# Repurposing of FDA Approved Drugs and Neuropep peptides as Anticancer Agents Against ErbB1 and ErbB2

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Key words
cytoscape, igemdock, hpepdock, datawarrior, *invitro* proliferation assay.

**received** 11.01.2023
**accepted** 30.01.2023
**published online** 17.04.2023

Bibliography
Drug Res 2023; 73: 341–348
**DOI** 10.1055/a-2030-4078
**ISSN** 2194-9379

Georg Thieme Verlag, Rüdigerstraße 14,
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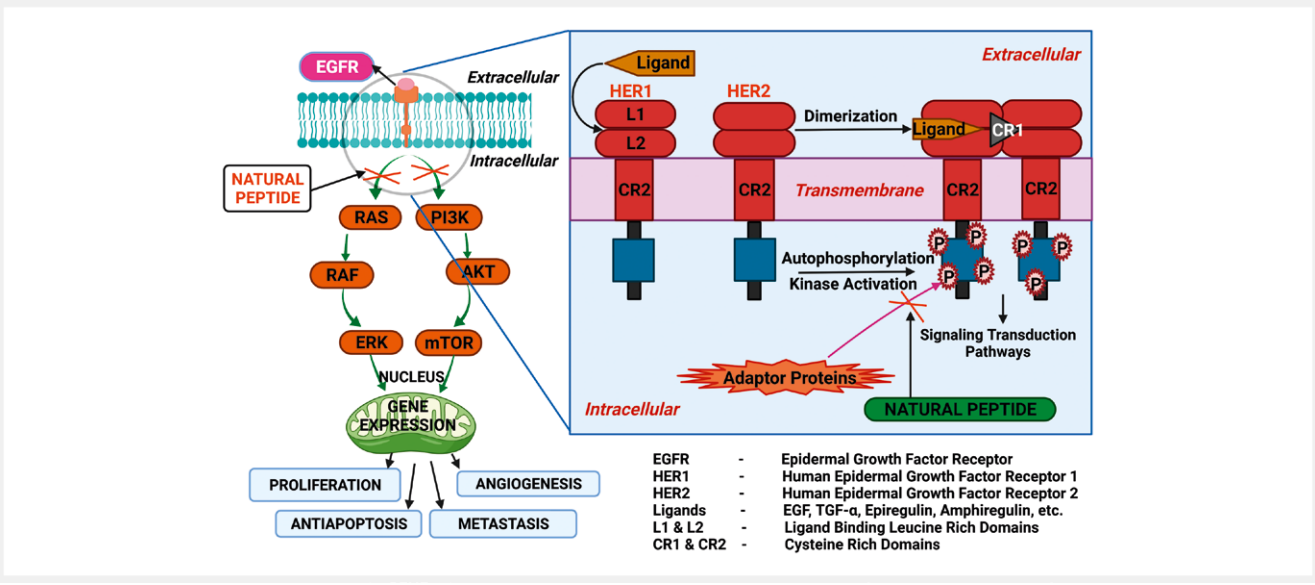
**ABSTRACT**

ErbB1 and ErbB2 are the most important biological targets in cancer drug discovery and development of dual inhibitors for the cancer therapy. FDA approved drugs and Neuropep peptides were used to fit into the ATP binding site of the tyrosine kinases; ErbB1 and ErbB2 proteins. Cytoscape, iGEMDOCK, HPEPDOCK and DataWarrior softwares were used to study the role of these agents as anticancer drugs. Eleven FDA approved drugs and eleven Neuropep peptides showed the strongest 2D interactions and significant binding energy with the proteins. *Invitro* MTT anticancer assay revealed that, the test compounds, peptide YSFGL and doxorubicin showed significant $IC_{50}$ value (μM) of 26.417 ± 0.660 and 7.675 ± 0.278 respectively which are compared with the lapatinib standard $IC_{50}$ value (μM) of 2.380 ± 0.357 against A549 cells and $IC_{50}$ value (μM) of 39.047 ± 0.770 and 8.313 ± 0.435 respectively which are compared with the lapatinib standard $IC_{50}$ value (μM) of 3.026 ± 0.180 against MDA-MB-231 cells.

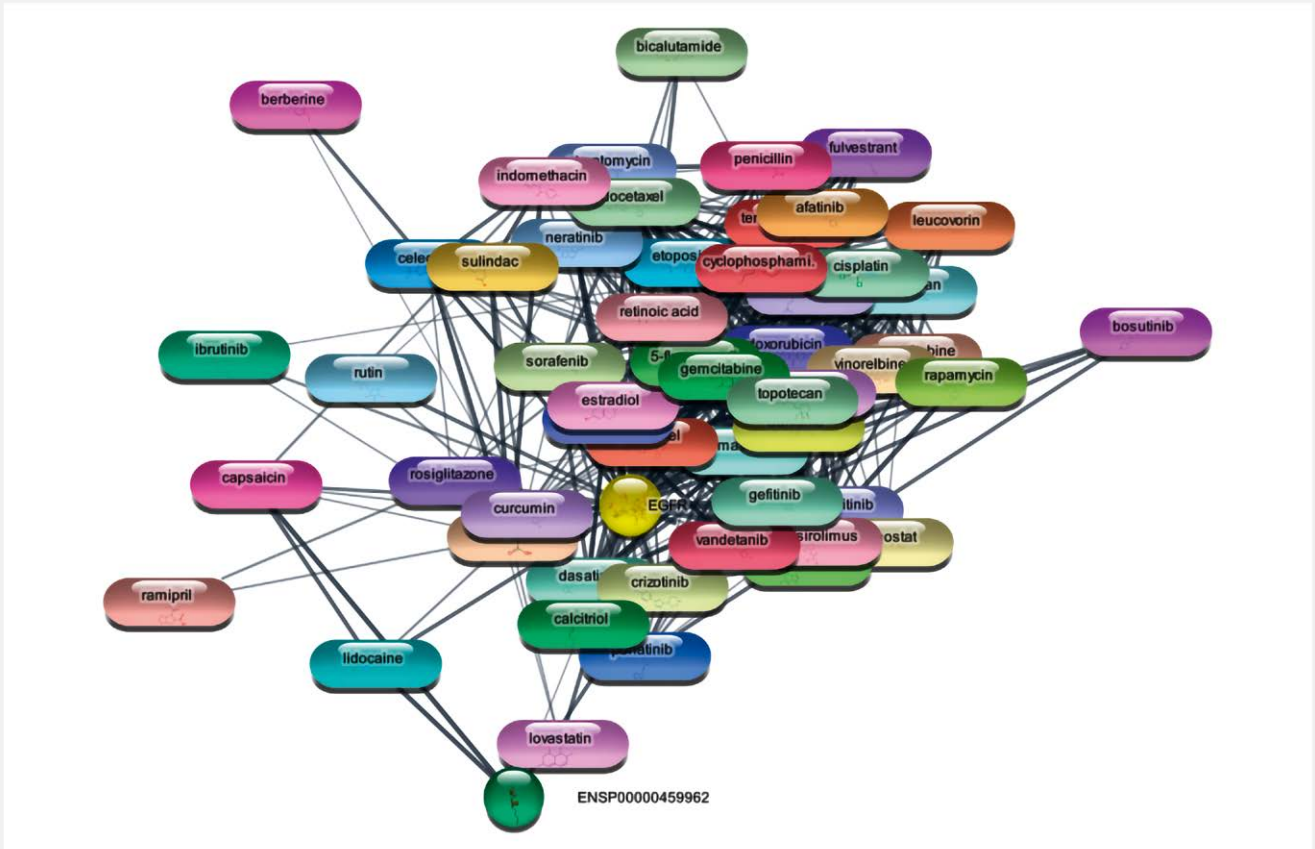
## Introduction

Cancer is one of the most dangerous diseases that have a serious risk to the mankind's health and a great challenge to the contemporary medicine [1]. In general physiology of body system, apoptosis plays a key role in the regulation of the cell cycle progression by leading the faulty cells to a programmed cell death. Check points in the cell cycle identify the faulty cells [2]. Surgery, radiotherapy, chemotherapy, and immunotherapy are the therapeutic strategies used for cancer treatment. Chemotherapy is still the major approach to treat cancer but has a drawback of increased chances of resistance and recurrence of the disease [3]. Protein kinases play a major role in apoptosis, cell cycle progression, cell division, cytoskeletal rearrangement, cell differentiation and development, the immune response, nervous system dynamics, transcription, and translation. Dysregulation of these protein kinases activity play a prominent role in the cancer [4]. Anti-apoptosis, angiogenesis, tumor vascularization and tyrosine kinase activity play a major role in cell proliferation and metastases [1]. The ErbB receptor protein-kinases regulate apoptosis, cell cycle progression, development, metastases and invasion [5]. The ErbB/HER receptor tyrosine kinases are one of the most researched category of cell signaling families in cancer biology because of their roles in signal transduction and oncogenesis [6]. EGFR/ErbB1/HER1, HER2/ErbB2, HER3/ErbB3 and HER4/ErbB4 are the four members belonging to the tyrosine kinase receptor family [7]. The ligands interacting with ErbB receptors include epigen (EPG), transforming growth factor-α (TGF-α), and Amphiregulin (AR) binding to EGFR; betacellulin (BTC), heparin-binding epidermal growth factor (HB-EGF), and Epiregulin (EPR)

binding to EGFR and ErbB4; neuregulin-1 (Nrg-1) and neuregulin-2 (Nrg-2) binding to ErbB3 and ErbB4; neuregulin-3 (Nrg-3) and neuregulin-4 (Nrg-4) binding to ErbB4 [5]. The EGFR family has been the most investigated receptor protein tyrosine kinase families because of their role in general signal transduction and in oncogenesis [8]. Out of all the four members of ErbB family, ErbB1 and ErbB2 are the attractive targets for cancers as they are involved in the development and metastases of different cancers [9]. These two pro-

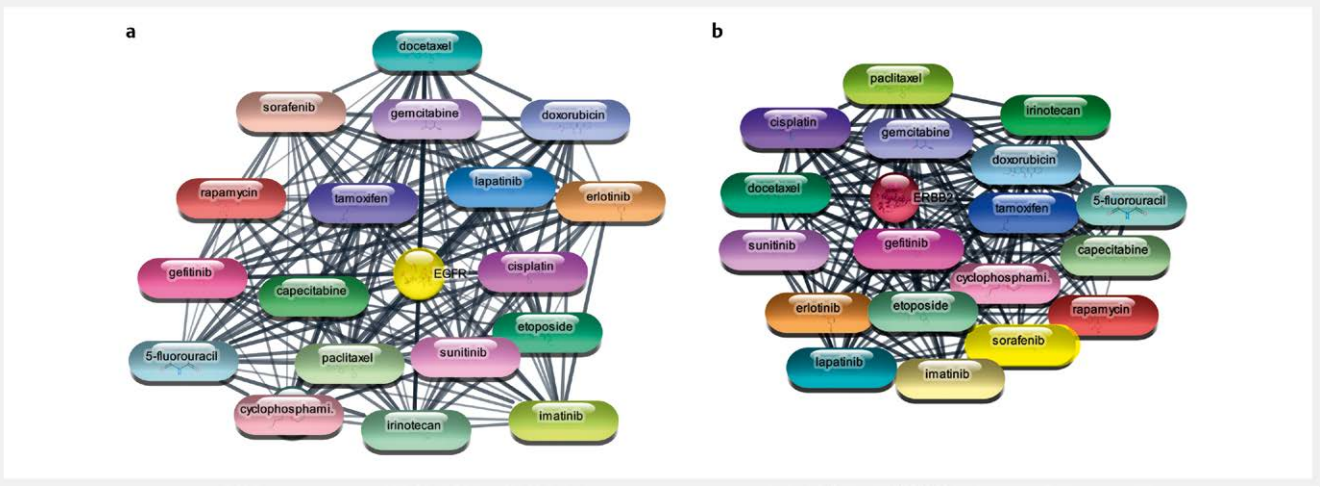



▶ **Fig. 1** Role of Natural Peptide/TKIs in RAS/mitogen activated protein kinase pathway, PI3K/AKT–mTOR, leading to the inhibition of the important hallmarks of cancer.




▶ **Fig. 2** Interaction of 58 FDA drugs with ErbB1.

teins share high sequence homology and structure, many catalytic and kinetic properties associating distinctly with the cancers [10]. There are many small molecular inhibitors reported as kinase inhibitors. The clinically available first-generation reversible EGFR-TKIs (EGFR-tyrosine kinase inhibitors) such as gefatinib, erlotinib, and icotinib; second generation irreversible EGFR-TKIs such as afatinib, and dacomitinib are being used [11]. Lapatinib and neratinib are clinically used dual inhibitors of ErbB1 and ErbB2. But, cancer cells can develop resistance against these anticancer agents [11, 12]. Hence there is a need to develop alternate drugs which can kill cancer cells effectively without resistance being developed by cancer cells. One such category of drugs includes use of peptides as anticancer drugs. Natural peptides have demonstrated selective cytotoxicity to human cancer cells without effecting the normal cells [11]. Natural peptides internalize in the intracellular region of EGFRs for the signal attenuation. They bind to the active intracellular kinase domain (ATP binding sites) at the C-terminal and thereby inhibit the phosphorylation at the tyrosine kinase domain which is the preliminary step in the progression of the cancer cells. When the phosphorylation step is inhibited, the adapter proteins do not have phosphorylated residues for further progression in downregulation pathways. This results in the prevention of the phosphotyrosine residues-activating molecules complex formation which further results in the inhibition of RAS/MAPK, PI3K/AKT-mTOR, signal transducers and activators of transcription signaling. This leads to the downregulation of proliferation, invasion, metastases, and angiogenesis of cancer cells (▶ **Fig. 1**) [11, 13–15]. Keeping all the facts in our mind, we wanted to identify new ErbB1 and ErbB2 dual




▶ **Fig. 3** **a** Interaction of 18 FDA drugs with ErbB1.; **b** Interaction of 18 FDA drugs with ErbB2.

▶ **Table.1** PDI Data using cytoscape against ErbB1.

| S. No | Name of the Drug | Degree | Closeness | Betweenness | MNC | Bottleneck | EcCentricity |
|---|---|---|---|---|---|---|---|
| 1. | Tamoxifen | 16 | 17.5 | 0.11765 | 16 | 1 | 0.5 |
| 2. | Doxorubicin | 18 | 18.5 | 0.36765 | 18 | 1 | 0.5 |
| 3. | Cisplatin | 18 | 18.5 | 0.36765 | 18 | 1 | 0.5 |
| 4. | Cyclophosphamide | 18 | 18.5 | 0.36765 | 18 | 1 | 0.5 |
| 5. | Docetaxel | 18 | 18.5 | 0.36765 | 18 | 1 | 0.5 |
| 6. | 5-flurouracil | 17 | 18 | 0.11765 | 17 | 1 | 0.5 |
| 7. | Irinotecan | 18 | 18.5 | 0.36765 | 18 | 1 | 0.5 |
| 8. | Paclitaxel | 17 | 18 | 0.25 | 17 | 1 | 0.5 |
| 9. | Imatinib | 1 | 10 | 0 | 1 | 1 | 0.5 |
| 10. | Gefatinib | 18 | 18.5 | 0.36765 | 18 | 1 | 0.5 |
| 11. | Erlotinib | 18 | 18.5 | 0.36765 | 18 | 1 | 0.5 |
| 12. | Sorafenib | 17 | 18 | 0.25 | 17 | 1 | 0.5 |
| 13. | Sunitinib | 18 | 18.5 | 0.36765 | 18 | 1 | 0.5 |
| 14. | Etoposide | 19 | 19 | 36.36765 | 18 | 2 | 1 |
| 15. | Gemcitabine | 17 | 18 | 0.11765 | 17 | 1 | 0.5 |
| 16. | Capecitabine | 18 | 18.5 | 0.36765 | 18 | 1 | 0.5 |
| 17. | Lapatinib | 18 | 18.5 | 0.36765 | 18 | 1 | 0.5 |
| 18. | Rapamycin | 18 | 18.5 | 0.36765 | 18 | 1 | 0.5 |

▶ **Table.2** PDI Data using cytoscape against ErbB2.

| S. No | Name of the Drug | Degree | Closeness | Betweenness | MNC | Bottleneck | EcCentricity |
|---|---|---|---|---|---|---|---|
| 1. | Tamoxifen | 18 | 18 | 0.36765 | 18 | 1 | 1 |
| 2. | Doxorubicin | 18 | 18 | 0.36765 | 18 | 1 | 1 |
| 3. | Cisplatin | 18 | 18 | 0.36765 | 18 | 1 | 1 |
| 4. | Cyclophosphamide | 18 | 18 | 0.36765 | 18 | 1 | 1 |
| 5. | Docetaxel | 18 | 18 | 0.36765 | 18 | 1 | 1 |
| 6. | 5-flurouracil | 18 | 18 | 0.36765 | 18 | 1 | 1 |
| 7. | Irinotecan | 18 | 18 | 0.36765 | 18 | 1 | 1 |
| 8. | Paclitaxel | 18 | 18 | 0.36765 | 18 | 1 | 1 |
| 9. | Imatinib | 18 | 18 | 0.36765 | 18 | 1 | 1 |
| 10. | Gefatinib | 18 | 18 | 0.36765 | 18 | 1 | 1 |
| 11. | Erlotinib | 18 | 18 | 0.36765 | 18 | 1 | 1 |
| 12. | Sorafenib | 18 | 18 | 0.36765 | 18 | 1 | 1 |
| 13. | Sunitinib | 18 | 18 | 0.36765 | 18 | 1 | 1 |
| 14. | Etoposide | 17 | 17.5 | 0.25 | 17 | 1 | 0.5 |
| 15. | Gemcitabine | 17 | 17.5 | 0.11765 | 17 | 1 | 0.5 |
| 16. | Capecitabine | 17 | 17.5 | 0.11765 | 17 | 1 | 0.5 |
| 17. | Lapatinib | 17 | 17.5 | 0.25 | 17 | 1 | 0.5 |
| 18. | Rapamycin | 16 | 17 | 0.11765 | 16 | 1 | 0.5 |

▶ **Table.3** Docking score of FDA approved drugs with ErbB1 and ErbB2 using iGEMDOCK.

| Ligand | Binding Energy (kcal/mol) | |
|---|---|---|
| | ErbB1 | ErbB2 |
| Flurouracil | −92.46 | −97.14 |
| Cyclophosphamide | −83.74 | −76.24 |
| Docetaxel | −105.38 | −82.59 |
| **Doxorubicin** | **−129.68** | **−127.28** |
| Erlotinib | −105.96 | −120.73 |
| Gefetinib | −106.01 | −109.60 |
| Imatinib | −123.87 | −118.31 |
| Paclitaxel | −89.63 | −100.11 |
| Sorafenib | −118.56 | −118.66 |
| Irinotecan | −115.59 | −132.97 |
| Sunitinib | −105.49 | −108.65 |
| Lapatanib (Standard) | −108.90 | −102.70 |

inhibitors from peptide origin. We also carried out the study with FDA approved drugs and compared the data with peptides.

# Materials and methods

## Collection and preparation of Proteins ErbB1 and ErbB2

The protein structure of EGFRs, ErbB1 (PDB ID: 1XKK) [16] and ErbB2 (PDB ID: 3PP0) [17], were obtained from the protein data bank (https://www.rcsb.org) [18].

## Collection of Peptides and FDA approved drugs

A library of natural peptides of five amino acid sequence from NeuroPep database, which is a comprehensive resource of neuropeptides originating from organisms [19] has been retrieved. The list of 2637 FDA approved drugs was obtained from the internet source.

## Protein drug interactions network by Cytoscape

The protein drug interaction networks (PDI) was visualized using the Cytoscape 3.9.1 software. Cytoscope 3.9.1 is an open source bioinformatics software used to visualize large sets of biological data and represent them as a network to better understand the relationship between the entities [20]. Our main focus was to establish a network for protein-drug interaction which would provide with a clear picture regarding the selected drugs that can directly interact with both the proteins ErbB1 and ErbB2 [21].

## Docking tools

Docking analysis was carried out using iGEMDOCK and online software HPEPDOCK. iGEMDOCK derives the pharmacological interactions of the selected ligands with proteins without the taking the known standard compounds. iGEMDOCK provides a post screening analysis module convenient for the clustering compounds and visualization of pharmacological interactions by interaction profiles [22]. HPEPDOCK is a server for blind peptide-protein docking by fast modeling of peptide conformations and global sampling of binding orientations [23]. FDA drugs were docked using iGEMDOCK, whereas, for peptides double docking was performed using iGEMDOCK and HPEPDOCK.

## ADMET analysis

ADMET analysis was performed using DataWarrior software, which is an open-source program for the data visualization and analysis

with chemical intelligence. DataWarrior combines dynamic graphical views and interactive row filtering with chemical intelligence [24].

### Invitro Proliferation assay (MTT assay)

Based on the docking results top peptide (YSFGL) and top FDA approved drug (Doxorubicin) have been selected for biological activity by MTT assay and compared with the standard lapatinib.

The obtained human lung cancer and breast cancer cell lines (A549 and MDA-MB-231) were cultured in DMEM medium supplemented with 10 percent fetal bovine serum (FBS) and 1 percent penicillin streptomycin at 37 °C in a humidified 5 percent $CO_2$ atmosphere. Cells were cultured ($1 \times 10^4$ cells/well) into flat-bottom 96-well plates (Corning$^R$ Cell Bind$^R$ Surface), in triplicate amount of 100 µL of cell suspension with media per each well. In order to determine the cytotoxicity effect of the peptide YSFGL, doxorubicin and standard lapatinib, the cell lines were treated with the compounds, which were freshly dissolved in the cell culture medium, at different concentrations (100, 50, 25, 12.50 and 6.25 µM) for 48 h. The cells of the control group and blank group were left untreated. After 48 h of treatment, MTT reagent at a final concentration of 0.5 mg/ml was added to each well, and incubated for 4 h at 37 °C. The blue-colored product was solubilized in DMSO and finally absorbance was measured at 570 nm using VarioskanTM Flash Multimode Reader (Thermo Scientific) [25]. Data obtained are expressed as the percentage of control mean ± SD of triplicate values. The $IC_{50}$ was determined by using GraphPad Prism software version 9.0.0 and nonlinear regression (curve fit).

## Results

### Protein drug interactions network by Cytoscape

All the 2637 FDA approved drugs were loaded to the cytoscape software and protein-drug interactions were recorded against ErbB1 and 58 drugs showed interaction with ErbB1 (▶ **Fig. 2**). These drugs were studied for the interactions with ErbB2 and 18 drugs showed interaction (▶ **Fig. 3b**). These 18 drugs can be the dual inhibitors of ErbB1 (▶ **Table.1**) and ErbB2 (▶ **Table.2**) (▶ **Fig. 3a, b**). The final drugs were then docked against ErbB1 and ErbB2 using iGEMDOCK and the results were compared with the docking scores of peptides.

### Molecular docking

All the FDA approved drugs and Neuropep peptides were subjected to the molecular docking using iGEMDOCK. The FDA approved drugs showed binding energy (▶ **Table.3**) ranging from −83.74 kcal/mol to −129.68 kcal/mol for ErbB1 and −76.24 kcal/mol to −132.97 kcal/mol for ErbB2. The average binding energy showed by doxorubicin is higher than all the other FDA approved drugs with −129.68 kcal/mol for ErbB1 and −127.28 kcal/mol for ErbB2. From the binding energies it may be noted that this drug can act as a dual inhibitor of ErbB1 and ErbB2. Double docking was done for the peptides using HPEPDOCK and iGEMDOCK (▶ **Table.4**). The average binding energy showed by YSFGL is higher than all the other peptides with −116.23 kcal/mol for ErbB1 and −107.06 kcal/mol for ErbB2 using HPEPDOCK; −114.63 kcal/mol for ErbB1 and −120.62 kcal/mol for ErbB2 using iGEMDOCK.

### ADMET analysis

The ADMET analysis by using DataWarrior for FDA approved drugs and Neuropep peptides are showed in ▶ **Table.5** and ▶ **Table.6**. The molecular weight of top 11 FDA drugs were in the range of 246.193 kDa to 853.915 kDa and molecular weight of top 11 peptides were in the range of 429.475 kDa to 683.828 kDa. Cyclophosphamide showed mutagenicity, tumorigenicity and effect on reproductive system, Doxorubicin and Sunitinib showed irritation whereas, peptides did not show any effect.

### Invitro Proliferation (MTT) Assay

After treatment against the cell lines, the cytotoxic activity of the test compounds was illustrated in ▶ **Table.7**, ▶ **Fig. 4,5**. The doxo-

▶ **Table.4** Docking score of Neuropep peptides with ErbB1 and ErbB2.

| Ligands | Binding Energy (kcal/mol) | | | |
|---|---|---|---|---|
| | HPEPDOCK | | iGEMDOCK | |
| | ErbB1 | ErbB2 | ErbB1 | ErbB2 |
| YAFGL | −103.24 | −100.28 | −119.86 | −116.44 |
| **YSFGL** | **−116.23** | **−107.06** | **−114.63** | **−120.62** |
| TLFRF | −108.4 | −104.82 | −105.66 | −118.59 |
| YLRF | −94.098 | −138.65 | −105.8 | −105.99 |
| YPFF | −99.352 | −110.88 | −101.77 | −100.08 |
| YGFL | −99.985 | −105.91 | −109.92 | −118.32 |
| YPWG | −97.51 | −102.85 | −101.09 | −101.35 |
| YPWT | −115.21 | −100.97 | −102.37 | −96.439 |
| FYRI | −110.24 | −98.285 | −113.96 | −105.61 |
| FLRN | −100.24 | −86.233 | −105.18 | −104.68 |
| APGW | −113.88 | −69.344 | −109.89 | −103.26 |
| Lapatanib (Standard) | – | – | −108.90 | −102.70 |
| (No peptide standards are available for the selected targets) | | | | |

▶ **Table.5** ADMET analysis data of FDA approved drugs.

| Drug name | Total Mol. weight | cLogP | cLogS | H-Acceptors | H-Donors | Polar Surface Area | Drug likeness | Mutagenic | Tumorigenic | Reproductive Effective | Irritant | Rotatable Bonds |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Flurouracil | 246.193 | −1.4898 | −1.503 | 7 | 3 | 99.1 | −3.4013 | None | None | None | None | 2 |
| Cyclophosphamide | 263.104 | −0.0289 | −2.823 | 4 | 2 | 44.73 | −9.8384 | High | High | High | None | 5 |
| Docetaxel | 807.887 | 2.609 | −5.811 | 15 | 5 | 224.45 | −55.654 | None | None | None | None | 13 |
| Doxorubicin | 543.523 | 0.1673 | −4.507 | 12 | 6 | 206.07 | 6.6484 | None | None | None | High | 5 |
| Erlotinib | 393.442 | 3.0713 | −3.527 | 7 | 1 | 74.73 | −5.9718 | None | None | None | None | 10 |
| Gefetinib | 446.909 | 3.9851 | −5.062 | 7 | 1 | 68.74 | 0.47937 | None | None | None | None | 8 |
| Imatinib | 493.613 | 3.9383 | −4.383 | 8 | 2 | 86.28 | 8.6128 | None | None | None | None | 7 |
| Paclitaxel | 853.915 | 3.188 | −6.289 | 15 | 4 | 221.29 | 0.82049 | None | None | None | None | 14 |
| Sorafenib | 464.83 | 4.1428 | −6.689 | 7 | 3 | 92.35 | −5.1185 | None | None | None | None | 6 |
| Irinotecan | 586.687 | 3.5596 | −4.504 | 10 | 1 | 112.51 | −0.08661 | None | None | None | None | 5 |
| Sunitinib | 398.48 | 1.836 | −3.471 | 6 | 3 | 77.23 | 8.335 | None | None | None | High | 7 |

▶ **Table.6** ADMET analysis data of Neuropep peptides.

| Peptide sequence | Total Molweight | cLogP | cLogS | H-Acceptors | H-Donors | Polar Surface Area | Druglikeness | Mutagenic | Tumorigenic | Reproductive Effective | Irritant | Rotatable Bonds |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **YGFL** | 498.578 | −1.3562 | −3.137 | 10 | 6 | 170.85 | −12.376 | None | None | None | None | 13 |
| **YLRF** | 598.722 | −2.0759 | −4.225 | 13 | 9 | 236.86 | −11.858 | None | None | None | None | 17 |
| **YPFF** | 572.66 | −0.0655 | −3.974 | 10 | 5 | 162.06 | −8.4144 | None | None | None | None | 12 |
| **YPWG** | 521.572 | −1.8273 | −2.986 | 11 | 6 | 177.85 | −1.3137 | None | None | None | None | 10 |
| **YPWT** | 565.625 | −2.0354 | −3.235 | 12 | 7 | 198.08 | −5.3323 | None | None | None | None | 11 |
| **YSFGL** | 585.656 | −2.8399 | −2.775 | 13 | 8 | 220.18 | −11.457 | None | None | None | None | 16 |
| **FYRI** | 598.722 | −2.0759 | −4.225 | 13 | 9 | 236.86 | −7.5668 | None | None | None | None | 17 |
| **TLFRF** | 683.828 | −2.8546 | −4.537 | 15 | 10 | 265.96 | −14.789 | None | None | None | None | 20 |
| **YAFGL** | 569.657 | −1.9132 | −3.282 | 12 | 7 | 199.95 | −12.516 | None | None | None | None | 15 |
| **APGW** | 429.475 | −2.9235 | −2.147 | 10 | 5 | 157.62 | −4.802 | None | None | None | None | 8 |
| **FLRN** | 549.651 | −4.3918 | −3.207 | 14 | 9 | 259.72 | −12.71 | None | None | None | None | 17 |

(Limits - Mol. Wt: < 500 Daltons [for small molecules]; cLogP: < 5; cLogS: > -5; H-acceptors: < 10; H-Donors: < 5; Polar Surface area: < 200; Mutagenecity: None; Tumorigenecity: None; Reproductive Effect: None; Irritation: None; Rotatable Bonds: < 5).

rubicin showed significant cytotoxic effect against A549 cells with $IC_{50}$ value of 7.675 ± 0.278 µM and YSFGL showed cytotoxicity with $IC_{50}$ value of 26.417 ± 0.660 µM, in comparison with the standard lapatinib (2.380 ± 0.357 µM). The $IC_{50}$ value of doxorubicin and YSFGL were found to be 8.313 ± 0.435 µM and 39.047 ± 0.770 µM respectively against MDA-MB-231 cell lines as compared with the standard lapatinib (3.026 ± 0.180 µM).

## Conclusion

Several biopharmaceutical agents have been approved by FDA for the treatment of cancer. A major shortcoming of these drugs is the development of resistance. So, there is an immediate need for the discovery of the alternate agents for treatment of cancer without developing resistance by cancer cells. In the present study, we focused mainly on the discovery of potent inhibitors of ErbB1 and ErbB2 as a potential therapy for treatment of cancer using *insilico* methods. The already existing FDA approved drugs against various diseases have been studied for interactions against ErbB1 and ErbB2 using cytoscape software. The results suggested that the drugs have interacted against the both proteins, and can be repurposed as anticancer agents. Then, molecular docking studies have been conducted to explore the possible binding of the FDA approved drugs and Neuropep peptides against ErbB1 and ErbB2 for their anticancer activity. Our binding results suggested the possible binding and the role of the selected drugs as dual inhibitors, thereby, leading for the development of these drugs as new entities for anticancer activity. The ADMET analysis of other drugs and peptides suggested that these drugs follows the limits of ADMET properties and can be established as therapeutic agents. The *invitro* MTT assay suggested that doxorubicin and peptide YSFGL showed significant anticancer activity against A549 and MDA-MB-231 cell lines. Further studies on these agents can be performed for exploring their role in treatment of cancer where ErbB1 and ErbB2 play a key role in progression of cancer.

▶ **Table.7** $IC_{50}$ values of test drugs against cell lines.

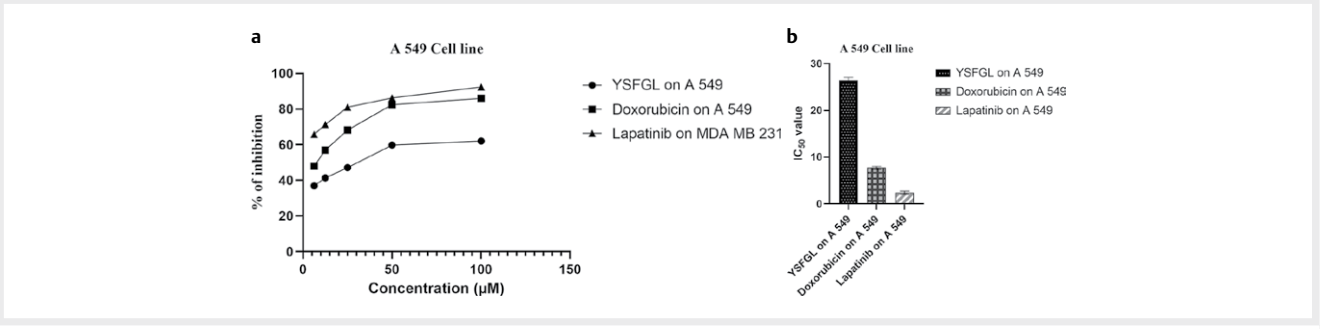
| Drug name | $IC_{50}$ Values (µM) | |
|---|---|---|
| | A549 | MDA-MB-231 |
| **YSFGL** | 26.417 ± 0.660 | 39.047 ± 0.770 |
| **Doxorubicin** | 7.675 ± 0.278 | 8.313 ± 0.435 |
| **Lapatinib (standard)** | 2.380 ± 0.357 | 3.026 ± 0.180 |

## Data availability statement

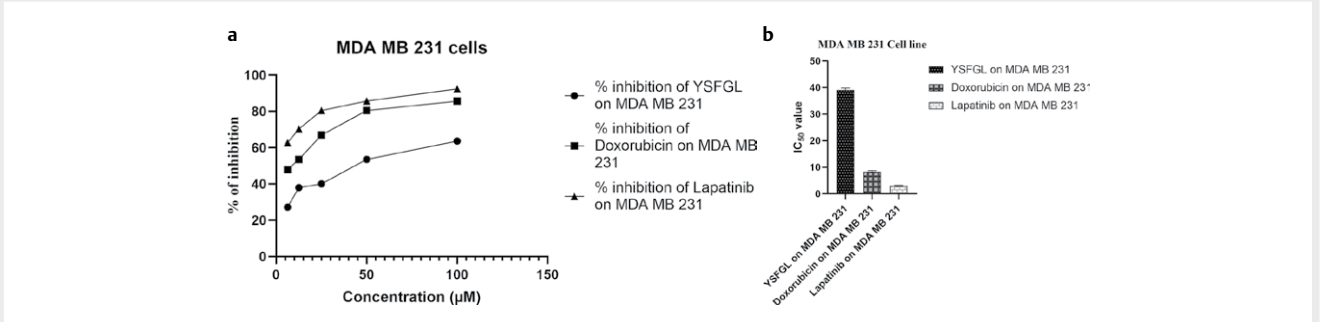
All data generated and analyzed during this study are included within this article

## Ethical Approval

Not Required




▶ **Fig. 4** **a** Plot showing % inhibition of A 549.; **b** Plot showing IC50 value on A 549.




▶ **Fig.5** **a** Plot showing % inhibition of MDA-MB-231; **b**. Plot showing IC50 value on MDA-MB-231

## Author Contributions

Conceptualization, methodology, software, validation, formal analysis, data curation: **Sunil Kumar Patnaik, Akey Krishna Swaroop, Mudavath Ravi Naik;** writing-original draft preparation: **Sunil Kumar Patnaik,** review, editing and supervision: **Dr. Moola Joghee Nanjan Chandrasekar, Dr. Jubie Selvaraj**

## Acknowledgments

Authors expresses their immense gratitude to JSS College of Pharmacy Ooty, JSS Academy of Higher Education and Research, Mysuru, and School of Life Sciences, JSS Academy of Higher Education & Research (Ooty Campus), Longwood, Mysuru Road, Ooty-643001, Tamilnadu, India for the facilities offered.

## Funding

No funding was provided for the above mentioned research

### Conflict of Interest

The authors declare that they have no conflict of interests

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