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One-pot three-component Biginelli-type reaction to synthesize 3,4-dihydropyrimidine-2-(1H)-ones catalyzed by Co phthalocyanines: Synthesis, characterization, aggregation behavior and antibacterial activity

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ABSTRACT

The synthesis of a novel phthalonitrile derivative with pyridine-2-thiol and 2,4,6-trimethylphenylamine substituents functionalized groups and its peripherally tetrasubstituted cobalt phthalocyanine and cationic phthalocyanines complexes were reported. The aggregation investigations carried out in different concentrations indicate that Co Phthalocyanines compounds **3,4** do not have any aggregation behavior for the concentration range of 6×10^{-4}–14×10^{-6} M in DMSO. The ion binding properties of Co Phthalocyanines compounds **3,4** show the formation of stable complex with Co^{2+}. In addition 3,4-Dihydropyrimidin-2(1H)-one derivatives were synthesized by modified Biginelli cyclocondensation reaction catalyzed by MPc as Lewis base. The structures of the synthesized compounds have been successfully characterized by the spectroscopic methods (IR, ^{1}H NMR, ^{13C}NMR, UV–Vis, mass spectrometry, elemental analysis and NMR 2D). The influence of substrate/catalyst ratio, solvent was also investigated to find optimal reaction on this synthesis for getting the highest conversion. Different parameters were examined for finding optimal conditions of catalysis. In addition; the compounds **3–11** were investigated for antimicrobial activity. Most of them exhibited important antimicrobial activity.

1. Introduction

Dihydropyrimidinones and their derivatives have attracted increasing interest owing to their.

therapeutic and pharmaceutical properties, such as antiviral, antibacterial, anti-inflammatory and antitumour activities [1–3]. Recently, functionalized dihydropyrimidinones have been successfully used as antihypertensive agents, calcium channel blockers, adrenergic and neuropeptide Y (NPY) antagonists [4,5]. In addition, some alkaloids containing the dihydropyrimidine core unit which also exhibit interesting biological properties have been isolated from marine sources [6,7]. One of the famous MCRs is synthesize of Dihydropyrimidinones (DHPMs) which was first reported by the Italian chemist Pietro Biginelli >100 years ago; it involves a three-component onepot condensation of benzaldehyde, ethyl acetoacetate and urea under strongly acidic conditions [8]. However, this method suffers from drawbacks such as low yields (20–40%) of the desired products, particularly in case of substituted aldehydes, and loss of acid sensitive functional groups during the reaction. This has led to multi-step synthetic strategies that produce somewhat better yields, but which lack the simplicity of the original one-pot Biginelli protocol [9]. The search for more suitable preparation of dihydropyrimidinones continues today. Recently, many synthetic methods for preparing these compounds have been developed to improve and modify this reaction by using Lewis acid catalysts, protic acids as well as ionic liquids [10–31].

On the others hand Multicomponent reactions (MCRs) have become an important component of the combinatorial chemistry, as wide varieties of biologically relevant compounds can be produced in a rapid parallel synthetic program [32–35]. The high atom economy, convergent character, operational simplicity, structural diversity and complexity of molecules are the major advantages associated with the MCRs. Multicomponent reactions contribute to the requirements of an environmentally friendly process by reducing the number of synthetic steps, energy consumption and waste production.

The scope of the Biginelli reaction has been extended by a long way by the variation of all building blocks, allowing access to a large number of multifunctionalzed pyrimidine derivatives with important biological properties. Therefore synthesis of this type of heterocyclic compounds

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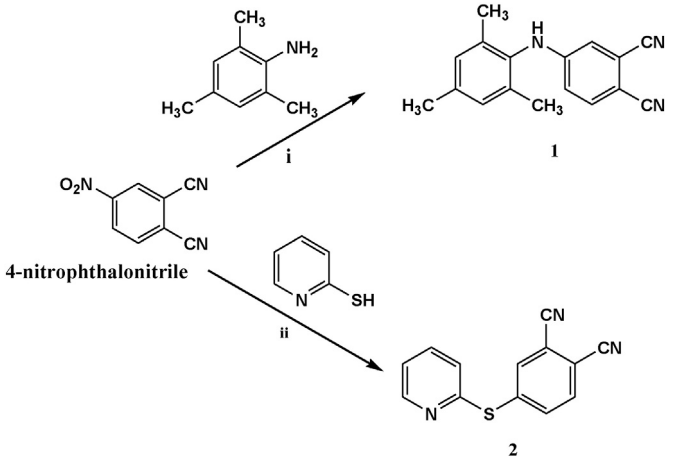
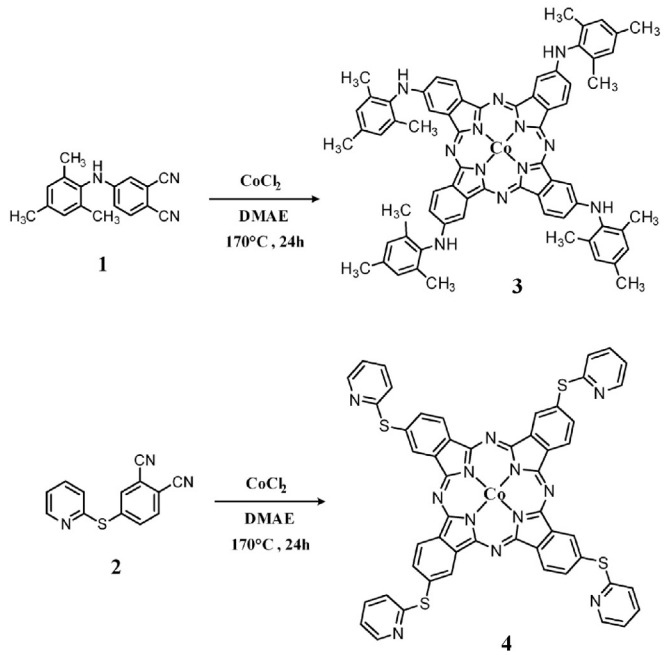


Scheme 1. Synthesis of the phthalonitriles 1–2.

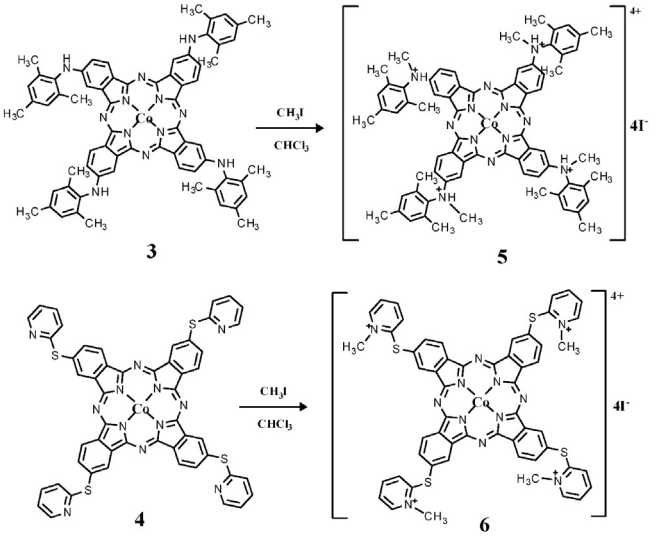
has been the focus of much interest from organic and medicinal chemistry. Many synthetic methods have been developed and Biginelli reaction has gained an active ongoing research.

As a continuation of our work [36,37], we report here firstly the synthesis and characterization of a new peripherally functionalized phthalonitrile **1,2** and Co metallophthalocyanines **3,4** and their quaternized derivatives **5,6** which contain different substituents groups on peripheral positions in the phthalocyanine framework. Secondly we report a facile and efficient multicomponent reaction route towards the synthesis of such multifunctionalized 3.4-dihydropyrimidin-2-ones by using methalophthalocyanines **3** as a catalyst. On the other hand we report also the binding properties of compounds **3,4** towards Co^{2+}. The studies were performed by UV–visible spectrophotometry absorption and by conductimetry.

In addition the compounds **1–5** were investigated for their antimicrobial activity. Most of the new compounds exhibited important antimicrobial activity.



Scheme 2. Synthesis of the Co metallophthalocyanines **3,4**.



Scheme 3. The synthesis of tetracationic metallophthalocyanine **5,6**.

2. Results and discussion

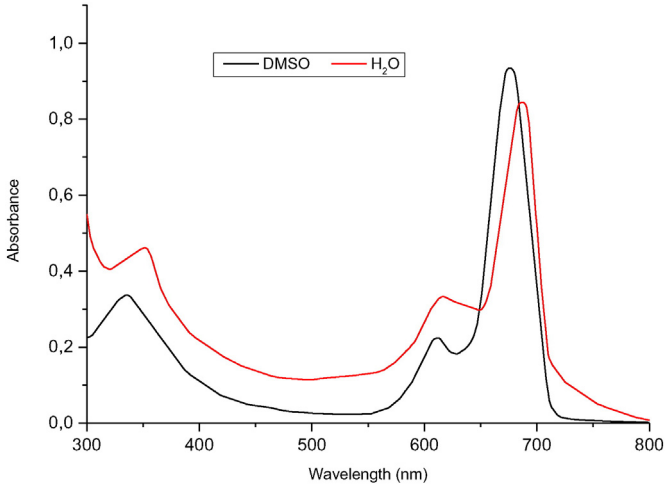
The phthalonitriles **1** and **2** were obtained via a based catalyzed (K_2CO_3) nucleophilic aromatic substitution reaction. The synthetic routes to novel phthalonitriles **1** and **2** are showed in Scheme 1.

The phthalonitriles **1–2** were characterized by the spectral data (IR, ^{1}H NMR, ^{13}C NMR, mass spectroscopies, elemental analysis and NMR 2D). The characterization data of the new compounds are consistent with the assigned formula.

In the ^{1}H NMR spectra of compound **1** the aromatic protons appear at 8.38–8.98, methylic protons appear at 2.02 (s), 2.09 (s) ppm respectively. In ^{13}C NMR, signal at δ149.5 ppm assigned to C_4, signal at δ116.4 is due to C_2 carbon. Signals that appeared at 114.5 and 114.8 correspond to the CN carbons. Other signals are in good agreement with the target compounds.

The ^{1}H NMR spectrum of compounds **2** showed a multiplet between 7.33 and 8.52 ppm for aromatic protons. In the mass spectra of compounds **1,2** the presence of molecular ions peaks at $m/z = 261$ and 237 respectively, confirmed the proposed structures.

Cyclotetramerization of **1** and **2** occurred in the presence of $CoCl_2 \cdot 6H_2O$ to form the desired Cocomplexes: **3** and **4**, respectively. All of these new cobalt phthalocyanines were purified by preparative thin layer and silica gel column chromatograph. They were obtained in a yield (55% for **3**, 65% for **4**) (Scheme 2).



Scheme 4. UV–Vis spectra of **5** in (DMSO, H_2O).

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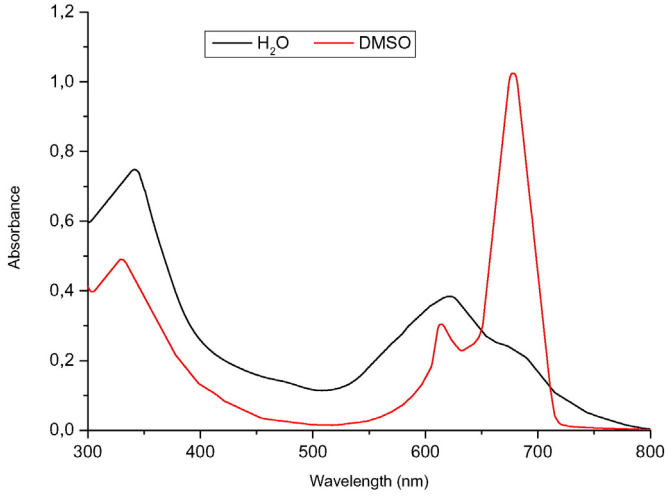


Scheme 5. UV–Vis spectra of **6** in (DMSO, H_2O).

After conversion of phthalonitriles **1**,**2** into cobalt phthalocyanine derivations, the characteristic CN stretch at 2235 cm^{-1} and 2233 cm^{-1} for **1** and **2** disappeared in the IR spectra, indicative of metallophthalocyanine formation. The characteristic vibration peaks of the Co—N and C═N appeared at 904, 1520 cm^{-1} respectively. The ^1H NMR spectra of cobalt phthalocyanines **3** and **4** could not be taken due to the paramagnetic cobalt (II) centers [38]. The elemental analyses for complexes **3**,**4** gave satisfactory results that were close to calculated values.

In the UV–vis spectrum of metallo phthalocyanines **3**,**4**, the Q bands causing by $\pi-\pi^*$ transitions were observed at 689, 687, 722 and 690 nm respectively [39]. The B bands causing from deeper π levels to LUMO were observed at: 364, 410, 384, and 414 nm for metallo phthalocyanines **3**,**4**.

The pyridine-2-thiol substituent on the complex **4** and 2.4.6-trimethyl phenylamine on the complex **3** are suitable for conversion into quaternary ammonium groups and this can increase the products' solubility in water so, quaternization of metallophthalocyanine complexes **3**,**4** was achieved by reaction with excess methyl iodide as a quaternization agent in $CHCl_3$ at room temperature. The yields of the products were 77% and 80% (Scheme 3**)**.

Quarternized metal-free **5**,**6** are very soluble in water as expected.

Infrared spectra of the quarternized complexes **5**,**6** showed the presence of C H stretching and bending alkyl groups bands around 2900 cm^{-1} and 1400 cm^{-1} respectively, and a CSC stretch between 800 and 990 cm^{-1}.

Typical UV–Vis spectra of **5** in DMSO showed a Q band at 677/614 nm and a B band at 329 nm (Scheme 4). Also UV–Vis spectra of **6** in H_2O showed a Q band at 687/615/ 678 nm and a B band at 351 nm (Scheme 5).

Also UV–Vis spectra of **6** in H_2O showed a Q band at 687/615/678 nm and a B band at 351 nm.

2.1. Catalytic activities of metallophthalocyanine 3,4 (CoMPc)

We are interested in studying Biginelli reaction with the aim to develop an operationally simple method for the synthesis of a large range of DHPMs. We started our study of the one-pot three-component Biginelli condensation using CoMPc as the catalyst by examining the conditions for the reaction using benzaldehyde, ethylacetoacetate and urea to afford the corresponding DHPM product **7–11** (Scheme 6).

We studied the reaction in different solvents including ethanol, acetonitrile, toluene, dichloromethane, THF and DMC conditions at 120 °C (Table 1). The best results were obtained in DMC (entry 6).

In order to investigate the scope of these conditions, we have undertaken the synthesis of different derivatives of 3,4-dihydropyrimidin-2(1H)-ones (**7–11**), from a variety of substrates from aromatic aldehydes, ethylacetoacetate and urea in the presence of CoMPc **3** as catalyst.

The benzaldehyde derivatives with substitutions in the aromatic ring with 4-methyl, 3-methoxy, 4-nitro and 4-N $(Me)_2$ positions were reacted with urea to furnish a series of products **7–11** (Table 2).

The new compounds **7–11** were characterized by IR, ^1H NMR spectroscopies and elemental analysis. The analyses are consistent with the predicted structures as shown in the experimental section.

The ^1H NMR spectrum of compound **7** shows a triplet at 1.14 ppm for the methylic protons (b), whereas the methylic protons (a) appeared at 2.19 ppm, 4.50 ppm attributed to the (H_d), H_6 appeared at 5.24 ppm. The spectrum also shows a multiplet at 7.2–8.5 ppm for the aromatic protons (Fig. 1).

^{13}C NMR spectroscopic analysis also confirmed structural identity, with resonances observed at δ_C 161.7 (O═C ester), 123.1–141.3(Carom), 150.2 (C_2), 150.2 (C_2),13.7(CH_3(a)), 17.3(CH_3(b)) ppm (Fig. 2).

Elemental analysis of compound **7** was within the range 0.4% and fully supported structural assignment.

The suggested mechanism for the Biginelli reaction catalyzed by MPc is outlined in Schemes 7–9.

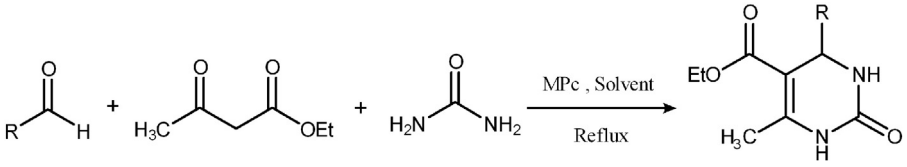
Step 1 Formation of Acylimine intermediate: This intermediate is formed by the reaction between an aldehyde and urea. Scheme 7.

Step 2 Enolisation of ethyl acetoacetate: CoMPc plays the role of a Lewis base by interaction with electrophilic carbon of aldehyde. The β–ketoester enolate can be formed by coordinating the aldehyde with MPc, which promotes deprotonation of the β–ketoester [40] Scheme 8.

Step 3 Condensation of Enol with the Acylimine to give an intermediate which undergoes cyclization followed by dehydration to afford the corresponding dihydropyrimidines. Scheme 9.

2.2. Aggregation study behaviors of methallophthalocyanines 3,4

Phthalocyanine compounds have a high aggregation tendency due to the interaction between their 18 electron systems and the aggregation decreases the solubility of these compounds in solvents. Aggregation is usually depicted as a coplanar association of rings progressing from monomer to dimer and higher order complex. It is dependent on the concentration, nature of the solvent, nature of the substituents, complexed metal ions and temperature. These compounds, normally with bulky substituents, possess good solubility, which can facilitate the purification and characterization processes. The non-aggregated nature can also prevent undesirable effects arising from stacking of molecules [41].Generally the increasing concentration of Pcs leads to aggregation, which is observed by the position of Q bands, which shift



7-11

Scheme 6. General synthetic scheme of compounds 7–11.

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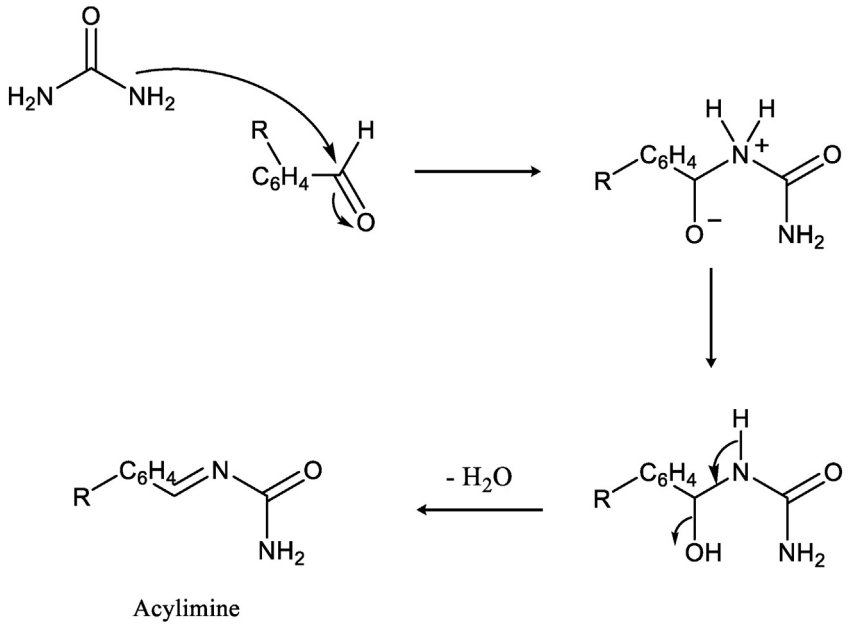


Scheme 7. Formation of Acylimine intermediate.

to higher energies by a parallel decrease in the molar absorption. In this work the aggregation behavior of the metallophthalocyanine complexes **3** and **4** were investigated at different concentrations from 6×10^{-4} to 14×10^{-6} M in DMSO for compounds **3** and **4** in DMSO (Figs. 3–4).

As the concentration was increased, the intensity of absorption of the Q band corresponding to monomeric species also increased and there were no new bands due to the aggregated species for both of the complexes. Beer–Lambert law was obeyed in the concentrations ranging from 6×10^{-4}–14×10^{-6} M for compound **3** and from for compound **4**. It can clearly be concluded that the phthalocyanines derivatives (**3** and **4**) did not show aggregation in DMSO for the studied concentrations.

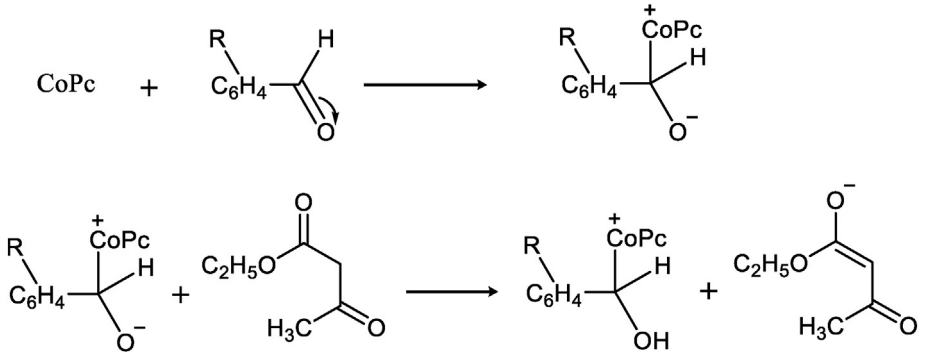
2.3. Antimicrobial activity of compounds 3–11

The synthesized compounds (**3—11**) were evaluated for in vitro antimicrobial activity by the well diffusion method. The antimicrobial activity of the tested compounds was presented in Table 3 by the formation of an inhibitory zone. In parallel, the MIC values were determinated in Table 4. The diameter of the zone of inhibition indicates the degree of sensitivity of the microorganisms to the compounds the well contains. It was obtained that, five compounds (**5**, **6**, **7**, **8** and **9**) present the best antimicrobial activity with a broad spectrum. The compound **9** showed antimicrobial activity against all bacteria and fungi tested with MIC values of 0.625–5 mg/ml. The compounds **5** and **6** exhibited an important antibacterial activity against *Micrococcus luteus*, *Staphylococcus aureus*, *Listeria monocytogenes* and *Polycystis aeruginosa* and antifungal activity against *Candida albicans* and *Candida tropicalis* with an important diameter ranging from 16 to 26 mm. The Compound **7** exhibited the highest in vitro antibacterial activity against *M. luteus* with MIC values of 0, 312 mg/ml while the Compound **8** showed a moderate antibacterial activity against *M. luteus*, *S. aureus*, *L. monocytogenes*, *S. Typhimurium* and *P. aeruginosa* with MIC values ranging from 5 to 10 mg/ml.

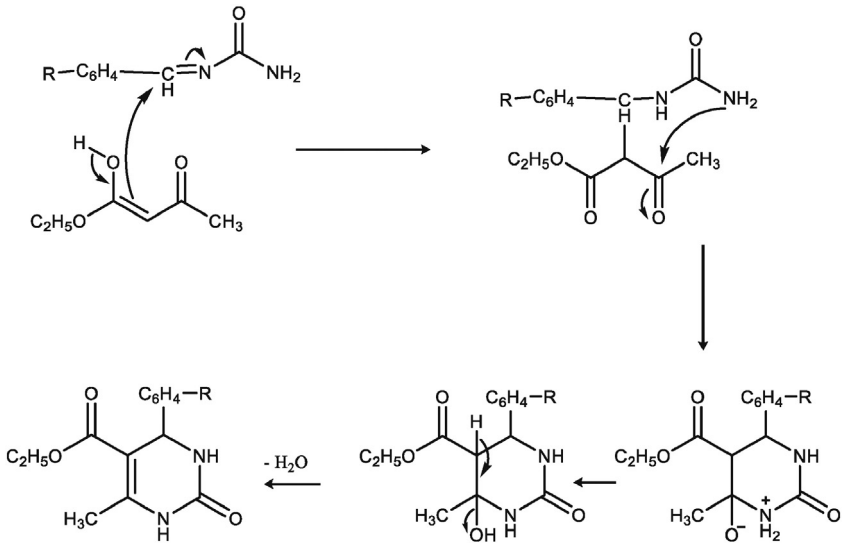
These results show that the most synthesized compounds have potent inhibitory activities against both Gram-positive and Gram-negative bacteria and fungi. Thus, they have an effective antimicrobial potential against food- borne pathogens and clinical microorganisms.

3. Complexation study

The complexation study of cobalt chloride by the free phthalocyanie **3,4** was followed by UV spectrophotometry. In fact, the titration of ligand solution in DMSO by a cobalt chloride solution in methanol shows a decrease of absorbance and a light hypsochromic displacement of the maximum of absorption ($\Delta\lambda \approx 3$ nm). The end of complexation between the phthalocyanine **3,4** and Co^{2+} is shown by the superposition of the spectra at approximately a ratio R ($R = C_M/C_L$) lower than **5** (see Fig. 5).



Scheme 8. Enolisation of ethyl acetoacetate.



Scheme 9. Suggested mechanism for the Biginelli reaction catalyzed by MPc **3**.

In addition, treatment of these spectral data by the digital program "Letagrop" [42] illustrates the stoichiometries of the formed complexes and their stability constants. The results show that the complexes formed in all cases are ML. The determination of stability constant shows the formation of stable complex (over 3.6 log units), however, $\mathbf{3{\cdot}Co^{2+}}$ is more stable than $\mathbf{4{\cdot}Co^{2+}}$ ($\log {}^{\beta}{}_{11}$ ($\mathbf{3{\cdot}Co^{2+}}$) = 3.77 and $\log {}^{\beta}{}_{11}$ ($\mathbf{4{\cdot}Co^{2+}}$) = 3.64) this result is expected given the given the preference of the N-donor site at cobalt [43].

In the other hand, the 1:1 stoichiometry of the complexes $\mathbf{3{\cdot}Co^{2+}}$ and $\mathbf{4{\cdot}Co^{2+}}$) were confirmed by conductimetric studies [44] (Fig. 6).

4. Conclusion

In the present work, we have presented the synthesis and characterized of a new phthalonitriles **1–2** and peripheral and non-peripheral substituted cobalt phthalocyanine **3** and **4** using spectroscopic methods (IR, UV–Vis, $^{1}H/^{13}C$ NMR, two-dimensional, mass spectroscopies, and as well as elemental analyses).

The cationic derivatives of the phthalocyanines were synthesized by the reaction of non-ionic phthalocyanines **3,4** and methyl iodide in chloroform. Quaternized derivatives **5,6** exhibited excellent solubility in water. **3,4** formed a mononuclear complex with cobalt in DMSO solution. The stability constant is determined by UV spectrophotometry.

The aggregation behaviors of compounds **3** and **4** were investigated. These phthalocyanines showed monomeric behaviors inTHF for studied concentration ranges.

In addition, a new method for the preparation of substituted dihydropyrimidinones-DHPMs was discovered that utilizes a multicomponent coupling reaction catalyzed by CoMPc, with a rapid and high yielding cyclocondensation to afford the corresponding DHPMs.

Table 1
MPc catalyzed synthesis of dihydropyrimidines in different solvents.

Entry	Solvent	Amount of MPc mol%)	Time (h)	Yield (%)
1	Ethanol	10	16	10
2	Acetonitrile	10	16	10
3	Toluene	10	16	30
4	Dichloromethane	10	16	22
5	THF	10	16	25
6	DMC	10	8	62
7	DMC	15	8	54
8	DMC	20	8	50
9	DMC	5	8	52

Most of the new compounds **3–11** exhibited an important antibacterial activity. The Compound **7** exhibited the highest in vitro antibacterial activity against *M. luteus* with MIC values of 0, 312 mg/ml while the Compound 8 showed a moderate antibacterial activity against *M. luteus*, *S. aureus*, *L. monocytogenes*, *S. Typhimurium* and *P. aeruginosa* with MIC values ranging from 5 to 10 mg/ml.

5. Experimental

All reagents were obtained from Fluka and Aldrich.The purity of the products was tested in each step by TLC (SiO_2, $CHCl_3$/MeOH and THF/MeOH). Melting points were determined using an Electrothermal apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were carried on a Varian Gemini 400 (400 MHz) spectrometer using TMS as internal standard ($\delta = 0$ ppm). IR spectra were recorded on a Perkin-Elmer 398 Spectrophotometer. MS were recorded on a LC-MS-MS 8030 Shimadzu. Elemental analyses were performed on Perkin-Elmer 2400 elemental analyzer, and the values found were within ±0.3% of the theoretical values. The UV spectra were recorded on a Perkin Elmer Lambda 11 spectrophotometer.

5.1. Synthesis of 4-(2.4.6-trimethylphenylamino)phthalonitrile 1

4-nitrophthalonitrile (0.38 g, 1.92 mmol), 2,4,6-trimethylphenylamine (0.55 g, 1.92 mmol) and anhydrous DMF (15 mL) were added to a round bottom flask under a nitrogen atmosphere. A fine powder of anhydrous potassium carbonate (0.8 g, 5.76 mmol) was added to this mixture. The resulting mixture was stirred at room temperature for 24 h. The crude product was collected by filtration, washed with distilled water, and then recrystallized. The crude product was recrystallized from THF-petroleum ether to afford a white powder. Yield: 0.77 g (98%). M.p. = 400 °C. IR (KBr pellet) ν_{max} cm^{-1}: 1305 (C—N), 1568 (C = C), 2235 (C≡N), 3049 (C—H, aromatic). ^{1}H NMR (DMSO-d_6): 8.38–8.98(m, 5H, Harom), 4.21(s, 1H, NH), 2.02(s, 3H,

Table 2
Synthesis of dihydropyrimidines 7-11 in different solvents.

Substrat	MPc	DHPM	Time (h)	Solvant	Amount of MPc mol%)	Yield (%)
Benzaldehyde	Co(II)Pc	7	3	CH_3CN	2	78
4-CH_3-Benzaldehyde	Co(II)Pc	8	4	EtOH	2	92
3-methoxyBenzaldehyde	Co(II)Pc	9	2	DMC	1	96
4-nitro-Benzaldehyde	Co(II)Pc	10	2	DMC	1	92
4-N(Me)$_2$-Benzaldehyde	Co(II)Pc	5	3	DMF	2	85

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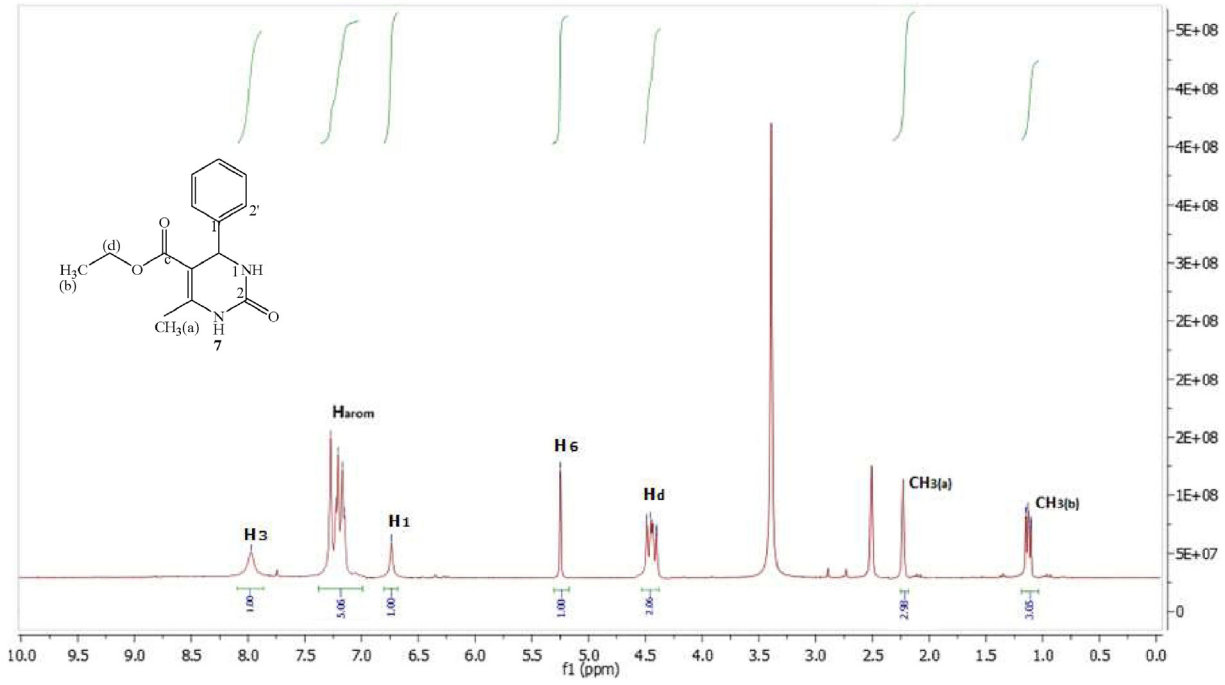

Fig. 1. [1]HNMR spectrum of compound 7 (DMSO, 300 MHz).

CH_3(a)), 2.09(s, 6H, CH_3(b,c)), 2.08(s, 3H, CH_3). [13]CNMR(DMSO-d_6,75 MHz)δ:17.5(C(a,b)),
19.9(Cb),114.5(CN),114.8(CN),116.4(C_2),
120.0(C_2'),120.5(C_6'),123.9(C4′),128.2(C_3',$_5'$),
128.3(C_3),128.6(C_5),135.4(C_6),141.3(C_{11}),149.5(C_4).
MS (LCMS-MS) *m/z*: Calc. 261.3; Found: 261.3. Anal. Calc. for C17H15N3: C, 78.135%; H, 5.786; N, 16.080, Found: C, 78.1; H, 5.6; N, 16.0%.

5.2. Synthesis of 4-(pyridine-2-ylsulfanyl) phthalonitrile 2

The synthesis of **2** was similar to **1** but the mixture was stirred for 72 h; pyridine-2-thiol (0.55 g, 1.92 mmol) was employed instead of 2,4,6-trimethylphenylamine. The amounts of the other reagents were 4-nitrophthalonitrile, 1 g (5.55 mmol) and anhydrous potassium carbonate, 2 g (13.88 mmol).

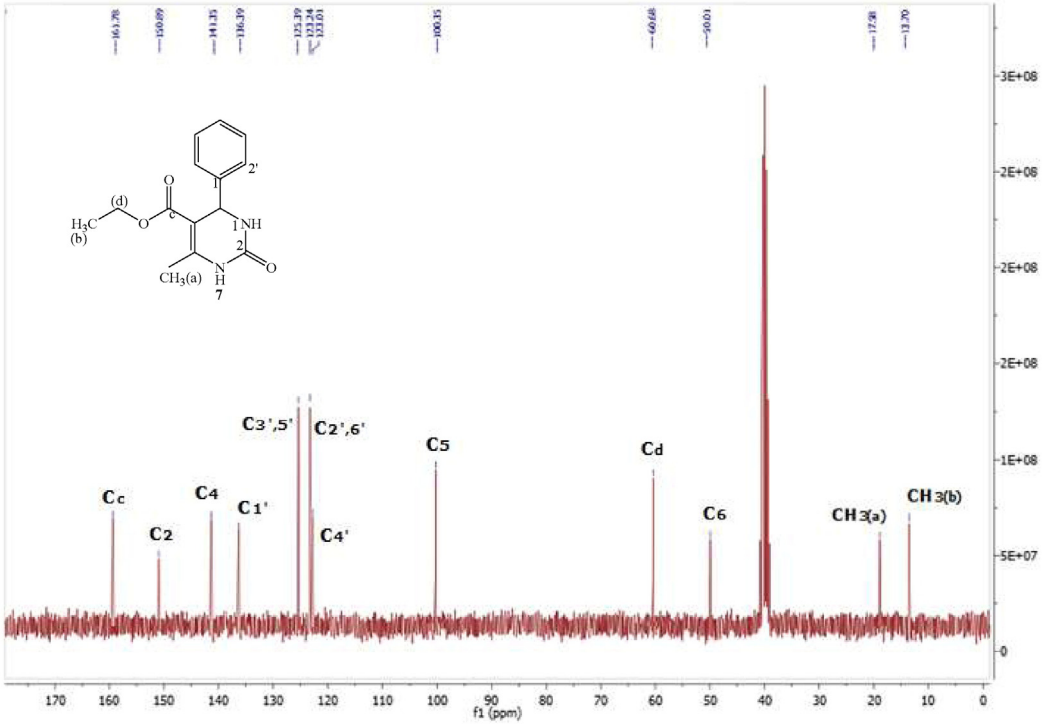

Fig. 2. [13]CNMR spectrum of compound 7 (DMSO, 75 MHz).

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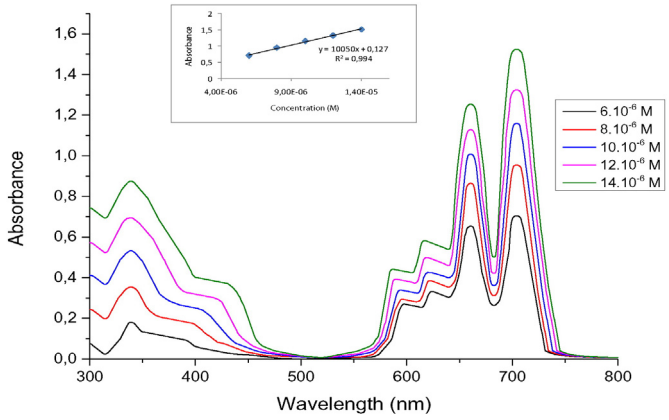

Fig. 3. The aggregation behavior of phthalocyanine **3** in DMSO.

Yield: 0.77 g (85%) M.p. = 370 °C. IR spectrum (cm^{-1}): 3077 (Ar-CH), 2233 (C—N), 1601 (C—C), 1263 (C-O-C), 1568 (C═C), 3049 (C—H, aromatic). ^{1}H NMR (DMSO-d_6): 7.33–8.52(m, H_{ar}, 7H). ^{13}CNMR(DMSO-d_6,75 MHz)δ: 113.5(C_2),115.9 (CN),116.2(*C*1),123.2(C2'), 125.3(C_4'),134.7(C_6),136.3(C_4),138.7(C_3'), 141.3(C_5),150.8(C_5'),154.8(C_1'). MS (LCMS-MS) *m/z*: Calc. 237.2; Found: 237.2. Calc. for C13H7N3S: C, 65.804%; H, 2.974%; N, 17.709%, Found: C, 65.8; H, 2.9; N, 17.7%.

5.3. General procedure for synthesis of metallophthalocyanines ***3,4***

Compound (**1**) (0.24 mmol) or compound **2** (0.24 mmol) *N,N*-dimethylaminoethanol (DMAE) (4 ml), 1,8-diazabicyclo [4.5.0]undec-7-ene (DBU) (3 drops) and (0.06 mmol) of $CoCl_2 \cdot 6H_2O$ were added in s shlink tube. The mixture was heated at reflux temperature of 170 °C for 24 h under N_2 atmosphere. Then the mixture was left for cooling at room temperature then treated with ethylacetate to precipitate the product which was then filtered off and suddenly washed with water. The green solid product was washed with hot ethanol and hot acetic acid and dried in vaccum. The raw product was purified by chromatography of silica gel column.

5.3.1. Co(II)pc (3)

Elution solvent system: chloroform: methanol (100:3) as eluent.
Yield: (55%).
M.p. = 315 °C.

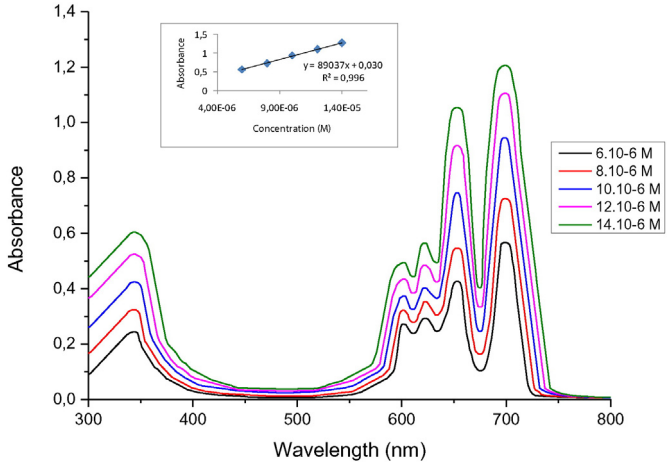

Fig. 4. The aggregation behavior of phthalocyanine **4** in DMSO.

FT-IR (KBr) n, cm-1: 3020 (C-Harom); 1403 (C—C); 1250 (C—N); 1602 (C═C); 1520 (C═N); 904 (Co—N).
UV/Vis (DMSO, λ_{max} nm (log ε)): 345 (4.780), 642 (4.863), 687 (5.082).
Calc. for C68H60N12Co: C, 73.964%; H, 5.477%, N, 15.222%; Found: C, 73.8; H, 5.4, N 15.1.

5.3.2. Co(II)pc (4)

Yield: (65%).
M.p. = 330 °C.
FT-IR (KBr) ν, cm^{-1}: 3048 (C-H_{arom}); 1420 (C—C); 1292 (C—N); 1620 (C═C); 1564 (C═N); 914 (Co—N).
UV/Vis (DMSO, λ_{max} nm (log ε)): 345 (4.90), 620 (4.69), 679(5.21).
Calc. for $C_{52}H_{28}N_{12}S_4Co$: C 61.957%; H, 2.800%,N 16.674% Found: C 61.8; H, 2.6, N16.5;

5.4. General procedure for the synthesis of quaternized metallophthalocyanines (5,6)

The methallophthalocyanines were dissolved in chloroform (10 ml) and excess amount of methyl iodide was added to these solutions. The reaction mixtures were stirred at ambient temperature for two days. The green precipitates were filtered off, washed with ethanol, acetone, diethyl ether and chloroform and dried.

5.4.1. Q Co(II)pc (5)

Elution solvent system: chloroform: methanol (100:3) as eluent.
Yield: (77%).
M.p. = 338 °C.
FT-IR (KBr) n, cm-1: 1520 (C = N), 1602 (C = C), 1250 (C—N), 1403 (C—C), 904 (Co—N).
UV–vis (DMSO): λ_{max}, nm (log ε): 629 (4.70), 690 (5.05), 316 (4.61), 388 (4.91).

5.4.2. Q Co(II)pc (6)

Elution solvent system: chloroform: methanol (100:3) as eluent.
Yield: (80%).
M.p. = 335 °C.
FT-IR (KBr) n, cm-1: 1565 (C = N), 1620 (C = C), 1292 (C—N), 1420 (C—C), 914 (Co—N).
UV–vis (DMSO): λ_{max}, nm (log ε): 629 (4.70), 690 (5.05), 316 (4.61), 388 (4.91).
Calc. for C56H40I4N12S4Co: C 46.465%; H, 2.785%,N 11.611% Found: C 46.6; H, 2.9, N11.5.

5.5. General procedure for preparation of the 7–11

A solution of ethyl acetoacetate (1 mmol), aldehyde (1 mmol) and urea, MPc (0.24 mmol), in DMC (2 mmol) was heated at 120 °C for appropriate duration of time (Table 1). The progress of the reaction was checked by TLC (chloroform/petroleum 2/1) and after completion of the reaction, the mixture was diluted with EtOH/H_2O (2/1) and then the crude product was recrystallized from EtOH (96%) to afford the pure product.

5.5.1. 6-Methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5–carboxylate 7

Yield: (96%).
M.p. = 320 °C.
^{1}HNMR (DMSO-d_6,300 MHz)δ ppm: 1.04 (t, 3H, CH_3(a)); 2.14 (s, 3H, CH_3(b)); 3.81 (q, 2H, Hd); 6.75 (s, 1H, H_3); 6.86 (s, 1H, H1); 6.99 (s, 1H, H_6);
^{13}CNMR(DMSO-d_6,75 MHz) δ ppm: 13.6 ($CH_{3(b)}$); 16.58 ($CH_{3(a)}$); 52.4 (C_b); 60.6 (C_d); 109.6 (C_5); 140.7 (C_4); 159.6 (CO ester); 156.5 (C_2), 128.5–145.1(Carom).

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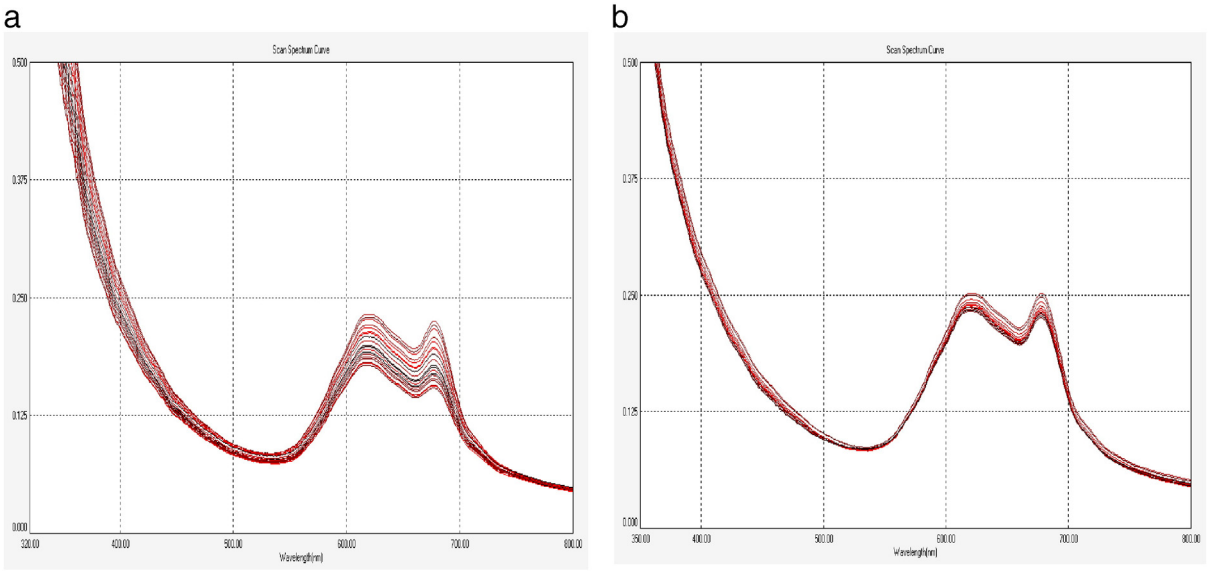

Fig. 5. UV absorption spectra on complexation of Co^{2+} with (a) **3** and (b) **4** in DMSO ($0 \le R_{M/L} \le 2.3$) at 25 °C.

Calc. for C14H1503N2 C 9.827%; H, 88.536%, N 1.637% Found: C 9.7; H, 88.4, N1.5;

5.5.2. 4-(3-Methylphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5–carboxylate 8

Yield: (92%).

M.p. = 220 °C.

^{1}HNMR (DMSO-d_6,300 MHz)δ ppm: 2.14 (s,3H, (CH_3(b)); 1.2 (s, 3H, (CH_3(c)); 3.4 (s, 3H, CH_3(a));4.5 (s, 2H, H_d); 6.72 (s, 1H, H_3); 7.2–8.5 (m, 5H, H_{arom}); 7.96 (s, 1H, H_6).

^{13}CNMR(DMSO-d_6,75 MHz) δ ppm: 13.6 (CH_3); 16.5 ($CH_{3(b)}$); 42.1 ($CH_{3(a)}$); 52.4 (C_6); 60.6 (C_d); 109.6 (C_5); 140.7 (C_4); 159.6 (COester); 156.5 (C_2); 127.5–139.4(Carom).

Calc. for C15H1703N2 C 9.360%; H, 89.184%,N 1.455% Found: C 9.4; H, 89.2, N 1.5;

5.5.3. 4-(3-Methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5–carboxylate 9

Yield: (96%).

M.p. = 310 °C.

^{1}HNMR (DMSO-d_6,300 MHz)δ ppm: 1.04 (t, 3H, $CH_{3(c)}$); 2.14 (s, 3H, $CH_{3(b)}$); 3.46 (s, 3H, $CH_{3(a)}$); 3.81 (q, 2H, H_d); 5.97 (s, 1H, H_b); 6.75 (dd, 1H, $H_{6'}$); 6.86 (s, 1H, $H_{2'}$); 6.99 (dd, 1H, $H_{4'}$); 7.24 (dd, 1H, $H_{5'}$); 7.48 (s, 1H, H_1); 8.68 (s, 1H, H_3).

^{13}CNMR (DMSO-d_6,75 MHz)δ ppm: 55.6 (OCH_3); 16.3 (CH_3(b)); 42.4 (CH_3(a)); 52.6 (C_6); 60.2 (Cd); 109.8 (C_5); 141.7 (C4); 159.6 (COester); 156.8 (C_2); 128.4–140.2(Carom).

Calc. for C15H1704N2 C 9.356%; H, 89.190%,N 1.455% Found: C 9.4; H, 89.2, N1.5.

5.5.4. 4-(4-Nitrophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5–carboxylate 10

Yield: (92%).

M.p. = 310 °C.

^{1}HNMR (DMSO-d_6, 300 MHz)δ ppm: 1.2 (t, 3H, $CH_{3(c)}$); 2.12 (s, 3H, $CH_{3(b)}$); 3.81 (q, 2H, H_d); 5.97 (s, 1H, H_6); 8.68 (s, 1H, H_3); 7.48 (s, 1H, H_1); 6.75–7.26(m,5H, Harom).

^{13}CNMR(DMSO-d_6,75 MHz)δ ppm: 14.8 (CH_3(b)); 42.6 (CH_3(a)); 52.6 (C_6); 60.2 (C_d); 109.3 (C_5); 141.2 (C_4); 159.7 (COester); 156.3 (C_2); 126.6–138.4(Carom).

Calc. for C14H1405N3 C 10.339%; H, 87.077%,N 2.584% Found: C 10.4; H, 87.2, N2.6.

5.5.5. 4-(4-Dimethylaminophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5–carboxylate 11

Yield: (85%).

M.p. = 310 °C.

1HNMR (DMSO-d_6, 300 MHz)δ ppm: 1.2 (t, 3H, CH_3(c)); 2.12 (s, 3H, CH_3(b)); 2.10 (s, 6H, $N(CH_3)_2$); 3.65 (q, 2H, Hd); 5.95 (s, 1H, H_6); 8.64 (s, 1H, H_3); 7.50 (s, 1H, H_1); 6.73–7.36(m,5H, Harom).

^{13}CNMR(DMSO-d_6,75 MHz)δ ppm: 16.4 ($N(CH_3)_2$); 14.5 ($CH_{3(b)}$); 42.4 ($CH_{3(a)}$); 52.8 (C_6); 60.,2 (C_d); 109.3 (C_5); 141.2 (C_4); 159.7 (COester); 156.3 (C_2); 126.6–138.4(Carom).

5.6. Antimicrobial activities

5.6.1. Microorganisms and growth conditions

Bacterial strains: Gram-positive bacteria (*Micrococcus luteus* LB 14110, *Staphylococcus aureus* ATCC 6538, *Listeria monocytogenes* ATCC 19117 and *Agrobacterium tumefaciens*), Gram-negative bacteria (*Salmonella* Typhimurium ATCC 14028 and *Pseudomonas aeruginosa* ATCC 49189) were used as indicator microorganisms for the

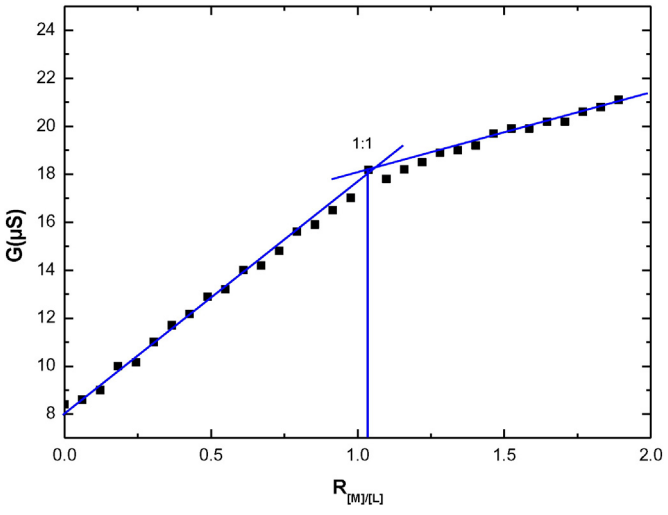

Fig. 6. Conductometric titration in the case of **3** with Co^{2+}.

Table 3
Antimicrobial activity spectrum of the synthesized compound.

Microrganism indicator	Compounds	Inhibition zone (mm)
Micrococcus luteus LB 14110	3	26
	4	26
	5	22
	6	14
	7	16
	8	18
	9	13
	10	14
	11	21
Staphylococcus aureus ATCC 6538	3	25
	4	23
	5	–
	6	14
	7	18
	8	17
	9	12
	10	13
	11	23
Listeria monocytogenes ATCC 19117	3	16
	4	20
	5	–
	6	13
	7	20
	8	19
	9	18
	10	17
	11	14
Agrobacterium tumefaciens	3	–
	4	–
	5	–
	6	–
	7	19
	8	17
	9	14
	10	13
	11	12
Salmonella typhimurium ATCC 14028	3	12
	4	12
	5	–
	6	12
	7	19
	8	16
	9	14
	10	13
	11	12
Pseudomonas aeruginosa ATCC 49189	3	16
	4	16
	5	–
	6	12
	7	20
	8	22
	9	18
	10	16
	11	14
Candida albicans	3	22
	4	12
	5	–
	6	–
	7	10
	8	12
	9	13
	10	16
	11	14
Candida tropicalis R2 CIP203.	3	20
	4	16
	5	–
	6	–
	7	15
	8	14
	9	13
	10	14
	11	–

Table 4
Determination of the Minimum Inhibitory Concentrations (MICs) expressed in mg/ml.

Microorganism indicator	Compounds	MIC(mg/ml)
Micrococcus luteus LB 14110	3	5
	4	5
	5	0.3125
	6	10
	7	1.25
	8	5
	9	0.4125
	10	4
	11	4
Staphylococcus aureus ATCC 6538	3	5
	4	5
	5	–
	6	5
	7	2.5
	8	–
	9	5
	10	10
	11	–
Listeria monocytogenes ATCC 19117	3	2.5
	4	5
	5	–
	6	5
	7	0.625
	8	–
	9	2.5
	10	5
	11	1.32
Salmonella Typhimurium ATCC 14028	3	5
	4	10
	5	–
	6	10
	7	5
	8	2.5
	9	5
	10	1.25
	11	–
Pseudomonas aeruginosa ATCC 49189	3	5
	4	5
	5	–
	6	10
	7	2.5
	8	–
	9	5
	10	10
	11	1.32
Candida albicans	3	2.5
	4	5
	5	10
	6	5
	7	–
	8	–
	9	2.3
	10	–
	11	2.1
Candida tropicalis R2 CIP203.	3	2.5
	4	5
	5	–
	6	–
	7	5
	8	2.5
	9	5
	10	1.32
	11	–

antibacterial activity assays. Antifungal activity was determined against the *Candida albicans* and *Candida tropicalis* R2 CIP203.

The bacterial strains using as indicator microorganisms were grown overnight in LB media under aerobic conditions and constant agitation (200 rpm) at 30 °C for *M. luteus* LB14110, *L. monocytogenes* ATCC 19117, and *A. tumefaciens*, and at 37 °C for *S. aureus* ATCC 6538, *S.* Typhimurium ATCC 14028 and *P. aeruginosa* ATCC 49189, and then diluted 1:100 in LB media and incubated for 5 h under constant agitation (200 rpm) at the appropriate temperature. *C. tropicalis* R2

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CIP203 was grown in YP10 medium (10 g/l yeast extract, 10 g/l peptone, 100 g/l glucose, 15 ml of 2 g/l adenine solution) and *C. albicans* was grown in YEPD medium (10 g/l yeast extract, 20 g/l peptone, 20 g/l dextrose) at 30 °C for 48 h in an orbital incubator with shaking at 200 rpm.

5.6.2. Agar well diffusion method

Agar well diffusion method was employed for the determination of the antimicrobials activities of the synthesized compounds. Briefly, the synthesized compounds are allowed to diffuse out into the appropriate agar medium (LB agar medium for bacterial strains and potato dextrose agar "PDA" for fungal strains) and interact in a plate freshly seeded with a suspension of the indicators microorganisms (0.1 ml of 10^8 cells per ml). The plate was incubated at the appropriate temperature after staying at 4 °C for 2 h. The resulting zones of inhibition will be uniformly circular as there will be a confluent lawn of growth. The antibacterial activity was assayed by measuring in millimeters the diameter of the inhibition zone formed around the well.

5.6.3. MIC determination

The antimicrobial activities of the synthesized compounds were determined by the minimum inhibitory concentration (MICs) in accordance with NCCLS guideline M7-A_6 and M38-P [42]. The test was performed in sterile 96-well microplates with a final volume in each microplate well of 100 μl. The synthesized compounds (20 mg/ml) were properly prepared in solution of dimethylsulfoxide (20%). The inhibitory activity of each synthesized compounds was transferred to each well in order to obtain a twofold serial dilution of the original sample and to produce the concentration range of 0.0781–10 mg/ml.

To each test well 10 μL of cell suspension were added to final inoculum concentrations of 10^6 CFU/ml for each microorganisms. Positive growth control wells consisted of microorganisms only in their adequate medium. Cells suspension at the same concentration supplemented with ampicillin (50 μg/ml) was used as negative control. The plates were then covered with the sterile plate covers and incubated at the appropriate temperature of each microorganism. The MIC was defined as the lowest concentration of the synthesized compounds at which the microorganism does not demonstrate visible growth after incubation. As an indicator of microorganism growth, 25 μl of Thiazolyl Blue Tetrazolium Bromide (MTT), indicator solution (0.5 mg/ml) dissolved in sterile water were added to the wells and incubated at room temperature for 30 min.

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