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Synthesis and biological evaluation of anti-cancer agents that selectively inhibit Her2 over-expressed breast cancer cell growth via down-regulation of Her2 protein

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ABSTRACT

Compound JCC76 selectively inhibited the proliferation of human epidermal growth factor 2 (Her2) over-expressed breast cancer cells. In the current study, a ligand based structural optimization was performed to generate new analogs, and we identified derivatives **16** and **17** that showed improved activity and selectivity against Her2 positive breast cancer cells. A structure activity relationship (SAR) was summarized. Compounds **16** and **17** were also examined by western blot assay to check their effect on Her2 protein. The results reveal that the compounds could decrease the Her2 protein, which explains their selectivity to Her2 over-expressed breast cancer cells. Furthermore, the compounds inhibited the chaperone activity of small chaperone protein that could stabilize Her2 protein.

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About 25–30% of breast cancer patients have human epidermal growth factor 2 (Her2) over-expressed tumors, and the tumor cells depend on the Her2 pathway to proliferate.[1] High expression of Her2 protein in tumors results in constitutive activation of the receptor and cell growth.[2,3] It has been well-documented that patients with over-expressed Her2 are associated with increased disease recurrence, worse prognosis and lower survival.[4] Targeting the extracellular domain of Her2 receptor could result in an efficient inhibition of breast cancer cell proliferation.[1,2,5,6] In addition, inhibition of intracellular signaling pathways of Her2 downstream could lead to suppression of cancer cell growth as well.[7] Currently, there are two types of drugs that target Her2 over-expressed cancer. The first group is Her2 monoclonal antibody drugs such as trastuzumab approved by FDA in 1998; the second type is intracellular tyrosine kinase inhibitors such as lapatinib approved in 2007.[8,9]

Although these drugs showed great efficiency in clinic for Her2 over-expressed breast cancer patients, resistance has been reported in patients with long term trastuzumab treatment.[9] There are multiple reasons for the resistance, and further increased Her2 expression in the cancer cells after the treatment is one of the resistant mechanisms.[10] Researchers used different strategies to reduce the Her2 level, and found that the cancer cells regained the sensitivity to trastuzumab.[10] Therefore, new agents that can decrease the amount of Her2 in breast cancer cells could be used for the Her2 over-expressed breast cancer treatment, and may also have the potential to overcome trastuzumab resistance.[11–13]

Our goal is to develop new anti-cancer compounds that could selectively inhibit the growth of Her2 over-expressed breast cancer cells, and then investigate the molecular mechanism of the pharmacological activity. Previously we identified a small molecule JCC76 that showed selectivity to inhibit the growth of Her2 over-expressed breast cancer cells.[14] In this study, structural optimization was performed to improve the biological activity and the selectivity of the lead compound (Fig. 1).

Compound JCC76 has been found to selectively inhibit the growth of SKBR-3 cells with an IC_{50} of 1–3 μM, and IC_{50}s of 20–25 μM to MCF-7 cells and MDA-MB-231 cells.[14] JCC76 was also found to inhibit a small chaperone protein heat shock protein 27 K_D (HSP27).[15] It has been reported that Her2 is a client protein of HSP27. The inhibition of HSP27 by JCC76 may affect the function of Her2, which explains the selectivity of JCC76 to Her2 over-expressed SKBR-3 cells.[10,16] To improve the potency, selectivity and ligand efficacy of JCC76, we further optimized the structure of this lead. Based on the structure activity relationship (SAR) summarized before, we either maintained the 2,5-dimethylbenzyl moiety or changed it to 2,5-dimethoxybenzyl group (Fig. 1),[15,17,18]

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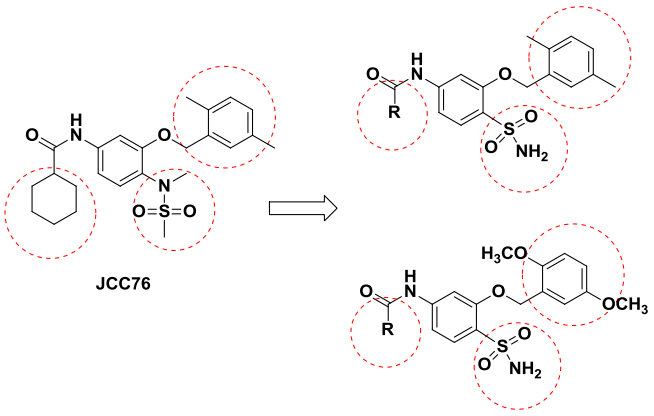


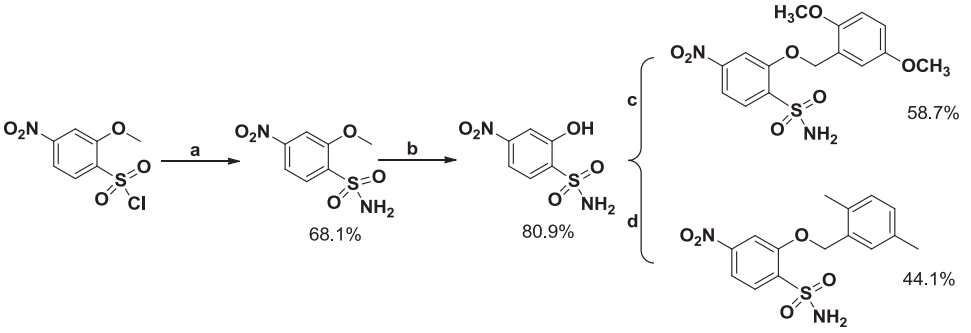
Fig. 1. Lead optimization of JCC76 to improve the ligand efficiency and biological activity.

followed by modification of the sulfonamide moiety via an orientation shift and removal of two methyl groups. These changes could increase the ligand efficacy and solubility. In addition, the amide moiety was constructed with various substituted benzamide to explore what the best functional group could be for this moiety. The synthesis of the new analogs is described in Schemes 1 and 2.

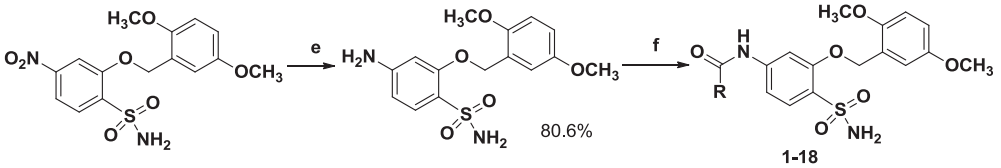
These new compounds were synthesized using methods adapted from previous studies.[15,17–20] Since the sulfonamide moiety was flipped in the new analogs compared to JCC76, the construction of the sulfonamide is different to previous synthetic methods. Twenty-three final compounds were synthesized.

The new derivatives were then examined for the potency and selectivity on the growth inhibition of three breast cancer cell lines including SKBR-3, MCF-7, and MDA-MB-231. SKBR-3 cells are Her2 positive and estrogen receptor (ER) negative, while MCF-7 cells are Her2 negative and ER positive, MDA-MB-231 cells are Her2 and ER negative. The activity of the compounds is summarized in Table 1.

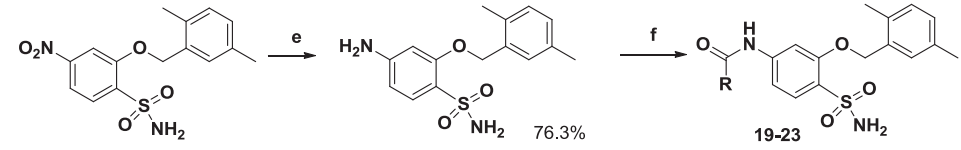
The IC_{50}s of the cell growth inhibition of the compounds range from 0.13 μM to 25.69 μM for SKBR-3 cells, 1.18 μM to 60.49 μM for MCF-7 cells, and 0.27 μM to 38.99 μM for MDA-MB-231cells. The selectivity is calculated by dividing the IC_{50}s of the compounds from different cell lines (Table 1). Most compounds exhibited higher growth inhibition in SKBR-3 cells compared to MCF-7 cells and MDA-MB-231cells, as indicated by the selective index (>1). For SKBR-3 cells, SAR analysis suggests that the benzamide group of



Scheme 1. (a) NH_3, H_2O, THF; (b) CH_2Cl_2, BBr_3; (c) 2,5-dimethoxybenzyl chloride, K_2CO_3, DMF; (d) 2,5-dimethylbenzyl chloride, K_2CO_3, DMF.



1. R=3-methoxyphenyl (71.7%)
2. R=3-methylphenyl(36.7%)
3. R=3-iodophenyl(46.3%)
4. R=3-bromophenyl(33.2%)
5. R=3-cyanophenyl(52.4%)
6. R=4-iodophenyl(37.5%)
7. R=2,4-trifluoromethylphenyl (24.3%)
8. R=4-trifluoromethoxyphenyl(61.3%)
9. R=3-cholophenyl(52.0%)
10. R=4-ethylphenyl (56.0%)
11. R=4-cyanophenyl (31.3%)
12. R=3-nitro 4-cholophenyl(52.1%)
13. R=3-ethoxyphenyl (52.5%)
14. R=4-bromophenyl (53.3%)
15. R=3,5-trifluoromethylphenyl(30.0%)
16. R=2-napthyl(52.5%)
17. R=4-methoxyphenyl (38.6%)
18. R=cyclohexanyl(77.0%)



19. R=4-iodophenyl(58.3%)
20 R=3-iodophenyl(55.8%)
21. R=cyclohexanyl(53.7%)
22. R=4-methoxyphenyl(64.2%)
23 R=4-bromophenyl(58.1%)

Scheme 2. (e) $FeCl_3$, Zn, DMF/H_2O; (f) RCOCl, K_2CO_3, 1,4-dioxane.