Science Academique

Science Academique
ISSN 2583-6889
Prasana JC, et al.
Pages: 77-96

Research Article

Rectifying ion channels and membrane potential for cancer therapy: A hypothesis

Johanan Christian Prasana[1*], E. Eunice[1,2], Dona Benny[1,2], B. Aysha Rifana[1,2], Freddy AJ[3]

[1]Department of Physics, Madras Christian College, East Tambaram 600059, Tamil Nadu, India
[2]University of Madras, Chennai, 600005, Tamil Nadu, India
[3]Department of Zoology, Madras Christian College, East Tambaram 600059, Tamil Nadu, India

[*]**Correspondence to:** Johanan Christian Prasana; reachjcp@gmail.com

Citation: Prasana, J. C., Eunice, E., Benny, D., Rifana, B. A., & Freddy, A. J. (2025). Rectifying ion channels and membrane potential for cancer therapy: A hypothesis. Sci Academique, 6(1), 77–96

Received: 29 April, 2025; **Accepted:** 11 June, 2025; **Published:** 27 June, 2025

Abstract

Cell membrane potential and ion channels are crucial for cancer cell proliferation. Deviations in membrane potential may lead to a depolarization state, favoring cancer cell growth. Targeting ion channels and ensuring appropriate signals can reactivate tumor suppressor protein p53. This reactivation helps prevent tumor cells from bypassing regulatory checkpoints and promotes apoptosis. Enhancing ion channel activity and unmasking p53 can boost the body's self-repair mechanisms. The optimization results for Levcromakalim are obtained through DFT calculations. UV-Vis, Frontier analysis, and Lipinski's Rule of 5 highlight its potential for effective and favorable pharmacological effects. Molecular docking studies reveal that Levcromakalim effectively binds to the K_ATP channel protein. These theoretical findings suggest that Levcromakalim may effectively regulate membrane potential and reactivate p53, triggering critical checkpoints in cell division. This theoretical approach could be a significant step toward more effective cancer treatments and the ultimate goal of a cancer-free society.

Introduction

In all their splendor and versatility, Multicellular organisms dwindle to the cell with their remarkable adaptability to diverse functions across different organs, systems, and tissues. It performs incredible functions like emotional responses, creativity, learning, parallel processing, and multitasking with astounding processivity speeds of approximately one exaFLOP ($1x10^{18}$ operation per second) in the brain, synthesizing proteins, hormones, immunological response, intra and inter-cellular communication and sending signals. Cellular function is challenging to comprehend in its entirety. Notwithstanding, cells respond

Science Academique
ISSN 2583-6889
Prasana JC, et al.
Pages: 77-96

dynamically to environmental stimuli, adapting their behavior and physiology to meet changing demands. Combined with all these activities, cellular division and homeostasis are a remarkable feat that the cell executes to survive, reproduce, and continue as a species. Figure 1 shows the schematic image of cell cycle checkpoints.

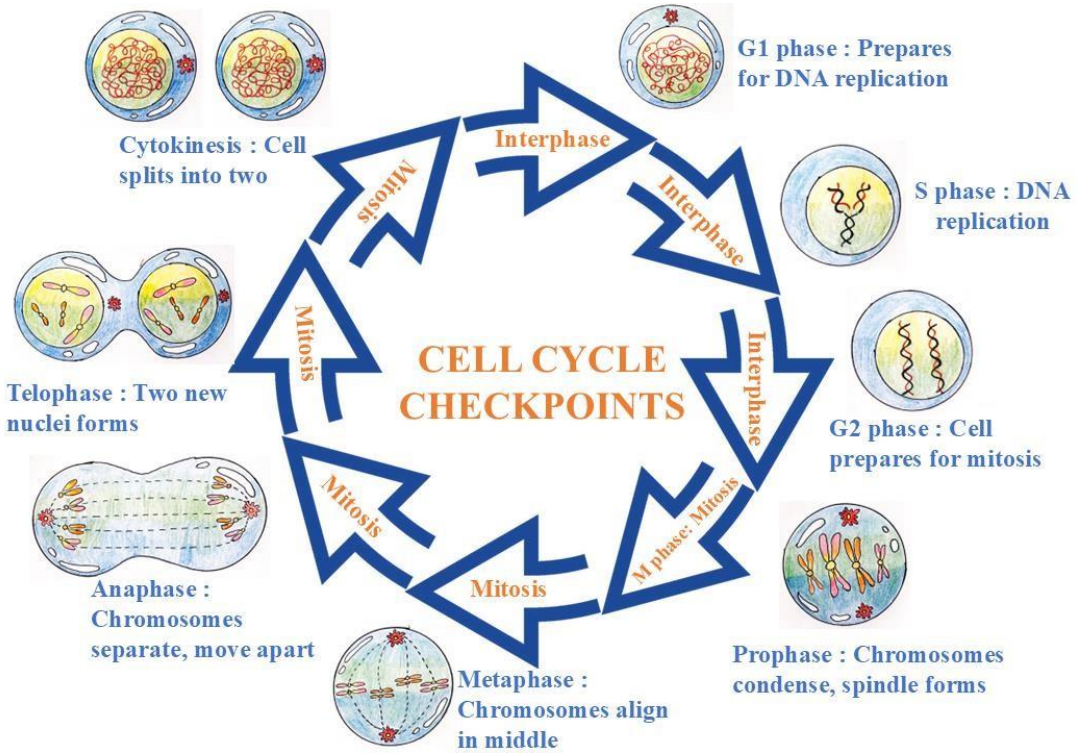

Figure 1: Schematic image of cell cycle checkpoints.

The cell cycle is a tightly coordinated and regulated event with G1, S, G2, and M, which ensures that each organism is genetically intact. This crucial regulatory maintenance of cell proliferation encompasses genetic stability and prevents uncontrolled cellular growth. TP53, often called p53, popularly termed the "guardian of the genome," is crucial in preserving cellular integrity. Activation of p53 to cellular stress, DNA damage, hypoxia, loss of tumor suppressor gene, or oncogene activation orchestrates several downstream genetic events directing the cell towards DNA repair or apoptosis to maintain cellular homeostasis. Mutations on p53 or masking of p53 are among the most frequent alterations in human cancers, often resulting in dysregulated cell proliferation and tumor development. Also, tumor cells frequently bypass cell cycle checkpoints due to improper signals that mask the p53 protein, failing to activate downstream proteins like p21 to arrest the cell cycle when conditions are unfavorable [1-8]. Molecular docking has shown promise by identifying small compounds capable of binding to and stabilizing p53, restoring its tumor-suppressing abilities [9]. Consequently, p53 has become a focal point in cancer research, with therapeutic strategies aimed at restoring its function or mimicking its activity showing promise in preclinical and clinical studies.

Science Academique
ISSN 2583-6889
Prasana JC, et al.
Pages: 77-96

The cell, with its remarkable versatility, precise regulation through the cell cycle, and the critical role of p53, characterizes the complexity and elegance of life. Understanding these processes provides insights into the mechanisms fundamental to health and disease, paving the way for innovations and evolution in medicine and biotechnology [10]. As scientists continue to unravel the mysteries of the cell, the potential for harnessing its capabilities to improve human health and combat diseases such as cancer grows ever brighter.

The cell membrane is a complex and dynamic structure essential for maintaining cellular function, communication through signaling, and homeostasis. The cellular barrier is enveloped with a differential voltage gradient called the membrane potential (V_m). Its selective permeability and the diverse roles of membrane proteins make it critical for numerous cellular processes. Separating the cellular contents from the extracellular environment is crucial for maintaining the cell's structural integrity. The cell membrane is tailored to serve as a physical barrier, protecting the cell from mechanical damage, pathogens, and harmful environmental factors. This separation is critical in maintaining intra and inter-cellular communication without compromising cellular health and homeostasis [11,12]. Ion channels within the membrane space create membrane potential and trigger electrical signals to communicate inside the human system [13,14]. Enclosed by a lipid bilayer functioning as a selective barrier, the membrane regulates the transport of substances to and from the cell. Membrane ion channels regulate ion flow, impacting membrane potential (V_m) and cellular function. Phospholipids, the primary components of the membrane, prevent the free passage of hydrophilic molecules. The Goldman-Hodgkin-Ktz equation provides a mathematical model for understanding the factors determining the V_m [15,16].

$$V_m = \frac{RT}{F}\, ln\, (P_{Na+}[Na^+]_0 + P_K + [K^+]_0 + P_{cl}^- [Cl^-]) / (P_{Na}^+ [Na]_i + P_{k+} [K]_i + P_{cl}^- [Cl^-]_i)$$

V_m is essential for regulating processes like cell growth, division, migration, and apoptosis, which is maintained by ion gradients by moving Na^+, K^+, Ca^{2+}, and Cl^- ions via specific channels. In normal cells, the membrane potential is tightly controlled and remains more negative, supporting normal cellular functions [17, 18].

Electrons play a crucial role in cell cycle checkpoints through their involvement in redox (reduction-oxidation) reactions, which are essential for maintaining the normal function of the p53 protein [19]. Disruptions in redox balance will impact membrane potential and may inhibit p53, potentially allowing damaged cells to proliferate uncontrollably [20,21]. Therefore, maintaining a proper redox state is vital for p53's stability and ability to regulate the cell cycle and prevent cancerous growth [22].

Membrane potential values due to ion channels and probable diseases are presented in Table 1 [18]. Ion channels exhibit specific functions in cancer progression. Voltage-gated sodium channels overexpressed in cancers like breast and prostate, promoting metastasis. Similarly, Potassium Channels [23 – 28] may create a depolarization state responsible for MCF-7 breast cancer, to name a few. Imbalances in calcium and chloride channels promote dysregulated cell growth and migration [19]. The normal range of membrane potential is between -40mv and -80mv, which may be obtained from the Gaussian Distribution Curve. From Table 1, it can be

Science Academique
ISSN 2583-6889
Prasana JC, et al.
Pages: 77-96

predicted that favorable equilibrium conditions arise when the membrane potential is closer to the higher side of the standard value. Fluctuations in membrane potential, which might be due to action and resting potentials, within a depolarized state or a depolarized state of ions may lead to enhanced proliferation and reduced apoptosis. Maintaining the membrane potential in the normal range is a vital parameter to send proper signals to activate the p53, restoring its function in regulating the cell cycle and inducing apoptosis. Therefore, targeting these ion channels to maintain appropriate membrane potential throws light on potential therapeutic strategies in cancer treatment [15].

S.No.	Membrane potential V_m(mV)	Probable diseases
1	0 to -10	Ovarian tumor Leukemic myeloblast
2	-10 to -20	Human hepatoma Hela MDA-MB-231 breast cancer, cervical tumor
3	-30 to -40	MDA-MB-468 breast cancer Quail fibrosarcoma MCF-7 breast cancer
4	-50 to -55	PC-3M prostate cancer

Table 1: Membrane potential scale and probable diseases [18].

Implications of Membrane Potential

Ion channels are highly selective, meaning they only allow specific ions to pass through. This selective permeability is essential for maintaining the proper balance of ions inside and outside the cell [29]. The uneven distribution of ions, causing V_m, is kept in balance by the K_ATP channel, which is K^+ ions-sensitive [30-33]. This maintains a membrane potential ranging from -40 mV to -80 mV [34]. Voltage-gated channels open or close in response to changes in V_m (charge difference across the membrane). Ligand-gated ion channels open or close when specific molecules (ligands) bind to them [35,36]. These channels help cells regulate the human system's proper functioning by sending appropriate signals. Deviations from the specified range in the membrane potential (Table 1) may lead to a depolarization state (less negative), favoring cancer cell growth [37-39].

Approach to Cancer Therapy - Hypothesis

The pathway for p53 Activation is presented in Figure 2. Depolarization conditions may inhibit tumor suppressor protein p53, leading to improper cell division. By restoring the suitable ion channels, the depolarization condition of the membrane potential may be corrected to restore proper electrical signals to p53. These corrected electrical signals may unmask p53 [40,41] and enhance p53's ability to control the cell cycle and promote cell apoptosis [38]. In light of this

Science Academique
ISSN 2583-6889
Prasana JC, et al.
Pages: 77-96

understanding, the hypothesis presented here focuses on controlling the electrical signals to activate p53, in order to control the cell cycle, rather than to focus on cancers that are assumed to suppress p53, which might lead to different types of cancers, in the present treatment.

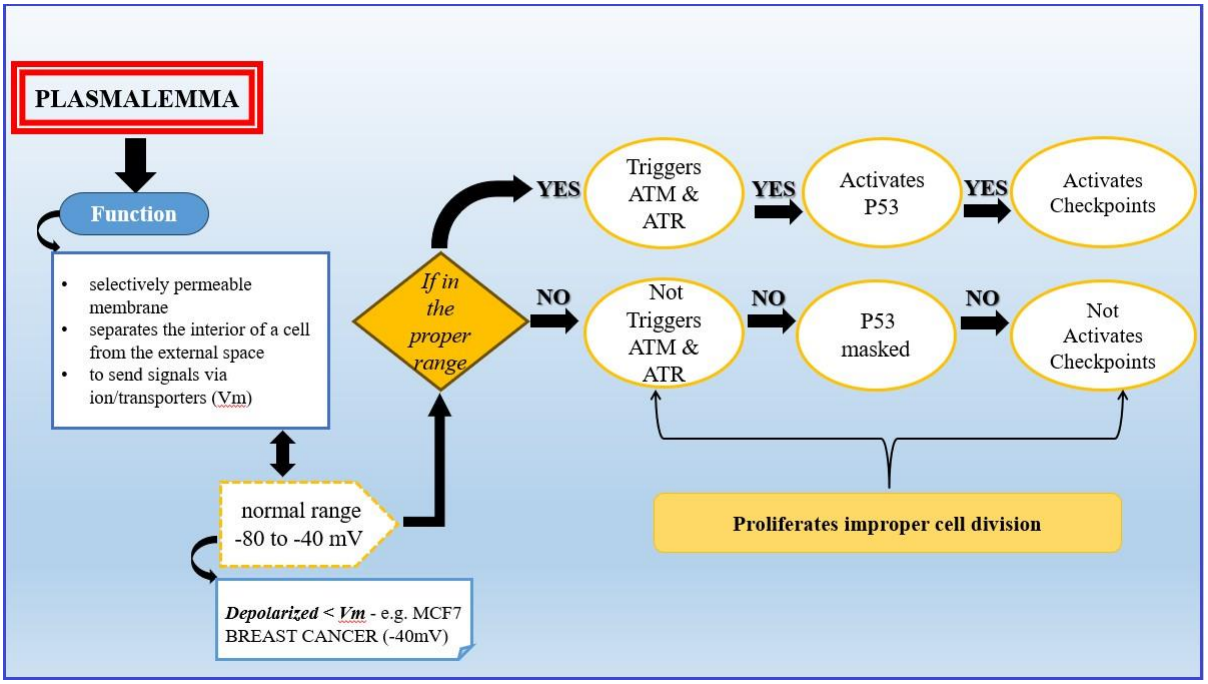

Figure 2: Approach to cancer therapy flowchart.

Therapeutic Potential and Mechanism of Action of Levcromakalim in Cancer Cells

Levcromakalim is an organic compound with the molecular formula $C_{16}H_{18}N_2O_3$ containing 39 atoms, and Pa activity is 90.5% [58]. IUPAC name is (3S,4R)-3-Hydroxy-2,2-Dimethyl-4-(2-Oxopyrrolidin-1-yl)-3,4-Dihydrochromene-6-Carbonitrile and molar mass of 286.33 g/mol [42]. It has therapeutic applications in vascular, neurological, metabolic, and cancer. The title compound contains functional groups such as methoxy, hydroxy, and nitrile, which are critical for interacting with K_ATP channels to modulate the membrane potential [43,44].

Levcromakalim activates ATP-sensitive potassium channels (K_ATP), inducing changes in membrane potential that are essential for proper intracellular signaling [45]. The proper signals help to restore an electrochemical environment favorable to the activation of DNA damage response pathways, particularly those mediated by ATM/ATR kinases [46]. These kinases phosphorylate and stabilize p53 by preventing MDM2-mediated degradation, thereby enabling p53 to translocate into the nucleus, activate p21 expression, and initiate cell cycle arrest or apoptosis [47]. This interaction between Levcromakalim and the membrane potential has been supported through molecular docking studies with the K_ATP channel, suggesting its potential to modulate ion channel function and restore appropriate signaling. The compound's influence on membrane potential and its role in the p53 reactivation pathway form the foundation of the

Science Academique
ISSN 2583-6889
Prasana JC, et al.
Pages: 77-96

proposed hypothesis, highlighting its therapeutic promise in targeting tumor suppressor pathways via ionic homeostasis.

This hypothesis work is an attempt made to bind human potassium channel K_ATP protein (5WTR-prokaryotic TRIC channel) with the ligand Levcromakalim. Levcromakalim is known to activate K_ATP channels, which regulate the flow of K^+ ions across the cell membrane [48] that may send proper signals to activate p53, thereby rectifying the cell cycle to promote cell apoptosis. This methodology could trigger the self-repair mechanism of the human body.
A comprehensive literature review indicates that no studies employing DFT and molecular docking have been documented regarding Levcromakalim's interaction with K_ATP channels [49-54].

Computational analysis

DFT is a computational method that provides insights into geometry, bonding, and reactivity [55]. GAUSSIAN 16W [56] package was employed in DFT calculations. B3LYP/6-311G++(d,p) is the basis set used. An optimized structure was obtained for Levcromakalim. UV-Vis spectra were performed using the TD-DFT method. Frontier analysis determines global reactivity parameters and evaluates toxicity. Pharmacological properties were assessed through the Swiss ADME online tool [57]. Bioactivity predictions were obtained using PASS online software [58]. Protein structure (5WTR) was sourced from the RCPDB [59]. Molecular docking was conducted using AutoDock Tools 1.5.6 and Discovery Studio software [60,61]. For Levcromakalim, docking studies predict the interaction with the K_ATP channel, helping identify key binding sites and assess binding energy. Docking can determine the most stable configuration through simulations of various binding poses [62,63].

Results and Discussion

- **Molecular Geometry**

Levcromakalim was optimized using DFT, providing a comprehensive understanding of the molecular structure and potential interactions with the ATP-sensitive potassium (K_ATP) channel. This computational approach helped refine the molecule's geometry by minimizing bond lengths and angles, crucial for effective binding and interaction with the K_ATP channel. The prominent bond lengths, C-N, C-O, and C-H, were within the typical range of 1.2 to 1.5 Å. The O1-C8, O1-C12, O2-C7, and N4-C6 bonds obtained bond lengths of 1.462 Å, 1.356 Å, 1.419 Å, and 1.462 Å, respectively. Bond angles, particularly those involving sp^2 hybridized carbon atoms, were optimized to ensure that Levcromakalim maintained the correct spatial arrangement for optimal interaction. The C8-O1-C12 bond angle was 118.9°, O1-C8-C7 was 107.2°, O1-C8-C15 was 104.7°, and O1-C8-C16 was 109.2°, all of which fell within the desired range of 110° to 120°. These angles suggested a favorable molecular geometry that supported the stability of Levcromakalim. Optimization also included adjustments to the dihedral angles to ensure that the title compound adopted the correct orientation for efficient binding to the K_ATP channel. The optimized structure of Levcromakalim is shown in Figure 3. Bond lengths (42 Å) and bond angles (75 °) are shown in Table 2.

Science Academique
ISSN 2583-6889
Prasana JC, et al.
Pages: 77-96

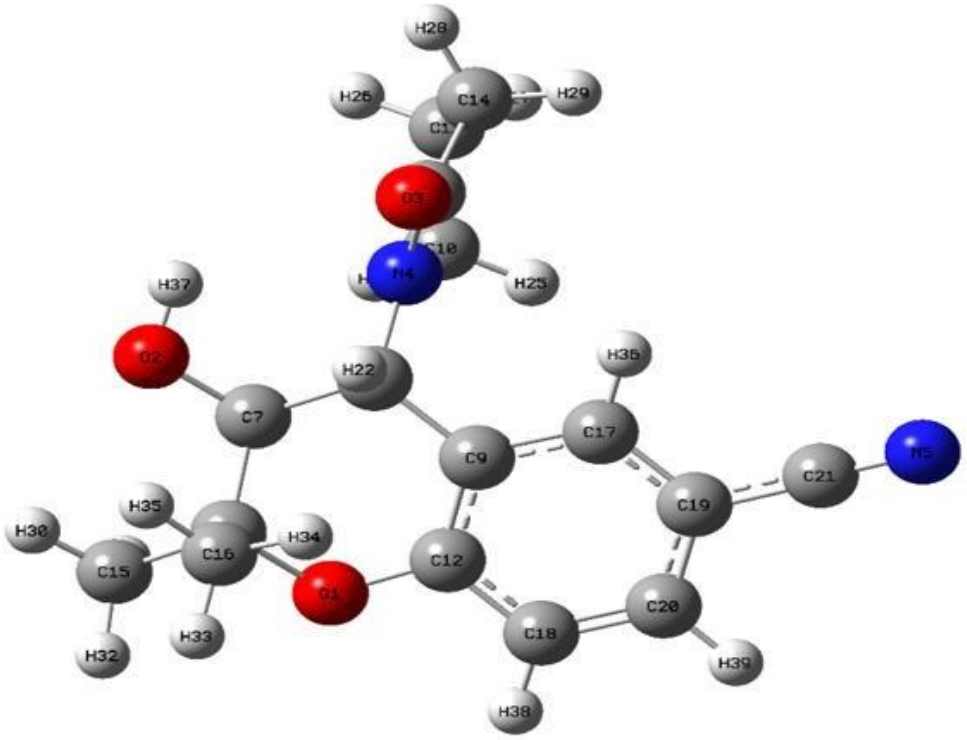

Figure 3: Optimized structure of Levcromakalim.

Bond Length(Å)	B3LYP/6-311++G (d,p)	Bond Angle (°)	B3LYP/6-311++G (d,p)
O1-C8	1.462	C8-O1-C12	118.9
O1-C12	1.356	C7-O2-H37	108.4
O2-C7	1.419	C6-N4-C10	124.1
O2-H37	0.964	C6-N4-C13	121.4
O3-C13	1.216	C10-N4-C13	113.0
N4-C6	1.462	N4-C6-C7	110.7
N4-C10	1.468	N4-C6-C9	113.6
N4-C13	1.383	N4-C6-H22	104.2
N5-C21	1.156	C7-C6-C9	110.4
C6-C7	1.536	C7-C6-H22	108.0
C6-C9	1.521	C9-C6-H22	109.5
C6-H22	1.095	O2-C7-C6	111.6
C7-C8	1.542	O2-C7-C8	108.3
C7-H23	1.1	O2-C7-H23	109.9
C8-C15	1.524	C6-C7-C8	111.4
C8-C16	1.53	C6-C7-H23	109.1
C9-C12	1.405	C8-C7-H23	106.4
C9-C17	1.392	O1-C8-C7	107.2
C10-C11	1.542	O1-C8-C15	104.7
C10-H24	1.092	O1-C8-C16	109.2
C10-H25	1.096	C7-C8-C15	110.7

Science Academique
ISSN 2583-6889
Prasana JC, et al.
Pages: 77-96

C11-C14	1.535	C7-C8-C16	113.3
C11-H26	1.093	C15-C8-C16	111.3
C11-H27	1.09	C6-C9-C12	119.9
C12-C18	1.402	C6-C9-C17	121.5
C13-C14	1.524	C12-C9-C17	118.6
C14-H28	1.09	N4-C10-C11	103.1
C14-H29	1.095	N4-C10-H24	111.2
C15-H30	1.09	N4-C10-H25	110.7
C15-H31	1.092	C11-C10-H24	112.4
C15-H32	1.092	C11-C10-H25	111.9
C16-H33	1.092	H24-C10-H25	107.7
C16-H34	1.092	C10-C11-C14	104.0
C16-H35	1.091	C10-C11-H26	109.7
C17-C19	1.399	C10-C11-H27	111.8
C17-H36	1.084	C14-C11-H26	110.1
C18-C20	1.382	C14-C11-H27	113.5
C18-H38	1.083	H26-C11-H27	107.8
C19-C20	1.406	O1-C12-C9	123.2
C19-C21	1.429	O1-C12-C18	116.4
C20-H39	1.083	C9-C12-C18	120.4
		O3-C13-N4	125.2
		O3-C13-C14	127.1
		N4-C13-C14	107.7
		C11-C14-C13	104.6
		C11-C14-H28	114.7
		C11-C14-H29	112.3
		C13-C14-H28	110.4
		C13-C14-H29	107.4
		H28-C14-H29	107.3
		C8-C15-H30	110.0
		C8-C15-H31	110.6
		C8-C15-H32	109.9
		H30-C15-H31	108.8
		H30-C15-H32	109.1
		H31-C15-H32	108.5
		C8-C16-H33	109.6
		C8-C16-H34	112.1
		C8-C16-H35	109.8
		H33-C16-H34	108.0
		H33-C16-H35	108.9
		H34-C16-H35	108.3
		C9-C17-C19	121.4
		C9-C17-H36	119.4
		C19-C17-H36	119.2

Science Academique
ISSN 2583-6889
Prasana JC, et al.
Pages: 77-96

		C12-C18-C20	120.4
		C12-C18-H38	118.4
		C20-C18-H38	121.2
		C17-C19-C20	119.3
		C17-C19-C21	120.2
		C20-C19-C21	120.5
		C18-C20-C19	119.9
		C18-C20-H39	120.3
		C19-C20-H39	119.8
		N5-C21-C19	179.7

Table 2: Optimized Geometrical Parameters for Levcromakalim.

For Levcromakalim, the minimized energy was found to be -955.9898433 a.u., indicating the most stable conformation. This energy value reflected an energetically favorable state for binding to the K_ATP channel, suggesting that the title compound was in a low-energy, stable configuration. Such a configuration was essential for efficient interactions with the protein target, ensuring that Levcromakalim could adopt the proper shape and orientation required for many pharmacological activities. This stable conformation further enhanced the potential for modulating the K_ATP channel, thereby supporting its therapeutic potential [64].

- **UV-Vis analysis**

UV-Vis analysis serves as a vital technique for investigating the absorption behavior of compounds in the ultraviolet and visible regions of the electromagnetic spectrum. This method typically covers the 200–600 nm range, with ultraviolet light spanning 10–400 nm and visible light from 400–600 nm [52,53]. In the present study, the UV-Vis absorption spectrum of Levcromakalim was theoretically predicted using the TD-DFT approach. Figure 4 illustrates the computed spectrum, while Table 3 summarizes the associated electronic transitions and properties.

Science Academique
ISSN 2583-6889
Prasana JC, et al.
Pages: 77-96

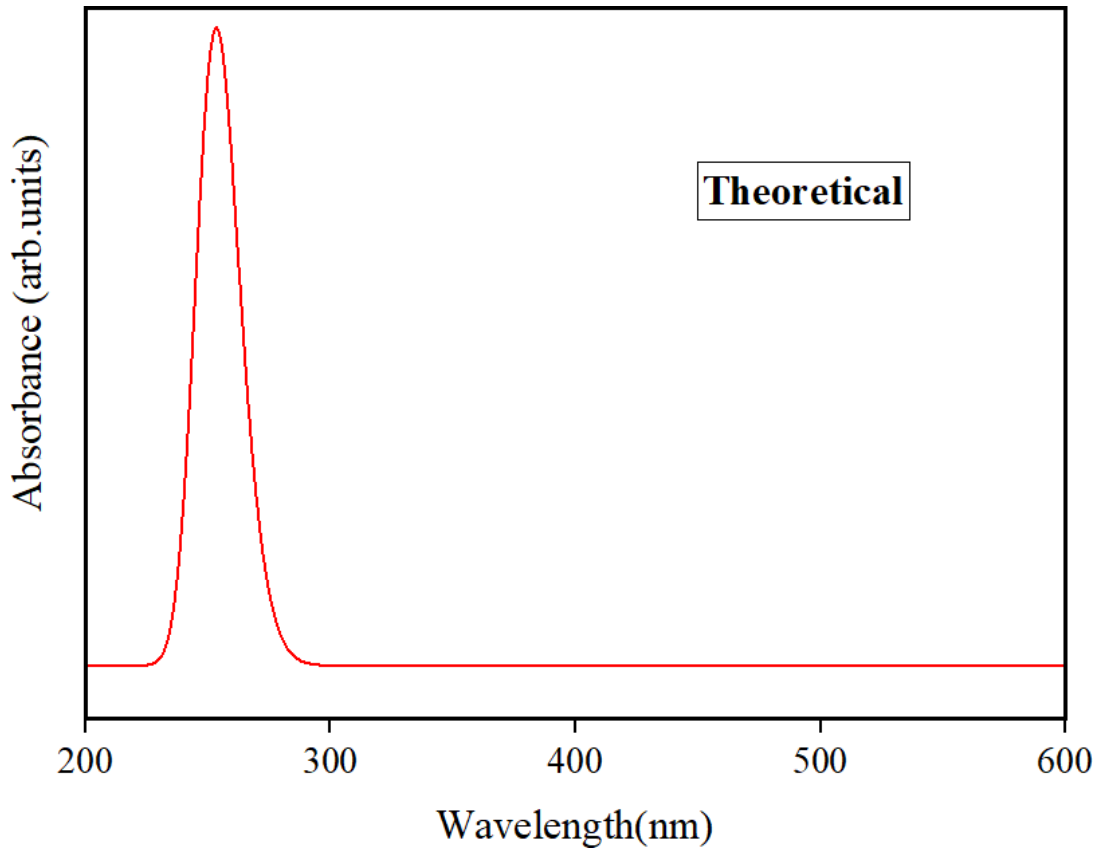

Figure 4: Theoretical UV-Vis spectrum for Levcromakalim.

	Theoretical		TD/DFT		6-311++G(d,p)
Phase	**Wavelength (nm)**	**Band gap (eV)**	**Energy (cm-1)**	**Oscillatory strength**	**Assignments**
GAS	252	4.67	39592.14	0.3551	HOMO->LUMO (69%)

Table 3: UV-Vis Properties of Levcromakalim using TD-DFT/B3LYP Method.

A prominent absorption peak was identified at 252 nm, which lies within the mid-UV region of the spectrum. This peak is attributed to an electronic transition from the HOMO to the LUMO, associated with an excitation energy of 4.67 eV and an oscillator strength of 0.3551, indicating a moderately allowed transition. This behavior reflects a $\pi \rightarrow \pi^*$ transition, which is characteristic of conjugated systems, suggesting that only a moderate energy input is required to promote electron excitation in the molecule.

- **Frontiers analysis (FMO)**

FMO analysis is crucial for assessing a compound's electronic properties, stability, and reactivity. HOMO indicates a molecule's electron donation ability, while the LUMO shows its

Science Academique
ISSN 2583-6889
Prasana JC, et al.
Pages: 77-96

electron acceptance tendency. The energy difference, or band gap, is crucial for assessing a compound's stability and reactivity. A larger HOMO–LUMO gap typically correlates with greater stability and lower reactivity, while a smaller gap suggests higher reactivity due to the reduced energy needed for electron excitation [65,66]. Table 4 provides Levcromakalim's computed global reactivity parameters, offering valuable insights into its electronic behavior. For Levcromakalim, the HOMO and LUMO energies were calculated to be –6.773 eV and –1.558 eV, respectively, yielding a HOMO–LUMO energy gap (ΔE) of 5.215 eV. This relatively large gap suggests that Levcromakalim is electronically stable and not highly reactive under typical physiological conditions. Using Planck's relation: $\lambda = hc/E$, where h is Planck's constant (6.626×10^{-34} J·s), c is the speed of light (3.0×10^{8} m/s), and E is the band gap energy, the corresponding wavelength is found to be 238 nm. This falls within the mid-UV range and aligns with the TD-DFT-predicted UV-Vis absorption peak, further confirming the compound's electronic characteristics.

Parameter	GAS PHASE
HOMO (eV)	-6.773
LUMO (eV)	-1.558
Ionization potential	6.773
Electron affinity	1.558
Energy gap (eV)	5.215
Electronegativity	4.166
Chemical potential	-4.166
Chemical hardness	2.608
Chemical softness	0.192
Electrophilicity index	3.327

Table 4: Calculated energy value and global reactivity parameters of Levcromakalim..

The Ionization Potential (IP), which is related to the HOMO, was determined to be 6.733 eV, representing the energy required to remove an electron. The Electron Affinity (EA), associated with the LUMO, was calculated at 1.558 eV, indicating the energy change upon electron addition. From these values, Levcromakalim's electronegativity (χ) is 4.166, suggesting a moderate tendency to attract electrons in bonding interactions [50]. The chemical hardness (η) was found to be 2.608 eV, implying significant resistance to changes in electron density and indicating enhanced molecular stability. In contrast, the chemical softness (S) was calculated to be 0.192, a relatively low value, consistent with the characteristics of biologically safe and low-toxicity molecules [67].

Moreover, Levcromakalim's electrophilicity index (ω) was computed as 3.327 eV, classifying it as a potent electrophile. This suggests that the compound strongly tends to accept electrons, making it potentially suitable for selective interactions with nucleophilic biological targets, such as enzymes or ion channels. Together, these parameters highlight Levcromakalim's chemical stability, low toxicity, and its promising potential in pharmaceutical applications, particularly those involving ion-channel modulation [68,69].

Science Academique
ISSN 2583-6889
Prasana JC, et al.
Pages: 77-96

- **Drug likeness**

Drug likeness refers to the set of chemical properties that have the potential to be developed into an effective pharmaceutical compound [70]. Levcromakalim demonstrated several key pharmacokinetic characteristics that align with these properties, making it a promising candidate to be developed into a drug. It adhered to Lipinski's Rule Of 5 (LRO5) [71], which includes criteria such as a molecular weight under 500 g/mol, fewer than 5 Hydrogen Bond Acceptors (HBA), fewer than 10 Hydrogen Bond Donors (HBD), and a logP value under 5 [72,73]. For Levcromakalim, an HBD value of 1 and an HBA count of 4 are within desirable limits, promoting good bioavailability. Molar logP (0.72) indicated balanced lipophilicity. The title compound's molar refractivity is 80.25, within the optimal range of 40-130, reflecting a suitable balance of size and flexibility for biological interactions. With only one rotatable bond, Levcromakalim exhibited enhanced stability. The molecular weight of 286.33 g/mol was well below the threshold (500 g/mol), suggesting favorable pharmacokinetics. A bioavailability score of 0.55 indicates the pharmaceutical nature of Levcromakalim. It also satisfies the Ghose, Veber, Egan, and Muegge filters, which collectively evaluate criteria such as molecular weight, lipophilicity, flexibility, and polarity for predicting oral bioavailability. Levocrakalim demonstrates high gastrointestinal (GI) absorption, suggesting it is well-suited for oral administration. It is not permeant to the blood-brain barrier (BBB), which limits its application for Central Nervous System (CNS) targeted therapies. Importantly, Levcromakalim is a P-glycoprotein (P-gp) substrate, indicating it may be subject to active efflux from cells, which can influence its bioavailability and tissue distribution. To evaluate the toxicity of Levcromakalim, toxicity prediction was performed using the ProTox 3.0 web server [74]. The analysis revealed that Levcromakalim falls under the "inactive" category for cytotoxicity (Table 5), predicting that the compound is non-toxic. This computational analysis suggests a favorable safety profile, which is essential for its consideration as a potential therapeutic agent in cancer treatment. Inactive-cytotoxicity implies that the compound is unlikely to induce cell damage at therapeutic concentrations. To experimentally verify this prediction, a cytotoxicity study using the MTT assay can be performed. These properties highlighted Levcromakalim as a promising candidate for drug development, with characteristics that supported effective oral administration and desirable pharmacological action. The pharmacokinetic properties for Levcromakalim are listed in Table 5.

Science Academique
ISSN 2583-6889
Prasana JC, et al.
Pages: 77-96

Descriptor	Desired range	Levcromakalim
Hydrogen Bond Donor (HBD)	<10	1
Hydrogen Bond Acceptor (HBA)	<5	4
MLogP	<4.15	0.72
Molar Refractivity	40-130	80.25
Number of rotatable bonds	<10	1
Molecular weight	<500	286.33 g/mol
Bioavailability score	≤0.85	0.55
Blood-Brain Barrier	Yes/ No	No
Gastrointestinal absorption	High/low	High
P-glycoprotein	Yes/ No	Yes
Lipinski's Rule of 5	0	0
Ghose	0	0
Veber	0	0
Egan	0	0
Muegge	0	0
Cytotoxicity	Active/Inactive	Inactive

Table 5: Drug Likeness Properties for Levcromakalim.

- **Molecular Docking**

Molecular docking is an advanced theoretical methodology to predict how a ligand interacts with a target protein, such as an enzyme, receptor, or ion channel [75]. Levcromakalim was docked with the 5WTR (prokaryotic TRIC channel) protein to regulate the flow of potassium ions (K+) across the cell membrane [76,77]. The docking results revealed that Levcromakalim binds effectively to the ion channel. The binding energy of Levcromakalim with the 5WTR of the K_ATP channel has a higher negative value of -6.59 kcal/mol (Table 6), indicating that the atoms come closer to create a strong interaction between the ligand and the protein to form a ligand-protein gated channel. This binding energy suggests that Levcromakalim facilitates activation of the K_ATP channel and regulates the flow of K^+ ions from the cytoplasm to extracellular space guided by the electrochemical gradient [42,78]. This might lead to proper membrane potential, which sends proper triggering signals to unmask p53 by triggering ATM & ATR, thus activating the checkpoint mechanisms in cell division and promoting cell apoptosis in cancerous tissues [79]. Figure 5 illustrates the docking pose of Levcromakalim with the 5WTR protein, showing the interaction and binding site. Table 6 summarizes the binding energy values, highlighting the optimal interaction between Levcromakalim and the K_ATP channel protein.

Science Academique
ISSN 2583-6889
Prasana JC, et al.
Pages: 77-96

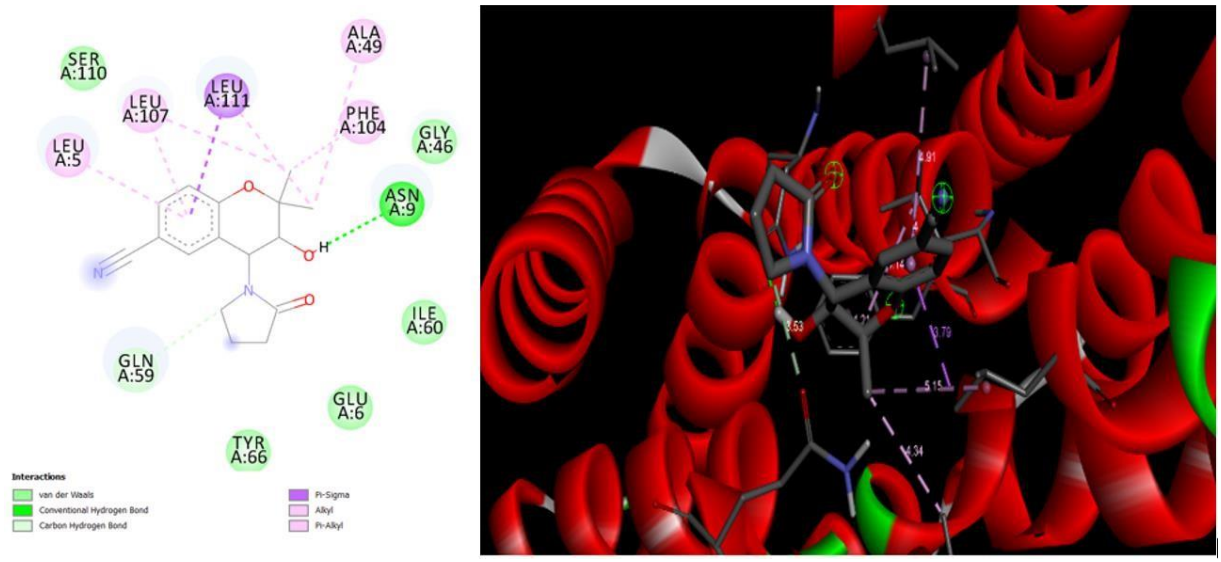

Figure 5: Docking pose of Levcromakalim with the 5WTR K+ channel protein.

Protein	Ligand	Bond residue	Interactions	Bond distance (Å)	Binding Energy (kcal/mol)	Inhibition constant (µm)	Ref. RMSD
5WTR	Levcromakalim	ASN9	Hydrogen bond	2.058	-6.59	14.71	109.83

Table 6: Molecular docking analysis for Levcromakalim.

Conclusion

The abnormality of cellular processes and organelles significantly contributes to cancer development and progression. Understanding the complex interactions between normal cells, organelles, and cancer cells is essential for creating effective therapeutic strategies. The hypothesis of this theoretical work emphasizes the importance of Levcromakalim's interactions with the potassium (K+) ion channel to maintain V_m between -40 mV and -80 mV for proper signals to reactivate p53, preventing tumor cells from evading regulatory checkpoints and thus, apoptosis. Activating the body's self-repair mechanism could significantly improve cancer treatment outcomes.

The optimization results obtained through DFT calculations show Levcromakalim's reactive nature and suitability for pharmacological applications. The UV-Vis and FMO analyses of Levcromakalim reveal its electronic stability and reactivity. Its moderate electrophilicity points to Levcromakalim's promising potential for pharmaceutical applications, particularly in the modulation of ion channels. Theoretical toxicity studies predict that the title compound is non-toxic in nature. Molecular docking of Levcromakalim with the 5WTR protein reveals that Levcromakalim effectively binds to the K_ATP channel, with a binding energy of -6.79 kcal/mol, indicating a strong interaction between the ligand (title compound) and the ion

Science Academique
ISSN 2583-6889
Prasana JC, et al.
Pages: 77-96

channel protein (5WTR). These theoretical outcomes predict that Levcromakalim may be a potential therapeutic compound for cancer treatment, highlighting the hypothesis of the work. This theoretical approach can be extended to molecular dynamics, experimental studies, such as in vitro and in vivo assay studies, and clinical studies. Rectification of ion channels that lead to proper membrane potential maybe a crucial step toward more effective cancer treatments and, ultimately, a cancer-free society.

References

1. Feroz, W., & Sheikh, A. M. A. (2020). Exploring the multiple roles of guardian of the genome: P53. *Egyptian Journal of Medical Human Genetics, 21*(1), Article 49. https://doi.org/10.1186/s43042-020-00089-x
2. Abubakar, M., & Rehman, B. (2024). Roles of mutant TP53 gene in cancer development and progression. *Proceedings of Anticancer Research, 8*(5), 165–181. https://doi.org/10.26689/par.v8i5.7826
3. Park, J. H., Zhuang, J., Li, J., & Hwang, P. M. (2016). p53 as guardian of the mitochondrial genome. *FEBS Letters, 590*(7), 924–934. https://doi.org/10.1002/1873-3468.12061
4. Chang, F., Syrjänen, S., Kurvinen, K., & Syrjänen, K. (1993). The p53 tumor suppressor gene as a common cellular target in human carcinogenesis. *The American Journal of Gastroenterology, 88*(2), 174–180. Google Scholar
5. Soussi, T. (2011). TP53 mutations in human cancer: Database reassessment and prospects for the next decade. *Advances in Cancer Research, 110*, 107–139. https://doi.org/10.1016/B978-0-12-386469-7.00005-0
6. Hientz, K., Mohr, A., Bhakta-Guha, D., & Efferth, T. (2017). The role of p53 in cancer drug resistance and targeted chemotherapy. *Oncotarget, 8*(5), 8921–8946. https://doi.org/10.18632/oncotarget.13475
7. Wang, H., Guo, M., Wei, H., & Chen, Y. (2023). Targeting p53 pathways: Mechanisms, structures and advances in therapy. *Signal Transduction and Targeted Therapy, 8*, Article 92. https://doi.org/10.1038/s41392-023-01347-1
8. Bykov, V. J. N., Eriksson, S. E., Bianchi, J., & Wiman, K. G. (2018). Targeting mutant p53 for efficient cancer therapy. *Nature Reviews Cancer, 18*(2), 89–102. Google Scholar
9. Bykov, V. J. N., Issaeva, N., Shilov, A., Hultcrantz, M., Pugacheva, E., Chumakov, P., Bergman, J., Wiman, K. G., & Selivanova, G. (2002). Restoration of the tumor suppressor function to mutant p53 by a low-molecular-weight compound. *Nature Medicine, 8*(3), 282–288. Google Scholar
10. Capuozzo, M., Santorsola, M., Bocchetti, M., Perri, F., Cascella, M., Granata, V., & Ottaiano, A. (2022). p53: From fundamental biology to clinical applications in cancer. *Biology, 11*(9), 1325. Google Scholar
11. Sachs, H. G., Stambrook, P. J., & Ebert, J. D. (1974). Changes in membrane potential during the cell cycle. *Experimental Cell Research, 83*(2), 362–366. https://doi.org/10.1016/0014-4827(74)90350-4
12. Mills, B., & Tupper, J. T. (1976). Cell cycle dependent changes in potassium transport. *Journal of Cellular Physiology, 89*(1), 123–132. https://doi.org/10.1002/jcp.1040890112
13. Becchetti, A. (2011). Ion channels and transporters in cancer. 1. Ion channels and cell proliferation in cancer. *American Journal of Physiology-Cell Physiology, 301*(2), C255–C265. Google Scholar

Science Academique
ISSN 2583-6889
Prasana JC, et al.
Pages: 77-96

14. Prevarskaya, N., Skryma, R., & Shuba, Y. (2010). Ion channels and the hallmarks of cancer. *Trends in Molecular Medicine, 16*(3), 107–121. https://doi.org/10.1016/j.molmed.2010.01.005

15. Cone, C. D. Jr. (1970). Variation of the transmembrane potential level as a basic mechanism of mitosis control. *Oncology, 24*(6), 438–470. https://doi.org/10.1159/000224545

16. Yang, M., & Brackenbury, W. J. (2013). Membrane potential and cancer progression. *Frontiers in Physiology, 4*, 185. Google Scholar

17. Wonderlin, W. F., & Strobl, J. S. (1996). Potassium channels, proliferation and G1 progression. *Journal of Membrane Biology, 154*(2), 91–107. https://doi.org/10.1007/s002329900135

18. Sundelacruz, S., Levin, M., & Kaplan, D. L. (2009). Role of membrane potential in the regulation of cell proliferation and differentiation. *Stem Cell Reviews and Reports, 5*(3), 231–246. https://doi.org/10.1007/s12015-009-9080-2

19. Sadiq, I. Z. (2023). Free radicals and oxidative stress: Signaling mechanisms, redox basis for human diseases, and cell cycle regulation. *Current Molecular Medicine, 23*(1), 13–35. Google Scholar

20. Mackova, V., Raudenska, M., Holcova Polanska, H., Jakubek, M., & Masarik, M. (2024). Navigating the redox landscape: Reactive oxygen species in regulation of cell cycle. *Redox Report, 29*(1), 2371173. Google Scholar

21. Sablina, A. A., Budanov, A. V., et al. (2005). The antioxidant function of the p53 tumor suppressor. *Nature Medicine, 11*(12), 1306–1313. Google Scholar

22. Franzese, O., Ancona, P., Bianchi, N., & Aguiari, G. (2024). Apoptosis, a metabolic "head-to-head" between tumor and T cells: Implications for immunotherapy. *Cells, 13*(11), 924. Google Scholar

23. Brackenbury, W. J. (2012). Voltage-gated sodium channels and metastatic disease. *Channels, 6*(5), 352–361. Google Scholar

24. Blackiston, D. J., McLaughlin, K. A., & Levin, M. (2009). Bioelectric controls of cell proliferation: Ion channels, membrane voltage and the cell cycle. *Cell Cycle, 8*(21), 3519–3528. https://doi.org/10.4161/cc.8.21.9888

25. Boonstra, J., Mummery, C. L., Tertoolen, L. G., Van Der Saag, P. T., & De Laat, S. W. (1981). Cation transport and growth regulation in neuroblastoma cells: Modulations of K+ transport and electrical membrane properties during the cell cycle. *Journal of Cellular Physiology, 107*(1), 75–83. https://doi.org/10.1002/jcp.1041070110

26. D'Amico, M., Gasparoli, L., & Arcangeli, A. (2013). Potassium channels: Novel emerging biomarkers and targets for therapy in cancer. *Recent Patents on Anti-Cancer Drug Discovery, 8*(1), 53–65. Google Scholar

27. Kunzelmann, K. (2005). Ion channels and cancer. *Journal of Membrane Biology, 205*(2), 159–173. https://doi.org/10.1007/s00232-005-0781-4

28. Zúñiga, L., Cayo, A., González, W., Vilos, C., & Zúñiga, R. (2022). Potassium channels as a target for cancer therapy: Current perspectives. *OncoTargets and Therapy, 15*, 783–797. Google Scholar

29. Ganser, K., Klumpp, L., Bischof, H., Lukowski, R., Eckert, F., & Huber, S. M. (2021). Potassium channels in cancer. In *Pharmacology of Potassium Channels* (pp. 253–275). Springer. Google Scholar

30. Purves, D., Augustine, G. J., Fitzpatrick, D., et al. (Eds.). (2001). Voltage-gated ion channels. In *Neuroscience* (2nd ed., pp. 157–176). Sinauer Associates.

Science Academique
ISSN 2583-6889
Prasana JC, et al.
Pages: 77-96

31. Morth, J. P., Pedersen, B. P., Buch-Pedersen, M. J., Andersen, J. P., Vilsen, B., Palmgren, M. G., & Nissen, P. (2011). A structural overview of the plasma membrane Na+, K+-ATPase and H+-ATPase ion pumps. *Nature Reviews Molecular Cell Biology, 12*(1), 60–70. https://doi.org/10.1038/nrm3031
32. Skou, J. C., & Esmann, M. (1992). The Na, K-ATPase. *Journal of Bioenergetics and Biomembranes, 24*, 249–261. Google Scholar
33. Stühmer, W., & Pardo, L. A. (2010). K+ channels as therapeutic targets in oncology. *Future Medicinal Chemistry, 2*(5), 745–755. Google Scholar
34. Sperelakis, N. (1995). Origin of resting membrane potentials. In *Cell Physiology Source Book* (pp. 67–90). Academic Press. Google Scholar
35. Bezanilla, F. (2007). Voltage-gated ion channels. In *Biological Membrane Ion Channels: Dynamics, Structure, and Applications* (pp. 81–118). Springer. Google Scholar
36. Iorio, J., Petroni, G., Duranti, C., & Lastraioli, E. (2019). Potassium and sodium channels and the Warburg effect: Biophysical regulation of cancer metabolism. *Bioelectricity, 1*(3), 188–200. Google Scholar
37. Suzuki-Karasaki, Y., Suzuki-Karasaki, M., Uchida, M., Ochiai, T. (2014). Depolarization controls TRAIL-sensitization and tumor-selective killing of cancer cells: Crosstalk with ROS. *Frontiers in Oncology, 4*, 128. https://doi.org/10.3389/fonc.2014.00128
38. Chen, J. (2016). The cell-cycle arrest and apoptotic functions of p53 in tumor initiation and progression. *Cold Spring Harbor Perspectives in Medicine, 6*(3), a026104. https://doi.org/10.1101/cshperspect.a026104
39. Foggetti, G., Ottaggio, L., Russo, D., Mazzitelli, C., Monti, P., Degan, P., Menichini, P. (2019). Autophagy induced by SAHA affects mutant P53 degradation and cancer cell survival. *Bioscience Reports, 39*(2), BSR20181345. https://doi.org/10.1042/BSR20181345
40. Zhang, L., Gu, H., Li, X., Wang, Y., Yao, S., Chen, X., Tuo, B. (2024). Pathophysiological role of ion channels and transporters in hepatocellular carcinoma. *Cancer Gene Therapy*, 1–8. https://doi.org/10.1038/s41417-024-00693-7
41. Lehen'Kyi, V. Y., Shapovalov, G., Skryma, R., Prevarskaya, N. (2011). Ion channels and transporters in cancer. 5. Ion channels in control of cancer and cell apoptosis. *American Journal of Physiology-Cell Physiology, 301*(6), C1281–C1289. https://doi.org/10.1152/ajpcell.00206.2011
42. National Center for Biotechnology Information. (2025). PubChem Compound Summary for CID 93504, Levcromakalim. Retrieved February 4, 2025, from https://pubchem.ncbi.nlm.nih.gov/compound/Levcromakalim
43. Leanza, L., O'Reilly, P., Doyle, A., Venturini, E., Zoratti, M., Szegezdi, E., Szabo, I. (2014). Correlation between potassium channel expression and sensitivity to drug-induced cell death in tumor cell lines. *Current Pharmaceutical Design, 20*(2), 189–200. Google Scholar
44. Moon, D. O. (2024). Exploring the role of surface and mitochondrial ATP-sensitive potassium channels in cancer: From cellular functions to therapeutic potentials. *International Journal of Molecular Sciences, 25*(4), 2129. https://doi.org/10.3390/ijms25042129
45. Kajioka, S., Nakayama, S., Asano, H., Seki, N., Naito, S., & Brading, A. F. (2008). Levcromakalim and MgGDP activate small conductance ATP-sensitive K^+ channels of K^+ channel pore 6.1/sulfonylurea receptor 2A in pig detrusor smooth muscle cells: Uncoupling of cAMP signal pathways. *The Journal of Pharmacology and Experimental Therapeutics, 327*(1), 114–123. https://doi.org/10.1124/jpet.108.140269

Science Academique
ISSN 2583-6889
Prasana JC, et al.
Pages: 77-96

46. Karakostis, K., Malbert-Colas, L., Thermou, A., Vojtesek, B., & Fåhraeus, R. (2024). The DNA damage sensor ATM kinase interacts with the p53 mRNA and guides the DNA damage response pathway. *Molecular Cancer, 23*(1), Article 21. https://doi.org/10.1186/s12943-024-01933-z

47. Stommel, J. M., & Wahl, G. M. (2004). Accelerated MDM2 auto-degradation induced by DNA-damage kinases is required for p53 activation. *The EMBO Journal, 23*(7), 1547–1556. https://doi.org/10.1038/sj.emboj.7600145

48. Al-Karagholi, M. A. M., Ghanizada, H., Hansen, J. M., Skovgaard, L. T., Olesen, J., Larsson, H. B. W., & Ashina, M. (2019). Levcromakalim, an adenosine triphosphate-sensitive potassium channel opener, dilates extracerebral but not cerebral arteries. *Headache: The Journal of Head and Face Pain, 59*(9), 1468–1480. https://doi.org/10.1111/head.13634

49. George, J., Prasana, J. C., Muthu, S., Kuruvilla, T. K., & Saji, R. S. (2020). Evaluation of vibrational, electronic, reactivity and bioactivity of propafenone—A spectroscopic, DFT and molecular docking approach. *Chemical Data Collections, 26*, 100360. https://doi.org/10.1016/j.cdc.2020.100360

50. Saji, R. S., Prasana, J. C., Muthu, S., & George, J. (2021). Experimental and theoretical spectroscopic (FT-IR, FT-Raman, UV-VIS) analysis, natural bonding orbitals and molecular docking studies on 2-bromo-6-methoxynaphthalene: A potential anti-cancer drug. *Heliyon, 7*(6), e07234. https://doi.org/10.1016/j.heliyon.2021.e07213

51. Prasana, J. C., Muthu, S., & Abraham, C. S. (2020). Wavefunction analysis, charge transfer and molecular docking studies on famciclovir and entecavir: Potential anti-viral drugs. *Chemical Data Collections, 26*, 100353. https://doi.org/10.1016/j.cdc.2020.100353

52. Jebapriya, J. C., Jonathan, D. R., Maidur, S. R., Nallamuthu, P., Patil, P. S., & Prasana, J. C. (2021). Crystal structure, synthesis, growth and characterization of a non-linear chalcone crystal: (2E)-1-(4-chlorophenyl)-3-(4-diethylaminophenyl)-prop-2-en-1-one. *Journal of Molecular Structure, 1246*, 131184. https://doi.org/10.1016/j.molstruc.2021.131184

53. Manjusha, P., Muthu, S., & Raajaraman, B. R. (2020). Density functional studies and spectroscopic analysis (FT-IR, FT-Raman, UV–visible, and NMR) with molecular docking approach on an antifibrotic drug Pirfenidone. *Journal of Molecular Structure, 1203*, 127394. https://doi.org/10.1016/j.molstruc.2019.127394

54. Manjusha, P., Prasana, J. C., Muthu, S., & Rizwana, B. F. (2019). A computational and spectroscopic interpretation (FT-IR, FT-Raman, UV–vis and NMR) with molecular docking studies on 3-carboxy-2-hydroxy-N,N,N-trimethyl-1-propanaminium hydroxide: A pharmaceutical drug. *Chemical Data Collections, 20*, 100191. Google Scholar

55. Jain, A., Shin, Y., & Persson, K. A. (2016). Computational predictions of energy materials using density functional theory. *Nature Reviews Materials, 1*(1), 15004. https://doi.org/10.1038/natrevmats.2015.4

56. Frisch, M. J., Trucks, G. W., Schlegel, H. B., Scuseria, G. E., Robb, M. A., Cheeseman, J. R., Scalmani, G., Barone, V., Petersson, G. A., Nakatsuji, H., & Li, X. (2016). *Gaussian 16 Revision A.03*. Gaussian Inc.

57. 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*(1), 42717. https://doi.org/10.1038/srep42717

58. Filimonov, D. A., Lagunin, A. A., Gloriozova, T. A., Rudik, A. V., Druzhilovskii, D. S., Pogodin, P. V., & Poroikov, V. V. (2014). Prediction of the biological activity spectra of

Science Academique
ISSN 2583-6889
Prasana JC, et al.
Pages: 77-96

organic compounds using the PASS online web resource. *Chemistry of Heterocyclic Compounds, 50*(3), 444–457. https://doi.org/10.1007/s10593-014-1496-1

59. Berman, H. M., Westbrook, J., Feng, Z., Gilliland, G., Bhat, T. N., Weissig, H., Shindyalov, I. N., & Bourne, P. E. (2000). The Protein Data Bank. *Nucleic Acids Research, 28*(1), 235–242. https://doi.org/10.1093/nar/28.1.235

60. Huey, R., Morris, G. M., & Forli, S. (2012). *Using AutoDock 4 and AutoDock Vina with AutoDockTools: A tutorial*. The Scripps Research Institute, Molecular Graphics Laboratory. Google Scholar

61. Jejurikar, B. L., & Rohane, S. H. (2021). Drug designing in discovery studio. *Asian Journal of Research in Chemistry, 14*(2), 135–138. Google Scholar

62. Ding, D., Wu, J. X., Duan, X., Ma, S., Lai, L., & Chen, L. (2022). Structural identification of vasodilator binding sites on the SUR2 subunit. *Nature Communications, 13*, 2675. https://doi.org/10.1038/s41467-022-30428-y

63. Dyhring, T., Jansen-Olesen, I., Christophersen, P., & Olesen, J. (2023). Pharmacological profiling of KATP channel modulators: An outlook for new treatment opportunities for migraine. *Pharmaceuticals, 16*(2), 225. https://doi.org/10.3390/ph16020225

64. Ecker, G., Fleischhacker, W., Wolf, C., Weiß-Greiler, P., & Wolschann, P. (1998). A quantum chemical study of levcromakalim. *Monatshefte für Chemie, 129*(6–7), 633–642. Google Scholar

65. Fukui, K., Yonezawa, T., & Shingu, H. (1952). A molecular orbital theory of reactivity in aromatic hydrocarbons. *The Journal of Chemical Physics, 20*(4), 722–725. https://doi.org/10.1063/1.1700523

66. Jolly, W. L. (1984). *Modern inorganic chemistry* (2nd ed.). McGraw-Hill. Google Scholar

67. Pearson, R. G. (2005). Chemical hardness and density functional theory. *Journal of Chemical Sciences, 117*(5), 369–377. https://doi.org/10.1007/BF02708340

68. LoPachin, R. M., & Gavin, T. (2014). Molecular mechanisms of aldehyde toxicity: A chemical perspective. *Chemical Research in Toxicology, 27*(7), 1081–1091. https://doi.org/10.1021/tx5001046

69. Edwards, G., Ibbotson, T., & Weston, A. H. (1993). Levcromakalim may induce a voltage-independent K-current in rat portal veins by modifying the gating properties of the delayed rectifier. *British Journal of Pharmacology, 110*(3), 1037–1048. Google Scholar

70. Schneider, G. (2013). Prediction of drug-like properties. In *Madame Curie Bioscience Database* [Internet]. Landes Bioscience. Google Scholar

71. Lipinski, C. A., Lombardo, F., Dominy, B. W., & Feeney, P. J. (2001). Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Advanced Drug Delivery Reviews, 46*(1–3), 3–26. https://doi.org/10.1016/S0169-409X(00)00129-0

72. Ghose, A. K., Viswanadhan, V. N., & Wendoloski, J. J. (1999). A knowledge-based approach in designing combinatorial or medicinal chemistry libraries for drug discovery. 1. A qualitative and quantitative characterization of known drug databases. *Journal of Combinatorial Chemistry, 1*(1), 55–68. https://doi.org/10.1021/cc9800071

73. Veber, D. F., Johnson, S. R., Cheng, H. Y., Smith, B. R., Ward, K. W., & Kopple, K. D. (2002). Molecular properties that influence the oral bioavailability of drug candidates. *Journal of Medicinal Chemistry, 45*(12), 2615–2623. https://doi.org/10.1021/jm020017n

74. Banerjee, P., Kemmler, E., Dunkel, M., & Preissner, R. (2024). ProTox 3.0: A webserver for the prediction of toxicity of chemicals. *Nucleic Acids Research*. Google Scholar

Science Academique
ISSN 2583-6889
Prasana JC, et al.
Pages: 77-96

75. Naqvi, A. A., Mohammad, T., Hasan, G. M., & Hassan, M. I. (2018). Advancements in docking and molecular dynamics simulations towards ligand-receptor interactions and structure-function relationships. *Current Topics in Medicinal Chemistry, 18*(20), 1755–1768. Google Scholar

76. Kajioka, S., Nakayama, S., Asano, H., Seki, N., Naito, S., & Brading, A. F. (2008). Levcromakalim and MgGDP activate small conductance ATP-sensitive K+ channels of K+ channel pore 6.1/sulfonylurea receptor 2A in pig detrusor smooth muscle cells: Uncoupling of cAMP signal pathways. *Journal of Pharmacology and Experimental Therapeutics, 327*(1), 114–123. Google Scholar

77. Ou, X., Guo, J., Wang, L., Yang, H., Liu, X., Sun, J., & Liu, Z. (2017). Ion- and water-binding sites inside an occluded hourglass pore of a trimeric intracellular cation (TRIC) channel. *BMC Biology, 15*, 17. Google Scholar

78. Ozaki, T., & Nakagawara, A. (2011). Role of p53 in cell death and human cancers. *Cancers, 3*(1), 994–1013. https://doi.org/10.3390/cancers3010994

79. Abdul, M., & Hoosein, N. (2002). Expression and activity of potassium ion channels in human prostate cancer. *Cancer Letters, 186*(1), 99–105. Google Scholar