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# Convenient synthesis of pyrrolo[3,4-*g*]indazole

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ABSTRACT

The synthesis of a novel class of tetrahydropyrrolo[3,4-*g*]indazoles is reported, by annelation of the pyrazole ring on the isoindole moiety by means of 5-hydroxymethylene tetrahydroisoindole-4-ones key intermediates, with good regioselectivity. Dihydroderivatives were also obtained by oxidation with DDQ of the corresponding tetrahydropyrrolo[3,4-*g*]indazoles. The growth inhibitory effect was evaluated at the National Cancer Institute of Bethesda and some derivatives showed modest activity.



## 1. Introduction

Due to their wide range of pharmacological applications, pyrazoles and their benzocondensed analogues, indazoles, have been the focus of much synthetic purpose in the past decades.[1] Fused tricyclic systems containing the pyrazole moiety have recently emerged as an important class of compounds with enhanced inhibitory activity targeting a variety of protein kinases, being thus useful in the treatment of several cell proliferative disorders, such as cancer, inflammatory, and autoimmune diseases.

In particular, compounds **1**–**3**, bearing the pyrazole ring condensed to dihydrobenzothiophene,[2] dihydrobenzothiazole[3] or dihydroquinazoline[4] are representative examples of potent kinase inhibitors (Chart 1). Over the past decades we have devoted our efforts to the study of pyrrole-containing ring systems some of which showed very promising antitumor properties.[5–10] Recently, we have reported the synthesis of dihydroisoxazolo[5,4-*e*]indazoles of type **4** using pyrazolo α-enamino ketones as key synthons for the annelation of the isoxazole moiety.[11] Thus, in this paper we focus our attention on the synthesis of the tetrahydropyrrolo[3,4-*g*]indazole ring system **5**, as part of our ongoing project aimed at exploring the versatility of α-substituted ketones of the pyrrole or pyrrolo-fused series, which gave us the entry to tricyclic systems with antitumor and/or photosensitizing properties.[12–20] Our purpose, in the present work, is the validation of a simple and straightforward method to obtain pyrrolo[3,4-*g*]indazoles either as tetrahydro- and as dihydro-derivatives with a variety of substitution patterns at the pyrrole and at the pyrazole moieties. The title ring system is not much represented in the literature, and in fact pyrrolo[3,4-*g*]indazoles were a new ring system at the time we started our synthetic work. Only two papers appeared in 2011 as a study of the 1,3-dipolar cycloaddition of an unstabilized *N*-methylazomethine ylide to nitrosulfones. However, few derivatives were prepared generally in modest yields by the ring closure of a pyrroline system to an indazole moiety.[21,22] Our

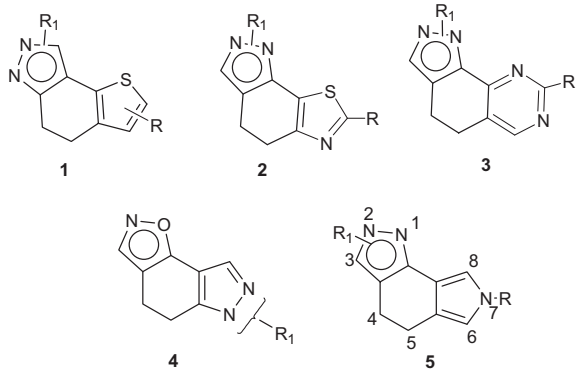


**Chart 1.** Structures of dihydrothieno[2,3-*e*]indazoles (**1**), dihydrothiazolo[4,5-*g*]indazoles (**2**), dihydropyrazolo[4,3-*h*]quinazolines (**3**), dihydroisoxazolo[5,4-*e*]indazoles (**4**), tetrahydropyrrolo[3,4-*g*]indazoles (**5**).

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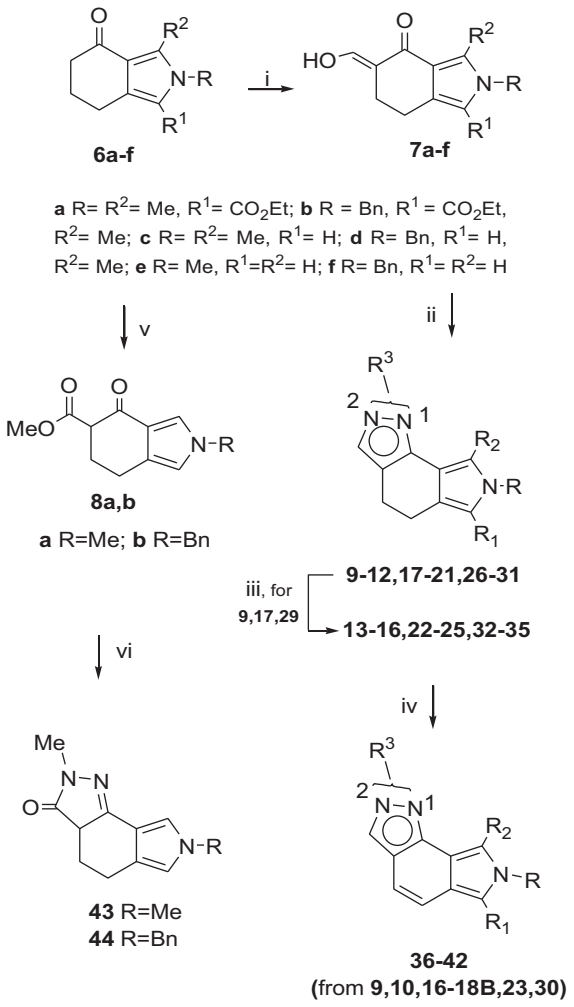
synthetic approach consists of the annelation of the pyrazole moiety on an isoindole system.

## 2. Results and discussion

Among the different methodologies used for the synthesis of the pyrazole framework, we became interested in the pyrazole ring closure on the isoindole moiety, by means of 5-hydroxymethyleneketones of type **7**. In fact, the reactivity of these type of intermediates is less investigated than that of enaminoketones, which are generally used as key intermediates for reaction with bidentate nucleophiles.[11–13,23–25]

Tetrahydroisoindole-4-ones **6**, suitable substrates for our purpose, were previously prepared by us decorated with various substituents on the pyrrole moiety.[26–29] Reaction of these latter with ethylformate and potassium *tert*-butoxide in benzene, under nitrogen atmosphere furnished in good yields hydroxymethyleneketones **7** (52–92%) (Scheme 1).[26] Spectroscopic data for compounds **7a**,**b** (see Supplementary data) are in agreement with a hydroxymethylene structure, supporting the ketone form of these compounds with respect to the possible enol form bearing a vicinal aldehydic group. In fact, the H NMR spectra show the signal at 14.41 (**7a**) and 14.66 (**7b**) ppm referring to the hydroxyl group coupling with the adjacent CH (7.49 ppm for **7a** and 7.76 for **7b**); in one case (**7b**) the coupling constant is also observable. Moreover, in the $^{13}C$ NMR spectrum, the typical signal of an aldehyde is missing. The synthesis of the desired indazoles was readily accomplished by boiling the proper hydroxymethyleneketone precursor in ethanol with hydrazine hydrate, or an alkyl- or aryl-substituted hydrazines.




**Scheme 1.** Synthesis of compounds **9**–**44** (see also Table 1). Reagents: (i) HCOOEt, *t*-BuOK, benzene, rt, 24 h, (52–92%); (ii); $NH_2NHR_3$, EtOH, 60 °C, 4 h, 20–86%; (iii) NaH, benzylchlorides, DMF, rt, 2–3 h, 12–98%; (iv) DDQ, benzene, rt, 4 h, 42–74%; (v) $(CH_3O)_2C{=}O$, *t*-BuOK, reflux, 1 h, 65–68%; (vi) $NH_2NHMe$, EtOH, reflux, 24 h, 38–45%.

In particular, when hydrazine hydrate was used as dinucleophile in the reaction of hydroxymethyleneketones bearing 1,3-disubstituted pyrroles (**7a**,**b**), tetrahydropyrrolo[3,4-*g*]indazoles **9** and **17** were obtained in 75% and 80% yields, respectively, as single products, with an N(1) substituted structure as supported by previous studies.[29–31] The same reaction carried out using other substrates gave mixed results. In fact, reaction of hydrazine hydrate with hydroxymethyleneketones **7c**,**e**, bearing a methyl substituent at the pyrrole nitrogen failed, giving a very complex mixture, from which it was not possible to isolate the corresponding indazole derivatives; the *N*-benzyl derivatives of the same series **7d**,**f** furnished compounds **27** and **29** in 68% and 80% yields, respectively, as single NH substituted isomers.

Reactions between hydroxymethyleneketones and alkyl-substituted hydrazines, could conceivably give a mixture of N(1)- and N(2)-alkylsubstituted pyrazoles. Since the substituted nitrogen in an alkylmonosubstituted hydrazine is the more nucleophilic of the two, we expected to obtain a mixture of the N(1)- and N(2)-substituted regioisomers with at least a preponderance of the N(2)-substituted one. Among the alkyl-substituted hydrazines, we investigated the reactivity toward methyl- and benzyl-hydrazines. In particular, from the reaction of **7b** with methylhydrazine, the corresponding ethyl tetrahydropyrrolo[3,4-*g*]indazole-6-carboxylate **18** was isolated, as a mixture of the N(1)- and N(2)-regioisomers **18A** (22%) and **18B** (70%).

In the cases of **7a**,**c**,**d**,**f** reacting with methylhydrazine a single indazole derivative, namely **10** (ethyl 2,7,8-trimethyl-2,4,5,7-tetrahydropyrrolo[3,4-*g*]indazole-6-carboxylate, 73%), **26** (2,7,8-trimethyl-2,4,5,7-tetrahydropyrrolo[3,4-*g*]indazole, 40%), **28** (7-benzyl-2,8-dimethyl-2,4,5,7-tetrahydropyrrolo[3,4-*g*]indazole, 45%), **30** (7-benzyl-2-methyl-2,4,5,7-tetrahydropyrrolo[3,4-*g*]indazole, 70%) corresponding to the N(2) substituted isomers were, respectively, isolated as expected. The hydroxymethyleneketone **7e**, bearing a methyl substituent at the pyrrole nitrogen, once again reacted with methylhydrazine furnishing a very complex mixture, from which it was not possible to isolate the corresponding indazole derivative as a pure compound. The modest yield of **26** and **28** (from **7c** and **7d**) and the unsuccessful ring closure of a hydroxymethyleneketone bearing a methyl group at the pyrrole moiety **7e**, induced us not to carry on further studies on these substrates (Table 1).

Reaction of **7a** with benzylhydrazine furnished in good yields the desired tetrahydropyrrolo[3,4-*g*]indazole derivative **11** (72%) as a single N(2) regioisomer, whereas the *N*-benzyl hydroxymethyleneketone **7b** furnished **19** as a mixture of the N(1)- and N(2)-substituted tetrahydroindazoles **19A** and **19B** in 20 and 72% yields, with a preponderance of the N(2) regioisomer as expected. Moreover, reaction of **7f** gave **31** as a single N(2) derivative (70%).

Considering that among the hydroxymethyleneketones, **7b** was the only one, which produced the two regioisomers in reactions with alkyl hydrazines, we investigated its reactivity toward phenylhydrazine to further confirm the previous assigned structures. In this case, we expected to obtain just the N(1)regioisomer. In fact, the experimental verification of this result can be found in the literature, in which it is demonstrated that, thanks to the higher nucleophilicity of the nitrogen atom β to the phenyl group of phenylhydrazine, a single N(1)-substituted pyrazole derivative is generally obtained.[29–31]

In accordance with this expectation, we were able to isolate from the above mentioned reaction of **7b** with phenylhydrazine,

**Table 1**
Tetrahydropyrrolo[3,4-*g*]indazoles **9**–**35** and dihydropyrrolo[3,4-*g*]indazoles **36**–**42**

| | R | $R^1$ | $R^2$ | $R^3$ | Yields (%) |
|---|---|---|---|---|---|
| **9** | Me | $CO_2Et$ | Me | 1-H | 75 |
| **10** | Me | $CO_2Et$ | Me | 2-Me | 73 |
| **11** | Me | $CO_2Et$ | Me | 2-Bn | 72 |
| **12** | Me | $CO_2Et$ | Me | 1-(4-OMe–$C_6H_4$) | 86 |
| **13** | Me | $CO_2Et$ | Me | 1-(4-OMe–Bn) | 96 |
| **14** | Me | $CO_2Et$ | Me | 1-(4-Cl–Bn) | 90 |
| **15** | Me | $CO_2Et$ | Me | 1-(3-Cl-Bn) | 98 |
| **16** | Me | $CO_2Et$ | Me | 1-(2,4-diCl–Bn) | 92 |
| **17** | Bn | $CO_2Et$ | Me | 1-H | 80 |
| **18A** | Bn | $CO_2Et$ | Me | 1-Me | 22 |
| **18B** | Bn | $CO_2Et$ | Me | 2-Me | 70 |
| **19A** | Bn | $CO_2Et$ | Me | 1-Bn | 20 |
| **19B** | Bn | $CO_2Et$ | Me | 2-Bn | 72 |
| **20** | Bn | $CO_2Et$ | Me | 1-$C_6H_5$ | 68 |
| **21** | Bn | $CO_2Et$ | Me | 1-(4-OMe–$C_6H_4$) | 80 |
| **22** | Bn | $CO_2Et$ | Me | 1-(4-OMe–Bn) | 88 |
| **23** | Bn | $CO_2Et$ | Me | 1-(4-Cl–Bn) | 84 |
| **24** | Bn | $CO_2Et$ | Me | 1-(3-Cl–Bn) | 86 |
| **25** | Bn | $CO_2Et$ | Me | 1-(2,4-diCl–Bn) | 82 |
| **26** | Me | H | Me | 2-Me | 40 |
| **27** | Bn | H | Me | 1-H | 68 |
| **28** | Bn | H | Me | 2-Me | 45 |
| **29** | Bn | H | H | 1-H | 80 |
| **30** | Bn | H | H | 2-Me | 70 |
| **31** | Bn | H | H | 2-Bn | 70 |
| **32A** | Bn | H | H | 1-(4-OMe–Bn) | 70 |
| **32B** | Bn | H | H | 2-(4-OMe–Bn) | 15 |
| **33A** | Bn | H | H | 1-(4-Cl–Bn) | 73 |
| **33B** | Bn | H | H | 2-(4-Cl–Bn) | 21 |
| **34A** | Bn | H | H | 1-(3-Cl–Bn) | 68 |
| **34B** | Bn | H | H | 2-(3-Cl–Bn) | 12 |
| **35A** | Bn | H | H | 1-(2,4-diCl–Bn) | 65 |
| **35B** | Bn | H | H | 2-(2,4-diCl–Bn) | 18 |
| **36** | Me | $CO_2Et$ | Me | 1-H | 50 |
| **37** | Me | $CO_2Et$ | Me | 2-Me | 54 |
| **38** | Me | $CO_2Et$ | Me | 1-(2,4-diCl–Bn) | 74 |
| **39** | Bn | $CO_2Et$ | Me | 1-H | 54 |
| **40** | Bn | $CO_2Et$ | Me | 2-Me | 72 |
| **41** | Bn | $CO_2Et$ | Me | 1-(4-Cl–Bn) | 60 |
| **42** | Bn | H | H | 2-Me | 42 |
| **43** | Me | H | H | — | 38 |
| **44** | Bn | H | H | — | 45 |

ethyl 7-benzyl-8-methyl-1-phenyl-1,4,5,7-tetrahydropyrrolo[3,4-*g*]indazole-6-carboxylate (**20**) in 68% yield.

In fact, the $^1$H NMR spectrum in $CDCl_3$ solution of **20** shows the signal for the H-3 proton at 7.59 ppm, which is in a typical range (7.45–7.59 ppm) of an N(1) substitution in this solvent for tetrahydropyrrolo[3,4-*g*]indazoles, whereas the same signal is generally found at higher field for an N(2) substitution (7.10–7.36 ppm).

Additionally **7a**,**b** were reacted with 4-methoxyphenylhydrazine furnishing the tetrahydroindazoles **12** and **21** in 86% and 80%, respectively, maintaining an N(1) structure confirmed by the slight variation of the H-3 chemical shift (compare **20** with **21**), attributable to the effect of the methoxy substituent at the phenyl ring.

Moreover, selected derivatives (**9**,**17** and **29**) bearing a free NH at the pyrazole moiety were subjected to alkylation with several benzylchlorides in anhydrous dimethylformamide in the presence of sodium hydride as base.

The *N*-methyl substituted derivative, **9** reacted with 4-methoxy-, 4-chloro-, 3-chloro-, and 2,4-dichloro-benzychlorides furnishing the corresponding tetrahydroindazoles in excellent yields **13** (96%), **14** (90%), **15** (98%), and **16** (92%) as exclusive products with an N(1) structure.

On the contrary, from the reaction of the *N*-benzyl derivative **17** with 4-methoxy- and 3-chloro-benzylchlorides, ethyl 7-benzyl-1-(4-methoxybenzyl)-8-methyl-1,4,5,7-tetrahydro pyrrolo[3,4-*g*]indazole-6-carboxylate **22** (88%), and ethyl 7-benzyl-1-(3-chlorobenzyl)-8-dimethyl-1,4,5,7-tetrahydro pyrrolo[3,4-*g*]indazole-6-carboxylate **24** (86%) were still isolated in very good yields as the main component of the reaction mixtures, despite TLC monitoring indicating the presence of traces of a secondary product, suggesting that the preferred site of alkylation was at the N(1). However, NMR studies indicated that the N(2) regioisomers, which were never isolated as pure compounds, were also formed in traces. A similar behavior was observed in the reaction of **17** with 4-chloro- and 2,4-dichlorobenzychlorides, giving the corresponding tetrahydroindazoles mainly as N(1)regioisomers **23** and **25** in 84% and 82%, respectively.

When **29**, bearing a benzyl substituent at the pyrrole nitrogen, was reacted with 4-methoxy-, 4-chloro-, 3-chloro-, and 2,4-dichloro-benzychlorides, tetrahydropyrrolo[3,4-*g*]indazoles were obtained as a mixture of the N(1) regioisomer **32A**–**35A** (65–73%), as the major component and the N(2)ones **32B**–**35B** (12–21%).

From an analysis of the results obtained, it can be observed that the *N*-benzyl substitution at the pyrrole nitrogen, in many cases, orients two possible ring closures yielding a mixture of N(1) and N(2) regioisomers. Moreover, for what concerns the alkylation reactions of the pyrazole moiety, a different behavior was observed depending on the substituent at the pyrrole nitrogen, influenced also by the substituents on the adjacent carbon atoms. The *N*-benzylsubstituted derivatives (**17**,**29**) produced two regioisomers always in favor of the N(1) substitution, indicating a tautomeric equilibrium in dimethylformamide between the two forms at variance of the ethyl 7,8-dimethyl-1,4,5,7-tetrahydropyrrolo[3,4-*g*]indazole-6-carboxylate **9**, which produced single products.

Incorporation of the carbonyl functionality into the heterocyclic system was also accomplished, through the preparation of pyrazolones **43** and **44.** Thus, the ketoesters **8a**,**b** (65–68 %) were prepared by boiling the corresponding tetrahydroisoindole-4-ones **7e** and **7f** in dimethylcarbonate in the presence of potassium *tert*-butoxide. Cyclization with methylhydrazine proceeded in moderate yields furnishing **43** (38%) and **44** (45%). Tetrahydropyrrolo[3,4-*g*]indazoles **9**–**17**, **18B**, **19B**, **29**–**31**, **32A**–**35A**, selected in terms of best yields when the two regioisomeric structures were available, were subjected to dehydrogenation to dihydropyrrolo[3,4-*g*]indazole by treatment with dichlorodicyanobenzoquinone (DDQ) in boiling benzene. Unfortunately only few aromatic compounds **36**–**42** in yields from modest to good (42–74%), could be isolated from the complex reaction mixtures, maintaining the regioisomeric structure of the starting tetrahydropyrroloindazoles.

Biological screenings on selected derivatives were performed at the National Cancer Institute (Bethesda, MD), at one dose concentration ($10^{-5}$ M), for the in vitro disease-oriented antitumor screenings against a panel of about 60 human tumor cell lines.[32] Among all of the derivatives, three tetrahydropyrrolo[3,4-*g*]indazoles **9**, **13** (of the 8-methyl-6-carboxylate series) and **27** (of the 7-benzyl-8-methyl series) showed modest activity. In particular, compounds **9**, **13** exhibited selectivity against the HOP-92 cell line of the non-small cell lung cancer with a growth inhibitory percentage of 79 and 88, respectively, whereas **27** showed selectivity against the MDA-MB-435 cell line of the melanoma sub-panel with a growth inhibitory percentage of 73. Among the dihydroindazole derivatives only compound **39** of the 8-methyl-6-carboxylate series showed selectivity against the HOP-92 cell line of the non-small cell lung cancer with growth inhibitory percentage of 82.

## 3. Conclusions

In conclusion, we have established a new efficient and versatile method for the synthesis of the tetrahydropyrrolo[3,4-*g*]indazole ring system, by addition of substituted hydrazines to 5-hydroxymethyleneketones. This kind of reactivity was never

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explored before in the isoindole series, and allowed the preparation of several derivatives of the ring system in very good yields. Moreover, our synthetic approach consisting of the annelation of the pyrazole ring to the tetrahydroisoindole moiety demonstrated a good regioselectivity. The antiproliferative activity shown in particular by four derivatives, although modest, makes this class of compounds interesting for further studies directed toward the synthesis of new compounds with an improved growth inhibitory effect.

## 4. Experimental section

### 4.1. General

All melting points were taken on a Buchi-Tottoli capillary apparatus and were uncorrected; IR spectra were determined in $CHBr_3$, with a Jasco FT/IR 5300 spectrophotometer; $^1H$ and $^{13}C$ NMR spectra were measured in DMSO-$d_6$ or $CDCl_3$ solutions, at 200 and 50.3 MHz, respectively, using a Bruker Avance II series 200 MHz spectrometer. Column chromatography was performed with Merck silica gel 230–400 mesh ASTM or with a SEPACORE chromatography apparatus BÜCHI. Elemental analyses (C, H, N) were within ±0.4% of the theoretical values and were performed with a VARIO EL III elemental analyzer. Compounds **7c**–**f** were prepared as previously described.[26]

### 4.2. General procedure for the preparation of 5-(hydroxyl methylidene)-2,5,6,7-tetrahydro-4*H*-isoindol-4-one (7a,b)

To a suspension of *t*-BuOK (36 mmol) in dry toluene (30 mL), a solution of **6a**,**b** (12 mmol) in dry toluene (40 mL) was added dropwise under $N_2$ at 0 °C. After 3 h stirring at room temperature the reaction was cooled at 0 °C and a solution of ethylformate (36 mmol) in toluene (20 mL) was added and the mixture was kept stirring at room temperature for 24 h, then the solvent was removed under vacuum. The residue was dissolved in water and the solution was washed with diethyl ether. The aqueous solution was then acidified with 6 M HCl and extracted with dichloromethane. The organic extracts were dried ($Na_2SO_4$) and evaporated under reduced pressure. The residue was purified by chromatography using dichloromethane/ethyl acetate (95:5) as eluent.

*4.2.1. Ethyl 5-(hydroxymethylidene)-2,3-dimethyl-4-oxo-4,5,6,7-tetrahydro-2H-isoindole-1-carboxylate (**7a**).* This compound was obtained from **6a**. White solid; $R_f$=0.66 ($CH_2Cl_2$); yield: 63%; mp: 63–65 °C; %; IR $cm^{-1}$: 2976 (OH), 1689 (CO), 1635 (CO); $^1H$ NMR ($CDCl_3$): δ 1.37 (3H, t, *J*=7.3 Hz, $CH_3$), 2.45 (2H, t, *J*=6.3 Hz, $CH_2$), 2.59 (3H, s, $CH_3$), 2.94 (2H, t, *J*=6.3 Hz, $CH_2$), 3.81 (3H, s, $CH_3$), 4.30 (2H, q, *J*=7.3 Hz, $CH_2$), 7.42 (1H, s, CH), 14.34 (1H, br s, OH); $^{13}C$ NMR ($CDCl_3$): δ 11.3 (q), 14.3 (q), 22.6 (t), 25.0 (t), 32.5 (q), 59.8 (t), 109.1 (s), 117.3 (s), 134.4 (s), 140.0 (s), 161.5 (s), 164.2 (d), 187.6 (s), 200.1 (s). Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.60; H, 6.78; N, 5.05.

*4.2.2. Ethyl 2-benzyl-5-(hydroxymethylidene)-3-methyl-4-oxo-4,5,6,7-tetrahydro-2H-isoindole-1-carboxylate (**7b**).* This compound was obtained from **6b**. White solid; $R_f$=0.64 ($CH_2Cl_2$); yield: 80%; mp: 78–79 °C; %; IR $cm^{-1}$: 2981 (OH), 1691 (CO), 1635 (CO); $^1H$ NMR ($CDCl_3$) δ 1.58 (3H, t, *J*=7.2 Hz, $CH_3$), 2.77 (2H, t, *J*=6.9 Hz, $CH_2$), 2.85 (3H, s, $CH_3$), 3.31 (2H, t, *J*=6.9 Hz, $CH_2$), 4.52 (2H, q, *J*=7.2 Hz, $CH_2$), 5.92 (2H, s, $CH_2$), 7.24 (2H, d, *J*=7.2 Hz, H-2′ and H-6′), 7.51–7.62 (3H, m, H-3′, H-4′ and H-5′), 7.76 (1H, s, CH), 14.66 (1H, br s, OH); $^{13}C$ NMR ($CDCl_3$): δ 11.5 (q), 14.2 (q), 22.8 (t), 25.0 (t), 48.2 (t), 60.0 (t), 109.3 (s), 117.7 (s), 125.7 (2×d), 127.2 (d), 128.7 (2×d), 134.9 (s), 137.1 (s), 140.4 (s), 161.3 (s), 164.8 (d), 187.7 (s), 201.2 (s). Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.65; H, 6.52; N, 4.35.

### 4.3. General procedure for the preparation of methyl-4-oxo-4,5,6,7-tetrahydro-2*H*-isoindole-5-carboxylates (8a,b)

Potassium *tert*-butoxide (2.69 g, 0.024 mol) was added to dry dimethylcarbonate (10.11 mL, 0.12 mol) followed by the relevant tetrahydroindol-4-one **6e**,**f** (0.006 mol). The mixture was boiled for 1 h with stirring under nitrogen atmosphere and evaporated under reduced pressure. Ice/water was added to the crude residue, made slightly acidic with 6 M HCl, and extracted with dichloromethane. Removing the organic solvent a crude residue formed, which was recrystallized from ethanol or purified by chromatography column.

*4.3.1. Methyl 2-methyl-4-oxo-4,5,6,7-tetrahydro-2H-isoindole-5-carboxylate (**8a**).* This product was obtained from **6e**. Yellow oil; $R_f$=0.54 ($CH_2Cl_2$); yield 68%; IR $cm^{-1}$: 1780 (CO), 1661 (CO). $^1H$ NMR ($CDCl_3$): δ 2.23–2.85 (4H, m, 2× $CH_2$), 3.44–3.45 (1H, m, CH), 3.65 (3H, s, $CH_3$), 3.75 (3H, s, $CH_3$), 6.37 (1H, s, H-1), 7.21 (1H, s, H-3). $^{13}C$ NMR ($CDCl_3$): δ 20.2 (t), 28.9 (t), 37.1 (q), 52.5 (q), 54.9 (d), 118.5 (d), 121.0 (s), 124.3 (d), 127.0 (s), 171.9 (s), 189.6 (s). Anal. Calcd for $C_{11}H_{13}NO_3$ (207.23): C, 63.76; H, 6.32; N, 6.76. Found: C, 63.44; H, 6.04; N, 7.02.

*4.3.2. Methyl 2-benzyl-4-oxo-4,5,6,7-tetrahydro-2H-isoindole-5-carboxylate (**8b**).* This product was obtained from **6f**. White solid; $R_f$=0.52 ($CH_2Cl_2$); mp 228–229 °C; yield 65%; IR $cm^{-1}$: 1782 (CO), 1682 (CO). $^1H$ NMR ($CDCl_3$): δ 2.21–2.78 (4H, m, 2× $CH_2$), 3.44–3.45 (1H, m, CH), 3.74 (3H, s, $CH_3$), 5.00 (2H, s, $CH_2$), 6.41 (1H, s, H-1), 7.14–7.31 (6H, m, Ar and H-3). $^{13}C$ NMR ($CDCl_3$): δ 20.3 (t), 28.9 (t), 52.5 (q), 54.4 (t), 55.0 (d), 117.7 (d), 121.1 (s), 123.8 (d), 127.1 (s), 127.9 (2×d), 128.7 (d), 129.3 (2×d), 136.5 (s), 171.8 (s), 189.8 (s). Anal. Calcd for $C_{17}H_{17}NO_3$ (283.32): C, 72.07; H, 6.05; N, 4.94. Found: C, 72.45; H, 5.88; N, 5.10.

### 4.4. General procedure for the tetrahydropyrrolo[3,4-*g*]indazoles (9–12, 17–21, 26–31)

To a solution of the relevant hydroxymethyl derivative **7** (0.03 mol) in anhydrous methanol (100 mL), the proper hydrazine (0.1 mol) was added dropwise at room temperature and under nitrogen atmosphere. The mixture was heated at 60 °C for 4 h and, upon cooling, evaporated to dryness. To the crude residue water was added and the insoluble material was filtered off, dried, and purified by chromatography column, to afford the desired compounds.

*4.4.1. Ethyl 7,8-dimethyl-1,4,5,7-tetrahydropyrrolo[3,4-g]indazole-6-carboxylate (**9**).* This product was obtained from 7a. Yellow solid; $R_f$=0.39 ($CH_2Cl_2$/EtOAc 70:30); mp 105–106 °C; yield: 75%; IR $cm^{-1}$: 3210 (NH), 1685 (CO). $^1H$ NMR (DMSO-$d_6$): δ 1.29 (3H, t, *J*=7.2 Hz, $CH_3$), 2.49 (3H, s, $CH_3$), 2.65 (2H, t, *J*=7.0 Hz, $CH_2$), 2.94 (2H, t, *J*=7.0 Hz, $CH_2$), 3.75 (3H, s, $CH_3$), 4.21 (2H, q, *J*=7.2 Hz, $CH_2$), 7.44 (1H, s, H-3), 12.28 (1H, s, NH). $^{13}C$ NMR (DMSO-$d_6$): δ 11.1 (q), 14.4 (q), 19.4 (t), 22.3 (t), 32.3 (q), 59.1 (t), 113.0 (s), 117.1 (s), 118.9 (s), 124.3 (s), 128.3 (s), 130.6 (d), 144.4 (s), 161.2 (s). Anal. Calcd for $C_{14}H_{17}N_3O_2$ (259.31): C, 64.85; H, 6.61; N, 16.20. Found: C, 64.64; H, 6.78; N, 16.01.

*4.4.2. Ethyl 2,7,8-trimethyl-2,4,5,7-tetrahydropyrrolo[3,4-g]indazole-6-carboxylate (**10**).* This product was obtained from **7a**. White solid; $R_f$=0.36 ($CH_2Cl_2$/EtOAc 70:30); mp 104–105 °C; yield: 73%; IR $cm^{-1}$: 1686 (CO). $^1H$ NMR ($CDCl_3$): δ 1.34 (3H, t, *J*=7.0 Hz, $CH_3$), 2.47 (3H, s, $CH_3$), 2.59 (2H, t, *J*=6.8 Hz, $CH_2$), 2.93 (2H, t, *J*=6.8 Hz, $CH_2$), 3.86 (3H, s, $CH_3$), 3.99 (3H, s, $CH_3$), 4.31 (2H, q, *J*=7.0 Hz, $CH_2$), 7.30 (1H, s, H-3). $^{13}C$ NMR ($CDCl_3$): δ 13.5 (q), 14.4 (q), 21.1 (t), 23.2 (t),

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32.7 (q), 39.6 (q), 59.7 (t), 111.7 (s), 116.6 (s), 128.8 (d), 130.9 (s), 136.0 (s), 136.1 (s), 136.3 (s), 161.9 (s). Anal. Calcd for $C_{15}H_{19}N_3O_2$ (273.33): C, 65.91; H, 7.01; N, 15.37. Found: C, 65.72; H, 7.38; N, 15.18.

*4.4.3. Ethyl 2-benzyl-7,8-dimethyl-2,4,5,7-tetrahydropyrrolo[3,4-g] indazole-6-carboxylate (**11**).* This product was obtained from **7a**. White solid; $R_f$=0.66 ($CH_2Cl_2$/EtOAc 95:5); mp 127–128 °C; yield: 72%; IR $cm^{-1}$: 1682 (CO). $^1H$ NMR ($CDCl_3$): $\delta$ 1.37 (3H, t, $J$=7.1 Hz, $CH_3$), 2.58 (3H, s, $CH_3$), 2.69 (2H, t, $J$=7.2 Hz, $CH_2$), 3.05 (2H, t, $J$=7.2 Hz, $CH_2$), 3.82 (3H, s, $CH_3$), 4.29 (2H, q, $J$=7.1 Hz, $CH_2$), 5.28 (2H, s, $CH_2$), 7.10 (1H, s, H-3), 7.22–7.38 (5H, m, Ar). $^{13}C$ NMR ($CDCl_3$): 11.7 (q), 14.5 (q), 20.0 (t), 22.5 (t), 32.6 (q), 55.7 (t), 59.5 (t), 113.4 (s), 115.7 (s), 117.8 (s), 125.6 (d), 127.6 (2×d), 127.7 (d), 128.6 (2×d), 129.5 (s), 131.2 (s), 137.4 (s), 145.8 (s), 162.2 (s). Anal. Calcd for $C_{21}H_{23}N_3O_2$ (349.43): C, 72.18; H, 6.63; N, 12.03. Found: C, 71.87; H, 6.85; N, 11.78.

*4.4.4. Ethyl 1-(4-methoxyphenyl)-7,8-dimethyl-1,4,5,7-tetrahydropyrrolo[3,4-g]indazole-6-carboxylate (**12**).* This product was obtained from **7a**. Brown solid; $R_f$=0.50 ($CH_2Cl_2$/EtOAc 95:5); mp 119–120 °C; yield: 86%; IR $cm^{-1}$: 1685 (CO). $^1H$ NMR (DMSO-$d_6$): $\delta$ 1.30 (3H, t, $J$=7.0 Hz, $CH_3$), 1.51 (3H, s, $CH_3$), 2.58 (2H, t, $J$=6.4 Hz, $CH_2$), 2.96 (2H, t, $J$=6.4 Hz, $CH_2$), 3.65 (3H, s, $CH_3$), 3.81 (3H, s, $CH_3$), 4.24 (2H, q, $J$=7.0 Hz, $CH_2$), 7.04 (2H, d, $J$=8.8 Hz, H-3′ and H-5′), 7.34 (2H, d, $J$=8.8 Hz, H-2′ and H-6′), 7.51 (1H, s, H-3). $^{13}C$ NMR (DMSO-$d_6$): $\delta$ 11.9 (q), 14.3 (q), 20.5 (t), 20.6 (t), 32.4 (q), 55.4 (q), 59.4 (t), 110.6 (s), 114.2 (2×d), 116.9 (s), 117.9 (s), 125.7 (2×d), 129.5 (s), 130.0 (s), 134.8 (s), 135.4 (s), 137.5 (d), 158.3 (s), 161.0 (s). Anal. Calcd for $C_{21}H_{23}N_3O_3$ (365.43): C, 69.02; H, 6.34; N, 11.50. Found: C, 69.32; H, 6.02; N, 11.75.

*4.4.5. Ethyl 7-benzyl-8-methyl-1,4,5,7-tetrahydropyrrolo[3,4-g]indazole-6-carboxylate (**17**).* This product was obtained from **7b**. Brown solid; $R_f$=0.46 ($CH_2Cl_2$/EtOAc 70:30); mp 181–182 °C; yield: 80%; IR $cm^{-1}$: 3210 (NH), 1683 (CO). $^1H$ NMR (DMSO-$d_6$): $\delta$ 1.22 (3H, t, $J$=7.3 Hz, $CH_3$), 2.44 (3H, s, $CH_3$), 2.71 (2H, t, $J$=6.9 Hz, $CH_2$), 3.03 (2H, t, $J$=6.9 Hz, $CH_2$), 4.16 (2H, q, $J$=7.3 Hz, $CH_2$), 5.61 (2H, s, $CH_2$), 6.94 (2H, d, $J$=6.9 Hz, H-2′ and H-6′), 7.20–7.30 (3H, m, H-3′, H-4′ and H-5′), 7.44 (1H, s, H-3), 12.38 (1H, s, NH). $^{13}C$ NMR (DMSO-$d_6$): $\delta$ 11.1 (q), 14.2 (q), 19.4 (t), 22.4 (t), 47.4 (t), 59.2 (t), 113.2 (s), 117.0 (s), 118.1 (s), 124.7 (s), 125.6 (2×d), 126.7 (d), 128.4 (s), 128.5 (2×d), 129.2 (s), 130.6 (d), 138.8 (s), 161.2 (s). Anal. Calcd for $C_{20}H_{21}N_3O_2$ (335.40): C, 71.62; H, 6.31; N, 12.53. Found: C, 71.90; H, 6.03; N, 12.75.

*4.4.6. Ethyl 7-benzyl-1,8-dimethyl-1,4,5,7-tetrahydropyrrolo[3,4-g] indazole-6-carboxylate (**18A**).* This product was obtained from **7b**. Yellow oil; $R_f$=0.67 ($CH_2Cl_2$/EtOAc 95:5); yield: 22%; IR $cm^{-1}$: 1686 (CO). $^1H$ NMR ($CDCl_3$): $\delta$ 1.29 (3H, t, $J$=6.9 Hz, $CH_3$), 2.39 (3H, s, $CH_3$), 2.64 (2H, t, $J$=6.9 Hz, $CH_2$), 3.00 (2H, t, $J$=6.9 Hz, $CH_2$), 3.96 (3H, s, $CH_3$), 4.93 (2H, q, $J$=6.9 Hz, $CH_2$), 5.64 (2H, s, $CH_2$), 6.94 (2H, d, $J$=6.9 Hz, H-2′ and H-6′), 7.19–7.31 (3H, m, H-3′, H-4′ and H-5′), 7.45 (1H, s, H-3). $^{13}C$ NMR ($CDCl_3$): $\delta$ 13.3 (q), 14.1 (q), 21.0 (t), 23.4 (t), 39.6 (q), 48.2 (t), 59.7 (t), 112.3 (s), 116.7 (s), 118.5 (s), 125.5 (2×d), 126.8 (d), 128.5 (2×d), 129.0 (s), 131.5 (s), 136.0 (d), 136.3 (s), 138.2 (s), 161.5 (s). Anal. Calcd for $C_{21}H_{23}N_3O_2$ (349.43): C, 72.18; H, 6.63; N, 12.03. Found: C, 72.40; H, 6.34; N, 12.36.

*4.4.7. Ethyl 7-benzyl-2,8-dimethyl-2,4,5,7-tetrahydropyrrolo[3,4-g] indazole-6-carboxylate (**18B**).* This product was obtained from **7b**. Brown solid; $R_f$=0.37 ($CH_2Cl_2$/EtOAc 95:5); mp 150–151 °C; yield: 70%; IR $cm^{-1}$: 1694 (CO). $^1H$ NMR ($CDCl_3$): $\delta$ 1.28 (3H, t, $J$=7.1 Hz, $CH_3$), 2.52 (3H, s, $CH_3$), 2.75 (2H, t, $J$=7.3 Hz, $CH_2$), 3.10 (2H, t, $J$=7.3 Hz, $CH_2$), 3.86 (3H, s, $CH_3$), 4.21 (2H, q, $J$=7.1 Hz, $CH_2$), 5.62 (2H, s, $CH_2$), 6.94 (2H, d, $J$=7.0 Hz, H-2′ and H-6′), 7.10 (1H, s, H-3), 7.17–7.30 (3H, m, H-3′, H-4′ and H-5′). $^{13}C$ NMR ($CDCl_3$): $\delta$ 11.6 (q), 14.4 (q), 19.9 (t), 22.7 (t), 38.7 (q), 48.1 (t), 59.6 (t), 113.9 (s), 115.4 (s), 117.6 (s), 125.7 (2×d), 126.6 (d), 126.7 (d), 128.5 (2×d), 130.2 (s), 131.1 (s), 138.7 (s), 145.8 (s), 161.8 (CO). Anal. Calcd for $C_{21}H_{23}N_3O_2$ (349.43): C, 72.18; H, 6.63; N, 12.03. Found: C, 72.53; H, 6.42; N, 12.22.

*4.4.8. Ethyl 1,7-dibenzyl-8-methyl-1,4,5,7-tetrahydropyrrolo[3,4-g] indazole-6-carboxylate (**19A**).* This product was obtained from **7b**. Brown oil; $R_f$=0.43 ($CH_2Cl_2$); yield 20%; IR $cm^{-1}$: 1682 (CO). $^1H$ NMR (DMSO-$d_6$): $\delta$ 1.21 (3H, t, $J$=7.1 Hz, $CH_3$), 2.40 (3H, s, $CH_3$), 2.68 (2H, t, $J$=7.3 Hz, $CH_2$), 3.00 (2H, t, $J$=7.3 Hz, $CH_2$), 4.14 (2H, q, $J$=7.1 Hz, $CH_2$), 5.27 (2H, s, $CH_2$), 5.60 (2H, s, $CH_2$), 6.92 (2H, d, $J$=6.7 Hz, H-2′ and H-6′), 7.20–7.38 (8H, m, 2× Ar), 7.57 (1H, s, H-3). $^{13}C$ NMR (DMSO-$d_6$): $\delta$ 11.1 (q), 14.1 (q), 19.4 (t), 22.4 (t), 47.4 (t), 54.6 (t), 59.2 (t), 113.7 (s), 114.4 (s), 117.0 (s), 125.5 (d), 125.6 (2×d), 126.7 (d), 127.4 (2×d), 127.5 (2×d), 128.4 (s), 128.5 (2×d), 129.0 (s), 130.7 (d), 138.1 (s), 138.7 (s), 144.7 (s), 161.9 (s). Anal. Calcd for $C_{27}H_{27}N_3O_2$ (425.52): C, 76.21; H, 6.40; N, 9.87. Found: C, 75.87; H, 6.67; N, 9.94.

*4.4.9. Ethyl 2,7-dibenzyl-8-methyl-2,4,5,7-tetrahydropyrrolo[3,4-g] indazole-6-carboxylate (**19B**).* This product was obtained from **7b**. Brown oil; $R_f$=0.25 ($CH_2Cl_2$); yield 72%; IR $cm^{-1}$: 1699 (CO). $^1H$ NMR (DMSO-$d_6$): $\delta$ 1.21 (3H, t, $J$=7.1 Hz, $CH_3$), 2.22 (3H, s, $CH_3$), 2.60 (2H, t, $J$=7.3 Hz, $CH_2$), 2.91 (2H, t, $J$=7.3 Hz, $CH_2$), 4.15 (2H, q, $J$=7.1 Hz, $CH_2$), 5.49 (2H, s, $CH_2$), 5.58 (2H, s, $CH_2$), 6.83 (2H, d, $J$=6.8 Hz, H-2′ and H-6′), 6.96 (2H, d, $J$=6.6 Hz, H-2″ and H-6″), 7.22–7.31 (6H, m, 2× Ar), 7.35 (1H, s, H-3). $^{13}C$ NMR (DMSO-$d_6$): $\delta$ 12.8 (q), 14.1 (q), 20.6 (t), 23.1 (t), 47.5 (t), 54.3 (t), 59.6 (t), 111.7 (s), 116.5 (s), 117.8 (s), 125.5 (2×d), 126.0 (2×d), 126.8 (d), 127.0 (d), 128.4 (2×d), 128.5 (2×d), 129.7 (d), 130.7 (s), 136.0 (s), 136.7 (s), 138.2 (s), 138.4 (s), 160.8 (s). Anal. Calcd for $C_{27}H_{27}N_3O_2$ (425.52): C, 76.21; H, 6.40; N, 9.87. Found: C, 76.45; H, 6.17; N, 10.04.

*4.4.10. Ethyl 7-benzyl-8-methyl-1-phenyl-1,4,5,7-tetrahydropyrrolo [3,4-g]indazole-6-carboxylate (**20**).* This product was obtained from **7b**. Brown solid; $R_f$=0.57 ($CH_2Cl_2$/EtOAc 95:5); mp 56–57 °C; yield 68%; IR $cm^{-1}$: 1685 (CO). $^1H$ NMR ($CDCl_3$): $\delta$ 1.35 (3H, t, $J$=7.1 Hz, $CH_3$), 1.45 (3H, s, $CH_3$), 2.73 (2H, t, $J$=6.6 Hz, $CH_2$), 3.12 (2H, t, $J$=6.6 Hz, $CH_2$), 4.24 (2H, q, $J$=7.1 Hz, $CH_2$), 5.52 (2H, s, $CH_2$), 6.85–7.53 (10H, m, Ar), 7.59 (1H, s, H-3). $^{13}C$ NMR ($CDCl_3$): $\delta$ 12.4 (q), 14.4 (q), 21.2 (t), 23.2 (t), 48.2 (t), 59.9 (t), 100.3 (s), 112.0 (s), 118.4 (s), 124.4 (2×d), 125.5 (2×d), 126.9 (d), 127.4 (d), 128.6 (2×d), 129.2 (2×d), 130.5 (s), 136.0 (s), 138.3 (s), 138.4 (s), 138.5 (d), 142.0 (s), 161.6 (s). Anal. Calcd for $C_{26}H_{25}N_3O_2$ (411.50): C, 75.89; H, 6.12; N, 10.21. Found: C, 75.94; H, 5.88; N, 10.44.

*4.4.11. Ethyl 7-benzyl-1-(4-methoxyphenyl)-8-methyl-1,4,5,7-tetrahydropyrrolo[3,4-g]indazole-6-carboxylate (**21**).* This product was obtained from **7b**. Brown oil; $R_f$=0.59 ($CH_2Cl_2$/EtOAc 95:5); yield 80%; IR $cm^{-1}$: 1693 (CO). $^1H$ NMR ($CDCl_3$): $\delta$ 1.31 (3H, t, $J$=7.1 Hz, $CH_3$), 1.49 (3H, s, $CH_3$), 2.72 (2H, t, $J$=6.6 Hz, $CH_2$), 3.11 (2H, t, $J$=6.6 Hz, $CH_2$), 3.81 (3H, s, $CH_3$), 4.26 (2H, q, $J$=7.1 Hz, $CH_2$), 5.52 (2H, s, $CH_2$), 6.85–6.91 (4H, m, H-2′ and H-6′, H-3″ and H-5″), 7.21–7.26 (3H, m, H-3′, H-4′ and H-5′), 7.38–7.43 (2H, d, $J$=6.9 Hz, H-2″ and H-6″), 7.56 (1H, s, H-3). $^{13}C$ NMR ($CDCl_3$): $\delta$ 12.2 (q), 14.4 (q), 21.1 (t), 23.3 (t), 48.2 (t), 55.5 (q), 59.9 (t), 112.0 (s), 114.3 (2×d), 117.9 (s), 118.4 (s), 125.5 (2×d), 125.9 (2×d), 126.9 (d), 128.6 (2×d), 130.5 (s), 131.4 (s), 135.4 (s), 136.1 (s), 137.9 (d), 138.3 (s), 158.8 (s), 161.6 (s). Anal. Calcd for $C_{27}H_{27}N_3O_3$ (441.52): C, 73.45; H, 6.16; N, 9.52. Found: C, 73.60; H, 5.96; N, 9.75.

*4.4.12. 2,7,8-Trimethyl-2,4,5,7-tetrahydropyrrolo[3,4-g]indazole (**26**).* This product was obtained from **7c**. Yellow solid; $R_f$=0.22 ($CH_2Cl_2$/EtOAc 95:5); mp 143–144 °C; yield: 40%. $^1H$ NMR (DMSO-$d_6$): $\delta$ 2.07 (3H, s, $CH_3$), 2.38–2.49 (4H, m, 2× $CH_2$), 3.48 (3H, s, $CH_3$), 3.89 (3H, s, $CH_3$), 6.55 (1H, s, H-6), 7.19 (1H, s, H-3). $^{13}C$ NMR

(DMSO-$d_6$): δ 12.6 (q), 21.8 (t), 22.3 (t), 33.7 (q), 39.4 (q), 109.9 (s), 115.2 (s), 117.9 (d), 119.3 (s), 122.9 (d), 135.7 (s), 137.4 (s). Anal. Calcd for $C_{12}H_{15}N_3$ (201.27): C, 71.61; H, 7.51; N, 20.88. Found: C, 71.86; H, 7.32; N, 20.82.

*4.4.13. 7-Benzyl-8-methyl-1,4,5,7-tetrahydropyrrolo[3,4-g]indazole (**27**).* This product was obtained from **7d**. Yellow solid; $R_f$=0.17 ($CH_2Cl_2$/EtOAc 95:5); mp 135–136 °C; yield: 68%; IR $cm^{-1}$: 3176 (NH). $^1H$ NMR (DMSO-$d_6$): δ 2.20 (3H, s, $CH_3$), 2.49–2.58 (4H, m, 2× $CH_2$), 5.02 (2H, s, $CH_2$), 6.58 (1H, s, H-6), 7.07 (2H, d, $J$=8.4 Hz, H-2′ and H-6′), 7.23–7.32 (3H, m, H-3′, H-4′ and H-5′), 7.38 (1H, s, H-3), 12.20 (1H, s, NH). $^{13}C$ NMR (DMSO-$d_6$): δ 10.8 (q), 20.4 (t), 21.2 (t), 49.2 (t), 113.1 (s), 116.6 (d), 118.2 (s), 121.2 (s), 121.6 (s), 125.4 (s), 126.6 (2×d), 127.1 (d), 128.5 (2×d), 136.2 (d), 139.0 (s). Anal. Calcd for $C_{17}H_{17}N_3$ (263.34): C, 77.54; H, 6.51; N, 15.96. Found: C, 77.68; H, 6.64; N, 15.60.

*4.4.14. 7-Benzyl-2,8-dimethyl-2,4,5,7-tetrahydropyrrolo[3,4-g]indazole (**28**).* This product was obtained from **7d**. Yellow solid; $R_f$=0.24 ($CH_2Cl_2$/EtOAc 95:5); mp 102–103 °C; yield: 45%. $^1H$ NMR (DMSO-$d_6$): δ 2.33 (3H, s, $CH_3$), 2.46–2.57 (4H, m, 2× $CH_2$), 3.88 (3H, s, $CH_3$), 5.09 (2H, s, $CH_2$), 6.71 (1H, s, H-6), 7.09 (2H, d, $J$=8.2 Hz, H-2′ and H-6′), 7.21 (1H, s, H-3), 7.25–7.37 (3H, m, H-3′, H-4′ and H-5′). $^{13}C$ NMR (DMSO-$d_6$): δ 12.6 (q), 21.4 (t), 21.9 (t), 39.3 (q), 49.8 (t), 110.1 (s), 115.1 (s), 117.6 (d), 119.6 (s), 121.3 (s), 126.5 (2×d), 127.1 (d), 128.6 (2×d), 135.5 (d), 136.8 (s), 138.7 (s). Anal. Calcd for $C_{18}H_{19}N_3$ (277.36): C, 77.95; H, 6.90; N, 15.15. Found: C, 78.06; H, 6.52; N, 15.30.

*4.4.15. 7-Benzyl-1,4,5,7-tetrahydropyrrolo[3,4-g]indazole (**29**).* This product was obtained from **7f**. Brown solid; $R_f$=0.39 ($CH_2Cl_2$/EtOAc 70:30); mp 171–172 °C; yield: 80%; IR $cm^{-1}$: 3128 (NH). $^1H$ NMR (DMSO-$d_6$): δ 2.50–2.59 (4H, m, 2× $CH_2$), 5.05 (2H, s, $CH_2$), 6.64 (1H, s, H-6), 6.90 (1H, s, H-8), 7.22–7.38 (6H, m, Ar and H-3), 12.26 (1H, s, NH). $^{13}C$ NMR (DMSO-$d_6$): δ 20.2 (t), 21.0 (t), 52.3 (t), 112.9 (s), 113.8 (d), 114.5 (s), 117.4 (d), 119.6 (s), 127.3 (2×d), 127.4 (d), 128.5 (2×d), 131.8 (s), 136.0 (d), 138.9 (s). Anal. Calcd for $C_{16}H_{15}N_3$ (249.31): C, 77.08; H, 6.06; N, 16.85. Found: C, 77.30; H, 5.84; N, 17.05.

*4.4.16. 7-Benzyl-2-methyl-2,4,5,7-tetrahydropyrrolo[3,4-g]indazole (**30**).* This product was obtained from **7f**. White solid; $R_f$=0.17 ($CH_2Cl_2$/EtOAc 95:5); mp 102–103 °C; yield: 70%. $^1H$ NMR ($CDCl_3$): δ 2.66–2.74 (4H, m, 2× $CH_2$), 3.90 (3H, s, $CH_3$), 5.05 (2H, s, $CH_2$), 6.53 (1H, s, H-6), 6.78 (1H, s, H-8), 7.14–7.35 (6H, m, Ar and H-3). $^{13}C$ NMR ($CDCl_3$): δ 21.0 (t), 21.4 (t), 37.3 (q), 53.4 (t), 112.8 (s), 113.8 (d), 114.0 (s), 114.6 (s), 118.0 (d), 121.0 (s), 127.0 (2×d), 127.8 (d), 128.8 (2×d), 135.8 (d), 137.8 (s). Anal. Calcd for $C_{17}H_{17}N_3$ (263.34): C, 77.54; H, 6.51; N, 15.96. Found: C, 77.40; H, 6.64; N, 15.80.

*4.4.17. 2,7-Dibenzyl-2,4,5,7-tetrahydropyrrolo[3,4-g]indazole (**31**).* This product was obtained from **7f**. Yellow oil; $R_f$=0.33 ($CH_2Cl_2$/EtOAc 95:5); yield: 70%. $^1H$ NMR ($CDCl_3$): δ 2.56–2.69 (4H, m, 2× $CH_2$), 4.87 (2H, s, $CH_2$), 5.36 (2H, s, $CH_2$), 6.45 (2H, d, $J$=7.4 Hz, Ar), 7.07–7.35 (11H, m, Ar and H-3). $^{13}C$ NMR ($CDCl_3$): δ 20.9 (t), 21.2 (t), 53.2 (t), 53.6 (t), 112.1 (s), 114.1 (d), 114.8 (s), 117.6 (d), 121.0 (s), 126.5 (2×d), 126.9 (2×d), 127.2 (d), 127.6 (d), 128.5 (2×d), 128.6 (2×d), 135.8 (s), 136.5 (d), 137.2 (s), 137.5 (s). Anal. Calcd for $C_{23}H_{21}N_3$ (339.43): C, 81.38; H, 6.24; N, 12.38. Found: C, 81.60; H, 6.02; N, 12.46.

### 4.5. General procedure for the preparation of *N*-benzylsubstituted tetrahydropyrrolo[3,4-g]indazoles (13–16, 22–25, 32–35)

To a solution of the relevant tetrahydropyrrolo[3,4-g]indazole **9**, **17**, **29** (0.0025 mol) dissolved in anhydrous DMF (10 mL), NaH (0.06 g, 0.0025 mol) was added at 0 °C and the reaction mixture was stirred at room temperature. After 1 h the benzylchloride (0.0025 mol) was added at 0 °C and the reaction mixture was stirred at room temperature for 2–3 h. Then, the reaction mixture was poured onto crushed ice and the precipitate was filtered off. The crude was purified by column chromatography of the residue, using DCM as eluent, to give the expected product.

*4.5.1. Ethyl 1-(4-methoxybenzyl)-7,8-dimethyl-1,4,5,7-tetrahydropyrrolo[3,4-g]indazole-6-carboxylate (**13**).* This product was obtained from **9**. White solid; $R_f$=0.21 ($CH_2Cl_2$/EtOAc 95:5); mp 74–75 °C; yield: 96%; IR $cm^{-1}$: 1681 (CO). $^1H$ NMR (DMSO-$d_6$): δ 1.28 (3H, t, $J$=7.1 Hz, $CH_3$), 2.47 (3H, s, $CH_3$), 2.61 (2H, t, $J$=7.3 Hz, $CH_2$), 2.92 (2H, t, $J$=7.3 Hz, $CH_2$), 3.72 (3H, s, $CH_3$), 3.73 (3H, s, $CH_3$), 4.20 (2H, q, $J$=7.1 Hz, $CH_2$), 5.17 (2H, s, $CH_2$), 6.89 (2H, d, $J$=8.7 Hz, H-3″ and H-5″), 7.22 (2H, d, $J$=8.7 Hz, H-2″ and H-6″), 7.46 (1H, s, H-3). $^{13}C$ NMR (DMSO-$d_6$): δ 11.2 (q), 14.3 (q), 19.3 (t), 22.1 (t), 32.2 (q), 54.1 (t), 55.0 (q), 59.1 (t), 113.1 (s), 113.8 (2×d), 114.1 (s), 117.1 (s), 126.2 (s), 128.2 (s), 129.0 (2×d), 130.0 (d), 130.6 (s), 144.7 (s), 158.6 (s), 161.1 (s). Anal. Calcd for $C_{22}H_{25}N_3O_3$ (379.45): C, 69.64; H, 6.64; N, 11.07. Found: C, 69.40; H, 7.02; N, 10.94.

*4.5.2. Ethyl 1-(4-chlorobenzyl)-7,8-dimethyl-1,4,5,7-tetrahydropyrrolo[3,4-g]indazole-6-carboxylate (**14**).* This product was obtained from **9**. White solid; $R_f$=0.67 ($CH_2Cl_2$/EtOAc 95:5); mp 100–101 °C; yield: 90%; IR $cm^{-1}$: 1685 (CO). $^1H$ NMR (DMSO-$d_6$): δ 1.29 (3H, t, $J$=7.0 Hz, $CH_3$), 2.46 (3H, s, $CH_3$), 2.64 (2H, t, $J$=6.9 Hz, $CH_2$), 2.93 (2H, t, $J$=6.9 Hz, $CH_2$), 3.73 (3H, s, $CH_3$), 4.21 (2H, q, $J$=7.0 Hz, $CH_2$), 5.27 (2H, s, $CH_2$), 7.25 (2H, d, $J$=8.2 Hz, H-2″ and H-6″), 7.40 (2H, d, $J$=8.2 Hz, H-3″ and H-5″), 7.53 (1H, s, H-3). $^{13}C$ NMR (DMSO-$d_6$): δ 11.2 (q), 14.3 (q), 19.3 (t), 22.0 (t), 32.3 (q), 53.7 (t), 59.1 (t), 112.9 (s), 114.3 (s), 117.2 (s), 126.7 (s), 128.2 (s), 128.4 (2×d), 129.2 (2×d), 130.7 (d), 132.0 (s), 137.2 (s), 145.1 (s), 161.1 (s). Anal. Calcd for $C_{21}H_{22}ClN_3O_2$ (383.88): C, 65.71; H, 5.78; N, 10.95. Found: C, 65.56; H, 5.94; N, 11.02.

*4.5.3. Ethyl 1-(3-chlorobenzyl)-7,8-dimethyl-1,4,5,7-tetrahydropyrrolo[3,4-g]indazole-6-carboxylate (**15**).* This product was obtained from **9**. White solid; $R_f$=0.53 ($CH_2Cl_2$); mp 98–99 °C; yield: 98%; IR $cm^{-1}$: 1689 (CO). $^1H$ NMR (DMSO-$d_6$): δ 1.29 (3H, t, $J$=7.1 Hz, $CH_3$), 2.46 (3H, s, $CH_3$), 2.64 (2H, t, $J$=6.9 Hz, $CH_2$), 2.94 (2H, t, $J$=6.9 Hz, $CH_2$), 3.74 (3H, s, $CH_3$), 4.21 (2H, q, $J$=7.1 Hz, $CH_2$), 5.29 (2H, s, $CH_2$), 7.18–7.42 (4H, m, H-2″, H-4″, H-5″and H-6″), 7.57 (1H, s, H-3). $^{13}C$ NMR (DMSO-$d_6$): δ 11.2 (q), 14.3 (q), 19.3 (t), 22.0 (t), 32.3 (q), 53.7 (t), 59.1 (t), 112.9 (s), 114.4 (s), 117.2 (s), 126.0 (d), 126.8 (d), 127.1 (d), 127.3 (d), 128.2 (s), 130.4 (d), 130.7 (s), 133.0 (s), 140.7 (s), 145.1 (s), 161.1 (s). Anal. Calcd for $C_{21}H_{22}ClN_3O_2$ (383.88): C, 65.71; H, 5.78; N, 10.95. Found: C, 65.85; H, 5.60; N, 10.80.

*4.5.4. Ethyl 1-(2,4-dichlorobenzyl)-7,8-dimethyl-1,4,5,7-tetrahydropyrrolo[3,4-g]indazole-6-carboxylate (**16**).* This product was obtained from **9**. White solid; $R_f$=0.20 ($CH_2Cl_2$); mp 151–152 °C; yield: 92%; IR $cm^{-1}$: 1680 (CO). $^1H$ NMR (DMSO-$d_6$): δ 1.29 (3H, t, $J$=7.1 Hz, $CH_3$), 2.44 (3H, s, $CH_3$), 2.65 (2H, t, $J$=7.3 Hz, $CH_2$), 2.94 (2H, t, $J$=7.3 Hz, $CH_2$), 3.74 (3H, s, $CH_3$), 4.21 (2H, q, $J$=7.1 Hz, $CH_2$), 5.35 (2H, s, $CH_2$), 6.95 (1H, d, $J$=8.3 Hz, H-6″), 7.41 (1H, dd, $J$=8.3 2.1 Hz, H-5″), 7.55 (1H, s, H-3), 7.66 (1H, d, $J$=2.1 Hz, H-3″). $^{13}C$ NMR (DMSO-$d_6$): δ 11.2 (q), 14.3 (q), 19.3 (t), 22.0 (t), 32.3 (q), 51.6 (t), 59.1 (t), 112.8 (s), 114.4 (s), 117.2 (s), 127.2 (d), 127.6 (d), 128.2 (s), 128.7 (d), 130.6 (d), 130.8 (s), 132.7 (s), 132.8 (s), 134.8 (s), 145.4 (s), 161.1 (s). Anal. Calcd for $C_{21}H_{21}Cl_2N_3O_2$ (418.32): C, 60.30; H, 5.06; N, 10.05. Found: C, 59.97; H, 5.28; N, 9.83.

*4.5.5. Ethyl 7-benzyl-1-(4-methoxybenzyl)-8-methyl-1,4,5,7-tetrahydropyrrolo[3,4-g]indazole-6-carboxylate (**22**).* This product

was obtained from **17**. Yellow oil; $R_f$=0.11 ($CH_2Cl_2$); yield: 88%; IR $cm^{-1}$: 1696 (CO). $^1H$ NMR ($CDCl_3$): $\delta$ 1.26 (3H, t, $J$=7.1 Hz, $CH_3$), 2.53 (3H, s, $CH_3$), 2.72 (2H, t, $J$=7.3 Hz, $CH_2$), 3.09 (2H, t, $J$=7.3 Hz, $CH_2$), 3.79 (3H, s, $CH_3$), 4.18 (2H, q, $J$=7.1 Hz, $CH_2$), 5.21 (2H, s, $CH_2$), 5.62 (2H, s, $CH_2$), 6.84 (2H, d, $J$=6.6 Hz, H-3″ and H-5″), 6.92 (2H, d, $J$=6.7 Hz, H-2′ and H-6′), 7.10–7.48 (6H, m, Ar and H-3). $^{13}C$ NMR (DMSO-$d_6$): $\delta$ 11.6 (q), 14.4 (q), 19.9 (t), 22.6 (t), 48.2 (t), 55.2 (t), 55.3 (q), 59.5 (t), 114.0 (s), 114.1 (2×d), 115.7 (s), 117.6 (s), 125.4 (d), 125.8 (2×d), 126.7 (s), 128.5 (2×d), 129.2 (s), 129.3 (2×d), 130.3 (d), 131.3 (s), 138.7 (s), 145.6 (s), 159.3 (s), 161.8 (s). Anal. Calcd for $C_{28}H_{29}N_3O_3$ (455.56): C, 73.82; H, 6.42; N, 9.22. Found: C, 73.65; H, 6.70; N, 9.05.

*4.5.6. Ethyl 7-benzyl-1-(4-chlorobenzyl)-8-methyl-1,4,5,7-tetrahydropyrrolo[3,4-g]indazole-6-carboxylate (**23**).* This product was obtained from **17**. White solid; $R_f$=0.51 ($CH_2Cl_2$/EtOAc 95:5); mp 75–76 °C; yield: 84%; IR $cm^{-1}$: 1682 (CO). $^1H$ NMR (DMSO-$d_6$): $\delta$ 1.22 (3H, t, $J$=7.1 Hz, $CH_3$), 2.39 (3H, s, $CH_3$), 2.68 (2H, t, $J$=7.3 Hz, $CH_2$), 3.00 (2H, t, $J$=7.3 Hz, $CH_2$), 4.14 (2H, q, $J$=7.1 Hz, $CH_2$), 5.27 (2H, s, $CH_2$), 5.60 (2H, s, $CH_2$), 6.92 (2H, d, $J$=6.7 Hz, H-2′ and H-6′), 7.21–7.42 (7H, m, Ar), 7.58 (1H, s, H-3). $^{13}C$ NMR (DMSO-$d_6$): $\delta$ 11.1 (q), 14.2 (q), 19.2 (t), 22.1 (t), 47.4 (t), 53.7 (t), 59.2 (t), 113.6 (s), 114.5 (s), 117.0 (s), 125.6 (2×d), 126.7 (d), 128.4 (2×d), 128.5 (2×d), 129.0 (s), 129.3 (2×d), 129.8 (d), 130.7 (s), 132.0 (s), 137.1 (s), 138.6 (s), 144.9 (s), 160.9 (s). Anal. Calcd for $C_{27}H_{26}ClN_3O_2$ (459.97): C, 70.50; H, 5.70; N, 9.14. Found: C, 70.28; H, 6.03; N, 8.90.

*4.5.7. Ethyl 7-benzyl-1-(3-chlorobenzyl)-8-methyl-1,4,5,7-tetrahydropyrrolo[3,4-g]indazole-6-carboxylate (**24**).* This product was obtained from **17**. Yellow oil; $R_f$=0.33 ($CH_2Cl_2$); yield: 86%; IR $cm^{-1}$: 1683 (CO). $^1H$ NMR (DMSO-$d_6$): $\delta$ 1.22 (3H, t, $J$=7.1 Hz, $CH_3$), 2.40 (3H, s, $CH_3$), 2.69 (2H, t, $J$=7.3 Hz, $CH_2$), 3.00 (2H, t, $J$=7.3 Hz, $CH_2$), 4.14 (2H, q, $J$=7.1 Hz, $CH_2$), 5.29 (2H, s, $CH_2$), 5.60 (2H, s, $CH_2$), 6.94 (2H, d, $J$=7.4 Hz, H-2′ and H-6′), 7.18–7.39 (7H, m, Ar), 7.61 (1H, s, H-3). $^{13}C$ NMR (DMSO-$d_6$): $\delta$ 11.1 (q), 14.2 (q), 19.2 (t), 22.1 (t), 47.4 (t), 53.8 (t), 59.2 (t), 113.6 (s), 114.6 (s), 117.0 (s), 125.6 (2×d), 126.1 (d), 126.7 (d), 126.9 (d), 127.2 (s), 127.3 (d), 127.4 (d), 128.5 (2×d), 130.4 (d), 130.8 (s), 133.0 (s), 138.6 (s), 140.6 (s), 145.0 (s), 160.9 (s). Anal. Calcd for $C_{27}H_{26}ClN_3O_2$ (459.97): C, 70.50; H, 5.70; N, 9.14. Found: C, 70.73; H, 5.64; N, 9.30.

*4.5.8. Ethyl 7-benzyl-1-(2,4-dichlorobenzyl)-8-methyl-1,4,5,7-tetrahydropyrrolo[3,4-g]indazole-6-carboxylate (**25**).* This product was obtained from **17**. White solid; $R_f$=0.44 ($CH_2Cl_2$); mp 107–108 °C; yield: 82%; IR 1686 $cm^{-1}$: (CO). $^1H$ NMR (DMSO-$d_6$): $\delta$ 1.22 (3H, t, $J$=7.1 Hz, $CH_3$), 2.38 (3H, s, $CH_3$), 2.70 (2H, t, $J$=7.4 Hz, $CH_2$), 3.02 (2H, t, $J$=7.4 Hz, $CH_2$), 4.14 (2H, q, $J$=7.1 Hz, $CH_2$), 5.36 (2H, s, $CH_2$), 5.59 (2H, s, $CH_2$), 6.92–7.01 (3H, m, Ar), 7.17–7.37 (3H, m, Ar), 7.40 (1H, dd, $J$=8.34, 2.14 Hz, H-5″), 7.58 (1H, s, H-3), 7.64 (1H, d, $J$=2.12 Hz, H-3″). $^{13}C$ NMR (DMSO-$d_6$): $\delta$ 11.1 (q), 14.2 (q), 19.2 (t), 22.1 (t), 47.4 (t), 51.6 (t), 59.2 (t), 113.5 (s), 114.4 (s), 117.1 (s), 125.6 (2×d), 126.7 (d), 127.3 (d), 127.6 (d), 128.5 (2×d), 128.7 (d), 129.1 (s), 130.7 (d), 130.8 (s), 132.7 (s), 132.9 (s), 134.7 (s), 138.6 (s), 145.2 (s), 160.9 (s). Anal. Calcd for $C_{27}H_{25}Cl_2N_3O_2$ (494.41): C, 65.59; H, 5.10; N, 8.50. Found: C, 65.29; H, 5.34; N, 8.28.

*4.5.9. 7-Benzyl-1-(4-methoxybenzyl)-1,4,5,7-tetrahydropyrrolo[3,4-g]indazole (**32A**).* This product was obtained from **29**. Yellow oil; $R_f$=0.67 ($CH_2Cl_2$/EtOAc 95:5); yield: 70%. $^1H$ NMR (DMSO-$d_6$): $\delta$ 2.52–2.58 (4H, m, 2× $CH_2$), 3.71 (3H, s, $CH_3$), 5.02 (2H, s, $CH_2$), 5.12 (2H, s, $CH_2$), 6.61 (1H, s, H-6), 6.86 (2H, d, $J$=8.4 Hz, Ar), 6.92 (1H, s, H-8), 7.14–7.33 (7H, m, Ar), 7.44 (1H, s, H-3). $^{13}C$ NMR (DMSO-$d_6$): $\delta$ 20.5 (t), 20.9 (t), 52.3 (t), 55.0 (t), 54.9 (q), 113.7 (2×d), 113.8 (d), 114.3 (s), 114.8 (s), 117.2 (d), 119.8 (s), 126.4 (d), 127.3 (s), 127.4 (2×d), 128.4 (2×d), 128.9 (2×d), 130.1 (d), 138.9 (s), 145.1 (s), 158.6 (s). Anal. Calcd for $C_{24}H_{23}N_3O$ (369.46): C, 78.02; H, 6.27; N, 11.37. Found: C, 77.84; H, 6.55; N, 11.46.

*4.5.10. 7-Benzyl-2-(4-methoxybenzyl)-2,4,5,7-tetrahydropyrrolo[3,4-g]indazole (**32B**).* This product was obtained from **29**. Yellow oil; $R_f$=0.56 ($CH_2Cl_2$/EtOAc 95:5); yield: 15%. $^1H$ NMR (DMSO-$d_6$): $\delta$ 2.68–2.73 (4H, m, 2× $CH_2$), 3.75 (3H, s, $CH_3$), 4.96 (2H, s, $CH_2$), 5.32 (2H, s, $CH_2$), 6.47 (1H, s, H-6), 6.54 (1H, s, H-8), 6.80 (2H, d, $J$=8.4 Hz, Ar), 7.03–7.12 (4H, m, Ar), 7.27–7.33 (3H, m, Ar), 7.35 (1H, s, H-3). $^{13}C$ NMR (DMSO-$d_6$): $\delta$ 21.1 (t), 21.4 (t), 53.3 (t), 53.4 (t), 55.2 (q), 112.4 (s), 114.1 (2×d), 114.3 (d), 115.0 (s), 117.8 (d), 121.2 (s), 127.1 (2×d), 127.8 (d), 128.0 (2×d), 128.8 (2×d), 129.5 (s), 135.7 (s), 136.6 (d), 137.6 (s), 158.8 (s). Anal. Calcd for $C_{24}H_{23}N_3O$ (369.46): C, 78.02; H, 6.27; N, 11.37. Found: C, 78.38; H, 5.94; N, 10.98.

*4.5.11. 7-Benzyl-1-(4-chlorobenzyl)-1,4,5,7-tetrahydropyrrolo[3,4-g]indazole (**33A**).* This product was obtained from **29**. White solid; $R_f$=0.62 ($CH_2Cl_2$/EtOAc 95:5); mp 126–127 °C; yield: 73%. $^1H$ NMR ($CDCl_3$): $\delta$ 2.68–2.71 (4H, m, 2× $CH_2$), 5.01 (2H, s, $CH_2$), 5.22 (2H, s, $CH_2$), 6.48 (1H, s, H-6), 6.98 (1H, s, H-8), 7.18–7.48 (10H, m, Ar and H-3). $^{13}C$ NMR ($CDCl_3$): $\delta$ 20.6 (t), 21.2 (t), 53.5 (t), 54.9 (t), 114.5 (d), 114.9 (s), 116.2 (s), 117.2 (d), 121.2 (s), 126.2 (d), 127.4 (2×d), 127.7 (s), 128.7 (2×d), 128.8 (2×d), 128.9 (2×d), 133.5 (s), 136.0 (d), 137.9 (s), 146.2 (s). Anal. Calcd for $C_{23}H_{20}ClN_3$ (373.88): C, 73.89; H, 5.39; N, 11.24. Found: C, 74.01; H, 5.00; N, 11.58.

*4.5.12. 7-Benzyl-2-(4-chlorobenzyl)-2,4,5,7-tetrahydropyrrolo[3,4-g]indazole (**33B**).* This product was obtained from **29**. Yellow oil; $R_f$=0.45 ($CH_2Cl_2$/EtOAc 95:5); yield: 21%. $^1H$ NMR ($CDCl_3$): $\delta$ 2.70–2.73 (4H, m, 2× $CH_2$), 4.95 (2H, s, $CH_2$), 5.35 (2H, s, $CH_2$), 6.46 (1H, s, H-6), 6.48 (1H, s, H-8), 7.00–7.34 (9H, m, Ar), 7.36 (1H, s, H-3). $^{13}C$ NMR ($CDCl_3$): $\delta$ 21.0 (t), 21.3 (t), 53.2 (t), 53.4 (t), 112.2 (s), 114.0 (d), 115.2 (s), 117.9 (d), 121.1 (s), 127.1 (2×d), 127.9 (d), 128.0 (2×d), 128.8 (2×d), 128.9 (2×d), 133.2 (s), 135.8 (s), 135.9 (s), 136.9 (d), 137.5 (s). Anal. Calcd for $C_{23}H_{20}ClN_3$ (373.88): C, 73.89; H, 5.39; N, 11.24. Found: C, 73.60; H, 5.02; N, 11.46.

*4.5.13. 7-Benzyl-1-(3-chlorobenzyl)-1,4,5,7-tetrahydropyrrolo[3,4-g]indazole (**34A**).* This product was obtained from **29**. White solid; $R_f$=0.20 ($CH_2Cl_2$); mp 115–116 °C; yield: 68%. $^1H$ NMR (DMSO-$d_6$): $\delta$ 2.50–2.58 (4H, m, 2× $CH_2$), 5.03 (2H, s, $CH_2$), 5.23 (2H, s, $CH_2$), 6.63 (1H, s, H-6), 6.94 (1H, s, H-8), 7.16–7.36 (9H, m, Ar), 7.54 (1H, s, H-3). $^{13}C$ NMR (DMSO-$d_6$): $\delta$ 20.0 (t), 20.8 (t), 52.3 (t), 53.7 (t), 100.0 (s), 113.9 (d), 114.5 (s), 117.2 (d), 119.8 (s), 126.1 (d), 127.0 (d), 127.1 (d), 127.2 (2×d), 127.3 (2×d), 127.4 (d), 128.5 (d), 130.4 (d), 133.0 (s), 138.9 (s), 140.8 (s), 145.5 (s). Anal. Calcd for $C_{23}H_{20}ClN_3$ (373.88): C, 73.89; H, 5.39; N, 11.24. Found: C, 73.70; H, 5.60; N, 11.46.

*4.5.14. 7-Benzyl-2-(3-chlorobenzyl)-2,4,5,7-tetrahydropyrrolo[3,4-g]indazole (**34B**).* This product was obtained from **29**. Brown oil; $R_f$=0.48 ($CH_2Cl_2$/EtOAc 95:5); yield: 12%. $^1H$ NMR (DMSO-$d_6$): $\delta$ 2.54–2.60 (4H, m, 2× $CH_2$), 5.02 (2H, s, $CH_2$), 5.41 (2H, s, $CH_2$), 6.68 (1H, s, H-6), 7.11–7.33 (11H, m, H-8, Ar and H-3). $^{13}C$ NMR (DMSO-$d_6$): $\delta$ 20.5 (t), 20.8 (t), 52.2 (t), 52.3 (t), 111.0 (s), 113.9 (s), 114.6 (d), 117.7 (d), 119.6 (s), 125.6 (d), 126.7 (d), 127.1 (d), 127.2 (2×d), 127.4 (d), 128.5 (2×d), 130.3 (d), 133.0 (s), 135.5 (s), 136.4 (d), 138.7 (s), 140.3 (s). Anal. Calcd for $C_{23}H_{20}ClN_3$ (373.88): C, 73.89; H, 5.39; N, 11.24. Found: C, 74.04; H, 5.02; N, 11.10.

*4.5.15. 7-Benzyl-1-(2,4-dichlorobenzyl)-1,4,5,7-tetrahydropyrrolo[3,4-g]indazole (**35A**).* This product was obtained from **29**. Yellow oil; $R_f$=0.67 ($CH_2Cl_2$/EtOAc 98:2); yield: 65%. $^1H$ NMR ($CDCl_3$): $\delta$ 2.72–2.76 (4H, m, 2× $CH_2$), 5.01 (2H, s, $CH_2$), 5.32 (2H, s, $CH_2$), 6.49 (1H, s, H-6), 6.82 (1H, d, $J$=8.3 Hz, H-6″), 6.98 (1H, s, H-8), 7.12–7.48 (7H, m, Ar and H-3), 7.58 (1H, d, $J$=2.1 Hz, H-3″). $^{13}C$ NMR ($CDCl_3$): $\delta$ 20.6 (t), 21.2 (t), 52.4 (t), 53.5 (t), 114.5 (d), 114.8 (s), 116.2 (s), 117.3

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(d), 121.2 (s), 126.8 (d), 127.4 (2×d), 127.5 (d), 127.7 (d), 128.7 (2×d), 129.1 (d), 130.2 (d), 133.0 (s), 134.0 (s), 134.2 (s), 137.8 (s), 146.6 (s). Anal. Calcd for $C_{23}H_{19}Cl_2N_3$ (408.32): C, 67.65; H, 4.69; N, 10.29. Found: C, 67.87; H, 4.40; N, 10.54.

*4.5.16. 7-Benzyl-2-(2,4-dichlorobenzyl)-2,4,5,7-tetrahydropyrrolo [3,4-g]indazole (**35B**).* This product was obtained from **29**. Yellow oil; $R_f$=0.57 ($CH_2Cl_2$/EtOAc 98:2); yield: 18%. $^1$H NMR ($CDCl_3$): δ 2.71–2.75 (4H, m, 2× $CH_2$), 4.93 (2H, s, $CH_2$), 5.43 (2H, s, $CH_2$), 6.38 (1H, s, H-6), 6.47 (1H, s, H-8), 6.58 (1H, d, *J*=8.4 Hz, H-6″), 7.06–7.10 (3H, m, Ar), 7.29–7.36 (4H, m, Ar), 7.30 (1H, s, H-3). $^{13}$C NMR ($CDCl_3$): δ 21.0 (t), 21.3 (t), 50.9 (t), 53.4 (t), 111.8 (s), 113.8 (d), 115.3 (s), 117.9 (d), 121.0 (s), 127.2 (2×d), 127.6 (d), 127.9 (d), 128.8 (2×d), 128.9 (d), 129.0 (d), 132.3 (s), 133.6 (s), 133.7 (s), 137.2 (d), 137.3 (s), 146.4 (s). Anal. Calcd for $C_{23}H_{19}Cl_2N_3$ (408.32): C, 67.65; H, 4.69; N, 10.29. Found: C, 67.38; H, 4.74; N, 10.02.

### 4.6. General procedure for the preparation of dihydropyrrolo [3,4-g]indazoles (36–42)

To a solution of tetrahydroindazole (**9**–**35**) (0.03 mol) in dry benzene (100 mL), DDQ (0.03 mol) was added. The mixture was stirred at room temperature for 4 h, then the solvent was removed under reduced pressure. The crude was purified by chromatography column.

*4.6.1. Ethyl 7,8-dimethyl-1,7-dihydropyrrolo[3,4-g]indazole-6-carboxylate (**36**).* This product was obtained from **9**. White solid; $R_f$=0.58 ($CH_2Cl_2$/EtOAc 70:30); mp 151–152 °C; yield: 50%; IR cm$^{-1}$: 3130 (NH), 1672 (CO). $^1$H NMR (DMSO-$d_6$): δ 1.39 (3H, t, *J*=6.9 Hz, $CH_3$), 2.73 (3H, s, $CH_3$), 4.04 (3H, s, $CH_3$), 4.32 (2H, q, *J*=6.9 Hz, $CH_2$), 7.36 (1H, d, *J*=9.2 Hz, H-5), 7.74 (1H, d, *J*=9.2 Hz, H-4), 8.10 (1H, s, H-3), 13.47 (1H, s, NH). $^{13}$C NMR (DMSO-$d_6$): δ 13.7 (q), 14.4 (q), 33.5 (q), 59.4 (t), 99.8 (s), 108.8 (s), 111.8 (s), 114.7 (s), 118.3 (d), 119.2 (s), 128.2 (s), 128.4 (d), 133.6 (d), 161.1 (s). Anal. Calcd for $C_{14}H_{15}N_3O_2$ (257.29): C, 65.35; H, 5.88; N, 16.33. Found: C, 65.02; H, 6.15; N, 16.50.

*4.6.2. Ethyl 2,7,8-trimethyl-2,7-dihydropyrrolo[3,4-g]indazole-6-carboxylate (**37**).* This product was obtained from **10**. White solid; $R_f$=0.33 ($CH_2Cl_2$/EtOAc 95:5); mp 168–169 °C; yield: 54%; IR cm$^{-1}$: 1672 (CO). $^1$H NMR (DMSO-$d_6$): δ 1.39 (3H, t, *J*=7.0 Hz, $CH_3$), 2.73 (3H, s, $CH_3$), 4.03 (3H, s, $CH_3$), 4.26 (3H, s, $CH_3$), 4.34 (2H, q, *J*=7.0 Hz, $CH_2$), 7.36 (1H, d, *J*=9.2 Hz, H-5), 7.74 (1H, d, *J*=9.2 Hz, H-4), 7.89 (1H, s, H-3). $^{13}$C NMR (DMSO-$d_6$): δ 13.7 (q), 14.4 (q), 33.5 (q), 41.4 (q), 59.4 (t), 99.8 (s), 108.8 (s), 111.9 (s), 114.7 (s), 118.3 (d), 119.2 (s), 128.2 (d), 128.4 (s), 133.6 (d), 161.2 (s). Anal. Calcd for $C_{15}H_{17}N_3O_2$ (274.31): C, 66.40; H, 6.32; N, 15.49. Found: C, 66.63; H, 6.60; N, 15.24.

*4.6.3. Ethyl 1-(2,4-dichlorobenzyl)-7,8-dimethyl-1,7-dihydropyrrolo [3,4-g]indazole-6-carboxylate (**38**).* This product was obtained from **16**. Yellow solid; mp 312–314 °C; $R_f$=0.19 ($CH_2Cl_2$/EtOAc 95:5); yield: 74%; IR cm$^{-1}$: 1682 (CO). $^1$H NMR (DMSO-$d_6$): δ 1.37 (3H, t, *J*=7.1 Hz, $CH_3$), 2.77 (3H, s, $CH_3$), 4.02 (3H, s, $CH_3$), 4.32 (2H, q, *J*=7.1 Hz, $CH_2$), 5.67 (2H, s, $CH_2$), 7.00 (1H, d, *J*=8.3 Hz, H-6″), 7.32 (1H, d, *J*=9.2 Hz, H-5), 7.41 (1H, d, *J*=8.3 1.9 Hz, H-5″), 7.62 (1H, d, *J*=9.2 Hz, H-4), 7.70 (1H, d, *J*=1.9 Hz, H-3″), 8.29 (1H, s, H-3). $^{13}$C NMR (DMSO-$d_6$): δ 11.9 (q), 14.4 (q), 33.2 (q), 52.7 (t), 59.2 (t), 111.5 (s), 112.7 (s), 116.6 (d), 117.0 (s), 118.3 (d), 125.8 (d), 126.7 (s), 127.8 (d), 128.8 (s), 130.3 (d), 130.9 (d), 133.0 (s), 133.2 (s), 134.1 (s), 143.6 (s), 161.2 (s). Anal. Calcd for $C_{21}H_{19}Cl_2N_3O_2$ (416.30): C, 60.59; H, 4.60; N, 10.09. Found: C, 60.63; H, 4.82; N, 9.94.

*4.6.4. Ethyl 7-benzyl-8-methyl-1,7-dihydropyrrolo[3,4-g]indazole-6-carboxylate (**39**).* This product was obtained from **17**. Yellow solid; $R_f$=0.61 ($CH_2Cl_2$/EtOAc 70:30); mp 199–200 °C; yield: 54%; IR cm$^{-1}$: 3129 (NH), 1676 (CO). $^1$H NMR (DMSO-$d_6$): δ 1.33 (3H, t, *J*=7.0 Hz, $CH_3$), 2.77 (3H, s, $CH_3$), 4.28 (2H, q, *J*=7.0 Hz, $CH_2$), 5.97 (2H, s, $CH_2$), 6.93 (2H, d, *J*=7.1 Hz, H-2′ and H-6′), 7.22–7.34 (3H, m, H-3′, H-4′ and H-5′), 7.47 (1H, d, *J*=9.1 Hz, H-5), 7.72 (1H, d, *J*=9.1 Hz, H-4), 8.10 (1H, s, H-3), 13.47 (1H, s, NH). $^{13}$C NMR (DMSO-$d_6$): 11.9 (q), 14.3 (q), 48.3 (t), 59.3 (t), 111.8 (s), 115.2 (s), 116.9 (s), 119.2 (d), 125.7 (2×d), 126.9 (d), 127.5 (s), 128.5 (s), 128.6 (2×d), 129.5 (s), 134.4 (d), 135.4 (d), 137.8 (s), 161.1 (s). Anal. Calcd for $C_{20}H_{19}N_3O_2$ (333.39): C, 72.05; H, 5.74; N, 12.60. Found: C, 72.32; H, 6.04; N, 12.43.

*4.6.5. Ethyl 7-benzyl-2,8-dimethyl-2,7-dihydropyrrolo[3,4-g]indazole-6-carboxylate (**40**).* This product was obtained from **18B**. Yellow solid; $R_f$=0.57 ($CH_2Cl_2$/EtOAc 95:5); mp 203–204 °C; yield: 72%; IR cm$^{-1}$: 1676 (CO). $^1$H NMR ($CDCl_3$): δ 1.41 (3H, t, *J*=6.9 Hz, $CH_3$), 2.77 (3H, s, $CH_3$), 4.36 (3H, s, $CH_3$), 4.39 (2H, q, *J*=6.9 Hz, $CH_2$), 6.02 (2H, s, $CH_2$), 6.90 (2H, d, *J*=6.8 Hz, H-2′ and H-6′), 7.22–7.34 (3H, m, H-3′, H-4′, H-5′), 7.42 (1H, d, *J*=9.2 Hz, H-5), 7.90 (1H, s, H-3), 7.96 (1H, d, *J*=9.2 Hz, H-4). $^{13}$C NMR ($CDCl_3$): δ 14.4 (q), 14.5 (q), 41.9 (q), 49.2 (t), 60.0 (t), 110.2 (s), 111.5 (s), 113.1 (s), 115.7 (d), 119.0 (d), 120.0 (s), 125.7 (2×d), 127.2 (d), 128.7 (2×d), 129.3 (s), 134.3 (s), 134.4 (d), 137.4 (s), 161.9 (s). Anal. Calcd for $C_{21}H_{21}N_3O_2$ (347.41): C, 72.60; H, 6.09; N, 12.10. Found: C, 72.65; H, 5.88; N, 11.86.

*4.6.6. Ethyl 7-benzyl-1-(4-chlorobenzyl)-8-methyl-1,7-dihydropyrrolo[3,4-g]indazole-6-carboxylate (**41**).* This product was obtained from **23**. White solid; $R_f$=0.33 ($CH_2Cl_2$); mp 139–140 °C; yield: 60%; IR cm$^{-1}$: 1674 (CO). $^1$H NMR (DMSO-$d_6$): δ 1.31 (3H, t, *J*=7.1 Hz, $CH_3$), 2.72 (3H, s, $CH_3$), 4.26 (2H, q, *J*=7.1 Hz, $CH_2$), 5.59 (2H, s, $CH_2$), 5.90 (2H, s, $CH_2$), 6.92 (2H, d, *J*=7.2 1.5 Hz, H-2″ and H-6″), 7.21–7.44 (8H, m, H-5 and Ar), 7.68 (1H, d, *J*=9.3 Hz, H-4), 8.34 (1H, s, H-3). $^{13}$C NMR (DMSO-$d_6$): δ 11.9 (q), 14.3 (q), 48.2 (t), 54.7 (t), 59.3 (t), 112.2 (s), 112.4 (s), 116.6 (d), 117.2 (s), 118.8 (d), 125.4 (d), 125.7 (2×d), 126.9 (s), 128.5 (2×d), 128.6 (2×d), 129.3 (2×d), 129.7 (s), 130.3 (s), 132.3 (s), 136.5 (d), 137.9 (s), 143.4 (s), 170.0 (s). Anal. Calcd for $C_{27}H_{24}ClN_3O_2$ (457.95): C, 70.81; H, 5.28; N, 9.18. Found: C, 71.06; H, 4.98; N, 9.24.

*4.6.7. 7-Benzyl-2-methyl-2,7-dihydropyrrolo[3,4-g]indazole (**42**).* This product was obtained from **30**. Yellow solid; $R_f$=0.37 ($CH_2Cl_2$/EtOAc 95:5); mp 107–108 °C; yield: 42%; $^1$H NMR ($CDCl_3$): δ 4.35 (3H, s, $CH_3$), 4.89 (2H, s, $CH_2$), 7.14–7.30 (5H, m, Ar, H-6 and H-8), 7.47–7.53 (3H, m, Ar and H-5), 7.89 (1H, s, H-3), 7.99 (1H, d, *J*=9.3 Hz, H-4). $^{13}$C NMR ($CDCl_3$): δ 41.3 (q), 41.4 (t), 114.6 (d), 125.4 (d), 127.1 (s), 127.4 (d), 127.5 (d), 127.7 (d), 128.6 (2×d), 128.7 (d), 128.8 (2×d), 132.2 (s), 136.7 (s), 141.5 (s), 169.3 (s). Anal. Calcd for $C_{17}H_{15}N_3$ (261.32): C, 78.13; H, 5.79; N, 16.08. Found: C, 78.46; H, 5.50; N, 16.04.

### 4.7. General procedure for the preparation of tetrahydropyrrolo[3,4-g]indazol-3(2*H*)-ones (43,44)

The relevant ketoester **8a**,**b** (0.002 mol) was dissolved in anhydrous ethanol (12 mL) and methylhydrazine (1.05 mL, 0.02 mol) was added. The reaction mixture was heated under reflux for 24 h. Upon cooling the solvent was removed in vacuo and water was added to the mixture. A solid precipitated, which was filtered, dried, and recrystallized from ethanol.

*4.7.1. 2,7-Dimethyl-3a,4,5,7-tetrahydropyrrolo[3,4-g]indazol-3(2H)-one (**43**).* This product was obtained from **8a**. White solid; $R_f$=0.37 ($CH_2Cl_2$/EtOAc 95:5); mp 226–228 °C; yield 38%; IR cm$^{-1}$: 1682 (CO). $^1$H NMR ($CDCl_3$): δ 1.10–1.92 (2H, m, $CH_2$), 2.30–3.14 (2H, m, $CH_2$), 3.29 (3H, s, $CH_3$), 3.64 (3H, s, $CH_3$), 4.17 (1H, s, CH), 6.43 (1H, s, H-6), 6.98 (1H, s, H-8). $^{13}$C NMR ($CDCl_3$): δ 17.0 (t), 31.1 (q), 32.0 (d),

32.2 (t), 36.6 (q), 74.0 (s), 110.4 (s), 118.4 (d), 118.8 (d), 122.9 (s), 173.3 (s). Anal. Calcd for $C_{11}H_{13}N_3O$ (203.24): C, 65.01; H, 6.45; N, 20.68. Found: C, 65.30; H, 6.24; N, 20.78.

*4.7.2. 7-Benzyl-2-methyl-3a,4,5,7-tetrahydropyrrolo[3,4-g]indazol-3(2H)-one (**44**).* This product was obtained from **8b**. White solid; $R_f$=0.49 ($CH_2Cl_2$/EtOAc 95:5); mp 112–114 °C; yield 45%; IR $cm^{-1}$: 1699 (CO). $^1H$ NMR ($CDCl_3$): $\delta$ 2.54–2.80 (4H, m, 2× $CH_2$), 3.32 (3H, s, $CH_3$), 4.98 (1H, s, CH), 5.01 (2H, s, $CH_2$), 6.48 (1H, s, H-6), 7.06–7.32 (6H, m, Ar and H-8). $^{13}C$ NMR ($CDCl_3$): $\delta$ 22.4 (t), 26.7 (t), 31.7 (q), 48.3 (d), 54.4 (t), 113.5 (s), 117.1 (d), 118.5 (d), 123.9 (s), 127.9 (2×d), 128.7 (d), 129.3 (2×d), 137.2 (s), 156.3 (s), 173.8 (s). Anal. Calcd for $C_{17}H_{17}N_3O$ (279.34): C, 73.10; H, 6.13; N, 15.04. Found: C, 73.40; H, 6.40; N, 14.86.

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## Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.09.003.

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