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N-2-Hydroxybenzaldehyde acylhydrazone–Fe(III) complex: synthesis, crystal structure and its efficient and selective N-methylation†

Zhiyou Li,[a] Lamei Wu,*[a] Tao Zhang,[a] Zhengxi Huang,[a] Guofu Qiu,[b] Zhongqiang Zhou[a] and Longfei Jin[a]

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N-Methyl-*N*′-2-hydroxybenzaldehyde acylhydrazones have been chemospecifically synthesized in good yield by N-methylation of the Fe(III) complexes of *N*-2-hydroxybenzaldehyde acylhydrazones with methyl iodide in tetrahydrofuran. The reaction proceeds with the exclusive formation of the *N*-methyl derivative without any concurrent O-methylation side reactions. In addition, the N-methylation reaction occurred simultaneously with a complete deprotection step (elimination of the metal ion). As a result, the *N*-methyl product was obtained in excellent purity without time-consuming chromatographic workup. A free *N*-2-hydroxybenzaldehyde acylhydrazone ligand could not be methylated under the same conditions.

Introduction

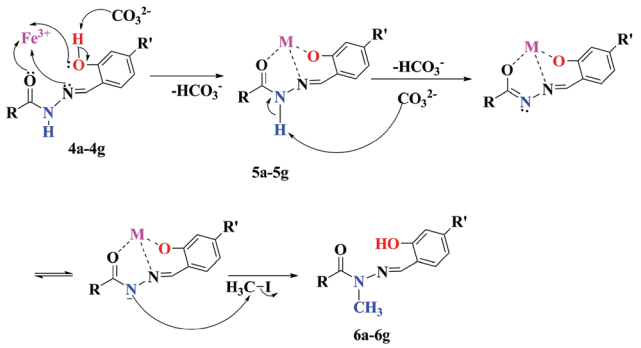
N-Acylhydrazone and *N*-methyl-*N*′-acylhydrazone derivatives have recently been applied in the synthesis of phosphodiesterase-4 (PDE4) inhibitors, cardiovascular drug candidates, nematicidal agents and antimycobacterials. The N-methylation of amide bonds can effectively improve the pharmacological properties of synthetic drugs[1–5] or peptides.[6–9] N-methylation of amides has always proven to be more difficult than for amines. Unlike the pyramidal arrangement of bonds in ammonia and amines, the bonds to the nitrogen in amides lie in the same plane. The electron-withdrawing inductive effect of the carbonyl group and the electron-releasing effect of the lone pair donation from the amide nitrogen decrease its nucleophilic character. Therefore, many researchers have been seeking simple and efficient methodologies for the N-methylation of amides. Currently, N-methylation of amides in the solid or solution phase is often achieved by one of two common approaches. One is direct methylation using a methylating agent, such as dimethyl sulfate, methyl iodide or diazomethane,[10] in the presence of various bases such as sodium hydride,[4,11–14] potassium *tert*-butoxide,[2] potassium carbonate,[1,15] LDA, NaHMDS, LiHMDS, or silver oxide (Ag_2O).[2] The other approach is indirect methylation either by way of intermediate 5-oxazolidinones,[16] or application of the intramolecular or intermolecular azomethine imine cycloaddition to the construction of *N*-alkyl-*N*′-acylhydrazone derivatives.[17–21] *N*-Methyl-*N*′-acylhydrazones have been synthesized by direct N-methylation of the corresponding *N*-acylhydrazones with methyl iodide in the presence of potassium carbonate.[1] However, this approach is unsuitable for N-methylation of *N*-2-hydroxybenzaldehyde acylhydrazone. The intramolecular hydrogen bonds of OH–N (imine) and NH–O (H)[22] are likely to cause difficulties in the methylation of amide and hydroxyl groups, respectively.

Complexation by metal ions can achieve selective synthesis by promoting or suppressing side reactions at the sites of complexation.[23] When an organic molecule contains several reactive sites, it often exhibits a considerably different reactivity when complexed with a metal ion compared to its uncomplexed state. This rationale prompted us to examine the effects of metal ions on the alkylation reaction of *N*-acylhydrazone. *N*-Acylhydrazone ligands can coordinate to various metal ions as tridentate ligands through the imine N, amide O and phenolate O atoms.[22,24] The two electron-withdrawing coordination bonds, imine-N-metal and amide-O-metal, stabilize the negative charge of the amide N ion, permitting it to be easily deprotonated and methylated with methylating agents in the presence of a weak base. At the same time, formation of such a phenolate-O-metal coordinate linkage could suppress the O-methylation side reactions of the phenol. The formation of ligand–metal ion coordinate bonds also interrupts the intramolecular hydrogen bonding of OH–N (imine) and NH–O (H) to facilitate the N-methylation of amides (Scheme 1).

[a]*Key Laboratory of Catalysis and Materials Science of the State Ethnic Affairs Commission & Ministry of Education, South-Central University for Nationalities, Wuhan, 430074, P. R. China. E-mail: wlm52875@163.com; Fax: +86-27-67842752; Tel: +86-27-67842752*

[b]*College of Pharmacy, Wuhan University, Wuhan, 430072, China. E-mail: 534801839@qq.com; Fax: +86-27-62754023; Tel: +86-27-68754629*

†Electronic supplementary information (ESI) available. CCDC 918855 and 910500. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4dt00121d



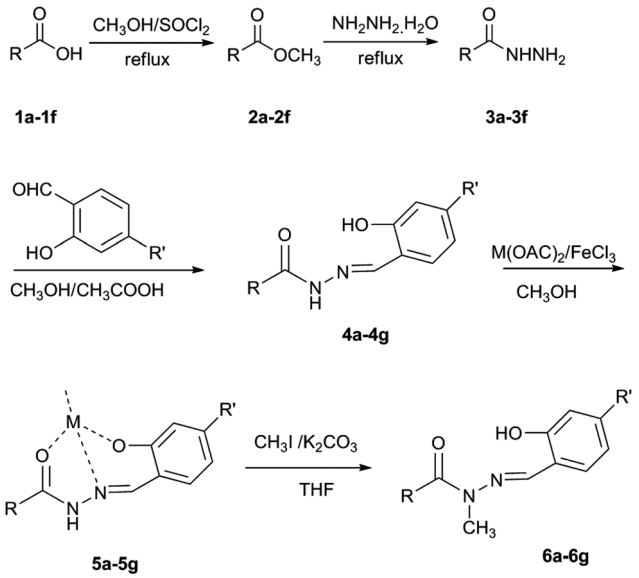
Scheme 1 Proposed selective N-methylation of amide bond of *N*-acylhydrazone by an iron complex.

In this study, the selective methylation of *N*-2-hydroxybenzaldehyde acylhydrazone was developed based on the formation of metal ion complexes. The effects of the metal ion coordination in the methylation of *N*-2-hydroxybenzaldehyde acylhydrazone were examined using methyl iodide as a methylating agent. It was found that metal complex formation increases the N-methylation of amides and suppresses the O-methylation of the hydroxyl group of the phenol. This method can be applied to the selective methylation of amides and avoids undesirable side reactions with the hydroxyl group.[2] The use of a protecting group on the hydroxyl was also unnecessary.

Results and discussion

Synthesis

The synthesis of *N*-2-hydroxybenzaldehyde acylhydrazones (**4a–4g**) was carried out according to the procedures depicted in Scheme 2. The compounds (**4a–4g**) were synthesized from the corresponding acylhydrazines (**3a–3g**), which were obtained from the esterification processing of carbonyl acids (**1a–1g**), followed by a hydrazinolysis reaction using hydrazine hydrate in ethanol. Thus, **4a–4g** were prepared *via* acid-catalyzed condensation of **3a–3g** with the corresponding aromatic aldehydes, as described in our previous work.[22] The *N*-methyl-*N*′-acylhydrazones were obtained from the corresponding *N*-methylhydrazides by slowly adding a dilute solution of the appropriate acid chloride as described in the literature.[13,26,27] In the literature method, the *N*-methylhydrazides are not readily available. We attempted to synthesize these *N*-methyl-*N*′-2-hydroxybenzaldehyde acylhydrazones (**6a–6g**) by direct methylation of the amide bonds of the corresponding *N*-2-hydroxybenzaldehyde acylhydrazones (**4a–4g**) with potassium carbonate using methyl iodide. The outcome of the experiment was less than satisfactory; neither the amide N nor the phenolate O was methylated. By analogy with the coordination mode of the *N*-acylhydrazone ligands with various metal ions,[24] we predicted that the metal complex formation should increase the N-methylation of the amides of **4a–4g**. Various metal ions, including Fe^{3+}, Zn^{2+}, Ni^{2+}, Mn^{2+} and Co^{2+}, were chosen to investigate the stability and the solubility of metal complexes of *N*-2-hydroxybenzaldehyde acylhydrazone in common organic solvents. The results indicated that the complexes with Fe^{3+} showed better stability and solubility in tetrahydrofuran (THF) and *N*,*N*-dimethylformamide (DMF). Hence, the *N*-2-hydroxybenzaldehyde acylhydrazones (**4a–4g**) were reacted with $FeCl_3{\cdot}6H_2O$, leading to the formation of metal complexes **5a–5g**. Subsequently, the *N*-methyl-*N*′-2-hydroxybenzaldehyde acylhydrazones (**6a–6g**) were synthesized by methylation of the Fe(III)-*N*-2-hydroxybenzaldehyde acylhydrazone complexes (**5a–5g**) with methyl iodide in the presence of potassium carbonate (Scheme 2). **6a–6g** were obtained as solid materials by removing the solvent under reduced pressure and recrystallizing from methanol. During the N-methylation process, the phenol group could not be methylated because a coordinate linkage between the oxygen atom of the phenol group and Fe(III) was formed, which suppressed the O-methylation of the phenol (see Fig. 1). The highly efficient N-methylation reaction and the rapid and complete metal elimination step allowed us to obtain the *N*-methyl-*N*′-2-hydroxybenzaldehyde acylhydrazones in high yields and excellent purity without time-consuming chromatographic workup. We substituted $Zn(OAc)_2{\cdot}2H_2O$



6a R=2-[4-(2-methylpropyl)phenyl] propane- R'=$(Et)_2N$-

6b R=2-(6-methoxynaphthyl) propane- R'=$(Et)_2N$-

6c R=2-[4-(2-methylpropyl)phenyl] propane- R'=H-

6d R=phenyl- R'=$(Et)_2N$-

6e R=4-methoxyphenyl- R'=$(Et)_2N$-

6f R=3,4,5-trimethoxyphenyl- R'=$(Et)_2N$-

6g R=4-Hydroxyphenyl- R'=$(Et)_2N$-

Scheme 2 The synthesis of the *N*-methyl-*N*′-2-hydroxybenzaldehyde acylhydrazones (**6a–6g**).

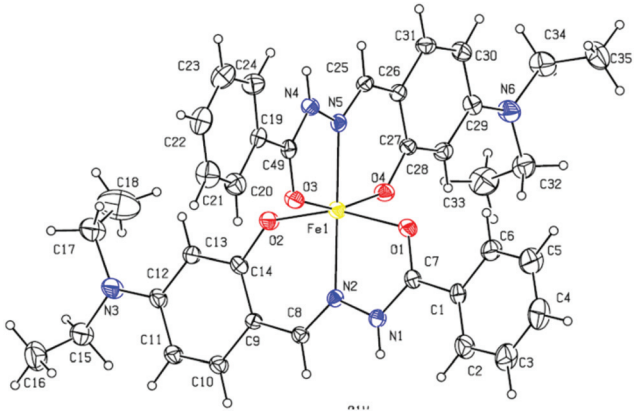


Fig. 1 ORTEP diagram of the Fe(III) complex of *N*-(4-diethylamino-2-hydroxy benzylidene)-benzohydrazide (**5d**).

for $FeCl_3{\cdot}6H_2O$, and the soluble Zn(II)-*N*-2-hydroxybenzaldehyde acylhydrazone complex **5a′** could be obtained. The same **6a** was synthesized by methylation of the Zn(II)-*N*-2-hydroxybenzaldehyde acylhydrazone complex **5a′**.

Structural features

The *N*-2-hydroxybenzaldehyde acylhydrazones (**4a–4c**) present two different sets of signals in the ^{1}H NMR spectrum in deuterated chloroform or dimethyl sulfoxide, showing the presence of two CO–NH bond-related *syn* and *anti*-periplanar conformers.[28] However, the *N*-methyl-*N′*-2-hydroxybenz-aldehyde acylhydrazones (**6a–6c**) present one set of signals in the ^{1}H NMR spectrum. Take **4a** and **6a**, for instance: their ^{1}H NMR spectra are shown in Fig. 2. In the spectrum of *N*-(4-diethyl amino-2-hydroxybenzylidene)-2-[4-(2-methylpropyl)phenyl]propane hydrazide (**4a**) (top in Fig. 2), the signal of the –OH proton appears at 11.426 ppm and 10.968 ppm; that of the –NH proton is at 11.241 ppm and 9.933 ppm; the N=CH proton appears at 8.154 ppm and 7.987 ppm, *etc.* As for the ^{1}H NMR spectrum of *N*-methyl-*N′*-(4-diethylamino-2-hydroxybenzylidene)-2-[4-(2-methylpropyl)phenyl]propane hydrazide (**6a**) (bottom in Fig. 2), one set of signals in the ^{1}H NMR appears, because the –NH proton is substituted by a methyl group. The CO–NH bond-related *syn* and *anti*-periplanar conformation rotation was restricted by N-methylation.

For the *N*-2-hydroxybenzaldehyde acylhydrazones (**4a–4g**), the moderate broad bands centered at approximately 3400 cm^{-1} and 3200 cm^{-1} in the IR spectra are ascribed to the stretching vibrations of O–H and N–H, respectively. The characteristic stretching band of C=O at 1630–1660 cm^{-1} is an indication that the keto-form is predominant in the solid state. The C=N bond is represented by the intense bands centered around 1600 cm^{-1}. For the complexes **5a–5g**, the absorption bands centered at approximately 3200 cm^{-1} due to N–H stretching were still present, and the absorption bands centered at approximately 3400 cm^{-1} may be ascribed to the O–H stretching vibration of solvent molecules (H_2O or CH_3OH). The moderate absorption bands at 1610 cm^{-1} are ascribed to the C=O stretching vibration, while the values found in the region

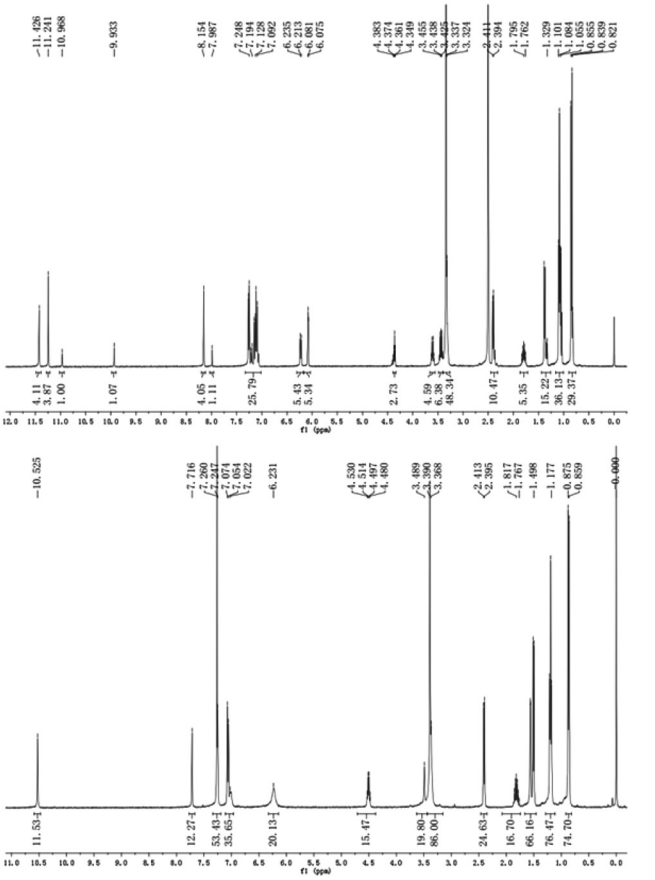


Fig. 2 ^{1}H NMR spectra of *N*-(4-diethylamino-2-hydroxybenzylidene)-2-[4-(2-methylpropyl)phenyl]propane hydrazide (**4a**) (top) and *N*-methyl-*N′*-(4-diethylamino-2-hydroxybenzylidene)-2-[4-(2-methylpropyl)phenyl]propane hydrazide (**6a**) (bottom).

from 1630 cm^{-1} to 1660 cm^{-1} for the free ligands **4a–4g** indicate that the ligands are coordinated in the keto-form. The C=N bond represented by the intense bands centered around 1600 cm^{-1} for the ligands **4a–4g** was shifted to 1510–1520 cm^{-1}, indicating that the imine N is coordinated to the metal. The single crystal structure of **5d** (see Fig. 1) confirms this coordination in the metal complexes **5a–5g**.

Single crystal structure of 5d

Complex **5d** $[Fe(III)(C_{18}N_3H_{20}O_2)_2]^+Cl^-(CH_3OH)$ (H_2O) crystallizes in the triclinic space group $P\bar{1}$. One water molecule and three methanol molecules involved are free from co-ordination and captured in the lattice, and the three methanol molecules are statistically disordered. Crystals of **5d** were unstable outside of the mother liquor and lost guest solvent molecules slowly. As shown in Fig. 1, the structure of complex **5d** is composed of Fe(III) and tridentate ligands **4d** in a 1 : 2 ratio. The coordination geometry around each metal center is distorted octahedral with two ligands bisecting each other at the central ferric ion, acting as tridentate ligands through the imine N, amide O and phenolate O atoms, which make two five-membered and two six-membered chelating rings. With the elec-

tron-withdrawing inductive effect of the neighboring imine-N-metal and amide-O-metal coordinate linkages, the amide could be deprotonated and methylated easily in the presence of potassium carbonate. Meanwhile, the formation of the phenolate-O-metal coordinate linkage efficiently suppressed the O-methylation side reaction of the phenol. As a result, the coordination of the *N*-acylhydrazone ligands with the metal atom increases the specific N-methylation of the amide bond and suppresses the O-methylation of the hydroxyl group of the phenol (Scheme 1). Although the tridentate behavior is absolutely normal for acylhydrazone ligands, in **5d** there are some interesting hydrogen-bond motifs. As shown in Fig. 3 and Table 2, each molecule of complex **5d** is linked to the hydrogen-bonded structure through the ligand amide N–H groups, intervening molecules of water O1W, methanol O1S, O2S and Cl^{-1}. The water molecule O1W acts as a single hydrogen-bonding acceptor from ligand amide N–H and as a double hydrogen-bonding donor to two methanol O1S and O2S. Two methanol molecules O1S and O2S respectively act as a single hydrogen-bonding acceptor from the water molecule O1W and a hydrogen-bonding donor to Cl^{-1}; Cl^{-1} acts as a quadruple hydrogen-bonding acceptor from ligand amide N–H and three methanol molecules O1S, O2S and O3S. Namely, one water molecule, two methanol molecules and a Cl^{-1} form a hydrogen-bonding cyclic tetramer, which interacts with two neighbouring complexes **5d** to form hydrogen-bonded 1-D chains by intermolecular hydrogen-bonding interactions. The H-bond network involving water, methanol, and the chloride ion makes the crystal of **5d** unstable outside of the mother liquor, and it loses water and methanol molecules slowly.

Single crystal structure of 6e

N-Methyl-*N*′-(4-diethylamino-2-hydroxybenzylidene)-4-methoxy-benzohydrazide (**6e**) crystallized in the monoclinic space group *P*2(1)/*c* with one molecule of **6e** in the asymmetric unit. As shown in Fig. 4 and Table 2, a strong intramolecular hydrogen bond existed between the N2 and O3 atoms [2.6501(17) Å], and intermolecular hydrogen bonds existed between the C9 and O3 atoms [3.198(2) Å] and the C6 and O2 atoms [3.419(2) Å]. These intramolecular and intermolecular hydrogen bonds caused **6e** to adopt the fully extended *E* isomer and *syn*-periplanar conformer in the solid state. In contrast with the *N*-2-hydroxybenzaldehyde acylhydrazones,[28] the CO–NH bond-related *syn* and *anti*-periplanar conformation rotation is restricted in **6e**, because the –NH proton is substituted by a methyl group. Without the CO–NH bond rotating, the *anti*-periplanar conformer disappears in solution. Therefore, one set of signals appears in the ^{1}H NMR spectra of **6a–6e** (bottom of Fig. 2).

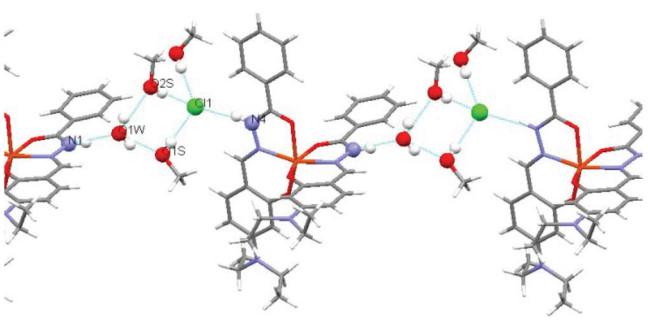


Fig. 3 The H-bond network of complex **5d**.

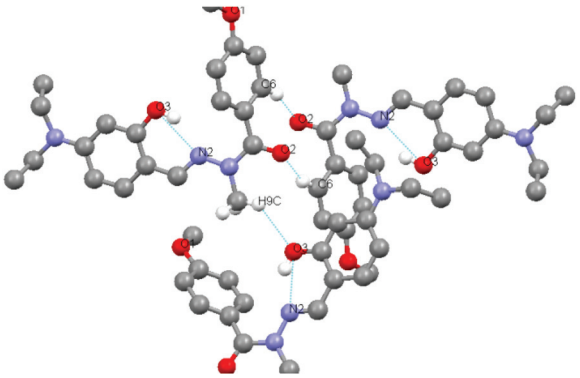


Fig. 4 The H-bond network of *N*-methyl-*N*′-(4-diethylamino-2-hydroxylbenzylidene)-4-methoxy-benzohydrazide (**6e**). Hydrogen atoms are omitted for clarity.

Conclusions

A novel and efficient method for site-specific N-methylation of *N*-2-hydroxybenzaldehyde acylhydrazones was developed. The coordinate linkages of *N*-2-hydroxybenzaldehyde acylhydrazones with Fe^{3+}/Zn^{2+} increase the specific N-methylation of the amide bonds and suppress the O-methylation of the hydroxyl group of the phenol. Consequently, the undesirable O-methylation side reaction was avoided. The chemospecific and quantitative N-methylation reaction and the rapid and complete elimination of the metal allowed us to obtain *N*-methyl-*N*′-2-hydroxybenzaldehyde-acylhydrazones in high yields and excellent purity without time-consuming chromatographic workup. A comparable effect was not observed in the methylation of *N*-2-hydroxybenzaldehyde acylhydrazone without a metal ion. These results demonstrated a synthetic technology that can effectively promote the specific N-methylation of amides while suppressing the O-methylation of the phenol groups without a prior protecting step.

Experimental

General methods

The starting materials were purchased from commercial sources and used without further purification. The IR spectra were recorded from KBr pellets in a range of 400–4000 cm^{-1} on a Perkin Elmer (Spectrum One) spectrometer. NMR spectra were obtained on a 400 MHz spectrometer. Chemical shifts are reported in δ relative to TMS. High-resolution mass spectra

(HRMS) were obtained using an ESI-QTOF mass spectrometer (ESI). Elemental analyses (C, H, N) were carried out on a Vario EL III. The melting points were determined on an XT-4 apparatus (uncorrected).

Single-crystal X-ray diffraction measurements for **5d** and **6e** were carried out on a Bruker Smart APEX CCD-based diffractometer equipped with a graphite crystal monochromator for data collection. The scattering intensity data were collected using MoKα radiation (λ = 0.71073 Å). The structure was solved by direct methods with SHELXS and refined with SHELXL.[25] All non-hydrogen atoms were refined anisotropically and H atoms isotropically with some restraints by full matrix least-squares. Crystallographic data and experimental details for structural analyses are summarized in Table 1. CCDC deposition no. 918855 and 910500.

General procedure for the synthesis of the *N*-2-hydroxybenzaldehyde acylhydrazones (4a–4g). The *N*-2-hydroxybenzaldehyde acylhydrazones were prepared according to a previously reported method.[22] Briefly, to an ethanol solution (20 ml) of the appropriate acylhydrazine (4.0 mmol) and 2-hydroxybenzaldehyde (4.0 mmol), a few drops of AcOH were added. The mixture was heated at reflux for 1 h and then cooled to r.t. The crystalline solid was collected by filtration, washed with cold ethanol, and dried in air (see ESI†).

General procedure for the synthesis of the metal complexes of *N*-2-hydroxybenzaldehyde acylhydrazones (5a–5g). Briefly, a THF solution (20 ml) of the appropriate *N*-2-hydroxybenzaldehyde acylhydrazone (4.0 mmol) was added into an ethanol solution (10 ml) of $FeCl_3{\cdot}6H_2O$ (1.07 g, 4.0 mmol). The mixture was heated at reflux for 0.5 h, and then part of the solvent was removed under vacuum, and the mixture was cooled to r.t. The crystalline solid was collected by filtration, washed with cold water, and dried in air. The melting points of the metal complexes of the *N*-2-hydroxybenzaldehyde acylhydrazones (**5a–5g**) exceed 300 °C. The elemental analyses and IR spectra of these metal complexes were recorded (see ESI†).

General procedure for the synthesis of the *N*-methyl-*N*′-2-hydroxybenzaldehyde-acylhydrazones (6a–6g). 0.55 g (4.0 mmol) potassium carbonate and 0.3 ml (4.0 mmol) methyl iodide were added into a THF solution (10 ml) of the appropriate metal complex of *N*-2-hydroxybenzaldehyde acylhydrazone (**5**) (obtained from 4.0 mmol *N*-2-hydroxybenzaldehyde acylhydrazones (**4**)). The mixture was heated at reflux for 8–16 h. After the removal of the solid by hot filtration, rotary evaporation was used to remove the solvent in the mother liquor. Then, the solid was collected and recrystallized from methanol, and a crystalline solid, *N*-methyl-*N*′-2-hydroxybenzaldehyde acylhydrazone (**6**), was obtained.

*N-Methyl-N′-(4-diethylamino-2-hydroxybenzylidene)-2-[4-(2-methylpropyl)phenyl]propane hydrazide (**6a**).* The title compound was obtained in a yield of 88.3%, 1.44 g, by the N-alkylation of metal complex **5a** with methyl iodide, as a thin yellow solid with mp 101–103 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.52 (s, 1H), 7.72 (s, 1H), 7.26 (d, 2H, J = 8.0 Hz), 7.06(d, 2H, J = 8.0 Hz), 7.01(d, 2H, J = 7.2 Hz), 6.23 (s, 2H), 4.50 (q, 1H, J = 6.8 Hz), 3.39 (s, 3H), 3.37 (q, 4H, J = 6.8 Hz), 2.40 (d, 2H, J = 7.2 Hz), 1.82 (m, 1H, J = 6.8 Hz), 1.50 (d, 3H, J = 6.8 Hz), 1.19 (t, 6H, J = 6.8 Hz), 0.90 (d, 6H, J = 6.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 159.2, 150.4, 144.5, 140.1, 138.5, 132.6, 129.3, 127.2, 106.8, 103.8, 98.2, 45.1, 44.5, 41.9, 30.1, 28.3, 22.4, 20.2, 12.6. IR (KBr) 3450 (w), 2967 (m), 2914 (m), 1660 (s), 1632 (vs), 1520 (m), 1405 (s). HRMS (ESI) m/z calcd for $[C_{25}H_{36}N_3O_2]^+$ $[M + H]^+$ 410.2802, found 410.2812. The same **6a** was obtained in a yield of 87.7%, 1.43 g, by the N-methylation of metal complex **5a**′ with methyl iodide.

*N-Methyl-N′-(4-diethylamino-2-hydroxybenzylidene)-2-(6-methoxynaphthyl)propane hydrazide (**6b**).* The title compound was obtained in a yield of 78.5%, 1.36 g, by the N-alkylation of metal complex **5b** with methyl iodide, as a thin yellow solid with mp 134–136 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.60 (s, 1H), 7.72 (s, 1H), 7.71 (m, 3H), 7.51 (dd, 1H, J_{ax} = 8.4 Hz, J_{bx} = 1.6 Hz), 7.11 (m, 2H), 7.00 (d, 1H, J = 7.6 Hz), 6.23 (d, 1H, J = 8.0 Hz), 4.68 (q, 1H, J = 6.8 Hz), 3.91 (s, 3H), 3.43 (s, 3H),

Table 1 Crystallographic data for **5d** and **6e**

	5d	6e
Empirical formula	$C_{37}H_{46}ClFeN_6O_6$	$C_{20}H_{25}N_3O_3$
Fw	762.10	355.43
Cryst syst	Triclinic	Monoclinic
a(Å)	12.311(4)	10.3190(15)
b(Å)	13.132(4)	15.155(2)
c(Å)	14.299(5)	13.3440(19)
α(°)	99.409(4)	90.00
β(°)	108.611(4)	109.348(2)
γ(°)	98.761(5)	90.00
V(Å^3)	2109.2(12)	1969.0(5)
Space group	$P\bar{1}$	$P2(1)/c$
Z value	2	4
ρ(calcd) (g cm^{-3})	1.200	1.199
Range of h, k, l	−14/14, −15/15, −16/14	−10/12, −18/18, −16/16
F(000)	802	760
Data/restraints/parameters	7284/1/483	3864/0/241
Θ min/max	1.61/25.01	2.10/26.00
μ(Mo Kα) (mm^{-1})	0.468	0.082
T(K)	150(2)	296(2)
R_1; w$R_2(I > 2\sigma(I))$	0.0888; 0.2195	0.0478; 0.1412
$R1$; w$R2(all)$	0.1335; 0.2463	0.0607; 0.1585
Goodness-of-fit	0.986	1.022

Table 2 Hydrogen bonds for **5d** and **6e** [Å and °]

D–H···A	d(D–H)	d(H···A)	d(D···A)	<(DHA)
5d				
N(1)–H(1)···O(1W)	0.88	1.98	2.820(6)	160.0
O(1W)–H(1W)···O(1S)	0.82	1.71	2.48(3)	155.9
O(1W)–H(2W)···O(2S)	0.82	2.07	2.832(9)	155.3
O(1S)–H(1S)···Cl(1)	0.82	2.52	3.342(17)	175.5
O(2S)–H(2S)···Cl(1)	0.82	2.39	3.207(9)	179.5
O(3S)–H(3S)···Cl(1)	0.82	2.33	3.146(17)	177.5
N(4)–H(4)···Cl(1)	0.88	2.32	3.171(5)	163.5
6e				
O(3)–H(3A)···N(2)	0.82	1.93	2.6501(17)	145.9
C (6)–H(6)···O(2)	0.93	2.55	3.419(2)	156.6
C (9)–H(9C)···O(3)	0.96	2.47	3.198(2)	132.5

3.39 (q, 4H, J = 6.8 Hz), 1.60 (d, 3H, J = 6.8 Hz). 1.21 (t, 6H, J = 6.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 159.2, 157.4, 150.4, 144.6, 136.6, 133.5, 132.6, 129.4, 129.0, 127.2, 126.7, 125.8, 118.7, 106.6, 105.5, 103.8, 97.9, 55.3, 44.5, 42.4, 28.3, 20.3, 12.7. IR (KBr) 3452 (w), 2971 (m), 2914 (m), 1654 (s), 1629 (vs), 1518 (s), 1469 (s), 1403 (s). HRMS (ESI) m/z calcd for $[C_{26}H_{32}N_3O_3]^+$ $[M + H]^+$ 434.2438, found 434.2435.

*N-Methyl-N′-(2-hydroxybenzylidene)-2-(6-methoxynaphthyl)-propane hydrazide (**6c**).* The title compound was obtained in a yield of 90.5%, 1.31 g, by the N-alkylation of metal complex **5c** with methyl iodide, as a white solid with mp 90–92 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.38 (s, 1H), 7.78 (s, 1H), 7.70 (t, 2H, J = 2.0 Hz), 7.68 (d, 1H, J = 2.0 Hz), 7.47 (dd, 2H, J_{ax} = 8.4 Hz, J_{bx} = 1.6 Hz), 7.28 (dd, 1H, J_{ax} = 8.0 Hz, J_{bx} = 1.6 Hz), 7.18 (dd, 1H, J_{ax} = 8.0 Hz, J_{bx} = 1.6 Hz), 7.09 (dd, 1H, J_{ax} = 8.8 Hz, J_{bx} = 2.4 Hz), 7.07 (m, 1H), 6.99 (d, 1H, J = 8.0 Hz), 6.89 (m, 1H, J = 2.0 Hz), 4.66 (q, 1H, J = 6.8 Hz), 3.88 (s, 3H), 3.44 (s, 3H), 1.60 (d, 3H, J = 6.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 157.7, 157.2, 143.5, 136.0, 133.6, 131.4, 131.3, 129.4, 129.0, 127.4, 126.4, 125.8, 119.7, 118.9, 117.9, 116.8, 105.5, 55.3, 42.6, 28.2, 20.4. IR (KBr) 3447 (w), 2968 (w), 2914 (w), 1674 (vs), 1605 (s), 1472 (s), 1399 (s). HRMS (ESI) m/z calcd for $[C_{22}H_{23}N_2O_3]^+$ $[M + H]^+$ 363.1703, found 363.1699.

*N-Methyl-N′-(4-diethylamino-2-hydroxybenzylidene)-benzohydrazide (**6d**).* The title compound was obtained in a yield of 88.6%, 1.15 g, by the N-alkylation of metal complex **5d** with methyl iodide, as a yellow solid with mp 97–98 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.81 (s, 1H), 7.77 (s, 1H), 7.54 (dd, 2H, J_{ax} = 7.6 Hz, J_{bx} = 1.6 Hz), 7.48 (m, 3H), 7.02 (d, 1H, J = 7.2 Hz), 6.20 (s, 1H), 6.08 (s, 1H), 3.55 (s, 3H), 3.31 (q, 4H, J = 6.8 Hz), 1.14 (t, 6H, J = 6.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 158.9, 150.3, 143.4, 135.5, 132.5, 130.2, 128.3, 127.8, 106.6, 103.6, 98.2, 44.5, 28.1, 12.6. IR (KBr) 3448 (w), 2973 (m), 1668 (s), 1627 (vs), 1521 (m), 1472 (m), 1404 (vs). HRMS (ESI) m/z calcd for $[C_{19}H_{24}N_3O_2]^+$ $[M + H]^+$ 326.1863, found 326.1862.

*N-Methyl-N′-(4-diethylamino-2-hydroxybenzylidene)-4-methoxy-benzohydrazide (**6e**).* The title compound was obtained in a yield of 91.1%, 1.29 g, by the N-alkylation of metal complex **5e** with methyl iodide, as a colorless solid with mp 110–111 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.11 (s, 1H), 7.80 (s, 1H), 7.62 (m, 1H), 7.59 (m, 1H), 7.04 (d, 1H, J = 8.4 Hz), 6.98 (m, 1H), 6.96 (m, 1H), 6.23 (d, 1H, J = 8.0 Hz), 6.11 (s, 1H), 3.87 (s, 3H), 3.55 (s, 3H), 3.35 (q, 4H, J = 7.2 Hz), 1.17 (t, 6H, J = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 161.2, 158.9, 150.3, 143.3, 132.4, 130.4, 127.2, 113.4, 106.7, 103.7, 98.2, 55.2, 44.4, 28.5, 12.6. IR (KBr) 3446 (w), 2968 (m), 1653 (vs), 1627 (vs), 1517 (s), 1466 (s), 1404 (vs). HRMS (ESI) m/z calcd for $[C_{20}H_{26}N_3O_3]^+$ $[M + H]^+$ 356.1969, found 356.1977.

*N-Methyl-N′-(4-diethylamino-2-hydroxybenzylidene)-3,4,5-trimethoxy-benzohydrazide (**6f**).* The title compound was obtained in a yield of 82.2%, 1.36 g, by the N-alkylation of metal complex **5f** with methyl iodide, as a gray solid with mp 130–132 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.06 (s, 1H), 7.81 (s, 1H), 7.04 (d, 1H, J_{ax} = 8.8 Hz), 6.86 (s, 2H), 6.23 (d, 1H, J = 7.6 Hz), 6.10 (s, 1H), 3.94 (s, 3H), 3.89 (s, 6H), 3.56 (s, 3H), 3.36 (q, 4H, J = 7.2 Hz), 1.18(t, 6H, J = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 159.1, 152.9, 150.4, 143.7, 139.7, 132.5, 130.2, 106.6, 105.8, 103.6, 98.1, 60.9, 56.1, 44.4, 28.5, 12.6. IR (KBr) 3447 (w), 2970 (m), 1627 (vs), 1587 (s), 1519 (m), 1465 (s), 1410 (s). HRMS (ESI) m/z calcd for $[C_{22}H_{30}N_3O_5]^+$ $[M + H]^+$ 416.2180, found 416.2190.

*N-Methyl-N′-(4-diethylamino-2-hydroxybenzylidene)-4-hydroxy-benzohydrazide (**6g**).* The title compound was obtained in a yield of 76.9%, 1.05 g, by the N-alkylation of metal complex **5 g** with methyl iodide, as a colorless solid with mp 213–215 °C. ^{1}H NMR (400 MHz, DMSO) δ 10.02 (s, 1H), 9.92 (s, 1H), 8.03 (s, 1H), 7.40 (d, 2H, J = 8.4 Hz), 7.20 (d, 1H, J = 8.8 Hz), 6.80 (d, 1H, J = 8.4 Hz), 6.22 (d, 1H, J = 8.8 Hz), 6.00 (s, 1H), 3.42 (s, 3H), 3.30 (q, 4H, J = 7.2 Hz), 1.06 (t, 6H, J = 7.2 Hz). ^{13}C NMR (100 MHz, DMSO) δ 169.6, 159.4, 158.7, 150.1, 143.3, 132.0, 130.8, 126.3, 115.0, 107.4, 104.0, 97.8, 44.2, 29.0, 12.9. IR (KBr) 3440 (m), 3292 (vs), 2971 (m), 1626 (vs), 1581 (s), 1516 (s). HRMS (ESI) m/z calcd for $[C_{19}H_{24}N_3O_3]^+$ $[M + H]^+$ 342.1812, found 342.1813.

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Notes and references

1 A. E. Kummerle, M. Schmitt, S. V. S. Cardozo, C. Lugnier, P. Villa, A. B. Lopes, N. C. Romeiro, H. Justiniano, M. A. Martins, C. A. M. Fraga, J.-J. Bourguignon and E. J. Barreiro, *J. Med. Chem.*, 2012, **55**, 7525.
2 H. K. R. Santhapuram, A. Datta, O. E. Hutt and G. I. Georg, *J. Org. Chem.*, 2008, **73**, 4705.
3 E. Biron, J. Chatterjee, O. Ovadia, D. Langenegger, J. Brueggen, D. Hoyer, H. A. Schmid, R. Jelinek, C. Gilon, A. Hoffman and H. Kessler, *Angew. Chem., Int. Ed.*, 2008, **47**, 2595.
4 D. C. Pryde, G. N. Maw, S. Planken, M. Y. Platts, V. Sanderson, M. Corless, A. Stobie, C. G. Barber, R. Russell, L. Foster, L. Barker, C. Wayman, P. V. D. Graaf, P. Stacey, D. Morren, C. Kohl, K. Beaumont, S. Coggon and M. Tute, *J. Med. Chem.*, 2006, **49**, 4409.
5 Z. Che, S. Zhang, Y. Shao, L. Fan, H. Xu, X. Yu, X. Zhi, X. Yao and R. Zhang, *J. Agric. Food Chem.*, 2013, **61**, 5696.
6 J. Chatterjee, C. Gilon, A. Hoffman and H. Kessler, *Acc. Chem. Res.*, 2008, **41**, 1331.
7 J. Chatterjee, O. Ovadia, G. Zahn, L. Marinelli, A. Hoffman, C. Gilon and H. Kessler, *J. Med. Chem.*, 2007, **50**, 5878.
8 J. Klages, C. Neubauer, M. Coles, H. Kessler and B. Luy, *ChemBioChem*, 2005, **6**, 1672.
9 O. Ovadia, S. Greenberg, J. Chatterjee, B. Laufer, F. Opperer, H. Kessler, C. Gilon and A. Hoffman, *Mol. Pharmaceutics*, 2011, **8**, 479.

10 E. Belsito, M. L. D. Gioia, A. Greco, A. Leggio, A. Liguori, F. Perri, C. Siciliano and M. C. Viscomi, *J. Org. Chem.*, 2007, **72**, 4798.
11 M. Prashad, D. Har, B. Hu, H.-Y. Kim, O. Repic and T. J. Blacklock, *Org. Lett.*, 2003, **5**, 125.
12 C. M. Crane and D. L. Boger, *J. Med. Chem.*, 2009, **52**, 1471.
13 L. Liu, M. H. Norman, M. Lee, N. Xi, A. Siegmund, A. A. Boezio, S. Booker, D. Choquette, N. D. DAngelo, J. Germain, K. Yang, Y. Yang, Y. Zhang, S. F. Bellon, D. A. Whittington, J.-C. Harmange, C. Dominguez, T.-S. Kim and I. Dussault, *J. Med. Chem.*, 2012, **55**, 1868.
14 G. Lawton, C. J. Moody and C. J. Pearson, *J. Chem. Soc., Perkin Trans. 1.*, 1987, 877.
15 S. Liu, W. Gu, D. Lo, X.-Z. Ding, M. Ujiki, T. E. Adrian, G. A. Soff and R. B. Silverman, *J. Med. Chem.*, 2005, **48**, 3630.
16 L. Aurelio, J. S. Box, R. T. C. Brownlee, A. B. Hughes and M. M. Sleebs, *J. Org. Chem.*, 2003, **68**, 2652.
17 W. Gan, P. J. Moon, C. Clavette, N. D. Neves, T. Markiewicz, A. B. Toderian and A. M. Beauchemin, *Org. Lett.*, 2013, **15**, 1890.
18 R. E. Dolle, M. C. Barden, P. E. Brennan, G. Ahmed, V. Tran and D. M. Ho, *Tetrahedron Lett.*, 1999, **40**, 2907.
19 E. C. Taylor, R. J. Clemens and H. M. L. Davies, *J. Org. Chem.*, 1983, **48**, 4567.
20 C. Clavette, W. Gan, A. Bongers, T. Markiewicz, A. B. Toderian, S. I. Gorelsky and A. M. Beauchemin, *J. Am. Chem. Soc.*, 2012, **134**, 16111.
21 A. D. Hunt, I. Dion, N. D. Neves, S. Taing and A. M. Beauchemin, *J. Org. Chem.*, 2013, **78**, 8847.
22 L. Wu, G. Qiu, H. Teng, Q. Zhu, S. Liang and X. Hu, *Inorg. Chim. Acta*, 2007, **360**, 3069.
23 K. Yamauchi, T. Nakagima and M. Kinoshita, *J. Org. Chem.*, 1980, **45**, 3868.
24 L.-M. Wu, H.-B. Teng, X.-C. Feng, X.-B. Ke, Q.-F. Zhu, J.-T. Su, W.-J. Xu and X.-M. Hu, *Cryst. Growth Des.*, 2007, **7**, 1337.
25 G. M. Sheldrick, *Acta Cryst. A.*, 2008, **64**, 112.
26 D. J. Benstead, A. N. Hulme, H. McNab and P. Wightb, *SYNLETT*, 2005, **10**, 1571.
27 Y. Xiong, J. Guo, M. R. Candelore, R. Liang, C. Miller, Q. Dallas. Yang, G. Jiang, P. E. McCann, S. A. Qureshi, X. Tong, S. S. Xu, J. Shang, S. H. Vincent, L. M. Tota, M. J. Wright, X. Yang, B. B. Zhang, J. R. Tata and E. R. Parmee, *J. Med. Chem.*, 2012, **55**, 6137.
28 A. B. Lopes, E. Miguez, A. E. Kümmerle, V. M. Rumjanek, C. A. M. Fraga and E. J. Barreiro, *Molecules*, 2013, **18**, 11683.