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Dedicated to Prof. Bogdan C. Simionescu on the occasion of his 75th anniversary

SYNTHESIS AND SPECTROSCOPIC PROPERTIES OF NOVEL INDOLIZINES AND AZAINDOLIZINES

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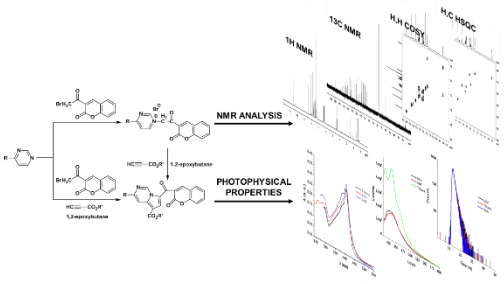
Novel indolizines and pyrrolo[1,2-*c*]pyrimidines bearing a 3-carbonylchromen-2-one moiety on the pyrrole rings were synthesized and spectroscopic properties of some of synthesized compounds were investigated. Synthetic procedures started from 4-substituted pyrimidines, 3-(2-bromoacetyl)-2*H*-chromen-2-one and electron-deficient alkynes *via* 3+2 dipolar cycloaddition of cycloimmonium-ylides, generated *in situ* from their corresponding quaternary salts, in the presence of an epoxide playing the role of acid scavenger and reaction solvent. The structures of novel compounds were confirmed by chemical analyses, IR and NMR spectroscopy. Spectroscopic properties of some of the synthesized compounds were investigated.



INTRODUCTION

Indolizines and azaindolizines are *N*-bridgehead [5,6]-fused ring systems with interesting properties for both medicinal chemistry and material sciences. Many compounds containing indolizine moiety have been investigated for their antibacterial and antifungal activity,[1,2] antimycobacterial,[3,4] antiinflammatory,[5,6] and psychotropic[7] activities. They proved to be HIV-1 VIF-Elongin C interaction inhibitors,[8] calcium entry blocker,[9] aromatase enzyme inhibitor,[10] and efficient inhibitors of farnesyltransferase.[11] Amongst azaindolizines, pyrrolo[1,2-*c*]pyrimidine is the core of some natural alkaloids such as arenaine,[12] batzelladine A,[13,14] crambescines A[15] and varioline B.[16,17] Pyrrolo[1,2-*c*]pyrimidine derivatives shown antifungal and antimicrobial properties,[18] antitumor activity,[19] and proved potent inhibitors of HIV-1 reverse transcriptase.[20] Many indolizines and azaindolizines have interesting fluorescent properties,[21–24] with applications as chemosensors.[25,26]

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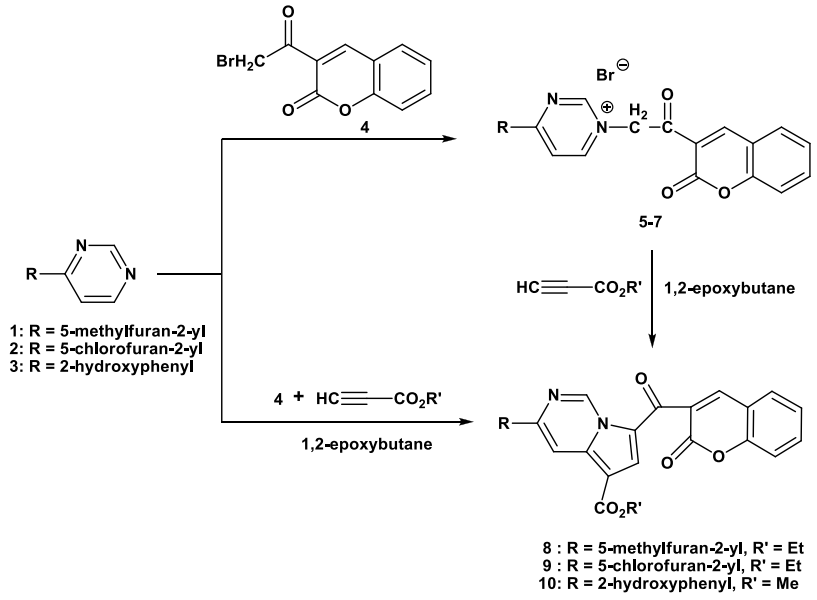
One accessible method to construct the indolizine and azaindolizine derivatives is based on the classical 3+2 dipolar cycloaddition reaction of heteroaromatic *N*-ylides as cyclic azomethine 1,3-dipoles with dipolarophiles.[27–30] Usually, this multistep process starts with the preparation of *N*-heterocyclic quaternary salts with α-halo carbonyl compounds, *in situ* conversion into corresponding heterocyclic *N*-ylides in the presence of an inorganic or organic base and 3+2 dipolar cycloaddition reactions of heterocyclic *N*-ylides with electron-deficient alkynes or alkenes.[31–45] Our group has developed a simple one-pot, multi-component synthetic strategy towards *N*-bridgehead heterocyclic compounds based on the consecutive quaternization of the *N*-heteroaromatic compound, *in situ* generation of the heterocyclic *N*-ylide, 3+2 dipolar cycloaddition reaction to an electron-deficient alkyne and aromatization sequence, using an epoxide as solvent and acid scavenger.[46–55] A range of new indolizines and azaindolizines were synthesized *via* 3+2 dipolar cycloaddition reactions of cycloimmonium ylides, generated from the various *N*-heterocycles such as pyridine, quinoline, isoquinoline, pyridazine, pyrimidine, phthalazine and benzimidazole derivatives with diverse phenacyl bromides, alkyl bromoacetates, 3-(2-bromoacetyl)-2*H*-chromen-2-one and electron-deficient alkynes. Continuing our interest in synthesis and fluorescent properties of imides, indolizine and azaindolizine derivatives,[56,57] here we report novel indolizine and azaindolizine derivatives containing a 3-carbonylchromen-2-one moiety on the pyrrole rings starting from 4-substituted pyrimidines *via* 3+2 dipolar cycloadditions of cycloimonium ylides, generated *in situ* from the corresponding *N*-heteroaromatic bromides with 3-(2-bromoacetyl)-2*H*-chromen-2-one, with activated alkynes.

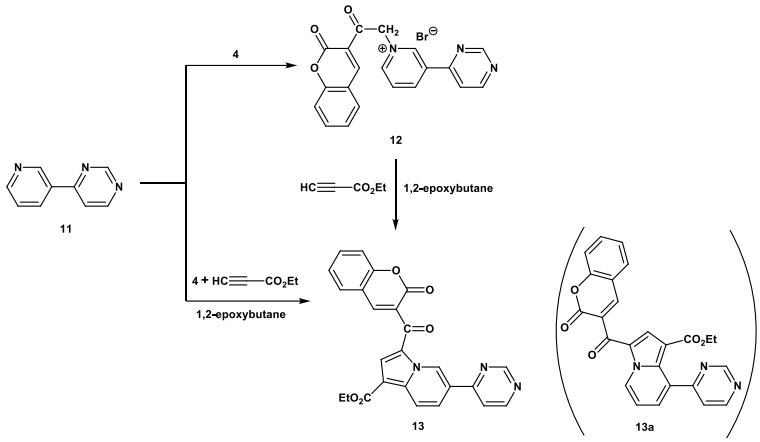
RESULTS AND DISCUSSION

Novel pyrrolo-fused heterocycles were obtained *via* 3+2 dipolar cycloaddition reactions starting from some 4-substituted pyrimidines with 3-(2-bromoacetyl)-2*H*-chromen-2-one and electron deficient alkynes such as methyl propiolate or ethyl propiolate in the presence of 1,2-epoxybutane as acid scavenger and reaction solvent. Synthetic strategies implied both classical multistep 1,3-dipolar cycloaddition reactions and the one-pot, three-component reactions of the 4-substituted pyrimidines, 3-(2-bromoacetyl)-2*H*-chromen-2-one and electron-deficient alkynes in 1,2-epoxybutane at reflux temperature. Therefore, the reactions of 4-substituted pyrimidines **1-3** with 3-(2-bromoacetyl)-2*H*-chromen-2-one (**4**) afforded the quaternary salts **5-7**. The one-pot reactions of resulted salts **5-7** with methyl propiolate or ethyl propiolate in the presence of 1,2-epoxybutane as acid scavenger and reaction solvent led directly to novel pyrrolo[1,2-*c*]pyrimidines with a 3-carbonylchreomene-2-one moiety substituted on the pyrrole rings **8-10** *via* 3+2 dipolar cycloaddition reactions of respective cycloimmonium ylides generated *in situ* from the quaternary salts **5-7** (Scheme 1). These compounds were also easily obtained *via* one-pot, three-component reactions of the 4-substituted pyrimidines **1-3**, 3-(2-bromoacetyl)-2*H*-chromen-2-one (**4**) and methyl or ethyl propiolate in 1,2-epoxybutane at reflux temperature (Scheme 1).



Scheme 1 – Synthesis of 3-carbonylchromen-2-one substituted pyrrolo[1,2-*c*]pyrimidines **8-10**.

Starting from 4-(3-pyridyl)pyrimidine (**11**) and 3-(2-bromoacetyl)-2*H*-chromen-2-one (**4**) we obtained the expected 3-(4-pyrimidinyl)pyridinium bromide **12**, the quaternization reaction taking place at the more basic nitrogen atom of pyridine. The one-pot reaction of resulted pyridinium bromide **12** with ethyl propiolate in 1,2-epoxybutane led directly to novel 6-(pyrimidin-4-yl)indolizine **13** containing a 3-carbonylchromen-2-one moiety on the pyrrole ring *via* 3+2 dipolar cycloaddition reactions of corresponding pyridinium-ylide with ethyl propiolate (Scheme 2). The reaction seems to be selective towards the indolizine **13**, the other possible indolizine (**13a**) never being separated.

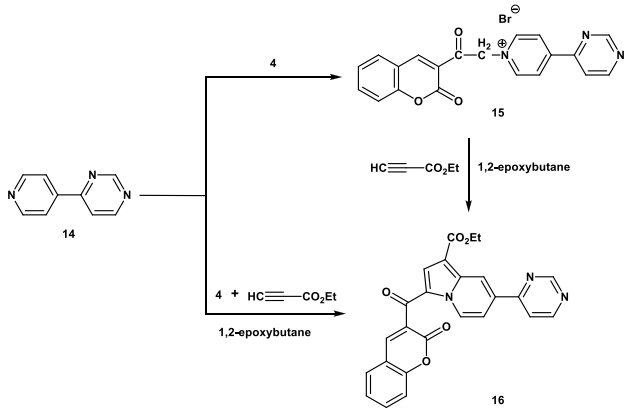


Scheme 2 – Synthesis of 3-carbonylchromen-2-one substituted indolizine **13**.

Under the same reaction conditions, the reaction of 4-(4-pyridyl)pyrimidine (**14**) with 3-(2-bromoacetyl)-2*H*-chromen-2-one (**4**) led to 4-(4-pyrimidinyl)pyridinium bromide **15**, from which the 7-(pyrimidin-4-yl)indolizine **16** with a 3-carbonylchromen-2-one on the pyrrole ring was accessed *via* 3+2 dipolar cycloaddition reaction of corresponding pyridinium-ylide with ethyl propiolate (Scheme 3).

Both indolizine derivatives **13** and **16** were also easily synthesized by the one-pot, three-components reaction of the 4-(3-pyridyl)pyrimidine **11**, 4-(4-pyridyl)pyrimidine **14**, respectively, with 3-(2-bromoacetyl)-2*H*-chromen-2-one (**4**) and ethyl propiolate in 1,2-epoxybutane at reflux temperature (Schemes 2 and 3).

The one-pot, three component synthetic procedure starting from 4-substituted pyrimidines, 3-(2-bromoacetyl)-2*H*-chromen-2-one and electron-deficient alkynes in the 1,2-epoxybutane as acid scavenger and reaction solvent led to higher yields for all synthesized azaindolizines and indolizines compared with the alternative procedure starting from the corresponding pyrimidinium salts **5** and electron deficient alkynes under the same reaction conditions. The one-pot, three component synthetic procedure has the advantages to avoid preparation and separation of pyrimidinium salts, as well as the formation of the inactivation products, tetrahydro-dipyirimido[1,2-b:4,5-b']pyrazine dimmers formed as a results of 3+3 cycloaddition reactions of highly reactive pyrimidinum *N*-ylides.[58–61]



Scheme 3 – Synthesis of 3-carbonylchromen-2-one substituted indolizine **16**.

All newly synthesized compounds were thoroughly analyzed by NMR and IR spectroscopy for chemical structure confirmation. Information about proton and proton-carbon spin systems were obtained from homo- and heteronuclear bidimensional correlation experiments. The success of *N*-quaternisation reaction was proven by the three-bond proton-carbon correlation signals between methylene group and pyrimidine/pyridine CH-1 and CH-4, observed in the H,C-HMBC spectra (exemplified in Fig. 1 for quaternary salt **5**). The chemical shifts values in both proton and carbon spectra have been unambiguously assigned in the proposed chemical structures. The quaternary salts **5–7**, **12** and **15** have well resolved proton spectra in which most of the protons resonate in the 6.0–11.0 ppm interval. Signals multiplicity together with proton-carbon correlations obtained from 2D experiments made it possible to assign each resonance to corresponding proton or carbon atom. For example, in the ^{1}H NMR spectrum of quaternary salt **5**, protons from chromen-2-one residue resonate in the interval 7.5–8.5 ppm and are readily recognized after the two triplets and two doublets with 8 Hz coupling constants. Two doublets and one singlet with chemical shifts values above 8.0 ppm characterize the 4-substituted pyrimidine ring, the two protons vicinal to nitrogen atom resonating at the lowest field (above 9.0 ppm) due to nitrogen's deshielding effect. For the furan ring protons, we assigned two doublets with 4 Hz coupling constants from 6.7 and 8.0 ppm.

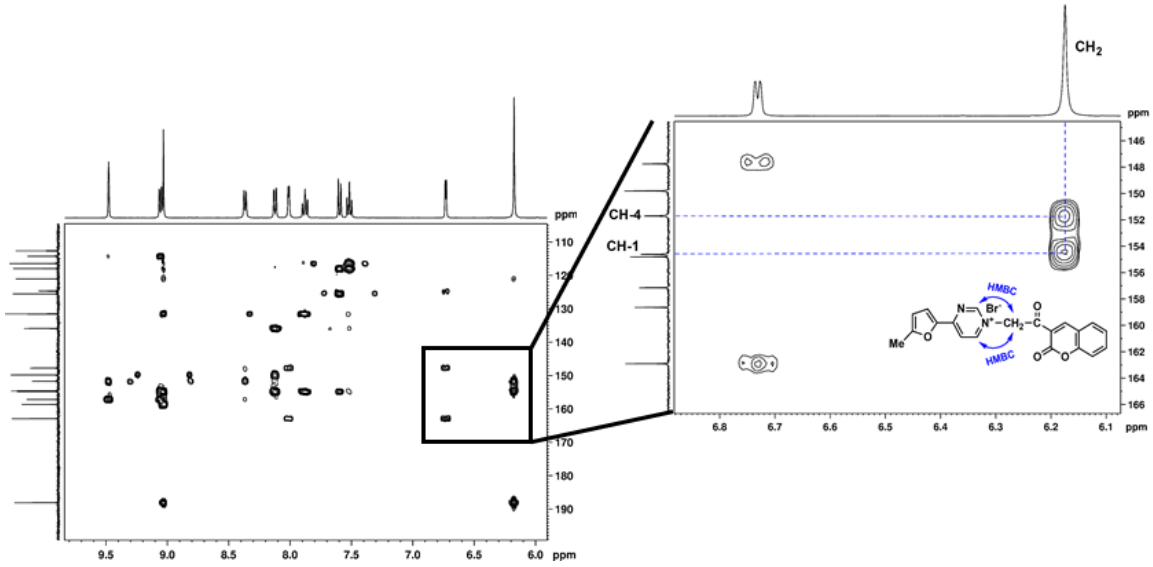


Fig. 1 – Low field region of the H,C-HMBC spectrum corresponding to quaternary salt **5** with insert showing main long-range proton-carbon correlation signals that prove the success of N-quaternisation reaction.

NMR analysis of newly synthesized azaindolizines **8-10** and indolizines **13** and **16** validate the proposed chemical structures. Compared with their quaternary salts precursors, cycloaddition products could be readily recognized in ^{1}H NMR spectra by the presence of characteristic signals for methyl (*e.g.* singlet at 4.05 ppm) or ethyl (*e.g.* triplet at 1.48 ppm and quartet at 4.49 pm) esters and disappearance of methylene signal (*e.g.* singlet at 6.20 ppm). The proton signals corresponding to pyrimidine and pyridine rings had new coupling patterns and chemical shifts values, associated with the cycloaddition-fused heterocycles. Three singlets in the low field region between 8.0-11.0 ppm characterize the newly formed azaindolizine *N*-fused heterocycle in compounds **8-10**. In the case of pyridine ring, after ethyl propiolate cycloaddition, two doublets and two singlets in the low field region support the newly formed indolizine *N*-fused heterocycle in compounds **13** and **16**.

For all newly synthesized compounds included in this study, the complete signals assignments together with specific NMR parameters are presented in the *Experimental* part.

The photophysical properties of the pyrrolopyrimidine derivatives were explored by performing absorption and fluorescence spectra, emission quantum yield and fluorescence lifetimes measurements. The electronic absorption spectra of the pyrrolopyrimidine derivatives **8** and **9** were studied in various solvents in a wide range of polarities (Table 1, Fig. 2). The pyrrolopyrimidine **8** displayed two prominent absorption bands in the

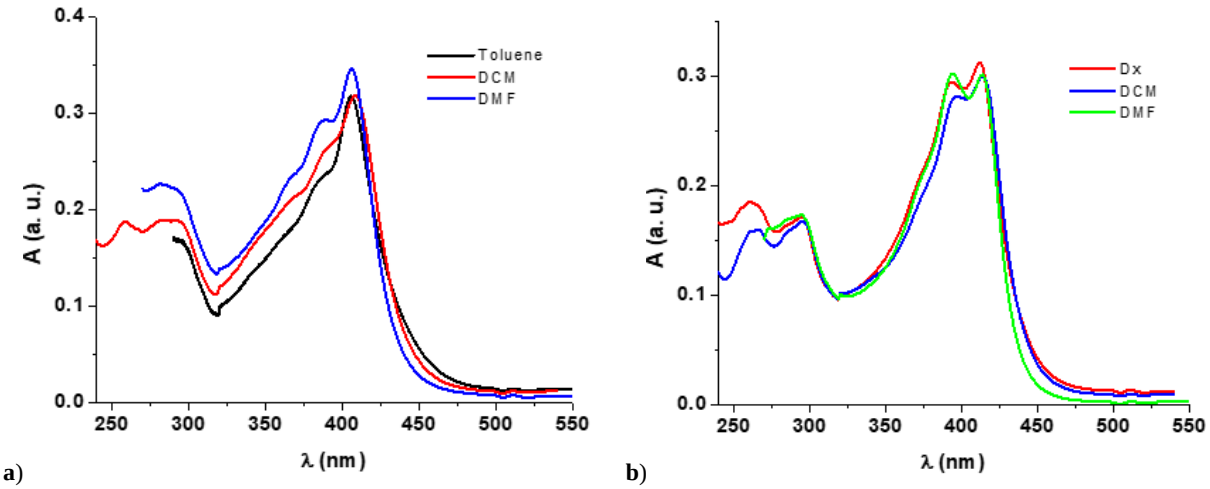
range 350–450nm and 275–325nm, respectively (Fig. 2a). According to the electronic absorption spectra shown in Fig. 2a, compound **8** exhibits an intense absorption band at 403 nm, accompanied by a shoulder around 385 nm, and an absorption band at 294 nm, in dichloromethane (DCM) (Fig. 2a). The substitution of the methyl donor group with chlorine (compound **9**) shifts to longer wavelengths the absorption maxima of **9** as compared to **8** (Fig. 2b). Compound **9** in DCM exhibits absorption maxima at 414 and 397 nm, while for compound **8** the absorption maximum is located at 409 nm.

Table 1

Spectral characteristics of pyrrolopyrimidine derivatives

Comp.	**8**				**9**		
Solvent	ε	λ_{max} (nm)	λ_{em} (nm)	Δν (cm^{-1})	λ_{max} (nm)	λ_{em} (nm)	Δν (cm^{-1})
Dioxane	2.21	403, 385sh, 281	430, 411	1558	412, 393, 294, 259	467sh, 443, 417	1699
Toluene	2.38	406, 385sh	435, 412	1642	415, 397	470sh, 445, 421	1624
$CHCl_3$	44.81	412, 390sh, 294, 258	429.5	989	416, 390sh, 297	446.5, 423	1692
DCM	8.93	409, 385sh, 293, 258	426.0	975	414, 397, 296, 261	470sh, 440, 420	1428
DMF	36.71	406, 385sh, 293	435.0	1642	414, 395, 294	470sh, 440, 420	1683
DMSO	46.68	408, 385sh, 294	437.5	1652	414, 396, 297	470sh, 447, 430	1725

sh – shoulder; DCM – dichloromethane; DMF – dimethylformamide; DMSO – dimethyl sulfoxide



a) **b**)

Fig. 2 – UV-Visible absorption spectra of pyrrolopyrimidine derivatives **8** (**a**, left) and **9** (**b**, right) in various solvents.

The fluorescence spectra of **8** present in non-polar solvents a vibrational structure that disappears in polar solvents (Fig. 3a). Thus, **8** shows violet emissions at 430 and 411 nm in dioxane, whereas in DMF (polar solvent) only one band at 435 nm was observed (Table 1). DMF solution of **9** shows blue emissions at 470 sh, 445 and 425 nm, respectively. The vibrational structure of this emission band is preserved in all solvents, regardless of the solvent polarity (Fig. 3b). The excitation wavelengths corresponding to longer wavelength maxima do not affect the shape of the emission spectra of compounds **8** and **9**, but only to some slight extent their intensities. As shown in Figs. 2 and 3 and Table 1, both the absorption spectra and emission spectra exhibited minor modifications with the solvent polarity variation. The absorption band of **8** is redshifted from 403 nm to 408 nm from dioxane to DMSO, while the emission band is also redshifted from 430 mm (dioxane) to 437.5 nm (DMSO). These insignificant changes of position with the solvent polarity suggest a non-polar ground state.[62] Given the small shifts in the absorption and emission maxima, and low Stokes shifts bellow 2 000 cm^{-1} (Table 1) these compounds did not present solvatochromic properties.

The fluorescence quantum yield values (Φ) were found to be modest in all studied solvents (Table 2). However, quite good fluorescence yield values were observed for **8** in nonpolar solvents (11.15% in toluene and 8.26% in dioxane), while smaller values in polar solvents were found (5.46% in DMF). Conversely, compound **9** exhibits the lowest values of fluorescence quantum yield ranging between 0.53 and 2.27%, regardless of the solvent polarity (Table 2). The observed behavior changes in fluorescence quantum yield of **9** as compared to **8** can be due to the electron

withdrawing effect of chlorine group leading to an increased charge separation in the excited state.[63,64]

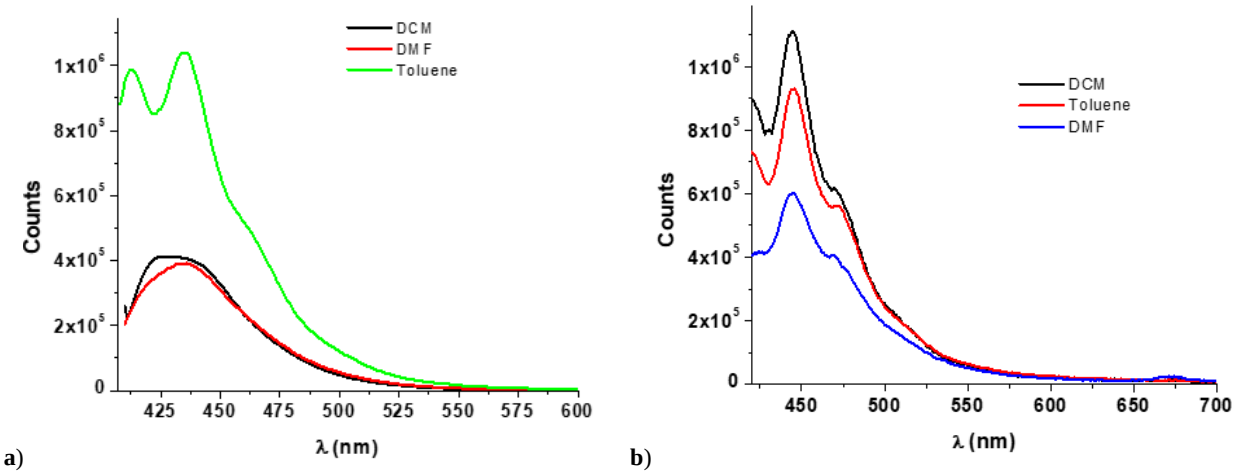


Fig. 3 – Emission spectra of pyrrolopyrimidine derivatives **8** (**a**, left) and **9** (**b**, right) in various solvents.

Table 2

Photophysical properties of pyrrolopyrimidine derivatives

Comp.	**8**			**9**		
Solvent	Φ (%)	τ (ns)	χ^2	Φ (%)	τ (ns)	χ^2
Dioxane	8.26	1.53	1.00	1.11	1.30	1.00
Toluene	11.15	1.45	1.00	0.53	1.25	1.00
Chloroform	11.33	1.44	0.99	2.27	1.08	0.99
DCM	3.63	1.54	1.00	0.67	1.15	1.00
DMF	5.46	1.64	1.00	0.82	2.07	1.00

The fluorescence decay curves require a monoexponential function to fit the experimental data (Fig. 4). The fluorescence lifetimes determined for pyrrolopyrimidine **8** is in the range 1.44–1.64 ns, while for **9** they span the range 1.08–2.07 ns (Table 2) which is characteristics for fluorescent organic compounds exhibiting significant radiative probability[65]. The values of the fluorescence lifetimes are affected in some slight extent by the solvent polarity (Table 2).

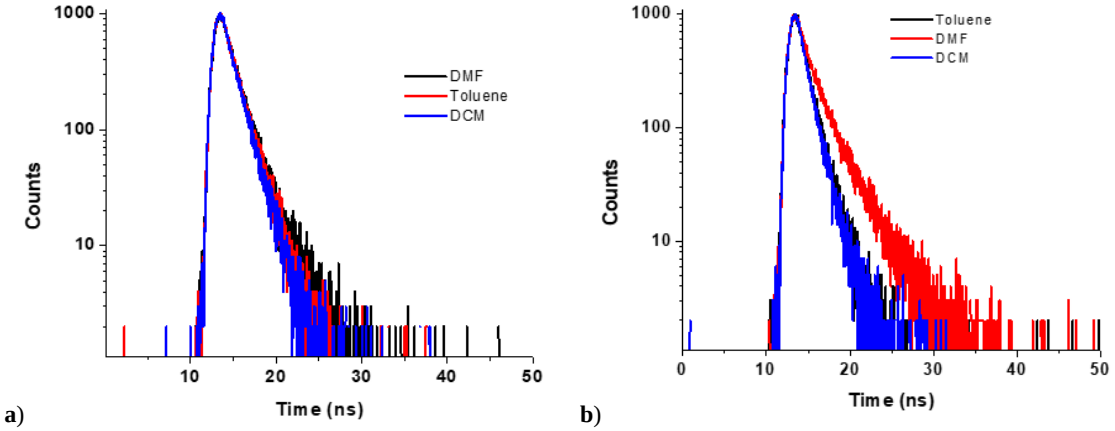


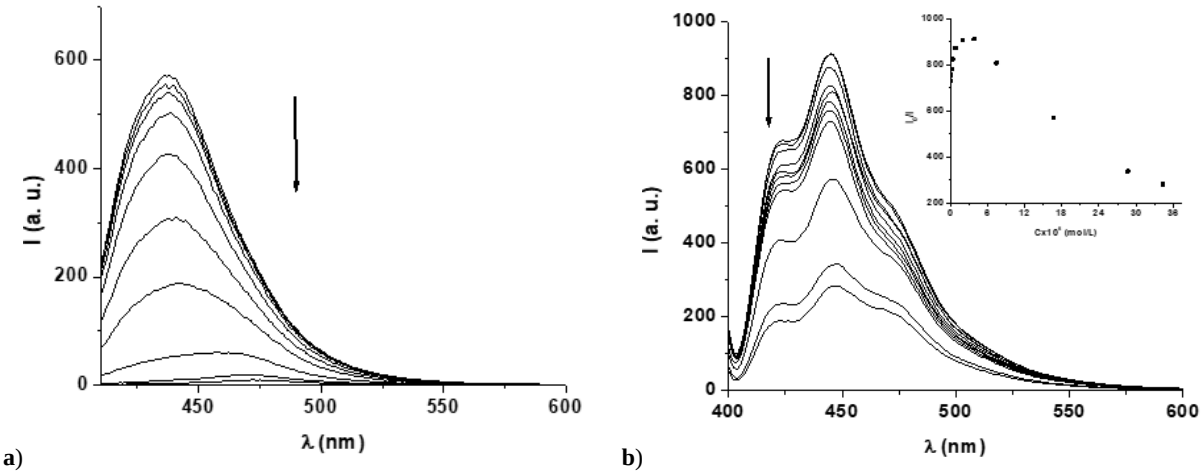
Fig. 4 – Fluorescence decay curves for pyrrolopyrimidine derivatives **8** (**a**, left) and **9** (**b**, right) in various solvents.

The sensing ability of these pyrrolopyrimidine derivatives towards picric acid (PA) was investigated using the fluorescence quenching process. In this way, fluorescence titration experiments were performed by progressive adding of the quenching agent (picric acid) in DMF and DMSO solutions of pyrrolopyrimidine derivatives. The fluorescence response of **8** and **9** toward the picric acid is illustrated in Figs. 4a and b. The emission intensity of **8** in DMSO gradually decreased with increased

amounts of picric acid (c_o = 9.73 × 10^{-4} mol/L) due to the electron transfer between them (Fig. 5a). The quenching efficiency can be expressed as:

$$(1 - I/I_o) \times 100$$

where I_o and I are the emission intensities in the absence and presence of quencher, respectively. The quenching efficiency reached a high value around 98.5% after the addition of 2.78 × 10^{-4} mol/L of PA for **8** in DMSO and 70% after the addition of 2.86 × 10^{-5} mol/L of PA in DMF for 683. Also, a high quenching efficiency was found for **9** in DMSO (95.8%, 1.6 × 10^{-4} mol/L). When **9** in DMF was titrated against picric acid initially an increase of the emission intensity of around 30% occurs. Then, a successive reduction of the intensity was observed until a conversion of 38% (Fig. 5b).



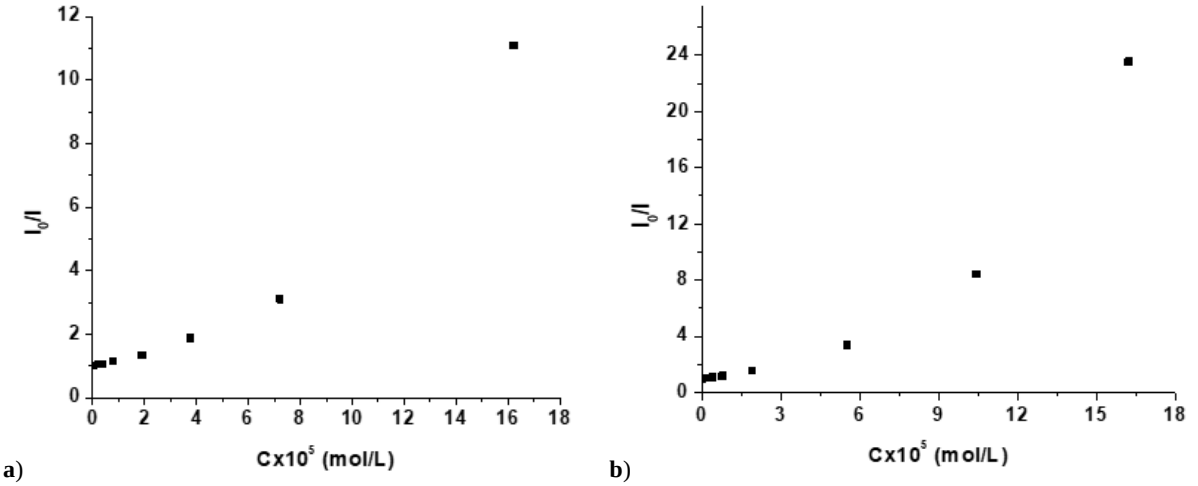
a) **b**)

Figure 5 – Changes in the emission spectra of pyrrolopyrimidine derivatives **8** upon gradual addition of picric acid in DMSO (**a**, left) and **9** (**b**, right) upon gradual addition of picric acid in DMF.

The quenching behavior was studied using the Stern-Volmer (S-V) equation:[62]

$$I_o/I = 1 + K_{SV}[Q]$$

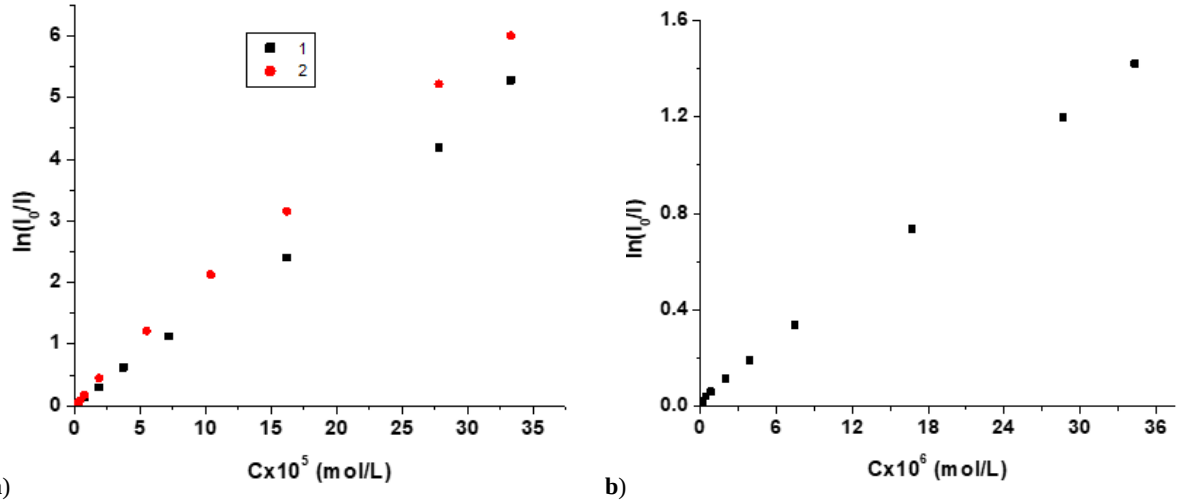
where I_o and I are the fluorescence intensities of the fluorophore in the absence and presence of quenching agent, [Q] represents the quencher concentration and K_{SV} is the Stern-Volmer constant. Typical S-V plots for the quenching process of these pyrrolopyrimidine derivatives are displayed in Fig. 6. It was observed that the S-V plots present a positive deviation from linearity at higher concentrations of picric acid indicating that the quenching process can be determined either by a static mechanism or by the combined effect of static and dynamic mechanism in the sensing process.[66-68]



a) **b**)

Fig. 6 – Stern-Volmer plots for fluorescence quenching of pyrrolopyrimidine derivatives **8** (**a**, left) and **9** (**b**, right) in DMSO.

However, the modified S-V plots as $ln(I_o/I)$ against quencher concentration are linear on the whole studied concentration range for both compounds **8** and **9** in DMSO (Fig. 7a) and for the compound **8** in DMF (Fig. 7b). This linearity of these Stern-Volmer plots indicated that the mechanism involved in the quenching process is sphere of action static model.



a) **b)**

Fig. 7 – Linear fitting plots between $ln(I_o/I)$ as a function of quencher concentration for both **8** (1) and **9** (2) in DMSO (**a**, left) and for **8** in DMF (**b**, right).

EXPERIMENTAL

Melting points were measured using a Boetius hot plate microscope.

The NMR spectra have been performed on either Varian Gemini 300 MHz or Bruker Avance NEO 400 and 600 MHz spectrometers, at room temperature. The newly synthesized compounds were soluble in DMSO-d_6 (quaternary salts) and $CDCl_3$ with TFA (cycloaddition products), chemical shifts values being reported relative to solvents residual signals. Unambiguous signals assignments in proton and carbon spectra were based on information obtained from homo- and heteronuclear bidimensional correlation experiments like COSY, HETCOR, HSQC and HMBC.

Fourier-transform IR spectra were recorded on a Bruker Vertex 70 spectrometer equipped with diamond crystal ATR accessory, on a spectral window ranging from 4000 to 400 cm^{-1} or on a Nicolet Impact 410 in KBr pellets.

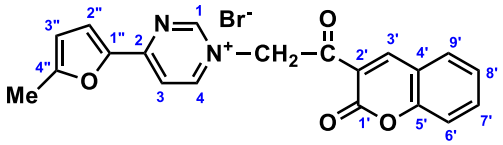
Elemental analysis was performed on a COSTECH Instruments EAS32 apparatus and the results were found to be in good agreement (± 0.3%) with the calculated values.

All starting materials and solvents were purchased from common commercial suppliers and were used without purification unless otherwise noted.

UV-Vis absorption spectra and fluorescence spectra were obtained using a SPECORD210Plus spectrometer (Analityk Jena, Germany) and Perkin Elmer LS55 luminescence spectrometer or an Edinburgh FS5 spectrometer, respectively, in rectangular 10 mm path length quartz cuvettes, at room temperature. The emission spectra were recorded on solutions having absorbance values lower than 0.1. The time resolved photoluminescence measurements were performed on a FLS980 spectrometer (Edinburgh Instruments) using time-correlation single photon counting (TCSPC) technique in 10 mm path length quartz cuvettes, equipped with a nanosecond diode laser for excitation with 405 nm wavelength. The experimental emission decay was fitted with a single function $I(t) = ae^{-t/\tau}$, where $I(t)$ is the fluorescence emission at time t, a and τ represent the pre-exponential factor and the decay time, respectively. The fitting quality was verified by calculated reduced chi-squared values (χ^2) close to 1 and the weight residual variance. The quantum yields were determined by FLS980 integration sphere accessory, using dilute solutions ($A < 0.1$) at excitation wavelengths corresponding to the absorption band maxima. The solvents for spectroscopy were purchased from Sigma Aldrich or Merck.

General procedure for obtaining quaternary salts. A solution of 4-substituted pyrimidine **1-3**, **11** and **14** (10 mmol) and 3-(2-bromoacetyl)-2*H*-chromen-2-one (2.67 g, 10 mmol) in 50 ml acetone was heated at reflux temperature for 30 min and subsequently left at room temperature for 24 h. The solid was filtered and washed on filter with acetone to obtain the corresponding salts **5-7**, **12**, and **15**.

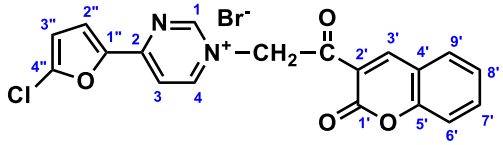
4-(5-Methylfuran-2-yl)-1-[2-oxo-2-(2-oxo-2H-chromen-3-yl) ethyl]pyrimidin-1-ium bromide (**5**)



Yellow crystals (3.98 g, 93%), mp 223-225°C. Anal. Calcd. for $C_{20}H_{15}BrN_2O_4$ (427.25): N, 6.56%. Found N, 6.82%. FT-IR (KBr, cm^{-1}): 3119, 3049, 1731, 1696, 1634, 1605, 1558, 1510, 1433, 1311, 1174. ^{1}H NMR (400.1 MHz, DMSO-d_6, δ (ppm)): 2.54 (3H, s, CH_3), 6.18 (2H, s, CH_2), 6.73 (1H, d, J = 4 Hz, H-3"), 7.52 (1H, t, J = 8 Hz, H-8'), 7.60 (1H, d, J = 8 Hz, H-6'), 7.88 (1H, t, J = 8 Hz, H-7'), 8.01 (1H, d, J = 4 Hz, H-2"), 8.12 (1H, d, J = 8 Hz, H-9'), 8.37 (1H, d, J = 7 Hz, H-3), 9.03 (1H, s, H-3'), 9.06 (1H, d, J = 7 Hz, H-4), 9.48 (1H, s, H-1). ^{13}C NMR (100.6 MHz, DMSO-d_6, δ (ppm)): 14.1 (CH_3), 64.7 (CH_2), 112.6 (CH-3"), 114.2 (CH-3), 116.4 (CH-6'), 117.9 (C-4'),

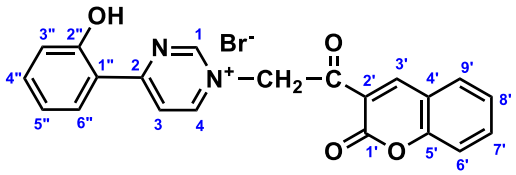
121.0 (C-2'), 124.7 (CH-2"), 125.5 (CH-8'), 131.5 (CH-9'), 135.9 (CH-7'), 147.8 (C-1"), 149.8 (CH-3'), 151.7 (CH-4), 154.6 (CH-1), 154.8 (C-5'), 157.2 (C-2), 158.6 (CO-1'), 162.9 (C-4"), 188.1 (CO).

4-(5-Chlorofuran-2-yl)-1-[2-oxo-2-(2-oxo-2H-chromen-3-yl) ethyl]yrimidin-1-ium bromide (**6**)



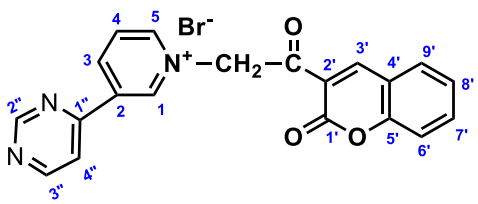
Brown crystals (3.94 g, 88%), mp 198-200°C. Anal. Calcd. for $C_{19}H_{12}BrClN_2O_4$ (447.67): N, 6.26. Found N, 6.58%. FT-IR (KBr, cm^{-1}): 3380, 3118, 3050, 1718, 1638, 1634, 1603, 1557, 1445, 1198. ^{1}H NMR (400.1 MHz, DMSO-d_6, δ (ppm)): 6.22 (2H, s, CH_2), 7.52 (1H, t, *J* = 8 Hz, H-8'), 7.59 (1H, d, *J* = 4 Hz, H-3"), 7.60 (1H, d, *J* = 8 Hz, H-6'), 7.88 (1H, t, *J* = 8 Hz, H-7'), 8.13 (1H, d, *J* = 8 Hz, H-9'), 8.51 (1H, d, *J* = 4 Hz, H-2"), 8.83 (1H, d, *J* = 7 Hz, H-3), 9.03 (1H, s, H-3'), 9.23 (1H, d, *J* = 7 Hz, H-4), 9.57 (1H, s, H-1). ^{13}C NMR (100.6 MHz, DMSO-d_6, δ (ppm)): 64.9 (CH_2), 115.7 (CH-3), 116.4 (CH-6'), 117.9 (C-4'), 120.9 (C-2'), 125.5 (CH-8'), 131.1 (CH-3"), 131.6 (CH-9'), 135.9 (CH-7'), 136.3 (CH-2"), 137.5 (C-1"), 141.3 (C-4"), 149.9 (CH-3'), 152.1 (CH-4), 154.7 (CH-1), 154.8 (C-5'), 158.6 (CO-1'), 162.2 (C-2), 187.7 (CO).

4-(2-Hydroxyphenyl)-1-[2-oxo-2-(2-oxo-2H-chromen-3-yl)ethyl]pyrimidin-1-ium bromide (**7**)



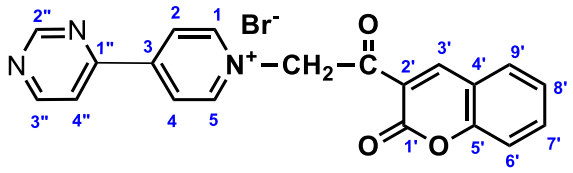
Yellow crystals (3.73 g, 85%), mp 254-256°C. Anal. Calcd. for $C_{21}H_{15}N_2BrO_4$ (439.26): C, 57.42; H, 3.44; N, 6.38. Found N, 6.70%. FT-IR (KBr, cm^{-1}): 3078, 3024, 1718, 1636, 1605, 1559, 1443, 1194. ^{1}H NMR (600.1 MHz, DMSO-d_6, δ (ppm)): 6.26 (2H, s, CH_2), 7.11 (1H, t, *J* = 8 Hz, H-5"), 7.19 (1H, d, *J* = 8 Hz, H-3"), 7.52 (1H, t, *J* = 8 Hz, H-8'), 7.59-7.62 (2H, m, H-6' and H-4"), 7.88 (1H, t, *J* = 8 Hz, H-7'), 8.12 (1H, d, *J* = 8 Hz, H-9'), 8.32 (1H, d, *J* = 8 Hz, H-6"), 9.01 (1H, d, *J* = 7 Hz, H-3), 9.03 (1H, s, H-3'), 9.15 (1H, d, *J* = 7 Hz, H-4), 9.65 (1H, s, H-1), 11.60 (1H, s, OH). ^{13}C NMR (150.9 MHz, DMSO-d_6, δ (ppm)): 65.0 (CH_2), 116.4 (CH-6'), 117.7 (CH-3"), 117.9 (C-4'), 119.4 (C-1"), 120.2 (CH-5"), 120.7 (CH-3), 121.1 (C-2'), 125.5 (CH-8'), 131.2 (CH-6"), 131.6 (CH-9'), 135.9 (CH-7'), 136.4 (CH-4"), 149.8 (CH-3'), 152.1 (CH-1), 153.6 (CH-1), 154.8 (C-5'), 158.7 (CO-1'), 159.9 (C-2"), 167.7 (C-2), 187.9 (CO).

1-[2-Oxo-2-(2-oxo-2H-chromen-3-yl)ethyl]-3-(pyrimidin-4-yl)pyridin-1-ium bromide (**12**)



Purple crystals (3.48, 82%), mp 227-230°C. Anal. Calcd. for $C_{20}H_{14}BrN_3O_3$ (424.25): N, 9.90%. Found N, 10.07%. FT-IR (KBr, cm^{-1}): 3089, 3026, 1721, 1696, 1610, 1572, 1465, 1189, 1103. ^{1}H-NMR (300 MHz, DMSO-d_6, δ (ppm)): 6.50 (2H, s, CH_2), 7.49 (1H, t, *J* = 8 Hz, H-8'), 7.57 (1H, d, *J* = 8 Hz, H-6'), 7.86 (1H, t, *J* = 8 Hz, H-7'), 8.10 (1H, d, *J* = 8 Hz, H-9'), 8.40 (1H, d, *J* = 5 Hz, H-4"), 8.48 (1H, t, *J* = 7 Hz, H-4), 9.01 (1H, s, H-3'), 9.13 (1H, d, *J* = 5 Hz, H-3"), 9.19 (1H, d, *J* = 7 Hz, H-5), 9.42 (1H, d, *J* = 7 Hz, H-3), 9.47 (1H, s, H-2"), 9.94 (1H, s, H-1). ^{13}C-NMR (75 MHz, DMSO-d_6, δ (ppm)): 69.3 (CH_2), 116.5 (CH-6'), 118.0 (C-4'), 118.5 (CH-4"), 121.2 (C-2'), 125.6 (CH-8') 128.0 (CH-4), 131.6 (CH-9'), 135.5 (C-2), 135.9 (CH-7'), 143.9 (CH-3), 145.3 (CH-5), 147.6 (CH-1), 149.7 (CH-3'), 154.8 (C-5'), 156.9 (C-1"), 158.6 (CO-1'), 159.0 (CH-2"), 159.4 (CH-3") 187.9 (CO).

1-[2-Oxo-2-(2-oxo-2H-chromen-3-yl)ethyl]-4-(pyrimidin-4-yl)pyridin-1-ium bromide (**15**)



Brown crystals (3.78 g, 89%), mp 188–190°C (dec.). Anal. Calcd. for $C_{20}H_{14}BrN_3O_3$ (424.25): N, 9.90%. Found N, 10.14%. FT-IR (KBr, cm^{-1}): 3094, 3028, 1725, 1692, 1607, 1570, 1488, 1202. 1194, 1109. ^{1}H NMR (400.1 MHz, DMSO-d_6, δ (ppm)): 6.42 (2H, s, CH_2), 7.52 (1H, td, *J* = 8 Hz, 1 Hz, H-8'), 7.61 (1H, d, *J* = 8 Hz, H-6'), 7.89 (1H, td, *J* = 8 Hz, 2 Hz, H-7'), 8.12 (1H, dd, *J* = 8 Hz, 2 Hz, H-9'), 8.55 (1H, dd, *J* = 5 Hz, 1 Hz, H-4"), 9.01 (2H, d, *J* = 7 Hz, H-2), 9.03 (1H, s, H-3'), 9.18 (2H, d, *J* = 7 Hz, H-1), 9.24 (1H, d, *J* = 5 Hz, H-3"), 9.55 (1H, d, *J* = 1 Hz, H-2").

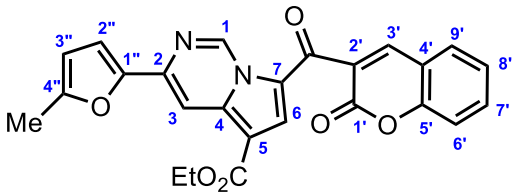
^{13}C NMR (100.6 MHz, DMSO-d_6, δ (ppm)): 68.8 (CH_2), 116.4 (CH-6'), 117.9 (C-4'), 119.8 (CH-4"), 121.1 (C-2'), 124.9 (CH-2), 125.5 (CH-8'), 131.6 (CH-9'), 135.9 (CH-7'), 147.2 (CH-1), 149.7 (CH-3'), 151.4 (C-3), 154.8 (C-5'), 157.0 (C-1"), 158.6 (CO-1'), 159.3 (CH-2"), 159.8 (CH-3"), 187.9 (CO).

General procedure for obtaining the 3-carbonylchromen-2-one substituted indolizines and azaindolizines from corresponding quaternary salts (A). A mixture of 5 mmol quaternary salt **5-7**, **12**, or **15** and 7 mmol methyl propiolate or ethyl propiolate in 60 ml 1,2-epoxybutane was heated at reflux temperature for 20 h. The solvent was partly removed under vacuum, 10 ml of MeOH was added and the mixture was left overnight at room temperature. The solid formed was filtered, washed on the filter with a mixture of MeOH/Et_2O 1:1 and crystallized from $CHCl_3$/MeOH.

General one-pot three components procedure for synthesis of 3-carbonylchromen-2-one substituted indolizines and azaindolizines (B). A mixture of 5 mmol of 4-substituted pyrimidine **1-3**, **11**, or **14**, 1.34 g (5 mmol) of 3-(2-bromoacetyl)-2*H*-chromen-2-one, and 7 mmol of methyl propiolate or ethyl propiolate in 60 ml 1,2-epoxybutane was heated at reflux temperature for 20 h. The solvent was partly removed under vacuum, 15 ml of MeOH was added and the mixture was left overnight at room temperature. The solid formed was filtered, washed on the filter

with a mixture of MeOH/Et_2O 1:1 and crystallized from $CHCl_3$/MeOH.

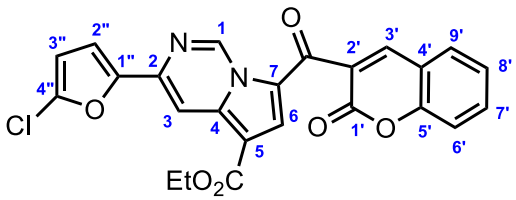
Ethyl 3-(5-methylfuran-2-yl)-7-(2-oxo-2H-chromene-3-carbonyl)pyrrolo[1,2-c]pyrimidine-5-carboxylate (**8**)



Yellow crystals, mp 260–263°C. Yield: 1.40 g, 62% (A); 1.51 g, 68% (B). Anal. Calcd. for $C_{25}H_{18}N_2O_6$ (442.42): C, 67.87; H, 4.10; N, 6.33%. Found C, 68.11; H, 4.34; N, 6.61%. FT-IR (KBr, cm^{-1}): 3111, 2985, 2924, 1724, 1618, 1559, 1524, 1464, 1340, 1245, 1206, 1116. ^{1}H NMR (400.1 MHz, $CDCl_3$+TFA, δ (ppm)): 1.47 (3H, t, *J* = 7 Hz, CH_3-Et), 2.47 (3H, s, CH_3), 4.50 (2H, q, *J* = 7 Hz, CH_2-Et), 6.33 (1H, d, *J* = 3 Hz, H-3"), 7.33 (1H, d, *J* = 3 Hz, H-2"), 7.49 (1H, t, *J* = 8 Hz, H-8'), 7.51 (1H, d, *J* = 8 Hz, H-6'), 7.75 (1H, d, *J* = 8 Hz, H-9'), 7.79 (1H, t, *J* = 8 Hz, H-7'), 8.26 (1H, s, H-6), 8.37 (1H, s, H-3'), 8.51 (1H, s, H-3), 11.03 (1H, s, H-1). ^{13}C NMR (100.6 MHz, $CDCl_3$+TFA, δ (ppm)): 13.8 (CH_3), 14.0 (CH_3-Et), 62.6 (CH_2-Et), 106.6 (CH-3), 109.3 (C-5), 110.7 (CH-3"), 116.7 (CH-2"), 117.2 (CH-6'), 118.0 (C-4'), 123.4 (C-7), 124.5 (C-2'), 126.2 (CH-8'), 130.0 (CH-9'), 133.9 (CH-6), 135.3 (CH-7'), 137.4 (C-2), 141.0 (C-4), 143.3 (CH-1), 144.9 (C-1"), 148.1 (CH-3'), 154.3 (C-5'), 158.7 (C-4"), 160.9 (CO-1'), 164.1 (COO), 179.8 (CO).

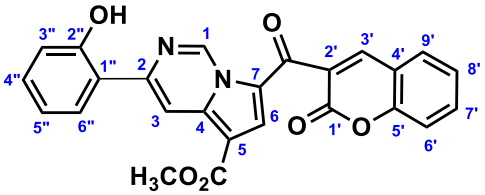
IR (KBr, cm^{-1}): 3111, 2985, 2924, 1724, 1618, 1559, 1524, 1464, 1340, 1245, 1206, 1116.

Ethyl 3-(5-chlorofuran-2-yl)-7-(2-oxo-2H-chromene-3-carbonyl)pyrrolo[1,2-c]pyrimidine-5-carboxylate (**9**)



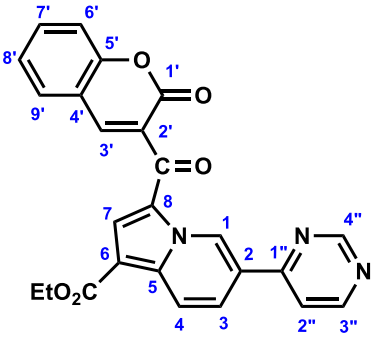
Mustard crystals, mp 316-319°C. Yield: 1.36 g, 59% (A); 1.48 g, 64% (B). Anal. Calcd. for $C_{24}H_{15}ClN_2O_6$ (462.84): C, 62.28; H, 3.27; N, 6.07%. Found C, 62.56; H, 3.34; N, 6.31%. FT-IR (KBr, cm^{-1}): 3090, 2986, 2915, 1724, 1616, 1554, 1526, 1475, 1426, 1357, 1329, 1251, 1209, 1115. ^{1}H NMR (400.1 MHz, $CDCl_3$+TFA, δ (ppm)): 1.48 (3H, t, *J* = 7 Hz, CH_3-Et), 4.49 (2H, q, *J* = 7 Hz, CH_2-Et), 7.07 (1H, d, *J* = 4 Hz, H-3"), 7.49 (1H, t, *J* = 8 Hz, H-8'), 7.51 (1H, d, *J* = 8 Hz, H-6'), 7.66 (1H, d, *J* = 3 Hz, H-2"), 7.75 (1H, d, *J* = 8 Hz, H-9'), 7.80 (1H, t, *J* = 8 Hz, H-7'), 8.20 (1H, s, H-6), 8.36 (1H, s, H-3'), 8.38 (1H, s, H-3), 10.76 (1H, s, H-1). ^{13}C NMR (100.6 MHz, $CDCl_3$+TFA, δ (ppm)): 14.0 (CH_3-Et), 62.6 (CH_2-Et), 107.7 (CH-3), 108.7 (C-5), 117.2 (CH-6'), 117.9 (C-4'), 122.9 (C-7), 124.5 (C-2'), 126.2 (CH-8'), 128.1 (CH-2"), 128.7 (CH-3"), 129.9 (CH-9'), 133.4 (CH-6), 135.3 (CH-7'), 136.4 (C-1"), 137.2 (C-4"), 141.6 (C-4), 142.6 (CH-1), 144.7 (C-2), 147.8 (CH-3'), 154.2 (C-5'), 161.5 (CO-1'), 164.8 (COO), 179.9 (CO).

Methyl 3-(2-hydroxyphenyl)-7-(2-oxo-2H-chromene-3-carbonyl)pyrrolo[1,2-c]pyrimidine-5-carboxylate (**10**)



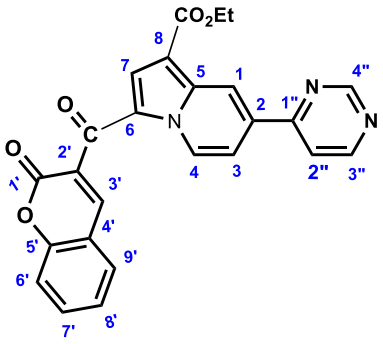
Orange crystals, mp 314-316 °C. Yield: 1.34 g, 61% (A); 1.49 g, 67% (B). Anal. Calcd. for $C_{25}H_{16}N_2O_6$ (440.40): C, 68.18; H, 3.66; N, 6.36%. Found C, 68.40; H, 3.44; N, 6.77%. FT-IR (KBr, cm^{-1}): 3080, 3019, 1723, 1624, 1606, 1520, 1453, 1354, 1230, 1207, 1110. ^{1}H NMR (600.1 MHz, $CDCl_3$+TFA, δ (ppm)): 4.05 (3H, s, CH_3), 7.13 (1H, d, *J* = 7 Hz, H-3"), 7.15 (1H, t, *J* = 7 Hz, H-5"), 7.48-7.53 (3H, m, H-6', H-8' and H-4"), 7.76 (1H, d, *J* = 7 Hz, H-9'), 7.81 (1H, t, *J* = 7 Hz, H-7'), 7.90 (1H, d, *J* = 7 Hz, H-6"), 8.32 (1H, s, H-6), 8.40 (1H, s, H-3'), 8.79 (1H, s, H-3), 11.00 (1H, s, H-1). ^{13}C NMR (150.9 MHz, $CDCl_3$+TFA, δ (ppm)): 53.1 (CH_3), 109.2 (C-5), 109.5 (CH-3), 115.7 (C-1"), 117.2 (CH-6'), 117.9 (C-4'), 118.6 (CH-3"), 121.9 (CH-5"), 123.2 (C-7), 124.4 (C-2'), 126.3 (CH-8'), 127.6 (CH-6"), 130.0 (CH-9'), 133.7 (CH-6), 134.6 (CH-4"), 135.4 (CH-7'), 140.8 (C-4), 141.4 (CH-1), 146.6 (C-2), 148.3 (CH-3'), 154.4 (C-5'), 156.4 (C-2"), 161.5 (CO-1'), 164.4 (COO), 180.1 (CO).

Ethyl 3-(2-oxo-2H-chromene-3-carbonyl)-6-(pyrimidin-4-yl)indolizine-1-carboxylate (**13**)



Beige crystals, mp 300–304°C. Yield: 1.15 g, 52% (A); 1.38 g, 63% (B). Anal. Calcd. for $C_{25}H_{17}N_3O_5$ (439.42): C, 68.33; H, 3.90; N, 9.56%. Found C, 68.12; H, 4.11; N, 9.78%. FT-IR (KBr, cm^{-1}): 3112, 2996, 2942, 1726, 1696, 1622, 1610, 1578, 1484, 1465, 1370, 1267, 1229, 1194, 1109, 1053. ^{1}H NMR (600.1 MHz, $CDCl_3$+TFA, δ (ppm)): 1.49 (3H, t, *J* = 7 Hz, CH_3-Et), 4.51 (2H, q, *J* = 7 Hz, CH_2-Et), 7.51 (1H, t, *J* = 7 Hz, H-8'), 7.53 (1H, d, *J* = 7 Hz, H-6'), 7.76 (1H, d, *J* = 7 Hz, H-9'), 7.81 (1H, t, *J* = 7 Hz, H-7'), 8.28 (1H, s, H-7), 8.33 (1H, s, H-3'), 8.45 (1H, dd, *J* = 10 Hz, 1 Hz, H-3), 8.59-8.60 (2H, m, H-4 and H-2"), 9.25 (1H, d, *J* = 7 Hz, H-3"), 9.66 (1H, s, H-4"), 11.05 (1H, s, H-1). ^{13}C NMR (150.9 MHz, $CDCl_3$+TFA, δ (ppm)): 14.1 (CH_3), 62.7 (CH_2), 109.3 (C-6), 117.3 (CH-6'), 117.9 (C-4'), 118.0 (CH-2"), 120.9 (CH-4), 123.3 (C-2), 123.6 (C-8), 124.7 (C-2'), 126.2 (CH-8'), 127.1 (CH-3), 129.9 (CH-9'), 133.2 (CH-7 and CH-1), 135.2 (CH-7'), 141.6 (C-5), 147.1 (CH-3'), 149.2 (CH-3"), 151.6 (CH-4"), 154.2 (C-5'), 161.5 (CO-1'), 164.9 (COO), 168.9 (C-1"), 180.7 (CO).

Ethyl 3-(2-oxo-2H-chromene-3-carbonyl)-7-(pyrimidin-4-yl)indolizine-1-carboxylate (**16**)



Beige crystals, mp 316-319°C. Yield: 1.24 g, 56% (A); 1.45 g, 66% (B). Anal. Calcd. for $C_{25}H_{17}N_3O_5$ (439.42): C, 68.33; H, 3.90; N, 9.56%. Found C, 68.61; H, 4.18; N, 9.82%. FT-IR (KBr, cm^{-1}): 3128, 2982, 1727, 1689, 1628, 1607, 1573, 1526, 1480, 1362, 1370, 1203, 1105, 1059. ^{1}H-NMR (300 MHz, $CDCl_3$+TFA, δ (ppm)):1.47 (3H, t, *J* = 7.1 Hz, CH_3), 4.49 (2H, q, *J* = 7 Hz, CH_2), 7.48-7.54 (2H, m, H-6' and H-8'), 7.74-7.83 (2H, m, H-7' and H-9'), 8.10 (1H, dd, *J* = 7 Hz, 2 Hz, H-3), 8.16 (1H, s, H-7), 8.34 (1H, s, H-3'), 8.68 (1H, d, *J* = 7 Hz, H-4), 9.28 (1H, d, *J* = 7 Hz, H-2"), 9.46 (1H, d, *J* = 2 Hz, H-1), 9.67 (1H, d, *J* = 7 Hz, H-3"), 10.06 (1H, s, H-5). ^{13}C-NMR (7 MHz, $CDCl_3$+TFA, δ (ppm)): 14.1 (CH_3), 62.8 (CH_2), 110.2 (C-8), 111.3 (CH-1), 114.1 (CH-6'), 118.0 (C-4'), 119.0 (CH-2"), 122.0 (CH-3), 124.1 (C-2), 125.2 (CH-4), 126.4 (C-2'), 128.7 (C-6), 130.1 (CH-8'), 130.7 (CH-7), 131.2 (CH-9'), 135.3 (CH-7'), 139.8 (C-5), 147.5 (CH-3'), 149.5 (CH-3"), 151.7 (CH-4"), 154.4 (C-5'), 161.6 (CO-1'), 165.2 (COO), 169.2 (C-1"), 181.0 (CO).

CONCLUSIONS

Novel indolizine and pyrrolo[1,2-*c*]pyrimidine compounds with a 3-carbonylchromen-2-one moiety on pyrrole rings were synthesized via 3+2 dipolar cycloaddition reactions of cycloimmonium-ylides, generated in situ from the corresponding quaternary salts of several 4-subsituted pyrimidines such as 4-(5-methylfuran-2-yl)pyrimidine, 4-(5-chlorofuran-2-yl)pyrimidine, 4-(2-hydroxyphenyl)pyrimidine, 4-(3-pyridyl)pyrimidine and 4-(4-pyridyl)pyrimidine with 3-(2-bromoacetyl)-2*H*-chromen-2-one and methyl or ethyl propiolate. Synthetic strategies involved both the one-pot, three-component reactions of the *N*-heterocycle, 3-(2-bromoacetyl)-2*H*-chromen-2-one and electron-deficient alkynes in 1,2-epoxybutane at reflux temperature and classical multistep 3+2 dipolar cycloaddition reactions. All structures have been fully characterized by IR, ^{1}H and ^{13}C NMR. The fluorescence decay was fitted to a monoexponential curve with fluorescence lifetimes between 1.08–2.07 ns. The modified Stern-Volmer plots are linear suggesting that the quenching mechanism is based on the sphere action static model. The ability of these pyrrolopyrimidine derivatives to sense the picric acid was proved by the significant quenching of the emission intensity.

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