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Substrate-dependent regiodivergent three-component condensation of 1*H*-pyrrole-2,3-diones, malononitrile and 4-hydroxyquinolin-2(1*H*)-ones

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ABSTRACT

An efficient regiodivergent three-component condensation of 1*H*-pyrrole-2,3-diones, malononitrile, and 4-hydroxyquinolin-2(1*H*)-ones was developed. The reaction can lead to the formation of spiro[pyrano[3,2-*c*]quinoline-4,3′-pyrrole] derivatives or the substituted 1,5-dihydropyrrole-2-ones depending on the substituents of 1*H*-pyrrole-2,3-diones and reaction conditions.

1. Introduction

Alkaloids bearing the pyranoquinoline core are omnipresent in nature. One of the best known representatives of pyranoquinoline alkaloids, haplamine, exhibits strong anti-proliferative and anti-cancer activities (Fig. 1) [1]. Another one, flindersine, demonstrates antifungal, antialgal and anti-inflammatory activities [2]. Furthermore, flindersine could be used as an ecofriendly pesticide due to its larvicidal and growth inhibitory activities against some species of insects [3]. Synthetic pyranoquinolines exhibit antibacterial [4], anti-proliferative [5], and multi-trypanosomatid [6] activities (Fig. 1).

One of the most popular approaches to the synthesis of pyranoquinolines involves multicomponent reactions (MCRs) of carbonyl compounds. MCRs have many advantages over step-by-step synthesis, such as simple implementation, step and atom economy [7]. In recent years, MCRs have become an indispensable tool in the synthesis of complex heterocyclic systems aimed at chemical diversity by combining the simplest reagents [8]. Examples of the pyranoquinoline synthesis via MCRs are Povarov reaction employing aldehydes, anilines and 3,4-dihydropyran [9] or three-component reaction of aldehydes, ethyl cyanoacetate or malononitrile and 4-hydroxyquinolin-2(1*H*)-ones [4,10]. Isatin was also used in the role of a highly activated carbonyl compound for the synthesis of pyranoquinolines (Scheme 1 (a)) [11], however, there are no literature examples describing the employment of its monocyclic analogues, 1*H*-pyrrole-2,3-diones.

It should be pointed out, that in contradistinction to isatin, 1*H*-pyrrole-2,3-diones could be viewed as vinylogous amides with a highly electrophilic C-5 atom, that preferably undergoes nucleophilic attack, especially if it is activated by additional EWGs [12]. Presence of at least three electrophilic centers (C-5, C-3 and C-2 atoms) in 1*H*-pyrrole-2,3-diones makes them attractive substrates for designing three-component reactions leading to the formation of several types of skeletally diverse scaffolds. Thus, reactions involving C-5 atom can lead to the products based on the poly-substituted 1,5-dihydropyrrole-2-one skeleton (Fig. 2) [13] which

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0040-4020/

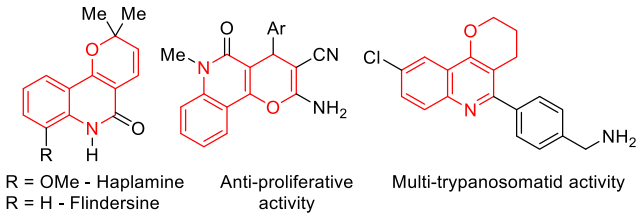
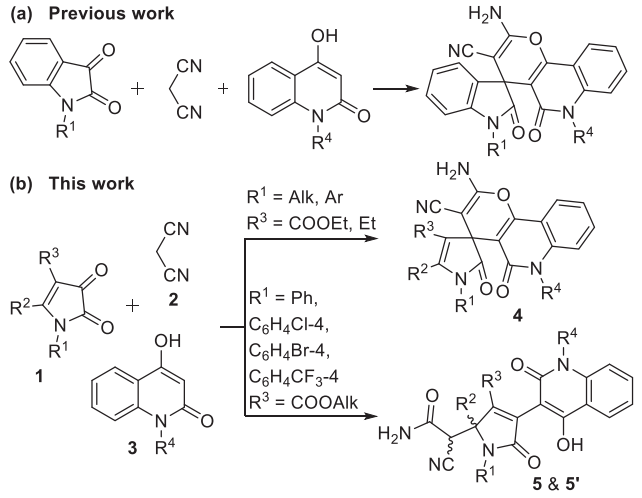


Fig. 1. Biologically active pyranoquinolines.



Scheme 1. Three-component reactions of activated ketones, malononitrile, and 4-hydroxyquinolin-2(1*H*)-ones.

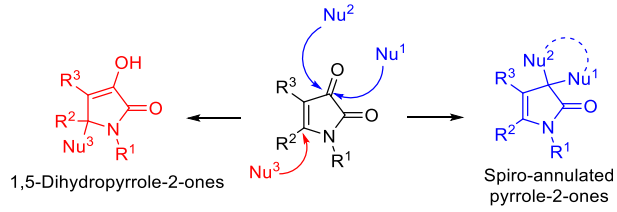


Fig. 2. Typical pathways for the reactions of 1*H*-pyrrole-2,3-diones with nucleophiles.

are of interest for medicinal chemistry and pharmaceutics due to their diverse biological activity [14]. At the same time, reactions proceeding selectively at C-3 atom (ketone carbonyl) can result in the spiro-annulated pyrrole-2-ones at the 3-position (Fig. 2) [15]. This structural motif is found in many natural products that have a wide variety of biological activities such as antiviral, antimicrobial and cytotoxic activities [16].

Herein, we report a regiodivergent three-component reaction of 1*H*-pyrrole-2,3-diones **1**, malononitrile **2**, and 4-hydroxyquinolin-2(1*H*)-ones **3** affording spiro[pyrano[3,2-*c*]quinoline-4,3′-pyrrole] derivatives **4** or a novel type of pyrrole-2-one derivatives **5** and **5'** (Scheme 1 (b)).

2. Results and discussion

We initially investigated the one-pot three-component reaction of 1*H*-pyrrole-2,3-dione **1a**, malononitrile **2**, and 4-hydroxy-1-methylquinolin-2(1*H*)-one **3a** catalyzed by Et_3N (20 mol %) in acetonitrile under reflux (Table 1, entry 1). The target product **4a** was isolated in a low yield of 28%, fully characterized, and its structure was confirmed by single crystal X-ray analysis (CCDC 2052374).

We examined this reaction under various conditions (Table 1). As expected, only trace amounts of product **4a** were detected in the reaction without any catalyst (Table 1, entry 2). Among the different protic and non-protic solvents, acetonitrile at 80 °C in the presence of Et_3N gave the maximum yield of 41% for 3 h (Table 1, entry 12).

Also, we investigated this reaction in acetonitrile in the presence of the other catalysts. Among the tested basic catalysts, DMAP was the most effective and allowed to improve the yield up to 65% (Table 1, entries 18–20). Thus, reflux in acetonitrile for 3 h in the presence of 20 mol % of DMAP was chosen as the optimal reaction conditions (conditions A).

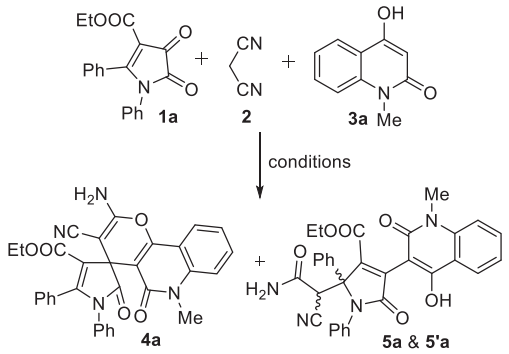
Notably, the concurrent isomeric products **5a** and **5′a** with molecular mass greater than that of product **4a** by 18 were detected by HPLC-MS in all cases during the optimization of reaction conditions. The highest yields of these products were observed when the reaction was carried out in THF with Et_3N as a catalyst (Table 1, entry 7). Applying these conditions, we isolated the substituted 1,5-dihydropyrrole-2-ones **5a** and **5′a** as inseparable diastereomeric mixture with total yield of 51% and established their structures. The structure of major diastereomers **5** was unequivocally proved by single crystal X-ray analysis by an example of compound **5b** (CCDC 2052375).

Considering the potential interest of poly-substituted 1,5-dihydropyrrole-2-ones for medicinal chemistry and pharmaceutics, we decided to try improving the yields of compounds **5a** and **5′a**, and testing various catalysts (Table 2) for its synthesis in THF. Unfortunately, the examined catalysts did not increase the product yields. Thus, we chose refluxing reagents in THF in the presence of 20 mol % of Et_3N as the optimal conditions for the preparation of products **5** and **5'** (conditions B).

After the optimization of the conditions for the synthesis of compounds **4**, this methodology (conditions A) was evaluated by using various 1*H*-pyrrole-2,3-diones **1** and 4-hydroxyquinolin-2(1*H*)-ones **3** (Table 3). The substituents in compounds **3** have a weak effect on the yield, while the substituents in 1*H*-pyrrole-2,3-diones have a significant effect. 4-Ethyl substituted 1*H*-pyrrole-2,3-diones **1g,h** reacted smoothly regardless of the substituents R^1 at the nitrogen atom. Concerning the reaction of 4-ethoxycarbonyl substituted 1*H*-pyrrole-2,3-diones **1a-e**, we observed that the yield of target products **4** depends on the electron-withdrawing properties of the substituent R^1. Thus, 1-alkyl substituted 1*H*-pyrrole-2,3-diones **1b,c** afforded products **4** with significantly higher yields compared to 1-aryl substituted 1*H*-pyrrole-2,3-diones **1a,d,e**. On the contrary, the electron-withdrawing strength of chlorophenyl is sufficient enough for 1*H*-pyrrole-2,3-dione **1f** to form the products **5b** and **5′b** (Table 4, entry 3) instead of the product **4i** (Table 3). Probably, in this case, two electron-withdrawing substituents (R^1 = chlorophenyl, R^3 = COOEt) increase electrophilicity of the C-5 atom in the pyrroledione **1f**, that leads to a change in the site of nucleophilic attack by malononitrile. It should be noted, that the compounds **5b** and **5′b** were isolated from both reaction conditions A and B (Table 4, entries 2, 3), however, the yield was higher in more optimal conditions B.

Next, we explored the substrate scope of the new approach to 1,5-dihydropyrrole-2-ones **5** and **5'** (Table 4). 4-Hydroxyquinolin-2(1*H*)-ones **3a,b** reacted with 4-alkoxycarbonyl-1*H*-pyrrole-2,3-diones **1a,f,i-l** having phenyl, halogenphenyl or trifluoromethylphenyl substituents at the nitrogen atom to afford compounds **5** and **5′** in reasonable yields. Unfortunately, less electron-deficient 1*H*-pyrrole-2,3-diones **1b-e** did not afford the compounds **5** and **5′** in isolable amounts. Therefore, the presence of several EWGs in pyrrolediones and fine-tuning its electronic properties are requisite for the successful implementation of this

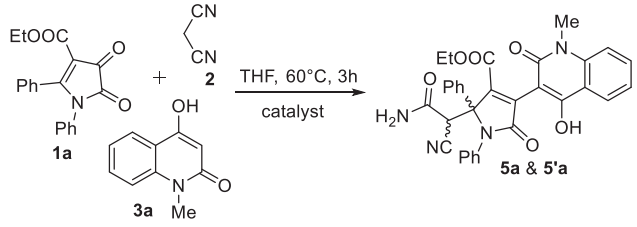
Table 1
Optimization of reaction conditions for the preparation of product **4a**.[a]



Entry	Solvent	Temp. (°C)	Catalyst (20 mol%)	Time (h)	Yield of 4a (%)[b]	Yield of 5a & 5′a (%)[b]
1[c]	MeCN	82	Et_3N	3	28	–
2	MeCN	80	–	7	trace	4
3	EtOH	60	Et_3N	7	6	21
4	HOAc	60	Et_3N	7	15	trace
5	Toluene	60	Et_3N	7	15	8
6	THF	60	Et_3N	7	16	54
7	THF	60	Et_3N	3	12	60
8	Ethyl acetate	60	Et_3N	7	18	30
9	DMSO	60	Et_3N	7	17	13
10	1,4-Dioxane	60	Et_3N	7	14	23
11	MeCN	60	Et_3N	7	29	19
12	MeCN	80	Et_3N	3	41	15
13	MeCN	80	Piperidine	3	23	2
14	MeCN	80	DBU	3	38	6
15	MeCN	80	NaOAc	3	46	8
16	MeCN	80	DABCO	3	13	5
17	MeCN	80	Pyridine	3	30	18
18	MeCN	80	DMAP	3	65	2
19	MeCN	80	DMAP	7	65	2
20[d]	MeCN	80	DMAP	3	66	5

[a] Reagents and conditions: **1a** (0.25 mmol), **2** (0.25 mmol), **3a** (0.25 mmol), catalyst (0.05 mmol), solvent (2.5 mL), in a capped vial.
[b] Yields were determined by HPLC.
[c] Reagents and conditions: **1a** (1 mmol), **2** (1 mmol), **3a** (1 mmol), Et_3N (0.2 mmol), MeCN (10 mL), in a flask, at reflux.
[d] 1 Equiv. of DMAP was used.

Table 2
Optimization of reaction conditions for the preparation of products **5a** and **5′a**.[a]



Entry	Catalyst (20 mol%)	Yield of 5a & 5′a (%)[b]
1	DMAP	22
2	DBU	35
3	NaOAc	28
4	Pyridine	8
5	HOAc	6
6[c]	Et_3N	42

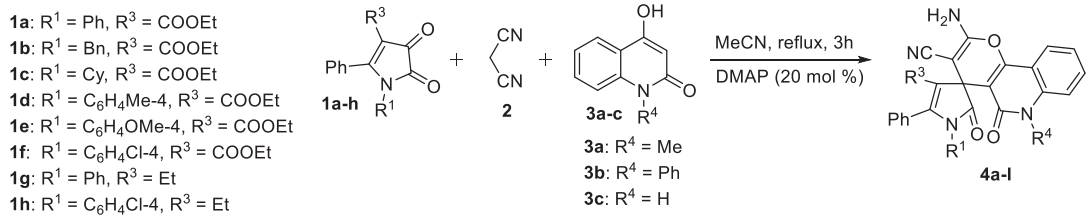
[a] Reagents and conditions: **1a** (0.25 mmol), **2** (0.25 mmol), **3a** (0.25 mmol), catalyst (0.05 mmol), THF (2.5 mL), in a capped vial, at 60 °C, 3 h.
[b] Yields were determined by HPLC.
[c] 1 Equiv. of Et_3N was used.

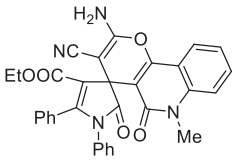
method. Notably, after recrystallization of compounds **5** and **5′**, we obtained mixtures with a higher dr value, which is probably associated with epimerization in solutions due to enolization of the cyanoacetamide fragment. To confirm the possibility of epimerization, we recorded ^{1}H NMR spectra of compounds **5h** and **5′h** immediately after dissolution in DMSO-d_6 and after 1 h. Indeed, the dr value changed from 5 : 1 to 2.5 : 1.

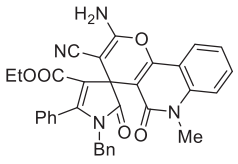
Our attempts to replace malononitrile with less reactive ethyl cyanoacetate or cyanoacetamide were unsuccessful both in the synthesis of derivatives of compounds **4** and **5**. The chemoselectivity of the reactions depended dramatically on the acidity of active methylene compounds. According to LC-MS data, in this case, the reaction mixtures were dominated by the products of the interaction of 1*H*-pyrrole-2,3-diones **1** with 4-hydroxyquinolin-2(1*H*)-ones **3** even when a stronger base (DBU) was used.

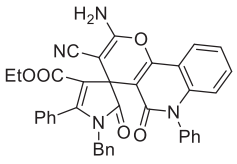
Previously, we reported the synthesis of analogues of spiro pyrroles **4** by the three-component reaction of 1*H*-pyrrole-2,3-diones and malononitrile with other enols such as 4-hydroxycoumarin, tetronic acid or 2-hydroxy-1,4-naphthoquinone [17]. Having discovered a new reaction pathway, we assumed that it could be realized with these enols. To test this, we investigated the three-component reaction of sufficiently electron-deficient pyrrolediones **1a,f** and malononitrile with 4-hydroxycoumarin, tetronic acid, and 2-hydroxy-1,4-naphthoquinone in conditions B (Scheme 2). To our satisfaction, we obtained products **6**–**8** and **6′-8′** with similar yields and higher diastereoselectivity compared to compounds **5** and **5'**. The

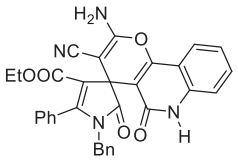
Table 3
Synthesis of the spiro[pyrano[3,2-*c*]quinoline-4,3′-pyrroles] **4a-l.**[a].

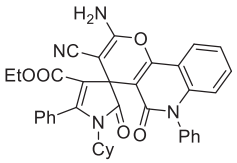


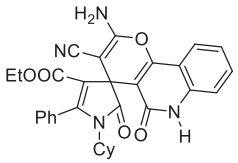

4a (56%)

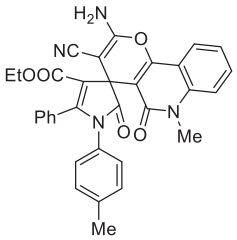

4b (87%)

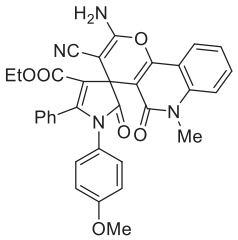

4c (93%)

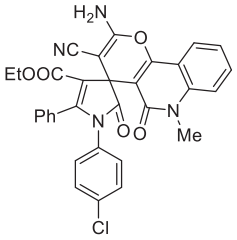

4d (83%)

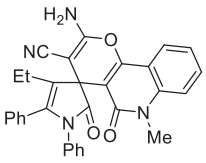

4e (72%)

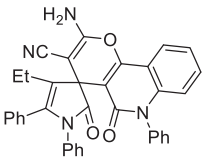

4f (67%)


4g (60%)


4h (65%)


4i (0%)


4j (74%)


4k (70%)

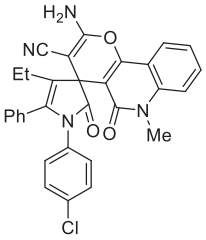
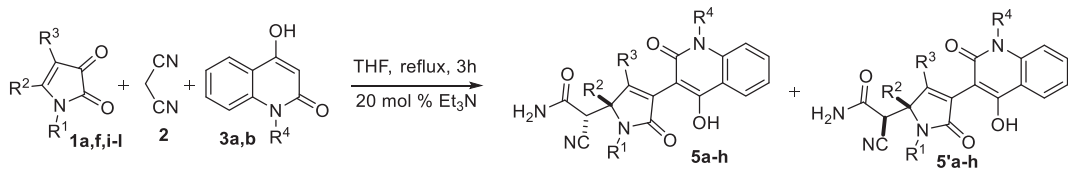
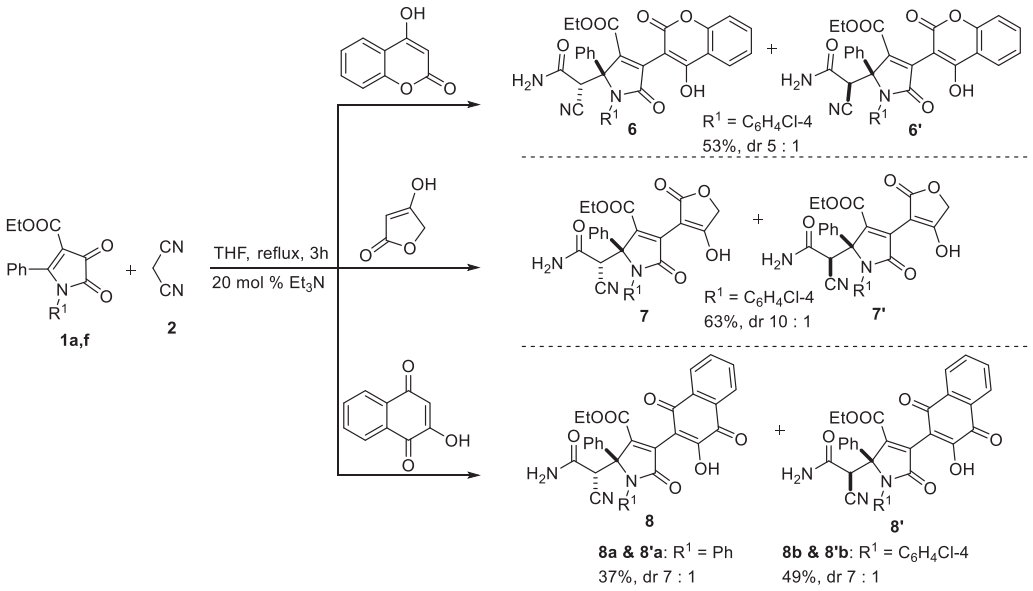

4l (68%)

Table 4
Synthesis of 1,5-dihydropyrrole-2-ones **5** and **5'**.[a]



Entry	1	3	R^1	R^2	R^3	R^4	5 and 5′	Yield of 5 and 5' (%)[b]	Ratio[c] 5/5' (dr)
1	**a**	**a**	Ph	Ph	COOEt	Me	**a**	51	2.1 : 1
2	**f**	**a**	C_6H_4Cl-4	Ph	COOEt	Me	**b**	56	2.8 : 1
3[d]	**f**	**a**	C_6H_4Cl-4	Ph	COOEt	Me	**b**	26	–
4	**i**	**a**	C_6H_4Br-4	Ph	COOEt	Me	**c**	49	2.9 : 1
5	**j**	**a**	Ph	C_6H_4Cl-4	COOMe	Me	**d**	47	2.4 : 1
6	**a**	**b**	Ph	Ph	COOEt	Ph	**e**	48	2.6 : 1
7	**f**	**b**	C_6H_4Cl-4	Ph	COOEt	Ph	**f**	58	3.2 : 1
8	**k**	**a**	$C_6H_4CF_3$-4	Ph	COOEt	Me	**g**	61	2.9 : 1
9	**l**	**a**	Ph	$C_6H_4NO_2$-4	COOEt	Me	**h**	49	3.4 : 1

[a] Conditions B: **1** (1 mmol), **2** (1 mmol), **3** (1 mmol), Et_3N (0.2 mmol), THF (10 mL), in a flask, at reflux, 3 h.
[b] Isolated yield.
[c] Determined by ^1H NMR spectroscopy for the crude mixtures.
[d] Conditions A: **1** (1 mmol), **2** (1 mmol), **3** (1 mmol), DMAP (0.2 mmol), MeCN (10 mL), in a flask, at reflux, 3 h.

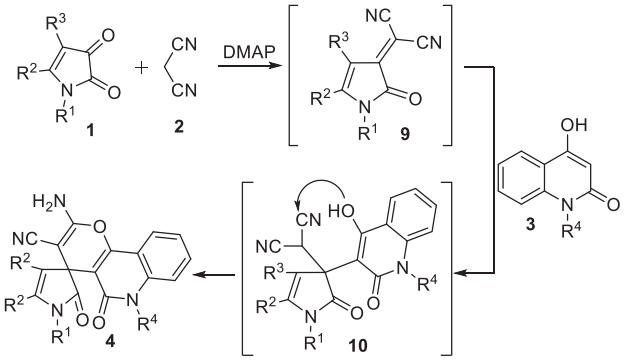


Scheme 2. Synthesis of 1,5-dihydropyrrole-2-ones **6**–**8** and **6′-8'**. Reaction scale: **1** (1 mmol), **2** (1 mmol), enols (1 mmol), Et_3N (0.2 mmol), THF (10 mL), in a flask. Yields are given for the isolated products.

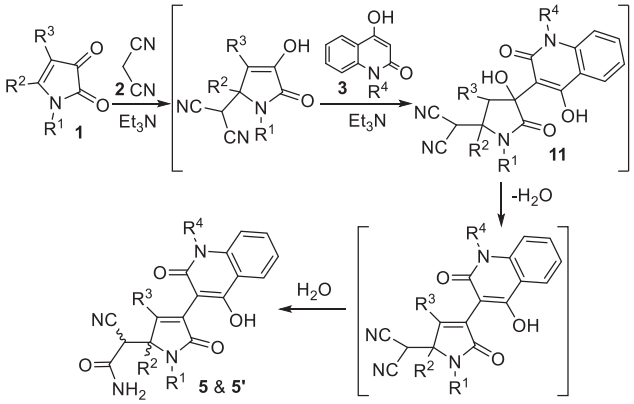
structure of the major diastereomer **6** was confirmed by X-ray analysis (CCDC 2052377).

The proposed mechanism for the synthesis of spiro[pyrano[3,2-*c*]quinoline-4,3′-pyrrole] derivatives **4** is described in Scheme 3. Knoevenagel condensation between 1*H*-pyrrole-2,3-diones **1** and malononitrile **2** leads to intermediate **9** of crimson or purple color. Michael addition of enols **3** to the exocyclic double bond of **9** gives intermediate **10,** which undergoes intramolecular cyclo-condensation to produce **4**. To confirm the reaction pathway, we independently prepared the intermediate **9a** (R^1 = Bn, R^2 = Ph, R^3 = COOEt) as crimson crystals, whose structure was established by single crystal X-ray analysis (CCDC 2052376). As expected, the compound **9a** was easily converted to **4c** under three-component reaction conditions with a yield of 96%.

The proposed mechanism for the synthesis of compounds **5** and **5′** is shown in Scheme 4. Malononitrile **2** and enols **3** successively attack C-5 and C-3 atoms of 1*H*-pyrrole-2,3-diones **1**, respectively, to form an intermediate **11** followed by dehydration and hydrolysis of one of the cyano-groups to obtain compounds **5** and **5'**. It should be noted, that the reactions in which two nucleophiles attack C-5 and C-3 atoms of 1*H*-pyrrole-2,3-diones have not been previously reported.



Scheme 3. The proposed mechanism for the formation of products **4**.



Scheme 4. The proposed mechanism for the formation of products **5** and **5'**.

3. Conclusions

In conclusion, a methodology for the synthesis of two distinct scaffolds of spiro[pyrano[3,2-*c*]quinoline-4,3′-pyrroles] and poly-substituted 1,5-dihydropyrrole-2-ones via the one-pot three-component reaction of 1*H*-pyrrole-2,3-diones, malononitrile, and 4-hydroxyquinolin-2(1*H*)-ones was developed. In the case of moderately electron-deficient 1*H*-pyrrole-2,3-diones, the reaction proceeds selectively via nucleophilic attack of both reagents on keto group affording spiro[pyrano[3,2-*c*]quinoline-4,3′-pyrroles] **4**, despite the presence of several electrophilic centers in 1*H*-pyrrole-2,3-diones. More electron-deficient 1*H*-pyrrole-2,3-diones react with malononitrile and 4-hydroxyquinolin-2(1*H*)-ones or other enols in a previously unknown way via nucleophilic attack of malononitrile at the C-5 atom and enol at the C-3 atom to form diastereomeric 1,5-dihydropyrrole-2-ones **5**–**8** and **5′-8'**.

4. Experimental section

4.1. General experimental information

^1H, ^{13}C, and ^{19}F NMR spectra were recorded on a Bruker Avance

III HD spectrometer (at 400, 101 or 377 MHz, respectively) using the residual solvent peak or C_6F_6 ($CDCl_3$: $\delta_F = -161.64$ ppm; DMSO-d_6: $\delta_F = -162.45$ ppm) [18] as internal standards. FT-IR spectra were recorded as mulls in mineral oil employing PerkinElmer Spectrum Two spectrometer. Elemental analyses were carried out on a Vario MICRO Cube analyzer. Melting points were measured with Mettler Toledo MP70 Melting Point apparatus. Reaction progress was monitored by LC-MS on a Waters UPLC-MS instrument Acquity I-Class equipped with a PDA eλ Detector and a Xevo TQD detector in ESI + ionization mode. The HRMS spectra were registered on a Bruker maXis Impact HD instrument operating in positive ion mode. X-ray structural analysis were performed on an Xcalibur Ruby diffractometer using Mo X-ray source (MoKα 0.71073 Å), scanning at 295(2) K. CCDC 2052374 (**4a**), 2052375 (**5b**), 2052377 (**6**), and 2052376 (**9a**) contain the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk. Column chromatography was performed on silica gel Acros Organics (35–70 μm). TLC was performed on plates Silica gel 60 F254 (Merck); spots were visualized with UV light (254 nm) and iodine vapors. Reagents were purchased from commercial sources and were used as received unless mentioned otherwise. Acetonitrile was dried over activated 4 Å molecular sieves. Anhydrous THF, toluene and hexane were obtained by heating at reflux over sodium and subsequent distillation under dry nitrogen atmosphere. Anhydrous $CHCl_3$ and CCl_4 were obtained by refluxing with phosphorus pentoxide followed by distillation under dry nitrogen atmosphere. 4-Hydroxyquinolin-2(1*H*)-ones **3a-c** [19], methyl 3-(4-chlorophenyl)-3-(phenylamino)acrylate [20], ethyl 3-(4-nitrophenyl)-3-(phenylamino)acrylate [21], and ethyl 1-benzyl-4-(dicyanomethylene)-5-oxo-2-phenyl-4,5-dihydro-1*H*-pyrrole-3-carboxylate **9a** [22] were prepared according to literature procedures. 1*H*-Pyrrole-2,3-diones **1a-f,i** were synthesized from oxalyl chloride and corresponding enamines in accordance with the known procedures [23].

4.2. Ethyl 3-phenyl-3-((4-(trifluoromethyl)phenyl)amino)acrylate (**12**) [24]

Ethyl phenylpropiolate (360 mg, 342 μL, 2.07 mmol), 4-(trifluoromethyl)aniline (500 mg, 389 μL, 3.11 mmol), $Cu(OTf)_2$ (75 mg, 0.207 mmol), molecular sieves 4 Å (600 mg), and anhydrous THF (2 mL) were placed in a round-bottomed flask. The reaction mixture was stirred at 50 °C for 24 h. The solution was cooled down to RT, and 20 mL of DCM were added. The mixture was washed sequentially with 1 M HCl (3 mL), water (20 mL) and brine. Organic phase was dried over Na_2SO_4, and solvent was evaporated. The residue was purified by column chromatography (hexane–toluene = 3:1, R_f 0.36), affording a white solid in 74% yield (510 mg), mp 84–85°C (hexane, toluene). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.39 (s, 1H), 7.42–7.28 (m, 7H), 6.68 (d, J = 8.3 Hz, 2H), 5.11 (s, 1H), 4.23 (q, J = 7.1 Hz, 2H), 1.33 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.0, 158.0, 143.9, 135.7, 130.0, 128.9 (2C), 128.2 (2C), 126.1 (q, J = 3.8 Hz, 2C), 124.5 (q, J = 32.6 Hz), 124.4 (q, J = 271.4 Hz), 121.0 (2C), 94.0, 59.8, 14.6.^{19}F NMR (377 MHz, $CDCl_3$) δ: −61.80 (s).

4.3. 4-Ethyl-1,5-diphenyl-1H-pyrrole-2,3-dione (**1g**)

Butyrophenone (14.82 g, 14.52 mL, 0.1 mol), aniline (9.31 g, 9.11 mL, 0.1 mol), $ZnCl_2$ (136 mg, 1 mmol) and *o*-xylene (15 mL) were placed in a round-bottomed flask equipped with Dean–Stark apparatus. The reaction mixture was refluxed for 15 h. The solution was cooled down to RT and decanted from insoluble salts. *o*-Xylene was evaporated and the oily residue, *N*,1-diphenylbutan-1-imine, was dissolved without additional purification in 150 mL of anhydrous CCl_4. Pyridine (15.82 g, 16.11 mL, 0.2 mol) was added to the resulted solution. The solution was cooled to 0 °C and oxalyl chloride (12.69 g, 8.57 mL, 0.1 mol) in 30 mL of anhydrous CCl_4 was added dropwise under stirring. Then, the mixture was heated to 50 °C and stirred for 1.5 h at this temperature. The mixture was cooled down to RT and washed sequentially with 1 M HCl (100 mL), water (50 mL) and brine. Organic phase was dried over Na_2SO_4, and 15 mL of anhydrous toluene was added to the solution. Then, CCl_4 was evaporated, and the formed precipitate was filtered off, affording a red solid in 51% yield (14.20 g), mp 164–165°C (toluene), lit. mp 162 °C [25]; IR ν, cm^{-1}: 1750, 1699, 1673.^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.43–7.32 (m, 3H), 7.29–7.17 (m, 5H), 7.00–6.95 (m, 2H), 2.34 (q, J = 7.5 Hz, 2H), 1.13 (t, J = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 184.9, 165.3, 158.2, 134.2, 131.1, 129.1 (2C), 128.7 (4C), 128.6, 127.5, 126.9 (2C), 115.7, 16.0, 13.9.

4.4. 1-(4-Chlorophenyl)-4-ethyl-5-phenyl-1H-pyrrole-2,3-dione (**1h**)

This compound was prepared according to the procedure listed for **1g** employing *p*-chloroaniline (12.76 g, 100 mmol) and isolated as red solid in 49% yield (15.42 g), mp 129–131°C (toluene); IR ν, cm^{-1}: 1752, 1704, 1670.^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.47–7.35 (m, 3H), 7.25–7.19 (m, 4H), 6.93–6.88 (m, 2H), 2.33 (q, J = 7.5 Hz, 2H), 1.12 (t, J = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 184.5, 164.6, 157.9, 133.3, 132.6, 131.3, 129.3 (2C), 128.9 (2C), 128.7 (2C), 128.2, 127.9 (2C), 116.1, 15.9, 13.8. HRMS (ESI+): *m/z* [M + H]$^+$ calcd for $C_{18}H_{14}ClNO_2$: 312.0786; found: 312.0787.

4.5. Methyl 2-(4-chlorophenyl)-4,5-dioxo-1-phenyl-4,5-dihydro-1H-pyrrole-3-carboxylate (**1j**)

To a stirred solution of methyl 3-(4-chlorophenyl)-3-(phenylamino)acrylate [19] (5.74 g, 20 mmol) in anhydrous $CHCl_3$ (12 mL), a solution of oxalyl chloride (2.67 g, 1.79 mL, 21.0 mmol) in anhydrous $CHCl_3$ (6 mL) was added dropwise at RT over 5 min. The mixture was heated for 2 h under reflux, cooled, and diluted with 20 mL of anhydrous hexane. The formed precipitate was filtered off, affording a red solid in 86% yield (5.85 g), mp 203–204°C (chloroform, hexane); IR ν, cm^{-1}: 1769, 1724, 1713.^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.39–7.27 (m, 7H), 7.00–6.95 (m, 2H), 3.73 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 177.7, 175.3, 161.4, 156.6, 138.8, 132.4, 130.8, 129.6 (2C), 129.0, 128.7 (2C), 127.7 (2C), 125.6, 104.4, 52.0. HRMS (ESI+): *m/z* [M + H]$^+$ calcd for $C_{18}H_{12}ClNO_4$: 342.0528; found: 342.0533.

4.6. Ethyl 4,5-dioxo-2-phenyl-1-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1H-pyrrole-3-carboxylate (**1k**)

The compound was prepared according to the procedure listed for **1j** employing ethyl 3-phenyl-3-((4-(trifluoromethyl)phenyl) amino)acrylate **12** (0.50 g, 1.5 mmol) and isolated as yellow solid in 86% yield (0.50 g), mp 175–176°C (chloroform, hexane); IR ν, cm^{-1}: 1771, 1747, 1695.^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.58–7.54 (m, 2H), 7.51–7.46 (m, 1H), 7.40–7.29 (m, 4H), 7.13–7.09 (m, 2H), 4.18 (q, J = 7.1 Hz, 2H), 1.17 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 177.5, 174.6, 160.8, 156.3, 136.0, 132.6, 130.7 (q, J = 33.2 Hz), 129.3 (2C), 128.5 (2C), 127.8 (2C), 127.2, 126.5 (q, J = 3.7 Hz, 2C), 123.6 (q, J = 272.5 Hz) 105.8, 61.1, 14.1.^{19}F NMR (377 MHz, $CDCl_3$) δ: −62.65 (s). Anal. calcd for $C_{20}H_{14}F_3NO_4$: C, 61.70; H, 3.62; N, 3.60. Found: C, 61.37; H, 3.87; N, 3.46.

*4.7. Ethyl 2-(4-nitrophenyl)-4,5-dioxo-1-phenyl-4,5-dihydro-1H-pyrrole-3-carboxylate (**1l**)*

The compound was prepared according to the procedure listed for **1j** employing ethyl 3-(4-nitrophenyl)-3-(phenylamino)acrylate [20] (3.12 g, 10 mmol) and isolated as orange solid in 69% yield (2.52 g), mp 199–201°C (toluene); IR ν, cm^{-1}: 1771, 1729, 1720, 1701.^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.18 (d, J = 8.4 Hz, 2H), 7.55 (d, J = 8.4 Hz, 2H), 7.36–7.27 (m, 3H), 7.00 (dd, J = 6.6, 2.9 Hz, 2H), 4.16 (q, J = 7.1 Hz, 2H), 1.17 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 177.7, 173.6, 160.5, 155.9, 149.4, 133.9, 132.1, 130.4 (2C), 129.8 (2C), 129.4, 127.7 (2C), 123.4 (2C), 105.1, 61.2, 14.1. Anal. calcd for $C_{19}H_{14}N_2O_6$: C, 62.30; H, 3.85; N, 7.65. Found: C, 62.24; H, 4.11; N, 7.52.

*4.8. General procedure for the preparation of products **4** (conditions A)*

To a solution of 1*H*-pyrrole-2,3-dione **1** (1 mmol), malononitrile **2** (1 mmol) and 4-hydroxyquinolin-2(1*H*)-one **3** (1 mmol) in anhydrous acetonitrile (10 mL) was added DMAP (0.2 mmol), and the reaction mixture was heated at reflux for 3 h. The resulting solution was cooled to RT, and the solvent was evaporated under reduced pressure. The residual solid was recrystallized from appropriate solvent (acetone or ethanol or their mixture) to afford **4** as white or yellow solid.

*4.8.1. Ethyl 2-amino-3-cyano-6-methyl-2′,5-dioxo-1′,5′-diphenyl-1′,2′,5,6-tetrahydrospiro[pyrano[3,2-c]quinoline-4,3′-pyrrole]-4′-carboxylate (**4a**)*

White crystalline solid, 56%, mp 289–291°C (ethanol); IR ν, cm^{-1}: 3457, 3353, 3306 (NH_2), 2189 (CN), 1738, 1672, 1630.^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.08 (dd, J = 8.0, 1.3 Hz, 1H), 7.78 (ddd, J = 8.6, 7.2, 1.5 Hz, 1H), 7.66 (d, J = 8.5 Hz, 1H), 7.57 (br s, 2H), 7.52–7.42 (m, 1H), 7.36–7.25 (m, 6H), 7.22–7.18 (m, 2H), 7.13–7.09 (m, 2H), 3.79–3.65 (m, 5H), 0.74 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 177.5, 161.6, 159.9, 159.1, 154.7, 151.8, 138.6, 134.4, 132.2, 129.6, 129.1, 129.0 (2C), 128.7 (2C), 128.1 (2C), 127.9, 127.5 (2C), 122.4, 122.1, 117.4, 115.1, 112.4, 110.9, 106.0, 58.8, 54.9, 49.1, 29.5, 13.2. HRMS (ESI+): m/z $[M + H]^+$ calcd for $C_{32}H_{24}N_4O_5$: 545.1819; found: 545.1819.

*4.8.2. Ethyl 2-amino-1′-benzyl-3-cyano-6-methyl-2′,5-dioxo-5′-phenyl-1′,2′,5,6-tetrahydrospiro[pyrano[3,2-c]quinoline-4,3′-pyrrole]-4′-carboxylate (**4b**)*

White solid, 87%, mp 311–313°C (acetonitrile); IR ν, cm^{-1}: 3396, 3320, 3254, 3207 (NH_2), 2201 (CN), 1732, 1668, 1634.^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.07 (dd, J = 8.0, 1.3 Hz, 1H), 7.81–7.74 (m, 1H), 7.65 (d, J = 8.6 Hz, 1H), 7.51 (br s, 2H), 7.48–7.31 (m, 4H), 7.25–7.11 (m, 7H), 4.61 (d, J = 16.3 Hz, 1H), 4.46 (d, J = 16.3 Hz, 1H), 3.75–3.61 (m, 5H), 0.68 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 178.5, 161.4, 160.0, 159.0, 155.4, 151.7, 138.5, 136.5, 132.2, 129.7, 129.3, 128.3 (2C), 127.9 (2C), 127.7 (2C), 126.8, 126.6 (2C), 122.4, 122.1, 117.6, 115.1, 112.3, 111.1, 105.9, 58.6, 54.9, 49.0, 44.2, 29.4, 13.2. Anal. calcd for $C_{33}H_{26}N_4O_5$: C, 70.96; H, 4.69; N, 10.03. Found: C, 71.19; H, 4.96; N, 10.03.

*4.8.3. Ethyl 2-amino-1′-benzyl-3-cyano-2′,5-dioxo-5′,6-diphenyl-1′,2′,5,6-tetrahydrospiro[pyrano[3,2-c]quinoline-4,3′-pyrrole]-4′-carboxylate (**4c**)*

The conditions A (from 1*H*-pyrrole-2,3-dione **1b** and malononitrile), white solid, 93%. The conditions A (from ethyl 1-benzyl-4-(dicyanomethylene)-5-oxo-2-phenyl-4,5-dihydro-1*H*-pyrrole-3-carboxylate **9a**), white solid, 96%. mp 248–250°C (ethanol, acetone); IR ν, cm^{-1}: 3675, 3393, 3320, 3212 (NH_2), 2201 (CN), 1738, 1674, 1644.^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.12 (dd, J = 8.0, 1.2 Hz, 1H), 7.68–7.55 (m, 6H), 7.45–7.37 (m, 2H), 7.34–7.29 (m, 4H), 7.19–7.05 (m, 7H), 6.63 (d, J = 8.2 Hz, 1H), 4.65 (d, J = 16.3 Hz, 1H), 4.29 (d, J = 16.3 Hz, 1H), 3.80–3.69 (m, 2H), 0.72 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 178.3, 161.4, 160.0, 159.0, 155.4, 152.3, 139.5, 136.8, 136.4, 131.9, 130.1 (2C), 129.5, 129.3, 129.0, 129.0, 128.9, 128.3 (2C), 127.9 (2C), 127.7 (2C), 126.8, 126.6 (2C), 122.7, 122.2, 117.6, 115.6, 112.3, 111.0, 106.2, 58.6, 54.9, 48.9, 44.2, 13.3. HRMS (ESI+): m/z $[M + H]^+$ calcd for $C_{38}H_{28}N_4O_5$: 621.2132; found: 621.2126.

*4.8.4. Ethyl 2-amino-1′-benzyl-3-cyano-2′,5-dioxo-5′-phenyl-1′,2′,5,6-tetrahydrospiro[pyrano[3,2-c]quinoline-4,3′-pyrrole]-4′-carboxylate (**4d**)*

White solid, 83%, mp 267–268°C (acetone); IR ν, cm^{-1}: 3391, 3322, 3198 (NH_2, NH), 2193 (CN), 1746, 1671, 1630.^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.83 (br s, 1H), 7.95 (dd, J = 8.1, 1.1 Hz, 1H), 7.64 (ddd, J = 8.4, 7.3, 1.4 Hz, 1H), 7.43–7.09 (m, 14H), 4.59 (d, J = 16.4 Hz, 1H), 4.47 (d, J = 16.4 Hz, 1H), 3.73–3.64 (m, 2H), 0.68 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 178.5, 161.4, 160.0, 159.7, 155.2, 152.6, 137.7, 136.6, 131.7, 129.7, 129.2, 128.3 (2C), 127.8 (2C), 127.7 (2C), 126.7, 126.6 (2C), 122.1, 121.7, 117.6, 115.5, 111.6, 111.2, 106.3, 58.6, 54.9, 48.7, 44.1, 13.2. HRMS (ESI+): m/z $[M + H]^+$ calcd for $C_{32}H_{24}N_4O_5$: 545.1819; found: 545.1821.

*4.8.5. Ethyl 2-amino-3-cyano-1′-cyclohexyl-2′,5-dioxo-5′,6-diphenyl-1′,2′,5,6-tetrahydrospiro[pyrano[3,2-c]quinoline-4,3′-pyrrole]-4′-carboxylate (**4e**)*

White solid, 72%, mp 205–206°C (ethanol); IR ν, cm^{-1}: 3669, 3410, 3296, 3176 (NH_2), 2197 (CN), 1728, 1686, 1656.^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.08 (dd, J = 8.0, 1.2 Hz, 1H), 7.68–7.44 (m, 9H), 7.42–7.37 (m, 1H), 7.34–7.17 (m, 4H), 6.57 (d, J = 8.3 Hz, 1H), 3.78–3.62 (m, 2H), 3.15–3.02 (m, 1H), 2.08–1.84 (m, 2H), 1.71–1.53 (m, 4H), 1.49–1.38 (m, 1H), 1.01–0.76 (m, 3H), 0.69 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 178.0, 161.4, 159.7, 158.9, 156.2, 152.3, 139.5, 137.0, 131.7, 130.5, 130.1 (2C), 129.3, 129.0, 129.0, 128.9, 128.4, 128.2 (2C), 127.9, 122.5, 122.1, 117.1, 115.5, 112.3, 110.7, 106.4, 58.4, 55.6, 54.4, 48.8, 29.1, 28.7, 25.3, 25.2, 24.6, 13.2. HRMS (ESI+): m/z $[M + H]^+$ calcd for $C_{37}H_{32}N_4O_5$: 613.2445; found: 613.2434.

*4.8.6. Ethyl 2-amino-3-cyano-1′-cyclohexyl-2′,5-dioxo-5′-phenyl-1′,2′,5,6-tetrahydrospiro[pyrano[3,2-c]quinoline-4,3′-pyrrole]-4′-carboxylate (**4f**)*

White solid, 67%, mp 306–308°C (acetone); IR ν, cm^{-1}: 3411, 3327, 3239, 3205 (NH_2, NH), 2191 (CN), 1743, 1671, 1630.^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.70 (br s, 1H), 7.92 (dd, J = 8.0, 0.9 Hz, 1H), 7.64–7.58 (m, 1H), 7.57–7.50 (m, 3H), 7.42–7.27 (m, 6H), 3.72–3.58 (m, 2H), 3.16–3.06 (m, 1H), 2.15–1.92 (m, 2H), 1.80–1.57 (m, 4H), 1.47 (br d, J = 10.3 Hz, 1H), 1.05–0.81 (m, 3H), 0.66 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 178.3, 161.4, 159.9, 159.5, 156.3, 152.5, 137.6, 131.5, 130.8, 129.3, 128.2 (3C), 127.9, 122.0, 121.6, 117.2, 115.3, 111.6, 110.5, 106.8, 58.4, 55.2, 54.5, 48.5, 28.9, 28.8, 25.4, 25.3, 24.7, 13.2. HRMS (ESI+): m/z $[M + H]^+$ calcd for $C_{31}H_{28}N_4O_5$: 537.2132; found: 537.2132.

*4.8.7. Ethyl 2-amino-3-cyano-6-methyl-2′,5-dioxo-5′-phenyl-1′-(p-tolyl)-1′,2′,5,6-tetrahydrospiro[pyrano[3,2-c]quinoline-4,3′-pyrrole]-4′-carboxylate (**4g**)*

White solid, 60%, mp 292–294°C (ethanol, acetone); IR ν, cm^{-1}: 3473, 3361, 3220 (NH_2), 2195 (CN), 1732, 1690, 1677, 1626.^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.08 (dd, J = 8.0, 1.3 Hz, 1H), 7.78 (ddd, J = 8.7, 7.2, 1.5 Hz, 1H), 7.65 (d, J = 8.5 Hz, 1H), 7.55 (br s, 2H), 7.49–7.42 (m, 1H), 7.34–7.27 (m, 3H), 7.23–7.18 (m, 2H), 7.15–7.10 (m, 2H), 7.03–6.96 (m, 2H), 3.79–3.67 (m, 2H), 3.67 (s, 3H), 2.24 (s, 3H), 0.73 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 177.6,

161.6, 159.9, 159.1, 154.9, 151.8, 138.5, 137.4, 132.1, 131.8, 129.8, 129.2 (2C), 129.0, 129.0 (2C), 127.9 (2C), 127.5 (2C), 122.4, 122.1, 117.4, 115.1, 112.4, 110.8, 106.0, 58.8, 54.9, 49.0, 29.4, 20.5, 13.2. HRMS (ESI+): *m/z* [M + H]$^+$ calcd for $C_{33}H_{26}N_4O_5$: 559.1976; found: 559.1970.

4.8.8. Ethyl 2-amino-3-cyano-1'-(4-methoxyphenyl)-6-methyl-2',5-dioxo-5'-phenyl-1',2',5,6-tetrahydrospiro[pyrano[3,2-c]quinoline-4,3'-pyrrole]-4'-carboxylate (**4h**)

Light yellow solid, 65%, mp 255–257°C (ethanol); IR ν, cm^{-1}: 3487, 3318 (NH_2), 2184 (CN), 1745, 1690, 1679, 1628.^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.07 (dd, J = 8.0, 1.4 Hz, 1H), 7.80–7.75 (m, 1H), 7.65 (d, J = 8.6 Hz, 1H), 7.61 (br s, 2H), 7.48–7.43 (m, 1H), 7.34–7.28 (m, 3H), 7.22–7.17 (m, 2H), 7.06–6.99 (m, 2H), 6.90–6.85 (m, 2H), 3.77–3.65 (m, 2H), 3.70 (s, 3H), 3.67 (s, 3H), 0.72 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 178.0, 161.7, 160.0, 159.2, 158.6, 155.2, 151.8, 138.6, 132.3, 129.8, 129.4 (2C), 129.1, 129.0 (2C), 127.7 (2C), 127.0, 122.6, 122.2, 117.5, 115.2, 114.1 (2C), 112.4, 110.7, 106.1, 58.9, 55.2, 54.9, 49.0, 29.5, 13.3. HRMS (ESI+): *m/z* [M + H]$^+$ calcd for $C_{33}H_{26}N_4O_6$: 575.1925; found: 575.1925.

4.8.9. 2-Amino-4'-ethyl-6-methyl-2',5-dioxo-1',5'-diphenyl-1',2',5,6-tetrahydrospiro[pyrano[3,2-c]quinoline-4,3'-pyrrole]-3-carbonitrile (**4j**)

White solid, 74%, mp 280–282°C (acetonitrile); IR ν, cm^{-1}: 3399, 3308, 3245, 3199 (NH_2), 2191, 2200 (CN), 1720, 1709, 1682, 1645, 1633.^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.06 (dd, J = 8.0, 1.3 Hz, 1H), 7.77 (ddd, J = 8.7, 7.2, 1.6 Hz, 1H), 7.64 (d, J = 8.4 Hz, 1H), 7.50 (br s, 2H), 7.44 (ddd, J = 8.1, 7.2, 0.9 Hz, 1H), 7.35–7.23 (m, 5H), 7.20–7.14 (m, 3H), 7.11–7.05 (m, 2H), 3.64 (s, 3H), 2.09–1.91 (m, 2H), 0.79 (t, J = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 177.5, 159.4, 159.0, 151.6, 138.7, 138.7, 136.0, 132.2, 130.4, 129.0 (2C), 128.3 (2C), 128.2, 128.1 (2C), 127.1 (2C), 126.5, 122.3, 122.2, 121.8, 117.1, 115.0, 112.1, 105.8, 55.9, 51.4, 29.4, 18.0, 13.9. Anal. calcd for $C_{31}H_{24}N_4O_3$: C, 74.39; H, 4.83; N, 11.19. Found: C, 74.58; H, 5.09; N, 11.05.

4.8.10. 2-Amino-4'-ethyl-2',5-dioxo-1',5',6-triphenyl-1',2',5,6-tetrahydrospiro[pyrano[3,2-c]quinoline-4,3'-pyrrole]-3-carbonitrile (**4k**)

Light yellow solid, 70%, mp 310–311°C (ethanol, acetone); IR ν, cm^{-1}: 3488, 3268, 3154 (NH_2), 2190 (CN), 1723, 1667, 1640, 1632.^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.11 (dd, J = 8.1, 1.2 Hz, 1H), 7.69–7.52 (m, 6H), 7.41 (ddd, J = 8.1, 7.3, 1.0 Hz, 1H), 7.37–7.19 (m, 7H), 7.16–7.08 (m, 3H), 7.02–6.93 (m, 2H), 6.60 (d, J = 8.3 Hz, 1H), 2.11–2.05 (m, 2H), 0.87 (t, J = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 177.2, 159.4, 159.1, 152.3, 139.7, 138.6, 137.0, 135.8, 132.0, 130.2, 130.2, 130.1, 129.1, 128.9 (3C), 128.8, 128.3 (2C), 128.2, 128.0 (2C), 127.0 (2C), 126.5, 122.6, 122.3, 122.0, 117.1, 115.5, 112.1, 106.0, 55.9, 51.2, 18.0, 14.0. HRMS (ESI+): *m/z* [M + H]$^+$ calcd for $C_{36}H_{26}N_4O_3$: 563.2078; found: 563.2068.

4.8.11. 2-Amino-1'-(4-chlorophenyl)-4'-ethyl-6-methyl-2',5-dioxo-5'-phenyl-1',2',5,6-tetrahydrospiro[pyrano[3,2-c]quinoline-4,3'-pyrrole]-3-carbonitrile (**4l**)

White solid, 68%, mp 184–187°C (ethanol, acetone); ethanol solvate 1 : 0.4; IR ν, cm^{-1}: 3422, 3315, 3247, 3201, 3169 (NH_2, OH), 2194 (CN), 1736, 1726, 1713, 1679, 1634.^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.06 (dd, J = 8.0, 1.6 Hz, 1H), 7.77 (ddd, J = 8.7, 7.0, 1.6 Hz, 1H), 7.64 (d, J = 8.7 Hz, 1H), 7.57 (br. s, 2H), 7.44 (t, J = 7.6 Hz, 1H), 7.39–7.27 (m, 5H), 7.19–7.15 (m, 2H), 7.09–7.03 (m, 2H), 3.64 (s, 3H), 2.08–1.90 (m, 2H), 0.79 (t, J = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 177.5, 159.4, 159.0, 151.7, 138.8, 138.3, 134.9, 132.3, 130.9, 130.1, 128.9 (2C), 128.7 (2C), 128.5 (2C), 128.4, 128.3 (2C), 122.4, 122.3, 122.2, 117.1, 115.1, 112.1, 105.7, 55.6, 51.5, 29.4, 18.0, 13.9. HRMS (ESI+): *m/z* [M + H]$^+$ calcd for $C_{31}H_{23}ClN_4O_3$: 535.1531; found: 535.1535.

4.9. General procedure for the preparation of products 5–8 and 5'-8' (conditions B)

To a solution of 1*H*-pyrrole-2,3-dione **1** (1 mmol), malononitrile **2** (1 mmol) and 4-hydroxyquinolin-2(1*H*)-one **3** or other enols (1 mmol) in anhydrous THF (10 mL) was added Et_3N (0.2 mmol), and the reaction mixture was heated at reflux for 3 h. The resulting solution was cooled to RT, and the solvent was evaporated under reduced pressure. The residue was purified re-crystallization or by preparative column chromatography to afford desired products as yellow or white solid.

4.9.1. Ethyl 2-(2-amino-1-cyano-2-oxoethyl)-4-(4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-5-oxo-1,2-diphenyl-2,5-dihydro-1H-pyrrole-3-carboxylate (**5a** & **5'a**)

Yellow solid, 51%, mp 195–196°C (ethanol); IR ν, cm^{-1}: 3454, 3419, 3288 (NH_2, OH), 2246 (CN), 1715, 1688, 1666. After crystallization dr ~100 : 1 (A: B). ^{1}H NMR (400 MHz, DMSO-d_6) δ (A + B): [10.55 (s, A), 9.47 (s, B), Σ1H], 8.09 (dd, J = 8.1, 1.3 Hz, 1H), 7.81 (br. s, 2H), 7.73–7.64 (m, 3H), 7.59–7.46 (m, 4H), 7.35–7.24 (m, 4H), 6.98–6.91 (m, 2H), [5.48 (s, A), 5.12 (s, B), Σ1H], 3.94–3.79 (m, 2H), 3.62 (s, 3H), 0.76 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (A): 168.0, 163.4, 161.3, 160.4, 158.2, 145.9, 139.3, 138.1, 135.1, 135.0, 131.8, 128.9, 128.6 (2C), 128.4 (2C), 128.3 (2C), 127.9, 127.0 (2C), 123.5, 121.6, 115.5, 115.0, 114.7, 103.3, 71.7, 60.4, 39.6, 29.1, 13.1. Anal. calcd for $C_{32}H_{26}N_4O_6$: C, 68.32; H, 4.66; N, 9.96. Found: C, 68.02; H, 4.55; N, 9.94.

4.9.2. Ethyl 2-(2-amino-1-cyano-2-oxoethyl)-1-(4-chlorophenyl)-4-(4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-5-oxo-2-phenyl-2,5-dihydro-1H-pyrrole-3-carboxylate (**5b** & **5'b**)

The conditions A, yellow solid, 26%. The conditions B, yellow solid, 56% mp 220–222°C (acetone); IR ν, cm^{-1}: 3457, 3377, 3329, 3274 (NH_2, OH), 2238 (CN), 1713, 1699, 1683, 1640. After crystallization dr ~37 : 1 (A: B). ^{1}H NMR (400 MHz, DMSO-d_6) δ (A + B): [10.58 (s, A), 9.53 (s, B), Σ1H], 8.09 (dd, J = 8.1, 1.3 Hz, 1H), 7.78 (br. s, 2H), 7.73–7.65 (m, 3H), 7.59–7.47 (m, 4H), 7.38–7.30 (m, 3H), [7.00–6.96 (m, A), 7.65–7.61 (m, B), Σ2H], [5.52 (s, A), 5.14 (s, B), Σ1H], 3.97–3.78 (m, 2H), [3.64 (s, B), 3.61 (s, A), Σ3H], 0.76 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (A): 167.9, 163.2, 161.3, 160.4, 158.3, 145.8, 139.3, 137.9, 134.9, 134.1, 132.4, 131.9, 129.9 (2C), 129.0, 128.8 (2C), 128.4 (2C), 127.0 (2C), 123.5, 121.6, 115.5, 115.1, 114.7, 103.1, 71.6, 60.5, 39.2, 29.1, 13.1. HRMS (ESI+): *m/z* [M + H]$^+$ calcd for $C_{32}H_{25}ClN_4O_6$: 597.1535; found: 597.1535.

4.9.3. Ethyl 2-(2-amino-1-cyano-2-oxoethyl)-1-(4-bromophenyl)-4-(4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-5-oxo-2-phenyl-2,5-dihydro-1H-pyrrole-3-carboxylate (**5c** & **5'c**)

White solid, 49%, mp 229–231°C (ethanol, acetone); acetone solvate 1 : 1; IR ν, cm^{-1}: 3469, 3393, 3268, 3170 (NH_2, OH), 2233 (CN), 1714, 1703, 1690, 1665, 1632. After crystallization dr ~3 : 1 (A: B). ^{1}H NMR (400 MHz, DMSO-d_6) δ (A + B): [10.58 (s, A), 9.52 (s, B), Σ1H], [8.26 (br. s, B), 7.78 (br. s, A), Σ2H], [8.09 (dd, J = 8.0, 1.5 Hz), 8.05 (dd, J = 8.0, 1.5 Hz), Σ1H], 7.76–7.45 (m, 9H), 7.38–7.30 (m, 1H), [6.95–6.87 (m, A), 6.56 (d, J = 8.7 Hz, B), Σ2H], [5.52 (s, A), 5.15 (s, B), Σ1H], 4.01–3.77 (m, 2H), [3.64 (s, B), 3.61 (s, A), Σ3H], 0.76 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ (A): 167.8, 163.2, 161.2, 160.3, 158.2, 145.8, 139.3, 137.8, 134.9, 134.5, 131.9, 131.4 (2C), 130.2 (2C), 129.0, 128.8 (2C), 126.9 (2C), 123.5, 121.6, 120.9, 115.5, 115.1, 114.7, 103.1, 71.5, 60.5, 39.2, 29.1, 13.1.^{13}C NMR (101 MHz, DMSO-d_6) δ (B): 167.0, 163.9, 160.7, 160.3, 158.1, 148.2, 139.4, 138.0, 135.0, 133.2, 131.9, 131.8 (2C), 130.1 (2C), 129.3, 128.9 (2C), 126.4 (2C), 123.3, 121.7, 121.3, 115.2, 115.0, 114.7, 101.8, 71.6, 60.6, 39.2, 28.9, 12.8. HRMS (ESI+): *m/z* [M + H]$^+$ calcd for $C_{32}H_{25}BrN_4O_6$: 643.1010; found: 643.1004.

*4.9.4. Methyl 2-(2-amino-1-cyano-2-oxoethyl)-2-(4-chlorophenyl)-4-(4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-5-oxo-1-phenyl-2,5-dihydro-1H-pyrrole-3-carboxylate (**5d** & **5′d**)*

White solid, 47%, mp 212–214°C (toluene, ethyl acetate); IR ν, cm^{-1}: 3482, 3288, 3240, 3156, 3105 (NH_2, OH), 2242 (CN), 1716, 1705, 1689, 1668, 1652, 1617. After crystallization dr ~11.5 : 1 (A: B). ^1H NMR (400 MHz, DMSO-d_6) δ (A + B): [10.81 (s, A), 9.71 (s, B), Σ1H], 8.24 (br. s, 0.08H, B), [8.10 (dd, J = 8.1, 1.5 Hz, A), 8.06 (dd, J = 8.0, 1.5 Hz, B), Σ1H], 7.81–7.55 (m, 7.76H), 7.45 (d, J = 8.7 Hz, 0.16H, B), 7.38–7.29 (m, 4H), [6.98–6.92 (m, A), 6.68–6.64 (m, B), Σ2H], [5.44 (s, A), 5.14 (s, B), Σ1H], [3.64 (s, B), 3.62 (s, A), Σ3H], [3.47 (s, B), 3.41 (s, A), Σ3H]. ^{13}C NMR (101 MHz, DMSO-d_6) δ (A): 167.7, 162.9, 162.0, 160.4, 158.6, 145.4, 139.4, 138.2, 134.7, 134.2, 133.6, 131.9, 129.1 (2C), 128.6 (2C), 128.5 (2C), 128.5 (2C), 128.1, 123.6, 121.6, 115.5, 114.9, 114.7, 103.0, 71.4, 51.7, 40.1, 29.2. HRMS (ESI+): *m/z* $[M + H]^+$ calcd for $C_{31}H_{23}ClN_4O_6$: 583.1379; found: 583.1380.

*4.9.5. Ethyl 2-(2-amino-1-cyano-2-oxoethyl)-4-(4-hydroxy-2-oxo-1-phenyl-1,2-dihydroquinolin-3-yl)-5-oxo-1,2-diphenyl-2,5-dihydro-1H-pyrrole-3-carboxylate (**5e** & **5′e**)*

The compound was purified by column chromatography (toluene–EtOAc = 1:1, R_f 0.29) followed by crystallization, yellow solid, 48%, mp 210–211°C (toluene, EtOAc); IR ν, cm^{-1}: 3449, 3313, 3169 (NH_2, OH), 2243 (CN), 1710, 1646, 1610. After crystallization dr ~24 : 1 (A: B). ^1H NMR (400 MHz, DMSO-d_6) δ (A + B): [10.87 (s, A), 9.75 (s, B), Σ1H], [8.30 (br. s, B), 7.78 (br. s, A), Σ2H], [8.14 (dd, J = 8.1, 1.5 Hz, A), 8.09 (dd, J = 8.0, 1.6 Hz, B), Σ1H], 7.67–7.40 (m, 9H), 7.33–7.22 (m, 6H), 6.97–6.92 (m, 2H), [6.65–6.61 (m, B), 6.58 (dd, J = 8.6, 1.0 Hz, A), Σ1H], [5.44 (s, A), 5.13 (s, B), Σ1H], 4.07–3.83 (m, 2H), 0.85 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ (A): 168.0, 163.2, 161.3, 160.4, 159.0, 146.0, 140.2, 137.7, 137.6, 135.0, 134.9, 131.5, 129.9 (2C), 129.1, 129.1, 128.8, 128.6 (2C), 128.5, 128.3 (4C), 128.0, 127.0 (2C), 123.4, 121.9, 115.4 (2C), 115.0, 103.4, 71.7, 60.5, 39.6, 13.3. HRMS (ESI+): *m/z* $[M + H]^+$ calcd for $C_{37}H_{28}N_4O_6$: 625.2082; found: 625.2084.

*4.9.6. Ethyl 2-(2-amino-1-cyano-2-oxoethyl)-1-(4-chlorophenyl)-4-(4-hydroxy-2-oxo-1-phenyl-1,2-dihydroquinolin-3-yl)-5-oxo-2-phenyl-2,5-dihydro-1H-pyrrole-3-carboxylate (**5f** & **5′f**)*

Yellow solid, 58%, mp 202–204°C (toluene, EtOAc); IR ν, cm^{-1}: 3439, 3313, 3172 (NH_2, OH), 2242 (CN), 1711, 1704, 1650, 1614. After crystallization dr ~100 : 1 (A: B). ^1H NMR (400 MHz, DMSO-d_6) δ (A + B): [10.89 (s, A), 9.84 (s, B), Σ1H], 8.14 (dd, J = 8.1, 1.5 Hz, 1H), 7.74 (br. s, 2H), 7.66–7.43 (m, 9H), 7.38–7.24 (m, 5H), 7.02–6.94 (m, 2H), [6.63 (d, J = 8.8 Hz, B), 6.58 (dd, J = 8.5, 1.0 Hz, A), Σ1H], [5.49 (s, A), 5.16 (s, B), Σ1H], 4.07–3.82 (m, 2H), 0.85 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ (A): 167.9, 163.1, 161.3, 160.3, 159.1, 145.9, 140.2, 137.6, 137.5, 134.8, 134.0, 132.4, 131.5, 130.0 (2C), 129.9 (2C), 129.1 (2C), 129.0, 128.8 (2C), 128.5, 128.4 (2C), 126.9 (2C), 123.5, 121.9, 115.4 (2C), 115.0, 103.3, 71.6, 60.6, 39.1, 13.3. HRMS (ESI+): *m/z* $[M + H]^+$ calcd for $C_{37}H_{27}ClN_4O_6$: 659.1692; found: 659.1701.

*4.9.7. Ethyl 2-(2-amino-1-cyano-2-oxoethyl)-4-(4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-5-oxo-2-phenyl-1-(4-(trifluoromethyl)phenyl)-2,5-dihydro-1H-pyrrole-3-carboxylate (**5g** & **5′g**)*

The compound was purified by column chromatography (toluene–EtOAc = 1:2, R_f 0.35) followed by crystallization, yellow solid, 61%, mp 208–211°C (acetone, hexane). After crystallization dr ~5 : 1 (A: B). ^1H NMR (400 MHz, DMSO-d_6) δ (A + B): [10.62 (br. s, A), 9.62 (br. s, B), Σ1H], [8.23 (br. s, B), 8.03 (br. s, B), 7.77 (br. s, A), Σ2H], 8.13–8.05 (m, 1H), 7.74–7.47 (m, 9H), 7.39–7.28 (m, 1H), [7.21 (d, J = 8.3 Hz, A), 6.90 (d, J = 8.3 Hz, B), Σ2H], [5.58 (s, A), 5.22 (s, B), Σ1H], 4.01–3.76 (m, 2H), [3.64 (s, B), 3.61 (s, A), Σ3H], 0.77 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ (A): 167.9, 163.1, 161.3, 160.4, 158.6, 145.8, 139.4, 139.1, 137.7, 135.0, 131.8, 129.1, 128.9 (2C), 128.5 (2C), 127.9 (q, J = 32.1 Hz), 126.9 (2C), 125.4 (q, J = 3.8 Hz, 2C), 123.9 (q, J = 272.1 Hz), 123.5, 121.5, 115.6, 115.1, 114.6, 102.9, 71.6, 60.5, 39.3, 29.1, 13.1.^{19}F NMR (377 MHz, $CDCl_3$) δ (A + B): −60.86 (s, A), −60.96 (s, B). Anal. calcd for $C_{33}H_{25}F_3N_4O_6$: C, 62.86; H, 4.00; N, 8.89. Found: C, 63.22; H, 4.18; N, 9.13.

*4.9.8. Ethyl 2-(2-amino-1-cyano-2-oxoethyl)-4-(4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-2-(4-nitrophenyl)-5-oxo-1-phenyl-2,5-dihydro-1H-pyrrole-3-carboxylate (**5h** & **5′h**)*

Yellow solid, 49%, mp 188–191°C (acetone). After crystallization dr ~5 : 1 (A: B). ^1H NMR (400 MHz, DMSO-d_6) δ (A + B): [10.77 (br. s, A), 9.80 (br. s, B), Σ1H], 8.38 (d, J = 8.4 Hz, 1.84H), 8.23 (s, 0.16H, B), 8.14–7.67 (m, 6H), 7.63–7.56 (m, 1H), 7.40–7.25 (m, 4H), [6.97 (dd, J = 6.9, 2.8 Hz, A), 6.76–6.69 (m, B), Σ2H], [5.49 (s, A), 5.22 (s, B), Σ1H], 4.02–3.77 (m, 2H), [3.65 (s, B), 3.62 (s, A), Σ3H], 0.78 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ (A): 167.7, 162.7, 161.2, 160.4, 158.5, 147.6, 145.0, 142.8, 139.4, 139.1, 134.6, 131.9, 128.7 (4C), 128.4 (2C), 128.2, 123.7 (2C), 123.5, 121.6, 115.5, 114.8, 114.7, 103.1, 71.3, 60.5, 40.0, 29.1, 13.0. Anal. calcd for $C_{32}H_{25}N_5O_8$: C, 63.26; H, 4.15; N, 11.53. Found: C, 63.40; H, 4.17; N, 11.41.

*4.9.9. Ethyl 2-(2-amino-1-cyano-2-oxoethyl)-1-(4-chlorophenyl)-4-(4-hydroxy-2-oxo-2H-chromen-3-yl)-5-oxo-2-phenyl-2,5-dihydro-1H-pyrrole-3-carboxylate (**6** & **6′**)*

Yellow solid, 53%, mp 208–211°C (toluene, ethanol); IR ν, cm^{-1}: 3471, 3358, 3331, 3247 (NH_2, OH), 2241 (CN), 1705, 1698, 1679, 1651, 1618, 1610. After crystallization dr ~9 : 1 (A: B). ^1H NMR (400 MHz, DMSO-d_6) δ (A + B): 11.82 (br. s, 1H), [8.08 (dd, J = 8.0, 1.6 Hz, A), 8.04 (dd, J = 8.0, 1.6 Hz, B), Σ1H], 7.94 (s, 0.1H, B), 7.79–7.30 (m, 11.9H), [7.02–6.94 (m, A), 6.70–6.63 (m, B), Σ2H], [5.46 (s, A), 5.17 (s, B), Σ1H], 4.08–3.81 (m, 2H), [0.84 (t, J = 7.1 Hz, B), 0.83 (t, J = 7.1 Hz, A), overlapped, Σ3H]. ^{13}C NMR (101 MHz, DMSO-d_6) δ (A): δ 167.3, 162.8, 162.7, 161.1, 159.7, 152.6, 145.7, 136.8, 134.8, 134.1, 133.2, 132.4, 130.0 (2C), 129.1, 128.9 (2C), 128.4 (2C), 126.8 (2C), 124.2, 123.7, 116.5, 115.5, 115.0, 97.0, 71.5, 60.7, 38.6, 13.2. HRMS (ESI+): *m/z* $[M + Na]^+$ calcd for $C_{31}H_{22}ClN_3O_7$: 606.1038; found: 606.1037.

*4.9.10. Ethyl 2-(2-amino-1-cyano-2-oxoethyl)-1-(4-chlorophenyl)-4-(4-hydroxy-2-oxo-2,5-dihydrofuran-3-yl)-5-oxo-2-phenyl-2,5-dihydro-1H-pyrrole-3-carboxylate (**7** & **7′**)*

Yellow solid, 63%, mp 214–215°C (acetone, ethanol); IR ν, cm^{-1}: 3484, 3425, 3381, 3312, 3245, 3177 (NH_2, OH), 2246 (CN), 1728, 1703, 1694, 1668, 1651, 1609. After crystallization dr > 99 : 1 (A: B). ^1H NMR (400 MHz, DMSO-d_6) δ (A): 13.06 (br. s, 1H), 7.58 (br. s, 1H), 7.56 (br. s, 1H), 7.55–7.45 (m, 5H), 7.36–7.31 (m, 2H), 7.03–6.98 (m, 2H), 5.41 (s, 1H), 4.86 (d, J = 16.7 Hz, 1H), 4.80 (d, J = 16.7 Hz, 1H), 4.00–3.85 (m, 2H), 0.94 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ (A): 178.0, 170.5, 168.1, 162.5, 161.6, 142.4, 134.5, 134.0, 132.4, 132.3, 130.0 (2C), 129.2, 128.9 (2C), 128.3 (2C), 126.7 (2C), 114.8, 91.8, 71.9, 67.2, 60.7, 37.6, 13.3. Anal. calcd for $C_{26}H_{20}ClN_3O_7$: C, 59.84; H, 3.86; N, 8.05. Found: C, 59.69; H, 4.22; N, 7.80.

*4.9.11. Ethyl 2-(2-amino-1-cyano-2-oxoethyl)-4-(3-hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-5-oxo-1,2-diphenyl-2,5-dihydro-1H-pyrrole-3-carboxylate (**8a** & **8′a**)*

Yellow solid, 37%, mp 223–225°C (acetone); IR ν, cm^{-1}: 3658, 3317, 3462, 3355, 3354, 3292, 3193 (OH, NH_2), 2248 (CN), 1716, 1683, 1674, 1660, 1628. After crystallization dr > 99 : 1 (A: B). ^1H NMR (400 MHz, DMSO-d_6) δ (A): 12.04 (br. s, 1H), 8.10 (d, J = 7.4 Hz, 1H), 8.05 (d, J = 7.5 Hz, 1H), 7.90 (dt, J = 20.5, 7.4 Hz, 2H), 7.78 (br. s, 1H), 7.66 (br. s, 1H), 7.61–7.42 (m, 5H), 7.32–7.21 (m, 3H), 6.93–6.85 (m, 2H), 5.34 (s, 1H), 3.96–3.77 (m, 2H), 0.76 (t, J = 7.1 Hz, 3H). ^{13}C

NMR (101 MHz, DMSO-d_6) δ (A): 181.5, 180.6, 166.3, 162.5, 161.0, 156.4, 145.9, 137.3, 135.2, 135.1, 135.0, 133.7, 131.8, 129.8, 129.0, 128.8 (2C), 128.5 (4C), 128.1, 126.8 (2C), 126.2, 126.0, 115.1, 114.6, 71.6, 60.6, 39.7, 13.2. HRMS (ESI+): *m/z* $[M + H]^+$ calcd for $C_{32}H_{23}N_3O_7$: 562.1609; found: 562.1610.

*4.9.12. Ethyl 2-(2-amino-1-cyano-2-oxoethyl)-1-(4-chlorophenyl)-4-(3-hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-5-oxo-2-phenyl-2,5-dihydro-1H-pyrrole-3-carboxylate (**8b** & **8′b**)*

Yellow solid, 49%, mp 223–225°C (ethanol); IR ν, cm^{-1}: 3457, 3344, 3293, 3189 (NH_2, OH), 2248 (CN), 1716, 1698, 1688, 1679, 1669, 1657, 1630. After crystallization dr > 99 : 1 (A: B). ^{1}H NMR (400 MHz, DMSO-d_6) δ (A): 11.93 (br. s, 1H), 8.12–8.08 (m, 1H), 8.05–8.02 (m, 1H), 7.90 (dtd, J = 19.9, 7.4, 1.5 Hz, 2H), 7.70 (br. s, 1H), 7.62 (br. s, 1H), 7.60–7.46 (m, 5H), 7.37–7.31 (m, 2H), 6.97–6.91 (m, 2H), 5.39 (s, 1H), 3.97–3.79 (m, 2H), 0.77 (t, J = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ (A): 181.3, 180.5, 166.4, 162.4, 160.8, 156.4, 145.7, 137.1, 135.0, 134.9, 134.0, 133.6, 132.5, 131.7, 130.0 (2C), 129.8, 129.1, 128.9 (2C), 128.5 (2C), 126.6 (2C), 126.1, 125.9, 115.0, 114.4, 71.4, 60.8, 38.6, 13.1. HRMS (ESI+): *m/z* $[M + H]^+$ calcd for $C_{32}H_{22}ClN_3O_7$: 596.1219; found: 596.1218.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2021.132129.

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