Computational studies of 2-(4-oxo-3-phenylthiazolidin-2-ylidene) malononitrile

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Abstract

The molecular structure of the 2-(4-oxo-3-phenylthiazolidin-2-ylidene) malononitrile (3) is calculated using DFT B3LYP/6-311G(d, p) method. The calculated geometric parameters are in good agreement with the experimental data. The NBO calculations were performed to predict the natural atomic charges at the different atomic sites and study the different intramolecular charge transfer (ICT) interactions occurring in the studied system. The BD(2)C17–C19 → BD*(2)C14–C15, LP(2)O2 → BD*(1)N5–C9 and LP(1)N5 → BD(2)C10–C11 ICT interactions causing stabilization of the system by 23.30, 30.63 and 52.48 kcal/mol, respectively. The two intense electronic transition bands observed experimentally at 249 nm and 296 nm are predicted using the TD-DFT calculations at 237.9 nm (f = 0.1618) and 276.4 nm (f = 0.3408), respectively. These electronic transitions are due to H-3 → L (94%) and H → L (95%) excitations, respectively.

Keywords: Thiazole, DFT/B3LYP calculations, Molecular docking, NBO calculations

Introduction

Thiazoles are an important class of heterocyclic compounds that possess the sulphur and nitrogen beside carbon atoms in its five member ring [1]. They are part of a number of pharmaceutical drugs that have analgesic (meloxicam) [2], antihistamine (nizatidine) [3], antibacterial (penicillin) [4], antifungal (thiabendazole) [5], anti-protozoal [6], and a number of other biological properties [1]. They are also part of the essential vitamin B1 or thiamine [7]. In the past, several thiazolidine derivatives have been synthesized and their molecular structural properties have been studied both experimentally and theoretically [8]. In this article we have selected a thiazole based derivative that we have synthesized previously and here we performed density functional theory (DFT) based calculation for its molecular structure [9–11]. The current studied will provide more chemical information about our previously synthesized compound that has good biological activities. These current theoretical studies will further assist in the design and syntheses of better bioactive analogues of thiazole in the future. The 2-(4-oxo-3-phenyl-1,3-thiazolidin-2-yl-idene)malononitrile is a thiazole based derivative that possess several biological properties [10]. We calculated both electronic and spectroscopic properties and compared with previous experimental results of its crystal structure [9, 10, 12, 13]. From the density functional theory (DFT) based calculations we predicted its non-linear optical properties etc. that are discussed below [10]. The DFT will provide information about geometry of the molecule, different orbitals calculations like frontier molecular orbitals will provide information about the π electronic system and intramolecular charge transfer, natural bond orbitals will provide information about different bond interactions and
their energies. Similarly, molecular electrostatic potential shows the reactive and non-reactive centers in the molecules while the ultra-violet visible (UV–Vis) spectrum and infra-red (IR) spectrum will also be obtained from these calculations.

**Computational methods**

**Quantum chemical calculations**

The DFT calculations for the thiazole derivative was performed with the hybrid function of B3LYP and basis set of 6-311G(d, p) [14–16] present in Gaussian 03 software [10, 17]. The coordinates file of the X-ray crystal structure of the thiazole derivative (compound 3) was downloaded from the online repository [10, 18]. The molecular geometry of the compound 3 was optimized through the energy minimization process without any geometrical parameters constraints [10]. The Gauss View 4.1 [19] and Chemcraft [20] softwares were used for drawing the refined structure of the compound 3 [10]. The energy minima of the optimized geometry of the selected molecule was established as there were no imaginary frequency modes. The electronic, orbital bonding and spectral properties of the selected molecule were also computed through DFT method [21–23]. The natural bond orbital and molecular electrostatic potential analyses for the thiazole derivative was carried out using the B3LYP/6-311G (d, P) level [14–16]. The NBO analyses provides the intramolecular interaction inside the thiazole derivative, stabilization energies and bond interactions. The second order perturbation energy calculation provided the donor and acceptor energies [21–23]. The molecular electrostatic potential analysis produced the most reactive sites in a molecule and thus it is easy to predict the electrophilic and nucleophilic attack sites.

**Docking studies**

The molecular docking was executed on the molecular operating environment (MOE) 2014.09 software [24–26]. The atomic coordinates of the human B-lactate dehydrogenase in complex with oxidized form of nicotinamide adenine dinucleotide and 4-hydroxy-1,2,5-oxadiazole-3-carboxylic acid having PDB ID Number 1T2F was downloaded from protein data bank website [27]. The structure of the protein and the selected ligand was optimized, and energy minimization was performed. The binding pockets in the protein receptor were determined with site finder module of MOE [24, 25]. The efficiency of the docking program was gauged by re-docking the original ligand into the established receptor active site for the determination of root mean square deviation (RMSD) [26]. After that, the malononitrile compound 3 was docked with the receptor protein and the conformer with best docking score and free energy was selected [26, 28].

**Results and discussion**

**Chemistry**

Malononitrile was stirred with phenyl isothiocyanate in K$_2$CO$_3$ in dimethylfluoride to afford an intermediary anionic compound 2, which on reacting with ethyl chloroacetate forming the targeted molecule 3 [9] (Fig. 1a).

**Optimization of the compound geometry**

The optimized molecular structure bond lengths and their angles were calculated through the hybrid function of B3LYP with 6-311G(d, p) basis set as tabulated in Table 1; and compared with the experimentally determined optimized molecular structure from the literature [9, 29]. This compound possess C$_1$ point group and its optimized structural information were compared with the crystallographic information file (CIF) [9, 10]. All the predicted geometric parameters agree with the experimental results. The bond distances of the compound 3 are a little overestimated except the C11–C12 bond which is shorter by 0.009 Å than the experimental one [30]. The main deviations in the values of calculated from the experimental bond length and angle are 0.041 Å (S1–C) and 1.3° (O2–C9–C6), respectively [30]. The predicted values of C–C–C bond angle of the phenyl ring of compound 3 are in the range of 119.1–120.3° while the experimental values are 117.9–120.8° [10, 31]. The calculated dihedral angles of the phenyl and thiazole rings of this molecule are close to 0° showing a planar structure [10] (Fig. 1b).

**Natural atomic charge on the molecule**

The charge distribution over a molecule has pivotal role in quantum chemistry. The atomic charges are related to the electronic density, charge distribution and dipole moment of a compound. The natural atomic charges (NAC) computed through DFT at the different atomic positions are tabulated in Table 2. The studied molecule has oxygen, nitrogen and sulfur-heteroatoms. The O and N-atoms are the most electronegative atomic spots in the malononitrile analogue [33]. In contrast, the S-atom is electropositive. The calculated natural atomic charge for the two N-sites of the nitrile groups (N3 and N4) are approximately equivalent [33]. While the NAC at the thiazole nitrogen atom is more negative than the N-atoms of the nitrile group. In the present compound 3, all the H-atoms are electropositive whereas the aliphatic protons (H7 and H8) are more positively charged than the aromatic ones [33]. The NAC on the aliphatic and aromatic protons are 0.2437 and 0.2080–0.2146, respectively. Most of the aromatic C-atoms are electronegative except C14 as this carbon bonded to the high electronegative
The most electropositive C-atom in the molecule is the carbonyl carbon [32].

**Molecular electrostatic potential**

The distribution of charge and its related properties of compounds can be obtained through the 3D electrostatic potential maps. The electrostatic potential map was produced by overlapping the Van der Waal’s radii of each atom present in the compound 3 so that it reveals the charged surface and thus one can visualize the morphological properties of the molecule [10, 35, 36]. Through these maps, we can forecast the reactive spots for electrophilic as well as the nucleophilic attack during the chemical reactions [10, 37, 38]. The malononitrile derivative electrostatic potential map was predicted through the same DFT hybrid function and basis set as other parameters were measured and is presented in Fig. 2. The charged surface map in Fig. 2 showed that the negative regions (red) contain the N3 and N4 atoms of the nitrile group, showing that these N-sites are the hot spots for electrophilic attack. While the blue regions in Fig. 2 represent the positive regions that contain the area of H7, H8 and C6-atoms of the compound 3 and are the hot spot of nucleophilic attacks. These results gave information about how compound 3 interact with receptor active sites.

| Parameter | Calc. | Exp | Parameter | Calc. | Exp |
|-----------|-------|-----|-----------|-------|-----|
| R(1-6)    | 1.824 | 1.783 | A(2-9-5)  | 124.0 | 123.6 |
| R(1-10)   | 1.769 | 1.739 | A(2-9-6)  | 124.9 | 126.2 |
| R(2-9)    | 1.199 | 1.191 | A(3-12-11)| 179.1 | 179.4 |
| R(3-12)   | 1.157 | 1.132 | A(4-13-11)| 175.2 | 175.1 |
| R(4-13)   | 1.156 | 1.137 | A(9-5-10) | 116.8 | 116.7 |
| R(5-9)    | 1.411 | 1.399 | A(9-5-14) | 118.8 | 119.1 |
| R(5-10)   | 1.377 | 1.357 | A(5-9-6)  | 111.1 | 110.2 |
| R(5-14)   | 1.447 | 1.444 | A(10-5-14)| 124.4 | 124.2 |
| R(6-9)    | 1.518 | 1.501 | A(5-10-11)| 127.9 | 126.9 |
| R(10-11)  | 1.376 | 1.367 | A(5-14-15)| 119.3 | 118.9 |
| R(11-12)  | 1.425 | 1.434 | A(5-14-23)| 119.3 | 119.0 |
| R(11-13)  | 1.423 | 1.426 | A(10-1112)| 118.1 | 118.1 |
| R(14-15)  | 1.391 | 1.370 | A(10-1113)| 126.0 | 126.8 |
| R(14-23)  | 1.391 | 1.368 | A(12-1113)| 115.9 | 115.0 |
| R(15-17)  | 1.391 | 1.384 | A(15-1423)| 121.4 | 122.1 |
| R(17-19)  | 1.393 | 1.366 | A(14-1517)| 119.1 | 117.9 |
| R(19-21)  | 1.393 | 1.361 | A(14-2321)| 119.1 | 119.0 |
| R(21-23)  | 1.391 | 1.365 | A(14-2324)| 120.0 | 120.4 |
| A(6-1-10) | 92.1  | 92.1  | A(15-1719)| 120.1 | 120.1 |
| A(6-6-9)  | 107.8 | 108.5 | A(17-1921)| 120.3 | 120.8 |
| A(10-5-5) | 112.1 | 112.3 | A(19-2123)| 120.1 | 120.1 |
| A(1-10-11)| 119.9 | 120.8 | A(19-2124)| 120.1 | 120.1 |

Fig. 1  a Synthesis of thiazole derivative 3 [3].  b Optimized chemical structure of the malononitrile analogue
Nonlinear optical properties

The nonlinear optical materials are important for photonic communications due to its use light for data transmission and thus are an actively used in industry nowadays [39–41]. Many organic based compounds are used in photonic communication instruments due to their superior polarizability ($\alpha_0$) and lower energy gap ($\Delta E$) between their highest occupied and lowest unoccupied molecular orbitals [40–42]. Here the $\alpha_0$ and $\Delta E$ values of the thiazole based malononitrile derivative are 162.89 Bohr³ and 4.6905 eV, while the polarizability value is approximately six times that of urea. Based on our calculations it has lower $\Delta E$ than urea. Thus, this thiazole based compound has superior nonlinear optical qualities than the reference molecules [33, 43, 44].

Frontier molecular orbitals (FMOs) of the malononitrile analogue

The electronic densities of FMOs are helpful in predicting the reactive positions and different reaction types for a $\pi$-electron systems containing molecules [33, 43]. Further, the energies of the two types of orbitals ($E_{\text{HOMO}}$ and $E_{\text{LUMO}}$) and their $\Delta E$ of a molecule showed its inherent chemical reactivity and intramolecular charge transfer (ICT) capacities [32, 45–48]. The $\Delta E$ for the FMOs of the thiazole based compound 3 was calculated through the hybrid function of B3LYP/6–311G (d, p) and its FMOs picture is presented in Fig. 3 [32]. It was observed that the molecular orbitals level are delocalized over the five member ring of the compound and the C10–C11–C–N $\pi$-electron systems. The $E_{\text{HOMO}}$ is $-6.9947$ eV while $E_{\text{LUMO}}$ is $-2.3043$ eV. The orbitals $\Delta E$ signifies a lower energy electronic transition with a value of 4.6905 eV for the thiazole based compound under study. This ICT of electron transition happens due to $\pi$–$\pi^*$ excitations. The 40 spin allowed singlet–singlet electronic transitions predicted are tabulated in Additional file 1: Table S1 and the electronic spectrum is presented in Additional file 1: Figure S4 [49]. Experimentally there are two intense electronic transition bands that are observed at 249 nm and 296 nm. On the basis of DFT calculations, these electronic spectral bands were observed at 237.9 nm ($f=0.1618$) and 276.4 nm ($f=0.3408$) on the spectrum and these can be assigned to the excitation from H-3 $\rightarrow$ L (94%) and H $\rightarrow$ L (95%) respectively.

Natural bond orbital (NBO) analysis

The stabilization energies $E^{(2)}$ for the relevant intramolecular charge transfer contacts were calculated through the NBO method (Table 3) [51, 52]. The different types of interactions between filled and empty orbitals in a complex molecule can be used to measure the intra-molecular electronic density delocalization. A larger stabilization energy showed high rate of electronic exchange between donor and acceptor NBOs, i.e. higher the amount of conjugation inside the molecule [53]. The second-order perturbation theory is used to describe the energetics of such interactions [10, 54, 55]. The intramolecular charge transfer exchange as a result of the orbital overlap between $\pi \rightarrow \pi^*$, $n \rightarrow \sigma^*$ and $n \rightarrow \pi^*$ orbitals helps in stabilization of the molecular system up to 23.30, 30.63 and 52.48 kcal/mol respectively, which are due to BD(2)C17–C19 $\rightarrow$ BD$^*(2)$C14–C15, LP(2)O2 $\rightarrow$ BD$^*(1)$.
N5–C9 and LP(1)N5 → BD*(2)C10–C11 ICT interactions, respectively [10]. These predicted results showed that there is strong electronic density spread from LP(1)

\[ E_{\text{LUMO}} = -2.3043 \text{ eV} \]

\[ E_{\text{HOMO}} = -6.9947 \text{ eV} \]

Table 3 The stabilization energies \( E^{(2)} \) in (kcal/mol) of the important charge transfer interactions between the donor and acceptor in the malononitrile analogue

| Donor NBO (i) | Acceptor NBO (j) | \( E^{(2)} \) kcal/mol |
|--------------|-----------------|-----------------------|
| BD(1)N3–C12  | BD*(1)C11–C12   | 8.09                  |
| BD(3)N3–C12  | BD*(2)C10–C11   | 7.66                  |
| BD(1)N4–C13  | BD*(1)C11–C13   | 8.49                  |
| BD(3)N4–C13  | BD*(2)C10–C11   | 8.50                  |
| BD(1)C10–C11 | BD*(1)C11–C12   | 5.29                  |
| BD(1)C10–C11 | BD*(1)C11–C13   | 5.93                  |
| BD(2)C10–C11 | BD*(3)N3–C12    | 20.67                 |
| BD(2)C10–C11 | BD*(3)N4–C13    | 19.65                 |
| BD(1)C10–C11 | BD*(2)C10–C11   | 6.94                  |
| BD(1)C11–C12 | BD*(1)N3–C12    | 8.23                  |
| BD(1)C11–C12 | BD*(1)N5–C10    | 6.32                  |
| BD(1)C11–C12 | BD*(1)C10–C11   | 5.01                  |
| BD(1)C11–C13 | BD*(1)N4–C13    | 8.66                  |
| BD(1)C11–C13 | BD*(1)C10–C11   | 6.46                  |
| BD(1)C14–C15 | BD*(2)C17–C19   | 17.82                 |
| BD(2)C14–C15 | BD*(2)C21–C23   | 20.47                 |
| BD(1)C15–C17 | BD*(1)N5–C14    | 5.05                  |
| BD(2)C17–C19 | BD*(2)C14–C15   | 23.30                 |
| BD(2)C17–C19 | BD*(2)C21–C23   | 20.11                 |
| BD(2)C21–C23 | BD*(1)N5–C14    | 5.05                  |
| BD(2)C21–C23 | BD*(2)C14–C15   | 21.81                 |
| BD(2)C21–C23 | BD*(2)C17–C19   | 20.50                 |
| LP(2)S1      | BD*(2)C10–C11   | 26.02                 |
| LP(2)O2      | BD*(1)N5–C9     | 30.63                 |
| LP(2)O2      | BD*(1)C6–C9     | 22.18                 |
| LP(1)N3      | BD*(1)C11–C12   | 12.47                 |
| LP(1)N4      | BD*(1)C11–C13   | 12.59                 |
| LP(1)N5      | BD*(2)O2–C9     | 44.57                 |
| LP(1)N5      | BD*(2)C10–C11   | 52.48                 |

N5 to the nearby C10–C11π*-NBO. Further, there is a \( \pi \rightarrow \pi^* \) electron delocalization between the nitrile group \( \pi \)-system to the nearby \( \pi^* \)-NBO of the C10–C11 bond in this thiazole based compound.

Vibrational spectrum analyses

The IR vibrational spectrum of the malononitrile analogue were computed through the same hybrid function and basis set as described previously and the vibrational modes were assigned through visual inspection through the GaussView software [10, 17, 56]. The comparison between theoretically computed and the experimental vibrational band frequencies of the compound 3 are tabulated in Additional file 1: Table S2 and the IR spectrum is shown in Fig. 5 [10]. The Additional file 1: Table S2
showed that there is close resemblance between the two IR vibrational frequencies [10, 57].

**Aromatic C–H bending vibrations**
The thiazole ring of the malononitrile derivative possesses the carbon–hydrogen stretching vibrations in 3100–3000 cm\(^{-1}\) region [10, 58]. In this study, the IR band recognized for the C–H stretching vibrations at 3042 cm\(^{-1}\) is present at 3097–3070 cm\(^{-1}\) [10, 59]. The in-plane and out-of-plane ring C–H bending vibrations bands are predicted in the region 1400–1000 and 1000–600 cm\(^{-1}\) respectively [10, 60, 61]. The DFT analyses also showed that the in-plane bending modes are at 1475, 1438, 1305, 1158, 1148, 1128, 1067 and 1013 cm\(^{-1}\) (exp. 1461, 1291, 1157 and 1024 cm\(^{-1}\)) [10]. Few of the in-plane C–H bending vibrational modes mixed with other bands [62]. On other hand, the out-of-plane bending modes for C–H are present at 980–904, 817, 739 and 684 cm\(^{-1}\) (exp. 991, 911, 791 and 698 cm\(^{-1}\)) [10]. Thus our theoretical calculated C–H vibrational frequencies agree very well with experimental data.

**Aliphatic C–H vibrations of the thiazole ring**

The compound under investigation has one methylene group at the thiazole ring. It will therefore exhibits two aliphatic C–H stretching vibration at lower frequencies in the spectrum than those of the aromatic C–H ring vibrations [63–65]. Both the symmetric and asymmetric stretching vibrations of the CH\(_2\) group are present at 3027 (exp. 2997 cm\(^{-1}\)) and 2979 cm\(^{-1}\) (exp. 2944 cm\(^{-1}\)), in the computed vibrational spectrum [62, 66, 67]. The theoretically computed CH\(_2\) scissoring, wagging, twisting and rocking vibrations are present at 1410 cm\(^{-1}\) (exp. 1384 cm\(^{-1}\)), 1285 cm\(^{-1}\) (exp. 1234 cm\(^{-1}\)), 1109 cm\(^{-1}\) and 888 cm\(^{-1}\) (exp. 886 cm\(^{-1}\)), respectively [10, 64].

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**Fig. 4** 2D representation showing the hydrogen bond interactions of the interesting compound and the targeting enzyme
C≡N vibrations

Generally the nitrile stretching vibration is present at 2250 ± 10 cm⁻¹ in saturated nitriles or in olefinic nitriles where no conjugation exists between the nitrile and the olefinic group [68, 69]. While in conjugated nitrile, the band moves to lower frequency of 2225 ± 7 cm⁻¹ [69, 70]. Here in this molecule, there are two nitrile groups attached to the C≡C so the symmetric and asymmetric υ_C≡N modes are predicted at 2251 and 2241 cm⁻¹ [71]. In agreement with literature, the υ_C≡N mode observed experimentally at 2215 cm⁻¹. In the IR spectrum of this compound 3, the symmetric and asymmetric δ_C≡N modes were predicted at 602 and 462 cm⁻¹ (exp. 468 cm⁻¹), respectively. Furthermore, the nitrile group out-of-plane torsion mode has a predicted at 454 cm⁻¹ (exp. 453 cm⁻¹) [10, 64, 65, 72].

C=O, C=C and C=S vibrations

In compounds that have aromaticity, the C=C stretching vibrations is mostly present at 1600–1500 cm⁻¹ [63, 73]. In the current system, these stretching vibrations are predicted at 1587–1438 cm⁻¹ while experimentally observed at 1597–1461 cm⁻¹ [10]. We also found that the aromatic rings breathing modes are at 987 cm⁻¹ (exp. 999 cm⁻¹) [10]. We noted, the υ_{C10=C11} stretching mode at 1520 cm⁻¹ while experimentally it is observed at 1527 cm⁻¹ [10]. The malononitrile analogue showed intense carbonyl vibration observed experimentally at 1745 cm⁻¹ (calc. 1769 cm⁻¹). The thiazole ring C=S stretching vibrational frequency mode is calculated at 758 cm⁻¹ while it is experimentally noted at 757 cm⁻¹ [69].

Molecular docking

Lactate dehydrogenase (LDH) has an active role in the metabolism of lactate during normal physiological process [74, 75]. The high levels of lactate are associated in different ways to several types of human cancers, as cancerous cells have increased metabolism [75]. The increase level of lactate ion may directly contributes to tumor growth and progression [75]. Molecular docking was conducted to find out the interaction of 2-(4-oxo-3-phenylthiazolidin-2-ylidene) malononitrile with the lactate dehydrogenase enzyme. The malononitrile derivative has good affinity for the LDH enzyme showing a total free energy of −4.6 kcal/mol on its interaction. It is clearly the cyano moiety that is the highly active group in the malononitrile by making two hydrogen acceptor interactions with Arg 106 with −3.0 kcal/mol and one hydrogen acceptor interaction with Thr 248 with −1.6 kcal/mol (Figs. 4, 5).
Pharmacophore studies
The pharmacophore analyses was done with the MOE software package (version 2014.010) using the default settings. The different conformers productions for the under test ligand was carried out using the conformational analysis algorithm, present in the MOE software package [76]. Pharmacophore modeling tools determine the different chemical properties and spatial arrangement in three dimensions that are essential for interaction between ligand and its receptor and thus for the drug action. Pharmacophore models can be generated from the structural data of protein–ligand complexes as well as from ligands when no receptor information is available and also from the receptor structure when no ligands are available. The generated models are usually used for virtual screening of online libraries of compounds that are the potentially active molecules. Also, the pharmacophoric feature may represent a specific property and is not necessarily related to a particular chemical structure; but different chemical groups may share the same property and possesses the same feature (Fig. 6 and Table 4) [77, 78].

Conclusions
The chemical structure of the 2-(4-oxo-3-phenylthiazolidin-2-ylidene) malononitrile was optimized through the hybrid B3LYP method and 6-311G (d, p) basis set. The predicted geometrical parameters of the malononitrile derivative agree well with the previous experimental results. From this study it was observed that this malononitrile compound has superior non-linear optical properties than urea. Thus, it can be used in photonic communication instruments.
synergistic experimental-computational analysis. J Phys Chem Solids 115:265–276. https://doi.org/10.1016/j.jpcs.2017.12.054
14. Curtiss LA, Raghavachari K, Trucks GW, Popele JA (1991) Gaussian-2 theory for molecular-energies of 1st-row and 2nd-row compounds. J Chem Phys. 104:7224–7230
15. McGrath MP, Radom L (1991) Extension of Gaussian-1 (G1) theory to bromine-containing molecules. J Chem Phys. https://doi.org/10.1063/1.460367
16. Curtiss LA, McGrath MP, Bludeau JP, Davis NE, Binning RC, Radom L (1995) Extension of Gaussian-2 theory to molecules containing third-row elements. J Chem Phys. https://doi.org/10.1063/1.471142
17. Frisch MJ, Trucks GW, Schlegel HB, Scuseria GE, Robb MA, Cheeseman JR, Montgomery AJJ, Vreven T, Kudin KN, Burant JC, Iyengar SS, Tomasi J, Barone V, Mennucci B, Cossi M, Scalmani G, Rega N, Petersen GA, Nakatsuji H, Hada M, Ehara M, Toyota K, Fukuda R, Hasegawa J, Ishida M, Nakajima T, Honda Y, Kitao O, Nakai H, Klene M, Li X, Knox JE, Hratchian HP, Cross JB, Bakken V, Adamo C, Jaramillo J, Gomperts R, Stratmann RE, Yazyev O, Juretschke J, Ayala P, Morokuma K, Voth GA, Salvador P, Dannenberg JJ, Zakrzewski VG, Dapprich S, Daniels AD, Strain MC, Farkas O, Malick DK, Rabuck AD, Raghavachari K, Foresman JB, Ortiz JV, Cui Q, Baboul AG, Clifford S, Cioslowski J, Stefanov B, Liu G, Liashenko A, Piskorz P, Komaromi I, Martin RL, Fox DJ, Keith T, Al-Laham MA, Peng CY, Nanayakkara A, Challacombe M, Gill PMW, Johnson B, Chen W, Wong MW, Gonzalez C, Pope JA (2004) Gaussian 03, Revision C.02, vol. 24. Gaussian Inc, Wallingford. ISBN: 9780898710796
18. Akkurt M, El-Saghier AM, Younes SH, Horton PN, Albayati MR (2013) 2-(4-Oxo-3-phenyl-1,3-thiazolid-2-ylidene)propanenitrile. Acta Crystallogr E Struct 69:o1315. https://doi.org/10.1107/s6003681301831-08
19. Frisch A, Nielsen AB, Holder JR (2000) Guassview users manual. Gaussian Inc, Wallingford
20. Zhurko GA, Zhurko DA (2017) Chemcraft. Lite Version Build 08. Available online: http://www.chemcraftprog.com/
21. Laurent AD, Jacquemin D (2013) TD-DFT benchmarks: a review. Int J Quantum Chem 113:2009–2039
22. Glendening ED, Badenhoop JK, Reed AD, Carpenter JE, Weinhold F (1996) Quantum Chem 113:2019–2039
23. Kurt M, Yurdakul M (2005) Molecular structure and vibrational spectra of 3-bromo-5-(2,5-difluorophenyl) pyridine and 3,5-bis(naphthalen-1-yl)pyridine: insight into the synthesis, spectroscopic, single crystal XRD, electronic, nonlinear optical and biological properties. J Mol Struct 1160:129–141. https://doi.org/10.1016/j.molstruc.2018.01.100
24. MOE (Molecular Operating Environment) (2009), Vol 2009.10.Re. Available online: http://www.chemcomp.com
25. Chemical Computing Group Inc (2004) Molecular operating environment (MOE). Sci Comput Instrum 22:32. https://doi.org/10.1017/CBO9781107415324.004
26. Gomha SM, Abbas IM, Elneairy MAA, Mahmoud ME, Mabrouk BKA (2017) Crystallographic Sect E Struct Rep Online 70:o1167. https://doi.org/10.1107/s1600536814022351
27. Farhat MF, El-Saghier AMM, Makhlouf MA, Kreddam KM, Elmezoughi AB (2007) Ketene N,5-acetals in heterocyclic synthesis: part I: synthesis of N-phenyl-2-ydine and 2,5-diydine-4-thiazolidinone derivatives. J Sulfur Chem 28:563–572. https://doi.org/10.1080/17415990701586823
28. Barakat A, Soliman SM, Al-Majid AM, Lotfy G, Mabrouk BKA (2017) Synthesis and structure investigation of novel pyrimidine-2,4,6-trione derivatives of highly potential biological activity as anti-diabetic agent. J Mol Struct 1098:365–376. https://doi.org/10.1016/j.molstruc.2018.01.100
29. Cameron A, Read J, Tranter R, Winter VJ, Sessions RB, Brady RL, Vivas L, Cameron A, Read J, Tranter R, Winter VJ, Sessions RB, Brady RL, Vivas L, Martin D, Chantraine F, Lakaye B, Wins P, Grisar T, Bettendorff L (2010) Extension of Gaussian-1 (G1) theory to bromine-containing molecules. J Chem Phys. https://doi.org/10.1063/1.470438
30. Barakat A, Soliman SM, Al-Majid AM, Lotfy G, Mabrouk BKA (2017) Crystallographic Sect E Struct Rep Online 69:o2350. https://doi.org/10.1107/s160053681700216x
31. Ahmad MS, Khalid M, Shafeen MA, Tahir MN, Khan MU, Braga AAC, Shah HA (2018) Synthesis and XRD, FT-IR vibrational, UV-vis, and nonlinear optical exploration of novel tetra substituted imidazole derivatives: a
68. McMurry HL, Thornton V (1952) Correlation of infrared spectra. Anal Chem 24:318–334. https://doi.org/10.1021/ac60062a018
69. Kitson RE, Griffith NE (1952) Infrared absorption band due to nitrile stretching vibration. J Anal Chem 24:334–337. https://doi.org/10.1021/ac60062a019
70. Islam MS, Al-Majid AA, Barakat A, Soliman S, Ghabbour H, Quah CK, Fun HK (2015) Synthesis, molecular structure and spectroscopic investigations of novel fluorinated spiro heterocycles. Molecules 20:8223–8241
71. Ebenezar J (ed) (2017) Recent trends in materials science and applications, vol 189. Springer Nature, New York. ISBN 978-3-319-44889-3
72. Barakat A, Ghabbour HA, Al-Majid AA, Soliman SM, Ali M, Mabkhot YN, Shaik MR, Fun HK (2015) Synthesis, spectroscopic investigations (X-ray, NMR and TD-DFT), antimicrobial activity and molecular docking of 2,6-bis((hydroxy(phenyl)methyl)cyclohexanone. Molecules 20:13240–13263. https://doi.org/10.3390/molecules200713240
73. Dorotíková S, Plevová K, Bučinský L, Malček M, Herich F, Kucková L, Bobenčiová M, Soralová S, Kozlíček J, Frinc M, Milata V, Dvoranová D (2014) Conformational, spectroscopic, and molecular dynamics DFT study of precursors for new potential antibacterial fluoroquinolone drugs. J Phys Chem A 118:9540–9551. https://doi.org/10.1021/jp506355f
74. Han T, Kang D, Ji D, Wang X, Zhan W, Fu M, Xin HB, Wang JB (2013) How does cancer cell metabolism affect tumor migration and invasion? Cell Adhes Migr 7:395–403
75. Dhup S, Dadhich RK, Porporato PE, Sonveaux P (2012) Multiple biological activities of lactic acid in cancer: influences on tumor growth, angiogenesis and metastasis. Curr Pharm Des 18:1319–1330. https://doi.org/10.2174/138161212799504902
76. Radwan AA, Abdel-Mageed WM (2014) In silico studies of quinoxaline-2-carboxamide 1,4-di-N-oxide derivatives as antimycobacterial agents. Molecules 19:2247–2260. https://doi.org/10.3390/molecules19022247
77. Papageorgiou L, Megalooikonomou V, Machakis D (2017) Genetic and structural study of DNA-directed RNA polymerase II of Trypanosoma brucei, towards the designing of novel antiparasitic agents. PeerJ 5:e3061. https://doi.org/10.7717/peerj.3061
78. Markley JL, Bax A, Arata Y, Hilbers CW, Kaptein R, Sykes BD, Wright PE, Wuthrich K (1998) Recommendations for the presentation of NMR structures of proteins and nucleic acids—IUPAC-IUBMB-IUPAB Inter-Union Task Group on the standardization of data bases of protein and nucleic acid structures determined by NMR spectroscopy. Eur J Biochem 256:1–15. https://doi.org/10.1023/a:1008290618449