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Discovery, Design and Synthesis of Some Novel Antitumor 1,2,4-Triazine Derivatives as C-Met Kinase Inhibitors

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Abstract : The receptor tyrosine kinase c-Met is an attractive target for therapeutic treatment of cancers nowadays. Among the wide variety of heterocycles that have been explored for developing c-Met kinase inhibitors, the 1,2,4-triazines have been rarely investigated, although they are well known in the literature to possess antitumor activities. Herein we describe the design and synthesis of a novel series of 1,2,4-triazine derivatives possessing N-acylarylhydrazone moiety and another series combining the 1,2,4-triazine scaffold to the well-known anticancer drug 6-MP in order to explore their “double-drug” effect. The synthesized compounds were evaluated for their in vitro antitumor activity against three c-Met addicted cancer cell lines (A549, HT-29 and MKN-45). Most compounds showed moderate to excellent antiproliferative activity and four compounds showed potent inhibitory activity more than the reference drug Foretinib against one or more cancer cell lines. The obtained results revealed that the potent compounds are highly selective to A549 (lung adenocarcinoma) cancer cell line. The c-Met kinase inhibitory activity of the potent derivatives is still under investigation. The present study clearly demonstrates that the 1,2,4-triazine core ring exhibits promising antitumor activity with potential c-Met kinase inhibitory activity.

Keywords : 1,2,4-triazine, antitumor, c-Met inhibitor, double-drug
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