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Design, Synthesis, Characterisation And Structural Insights Into The Drug-Likeness Of Substituted Chalcones

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ABSTRACT: A series of substituted chalcone derivatives (2a–2j) were synthesized in excellent yields and thoroughly characterized using IR, ^{1}H NMR, ^{13}C NMR, and HRMS techniques. The physicochemical properties, drug-likeness, and ADME (absorption, distribution, metabolism, and excretion) profiles of these compounds were evaluated using SwissADME analysis. Compounds 2a, 2b, and 2d exhibited promising drug-like characteristics, showing no violations of Lipinski's Rule of Five, moderate Log P values, and relatively low TPSA, indicating their potential for good oral bioavailability and membrane permeability. In contrast, compounds 2c, 2g, 2h, and 2i displayed violations of Lipinski's criteria, suggesting possible limitations in their drug efficacy and absorption profiles. Compounds 2e and 2f, despite having higher TPSA values and increased hydrophobicity, demonstrated good synthetic accessibility; however, their elevated polarity may reduce their membrane permeability and thus limit their therapeutic potential. These findings provide a valuable foundation for further structural optimization and biological evaluation of these chalcone derivatives.

Key words: Chalcones, Spectro-analytical characterization, Swiss ADME, Swiss Boiled-Egg Model.

1. INTRODUCTION

Chalcones are an important class of naturally occurring and synthetically accessible organic compounds that have attracted considerable attention in recent decades due to their broad spectrum of biological and pharmacological activities. Structurally, chalcones are characterized by the presence of an α, β-unsaturated carbonyl system linking two aromatic rings (ring A and ring B), forming the core structure of 1,3-diaryl-2-propen-1-one. This conjugated enone system contributes significantly to the reactivity and biological activity of chalcones, as it facilitates interactions with various biological targets through Michael addition and hydrogen bonding (Nowakowska, 2007).

Chalcones are biosynthetically precursors to flavonoids and isoflavonoids in plants, playing a pivotal role in the biosynthesis of numerous polyphenolic compounds. The presence of hydroxyl, methoxy, halogen, and other electron-donating or electron-withdrawing groups on the aromatic rings allows for extensive derivatization and structure–activity relationship (SAR) studies (Singh et al., 2014). Their straightforward synthesis via Claisen–Schmidt condensation between substituted benzaldehydes and acetophenones under basic or acidic conditions has enabled the preparation of numerous chalcone derivatives with enhanced or novel bioactivities (Go et al., 2005).

Due to their simple structure and synthetic versatility, chalcones serve as key intermediates in the synthesis of various heterocyclic compounds such as flavones, flavanones, aurones, pyrazolines, isoxazoles, and oxadiazoles (Batovska & Todorova, 2010). This synthetic accessibility, combined with their significant biological potential, has led to the widespread exploration of chalcones in drug discovery and development.

1.1 Biological and Pharmacological Applications of Chalcones

Chalcones are compounds with a broad spectrum of biological activities, including antimicrobial, anticancer, anti-inflammatory, antioxidant, antidiabetic, antiviral, and antiparasitic effects. These properties are attributed to their ability to modulate enzymes, interfere with protein–protein interactions, and induce apoptosis in cancer cells.

Antimicrobial Activity: Chalcones have shown effectiveness against both Gram-positive and Gram-negative bacteria, as well as fungal species, by damaging microbial membranes, inhibiting efflux pumps, or binding to key enzymes like DNA gyrase.

Anticancer Activity: Some chalcones inhibit tubulin polymerization, preventing mitosis, and modulate apoptosis-regulating proteins, thus exerting antimitotic and antiproliferative effects.

Anti-inflammatory and Antioxidant Activity: Chalcones reduce inflammation by inhibiting enzymes like cyclooxygenase (COX), lipoxygenase (LOX), and nitric oxide synthase (NOS). Their antioxidant properties arise from phenolic hydroxyl groups that scavenge free radicals.

Antidiabetic Activity: Chalcones have been found to inhibit enzymes such as α-glucosidase, aldose reductase, and DPP-IV, which are involved in diabetes mellitus.

Antiviral and Antiparasitic Activity: Chalcones and their derivatives show promise as antiviral agents against HIV, dengue, and SARS-CoV, as well as antiparasitic agents against malaria and Leishmania spp.

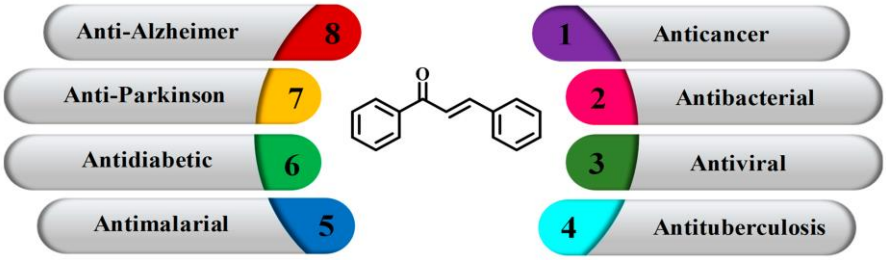


Figure 1: Pharmacological activity of Chalcones

1.2 Structural Modifications and SAR Studies

Structure–activity relationship (SAR) studies have shown that the substitution pattern on both aromatic rings plays a critical role in modulating the activity of chalcones. For example, electron-donating groups like hydroxyl and methoxy on ring A are often associated with increased antioxidant and anticancer properties, while electron-withdrawing groups on ring B (such as nitro or halogens) may enhance antimicrobial or antitumor effects (Singh et al., 2014). Hybrid chalcone scaffolds incorporating pharmacophores such as azoles, quinolines, or thiazoles have further expanded their biological profile (Zhang et al., 2021).

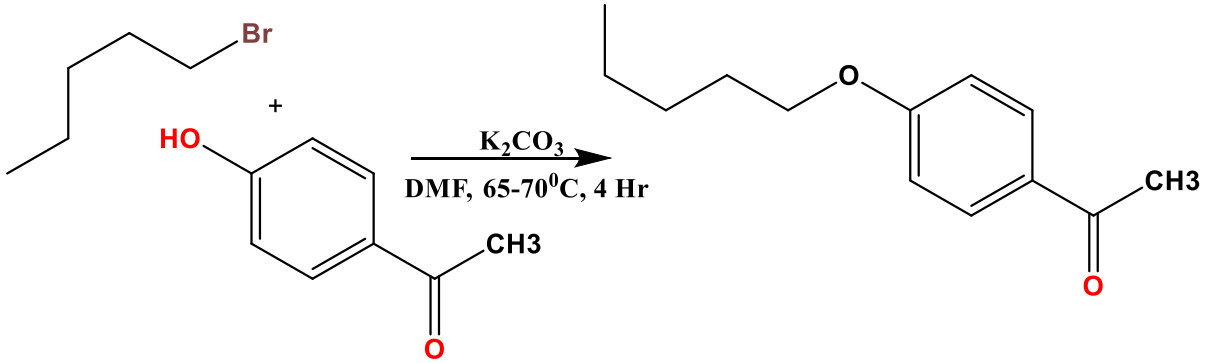
2. MATERIALS & METHODS:

2.1. Experimental:

The chemicals and reagents used in the experimental work were of AR grade, sourced from Sigma Aldrich, Molychem, and Himedia. Silica gel G for analytical chromatography (TLC) was obtained from E. Merck India Ltd. Chemicals were purified by distillation before use. Elemental analysis (C, H, N, & S) was performed using a Perkin-Elmer 240C elemental analyzer. UV-Vis spectra were recorded on a Perkin-Elmer 240 C spectrophotometer, while IR spectra were obtained using a Perkin-Elmer 435 spectrophotometer in the 4000-400 cm-1 range. 1H and 13C NMR spectra were recorded on a Bruker 400 MHz spectrometer in DMSO-d6. Mass spectra were measured with an LC-MSD-Trap-SL instrument using the ESI method. For in-silico molecular modeling, AutoDock Vina and PyRx tools were used, with docking images generated via BIOVIA Discovery Studio Visualizer 2021. SwissADME was employed to predict the pharmacokinetic and drug-like properties of the compounds.

2.2. Synthesis:

2.2.1. Preparation of 1-(4-(pentyloxy)phenyl)ethan-1-one:



2.2.2. Preparation of Chalcone derivatives:

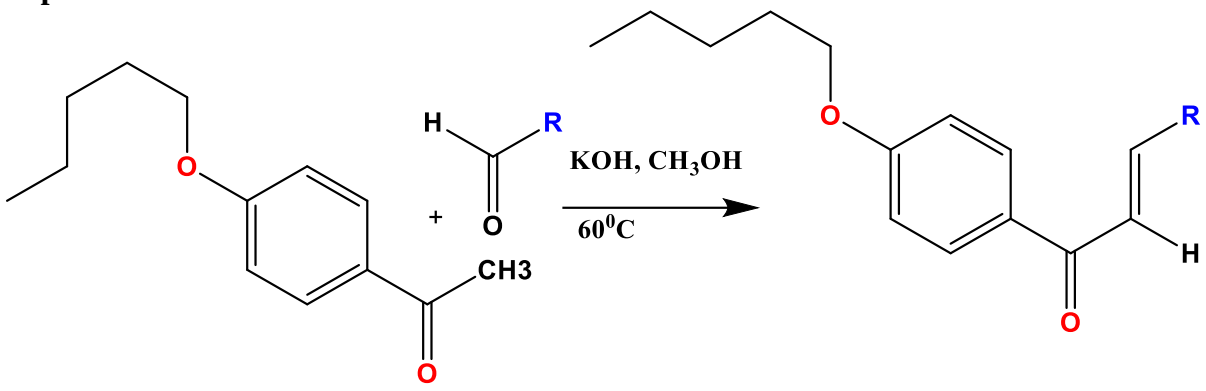
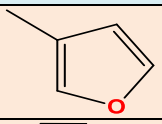
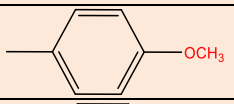
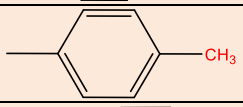
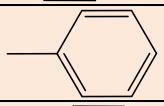
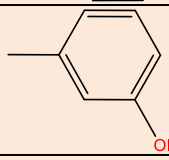
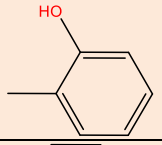
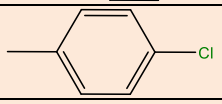
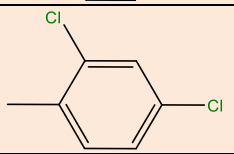
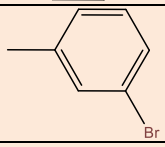
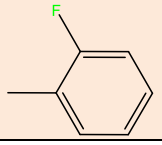


Table 1: List of Chalcone derivatives and their IUPAC names

Compound	R	IUPAC Name
2a		(E)-3-(furan-3-yl)-1-(4-(pentyloxy)phenyl)prop-2-en-1-one
2b		(E)-3-(4-methoxyphenyl)-1-(4-(pentyloxy)phenyl)prop-2-en-1-one
2c		(E)-1-(4-(pentyloxy)phenyl)-3-(p-tolyl)prop-2-en-1-one
2d		(E)-1-(4-(pentyloxy)phenyl)-3-phenylprop-2-en-1-one
2e		(E)-3-(3-hydroxyphenyl)-1-(4-(pentyloxy)phenyl)prop-2-en-1-one
2f		(E)-3-(2-hydroxyphenyl)-1-(4-(pentyloxy)phenyl)prop-2-en-1-one
2g		(E)-3-(4-chlorophenyl)-1-(4-(pentyloxy)phenyl)prop-2-en-1-one
2h		(E)-3-(2,4-dichlorophenyl)-1-(4-(pentyloxy)phenyl)prop-2-en-1-one
2i		(E)-3-(3-bromophenyl)-1-(4-(pentyloxy)phenyl)prop-2-en-1-one
2j		(E)-3-(2-fluorophenyl)-1-(4-(pentyloxy)phenyl)prop-2-en-1-one

3. Result & Discussion:

3.1. Spectro Analytical Characterization:

(E)-3-(furan-3-yl)-1-(4-(pentyloxy)phenyl)prop-2-en-1-one (2a):

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, 1H), 7.78 (s, 1H), 7.74 (d, *J* = 5.4 Hz, 2H), 7.55 (d, *J* = 5.7 1H), 7.41 (d, 1H), 7.06 (d, 1H), 6.44 (d, *J* = 5.7 Hz, 1H), 4.0 (t, *J* = 8.1 Hz, 2H), 1.76 (m, *J* = 8.1 Hz, 2H), 1.50 (m, *J* = 18.1 Hz, 2H), 1.34 (m, *J* = 30.1, 14.0 Hz, 2H), 0.94 (t, *J* = 11.1 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 191.43, 163.56, 145.64, 145.19, 140.22, 132.16, 130.29, 130.26, 118.03, 114.84, 109.88, 69.64, 29.21, 28.44, 22.94, 14.02. **IR (cm^{-1})**: ν_{max} 3050, 2976, 2903, 1674, 1590, 1443, 1362, 1020. HRMS (ESI, m/z): 284.36, 284.14, 285.14, 286.15. Elemental Analysis Calcd. For $C_{18}H_{20}O_3$: C, 76.03; H, 7.09; O, 16.88

(E)-3-(4-methoxyphenyl)-1-(4-(pentyloxy)phenyl)prop-2-en-1-one (2b):
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, 1H), 7.77 (d, 2H), 7.45 (d, 2H), 7.37 (d, 1H), 7.08 (d, 1H), 7.01 (d, 1H), 3.96 (s, 3H), 3.81 (t, *J* = 10.1 Hz, 2H), 1.73 (m, *J* = 10.1 Hz, 2H), 1.37 (m, 2H), 1.32 (m, 2H), 0.99 (t, *J* = 11.1 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 188.76, 162.95, 161.51, 143.72, 131.14, 130.71, 130.11, 127.69, 119.63, 114.77, 114.34, 68.29, 55.43, 28.86, 28.18, 22.47, 14.04. **IR (cm^{-1})**: ν_{max} 3027, 2928, 2896, 1687, 1540, 1428, 1343, 1103, 1023. HRMS (ESI, m/z): 324.42, 324.17 (100.0%), 325.18 (22.7%), 326.18 (2.5%). Elemental Analysis Calcd. For $C_{21}H_{24}O_3$: C, 77.75; H, 7.46; O, 14.79.

(E)-1-(4-(pentyloxy)phenyl)-3-(p-tolyl)prop-2-en-1-one (2c):
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, 1H), 7.76 (d, 2H), 7.42 (d, *J* = 5.21 Hz, 2H), 7.41 (d, 1H), 7.27 (d, *J* = 5.21 Hz, 1H), 7.06 (d, 2H), 4.0 (t, *J* = 9.2 Hz, 2H), 2.35 (s, 3H), 1.76 (m, *J* = 9.2 Hz, *J* = 16.1, 2H), 1.50 (m, *J* = 16.1, 14.0 Hz, 2H), 1.34 (m, *J* = 18.3, 16.1 Hz, 2H), 0.99 (t, *J* = 18.3 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 188.82, 163.03, 143.97, 140.80, 132.41, 130.94, 130.79, 129.69, 128.41, 120.94, 114.30, 68.30, 28.98, 28.86, 22.48, 21.55, 14.13. **IR (cm^{-1})**: ν_{max} 3050, 2906, 2806, 1727, 1654, 1590, 1443, 1362, 1042. HRMS (ESI, m/z): 308.42, 308.18, 309.18, 310.18. Elemental Analysis: Calcd. For $C_{21}H_{24}O_2$: C, 81.78; H, 7.84; O, 10.37.

(E)-1-(4-(pentyloxy)phenyl)-3-phenylprop-2-en-1-one (2d):
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, 1H), 7.77 (d, 2H), 7.57 (d, *J* = 6.2 Hz, 2H), 7.42 (d, *J* = 6.2 Hz, 2H), 7.41 (t, *J* = 6.2 Hz, 1H), 7.10 (d, *2*H), 6.90 (d, 1H), 3.98 (t, *J* = 8.1 Hz, 2H), 1.74 (m, *J* = 8.1 Hz, 2H), 1.37 (m, *J* = 12.3 Hz, 2H), 1.28 (m, *J* = 12.3, 11.0 Hz, 2H), 0.99 (t, *J* = 11.0 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 188.72, 163.13, 143.88, 135.16, 130.84, 130.32, 128.94, 128.38, 121.97, 114.34, 68.32, 28.85, 28.18, 22.47, 14.05. **IR (cm^{-1})**: ν_{max} 3005, 2986, 2916, 1664, 1525, 1396, 1362, 1023. HRMS (ESI, m/z): 294.39, 294.16, 295.17, 296.17. Elemental Analysis Calcd. For $C_{20}H_{22}O_2$: C, 81.60; H, 7.53; O, 10.87

(E)-3-(3-hydroxyphenyl)-1-(4-(pentyloxy)phenyl)prop-2-en-1-one (2e):
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, 1H), 7.76 (d, 2H), 7.22 (dd, *J* = 5.7 Hz, 1H), 7.07 (s, 1H), 7.06 (d, 2H), 6.98 (d, *J* = 5.7 Hz, 1H), 6.87 (d, 1H), 6.85 (d, 1H), 5.64 (s, 1H), 4.01 (t, *J* = 8.1 Hz, 2H), 1.76 (m, *J* = 8.1 Hz, 2H), 1.50 (m, *J* = 18.1 Hz, 2H), 1.34 (m, *J* = 19.1, 14.0 Hz, 2H), 0.99 (t, *J* = 11.1 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 189.04, 163.27, 156.42, 143.98, 136.60, 130.81, 130.12, 122.04, 120.73, 117.65, 115.13, 114.29, 68.34, 28.83, 28.16, 22.46, 14.03. **IR (cm^{-1})**: ν_{max} 3496, 3008, 2974, 2916, 1707, 1525, 1413, 1362, 1012. HRMS (ESI, m/z): m/z: 310.16, 311.16, 312.16. Elemental Analysis Calcd. For $C_{20}H_{22}O_3$: C, 77.39; H, 7.14; O, 15.46

(E)-3-(2-hydroxyphenyl)-1-(4-(pentyloxy)phenyl)prop-2-en-1-one (2f):
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, 1H), 7.73 (d, 2H), 7.36 (d, 1H), 7.06 (d, 2H), 6.98 (dd, 1H), 6.87 (d, 1H), 6.75 (d, 1H), 5.47 (s, 1H), 4.01 (t, *J* = 8.1 Hz, 2H), 1.76 (m, *J* = 8.1 Hz, 2H), 1.49 (m, *J* = 12.1 Hz, 2H), 1.34 (m, *J* = 12.1, 11.4 Hz, 2H), 0.99 (t, *J* = 11.4 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 190.13, 184.73, 163.14, 140.21, 131.63, 130.98, 129.18, 122.36, 120.58, 116.79, 114.32. **IR (cm^{-1})**: ν_{max} 3465, 3024, 2942, 2896, 1623, 1582, 1405, 1312, 1036. HRMS (ESI, m/z): 310.16, 311.16, 312.16. Elemental Analysis Calcd. For $C_{20}H_{22}O_3$: C, 77.39; H, 7.14; O, 15.46.

(E)-3-(4-chlorophenyl)-1-(4-(pentyloxy)phenyl)prop-2-en-1-one (2g):
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 4.9 Hz,1H), 7.75 (d, 2H), 7.59 (d, *J* = 4.9 Hz, 1H), 7.51 (d, *J* = 5.7 Hz, 2H), 7.44 (d, *J* = 5.7 Hz, 2H), 7.06 (d, 2H), 3.97 (t, *J* = 9.3 Hz, 2H), 1.75 (m, *J* = 9.3 Hz, 2H), 1.39 (m, *J* = 10.4 Hz, 2H), 1.32 (m, *J* = 10.4, 9.7 Hz, 2H), 0.99 (t, *J* = 9.7 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 188.36, 163.23, 142.35, 136.16, 133.66, 130.77, 129.51, 129.21, 114.37, 114.03, 112.36, 87.53**IR (cm^{-1})**: ν_{max} 3022, 2912, 2897, 1674, 1546, 1421, 1293, 1009, 810. HRMS (ESI, m/z): 328.12, 330.12, 329.13, 331.12. Elemental Analysis Calcd. For $C_{20}H_{21}ClO_2$: C, 73.05; H, 6.44; Cl, 10.78; O, 9.73

(E)-3-(2,4-dichlorophenyl)-1-(4-(pentyloxy)phenyl)prop-2-en-1-one (2h):
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, 1H), 7.76 (d, 2H), 7.51 (s, 1H), 7.49 (d, 1H), 7.44 (d, *J* = 5.2 Hz, 2H), 7.32 (d, *J* = 5.2 Hz, 1H), 7.06 (d, 2H), 4.0 (t, *J* = 8.1 Hz, 2H), 1.74 (m, *J* = 8.1 Hz, 2H), 1.38 (m, *J* = 10.1 Hz, 2H), 1.35 (m, *J* = 10.1, 2H), 0.99 (t, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 184.67, 148.20, 132.81, 132.27, 131.59, 131.07, 130.73, 129.64, 128.51, 126.31, 123.31, 120.71, 114.53, 68.30, 50.88, 45.00. **IR (cm^{-1})**: ν_{max} 3024, 2975, 2880, 1681, 1525, 1336, 1263, 1070, 993 and 840. HRMS (ESI, m/z): 362.08, 364.08, 363.09, 366.08, 365.08, 367.08. Elemental Analysis Calcd. For $C_{20}H_{20}Cl_2O_2$: C, 66.13; H, 5.55; Cl, 19.52; O, 8.81

(E)-3-(3-bromophenyl)-1-(4-(pentyloxy)phenyl)prop-2-en-1-one (2i):
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 5.4 Hz, 1H), 7.81 (s, 1H), 7.75 (d, 2H), 7.61 (d, *J* = 5.4 Hz, 1H), 7.59 (d, *J*= 5.3 Hz, 1H), 7.52 (d, *J* = 5.7 Hz, 2H), 7.31 (dd, *J* = 5.7 Hz, *J*= 5.3 Hz, 1H), 7.07 (d, 2H), 3.96 (t, *J* = 8.5 Hz, 2H), 1.74 (m, *J* = 8.5 Hz, 2H), 1.37 (m, *J* = 12.3 Hz, 2H), 1.32 (m, *J* = 12.3, 10.6 Hz, 2H), 0.99 (t, *J* = 10.6 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 188.08, 163.29, 141.94, 137.28, 133.03,

132.99, 131.12, 131.02, 130.85, 130.66, 127.20, 123.09, 114.40, 114.39. **IR (cm^{-1})**: ν_{max} 3026, 2942, 2895, 1672, 1540, 1428, 1302, 1012, 620. HRMS (ESI, m/z): 372.07, 374.07, 375.07, 373.08. Elemental Analysis Calcd. For $C_{20}H_{21}BrO_2$: C, 64.35; H, 5.67; Br, 21.41; O, 8.57

(E)-3-(2-fluorophenyl)-1-(4-(pentyloxy)phenyl)prop-2-en-1-one (2j)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 5.7 Hz, 1H), 7.75 (d, *J*= 4.9 Hz, 2H), 7.50 (d, *J* = 5.4 Hz, 1H), 7.36 (dd, 1H), 7.27 (d, *J* = 5.7 Hz, 1H), 7.17 (dd, *J*= 5.4 Hz,1H), 7.12 (d, 1H), 7.06 (d, *J*= 4.9 Hz, 2H), 4.0 (t, *J* = 8.1 Hz, 2H), 1.76 (m, *J* = 8.1 Hz, 2H), 1.50 (m, *J* = 10.1 Hz, 2H), 1.34 (m, *J* = 10.1, 9.7 Hz, 2H), 0.99 (t, *J* = 9.7 Hz, 3H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ 188.69, 163.21, 162.74, 160.72, 136.61, 131.57, 130.93, 130.58, 129.85, 129.61, 124.55, 123.26, 116.40, 116.29, 114.36, 114.18, 68.32, 28.84, 28.17, 22.47, 14.04. **IR (cm^{-1})**: ν_{max} 3021, 2965, 2897, 1645, 1508, 1423, 1262, 1102, 1013, 998. HRMS (ESI, m/z): 312.15, 313.16, 314.16. Elemental Analysis Calcd. For $C_{20}H_{21}FO_2$: C, 76.90; H, 6.78; F, 6.08; O, 10.24

3.2. Swiss ADME:

Table 2: Swiss ADME properties of the compounds 2a – 2j

Compound	MW	Violation of Lipinski's rule	The polar surface area (TPSA)	No. of Hydrogen Bond Acceptors	No. of Hydrogen Bond Donors	Log P	Synthetic accessibility
2a	284.35	No	39.44	3	0	3.64	3.08
2b	324.41	No	35.53	3	0	4.09	2.98
2c	308.41	Yes	26.30	2	0	4.08	2.96
2d	294.39	No	26.30	2	0	3.82	2.83
2e	310.39	No	46.53	3	1	3.47	2.93
2f	310.39	No	46.53	3	1	3.60	3.03
2g	328.83	Yes	26.30	2	0	4.08	2.86
2h	363.28	Yes	26.30	2	0	4.28	3.08
2i	373.28	Yes	26.30	2	0	4.21	2.95
2j	312.38	No	26.30	3	0	3.91	2.86

The table provides a Swiss ADME (Absorption, Distribution, Metabolism, and Excretion) analysis for ten compounds **(2a to 2j)**, detailing their physicochemical properties, their adherence to Lipinski's Rule of Five, and other related parameters.

MW (Molecular Weight): This represents the molecular weight of each compound. Compounds with a lower molecular weight are typically easier to absorb and may have better bioavailability.

Violation of Lipinski's Rule: Lipinski's Rule of Five is a set of criteria used to evaluate the drug-likeness of compounds based on their molecular properties. If a compound violates one or more of the rules, it may be less likely to be an effective drug. The rule includes parameters like molecular weight, hydrogen bond donors/acceptors, and Log P.

"No" indicates the compound does not violate the rule, suggesting better drug-likeness.

"Yes" indicates a violation, which could affect the compound's ability to function effectively as a drug.

Polar Surface Area (TPSA): TPSA reflects the surface area of a molecule that is polar and typically indicates how well a compound will permeate biological membranes, like the blood-brain barrier or intestinal absorption. A higher TPSA generally means poorer membrane permeability. **2a**, **2e**, and **2f** have higher TPSA values (≥ 39), which may affect absorption and permeability. **2c**, **2g**, **2h**, and **2i** have lower TPSA values (around 26), which may be more permeable.

No. of Hydrogen Bond Acceptors: This indicates the number of atoms in the molecule that can accept hydrogen bonds, which influences the compound's ability to interact with water and other molecules. Most compounds have **2 or 3 hydrogen bond acceptors**, which is typical for small molecules intended for absorption.

No. of Hydrogen Bond Donors: This indicates the number of hydrogen atoms available to donate to form hydrogen bonds. **2e** and **2f** have **1 hydrogen bond donor**, while most other compounds do not have any hydrogen bond donors, indicating a more hydrophobic character.

Log P (Partition Coefficient): Log P indicates the compound's hydrophobicity or lipophilicity. A value between **1 and 3** generally indicates good oral bioavailability and ability to cross cell membranes. **2a**, **2b**, and **2h** have higher Log P values (around 4), which may indicate higher lipophilicity and better cell

membrane permeability, but they may also pose challenges for water solubility. Lower Log P values (**2e** and **2d**) suggest moderate hydrophobicity, balancing solubility and membrane permeability.

Synthetic Accessibility: This score represents the ease with which a compound can be synthesized, with lower values indicating more challenging synthesis. It's a practical measure in drug discovery, as compounds that are difficult to synthesize may not be viable candidates for development. Most compounds have scores ranging from **2.83 to 3.08**, indicating that they are relatively easy to synthesize but not trivial.

2a, 2b, and 2d appear to have good drug-likeness, with no violations of Lipinski's Rule, moderate Log P values, and relatively low TPSA. **2c, 2g, 2h, and 2i** violate Lipinski's Rule, which may suggest reduced drug-likeness and potential challenges in absorption or bioavailability. **2e and 2f** have higher TPSA values, suggesting they might have reduced ability to permeate membranes, but they maintain good synthetic accessibility and low hydrogen bond donors.

3.3. Boiled Egg Model:

The Boiled Egg model is used to predict a compound's ability to cross biological barriers, focusing on its potential to penetrate the blood-brain barrier (BBB) and be absorbed in the human intestine (HIA). The model uses two axes: WLOGP (hydrophobicity) and TPSA (polar surface area), which help assess the compound's permeability.

Yellow Zone (BBB): Compounds in this zone are likely to cross the BBB, indicating potential for central nervous system (CNS) activity.

White Zone (HIA): Compounds here are likely to be well-absorbed in the human intestine, suggesting good bioavailability.

Additionally, the graph points show compounds that are substrates for the P-glycoprotein (PGP) transporter. PGP+ compounds may be actively effluxes, reducing bioavailability, while PGP- compounds are less affected by this transporter.

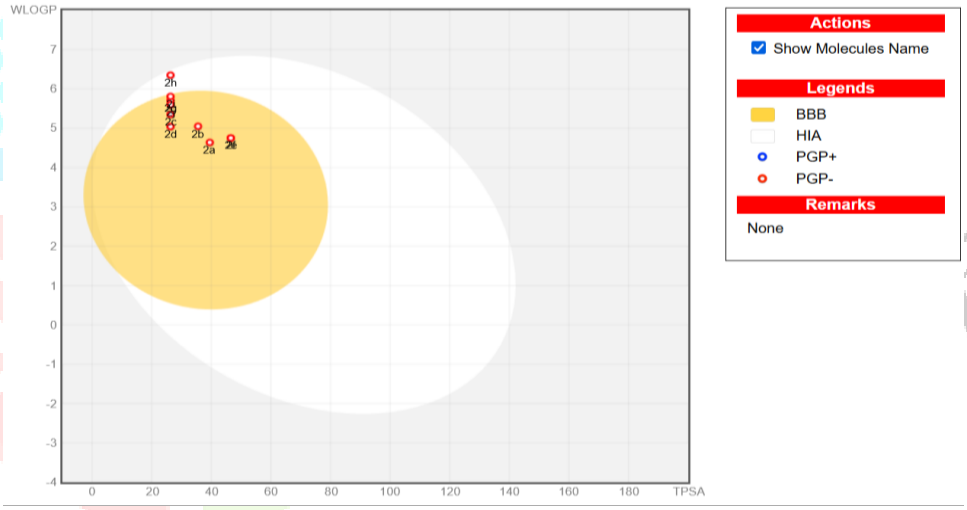


Figure 2: Swiss Boiled Egg model of the compounds 2a – 2j

4. Conclusion:

In this study, we have successfully developed chalcone derivatives (2a–2j). The methodology has proved to be advantageous owing to the use of inexpensive precursors and an organic base as the catalyst. The Swiss ADME analysis for compounds 2a to 2j provides valuable insights into their physicochemical properties, drug-likeness, and potential for absorption, distribution, metabolism, and excretion. Compounds like 2a, 2b, and 2d demonstrate good drug-likeness with no violations of Lipinski's Rule, moderate Log P values, and relatively low TPSA, suggesting they may have favorable bioavailability and permeability. On the other hand, compounds 2c, 2g, 2h, and 2i violate Lipinski's Rule, which could indicate challenges in their drug efficacy and absorption. Compounds 2e and 2f, while having higher TPSA values, show good synthetic accessibility and a more hydrophobic character, but their reduced membrane permeability might limit their efficacy.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest regarding the publication of this work.

References

1. Batovska, D. I., & Todorova, I. T. (2010). Trends in chalcone research: a short survey. *Current Clinical Pharmacology*, **5**(1), 1–29. https://doi.org/10.2174/157488410790410571
2. da Silva, C. G., Gomes, B. S., Pinto, M. C. F. R., et al. (2020). Chalcone derivatives: promising starting points for drug design. *Molecules*, **25**(15), 3624. https://doi.org/10.3390/molecules25153624
3. Go, M. L., Wu, X., & Liu, X. L. (2005). Chalcones: an update on cytotoxic and chemoprotective properties. *Current Medicinal Chemistry*, **12**(4), 483–499. https://doi.org/10.2174/0929867053363207
4. Nowakowska, Z. (2007). A review of anti-infective and anti-inflammatory chalcones. *European Journal of Medicinal Chemistry*, **42**(2), 125–137. https://doi.org/10.1016/j.ejmech.2006.10.006
5. Singh, P., Anand, A., & Kumar, V. (2014). Recent developments in biological activities of chalcones: A mini review. *European Journal of Medicinal Chemistry*, **85**, 758–777. https://doi.org/10.1016/j.ejmech.2014.08.023
6. Yadav, V. R., Suresh, S., Devi, K., & Yadav, S. (2012). Chalcone derivatives as potential inhibitors of aldose reductase and advanced glycation end product formation. *Bioorganic & Medicinal Chemistry Letters*, **22**(3), 1170–1174. https://doi.org/10.1016/j.bmcl.2011.11.107
7. Zhang, B., Ma, Y., Wang, J., & Wang, X. (2021). Design, synthesis and biological evaluation of chalcone-based hybrids as multifunctional agents. *Bioorganic & Medicinal Chemistry*, **30**, 115935. https://doi.org/10.1016/j.bmc.2020.115935
8. Kappe, C. O. (2004). Controlled microwave heating in modern organic synthesis. *Angewandte Chemie International Edition*, **43**(46), 6250–6284. https://doi.org/10.1002/anie.200400655
9. Sharma, R. A., et al. (2014). Microwave-assisted synthesis and pharmacological activities of chalcones: A review. *Asian Journal of Pharmaceutical Sciences*, **9**(6), 336–351. https://doi.org/10.1016/j.ajps.2014.06.003
10. Go, M. L., Wu, X., & Liu, X. L. (2005). Chalcones: cytotoxic and chemoprotective properties. *Current Medicinal Chemistry*, **12**(4), 483–499. https://doi.org/10.2174/0929867053363207
11. Nowakowska, Z. (2007). A review of anti-infective and anti-inflammatory chalcones. *Eur J Med Chem*, **42**(2), 125–137. https://doi.org/10.1016/j.ejmech.2006.10.006
12. Batovska, D. I., & Todorova, I. T. (2010). Trends in chalcone research: a short survey. *Current Clinical Pharmacology*, **5**(1), 1–29. https://doi.org/10.2174/157488410790410571
13. Yadav, V. R., et al. (2012). Chalcones as aldose reductase inhibitors. *Bioorganic & Medicinal Chemistry Letters*, **22**(3), 1170–1174. https://doi.org/10.1016/j.bmcl.2011.11.107
14. Zhang, B., et al. (2021). Design, synthesis and biological evaluation of chalcone-based hybrids as multifunctional agents. *Bioorganic & Medicinal Chemistry*, **30**, 115935. https://doi.org/10.1016/j.bmc.2020.115935
15. Daina, A., Michielin, O., & Zoete, V. (2017). SwissADME: A free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. *Scientific Reports*, *7*, 42717. https://doi.org/10.1038/srep42717
16. Daina, A., Michielin, O., & Zoete, V. (2019). The SwissADME web tool to predict the drug-likeness and pharmacokinetic properties of small molecules. *Scientific Reports*, *9*(1), 1-11. https://doi.org/10.1038/s41598-019-43805-1
17. S. Hymavathi, Ameena Husain, N. Swathi, P. Sateesh Kumar, B. Anupama, Alia Begum. 2024. Asian Journal of Chemistry, Vol. 36, No. 12 (2024), 2801-2808. https://doi.org/10.14233/ajchem.2024.32630