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4-acyl-1-phenylaminothiocarbonyl-2-methylpiperazine derivatives as potent inhibitors of adenovirus infection

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Background: Human adenoviruses (HAdV) are the cause of many different acute infections mostly in the respiratory and gastrointestinal tracts, as well as conjunctivitis. HAdV disease is a cause of potentially life-threatening viral diseases in immunosuppressed patients as well as in immunocompetent patients suffering community-acquired pneumonia. Unfortunately, despite the significant clinical impact, there are no antiviral agents currently approved for the treatment of HAdV infections. In previous works (Sanchez-Cespedes *et al.*, *J Med Chem.* 2016 and Sanchez-Cespedes *et al.*, *Antiviral Res.* 2014) we used high-throughput screening (HTS) of synthetic small molecule libraries to identify piperazine derivatives that restrict HAdV infection. Methyllpiperazine derivatives containing thioureas substitutions at N1 demonstrated a very high activity blocking HAdV infection, but they were dismissed because of their high cytotoxicity. Here, we show the design and evaluation of a new set of methylpiperazine derivatives with thiourea substitutions at N1, aiming to keep their high anti-HAdV activity but decreasing their cytotoxicity.

Material/methods: HAdV inhibition of infection was evaluated by plaque and entry assays. HAdV DNA replication efficiency in the presence of the compounds was evaluated by quantitative real-time

PCR (qPCR). Virus yield in presence of the selected derivatives was evaluated in a burst assay where the $TCID_{50}$ values were calculated using an endpoint dilution method (Lee, A. *et al*., *J Biol Chem.* 2008). Statistical analyses were performed with the GraphPad Prism 5 suite.

Results: We have identified seven 4-acyl-1-phenylaminothiocarbonyl-2-methylpiperazine derivatives, by the screening of four generations of designed analogues that significantly inhibited HAdV infection. Main results for their anti-HAdV activity and their mechanistic assays are showed in the following table:

COMPOUND	Plaque assay inhibition	IC_{50}	Yield reduction	% DNA replication inhibition	CC_{50}
585	92.91±3.82	1.78±0.87	12.08±2.78	0.00±0.00	200.00
613	100.00±0.00	2.53±0.77	9.30±2.90	0.00±0.00	193.04
616	100.00±0.00	0.57±0.23	30.53±12.94	0.00±0.00	143.36
619	95.79±4.82	2.06±0.42	39.05±15.95	46.57±14.79	122.21
628	98.21±3.57	2.04±0.39	25.59±10.45	17.55±30.80	210.38
634	99.50±1.58	5.12±0.47	33.42±10.16	87.98±11.78	129.74
635	98.36±2.13	4.59±0.10	18.39±5,44	21.2±5.46	174.69

Conclusions: The selected seven 4-acyl-1-phenylaminothiocarbonyl-2-methylpiperazine derivatives showed potent anti-HAdV activity at low micromolar concentrations, showing low cytotoxicity. Based on our mechanism studies these molecules block HAdV infections at different points of the HAdV life cycle. Compounds 634 and 619 target the DNA replication process and compounds 585, 613, 616, 628 and 635 target later steps on the HAdV life cycle. Although further optimization and characterization of the mechanisms of action will be required for these compounds, they could represent hit candidates for the development of a new class of antiviral compounds.