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Cyanoacetylazoles and salicylic aldehydes promoting the synthesis of new trifluoromethyl-substituted azolecarbonyl-2*H*-chromen-2-ones through the Knoevenagel condensation reaction

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ABSTRACT

The results of the chemical behavior of three substituted cyanoacetylazoles and some salicylic aldehydes used to obtain new trifluoromethylated azolecarbonyl-2*H*-chromen-2-ones through Knoevenagel condensation reactions, are reported. First, a new series of four 3-(5-hydroxy-3-methyl-5-trifluoromethyl-4,5-dihydro-1*H*-pyrazole-1-carbonyl)-2-imino-2*H*-chromenes were efficiently synthesized, in yields of 50–78%, using 0.4 M NaOH/EtOH as the catalyst. They were then subjected to an acid hydrolysis reaction, which produced the respective trifluoromethyl-substituted pyrazolinecarbonyl coumarins in good yields (80–91%). In order to study the influence of the CF_3 substituent, reactions involving 1-cyanoacetyl-3,5-dimethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazole were also performed, but they did not provide the desired coumarins. On the other hand, attempts to synthesize some pyrrolecarbonyl coumarins not containing trifluoromethyl groups, but using the same methodology, directly resulted in a new series of five 3-(1-methyl-1*H*-pyrrol-2-carbonyl)-2*H*-chromen-2-ones in good yields (40–60%).

1. Introduction

2*H*-Chromen-2-one derivatives (coumarins or benzo [*b*] pyrones) are found in several plant species in nature. Coumarins are a class of secondary metabolites widely distributed in the plant kingdom and can also be found in fungi and bacteria [1]. These kinds of compounds have a large range of applications in the food, cosmetic and perfume industries, as well as a major role in technological advances. Coumarins have been studied by many research groups and reported as biological agents with anticoagulant, antibacterial, antifungal, antibiotic, anti-inflammatory, antidepressant, and antimalarial activities, among other things [2–6]. Coumarins are part of an important class of fluorescent and laser dyes and are used for synthesizing brighteners and fluorescent labels, as well as in probes for measuring physiological [7–9], organic nonlinear optical materials, and they are widely used in the emission layers of organic light-emitting diodes (OLED) [10–31]. Their photophysical and spectroscopic properties can be easily modified by the introduction of substituents into the coumarin ring, giving them more flexibility to adapt well to various applications [17,32–34].

Different substituted coumarin derivatives can be obtained by several synthetic methods. In the field of synthetic organic chemistry, salicylic aldehydes have been used as substrates in organic synthesis in order to obtain coumarins. Despite all the interesting uses of coumarins, a brief review of the literature has shown that the synthesis of more complex heterocyclic compounds (e.g., those containing a benzo [*b*] pyrone moiety associated to a pyrazole or a pyrrole nucleus and both linked to a carbonyl function) has been little explored, but coumarin systems directly related to pyrazoles and pyrroles without a carbonyl spacer are commonly found in the literature [18,35,36].

On the other hand, a very important substituent in medicinal chemistry is the trifluoromethyl group [37], due to its stereoelectronic properties and increase in molecular lipophilicity [38–45]. Thus, the introduction of trifluoromethyl groups into bioactive molecules has become very important in pharmaceutical studies [46–48], stimulating work directed towards the elaboration of synthetic methodology for compounds containing these groups. Due to all these factors, organofluorine chemistry has been vigorously developing over the past two decades [49–57]. Our research group and a few others around the world have been studying the synthetic potential of β-alkoxyvinyl trifluoromethyl

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ketones for obtaining new trifluoromethylated heterocycles, as well as other molecules that could provide chemical derivatizations, thus leading to substances, or the substances structural analogues, with proven applications [54–57].

Among the various classes of known heterocycles, pyrazoles and their derivatives possess a diversity of functional groups and they have attracted a great deal of interest because of their wide range of pharmacological properties [58–63]. In recent years we have performed the syntheses of some tosylpyrazoles containing the CF_3 group. The syntheses showed good results for pathological pain in comparison with the drug Celecoxib [64]. Also, in 2006 the biological activities of pyrazoles containing the CF_3 group were explored [65]. A series of pyrazolyl-quinolines were synthesized and biological assays showed antimalarial activity stronger than chloroquine, which is one of the drugs commonly prescribed for malaria. Taking into consideration recently developed works, we confirm the importance of the study of new pyrazoles containing the CF_3 group due to their wide range of pharmacological properties [66,67,45,68,69].

On the other hand, it is also reported in the literature some computational and experimental approaches that can estimate the permeability and solubility of organic compounds. One such approach would be the study reported as the Lipinski rules of five [70]. This rule predicts that the bad absorption or permeation is more likely when the compounds have more than five H-bonds donors, ten H-bonds acceptors, the molecular weight of the compounds is higher than 500 g/mol and when a calculated log P (ClogP) is greater than 5. This study has recently been applied to many compounds containing the trifluoromethyl group to predict the performance of these in the organism [71–73].

In this context, and aiming for the synthesis of new trifluoromethyl-substituted molecules, we synthesized 1-cyanoacetyl-5-hydroxy-3-methyl-5-trifluoromethyl-4,5-dihydro-1*H*-pyrazole (**3**) – a trifluoromethylated heterocyclic molecule that has a cyanoacetyl group attached to the N-1 – as well as a 2-cyanoacetyl-1-methylpyrrole system (**9**), both of which were used as precursors in reactions with salicylic aldehydes. The structural chemical characteristics of these two cyanoacetylazoles (**3** and **9**) allowed them to be studied in synthetic applications for the obtainment of new iminochromene and coumarinic pyrazoline/pyrrole substituent [74].

Thus, considering the biological importance and application of coumarins, the known synthetic potential of the pyrazoline **3**, the importance of heterocycles containing the CF_3 group, and the study of the reactivity of these systems when compared to non trifluoromethyl-substituted heterocycles, we wish to report here the synthesis of a new series of 3-(5-hydroxy-3-methyl-5-trifluoromethyl-4,5-dihydro-1*H*-pyrazol-1-carbonyl)-2-imino-2*H*-chromenes (**5**) and 3-(3-methyl-5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazol-1-carbonyl)-2*H*-chromen-2-ones (**6**) obtained from an initial Knoevenagel condensation reaction involving 1-cyanoacetyl-5-hydroxy-3-methyl-5-trifluoromethyl-4,5-dihydro-1*H*-pyrazole (**3**) and substituted salicylic aldehydes (**4**) under conventional heating. Subsequently, in order to establish a comparative study, we present the synthesis of 3-(1-methyl-1*H*-pyrrol-2-carbonyl)-2*H*-chromenes (**10**) using 2-cyanoacetyl-1-methylpyrrole (**9**) and the same substituted salicylic aldehydes (**4**) as precursors.

2. Results and discussion

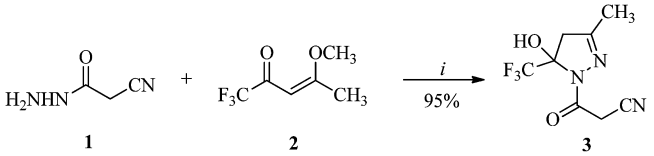
In order to achieve the first synthetic target of this work, it was necessary to synthesize the precursor 1-cyanoacetyl-4,5-dihydro-1*H*-pyrazole (**3**), which was obtained from the cyclocondensation of cyanoacetic hydrazide (**1**) and 4-methoxy-1,1,1-trifluoropent-3-en-2-one (**2**) [75,76], in accordance with the literature (Scheme 1) [77,78], with it being necessary to introduce small experimental modifications; for example, the use of methanol as the reaction solvent, under reflux for 16 h and further purification by extraction with ethyl acetate (see experimental section).

Subsequently, when pure 4,5-dihydropyrazole (**3**) reacted with some selected substituted salicylic aldehydes (**4a–d**), regiospecifically and in a one-step reaction, pyrazolinyl-iminochromenes (**5a–d**) were obtained through a typical Knoevenagel condensation reaction, due to the existence of an active methylenic center in the precursor **3** (Scheme 2).

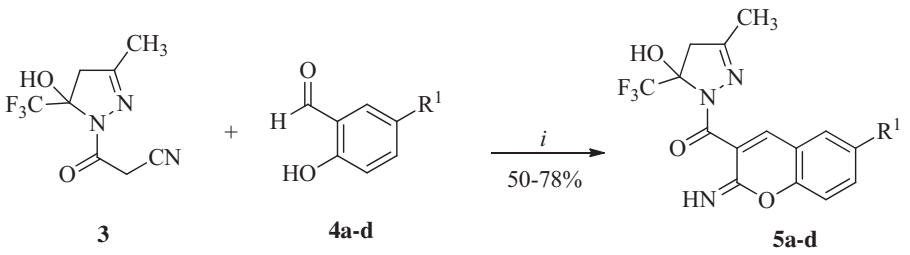
Based on the methodology described in the literature [79], we started the optimization of the reaction conditions using **4b** as the aldehyde precursor. In order to obtain the desired iminochromene **5b**, different catalysts were tested. When piperidine or triethylamine were used, the imino compounds were isolated at low yields. However, when the reaction was done employing 0.4 M NaOH/EtOH, the product **5b** was obtained at better yields (78%). The presence of 0.4 M NaOH/EtOH was the best methodology for generating the active methylenic center, which is essential for beginning the condensation reaction and providing the desired pyrazolinyl-iminochromenes **5**. We also tested different solvents, such as ethanol and acetone, but ethanol was the most efficient medium—it contributed to a significant increase in product yields. Interestingly, the initial condensation reaction enabled the isolation of the products, with the imino function being preserved at position 2 of the coumarin ring. The conversion to the product was followed by TLC, checking of the consumption of the starting materials over time, and choosing the best reaction time that would lead to a higher yield in a shorter amount of time. Thus, the optimal conditions enabled the isolation of a new series of pyrazolinyl-iminochromenes **5a-d**.

The reactions were done at a molar ratio of 1:1, with ethanol as the solvent, at 78 °C for 2 h, using drops of 0.4 M NaOH/EtOH as the catalyst. After the reaction time, compounds **5a–d** precipitated and were isolated in yields of 50–78% by simple filtration and washing with acetone/dichloromethane (Scheme 2). Compounds **5a–d** were obtained with small amounts of the carbonyl compounds **6a-d**, which were easily discarded by washing with a mixture of acetone and dichloromethane. Unfortunately, when we performed the reaction with the cyanoacetylated precursor **3** and the 2-hydroxy-4-methoxybenzaldehyde, which contains the electron-donating group 4-OCH_3, it was not possible to isolate the corresponding product **5e**. The electrophilicity is lower of this aldehyde, which leads to the formation of a complex mixture with difficult isolation and identification of the products by proton NMR.

It should also be noted that the compounds **5a–d** (iminochromenes) had very low solubility in many common organic solvents and were completely insoluble in water. Thus, the **5** series could not be completely characterized by GC–MS or LC–MS, and the ^1H and ^{13}C NMR spectra could only be recorded for compounds **5a–c**, with the limitation being due to the low solubility of compounds **5a–c**. The compounds **5a–c** were then identified by ^1H NMR in a highly diluted solution in DMSO-d_6; however, only **5b** and **5c** could be identified by ^{13}C NMR. Contrastingly, the whole of series **5** had its purity confirmed by satisfactory data from CHN elemental



Scheme 1. Cyclocondensation reaction involving cyanoacetic hydrazide (1) and 4-methoxy-1,1,1-trifluoropent-3-en-2-one (2). Reagents and conditions: (*i*) MeOH, reflux, 16 h.



4,5	a	b	c	d
R^1	H	NO_2	Br	OCH_3

Scheme 2. Knoevenagel condensation reaction involving 4,5-dihydropyrazole (3) and salicylic aldehydes (4). Reagents and conditions: (*i*) EtOH, 0.4 M NaOH/EtOH, reflux, 2 h.

analysis. All the coumarins of the **6** series showed good solubility in various solvents and could be completely characterized by the previously mentioned spectral methods.

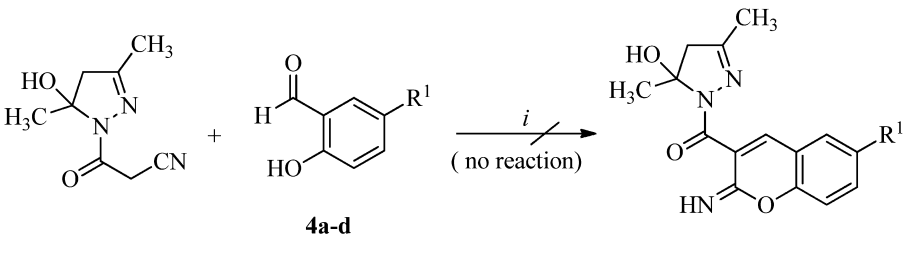
Subsequently, and with the aim of trying to expand the reaction scope, some reaction tests were performed to synthesize pyrazolinyl-iminochromenes without the trifluoromethyl substituent, in order compare the reactivity of the precursors and the structure of the isolated products. The reaction tests were performed using a structural analogue, 1-cyanoacetyl-5-hydroxy-3,5-dimethyl-4,5-dihydro-1*H*-pyrazole, and the same aldehydes **4** (Scheme 3). Unfortunately, under the standard methodology optimized to obtain the compounds of **5**, no reactions were observed by TLC in any case—only the starting materials **4** were recovered. We believe that the absence of the trifluoromethyl group, which was substituted by a methyl group at the pyrazoline ring, clearly reduces the electron-withdrawing effect in relation to the trifluoromethyl-substituted group that existed in the precursor **3**. This electronic effect minimizes the electronic deficiency of the carbonyl carbon that directly affects the acidity of the methylene protons of the cyanoacetyl group. This reactivity test shows that the CF_3 group in pyrazole **3** is extremely important for the cyclocondensation reaction being studied and decisive in the formation of the coumarin when a Knoevenagel condensation is involved.

On the other hand, the influence that the substituents attached to the aldehyde moiety had on the yields for the synthesis of compounds **5a-d** was also verified. It was observed that the electron-donating groups at the C-5 position in the aromatic aldehydes (e.g., **4d**) lead to lower yields, because these groups have a direct influence on the reactivity of the aldehyde carbonyl group present in this precursor. However, when either a non-substituted aromatic ring (e.g., **4a**) or aromatic aldehydes containing electron-withdrawing groups are employed as the substituents at the same position (e.g., **4b**–**c**), higher yields are obtained.

Due to the presence of the imino group, compounds **5a–d** exhibited very low solubility in the majority of organic solvents. In order to improve the solubility of these compounds and thus obtain better resolution for NMR analysis, the imino function of these molecules was converted into a carbonyl group, generating the pyrazolinyl-coumarins (**6a-d**) in 80–91% yields. The synthesis of **6** was done in ethanol, using 36% HCl as the catalyst for 1 h at reflux, in accordance with the methodology reported by Bonacorso et al. [80] in 2003 (Scheme 4). After the reaction time, the reaction mixtures were refrigerated and the products were isolated by precipitation and filtration, followed by washing with cold ethanol.

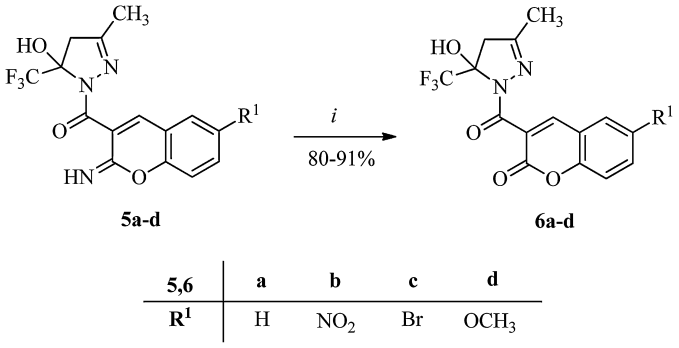
Attempts to obtain the aromatic pyrazoles by dehydration reactions of the pyrazolines **3**, and compounds **5** and **6** were performed according to the appropriated methodology described in literature [81], but the cleavage of the amide bond occurred, poor yields were registered and some non-identified byproducts observed. So, as expected, compounds **3**, **5** and **6** were resistant to dehydration reactions.

According to the literature reports, reactions involving compounds that contain a cyanoacetyl moiety and aldehydes (e.g., **3**), respectively, could generate two isomer intermediates in the *Z* and *E*-styryl forms [82]. The intermediates formed can be worked through the *E*-styryl intermediate (Scheme 4), since the intermediate *E* would be less sterically hindered and would have the cyano group close to the hydroxyl group, thereby facilitating the cyclization step of this reaction. Therefore, we propose a mechanism for condensation reactions involving the obtainment



4	a	b	c	d
R^1	H	NO_2	Br	OCH_3

Scheme 3. Knoevenagel condensation reaction involving 1-cyanoacetyl-5-hydroxy-3,5-dimethyl-4,5-dihydro-1*H*-pyrazole and salicylic aldehydes 4. Reagents and conditions: (*i*) EtOH, 0.4 M NaOH/EtOH, reflux, 2 h.



5,6	a	b	c	d
R^1	H	NO_2	Br	OCH_3

Scheme 4. New Coumarins 6 from hydrolysis reaction of pyrazolinyl-iminochromenes 5. Reagents and conditions: (*i*) EtOH, 36% HCl, reflux, 1 h.

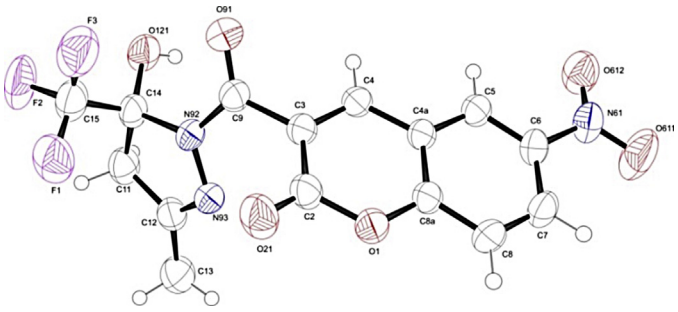


Fig. 1. ORTEP obtained from the crystal structure of 3-(5-hydroxy-3-methyl-5-trifluoromethyl-4,5-dihydro-*1H*-pyrazol-1-carbonyl)-6-nitro-*2H*-chromen-2-one (**6b**) with atoms labeled (CCDC 1056179) [83]. Displacement ellipsoids are drawn at the 50% probability level.

of pyrazolinyl- iminochromenes systems and their acid hydrolysis, leading to coumarin systems, as shown in Scheme 5.

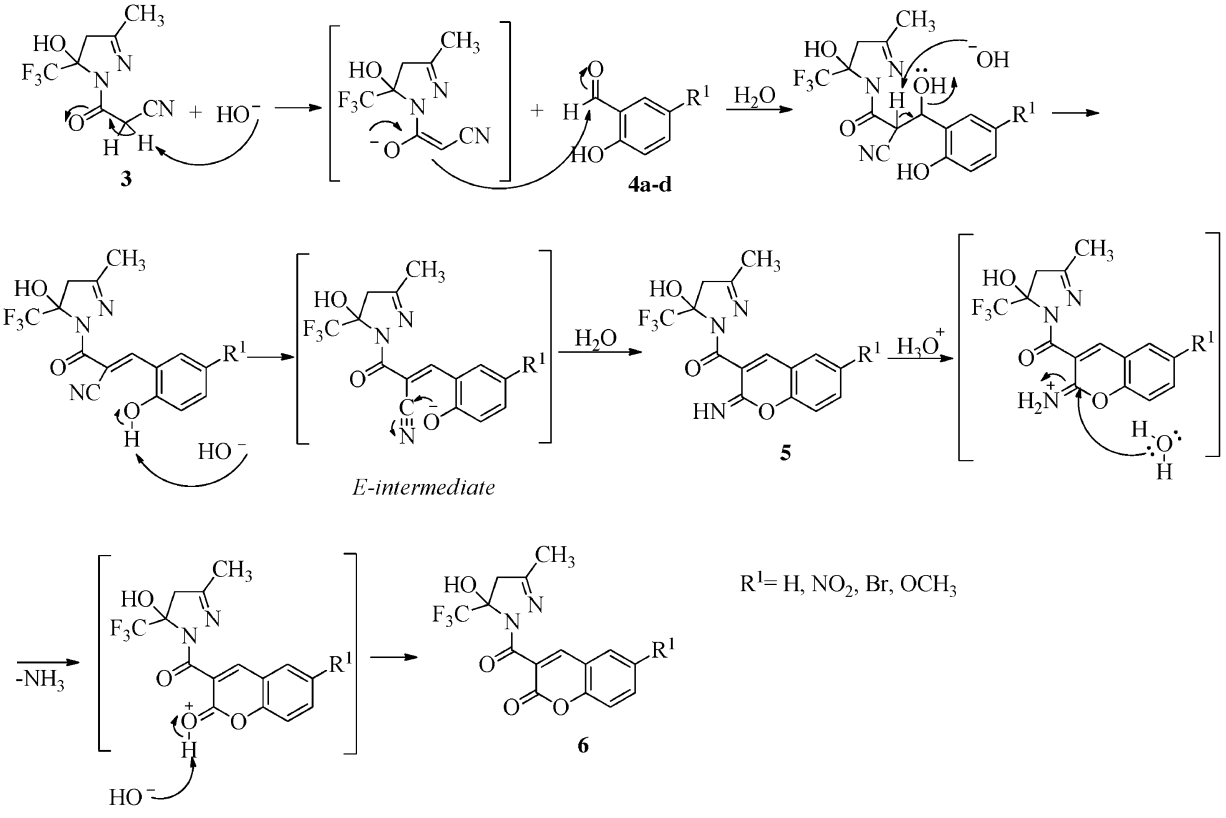
Products **5** and **6** were identified by ^{1}H and ^{13}C NMR, elemental analysis, and GC–MS. Also, through FT-IR analysis it was possible to confirm the presence of the imino group (=NH) in compounds **5a–d** and the corresponding carbonyl group in compounds **6a–d**, at position 2 of the coumarin nucleus. The infrared analysis shows a characteristic NH band in the region of $\nu = 3000\ cm^{-1}$, which characterizes the compounds **5a–d**, and for compounds **6a–d** it is possible to verify the presence of the carbonyl group of the lactone function due to the band in the region of $\nu = 1700\ cm^{-1}$.

The analysis of the ^{1}H NMR spectrum data for compounds **5** and **6** shows the signals of protons the aromatic and pyran rings in the characteristic region at δ 7.00–8.20 ppm for these moieties, which are important for proving the structures.

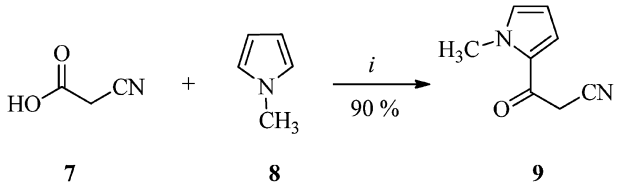
Through the crystal X-ray diffraction obtained for coumarin **6b** (Fig. 1), it was possible to confirm the structure and establish the product structure and the presence of the lactone carbonyl at the C-2 position. Also, the existence of the pyran and pyrazoline rings (shown in the ORTEP) confirms the formation of the compound and the relative position at which there are two rings, wherein the plane of the pyrazoline ring is 62.4° from the plane of the coumarin ring.

In order to expand the scope of the products and prove the feasibility of this synthesis for another heterocyclic system attached to the coumarin moiety, reactions using the standard methodology and involving 2-cyanoacetyl-1-methylpyrrole (**9**) and salicylic aldehydes (**4a–e**) were performed in order to obtain the pyrrolyl-coumarins (**10a–e**). The precursor **9** was synthetized by a reaction involving refluxing of cyanoacetic acid and 1-methylpyrrole in acetic anhydride for 1 h, in accordance with the methodology described in the literature (Scheme 6) [84].

It was possible to directly obtain a series of pyrrolyl-coumarins (**10a–e**) and only traces of pyrrolyl-iminochromene intermediate derivatives, in accordance with Scheme 7.



Scheme 5. Proposed mechanism for the Knoevenagel condensation reactions of the compounds 5 and 6.



7 8 9

Scheme 6. Reagents and conditions: (*i*) acetic anhydride, reflux, 1 h.

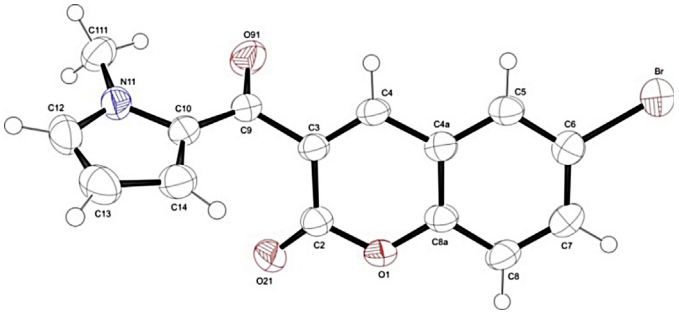
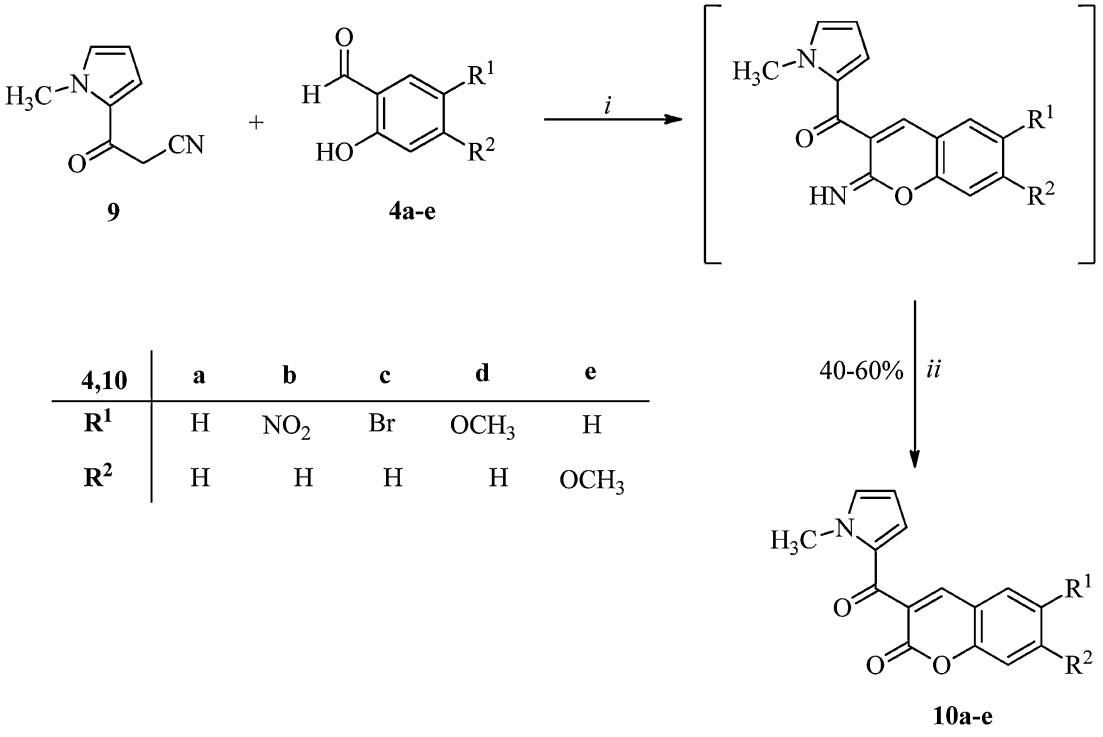


Fig. 2. ORTEP obtained from the crystal structure of 6-bromo-3-(1-methyl-1*H*-pyrrol-2-carbonyl)-2*H*-chromen-2-one (**10c**) with atoms labeled (CCDC 1056083) [83]. Displacement ellipsoids are drawn at the 50% probability level.

Initially, we expected that the pyrrolyl-iminochromenes would be the first products and that they would be similar to **5a–d**, but the reactivity of the cyanoacetylated pyrrole **9** proved to be very different. The pyrrole precursor **9** has an active methylenic group neighboring a ketone function, while the pyrazoline **3** has an hydrazide function. This fact makes β-ketonitrile **9** more reactive than **3** in the first step of the condensation reaction, despite not having a trifluoromethyl group attached to the pyrrole ring of **9**. To ensure total conversion into pyrrolyl-coumarin compounds (**10a–e**), after 2–3 h of reaction time, drops of 36% HCl were added and the resulting solution was kept under reflux for one additional hour. Compounds **10a–e** were obtained by precipitation in reaction solvent at a low temperature, as black or pale brown solids in yields of 40–60%, according to the substituent in the salicylic aldehydes (**4a–e**). Table 1 shows the yields and melting points of the compounds belonging to the **5**, **6**, and **10** series.

The single-crystal X-ray diffraction obtained for compound **10c** confirms the presence of the lactone carbonyl at the C-2 position and also the existence of the pyran and pyrrole rings, thus proving the structure of the compound. The torsion angles measured for **10c** show that the C-2, C-3, C-9, and C-10 carbons are located with a 58° dihedral angle between the planes of the pyrrole and pyran ring (Fig. 2).

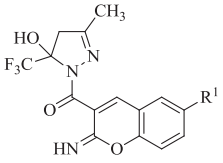
In order to evaluate the performance as new drugs in the synthesized compounds, the parameters of Lipinski [70] were applied to the thirteen chromenones (**5a–d**, **6a–d** and **10a–e**). These parameters have the ability to estimate the activities of the compounds in the organism by the evaluation of hydrogen donor and receptor interactions and estimated lipophilicity by the use of the partition coefficient calculations. Through the results obtained, we could verify that the all studied compounds remain within the established limits according the following data: (i) the molecular weights were under 500: 253,07 $\leq MW_{\mathbf{5,6,10}} \leq$ 417,98; (ii) a limited lipophilicity (expressed by Log $P < 5$): $-1{,}36 \leq ClogP_{\mathbf{5,6,10}} \leq 4{,}99$ (calculated with ChemDraw™ Ultra, version 12.0); (iii) maximum 5 H-bond donors (expressed as the sum of OHs and NHs groups): the values are 02 for compounds **5a–d**, 01 for compounds **6a–d** and 0(zero) for compounds **10a–e** and (iv) a maximum 10 H-bond acceptors (expressed as the sum of Os and Ns atoms): the values remained within the range 04 to 09 atoms for the compounds **5**, **6** and **10**.



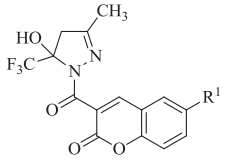
4,10	a	b	c	d	e
R1	H	NO_2	Br	OCH_3	H
R2	H	H	H	H	OCH_3

Scheme 7. Synthsis of coumarins 10 via Knoevenagel condensation reaction of cyanoacetylpyrrole 9 and salicylic aldehydes 4. Reagents and conditions: (*i*) EtOH, 0.4 M NaOH/EtOH, reflux, 2-3 h. (*ii*) EtOH/36% HCl, reflux, 1 h.

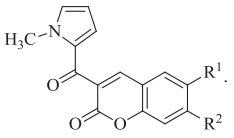
Table 1
Yields and melting points of compounds **5**, **6**, and **10**.



5a–d



6a–d



10a–e

Compound	R^1	R^2	Molecular Weight (g/mol)	m.p. (°C)[a]	Yield (%)[a]
5a	H	H	$C_{15}H_{12}F_3N_3O_3$ (339.08)	208–211	64
6a	H	H	$C_{15}H_{11}F_3N_2O_4$ (340.07)	212–214	80
10a	H	H	$C_{15}H_{11}NO_3$ (253.07)	162–163	40
5b	NO_2	H	$C_{15}H_{11}F_3N_4O_5$ (384.07)	203–205	78
6b	NO_2	H	$C_{15}H_{10}F_3N_3O_6$ (385.05)	218–219	91
10b	NO_2	H	$C_{15}H_{10}N_2O_5$ (295.06)	200–203	45
5c	Br	H	$C_{15}H_{11}BrF_3N_3O_3$ (416.99)	228–231	60
6c	Br	H	$C_{15}H_{10}BrF_3N_2O_4$ (417.98)	230–231	86
10c	Br	H	$C_{15}H_{10}BrNO_3$ (330.98)	222–224	60
5d	OCH_3	H	$C_{16}H_{14}F_3N_3O_4$ (369.09)	213–216	50
6d	OCH_3	H	$C_{16}H_{13}F_3N_2O_5$ (370.08)	(219–222)[b]	81
10d	OCH_3	H	$C_{16}H_{13}NO_4$ (283.28)	193–196	53
10e	H	OCH_3	$C_{16}H_{13}NO_4$ (283.28)	188–190	51

[a] Data for isolated pure products.
[b] Product decomposition by melting point.

3. Conclusions

In summary, we presented the synthesis of a series of 3-(5-hydroxy-3-methyl-5-trifluoromethyl-4,5-dihydro-1*H*-pyrazol-1-carbonyl)-2-imino-2*H*-chromenes (**5a–d**), 3-(3-methyl-5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazol-1-carbonyl)-2*H*-chromen-2-ones (**6a–d**), and also a series of 3-(1-methyl-1*H*-pyrrol-2-carbonyl)-2*H*-chromenes (**10a–e**) via a Knoevenagel condensation reaction, which was derived from 4,5-dihydropyrazole (**3**) or 2-cyanoacetyl-1-methylpyrrole (**9**) and five selected salicylic aldehydes (**4a–e**). The synthesis of four series of allyl coumarins was attempted but only three series (**5**, **6**, and **10**) were successfully obtained through the use of two different cyanoacetylated azoles (starting materials), in which the methylene group attached to a ketone or hydrazide function, as well as the presence or absence of CF_3 units, were decisive and demonstrate the specific chemical behavior. Also, the influence of the substituents presented in the salicylic aldehydes **4** used as precursors, was observed. Finally, a quick and efficient synthesis for the preparation of 13 new interesting carbonyl-spaced azolecarbonyl coumarins in yields of up to 91%, under conventional heating and in short reaction times, was reported.

4. Experimental

4.1. Analytical equipment and procedures

Unless otherwise indicated, all common reagents and solvents were used as obtained from commercial suppliers without further purification. All melting points were determined using coverslips on a Microquímica MQAPF-302 apparatus, and are uncorrected. Mass spectra were registered in a HP 5973 MSD connected to a HP 6890 GC and interfaced by a Pentium PC. The GC was equipped with a split-splitless injector, auto sampler, and cross-linked HP-5 capillary column (30 m, 0.32 mm internal diameter), and helium was used as the carrier gas. The high-resolution mass spectrometry (HRMS) spectra were obtained using an Agilent-QTOF 6530 spectrometer (LARP/UFSM). ^{1}H and ^{13}C NMR spectra were acquired on a Bruker DPX 400 spectrometer and Bruker Avance III 600 MHz, using 5 mm sample tubes, 298 K, digital resolution of±0.01 ppm, in DMSO-d_6, with TMS as internal reference. The CHN elemental analyses were performed on a Perkin-Elmer 2400 CHN elemental analyzer (University of São Paulo, Brazil). To obtain the infrared spectrum of the samples, we used a Perkin Elmer FTIR Spectrum 100 spectrophotometer (Federal Technical University of Paraná, Brazil). The diffraction measurements were done by graphite-monochromatized Mo *K*α radiation, with λ = 0.71073 Å, on a Bruker SMART CCD diffractometer [85]. The structures of **6b** and **10c** were solved by direct methods using the SHELXS-97 program [86], and refined on F^2 by full-matrix least-squares using the SHELXL-97 package [87]. The absorption correction was done by Gaussian methods [88]. Anisotropic displacement parameters for non-hydrogen atoms were applied. The hydrogen atoms were placed at calculated positions with 0.96 Å (methyl CH_3) and 0.93 Å (aromatic CH), using a riding model. The hydrogen isotropic thermal parameters were kept at $U_{iso}(H) = \chi U_{eq}$ (carrier C atom), with $\chi = 1.5$ for the methyl groups and $\chi = 1.2$ for the other groups. The valence angles C–C–H and H–C–H of the methyl groups were set to 109.5°, and the H atoms were allowed to rotate around the C–C bond. The molecular graph was prepared using ORTEP-3 for Windows [89].

4.2. Synthesis

4.2.1. General procedure for the synthesis of 1-cyanoacetyl-5-hydroxy-3-methyl-5-trifluoromethyl-4,5-dihydro-1H-pyrazole (3)

To a flask containing cyanoacetohydrazide (**1**) (1.2 mmol, 0.119 g) and being magnetically stirred, methanol (10 mL) and 4-methoxy-1,1,1-trifluoropent-3-en-2-one (**2**) (1.2 mmol, 0.202 g) were added at room temperature. The resulting mixture was refluxed for 16 h. The reaction solvent was then removed in a rotary evaporator and to the resulting oil, distilled water (10 mL) was added and extracted with ethyl acetate (3 × 10 mL). The organic layer was separated, dried with anhydrous sodium sulfate (15 g), and the solvent was removed in a rotary evaporator under reduced pressure. Compound **3** was isolated as a brown oil in a yield of 95%; Literature [77] 80%.

4.2.2. General procedure for the synthesis of 3-(5-hydroxy-3-methyl-5-trifluoromethyl-4,5-dihydro-1H-pyrazol-1-carbonyl)-2-imino-2H-chromenes (5a–d)

In a flask containing 4,5-dihydropyrazole (**3**) (1 mmol, 0.235 g), ethanol (10 ml) and 0.4 M NaOH/EtOH (0.036 g or 0.075 mL) were

added under magnetic stirring at room temperature. The temperature of the mixture was elevated to 78 °C and maintained in this condition under magnetic stirring for 15 min. Subsequently, to each reaction, the corresponding salicylic aldehydes (**4a–d**) (1 mmol) were added and the reactions were then refluxed for an additional 2 h. During this period, the precipitation of the respective compounds of **5** was observed. The resulting solids were filtered under atmospheric pressure and washed with a mixture of acetone and dichloromethane 1:1 (1 × 30 mL) at room temperature. Finally, the solids were isolated in a pure form when left under reduced pressure at room temperature for several hours.

*4.2.2.1. 3-(5-Hydroxy-3-methyl-5-trifluoromethyl-4,5-dihydro-1H-pyrazol-1-carbonyl)-2-imino-2H-chromene (**5a**).* red solid, yield 64%, mp. 208–211 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ 8.27 (s, 1*H*, H-4); 8.15 (s, 1*H*, OH); 8.09 (d, *J* = 8 Hz, 1*H*, H-8); 7.43 (td, *J* = 2 Hz, *J* = 7 Hz, 1*H*, H-6), 7.01 (d, *J* = 8 Hz, 1*H*, H-5); 6.96 (t, *J* = 7 Hz, 1*H*, H-7); 3.54 (d, *J* = 19 Hz, 1*H*, H-13a); 3.13 (d, *J* = 19 Hz, 1*H*, H-13b); 2.04 (s, 3*H*, CH_3).

Anal. Calc. for $C_{15}H_{12}F_3N_3O_3$ (339.1): C, 53.10, H, 3.57, N, 12.39. Found: C, 52.95, H, 3.75, N, 11.92.

*4.2.2.2. 3-(5-Hydroxy-3-methyl-5-trifluormethyl-4,5-dihydro-1H-pyrazol-1-carbonyl)-6-nitro-2-imino-2H-chromene (**5b**).* black solid, yield 78%, mp. 203–205 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.96 (d, *J* = 3 Hz, 1*H*, H5); 8.27 (dd, *J* = 3 Hz, *J* = 9 Hz, 1*H*, H-7); 8.20 (s, 1*H*, H-4); 7.13 (d, *J* = 9 Hz, 1*H*, H-8); 3.54 (d, *J* = 19 Hz, 1*H*, H-13a); 3.14 (d, *J* = 19 Hz, 1*H*, H-13b); 2.04 (s, 3*H*, CH_3).

^{13}C NMR (400 MHz, DMSO-d_6): 161.5 (C-9); 157.5 (C-2); 156.3 (C-12); 155.8 (C-8a); 144.5 (C-6); 140.8 (C-7); 127.7 (C-4a); 125.6 (C-4); 123.3 (q, *J* = 286 Hz, CF_3); 118.9 (C-8); 118.4 (C-5); 102.5 (C-3); 91.4 (q, *J* = 34 Hz, C-14); 48.4 (C-13); 15.6 (CH_3).

Anal. Calc. for $C_{15}H_{11}F_3N_4O_5$ (384.1): C, 46.88, H, 2.89, N, 14.58. Found: C, 46.83, H, 2.89, N, 14.36.

*4.2.2.3. 6-Bromo-3-(5-hydroxy-3-methyl-5-trifluoromethyl-4,5-dihydro-1H-pyrazol-1-carbonyl)-2-imino-2H-chromene (**5c**).* red solid, yield 60%, mp. 228–231 °C. ^{1}H NMR (600 MHz, DMSO-d_6): 8.22 (s, 1*H*, OH); 8.19 (s, 1*H*, H-4); 8.17 (d, *J* = 2 Hz, 1*H*, H-5); 7.58 (dd, *J* = 2 Hz, *J* = 9 Hz, 1*H*, H-7); 6.90 (d, *J* = 9 Hz, 1*H*, H-8); 3.54 (d, *J* = 19 Hz, 1*H*, H-13a); 3.14 (d, *J* = 19 Hz, 1*H*, H-13b); 2.05 (s, 3*H*, CH_3).

^{13}C NMR (600 MHz, DMSO-d_6): δ 160.1 (C-9); 157.5 (C-2); 155.9 (C-12); 145.9 (C-8a); 136.8 (C-7); 130.3 (C-4a); 123 (q, *J* = 286 Hz, CF_3); 121.4 (C-6); 119.0 (C-4,C-5); 116.0 (C-10); 110.8 (C-8); 107.5 (C-3); 92.0 (q, *J* = 34 Hz, C-14); 48.1 (C-13); 15.7 (CH_3).

Anal. Calc. for $C_{15}H_{11}BrF_3N_3O_3$ (417): C, 43.08, H, 2.65, N, 10.05. Found: C, 42.95, H, 2.58, N, 9.66.

*4.2.2.4. 6-Methoxy-3-(5-hydroxy-3-methyl-5-trifluoromethyl-4,5-dihydro-1H-pyrazol-1-carbonyl)-2-imino-2H-chromene (**5d**).* Yield 50%, red solid, mp. 213–216 °C. Anal. Calc. for $C_{16}H_{14}F_3N_3O_4$ (369.1): C, 52.04, H, 3.82; N, 11.38. Found: C, 52.04; H, 3.82; N, 11.35.

*4.2.3. General procedure for the synthesis of 3-(3-methyl-5-trifluoromethyl-5-hydroxy-4,5-dihydro-1H-pyrazol-1-carbonyl)-2H-chromen-2-ones (**6a–d**)*

To a magnetically stirred solution of the compounds **5a–d** (1 mmol) in ethanol (10 mL), 1.8 mL of 36% HCl was added. The resulting mixture was subjected to a temperature of 78 °C for 1 h under magnetic stirring. Subsequently, the solution was cooled and precipitation of the product occurred. The solids were then filtered under atmospheric pressure, washed with cold ethanol (1 × 20 mL), and dried under reduced pressure, which led to yellow solids as the pure products of **6**.

*4.2.3.1. 3-(5-Hydroxy-3-methyl-5-trifluoromethyl-4,5-dihydro-1H-pyrazol-1-carbonyl)-2H-chromen-2-one (**6a**).* yellow solid, yield 80%, mp. 212–214 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.18 (s, 1*H*, H-4), 8.08 (s, 1*H*, OH), 7.81 (d, *J* = 8 Hz, 1*H*, H-5), 7.67 (t, *J* = 8 Hz, 1*H*, H-7), 7.43 (d, *J* = 8 Hz, 1*H*, H-8), 7.39 (t, *J* = 8 Hz, 1*H*, H-6), 3.48 (d, *J* = 19 Hz, 1*H*, H-13a), 3.14 (d, *J* = 19 Hz, 1*H*, H-13b), 1.92 (s, 3*H*, CH_3).

^{13}C NMR (400 MHz, DMSO-d_6): δ 162.4 (C-9), 157.2 (C-12), 155.3 (C-2), 153.9 (C-8a); 141.6 (C-4), 133.2 (C-7), 129.6 (C-6), 126.3 (C-4a), 125.3 (C-5), 123.6 (q, *J* = 286 Hz, CF_3), 119.4 (C-3), 118.4 (C-8), 91.2 (q, *J* = 34 Hz, C-14), 48.3 (C-13), 15.5 (CH_3).

MS, m/z (%), 340 (M^+,1.4), 173 (100), 229 (14), 89 (17).

IR (KBr): ν = 3262 cm^{-1}(OH), 2972 cm^{-1} (CH), 1698 cm^{-1} (lactone C=O), 1662 cm^{-1} (C = O amide)

Anal. Calc. for $C_{15}H_{11}F_3N_2O_4$ (340.1): C, 52.95, H, 3.26, N, 8.23; Found: C, 53.46, H, 3.31, N, 8.09.

*4.2.3.2. 3-(5-Hydroxy-3-methyl-5-trifluoromethyl-4,5-dihydro-1H-pyrazol-1-carbonyl)-6-nitro-2H-chromen-2-one (**6b**).* pale yellow solid, yield 91%, mp. 218–219 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 8.82 (d, *J* = 3 Hz, 1*H*, H-5), 8.46 (dd, *J* = 3 Hz, *J* = 9 Hz, 1*H*, H-7), 8.39 (s, 1*H*, H-4), 8.24 (s, 1*H*, OH), 7.67 (d, *J* = 9 Hz, 1*H*, H-8) 3.49 (d, *J* = 19 Hz, 1*H*, H-13a), 3.21 (d, *J* = 19 Hz, 1*H*, H-13b), 1.93 (s, 3*H*, CH_3).

^{13}C NMR (400 MHz, DMSO-d_6): δ 161.5 (C-9), 157.4 (C-12), 156.3 (C-2), 155.9 (C-8a); 144.3 (C-4), 140.8 (C-7), 127.9 (C-4a), 127.7 (C-6), 125.5 (C-5), 123.5 (*J* = 285 Hz, CF_3), 118.8 (C-3), 118.3 (C-8), 91.1 (q, *J* = 34 Hz, C-14), 48.2 (C-13), 15.6 (CH_3).

MS, m/z (%), 385 (M^+,1.3), 218 (100), 172 (47), 274 (33).

IR (KBr): ν = 1742 cm^{-1} (C = O, lactone), 1674 cm^{-1} (C = O, amide), 1619 cm^{-1} (C–C aromatic ring), 1345 cm^{-1} (CN)

Anal. Calc. for $C_{15}H_{10}F_3N_3O_6$ (385.1): C, 46.76, H, 2.62, N, 10.91, Found: C, 46.68, H, 2.62, N, 10.91.

*4.2.3.3. 6-Bromo-3-(5-hydroxy-3-methyl-5-trifluoromethyl-4,5-dihydro-1H-pyrazol-1-carbonyl)-2H-chromen-2-one (**6c**).* pale yellow solid, yield 86%, mp 230–231 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.16 (s, 2*H*, OH, H-4), 8.07 (d, *J* = 2 Hz, 1*H*, H-5), 7.82 (dd, *J* = 2 Hz, *J* = 9 Hz, 1*H*, H-7), 7.43 (d, *J* = 9 Hz, 1*H*, H-8), 3.49 (d, *J* = 19 Hz, 1*H*, H-13a), 3.14 (d, *J* = 19 Hz, 1*H*, H-13b), 1.92 (s, 3*H*, CH_3);

^{13}C NMR (400 MHz, DMSO-d_6): δ 161.9 (C-9), 156.8 (C-12), 155.7 (C-2), 152.9 (C-8a); 140.4 (C-7), 135.6 (C-4), 131.6 (C-5), 127.3 (C-4a), 123.6 (q, *J* = 286 Hz, CF_3); 120.2 (C-6), 119.0 (C-8), 116.9 (C-3), 91.1 (q, *J* = 34 Hz, C-14), 48.2 (C-13), 15.6 (CH_3).

MS, m/z (%), 420 [(M^++2) 1], 253 (100), 309 (19), 167 (15).

IR (KBr): ν = 3350 cm^{-1} (OH), 1734 cm^{-1} (lactone C = O), 1657 cm^{-1}(C = O amide).

Anal. Calc. for $C_{15}H_{10}BrF_3N_2O_4$ (418): C, 42.98, H, 2.40, N, 6.68; Found: C, 42.81, H, 2.64, N, 6.38.

*4.2.3.4. 3-(5-Hydroxy-3-methyl-5-trifluoromethyl-4,5-dihydro-1H-pyrazol-1-carbonyl)-6-methoxy-2H-chromen-2-one (**6d**).* yellow solid, yield 82%, mp. 222–223 °C. ^{1}H NMR (400 MHz, DMSO-d_6): 8.08 (s, 1*H*, H-4); 7.73 (d, *J* = 9 Hz, 1*H*, H-8); 7.02 (d, *J* = 2 Hz, 1*H*, H-5); 6.99 (dd, *J* = 3 Hz, *J* = 9 Hz, 1*H*, H-6); 3.89 (s, 3*H*, OCH_3); 3.46 (d, *J* = 19 Hz, 1*H*, H-13a); 3.13 (d, *J* = 19 Hz, 1*H*, H-13b); 1.90 (s, 3*H*, CH_3).

^{13}C NMR (400 MHz, DMSO-d_6): 163.8 (C-9); 162.8 (C-2); 157.5 (C-12); 156.0 (C-6); 155.0 (C-8a); 142.2 (C-7); 130.8 (C-4); 123.7 (q, *J* = 286 Hz, CF_3); 122.7 (C-4a); 113.4 (C-5); 112.0 (C-3); 101.2 (C-8); 91.2 (q, *J* = 34 Hz, C-14); 56.6 (OCH_3); 48.4 (C-13); 15.6 (CH_3).

MS, m/z (%), 370 [(M^+ +1) 5]; 208 (100); 259 (10); 119 (12). Anal. Calcd. for $C_{16}H_{14}F_3N_2O_4$ (369.1): C, 51.90, H, 3.54, N, 7.57; Found: C, 52.18, H, 3.68, N, 7.46.

*4.2.4. General procedure for the synthesis of 3-(1-methyl-1*H*-pyrrol-2-carbonyl)-2*H*-chromenes (**10a–e**)*

To a flask containing 2-cyanoacetyl-1-methylpyrrole (**9**) (1 mmol, 0.148 g) and under magnetic stirring, ethanol (10 mL) and 0.4 M NaOH/EtOH (0.036 g or 0.075 mL) were added at room temperature. The temperature of the resulting mixture was elevated to 78 °C and maintained in this condition under magnetic stirring for 15 min. The corresponding salicylic aldehyde (**4a–e**) was then added (1 mmol) and the reaction was refluxed for further 2 h. Subsequently, 1.8 mL of 36% HCl was added and the resulting mixture was refluxed for 1 h. The products **10** precipitated from the reaction mixture immediately after cooling. These products were filtered under atmospheric pressure, washed with cold ethanol (20 mL), and then dried under reduced pressure, which led to brown solids as the pure products **10**.

*4.2.4.1. 3-(1-Methyl-1*H*-pyrrol-2-carbonyl-2*H*-chromen-2-one (**10a**).* brown solid, yield 40%, mp. 162–163 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.21 (s, 1*H*, H-4); 7.78 (dd, *J* = 1 Hz, *J* = 7 Hz, 1*H*, H-5); 7.67 (td, *J* = 2 Hz, *J* = 8 Hz, 1*H*, H-7); 7.42 (d, *J* = 8 Hz, 1*H*, H-8); 7.37 (td, *J* = 1 Hz, *J* = 7 Hz, 1*H*, H-6); 7.27 (t, *J* = 2 Hz, 1*H*, H-13); 6.88 (dd, *J* = 1 Hz, *J* = 2 Hz, 1*H*, H-12); 6.15 (dd, *J* = 2 Hz, 1*H*, H-14); 3.96 (s, 3*H*, NCH_3).

^{13}C NMR (400 MHz, DMSO-d_6): δ 180.1 (C-9); 158.4 (C-2); 154.3 (C-8a); 142.9 (C-4); 134.1 (C-3); 133.3 (C-5); 130.2 (C-10); 129.8 (C-6); 127.9 (C-4a); 125.2 (C-12); 123.9 (C-14); 118.7 (C-8); 116.7 (C-7); 109.1 (C-13); 37.3 (CH_3).

MS, m/z (%), 253 (M^+, 55); 173(26); 108(100); 80(97); 53(89);
HRMS (ESI): m/z Calcd. 254.0812 (M + H); Found 254.0803.

*4.2.4.2. 3-(1-Methyl-1*H*-pyrrol-2-carbonyl)-6-nitro-2*H*-chromen-2-one (**10b**).* brown solid, yield 45%, mp. 200–203 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.80 (d, *J* = 3 Hz, 1*H*, H-5); 8.47 (dd, *J* = 3 Hz, *J* = 9 Hz, 1*H*, H-7); 8.41 (s, 1*H*, H-4); 7.68 (d, *J* = 9 Hz, 1*H*, H-8); 7.37 (t, *J* = 1 Hz, 1*H*, H-13); 7.02 (dd, *J* = 1 Hz, *J* = 4 Hz, 1*H*, H-12); 6.18 (dd, *J* = 2 Hz, *J* = 4 Hz, 1*H*, H-14); 3.96 (s, 3*H*, NCH_3).

^{13}C NMR (400 MHz, DMSO-d_6): δ 179.2 (C-9); 157.8 (C-2); 157.6 (C-8a); 144.1 (C-6); 141.9 (C-7); 134.8 (C-3); 129.8 (C-5); 129.2 (C-10); 127.7 (C-4a); 125.6 (C-12); 124.8 (C-14); 119.2 (C-8); 118.3 (C-4); 109.4 (C-13); 37.4 (CH_3).

MS, m/z (%), 299 [(M^+ + 1)39]; 57 (100); 69 (33); 82 (39);
HRMS (ESI): m/z Calcd. 299.0662 (M + H); Found 299.0682.

*4.2.4.3. 6-Bromo-3-(1-methyl-1*H*-pyrrol-2-carbonyl)-2*H*-chromen-2-one (**10c**).* brown solid, yield 60%, mp. 222–224 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.19 (s, 1*H*, H-4); 8.05 (d, *J* = 2 Hz, 1*H*, H-5); 7.82 (dd, *J* = 2 Hz, *J* = 9 Hz, 1*H*, H-7); 7.42 (d, *J* = 9 Hz, 1*H*, H-8); 7.33 (t, *J* = 1 Hz, 1*H*, H-13); 6.95 (dd, *J* = 1 Hz, *J* = 4 Hz, 1*H*, H-12); 6.16 (dd, *J* = 2 Hz, *J* = 4 Hz, 1*H*, H-14); 3.96 (s, 3*H*, NCH_3).

^{13}C NMR (400 MHz, DMSO-d_6): δ 179.6 (C-9); 157.9 (C-2); 153.2 (C-8a); 141.6 (C-7) 135.5 (C-4); 134.4 (C-3); 131.7 (C-5); 129.9 (C-10); 128.7 (C-4a); 124.3 (C-12); 120.6 (C-14); 118.9 (C-8); 116.6 (C-6); 109.2 (C-13); 37.3 (CH_3).

MS, m/z (%), 331 [(M^+ + 1)23]; 108 (100); 80 (75); 53 (63); 167 (11);

IR (KBr): ν = 1720 cm^{-1} (C = O lactone); 1627 cm^{-1} (C = O ketone); 1593 cm^{-1} (C–C aromatic ring).

HRMS (ESI): m/z Calcd. 331.9917 (M + H); Found 331.9905.

*4.2.4.4. 3-(1-Methyl-1*H*-pyrrol-2-carbonyl)-6-methoxy-2*H*-chromen-2-one (**10d**).* brown solid, yield 53%, mp. 193–196 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.19 (s, 1*H*, H-4); 7.39 (d, *J* = 9 Hz, 1*H*, H-8); 7.37 (d, *J* = 3 Hz, 1*H*, H-5); 7.32 (t, *J* = 2 Hz, 1*H*, H-13); 7.27 (dd, *J* = 3 Hz, *J* = 9 Hz, 1*H*, H-7); 6.89 (dd, *J* = 2 Hz, *J* = 4 Hz, 1*H*, H-12); 6.16 (dd, *J* = 3 Hz, *J* = 4 Hz, 1*H*, H-14); 3.96 (s, 3*H*, NCH_3); 3.81 (s, 3*H*, OCH_3).

^{13}C NMR (400 MHz, DMSO-d_6): δ 180.2 (C-9); 158.5 (C-2); 156.2 (C-6); 148.5 (C-8a); 142.8 (C-7); 134.2 (C-5); 130.0 (C-10); 128.0 (C-3); 124.0 (C-12); 120.9 (C-14); 119.1 (C-4a); 117.7 (C-8); 111.2 (C-4); 109.1(C-13); 56.2 (OCH_3); 37.3 (CH_3).

MS, m/z (%), 283 (M^+,100); 203 (26); 108 (82); 80 (22);
HRMS (ESI): m/z Calcd. 284.0917 (M + H); Found 284.0916.

*4.2.4.5. 3-(1-Methyl-1*H*-pyrrol-2-carbonyl)-7-methoxy-2*H*-chromen-2-one (**10e**).* black solid, yield 51%, mp. 188–190 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.21 (s, 1*H*, H-4); 7.72 (d, *J* = 9 Hz, 1*H*, H-8); 7.30 (t, *J* = 2 Hz, 1*H*, H-13); 7.04 (d, *J* = 2 Hz, 1*H*, H-5); 6.99 (dd, *J* = 2 Hz, *J* = 9 Hz, 1*H*, H-6); 6.87 (dd, *J* = 2 Hz, *J* = 4 Hz, 1*H*, H-12); 6.15 (dd, *J* = 2 Hz, *J* = 4 Hz, 1*H*, H-14); 3.95 (s, 3*H*, NCH_3); 3.89 (s, 3*H*, OCH_3).

^{13}C NMR (400 MHz, DMSO-d_6): δ 180.5 (C-9); 163.9 (C-2); 158.7 (C-7); 156.3 (C-8a); 143.8 (C-4); 133.9 (C-10); 131.1 (C-5); 130.2 (C-3); 124.1 (C-4a); 123.7 (C-6); 113.3 (C-12); 112.1 (C-8); 109.0 (C-14); 101.0 (C-13); 56.6 (OCH_3); 37.3 (CH_3).

MS, m/z (%), 283 (M^+, 100); 203 (26); 108 (82); 80 (22);
HRMS (ESI): m/z Calcd. 284.0917 (M + H); Found 284.0944.

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References

[1] A.E.H. Machado, R. Paula, J.A. Miranda, 3-Benzoxazol-2-yl-7-(N,N-diethylamino)-chromen-2-one as a fluorescence probe for the investigation of micellar microenvironments, J. Photochem. Photobiol. A 165 (2004) 109–114.
[2] R.D. Murray, J. Mendez, S.A. Brown, in: R. Murray, J. Mendez, S. Brown (Eds.), The Natural Coumarins: Occurrence, Chemistry and Biochemistry, John Wiley and Sons, New York, NY, 1982, p. 227.
[3] M.S.Y. Khan, P. Sharma, Synthesis of new α-pyronochalcones and related cyclization products, Indian J. Chem., Sect B. 32 (1993) 374–376.
[4] J.A.A. Miky, A.A. Farrag, Synthesis and reactions of 3-cinnamoylcoumarin derivatives with activated nitriles, Indian J. Chem., Sect B. 36 (1997) 357–360.
[5] L. Bonsignore, G. Loy, D. Secci, A. Calignano, Synthesis and pharmacological activity of 2-oxo-(2*H*)-1-benzopyran-3-carboxamide derivatives, Eur. J. Med. Chem. 28 (1993) 517–520.
[6] M.V. Kulkarni, V.D. Patil, Studies on coumarins I, Arch. Pharm. 314 (1981) 708–711.
[7] D.R. Buckle, D.G. Outred, J.W. Ross, H. Smith, R.J. Smith, B.A. Spicer, B.C. Gasson, Aryloxyalkyloxy- and Aralkyloxy-4-hydroxy-3-nitrocoumarins Which Inhibit Histamine Release in the Rat and Also Antagonize the Effects of a Slow Reacting Substance of Anaphylaxis, J. Med. Chem. 22 (1979) 158–168.
[8] A.S. Gupta, J.R. Merchant, Antimicrobial activity of phenoxycoumarins, Indian J. Chem., Sect B. 17 (1979) 410–411.
[9] G.S. Bajwa, K.E. Hartman, M.M. Joullie, Antimalarials. 1. Heterocyclic analogs of *N*-substituted naphthalenebisoxazines, J. Med. Chem. 16 (1973) 134–138.
[10] X. Luo, J. Song, L. Cheng, D. Huang, Preparation of some new coumarin dyes, Sci. China. Ser. B. 44 (2001) 532–539.
[11] M. Min, B. Kim, S. Hong, Direct C-H cross-coupling approach to heteroaryl coumarins, Org. Biomol. Chem. 10 (2012) 2692–2698.
[12] J. Donovalová, M. Cigáň, H. Stankovičová, J. Gašpar, M. Danko, A. Gáplovský, P. Hrdlovič, Spectral properties of substituted coumarins in solution and polymer matrices, Molecules 17 (2012) 3259–3276.
[13] M.-S. Schiedel, C.A. Briehn, P. Bäuerle, Single-Compound Libraries of Organic Materials: Parallel Synthesis and Screening of Fluorescent Dye, Angew. Chem. Int. Edit. 40 (2001) 4677–4680.
[14] G. Jones, W.R. Jackson, C.Y. Choi, W.R. Bergmark, Solvent effects on emission yield and lifetime for coumarin laser dyes. Requirements for a rotatory decay mechanism, J. Phys. Chem. 89 (1985) 294–300.
[15] R.S. Koefod, K.R. Mann, Preparation, photochemistry, and electronic structures of coumarin laser dye complexes of cyclopentadienylruthenium(II), Inorg. Chem. 28 (1989) 2285–2290.
[16] A.R. Jagtap, V.S. Satam, R.N. Rajule, V.R. Kanetkar, The synthesis and characterization of novel coumarin dyes derived from 1,4-diethyl-1,2,3,4-tetrahydro-7-hydroxyquinoxalin-6-carboxaldehyde, Dyes Pigments 82 (2009) 84–89.

[17] B.D. Wagner, The use of coumarins as environmentally-sensitive fluorescent probes of heterogeneous inclusion systems, Molecules 14 (2009) 210–237.
[18] K. Hara, M. Kurashige, Y. Dan-oh, C. Kasada, A. Shinpo, S. Suga, K. Sayama, H. Arakawa, Design of new coumarin dyes having thiophene moieties for highly efficient organic-dye-sensitized solar cells, New J. Chem. 27 (2003) 783–785.
[19] M.-T. Lee, C.-K. Yen, W.-P. Yang, H.-H. Chen, C.-H. Liao, C.-H. Tsai, C.H. Chen, Efficient Green Coumarin Dopants for Organic Light-Emitting Devices, Org. Lett. 6 (2004) 1241–1244.
[20] S.A. Swanson, G.M. Wallraff, J.P. Chen, W. Zhang, L.D. Bozano, K.R. Carter, J.R. Salem, R. Villa, J.C. Scott, Stable and Efficient Fluorescent Red and Green Dyes for External and Internal Conversion of Blue OLED Emission, Chem. Mater. 15 (2003) 2305–2312.
[21] C.-H. Chang, H.-C. Cheng, Y.-J. Lu, K.-C. Tien, H.-W. Lin, C.-L. Lin, C.-J. Yang, C.-C. Wu, Enhancing color gamut of white OLED displays by using microcavity green pixels, Org. Electron. 11 (2010) 247–254.
[22] T. Yu, P. Zhang, Y. Zhao, H. Zhang, J. Meng, D. Fan, Synthesis, characterization and high-efficiency blue electroluminescence based on coumarin derivatives of 7-diethylamino-coumarin-3-carboxamide, Org. Electron. 10 (2009) 653–660.
[23] A. Dorlars, C.-W. Schellhammer, J. Schroeder, Heterocycles as building blocks of new fluorescent whiteners, Angew. Chem. Int. Edit. 87 (1975) 693–707.
[24] S.S. Keskin, N. Aslan, F. Bayrakeken, Optical properties and chemical behavior of laser-dye Coumarin-500 and the influence of atmospheric corona discharges, Spectrochim. Acta. Part A. 72 (2009) 254–259.
[25] J. Kido, Y. Iizumi, Fabrication of highly efficient organic electroluminescent devices, Appl. Phys. Lett. 73 (1998) 2721–2723.
[26] C.R. Moylan, Molecular hyperpolarizabilities of coumarin dyes, J. Phys. Chem. 98 (1994) 13513–13516.
[27] A. Painelli, F. Terenziani, Linear and non-linear optical properties of push-pull chromophores: vibronic and solvation effects beyond perturbation theory, Synth. Met. 124 (2001) 171–173.
[28] K.A. Wilze, A.K. Johnson, In Handbook of Detergents, Chemistry, Production, and Application of Fluorescent Whitening Agents, Part F: Production;, 28, CRC Press, Taylor & Francis, Boca Raton, FL, 2007p. 554.
[29] J.H. Kim, H.J. Kim, S.H. Kim, J.H. Lee, J.H. Do, H.-J. Kim, J.H. Lee, J.S. Kim, Fluorescent coumarinyldithiane as a selective chemodosimeter for mercury (II) ion in aqueous solution, Tetrahedron Lett. 50 (2009) 5958–5961.
[30] H.S. Jung, P.S. Kwon, J.W. Lee, J.I.I. Kim, C.S. Hong, J.W. Kim, S. Yan, J.Y. Lee, J.H. Lee, T. Joo, J.S. Kim, Coumarin-Derived Cu^{2+} -Selective Fluorescence Sensor: Synthesis, Mechanisms, and Applications in Living Cells, J. Am. Chem. Soc. 131 (2009) 2008–2012.
[31] R. Sheng, P. Wang, Y. Gao, Y. Wu, W. Liu, J. Ma, H. Li, S. Wu, Colorimetric Test Kit for Cu^{2+} Detection, Org. Lett. 10 (2008) 5015–5018.
[32] H.-J. Kim, J.-E. Park, M.-G. Choi, S. Ahn, S.-K. Chang, Selective chromogenic and fluorogenic signalling of Hg^{2+} ions using a fluorescein-coumarin conjugate, Dyes Pigments 84 (2010) 54–58.
[33] W. Lin, L. Yuan, X. Cao, W. Tan, Y. Feng, A coumarin-based chromogenic sensor for transition-metal ions showing ion-dependent bathochromic shift, Eur. J. Org. Chem. 29 (2008) 4981–4987.
[34] S. Mizukami, S. Okada, S. Kimura, K. Kikuchi, Design and Synthesis of Coumarin-Based Zn^{2+} Probes for Ratiometric Fluorescence Imaging, Inorg. Chem. 48 (2009) 7630–7638.
[35] M. Çamur, M. Bulut, M. Kandaz, O. Guney, Effects of coumarin substituents on the photophysical properties of newly synthesised phthalocyanine derivatives, Supramol. Chem. 21 (2009) 624–631.
[36] F.M.A.A. El-Taweel, M.H. Elnagdi, Studies with enaminones: synthesis of new coumarin-3-yl azoles, coumarin-3-yl azines, coumarin-3-yl azoloazines, coumarin-3-yl pyrone, and coumarin-2-yl benzo[*b*]furans, J. Heterocycl. Chem. 38 (2001) 981–984.
[37] W. Zhu, J. Wang, S. Wang, Z. Gu, J.L. Aceña, K. Izawa, H. Liu, V.A. Soloshonok, Recent advances in the trifluoromethylation methodology and new CF_3-containing drugs, J. Fluorine Chem. 167 (2014) 37–54.
[38] R.D. Chambers, Fluorine in Organic Chemistry;, Blackwell, Oxford, 2004, pp. 259–264.
[39] P. Kirsch, Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Aplications;, Wiley-VCH, Weinheim, Germany, 2004.
[40] J.P. Begué, D. Bonnet-Delpon, Bioorganic and Medicinal Chemistry of Fluorine Wiley, John Willey & Sons, Inc, Hoboken, NJ, 2008.
[41] P. Maienfish, R.G. Hall, The importance of fluorine in the life science industry, Chimia 58 (2004) 93–99.
[42] Z.-P. Liu, Chiral nonracemic fluorinated compounds, the synthesis and applications, Curr. Org. Chem. 14 (2010) 888.
[43] K. Mikami, Y. Itoh, M. Yamanaka, Fluorinated Carbonyl and Olefinic Compounds: Basic Character and Asymmetric Catalytic Reactions, Chem. Rev. 104 (2004) 1–16.
[44] M.A. McClinton, D.A. McClinton, Trifluoromethylations and related reactions in organic chemistry, Tetrahedron 48 (1992) 6555–6666.
[45] P. Lin, J. Jiang, Synthesis of mono(trifluoromethyl)-substituted saturated cycles, Tetrahedron 56 (2000) 3635–3671.
[46] E.L. Luzina, A.V. Popov, Synthesis and anticancer activity of N-bis(trifluoromethyl)alkyl-N'-thiazolyl and N-bis(trifluoromethyl)alkyl-N'-benzothiazolyl ureas, Eur. J. Med. Chem. 44 (2009) 4944–4953.
[47] E.L. Luzina, A.V. Popov, Anticancer activity of N-bis(trifluoromethyl)alkyl-N'-(polychlorophenyl) and N'-(1,2,4-triazolyl) ureas, Eur. J. Med. Chem. 45 (2010) 5507–5512.
[48] E.L. Luzina, A.V. Popov, Synthesis, evaluation of anticancer activity and COMPARE analysis of *N*-bis(trifluoromethyl)alkyl-*N'*-substituted ureas with pharmacophoric moieties, Eur. J. Med. Chem. 53 (2012) 364–373.
[49] R. Filler, Y. Kobayashi (Eds.), Biomedicinal Aspects of Fluorine Chemistry, Elsevier, Amsterdam, 1982.
[50] J.T. Welch, S. Eswarakrishnan, Fluorine in Bioorganic Chemistry, John Wiley & Sons, New York, 1990.
[51] R.E. Filler, Organic Chemistry in Medicinal Chemistry and Applications, Plenum and Elsevier, Amsterdam, 1993.
[52] R. Ling, M. Yoshida, P.S. Mariano, Exploratory Investigations Probing a Preparatively Versatile, Pyridinium Salt Photoelectrocyclization-Solvolytic Aziridine Ring Opening Sequence, J. Org. Chem. 61 (1996) 4439–4449.
[53] V.G. Nenajdenko, E.S. Balenkova, Preparation of α,β-unsaturated trifluoromethyl ketones and their application in the synthesis of heterocycles, ARKIVOC i (2011) 246–328.
[54] J.C. Sloop, C.L. Bumgardner, W.D. Loehle, Synthesis of fluorinated heterocycles, J. Fluorine Chem. 118 (2002) 135–147.
[55] Y. Inouye, K. Tezuka, W. Takeda, S. Sugai, Synthetic utilization of methyl 2-(F-methyl)-2-hydryl-F-propyl ether. Part III. A simple one-pot preparation and derivatization of 2-(alkylthio)-5-(F-methyl)-6-fluoro-3,4-dihydro-4(3*H*)-pyrimidinones, J. Fluorine Chem. 35 (1987) 275–285.
[56] M.E. Pierce, R.L. Parsons, L.A. Radesca, Y.S. Lo, S. Silverman, J.R. Moore, Q. Islam, A. Choudhury, J.M.D. Fortunak, D. Nguyen, C. Luo, S.J. Morgan, W.P. Davis, P.N. Confalone, C. Chen, R.D. Tillyer, L. Frey, L. Tan, F. Xu, D. Zhao, A.S. Thompson, E.G. Corley, E.J.J. Grobowski, R. Reamer, P.J. Reider, Practical Asymmetric Synthesis of Efavirenz (DMP 266), an HIV-1 Reverse Transcriptase Inhibitor, J. Org. Chem. 63 (1998) 8536–8543.
[57] J.T. Welch, Advances in the preparation of biologically active organofluorine compounds, Tetrahedron 43 (1987) 3123–3197.
[58] A.A. Bekhit, T. Abdel-Azien, Design, synthesis and biological evaluation of some pyrazole derivatives as anti-inflammatory-antimicrobial agents, Bioorg. Med. Chem. 12 (2004) 1935–1945.
[59] C.C. Cheng, E.F. Elslager, L.M. Werbel, S.R. Priebe, W.R. Leopold, Pyrazole derivatives. 5. Synthesis and antineoplastic activity of 3-(2-chloroethyl)-3,4-dihydro-4-oxopyrazolo[5,1-d]-1,2,3,5-tetrazine-8-carboxamide and related compounds, J. Med. Chem. 29 (1986) 1544–1547.
[60] H.G. Bonacorso, S. Cavinatto, P.T. Campos, L.M.F. Porte, J. Navarini, G.R. Paim, M.A.P. Martins, N. Zanatta, C.Z. Stuker, New trifluoromethyl-containing (*E*)-*N'*-arylidene-[3-alkyl(aryl/heteroaryl)-4,5-dihydro-1*H*-pyrazol-1-yl]carbohydrazides: Synthesis, crystal structure and antimicrobial/antioxidant activity, J. Fluorine Chem. 135 (2012) 303–314.
[61] P. Machado, P.T. Campos, G.R. Lima, F.A. Rosa, A.F.C. Flores, H.G. Bonacorso, N. Zanatta, M.A.P. Martins, Experimental and calculated structural parameters of 5-trihalomethyl-4,5-dihydro-1H-pyrazole derivatives, novel analgesic agents, J. Mol. Struct. 15 (2009) 176–182.
[62] P.D. Sauzem, G.S. Sant'Anna, P. Machado, M.M.M.F. Duarte, J. Ferreira, C.F. Mello, P. Beck, H.G. Bonacorso, N. Zanatta, M.A.P. Martins, M.A. Rubin, Effect of 5-trifluoromethyl-4,5-dihydro-1H-pyrazoles on chronic inflammatory pain model in rats, Eur. J. Pharmacol. 616 (2009) 91–100.
[63] D.M. Martins, B.G. Torres, P.R. Spohr, P. Machado, H.G. Bonacorso, N. Zanatta, M.A.P. Martins, T. Emanuelli, Antioxidant potential of new pyrazoline derivatives to prevent oxidative damage, Basic Clin. Pharmacol. Toxicol. 104 (2009) 107–112.
[64] S.M. Oliveira, C.R. Silva, A.P. Wentz, G.R. Paim, M.S. Correa, H.G. Bonacorso, A.S. Prudente, M.F. Otuki, J. Ferreira, Antinociceptive effect of 3-(4-fluorophenyl)-5-trifluoromethyl-1*H*-1-tosylpyrazole. A Celecoxib structural analog in models of pathological pain, Pharmacol. Biochem. Behav. 124 (2014) 396–404.
[65] W. Cunico, C.A. Cechinel, H.G. Bonacorso, M.A.P. Martins, N. Zanatta, M.V.N. de Souza, I.O. Freitas, R.P.P. Soares, A.U. Kretlli, Antimalarial activity of 4-(5-trifluoromethyl-1*H*-pyrazol-1-yl)-chloroquine analogues, Bioorg. Med. Chem. Lett. 16 (2006) 649–653.
[66] R. Filler, Organofluorine Chemicals and Their Industrial Applications, Banks, Ellis Harwood, London, 1979, R.E. (Ed.).
[67] H. Amii, Y. Kishikawa, K. Uneyama, Rh(I)-Catalyzed Coupling Cyclization of N-Aryl Trifluoroacetimidoyl Chlorides with Alkynes: One-Pot Synthesis of Fluorinated Quinolines, Org. Lett. 3 (2001) 1109–1112.
[68] Y. Zhao, A. Bacher, B. Illarionov, M. Fischer, G. Georg, Q. Ye, P.E. Fanwick, S.G. Franzblau, B. Wan, M. Cushman, Discovery and Development of the Covalent Hydrates of Trifluoromethylated Pyrazoles as Riboflavin Synthase Inhibitors with Antibiotic Activity Against Mycobacterium tuberculosis, J. Org. Chem. 74 (2009) 5297–5303.
[69] M.A.P. Martins, P. Machado, F.A. Rosa, M. Rossatto, P.D. Sauzem, R.M.S. Silva, M.A. Rubin, J. Ferreira, H.G. Bonacorso, N. Zanatta, Synthesis and structure of novel 4,5-dihydro-1H-pyrazoles. Salicylic acid-based analgesic agents, ARKIVOC xvi (2007) 281–297.
[70] C.A. Lipinski, F. Lombardo, B.W. Dominy, P.J. Freeney, Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings, Adv. Drug Deliver. Rev. 23 (1997) 3–25.
[71] E.L. Luzina, A.V. Popov, Synthesis of 3,3,3-trifluoroethyl isocyanate, carbamate and ureas. Anticancer activity evaluation of N-(3,3,3-trifluoroethyl)-N'-substituted ureas, J. Fluorine Chem. 176 (2015) 82–88.
[72] E.L. Luzina, A.V. Popov, Synthesis of 1-aroyl(1-arylsulfonyl)-4-bis(trifluoromethyl)alkyl semicarbazides as potential physiologically active compounds, J. Fluorine Chem. 148 (2013) 41–48.

[73] E.L. Luzina, A.V. Popov, Synthesis and anticancer activity evaluation of 3,4-mono- and bicyclosubstituted N-(het)aryl trifluoromethyl succinimides, J. Fluorine Chem. 168 (2014) 121–127.
[74] G.E.H. Elgemeie, A.H.H. Elghandour, Activated nitriles in heterocyclic synthesis. Novel synthesis of 5-imino-5H-[1]benzopyrano[3,4-c]pyridine-4(3H)-thiones and their oxo analogs, B. Chem. Soc. Jpn. 63 (1990) 1230–1232.
[75] A. Colla, G. Clar, M.A.P. Martins, S. Krimmer, P. Fischer, Trihaloacetylated enol ethers. General synthetic procedure and heterocyclic ring closure reactions with hydroxylamine, Synthesis (1991) 483–486.
[76] M.A.P. Martins, W. Cunico, C.M.P. Pereira, A.P. Sinhorin, A.F.C. Flores, H.G. Bonacorso, N. Zanatta, 4-Alkoxy-1,1,1-trichloro-3-alken-2-ones: Preparation and applications in heterocyclic synthesis, Curr. Org. Synth. 1 (2004) 391–403.
[77] M.A.P. Martins, H.G. Bonacorso, N. Zanatta, D.N. Moreira, C.P. Frizzo, K. Longhi, Reaction of (-alkoxyvinyl halomethyl ketones with cyanoacetohydrazide, J. Braz. Chem. Soc. 19 (2008) 1361–1368.
[78] D.N. Moreira, C.P. Frizzo, K. Longhi, A.B. Soares, M.R.B. Marzari, L. Buriol, S. Brondani, N. Zanatta, H.G. Bonacorso, M.A.P. Martins, Ionic liquid and Lewis acid combination in the synthesis of novel (E)-1-(benzylideneamino)-3-cyano-6-(trifluoromethyl)-1H-2-pyridones, Monatsh Chem. 142 (2011) 1265–1270.
[79] T.M.A. Elmaati, F.M. El-Taweel, S.M. Elmougi, A. Elagamey, The condensation of active methylene reagents with salicylaldehyde: Novel synthesis of chromene, azaanthracene, pyrano[3,4-*c*]chromene and chromeno[3,4-*c*]pyridine derivatives, J. Heterocycl. Chem. 41 (2004) 655–658.
[80] H.G. Bonacorso, H. Lewandowski, R.L. Drekener, M.B. Costa, C.M.P. Pereira, A.D. Wastowski, C. Peppe, M.A.P. Martins, N. Zanatta, Reactions of β-methoxyvinyl trifluoromethyl ketones with 2-pyridinecarboxamidrazone. A convenient route to trifluoromethylated 4,5-dihydro-1H-1-picolinoylpyrazole hydrochlorides, J. Fluorine Chem. 122 (2003) 159–163.
[81] A. Padwa, A Novel 2,2,1-Bicyclic Elimination of a N-Tosylpyrazoline, J. Org. Chem. 30 (1965) 1274–1275.
[82] G. Volmajer, R. Toplak, I. Leban, A. Majcen Le Marechal, Synthesis of new iminocoumarins and their transformations into N-chloro and hydrazono compounds, Tetrahedron 61 (2005) 7012–7021.
[83] Crystallographic data for the structure of 6b and 10c, reported in this paper have been deposited with the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 1056179 and CCDC 1056083. Copies of the data can be obtained free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. (fax: +44 1223 336033 or deposit@ccdc.com.ac.uk).
[84] H.M. Al-Matar, A.Y. Adam, K.D. Khalil, M.H. Elnagdi, Studies with 3-oxoalkanenitriles: novel rearrangements observed while exploring the utility of 2-cyanoacetyl-1-methylpyrrole as a precursor to pyrrole substituted heterocyclic compounds, ARKIVOC vi (2012) 1–15.
[85] Bruker, APEX2 (Version 2.1), COSMO (Version 1.56), BIS (Version 2.0.1.9), SAINT (Version 7. 3A) and SADABS (Version 2004/1) and XPREP9 (Version 2005/4), Bruker AXS Inc, Madison, WI, USA, 2006.
[86] G.M. Sheldrick, SHELXS-97, Program for Crystal Structure Solution, University of Göttingen, Germany, 1997.
[87] G.M. Sheldrick, SHELXL-97, Program for Crystal Structure Refinement, University of Göttingen, Germany, 1997.
[88] P. Coppens, L. Leiserowitz, D. Rabinovich, Calculation of absorption corrections for camera and diffractometer data, Acta Crystallogr. 18 (1965) 1035–1038.
[89] L.J. Farrugia, ORTEP-3 for windows - a version of ORTEP-III with a graphical user interface (GUI), Appl. Crystallogr. 30 (1997) 565.