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THIORIDAZINE@CUCURBIT[7]URIL COMBINATION FOR ENHANCED ANTIPSYCHOTIC TREATMENT

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Abstract

Thioridazine, a first-generation antipsychotic, has demonstrated effectiveness in addressing psychotic symptoms. Cucurbit[n]urils (CB[n]), a group of macrocyclic molecules shaped like pumpkins, are renowned for their remarkable host-guest chemistry and compatibility with biological systems. This work explores the possibility of augmenting the first-generation antipsychotic thioridazine by incorporating it into a Cucurbit[7]uril (CB[7]) complex, which is well-known for its host-guest chemistry. A detailed analysis of the development of the thioridazine@Cucurbit[7]uril inclusion complex was conducted using UV-V is spectrophotometry and density functional theory. Because thioridazine has a low oral bioavailability and inhibits systemic absorption, researchers have been looking into CB[7]'s potential to form inclusion complexes with a variety of medications, including thioridazine. The thioridazine@Cucurbit[7]uril inclusion complex is successfully formed, as evidenced by the study, suggesting that it may have enhanced antipsychotic action. Through the utilization of CB's distinct characteristics, this complex presents opportunities to improve medication solubility, stability, and targeted delivery. According to the results, thioridazine's bioavailability limitations may be addressed by this complex formation, which could increase the medication's therapeutic efficacy in treating psychotic symptoms. The results of this study pave the way for the potential use of CB[7] complexes as a means of improving the efficacy of antipsychotic drugs such as thioridazine and enhancing psychiatric disease treatment approaches.

Keywords: Thioridazine, Cucurbit[7]Uril, Antipsychotic Treatment, Antipsychotic Activity, Spectrophotometer, Oral Bioavailability.

INTRODUCTION

Thioridazine, a derivative of phenothiazine, became well-known as an antipsychotic drug in the 1950s after chlorpromazine's commercial success[1]. Because it was effective at treating psychotic symptoms and had a reduced risk of extrapyramidal side effects than other antipsychotics of the time, its introduction marked a significant advancement in the field of psychiatric treatment. Thioridazine's efficacy in treating schizophrenia was confirmed in a ground-breaking study carried out by the National Institute of Mental Health (NIMH) and the NIMH PSC Collaborative Study Group. The trial showed that thioridazine was as effective at reducing symptoms of schizophrenia when compared to fluphenazine, chlorpromazine, and a placebo[2]. This crucial discovery made thioridazine's position in the treatment of psychotic diseases much more certain. Phenothiazines, such as thioridazine, have demonstrated exceptional antibacterial activity against a range of intracellular microbes in addition to its core role as an antipsychotic[3]. Research has demonstrated their efficacy in combating bacteria, protozoa, and certain viral illnesses. Their surprising antibacterial action has sparked research into possible uses outside of mental medicine. Thioridazine's antipsychotic

actions are mediated through altering dopamine neurotransmission, whereby it functions as an antagonist for the D2 family of dopamine receptor proteins[4]. New findings about the pharmacological activity of thioridazine have illuminated new aspects of its potential as an anticancer drug. Research indicates that it has the ability to cause cancer cells to undergo apoptosis, prevent angiogenesis, and alter several signalling pathways that are connected to the advancement of cancer[5]. Thioridazine's complex pharmacological profile has led to interest in repurposing this drug for a range of medicinal uses. Its adaptability is demonstrated by its capacity to function across several biological domains, including mental illnesses, antimicrobials, and possibly even cancer. The use of thioridazine has encountered significant obstacles in spite of these encouraging features[6]. Its clinical use has been limited because to concerns about cardiac adverse effects, including QT interval lengthening that can result in potentially deadly arrhythmias. Consequently, when using thioridazine in clinical practice, care and constant observation are necessary. In an effort to maximise thioridazine's therapeutic advantages while reducing related hazards, research on the drug's many pharmacological characteristics and possible uses is now underway. The progression of thioridazine from its original use as an antipsychotic to its investigation in the fields of antibacterial and anticancer therapy is evidence of the fluidity of medication repurposing and the ongoing pursuit of the most effective therapeutic treatments across a range of medical specialties[7].

In fact, throughout the past 10 years, cucurbit[n]urils (CB[n]) have become a well-known class of molecular containers, drawing interest from a variety of scientific fields[8]. These macrocyclic molecules have a unique structure consisting of n glycoluril units connected by methylene groups. Their interesting host-guest chemistry has created opportunities for a great deal of basic and applied study. Because of their innate architecture, CB[n]s possesses unique characteristics that are essential for molecule identification in aquatic conditions[9]. These containers, whose n values vary from 5 to 10, have carbonyl group-lined entrances and a hydrophobic cavity whose volume increases as the number of glycoluril units increases. Through noncovalent interactions, CB[n]s can form stable and reversible complexes with a variety of cationic or neutral guest molecules thanks to their structural diversity[10]. These host-guest complexes are made possible by a variety of interactions, including ion-dipole interactions, hydrophobic effects, and hydrogen bonding. Because of their adaptable binding capabilities, CB[n]s may manage and encapsulate a variety of guest molecules with selectivity, which makes them useful instruments for studying molecular recognition processes[11]. Cucurbit[7]uril (CB[7]) is one among the members of the CB[n] family that has attracted the most attention because of its remarkable water solubility, which may reach concentrations of up to 30 mM. Its excellent aqueous solubility is a major factor in its applicability in nanotechnology and the biological sciences[12]. Furthermore, CB[7] has a suitably sized cavity that can hold a wide variety of molecules, which increases its applicability in a number of different domains. Because CB may form stable compounds with molecules that are important to biology, it has a considerable biomedical importance[13]. These could be medicinal substances, peptides, amino acids, or even specific proteins, providing chances for targeted therapies, biomolecule recognition, and drug delivery systems. Furthermore, the aqueous environment compatibility of CB[7] is in line with biological systems, further augmenting its potential for biomedical applications. CB[7] is a useful building component in nanotechnology that can be used to create supramolecular structures. Its capacity to precisely and steadily encapsulate guest molecules makes it easier to

create functional nanostructures, such as drug delivery systems, molecular switches, and sensors[14]. These uses demonstrate how crucial CB[7] is to the advancement of solutions based on nanotechnology. The ongoing investigation of CB[n]urils, in particular CB[7], highlights their importance in influencing scientific inquiry into everything from basic molecular interactions to cutting-edge real-world applications. These molecular containers have the potential to further revolutionise a variety of scientific areas and open up new avenues for investigation and discovery as knowledge expands and creative methods arise[15].

CB[n]urils, or the family of cucurbit[n]urils, are an intriguing class of molecular containers that are created when formaldehyde and glycoluril mix in a very acidic environment. Their structural uniqueness is attributed to the inclusion of a hydrophobic cavity and two identical uridyl CO gateways, which provide them exceptional binding capabilities, particularly in aquatic conditions[16]. By utilising a mix of ion-dipole interactions and the hydrophobic effect, CB[n] compounds show a remarkable capacity to bind both cationic and hydrophobic molecules in water. Their host-guest chemistry is based on these interactions, which enable different molecules to be encapsulated within their cavities. Theory research have focused on understanding the subtleties of interactions between guest molecules and cucurbiturils[17]. Numerous key mechanisms influencing these interactions have been postulated by these investigations. When using a cationic host, charge-dipole interactions are more important, but hydrogen bonding between the hydrogen atoms in the guest and the carbonyl portal of the host is also quite important[18]. Moreover, the binding process is greatly aided by hydrogen interactions involving the hydrogen atoms in the cucurbituril's methylene unit and hydrophobic interactions inside the concave cavity of the compound. The cucurbituril cavity's guest molecule complexation is determined by these mechanisms, or a combination of them. This work focuses on investigating the complex formation between the host molecules cucurbit[7]uril and the guest molecule thioridazine[19]. The main goals are to comprehend the factors that drive the formation of complexes and assess the stability of the guest molecule after complexation.

Our study attempts to determine the stoichiometry of the complexes generated between Thioridazine and cucurbit[7]uril by using the UV-Vis-based Jobs approach[20]. We hope to clarify the details of these complexes' interactions and provide insight into the binding forces that promote their stability by defining the precise ratio at which they develop. These results have important ramifications, especially for the field of drug delivery. Understanding the ways in which cucurbiturils and thioridazine interact may help us better understand how to use these molecular carriers to increase medication delivery[21]. Through the clarification of the complexation mechanism and evaluation of the stability of the resultant complexes, we open up new avenues for creative approaches to the development of drug delivery systems that maximise therapeutic effects.The results of this work have the potential to further our basic knowledge of molecular interactions and to direct future research efforts towards more effective and focused medication delivery approaches. The utilisation of cucurbiturils' host-guest chemistry holds promise for transforming drug delivery by providing increased effectiveness and reduced negative effects for a wide range of medicinal agents[22].

MATERIALS AND METHODS

- JascoV-730 Spectrophotometer was used for recording the UV-Vis spectra. 1x10-5molar of Cucurbit[7]uril is dissolved in water.In that solution, 1×10-4 molar of thioridazine is added.
- Gaussian G16 Code was used for optimisation. The structures were optimized both in gas and liquid state with the wb97xd/6-31+g(d) method. The Highest occupied molecular orbital (HOMO) and Lowest unoccupied molecular orbital (LUMO) were analyzed using chemcraft software. The most stable geometries have only positive frequencies that indicate they are all in the minima in the potential energy surface and are not the saddle points.

The materials utilized in this synthesis process encompassed:

Paraformaldehyde (reagent grade, Aldrich): Employed in its as-received state, without further purification, as a key reactant in the synthesis.1,4-dimethoxybenzene (1.38 g, 10 mmol): Dissolved in 20 ml of 1,2-dichloroethane, serving as a foundational component for the synthesis. Boron trifluoride diethyl etherate (1.25 ml, 10 mmol): Added dropwise to the mixture of 1,4-dimethoxybenzene and paraformaldehyde under a nitrogen atmosphere, facilitating the reaction process. Dry methanol (50 ml): Introduced into the resulting solution to advance the synthesis.

The synthetic procedure for cucurbit[7]uril involved sequential steps:

Preparation of Reaction Mixture: Dissolving 1,4-dimethoxybenzene in 20 ml of 1,2-dichloroethane within a nitrogen atmosphere. Addition of Paraformaldehyde: Incorporating paraformaldehyde into the solution and stirring the mixture for 10 minutes to initiate the reaction. Introduction of Boron Trifluoride Diethyl Etherate: Adding boron trifluoride diethyl etherate dropwise under a nitrogen atmosphere to continue the reaction, followed by additional stirring under nitrogen for 10 minutes and subsequent exposure to air for 20 minutes. Inclusion of Dry Methanol: Incorporating dry methanol into the resultant solution.Filtration and Isolation: Separating the solid material obtained through filtration, then dissolving it in chloroform. Evaporation and Drying: Evaporating the chloroform solvent and drying the solid product at room temperature for 12 hours to yield cucurbit[7]uril. Characterization of the synthesized cucurbit[7]uril involved analytical techniques:

1H NMR Spectroscopy: Utilized a Bruker NMR operating at 300 MHz, recording spectra in CDCl3 with tetramethylsilane as an internal standard. This technique helped ascertain the structural properties of the synthesized compound. 2D COZY Spectroscopy: Employed as an additional analytical method for a more comprehensive understanding of the synthesized compound's structure and properties. These analytical approaches, particularly NMR spectroscopy, are pivotal in verifying the successful synthesis of organic compounds like cucurbit[7]uril, providing invaluable insights into their molecular structures and functional groups, essential for their characterization and subsequent applications.

DISCUSSION

Computational analysis of the inclusion complex between cucurbituril and thioridazine has provided interesting new information about their possible interactions and consequences. This complex's 1:1 stoichiometry has been investigated using Density Functional Theory (DFT), which has provided a sophisticated insight of the molecular-

level behaviour. Finding the lowest energy optimised geometries for the compounds generated between thioridazine and cucurbituril was one of the study's main conclusions[24]. Interestingly, the majority of these optimised geometries showed the guest thioridazine partially contained within the host cucurbituril molecule. This encapsulation state indicates a particular binding interaction in which the cucurbituril's cavity partially encloses the thioridazine molecule, pointing to a different way in which the two entities interact. When cucurbituril was titrated with thioridazine, the UV-Vis spectra that were acquired showed isosbestic spots, which suggested a substantial alteration in the electronic structure or environment during complex formation[25]. These points indicate a particular equilibrium between the bound and free versions of the molecules, implying that the complexation process resulted in a uniform and defined state. This spectrum observation is consistent with the knowledge that the molecules involved undergo electronic property changes as a result of the complexation. The computed infrared spectra demonstrated alterations in the thioridazine molecules' spectrum frequencies during complexation with cucurbituril, which offered additional proof of complex formation. These changes in spectrum frequencies show that the thioridazine molecule's vibrational modes have changed as a result of its interaction with the host molecule. Such vibrational frequency shifts frequently indicate alterations to the molecular contacts and chemical environment, confirming the complexation process. This work highlights an interesting feature: complex formation enhances the solubility of thioridazine molecules. Cucurbituril's capacity to fully or partially encapsulate thioridazine provides information about possible uses for increasing the medication's solubility. A solubility boost of this kind is critical to pharmaceutical formulations because it can have a favourable effect on drug transport, bioavailability, and ultimately therapeutic efficacy[26]. The optimised geometries' partial encapsulation suggests a particular binding mode that may have an impact on thioridazine's pharmacokinetics. Understanding the possible behaviour of these complexes in biological systems and their possible influence on medication distribution and metabolism requires knowledge of this kind. All things considered, our computational study clarifies the complex structure of the thioridazine-cucurbituril inclusion complex. Cucurbiturils may be used to increase the pharmacological qualities of thioridazine, as suggested by the observed changes in spectroscopic properties and the hint of improved solubility. To validate our computational results and investigate the potential applications of these interactions in medication delivery and therapeutic interventions, further thorough research and experimental validation are required[27].

CONCLUSION

The structural features, spectrum shifts, and possible consequences of thioridazine and cucurbituril's interaction have been clarified by the computational study of their inclusion complex. Utilising Density Functional Theory (DFT) to investigate the complex's 1:1 stoichiometry, this study has produced noteworthy results that highlight the interaction's possible medicinal significance. The discovery of the lowest energy optimal geometries is a significant finding of this work, which indicates that the most stable complexes involving thioridazine and cucurbituril required the encapsulation of the guest molecule within the host. In particular, the finding that thioridazine is present in the cucurbituril cavity in a partially enclosed form indicates a distinct and particular binding mode between these entities[28]. Furthermore, after complexing with cucurbituril, the computed infrared spectra showed alterations in the spectrum frequencies of thioridazine molecules. These spectral variations point to adjustments

in the thioridazine vibrational modes, supporting the complicated creation event and emphasising the changes in the chemical environment brought about by this interaction. The enhancement in thioridazine molecule solubility that is observed upon complexation with cucurbituril is particularly noteworthy. Improved solubility affects bioavailability, which in turn affects therapeutic efficacy, making it a critical component in medication development. Cucurbituril's capacity to aid in thioridazine's improved solubility raises the possibility of boosting the medication's medicinal qualities. This discovery raises the possibility of using cucurbiturils as enhancers or transporters in medication formulations to solve solubility-related problems[29]. To sum up, our computational study offers strong proof of the complexation between cucurbituril and thioridazine, clarifying its structural, spectral, and possible medicinal consequences. The importance of this interaction is highlighted by the discovery of encapsulated complexes, modifications in spectroscopic characteristics, and an increase in thioridazine solubility. By providing prospective possibilities for utilising cucurbiturils in drug delivery and pharmaceutical development, as well as encouraging additional research into their uses in increasing drug solubility and efficacy, these findings establish the foundation for further experimental validation and exploration[30].

Future Scope of The Study

Further research and rigorous clinical trials are imperative to comprehensively assess the safety, efficacy, and practical applications of the thioridazine-cucurbituril complex in treating psychotic disorders. While computational investigations provide valuable insights into molecular interactions, their translation into real-world therapeutic interventions requires robust empirical evidence.Clinical trials involving this complex are essential to validate its therapeutic potential in treating psychotic disorders. These trials would involve careful assessments of safety profiles, dosing strategies, pharmacokinetics, and therapeutic outcomes in patients. Comprehensive evaluations would ascertain the complex's efficacy in managing psychotic symptoms while monitoring for any adverse effects or interactions[31]. Moreover, examining the complex's stability in biological systems and its potential for targeted drug delivery is crucial. Understanding its behavior in vivo, including its absorption, distribution, metabolism, and excretion, is pivotal in determining its clinical viability and optimizing its therapeutic application. Furthermore, comparative studies against existing treatments for psychotic disorders would provide essential benchmarks, evaluating the complex's efficacy and safety in relation to standard therapies[32]. Ethical considerations, patient safety, and regulatory approvals are paramount throughout this process. Rigorous adherence to ethical guidelines and regulatory protocols ensures the safety and well-being of participants in clinical trials and validates the credibility of the findings. Concurrently, long-term studies assessing the durability of therapeutic effects and monitoring for any unforeseen effects or complications are crucial for establishing the complex's sustained efficacy and safety over extended treatment periods[33].

In conclusion, while the computational investigation highlights promising aspects of the thioridazine-cucurbituril complex, thorough clinical evaluation is imperative. Rigorous clinical trials, coupled with comprehensive assessments of safety, efficacy, pharmacokinetics, and long-term effects, are necessary steps in determining its viability as a valuable addition to the treatment landscape for psychotic disorders. These endeavors would not only validate its potential therapeutic benefits but also ensure patient safety and guide its eventual clinical application[34]

RESULTS AND DISCUSSION

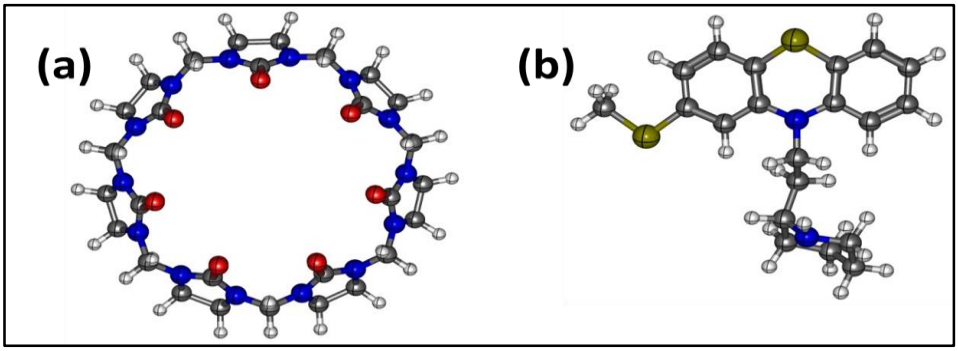
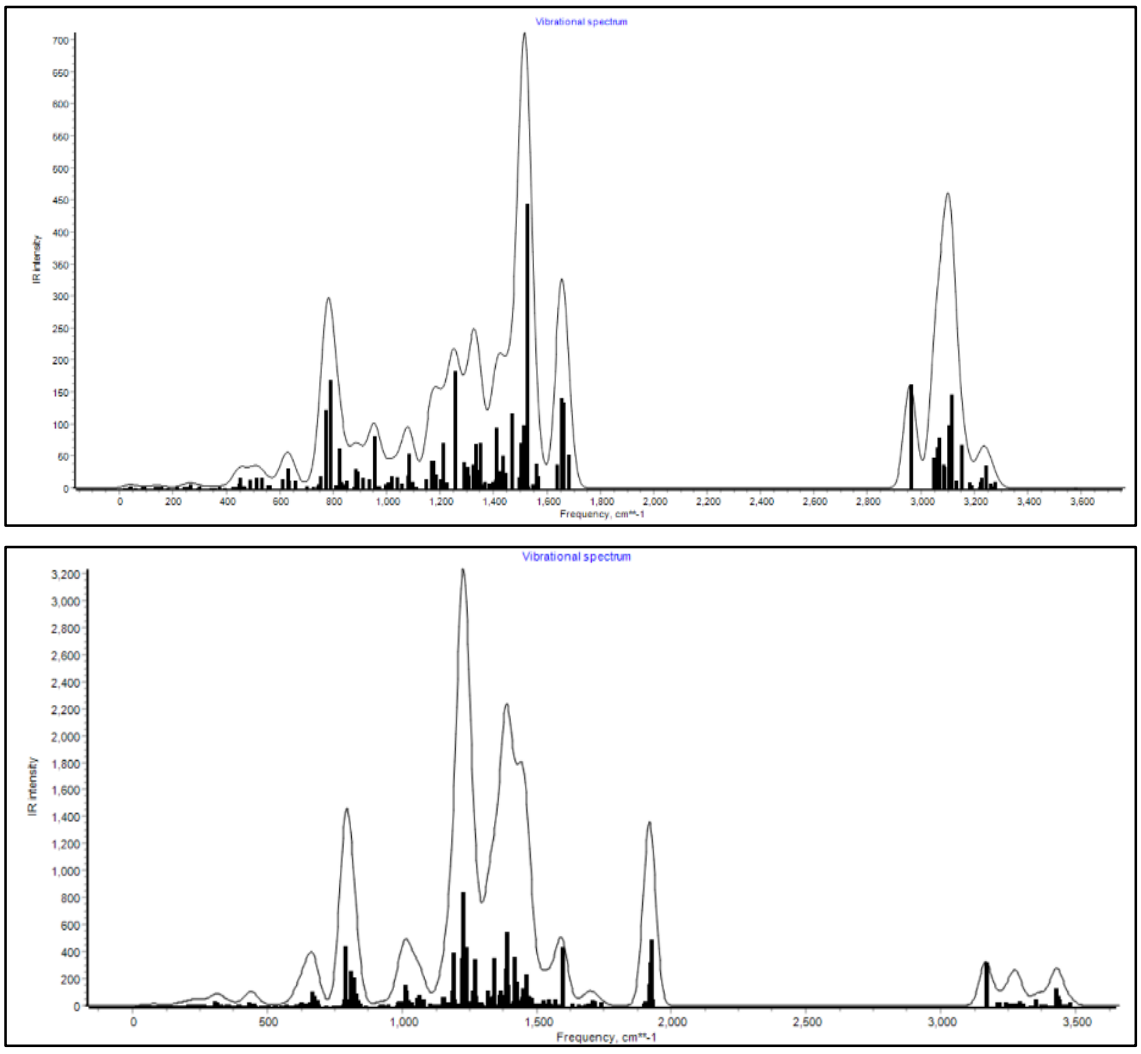


Figure 1: Optimized structures of (a) cucurbit[7]uril and (a) thioridazine molecule in gas phase

The optimized structures of cucurbit[6]uril CB[7] is shown in Fig. 1a in lateral view and The computed cavity diameter between the oxygen portals and the cavity depth of CB[7] is 6.92 Å and 6.09 Å respectively with D7h symmetry. The observed values are in close agreement with the previously reported theoretical values. The computed oxygen portals diameter in CB6 is 6.77 Å and its cavity diameter is 5.96 Å, which are shorter than the values computed for the Q[6] molecule.



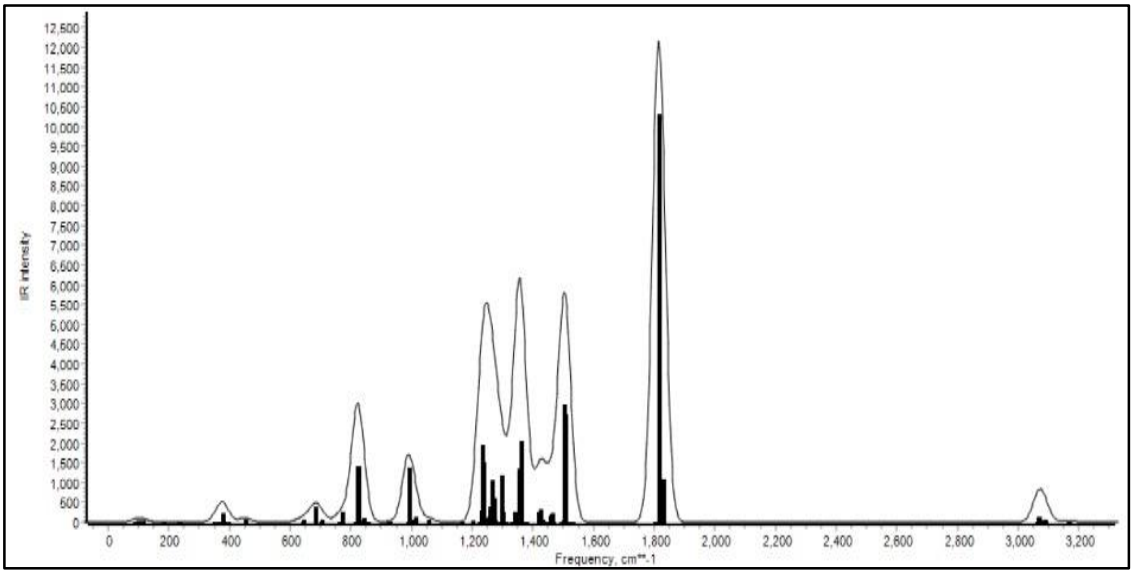


Figure 2: IR spectra of (a) cucurbit[7]uril (b) thioridazine and (c) thioridazine@CB[7] complex computed in gas phase.

As shown in figure 2, the vibration of CB[7] in the vicinity of the wave number of 2800 cm-1 is the stretching vibration of ν(β-H) and ν(γ-H). The pure thioridazine shows spectra in the regions close to 2000 cm-1. Upon complexation the frequencies undergo a spectral shift toward the red region, which clearly establishes the complex formation. The absorption peak frequencies of the vibrational mode ν(β-H) , ν(α=O)+δ(β-H), ν(N-β) and δ(γ-H)+ δ(β-H)+ ν(β-N-β) gradually decrease in turn with the addition of thioridazine[23].

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Conflict of Interest

The authors declare no conflict of Interest

References

1) Thanacoody RH. Thioridazine: the good and the bad. Recent Pat Antiinfect Drug Discov. 2011 May;6(2):92–8.

2) Guttmacher ms. Phenothiazine treatment in acute schizophrenia; effectiveness: the national institute of mental health psychopharmacology service center collaborative study group. Arch gen psychiatry. 1964 mar;10:246–61.

3) Thanacoody HKR. Thioridazine: resurrection as an antimicrobial agent? Br J Clin Pharmacol. 2007 Nov;64(5):566–74.

4) Amaral L, Viveiros M, Kristiansen JE. “Non-Antibiotics”: alternative therapy for the management of MDR TB and MRSA in economically disadvantaged countries. Curr Drug Targets. 2006 Jul;7(7):887–91.

5) Mu J, Xu H, Yang Y, Huang W, Xiao J, Li M, et al. Thioridazine, an antipsychotic drug, elicits potent antitumor effects in gastric cancer. Oncol Rep. 2014 May;31(5):2107–14.

6) Cao L, Śekutor M, Zavalij PY, Mlinarić-Majerski K, Glaser R, Isaacs L. Cucurbit[7]uril·guest pair with an attomolar dissociation constant. Angew Chem Int Ed Engl. 2014 Jan 20;53(4):988–93.

7) Kuok KI, Li S, Wyman IW, Wang R. Cucurbit[7]uril: an emerging candidate for pharmaceutical excipients. Ann N Y Acad Sci. 2017 Jun;1398(1):108–19.

8) Barrow SJ, Kasera S, Rowland MJ, Del Barrio J, Scherman OA. Correction to Cucurbituril-Based Molecular Recognition. Chem Rev. 2016 Oct 12;116(19):12651–2.

9) Lee JW, Samal S, Selvapalam N, Kim HJ, Kim K. Cucurbituril homologues and derivatives: new opportunities in supramolecular chemistry. Acc Chem Res. 2003 Aug;36(8):621–30.

10) Lagona J, Mukhopadhyay P, Chakrabarti S, Isaacs L. The cucurbit[n]uril family. Angew Chem Int Ed Engl. 2005 Aug 5;44(31):4844–70.

11) Nithya, P., Jeyaram, C., Sundaram, K. M., Chandrasekar, A., & Ramasamy, M. S. (2014). Anti-dengue viral compounds from Andrographis paniculata by insilico approach. World Journal of Alternative Medicine, 1(2), 10-16.

12) Subramanian, U., Kishorekumar, M. S., Muthuraman, S., Munusamy, A. P., & Sundaram, R. (2018). Marine algal secondary metabolites promising anti-angiogenesis factor against retinal neovascularization in CAM model. *Research and Reviews: A Journal of Life Sciences*, *8*, 19-25.

13) Saravanan, K. M., & SUNDARAM, K. M. (2021). Effect of bromocriptine in diabetes mellitus: a review. *Uttar pradesh journal of zoology*, 1166-1170.

14) Meenakshi Sundarm, K., Devi, U., & Manivannan, R. (2015). In silico Discovery of Seaweed Molecules against Matrixmet all oproteinase-26. *Journal of Advanced Bioinformatics Applications and Research*, *6*(2), 52-61.

15) Murray, M. T., & Pizzorno, J. (2010). The encyclopedia of healing foods. Simon and Schuster. https://books.google.co.in/books/about/The_Encyclopedia_of_Healing_Foods.html?id=UKtAMVUT57EC&redir_esc=y

16) Padmapriya, A., Preetha, S., Selvaraj, J., & Sridevi, G. (2022). Effect of Carica papaya seed extract on IL-6 and TNF-α in human lung cancer cell lines-an In vitro study. Research Journal of Pharmacy and Technology, 15(12), 5478-5482. https://www.semanticscholar.org/paper/Effect-of-Carica-papaya-seed-extract-on-IL-6-and-in-P.-P./38de57e0cd65f15736e93664c186c2349d8200ab

17) Prathap, L., & Jayaraman, S. (2022). Anti Proliferative Effect of Endogenous Dopamine Replica in Human Lung Cancer Cells (A549) Via Pi3k and Akt Signalling Molecules. Journal of Pharmaceutical Negative Results, 1380-1386. https://www.pnrjournal.com/index.php/home/article/view/1228

18) Prathap, L., & Lakshmanan, G. (2022). Evaluation of Incidence of Various Types of Coronoid Process in South Indian Population. Journal of Pharmaceutical Negative Results, 1387-1390. https://www.pnrjournal.com/index.php/home/article/view/1230

19) Santhi, M. P., Bupesh, G., SenthilKumar, V., Meenakumari, K., Prabhu, K., Sugunthan, S., . . . Saravanan, K. (2016). Anticancer activity and drug likeliness of quinoline through insilico docking against cervical and liver cancer receptors. Ind J Med Res Pharm Sci, 3(9). https://www.researchgate.net/publication/309202439_Anticancer_Activity_And_Drug_Likeliness_Of_Quinoline_Through_Insilico_Docking_Against_Cervical_And_Liver_Cancer_Receptors

20) Schirrmacher, V. (2020). Mitochondria at work: new insights into regulation and dysregulation of cellular energy supply and metabolism. Biomedicines, 8(11), 526. https://pubmed.ncbi.nlm.nih.gov/33266387/

21) Shi, Z., Chen, T., Yao, Q., Zheng, L., Zhang, Z., Wang, J., . . . Han, X. (2017). The circular RNA ci RS-7 promotes APP and BACE 1 degradation in an NF-κB-dependent manner. The FEBS journal, 284(7), 1096-1109. https://onlinelibrary.wiley.com/doi/abs/10.1002/adma.201700990

22) Sobczuk, P., Łomiak, M., & Cudnoch-Jędrzejewska, A. (2020). Dopamine D1 receptor in cancer. Cancers, 12(11), 3232. https://pubmed.ncbi.nlm.nih.gov/33147760/

23) Vijaya Anand, A., Bharathi, V., Bupesh, G., Lakshmi, J., Meenakshi Sundaram, K., & Saradhadevi, M. (2021). Identification of novel potent pancreatic lipase inhibitors from Ficus racemosa. Biomedicine, 41(1), 23-30. https://doi.org/10.51248/.v41i1.528

24) Wu, Y., Hu, Y., Wang, B., Li, S., Ma, C., Liu, X., . . . Yang, S. (2020). Dopamine uses the DRD5-ARRB2-PP2A signaling axis to block the TRAF6-mediated NF-κB pathway and suppress systemic inflammation. Molecular cell, 78(1), 42-56. e46. https://www.cell.com/molecular-cell/pdf/S1097-2765(20)30043-5.pdf

25) Yin, T., He, S., Shen, G., Ye, T., Guo, F., & Wang, Y. (2015). Dopamine receptor antagonist thioridazine inhibits tumor growth in a murine breast cancer model. Molecular medicine reports, 12(3), 4103-4108. https://www.spandidos-publications.com/mmr/12/3/4103

26) Sundaram, K. K. M., Bupesh, G., & Saravanan, K. M. (2022). Instrumentals behind embryo and cancer: a platform for prospective future in cancer research. AIMS Molecular Science, 9(1), 25-. https://www.aimspress.com/article/doi/10.3934/molsci.2022002?viewType=HTML

27) Phukan, M. M., Sangma, S. R., Kalita, D., Bora, P., Das, P. P., Manoj, K., ... & Sundaram, K. M. (2023). Alkaloids and terpenoids: Synthesis, classification, isolation and purification, reactions, and applications. In Handbook of Biomolecules (pp. 177-213). Elsevier.

28) Borniger, J. C. (2019). Central regulation of breast cancer growth and metastasis. Journal of cancer metastasis and treatment, 5. https://pubmed.ncbi.nlm.nih.gov/31773065/

29) Ch Beck, G., Brinkkoetter, P., Hanusch, C., Schulte, J., van Ackern, K., van der Woude, F. J., & Yard, B. A. (2004). Clinical review: Immunomodulatory effects of dopamine in general inflammation. Critical Care, 8(6), 485. https://doi.org/10.1186/cc2879

30) Chockalingam, S., Sasanka, K., Babu K, Y., Ramanathan, V., & Ganapathy, D. (2020). Role of Bruxism in Prosthetic Treatments-A Survey. Indian Journal of Forensic Medicine & Toxicology, 14(4). https://agupubs.onlinelibrary.wiley.com/doi/abs/10.1029/2001JD90013

31) Fleming, B., Edison, P., & Kenny, L. (2023). Cognitive impairment after cancer treatment: mechanisms, clinical characterization, and management. bmj, 380. https://bmjecomm.bmj.com/content/380/bmj-2022-071726