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Synthesis and biological prospection of new derivatives 4-quinolone-3-hydroxamic acids with potential activity anti-HSV

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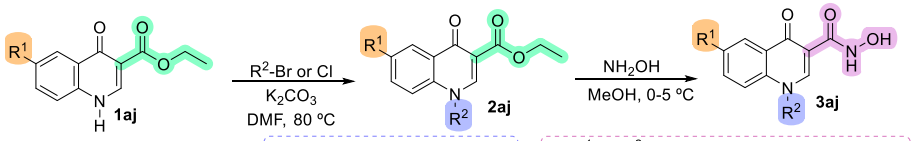
ABSTRACT

4-quinolones are studied for their broad biological spectrum[1]. In this context Elvitegravir exemplifies a 4-quinolone used in clinical HIV treatment. Hydroxamic acids (HA) are studied as antiviral agents due to their coordination properties[2,3]. Thus, this study aim is to modify the 4-quinolone nucleus by introducing the HA group, resulting in derivatives **3aj** evaluated for their anti-HSV activity. The synthesis initially involved an alkylation reaction of 4-quinolones **1aj** followed by a S_N2 reaction with different alkylation reagents. The HA **3aj** were obtained through nucleophilic displacement on **2aj** previously synthesized, using hydroxylamine solution (NH_2OH) as the nucleophile, prepared *in situ* by treating $NH_2OH.HCl$ with KOH using methanol as solvent (Scheme 1). The synthesis was realized after methodological optimization and the newly **3aj** synthesized were structurally characterized (IR, MS, ^1H,^{13}C NMR and m.p.), yielding 18-67%. Ultimately the HA were subjected to anti-HSV activity tests, showing significant results with inhibition 60% to 100%.



2a: R^1:Cl; R^2: pr - 91% - 127 °C
b R^1:Br; R^2: pr - 89% - 140 °C
c R^1:F; R^2: pr - 80% - 132 °C
d R^1:Cl; R^2: pe - 87% - 103 °C
e R^1:CH_3; R^2: pe - 87% - 95 °C
f R^1:Cl; R^2: bn - 88% - 185 °C
g R^1:Br; R^2: bn - 87% - 165 °C
h R^1:F; R^2: bn - 88% - 210 °C
i R^1:H; R^2: bn - 80% - 121 °C
j R^1:I; R^2: bn - 79% - 129 °C

3a: R^1:Cl; R^2:pr - 63% - 201 °C (inhib 72%)
b R^1:Br; R^2:pr - 45% - 193-195 °C (inhib 81%)
c R^1:F; R^2:pr - 67% - 212 °C (inhib 60%)
d R^1:Cl; R^2:pe - 42% - 223-225 °C (inhib 61%)
e R^1:CH_3; R^2:pe - 51% - 220-222 °C (inhib 85%)
f R^1:Cl; R^2:bn - 42% - 223-225 °C (inhib100%)
g R^1:Br; R^2:bn - 44% - 214-215 °C (inhib 100%)
h R^1:F; R^2:bn - 18% - 224-226 °C (inhib 96%)
i R^1:H; R^2:bn - 54% - 202-203 °C (inhib 95%)
j R^1:I; R^2:bn - 32% - 196-198 °C (inhib 72%)

Scheme 1. Synthesis methodology for obtaining HA **3aj**.

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