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Research Article

ADMET Prediction of synthesized Heterocyclic derivatives to treat renal cancer

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Abstract

A library of 121 potent, synthesized, and characterized compounds from different heterocyclic derivatives such as pyrimidine, phthalazine, benzothiazole, benzpyrazoline, indoline, benzimidazole, phthalazine, indole, quinoline, quinazoline were selected based on their anti-renal cancer activity. The Drug likeness, Bioactivity, Absorption, Distribution, Metabolism, Excretion, and Toxicity of all the screened compounds were predicted through Molinspiration, PreADMET, and Osiris software. After screening 121 compounds, 19 compounds showed drug-like properties and an absorption percentage better than the standard drug Sorafenib. These compounds were further assessed based on their distribution parameter and the compounds that showed plasma protein binding equal to or below 90% and blood-brain barrier penetration below 1.000 were selected, i.e., compounds 3, 23, 64, 65 were then further assessed for the toxicity. Osiris property explorer was used to predict drug relevance and toxicity of the synthesized compounds. Compounds 3 and 23 were non-toxic similar to the standard drug Sorafenib. Compounds 3 and 23 were found to be active as Kinase Inhibitors, with a bioactivity score of 0.2 and 0.6 compared to standard drug sorafenib, which scored 0.44. Therefore Compound 3 N-(4-fluoro-2-methoxyphenyl)-7-methyl-5,6,7,8-tetrahydropyrido [4',3':4,5] thieno[2,3-d] pyrimidin-4-amine and compound 23 1-(4-fluorophenyl)-3-methyl-N-phenyl-3a,7a-dihydro-1H-pyrazolo[3,4-d] pyrimidin-4-amine belonging to pyrimidine derivatives were considered as best and suggested to be taken further for preclinical and clinical trials. The pyrimidine derivatives with anti-renal cancer activity can serve as a scaffold for the design of renal cancer targeting agents and motivates the further development of effective and safer compounds.

Keywords: renal cancer; pyrimidine; Osiris; PreADMET; Molinspiration; kinase inhibitors

Introduction

Cancer is a worldwide health issue that leads to death in both developing and developed countries [1]. It is defined by a rise in the number of aberrant cells produced from a particular normal tissue, their invasion of neighbouring tissue, and the lymphatic or blood-borne dissemination of malignant cells to regional lymph nodes and distant locations (metastasis) [2]. Cancer is a very hazardous illness characterized by uncontrolled cell proliferation and the fast spread of abnormal cells [3]. Various internal and external factors contribute to aberrant cell growth and the development of various malignancies [4].

Cancer is the leading cause of mortality worldwide [5]. Low- and middle-income countries accounted for 65% of cancer deaths worldwide, which is expected to rise to 75% by 2030. As a result, much work has gone into developing new powerful chemotherapeutic drugs that are more selective for cancer cells [6].

Kidney cancer, also known as renal cancer, is a condition in which tumours begin in kidney cells, become malignant (cancerous), and grow out of control, resulting in a tumour [7]. Renal cancer is

divided into two types: renal cell carcinoma and renal pelvis transitional cell carcinoma [8]. Renal cancer can be caused by various factors, including smoking, obesity, long-term use of pain relievers, severe kidney disease, long-term dialysis, high blood pressure, lymphoma, certain genetic disorders, chemical exposure, and a family history of kidney cancer [9]. According to the American Cancer Society, 76,080 new instances of kidney cancer have been identified (48,780 men and 27,300 women), with 13,780 individuals (8,790 men and 4,990 women) dying from the disease [10].

The National Cancer Institute Anticancer Drug Screen (NCI-60) cell lines are the most thoroughly described in-vitro cancer cell model cell lines, and they are an essential tool in applying the 3Rs approach of animal research - Replacement, Reduction, and Refinement [11]. A-498,786-O, UOK262, UOK268, TK-10, UO-31, CAK-1, and SN12C are some of the NCI-60 panel's renal cancer cell lines [12].

Heterocyclic compounds are cyclic structures containing carbon and at least one heteroatom, such as oxygen, nitrogen, and sulfur [13]. Heterocycles are important pharmacophores and have the significance of creating privileged chemical structures possessing pharmacological activities [14]. Hence, heterocycles play an important role in current drug design as they are present in most marketed drugs [15]. Around 60% of the medications used for cancer treatment are based on heterocyclic moieties [13]. Heterocyclic compounds like pyrimidine [16-22], phthalazine [23], benzothiazole [24], Benzpyrazoline [25,26], indoline [27-31], benzimidazole [32], phthalazone [33], indole [34,35], quinoline [36,37], quinazoline [38] find application in the treatment of renal cancer. Many synthetic nitrogen heterocycles are extremely relevant to pharmacology and medicine. Benzimidazole has immense importance among all nitrogen-based heterocyclic compounds [39]. Quinoline scaffold has become an important construction motif that shows significant anti-renal activity [40].

This study aims to overcome the challenges faced during the clinical trials of drug development and reduce the chances of drug failure at a later stage. ADMET profiling is required to decide whether or not a compound is suitable to proceed to the clinical stage since effectiveness or safety problems can result in drug development failures. Hence, the present study involves screening of 648 heterocyclic drug candidates and selecting 121 potential candidates based on their IC_{50} value and cell inhibition (%) against renal cancer cell lines. They were screened for their ADMET properties using computational software like Molinspiration, PreADMET, and Osiris, to furnish safe leads for drug approvals.

Computational studies

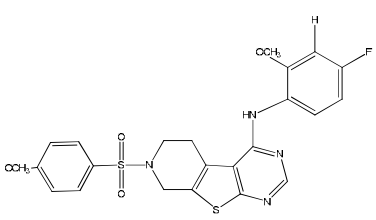
Methodology

An extensive review study was carried out on heterocyclic derivatives designed, synthesized, characterized, and evaluated against renal carcinoma cell lines. The study focused on selecting potent compounds from the synthesized heterocyclic moieties such as pyrimidine[16-22], phthalazine [23], benzothiazole [24], Benzpyrazoline [25,26], indoline[27-31], benzimidazole [32], phthalazone [33], indole [34,35], quinoline [36,37], quinazoline [38] based on their IC_{50} value and cell inhibition (%) against renal cancer cell line such as 786-O, A-498, TK-10, UO-31, ACHN, SKNEP-1, HEK-293, CAK-1, RCC, 760-O, RXF393, SN12C and CAKi-1. Around 648 synthesized compounds were studied, and 121 potent compounds were selected.

Libraries of the selected compounds were then screened to predict Absorption, Distribution, Metabolism, Excretion and Toxicity of the compounds using software such as Molinspiration, PreADMET, and Osiris. The structures of heterocyclic compounds selected for the study and the reasons for choosing the compounds from various literature studies are given below, along with their anti-renal cancer activity.

Heterocyclic moiety:

A. *Pyrimidine*



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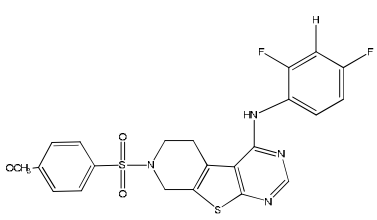

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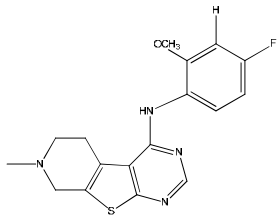

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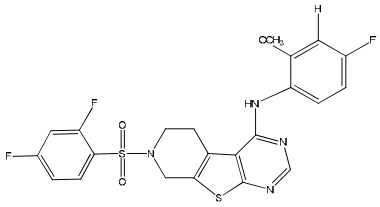

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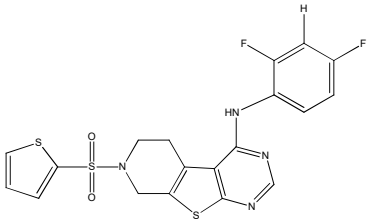

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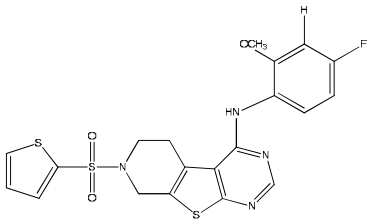

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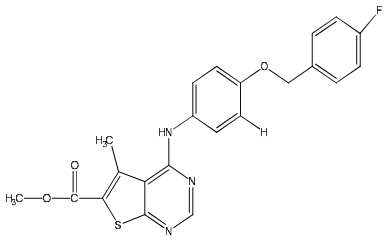
Compounds 1-6 showed an IC_{50} value of less than 1 μm and cell viability ranging from less than 50% against the renal cancer cell line 786-O [16].



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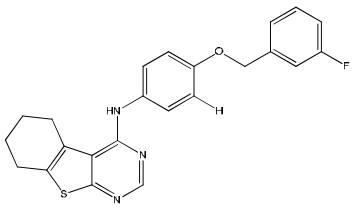

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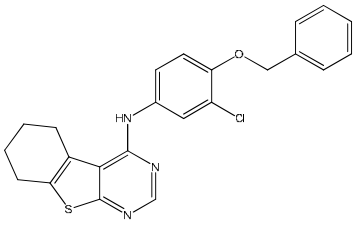

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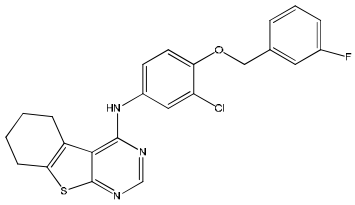

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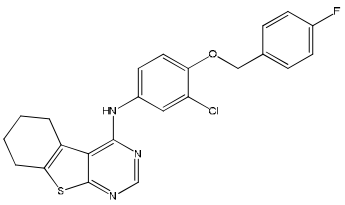

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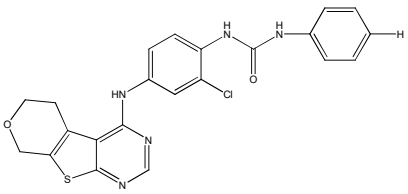

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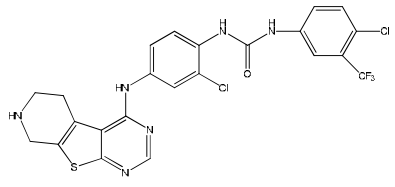
Compounds 7-11 showed cell inhibition ranging from 16%-77%, 6%-54.67% and 21%-59 % against A498, TK-10, UO-31 respectively [17].



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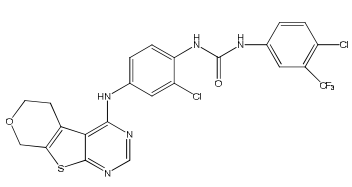

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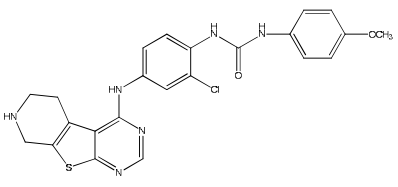

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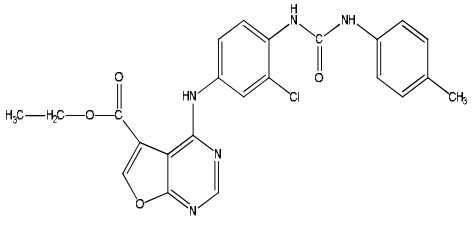

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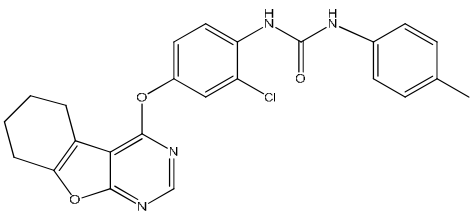
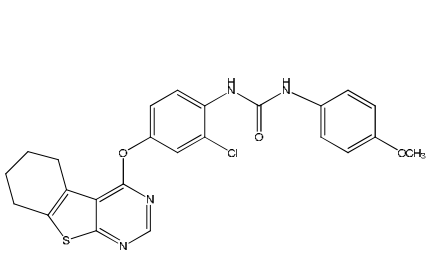


(17)

Compounds 12-15 showed IC_{50} value of 2.5 μm-5.48 μm and good cell inhibition of 77.65% and 59.81% against A498 and UO-31 respectively [18].



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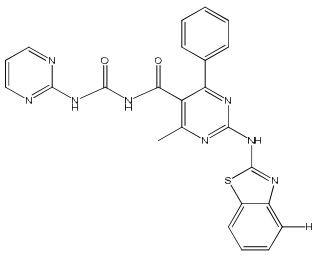

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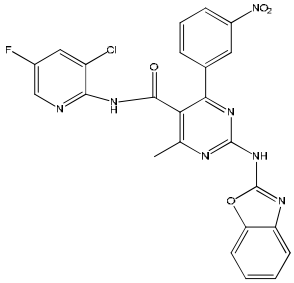

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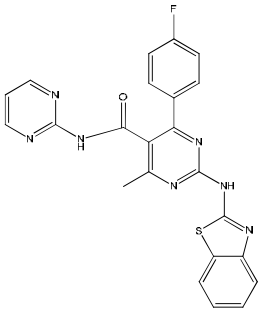
Compounds 16-18 showed 99.50% cell inhibition and IC_{50} value ranging from 33.4 nm-946 nm against UO-31 [19].



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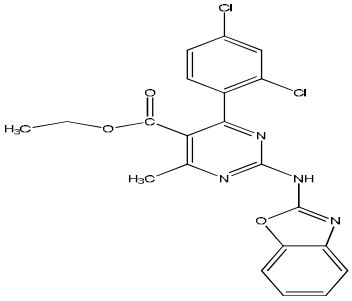

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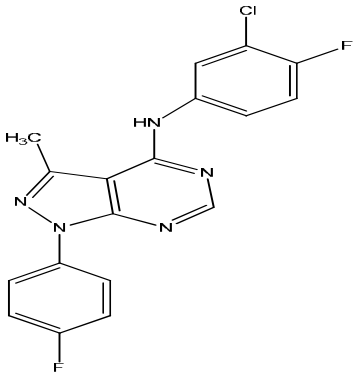
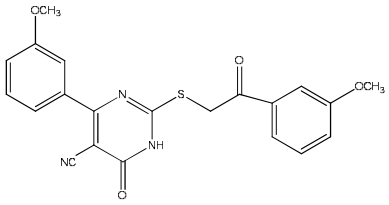


(23)

Compounds 19-22 showed % Growth inhibition of less than 70% against the UO-31 cell line and an IC_{50} value of less than 10 μm [20].

Compound 23 showed % Growth inhibition of 60.41 and 21.33% against ACHN and 786-O respectively and with an IC_{50} value of 5.53 μm against renal cancer cell line ACHN [21].



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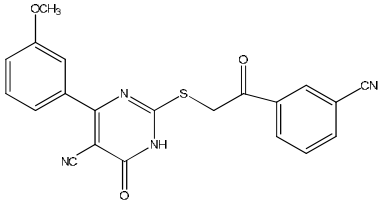

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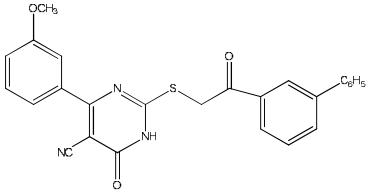
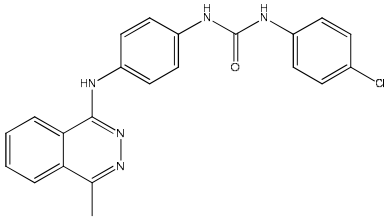


(26)

Compounds 24-26 showed an IC_{50} value from 1.23 μm-4.30 μm and also a % Growth inhibition value of 23% against renal cancer line UO-31 [22].

B. *Pthalazine*



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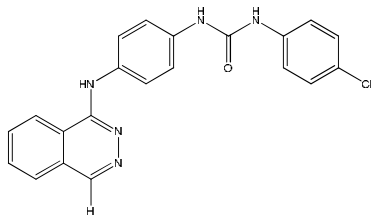

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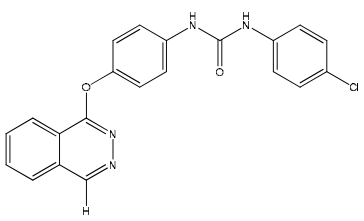

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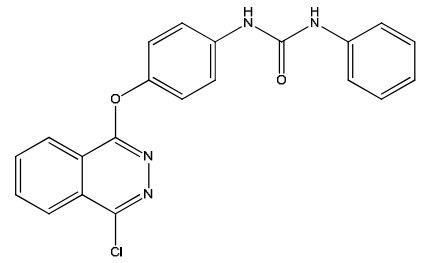

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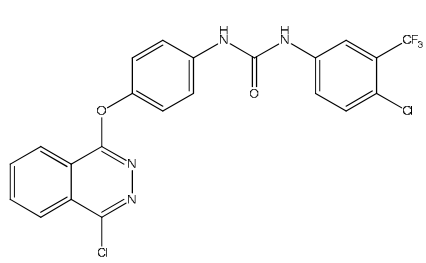

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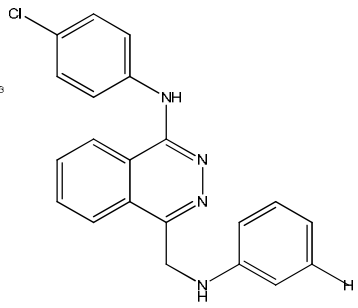

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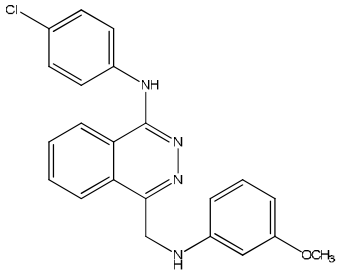

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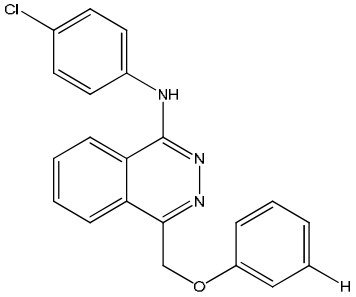
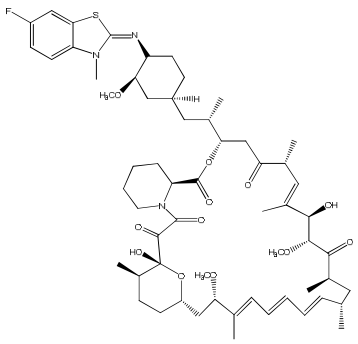


(34)

Compounds 27-34 exhibited remarkable broad spectrum cell growth inhibition (above 90%) against various renal cancer cell lines with GI_{50} values ranging from 0.15- 8.41 μm [23].

C. *Benzothiazole*



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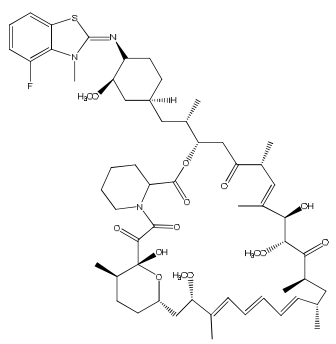

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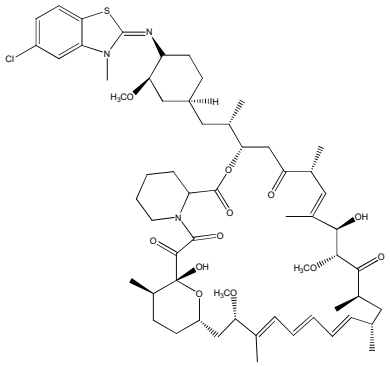

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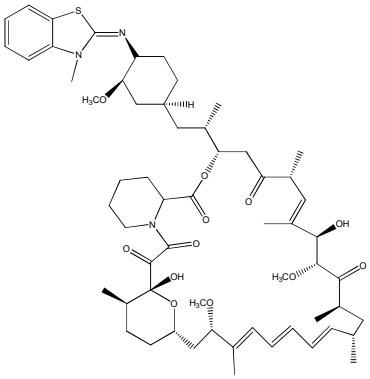

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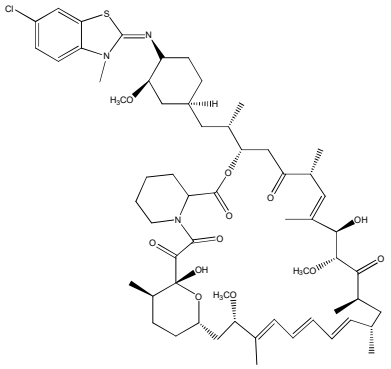

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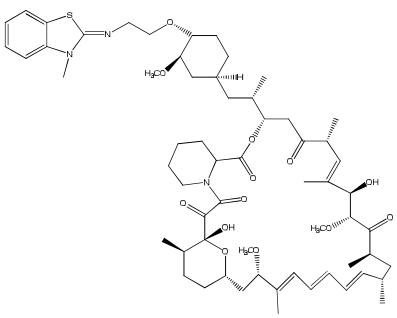
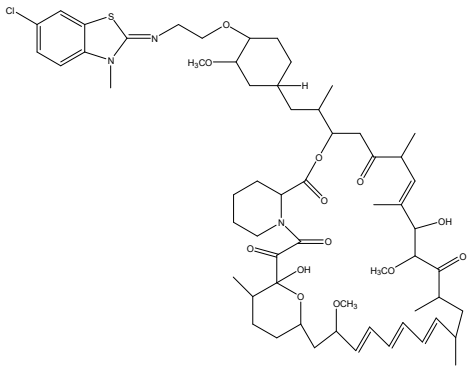


(40)

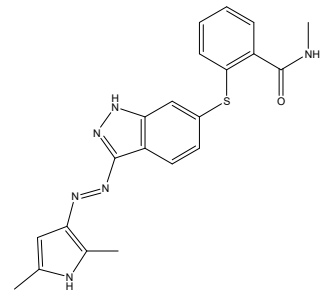
Compounds 35-39 containing N-methyl group on thiazole ring displayed more potent activity than Rapamycin against SKNEP-1 (renal cancer cell line) with a growth inhibition rate of 47.09-52.3% [24].



(41)

Compounds 40 and 41 containing N- methyl group on thiazole ring displayed potent activity against SKNEP-1 (renal cancer cell line) with IC_{50} value 10.1 ± 1.09 μm and 9.6 ± 0.96 μm respectively [24].

D. *Benzpyrazoline*



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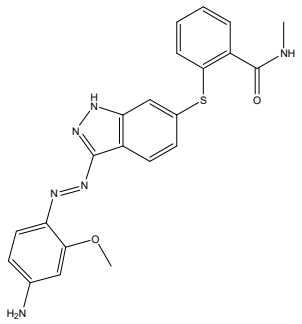

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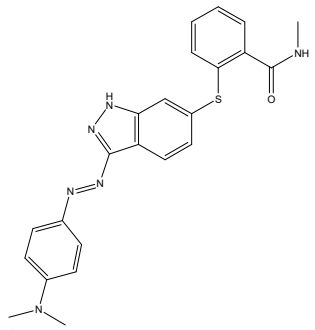

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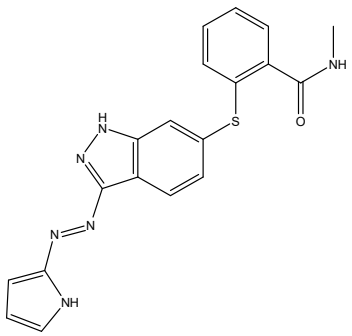

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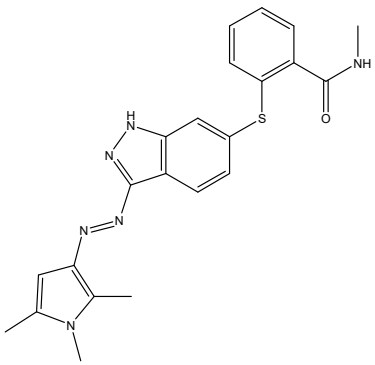

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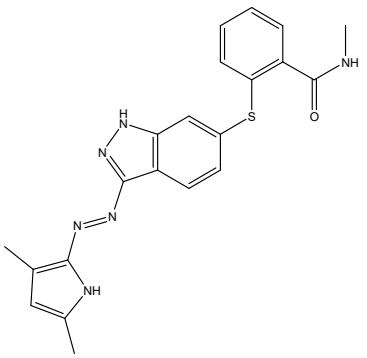

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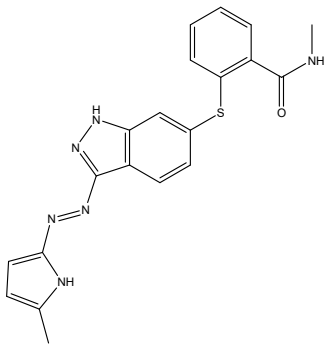

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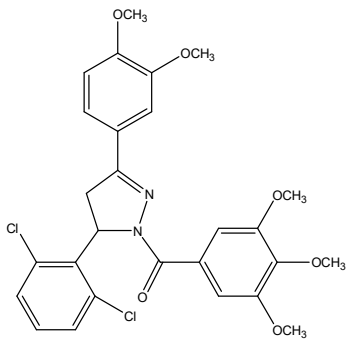

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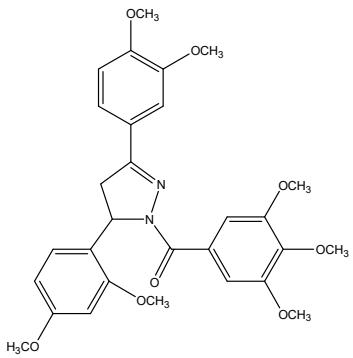
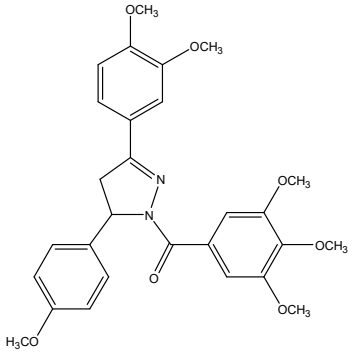


(50)

Compound 42 showed the highest inhibition activity in the VEGFR-2 Kinase assay with an IC_{50} value= of 44 nm [25].

As per the reported literature, Compounds 43-48 displayed favourable inhibitory activity in the VEGFR-2 Kinase assay with IC_{50} values ranging from 100-300 nm [25].

Benzpyrazoline derivative 49 exhibited moderate cell growth inhibition activity against renal cancer UO-31 cell line [26].



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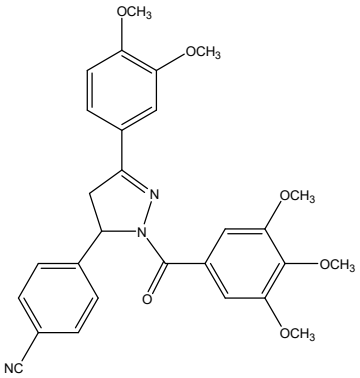
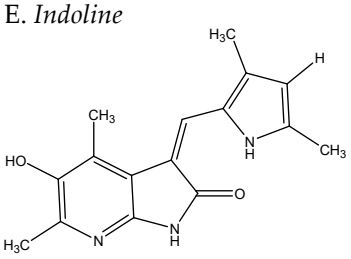


(52)

Compound 50 exhibited broad-spectrum cell growth inhibition activity against renal cancer CAKI-1 and moderate cell growth inhibition against renal cancer UO-31 cell lines [26].

As per the reported literature, Compounds 51 and 52 had the highest ability to inhibit the proliferation of various renal cancer cell lines with IC_{50} values of 40 μm and 17 μm, respectively [26].

E. *Indoline*



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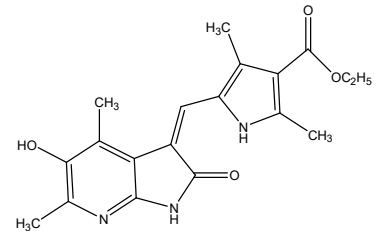

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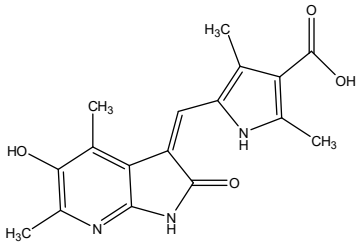

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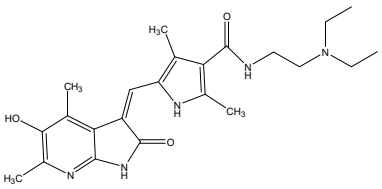

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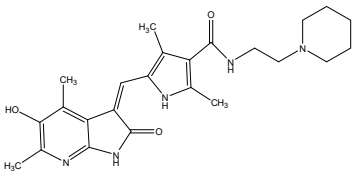

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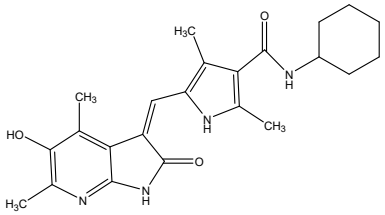

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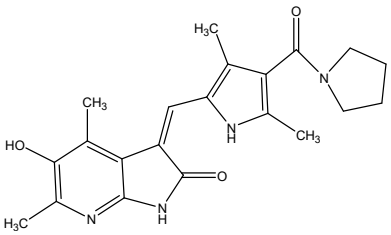

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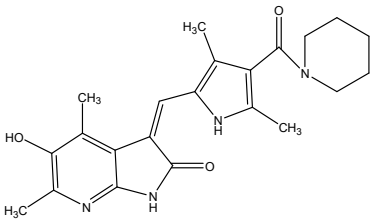

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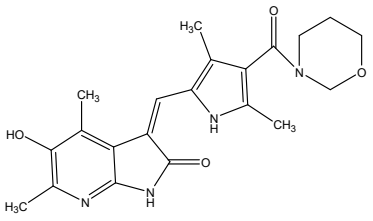

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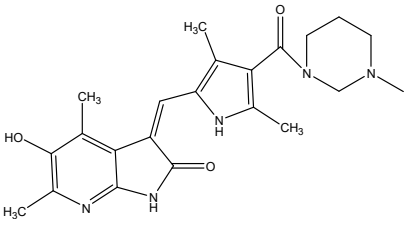
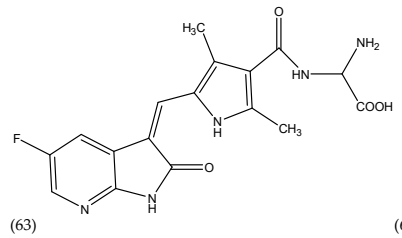


(62)

The IC_{50} value of compounds 53-62 was found to be in a range of 7.30-45.70 μm against renal cancer cell line HEK293 [27].



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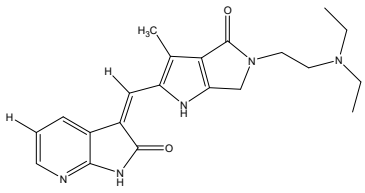

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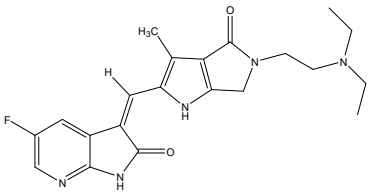

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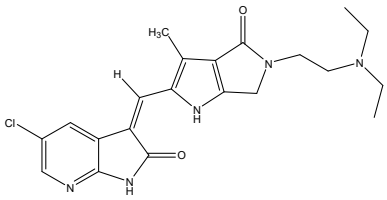

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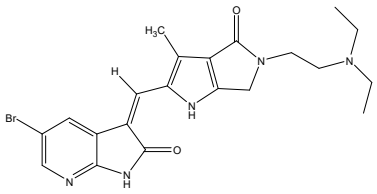

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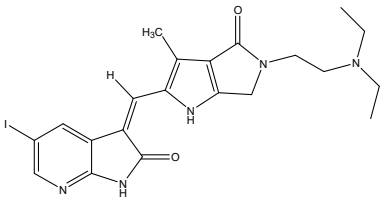
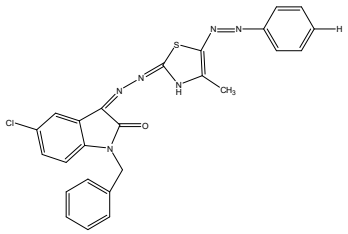


(68)

The compound 63 showed an IC_{50} value of 2.5 μm when screened against renal cancer cell line RCC 760-O. It showed activity equal to sunitinib (control) [28].

The IC_{50} value of compounds 64-68 was found to be below 10 μm against renal cancer cell line 786-O. The % inhibition against VEGFR-2 was in the range of 35%-64% and PDGFRβ was in the range of 36%-68% [29].



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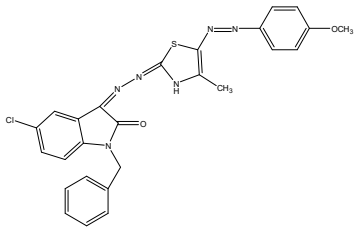

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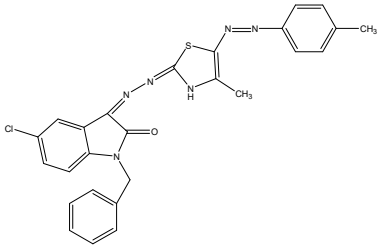

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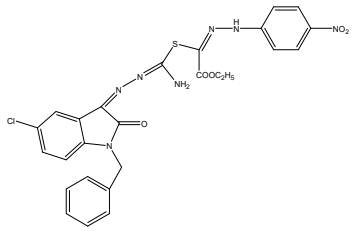

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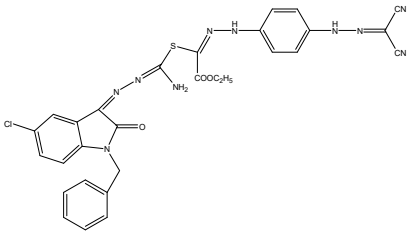

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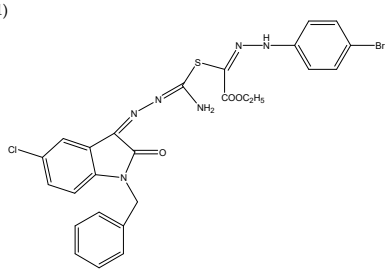

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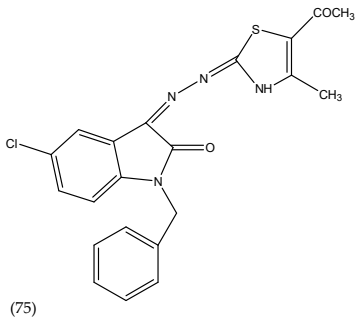

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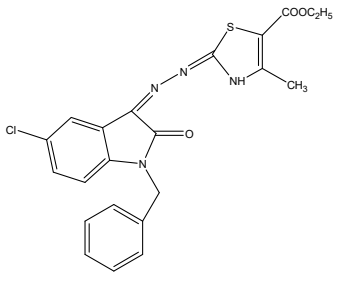

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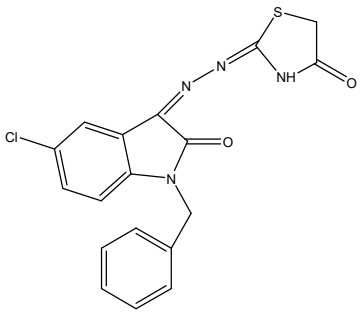
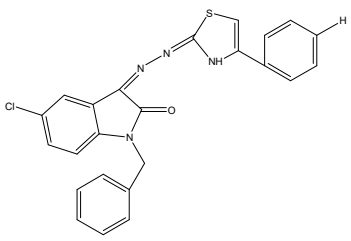


(77)

The IC_{50} value of compounds 69-81 was found to be below 10μM against renal cancer cell line A498. The IC_{50} value of the VEGFR-2 kinase inhibitory activity was found in the range of 0.067-0.422 μm [30].

The growth inhibition percentage of compounds 82-89 was found to be above 35% against renal cancel cell lines RXF393 and ACHN [31].



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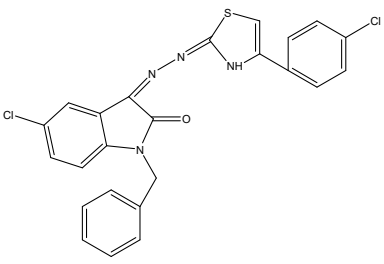

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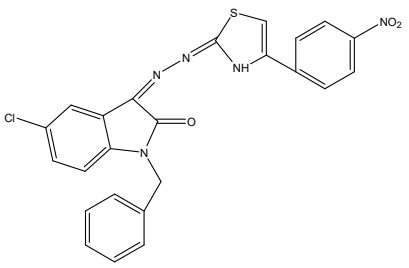

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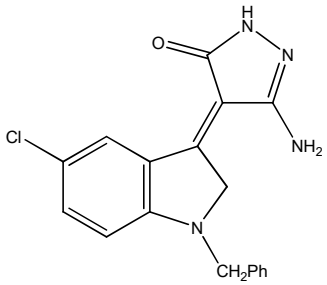

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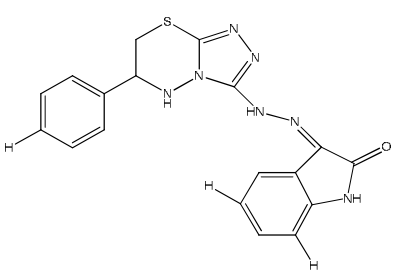

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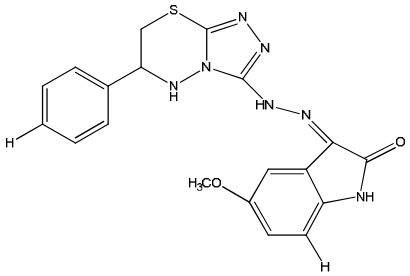

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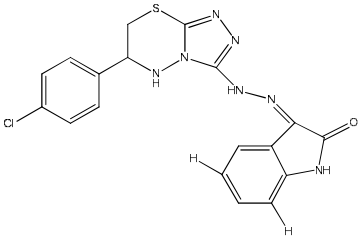

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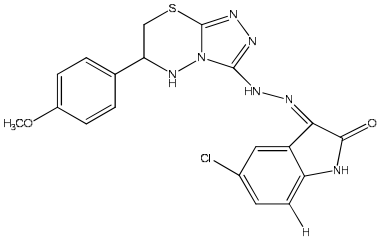

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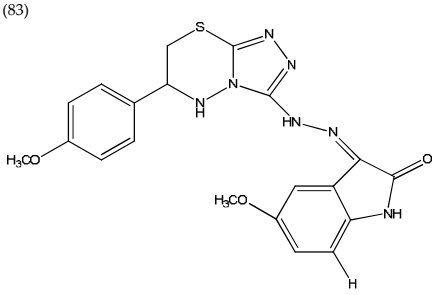

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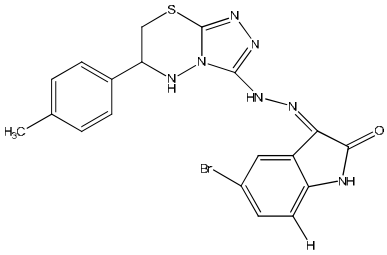

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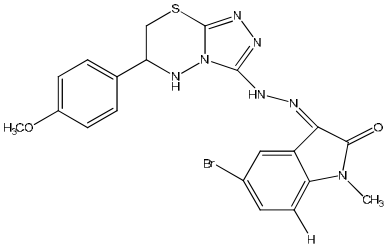

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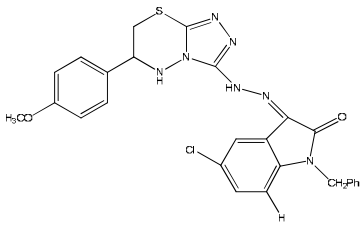
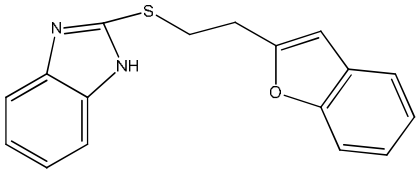


(89)

F. *Benzimidazole*



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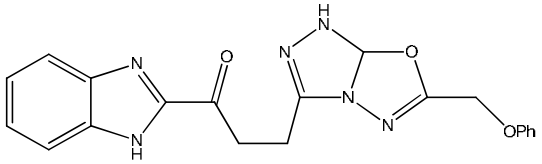
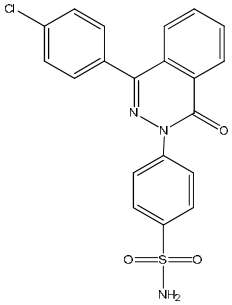


(91)

G. *Pthalazones*



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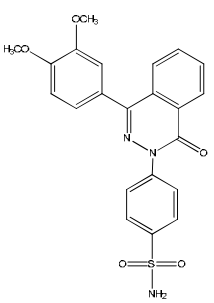
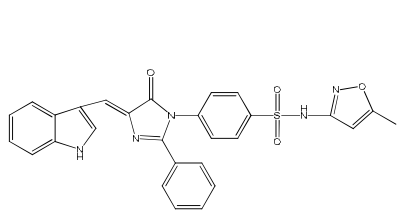


(93)

Compounds 90 and 91 showed IC_{50} values in the range of 0.2-0.3 μm against renal cancer cell line A498 and UO-31. Cytotoxic against renal cancer cell line A498 and UO-31 [32].

Compounds 92 and 93 showed IC_{50} values below 10 μm against renal cancer cell line UO-31 [33].

H. *Indole*



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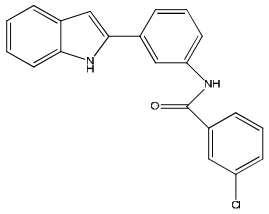

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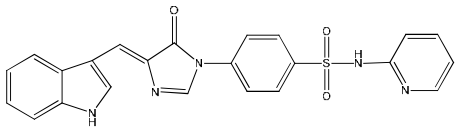

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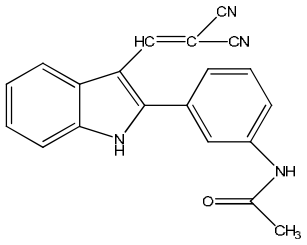
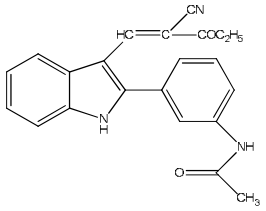
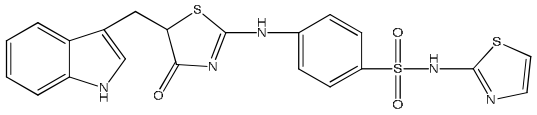


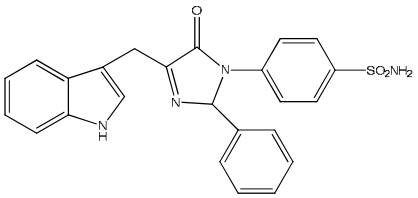
(97)



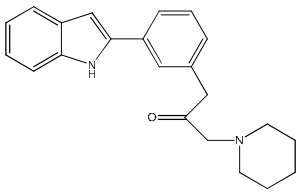
(98)



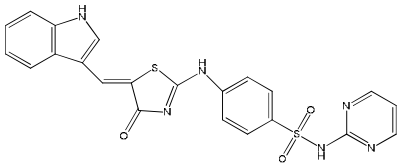
(99)



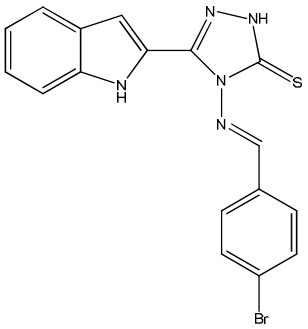
(100)



(101)



(102)



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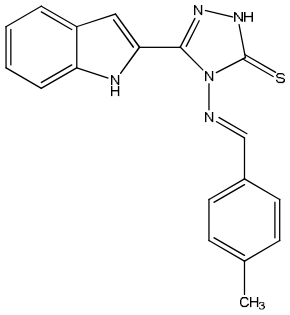
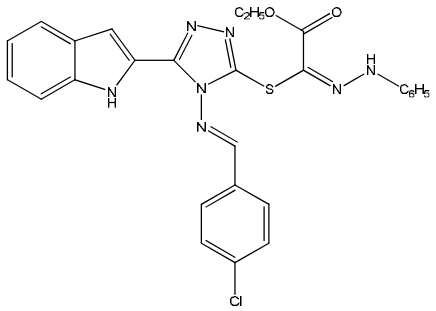


(104)



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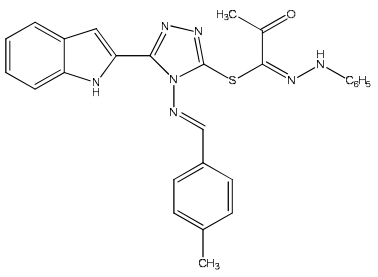

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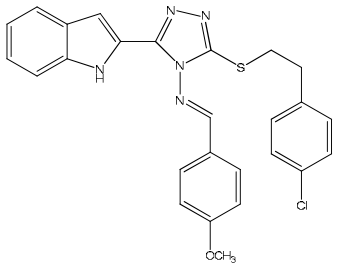


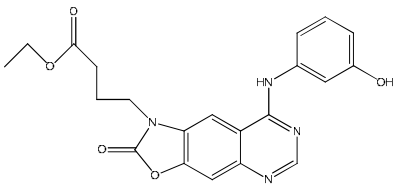
(107)

Compound 94 showed a growth inhibition percentage above 30% against renal cancer cell lines UO-31,786-0, SN12C, and A498 [34]. Compounds 95 and 96 showed growth inhibition percentage above 30% against renal cancer cell lines A498 and UO-31 [34].

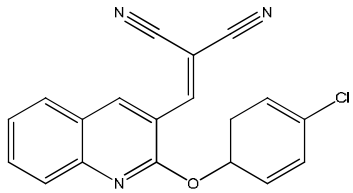
Compounds 97-102 showed growth inhibition percentage above 30% against renal cancer cell line UO-31 [34].

Compounds 103-107 showed an IC_{50} value below 10 μm against renal cancer cell lines CAK1 and A-498. Compounds 106 and 107 showed a better safety profile against non-cancer human renal cells [35].

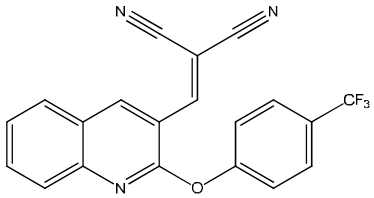
I. Quinoline



(108)



(109)



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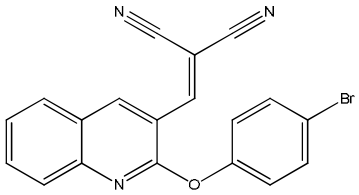
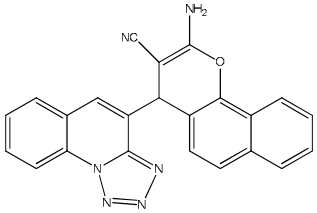
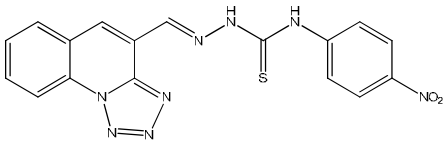


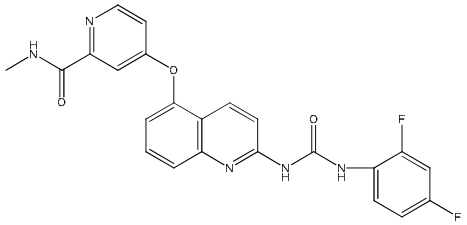
(111)



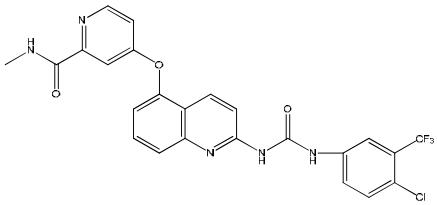
(112)



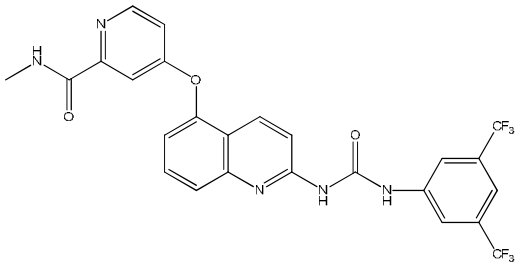
(113)



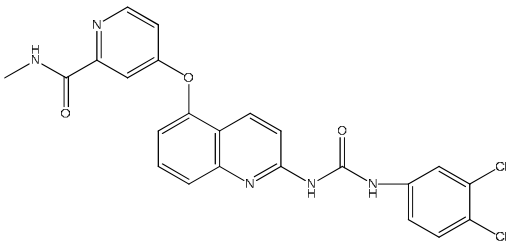
(114)



(115)

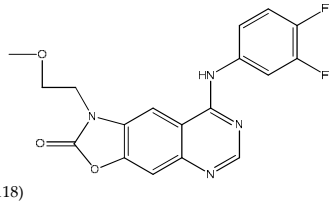


(116)

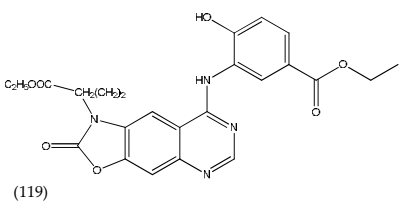


(117)

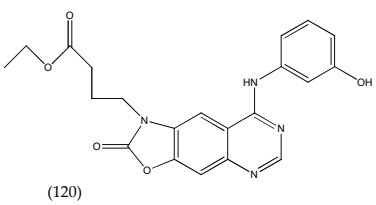
J. *Quinazoline*



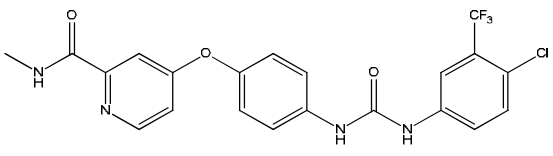
(118)



(119)



(120)



(121)

Compound 108-111 showed % growth inhibition from 46.23%-64.92% against the UO-31 cell line [36]. Compound 112 exhibited high selectivity and potency against A498 (renal cancer cell line) showing 100% inhibition of tumour cell growth, with a growth inhibition (GI_{50}) values <1.0 μm and its EGFR IC_{50} (μg/ml) value is 0.729, VEGFR IC_{50} (μg/ml) value is 0.412 and TOPO 1 IC_{50} (μg/ml) value is 0.278 [36]. Compound 113 shows 100% growth inhibition against the UO-31 cell line [36]. Compounds 114-117 showed IC_{50} values ranging from 0.42-5.94 μm against the renal cancer cell line A498 [37]. Compounds 118-120 showed 97%-100% cell inhibition and IC_{50} value ranging from 0.0073-0.026 μm against A498 [38]. The compound 121 (sorafenib) is an approved drug for the treatment of metastatic renal cell cancer. It is classified as a tyrosine kinase inhibitor and VEGFR inhibitor [39,40].

Cheminformatics Prediction

Molinspiration cheminformatics

Molinspiration provides a wide range of cheminformatics tools that assist molecule manipulation and processing, involves SMILES and SD file conversion, normalization of molecules, creation of tautomer, molecule fragmentation, determining various molecular properties needed in QSAR (Quantitative structure-activity relationship), molecular modelling and drug design, high-quality molecule depiction, molecular database tools assisting substructure and related searches. These products also help with fragment-based virtual screening, bioactivity prediction, and data visualization. Molinspiration tools are put down in Java and thus can be used practically on any computer platform. Computed molecular descriptors may be used for property-based virtual screening of large collections of molecules to discard structures with non-drug-like properties and to elect potential drug candidates. These are the following molecular properties which are calculated with the help of Molinspiration [41].

Drug Likeness calculation based on Lipinski rule of five

The structures of the compounds from the generated library were screened using Molinspiration software (2018.02 version). This software predicts bioactivity scores based on the ability of the compound to behave as drug targets such as enzyme inhibitors, nuclear receptors, kinase inhibitors, GPCR ligands, and ion channel modulators [42]. The software also calculates molecular properties based on Lipinski's Rule of Five, which Christopher A. Lipinski conveyed in 1997. According to the RO5, a drug-like compound should have a molecular weight (MW) of <500 g/mol, a log p value of <5 representing its hydrophobicity, no >5 hydrogen bond donors (HBDs), and no >10 hydrogen bond acceptor (HBA) sites, a polar surface area (PSA) of ≤140 A° and <10 rotatable bonds [43]. Molecular properties such as log P, topological polar surface area (TPSA), hydrogen bond donors and acceptors, rotatable bonds, number of atoms, molecular weight, and violations of Lipinski's rule of five were calculated to analyse the drug-likeness of the compounds. The absorption percentage (% Ab) was as well estimated by using the subsequent formula: %Ab = 109 − [0.345 × TPSA] [44]. All 121 compounds were screened for drug-likeness and bioactivity scores, which are represented in Table 1 and Table 2.

LogP (Octanol/water partition coefficient)

This characteristic is used in QSAR studies and rational drug design to estimate molecular Hydrophobicity. Hydrophobicity influences drug absorption, bioavailability, drug-receptor interactions, metabolism of molecules, as well as the toxicity of compounds. LogP is computed by the methodology developed by Molinspiration as a sum of fragment-based contributions and correction factors. This method is robust and can process practically all organic and most organometallic molecules [45].

TPSA (Topological polar surface area)

In TPSA sum of O− and N− centered polar fragments are considered. TPSA is a perfect descriptor for characterizing drug absorption, including intestinal absorption, bioavailability, Caco-2 permeability, and blood-brain barrier penetration [46].

Table 1. Physicochemical properties of the compounds using Molinspiration software.

Sr No.	miLog	TPSA	n atoms	MW	n ON	n OH NH	n violations	n rotb	Vol	% Absorption
1	4.54	93.66	34	500.58	8	1	1	6	405.45	76.6873
2	4.64	84.42	33	488.54	7	1	0	5	384.84	79.8751
3	3.57	50.28	24	344.2	5	1	0	3	293.63	91.6534
4	4.74	84.42	34	506.53	7	1	1	5	389.77	79.8751
5	4.54	75.19	30	464.54	6	1	0	4	350.01	83.05945
6	4.43	84.42	31	476.58	7	1	0	5	370.62	79.8751
7	5.68	73.35	30	423.47	6	1	1	7	357.46	83.69425
8	6.38	47.05	29	405.5	4	1	1	5	352.74	92.76775
9	6.84	47.05	29	421.95	4	1	1	5	361.34	92.76775
10	6.99	47.05	30	439.94	4	1	1	5	366.27	92.76775
11	7.01	47.05	30	439.94	4	1	1	5	366.27	92.76775
12	5.39	88.17	31	451.94	7	3	1	4	371.53	78.58135
13	6.49	90.96	36	553.4	7	4	2	5	419.78	77.6188
14	6.49	90.96	36	553.4	7	4	2	5	419.78	77.6188
15	5.05	100.2	33	480.98	8	4	1	5	400.49	74.431
16	5.05	100.2	33	480.98	8	4	1	5	400.49	74.431
17	5.97	89.28	32	448.91	7	2	1	4	383.34	78.1984
18	6.22	85.38	33	480.98	7	2	1	5	401.47	79.5439
19	4.06	134.68	35	482.53	10	3	0	5	403.93	62.5354
20	5.15	151.66	37	519.88	11	2	3	6	409.35	56.6773
21	4.57	105.58	33	457.49	8	2	0	5	377.47	72.5749
22	5.77	90.15	30	443.29	7	1	1	6	357.32	77.89825
23	4.63	55.64	26	371.78	5	1	0	3	296.11	89.8042
24	-2.78	85.66	29	407.45	7	1	0	7	353.77	79.4473
25	-3.08	100.21	29	402.44	7	1	0	6	345.08	74.42755
26	-3.08	100.21	29	402.44	7	1	0	6	345.08	74.42755
27	5.95	78.94	29	403.87	6	3	1	4	348.83	81.7657
28	5.32	78.94	28	389.85	6	3	1	4	332.27	81.7657
29	5.08	76.14	28	390.83	6	2	1	4	328.85	82.7317
30	5.62	76.14	28	390.83	6	2	1	4	328.85	82.7317
31	7.12	76.14	33	493.27	6	2	1	5	373.68	82.7317
32	6.02	49.84	26	360.85	4	2	1	5	317.68	91.8052
33	6.05	59.07	28	390.87	5	2	1	6	343.23	88.62085
34	6.42	47.05	26	361.83	4	1	1	5	314.26	92.76775
35	8.54	192.54	76	1078.39	15	2	3	7	1019.95	42.5806
36	8.53	192.54	76	1078.39	15	2	3	7	1019.95	42.5806
37	8.8	192.52	76	1094.85	15	2	3	7	1028.56	42.5806
38	8.46	192.52	75	1060.4	15	2	3	7	1015.02	42.5806
39	8.8	192.52	76	1094.85	15	2	3	7	1028.56	42.5806
40	8.45	201.75	78	1104.46	16	2	3	10	1057.61	39.39625
41	8.8	201.75	79	1138.9	16	2	3	10	1057.61	39.39625
42	4.32	98.3	29	404.5	7	3	0	5	354.97	75.0865
43	4.09	117.77	31	432.51	8	4	0	6	373.69	68.36935
44	5.13	85.75	31	430.54	7	2	1	6	382.77	79.41625
45	4.07	98.3	27	376.44	7	3	0	5	321.85	75.0865
46	4.38	87.44	30	418.53	7	2	0	5	371.91	78.83332
47	4.67	98.3	29	404.5	7	3	0	5	354.97	75.0865
48	4.29	98.3	28	390.47	7	3	0	5	338.41	75.0865
49	5.13	78.84	37	545.42	8	0	2	8	459.48	81.8002
50	3.91	97.31	39	536.58	10	0	1	10	483.5	75.42805
51	3.93	88.08	37	506.56	9	0	1	9	457.95	78.6124
52	3.63	102.64	37	501.54	9	0	1	8	449.26	73.5892
53	2.51	81.77	21	283.33	5	3	0	1	258.5	80.78935

54	2.65	108.08	26	355.39	7	3	0	4	319.83	71.7124
55	2.01	119.07	24	327.34	7	4	0	2	285.5	67.92085
56	2.41	114.11	31	425.53	8	4	0	7	403	69.63205
57	2.57	114.11	32	437.54	8	4	0	5	409.44	69.63205
58	3.54	110.87	30	408.5	7	4	0	3	379.88	70.74985
59	1.81	102.08	28	380.45	7	3	0	2	346.64	73.7824
60	2.31	102.08	29	394.48	7	3	0	2	363.44	73.7824
61	1.51	111.32	29	396.45	8	3	0	2	355.62	70.5946
62	1.55	105.32	30	409.49	8	3	0	2	375.98	72.6646
63	-0.2	141.07	27	372.36	8	6	1	4	312.95	60.33085
64	2.69	72.2	28	378.48	6	2	0	6	355.8	84.091
65	1.85	72.2	29	396.47	6	2	0	6	360.73	84.091
66	3.34	72.2	29	412.92	6	2	0	6	369.34	84.091
67	3.47	72.2	29	457.37	6	2	0	6	373.69	84.091
68	3.74	72.2	29	504.37	6	2	1	6	379.79	84.091
69	7.83	87.25	34	486.99	7	1	1	5	4007.42	78.89875
70	7.89	96.49	36	517.01	8	1	2	6	432.96	75.71095
71	8.25	87.25	35	501.01	7	1	2	5	423.98	78.89875
72	6.79	169.28	40	580.03	12	3	3	11	474.39	50.5984
73	7.7	195.43	44	627.09	13	4	3	12	520.44	41.57665
74	7.64	123.45	38	613.92	9	3	2	10	468.94	66.40975
75	5.66	79.59	29	424.91	6	1	1	4	352.45	81.54145
76	5.96	88.83	31	454.94	7	1	1	6	378.23	78.35365
77	3.24	75.83	26	384.85	6	1	0	3	308.71	82.83865
78	6.97	62.52	31	444.95	5	1	1	4	371.75	87.4306
79	7.65	62.52	32	479.39	5	1	1	4	385.29	87.4306
80	6.93	108.35	34	489.94	8	1	1	5	395.08	71.61925
81	2.94	75.02	24	338.8	5	3	0	2	287.04	83.1181
82	2.96	100	27	377.43	8	3	0	3	313.44	74.5
83	2.99	109.23	29	407.46	9	3	0	4	338.99	71.31565
84	3.64	100	28	411.88	8	3	0	3	326.98	74.5
85	3.67	109.23	30	441.9	9	3	0	4	352.52	71.31565
86	3.05	118.47	31	437.49	10	3	0	5	364.53	68.12785
87	3.8	109.23	30	486.36	9	3	0	4	356.87	71.31565
88	3.87	98.38	31	500.38	9	2	1	4	373.81	75.0589
89	5.33	98.38	37	532.03	9	2	2	6	441.11	75.0589
90	4.72	41.82	21	294.38	3	1	0	4	257.56	94.5721
91	3.1	94.98	29	406.47	8	2	0	7	343.63	76.2319
92	3.57	95.06	28	411.87	6	2	0	3	327.3	76.2043
93	2.54	113.53	31	437.48	8	2	0	5	364.86	69.83215
94	4.3	122.89	38	523.57	9	2	1	6	436.66	66.60295
95	5.35	44.89	25	346.82	3	2	1	3	300.76	93.51295
96	2.45	109.75	32	443.49	8	2	0	5	367.12	71.13625
97	3.01	92.47	25	326.36	5	2	0	3	293.51	77.09785
98	3.01	92.47	25	326.36	5	2	0	3	293.51	77.09785
99	3.17	116.31	32	483.6	8	3	0	7	381.79	68.87305
100	3.38	108.63	32	444.52	7	3	0	5	376.37	71.52265
101	4.29	48.13	25	333.44	4	2	0	4	318.57	92.39515
102	3.52	95.06	30	414.49	7	3	0	6	355.49	76.2043
103	3.91	61.77	24	398.29	5	2	0	3	291.04	87.68935
104	3.54	61.77	24	333.42	5	2	0	3	289.72	87.68935
105	7.86	109.57	38	544.04	9	2	2	10	456.22	71.19835
106	6.94	100.33	36	493.6	8	2	1	8	433.46	74.38615
107	6.57	68.11	34	488.02	6	1	1	8	418.38	85.50205
108	4.65	39.2	23	317.27	3	0	0	4	254.55	95.476
109	4.7	69.71	24	331.76	4	0	0	3	278.94	84.95005

110	4.92	69.71	27	365.31	4	0	0	3	296.71	84.95005
111	4.83	69.71	24	376.21	4	0	0	3	283.29	84.95005
112	3.52	114.73	31	406.45	7	4	0	2	357.46	69.41815
113	3.25	135.76	29	408.45	10	3	0	7	342.04	62.1628
114	4.12	105.24	33	449.42	8	3	0	5	371.12	72.6922
115	5.36	105.24	36	515.88	8	3	2	6	408.09	72.6922
116	5.58	105.24	39	549.43	8	3	2	7	425.86	72.6922
117	5.14	105.24	33	482.33	8	3	1	5	390.33	72.6922
118	3.15	82.19	27	372.33	7	1	0	5	302.46	80.64445
119	3.4	145.79	33	452.42	11	2	1	9	380.93	58.70245
120	2.88	119.49	30	408.41	9	2	0	8	353.2	67.77595
121 (S)	4.76	92.35	32	464.83	7	3	0	6	368.26	77.13925

(S)- Standard compound – Sorafenib
Mol Wt.: Molecular weight. For a candid to be drug-like, its Molecular weight should be less than 500 Low molecular weight drug molecules (<500) are easily transported, diffuse, and absorbed as compared to heavy molecules.
mi Log P: Octanol-Water Partition Coefficient. Drug candid must have a log P value less than 5. TPSA: Total Polar Surface Area. TPSA of the drug candid must be below the 160 A^0 limit.
n Atoms: Number of atoms in the drug candid
n ON: Number of hydrogen bond acceptors. Drug candid must have less than 10 hydrogen bond acceptors
n OH, NH: Number of hydrogen bond donors. Drug candid must have less than 5 hydrogen bond donors
n violation: Violations to the rule of Lipinski's rule of five: Drug candid must have not more than 1 violations (n=0-1) for drug-likeness
n rotb: Number of rotatable bonds: Drug candid must have less than 10 rotatable bonds
Mol vol: Molecular volume % Absorption

Molecular volume

Molecular volume determines transport characteristics of molecules, such as intestinal absorption or blood-brain barrier penetration. Volume is, therefore, often used in QSAR studies to model molecular properties and biological activity. Methods for calculating molecule volume, developed at Molinspiration, are based on group contributions. These have been obtained by fitting a sum of fragment contributions to "real" 3D volume for a training set of about twelve thousand, mostly drug-like molecules. 3D molecular geometries for a training set were fully optimized by the semi-empirical AM1 method. Calculated volume is expressed in cubic Angstroms [47].

Number of rotatable bonds (n-rotb)

The number of rotatable bonds (RBN) is the number of bonds that allow free rotation around themselves. These are defined as any single bond, not in a ring, bound to a nonterminal heavy atom. Excluded from the count are amide C–N bonds because of their high rotational energy barrier [48].

Bioactivity Score

G Protein-coupled receptors (GPCRs) ligand

GPCRs represent one of the largest and most important integral membrane protein families. These receptors serve as increasingly attractive drug targets for their relevance in treating various diseases, such as inflammatory disorders, metabolic imbalances, cardiac disorders, cancer, monogenic disorders, etc. [49].

Ion channel modulator

Ion channels play an essential role in numerous cell types. Several disease states are related to dysfunctional ion channels. Prominent among these are cardiac arrhythmias, diabetes, hypertension, angina pectoris, and epilepsy. Drugs have been developed to target ion channels and to prevent the channels from conducting ions. They are widely used as local anaesthetics, anti-arrhythmic, antihypertensives, and antiepileptics [50].

Kinase inhibitors

Protein kinases are involved in various cellular functions, including metabolism, cell cycle regulation, survival, and differentiation. Dysregulation of protein kinases is implicated in multiple processes of carcinogenesis. There are many types of protein kinases that take part in many cell functions. These include cell signalling, growth, and division. Blocking specific protein kinases may help keep cancer

cells from growing. Some protein kinase inhibitors, such as imatinib, vemurafenib, and gefitinib, are used to treat cancer [51].

Nuclear receptor (NR) ligand

NR pleiotropically regulate several physiological processes, including metabolism, immune function, reproduction, and development. Therefore, NRs have significant roles in the pathology of human diseases, including diabetes, cancer, autoimmune disease, and ageing. Ligands that bind to and activate nuclear receptors include lipophilic substances such as endogenous hormones, vitamins A and D, and xenobiotic endocrine disruptors [52,53].

Protease inhibitors

Protease inhibitors bind to the active site of the protease enzyme and prevent the maturation of the newly produced virions so that they remain non-infectious. Protease inhibitors are used in the treatment of human immunodeficiency virus (HIV infection) and acquired immune deficiency syndrome (AIDS) [54].

Enzyme inhibitors

Enzyme inhibitors are molecules that bind to enzymes and decrease their activity. This is the most common use for enzyme inhibitors because they target human enzymes and try to correct a pathological condition. Uses of enzyme inhibitors are erectile dysfunction, chemotherapy for cancer, Anaesthesia, myasthenia gravis and viral infections [55].

Table 2. Bioactivity score of compounds based on Molinspiration cheminformatics software.

Sr No.	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor (antivirals)	Enzyme inhibitor
1	-0.17	-0.61	-0.09	-1.04	-0.4	-0.22
2	-0.25	-0.6	-0.05	-1.08	-0.35	-0.23
3	-0.04	-0.54	0.2	-1.4	-0.71	-0.24
4	-0.16	-0.69	-0.07	-1.05	-0.4	-0.22
5	-0.24	-0.74	-0.12	-1.3	-0.33	-0.23
6	-0.18	-0.8	-0.18	-1.27	-0.44	-0.25
7	-0.32	-0.42	0.01	-1.07	-0.62	-0.29
8	-0.13	-0.27	0.14	-0.91	-0.51	-0.18
9	-0.18	-0.32	0.15	-0.95	-0.61	-0.22
10	-0.17	-0.32	0.17	-0.89	-0.6	-0.23
11	-0.17	-0.32	0.17	-0.9	-0.62	-0.23
12	-0.15	-0.28	0.2	-1.1	-0.53	-0.25
13	-0.07	-0.24	0.25	-0.89	-0.48	-0.19
14	-0.12	-0.24	0.2	-0.85	-0.5	-0.25
15	-0.12	-0.33	0.2	-1.09	-0.53	-0.21
16	-0.24	-0.21	0.34	-0.73	-0.53	0.01
17	-0.13	-0.39	0.05	-0.6	-0.37	-0.11
18	-0.16	-0.32	0.03	-0.94	-0.46	-0.32
19	0.04	-0.18	0.45	-0.5	-0.28	0.12
20	0	-0.05	0.39	-0.29	-0.34	-0.01
21	-0.04	-0.17	0.49	-0.45	-0.27	0
22	0	0.08	0.18	-0.13	-0.25	-0.04
23	0.03	-0.28	0.62	-0.81	-0.54	-0.05
24	-0.51	-0.72	-0.42	-0.73	-0.58	-0.19
25	-0.48	-0.71	-0.33	-0.65	-0.56	-0.15
26	-0.4	-0.6	-0.31	-0.59	-0.47	-0.12
27	-0.14	0.07	0.24	-0.56	-0.24	0.04
28	-0.01	0.18	0.48	-0.65	-0.17	0.07
29	-0.01	0.12	0.32	-0.43	-0.13	0.09
30	-0.06	0.15	0.11	-0.33	-0.14	0.14
31	-0.04	0.16	0.12	-0.17	-0.17	0.7
32	-0.13	0.04	0.32	-0.46	-0.26	0.04
33	-0.18	-0.05	0.27	-0.47	-0.32	-0.02
34	-0.1	0.09	0.27	-0.32	-0.22	0.11

35	-3.72	-3.8	-3.86	-3.83	-3.69	-3.67
36	-3.72	-3.8	-3.85	-3.82	-3.68	-3.67
37	-3.71	-3.8	-3.86	-3.82	-3.69	-3.67
38	-3.69	-3.79	-3.84	-3.81	-3.66	-3.65
39	-3.72	-3.8	-3.86	-3.82	-3.68	-3.67
40	-3.75	-3.82	-3.88	-3.84	-3.72	-3.71
41	-3.76	-3.83	-3.89	-3.85	-3.74	-3.73
42	0.23	-0.11	0.59	-0.41	0.07	0.11
43	0.2	-0.12	0.5	-0.6	0.11	0.13
44	0.2	-0.07	0.46	-0.51	0.14	0.1
45	0.32	0	0.57	-0.33	0.19	0.17
46	0.21	-0.2	0.43	-0.48	0.02	0.11
47	0.19	-0.16	0.51	-0.43	0.07	0.08
48	0.26	-0.09	0.52	-0.35	0.12	0.1
49	-0.33	-0.71	-0.39	-0.37	-0.41	-0.31
50	-0.3	-0.75	-0.39	-0.4	-0.39	-0.29
51	-0.3	-0.68	-0.36	-0.4	-0.38	-0.26
52	-0.28	-0.67	-0.28	-0.34	-0.37	-0.23
53	-0.26	-0.43	0.84	-0.5	-0.76	0.04
54	-0.35	-0.56	0.38	-0.69	-0.83	-0.2
55	-0.21	-0.53	0.56	-0.6	-0.76	-0.05
56	-0.03	-0.36	0.55	-0.64	-0.51	-0.03
57	0.01	-0.31	0.55	-0.6	-0.44	0
58	-0.03	-0.36	0.54	-0.64	-0.43	0.01
59	-0.04	-0.39	0.59	-0.58	-0.51	-0.02
60	-0.03	-0.4	0.55	-0.6	-0.52	0
61	-0.01	-0.46	0.62	-0.65	-0.49	-0.07
62	0.01	-0.43	0.42	-0.84	-0.56	-0.06
63	-0.15	-0.5	0.39	-0.9	-0.52	-0.04
64	-0.12	-0.6	0.53	-0.74	-0.31	-0.24
65	-0.1	-0.59	0.53	-0.68	-0.33	-0.23
66	-0.12	-0.59	0.49	-0.73	-0.33	-0.26
67	-0.23	-0.68	0.46	-0.84	-0.43	-0.31
68	-0.14	-0.57	0.54	-0.7	-0.38	-0.29
69	-0.41	-0.74	-0.24	-0.95	-0.66	-0.48
70	-0.41	-0.78	-0.25	-0.91	-0.66	-0.49
71	-0.42	-0.77	-0.25	-0.95	-0.67	-0.49
72	-0.5	-0.91	-0.53	-0.97	-0.55	-0.51
73	-0.57	-1.31	-0.77	-1.22	-0.56	-0.68
74	-0.49	-0.85	-0.44	-0.98	-0.57	-0.46
75	-0.39	-1	-0.51	-0.92	-0.87	-0.65
76	-0.55	-1.01	-0.54	-1	-0.81	-0.62
77	-0.62	-1	-0.74	-1.29	-0.87	-0.62
78	-0.32	-0.69	-0.25	-0.82	-0.67	-0.4
79	-0.3	-0.67	-0.24	-0.79	-0.65	-0.39
80	-0.41	-0.67	-0.34	-0.83	-0.73	-0.46
81	-0.19	-0.44	0.34	-0.57	-0.22	-0.12
82	-0.86	-1.14	-0.29	-1.55	-1.08	-0.58
83	-0.84	-1.13	-0.29	-1.44	-1.07	-0.57
84	-0.83	-1.11	-0.3	-1.52	-1.08	-0.59
85	-0.82	-1.1	-0.32	-1.43	-1.05	-0.59
86	-0.79	-1.06	-0.27	-1.35	-1	-0.53
87	-0.93	-1.19	-0.34	-1.54	-1.15	-0.64
88	-0.92	-1.34	-0.47	-1.51	-1.08	-0.72
89	-0.58	-1.12	-0.33	-1.18	-0.79	-0.53
90	-0.2	-0.34	-0.33	-0.57	-0.48	-0.1
91	0.22	-0.1	-0.14	-0.25	0.09	0.08
92	-0.18	-0.38	0.06	-0.66	-0.2	0.05
93	-0.21	-0.4	0.07	-0.62	-0.23	0.03
94	-0.15	-0.79	-0.07	-0.71	-0.5	-0.31
95	0.19	-0.09	0.44	0.07	0.04	0.06
96	-0.01	-0.52	0.06	-0.66	-0.23	-0.09
97	-0.05	-0.34	0.15	-0.18	-0.24	-0.13
98	-0.05	-0.34	0.15	-0.18	-0.24	-0.13

99	-0.33	-0.85	-0.38	-0.96	-0.43	-0.07
100	-0.01	-0.24	-0.08	-0.34	0.06	0.07
101	0.27	-0.07	0.39	0.1	0.14	0.09
102	-0.1	-0.55	-0.01	-0.91	-0.42	0.01
103	-0.93	-1.05	-0.78	-1.09	-1.1	-0.76
104	-0.87	-1.05	-0.78	-1.01	-1.04	-0.74
105	-0.78	-0.94	-0.57	-0.98	-0.86	-0.57
106	-0.87	-0.97	-0.63	-1.06	-0.93	-0.59
107	-0.61	-0.76	-0.37	-0.71	-0.76	-0.4
108	0.11	0.19	0.25	0.21	-0.2	0.07
109	-0.1	-0.15	0.07	-0.17	-0.33	-0.09
110	-0.03	-0.05	0.14	0	-0.22	-0.05
111	-0.2	-0.22	0.05	-0.27	-0.41	-0.13
112	-0.81	-0.96	-0.78	-0.7	-0.86	-0.42
113	-0.6	-0.62	-0.69	-0.93	-0.71	-0.35
114	0.28	0.08	0.73	-0.28	0.21	0.24
115	0.29	0.07	0.65	-0.16	0.12	0.17
116	0.31	-0.04	0.59	-0.15	-0.18	0.17
117	0.31	0.08	0.68	-0.29	0.14	0.21
118	0.03	-0.3	0.22	-0.31	-0.68	0.09
119	-0.07	-0.46	-0.09	-0.28	-0.67	-0.01
120	0.08	-0.19	0.08	-0.15	-0.58	0.15
121 (S)	0.18	0	0.44	-0.07	0.11	0.08

GPCR: G-Protein Coupled Receptor; (S)- Standard compound – Sorafenib
Compounds with bioactive scores >0 were considered active, -5.0-0 were found moderately active, while <-5.0 were considered inactive

PreADMET

Analysis of ADMET is essential for assessing a drug candidate's Pharmacokinetic and toxicity profile [56]. Due to deficiencies in ADME/Toxicity, over 50% of the drug candidates fail in the drug development stage [42]. Online computational tools can assist in predicting and analysing ADMET profiles [56]. PreADMET is a web-based application for predicting ADME data and building a drug-like library using in silico method [57]. Failure in the drug development stage has been reduced because of this early-stage in-vitro ADME [58].

Parameters of PreADMET

PreADMET offers an in-silico estimation of human intestinal absorption (HIA), blood-brain barrier (BBB) permeability, and plasma protein binding. Caco2 cell model and MDCK (Madin Darby canine kidney) cell models for determining the oral drug absorption of a molecule [42,56]. It also predicts metabolism by classifying compounds as enzyme CYP 450 2C19 Inhibitor, CYP 450 2C9 Inhibitor, CYP 450 2D6 Inhibitor and substrate, CYP 450 3A4 Inhibitor and substrate, and P-gp Inhibitor [57].

Absorption, Distribution, and Excretion

Human Intestinal Absorption (HIA) refers to the process through which orally administered drugs are absorbed from GIT into the bloodstream [59]. High values of HIA indicate that the drug is better absorbed from the gastrointestinal tract into the bloodstream upon oral administration and hence affects bioavailability [58,59]. Human intestinal absorption data are the sum of bioavailability and absorption evaluated from the ratio of excretion or cumulative excretion in urine, bile, and faeces. For the prediction of HIA in PreADMET, chemical structures at pH 7.4 are applied because HIA is measured by *in vivo* test [57].

PreADMET uses the Caco-2 (Cancer coli-2) cell and MDCK (Madin-Darby canine kidney) cell model for the prediction of oral drug absorption [57]. The Caco-2 cell line is isolated from a human colon adenocarcinoma, whereas the MDCK cell line is isolated from canine distal renal tissue. The Caco-2 and MDCK cell models parallel human intestinal absorption and allow for the mechanistic evaluation of drug permeability, such as passive diffusion (paracellular, transcellular), carrier-mediated uptake, and carrier-mediated efflux. Thus, they serve as rapid screening tools for drug permeability and transport, delivering information at the cellular level [60].

The unbound drug is available for diffusion or transport across cell membranes and interaction with a pharmacological target. As a result, a drug's degree of plasma protein binding affects not only the drug's activity but also its disposition and efficacy. PreADMET can predict the percent drug bound in plasma protein as *in vitro* data on humans [57].

Predicting Blood Brain Barrier (BBB) penetration means predicting whether compounds pass across the blood-brain barrier. This is important in the pharmaceutical sphere because CNS-active compounds must pass across it, and CNS-inactive compounds should not pass across it to avoid CNS side effects. PreADMET can anticipate *in vivo* data on rates for BBB penetration [57]. Table 3 gives details on the prediction of the above parameters by PreADMET.

Table 3. Prediction of parameters by PreADMET software.

Classification	**HIA (Human Intestinal Absorption)**
Poorly absorbed compounds	0 - 20 %
Moderately absorbed compounds	20 - 70 %
Well absorbed compounds	70 - 100 %
Classification	**P_{Caco-2}/ P_{MDCKP} (nm/sec)**
Low permeability	Less than 4
Middle permeability	4 - 70
High permeability	more than 70
Classification	**Plasma Protein Binding (%PPB)**
Chemicals strongly bound	more than 90%
Chemicals weakly bound	less than 90%
Classification	**Blood Brain Barrier Penetration (C brain/ C blood)**
High absorption to CNS	more than 2.0
Middle absorption to CNS	2.0 - 0.1
Low absorption to CNS	less than 0.1

HIA-Human Intestinal absorption; Caco2- Cancer coli-2 Cell Model

All 121 compounds were screened through PreADMET software for predicting the above parameter, which are represented in Table 4.

Table 4. Prediction of Absorption, Distribution, and Excretion by PreADMET.

Compounds	**Toxicity Prediction**				
	Absorption			**Distribution**	
	Human intestinal absorption (HIA, %)	**In-vitro Caco-2 cell permeability (nm/sec)**	**In-vitro MDCK cell permeability (nm/sec)**	**In-vitro plasma protein binding (%)**	**In-vivo blood-brain barrier penetration (C_{brain}/C_{blood})**
1	97.880635	21.6781	0.0602901	100	0.0170939
2	97.331982	21.664	0.0584867	100	0.0141756
3	96.412822	25.2551	7.08779	70.858559	0.0196489
4	97.323363	21.6676	0.0532635	100	0.0129214
5	98.581688	20.9295	0.143826	100	0.0145888
6	98.912423	21.0727	0.154837	98.877895	0.0192742
7	96.956031	24.9058	0.0600658	88.297401	0.0221109
8	96.854787	28.3887	3.91017	100	0.194175
9	97.241674	57.7117	2.38948	99.570554	0.395025
10	97.247615	57.8262	4.41998	100	0.542351
11	97.247615	57.5634	0.822475	99.673747	0.614157
12	94.820126	42.2174	0.173313	88.548197	0.112335
13	94.699578	34.9982	0.0529568	87.753473	0.95459
14	95.821668	42.5676	0.0523966	86.801272	1.00221
15	93.2667	37.3975	0.171207	74.395416	0.113842
16	93.770849	21.096	0.104188	93.557641	0.142072
17	95.912887	27.8711	0.0718274	88.608448	0.67919
18	95.938419	52.5508	0.0708814	89.010964	0.0791107
19	94.32872	10.7379	0.614361	97.913652	0.133981
20	96.636988	16.869	0.0443809	94.393622	0.0971003

21	96.09712	16.6806	0.046033	97.879101	0.141368
22	96.732612	32.0306	0.0854821	89.000243	0.514374
23	96.68247	40.1424	0.0895796	90.8642	0.299271
24	98.499546	16.1635	0.070819	93.997810	0.25781
25	98.191465	15.3675	0.0726968	97.430577	0.139526
26	97.110137	15.8454	0.315386	98.120192	0.297958
27	94.440184	21.9865	0.195618	87.893524	1.65135
28	94.317723	21.4932	0.241822	89.50665	1.43146
29	95.913593	23.0756	0.268029	88.785074	0.409816
30	95.913593	22.0756	0.254047	92.2681	0.561649
31	96.434924	25.7649	0.0661058	90.533107	3.74418
32	95.356398	32.1458	72.0899	96.332301	6.97287
33	95.747877	33.9831	16.3424	95.438914	4.32328
34	96.867282	42.0341	71.0078	95.251521	1.50839
35	98.519604	39.9235	0.0434155	89.607585	0.108969
36	98.519604	40.9834	0.0434155	89.558573	0.113297
37	97.922104	47.4763	0.0434155	89.312731	0.141571
38	98.52394	38.1127	0.0434155	89.667415	0.105198
39	97.922104	47.4763	0.0434155	89.31307	0.141485
40	98.693071	39.3086	0.0434155	89.685019	0.167382
41	98.327154	49.5262	0.0434155	89.498525	0.145154
42	87.88792	16.0049	20.5177	93.273759	1.6171
43	90.864519	8.0401	9.40062	86.370134	0.577642
44	94.26837	21.0538	0.270844	94.271451	1.67094
45	86.853766	12.3444	41.249	95.673402	1.20849
46	93.717687	20.4779	10.2303	97.517683	1.53106
47	87.877775	15.7485	19.6359	93.465216	2.06721
48	87.835034	19.6378	45.2221	91.152057	3.39969
49	97.643117	50.8755	0.0456045	90.081875	1.3586
50	99.109766	54.7381	0.0435041	89.727596	0.800914
51	98.476276	54.8117	0.0447372	89.590345	0.964275
52	99.582123	42.8571	0.0448468	90.044039	0.756216
53	85.996264	3.7756	80.508	75.238458	1.37682
54	84.992654	20.3535	1.14756	80.848889	0.433002
55	81.059802	20.534	23.587	76.056562	0.253821
56	84.138961	21.8822	1.52474	51.860977	0.26068
57	85.008418	20.7427	0.631828	57.241105	0.255913
58	84.469072	20.5442	0.0885302	85.56032	0.876223
59	87.500791	21.0335	1.66631	77.966559	0.353447
60	88.084644	21.7245	0.350723	83.040578	0.541989
61	86.623298	20.3648	7.89135	65.531118	0.137431
62	88.072028	22.4928	1.30982	42.056534	0.195017
63	74.494637	16.1255	0.846714	45.597723	0.0528776
64	92.380619	43.9915	33.1136	66.145741	0.783161
65	92.400861	41.5318	4.40579	67.300368	1.05918
66	93.331695	34.5754	3.55378	75.965554	1.55791
67	93.801568	35.5388	0.0494869	77.31037	1.66464
68	97.2353	39.5668	2.4595	93.882817	0.0419489
69	97.2353	39.5668	2.4595	93.882817	0.0419489
70	97.376717	42.3518	0.108732	95.254742	0.0679249
71	97.252117	41.1484	4.11133	95.292593	0.0367087
72	95.771763	9.4821	0.04359	90.980019	0.0846115
73	93.928354	18.0984	0.0442369	93.149412	0.0842652
74	96.541733	21.8453	0.0181884	87.944885	0.0226835
75	97.369757	37.6555	0.0779213	90.3742	0.440809
76	97.867605	42.0625	0.0523123	93.003099	0.313414
77	96.874819	23.6095	10.4702	93.680222	0.200301
78	97.463445	43.3813	20.063	94.129734	0.386376
79	97.784239	44.0468	15.8948	92.080805	0.233188
80	98.68608	22.5634	0.179962	93.76858	0.554902
81	95.233265	20.5837	161.25	92.294282	0.172281
82	93.51087	18.8465	67.1464	95.866973	0.0389898

83	93.804181	18.7585	1.11221	94.576899	0.0369458
84	94.05226	19.0572	38.1524	94.676176	0.0629572
85	94.077729	19.4857	0.990437	95.056502	0.0441762
86	94.068725	16.8795	0.164357	92.655109	0.0571311
87	94.412081	20.6623	0.0247349	95.502461	0.0457372
88	95.723702	21.231	0.0192071	98.551638	0.0340618
89	96.425262	23.3598	0.316366	95.002362	0.041234
90	94.611073	4.6705	0.55867	93.373811	3.36768
91	92.213923	13.3405	56.142	87.407879	0.49962
92	96.804375	4.7705	0.0964651	95.827097	0.0095595
93	98.06656	6.5002	0.10615	85.99455	0.0135795
94	94.915026	10.8523	0.0486999	95.851612	0.074633
95	93.848985	43.2819	0.699548	93.81326	11.6456
96	93.903976	10.3928	2.77534	100	0.039503
97	91.313272	2.86526	0.542633	89.914418	0.436712
98	92.093786	4.25203	0.0904015	87.986214	0.880675
99	90.69694	12.0775	0.566884	100	0.0716918
100	94.161289	1.00242	0.095911	99.589003	0.134976
101	92.68774	49.912	100.325	82.562571	5.65471
102	99.700804	20.734	0.417296	100.000000	0.264511
103	94.974876	27.5883	0.314936	89.702116	3.68211
104	94.125479	23.0907	81.6016	96.03967	2.72605
105	95.730257	14.1039	4.25395	93.441285	1.8767
106	95.266778	17.4181	6.91859	97.974934	1.39758
107	96.710201	47.8326	26.1632	97.562083	3.82479
108	98.002147	32.005	0.0604341	92.217373	0.133761
109	97.595288	23.2786	0.1669	93.059766	0.0299508
110	97.968514	22.2165	0.0437606	93.807035	0.0340314
111	97.483016	23.6219	0.0284336	97.729626	0.0329311
112	96.313603	4.71105	34.9652	94.608965	0.231337
113	80.735265	17.0365	5.57453	74.283788	0.0723951
114	93.616922	20.5184	0.0863542	91.61803	0.145856
115	94.845768	22.4401	0.0484168	92.944603	0.636003
116	94.139832	21.5713	0.0447487	97.108007	0.877513
117	95.414521	22.343	0.0640813	90.875815	0.459374
118	96.359923	30.2546	0.0831065	95.317634	0.115123
119	95.213095	20.8031	0.0508489	95.628783	0.036131
120	95.321958	17.9898	0.23246	89.119592	0.0590691
121 (S)	93.500451	22.5596	0.0822323	89.865177	1.00027

MDCK-Madin-Darby Canine Kidney Cell Model

The Caco-2 and MDCK cell models are parallel to human intestinal absorption, which serve as rapid screening tools for drug permeability and transport delivering information at the cellular level; (S)- Standard compound – Sorafenib

Metabolic Prediction

Metabolism of drugs impacts multidrug resistance in cancer chemotherapy and infectious diseases. Drugs as substrates or inhibitors of Cytochrome P450 enzymes (CYP2C19, CYP2C9, CYP2D6, CYP3A4) involved in phase I metabolism (xenobiotic metabolism) influence the potency and duration of many drugs and lead to various hazardous drug interactions [58].

Drugs that inhibit these cytochrome p-450 enzymes tend to increase the plasma concentration of other drugs, while substrates of these enzymes stimulate the metabolic pathways of other drugs, thereby decreasing their plasma concentration [61].

P-glycoprotein is also multidrug resistance protein 1 (MDR1) [62]. P-glycoprotein (P-gp) is a plasma membrane protein that actively exports, pumps, or expels drugs out of the cell and thus affects the distribution, metabolism, and excretion of many drugs. This efflux of drugs helps develop drug resistance by decreasing their intracellular concentration inside the cell. Hence P-gp inhibition finds application in cancer therapy [58].

All 121 compounds were screened for predicting whether the compounds were substrates or inhibitors of cytochrome p-450 enzymes and P-gp, which are represented in Table 5.

Table 5. Metabolic prediction of the compounds by Pre ADMET software.

Compounds	CYP_2C19 inhibition	CYP_2C9 inhibition	CYP_2D6 inhibition	CYP_2D6 substrate	CYP_3A4 inhibition	CYP_3A4 substrate	P-gp inhibition
1	Non	Inhibitor	Non	Non	Non	Substrate	Inhibitor
2	Non	Inhibitor	Non	Non	Non	Substrate	Inhibitor
3	Non	Non	Inhibitor	Substrate	Non	Substrate	Inhibitor
4	Non	Inhibitor	Non	Non	Non	Substrate	Inhibitor
5	Non	Inhibitor	Non	Non	Non	Weakly	Inhibitor
6	Non	Inhibitor	Non	Non	Non	Substrate	Inhibitor
7	Non	Inhibitor	Non	Non	Non	Substrate	Inhibitor
8	Non	Non	Non	Non	Non	Substrate	Inhibitor
9	Non	Non	Non	Non	Non	Substrate	Inhibitor
10	Non	Non	Non	Non	Non	Substrate	Inhibitor
11	Non	Non	Non	Non	Non	Substrate	Inhibitor
12	Non	Inhibitor	Inhibitor	Non	Inhibitor	Substrate	Inhibitor
13	Non	Inhibitor	Non	Non	Inhibitor	Substrate	Inhibitor
14	Non	Inhibitor	Non	Non	Inhibitor	Substrate	Inhibitor
15	Non	Inhibitor	Non	Non	Inhibitor	Weakly	Inhibitor
16	Non	Inhibitor	Non	Non	Inhibitor	Weakly	Inhibitor
17	Non	Inhibitor	Inhibitor	Non	Non	Non	Inhibitor
18	Non	Inhibitor	Inhibitor	Non	Non	Substrate	Inhibitor
19	Non	Inhibitor	Non	Non	Non	Substrate	Inhibitor
20	Non	Inhibitor	Non	Non	Inhibitor	Substrate	Inhibitor
21	Non	Inhibitor	Non	Non	Inhibitor	Substrate	Inhibitor
22	Non	Inhibitor	Non	Non	Non	Substrate	Inhibitor
23	Non	Non	Non	Non	Non	Weakly	Inhibitor
24	Inhibitor	Inhibitor	Non	Non	Inhibitor	Non	Non
25	Inhibitor	Inhibitor	Non	Non	Inhibitor	Non	Inhibitor
26	Inhibitor	Inhibitor	Non	Non	Inhibitor	Non	Inhibitor
27	Non	Inhibitor	Non	Non	Inhibitor	Weakly	Inhibitor
28	Non	Inhibitor	Non	Non	Inhibitor	Weakly	Inhibitor
29	Non	Inhibitor	Non	Non	Non	Non	Inhibitor
30	Non	Inhibitor	Non	Non	Non	Non	Inhibitor
31	Non	Inhibitor	Non	Non	Non	Weakly	Inhibitor
32	Non	Non	Non	Non	Non	Weakly	Inhibitor
33	Non	Non	Non	Non	Non	Weakly	Non
34	Non	Non	Non	Non	Non	Weakly	Inhibitor
35	Non	Non	Non	Weakly	Inhibitor	Substrate	Inhibitor
36	Non	Non	Non	Weakly	Inhibitor	Substrate	Inhibitor
37	Non	Non	Non	Weakly	Inhibitor	Substrate	Inhibitor
38	Non	Non	Non	Weakly	Inhibitor	Substrate	Inhibitor
39	Non	Non	Non	Weakly	Inhibitor	Substrate	Inhibitor
40	Non	Non	Non	Weakly	Inhibitor	Substrate	Inhibitor
41	Non	Non	Non	Weakly	Inhibitor	Substrate	Inhibitor
42	Non	Inhibitor	Non	Non	Inhibitor	Substrate	Inhibitor
43	Non	Inhibitor	Non	Non	Inhibitor	Weakly	Inhibitor
44	Non	Inhibitor	Non	Non	Non	Non	Inhibitor
45	Non	Inhibitor	Non	Non	Inhibitor	Weakly	Inhibitor
46	Non	Inhibitor	Non	Non	Non	Substrate	Inhibitor
47	Non	Inhibitor	Non	Non	Inhibitor	Substrate	Inhibitor
48	Non	Inhibitor	Non	Weakly	Inhibitor	Substrate	Inhibitor
49	Non	Inhibitor	Non	Non	Inhibitor	Substrate	Inhibitor
50	Non	Inhibitor	Non	Non	Inhibitor	Substrate	Inhibitor
51	Non	Inhibitor	Non	Non	Inhibitor	Substrate	Inhibitor
52	Non	Inhibitor	Non	Non	Inhibitor	Substrate	Inhibitor
53	Inhibitor	Inhibitor	Non	Non	Inhibitor	Substrate	Non

54	Inhibitor	Inhibitor	Non	Non	Inhibitor	Substrate	Non
55	Non	Inhibitor	Non	Non	Non	Weakly	Non
56	Non	Inhibitor	Non	Weakly	Inhibitor	Substrate	Non
57	Non	Inhibitor	Non	Weakly	Inhibitor	Substrate	Non
58	Non	Inhibitor	Non	Non	Inhibitor	Substrate	Non
59	Non	Non	Inhibitor	Non	Inhibitor	Substrate	Non
60	Non	Non	Inhibitor	Non	Inhibitor	Substrate	Non
61	Non	Inhibitor	Inhibitor	Non	Inhibitor	Substrate	Non
62	Non	Inhibitor	Non	Weakly	Inhibitor	Substrate	Non
63	Non	Inhibitor	Non	Non	Non	Weakly	Non
64	Non	Non	Non	Weakly	Non	Weakly	Non
65	Non	Non	Non	Weakly	Non	Weakly	Non
66	Non	Non	Non	Weakly	Non	Weakly	Non
67	Non	Non	Non	Weakly	Non	Weakly	Non
68	Non	Inhibitor	Non	Non	Non	Substrate	Inhibitor
69	Non	Inhibitor	Non	Non	Non	Substrate	Inhibitor
70	Non	Inhibitor	Non	Non	Non	Substrate	Inhibitor
71	Non	Inhibitor	Non	Non	Non	Substrate	Inhibitor
72	Non	Inhibitor	Non	Non	Inhibitor	Weakly	Inhibitor
73	Non	Inhibitor	Non	Non	Inhibitor	Non	Inhibitor
74	Non	Inhibitor	Non	Non	Inhibitor	Non	Inhibitor
75	Inhibitor	Inhibitor	Non	Non	Inhibitor	Substrate	Inhibitor
76	Inhibitor	Inhibitor	Non	Non	Inhibitor	Substrate	Inhibitor
77	Non	Inhibitor	Non	Non	Non	Weakly	Inhibitor
78	Inhibitor	Inhibitor	Non	Non	Inhibitor	Substrate	Inhibitor
79	Inhibitor	Inhibitor	Non	Non	Inhibitor	Substrate	Inhibitor
80	Non	Inhibitor	Non	Non	Non	Substrate	Inhibitor
81	Non	Inhibitor	Non	Non	Non	Weakly	Non
82	Non	Inhibitor	Non	Non	Non	Substrate	Non
83	Non	Inhibitor	Non	Non	Inhibitor	Substrate	Non
84	Non	Inhibitor	Non	Non	Non	Substrate	Non
85	Non	Inhibitor	Non	Non	Inhibitor	Substrate	Non
86	Non	Inhibitor	Non	Non	Inhibitor	Substrate	Non
87	Non	Inhibitor	Non	Non	Inhibitor	Substrate	Non
88	Non	Inhibitor	Non	Non	Non	Weakly	Inhibitor
89	Non	Inhibitor	Non	Non	Non	Weakly	Inhibitor
90	Inhibitor	Inhibitor	Non	Non	Inhibitor	Weakly	Non
91	Non	Non	Non	Substrate	Non	Substrate	Inhibitor
92	Non	Non	Non	Non	Non	Non	Inhibitor
93	Non	Inhibitor	Non	Non	Non	Non	Inhibitor
94	Non	Inhibitor	Non	Non	Inhibitor	Weakly	Non
95	Non	Non	Non	Non	Non	Non	Inhibitor
96	Non	Inhibitor	Non	Non	Non	Substrate	Non
97	Non	Non	Non	Non	Non	Weakly	Non
98	Non	Non	Non	Non	Non	Weakly	Non
99	Non	Inhibitor	Non	Non	Non	Weakly	Non
100	Non	Inhibitor	Non	Non	Non	Weakly	Non
101	Non	Non	Inhibitor	Substrate	Non	Weakly	Inhibitor
102	Non	Inhibitor	Non	Weakly	Inhibitor	Weakly	Inhibitor
103	Inhibitor	Inhibitor	Non	Non	Inhibitor	Weakly	Inhibitor
104	Inhibitor	Inhibitor	Non	Non	Inhibitor	Weakly	Inhibitor
105	Inhibitor	Inhibitor	Non	Non	Inhibitor	Weakly	Inhibitor
106	Inhibitor	Inhibitor	Non	Non	Inhibitor	Substrate	Inhibitor
107	Inhibitor	Inhibitor	Non	Non	Inhibitor	Weakly	Inhibitor
108	Inhibitor	Inhibitor	Non	Non	Inhibitor	Substrate	Inhibitor
109	Inhibitor	Inhibitor	Non	Non	Inhibitor	Weakly	Inhibitor

110	Inhibitor	Inhibitor	Non	Non	Inhibitor	Weakly	Inhibitor
111	Inhibitor	Inhibitor	Non	Non	Inhibitor	Weakly	Inhibitor
112	Non	Inhibitor	Non	Weakly	Inhibitor	Substrate	Non
113	Non	Non	Inhibitor	Weakly	Inhibitor	Substrate	Inhibitor
114	Non	Inhibitor	Non	Non	Inhibitor	Weakly	Inhibitor
115	Non	Inhibitor	Non	Non	Inhibitor	Weakly	Inhibitor
116	Non	Inhibitor	Non	Non	Inhibitor	Substrate	Inhibitor
117	Non	Inhibitor	Non	Non	Inhibitor	Weakly	Inhibitor
118	Non	Inhibitor	Non	Non	Non	Substrate	Inhibitor
119	Non	Inhibitor	Non	Weakly	Inhibitor	Substrate	Inhibitor
120	Non	Inhibitor	Non	Non	Non	Substrate	Inhibitor
121 (S)	Non	Inhibitor	Non	Non	Non	Weakly	Inhibitor

CYP-Cytochrome P-450 enzymes involved in Phase-I metabolism; (S)- Standard compound – Sorafenib
Pgp- P-glycoprotein: It is a plasma membrane protein that actively exports, pumps, or expels drugs out of the cell and thus affects the distribution, metabolism, and excretion of many drugs. Inhibition finds application in cancer.

Osiris property explorer

Osiris property explorer is an online cheminformatics tool developed by Actelion Pharmaceuticals Ltd. and needs a Java-run environment for its real-time cheminformatics applications [63]. The genetic information must be the same in all cells of living creatures. However, mutation may occur in genetic information and result in abnormalities in future generations. Teratogenicity can cause birth death, abnormalities, developmental delays, or death. Reproductive toxins can cause sterility, reduced fertility, or adverse reproductive effects. Many occupational cancers may develop 10-20 years longer after explosive to the carcinogen. Primary irritant dermatitis is caused by chemical substances that directly irritate the skin. All these toxicity parameters are evaluated using Osiris property explorer [64].

The toxicity prediction results obtained by virtual screening are valued and colour-coded as green, red, and yellow for properties such as effect on mutagenicity, reproductive system, skin irritant effect, and tumorigenicity. Properties in red indicate high risks of undesired effects like mutagenicity or poor intestinal absorption and a high probability of toxicity. In contrast, yellow indicates moderate toxicity, green shows good drug-conform behaviour and compatibility, and suggests no toxicity or low toxicity potential [65]. The Osiris software also calculates various parameters like the log P value of a compound, which measures its hydrophilicity, and the log S value, which signifies the aqueous solubility of a compound, and other parameters like molecular weight and drug likeness [63]. It combines these parameters along with toxicity risks and generates a 'Drug score' for a compound to judge its overall potential to qualify for a drug [42].

All 121 compounds were screened through Osiris software to assess their toxicities and drug score (Table 6).

Table 6. Prediction of toxicity by Osiris software.

Compounds	**Toxicity**				**Drug Score**
	Mutagenicity	**Tumorigenic**	**Irritant**	**Reproductive effect**	
1	Green	Green	Green	Green	0.53
2	Green	Green	Green	Green	0.63
3	Green	Green	Green	Green	0.81
4	Green	Green	Green	Green	0.46
5	Green	Green	Green	Green	0.64
6	Green	Green	Green	Green	0.53
7	Green	Green	Green	Green	0.39
8	Green	Green	Green	Green	0.29
9	Green	Green	Green	Green	0.26
10	Green	Green	Green	Green	0.25
11	Green	Green	Green	Green	0.25
12	Green	Green	Yellow	Green	0.27
13	Green	Green	Yellow	Green	0.18
14	Green	Green	Yellow	Green	0.17
15	Green	Green	Yellow	Green	0.32

16	Green	Green	Yellow	Green	0.24
17	Red	Green	Yellow	Green	0.13
18	Red	Green	Yellow	Green	0.12
19	Green	Green	Green	Green	0.6
20	Green	Yellow	Green	Yellow	0.18
21	Green	Green	Green	Green	0.58
22	Green	Green	Green	Green	0.3
23	Green	Green	Green	Green	0.51
24	Green	Green	Green	Green	0.48
25	Green	Green	Green	Green	0.43
26	Green	Green	Green	Green	0.41
27	Red	Red	Green	Green	0.16
28	Red	Red	Green	Red	0.1
29	Green	Green	Green	Green	0.7
30	Green	Green	Green	Green	0.56
31	Green	Green	Green	Green	0.24
32	Green	Green	Green	Green	0.43
33	Green	Green	Green	Green	0.64
34	Green	Green	Green	Green	0.6
35	Green	Green	Green	Green	0.24
36	Green	Green	Green	Green	0.25
37	Green	Green	Green	Green	0.25
38	Green	Green	Green	Green	0.26
39	Green	Green	Green	Green	0.25
40	Green	Green	Green	Green	0.26
41	Green	Green	Green	Green	0.26
42	yellow	Red	Green	Red	0.17
43	Red	Red	Red	Red	0.05
44	Red	Red	Green	Red	0.07
45	yellow	Red	Green	Red	0.17
46	yellow	Red	Green	Red	0.18
47	yellow	Red	Green	Red	0.17
48	yellow	Red	Green	Red	0.17
49	Green	Green	Green	Green	0.47
50	Green	Green	Green	Green	0.59
51	Green	Green	Green	Green	0.62
52	Green	Green	Green	Green	0.63
53	Green	Green	Green	Green	0.61
54	Green	Green	Green	Green	0.36
55	Green	Green	Green	Green	0.93
56	Green	Green	Red	Green	0.51
57	Green	Green	Green	Green	0.82
58	Green	Green	Green	Green	0.59
59	Green	Green	Green	Green	0.88
60	Green	Green	Green	Green	0.85
61	Green	Green	Green	Green	0.87
62	Green	Red	Green	Green	0.51
63	Green	Green	Green	Green	0.47
64	Green	Green	Red	Green	0.54
65	Green	Green	Red	Green	0.53
66	Green	Green	Red	Green	0.51
67	Green	Green	Red	Green	0.48
68	Green	Green	Red	Green	0.44
69	Yellow	Yellow	Yellow	Yellow	0.12
70	Yellow	Red	Green	Green	0.12
71	Yellow	Red	Green	Green	0.11
72	Green	Green	Green	Green	0.22
73	Red	Red	Green	Green	0.06
74	Green	Green	Green	Green	0.31
75	Green	Green	Green	Green	0.67
76	Green	Green	Green	Green	0.62
77	Green	Green	Green	Green	0.81
78	Green	Green	Green	Green	0.51
79	Green	Green	Green	Green	0.44

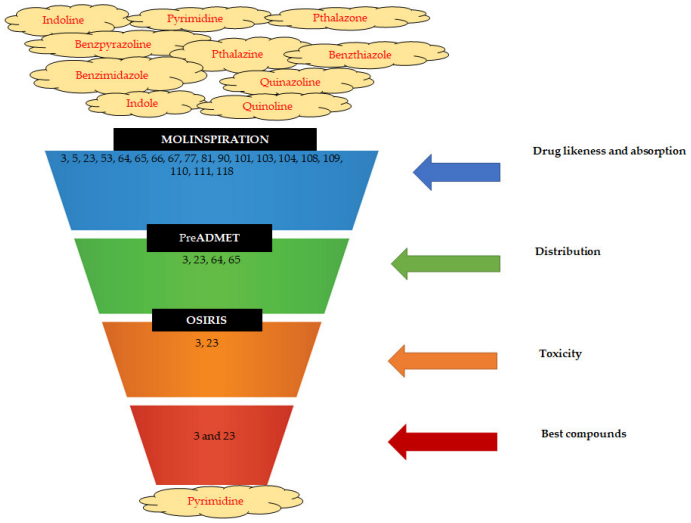
80	Green	Green	Green	Green	0.28
81	Green	Green	Red	Green	0.55
82	Green	Green	Green	Yellow	0.69
83	Green	Green	Green	Yellow	0.67
84	Green	Green	Green	Yellow	0.64
85	Green	Green	Green	Yellow	0.62
86	Green	Green	Green	Yellow	0.64
87	Green	Green	Green	Yellow	0.56
88	Green	Green	Green	Yellow	0.29
89	Green	Green	Green	Yellow	0.22
90	Green	Green	Green	Green	0.75
91	Green	Green	Green	Green	0.84
92	Green	Green	Green	Green	0.74
93	Green	Green	Green	Green	0.77
94	Green	Green	Green	Green	0.64
95	Green	Green	Green	Green	0.61
96	Red	Red	Green	Red	0.17
97	Green	Green	Green	Red	0.26
98	Green	Green	Green	Red	0.26
99	Green	Yellow	Green	Yellow	0.47
100	Green	Green	Green	Green	0.8
101	Green	Green	Red	Green	0.5
102	Red	Red	Green	Green	0.27
103	Red	Green	Green	Red	0.27
104	Red	Green	Green	Red	0.3
105	Green	Red	Green	Green	0.23
106	Green	Red	Green	Green	0.28
107	Green	Green	Green	Green	0.47
108	Green	Green	Green	Green	0.15
109	Green	Green	Green	Green	0.38
110	Green	Green	Green	Green	0.36
111	Green	Green	Green	Green	0.36
112	Yellow	Yellow	Green	Green	0.23
113	Red	Green	Green	Red	0.15
114	Green	Green	Green	Green	0.66
115	Green	Green	Green	Green	0.28
116	Green	Green	Green	Green	0.25
117	Green	Green	Green	Green	0.57
118	Green	Green	Green	Green	0.42
119	Green	Green	Green	Red	0.2
120	Green	Green	Green	Green	0.39
121 (S)	Green	Green	Green	Green	0.35

Drug Score: Gives overall potential to qualify for a drug; (S)- Standard compound – Sorafenib
Green: Non-toxic or Low Toxic Potential
Yellow: Moderate Toxicity
Red: High Toxic potentials

Results and Discussion

The Drug likeness, Absorption, Distribution, Metabolism, Excretion, and Toxicity of all the screened compounds were predicted through Molinspiration, PreADMET, and Osiris software. The compounds that showed drug-likeness properties through Molinspiration software were screened further for their ADMET properties. When 121 compounds were screened for drug-likeness, only 19 compounds i.e., 3, 5, 23, 53, 64, 65, 66, 67, 77, 81, 101, 103, 104, 108, 109, 110, 111, 118, 121 (Standard drug) had drug-like property. All the above-screened compounds showed excellent absorption with a Human Intestinal Absorption (HIA) value above 70% and Caco-2 permeability between 4-70 nm/sec with Pre ADMET software, which was similar to the standard drug Sorafenib 121. The percentage of all the above compounds was found to be above 80% compared to standard drug 121 (Sorafenib), which had an absorption of 77.13.

The above-selected compounds were further screened based on their distribution parameter results. The compounds that showed plasma protein binding equal to or below 90% and blood-brain barrier penetration below 1.000 were selected, i.e., compounds 3, 23, 64, 65. The standard drug sorafenib also



showed plasma protein binding equal to or below 90% and blood-brain barrier penetration of 1.000. The screened compounds had lower blood-brain barrier penetration than the standard (below 1.00), indicating lesser CNS side effects.

Figure 1. Screening of ADMET properties of Heterocyclic Compounds for anti-renal cancer activity.

The above-selected compounds were further screened based on their toxicity parameter results. Most compounds were eliminated because of toxicity results, determined through Osiris property explorer. Compounds 64 and 65 were found to be irritants and hence eliminated, while compounds 3 and 23 were found to be non-toxic similar to the standard drug Sorafenib. Metabolism was predicted using PreADMET. Compound 3 was found to be the non- inhibitor of enzymes CYP_2C19, CYP_2C9, and CYP_3A4. Compound 23 was noted as a non-inhibitor of CYP_2C19, CYP_2C9, CYP_2D6, and CYP_3A4. Both compounds 3 and 23 showed Pgp inhibition similar to standard 121.

Compounds 3 and 23 showed a bioactivity score of 0.2 and 0.6 as kinase inhibitors compared to standard drug sorafenib, which scored 0.44. The bioactive score above 0 indicated that the compounds were active as kinase inhibitors, one of the primary targets for renal cancer. After screening a library of 121 compounds, two compounds belonging to Pyrimidine derivatives 3 and 23 were considered best and suggested to be taken further for preclinical and clinical trials. Figure 1 represents the funnel that screens the ADMET properties of heterocyclic compounds based on Molinspiration, PreADMET, and Osiris software.

Conclusion

Through these studies, we were able to discover ADMET parameters of potential heterocyclic drug candidates for renal cancer using computational software like Pre-ADMET, Osiris, and Molinspiration. After screening a library of 121 compounds, two compounds belonging to Pyrimidine derivatives 3 and 23 are considered best and suggested to be taken further for preclinical and clinical trials. These parameters have been found essential during drug development and also reduce the chances of drug failure at the later stage.

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Authors contribution

All the authors have contributed equally.

Conflict of interest

The authors declare no conflict of interest.

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