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Biological activity, Molecular Docking Studies and Molecular Dynamics Simulations of 2,3,4,5-Tetrahydro-1*H*-pyrido[4,3-b] indoles as c-Met inhibitors

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SUMMARY. c-Met has been deregulated in many cancers and become one of the leading molecular targets in cancer. In our previous research, we designed and synthesized six novel 2,3,4,5-tetrahydro-*1*H-pyrido[4,3-b] indoles as c-Met inhibitors. In this study, we evaluated their biological activity at cellular and molecular level. The results showed that the majority of the compounds exhibited significant inhibitory effect on c-Met with IC_{50} values of 0.0145-0.5 μM in TR-FRET-based assay and IC_{50} values of 1.34-34 μM in cell-based assay. Furthermore, our docking experiments analyzed the results and explained the molecular mechanism of eminent activities to c-Met and molecular dynamics simulations method was then applied to perform further evaluation of the binding stabilities between the compounds **4a**, **5a** and their receptor 3dkf.

RESUMEN. c-Met se ha desregulado en muchos tipos de cancer, por lo que se ha convertido en uno de los blancos moleculares en el tratamiento del cáncer. En una investigación anterior hemos sintetizado seis nuevos 2,3,4,5-tetrahidro-*1*H-pirido[4,3-b] indoles como inhibidores de c-Met. En este estudio se evaluó su actividad biológica a nivel celular y molecular. Los resultados mostraron que la mayoría de los compuestos exhiben efecto inhibidor significativo sobre c-Met con valores de IC_{50} de 0,0145 a 0,5 μM en el ensayo basado en TR-FRET-y valores de CI_{50} de 1.34-34 μM en el ensayo basado en células. Además, nuestros experimentos de anclaje analizaron los resultados y permiten explicar el mecanismo molecular de actividades eminentes para c-Met; el método de simulaciones de dinámica molecular se aplicó para realizar una evaluación adicional de las estabilidades de unión entre los compuestos **4a**, **5a** y su receptor 3dkf.

KEY WORDS: biological activity, c-Met inhibitors, molecular docking, molecular dynamics simulations, molecular mechanism, 2,3,4,5-tetrahydro-*1*H-pyrido[4,3-b] indoles.

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