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Design, synthesis, and biological evaluation of cyanopyrimidine-based chalcones targeting lysine-specific demethylase 1 as anticancer agents

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ABSTRACT A new series of 12 cyanopyrimidine-based chalcone derivatives was rationally designed, synthesized, characterized, and evaluated as promising anticancer agents targeting lysine-specific demethylase 1 (LSD1). The synthesis of the derivatives involved nucleophilic substitution of the chloro group in the cyanopyrimidine moiety by the hydroxyl group bearing chalcones using cesium carbonate as a catalytic base and acetonitrile as the solvent. *In silico* molecular docking and Molecular Mechanics–Generalized Born Surface Area calculations revealed excellent binding affinities of the compounds to LSD1, complemented by highly favorable ADMET profiles. *In vitro* anticancer activity was assessed using the National Cancer Institute one-dose sulforhodamine B assay at 10 μM, where most compounds demonstrated moderate to potent growth inhibition. Notably, compound **5a** emerged as the lead candidate, exhibiting the strongest anticancer efficacy against RPMI-8226, MCF7, and HCT-116 cell lines. Further validation through the MTT assay confirmed the exceptional potency of **5a** in HCT-116 colorectal cancer cells, where it effectively induced apoptosis and G2/M phase cell cycle arrest, thereby robustly suppressing tumor cell proliferation. Compound **5a** also potently inhibited LSD1 enzymatic activity with an impressive IC_{50} value of 0.52 μM, underscoring its direct target engagement. These compelling findings establish this scaffold as a privileged structure for LSD1 inhibition and highlight **5a** as a promising therapeutic candidate.

KEY WORDS Cancer, Chalcone, Lysine-specific demethylase 1, MD simulation, Molecular docking, Pyrimidine.

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