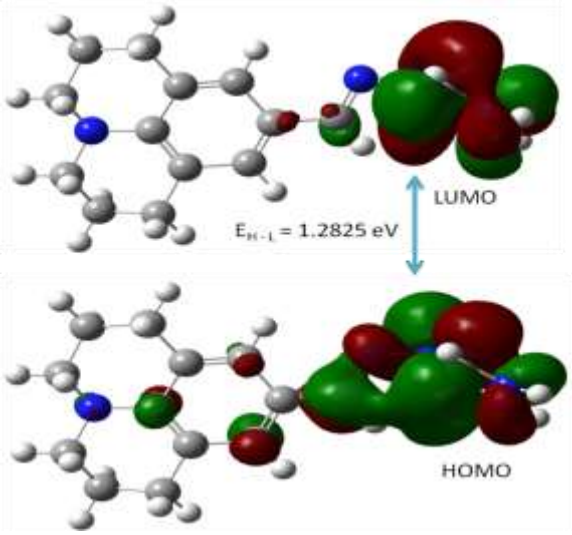

Figure. 2. The HOMO, LUMO, and energy gap of QTM.

3.3. Molecular Electrostatic Potential

A Molecular Electrostatic Potential (MEP) map shows the charge distribution in a molecule, highlighting electron-rich regions (negative, red/yellow) or electron-deficient (positive, blue) areas. It helps to predict molecular reactivity and interactions with other molecules [1]. Figure 3 displays the MEP of QTM with color limit -8.841e2 to 8.841e2. The negative part of the map is associated with the nitrogen atom, which is also partially spread over Julolidine moiety and on the pi-space of QTM, whereas the positive part of the map is allocated to carbon and hydrogen atoms.

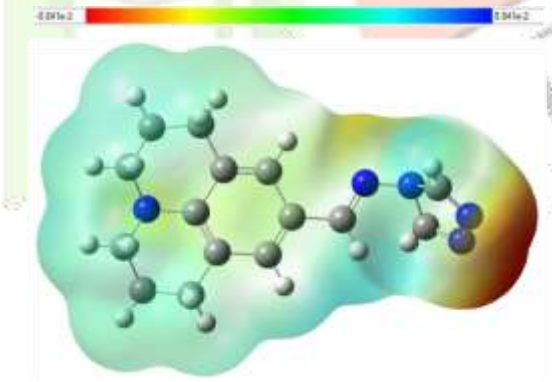

Figure 3 MEP of QTM

3.4 NLO response

Nonlinear Optics (NLO) is the study of how light interacts with materials in a way that changes its properties, like frequency or phase, when the material's response is not directly proportional to the light's intensity. NLO effects, such as frequency doubling, are important in applications like lasers, telecommunications, and optical computing, and usually occur at high intensity of light, such as those produced by lasers [1, 13-15]. Polarizability (α), hyperpolarizability (β), and dipole moment (μ) can be obtained as follows, and their calculated values are given in Table 2.

$$\mu = \sqrt{(\mu_x^2 + \mu_y^2 + \mu_z^2)}$$

$$\alpha_{tot} = \frac{\alpha_{xx} + \alpha_{yy} + \alpha_{zz}}{3}$$

$$\text{Hyper polarizability } \beta_{total} = \sqrt{\beta_1^2 + \beta_2^2 + \beta_3^2}$$

Where, $\beta_x = \beta_{xxx} + \beta_{xyy} + \beta_{xzz}$, $\beta_y = \beta_{yyy} + \beta_{xxy} + \beta_{yyz}$, $\beta_z = \beta_{zzz} + \beta_{xxz} + \beta_{yyz}$

The computed polarizability (α) value for the title compound (QTM) is 19.54×10^{-23}esu. The calculated hyperpolarizability (β) of QTM is 4.688×10^{-30} esu, which is six times higher than the β (0.7803×10^{-30} esu [16]) of urea. At the same time, the calculated dipole moment (μ) of QTM is 7.2938 D, which is also higher than the μ (1.5256 Debye [16]) value of urea. These results suggest that the QTM could become a good NLO active agent for the development of NLO active materials. All calculated values for NLO parameters (dipole moment, polarizability, and hyperpolarizability) are given in Table 2.

Table 2. Calculated dipole moment (μ), polarizability (α), and first-order hyperpolarizability (β_{total}) of QTM.

Parameter	Value (Debye)	Parameter	Value (au)	Parameter	Value (au)
μ_x	5.4323	α_{xx}	-149.8571	β_{xxx}	411.9905
μ_y	-4.0289	α_{yy}	-122.8587	β_{yyy}	-10.0284
μ_z	2.7308	α_{zz}	-146.8460	β_{zzz}	8.0815
μ_{total}	7.2938	α_{xy}	-22.7321	β_{xyy}	2.7479
		α_{xz}	6.8445	β_{xxy}	-123.6425
		α_{yz}	4.5905	β_{xxz}	85.6584
		α_{total}	19.54×10^{-23} esu	β_{xzz}	39.7367
				β_{yzz}	-2.0494
				β_{yyz}	0.3500
				β_{xyz}	23.0769
				β_{total}	4.688×10^{-30} esu

3.5. Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET)

Several characteristics related to drug-likeness for the designed compound in the current era are frequently studied by in silico ADMET analysis utilizing the Swiss online server AdmetSAR. Characteristics like water-solubility, pharmacokinetics, lipophilicity, and medicinal chemistry confirm whether or not the designed compound possesses a drug-likeness nature [1, 13]. Lipinski's rule reveals that the calculated value of log Po/w (iLOGP) is found to be 2.99 whereas. Solubility/log S (ESOL) is -2.81. However, this compound exhibits zero violation of Lipinski. QTM possesses 3.31 synthetic accessibility values, which confirms it (synthetic accessibility) is in a good range. This compound (QTM) demonstrates a high GI (gastrointestinal absorption) absorption rate and could inhibit cytochrome (CYP1A2 CYP2C19, CYP2D6, and CYP3A4). The calculated physicochemical parameters are given in Table 3-5. On the basis of Lipinski's rule, the bio-availability radar for QTM is illustrated in Figure 4.

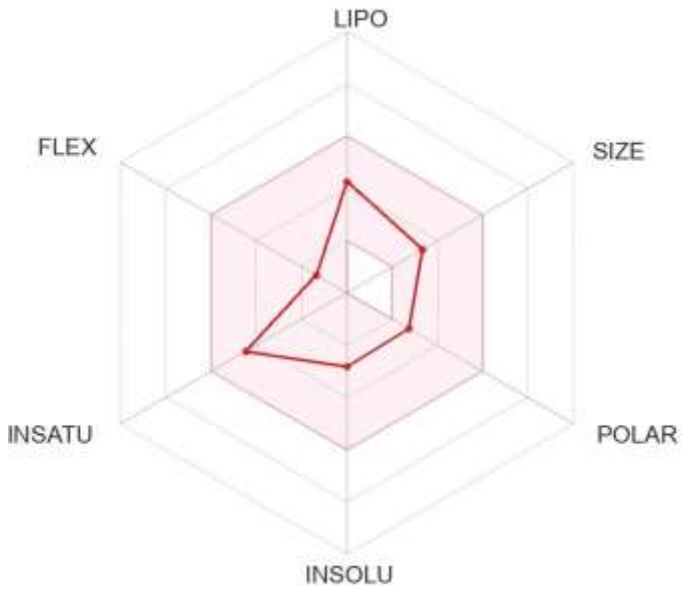

Figure 4. Bio-availability radar for QTM

Table 3 Physicochemical Parameters and Lipophilicity of QTM

Physicochemical Properties	Value	Lipophilicity	Value
Formula	C16H18N4	Log $P_{o/w}$ (iLOGP)	2.99
Molecular weight	266.34 g/mol	Log $P_{o/w}$ (XLOGP3)	1.95
Num. heavy atoms	20	Log $P_{o/w}$ (WLOGP)	1.10
Num. arom. heavy atoms	6	Log $P_{o/w}$ (MLOGP)	1.88
Fraction Csp3	0.44	Log $P_{o/w}$ (SILICOS-IT)	4.18
Num. rotatable bonds	2	Consensus Log $P_{o/w}$	2.42
Num. H-bond acceptors	3		
Num. H-bond donors	0		
Molar Refractivity	93.88		
TPSA	40.32 Å^2		

Table 4 Water Solubility and Pharmacokinetics of QTM

Water Solubility		Pharmacokinetics	
Log S (ESOL)	-2.81	GI absorption	High
Solubility	4.13e-01 mg/ml ; 1.55e-03 mol/l	BBB permeant	Yes
Class	Soluble	P-gp substrate	No
Log S (Ali)	-2.42	CYP1A2 inhibitor	Yes
Solubility	1.01e+00 mg/ml ; 3.79e-03 mol/l	CYP2C19 inhibitor	Yes
Class	Soluble	CYP2C9	No

		inhibitor	
Log S (SILICOS-IT)	-3.72	CYP2D6 inhibitor	Yes
Solubility	5.12e-02 mg/ml ; 1.92e-04 mol/l	CYP3A4 inhibitor	Yes
Class	Soluble	Log K_p (skin permeation)	-6.54 cm/s
Log S (ESOL)	-2.81	GI absorption	High

Table 5 Druglikeness and Medicinal Chemistry

Druglikeness		Medicinal Chemistry	
Lipinski	Yes; 0 violation	PAINS	0 alert
Ghose	Yes	Brenk	1 alert: imine_1
Veber	Yes	Leadlikeness	Yes
Egan	Yes	Synthetic accessibility	3.31
Muegge	Yes		
Bioavailability Score	0.55		

3.6. Docking studies

Molecular docking is a computational technique used in drug discovery and structural biology to predict how a small molecule (such as a drug or ligand) binds to a receptor, typically a protein. The primary goal of molecular docking is to understand the interaction between the ligand and receptor, which helps predict the strength, type, and biological effect of this binding [1, 13]. In the case of **QTM** and **AChE**, the active receptor sites are PHE331, PHE330, TRP84, TYR334, ILE287, and ARG289, which bind with the triazole ring and imine nitrogen through hydrogen bonds with a binding affinity of **-9.3 kcal/mol**. On the other hand, **BChE** binds with **QTM** at the active sites GLY117, TRP231, LEU286, SEP198, HIS438, PHE328, and SER287, with a binding affinity of -8.3 kcal/mol. The above results suggest that the designed compound QTM can become a moderate anti-Alzheimer agent. 2D and 3D representations of molecular docking are shown in Figures 5 and 6. For molecular docking, the first PDB file of the receptor AChE (PDB ID-**1EVE)**and BChE (PDB ID-**10PI)** have been downloaded from the protein data bank site and prepared for docking in the Discover studio (visualizer), and docking results are displayed in Discover studio.

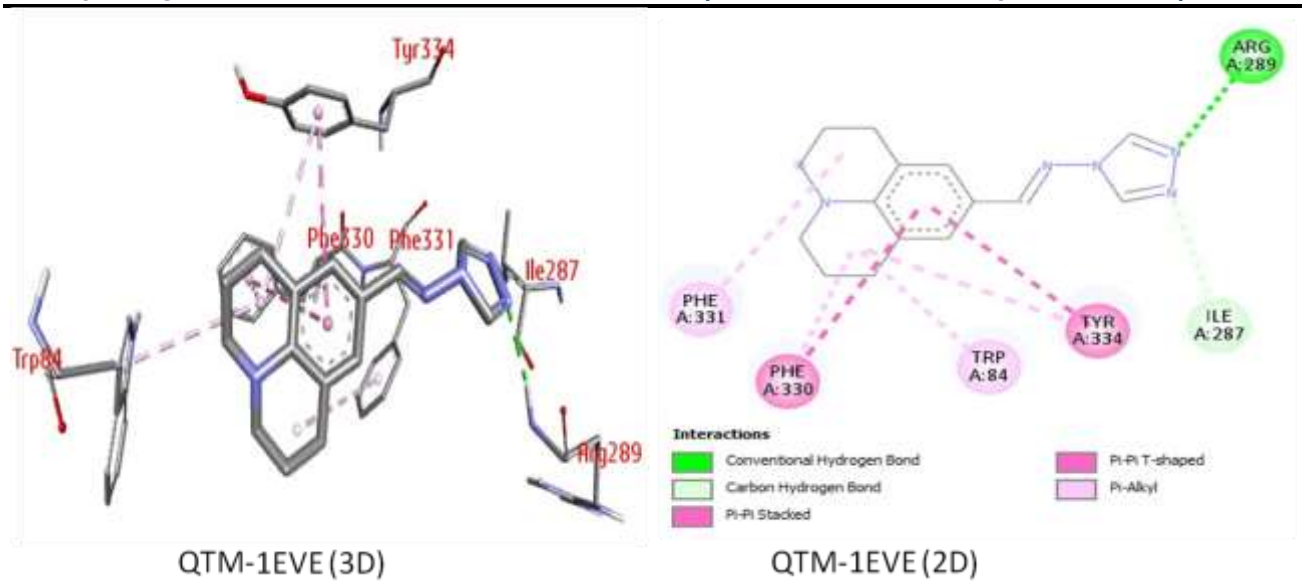

Figure 5. Docking of QTM with 1EVE/AChE

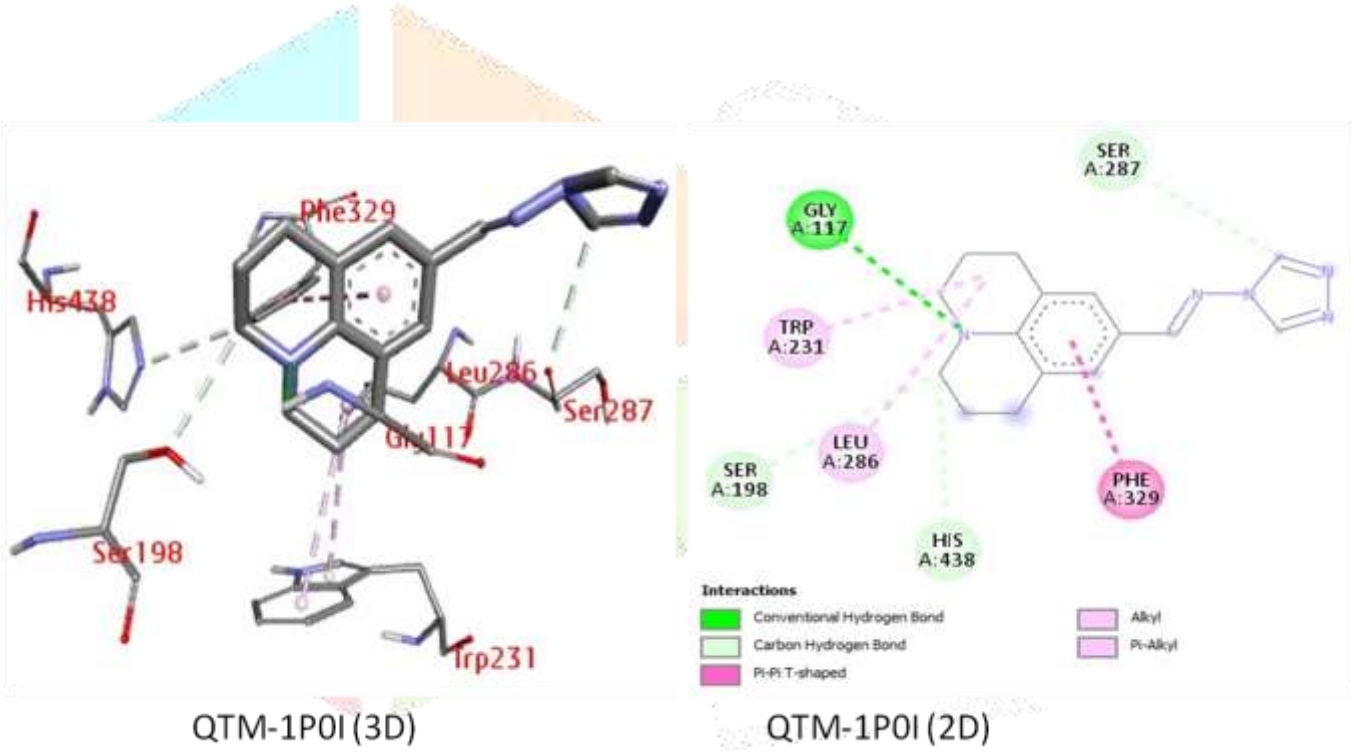

Figure 6 Docking of QTM with 10PI/BChE.

4. Conclusions

A heterocyclic compound (E)-1-(2,3,6,7-tetrahydro-1H,5H-pyrido[3,2,1-ij]quinolin-9-yl)-N-(4H-1,2,4-triazol-4-yl) methenamine (QTM) has been designed, and its optical and biological properties and structural characterization has been studied theoretically. The frontier molecular orbital analysis reveals that the compound possesses 1.2825 eV(E_{H-L}/HOMO-LUMO energy gap), promising that this molecule can show NLO response and biological activity. The hyperpolarizability value is found to be six times higher than urea, which is appropriate for NLO active character of QTM. ADMET results show that QTM possesses drugs like nature. A docking study revealed that QTM can become a moderate anti-Alzheimer agent.

Declaration of competing interest

None.

References

[1]. Jamal, A., Ferjani, H., Faizi, M.S.H. and Alzahrani, A.Y.A., 2024. DFT calculation and molecular docking studies of designing quinoline-derived anti-Alzheimer agents with NLO response. Journal of the Indian Chemical Society, 101(8), p.101181.

[2]. Lai, C.C., Lo, C.Y., Huang, J.Z., Chiang, C.C.F., Nguyen, D.H., Chen, Y.P. and Liao, C.D., 2018. Architecting a nonlinear hybrid crystal–glass metamaterial fiber for all-optical photonic integration. Journal of Materials Chemistry C, 6(7), pp.1659-1669.

[3]. Lei, J., Guo, C., Liu, F., Chen, S., Shi, W.J., Wang, Z., Zhai, Z., Mo, S. and Wang, J., 2019. Enhancement of electro-optic properties of nonlinear optical chromophores by introducing pentafluorobenzene group into the donor and π-bridge. Dyes and Pigments, 170, p.107607.

[4]. Gong, L., Ma, C., Liu, T., Lv, J. and Xun, X., 2020. Theoretical study on functionalized acrylonitrile compounds with a large second-order nonlinear optical response. New Journal of Chemistry, 44(45), pp.19623-19629.

[5]. Yang, Y., Zhang, W., Xu, W., Li, Y. and Xiao, H., 2019. Achieving excellent electro-optic activity of chromophores by introducing a stronger electron donor and modifying the π-bridge. Dyes and Pigments, 163, pp.740-748..

[6] Ali, B., Khalid, M., Asim, S., Usman Khan, M., Iqbal, Z., Hussain, A., Hussain, R., Ahmed, S., Ali, A., Hussain, A. and Imran, M., 2021. Key electronic, linear and nonlinear optical properties of designed disubstituted quinoline with carbazole compounds. Molecules, 26(9), p.2760..

[7] Kotowicz, S., Siwy, M., Filapek, M., Malecki, J.G., Smolarek, K., Grzelak, J., Mackowski, S., Slodek, A. and Schab-Balcerzak, E., 2017. New donor-acceptor-donor molecules based on quinoline acceptor unit with Schiff base bridge: Synthesis and characterization. Journal of Luminescence, 183, pp.458-469.

[8] Jasiecki, J. and Wasąg, B., 2019. Butyrylcholinesterase protein ends in the pathogenesis of Alzheimer's disease—could BCHE genotyping be helpful in Alzheimer's therapy?. Biomolecules, 9(10), p.592.

[9] Darvesh, S., 2016. Butyrylcholinesterase as a diagnostic and therapeutic target for Alzheimer's disease. Current Alzheimer Research, 13(10), pp.1173-1177.

[10] Mushtaq, G., H Greig, N., A Khan, J. and A Kamal, M., 2014. Status of acetylcholinesterase and butyrylcholinesterase in Alzheimer's disease and type 2 diabetes mellitus. CNS & Neurological Disorders-Drug Targets (Formerly Current Drug Targets-CNS & Neurological Disorders), 13(8), pp.1432-1439.

[11]. Raza, M.A., Fatima, K., Saqib, Z., Maurin, J.K. and Budzianowski, A., 2019. Designing of diamino based esterases inhibitors; synthesis, characterization, density functional theory and molecular modeling. Journal of Molecular Structure, 1195, pp.712-722.

[12] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, et al. Gaussian 09 Revision E.01; Gaussian, Inc.: Wallingford, CT, 2010.6.

[13] Tatlidil, D., Raza, M.A., Dege, N., Agar, A.A., Farwa, U. and Rehman, S.U., 2022. Therapeutical potential of imines; synthesis, single crystal structure, computational, molecular modeling, and ADMET evaluation. ACS omega, 7(12), pp.10568-10579.

[14] Khalid, M., Ali, A., Jawaria, R., Asghar, M.A., Asim, S., Khan, M.U., Hussain, R., ur Rehman, M.F., Ennis, C.J. and Akram, M.S., 2020. First principles study of electronic and nonlinear optical properties of A–D–π–A and D–A–D–π–A configured compounds containing novel quinoline–carbazole derivatives. RSC advances, 10(37), pp.22273-22283.

[15] Suresh, S., Ramanand, A., Jayaraman, D. and Mani, P., 2012. Review on theoretical aspect of nonlinear optics. Rev. Adv. Mater. Sci, 30(2), pp.175-183.

[16] Ramalingam, S., Karabacak, M., Periandy, S. and Puviarasan, N., 2012. Spectroscopic analysis (FT-IR/FT-Raman) and molecular structure investigation on m-fluoronitrobenzene using hybrid computational calculations. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, 94, pp.318-330.