Design and Synthesis of Novel Tricyclic Oxazine Fused Quinazolines as Dual EGFR/HER2 Inhibitors
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Purpose
Kinase inhibitors are clinically utilized in cancer therapy; patients may develop resistance to these agents via secondary mutations or alternative mechanisms. Based on Lapatinib as a leading compound, we synthesized a series of new tricyclic oxazine fused quinazolines and evaluated their antitumor activity in this study.

Methods
A series of new tricyclic oxazine fused quinazolines were synthesized through intramolecular cyclization, all of which possessed functional Michael acceptor group in order to achieve potent antitumor activity. The structure of the compounds was determined using 1H NMR and MS. Antitumor effect of the compounds was screened on A431 (EGFR overexpression), BT474 (HER2 overexpression), N87 (HER2 overexpression), and H1975 (EGFR L858R/T790M mutation) cell lines by MTT assay in vitro. Inhibition of EGF-induced receptor autophosphorylation in the KB cell line was also assessed using a sandwich ELISA approach in vitro.

Results
The test compounds possessed variable degrees of cytotoxicity against A431 (IC50 0.13-2.49µM), BT474 (IC50 0.01-0.20µM), N87 (IC50 0.01-0.14µM), and H1975 (IC50 1.20-4.40µM), respectively. Compared to reference Lapatinib (IC50 0.04-7.37µM), most target compounds demonstrated higher antitumor activities in vitro. In addition, all test compounds counteracted EGF-induced receptor autophosphorylation in the KB cell line, and their potency (IC50 0.01-0.57µM) was comparable to Lapatinib (IC50 0.06µM). Structure-activity relationship (SAR) of the target compounds indicated that side chain with different aliphatic amines did not show significant effect on inhibitory activity of the molecules.

Conclusion
New tricyclic oxazine fused quinazolines from this study demonstrated potent and broad-spectrum anticancer activity in vitro.