Synthesis, *In vitro* Anti-HIV Activity, Cytotoxicity and Computational Studies of Some New Steroids, Their Pyrazoline and Oxime Analogues

Wasfi A. Al-Masoudi[a], Najim A. Al-Masoudi[b, 1], Bahjat A. Saeed[c], Rainer Winter[d], and Christophe Pannecouque[e]

[a]*Department of Physiology, Pharmacology and Chemistry, College of Veterinary, University of Basrah, Basrah 61001, Iraq*

[b]*Department of Chemistry, College of Science, University of Basrah, Basrah 61001, Iraq, Present address: 78464 Konstanz, Germany*

[c]*Department of Chemistry, College of Education, University of Basrah, Basrah 61001, Iraq*

[d]*Department of Chemistry, University of Konstanz, P.O. Box 5560, D-78464 Konstanz, Germany*

[e]*Rega Institute for Medical Research, Katholieke Universiteit Leuven, B-3000 Leuven, Belgium*

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Abstract—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 by development of new non-nucleoside reverse transcriptase inhibitors (NNRTIs). A series of pregnenolone analogues, 3-((aryl)-1-(5-pregnen-3β-ol-17-yl)prop-2-en-1-ones, were synthesized. Further, treatment of 3-((4-bromo-, 4-trifluoromethyl, or 4-methylphenyl)-1-(preg-5-en-3β-ol-17-yl)prop-2-en-1-ones with thiosemicarbazide in ethanolic KOH or hydrazine hydrate in HOAc gave 5-(4-bromo-, 4-trifluoromethyl, or 4-methylphenyl)-3-(preg-5-en-3β-ol-17-yl)-4,5-dihydro-1*H*-pyrazoline-1-carbothioamides and 1-*O*-acetyl-(5-(4-bromophenyl)-3-(preg-5-en-3β-ol-17-yl)-4,5-dihydro-1*H*-pyrazoline, respectively. Analogously, treatment of 3-((4-bromophenyl)-1-(preg-5-en-3β-ol-17-yl)prop-2-en-1-one with hydroxylamine afforded the *Z/E* isomers of 3-(4-bromophenyl)-1-(preg-5-en-3β-ol-17-yl)prop-2-en-1-one oxime. The new compounds were assayed against HIV-1 and HIV-2 in MT-4 cells. Compounds 3-(thiophene-2-yl)-1-(preg-5-en-3β-ol-17-yl)prop-2-en-1-one and 1-*O*-acetyl-(5-(4-bromophenyl)-3-(preg-5-en-3β-ol-17-yl)-4,5-dihydro-1*H*-pyrazoline were the most active in inhibiting HIV-1 and HIV-2 with IC_{50} = 60.5 μM (SI > 2, against HIV-2 and SI < I against HIV-1), and > 0.29 μM (SI < I), respectively, suggesting to be new leads in the development of antiviral agents. QSAR of 3-((aryl)-1-(5- pregnen-3β-ol-17-yl)prop-2-en-1-ones and 5-(substituted phenyl)-3-(5-preg-5-3β-ol-17-yl)-4,5- dihydro-1*H*-pyrazole-1-carbothioamides has been studied. The conformational analysis of 5-(4-trifluoromethylphenyl)-3-(preg-5-en-3β-ol-17-yl)-4,5-dihydro-1*H*-pyrazoline-1-carbothioamide and 1-*O*-acetyl-(5-(4-bromophenyl)-3-(preg-5-en-3β-ol-17-yl)-4,5-dihydro-1*H*-pyrazoline as well as the molecular docking study of the latter compound have been investigated

Keywords: *anti-HIV activity, α-unsaturated ketones, cytotoxicity, molecular docking study, QSAR, pregnenolone*

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[1] Corresponding author: e-mail: najim.al-masoudi@gmx.de (web: www.al-masoudi.de).

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