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ORIGINAL ARTICLE

# Discovery of Novel Human Epidermal Growth Factor Receptor-2 Inhibitors by Structure-based Virtual Screening

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Submitted: 13-10-2015 Revised: 25-11-2015 Published: 02-03-2016

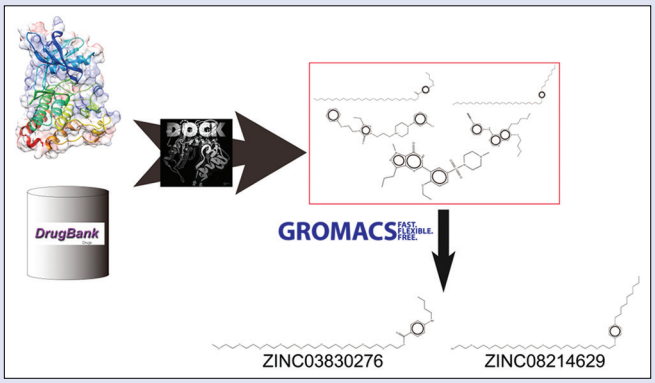
## ABSTRACT

**Background:** Human epidermal growth factor receptor-2 (HER2) is a transmembrane receptor like protein, and aberrant signaling of HER2 is implicated in many human cancers, such as ovarian cancer, gastric cancer, and prostate cancer, most notably breast cancer. Moreover, it has been in the spotlight in the recent years as a promising new target for therapy of breast cancer. **Objective:** Since virtual screening has become an integral part of the drug discovery process, it is of great significant to identify novel HER2 inhibitors by structure-based virtual screening. **Materials and Methods:** In this study, we carried out a series of elegant bioinformatics approaches, such as virtual screening and molecular dynamics (MD) simulations to identify HER2 inhibitors from Food and Drug Administration-approved small molecule drug as potential "new use" drugs. **Results:** Molecular docking identified top 10 potential drugs which showed spectrum affinity to HER2. Moreover, MD simulations suggested that ZINC08214629 (Nonoxynol-9) and ZINC03830276 (Benzonatate) might exert potential inhibitory effects against HER2-targeted anti-breast cancer therapeutics. **Conclusion:** Together, our findings may provide successful application of virtual screening studies in the lead discovery process, and suggest that our discovered small molecules could be effective HER2 inhibitor candidates for further study.

**Key words:** Drug development, human epidermal growth factor receptor-2, kinase, kinase inhibitor, virtual screening

## SUMMARY

- A series of elegant bioinformatics approaches, including virtual screening and molecular dynamics (MD) simulations were took advantage to identify human epidermal growth factor receptor-2 (HER2) inhibitors. Molecular docking recognized top 10 candidate compounds, which showed spectrum affinity to HER2. Further, MD simulations suggested that ZINC08214629 (Nonoxynol-9) and ZINC03830276 (Benzonatate) in candidate compounds were identified as potential "new use" drugs against HER2-targeted anti-breast cancer therapeutics.




**Abbreviations used:** HER2: Human epidermal growth factor receptor-2, FDA: Food and Drug Administration, PDB: Protein Database Bank, RMSDs: Root mean square deviations, SPC: Single point charge, PME: Particle mesh Ewald, NVT: Constant volume, NPT: Constant pressure, RMSF: Root-mean-square fluctuation.

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**DOI :** 10.4103/0973-1296.177912

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## INTRODUCTION

The human epidermal growth factor receptor (HER) family of transmembrane type I receptor, tyrosine kinase are enzymes which play a vital role in various fundamental processes, such as cell proliferation, differentiation, and survival. There are four receptors in this family, including HER1, HER2, HER2, and HER4.[1] Accumulating evidence has indicated that deregulation of HER family signaling promotes proliferation, invasion, metastasis, angiogenesis, and tumor cell survival.

As one of the most attention-getting HER families, HER2 is overexpressed and/or amplifies in 25–30% of all breast cancers, portends poor clinical outcome.[2] HER2 has no identified ligand, which allows it to always be in open conformation to dimerize with HER1, HER3, or HER4. Thus, when the HER2 gene is amplified and overexpressed, it allows for cell growth, survival, and cell differentiation via a signal transduction cascade mediated by the activation of PI3K/AKT and the Ras/Raf/MEK/MAPK pathways.[3]

Previous studies have indicated that HER2 is only expressed at low levels in normal human tissues which make it as an attractive target for tumor-specific therapeutics. Therefore, HER2 represents a class of rational target for anti-cancer drug development, and a number of small molecules targeting HER2 are urgently needed in future drug discovery.[4] Previous evidence has indicated that trastuzumab (Herceptin®)



**Cite this article as:** Shi Z, Yu T, Sun R, Wang S, Chen XQ, Cheng LJ, *et al*. Discovery of novel human epidermal growth factor receptor-2 inhibitors by structure-based virtual screening. Phcog Mag 2016;12:139-44.

and lapatinib (Tykerb®) are two most successful advanced drugs used clinically in breast cancer. Notably, trastuzumab is a humanized IgG1 monoclonal antibody, which selectively binds to extracellular domain of HER2, inhibiting cell proliferation and survival in HER2-dependent tumors that inhibits over-expression of HER2.[5] After binding to HER2, trastuzumab inhibits HER2-activated cell signaling pathways necessary for cellular proliferation and survival in HER2-dependant cells.[6] In addition, lapatinib inhibits HER2 autophosphorylation by competing with adenosine triphosphate (ATP) for the HER2 protein kinase domain, thus preventing further signal transduction.[7] Although tremendous advance has been made in the treatment of breast cancer and notably HER2 positive breast cancer, this disease has not been conquered yet due to severe side effects. There are diverse potential mechanisms which make the current Food and Drug Administration (FDA)-approved agents to be refractory.

Currently, virtual screening which aims to screen the potential inhibitors of target proteins has become a frequent practice in drug discovery. It takes advantage of fast algorithms to filter chemical space and successfully select potential drug candidates.[8] Hitherto, a number of small molecule kinase inhibitors were identified by using above-mentioned approach, such as SRC inhibitors, cyclin-dependent kinases inhibitors, and epidermal growth factor receptor (EGFR) inhibitors.[9,10] However, those researches aimed to recognize new lead compound; our research tried to identify new potential uses for FDA-approved drugs, exhibiting the novelty of our study. Interestingly, Bao's group utilized a series of bioinformatics approaches to successfully identify chlorhexidine and sorafenib as potential "new use" drugs targeting wild-type ABL1, whereas nicergoline and plerixafor targeted T315I ABL1.

In the current study, according to the idea "new uses for old drugs," virtual screening was proposed to recognize HER2 inhibitors from FAD-approved small molecule drugs, and five potential drugs were further chosen based upon their amber scores. In addition, molecular dynamics (MD) simulations were further used to investigate the affinities and stabilities of HER2 with above-mentioned drugs. Finally, several old drugs, including ZINC08214629 (Nonoxynol-9) and ZINC03830276 (Benzonatate), were predicted to exert potential inhibitory effects against HER2 protein by targeting the intracellular tyrosine kinase domain of HER2, and thus preventing further signal transduction. In summary, our study may not only serve as a paradigm for the repositioning of existing approved drugs, but also improve the outcome for patients with HER2 positive breast cancer.

# MATERIALS AND METHODS

## Virtual screening

The initial three-dimensional (3D) geometric co-ordinates of the X-ray crystal structure of HER2 (PDB: 3PP0) was downloaded from the Protein Database Bank (PDB) (http://www.rcsb.org/pdb/home/home.do). Subsequently, we built screening library from FDA-approved small molecule compounds that totally 1408 small molecule drugs were selected to predict novel kinase inhibitors targeting HER2. The 3D format structure of our candidate compounds was downloaded from ZINC database, which is a free database of commercially available compounds for virtual screening and it contains over 35 million compounds in ready-to-dock. The 3D structure of these molecules in ZINC database was initially generated by OpenEye's Omega program, and the relevant, correctly protonated forms of the molecules were then created by Schrödinger's LigPrep program.[11] At last, the 3D conformations generated by OpenEye's program Omega were distilled into a flexibase format using program mol2db.[12,13] Accordingly, the 3D structure of compounds that we used for molecular docking simulation have primarily optimized by ZINC database.[14]

Subsequently, the molecular docking calculations were performed using UCSF DOCK6.4 program with flexible ligand docking method in which the ligand would be allowed to be structurally rearranged in response to the receptor.[15] To improve the accuracy, the binding site was selected within 10.0 Å root mean square deviations (RMSDs) of original ligand. In addition, we carried out flexible ligand docking to a rigid receptor with grid-based scoring, in which the ligands (small molecule drugs) were allowed to be structurally rearranged in response to the kinase.

In docking processes, maximum number of orientations was set to 500.[16] Subsequently, amber scoring function in DOCK 6.4 was used to re-rank the top 100 small molecule compounds from the previous grid-based scoring. During the amber score calculation, the PDB2PQR server was utilized to assign the protonation state of PDB files with AMBER force field, and PROPKA was applied to maintain protonation state at pH = 7.0.[17] Regarding amber scores and binding modes, we eventually selected 5 HER2-small molecule drug complexes for further MD simulations analysis.

## Molecular dynamics simulations

The GROMACS (version 4.5) (GROMACS was first developed in Herman Berendsen's group, department of Biophysical Chemistry of Groningen University, and now lead in Stockholm from the Science for Life Laboratory. http://www.gromacs.org/) package was employed to perform MD simulation analysis of the dynamic behavior of HER2 complexed with top 5 potential drugs, and the protein topology was constructed by pdb2 gmx with GROMOS96 43a1 force field whereas the ligand topology was generated using PRODRG2 server.[18,19] With a 1.0 solute-wall minimum distance, we defined the unit cell as cubic box and filled it with single point charge water molecules.[20] Following a steepest descent energy minimization with particle mesh Ewald at every step, HER2-small molecule drug complexes were equilibrated 100ps under constant volume (NVT) and constant pressure (NPT) condition, respectively, during which position restraints were simultaneously applied to HER2 kinase domain and its ligands. In NVT equilibration, the temperature was maintained at 300K by the Berendsen weak coupling method.[21] In addition, under NPT equilibration, the temperature was controlled by the Berendsen weak coupling method and the pressure was maintained at 1 bar by Parrinello-Rahman barostat method.[22] Upon completion of the two equilibration phases, production of MD simulations was conducted for 5ns after taking away the position restraints. In this data collection phase, the temperature and pressure were maintained by the same methods as in NPT phase, and the coordinates were saved every 0.2 ps.[23] For all simulations, LINCS algorithm was applied to constrain all bonds. The resulting trajectory files were viewed and analyzed using UCSF Chimera.[24]

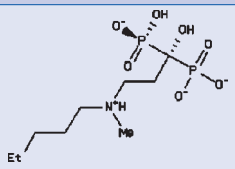
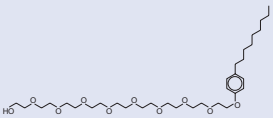
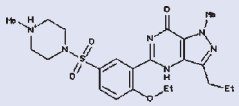
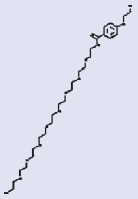
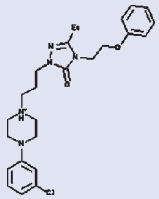
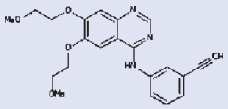
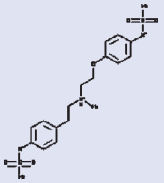
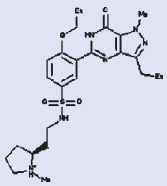
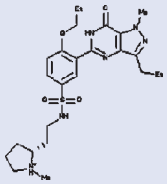
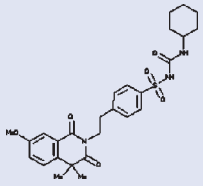
# RESULTS AND DISCUSSION

## Molecular docking

To study the ligand–protein interactions, we totally collected 1408 small molecule drugs (ligands) and docked them to HER2 kinase domain. To make the results more accurate, the results were scored twice. The first score is Gird score, and based on this score, we used Amber score to score again. The docking pose was ranked based upon grid score, then the top ranked 100 small molecular natural products were rescored by amber score function. Amber score has the advantage that both the ligand and the active site (s) of the receptor can be flexible, allowing small structure rearrangements to reproduce the so-called "induced fit" when performing the score.[16,25]

Herein, top-ranking 100 potential drugs were selected according to the grid score and subsequently we re-scored using amber score. Consequently, we finally collected top 10 drugs and the amber scores

**Table 1:** Molecular docking results of human epidermal growth factor receptor-2 in complex with Food and Drug Administration-approved small molecule drugs

| ZINC number | Amber score | Name | Structure |
|---|---|---|---|
| ZINC20444137 | −72.9880064 | Ibandronate sodium |  |
| ZINC08214629 | −71.671036 | Nonoxynol-9 |  |
| ZINC19796168 | −53.634178 | Sildenafil citrate |  |
| ZINC03830276 | −52.336391 | Benzonatate |  |
| ZINC00538065 | −52.226681 | Nefazodone hydrochloride |  |
| ZINC01546066 | −51.979027 | Erlotinib |  |
| ZINC49583080 | −47.824524 | Dofetilide |  |
| ZINC04824235 | −47.349358 | Udenafil |  |
| ZINC13916432 | −45.719276 | Udenafil |  |
| ZINC01482077 | −44.779125 | Gliquidone |  |

of these 10 drugs in complex with HER2 ranged from −72.9880064 to −44.779125. The detailed information of top 10 drugs and their amber scores were shown in Table 1. In general, the negative lower amber score and the appropriate binding modes of these drugs indicated they might target HER2 with higher affinity. Based upon their amber score, top 5 docking results, including nonoxynol-9, sildenafil citrate, benzonatate, nefazodone, hydrochloride, and erlotinib were selected for the further MD simulations analysis.

## Molecular dynamics simulations

MD simulations could evaluate the dynamic interactions between receptors and ligands within the given period of time. Herein, to further verify whether the conformational stability between top 5 potential small molecule drugs and HER2 could maintain stable, we performed a MD simulations through the protocol described above, which indicated that the time-evolving structure ensemble, representing the solution conformation of the proteins, exhibited different dynamic processes according to different ligands. The interaction energy (the sum of electrostatic and van der Waals interactions)[26] between the HER2 and its ligands was subsequently considered [Figure 1 and Table 2].

To assess the dynamic stability of each in 5 ligands, the RMSD of the atomic positions to examine the conformational variations of HER2 complexes for 5ns was developed. RMSD value is an important indicator of stability of drug–target interaction. The overall conformational evolution of the HER2-ligand complexes during the room temperature simulation was analyzed. From their starting structures, HER2-ZINC00538065 and HER2-ZINC01546066 have a similarly sharp rise during the first 0.5ns [Figure 2]. Notably, the HER2-ZINC08214629 system could reach its stability after 1.5ns, and the HER2-ZINC03830276 system had the trend of rise within 4.5ns, while the HER2-ZINC19796168 system exhibited maximum deviation. Seen from Table 2 and Figure 2, we can infer that the HER2-ZINC08214629 system and the HER2-ZINC03830276 system were much more stable than the others, which suggested that these two small molecules might exert a stronger affinity toward HER2.

To compare the flexibility of each residue in HER2-ligand complexes, a detailed analysis of the root-mean-square fluctuation versus the residue number in the complex is illustrated in Figure 3. As seen from this figure, HER2-ZINC19796168 complex exhibited higher flexibility while

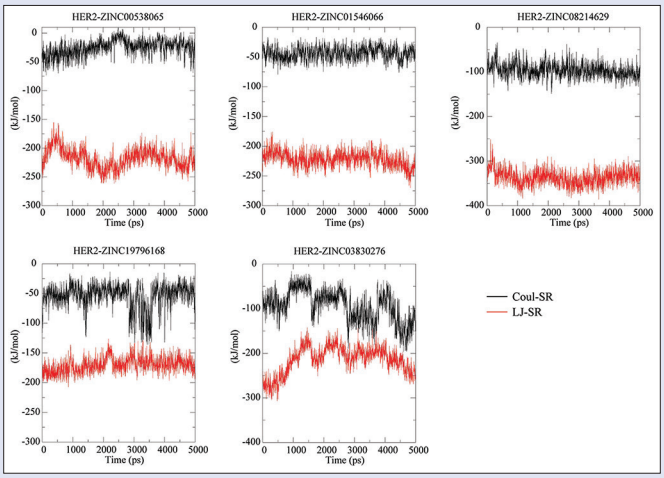



**Figure 1:** Root mean square deviations of human epidermal growth factor receptor-2-drug complexes backbone atoms during the molecular dynamics simulations

**Table 2:** Molecular dynamics simulations results of human epidermal growth factor receptor-2 in complex with Food and Drug Administration-approved small molecule drugs

| Ligand number | $E_{coul}$ | $E_{vdw}$ | Potential energy | Kinetic energy | Total energy | Interaction energy |
|---|---|---|---|---|---|---|
| ZINC00538065 | −24.8569 | −217.953 | −894,124 | 162,858 | −731,266 | −242.810 |
| ZINC01546066 | −43.8386 | −221.607 | −894,974 | 162,845 | −732,129 | −265.446 |
| ZINC08214629 | −96.5783 | −337.094 | −893,671 | 162,922 | −730,748 | −433.672 |
| ZINC19796168 | −54.1139 | −170.785 | −894,868 | 162,848 | −732,020 | −224.899 |
| ZINC03830276 | −93.5986 | −215.538 | −893,824 | 162,919 | −730,905 | −309.137 |

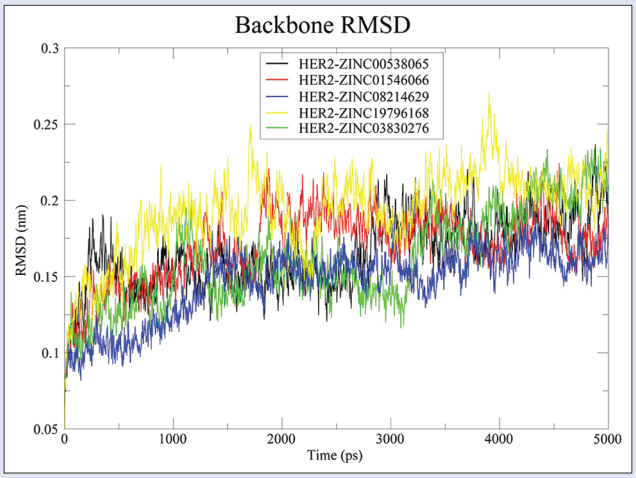



**Figure 2:** Root mean square fluctuations of the backbone atoms versus the residue number of the human epidermal growth factor receptor-2-drug complexes during molecular dynamics simulations

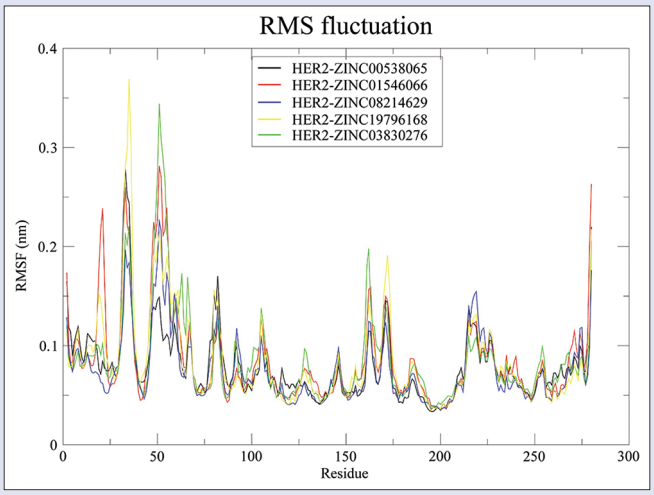



**Figure 3:** Secondary structural variations of human epidermal growth factor receptor-2-drug complexes during molecular dynamics simulations

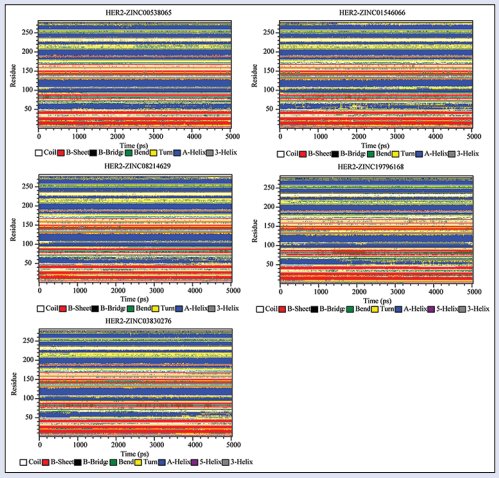



**Figure 4:** Plots for the composition of interaction energy of human epidermal growth factor receptor-2 with different small molecules during the molecular modeling

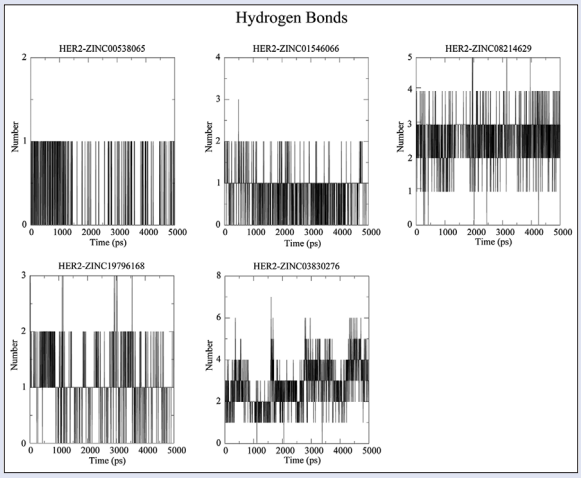



**Figure 5:** Hydrogen-bonding variations in human epidermal growth factor receptor-2-drug complexes during molecular dynamics simulations

HER2-ZINC0821469 complex exerted low flexibility in HER2-ligand complexes. In addition, the secondary structure could also depict the stability of such complexes. Figure 4 indicates that the residues 50–60 of HER2-ZINC03830276 change from A-helix to turn or 5-helix, and the residues 5–10 of HER2-ZINC19796168 vary from 3-helix to turn at 0.6ns while the other systems remain relatively stable. Moreover, hydrogen bonding variations in HER2-drug complexes during MD simulations were also shown in Figure 5. No water molecules are observed within the hydrophobic cavity throughout the whole simulations.

## DISCUSSION

It is known to all that kinase provides a rich and diverse source of potential targets for blocking tumor growth and survival. Moreover, protein kinase inhibitors have made a substantial beneficial impact on the therapeutic care of cancer patients. HER2 in a member of the

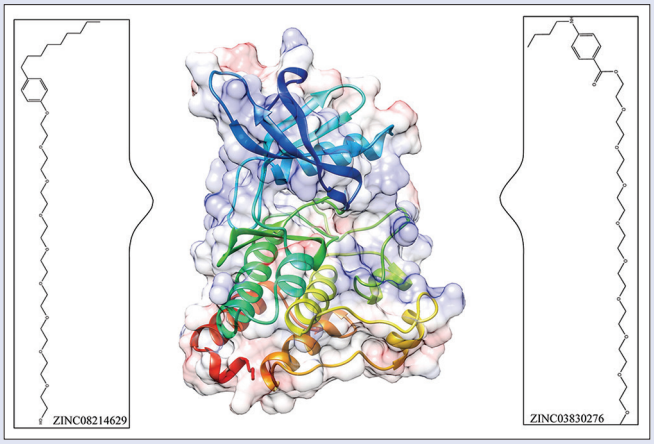



**Figure 6:** Potential Food and Drug Administration-approved small molecule drugs targeting human epidermal growth factor receptor-2

EGFR family of tyrosine kinases and aberrant signaling of HER2 is implicated in many human cancers. The gene is amplified in a subtype of breast cancers in which the HER2 network is the major driver of tumor cancer proliferation and survival, thus making it an attractive target for cancer therapy. To date, a limited number of HER2 kinase inhibitors have been assessed in clinical trials. Nevertheless, emerging data suggest that some HER2 mutant cancers show intrinsic resistances to current HER2 inhibitors with a number of mechanisms. Therefore, it is an urgent need to discover novel and potent novel kinase inhibitors.

Computer-aided drug design has been emerged as a promising and effective approach in drug discovery over the past two decades. Moreover, molecular docking is a standard computational tool to predict the experimental binding orientations and affinities of small molecules within the receptor-binding site. In this study, we recognized that 10 small molecules might potentially bind HER2 based upon their docking score. Subsequently, top 5 small molecules were manually selected for further MD simulation analysis due to their higher affinity with HER2. ZINC08214629 (Nonoxynol-9) and ZINC03830276 (Benzonatate) exerted relatively stable affinity and they were successfully chosen according to their MD analysis.

## CONCLUSION

Herein, we identified ZINC08214629 (Nonoxynol-9) and ZINC03830276 (Benzonatate) as the novel potential inhibitors of HER2 through targeting the intracellular tyrosine kinase domain of HER2 [Figure 6]. Moreover, these two small molecule compounds could potentially compete with ATP binding at the cytoplasmic catalytic kinase domain of HER-2 block autophosphorylation and activation of HER-2, resulting in the inhibition of downstream proliferation and survival signals, leading to an increase in apoptosis and decrease in cellular proliferation. In conclusion, our findings may not only serve as a paradigm for the repositioning of existing approved drugs, but also instill new vitality to HER2-targeted anti-cancer drugs.

## Acknowledgment

We are grateful to Miss. Wen-wen Li (University College London) for providing constructive suggestions. This work was supported in part by the National Natural Science Foundation of China (No. 51402027 and No. 51203157), science and technology support program of Science and Technology Department of Sichuan Province (2016NZ0060), open foundation of Sichuan Industrial Institute of Antibiotics, Antibiotics Research and Re-evaluation Key Laboratory of Sichuan Province (ARRLKF15-05) and Project of Department of Education of Sichuan Province and Project of Department of Education of Sichuan Province (16ZB0424 ).

## Financial support and sponsorship

This work was supported in part by the National Natural Science Foundation of China (No. 51402027 and No.51203157), science and technology support program of Science and Technology Department of Sichuan Province (2016NZ0060), open foundation of Sichuan Industrial Institute of Antibiotics, Antibiotics Research and Re-evaluation Key Laboratory of Sichuan Province (ARRLKF15-05) and Project of Department of Education of Sichuan Province, and Project of Department of Education of Sichuan Province (16ZB0424 ).

## Conflicts of interest

There are no conflicts of interest.

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