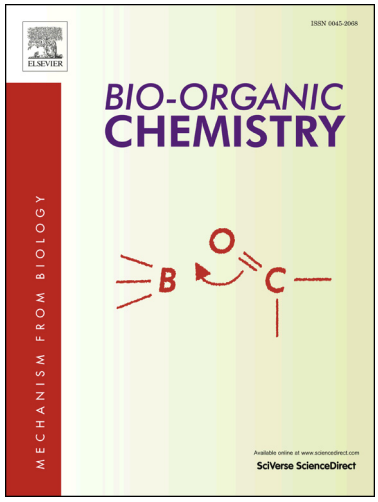

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Evaluation of 4-thiazolidinone derivatives as potential reverse transcriptase inhibitors against HIV-1 drug resistant strains

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ABSTRACT

Rapid emergence of drug resistance is crucial in management of HIV infection limiting implementation of efficacious drugs in the ART regimen. Designing new molecules against HIV drug resistant strains is utmost essential. Based on the anti-HIV-1 activity, we selected four 4-thiazolidinone derivatives (S009-1908, S009-1909, S009-1911, S009-1912) and studied their interaction with reverse transcriptase (RT) from a panel of 10 clinical isolates (8 nevirapine resistant and two susceptible) using in-silico methods, and inhibition pattern using in-vitro cell based assays. On the basis of binding affinity observed in in-silico analysis, 2-(2-chloro-6-nitrophenyl)-3-(4, 6-dimethylpyridin-2-yl) thiazolidin-4-one (S009-1912) was identified as the lead molecule followed by S009-1908, S009-1909 and S009-1911. The in-vitro activity against the same panel was assessed using TZM-bl assay (IC50: 0.4 to 11.44 µg/ml, TI: 4 to 126) and subsequently in PBMC assay against a nevirapine resistant clinical isolate (IC50: 0.8 to 6.65 µg/ml, TI: 8.31 to 11.43) and standard strain from NIH ARRRP (IC50: 0.95 to 3.6 µg/ml, TI: 9 to 26). The study shows analogue with pyrimidin-2-yl amino substitution at N-3 position of thiazolidin-4-one ring (S009-1908, S009-1909, S009-1911) exhibited enhanced activity as compared to pyridin-2-yl substituted