3,5-Disubstituted Thiadiazine-2-thiones: New Cell-Cycle Inhibitors

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Abstract:

Two series, a and b, of 3-cyclopentyl or (3-cyclohexyl)-5-substituted-3,4,5,6-tetrahydro-2H-1,3,5-thiadiazine-2-thiones (THTT) 2a-9a and 3b, 4b, 6b-9b, were synthesized to develop new cell cycle inhibitors. Variable and promising in vitro antiproliferative activities were shown with the synthesized THTT derivatives. Compound 5a with a 5-cyclopentyl group on position-3 and a glutamine residue on position-5 of the THTT moiety showed maximum activity (IC50 = 8.98 μM). Compound 5a possessed notable cell cycle disrupting and apoptotic activities with enhanced selectivity against cancer cells, suggesting the potential for the development of new selective cell cycle inhibitors. There is no evident relationship between the cytotoxic activity of the tested compounds and their lipophilicity. In addition, a pharmacophore based study was performed to explain the biological activity on structural bases. A successful model was generated with a good correlation with the observed activity.

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