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Computational pharmacokinetic analysis on some newly designed 2-anilinopyrimidine derivative compounds as anti-triple-negative breast cancer drug compounds

Hadiza Lawal Abdulrahman*, Adamu Uzairu and Sani Uba

Abstract

Introduction: Worldwide, cancer of the breast is the most commonly diagnosed disease and the second leading cause of cancer-related mortality amongst women yearly (Miller et al., 2016). Computer-aided drug discovery (CADD) is a fundamental shortcut in drug discovery arena. CADD tools ascertain key molecule for testing, predicting the effectiveness, the possible side effect, and also assist in upgrading drug-likeliness of drug molecules (Leelananda and Lindert, 2016). The propose of carrying out this research is to design new 2-anilinopyrimidine derivative compounds based on the interaction of the derivative compounds (ligand) and thyroid hormone receptor (TRβ1), and also analyze their pharmacokinetic properties as drug compounds that would be used by the pharmaceuticals against triple-negative breast cancer (MDA-MB-468 cell line).

Results: Three compounds (12, 17, and 18) had the highest docking score ranging from − 7.3 to − 7.4 kcal/mol. This showed that the compounds (ligands) bind tightly with the active site of the thyroid hormone receptor (TRβ1). Based on their tight interactions with the receptor, the compounds were chosen as lead compounds in the design of fourteen new compounds by incorporating some fragments found to bind intensely with the active site of the thyroid hormone receptor (TRβ1). All the newly designed compounds passed the pharmacokinetic analysis (adsorption, distribution, metabolism, excretion, and other physicochemical test) passed the drug-likeness test, and they also adhered to the Lipinski rule of five.

Conclusions: New derivative compounds of 2-anilinopyrimidine against MDA-MB-468 cell line were designed based on the information obtained from the molecular docking studies. Furthermore, the pharmacokinetics analysis (adsorption, distribution, metabolism, excretion (ADME) and other physicochemical properties) carried out on the newly designed compounds showed this compounds can be made into oral drugs for patients with triple-negative breast cancer (MBA-MD-468 cell line) as they serve as most promising inhibitors against thyroid hormone receptor (TRβ1).

Keywords: Molecular docking studies, 2-anilinopyrimidine, MDA-MB-468 cell line, Thyroid hormone receptor (TRβ1), Structure-based design, Pharmacokinetic analysis

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Introduction

Mammary tumor is a tumor initiating from the mammary tissues, frequently from the inside lining of milk ducts or the lobules that supply the ducts with milk (Sharma et al., 2010). Worldwide, breast cancer is the commonly identified disease and the second cancer-related mortality amongst the women folk yearly (Miller et al., 2016). Breast cancer can be categorized into invasive and non-invasive types; non-invasive breast cancer is a cancer type that does not stretch out of the lobule or ducts where it situated (estrogen receptor (ER)-/progesterone receptor (PR)- positive type (~ 80%) and human epidermal growth factor receptor 2 (HER2+) positive type (~ 5%)) while the invasive breast cancer type extends into the neighboring tissues outside the milk duct (triple-negative type (10–15%)) (Akram et al., 2017).

The traditional process of discovering and developing drugs is very costly and consumes a lot of time. Traditional methods of drug findings depend on a step by step synthesis and filtering of many molecules to find a lead molecule (Kapetanovic, 2008).

Computer-aided drug discovery (CADD) and design confirms the best potential compound; it reduces the cost related to discovering a drug, and it also reduces the time taken for a drug to get to the consumer market. It is a fundamental shortcut in the drug discovery arena. CADD tools ascertain potential molecule to be tested, predicting the efficacy, the possible side effect, and also aid to upgrade the drug-likeliness of drug molecules (Leelananda and Lindert, 2016). The frequently used CADD techniques are the structure-based drug discovery (SBDD). The propose is to obtain ligands with specific electrostatic and physicochemical properties to gain higher docking score. In SBDD, the therapeutics are designed based on the information of the crystalized macromolecule also known as a receptor (Ferreira et al., 2015).

There are lots of drug compounds that do not pass the drug-likeness analysis. Efficiency and safety of the drug to the human system are the main cause of drug failure, which indicates the absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties of molecules plays an essential role in every stage of drug discovery and development. Therefore, it is compulsory to find potent molecules with better ADMET properties (Guan et al., 2019).

Recently, thirty derivative compounds of 2-anilinopyrimidine were reported by Jo et al., 2019 as inhibitors against MDA-MB-468 cell line. This study is aimed to design new derivative compounds based on the interaction of the derivative compounds (ligand) and thyroid hormone receptor (TRβ1), and also analyze their pharmacokinetic properties as drug compounds that would be used by the pharmaceuticals against triple-negative breast cancer (MDA-MB-468 cell line).

Methods

Data collection

Thirty (30) novel derivative compounds of 2-anilinopyrimidine with their inhibitory concentration (IC_{50}), against triple breast cancer (MDA-MB-468) cell line, were acquired from (Jo et al., 2019) reports. Figure 1 shows the template of the 2-anilinopyrimidine derivatives compounds while Table 1 shows the structures that was attached to the Fig. 1.

Molecular docking studies

2-Anilinopyrimidine derivative compounds (Table 1) underwent molecular docking studies with the thyroid hormone receptor (TRβ1). The crystal structure was obtained from RCSB PDB (https://www.rcsb.org) with the ID, 1Y0X. The docking scores of the ligand-receptor complex were calculated with Autodock Vina of the Pyrx software (Abdulfatai et al., 2018; Abdullahi et al., 2019). Visualizer of Discovery Studio was used to understand the ligand-protein target interactions.

Computational pharmacokinetics (drug-likeness)

The SwissADME, a free web tool used in evaluating the pharmacokinetics, drug-likeness (physicochemical and ADME properties) and medicinal chemistry friendliness of small molecules (Diana et al., 2017) was used in testing the drug-likeness of the newly designed compounds. Furthermore, some physicochemical properties and positive controls of the designed compounds were checked using the on-line tool for their familiarity with Lipinski's

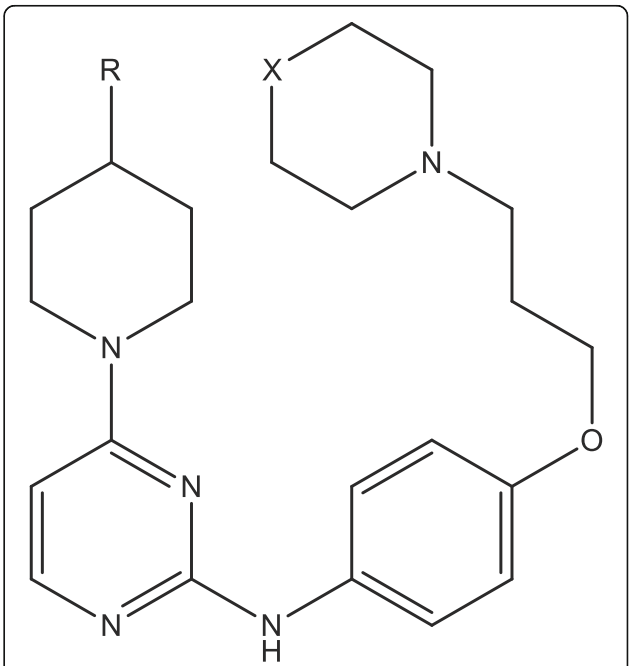


Fig. 1 Template of 2-anilinopyrimidine derivatives

Table 1 : 2-anilimopyrimidine derivatives compounds

Structure	R	X
1	H	O
2	-	O
3	-	S
4	-	CH_2
5	-	O
6	-	S
7	-	CH_2
8	-	O
9	-	S
10	-	CH_2
11	H	O
12	H	CH_2
13	Me	O
14	Me	S
15	Cl	CH_2
16	Cl	O
17	Cl	S
18	Cl	CH_2
19	-	O
20	-	S
21	-	CH_2
22	-	O
23	-	S
24	-	CH_2
25		-
26		-
27		-
28		-
29		-
30		-

Table 2 Binding affinities, interaction types, bond types, and bond distances between some compounds and the receptor

Complex	Binding affinity (kcal/mol)	Amino acid	Bond type	Interaction	Distance (A^0)
30	− 5.9	LEU360	Hydrogen bond	Conventional hydrogen bond	2.19527
		LEU360	Hydrogen bond	Conventional hydrogen bond	2.08848
		VAL319	Hydrogen bond	Carbon hydrogen bond	3.03818
		SER361	Hydrogen bond	Pi-donor hydrogen bond	3.21568
		VAL319	Hydrophobic	Alkyl	5.40031
		TRP239	Hydrophobic	Pi-alkyl	5.30319
		TRP239	Hydrophobic	Pi-alkyl	4.57531
12	− 7.2	GLY432	Hydrogen bond	Conventional hydrogen bond	2.96575
		GLY432	Hydrophobic	Amide-Pi stacked	3.88004
		ILE303	Hydrophobic	Alkyl	5.23513
		LYS306	Hydrophobic	Alkyl	4.84663
		ARG383	Hydrophobic	Alkyl	5.07109
		PRO384	Hydrophobic	Alkyl	5.29712
		ALA433	Hydrophobic	Pi-alkyl	4.14051
		ALA436	Hydrophobic	Pi-alkyl	5.48801
18	− 7.3	GLU311	Hydrogen bond	Conventional hydrogen bond	2.10982
		ARG429	Hydrogen bond	Conventional hydrogen bond	2.68544
		GLY307	Hydrogen bond	Conventional hydrogen bond	2.97669
		GLU311	Hydrogen bond	Conventional hydrogen bond	2.85424
		VAL458	Hydrogen bond	Carbon hydrogen bond	3.34145
		ILE303	Hydrophobic	Alkyl	5.28774
		LYS306	Hydrophobic	Alkyl	4.9622
		ARG383	Hydrophobic	Alkyl	5.40494
		PRO384	Hydrophobic	Alkyl	4.84454
		PRO384	Hydrophobic	Alkyl	5.15235
		ALA436	Hydrophobic	Pi-alkyl	4.91503
15	− 7.4	GLU311	Hydrogen bond	Conventional hydrogen bond	2.15506
		ARG429	Hydrogen bond	Conventional hydrogen bond	2.57929
		GLU311	Hydrogen bond	Conventional hydrogen bond	2.76094
		VAL458	Hydrogen bond	Carbon hydrogen bond	3.37649
		ILE303	Hydrophobic	Alkyl	5.43788
		LYS306	Hydrophobic	Alkyl	5.04683
		ARG383	Hydrophobic	Alkyl	5.3858
		PRO384	Hydrophobic	Alkyl	5.11068
		PRO384	Hydrophobic	Alkyl	4.78448
		PRO384	Hydrophobic	Alkyl	4.75312
17	− 7.4	GLY432	Conventional hydrogen bond	Alkyl	2.88081
		GLY432	Carbon hydrogen bond		3.57426
		GLY432	Hydrophobic	Alkyl	3.93288
		ILE303	Hydrophobic	Alkyl	5.3903
		LYS306	Hydrophobic	Alkyl	5.01206
		ARG383	Hydrophobic	Alkyl	4.96917
		PRO384	Hydrophobic	Alkyl	5.19799
		ARG429	Hydrophobic	Alkyl	5.05991
		MET430	Hydrophobic	Alkyl	5.44203
		ALA433	Hydrophobic	Pi-alkyl	4.23025
		ALA436	Hydrophobic	Pi-alkyl	5.44549

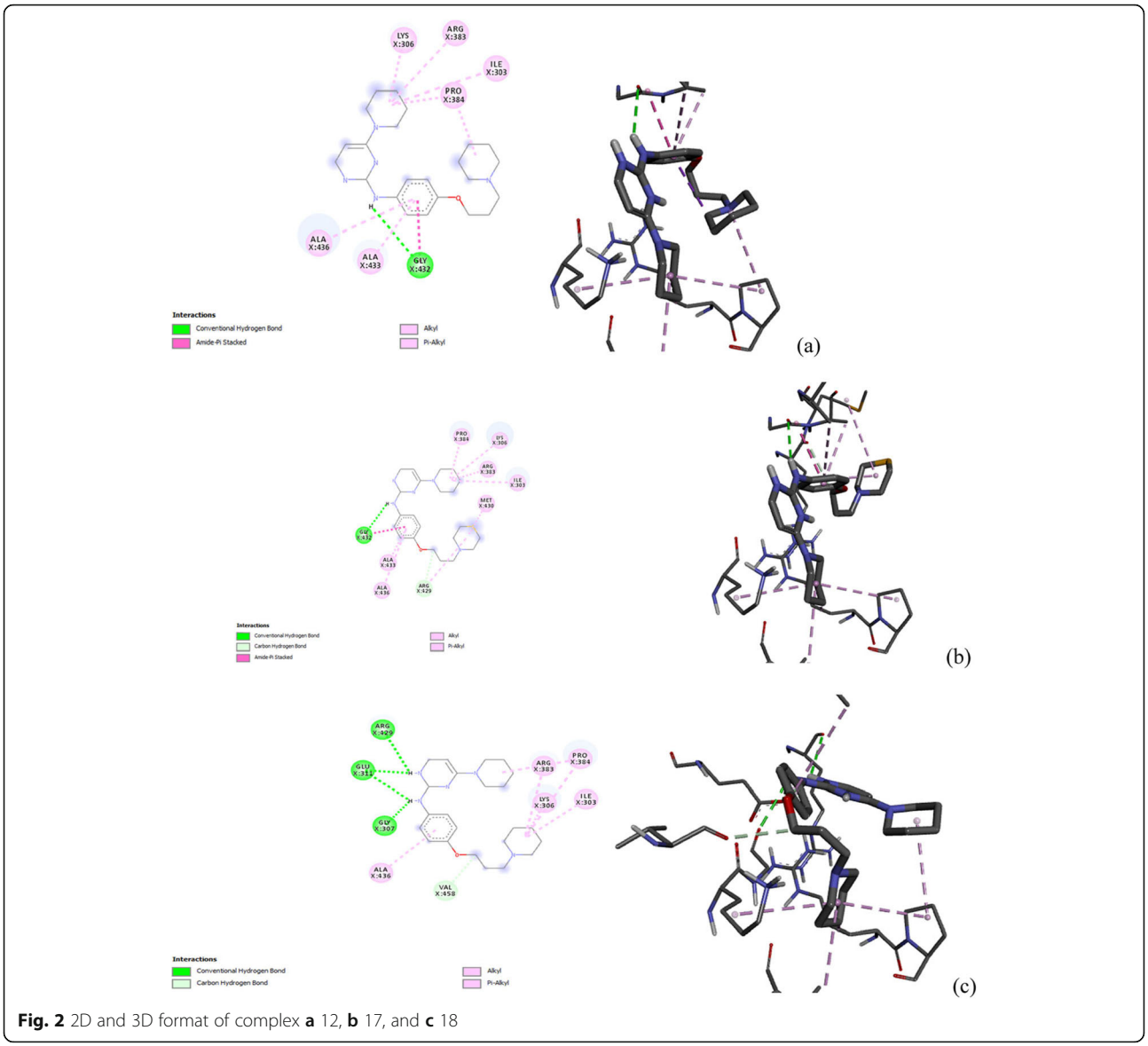


Fig. 2 2D and 3D format of complex **a** 12, **b** 17, and **c** 18

rule of five (Hou et al., 2019). Lipinski and co-workers proposed the "Rule of Five" in 1997, which was the geniune- and most famous rule-based filter for drug-likeness of a molecule, distinguishing whether a molecule can be orally absorbed well or not, following the criteria: molecular weight (MW) ≤ 500, octanol/water partition coefficient (AlogP) ≤ 5, number of hydrogen bond donors (HBDs) ≤ 5, and number of hydrogen bond acceptors (HBAs) ≤ 10.6. According to the rule of five, a compound fails to be active orally when it breaks two or more rules out of the Lipinski's rule of five (Guan et al., 2019).

Results

Table 2 shows a summary of the docking scores, the various interactions (hydrogen and hydrophobic), and their bond lengths that occurred between some selected 2-anilinopyrimidine derivatives compounds (ligand) that had the highest docking scores and the amino acid residues of the thyroid hormone (TRβ1) receptor. The docking scores of the ligand-receptor to form a complex were calculated with Autodock Vina of the Pyrx software and visualized using the Discovery Studio Software. Figure 2 showed the ligand-receptor interaction of complexes 12, 17, and 18 in both 2D and 3D format.

Structure-based design

Using the results obtained from the molecular docking studies, compounds 12, 17, and 18 had the highest docking scores and were used in the design of fourteen (14) new 2-anilinopyrimidine derivative compounds using the structure-based design technique, based on the information obtained from the binding site of the crystalized

macromolecule known as a receptor. The newly designed compounds are shown in Table 3.

Computational pharmacokinetic analysis (physicochemical and ADME properties) of the newly designed 2-anilinopyrimidine compounds

All the newly designed compounds were tested for their drug-likeliness "drug-likeliness, assess quantitatively the chance for a molecule to become an oral drug with respect to bioavailability." SwissADME on-line software was used to ascertain the drug-likeness of the designed compounds before the can proceed to pre-clinical trials. Table 4 shows the pharmacokinetic results of the designed compounds. Figure 3 shows the bioavailability radar of molecules 3, 12, and 14. The bioavailability radar gives a main scan at the drug-likeness of a compound (Diana et al., 2017).

Discussion

Molecular docking studies

Molecular docking on compounds of 2-anilinopyrimidine with the protein target, thyroid hormone receptor (TRβ1), was performed. Amongst all the derivatives, compounds 12, 15, 17, 18, and 30 had high docking scores ranging from − 5.9 to − 7.4 kcal/mol. The visual examination of the docked complexes was carried out by a careful examination of hydrogen bond interaction, hydrogen bond length, and hydrophobic interaction.

Compound 12 exhibited hydrogen bonding with GLY432 (2.96575 A^0) amino acid residue. Furthermore, the pi-orbital containing delocalized electrons in the benzene ring interact with the alkyl groups of ILE303 (5.23513 A^0), LYS306 (4.84663 A^0), ARG383 (5.07109 A^0), PRO384 (5.29712 A^0), ALA433 (4.14051 A^0), and ALA436 (5.48801 A^0) amino acid residue to form hydrophobic bond.

Compound 18 also showed the same hydrogen bonding with amino acid residues of GLU311 (2.10982 A^0), ARG439 (2.68544 A^0), GLY307 (2.97669 A^0), GLU311 (2.85424 A^0), and carbon hydrogen bonding with VAL458 (3.34145 A^0). Also, the compound formed hydrophobic bond with the amino acids of ILE303 (5.28774 A^0), LYS306 (4.9622 A^0), ARG383 (5.40494 A^0), PRO384 (4.84454 A^0 and 5.15235 A^0), and ALA436 (4.91503 A^0).

Compound 17 also showed two hydrogen bonding with GLY4432 (2.88081 and 3.57426 A^0) of the active site of the receptor. The derivative also formed hydrophobic bonds (3.93288, 5.3903, 5.01206, 4.96917, 5.19799, 5.05991, 5.44203, 4.23025, and 5.44549 A^0) with amino acids of GLY432, ILE303, LYS306, ARG383, PRO384, ARG429, MET430, ALA433, and ALA436 of the protein target. The carbonyl of the compound attached to 3-methylenedihydrofuran-2(3H)-one act as a hydrogen acceptor to form one hydrogen bond with LSY134.

Table 3 Newly designed 2-anilinopyrimidine compounds against MBA-MB-468 cell line

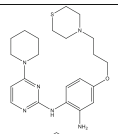
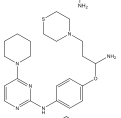
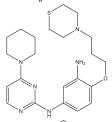
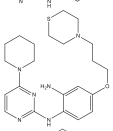
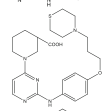
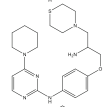
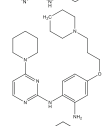
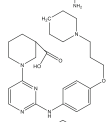
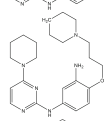
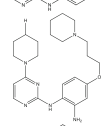
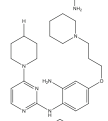
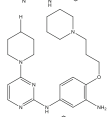
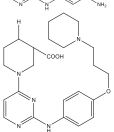
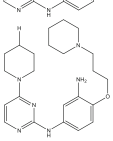
No.	Structure	New binding affinity (kcal/mol)
1		-7.8
2		-7.6
3		-7.6
4		-7.8
5		-7.7
6		-7.8
7		-8.0
8		-7.9
9		-7.7
10		-7.4
11		-7.5
12		-7.6
13		-7.5
14		-7.5

Table 4 Pharmacokinetic properties of the newly designed 2-anilinopyrimidine compounds against MDA-MB-468 cell line

No.	MW (g/mol)	nHA	nRA	HBA	HBD	MR	TPSA	iLOGP	BBB	PAINS	Brenk
17a	428.59	12	8	4	2	133.05	104.84	3.77	No	0	1
17b	428.59	12	8	5	2	131.35	104.84	3.67	No	0	1
17c	425.59	12	8	4	2	133.05	104.84	3.66	No	0	1
17d	428.59	12	8	4	2	133.05	104.84	3.77	No	0	1
17f	457.59	12	9	6	2	135.23	116.12	3.53	No	0	1
18a	410.56	12	8	4	2	130.54	79.54	3.87	No	0	1
18b	439.55	12	9	6	2	132.44	90.82	3.67	No	0	0
18c	410.56	12	8	4	2	130.27	79.54	3.97	No	0	1
17h	428.59	12	8	5	2	131.35	104.84	3.87	No	0	0
12a	410.56	12	8	4	2	130.27	79.54	3.87	No	0	1
12b	410.56	12	8	4	2	130.27	79.54	3.87	No	0	1
12c	410.56	12	8	4	2	130.27	79.54	3.97	No	0	1
12d	439.55	12	9	6	2	132.44	90.82	3.67	No	0	0
12e	410.56	12	8	4	2	130.27	79.54	3.97	No	0	1

MW molecular weight (< 500mg/mol), *nAH* number of aromatic heavy atoms, *nRB* number of rotatable bonds, *HBA* hydrogen bond acceptors, *HBD* hydrogen bond donors, *MR* molecular refractivity, *TPSA* topological polar surface area, *BBB* blood-brain barrier

All the compounds showed the same hydrogen bond and hydrophobic bond interactions with the amino acid residues of the receptor at different distances. The binding affinity of the ligands was higher than that of the standard drug Gefitinib (– 5.3 kcal/mol). From the compounds interaction with the receptor, it proves the ability of the compounds to inhibit thyroid hormone (TRβ1) receptor.

Structure-based design

Compounds 12, 17, and 18 were chosen as lead compounds because they had the highest docking scores. The ligand-receptor interactions as shown in Fig. 2 indicate the points of interactions between the compounds and the amino acid residues of the receptor. Therefore, modifications were made on the lead compounds by incorporating some fragments found to bind intensely with the active-site of thyroid hormone (TRβ1) based on the mode of interactions that occurred between the ligand and receptor as shown in Table 3.

Pharmacokinetics analysis (physicochemical and ADME properties) of the newly designed 2-anilinopyrimidine compounds

All the fourteen (14) designed compounds passed the drug-likeliness test as shown in Table 4; they also passed the Lipinski rule of five, a criteria used as a guide in drug design (the molecules that adhere to three rules out of the four rules are said to obey to Lipinski rule (Diana et al., 2017)). The gastrointestinal absorption of all the new compounds was found to be high, making the compounds a breakthrough in finding the cure for triple-negative breast cancer.

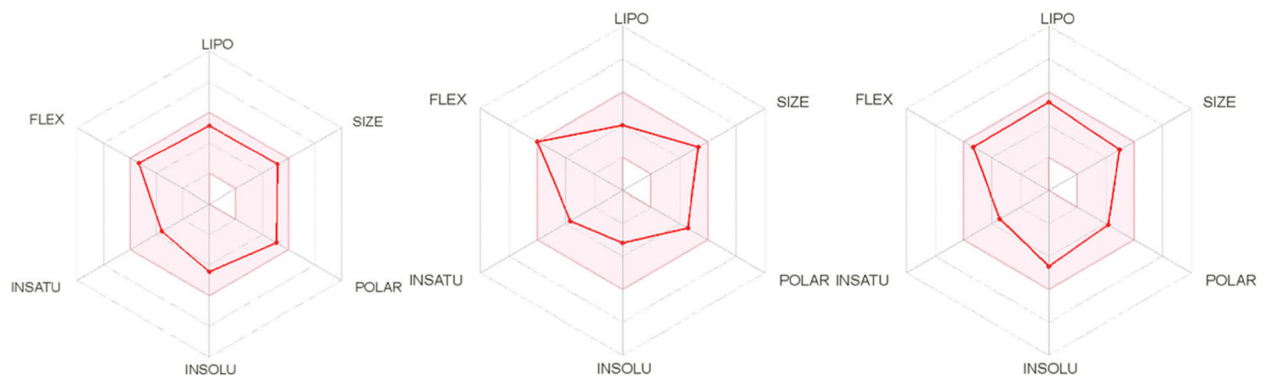


Fig. 3 The bioavailability radar for compounds 3, 13, and 14

Conclusion

New derivative compounds of 2-anilinopyrimidine against MDA-MB-468 cell line were designed based on the information obtained from the molecular docking studies. Molecular docking studies were used in understanding the interaction in details between the compounds (ligands) and thyroid hormone receptor (TRβ1). From the docking score, compounds 12, 17, and 18 were used as lead compounds in designing twelve new derivative compounds due to their high docking scores. Modifications were made on the lead compounds by incorporating some fragments found to bind intensely with the active site of the receptor (TRβ1).

Furthermore, the pharmacokinetics analysis (ADME and other physicochemical properties) carried out on the newly designed compounds showed this compounds can be made into oral drugs for patients with triple-negative mammary tumor (MBA-MD-468 cell line) because they passed the drug-likeness test, and they also obey the Lipinski rule of five. This gives a great development to rescuing the female race by developing more effective anti-breast cancer drug to concur this deadly disease.

Abbreviations

IC_{50}: Inhibitory concentration; TRβ1: Thyroid hormone receptor; ADMET: Adsorption, distribution, metabolism, excretion, and toxicity; MW: Molecular weight (< 500mg/mol); nAH: Number of aromatic heavy atoms; nRB: Number of rotatable bonds; HBA: Hydrogen bond acceptors; HBD: Hydrogen bond donors; MR: Molecular refractivity; TPSA: Topological polar surface area; BBB: Blood-brain barrier

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Authors' contributions

HAL gathered the data sets and analyzed it computationally in accordance with the methodology to get a model of high performance and was a major contributor in drafting the manuscript. AU carried out statistical analysis on the model to ensure its stability and also participated in the write up, and SU re-edited the work and ensured it conforms with the manuscript's guide. All the authors read and approved the final manuscript.

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Availability of data and materials

Not applicable

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Competing interests

The authors declare no conflict of interest.

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