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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,N*-dimethyl-2-thioxo-pyrimidin-4-one derivatives **17–27** and the *N*-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,N*-methyl-6-oxo-2-thioxo-pyrimidin-1-yl)]Pt(II) (**29**) and [(6-amino-5-(4-*R*-phenyl)diazenyl)-*N,N*-dimethyl-2-thioxo-pyrimidin-4-one]Pt(II)Cl₂ derivatives **30–33** were prepared from the treatment of **5** and the azo analogs **17** and **21–23** with PtCl₂, respectively. Analogously, **5** and **17** were treated with RuCl₃·3H₂O 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 IC₅₀ 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-diphenylumazine [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)(PF₆)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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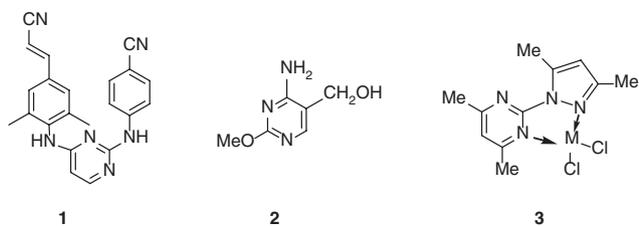


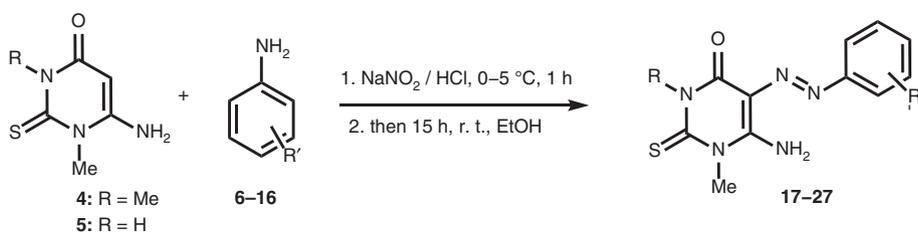
Fig. 1: Chemical structures of rilpivirine (1), bacimethrin (2) and $[M(\text{pyrimidinyl-pyrazole})\text{Cl}_2]$ [$M=\text{Pt}, \text{Ru}(\text{Cl})$] complexes (3).

2 Results and discussion

6-Amino-5-(aryldiazenyl)- N^1, N^3 -dimethyl-2-thioxo-pyrimidin-4-one derivatives **17–27** were prepared in 40–92 % yield via diazotization reaction by treatment of 6-amino- N^1, N^3 -dimethyl-2-thioxo-pyrimidin-4-one (**4**) with various substituted amines – 4-chloro- (**6**), 4-bromo- (**7**), 4-nitro- (**8**), 4-methyl- (**9**), 4-sulfonamido- (**10**) and 4-sulfonolactamido- (**11**) anilines – as well as with *p*-aminobenzoic acid (**12**), *p*-aminosulfonic acid (**13**), sulfadiazine (**14**), sulfamerazine (**15**) and sulfamethazine (**16**), in the presence of NaNO_2 and HCl at 0–5 °C, then at ambient temperature for 15 h. Under similar conditions, azothiopyrimidine **28** was prepared in 68 % yield from diazotization of 6-amino- N^1 -methyl-2-thioxo-pyrimidin-4-one (**5**) (Scheme 1).

The structures of **17–28** were assigned on the basis of their ^1H , ^{13}C NMR and mass spectra. The ^1H NMR spectra showed similar patterns for the aromatic and pyrimidine protons and carbon atoms, where the NH_2 group of **17**, **18**, **20** and **23–25** resonated as two separated singlets at the regions $\delta = 9.14\text{--}11.75$ ppm and $\delta = 8.64\text{--}9.02$ ppm, and

this pattern was due to the hydrogen bonding between the NH_2 group and the nitrogen atom of the azo residue. Compound **20** was selected for ^1H NMR measurement at high temperature (364 K), which revealed the appearance of a broad singlet at $\delta = 9.99$ ppm assigned to the NH_2 group, which was exchangeable with D_2O , and the disappearance of NH_2 protons at $\delta = 11.64$ and 8.65 ppm (92 K). The aromatic, pyrimidine and methyl protons were fully analyzed (see Experimental Section). In the ^{13}C NMR spectra of **17–28**, the resonances at the regions $\delta = 177.2\text{--}179.1$ and 157.0–151.0 ppm were assigned to C-2 (C=S) and C-4 of the thiopyrimidine ring, whereas the resonances at the regions $\delta = 75.0\text{--}82.7$ and 157.1–165.5 ppm were attributed to C-5 and C-6 of the same ring, respectively. The other carbon atoms of the pyrimidine and aromatic substituents were fully assigned (see Experimental Section), whereas all the synthesized compounds were confirmed from their ^1H and ^{13}C HSQC NMR spectra [35]. Compound **27** was selected for further NMR experiments. The gradient HMBBC [36] NMR spectrum of **27** revealed two $^2J_{\text{C,H}}$ couplings: the aromatic carbon atom C-1' at $\delta = 143.5$ ppm showed a $^2J_{\text{C,H}}$ coupling with 2'-H and 6'-H of the same ring at $\delta = 8.08$ ppm, whereas the other one was observed between 5''-H of the pyrimidine ring at $\delta = 6.67$ ppm and two methyl carbon atoms attached to C-4' and C-6'' of the same ring at $\delta = 23.0$ ppm. Furthermore, C-2 (C=S) of the pyrimidine ring at $\delta = 177.5$ ppm showed two $^3J_{\text{C,H}}$ couplings, one with N^1 -Me protons at $\delta = 3.69$ ppm and the other with N^3 -Me protons at $\delta = 3.89$ ppm. In addition, a $^3J_{\text{C,H}}$ coupling was observed between C-5'' of the pyrimidine scaffold at $\delta = 113.1$ ppm and the two methyl carbon atoms attached to C-4'' and C-6'' of the same ring at $\delta = 23.0$ ppm (Fig. 2).



Compd.	R'	R'	Compd.
6, 17	4-Cl	4-SO ₃ H	12, 23
7, 18	4-Br	4-SO ₂ NHCOMe	13, 24
8, 19	4-NO ₂	4-(SO ₂ NH-2-pyrimidine)	14, 25
9, 20	4-Me	4-(SO ₂ NH-2-(4-methylpyrimidine))	15, 26
10, 21	4-CO ₂ H	4-(SO ₂ NH-2-(4,6-dimethylpyrimidine))	16, 27
11, 22	4-SO ₂ NH ₂		

17–27: R = Me

28: R = H; R' = 4-SO₂NH₂

Scheme 1: Synthesis of the 6-amino-5-aryl-diazenyl- N^1, N^3 -dimethyl-2-thioxo-pyrimidin-4-one derivatives (**17–27**) and of the N^1 -methyl analog (**28**).

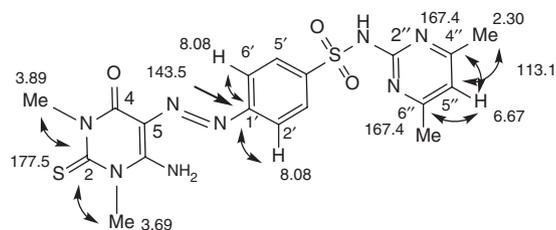


Fig. 2: Chemical shifts (δ , ppm) and $J_{C,H}$ correlations in the HMBC NMR spectrum of **27**.

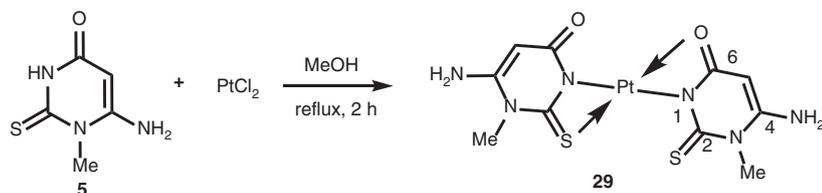
Our procedure was modified by preparing some new platinum(II) and ruthenium(III) complexes. Thus, compound **5** was selected as a precursor for the synthesis of the new platinum(II) complex **29** in 48 % yield from the treatment of **5** with $PtCl_2$ in hot MeOH, aiming to examine its antiviral activity (Scheme 2). The structure of **29** was determined from the elemental analysis, 1H , ^{13}C NMR and IR spectra (see Experimental Section). In the ^{13}C NMR spectrum of **5**, carbon atoms 2 and 4–6 appeared at $\delta = 179.7$, 164.4, 160.1 and 79.6 ppm, respectively. In the IR spectrum, $\nu(C=O)$ and $\nu(C=S)$ of the free ligand **5** were observed at 1630 and 1099 cm^{-1} , respectively, which shifted to 1649 and 1134 cm^{-1} for complex **29**. This indicated that the $>C=O$ and $>C=S$ groups of the ligand are involved in the bonding with metal ions. The $\nu(NH_2)$ observed at 3100 and 3400 cm^{-1} in the spectrum of free ligand remained constant in the spectrum of the complex. This observation is in agreement with the data reported by Masouda et al. [37] and Parthasarathi et al. [38] concerning the metal complexes of some thiouracil derivatives. The spectrum of **29** also showed a low wavenumber band at 448 cm^{-1} , characteristic for a $\nu(Pt-O)$ coordinated bond, as expected [39], whereas a band at 706 cm^{-1} was probably due to a pyrimidine-ring vibration [40]. These data suggested that the geometrical structure of **29** is a distorted square planar. The chelation via N and S donor atoms and the formation of a four-membered ring at **29** are in agreement with the X-ray data of the related complex $Pt(\eta^2-N,S\text{-pymS})(\eta^1-S\text{-pymS})(PPh_3)_2$ reported by Lobana et al. [41].

The platinum complexes of some synthesized azothiopyrimidine analogs had been explored, aiming to study

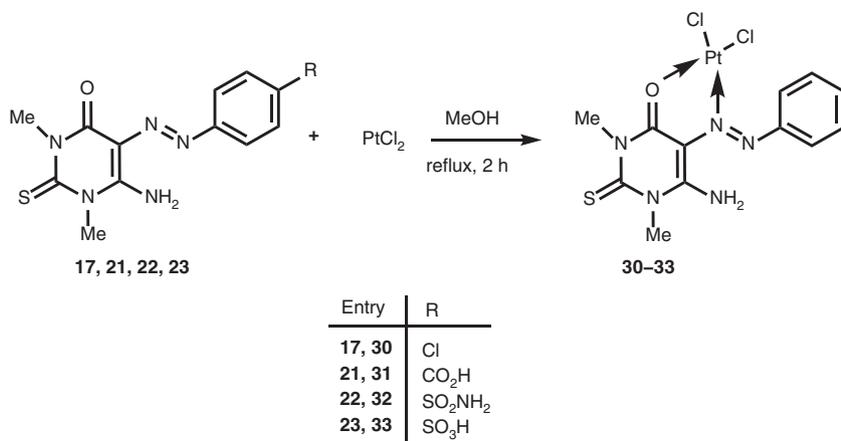
their stereochemical geometry in addition to evaluating their anti-HIV activity. Thus treatment of the azo ligands **17** and **21–23** with $Pt(II)Cl_2$ in refluxing MeOH gave, after purification, the desired $Pt(II)$ complexes $[(AzPym-Cl)PtCl_2]$ **30–33** in 55 %, 46 %, 45 % and 58 % yield, respectively (Scheme 3).

The structures of **30–33** were assigned from the elemental analysis, 1H , ^{13}C NMR and IR spectra, since they showed similar patterns of aromatic and pyrimidine protons. In the ^{13}C NMR spectra, the lower field resonances at $\delta = 178.2$ – 177.4 ppm were assigned to C-2, whereas the resonances at $\delta = 154.8$ – 153.2 ppm were attributed to C-4 of the pyrimidine ring, respectively. The resonances at $\delta = 84.1$ – 77.8 and 158.5– 156.7 ppm were assigned to C-5 and C-6 of the same ring, respectively. The aromatic carbon atoms were fully analyzed (see Experimental Section). The IR spectra of the free ligands **17** and **21–23** showed the characteristic $\nu(C=O)$ bands in the 1626, 1629, 1630 and 1641 cm^{-1} region, respectively, which shifted to higher wavenumbers in the spectra of the metal complexes **30–33** (1656, 1675, 1653 and 1657 cm^{-1} , respectively) [41–43]. In addition, the bands at 1414, 1416, 1406 and 1414 cm^{-1} were due to the azo group $\nu(N=N)$, respectively, which shifted to higher wavenumbers of the metal complexes in the 1420, 1421, 1425 and 1427 cm^{-1} range, respectively, indicating the coordination of C=O with one nitrogen atom of the azo group with platinum(II). Furthermore, the bands of the free ligands of $\nu(C=S)$ vibrated at 1091, 1100, 1101 and 1122 cm^{-1} , which almost vibrated at the same wavenumbers for the complexes at 1088, 1104, 1100 and 1120 cm^{-1} , respectively. The wavenumbers at ~ 800 cm^{-1} are characteristic for the pyrimidine ring stretching. The band at 554 cm^{-1} of complex **32** probably belongs to the Pt–N coordinated bond. In conclusion, the above spectral data suggested that the complexes **30–33** exist in square-planar geometries.

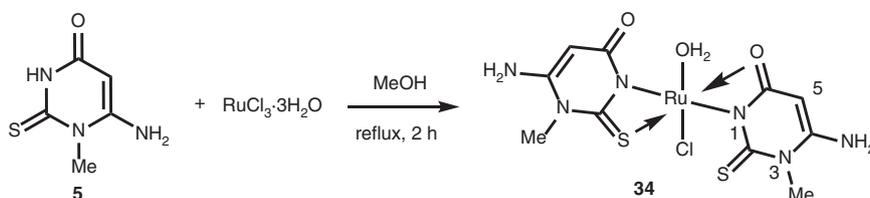
Owing to the biological importance of ruthenium complexes [44, 45], we focused our work on the synthesis of a new derivative of ruthenium(III) pyrimidine complex **34** in 43 % yield by treatment of **5** with $RuCl_3 \cdot 3H_2O$ in a 2:1 ratio (Scheme 4). The structure of **34** was confirmed by the elemental analysis, 1H , ^{13}C NMR and IR spectra. In



Scheme 2: Synthesis of the bis(4-amino-*N*³-methyl-6-oxo-2-thioxo-pyrimidin-1-yl)platinum(II) complex $[Pt(ThPym)_2]$ (**29**).



Scheme 3: Synthesis of the bis(4-amino-*N*¹,*N*³-dimethyl-6-oxo-2-thioxo-pyrimidin-1-yl)Pt(II)Cl₂ complexes [(ADiThPym)₂PtCl₂] (**29–33**).

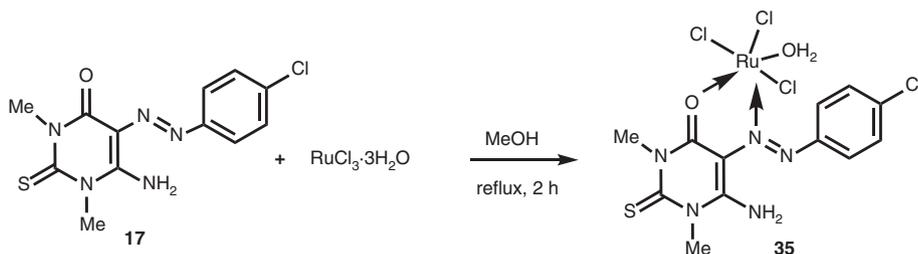


Scheme 4: Synthesis of the bis(4-amino-*N*¹-methyl-6-oxo-2-thioxo-pyrimidine)RuCl₃·H₂O complex [(AMThPym)₂RuCl₃·H₂O] (**34**).

the ¹³C NMR spectrum of **34**, the low field frequency at $\delta = 182.8$ ppm was assigned to C-2 (C=S), whereas C-4–C-6 appeared at $\delta = 156.6$, 82.3 and 162.5 ppm, respectively (see Experimental Section). In the IR spectrum, the C=O at C-6 showed two bands: one band appeared at wavenumber 1646 cm⁻¹, which was higher than that of the starting material **5** (1630 cm⁻¹), indicating a coordination of the C=O group of **34** with Ru(III), whereas the other band vibrated at 1600 cm⁻¹ as a non-coordinated C=O group. Similarly, the C=S group showed two bands as well: one band vibrated at 1124 cm⁻¹, which is a higher wavenumber than that for **5** (1100 cm⁻¹), indicating the coordination of the C=S group at C-2 with Ru, whereas the second band at 1100 cm⁻¹ was attributed to the non-coordinated C=S

group. The above data suggested that **34** exists as a distorted compressed octahedron.

Next, the treatment of **17** with RuCl₃·3H₂O (1:1 molar ratio) in refluxing MeOH afforded, after purification, the Ru(III) complex **35** (54 %) (Scheme 5). The ¹³C NMR spectrum showed two lower field resonances at $\delta = 177.8$ and 163.2 ppm assigned to C-2 and C-6 of the pyrimidine ring, respectively, whereas the resonances at $\delta = 158.2$ and 80.4 ppm were attributed to C-4 and C-5 of the same ring, respectively. The aromatic and methyl carbon atoms were fully assigned (see Experimental Section). The IR spectrum of ligand **17** revealed bands at 1626 and 1414 cm⁻¹ assigned to ν (C=O) and ν (N=N), respectively, which shifted to higher wavenumbers (1649 and 1134 cm⁻¹) in



Scheme 5: Synthesis of the [6-amino-5-((4-chlorophenyl)diazenyl)-*N*¹,*N*³-dimethyl-2-thioxo-pyrimidin-4-one)Ru(III)Cl₃·H₂O complex [(AzPym-Cl)RuCl₃·H₂O] (**34**).

the spectrum of complex **35**. These differences in wave-numbers indicate that the $>C=O$ and $>N=N$ groups of **17** are involved in the bonding with metal ions. The $\nu(C=S)$ vibration of **17** was observed at 1091 cm^{-1} , which remained constant in the spectrum of the complex at 1088 cm^{-1} . The above spectral data suggest the geometrical structure of Ru(III) complex **35** as a distorted octahedral one.

2.1 In vitro anti-HIV activity

Compounds **17–35** were tested for their in vitro anti-HIV-1 (strain III_B) and anti-HIV-2 (strain ROD) activity in human T-lymphocyte (MT-4) cells based on an MTT assay [46]. The results are summarized in Table 1, where the data for nevirapine (BOE/BIRG587) [47] and azidothymidine (DDN/AZT) [48] are included for comparison. Compounds **26** and **30** were found to be the only compounds from the series inhibiting HIV-1 and HIV-2 replication in a cell culture, which showed an IC_{50} value of >2.07 , and $>3.02\text{ }\mu\text{g mL}^{-1}$, respectively, whereas the analogs **22**, **25**, **27**, **29** and **35** exhibited moderate activity against both virus types, with an IC_{50} value of >9.56 , 8.11 , 5.23 , 8.06 and $10.01\text{ }\mu\text{g mL}^{-1}$, respectively.

In conclusion, the data in Table 1 suggested that the incorporation of sulfadiazine, sulfamerazine or sulfamethazine into the C-5 of the pyrimidine backbone, via the azo group, would enhance the anti-HIV activity. In addition, the coordination of $PtCl_2$ with the carbonyl oxygen atom ($C_4=O$) and the (C-5-) N atom of the azo group in compound **30** enhanced the anti-HIV activity as well. Therefore, the in vitro screening led to the identification of the new pyrimidines **26** and **30** as new anti-HIV candidates, being promising agents for further structural modification and pharmacological evaluation.

2.2 Molecular modeling analysis

The azothiopyrimidine analog **26**, owing to its anti-HIV activity, was selected for the molecular modeling study, which was performed to understand the binding mode of these analogs with the HIV-RT binding pocket (NIBP) (PDB code: 1DTT [49]). The SYBYL-X 1.1 software was used, and the results were visualized with PYMOL [50].

The molecular modeling study of compound **26** showed a binding energy score of -8.0 , which revealed a selective interaction with the amino acids of the RT HIV enzyme. As shown in Figure 3, the aromatic ring of the sulfonamide group of **26** fitted into an aromatic-rich sub-pocket surrounded by the aromatic side chains of Tyr179,

Table 1: In vitro anti-HIV-1^a and anti-HIV-2^b activity of the new pyrimidines [Pt(II) and Ru(III) complexes **17–35**].

Compound	Virus strain	EC_{50} ($\mu\text{g mL}^{-1}$) ^c	CC_{50} ($\mu\text{g mL}^{-1}$) ^d	SI ^e
17	III _B	>28.83	28.83	<1
	ROD	>28.83	28.83	<1
18	III _B	>36.21	36.21	<1
	ROD	>36.21	36.21	<1
19	III _B	>65.34	65.34	<1
	ROD	>65.34	65.34	<1
20	III _B	>95.77	95.77	<1
	ROD	>92.68	95.77	<1
21	III _B	>87.22	87.22	<1
	ROD	>87.22	87.22	<1
22	III _B	>9.56	9.56	<1
	ROD	>9.56	9.56	<1
23	III _B	>37.56	37.56	<1
	ROD	>37.56	37.56	<1
24	III _B	>15.45	15.45	<1
	ROD	>15.45	15.45	<1
25	III _B	>8.11	8.11	<1
	ROD	>8.11	8.11	<1
26	III _B	>2.07	2.07	<1
	ROD	>2.07	2.07	<1
27	III _B	>5.23	5.23	<1
	ROD	>5.23	5.23	<1
28	III _B	>8.06	8.06	<1
	ROD	>8.06	8.06	<1
29	III _B	>54.23	54.23	<1
	ROD	>54.23	54.23	<1
30	III _B	>3.02	3.02	<1
	ROD	>3.02	3.02	<1
31	III _B	>21.25	21.25	<1
	ROD	>21.25	21.25	<1
32	III _B	>39.34	39.34	<1
	ROD	>39.34	39.34	<1
33	III _B	>31.22	31.22	<1
	ROD	>31.22	31.22	<1
34	III _B	>29.34	29.34	<1
	ROD	>29.34	29.34	<1
35	III _B	>10.01	10.01	<1
	ROD	>10.01	10.01	<1
AZT	III _B	0.0022	>25	$>11\ 363$
	ROD	0.00094	>25	$>26\ 596$
Nevirapine	III _B	0.050	>4.00	>80
	ROD	>4.00	>4.00	>1

^aAnti-HIV-1 activity measured with strain III_B.

^bAnti-HIV-2 activity measured with strain ROD.

^cCompound concentration required to achieve 50 % protection of the MT-4 cells from the HIV-1- and HIV-2-induced cytopathogenic effect.

^dCompound concentration that reduces the viability of mock-infected MT-4 cells by 50 %.

^eSI: selectivity index (CC_{50}/EC_{50}).

and a hydrogen bond between the hydroxyl group of Tyr179 and the nitrogen atom of the azo group was observed. The sulfonamide moiety was located in a favorable position

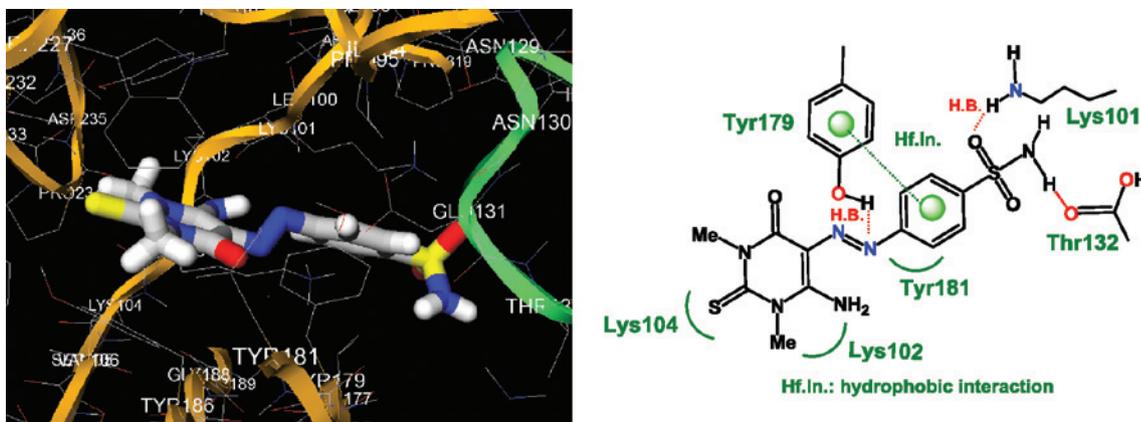


Fig. 3: Docked conformation of **26** showing three hydrogen bonds: Lys101 with the oxygen atom of the SO_2 group, Thr132 with the NH group of the sulfonamide residue and OH of Tyr179 with the nitrogen atom of the azo group. In addition, a hydrophobic interaction was observed between the phenyl group of the benzenesulfonamido moiety and the aromatic ring of Tyr179 of the reverse transcriptase (RT) enzyme residues.

of the pocket of RT enzyme, leading to the formation of a hydrogen bond between the oxygen atom of the SO_2 group and the NH_2 of Lys101, in addition to the hydrogen bond between the NH_2 of the sulfonamide group and the oxygen atom of the carboxylic group of Thr132 of the RT enzyme. Overall, the combination of hydrophobic interaction and π stacking appears to govern the binding of **130** with HIV RT.

2.3 In vitro antibacterial activity

The thiopyrimidines **17–35** and **31–33** were screened in vitro for the presence of antibacterial constituents against two strains of bacteria, *Staphylococcus aureus* and *Escherichia coli*, by the disc diffusion method [51]. Muller-Hinton agar (MH) was used as the culture media for antibacterial activity. Recommended concentrations of 100, 200 and 300 and 500 $\mu\text{g mL}^{-1}$ of the test samples in DMSO as a solvent were introduced in the respective method. The bacterial inoculum was uniformly spread using a sterile cotton swab on a sterile Petri dish MH agar. Fifty microliters from 1 mg mL^{-1} concentration of chemical products was added to each well (7-mm-diameter holes were cut in the agar gel, 20 mm apart from one another). The plates were incubated for 24 h at 36 ± 1 °C under aerobic conditions. After incubation, confluent bacterial growth was observed. Inhibition of the bacterial growth was measured in millimeters using a caliper vernia.

Compound **26**, carrying a sulfamerazine scaffold, was the most active candidate in the series, with inhibition zones of 12–13 and 16 mm against *S. aureus* and *E. coli* bacteria, at a concentration of 100 $\mu\text{g mL}^{-1}$, respectively, in comparison with the antibacterial drug sulfamerazine itself [52]. The docking study of **26** showed a binding energy score of -9.2 with the aspartate transaminase (AST) enzyme

of *E. coli*, indicating highly selective interactions with the enzyme pocket, which led to a higher binding energy score.

3 Experimental section

3.1 General

Melting points were uncorrected and were measured on a Büchi melting point apparatus (B-545, Büchi Labortechnik AG, Flawil, Switzerland). Microanalytical data were obtained with a Vario elemental analyzer (Shimadzu, Kyoto, Japan). NMR spectra were recorded on a spectrometer (Bruker, Rheinstetten, Germany) at 400 and 600 MHz for ^1H and at 150.91 MHz for ^{13}C , with tetramethylsilane as an internal standard, and on a δ scale in parts per million. Signal assignments for protons were performed by selective proton decoupling or by COSY spectra. Heteronuclear assignments were verified by HSQC, HMBC and DFQ-COSY experiments. Mass spectra (EI, 70 eV, and fast atom bombardment) were recorded on a MAT 8200 spectrometer (Finnegan MAT, Ringoes, NJ, USA). TLC plates (60 F254) were purchased from Merck.

3.2 General procedure for the preparation of 6-amino-5-(aryldiazenyl)- N^1 , N^3 -dimethyl-2-thioxo-pyrimidin-4-one derivatives **17–27**

A solution of substituted aniline **6–16** (2.90 mmol) in 6 mol/L of HCl (4.0 mL) was cooled to 0–5 °C, and then NaNO_2 (58 mg, 0.84 mmol) in water (2.0 mL) was added

dropwise with stirring. After the addition was completed, the solution was stirred for another 15 min and checked with iodine-starch paper to destroy the excess of HNO_2 . The diazonium salt solution was then poured onto a solution of 6-amino- N^1,N^3 -dimethyl-2-thioxo-pyrimidin-4-one (**4**) (500 mg, 2.90 mmol) or of the N^1 -methyl analog **5** in EtOH and stirred for 30 min. Potassium acetate (485 mg) was then added, and the mixture was stirred for 16 h at room temperature. The resulting precipitate was filtered, washed with water and dried in a vacuum desiccator over P_2O_5 to give the desired azothiopyrimidine derivatives.

3.2.1 6-Amino-5-((4-chlorophenyl)diazanyl)- N^1,N^3 -dimethyl-2-thioxo-pyrimidin-4-one (**17**)

From 4-chloroaniline **6** (450 mg). Yield: 704 mg (82 %), m. p. 226–228 °C (dec.), $R_f = 0.9$. – IR (KBr, v, cm^{-1}): 3297 (NH_2 , br.), 1626 (C=O), 1509 (C=C), 1414 (N=N), 1091 (C=S). – ^1H NMR ($[\text{D}_6]$ DMSO): $\delta = 9.14, 8.84$ (2 × s, 2H, NH_2), 7.75 (d, 2H, $J_{5',6'} = 8.0$ Hz, $\text{H}_{\text{arom.}-3'} + \text{H}_{\text{arom.}-5'}$), 7.55 (d, 2H, $J_{2,3'} = 8.0$ Hz, $\text{H}_{\text{arom.}-2'} + \text{H}_{\text{arom.}-6'}$), 3.89 (s, 3H, N3-CH_3), 3.69 (s, 3H, N1-CH_3) ppm. – ^{13}C NMR ($[\text{D}_6]$ DMSO): $\delta = 177.4$ (C(2)_{pyrimid.}), 165.5 (C(6)_{pyrimid.}), 157.5 (C(4)_{pyrimid.}), 148.4 (C(1')_{arom.}), 134.5 (C(4')_{arom.}), 129.8 (C(2')_{arom.} + C(6')_{arom.}), 123.1 (C(3')_{arom.} + C(5')_{arom.}), 77.8 (C(5)_{pyrimid.}), 37.6 (N3-CH_3), 36.1 (N1-CH_3) ppm. – Anal. for $\text{C}_{12}\text{H}_{12}\text{ClN}_5\text{OS}$ (309.77): calcd. C 46.53, H 3.09, N, 22.61; found: C 46.33, H 2.94, N 22.39.

3.2.2 6-Amino-5-((4-bromophenyl)diazanyl)- N^1,N^3 -dimethyl-2-thioxo-pyrimidin-4-one (**18**)

From 4-bromoaniline **7** (502 mg). Yield: 631 mg (61 %), m. p. 205–209 °C, $R_f = 0.71$. – IR (KBr, v, cm^{-1}): 3294 (NH_2 , br.), 1630 (C=O), 1511 (C=C), 1416 (N=N), 1096 (C=S). – ^1H NMR ($[\text{D}_6]$ DMSO): $\delta = 9.16, 8.83$ (2 × s, 2H, NH_2), 7.76 (d, 2H, $J_{5',6'} = 8.6$ Hz, $\text{H}_{\text{arom.}-3'} + \text{H}_{\text{arom.}-5'}$), 7.46 (d, 2H, $J_{2,3'} = 8.6$ Hz, $\text{H}_{\text{arom.}-2'} + \text{H}_{\text{arom.}-6'}$), 3.88 (s, 3H, N3-CH_3), 3.68 (s, 3H, N3-CH_3) ppm. – ^{13}C NMR ($[\text{D}_6]$ DMSO): $\delta = 177.4$ (C(2)_{pyrimid.}), 164.8 (C(6)_{pyrimid.}), 157.4 (C(4)_{pyrimid.}), 148.4 (C(1')_{arom.}), 132.8 (C(3')_{arom.} + C(5')_{arom.}), 129.8 (C(2')_{arom.} + C(6')_{arom.}), 123.4 (C(4')_{arom.}), 78.1 (C(5)_{pyrimid.}), 37.6 (N3-CH_3), 36.1 (N1-CH_3) ppm. – Anal. for $\text{C}_{12}\text{H}_{12}\text{BrN}_5\text{OS}$ (354.23): calcd. C 40.69, H 3.41, N 19.77; found: C 46.48, H 3.38, N 19.53.

3.2.3 6-Amino- N^1,N^3 -dimethyl-5-(4-nitrophenyl)diazanyl)-2-thioxo-pyrimidin-4-one (**19**)

From 4-nitroaniline **8** (390 mg). Yield: 806 mg (92 %), m. p. 228–230 °C (dec.), $R_f = 0.63$. – IR (KBr, v, cm^{-1}):

3297 (NH_2 , br.), 1626 (C=O), 1509 (C=C), 1414 (N=N), 1091 (C=S). – ^1H NMR ($[\text{D}_6]$ DMSO): $\delta = 9.09$ (s, 2H, NH_2), 8.34 (d, 2H, $J_{5',6'} = 9.0$ Hz, $\text{H}_{\text{arom.}-3'} + \text{H}_{\text{arom.}-5'}$), 7.91 (d, 2H, $J_{2,3'} = 9.0$ Hz, $\text{H}_{\text{arom.}-2'} + \text{H}_{\text{arom.}-6'}$), 3.89 (s, 3H, N3-CH_3), 3.69 (s, 3H, N1-CH_3) ppm. – ^{13}C NMR ($[\text{D}_6]$ DMSO): $\delta = 177.7$ (C(2)_{pyrimid.}), 163.8 (C(6)_{pyrimid.}), 157.3 (C(4)_{pyrimid.}), 148.7 (C(1')_{arom.}), 148.4 (C(4')_{arom.}), 125.5 (C(3')_{arom.} + C(5')_{arom.}), 122.1 (C(2')_{arom.} + C(6')_{arom.}), 75.0 (C(5)_{pyrimid.}), 37.7 (N3-CH_3), 36.2 (N1-CH_3) ppm. – Anal. for $\text{C}_{12}\text{H}_{12}\text{N}_5\text{O}_5\text{S}$ (320.33): calcd. C 44.99, H 3.78, N 26.24; found: C 44.72, H 3.61, N 26.02.

3.2.4 6-Amino- N^1,N^3 -dimethyl-2-thioxo-5-(*p*-tolyl-diazanyl)-2-thioxo-pyrimidin-4-one (**20**)

From 4-methylaniline **9** (312 mg). Yield: 540 mg (70 %), m. p. 235–237 °C (dec.), $R_f = 0.76$. – IR (KBr, v, cm^{-1}): 3297, 3257 (NH_2), 1630 (C=O), 1511 (C=C), 1418 (N=N), 1101 (C=S). – ^1H NMR ($[\text{D}_6]$ DMSO): $\delta = 11.64, 8.64$ (2xbr s., 2H, NH_2), 7.61 (d, 2H, $J_{5',6'} = 8.0$ Hz, $\text{H}_{\text{arom.}-3'} + \text{H}_{\text{arom.}-5'}$), 7.29 (d, 2H, $J_{2,3'} = 8.0$ Hz, $\text{H}_{\text{arom.}-2'} + \text{H}_{\text{arom.}-6'}$), 3.88 (s, 3H, N3-CH_3), 3.69 (s, 3H, N1-CH_3), 2.36 (s, 3H, Ph-Me) ppm. – ^{13}C NMR ($[\text{D}_6]$ DMSO): $\delta = 177.2$ (C(2)_{pyrimid.}), 163.9 (C(6)_{pyrimid.}), 157.6 (C(4)_{pyrimid.}), 148.2 (C(1')_{arom.}), 138.8 (C(4')_{arom.}), 130.6 (C(3')_{arom.} + C(5')_{arom.}), 128.1 (C(2')_{arom.} + C(6')_{arom.}), 76.8 (C(5)_{pyrimid.}), 37.5 (N3-CH_3), 36.1 (N1-CH_3), 21.3 (Me) ppm. – Anal. for $\text{C}_{13}\text{H}_{15}\text{N}_5\text{OS}$ (289.10): calcd. C 53.96, H 5.23, N 24.20; found: C 53.72, H 5.16, N 24.03.

3.2.5 4-((6-Amino- N^1,N^3 -dimethyl-4-oxo-2-thioxo-pyrimidin-5-yl)diazanyl)benzoic acid (**21**)

From *p*-aminobenzoic acid **10** (402 mg). Yield: 800 mg (86 %), m. p. 247–249 °C, $R_f = 0.42$. – IR (KBr, v, cm^{-1}): 3381 (NH_2 , br.), 1629 (C=O), 1503 (C=C), 1416 (N=N), 1100 (C=S). – ^1H NMR ($[\text{D}_6]$ DMSO): $\delta = 12.63$ (s, 1H, CO_2H), 11.80 (br s., 2H, NH_2), 8.04 (d, 2H, $J_{5',6'} = 8.0$ Hz, $\text{H}_{\text{arom.}-3'} + \text{H}_{\text{arom.}-5'}$), 7.78 (d, 2H, $J_{2,3'} = 8.0$ Hz, $\text{H}_{\text{arom.}-2'} + \text{H}_{\text{arom.}-6'}$), 3.73 (s, 3H, N3-CH_3), 3.69 (s, 3H, N1-CH_3) ppm. – ^{13}C NMR ($[\text{D}_6]$ DMSO): $\delta = 179.1$ (C(2)_{pyrimid.}), 167.5 (CO_2H), 159.5 (C(6)_{pyrimid.}), 157.0 (C(4)_{pyrimid.}), 153.0 (C(1')_{arom.}), 141.1 (C(4')_{arom.}), 131.0 (C(3')_{arom.} + C(5')_{arom.}), 121.4 (C(2')_{arom.} + C(6')_{arom.}), 75.0 (C(5)_{pyrimid.}), 36.4 (N3-CH_3), 35.7 (N1-CH_3) ppm. – Anal. for $\text{C}_{13}\text{H}_{13}\text{N}_5\text{O}_3\text{S}$ (319.34): calcd. C 48.89, H 4.10, N 21.93; found: C 48.68, H 4.02, N 21.78.

3.2.6 4-((6-Amino- N^1,N^3 -dimethyl-4-oxo-2-thioxo-pyrimidin-5-yl)diazanyl)benzenesulfonamide (**22**)

From *p*-aminobenzenesulfonamide **11** (502 mg). Yield: 740 mg (81 %), m. p. 259–60 °C, $R_f = 0.75$. – IR (KBr, v, cm^{-1}):

3372, 3247 (NH₂), 1630 (C=O), 1502 (C=C), 1406 (N=N), 1101 (C=S). – ¹H NMR ([D₆]DMSO): δ = 11.70, 8.92 (2 × s, 2H, NH₂), 7.93 (d, 2H, J_{5,6'} = 8.5 Hz, H_{arom.}-3' + H_{arom.}-5'), 7.86 (d, 2H, J_{2,3'} = 8.5 Hz, H_{arom.}-2' + H_{arom.}-6'), 7.41 (s, 2H, SO₂NH₂), 3.89 (s, 3H, N3-CH₃), 3.69 (s, 3H, N1-CH₃) ppm. – ¹³C NMR ([D₆]DMSO): δ = 177.5 (C(2)_{pyrimid.}), 157.4 (C(6)_{pyrimid.}), 154.4 (C(4)_{pyrimid.}), 148.5 (C(1')_{arom.}), 143.5 (C(4')_{arom.}), 127.4 (C(2')_{arom.} + C(6')_{arom.}), 121.7 (C(3')_{arom.} + C(5')_{arom.}), 77.5 (C(5)_{pyrimid.}), 37.6 (N3-CH₃), 36.1 (N1-CH₃) ppm. – Anal. for C₁₂H₁₄N₆O₃S₂ (354.40): calcd. C 40.67, H 3.98, N 23.71; found: C 40.23, H 3.89, N 23.50.

3.2.7 4-((6-Amino-N¹,N³-dimethyl-4-oxo-2-thioxo-pyrimidin-5-yl)diazenyl)benzenesulfonic acid (23)

From *p*-aminobenzenesulfonic acid **12** (400 mg). Yield: 830 mg (80 %), m. p. 273–275 °C, R_f = 0.2. – IR (KBr, v, cm⁻¹): 3442 (NH₂, br.), 1641 (C=O), 1508 (C=C), 1414 (N=N), 1120 (C=S). – ¹H NMR ([D₆]DMSO): δ = 11.71, 8.86 (2 × s, 2H, NH₂), 7.72 (d, 2H, J_{2,3'} = 8.5 Hz, H_{arom.}-2' + H_{arom.}-6'), 7.68 (d, 2H, J_{5,6'} = 8.5 Hz, H_{arom.}-3' + H_{arom.}-5'), 3.90 (s, 3H, N3-CH₃), 3.70 (s, 3H, N1-CH₃) ppm. – ¹³C NMR ([D₆]DMSO): δ = 177.3 (C(2)_{pyrimid.}), 158.9 (C(6)_{pyrimid.}), 157.5 (C(4)_{pyrimid.}), 148.5 (C(4')_{arom.}), 127.1 (C(2')_{arom.} + C(6')_{arom.}), 121.0 (C(3')_{arom.} + C(5')_{arom.}), 77.3 (C(5)_{pyrimid.}), 36.4 (N3-CH₃), 35.7 (N1-CH₃) ppm. – Anal. for C₁₂H₁₃N₅O₄S₂ (355.39): calcd. C 40.27, H 3.55, N 19.49; found: C 40.27, H 3.55, N 19.49.

3.2.8 N-((4-((6-Amino-N¹,N³-dimethyl-4-oxo-2-thioxo-pyrimidin-5-yl)diazenyl)phenyl)sulfonyl)acetamide (24)

From *N*-((4-aminophenyl)sulfonyl)acetamide (**13**) (625 mg). Yield: 650 mg (56 %), m. p. 261–263 °C (dec.), R_f = 0.52. – IR (KBr, v, cm⁻¹): 3385, 3279 (NH₂), 1631 (C=O), 1502 (C=C), 1408 (N=N), 1099 (C=S). – ¹H NMR ([D₆]DMSO): δ = 11.75, 9.02 (2 × br s, 2H, NH₂), 8.00 (d, 2H, J_{2,3'} = 7.8 Hz, H_{arom.}-2' + H_{arom.}-6'), 7.88 (d, 2H, J_{5,6'} = 7.8 Hz, H_{arom.}-3' + H_{arom.}-5'), 3.90 (s, 3H, N3-CH₃), 3.70 (s, 3H, N1-CH₃), 1.96 (s, 3H, NHCOMe) ppm. – ¹³C NMR ([D₆]DMSO): δ = 177.8 (C(2)_{pyrimid.}), 169.3 (C=O), 157.3 (C(6)_{pyrimid.}), 156.6 (C(4)_{pyrimid.}), 148.8 (C(1')_{arom.}), 138.2 (C(4')_{arom.}), 129.4 (C(2')_{arom.} + C(6')_{arom.}), 121.7 (C(3')_{arom.} + C(5')_{arom.}), 77.3 (C(5)_{pyrimid.}), 37.6 (N3-CH₃), 36.2 (N1-CH₃), 23.8 (NHCOMe) ppm. – Anal. for C₁₂H₁₃N₅O₄S₂ (396.44): calcd. C 42.41, H 4.07, N 21.2; found: C 42.20, H 3.95, N 20.92.

3.2.9 4-((6-Amino-N¹,N³-dimethyl-4-oxo-2-thioxo-pyrimidin-5-yl)diazenyl)-*N*-pyrimidin-2-yl-benzene sulfonamide (25)

From sulfadiazine (**14**) (731 mg). Yield: 750 mg (59 %), m. p. 158–160 °C (dec.), R_f = 0.57. – IR (KBr, v, cm⁻¹): 3385, 3279 (NH₂), 1630 (C=O), 1514 (C=C), 1421 (N=N), 1099 (C=S). – ¹H NMR ([D₆]DMSO): δ = 11.65 (s, 2H, NH₂), 9.07 (s, H, NH), 8.52 (d, 2H, J_{4,5''} = 5.0 Hz, H_{pyrimid.}-4'' + H_{pyrimid.}-6''), 8.08 (d, 2H, J_{2,3'} = 7.5 Hz, H_{arom.}-2' + H_{arom.}-6'), 7.88 (d, 2H, J_{5,6'} = 7.5 Hz, H_{arom.}-3' + H_{arom.}-5'), 7.06 (t, 1H, J_{5,6'} = 5.0 Hz, H-5''_{pyrimid.}), 3.90 (s, 3H, N3-CH₃), 3.69 (s, 3H, N1-CH₃) ppm. – ¹³C NMR ([D₆]DMSO): δ = 176.4 (C(2)_{pyrimid.}), 168.2 (C(2'')_{pyrimid.}), 157.1 (C(6)_{pyrimid.}), 156.7 (C(4'')_{pyrimid.} + C(6'')_{pyrimid.}), 155.3 (C(4)_{pyrimid.}), 149.9 (C(1')_{arom.}), 139.6 (C(4')_{arom.}), 131.3 (C(2')_{arom.} + C(6')_{arom.}), 123.8 (C(3')_{arom.} + C(5')_{arom.}), 100.0 (C(5'')_{pyrimid.}), 82.7 (C(5)_{pyrimid.}), 38.7 (N3-CH₃), 36.2 (N1-CH₃) ppm. – Anal. for C₁₆H₁₆N₈O₃S₂ (432.48): calcd. C 44.43, H 3.73, N 25.91; found: C 44.17, H 3.69, N 25.63.

3.2.10 4-((6-Amino-N¹,N³-dimethyl-4-oxo-2-thioxo-pyrimidin-5-yl)diazenyl)-*N*-(4-methylpyrimidin-2-yl)benzenesulfonamide (26)

From sulfamerazine (**15**) (772 mg). Yield: 520 mg (40 %), m. p. 207–209 °C (dec.), R_f = 0.76. – IR (KBr, v, cm⁻¹): 3392, 3282 (NH₂), 1624 (C=O), 1512 (C=C), 1418 (N=N), 1100 (C=S). – ¹H NMR ([D₆]DMSO): δ = 12.78, 9.14 (2 × s, 2H, NH₂), 8.36 (d, H, J_{5,6''} = 5.5 Hz, H_{pyrimid.}-6''), 8.18 (d, 2H, J_{2,3'} = 7.5 Hz, H_{arom.}-2' + H_{arom.}-6'), 7.83 (d, 2H, J_{5,6'} = 7.5 Hz, H_{arom.}-3' + H_{arom.}-5'), 7.05 (d, 1H, H-5''_{pyrimid.}), 3.75 (s, 3H, N3-CH₃), 3.72 (s, 3H, N1-CH₃), 2.39 (s, 3H, C4''-Me) ppm. – ¹³C NMR ([D₆]DMSO): δ = 179.0 (C(2)_{pyrimid.}), 171.9 (C(4'')_{pyrimid.}), 167.4 (C(2'')_{pyrimid.}), 158.8 (C(6)_{pyrimid.}), 155.2 (C(4)_{pyrimid.}), 153.2 (C(6'')_{pyrimid.}), 148.1 (C(1')_{arom.}), 140.6 (C(4')_{arom.}), 128.3 (C(2')_{arom.} + C(6')_{arom.}), 122.6 (C(3')_{arom.} + C(5')_{arom.}), 109.3 (C(5'')_{pyrimid.}), 82.8 (C(5)_{pyrimid.}), 38.6 (N3-CH₃)_{pyrimid.}, 35.8 (N1-CH₃)_{pyrimid.}, 23.0 (Me)_{pyrimid.} ppm. – Anal. for C₁₇H₁₈N₈O₃S₂ (446.51): calcd. C 45.73, H 4.06, N 25.10; found: C 45.47, H 4.01, N 24.89.

3.2.11 4-((6-Amino-N¹,N³-dimethyl-4-oxo-2-thioxo-pyrimidin-5-yl)diazenyl)-*N*-(4,6-dimethyl-pyrimidin-2-yl)benzenesulfonamide (27)

From sulfamethazine (**16**) (813 mg). Yield: 560 mg (42 %), m. p. 199–200 °C (dec.), R_f = 0.6. – IR (KBr, v, cm⁻¹): 3389, 3274 (NH₂), 1622 (C=O), 1509 (C=C), 1422 (N=N), 1108 (C=S). – ¹H NMR ([D₆]DMSO): δ = 11.72 (br s., 2H, NH₂), 8.96 (br s., 1H, NH), 8.08 (d, 2H, J_{2,3'} = 8.0 Hz, H_{arom.}-2' +

$H_{\text{arom.}-6'}$, 7.83 (d, 2H, $J_{5',6'} = 8.0$ Hz, $H_{\text{arom.}-3'} + H_{\text{arom.}-5'}$), 6.67 (s, 1H, $H_{5''}$ pyrimid.), 3.89 (s, 3H, N3-CH₃), 3.69 (s, 3H, N1-CH₃), 2.30 (2 × s, 6H, 2 × Me pyrimid.) ppm. – ¹³C NMR ([D₆]DMSO): $\delta = 177.5$ (C(2) pyrimid.), 169.6 (C(2'') pyrimid.), 167.4 (C(4'') pyrimid.) + C(6'') pyrimid.), 164.9 (C(6) pyrimid.), 151.0 (C(4) pyrimid.), 143.5 (C(1') arom.), 140.6 (C(4') arom.), 129.0 (C(2') arom. + C(6') arom.), 121.1 (C(3') arom. + C(5') arom.), 113.1 (C(5'') pyrimid.), 72.2 (C(5) pyrimid.), 37.6 (N3-CH₃ pyrimid.), 36.1 (N1-CH₃ pyrimid.), 23.0 (2 × Me pyrimid.) ppm. – Anal. for C₁₈H₂₀N₆O₃S₂ (460.53): calcd. C 46.94, H 4.38, N 24.33; found: C 46.73, H 4.27, N 24.07.

3.2.12 4-((6-Amino-N¹-methyl-4-oxo-2-thioxo-pyrimidin-5-yl)diazenyl)benzenesulfonamide (28)

From 4-amino-benzenesulfonamide (**11**) (546 mg). Yield: 742 mg (68 %), m. p. 251–253 °C, $R_f = 0.13$. – IR (KBr, v, cm⁻¹): 3388, 3279 (NH₂), 1627 (C=O), 1515 (C=C), 1420 (N=N), 1094 (C=S). – ¹H NMR ([D₆]DMSO): $\delta = 11.87, 8.93$ (2 × s, 2H, NH₂), 7.93 (d, 2H, $J_{5',6'} = 8.7$ Hz, $H_{\text{arom.}-3'} + H_{\text{arom.}-5'}$), 7.85 (d, 2H, $J_{2,3'} = 8.7$ Hz, $H_{\text{arom.}-2'} + H_{\text{arom.}-6'}$), 7.40 (s, 2H, SO₂NH₂), 3.81 (s, 3H, N1-CH₃) ppm. – ¹³C NMR ([D₆]DMSO): $\delta = 176.8$ (C(2) pyrimid.), 164.1 (C(6) pyrimid.), 157.4 (C(4) pyrimid.), 149.6 (C(1') arom.), 143.3 (C(4') pyrimid.), 127.4 (C(3') arom. + C(5') arom.), 121.6 (C(2') arom. + C(6') arom.), 78.8 (C(5) pyrimid.), 35.7 (N1-CH₃ pyrimid.) ppm. – Anal. for C₁₁H₁₂N₆O₃S₂ (340.38): calcd. C 38.81, H 3.55, N 24.69; found: C 38.60, H 3.46, N 24.45.

3.2.13 [Bis(4-amino-N³-methyl-6-oxo-2-thioxo-pyrimidin-1-yl)]Pt(II), [(AMeThPyrm)₂Pt] (29)

To a stirred solution of **5** (116 mg, 0.74 mmol) in MeOH (2 mL) was added a solution of PtCl₂ (99 mg, 0.34 mmol) in MeOH (3 mL) (2:1 molar ratio), and the mixture was heated under reflux for 2 h. The solid was separated on cooling, filtered, washed with MeOH and dried in a vacuum desiccator to give **138** (90 mg, 48 %), m. p. 270–271 °C (dec.). – IR (KBr, v, cm⁻¹): 3348, 3169 (NH₂), 1650 (C=O), 1602 (C=C), 1134 (C=S). – ¹H NMR ([D₆]DMSO): $\delta = 6.90$ (br s, 2H, NH₂), 4.88 (s, 1H, H-5), 3.88 (s, 3H, N3-CH₃) ppm. – ¹³C NMR ([D₆]DMSO): $\delta = 179.7$ (C(2) pyrimid.), 164.4 (C(6) pyrimid.), 160.1 (C(4) pyrimid.), 79.6 (C(5) pyrimid.), 34.6 (N3-CH₃) ppm. – Anal. for C₁₀H₁₂N₆O₂PtS₂ (507.46): calcd. C 23.67, H 2.38, N 16.56; found: C 23.43, H 2.21, N 15.28.

3.3 General procedure for the preparation of metal pyrimidine complexes 30–33

To a solution of the aryl-azothiopyrimidine (0.37 mmol) in MeOH (3 mL) was added a solution of PtCl₂ (99 mg,

0.37 mmol) in MeOH (3 mL) (1:1 molar ratio), and the mixture was heated under reflux for 2 h. After cooling, the solid was filtered and dried in a vacuum desiccator.

3.3.1 [(6-Amino-5-(4-chlorophenyl)diazenyl)-N¹,N³-dimethyl-2-thioxo-pyrimidin-4-one)]Pt(II)Cl₂, [(AzPyrm-Cl)PtCl₂] (30)

From **17** (115 mg). Yield: 120 mg (55 %), m. p. 245–247 °C (dec.). – IR (KBr, v, cm⁻¹): 3433, 3303 (NH₂), 1656 (C=O), 1488 (C=C), 1437 (N=N), 1088 (C=S). – ¹H NMR ([D₆]DMSO): $\delta = 10.95, 9.26$ (2 × s, 2H, NH₂), 7.96 (d, 2H, $J_{2,3'} = 7.0$ Hz, $H_{\text{arom.}-2'} + H_{\text{arom.}-6'}$), 7.58 (d, 2H, $J_{5',6'} = 7.0$ Hz, $H_{\text{arom.}-3'} + H_{\text{arom.}-5'}$), 3.92 (s, 3H, N3-CH₃), 3.68 (s, 3H, N1-CH₃) ppm. – ¹³C NMR ([D₆]DMSO): $\delta = 177.6$ (C(2) pyrimid.), 156.7 (C(6) pyrimid.), 154.8 (C(4) pyrimid.), 149.8 (C(1') arom.), 133.1 (C(4') arom.), 129.9 (C(2') arom. + C(6') arom.), 122.3 (C(3') arom. + C(5') arom.), 38.6 (N3-CH₃), 35.8 (N1-CH₃), 77.8 (C(5) pyrimid.) ppm. – Anal. for C₁₂H₁₂Cl₂N₅OPTS (575.76): calcd. C 25.03, H 2.10, N 12.16; found: C 24.82, H 2.01, N 11.89.

3.3.2 [(4-((6-Amino-N¹,N³-dimethyl-4-oxo-2-thioxo-pyrimidin-5-yl)diazenyl)benzoic acid)]Pt(II)Cl₂, [(AzPyrm-CO₂H)PtCl₂] (31)

From **21** (118 mg). Yield: 103 mg (46 %), m. p. 251–253 °C. – IR (KBr, v, cm⁻¹): 3452 (NH₂, br.), 1675 (C=O), 1503 (C=C), 1421 (N=N), 1104 (C=S). – ¹H NMR ([D₆]DMSO): $\delta = 12.36$ (s, 1H, CO₂H), 11.14, 9.38 (2 × s, 2H, NH₂), 8.04–8.00 (m, 4H, $H_{\text{arom.}-2'} + H_{\text{arom.}-6'} + H_{\text{arom.}-3'} + H_{\text{arom.}-5'}$), 3.93 (s, 3H, N3-CH₃), 3.69 (s, 3H, N1-CH₃) ppm. – ¹³C NMR ([D₆]DMSO): $\delta = 178.2$ (C(2) pyrimid.), 167.4 (C₂OH), 157.4 (C(6) pyrimid.), 154.6 (C(4) pyrimid.), 154.2 (C(1') arom.), 131.1 (C(2') arom. + C(6') arom.), 128.1 ((C(4') arom.)), 121.3 (C(3') arom. + C(5') arom.), 82.0 (C(5) pyrimid.), 38.0 (N3-CH₃), 36.9 (N1-CH₃) ppm. – Anal. for C₁₃H₁₅Cl₂N₅O₄PtS₂ (603.34): calcd. C 25.88, H 2.51, N 11.61; found: C 25.88, H 2.51, N 11.78.

3.3.3 [4-((6-Amino-N¹,N³-dimethyl-4-oxo-2-thioxo-pyrimidin-5-yl)diazenyl)benzenesulfonamide]Pt(II)Cl₂, [(AzPyrm-SO₂NH₂)PtCl₂] (32)

From **22** (118 mg). Yield: 110 mg (45 %), m. p. 249–250 °C (dec.). – IR (KBr, v, cm⁻¹): 3362, 3268 (NH₂), 1653 (C=O), 1484 (C=C), 1450 (N=N), 1100 (C=S). – ¹H NMR ([D₆]DMSO): $\delta = 11.70, 8.92$ (2 × s, 2H, NH₂), 8.11 (d, 2H, $J_{5',6'} = 8.0$ Hz, $H_{\text{arom.}-3'} + H_{\text{arom.}-5'}$), 7.93 (d, 2H, $J_{2,3'} = 8.0$ Hz, $H_{\text{arom.}-2'} + H_{\text{arom.}-6'}$), 7.45 (s, 2H, SO₂NH₂), 3.94 (s, 3H, N3-CH₃),

3.60 (s, 3H, N1-CH₃) ppm. – ¹³C NMR ([D₆]DMSO): δ = 177.4 (C(2)_{pyrimid.}), 158.5 (C(6)_{pyrimid.}), 153.2 (C(4)_{pyrimid.}), 149.6 (C(1')_{arom.}), 149.3 (C(4')_{arom.}), 127.5 (C(2')_{arom.} + (C(6')_{arom.}), 120.4 (C(3')_{arom.} + (C(5')_{arom.}), 82.6 (C(5)_{pyrimid.}), 38.4 (N3-CH₃), 35.8 (N1-CH₃) ppm. – Anal. for C₁₂H₁₆Cl₂N₆O₂PtS₂ (638.41): calcd. C 22.58, H 2.58, N 13.16; found: C 22.36, H 2.39, N 13.31.

3.3.4 [4-((6-Amino-N¹,N³-dimethyl-4-oxo-2-thioxo-pyrimidin-5-yl)diazényl)benzenesulfonic acid] Pt(II)Cl₂, [(AzPyrm-SO₃H)PtCl₂] (33)

From **23** (131 mg). Yield: 140 mg (58 %), m. p. 281–283 °C. – IR (KBr, ν, cm⁻¹): 3432, 3067 (NH₂), 1657 (C=O), 1488 (C=C), 1443 (N=N), 1120 (C=S). – ¹H NMR ([D₆]DMSO): δ = 11.23 (br s, 2H, NH₂), 7.91 (d, 2H, J_{3',5'} = 8.3 Hz, H_{arom.}-3' + H_{arom.}-5'), 7.71 (d, 2H, J_{2',3'} = 8.3 Hz, H_{arom.}-2' + H_{arom.}-6'), 3.94 (s, 3H, N3-CH₃), 3.68 (s, 3H, N1-CH₃) ppm. – ¹³C NMR ([D₆]DMSO): δ = 177.5 (C(2)_{pyrimid.}), 157.1 (C(6)_{pyrimid.}), 153.4 (C(4)_{pyrimid.}), 148.6 (C(1')_{arom.}), 143.8 (C(4')_{arom.}), 127.2 (C(2')_{arom.} + (C(6')_{arom.}), 122.0 (C(3')_{arom.} + (C(5')_{arom.}), 84.1 (C(5)_{pyrimid.}), 36.4 (N3-CH₃), 35.7 (N1-CH₃) ppm. – Anal. for C₁₂H₁₅Cl₂N₅O₅PtS₂ (639.40): calcd. C 22.54, H 2.36, N 10.95; found: C 22.37, H 2.48, N 10.80.

3.3.5 [Bis(4-amino-N³-methyl-6-oxo-2-thioxo-pyrimidin-1-yl)]Ru(III)Cl·H₂O, [(AMeThPyrm)₂RuCl·H₂O] (34)

To a stirred solution of **5** (116 mg, 0.74 mmol) in MeOH (3 mL) was added a solution of RuCl₃·3H₂O (97 mg, 0.37 mmol) in MeOH (3 mL) (2:1 molar ratio), and the mixture was heated under reflux for 2 h. After cooling, the solid complex was filtered, washed with MeOH and dried in a vacuum desiccator to give **34** (150 mg, 43 %), m. p. >295 °C (dec.). – IR (KBr, ν, cm⁻¹): 3351, 3183 (NH₂), 1646 (coord. C=O), 1600 (non-coord. C=O), 1509 (C=C), 1124 (coord. C=S), 1100 (non-coord. C=S). – ¹H NMR ([D₆]DMSO): δ = 7.42 (br s, 2H, NH₂), 7.30 (br s, 2H, NH₂), 5.72 (s, H, H-5), 3.68 (s, 3H, N1-CH₃) ppm. – ¹³C NMR ([D₆]DMSO): δ = 182.8 (C(2)_{pyrimid.}), 162.5 (C(6)_{pyrimid.}), 156.6 (C(4)_{pyrimid.}), 82.3 (C(5)_{pyrimid.}), 34.9 (N1-CH₃) ppm. – Anal. for C₁₀H₁₄ClN₆O₃RuS₂ (466.91): calcd. C 25.72, H 3.02, N 18.00; found: C 25.41, H 3.14, N 17.38.

3.3.6 [6-Amino-5-((4-chlorophenyl)diazényl)-N¹,N³-dimethyl-2-thioxo-pyrimidin-4-one]Ru(III)Cl₃·H₂O, [(AzPyrm-Cl)RuCl₃·H₂O] (35)

This complex was prepared by following the procedure for the preparation of **34**, from the azo-pyrimidine **17** (109 mg,

0.37 mmol) and RuCl₃·3H₂O (97 mg, 0.37 mmol) (1:1 molar ratio). Yield: 107 mg (54 %), m. p. 241–244 °C (dec.). IR (KBr, ν, cm⁻¹): 3418 br. (NH₂, br.), 1649 (C=O), 1489 (C=C), 1437 (N=N), 1088 (C=S). – ¹H NMR ([D₆]DMSO): δ = 8.28 (br s, 2H, NH₂), 7.99 (d, 2H, J_{5',6'} = 7.6 Hz, H_{arom.}-3' + H_{arom.}-5'), 7.56 (d, 2H, J_{2',3'} = 7.6 Hz, H_{arom.}-2' + H_{arom.}-6'), 3.94 (s, 3H, N3-CH₃), 3.56 (s, 3H, N1-CH₃) ppm. – ¹³C NMR ([D₆]DMSO): δ = 177.8 (C(2)_{pyrimid.}), 163.2 (C(6)_{pyrimid.}), 158.2 (C(4)_{pyrimid.}), 150.0 (C(1')_{arom.}), 133.1 (C(4')_{arom.}), 129.9 (C(2')_{arom.} + (C(6')_{arom.}), 122.3 (C(3')_{arom.} + (C(5')_{arom.}), 80.4 (C(5)_{pyrimid.}), 36.5 (N3-CH₃), 35.8 (N1-CH₃) ppm. – Anal. for C₁₂H₁₄Cl₄N₅O₂RuS (535.22): calcd. C 26.93, H 2.64, N 13.09; found: C 26.61, H 2.54, N 13.21.

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