Structural, Electronic, Vibrational and Pharmacological Investigations of Highly Functionalized Diarylmethane Molecules Using DFT Calculations, Molecular Dynamics and Molecular Docking


To cite this article: Priyanka B. Kole, Shiva Prasad Kollur, H. D. Revanasiddappa, Chandan Shivamallu, Renyer A. Costa, Earle S. A. Junior, Lucas M. Anselmo, Jonathas N. da Silva, Chandrashekar Srinivasa, Asad Syed & Fateh V. Singh (2022): Structural, Electronic, Vibrational and Pharmacological Investigations of Highly Functionalized Diarylmethane Molecules Using DFT Calculations, Molecular Dynamics and Molecular Docking, Polycyclic Aromatic Compounds, DOI: 10.1080/10406638.2022.2041050

To link to this article: https://doi.org/10.1080/10406638.2022.2041050

Published online: 16 Feb 2022.
Structural, Electronic, Vibrational and Pharmacological Investigations of Highly Functionalized Diarylmethane Molecules Using DFT Calculations, Molecular Dynamics and Molecular Docking


ABSTRACT
Present work describes the UV–Visible and FT-IR spectral behavior of highly functionalized diarylmethanes via theoretical investigations. Analyses of both theoretical and experimental UV data were in good agreement with the assigned bands. In addition, calculations pertaining to natural bond orbitals (NBOs) and mapped molecular electrostatic potential surface (MEPS) were also performed, revealing that the strongest hyperconjugative intramolecular interactions involves the $\pi \rightarrow \pi^*$, $\sigma^* \rightarrow \pi^*$ and $\pi \rightarrow \sigma^*$ transitions in the D and A rings. Further, the theoretical vibrational analysis revealed several characteristic vibrations that may be used as a diagnostic tool for other diarylmethanes and also indicated that the experimental bands related to the nitrile group occur in regions lower than usual, which confirms high conjugation of the triple bond with the aromatic system. Molecular dynamics (MD) and molecular docking calculations were performed in order to evaluate the behavior of such molecules in aqueous medium and the pharmacological potential. Another interesting observation in this study is the HOMO–LUMO analysis, which showed that the global reactivity values changed according to the type of substituent groups.

ARTICLE HISTORY
Received 3 February 2020
Accepted 3 February 2022

KEYWORDS
DFT calculations; diarylamethanes; molecular docking; pyran-2-ones; Topoisomerase-II

1. Introduction
Diarylmethanes are key structural motifs found in various biologically active and naturally occurring compounds. These scaffolds are known to exhibit various remarkable biological activities including anti-diabetic, antiviral, anti-breast cancer, anti-allergic, antispasmodic, anti-
hypolipidemic agent\textsuperscript{12} and antibiotic activity.\textsuperscript{13,14} In the past few years, similar highly conjugated systems equipped with electron-donating and withdrawing functionalities have been found as interesting research objects in the area of photophysical chemistry.\textsuperscript{15,16} Various polyaromatic scaffolds bearing electronic Push–Pull system have been identified as remarkable fluorescent probes for lipid droplets (LDs) markers\textsuperscript{17,18} and fluorescent chemosensors.\textsuperscript{19–21} Additionally, various organic light emitting devices have been fabricated using different donor–acceptor based organic scaffolds including 1,2,3-triarylbenzenes,\textsuperscript{22,23} benzo[\textit{f}]quinolines and benzo[\textit{a}]acridines,\textsuperscript{24} fluoranthenes,\textsuperscript{25} fluorenes and fluorenones.\textsuperscript{26}

Various routes are available in the literature to achieve the synthesis of diarylmethanes but most of them are linked with transition metal–catalyzed cross–coupling reactions\textsuperscript{27–32} and Friedel–Craft benzylation of arenes using benzylic alcohols/halides.\textsuperscript{33,34} Recently, Singh and Kole developed a metal-free approach for the synthesis of functionalized diarylmethanes by the ring transformation of 2\textit{H}-pyran-2-ones with 1,3-diphenylacetone under mild reaction conditions.\textsuperscript{35} The synthesis of highly functionalized diarylmethanes 7 was achieved in three chemical steps starting from ethyl-2-cyano-3,3-bis(methylthio)acrylate 2\textit{H}-pyran-2-ones 1 (Scheme 1).\textsuperscript{35,36} The details of all the synthesized diarylmethanes 7\textit{a–j} is summarized in Table 1.

Present work analyses the synthetized diarylmethanes 7\textit{a, c} and 7\textit{g} (Figure 1) from a theoretical view (geometry optimization, NBO, theoretical IR, UV gaps and MEPS calculations) using density functional theory (DFT) approach, comparing the calculated data with the experimental result, providing complete description of the vibrational, structural and quantum properties of molecular structures under study. Molecular dynamics (MD) calculations were performed in aqueous medium in order to evaluate the interaction of these molecules with water, considering that biological processes and biological disposal occur in this medium. Molecular docking calculations were also analyzed with DNA Topoisomerase-II, for being an essential ubiquitous nuclear enzyme which manages the topology of DNA during cellular processes such as, replication. To the best of our knowledge, no theoretical molecular modeling study that discusses the geometrical

![Scheme 1](image_url)

Scheme 1. The synthesis of highly functionalized diarylmethanes 7 starting from ethyl-2-cyano-3,3-bis(methylthio)acrylate 2\textit{H}-pyran-2-ones 1.
parameters of diarylmethane derivatives under investigation has been reported previously. Furthermore, in this work we have performed a detailed description of the spectroscopic (FT-IR and UV–Vis) behavior with the help of quantum (DFT) calculations along with NBO, MEPS and HOMO–LUMO, MD and docking calculations.

2. Materials and methods

The detailed experimental procedure and spectroscopic characterization of all the compounds under study are discussed in our previous report. The experimental electronic absorption spectra of the compounds under study were measured in chloroform solution using UV-1800 spectrophotometer (Shimadzu). The FT-IR spectra of compounds were recorded using Perkin Elmer FT-IR type 1650 spectrophotometer in the region 4000–400 cm⁻¹ using KBr pellets.

2.1. Computational methods

The theoretical quantum chemical calculations were performed using the Gaussian 09 Program (Revision D.01) on the Debian LINUX (8.0 version) platform on a Dell XPS 8900-A10 Intel® Core™ PC with 16GB Ram. The DFT approach using 6-311G(2d,p) basis sets and the B3LYP hybrid functional was chosen to perform the all calculations (Geometry optimization,
HOMO–LUMO analysis and IR spectra). The theoretical IR spectra were obtained from the DFT intensities in combination with the calculated vibrational wavenumbers uniformly scaled by factor of 0.98 (no imaginary frequencies or negative eigenvalues were registered). The assignments of the calculated IR wavenumbers are aided by the animation option of GAUSSVIEW 5.0 program, which gives a visual presentation of the vibrational modes. The potential energy distribution (PED) was calculated with the help of VEDA4 software package. The UV spectra were calculated using the B3LYP functional with 6-311G(2d,p) basis set in chloroform using PCM model by TD-DFT method. The NBO values were calculated with NBO 3.1 program (implemented in the GAUSSIAN 09 package) at the same theory level.

For MD calculations, the were set up using the official CHARMM General Force Field server (CGenFF) and the TIP3 model was used for water. The simulations of structures were performed with CHARMM36 force field using GROMACS version 2019. Particle Mesh Ewald (PME) was used to calculate the long-range ionic interactions. For each system, a 50,000-step minimization was used followed by 100 ps equilibration runs with 2 fs step size. This was followed by the NPT (constant pressure/temperature) production runs at 300 K using 0.5 fs time steps for 10 ns. The reference pressure (1 bar) was controlled using the Berendsen method with a coupling every 2 ps. The temperature was controlled using the modified Berendsen thermostat with coupling every 0.1 ps. The systems for MD simulations were modeled by placing one molecule (structures 1, 2, 3 and 4) to the simulation box solvated with approximately 3047 water molecules. In all cases were used cubic boxes of 98 nm³ for the simulations.

3. Results and discussion

3.1. Geometrical analysis

The geometrical optimization of the studied molecules was calculated at B3LYP/6-311G(2d,p) approach (Figure 2), and compared with X-ray data of a similar molecules reported in the literature (Table S1). The closeness of values between the calculated and experimental geometric parameters indicates the accuracy of the theoretical calculations, making them reliable for the discussion of the geometry for the studied structures. All molecules showed C1 symmetry for the most stable conformations, showing energy electronic values of −1308.00, −1347.34 and −3881.55 a.u. for structures 7a, 7c and 7g, respectively.

All the structures showed uniformity in bond lengths and angles, and since they have a characteristic poly-substituted central benzene besides other benzene rings, their structures are not planar, which hinders intermolecular pi–pi interactions. Structure 7a showed bond length values with small distortions in its rings. Ring A presents very similar bond lengths with values of 1.400 Å (C1–C3), 1.399 Å (C5–C6) and 1.387 Å (C2–C1) with the exception for the bonds C3–C4 (1.417 Å), C4–C5 (1.416 Å) and C6–C2 (1.415 Å). Ring B shows similar bond lengths too with
values of 1.397 Å (C14–C19), 1.392 Å (C19–C18), 1.391 Å (C17–C16) and 1.396 Å (C15–C14), except for the bonds C18–C17 (1.388 Å) and C16–C15 (1.387 Å). Rings C and D showed close bond length values (~1.39 Å) with exception for the bonds C11–C12 (1.389 Å), C9–C10 (1.389 Å), C21–C25 (1.388 Å) and C24–C23 (1.389 Å). Concerning to the bond angles, structure 7a did not show large distortions, revealing angles values around 120°, except for the angles C5–C6–C2 (118.87°), C1–C3–C4 (116.55°), C15–C14–C19 (118.29°), C12–C7–C8 (118.38°) and C22–C20–C21 (118.38°). In addition, the geometry of the Ring E (which has a chair conformation), the C–C bonds showed bond lengths of 1.53 Å and the N–C bonds showed bonds values of 1.46 Å. This values clearly justifies the distortion in the bond angle values in Ring E, highlighted by different values 110.26° (N26–C31–C30), 111.68° (C31–C30–C29), 110.55° (C30–C29–C28), 110.53° (C29–C28–C27), 111.91° (C28–C27–N26), 114.30° (C27–N26–C31).

3.2. Electrostatic potential maps

The Molecular Electrostatic Potential Surface (MEPS) is a plot of electrostatic potential mapped onto the constant electron density surface. The MEPS has been particularly useful as an indicator of nucleophilic sites of a molecule (which an approaching electrophile is initially attracted), for biological recognition, and has also been successfully applied to the study of interactions involving some optimal relative orientation between molecules.42 Besides its usefulness, its interpretation is very simple, showing red colored regions, which indicate regions with high electron density, blue colored regions representing zones with low electronic density, and green colored regions that indicate neutral.

The calculated MEPS (Figure 3) for structure 7a showed polarized regions with negative potentials over the nitrogen atom N33 (−0.0570 a.u.) and over Rings B (−0.0360 a.u.), C (−0.0240 a.u.) and D (−0.0180 a.u.). In relation to the positive potentials, the structure does not present expressive values, indicating absence of electrophilic regions, however it is worth highlighting the potentials over hydrogen atoms H60 (0.0182 a.u.), H47 (0.0160 a.u.), H48 (0.0170 a.u.), H61 (0.016 a.u.) and H51 (0.018 a.u.). Structure 7c presented less expressive negative potentials, indicated by the values of over the nitrogen atom N33 (−0.0546 a.u.), over Rings B (−0.0331 a.u.), C

Figure 3. Molecular electrostatic potential surfaces (MEPS) calculated for 7a, 7c and 7g.
In fact, the presence of a Br atom delocalizes electron density over the D ring, because Br atom withdraw electron density of the resonant system due to its electronegativity. This can be easily observed comparing the potential over Ring D, which in structure the electrostatic potential is −0.0180 a.u. Concerning the positive potentials, more expressive values are presented, deserving prominence the potentials over the atoms H60 (0.0242 a.u.), H47 (0.0225 a.u.), H48 (0.0201 a.u.), H49 (0.0175 a.u.) and H46 (0.0166 a.u.). Structure did not present significant changes in the potentials over the atoms in relation to structure , presenting similar values, except for the negative potential over the Ring D which is slightly more negative, −0.0184 a.u., due to the fact that methyl group is an electron-donating group, signaling that the presence of an additional methyl group does not interfere in the delocalization of the electronic density expressively.

### 3.3. HOMO and LUMO analysis

The determination of the HOMO (Highest Occupied Molecular Orbital) and LUMO (Lowest Unoccupied Molecular Orbital) energies is of fundamental importance for obtaining several molecular properties, such as hardness, electrophilicity, electronegativity and chemical potential, being a fundamental research subject for theoretical chemists. Within the Kohn–Sham (KS) DFT framework, the KS orbitals are a mathematical object used to build the electron density of the chemical system and in order to promote an appealing meaning for the eigenvalues of the Kohn–Sham equation, Janak introduced a generalization, \( \frac{\partial E}{\partial \eta_i} \), called Janak theorem. Based on this theorem, Perdew et al. showed that \( \bar{\epsilon}_i = -\text{IP} \) (\( Z - 1 < N < Z \)) and \( \bar{\epsilon}_i = -\text{EA} \) (\( Z < N < Z + 1 \)) for the exact KS functional, however the available functions allow only express approximate values of IP and EA, and consequently approximate values of hardness (\( \eta \)), chemical potential (\( \mu \)), electronegativity (\( \chi \)) and electrophilicity index (\( \omega \)), which defined as follows:

\[
\eta = \frac{(I - A)}{2}
\]
\[
\mu = -\frac{(I + A)}{2} = -\chi
\]
\[
\omega = \left( \frac{\mu^2}{2\eta} \right)
\]

where \( A \) is the electron affinity and \( I \) is the ionization potential of the molecule. The ionization energy and electron affinity are obtained from the HOMO and LUMO energies as \( I = -E_{\text{HOMO}} \) and \( A = -E_{\text{LUMO}} \).
All these properties were calculated for the studied compounds using TD-DFT approach and are summarized in Table 2. Guided by the plots of the HOMO and LUMO surfaces (Figure 4), the calculated HOMO orbital for structure 7a comprise Rings A and D and the N33, C32 and N26 atoms, while the LUMO orbital comprise Rings A and E and the N33 atom. In other words these groups are susceptible for reactions, due to the fact that HOMO orbitals are electron donors and LUMO orbitals are electron acceptors. This explanation was very explored by Fukui, and can be observed through the 7a derivatives. The HOMO and LUMO orbitals of structures 7c and 7g shown the same pattern of structure 7a, however the energy gap values are changed according to the type of substituent groups attached to Ring D, following the order: Methyl > Br > H. The HOMO–LUMO gap values is directly related to the reactive descriptor of a molecule, in this case, structure 7a, that presents the lowest energy gap, has the lowest hardness value (1.89 eV) and higher electrophilicity index (3.56 eV), indicating that this molecule is more polarizable with more electrons further from the nucleus. 7g shows hardness and electrophilicity values of 2.057 and 3.12 eV respectively, indicating to be a slightly less polarizable structure, with fewer electrons available. In a general way, the reactivity tends to increase in the order 7g < 7c < 7a.

3.4. UV–Visible analysis

The electronic spectra of the substances (recorded in chloroform) were compared to the calculated spectra at Time Dependent Density Functional Theory (TD-DFT) using the B3LYP/6-311G(2d,p) basis set in methanol (PCM model) as shown in Figure 5. Initially, the experimental UV–Vis spectrum of structure 7a showed bands at 261, 287 and 354 nm, which are assigned to $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ of the aromatic rings and the nitrogen atoms. The calculated UV–Vis spectrum showed close values in relation to the experimental, deserving prominence electronic transitions at 273.95 nm (with electronic transition of 4.53 eV and oscillator strength $f = 0.16$), 291.01 nm (with electronic transition of 4.26 eV and oscillator strength $f = 0.443$), 298.27 nm (4.15 eV and $f = 0.225$) and 395.67 nm
(3.13 eV and $f = 0.125$). The transitions involved in the bands showed major contributions from $H - 3 \rightarrow L$ (65.62%), $H \rightarrow L + 1$ (74.93%), $H - 1 \rightarrow L$ (76.12%) and $H \rightarrow L$ (97.74%), respectively. The experimental UV spectrum of structure 7c revealed bands at 267, 288 and 353 nm that are related to the calculated electronic transitions at 262.36 nm (with electronic transition of 4.73 eV and oscillator strength $f = 0.2324$), 283.85 nm (with electronic transition of 4.367 eV and oscillator strength $f = 0.4535$), 293.21 nm (4.23 eV and $f = 0.1516$) and 363.48 nm (3.41 eV and $f = 0.144$) with contributions from $H - 4 \rightarrow L$ (76.11%) (262.36), $H - 1 \rightarrow L$ (86.6%) (283.85 nm), $H \rightarrow L + 1$ (92.6%) (293.21 nm) and $H \rightarrow L$ (97.1%) (363.48 nm).

The UV spectrum of structure 7g revealed bands at 265, 275 and 349 nm, very similar to previous structures. The theoretical spectrum presented intense electronic transitions at 261.30 (with excitation energy of 4.75 eV and oscillator strength $f = 0.1064$), 284.83 nm (with excitation energy of 4.35 eV and oscillator strength $f = 0.559$), 289.52 nm (with 4.28 eV and $f = 0.1689$) and 357.77 nm (3.46 eV and $f = 0.149$), which are very close to the experimental UV bands. The calculated bands showed contributions from $H - 4 \rightarrow L$ (46%) (261.30 nm), $H \rightarrow L + 1$ (54.9%) (284.83 nm), $H - 1 \rightarrow L$ (56.1%) (289.52 nm) and $H \rightarrow L$ (96.8%) (357.77 nm). It is important to emphasize that structure 7g show a hypsochromic shift in the secondary absorption bands in relation to structures 7a and 7c, which is evidenced by the band 357 nm, related to the experimental band at 349 nm. Actually such spectroscopic behavior is justified by the highest HOMO–LUMO energy gap of structure 7g compared to the others, in view of such bands have as major contribution $H \rightarrow L$ transitions, is justifiable for such structure that the secondary band be shifted to a lower wavelength. The UV spectrum of structure 7g revealed bands at 265, 275 and 349 nm, very similar to previous structures. The theoretical spectrum presented intense electronic transitions at 261.30 (with excitation energy of 4.75 eV and oscillator strength $f = 0.1064$), 284.83 nm (with excitation energy of 4.35 eV and oscillator strength $f = 0.559$), 289.52 nm (with 4.28 eV and $f = 0.1689$) and 357.77 nm (3.46 eV and $f = 0.149$), which are very close to the experimental UV bands. The calculated bands showed contributions from $H - 4 \rightarrow L$ (46%) (261.30 nm), $H \rightarrow L + 1$ (54.9%) (284.83 nm), $H - 1 \rightarrow L$ (56.1%) (289.52 nm) and $H \rightarrow L$ (96.8%) (357.77 nm). It is important to emphasize that structure 7g show a hypsochromic shift in the secondary absorption bands in relation to structures 7a and 7c, which is evidenced by the band 357 nm, related to the experimental band at 349 nm. Such spectroscopic behavior is justified by the highest HOMO–LUMO energy gap of structure 7g compared to the others (see Section 3.2), in view of such bands have as major contribution $H \rightarrow L$ transitions.

### 3.5. Infrared analysis

The assignments of the experimental bands to the theoretical wavenumber were made by PED calculations using the optimized structures at B3LYP/6-311(2d,p) theory level, where only modes...
between 400 and 4000 cm\(^{-1}\) were analyzed (see Tables S2–S4). Discrepancies between the spectra can be attributed to the fact that the theoretical DFT calculations are made in gas phase, whereas experimentally the molecules are in the solid phase, however this situation is bypassed using scaling factors. Scaling factors has been targeted for discussion over the years, varying accord to the applied method, however without a consensus in the literature about a fixed value and how to use them. Restricting to DFT approach, some authors recommend the use of two different scale factors, one for low frequencies and one for high frequencies.\(^{46-55}\) Hirst and Watson, in 2002, commented that scaling factors are not very reliable, because the studies are centered on molecules with less than 10 atoms, not being tested in more complex systems.\(^{56}\) Also, there are studies that recommend the use of uniform scale factors (varying from 0.96 to 0.99), especially when working with complex molecules.\(^{57-60}\) In this work, we have chosen to correct uniformly the theoretical wavenumbers by 0.98,\(^{61-70}\) revealing a good correlation between the theoretical and experimental data. The comparison between the experimental and the calculated IR spectra for the studied molecules is depicted in Figure 6.

The analysis showed that modes between 3200 and 2200 cm\(^{-1}\) are related to H–C stretching (assigned to the experimental bands at 3111.5, 3060.8 and 2932.12 cm\(^{-1}\) for structure 7a, 3112.5 and 3070.8 cm\(^{-1}\) for structure 7c, 3080.53 and 2935.92 cm\(^{-1}\) for structure 7g) and N=C stretching vibrations (assigned to the experimental bands at 2214.99, 2217.06 and 2210.61 cm\(^{-1}\) for structures 7a, 7c and 7g, respectively). Bands between 1600 and 900 cm\(^{-1}\) are mostly related to C=C stretching modes of the benzene rings (assigned to the experimental bands at 1586.76, 1572.02, 1536.34, 1401.74 and 1079.60 cm\(^{-1}\) for structure 7a, 1587.76, 1547.76, 1513.26, 1065.75 and 1029.22 cm\(^{-1}\) for structure 7c and 1581.60, 1513.62 and 991.02 cm\(^{-1}\) for structure 7g), N–C stretching vibration of Ring E (related to the experimental bands at 1401.47 and 1216 cm\(^{-1}\) for structure 7a, 1216.19 cm\(^{-1}\) for structure 7c and 1214.62, 1112.42 cm\(^{-1}\) for structure 7g), H–C–C bend vibrations (related to the experimental bands at 1494.98, 1451.99, 1442.90, 1261.06 and 1079.60 cm\(^{-1}\) for structure 7a, 1493.62, 1449.76, 1231.16, 1216.19 and 1009.54 cm\(^{-1}\) for structure 7c, 1492.96, 1444.04, 1347.81 and 1227.61 cm\(^{-1}\) for structure 7g) and C–C–C bend vibration modes (experimental bands at 1536.34 cm\(^{-1}\) for structure 7a and 1513.26, 1099.54 and 992.60 cm\(^{-1}\) for structure 7c). Bands between 900 and 400 cm\(^{-1}\) are mostly related to H60–C1–C3–N26 torsion (experimental bands at 878.15, 879.27, 874.19 cm\(^{-1}\) for structures 7a, 7c and 7g, respectively), C=C–C=C torsions (experimental bands at 755 and 512 cm\(^{-1}\) for 7a, 778.42 and 698.99 cm\(^{-1}\) for 7c and 746.15, 697.19 cm\(^{-1}\) for 7g) and H–C–C–C torsions (experimental bands at 729.83 and 701.35 cm\(^{-1}\) for 7a, 823.63 and 722.37 cm\(^{-1}\) for 7c and 697.19 cm\(^{-1}\) for 7g). It is important to note that the band referred to nitrile groups stretching occurs at about 2250 cm\(^{-1}\) and for aromatic nitriles, the absorption occurs at lower frequencies, around

Figure 6. Comparison between experimental (red) and calculated (blue) IR spectra of structures 7a, 7c and 7g.
2230 cm\(^{-1}\). However, for the studied structures, the experimental bands occur in regions lower than usual, at 2214.99, 2217.06 and 2210.61 cm\(^{-1}\), for structures 7a, 7c and 7g, respectively. Such bands occur in these regions due to the high conjugation of the triple bond with the aromatic system of each molecule, which decreases the stretching force constant of such bonds, resulting in lower frequency absorptions (see Section 3.6).

### 3.6. NBO analysis

Natural bond orbitals (NBOs) are theoretical bonding orbitals with maximum electron density which describes the Lewis-like molecular bonding pattern of electron pairs (or of individual electrons in the open-shell case). NBOs are commonly used in computational chemistry to calculate the distribution of electron density in atoms and in bonds between atoms and describe the residual “delocalization effects” in molecules by the second-order perturbation energies \( E(2) \) [donor \((i) \rightarrow \) acceptor \((j)\)], that involve the most important delocalization instances, and are given by\(^{71-74}\):

\[
E(2) = \Delta_{ij} = q_i \frac{F_{ij}}{\varepsilon_{ij} - \varepsilon_i}
\]

NBOs provide a valence bond-type description of the wave function, closely linked to classical Lewis concepts being a useful tool for understanding the delocalization of electron density. The second-order perturbation energies (summarized in Tables S5–S7) revealed strong hyperconjugative intramolecular interactions of \( \pi \rightarrow \pi^* \), \( \text{LP} \rightarrow \sigma^* \) and \( \text{TB} \rightarrow \sigma^* \) type, with special emphasis on those occurring in benzene rings and involving the nitrile group. For structure 7a, the strongest hyperconjugative interactions involve the bonds: \( \text{C3–C4} \rightarrow \text{C5–C6} (\pi \rightarrow \pi^*, 15.31 \text{ kcal/mol}) \), \( \text{C3–C4} \rightarrow \text{C32–N33} (\pi \rightarrow \pi^*, 16.53 \text{ kcal/mol}) \), \( \text{C5–C6} \rightarrow \text{C1–C2}(\pi \rightarrow \pi^*, 15.99 \text{ kcal/mol}) \), \( \text{C7–C12} \rightarrow \text{C10–C11} (\pi \rightarrow \pi^*, 14.37 \text{ kcal/mol}) \), \( \text{C24–C25} \rightarrow \text{C22–C23}(\pi \rightarrow \pi^*, 14.48 \text{ kcal/mol}) \), \( \text{N26} \rightarrow \text{C1–C3} (\text{LP1} \rightarrow \sigma^*, 12.16 \text{ kcal/mol}) \), \( \text{C32–N33} \rightarrow \text{C3–C4} (\text{TB} \rightarrow \pi^*, 7.73 \text{ kcal/mol}) \) and \( \text{N33} \rightarrow \text{C4–C32} (\text{LP1} \rightarrow \sigma^*, 12.69 \text{ kcal/mol}) \). For structure 7c, the highest second-order perturbation energies involves the bonds: \( \text{C5–C6} \rightarrow \text{C1–C2}(\pi \rightarrow \pi^*, 16.06 \text{ kcal/mol}) \), \( \text{C8–C9} \rightarrow \text{C7–C12}(\pi \rightarrow \pi^*, 15.70 \text{ kcal/mol}) \), \( \text{C14–C15} \rightarrow \text{C16–C17} (\pi \rightarrow \pi^*, 14.62 \text{ kcal/mol}) \), \( \text{C18–C19} \rightarrow \text{C14–C15}(\pi \rightarrow \pi^*, 15.21 \text{ kcal/mol}) \), \( \text{C20–C22} \rightarrow \text{C20–C21} (\pi \rightarrow \pi^*, 15.71 \text{ kcal/mol}) \), \( \text{N33} \rightarrow \text{C14–C15} (\text{LP} \rightarrow \sigma^*, 12.71 \text{ kcal/mol}) \) and \( \text{C3–C4} \rightarrow \text{C32–N33} (\pi \rightarrow \pi^*, 16.41 \text{ kcal/mol}) \). For this particular structure, it is worth mentioning the interaction involving the Br atom and the D ring, \( \text{Br} \rightarrow \text{C14–C15} (\text{LP} \rightarrow \pi^*, 10.38 \text{ kcal/mol}) \), \( \text{C12–C25} \rightarrow \text{C24–Br} (\pi \rightarrow \sigma^*, 6.80 \text{ kcal/mol}) \) and \( \text{C22–C23} \rightarrow \text{C24–Br} (\pi \rightarrow \sigma^*, 6.00 \text{ kcal/mol}) \). Through second-order energies data, although the bromine atom removes electron density from Ring D (explained in the map values) the extension of the conjugation promoted by its presence, which is evidenced from the transitions mentioned earlier, justifies lower HOMO–LUMO gap compared when it presents a methyl group (see Figure 5). Concerning to structures 7g, the same framework is perceptible, in which the interactions that stand out are: \( \text{C1–C3} \rightarrow \text{C2–C6} (\pi \rightarrow \pi^*, 24.89 \text{ kcal/mol}) \), \( \text{C2–C6} \rightarrow \text{C4–C5} (\pi \rightarrow \pi^*, 28.17 \text{ kcal/mol}) \), \( \text{C4–C5} \rightarrow \text{C32–N33} (\pi \rightarrow \pi^*, 21.15 \text{ kcal/mol}) \), \( \text{C11–C12} \rightarrow \text{C7–C8}(\pi \rightarrow \pi^*, 20.85 \text{ kcal/mol}) \), \( \text{N26} \rightarrow \text{C1–C3} (\text{LP} \rightarrow \pi^*, 24.63 \text{ kcal/mol}) \), \( \text{N33} \rightarrow \text{C32–C4} (\pi \rightarrow \sigma^*, 12.53 \text{ kcal/mol}) \).

### 3.7. MD studies

MD calculations serve as a very important tool for understanding the interactions between atoms of a given molecule with a large sample of solvent atoms. Radial distribution function, \( g(r) \), describes how the density of the surrounding solvent molecules varies as a function of a distinct point. The tested solvent was water, and it can be said that the radial distribution function takes
into account the forces that the molecules exert on each other, and in the case of our study, between the solvent molecules of water and the tested structures. For the calculation of \( g(r) \) involving atoms that play a similar role (such as water hydrogen atoms and chloroform chlorine atoms), only one was used as reference for the calculation and not the average \( g(r) \) of each, since the average relative deviation from the average \( g(r) \) of similar atoms was less than 2%. It can be seen from Figures 6 and 7 that the solute–solvent radial distribution function of the interaction between selected atoms of structures 7a, 7c and 7g the hydrogen atom of water.

Concerning to the interactions between the water hydrogen atoms and N26 (structures 7a and 7c) and N27 (structure 7g) atoms, the pair correlation function showed very small peaks at \( \sim 2 \text{ Å} \), indicating that the density of the surrounding solvent is small, whereas at \( \sim 5 \text{ Å} \) the density of the surrounding solvent is relatively higher (Figure 7a). For nitrogen atoms N33 (structures 7a and 7c) and N34 (structure 7g), were observed very fairly small peaks at \( \sim 2 \text{ Å} \) (first solvation shell) and \( \sim 3.5 \text{ Å} \) (second solvation shell), indicating low concentration of solvent molecules around these atoms as well (see Figure 7b). Such phenomenon can reasonable be interpreted due to the hydrogen-bonding interaction of the N atom's lone pair orbital occurs with one water hydrogen, which excludes any other H-bonding interactions between the CN orbitals and water molecules.75 Nuclear quantum effects are also involved, resulting in transient protonation of nitrogen atoms, thus revealing small peaks.76 Regarding to C ring substituent groups (see Figure 7c), Br61 and C26 atoms showed broad peaks between 3.5 and 4.5 Å, without a defined shell, thus indicating very weak interactions with water. H61 atom of structure 7g did not show a defined solvation shell, indicating that this region of this molecule interacts poorly with water.

Analyzing the radial distribution functions between the nitrile nitrogen atoms and water oxygen (Figure 8), the first solvation shells are well defined showing high peaks at \( \sim 3 \text{ Å} \). This RDF can be explained due to the fact that the nitrile groups are hydrogen bond acceptor, when they interact with water hydrogens, the oxygen atoms has freedom to orient itself, thus, not repulsing the other neighbor water molecules, having as a final result several water molecules forming a solvation shell at \( \sim 3 \text{ Å} \).

3.8. Molecular docking studies

Guided by the anti-cancer activity showed by diarylmethane molecules2,9,10 molecular docking calculations were performed on AutoDock-Vina77 with DNA Topoisomerase-II–DNA complex (topo II-DNA) due to the fact that a wide variety of molecules used for the treatment of human cancers are topo II inhibitors. Autodock Vina uses a scoring function, which approximate the standard chemical potentials of the system, through the number of sequential steps that involves
a random perturbation of the conformation followed by local optimizations. X-ray crystal structure of human DNA Topoisomerase-II beta complexed with DNA and amsacrine (PDB ID: 4G0U) was obtained from the Protein Data Bank website (http://www.rcsb.org/pdb/). For the calculations, water molecules and amsacrine were removed, Gasteiger charges were assigned and the macromolecule was saved in PDBQT file format. A Grid box size of $24 \times 24 \times 18 \text{Å}$ was centered at the site of DNA cleavage of topo II–DNA complex ($x = 26.868$, $y = 101.189$, $z = 33.652$). The docking protocol was tested by removing the co-crystallized inhibitor from the complex and then docking it at the same site, showing RMSD value below 2.

Free energy of binding ($\Delta G$) analysis demonstrated that molecules 7a, 7c and 7g docked with $\Delta G$ values of $-8.8$, $8.6$ and $-7.9 \text{kcal/mol}$, respectively while the known inhibitor, amsacrine, docked with $\Delta G = -10.0 \text{kcal/mol}$ (Figure 9). Bind mode analysis showed that the three structures form intermolecular hydrogen bond with Arg 503 and weak $\pi$–alkyl and alkyl–alkyl type interactions with Ile 454, Ala 521, DG13 and DG12 (Figure 10). Although the binding affinity values shown by the structures be lower than the value recorded for Amsacrine, all structures binds at the Topoisomerase-II DNA complex by alkyl–$\pi$ interactions between E ring with both upstream and downstream base pairs, which allied to the hydrogen bonds with Arg 503, indicate an inhibitory potential for DNA replication in tumor cells.

3.9. Photophysical study of diarylmethanes

The photophysical behavior of synthesized diarylmethanes 7a–j was studied owing conjugated aromatic systems. The absorbance and emission was deliberated by means of UV–Vis and fluorescence spectroscopy. The derivatives analyzed 7a–j absorbed maxima in the range of 242–269 nm (short range) and 301–347 nm (long range) in MeCN and data was verified for $1 \times 10^{-5}$ concentration (Figure 11 and Table 3). Usually, the red shift in the absorption and emission is directly proportional to the transition of charges in the compound, which depends on the structural conjugation in donor–$\pi$–acceptor arrangement within molecule. The band gap was calculated by using formula in $E_g = 1240/\lambda_{\text{max}} \text{(eV)}$ with respect to long-range absorbance and found between the range of $3.57$–$4.11 \text{eV}$ (Table 3).

The fluorescent emission spectra for synthesized diarylmethanes is presented below (Figure 12). The fluorescent emission spectrum diarylmethanes 7a–j showed sky blue fluorescence with emission maxima from 431 to 455 nm when excited at 348 nm. The $\pi \rightarrow \pi^*$ transitions results in shifting of emission toward red shift (Table 3). All the synthesized diarylmethanes already contain one electron donor group like tert-amino and electron acceptor group such as nitrile in proper
**Figure 9.** Superimposition of the docked structures Amsacrine (red), 7a (yellow), 7c (blue) and 7g (green) into DNA cleavage site in Topoisomerase-II enzyme.

**Figure 10.** Ligand–protein interaction of 7a, 7c and 7g structures with Topoisomerase-II–DNA complex.

**Figure 11.** Absorbance spectra diarylmethanes 7a–j.
conjugation with other aromatic rings and are responsible for the red shifted emission in all the studied compounds.

The aromaticity of all the rings is conserved with different resonances. As a result, the presence of additional functional group in the synthesized diarylmethanes \(7a\)–\(j\) plays a vital role directed to change the emission pattern. The emission patterns govern on the type of structural changes appeared by the derivatives at their excited states. Hence, the presence of electron-donating group in synthesized scaffolds \(7d,e\) enhances the intensity of fluorescent as compared to compounds bearing electron withdrawing groups \(7f–h\) depending upon the charge transfer and push-pull electronic effect. The compounds with methyl group \(7i,j\) attached in direct proper conjugation with central benzene ring exhibits good broad emission is due to \(\pi \rightarrow \pi^*\) intramolecular charge transfer.

### 3.10. Thermal analysis of diarylmethane derivative \(7h\)

The thermal characteristics consisting of thermogravimetric analysis (TGA) and differential thermal analysis (DTA) was performed on synthesized diarylmethane derivative \(7h\) to evaluate thermal behavior (Figure 13) using alumina as reference. The TG-DTA curve for compound \(7h\) exposed that this compound stay thermally stable up to \(310^\circ C\) and underwent single step weight...
reduction and subsequent decomposition in the temperature range of 310–500 °C. Further, DTA curve showed one sharp endothermic peak at 173 °C due to melting of compound and one sharp exothermic peak at 365 °C due to chemical change in the studied compound 7h.

4. Conclusions

To sum up, structures 7a, 7c and 7g were comprehensively characterized with their spectral behavior and quantum properties described. The theoretical geometry compared to the X-ray data with similar molecules in the literature showed close values, revealing that the methodology applied is reliable for the analysis of the structures of the studied molecules. The HOMO–LUMO analysis showed that the energy gap values are changed according to the type of substituent groups attached to ring D, following the order: H < Br < Methyl, which directly influences their reactivity, revealing to increase in the order 7g < 7c < 7a. The molecular electrostatic maps showed significant differences between the studied molecules, which are justified by the presence of different substituents in the D ring. Such observations were evidenced by the electrostatic potential values on the D ring of each structure which are −0.0180, −0.009 and −0.0189 a.u. for structures 7a, 7c and 7g, respectively. The comparative IR studies revealed that the experimental bands related to the nitrile groups occur in regions below than the usual, due to the decreasing of the stretching force constant provoked by the high conjugation of the triple bond with the aromatic system. The major significance of NBO analysis has proved that the second-order perturbation energies of the molecules under study has strong hyperconjugative intramolecular interactions, with special emphasis on those occurring in benzene rings and involving the nitrile group. This observation is also confirmed by hyperconjugative interactions involving the bonds C3–C4 ⟷ C32–N33, C4–C5 ⟷ C32–N33 and C4–C32 ⟷ C32–N33 in NBO analysis. MD calculations combined with molecular docking studies indicates that the reported molecules are potential for pharmacological applications.

Acknowledgments

Authors are thankful to the VIT University (both Chennai and SAIF, Vellore campus) for providing fellowship and spectroscopic analysis. We are highly grateful to the Federal University of Amazonas, Brazil for their
appreciative support. SPK thank the Director, Amrita Vishwa Vidyapeetham for supporting and providing infra-
structure facilities.

**Disclosure statement**

There is no conflict of interest to declare.

**Funding**

Authors are thankful to the VIT University (both Chennai and SAIF, Vellore campus) for providing fellowship and spectroscopic analysis. RC thank Capes and Finep for the financial support.

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