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ARTICLE

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Three-component, one-pot synthesis of pyrano[3,2-c] chromene derivatives catalyzed by ammonium acetate: Synthesis, characterization, cation binding, and biological determination

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Abstract

Three-component reaction of arylaldehydes with malononitrile and 4-hydroxycoumarine using CH_3COONH_4 as a catalyst at reflux was used for the synthesis of novel substituted pyrano[3,2-c]chromene derivatives. The structure of these compounds was assigned by spectroscopic data such as (IR, ^{1}HNMR, ^{13}CNMR, and mass spectral data). The cation binding properties of chromene derivatives **4a-c** towards Cu^{2+}, Ni^{2+}, and Zn^{2+} were studied in methanol. The results showed that Zn^{2+} is the most complexed in this series of cations, and **4c** is best complexed with either Ni^{2+} and Zn^{2+}. Antimicrobial properties of new pyrano[3,2-c]chromene derivatives are investigated, the compound **4c** presents against *Micrococcus luteus* LB 14110 an MIC value of 0.0185 mg/mL quite better to that of ampicillin (0.0195 mg/mL) used as standard. Concerning acetylcholinesterase inhibition activity (AChEI), compound **4c** presents an interesting AChEI activity with an inhibition of 52%.

1 | INTRODUCTION

There has been a growing interest to use the 4-hydroxycoumarin as a heterocyclic motif to generate molecular structures possessing a multitude of biological activities such as anti-HIV, antifungal, phytotoxic, antimicrobial, cytotoxic, and neurotoxic activities.[1–7] The incorporation of other heterocyclic moieties into pyran-2-ones either in the form of an extra cyclic substituent or as a fused structure has often led to enhanced biological effects. For instance, furo[3,2-c]pyran-4-ones and their derivatives have been recognized to possess a wide range of medicinal benefits.[8–15]

Multicomponent reactions (MCRs) have emerged as useful tools for exploring chemical space. They involve domino processes in which at least three different reactants are directly converted into products in a one-pot fashion.[16–20] Compared with classical multistep synthesis, MCRs offer higher atom economy and selectivity and give easy access to molecular complexity and diversity while generating fewer by-products. As a result, the importance of MCRs in modern organic chemistry is growing,[21–23] and MCRs are being developed for the efficient production

of medicinally relevant scaffolds. In the course of our continuing interest in the synthesis of condensed coumarin derivatives with anti-inflammatory and antioxidant activities,[24,25] we have extended our research to the synthesis, characterization, and biological evaluation of novel bioactive new substituted pyrano[3,2-c]chromene derivatives via an environmentally friendly reaction condition. In addition, their biological activities were studied.

2 | RESULTS AND DISCUSSIONS

The reaction of an equimolecular amounts of 4-hydroxycoumarine **1** with malononitrile and arylaldehydes using different solvents such as DMC, DEC, ethanol, tetrahydrofuran (THF), dichloromethane, and toluene (Table 1, entries 1-7) was investigated in the presence of a catalytic amount of ammonium acetate. The results are presented in Table 1.

The results indicated that solvents also affected the yield of compounds (Table 1, entries 1-7). In the organic solvents such as dichloromethane, THF, ethanol, or toluene, the yields of **3** were lower, and longer reaction times were required, the best result was obtained when using DMC.

The reaction was also performed with different amounts of catalyst at ambient temperature. The results are summarized in Table 2

A total of 20 mol% of catalyst was found more suitable for this reaction. In addition, when we increase the percentage of the catalyst to 10, 15, and 20 mol%, the yields were found to be increased up to 85%, 82%, and 95%, respectively.

Table 3 shows that 30 minutes are not enough for the reaction to be complete. On the other hand, beyond 120 minutes, we have no improvement in the reaction yield. With the optimized reaction conditions in hand, we then investigated the scope of this reaction with substituted aromatic aldehydes as substrates. The results are summarized in Scheme 1 and Table 4.

All the aromatic aldehydes afforded the corresponding products **4** in good yields.

The structure of the new compounds **4** was identified by their ^{1}H-NMR and ^{13}C-NMR data as well as by their mass spectra and their elemental analysis. In ^{1}H-NMR of compound **4a**, a characteristic singlet at about 3.07 ppm is assigned to the methyl protons (a,b), whereas the proton NH appears as a singlet at about 9.98 ppm in accordance with the previous data (Figure 1).[26–33]

^{13}C-NMR showed the amide (NH–C) signal at δ 177.8 ppm, the $C_{1'}$ signal had a chemical shift of $\delta = 61.9$, while the C_4 signal was assigned further upfield at $\delta = 96.1$. However, the C_2 signal was further upfield, $\delta = 180.1$, than was the $C_{4'}$ signal was assigned as $\delta = 134.4$ ppm (Figure 2).

The MS spectrum of complex **4a** is given in Figure 3.

The fragmentation leading to $m/z = 79$ can occur via the mechanism fragmentation given in Scheme 2.

The formation of compound **4** could be explained by the reaction sequence in Scheme 3. First, condensation of ammonium acetate with malonitrile is proposed to give intermediate (**i**), The Michael addition of 4-hydroxycoumarine to the intermediate (**ii**) occur to

TABLE 1 Synthesis of pyrano[3,2-c]chromene derivatives in the presence of different solvents

Entry	Solvent	T, °C	Yield, %[a]
1	DMC	90	85
2	DEC	128	75
3	EtOH	78	72
4	$CHCl_3$	61	60
5	Bmin[triflate]	>100	90
6	THF	66	65
7	Toluene	110	60
8	CH_2Cl_2	40	62

Note. Reaction conditions: 4-hydroxycomarine (1 mmol), malononitrile (1 mmol), benzaldehyde (1 mmol), NH_4OAc (2,5 mol%), solvant (5 ml), t (2 h).

[a]Isolated yield of product.

TABLE 2 Effect of catalyst amount on the condensation of benzaldehyde 1, malononitrile 2, and 4-hydroxycoumarin **3** in Bmim[triflate]

Entry	Catalyst	Mole, %	Yield, %[a]
1	NH_4OAc	5	55
2	NH_4OAc	10	90
3	NH_4OAc	15	92
4	NH_4OAc	20	94
5	NH_4OAc	30	92
6	NH_4OAc	35	90
7	NH_4OAc	40	88

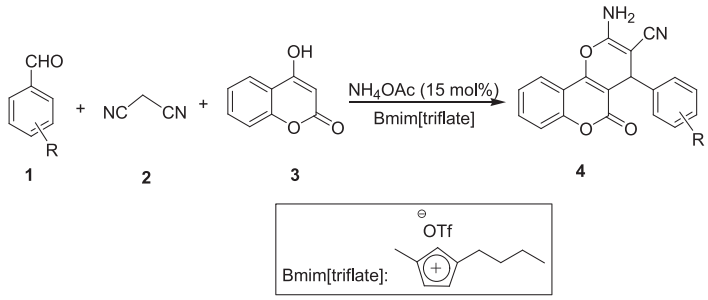
Note. Reaction conditions: 4-hydroxycomarine (1 mmol), malononitrile (1 mmol), benzaldehyde (1 mmol), Bmim[triflate] (5 ml), t (2 h).

[a]Isolated yields after purification.

TABLE 3 Effect of reaction time on the yield of compounds

t, min	30	40	60	90	120	130
Yield, %	68	75	76	72	95	80

Note. Reaction conditions: 4-hydroxycomarine (1 mmol), malononitrile (1 mmol), benzaldehyde (1 mmol), NH_4OAc (15 mol%), Bmim[triflate] (5 mL).



SCHEME 1 Synthesis of pyrano[3,2-c] chromene derivatives **4** catalyzed by NH_4OAc

TABLE 4 Physico-chemical characteristics of pyrano[3,2-c] chromene derivatives **4**

Entry	R	Product	t, min	Yield, %[a]	mp, °C
1	3,5-OCH_3-4-$COOCH_3$	**4a**	180	92	240
2	2,3-OH	**4b**	100	90	258
3	2-OH-5-NO_2	**4c**	120	85	250
4	H	**4d**	50	94	260
5	*m*-OCH_3	**4e**	45	90	325

Note. Reaction conditions: Aromatic aldehyde 1a (1 mmol), malononitrile 2 (1 mmol), and 4-hydroxycoumarin 3 (1 mmol), Bmim[triflate] (5 mL) NH_4OAc (15 mol%).

[a]Isolated yields after purification.

provide the intermediate (**iii**), which undergoes isomerization to form the target **4**.

3 | BIOLOGICAL ACTIVITIES

3.1 | Antibacterial activity

The antimicrobial activity of the pyrano[3,2-c]chromene derivatives **4** was tested at three different concentrations: 0.1, 0.3, and 0.5 mg/mL. The obtained results of the synthesized coumarins are shown in Table 5.

Compound **4a** showed activity against *Micrococcus luteus* LB 14110 at three different concentrations 0.1, 0.3, and 0.5 mg/mL. We found also that if we increase the concentration of compound **3a**, the diameter of inhibition zone will not increase as we have expected. Compound **4b** showed activity against bacteria *M. luteus* LB 14110 and *Agrobacterium tumifaciens* only in concentration of 0.5 mg/mL. Compound **4c** did not show activity against *Listeria monocytogenes* ATCC 19117. In the case of *L. monocytogenes* ATCC 19117, by increasing the concentration of compound **4c**, the activity will not change. The Minimal Inhibitory Concentrations (MICs) values of pyrano[3,2-c]chromene derivatives **4** were determined. The most active compound was **4c**, which presents against *M. luteus* LB 14110 the same MIC value of 0.0195 mg/mL than the used standard (ampicillin) (Table 6).

3.2 | Acetylcholinesterase inhibition

The acetylcholinesterase enzyme (AChE) was done using some previously reported methods.[34–37]

The results of AChEI of the synthesized compounds **4** are presented in Table 8. Three compounds (**4a**, **4b**, and **4c**) exhibited moderate AChEI activity at 100 μg/mL. As

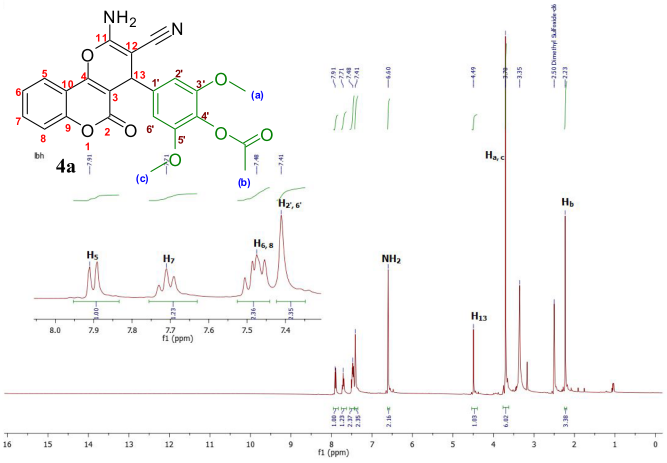


FIGURE 1 ^1H NMR spectra of compound **4a** (400 MHz, DMSO-d_6) [Color figure can be viewed at wileyonlinelibrary.com]

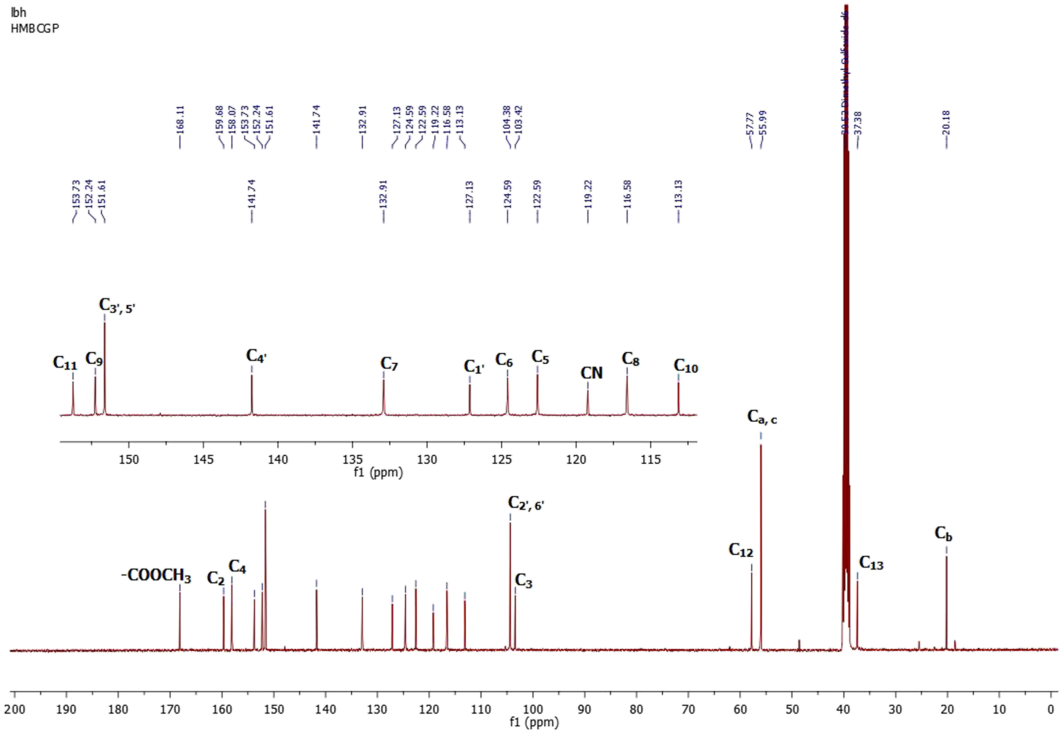


FIGURE 2 ^{13}C NMR spectra of compound **4a** (100 MHz, DMSO-d_6) [Color figure can be viewed at wileyonlinelibrary.com]

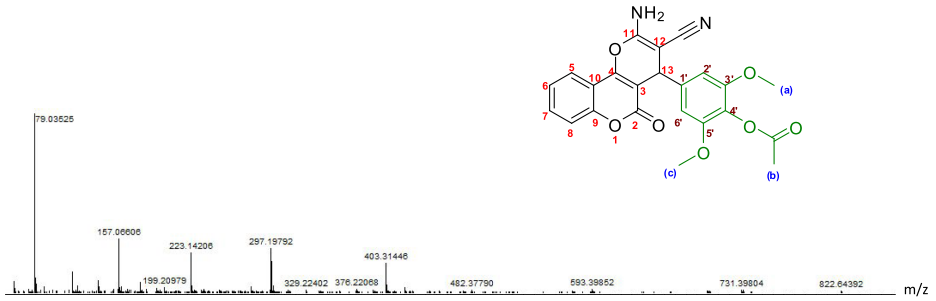
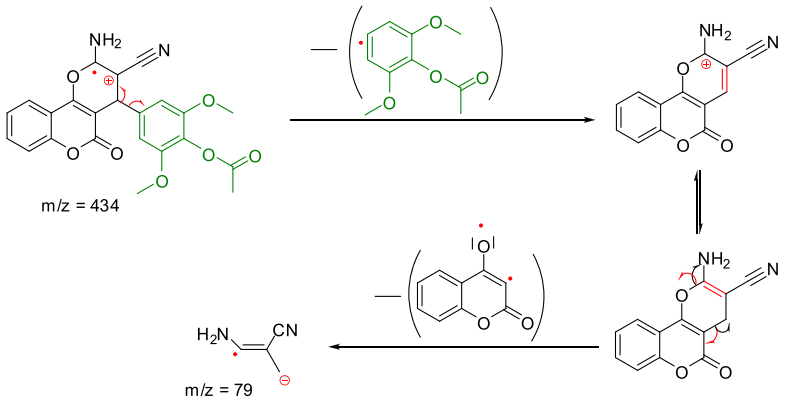
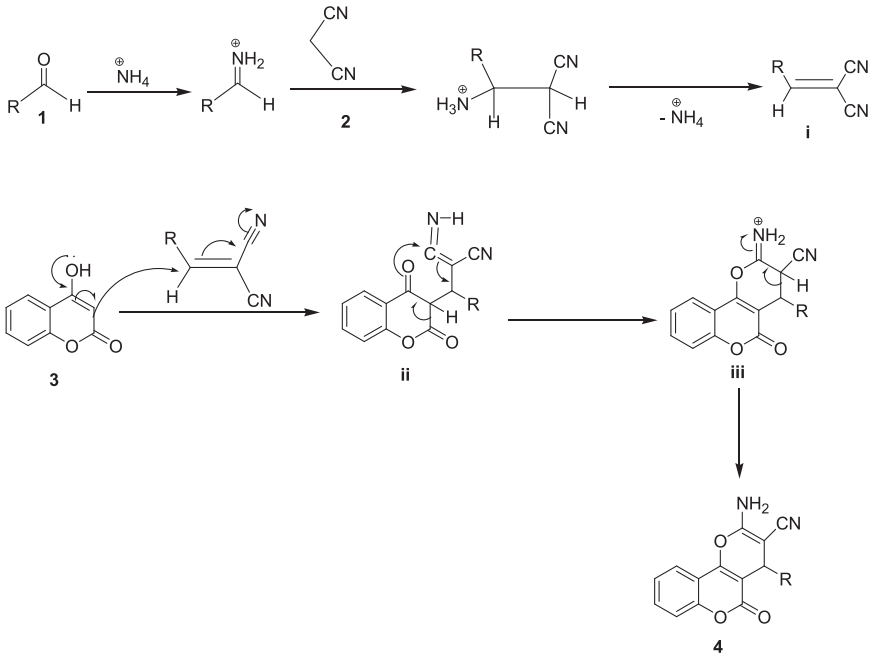


FIGURE 3 DART MS spectrum (DART-TOF-MS) of compound **4a** [Color figure can be viewed at wileyonlinelibrary.com]



SCHEME 2 Mechanism of the fragmentation leading to the $m/z = 79$ peak [Color figure can be viewed at wileyonlinelibrary.com]



SCHEME 3 A proposed mechanism for the three-component synthesis of pyrano[3,2-c]chromene derivatives **4**

TABLE 5 Antibacterial activity of the synthesized pyrano[3,2-c]chromene derivatives **4** against the tested indicator microorganisms

Bacteria	Conc, mg/mL	4a	4b	4c	4d	4e	AMC
Micrococcus luteus	0.1	19	0	16	15	14	25
LB 14110	0.3	23	0	16	13	12	
	0.5	23	24	16	14	13	
Staphylococcus aureus	0.1	24	0	40	36	**28**	
ATCC 6538	0.3	24	0	36	35	**23**	
	0.5	33	0	33	34	**29**	
Listeria monocytogenes	0.1	0	0	0	0	0	
ATCC 19117	0.3	0	0	0	0	0	
	0.5	22	0	0	0	0	
Salmonella Typhimurium	0.1	0	0	0	0	0	
ATCC 14028	0.3	0	0	0	0	0	
	0.5	16	0	22	0	0	
Agrobacterium tumifaciens	0.1	21	21	0	0	0	
	0.3	20	19	16	0	0	
	0.5	21	18	0	0	0	

the antibacterial and antioxidant activities, the compound **4b** possesses the most active AChEI activity (Table 7).

4 | CATION BINDING PROPERTIES

4.1 | Complexation of heavy metals cations by compounds 4a-c

4.1.1 | Spectrophotometric study

The complexation of divalent metal cations (Cu^{2+}, Ni^{2+}, and Zn^{2+}) by ligands **4a-c** was interpreted by spectral variations throughout the titration of ligand by metal solution. Generally, a decrease of absorbances was observed as shown in Figure 4, which corresponds to the complexation of Ni^{2+} by ligand **4c.**

The interpretation of these spectrophotometric data by means of the Letagrop calculation program made it possible to determine the stoichiometries of the species formed and to calculate their stability constants.[37] These species are of stoichiometry ML for the two series of ligands. All these results are presented in Table 8.

The stability constants of the ML complexes vary between 2.92 and 3.58 logarithmic units. Small spectral variations with Cu^{2+} prevented the formation of the complex.[38] The stability profiles of the three ligands **4a-c** are shown in Figure 5.

TABLE 6 Determination of the Minimum Inhibitory Concentrations (MICs) expressed in mg/ml of compounds **4**

Microorganism Indicator	Compounds	MIC, mg/mL
Micrococcus luteus LB 14110	Ampicillin	0.0195
	4a	0.02
	4b	0.025
	4c	0.0185
	4d	0.0196
	4e	0.197
Listeria monocytogenes ATCC 19117	Ampicillin	0.039
	4a	0.040
	4b	0.042
	4c	0.032
	4d	0.041
	4e	0.042
Salmonella Typhimurium ATCC 14028	Ampicillin	0.625
	4a	0.650
	4b	0.635
	4c	0.621
	4d	0.626
	4e	0.627

TABLE 7 Acetylcholinesterase inhibitory activity (AChEI) (%) of pyrano[3,2-c]chromene derivatives **4**

Compound	(AChEI) (%)
4a	-
4b	48.5
4c	52
4d	47.5
4e	49.1

TABLE 8 Stability constants log β_{xy} of complexes of Cu^{2+}, Ni^{2+}, and Zn^{2+} in MeOH at 25°C, I = 10^{-2} M, ($0.01 \leq \sigma_{n-1} \leq 0.16$)

	M:L	Cu^{2+}	Ni^{2+}	Zn^{2+}
4a	1:1	a	2.92	3.27
4b	1:1	a	3.01	3.38
4c	1:1	a	3.07	3.58

Note. a: Absorbance changes too small to enable satisfactory fitting.

Figure 5 depicts the increase of complexes stabilities in favor of Zn^{2+}.

Zn^{2+} is the most complex in the series of cations considered, but its constants of stabilities are of the same order of magnitude as those with Ni^{2+}. However, the absence of complexation affinity of Cu^{2+} suggests a probable application for the separation of Ni^{2+} and Zn^{2+} in solution with Cu^{2+}.

It is noted that chromene **4c** is the best complexant for either Ni^{2+} and Zn^{2+}. In comparison with the results of the biological activities, we can suggest this phenomenon can be in agreement with its answer towards *S. Typhimurium* at high concentration (0.5 mg/mL) and with staphylococcus aureus in all studied concentrations (0.1-0.5 mg/mL).

5 | CONCLUSION

In summary, we presented an efficient, mild, and rapid approach for the synthesis of pyrano[3,2-c]chromene derivatives via three component reaction of aromatic aldehydes, ethyl cyanoacetoacetate, and 4-hydroxycumarine using cheap and readily available low toxic organocatalyst

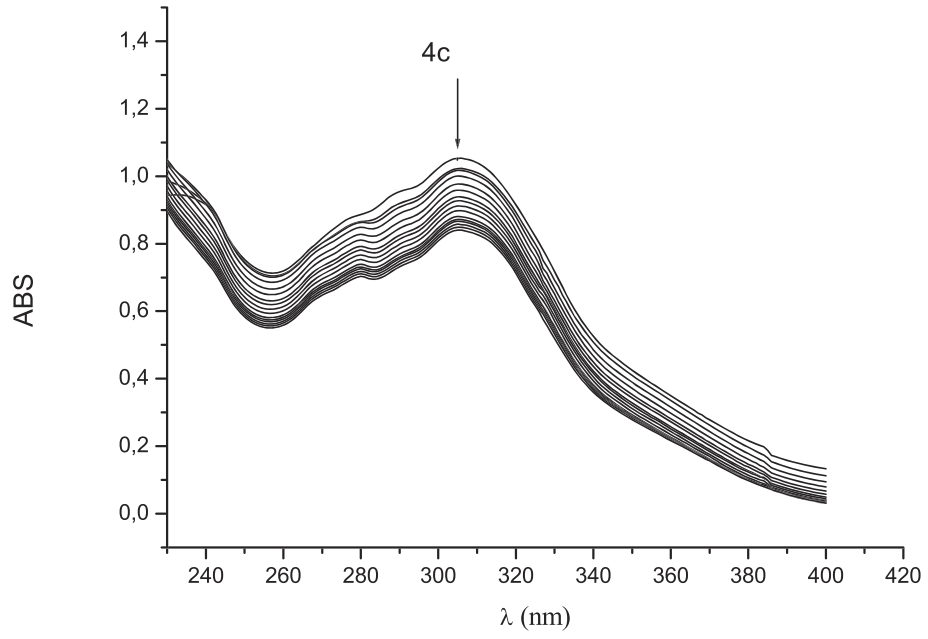


FIGURE 4 UV absorption spectra on complexation of Ni^{2+} with **4c**, in MeOH, ($0 \leq RM/L \leq 2$) at 25°C

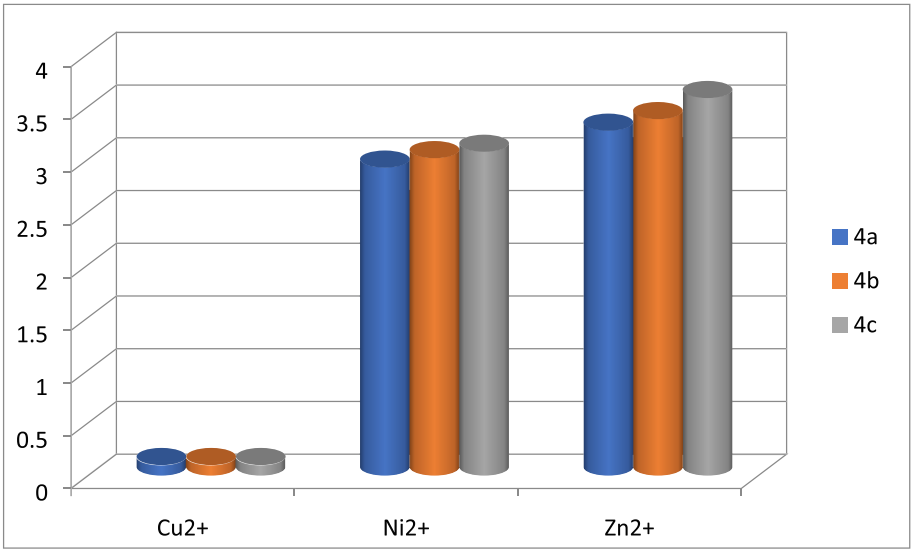


FIGURE 5 Stability constants log β_{11} (determined in MeOH) for Cu^{2+}, Ni^{2+}, and Zn^{2+} with **4a-c** [Color figure can be viewed at wileyonlinelibrary.com]

ammonium acetate. The advantages of this procedure are clean. The structure of the new compounds **4** was identified by their ^{1}H-NMR and ^{13}C-NMR data as well as by their mass spectra and their elemental analysis. The complexation properties of the derivatives prepared towards Cu^{2+}, Ni^{2+} and Zn^{2+} show that Zn^{2+} is the most complex in this series of cations, and **4c** is best complexant with either Ni^{2+} or Zn^{2+}. The obtained products were tested for their antibacterial and acetylcholinesterase activities. Most of the synthesized compounds are more active against *Escherichia coli* and *Staphylococcus aureus* than standard references.

6 | EXPERIMENTAL SECTION

General Procedures were done regarding our previous work.[24]

The synthesis and characterization of compounds **4d** and **4e** were done regarding our previous work.[24]

The synthesis of 3,4-dihydropyrano[3,2-c]chromenes **4** was done as our previous reports.[24]

6.1 | 2-Amino-4-(4-acetoxy-3,5-dimethoxyphenyl)-5-oxo-4,5-dihydropyrano [3,2-c] chromene-3-carbonitrile (4a)

Yield: 92%, mp = 240°C, $C_{23}H_{18}N_2O_7$, FT-IR (KBr) ν, cm^{-1}: 3326 (NH_2), 3175 (C—H)$_{arom}$, 2196 (CN), 1710 (C═O) . ^{1}H NMR. (DMSO-d_6, 400 MHz) (δ : ppm):7.91 (d, 1H, H_5, arom CH); 7.71 (m, 1H, H_7, arom CH); 7.48 (m, 2H, $H_{6,\ 8}$, arom CH); 7.41(s, 2H, $H_{2',\ 6'}$, arom CH); 6.60 (s, 2H, NH_2); 4.49 (s, 1H, H_{13}, arom CH); 3.70 (s, 6H, $H_{a,c}$, OCH_3); 2.23 (s, 3H, H_b, $OCOCH_3$). ^{13}C NMR. (DMSO-d_6, 100 MHz) (δ: ppm):168.11 ($COOCH_3$, ester); 159.68 (-C_2OOC-, ester); 158.07 (C_4); 153.73 (C_{11}); 152.24 (C_9); 151.61 ($C_{3',\ 5'}$); 141.74 ($C_{4'}$); 132.91 (C_7); 127.13 ($C_{1'}$); 124.59 (C_6); 122.59 (C_5); 119.22 (CN); 116.58 (C_8); 113.13 (C_{10}); 104.38 ($C_{2',\ 6'}$); 103.42 (C_3); 57.77 (C_{12}); 55.99 ($C_{a,\ c}$); 37.38 (C_{13}); 20.18 (C_b). DART-TOF-MS: m/z = 403, 297, 223, 157 et 79.

6.2 | 2-Amino-4-(2,3-dihydroxyphenyl)-5-oxo-4,5-dihydropyrano [3,2-c] chromene-3-carbonitrile (4b)

Yield: 90%, mp = 258°C, $C_{19}H_{12}N_2O_5$, FT-IR (KBr) ν, cm^{-1}: 3443 et 3380 (NH_2), 3274 (C—H)$_{arom}$, 2221 (CN), 1714 (C═O) cm^{-1}. ^{1}H NMR. (DMSO-d_6, 400 MHz) (δ : ppm): 9.85 (s, 1H, OH); 9.56 (s, 1H, OH); 7.90 (m, 1H, Ar—H); 7.77 (m, 1H, Ar—H); 7.57 (m, 1H, Ar—H); 7.43 (m, 1H, Ar—H); 7.30 (m, 1H, Ar—H); 7.18 (m, 2H, Ar—H); 7.00 (s, 2H, NH2); 4.66 (s, 1H, C—H). ^{13}C NMR. (DMSO-d_6, 100 MHz) (δ: ppm): 160.6 (C_2OOC-, ester); 158.2 ($C_{2'}$); 155.1 ($C_{3'}$); 152.4 (C_4); 151.1 (C_{11}); 146.8 (C_9); 134.2 (C_7); 129.8(C_6); 129.4($C_{1'}$); 125.4 (C_5); 124.6 ($C_{6'}$); 124.6 ($C_{5'}$); 123.9 (C_8); 123.1 ($C_{4'}$); 119.7 (CN); 117.8 (C_{10}); 113.6 (C_3); 103.8 (C_{12}); 57.3 (C_{13}).

6.3 | 2-Amino-4-(2-hydroxy-5-nitrophenyl)-5-oxo-4,5-dihydropyrano [3,2-c] chromene-3-carbonitrile (4c)

Yield: 85%, mp = 250°C, $C_{19}H_{11}N_3O_6$ FT-IR (KBr) ν, cm^{-1}: 3435 and 3375 (NH_2), 3275 (C—H)$_{arom}$, 2215 (CN), 1709 (C═O) cm^{-1}. ^{1}H NMR. (DMSO-d_6, 400 MHz) (δ : ppm): 9.91 (s, 1H, OH); 8.04 (m, 1H, H_5, arom CH); 782 (m, 2H, $H_{4',6'}$, arom CH); 7.48 (m, 1H, H_7, arom CH); 6.79 (m, 2H, $H_{6,\ 8}$, arom CH); 6.72 (d, 1H, $H_{3'}$, arom CH); 6.20 (s,

2H, NH_2); 5.43 (s, 1H, H_{13}, C—H). ^{13}C NMR. (DMSO-d_6, 100 MHz) (δ: ppm): 160.7 (C_2OOC-, ester); 158.3 ($C_{2'}$); (−155.0 (C_4); 152.6 (C_{11}); 150.8 (C_9); 147.2 ($C_{5'}$); 134.3 (C_7); 129.9 ($C_{4'}$); 129.2 ($C_{6'}$); 125.2 (C_6); 125.2 ($C_{1'}$); 124.8 (C_5); 124.5 (C_8); 122.8 ($C_{3'}$); 119.6 (CN); 117.6 (C_{10}); 113.8 (C_3); 104.0 (C_{12}); 57.1 (C_{13}).

Stability Constant Measurements were determined regarding our previous work.[25]

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