Computational efforts towards the analysis of synthetic preference of cis and trans isomers of o-anisaldehyde chalcone derivatives

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Abstract

Chalcones are widely diverse naturally and synthetically produced biological compounds. Chalcones function as pharmaceutical agents treating many disorders and diseases such as viral and cardiovascular diseases, infections, and cancers. In this study we are aiming to computational synthesize chalcone isomers of biological importance and understand the chemical properties regulating the production of various chemical arrangements of the same molecule, also known as isomers. A variation in three dimensional atom arrangement can drastically effect chalcone function. Computational methods expand the use of produced models in synthetic questions while minimizing use of resources and organic waste production. We are specifically aiming to analyze the effect of ketone starting material on chalcone stability as well as comparing the stability and energetic characteristics of chalcone isomers. The experimental data collected, carbonyl frequencies and reaction energies will identify the most likely isomer produced when chalcone condensation it completed. Our results suggest the production of both trans and cis chalcone isomer is thermodynamically possible, however the favored isomer is dependent upon the starting material.

Introduction

Chalcones are chemical compounds found in plants that function as a natural defense mechanism or relevant intermediates and have demonstrated valuable biological properties (9). Chalcones are clinically used for their anti-cancer, anti-diabetic and anti-inflammatory properties (9). Preliminary data has demonstrated chalcones may inhibit SARS-CoV-2 proteins responsible for COVID-19 (12).

Containing both an aromatic ketone and b-unsaturated moiety, chalcones produce the compound class known as chalconoids (9). Chalcones are produced using an aldol condensation reaction of an aromatic ketone and aromatic aldehyde (Scheme 1) (10). Condensation reactions consist of the combination of two molecules to form one larger molecule (8). An aromatic ketone is a functional group containing a carbonyl with two carbon substituents, one of which must be an aromatic ring (8). An aromatic aldehyde is also characterized by containing a carbonyl group with two substituents (8). One substituent is an aromatic ring while the other is a hydrogen atom (8). The condensation reaction begins by activation of an aryl ketone to form an activated ketone also known as an enolate intermediate (Scheme 1). The activated ketone will then condense with an aldehyde to produce the skeleton of a final product (Scheme 1).
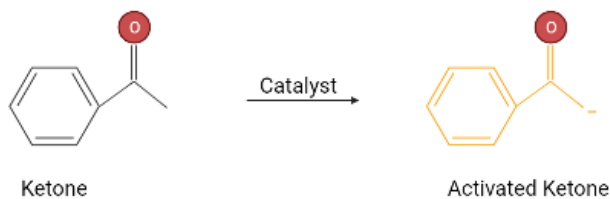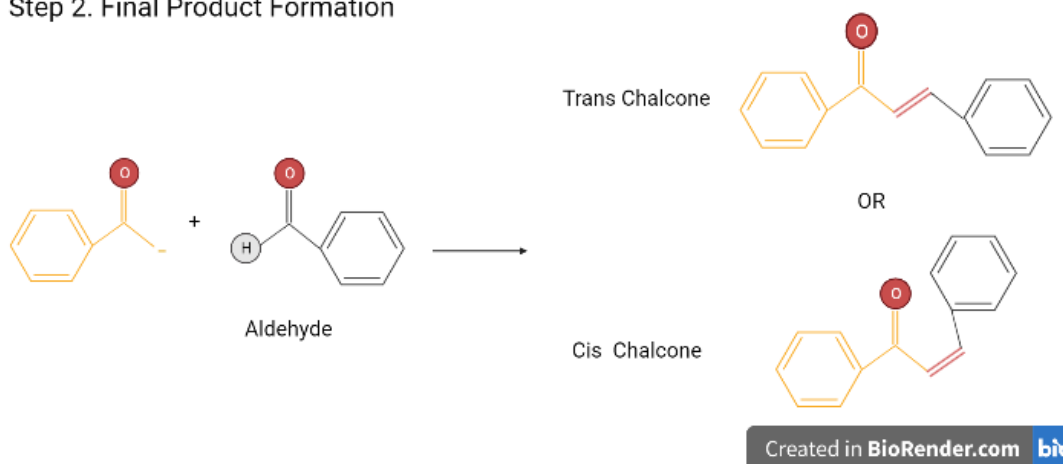
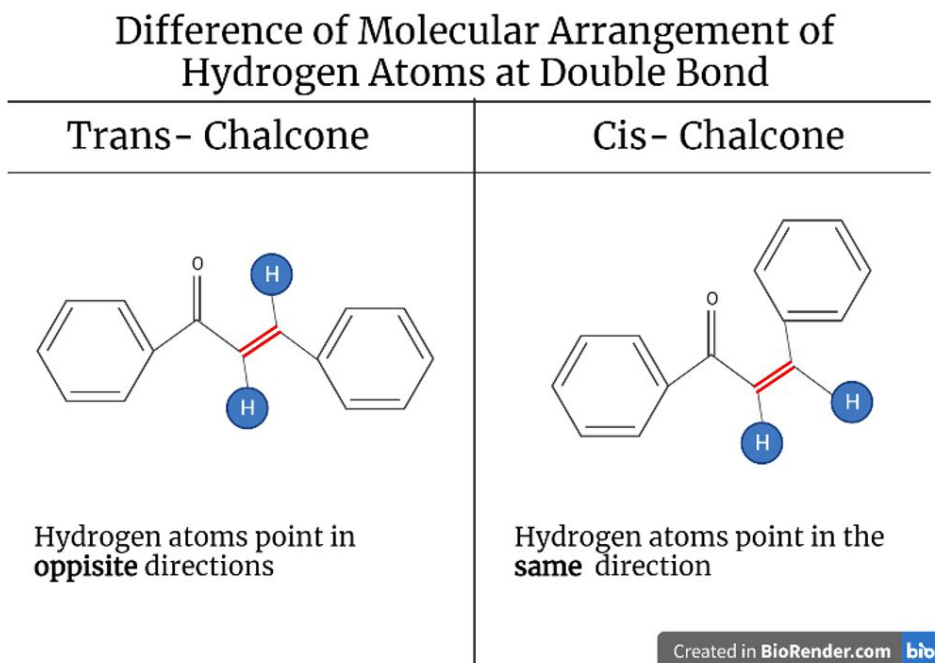Scheme 1. Summary of chalcone synthesis via an aldol condensation. Produced in BioRender

The geometry of a chalcone produces substantial differences that may affect the molecule's function. The orientation of the double bond (shown in red) determines if the compound is characterized as a trans or cis isomer (Scheme 2). Trans isomers are produced if the hydrogen atoms found on opposing sides of the double bond point in opposite directions (Scheme 2). In contrast, cis isomers are produced if the hydrogen atoms of the double bond are oriented in the same direction (Scheme 2).

Difference of Molecular Arrangement of Hydrogen Atoms at Double Bond

Trans- Chalcone	Cis- Chalcone
Hydrogen atoms point in **oppisite** directions	Hydrogen atoms point in the **same** direction

Created in **BioRender.com**

Scheme 2. Illustration of two possible isomers. Produced in BioRender

Starting materials and products were modeled and analyzed for chemical characteristics to determine final product stability and favorability. Intermediates are compounds found between the transition of the starting material to product while the transition state is the highest energy compound between the starting materials and products. Transition states and intermediate steps were not deemed important for determination of isomer chalcone production, and thus were not modeled. In this study, three computationally synthesized chalcones with antiproliferative properties were produced and analyzed to understand the chemical properties regulating the synthetic preference of isomer production (7).

Experimental procedure
Model Synthesis

All structures were modeled using Avogadro (Version 1.2.0n, 2012) (1,6). Structures were optimized using an UFF force field and 4 steps per update. Optimization includes inducing correct bond lengths and molecule orientations. Files were saved as a chemical markup language (CML) file. Input files were then produced using the computational chemistry suite GAMESS (5 Dec 2014 R1) (2). Input file generator header was provided by Valeria Stepanova Inc (2021).

Structure Analysis

Input structures produced by input generator were ran in computational chemistry suite GAMESS extension within Mo-Calc2012 (2). Programs analyzed each molecule for thermodynamic parameters such as total enthalpy (H°), entropy (S°) and energy (G°). All starting material, aldehydes and ketones, and trans and cis configurations of the chalcone products were ran and analyzed.

Vibrational Frequencies and Final Images

Output structure files produced by GAMESS were open and analyzed in MaxMol (4). Vibrational frequencies of carbonyl groups and 3-dimensional configuration images of all starting materials and products were produced and analyzed.

Characterization of energies

Using energies produced by GAMEES, changes in enthalpy ($\Delta H°_{rxn}$) and total change of energy of reaction ($\Delta G°_{rxn}$) were calculated using formula 1 (5). The resulting values were analyzed for significance.

$$\Delta G°_{rxn}= \sum \Delta G°_{products} - \sum \Delta G°_{reactants}$$

$$\Delta H°_{rxn}= \sum \Delta H°_{products} - \sum \Delta H°_{reactants}$$

$$\Delta S°_{rxn}= \sum \Delta S°_{products} - \sum \Delta S°_{reactants}$$

Formula 1. General formulas used for calculation of thermodynamic preferences.

Results and discussion

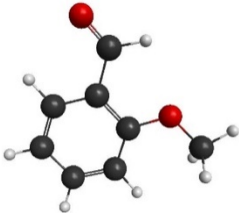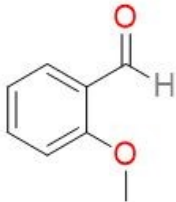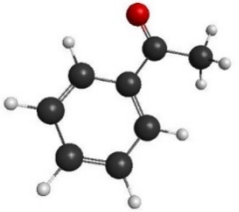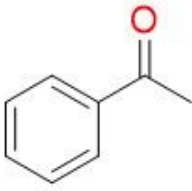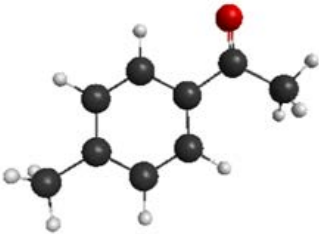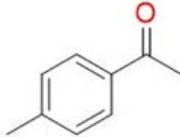All bonds within molecules vibrate and absorb various lengths of light. Specifically, the carbonyl functional group, (C=O bond) strongly absorbs light in the IR spectrum and can be read and analyzed. The frequencies of vibrations are extremely sensitive to changes in their neighboring functional groups and correlate to the electron density between the carbon and oxygen atoms (12). More electrons present between the atoms lead to decreased frequencies. Fewer electrons present lead to the bond vibrating faster. A carbonyl group is described as an electron withdrawing group, thus increasing stability as electron density increases (12).
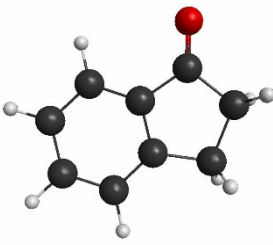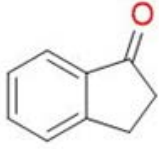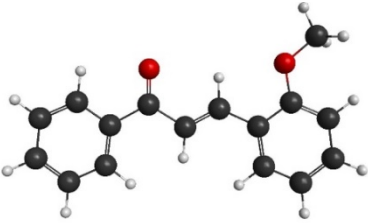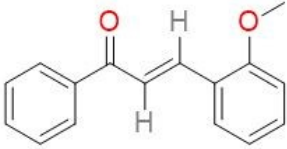
Gibbs free energy is an important reaction characteristic that is calculated by the sum of the reaction's enthalpy and entropy (11). Enthalpy is a representation of the heat within a reaction system. This can be correlated to the energy associated with breaking and forming bonds. Entropy is a value that describes the disorder within a reaction system. Another important characteristic is the change in enthalpy ($\Delta H°rxn$). This value describes the change in energy associated with the breaking of old bonds and forming new bonds (11). The change in Gibbs free energy ($\Delta G°rxn$) is used to predict if a reaction occurs spontaneously as written (11). A spontaneous reaction is characterized by a negative $\Delta H°rxn$ and $\Delta G°rxn$.

To ensure the accuracy of the data, the first compound o-Anisaldehyde, was calculated by each researcher. The calculated values for vibrational frequencies were found to correlate to one another with an average of 1887 ± 9

cm^{-1} and a range of 1876 cm^{-1} to 1892 cm^{-1}. Total enthalpy and free energy also correlated within the members. Total enthalpy values averaged 428±2 kJ/mol and ranged from 427 kJ/mol to 429kJ/mol. Free energies ranged 317 kJ/mol to 320 kJ/mol and averaged 318±2 kJ/mol.

Molecule ID	IUPAC Name	3D Drawing	2D - Drawing
o-Anisaldehyde			
Acetophenone			
p-Methylacetophenone			
1-Indadanone			
Chalcone product 1	Trans -3-(2-methoxyphenyl)-1-phenylprop-2-en-1-one		

Chalcone product 2	Cis -3-(2-methoxyphenyl)-1-phenylprop-2-en-1-one		
Chalcone product 3	Trans-3-(2-methoxyphenyl)-1-(4-methylphenyl)prop-2-en-1-one		
Chalcone product 4	Cis -3-(2-methoxyphenyl)-1-(4-methylphenyl)prop-2-en-1-one		
Chalcone 5	Trans-2-[(2-methoxyphenyl)methylidene]-2,3-dihydro-1H-inden-1-one		
Chalcone 6	Cis -2-[(2-methoxyphenyl)methylidene]-2,3-dihydro-1H-inden-1-one		
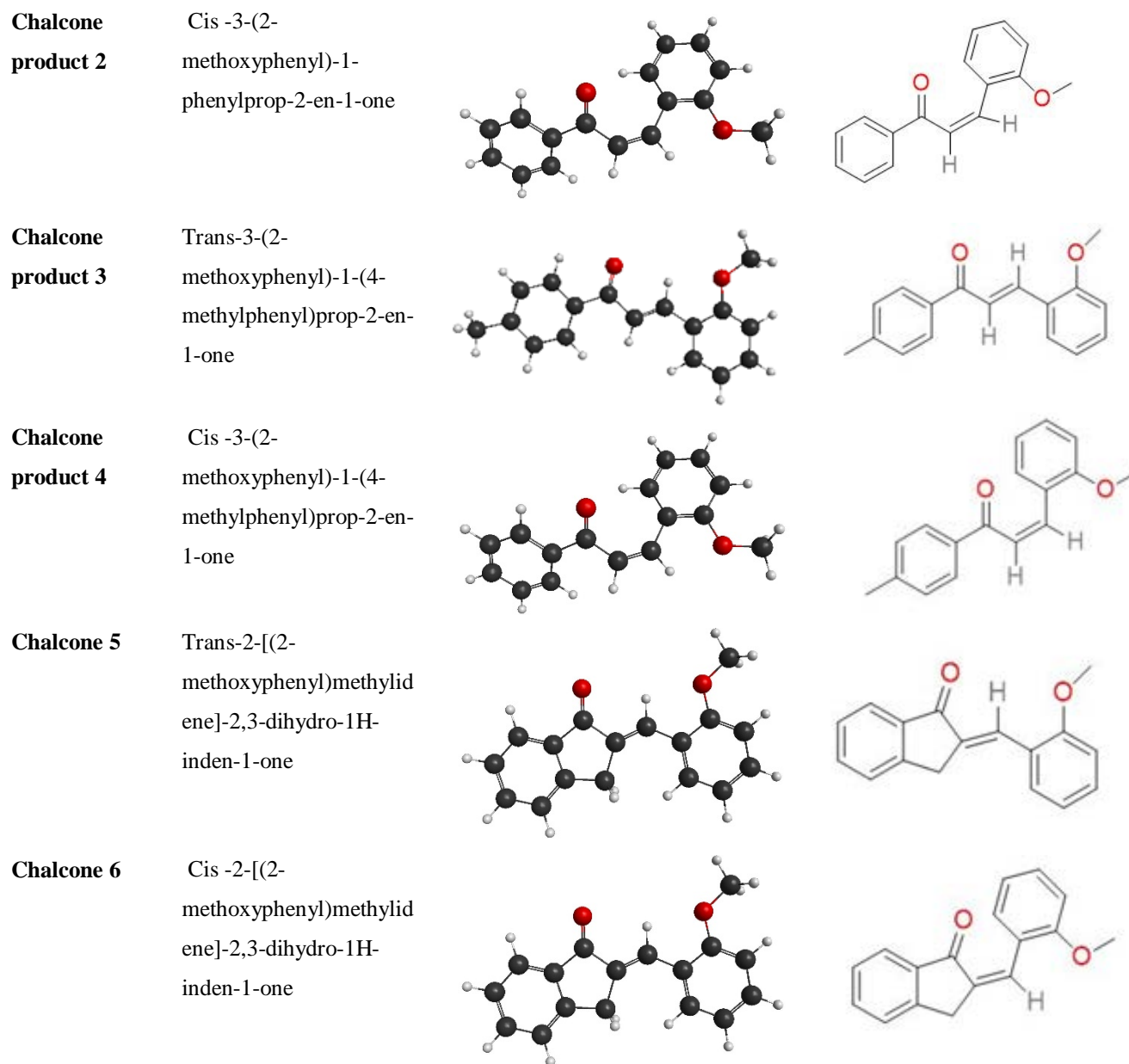
Figure 2. Chemical images of reactants and products of chalcones of interest. 3D images produced in wxMacMol. 2D image produced in ChemDraw.

Table 1. Vibrational frequencies of carbonyl groups of target molecules

Starting Material Name	Vibrational Frequency (cm^{-1})	Chalcone ID	Vibrational Frequency (cm^{-1})
o-Anisaldehyde	1887±9	1	1884.989990
Acetophenone	1913.9399411	2	1883.949951
p-Methylacetophenone	1909.859985	3	1783.089966

1-Indadanone	1952.239990

4	1872.869995
5	1945.469971
6	1942.430054

Table 2. Computationally determined energetic properties of suspected molecules

Starting Material Name	Total H (kJ/mol)	Total G (kJ/mol)
o-Anisaldehyde	428 ± 2	318 ± 2
Acetophenone	413.337	308.159
p-Methylacetophenone	494.731	376.685
1-Indadanone	433.626	328.360

Chalcone ID	Total H (kJ/mol)	Total G (kJ/mol)
1	774.216	614.301
2	771.154	623.016
3	852.857	688.369
4	855.540	682.305
5	790.865	636.796
6	786.862	638.298

Table 3. Calculated thermodynamic parameters for chalcones of interest.

Chalcone ID	ΔH°_{rxn}[a](kJ/mol)	ΔG°_{rxn} [b] (kJ/mol)
1	-66.611	-14.319
2	-69.673	-5.604
3	-71.765	-6.188
4	-69.082	-12.252
5	-72.634	-9.366
6	-92.346	-7.864

a. Calculated using Equation 1: $\Delta H^{\circ}_{rxn} = \sum \Delta H^{\circ}_{products} - \sum \Delta H^{\circ}_{reactants}$

b. Calculated using Equation 2: $\Delta G^{\circ}_{rxn} = \sum \Delta G^{\circ}_{products} - \sum \Delta G^{\circ}_{reactants}$

Chalcone 1 and 2 are the resulting isomer chalcones when o-Anisaldehyde and Acetophenone are condensed (Fig2). The trans chalcone (chalcone 1) has a carbonyl vibrational frequency characterized by 1885 cm^{-1} while the cis chalcone (chalcone 2) is characterized as 1884 cm^{-1}(Table 1). This suggests the trans and cis isomers contain similar electrons between the carbonyl atoms and therefore are similar in stability. There was a slight decrease in ΔH°rxn when comparing chalcone 1 (-67 kJ/mol) and chalcone 2 (-70 kJ/mol) (Table2). The ΔG°rxn increased from chalcone 1 (-14 kJ/mol) to the chalcone 2 (-6 kJ/mol) (Table3). Though the small decrease in enthalpy, the greater changes in reaction free energy suggests the production of the trans chalcone isomer from o-Anisaldehyde and Acetophenone is favored over the formation of the cis isomer.

The production of 3-(2-methoxyphenyl)-1-(4-methylphenyl)prop-2-en-1-one (chalcones 3 and 4) includes the condensation of o-Anisaldehyde and p-Methylacetophenone. In comparison, chalcone 3's and chalcone 4's carbonyl frequencies are significantly different (1783cm^{-1} vs 1873cm^{-1}) (Table 1). The increased carbonyl frequency of cis chalcone 4 suggests it, chalcone 4, is significantly less stable then chalcone 3. Minor differences were seen when analyzing the ΔH°rxn of chalcone 3 (-71 kJ/mol) and chalcone 4 (-69 kJ/mol) (Table 2). A larger variation was seen when analyzing ΔG°rxn. Chalcone 3 showed an increase of 6 kJ/mol compared to chalcone 4 (Table3).

Significant changes in carbonyl frequency suggest the production of the trans chalcone (chalcone 3) from o-Anisaldehyde and p-Methylacetophenone is favored over the cis isomer (chalcone 4).

Condensation of o-Anisaldehyde and 1-Indandanone produces cis and trans isomers of 2-[(2-methoxyphenyl)methylidene]-2,3-dihydro-1H-inden-1-one (chalcones 5 and 6) (Fig4). When analyzing carbonyl vibrational frequencies of the two isomers, a destabilization of the chalcone 6 can be observed. There was a decrease from 1945cm^{-1} (chalcone 5) to 1942cm^{-1} (chalcone 6). Although the two values are very similar, this suggests that the trans isomer contains slightly fewer electrons between the atoms of carbonyl group. (Table1). The most noticeable difference between chalcone 6 and 5 is observed when analyzing the change of enthalpy of reaction. The chalcone 5 is characterized by an ΔH°rxn of -73kJ/mol while chalcone 6 is characterized by -92kJ/mol (Table3). This data suggests that the cis isomer requires less energy to form and break new bonds. The change in free energy, ΔG°rxn, of chalcone 5 was -9kJ/mol and increased for chalcone 6 to -8kJ/mol (Table3). The conjunction of these results suggests the production of the cis chalcone isomer from o-Anisaldehyde and 1-Indanone is slightly more stable and favored than the formation of the trans isomer.

Though little change is seen between the isomers of all the chalcones analyzed, large variations are seen between chalcones of varying ketone starting material. A direct correlation between starting material and chalcone product reactivity is observed. p-Methylacetophenone derived chalcones 3 and 4 presents with the lowest carbonyl frequencies which correlates to the least reactive and most stable chalcone (Table 1). In contrast, 1-indanone derived chalcones 5 and 6 are characterized by the largest carbonyl frequencies and can be characterized as the most reactive, least stable chalcones tested (Table 1). Starting material p-Methylacetophenone and its derived chalcones, 3 and 4, are characterized as the most stable compounds tested. Though these results comment on stability, there is not an observed correlation to isomer preference.

The acetophenone and p-Methylacetophenone derived chalcones isomers (chalcones 1-4) as well as unfavored chalcone 5 are represented by similar changes in enthalpy (Table 3). The favored cis 1-Indanone derived chalcone 6 is defined by the most negative change in enthalpy (Table 3). These results suggest the 1-Indanone derided chalcone 6 requires the least amount of energy to form, and thus is the most favored.

Starting material, Acetophenone is characterized by the most spontaneous, chalcone 1, as well as the least spontaneous, chalcone 2, condensations (Table 3). Values ranging from –5 kJ/mol to -14 kJ/mol, the change of free energy has the smallest variations between chalcones produced.

Conclusion

Chalcones are widely structurally diverse compounds with numerous pharmaceutical applications. Although they can exist as cis and trans isomers the general synthesis produces exclusively trans-product. In this study, we attempted to identify a possibility of obtaining a cis-isomer for several chalcones and studied factors that govern the process using computational modeling. Our results demonstrate a pattern of thermodynamic preference for various chalcone isomers and a strong dependance to the starting materials used. According to our calculations synthesis of chalcone 6 favors the formation of cis-isomer due to the stability of the product and the starting ketone,

1-Indanone. The least stable and energetically costly chalcones, such as compounds 1-4, favor the trans-isomer. Further research combining synthetic and computational perspectives will be needed to expand the variety of chalcones, however, our initial results suggest that reactions of thermodynamically stable ketone starting materials favor the cis-configuration of the final chalcone.

References

1. Avogadro: an open-source molecular builder and visualization tool. Version 1.2.0n http://avogadro.cc/
2. Barca, G. M. J.; Bertoni, C.; Carrington, L.; Datta, D.; De Silva, N.; Deustua, J. E.; Fedorov, D. G.; Gour, J. R.; Gunina, A. O.; Guidez, E.; Harville, T.; Irle, S.; Ivanic, J.; Kowalski, K.; Leang, S. S.; Li, H.; Li, W.; Lutz, J. J.; Magoulas, I.; Mato, J.; Mironov, V.; Nakata, H.; Pham, B. Q.; Piecuch, P.; Poole, D.; Pruitt, S. R.; Rendell, A. P.; Roskop, L. B.; Ruedenberg, K.; Sattasathuchana, T.; Schmidt, M. W.; Shen, J.; Slipchenko, L.; Sosonkina, M.; Sundriyal, V.; Tiwari, A.; Vallejo, J. L. G.; Westheimer, B.; Wloch, M.; Xu, P.; Zahariev, F.; Gordon, M. S. Recent developments in the general atomic and molecular electronic structure system. J. Chem. Phys. 2020, 152, 154102. https://doi.org/10.1063/5.0005188
3. Binkley, J. S.; Pople, J. A.; Hehre, W. J. Self-consistent molecular orbital methods. 21. Small split-valence basis sets for first-row elements. *J. Am. Chem. Soc.* **1980**, *102*, 939-947. https://doi.org/10.1021/ja00523a008.
4. Bode, B. M., and Gordon, M. S. MacMolPlt: a graphical user interface for GAMESS *J. Mol. Graphics and Modeling* **1999**, *16*, 133-138. https://doi.org/10.1016/s1093-3263(99)00002-9
5. Hanwell, M. D.; Curtis, D. E.; Lonie, D. C.; Vandermeersch, T.; Zurek, E.; Hutchison, G. R. "Avogadro: An advanced semantic chemical editor, visualization, and analysis platform" *J. Cheminformatics* **2012**, *4*:17.
6. Gaonkar, S.L., Vignesh, U.N. Synthesis and pharmacological properties of chalcones: a review. *Res Chem Intermed,* **2017**, 43**,** 6043–6077 https://doi.org/10.1007/s11164-017-2977-5
7. Mellado, M., Madrid, A., Reyna, M. Synthesis of chalcones with antiproliferative activity on the SH-SY5Y neuroblastoma cell line: Quantitative Structure–Activity Relationship Models. *Med Chem Res* 2018, 27**,** 2414–2425 https://doi.org/10.1007/s00044-018-2245-2
8. Perrin, C. L, Chang, K-L., The Complete Mechanism of an Aldol Condensation. *Journal of Organic Chemistry*, **2016**, 81(12), 5631-5635 doi: 10.1021/acs.joc.6b00959
9. Shakil, N.A.; Singh, M.K.; Sathiyendiran, M.; Kumar, J.; Padaria, J.C. Microwave synthesis, characterization and bio-efficacy evaluation of novel chalcone based 6-carbethoxy-2-cyclohexen-1-one and 2H-indazol-3-ol derivatives. *European Journal of Medicinal Chemistry,* **2013**, 59, 120-131
10. Shapiro, N.Z.; Shapley, L. S. Mass Action Laws and the Gibbs Free Energy Function. *Journal of the Society for Industrial and Applied Mathematics,* **1965**, 13:2, 353-375 https://doi.org/10.1137/0113020
11. Shiraz, A. K.; Goharrizi, A. Y.; Hamidi, S. M. Structural stability and electron density analysis of doped germanene: a first-principles study. *Res. Express, 2019, 6:10*
12. Vijayakumar, B. G., Ramesh, D., Joji, A., Jayachandra Prakasan, J., & Kannan, T. In silico pharmacokinetic and molecular docking studies of natural flavonoids and synthetic indole chalcones against essential proteins of SARS-CoV-2. E*uropean journal of pharmacology*, **2020**, 886, 1-12. https://doi.org/10.1016/j.ejphar.2020.173448
13. Yerragunta V, Kumaraswamy T, Suman D, Anusha V, Patil P, Samhitha T, A review on Chalcones and its importance, PharmaTutor, 2013, 1(2), 54-59