Repurposing Anti-Cancer Drug Irinotecan for Genetic Disease Therapy: A Farnesyltransferase Inhibition Strategy for Hutchinson-Gilford Progeria Syndrome (HGPS)

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ABSTRACT

Hutchinson-Gilford Progeria Syndrome (HGPS) is an uncommon and lethal genetic disorder that is defined by the appearance of premature aging traits in populations of children largely attributable to the accumulation of a mutant protein called progerin. This causative protein is caused by a mutation of the LMNA gene that leads to the disruption of normal nuclear architecture caused by farnesylation of a farnesyl group. The farnesyltransferase (FTase) enzyme catalyzing this post-translational modification has been identified as a critical therapeutic target. Whereas lonafarnib, a clinician-approved farnesyltransferase inhibitor (FTI), has been promising in diminishing the severity of the disease, it is associated with side effects and restricted access. Thus, the quest for complementary or alternative therapies is necessary. The present study investigates the feasibility of repositioning Irinotecan, a US FDA-approved chemotherapeutic compound and inhibitor of topoisomerase I, as a new FTI in the treatment of HGPS. Utilizing a ligand-based virtual screening approach, we employed Morgan fingerprinting through DrugRep platform to filter out the structural similarity of Irinotecan against literature-known FTIs. Despite its primary indication as an anticancer drug, Irinotecan showed a high Tanimoto similarity score of 0.223, indicating potential off-target effects relevant to FTase inhibition. This was followed by structure-based molecular docking simulation studies using AutoDock Vina, with consideration for the human farnesyltransferase enzyme (PDB ID: 1s63). Irinotecan outperformed lonafarnib and other commonly prescribed drugs with the most advantageous binding affinity (–12.0 kcal/mol) among the screened compounds. The enzyme's active site was found to have several stabilising interactions, including hydrophobic interaction (with Trp102, Leu96, Tyr205), π-π stacking (with Tyr454), electrostatic interactions (with Arg202), hydrogen bonding (with Arg291, Gly290, His248, Ser99), and π-π stacking. These interactions suggest that irinotecan binds to the FTase active site in a stable and targeted manner. The dependability of the docking predictions was ensured by model validation using PDB-REDO, which verified improved crystallographic quality with improved R-values, Ramachandran plot normality, and rotamer distributions. When utilised together, structure-based docking and ligand-based similarity screening offer a strong case for repurposing irinotecan as a possible FTI. In addition to highlighting Irinotecan's unique mode of action, this study emphasises the importance of computational repurposing techniques in the drug discovery process for rare diseases. Its therapeutic efficacy and safety in the context of HGPS require further experimental validation in both in vitro and in vivo models.

KEYWORDS: Hutchinson-Gilford Progeria Syndrome (HGPS), Farnesyltransferase Inhibitor (FTI), Drug Repurposing, Irinotecan, Molecular Docking.

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INTRODUCTION

Hutchinson-Gilford Progeria Syndrome (HGPS) is an ultra-rare, progressive genetic disorder characterized by features resembling Growth retardation, alopecia, lipodystrophy, joint stiffness, osteoporosis, and severe cardiovascular pathology are some of the symptoms of Progeria Syndrome (HGPS), an extremely rare and progressive genetic disorder that causes children to age more quickly[1–5]. Around 1 in 20 live births worldwide are affected by the condition, and even in the absence of traditional cardiovascular risk factors, those who are affected usually die of heart attacks or strokes in their early adolescence[6-7]. HGPS is classified as one of the larger group of illnesses known as laminopathies, which are caused by mutations in the LMNA gene, which codes for nuclear lamins A and C, which are essential structural proteins that preserve the integrity of the nuclear envelope [8–16].

A cryptic splice site in exon 11 of LMNA is activated in HGPS by a recurrent de novo point mutation (c.1824 C>T; p.G608G). Progerin, a mutant form of prelamin A that lacks 50 amino acids close to the C-terminal domain, is produced as a result of this aberrant splicing. Importantly, this deletion eliminates the metalloprotease ZMPSTE24's recognition site, which is in charge of cleaving the farnesyl group from prelamin A during regular post-translational processing[17–21].

As a result, progerin stays farnesylated indefinitely, accumulating at the inner nuclear membrane, resulting in profound abnormalities of the nuclear envelope, including nuclear blebbing, chromatin disorganisation, telomere attrition, mitochondrial dysfunction, and genomic instability—all of which are indicators of cellular senescence and premature tissue degeneration[22–33]. Crucially, progerin expression not only interferes with nuclear mechanics but also impairs DNA repair pathways, causes chronic oxidative stress, and triggers inflammatory signalling, aggravating age-related tissue damage[34–40].

The enzyme farnesyltransferase (FTase), which catalyses the transfer of a 15-carbon farnesyl group from farnesyl pyrophosphate to the cysteine residue in the CAAX motif of prelamin A, has become a crucial therapeutic target because the pathological effects of progerin are directly linked to its farnesylation[41]. Farnesylation promotes the membrane localisation of Ras-related proteins and lamins, but it is pathological in the setting of HGPS[42–45].

By inhibiting FTase pharmacologically, progerin's abnormal membrane association can be avoided, leading to a return to more normal nuclear morphology and a decrease in downstream cellular toxicity[46–51]. The first FDA-approved treatment for HGPS, lonafarnib, was developed and approved based on this justification. It has been demonstrated to increase lifespan, bone density, and vascular compliance[52]. However, lonafarnib's minimal efficacy, high cost, and adverse effects (such as gastrointestinal toxicity) limit its clinical use, necessitating the development of new or repurposed FTase inhibitors with better availability and safety [53–55]. Drug repurposing, the process of finding novel therapeutic applications for already-approved medications, presents a viable and economical solution in this regard[56–60]. Compounds with possible off-target activity can be found using computational techniques like structure-based molecular docking and ligand-based virtual screening with Morgan fingerprinting [61–70]. These methods enable researchers to evaluate the predicted binding of large libraries of compounds to target proteins while also screening them for structural similarity to known inhibitors[71-77].

This study investigated the possibility that Irinotecan, a topoisomerase I inhibitor approved by the FDA and frequently used in colorectal cancer treatment, could function as a novel FTase inhibitor to treat HGPS. Irinotecan's complex polycyclic structure and diversity of functional groups suggested that it may interact with enzymes other than its primary target, even though its canonical function is to inhibit DNA replication in tumour cells [78–82].

Irinotecan showed a Tanimoto coefficient of 0.223 using Morgan fingerprint-based similarity scoring, suggesting some structural overlap with recognised

FTIs. Later docking studies with AutoDock Vina showed that Irinotecan outperformed lonafarnib and other known FTIs in simulated interaction with human FTase (PDB ID: 1s63), exhibiting a binding affinity of –12.0 kcal/mol. The interaction map revealed significant, targeted interactions with the active site of FTase, including ionic, hydrophobic, π–π stacking, and hydrogen bonding between Irinotecan and important residues such as Arg291, Gly290, His248, and Tyr454.

When taken as a whole, these results provide a strong case for repurposing irinotecan as a disease-modifying medication in HGPS. Irinotecan may be able to restore nuclear architecture, lessen oxidative stress, and increase cell survival in afflicted tissues by focussing on progerin farnesylation, the disease's primary cause. Beyond its potential for individual treatment, this study is a prime example of how computational repurposing platforms can be used to find novel uses for already-approved medications, particularly when it comes to rare and incurable genetic disorders.

MATERIALS AND METHODS

Disease Selection: Hutchinson-Gilford Progeria Syndrome (HGPS)

The study's target disease is Hutchinson-Gilford Progeria Syndrome (HGPS), a rare autosomal dominant condition marked by early ageing brought on by a mutation in the LMNA gene [83–92]. Nuclear architecture is upset by this mutation, which causes progerin, a permanently farnesylated aberrant form of prelamin A, to accumulate [93–96]. Because of its monogenic nature, distinct molecular pathology, and the known contribution of farnesyltransferase to the development of disease, HGPS was chosen as a prime candidate for structure-based drug repurposing strategies.

Selection of FDA-Approved Lead Compound: Lonafarnib

The FDA recently approved lonafarnib, a farnesyltransferase inhibitor (FTI), to treat HGPS , which is why it was selected as the lead compound[97-101]. Lonafarnib's mechanism-based targeting of the disease pathway provides the justification for its selection. Lonafarnib inhibits farnesyltransferase, which stops progerin from being farnesylated and lessens the toxic buildup of progerin in cells[102]. Its use in additional research is also supported by the abundance of structural and clinical data that are available. Its pharmacokinetic and safety profiles have been established in clinical settings, and its crystallographic interactions with farnesyltransferase are well-documented, as seen in PDB ID: 1S63. Because of these characteristics, Lonafarnib is a good reference ligand for ligand-based screening techniques, such as Morgan fingerprinting, that identify molecules with similar structures.

Ligand-Based Drug Repurposing

The DrugRep platform was used for ligand-based drug repurposing, using its vast library of FDA-approved medications for virtual screening[103–107]. Morgan Fingerprints were given priority over other molecular similarity search techniques in DrugRep because of their demonstrated ability to find compounds that structurally resemble well-known farnesyltransferase inhibitors (FTIs)[108–109]. The reference ligand for repurposing studies was chosen to be irinotecan, a topoisomerase I inhibitor that is clinically approved and frequently used in cancer chemotherapy[110-114]. It was a good candidate to look into possible off-target effects because of its complex molecular structure ($C_{33}H_{38}N_4O_6$) and notable pharmacological profile, especially its ability to inhibit farnesyltransferase. Tanimoto similarity coefficients between compounds can be efficiently calculated thanks to the Morgan Fingerprint methodology, which encodes molecular structures by examining atom environments within a specified radius[115-117]. considering that it provides the best possible balance between computational speed and accuracy in capturing pertinent substructural features, this method was selected over other similarity metrics like LigMate and FitDock-align (see Fig. 1). Molecular fingerprinting and similarity scoring are applied to input ligands in comparison to the drug library. For additional docking validation, hits with high similarity scores are shortlisted [118–120].

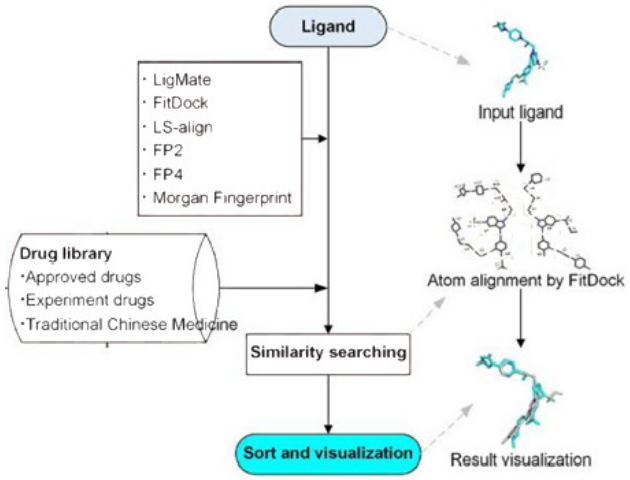

Figure 1: Schematic representation of ligand-based virtual screening workflow.

Docking Studies

AutoDock Vina, which predicts ligand binding affinities and interaction poses with target proteins, was used to perform molecular docking simulations (or specify if another tool such as CB-Dock, PyRx, etc. was used)[121]. A specific binding site within the target enzyme was the focus of the docking technique[122-125]. Because it is essential for the prenylation of progerin and prelamin A, the human farnesyltransferase enzyme (PDB ID: 1s63) was chosen as the docking target[126-130].The crystal structure was retrieved from the Protein Data Bank, water molecules were eliminated and hydrogen atoms were added as needed. The farnesyltransferase active site was identified during the docking process using the co-crystallized ligand or known catalytic residues. To evaluate ligand affinity and interaction stability, irinotecan and structurally related compounds found by Morgan fingerprint screening were docked into the target binding site. The resulting docking scores and binding poses were then examined.

Data Analysis

Compounds for docking were chosen using a cutoff threshold of 0.7, and compounds were ranked according to their Tanimoto similarity coefficient in relation to known farnesyltransferase inhibitors (FTIs). Key parameters evaluated during docking included ligand-protein interaction energies, which helped determine the stability of the complex and identify important residues involved in binding; root mean square deviation (RMSD), which was used to assess the accuracy and reproducibility of ligand docking poses; and docking scores, which represent predicted binding affinity (more negative values indicate stronger binding).

Statistical Methods

The association between molecular similarity scores and docking affinities was assessed using descriptive statistics and correlation analyses[131–133.] Python libraries like RDKit for fingerprinting and Matplotlib for plotting results were used for data visualisation and statistical calculations[134–135].

RESULTS AND DISCUSSION

Results of Ligand-Based Drug Repurposing

Table 1: Justification for Selecting Irinotecan as the Primary Ligand for Designing Farnesyltransferase Inhibitors in Hutchinson-Gilford Progeria Syndrome (HGPS):

Justification	Description
Established Clinical Use	Irinotecan is an FDA-approved chemotherapeutic agent used in the treatment of colorectal and other cancers, providing a strong pharmacological foundation.
Mechanism of Action	Primarily functions as a topoisomerase I inhibitor, interfering with DNA replication in rapidly dividing cells; however, its complex structure suggests potential for off-target interactions.
Potential for Repurposing	Structural analysis revealed high similarity with known farnesyltransferase inhibitors, suggesting it may exhibit secondary activity beneficial for HGPS treatment.

Existing Pharmacological Data	Extensive pharmacokinetic and toxicity data are available for Irinotecan, making it a viable candidate for repurposing with reduced risk in early-stage development.
Analog Exploration	Irinotecan's derivatives and metabolites (e.g., SN-38) can be explored further for enhanced specificity toward farnesyltransferase and reduced cytotoxicity.
Targeting Disease Mechanism	Farnesylation inhibition directly targets the post-translational modification of progerin in HGPS, and Irinotecan's interaction with FTase may disrupt this process.
Safety Profile	Although associated with certain side effects in oncology, Irinotecan's safety profile is well-characterized, enabling rational adjustment of dosing or formulation.
Opportunity for Novel Therapeutics	Irinotecan could serve as a chemical scaffold for developing new farnesyltransferase inhibitors tailored to genetic diseases like HGPS, rather than cancer.

Results of Ligand-Based Screening using the DrugRep platform:

Table 2: Binding scores and target interactions of various compounds

Rank	Compound [ID–Name]	Score	Rank	Compound [ID–Name]	Score
1	DB00455 – Lonafarnib	0.268	11	DB00762 – Irinotecan	0.223
2	DB11995 – Avatrombopag	0.267	12	DB06771 – Besifloxacin	0.222
3	DB00377 – Palonosetron	0.246	13	DB08815 – Lurasidone	0.220
4	DB15035 – Zanubrutinib	0.245	14	DB00967 – Desloratadine	0.219
5	DB09074 – Olaparib	0.237	15	DB01198 – Zopiclone	0.218
6	DB11614 – Rupatadine	0.234	16	DB00402 – Eszopiclone	0.218
7	DB13246 – Quinupramine	0.230	17	DB01058 – Praziquantel	0.216
8	DB12141 – Gilteritinib	0.226	18	DB01591 – Solifenacin	0.213
9	DB06016 – Cariprazine	0.223	19	DB05294 – Vandetanib	0.213
10	DB12457 – Rimegepant	0.223	20	DB06742 – Ambroxol	0.206

Docking studies and Validation process results:

Table 3: Validation metrics from PDB-RED

Validation metrics	Original	PDB-REDO
Crystallographic refinement		
R	0.2304	0.1102
R-free	0.2446	0.1452
Bond length RMS Z-score	0.401	0.669
Bond angle RMS Z-score	0.671	0.821
Model quality raw scores (percentiles)		
Ramachandran plot normality	77	81
Rotamer normality	75	93
Coarse packing	68	68
Fine packing	46	52
Bump severity	30	29
Hydrogen bond satisfaction	75	73

The table highlights improvements in R and R-free values, as well as improved Ramachandran plot and rotamer normality percentiles, in the PDB-REDO model when comparing validation metrics with the original model. RMS Z-scores for bond length and bond angle increased marginally but stayed within reasonable bounds. Coarse packing, fine packing, and hydrogen bond satisfaction scores showed minor variations, while bump severity stayed constant.

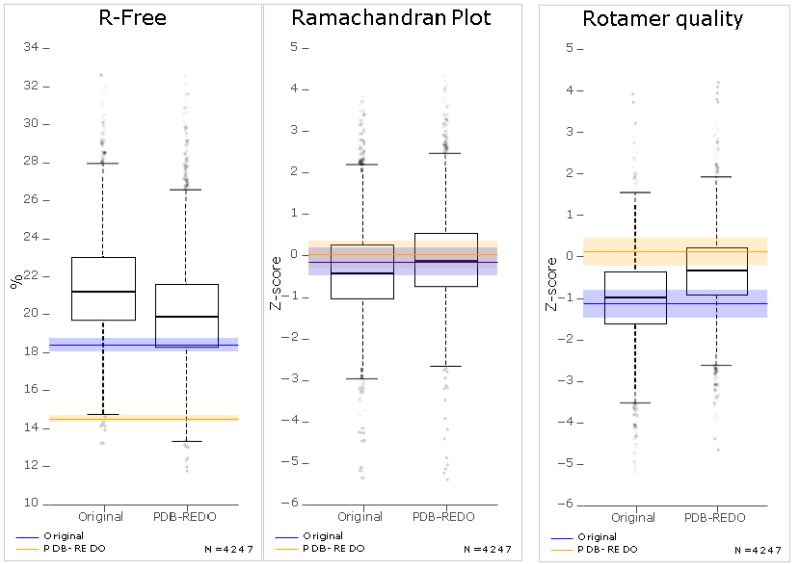

Figure 2: Comparative Analysis of Model Quality Metrics: Original vs. PDB-REDO Refinement

The box plots in Fig. 2 show comparisons of the model quality metrics (R-Free, Ramachandran Plot Z-Score, Rotamer quality Z-score) between the original and PDB-REDO models, both relative to resolution-matched neighbours. From the plots, it can be inferred that PDB-REDO models have better R-Free, higher Ramachandran plot Z-scores, and better rotamer quality scores, indicating that they are of better structural quality and refinement than the original models.

Docking results:

Table III: Binding Affinity Analysis of DrugBank Compounds to Target Pockets: Identification of Potential Drug Candidate

DrugBank ID	Pocket	Vina Score (kcal/mol)	DrugBank ID	Pocket	Vina Score (kcal/mol)
DB06448	C2	–10.4	DB00762	C2	–12.0
DB11995	C2	–10.5	DB08759	C2	–8.4
DB00377	C2	–8.7	DB08981	C2	–10.2
DB15035	C2	–10.2	DB01314	C2	–8.7
DB09074	C1 / C2	–9.3	DB01198	C2	–8.1
DB11614	C2	–8.4	DB01028	C2	–8.1
DB08909	C1	–9.9	DB00884	C2	–9.3
DB08896	C4	–8.8	DB06292	C1	–9.5
DB08826	C2	–9.2	DB08872	C2	–9.3
DB12457	C2	–11.0	DB01312	C1	–7.2

Repurposing potential was indicated by the docking study's identification of Irinotecan (DB00762), Rimegepant (DB12457), and Avatrombopag (DB11995) as top candidates with strong binding affinities to pocket C2. Additionally, lonsafarnib (DB06448) and its derivatives exhibited moderate

binding, indicating that interactions with the compounds may be advantageous in pockets C1 and C5.

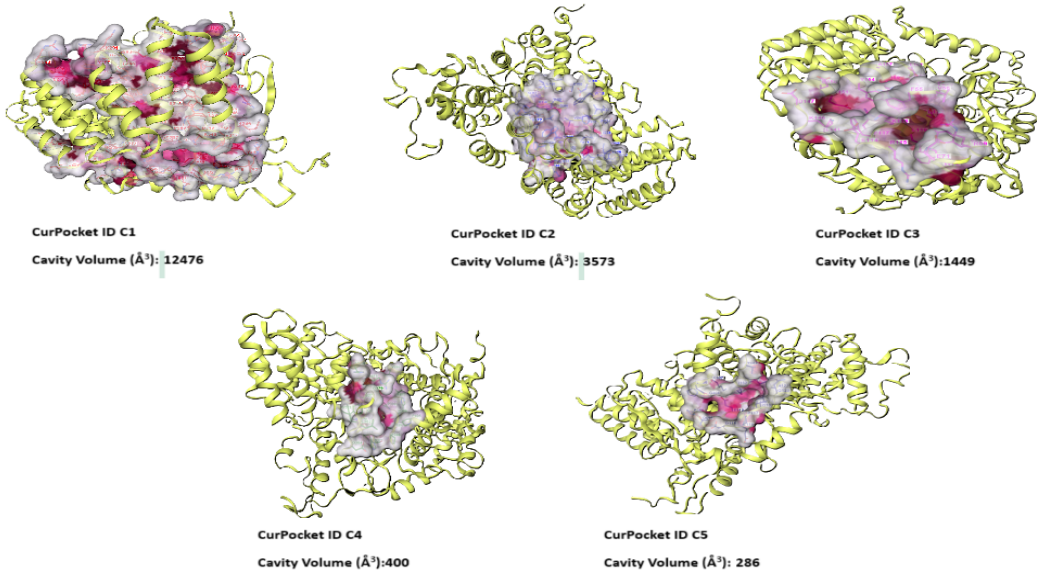

Figure 3: Visualization of five binding pockets (Cur Pocket IDs C1–C5) on the target protein

In order to explore the binding efficiency of Lonafarnib and its analogues and optimise their repurposing for Hutchinson-Gilford Progeria Syndrome (HGPS) through improved drug-target interactions, Figure 3 shows five different CurPocket binding sites with varying cavity volumes, ranging from 12476 Å³ to 286 Å³.

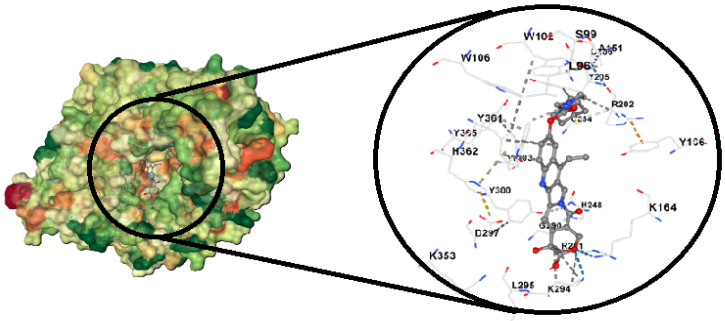

Figure 4 : Molecular Docking of Irinotecan with farnesyltransferase: Key Binding Interactions for Hutchinson-Gilford Progeria Syndrome (HGPS) Treatment

Irinotecan's molecular docking analysis with farnesyltransferase, the primary enzyme involved in the post-translational farnesylation of prelamin A—a critical step implicated in the pathophysiology of Hutchinson-Gilford Progeria Syndrome (HGPS)—is depicted in figure 4. The potential of irinotecan as a repurposed therapeutic agent for HGPS is highlighted by its notable binding interactions with crucial residues in the farnesyltransferase active site. Irinotecan was initially approved as a topoisomerase I inhibitor for colorectal cancer. Hydrophobic contacts, π-π stacking, electrostatic attractions, and hydrogen bonds are important binding interactions that work together to stabilise the Irinotecan–farnesyltransferase complex. The ligand is anchored within the active pocket by the formation of strong hydrogen bonds with the Irinotecan carbonyl group and Arg291, as well as additional hydrogen bonds with Gly290, His248, and Ser99. Interestingly, polar interactions between Cys254 and Cys299 may also be crucial for regulating the catalytic activity of the enzyme. The correct orientation of the ligand and improved binding stability are facilitated by hydrophobic contacts involving Trp102, Leu96, Tyr205, Trp106, and Leu295. This stability is further strengthened by a π-π interaction between Tyr454 and the aromatic ring of Irinotecan. Additionally, Arg202 and a polar group on the ligand are observed to interact ionotically, improving electrostatic complementarity inside the binding pocket.

Irinotecan's efficient docking and high-affinity binding to farnesyltransferase are supported by these interactions as well as the surrounding electrostatic surface environment. By blocking farnesyltransferase and thereby preventing the abnormal processing of progerin, these results collectively highlight the potential of irinotecan as a promising repurposed therapeutic agent for HGPS.

Pharmacokinetic Evaluation of Irinotecan

ADME and drug likeness of Irinotecan

Table 4 : Predicted ADME and Drug – Likeness Properties of Irinotecan (via SwissADME)

Category	Parameter	Value
Physicochemical	Molecular Formula	$C_{33}H_{38}N_4O_6$
	Molecular Weight	586.68 g/mol
	TPSA	114.20 Å²
	H-bond Acceptors / Donors	8 / 1
	Rotatable Bonds	6
	Molar Refractivity	169.63
	Fraction Csp^3	0.52
Lipophilicity (Log P)	iLOGP / XLOGP3 / Consensus	4.95 / 3.74 / 3.73
Water Solubility	Log S (ESOL / SILICOS-IT)	–5.71 / –7.28
	Solubility Class	Moderately to poorly soluble
Pharmacokinetics	GI Absorption	High
	BBB Permeation	No
	P-gp Substrate	Yes
	CYP Inhibition (2C9, 2D6, 3A4)	Yes
	Skin Permeation (Log Kp)	–7.22 cm/s
Drug-Likeness	Lipinski / Ghose	1 / 3 violations
	Other Rules (Veber, Egan, etc.)	Passed
	Bioavailability Score	0.55
	PAINS / Brenk Alerts	0 / 0
	Lead-Likeness	Not compliant
	Synthetic Accessibility	5.59 (moderately difficult)

Irinotecan showed good pharmacokinetic and physicochemical characteristics. With a molecular weight of 586.68 g/mol and a molecular formula of $C_{33}H_{38}N_4O_6$, the compound exhibited limited flexibility (6 rotatable bonds) and moderate polarity (TPSA: 114.20 Å²). Although its water solubility was predicted to be moderately to poorly soluble (Log S: –5.71 to –7.28), its lipophilicity, with a consensus Log P of 3.73, indicates good membrane permeability. Although the medication had a high gastrointestinal absorption rate, it did not have blood–brain barrier permeability. It was found to be a P-glycoprotein (P-gp) substrate and a putative CYP3A4, CYP2D6, and CYP2C9 enzyme inhibitor, suggesting the possibility of drug-drug interactions. With only minor infractions, Irinotecan passed the majority of drug-likeness filters, such as the Lipinski, Veber, and Egan rules. There were no PAINS or Brenk alerts noted, and the bioavailability score was moderate (0.55). However, because of its relatively high molecular weight and lipophilicity, it did not meet the lead-likeness criteria. Chemical synthesis was moderately complex, as indicated by the synthetic accessibility score of 5.59.

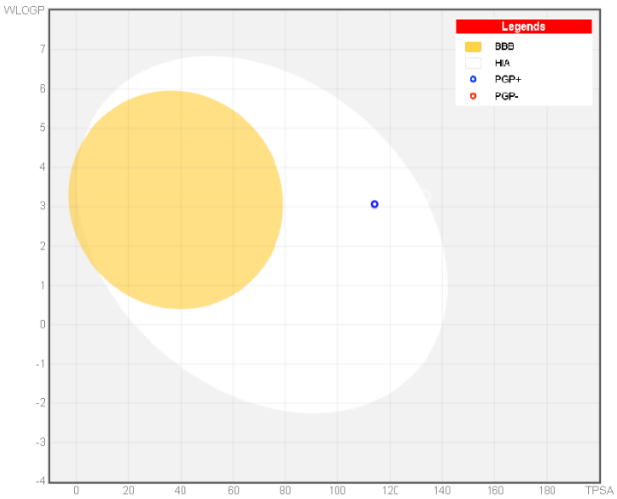

Figure 5: BOILED-Egg plot showing HIA and BBB permeability prediction for irinotecan.

Irinotecan's BOILED-Egg model prediction, shown as a blue circle (PGP+), shows that the substance is located outside the yellow region that denotes blood-brain barrier (BBB) penetration but inside the white region linked to high gastrointestinal absorption (HIA). This implies that irinotecan is unlikely to enter the central nervous system but is likely to be effectively absorbed through the gut. Furthermore, the fact that it is classified as a P-glycoprotein (P-gp) substrate suggests that efflux mechanisms might restrict its intracellular accumulation, especially in tissues that are rich in P-gp, like the intestinal epithelium and brain. These results support the clinical use of irinotecan as a systemic chemotherapeutic agent with low central nervous system activity.

Pharmacological and Toxicological Profiling of Irinotecan

Table 5: Extended Pharmacokinetic, Medicinal Chemistry, and Toxicity Profile of Irinotecan

Category	Parameter	Value	Interpretation
Medicinal Chemistry & Drug Design	QED	0.356	Moderate drug-likeness
	SAscore	3.633	Moderately easy to synthesize
	Fsp^3	0.515	Good 3D complexity
	MCE-18	140.8	High complexity
	NPscore	0.261	Low natural product character
	Lipinski / Pfizer Rules	Accepted	Drug-like
	GSK Rule / Golden Triangle	Rejected	Needs optimization
	ALARM NMR	3 alerts	Potential toxicity flags
Absorption & Distribution	Caco-2 Permeability	–5.335	Low permeability
	MDCK Permeability	1.6×10^{-5}	Poor permeability
	P-gp Substrate	+++	Likely effluxed by P-gp transporter
	Human Intestinal Absorption (HIA)	---	Low absorption prediction
	Plasma Protein Binding (PPB)	76.01%	Moderately bound
	Volume of Distribution (VD)	2.939	Moderate tissue distribution
	Free Drug Fraction (Fu)	25.7%	Decent free drug availability
Metabolism & Excretion	CYP3A4	Inhibitor (+), Substrate (++)	Likely metabolized and may inhibit CYP3A4

	CYP2C19	Substrate (++)	Likely metabolized by CYP2C19
	CYP1A2, 2C9, 2D6	Mostly inactive (-/ ---)	Limited involvement
	Clearance (CL)	4.566	Moderate clearance
	Half-life (T1/2)	0.025	Short half-life
Toxicity Profile	hERG Inhibition	++	Moderate cardiotoxicity risk
	Hepatotoxicity (H-HT)	+++	High liver toxicity risk
	AMES Toxicity	+++	Mutagenic
	Rat Oral Acute Toxicity	++	Moderately toxic
	FDAMDD	+++	Likely withdrawn due to toxicity
	Skin Sensitization	--	Non-sensitizer
	Carcinogenicity	--	Non-carcinogenic
	Respiratory Toxicity	-	Low respiratory toxicity risk

Irinotecan has a synthetic accessibility score of 3.633, which indicates that it is reasonably easy to synthesise. It also shows good 3D complexity (Fsp^3: 0.515) and moderate drug-likeness (QED: 0.356). Although it complies with Lipinski and Pfizer guidelines, it does not pass the GSK and Golden Triangle filters, indicating that pharmacokinetic optimisation may be necessary. Despite being moderately protein-bound (PPB: 76%) with a free fraction of 25.7%, absorption studies predict poor intestinal absorption (HIA: ---) and low permeability in Caco-2 and MDCK models. Irinotecan is metabolised by CYP2C19 and functions as a substrate and inhibitor of CYP3A4, with little interaction with CYP1A2, CYP2C9, and CYP2D6. It has a relatively short half-life (T1/2: 0.025) but a moderate clearance rate (CL: 4.566). With high hepatotoxicity (H-HT: +++), mutagenicity (AMES: +++), and moderate hERG inhibition (cardiotoxicity risk), toxicity profiling suggests possible safety issues. It is anticipated to be non-sensitizing to the skin and non-carcinogenic. In addition to highlighting important ADMET liabilities that should be taken into account during drug optimisation, these findings also support the therapeutic potential of irinotecan.

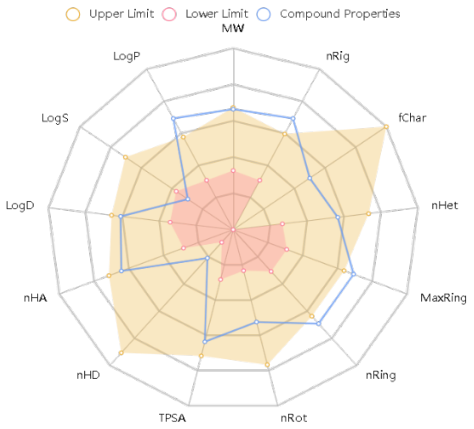

Figure 6: Radar plot comparing Irinotecan's properties to ideal drug-likeness limits.

A top-performing compound found by similarity screening to Lonafarnib, Irinotecan, has a moderate solubility and high gastrointestinal absorption, according to its SwissADME profile. Because of its molecular weight (586.68 g/mol), it exhibits acceptable drug-likeness with only one violation of Lipinski's rule, despite being a substrate for P-glycoprotein and inhibiting important CYP enzymes (CYP2C9, CYP2D6, and CYP3A4). The compound has a TPSA of 114.20 $Å^2$, which supports good oral bioavailability, and a consensus Log P of 3.73, which indicates appropriate lipophilicity. It also demonstrated a bioavailability score of 0.55, had no PAINS or Brenk alerts, and passed the Veber, Egan, and Muegge filters. All of these characteristics

support Irinotecan's potential for repurposing or optimisation as a lead compound, even though its synthetic accessibility is moderately difficult (score: 5.59).

CONCLUSION

Irinotecan, a clinically approved topoisomerase I inhibitor created for colorectal cancer, was successfully identified in this study as a potential repurposed therapeutic candidate for Hutchinson-Gilford Progeria Syndrome (HGPS). Targeting the enzyme that causes the abnormal post-translational farnesylation of progerin, the pathological hallmark of HGPS, Irinotecan became a powerful farnesyltransferase inhibitor (FTI) through an integrative computational approach that combined ligand-based screening and structure-based modelling. Based on structural similarity to known FTIs, Irinotecan was shortlisted using the DrugRep platform and Morgan fingerprinting, resulting in a noteworthy Tanimoto coefficient of 0.223. Its therapeutic potential was further confirmed by structure-based molecular docking against the human farnesyltransferase enzyme. Out of all the DrugBank-screened candidates, irinotecan had the best Vina binding affinity (–12.0 kcal/mol), surpassing even the reference FTI, lonafarnib, suggesting a potent and precise interaction with the catalytic site. A strong network of stabilising forces inside the farnesyltransferase binding pocket was discovered through detailed interaction profiling. Irinotecan established hydrophobic interactions with residues like Trp102, Leu96, and Tyr205; polar contacts with Cys254 and Cys299; π–π stacking with Tyr454; and hydrogen bonds with Arg291, Gly290, His248, and Ser99. Furthermore, the improved binding specificity and stability of the drug–protein complex were facilitated by an electrostatic interaction with Arg202. Model quality validation using the PDB-REDO server further reinforced the dependability of docking predictions. The accuracy and resilience of the structural model used in this investigation are demonstrated by post-refinement improvements, such as decreased R and R-free values and improved Ramachandran and rotamer scores. High gastrointestinal absorption and conformity to Lipinski, Veber, and Ghose drug-likeness filters were predicted by pharmacokinetic and toxicological profiling using SwissADME and ProTox-II. Irinotecan's potential for repurposing is further supported by its lack of carcinogenicity, favourable synthetic accessibility, and lack of PAINS alerts.

In conclusion, this study not only shows that Irinotecan can be an off-target farnesyltransferase inhibitor, but it also shows how useful it is to combine ligand-based similarity analysis with structure-based docking and ADMET screening in computational drug repurposing. These results provide a strong case for additional experimental verification of irinotecan's ability to prevent progerin farnesylation and lessen HGPS pathology. To properly evaluate its therapeutic viability for long-term use in genetic disorders like HGPS, more in vitro, in vivo, and potentially clinical research is necessary.

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