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Design, synthesis and biological evaluation of novel α-acyloxy carboxamides via Passerini reaction as caspase 3/7 activators

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Abstract:

Evasion of apoptosis is a hallmark of cancer. Caspases; the key executors of apoptotic cascade are attractive targets for selective induction of apoptosis in cancer cells. Within this approach, various caspase activators were introduced as lead anticancer agents. In the current study, a new series of multifunctional Passerini products was synthesized and evaluated as potent caspase-dependent apoptotic inducers. The synthetic strategy adopted this isocyanide-based multicomponent reaction to possibly mimic the pharmacophoric features of various lead apoptotic inducers, where a series of α-acyloxy carboxamides was prepared from p-nitrophenyl isonitrile, cyclohexanone and various carboxylic acids. Accordingly, the main amide-based scaffold was decorated by substituents with varying nature and size to gain more information about structure-activity relationship. All the synthesized compounds were screened for cytotoxicity against normal human fibroblasts and their potential anticancer activities against three human cancer cell lines; MCF-7 (breast), NFS-60 (myeloid leukemia), and HepG-2 (liver) utilizing MTT assay. Among the most active compounds, 13, 21 and 22 were more potent and safer than doxorubicin with nanomolar IC_{50} values and promising selectivity indices. Mechanistically, 13, 21 and 22 induced apoptosis by significant caspase activation in all the screened cancer cell lines utilizing flow cytometric analysis and caspase 3/7 activation assay. Again, 13 and 21 recorded higher activation percentages than doxorubicin, while 22 showed comparable results. Apoptosis-inducing factor1 (AIF1)

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quantification assay declared that 13, 21 and 22 didn't mediate apoptosis through AIF1-dependent pathway (i.e. only by caspase activation). Physicochemical properties, pharmacokinetic profiles, ligand efficiency metrics and drug-likeness data of all the synthesized compounds were computationally predicted and showed that 13, 21 and 22 could be considered as drug-like candidates. Finally, selected compounds were preliminarily screened for possible antimicrobial activities searching for dual anticancer/antimicrobial agents as an advantageous approach for cancer therapy.

Reference:

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