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Journal Name:	Journal of Advances in Medical and Pharmaceutical Sciences
Manuscript Number:	Ms_JAMPS_22801
Title of the Manuscript:	THEORITICAL INVESTIGATION OF MOLECULAR AND ELECTRONIC STRUCTURE OF ANTIFUNGAL ACTIVITY OF KETONE COMPOUNDS: COMBINING QSAR AND DFT STUDIES.
Type of the Article	Original research Articles

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This journal's peer review policy states that **NO** manuscript should be rejected only on the basis of '**lack of Novelty**', provided the manuscript is scientifically robust and technically sound.

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PART 1: Review Comments

	Reviewer's comment	Author's comment (if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)
Compulsory REVISION comments	The authors have reported on the development, use and validity of DFT calculations using the GFA approximation to determine QSAR in a series of coumarin derivatives and compare those values with experimentally determined MICs. While the findings have merit, I have multiple concerns with this paper that are both editorial in nature and content-based. Taken together, this paper must be substantially rewritten. I describe some key concerns below: 1. Editorial Comments: a. This paper is littered with errors in spelling, omissions of spacing between words and sentences, word choice, sentence fragments and punctuation. I counted at least 20 such errors from the Title through line 55 alone. The manuscript as a whole is replete with errors of this type and I cannot enumerate them all here. In the minor revisions section, I identify some of these errors. Recommendation: A thorough rewrite and editing to correct these errors by someone who reads and writes fluently in English. b. The authors' use of English composition in the construction of this work is imprecise. There are numerous examples where euphemisms are used to describe or explain the work that is unscientific. I have identified some of these errors in the minor revisions section. 2. Content Comments: a. Title – The title THEORITICAL INVESTIGATION OF	



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	ANTIFUNGAL ACTIVITY OF KETONE COMPOUNDS: COMBINING QSAR AND DFT STUDIES] has several issues. (1) Theoretical is misspelled in the title! (2) The term ketone is not correct. The subject compounds are actually coumarin derivatives (esters). (3) The title has a period at the end and should not have any punctuation. Recommendation: Retitle the paper to something along the lines of: THEORETICAL INVESTIGATION OF CORRELATIONS BETWEEN MOLECULAR AND ELECTRONIC STRUCTURE AND ANTIFUNGAL ACTIVITY IN COUMARIN DERIVATIVES: COMBINING QSAR AND DFT STUDIES b. Abstract – Should recapitulate key findings and give the reader enough detail to understand the focus of the paper. As written, the reader is presented with a series of acronyms that have not been identified and while these terms are well known to the authors, the target audience may not be familiar with them. Recommendation: Reword the Abstract: Quantitative structure-activity relationship (QSAR) models were combined with density functional computations and used to predict anti-fungi activities in a series of coumarin derivatives. Essential descriptors employed in this study were chosen based on the use of the Genetic Function Approximation (GFA) method. Leave-N-Out (LNO) and Y-randomization techniques affirmed the model's robustness and validity. Computed pMIC values were found to be in good agreement (+/- XX%) with experimentally determined values. The proposed model may be a superior predictor of the counter-parasitic action of coumarin analogs and can be utilized for recommendation of new chemopreventive species. c. Materials and Methods – Lines 46-48 – Sentence structure is awkward. Recommendation: Reword to read: The purpose of the present work is to perform a quantum chemical QSAR study on	
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	the series of coumarin derivatives in Table 1[13], to compare the computed values with the experimental activities of the compounds as Antifungal Agents...” d. Chemical Data – Lines 50-53 – Sentence structure is awkward. Recommendation: Reword to read: Biological data on the activity of coumarin derivatives has been obtained[13] and is reported in Table 1. The activity data refers to pMIC (–log MIC), which indicates the experimentally determined biological activity of the compounds necessary for the inhibition of <i>candida albicans</i>. Fluconazole was used in Table 1 as an assay control. e. Computational and statistical details – Lines 70-72 – Sentences awkward. Recommendation: Change the sentences to read: “The molecular geometry of all the derivatives from the dataset (Table 1) was determined via energy minimization[14] and geometry optimization using a Merck Molecular Force Field (MMFF) with the B3LYP/6-311+G(d) method. This same density functional level was used to study QSAR[15-18].” f. Conclusion – To complete the paper and highlight the major findings of this work, the authors need to quantify and state the success of this model in its predictive ability of antifungal activity in coumarin derivatives.	
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Minor REVISION comments	a. Introduction – Line 26 – What does the term “phones” mean? Line 28 - I believe “Wnger” is supposed to be “finger”. Line 30 – Should read “...suffering from AIDS...” Line 38 – delete “kinds of” Lines 40-42 – Incomplete sentence. Rework: In this study, we use the genetic function approximation (GFA), a statistical modeling algorithm to build a functional model of experimental data. Table 1 – One of the columns labeled pMIC (□g/mL) is actually MIC and should be corrected. - The nomenclature of these entries should be corrected. These are not chromenone derivatives and should be named as coumarin derivatives. b. Computational and statistical details – Lines 64-66 – spacing between Windows 7 is missing, spacing between Descriptor (A...), version is missing. c. Calculations- Lines 76, 83, 86, 88 – delete the hyphen in determine, interactions, complexity, Schrödinger, respectively. d. Density functional theory (DFT)- This part of the manuscript does not add substantially to the worth of the paper, and should be substantially reduced in length. In addition, the authors use phraseology that is unscientific. For example, Lines 92-95 read: Density function theory is an abdominal muscle abinitio estimation strategy for the Schrödinger mathematical statement that depends on the thickness or likelihood of electrons around a molecule as an element of the range from that molecule, rather than wave capacities as different speculations utilize. -what does the term abdominal muscle mean? Delete this, as it does not add to the description of DFT. - ab initio is two words, not one. - use electron density to describe the presence of electron surrounding an atom. -What does “...as an element of the range from that	
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	molecule..." refer to? Recommendation: Reword - Density functional theory is an ab initio estimation for a solution to the Schrödinger equation that depends on the electron density around the nuclei in a molecule, rather than actual wave functions that other methods use. Lines 95, 96, 98, 100, 132 – Delete spaces in the following words: functional, mathematical, electrons, potential, reassessed. Lines 103-105 – This sentence is worded awkwardly and has some phrases that do not make sense. "DFT is a well known technique for estimate today in the computational science world on the grounds that it has a high precision for every unit PC ace cessor (CPU) time proportion in examination to different system [19]." -What does the highlighted words "ace cessor" refer to – is this supposed to be "processor"? The word "system" should be plural in this context. e. GFA discussion (Lines 109-158). This section is pivotal to the paper and should be more directly related to DFT. While the authors lay out a discussion of what GFA can do, it seems that this part of the paper is stand-alone. In other words, what is it about DFT that permits the authors to use the GFA approximation? In addition, lines 142-143 contain an unfinished sentence: "At the point when this rule has been fulfilled, no further eras are figure" This must be reworded and completed. f. Results and Discussion- Lines 162-163 – Sentence is awkward. Recommendation: Reword to read: In a general sense, QSAR addresses two inquiries: what auxiliary and electronic properties of an atom decide its movement and what can be modified to enhance this action? Lines 165-166 – Imprecise wording. Recommendation: Reword to read: This saves both time and money, permitting the exclusion of subpar competitors without expending	
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	research facility resources [24]. QSAR Study Lines 171-174 – Sentence structure and wording is awkward: Most relapse calculation depends on the information that is, in effect, typically examined, on the off chance that the information is not ordinarily disseminated, we ought to think about applying as a numerical change to accomplish an ordinary circulation. -Missing commas -subject-verb agreement requires “is” - What does the last highlighted phrase mean? Reword. Lines 174-177 – The commas after Table 4 are incorrect punctuation marks and should be deleted. - Line 183 – insert the word “a” between Developing & QSAR Line 185 - delete the phrase As of right now, and begin the sentence with “In a normal...” Line 187 – Correct the sentence beginning with “Table Shows...” to “Table 5 shows...” Line 188 – Delete the last sentence – it is redundant. Line 193 – Delete the period after Table 6. Line 195 – What do you mean by “...predetermined number of eras.” Do you mean areas? Clarify. Line 206 – Insert a period after [26]. Line 219 – Table 7 should be deleted and the best fit equation should identified as a equation (3). Line 224 – change eq (3) to eq (4). Line 241 – The word define should be plural – change to defines. The word samples should be singular – change to sample. Line 245 – The word should be cross-validated, not crossvalidated. Line 246 – delete the extra space between LOO and the period. Line 252 – capitalize the y term in (in X and y simultaneously). Line 254 – yield should be plural, change to yields. Line 261 – Delete the fragment “The y-randomization test.” It	
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	serves no purpose. Line 264 – Sentence is awkwardly worded. Recommend changing to “There are different ways to judge whether the genuine model is described by a chance relationship.” Line 282 – The word prediction should be plural. Change to predictions. Line 283 – The word “term” should be changed to “termed”. Line 284 – Delete the space between the word domain and the period. Lines 288-290, 297, 309. Change the numbers assigned to these equations to 5, 6, 7, 8 and 9, respectively. Line 294 – modeling is misspelled. Correct it. Line 296 – The word “value” should be plural. Change to “values”. Line 310 – Change the sentence to read: “All (h_{ii}, t_e or t_{ext}, h_{ii}, t_r) leverages...” Lines 312-314 – Sentence structure is poor. Reword to read “Along the ordinate ± 2.5-3 standard deviation units will used as the boundary because points that lie within a ± 3 standardized residual from the mean covers 99% of the normally distributed data [37-39]. Lines 317-319 – Figure 1. Relabel Y-axis as Standardized Residuals. In the legend, the word training is not complete. Recommend retitling - Figure 1. Williams plot of the standardized residuals v. leverage values. Line 320-322 – Reword sentence to clarify: “As Figure 1 shows, all compounds of the training set and test set are inside an area bounded by 3 standardized residuals (Y axis) and the warning h^* value of 0.714 (X-axis) with the exception of compound X. This means that all evaluated compounds except one have a leverage lower than the warning h value of 0.714. Line 327 – Change Figure 2 title to : Predicted pMIC v. Observed pMIC. Line 328 – Delete the colon after the number 2 and drop the capital letter in the word observed. Line 345 – Rename Figure to Figure 4. Outlier analysis	
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	The individual graphs should be labeled a and b. Line 358 – Reaname Figure 5 to Figure 5. Variable usage count v. Generation number. Line 363 – Delete the spaces after population, and parents,. Conclusion Line 372 – delete the comma in the word correlations. - Change the words ketones to coumarin. Lines 373-374 – hyphenate the word cross-validation. Line 375 – change the word built to constructed. Line 378 – change the wording of the sentence: "...role in the antifungal activity of the compounds." to "...role in the predicting the antifungal activity of coumarin derivatives."	
<u>Optional/General</u> comments		

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