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Novel method for synthesis of aryl hydrazones from α-diazo esters: scope and limitations of nucleophiles

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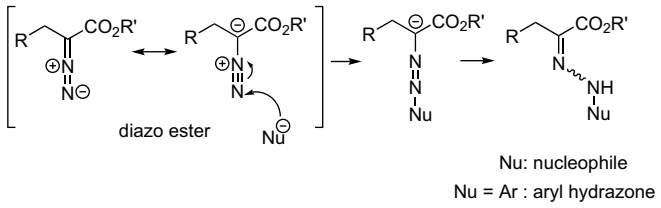
ABSTRACT

Aryl hydrazones, the precursor of Fischer indole synthesis, were easily obtained by nucleophilic addition of aryllithium reagents to diazo esters. The aryl hydrazones were converted into indoles in good yields by heating with thionyl chloride in alcohol. Grignard reagent was also a good nucleophile, whereas organozinc reagent did not react with diazo esters. Aryllithium reagents were prepared by reacting aryl bromides having various substitutions at 2-, 3-, 4-, or multi positions with *n*-BuLi. The addition of nucleophiles derived from bromopyridines to diazo esters also gave hydrazones.

1. Introduction

Due to their superior biological activities, the development of new methods for the synthesis of indoles has been attracting a lot of attention ever since.[1] Fischer indole synthesis developed in 1883 is still being used today.[2] In this synthesis, heating an aryl hydrazone with protic or Lewis acid yields an indole compound. Meanwhile, our group found that the terminal nitrogen of diazo ester was easily attacked by a nucleophile.[3] We thought that if many kinds of aryl lithium compounds reacted with the diazo group, various aryl hydrazones could be easily prepared (Scheme 1). Here we report a novel method for the synthesis of aryl hydrazones, the precursor of Fischer indole synthesis.



Scheme 1.

2. Results and discussion

2.1. Fischer indole synthesis utilizing novel hydrazone preparation

According to the above-mentioned strategy (Scheme 1), we prepared several hydrazones. To diazo ester **1a** derived from phenylalanine ethyl ester in THF was added 1.0 equiv of phenyllithium at −68 °C. After the disappearance of the starting material, the reaction mixture was neutralized with acetic acid and purified by silica gel column chromatography to give desired phenyl hydrazone **2a** in 86% yield. *anti*-Hydrazone was produced as the major product but a small amount of *syn*-hydrazone **2a′** was also detected. These isomers were easily separated by silica gel column chromatography. The stereochemistry of the hydrazones was assigned according to a reported procedure using NMR analysis.[4] The hydrogen of *syn*-hydrazone forms a hydrogen bond with the ester carbonyl group and thus, the chemical shift of the hydrogen appears at a lower field. The resulting *anti*-hydrazone **2a** was heated in a sealed tube with thionyl chloride in ethanol[5] to give indole **3a** in 95% yield. *syn*-Hydrazone **2a′**[6] also gave indole **3a** in 97% yield (Scheme 2).

Other diazo esters were converted into corresponding hydrazones in the same manner. All diazo esters, which are useful synthetic units comprising several functional groups and an appropriate carbon frame, were easily prepared by our reported procedure[7] from α-amino acid esters. As shown in Table 1, diazo esters reacted with phenyllithium to give desired phenyl hydrazones **2a**–**2g** in good yields. Even glutamic acid and lysine derivatives (**1e** and **1f**) having an acidic proton in the molecule gave hydrazones **2e** and **2f**, respectively. From NMR analysis, the

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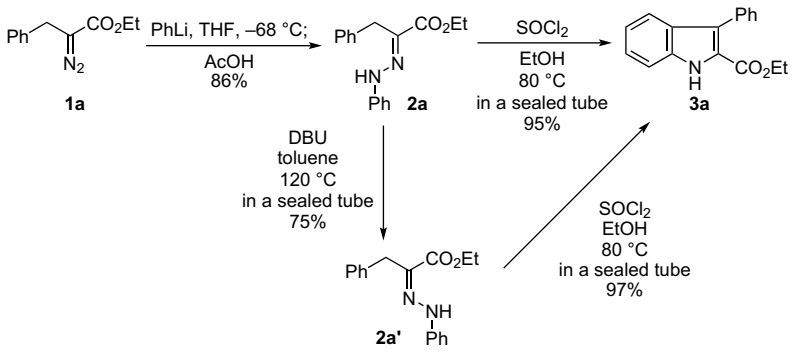
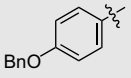
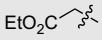
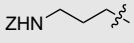


Scheme 2.

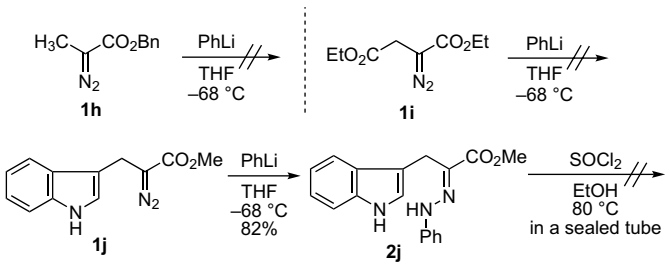
stereochemistry of all hydrazones except **2g** was confirmed to be anti.[8] Hydrazones **2a**–**2g** were then subjected to the indole cyclization reaction. Most substrates gave the desired indoles in moderate to good yields. The cyclization reaction of **2b** hardly proceeded at 80 °C, whereas **3b** was obtained in 86% yield when **2b** was cyclized at 100 °C.

Unfortunately, several reactions ended in failure (Scheme 3). Diazo esters derived from alanine benzyl ester **1h** and aspartic acid ester **1i** did not give the desired hydrazones when they were treated with phenyllithium. Diazo ester derived from tryptophan methyl ester **1j** gave hydrazone **2j** in good yield, but Fischer indole cyclization reaction of **2j** did not proceed.

Table 1

Amino acid	R	R′	1	2	3
Phenylalanine		Et	**1a**, 93%	**2a**, 86%	**3a**, 95%
Leucine		Et	**1b**, 94%	**2b**, 67%	**3b**, 86%[b]
Tyrosine		Me	**1c**, 97%	**2c**, 72%	**3c**, 70%
Methionine		Me	**1d**, 85%	**2d**, 79%	**3d**, 59%
Glutamic acid		Et	**1e** 73%	**2e**, —[a]	**3e**, 47%[c]
Lysine		Me	**1f**, 89%	**2f**, 88%[a]	**3f**, 78%
Cysteine		Et	**1g** 80%	**2g**, 97%	**3g**, 67%

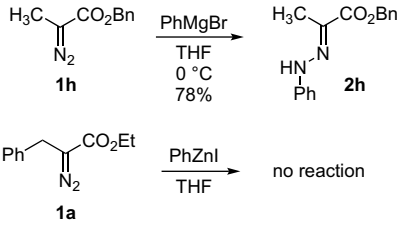
[a] PhLi (2 equiv) was used.
[b] The reaction was performed at 100 °C.
[c] Isolation yield for two steps.



Scheme 3.

2.2. Trials on another metal reagent: examination of nucleophile 1

Instead of lithium reagents, Grignard reagent, and an organozinc reagent were examined. To a cooled (−68 °C) solution of **1a** in THF was added phenylmagnesium bromide to give *anti*-hydrazone as the major product. The reaction rate seemed to be lower than that when lithium reagent was used. What is interesting is that the diazo ester derived from alanine benzyl ester **1h** reacted with phenylmagnesium bromide (at 0 °C) to give hydrazone **2h** in 78% yield, although it did not react with PhLi (Schemes 3 and 4). On the other hand, **1i** derived from aspartic acid ester did not produce hydrazone despite use of Grignard reagent.



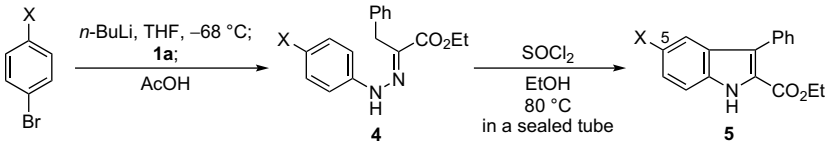
Scheme 4.

Next, an organozinc reagent was examined to determine whether it would work as a nucleophile with diazo ester. Phenylzinc iodide (1.0 equiv) was added to a solution of diazo ester **1a** in THF at 0 °C, and then the ice bath was removed. The reaction mixture was allowed to warm to room temperature, but the reaction did not proceed. Neither increasing reagent amount nor heating promoted the reaction.

2.3. Application of hydrazone synthesis: examination of nucleophile 2

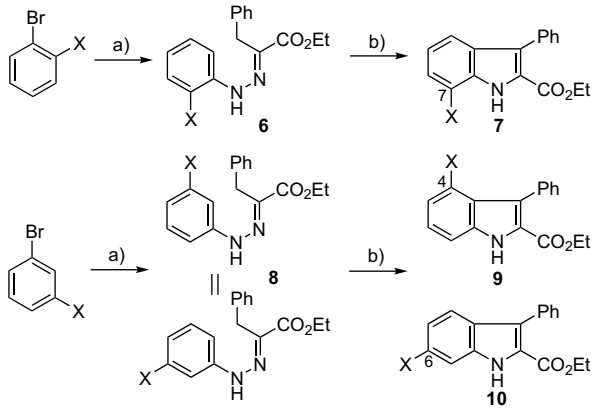
The diversity of aryllithium reagents was examined next. If aryllithium reagents generated in situ could react with diazo esters, the application of this reaction would be extended because commercially available aryllithium reagents are limited in number. At first, 4-substituted aryl bromides (1.5 equiv) were treated with *n*-BuLi (1.5 equiv) in THF at −68 °C to produce aryllithium reagents. To the mixture was added diazo ester **1a** (1.0 equiv). Lithiation of aryl bromides and subsequent nucleophilic addition of the lithium reagents to diazo compound **1a** proceeded successfully. Resulting hydrazone **4** easily gave indole **5** on treatment with an acid (Scheme 5).

In the same manner, 2-substituted phenyl bromides, 3-substituted phenyl bromides, and multi-substituted phenyl bromides



Scheme 5.

were converted into nucleophiles to give corresponding hydrazones. Although all lithium reagents gave the desired hydrazones, the yield of hydrazone **6a** was low compared to others. During the cyclization of hydrazone **6b**, indole **3a** was also produced in 21% yield besides major indole **7b**. It seems that the methyl group was eliminated by aromatization of the indole ring, and the same example has already been reported.[9] Hydrazone **6** derived from 2-substituted phenyl bromides gave only one isomer, 7-substituted indole **7**, but hydrazone **8** derived from 3-substituted phenyl bromides gave two isomers, 4-substituted indole **9** and 6-substituted indole **10** (Scheme 6). The regioisomers (**9** and **10**) were determined by NMR analysis. There seemed to be no rule regarding the substituent group and the production rate (**9**/**10**). Furthermore, multi-substituted phenyllithium prepared from 3,5-dichlorophenyl bromide reacted with diazo ester **1a**, and resulting hydrazone **11** gave desired indole **12**. These results are listed in Table 2.



Scheme 6. (a) *n*-BuLi, THF, −68 °C, **1a**, AcOH; (b) $SOCl_2$, EtOH, 80 °C in a sealed tube.

2.4. Nucleophiles derived from heteroaromatic compounds: examination of nucleophile 3

Now that it has become clear that many kinds of phenyl bromides can be converted into nucleophiles for diazo esters, we investigated another type of nucleophile. As a typical example of heteroaromatic bromide, bromopyridines were examined to determine if they could function as a nucleophile. Each bromopyridine (2-, 3-, and 4-bromopyridine) was lithiated by known procedures.[10] Desired hydrazones were produced after adding a solution of **1a** to pyridyl lithium reagents, although the yields were low (Scheme 7). Subsequent cyclization did not proceed under the same reaction conditions to obtain azaindoles, as reported.[11]

Table 2

	X	4	5		X	6	7
4-	OMe	**4a**, 79%	**5a**, 92%	2-	OMe	**6a**, 28%	**7a**, 60%
	CN	**4b**, 77%	**5b**, 82%		Me	**6b**, 72%	**7b**, 71%[a]
	n-Bu	**4c**, 74%	**5c**, 92%		Cl	**6c**, 96%	**7c**, 50%
	t-Bu	**4d**, 78%	**5d**, 83%		F	**6d**, 72%	**7d**, 54%
	Br	**4e**, 69%	**5e**, 81%		X	**8**	**9**/**10**
	CF_3	**4f**, 76%	**5f**, 76%	3-	OMe	**8a**, 66%	**9a**/**10a**, 84% (2:1)
	CN	**4g**, 46%	**5g**, 49%		Me	**8b**, 78%	**9b**/**10b**, 88% (1:1)
	X	**11**	**12**		Br	**8c**, 91%	**9c**/**10c**, 98% (2:3)
Multi	3,5-Dichloro	64%	65%		F	**8d**, 68%	**9d**/**10d**, 90% (2:1)

[a] Compound **3a** was also isolated in 21% yield.

3. Conclusion

We have developed a novel method for the synthesis of aryl hydrazones from α-diazo esters. As a result, many new aryl hydrazones and indoles were synthesized utilizing this methodology.[12] The terminal nitrogen of the diazo group easily reacted with various nucleophiles to give aryl hydrazones. Although aryl lithium reagents and phenyl Grignard reagent worked as nucleophiles, organozinc reagent did not react with diazo esters. Aryl lithium reagents having substitutions at 2-, 3-, 4-, or multi positions gave corresponding hydrazones and indoles by subsequent Fischer indole cyclization. Nucleophiles derived from bromopyridines also gave hydrazones.

4. Experimental

4.1. General

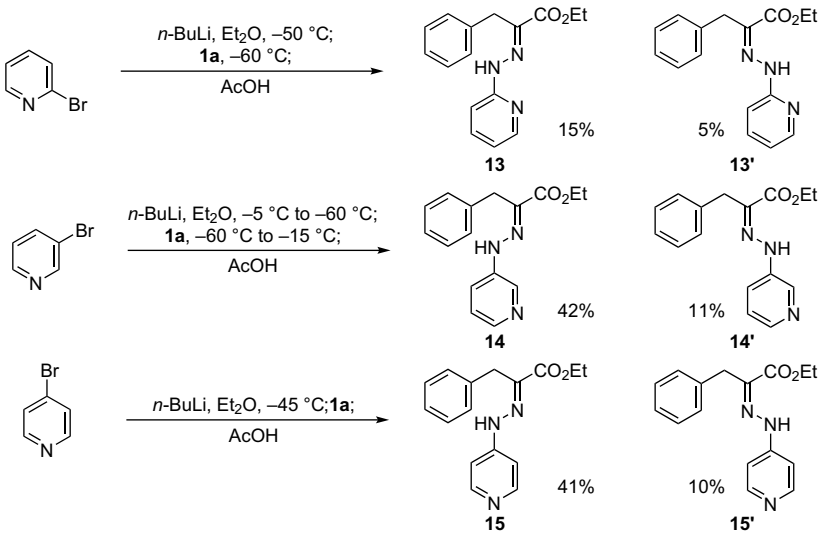
^1H and ^{13}C NMR spectra were recorded on a JEOL JNM-ECX-400 spectrometer at 400 and 100 MHz, respectively. Chemical shifts were expressed in δ parts per million with tetramethylsilane as an internal standard (δ=0 ppm) for ^1H NMR. Chemical shifts of carbon signals were referenced to $CDCl_3$ (δ_c=77.0 ppm). IR spectra were recorded on a JASCO FT/IR-4100. Mass spectra were recorded on a JEOL JMS-GCmate II. Melting points were measured on a Yanaco MP-500P micro melting point apparatus and are not corrected.

4.2. Materials

Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from benzophenone ketyl immediately before use. All other reagents and solvents were purchased from commercial sources and used without further purification.

4.3. Synthesis of aryl hydrazones

The typical procedure for synthesis of aryl hydrazones **2**: diazo ester **1a** (204 mg, 1 mmol) was dissolved in THF (10 ml) and stirred at −68 °C under nitrogen atmosphere. To this solution was added slowly phenyllithium (0.48 ml, 2.1 M in Bu_2O). The reaction mixture was stirred for 20 min at the same temperature, neutralized with acetic acid (0.06 ml, 1 mmol), diluted with an aqueous saturated $NaHCO_3$ solution and extracted three times with ethyl acetate. The combined organic phase was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate: 5:1) to give **2a** as pale yellow crystals (242 mg, 86%). Recrystallization from isopropylether afforded slightly yellow crystals, mp (88–89 °C) (lit:[13] 89 °C, lit:[4] 92–94 °C).



Scheme 7.

*4.3.1. (E)-Ethyl 3-phenyl-2-(2-phenylhydrazono)propanoate (**2a**)*

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.08 (s, 1H), 7.29–7.20 (m, 7H), 7.06 (m, 1H), 6.91 (m, 1H), 4.31 (q, J=7.2 Hz, 2H), 3.98 (s, 2H), 1.35 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.33, 142.87, 135.00, 133.59, 129.08, 129.04, 127.85, 126.93, 122.04, 113.90, 61.23, 30.87, 14.20; IR (KBr) 3300, 3244, 1701, 1669 cm^{-1}; HRMS (EI) calculated for $C_{17}H_{18}N_2O_2$ (M^+) 282.1368, found 282.1360.

*4.3.2. (Z)-Ethyl 3-phenyl-2-(2-phenylhydrazono)propanoate (**2a′**)*

^{1}H NMR ($CDCl_3$, 400 MHz) δ 12.14 (s, 1H), 7.31–7.18 (m, 9H), 6.95 (m, 1H), 4.18 (q, J=7.2 Hz, 2H), 3.82 (s, 2H), 1.24 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.59, 143.45, 139.13, 129.26, 128.92, 128.16, 127.85, 126.12, 121.84, 113.69, 60.57, 39.34, 13.99.

*4.3.3. (E)-Ethyl 4-methyl-2-(2-phenylhydrazono)pentanoate (**2b**)*

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.14 (s, 1H), 7.28–7.19 (m, 4H), 6.92 (m, 1H), 4.29 (q, J=7.2 Hz, 2H), 2.49 (d, J=7.2 Hz, 2H), 2.05 (m, 1H), 1.36 (t, J=7.2 Hz, 3H), 0.97 (d, J=6.4 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.38, 143.17, 135.52, 129.04, 121.63, 113.75, 60.82, 32.88, 26.20, 22.64, 14.11; IR (film) 3308, 1701, 1574, 1221 cm^{-1}; HRMS (EI) calculated for $C_{14}H_{20}N_2O_2$ (M^+) 248.1525, found 248.1521.

*4.3.4. (E)-Methyl 3-(4-(benzyloxy)phenyl)-2-(2-phenylhydrazono)propanoate (**2c**)*

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.00 (s, 1H), 7.41–7.22 (m, 7H), 7.15 (d, J=8.8 Hz, 2H), 7.04 (d, J=8.8 Hz, 2H), 6.92 (m, 3H), 5.01 (s, 2H), 3.95 (s, 2H), 3.88 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.89, 157.80, 142.80, 136.75, 133.82, 129.21, 128.96, 128.52, 127.94, 127.40, 126.89, 122.22, 115.59, 114.02, 69.98, 52.43, 30.25; IR (film) 3450, 1604, 1238 cm^{-1}; HRMS (EI) calculated for $C_{23}H_{22}N_2O_3$ (M^+) 374.1630, found 374.1628.

*4.3.5. (E)-Methyl 4-(methylthio)-2-(2-phenylhydrazono)-butanoate (**2d**)*

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.69 (s, 1H), 7.29 (m, 2H), 7.20 (m, 2H), 6.98 (m, 1H), 3.86 (s, 3H), 2.94 (t, J=6.8 Hz, 2H), 2.72 (t, J=6.8 Hz, 2H), 2.18 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.51, 143.11, 134.33, 129.28, 122.19, 114.06, 52.28, 30.48, 25.65, 16.02; IR (film) 1701, 1241 cm^{-1}; HRMS (EI) calculated for $C_{12}H_{16}N_2O_2S$ (M^+) 252.0932, found 252.0933.

*4.3.6. (E)-Diethyl 2-(2-phenylhydrazono)pentanedioate (**2e**)*

^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.60 (s, 1H), 7.35–7.20 (m, 4H), 6.95 (m, 1H), 4.30 (q, J=7.2 Hz, 2H), 4.14 (q, J=7.2 Hz, 2H), 2.86 (t, J=6.4 Hz, 2H), 2.66 (t, J=6.4 Hz, 2H), 1.38 (t, J=7.2 Hz, 3H), 1.23 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 175.14, 165.19, 143.71, 134.47, 129.17, 121.74, 113.97, 61.42, 61.05, 31.45, 19.74, 14.30, 14.06; IR (film) 3279, 1699, 1237 cm^{-1}; HRMS (EI) calculated for $C_{15}H_{20}N_2O_4$ (M^+) 292.1423, found 292.1428.

*4.3.7. (E)-Methyl 6-(benzyloxycarbonylamino)-2-(2-phenylhydrazono)hexanoate (**2f**)*

^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.01 (s, 1H), 7.40–7.25 (m, 9H), 6.92 (t, J=7.2 Hz, 1H), 5.08 (s, 2H), 4.97 (m, 1H), 3.83 (s, 3H), 3.34 (dd, J=11.2, 6.0 Hz, 1H), 2.67 (m, 1H), 1.58 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.97, 157.72, 143.82, 136.16, 134.78, 129.05, 128.50, 128.14, 127.79, 121.53, 114.16, 67.02, 52.11, 38.64, 30.89, 23.76, 21.18; IR (film) 3282, 2947, 1701, 1240 cm^{-1}; HRMS (EI) calculated for $C_{21}H_{25}N_3O_4$ (M^+) 383.1845, found 383.1847.

*4.3.8. (Z)-Ethyl 3-(benzylthio)-2-(2-phenylhydrazono)-propanoate (**2g**)*

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.71 (s, 1H), 7.31–7.22 (m, 7H), 7.12 (d, J=8.8 Hz, 2H), 6.96 (t, J=7.2 Hz, 1H), 4.26 (q, J=7.2 Hz, 2H), 3.69 (s, 2H), 3.66 (s, 2H), 1.32 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.56, 142.85, 137.31, 129.48, 129.09, 128.71, 128.53, 127.32, 122.36, 114.17, 61.23, 36.00, 24.26, 14.15; IR (film) 3295, 1698, 1227, 1170 cm^{-1}; HRMS (EI) calculated for $C_{18}H_{20}N_2O_4S$ (M^+) 328.1245, found 328.1253.

*4.3.9. (E)-Benzyl 2-(2-phenylhydrazono)propanoate (**2h**)*

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.78 (s, 1H), 7.46–7.18 (m, 9H), 6.95 (t, J=7.2 Hz, 1H), 5.30 (s, 2H), 2.09 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.01, 143.11, 136.21, 131.94, 129.26, 128.45, 128.01, 127.93, 122.05, 113.99, 66.59, 10.25; IR (KBr) 3451, 3291, 1673, 1243, 1152 cm^{-1}; HRMS (EI) calculated for $C_{16}H_{16}N_2O_2$ (M^+) 268.1212, found 268.1216; mp 91.8–93.0 °C.

The typical procedure for synthesis of aryl hydrazones **4**, **6**, **8**, **11**, **13**–**15**: 4-bromoanisole (0.19 ml, 1.5 mmol) was dissolved in THF (10 ml) and stirred at −68 °C under nitrogen atmosphere. To this solution was added slowly *n*-butylllithium (0.96 ml, 1.56 M in hexane, 1.5 mmol) and stirred for 10 min at the same temperature. Then to this solution was added **1a** (1.0 ml, 1.0 M in THF, 1.0 mmol) keeping the temperature not to rise over −60 °C. After 40 min, the reaction mixture was neutralized with acetic acid (0.09 ml, 1.5 mmol), diluted with an aqueous saturated $NaHCO_3$ solution and extracted three times with ethyl acetate. The combined organic phase was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The resulting residue was purified by silica gel column

chromatography (hexane/ethyl acetate: 5:1) to give **4a** as pale yellow oil (246.0 mg, 79%).

*4.3.10. (E)-Ethyl 2-(2-(4-methoxyphenyl)hydrazono)-3-phenylpropanoate (**4a**)*

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.89 (s, 1H), 7.33–7.20 (m, 5H), 6.98 (d, J=9.0 Hz, 2H), 6.80 (d, J=9.0 Hz, 2H), 4.33 (q, J=7.2 Hz, 2H), 4.00 (s, 2H), 3.74 (s, 3H), 1.38 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.50, 155.19, 136.85, 135.15, 132.67, 129.16, 127.93, 127.02, 115.21, 114.53, 61.26, 55.54, 31.01, 14.32; IR (film) 3298, 1698, 1514, 1231 cm^{-1}; HRMS (EI) calculated for $C_{18}H_{20}N_2O_3$ (M^+) 312.1474, found 312.1472.

*4.3.11. (E)-Ethyl 3-phenyl-2-(2-p-tolylhydrazono)propanoate (**4b**)*

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.92 (s, 1H), 7.35–7.18 (m, 5H), 7.04 (d, J=8.0 Hz, 2H), 6.95 (d, J=8.0 Hz, 2H), 4.34 (q, J=7.2 Hz, 2H), 4.00 (s, 2H), 2.25 (s, 3H), 1.38 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.47, 140.62, 135.10, 133.04, 131.62, 129.68, 129.17, 127.93, 127.03, 113.93, 61.31, 31.01, 20.63, 14.32; IR (film) 3299, 1698, 1239 cm^{-1}; HRMS (EI) calculated for $C_{18}H_{20}N_2O_2$ (M^+) 296.1525, found 296.1537.

*4.3.12. (E)-Ethyl 2-(2-(4-butylphenyl)hydrazono)-3-phenylpropanoate (**4c**)*

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.92 (s, 1H), 7.32–7.20 (m, 5H), 7.05 (d, J=8.8 Hz, 2H), 6.96 (d, J=8.8 Hz, 2H), 4.34 (q, J=6.8 Hz, 2H), 4.01 (s, 2H), 2.51 (t, J=8.0 Hz, 2H), 1.52 (m, 2H), 1.39 (t, J=6.8 Hz, 3H), 1.30 (m, 2H), 0.89 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.50, 140.80, 136.86, 135.14, 133.08, 129.19, 129.08, 127.95, 127.04, 113.97, 61.30, 34.84, 33.74, 31.04, 22.19, 14.32, 13.90; IR (film) 3301, 2929, 1700, 1520, 1239 cm^{-1}; HRMS (EI) calculated for $C_{21}H_{26}N_2O_2$ (M^+) 338.1994, found 338.2003.

*4.3.13. (E)-Ethyl 2-(2-(4-tert-butylphenyl)hydrazono)-3-phenylpropanoate (**4d**)*

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.93 (s, 1H), 7.35–7.15 (m, 7H), 7.00 (d, J=8.8 Hz, 2H), 4.33 (q, J=7.2 Hz, 2H), 4.00 (s, 2H), 1.38 (t, J=7.2 Hz, 3H), 1.26 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.50, 145.16, 140.56, 135.14, 133.15, 129.17, 127.95, 127.02, 125.99, 113.73, 61.27, 34.16, 31.37, 31.03, 14.32; IR (KBr) 3435, 2964, 1698, 1673, 1561, 1522, 1246, 1209, 1184 cm^{-1}; HRMS (EI) calculated for $C_{21}H_{26}N_2O_2$ (M^+) 338.1994, found 338.2005; mp 115.3–115.9 °C.

*4.3.14. (E)-Ethyl 2-(2-(4-bromophenyl)hydrazono)-3-phenylpropanoate (**4e**)*

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.99 (s, 1H), 7.36–7.16 (m, 7H), 6.93 (d, J=9.2 Hz, 2H), 4.33 (q, J=7.2 Hz, 2H), 3.99 (s, 2H), 1.37 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.16, 142.02, 134.75, 134.58, 132.00, 129.22, 127.87, 127.15, 115.53, 114.27, 61.46, 31.10, 14.26; IR (film) 3297, 1699, 1486, 1239 cm^{-1}; HRMS (EI) calculated for $C_{17}H_{17}BrN_2O_2$ (M^+) 360.0473, found 360.0473.

*4.3.15. (E)-Ethyl 3-phenyl-2-(2-(4-(trifluoromethyl)phenyl)-hydrazono)propanoate (**4f**)*

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.06 (s, 1H), 7.48 (d, J=8.4 Hz, 2H), 7.36–7.22 (m, 5H), 7.10 (d, J=8.4 Hz, 2H), 4.36 (q, J=7.2 Hz, 2H), 4.04 (s, 2H), 1.40 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.08, 145.57 (d, J_{C-F}=1.9 Hz), 135.99, 134.60, 129.37, 127.93, 127.34, 126.57 (q, J_{C-F}=3.8 Hz), 124.32 (q, J_{C-F}=269.8 Hz), 123.72 (t, J_{C-F}=32.5 Hz), 113.69, 61.66, 31.31, 14.28; IR (KBr) 3297, 1688, 1318 cm^{-1}; HRMS (EI) calculated for $C_{18}H_{17}F_3N_2O_2$ (M^+) 333.0977, found 333.0952; mp 104.5–105.5 °C.

*4.3.16. (E)-Ethyl 2-(2-(4-cyanophenyl)hydrazono)-3-phenylpropanoate (**4g**)*

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.37 (s, 1H), 7.47 (d, J=8.4 Hz, 2H), 7.35–7.20 (m, 5H), 7.12 (d, J=8.4 Hz, 2H), 4.33 (q, J=7.2 Hz, 2H), 4.03 (s, 2H), 1.38 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.82, 146.44, 137.10, 134.48, 133.47, 129.22, 127.87, 127.21, 119.35, 114.08, 104.16, 61.65, 31.20, 14.17; IR (film) 3283, 2220, 1700, 1607 cm^{-1}; HRMS (EI) calculated for $C_{18}H_{17}N_3O_2$ (M^+) 307.1321, found 307.1317.

*4.3.17. (E)-Ethyl 2-(2-(2-methoxyphenyl)hydrazono)-3-phenylpropanoate (**6a**)*

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.49 (s, 1H), 7.53 (dd, J=7.6, 1.2 Hz, 1H), 7.34–7.18 (m, 5H), 6.93 (dt, J=7.6, 1.2 Hz, 1H), 6.86 (dt, J=8.0, 1.2 Hz, 1H), 6.76 (dd, J=8.0, 1.2 Hz, 1H), 4.36 (q, J=7.2 Hz, 2H), 4.01 (s, 2H), 3.72 (s, 3H), 1.40 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.59, 146.13, 135.23, 134.68, 132.43, 128.90, 128.37, 126.87, 121.47, 121.46, 113.47, 110.35, 61.30, 55.60, 31.53, 14.33; IR (film) 3347, 1698 cm^{-1}; HRMS (EI) calculated for $C_{18}H_{20}N_2O_3$ (M^+) 312.1474, found 312.1478.

*4.3.18. (E)-Ethyl 3-phenyl-2-(2-o-tolylhydrazono)propanoate (**6b**)*

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.79 (s, 1H), 7.54 (d, J=7.6 Hz, 1H), 7.35–7.22 (m, 5H), 7.17 (t, J=7.6 Hz, 1H), 6.97 (d, J=7.2 Hz, 1H), 6.84 (dt, J=7.2, 0.8 Hz, 1H), 4.38 (q, J=7.2 Hz, 2H), 4.06 (s, 2H), 1.77 (s, 3H), 1.42 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.63, 140.85, 134.84, 134.37, 130.32, 129.31, 128.14, 127.27, 127.23, 121.76, 121.67, 113.80, 61.43, 31.76, 16.37, 14.36; IR (KBr) 3353, 1694, 1571, 1242, 1196 cm^{-1}; HRMS (EI) calculated for $C_{18}H_{20}N_2O_2$ (M^+) 296.1525, found 296.1520; mp 80.7–81.5 °C.

*4.3.19. (E)-Ethyl 2-(2-(2-chlorophenyl)hydrazono)-3-phenylpropanoate (**6c**)*

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.38 (s, 1H), 7.62 (dd, J=8.4, 1.2 Hz, 1H), 7.36–7.16 (m, 7H), 6.83 (dt, J=8.0, 1.6 Hz, 1H), 4.38 (q, J=7.2 Hz, 2H), 4.04 (s, 2H), 1.41 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.26, 139.05, 136.53, 134.46, 129.14, 129.01, 128.32, 127.88, 127.16, 122.08, 118.66, 115.19, 61.52, 31.66, 14.29; IR (film) 3337, 1699, 1238 cm^{-1}; HRMS (EI) calculated for $C_{17}H_{17}ClN_2O_2$ (M^+) 316.0979, found 316.0966.

*4.3.20. (E)-Ethyl 2-(2-(2-fluorophenyl)hydrazono)-3-phenylpropanoate (**6d**)*

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.15 (s, 1H), 7.60 (dt, J=8.4, 1.2 Hz, 1H), 7.50–7.20 (m, 5H), 7.07 (t, J=8.0 Hz, 1H), 6.95 (ddd, J=11.2, 8.0, 1.2 Hz, 1H), 6.84 (m, 1H), 4.37 (q, J=7.2 Hz, 2H), 4.02 (s, 2H), 1.40 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.21, 150.39 (d, J_{C-F}=240.3 Hz), 136.35, 134.72, 131.38 (d, J_{C-F}=8.5 Hz), 129.22, 128.16, 127.15, 124.82 (d, J_{C-F}=2.9 Hz), 121.64 (d, J_{C-F}=6.7 Hz), 115.39 (d, J_{C-F}=1.9 Hz), 114.85 (d, J_{C-F}=17.2 Hz), 61.50, 31.48, 14.29; IR (film) 3353, 1700, 1254, 1189, 1105 cm^{-1}; HRMS (EI) calculated for $C_{17}H_{17}FN_2O_2$ (M^+) 300.1274, found 300.1271.

*4.3.21. (E)-Ethyl 2-(2-(3-methoxyphenyl)hydrazono)-3-phenylpropanoate (**8a**)*

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.95 (s, 1H), 7.35–7.20 (m, 5H), 7.12 (t, J=8.0 Hz, 1H), 6.71 (t, J=2.4 Hz, 1H), 6.56 (m, 1H), 6.49 (m, 1H), 4.34 (q, J=7.2 Hz, 2H), 4.01 (s, 2H), 3.77 (s, 3H), 1.38 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.38, 160.64, 144.23, 134.96, 133.82, 129.98, 129.22, 127.93, 127.10, 107.82, 106.58, 99.81, 61.39, 55.20, 31.07, 14.28; IR (film) 3300, 1699, 1600, 1200, 1152 cm^{-1}; HRMS (EI) calculated for $C_{18}H_{20}N_2O_3$ (M^+) 312.1474, found 312.1468.

*4.3.22. (E)-Ethyl 3-phenyl-2-(2-m-tolylhydrazono)propanoate (**8b**)*

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.98 (s, 1H), 7.35–7.20 (m, 5H), 7.13 (t, J=8.0 Hz, 1H), 6.92 (s, 1H), 6.85 (d, J=8.0 Hz, 1H), 6.76 (d, J=8.0 Hz, 1H), 4.36 (q, J=7.2 Hz, 2H), 4.02 (s, 2H), 2.30 (s, 3H), 1.40 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.40, 142.81, 139.20, 135.03, 133.47, 129.16, 129.00, 127.90, 127.03, 123.05, 114.51, 111.18, 61.34, 30.99, 21.41, 14.29; IR (film) 3297, 2981, 1697, 1569,

1191 cm^{-1}; HRMS (EI) calculated for $C_{18}H_{20}N_2O_2$ (M^+) 296.1525, found 296.1555.

*4.3.23. (E)-Ethyl 2-(2-(3-bromophenyl)hydrazono)-3-phenylpropanoate (**8c**)*

^1H NMR ($CDCl_3$, 400 MHz) δ 7.90 (s, 1H), 7.36–7.20 (m, 6H), 7.05 (m, 2H), 6.92 (m, 1H), 4.36 (q, J=7.2 Hz, 2H), 4.01 (s, 2H), 1.40 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.16, 144.17, 135.17, 134.67, 130.48, 129.34, 127.90, 127.27, 125.01, 123.13, 116.95, 112.63, 61.59, 31.24, 14.31; IR (film) 3298, 1700, 1593, 1233 cm^{-1}; HRMS (EI) calculated for $C_{17}H_{17}N_2O_2$ (M^+) 360.0473, found 360.0463.

*4.3.24. (E)-Ethyl 2-(2-(3-fluorophenyl)hydrazono)-3-phenylpropanoate (**8d**)*

^1H NMR ($CDCl_3$, 400 MHz) δ 8.01 (s, 1H), 7.35–7.10 (m, 6H), 6.89 (dt, J=10.8, 2.0 Hz, 1H), 6.70 (dd, J=8.0, 2.4 Hz, 1H), 6.60 (dt, J=8.4, 2.4 Hz, 1H), 4.33 (q, J=7.2 Hz, 2H), 4.00 (s, 2H), 1.38 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.25, 163.71 (d, J_{C-F}=244.1 Hz), 144.80, 144.69, 134.85 (d, J_{C-F}=9.5 Hz), 130.40 (d, J_{C-F}=9.5 Hz), 129.30, 127.95, 127.22, 109.58 (d, J_{C-F}=1.9 Hz), 108.74 (d, J_{C-F}=21.9 Hz), 101.46 (d, J_{C-F}=26.7 Hz), 61.56, 31.18, 14.30; IR (KBr) 3451, 3289, 1698, 1670, 1136 cm^{-1}; HRMS (EI) calculated for $C_{17}H_{17}FN_2O_2$ (M^+) 300.1274, found 300.1275.

*4.3.25. (E)-Ethyl 2-(2-(3,5-dichlorophenyl)hydrazono)-3-phenylpropanoate (**11**)*

^1H NMR ($CDCl_3$, 400 MHz) δ 7.92 (s, 1H), 7.36–7.18 (m, 5H), 6.93 (d, J=2.0 Hz, 2H), 6.89 (t, J=1.6 Hz, 1H), 4.35 (q, J=7.2 Hz, 2H), 4.00 (s, 2H), 1.40 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.93, 144.69, 136.32, 135.60, 134.38, 129.41, 127.86, 127.40, 121.84, 112.45, 61.74, 31.33, 14.28; IR (KBr) 3325, 1703, 1589, 1559 cm^{-1}; HRMS (EI) calculated for $C_{17}H_{16}Cl_2N_2O_2$ (M^+) 350.0589, found 350.0573; mp 121.3–121.7 °C.

*4.3.26. (E)-Ethyl 3-phenyl-2-(2-(pyridin-2-yl)hydrazono)-propanoate (**13**)*

^1H NMR ($CDCl_3$, 400 MHz) δ 8.62 (s, 1H), 8.10 (d, J=4.4 Hz, 1H), 7.63 (m, 1H), 7.44 (d, J=8.8 Hz, 1H), 7.34–7.19 (m, 5H), 6.86 (m, 1H), 4.35 (q, J=7.2 Hz, 2H), 4.03 (s, 2H), 1.39 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.03, 155.32, 147.48, 138.32, 136.10, 134.62, 129.10, 128.07, 127.01, 117.73, 108.48, 61.54, 31.03, 14.25; IR (film) 2980, 1702, 1595, 1577 cm^{-1}; HRMS (EI) calculated for $C_{16}H_{17}N_3O_2$ (M^+) 283.1321, found 283.1296.

*4.3.27. (E)-Ethyl 3-phenyl-2-(2-(pyridin-3-yl)hydrazono)-propanoate (**14**)*

^1H NMR ($CDCl_3$, 400 MHz) δ 8.24 (d, J=2.8 Hz, 1H), 8.18 (dd, J=4.8, 1.6 Hz, 1H), 7.97 (s, 1H), 7.52 (m, 1H), 7.47–7.22 (m, 5H), 7.19 (dd, J=8.4, 4.8 Hz, 1H), 4.36 (q, J=7.2 Hz, 2H), 4.05 (s, 2H), 1.40 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.05, 143.45, 139.49, 136.51, 136.22, 134.60, 129.38, 127.95, 127.35, 123.84, 121.01, 61.63, 31.31, 14.29; IR (KBr) 3448, 1699, 1585, 1100 cm^{-1}; HRMS (EI) calculated for $C_{16}H_{17}N_3O_2$ (M^+) 283.1321, found 283.1310; mp 153.0–154.0 °C.

*4.3.28. (Z)-Ethyl 3-phenyl-2-(2-(pyridin-3-yl)hydrazono)-propanoate (**14′**)*

^1H NMR ($CDCl_3$, 400 MHz) δ 12.13 (s, 1H), 8.46 (d, J=2.8, 1H), 8.21 (d, J=4.8 Hz, 1H), 7.56 (m, 1H), 7.32–7.17 (m, 6H), 4.22 (q, J=7.2 Hz, 2H), 3.83 (s, 2H), 1.27 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.46, 142.77, 139.89, 138.46, 136.22, 130.25, 128.91, 128.22, 126.29, 123.90, 120.41, 60.94, 39.30, 13.91.

*4.3.29. (E)-Ethyl 3-phenyl-2-(2-(pyridin-4-yl)hydrazono)-propanoate (**15**)*

^1H NMR ($CDCl_3$, 400 MHz) δ 8.35 (dd, J=5.2, 1.2 Hz, 2H), 8.10 (s, 1H), 7.37–7.20 (m, 5H), 6.93 (dd, J=5.2, 1.2 Hz, 2H), 4.37 (q, J=7.2 Hz, 2H), 4.04 (s, 2H), 1.40 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.85, 150.48, 149.13, 137.63, 134.37, 129.43, 127.93, 127.43, 108.75, 61.81, 31.44, 14.26; IR (KBr) 3448, 2979, 1703, 1595 cm^{-1}; HRMS (EI) calculated for $C_{16}H_{17}N_3O_2$ (M^+) 283.1321, found 283.1328.

4.4. Synthesis of indoles

The typical procedure for synthesis of indoles **3**, **5**, **7**, **9**, **10**, **12**: ethanol (1.1 ml) was cooled in an ice bath and thionyl chloride (0.08 ml, 1.1 mmol) was added dropwise. This solution was poured into hydrazone **2a** (30.0 mg, 0.106 mmol) in a sealed tube. The reaction solution was stirred at 80 °C for 40 min, cooled, diluted with chloroform and washed with an aqueous saturated $NaHCO_3$ solution. The separated water phase was further extracted with chloroform twice and the combined organic phase was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate: 9:1) to give **3a** as pale yellow crystals (26.7 mg, 95%). Recrystallization from ethanol afforded slightly yellow crystals, mp (137–138 °C) (lit:[4] 137–138 °C).

*4.4.1. Ethyl 3-phenylindole-2-carboxylate (**3a**)*

^1H NMR ($CDCl_3$, 400 MHz) δ 9.34 (s, 1H), 7.63 (d, J=7.6 Hz, 1H), 7.55 (m, 2H), 7.45–7.31 (m, 5H), 7.13 (m, 1H), 4.29 (q, J=7.2 Hz, 2H), 1.22 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.22, 135.78, 133.53, 130.62, 127.86, 127.67, 127.11, 125.69, 124.16, 122.74, 121.67, 120.76, 111.72, 60.88, 13.96; IR (KBr) 3344, 1668, 1252 cm^{-1}; HRMS (EI) calculated for $C_{17}H_{15}NO_2$ (M^+) 265.1103, found 265.1103.

*4.4.2. Ethyl 3-isopropyl-1H-indole-2-carboxylate (**3b**)*

^1H NMR ($CDCl_3$, 400 MHz) δ 8.70 (s, 1H), 7.89 (d, J=8.4 Hz, 1H), 7.38 (d, J=8.0 Hz, 1H), 7.30 (m, 1H), 7.10 (m, 1H), 4.42 (q, J=7.2 Hz, 2H), 4.11 (m, 1H), 1.48 (d, J=7.2 Hz, 6H), 1.43 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.41, 136.20, 130.96, 126.40, 125.08, 122.70, 121.84, 119.46, 111.89, 60.66, 25.66, 22.72, 14.37; IR (KBr) 3327, 1678 cm^{-1}; HRMS (EI) calculated for $C_{14}H_{17}NO_2$ (M^+) 231.1259, found 231.1256; mp 60.6–61.2 °C.

*4.4.3. Methyl 3-(4-(benzyloxy)phenyl)-1H-indole-2-carboxylate (**3c**)*

^1H NMR ($CDCl_3$, 400 MHz) δ 8.99 (s, 1H), 7.65 (d, J=8.0 Hz, 1H), 7.51–7.34 (m, 9H), 7.14 (m, 1H), 7.08 (d, J=8.8 Hz, 2H), 5.13 (s, 2H), 3.83 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.38, 158.16, 137.04, 135.73, 131.65, 128.59, 127.97, 127.92, 127.56, 125.86, 125.83, 124.22, 122.13, 121.81, 120.78, 114.27, 111.65, 70.04, 51.75; IR (KBr) 3350, 1684, 1254 cm^{-1}; HRMS (EI) calculated for $C_{23}H_{19}NO_3$ (M^+) 357.1365, found 357.1355; mp 157.0–158.0 °C.

*4.4.4. Methyl 3-(methylthiomethyl)-1H-indole-2-carboxylate (**3d**)*

^1H NMR ($CDCl_3$, 400 MHz) δ 8.96 (s, 1H), 7.79 (dd, J=8.4, 0.8 Hz, 1H), 7.35 (m, 2H), 7.16 (m, 1H), 4.27 (s, 2H), 3.96 (s, 3H), 2.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.50, 135.90, 127.33, 125.87, 123.56, 121.04, 120.46, 120.39, 111.83, 51.82, 26.95, 15.14; IR (KBr) 3323, 1683, 1253 cm^{-1}; HRMS (EI) calculated for $C_{12}H_{13}NO_2S$ (M^+) 235.0667, found 235.0662; mp 131.0–131.5 °C.

*4.4.5. Ethyl 3-(2-ethoxy-2-oxoethyl)-1H-indole-2-carboxylate (**3e**)*

^1H NMR ($CDCl_3$, 400 MHz) δ 9.22 (s, 1H), 7.63 (d, J=8.0 Hz, 1H), 7.31 (m, 2H), 7.15 (m, 1H), 4.35 (q, J=7.2 Hz, 2H), 4.19 (q, J=7.2 Hz, 2H), 4.18 (s, 2H), 1.40 (t, J=7.2 Hz, 3H), 1.26 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.34, 162.02, 135.77, 127.81, 125.48, 124.38, 120.39 (×2), 115.58, 111.91, 60.87, 60.74, 30.67, 14.21, 14.14; IR (KBr) 3317, 1719, 1684, 1259 cm^{-1}; HRMS (EI) calculated for $C_{15}H_{17}NO_4$ (M^+) 275.1158, found 275.1162; mp 80.0–81.0 °C.

*4.4.6. Methyl 3-(3-(benzyloxycarbonylamino)propyl)-1H-indole-2-carboxylate (**3f**)*

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.79 (s, 1H), 7.65 (d, J=8.0 Hz, 1H), 7.34 (m, 7H), 7.13 (m, 1H), 5.26 (m, 1H), 5.11 (s, 2H), 3.91 (s, 3H), 3.18 (m, 4H), 1.90 (quint, J=6.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.55, 156.46, 136.78, 135.94, 128.43, 128.02, 127.96, 125.81, 124.12, 122.96, 120.64, 120.20, 111.83, 66.44, 51.79, 40.08, 30.40, 21.38; IR (KBr) 3337, 1683 cm^{-1}; HRMS (EI) calculated for $C_{21}H_{22}N_2O_4$ (M^+) 366.1580, found 366.1588; mp 106.0–107.0 °C.

*4.4.7. Ethyl 3-(benzylthio)-1H-indole-2-carboxylate (**3g**)*

^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.13 (s, 1H), 7.77 (dd, J=0.8, 8.4 Hz, 1H), 7.39–7.31 (m, 2H), 7.19–7.10 (m, 6H), 4.39 (q, J=7.2 Hz, 2H), 4.05 (s, 2H), 1.42 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.24, 138.23, 135.26, 130.63, 128.85, 128.84, 128.09, 126.80, 125.88, 121.41, 121.12, 112.90, 111.85, 61.25, 40.87, 14.34; IR (KBr) 3320, 1677, 1252 cm^{-1}; HRMS (EI) calculated for $C_{18}H_{17}NO_2S$ (M^+) 311.0980, found 311.0983; mp 99.8–100.5 °C.

*4.4.8. Ethyl 5-methoxy-3-phenyl-1H-indole-2-carboxylate (**5a**)*

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.92 (s, 1H), 7.56–7.33 (m, 6H), 7.03 (dd, J=8.8, 2.4 Hz, 1H), 6.99 (d, J=2.4 Hz, 1H), 4.27 (q, J=7.2 Hz, 2H), 3.78 (s, 3H), 1.23 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.87, 154.94, 133.71, 130.99, 130.52, 128.15, 127.81, 127.10, 123.74, 123.30, 117.50, 112.65, 101.47, 60.79, 55.71, 14.04; IR (KBr) 3315, 1677 cm^{-1}; HRMS (EI) calculated for $C_{18}H_{17}NO_3$ (M^+) 295.1208, found 295.1209; mp 113.5–114.5 °C.

*4.4.9. Ethyl 5-methyl-3-phenyl-1H-indole-2-carboxylate (**5b**)*

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.91 (s, 1H), 7.55 (m, 2H), 7.45 (m, 2H), 7.36 (m, 3H), 7.19 (dd, J=8.4, 1.6 Hz, 1H), 4.28 (q, J=6.8 Hz, 2H), 2.41 (s, 3H), 1.23 (t, J=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.02, 134.07, 133.67, 130.62, 130.26, 128.12, 127.72, 127.70, 127.08, 123.72, 122.81, 120.85, 111.34, 60.78, 21.43, 14.03; IR (KBr) 3325, 1683 cm^{-1}; HRMS (EI) calculated for $C_{18}H_{17}NO_2$ (M^+) 279.1259, found 279.1245; mp 124.0–125.0 °C.

*4.4.10. Ethyl 5-butyl-3-phenyl-1H-indole-2-carboxylate (**5c**)*

^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.21 (s, 1H), 7.55 (m, 2H), 7.45 (m, 2H), 7.36 (m, 3H), 7.18 (dd, J=8.8, 2.0 Hz, 1H), 4.28 (q, J=6.8 Hz, 2H), 2.65 (t, J=7.6 Hz, 2H), 1.58 (m, 2H), 1.33 (m, 2H), 1.21 (t, J=6.8 Hz, 3H), 0.90 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.21, 135.48, 134.37, 133.77, 130.65, 127.99, 127.66, 127.09, 127.00, 123.78, 122.81, 120.22, 111.42, 60.77, 35.77, 34.26, 22.38, 13.97, 13.92; IR (KBr) 3336, 1685 cm^{-1}; HRMS (EI) calculated for $C_{21}H_{23}NO_2$ (M^+) 321.1729, found 321.1690; mp 110.0–111.0 °C.

*4.4.11. Ethyl 5-tert-butyl-3-phenyl-1H-indole-2-carboxylate (**5d**)*

^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.01 (s, 1H), 7.56 (m, 2H), 7.46 (m, 3H), 7.39 (m, 3H), 4.28 (q, J=7.2 Hz, 2H), 1.33 (s, 9H), 1.22 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.21, 143.79, 134.06, 133.75, 130.66, 127.70, 127.57, 127.01, 124.51, 124.29, 122.89, 116.78, 111.29, 60.77, 34.67, 31.65, 13.98; IR (KBr) 3331, 1678, 1261 cm^{-1}; HRMS (EI) calculated for $C_{21}H_{23}NO_2$ (M^+) 321.1729, found 321.1732; mp 172.0–173.0 °C.

*4.4.12. Ethyl 5-bromo-3-phenyl-1H-indole-2-carboxylate (**5e**)*

^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.15 (s, 1H), 7.75 (d, J=1.2 Hz, 1H), 7.52–7.31 (m, 7H), 4.29 (q, J=7.2 Hz, 2H), 1.23 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.70, 134.15, 132.77, 130.49, 129.52, 128.75, 127.88, 127.48, 124.12, 123.76, 123.51, 114.11, 113.22, 61.11, 13.98; IR (KBr) 3311, 1684, 1258 cm^{-1}; HRMS (EI) calculated for $C_{17}H_{14}BrNO_2$ (M^+) 343.0208, found 343.0170; mp 174.0–175.0 °C.

*4.4.13. Ethyl 3-phenyl-5-(trifluoromethyl)indole-2-carboxylate (**5f**)*

^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.33 (s, 1H), 7.91 (s, 1H), 7.60–7.40 (m, 7H), 4.31 (q, J=7.2 Hz, 2H), 1.23 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.71, 136.75, 132.53, 130.52, 127.99, 127.68, 127.27, 126.24, 124.93, 124.43, 123.43 (q, J_{C-F}=32.4 Hz), 122.24 (q, J_{C-F}=3.8 Hz), 119.76 (q, J_{C-F}=1.9 Hz), 112.25, 61.26, 13.96; IR (KBr) 3312, 1682, 1265, 1161, 1098 cm^{-1}; HRMS (EI) calculated for $C_{18}H_{14}F_3NO_2$ (M^+) 333.0977, found 333.0952; mp 204.1–205.1 °C.

*4.4.14. Ethyl 5-cyano-3-phenylindole-2-carboxylate (**5g**)*

^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.51 (s, 1H), 7.99 (s, 1H), 7.57–7.40 (m, 7H), 4.32 (q, J=7.2 Hz, 2H), 1.23 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.46, 136.92, 131.95, 130.43, 128.04, 127.99, 127.92, 127.89, 127.75, 124.78, 124.56, 119.96, 112.84, 104.27, 61.44, 13.94; IR (KBr) 3293, 2992, 2217, 1681, 1265 cm^{-1}; HRMS (EI) calculated for $C_{18}H_{14}N_2O_2$ (M^+) 290.1055, found 290.1051; mp 219.0–220.0 °C.

*4.4.15. Ethyl 7-methoxy-3-phenyl-1H-indole-2-carboxylate (**7a**)*

^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.17 (s, 1H), 7.57–7.33 (m, 5H), 7.22 (d, J=8.0 Hz, 1H), 7.05 (t, J=8.4 Hz, 1H), 6.75 (d, J=7.6 Hz, 1H), 4.28 (q, J=7.2 Hz, 2H), 3.98 (s, 3H), 1.23 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.72, 146.33, 133.60, 130.59, 129.03, 127.68, 127.11, 126.92, 124.48, 122.48, 121.21, 113.87, 104.42, 60.77, 55.45, 14.06; IR (film) 3294, 1694 cm^{-1}; HRMS (EI) calculated for $C_{18}H_{17}NO_3$ (M^+) 295.1208, found 295.1218; mp 96.1–97.1 °C.

*4.4.16. Ethyl 7-methyl-3-phenyl-1H-indole-2-carboxylate (**7b**)*

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.92 (s, 1H), 7.54 (m, 2H), 7.45 (m, 3H), 7.37 (m, 1H), 7.15 (d, J=6.8 Hz, 1H), 7.06 (t, J=7.2 Hz, 1H), 4.29 (q, J=7.2 Hz, 2H), 2.56 (s, 3H), 1.23 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.21, 135.45, 133.70, 130.63, 127.67, 127.56, 127.12, 125.93, 124.66, 122.60, 121.12, 120.99, 119.38, 60.87, 16.59, 14.02; IR (KBr) 3338, 1672 cm^{-1}; HRMS (EI) calculated for $C_{18}H_{17}NO_2$ (M^+) 279.1259, found 279.1259; mp 117.8–118.3 °C.

*4.4.17. Ethyl 7-chloro-3-phenyl-1H-indole-2-carboxylate (**7c**)*

^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.11 (s, 1H), 7.53–7.20 (m, 7H), 7.08 (t, J=8.4 Hz, 1H), 4.31 (q, J=7.2 Hz, 2H), 1.24 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.51, 133.06, 132.97, 130.52, 129.20, 127.81, 127.45, 124.92, 124.79, 123.49, 121.48, 120.36, 117.10, 61.11, 14.01; IR (KBr) 3318, 1697, 1316, 1236 cm^{-1}; HRMS (EI) calculated for $C_{17}H_{14}ClNO_2$ (M^+) 299.0713, found 299.0709; mp 88.9–89.7 °C.

*4.4.18. Ethyl 7-fluoro-3-phenyl-1H-indole-2-carboxylate (**7d**)*

^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.22 (s, 1H), 7.54 (m, 2H), 7.45 (m, 2H), 7.38 (m, 2H), 7.04 (m, 2H), 4.31 (q, J=7.2 Hz, 2H), 1.24 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.56, 149.47 (d, J_{C-F}= 245 Hz), 132.98, 131.31 (d, J_{C-F}=4.8 Hz), 130.53, 127.80, 127.43, 124.61 (d, J_{C-F}=13.4 Hz), 124.60 (d, J_{C-F}=2.9 Hz), 123.60, 120.88 (d, J_{C-F}=5.7 Hz), 117.42 (d, J_{C-F}=3.8 Hz), 109.89 (d, J_{C-F}=16.2 Hz), 61.11, 14.01; IR (KBr) 3303, 1685, 1322, 1235 cm^{-1}; HRMS (EI) calculated for $C_{17}H_{14}FNO_2$ (M^+) 283.1009, found 283.1009; mp 160.6–161.6 °C.

*4.4.19. Ethyl 4-methoxy-3-phenyl-1H-indole-2-carboxylate (**9a**)*

^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.00 (s, 1H), 7.46 (m, 2H), 7.35 (m, 3H), 7.25 (t, J=8.0 Hz, 1H), 7.03 (d, J=8.0 Hz, 1H), 6.47 (d, J=8.0 Hz, 1H), 4.20 (q, J=7.2 Hz, 2H), 3.66 (s, 3H), 1.13 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.90, 155.95, 137.09, 134.81, 130.96, 126.59, 126.56, 126.50, 124.34, 122.30, 117.89, 104.56, 100.33, 60.63, 55.12, 13.91; IR (KBr) 3328, 1662, 1261 cm^{-1}; HRMS (EI) calculated for $C_{18}H_{17}NO_3$ (M^+) 295.1208, found 295.1217; mp 182.0–183.0 °C.

*4.4.20. Ethyl 6-methoxy-3-phenyl-1H-indole-2-carboxylate (**10a**)*

^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.07 (s, 1H), 7.55 (m, 2H), 7.50 (d, J=8.8 Hz, 1H), 7.43 (m, 2H), 7.37 (m, 1H), 6.84 (d, J=2.4 Hz, 1H), 6.80 (dd, J=8.8, 2.4 Hz, 1H), 4.27 (q, J=7.2 Hz, 2H), 3.85 (s, 3H), 1.22 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.04, 159.14, 136.75, 133.54, 130.53, 127.67, 127.13, 124.64, 122.59, 122.30, 121.54, 112.27,

93.36, 60.63, 55.45, 14.04; IR (KBr) 3324, 1670, 1261 cm^{-1}; HRMS (EI) calculated for $C_{18}H_{17}NO_3$ (M^+) 295.1208, found 295.1208; mp 131.0–132.5 °C.

*4.4.21. Ethyl 4-methyl-3-phenyl-1H-indole-2-carboxylate (**9b**)*

^1H NMR ($CDCl_3$, 400 MHz) δ 8.99 (s, 1H), 7.37 (m, 5H), 7.29 (d, J=8.4 Hz, 1H), 7.22 (t, J=8.4 Hz, 1H), 6.84 (m, 1H), 4.16 (q, J=7.2 Hz, 2H), 2.05 (s, 3H), 1.05 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.05, 136.14, 135.71, 133.67, 130.61, 127.17, 126.99, 126.49, 125.59, 125.09, 123.60, 122.01, 109.54, 60.54, 20.19, 13.78; IR (KBr) 3314, 1678, 1254 cm^{-1}; HRMS (EI) calculated for $C_{18}H_{17}NO_2$ (M^+) 279.1259, found 279.1268; mp 157.5–158.9 °C.

*4.4.22. Ethyl 6-methyl-3-phenyl-1H-indole-2-carboxylate (**10b**)*

^1H NMR ($CDCl_3$, 400 MHz) δ 8.85 (s, 1H), 7.55 (m, 2H), 7.52 (d, J=8.0 Hz, 1H), 7.44 (m, 2H), 7.36 (m, 1H), 7.22 (s, 1H), 6.98 (dd, J=8.0, 1.2 Hz, 1H), 4.28 (q, J=7.2 Hz, 2H), 2.49 (s, 3H), 1.23 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.04, 159.14, 136.75, 133.54, 130.53, 127.67, 127.13, 124.64, 122.59, 122.30, 121.54, 112.27, 93.36, 60.63, 55.45, 14.04; IR (KBr) 3335, 1677, 1255 cm^{-1}; HRMS (EI) calculated for $C_{18}H_{17}NO_2$ (M^+) 279.1259, found 279.1270; mp 166.0–167.0 °C.

*4.4.23. Ethyl 4-bromo-3-phenyl-1H-indole-2-carboxylate (**9c**)*

^1H NMR ($CDCl_3$, 400 MHz) δ 9.17 (s, 1H), 7.42 (dd, J=8.4, 0.8 Hz, 1H), 7.38 (s, 5H), 7.31 (dd, J=7.2, 0.8 Hz, 1H), 7.16 (t, J=8.0 Hz, 1H), 4.17 (q, J=7.2 Hz, 2H), 1.05 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.77, 136.42, 133.95, 131.36, 127.20, 126.88, 126.08, 125.66, 125.54, 124.99, 124.70, 116.34, 111.13, 60.89, 13.71; IR (KBr) 3347, 1673, 1259 cm^{-1}; HRMS (EI) calculated for $C_{17}H_{14}BrNO_2$ (M^+) 343.0208, found 343.0221; mp 167.5–168.7 °C.

*4.4.24. Ethyl 6-bromo-3-phenyl-1H-indole-2-carboxylate (**10c**)*

^1H NMR ($CDCl_3$, 400 MHz) δ 8.97 (s, 1H), 7.61 (d, J=2.0 Hz, 1H), 7.53–7.37 (m, 6H), 7.24 (dd, J=8.4, 1.2 Hz, 1H), 4.29 (q, J=7.2 Hz, 2H), 1.23 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.68, 136.20, 132.85, 130.52, 127.83, 127.46, 126.83, 124.42, 124.28, 123.23, 123.08, 119.62, 114.52, 61.07, 14.01; IR (KBr) 3429, 3314, 1678, 1237, 1049 cm^{-1}; HRMS (EI) calculated for $C_{17}H_{14}BrNO_2$ (M^+) 343.0208, found 343.0224; mp 205.9–207.0 °C.

*4.4.25. Ethyl 4-fluoro-3-phenyl-1H-indole-2-carboxylate (**9d**)*

^1H NMR ($CDCl_3$, 400 MHz) δ 9.26 (s, 1H), 7.54 (m, 3H), 7.45 (m, 2H), 7.38 (m, 1H), 7.10 (dd, J=9.2, 2.4 Hz, 1H), 6.91 (dt, J=9.2, 2.4 Hz, 1H), 4.29 (q, J=7.2 Hz, 2H), 1.23 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.25, 161.37 (d, J_{C-F}=108.7 Hz), 135.81 (d, J_{C-F}=13.3 Hz), 133.14, 130.53, 127.79, 127.38, 124.65, 124.44 (d, J_{C-F}=1.9 Hz), 123.21 (d, J_{C-F}=3.8 Hz), 123.11 (dd, J_{C-F}=10.4, 2.0 Hz), 110.41 (dd, J_{C-F}=24.8, 2.8 Hz), 97.53 (d, J_{C-F}=25.7 Hz), 60.96, 13.99; IR (KBr) 3316, 1671, 1260, 1240 cm^{-1}; HRMS (EI) calculated for $C_{17}H_{14}FNO_2$ (M^+) 283.1009, found 283.1012; mp 181.5–182.5 °C.

*4.4.26. Ethyl 6-fluoro-3-phenyl-1H-indole-2-carboxylate (**10d**)*

^1H NMR ($CDCl_3$, 400 MHz) δ 9.22 (s, 1H), 7.50 (m, 3H), 7.40 (m, 3H), 7.24 (m, 2H), 6.76 (ddd, J=11.2, 6.8, 1.2 Hz, 1H), 4.25 (q, J=7.2 Hz, 2H), 1.17 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.72, 157.93 (d, J_{C-F}=251.7 Hz), 137.75 (d, J_{C-F}=8.5 Hz), 133.54 (d, J_{C-F}=1.9 Hz), 130.72 (d, J_{C-F}=1.9 Hz), 127.26, 127.10, 126.11 (d, J_{C-F}=8.6 Hz), 123.35, 122.38, 116.97 (d, J_{C-F}=18.1 Hz), 107.78 (d, J_{C-F}=4.7 Hz), 105.75 (d, J_{C-F}=19.17 Hz), 61.03, 13.89; IR (KBr) 3317, 1672, 1258, 1243 cm^{-1}; HRMS (EI) calculated for $C_{17}H_{14}FNO_2$ (M^+) 283.1009, found 283.1008; mp 149.0–150.5 °C.

*4.4.27. Ethyl 4,6-dichloro-3-phenyl-1H-indole-2-carboxylate (**12**)*

^1H NMR ($CDCl_3$, 400 MHz) δ 9.36 (s, 1H), 7.36 (m, 6H), 7.10 (d, J=1.6 Hz, 1H), 4.19 (q, J=7.2 Hz, 2H), 1.06 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.67, 136.49, 133.50, 131.09, 130.98, 129.21, 127.34, 126.96, 125.30, 124.10, 123.27, 122.50, 110.42, 61.12, 13.70; IR (KBr) 3303, 1683, 1248 cm^{-1}; HRMS (EI) calculated for $C_{17}H_{13}Cl_2NO_2$ (M^+) 333.0323, found 333.0326; mp 202.2–202.7 °C.

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