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# Iodine catalyzed one-pot multi-component reaction to $CF_3$-containing spiro[indene-2,3′-piperidine] derivatives

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One-pot multi-component reactionDedicated to Professor Wei-Yuan Huang on the occasion of his 90th birthday.

ABSTRACT

In the presence of a catalytic amount of molecular iodine (0.1 equiv.), the one-pot multi-component reaction of ethyl trifluoroacetoacetate **1**, indan-1,3-dione **2**, ammonium acetate **3** and aromatic aldehyde **4** mainly gave the ethyl-6′-hydroxy-1,3-dioxo-2′,4′-diaryl-6′-(trifluoromethyl)-1,3-dihydrospiro[indene-2,3′-piperidine]-5′-carboxylate derivatives **5**, along with the minor product 2-trifluoromethyl-2,3,4,5-tetrahydro-1*H*-indeno[1,2-*b*]pyridine derivatives **6**. A plausible reaction mechanism for the formation of **5**, **6** was presented. The structures of compounds **5**, **6** were fully confirmed by $^1$H NMR, $^{19}$F NMR, MS, IR spectroscopies and elemental analysis or high resolution mass spectra (HRMS). Meanwhile, the representative **5a** and **6h** were further confirmed by XRD analysis.



## 1. Introduction

In recent times, the use of molecular iodine has received considerable attention as an inexpensive, nontoxic, readily available catalyst for various organic transformations to afford the corresponding products in excellent yields with high selectivity [1]. The mild Lewis acidity associated with iodine enhanced its usage in organic synthesis to realize several organic transformations using stoichiometric levels to catalytic amounts. Owing to numerous advantages associated with this eco-friendly element, iodine has been explored as a powerful catalyst for various organic transformations [2]. So the development of a reaction that uses catalytic amounts of mild toxic and readily available iodine should greatly contribute to the creation of environmentally benign processes. Interestingly, to some extent, the reactions promoted by iodine usually afford the unexpected results [3].

The spiropiperidine and its derivatives are important biologically active compounds [4], which have profound medical applications. In addition, spiropiperidinyl ring systems have been isolated from various plant alkaloids and animal toxins [5]. For example, some neurotoxic spirofused piperidines were isolated from the neotropical poisonous frog Dendrobates histrionicus and their spirofused analogues, the alkaloids sibirine, nitramine, isonitramine and nitrabirine, were isolated from plants of the genus Nitraria [6].

Fluorine-containing compounds have attracted much interest because of their unique chemical, physical, and biological activities [7]. In particular, fluorine-containing heterocycles are now widely recognized as important organic molecules showing interesting biological activities with potential for applications in the medicinal and agricultural fields [8]. With the aim to develop more efficient synthetic processes, environmental friendly, shorten the synthetic route, and in the continuation of our recent interest in the construction of fluorine-containing heterocycles scaffolds [9], we develop a facile, multi-component reaction involving condensation of ethyl trifluoroacetoacetate (**1**), 1,3-indanedione (**2**), ammonium acetate (**3**), and aromatic aldehyde (**4**) in the presence of catalytic amount of molecular iodine under mild reaction conditions to afford a series of novel trifluoromethyl-containing

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spiro[indene-2,3′-priperindine] scaffolds **5** in moderate yields, along with the minor product **6**, respectively.

## 2. Results and discussion

In an initial endeavour, we carried out the one-pot, four-component reaction of equivmolar amounts of ethyl trifluoroacetoacetate (**1**), 1,3-indanedione (**2**), ammonium acetate (**3**), and benzaldehyde (**4**) in ethanol as solvent. The reaction mixture was stirred for 12 h at room temperature, however, TLC showed that there was no reaction occurred, even though the reaction mixture was heated to reflux with prolonged reaction time. Subsequently, a catalytic amount of molecular iodine (0.2 equivmolar) was introduced into the reaction mixture, after stirring for 4 h at room temperature, TLC analysis showed that two new compounds were formed, however the starting materials did not disappeared completely. After simple workup, one major product was isolated in 42% yield, and the amount of the other minor product was insufficient to be identified. The $^1$H NMR spectra of the major product was not consistent with the one molecular aryl group, Further analysis of the NMR spectra revealed that this compound might contain two molecular aryl groups framework. Finally, the structure of major product **5a** was unequivocally established by the X-ray diffraction analysis of its single crystal (Fig. 1). The formation of a trifluoromethyl-containing spiro[indene-2,3′-piperidine] structure is very unusual and may find its application in related transformation leading to useful products. Encouraged by this unexpected result, we initially optimized the reaction conditions by varying the molecular ratio of the starting materials. So the molecular ratio of the starting materials was modified to equivmolar amount of ethyl trifluoroacetoacetate (**1**), 1,3-indanedione (**2**), ammonium acetate (**3**), and 2.0 equivmolar of benzaldehyde (**4**), and the reaction was performed under the same reaction conditions. After stirring for 4 h at room temperature, TLC analysis showed the reaction was completed. General workup afforded the major product **5a** in 70% yield, along with the minor product **6a** in 9% yield, respectively.

Based on the results above, the reaction conditions were further optimized to improve the yield by changing the catalytic amounts of molecular iodine and solvent. We first investigated the relation of the reaction outcome with the catalytic amounts of molecular iodine. As shown in Table 1, in the absence of a catalytic amount of molecular iodine, the reaction did not occur even after reflux for 12 h in ethanol (entry 1, Table 1). The 0.05 equivmolar amount of molecular iodine was insufficient to push the reaction forward, resulting in the decrease of the yields of products **5a** and **6a**, even though the reaction was carried out with prolonged the reaction time to 6 h (entry 2, Table 1). Higher catalyst loading (from 0.2 to 0.4 equivmolar amount of molecular iodine) neither shortened the reaction time, nor increased the products yields obviously (entries 5–6, Table 1). Thus, we choosed 0.1 equivmolar amount of molecular iodine as the catalyst loading for this one-pot, four-component reaction. Meanwhile, we also investigated the reaction temperature affecting the reaction efficiency and the products yields. It was found that the reaction time might be shortened to 3.5 h in refluxing temperature, however, the products yields were not increased significantly (entry 4, Table 1).

Solvent effect was the next considered factor. As shown in Table 1, generally, the reactions gave the better yield in polar protic solvents such as EtOH and MeOH than those in aprotic solvents (entries 2–8 and 9–11, Table 1). Moreover, the reaction in absolute ethanol under the nitrogen atmosphere gave almost the same product yields as that in the commercially available ethanol, indicating that the trace of water in ethanol did not accelerate the reaction obviously (entry 7, Table 1).

With the optimal results in hand as shown in entry 3, Table 1, we investigated the scope and limitation of this one-pot, four-component reaction with a variety of aromatic aldehydes, and the

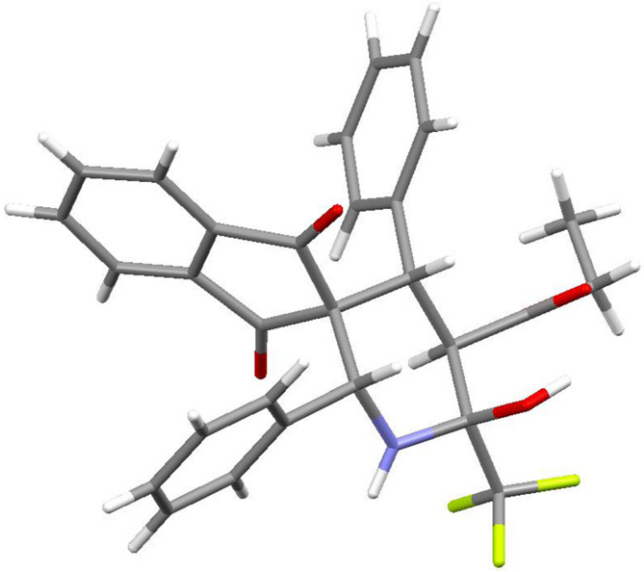


**Fig. 1.** X-ray crystal structure of **5a**.

**Table 1**
The effect of a variety of the amounts of iodine and solvents on this one-pot reaction.[a]

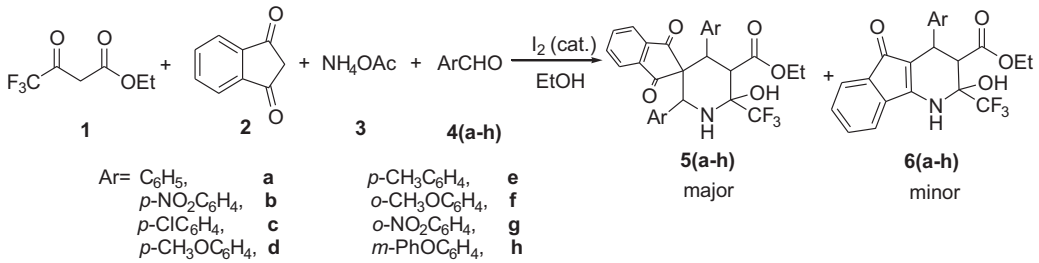
| Entry | Solvent | Iodine (mol%) | Time (h) | Yields[b] (%) | | | |
|---|---|---|---|---|---|---|---|
| | | | | Products **5** and **6** | | | |
| 1 | EtOH | 0 | 12 | **5a** | – | **6a** | – |
| 2 | EtOH | 5 | 6 | **5a** | 52 | **6a** | 7 |
| 3 | EtOH | 10 | 4 | **5a** | 70 | **6a** | 9 |
| 4[c] | EtOH | 10 | 3.5 | **5a** | 71 | **6a** | 9 |
| 5 | EtOH | 20 | 4 | **5a** | 70 | **6a** | 9 |
| 6 | EtOH | 40 | 4 | **5a** | 69 | **6a** | 9 |
| 7[d] | EtOH | 10 | 4 | **5a** | 71 | **6a** | 9 |
| 8 | MeOH | 10 | 4.5 | **5a** | 70 | **6a** | 8 |
| 9 | $CH_2Cl_2$ | 10 | 6 | **5a** | 40 | **6a** | Trace |
| 10 | $CH_3CN$ | 10 | 6 | **5a** | 40 | **6a** | Trace |
| 11 | DME | 10 | 8 | **5a** | 45 | **6a** | Trace |

[a] Reaction conditions: ethyl 4,4,4-trifluoro-3-oxobutanoate **1** (1.0 mmol), 1,3-indanedione **2** (1.0 mmol), ammonium acetate **3** (1.0 mmol), and benzaldehyde **4** (2.0 mmol), solvent: 10 mL.
[b] Isolated yield.
[c] The reaction was carried out in freshly distilled absolute EtOH under nitrogen.
[d] The reaction was carried out in refluxing in EtOH as solvent.

**Table 2**
Results of the one-pot, four-component reaction.[a]

| Entry | Ar= | Time (h) | Yields[b] (%) | | | |
|---|---|---|---|---|---|---|
| | | | Product **5** and **6** | | | |
| 1 | **4a** $C_6H_5$ | 4 | **5a** | 70 | **6a** | 9 |
| 2 | **4b** $p$-$NO_2C_6H_4$ | 6 | **5b** | 55 | **6b** | 8 |
| 3 | **4c** $p$-$ClC_6H_4$ | 4 | **5c** | 68 | **6c** | 9 |
| 4 | **4d** $p$-$CH_3OC_6H_4$ | 4 | **5d** | 71 | **6d** | 11 |
| 5 | **4e** $p$-$CH_3C_6H_4$ | 4 | **5e** | 70 | **6e** | 10 |
| 6 | **4f** $o$-$CH_3OC_6H_4$ | 4 | **5f** | 72 | **6f** | 10 |
| 7 | **4g** $o$-$NO_2C_6H_4$ | 6 | **5g** | 53 | **6g** | 9 |
| 8 | **4h** $m$-$phOC_6H_4$ | 4 | **5h** | 75 | **6h** | 10 |
| 9 | **4g** 3,4-$(MeO)_2C_6H_3$ | 10 | –[c] | | –[c] | |

[a] Reaction conditions: ethyl 4,4,4-trifluoro-3-oxobutanoate **1** (1.0 mmol), 1,3-indanedione **2** (1.0 mmol), ammonium acetate **3** (1.0 mmol), and aromatic aldehyde **4** (2.0 mmol), ethanol (10 mL, AR), room temperature.
[b] Isolated yields.
[c] Not isolated.




**Scheme 1.** Reaction of ethyl trifluoroacetoacetate (**1**) with 1,3-indanedione (**2**), ammonium acetate (**3**), and aromatic aldehyde (**4**).

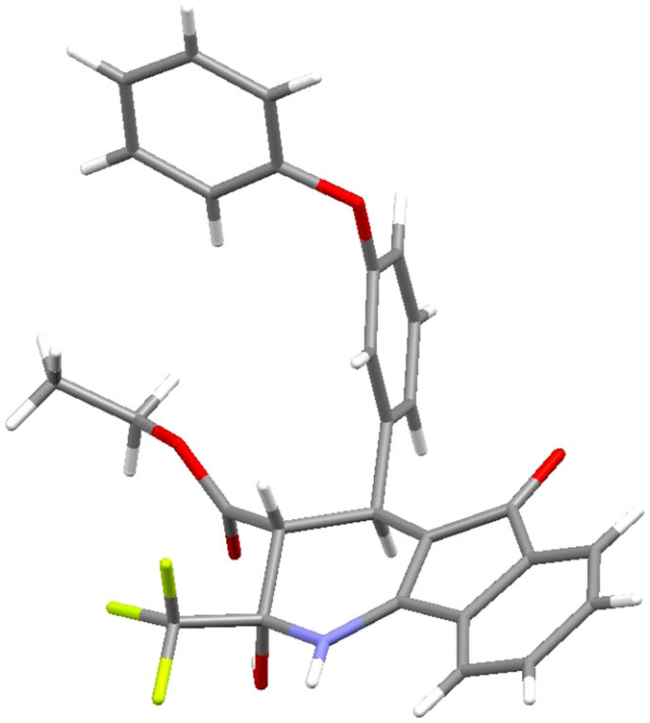


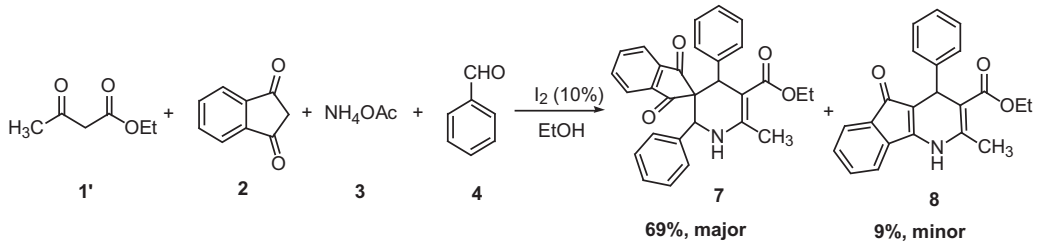
**Fig. 2.** X-ray crystal structure of **6h**.

corresponding expected products were obtained, in which the compounds **5**(**a**–**h**) were the major products, along with the minor products **6**(**a**–**h**). The reaction results are summarized in Table 2. Various aromatic aldehydes bearing either electron-donating or electron-withdrawing group have not shown the obvious effort on the formation of the products. On the other hand, the substituents located at para, meta or ortho positions of aryldehydes have not shown the much effort on the formation of products, either (entries 2–8). Surprisingly, the reactions of electron-rich aromatic aldehyde were not successful. That is, the corresponding products were not formed. For example, in the case of 3,4-dimethoxy-benzaldehyde, there was no corresponding products were formed. The above results have shown that the reactivity of the aromatic aldehyde differs significantly depending on the nature of electronic effect, other than of the steric effect of the substituents (Scheme 1).

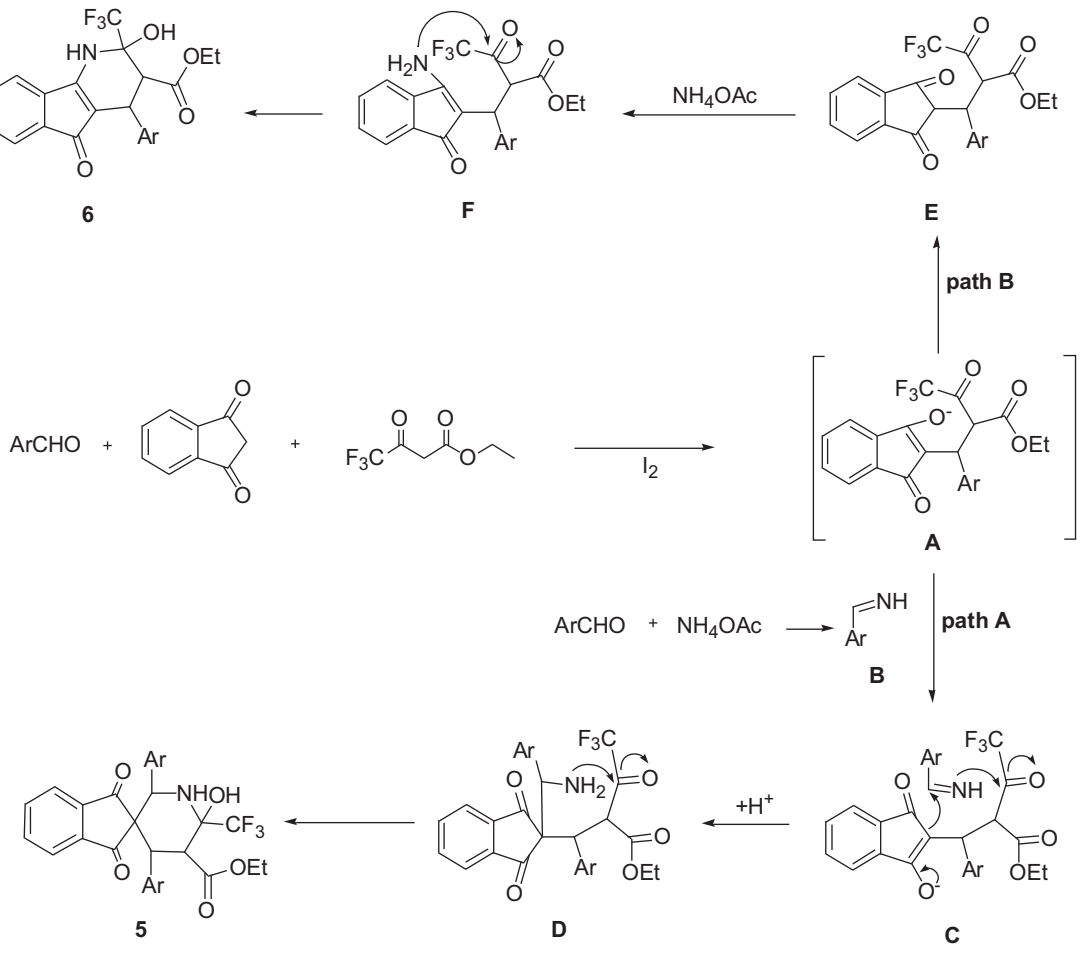
The structures of compounds **5** and **6** were fully confirmed by $^{1}$H NMR, $^{19}$F NMR, MS, IR spectroscopies and elemental analysis. For instance, the characteristic features of $^{1}$H NMR in $CDCl_3$ spectra of **5a** were the appearances of doublets at $\delta$ 4.54 and 4.12 ppm with $J_{H-H}$ = 12.5 Hz for 3-H and 4-H protons, respectively, indicating that a trans configuration of the vicinal two hydrogen atoms. The chemical shift of $CF_3$ group in $^{19}$F NMR was a singlet peak at $\delta$ −84.01 ppm (s, 3F), which indicated that the $CF_3$ group was bonded to a quaternary carbon atom. The similar pattern of characteristic doublet peaks in $^{1}$H NMR spectra and the singlet peak in $^{19}$F NMR spectra were also observed in compounds **6**. Furthermore, the structure of compound **6h** was further confirmed by XRD analysis, and crystal structure of compound **6h** was shown in Fig. 2.

Singh and his co-workers reported the comparable one-pot multicomponent reaction to functionalized unsymmetrical dihydro-1*H*-indeno[1,2-*b*]pyridines by grinding under the solvent- and catalyst-free conditions [10]. Dihydro-1*H*-indeno[1,2-*b*]pyridine derivative was also obtained in four-component reaction catalyzed by $Yb(OTf)_3$ [11]. By comparison, we also investigated that the one-pot, multicomponent reaction involving condensation of non-fluorinated substrate instead of ethyl trifluoroacetoacetate catalyzed by molecular iodine under the present reaction conditions. To our surprise, the reaction results were consistent with the previous results using the fluorinated substrates. It gave the corresponding spiro[indene-2,3′-piperidine] **7** as a major product in 69% yield, along with the a minor product **8** in 9% yield [10]. The slight difference between the fluorinated and non-fluorinated substrates was that the reaction directly gave the corresponding dehydrated products **7** and **8** (Scheme 2). This difference was attributed to unique catalytic activity of molecular iodine.

Based on the above results, A plausible mechanism for the formation of **5** and **6** was illustrated in Scheme 3, it is conceivable that the initial event is the formation of intermediate "**A**" form ethyl trifluoroacetoacetate (**1**) with 1,3-indanedione (**2**), and aromatic aldehyde (**4**) *via* Knoevenagel condensation reaction, followed by Michael addition reaction. The second key intermediate is aldehyde imine, produced by the condensation of aromatic aldehyde with ammonia. And then there were two pathways to




**Scheme 2.** Reaction result of non-fluorinated substrate.




**Scheme 3.** A plausible mechanism of one-pot, four-component reaction.

proceed. Condensation of intermediate "**A**" with intermediate "**B**" give the acyclic intermediate "**D**", which undergoes intramolecular cyclization to form the major product spiro[indene-2,3′-piperidine] derivatives **5** (Path A). Alternatively, intermediate "**A**" reacts with ammonia to afford the intermediate "**F**", which undergoes intramolecular cyclization with participation of amino function and carbonyl group to form the minor product tetrahydroindeno[1,2-*b*]pyridine derivatives **6** (Path B).

## 3. Conclusion

In conclusion, we have developed a convenient one-pot, four-component reaction to trifluoromethyl-containing spiro[indene-2,3′-piperidine] derivatives and tetrahydroindeno[1,2-*b*]pyridine derivatives from ethyl trifluoroacetoacetate (**1**), 1,3-indanedione (**2**), ammonium acetate (**3**), and benzaldehyde (**4**) in the presence of catalytic amount of molecular iodine (10%) under the mild reaction conditions. These molecular iodine catalyzed one-pot, multi-component reactions provide a rapid and efficient route to the preparation of a variety of unusual fluorinated heterocycles.

## 4. Experimental

### 4.1. General

Melting points were measured with digital melting point apparatus (WRS-1B, Shanghai precision & scientific instrument CO., LTD.) and were uncorrected. $^1$H and $^{19}$F NMR spectra were recorded in $CDCl_3$ on Bruker AM-500 instruments with $Me_4Si$ and $CFCl_3$ (with upfield negative) as the internal and external standards, respectively. IR spectra were obtained with a Nicolet AV-360 spectrophotometer. Lower resolution mass spectra were determined with Agilent 1100 LC/MSD SL instrument using ESI technique. High resolution mass spectra were run on Ionspec 4.7 T FTMS using MALDI/DHB. Elemental analyses were performed using a Vario EL III Analyzer. X-ray crystal structure data were collected on a Bruck SMART Apex2 CCD area-detector diffractometer using graphite monochromatized Mo $K\alpha$ radiation ($\lambda$ = 0.71073 Å) at 296(2) K.

### 4.2. Typical experimental procedure for the synthesis of compounds 5a–h and 6a–h

To a 10 mL ethanol solution containing ethyl trifluoroacetoacetate (1.0 mmol), 1,3-indanedione (1.0 mmol), ammonium acetate (1.0 mmol) and benzaldehyde (2.0 mmol) was added a catalytic amount of molecular iodine (0.1 mmol). The reaction mixture was stirred at room temperature for 4 h. After the reaction was completed (Monitored by TLC), the solution was concentrated under reduced pressure and the residue was re-dissolved in 30 mL of ethyl acetate. The solution was washed with aq. $Na_2S_2O_3$ solution to remove iodine, followed by $H_2O$ (20 mL × 2). The organic layer was dried over anhydrous $Na_2SO_4$ and evaporated to dryness. The residue was purified by column chromatography on silica gel using petroleum/ethyl acetate = 6:1 (v/v) as eluent to afford **5a** as a white solid in 70% yield and **6a** as a red solid in 9% yield.

*4.2.1. Ethyl 1,3-dihydro-6′-hydroxy-1,3-dioxo-2′,4′-diphenyl-6′(trifluoromethyl)-spiro [indene-2,3′-piperidine]-5′-carboxylate (**5a**)*

White solid, mp: 171–173 °C. IR (KBr, $cm^{-1}$): 3400, 2922, 2852, 1787, 1742, 1711, 1510, 1247, 1190, 1163, 836, 754. $^1H$ NMR ($CDCl_3$, 500 MHz): $\delta$ 0.77 (t, $J$ = 7.0 Hz, 3H, $OCH_ACH_B$); 2.63 (s, 1H, NH); 3.85 (qd, $J_1$ = 7.0 Hz, $J_2$ = 2.0 Hz, 2H, $OCH_ACH_B$); 4.12 (d, $J$ = 12.5 Hz, 1H, CH); 4.54 (d, $J$ = 12.5 Hz, 1H, CH); 5.04 (s, 1H, OH); 5.58 (s, 1H, CH); 6.95–7.02 (m, 8H, ArH); 7.10–7.17 (m, 2H, ArH); 7.38–7.45 (m, 3H, ArH); 7.56–7.54 (m, 1H, ArH). $^{19}F$ NMR ($CDCl_3$, 470 MHz): $\delta$ −84.02 (s, 3F, $CF_3$). MS (ESI) $m/z$: 524 $[M+H]^+$. Anal. Calcd for: $C_{29}H_{24}F_3NO_5$ (%): C, 66.53; H, 4.62; N, 2.68. Found: C, 66.23; H, 4.94; N, 2.54.

*4.2.2. Ethyl 1,3-dihydro-6′-hydroxy-1,3-dioxo-2′,4′-di(4-nitrophenyl)-6′(trifluoromethyl)-spiro[indene-2,3′-piperidine]-5′-carboxylate (**5b**)*

White solid, mp: 174–175 °C. IR (KBr, $cm^{-1}$): 3416, 3301, 3019, 2975, 1942, 1737, 1701, 1527, 1348, 1242, 1185, 1086, 861, 695. $^1H$ NMR ($CDCl_3$, 500 MHz): $\delta$ 0.86 (t, $J$ = 7.5 Hz, 3H, $OCH_ACH_B$); 2.67 (s, 1H, NH), 3.89 (q, $J$ = 7.5 Hz, 2H, $OCH_ACH_B$), 4.27 (d, $J$ = 13.0 Hz, 1H, CH), 4.57 (d, $J$ = 13.0 Hz, 1H, CH), 5.17 (s, 1H, OH), 5.46 (s, 1H, CH), 7.30–7.39 (m, 4H, ArH), 7.48–7.58 (m, 4H, ArH), 7.94–7.87 (m, 4H, ArH). $^{19}F$ NMR ($CDCl_3$, 470 MHz): $\delta$ −83.91 (s, 3F, $CF_3$); MS (ESI) $m/z$: 614 $[M+H]^+$, 615 $[M+2H]^+$. HRMS for $[C_{29}H_{22}F_3N_3O_9+H]^+$ Calcd: 614.1386; Found: 614.1381.

*4.2.3. Ethyl 1,3-dihydro-6′-hydroxy-1,3-dioxo-2′,4′-di(4-chloroophenyl)-6′(trifluoromethyl)-spiro[indene-2,3′-piperidine]-5′-carboxylate (**5c**)*

White solid, mp: 172–175 °C. IR (KBr, $cm^{-1}$): 3437, 3339, 2983, 1725, 1705, 1595, 1492, 1741, 1373, 1339, 1254, 1203, 1015, 986, 832, 759. $^1H$ NMR ($CDCl_3$, 500 MHz): $\delta$ 0.85 (t, $J$ = 7.5 Hz, 3H, $OCH_ACH_B$); 2.56 (s, 1H, NH); 3.88 (q, $J$ = 7 .5 Hz, 2H, $OCH_ACH_B$); 4.08 (d, $J$ = 12.5 Hz, 1H, CH); 4.48 (d, $J$ = 12.5 Hz, 1H, CH); 5.00 (s, 1H, OH); 5.51 (s, 1H, CH); 6.96–7.12 (m, 8H, ArH); 7.48–7.53 (m, 3H, ArH); 7.57–7.59 (m, 1H, ArH). $^{19}F$ NMR ($CDCl_3$, 470 MHz): $\delta$ −84.01 (s, 3F, $CF_3$). MS (ESI) $m/z$: 592 $[M+H]^+$. Anal. Calcd for: $C_{29}H_{22}Cl_2F_3NO_5$ (%): C, 58.80; H, 3.74; N, 2.36. Found: C, 58.86; H, 3.68; N, 2.30.

*4.2.4. Ethyl 1,3-dihydro-6′-hydroxy-1,3-dioxo-2′,4′-di(4-methoxyophenyl)-6′(trifluoromethyl)-spiro[indene-2,3′-piperidine]-5′-carboxylate (**5d**)*

White solid, mp: 178–180 °C. IR (KBr, $cm^{-1}$): 3420, 3353, 3030, 2982, 2926, 1919, 1742, 1706, 1464, 1342, 1255, 1183, 1156, 1080, 809, 567. $^1H$ NMR ($CDCl_3$, 500 MHz): $\delta$ 0.82 (t, 3H, $J$ = 7.0 Hz, $OCH_ACH_B$); 2.54 (s, 1H, NH); 3.57 (s, 3H, $OCH_3$); 3.58 (s, 3H, $OCH_3$); 3.85 (q, $J$ = 7.0 Hz, 2H, $OCH_ACH_B$); 4.04 (d, $J$ = 12.5 Hz, 1H, CH); 4.48 (d, $J$ = 12.5 Hz, 1H, CH); 4.96 (s, 1H, OH); 5.53 (s, 1H, CH); 6.48–6.54 (m, 4H, ArH); 7.00–7.08 (m, 4H, ArH); 7.40–7.47 (m, 3H, ArH); 7.56–7.58 (m, 1H, ArH). $^{19}F$ NMR ($CDCl_3$, 470 MHz): $\delta$ −84.02 (s, 3F, $CF_3$). MS (ESI) $m/z$: 584 $[M+H]^+$; Anal. Calcd for: $C_{31}H_{28}F_3NO_7$ (%): C, 63.80; H, 4.84; N: 2.40. Found: C, 63.94; H, 4.71; N, 2.45.

*4.2.5. Ethyl spiro-1,3-dihydro-6′-hydroxy-1,3-dioxo-2′,4′-di(p-tolyl)-6′(trifluoromethyl)-[indene-2,3′-piperidine]-5′-carboxylate (**5e**)*

White solid, mp: 170–172 °C. IR (KBr, $cm^{-1}$): 3421, 3354, 3030, 2982, 1919, 1742, 1707, 1515, 1461, 1254, 1183, 1081, 809, 569. $^1H$ NMR ($CDCl_3$, 500 MHz): $\delta$ 0.78 (t, 3H, $J$ = 7.0 Hz, $OCH_ACH_B$); 2.04 (s, 3H, $ArCH_3$); 2.06 (s, 3H, $ArCH_3$); 2.57 (s, 1H, NH); 3.84 (q, $J$ = 7.0 Hz, 2H, $OCH_ACH_B$); 4.07 (d, 1H, $J$ = 12.5 Hz, CH); 4.50 (d, $J$ = 12.5 Hz, 1H, CH); 4.98 (s, 1H, OH); 5.55 (s, 1H, CH); 6.76–6.80 (m, 3H, ArH); 6.82–6.85 (m, 3H, ArH); 6.88–7.04 (m, 2H, ArH); 7.38–7.40 (m, 1H, ArH); 7.42–7.48 (m, 2H, ArH); 7.53–7.57 (m, 1H, ArH). $^{19}F$ NMR ($CDCl_3$, 470 MHz): $\delta$ −84.02 (s, 3F, $CF_3$). MS (ESI) $m/z$: 552 $[M+H]^+$; Anal. Calcd for: $C_{31}H_{28}F_3NO_5$ (%): C, 67.51; H, 5.12; N, 2.54. Found: C, 67.48; H, 5.22; N, 2.47.

*4.2.6. Ethyl 1,3-dihydro-6′-hydroxy-1,3-dioxo-2′,4′-di(2-methoxyphenyl)-6′(trifluoromethyl)-spiro[indene-2,3′-piperidine]-5′-carboxylate (**5f**)*

White solid, mp: 168–170 °C. IR (KBr, $cm^{-1}$): 3367, 3305, 3003, 2965, 2919, 1742, 1707, 1599, 1495, 1250, 1171, 1028, 759. $^1H$ NMR ($CDCl_3$, 500 MHz): $\delta$ 0.73 (t, $J$ = 7.0 Hz, 3H, $OCH_ACH_B$); 2.73 (br, 1H, NH); 3.63 (s, 3H, $OCH_3$); 3.79 (q, $J$ = 7.0 Hz, 2H, $OCH_ACH_B$); 3.85 (s, 3H, $OCH_3$); 4.42 (d, $J$ = 13.0 Hz, 1H, CH); 5.05 (d, $J$ = 13.0 Hz, 1H, CH); 5.51 (s, 1H, OH); 5.72 (s, 1 H, CH); 6.38–6.41 (m, 1H, ArH), 6.57–6.69 (m, 3H, ArH); 6.88–7.02 (m, 3H, ArH); 7.19–7.21 (m, 1H, ArH); 7.32–7.33 (m, 1H, ArH); 7.40–7.45 (m, 2H, ArH); 7.58–7.59 (m, 1H, ArH). $^{19}F$ NMR ($CDCl_3$, 470 MHz): $\delta$ −83.97 (s, 3F, $CF_3$). MS (ESI) $m/z$: 584 $[M+H]^+$. Anal. Calcd for: $C_{31}H_{28}F_3NO_7$ (%): C, 63.80; H, 4.84; N, 2.40. Found: C, 63.44, H 4.87, N: 2.29.

*4.2.7. Ethyl 1,3-dihydro-6′-hydroxy-1,3-dioxo-2′,4′-di(2-nitrophenyl)-6′(trifluoromethyl)-spiro[indene-2,3′-piperidine]-5′-carboxylate (**5g**)*

White solid, mp: 173–175 °C. IR (KBr, $cm^{-1}$): 3415, 3311, 2988, 1736, 1704, 1535, 1353, 1248, 1189, 789, 768, 719. $^1H$ NMR ($CDCl_3$, 500 MHz): $\delta$ 0.84 (t, $J$ = 7.5 Hz, 3H, $OCH_ACH_B$); 2.69 (s, 1H, NH); 3.97 (qd, $J_1$ = 7.5 Hz, $J_2$ = 2.5 Hz, 2H, $OCH_ACH_B$); 4.68 (d, $J$ = 12.5 Hz, 1H, CH); 5.19 (d, $J$ = 12.5 Hz, 1H, CH); 5.81 (s, 1H, OH); 5.86 (s, 1H, CH); 7.10–7.17 (m, 2H, ArH); 7.19–7.25 (m, 2H, ArH); 7.36–7.38 (m, 1H, ArH); 7.49–7.61 (m, 6H, ArH); 7.73–7.74 (m, 1H, ArH). $^{19}F$ NMR ($CDCl_3$, 470 MHz): $\delta$ −83.70 (s, 3F, $CF_3$). MS (ESI) $m/z$: 614 $[M+H]^+$; HRMS for $[C_{29}H_{22}F_3N_3O_9+H]^+$ Calcd: 614.1386. Found: 614.1381.

*4.2.8. Ethyl 1,3-dihydro-6′-hydroxy-1,3-dioxo-2′,4′-di(3-phenoxyphenyl)-6′(trifluoromethyl)-spiro[indene-2,3′-piperidine]-5′-carboxylate (**5h**)*

White solid, mp: 187–190 °C. IR (KBr, $cm^{-1}$): 3432, 3307, 3065, 2982, 1740, 1705, 1586, 1487, 1240, 1187, 1091, 1019, 777, 750, 692. $^1H$ NMR ($CDCl_3$, 500 MHz): $\delta$: 0.88 (t, $J$ = 7.0 Hz, 3H, $OCH_ACH_B$); 2.61 (s, 1H, NH); 3.92 (qd, $J_1$ = 7.0 Hz, $J_2$ = 2.0 Hz, 2H, $OCH_ACH_B$); 4.09 (d, 1H, $J$ = 12.5 Hz, CH); 4.48 (d, $J$ = 12.5 Hz, 1H, CH); 4.99 (s, 1H, OH); 5.50 (s, 1 H, CH); 6.59–6.66 (m, 5H, ArH); 6.77–6.86 (m, 3H, ArH); 6.93–7.01 (m, 3H, ArH); 7.06–7.09 (m, 2H, ArH); 7.23–7.28 (m, 5H, ArH); 7.55–7.62 (m, 4H, ArH). $^{19}F$ NMR ($CDCl_3$, 470 MHz): $\delta$ −83.95 (s, 3F, $CF_3$). MS (ESI) $m/z$: 708 $[M+H]^+$, Anal. Calcd for $C_{41}H_{32}F_3NO_7$ (%): C, 69.58; H, 4.56; N, 1.98. Found: C, 69.57; H, 4.75, N, 1.86.

*4.2.9. Ethyl 2,3,4,5-tetrahydro-2-hydroxy-5-oxo-4-phenyl-2-(trifluoromethyl)-1H-indeno[1,2-b]pyridine-3-carboxylate (**6a**)*

Red solid, mp: 197–200 °C. IR (KBr, $cm^{-1}$): 3394, 3237, 3060, 2997, 1702, 1666, 1574, 1543, 1381, 1233, 1177, 768, 717, 702. $^1H$ NMR ($CDCl_3$, 500 MHz): $\delta$ 0.91 (t, $J$ = 7.0 Hz, 3H, $OCH_ACH_B$); 3.07 (d, $J$ = 11.5 Hz, 1H, CH); 3.98 (qd, $J_1$ = 7.0 Hz, $J_2$ = 3.5 Hz, 2H, $OCH_ACH_B$); 4.10 (d, $J$ = 11.5 Hz, 1H, CH); 5.71 (s, 1H, NH); 5.95 (s, 1H, OH); 7.13–7.14 (m, 1H, ArH); 7.22–7.24 (m, 2H, ArH); 7.31–7.38 (m, 6H, ArH). $^{19}F$ NMR ($CDCl_3$, 470 MHz): $\delta$ −82.69 (s, 3F, $CF_3$). MS (ESI) $m/z$: 418 $[M+H]^+$. Anal. Calcd for: $C_{22}H_{18}F_3NO_4$ (%): C, 63.31; H, 4.35; N, 3.36. Found: C, 63.13; H, 4.36; N, 3.20.

*4.2.10. Ethyl 2,3,4,5-tetrahydro-2-hydroxy-5-oxo-4-(4-nitrophenyl)-2-(trifluoromethyl)-1H-indeno[1,2-b]pyridine-3-carboxylate (**6b**)*

Red solid, mp: 183–184 °C. IR (KBr, $cm^{-1}$): 3421, 3334, 2987, 2941, 1943, 1723, 1668, 1573, 1524, 1347, 1199, 1083, 1019, 716, 699. $^1H$ NMR ($CDCl_3$, 500 MHz): $\delta$ 0.94 (t, $J$ = 7.0 Hz, 3H, $OCH_ACH_B$); 3.05 (d, $J$ = 11.5 Hz, 1H, CH); 3.99 (qd, $J_1$ = 7.0 Hz, $J_2$ = 3.5 Hz, 2H, $OCH_ACH_B$); 4.01 (d, $J$ = 11.5 Hz, 1H, CH); 5.55 (s, 1H, NH); 5.97 (s, 1H, OH); 7.16–7.17 (m, 1H, ArH); 7.35–7.42 (m, 5H, ArH); 8.19–8.20 (m, 1H, ArH). $^{19}F$ NMR ($CDCl_3$, 470 MHz): $\delta$ −82.55 (s, 3F, $CF_3$). MS (ESI) $m/z$: 463 $[M+H]^+$; HRMS for $[C_{22}H_{17}F_3N_2O_6+H]^+$ Calcd: 463.1117. Found: 463.1112.

*4.2.11. Ethyl 2,3,4,5-tetrahydro-2-hydroxy-5-oxo-4-(4-chlorophenyl)-2-(trifluoromethyl)-1H-indeno[1,2-b]pyridine-3-carboxylate (**6c**)*

Red solid, mp: 179–180 °C. IR (KBr, $cm^{-1}$): 3426, 3336, 2989,1895, 1729, 1669, 1574, 1529, 1227, 1197, 1086, 716. $^1H$ NMR($CDCl_3$, 500 MHz): $\delta$ 0.94 (t, $J$ = 7.5 Hz, 3H, $OCH_ACH_B$); 2.97 (d, $J$ = 11.5 Hz, 1H, CH); 3.98 (qd, $J_1$ = 7.5 Hz, $J_2$ = 3.5 Hz, 2H, $OCH_ACH_B$); 4.04 (d, $J$ = 11.5 Hz, 1H, CH); 5.58 (s, 1H, NH); 5.96 (s, 1H, OH); 7.08–7.17 (m, 3H, ArH); 7.26–7.28 (m, 2H, ArH); 7.28–7.34 (m, 3H, ArH). $^{19}F$ NMR ($CDCl_3$, 470 MHz): $\delta$ −82.62 (s, 3F, $CF_3$). MS (EI) ($m/z$, %): 451 ($[M]^+$, 3.39). 362/360 ($[M-H_2O-CO_2C_2H_5]^+$, 39/100). Anal. Calcd for: $C_{22}H_{17}ClF_3NO_4$ (%): C, 58.48; H, 3.79; N, 3.10. Found: C, 58.82; H, 4.14; N 2.96.

*4.2.12. Ethyl 2,3,4,5-tetrahydro-2-hydroxy-5-oxo-4-(4-methoxyphenyl)-2-(trifluoromethyl)-1H-indeno[1,2-b]pyridine-3-carboxylate (**6d**)*

Red solid, mp: 201–202 °C. IR (KBr, $cm^{-1}$): 3421, 3273, 2986, 2930, 1721, 1671, 1576, 1535, 1207, 1185, 1081, 715. $^1H$ NMR ($CDCl_3$, 500 MHz): $\delta$ 0.94 (t, $J$ = 7.0 Hz, 3H, $OCH_ACH_B$); 3.01 (d, $J$ = 11.5 Hz, 1H, CH); 3.77 (s, 3H, $OCH_3$); 3.98 (qd, 2H, $J_1$ = 7.0 Hz, $J_2$ = 3.5 Hz, $OCH_ACH_B$); 4.04 (d, $J$ = 11.5 Hz, 1H, CH); 5.66 (s, 1H, NH); 6.04 (s, 1H, OH); 6.81–6.84 (m, 2H, ArH); 7.09–7.13 (m, 3H, ArH); 7.27–7.38 (m, 3H, ArH). $^{19}F$ NMR ($CDCl_3$, 470 MHz): $\delta$ −82.63 (s, 3F, $CF_3$); MS (EI) ($m/z$, %): 447 ($[M]^+$, 5.83); 356 ($[M-H_2O-CO_2C_2H_5]^+$, 100). Anal. Calcd for: $C_{23}H_{20}F_3NO_5$ (%): C, 61.74; H, 4.51; N, 3.13. Found: C: 61.33, H, 4.77; N, 3.28.

*4.2.13. Ethyl 2,3,4,5-tetrahydro-2-hydroxy-5-oxo-4-(4-methyphenyl)-2-(trifluoromethyl)-1H-indeno[1,2-b]pyridine-3-carboxylate (**6e**)*

Red solid, mp: 196–198 °C. IR (KBr, $cm^{-1}$): 3421, 3273, 3051, 2986, 1721, 1671, 1575, 1536, 1206, 1185, 715, 536. $^1H$ NMR ($CDCl_3$, 500 MHz): $\delta$ 0.92 (t, $J$ = 7.0 Hz, 3H, $OCH_ACH_B$); 2.31 (s, 3H, $ArCH_3$); 3.02 (d, $J$ = 11.5 Hz, 1H, CH); 3.97 (qt, $J_1$ = 7.0 Hz, $J_2$ = 3.5 Hz, 2H, $OCH_ACH_B$); 4.04 (d, $J$ = 11.5 Hz, 1H, CH); 5.67 (s, 1H, NH); 5.94 (s, 1H, OH); 7.07–7.11 (m, 5H, ArH); 7.28–7.34 (m, 3H, ArH). $^{19}F$ NMR ($CDCl_3$, 470 MHz): $\delta$ −82.69 (s, 3F, $CF_3$). MS (ESI) $m/z$: 432 $[M+H]^+$. Anal. Calcd for: $C_{23}H_{20}F_3NO_4$ (%): C, 64,03; H, 4.67; N, 3.25, Found: C, 64.35; H, 4.50; N, 3.19.

*4.2.14. Ethyl 2,3,4,5-tetrahydro-2-hydroxy-5-oxo-4-(2-methoxyphenyl)-2-(trifluoromethyl)-1H-indeno[1,2-b]pyridine-3-carboxylate (**6f**)*

Red solid, mp: 203–205 °C; IR (KBr, $cm^{-1}$): 3547, 3411, 3227, 3172, 3060, 2982, 1701, 1631, 1590, 1558, 1208, 1187, 1089, 752, 718. $^1H$ NMR ($CDCl_3$, 500 MHz): $\delta$ 0.83 (br, 3H, $OCH_ACH_B$); 3.05 (d, $J$ = 11.5 Hz, 1H, CH); 3.73 (br, 2H, $OCH_ACH_B$); 3.91 (br, 3H, $OCH_3$); 4.80 (d, $J$ = 11.5 Hz, 1H, CH); 5.84 (br, 1H, NH); 6.12 (s, 1H, OH); 6.86–6.90 (m, 2H, ArH); 7.08–7.14 (m, 2H, ArH); 7.26–7.31 (m, 4H, ArH). $^{19}F$ NMR ($CDCl_3$, 470 MHz): $\delta$ −82.85 (s, 3F, $CF_3$). MS(EI): ($m/z$, %): 447 ($[M]^+$, 5.27); 356 ($[M\text{-}CO_2C_2H_5\text{-}H_2O]^+$, 100). HRMS for $[C_{23}H_{20}F_3NO_5]^+$ Calcd: 447.1294. Found: 447.1292.

*4.2.15. Ethyl 2,3,4,5-tetrahydro-2-hydroxy-5-oxo-4-(4-nitrophenyl)-2-(trifluoromethyl)-1H-indeno[1,2-b]pyridine-3-carboxylate (**6g**)*

Red solid, mp: 195–197 °C. IR (KBr, $cm^{-1}$): 3423, 3309, 3919, 2851, 1736, 1699, 1533, 1353, 1201, 788, 793. $^1H$ NMR ($CDCl_3$, 500 MHz): $\delta$ 0.91 (t, $J$ = 7.0 Hz, 3H, $OCH_ACH_B$); 3.09 (d, $J$ = 11.5 Hz, 1H, CH); 3.99 (qd, $J_1$ = 7.0 Hz, $J_2$ = 3.5 Hz, 2H, $OCH_ACH_B$); 4.89 (d, $J$ = 11.5 Hz, 1H, CH); 6.01 (s, 1H, NH); 6.58 (s, 1H, OH); 7.16–7.26 (m, 3H, ArH); 7.32–7.42 (m, 3H, ArH); 7.51–7.55 (m, 1H, ArH); 7.78–7.86 (m, 1H, ArH). $^{19}F$ NMR ($CDCl_3$, 470 MHz): $\delta$ −81.96 (s, 3F, $CF_3$). MS (ESI): $m/z$: 463 $[M+H]^+$. HRMS for $[C_{22}H_{17}F_3N_2O_6+Na]^+$ Calcd: 485.0936; Found: 485.0931.

*4.2.16. Ethyl 2,3,4,5-tetrahydro-2-hydroxy-5-oxo-4-(3-phenoxyphenyl)-2-(trifluoromethyl)-1H-indeno[1,2-b]pyridine-3-carboxylate (**6h**)*

Red solid, mp: 184–186 °C. IR (KBr, $cm^{-1}$): 3388, 3221, 3056, 2919, 1932, 1702, 1666, 1576, 1543, 1489, 1300, 1243, 1199, 1179, 1085, 751, 718, 701. $^1H$ NMR($CDCl_3$, 500 MHz): $\delta$ 1.03 (t, 3H, $J$ = 7.0 Hz, $OCH_ACH_B$); 3.05 (d, 1H, $J$ = 11.5 Hz, CH); 4.05 (q, $J$ = 7.0 Hz, 2H, $OCH_ACH_B$); 4.09 (d, $J$ = 11.5 Hz, 1H, CH); 5.67 (s, 1H, OH); 5.89 (s, 1H, NH); 6.94–6.95 (m, 2H, ArH); 6.99–6.71 (m, 3H, ArH); 7.07–7.13 (m, 2H, ArH); 7.29–7.39 (m, 6H, ArH). $^{19}F$ NMR ($CDCl_3$, 470 MHz): $\delta$ −82.68 (s, 3F, $CF_3$). MS (ESI) $m/z$: 510 $[M+H]^+$. Anal. Calcd for: $C_{28}H_{22}F_3NO_5$ (%): C, 66.01; H, 4.35; N, 2.75. Found: C, 65.87; H, 4.56; N, 2.31.

*4.2.17. Ethyl 1,3-dihydro-2′,3′dihydro-6′-methyl-1,3-dioxo-2′,4′-diphenyl-spiro[indene-2,3′-4′H-pyridine]-5′-carboxylate (**7**)*

Yellow solid, mp: 169–171 °C. IR (KBr, $cm^{-1}$): 3422, 3070, 3028, 2973, 2899, 2872, 1989, 1736, 1701, 1613, 1491, 1253, 763, 705. $^1H$ NMR ($CDCl_3$, 500 MHz): $\delta$ 0.58 (t, $J$ = 7.0 Hz, 3H, $OCH_ACH_B$); 2.48 (s, 3H, $CH_3$); 3.69 (qd, $J_1$ = 7.0 Hz, $J_2$ = 3.5 Hz, 2H, $OCH_ACH_B$); 4.52 (s, 1H, NH); 4.70 (s, 1H, CH); 4.86 (s, 1H, CH); 6.80–6.97 (m, 4H, ArH); 7.01–7.07 (m, 4H, ArH); 7.13–7.15 (m, 2H, ArH); 7.35–7.41 (m, 3H, ArH); 7.46–7.48 (m, 1H, ArH). MS (ESI) $m/z$: 452 $[M+H]^+$. Anal. Calcd for: $C_{29}H_{25}NO_4$ (%): C, 77.14; H, 5.58; N, 3.10. Found: C, 77.09; H, 5.62; N, 3.14.

*4.2.18. Ethyl 4,5-dihydro-2-methyl-5-oxo-4-phenyl-1H-indeno[1,2-b]pyridine-3-carboxylate (**8**)*

Orange solid, mp: 153–155 °C. IR (KBr, $cm^{-1}$): 3443, 3272, 2976, 2924, 1704, 1637, 1511, 1180, 1088, 705. $^1H$ NMR ($CDCl_3$, 500 MHz): $\delta$ 1.15 (t, $J$ = 7.0 Hz, 3H, $OCH_ACH_B$); 2.53 (s, 3H, $CH_3$); 4.06 (d, $J$ = 7.0 Hz, 2H, $OCH_ACH_B$); 5.04 (s, 1H, CH); 6.83 (s, 1H, NH); 7.09–7.11 (m, 2H, ArH); 7.15–7.31 (m, 4H, ArH); 7.35–7.39 (m, 3H, ArH). MS (EI) ($m/z$, %): 345 ($[M]^+$, 16.78), 272 ($[M-CO_2C_2H_5]^+$, 4.58), 268 ($[M-C_7H_6]^+$, 100). Anal. Calcd for: $C_{22}H_{19}NO_3$ (%): C, 76.50; H, 5.54; N, 4.06. Found: C, 76.31; H, 5.36; N, 4.12.

### *4.3. X-ray crystal structure data of compounds **5a** and **6h***

CCDC 723103, 723104 contain the supplementary crystallographic data for this paper. These results can be obtained free of charge *via* www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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