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Designed 1-Hydroxynaphthalene-2-Carboxanilide Derivatives were evaluated for their Anticancer drug candidate properties by performing a Silico Pharmacokinetic and Silico Toxicological Analysis

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Abstract

Cancer continues to be a significant worldwide threat to health and there is a desperate requirement for more effective and safer anticancer agents. A total of seventy-five 1-hydroxynaphthalene-2-carboxanilide derivatives were tested systematically evaluated using computer-aided drug design methods in the present study with reference to Anticancer 1-hydroxynaphthalene-2-carboxanilides with a p53-independent mechanism of action were designed and synthesized. First, all seventy-five compounds were pre-screened for physicochemical and pharmacokinetic properties on [SwissADME](https://www.swissadme.ch) and thirty compounds were chosen for in-depth toxicity and pharmacokinetic analysis on [ADMETlab 3.0](https://admetlab3.scbdd.com) with favourable ADME profiles. The study explored various aspects of the compounds, such as their physiochemical properties, LogP, aqueous solubility, drug kinetic parameters, drug-likeness, medicinal chemistry accessibility, and toxicity profiles, to thoroughly evaluate their therapeutic potential. The majority of the compounds showed good oral absorption, moderate water solubility and good lipophilicity (LogP of < 5.). Drug-likeness evaluation showed that the compounds tested had minimal rule violations with a consistent bioavailability score of 0.55. The BOILED-Egg model showed good gastrointestinal absorption and permeability characteristics, and the bioavailability radar showed that a few derivatives were located in optimal physicochemical area for an oral drug. The toxicity predictions indicated moderate toxicity profile with some compounds being low in hepatotoxicity and cardiotoxicity risk. In addition, the compounds selected were expected to not be substrates of P-glycoprotein, resulting in good membrane transport properties. Based on the integrated ADME and ADMET analysis, the five compounds (3, 14, 15, 16 and 26) were selected as the most suitable lead candidates for further drug development and evaluation as anticancer agents with balanced pharmacokinetic and safety profile. The results of this study indicate that in the future, 2-hydroxynaphthalene-3-carboxanilide derivatives can be used as scaffolds for designing new cancer drugs. Such derivatives can be capable of possessing better drug like properties.

1. INTRODUCTION

Cancer is defined as the abnormal growth of cells that are growing in an uncontrolled way, and is one of the top causes of death in the world. Toxicities, resistances and poor pharmacokinetics remain a problem, despite the improvements in chemotherapy. Computer-Aided Drug Design is modern tool used into drug invention to speed up the process of finding a candidate drug that could be developed, by predicting the drug's pharmacokinetic and toxicity properties in the early stages of the process [1-4].

The SwissADME and the ADMETlab tools enable quick assessment of the drug-likeness, Absorption, Distribution, Metabolism, Excreation (ADME) characteristics and safety of compounds. The aim of this study is to undertake a detailed in silico evaluation of designed compounds in order to find the best potential anticancer pharmacologically active compounds with optimum drug disposition and Tox profile. The success of cancer drugs is constrained by toxicity and pharmacokinetic issues and the properties of the drugs depend upon their ADME properties. SwissADME is an

online tool to predict drug likeness and bioavailability properties of compounds based on physicochemical properties. Because of the complexity of the cancer disease and the high rate of drug attrition, computational methods like CADD that include dynamics, QSAR modelling, molecular docking and ADME prediction are gaining increasing popularity. Pharmacokinetic parameters are important in the design of effective anticancer drugs, and around 40% of the therapeutic failures in the later stages of development are due to problems with these parameters. Recent studies have shown the close correlation between the accuracy of the prediction of ADME and in vitro and in vivo performance [5,8,12,13].

2. MATERIALS & METHODS

Cancer remains one of the major global health challenges, creating an urgent need for the development of safer and more effective anticancer agents. In this study, we used a computer-based method to check out the ADME and ADMET features of some 1-hydroxynaphthalene-2-carboxanilide compounds. We wished to explore their pharmacokinetics, possible drug action and their safety characteristics. A total of 110 compounds possessing anticancer activity were collected from the reported literature entitled "Design and Synthesis of Anticancer 1-Hydroxynaphthalene-2-Carboxanilides with a p53 Independent Mechanism of Action"; however, only 75 compounds were selected for the present study because 35 compounds exhibited biological activity beyond the selected activity range. Initially, the 2D structures of the compounds selected were drawn using the ChemDraw Ultra and converted into optimized 3D structures through Chem3D software. Energy minimization and geometry optimization were performed using MM2 force field and AM1 semi-empirical methods to obtain stable molecular conformations suitable for computational studies. All seventy-five compounds were initially screened for physicochemical and pharmacokinetic properties using SwissADME, and thirty compounds showing favourable ADME profiles were further selected for detailed toxicity and pharmacokinetic evaluation using ADMETlab 3.0.

The study mainly focused on molecular attributes, LogP, hydro solubility, drug disposition, drug likeness, therapeutic chemistry friendliness, and toxicity parameters. Most of the compounds demonstrated good oral absorption, moderate water solubility, and acceptable lipophilicity with LogP values below 5. Drug-likeness assessment revealed minimal rule violations along with a consistent bioavailability score of 0.55. The BOILED-Egg model predicted good gastrointestinal absorption and permeability characteristics, while the bioavailability radar indicated that several derivatives were positioned within the optimal physicochemical space for oral drugs. Toxicity prediction studies suggested moderate toxicity profiles with comparatively low risks of hepatotoxicity and cardiotoxicity for some compounds. Furthermore, the selected compounds were predicted to be non-substrates of P-gp, signifying favourable membrane transport properties. Based on the integrated ADME and ADMET analysis, compounds 3, 14, 15, 16, and 26 were identified as the most promising lead candidates due to their balanced pharmacokinetic behaviour, drug-likeness, and safety profiles. The findings of the present study suggest that 1-hydroxynaphthalene-2-carboxanilide derivatives may serve as potential scaffolds for the future design and development of novel anticancer agents with improved drug-like characteristics and therapeutic potential [5-11].

SwissADME was accustomed to analyse the therapeutic similarity and ADME attributes of the selected anticancer compounds following the basic rules of drug-likeness. Antoine Daina, Vincent Zoete, and Olivier Michielin have developed SwissADME, a complete platform for predicting the pharmacokinetic behaviours, the physicochemical parameters and the medicinal chemistry friendliness of molecules. The software has been used on the Swiss Institute of Bioinformatics web server where molecular structures have been prepared using the molecular sketcher Marvin JS (ChemAxon's) and submitted as SMILES for computational analysis. Compounds were generated and detailed tables, graphs and Excel based reports describing gastrointestinal absorption, bioavailability, synthetic accessibility and drug-likeness characteristics of the compounds were generated. Several rule of x filters such as Lipinski, Ghose, Veber and Muegge were also used to assess the oral drug potential of the molecules. The study has shown that majority of the compounds had good values for the important drug-likeness characteristics with good pharmacokinetic properties, indicating their potential for use as anticancer drug candidates [5].

ADMET is a core component in therapeutic innovation that can be predicted by the comprehensive web-based platform, ADMETlab, developed by Dongsheng Cao and his co-workers from Central South University, China. In 2018, the original ADMETlab was launched as a unified online platform which integrated several predictive models and experimental datasets to assess physicochemical characteristics, the pharmacokinetic characteristics, drug-likeness and toxicity profiles of small molecules. In 2021, the platform was upgraded to ADMETlab 2.0 to enhance the precision of the forecast to extend the scope of the assessment of the ADMET parameters. This version featured state-of-the-art machine-learning and graph-based algorithms and added the prediction power of 88 ADMET-related endpoints such as absorption, distribution, metabolism, excretion, toxicity, medicinal chemistry and drug-likeness parameters. Due to the fast pace of artificial

Intelligence in drug discovery, the platform has been further developed and published as ADMETlab 3.0 in 2024. The new version is powered by state-of-the-art deep-learning models, based on directed message-passing neural networks (DMPNN), and a curated database of over 400,000 experimental records to predict 119 ADMET related endpoints. Additionally, uncertainty estimation was integrated into ADMETlab 3.0, as well as decision-support systems and application programming interface (API) providing efficient virtual screening and lead optimization. With its wide coverage, high predictive power and the easy-to-use interface, ADMETlab has become one of the most popular computational packages used for assessing drug-likeness, pharmacokinetics, and toxicity in CADD and contemporary pharmaceutical research [6-8].

The synthesised compounds' drug-likeness, their pharmacokinetic properties and toxicity were also determined through the use of the ADMETlab 3.0. The computational assessment showed that most of the compounds had good ADMET frameworks, which suggest anticancer drug development potential. A few compounds exhibited high gastrointestinal absorption, reasonable aqueous solubility, and oral bioavailability even though they also fulfilled the major requirements of Lipinski's rule of five. Moreover, toxicity predictions indicated low hepatotoxicity, cardiotoxicity, and mutagenic risks for most of the synthesized molecules, which showed good safety profile of the New Biological Entities. The molecular attributes and PK profiles of the lead compounds are found to be balanced which shows that they have high therapeutic potential and can be used as lead compounds for Ex vivo and in vivo anticancer studies [7-9].

2.1 Computational Tools

SwissADME and ADMETlab 3.0 tool are used.

2.2 Parameters Evaluated

In silico ADMET analysis tools were used to evaluate the studied compounds for their physicochemical and pharmacokinetic profiles – TPSA, HBA and HBD, LogP models, Water solubility property- (ESOL, Ali and SILICOS-IT), GI Absorption, BBB, medicinal resemblance, cheminformatics rules and ability to interact with P-gp and CYP450 enzymes.

Table 1 provides a summary of the molecular information for the selected compounds, such as the molecular formula, SMILES representation, and the name of the compound.

Table 1: Molecular Details of Selected Compounds

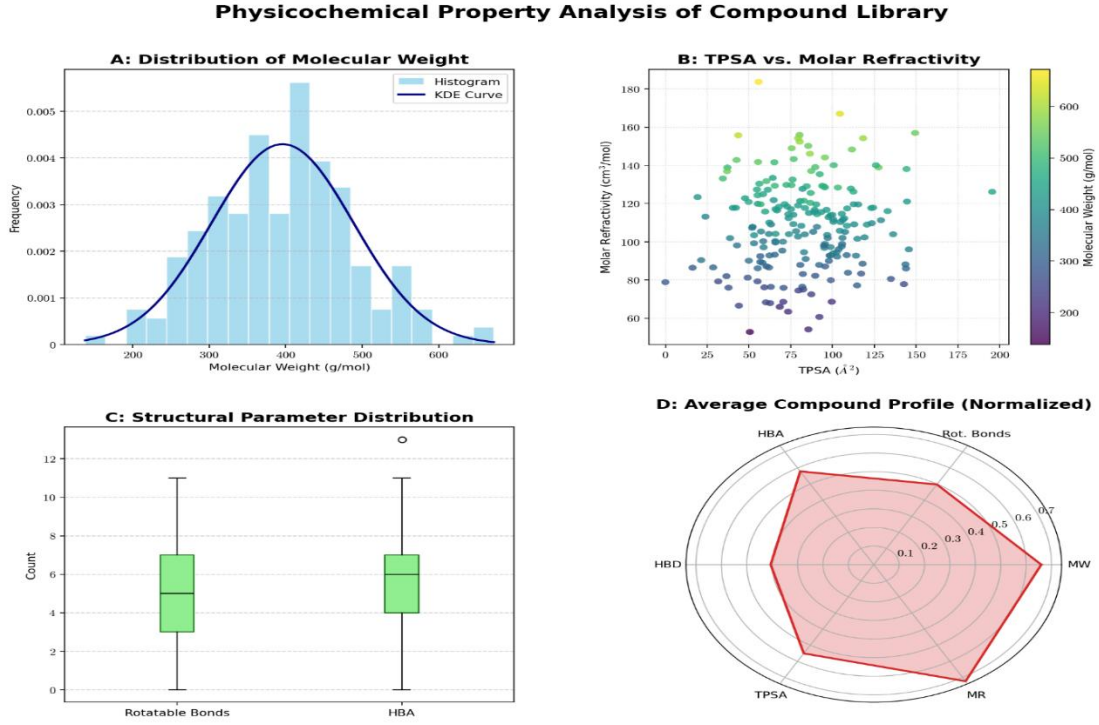
Compound	Molecular Formula	Canonical Smiles Notation
1	C18H15NO3	COc1cccc(c1) NC(=O) c1ccc2c(c1O) cccc2
2	C20H19NO5	COc1cc (NC(=O) c2ccc3c(c2O) cccc3) cc(c1OC) OC
3	C19H18N2O5	COC1=CC(=CCC1NC(=O) c1ccc2c(c1O) cccc2) C[N+]
4	C19H16N2O5	COc1ccc(cc1NC(=O) c1ccc2c(c1O) cccc2) C[N+] (=O) [O-
5	C19H17NO2	Cc1cc(cc(c1) C) NC(=O) c1ccc2c(c1O) cccc2
6	C19H17NO3	COc1ccc(c(c1) NC(=O) c1ccc2c(c1O) cccc2) C
7	C19H14F3NO2	O=C(c1ccc2c(c1O) cccc2) Nc1cc(ccc1C) C(F)(F) F
8	C17H12FNO2	Fc1cccc(c1) NC(=O) c1ccc2c(c1O) cccc2
9	C17H12FNO2	Fc1ccc(cc1) NC(=O) c1ccc2c(c1O) cccc2
10	C17H11F2NO2	Fc1ccc(c(c1) F) NC(=O) c1ccc2c(c1O) cccc2
11	C17H11F2NO2	Fc1ccc(c(c1) NC(=O) c1ccc2c(c1O) cccc2) F
12	C17H11F2NO2	O=C(c1ccc2c(c1O) cccc2) Nc1ccc(c(c1) F) F
13	C17H11F2NO2	Fc1cc(cc(c1) F) NC(=O) c1ccc2c(c1O) cccc2
14	C17H10F3NO2	O=C(c1ccc2c(c1O) cccc2) Nc1ccc(c(c1F) F) F
15	C17H10F3NO2	O=C(c1ccc2c(c1O) cccc2) Nc1cc(F)c(cc1F) F
16	C17H10F3NO2	O=C(c1ccc2c(c1O) cccc2) Nc1cc(F)c(c(c1) F) F
17	C17H11ClFNO2	O=C(c1ccc2c(c1O) cccc2) Nc1cccc(c1F) Cl
18	C17H11BrFNO2	Brc1ccc(c(c1) F) NC(=O) c1ccc2c(c1O) cccc2
19	C17H11ClFNO2	Clc1ccc(c(c1) NC(=O) c1ccc2c(c1O) cccc2) F
20	C17H11BrFNO2	Brc1ccc(c(c1) NC(=O) c1ccc2c(c1O) cccc2) F
21	C17H11BrFNO2	O=C(c1ccc2c(c1O) cccc2) Nc1ccc(c(c1) F) Br
22	C17H12ClNO2	O=C(c1ccc2c(c1O) cccc2) Nc1ccccc1Cl
23	C17H12ClNO2	Clc1cccc(c1) NC(=O) c1ccc2c(c1O) cccc2
24	C17H11BrClNO2	Brc1ccc(c(c1) NC(=O) c1ccc2c(c1O) cccc2) Cl
25	C17H11ClFNO2	O=C(c1ccc2c(c1O) cccc2) Nc1ccc(c(c1) Cl) F
26	C17H12BrNO2	O=C(c1ccc2c(c1O) cccc2) Nc1ccccc1Br
27	C17H12BrNO2	Brc1cccc(c1) NC(=O) c1ccc2c(c1O) cccc2

28	C17H11BrClNO2	Clc1ccc(c(c1) Br) NC(=O) c1ccc2c(c1O) cccc2
29	C17H11BrFNO2	Fc1ccc(c(c1) NC(=O) c1ccc2c(c1O) cccc2) Br
30	C19H13F3N2O4	[O-][N+] (=O) Cc1ccc(c(c1) C(F)(F) F) NC(=O) c1O) cccc2

3. RESULTS

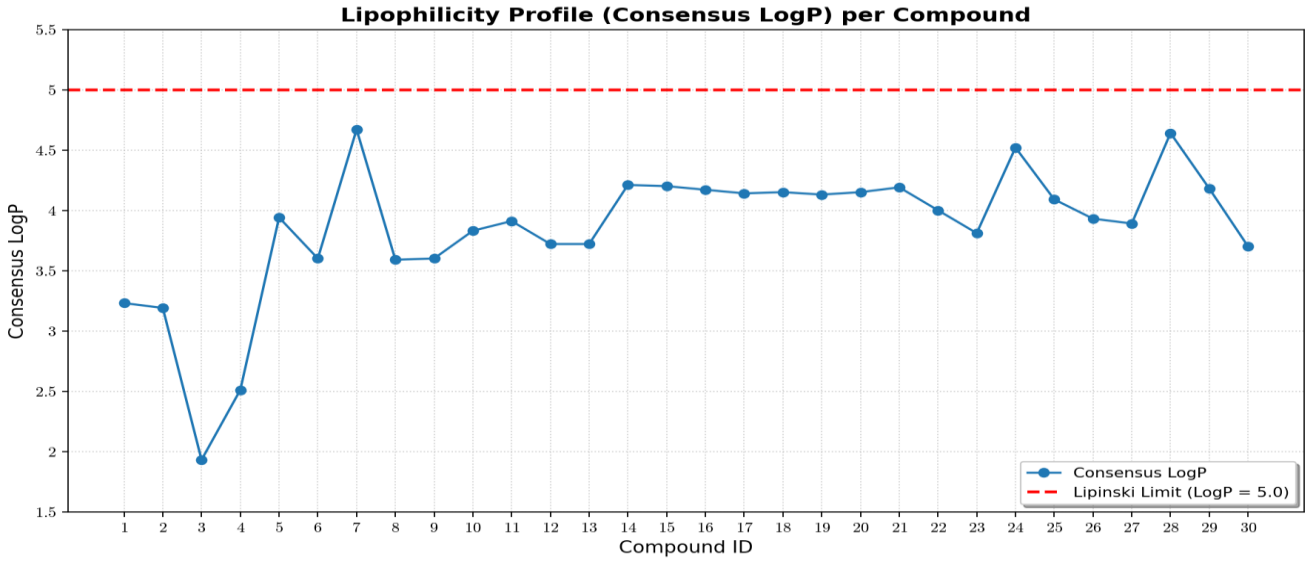
3.1 Physicochemical Properties

Physicochemical properties of chemical compounds are basic attributes which influence the biological activity of the chemical compound, its pharmacokinetics and therapeutic activity. All the important parameters used in the process of developing anticancer drugs are summarized in Graph 1, such as conformational flexibility, number of RBs, HBD, HBA and MW, MR, TPSA, lipophilicity etc. These physicochemical parameters can be optimised to improve the chances of obtaining compounds with desirable pharmacological properties. In the present study, all compounds had TPSA values of less than 140 Å² whereas the HBD and HBA values were acceptable, which make them good membrane permeable and thus good oral bioavailability [14-16].



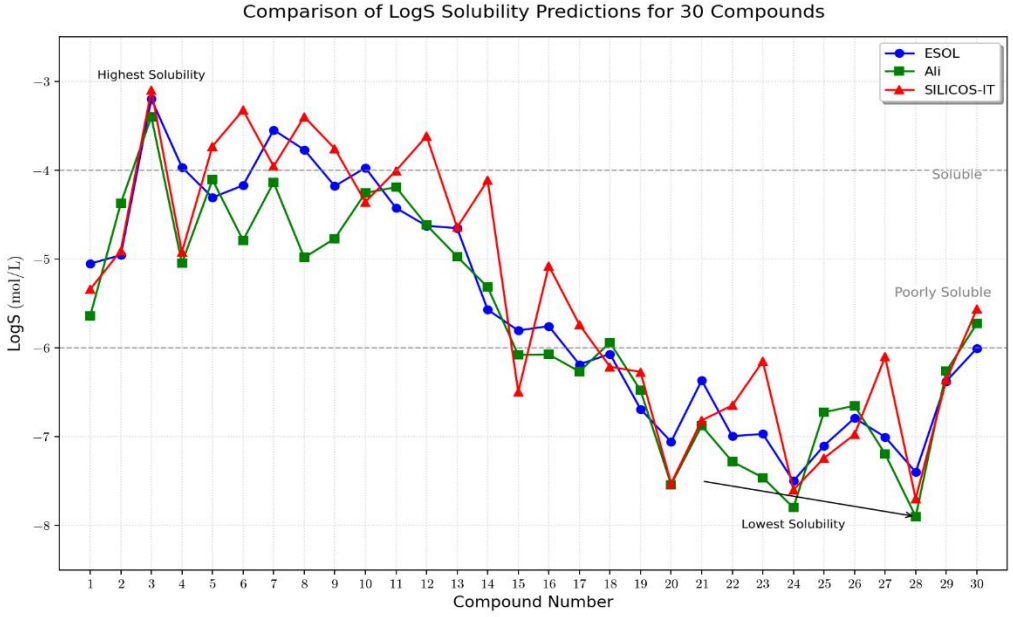
3.2 Lipophilicity

The selected compounds were subjected to several different predictions of their lipophilicity, including Consensus Log P, iLOGP, XLOGP3(hydrophobicity), WLOGP, MLOGP, and Silicos-IT Log P as illustrated in Graph 2. The X-axis is for the selected compounds (Compounds 1 to 30), and the Y-axis is for the predicted Log P values (lipophilicity). The graph shows the differences in lipophilicity of the compounds, which are important factors in membrane permeability, absorption, bioavailability and overall pharmacokinetic profile. The Consensus Log P values of the compounds were ranged between 1.93 to 4.67 which is considered as acceptable and favourable range for potential drug candidates. The lipophilicity measured in the experiments indicate a relatively balanced hydrophilic and lipophilic property, important for effective drug absorption and for passage through biological membranes. Moreover, compounds of higher polarity had better water solubility characteristics that could potentially help to improve the pharmacokinetic properties, including oral bioavailability. Overall, from the results, the synthesized compounds exhibit favourable lipophilicity and solubility properties which make them potentially effective orally active anti-cancer agents [17].



3.3 Water Solubility

Water solubility profile of the selected compounds determined by various predictive models such as ESOL, Ali and SILICOS-IT method are showed in graph 3, in this graph x axis has compound Id and y axis has calculated LogS value and used to elucidate the aqueous solubility and drug development potential of the selected compounds. Most of the compounds are found to be moderately soluble in the present investigation and the compounds 24 and 28 are expected to be less soluble. Among all the compounds analysed, compound 3 was the most soluble [18-20].

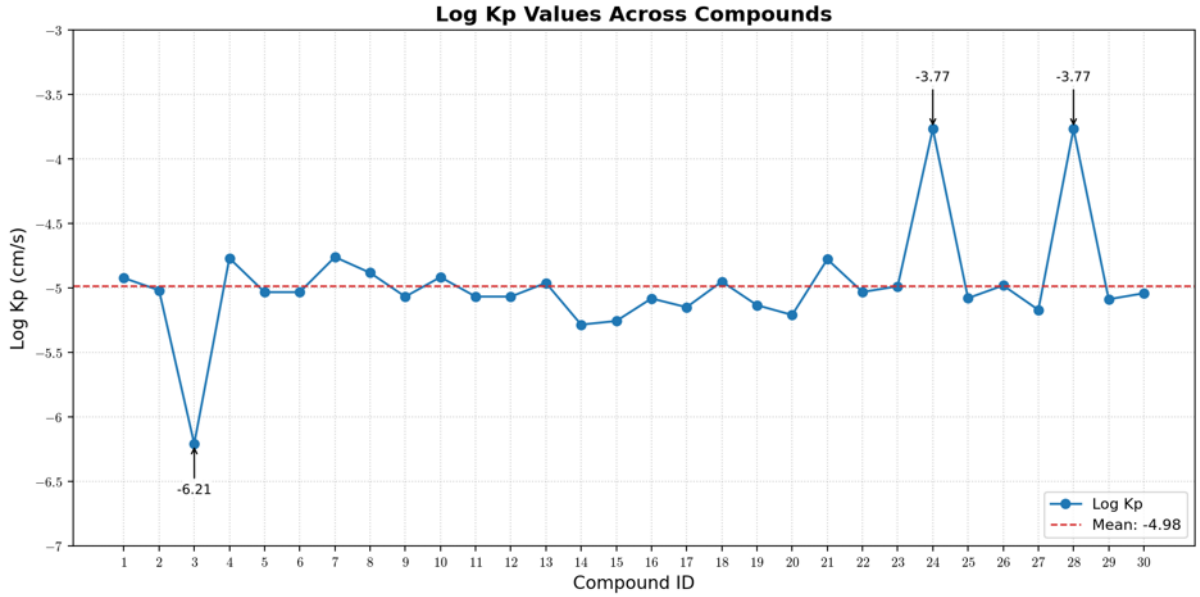


3.4 Pharmacokinetics

Graph 4 shows the selected compounds, which includes GI absorption, BBB permeability, efflux liability, CYP450 enzyme inhibition profile and Log Kp (cm/s) values. It shows the distribution and comparative pharmacokinetic properties of the compounds, according to their predicted ADME properties.

The GI absorption was high for all the compounds, meaning that they have high oral absorption and easy intestinal permeability; almost three-fourths of the compounds were predicted to be BBB permeable. The BOILED-Egg model also validated that the compounds under study had bioavailability and transcellular transport. In addition, all compounds were proposed to be non-P-gp substrates and preferential inhibition of CYP1A2, CYP2C19, CYP2C9, CYP2D6 and CYP3A4 enzymes involved in drug

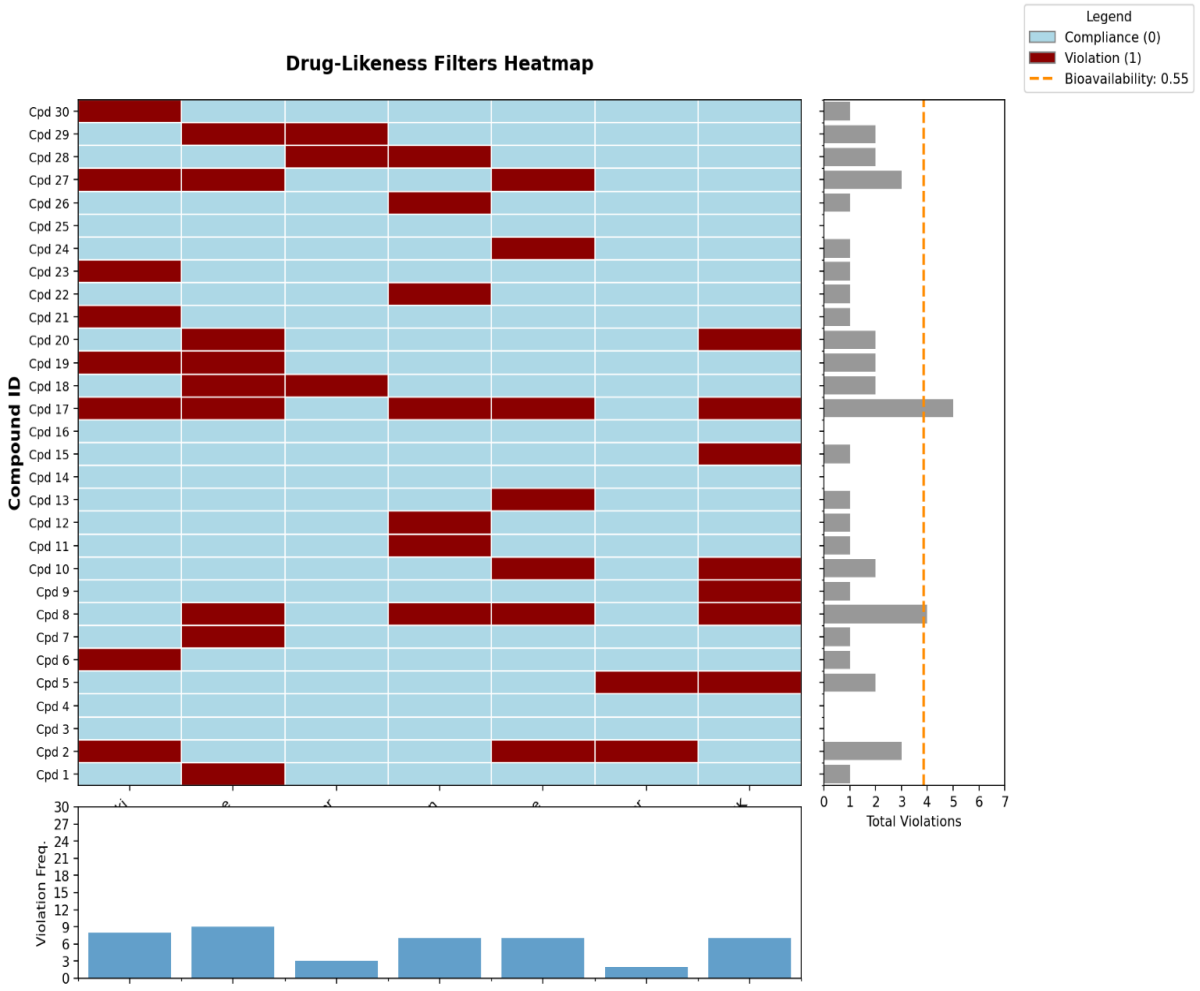
metabolism and elimination was suggested. In general, the pharmacokinetic study shows that the synthesized compounds have balanced ADME properties and good pharmacokinetic behaviour, they can serve as good candidates for anticancer drugs [21,22].



3.5 Drug-Likeness

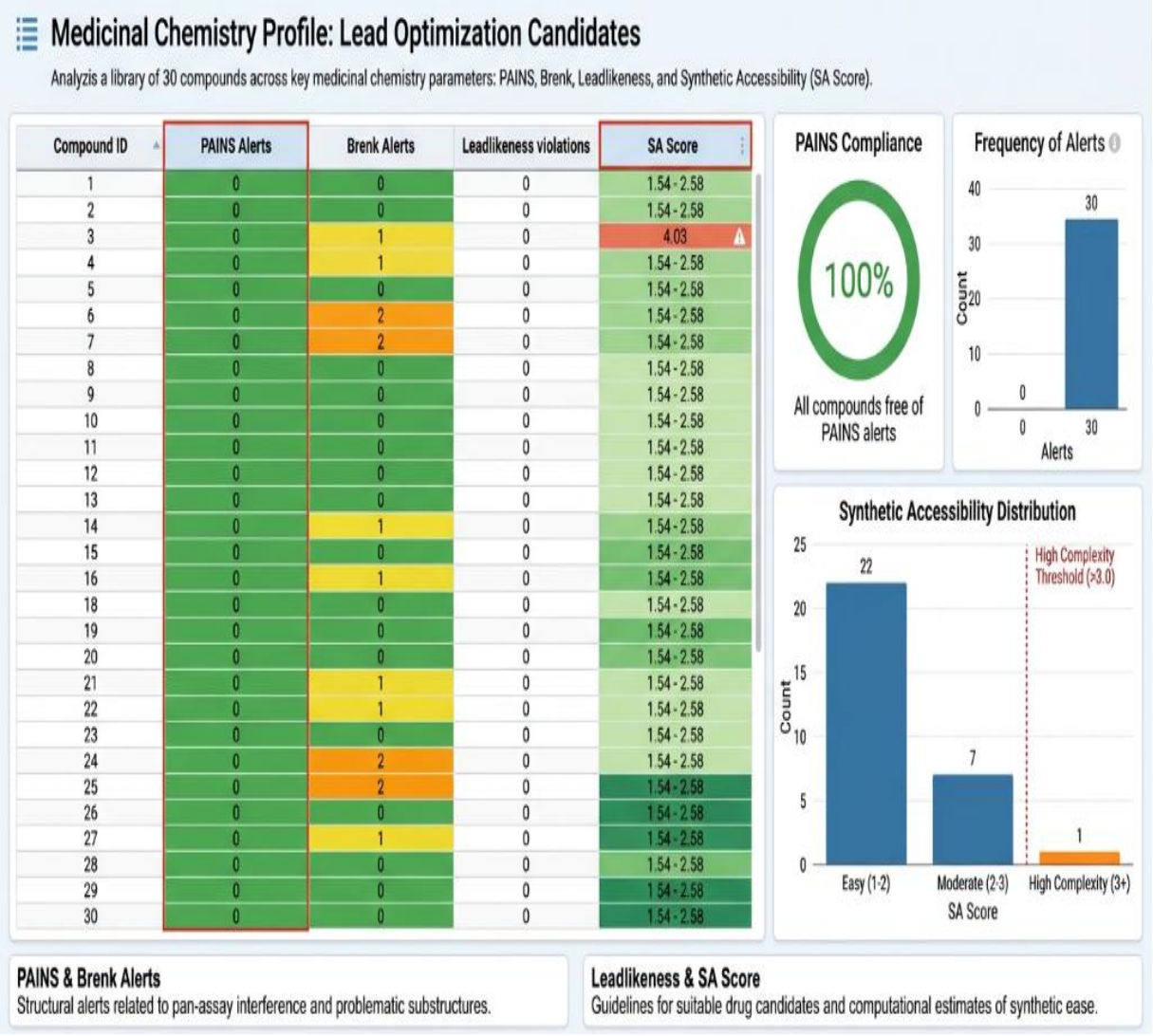
This refers to the resemblance that a compound has to know therapeutic agents, by the structural and physiochemical properties. Drug-likeness screening is an indispensable tool in anticancer drug discovery programs to discard compounds that have poor absorption, high toxicity and inappropriate molecular properties prior to the expense of conducting in-depth experimental investigations. Most of the evaluated compounds did not have any significant violations of the drug-likeness rules, suggesting good pharmacological properties.

The extent of medicinal resemblance of the selected compounds to a drug is described in Graph4.It checks against different guidelines like Lipinski, Ghose, Veber, Egan, and Muegge rules, plus Pfizer and GSK filters. There's also a look at their bioavailability scores to see if these compounds are suitable as oral drugs. All the compounds showed bioavailability score of 0.55, suggesting the compounds have good potential for drug development through the oral route and are good candidates to be further developed as anti-cancer drugs. There was a good agreement of the toxicity predictions from Pfizer and GSK (96.7%). The toxicity classification for 29 of the 30 compounds was the same: In 30 compounds only one compound had a discordant classification (Pfizer: non-toxic; GSK: toxic). The two models had almost perfect agreement (Cohen's kappa coefficient ~ 0.85). It is possible that the one outlier case is due to the difference in model sensitivity and/or threshold between the two models, so the model from the GSK might be a bit more conservative for predicting toxicity [23-25].



3.6 Medicinal Chemistry

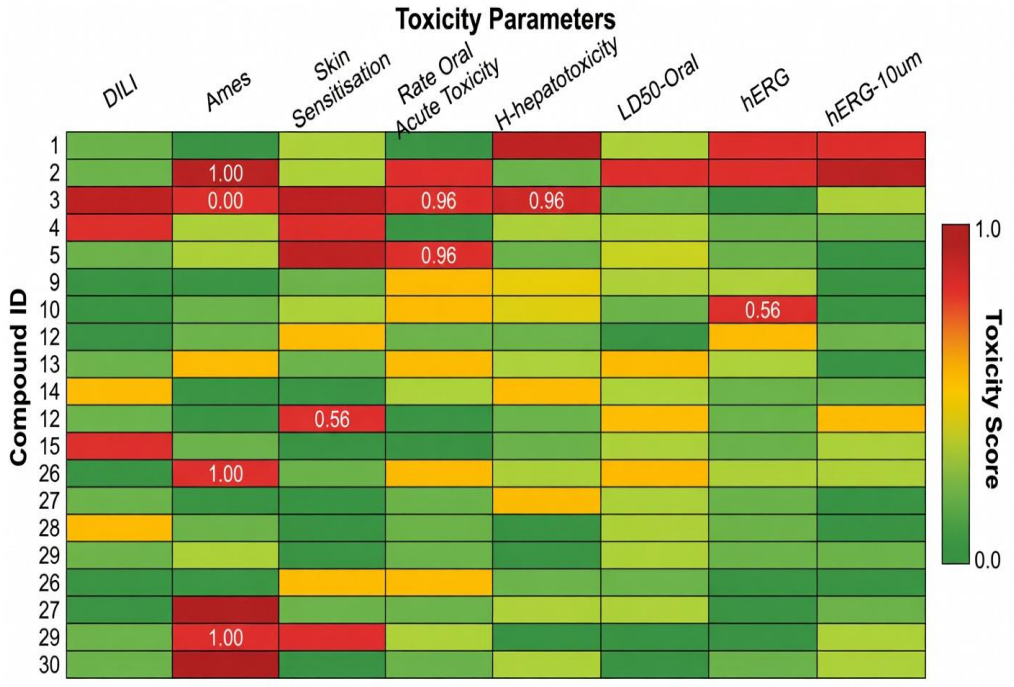
Medicinal Chemistry is the design, synthesis, optimization and evaluation of biologically active molecules for therapeutic uses. Medicinal chemistry is the main challenge in anticancer drug development to intensify the selectivity, energy, safety and the drug kinetics profile of developmental candidate. Structural modifications are made to improve the anticancer activity, but not causing too much toxicity to normal cells. In this context, computational pharmacokinetics like molecular docking, ADMET prediction, CADD, and SAR analysis are widely used to rapidly discover and optimize new and improved anticancer drugs. In Table 2 you'll find the medicinal chemistry aspects of these compounds. It highlights alerts for PAINS and Brenk, assesses lead-likeness, and looks at how easy they are to make. This gives an idea of how they perform in terms of medicinal chemistry and production. The medicinal chemistry evaluation showed that all compounds were not showing any PAINS alerts, thus a low probability of false-positive biological activity. Low Brenk alerts were only seen in a handful of compounds indicating limited structural toxicity concerns and/or instability. Additionally, the synthetic accessibility scores indicated that the compounds have good to moderate synthetic feasibility, which suggests that they are good candidates to undergo synthetic reactions in the laboratory and further studies for drug development [26-28].



3.7 Toxicity Analysis

Assessment of the toxicity of chemical compounds and therapeutic agents is an important part of the process of determining chemical safety. Human exposure to chemicals can lead to genotoxic, carcinogenic and immunotoxic, reproductive and developmental toxic effects. So, a mixture of in vitro, ex vivo and via computer simulation methods is extensively accustomed for the identification of the hazardous potential of new drug candidates. With recent developments in computational toxicology, the reliance on animal testing has been reduced significantly to the potential for prediction of toxicity parameters during early drug discovery in a quick and economical way. Knowing the various types of toxicity and what affects drug induced adverse effects is very important for the successful development of safe and effective anticancer agents.

Graph 6 provides details about the safety of the selected compounds. It covers skin sensitization, rat oral acute toxicity, human liver toxicity, lethal dose values, and predictions for heart-related toxicity. This helps understand their safety and potential risks. Based on the toxicity prediction results, most of the compounds that were analysed had moderate toxicity profiles. Several compounds showed hepatotoxicity and may have liver side effects. The hERG protein was also moderately inhibited, suggesting a moderate, but significant, risk of cardiotoxicity. Based on the evaluated toxicity, compounds 7, 24, 26 and 28 showed relatively safer toxicity profile and could be considered as potential candidates for further anticancer drug development studies [8,29-30]



3.8 Bioavailability Radar and BOILED-Egg Analysis were constructed

Most compounds were found to be in the druglike region using radar plots. The BOILED-Egg diagram showed good gastrointestinal absorption and BBB permeability, thus suggesting oral bioavailability [5].

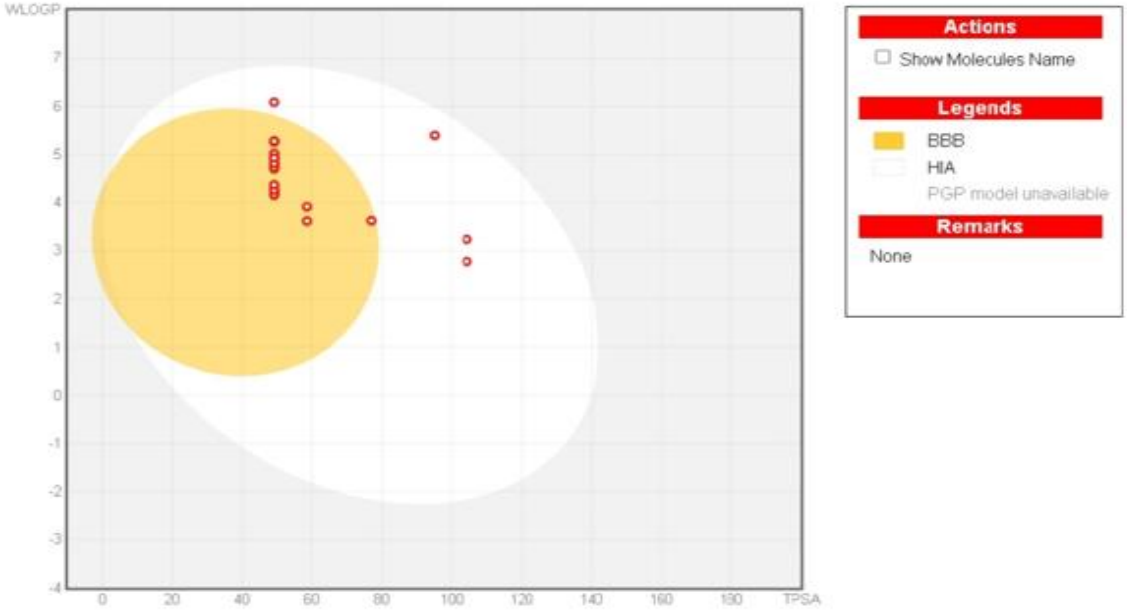


Fig. 1. The BOILED-Egg model diagram for the predictive evaluation of passive gastrointestinal absorption (HIA) and blood–brain barrier (BBB) penetration of compounds 1–30. The BOILED-Egg model represents a plot of molecules in the WLOGP versus TPSA physicochemical space and estimates the likelihood of intestinal absorption and brain permeation.


LIPO
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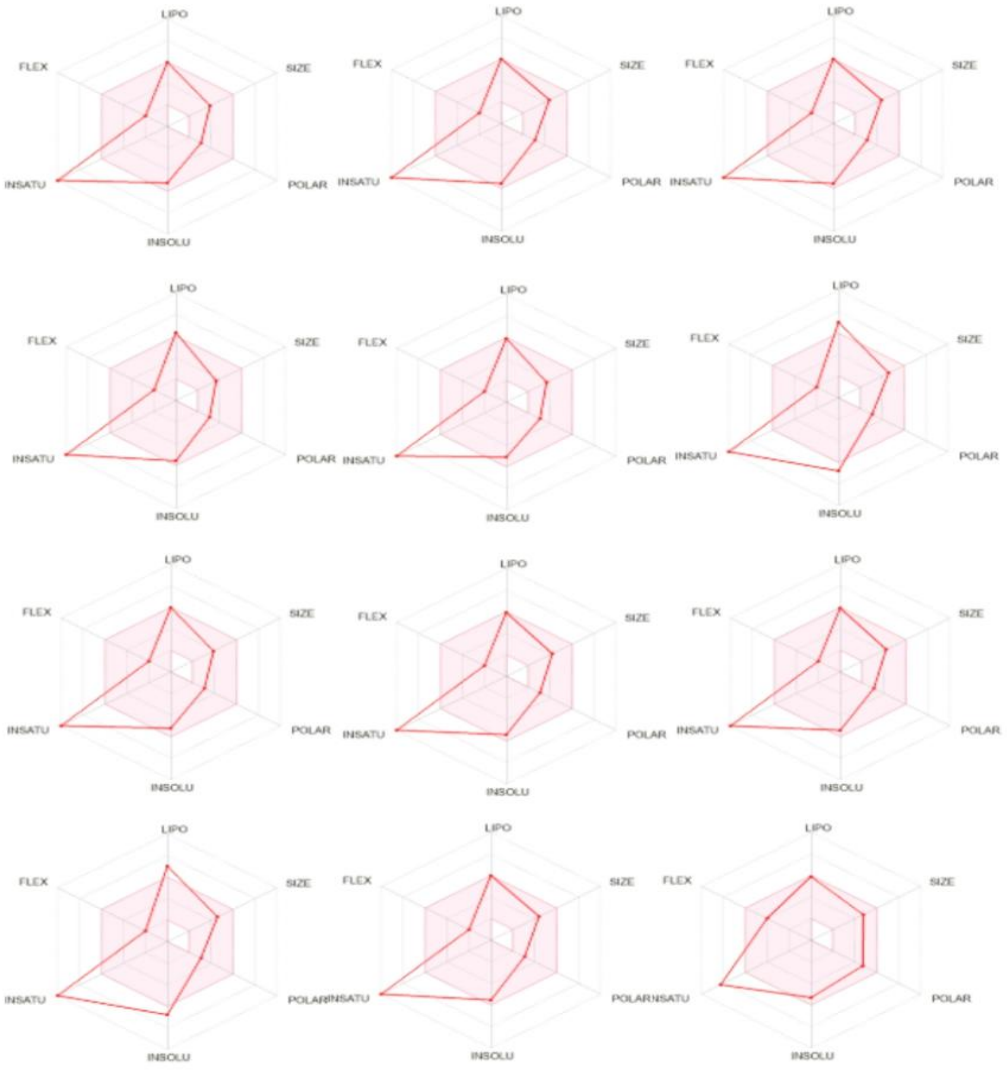

Fig. 2. Bioavailability Radar representing the drug-likeness profile of compounds 1–30. Six physicochemical parameters (lipophilicity (LIPO), molecular size (MW), polarity (TPSA), solubility (INSOLU), saturation (INSATU) and flexibility (FLEX)) are evaluated using the radar plot to determine the potential of the molecules to be well absorbed in the human gastrointestinal tract. The grey area (shaded pink) represents the optimal range of physicochemical properties needed for good oral bioavailability.

SwissADME was used for in silico evaluation of anticancer agents-

Anti-cancer drug discovery and development are fields in which SwissADME and ADMETlab 3.0 are invaluable computational tools used widely.

These systems enable rapid assessment of pk, chemicophysical, ADME/Tox characteristics of chemical entities, which helps to optimize the therapeutic discovery by diminish the time and resources channelled, and the risk of failure. These tools can be used in a variety of applications, including prediction of blood clearance of anticancer agents, which falls under the category of ADMET. They also allow for the determination of oral bioavailability, gastrointestinal tract absorption and compound permeability to the blood-brain barrier. Lipinski's Rule of 5 and other guidelines of medicinal chemistry are used to assess drug-likeness. The interactions with cytochrome P450 enzymes and metabolic stability of compounds can also be predicted. In addition, these

platforms offer indications of toxicity through the assessment of hepatotoxicity, cardiotoxicity, mutagenicity, carcinogenicity, and more. They play a key role in virtual screening, structure-activity relationships of lead compounds, and the identification of most promising antiviral candidates. Overall, SwissADME and ADMETlab 3.0 are valuable tools for researchers involved in the development of new anticancer agents, as they can help improve the safety and effectiveness of these compounds [5,8,12].

4. FINAL LEAD IDENTIFICATION

Then, various computational platforms have been used for ADME and ADMET predictions, including SwissADME and ADMETlab. Pharmacokinetic parameters such as MW, LogP, HBA and HBD, TPSA, GI absorption, BBB permeability, CYP450 inhibition, P-gp interaction, biodisponibility, therapeutic similarity, and toxicity parameters were considered. Of 75 compounds screened, almost 30 compounds showed good drug-likeness and favourable pharmacokinetic properties, suggesting them as potential drug candidates for further biological and experimental studies as anticancer agents. Several compounds were found to have desirable properties based on physical chemical properties, pharmaceutics, drug-likeness, chemical biology parameters and toxicity predictions, which led to their consideration as potential anticancer drug candidates. The aqueous solubility profile was the best for Compound 3, potentially enhancing dissolution, absorption and bioavailability. The compounds (14, 15 and 16) exhibited favourable pharmacological similarity and drug disposition and clasp enormous promise for further refinement and estimation for bio efficacy. The overall toxicity profiles of all the investigated compounds were compared, and Compound 26 proved to be the safest compound with relatively low predicted toxicological risk, and would therefore be a promising lead compound for further studies for development of anticancer compounds [5,8-9].

5. CONCLUSION

Results obtained from a detailed in silico evaluation revealed optimal physicochemical, pharmacokinetic and physiochemical descriptors and toxicological profile of the synthesized compounds, making them promising anticancer agents. The resulting TPSA, HBD, HBA, MR and Nrotb were all admissible for most of the compounds, suggesting good membrane permeability and oral bioavailability. Consensus LogP values between 1.93 and 4.67 indicated balanced lipophilicity which is essential for the efficient drug absorption, distribution and cellular penetration. The water solubility analysis showed that most of the compounds were moderately soluble in water and compounds 24 and 28 were poorly soluble in water, among all the compounds compound 3 had the best solubility profile indicating better bioavailability potential. ADME projection revealed excellent GI absorption for all compounds, and most compounds had BBB permeability and none was a P-gp substrate, which reduces the possibilities of oncology. The favourable absorption and permeability property were also verified with the BOILED-Egg model. DLE showed compounds to have either no violations of Lipinski, Ghose, Veber, Egan and Muegge rules (minimal) or a score of 0.55, indicating good oral drug development potential. Medicinal chemistry assessment revealed no PAINs alerts, minimal Brenk alerts and low synthetic accessibility, providing good chemical stability and synthetic ease. Most of the compounds were predicted to have moderate toxicity in toxicity prediction studies, while some were predicted to be hepatotoxic, and low-to-moderate hERG inhibitors; compounds 7, 24, 26, and 28, however, had comparatively safer toxicity profiles. Based on integrated analysis, Compound 3 had the highest aqueous solubility while compounds 14, 15, and 26 had a balanced ADME property, and Compound 26 was the safest overall compound. Overall, these results suggest that the tested compounds have great potential for future molecular docking, in vitro and in vivo experimental studies to develop effective anticancer drugs.

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