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Preparation, characterization, crystal structure and bioactivity determination of ferrocenyl–thiazoleacylhydrazones

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4-Methylthiazole-5-carbohydrazide was synthesized by heating 85% hydrazine hydrate and methyl 4-methylthiazole-5-carboxylate in ethanol. Ferrocenyl–thiazoleacyl hydrazones were synthesized by condensing hydrazide with formylferrocene or acetylferrocene in the presence of a few drops of ice acetic acid. The structures of the synthetical compounds were confirmed using elemental analysis, IR and ^{1}H-NMR. In addition, the structure of (*E*)-*N*′-ferrocenylidene-4-methylthiazole-5-carbohydrazide was confirmed by single crystal X-ray diffraction analyse. The compound crystallized in the tetragonal space group, P4(2)/*n* with cell dimensions $a = 21.041(3)$ Å, $b = 21.041(3)$ Å, $c = 7.1212(14)$ Å, $\beta = 90.00°$, $V = 3152.6(9)$ Å^3, $D_{calc} = 1.488$ g cm^{-3}, $Z = 8$, $\mu = 1.093$ mm^{-1} and $F(000) = 1456$, and its structure was refined to $R_1 = 0.0423$ and $wR_2 = 0.0871$ for 2906 observed reflections ($I > 2\sigma(I)$). It showed the substituted cyclopentadiene ring to be approximately coplanar with the thiazole ring but a small twist between its two ring systems. In the crystal structure, molecules were linked by intermolecular hydrogen bonds N–H···O bonds into closed eight-membered loops and centrosymmetric dimers. The ferrocenyl–thiazoleacylhydrazone compounds were tested for their anti-Human Immunodeficiency Virus Type 1 Reverse Transcriptase, anti-Human Lung Cancer A549 cells and antibacterial bioactivities. It was found that they showed significant activity against *Staphylococcus aureus*, *Esherichia coli* and *Pseudomonas aeruginosa* with minimum inhibitory concentration values in the range of 25.0–100.0 μg/ml.

Keywords: hydrazones; ferrocenyl; crystal structure; bioactivity, preparation

Introduction

Ferrocene, a compound containing iron and two cyclopentadiene ligands was reported in 1951.[1,2] The discovery of ferrocene and elucidation of its remarkable structure was arguably the starting point for modern organometallic chemistry. In recent years, bioorganometallic chemistry has developed as a rapidly growing and maturing area which links classical organometallic chemistry to biology, medicine and molecular biotechnology.[3–6] The stability of the ferrocenyl group in aqueous, aerobic media, the accessibility of a large variety of derivatives and its favorable electrochemical properties, have made ferrocene and its derivatives very popular molecules for biological applications and for conjugation with biomolecules.[7–10]

Hydrazide–hydrazones, which are readily obtained by the condensation of aldehydes or ketones with hydrazines in the presence of an acid catalyst, represent a class of azomethine compounds.[11,12] Hydrazide–hydrazones have been demonstrated to possess antibacterial,[13–15] anti-HIV-1,[16–18] anticonvulsant[19,20] and antitubercular[21,22] activities.

In addition, the class of heterocyclic compounds known as thiazoles has been found in many natural and synthetic products with a wide range of pharmacal activities, such as antiviral, anticancer, antibacterial, antifungal, anticonvulsant, antiparkinsonian and anti-inflammatory activities, which is well illustrated by the large number of drugs on the market containing this function group.[23,24] Recently, Yu *et al*. reported some bioactivities of ferrocenyl-containing thiazole imine derivatives.[25]

The novel bioactivity properties of the derivatives of ferrocene, hydrazide-hydrazones and thiazoles have been reported separately. However, until now, the bioactivity of ferrocenyl–thiazoleacylhydrazones has not been reported. These observations led us to design and synthesize novel ferrocenyl–thiazoleacylhydrazones which contain the three kinds of moieties (ferrocene, hydrazone and thiazole) and to investigate their possible anti-Human Immunodeficiency Virus Type 1 Reverse Transcriptase (HIV-1 RT), anti-Human Lung Cancer A549 cells (HLC A549) and antibacterial bioactivities. The structures of the synthetical compounds were confirmed using elemental analysis, IR, ^{1}H-NMR and single crystal X-ray diffraction.

Results and Discussion

Synthetic routes to compounds **2, 3, 4a** and **4b** are shown in Fig. 1. The compound 4-methylthiazole-5-carboxylic acid (**1**) was chosen as the starting compound to design two novel hydrazide–hydrazones. Methyl 4-methylthiazole-5-carboxylate (**2**) was prepared by the reaction of 4-methylthiazole-5- carboxylic acid and methanol in the presence of a few drops of concentrated sulfuric acid. 4-Methylthiazole-5-carbohydrazide (**3**) was synthesized

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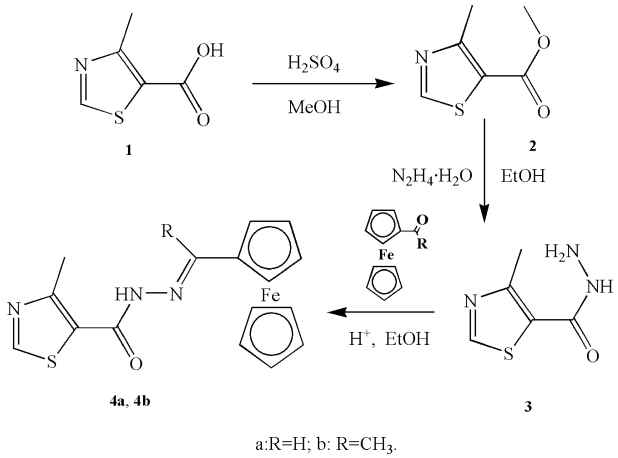

Figure 1. Synthetic route of **2, 3, 4a** and **4b**.

by heating 85% hydrazine hydrate and **2** in ethanol. After condensing hydrazide (**3**) with formylferrocene or acetylferrocene in the presence of a few drops of ice acetic acid, ferrocenyl–thiazoleacylhydrazone derivatives were obtained.

The two ferrocenyl–thiazoleacylhydrazones are red and air-stable for extended periods; they are slightly soluble in ordinary organic solvent like methanol, ethanol, acetone, ethyl acetate, THF and H_2O and freely soluble in DMF and DMSO. They also have a high dipole moment from TLC evaluate.

IR spectra

The IR spectra of **4a** and **4b** showed N–H bands at 3179 and 3197 cm^{-1}, which were attributed to the stretching of N–H.[26] The bands representing carbonyl groups and azomethine appeared at 1670, 1670, 1603 and 1596 cm^{-1}, respectively.[26] These indicate the existence of hydrazone configuration. In addition, the characteristic bands of the ferrocenyl group in compounds **4a** and **4b** appeared at 3092, 1102, 819, 499; and 3095, 1108, 821, 503, respectively.[27,28]

^{1}H-NMR spectra

^{1}H-NMR spectra of **3** displayed the –NH– and $-NH_2$ resonance of the hydrazide at 8.00 and 3.96 ppm, respectively. These two signals disappeared when the compound was exchanged for heavy water.

The ^{1}H-NMR spectra of **4a** and **4b** showed broad single signals corresponding to resonances of azomethine protons at 10.34 and 10.29 ppm in accordance with the literature.[29] These signals disappeared when the compounds were exchanged for heavy water. The proton signal at 7.84 ppm of compound **4a** was assignable to the –CH═N– group.[30] The ^{1}H-NMR spectrum of compound **4a** showed a chemical shift of five protons on the unsubstituted cyclopentadienyl ring at 4.22 ppm as a singlet. The signals at 4.44 and 4.69 ppm (two multiplets, 2H each) were due to the proton on the substituted cyclopentadienyl ring.[29] The chemical shift of cyclopentadienyl ring of compound **4b** was similar to that of **4a**.

Crystallographic studies

The crystal data and experimental parameters are given in Table 1. The selected bond lengths and bond angles are given in Table 2. The ellipsoid and packing drawings of **4a** are illustrated in Figs 2 and 3.

Table 1. The crystal structure information of **4a**

CCDC no.	648 138
Empirical formula	$C_{16}H_{15}FeN_3OS$
Formula weight	353.22
Description	dark red
Crystal size (mm)	0.360 × 0.350 × 0.310
Temperature (K)	293(2)
Crystal system	tetragonal
Space group	P4(2)/*n*
Unit cell dimensions	
a (Å)	21.041(3)
b (Å)	21.041(3)
c (Å)	7.1212(14)
α (deg)	90.00
β (deg)	90.00
γ (deg)	90.00
Volume (Å^3)	3152.6(9)
Z	8
D_{Calc} (g cm^{-3})	1.488
F(000)	1456
Absorption coefficient (mm^{-1})	1.093
Absorption correction	semi-empirical from equivalents
Maximum and minimum transmission	0.682, 0.712
Theta range for data collection(deg)	3.02–27.47
Refinement method	full matrix least-squares on F^2
Reflections collected	3607
Unique reflections (R_{int})	2906(0.0260)
Data/parameters/restraints	3607/199/0
Goodness-of-fit on F^2	1456
R_1, wR_2 [$I \geq \sigma(I)$][a]	0.0324, 0.0871
R_1, wR_2 (all data)[a]	0.0423, 0.0918
Largest difference peak and hole (e Å^{-3})	0.299, −0.267
$(\Delta/\sigma)_{max}$	0.001
Measurement	Rigaku R-AXIS RAPID
Program system	SHELXL-97
Structure determination	direct method

[a] $R_1 = \sum(|F_O| - |F_C|) \sum |F_0| wR_2 = \left[\sum w(F_O^2 - F_C^2)^2 / \sum w(F_O^2)^2\right]^{1/2}$.

The molecular structure of **4a** is essentially planar, albeit with a small twist about the C12–C13 bond. This is substantiated by the values of the N2–C12–C13–C15, N1–N2–C12–C13, C11–N1–N2–C12, C10–C11–N1–N2 and C6–C10–C11–N1 torsion angles of −171.11(18)°, −3.0(3)°, −179.69(18)°, 176.74(16)° and 7.1(3)°, respectively. The N1–N2, N1–C11, N2–C12 and C12–O1 bond distances are suggestive of limited delocalization of π-electron density over the central chromophore. The H atom bound to atom N2 is involved in an intermolecular interaction with atom O1 of another molecular, with H–N2 = 0.860 Å, H···O1 = 1.964 Å and N2–H···O1 = 2.819 Å. The O1 atom also forms a intermolecular hydrogen bond with H atom bound to atom N2 of another molecular. Thus, the molecules of **4a** are interlinked by intermolecular hydrogen bonds N2–H···O1 and O1···H–N2 into centrosymmetric dimers, which also form a closed eight-membered loop between two molecule. It appears that weak interactions of N1–S and N3–S exist in intramolecule and intermolecule with bond lengths 2.739 and 3.279 Å, respectively.[36]

Table 2. Selected bond lengths Å and bond angles (deg) for **4a**

Bond	Length	Bond	Length
Fe–C1	2.034(2)	N1–C11	1.270(2)
C1–C2	1.403(3)	N1–N2	1.373(2)
C2–C3	1.396(3)	N2–C12	1.348(2)
S–C14	1.694(2)	N3–C14	1.299(3)
S–C13	1.7334(17)	N3–C15	1.376(2)
O1–C12	1.238(2)	C13–C15	1.375(2)

Hydrogen bond

D–H	d(D–H)	d(H..A)	<DHA	d(D..A)	A
N2–H2B	0.860	1.964	172.43	2.819	O1

Bond angle	Angle	Bond angle	Angle
C5–Fe–C1	40.38(11)	C11–N1–N2	116.23(15)
C5–Fe–C9	157.32(10)	C12–N2–N1	122.24(15)
C5–Fe–C2	67.80(11)	C14–N3–C15	110.06(16)
C5–Fe–C7	106.69(11)	N1–C11–C10	120.75(17)
C5–Fe–C6	122.60(10)	N2–C12–C13	121.07(15)
C5–C1–Fe	69.80(13)	N3–C14–S	116.94(14)
C6–C10–C11	127.28(17)	C13–C15–N3	114.73(16)
C11–C10–Fe	126.73(13)	C13–C15–C16	128.44(16)
C14–S–C13	88.71(9)	N3–C15–C16	116.82(16)

Torsion angle	Angle	Torsion angles	Angle
C6–C10–C11–N1	7.1(3)	N1–N2–C12–C13	–3.0(3)
C10–C11–N1–N2	176.74(16)	N2–C12–C13–C15	–171.11(18)
C11–N1–N2–C12	–179.69(18)		

The H atoms were included in the riding-model approximation, with C–H(aromatic) = 0.93 Å and C–H(methyl) = 0.96 Å, and with Uiso(H) = 1.2 and 1.5 Ueq(C) for aromatic and methyl-H, respectively. Data collection, SMART[31]; cell refinement, SAINT[31]; data reduction, SAINT; program(s) used to solve structure, SIR92[32]; program(s) used to refine structure, SHELXL97[33]; molecular graphics, ORTEPII[34] and DIAMOND[35]; software used to prepare material for publication, SHELXL97.

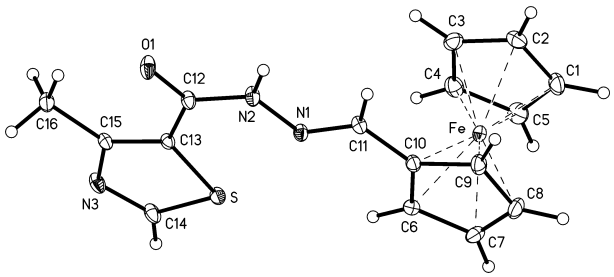

Figure 2. The molecular structure of $C_{16}H_{15}FeN_3OS$ (**4a**), showing the atom-labeling scheme and displacement ellipsoids drawn at the 50% probability level.

In cyclopentadiene ring part, the maximum C–C bond length is 1.426(3) Å, and the minimum is 1.397(3) Å. The average bond length with C–C and C–Fe of the ferrocnenyl group is 1.406(3) and 2.040(2) Å, respectively. In the thiazole ring part, the C14–S bond is 1.694(2) Å, the C14–N3 double bond is 1.299(3) Å and the C13–C15 double bond is 1.375(2) Å. The other bond lengths and angles are in the normal range.

Anti-HIV RT activity

The two ferrocenyl–thiazoleacylhydrazones were evaluated for inhibitory activity against HIV-1 RT in comparison with nevirapine (NVP) used as reference drug. The results are summarized in Table 3, expressed as IC_{50} values. In general, it was found that the two synthetical compounds **4a** and **4b** showed a little activity against HIV-1 RT with IC_{50} values of 48.38 and 51.22 μg/ml, respectively. In contrast, the reference compound (NVP) exhibited more potent activity than the synthetical compounds.

Anti-HLC A549 activity

The two ferrocenyl–thiazoleacylhydrazones were evaluated for their bioactivity against HLC A549. The SRB assay was used for HLC A549 density determination, based on the measurement of cellular protein content. When the concentration of **4a** and **4b** was 10^{-5} mol/l, the inhibition rate (%) was 14.81 and 45.1 (both less than 50%). Therefore, the evaluation result of anti-HLC A549 activity of **4a** and **4b** was not significant (Table 4).

Antibacterial activity

The two ferrocenyl–thiazoleacylhydrazones and compound **3** were evaluated for their activity against *Staphylococcus aureus* (*S. aureus*), *Esherichia coli* (*E. coli*) and *Pseudomonas aeruginosa* (*P. aeruginosa*) *in vitro*. The antimicrobial activity was determined by the double dilution method.[37] Ciprofloxacin, which has excellent activity against most Gram-negative and Gram-positive bacteria, and is known as an important antibacterial drug in the treatment of a wide range of infections, was chosen as a reference drug in antibacterial activity measurements.[38,39] The results are summarized in Table 5 expressed as minimum

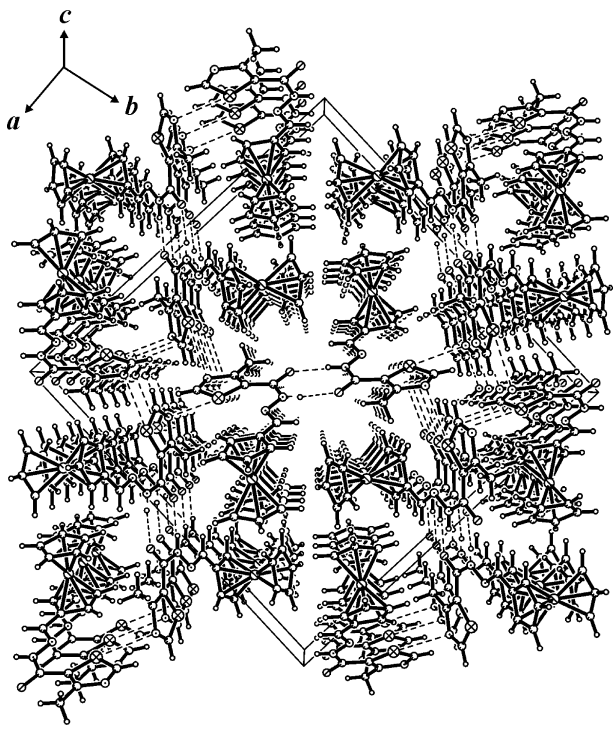

Figure 3. The crystal packing in $C_{16}H_{15}FeN_3OS$ (**4a**), viewed down the *c*-axis.

Table 3. Anti-HIV RT activity of **4a** and **4b**

Compound	Initial concentration	IC_{50}
4a	200 μg/ml	48.38 μg/ml
4b	200 μg/ml	51.22 μg/ml
NVP	10 μg/ml	0.21 μg/ml

Table 4. Anti-HLC A549 activity of **4a** and **4b** (inhibition rate %)

	Concentrations (mol/l)				
Compounds	10^{-4}	10^{-5}	10^{-6}	10^{-7}	10^{-8}
4a	66.6	14.8	9.8	11.4	9.0
4b	53.2	45.1	8.7	12.1	0

inhibitory concentrations (MIC) values. In general, the synthetical compounds including **3** were very active in *in vitro* assay. It was found that **4a, 4b** and **3** showed notable activity against *S. aureus, E. coli* and *P. aeruginosa* with MIC values in the range of 25.0–100.0 μg/mL. It was also observed from these studies that **4a** and **4b**, which contained hydrazone configuration had a higher activity than **3**, which contained hydrazide configuration.

Experimental

Instrumentation and materials

Melting points (m.p.) were determined using an X-4 digital display binocular microscope and were uncorrected. The C, H and N microanalyses were performed with a Carlo Erba 1106 elemental analyzer. The FT-IR spectra were recorded at room temperature in the region of 4000–400 cm^{-1} with a Bruker Vector-22 spectrometer using KBr pellets. ^{1}H-NMR spectra were recorded in chloroform ($CDCl_3$) on a Mercury Plus 400 MHz NMR spectrometer; chemical shifts are reported in δ (ppm) units relative to the internal standard tetramethylsilane (TMS). The ELISA reader was produced by Boehringer Mannheim, Germany. Cell culture medium (RPMI1640) was purchased from Gibco company. Sulforhodamine B (SRB) was purchased from Sigma. NVP (non-nucleoside RT inhibitor) was produced by Ze Zhong Yi Hua Information Research Center, Nanjing, China. All the solvents and other reagents were analytical grade.

Formyl ferrocene and acetyl ferrocene were prepared by the literature methods.[40,41]

Table 5. Antibacterial activity of **4a, 4b** and **3**

	MIC (μg/ml)		
Compound	*S. aureus*	*E. coli*	*P. aeruginosa*
3	100.0	100.0	100.0
4a	50.0	50.0	25.0
4b	50.0	50.0	50.0
Ciprofloxacin	12.5	25.0	12.5

Preparation of the methyl 4-methylthiazole-5-carboxylate (2)

4-Methylthiazole-5-carboxylic acid 10 g (69.85 mmol) and methanol (50 ml) were refluxed for 2 h in a few drops of concentrated sulfuric acid. The obtained mixture was washed neutral with sodium carbonate solution (5%), extracted with toluene (25 ml) three times, dried and recrystallized from ethanol. It gave 9.34 g (85.1%) of **2**, m.p. 65–66 °C (lit. 63.9–65.1 °C[42]).

Preparation of the 4-methylthiazole-5-carbohydrazide (3)

Hydrazine-hydrate (5.8 ml, 101.79 mmol), 85%, was added to ethanolic solution of **2** (8 g, 50.90 mmol) and stirred for 3 h at room temperature. The reaction mixture was allowed to stand overnight. The solid precipitate was collected on a filter, washed three times with 95% ethanol and recrystallized from 20 ml ethanol. It gave 7.13 g of **3**.

Compound **3**: yellow crystal, yield 89.1%, m.p.166–167 °C, R_f (distance component traveled/distance solvent traveled) = 0.55 (petroleum ether : ethyl acetate = 1 : 1, v/v). ^{1}H-NMR ($CDCl_3$) δ: 9.27 (1H, s, S–CH=N), 8.00 (1H, s, NH), 3.96 (2H, s, NH_2), 2.40(3H, s, CH_3). IR (KBr) cm^{-1}: 3310, 3276, 3132, 3102, 2950, 2870, 1679, 1563, 1544, 960, 830, 701. Anal. calcd for $C_5H_7N_3OS$: C, 38.20; H, 4.49; N, 26.73. Found C, 38.88; H, 4.86; N, 26.55.

Procedure for the synthesis of (*E*)-*N*′-ferrocenylidene-4-methylthiazole-5- carbohydrazide (4a)

A solution of 1 g (6.36 mmol) of **3**, an equimolar amount of formyl ferrocene (1.36 g) and a few drops of ice acetic acid in 20 ml of EtOH were heated under reflux for 8 h with stirring and thin-layer chromatography (TLC) indicating. The solution was concentrated to half of its original volume, cooled to room temperature and allowed to stand overnight. The red solid precipitate was collected on a filter, washed three times with 95% EtOH, dried and recrystallized from 30 ml mixed solvent (DMF : ethanol = 1 : 2,

v/v). After drying *in vacuo*, crystals were obtained, giving 1.98 g of **4a**, yield 88.2%, m.p. 194–195 °C.

The preparation method of **4b** was similar to that of **4a**.

Compound **4a**: dark red crystal, yield 88.2%, m.p. 194–195 °C, $R_f = 0.53$ (petroleum ether : ethyl acetate = 4 : 1, v/v). ^{1}H-NMR ($CDCl_3$) δ: 10.34 (1H, s, S-CH═N), 8.94 (1H, s, NH), 7.84 (1H, s, CH═N), 4.69 (2H, m, C_5H_4–H), 4.44 (2H, m, C_5H_4–H), 4.22 (5H, s, C_5H_5–H), 2.96 (3H, s, CH_3). IR (KBr) cm^{-1}: 3179, 3092, 1670, 1603, 1547, 1102, 940, 819, 499. Anal. calcd for $C_{16}H_{15}FeN_3OS$: C, 54.41; H, 4.28; N, 11.90. Found C, 54.02; H, 3.89; N, 12.34.

Compound **4b**: dark red crystal, yield 80.0%, m.p. 118–120 °C, $R_f = 0.50$ (petroleum ether : ethyl acetate = 4 : 1, v/v). ^{1}H-NMR ($CDCl_3$) δ: 10.29 (1H, s, S–CH═N), 8.93 (1H, s, NH), 4.71 (2H, m, C_5H_4–H), 4.41 (2H, m, C_5H_4–H), 4.18 (5H, s, C_5H_5–H), 2.91 (3H, s, CH_3), 1.48 (3H, s, CH_3). IR (KBr) cm^{-1}: 3197, 3095, 1670, 1596, 1537, 1108, 945, 821, 503. Anal. calcd for $C_{17}H_{17}FeN_3OS$: C, 55.60; H, 4.67; N, 11.44. Found C, 55.77; H, 3.22; N, 12.44.

Crystallographic measurements

Crystal of **4a** was mounted in thin-walled glass capillaries for crystallographic studies (see Table 1 for details). The data were collected on a Rigaku RAXIS RAPID IP diffractometer with graphite-monochromated MoKα radiation ($\lambda = 0.71073$ Å) at 293(2) K. A total of 29 348 reflections and 3607 independent ones ($R_{int} = 0.0260$) were collected within the range $3.02^\circ < \theta < 27.47^\circ$ using ω scan technique, of which 2906 observed reflections with $I > 2\sigma(I)$ were used in the structural analysis. The structure was solved by direct methods and refined by full matrix least-squares techniques, using anisotropic thermal parameters for all non-hydrogen atoms. The hydrogen atoms were calculated and included as riding atoms in the refinements. The final cycle of full-matrix least-squares refinement gave $R_1 = 0.0423$, $wR_2 = 0.0918$, $S = 1.073$ and $(\Delta/\sigma)_{max} = 0.001$. The maximum peak on the final difference Fourier map was 0.299 and the minimum peak was -0.267 e/Å^3. The program used was SHELXL-97. Figure 2 shows the molecular structure of **4a** and Fig. 3 depicts the packing diagram of the molecules in a unit cell.

Anti-HIV-1 RT assay *in vitro*

The HIV-RT inhibition assay was performed using a reverse transcriptase (RT) assay kit, and the procedure for assaying RT inhibition was performed as described in the kit protocol.[43] Briefly, the reaction mixture consists of template/primer complex, 2′-deoxy-nucleotide- 5′- triphosphates(dNTPs) and RT enzyme in the lysis buffer with or without inhibitors. After 1 h incubation at 37 °C, the reaction mix was transferred to streptavidine-coated microtiter plate (MTP). The biotin-labeled dNTPs that are incorporated in the template due to the activity of RT were bound to streptavidine. The unbound dNTPs were washed using wash buffer and anti-digoxigenin–peroxidase (DIG–POD) was added in MTP. The DIG-labeled dNTPs incorporated in the template were bound to the anti-DIG–POD antibody. The unbound anti-DIG–POD was washed and the peroxide substrate (ABST) was added to the MTP. A colored reaction product was produced during the cleavage of the substrate catalyzed by a peroxide enzyme. The absorbance of the sample was determined at OD_{405} nM using a microtiter plate ELISA reader. The resulting color intensity was directly proportional to the actual RT activity. The percentage inhibitory activity of RT inhibitors was calculated by comparison with a sample that did not contain an inhibitor. The percentage inhibition was calculated by the formula given below:

$$\%\text{Inhibition} = 100 - \left[\frac{OD_{405}\text{ nm with inhibitor}}{OD_{405}\text{ nm without inhibitor}} \times 100\right]$$

The results were presented as 50% inhibitory concentrations (IC_{50}) by the median effect equation.[44]

Anti-HLC A549 activity

Ferrocenyl–thiazoleacylhydrazones of **4a** and **4b** were dissolved in physiological salt water with suitable concentrations and were added in the cultures (RPMI1640) of HLC A549. After an incubation period, cultures were fixed with 10% (w/v) trichloroacetic acid and stained for 30 min with 0.4% (w/v) SRB dissolved in 1% acetic acid.[45] Unbound dye was removed with four washes with 1% acetic acid, and protein-bound dye was extracted with 10 mmol/l unbuffered Tris base [tris (hydroxyl methyl) aminomethane] for optical density determination at 510 nm using a microplate reader.

Antibacterial activity assay *in vitro*[37]

The following standard organisms were used in the antimicrobial screening: *S. aureus* (ATCC 25923), *E. coli* (ATCC 25922) and *P. aeruginosa* (ATCC 27853). The bacterial strains were grown in Hottinger's broth (0.1% amine nitrogen and 0.5% NaCl, pH 7.0). Briefly, 10 tubes were filled with 2 ml seeded broth. Then the synthetical compound (2 ml of 1 mg/ml solution in DMF) was added to the first tube and 2 ml of this solution was transferred to the second tube and so on so forth. Then bacterial strains (2×10^5 cfu/ml) were inoculated into the tubes and incubated at 37 °C for 20 h. The results were presented as MIC values by visual observation.

Conclusions

Taken together, the novel ferrocenyl–thiazoleacylhydrazones were prepared and fully characterized. The crystal and molecular structure of **4a** was examined by X-ray crystal diffraction. The bioactivity of the synthetical compounds was tested for anti-HIV-1 RT, anti-HLC A549 and anti-bacterial activities; **4a, 4b** and **3** showed notable activity against *S. aureus, E. coli* and *P. aeruginosa*, with MIC values in the range 25.0–100.0 μg/ml whereas **4a** and **4b** demonstrated low activity against HIV-1 RT and HLC A549. Further structure modification and optimization of these ferrocenyl–thiazoleacylhydrazones derivatives are necessary.

Acknowledgment

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Supplementary Material

Crystallographic data for the structure analysis have been deposited with the Cambridge Crystallographic Data Center, CCDC no. 648138. Copies of this information may be obtained free of charge from the director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK. E-mail: linstead@ccdc.cam.ac.uk; deposit@ccdc.cam.ac.uk; http://www.ccdc.cam.ac.uk; Tel: 44-1223-336408; Fax: +44-1223-336033.

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