Spectroscopic and computational study of chromone derivatives with antitumor activity: detailed DFT, QTAIM and docking investigations

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Abstract

Theoretical investigations of three pharmaceutically active chromone derivatives, (E)-3-((2,3,5,6-tetrafluorophenyl)hydrazono)methyl)-4H-chromen-4-one (TPC), (E)-3-((2-(2,4,6-trifluorophenyl)hydrazono)methyl)-4H-chromen-4-one (FHM) and (E)-3-((2-(perfluorophenyl)hydrazono)methyl)-4H-chromen-4-one (PFH) are reported. Molecular geometries, vibrational spectra, electronic properties and molecular electrostatic potential were investigated using density functional theory. Quantum theory of atoms in molecules (QTAIM) study shows that the maximum of ellipticity parameters in the existing bonds in TPC, FHM and PFH, attributes to the bonds involving in aromatic region points toward the π -bond interactions in the molecules. Based on energy gap (1.870, 1.649 and 1.590 eV) and electrophilicity index (20.233, 22.581 and 23.203 eV) values of TPC, FHM and PFH, we can conclude that all molecules have more biological activity. The molecular electrostatic potential maps were calculated to provide information on the chemical reactivity of the molecule and also to describe the intermolecular interactions. All these studies including docking studies, help a lot in determining the biological activities of chromone derivatives. Activities of chromone derivatives are compared with 5-fluorouracil and azathioprine (antitumor, antiproliferative standards) and were found to be higher than reference ones.

Keywords DFT · Chromone · QTAIM · Docking · Antitumor activity

1 Introduction

Hydrazine is an industrial raw material that is widely used and toxic biochemical reagent. Hydrazine is widely used for manufacture of drugs, pesticides and chemical dye etc. [1]. Functions such as anti-inflammatory, antibacterial, antitumor, antioxidant, anti-HIV, antiviral and antiallergic are among the various biological properties of hydrazines [2–5]. Hydrazine, colourless inorganic liquid compound, is highly reductive and simple, used as a heating system corrosion inhibitors [6]. Because of the existence

of hydrazine structural units in natural and medicinal products, chromones including flavones and related ones create interest in medicinal chemistry [7–9]. The ring system of benzopyrrons is fundamental in natural products such as chromones and flavanoids which are common class of compounds which occur naturally and beneficial for human [10, 11]. The nanocrystalline metal oxide catalyst for styrylchromones preparation was reported by Kunde et al. [12]. Chromone derivatives also act as intermediates to several pharmaceutical, agrochemical and dye stuffs products. Due to chromone derivative's biological

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activities and natural occurrence, these derivatives are important for researchers [13–15]. Arjunan et al. [16] reported the spectroscopic analysis of a formylchromone derivative. Metal complexes from chromone bases have gained significant attention due to their chelating capacity to exhibit successful DNA binding [17]. Mariappan and Sundaraganesan [18] reported the study of a methylchromone derivative. Recently research has been reported on the photophysical behaviour and antimicrobial activity of chromone derivatives [19–21]. Combining pyrone with benzene ring results in two distinct types of benzopyrone rings which are recognized as coumarins and chromones [21]. Kulackowska and Bartyzel [22, 23] reported structural analysis of a chromanone derivatives. Chromanones and flavones are an important part of the diet of humans and play a role in the response to biotic and abiotic stress in plants [24, 25]. Kornev et al. [26] reported the reactions

of functionalized chromones with triacetic acid lactone. The chromone system's reactivity is determined mainly by the existence and position of a substitute in the pyrone chain [27]. Here we analyzed structural, electronic, biochemical properties of TPC, FHM and PFH chromones theoretically. Antitumor- antibacterial effects of chromone derivatives were compared with 5-fluorouracil (FU) and azathioprine (AP).

1.1 Computational procedure

Gaussview program is used to draw the molecular structures (Fig. 1) of TPC, FHM and PFH [28]. Optimizations were made in Gaussian09 at B3LYP/6–311++G(d,p) and no imaginary frequency was obtained [29]. NMR, UV and chemical descriptors were also calculated [30–33]. Chromone derivatives, 5-fluorouracil and azathioprine

Fig.1 Optimized geometries of
a TPC, **b** FHM, **c** PFH

(antitumor-antibacterial references) were docked with cancer cell line and references, against PDB ID: 4AT9, 6DM8, 2AYN and 5NAD [34]. Docking were performed by Autodock [35, 36] and spectral data were from Słomiak et al. [37]. In the following discussion phenyl and chromone rings are designated as ring1 and ring2, respectively.

QTAIM as a strong method was utilized to examine the atom–atom interactions in the studied compounds [38, 39]. This method is beneficial to achieve the amounts of electron density and bonding characteristics. AIM analysis was used to find inter-molecular interactions. The electron density (ρ), Laplacian of electron densities ($\nabla^2\rho$) and ellipticity parameters (ϵ) at the bond critical points for TPC, FHM and PFH were obtained from AIM calculations through AIM2000 program (Fig. 2 and table S1), for the evaluation of nature of the interaction. According to QTAIM method, each two interacting atoms were linked by the bond path, and saddle point in BP

had a maximum value of electron density (bond critical point—BCP). All assets of each bond were obtained at BCP.

2 Results and discussion

2.1 Molecular structures

The C–O bond lengths (DFT) are: 1.3473 Å, 1.3736 Å (TPC), 1.3730 Å, 1.3983 Å (FHM) and 1.3708 Å, 1.3998 Å (PFH) and experimental values are in the ranges 1.3477–1.3483 Å and 1.3766–1.3738 Å [37]. The carbonyl bond lengths (DFT) are 1.2313 Å, 1.2585 Å, 1.2582 Å for TPC, FHM and PFH while the experimental values are from 1.2364 Å to 1.2360 Å [37]. The CN bond lengths are 1.3797 Å, 1.2871 Å for TPC, 1.3869 Å, 1.2974 Å for FHM and 1.3810 Å, 1.2966 Å for PFH with experimental values in the ranges, 1.3788–1.3905 Å and 1.2831–1.2816 Å [37]. The NN bond length is 1.3356 Å,

Fig. 2 The molecular graphs of **a** TPC, **b** FHM, **c** PFH. Nuclei and bond critical points are represented by big and small spheres small, respectively (green and red circles are bond and ring critical points, respectively). The lines are bond paths

1.3632 Å, 1.3686 Å for TPC, FHM and PFH and reported experimental values are from 1.3677 Å to 1.3503 Å [37]. The CF bond lengths lie in the ranges 1.3428–1.3425 Å for TPC, 1.3984–1.3857 Å for FHM and 1.3899–1.3745 Å for PFH which are in agreement with experimental results in the range 1.377–1.3618 Å [37]. The C=C lengths are 1.3593 Å, 1.3621 Å, 1.3622 Å for TPC, FHM and PFH with experimental values in the range 1.3498–1.3550 Å [37]. The COC bond angles are 119.1° (TPC), 119.3° (FHM), 119.4° (PFH) and 118.3° (experimental) and CNN angles are 123.3°, 117.2° (TPC), 122.6°, 117.1° (FHM), 120.3°, 118.2° (PFH) with experimental values as 122.8°, 116.7° [37]. The experimental values of the angle, CC=O are 125.2° and 122.4° and for the title compounds, the corresponding angles are, 122.9°, 122.9° (TPC), 122.2°, 122.4° (FHM) and 122.2°, 122.5° (PFH) [37]. Also the CCN angles are in agreement with the reported values: 119.5° (experimental), 121.3° (TPC), 120.5° (FHM) and 120.7° (PFH) [37]. Most of the dihedral angles are nearly agrees with the experimental results [37].

2.2 IR and NMR spectra

The experimental IR spectral data of the title compounds are from Slomiac et al. [37].

The vibrations (table S2) at 3388 cm⁻¹ (IR), 3372 cm⁻¹ (DFT) for TPC, 3387 cm⁻¹ (IR), 3383 cm⁻¹ (DFT) for FHM and 3388 cm⁻¹ (IR), 3382 cm⁻¹ (DFT) for PFH are uNH [40]. Also these IR band has doublet at 3243, 3247, 3250 cm⁻¹ respectively for TPC, FHM and PFH with red shift from the computed value showing weakening of NH bond [41, 42]. The NH deformation is assigned at 1537/1541 cm⁻¹ (IR/DFT) for TPC, 1536/1543 cm⁻¹ (IR/DFT) for FHM and 1547/1548 cm⁻¹ (IR/DFT) for PFH. The NH stretching modes are reported at 3393 cm⁻¹ (DFT) and at 3380 cm⁻¹ (IR) [43]. The vibrations at 1656, 1619, 1586 cm⁻¹ (IR), 1671, 1617, 1590 cm⁻¹ (DFT) for TPC, 1644, 1590, 1564 cm⁻¹ (IR), 1629, 1589, 1562 cm⁻¹ (DFT) for FHM and 1649, 1596, 1562 cm⁻¹ (IR), 1635, 1594, 1563 cm⁻¹ (DFT) for PFH are the C=O, C=N and C=C stretches [40]. The C=O stretching modes are reported at 1682 cm⁻¹ (DFT), 1688 cm⁻¹ (IR) and at 1681 cm⁻¹ (Raman) [54]. uC-O is assigned at 1163, 961 cm⁻¹ (IR), 1161, 962 cm⁻¹ (DFT) for TPC, 1147, 958 cm⁻¹ (IR), 1144, 963 cm⁻¹ (DFT) for FHM and 1137, 930 cm⁻¹ (IR) 1143, 921 cm⁻¹ (DFT) for PFH [40]. The CO stretching modes are reported at 1082 cm⁻¹ and 997 cm⁻¹ theoretically [45]. NBO interactions produces the downshift of the modes. CF stretches are assigned at 1266, 1201, 1108, 1070 cm⁻¹ for TPC, 1252, 1205, 1115 cm⁻¹ for FHM and at 1200, 1097, 989 cm⁻¹ for PFH experimentally [40]. The CF stretching modes are reported at 1112, 1076, 1060 cm⁻¹ [46] and at 1239, 1223 cm⁻¹ theoretically [47, 48]. The bands at 1095, 1315 cm⁻¹ for TPC, 1082, 1313 cm⁻¹

for FHM and 1075, 1317 cm⁻¹ for PFH in the IR spectrum are the N–N and C–N stretching modes of the derivatives [40]. The corresponding DFT values are 1083, 1322 cm⁻¹ (TPC), 1083, 1304 cm⁻¹ (FHM) and 1075, 1303 cm⁻¹ (PFH). The N–N stretching mode is reported at 1138 cm⁻¹ theoretically [49].

¹H and ¹³C NMR spectra of TPC, FHM and PFH were calculated and it is seen that the chemical shifts are quite similar for TPC, FHM and PFH molecules (table S3). There are four groups of hydrogen in the studied molecules, aromatic, chromone ring, H atom of NH and hydrazine group. H8, H12 (TPC and PFH) and H9, H13 (FHM) near to O atoms which high electronegativity and its core is less shielded and have high chemical shifts [50]. H22 (TPC and PFH) and H23 (FHM) are less shielded as it is near to C and N (high electronegativity) atoms. For all carbon atoms, near to electronegative atoms, high C NMR chemical shifts. Among the ¹³C NMR shifts, C10, C19 (TPC and PFH) and C11, C20 (FHM) have the high chemical shift value due to presences of neighbors of high electronegativity [51, 52].

2.3 AIM analysis

It is established that size of electron density function appraised at BCP can reveal power of a specific bond. This relation has been seen for strong bonds, covalent in nature, and for weak interactions, such as hydrogen bonds. Commonly, higher electron density (ρ) at BCP results in the stronger the bond [53, 54]. Each of interacting atoms shares electrons in the case of the covalent bond, therefore generating a shared electron pair that is significantly confined in the region between these two atoms. This is additionally accompanied by negative values of Laplacian of electron densities ($\nabla^2\rho$) given that at BCP of covalent bond, concentration of electron density can be seen. Positive electron density values gives interaction between the corresponding atoms of each compound. The minimum and maximum Electron density are +0.013576 au (for N3–F31) and +0.394356 au (for O2–C10) in TPC, +0.013569 au (for N3–F7) and +0.357139 au (for O2–C11) in FHM, and +0.013743 au (for N3–F32) and +0.357454 au (for O2–C10) in PFH, respectively. It can be concluded that the ρ value for all bonds except N3–F31 (in TPC), N3–F7 (in FHM), and N3–F32 (in PFH) are in the range of covalent. For the stated bonds, no strongly connection is expected because of their low electron densities. There is good agreement between charge density and Laplacian of charge density ($\nabla^2\rho$). The $\nabla^2\rho(r)$ indicates bond interaction energy which designated on the interaction nature. A positive value of $\nabla^2\rho(r)$ can be an indication of non-interaction, whereas a negative value is proof of the covalent interaction. Normally, the negative value of $\nabla^2\rho$ associates with covalent interaction and hence the positive values

for the stated bonds confirms non-covalent interaction. From tables, the maximum of ϵ in the existing bonds in TPC, FHM and PFH, attributes to the bonds involving in aromatic region for example C23–C24 and C23–C29 in TPC, C24–C25 and C24–C31 in FHM, and C24–C25, and C7–C9 in PFH, respectively that points toward the π -bond interactions between the corresponding atoms [55].

2.4 NBO, electronic and chemical properties

Due to NBO activity [56, 57] the interactions (energies in kcal/mol) are (Table 1): from chromone ring oxygen atom to O1 $\rightarrow$ BD*(C7–C9, C19–C20) (33.63, 27.31) for TPC; O1 $\rightarrow$ BD*(C8–C10, C20–C21) (31.39, 25.58) for FHM and O1 $\rightarrow$ BD*(C7–C9, C19–C20) (32.02, 25.30) for PFH. Also due to the other oxygen atom, BD*(C9–C10, C10–C20) (19.70, 19.97) for TPC; BD*(C10–C11, C11–C21) (17.13, 17.42) for FHM and BD*(C9–C10, C10–C20) (17.20, 17.42) for PFH due to to carbonyl oxygen atom. Nitrogen atom N4 in all cases produce high interaction given as: N4 $\rightarrow$ BD*(N3–C21, C23–C29) (30.91, 43.23) for TPC, N4 $\rightarrow$ BD*(N3–C22, C24–C31) (31.86, 42.09) for FHM and N4 $\rightarrow$ BD*(N3–C21, C23–C28) (29.52, 45.69) for PFH. Due to fluorine atoms, the interactions are: F5 $\rightarrow$ BD*(C24–C25) (17.36), F6 $\rightarrow$ BD*(C26–C28) (20.56), F31 $\rightarrow$ BD*(C23–C29) (18.70), F32 $\rightarrow$ BD*(C24–C25) (20.96) for TPC; F5 $\rightarrow$ BD*(C25–C26) (16.17), F6 $\rightarrow$ BD*(C28–C29) (17.78), F7 $\rightarrow$ BD*(C24–C31) (17.77) for FHM and F5 $\rightarrow$ BD*(C24–C25) (16.46), F6 $\rightarrow$ BD*(C26–C27) (18.87), F30 $\rightarrow$ BD*(C24–C25) (19.22), F31 $\rightarrow$ BD*(C26–C27) (18.06), F32 $\rightarrow$ BD*(C27–C28) (17.42) for PFH.

FMOs often play dominant roles in molecular systems. The fundamental idea of this theory can be abridged in the form of a simple rule telling the condition for a simple course of the reaction by the requirement of the maximal positive overlap between LUMO (empty state) and HOMO (filled state) orbitals. LUMO and HOMO are related to electron affinity and ionization potential [58, 59]. These orbitals help to understand the chemical stability and the reactivity (Fig. 3). HOMO is over the ring1 and oxygen containing portion of ring2 for all molecules and over fluorine atoms of FHM and PFH while for TPC, it is over the fluorine atoms near to the CN attached bond. For all compounds, LUMO is over the ring2. HOMO and LUMO levels are -7.086 eV, -5.216 eV for TPC, -6.928 eV, -5.279 eV for FHM, -6.869 eV, -5.279 eV for PFH and energy gap varies in the order, TPC > FHM > PFH (Table 2). A molecule with a small energy gap is more polarizable and is generally associated with high chemical reactivity and low kinetic stability and is also termed as the soft molecule. It ensures an increase in chemical stability of the molecule because the smaller value of energy gap indicates easiness of the electron excitation from HOMO to LUMO and it reflects

Table 1 Interaction energies from NBO analysis for (a) TPC (b) FHM (c) PFH

Donor NBO	Acceptor NBO	Interaction energy E(2) kcal/mol
<i>(a) TPC</i>		
BD(C7–C9)	BD*(O2–C10)	22.46
BD(C7–C9)	BD*(N3–C21)	16.15
BD(C11–C13)	BD*(C15–C17)	21.56
BD(C11–C13)	BD*(C19–C20)	18.14
BD(C15–C17)	BD*(C11–C13)	16.29
BD(C15–C17)	BD*(C19–C20)	21.88
BD(C19–C20)	BD*(C02–C10)	21.24
BD(C19–C20)	BD*(C11–C13)	18.37
BD(C19–C20)	BD*(C15–C17)	16.43
BD(C23–C29)	BD*(C24–C25)	16.85
BD(C23–C29)	BD*(C26–C28)	23.58
BD(C24–C25)	BD*(C23–C29)	19.84
BD(C24–C25)	BD*(C26–C28)	15.30
BD(C26–C28)	BD*(C23–C29)	16.86
BD(C26–C28)	BD*(C24–C25)	22.56
LPO1	BD*(C7–C9)	33.63
LPO1	BD*(C19–C20)	27.31
LPO2	BD*(C9–C10)	19.70
LPO2	BD*(C10–C20)	19.97
LPN4	BD*(N37–C21)	30.91
LPN4	BD*(C23–C29)	43.23
LPF5	BD*(C24–C25)	17.36
LPF6	BD*(C26–C28)	20.56
LPF31	BD*(C23–C29)	18.70
LPF32	BD*(C24–C25)	20.96
<i>(b) FHM</i>		
BD(C8–C10)	BD*(O2–C11)	23.80
BD(C8–C10)	BD*(N3–C22)	16.59
BD(C12–C14)	BD*(C16–C18)	21.55
BD(C12–C14)	BD*(C20–C21)	18.89
BD(C16–C18)	BD*(C12–C14)	16.62
BD(C16–C18)	BD*(C20–C21)	22.34
BD(C20–C21)	BD*(O2–C11)	23.02
BD(C20–C21)	BD*(C12–C14)	18.06
BD(C20–C21)	BD*(C16–C18)	16.81
BD(C24–C31)	BD*(C25–C26)	20.54
BD(C24–C31)	BD*(C28–C29)	19.84
BD(C25–C26)	BD*(C24–C31)	17.71
BD(C25–C26)	BD*(C28–C29)	19.06
BD(C28–C29)	BD*(C24–C31)	20.49
BD(C28–C29)	BD*(C25–C26)	19.55
LPO1	BD*(C8–C10)	31.39
LPO1	BD*(C20–C21)	25.58
LPO2	BD*(C10–C11)	17.13
LPO2	BD*(C11–C21)	17.42
LPN4	BD*(N3–C22)	31.86

Table 1 (continued)

Donor NBO	Acceptor NBO	Interaction energy E(2) kcal/mol
LPN4	BD*(C24–C31)	42.09
LPF5	BD*(C25–C26)	16.17
LPF6	BD*(C28–C29)	17.78
<i>(c)PFH</i>		
BD(C7–C9)	BD*(O25–C10)	23.79
BD(C7–C9)	BD*(N35–C21)	17.39
BD(C11–C13)	BD*(C15–C17)	21.52
BD(C11–C13)	BD*(C19–C20)	19.06
BD(C15–C17)	BD*(C11–C13)	16.63
BD(C15–C17)	BD*(C19–C20)	22.54
BD(C19–C20)	BD*(O25–C10)	23.11
BD(C19–C20)	BD*(C11–C13)	17.95
BD(C19–C20)	BD*(C15–C17)	16.76
BD(C23–C28)	BD*(C24–C25)	18.34
BD(C23–C28)	BD*(C26–C27)	23.12
BD(C24–C25)	BD*(C23–C28)	18.40
BD(C24–C25)	BD*(C26–C27)	16.97
BD(C26–C27)	BD*(C23–C28)	17.04
BD(C26–C27)	BD*(C24–C25)	20.95
LPO1	BD*(C7–C9)	32.02
LPO1	BD*(C19–C20)	25.30
LPO2	BD*(C9–C10)	17.20
LPO2	BD*(C10–C20)	17.42
LPN4	BD*(N3–C21)	29.52
LPN4	BD*(C23–C28)	45.69
LPF5	BD*(C24–C25)	16.46
LPF6	BD*(C26–C27)	18.87
LPF30	BD*(C24–C25)	19.22
LPF31	BD*(C26–C27)	18.06
LPF32	BD*(C23–C28)	17.42

the biological activity of the molecule [43, 60, 61]. The title molecules are electrophilic 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 title compounds are inherently reactive and this feature is responsible for various biological activities [62–65].

To estimate the antitumor-antiproliferative activities of TPC, FHM and PFH, chemical descriptors were noted for 5-fluorouracil (anticancer) and azathioprine (antiproliferative drug). Dipole moment of 5-fluorouracil is in between the values of title compounds. From the results, if 5-fluorouracil is an antitumor drug, the title compounds may also have same activity. Similar explanation is applicable for antiproliferative activity [66].

MEP allows us to search the most reactive nucleophilic and electrophilic sites of a molecule against the reactive biological potentials [67]. Electrophilic portions show attraction, while nucleophilic indicates repulsion. Electrostatic potential diagrams are illustrated in Fig. 4. The red and yellow colours represent the most electronegative electrostatic potential. That is atoms in this region have a tendency to attract electrons (electrophilic). In the MEP plot, blue colour indicates the most electropositive potential and the red colour indicates the most electronegative potential. Regions where the potentials are zero are denoted by green colour. As from MEP surface negative region is on O, F atoms and phenyl rings for FHM, TPC and PFH with nucleophilic portions near H atoms with NH group showing the biological activity [44].

The UV–Vis absorption (Fig.S1) are at 310 nm, 278 nm for TPC, 312 nm, 284 nm for FHM and at 311 nm, 281 nm for PFH. DOS spectrum (Fig.S2) characterize the energy levels per unit energy increment and its composing energy. The displaying study per orbital shows that the green and red line in these curves correspond to HOMO and LUMO energy levels.

NLO properties are presented in table S4 [68]. First order hyperpolarizability ($\times 10^{-30}$ esu) varies as: FHM > TPC > PFH which are 140, 134 and 69 times that of urea and second order value is also high for all derivatives [69, 70].

2.5 Molecular docking

PASS analysis [71] gives activities, HMGCS2 expression enhancer, Mcl-1 antagonist, Thiol protease inhibitor and antiproliferative activities. Receptors, 4AT9, 6DM8, 2AYN and 5NAD were obtained from protein data bank website. ILF3 promotes proliferation and migration in breast

Fig.3 HOMO–LUMO plots of **a** TPC, **b** FHM, **c** PFH

Table 2 Chemical descriptors

Molecule	$I = -E_{\text{HOMO}}$	$A = -E_{\text{LUMO}}$	ΔE	$\eta = (I-A)/2$	$\chi = (I+A)/2$	ω	Dipole moment
TPC	7.086	5.216	1.870	0.935	6.151	20.233	2.7693
FHM	6.928	5.279	1.649	0.825	6.104	22.581	2.3525
PFH	6.869	5.279	1.590	0.795	6.074	23.203	4.7226
5-Fluorouracil (FU)	7.915	3.999	3.916	1.958	5.957	9.062	4.2979
Azathioprine (AP)	7.268	4.493	2.775	1.388	5.881	12.459	5.2752

Dipole moment is in Debye and all other in eV

Fig.4 MEP plots of **a** TPC, **b** FHM, **c** PFH

cancer cells, at least partly by promoting CDH11 expression [72]. Frequent over expression of MCL-1 in primary and drug-resistant human cancer cells makes it an attractive therapeutic target for cancer [73–75]. Anticancer and antibacterial properties of chromone derivatives were investigated using selected PDB by using Audock software [35, 36] and Patchdock server [76–78]. 2D Interactions are shown in Fig.S3. With these the docked ligands form stable complex and has high binding affinity values (Table 3). From the results of Autodock, TPC and PFH have maximum binding energy values of -9.6 kcal/mol for 6DM8 while for FHM binding energy is -8.6 kcal/mol for 5NAD. For all the PDBs, the binding energies vary from -7.9 kcal/mol to -9.6 kcal/mol. For AP and FU according to Autodock results, the binding energies are in the range -6.6 kcal/mol to -7.4 kcal/mol and -5.0 kcal/mol to -5.7 kcal/mol. For TPC and FHM, Patchdock server docking give maximum binding energy (table S5) for the PDB:6DM8 with values -41.41 kcal/mol and -43.70 kcal/mol. For PFH the energy is high for 2AYN with a value -38.46 kcal/mol. AP and FU also have energies in the ranges -39.44 kcal/mol to -45.62 kcal/mol (AP) and -20.80 kcal/mol to -23.03 kcal/mol (FU). Consequently, all derivatives show activity against these inhibitors and can develop new lead medication as in cancer treatment and antiproliferative

effects. As seen in table S6 of Autodock results, TPC, FHM and PFH are interacting with the all target proteins.

2.6 Interactions of TPC, FHM, PFH with 4AT9

2.6.1 For TPC

The active amino acid Gln358, Ile359 forms conventional H-bond interaction with same fluorine atom at the distance of 3.39, 3.29 Å whereas Arg94 shows conventional H-bond and carbon hydrogen bond interaction with C=N bond at the distance of 3.39, 3.63 Å. Val98 have two halogen interactions and Ile395 has a halogen interaction with fluorine atoms at the distance of 2.84, 3.34 and 3.18 Å. Arg94 form hydrophobic π -sigma interaction and Met93 having a π -sulfur interaction with ring centres of chromone structure are at the distance of 3.94, 5.69 Å. Val357, Pro361 shows hydrophobic π -alkyl interaction having the distances of 4.38, 5.47 Å with tetra fluoro phenyl ring centre while Ala99 forms two hydrophobic π -alkyl interaction with ring centres of chromone structure are at the distance of 4.64, 4.86 Å. Arg94, Ala213, Lys214 shows hydrophobic π -alkyl interaction with ring centres of chromone structure are at the distance of 5.44, 4.42, 5.39 Å and Gly101 form a carbon hydrogen bond interaction with fluorine atom at the distance of 3.34 Å.

2.6.2 For FHM

The active amino acid Ser200, His207 forms conventional H-bond interaction with fluorine atoms at the distance of 3.41, 3.38 Å whereas Ser200, Thr241 shows conventional H-bond with NH bond, oxygen atom in a ring at the distance of 2.32, 3.12 Å. Asp121, Ser200 have halogen interaction with fluorine atoms at the distance of 3.51, 3.29 Å while Trp243 forms two hydrophobic π - π T shaped interaction with ring centres of chromone structure are at the distance of 4.65, 4.68 Å. Ala204, Trp243 form hydrophobic π -sigma interaction having the distances 3.74, 3.54 Å with ring centres of tetra fluoro phenyl and phenyl ring respectively. Val298, Val301 shows hydrophobic π -alkyl interaction with phenyl ring centre are at the distance of 5.42, 4.52 Å.

2.6.3 For PFH

The amino acid Tyr35, Gln237 forms conventional H-bond interaction with same fluorine atom at the distance of 3.29, 3.24 Å whereas val44, Lys45 shows conventional H-bond with oxygen atom in a ring at the distance of 3.16, 3.01 Å. Pro48 having two carbon hydrogen bond interaction with fluorine atom and C=O group at the distance of 3.43, 3.54 Å while Glu50, Arg269 shows halogen interaction

Table 3 The binding affinity values of different poses the compounds predicted by Autodock Vina

Compound	Protein	Affinity (kcal/mol)	Distance from best mode (Å)	
			RMSD l.b	RMSD u.b
TPC	4AT9	-8.2	0.000	0.000
TPC	6DM8	-9.6	0.000	0.000
TPC	2AYN	-8.6	0.000	0.000
TPC	5NAD	-8.8	0.000	0.000
FHM	4AT9	-7.9	0.000	0.000
FHM	6DM8	-8.0	0.000	0.000
FHM	2AYN	-8.4	0.000	0.000
FHM	5NAD	-8.6	0.000	0.000
PFH	4AT9	-8.4	0.000	0.000
PFH	6DM8	-9.6	0.000	0.000
PFH	2AYN	-8.7	0.000	0.000
PFH	5NAD	-9.1	0.000	0.000
AP	4AT9	-6.8	0.000	0.000
AP	6DM8	-7.4	0.000	0.000
AP	2AYN	-7.1	0.000	0.000
AP	5NAD	-6.6	0.000	0.000
FU	4AT9	-5.0	0.000	0.000
FU	6DM8	-5.3	0.000	0.000
FU	2AYN	-5.6	0.000	0.000
FU	5NAD	-5.7	0.000	0.000

with fluorine atoms at the distance of 3.68, 3.60 Å. Gly288 form a conventional H-bond interaction with C=O group and Arg269 has a carbon hydrogen bond interaction with fluorine atom at the distance of 3.20 and 3.26 Å. Gly288 forms hydrophobic π -sigma interaction with ring centre of tetra fluoro phenyl and hydrophobic amide π -stacked interaction with ring centre of chromone structure at the distance of 3.59 and 3.97 Å. Arg43, Val44 shows hydrophobic π -alkyl interaction with ring centres of chromone structure are at the distance of 4.84, 5.34 Å.

2.7 Interactions of TPC, FHM, PFH with 6DM8

2.7.1 For TPC

The amino acids Asp200 shows two salt-bridge H-bond with NH bond at the distances of 2.66, 2.17 Å but Asn64 form conventional H-bond and Asp200 form halogen interaction with fluorine atoms at the distance of 3.33, 3.22 Å. Tyr59 shows two hydrophobic interactions with ring centres of chromone structure at the distances of 3.74, 4.31 Å whereas Tyr5 form hydrophobic π - π stacked interaction with tetra fluoro phenyl ring at the distance of 4.41 Å. Trp125 has a hydrophobic π - π T shaped interaction and Ala151 form hydrophobic π -alkyl interaction with chromone ring structure having the distances of 5.06, 5.41 Å respectively.

2.7.2 For FHM

The amino acid Asp200 show conventional H-bond with NH bond and halogen interaction with fluorine atom at the distances of 2.48, 3.26 Å. Tyr59 shows two hydrophobic π - π stacked interactions with ring centres of chromone structure at the distances of 3.74, 4.36 Å whereas Tyr5 form hydrophobic π - π stacked interaction with tetra fluoro phenyl ring at the distance of 4.51 Å. Trp125 has a hydrophobic π - π T shaped interaction and Ala151 form hydrophobic π -alkyl interaction with chromone ring structure having the distances of 5.06, 5.43 Å respectively.

2.7.3 For PFH

The amino acid Asp200 shows two conventional H-bond with NH bond and Asn64, Asp200 halogen interaction with fluorine atom at the distances of 2.63, 2.25 and 3.31, 3.37 Å. Tyr59 shows two hydrophobic π - π stacked interactions with ring centres of chromone structure at the distances of 3.67, 4.09 Å whereas Tyr5, Trp15 form hydrophobic π - π stacked interaction with tetra fluoro phenyl ring, second ring centre at the distance of 4.43, 5.93 Å. Trp152 has a hydrophobic π - π T shaped interaction and Ala151 form

hydrophobic π -alkyl interaction with phenyl ring centre having the distances of 5.56, 5.12 Å respectively.

2.8 Interactions of TPC, FHM, PFH with 2AYN

2.8.1 For TPC

The active residues Arg123, Lys129, Arg441 forms conventional H-bond interaction with C=N, fluorine atom and C=O group at the distance of 2.94, 3.24, 3.00 Å and Cys104 forms conventional and π -donor H-bond with oxygen atom and centre of the ring of chromone structure at the distance of 3.30, 4.01 Å. Pro103 formulates two hydrophobic π -alkyl interaction with the ring centres of chromone structure at the distances are 5.38, 5.32 Å. Val439, Arg441, Pro103 shows hydrophobic π -alkyl interaction with centre of tetra fluoro phenyl ring at the distance of 4.54, 4.86, 4.41 Å while Lys440 has a halogen interaction at the distance of 3.67 Å with one of the fluorine atom attached with tetra fluoro phenyl ring.

2.8.2 For FHM

The active residues Asn413, Tyr416 forms conventional H-bond interaction and Phe405, Cys414 shows halogen interaction with fluorine atoms at the distance of 3.30, 3.24 and 3.26, 3.03 Å and Arg482 form a π -donor H-bond with centre of tetra fluoro phenyl ring at the distance of 3.66 Å. Phe373 formulates two hydrophobic π - π stacked interaction and Pro402 shows two with hydrophobic π -alkyl interaction the ring centres of chromone structure at the distances are 3.78, 4.01 Å and 4.38, 5.27 Å. Pro481, Arg482 forms hydrophobic π -alkyl interaction with centre of tetra fluoro phenyl ring at the distance of 5.48, 4.79 Å.

2.8.3 For PFH

The active residues Leu174 forms two conventional H-bond interaction with fluorine atom and Thr165 has a conventional H-bond interaction with C=O group are at the distance of 3.02, 3.48 and 3.08 Å. Ala154, Asp157 shows two halogen interactions with fluorine atoms at the distance of 3.50, 3.02, 3.59, 3.48 Å whereas Pro170 forms two hydrophobic π -alkyl interaction the ring centres of chromone structure at the distances are 4.83, 5.07 Å. Ile173 displays a π -sigma interaction and Asp157 indicates amide π -stacked interaction with tetra fluoro phenyl ring centre at the distances of 3.33, 4.20 Å but Ala154 forms a carbon hydrogen bond interaction with fluorine atom at the distance 3.56 Å. Leu158, Ile169 forms hydrophobic π -alkyl interaction with ring centres of tetra fluoro phenyl and chromone structure respectively at the distances of 4.56, 4.36 Å.

2.9 Interactions of TPC, FHM, PFH with 5NAD

2.9.1 For TPC

Amino acids Asp608, Ile531 form conventional H-bond with NH bond at the distance of 2.57, 2.85 Å and Met671, Val539, Lys553, Ile663 shows hydrophobic π -alkyl interaction with centres of the rings of chromone structure at the distances are 5.10, 5.11, 5.16, 5.33 Å. Ile663, form hydrophobic π -sigma interaction and Met671 form π -sulfur interaction with centre of chromone structure at the distance of 3.84, 3.65 Å. Asp608 formulate halogen interaction with one of the fluorine atom attached with tetra fluoro phenyl ring and Ile531 has a hydrophobic π -alkyl interaction with centre of tetra fluoro phenyl ring are at the distance of 3.13, 4.60 Å respectively.

2.9.2 For FHM

Amino acid Asp608 form halogen interaction with fluorine atom and electrostatic π -anion interaction with tetra fluoro phenyl ring centre at the distance of 3.21, 4.95 Å and Ile663 shows hydrophobic π -sigma and π -alkyl interaction with centres of the rings of chromone structure at the distances are 3.73, 5.23 Å. Met671 shows a π -sulfur and hydrophobic π -alkyl interaction whereas Val539 forms two hydrophobic π -alkyl interaction with centres of the rings of chromone structure at the distances of 3.73, 5.47 and 4.52, 5.43 Å. Ile531, Lys553 have hydrophobic π -alkyl interaction with tetra fluoro phenyl ring centre, phenyl ring centre at the distance of 4.69, 5.33 Å respectively.

2.9.3 For PFH

Amino acid Gln670 forms two halogen interaction both are at the distances 3.49 Å and Glu571, Asp664 shows a halogen interaction are at the distances of 3.27, 3.30 Å with fluorine atoms. Lys553 electrostatic π -cation interaction with tetra fluoro phenyl ring centre and Cys604 shows a π -sulfur interaction with centre of phenyl ring at the distance of 4.61, 5.79 Å. Lys553, Ile663, Met671 shows hydrophobic π -alkyl interaction with tetra fluoro phenyl ring centre and Ile 531 indicates two hydrophobic π -alkyl interaction with ring centres of chromone structure are at the distances of 4.91, 5.24, 4.76 and 5.14, 4.98 Å. Leu654, Pro673 forms hydrophobic π -alkyl interaction with ring centres of tetra fluoro phenyl and chromone structure respectively at the distances of 5.16, 5.37 Å.

2.10 Interactions of 5-fluorouracil (FU) and azathioprine (AP) with 4AT9, 6DM8, 2AYN and 5NAD

2.10.1 AP and 4AT9

Amino acids Gly106, Lys110 forms conventional H-bond interaction with NO₂ group at the distance of 3.12, 3.16 Å whereas Thr112, Asp246 shows carbon hydrogen bond interaction with H(2) atom of imidazole ring at the distance of 2.87, 2.82 Å. His207 gives π -sulfur interaction with sulphur atom and hydrophobic π - π T shaped interaction with imidazole ring centre at the distances of 5.58, 5.42 Å. Pro242 forms two hydrophobic π -alkyl interaction at the distance of 5.30, 4.76 Å with centre of purine structure and Ala204 has a hydrophobic π -alkyl interaction with imidazole ring centre at the distance of 4.35 Å. Asp246 shows conventional H-bond with NH bond of imidazole ring and Ser107 form a carbon hydrogen bond with nitrogen atom of pyrimidine ring are at the distance of 1.86 Å and 3.38 Å.

2.10.2 FU and 4AT9

Amino acids Ser281, Ser289 forms conventional H-bond interaction with OH bond, fluorine atom at the distances of 3.00, 3.13 Å whereas Gly282, Ile283 indicates carbon hydrogen bond interaction with H(1), nitrogen atom attached with H(3) are at the distances of 2.76, 3.39 Å. Phe 34 formulate a π -donor H-bond having 3.15 Å distance with H(4) atom.

2.10.3 AP and 6DM8

The active Amino acids Arg148 shows two conventional H-bond interaction with nitrogen atoms of purine ring structure at the distance of 3.27, 3.19 Å whereas Asp200 forms two carbon hydrogen bond with H(4) atom of imidazole ring, H(7) atom of CH₃ group respectively are at the distance of 3.00, 2.80 Å. Glu170, Glu61 form carbon hydrogen bond with H(2) atom of imidazole ring are at the distance of 2.52, 3.06 Å and Met115 has a π -sulfur interaction with sulphur atom of the ligand with the distance of 5.99 Å. Trp152 forms different categories of hydrophobic interactions are four π - π T shaped; two π - π stacked and a π -alkyl with ring centres of purine structure are at the distances 5.62, 5.12, 5.47, 5.31; 5.09, 4.58 and 3.71 Å respectively. Arg129, Glu61 forms electrostatic π -cation, π -anion interaction with imidazole ring centre at the distances 3.78, 3.84 Å.

2.10.4 FU and 6DM8

Amino acid Gln290 shows a conventional H-bond and carbon hydrogen bond interactions with H(3), H(2) atoms at the distance of 2.76, 3.07 Å while Thr240 form a carbon hydrogen bond interaction with H(4) atom attaching CH₃ group at the distance of 3.09 Å. Gly295 forms a conventional H-bond interaction with H(4) atom and two halogen interaction with fluorine atom are at the distance of 2.06, 2.84, 3.44 Å. Arg291, Glu298 formulates conventional H-bond, halogen interaction respectively with same fluorine atom at the distance of 3.06, 2.98 Å.

2.10.5 AP and 2AYN

The active residues Cys414, arg482 forms conventional H-bond interaction with nitrogen atom and hydrogen atom of imidazole ring attached with pyrimidine ring and Tyr416 form carbon hydrogen bond interaction with H(2) atom at the distance of 2.29, 2.98 Å and 2.35 Å. Arg482 formulate hydrophobic π -alkyl interaction with the attached ring centres at the distances are 4.34, 5.49 Å. Phe373 has a hydrophobic π - π stacked interaction and Pro402 shows a hydrophobic π -alkyl interaction with centre of imidazole ring at the distance of 3.84, 4.80 Å.

2.10.6 FU and 2AYN

The active residue Phe405 forms two conventional H-bond interaction with H(3), H(4) atoms and halogen interaction with fluorine atom at the distance of 2.40, 2.05, 3.09 Å whereas Cys414 two conventional H-bond interaction with H(3), oxygen atom attached with H(2) at the distance of 3.09, 3.56 Å. Amino acid Asn413 formulates two conventional H-bond interaction with oxygen atom attached with H(1), fluorine atom at the distance of 3.33, 2.98 Å and Ser404 has a H-bond interaction with H(4) atom at the distance of 2.80 Å.

2.10.7 AP and 5NAD

Amino acid Ile531 form conventional H-bond with NH bond of imidazole ring attached with pyridine ring at the distance of 2.36 Å and Asp664 shows a carbon hydrogen bond at the distance of 2.68 Å with H(4) atom of imidazole ring attached with pyridine ring. Ile531, Ile663 forms hydrophobic π -sigma interaction with centre of imidazole ring attached with pyridine ring at the distance of 3.55, 3.82 Å. Val539 formulate two hydrophobic π -alkyl interaction with centres of purine ring are at the distance of 5.20, 5.13 Å while Met671 has a hydrophobic π -alkyl interaction with centre of imidazole ring. Leu654, Ile663 shows

hydrophobic π -alkyl interaction with centres of pyrimidine ring at the distance of 5.17, 4.80 Å respectively.

2.10.8 Fu and 5NAD

Amino acid Tyr725 forms conventional H-bond with H(2), H(3), fluorine atoms are at the distances of 2.30, 2.14, 3.14 Å respectively and Glu755 show a conventional H-bond with H(3) atom at the distance of 2.99 Å.

TPC, FHM and PFH molecules formed hydrophobic and hydrogen bond interactions with the targets and with more negative binding energy showing high inhibition efficiency. Also interaction energies are higher than that of 5-fluorouracil and azathioprine. Hence chromone derivatives have anticancer and antiproliferative properties similar to that of reference drugs.

3 Conclusion

The optimized structures of chromones have been carried out using DFT method and their frequencies and geometrical parameters were also determined. Maximum of ϵ in the existing bonds in TPC, FHM and PFH, attributes to the bonds involving in aromatic region for C23–C24 and C23–C29 in TPC, C24–C25 and C24–C31 in FHM and C24–C25, and C7–C9 in PFH respectively that points toward the π -bond interactions between the corresponding atoms. First order hyperpolarizability of FHM, TPC and PFH are 140, 134 and 69 times that of urea. Molecular properties such as frontier orbitals, gap energies and reactivity descriptors have also been discussed. The decrease in gap energy makes the flow of electrons easier so the molecules becomes soft and reactive. The calculated MEP maps show the positive potential sites are favourable for nucleophilic attack, whereas the negative potential sites are favourable for the electrophilic attack. Docking results were discussed based on the different interactions between the ligands and proteins. From the results of Autodock, TPC and PFH have maximum binding energy values of –9.6 kcal/mol for 6DM8 while for FHM binding energy is –8.6 kcal/mol for 5NAD. Antitumor and antiproliferative activities of hydrazine's were found to be higher than standard molecules.

Author contributions All authors conceived and designed the calculations. Analyzed and interpreted the data; contributed materials, analysis tools or data and software; wrote the paper.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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