Synthesis and anti-HIV Activity of New Benzimidazole, Benzothiazole and Carbohyrazide Derivatives of the anti-Inflammatory Drug Indomethacin

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There is an urgent need for the design and development of new and safer drugs for the treatment of HIV infection, active against the currently resistant viral strains. New derivatives of the non-steroidal anti-inflammatory drug indomethacin bearing benzimidazoles, benzothiazole, purine and pyridine residues \textsuperscript{8}–\textsuperscript{13} were synthesized with the aim of developing new non-nucleoside reverse transcriptase inhibitors (NNRTIs). Alternatively, new imine analogs \textsuperscript{16}–\textsuperscript{20} were synthesized from condensation of indomethacinyl hydrazide \textsuperscript{15}, prepared from the ester \textsuperscript{14}, with various ketone precursors. Treatment of \textsuperscript{15} with phenyl isothiocyanate or triethyl orthoformate afforded the phenylcarbonothioyl and the oxadiazole derivatives \textsuperscript{21} and \textsuperscript{22}, respectively. The new compounds were assayed against HIV-1 and HIV-2 in MT-4 cells. Compounds \textsuperscript{9} and \textsuperscript{10} were the most active in inhibiting HIV-2 and HIV-1, respectively, with $EC_{50} \geq 17.60 \, \mu g \, mL^{-1}$ and $> 1.15 \, \mu g \, mL^{-1}$ (therapeutic indexes (SI) of $\geq 3$ and $< 1$, respectively), and are leading candidates for further development.

\textit{Key words:} Anti-HIV Activity, Benzimidazole, Indomethacin, Non-nucleoside Reverse Transcriptase Inhibitors