Research Square

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Phytochemical Screening and Computational Evaluation of Artemisia maciverae Compounds Targeting HER2 in Breast Cancer

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Abstract

Introduction

Breast cancer remains a leading cause of cancer-related mortality among women worldwide. Although HER2-targeted therapies have improved outcomes, drug resistance and toxicity limit their long-term effectiveness. *Artemisia maciverae* is traditionally used in northern Nigeria for the treatment of cancer, but its phytochemical profile and molecular activity against HER2 remain poorly characterized. This study investigated the phytochemical constituents of the methanol leaf extract of *A. maciverae* and evaluated their potential HER2 inhibitory activity using computational approaches.

Methodology

Leaves of *A. maciverae* were extracted with 70% methanol by cold maceration. Phytochemical constituents were identified using GC-MS. The HER2 receptor (PDB: 3POZ) was prepared, and molecular docking was performed using Glide (HTVS, SP and XP). Binding free energy was estimated using MM-GBSA, while pharmacokinetic and toxicity properties were predicted using QikProp and ADMETlab.

Results

GC-MS analysis identified 22 phytochemical compounds. Virtual screening selected six lead compounds for extra-precision docking. The best-performing compounds included 1,1'-Bis(cyclooct 2-en-4-one), 3-Methyl-4-(phenylthio)-2-prop-2-enyl-2,5-dihydrothiophene 1,1-dioxide, 9,10-Anthracenedibutanol, 9,10-dihydro-, 4,4-Dimethyl-3-oxopentanenitrile and Benzo[h]quinoline, 2,4-dimethyl. MM-GBSA analysis indicated favorable binding energies, and ADMET predictions showed that all lead compounds complied with Lipinski's rule and exhibited acceptable pharmacokinetic profiles and manageable predicted toxicity.

Conclusion

The study demonstrates that *Artemisia maciverae* contains phytochemicals with promising *in silico* affinity for the HER2 receptor. These findings support the plant's ethnomedicinal use and suggest that the identified compounds could serve as lead molecules for anti-breast cancer drug development. Experimental *in vitro* and *in vivo* validation is recommended.

1. Introduction

Breast cancer is the second most common malignant tumor in the world, with a high mortality and morbidity rate[1]. It is the most common cancer in women in 157 out of 185 countries, causing 670,000 deaths worldwide by 2022. The vast repercussions of breast cancer, including its financial, physical, emotional, and societal costs and challenges, make it one of the major public health problems [2, 1]. Despite progress in the development of cancer drugs, the number of deaths from cancer is rising. This is due in particular to the side effects of anti-cancer drugs, linked to their non-selectivity, and to the development of resistance to these drugs [3]. This is why the search for new anti-cancer drugs capable of overcoming all these barriers, including toxicity, resistance, and accessibility (especially for developing countries), constitutes a major objective of anti-cancer pharmacology research.

Human epidermal growth factor receptors (HER), including HER1 (also known as EGFR), HER2, HER3, and HER4, play a central role in regulating cell proliferation, survival, differentiation, and migration. Their overexpression is recognised as one of the most common cellular disorders associated with a wide variety of tumors [4] [5]. Several drugs have been approved in recent decades, including Erlotinib, Gefitinib, Lapatinib, Trastuzumab, and Pertuzumab, demonstrating the importance of this therapeutic target [6].

Phytochemicals are natural compounds found in plants [7]. They represent one of the main sources of drugs. More than 60% of clinically approved anti-cancer drugs come from medicinal plants [8, 9]. Exploiting the cytotoxic potential of natural products of plant origin, therefore, remains a promising avenue for discovering new anti-cancer agents[3].

The genus Artemisia belongs to the Asteraceae family and includes 250 to 500 species and varieties. Artemisia species have been known as medicinal plants and condiments since ancient times. Almost all species contain numerous bitter substances and essential oils [10]. *Artemisia maciverae* is one of the species found in northern Nigeria, where it is locally known as "Tazargade" in the Hausa language. The Hausa people of northern Nigeria use this plant to treat malaria as well as several types of cancer, including breast cancer [11]. Although the plant is used by the population to treat breast cancer, the phytochemical compounds have not been identified, and the assessment of its pharmacological activity has never been validated. This study aims to identify the phytochemical compounds present in *A.maciverae* and to evaluate their anti-cancer potential by targeting HER2 using a computational modelling approach against breast cancer.

2. Materials and methods

2.1. Plant Preparation and Extraction

The plant was collected in August 2025 in Samaru, Zaria Local Government Area, Kaduna State, Nigeria using standard plant collection procedures. It was identified and authenticated by Dr Namadi Sanusi of the Herbarium Unit of the Department of Botany, Ahmadu Bello University, Zaria. A voucher number (ABUH06883) was assigned to the specimen after comparison with an existing sample. The plant was then dried in the shade (room temperature) and ground to a fine powder using a pestle and mortar. A total of 926 g of powder was extracted with 9.26 litres of solvent (70% methanol) at a ratio of 1:10, by

cold maceration for 72 hours with intermittent mechanical agitation. The maceration was then filtered using Whatman No. 1 filter paper, and the filtrate obtained was dried in a water bath at 50°C [12].

2.2. Phytochemical Screening

The phytochemical screening of MLEAM was carried out using the methods described by Evans and Trease. The presence of tannins, flavonoids, saponins, Terpenoids, alkaloids, cardiac glycosides, steroids, phenolic compounds, and anthraquinones was tested [13].

2.3. Gas Chromatography-mass Spectrometry

Analysis by gas chromatography-mass spectrometry (GC-MS) was carried out using a mass spectrum detector (GC 7890B system, 5977A, Agilent Technologies, USA). Chromatography was performed on an HP-5 MS capillary column (30 m × 250 µm × 0.25 µm). High-purity helium was used as the carrier gas, with a continuous flow rate of 3.6839 mL/min and a split-mode injection ratio of 5:1. The chromatograph temperature was started at 50°C for 1 minute, then increased to 200°C at a rate of 3°C/min, then increased to 300°C at the same rate for 15 minutes, and finally maintained at 325°C for 1 minute. Other GC-MS parameters included an ionisation voltage of 70 eV, an ionisation current of 150 µA, and mass spectrum analysis in the range 30–600 m/z. The temperature of the quadrupole and ion source was set at 150°C and 230°C, respectively. The compounds present in the sample (extract) were identified on the basis of standards, isolation, and structural determination using the National Institute of Standards and Technology (NIST) database [14].

2.4. Protein Preparation and Grid Generation

The HER2 (human epidermal growth factor 1 or EGFR) receptor bound cocrystallized ligand was downloaded in its X-ray crystallographic structure from https://www.rcsb.org with ID PDB: 3POZ and a resolution of 1.50 Å, complex with the inhibitor. The protein was imported into the workspace of the Maestro software (Schrödinger suite), then missing loops and chains were filled in using Prime. The water molecules were then removed along with the SO4cofactor during chain refinement. A pH of 7.5 was applied with PROPKA to optimise the protein; water beyond a 5 Å radius was also removed, and the protein was minimised. Using the OPLS3e force field, the energy minimisation process was performed to obtain a lower energy state for the protein[15]. A docking grid was then created at the co-crystallised ligand binding site at the specific coordinates x = 18.32, y=-33.01, and z = 12.28.

2.5. Molecular Docking Analysis

This analysis was carried out using the Glide module of Schrödinger's Maestro interface. Ligands (phytocompounds from *A. maciverae*) previously filtered and prepared via the LigPrep node were docked with the generated receptor grid to study their interactions within the target protein binding site (HER2), highlighting key biochemical processes. The programme was first run in HTVS (High Throughput Virtual Screening) mode for rapid screening; then the highest-scoring molecules were selected for more precise docking in SP mode. Finally, the 6 best-performing compounds were docked in XP (Extra Precision) mode, leading to an in-depth analysis [15].

2.6. Estimation of Binding Energy

This analysis was carried out to provide information on the stability of the complex (LigandProtein) and to determine whether the association between the ligands and the target protein is strong enough to induce a potential biological response. The free binding energy was calculated using Molecular Mechanics-Generalized Born Surface Area (MM-GBSA) with Maestro's Prime module. The five top-ranked compounds, including the standard drug and the cocrystallize ligand, were selected for this analysis.

The free binding energy was calculated with: $\Delta^{Gbind} = G^{complex}X - (G^{protéine} + G^{Ligand})$ [16]

2.7. Pharmacokinetics and Toxicity Analyses

ADMET properties (absorption, distribution, metabolism, excretion, and toxicity) were assessed using Maestro's QikProp module and the admetLAB web server on the 6 six compounds. The parameters: hERG (hERG Blockers), H-HT (Human Hepatotoxicity), and AMES (Ames Mutagenicity) were evaluated to predict associated toxicities[17] (See Fig. 1 workflow).

3. Results

3.1. Phytochemical Screening and GC-MS analysis

Phytochemical screening revealed tannins, saponins, flavonoids, glycosides, terpenoids, steroids, carbohydrates, phenols, and alkaloids. The anthraquinone class was not identified (Table 1). GC-MS analysis identified 22 compounds, as reported in Table 2.

Table 1
Phytoconstituents of MLEAM

Phytochemicals	Test	Inference
Anthraquinones	Bornträger's test	-
Tannins	Bromine water test	+
Saponins	Frothing test	+
Flavonoids	Shinoda test	+
	Alkaline Reagent test	+
Cardiac glycosides	Keller-killiani test	+
Terpenoids	Liebermann-Burchard 's test	+
Steroids	Salkowski test	+
Carbohydrates	Molisch's test	+
Phenols	Lead acetate test	+
Alkaloids	Mayer's test	+
+ = Presence - = Absence		

Table 2
GC-MS results for identified compounds.

PK	RT	Area Pct	Library/ID
1	6.2927	0.1503	.beta.-copaene
2	7.9201	2.0517	Dodecanoic acid, methyl ester
3	9.7512	1.6038	Methyl tetradecanoate
4	10.2624	0.1582	Z-8-Methyl-9-tetradecenoic acid
5	11.6706	7.2371	Hexadecanoic acid, methyl ester
6	12.2885	0.6169	Dibutyl phthalate
7	12.4187	0.5898	Pentanoic acid, 4-methyl-, ethyl ester
8	13.6363	22.2716	9-Octadecenoic acid (Z)-, methyl ester
9	13.9619	7.8318	Methyl stearate
10	14.4509	3.9808	Ambrosin
11	14.5148	12.0839	1,1'-Bis(cyclooct-2-en-4-one)
12	16.7379	0.8438	(Z)-Methyl hexadec-11-enoate
13	16.9629	3.5046	2(1H)-Benzocyclooctenone, decahydro-4a-methyl-, trans-(-)-
14	17.5983	25.7569	3,4-Pentadienal, 2,2-dimethyl-
15	19.3203	0.5198	9,10-Anthracenedibutanol, 9,10-dihydro-
16	19.5622	0.3707	7-Pentadecyne
17	19.7784	2.0881	Bis(2-ethylhexyl) phthalate
18	23.6662	0.2875	2-Methyl-Z,Z-3,13-octadecadienol
19	24.6371	4.5414	4,4-Dimethyl-3-oxopentanenitrile
20	27.6934	2.466	1-Methoxy-3-(2-hydroxyethyl)nonane
21	28.3776	0.8133	3-Methyl-4-(phenylthio)-2-prop-2-enyl-2,5-dihydrothiophene 1,1-dioxide
22	29.3296	0.232	Benzo[h]quinoline, 2,4-dimethyl
RT: Retention Time; **GC-MS**: Gas Chromatography-Mass Spectrometry			

3.2. Prediction Results for Pharmacokinetic and Toxicity Parameters

The ADME (Absorption, Distribution, Metabolism, and Elimination) parameters of the compounds are presented in Table 3 and were assessed using ADME Lab. All compounds were Lipinski-compliant (Table 3).

Table 3
Prediction of pharmacokinetics and toxicity.

Absorption		Distribution		Metabolism			Elimination		Toxicity		
LIGAND	Papp(CACO-2 Permeability) cm/s	HIA(Human Intestinal Absorption)	PPB(Plasma Protein Binding)%	BBB(Blood Brain Barrier)	P450 CYP3A4 substrate	P450 CYP3A4 inhibitor	P450 CYP2C9 inhibitor	T ½(Hr)	Clearance Rate: mL/min/kg	hERG Blockers	H-HT (Human Hepatotox
A	-5.236	---	99.1	--	+++	---	----	0.545	5.96	0.718	0.894
B	-4.514	---	88.3	+++	---	---	--	1.198	8.535	0.056	0.889
C	-4.946	---	96.9	++	+	--	--	1.09	6.151	0.011	0.571
D	-5.067	---	98.4	+++	+++	+++	---	0.473	8.46	0.24	0.77
E	-4.564	--	44.5	--	+++	-	++	0.867	8.823	0.038	0.339
F	-4.393	---	98.4	+++	+++	+++	+	---	0.548	0.352	0.28
G	-5.304	---	99	---	+++	+++	--	0.685	3.811	0.86	0.932
Legends:											

A : Tak-285, **B**: 1,1'-Bis(cyclooct-2-en-4-one), **C**: 3-Methyl-4-(phenylthio)-2-prop-2-enyl2,5-dihydrothiophene 1,1-dioxide, **D**: 9,10-Anthracenedibutanol, 9,10-dihydro-, **E**: 4,4Dimethyl-3-oxopentanenitrile, **F**: Benzo[h]quinoline, 2,4-dimethyl-, **G**: Lapatinib, **Ac**: Accepted.

Papp Caco2 permeability: **High permeability**: >-5.15 Log Papp (log cm/s); **Moderate permeability**:-6.0 to -5.0 log Papp; **Low permeability** :< -6.0 Log Papp. **HIA** -: ≥ 30%: HIA+: < 30%; affinity. **PPB**: optimal < 90%; > 90%: highly protein-bound; **BBB+**: the compound is considered capable of penetrating the brain. **BBB-**: brain penetration is poor or absent. **T ½**: > 8 h: long half-life; 4–8 h: moderate; < 4 h: short half-life. **CL_{plasma}** > 15 mL/min/kg: high; 5 mL/min/kg < Cl < 15 mL/min/kg: moderate; < 5 mL/min/kg; **hERG Blockers**: 0-0.3 excellent, 0.3–0.7 medium; 0.7-1.0 poor

human hepatotoxicity: Category 0: H-HT negative(-); Category 1: H-HT positive(+). The output value is the probability of being toxic, within the range of 0 to 1; **AMES Toxicity**: Category 0: AMES negative (-); Category 1: AMES positive(+). The output value is the probability of being toxic, within the range of 0 to 1 [16].

3.3. Molecular Docking Results

All the compounds (22) identified, as well as the co-crystallised ligand (Tak-285), were screened using THVS Precision, with a threshold of -7 kcal/mol for docking to filter out the best compounds, which enabled us to retain 9 compounds. These 9 compounds were evaluated using the Standard Precision (SP) method, and finally six (6) of these nine (9) were screened using the Extra Precision (XP) method (Table 4). The co-crystallised ligand (Tak-285) was used as the standard to compare results. The docking protocol validation was performed by superimposing the redocked Co-crystallized ligand (Tak-285) with its primary position. The post-docking analysis showing the 2D interactions between the key amino acid residues of the target protein and the compounds is presented in Fig. 2.

Table 4
Docking scores and MMBGSA scores of compounds derived from *A. maciverae* with the HER2 complex (PDB: 3POZ), with Tak-285 and Lapatinib.

N	Compounds	PubChem Id	Docking Score XP (kcal/mol)	MMGBSA: BE (ΔG)(kcal/mol)
1	Cocrystallize_Ligand_Tak-285	11620908	-14.375	-9.98
2	1,1'-Bis(cyclooct-2-en-4-one)	5368987	-6.199	-35.23
3	3-Methyl-4-(phenylthio)-2-prop-2-enyl-2,5-dihydrothiophene 1,1-dioxide	6420230	-5.933	-40.63
4	9,10-Anthracenedibutanol, 9,10-dihydro-	11940	-5.632	-40.13
5	4,4-Dimethyl-3-oxopentanenitrile	108871	-5.260	-29.48
6	Benzo[h]quinoline, 2,4-dimethyl	610182	-4.932	-25.74
7	Lapatinib	208908	-13.426	-98.25

MMGBSA: Molecular Mechanics-Generalized Born Surface Area, **XP**: Extra Precision, **BE**: Binding Energy.

3.4. Docking Interaction of *A.maciverae* Compounds with Protein Target

A:Tak-285.1; **B**:1,1'-Bis(cyclooct-2-en-4-one); **C**: 3-Methyl-4-(phenylthio)-2-prop-2-enyl-2,5-dihydrothiophene 1,1-dioxide; **D**: 9,10-Anthracenedibutanol, 9,10-dihydro; **E**:4, 4-Dimethyl-3-oxopentanenitrile; **F**: Benzo[h]quinoline, 2,4-dimethyl; **G**: Lapatinib

4. Discussion

The molecular docking technique uses energy-based scoring functions to predict interactions between ligand and receptor active sites [18]. It simulates the interaction between small molecule ligands and bio-macromolecular receptors based on the “lock-and-key” principle. Ligand-receptor interaction is a process of molecular recognition, which mainly includes electrostatic interaction, hydrogen bonding, hydrophobic interaction, van der Waals interaction, etc. Through calculations, the combination mode and affinity between them can be predicted to perform virtual screening of drugs [19].

In the present study, the extraction of *A. maciverae* leaves harvested in Samaru, Nigeria, and subsequent submission to phytochemical screening and GC-MS analysis successfully revealed the presence of some secondary metabolites and identified 22 distinct phytochemical compounds, indicating a diverse range of bio-active constituents within the extract. The detection of the presence of tannins, saponins, flavonoids, glycosides, terpenoids, steroids, carbohydrates, phenols, and alkaloids in the MLEAM, as reported in Table 1, suggests that the plant contains several metabolite classes reported to have anti-tumour activities through modulation of key processes in cancer development, including oxidative stress, cell proliferation, apoptosis, angiogenesis, invasion, and metastasis [20, 21]. Flavonoids and other phenolic constituents may contribute through antioxidant and anti-inflammatory actions, as well as by regulating cancer-related signalling pathways, whereas alkaloids, terpenoids, and saponins have been associated with cell-cycle arrest, apoptosis induction, inhibition of tumour growth, and reduced metastatic behavior [22–24]. Additionally, the presence of cardiac glycosides is noteworthy because compounds in this class have demonstrated preclinical anti-proliferative and pro-apoptotic effects by inhibiting the Na+/k+-ATPase, resulting in reduced intracellular K^+ and increased Na^+ and $Ca2^+$. Also, they were known to act as inhibitors of IL8 production, DNA topoisomerase I and II, anoikis prevention and suppression of several target genes responsible for the inhibition of cancer cell proliferation [25].

Among the identified compounds, three (β-copaene, ambrosin, and benzo[h]quinoline, 2,4-dimethyl) have been reported in the literature to possess antitumor activities. Ambrosin exhibits anticancer activity by inducing apoptosis via mitochondrial pathways and ROS generation, while also inhibiting EGFR and RhoC signalling, suggesting its potential as a therapeutic agent for advanced bladder and breast cancers [26]. Yadav *et al*. reported that benzo[h]quinolines exhibit cytotoxic activity against human cancer cell lines by inducing oxidative stress-mediated DNA damage [27]. Also, essential oils containing copaene have been reported to show *in vitro* cytotoxic effects on human lymphocytes [28]. The cytotoxic activity may be attributed to these three compounds.

For pharmacokinetic analysis, overall, all compounds exhibited good absorption properties. Most compounds showed high protein-binding affinity, except 1,1'-bis(cyclooct-2-en-4-one) and 4,4-dimethyl-3-oxopentanenitrile. Regarding blood-brain barrier (BBB) permeability, all compounds were able to cross the BBB, except the co-crystallised ligand, 4,4-dimethyl-3-oxopentanenitrile, and the standard drug (lapatinib). This ability to cross the blood-brain barrier suggests their potential as candidates for brain tumor therapy. The ability of some compounds to inhibit cytochrome P450 enzymes may lead to potential plant–drug interactions. CYP3A4 inhibition is clinically very important, as this enzyme is responsible for the metabolism of half of all drugs (Zhang et al., 2024). All compounds demonstrated a short half-life, indicating rapid elimination from the body; therefore, frequent dosing may be required to maintain therapeutic levels. Their clearance rates ranged from low to moderate. In addition, all compounds complied with Lipinski’s rule of five, indicating good oral bioavailability when administered orally.

In the present study, the compounds identified using the GC-MS method were docked with the HER-2 receptor to predict the possible mechanism of action of MLEAM. Activation of the HER-2 receptor leads to the initiation of three major signalling pathways: MAPK, PI3K/AKT/mTOR, and JAK-STAT, which are involved in cell growth, survival, differentiation, metabolism, and angiogenesis [29]. The docking scores of the MLEAM compounds targeting HER-2 showed binding energies comparable to those of the standard drug and the co-crystallised ligand. Compound 18 (2-methyl-Z, Z-3,13-octadecadienol) was found to interact with four key amino acid residues, while compound 22 (benzo[h]quinoline, 2,4-dimethyl) interacted with three key residues, indicating strong binding affinity and good stability within the HER-2 active site. This may predict the mechanistic pathway through which the MLEAM exerts its cytotoxic activity.

A limitation of this study is that molecular dynamics (MD) simulation was not performed to further evaluate the stability, flexibility and dynamic behaviour of the selected phytochemicals-HER2 complexes under physiological conditions.

5. Conclusion

This study offers the first robust computational and phytochemical validation of the ethnopharmacological use of *Artemisia maciverae* leaf extracts against breast cancer. GC-MS analysis identified 22 phytochemicals, and virtual screening against EGFR kinase selected six promising lead compounds with favourable docking interactions, MM-GBSA binding stability, and drug-like pharmacokinetic properties. Lead compounds, including 3-methyl-4-(phenylthio)-2-prop-2-enyl-2,5-dihydrothiophene 1,1-dioxide and 9,10-anthracenedibutanol, 9,10-dihydro-, exhibited MM-GBSA binding energy values comparable to that of the standard drug. Additionally, several compounds demonstrated outstanding blood-brain barrier permeability. These findings present *A. maciverae* as a rich reservoir of drug-like leads for targeting EGFR, laying a solid foundation for future *in vitro* and *in vivo* investigations to advance these compounds toward clinical evaluation.

Declarations

Animal ethics

Not applicable.

Plant collection and authentication: Plant collection and authentication: The plant material, *Artemisia maciverae*, was collected from naturally growing vegetation in an accessible, non-protected area of Samaru, Zaria Local Government Area, Kaduna State, Nigeria. The collection was conducted in accordance with applicable local and national requirements governing plant collection and utilisation. No formal collection permit or licence was required for this collection. The plant specimen was authenticated, and a voucher specimen was deposited at the Herbarium of the Department of Botany, Ahmadu Bello University, Zaria, Nigeria (Voucher No.: ABUH06883).

Consent for publication:

Not Applicable

Competing interests:

The authors declare no conflicts of interest

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Author Contribution

HI provided the plant material. MSFS conceptualised the study, conducted the research, analysed and interpreted the data, and drafted the manuscript. AO provided guidance and advice. JY and MZ supervised the work, provided scientific guidance and advice and reviewed the final manuscript. All authors reviewed and approved the final manuscript.

Data Availability

The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

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Figures

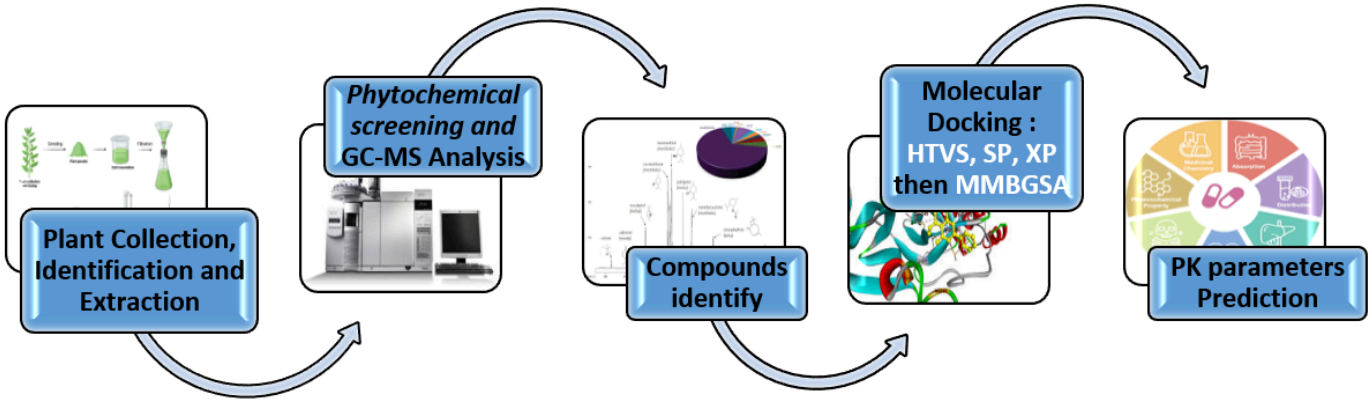

Figure 1

Workflow of the research

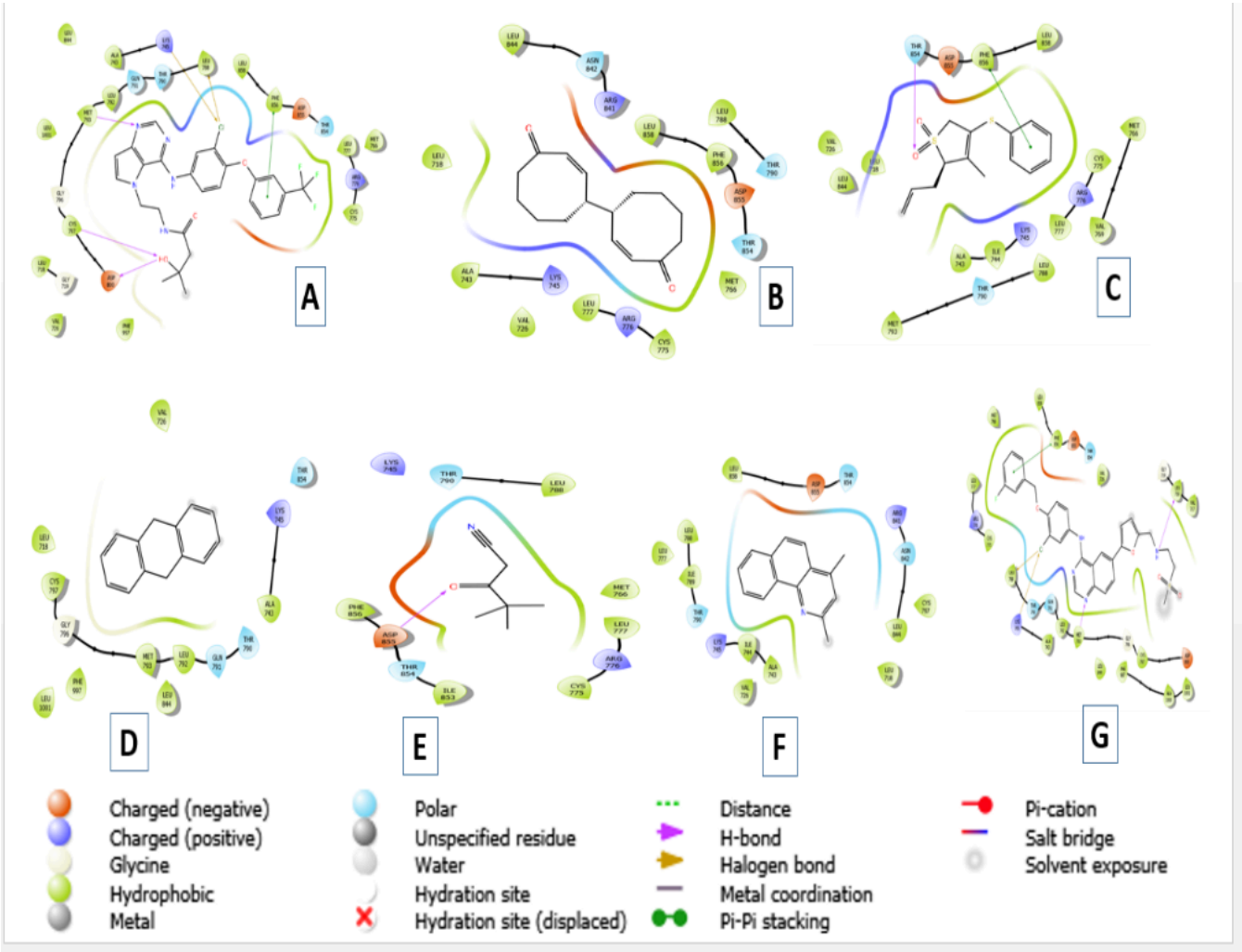

Figure 2

2D Docking interactions of *A. maciverae* compounds, Lapatinib, and the Co-Crystallised Ligand with amino acid residues at the active site of HER2.

A:Tak-285.1; **B**:1,1'-Bis(cyclooct-2-en-4-one); **C**: 3-Methyl-4-(phenylthio)-2-prop-2-enyl-2,5-dihydrothiophene 1,1-dioxide; **D**: 9,10-Anthracenedibutanol, 9,10-dihydro; **E**:4, 4-Dimethyl-3-oxopentanenitrile; **F**: Benzo[h]quinoline, 2,4-dimethyl; **G**: Lapatinib