Modelling the structural and reactivity landscapes of tucatinib with special reference to its wavefunction-dependent properties and screening for potential antiviral activity

Ali Alsalme 1 · T. Pooventhiran 2 · Nabil Al-Zaqri 1 · D. Jagadeeswara Rao 3 · Siriki Srinivasa Rao 4 · Renjith Thomas 2

Received: 26 August 2020 / Accepted: 8 November 2020
© Springer-Verlag GmbH Germany, part of Springer Nature 2020

Abstract
HER-2 type breast cancer is one of the most aggressive malignancies found in women. Tucatinib is recently developed and approved as a potential medicine to fight this disease. In this manuscript, we present the gross structural features of this compound and its reactivity and wave function properties using computational simulations. Density functional theory was used to optimise the ground state geometry of the molecule and molecular docking was used to predict biological activity. As the electrons interact with electromagnetic radiations, electronic excitations between different energy levels are analysed in detail using time-dependent density functional theory. Various intermolecular and intramolecular interactions are analysed and reaction sites for attacking electrophiles and nucleophiles identified. Information entropy calculations show that the compound is inherently stable. Docking with COVID-19 proteins show docking score of $-9.42$, $-8.93$, $-8.45$ and $-8.32$ kcal/mol respectively indicating high interaction between the drug and proteins. Hence, this is an ideal candidate to study repurposing of existing drugs to combat the pandemic.

Keywords DFT · Tucatinib · Docking · NCI · LIE

Introduction
Breast cancer is one of the most common type of neoplasm found in women and it is divided basically into different subtypes, viz., Luminal A, Luminal B, HER2-enriched, Basal-like and the human epidermal growth factor receptor-2-enriched (HER2-E) is indicated by the overexpression of growth factor receptor–related genes and cell cycle–related genes along with low presence of oestrogen-related and basal-related genes [1–3]. Always, there is a risk of metastatic spread to other interorgans like lungs, brain and bone [4, 5].

HER2 tyrosine kinase inhibitor Lapatinib is widely used for the management of this disease [6]. Tucatinib is recently developed as a promising drug for the management of HER2-positive breast cancer [7]. It is also used along with trastuzumab in patients with HER2-positive colorectal cancer [8]. Tucatinib even showed extensive anti-tumour activity and tumour regression in N87 gastric cancer cell line and HER2-amplified colorectal, oesophageal and gastric cancers [9, 10]. The drug is also well tolerated in patients also along with trastuzumab [11].

Recently, the new strain of coronavirus, n-CoV-2, is devastating human life in entire globe which now emerged to the dimensions of a pandemic and had impacted the life style and health of almost all the people [12]. Scientists through the globe are tirelessly working for establishing the pathology [13], epidemiology [13] and many are try to develop novel molecules, antibodies and vaccines [14]. As it is difficult to come with a new magic molecule which could cure this disease in a short period of time, scientists are looking to reroute the existing drugs with known pharmacokinetics and pharmacodynamics for the management of COVID [15–17]. Chloroquine was once highlighted as a wonder medicine for the management of COVID, in spite of several differences in
opinions about its effectiveness and now discontinued [18]. Remdesivir is now presently used widely to get rid of the pneumonia associated with COVID [19]. Lopinavir, umifenovir, favipiravir and oseltamivir molecules are also used now as a potentially active compound against the virus [15]. Thomas and coworkers recently reported that the sleep hormonemelatonin has preferential binding over the COVID proteins [20]. As it is time consuming to design and develop a drug for the treatment, it will be a wise decision to do research to reroute the existing drugs as a molecular target against the virus. We also thought in this direction and decided to screen tucatinib as a potential candidate for the management of COVID.

Understanding the electronic structure of a compound is very important for analysing the potential applications of a compound. Literature analysis showed that no studies have been reported in this direction. This manuscript attempts to study the detailed geometry, electronic structure, physical and chemical properties, orbital characteristics, surface topology, non-covalent interactions, electronic excitations, intermolecular stabilisations and information entropy analysis. It is followed by molecular modelling studies of the interaction of the molecule with four prominent n-CoV-19 proteins. We believe that this manuscript will be an addition to the scientific data.

Methods

We report the detailed study of the molecule using molecular simulations. Tucatinib molecule was optimised using Gaussian-09 [21] software, a package using DFT methodology with ωB97XD [22–24] functional and cc-pVDZ basis set [25]. We performed the frequency calculations to ensure that there exists no imaginary frequency such that the obtained geometry corresponds to a global minimum for reaching the optimised geometry. We used the same geometry for calculating frontier molecular analysis, natural bonding orbitals and non-linear optical studies. For UV-visible spectrum simulation, we used time-dependent density functional theory (TD-DFT) with long-range corrected CAM-B3LYP functional [26, 27] and aug-cc-pVDZ basis set as the electronic transitions are time-dependent phenomena with GaussSum [28]. Reaction sites of tucatinib calculated using Multiwavefunction [29] software for calculating total electrostatic, average localised ionisation energy, electron localisation functions, localised orbital locator, reduced density gradient, localised entropy interaction, electron delocalisation functions, local electron locator, reduced density gradient and non-covalent interactions for tucatinib’s anti-coronovirus2 biological activity were analysed by using suitable proteins in the PDB format downloaded from RCSB [30] site, the energy received from SwissDock and the score values received from PatchDock [31] after docking and the docked results analysed using bio-discovery studio.

Results and discussion

Geometry structure for tucatinib

Tucatinib molecular structure was optimised by using density functional theory method for structural confirmation, DFT-ωB97XD as a method, and cc-pVDZ as a basis set. The optimised structure for tucatinib is shown in Fig. 1 and Table 1 shows important bond distances and angles for tucatinib. The optimised structure for tucatinib is shown in Fig. 1 and Table 1 shows important bond distances and angles for tucatinib.

Table 1 Structural parameters of tucatinib

| Definition | Value (in Å) | Definition | Value (in °) |
|------------|-------------|-----------|-------------|
| R(1O–12C) | 1.44        | A(12C–1O–15C) | 105.18     |
| R(1O–15C) | 1.36        | A(26C–2O–31C) | 118.20     |
| R(2O–26C) | 1.39        | A(11C–3N–15C) | 106.35     |
| R(2O–31C) | 1.36        | A(15C–4N–16C) | 127.74     |
| R(3N–11C) | 1.48        | A(15C–4N–45H) | 114.54     |
| R(3N–15C) | 1.28        | A(16C–4N–45H) | 117.67     |
| R(4N–15C) | 1.36        | A(21C–5N–23C) | 131.47     |
| R(4N–16C) | 1.39        | A(21C–5N–49H) | 114.73     |
| R(4N–45H) | 1.01        | A(23C–5N–49H) | 113.77     |
| R(5N–21C) | 1.37        | A(20C–6N–29C) | 115.19     |
| R(5N–23C) | 1.40        | A(21C–7N–29C) | 117.13     |
| R(5N–49C) | 1.01        | A(10N–8N–33C) | 110.27     |
| R(6N–20C) | 1.37        | A(10N–8N–35C) | 126.30     |
| R(6N–29C) | 1.31        | A(33C–8N–35C) | 123.43     |
| R(7N–21C) | 1.32        | A(33C–9N–36C) | 102.33     |
| R(7N–29C) | 1.36        | A(8N–10N–36C) | 101.28     |
| R(8N–10C) | 1.35        | A(1O–15C–3N)  | 119.22     |
| R(8N–33C) | 1.38        | A(1O–15C–4N)  | 112.02     |
| R(8N–35C) | 1.36        | A(3N–15C–4N)  | 128.77     |
| R(9N–33C) | 1.33        | A(18C–17C–20C) | 120.68    |
| R(9N–36C) | 1.35        | A(18C–17C–21C) | 124.02    |
| R(10N–36C) | 1.33    | A(20C–17C–21C) | 115.29    |
| R(24C–30C) | 1.50   | A(5N–21C–7N)  | 120.56     |
| R(26C–28C) | 1.39    | A(5N–21C–17C) | 118.20     |
| R(28C–52H) | 1.09   | A(7N–21C–17C) | 121.24     |
| R(31C–32C) | 1.37   | A(5N–23C–25C) | 124.34     |

© Springer
tucatinib. The molecule possesses three heterocyclic rings, ether and secondary anime linkages connecting the rings.

The bond distances for 1O–12C, 1O–15C, 2O–26C, 2O–31C, 3N–11C, 3N–15C, 4N–15C, 4N–16C, 4N–45H, 5N–21C, 5N–23C, 5N–49C, 6N–20C, 6N–29C, 7N–21C, 7N–29C, 8N–10C, 8N–33C, 8N–35C, 9N–33C, 9N–36C, 10N–36C, 24C–30C, 26C–28C, 28C–52H and 31C–32C having 1.44, 1.36, 1.39, 1.48, 1.28, 1.36, 1.39, 1.01, 1.37, 1.40, 1.01, 1.37, 1.31, 1.32, 1.36, 1.35, 1.38, 1.36, 1.33, 1.35, 1.33, 1.50, 1.39, 1.09 and 1.37 Å respectively. The bond angles for 12C–1O–15C, 26C–2O–31C, 11C–3N–15C, 15C–4N–16C, 15C–4N–45H, 16C–4N–45H, 21C–5N–23C, 21C–5N–49H, 23C–5N–49H, 20C–6N–29C, 21C–7N–29C, 10N–8N–33C, 10N–8N–35C, 33C–8N–35C, 33C–9N–36C, 8N–10N–36C, 1O–15C–3N, 1O–15C–4N, 3N–15C–4N, 18C–17C–20C, 18C–17C–21C, 20C–17C–21C, 5N–21C–7N, 5N–21C–17C, 7N–21C–17C, 5N–23C–25C, 5N–23C–27C, 25C–23C–27C, 31C–32C–33C, 31C–32C–57H, 33C–32C–57H, 8N–33C–9N, 8N–33C–32C and 9N–33C–32C, having 105.18, 118.20, 106.35, 127.74, 114.54, 117.67, 131.47, 114.73, 113.77, 115.19, 117.13, 110.27, 126.30, 123.43, 102.33, 101.28, 119.22, 112.02, 128.77, 120.68, 124.02, 115.29, 120.56, 118.20, 121.24, 124.34, 116.38, 119.28, 117.93, 122.84, 119.23, 109.08, 118.91 and 132.01° respectively.

**Frontier molecular orbital (FMO) properties for tucatinib**

Frontier molecular orbitals can provide valuable information about the energy band gap and using the HOMO and LUMO energy, one can predict various physical and chemical descriptors of the molecule, which enables us to comment on the reactivity, stability and biological activity [32]. The energies are calculated in the DFT-ωB97XD/cc-pVDZ basis set and the related data is presented in Table 2. HOMO is the molecule is found to have energy $-5.59$ eV and LUMO $-1.50$ eV. The energy gap is only 4 eV. The ionisation energy [33, 34] is 5.50 eV and electron affinity 1.59 eV [35–38]. Global hardness [39, 40] and softness [41] are widely regarded as an indicator of the reactivity of compounds, whose values are 2.00 eV and 0.50 eV respectively. The softness value is high such that the compound is polarisable and hence more chance to be biologically active. The chemical potential, which is the average of ionisation energy and electron affinity is found to be $-3.59$ eV, which indicates that the molecule is reactive [42]. The electronegativity [43] was 3.59 eV. The compound is electrophilic (see the [44, 45] and nucleophilicity index [46–49] values) in nature with a negative electron donating power. This is in agreement with the high electron affinity values. Hence, it can be concluded that the compound is
The electronic transitions in tucatinib and their properties are shown in Table 3. The first transition at 309.24 nm has an oscillator strength of 0.44, indicating good light-harvesting efficiency. The second transition at 267.56 nm has an oscillator strength of 0.26. The third transition at 265.44 nm has a much smaller oscillator strength of 0.0032. The transitions from the second last higher occupied molecular orbital (HOMO) to lower unoccupied molecular orbital (LUMO) with contribution 12 percentage, and from higher occupied molecular orbital (HOMO) to second lower unoccupied molecular orbital (LUMO+2) with 60 percentage contribution. For the first transition, oscillator strength (f) is 0.4431, which means, the molecule is having good light-harvesting efficiency (LHE), which is expressed as a function of the oscillator strength related as LHE = 1−10−f [53–56]. The value is 0.6395 for the first transition, which indicate that the compound can absorb 63.95% of the incident light energy for electronic excitation at that particular wavelength [57, 58].

### Non-linear optical properties for tucatinib

Study of light matter interactions is very important especially for organic molecules. Recently, a large number of organic non-linear optical (NLO) compounds have been extensively studied using various computational tools for their potential industrial use [59–61]. The ability of the molecule to bend the linear light can be done using the polarisability and hyperpolarisability values obtained from the Raman spectrum simulation. This type of non-linear optical activity is very important for using the compound in organic electronics industry [62–64]. The simulation is carried out in the same theoretical level as of the optimisation and is compared with a standard non-linear optically active substance urea and p-nitroacetanilide (PNA) [65, 66]. The non-linear optical property parameters for tucatinib are shown in Table 4. Tucatinib is found to have dipole moment (μ) of 2.74 D, which is 1.58 times greater than urea and 3.01 times greater than p-nitroacetanilide. Hyperpolarisability (β) is 51.60*10−31 e.s.u., which is 6.79 times greater than urea and 0.21 times than p-nitroacetanilide. The high values of values are due to the highly non-symmetric structure of the compound (C₄ point group).

### Nature bond orbital analysis for tucatinib

Intramolecular electron displacements are very important as they decide the inherent stability of a compound. Natural bond orbital analysis is an excellent tool to study such interactions via hyperconjugation [67–72]. The occupancy values of the natural bond orbitals and their delocalisation energy provide valuable information about the above-mentioned stabilisations. Nature bond orbital (NBO) calculations were

### Table 2 Frontier molecular orbitals properties for tucatinib

| Property                              | Values       |
|---------------------------------------|--------------|
| HOMO (eV)                             | -5.59        |
| LUMO (eV)                             | -1.59        |
| Energy gap ΔE (eV)                    | 4.00         |
| Ionisation energy (I = eHOMO - HOMO) (eV) | 5.59        |
| Electron affinity (A = ELUMO - LUMO) (eV) | 1.59        |
| Global hardness (η = (I - A)/2) (eV)  | 2.00         |
| Global softness (S = 1/η)             | 0.50         |
| Chemical potential (μ = -(I + A)/2) (eV) | -3.59       |
| Electronegativity (χ = -μ) (eV)       | 3.59         |
| Electrophilicity index (ω = μ/2/η)    | 3.22         |
| Nucleophilicity index (N = 1/ω)       | 0.31         |
| ΔNmax                                 | 1.79         |
| Electroaccepinging power ω+ = A/2(I - A) | 0.31        |
| Electrodonating power ω+ = A/2(I - A) | -37.63       |

| No. | Wavelength (nm) | Osc. Strength | Symmetry      | Major contributions              |
|-----|-----------------|---------------|---------------|----------------------------------|
| 1   | 309.24          | 0.44          | Singlet-A     | HOMO → LUMO (90%)                |
| 2   | 267.56          | 0.26          | Singlet-A     | H-2 → LUMO (12%), HOMO → L + 2 (60%) |
| 3   | 265.44          | 0.0032        | Singlet-A     | H-6 → LUMO (84%)                |
done using the NBO suite available within the Gaussian 09 software.

Table S1 shows the natural atomic orbital (NAO) occupancies for tucatinib. In general, the decreasing order of atomic orbitals by the occupancies are core orbital > valence orbital > Rydberg orbital. Table S1 shows the number of atomic orbitals, the symbol of atoms, number of atoms, angular momentum, type of atomic orbital, occupancies, and energy in a.u. unit Tucatinib having 624 nature atomic orbitals (NAOs), the oxygen atoms label numbers from 1 to 2 atoms nature atomic orbital numbers are 6, 18 having py, and px angular momentum with atomic orbital type is valence 2p, occupancies are 1.40 and 1.11, and energies are $-0.37$ and $-0.37$ a.u. respectively, the nitrogen atoms label numbers from 3 to 10 are having atomic orbital numbers are 34, 46, 60, 78, 90, 102, 118 and 134 having py, px, px,pz, py, px, py and pz angular momentum with atomic orbital type is valence 2p, occupancies are 1.31, 1.41, 1.36, 1.24, 1.25, 1.28, 1.29 and 1.08, and energies are $-0.20$, $-0.29$, $-0.28$, $-0.19$, $-0.20$, $-0.30$, $-0.18$ and $-0.15$ a.u. respectively, the carbon atoms label numbers from 11 to 36 are having atomic orbital numbers are 146, 160, 174, 190, 198, 216, 230, 242, 258, 272, 284, 298, 312, 326, 340, 354, 370, 382, 398, 412, 428, 442, 456, 466, 484 and 498 having py, py, pz, S, py, py, px, py,
Table 4 Non-linear optics property for tucatinib

| Non-linear property          | Tucatinib | Urea   | p-nitro acetanilide | Comparison of tucatinib with urea and PNA |
|------------------------------|-----------|--------|---------------------|------------------------------------------|
| Dipole moment (μ)            | 2.74 D    | 1.73 D | 0.91 D              | 1.58 times urea and 3.01 times PNA       |
| Hyperpolarisability (β) (esu)| 51.6*10^{-31} | 7.60*10^{-31} | 237.67*10^{-31} | 6.79 times urea and 0.21 times PNA       |
| Mean polarisability (α)      | 373.08*10^{-23} | 24.30*10^{-23} | 113.86*10^{-23} | 15.5 times greater than urea and 3.27 times PNA |
| Anisotropy of the polarisability (Δα) (esu) | 897.38*10^{-23} | 0.85*10^{-23} | 5.29*10^{-23} | 1055 times greater than urea and 169 times PNA |
| Molar refractivity (MR) (esu) | 9412.26 | 613.31 | 2873.74 | 15.34 times greater than urea and 3.2 times PNA |

- py, px, px, px, px, px, px, py, py, py, pz, pz, pz, px, px, pz and
- px angular momentum with atomic orbital type is valence 2p,
- occupancies are 0.87, 0.79, 1.18, 1.09, 0.71, 0.93, 1.11, 1.09,
- 1.06, 0.95, 0.97, 1.08, 0.89, 1.08, 0.78, 1.11, 1.07, 1.00,
- 1.16, 0.94, 1.09, 0.89, 1.06, 0.84 and 1.03, and energies are
- -0.15, -0.06, -0.06, -0.09, -0.08, -0.08, -0.03, -0.07,
- -0.06, -0.06, -0.01, -0.03, -0.05, -0.01, -0.05, -0.03,
- -0.01, -0.06, -0.05, -0.02, -0.08, -0.03, -0.07, -0.01,
- -0.07, -0.01 and -0.02 respectively, and the hydrogen atoms
- label numbers from 37 to 60 are having atomic orbital num-
- bers 505, 510, 515, 520, 525, 530, 535, 540, 545, 550,
- 555, 560, 565, 570, 575, 580, 585, 590, 595, 600, 605, 610,
- 615 and 620 having S angular momentum with atomic orbital
- type is valence 1S, occupancies are 0.79, 0.78, 0.77, 0.77,
- 0.76, 0.77, 0.77, 0.76, 0.56, 0.74, 0.76, 0.74, 0.57, 0.72,
- 0.76, 0.75, 0.79, 0.76, 0.75, 0.75, 0.72, 0.73, 0.74 and 0.78,
- and energies are 0.07, 0.07, 0.08, 0.09, 0.09, 0.08, 0.09,
- 0.11, 0.11, 0.07, 0.10, 0.12, 0.13, 0.08, 0.09, 0.09, 0.10, 0.09,
- 0.09, 0.11, 0.09, 0.08 and 0.09 a.u. respectively.

Table S2 provides the summary of natural population charge analysis for tucatinib. Each atom having particular nat-
- ural charges and population charges is core, valence and
- Rydberg populations. Tucatinib molecule’s total natural charge is zero, and total natural populations in the core
- is 71.97, valence is 179.24 and the Rydberg population is 0.79
- and the total population is 252.00. Table S3 shows the natural populations between natural minimal basis and natural
- Rydberg basis for tucatinib. Total core population is 71.97
- out of 72 basis, which is more than 99.50 percentage; valence
- population is 179.24 out of 180 basis, which is more than
- 99.50 percentage; the natural minimal basis (NMB) is
- 251.21 out of 252 basis, which is more than 99.50 percentage;
- and natural Rydberg basis (RYB) is 0.79 out of 252 basis,
- which is below 0.50 percentage. Table S4 shows the electron-
- ic configurations for all the elements in tucatinib. Table S5
- explains natural bond analysis by occupancy threshold energy for in tucatinib. For the cycles 1 and 2, having the same occu-
- pancy threshold energy 1.9, Lewis occupancy is 238.24, non-
- Lewis occupancy is 13.76 and deviation is 0.63. Table S6
- shows the total Lewis and non-Lewis contributions for tucatinib. The contributions for core orbital are 71.97 out of
- 72 basis, which is more than 99.50 percentage, valence Lewis
- orbital is 173.56 out of 180 basis, which is 96.42 percentage
- and total Lewis contribution is 245.53 out of 252 basis, which
- is 97.43 percentage. The contribution of valence non-Lewis
- orbital is 5.92 out of 252 basis, which is 2.35 percentage,
- Rydberg non-Lewis orbital is 0.55 out of 252 basis, which is
- 0.22 percentage and total non-Lewis contribution is 6.47 out
- of 252 basis, which is 2.57 percentage.

The local l(r) average energy of ionisation is the energy needed to remove an electron from point r the system. The lowest
- values show the positions of the least tightly held electrons and therefore the chosen reaction sites by electrophiles or radicals [74–77]. The 2D representation of average localised ionisation energy (ALIE) of tucatinib is given in Fig. 4.

The colour greenish-blue is denoted delocalised electrons appearing in 4,4-dimethyloxazole, 4,4-dimethylozazolamin, quinazolin, quinazolinamin and triazolepyridin groups; these are giving the number of resonance structure and explain stability of tucatinib. The colour blue is denoted sigma or stable bonds occur in all the carbons, which are having protons. The colour red indicates multiple bonds; fortunately, there are no multiple bonds present in the tucatinib.

This study explains the electronic structure for tucatinib. The higher value of electron localisation function is strongly localised and low value is strong delocalisation of electron in this molecule [78–80]. The electron localised function (ELF) for tucatinib is shown in Fig. 5. Tucatinib has the range between −16.34 and 16.34 Bohr³, the probability value between 0.000 and 1.000, and the colour blue to red shown in Fig. 5.

The red in colour shows that high probability to strong n
- localised electrons occurs on the carbon, nitrogen and oxygen atoms core and lone-pair of electrons, and all the protons in the molecule. The blue in colour that high probability to

 Springer
strong π-delocalised electrons occurs on carbons and nitrogen atoms in 4,4-dimethyloxazolamin and quinolinamin rings, and 4,4-dimethyloxazolamin, quinolinamin and methylphenyl rings.

**Localised orbital locator for tucatinib**

Localised orbital locator (LOL) study explains the orbital locations for tucatinib [81, 82] and is represented in Fig. 6. The value ranges between −16.34 and 16.34 Bohr$^3$, values between 0.000 and 0.800, and colour from blue to red shown in Fig. 6.

The colour red denotes strongly localised π-orbitals which occur between carbons and oxygens, carbons and nitrogens, and carbons and carbons in 4,4-dimethyloxazolamin, quinolinamin, methylphenyl and triazoxylpyridin groups. The colour blue denotes strong delocalised π-orbitals which occurs in 4,4-dimethyloxazolamin, quinolinamin, methylphenyl, triazoxylpyridin rings and all the hydrogens in the whole molecule.
Molecular electrostatic potentials (MESP) from electronic charges for tucatinib

The electrostatic potential $V(r)$ generated around a molecule by its nuclei and electrons which are treated as static charge distribution is a very useful property for studying and predicting molecular reactive actions [83–87]. The capacity has been especially useful as an indication of the positions or regions of the molecule to which the advancing electrophile is initially drawn, and has also been effectively extended to the analysis of associations requiring a certain optimal relative orientation of the reactants, such as between the product and its cellular receptor. Tucatinib molecule’s MESP was generated using the data obtained in the previous calculation and is represented in Fig. 7. Figure 7 shows those sites within the range between −16.26 and 16.26 Bohr$^3$, the numerical value from −0.100 to 0.100 and the colour from blue to red.

The colour blue on all the nitrogen atoms in amin-oxazole and amin-quinazolin groups is electron-rich sites, and therefore electrophiles can easily attack these sites. The colour red on all the carbons which are having protons in 4,4-dimethyloxazolamin, quinazolinamin and triazoxylpyridin groups is electron-poor sites, and therefore nucleophiles can easily attack these sites.

Molecular electrostatic potentials (MESP) from nuclear charges for tucatinib

The electrostatic potentials from nuclear charges [85, 87] for tucatinib are shown in Fig. 8. Tucatinib has the range between −15.88 and 17.67 Bohr$^3$, values between 0.000 and 0.800, and colour from blue to red shown in Fig. 8.

The colour red denotes negative electrostatic potentials between the range 47.000 and 50.000 and shows strong attraction between protons and nuclei core and lone-pair of electrons in carbons, nitrogens and oxygens in 4,4-dimethyloxazolamin, quinazolinamin and triazoxylpyridin groups. The colour blue denotes positive electrostatic potentials between the range 15.000 and 23.000 and shows strong repulsions between protons and nuclei in all the hydrogens in the whole molecule.

Reduced density gradients (RDG) for tucatinib

The reduced density gradient is directly proportional to the electronic density of the molecule. Which means a small reduced density gradient is low electronic density [88–92]. Figure 9 shows the reduced density gradient for tucatinib. Tucatinib has the range between −14.88 and 16.34 Bohr$^3$, values between 0.000 and 1.000, and colour from blue to red shown in Fig. 9.

The colour red range between 0.800 and 1.000 shows the most probability of the reduced density gradients which occur in higher molecular weight elements which are oxygens, nitrogens and carbons in 4,4-dimethyloxazolamin, quinolinamin, methylphenyl and triazoxylpyridin groups.

Local information entropy (LIE) for tucatinib

This study explains the stability of the molecule. Entropy is a feature of probability distributions and can take to be a qualification of uncertainty. The high value of local information entropy is directionally proportional to the uncertainty of electrons in spatial distribution [93, 94]. Figure 10 shows local...
information entropy for tucatinib. Tucatinib has the range between $-16.34$ and $16.34$ Bohr$^3$, values between 0.000 and 0.100, and colour from blue to red shown in Fig. 10.

The colour blue shows the entropy value between 0.000 and 0.015 which denotes low uncertainty regions in 4,4-dimethyloxazolamin, quinolinamin, methylphenyl and triazoxylpyridin groups. The colour bluish-green shows the moderated entropy values between 0.035 and 0.045 which denotes moderated uncertainty of the elements which are carbons, nitrogens and oxygens in 4,4-dimethyloxazolamin and quinolinamin groups.

**Non-covalent interactions (NCI) for tucatinib**

A non-covalent interaction differs from a covalent bond by not involving the sharing of electrons but involving more dispersed variations of electromagnetic interactions between molecules or within a molecule. The three-dimensional arrangement of large molecules, such as protein and nucleic acids, is important to non-covalent interactions. Additionally, they are also involved in many biological processes where large molecules bind to each other specifically but transiently. These
interactions also have a strong impact on drug design, crystallinity and material design, self-assembly and the design of synthesis of tailor-made organic molecules [89, 95]. The non-covalent interactions for tucatinib are shown in Fig. 11.

This study explains the non-covalent bonds which occur in the molecule. Figure 11 shows the non-covalent bonds which are hydrogen-bond, van der Waals and steric force type of bonds which occurs in the tucatinib; a graph plotted energy against reduced density gradient.

The hydrogen bonds appear between the range −0.020 and −0.005 a.u. from secondary amine-nitrogen attached in 4,4-dimethyloxazol to hydrogens in methyl in 4,4-dimethyloxazol and quinazolin groups, and from secondary amine-nitrogen attached in quinazolin to hydrogens in quinazolin and 2-methylphenoate groups, the van der Waals force between the range −0.005 and 0.003 a.u. from oxygen in 2-methylphenolat to hydrogens in methyl in 2-methylphenoate and triazolepyridin groups, and steric force between the range 0.004 and 0.050 a.u. within the rings for 4,4-dimethyloxazol,
quinazolin, 2-methylphenoate and triazolepyridin groups, and between 4,4-dimethyloxadol and quinazol, quinalolin and 2-methylphenolat, and 2-methylphenolat and triazolepyridin groups.

**Molecular docking study for tricatinib**

Scientists around the globe are looking medicines for managing the COVID pandemic. It is always better to reroute the existing drugs for this pandemic as it could save lot of precious time for new drug discovery. We also thought in this direction and checked the activity of this drug against known COVID proteins. Molecular docking can be used as a tool to screen the biological activity of a compound [96, 97]. Molecular docking explains the structure relative activity of tucatinib against coronavirus2 proteins (PDB IDs: 6M03 [98], 6W63 [99], 6LZG [100] and 6LU7 [99]) deposited in the RSC database [30].

Table 5 shows the docking result from SwissDock server, tucatinib with coronavirus2 proteins are 6LU7, 6W63, 6M03 and 6LZG having full fitness values are $-1276.22$, $-1238.58$, $-1243.04$ and $-3497.47$ kcal/mol respectively, and estimated $\Delta G$ are $-9.42$, $-8.94$, $-8.45$ and $-8.32$ kcal/mol respectively. The interactions tucatinib with 6LU7 having greater interfull fitness, intrafull fitness, $\Delta G$ ligand solvent non-polar and $\Delta G$ van der Waals force energies than other compared proteins, and protein 6LZG having greater energy, simple fitness, solvent full fitness, surface full fitness, $\Delta G$ complex solvent polar, $\Delta G$ complex solvent nonpolar, $\Delta G$ protein solvent polar, $\Delta G$ protein solvent non-polar and $\Delta G$ ligand solvent polar energies than other compared proteins.

The results from the docking of tucatinib and coronavirus2 proteins with PDB IDs: 6LU7, 6W63, 6M03 and 6LZG using PatchDock gives the docking score values as 5640, 5594, 5470 and 6182 respectively. The interacting areas are 706.70, 74,840, 573.90 and 716.40 Å$^2$ respectively; minimum atomic contact energies are $-348.62$, $-416.91$, $-151.45$ and $-128.30$ kcal/mol respectively; and molecule solvent accessibilities are 3158.43, 2819.61, 2753.54 and 3748.54 Å$^2$ respectively for different proteins used. Figure 12 shows the skeletal structure and residues with labels of interactions between tucatinib with coronavirus2 proteins, and Table S8 explains the coronavirus2 protein labels, name, hydrophobicity, pKa, average isotropic displacement, secondary structure, residue solvent accessibility, sidechain solvent accessibility, percent solvent accessibility and percent sidechain solvent accessibility values.

Table S9 explains the non-covalent bonds which occur between tucatinib with coronavirus2 proteins are favourable non-bond, unfavourable non-bond and unsatisfied bond within tucatinib interacting with coronavirus2 proteins. Table S8 explains the non-covalent bonds are hydrophobicity, hydrophilicity, neutral, acidic and basic group label interactions between tucatinib with coronavirus2 proteins.

Figure S1, Table S2 and Table 4 explain the water-resistant as well as called hydrophobic interactions between tucatinib with coronavirus2 proteins. Figure S2, Table S9 and Table 6 show water-loving groups of interactions between tucatinib with coronavirus2 proteins. Table S9 and Table 6 with...
Fig. S3, S4 and S5 explain the neutral, acidic and basic groups
of interactions between tucatinib with coronavirus2 proteins
respectively.

Conclusions

Tucatinib molecule having good HOMO-LUMO values, which show good chemical parameters energy gap, ionisation energy, electron affinity, global hardness, global softness, chemical potentials, electronegativity, electrophilicity index and nucleophilicity index. From the UV-Visible spectrum result, tucatinib has shown absorption peaks at 309.1468 and 267.5687 nm with 0.4431 and 0.2633 oscillator strengths.

From the NLO property of tucatinib, the dipole moment is 2.1797 times greater than urea and 7.9092 times greater than p-nitro acetanilide, hyperpolarisability is 10.9881 times greater than urea and 1.2032 times greater than p-nitro acetanilide, mean polarisability is 15.3529 times greater than urea and 3.0367 times greater than p-nitro acetanilide, the anisotropy of the polarisability is 16.9187 times greater than urea and 2.5999 times greater than p-nitro acetanilide, and molar refractivity (MR) is 15.3494 times greater than urea and 3.0360 times greater than p-nitro acetanilide. The NBO result explains the molecular bonding property of tucatinib having suitable occupancies with energies. The reaction site properties were electrostatic potentials, average localised ionisation energy and non-covalent interactions mostly occur on 4,4-

Table 5 Docking result for tucatinib with coronavirus2 proteins

| Parameters                  | 6LU7       | 6W63       | 6M03       | 6LGZ       |
|-----------------------------|------------|------------|------------|------------|
| Energy                      | 58.0421 kcal/mol | 54.9743 kcal/mol | 60.3017 kcal/mol | 61.3409 kcal/mol |
| Simple fitness              | 58.0421 kcal/mol | 54.9743 kcal/mol | 60.3017 kcal/mol | 61.3409 kcal/mol |
| Full fitness                | -1276.2 kcal/mol | -1238.6 kcal/mol | -1243 kcal/mol | -3497.5 kcal/mol |
| Interfull fitness           | -68.14 kcal/mol              | -58.674 kcal/mol          | -59.893 kcal/mol          | -62.734 kcal/mol          |
| Intrafull fitness           | 11.7314 kcal/mol            | 5.60706 kcal/mol          | 9.84711 kcal/mol          | 9.53814 kcal/mol          |
| Solvent full fitness        | -1439 kcal/mol              | -1405.4 kcal/mol          | -1413.6 kcal/mol          | -3978 kcal/mol            |
| Surface full fitness        | 219.201 kcal/mol            | 219.847 kcal/mol          | 220.597 kcal/mol          | 533.718 kcal/mol          |
| Extra full fitness          | 0 kcal/mol                  | 0 kcal/mol                | 0 kcal/mol                | 0 kcal/mol                |
| ΔG complex solvent polar    | -1439 kcal/mol              | -1405.4 kcal/mol          | -1413.6 kcal/mol          | -3978 kcal/mol            |
| ΔG complex solvent non-polar| 219.201 kcal/mol            | 219.847 kcal/mol          | 220.597 kcal/mol          | 533.718 kcal/mol          |
| ΔG protein solvent polar    | -1411.4 kcal/mol            | -1372.1 kcal/mol          | -1385.7 kcal/mol          | -3956.8 kcal/mol          |
| ΔG protein solvent non-polar| 221.095 kcal/mol            | 222.123 kcal/mol          | 221.3 kcal/mol            | 533.989 kcal/mol          |
| ΔG ligand solvent polar     | -62.539 kcal/mol            | -61.961 kcal/mol          | -64.017 kcal/mol          | -63.078 kcal/mol          |
| ΔG ligand solvent non-polar | 10.0198 kcal/mol            | 9.94932 kcal/mol          | 9.90626 kcal/mol          | 9.90859 kcal/mol          |
| ΔG van der Waals force      | -68.14 kcal/mol             | -58.674 kcal/mol          | -59.893 kcal/mol          | -62.734 kcal/mol          |
| ΔG electric force           | 0 kcal/mol                  | 0 kcal/mol                | 0 kcal/mol                | 0 kcal/mol                |
| Total ΔG                    | -9.4248 kcal/mol            | -8.9381 kcal/mol          | -8.4504 kcal/mol          | -8.3247 kcal/mol          |

Fig. 12 Skeletal structure of interactions between tucatinib and coronavirus2 proteins
dimethyloxazol, amin- in 4,4-dimethyloxazole, quinazolin, amin- in quinazoline, 2-methylphenolat and triazolepyridin groups in tucatinib. From the molecular docking result, it explains types of interactions, hydrophilicity, and hydrophobicity, acidic, basic and neutral group residues of referred coronovirus2 proteins (6LU7, 6W63, 6M03 and 6LZG) with tucatinib.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s00894-020-04603-1.

**Authors’ contributions** Ali Alsalme: Problem selection, writing and data analysis.
T. Pooventhiran: Simulations, analysis, manuscript first draft.
Nabil Al-Zaqri: Methods, project management, result analysis, manuscript editing.
D. Jagadeeswara Rao: Result analysis, manuscript editing.
Siriki Srinivasa Rao: Data analysis, writing.
Ranjith Thomas: Conceiving problem, project management, software, simulations, supervision.

**Funding** This work was financially supported by Researchers Supporting Project number (RSP-2020/78), King Saud University, Riyadh, Saudi Arabia.

**Data availability** Related data are provided in the Supplementary materials.

**Compliance with ethical standards**

**Conflict of interest** The authors declare that they have no competing interests.

**Ethics approval** NA.

**Consent to participate** NA.

**Consent for publication** NA.

**Code availability** NA.

**References**

1. Brasó-Maristany F, Griguolo G, Pascual T, Paré L, Nuciforo P, Llombart-Cussac A, Bermejo B, Oliveira M, Morales S, Martínez N, Vidal M, Adamo B, Martínez O, Pernas S, López R, Muñoz M, Chic N, Galván P, Garau I, Manso L, Alarcón J, Martínez E, Gregorio S, Gomis RR, Villagrasa P, Cortés J, Ciruelos E, Prat...
2. Koboldt DC, Fulton RS, McLellan MD, Schmidt H, Kalicki-Veizer J, McMichael JF, Fulton LL, Dooling DJ, Ding L, Mardis ER, Wilson RK, Ally A, Balasundaram M, Butterfield YSN, Carl森 R, Carter C, Chu A, Chua E, Chun HJE, Cooпе RJN, Dhallя N, Guин R, Hirst C, Hirst M, Holt RA, Lee D, Li H, Mayo M, Moore RA, Mungall AJ, Pleasance E, Robertson AG, Scheиn JE, Shafieи A, Sipahimalаni P, Slobodаn JB, Stoll D, Tam A, Thiessen N, Varhol RJ, Wye N, Zeng T, Zhao Y, Bиol I, Jones SJM, Marra MA, Cшiernаickаi А, Saksеnа G, Onоfriо R, Phо NH, Carter SL, Schumаcher SE, Tabаk B, Хаmеnder B, Gеntу J, Nguеn H, Cшrеnаsh A, Ardlie K, Berоzikhm R, Вinekler W, Gеtz G, Gabriel SB, Муrеvоnь M, Chin L, Kучеrаlаti P, Hоadleу KA, Ausion JТ, Faн С, Turman JY, Shи V, Li L, Tопаl MD, He X, Chоа HН, Prаt A, Silvа G, ИОGеlsеd MD, Zhao W, Usаry J, Berg JS, Adams M, Bookеr J, Wu J, Gulаbаni A, Bodеnheimeг T, Hoyle AP, Solоwаy MG, Mоse ME, Lеffеrуs SR, Bаlu S, Parker JS, Хаyes DN, Perоu CM, Mаlik S, Mаhurkаr S, Shеn H, Wеinеdеrger J, Trиche T, Lаi PH, BоOtwallа MS, Маglimtе DT, Bеrmаn BP, Vaн Dеn Berg DС, Barаin SB, Lаird PW, Cгеightоn JС, Dоеnhraуer LA, Nоblе M, Vеоt D, Gеhеlbrоn N, Dі Саrа D, Zаng J, Zаng H, Wу CJ, Yingchun Lius, Lаwеnе S, Lоu L, Sivаchеnko A, Lіn P, Stоjanоv P, Jing R, Cho J, Sinha R, Park RW, Nаzаrе MD, Rоbinsoн J, Thоrаvldоthоlt J, Hеsіrvо L, Pаrк JР, Реylеr J, Skreіsbеrg RB, Bеrnаrd B, Brеllеr R, Еrrkіlа T, Lin J, Тhоrsoн V, Zаng W, Shmулевіч І, Сhіlіоtі G, Wеinхоld N, Sсhultу N, Gао G, Cеrami Е, Gross B, Іасеbаскіс A, Sinха R, Саndуsh G, Windоrі C, Lуlе T, Tоpa с, Сhuа T, Yаn C, Hu Y, Mееrzаmаn D, Gаstier-Fоstоr JМ, Боnуn J, Rаmіrez NC, Blаck АD, Руаtе RE, Whіtе P, Зmунda ЕJ, Frісk J, Lichtenberg TM, Brоокеns R, Gеорге MM, Gerken MA, Hаu bеs TJA (2020) Therapy for HER2-positive metastatic breast cancer. N Engl J Med 382:E98. https://doi.org/10.1056/NEJMoa1914609

3. Prаt A, Pасsuaіl T, Аdаmо B (2017) Intrinsic molecular subtypes of HER2+ breast cancer. Oncotarget 8:73363–73366. https://doi.org/10.18632/oncotarget.20629

4. Gil-Gil MJ, Martínez-García M, Sierra A, Conesa G, Del Barco S, González-Jimenez S, Víllal S (2014) Breast cancer brain metastasis: a review of the literature and a current multidisciplinary management guideline. Clin Transl Oncol 16:436–446. https://doi.org/10.1007/s12094-013-1110-5

5. Tanaka Y, Hirata M, Shinonome S, Torii M, Nezasa K, Tanaka H (2018) Distribution analysis of epibrin in brain metastasis of HER2-positive breast cancer by imaging mass spectrometry and prospect for antitumor activity. Sci Rep 8:1–12. https://doi.org/10.1038/s41598-017-18702-2

6. Mуkherjeeса J, Dхaddа AS, Shеhаtа M, Chаn S (2007) Lapatinib: a tyrosine kinase inhibitor with clinical role in breast cancer. Expert Opin Pharmacother 8:2189–2204. https://doi.org/10.1517/14656566.8.13.2189

7. Baltschukаt S, Еngstlеr BS, Huang А, Hao ХА, Taм A, Wаng HQ, Liаng J, DiMаre MТ, Bhаng HЕС, Wаng Y, Furet Р, Сеllеrs WR, Hoффmаn F, Соelpsеr J, Тiedt R (2019) Capmatinib (INC280) is active against models of non-small cell lung cancer and other cancer types with defined mechanisms of MET activation. Clin Cancer Res 25:3164–3175. https://doi.org/10.1158/1078-0432.CCR-18-2814

8. Bekаii-Saab T, Kіm R, Kim ТW, О’Connor JM, Strіckеl JH, Malkа D, Sаrtоre-Blіаnсhi А, Bі F, Yаmаguchi K, Yоshіtо S, Prаger GW (2019) Third- or later-line therapy for metastatic colorectal cancer: reviewing best practice. Clin Colorectal Cancer 18:e117–e129. https://doi.org/10.1016/j.ccc.2018.11.002

9. Murthy RK, Loі S, Оkіnеs А, Pаlapmаtо E, Хаmiltoп H, Еrvurtі SA, Lin NU, Вороғ S, Врαmонv A, Вnсrds C, Bedаl P, Оlivеrа M, Jakоbsеn B, Еrtеnthо S, Сhаrаr S, Mvllеr V, Вragа S, Dухоus ЕР, Grеіl R, Саmеrоn D, Саrеу LA, Сurіglіаnо G, Gеlmоn K, Hоrtосbаgуу G, Knор I, Lоіlі Ѕ, Реgrаm M, Sаmоn D, PaІаnса-Wеlsесs MC, Ваllеr L, Fеnw W, Wіnеr ЕР (2020) Tuсatinib, trаstuzumаb, and саpecitаbine for HER2-positive metastаtic breast cancer. N Engl J Med 382:597–609. https://doi.org/10.1056/NEJMoa1914609

10. Dekker ТJA (2020) Therapy for HER2-positive metastatic breast cancer. N Engl J Med 382:E98. https://doi.org/10.1056/NEJMoa2004854

11. Metzgеr Filhо О, Lеоnе JР, Li Т, Таn-Wаsіеlewіskі Z, Trіppа L, Ваrr ВT, Yоungеr J, Lаwler Е, Ваllеr L, Freedmaн RA, Тоlаmеn SM, Кnор I, Віnr ЕР, Lin NU (2020) Phase I dose-escalation trial of tuсatinib in combination with trаstuzumаb in patients with HER2-positive breast cancer brain metastases. Ann Oncol 0. https://doi.org/10.1016/j.annonc.2020.05.014

12. Yuen K-S, Yе Z-W, Fung S-Y, Чаn С-Р, Jin D-Y (2020) SАRS-CoV-2 and COVID-19: the most important research questions. Cell Biosi 10:40. https://doi.org/10.1186/s13578-020-00404-4

13. Xu Z, Shі L, Wаng Y, Zаng J, Huаng L, Zаng C, Liу S, Zhao P, Lіu H, Zhu L, Таі Y, Bаі C, Gао T, Song J, Хаі P, Dоng J, Zhao J, Wаng F-S (2020) Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respіr Med 8:420–422. https://doi.org/10.1016/S2213-2600(20)30076-X

14. Lake MA (2020) What we know so far: COVID-19 current clinical knowledge and research. Clin Med 20:124–127. https://doi.org/10.7863/ciіmed.2019-сorn

15. Wu R, Wаng L, Kuo H-CD, Shаnnаr A, Pеrеt Р, Chоu Р, Li S, Huldіkаr R, Liу X, Liу Z, Поіаnі GJ, Аmоrosа L, Brunеlтtі LH, Knоg А-Н (2020) An update on current therapeutic drugs treating COVID-19. Curr Pharmacoі Rep 6:56–70. https://doi.org/10.1007/s40495-020-00216-7
16. Gorbalenya A, Baker S, Baric R, de Groot R, Drosten C, Gulyaeva A, Haagmans B, Lauber C, Leontovich A, Neuman B, Penzar D, Perlman S, Poon L, Samborskiy D, Sidorov I, Sola I, Ziebuhr J (2020) Severe acute respiratory syndrome-related coronavirus : the species and its viruses – a statement of the Coronavirus Study Group. Nat Microbiol. https://doi.org/10.1038/s41564-020-0827-7

17. Harapan H, Itoh N, Yufika A, Winardi W, Keam S, Te H, Megawati D, Hayati Z, Wagner AL, Mudarris M (2020) Coronavirus disease 2019 (COVID-19): a literature review. J Infect Public Health 13:667–673. https://doi.org/10.1016/j.jiph.2020.03.019

18. Touret F, de Lamberliere X (2020) Of chloroquine and COVID-19. Antivir Res 177:104762. https://doi.org/10.1016/j.antiviral.2020.104762

19. Wang Y, Zhang D, Du R, Zhao J, Jin Y, Fu S, Gao L, Cheng Z, Lu Q, Hu Y, Luo G, Wang K, Lu Y, Li H, Wang S, Ruan S, Yang C, Mei C, Wang Y, Ding D, Wu F, Tang X, Ye X, Ye Y, Liu B, Yang J, Yin W, Wang A, Fan G, Zhou F, Liu Z, Gu X, Xu J, Shang L, Zhang Y, Cao L, Guo T, Wan Y, Qiu H, Jiang Y, Jaki T, Hayden FG, Horby PW, Cao B, Wang C (2020) Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet 395:1569–1578. https://doi.org/10.1016/S0140-6736(20)31022-9

20. Al-Otaibi JS, Almuqrin AH, Sheena Mary Y, Mary YS, Thomas R (2020) Modeling the conformational preference, spectral analysis and other quantum mechanical studies on three bioactive aminobenzoate derivatives and their SERS active graphene complexes. Polycycl Aromat Compd:1–11. https://doi.org/10.1016/j.pac2020.1827270

21. 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, H. Nakatsuji, M. Caricato, X. Li, H.P. Hratchian, A.F. Izmaylov, J. Bloino, G. Zheng, J.L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J.A. Montgomery Jr., J.E. Peralta, F. Ogliaro, M. Bearpark, J.J. Heyd, E. Brothers, K.N. Kudin, V.N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J.C. Burant, S.S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J.M. Millam, M. Klene, J.E. Knox, J.B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R.E. Stratmann, O. Yazyev, A.J. Austin, R. Cammi, C. Pomelli, J.W. Ochterski, R.L. Martin, K. Morokuma, V.G. Zakrzewski, G.A. Voth, P. Salvador, J.J. Dannenberg, S. Dapprich, A.D. Daniels, M. Farkas, J.B. Foresman, J. V. Ortiz, J. Cioslowski, D.J. Fox, Gaussian09 Revision D.01, (2013)

22. Orio M, Pantazis DA, Neese F (2009) Density functional theory. Photosynth Res 102:443–453. https://doi.org/10.1007/s11103-009-9404-8

23. Stephens PJ, Devlin FJ, Chabalowski CF, Frisch MJ (1994) Ab initio calculation of vibrational absorption and circular dichroism spectra using density functional force fields. J Phys Chem 98:11623–11627. https://doi.org/10.1021/j100096a001

24. Foresman JB, Frisch JE (2015) Exploring chemistry with electron–lecular calculations. I. The atoms boron through neon and hydro- gen. J Chem Phys 90:1007–1023. https://doi.org/10.1063/1.456153

25. Dunning TH (1989) Gaussian basis sets for use in correlated molecular calculations. I. The atoms boron through neon and hydro- gen. J Chem Phys 90:1007–1023. https://doi.org/10.1063/1.456153

26. Yanai T, Tew DP, Handy NC (2004) A new hybrid exchange–correlation functional using the Coulomb-attenuating method (CAM-B3LYP). Chem Phys Lett 393:51–57. https://doi.org/10.1016/j.cplett.2004.06.011

27. Okuno K, Shigeta Y, Kishi R, Miyasaka H, Nakano M (2012) Tuned CAM-B3LYP functional in the time-dependent density functional theory scheme for excitation energies and properties of diarylethene derivatives. J Photochem Photobiol A Chem 235:29–34. https://doi.org/10.1016/j.jphotochem.2012.03.003

28. O’boyle NM, Tenderholt AL, Langner KM (2008) CCLIB: a library for package-independent computational chemistry algorithms. J Comput Chem 29:839–845. https://doi.org/10.1002/jcc.20823

29. Lu T, Chen F (2012) Multiwfn: a multifunctional wavefunction analyzer. J Comput Chem 33:580–592. https://doi.org/10.1002/jcc.22885

30. Burley SK, Berman HM, Bhikadiya C, Bi C, Chen L, Di Costanzo L, Christie C, Dalenberg K, Duarte JM, Dutta S, Feng Z, Ghosh S, Goodsell DS, Green RK, Guranovic V, Guzenko D, Hudson BP, Karlo T, Liang Y, Lowe R, Namkoong H, Peisach E, Persikova I, Prlic A, Randle C, Rose A, Rose P, Sala R, Sekharan M, Shao C, Tan L, Tao Y-P, Valasatava Y, Voigt M, Westbrook J, Woo J, Yang H, Young J, Zhuravleva M, Zardecki C (2018) RCSB Protein Data Bank: biological macromolecular structures enabling research and education in fundamental biology, biomedicine, biotechnology and energy. Nucleic Acids Res 47:D464–D474. https://doi.org/10.1093/nar/gky1004

31. Schneidman-Duhovny D, Inbar Y, Nussinov R, Wolfson HJ (2005) PatchDock and SymmDock: servers for rigid and symmetric docking. Nucleic Acids Res 33:W363–W367. https://doi.org/10.1093/nar/gki481

32. Frisch MJ, Trucks GW, Schlegel HB, Scuseria GE, Robb MA, Cheeseman JR, Scalmani G, Barone V, Mennucci B, Petersson GA, Nakatsuji H, Caricato M, Li X, Hratchian HP, Izmaylov AF, Bloino J, Zheng G, Sonnenberg JL, Hada M, Ehara M, Toyota K, Fukuda R, Hasegawa J, Ishida M, Nakajima T, Honda Y, Kitao O, Nakai H, Vreven T, Montgomery Jr., JA, Peralta JE, Ogliaro F, Bearpark M, Heyd JJ, Brothers E, Kudin KN, Staroverov VN, Kobayashi R, Normand J, Raghavachari K, Rendell A, Burant JC, Iyengar SS, Tomasi J, Coss M, Rega N, Millam JM, Klene M, Knox JE, Cross JB, Bakken V, Adamo C, Jaramillo J, Gomperts R, Stratmann RE, Yazyev O, Austin AJ, Cammi R, Pomelli C, Ochterski JW, Martin RL, Morokuma K, Zakrzewski VG, Voth GA, Salvador, Dannenberg JJ, Dapprich S Daniels A.D., Farkas O., Foresman, J.B., Ortiz, J.V., Cioslowski, J., and Fox DJ (2010) Gaussian 09, Revision D.01. Gaussian Inc., Wallingford

33. Kälsem S, Kronik L (2008) Orbital-dependent density functionals: theory and applications. Rev Mod Phys 80:3–60. https://doi.org/10.1103/RevModPhys.80.3

34. Zhang G, Musgrave CB (2007) Comparison of DFT methods for molecular orbital eigenvalue calculations. J Phys Chem A 111:1554–1561. https://doi.org/10.1021/jp0616330

35. Teale AM, De Proft F, Tozer DJ (2008) Orbital energies and negative electron affinities from density functional theory: insight from the integer discontinuity. J Phys Chem A 129:044110. https://doi.org/10.1021/jp802941r

36. De Proft F, Sablon N, Tozer DJ, Geerlings P (2007) Calculation of negative electron affinity and aqueous anion hardness using Kohn-Sham HOMO and LUMO energies. In: Faraday Discuss., Royal Society of Chemistry, pp. 151–159. https://doi.org/10.1039/b605302p

37. Louis E, San-Fabián E, Díaz-García MA, Chiappe G, Vergés JA (2017) Are Electron affinity and ionization potential intrinsic pa- rameters to predict the electron or hole acceptor character of amor- phous molecular materials? J Phys Chem Lett 8:2445–2449. https://doi.org/10.1021/acs.jpclett.7b00681

38. Zhan CG, Nichols JA, Dixon DA (2003) Ionization potential, electron affinity, electronegativity, hardness, and electron excita- tion energy: molecular properties from density functional theory orbital energies. J Phys Chem A 107:4184–4195. https://doi.org/10.1021/jp0225774
39. Parr RG, Pearson RG (1983) Absolute hardness: companion parameter to absolute electronegativity. J Am Chem Soc 105:7512–7516. 
   https://doi.org/10.1021/ja0364a005
40. Politzer P, Murray JS (2018) An Occam’s razor approach to chemical hardness: lex parsimoniae. J Mol Model 24:332. 
   https://doi.org/10.1007/s00894-018-3864-8
41. Xu H, Xu DC, Wang Y (2017) Natural indices for the chemical hardness/solventness of metal cations and ligands: 
   https://doi.org/10.1021/acs.cejc.6b01039
42. Schneider HL, Becke AD (2000) Chemical content of the kinetic energy density. J Mol Struct THEOCHEM 527:51–61. 
   https://doi.org/10.1016/S0166-0226(00)00477-2
43. Pearson RG (1988) Absolute electronegativity and hardness: application to inorganic chemistry. Inorg Chem 27:734–740. 
   https://doi.org/10.1021/ic00277a030
44. Chattaraj PK, Sarkar U, Roy DR (2006) Electrophilicity index. Chem Rev 106:2065–2091. 
   https://doi.org/10.1021/cr040109f
45. Chattaraj PK, Giri S (2009) Electrophilicity index within a conceptual DFT framework. Annu Rep Prog Chem, Sect C: Phys 
   Chem 105:13–39. https://doi.org/10.1039/B808232J
46. Domingo LR, Ríos-Gutiérrez M, Pérez P (2016) Applications of the conceptual density functional theory indices to organic 
   chemistry reactivity. Molecules. 21:748. https://doi.org/10.3390/ 
   20160748
47. Al-Otaibi JS, Mary YS, Thomas R (2019) Quantum mechanical and photovoltaic studies on the cocrysalts of hydro-
   chlorothiazide with isonazid and malonamide. J Mol Struct 1197: 
   719–726. https://doi.org/10.1016/j.molstruc.2019.07.110
48. Al-Otaibi JS, Shema Mary Y, Shyma Mary Y, Panicker CY, Thomas R (2019) Cocrysalts of pyrazinamide with p-
   toluenesulfonic and furic acids: DFT investigations and molecular 
   docking studings. J Mol Struct 1175:916–926. https://doi.org/ 
   10.1016/j.molstruc.2018.08.055
49. Al-Otaibi JS, Mary YS, Armakovic S, Thomas R (2020) Hybrid 
   and bioactive cocrysalts of pyrazinamide with hydroxybenzoic 
   acids: detailed study of structure, spectroscopic characteristics, 
   other potential applications and noncovalent interactions using 
   SAPT. J Mol Struct 1202:127316. https://doi.org/10.1016/j. 
   molstruc.2019.127316
50. Majumdar D, Agrawal Y, Thomas R, Ullah Z, Santra MK, Das S, Pal TK, Bankura K, Mishra D (2020) Syntheses, 
   characterizations, crystal structures, DFT/TD-DFT, luminescence behaviors and cy-
   totoxic effect of bicompartamental Zn (II)-dicyanamide Schiff 
   base coordination polymers: an approach to apoptosis, autophagy 
   and necrosis type classical cell death. Acta Biomater Chem 34. 
   https://doi.org/10.1016/j.acbmc.2020.05.050
51. Majumdar D, Das S, Thomas R, Ullah Z, Sreejith SS, Thomas R (2019) Structure, spectral features, bioactivity 
   and light harvesting properties of methyl and dimethyl anthracene: experimental and first principle 
   studies. Polycycl Aromat Compd:1–15. https://doi.org/ 
   10.1080/10406638.2019.1709083
52. Scholes GD (2017) Introduction: light harvesting. Chem Rev 117: 
   247–248. https://doi.org/10.1021/acs.chemrev.6b00826
53. Curutchet C, Mennucci B (2017) Quantum chemical studies of light harvesting. Chem Rev 117:294–343. 
   https://doi.org/10.1021/acs.chemrev.5b00700
54. Majumdar D, Das S, Thomas R, Ullah Z, Sreejith SS (2019) Syntheses . X-ray crystal structures of two new Zn ( II )-
   dicyanamide complexes derived from H 2 vanen-type compartmental ligands : Investigation of thermal, photoluminescence, 
   in vitro cytotoxic c ef f ct and DFT-TDDFT studies. Inorg Chim 
   Acta 492:221–234. https://doi.org/10.1016/j.ica.2019.04.041
55. Thadathil DA, Varghese S, Akshaya KB, Thomas R, Varghese A (2019) An insight into photophysical investigation of 
   (E)-2-
   fluoro-N′-(1-(4-nitrophenyl) ethylidyne) benzoylhydrazone through 
   solvatochromism approaches and computational studies. J Fluoresc 29:1013–207
56. Irfan A, Imran M, Thomas R, Mumtaz MW, Basra MAR, Ullah S, 
   Assiri MA, Al-Sehemi AG, Assiri MA (2020) Exploring the effect of oligothiophene and 
   acene cores on the optoelectronic properties and enhancing p- 
   and n-type ability of semiconductor materials. J Sulfur Chem:1–13. 
   https://doi.org/10.1080/17415993.2020.1830401
57. Irfan A, Imran M, Thomas R, Mumtaz MW, Qayyum MA, Ullah S, 
   Assiri MA, Al-Sehemi AG (2020) Exploration of electronic 
   nature and intrinsic mobility of 10-(1,3-dithiol-2-
   ylidene)anthracene based organic semiconductor materials. 
   Optik (Stuttgart):165530. https://doi.org/10.1016/j.ijleo.2020. 
   165530
58. Andijani N, Al-Qurashi O, Wazzan N, Irfan A (2019) Modeling of 
   efficient pyrene-core substituted with electron-donating groups as 
   hole-transporting materials in perovskite solar cells. Sol Energy 
   188:898–912. https://doi.org/10.1016/j.solener.2019.06.074
59. Irfan A, Assiri MA, Al-Sehemi AG (2018) Exploring the optoelec-
   tronic and charge transfer performance of diaza[5]helicenes at 
   molecular and bulk level. Org Electron 57:211–220. 
   https://doi.org/10.1016/j.orgel.2018.03.022
60. Irfan A, Al-Sehemi AG, Assiri MA, Ullah S (2020) Exploration 
   the effect of metal and electron withdrawing groups on charge 
   transport and optoelectronic nature of Schiff base Ni(II), Cu(II) 
   and Zn(II) complexes at molecular and solid-state bulk scales. 
   Mater Sci Semicond Process 107:104855. 
   https://doi.org/10.1016/j.mssp.2019.104855
61. Wazzan N, Irfan A (2020) Promising architectures modifying the D-
   π-A architecture of 2,3-dipentyldithieno[3,2-Fe,2'-3']-
   hquinoline-based dye as efficient sensitizers in dye-sensitized 
   solar cells: a DFT study. Mater Sci Semicond Process 120: 
   105260. https://doi.org/10.1016/j.mssp.2020.105260
62. Kavitha KR, Mary YS, Fernandez A, Anu Priya S, Mary YS, 
   Thomas R (2019) Single crystal XRD, DFT investigations and 
   molecular docking study of 2- 
   ((1-(5-dimethyl-3-oxo-2-phenyl-2, 
   3-dihydro-1H-pyrazol-4-yl)amino)naphthalene-1,4-dione as a po-
   tential anti-cancer lead molecule. Comput Biol Chem 78:153– 
   164. https://doi.org/10.1016/j.compbiolchem.2018.11.022
63. Reed AE, Cartis LA, Weinhold F (1988) Intra- and intermolecular 
   interactions from a natural bond orbital, donor-acceptor viewpoint. Chem 
   Rev 88:899–926. https://doi.org/10.1021/cr0008a005
64. Weinhold F (2012) Natural bond orbital analysis: a critical overview 
   of relationships to alternative bonding perspectives. J 
   Comput Chem 33:2363–2379. https://doi.org/10.1002/jcc.23060
65. Matondo A, Thomas R, Tsalu PV, Mukeba CT, Mudogo V (2019) 
   θ-methylation and θ-fluorination electronic effects on the regio-
   selectivity of carbonyl groups of uracil by H and triol bonds in 
   the interaction of U, T and 5FU with HCl and TrH 3 (Tr = B, Al). J
Breneman CM, Martinov M (1996) 3 - The use of electrostatic potential fields in QSAR and QSRR. In: Murray JS, K.B.T.-T, Sen CC (eds) Mol. Electrost. Potentials. Elsevier, pp 143–179. https://doi.org/10.1016/S1380-7323(96)80043-4

Politzer P, Laurence PR, Jayasuriya K (1985) Molecular electrostatic potentials: an effective tool for the elucidation of biochemical phenomena. Environ Health Perspect 61:191–202. https://doi.org/10.1289/ehp.8561191

Orozco M, Luque FJ (1996) Generalization of the molecular electrostatic potential for the study of noncovalent interactions. In: Murray JS, K.B.T.-T, Sen CC (eds) Mol. Electrost. Potentials. Elsevier, pp 181–218. https://doi.org/10.1016/S1380-7323(96)80044-6

Del Campo JM, Gázquez JL, Alvarez-Mendez RJ, Vela A (2012) The reduced density gradient in atoms. Int J Quantum Chem 112:3594–3598. https://doi.org/10.1002/qua.24241

100. Wang Q, Zhang Y, Wu L, Niu S, Song C, Zhang Z, Lu G, Qiao C, Hu Y, Yuen K-Y, Wang Q, Zhou H, Yan J, Qi J (2020) Structural and functional basis of SARS-CoV-2 entry by using human ACE2. Cell 181:894–904.e9. https://doi.org/10.1016/j.cell.2020.03.045

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.