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ORIGINAL PAPER

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

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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 intermolecular 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

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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

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
		A(5N–23C–27C)	116.38
		A(25C–23C–27C)	119.28
		A(31C–32C–33C)	117.93
		A(31C–32C–57H)	122.84
		A(33C–32C–57H)	119.23
		A(8N–33C–9N)	109.08
		A(8N–33C–32C)	118.91
		A(9N–33C–32C)	132.01