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Theoretical Study of Flavopiridol Binded to Transition Metals

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ABSTRACT

More recently medical chemistry research has been focused on proteins that drive and control cell cycle progression. Among them, the cyclin dependent kinases (cdk's) are a group of serine/threonine kinases, which rule the transition between successive stages of the cell cycle. The activity of cdk's is regulated by multiple mechanisms, including binding to cyclins, which is a broad class of positive regulatory cdk-binding proteins. Among the chemical agents that act selectively as cdk inhibitors are flavonoids,flavopiridol is a semisynthetic flavonoid.Theoretical study is performed on flavopiridol using quantum chemical calculations. Interactions between flavopiridol with transition metals were studied at HF/6-31G*, and HF/6-311G** levels of theory.

Method: *Ab initio* method at HF level of theory was used.
***Results*:** Conformations, optimized parameters, bond length, were computed for metalated and isolated flavopiridol.
Conclusions: Flavopiridol can be Metalated from its binding sites (oxo and hydroxyl groups) and the energies of these compounds were computed.
***Abbreviations and notations*:** HF, Hartree-Fock; Cdk , Cyclin dependent kinases.
***Keywords*:**conformations; comformational analysis; metalated flavopiridol; flavopiridol; transition metal; Ab initio ;HF

INTRODUCTION

Flavonoids are poly phenolic substances naturally present in vegetables, fruits and tea(figure1)[1].A large number of epidemiological studies have suggested that flavonoids exhibit biological activities, including antiallergenic antiviral, anti-inflammatory, and vasodilating actions. The antioxidant activity of flavonoids, is due to their ability to reduce free radical formation and to scavenge free radicals (figure2)[2].

A number of flavonoids efficiently chelate trace metals, which play an important role in oxygen metabolism (figure3). Free iron, copper and other transition metals are potential enhancers of reactive oxygen species formation, as exemplified by the reduction of hydrogen peroxide with generation of the highly aggressive hydroxyl radical, which is very reactive and rapidly attack the molecules in nearby cells, and probably the damage caused by is unavoidable and is dealt with by repair process.

The various classes of flavonoids differ in the level of oxidation and pattern of substitution of its rings. Flavopiridol, also known as L86-8275,[(-)-cis-5,7-dihydroxy - 2 - (2 – chlorophenyl) -8- [4- (3- hydroxy l -1-methyl)-piperidinyl]-4H-benzopyran-4-one] or HMR 1275 is a semi synthetic flavonoid [3] derived from rohitukine,an alkaloid isolated from a plant indigenous to India[4](figure4) However most interest has been devoted to flavopiridol because of:

1. Its high potency to inhibit the proliferation of a broad range of human tumor cell lines after prolonged exposure time
2. Its potency to inhibit tyrosine kinases and serine kinases[5,6]
3. The discrepancies between its high degree of cytoxicity
4. Its potency to inhibit known kinases as well as the lack of correlation between its cytoxicity and the sensitivity of the respective test cells to growth factors
5. Its potency to inhibit in vivo a broad type range of human tumors, leukemias and lymphomas [7-13].

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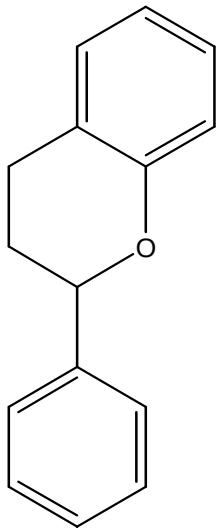

Fig.1. Flavonoid

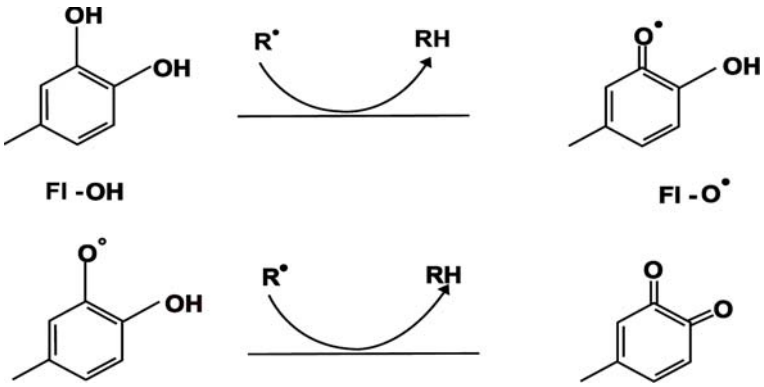

Fig. 2. Scavenging of free radicals by flovonoids

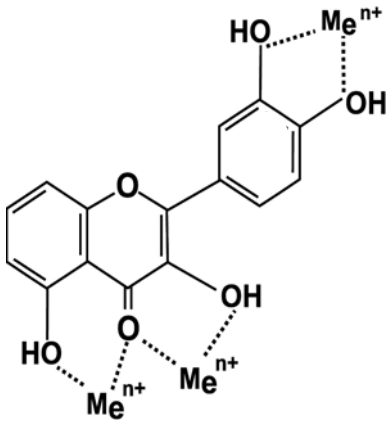

Fig.3. Binding sites for trace metals

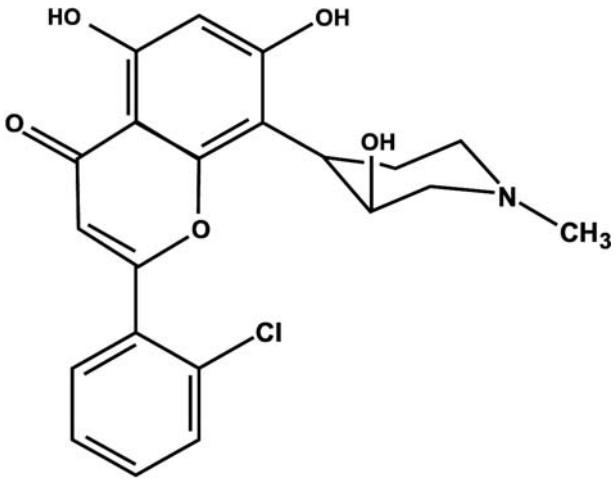

Fig. 4. Flovopiridol

COMPUTATIONAL METHODS

GAUSSIAN 98 is used to perform Hartree-Fock (HF) calculations on flavopiridol [14]. First for conformational analysis the molecule was divided in two parts :in one part rotation of cyclohexzene group around ω_1 for every 15° (0°-180°) and in another part rotation of *o*-chlorophenyl group around ω_2 for every 15° (-77°-148°) with respect to the rest of the molecule were carried out (Figure 5). Metalation of flavopiridol was performed at HF/6-31G*, and HF/6-311G** levels of theory. Transition metals are described by effective core potential (ECP) of Wadt and Hay pseduopotential with a double ζ valance using the LANL2DZ.

RESULTS AND DISCUSSION

1. Isolated flavoropriridol

1.1 Rotational Energies

Graphical representation of cyclohexazene and o-chlorophenyl torsional potential are shown in Figure 6. We suggested that the barrier at 45° and 150° of rotation of cyclohexazene and at 0° and 180° of rotation of o-chlorophenyl show the transition states.

1.2 Geometry Parameters.

The optimized geometries are summarized in Tables 1and 2 .Excluding C1-C6, C3-C4, C4-C5, C5-C6, C5C15, C24-C25, C25-C27 and C27-C28 bonds the rest of the bond lengths in flavopiridol range from1.37 to1.39 Å(figure7) this may suggest that flavopiridol is a conjugated molecule with a Л electron delocalized system[15].

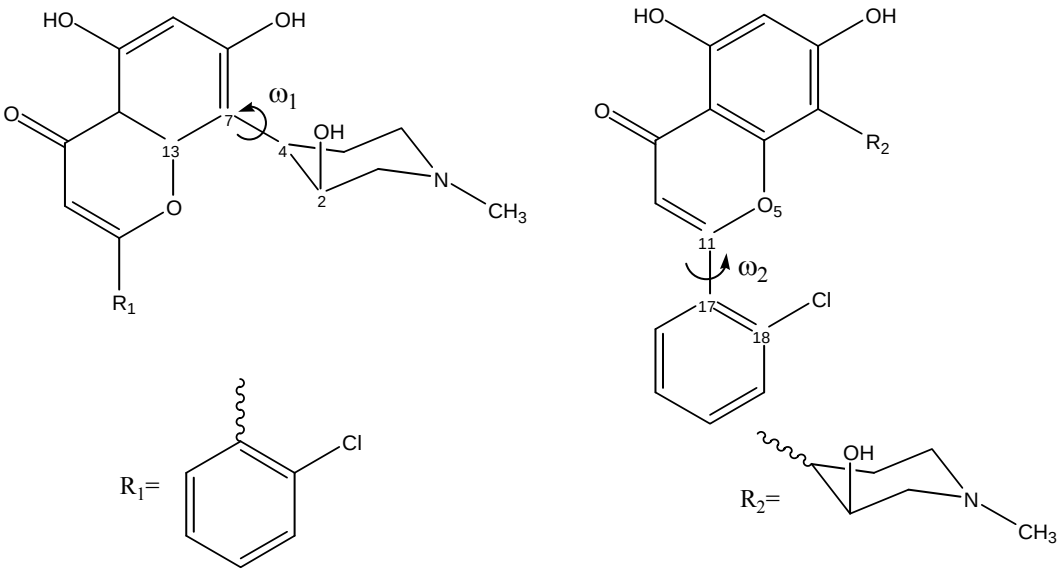

Fig.5. Rotation around ω_1 and ω_2.

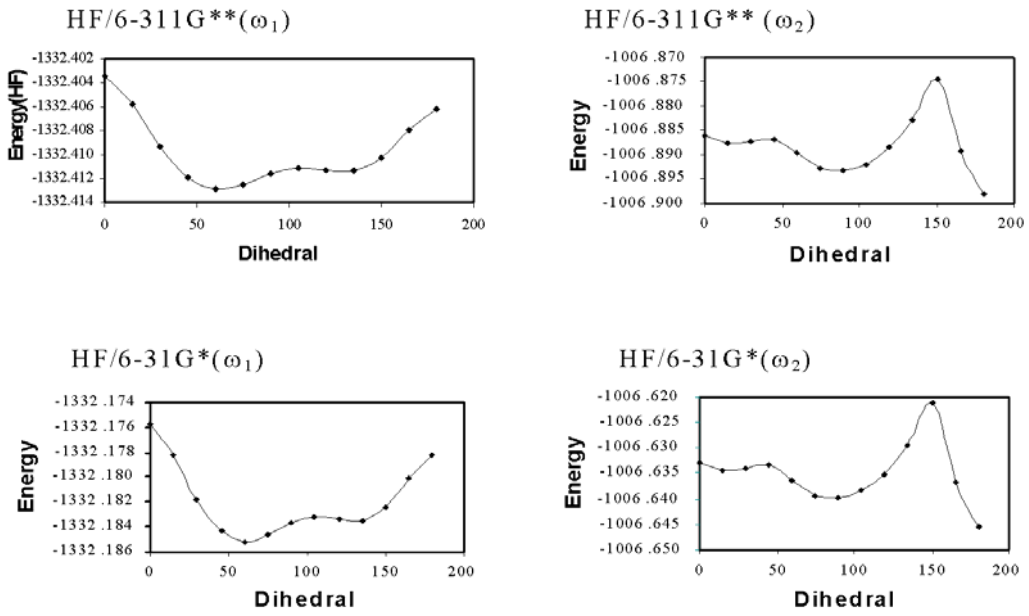

Fig. 6. Torsional energy profile plots

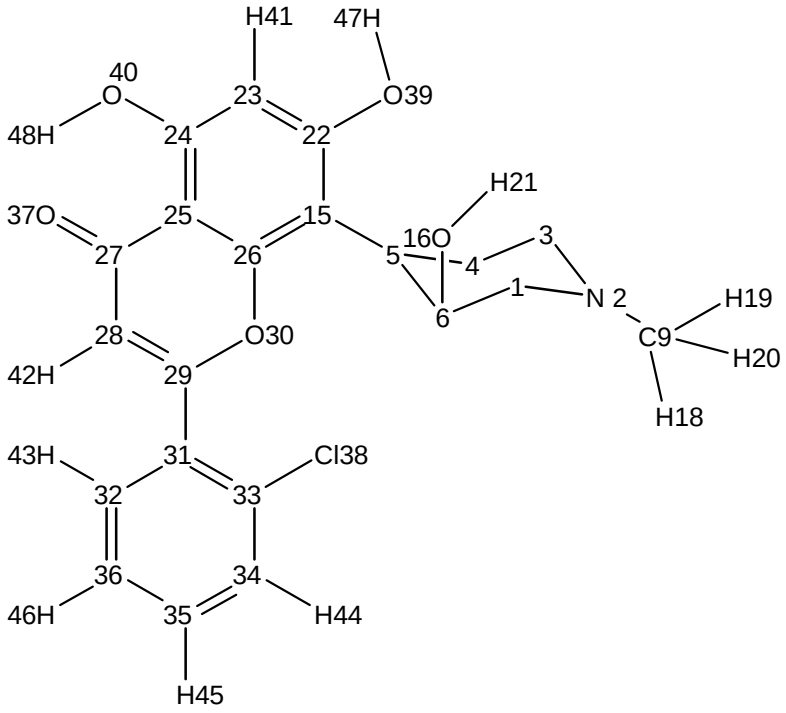

Fig. 7. Nomenclatured Flovopiridol

Table 1. Optimized bond lengths (rotation around ω_1)

	Minimum		Transition state	
	Regular optimization		HF/6-311G**	
	HF/6-31G*	HF/6-311G**	at 45 degree	at 150 degree
bond length (A^0)				
C6-O16	1.4169	1.4162	1.3969	1.4007
O16-H21	0.9529	0.9457	0.9431	0.9427
O16-H47	1.7556	1.7545	-	-
C5-C6	1.538	1.5374	1.5524	1.5578
C1-C6	1.5258	1.5246	1.5321	1.5242
C6-H17	1.0822	1.0827	1.0838	1.0729
C5-C15	1.5286	1.5284	1.5314	1.5547
C4-C5	1.5396	1.5389	1.5371	1.5442
C5-H14	1.0803	1.08	1.0874	1.0945
C1-N2	1.4534	1.4527	1.4547	1.4457
C1-H7	1.0842	1.0847	1.0838	1.0843
C1-H8	1.0929	1.0941	1.0947	1.0971
C15-C26	1.401	1.4007	1.4015	1.4091
C15-C22	1.3958	1.3941	1.3907	1.3969
C3-C4	1.5295	1.5286	1.5299	1.5269
C4-H13	1.0837	1.0842	1.0847	1.0853
C4-H12	1.0849	1.0853	1.0867	1.0755
N2-C3	1.4578	1.4574	1.4543	1.4479
N2-C9	1.4482	1.4481	1.4472	1.4464
C26-O30	1.3558	1.3541	1.3377	1.3496
C25-C26	1.3982	1.3968	1.3954	1.4004
C22-C23	1.3924	1.392	1.3912	1.3876
C22-O39	1.3338	1.332	1.3445	1.35
C3-H11	1.0841	1.0845	1.0847	1.085
C3-H10	1.0951	1.0966	1.0985	1.0982
C9-H19	1.0835	1.0841	1.0843	1.0844
C9-H18	1.0926	1.0943	1.0947	1.095
C9-H20	1.0837	1.0843	1.0841	1.0842
C29-O30	1.3409	1.3388	1.3335	1.3365
C24-C25	1.4107	1.4104	1.4102	1.4067
C25-C27	1.4806	1.4811	1.4838	1.4841
C23-C24	1.3737	1.3722	1.3723	1.37
C23-H41	1.0749	1.0749	1.0747	1.0746
O39-H47	0.9583	0.9522	0.9382	0.9388
C24-O40	1.3334	1.3311	1.3304	1.3304
C27-O37	1.1981	1.1924	1.1929	1.1923
C27-C28	1.4713	1.4718	1.47	1.4686
C28-C29	1.3193	1.3182	1.3204	1.3175
C29-H31	1.0717	1.0724	1.0718	1.0725
O40-H48	0.9476	0.941	0.941	0.9411
C28-H42	1.072	1.0722	1.0721	1.072
E(Hartree)	-1006.64559822	-1006.897923170	-1006.88663047	-1006.87451600
E(kcal/mol)	-632173.43568216	-632331.89575076	-632324.80393516	-632317.19604800
ΔE(kcal/mol)	0	0	-7.09181560	-14.69970276

Table 2. Optimized bond lengths (rotation around ω_2)

	Minimum		Transition state	
	Regular optimization		HF/6-311G**	
	HF/6-31G*	HF/6-311G**	At 0 degree	At 180 degree
bond length (A^0)				
C15-C26	1.3878	1.3876	1.3881	1.3891
C15-C22	1.3782	1.3768	1.3766	1.3771
C15-H5	1.0739	1.0737	1.0732	1.0738
C26-O30	1.3472	1.3453	1.344	1.3427
C25-C26	1.3921	1.3903	1.3874	1.3866
C22-C23	1.3925	1.3921	1.3929	1.3922
C22-O39	1.3402	1.338	1.338	1.338
C29-O30	1.3467	1.3444	1.3394	1.3555
C24-C25	1.4151	1.415	1.4149	1.4147
C27-C25	1.4782	1.4787	1.474	1.4737
C23-C24	1.3784	1.377	1.3763	1.3768
C23-H41	1.0747	1.0747	1.0747	1.0746
O39-H47	0.9477	0.9412	0.9412	0.9411
C24-O40	1.3322	1.3295	1.3295	1.3287
C27-O37	1.1979	1.1922	1.1935	1.1925
C27-C28	1.4728	1.4734	1.4711	1.4748
C28-C29	1.3256	1.3237	1.3309	1.3282
C29-C31	1.4861	1.4863	1.495	1.4951
O40-H48	0.9476	0.9411	0.9411	0.9411
C28-H42	1.0719	1.0719	1.0676	1.0629
C31-C33	1.3924	1.3905	1.3984	1.4001
C31-C32	1.3906	1.3893	1.4013	1.4001
C33-Cl38	1.7423	1.7423	1.7483	1.7456
C33-C34	1.3826	1.3812	1.3897	1.3847
C32-C36	1.3837	1.3829	1.3741	1.3783
C32-H43	1.0741	1.0742	1.0698	1.0685
C34-C35	1.3846	1.3835	1.3751	1.3786
C34-H44	1.0731	1.0731	1.0725	1.0727
C35-C36	1.3831	1.3822	1.3842	1.3809
C36-H46	1.0744	1.0745	1.0743	1.0745
C35-H45	1.0747	1.0749	1.0746	1.0747
E(Hartree)	-1332.18514832	-1332.41286963	-1332.40344155	-1332.40619701
E(kcal/mol)	-836612.27314496	-836755.28212764	-836749.36129340	-836751.09172228
ΔE(kcal/mol)	0	0	-5.92083424	-4.19040536

2. Metalated flavoropriridol

Energies of metalated flavopiridol were computed (table3) and the optimized geometry parameteres are in good agreement with geometry parameters of suggested transition states.

Table 3. Computed energies of flavopiridol-transition metal compounds

Complex	**Energy**(Hartreee)
Flavopiridol-W	-1761.2157666
Flavopiridol-Re	-1771.8465315
Flavopiridol-Os	-1784.3588231
Flavopiridol-Ir	-1797.4388279
Flavopiridol-Pt	-1812.4795186
Flavopiridol-Au	-1829.2313873
Flavopiridol-Hg	-1735.4702723

CONCLUSIONS

In this paper we concluded that:

1. There are four transition states at 45º, 150º, 0 ºand 180º tortional angles.
2. We are dealing with a JI electron delocalized system.
3. All structural parameters were calculated for isolated and metalated flavopiridol
4. Complexes of lavopiridol with Pt and Au are more stabilized than the others.

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