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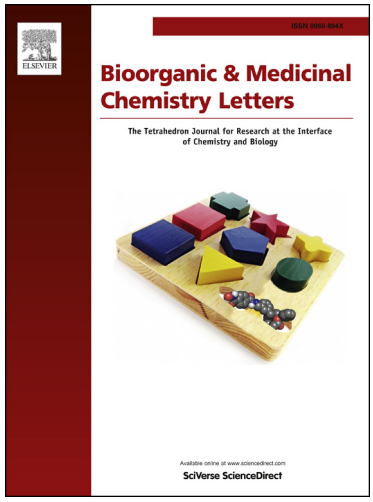


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# Identification of triazolo[4,5-b]pyrazine derivatives as hepatocyte growth factor receptor inhibitors through structure-activity relationships and molecular docking simulations

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ABSTRACT

c-MET is a receptor tyrosine kinase and potential oncological target for cancer therapy. Th e activities of 1,2,3-triazolo[4,5-b]pyrazine series of c-MET inhibitors were analyzed accor ding to the three-dimensional quantitative structure-activity relationship and molecular doc king methods.The results indicated that the hydrophobic and electrostatic fields play key ro les in activity and QSAR model was reliable enough for activity prediction. Moreover, the docking results do validate the predicted 3D-QSAR scores, vital residues Asp1222, Asp12 31, Met1160, Tyr1259 and Tyr1230 found in binding site. Four new c-MET inhibitor anal ogues designed in this letter which are being currently synthesized by our laboratories.



Cancer is a leading cause of death worldwide, thereby urging medical researchers to discover efficient drugs for this disease. c-Met or hepatocyte growth factor receptor is a receptor tyrosine kinase (RTK) structurally distinct from other RTK families and normally expressed by epithelial cells of organs (e.g., liver, pancreas, prostate, kidneys, muscle, and bone narrow) during embryogenesis and adulthood.[1,2]

c-MET is an important target for targeted cancer therapies.The normal HGF/c-Met signaling pathway exhibits important functions in invasive growth during embryonic development and postnatal organ regeneration; this signaling pathway is only fully active in adults for wound healing and tissue regeneration.[3] Aberrant HGF/c-Met signaling has been identified in human cancers of the bladder, breast, cervix, colorectum, endometrium, stomach, kidneys, liver, lung, pancreas, prostate, and thyroid.[4-10] Various c-Met mutations have been identified in several tumors, including hereditary and sporadic human papillary renal carcinomas, ovarian cancer, childhood hepatocellular carcinomas, gastric cancer, and lung cancer.[11] Given the increased cases of c-Met mutations in tumors, research institutions and pharmaceutical companies have focused on the development of c-MET inhibitors since the first crystal c-MET structures were published.[12] Clinical studies have analyzed the regulation of the HGF/c-MET pathway for oncological applications, such as c-Met monoclonal antibody (e.g., MetMab[13]), anti-HGF antibody (e.g., AMG 102, rilotumumab[14]), and small-molecule inhibitors (e.g., cabozantinib[15], crizotinib[16], and SU11274[17]; Fig. 1). Here, the small-molecule inhibitor through occupy the active site of the c-Met kinase domain, thereby prohibiting downstream phosphorylation.[18] Targeted cancer therapies have been more effective than current treatments and less harmful to normal cells. This strategy has elicited extensive attention as a consequence of potential inhibitor compounds that reach clinical trials, the success of Pfizer's PF-2341066 (crizotinib) in clinical treatments confirms the rational of this strategy.[19] However, these inhibitors exhibit limitations despite their excellent potencies. For example, people using crizotinib and cabozantinib experience side effects, such as sudden diarrhea and nausea. Therefore, these drugs may not fully provide protection, and a new generation of c-MET inhibitors is needed.