Spectroscopic and Physical Properties of Novel Tetrazoles Derivatives as Anti-Tuberculosis Drugs: A computational approach

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Abstract

Tuberculosis is a deadly disease spreading all over the world. Word health data indicated that every year, approximately 2 million people are dead due to tuberculosis. There are many reasons of spreading of mycobacterium tuberculosis infection, but major factor is interaction with the Human Immunodeficiency Virus (HIV). Hence treatment of tuberculosis is quite important worldwide. Tetrazoles derivatives are anti-fungal drugs, but they are also used in treatment of tuberculosis (TB). Finding the better drug for further treatment of TB amongst all tetrazoles is a big task, because structure and some properties of tetrazoles derivatives are almost same. So, here we studied spectroscopic property, like- IR spectra, and physical properties like- HOMO-LUMO energy band gap as well ground state energy, which might be helpful for finding the better drug for further treatment of TB.

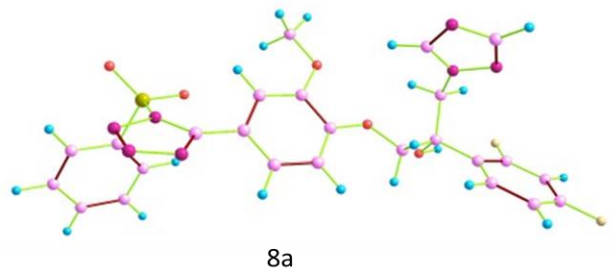
Introduction

Tuberculosis (TB) is one of the most contagious and deadliest diseases caused due to tenacious pathogen Mycobacterium tuberculosis (MTB). This disease usually affects when as few as 10 bacteria are inhaled into the deep lung [1]. Pulmonary system is the prime target of this bacteria but it can also invade extra-pulmonary systems like lymphatic, gastrointestinal, urogenital, cental nervous system and skeletal system. Early symptoms are night sweats, fever and weight loss, whereas severe symptoms of advanced stage include chest pain, shortness of breath, and blood while cough [2] first line drugs for the treatment of TB include isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA) and ethambutol (EMB). Combination of these drugs is given for 6-8 months for the treatment of TB. New problem has emerged in form of multidrug-resistance TB (MDRTB) in which TB pathogen develops resistance towards two most powerful drugs ioniazid and rifampicin. The treatment of drug resistance TB is longer and expensive and drugs used are toxic too. According to WHO the success rate of drugs used for MDR-TB is lower [3]. These major problems pointed in urgent need for the search of better drugs which are less expensive

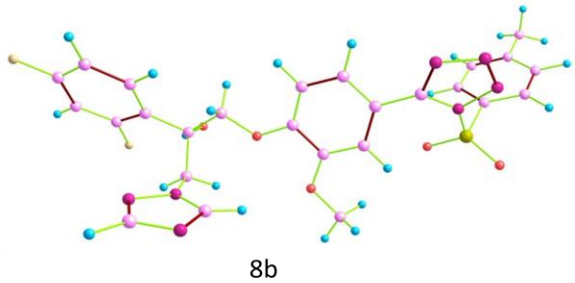
and show faster recovery of patients [4]. But, development of drug resistant strains of Mycobacterium species has contributed to the lack of efficiency of the conventional anti-TB therapy, and hence the search for new anti-tubercular agents is still on. Tetrazoles and its derivatives have shown potency as anti-TB drugs. These compounds show wide variety of biological activities as antibacterial [5-7], antifungal [8-10], anti-inflammatory, antiviral [11, 12] , antinociceptive, hypoglycemic and anti-cancer [13,14]. The tetrazole ring present in these compounds is resistant to biological degradation and hence can be used as isoteric substituent of various functional groups [15]. In this present work we have studied some of their spectroscopic and physical properties. The structure were collected from literature survey [16], this study might lead us to understand why they show anti-bacterial and most importantly anti-tuberculosis activity.

Methodology

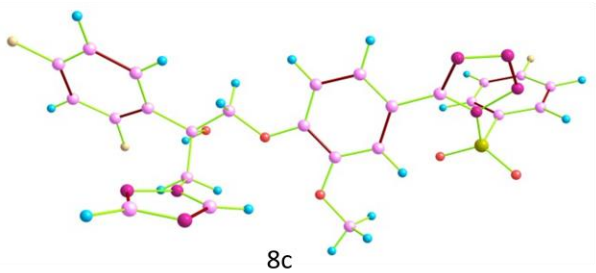
All structures were designed using gauss view 5.0 and structure were optimized by Gaussian 09 [17] using B3LYP function at 6-31 G ** basis set. Frequency calculations were performed to check the stability of the compounds, which was confirmed as no structure showed imaginary frequencies. HOMO-LUMO gap is calculated using spin density calculations. The figures were



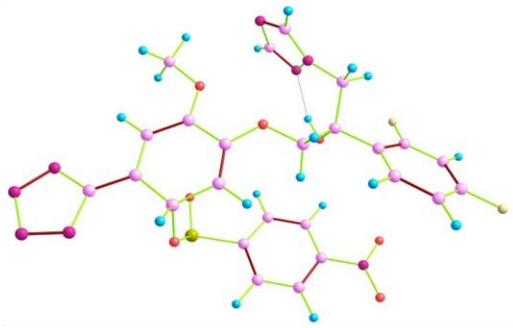
8a



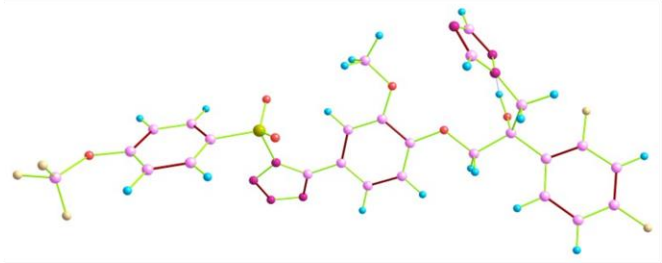
8b



8c



8f



8i

assembled using Chemcraft [18]. The molecular orbitals were visualized using gauss view itself.

Figure: 1 Optimized structures of sulphonamide tetrazole analogues 8a, 8b, 8c, 8f and 8i respectively.

Results and Discussion

Optimization results depicted the most stable compound to be 8i on the basis of free energy calculations, whose energy was found to be -7.44x 10^4 eV and second most stable is 8f compound with value of -6.87x 10^4 eV, this can be seen in **table: 1**. Band gap calculated by HOMO- LUMO difference showed that these selected compounds are wide band gap materials with only exception being 8f whose band gap came quite less than other compounds i.e. 2.98 eV; assembled in **table: 1**.The complexes 8a, 8b, & 8c optimization energy were of nearly same value.

Compound	HOMO-LUMO gap (au)	HOMO-LUMO gap (ev)	Energy (ev)
8a	**0.14913**	**4.04**	**-6.33x 10^4**
8b	**0.15180**	**4.12**	**-6.43x 10^4**
8c	**0.15045**	**4.08**	**-6.59x 10^4**
8f	**0.10998**	**2.98**	**-6.87x 10^4**
8i	**0.14414**	**3.91**	**-7.44x 10^4**

Table: 1 Above table shows values of HOMO- LUMO gap both in (eV and au), ground state energies (in eV) of structures chosen for present studies.

Furthermore, from the IR- absorption spectrum compound 8a, 8b and 8c graph depicted similar absorption pattern and peaks. Although slight lateral shift is observed in entire pattern as we move from compound 8a, 8b and 8c respectively. Infrared spectroscopy (IR spectra) is basically obtained by absorption of frequencies in IR region by various (functional) groups and bonds present in molecule when light is irradiated on them. There are many modes of vibrations of molecules. 8a derivatives has maximum absorption at 1314.21 cm^{-1} which can be seen from fig: 3 and is basically due to rocking, waging and twisting of C-H bonds present in various groups like CH_3 and C-H bonds present in benzene ring. Similarly, 8b represented in fig: 4 shows major

peak at 1314.46 cm^{-1}, which also corresponds to same vibrations and groups as those present in 8a with nearly same IR intensity. Highest peak of 8c was observed at 1314.78 cm^{-1}. Hence it can be seen and inferred that these three molecules shows major IR activity in same region, this is shown in fig: 5. Although 8f shows one peak at 676.89 cm^{-1} due to stretching vibrations of N-N bond in tetrazole ring and highest peak for C=C bond streching in benzene at 1606.37 cm^{-1}. 8i was most active at 1308.67 for rocking in benzene C-H bonds and wagging of carbon of CF_3 group. Also, both 8i and 8f (fig: 6 & 7 respectively) showed a moderate peak between 3500-3600 cm-1 for O-H functional group stretching vibrations, whereas in 8a, 8b and 8c this peak was rather small.

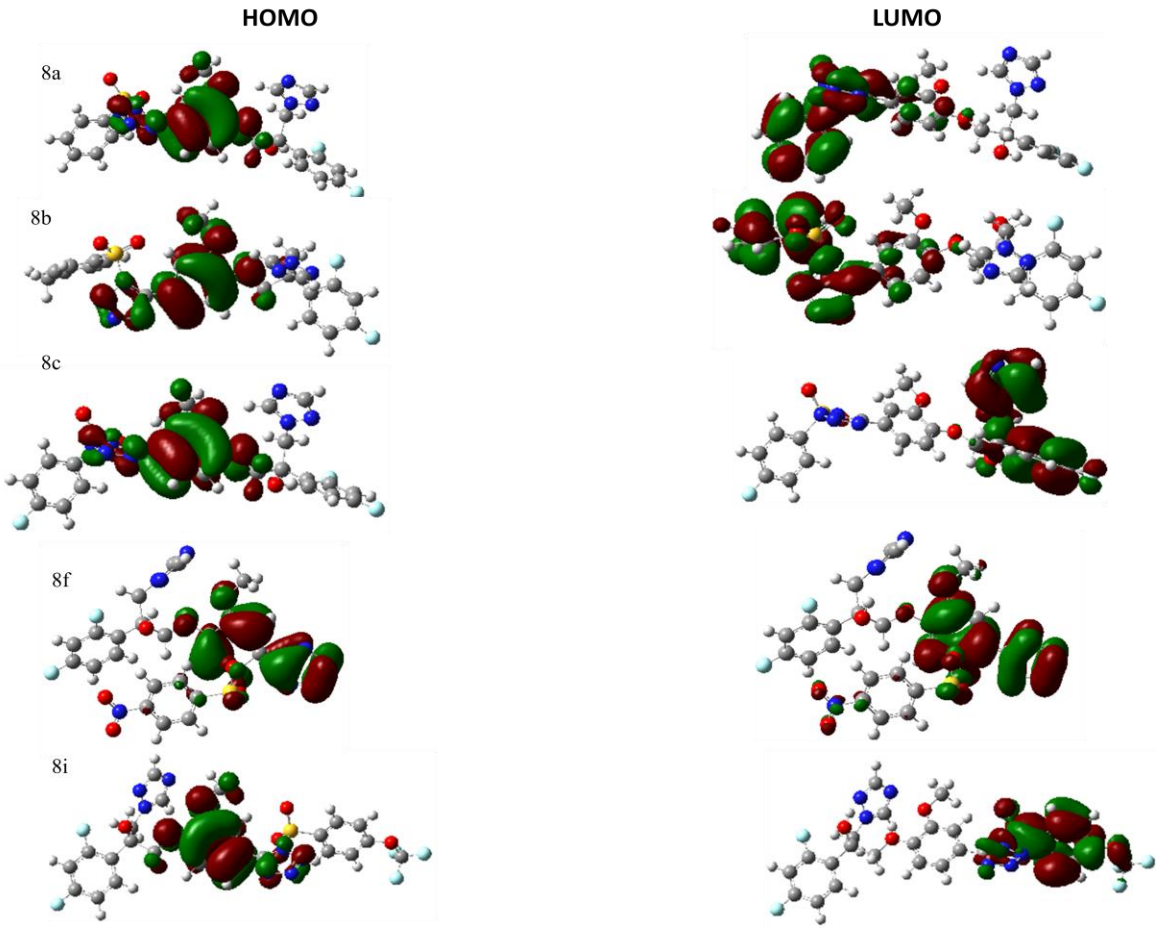


Figure: 2 HOMO –LUMO structures of Sulphonamide tetrazoles analogues.

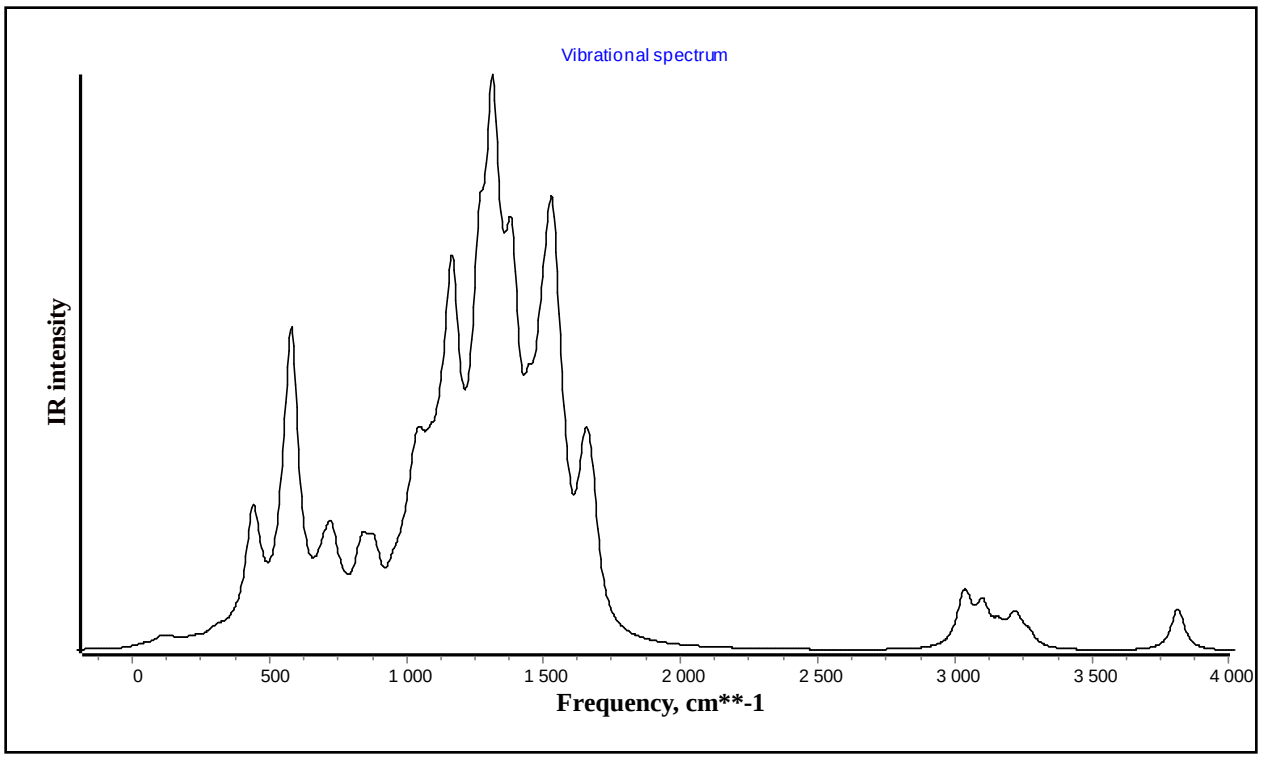


Figure: 3 IR spectrum of 8a.

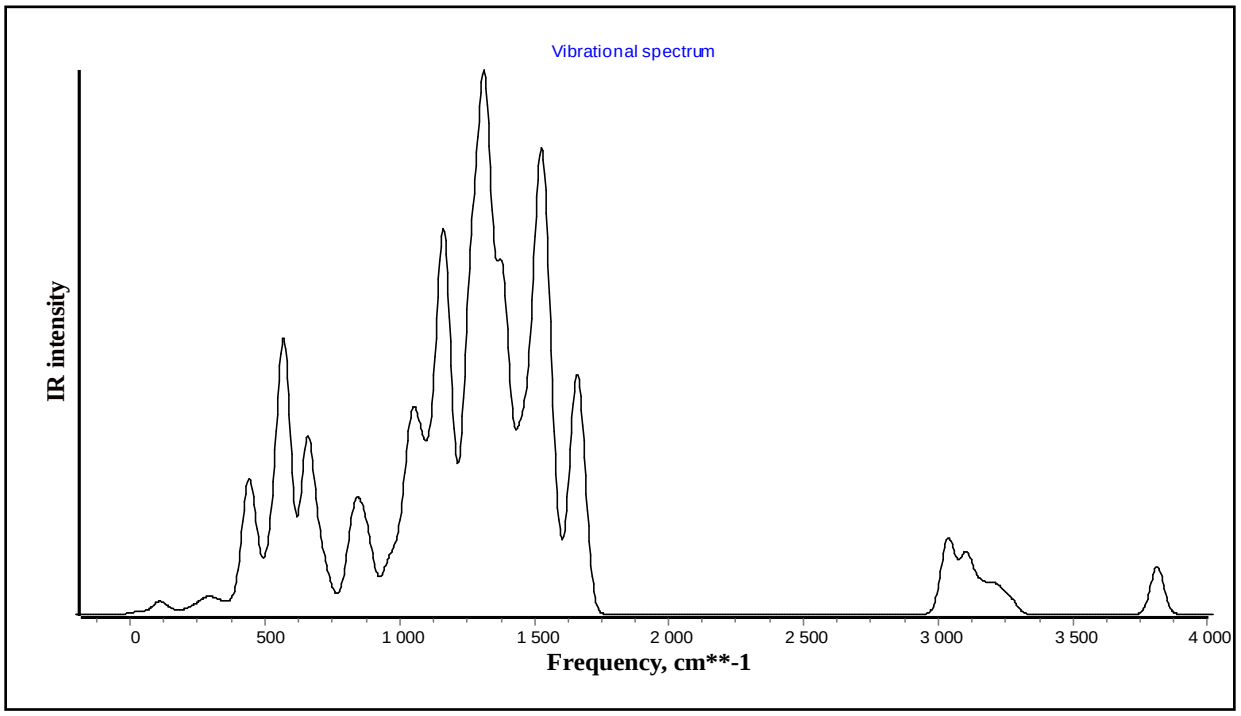


Figure: 4 IR spectrum of 8b.

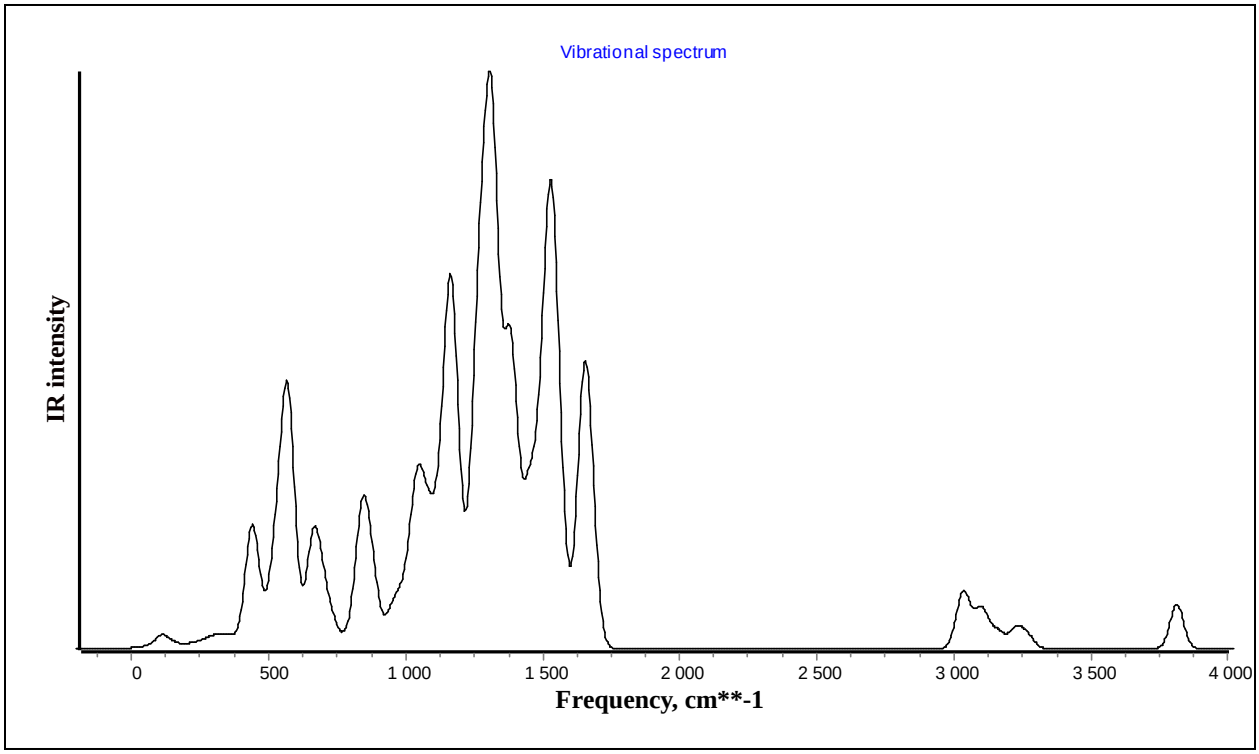


Figure: 5 IR spectrum of 8c

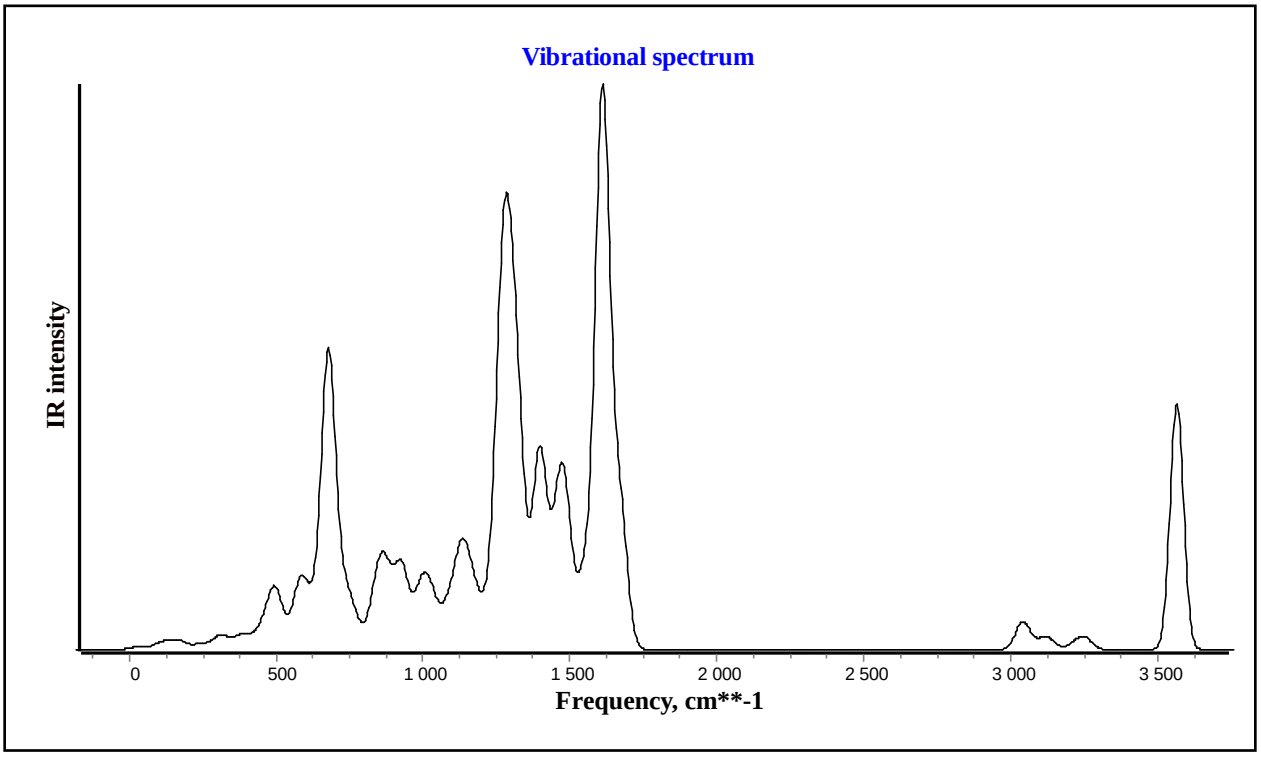


Figure: 6 IR spectrum of 8f

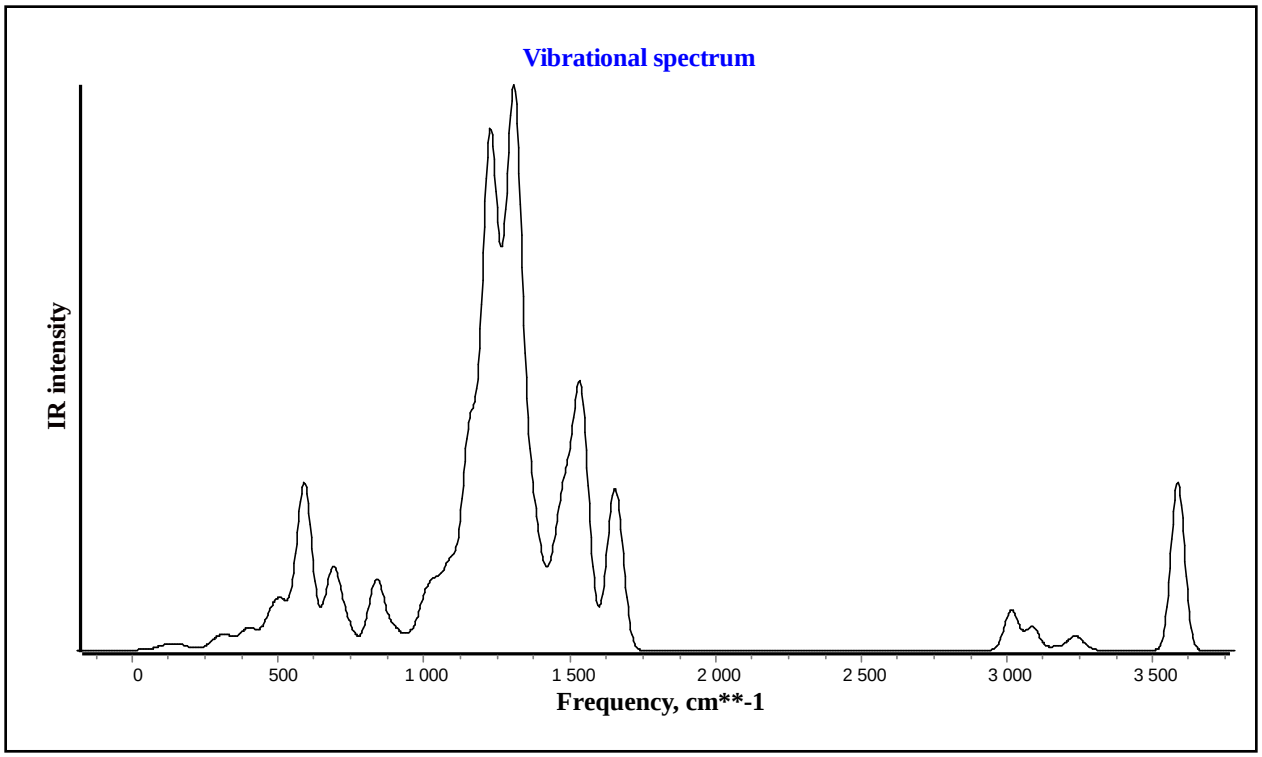


Figure: 7 IR spectrum of 8i

Conclusion

As mentioned earlier, the minimum potential energy of 8a is -6.33x 10^4 eV, this structure could be regarded as least stable in terms of ground state energy between all of the rest complexes. 8i has most stable structure, as it has energy came out to be -7.44x 10^4 eV. The minimum potential energy of 8b is -6.43 x 10^4 which is less stable than 8c having energy value of -6.59x 10^4 eV. Derivative 8f has energy -6.87x 10^4 eV. Amongst all derivatives 8i is most stable molecule, hence it might be more useful to test its potency as anti-tuberculosis drug. The HOMO-LUMO band-gap is also reported in table 1. 8f has HOMO-LUMO band-gap of 2.98 eV, band-gap of 8i is 3.91 eV, which is greater than 8f. 8a, 8b and 8c showed band-gap similar band-gaps and they also displayed nearly same intensity peaks at same vibrations frequencies in IR spectrum graph.

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References

1.Strohmeier GR, Fenton JM (1999) Roles of lipoarabinomannan in the pathogenesis of tuberculosis. Microbes & Infection 1: 709-717.

2.Sarkar S, Ganguly A, Sunwoo HH (2016) Current Overview of Anti-Tuberculosis Drugs: Metabolism and Toxicities. Mycobact Dis 6: 209.

3.World Helath organization (WHO), Global Tuberculosis Controls Report, 2014, http://www.who.int/tb/publications/factsheet_global.pdf.

[4.] P. K. Ranjith, R. Pakkath, K.R. Haridas, S. N. Kumari, Eur. J. Med. Chem. 2014, 71, 354-365.

[5] I. Kucukguzel, S. G. Kucukguzel, Rollasa, S. Rollasa, M. Kiraz, Bioorg. Med. Chem. Lett. 2001, 11, 1703-1707.

[6] L. Zahajska, V. Klimesova, J. Koci, K. Waisser, J. Kaustova, Arch. Pharm. pharm. Med. Chem. 2004, 337, 549-555.

[7] N. U. Guzeldemirci, O. Kucukbasma, Eur. J. Med. Chem 2010, 45, 63-68.

[8] G. T. Zitouni, Z. A. Kaplancikli, M. T. Yildiz, P. Chevallet, D. Kaya, Eur. J. Med. Chem. 2005, 40, 607-613.

[9] B. S. Holla, R. Gonsalves, S. Shalini, Eur. J. Med. Chem. 2000, 35, 267-271.

[10] S. P. Garoufalias, N. Pouli, V. Marakos, A. C. Ladas, II Farmaco. 2002, 57, 973-977.

[11] M. T. Abdel-Aal, W. A. El-Sayed, S.M. El-Kosy, E. S. H. El-Ashry, Arch. Pharm. Chem. Life Sci. 2008, 341, 307-313.

[12] M. Krisanida, A. Mouroutsou, P. Marakos, P. Pouli, S. P. Garoufalias, C. Pannecouque, M. Witvrouw, E. D Clercq, II Farmaco. 2002, 57, 253-257.

[13] B. K. Kaymakcioglu, S. Rollas, II Farmaco. 2002, 57, 595-599.

[14] B. S. Holla, B. Veerendra, M. K. Shivananda, B. Poojary, Eur. J. Med. Chem. 2003, 38, 759-767.

[15] K. Chauhan, M. Sharma, P. Trivedi, V. Chaturvedi, P. M .S. Chauhan, Bioorg.

Med. Chem. Lett. 2014, 24, 4166-4170.

[16] A. Suresh, N. Suresh, S. Misra, N.M.K Kumar, & K.V.G.C. Shekhar, Chemistry Select, 2016, 1, 1705-1710.

[17] Gaussian 09, Revision E.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski and D. J. Fox, Gaussian, Inc., Wallingford CT ***(2009)****.*

[18] Chemcraft - graphical software for visualization of quantum chemistry computations. https://www.chemcraftprog.com