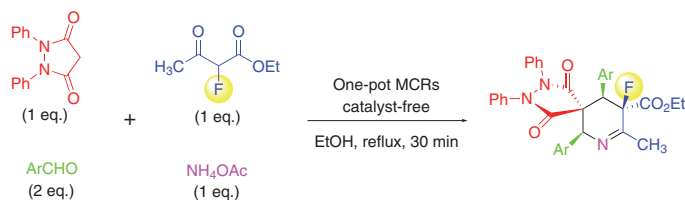


Concise One-Pot Multicomponent Reaction Approach to Mono-fluorinated Spiro-pyrazole-pyridine Derivatives without Additional Catalyst

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Abstract Monofluorinated bis-heterocyclic spirocycles: functionalized ethyl 9-fluoro-8-methyl-1,4-dioxo-2,3,6,10-tetraphenyl-2,3,7-triazaspiro[4.5]dec-7-ene-9-carboxylate derivatives were efficiently synthesized from readily available 1,2-diphenylpyrazolidine-3,5-dione, ethyl 2-fluoroacetoacetate, aromatic aldehydes, and ammonium acetate via one-pot four-component reactions in the absence of additional catalyst. In the protocols, ammonium acetate serves not only as the fourth component but also as the catalyst.

Key words one-pot multicomponent reaction, ethyl 2-fluoroacetoacetate, 1,2-diphenylpyrazolidine-3,5-dione, fluorinated spiro-pyrazole-pyridine derivatives

It is well known that the introduction of fluorine into organic molecules often results in a dramatic modification of the physical, chemical, and biological properties due to the properties of the fluorine atom.¹ For example, incorporation of fluorine atoms or fluoroalkyl groups generally results in increased lipid solubility of the molecule, which improves the rate of absorption and thus promotes the ease of drug transport *in vivo*.² As such, fluorinated compounds find wide applications in fields such as the pharmaceutical and agrochemical industries. Therefore, the exploration of new efficient methods for incorporating fluorine atoms or fluoroalkyl groups into organic frameworks has attracted considerable attention.³

Spiro-heterocycles possess diverse biological properties ranging from central nervous system activity to antitumor and antifungal properties.⁴ Furthermore, spiro-piperidines are useful tools for studying the mechanism of interaction of small non-peptidic molecules.⁵ Therefore, the synthesis of fluorine-containing *N*-heterocyclic compounds is particularly important.⁶

Recently, the synthesis of polyheterocyclic compounds by one-pot, multicomponent reactions (MCRs) has attracted significant interest.⁷ MCRs are generally considered to be one of the most important and useful methods in conventional chemical reactions, because they reduce operative steps and enhance synthetic efficiency.^{8,9} Hence, design and development of MCRs for the preparation of new bioactive heterocyclic compounds remains in great demand.¹⁰

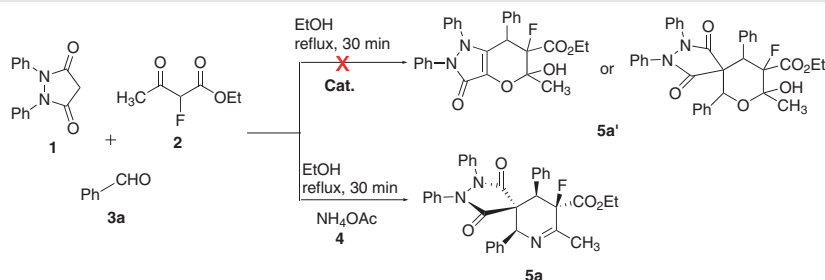
Ethyl 2-fluoroacetoacetate is a readily available reagent and less hazardous than ethyl fluoroacetate.¹¹ Recently, great progress has been made in applications of α -fluoro- β -keto esters and/or their analogues to serve as monofluorinated building blocks in the construction of monofluorinated products. Generally, the protocols produce acyclic or cyclic products by reaction of the monofluorinated substrates with various substrates by organocatalysis and metallic catalysis as well as by electrocatalysis.¹²

Pyrazolidine-3,5-dione derivatives have attracted considerable attention due to their diverse biological activities, including anticardiovascular, anti-HIV, antihyperglycemic, antitumor, and anti-inflammatory activities.¹³ Interestingly, the pyrazolidine-3,5-dione moiety has also been found to act as a carbon acid receptor for donor-acceptor Stenhouse adducts (DASAs) with photoswitching properties¹⁴ and as a key acceptor terminal group for merocyanines.¹⁵

However, to the best of our knowledge, protocols using ethyl 2-fluoroacetoacetate as a monofluorinated building block with pyrazolidine-3,5-diones to construct monofluorinated spiro-pyrazole-pyridine derivatives via one-pot MCRs has not been explored systematically in the literature. Considering the importance of 3-fluoropiperidine derivatives,⁶ and in continuation of our interest in the synthesis of various fluorinated polyheterocyclic compounds based on the MCR strategy,¹⁶ herein, we wish to report our recent studies on the efficient synthesis of monofluorinated functionalized spiro-pyrazole-pyridine derivatives via one-pot four-component reactions of 1,2-diphenylpyrazolidine-3,5-dione (**1**), ethyl 2-fluoroacetoacetate (**2**), aromatic aldehydes **3**, and ammonium acetate (**4**) without need for additional catalyst.

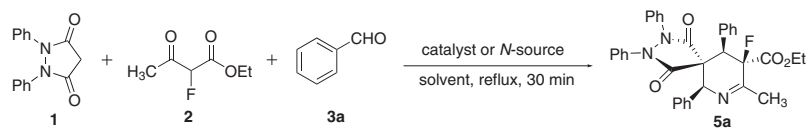
In our preliminary experiments, we carried out the three-component reaction of equivalent molar amounts of 1,2-diphenylpyrazolidine-3,5-dione (**1**) and ethyl 2-fluoroacetoacetate (**2**) with benzaldehyde (**3a**) in EtOH under refluxing conditions catalyzed by commonly used catalysts

such as piperidine, *p*-TSA, NEt₃, or pyridine (Scheme 1). Unfortunately, TLC analysis showed that no reaction had occurred (Table 1, entries 1–4). Interestingly, a further attempt produced the unexpected product **5a** in 12% yield when a 0.5 equivalent amount of NH₄OAc was used as the catalyst in EtOH under reflux conditions (Table 1, entry 5). Further increasing the NH₄OAc loading to 1.0 equivalent afforded product **5a** in 28% yield (Table 1, entry 6). The ¹H NMR spectrum of product **5a** revealed that, except for the ethyl group, this compound contained a four molecular phenyl group framework and three types of aliphatic hydrogen atoms. Based on these observations and in combination with the MS data, we speculated that the structure of the obtained compound was spiro-*N*-heterocyclic compound **5a**. The above results also showed that the addition of 2.0 equivalents of benzaldehyde was necessary if the reaction were to occur smoothly. Furthermore, 0.5 equivalents of NH₄OAc catalyst loading was insufficient to push the reaction to completion due to NH₄OAc being involved both as the fourth component and as the catalyst.



Scheme 1 One-pot MCR approach for the synthesis of **5**

Table 1 Optimization of the One-Pot Reaction^a



Entry	Solvent	3a (equiv.)	Catalyst (equiv.)	<i>N</i> -Source (equiv.)	Yield ^b (%)
1	EtOH	1	piperidine (0.5)	–	–
2	EtOH	1	<i>p</i> -TSA (0.5)	–	–
3	EtOH	1	NEt ₃ (0.5)	–	–
4	EtOH	1	pyridine (0.5)	–	–
5	EtOH	1	NH ₄ OAc (0.5)	–	12
6	EtOH	1	–	NH ₄ OAc (1.0)	28
7	EtOH	2	–	NH ₄ OAc (1.0)	54
8	EtOH	2	–	NH ₄ OAc (1.2)	54
9	EtOH	2	–	NH ₄ OAc (2.0)	55
10	THF	2	–	NH ₄ OAc (1.0)	49
11	CH ₃ CN	2	–	NH ₄ OAc (1.0)	–

^a Reaction conditions: **1** (1.0 mmol), **2** (1.0 mmol), **3a** (as indicated), solvent (10.0 mL), reflux, 30 min.

^b Isolated yield.

Encouraged by this unexpected result, we subsequently optimized the reaction conditions by changing the molecular ratio of the starting materials. When a stoichiometric amount of NH_4OAc and 2.0 equivalents of benzaldehyde (**3a**) were used, the yield of product **5a** could be improved to 54% (Table 1, entry 7).

Based on the above results, the reaction conditions were further optimized to improve the yield by changing the amount of NH_4OAc and solvent. The effects of the amount of NH_4OAc loading on the reaction efficiency were first screened. After screening different NH_4OAc loadings, it was found that 1.0 equivalent of NH_4OAc gave a yield of 54% (Table 1, entry 7). Further increase in the amount of NH_4OAc loading had no significant effect on the reaction (Table 1, entries 8 and 9). It should be noted that no corresponding *O*-heterocyclic analogues **5a'** were detected when the reaction was performed in the absence of NH_4OAc despite the presence of other catalysts (Table 1, entries 1–4).

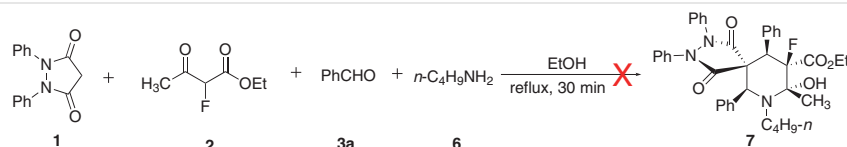
The solvent effect on reaction efficiency was also investigated. After briefly screening various common organic solvents, we found that the reaction proceeded most efficiently in EtOH. Reactions performed in THF produced diminished product yields (Table 1, entry 10), whereas other solvents such as CH_3CN did not provide any product (Table 1, entry 11). Thus, EtOH was selected as the preferred solvent as a result of its efficiency in the reaction and ease of handling during the workup procedure.

To examine the effects of other nitrogen sources, we performed two parallel reactions using different sources: ammonium chloride as well as aqueous ammonia (Table 2). The results showed that product **5a** could not be obtained

in the reaction with NH_4Cl as nitrogen source under similar reaction conditions. However, reaction with aqueous ammonia as nitrogen source gave the expected product **5a**, but the reaction yield was relatively low at 30%. These results illustrate the twofold catalytic effect of ammonium acetate in the transformation.

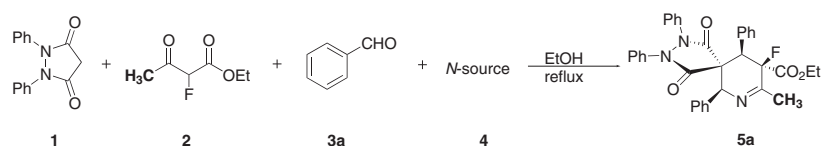
With the optimized conditions in hand, the generality and scope of this reaction was subsequently investigated, as shown in Table 3. Aromatic aldehydes bearing electron-neutral, electron-rich, or electron-deficient substituents were smoothly converted into the corresponding products in moderate yields. The results indicated that steric effects of the substituents on the aromatic aldehydes showed little influence on the efficiency of this reaction (Table 3; entries 2–4, 5–7, and 9–11), regardless of the electronic nature of the substituent groups. Unfortunately, reactions using aromatic aldehydes with a strongly electron-donating or with a strongly electron-withdrawing group (Table 3, entries 16 and 17), the sterically hindered 1-naphthylaldehyde (Table 3, entry 18), or an aliphatic aldehyde (Table 3, entry 19) failed to provide any product, even if the reaction time was prolonged.

After completing the above reaction, we considered whether we could obtain the corresponding hemiaminal analogues using primary aliphatic amines as raw materials under similar reaction conditions. With this in mind, we attempted the four-component reaction with *n*-butylamine (**6**) instead of NH_4OAc (**4**) (Scheme 2). Unfortunately, the reaction did not afford the corresponding hemiaminal analogue **7**. Therefore, it can be concluded that NH_4OAc plays a crucial role in this one-pot four-component reaction.



Scheme 2 One-pot MCR using $\text{C}_4\text{H}_9\text{NH}_2$ as substrate

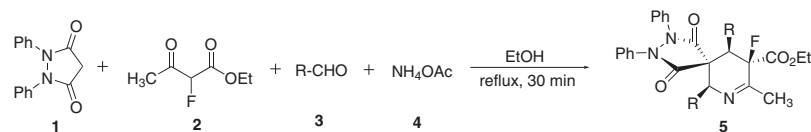
Table 2 Optimization of the *N*-Source^a



Entry	<i>N</i> -Source	Yield of 5a (%) ^b
1	NH_4OAc	54
2	$\text{NH}_3 \cdot \text{H}_2\text{O}$	30
3	NH_4Cl	–

^a Reaction conditions: **1** (1.0 mmol), **2** (1.0 mmol), **3a** (2.0 mmol), **4** (1.0 equiv.), EtOH (10.0 mL), reflux, 30 min.

^b Isolated yield.

Table 3 Scope of Substrates for the Synthesis of Compound **5**^a

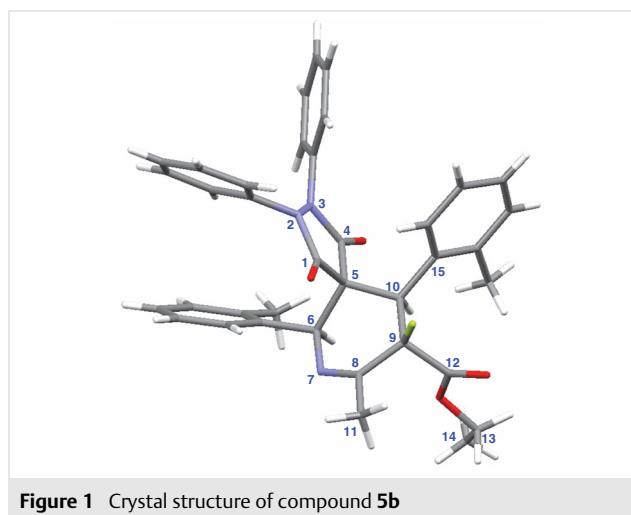
Entry	R	Time (h)	Product	Yield of 5 (%) ^b
1	C ₆ H ₅	0.5	5a	54
2	2-MeC ₆ H ₄	0.5	5b	63
3	3-MeC ₆ H ₄	0.5	5c	60
4	4-MeC ₆ H ₄	0.5	5d	58
5	2-ClC ₆ H ₄	0.5	5e	60
6	3-ClC ₆ H ₄	0.5	5f	62
7	4-ClC ₆ H ₄	0.5	5g	61
8	2,4-(Cl) ₂ C ₆ H ₃	0.5	5h	49
9	2-BrC ₆ H ₄	0.5	5i	52
10	3-BrC ₆ H ₄	0.5	5j	56
11	4-BrC ₆ H ₄	0.5	5k	57
12	2-FC ₆ H ₄	0.5	5l	64
13	3-FC ₆ H ₄	0.5	5m	56
14	2-MeOC ₆ H ₄	0.5	5n	67
15	3-MeOC ₆ H ₄	0.5	5o	63
16	4-(Me ₂ N)C ₆ H ₄	1.0	5p	–
17	4-NO ₂ C ₆ H ₄	1.0	5q	–
18	1-naphthyl	1.0	5r	–
19	CH ₃	1.0	5s	–

^a Reaction conditions: **1** (1.0 mmol), **2** (1.0 mmol), **3** (2.0 mmol), **4** (1.0 equiv.), EtOH (10.0 mL), reflux, 30 min.

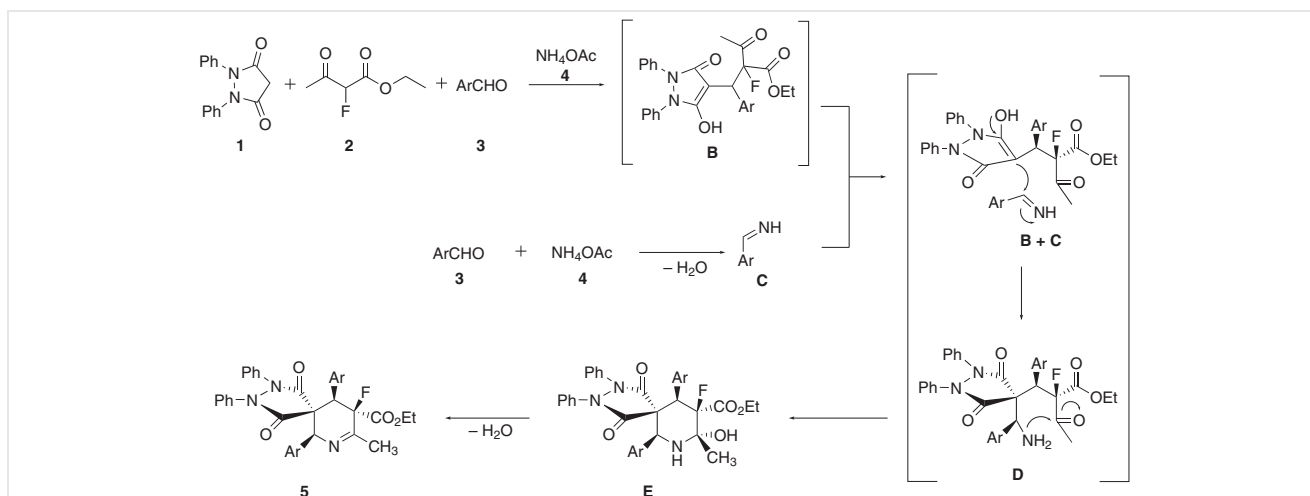
^b Isolated yield.

The structures of compounds **5** were fully characterized by spectroscopic methods. For example, in the ¹H NMR spectrum of **5a**, a doublet at δ 4.29 ppm was observed with a coupling constant of 30.5 Hz between 10-H and 9-F. Alternatively, the ¹⁹F NMR spectrum showed the 9-F signal, in most cases, as a double doublet at δ –155.5 ppm with a similar coupling constant $J_{H-F} = 30.5$ Hz. Meanwhile, the structure of compound **5b** was unambiguously assigned by single crystal X-ray diffraction analysis (Figure 1).¹⁷

Concerning the stereochemistry of products **5**, although the reaction generates three carbon-based stereogenic centers, it exclusively gave products **5** as a single diastereomer. The relative stereochemistry of the representative product **5b** was clearly confirmed by XRD analysis, with a stereochemistry of 6*S**,9*R**,10*R**. This could be due to the fact that the intramolecular cyclization proceeds under thermodynamic control, leading to formation of the most stable product. This conclusion is based on the fact that, in the solid state, the tetrahydropyridine ring adopts a nearly ideal half-chair conformation, whereas the three larger substituents,

**Figure 1** Crystal structure of compound **5b**

namely the 6-phenyl, 10-phenyl, and 9-ethoxycarbonyl groups, occupy *pseudo*-equatorial sites. It is noteworthy that all products **5** exhibited similar characteristic features



Scheme 3 A plausible mechanism for formation of **5**

in their ^1H NMR, ^{19}F NMR, and ^{13}C NMR spectra, indicating that all the products have the same relative stereochemistry.

Based on the above results, a plausible mechanism for the formation of products **5** is illustrated in Scheme 3. Firstly, intermediate **B** is formed via initial Knoevenagel condensation, followed by Michael addition reaction with the third component. Subsequently, intermediate **B** reacts with arylmethanimine **C**, derived from the second molar aromatic aldehyde **3** with NH_4OAc (**4**), to give the acyclic intermediate **D**, which undergoes intramolecular cyclization to give the spiro-heterocyclic intermediate **E**. Finally, dehydration of spiro-heterocyclic intermediate **E** affords the ultimate product **5**.

In conclusion, we have demonstrated a one-pot, four-component reaction to provide a facile and convenient approach to monofluorinated spiro-pyrazole-pyridine derivatives **5** from readily available starting materials. NH_4OAc plays a dual role both as the fourth component and as a catalyst in this MCR. This protocol will be useful for the synthesis of monofluorinated bis-heterocyclic spirocycles that could find further applications as biologically active compounds.

Melting points were measured with a digital melting point apparatus (WRS-1B, Shanghai Precision & Scientific Instrument Co., Ltd) and are uncorrected. IR spectra were obtained with a Nicolet AV-360 spectrophotometer. ^1H , ^{13}C , and ^{19}F NMR spectra were recorded in CDCl_3 on a Bruker AM-500 instrument with Me_4Si or CFCl_3 as internal and external standards, respectively. Low-resolution mass spectra were recorded with a Finnigan GC-MS 4021 instrument using electron impact ionization (70 eV) or an Agilent 1100 LC/MSD SL instrument using ESI. High-resolution mass spectra were obtained on a Bruker Daltonics, Inc. APEXIII 7.0 T FTMS using ESI. Flash column chromatography

was performed on silica gel (particle size 200–400 mesh) purchased from Qingdao Haiyang, eluting with petroleum ether (PE)/ethyl acetate (EA) (10:1, v/v). X-ray crystal structure data were collected on a Bruker SMART CCD area detector diffractometer using graphite monochromated $\text{Mo K}\alpha$ radiation ($\lambda = 0.71073 \text{ \AA}$) at 296(2) K.¹⁷

Ethyl 9-Fluoro-8-methyl-1,4-dioxo-2,3,6,10-tetraphenyl-2,3,7-triazaspiro[4.5]dec-7-ene-9-carboxylate (**5a**); Typical Procedure for Preparation of Compounds **5**

To a mixture of 1,2-diphenylpyrazolidine-3,5-dione (**1**; 256.0 mg, 1.0 mmol), ethyl 2-fluoroacetoacetate (**2**; 148.0 mg, 1.0 mmol), and benzaldehyde (**3b**; 212.0 mg, 2.0 mmol) in EtOH (10.0 mL) was added ammonium acetate (**4**; 77.0 mg, 1.0 mmol). The resultant mixture was stirred at reflux for 30 min. The progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was evaporated and the residue was purified by column chromatography on silica gel using PE/EA (10:1, v/v) as eluent to afford the pure product **5a**. White solid; yield: 311.0 mg (54%); mp 219.2–220.6 °C; $R_f = 0.49$ (PE/EA, 4:1 (v/v)).

IR (KBr): 1762, 1731, 1690, 1492, 1376, 1244 cm^{-1} .

^1H NMR (500 MHz, CDCl_3): $\delta = 7.40$ – 7.22 (m, 10 H, Ar-H), 7.10–6.98 (m, 6 H, Ar-H), 6.52–6.46 (m, 2 H, Ar-H), 6.38–6.33 (m, 2 H, Ar-H), 5.27–5.22 (m, 1 H, CH), 4.31 (q, $J = 7.0$ Hz, 2 H, CH_2), 4.29 (d, $J_{\text{H-F}} = 30.5$ Hz, 1 H, CH), 2.32 (d, $J = 2.5$ Hz, 3 H, CH_3), 1.27 (t, $J = 7.0$ Hz, 3 H, CH_3).

^{19}F NMR (470 MHz, CDCl_3): $\delta = -155.47$ (dd, $J = 30.5, 4.5$ Hz, C-F).

^{13}C NMR (125 MHz, CDCl_3): $\delta = 169.4$ (s, pyrazole-C=O), 168.3 (d, $^2J_{\text{C-F}} = 27.9$ Hz, C=O), 167.4 (s, pyrazole-C=O), 162.8 (d, $^2J_{\text{C-F}} = 21.0$ Hz, C=N), 137.8 (s, Ar-C), 134.3 (s, Ar-C), 131.5 (s, Ar-C), 131.4 (s, Ar-C), 130.9 (d, $^3J_{\text{C-F}} = 3.0$ Hz, C-C-F), 128.8 (s, Ar-C), 128.7 (s, Ar-C), 128.6 (s, Ar-C), 128.5 (s, Ar-C), 128.2 (s, Ar-C), 127.4 (s, Ar-C), 127.2 (s, Ar-C), 123.9 (s, Ar-C), 123.8 (s, Ar-C), 86.8 (d, $^1J_{\text{C-F}} = 205.9$ Hz, C-F), 66.8 (d, $^3J_{\text{C-F}} = 1.3$ Hz, $-\text{CH}_3$), 63.0 (s, spiro-C), 55.5 (s, $-\text{CH}_2$), 50.8 (d, $^2J_{\text{C-F}} = 19.0$ Hz, $-\text{CH}$), 21.7 (s, $-\text{CH}$), 14.2 (s, $-\text{CH}_3$).

MS (ESI): $m/z = 598$ [$\text{M} + \text{Na}$] $^+$.

HRMS (ESI): m/z [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{35}\text{H}_{30}\text{FN}_3\text{O}_4$: 576.2299; found: 576.2295.

Ethyl 9-Fluoro-8-methyl-1,4-dioxo-2,3-diphenyl-6,10-di-o-tolyl-2,3,7-triazaspiro[4.5]dec-7-ene-9-carboxylate (5b)

White solid; yield: 380.0 mg (63%); mp 168.5–169.2 °C; $R_f = 0.43$ (PE/EA, 4:1 (v/v)).

IR (KBr): 1761, 1719, 1492, 1306, 1238 cm^{-1} .

^1H NMR (500 MHz, CDCl_3): $\delta = 7.56$ – 7.50 (m, 1 H, Ar-H), 7.44 – 7.38 (m, 1 H, Ar-H), 7.21 – 7.04 (m, 9 H, Ar-H), 7.00 – 6.94 (m, 3 H, Ar-H), 6.67 – 6.62 (m, 2 H, Ar-H), 6.33 – 6.25 (m, 2 H, Ar-H), 5.57 – 5.51 (m, 1 H, CH), 4.72 (d, $J_{\text{H-F}} = 30.0$ Hz, 1 H, CH), 4.41 – 4.32 (m, 1 H, CH-H), 4.31 – 4.23 (m, 1 H, CH-H), 2.40 (s, 3 H, CH_3), 2.36 (s, 3 H, CH_3), 2.31 (d, $J = 2.0$ Hz, 3 H, CH_3), 1.29 (t, $J = 7.0$ Hz, 3 H, CH_3).

^{19}F NMR (470 MHz, CDCl_3): $\delta = -155.57$ (dt, $J = 30.0, 4.0$ Hz, C-F).

^{13}C NMR (125 MHz, CDCl_3): $\delta = 169.2$ (s, pyrazole-C=O), 168.8 (d, $^2J_{\text{C-F}} = 28.1$ Hz, C=O), 167.7 (s, pyrazole-C=O), 163.0 (d, $^2J_{\text{C-F}} = 21.0$ Hz, C=N), 137.9 (s, Ar-C), 136.2 (s, Ar-C), 136.0 (s, Ar-C), 134.6 (s, Ar-C), 134.3 (s, Ar-C), 130.8 (s, Ar-C), 130.7 (s, Ar-C), 130.6 (s, Ar-C), 130.5 (s, Ar-C), 130.3 (d, $^3J_{\text{C-F}} = 2.4$ Hz, Ar-C), 130.2 (s, Ar-C), 128.5 (s, Ar-C), 128.4 (s, Ar-C), 128.3 (s, Ar-C), 128.1 (s, Ar-C), 127.2 (s, Ar-C), 127.1 (s, Ar-C), 126.3 (s, Ar-C), 126.0 (s, Ar-C), 123.9 (s, Ar-C), 123.7 (s, Ar-C), 86.8 (d, $^1J_{\text{C-F}} = 207.5$ Hz, C-F), 63.0 (s, spiro-C), 60.3 (s, $-\text{CH}_2$), 55.2 (d, $^3J_{\text{C-F}} = 1.3$ Hz, $-\text{CH}_3$), 50.8 (s, $-\text{CH}$), 21.7 (s, $-\text{CH}$), 21.3 (s, $-\text{CH}_3$), 21.2 (s, $-\text{CH}_3$), 14.1 (s, $-\text{CH}_3$).

MS (ESI): $m/z = 604$ [M + H] $^+$.

HRMS (ESI): m/z [M + H] $^+$ calcd for $\text{C}_{37}\text{H}_{34}\text{FN}_3\text{O}_4$: 604.2612; found: 604.2608.

Ethyl 9-Fluoro-8-methyl-1,4-dioxo-2,3-diphenyl-6,10-di-m-tolyl-2,3,7-triazaspiro[4.5]dec-7-ene-9-carboxylate (5c)

White solid; yield: 362.0 mg (60%); mp 176.4–177.2 °C; $R_f = 0.48$ (PE/EA, 4:1 (v/v)).

IR (KBr): 1758, 1719, 1674, 1490, 1302, 1232 cm^{-1} .

^1H NMR (500 MHz, CDCl_3): $\delta = 7.21$ – 7.16 (m, 2 H, Ar-H), 7.15 – 6.97 (m, 12 H, Ar-H), 6.58 – 6.52 (m, 2 H, Ar-H), 6.43 – 6.37 (m, 2 H, Ar-H), 5.20 – 5.15 (m, 1 H, CH), 4.32 (q, $J = 7.0$ Hz, 2 H, CH_2), 4.24 (d, $J_{\text{H-F}} = 30.5$ Hz, 1 H, CH), 2.32 (d, $J = 2.5$ Hz, 3 H, CH_3), 2.17 (s, 3 H, CH_3), 2.12 (s, 3 H, CH_3), 1.29 (t, $J = 7.0$ Hz, 3 H, CH_3).

^{19}F NMR (470 MHz, CDCl_3): $\delta = -155.41$ (dt, $J = 30.5, 4.7$ Hz, C-F).

^{13}C NMR (125 MHz, CDCl_3): $\delta = 169.6$ (s, pyrazole-C=O), 168.4 (d, $^2J_{\text{C-F}} = 28.0$ Hz, C=O), 167.8 (s, pyrazole-C=O), 162.8 (d, $^2J_{\text{C-F}} = 20.7$ Hz, C=N), 138.4 (s, Ar-C), 138.2 (s, Ar-C), 137.6 (s, Ar-C), 134.6 (s, Ar-C), 131.5 (s, Ar-C), 131.4 (s, Ar-C), 131.3 (s, Ar-C), 131.2 (s, Ar-C), 129.6 (s, Ar-C), 129.2 (s, Ar-C), 128.9 (s, Ar-C), 128.6 (s, Ar-C), 128.5 (s, Ar-C), 128.4 (s, Ar-C), 128.3 (s, Ar-C), 127.9 (d, $^3J_{\text{C-F}} = 2.0$ Hz, Ar-C), 127.1 (s, Ar-C), 126.9 (s, Ar-C), 125.8 (s, Ar-C), 123.4 (s, Ar-C), 123.3 (s, Ar-C), 86.9 (d, $^1J_{\text{C-F}} = 205.1$ Hz, C-F), 67.0 (s, spiro-C), 62.9 (s, $-\text{CH}_2$), 55.4 (d, $^3J_{\text{C-F}} = 1.4$ Hz, $-\text{CH}_3$), 50.7 (d, $^2J_{\text{C-F}} = 19.2$ Hz, $-\text{CH}$), 21.7 (s, $-\text{CH}$), 21.4 (s, $-\text{CH}_3$), 21.2 (s, $-\text{CH}_3$), 14.2 (s, $-\text{CH}_3$).

MS (ESI): $m/z = 604$ [M + H] $^+$.

HRMS (ESI): m/z [M + H] $^+$ calcd for $\text{C}_{37}\text{H}_{34}\text{FN}_3\text{O}_4$: 604.2612; found: 604.2611.

Ethyl 9-Fluoro-8-methyl-1,4-dioxo-2,3-diphenyl-6,10-di-p-tolyl-2,3,7-triazaspiro[4.5]dec-7-ene-9-carboxylate (5d)

White solid; yield: 350.0 mg (58%); mp 188.1–189.2 °C; $R_f = 0.47$ (PE/EA, 4:1 (v/v)).

IR (KBr): 1724, 1487, 1302, 1256 cm^{-1} .

^1H NMR (500 MHz, CDCl_3): $\delta = 7.25$ – 7.17 (m, 2 H, Ar-H), 7.11 – 6.98 (m, 12 H, Ar-H), 6.55 – 6.50 (m, 2 H, Ar-H), 6.44 – 6.39 (m, 2 H, Ar-H), 5.22 – 5.16 (m, 1 H, CH), 4.31 (q, $J = 7.0$ Hz, 2 H, CH_2), 4.22 (d, $J_{\text{H-F}} = 30.5$ Hz, 1 H, CH), 2.31 (s, 3 H, CH_3), 2.30 (d, $J = 2.5$ Hz, 3 H, CH_3), 2.28 (s, 3 H, CH_3), 1.28 (t, $J = 7.0$ Hz, 3 H, CH_3).

^{19}F NMR (470 MHz, CDCl_3): $\delta = -155.46$ (dd, $J = 30.5, 4.6$ Hz, C-F).

^{13}C NMR (125 MHz, CDCl_3): $\delta = 169.8$ (s, pyrazole-C=O), 168.4 (d, $^2J_{\text{C-F}} = 28.3$ Hz, C=O), 167.8 (s, pyrazole-C=O), 162.7 (d, $^2J_{\text{C-F}} = 20.9$ Hz, C=N), 138.6 (s, Ar-C), 137.8 (s, Ar-C), 134.8 (s, Ar-C), 134.7 (s, Ar-C), 130.7 (d, $^3J_{\text{C-F}} = 3.2$ Hz, Ar-C), 129.4 (s, Ar-C), 129.1 (s, Ar-C), 128.5 (s, Ar-C), 128.4 (s, Ar-C), 128.3 (s, Ar-C), 127.2 (s, Ar-C), 127.0 (s, Ar-C), 123.6 (s, Ar-C), 123.5 (s, Ar-C), 86.9 (d, $^1J_{\text{C-F}} = 204.5$ Hz, C-F), 66.7 (s, spiro-C), 62.9 (s, $-\text{CH}_2$), 55.6 (d, $^3J_{\text{C-F}} = 1.5$ Hz, $-\text{CH}_3$), 50.4 (d, $^2J_{\text{C-F}} = 19.2$ Hz, $-\text{CH}$), 21.7 (s, $-\text{CH}$), 21.2 (s, $-\text{CH}_3$), 21.1 (s, $-\text{CH}_3$), 14.2 (s, $-\text{CH}_3$).

MS (ESI): $m/z = 604$ [M + H] $^+$.

HRMS (ESI): m/z [M + H] $^+$ calcd for $\text{C}_{37}\text{H}_{34}\text{FN}_3\text{O}_4$: 604.2612; found: 604.2606.

Ethyl 6,10-Bis(2-chlorophenyl)-9-fluoro-8-methyl-1,4-dioxo-2,3-diphenyl-2,3,7-triazaspiro[4.5]dec-7-ene-9-carboxylate (5e)

White solid; yield: 386.0 mg (60%); mp 164.2–165.8 °C; $R_f = 0.52$ (PE/EA, 4:1 (v/v)).

IR (KBr): 1763, 1720, 1680, 1489, 1304, 1246 cm^{-1} .

^1H NMR (500 MHz, CDCl_3): $\delta = 7.69$ – 7.62 (m, 1 H, Ar-H), 7.36 – 7.30 (m, 3 H, Ar-H), 7.22 – 7.14 (m, 3 H, Ar-H), 7.12 – 6.96 (m, 7 H, Ar-H), 6.66 – 6.62 (m, 2 H, Ar-H), 6.59 – 6.54 (m, 2 H, Ar-H), 5.96 – 5.92 (m, 1 H, CH), 5.15 (d, $J_{\text{H-F}} = 30.0$ Hz, 1 H, CH), 4.48 – 4.39 (m, 1 H, CH-H), 4.32 – 4.23 (m, 1 H, CH-H), 2.30 (d, $J = 2.5$ Hz, 3 H, CH_3), 1.34 (t, $J = 7.0$ Hz, 3 H, CH_3).

^{19}F NMR (470 MHz, CDCl_3): $\delta = -155.41$ (dt, $J = 30.5, 3.9$ Hz, C-F).

^{13}C NMR (125 MHz, CDCl_3): $\delta = 168.1$ (s, pyrazole-C=O), 167.6 (d, $^2J_{\text{C-F}} = 28.1$ Hz, C=O), 167.4 (s, pyrazole-C=O), 163.4 (d, $^2J_{\text{C-F}} = 20.6$ Hz, C=N), 135.8 (s, Ar-C), 135.4 (s, Ar-C), 134.8 (s, Ar-C), 134.4 (s, Ar-C), 133.4 (s, Ar-C), 132.3 (s, Ar-C), 131.6 (s, Ar-C), 131.5 (s, Ar-C), 130.2 (s, Ar-C), 129.9 (d, $^3J_{\text{C-F}} = 2.8$ Hz, Ar-C), 129.8 (s, Ar-C), 129.7 (s, Ar-C), 129.4 (s, Ar-C), 128.7 (s, Ar-C), 128.5 (s, Ar-C), 127.2 (s, Ar-C), 127.1 (s, Ar-C), 126.9 (s, Ar-C), 126.8 (s, Ar-C), 123.1 (s, Ar-C), 122.7 (s, Ar-C), 85.7 (d, $^1J_{\text{C-F}} = 203.6$ Hz, C-F), 63.3 (s, spiro-C), 63.2 (s, $-\text{CH}_2$), 54.4 (d, $^3J_{\text{C-F}} = 1.4$ Hz, $-\text{CH}_3$), 44.6 (d, $^2J_{\text{C-F}} = 19.2$ Hz, $-\text{CH}$), 21.7 (s, $-\text{CH}$), 14.0 (s, $-\text{CH}_3$).

MS (ESI): $m/z = 644$ [M + H] $^+$.

HRMS (ESI): m/z [M + H] $^+$ calcd for $\text{C}_{35}\text{H}_{28}\text{Cl}_2\text{FN}_3\text{O}_4$: 644.1519; found: 644.1518.

Ethyl 6,10-Bis(3-chlorophenyl)-9-fluoro-8-methyl-1,4-dioxo-2,3-diphenyl-2,3,7-triazaspiro[4.5]dec-7-ene-9-carboxylate (5f)

White solid; yield: 399.0 mg (62%); mp 192.3–193.6 °C; $R_f = 0.54$ (PE/EA, 4:1 (v/v)).

IR (KBr): 1761, 1735, 1703, 1482, 1366, 1247 cm^{-1} .

^1H NMR (500 MHz, CDCl_3): $\delta = 7.41$ – 7.37 (m, 2 H, Ar-H), 7.31 – 7.27 (m, 2 H, Ar-H), 7.25 – 7.01 (m, 10 H, Ar-H), 6.60 – 6.54 (m, 2 H, Ar-H), 6.51 – 6.45 (m, 2 H, Ar-H), 5.22 – 5.17 (m, 1 H, CH), 4.33 (q, $J = 7.0$ Hz, 2 H, CH_2), 4.26 (d, $J_{\text{H-F}} = 30.0$ Hz, 1 H, CH), 2.32 (d, $J = 2.0$ Hz, 3 H, CH_3), 1.30 (t, $J = 7.0$ Hz, 3 H, CH_3).

^{19}F NMR (470 MHz, CDCl_3): $\delta = -155.49$ (dd, $J = 30.0, 4.6$ Hz, C-F).

^{13}C NMR (125 MHz, CDCl_3): $\delta = 168.9$ (s, pyrazole-C=O), 168.1 (d, $^2J_{\text{C-F}} = 28.2$ Hz, C=O), 167.0 (s, pyrazole-C=O), 163.4 (d, $^2J_{\text{C-F}} = 20.7$ Hz, C=N), 139.7 (s, Ar-C), 134.8 (s, Ar-C), 134.7 (s, Ar-C), 134.1 (s, Ar-C), 133.4 (s, Ar-C), 133.3 (s, Ar-C), 130.7 (d, $^3J_{\text{C-F}} = 3.7$ Hz, Ar-C), 130.2 (s, Ar-C),

130.0 (s, Ar-C), 129.3 (s, Ar-C), 129.0 (s, Ar-C), 128.9 (s, Ar-C), 128.8 (s, Ar-C), 128.6 (s, Ar-C), 127.6 (s, Ar-C), 127.5 (s, Ar-C), 127.1 (s, Ar-C), 123.7 (s, Ar-C), 123.5 (s, Ar-C), 86.6 (d, $^1J_{C-F}$ = 206.7 Hz, C-F), 66.3 (s, spiro-C), 63.4 (s, -CH₂), 55.1 (s, -CH₃), 50.4 (d, $^2J_{C-F}$ = 19.2 Hz, -CH), 21.8 (s, -CH), 14.3 (s, -CH₃).

MS (ESI): m/z = 644 [M + H]⁺.

HRMS (ESI): m/z [M + H]⁺ calcd for C₃₅H₂₈Cl₂FN₃O₄: 644.1519; found: 644.1519.

Ethyl 6,10-Bis(4-chlorophenyl)-9-fluoro-8-methyl-1,4-dioxo-2,3-diphenyl-2,3,7-triazaspiro[4.5]dec-7-ene-9-carboxylate (5g)

White solid; yield: 392.0 mg (61%); mp 174.0–174.5 °C; R_f = 0.57 (PE/EA, 4:1 (v/v)).

IR (KBr): 1722, 1675, 1490, 1298, 1254 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 7.31–7.20 (m, 2 H, Ar-H), 7.16–7.12 (m, 2 H, Ar-H), 7.11–7.02 (m, 10 H, Ar-H), 6.56–6.51 (m, 2 H, Ar-H), 6.47–6.42 (m, 2 H, Ar-H), 5.22–5.15 (m, 1 H, CH), 4.31 (q, J = 7.0 Hz, 2 H, CH₂), 4.25 (d, J_{H-F} = 30.0 Hz, 1 H, CH), 2.32 (d, J = 2.0 Hz, 3 H, CH₃), 1.28 (t, J = 7.0 Hz, 3 H, CH₃).

¹⁹F NMR (470 MHz, CDCl₃): δ = -155.42 (dd, J = 30.0, 4.7 Hz, C-F).

¹³C NMR (125 MHz, CDCl₃): δ = 169.3 (s, pyrazole-C=O), 168.0 (d, $^2J_{C-F}$ = 28.2 Hz, C=O), 167.3 (s, pyrazole-C=O), 163.2 (d, $^2J_{C-F}$ = 21.0 Hz, C=N), 136.1 (s, Ar-C), 135.2 (s, Ar-C), 134.4 (s, Ar-C), 134.3 (s, Ar-C), 134.2 (s, Ar-C), 132.3 (s, Ar-C), 132.2 (s, Ar-C), 130.1 (s, Ar-C), 129.8 (d, $^2J_{C-F}$ = 2.7 Hz, Ar-C), 129.0 (s, Ar-C), 128.8 (s, Ar-C), 128.7 (s, Ar-C), 127.5 (s, Ar-C), 127.4 (s, Ar-C), 123.2 (s, Ar-C), 123.1 (s, Ar-C), 86.6 (d, $^1J_{C-F}$ = 205.9 Hz, C-F), 66.1 (s, spiro-C), 63.2 (s, -CH₂), 55.4 (d, $^3J_{C-F}$ = 1.6 Hz, -CH₃), 50.1 (d, $^2J_{C-F}$ = 19.1 Hz, -CH), 21.7 (s, -CH), 14.2 (s, -CH₃).

MS (ESI): m/z = 644 [M + H]⁺.

HRMS (ESI): m/z [M + H]⁺ calcd for C₃₅H₂₈Cl₂FN₃O₄: 644.1519; found: 644.1513.

Ethyl 6,10-Bis(2,4-dichlorophenyl)-9-fluoro-8-methyl-1,4-dioxo-2,3-diphenyl-2,3,7-triazaspiro[4.5]dec-7-ene-9-carboxylate (5h)

White solid; yield: 348.0 mg (49%); mp 205.1–206.5 °C; R_f = 0.52 (PE/EA, 4:1 (v/v)).

IR (KBr): 1728, 1681, 1590, 1482, 1292 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 7.58 (dd, J = 11.0, 2.0 Hz, 1 H, Ar-H), 7.36 (dd, J = 8.5, 2.0 Hz, 2 H, Ar-H), 7.23–7.02 (m, 8 H, Ar-H), 6.63 (dd, J = 8.5, 2.0 Hz, 1 H, Ar-H), 6.69–6.62 (m, 4 H, Ar-H), 5.89–5.83 (m, 1 H, CH), 5.06 (d, J_{H-F} = 30.0 Hz, 1 H, CH), 4.47–4.38 (m, 1 H, CH-H), 4.32–4.23 (m, 1 H, CH-H), 2.28 (d, J = 2.5 Hz, 3 H, CH₃), 1.34 (t, J = 7.0 Hz, 3 H, CH₃).

¹⁹F NMR (470 MHz, CDCl₃): δ = -155.31 (dt, J = 30.0, 3.6 Hz, C-F).

¹³C NMR (125 MHz, CDCl₃): δ = 167.9 (s, pyrazole-C=O), 167.3 (s, pyrazole-C=O), 167.2 (d, $^2J_{C-F}$ = 28.4 Hz, C=O), 163.7 (d, $^2J_{C-F}$ = 20.6 Hz, C=N), 136.6 (s, Ar-C), 135.4 (s, Ar-C), 135.2 (s, Ar-C), 134.7 (s, Ar-C), 134.4 (s, Ar-C), 134.0 (s, Ar-C), 133.8 (s, Ar-C), 133.2 (s, Ar-C), 132.3 (s, Ar-C), 132.2 (s, Ar-C), 130.0 (s, Ar-C), 129.0 (s, Ar-C), 128.9 (s, Ar-C), 128.6 (s, Ar-C), 128.5 (d, $^3J_{C-F}$ = 3.2 Hz, Ar-C), 127.5 (s, Ar-C), 127.3 (s, Ar-C), 127.2 (s, Ar-C), 127.1 (s, Ar-C), 122.6 (s, Ar-C), 122.1 (s, Ar-C), 85.4 (d, $^1J_{C-F}$ = 204.1 Hz, C-F), 63.4 (s, spiro-C), 62.8 (s, -CH₂), 54.3 (s, -CH₃), 44.0 (d, $^2J_{C-F}$ = 19.2 Hz, -CH), 21.7 (s, -CH), 14.0 (s, -CH₃).

MS (ESI): m/z = 712 [M + H]⁺.

HRMS (ESI): m/z [M + H]⁺ calcd for C₃₅H₂₆Cl₄FN₃O₄: 712.0740; found: 712.0737.

Ethyl 6,10-Bis(2-bromophenyl)-9-fluoro-8-methyl-1,4-dioxo-2,3-diphenyl-2,3,7-triazaspiro[4.5]dec-7-ene-9-carboxylate (5i)

White solid; yield: 380.6 mg (52%); mp 228.7–229.3 °C; R_f = 0.52 (PE/EA, 4:1 (v/v)).

IR (KBr): 1758, 1680, 1592, 1488, 1292 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 7.66–7.64 (m, 1 H, Ar-H), 7.54–7.51 (m, 2 H, Ar-H), 7.35–7.33 (m, 1 H, Ar-H), 7.23 (t, J = 7.5 Hz, 1 H, Ar-H), 7.13–6.97 (m, 9 H, Ar-H), 6.66 (d, J = 7.7 Hz, 2 H, Ar-H), 6.6 (d, J = 7.1 Hz, 2 H, Ar-H), 5.93–5.91 (m, 1 H, CH), 5.15 (d, J_{H-F} = 29.7 Hz, 1 H, CH), 4.49–4.43 (m, 1 H, CH-H), 4.33–4.26 (m, 1 H, CH-H), 2.30 (d, J = 2.2 Hz, 3 H, CH₃), 1.34 (t, J = 7.2 Hz, 3 H, CH₃).

¹⁹F NMR (470 MHz, CDCl₃): δ = -155.22 (dt, J = 32.2, 3.6 Hz, C-F).

¹³C NMR (125 MHz, CDCl₃): δ = 168.0 (s, pyrazole-C=O), 167.6 (s, pyrazole-C=O), 167.3 (d, $^2J_{C-F}$ = 28.3 Hz, C=O), 163.7 (d, $^2J_{C-F}$ = 21.0 Hz, C=N), 137.3 (s, Ar-C), 134.9 (s, Ar-C), 134.5 (s, Ar-C), 133.7 (s, Ar-C), 133.0 (s, Ar-C), 132.5 (s, Ar-C), 131.8 (s, Ar-C), 131.7 (s, Ar-C), 130.1 (d, $^2J_{C-F}$ = 20.0 Hz, Ar-C), 128.7 (s, Ar-C), 128.6 (s, Ar-C), 127.9 (s, Ar-C), 127.4 (s, Ar-C), 127.14 (s, Ar-C), 127.05 (s, Ar-C), 127.0 (s, Ar-C), 123.7 (s, Ar-C), 123.1 (s, Ar-C), 122.8 (s, Ar-C), 85.7 (d, $^1J_{C-F}$ = 163.5 Hz, C-F), 65.6 (s, spiro-C), 63.4 (s, -CH₂), 54.7 (s, -CH₃), 47.5 (d, $^2J_{C-F}$ = 19.2 Hz, -CH), 21.7 (s, -CH), 14.1 (s, -CH₃).

MS (ESI): m/z = 732 [M + H]⁺.

HRMS (ESI): m/z [M + H]⁺ calcd for C₃₅H₂₆⁷⁹Br₂FN₃O₄: 732.0509; found: 732.0496.

Ethyl 6,10-Bis(3-bromophenyl)-9-fluoro-8-methyl-1,4-dioxo-2,3-diphenyl-2,3,7-triazaspiro[4.5]dec-7-ene-9-carboxylate (5j)

White solid; yield: 409.4 mg (56%); mp 178.3–179.7 °C; R_f = 0.48 (PE/EA, 4:1 (v/v)).

IR (KBr): 1758, 1712, 1585, 1487, 1241 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 7.56–7.53 (m, 2 H, Ar-H), 7.46–7.43 (m, 2 H, Ar-H), 7.28 (d, J = 7.8 Hz, 1 H, Ar-H), 7.20–7.18 (m, 1 H, Ar-H), 7.16–7.02 (m, 8 H, Ar-H), 6.59–6.56 (m, 2 H, Ar-H), 6.51–6.49 (m, 2 H, Ar-H), 5.19–5.18 (m, 1 H, CH), 4.33 (q, J = 7.1 Hz, 2 H, CH₂), 4.24 (d, J_{H-F} = 29.8 Hz, 1 H, CH), 2.32 (d, J = 2.4 Hz, 3 H, CH₃), 1.30 (t, J = 7.1 Hz, 3 H, CH₃).

¹⁹F NMR (470 MHz, CDCl₃): δ = -155.48 (dd, J = 36.2, 4.8 Hz, C-F).

¹³C NMR (125 MHz, CDCl₃): δ = 168.8 (s, pyrazole-C=O), 168.1 (s, pyrazole-C=O), 167.9 (d, $^2J_{C-F}$ = 28.2 Hz, C=O), 163.4 (d, $^2J_{C-F}$ = 20.9 Hz, C=N), 139.9 (s, Ar-C), 134.1 (s, Ar-C), 133.6 (s, Ar-C), 133.5 (d, $^3J_{C-F}$ = 4.1 Hz, Ar-C), 132.3 (s, Ar-C), 131.6 (s, Ar-C), 131.5 (s, Ar-C), 130.4 (s, Ar-C), 130.3 (s, Ar-C), 129.81 (s, Ar-C), 129.80 (s, Ar-C), 128.9 (s, Ar-C), 127.6 (s, Ar-C), 127.5 (s, Ar-C), 123.7 (s, Ar-C), 123.5 (s, Ar-C), 123.0 (s, Ar-C), 122.9 (s, Ar-C), 122.8 (s, Ar-C), 86.6 (d, $^1J_{C-F}$ = 205.9 Hz, C-F), 66.2 (s, spiro-C), 63.4 (s, -CH₂), 55.1 (d, $^3J_{C-F}$ = 1.5 Hz, -CH₃), 50.4 (d, $^2J_{C-F}$ = 19.3 Hz, -CH), 21.8 (s, -CH), 14.3 (s, -CH₃).

MS (ESI): m/z = 732 [M + H]⁺.

HRMS (ESI): m/z [M + H]⁺ calcd for C₃₅H₂₆⁷⁹Br₂FN₃O₄: 732.0509; found: 732.0499.

Ethyl 6,10-Bis(4-bromophenyl)-9-fluoro-8-methyl-1,4-dioxo-2,3-diphenyl-2,3,7-triazaspiro[4.5]dec-7-ene-9-carboxylate (5k)

White solid; yield: 417.2 mg (57%); mp 176.1–177.2 °C; R_f = 0.46 (PE/EA, 4:1 (v/v)).

IR (KBr): 1721, 1591, 1488, 1298, 1252 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 7.53 (t, *J* = 7.2 Hz, 1 H, Ar-H), 7.37–7.34 (m, 1 H, Ar-H), 7.27–7.23 (m, 2 H, Ar-H), 7.12–6.98 (m, 10 H, Ar-H), 6.63 (d, *J* = 7.4 Hz, 2 H, Ar-H), 6.54 (d, *J* = 7.2 Hz, 2 H, Ar-H), 5.73–5.72 (m, 1 H, CH), 4.88 (d, *J*_{H-F} = 30.2 Hz, 1 H, CH), 4.40–4.30 (m, 2 H, CH₂), 2.31 (d, *J* = 2.3 Hz, 3 H, CH₃), 1.33 (t, *J* = 7.2 Hz, 3 H, CH₃).

¹⁹F NMR (470 MHz, CDCl₃): δ = -155.40 (dd, *J* = 31.1, 4.7 Hz, C-F).

¹³C NMR (125 MHz, CDCl₃): δ = 169.4 (s, pyrazole-C=O), 168.2 (s, pyrazole-C=O), 167.4 (d, ²*J*_{C-F} = 28.3 Hz, C=O), 163.3 (d, ²*J*_{C-F} = 21.0 Hz, C=N), 136.6 (s, Ar-C), 134.34 (s, Ar-C), 134.33 (s, Ar-C), 132.6 (d, ³*J*_{C-F} = 3.5 Hz, Ar-C), 132.0 (s, Ar-C), 131.8 (s, Ar-C), 130.5 (s, Ar-C), 130.4 (s, Ar-C), 128.9 (s, Ar-C), 128.8 (s, Ar-C), 127.6 (d, ²*J*_{C-F} = 18.0 Hz, Ar-C), 123.5 (s, Ar-C), 123.3 (s, Ar-C), 123.2 (s, Ar-C), 122.7 (s, Ar-C), 86.6 (d, ¹*J*_{C-F} = 205.7 Hz, C-F), 66.2 (s, spiro-C), 63.3 (s, -CH₂), 55.4 (d, ³*J*_{C-F} = 1.4 Hz, -CH₃), 50.2 (d, ²*J*_{C-F} = 19.0 Hz, -CH), 21.8 (s, -CH), 14.2 (s, -CH₃).

MS (ESI): *m/z* = 732 [M + H]⁺.

HRMS (ESI): *m/z* [M + H]⁺ calcd for C₃₅H₂₉Br₂FN₃O₄: 732.0509; found: 732.0498.

Ethyl 9-Fluoro-6,10-bis(2-fluorophenyl)-8-methyl-1,4-dioxo-2,3-diphenyl-2,3,7-triazaspiro[4.5]dec-7-ene-9-carboxylate (5I)

Yellow solid; yield: 391.7 mg (64%); mp 188.7–190.1 °C; *R*_f = 0.53 (PE/EA, 4:1 (v/v)).

IR (KBr): 1756, 1713, 1594, 1491, 1236 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 7.53 (t, *J* = 7.2 Hz, 1 H, Ar-H), 7.37–7.34 (m, 1 H, Ar-H), 7.27–7.23 (m, 2 H, Ar-H), 7.12–6.98 (m, 10 H, Ar-H), 6.63 (d, *J* = 7.4 Hz, 2 H, Ar-H), 6.54 (d, *J* = 7.2 Hz, 2 H, Ar-H), 5.73–5.72 (m, 1 H, CH), 4.88 (d, *J*_{H-F} = 30.2 Hz, 1 H, CH), 4.40–4.30 (m, 2 H, CH₂), 2.31 (d, *J* = 2.3 Hz, 3 H, CH₃), 1.33 (t, *J* = 7.2 Hz, 3 H, CH₃).

¹⁹F NMR (470 MHz, CDCl₃): δ = -115.50 to -115.70 (m, 1 F, Ar-F), -115.78 to -115.83 (m, 1 F, Ar-F), -155.28 (d, *J* = 31.4 Hz, 1 F, C-F).

¹³C NMR (125 MHz, CDCl₃): δ = 168.5 (s, pyrazole-C=O), 167.6 (d, ²*J*_{C-F} = 28.5 Hz, C=O), 167.4 (s, pyrazole-C=O), 163.7 (d, ²*J*_{C-F} = 20.7 Hz, C=N), 160.8 (d, ¹*J*_{C-F} = 247.3 Hz, Ar-C), 159.9 (d, ¹*J*_{C-F} = 248.1 Hz, Ar-C), 134.7 (s, Ar-C), 134.4 (s, Ar-C), 131.6 (d, ³*J*_{C-F} = 2.6 Hz, Ar-C), 131.2 (d, ³*J*_{C-F} = 2.8 Hz, Ar-C), 130.6 (d, ³*J*_{C-F} = 8.5 Hz, Ar-C), 130.2 (d, ³*J*_{C-F} = 8.1 Hz, Ar-C), 128.8 (s, Ar-C), 128.6 (s, Ar-C), 127.2 (d, ²*J*_{C-F} = 15.9 Hz, Ar-C), 124.8 (d, ²*J*_{C-F} = 13.5 Hz, Ar-C), 124.7 (d, ³*J*_{C-F} = 3.4 Hz, Ar-C), 124.3 (d, ³*J*_{C-F} = 3.4 Hz, Ar-C), 123.2 (s, Ar-C), 123.0 (s, Ar-C), 119.2 (d, ³*J*_{C-F} = 3.4 Hz, Ar-C), 119.1 (d, ³*J*_{C-F} = 3.3 Hz, Ar-C), 116.0 (d, ²*J*_{C-F} = 23.1 Hz, Ar-C), 115.3 (d, ²*J*_{C-F} = 22.0 Hz, Ar-C), 86.3 (d, ¹*J*_{C-F} = 203.5 Hz, C-F), 63.3 (s, spiro-C), 60.3 (s, -CH₂), 53.9 (s, -CH₃), 41.0 (d, ²*J*_{C-F} = 19.6 Hz, -CH), 21.7 (s, -CH), 14.0 (s, -CH₃).

MS (ESI): *m/z* = 612 [M + H]⁺.

HRMS (ESI): *m/z* [M + H]⁺ calcd for C₃₅H₂₉F₃N₃O₄: 612.2110; found: 612.2095.

Ethyl 9-Fluoro-6,10-bis(3-fluorophenyl)-8-methyl-1,4-dioxo-2,3-diphenyl-2,3,7-triazaspiro[4.5]dec-7-ene-9-carboxylate (5m)

White solid; yield: 342.7 mg (56%); mp 168.2–169.5 °C; *R*_f = 0.35 (PE/EA, 5:1 (v/v)).

IR (KBr): 1721, 1589, 1491, 1301, 1238 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 7.25–7.20 (m, 2 H, Ar-H), 7.15–7.00 (m, 12 H, Ar-H), 6.56–6.54 (m, 2 H, Ar-H), 6.48–6.46 (m, 2 H, Ar-H), 5.24–5.22 (m, 1 H, CH), 4.35 (q, *J* = 7.0 Hz, 2 H, CH₂), 4.25 (d, *J* = 30.0 Hz, 1 H, CH), 2.33 (d, *J* = 2.5 Hz, 3 H, CH₃), 1.29 (t, *J* = 7.0 Hz, 3 H, CH₃).

¹⁹F NMR (470 MHz, CDCl₃): δ = -112.18 to -112.28 (m, 1 F, Ar-F), -112.29 to -112.39 (m, 1 F, Ar-F), -155.50 (d, *J* = 31.4 Hz, 1 F, C-F).

¹³C NMR (125 MHz, CDCl₃): δ = 169.0 (s, pyrazole-C=O), 168.0 (d, ²*J*_{C-F} = 27.5 Hz, C=O), 167.1 (s, pyrazole-C=O), 163.3 (d, ²*J*_{C-F} = 20.9 Hz, C=N), 163.0 (d, ¹*J*_{C-F} = 245.4 Hz, Ar-C), 162.6 (d, ¹*J*_{C-F} = 245.3 Hz, Ar-C), 140.2 (d, ³*J*_{C-F} = 7.1 Hz, Ar-C), 134.2 (d, ³*J*_{C-F} = 3.4 Hz, Ar-C), 130.4 (d, ³*J*_{C-F} = 8.1 Hz, Ar-C), 130.2 (d, ³*J*_{C-F} = 8.1 Hz, Ar-C), 128.8 (d, ³*J*_{C-F} = 4.4 Hz, Ar-C), 128.7 (s, Ar-C), 128.6 (s, Ar-C), 127.6 (s, Ar-C), 127.5 (s, Ar-C), 126.8 (s, Ar-C), 124.5 (d, ³*J*_{C-F} = 2.7 Hz, Ar-C), 123.5 (s, Ar-C), 123.4 (s, Ar-C), 118.0 (d, ³*J*_{C-F} = 3.7 Hz, Ar-C), 117.8 (d, ³*J*_{C-F} = 4.0 Hz, Ar-C), 116.1 (d, ²*J*_{C-F} = 20.8 Hz, Ar-C), 115.9 (d, ²*J*_{C-F} = 22.5 Hz, Ar-C), 115.3 (d, ²*J*_{C-F} = 20.9 Hz, Ar-C), 86.6 (d, ¹*J*_{C-F} = 206.0 Hz, C-F), 66.2 (s, spiro-C), 63.3 (s, -CH₂), 55.2 (s, -CH₃), 50.5 (d, ²*J*_{C-F} = 18.9 Hz, -CH), 21.8 (s, -CH), 14.2 (s, -CH₃).

MS (ESI): *m/z* = 612 [M + H]⁺.

HRMS (ESI): *m/z* [M + H]⁺ calcd for C₃₅H₂₉F₃N₃O₄: 612.2110; found: 612.2093.

Ethyl 9-Fluoro-6,10-bis(2-methoxyphenyl)-8-methyl-1,4-dioxo-2,3-diphenyl-2,3,7-triazaspiro[4.5]dec-7-ene-9-carboxylate (5n)

Yellow solid; yield: 426.1 mg (67%); mp 188.2–189.3 °C; *R*_f = 0.46 (PE/EA, 3:1 (v/v)).

IR (KBr): 1753, 1710, 1593, 1493, 1255 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 7.37–7.33 (m, 2 H, Ar-H), 7.23–7.20 (m, 2 H, Ar-H), 7.13–7.09 (m, 2 H, Ar-H), 7.06–6.95 (m, 4 H, Ar-H), 6.88 (t, *J* = 7.4 Hz, 1 H, Ar-H), 6.83 (d, *J* = 7.9 Hz, 1 H, Ar-H), 6.78 (t, *J* = 7.6 Hz, 1 H, Ar-H), 6.70 (dd, *J* = 16.7, 7.6 Hz, 3 H, Ar-H), 6.49 (d, *J* = 7.6 Hz, 2 H, Ar-H), 5.85–5.83 (m, 1 H, CH), 5.12 (d, *J*_{H-F} = 31.1 Hz, 1 H, CH), 4.42–4.19 (m, 2 H, CH₂), 3.81 (s, 3 H, CH₃), 3.44 (s, 3 H, CH₃), 2.28 (d, *J* = 2.5 Hz, 3 H, CH₃), 1.32 (t, *J* = 7.2 Hz, 3 H, CH₃).

¹⁹F NMR (470 MHz, CDCl₃): δ = -155.46 (dd, *J* = 30.5, 4.6 Hz, C-F).

¹³C NMR (125 MHz, CDCl₃): δ = 169.4 (s, pyrazole-C=O), 168.5 (s, pyrazole-C=O), 168.2 (d, ²*J*_{C-F} = 29.0 Hz, C=O), 163.1 (d, ²*J*_{C-F} = 20.3 Hz, C=N), 157.6 (s, Ar-C), 156.3 (s, Ar-C), 135.6 (s, Ar-C), 135.0 (s, Ar-C), 131.4 (s, Ar-C), 130.6 (d, ³*J*_{C-F} = 3.8 Hz, Ar-C), 129.6 (s, Ar-C), 129.3 (s, Ar-C), 128.5 (s, Ar-C), 128.4 (s, Ar-C), 126.8 (s, Ar-C), 126.5 (s, Ar-C), 126.3 (s, Ar-C), 123.0 (s, Ar-C), 122.9 (s, Ar-C), 121.0 (s, Ar-C), 120.8 (s, Ar-C), 120.7 (s, Ar-C), 111.2 (s, Ar-C), 110.4 (s, Ar-C), 86.4 (d, ¹*J*_{C-F} = 202.4 Hz, C-F), 62.5 (s, spiro-C), 60.5 (s, -CH₂), 56.1 (s, CH₃), 54.9 (s, OCH₃), 54.5 (s, OCH₃), 40.6 (d, ²*J*_{C-F} = 20.1 Hz, -CH), 21.7 (s, -CH), 14.1 (s, -CH₃).

MS (ESI): *m/z* = 636 [M + H]⁺.

HRMS (ESI): *m/z* [M + H]⁺ calcd for C₃₇H₃₅FN₃O₆: 636.2510; found: 636.2503.

Ethyl 9-Fluoro-6,10-bis(3-methoxyphenyl)-8-methyl-1,4-dioxo-2,3-diphenyl-2,3,7-triazaspiro[4.5]dec-7-ene-9-carboxylate (5o)

White solid; yield: 400.7 mg (63%); mp 167.8–168.6 °C; *R*_f = 0.39 (PE/EA, 4:1 (v/v)).

IR (KBr): 1755, 1671, 1596, 1489, 1264 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 7.18 (dt, *J* = 27.4, 7.9 Hz, 2 H, Ar-H), 7.12–6.98 (m, 7 H, Ar-H), 6.87–6.76 (m, 5 H, Ar-H), 6.59–6.58 (m, 2 H, Ar-H), 6.48–6.46 (m, 2 H, Ar-H), 5.19–5.18 (m, 1 H, CH), 4.32 (q, *J* = 7.1 Hz, 2 H, CH₂), 4.26 (d, *J*_{H-F} = 30.3 Hz, 1 H, CH), 3.48 (s, 3 H, CH₃), 3.45 (s, 3 H, CH₃), 2.33 (d, *J* = 2.4 Hz, 3 H, CH₃), 1.29 (t, *J* = 7.1 Hz, 3 H, CH₃).

¹⁹F NMR (470 MHz, CDCl₃): δ = -155.15 (dd, *J* = 32.3, 4.9 Hz, C-F).

¹³C NMR (125 MHz, CDCl₃): δ = 169.6 (s, pyrazole-C=O), 168.3 (d, ²*J*_{C-F} = 27.3 Hz, C=O), 168.0 (s, pyrazole-C=O), 163.0 (d, ²*J*_{C-F} = 21.0 Hz, C=N), 159.9 (s, Ar-C), 159.6 (s, Ar-C), 139.1 (s, Ar-C), 134.74 (s, Ar-C), 134.71 (s, Ar-C), 132.8 (d, ³*J*_{C-F} = 2.8 Hz, Ar-C), 129.7 (s, Ar-C), 129.6 (s, Ar-C), 128.64 (s, Ar-C), 128.59 (s, Ar-C), 127.2 (s, Ar-C), 127.0 (s, Ar-C), 123.31 (s, Ar-C), 123.27 (s, Ar-C), 123.1 (s, Ar-C), 121.0 (s, Ar-C), 115.5

(s, Ar-C), 115.42 (s, Ar-C), 115.35 (s, Ar-C), 112.9 (s, Ar-C), 86.9 (d, $^1J_{C-F}$ = 205.7 Hz, C-F), 67.0 (s, spiro-C), 63.1 (s, -CH₂), 55.7 (s, -CH₃), 55.0 (s, OCH₃), 54.9 (s, OCH₃), 50.7 (d, $^2J_{C-F}$ = 18.9 Hz, -CH), 21.8 (s, -CH), 14.3 (s, -CH₃).

MS (ESI): m/z = 636 [M + H]⁺.

HRMS (ESI): m/z [M + H]⁺ calcd for C₃₇H₃₅FN₃O₆: 636.2510; found: 636.2503.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

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- (17) CCDC 2152316 contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.