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CADD ANALYSIS OF NOVEL COUMARINE DERIVATIVES

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ABSTRACT

Coumarine are reported as ntifungal,antibacterial,chemotherapeutic,antiinflammantory,antioxidant agent and HIV inhibitors. It also reported as antitumor anticancers activity due to inhibition of cyclin D1and protein kinase(CK2). Theoretical and computational methods are widely used to analyze, investigate, and predict Biological activity. The present study is focused on exploration of electronic properties including molecular structure, NBO analysis, and vibrational assignments of coumarin derivatives .In order to better understand the structural requirements of coumarine derivatives we were examined CK2 enzyme interaction to gain information about their anticancer aspect using dockin techni/ues.

Keywords: Cyclin D1, CK2, NBO and Anticacers

I. INTRODUCTION

Coumarins are naturally occurring compounds found in all parts of plants and mainly can be found in grasses, legumes and among others [1]. Various studies of coumarins have been conducted in past due to their wide range of applications. They are widely used as antifungal [2], antibacterial [3], chemotherapeutics [4], anti-inflammatory, antioxidant agents, and HIV inhibitors. Hence, because of wide range applications coumarins are very interesting compounds to study since a long time. In particular, one of the studies has shown that 7-dihydroxycoumarin has antitumor activity due to inhibition of cyclin D1 which is known to over expressed in many tumors [5]. Also, their anticancer activity has been identified as the attractive inhibitors of protein kinase (CK2) by virtual screening methodology [6].

CK2, a pleiotropic enzyme, is involved in variety of cellular functions [7] and it has been also reported that they display an antiapoptotic effect in cancer cell lines [8]. They are invariably more abundant in tumors compared with normal tissues, and their overexpression causes alterations in the expression of cellular oncogenes or tumor suppressor genes [9]. Hence, CK2 is a potential target for antitumor drugs. Various in-silico studies have been reported in last few years for screening inhibitors of CK2 [10]. From the one of the virtual screening approaches, important inhibitor features of coumarins for CK2 has been identified [6].

Molecular modeling studies have been widely employed for coumarin derivatives. The electronic descriptors and vibrational data of molecules are the important parameters to for the investigation of biological property. The present study is focused on exploration of electronic properties including molecular structure, NBO analysis, and vibrational assignments of coumarin derivatives. A molecular docking study has been performed with CK2 enzyme to gain information about their anticancer aspects due to interaction with CK2 enzyme.

II. MATERIALS AND METHODS

All calculations were performed on a Linux workstation equipped with eight parallel Intel Xeon X5460 processors (3.16 GHZ) with 16 GB total RAM.

DFT methodology: DFT calculations were performed with the Jaguar v7.9 quantum chemistry module of Schrödinger software [11]. Coumarin derivatives were fully optimized in *vacuum* at DFT level without imposing constraints using Becke's three-parameter and Lee-Yang-Parr functional (B3LYP) level hybrid functional with basis set *ps*6-311G with ** polarization. In general ** option places polarization functions on all atoms except for transition metals, H and He and *ps*6-311G basis set is used for C, H, N, O, and P. Effective core potential used for heavy atoms and Non-ECP atoms uses 6-311G basis. The calculated stationary points were characterized by calculating vibrational frequencies with the Hessian obtained during the geometry optimization. Real frequencies were obtained for optimized structures.

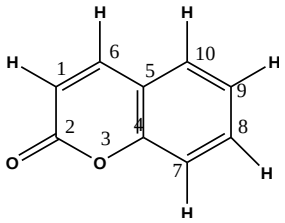
Docking: For the docking study, X-ray crystallographic coordinates of PDB entry 2QC6 (downloaded from RCSB) having resolution of 2.20 Å. Docking analysis was performed with Glide after preparing the protein structures with Preparation Wizard [11]. During pre-processing, bond orders were assigned; hydrogens were added to all atoms in the protein structure. Water molecules beyond 5 Å from hetero (het) groups were deleted and missing loops were filled up. States were generated for these hetero atoms at pH=7.0 ± 3.0. In the presence of force field OPLS2005, hydrogen atoms of protein structure were minimized, orientations of retained water molecules were sampled and pKa's were determined. Grid calculations were performed for the protein active site by generating the with default size of grid box x=33.8893 Å, y= 22.068 Å and z=10.424 Å. No constraints were applied and rotations of rotatable groups were disallowed.

The coumarin derivatives were prepared using the Ligprep v2.6 module [11]. All the possible protonation states at pH=7.0 ± 2.0 were generated using ionization tool. Specified chiralities of these ligands were retained while ligand preparation. Low energy conformers were obtained in the force field OPLS2005 without any constraints. These conformers were retained for docking studies. Five thousand poses were kept in the initial phase of the docking keeping the default scoring window cut-off value at 100. Ligand Van der Waals radii were scaled to a factor of 0.80 (default value) for non-polar atoms with a partial charge cut-off level of 0.15 (absolute value). Post docking minimizations were performed by including five poses per ligand.

Glide v5.8 [11] was used for docking analysis. Glide's workflow predicts the binding mode of the ligand with high accuracy. The docking study was initiated by bringing specified prepared proteins and ligand molecules together..

III. RESULT AND DISCUSSION

Molecular Geometry: DFT calculations were performed on Coumarin derivatives: 7-diethyl amino coumarin, 7-diethylamino-4-methyl coumarin, 7-hydroxy-4-trifluoromethyl coumarin, 7-methoxy-4-trifluoromethyl coumarin, 6, 7-dihydroxy-4-trifluoromethyl coumarin, 5, 7-dimethoxy coumarin and 5, 7-dihydroxy-4-methyl coumarin shown in table. The coumarin derivatives were DFT optimized at B3LYP level at *ps*6-311G basis set.



Name	Structure	Name	Structure
7-diethylamino coumarin		5,7-dimethoxy coumarin	
7-diethylamino-4-methyl coumarin		5,7-dihydroxy-4-methyl coumarin	
7-hydroxy-4-trifluoromethyl coumarin		6,7-dihydroxy-4-trifluoromethyl coumarin	
7-methoxy-4-trifluoromethyl coumarin			

The optimized bond lengths of derivatives were observed. Subsequent vibrational frequency showed that minima on their respective potential energy surfaces were obtained. The optimized hydrogen bond length for C_6-R_{13} (where R is hydrogen or trifluoromethyl group) differs for coumarin derivatives due to presence of different functional groups. Bond length of C_6-R_{13} bond for 7-diethylamino-4-methyl coumarin (R = CF_3) is about 1.505 Å, which is shorter than the length of a normal C-C single bond (1.54Å) and longer than the length of a normal C-C double bond (1.34 Å). It indicates that bonds C-C bond lengths of 7-diethylamino-4-methyl coumarin have partly the characteristic of single bond. 7-diethyl amino coumarin's bond length for C_6-R_{13} (R = H) is 1.087 Å, which is approx C (sp^3) – H bond (1.09 Å). Bond lengths for C_2-O_{11} bond of coumarin derivates are approximately same because all seven compounds have bond length in the range of 1.183 – 1.210 Å. It is reported that the bond length between C-atom and O-atom for single bond is 1.42 Å and for double bond is 1.20 Å thus this bond is single bond between C=O bond of coumarin compound. Bond length for O_3-C_4 bond for coumarin derivatives are approx same because all seven coumarin compounds have bond length of 1.342–1.365 Å. So this bond of coumarin compound is partly double bond. Bond length for C_8-C_9 bond for coumarin compounds are approx same. Coumarin compounds have bond length in the range of 1.324–1.423 Å. It is reported that the bond length of aromatic compound at C-C bond for single bond is 1.54 Å, for double bond is 1.34 Å and for triple bond is 1.20 Å. Thus this is partially double bond.

HOMO-LUMO Gap: HOMO and LUMO energy of any molecule determined by DFT theory. There are some amino coumarins and nitrogen atom has two unshared electron pairs. It was found that 5, 7-dimethoxy coumarin has the highest HOMO-LUMO energy gap (-0.12464au at B3LYP/6-31G) so 5-7-dimethoxy coumarin is more

stable molecule than the other coumarin derivatives. 5, 7-dihydroxy-4-trifluoromethyl coumarin has the lowest HOMO-LUMO energy gap (-0.16557 au at B3LYP/6-31G) so 5, 7-dihydroxy-4-trifluoromethyl coumarin is less stable and has less reactivity then the other coumarin derivatives. 7-diethyl amino -4-methyl coumarin is more stable than the 7-diethyl amino coumarin because 7-diethyl-4-methyl coumarin has high HOMO-LUMO energy gap (-0.14933) while 7-diethyl amino coumarin has low HOMO-LUMO energy gap (-0.15089). In comparison of 7-diethyl amino-4-methyl coumarin and 7-diethyl amino coumarin, there is a methyl group attach on C_4 atom in 7-diethyl amino 4-methyl coumarin while 7-diethyl amino coumarin do not has methyl group which is an electron donating molecule. 7-hydroxy-4-trifluoromethyl coumarin is less stable than the 7-methoxy-4-trifluoromethyl coumarin because 7-hydroxy-4-trifluoromethyl coumarin has low HOMO-LUMO energy gap (-0.15747) while 7-methoxy-4-trifluoromethyl coumarin has high HOMO-LUMO energy gap (-0.15553). Both molecules have trifluoromethyl group on C_4 but 7-methoxy-4-trifluoromethyl coumarin has methoxy group on C-atom while 7-hydroxy-4-trifluoromethyl coumarin has –OH group of C_7 of 6, 7-dihydroxy-4-trifluoromethyl coumarin have two OH group on C_6 and C_7-atom. In comparison of 6, 7-dihydroxy-4-trifluoromethyl coumarin, 7-hydroxy-4-triflouromethyl coumarin and 7-methyoxy-4-triflouromethyl coumarin, the 6, 7-dihydroxy-4-trifluoromethyl coumarin has high HOMO-LUMO energy gap than the other molecules because both molecules have two functional groups. One functional group is on the C_7-atom and other is on C_4-atom same as 6, 7-dihydroxy-4-triflouromethyl coumarin while 6, 7-dihydroxy-4-trifluoromethyl coumarin also has an extra functional group on C_6-atom.

Vibrational spectra: The simultaneous IR activation of the benzene ring mode and carbonyl (C=O) of the coumarin derivatives mode explains the charges transfer interaction between the electron donating group and the acceptor group through the π-conjugated system. The π-electron cloud movement from the donor to the acceptor can make the molecule highly polarized through the single or double path, when it changes from the ground state into the first excited state.

C-H Vibrations: The aromatic structure shows the C-H bonding and this C-H bonds show the presence of stretching vibrations in the region 3100-3000cm^{-1} and multiple weak bands recorded in this region [12]. However, these bands are useful because they overlap with the other atom or molecule resulting in stronger peak in this region [13]. It is characteristic region for identification of C-H stretching region. The C-H stretching vibration values of coumarin compounds at C_7-H_{17} bond are 3247.6, 3238.8, 3236.8, 3217.4, 3227.5, 3099.5 and 3222.8 cm^{-1} for 7-diethyl amino -4-methyl coumarin, 7-hydroxy-4-trifluoromethyl coumarin, 7-methoxy-4-trifluoromethyl coumarin, 6,7-dihydroxy-4-trifluoromethyl coumarin, 7-diethyl amino coumarin and 5,7-dihydroxy coumarin respectively. We determine via the DFT study that the stretching vibration of C_7-H_{17} bond of these 6 coumarin derivatives comes out of this range (3100 -3000 cm^{-1}). It means there are no weak bands so this bond cannot overlap with one another.

Ring (C-C and C=C) Vibrations: The benzene ring of coumarin derivative has 6 stretching vibrations at C-C bond. Generally, the C-C bond gives stretching vibration in the region of 1430-1650 cm^{-1} [13]. The C-C stretching vibrations of coumarin derivatives at C_4-C_5 bond are 1631.0, 1597.3, 1450.1 and 1588.0 cm^{-1} for 7-hydroxy-4-trifluoromethyl coumarin, 7-methoxy-4-trifluoromethyl coumarin, 6, 7-dihydroxy-4-trifluoromethyl coumarin and 7-diethyl amine coumarin respectively [14]. The C-C stretching vibrations of the 7-diethyl amino-

4-methyl coumarin, 5, 7-dimethoxy coumarin and 5, 7-dihydroxy-4-methyl coumarin are 1380.3, 895.6 and 1374.0 cm^{-1} respectively. These are weak bonds.

C=O Vibration: The carbonyls stretching peak or organic compounds are found in the range of 1780 -1700 cm^{-1}. The carbonyl ($C_2 - O_{11}$) stretching peak of the coumarin derivatives are 1835.6, 1846.1, 1844.9, 1824.9, 1840.5, 1905.2, and 1824.7 cm^{-1} for 7-diethyl amino-4-methyl coumarin, 7-hydroxy-4-trifluoromethyl coumarin, 7-methoxy-4-trifluoromethyl coumarin, 6,7-dihydroxy-4-trifluoromethyl coumarin, 7-diethyl amino coumarin, 5,7- dimethoxycoumarin, and 5,7-dihydroxy-4-methyl coumarin respectively.

NBO analysis:. The most important role of NBO analysis is that it gives information about interactions in both filled and virtual orbital spaces that could enhance the analysis of the intermolecular interaction and intra molecular interaction. The interaction result is the loss of occupancy from the localized NBO of the idealized Lewis structure into an empty non- Lewis orbital. Delocalization of electron density between occupied Lewis type (bond or lone pair) NBO orbital and formally unoccupied (antibonding) non- Lewis NBO orbital correspond to a stabilizing donor-acceptor interaction. The NBO analysis at C_1-C6, C_2-O_{14}, O_3-C_4, C_5-C_{10} and C_8-C_9 orbitals of coumarin derivatives. The electron density of six conjugated single bond of aromatic ring (~1.9 e) demonstrate strong delocalization [12].The C-C bond of the seven coumarin compounds in benzene ring leads to the σ bond and have approx 1.9 electron density thus these bonds are work as electron donor.

IV. CONCLUSION

Glide docking uses a series of hierarchical filters to find the best possible ligand binding locations in a prebuilt receptor grid space that represents the shape and properties of receptors. It evaluates the energy interactions of the ligand with the protein in terms of Gscore value which is used for predicting binding affinity. All the possible interactions of the investigated compounds at the active site and the probable ligand binding conformations then will help in providing an improved basis for structure-based rational design. NBO analysis provided the accurate 'natural Lewis structure' picture of molecule, because all the orbital are mathematically chosen to include the highest possible percentage of the electron density.

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REFERENCES

[1] Murray, R. D. H.; Mendez, J.; Brown, S. A. In The Natural Coumarins: Occurrence Chemistry and Biochemistry; John Wiley& Sons: New York, 1982.

[2] T. Patonay, G. Litkei, R. Bognar, J. Eredi, C. Miszti, Pharmazie ,39, 1984, 86–91

[3] A.H. Bedair, N.A. El-Hady, M.S. Abd El-Latif, A.H. Fakery, A.M. El-Agrody, Farmaco ,55 2000, 708.

[4] D.A. Egan, P. James, D. Cooke, R. O'Kennedy, Cancer Lett, 118,1997, 201.

[5] Lacy, A.; O'Kennedy, R. Studies on coumarins and coumarin-related compounds to determine their therapeutic role in the treatment of cancer. Curr. Pharm. Des, 10,2004, 3797–3811.

[6] Coumarin as Attractive Casein Kinase 2 (CK2) Inhibitor Scaffold: An Integrate Approach To Elucidate the Putative Binding Motif and Explain Structure–Activity Relationships, J. Med. Chem. , 51,2008, 752–759

[7] Litchfield, D. W. Protein kinase CK2: Structure, regulation and role in cellular decisions of life and death. Biochem. J., 369,2003, 1–15.\

[8] Guo, C.; Yu, S.; Wang, H.; Davis, A. T.; Green, J. E.; Ahmed, K. A potential role of nuclear matrix-associated protein kinase CK2 in protection against drug-induced apoptosis in cancer cells. J. Biol. Chem., 276, 2001,5992–5999.

[9] Tawfic, S.; Yu, S.; Wang, H.; Faust, R.; Davis, A.; Ahmed, K. Protein kinase CK2 signal in neoplasia. Histol. Histopathol ,16, 2001,573–582.

[10] a. De Moliner, E.; Moro, S.; Sarno, S.; Zagotto, G.; Zanotti, G.; Pinna,L. A.; Battistutta, R. Inhibition of protein kinase CK2 by anthraquinone- related compounds. A structural insight. J. Biol. Chem,, 278,2003, 1831–1836.

[10] b. Meggio, F.; Pagano, M. A.; Moro, S.; Zagotto, G.; Ruzzene, M.; Sarno,S.; Cozza, G.; Bain, J.; Elliott, M.; Deana, A. D.; Brunati, A. M.; Pinna, L. A. Inhibition of protein kinase CK2 by condensed polyphenolic derivatives. An in vitro and in vivo study. Biochemistry, 43,2004, 12931–12936.

[11] Schrödinger, LLC, New York, NY, 2012; Jaguar version 7.9, Lig prep version 2.6, Glide version 5.8.

[12] R.N singh, Amit Kumar, R.K. Tiwari, Poonum Rawat, Vikas Baboo, Divya Verma , Spectrochimica Acta Part A 92, 2012**,** 295-304.

[13] D.Sajan, Y. Erdogdu, R. Reshmy, O. Dereli, K. Kurien Thomas, I. Hubert Joe, Spectrochimica Acta Part A 82,2011**,** 118-125.

[14] S. Muthu, J. Uma Maheswari, spectrochimica Acta Part A, 92, 2012, 154-163.