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Synthesis, biological activity and modeling study of some thiopyrimidine derivatives and their platinum(II) and ruthenium(III) metal complexes

Abstract: A new series of 6-amino-5-(aryldiazenyl)-N^1,N^3-dimethyl-2-thioxo-pyrimidin-4-one derivatives **17**–**27** and the N^1-methyl-azothiopyrimidine analog **28** were synthesized from the pyrimidine derivatives **4** and **5**, respectively, via diazotization reaction, with various amines. The platinum(II) metal complexes [bis(4-amino-N^3-methyl-6-oxo-2-thioxo-pyrimidin-1-yl)]Pt(II) (**29**) and [(6-amino-5-(4-*R*-phenyl)diazenyl)-N^1,N^3-dimethyl-2-thioxo-pyrimidin-4-one)]Pt(II)Cl_2 derivatives **30**–**33** were prepared from the treatment of **5** and the azo analogs **17** and **21**–**23** with $PtCl_2$, respectively. Analogously, **5** and **17** were treated with $RuCl_3 \cdot 3H_2O$ to give the Ru(III) complexes **34** and **35**, respectively. The newly synthesized compounds were assayed against HIV-1 and HIV-2 in MT-4 cells. The results revealed that **26** and **30** were the only compounds in the series inhibiting HIV replication in cell cultures with an IC_{50} value of >2.07 and >3.02 μg mL^{-1}, respectively. The molecular modeling interactions of **26** with some amino acids of HIV reverse transcriptase were studied. In addition, the antibacterial activity of **17**–**35** and **31**–**33** against *Staphylococcus aureus* and *Escherichia coli* was evaluated.

Keywords: antibacterial activity; anti-HIV activity; diazotization; molecular modeling study; thiopyrimidines.

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1 Introduction

The pyrimidine molecule is a promising structural moiety for drug design because it forms a component in a number of useful drugs and is associated with many biological and therapeutic activities [1]. Besides the biological significance of pyrimidine, several of its derivatives have been developed as chemotherapeutic agents and have found wide clinical applications such as antiviral [2, 3], antiprotozoal [4], antimicrobial, anti-insecticidal [5–8], anticancer [9–14], antihypertensive [15], antihypoglycemic and hypolipidemic [16], and anti-HIV agents [17–19], in addition to their cardiovascular [20] and diuretic [21, 22] properties. Furthermore, some pyrimidines are used as hypnotic and sedative drugs [23, 24]. Two diarylpyrimidines (DAPY), rilpivirine (**1**) [25] and etravirine [26, 27], have been classified as non-nucleoside reverse transcriptase inhibitors, whereas bacimethrin (4-amino-5-(hydroxymethyl)-2-methoxypyrimidine) (**2**) (Fig. 1) is a pyrimidine antibiotic that is active against several staphylococcal bacteria [28].

Some platinum and ruthenium complexes play a crucial role in preclinical as well as in clinical studies. Saha and Muherjee [29] have reported the metal complexes of palladium(II) and platinum(II) **3** of (3,5-dimethyl-2′-pyrimidyl)pyrazole as potent anticancer agents (Fig. 1). Furthermore, we have reported the synthesis and anti-HIV activity of a new series of Pt(II), as well as those of other metal complexes with 3-methyl-6,7-diphenyllumazine [30]. In addition, Joshi et al. [31] have discussed the selectivity of anticancer drugs toward cancer cells as one of the main goals of drug optimization, by using the complexes $Ru(dppz)_2(CppH)](PF_6)_2$ [where CppH = 2-(2-pyridyl)pyrimidine-4-carboxylic acid and dppz = dipyrido[3,2-*a*:2′,3′-c] phenazine)] as a "photocaging" agent to give a light illumination at 350 nm for detection of cancer cells. This is the first substitutionally inert cytotoxic metal complex to be used as a light-triggered prodrug candidate.

In continuation of our ongoing work on the synthesis of a new anti-HIV agent and our recent antiviral data on new pyrimidine derivatives [32–34], we report here the synthesis of a new series of pyrimidines having arylazo residues, including some of their Pt(II) and Ru(III) metal complexes, and the evaluation of their anti-HIV and antibacterial activities, together with a molecular modeling study.

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