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The Interactions between Heterocyclic Compounds and Target Proteins Involved with Cancer

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Abstract

Worldwide, cancer ranks as the second most lethal disease. The World Health Organisation predicts that by 2030, there will be 22 million new instances of cancer worldwide. Cancer prevention, diagnostic, and treatment procedures are the subject of extensive global research. The metabolic profile of cancer cells differs from that of normal cells due to epigenetic and genetic abnormalities. Many anti-cancer medications on the market include heterocycles as their primary structural component. Additionally, anticancer medications that were authorised by the FDA between 2010 and 2015 have heterocyclic rings in their structural makeup. Their massive cellular processes and mechanisms, together with their abundance in nature, explain why they are present in anti-cancer medications. This study sheds light on several heterocyclic compounds that have anticancer effect on various cell lines. These compounds have rings that contain nitrogen, sulphur, and oxygen. Collecting information on heterocyclic rings can pave the path for the discovery of novel compounds with cancer-fighting potential in the future.

Keywords: Heterocyclic compounds, Anticancer activity, Cell lines, Cytotoxicity, Natural product

Introduction

The majority of study has focused on VEFG as an initiator; however several cancer targets have been discovered, including enzymes that deacetylate histones, the enzyme tyrosine kinase, the growth factor TGF-α, fibroblast growth factor (FGF), phosphoglycerate geranylgeranyl transferase (PGF), epidermal growth factor (EGF), and phosphodiesterase type I and II. Although there have been several cases of illness progression following therapy, blocking VEFG signalling has not shown to be highly successful.Several heterocyclic anticancer drugs, derived from both natural and synthetic sources, are now in use, and researchers are actively searching for additional. As seen in Figure 1, there are a few instances. The therapeutic characteristics of heterocyclic compounds, which are ring compounds containing carbon and one or more atoms of nitrogen, oxygen, or sulphur, have been investigated for the treatment of cancer and other disorders. Druggable candidates are optimised for ADMET (Adsorption, Distribution, Metabolism, Excretion, and Toxicity) when these heteroatoms are introduced, which increases their solubility, polarity, and hydrogen bonding capacities.

One natural substance derived from Centipeda minimum, one heterocyclic sesquiterpene lactone that has anticancer properties is Brevilin A, 11, also known as 11. Scientists have shown that by decreasing the activity of tyrosine kinase, signal, and Janus kinase transcriptional transducer and activator 3 (STATS 3), Brevilin A may suppress cell growth, induce cell death, and decrease cell metastasis. Lee, Chan, and colleagues synthesised Brevilin A analogues for their investigation. They discovered that 13 and 14, which were derived from paraformaldehyde and 11 through an aldol reaction with sodium carbonate, had stronger anticancer effects than 11.

Problems with cancer therapies are common and include things like drug resistance, systemic toxicity from medications, and drugs that don't work. It is critical to find novel anticancer agents as drug leads immediately because of the difficulty in finding an effective therapeutic agent for fighting tumours due to variables such as the tendency of most cancer cells to change and the complex nature of signalling networks. One potential solution to these problems is the use of multi-target heterocyclic inhibitors in the battle against cancer.

That there are a number of new heterocyclic compounds with proven anticancer effects, such as Midostaurin (16), Vorinostat (17), and Sunitinib (15). Theirs is the ability to regulate many growth factors at once, including VEGFR, c-Kit from PDGFRA, and FLT-3. Figure 1.2 shows that many drugs with promising inhibitory potentials against Phase 3 clinical trials are now being conducted on a number of HER1 and HER2 inhibitors, including sotagliflozin (21), lapatinib (20), erlotinib (19), and gefitinib (18).

Literature Review

Ledade (2022) Fused nitrogen heterocyclic molecules have gained attention for their therapeutic properties in recent years. N-Heterocyclic scaffolds, which are versatile and easily synthesized, have numerous potential applications in synthetic organic chemistry and the biological domain. These compounds offer broad-spectrum antibacterial and anticancer medicines with low toxicity levels, but cytotoxicity levels are higher than those of cisplatin, the gold standard anticancer drug. Numerous synthetic techniques have been developed to synthesize N-heterocycles and their derivatives, offering a range of structural flexibility for targeted biological uses.

Martins (2015) Heterocycle molecules and fragments are essential in medicinal chemistry due to their adaptability, physicochemical characteristics, and prevalence in medicines. They are being studied for their potential effectiveness against various types of cancer. Their unique flexibility and dynamic structure have been specifically used in anticancer research. However, these compounds have drawbacks, including potential limiting concerns. This summary discusses the key biological objectives, structure-activity relationships, biochemical processes of action, and intrinsic limiting concerns with heterocyclic compounds, focusing on those beneficial for cancer treatment. The article also discusses the potential of nano vectorization to enhance the pharmacokinetic and pharmacodynamic features of heterocycles, particularly with the introduction of nanotechnology for effective selective drug targeting.

Didehban (2018) Heterocyclic systems are essential building blocks in organic synthesis and are found in numerous compounds, including over 90% of new drug structures. Researchers are working on innovative one-pot methods to synthesize these organic molecules using basic, cheap, and easily accessible building blocks. One of the most intriguing and encouraging synthetic operations is the chemical fixation of carbon dioxide onto organic molecules. This approach has evolved over the last five years, allowing for the synthesis of several biologically significant heterocyclic

systems. This brief overview focuses on recent developments in this field of chemistry, particularly in terms of reactions' mechanisms.

Naturalista (2024) Pyrazole derivatives are heterocyclic compounds with diverse biological and therapeutic applications. They have a broad range of effects, including antibacterial, anti-inflammatory, antioxidant, antiviral, antidiabetic, and neuroprotective effects. Contemporary techniques, such as solvent-free methods, microwave-assisted synthesis, green chemistry, catalytic methods, and multicomponent reactions, have replaced traditional methods in synthesis. These developments have made pyrazole-based compounds more efficient and selective, improving their use in the pharmaceutical industry. This article provides a comprehensive overview of the synthetic processes used to generate pyrazole derivatives and investigates the structure-activity relationship (SAR) of these compounds. It highlights the importance of pyrazole derivatives in developing novel medicinal medicines and provides guidance for future studies. The comprehensive analysis aims to highlight the potential of pyrazole derivatives as flexible candidates for creating new medications, contributing to continuous advancements in medicinal chemistry.

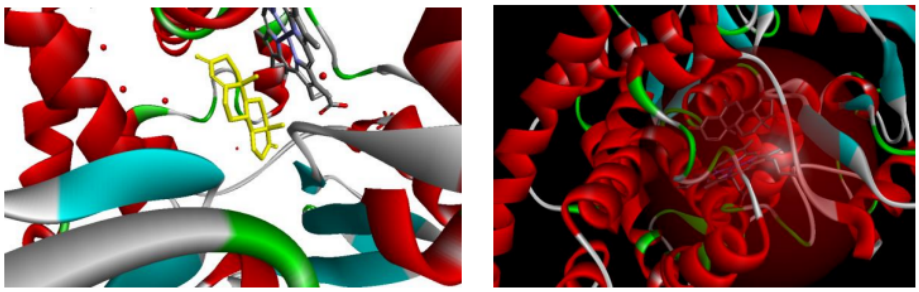
Mirza, Agha Zeeshan. (2019). Cancer is a major public health issue with millions of deaths annually. Chemotherapeutic medications, including synthetic versions of natural molecules, are effective in treating cancer. Nucleoside analogues, which have been used in antitumor chemotherapy, neoplasm treatment, and viral infection management, have become essential in cancer therapy. This review examines nucleosides and their potential utility in cancer treatment, including those pending FDA approval. The article also discusses the impact of substitution on nucleoside analogues and discusses the progress of computational chemistry in this field.

Material and Methods

Investigating Novel Non-Estradiol Chemo-Types as Aromatase Inhibitors in a Controlled Environment

The rapid need for novel pharmaceutical discoveries necessitates the development of new drug models, and in-silico trials provide a proactive means of doing so. The activity of the aromatase enzyme was better understood, and new and powerful artificial intelligences were developed, thanks to in-silico studies performed by several researchers employing cutting-edge tools like Structure-Guided Design, High-Throughput Docking, and pharmacophore-based modelling approaches. A better knowledge of aromatase's structure and function has been made possible by increasingly complex approaches, such as membrane-bound molecular dynamic simulations.

Some results show that aromatase's charged amino acid sequence, which includes alkyl and aryl amino acids, is critical for AI interaction. Heme porphyrin, when present at the active site, stabilises the substrate's transition state via its oxidation state and serves as an electron donor. In their work on molecular modelling of the aromatase active site, Park et al. revealed that the Aspartic acid 309 residue near the entrance of the active site is crucial for substrate access to the active site channel. Furthermore, it should be mentioned that the aromatase active site is often coordinated by the heme-porphyrin complex when sp2 nitrogen is present in the heterocyclic structure of AIs. Amino acid residues 133, 235, 395, 474, 302, 308, 309, Threonine, Serine 478, and 480 were shown to include sixteen distinct aromatase mutations. Ligand binding affinity with aromatase active site amino acid residues is either drastically increased or decreased by these mutations.



A B

Figure 1. The 3S7S and 3EQM aromatase proteins

• Creating a QSAR prototype

The IC50 activity and chemical diversity of the ligands in the aligned training set were used to verify the model. The goal was to generate meaningful predictions. A series of models were developed using four distinct PLS components to accomplish the regression using a partial least squares (PLS) approach. According to Table 3.1, the greatest overall model significance and statistical significance were achieved with PLS factor 4 (# Factor), which was selected due to the strong correlation between the training set and Partial Least Square factors. With these characteristics, we were able to assess the predictive power of the test set with a Q2 of 0.7854, RMSE of 0.5284, and Pearson R of 0.9111. A measure of variance is F. Regressions with larger values of F are considered to be more statistically significant. The variance ratio's significance level is denoted by P. A higher level of certainty was indicated by smaller P values. The expected activities' Q-squared value is Q2 multiplied by themselves. Pearson-R measures the degree of agreement between the test set's expected and actual activity. The most promising 3D QSAR models for prediction were those that met all of these criteria simultaneously.

Table 1. Assessment of the best pharmacophore hypothesis ARR.1 using partial Least Squares

S. No.	# Factors	SD	R-Squared	F	P	Stability	RMSE	Q-Squared	Pearson-R
1	1	0.7851	0.5544	27.4	3.014e-005	0.6157	0.8218	0.4809	0.7716
2	2	0.5422	0.7972	41.3	5.313e-008	0.3104	0.6054	0.7183	0.8589
3	3	0.2807	0.9482	122.1	5.006e-013	0.1769	0.5096	0.8003	0.9302
4	4	0.1265	0.99	470.6	1.033e-018	0.094	0.5284	0.7854	0.9111

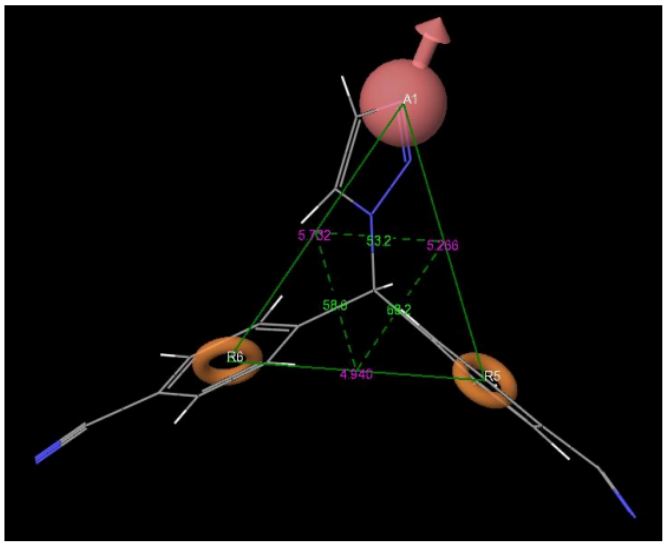
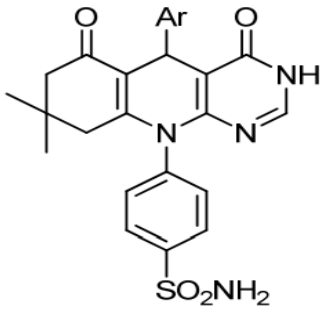


Figure 2. Potential structure of a pharmacophore

Table 2: Analysis of compounds 6a and 6b using microscopy and physical data

Compd. No.	Ar	M.p. (˚C)	Yield (%)	Mol. Formula(M. wt.)	Microanalysis	
					Calculated	Found
6a	C_6H_4F-4	282-4	86	$C_{24}H_{23}FN_4O_3S$ (466.53)	C: 61.79 H: 4.97 N: 12.01	C: 61.91 H: 4.73 N: 11.80
6b	C_6H_4Cl-4	280-2	85	$C_{24}H_{23}ClN_4O_3S$ (482.98)	C: 59.68 H: 4.80 N: 11.60	C: 59.92 H: 5.00 N: 11.33

5-[5-(4-fluorophenyl)-8,8-dimethyl-4,6-dioxo-3,4,6,7,8,9-hexahydro-pyrimido[4,5-b]quinolin-10(5H)-yl]`(7a) benzenesulfonamide and 4–[5-(4-chlorophenyl)-8,8-dimethyl-4,6-dioxo-3,4,6,7,8,9-hexahydropyrimido[4,5- b]quinolin-10(5H)-yl]isothiocyanate (7b)



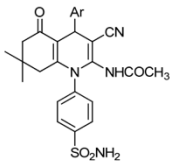
(7a & 7b)

After refluxing a solution of compound 6a or 6b (0.001 mol) in 20 ml of formic acid for 5 hours, cooling the mixture, and 7a and 7b were produced when the ensuing solid was crystallised from dioxane after it was ultimately poured into cold water.

Table 3: Microanalysis and physical data of molecules 7a and 7b

Compd. No.	Ar	M.p. (°C)	Yield (%)	Mol. Formula (M. wt.)	Microanalysis	
					Calculated	Found
7a	C_6H_4F-4	168-70	79	$C_{25}H_{23}FN_4O_4S$ (494.54)	C: 60.72 H: 4.69 N: 11.33	C: 60.82 H: 4.84 N: 11.49
7b	C_6H_4Cl-4	162-4	78	$C_{25}H_{23}ClN_4O_4S$ (510.99)	C: 58.76 H: 4.54 N: 10.96	C: 58.94 H: 4.38 N: 11.18

1,4,5,6,7,8-hexahydroquinolin-2-yl -[3-Cyano-4-(4-fluorophenyl)-7,7-dimethyl-5-oxo-1-(4-sulfamoyl-phenyl)] Eighthly, acetamide in addition to N-[4-(4-chlorophenyl)-3- cyano-7,7-dimethyl-5-oxo-1-(4-sulfamoylphenyl)-1,4,5,6,7,8-hexahydroquinolin-2-yl]8-benzoic acid



(8a & 8b)

For the preparation of 8a and 8b, respectively, after a solution of compound 6a or 6b (0.001 mol) was refluxed in 20 ml of acetic anhydride for 5 hours, the reaction mixture was concentrated. The solid that had separated was then crystallised from ethanol.

Table 4: Analysis of compounds 8a and 8b using microscopy and physical data

Compd. No.	Ar	M.p. (°C)	Yield (%)	Mol. Formula(M. wt.)	Microanalysis	
					Calculated	Found
8a	C_6H_4F-4	150-2	97	$C_{26}H_{25}FN_4O_4S$ (508.56)	C: 61.40 H: 4.95 N: 11.02	C: 61.68 H: 5.11 N: 10.83
8b	C_6H_4Cl-4	149-51	82	$C_{26}H_{25}ClN_4O_4S$ (525.02)	C: 59.48 H: 4.80 N: 10.67	C: 59.31 H: 5.05 N: 10.49

Results

3D QSAR

The ARR three-point pharmacophore model consists of one hydrogen bond acceptor (A) and two aromatic rings (R). Based on the hypothesis for pharmacophore-based alignment, the 3D-QSAR model was able to predict the performance of both the training and test sets.

By examining the 3DQSAR model that is shown in the Workspace (Figure 4.8), one may determine whether ligand properties

have a favourable or negative impact on the anticipated activity. This 3D QSAR model represents letrozole in its prototype form. The presence of oxygen and nitrogen in the blue cubes on the hydrogen bond acceptor area suggests an ideal setting for the attachment of these atoms, which in turn has a beneficial effect on biological activity. A less-than-ideal environment for attaching functional groups, as shown in the red cubes just outside the H-bond acceptor zone, has a deleterious impact on biological activity. Vector characteristics, such as aromatic rings and acceptors, have a significant influence in the aligned structures, as seen by greater vector score values. Overlapping van der Waals models of non-hydrogen atoms determine the volume score of each pair of structures. In order to boost the efficacy of the ligand, a hydrogen bond acceptor (A)—which might be either nitrogen or oxygen—is required.

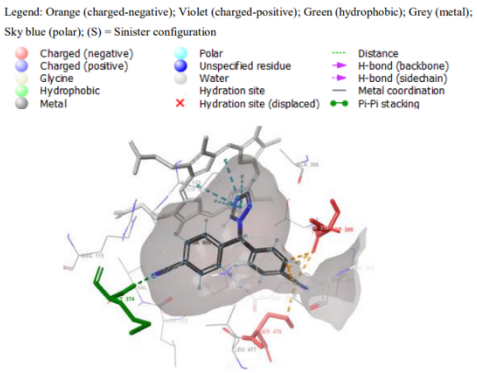
Table 5. Novel chemotypes' 3D QSAR findings (compound 35-66)

S.No.	Ligand	Predicted Activity	Align Score	Vector Score	Volume Score	Fitness
1	35	0.8697	0.043914	0.923434	0.553571	2.440411
2	36	-0.80296	0.256423	0.784339	0.442922	2.013576
3	37	-0.80296	0.2564	0.784376	0.454333	2.025042
4	38	-0.80296	0.256671	0.784165	0.457547	2.02782
5	39	-0.80296	0.256245	0.78448	0.456471	2.027413
6	40	0.737991	0.044625	0.923212	0.425	2.311024
7	41	0.852453	0.043946	0.923415	0.563636	2.450429
8	42	-0.73642	0.256497	0.784367	0.464115	2.034734
9	43	-0.73642	0.25638	0.784372	0.460808	2.03153
10	44	-0.70664	0.277472	0.772249	0.478673	2.019696
11	45	0.800144	0.277472	0.772249	0.478673	2.019696
12	46	-0.7974	0.043947	0.92334	0.570552	2.457269
13	47	-0.7974	0.25642	0.784365	0.468599	2.03928
14	48	-0.7974	0.256828	0.784019	0.454333	2.024329
15	49	-0.76701	0.256095	0.784621	0.465228	2.036436
16	50	0.965794	0.428475	0.805351	0.5075	1.955788
17	51	-0.47892	0.066766	0.949119	0.566265	2.459746
18	52	-0.81155	0.407089	0.839301	0.453488	1.953549
19	53	-0.69853	0.407735	0.839245	0.447005	1.946471
20	54	-0.59219	0.40921	0.839001	0.450935	1.948927
21	55	0.633341	0.406863	0.834213	0.44213	1.93729
22	56	-0.66154	0.066775	0.9491	0.583851	2.477305
23	57	-0.654	0.417373	0.760761	0.459135	1.872085
24	58	-0.654	0.407764	0.839176	0.455399	1.954771
25	59	-0.654	0.407765	0.839127	0.46747	1.966792
26	60	0.791436	0.4078	0.839162	0.472019	1.971348
27	61	0.767623	0.044013	0.923331	0.561934	2.448587
28	62	-0.61032	0.066866	0.949051	0.582043	2.475373

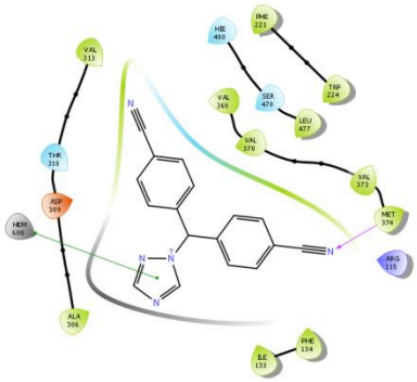
Docking Results

In order to enhance the interactions between ligands and receptors, the maestro workspace's Glide XP Visualiser was used to construct the active site surface mesh. Among the intriguing discoveries is the geometry of the aromatase receptor site. It resembles a standard iodine flask in appearance. The active cite is hydrophobic

and has a conical entrance composed of L-phenylalanine 221 and L-Valine 313. The flat base of the flask, formed by the heme prosthatic group (grey), is essential for aromatisation because it provides electrons to the substrate.



Letrozole 3D docking



Letrozole 2D docking

Biological Activity

- **In vitro anticancer screening**

The pharmacology branch of Cairo University's National Cancer Institute carried out the in vitro anticancer screening. A human tumor breast cell line known as MCF7 was used in this study. The cytotoxic activity of the newly synthesized compounds was evaluated in vitro using the Sulfo-Rhodamine-B stain (SRB) assay, as described by Skehan et al. One of the most used approaches of in vitro cytotoxic screening is the SRB test, which has been around since 1990. Tested here is SRB's binding affinity for trichloroacetic acid (TCA)-fixed cell protein components on tissue-culture plates. In somewhat acidic circumstances, the bright-pink aminoxanthene dye SRB binds to basic amino acid residues, but in basic conditions, it dissociates. The dye contains two sulfonic groups.

Before being treated with the compound(s) under investigation, cells were allowed to adhere to the plate wall by plating them on a 96-well plate (10 4 cells/well) for 24 hours. For every concentration, three separate wells were made. The cells were left to incubate with the substance(s) for 48 hours at 37 ˚C in a 5% CO2 environment. Following the passage of 48 hours, the cells were fixed, washed, and stained for 30 minutes with a solution containing 0.4% (wt/vol) SRB in 1% acetic acid. It took four washes with 1% acetic acid to get rid of the excess unbound color, and then Tris-EDTA buffer helped get the attached stain back. The 570 nm wavelength was used to detect the colour intensity in an ELISA reader.

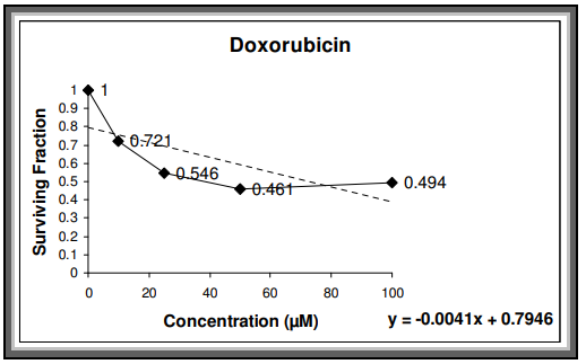


Figure 3: Time to death plot for doxorubicin

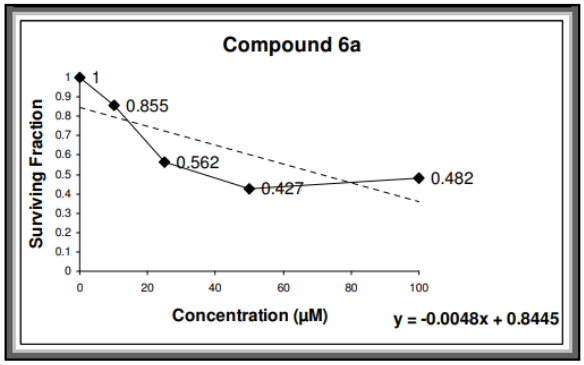


Figure 4 Time required for component 6a to degrade

Conclusion

Recent advances in the synthesis of derivatives with anticancer qualities incorporating heterocyclic rings have been the primary topic of this study, with an emphasis on the creation of target based anticancer medicines. Anticancer medicines' pharmacokinetic and pharmacodynamic qualities are enhanced by the presence of heterocyclic moieties, which are found in the majority of medications. One or more heterocyclic rings comprising oxygen, nitrogen, and sulphur are present in about 30% of the anticancer medications authorised by the FDA. In the metabolism of all living things, heterocyclic moieties are involved in a great number of the metabolic reactions that are essential to life. About two-thirds of the anticancer medications authorised by the FDA in the first half of the decade included them, demonstrating their central position in cancer research and the battle against cancer. Recent breakthroughs in the use of heterocyclic compounds as anticancer medicines and a novel approach to the development of such compounds have also been the focus of these endeavours.

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