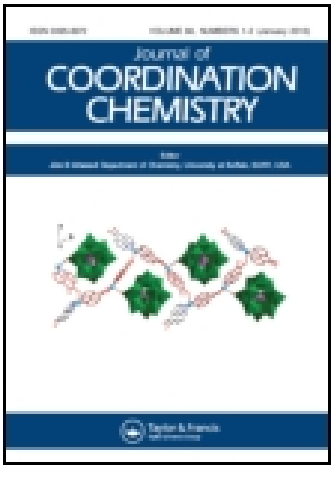

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New chelating agents for Cu(II), Fe(III), Al(III), and Zn(II) based on β-diketonate-3-substituted phthalide (isobenzofuranone) and isoindolinone

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New chelating agents for Cu(II), Fe(III), Al(III), and Zn(II) based on β-diketonate-3-substituted phthalide (isobenzofuranone) and isoindolinone

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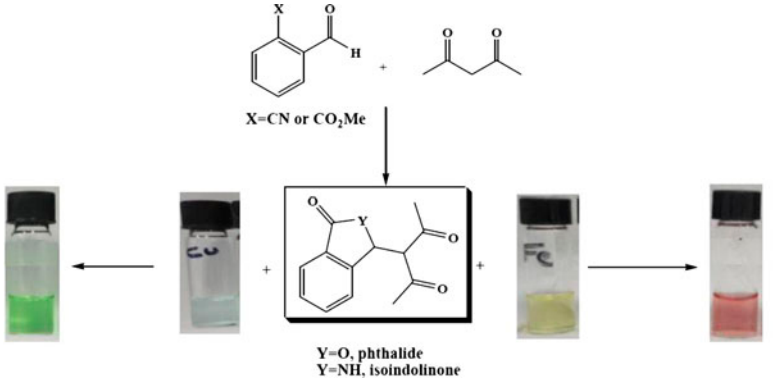

The complexing capability of β-diketone-3-substituted phthalides (isobenzofuranone) or isoindolinones toward Cu(II), Fe(III), Al(III), and Zn(II) salts has been highlighted by UV–vis spectroscopic studies. Conversely, heterocyclic analogs substituted with dimethyl malonate showed no complexing ability. Further insights have been given by the determination of equilibrium constants and distribution diagram, while the synthesis, isolation, and characterization of Cu(II)-β-diketonate-isoindolinone complex has been achieved via a convenient modification of standard procedures. Moreover, *in silico* evaluation of bioavailability of the ligands is also discussed for potential pharmacological applications.

Keywords: β-diketonate; Metal complexes; Heterocycles

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1. Introduction

The identification of new chelating agents is of paramount importance not only for organometallic chemistry and catalysis, but also for bio-inorganic-based therapeutic approaches [1]. Metal ions play an important role in modulation of several biological processes [1, 2]. However, high concentrations, accumulation, and dyshomeostasis are pathogenic factors for several diseases. For example, iron supplementation is an important treatment for blood anemia, but accumulation of externally administered iron in the body can have deleterious effects, such as increasing the risk of several types of tumors. In such cases, chelation therapy with deferasirox is a recommended treatment [3].

Abnormal concentrations, accumulation, and dyshomeostasis of metal ions like Al(III) and bioelements like Fe(III), Cu(II), and Zn(II) in brain tissues have also been highlighted in several neurodegenerative diseases such as Alzheimer (AD) [1], Parkinson (PD) [1], Prion disease [1], and multiple sclerosis [4]. This renders chelation therapy particularly promising, stimulating a great number of studies about possible *in vivo* treatments, using more or less selective chelating agents [1, 5]. Actually, apart from selectivity, bioavailability and blood–brain barrier (BBB) permeability are major requirements that a suitable chelating agent for the treatment of neurodegenerative disorders should fulfill [1, 5]. Unfortunately, very few molecules have been shown to possess these features [1, 3]. Obtaining these compounds requires long synthetic strategies, which restricts their possible application on a large scale [1, 5].

Among chelating molecules, β-diketonate derivatives are of particular interest. Neuroprotective activity of curcumin [1], which possesses a β-diketone group, seems to be related also to the ability to easily chelate Cu(II), Fe(III), Zn(II), and Al(III) [6]. However, its low bioavailability is a limit, and efforts are undertaken to improve this feature [6(c)]. Moreover, β-diketonate metal complexes are reported to show interesting biological activities in cancer therapy [7], and to be useful in the development of effective electroluminescent devices [8]. In the present work, the chelating properties of recently reported phthalides and isoindolinone heterocyclic compounds 3-substituted with β-diketones and malonates are investigated. Phthalide and isoindolinone scaffolds have been identified as active compounds showing a range of activities [9] also in AD and PD [10, 11]. Thus, the combination in a single molecule of potential biologically active heterocycle and chelating groups can confer additional properties as a multifunctional approach.

2. Experimental

2.1. *General remarks*

Column chromatographic purification of products was carried out using silica gel 60 (70–230 mesh, Merck). All the reagents were commercially available and used without purification. The syntheses of the ligands have been performed according to the reported procedures [9]; their NMR spectra were in agreement with those reported [9]. Yields are given for isolated products showing one spot on a TLC plate and no impurities detectable in the NMR spectrum. Mass spectral analyses were carried out using an electrospray spectrometer, Waters 4 micro quadrupole. Elemental analyses were performed with FLASHEA 1112 series-Thermo Scientific for CHNS-O apparatus. UV–vis spectra were recorded with a

double ray spectrophotometer Cary 1E Varian. FT-IR spectra were performed on Bruker Vertex 70 model on KBr pellets.

2.2. *Stoichometric Cu(II)-1a complex determination by Job's method and determination of the formation constants*

Two equimolar solutions of isoindolinone **3a** and $CuSO_4 \cdot 5H_2O$ (30 mM) in CH_3OH were prepared. Aliquots were taken from the two solutions keeping constant the volume and concentrations. In table S1 of supporting information, the mixtures composition and the **3a**/Cu ratios are reported. Each mixture was analyzed by UV–vis.

2.3. *Spectrophotometric titration of Cu(II) with 3a*

Two different solutions in CH_3OH were prepared: isoindolinone **3a** (0.120 M) and $CuSO_4 \cdot 5H_2O$ (20.08 mM). Starting from 2.000 mL of the Cu(II) solution, 50 µL additions of isoindolinone solution were done, till reaching 1.000 mL of titrant volume. After each addition, the UV–vis spectrum of the solution was recorded, in the visible wavelength interval.

2.4. *Synthesis and characterization of the Cu(II)-3a complex*

This complex was prepared following a slight modification of the literature procedure [8(a), 12]. Under air at room temperature, $CuSO_4 \cdot 5H_2O$ (55 mg, 0.22 mmol) was added to a solution of **3a** (110 mg, 0.47 mmol) and triethylamine (0.44 mmol) in methanol (1.7 mL). The homogeneous mixture was stirred at RT for 2 h until formation of a blue precipitate and then filtered. The copper complex was washed with methanol and dried in vacuo, giving a light blue powder. Yield: 85 mg (74%). Anal. Calcd for $C_{26}H_{24}CuN_2O_6$: C, 59.59; H, 4.62; N, 5.35. Found: C, 59.71; H, 4.48; N, 5.44. ESI, 524 ($M + H^+$). FT-IR (KBr), 1689, 1575 cm^{-1}.

3. Results and discussion

3.1. *Evaluation of complexing capability of isoindolinones 3a, 3b and phthalides 5a, 5b spectrophotometrically*

Isoindolinones **3a**, **3b** and isobenzofuranones **5a**, **5b** (scheme 1) substituted with 1,3-dicarbonyl groups were easily synthesized according to procedures recently described by our group, starting from readily available compounds [9]. These methods are particularly convenient for large-scale synthesis as well as for the development of asymmetric versions [9(e)–(g)].

The coordination of **3a**, **3b** and **5a**, **5b** towards Cu(II), Al(III), Fe(III), and Zn(II) salts has been investigated spectrophotometrically by UV–vis spectroscopy. All the experiments were performed using methanol as solvent, owing to the scarce solubility in water of isoindolinones **3a**, **3b** and phthalides **5a**, **5b**. For the sake of comparison, single spectra of the metal ions and of the tested heterocyclic compounds, all of them at the same concentration, have been recorded.

3.1.1. Fe(III). In a first set of experiments, 1 : 1 mixtures of Fe^{3+} with each of the compounds **3a**, **3b**, **5a**, **5b**, were examined. In the presence of **3a** (figure 1) and **5a** (see SI for details), the color of the MeOH solution immediately turned from the characteristic light yellow, typical of $FeCl_3$ solutions, to dark red. In the resulting spectra, a new broad band appeared around 550 nm (figure 1 for Fe(III)/**3a** mixture, see SI for the similar spectrum of Fe(III)/**5a**). In the presence of **3b** or **5b**, however, no difference in the color and in the spectra of the resulting solutions was observed with respect to the $FeCl_3$, highlighting weak coordination capability of the malonate derivatives (see SI).

3.1.2. Al(III) and Zn(II). The spectra of 1/1 complexes of Al(III) with **3a** (figure 2) and **5a** (see SI) showed new peaks at 302 and 293 nm, respectively, while once again no differences were observed between $Al(NO_3)_3$ and its mixtures with **3b** and **5b**. Modifications of the recorded spectra were also observed for mixtures between $Zn(OAc)_2$ with **3a** (figure 3) and **5a**, respectively, but not for **3b** and **5b** (see Supporting Information for details).

3.1.3. Cu(II) spectra and stoichiometry with 3a. A similar general trend emerged in the formation of complexes with 1 : 2 mixtures of Cu^{2+} with each of the compounds **3a**, **3b**, **5a**, **5b**. In the presence of **3a** and **5a**, the color of the MeOH solution immediately turned from the characteristic light blue of $CuSO_4$ to bright green. The spectra show bathochromic and iperchromic effects, with the absorbance maximum of Cu(II) shifting from 820 to 772 nm in the presence of 1 : 2 **3a** (see figure S1 (see online supplemental material at http://dx.doi.org/10.1080/00958972.2014.939075) and figures 5–7) and to 749 nm in the presence of 1 : 2 **5a** (figure S2 in SI). New strong absorptions appear in the near-UV region. Such effects provide evidence about the formation of complexes in solution. The similar effects on spectra of Cu (II) complexes obtained in the presence of both **3a** and **5a** and the relatively small decrease of λ_{max} indicate that only oxygens are involved in coordination, as highlighted by studies on

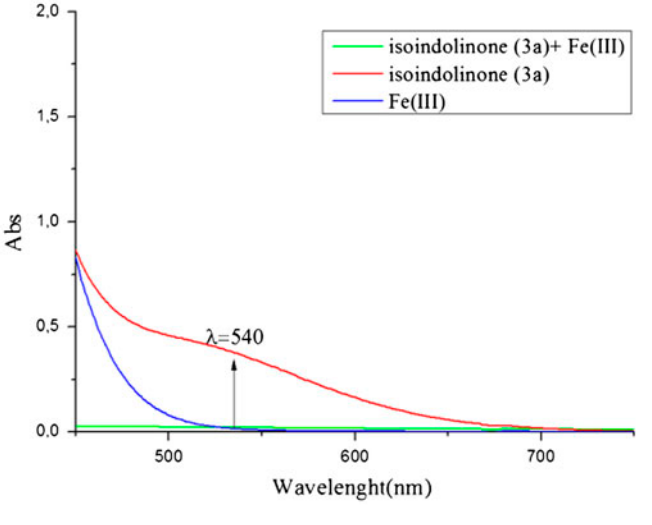


Figure 1. Molecular absorption spectra recorded at 25 °C in CH_3OH. [Fe(III)] = 0.35 mM; Fe(III)/**3a** = 1 : 1. Optical path: 1 cm.

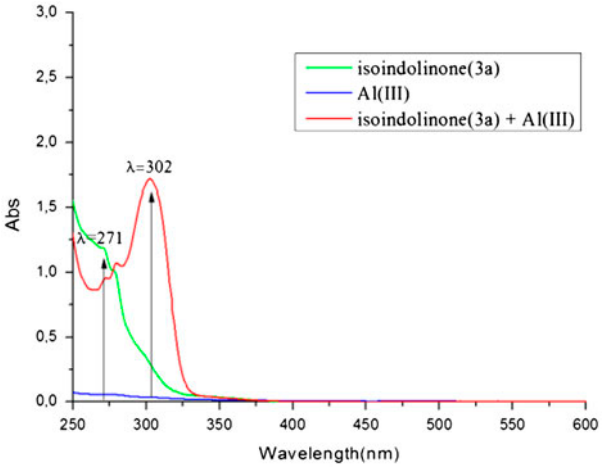


Figure 2. Molecular absorption spectra recorded at 25 °C in CH_3OH. [Al(III)] = 0.44 mM; Al(III)/**3a** = 1 : 1. Optical path: 1 cm.

coordination of Cu(II) with other O-donor ligands [13]. Conversely, as observed for the other metal ions, when the heterocyclic derivatives of dimethyl malonate **3b** and **5b** were mixed with $CuSO_4$, no difference in the color of the solution and in the spectra was observed at every wavelength (see figures S3 and S4 in the SI).

Considering the relevance of copper speciation in biochemistry and catalysis, the stochiometry of Cu(II)-**3a** complexes in solution was further investigated using Job's method [5(c), 14]. UV–vis spectra were recorded of solutions containing **3a** and $CuSO_4$ so that the sum of the concentrations of both species was constant in all the samples, the proportions of both components varied between 0 and 100% and recording the UV–vis spectra (see SI). The continuous variation plot obtained (see Supporting Information) could be interpreted

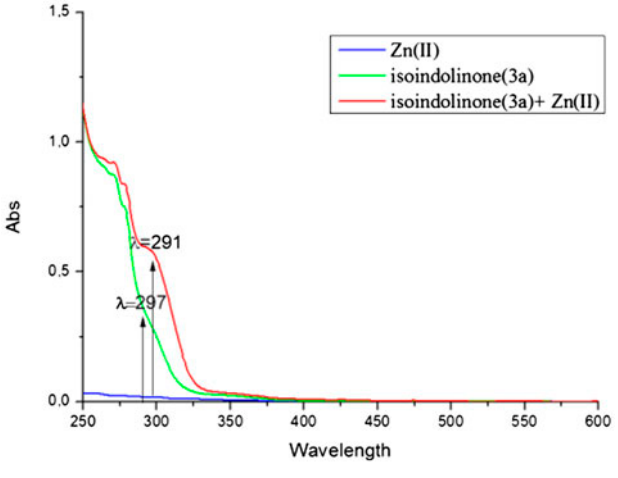


Figure 3. Molecular absorption spectra recorded at 25 °C in CH_3OH. [Zn(II)] = 0.16 mM; Zn(II)/**3a** = 1 : 2. Optical path: 1 cm.

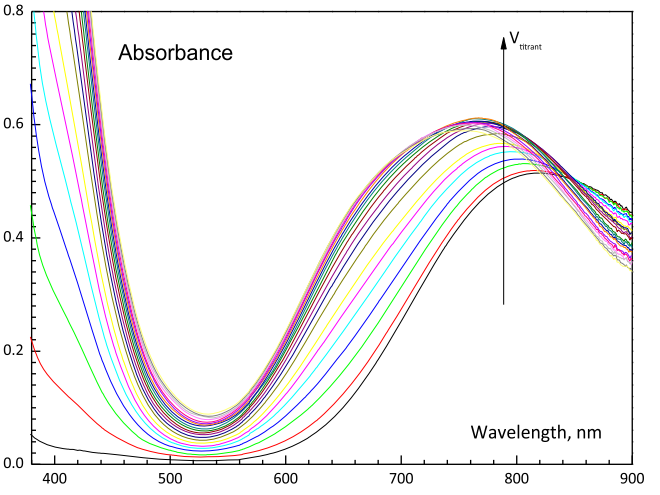


Figure 4. Spectrophotometric titration of $CuSO_4$/**3a** mixtures.

assuming Cu(II)-**3a** complexes having both 1 : 1 and 1 : 2 stoichiometries in the analyzed solution. This is also in agreement with the ^{1}H NMR spectrum, which provided evidence for the existence of more than a single enol form (see *infra*).

A consistent picture was given by the stability constants determined spectrophotometrically by titrating Cu(II) solutions with known amounts of a **3a** solution, and recording the molecular absorption spectra after each addition in the 380–900 nm range. Spectra relative to 21 solutions, reported in figure 4, were analyzed using the HypSpec software [15] based on a non-linear least-square minimization algorithm. The best fit of the data was obtained assuming the existence of two species, Cu(II)L and $Cu(II)L_2$ (HL: **3a**, charges are omitted for simplicity) with the stability constants of the supposed species reported in table 1.

A further result of the equilibrium constant refinement was the molar extinction coefficients of HL (**3a**), Cu(II), Cu(II)L, and $Cu(II)L_2$ at each wavelength, highlighting the contribution of each species (figure 5). From the distribution diagram of the simple Cu(II)-**3a** system presented in figure 6, it may be inferred that when considering 1 μM Cu(II) and 1 mM total HL not less than 65% of Cu(II) is bonded to **3a**, giving the mono-ligated species predominantly. Notably, similar values of the stability constants for several Cu(II)-β-diketonate complexes in different solvents and mixture of solvents have been determined by UV–vis spectroscopy [16], even if the contribution of every species has not been highlighted. Conversely, a somewhat similar picture showing the coexistence of different species

Table 1. Survey of the equilibrium constants in the Cu(II)-**3a** system at 25 °C in CH_3OH, determined by spectrophotometry. HL indicates **3a**.

Reaction	log(constant) ± 3σ
$Cu(II) + L = CuL^+$	3.26 ± 0.05
$Cu(II) + 2L = CuL_2$	5.3 ± 0.1

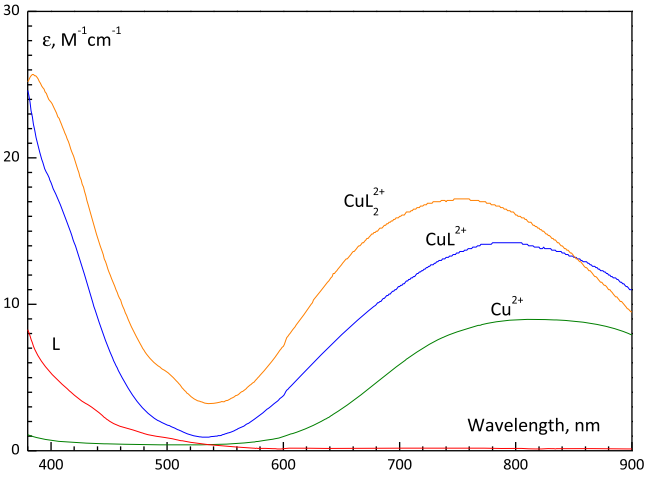


Figure 5. Molar extinction coefficients of Cu^{2+}, **3a** (L), CuL^{+}, and CuL_2 as a function of wavelength.

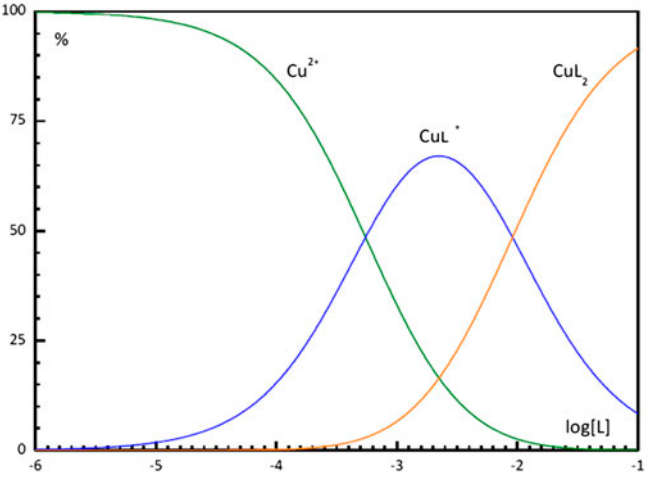


Figure 6. Distribution diagram for Cu(II)-**3a** system (1/2 ratio). The percentage of the species refers to the relative concentration of the metal. The plot is drawn assuming the constants reported in table 2, valid at 25 °C in CH_3OH.

in solution has been given by recent studies about Cu(II) complexes with several ligands in aqueous solution by the combination of UV–vis spectroscopy and HypSpec analysis [17] and by studies about stability constants of several Fe(III) β-diketonates [18].

3.2. *Synthesis and characterization of Cu(II)-3a complex*

Two main routes have been described for the synthesis and isolation of β-diketonate complexes: employing stoichiometric amounts of an organic base [8(a), 12] or by displacement of anion by the sodium salt of the β-diketonate derivatives [8(a), 19]. The former method is

somewhat preferable since the use of sodium usually leads to mixtures more difficult to purify. Thus, according to scheme 2, a modification of the first method was employed in the case of Cu(II) and in the presence of **3a**, using two equivalents of Et_3N in MeOH (scheme 2).

From an initial homogeneous solution after 30 min of reaction at RT, precipitation of a blue solid was observed. The reaction was conducted for an additional 1.5 h, giving the expected complex as a blue powder in a 74% yield. The solid was poorly soluble in common solvents, while ^{1}H NMR analysis of the residual solution highlighted the presence of ethylammonium salt and unreacted starting materials. FT-IR of **6** performed on KBr pellets revealed the typical vibration of β-diketonate complexes with new bands at 1689 and 1575 cm^{-1}, while the spectrum of **3a** is characterized by a strong band belonging to carbonyls stretch at 1718 cm^{-1} (figure 7). As described for other β-diketonate metal complexes [8(b), 20] the lowering of the stretching of carbonyls for the metal complex is due to coordination of Cu(II) to the β-diketonate in a quasi-aromatic fashion of the ring, weakening the character of the double bond as represented by the structure **6** of scheme 2 (R is the heterocyclic moiety) [19].

The good purity of **6** and the described stoichiometry were confirmed by elemental analysis and by the ESI-MS spectrum, respectively, the latter showing a molecular peak at $m/z = 524$ corresponding to the species $[CuL_2 + H^+]$. The peak at $m/z = 526$ of the isotopic $[^{65}CuL_2 + H^+]$ at natural abundance was also evident (see SI for details).

The low solubility of **6** in solvents like methanol is somewhat surprising in comparison with the just reported studies about equilibria and UV–vis spectra performed in the same solvent. β-diketones like **3a** are characterized by the tautomerism between the keto and enol forms as well as by the anionic form (scheme 3) [18]. ^{1}H NMR spectrum of **3a** in MeOD

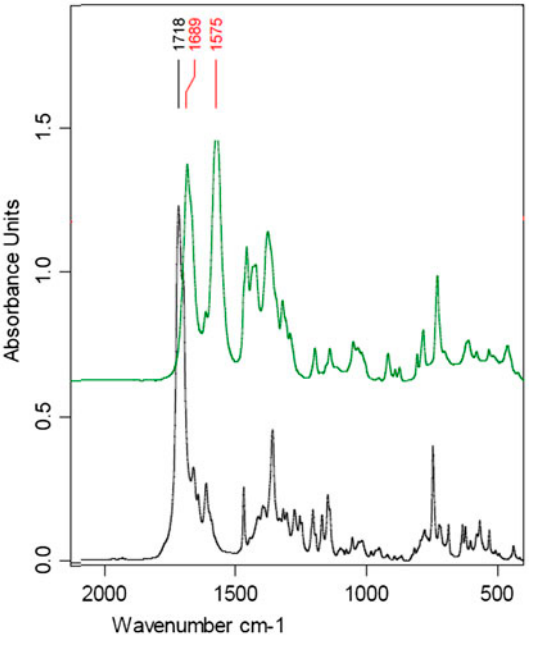
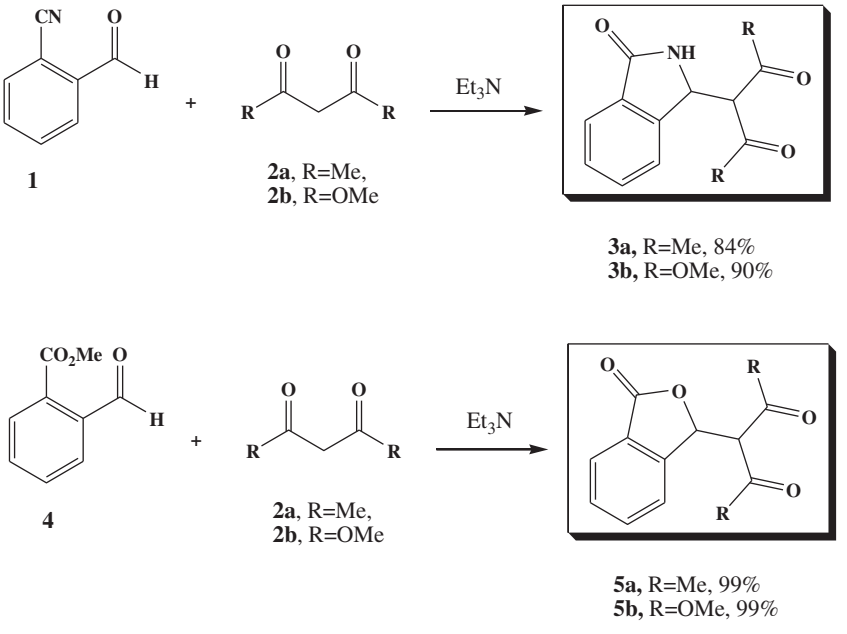
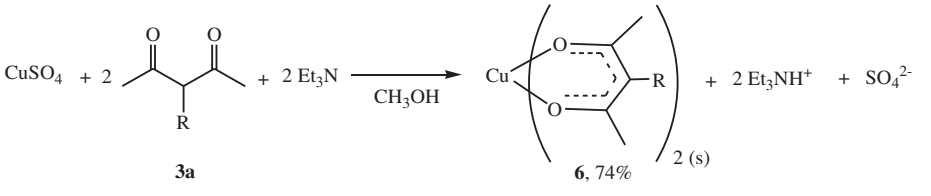


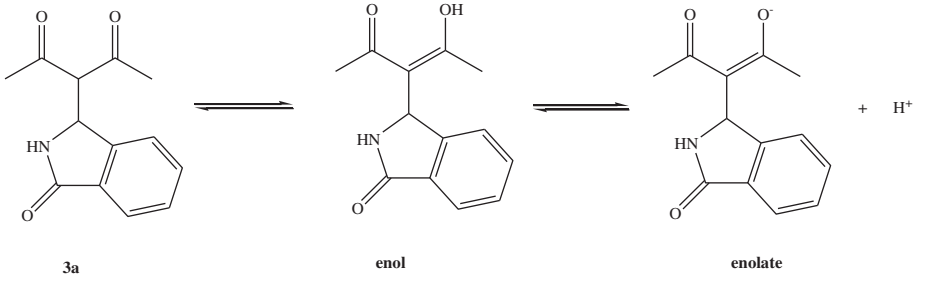
Figure 7. In green the FT-IR spectrum of **6**, in black the one of **3a**.



Scheme 1. Synthetic approach to 3-substituted isoindolinones and isobenzofuranones.



Scheme 2.



Scheme 3. Keto–enol tautomerism of **3a**.

clearly points out the equilibrium between the β-diketone and the corresponding enol in about 25% (see Supporting Information). The formation of β-diketonate complexes in

solution may be affected by several factors, i.e. by keto–enol tautomerism, pH, and the solvent, yielding a complicated picture as previously highlighted by Job's analysis and by the stability constants [18]. Reported studies about Job's plot and the determination of stability constants of several Fe(III) β-diketonates support this picture in favor of mono-ligated species, since several competing reactions have been hypothesized [18].

On the other hand, the use of a base like Et_3N favors the enolate of **3a** (see scheme 3) leading to **6** in high yield as an insoluble solid (scheme 2). Thus, focusing on **6**, additional experiments gave some insights on the relationships between its solubility and the presence of different species in solution depending on the reaction conditions. In particular, a stoichiometric amount of acetic acid added to a suspension of **6** in methanol dissolved the solid, giving a homogeneous solution. Nicely enough ^{1}H NMR spectra in MeOD of 1/2 mixture of Cu(II)/**3a** were similar to the spectra of **6** dissolved in MeOD and stoichiometric amount of deuterated acetic acid. Even if Cu(II) NMR spectra are recorded with difficulty and usually are not reported because of broad signals, these spectra show the disappearance of the doublets of **3a** and the appearance of a series of singlets, the more intense at 5.34 and 5.09, and smallest at 5.66 and 5.83 ppm (see SI).

3.3. *Evaluation of bioavailability by in silico methods*

As an appendix to the present study, the bioavailability of **3a** and **5a** through *in silico* calculations has been evaluated, with the aid of Molinspiration Cheminformatics (Bratislava, Slovak Republic) [21], taking into account Lipinski's "rule-of-five" [22].

Bioactive compounds have to cross several barriers to reach their target sites. Their availability in a biological system (bioavailability) depends upon several physicochemical parameters often associated to Lipinski's "rule-of-five" [21]. Bioavailability is likely to occur if at least three of the following rules are obeyed: molecular weight <500, logarithm of the calculated octanol–water partition coefficient (clogP) < 5, the number of hydrogen-bond donors (HBD) < 5, and the number of hydrogen-bond acceptors (HBA) < 10, indicating that only "not too polar" molecules are good drug candidates, in consideration of the lipophilic nature of biological membranes. With the aim of improving the prediction of drug-likeness, the rules have spawned many extensions considering the log P in −0.4 to + 5.6 range [23]. Moreover, the additional strict criteria proposed by Veber *et al.*, the topological polar surface area (TPSA) and the number of rotatable bonds (nRotb) are mostly related to the capability to cross the BBB (blood brain barrier) [20]. Optimal values for good drug candidates are considered not exceeding 140 for TPSA and a nRotb smaller than 10, adding further limits for polarity and molecular flexibility [24].

As shown in table 2, both **3a** and **5a** exhibited physicochemical parameter values within the limits proposed by Lipinski's "rule-of-five" and by its following additional criteria, highlighting a good drug-likeness as possible drug candidates.

Table 2. Physicochemical parameters associated to Lipinski's "rule-of-five".

Comp.	X	cLogP	MW	TPSA	HBD	HBA	nRotB
3a	NH	0.362	231	63.24	1	4	3
5a	O	1.001	232	60.45	0	4	3

4. Conclusion

The formation of complexes of recently reported β-diketone-3-substituted isoindolinone **3a** and isobenzofuranone **5a** with Cu^{2+}, Fe^{3+}, Al^{3+}, and Zn^{2+} has been established by UV–vis spectroscopy. Conversely, the analog heterocyclic compounds **3b** and **5b** substituted with dimethylmalonate moiety have not shown coordination ability. Focusing on Cu(II)-**3a**, further insights have been given by Job's plot, by ^{1}H NMR studies and by the determination of stability constants. Furthermore, the β-diketonate-isoindolinone-Cu(II) complex has been synthesized, isolated, and characterized by modifying reported procedures. Good agreement of the results obtained by ESI-MS, UV–vis, and FT-IR spectroscopies permits description of the ligand arrangement in the complex with high probability, highlighting the coordination of Cu(II) to two molecules of the β-diketone **3a** in a quasi-aromatic fashion of the rings. Finally, the reported favorable *in silico* evaluation of bioavailability of **3a** and **5a** can offer new inspiration for bioinorganic drug design and in chelation therapy. On the basis of this work, other developments and applications can be envisioned and the results will be communicated in due course.

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Supplemental data

Supplemental data for this article can be accessed here http://dx.doi.org/10.1080/00958972.2014.939075.

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