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MICROWAVE-ASSISTED SYNTHESIS OF *N*-2-BENZYL-3-(4-ETHOXYCARBONYLPHENYL)INDAZOLE DERIVATIVES

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Abstract – The microwave-assisted synthesis for promoting *N*-2 substituted indazoles as the major products were successfully developed by treating 3-(4-ethoxycarbonylphenyl)indazoles with various substituted benzyl chloride (benzyl, *o*-chlorobenzyl, *m*-chlorobenzyl, and *p*-chlorobenzyl chloride) in the presence of two equivalents of triethylamine. The result was better than two trandional methods including the directly substitution with benzyl chloride and Mitsunobu reaction with benzyl alcohol.

INTRODUCTION

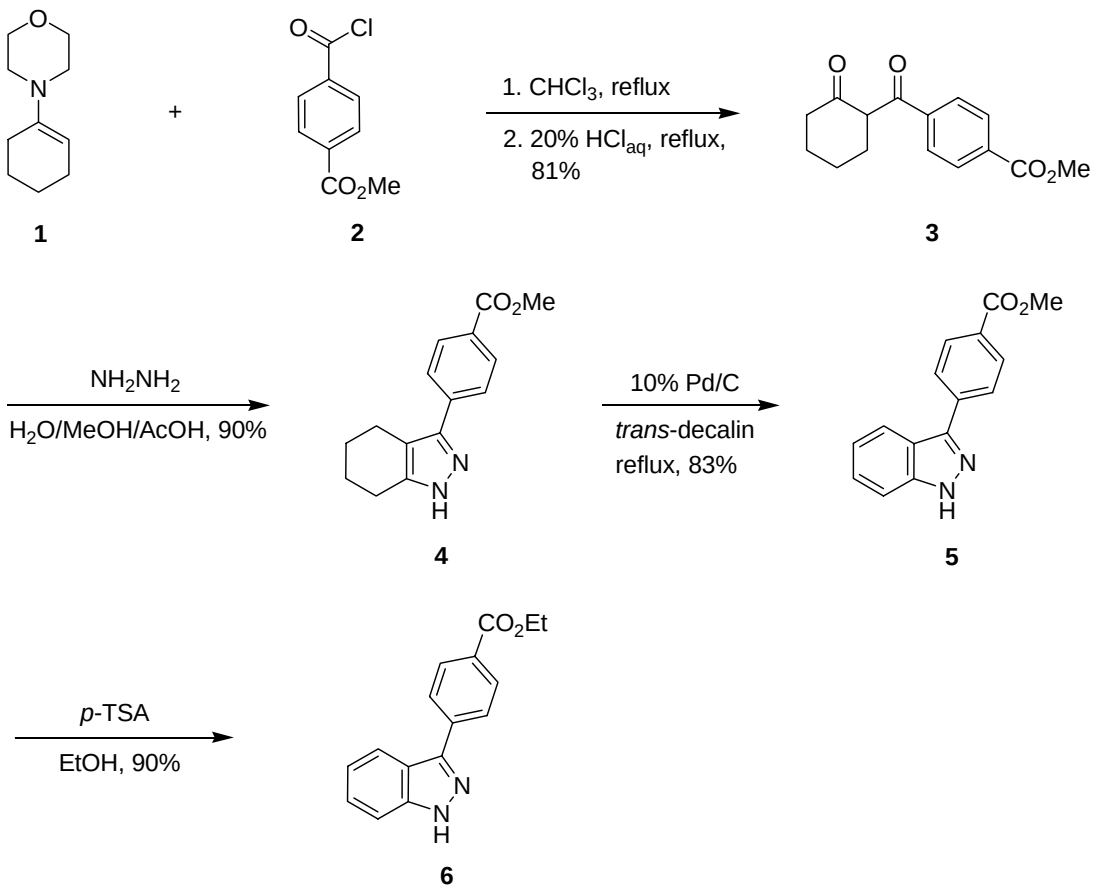
The indazole nucleus[1] is an effective pharmacophore in medicinal chemistry as illustrated by its application in pharmaceutical agents in fields as diverse as CNS discords (granisetron), anti-inflammatory area,[2] anti-tumor[3] and HIV protease inhibitor.[4] Most syntheses of indazoles reported in literature are proceeded from benzene derivatives where pyrazole moiety was generated by ring closure starting from isatines, *o*-substituted aniline, or phenylhydrazines.[1] However, indazole chemistry remains almost studied in *N*-1 substitutents.

In split of the indazole derivatives were important in the pharmaceutical development, the efficient and selectivity synthetic methodologies of *N*-2 substituted indazoles has met with limited success.[5] As a result, many approaches to synthesis of *N*-2 substituted indazoles have been studied.[6] In this paper, we investigated the microwave-assisted synthetic technique to promote *N*-2 substituted indazole derivatives and compared to two traditional chemical reactions – the directly substitution with benzyl chloride and Mitsunobu reaction with benzyl alcohol. Eventually, we found the *N*-2-benzyl-3-(4-ethoxycarbonylphenyl)indazoles can be successfully promoted as the major products by the microwave-assisted synthetic technique in 49–54% yields.

RESULTS AND DISCUSSION

3-(4-Ethoxycarbonylphenyl)indazole (**6**) were prepared by following our previous publication procedure via substitution, cyclodehydration, dehydrogenation, and transesterification (see Scheme 1).[7] 1-(*N*-Morpholino)cyclohexene (**1**) was reacted with methyl 4-(chlorocarbonyl)benzoate (**2**) to give the corresponding 4-[2-(4-ethoxycarbonylbenzoyl)cyclohexylidene]-morpholin-4-ium intermediate. After the further hydrolysis in acidic condition, 1,3-dicarbonyl compound **3** was obtained as white powder in 81% yield. The typically ring formation of pyrazole **4** involves cyclodehydration from the corresponding ketone *N*-acylhydrazine intermediate, preparing from dicarbonyl compound **3** with hydrazine in acidic aqueous solution.[7] Compound **4** was performed the dehydrogenation in the presence of catalytic amount of Pd/C and *trans*-decalin to give the corresponding product **5** in 83% yield. According to the ethyl carboxylates are more stable ester;[8] the transesterification has been carried out with *p*-toluenesulfonic acid in EtOH solution to afford 3-(4-ethoxycarbonylphenyl)indazole (**6**) in 90% yield.

In the benzylation studies, we treated 3-(4-ethoxycarbonylphenyl)indazoles (**6**) with various substituted benzyl chloride (benzyl, *o*-chlorobenzyl, *m*-chlorobenzyl, and *p*-chlorobenzyl chloride) in the presence of EtONa to provide the corresponding *N*-1-benzyl-3-(4-hydroxymethylphenyl)indazoles (**7a – 10a**) and *N*-2- benzyl-3-(4-hydroxymethylphenyl)indazoles (**7b – 10b**) products in 49–58% and 5–9% yields, respectively (see Table 1 and Scheme 2). By applying the Mitsunobu reaction procedure involving various substituted benzyl alcohol, 1,1-(azodicarbonyl)dipiperidine, and P(*n*-Bu)$_3$, the corresponding *N*-1 substituted products (**7a – 10a**) as a major component and *N*-2 substituted products (**7b – 10b**) as a minor component (see Table 1). Two methods of benzylation were obtained in similar results and the data was shown in Table 1. The microwave-assisted synthetic technique is applicable to benzylation reaction, only the *N*-2 corresponding products (**7b – 10b**) were isolated in low yields (24–27%) without detecting *N*-1 products. Most of residual compounds are the corresponding starting material **6**.

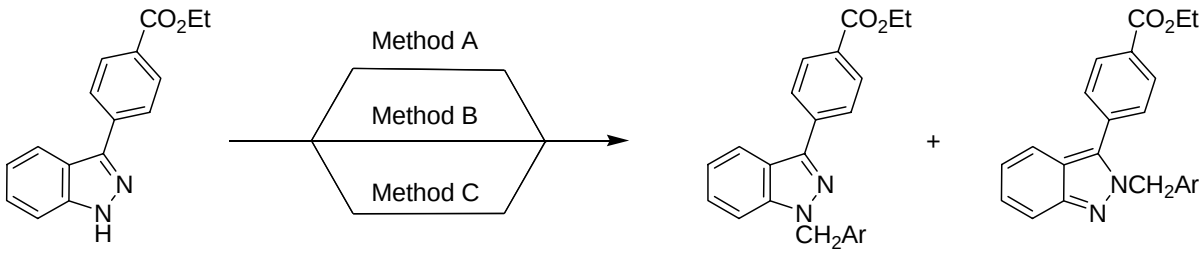


Scheme 1

Table 1. The results of the different benzylation methods

N-Ar	The directly substitution		The Mitsunobu reaction		The microwave-assisted synthetic technique	
	Product Yields (%)		Product Yields (%)		Product Yields (%)	
	***N*-1**	***N*-2**	***N*-1**	***N*-2**	***N*-1**	***N*-2**
Ph	54 (**7a**)	9 (**7b**)	50 (**7a**)	6 (**7b**)	_*a*	27 (**7b**)
o-ClPh	55 (**8a**)	8 (**8b**)	51 (**8a**)	7 (**8b**)	_*a*	24 (**8b**)
m-ClPh	49 (**9a**)	5 (**9b**)	50 (**9a**)	5 (**9b**)	_*a*	24 (**9b**)
p-ClPh	58 (**10a**)	8 (**10b**)	57 (**10a**)	7 (**10b**)	_*a*	26 (**10b**)

[a]non-detectable.



6

A: benzyl chloride/EtONa/EtOH
B: benzyl alcohol/1,1-(azodicarbonyl)-dipiperidine/P(*n*-Bu)$_3$
C: benzyl chloride, microwave

7a. Ar = Ph
8a. Ar = *o*-ClPh
9a. Ar = *m*-ClPh
10a. Ar = *p*-ClPh

7b. Ar = Ph
8b. Ar = *o*-ClPh
9b. Ar = *m*-ClPh
10b. Ar = *p*-ClPh

Scheme 2

To search for optimum condition and to establish reproduciblity for benzylation of 3-(4-ethoxycarbonylphenyl)indazole (**6**) by using microwave-assisted technique. Compound **6** was treated with benzyl chloride as model study in the different solvents, including *p*-dioxane, DMEU, DMF, DMSO, EtOH, THF, and toluene. We found that the use of *p*-dioxane gave the better result and *N*-2 substitutent **7b** was major product in 41% isolated yield. We applied this better condition to 3-(4-ethoxycarbonylphenyl)indazole (**6**) and various substituted benzyl chloride (benzyl, *o*-chlorobenzyl, *m*-chlorobenzyl, and *p*-chlorobenzyl chloride). The corresponding *N*-2 substituted indazoles (**8b – 10b**) were promoted as major products in 40–44% yields and low yields of *N*-1 substitutents **8a – 10a** were isolated (4–7%). Unfortunately, most of starting materials **6** was residue in benzylation precedure (45–51%, see Table 2). While the reaction time was prolonged to more than 4 h, the starting material also can not fully consume.

In addition to the solvent control experiments, we also carried out benzylation reactions by varying the base agents, including cesium carbonate, pyridine, tributylamine, trimethylamine, and a mixture of *p*-dioxane/triethylamine. A reliable procedure for the microwave-assisted benzylation reaction involved treatment of 3-(4-ethoxycarbonylphenyl)indazole **6** in neat with two equivalents of triethylamine under N_2 atmosphere. The desired *N*-2 substituted indazole **7b** was produced in 51% yield and 31% of *N*-1 substitutent **7b** was yielded. And about 13% of starting material **6** was residue.

By employing this conditions for benzylation of 3-(4-ethoxycarbonylphenyl)indazole (**6**) with various substituted benzyl chloride agents containing chloro group at ortho-, meta-, and para-positions, we were able to obtain the similar substitution results to give the corresponding *N*-2 substituted indazoles (**8b – 10b**) as major products in 49–54% yields and *N*-1 substitutents (8**a – 10a**) as minor products in 30–32% yields (see Table 2). Little amounts of the starting materials **6** were residue in the benzylation procedure (10–14%, see Table 2).

Table 2. The results of the benzylation by the microwave-assisted synthetic technique

N-Ar	Yields (%)[a]			Yields (%)[b]		
	***N*-1**	***N*-2**	**S.M. (6)**	***N*-1**	***N*-2**	**S.M. (6)**
Ph	4 (**7a**)	41 (**7b**)	50	31 (**7a**)	51 (**7b**)	13
o-ClPh	7 (**8a**)	44 (**8b**)	45	32 (**8a**)	54 (**8b**)	10
m-ClPh	4 (**9a**)	40 (**9b**)	51	30 (**9a**)	49 (**9b**)	14
p-ClPh	5 (**10a**)	42 (**10b**)	48	30 (**10a**)	52 (**10b**)	11

[a]*p*-dioxane was used as reaction solvent. [b]the reaction condition is neat with two equiv. of triethylamine.

In conclusion, three benzylation methods were investigated to improving *N*-2 substituted indazole products and diminishing the *N*-1 subsitutent products, involving the directly substitution, Mitsunobu reaction, and the microwave-assisted substitution. However, the microwave-assisted synthetic technique can be successfully promoted *N*-2-benzyl-3-(4-ethoxycarbonylphenyl)indazoles as the major products by using two equivalents of triethylamine in the neat condition.

EXPERIMENTAL

General. Methyl 4-(4,5,6,7-tetrahydro-1*H*-indazol-3-yl)benzoate (**4**) was synthesized according to literature procedures via substitution and cyclodehydration.[7] All chemicals were reagent Analytical thin-layer chromatography (TLC) was performed on precoated plates (silica gel 60 F-254), purchased from Merck Inc. Purification by gravity column chromatography was carried out by use of Merck Reagents Silica Gel 60 (particle size 0.063–0.200 mm, 70–230 mesh ASTM). Infrared (IR) spectra were measured on a Bomem Michelson Series FT-IR spectrometer. The wavenumbers reported are referenced to the polystyrene 1601 cm^{-1} absortion. Absorption intensities are recorded by the following abbreviations: s, strong; m, medium; w, weak. Proton NMR spectra were obtained on a Bruker (200 MHz) spectrometer by use of $CDCl_3$ and DMSO-d_6 as solvent. Carbon-13 NMR spectra were obtained on a Bruker (50 MHz) spectrometer by used of $CDCl_3$ as solvent. Carbon-13 chemical shifts are referenced to the center of the $CDCl_3$ triplet (δ 77.0 ppm). Multiplicities are recorded by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; *J*, coupling constant (Hz). Microwave irradiation instrument was purchase order from CEM Discover. The microwave irradiation condition was set in 100

W at 90 °C for 1 h. Elemental analyses were carried out on a Heraeus CHN–O RAPID element analyzer.

3-(4-Methoxycarbonylphenyl)indazole (5). To a solution of compound **4** (13.0 g, 50.0 mmole, 1.0 equiv), *trans*-decahydronaphthalene (*trans*-decalin) (160 mL) and 10 % Pd/C (2.71 g) were stirred and heated to reflux for 24 h. When the reaction was completed, the reaction mixture was concentrated to about 20 mL under reduced pressure. Petroleum ether (80 mL) was added into the residual solution while hot, and the mixture was well mixed. The resulting solution was precipitated upon cooling to give the corresponding product **5** as a light yellow solid in 83% isolated yield (10.4 g): ^{1}H NMR (DMSO-d_6, 200 MHz) δ 3.88 (3H, *s*, H-19), 7.20–7.28 (1H, *m*, H-8), 7.34–7.46 (1H, *m*, H-7), 7.62 (1H, *d*, *J* = 8.2 Hz, H-6), 8.08 (2H, *d*, *J* = 8.6 Hz, H-12, 14), 8.13 (1H, *d*, *J* = 9.6 Hz, H-9), 8.17 (2H, *d*, *J* = 8.6 Hz, H-11, 15), 13.48 (1H, *s*, H-1); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 52.36, 111.06, 120.35, 120.79, 121.78, 126.55, 126.86, 128.566, 130.05, 138.59, 141.89, 142.15, 166.30; IR (KBr) 3306 (b, NH), 1697 (C=O), 1609 (C=N) cm^{-1}; Anal. Calcd for $C_{15}H_{12}N_2O_2$; C: 71.42, H: 4.79, N: 11.10. Found: C: 71.40, H: 4.77, N: 11.11.

3-(4-Ethoxycarbonylphenyl)indazole (6). To a solution of compound **5** (0.94 g, 3.99 mmole, 1.0 equiv) and *p*-toluenesulfonic acid (0.52 g) in EtOH (100 mL) was stirred and heated to reflux for 2 h. When the transesterification was completed, the reaction mixture was concentrated under reduced pressure to afford 3-(4-ethoxycarbonylphenyl)indazole (**6**) in 90% yield: ^{1}H NMR (DMSO-d_6, 200 MHz) δ 1.33 (3H, *t*, *J* = 7.0 Hz, H-20), 4.32 (2H, *q*, *J* = 7.0 Hz, H-19), 7.20–7.27 (1H, *m*, H-8), 7.38–7.45 (1H, *m*, H-7), 7.62 (1H, *d*, *J* = 8.4 Hz, H-6), 8.08 (2H, *d*, *J* = 8.4 Hz, H-12, 14), 8.12 (1H, *d*, *J* = 9.2 Hz, H-9), 8.16 (2H, *d*, *J* = 8.4 Hz, H-11, 15), 13.47 (1H, *s*, H-1); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 14.41, 60.94, 111.05, 120.37, 120.78, 121.77, 126.53, 126.84, 128.86, 130.00, 138.53, 141.91, 142.21, 165.80; IR (KBr) 3306 (b, NH), 1697 (C=O), 1609 (C=N) cm^{-1}; Anal. Calcd for $C_{16}H_{14}N_2O_2$; C: 72.16, H: 5.30, N: 10.52. Found: C: 72.18, H: 5.29, N: 10.52.

Standard Procedure for Benzylation to Prepare *N*-1 -Benzyl-3-(4-ethoxycarbonylphenyl)indazoles (7a – 10a) and *N*-2-benzyl-3-(4-ethoxycarbonylphenyl)indazole derivatives (7b – 10b).

The Directed Substitution. To a solution of compound **6** (4.02 g, 15.1 mmole, 1.0 equiv), various substituted benzyl chloride (benzyl, *o*-chlorobenzyl, *m*-chlorobenzyl, and *p*-chlorobenzyl chloride, 10.0 equiv.), and EtONa (3.51 g, 52.0 mmole, 3.5 equiv) in EtOH (150 mL) was stirred at rt for 30 min. After the reaction was completed, the reaction mixture was concentrated under reduced pressure to remove EtOH. The residue was added with water (150 mL), and extracted with $CHCl_3$ (200 mL). The combined organic solutions were washed with water and saturated aqueous NaCl. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residual solution was purified by column chromatography on silica gel (CH_2Cl_2 as eluant) to give

N-1-benzyl-3-(4-hydroxymethylphenyl)indazoles (**7a – 10a**) and *N*-2- benzyl-3-(4-hydroxymethyl-phenyl)indazoles (**7b – 10b**) products in 49–58% and 5–9% yields.

The Mitsunobu Reaction Procedure. To a solution of compound **6** (4.01 g, 15.1 mmole, 1.0 equiv), various substituted benzyl alcohol (benzyl, *o*-chlorobenzyl, *m*-chlorobenzyl, and *p*-chlorobenzyl alcohol, 2.0 equiv), and 1,1-(azodicarbonyl)dipiperidine (7.49 g, 29.9 mmole, 2.0 equiv), and $(n\text{-Bu})_3P$ (7.3 mL, 30 mmole, 2.0 equiv) in toluene (50 mL) was stirred and heated at reflux for 16 h. After the reaction was completed, the reaction mixture was concentrated under reduced pressure to remove toluene. The residue was added with water (100 mL), and extracted with CH_2Cl_2 (150 mL). The combined organic solutions were washed with water and saturated aqueous NaCl. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residual solution was purified by column chromatography on silica gel (CH_2Cl_2 as eluant) to give *N*-1-benzyl-3-(4-hydroxymethylphenyl)indazoles (**7a – 10a**) and *N*-2-benzyl-3-(4-hydroxymethylphenyl)indazoles (**7b – 10b**) products in 50–57% and 5–7% yields.

The Microwave-assisted Synthesis Procedure. To a solution of compound **6** (0.48 g, 1.89 mmole, 1.0 equiv) and various substituted benzyl chloride (benzyl, *o*-chlorobenzyl, *m*-chlorobenzyl, and *p*-chlorobenzyl chloride, 1.0 equiv.) in *p*-dioxane (5 mL) or in neat condition with triethylamine (0.42 g, 3.81 mmole, 2.0 equiv) was heated in the Smith Synthesizer™ microwave at reflux for 1 h. After the reaction was completed, the reaction mixture was diluted with water (30 mL) and extracted with CH_2Cl_2 (50 mL). The combined organic solutions were washed with water and saturated aqueous NaCl. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residual solution was purified by column chromatography on silica gel (CH_2Cl_2 as eluant) to give *N*-2-benzyl-3-(4-hydroxymethylphenyl)indazoles (**7b – 10b**) as major products in 49–54% yields and *N*-1-benzyl-3-(4-hydroxymethylphenyl)indazoles (**7a – 10a**) in 30–32% yields.

***N*-1-Pheyl-3-(4-ethoxycarbonylphenyl)indazole (7a)**. ^{1}H NMR (DMSO-d_6, 200 MHz) δ 1.32 (3H, *t*, *J* = 7.1 Hz, H-27), 4.33 (2H, *q*, *J* = 7.1 Hz, H-26), 5.75 (2H, *s*, H-10), 7.22–7.30 (6H, *m*, H-8, 12, 13, 14, 15, 16), 7.44 (1H, *t*, *J* = 7.0 Hz, H-7), 7.78 (1H, *d*, *J* = 8.5 Hz, H-6), 8.06–8.10 (2H, *m*, H-19, 21), 8.12 (1H, *d*, *J* = 7.5 Hz, H-9), 8.15–8.18 (2H, *m*, H-18, 22); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 14.40, 52.33, 60.97, 110.77, 121.14, 121.30, 122.14, 126.85, 126.95 (C×2), 127.60 (C×2), 127.83, 128.82 (C×2), 129.03, 130.03 (C×2), 137.41, 137.91, 141.23, 141.71, 165.75; IR (KBr) 1721 (C=O), 1611 (C=N) cm^{-1}; Anal. Calcd for $C_{23}H_{20}N_2O_2$; C: 77.51, H: 5.66, N: 7.86. Found: C: 77.48, H: 5.68, N: 7.88.

***N*-2-Pheyl-3-(4-ethoxycarbonylphenyl)indazole (7b)**. ^{1}H NMR (DMSO-d_6, 200 MHz) δ 1.31 (3H, *t*, *J* = 7.1 Hz, H-27), 4.33 (2H, *q*, *J* = 7.1 Hz, H-26), 5.70 (2H, *s*, H-10), 6.98–7.04 (2H, *m*, H-12, 16), 7.09–7.14 (1H, *m*, H-8), 7.19–7.24 (3H, *m*, H-13, 14, 15), 7.27–7.34 (1H, *m*, H-7), 7.56 (1H, *d*, *J* = 8.4 Hz, H-9), 7.69 (3H, *d*, *J* = 8.3 Hz, H-6, 18, 22), 8.09 (2H, *d*, *J* = 8.3 Hz, H-19, 21); ^{13}C NMR (DMSO-d_6, 50 MHz)

δ 14.35, 54.39, 61.20, 117.51, 120.12, 121.19, 122.62, 126.52, 127.15 (C×2), 127.84, 128.78 (C×2), 129.84 (C×2), 130.07 (C×3), 133.75, 134.62, 137.04, 147.80, 165.48; IR (KBr) 1708 (C=O), 1607 (C=N) cm^{-1}; Anal. Calcd for $C_{23}H_{20}N_2O_2$; C: 77.51, H: 5.66, N: 7.86. Found: C: 77.49, H: 5.65, N: 7.87.

***N*-1-(2-Chlorobenzyl)-3-(4-ethoxycarbonylphenyl)indazole (8a)**. ^{1}H NMR (DMSO-d_6, 200 MHz) δ 1.32 (3H, *t*, *J* = 7.1 Hz, H-28), 4.32 (2H, *q*, *J* = 7.1 Hz, H-27), 5.82 (2H, *s*, H-10), 6.87 (1H, *dd*, *J* = 1.7, 7.6 Hz, H-14), 7.18–7.34 (3H, *m*, H-8, 15, 16), 7.42–7.51 (2H, *m*, H-7, 13), 7.74 (1H, *d*, *J* = 8.5 Hz, H-6), 8.04–8.18 (5H, *m*, H-9, 18, 19, 21, 22); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 14.41, 49.96, 60.98, 110.65, 121.16 (C×2), 122.27, 127.00 (C×3), 127.74, 129.11, 129.38, 129.72 (C×2), 130.02 (C×2), 132.23, 134.74, 137.73, 141.62, 142.16, 165.72; IR (KBr) 1711 (C=O), 1609 (C=N) cm^{-1}; Anal. Calcd for $C_{23}H_{19}ClN_2O_2$; C: 70.68, H: 4.90, N: 7.17. Found: C: 70.70, H: 4.89, N: 7.15.

***N*-2-(2-Chlorobenzyl)-3-(4-ethoxycarbonylphenyl)indazole (8b)**. ^{1}H NMR (DMSO-d_6, 200 MHz) δ 1.29 (3H, *t*, *J* = 7.0 Hz, H-28), 4.30 (2H, *q*, *J* = 7.0 Hz, H-27), 5.73 (2H, *s*, H-10), 6.86–6.90 (1H, *m*, H-14), 7.08–7.19 (1H, *m*, H-8), 7.20–7.25 (3H, *m*, H-13, 15, 16), 7.26–7.34 (1H, *m*, H-7), 7.54–7.66 (2H, *m*, H-6, 9), 7.69 (2H, *d*, *J* = 8.2 Hz, H-18, 22), 8.07 (2H, *d*, *J* = 8.2 Hz, H-19, 21); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 14.59, 52.41, 61.44, 117.78, 120.40, 121.19, 122.97, 126.88, 127.97, 129.65, 129.77, 130.03 (C×3), 130.19, 130.32 (C×2), 132.13, 133.90, 134.62, 135.39, 148.14, 165.70; IR (KBr) 1704 (C=O), 1611 (C=N) cm^{-1}; Anal. Calcd for $C_{23}H_{19}ClN_2O_2$; C: 70.68, H: 4.90, N: 7.17. Found: C: 70.66, H: 4.90, N: 7.16.

***N*-1-(3-Chlorobenzyl)-3-(4-ethoxycarbonylphenyl)indazole (9a)**. ^{1}H NMR (DMSO-d_6, 200 MHz) δ 1.33 (3H, *t*, *J* = 7.0 Hz, H-28), 4.33 (2H, *q*, *J* = 7.0 Hz, H-27), 5.78 (2H, *s*, H-10), 7.20–7.37 (5H, *m*, H-8, 12, 14, 15, 16), 7.44–7.52 (1H, *m*, H-7), 7.83 (1H, *d*, *J* = 8.4 Hz, H-6), 8.06–8.17 (5H, *m*, H-9, 18, 19, 21, 22); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 14.42, 51.52, 61.01, 110.71, 121.25 (C×2), 122.32, 126.27, 127.03 (C×3), 127.45, 127.86, 129.12, 130.07 (C×2), 130.83, 133.40, 137.75, 139.91, 141.28, 142.02, 165.74; IR (KBr) 1713 (C=O), 1609 (C=N) cm^{-1}; Anal. Calcd for $C_{23}H_{19}ClN_2O_2$; C: 70.68, H: 4.90, N: 7.17. Found: C: 70.71, H: 4.89, N: 7.16.

***N*-2-(3-Chlorobenzyl)-3-(4-ethoxycarbonylphenyl)indazole (9b)**. ^{1}H NMR (DMSO-d_6, 200 MHz) δ 1.28 (3H, *t*, *J* = 7.1 Hz, H-28), 4.30 (2H, *q*, *J* = 7.1 Hz, H-27), 5.69 (2H, *s*, H-10), 6.89–6.91 (1H, *m*, H-16), 7.07–7.11 (2H, *m*, H-8, 12), 7.22–7.28 (2H, *m*, H-14, 15), 7.28–7.29 (1H, *m*, H-7), 7.53 (1H, *d*, *J* = 8.4 Hz, H-9), 7.65 (3H, *d*, *J* = 8.3 Hz, H-6, 18, 22), 8.06 (2H, *d*, *J* = 8.3 Hz, H-19, 21); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 14.57, 53.93, 61.42, 117.76, 120.39, 121.38, 122.96, 126.11, 126.89, 127.38, 128.09, 130.08 (C×2), 130.34 (C×3), 130.92, 133.62, 133.77, 135.05, 139.61, 148.12, 165.69; IR (KBr) 1717 (C=O), 1611 (C=N) cm^{-1}; Anal. Calcd for $C_{23}H_{19}ClN_2O_2$; C: 70.68, H: 4.90, N: 7.17. Found: C: 70.70, H: 4.87, N: 7.19.

***N*-1-(4-Chlorobenzyl)-3-(4-ethoxycarbonylphenyl)indazole (10a)**. ^{1}H NMR (DMSO-d_6, 200 MHz) δ

1.33 (3H, *t*, *J* = 7.1 Hz, H-28), 4.33 (2H, *q*, *J* = 7.1 Hz, H-27), 5.76 (2H, *s*, H-10), 7.24–7.39 (5H, *m*, H-8, 12, 13, 15, 16), 7.43–7.50 (1H, *m*, H-7), 7.80 (1H, *d*, *J* = 8.4 Hz, H-6), 8.06–8.17 (5H, *m*, H-9, 18, 19, 21, 22); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 14.42, 51.51, 61.00, 110.72, 121.20, 121.28, 122.25, 126.99 (C×3), 128.84 (C×2), 129.08, 129.49 (C×2), 130.04 (C×2), 132.53, 136.43, 137.80, 141.22, 141.92, 165.74; IR (KBr) 1719 (C=O), 1611 (C=N) cm^{-1}; Anal. Calcd for $C_{23}H_{19}ClN_2O_2$; C: 70.68, H: 4.90, N: 7.17. Found: C: 70.70, H: 4.88, N: 7.18.

***N*-2-(4-Chlorobenzyl)-3-(4-ethoxycarbonylphenyl)indazole (10b)**. ^{1}H NMR (DMSO-d_6, 200 MHz) δ 1.28 (3H, *t*, *J* = 7.1 Hz, H-28), 4.30 (2H, *q*, *J* = 7.1 Hz, H-27), 5.66 (2H, *s*, H-10), 7.00 (2H, *d*, *J* = 8.0 Hz, H-12, 16), 7.07–7.11 (1H, *m*, H-8), 7.27 (2H, *d*, *J* = 8.0 Hz, H-13, 15), 7.29–7.30 (1H, *m*, H-7), 7.53 (1H, *d*, *J* = 7.5 Hz, H-9), 7.65 (3H, *d*, *J* = 8.0 Hz, H-6, 18, 22), 8.06 (2H, *d*, J = 8.0 Hz, H-19, 21); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 14.58, 53.91, 61.43, 117.74, 120.36, 121.41, 122.93, 126.85, 129.01 (C×2), 129.32 (C×2), 130.06 (C×2), 130.34 (C×3), 132.75, 133.82, 134.93, 136.23, 148.09, 165.70; IR (KBr) 1717 (C=O), 1611 (C=N) cm^{-1}; Anal. Calcd for $C_{23}H_{19}ClN_2O_2$; C: 70.68, H: 4.90, N: 7.17. Found: C: 70.71, H: 4.88, N: 7.19.

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