Synthesis and antibacterial, antimycobacterial and antifungal activities of Fe(II), Fe(III), Cu(II), Zn(II) and Ni(II) complexes of aliphatic hydroxamic acids

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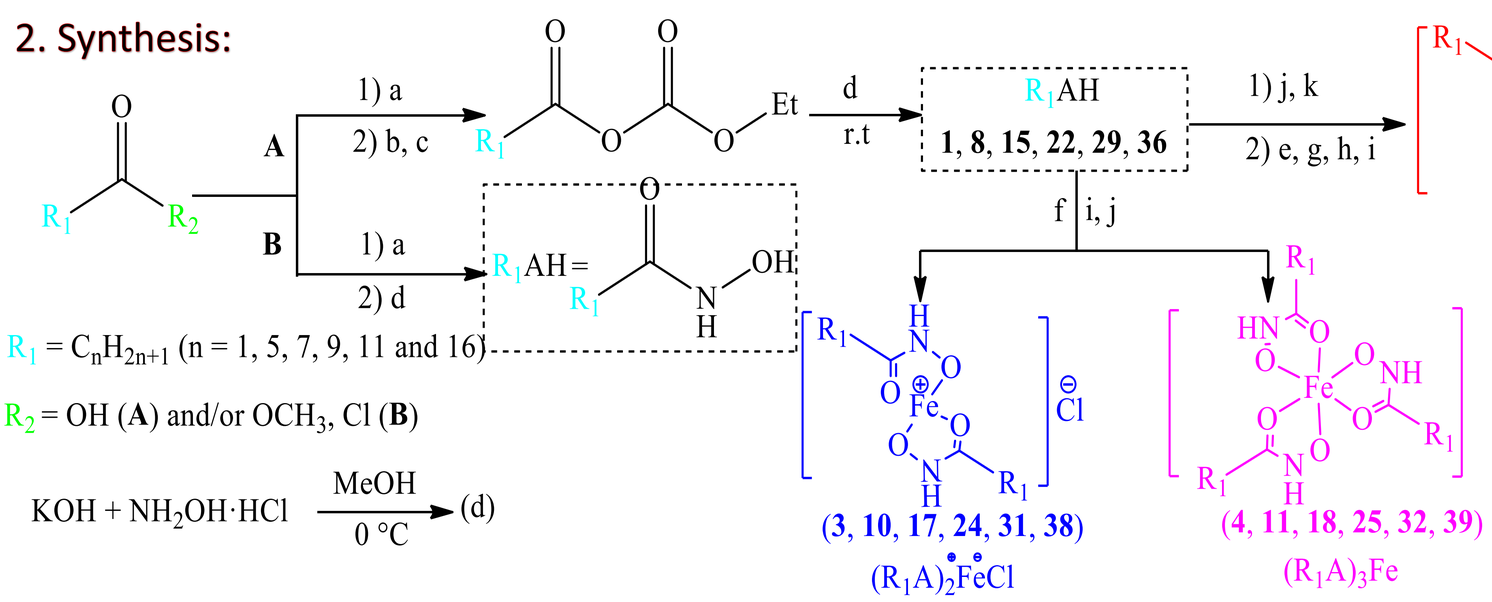
1. Introduction: Hydroxamic acids show interesting biological properties described in the literature [1], particularly against bacteria, tumoral cells, fungi [2,3,4] and mycobacteria [5,6]. In the present project we aim at more deeply and systematically exploring the biological properties of Fe(II), Fe(III), Cu(II), Zn(II) and Ni(II) complexes of aliphatic hydroxamic acids with variable chain lengths [7]. We investigate the effect of lipophilicity on the biological activity. The synthesis of Fe(II), Fe(III), Cu(II), Zn(II), Ni(II) complexes with C_2, C_6, C_8, C_{10}, C_{12} and C_{17} hydroxamic acids and their effects on bacteria, mycobacteria and yeasts are described.

2. Synthesis:



Scheme 1: Synthetic routes for preparation of hydroxamic acids and complexes **1**—**42**.

Reagents and conditions: a = Et_2O, b = ClCOOEt, c = $O(CH_2CH_2)NCH_3$, d = NH_2OH, e = $FeCl_2$ (**43**), f = $FeCl_3$ (**44**), g = $CuCl_2.2H_2O$ (**45**), h = $ZnCl_2$ (**46**), i = $NiCl_2.6H_2O$ (**47**), j = MeOH, k = NaOH (1 M), 0°C and room temperature (r.t).

Table 1: Formula of R_1

Formula	R_1 (N° compounds)					
R_1AH	CH_3 (**1**)	C_5H_{11} (**8**)	C_7H_{15} (**15**)	C_9H_{19} (**22**)	$C_{11}H_{23}$ (**29**)	$C_{16}H_{33}$ (**36**)
$(R_1A)_2Fe$	CH_3 (**2**)	C_5H_{11} (**9**)	C_7H_{15} (**16**)	C_9H_{19} (**23**)	$C_{11}H_{23}$ (**30**)	$C_{16}H_{33}$ (**37**)
$(R_1A)_2Fe^+Cl^-$	CH_3 (**3**)	C_5H_{11} (**10**)	C_7H_{15} (**17**)	C_9H_{19} (**24**)	$C_{11}H_{23}$ (**31**)	$C_{16}H_{33}$ (**38**)
$(R_1A)_3Fe$	CH_3 (**4**)	C_5H_{11} (**11**)	C_7H_{15} (**18**)	C_9H_{19} (**25**)	$C_{11}H_{23}$ (**32**)	$C_{16}H_{33}$ (**39**)
$(R_1A)_2Cu$	CH_3 (**5**)	C_5H_{11} (**12**)	C_7H_{15} (**19**)	C_9H_{19} (**26**)	$C_{11}H_{23}$ (**33**)	$C_{16}H_{33}$ (**40**)
$(R_1A)_2Zn$	CH_3 (**6**)	C_5H_{11} (**13**)	C_7H_{15} (**20**)	C_9H_{19} (**27**)	$C_{11}H_{23}$ (**34**)	$C_{16}H_{33}$ (**41**)
$(R_1A)_2Ni$	CH_3 (**7**)	C_5H_{11} (**14**)	C_7H_{15} (**21**)	C_9H_{19} (**28**)	$C_{11}H_{23}$ (**35**)	$C_{16}H_{33}$ (**42**)

3. Results. Table 2: Minimum inhibitory concentration (µM) values biological assays against: Gram-positive/-negative bacteria, mycobacteria and yeasts of hydroxamic acids and their complexes (**1**–**42**) (see **Table 1**).

N°	Code	Gram- + bacteria			Gram- - bacteria			Mycobacteria	Yeasts	
		S.a MSSA	*S.a MRSA*	*C.g*	*E.c*	*P.a*	*K.p*	*M.s*	*C.a*	*C.t*
1	HA2	>500	>500	>500	>500	>500	>500	>500	>500	>500
2	A2Fe2	>500	>500	>500	>500	>500	>500	>500	>500	>500
3	A2FeCl	>500	>500	>500	>500	>500	>500	>500	>500	>500
4	A2Fe3	>500	>500	>500	>500	>500	>500	>500	>500	>500
5	A2Cu2	>500	>500	>500	>500	>500	>500	>500	>500	>500
6	A2Zn2	>500	>500	>500	>500	>500	>500	>500	>500	>500
7	A1Ni2	>500	>500	>500	>500	>500	>500	>500	>500	>500
8	HA6	>500	>500	>500	>500	>500	>500	>500	>500	>500
9	A6Fe2	>500	>500	>500	>500	>500	>500	>500	>500	>500
10	A6FeCl	156.25	>500	>500	312.5	>500	>500	>500	>500	>500
11	A6Fe3	78.125	>500	>500	>500	>500	>500	>500	>500	>500
12	A6Cu2	>500	>500	>500	>500	>500	>500	>500	>500	>500
13	A6Zn2	>500	>500	>500	78.125	>500	>500	>500	>500	>500
14	A6Ni2	>500	>500	>500	>500	>500	>500	>500	>500	>500
15	HA8	>500	>500	>500	312.5	>500	>500	>500	>500	>500
16	A8Fe2	312.5	>500	>500	156.25	>500	>500	>500	>500	>500
17	A8FeCl	78.125	>500	250	156.25	>500	>500	>500	>500	>500
18	A8Fe3	78.125	>500	250	156.25	>500	>500	>500	>500	>500
19	A8Cu2	>500	>500	>500	>500	>500	>500	>500	>500	>500
20	A8Zn2	>500	>500	>500	78.125	>500	>500	>500	250	>500
21	A8Ni2	>500	>500	>500	>500	>500	>500	>500	>500	>500
22	HA10	312.5	>500	500	312.5	>500	>500	>500	31.25	>500
23	A10Fe2	125	>500	125	>500	>500	>500	>500	>500	>500
24	A10FeCl	78.125	>500	250	312.5	>500	>500	>500	>500	>500
25	A10Fe3	78.125	>500	125	<78.125	>500	>500	>500	>500	>500
26	A10Cu2	>500	>500	>500	>500	>500	>500	>500	>500	>500
27	A10Zn2	>500	>500	>500	78.125	>500	>500	>500	125	>500
28	A10Ni2	>500	>500	>500	>500	>500	>500	>500	250	>500
29	HA12	62.5	125	62.5	62,5	>500	>500	62.5	15.625	62.5
30	A12Fe2	>500	>500	>500	>500	>500	>500	125	>500	125
31	A12FeCl	>500	>500	>500	>500	>500	>500	125	>500	250
32	A12Fe3	>500	>500	>500	156.25	>500	>500	31.25	>500	125
33	A12Cu2	>500	>500	>500	>500	>500	>500	>500	15.625	>500
34	A12Zn2	>500	>500	>500	156.25	>500	>500	>500	15.625	>500
35	A12Ni2	>500	>500	>500	>500	>500	>500	>500	31.25	>500
36	HA17	>500	>500	>500	>500	>500	>500	>500	>500	>500
37	A17Fe2	>500	>500	>500	312,5	>500	>500	>500	>500	>500
38	A17FeCl	>500	>500	>500	>500	>500	>500	>500	>500	>500
39	A17Fe3	>500	>500	>500	>500	>500	>500	>500	>500	>500
40	A17Cu2	>500	>500	>500	>500	>500	>500	>500	>500	>500
41	A17Zn2	>500	>500	>500	>500	>500	>500	>500	>500	>500
42	A17Ni2	>500	>500	>500	>500	>500	>500	>500	>500	>500
43	Fe2	>500	>500	>500	>500	>500	>500	>500	>500	>500
44	Fe3	>500	>500	>500	>500	>500	>500	>500	>500	>500
45	Cu2	312.5	>500	500	>500	>500	>500	>500	>500	>500
46	Zn2	>500	>500	250	<78.125	>500	>500	>500	>500	>500
47	Ni2	>500	>500	>500	>500	>500	>500	>500	>500	>500
48	Vanc	<1.048	1.725	0.215	<1.048	>3.45	>3.45	0.431	>3.45	0.215
49	Cetr	--	<0.0928	<0.00219	--	0.3715	0.0928	0.372	0.0928	<0.0928
50	Rifa	--	--	0.00918	--	--	>6.079	<0.189	--	<0.0189

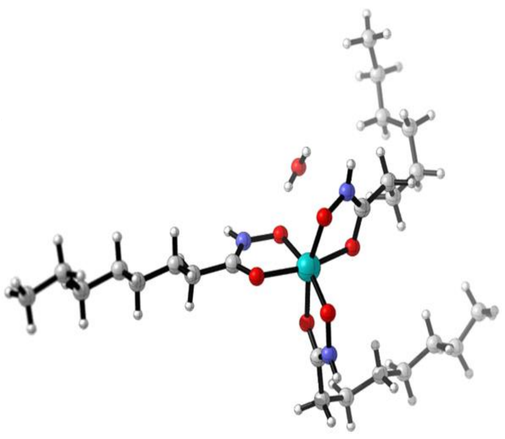


Figure 1: Crystal structure obtained by X-ray diffraction of A8Fe3 (**18**).

S.a MSSA: methicillin-sensitive *Staphylococcus aureus*,
S.a MRSA: methicillin-resistant *Staphylococcus aureus*,
C.g: *Corynebacterium glutamicum*,
E.c: *Escherichia coli*,
P.a: *Pseudomonas aeruginosa*,
K.p: *Klebsiella pneumoniae*,
M.s: *Mycobacterium smegmatis*,
C.a: *Candida albicans*
C.t: *Candida tropicalis*,
Van: Vancomycin (**48**),
Cetr: Cetrimide (**49**)
Rifa: Rifampicin (**50**).

4. Conclusion and perspective : The results of the *in vitro* test carried out support the hypothesis that the length of the R_1 group chain and the type of coordination metal have an effect on antimicrobial activity. The toxicity of compounds with significant antibacterial and antifungal activity will be investigated on cervical cancer cells and the cell penetration of the most promising compounds will be determined.

[1] Alam et *al*. *Cur. Org. Chem.* 2019, [2] Karger, *Horst Kehl* N.Y 1982.; [3] Maehr et *al*. *Pure Appl. Chem*. 1971; [4] Hase et *al. Chem. Pharm. Bull.* 1971; [5] Urbanski, *Nature*, 1950; [6] Urbanski et *al*. *Nature*, 1952; [7] O'Brien et *al. J. of Inorg. Biochem.* 2000; [8] Brown et *al*. *Inorg. Chem*. 1983; [9] Aliyu et *al*. *Asian J. of Chem.* 2011; [10] Bayer et al. from *Patentschrift*, 1967; [11] Zhu et *al*. *N.P.C*, 2011; [12] Darren et *al*. *J. of Inorg. Biochem*., 2011; [13] Reddy et *al*. *Tetrahedron letters*, 2000; [14] Cerniauskaite et *al. Eur. J. Org. Chem*. 2011; [15] Brown et *al*. *M.R. In Chemi.* 1988; [16] Devlin et al. *J. Chem. Soc.* 1975.

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