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Novel Polydentate Macroacyclic Schiff Base Ligands Based on 2,6−Diformylphenol

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Dedicated to Academician Oleg Chupakhin on the occasion of his 80th birthday

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*[1+2] Condensation of 2,6-diformylphenol (**1**) with ethyl-2-[(2-aminophenyl)aminomethylidene]-1,3-dicarbonyl compounds (**2**) resulted in new macroacyclic bisazomethines **3** having 2-hydroxyphenyl spacer. They are capable of regulated selective modes of mono- and binuclear complexes **4**, **5** with 3d metal ions in proper conditions. Crystal structure of **4d** was confirmed with X-Ray data. A moderate tuberculostatic activity of Schiff base ligands **3c,d** is reported.*

Keywords: Schiff bases, 2,6-diformylphenol, condensation, tuberculostatic activity, 3d metal complexes.

Новые полидентатные макроациклические основания Шиффа на основе 2,6−диформилфенола

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*В результате [1+2] конденсации 2,6-диформилфенола **1** с этил-2-[(2-аминофенил)аминометилиден]-1,3-дикарбонильными соединениями **2** получены новые макроациклические бис-азометины **3** с 2-гидроксифенильным спейсером, способные к регулируемому селективному формированию на их основе моно- и биядерных металлокомплексов **4**, **5** с катионами переходных металлов. Выявлено умеренное туберкулостатическое действие синтезированных лигандов на лабораторный штамм микобактерий туберкулеза $H_{37}Rv$.*

Ключевые слова: Основания Шиффа, 2,6-диформилфенол, конденсация, туберкулостатическая активность, комплексы 3d металлов.

Introduction

Directed synthesis of polydentate organic compounds with various donor centers followed by metal complexes formation, their structures' definition and evaluation of regioselective coordination factors play an important role in design of artificial models of biologically important objects[1,2] and searching for compounds with required physicochemical and applied properties,[3-5] *e.g.* magnetic,[6,7] catalytic,[8-10] medicobiological,[11] *etc*.

Previously we have reported on macroacyclic polydentate ligands via diethyl-2-[(2-aminophenyl)-aminomethylidene]malonate or ethyl-2-[(2-aminophenyl)aminomethylidene]-3-oxo-3-(polyfluoro)alkylpropionates with thiophene-2,5-dicarboxaldehyde.[12,13] It was shown the structure of their coordination centers depends on the symmetry of 1,3-dicarbonyl fragment. These compounds were expected to form complexes with 3d metal ions; however our attempts to isolate stable chelates were unsuccessful because of sulfur atom in thiophene cycle seems to have the low donor ability for the formation of strong donor-acceptor bond with metal ion.[14]

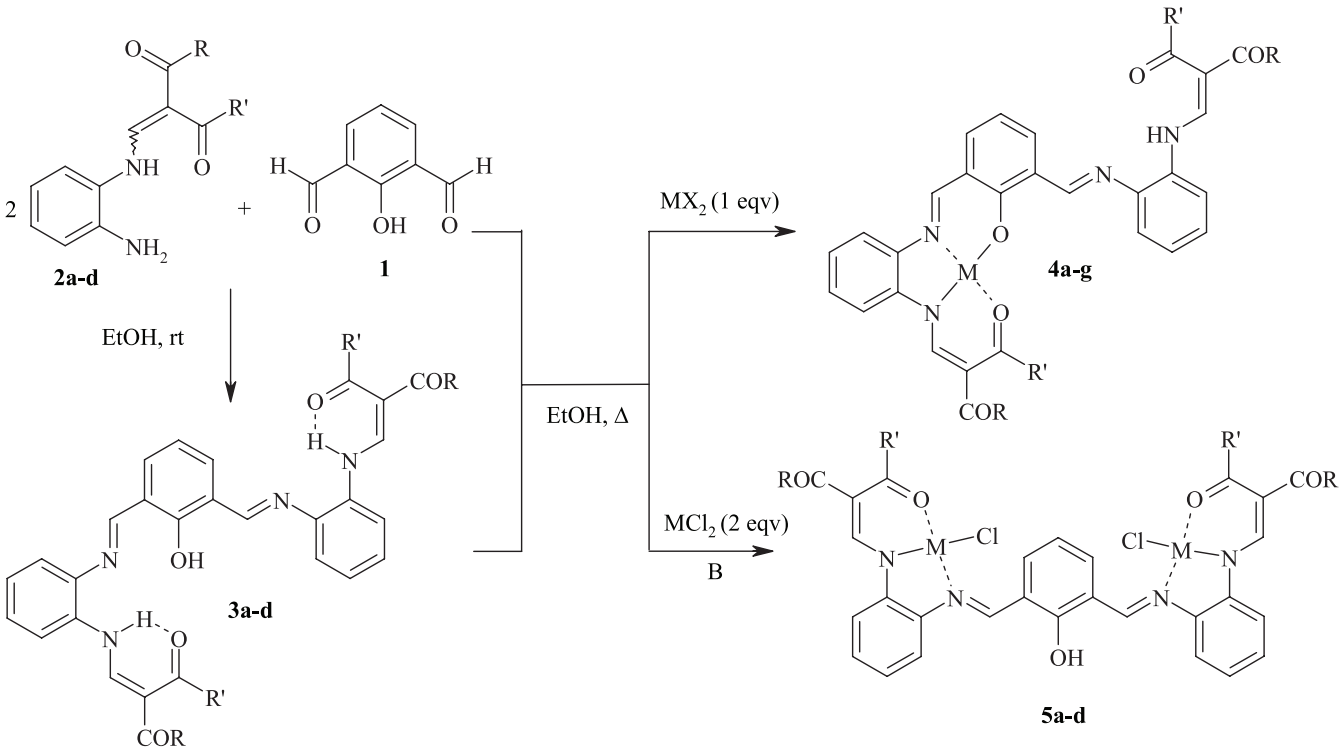
Unlike thiophene-2,5-dicarboxaldehyde 2,6-diformylphenol have a hydroxy group that can provide the covalent bonding with metal ions. It is worth noting that 2,6-diformylphenol and its derivatives are widely used in the design of polydentate ligands which can form polynuclear complex systems having magnetic interaction between the metal centers. Due to the study of stereochemical, electronic, magnetic, catalytic, spectroscopic and biological properties one can suggest for them some important applications.[15-18]

In this paper we describe the synthesis, coordination properties and tuberculostatic activity of new macroacyclic Schiff base ligands based on 2,6-diformylphenol **1** and ethyl-2-[(2-aminophenyl)aminomethylidene]-1,3-dicarbonyl compounds **2a-d**.

Results and Discussion

It was found the reaction of dialdehyde **1** with amines **2a-d** in ethanol at room temperature proceeds regioselectively and gives [1+2] condensation products – diazomethines **3a-d** in good yields (Scheme 1). Structures of **3a-d** were characterized by IR, ^{1}H, ^{19}F NMR spectroscopy and elemental analysis.

An important point is that compounds **3a-d** have labile hydrogen atom and therefore they can be involved in keto-enol and amine-imine tautomerism. The imino-enone, imino-enol, and/or amino-enone tautomers are possible for their structure. Furthermore, amino-enone tautomers of 3-oxoesters derivatives **3c,d** can exhibit *Z,E*-isomerism because of different position of non-equivalent substituents relative to C=C bond.



2, 3: R = R' = OEt (**a**); R = R' = Me (**b**); R = OEt: R' = Me (**c**), CF_3 (**d**).

4: R = R' = OEt: M = Ni (**a**), Cu (**b**); R = R' = Me: M = Ni (**c**); R = OEt, R' = Me: M = Ni (**d**), Cu (**e**); R = OEt, R' = CF_3: M = Ni (**f**), Cu (**g**).

5: R = R' = Me, M = Ni (**a**); R = OEt: R' = Me, M = Ni (**b**), Cu (**c**); R = OEt: R' = CF_3, M = Ni (**d**).

B = Py, DBU; X = Cl, OAc.

Scheme 1.

Table 1. ^{1}H NMR spectral data (δ, ppm) of compounds **3c**,**d** in $CDCl_3$.

Compound	R	R′	Isomer	Methylene (=CH-)	Azomethine (-HC=N-)	Amine (-NH)	Content, %
3c	Me	OEt	EE	8.59	9.00	13.19	85
			ZZ	8.58	8.89	12.59	15
3d	CF_3		EE	8.71	9.02	12.77	80
			ZZ	8.57		12.08	20

A comparative analysis of IR spectra of azomethines **3a**,**b** with symmetrical 1,3-dicarbonyl fragments revealed no substantial differences between them. Thus, their IR spectra have two high-frequency absorption bands corresponding to vibrations of ester (-CO_2Et for **3a**) or keto-groups (-COMe for **3b**) of two types: free carbonyl group (1709-1655 cm^{-1}) and carbonyl group involved in the formation of intramolecular hydrogen bond (IMHB) (1690-1619 cm^{-1}) with the NH-group. The absorption bands of NH-groups are observed at 3208-3069 cm^{-1}. Based on this analyze one can conclude the existence of compounds **3a**,**b** as *bis*(amino-enone) tautomer in solid state. ^{1}H NMR spectra of **3a**,**b** in $CDCl_3$ have one set of signals corresponds to *bis*(amino-enone) tautomer that confirmed the molecule symmetry preservation under dissolution.

The IR spectra of compounds **3c,d**, having 3-oxoester fragment, are characterized by absorption bands of free ethoxycarbonyl groups (1700-1697 cm^{-1}) and (fluoro)acyl carbonyl groups (1689-1633 cm^{-1}) participated in IMHB with NH-groups (3176-3154 cm^{-1}). In this case absorption bands are either doublet or broadened. Based on the IR spectra analogy we suggested for compounds **3c**,**d** *E,E*-isomeric structure in which *bis*(amino-enone) fragments stabilized with IMHB are in *trans*-position relative to aromatic spacer similarly to described earlier[13] thiophene derivatives.

According to the ^{1}H and ^{19}F NMR spectral data azomethines **3c**,**d** in $CDCl_3$ solutions exist as mixtures of *E,E*- and *Z,Z*-isomers and *E,E*-isomer is prevalent (Table 1). The *E,E*- and *Z,Z*-isomeric forms in the ^{1}H and ^{19}F NMR spectra were attributed in accordance with our previous work[19] in which CH- and NH-protons of *EE*-isomer are observed at lower field compared to that of *Z,Z*-isomer.

There are two (N_2O_2- and N_2O-) coordination centers capable of complex formation in the structure of compounds **3a-d**. Their treatment with nickel(II) and copper(II) salts in equimolar ratio was shown to give mononuclear complexes **4a-g** (yields 89-93 %). We were also succeeded in template synthesis of **4a-g** from dialdehyde **1** and amines **2a-d** with 3d metal ions (yields 80-95 %). In both cases tetradentate N_2O_2-center participated in the complex formation.

Elemental analyses data of complexes **4a-g** correspond to M[L-H] structure (M = metal, L = ligand). IR spectra of **4a-g** contain both high-frequency absorption bands (1727-1690 cm^{-1}) corresponding to the vibrations of free carbonyl groups (CO_2Et and $R^{(F)}C$=O) and absorption bands of carbonyl groups which participate in the coordination with metal ions. The latter are characterized with low-frequency shift (1665-1615 cm^{-1}). Absorption intensity decreasing of NH- and OH-groups in the field of stretching vibrations is also observed (3206-3125 cm^{-1}).

^{1}H NMR spectra of nickel(II) complexes **4a**,**c** were suitable for the structure determination in solution. The absence of OH-group low field singlet and the presence of only one NH-group doublet indicate their involvement in covalent bonding with metal. Probably owing to the nickel(II) ion coordination only on one N_2O_2-center protons of symmetrical 1,3-dicarbonyl groups (-OEt for **4a** and -Me for **4c**) as well as protons of two H-C=N- and two =CH- groups become not equal (Figure 1). Thereby in ^{1}H NMR spectra of **4a,c** there are three different sets of signals corresponding to protons of ethyl and methyl groups respectively. ^{1}H NMR spectrum of complex **4a** in $CDCl_3$ solution contains signals of H-C=N- and =CH-groups of chelate moiety as singlets with different chemical shifts while =CH-group of free N_2O-site appears as doublet due to the spin-spin coupling with proton of NH-group.

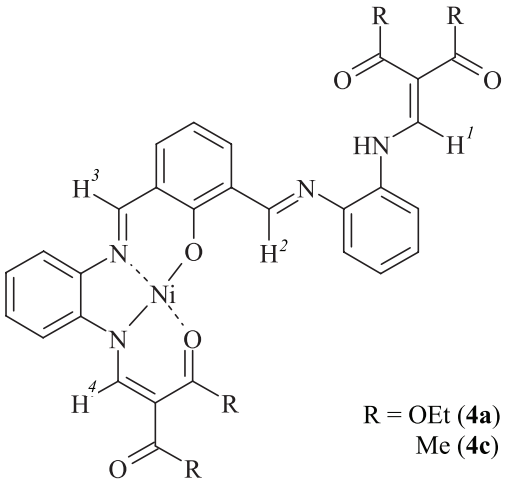


Figure 1. Non-equal protons in **4a**,**c**.

^{1}H NMR spectra of complexes **4d**,**f** were uninformative because of strong signals broadening.

According to single-crystal X-Ray diffraction, nickel(II) atom in **4d** has slightly distorted square-planar coordination with two (N(3) and N(4)) nitrogen atoms of phenylenediamine fragment and two (O(3) and O(4)) oxygen atoms of acyl and hydroxy groups belong to 1,3-dicarbonyl fragment and dialdehyde respectively (Figure 2). The distortion is caused by the difference between the lengths of a square N(3)-N(4)-O(3)-O(4) sides (maximum difference between N(3)-O(4) and O(3)-O(4) sides is 0.233 Å).

N_2O-center not participating in complex formation contains an intramolecular hydrogen bond (IMHB) N(2)-H(2)···O(7). This IMHB is characterized by the following parameters: intramolecular distance O(7)···H(2) is 1.89(5)

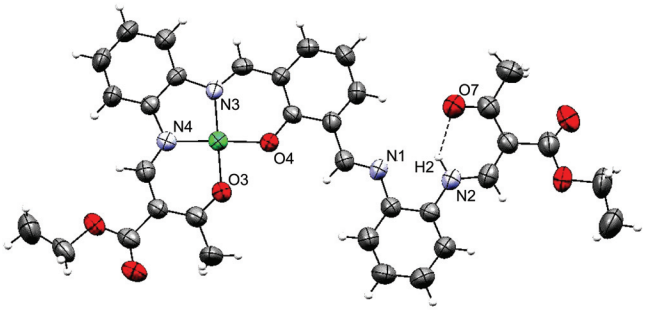


Figure 2. X-Ray structure of **4d** (thermal ellipsoids at 50 % probability level, ORTEP drawing).

Å, N(2)–H(2) is 0.92(3) Å, N(2)···O(7) is 2.61(8) Å, angles N(2)–H(2)···O(7) and C(10)–O(7)···H(2) are 133.5(0)° and 105.0(7)° respectively.

The molecule of **4d** has an approximately planar conformation; bonds of metal cycle are coplanar with adjacent aryl moieties. The deviation of atoms Ni-N(3)-N(4)-O(3)-O(4), which form chelate center of the molecule, from its mean plane is not more than 0.10(5) Å.

Three conjugated metal cycles (two six- and one five-membered) are formed in the molecule as a result of tetradentate coordination. Electron density of six-membered metal cycles is strongly delocalized that leads to the equalization of Ni–X, C–X and C–C bond lengths (X = N, O) of the metal cycle.

Molecular packing of **4d** is formed by translational molecules stacks with the interplanar distance 3.43(1) Å (Figure 3). The cavities between the stacks are occupied by pyridine molecules. Stacks are packed in parallel layers owing to π-π stacking of phenyl rings of adjacent molecules.[20]

Reaction of ligand **3d** with two equivalents of nickel(II) chloride and pyridine resulted in binuclear nickel complex **5d**. The main requirement providing complex formation on two N_2O-centers was the use of pyridine as a base in equimolar quantity that facilitates the deprotonation of *NH*-groups. One-pot synthesis of binuclear complexes **5a-c** from dialdehyde **1** and ethyl-2-[(2-aminophenyl)aminomethylidene]-1,3-dicarbonyl compounds **2b**,**c** on the nickel(II)/copper(II) ions template was also successful and in this case DBU was used as a base. Advantage of one-pot method is absence of additional stages of ligand isolation and purification and as a result a higher yield of metal complex.

Spectral data of **5a-d** demonstrated both coordination centers involved in complex formation. Elemental composition of **5a-d** corresponds to $M_2[L\text{-}OH]Cl_2$ structure (M = metal, L = ligand). IR spectra have high-frequency absorption bands at 1727-1668 cm^{-1} corresponding to the vibrations of carbonyl groups in ester and (fluoro)acyl moieties. A comparison of **4a-f** and **5a-d** IR spectra reveal their differences: in complexes **5a-d** spectra there are no high-frequency absorption bands at 3100-3300 cm^{-1} corresponds to the stretching vibrations of NH-groups that denotes the participation of both N_2O-coordination centers in complexation.

The structure of binuclear nickel(II) metal complexes **5a**,**b**,**d** in solution was defined by means of ^1H, ^{19}F NMR

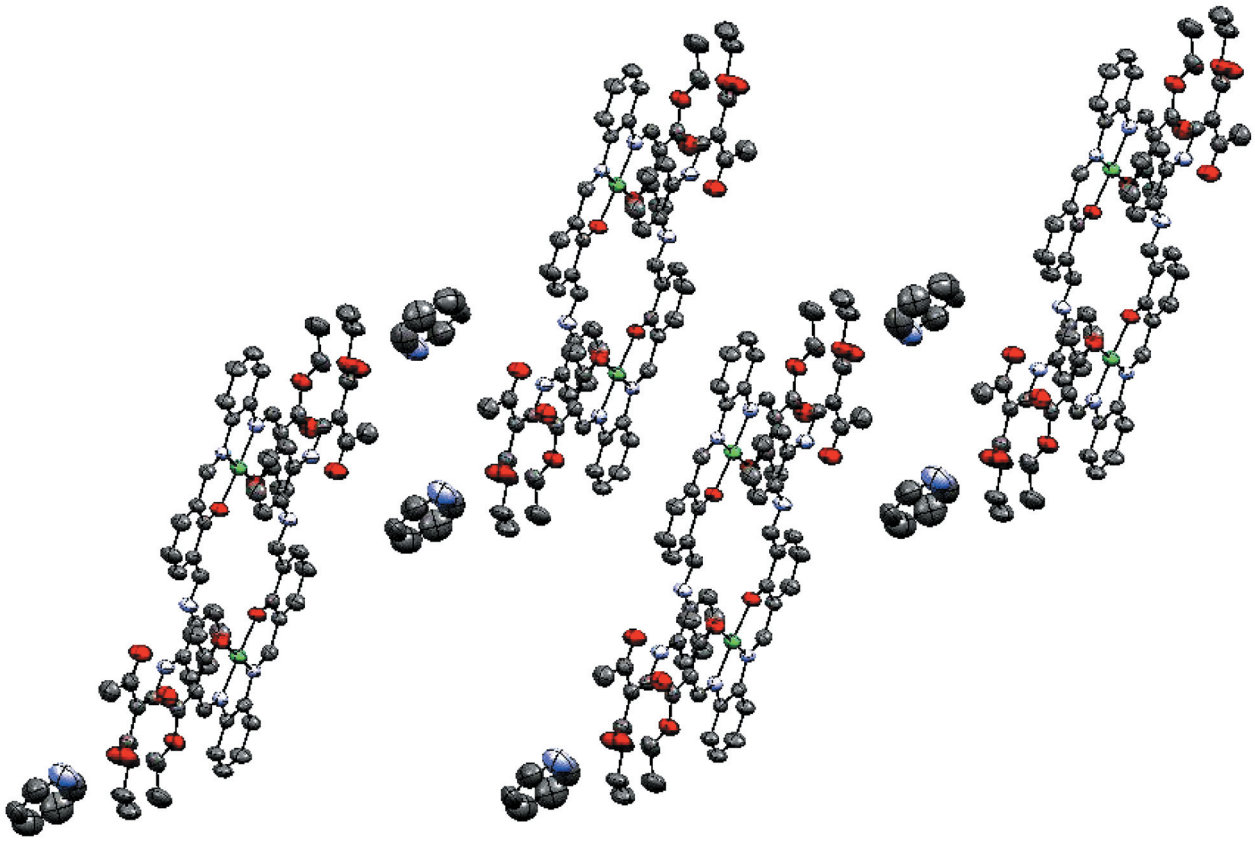


Figure 3. Molecular packing of nickel(II) complex **4d** (along the *b* axis).

spectroscopy. In consequence of nickel(II) coordination on two N_2O-centers protons of symmetrical 1,3-dicarbonyl groups as well as H-C=N- and =CH-groups become equal and this fact is confirmed by the presence of one set of signals in spectra. It should be noted the covalent bond with metal ions in binuclear complexes **5** is realized via two NH-groups of the ligand **3** and counterions of corresponding salts (Cl^-). In this case oxygen atoms of (fluoro)acyl C=O groups participate in coordination bonding. ^{1}H NMR spectra of nickel(II) complexes **5a**,**b**,**d** have low-field singlets correspond to free hydroxy-group of 2,6-diformylphenol **1** (δ_{OH} ~10.3-10.5 ppm). Complexation occurs on ketoendiimine fragment to form a symmetrical structure. The symmetry of functional groups' signals in ^{1}H, ^{19}F NMR spectra points out at the equivalence of coordination centers.

To our best knowledge one of the antituberculous aspects of *isoniazid* (isonicotinic acid hydrazide) action is the ability to form metal complexes which alters the normal microorganisms' activity and prevents mycobacteria multiplication.[21] Within this context and taking into account the complexing properties of diazomethines **3** we were estimated tuberculostatic activity of **3c**,**d** *in vitro* by their effect on the growth inhibition of *Mycobacterium tuberculosis* H_{37}Rv. Isoniazid was used as a reference drug with minimum inhibition concentration (MIC) 0.15 μg/ml. The MIC was defined as the lowest concentration of drug required for *M. tuberculosis* H_{37}Rv growth inhibition. Both non-fluorinated diazomethine **3c** and fluorinated one **3d** demonstrated a moderate effect against *M. tuberculosis* H_{37}Rv with MIC 6.2 μg/ml.

Experimental

Equipment

Melting points were measured in open capillaries with a Stuart SMP3 apparatus for melting temperature determination. The IR diffuse reflectance spectra were recorded on a Perkin Elmer Spectrum One Fourier FT-IR instrument in the interval 400-4000 cm^{-1} in the solid state as powders on a stick using a diffuse reflectance attachment (DRA). The ^{1}H (400 MHz) and ^{19}F (376 MHz) NMR spectra were recorded on a Bruker DRX-400 spectrometer with $(CH_3)_4Si$ and C_6F_6 as internal standarts, respectively. Elemental analyses were performed on a Perkin Elmer PE 2400 series II elemental analyzer.

Tuberculostatic Activity Determination Method

Determination of **3c**,**d** tuberculostatic activity was carried out with the use of solid culture medium *Novaya* by vertical diffusion method. For inoculation the laboratory strain H_{37}Rv was prepared. The culture of laboratory strain was weighed on a torsion balance and sample (10 mg) was placed into porcelain mortar and triturated thoroughly; then the culture suspension was prepared by bacterial turbidity standard (100 million microbial bodies/ml). The suspension obtained (2 ml) was inoculated into tubes containing culture medium and a test compound (5 ml) of appropriate dilution. Prepared by serial dilution the following concentrations were used: 100, 50, 12.5, 6.2, 3.5, 1.5, 0.7, 0.3, 0.15 μg/ml. The tube was incubated in calorstat for 7-10 days at 37 °C. Study of test substances effect on the growth of *Mycobacterium tuberculosis* H_{37}Rv was performed in three parallel tubes at each concentration.

Materials

Reactions were monitored by thin layer chromatography (TLC) with 0.20 mm Alugram Sil G/UV_{254} pre-coated silica gel plates (60 F254). The column chromatography was carried out on Merck silica gel 60 (0.063-0.200 mm). Unless otherwise mentioned, all commercially available compounds and solvents were used as received (2,6-diformylphenol **1** (>98.0 %) was purchased from Tokio Chemical Industry Co., Ltd., pyridine (ACS 99 %) from Alfa Aesar, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (98 %) from Acros Organics). Ethanol was purified and dried according to standard procedures.[22] Diethyl 2-[(2-aminophenyl)aminomethylidene]-malonate **2a**,[12] 3-[(2-aminophenyl) aminomethylidene]pentane-2,4-dione **2b**[23] and ethyl 2-[(2-aminophenyl)aminomethylidene]-3-oxo-3-(polyfluoro)alkylpropionates **2c**,**d**[24,25] were synthesized according to previously reported procedures.

X-Ray Crystallography

Crystallographic data for **4d**: $C_{34}H_{32}N_4NiO_7 \cdot C_5H_5N$, M = 746.45, triclinic, space group P-1, a = 11.6344(5), b = 11.7919(11) and c = 14.4670(14) Å, α = 74.476(9)º, β = 68.460(8)º, γ = 76.303(8)º, V = 1757.4(2) Å^3, Z = 2, d_{calc} = 1.411 g·cm^{-3}, μ(MoKα) = 0.611 cm^{-1}, F(000) = 780. A total number of 12747 reflections were measured on an Xcalibur 3 diffractometer at 295(2) K [(ω/2θ-scanning technique, MoKα radiation (λ = 0.71073 Å), graphite monochromator, CCD detector], 7084 independent reflections (R_{int} = 0.0394), 3602 reflections with F_o>4σ(F_o). The structure was solved by direct methods and refined by the least-squares method with the use of SHELXL-97[26] program package to R_1 = 0.0440, wR_2 = 0.0653 and GOOF = 1.005 [based on reflections with I > 2σ(I)].

CCDC 961402 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via *www.ccdc.cam.ac.uk/data_request/cif.*

Synthesis

*Diazomethines **3a-d** (general procedure)*. To a solution of 2,6-diformylphenol **1** (0.75 g, 5 mmol) in anhydrous EtOH (40 ml) the corresponding ester **2** (10 mmol) was added. After stirring for 4 h the precipitate formed was separated by filtration, crystallized from MeCN and dried to give products **3a-d** as bright yellow powders.

*Tetraethyl 2,2'-[1,3-(2-hydroxybenzylidene)-bis(aminomethylidene-2-iminophenylene)] dimalonate **(3a)***. Prepared from ester **2a** (2.78 g). Yield 3.19 g (95 %), mp 152-153 °C. Found: C 64.34, H 5.67, N 8.40 %. $C_{36}H_{38}N_4O_9$ requires C 64.47, H 5.71, N, 8.35. IR ν cm^{-1}: 3208, 3195 (N-H, O-H); 3065, 2978 (C-H); 1709, 1690 (C=O); 1647 (C=N); 1614, 1566 (C=C, N-H). ^{1}H NMR ($CDCl_3$) δ ppm: 1.33, 1.36 (two t, J = 7.1 Hz, both 6H, 4 OCH_2CH_3), 4.26, 4.34 (two q, J = 7.1 Hz, both 4H, 4 OCH_2CH_3), 7.10-7.36 (m, 10H, Ar), 8.17 (m, 1H, Ar), 8.60 (d, J = 13.9 Hz, 2H, 2 =CH), 9.00 (s, 2H, 2 H-C=N), 11.67 (br d, J = 13.9 Hz, 2H, 2 NH)

*3,3'-[1,3-(2-Hydroxybenzylidene)-bis(aminomethylidene-2-iminophenylene)]-bis(pentane-2,4-dione) **(3b)***. Prepared from ester **2b** (2.18 g). Yield 2.48 g (90 %), mp 260-261 °C. Found: C 69.70, H 5.20, N 10.03 %. $C_{32}H_{30}N_4O_5$ requires C 69.80, H 5.49, N 10.18. IR ν cm^{-1}: 3069 (N-H); 2923, 2852 (C-H); 1655, 1619 (C=O); 1597 (C=N); 1580, 1560 (C=C, N-H). ^{1}H NMR ($CDCl_3$) δ ppm: 2.40, 2.58 (two s, both 6H, 4 Me), 6.82-6.89, 7.08-7.37, 7.88-7.90, 8.13-8.16 (all m, 10H, Ar), 8.25 (br s, 1H, Ar), 8.33 (d, J = 12.9 Hz, 2H, 2 =CH), 9.01 (s, 2H, 2 H-C=N), 12.88 (s, 1H, OH), 13.18 (br d, J = 12.9 Hz, 2H, 2 NH).

*Diethyl 2,2'-[1,3-(2-hydroxybenzylidene)-bis(aminomethylidene-2-iminophenylene)]bis(3-oxobutanoate) **(3c)***. Prepared from ester **2c** (2.48 g). Yield 2.99 g (98 %), mp 204-205 °C. Found: C 66.80, H 5.61, N 9.18 %. $C_{34}H_{34}N_4O_7$ requires C 66.87, H 5.61, N

9.17. IR ν cm^{-1}: 3210, 3185 (N-H, O-H); 2983 (C-H); 1700, 1689 (C=O); 1619 (C=N); 1597, 1586, 1560 (C=C, N-H). ^{1}H NMR ($CDCl_3$) δ ppm: 7.15-7.25, 7.30-7.41 (two m, 10H, Ar), 8.20 (br s, 1H, Ar); *E,E* (85 %): 1.35 (t, *J* = 7.1 Hz, 6H, 2 OCH_2CH_3), 2.57 (s, 6H, 2 Me), 4.29 (q, *J* = 7.1 Hz, 4H, 2 OCH_2CH_3), 8.59 (d, *J* = 13.4 Hz, 2H, 2 =CH), 9.00 (br s, 2H, 2 H-C=N), 13.19 (br d, *J* = 13.4 Hz, 2H, 2 NH); *Z,Z* (15 %): 1.30 (t, *J* = 7.1 Hz, 6H, 2 OCH_2CH_3), 2.51 (s, 6H, 2 Me), 4.41 (q, *J* = 7.1 Hz, 4H, 2 OCH_2CH_3), 8.58 (d, *J* = 13.4 Hz, 2H, 2 =CH), 8.89 (s, 2H, 2 H-C=N), 12.59 (br d, *J* = 13.4 Hz, 2H, 2 NH).

*Diethyl 2,2'-[1,3-(2-hydroxybenzylidene)-bis(aminomethylidene-2-iminophenylene)]bis(3-oxo-4,4,4-trifluorobutanoate) (**3d**).* Prepared from ester **2d** (3.02 g). Yield 2.44 g (68 %), mp 140-141 °C. Found: C 56.72, H 3.88, F 15.80, N 7.86 %. $C_{34}H_{28}F_6N_4O_7$ requires C 56.83, H 3.93, F 15.86, N 7.80. IR ν cm^{-1}: 3200, 3176 (N-H, O-H); 3074, 2986 (C-H); 1697 br (C=O); 1633 (C=N); 1603, 1587, 1564 (C=C, N-H); 1276-1149 (C-F). ^{1}H NMR ($CDCl_3$) δ ppm: 7.18-7.24, 7.30-7.41, 7.45-7.47 (all m, 10H, Ar), 8.22 (br s, 1H, Ar), 9.02 (m, 2H, 2 H-C=N); *E,E* (80 %): 1.34 (t, *J* = 7.1 Hz, 6H, 2 OCH_2CH_3), 4.30 (q, *J* = 7.1 Hz, 4H, 2 OCH_2CH_3), 8.71 (d, *J* = 14.3 Hz, 2H, 2 =CH), 12.75 (s, 1H, OH), 12.77 (br d, *J* = 14.3 Hz, 2H, 2 NH); *Z,Z* (20 %): 1.35 (t, *J* = 7.1 Hz, 6H, 2 OCH_2CH_3), 4.31 (q, *J* = 7.1 Hz, 4H, 2 OCH_2CH_3), 8.57 (d, *J* = 14.3 Hz, 2H, 2 =CH), 12.08 (br d, *J* = 14.3 Hz, 2H, 2 NH), 12.77 (s, 1H, OH). ^{19}F NMR ($CDCl_3$) δ_F ppm: *E,E* (80 %): 89.12 (s, 6F, 2 CF_3); *Z,Z* (20 %): 90.00 (s, 6F, 2 CF_3).

*Mononuclear complexes **4** (general procedure):*

A. To a solution of ester **3** (4 mmol) in refluxing ethanol (30 ml) the appropriate metal salt ($Ni(OAc)_2 \cdot 4H_2O$ or $CuCl_2 \cdot 2H_2O$, 2 mmol) was added and the reaction mixture was cooled to room temperature under stirring. The precipitate formed was separated by filtration and crystallized from EtOH.

B. To a solution of 2,6-diformylphenol **1** (0.30 g, 2 mmol) in EtOH (20 ml) the appropriate metal salt ($Ni(OAc)_2 \cdot 4H_2O$ or $CuCl_2 \cdot 2H_2O$, 2 mmol) was added. Mixture was slightly heated under stirring until reactants dissolved followed by the dropwise addition of solution of ester **2** (4 mmol) in EtOH (15 ml). The reaction mixture was stirred for 2 h at room temperature and the precipitation formed was filtered and crystallized from EtOH.

*Mononuclear nickel(II) complex **4a***. Yield 1.32 g (91 %) (*A*), 1.24 g (85 %) (*B*), mp 234-235 °C (red powder). Found: C 59.34, H 4.60, N 7.30, Ni 8.10 %. $C_{36}H_{36}N_4NiO_9$ requires C 59.44, H 4.99, N 7.70, Ni, 8.07. IR ν cm^{-1}: 3183 (N-H); 3054, 2979 (C-H); 1711, 1676, 1665 (C=O); 1648 (C=N); 1599, 1581, 1532 (C=C, N-H). ^{1}H NMR ($CDCl_3$) δ ppm: 1.33, 1.35, 1.40 (all t, *J* = 7.1 Hz, 12H, 4 OCH_2CH_3), 4.21, 4.27, 4.36 (all q, *J* = 7.1 Hz, 8H, 4 OCH_2CH_3), 6.68-6.76, 6.94-7.22, 7.28-7.38, 7.49-7.56 (all m, 9H, Ar), 7.85 (dd, *J* = 7.4, 1.4 Hz, 1H, Ar), 7.98 (s, 1H, H^2-C=N), 8.29 (s, 1H, =CH^4), 8.52 (dd, *J* = 7.4, 1.4 Hz, 1H, Ar), 8.59 (d, *J* = 14.2 Hz, 2H, =CH^1), 9.05 (s, 1H, H^3-C=N), 11.97 (br d, *J* = 14.2 Hz, 1H, NH).

*Mononuclear copper(II) complex **4b***. Yield 1.36 g (93 %) (*A*), 1.27 g (87 %) (*B*), mp 203-204 °C (dark brown powder). Found: C 57.51, H 4.60, N 7.15, Cu 8.76 %. $C_{36}H_{36}CuN_4O_9 \cdot H_2O$ requires C 57.63, H 5.11, N 7.47, Cu 8.47. IR ν cm^{-1}: 3206 (N-H); 3064, 2977 (C-H); 1708, 1658 (C=O); 1605 (C=N); 1582, 1535 (C=C, N-H).

*Mononuclear nickel(II) complex **4c***. Yield 1.09 g (90 %) (*A*), 1.13 g (93 %) (*B*), mp 304-305 °C (red powder). Found: C 63.11, H 4.56, N 9.23, Ni 9.60 %. $C_{32}H_{28}N_4NiO_5$ requires C 63.29, H 4.65, N 9.23, Ni 9.66. IR ν cm^{-1}: 3159 (N-H); 3059, 2994 (C-H); 1640, 1615 (C=O); 1599 (C=N); 1580, 1561, 1532 (C=C, N-H). ^{1}H NMR (Py-d_5) δ ppm: 2.55, 2.57, 1.69 (all s, 12H, 4 Me), 7.14, 7.17 (two br s, 4H, Ar), 7.36-7.39, 7.43, 7.51, 7.76-7.78, 7.85 (all m, 7H, Ar), 8.50-8.55 (m, 2H, 2 H-C=N), 8.62 (d, *J* = 13.2 Hz, 2H, 2 =CH), 13.50 (br d, *J* = 13.2 Hz, 1H, NH).

*Mononuclear nickel(II) complex **4d***. Yield 1.18 g (89 %) (*A*), 1.07 g (80 %) (*B*), mp 262-263 °C (red powder). Found: C 61.05, H 4.76, N 8.39, Ni 9.03 %. $C_{34}H_{32}N_4NiO_7$ requires C 61.19, H 4.83, N 8.40, Ni 8.80. IR ν cm^{-1}: 3125 (N-H); 2981, 2928 (C-H); 1701 br (C=O); 1643 (C=N); 1606, 1535 (C=C, N-H).

*Mononuclear copper(II) complex **4e***. Yield 1.22 g (91 %) (*A*), 1.28 g (95 %) (*B*), mp 248-249 °C (dark brown powder). Found: C 60.30, H 4.58, N 8.20, Cu 9.51 %. $C_{34}H_{32}CuN_4O_7$ requires C 60.75, H 4.80, N 8.34, Cu 9.45. IR ν cm^{-1}: 3163 (N-H); 3062, 2978 (C-H); 1700, 1689 (C=O); 1632 (C=N); 1602, 1539 (C=C, N-H).

*Mononuclear nickel(II) complex **4f***. Yield 1.38 g (89 %) (*A*), 1.41 g (91 %) (*B*), mp 253-254 °C (red powder). Found: C 52.77, H 3.19, F 14.39, N 7.38 %. $C_{34}H_{26}F_6N_4NiO_7$ requires C 52.67, H 3.38, F 14.70, N 7.23. IR ν cm^{-1}: 3175 (N-H); 2985 (C-H); 1727, 1704 (C=O); 1639 (C=N); 1617, 1605, 1588 (C=C, N-H); 1282-1156 (C-F).

*Mononuclear copper(II) complex **4g***. Yield 1.36 g (87 %) (*A*), 1.40 g (90 %) (*B*), mp 265-266 °C (dark brown powder). Found: C 52.66, H 3.45, F 14.51, N 7.54 %. $C_{34}H_{26}CuF_6N_4O_7$ requires C 52.35, H 3.36, F 14.61, N 7.18. IR ν cm^{-1}: 3182 (N-H); 3076, 2982 (C-H); 1726, 1704 (C=O); 1640 (C=N); 1607, 1590,1538 (C=C, N-H).

*Binuclear complexes **5a-c** (general procedure).* To a solution of 2,6-diformylphenol **1** (0.30 g, 2 mmol) in EtOH (20 ml) the appropriate metal salt ($NiCl_2$ or $CuCl_2 \cdot 2H_2O$, 5 mmol) was added. Mixture was slightly heated under stirring until salt completely dissolved followed by the dropwise addition of DBU (0.61 g, 4 mmol) and solution of corresponding ethyl 2-[(2-aminophenyl) aminomethylidene]-1,3-dicarbonyl compound **2** (4 mmol) in EtOH (10 ml). The reaction mixture was stirred for 5 h at room temperature and the precipitation formed was filtered. Products were purified by column chromatography (eluent $CHCl_3$:EtOH (5:1)).

*Binuclear nickel(II) complex **5a***. Prepared from ester **2b** (0.87 g) and $NiCl_2$ (0.65 g). Yield 1.03 g (70 %), mp 320-321 °C (orange powder). Found: C 52.36, H 3.90, N 7.55, Ni 16.00 %. $C_{32}H_{28}Cl_2N_4Ni_2O_5$ requires C 52.16, H 3.83, N 7.60, Ni 15.93. IR ν cm^{-1}: 2994, 2924, 2855 (C-H); 1668 br (C=O); 1642 (C=N); 1601, 1562 (C=C). ^{1}H NMR ($CDCl_3$) δ ppm: 2.46, 2.60 (two m, both 6H, 4 Me), 6.79 (br t, *J* = 7.6 Hz, 1H, Ar), 7.13-7.15 (m, 1H, Ar), 7.20, 7.29 (two br t, *J* = 7.6 Hz, 3H, Ar), 7.52-7.54 (m, 2H, Ar), 7.57 (br d, *J* = 8.3 Hz, 1H, Ar), 7.64 (dd., *J* = 7.6, 1.7 Hz, 1H, Ar), 7.71 (br d, *J* = 7.9 Hz, 1H, Ar), 7.96 (dd, *J* = 7.4, 1.7 Hz, 1H, Ar), 8.27, 8.28 (two s, both 1H, 2 =CH), 8.29 (s, 2H, 2 H-C=N), 10.59 (s, 1H, OH).

*Binuclear nickel(II) complex **5b***. Prepared from ester **2c** (0.99 g) and $NiCl_2$ (0.65 g). Yield 1.19 g (78 %), mp 212-213 °C (orange powder). Found: C 51.36, H 4.12, N 6.95, Ni 14.80 %. $C_{34}H_{32}Cl_2N_4Ni_2O_7$ requires C 51.24, H 4.05, N 7.03, Ni 14.73. IR ν cm^{-1}: 2983, 2862 (C-H); 1672 br (C=O); 1607 (C=N); 1575 (C=C). ^{1}H NMR ($CDCl_3$) δ ppm: 1.37 (t, *J* = 7.1 Hz, 6H, 2 OCH_2CH_3), 2.55 (s, 6H, 2 Me), 4.27 (q, *J* = 7.1 Hz, 4H, 2 OCH_2CH_3), 6.75, 7.14, 7.24 (all br t, *J* = 7.5 Hz, 5H, Ar), 7.54, 7.60, 7.66, 7.91 (all dd, *J* = 7.9, 1.7 Hz, 6H, Ar), 8.25 (s, 2H, 2 =CH), 8.38 (s, 2H, 2 H-C=N), 10.53 (s, 1H, OH).

*Binuclear copper(II) complex **5c***. Prepared from ester **2c** (0.99 g) and $CuCl_2 \cdot 2H_2O$ (0.85 g). Yield 1.34 g (87 %), mp 275-276 °C (dark brown powder). Found: C 50.51, H 4.08, Cu 15.80, N 6.97 %. $C_{34}H_{32}Cl_2Cu_2N_4O_7$ requires C 50.63, H 4.00, Cu 15.76, N 6.95. IR ν cm^{-1}: 2979 (C-H); 1697 br (C=O); 1607 (C=N); 1582, 1540 (C=C).

*Binuclear nickel(II) complex **5d***. $NiCl_2$ (0.52 g, 4 mmol) was dissolved in EtOH and added dropwise to a solution of ester **3d** (1.44 g, 2 mmol) and pyridine (0.32 g, 4 mmol) in $CHCl_3$ (30 ml). The reaction mixture was stirred for 3 h at room temperature; the precipitation formed was filtered, crystallized from EtOH and dried to give complex **5d** as crystal red powder. Yield 1.60 g (92 %), mp 265-266 °C. Found: C 45.29, H 2.89, F 12.67, N 6.30 %. $C_{34}H_{26}Cl_2F_6N_4Ni_2O_7$ requires C 45.13, H 2.90, F 12.60, N 6.19. IR ν cm^{-1}: 2953, 2923 (C-H); 1727, 1703 (C=O); 1637 (C=N); 1603, 1585 (C=C); 1281-1156 (C-F). ^{1}H NMR ($CDCl_3$) δ ppm: 1.37 (t, *J* = 7.1 Hz, 6H, 2 OCH_2CH_3), 4.32 (q, *J* = 7.1 Hz, 4H, 2 OCH_2CH_3), 6.77 (t, *J* = 7.9 Hz, 2H, Ar), 7.23-7.30 (m, 3H, Ar), 7.56, 7.60, 7.69,

7.92 (all dd, J = 7.9, 1.7 Hz, 6H, Ar), 8.21 (s, 2H, 2 =CH), 8.33 (s, 2H, 2 H-C=N), 10.33 (s, 1H, OH). ^{19}F NMR ($CDCl_3$) δ_F ppm: 93.87 (s, 6F, 2 CF_3).

Conclusions

Perspective approach to the polydentate acyclic ligands **3** based on [1+2]condensation of 2,6-diformylphenol **1** with ethyl-2-[(2-aminophenyl)aminomethylidene]-1,3-dicarbonyl compounds **2a-d** was reported. Compounds **3a-d** can form both mono- and binuclear complexes with 3d metal ions due to the presence of two coordination centers (N_2O_2- and N_2O-) in structure. Directed one-pot method of metal complexes synthesis is more efficient. Unequal structure of coordination units accounts for different conditions of complexes formation: mononuclear complexes **4** were shown to be formed as a result of N_2O_2-center coordination with the participation of 2,6-diformylphenol OH-group in covalent bonding with the metal ion. In the case of binuclear complexes **5** two metal ions bind two N_2O-centers and counterions are participated in covalent bonding leaving free OH-group. Diazomethines **3c,d** exhibited the moderate inhibitor activity against growth of *M. tuberculosis* H_{37}Rv (MIC 6.2 μg/ml). Further work will be directed at the synthesis of supramolecular systems containing ions of different metals besides 3d metals, *e.g*. Pd(II) or Zn(II), and their applied properties study (catalytic, photoluminescent, *etc*.).

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