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New Insight to Hair-Loss as a Side Effect of Some Drugs

AHMAD R. BEKHRADNIA*, MOHAMMAD ALI EBRAHIMZADEH†,
VAHID HEJAZI†, REZA GORJI† and ESMAEEL VESSALLY†
Department of Chemistry and Pharmaceutical Science Research Center
Mazandaran University of Medical Sciences, Sari, Iran
E-mail: reza_bnia@yahoo.com

Geometrical optimizations and frequency calculations were performed for some drugs with hair-loss as side effect. Cimetidine, metoprolol, etretinate and doxepin apart from the more common effects, were selected. The calculations were carried out at the Hartree-Fock (HF) level of theory using 6-31G* basis sets. All of the mentioned drugs were portrayed that the structural requirements include an electron-rich functional group in the plane of and separated from the center of an aromatic ring by *ca.* 7.68 Å. On the basis, one may realize that the related distance, is important and effective factor in structure of drugs with hair-loss side effect. The *ab initio* calculated thermodynamic data and geometrical parameters are also given for clear molecular structures.

Key Words: *ab initio*, Hair-loss (Alopecia), Conformation, Electron-rich functional group.

INTRODUCTION

Alopecia (hair-loss) has many causes. Alopecia may also be congenital, be associated with systemic disorders, severe emotional and physical stress, or skin disorders, or due to nutritional deficiencies. The most common form, male-pattern alopecia, is androgen-related[1-4]. Some drugs may cause alopecia *e.g.*, some H_2-blockers, β-blockers, anti-depressants and retinoids[5-7]. In some cases there is destruction of the hair follicles (scarring) resulting in permanent hair-loss. If the hair follicles remain intact (non-scarring alopecia) then treatment of the underlying condition or removal of the suspected drug may produce hair regrowth. Drug treatment may be tried in alopecia areata and male-pattern alopecia, although it is often unsuccessful[8]. Cytotoxic drugs may cause alopecia by eigher anagen or telogen effluvium[9-11]. In continuation of our research program dealing with molecular modelling of chemical molecules[12-14], we were interested in molecular structure relationship and side effect of the drugs. In this study, some drugs apart from more common effects and their patterns of drug-induced hair-loss (as side effect) were selected. These are included cimetidine (2-cyano-1-methyl-3-[2-(5-methylimidazol-4-ylmethylthio)ethyl]guanidine) as a H_2-blocker, metoprolol 1-isopropylamino-3-[4-(2-methoxyethyl)phenoxy]propan-2-ol as a β-blocker, etretinate ethyl (all-*trans*)-9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethylnona-2,4,6,8-tetra-enoate with retinoid structure and doxepin (E)-3-

†Payame Nour University (PNU), Zanjan, Iran.

(dibenz[b,e]oxepin-11-ylidene)propyldimethyl-amine as a tricyclic anti-depressant drug. Up to now, no report has appeared on the conformational analysis of the mentioned drugs. In this paper, geometrical optimization, thermodynamic data and hair-loss effects relationship with molecular structure were reported for cimetidine, metoprolol, etretinate and doxepin at the Hartree-Fock (HF) level of theory using 6-31G* basis set (Fig. 1).

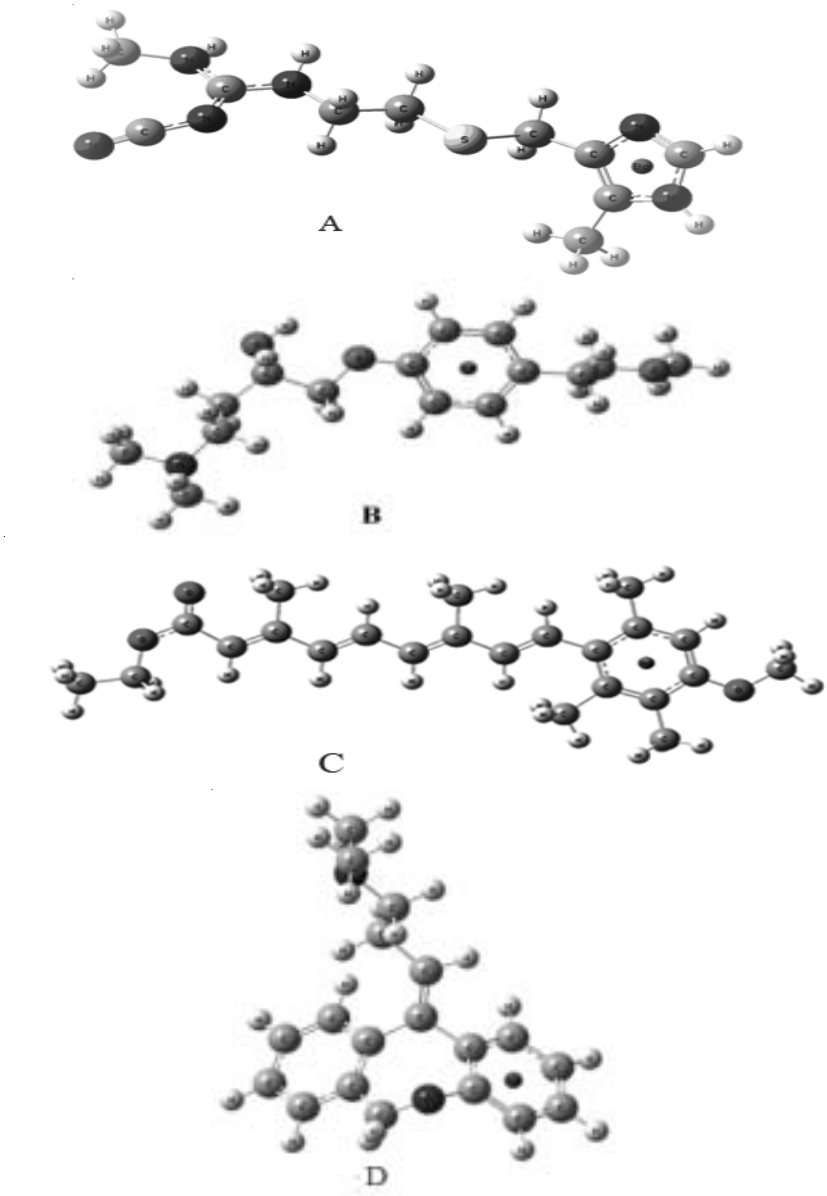


Fig. 1. Final optimized conformers of cimetidin (A), metoprolol (B), etretinate (C) and doxepin (D) obtained through HF/6-31G* calculations

RESULTS AND DISCUSSION

Complete geometry optimizations were performed on the cimetidine, metoprolol, etretinate and doxepin molecules. All structures were optimized at the Hartree-Fock[15] level of theory with the 6-31G* basis set[16]. The frequency calculations were done at the same level to determine the nature of the optimized structures to obtain zero-point energies (un-scaled) and thermo-chemical corrections. All calculations were carried out using the Gaussian 98 program[17]. Thermodynamic data of these drugs were calculated at HF/6-31G* level and are shown in Table-1.

TABLE-1
HF/6-31G* OPTIMIZED THE CORRECTED THERMAL ENERGIES (E), THERMAL ENTHALPIES (H) AND THERMAL FREE ENERGIES (G), IN kcal mol^{-1}, FOR CIMETIDINE, METOPROLOL, ETRETINATE AND DOXEPIN MOLECULES

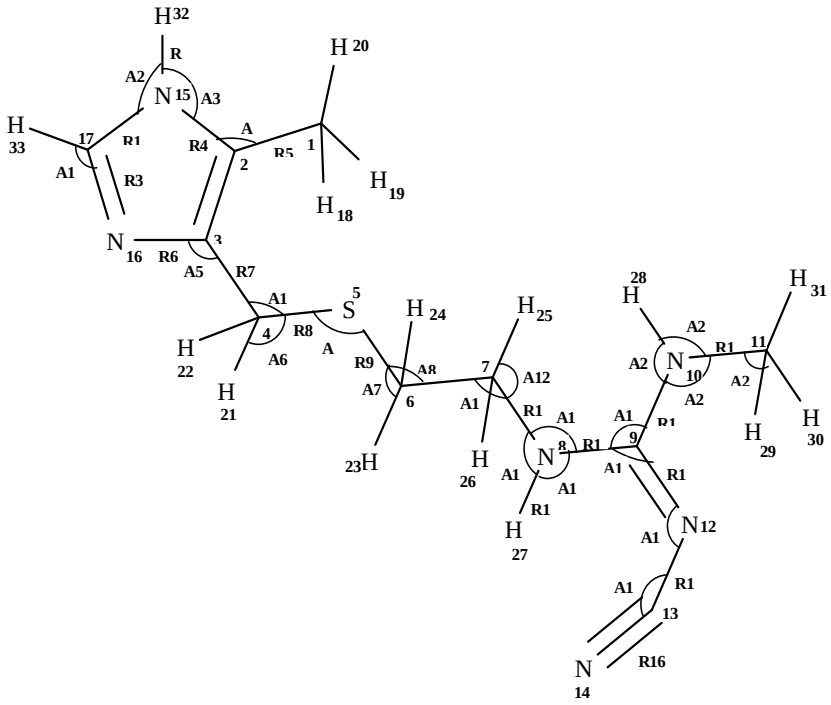
Drug molecule	Thermal energies (E)	Thermal enthalpies (H)	Gibbs free energies (G)
Cimetidine	-697531.2906	-697530.1710	-697613.2142
Metoprolol	-540115.8148	-540114.6952	-540202.6217
Etretinate	-575468.1817	-575467.0621	-575557.6516
Doxepin	-539799.9557	-539798.8362	-539876.3918

The calculation of thermal energies (E), thermal enthalpies (H) and thermal Gibbs free energies (G) have also included in present work. These are along with the calculated geometrical parameters such as bond length, bond angles and dihedral angles (Tables 2-5). In order to evaluate scope and investigation of these different drugs as their similar side effect, the geometrical center of the aromatic rings were served as the most easily defined reference point. The electron-rich functional group was considered in the plane of and separated from the aromatic ring center. The measurement of distance parameter between the related electron functional group and defined reference point was employed Gaussian and its correlated softwares. This parameter is one of the most important factors in description of relationships in structure and reactivity and it is used to explain some pharmacokinetic properties and biological effects of drugs[8,18].

The major structural features of these molecules are briefly summarized in Fig. 1. For the best selection of electron-rich functional group in mentioned drugs and also a deeper investigation, it was used the calculated NBO atomic charges shown in Tables 2-5.

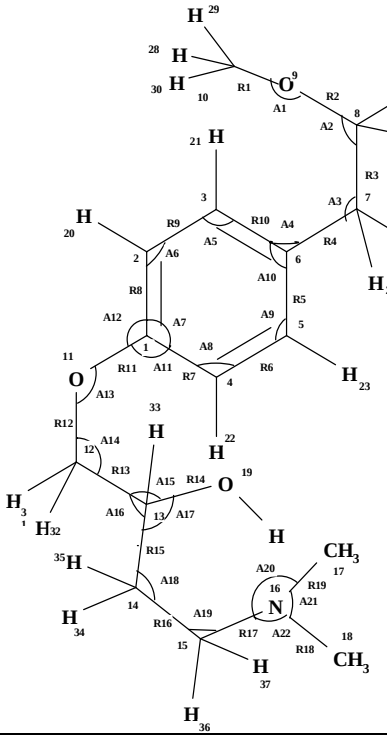
The related atom in each drugs were selected as follows: the nitrogen atom which is connected to ethyl group in cimetidine, the nitrogen atom of isopropylamine group in metoprolol, the C_5 of ethylenic carbon in etretinate, the nitrogen atom of dimethylamine group in doxepin. Accordingly, the calculated distance of aromatic ring center from a desired hetero-atom was 7.65 Å for cimetidine, 7.98 Å for metoprolol, 7.68 Å for etretinate and 7.40 Å for doxepin.

TABLE-2
HF/6- 31G* OPTIMIZED CONFORMER, OPTIMIZED BOND LENGTH (Å), OPTIMIZED ANGLES (DEGREE), OPTIMIZED DIHEDRAL ANGLES (DEGREE) AND NATURAL CHARGES ARE SHOWN FOR CIMETIDIN MOLECULE



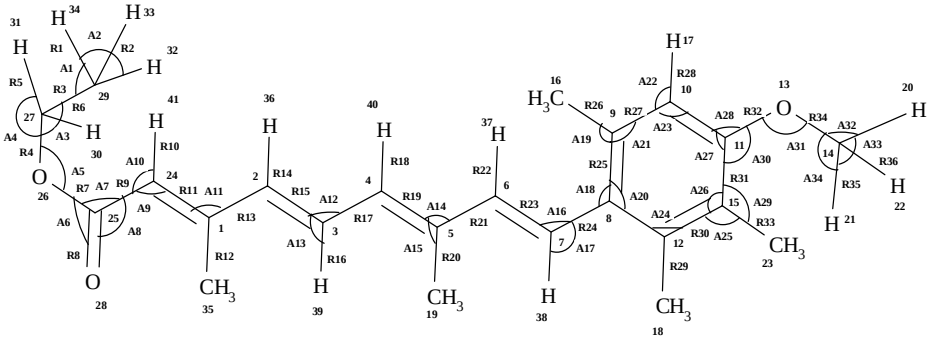
Entry	Dihedral angles (º)	Entry	Bonding angles (º)	Entry	Bonding length (Å)	Entry	Natural charge
33,17,15,32	0.648	A_1	125.778	R_1	1.3507	1	-0.66245
33,17,16,3	179.721	A_2	126.328	R_2	0.9944	2	0.14698
33,17,15,2	179.845	A_3	126.324	R_3	1.2851	3	0.08013
16,17,15,2	-0.112	A_4	122.452	R_4	1.3735	4	-0.57533
17,15,2,3	0.174	A_5	120.535	R_5	1.4950	5	0.22681
15,2,3,16	-0.1803	A_6	108.934	R_6	1.3761	6	-0.59283
16,3,2,1	179.733	A_7	108.889	R_7	1.4959	7	-0.20729
17,15,2,1	-179.751	A_8	110.016	R_8	1.8260	8	-0.72070
1,2,3,4	0.197	A_9	99.630	R_9	1.8154	9	0.84672
2,3,16,17	0.116	A_{10}	111.024	R_{10}	1.4556	10	-0.73036
16,3,4,22	141.369	A_{11}	109.059	R_{11}	0.9971	11	-0.40585
16,3,4,5	-97.530	A_{12}	108.050	R_{12}	1.3604	12	-0.76241
2,3,4,5	81.965	A_{13}	115.277	R_{13}	1.2883	13	0.50932
2,3,4,22	-39.135	A_{14}	114.953	R_{14}	1.3518	14	-0.49099
21,4,5,6	56.732	A_{15}	122.045	R_{15}	1.3269	15	-0.63260
22,4,5,6	-61.207	A_{16}	117.922	R_{16}	1.1426	16	-0.55027
4,5,6,7	176.455	A_{17}	113.521	R_{17}	1.4538	17	0.27686

TABLE-3
HF/6- 31G* OPTIMIZED CONFORMER, OPTIMIZED BOND LENGTH (Å), OPTIMIZED ANGLES (DEGREE), OPTIMIZED DIHEDRAL ANGLES (DEGREE) AND NATURAL CHARGES ARE SHOWN FOR METOPROLOL MOLECULE



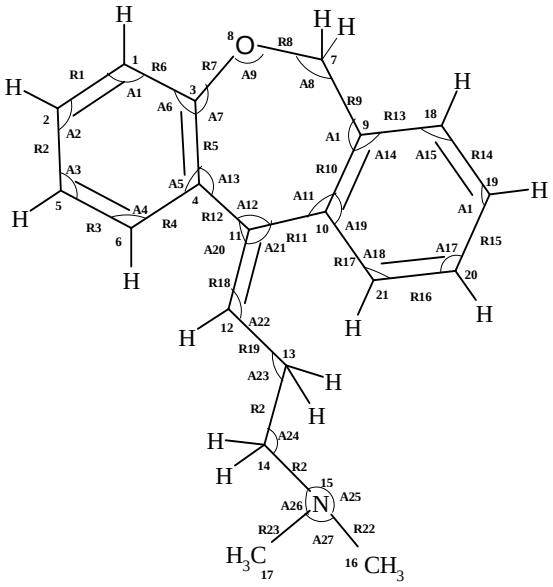
Entry	Dihedral angles (º)	Entry	Bonding angles (º)	Entry	Bonding length (Å)	Entry	Natural charge
33,27,20,16	179.923	A_1	114.247	R_1 (33,27)	1.39242	1	0.37912
27,20,16,10	179.791	A_2	108.337	R_2 (27,20)	1.39527	2	-0.27495
20,16,10,5	-86.9208	A_3	112.325	R_3 (20,16)	1.52419	3	-0.19114
20,16,10,6	91.8066	A_4	121.137	R_4 (16,10)	1.51343	4	-0.31993
6,10,5,2	-0.225859	A_5	121.569	R_5 (10,5)	1.39596	5	-0.18726
10,5,2,1	0.0435622	A_6	120.122	R_6 (5,2)	1.37694	6	-0.08266
5,2,1,3	0.144322	A_7	119.437	R_7 (2,1)	1.39200	7	-0.44859
2,1,3,6	-0.141923	A_8	119.501	R_8 (1,3)	1.38363	8	-0.01471
1,3,6,10	-0.0482928	A_9	122.016	R_9 (3,6)	1.39154	9	-0.64817
3,6,10,5	0.22849	A_{10}	117.356	R_{10} (6,10)	1.38320	10	-0.22042
3,1,4,7	0.2899	A_{11}	124.528	R_{11} (1,4)	1.35334	11	-0.63436
2,1,4,7	-179.411	A_{12}	116.035	R_{12} (7,4)	1.40721	12	-0.05892
1,4,7,11	-177.934	A_{13}	120.438	R_{13} (7,11)	1.52043	13	0.14694
4,7,11,18	59.6689	A_{14}	106.453	R_{14} (11,18)	1.40298	14	-0.46013
4,7,11,17	178.957	A_{15}	109.432	R_{15} (11,17)	1.52649	15	-0.20237
7,11,17,21	75.6009	A_{16}	113.155	R_{16} (17,21)	1.52937	16	-0.56042
18,11,17,21	-163.754	A_{17}	107.059	R_{17} (21,28)	1.45249	17	-0.40117
11,17,21,28	-172.162	A_{18}	113.783	R_{18} (28,35)	1.44790	18	-0.40683
17,21,28,34	166.769	A_{19}	113.057	R_{19} (28,34)	1.44787	19	-0.80654
17,21,28,35	-67.2597	A_{20}	111.374	–	–	20	0.23765
–	–	A_{21}	113.379	–	–	21	0.22772

TABLE-4
HF/6- 31G* OPTIMIZED CONFORMER, OPTIMIZED BOND LENGTH (Å), OPTIMIZED ANGLES (DEGREE), OPTIMIZED DIHEDRAL ANGLES (DEGREE) AND NATURAL CHARGES ARE SHOWN FOR ETRETINATE MOLECULE



Entry	Dihedral angles (º)	Entry	Bonding angles (º)	Entry	Bonding length (Å)	Entry	Natural charge
32,29,27,30	60.0929	A_1	110.411	R_1	1.08392	1	-0.09411
34,29,27,30	-59.9937	A_2	108.738	R_2	1.83920	2	-0.26375
32,29,27,26	180.0000	A_3	107.091	R_3	1.51513	3	-0.15969
33,29,27,26	-59.9134	A_4	110.066	R_4	1.41466	4	-0.24777
34,29,27,26	59.9134	A_5	124.132	R_5	1.08417	5	-0.17695
29,27,26,25	180.0000	A_6	118.581	R_6	1.08417	6	-0.23856
30,27,26,25	-59.7839	A_7	118.590	R_7	1.33828	7	-0.16857
31,27,26,25	59.7839	A_8	122.829	R_8	1.50000	8	-0.12052
27,26,25,28	180.0000	A_9	119.497	R_9	1.46000	9	-0.16741
27.26.25.24	0.0000	A_{10}	120.207	R_{10}	1.07232	10	-0.27716
26,25,24,41	0.0000	A_{11}	124.597	R_{11}	1.33145	11	0.39313
28,25,24,41	180.0000	A_{12}	124.556	R_{12}	1.07566	12	-0.16420
28,25,24,1	0.0000	A_{13}	118.915	R_{13}	1.45400	13	-0.60664
26,25,24,1	180.0000	A_{14}	124.501	R_{14}	1.07747	14	-0.22780
24,1,2,3	180.0000	A_{15}	119.003	R_{15}	1.33399	15	-0.33371
35,1,2,3	0.0000	A_{16}	127.905	R_{16}	1.07790	16	0.22607
7,8,9,16	0.0000	A_{17}	114.529	R_{17}	1.45479	17	0.24195
12,8,9,10	0.0000	A_{18}	123.723	R_{18}	1.07775	18	0.22622
9,10,11,15	0.0000	A_{19}	120.117	R_{19}	1.33363	19	0.21451
10,11,15,12	0.0000	A_{20}	117.112	R_{20}	1.07874	20	0.21212
8,12,15,11	0.0000	A_{21}	121.454	R_{21}	1.45598	21	0.18458
18,12,15,11	180.0000	A_{22}	121.174	R_{22}	1.07716	22	0.18458
12,15,11,13	180.0000	A_{23}	120.426	R_{23}	1.33153	23	0.23270
10,11,13,14	180.0000	A_{24}	122.266	R_{24}	1.47094	24	-0.41717
15,11,13,14	0.0000	A_{25}	118.347	R_{25}	1.40181	25	0.97296
11,13,14,20	180.0000	A_{26}	119.490	R_{26}	1.07518	26	-0.64801
11,13,14,22	61.2188	A_{27}	119.252	R_{27}	1.37152	27	-0.03828
11,13,14,21	-61.2188	A_{28}	115.805	R_{28}	1.07346	28	-0.69153
–	–	A_{29}	121.317	R_{29}	1.07580	29	-0.65080
–	–	A_{30}	124.943	R_{30}	1.38950	30	0.19161
–	–	A_{31}	119.724	R_{31}	1.38315	31	0.19161

TABLE-5
HF/6- 31G* OPTIMIZED CONFORMER, OPTIMIZED BOND LENGTH (Å), OPTIMIZED ANGLES (DEGREES), OPTIMIZED DIHEDRAL ANGLES (DEGREES) AND NATURAL CHARGES ARE SHOWN FOR DOXEPIN MOLECULE



Entry	Dihedral angles (º)	Entry	Bonding angles (º)	Entry	Bonding length (Å)	Entry	Natural charge
3,1,2,5	-0.190667	A_1	120.531	R_1 (1,2)	1.38700	1	-0.20316
1,2,5,6	0.0482365	A_2	115.642	R_2 (2,5)	1.38300	2	-0.22957
2,5,6,4	0.336578	A_3	120.152	R_3 (5,6)	1.38738	3	-0.07722
5,6,4,3	-0.382939	A_4	120.370	R_4 (6,4)	1.38702	4	-0.02544
6,4,3,1	0.14429	A_5	119.432	R_5 (4,3)	1.39503	5	-0.21353
4,3,1,2	0.142093	A_6	119.872	R_6 (3,1)	1.38386	6	-0.21401
4,3,7,8	71.4701	A_7	118.151	R_7 (3,7)	1.50659	7	-0.03068
3,7,8,9	-65.3046	A_8	112.990	R_8 (7,8)	1.40837	8	-0.61739
7,8,9,10	8.73278	A_9	122.555	R_9 (8,9)	1.35161	9	0.40088
8,9,10,11	1.48959	A_{10}	126.539	R_{10} (9,10)	1.39838	10	-0.14960
9,10,11,4	46.9547	A_{11}	124.263	R_{11} (10,11)	1.49955	11	-0.05478
10,11,4,3	-61.3466	A_{12}	115.941	R_{12} (11,4)	1.49655	12	-0.17066
11,4,3,7	-0.210142	A_{13}	118.177	R_{13} (9,18)	1.39441	13	-0.45950
10,9,18,19	0.896328	A_{14}	120.132	R_{14} (18,19)	1.37534	14	-0.19526
9,18,19,20	0.241522	A_{15}	121.100	R_{15} (19,20)	1.38708	15	-0.56217
18,19,20,21	-0.41018	A_{16}	119.835	R_{16} (20,21)	1.37791	16	-0.40049
19,20,21,10	-0.568084	A_{17}	118.946	R_{17} (21,10)	1.39934	17	-0.40488
20,4,10,9	1.65385	A_{18}	122.776	R_{18} (11,12)	1.32952	18	-0.27846
4,10,9,18	-1.78401	A_{19}	117.186	R_{19} (12,13)	1.50692	19	-0.19355
10,11,12,13	5.27032	A_{20}	119.409	R_{20} (13,14)	1.53231	20	-0.26667
4,11,12,13	-175.429	A_{21}	124.646	R_{21} (14,15)	1.45121	21	-0.17799
11,12,13,14	131.400	A_{22}	128.960	R_{22} (15,16)	1.44771	22	0.22746
12,13,14,15	-176.634	A_{23}	110.709	R_{23} (15,17)	1.44709	23	0.22939
13,14,15,16	161.357	A_{24}	113.242	–	–	24	0.22921
13,14,15,17	-72.4008	A_{25}	111.730	–	–	25	0.23278

TABLE-6
CALCULATED DISTANCE OF AN ELECTRON-RICH FUNCTIONAL GROUP FROM AROMATIC RING CENTER (A DEFINED REFERENCE POINT) WITH 95 % CONFIDENCE LIMITS ARE SHOWN FOR EACH DRUG MOLECULE

Drug molecules	Calculated distance of an electron-rich functional group from aromatic ring center (a defined reference point)	Calculated distances with 95 % confidence limits
Cimetidine	7.65 Å	7.68 ± 0.37 Å
Metoprolol	7.98 Å	
Etretinate	7.68 Å	
Doxepin	7.40 Å	

The arithmetic mean of the related calculated distance of above 4 drugs was found. The corresponding standard deviation was calculated in order to degrees of freedom. Then the calculated distances were extracted with 95 % confidence limits. As a result, it was found 7.68 ± 0.37 Å. Consequently, noticeable consistency was obtained between all of mentioned 4 molecules on these theoretical results (Table-6).

Conclusion

Ab initio calculations revealed a clear picture of these 4 drugs. The best related conformers were found in order of the calculated geometrical parameters in Tables 2-5. All optimized structures and thermodynamic data showed minimal structural requirements include an electron-rich functional group (amino nitrogen or ethylenic carbon) in the plane and separated from the center of an aromatic ring by *ca.* 7.68 ± 0.37 Å. Therefore, a theoretical attempt is made to avoid to hair-loss side effect and paving the way for the future synthesis in the laboratory.

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REFERENCES

1. V.H. Price, M. Angell and A.J.J. Wood, *N. Engl. J. Med.*, **341**, 964 (1999).
2. S.P. MacDonald Hull M.L. Wood, P.E. Hutchinson, M. Sladden and A.G. Mossenger, *Br. J. Dermatol.*, **149**, 692 (2003).
3. W.F. Bergfeld, *Am. J. Med.*, **98 (suppl 1A)**, 95S (1995).
4. R. Sinclair, *Br. Med. J.*, **317**, 865 (1998).
5. A. Levantine and J. Almeyda, *Br. J. Dermatol.*, **89**, 549 (1973).
6. M.L. Blankenship, *Australas J. Dermatol.*, **24**, 100 (1983).
7. M.B. Brodin, *Dermatol. Clin.*, **5**, 571 (1987).
8. S. Sweet, Martindale: The Complete Drug Reference, Pharmaceutical Press, China (2007).
9. B.J. Kerker and A.F. Hood, *Semin Dermatol.*, **8**, 173 (1989).

10. A. Rook and R. Dewber, Disease of the Hair and Scalp, Blackwell Scientfic Publication: Oxford, edn. 2 (1990).
11. P.K. Kutty, K.R.K. Raman, K. Hawken and J.A. Barrowman, *Ann. Intern. Med.*, **97**, 758 (1982).
12. M.Z. Kassaee, A.R. Bekhradnir and S. Arshadi, *Asian J. Chem.*, **20**, 43 (2008).
13. A.R. Bekhradnia and S. Arshadi, *Asian J. Chem.*, **19**, 5251 (2007).
14. A.r. Bekhradnia and S. Arshadi, *Monatsh. Chem.*, **138**, 725 (2007).
15. R. Weeny and G. Dierksen, *J. Chem. Phys.*, **49**, 4852 (1968).
16. P. Hariharan and J. Pople, *Mol. Phys.*, **27**, 209 (1974).
17. M. Frisch, G. Trucks, H. Schlegel, G. Scuseria, M. Robb, J. Cheeseman, V. Znkrzewski, G. Montgomery, R. Startmann, J. Burant, S. Dapprich, J. Millam, A. Daniels, K. Kudin, M. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pamelli, G. Adamo, S. Clifford, J. Ochterski, G. Petersson, P. Ayala, Q. Cui, K. Morokoma, D. Malick, A. Rubuck, K. Raghavachari, J. Foresman, J. Cioslawski, J. Oritz, B. Stlefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Comperts, R. Martin, P. Fox, T. Keith, M. Al-laham, C. Peng, A. Akkara, C. Gonzales, M. Combe, P. Gill, B. Johnson, W. Chem, M. Wong J. Andres, C. Gonzales, M. Head-Gordon, E. Replogle and J. Pople, Gaussian Inc., Pittsburgh PA (1998).
18. W. Foye, Th. Lemek and D. Williams, FOYE's Principales of Medicinal Chemistry, Lippitcott: Philadelphia (2002)

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