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A FACILE SYNTHESIS OF 4-ARYL-5-ALKOXYCARBONYL-6-HYDROXY-6-METHYL-4,5,6,7-TETRAHYDRO-3-HYDROXY-2-(PYRIDIN-2-YL)-INDAZOLES AND THEIR NMR CHARACTERIZATIONS

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Abstract - A series of *N*-pyridinyl tetrahydroindazoles have been synthesized by a convenient and regioseletive method by taking cyclic β-ketoesters as scaffolds. An optimum reaction condition was achieved by monitoring the reaction in different reaction condition. One and two dimensional NMR spectroscopic investigations evidenced the formation and structure of the compounds. Besides, all the compounds have been achieved as a single isomer with pyridyl group at *N*(2). A suitable reaction mechanism was proposed.

INTRODUCTION

Tetrahydroindazoles are cycloalkane derivatives of pyrazoles. Pyrazoles are well known skeleton having much importance in the field of medicinal chemistry owing to their remarkable biological potencies.[1–4] Moreover, substituted pyrazoles and pyrazole derivatives such as benzindazoles[5] (aromatic derivatives of pyrazoles), tetrahydroindazoles along with several substituents are also well known for their unique pharmacological properties.[6–8] Several reports have been proved that pyrazoles are being in annular tautomerism[9] and unsymmetrical pyrazoles and indazoles are showing regioisomerism with respect to *N*-substitution like *N*-arylation[10] and *N*-alkylation[11] which are inevitably yielded a mixture of *N*(1) and *N*(2) regioisomers with poor selectivities during substitutions. Numerous methods have been developed to achieve a regioselective synthesis of *N*-substituted pyrazole derivatives and to crossover the harsh reactionconditions.

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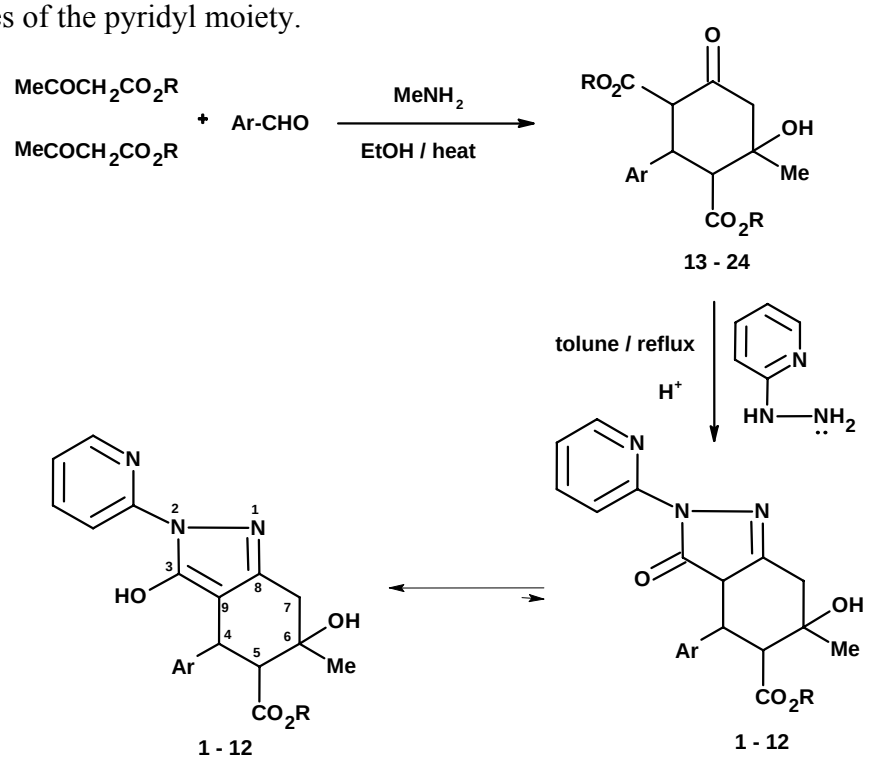
Chemistry

Generally pyrazole ring have been synthesized by the reaction of β-dicarbonyl compounds with hydrazine.[1,12,13] Tetrahydroindazoles are usually prepared from cyclohexanone and its derivatives.[14–18] Instead of cyclohexanones, 1,3-cylohexanedione and its derivatives were used to afford tetrahydroindazole-4-ones.[19-21] The reaction of Baylis-Hillman adduct and phenylhydrazine results in diphenylpyrazole[22] formation via the successive hydrazone formation, acid catalyzed cyclization, and subsequent 1,3-hydrogen transfer. Heterogeneous catalysts have also been used for the synthesis of both pyrazoles and tetrahydroindazoles derivatives (1,2-disubstituted cycloalkanopyrazole), starting from hydrazine and 1,3-diketone.[14b,23,24] Even though there are several methods, there is still a lack of general and efficient methodologies for the regioselective synthesis of *N*-substituted tetrahydroindazoles with various substituents in saturated ring.

Here, we described a convenient synthetic technique for the synthesis of 4-aryl-5-alkoxycarbonyl-6-hydroxy- 6-methyl-4,5,6,7-tetrahydro-3-hydroxy-2(pyridin-2-yl)indazoles as a single isomer. We proved that alicyclic keto esters are being suitable scaffolds for the regioselective synthesis of *N*-substituted indazoles and the preferable reaction condition has been found. The formation of the series of title compounds and their structural elucidations have been carried out by using NMR tool. 2,4-Bis(alkoxycarbonyl)-3-aryl-5-hydroxy-5-methylcyclohexanoes[25] have been used as a scaffolds and 2-hydrazinopyridine was used as hydrazine derivative, for its efficient reactivity and also in lieu of the biological properties of the pyridyl moiety.



Scheme 1. Synthesis of compounds **1-12**

Entry		R	Ar
1	**13**	Me	Ph
2	**14**	Me	4-Cl-Ph
3	**15**	Me	3-Cl-Ph
4	**16**	Me	4-MeO-Ph
5	**17**	Me	3,5-$(MeO)_2$-Ph
6	**18**	Me	3-NO_2-Ph
7	**19**	Me	3-PhOPh-Ph
8	**20**	Et	Ph
9	**21**	Et	4-MeO-Ph
10	**22**	Et	3-Cl-Ph
11	**23**	Et	4-Cl-Ph
12	**24**	Et	4-NO_2-Ph

RESULTS AND DISCUSSION

A series of *N*-pyridinyl tetrahydroindazoles were synthesized by the reaction of corresponding cyclic ketoesters with 2-hydrazinopyridine as shown in the Scheme 1. It was helped us that the synthesis of 1*H*-indazoles from the reaction of cyclic ketoesters with the dinucleophile hydrazine, to find the optimum reaction conditions and also for the structural elucidations of *N*-pyridylindazoles. The 1*H*-tetrahydroindazoles (**25**) synthesis has been carried out in EtOH medium by refluxing at 70-80 ˚C for about two hours with good yield (75%). It was observed that there is no appreciable improvement in yield by the addition of acid catalyst (acetic acid) or weak base (sodium acetate) and also by changing the solvents. The resultant product was characterized by one and two dimensional NMR spectral results and found as 5-methoxycarbonyl-6-hydroxy-6-methyl-4-phenyl-4,5,6,7-tetrahydro-3-hydroxy-1*H*-indazole (**25**) as a single isomer.[26]

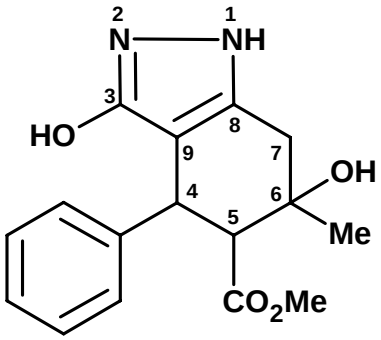


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Table 1. Spectral assignments of 1*H*-indazole (**25**) recorded in DMSO-d_6

Carbon chemical shifts, δ (ppm)	Proton resonances,* δ (ppm) and HSQC Correlations	HMBC Correlations
157.9, C-3	no correlations	4.27, H-4a
38.7, C-4	4.06, H-4a	7.25 (ph-*ortho* 2H), 2.73 (H-5a)
59.9, C-5	2.57, H-5a	4.27 (H-4a), 2.98 (H-7e), 1.38 (Me at C-6)
69.9, C-6	no correlations	2.76 (H-7a), 2.98 (H-7e), 1.38 (Me at C-6)
36.5, C-7	2.52, H-7a; 2.77, H-7e	2.73 (H-5a), 1.38 (Me at C-6)
138.8, C-8	no correlations	2.76 (H-7a), 2.98 (H-7e), 4.27 (H-4a), 1.38 (Me at C-6)
99.2, C-9	no correlations	4.27 (H-4a), 2.76 (H-7a), 2.98 (H-7e)
28.4, Me at C-6	1.21 (Me at C-6)	2.76 (H-7a), 2.98 (H-7e)
50.8, Me of CO_2 Me	3.43 (Me of CO_2Me)	2.73 (H-5a) weak
172.0, C=O of CO_2Me	no correlations	2.73 (H-5a), 4.27 (H-4a), 3.51 (Me of CO_2 Me), 2.98 (H-7e)
126.0, 127.7, 128.0, 143.0 - phenyl *ipso*	7.07-7.21 no correlations for *ipso* carbon	4.27 (H-4a), 2.73 (H-5a)

***** δ OH at C-6 (4.48 ppm), OH at C-3 (11.0 ppm) and N-H at 1 (9.0 ppm)

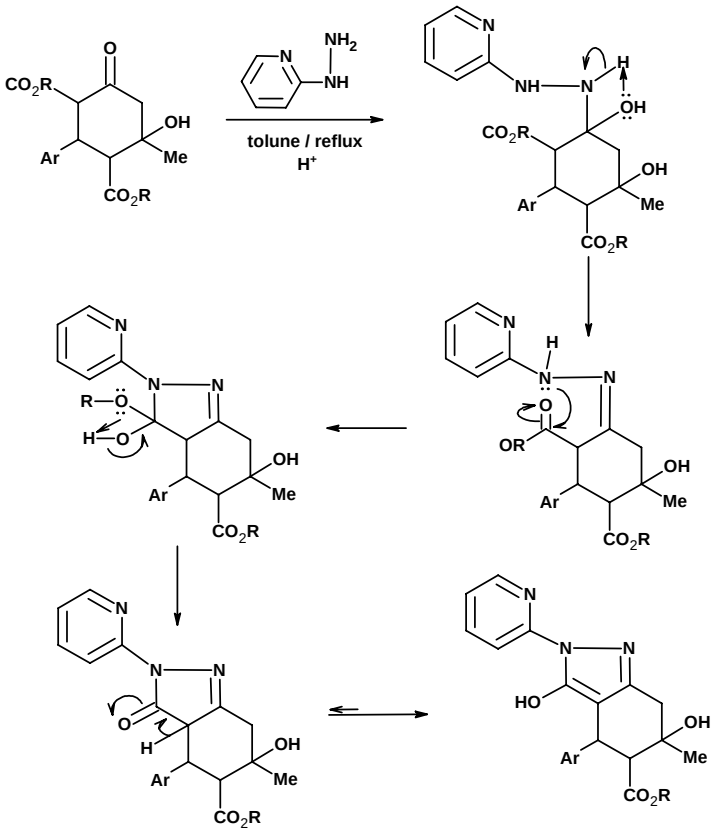
To find the optimum reaction condition, *N*-pyridyl tetrahydroindazoles synthesis was performed in different solvents with and without the addition of acid or base catalyst (Table 1). The reaction was not progressed in EtOH medium more than 5% and there was no improvement by the addition of acid or base catalysts and also when allowed in prolonged heating. Also, very poor yield observed in methanol medium suggested that the alcoholic medium is not a desirable solvent even for the hydrazone formation from the condensation of hydrazinopyridine with cyclic ketoesters. When the reaction was carried out in benzene or toluene, a substantial improvement in the yield was noted. Moreover, the addition of catalytic amount of glacial acetic acid in toluene medium was found to be advantageous in enhancing the yield and reducing the reaction time. Addition of excess acetic acid or HCl leads to the dehydration of OH at C-6. A preliminary monitoring through TLC and GC/MS supports the formation of the product as a single isomer.

All the products were purified by the straight forward recrystalization in EtOH after evaporating the solvent by vacuum distillation.

Table 2. Different reaction conditions and the results (for compounds **1** and **7**)

Reaction conditions	EtOH 70-80 ˚C, 30 h	EtOH /AcOH 70-80 ˚C 30 h	MeOH/AcOH 80-85 ˚C 30 h	benzene/ AcOH 75-80 ˚C 24 h	toluene 85-90 ˚C 24 h	toluene/sodium acetate 85-90 ˚C 24 h	toluene/ AcOH 85-90 ˚C 6-8 h
Yield	< 5%	< 5%	9-11%	35-40%	50-55%	ca. 55%	> 65%

The reaction mechanism was proposed with the support of literature and in connection with the maintained reaction conditions. It is obvious that the direct condensation of pyridinyl hydrazine with the keto functionality through its NH_2 group is kinetically more favorable, subsequently the ester group carbonyl should prefer bond formation with secondary amine nature like NH. The improvement in the yield and lessen in reaction time duration after the addition of catalytic amount of acetic acid may be due to the faster reaction rate of the NH_2 condensation with keto group initially, after, followed by the dehydration, cycloaddition through NH with ester group and hydrogen transfer yielded the *N*-pyridinyltetrahydro indazole with the pyridinyl moiety positioned at *N*-2 (Scheme 2).



Scheme 2. Plausible mechanism for the formation of products **1**-**12**

For all the compounds, ^{1}H and ^{13}C NMR spectra were recorded. For compound **1** HSQC, HMBC, NOESY and for compound **8** HMBC spectra were also recorded. Mass spectrum was recorded for compounds **1**, **8**, and **10.**

Mass spectral analysis ensured the proposed molecular formulae with the observation of corresponding molecular ion peaks at m/e 379, 393 and 423 respectively for the compounds **1**, **8** and **10.**

Structural elucidation through NMR

^{1}H NMR results evidenced the formation of regioselective isomer. Proton resonances were investigated through its chemical shift, multiplicity and coupling constants values. All the compounds recorded in $CDCl_3$ showed almost similar resonances for all the protons except the aromatic protons and ester group protons with respect to the substituents, and the compound (**6**) recorded in DMSO-d_6 having appreciable difference in the chemical shift of OH at C-6 due to solvent effect. The pyridinyl protons resonances observed in the aromatic region and the absence of one ester group signals observed in parent ketoesters supports the cyclization. The calculated coupling constants from the four doublets observed in the aliphatic region facilitated the assignments. A convenient assignment was made for the methylene and methine protons on the basis of their coupling constants and position. Two doublets were observed in the range of 2.74-2.77 ppm and 2.96-2.99 ppm with the coupling constants (*J*) of around 16Hz and another two doublets in the range of 4.21-4.27 ppm and 2.66-2.73 ppm with the coupling constant of around 12Hz showed closer proximity to the corresponding geminal and vicinal coupling constants of cyclohexane ring, were conveniently assigned for methylene protons at C-7 and methine protons at C-4 and C-5 respectively. Among the two methine protons, H-4a was assigned from its downfield resonance due to the deshielding aroused from the fused ring formation at C-8 and C-9. Carbon resonances showed pyridyl carbons along with the saturated ring carbons, aromatic carbons and ester carbons. The individual assignments of carbons and protons, position of pyridinyl moiety and the stereochemistry of indazole have been succeeded by NOESY, HSQC and HMBC spectrum.

From the HSQC (Figure 1) spectral results of compound **1** we have found that there are seven quaternary carbons for the anticipated structure. The individual assignments of methyl, methylene and methine carbons and their associated protons were carried out from their corresponding cross peaks observed at 1.38/28.7 ppm (Me at C-6), 3.51/51.5 ppm (Me of CO_2Me), 2.76, 2.98/37.1 ppm (CH_2 of C-7), 4.27/39.8 ppm (CH of C-4) and 2.73/59.0 ppm (CH of C-5). Pyridinyl protons and their respective carbons also predicted from their corresponding cross peaks 8.09/144.8 ppm, 7.83/111.7 ppm, 139.7 ppm and 7.07/119.5 ppm. Likewise, aromatic protons were also assigned (Table 3).

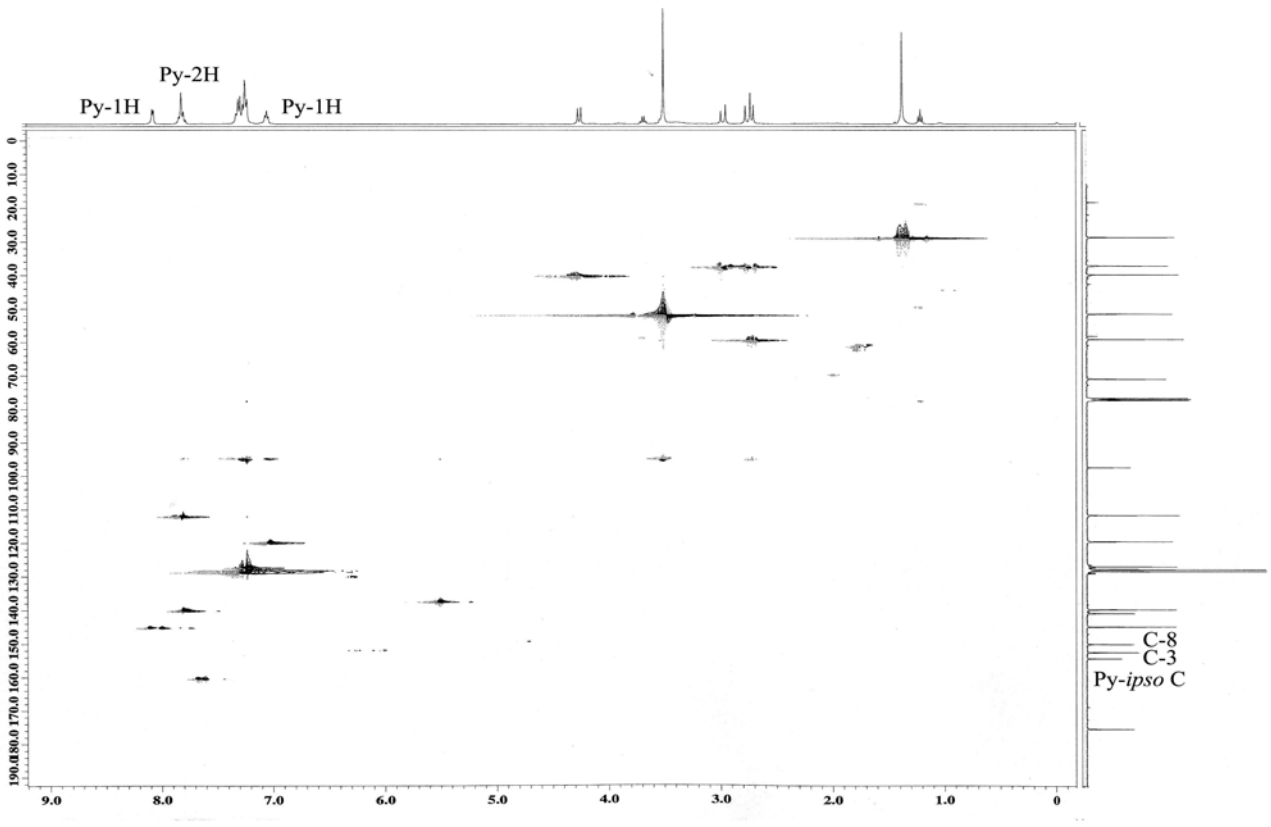


Figure 1. HSQC spectrum of compound **1**

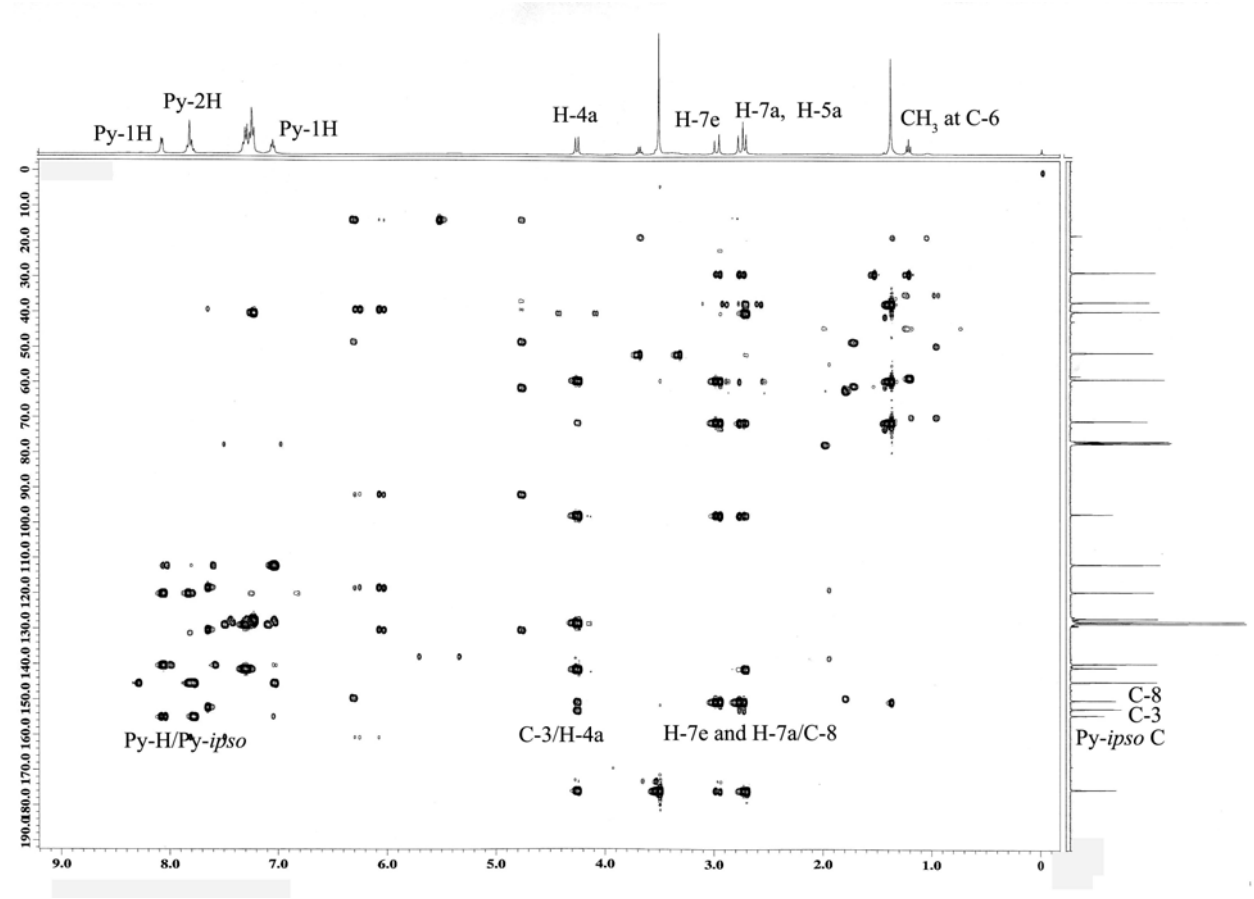


Figure 2. HMBC spectrum of compound **1**

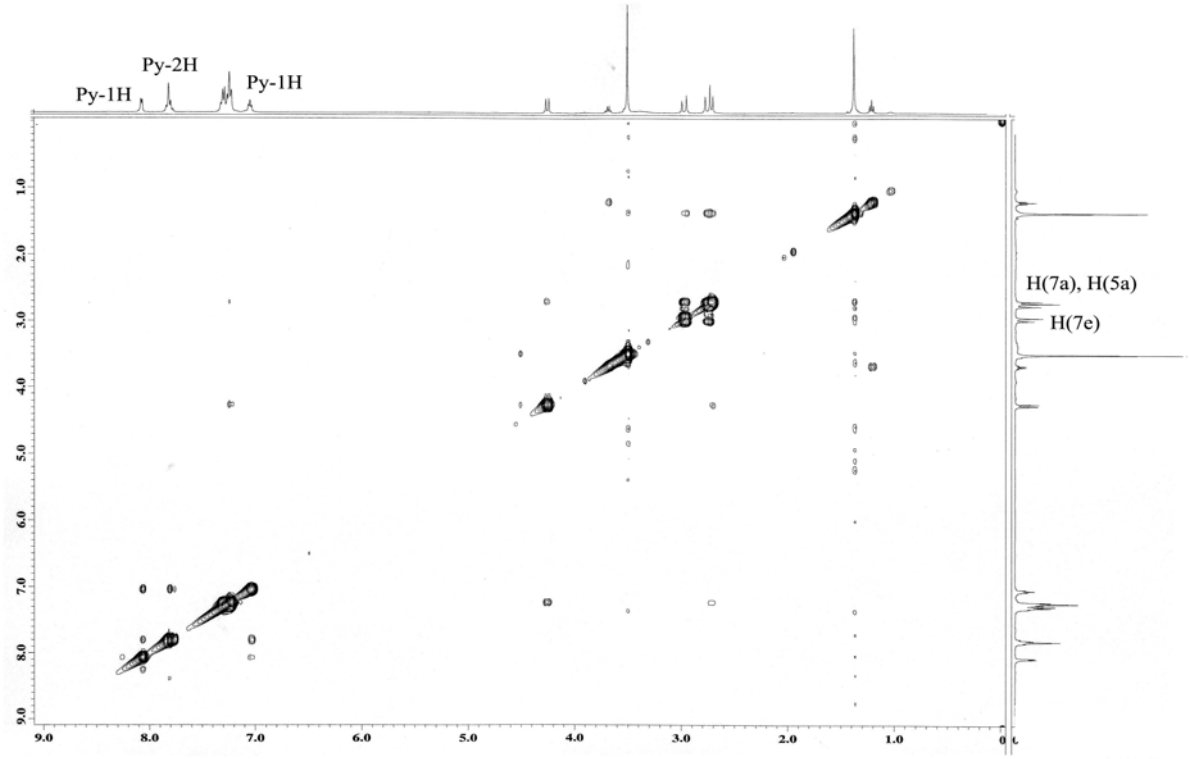


Figure 3. NOESY spectrum of compound **1**

The HMBC (Figure 2) correlations observed for compound **1** furnished the quaternary carbons assignments and also supports for the elucidation of structure. The individual assignment of three closer carbon resonances achieved from their corresponding multiple bond correlations marked as δ 152.4 /H-4a, δ 150.0/H-7a, H-7e, H-4a, Me at C-6 and δ 154.3/pyridinyl protons for C-3, C-8/C=N and ″C-1 (pyridinyl *ipso* carbon) respectively. Remaining correlations supported for the individual assignments are tabulated (Table-2). The HMBC correlations observed for compound **8** are given in Table 4.

The absence of OH (C-3) signal in ^{1}H NMR recorded in $CDCl_3$ is due to proton exchange with solvent, is confirmed by recording compound (**1**) in DMSO-d_6 in which the OH signal is observed at 11.7 ppm as a broad singlet. The downfield shift observed for pyridinyl protons in DMSO-d_6 was due to the strong interaction between sulphoxide and nitrogen.

Although all the assignments of *N*-pyridinylindazoles were carried out from the observed NMR results, it was further confirmed by comparing the one and two dimensional results observed for compound **1** with 1*H*-indazole **25** (Table-2). Apart from the solvent effect there was no appreciable difference found in the proton resonances. But carbon resonances of C-3 and C-8 showed a significant difference. The upfield shift of C-3 for about 5.5 ppm and the downfield shift of C-8 for about 11.2 ppm in *N*-pyridinylindazole cleared the structure of the fused pyrazole ring with pyridinyl group positioned at N-2.

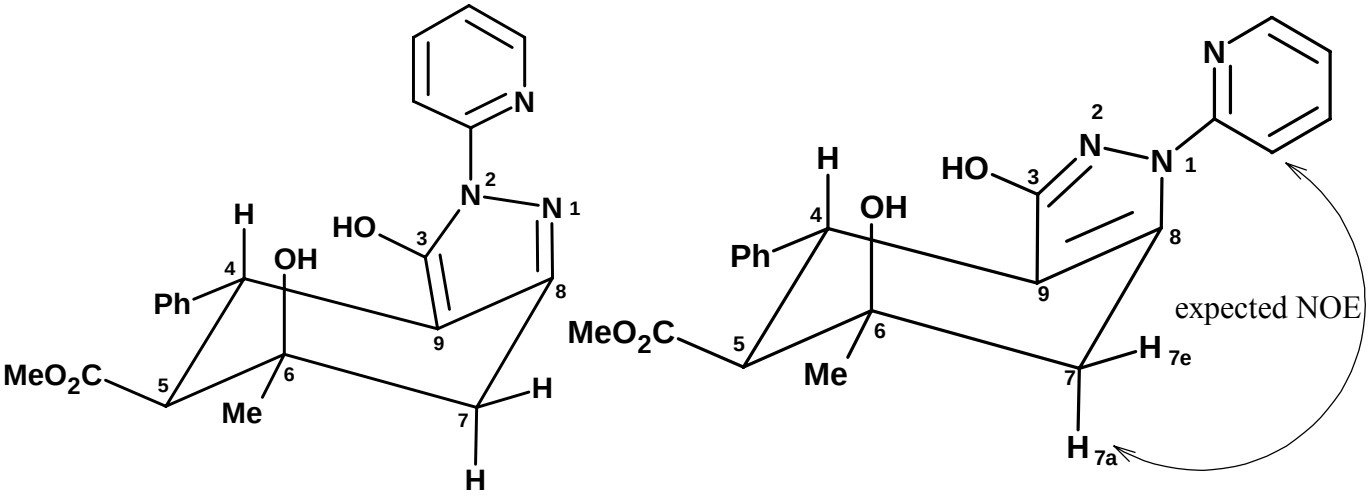
Table 3. HSQC and HMBC Correlations of compound **1**

Carbon chemical shifts	HSQC Correlations	HMBC Correlations
152.4, C-3	no Correlations	4.27, H-4a
39.8, C-4	4.27, H-4a	7.25 (ph-*ortho* 2H), 2.73 (H-5a)
59.0, C-5	2.73, H-5a	4.27 (H-4a), 2.98 (H-7e), 1.38 (Me at C-6)
70.9, C-6	no Correlations	2.76 (H-7a), 2.98 (H-7e), 1.38 (Me at C-6)
37.1, C-7	2.76, H-7a ; 2.98, H-7e	2.73 (H-5a), 1.38 (Me at C-6)
150.0, C-8	no correlations	2.76 (H-7a), 2.98 (H-7e), 4.27 (H-4a), 1.38 (Me at C-6)
97.4, C-9	no correlations	4.27 (H-4a), 2.76 (H-7a), 2.98 (H-7e)
28.7, Me at C-6	1.38 (Me at C-6)	2.76 (H-7a), 2.98 (H-7e)
51.5, Me of CO_2Me	3.51 (Me of CO_2Me)	2.73 (H-5a) weak
175.4, C=O of CO_2Me	no correlations	2.73 (H-5a), 4.27 (H-4a), 3.51 (Me of CO_2Me), 2.98 (H-7e)
140.8, phenyl *ipso*	no correlations	4.27 (H-4a), 2.73 (H-5a)
154.3, pyridinyl *ipso*	no correlations	8.09, 7.83, 7.07 (pyridinyl protons)

Table 4. HMBC Correlations of compound **7**

Carbon chemical shifts, δ (ppm)	HMBC Correlations, δ (ppm)
152.5, C-3	4.26, H-4a
40.0, C-4	7.25 (ph-*ortho* 2H), 2.71 (H-5a),
58.8, C-5	4.26 (H-4a), 2.98 (H-7e), 1.40 (Me at C-6)
70.9, C-6	2.76 (H-7a), 2.98 (H-7e), 1.40 (Me at C-6)
37.2, C-7	2.71 (H-5a), 1.40 (Me at C-6)
150.1, C-8	2.76 (H-7a), 2.98 (H-7e), 4.26 (H-4a), 1.40 (Me at C-6)
97.5, C-9	4.26 (H-4a), 2.76 (H-7a), 2.98 (H-7e), 2.71 (H-5a)
28.7 (Me at C-6)	2.76 (H-7a), 2.98 (H-7e)
13.8 (Me of CO_2Et)	4.0 (CH_2 of CO_2Et)
60.6 (CH_2 of CO_2Et)	0.97 (Me of CO_2Et)
175.0, C=O of CO_2Et	2.71 (H-5a), 4.26 (H-4a), 4.0 (CH_2 of CO_2Et), 2.98 (H-7e)
140.8, phenyl *ipso*	4.26 (H-4a), 2.71 (H-5a) - aromatic protons
154.4, pyridinyl *ipso*	8.09, 7.83, 7.06 (pyridinyl protons)

Stereochemistry of the products suggested from their calculated coupling constants of protons, and NOEs (Figure 3) observed. Coupling constants of methylene protons at C-7 and methine protons H-4a and H-5a are almost closer to the parent cyclic ketoesters suggested that the cycloalkane ring should be in chair conformation (Figure 4). None of the NOEs observed for the pyridinyl protons with the saturated ring protons, especially with H-7a and H-7e (Figure 5) proved that the pyridinyl ring should be positioned in N(2).



CONCLUSION

A convenient and regioselective synthetic route to afford the *N*(2)-pyridyltetrahydroindazoles as a single isomer from cyclic β-ketoesters was described. The reaction was consistent while using toluene as solvent with the addition of catalytic amount of acetic acid by refluxing at 80-90 ˚C to get a series of products. NMR analysis supports the pyridyl group at *N*(2) and C-3 having OH. The stereochemistry was found as normal chair conformation.

EXPERIMENTAL

Melting points were measured in Electrothermal-9100 (Japan) instrument and were uncorrected. NMR was recorded in $CDCl_3$ (except **6** in DMSO-d_6) with Me_4Si as internal standard in JEOL (Japan) JNM ECP-400 instrument operating at 400 MHz for ^1H and 100.6 MHz for ^{13}C. Mass spectrum was recorded in JEOL, JMS-700.

General procedure for synthesis of 2,4-bis(alkoxycarbonyl)-3-aryl-5-hydroxy-5-methylcyclohexanoes (13-24)

A mixture of acetoacetic esters (10 mmol), aromatic aldehydes (5 mmol) and methylamine (5 mmol) was heated to boiling. The reaction mixture was kept for overnight. The separated solid was filtered and recrystalized from EtOH.[25]

Synthesis of 5-methoxycarbonyl-6-hydroxy-6-methyl-4-phenyl-4,5,6,7-tetrahydro-3-hydroxy-1*H*-indazole(25)

A mixture of respective ketoester **13** (1 mmol) and hydrazine hydrate (1.3 mmol) in EtOH was refluxed for 2 h, and it was poured in ice. The separated solid was filtered and recrystalized from EtOH.

General procedure for synthesis 4-aryl-5-alkoxycarbonyl-6-hydroxy-6-methyl-4,5,6,7-tetrahydro-3-hydroxy-2-(2-pyridinyl)indazoles (1-12)

A mixture of cyclic keto ester (1 mmol) and 2-hydrazinopyridine(1.2 mmol) in dry toluene with the addition of catalytic amount of acetic acid were refluxed for about 6-8 h under nitrogen atmosphere. Duration of the reaction period varied for every reaction, and it was monitored by TLC. After completion of the reaction, the solvent was evaporated under vacuum and the resultant residue was recrystalized from EtOH.

Synthesis of *t*(5)-methoxycarbonyl-*t*(6)-hydroxy-*c*(6)-methyl-r(4)-phenyl-4,5,6,7-tetrahydro-3-hydroxy-2-(pyridin-2-yl)indazole (1): This compound was obtained as white crystals (284 mg, 75%) with mp 157-158 ˚C. EI-MS (70 eV): m/e = 379 (M^+), 302 (bp), 262, 78. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23-7.33 (m, 5H, ArH), 4.27 (d, ^3J = 11.0 Hz, 1H, H-4a), 2.73 (d, ^3J = 11.0 Hz, 1H, H-5a), 2.76 (d, ^2J = 16.84 Hz, 1H, H-7a), 2.98 (d, ^2J = 16.88 Hz, 1H, H-7e), 1.38 (s, 3H, Me at C-6), 3.36 (bs, 1H, OH at C-6), 3.51 (s, 3H, Me of CO_2Me), 8.09 (d, 1H, PyH), 7.83 (m, 2H, PyH), 7.07 (t, 1H, PyH) ppm. ^{13}C NMR(100.6 MHz, $CDCl_3$):δ = 152.4 (C-3), 39.8 (C-4), 59.0 (C-5), 70.9 (C-6), 37.1 (C-7), 150.0 (C-8), 97.4 (C-9), 28.7 (Me at C-6), 51.5 (Me of CO_2Me), 175.4 (C=O), 140.8 (*ipso* Ph-C), 127.0, 127.8, 128.3 (Phenyl), 154.3 (*ipso* Py-C), 111.7, 139.7, 119.5, 144.8 (Pyridyl) ppm. Anal. Calcd for $C_{21}H_{21}N_3O_4$ (379.41): C 66.48, H 5.58, N 11.08. Found: C 66.51, H 5.57, N 11.06.

Synthesis of 5-methoxycarbonyl-6-hydroxy-6-methyl-4-(*p*-chlorophenyl)-4,5,6,7-tetrahydro-3-hydroxy-2-(pyridinyl)indazole (2): This compound was obtained as white solid (289 mg, 70%) with mp 143-145 ˚C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25-7.29 (m, 5H, ArH), 4.26 (d, ^3J = 11.36 Hz, 1H, H-4a), 2.68 (d, ^3J = 11.0 Hz, 1H, H-5a), 2.76 (d, ^2J = 16.84 Hz, 1H, H-7a), 2.98 (d, ^2J = 16.84 Hz, 1H, H-7e), 1.38 (s, 3H, Me at C-6), 3.17 (bs, 1H, OH at C-6), 3.55 (s, 3H, Me of CO_2Me), 8.12 (d, 1H, PyH), 7.84 (m, 2H, PyH), 7.09 (t, 1H, PyH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.5 (C-3), 39.2 (C-4), 58.9 (C-5), 71.0 (C-6), 37.1 (C-7), 149.9 (C-8), 96.9 (C-9), 28.7 (Me at C-6), 51.7 (Me of CO_2Me),175.2 (C=O), 139.5 (*ipso* Ph-C), 128.6, 129.2, 132.6 (Phenyl), 154.3 (*ipso* Py-C), 111.7, 139.8, 119.6, 144.9 (Pyridyl). Anal. Calcd for $C_{21}H_{20}ClN_3O_4$ (413.85): C 60.95, H 4.87, N 10.15. Found: C 60.98, H 4.86, N 10.14.

Synthesis of 5-methoxycarbonyl-6-hydroxy-6-methyl-4-(*m*-chlorophenyl)-4,5,6,7-tetrahydro-3-hydroxy-2-(2-pyridinyl)indazole (3): This compound was obtained as grayish white powder (297 mg, 72%) with mp 194-196 ˚C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.13-7.15, 7.23-7.26 (m, 5H, ArH), 4.25 (d, ^3J = 11.36 Hz, 1H, H-4a), 2.69 (d, ^3J = 11.36 Hz, 1H, H-5a), 2.75 (d, ^2J = 16.84 Hz, 1H, H-7a), 2.98 (d, ^2J = 16.84 Hz, 1H, H-7e), 1.38 (s, 3H, Me at C-6), 3.35 (bs, 1H, OH at C-6), 3.55 (s, 3H, Me of CO_2Me),

8.11 (d, 1H, PyH), 7.84 (m, 2H, PyH), 7.08 (t, 1H, PyH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 152.5 (C-3), 39.6 (C-4), 58.8 (C-5), 70.9 (C-6), 37.1 (C-7), 149.8 (C-8), 96.6 (C-9), 28.6 (Me at C-6), 51.6 (Me of CO_2Me), 175.1 (C=O), 143.1 (*ipso* Ph-C), 134.1, 129.5, 127.9, 127.2, 126.1 (Phenyl), 154.3 (*ipso* Py-C), 111.7, 139.8, 119.6, 144.9 (Pyridyl). Anal. Calcd for $C_{21}H_{20}ClN_3O_4$ (413.85): C 60.95, H 4.87, N 10.15. Found: C 6.98, H 4.89, N 10.14.

Synthesis of 5-methoxycarbonyl-6-hydroxy-6-methyl-4-(*p*-methoxyphenyl)-4,5,6,7-tetrahydro-3-hydroxy-2-(2-pyridinyl)indazole (4): This compound was obtained as white needles (306 mg, 75%) with mp 191-192 ˚C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.05-7.09, 7.79-7.85 (m, 5H, ArH), 4.23 (d, ^3J = 11.36 Hz, 1H, H-4a), 2.70 (d, ^3J = 11.36 Hz, 1H, H-5a), 2.75 (d, ^2J = 16.88 Hz, 1H, H-7a), 2.97 (d, ^2J = 16.84 Hz, 1H, H-7e), 1.38 (s, 3H, Me at C-6), 3.34 (bs, 1H, OH at C-6), 3.54 (s, 3H, Me of CO_2Me), 8.11 (d, 1H, PyH), 7.83 (m, 2H, PyH), 7.07 (t, 1H, PyH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 152.4 (C-3), 39.0 (C-4), 59.2 (C-5), 70.9 (C-6), 37.2 (C-7), 150.1 (C-8), 97.6 (C-9), 28.7 (Me at C-6), 51.6 (Me of CO_2Me), 175.5 (C=O), 132.9 (*ipso* Ph-C), 128.7, 113.7, 158.4 (Phenyl), 55.0 (Ph-OMe), 154.4 (*ipso* Py-C), 111.7, 139.7, 119.4, 144.8 (Pyridyl). Anal. Calcd for $C_{22}H_{23}N_3O_5$ (409.44): C 64.54, H 5.66, N 10.26. Found: C 64.51, H 5.68, N 10.28.

Synthesis of 5-methoxycarbonyl-6-hydroxy-6-methyl-4-(*2,4*-methoxyphenyl)-4,5,6,7-tetrahydro-3-hydroxy-2-(2-pyridinyl)indazole (5): This compound was obtained as white needles (351 mg, 80%) with mp 181-183 ˚C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.36-6.40 (m, 3H, ArH), 4.21 (d, ^3J = 11.32 Hz, 1H, H-4a), 2.72 (d, ^3J = 10.96 Hz, 1H, H-5a), 2.75 (d, ^2J = 15.04 Hz, 1H, H-7a), 2.97 (d, ^2J = 16.84 Hz, 1H, H-7e), 1.37 (s, 3H, Me at C-6), 3.35 (bs, 1H, OH at C-6), 3.57 (s, 3H, Me of CO_2Me), 8.12 (d, 1H, PyH), 7.84 (m, 2H, PyH), 7.08 (t, 1H, PyH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 152.5 (C-3), 40.0 (C-4), 58.9 (C-5), 71.0 (C-6), 37.1 (C-7), 150.0 (C-8), 97.0 (C-9), 28.7 (Me at C-6), 51.6 (Me of CO_2Me), 175.4 (C=O), 98.8, 105.8, 143.5, 160.6 (Phenyl), 55.1 (2,4-MeO -Ph), 154.3 (*ipso* Py-C), 111.7, 139.7, 119.5, 144.9 (Pyridyl). Anal. Calcd for $C_{23}H_{25}N_3O_6$ (439.46): C 62.86, H 5.73, N 9.56. Found: C 62.89, H 5.75, N 9.57.

Synthesis of 5-methoxycarbonyl-6-hydroxy-6-methyl-4-(*m*-nitrophenyl)-4,5,6,7-tetrahydro-3-hydroxy-2-(2-pyridinyl)indazole (6): This compound was obtained as yellow crystals (288 mg, 68%) with mp 223-226 ˚C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.56, 7.66, 8.0, 8.08 (m, 5H, ArH), 4.22 (d, ^3J = 9.88 Hz, 1H, H-4a), 2.85 (d, ^3J = 10.6 Hz, 1H, H-5a), 2.63 (d, ^2J = 16.84 Hz, 1H, H-7a), 2.96 (d, ^2J = 16.84 Hz, 1H, H-7e), 1.28 (s, 3H, Me at C-6), 4.87 (bs, 1H, OH at C-6), 3.46 (s, 3H, Me of CO_2Me), 8.37 (d, 1H, PyH), 8.20 (m, 2H, PyH), 7.17 (t, 1H, PyH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 152.5 (C-3), 39.2 (C-4), 58.4 (C-5), 69.5 (C-6), 39.0 (C-7), 149.0 (C-8), 96.6 (C-9), 28.1 (Me at C-6), 51.1 (Me of CO_2Me), 171.9 (C=O), 147.7, 144.6, 135.4, 129.5, 122.6, 121.5 (Phenyl and *ipso* Py-C), 111.0, 138.8,

119.8 (Pyridyl). Anal. Calcd for $C_{21}H_{20}N_4O_6$ (424.41): C 59.43, H 4.75, N 13.20. Found: C 59.47, H 4.76, N 13.21.

Synthesis of 5-methoxycarbonyl-6-hydroxy-6-methyl-4-(*m*-phenoxyphenyl)-4,5,6,7-tetrahydro-3-hydroxy-2-(2-pyridinyl)indazole (7): This compound was obtained as white needles (339 mg, 72%) with mp 201-203 ˚C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.91-7.09, 7.24-7.30 (m, 5H, ArH), 4.26 (d, ^3J = 11.36 Hz, 1H, H-4a), 2.70 (d, ^3J = 11.36 Hz, 1H, H-5a), 2.73 (d, ^2J = 16.84 Hz, 1H, H-7a), 2.96 (d, ^2J = 16.84 Hz, 1H, H-7e), 1.37 (s, 3H, Me at C-6), 3.32 (bs, 1H, OH at C-6), 3.56 (s, 3H, Me of CO_2Me), 8.12 (d, 1H, PyH), 7.81 (m, 2H, PyH), 6.91-7.09 (m, 1H, PyH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 152.4 (C-3), 39.6 (C-4), 58.9 (C-5), 70.9 (C-6), 37.1 (C-7), 149.9 (C-8), 97.0 (C-9), 28.6 (Me at C-6), 51.6 (Me of CO_2Me), 175.1(C=O), 157.5, 156.7, 143.1, 129.6, 129.4, 123.1, 122.6, 119.0, 118.0, 117.9 (Phenyl), 154.3 (*ipso* Py-C), 111.7, 139.7, 119.5, 144.8 (Pyridyl). Anal. Calcd for $C_{27}H_{25}N_3O_5$ (471.5): C 68.78, H 5.34, N 8.91. Found: C 68.80, H 5.34, N 8.90.

Synthesis of 5-ethoxycarbonyl-6-hydroxy-6-methyl-4-phenyl-4,5,6,7-tetrahydro-3-hydroxy-2-(2-pyridinyl)indazole (8): This compound was obtained as white crystals (290 mg, 74%) with mp EI-MS (70 eV): m/e = 393 (M^+), 302 (bp), 262, 121, 78. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25-7.32 (m, 5H, ArH), 4.26 (d, ^3J = 11.36 Hz, 1H, H-4a), 2.71 (d, ^3J = 11.36 Hz, 1H, H-5a), 2.76 (d, ^2J = 16.84 Hz, 1H, H-7a), 2.98 (d, ^2J = 16.84 Hz, 1H, H-7e), 1.40 (s, 3H, Me at C-6), 3.41 (bs, 1H, OH at C-6), 0.97 (t, 3H, Me of CO_2Et),4.0 (m, 2H, CH_2 of CO_2Et), 8.09 (d, 1H, PyH), 7.83 (m, 2H, PyH), 7.06 (m, 1H, PyH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 152.5 (C-3), 40.0 (C-4), 58.8 (C-5), 70.9 (C-6), 37.2 (C-7), 150.1 (C-8), 97.5 (C-9), 28.7 (Me at C-6), 13.8 (Me of CO_2Et), 60.6 (CH_2 of CO_2Et), 175.0 (C=O), 140.8 (*ipso* Phenyl), 128.3, 128.0, 126.9 (Phenyl-C), 154.4 (*ipso* Py-C), 111.7, 139.7, 119.4, 144.9 (Pyridyl). Anal. Calcd for $C_{22}H_{23}N_3O_4$ (393.44): C 67.16, H 5.89, N 10.68. Found: C 67.18, H 5.90, N 10.69.

Synthesis of 5-ethoxycarbonyl-6-hydroxy-6-methyl-4-(*p*-methoxyphenyl)-4,5,6,7-tetrahydro-3-hydroxy-2-(2-pyridinyl)indazole (9): This compound was obtained as white needles (334 mg, 79%) with mp 173-175 ˚C. EI-MS (70 eV): m/e = 423 (M^+), 332 (bp), 292, 262, 166, 121, 78. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.84-6.86, 7.16-7.19 (m, 5H, ArH), 4.23 (d, ^3J = 11.36 Hz, 1H, H-4a), 2.68 (d, ^3J = 11.36 Hz, 1H, H-5a), 2.74 (d, ^2J = 16.84 Hz, 1H, H-7a), 2.97 (d, ^2J = 17.20 Hz, 1H, H-7e), 1.39 (s, 3H, Me at C-6), 3.38 (bs, 1H, OH at C-6), 1.02 (t, 3H, Me of CO_2Et), 4.03 (m, 2H, CH_2 of CO_2Et), 3.79 (s, 3H, MeO-Ph) 8.10 (d, 1H, PyH), 7.82 (m, 2H, PyH), 7.06 (m, 1H, PyH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 152.5 (C-3), 39.1 (C-4), 59.1 (C-5), 70.9 (C-6), 37.2 (C-7), 150.1 (C-8), 97.8 (C-9), 28.7 (Me at C-6), 13.9 (Me of CO_2Et), 60.6 (CH_2 of CO_2Et), 55.1 (MeO-Ph), 175.1 (C=O), 158.4, 132.9, 128.9, 113.7 (Phenyl-C), 154.4 (*ipso* Py-C), 111.7, 139.7, 119.4, 144.9 (Pyridyl). Anal. Calcd for $C_{23}H_{25}N_3O_5$ (423.46): C 65.24, H 5.95, N 9.92. Found: C 65.22, H 5.96, N 9.91.

Synthesis of 5-ethoxycarbonyl-6-hydroxy-6-methyl-4-(*m*-chlorophenyl)-4,5,6,7-tetrahydro-3-hydroxy-2-(2-pyridinyl)indazole (10): This compound was obtained as white solid (286 mg, 67%) with mp 163-166 ˚C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.15-7.17, 7.23-7.26 (m, 5H, ArH), 4.25 (d, ^3J = 11.36 Hz, 1H, H-4a), 2.66 (d, ^3J = 11.36 Hz, 1H, H-5a), 2.75 (d, ^2J = 16.84 Hz, 1H, H-7a), 2.98 (d, ^2J = 16.84 Hz, 1H, H-7e), 1.40 (s, 3H, Me at C-6), 3.39 (bs, 1H, OH at C-6), 1.02 (t, 3H, Me of CO_2Et), 4.03 (m, 2H, CH_2 of CO_2Et), 8.11 (d, 1H, PyH), 7.84 (m, 2H, PyH), 7.08 (m, 1H, PyH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 152.5 (C-3), 39.7 (C-4), 58.7 (C-5), 70.9 (C-6), 37.1 (C-7), 149.9 (C-8), 96.8 (C-9), 28.6 (Me at C-6), 13.9 (Me of CO_2Et), 60.7 (CH_2 of CO_2Et), 174.8 (C=O), 143.1, 134.1, 126.2, 127.1, 128.1 (Phenyl-C), 154.3 (*ipso* Py-C), 111.7, 139.8, 119.6, 144.9 (Pyridyl). Anal. Calcd for $C_{22}H_{22}ClN_3O_4$ (427.88): C 61.75, H 5.18, N 9.82. Found: C 61.78, H 5.20, N 8.83.

Synthesis of 5-ethoxycarbonyl-6-hydroxy-6-methyl-4-(*p*-chlorophenyl)-4,5,6,7-tetrahydro-3-hydroxy-2-(2-pyridinyl)indazole (11): This compound was obtained as white solid (311 mg, 73%) with mp 187-189 ˚C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19-7.21, 7.26-7.29 (m, 5H, ArH), 4.25 (d, ^3J = 11.36 Hz, 1H, H-4a), 2.66 (d, ^3J = 11.36 Hz, 1H, H-5a), 2.75 (d, ^2J = 16.88 Hz, 1H, H-7a), 2.99 (d, ^2J = 16.84 Hz, 1H, H-7e), 1.40 (s, 3H, Me at C-6), 3.33 (bs, 1H, OH at C-6), 1.02 (t, 3H, Me of CO_2Et), 4.03 (m, 2H, CH_2 of CO_2Et), 8.12 (d, 1H, PyH), 7.83 (m, 2H, PyH), 7.09 (m, 1H, PyH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 152.5 (C-3), 39.4 (C-4), 58.8 (C-5), 71.0 (C-6), 37.1 (C-7), 149.9 (C-8), 97.1 (C-9), 28.7 (Me at C-6), 13.9 (Me of CO_2Et), 60.8 (CH_2 of CO_2Et), 174.8 (C=O), 139.5, 128.5, 129.4, 132.6 (Phenyl-C), 154.4 (*ipso* Py-C), 111.7, 139.8, 119.6, 144.9 (Pyridyl). Anal. Calcd for $C_{22}H_{22}ClN_3O_4$ (427.88): C 61.75, H 5.18, N 9.82. Found: C 61.78, H 5.19, N 9.82.

Synthesis of 5-ethoxycarbonyl-6-hydroxy-6-methyl-4-(*p*-nitrophenyl)-4,5,6,7-tetrahydro-3-hydroxy-2-(2-pyridinyl)indazole (12): This compound was obtained as yellow crystals (284 mg, 65%) with mp 167-169 ˚C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42-7.44, 8.16-8.18 (m, 5H, ArH), 4.39 (d, ^3J = 11.36 Hz, 1H, H-4a), 2.68 (d, ^3J = 11.36 Hz, 1H, H-5a), 2.77 (d, ^2J = 16.88 Hz, 1H, H-7a), 2.99 (d, ^2J = 16.88 Hz, 1H, H-7e), 1.41 (s, 3H, Me at C-6), 3.32 (bs, 1H, OH at C-6), 1.0 (t, 3H, Me of CO_2Et), 4.03 (m, 2H, CH_2 of CO_2Et), 8.11 (d, 1H, PyH), 7.84 (m, 2H, PyH), 7.1 (m, 1H, PyH) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 152.5 (C-3), 39.7 (C-4), 58.3 (C-5), 71.0 (C-6), 37.1 (C-7), 149.7 (C-8), 96.3 (C-9), 28.6 (Me at C-6), 14.0 (Me of CO_2Et), 60.9 (CH_2 of CO_2Et), 174.3 (C=O), 148.9, 147.0, 129.0, 123.6 (Phenyl-C), 154.2 (*ipso* Py-C), 111.7, 139.9, 119.7, 144.9 (Pyridyl). Anal. Calcd for $C_{22}H_{22}N_4O_6$ (438.43): C 60.27, H 5.06, N 12.78. Found: C 60.27, H 5.07, N 12.77.

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