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Original article

Synthesis and anti-tuberculosis activity of new hetero(Mn, Co, Ni)trinuclear iron(III) furoates

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ABSTRACT

New hetero(μ_3-oxo)trinuclear iron(III) furoates with the general formulas $[Fe_2MO(\alpha\text{-Fur})_6(L)(H_2O)_2]$, where L = THF (**1**–**3**), DMF (**4**–**5**), M = Mn^{2+} (**1**, **4**), Co^{2+} (**2**, **5**), Ni^{2+} (**3**, **6**) and $[Fe_2MO(\alpha\text{-Fur})_6(3Cl\text{-}Py)_3]$, where M = Mn^{2+} (**7**), Co^{2+} (**8**), Ni^{2+} (**9**); have been synthesised and investigated by Mössbauer and IR spectroscopies. The X-ray crystal structure has been determined for the **4** and **8** complexes, indicating that they are related to the monoclinic crystal system ($P2_1/n$) and have a structure typical of μ_3-O-bridged trinuclear iron (III) compounds. The ^{57}Fe Mössbauer spectra of microcrystalline samples of the compounds indicate the presence of high-spin iron (III) ($S = 5/2$) with a near symmetrical environments. The iron(III)–cobalt(II) containing compounds **2**, **5** and **8** displayed MIC values between 0.83 ÷ 4.00 μg/mL.

1. Introduction

Mycobacterium tuberculosis, the causative agent of tuberculosis (TB), continues to be the greatest infectious cause of persistent widespread disease, whereas drugs, currently use to treat TB, are more than 40 years old and are only poorly effective against it [1–3]. Appearance of dramatic health problems such as multi-drug resistance and other different forms of diseases have made the research for new anti-TB drugs even more urgent. It is well known what important role metal ions play in biological phenomena. Being based on it, it has been synthesised a wide number of metals complexes that posses anti-tubercular activity [4–6]. Recently Vigorita et al. have presented some isonicotinoylhydrazones of cobalt (II) which are more promising then copper(II) and nickel(II) analogues [7a–b] as anti-mycobacterial agents against *M. tuberculosis* $H_{37}Rv$ [7c–d]. It has been studied the effect of some transition metal complexes on the structure of fungal and mammalian cell organelles, and they have been found to be potential to damage mitochondrial function and to uncouple respiration [8]. It should be noted that, coordination to a metal ion, as has often been reported, enhances the anti-mycobacterial and anti-proliferative properties of several ligands [9a–c]. Bioinorganic chemists tackle such problems at first focusing on the elucidation of the structure of the metal complex of interest and then try to discover it biological properties. Here, we report synthesis and structural investigation of new nine hetero(μ_3-oxo)trinuclear iron (III) furoates and their evaluation as novel class of anti-tubercular agents against *M. tuberculosis* $H_{37}Rv$.

2. Chemistry

The heterotrinuclear complexes of the general formula $[Fe_2MO(\alpha\text{-fur})_6(THF)(H_2O)_2]\cdot H_2O$, where M = Mn, Co, Ni, were obtained via substitution reactions, where the acetate anions in $[Fe_2MO(CH_3COO)_6(H_2O)_3]$ are easily replaced by α-furoic acid anions in THF. At the same time re-crystallization of these heteronuclear complexes in DMF or 3Cl-Py leads to new compounds of formulae $[Fe_2MO(\alpha\text{-fur})_6(DMF)(H_2O)_2]$ and $[Fe_2MO(\alpha\text{-fur})_6(3Cl\text{-}Py)_3]$, where M = Mn, Co, Ni.

2.1. Methods

2.1.1. Synthesis of $[Fe_2MO(\alpha\text{-fur})_6(THF)(H_2O)_2]\cdot H_2O$, where M = Mn ($1\cdot H_2O$), Co ($2\cdot H_2O$), Ni ($3\cdot H_2O$)

To a THF (tetrahydrofuran) (20 mL) solution of α-furoic acid (0.56 g, 5 mmol) was added $[Fe_2MnO(CH_3COO)_6(H_2O)_3]$ (1.18 g, 2 mmol). After

Abbreviations: M. tuberculosis, *Mycobacterium tuberculosis*; α-fur, Furoate; THF, Tetrahydrofuran; DMF, *N*,*N*-Dimethylformamide; 3Cl-Py, 3-Chloropyridine; MIC, Minimum Inhibitory Concentration.

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1 h of heating the solution was filtrated and was then kept standing at room temperature. Dark-brown crystals precipitated overnight. Calc. for $C_{34}H_{32}O_{23}Fe_2Mn$ (**1**·H_2O): C, 41.87; H, 3.31; Fe, 11.45%; Mn, 5.63%. Found: C, 41.55; H, 3.55; Fe, 11.33%; Mn, 5.52%. Yield: ~560 mg (~29%). IR (cm^{-1}): 3429b, 3145sh, 1598b, 1474s, 1411b, 1371s, 1230w, 1199s, 1140m, 1078w, 1017s, 934m, 884w, 799sh, 782b, 759m, 712w, 662w, 614m, 495b. The IR spectra of other complexes have the same characteristic bands. The syntheses of compounds **2** and **3** were carried out as described above for compound **1**, but starting with [$Fe_2CoO(CH_3COO)_6(H_2O)_3$] and [$Fe_2NiO(CH_3COO)_6(H_2O)_3$], respectively. Calc. for $C_{34}H_{32}O_{23}Fe_2Co$ (**2**·H_2O): C, 41.70; H, 3.29; Fe, 11.41%; Co, 6.02%. Found: C, 41.72; H, 2.93; Fe, 11.47%; Co, 5.94%. Yield: ~520 mg (~27%). Calc. for $C_{34}H_{32}O_{23}Fe_2Ni$ (**3**·H_2O): C, 41.71; H, 3.29; Fe, 11.41%; Ni, 6.00%. Found: C, 41.74; H, 3.98; Fe, 11.76%; Ni, 5.92%. Yield: ~560 mg (~29%).

2.1.2. Synthesis of [$Fe_2MO(\alpha$-fur$)_6$(DMF)$(H_2O)_2$]·2DMF, where M = Mn (4·2DMF·1.7H_2O), Co (5·2DMF), Ni (6·2DMF)

The starting compound [$Fe_2MO(\alpha$-fur$)_6$(THF)$(H_2O)_2$]·H_2O, where M = Mn, Co, Ni; was dissolved in DMF. Brown crystals were obtained by allowing the solvent to slowly evaporate for about a month. Calc. for $C_{39}H_{46.40}Fe_2MnN_3O_{25.70}$ (**4**): C, 41.27; H, 4.12; N, 3.70; Fe, 9.84%; Mn, 4.84%. Found: C, 41.05; H, 3.97; N, 3.65; Fe, 9.93%; Mn, 4.89%. Yield: ~63%. IR (cm^{-1}): 3124b, 2934b, 1604s, 1569m, 1474s, 1409b, 1393sh, 1365s, 1255w, 1226m, 1196s, 1142m, 1100b, 1078m, 1044w, 1009b, 932m, 883m, 797sh, 781b, 754m, 699b. The IR spectra of other complexes have the same characteristic bands. Calc. for $C_{39}H_{43}N_3O_{24}Fe_2Co$ (**5**): C, 42.26; H, 3.91; N, 3.79; Fe, 10.07%; Co, 5.32%. Found: C, 42.10; H, 3.76; N, 3.44; Fe, 9.97%; Co, 5.13%. Yield: ~58%. Calc. for $C_{39}H_{43}N_3O_{24}Fe_2Ni$ (**6**): C, 42.27; H, 3.91; N, 3.79; Fe, 10.08%; Ni, 5.30%. Found: C, 41.78; H, 3.99; N, 3.83; Fe, 9.90%; Ni, 5.32%. Yield: ~61%.

2.1.3. Synthesis of [$Fe_2MO(\alpha$-fur$)_6$(3Cl-Py$)_3$], where M = Mn (**7**), Co (**8**), Ni (**9**)

To a suspension of [$Fe_2MO(\alpha$-fur$)_6$(THF)$(H_2O)_2$] (0.3 mmol), where M = Co, Mn, Ni in acetone (10 ml) was added dropwise a 3Cl-Py (3 mmol, 0.28 ml). After stirring and heating for 30 min, the solution was filtered and the filtrate kept standing at room temperature. Dark-brown crystals were obtained after several weeks in ca. 80% yield (~290 mg). Calc. for $C_{45}H_{32}N_3O_{20}Cl_3Fe_2Mn$ (**7**·H_2O): C, 44.75; H, 2.67; N, 3.48; Fe, 9.25%; Mn, 4.55%. Found: C, 44.67; H, 2.63; N, 3.41; Fe, 9.30%; Mn, 4.38%. IR (cm^{-1}): 3100b, 1632m, 1608s, 1574m, 1476s, 1408b, 1364s, 1322sh, 1226m, 1197s, 1143w, 1117m, 1099w, 1079w, 1044n, 1033n, 1009s, 933s, 884m, 837w, 800m, 778s, 750b, 692b, 658sh. Calc. for $C_{45}H_{32}N_3O_{20}Cl_3Fe_2Co$ (**8**·H_2O): C, 44.60; H, 2.66; N, 3.47; Fe, 9.22%; Co, 4.86%. Found: C, 43.98; H, 2.47; N, 3.45; Fe, 9.15%; Co, 4.69%. The IR spectra of other complexes have the same characteristic bands. Yield: ~81%. Calc. for $C_{45}H_{32}N_3O_{20}Cl_3Fe_2Ni$ (**9**·H_2O): C, 44.61; H, 2.66; N, 3.47; Fe, 9.22%; Ni, 4.84%. Found: C, 44.95; H, 2.61; N, 3.49; Fe, 9.10%; Ni, 4.77%. Yield: ~78%.

3. Pharmacology

Data from the primary assay (level 1) revealed three active compounds (effecting >90% inhibition). Afterwards they have been tested in minimum inhibitory concentration (MIC) assay (level 2). Three of them, namely **2**, **5** and **8** were also tested at level 2 in cytotoxicity (EC50) assays. MIC and IC50 values for those three {Fe_2CoO}-furoates to VERO cell line in culture media were determined and selectivity indexes (SI = EC50/MIC) were calculated.

3.1. Primary screen (Dose response): determination of a 90% inhibitory concentration (IC90)

The initial screen is conducted against *M. tuberculosis* H37Rv (ATCC 27294) in BACTEC 12B medium using the Microplate Alamar Blue Assay (MABA) [10]. All titled compounds are tested in ten 2-fold dilutions, typically from 100 μg/mL to 0.19 μg/mL. The IC90 is defined as the concentration effecting a reduction in fluorescence of 90% relative to controls. This value is determined from the dose-response curve using a curve-fitting program. Any IC90 value of ≤10 μg/mL is considered "Active" for anti-tubercular activity.

3.2. Secondary screen: determination of mammalian cell cytotoxicity (EC50)

The VERO cell cytotoxicity assay is done in parallel with the TB Dose Response assay. After 72 h exposure, viability is assessed using Promega's Cell Titer Glo Luminescent Cell Viability Assay, a homogeneous method of determining the number of viable cells in culture based on quantitation of the ATP present. Cytotoxicity is determined from the dose-response curve as the EC50 using a curve-fitting program. Ultimately, the EC50 is divided by the IC90 to calculate an SI (Selectivity Index) value. SI values of ≥10 are considered for further testing.

4. Results and discussion

By means of the strategies described above nine new coordination compounds with α-furoic acid were prepared. All complexes give good elemental analyses results as shown in Methods (2.1) and were obtained as polycrystalline samples.

4.1. Structural analysis of [$Fe_2MnO(\alpha$-fur$)_6$(DMF$)(H_2O)_2$]·2DMF·1.7H_2O (**4**) and [$Fe_2CoO(\alpha$-fur$)_6$(3Cl-Py$)_3$] (**8**)

Both μ_3-oxo-heterotrinuclear compounds **4** and **8** have the same crystal and molecular structures. Complex [$Fe_2MnO(\alpha$-fur$)_6$(DMF$)(H_2O)_2$] (**4**) crystallizes with dimethylformamide and water as solvate molecules in a 1:2:1.7 ratio, while the crystal of **8** consists of [$Fe_2CoO(\alpha$-fur$)_6$(3Cl-Py$)_3$] and does not contain any solvate molecule. Molecular structures of complexes **4** and **8** are depicted in Fig. 1. Three metal atoms describe a typical triangular structure with M–Fe1, M–Fe2, Fe1–Fe2 separations equal to 3.4035(9), 3.3372(9), 3.2807(8)Å and 3.315(5), 3.3321(5), 3.259(5)Å for **4** and **8**, respectively. The central μ_3-oxygen atom and six furoate anions as bidentate ligands fulfil the bridge functions consolidating trinuclear skeleton. The three metal ions have an octahedral coordination, completed by the water molecules for Mn and Fe2 atoms and by DMF for the Fe3 atom in structure **4** and by three 3Cl-Py molecules in **8**. The position for each metal ion in the trinuclear core, as shown in Fig. 1, was possible to determine on the basis of geometric characteristics of the coordination sites. Indeed, Mn–O1 = 2.044(3), Mn–O1w = 2.177(3) and average Mn—$O_{(COO)}$ = 2.154(3) Å for **4**, Co–O1 = 1.937(4), and average Co—$O_{(COO)}$ = 2.070(4) Å for **8** bond distances exhibit larger values in comparison with the analogous for the Fe1 (**4**, 1.895(3) and 1.891(4) Å, **8**) and Fe2 (**4**, 1.847(3) and 1.884(4) Å, **8**) coordination sites.

These values are in a good agreement with the corresponding ionic radii (0.83 Å for Mn^{2+}, 0.83 Å for Co^{2+} and 0.65 Å for Fe^{3+} [13]) and clearly confirm the localization of the heteroatom in the trinuclear fragment.

4.2. IR spectra

All the above given structural data are in close conformity with the data of IR spectroscopy. The assignments of the observed bands have been done according to [11]. The analytical frequencies for the carboxylic ligands are the asymmetric and symmetric stretching vibrations of the COO group. For our new compounds, these two intensive bands are in the range 1608–1594 cm^{-1} and 1403–1418 cm^{-1}, respectively. The values of the frequency shifts of the

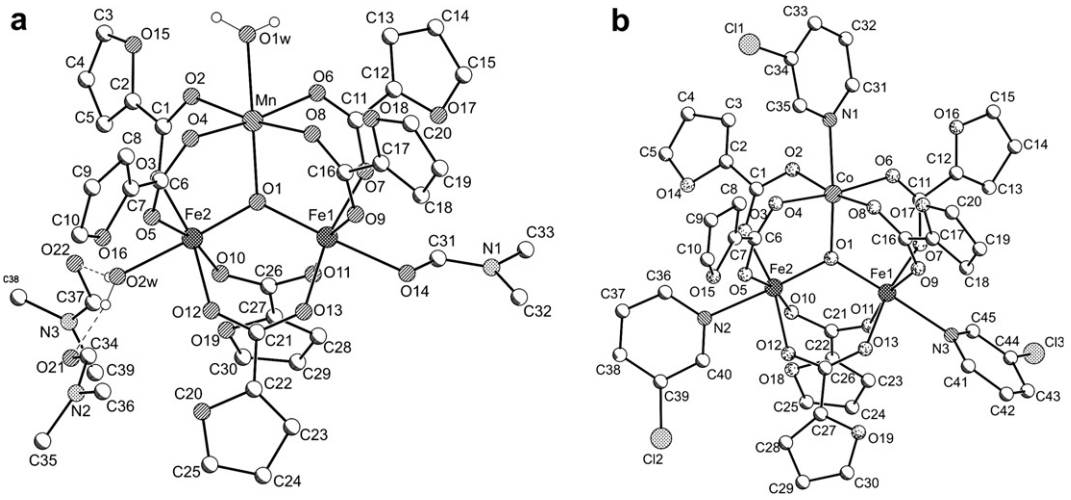

Fig. 1. Molecular structure of $[Fe_2MnO(\alpha\text{-fur})_6(DMF)(H_2O)_2]$ (**4**) associated with two H-bonded solvate molecule of DMF. Some outer sphere DMF molecules and the disordered water molecules of crystallization have been omitted for clarity (a); Molecular structure of $[Fe_2CoO(\alpha\text{-fur})_6(3Cl\text{-}Py)_3]$ (**8**) (b).

symmetric and antisymmetric carboxyl bands are characteristic for furoate carboxylates [12]. The infrared data support the proposal of similar electronic structures of the complexes. The C–O–C stretching frequency in furoates is the same as in the "origin" acid 1009–1017 cm^{-1}, indicating that the ring oxygen does not participate in coordination. Except the above mentioned bands, there are a great number of other bands specific for THF, DMF and 3Cl-Py.

4.3. Mössbauer spectra

The parameters of the Mössbauer spectra (MS) of all the studied compounds indicate the presence of high-spin iron(III) ($S = 5/2$).

The analysis of isomer shift values (δ_{Na+}) (Table 1) at 300 K and 80 K shows that the monodentate ligands and M^{2+} ions in the inner sphere as well as the anions and solvent molecules in the external sphere do not influence the total density of s-electrons on the nucleus. Depending on their structure all titled complexes can be divided in 3 classes: molecular heterotrinuclear complexes with the following fragment $\{Fe_2MO\}$, where M = Mn^{2+}, Co^{2+}, Ni^{2+}, and different monodentate ligands H_2O, (THF, DMF), 3Cl-Py in the inner spheres.

The values of quadrupol splitting (ΔE_Q) of MS in the case of homotrinuclear complexes are in the limits 0.54–0.59 mm/s (80 K) and increases to 0.85–1.02 mm/s (80 K) in the case of heterotrinuclear clusters. There is no evidence of any change of the ΔE_Q values within the limits of a given class of studied substances. According to the analysis of ΔE_Q (Table 1) it can be concluded that replacement of the ion Fe^{3+} with the ion M^{2+} (M = Mn, Co, Ni) in the structure of a fragment $\{Fe_2MO\}$ leads to a reduction of symmetry of the electronic cloud surrounding the Fe-57 nucleus. It is possible to explain by turning symmetry C_{3V} of a fragment $\{Fe_3O\}$ into symmetry C_{2V} of a fragment $\{Fe_2MO\}$. At the same time, practically, the influence on a gradient of electric field of the nature of the metal as well as the change in structure of the coordination centre is not observed.

Table 1
The Mössbauer spectra parameters of the investigated complexes at 80 and 300 K.

Nr	Substance	T, K	mm/s		
			δ_{Na+}, (±0.03)	ΔE_Q, (±0.03)	Γ, (±0.03)
1	[Fe2MnO(α-fur)6(THF)(H2O)2]·H2O	300	0.68	1.03	0.32
		80	0.78	0.86	0.37
2	[Fe2CoO(α-fur)6(THF)(H2O)2]·H2O	300	0.68	0.92	0.37
		80	0.78	1.02	0.39
3	[Fe2NiO(α-fur)6(THF)(H2O)2]·H2O	300	0.68	0.97	0.31
		80	0.81	1.01	0.41
4	[Fe2MnO(α-fur)6(DMF)(H2O)2]·2DMF	300	0.69	1.07	0.37
		80	0.78	0.98	0.26
5	[Fe2CoO(α-fur)6(DMF)(H2O)2]·2DMF	300	0.71	0.86	0.35
		80	0.79	0.97	0.27
6	[Fe2NiO(α-fur)6(DMF)(H2O)2]·2DMF	300	0.69	1.06	0.30
		80	0.78	0.99	0.28
7	[Fe2MnO(α-fur)6(3Cl-Py)3]	300	0.69	1.08	0.31
		80	0.78	0.86	0.22
8	[Fe2CoO(α-fur)6(3Cl-Py)3]	300	0.68	1.03	0.30
		80	0.79	0.86	0.21
9	[Fe2NiO(α-fur)6(3Cl-Py)3]	300	0.69	1.03	0.31
		80	0.78	0.85	0.24

4.4. Anti-tuberculosis activity

Anti-mycobacterial data concerning nine new heterotrinuclear tested as inhibitors against *M. tuberculosis* ($H_{37}Rv$) are collected in Table 2. In the primary assay three compounds shown distinctive activity. Surprisingly, but among these three clusters all is representatives of heteroclusters containing cobalt as bivalent 3d-metal (**2**, **5**, **8**) which have demonstrated sufficient activity; others complexes were considered as inactive. Among all complexes of the series under test for determination of minimum inhibitory concentration complex **2** was found to be the most potent. More promising tuberculosis inhibitors **2**, **5** and **8** were tested at level 2 in MIC and cytotoxicity

Table 2
Tuberculosis inhibition activity and cytotoxicity assays summary[a] concerning compounds **2**, **5** and **8**.

Compound/TAACF code	MIC assay (level 2) and cytotoxicity assay			
	Inhib. (%)	MIC (μg/mL)	EC_{50} (μg/mL)	SI
2/412 305	Active	0.827	>30.0	>36.2
5/412 313	Active	3.999	>30.0	>7.5
8/412 327	Active	3.344	>30.0	>8.9
INH	Active	<0.05	>1000.0	>40 000
RMP	Active	<0.125	>100.0	>800

[a] Inhib.- inhibition; MIC-minimum inhibitory concentration (value of MIC<1 μg/mL is an excellent result); EC_{50} – cytotoxicity to a VERO cell line; SI-selectivity index defined as the ratio of EC_{50} to MIC (it should be >10 for further testing).

Table 3
Crystallographic data, experiment details and structure refinement parameters for [Fe2MnO(α-fur)6(DMFA)(H2O)2]·2DMFA·1.7H2O (4) and [Fe2CoO(α-fur)6(3Cl-Py)3] (8) complexes.

	4	**8**
Empirical formula	$C_{39}H_{46.40}Fe_2MnN_3O_{25.70}$	$C_{45}H_{30}N_3O_{19}Cl_3Fe_2Co$
Formula mass	1135.03	1193.72
Space group	$P2_1/n$	$P2_1/n$
a [Å]	10.5566 (6)	14.9215 (12)
b [Å]	20.4437 (11)	14.1352 (12)
c [Å]	22.5004 (14)	23.9978 (16)
β [°]	90.661 (4)	100.358 (8)
V [Å^3]	4855.6 (5)	4979.1 (7)
Z	4	4
λ [Å]	0.71073	0.71073
$\rho_{(calcd.)}$ [g·cm^{-3}]	1.553	1.592
Crystal size [mm]	0.2 × 0.15 × 0.12	0.25 × 0.2 × 0.20
T [K]	100	173
μ [cm^{-1}]	0.937	1.144
R_1[a]	0.0570	0.0602
wR_2[b]	0.1354	0.1106
GOF[c]	1.064	0.881

[a] $R_1 = \Sigma||Fo| - |Fc||/\Sigma|Fo|$.
[b] $wR_2 = \{\Sigma[w(Fo^2 - Fc^2)^2]/\Sigma[w(Fo^2)^2]\}^{1/2}$.
[c] GOF $= \{\Sigma[w(Fo^2 - Fc^2)^2]/(n-p)\}^{1/2}$, where n is the number of reflections and p is the total number of parameters refined.

assays. Important results of those assays are disclosed in Table 2 together with the data for control drugs INH and RMP.

The iron(III)–cobalt(II) containing compounds **2**, **5** and **8** exhibited activity between 0.83 ÷ 4.00 μg/mL, which is unexpected result for these class of compounds. According to the statistic data [14], the results obtained for compound [Fe_2CoO(α-Fur)$_6$(THF)$(H_2O)_2$] (**2**) in average is characteristic for 32 successful tests from 10 000 screenings.

5. Conclusion

In conclusion, we have demonstrated the syntheses of new hetero(μ$_3$-oxo)trinuclear iron (III) furoates with the formulas [Fe_2MO(α-Fur)$_6$(L)$(H_2O)_2$], where L = THF (**1**–**3**), DMF (**4**–**5**), M = Mn^{2+} (**1**, **4**), Co^{2+} (**2**, **5**), Ni^{2+} (**3**, **6**) and [Fe_2MO(α-Fur)$_6$(3Cl-Py)$_3$], where M = Mn^{2+} (**7**), Co^{2+} (**8**), Ni^{2+} (**9**); have been prepared and investigated by X-ray, Mössbauer and IR spectroscopies.

The iron(III)–cobalt(II) containing compounds **2**, **5** and **8** exhibited activity between 0.83 ÷ 4.00 μg/mL, were compared with well known drugs such as isoniazid (INH) and rifampicin (RMP). Only one of the tested compounds, [Fe_2CoO(α-Fur)$_6$(THF)$(H_2O)_2$] (**2**), has demonstrated tuberculosis inhibition activity and cytotoxicity results acceptable for further screening, which could be a nice start "stone" to further studies, as well as find new class of lead compounds. Other TAACF screening levels, i.e. on TB-infected macrophages culture, are underway.

6. Experimental protocol

The carbon, hydrogen and nitrogen contents of the complex were determined by standard micro-methods by the microanalysis group of the Institute of Chemistry using a Vario-EL-III-CHNOS Elemental Analyzer; iron, manganese, cobalt and nickel determinations were carried out using the Atomic Absorption Spectroscopy (Spectrophotometer AAS-3N Karl Zeiss Jena® DDR) in the Centre of Physical Methods of Research of the Institute of Chemistry ASM.

IR spectra of polycrystalline samples were recorded using a Perkin Elmer Spectrum 100 FT-IR Spectrometer.

The Mössbauer spectra for **1**–**9** were acquired using a constant acceleration system with asymmetrical waveform. A ^{57}Co (1.0 MBq) source in a Rh matrix was used; isomer shifts are referenced to sodium nitroprusside $Na_2[Fe(CN)_5(NO)]\cdot 2H_2O$.

X-ray diffraction measurements for **4** were performed with an X8 APEXII CCD diffractometer. Single crystals were positioned at 40 mm from the detector and 2310 frames were measured for 30 s with a 1° scan-width. The data were processed using the SAINT software package [15]. The structures were solved by direct methods and refined by full-matrix least-squares techniques. Non-hydrogen atoms were refined with anisotropic displacement parameters. The hydrogen atoms were included in calculated positions and treated as riding atoms using SHELXL default parameters. The following computer programs were used: structure solution: SHELXS-97 [16]; refinement: SHELXL-97 [17]; molecular diagrams: ORTEP [18]; computer CPU: Pentium IV; scattering factors were taken from the literature [19]. A black-grey crystal of **8** was mounted on a Stoe Mark-II Image Plate diffractometer system equipped with a graphitemonochromator. Data collections were performed using Mo-K_α radiation (λ = 0.71073 Å) at 173 K. Crystal data, data collection parameters, and structure refinement details are given in Table 3. The structures were solved by direct methods using the program SHELXS-97 [16] and refined by full-matrix least-squares on $F2$ with SHELXL-97 [17].

7. Supplementary material

Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC-696082 (for **4**), -696081 (for **8**). Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44 1223 336 033; e-mail:deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

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