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SYNTHESES OF 10-ISOBUTOXY-6-(SUBSTITUTED PHENYL)-3,4-DIMETHYL-7,12-DIHYDROINDENO [2′,1′ : 4,5] PYRROLO [3,2-*c*] QUINOLINES AND N-(SUBSTITUTED PHENYL)-10-ISOBUTOXY-3,4-DIMETHYL-7,12-DIHYDROINDENO [2′,1′:4,5] PYRROLO [3,2-*c*] QUINOLIN-6-AMINE DERIVATIVES

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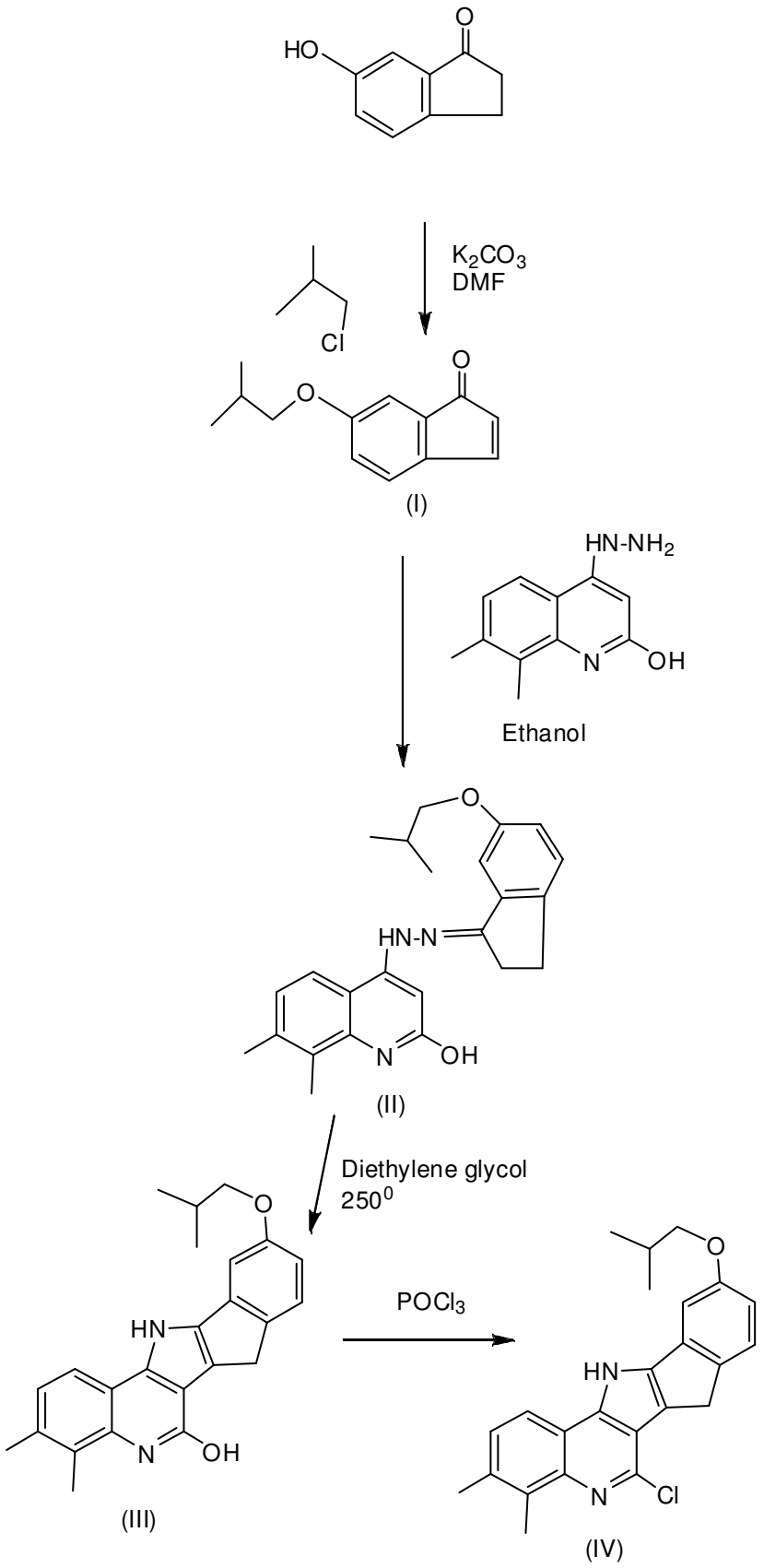
A series of pyrrolo [3,2-*c*] quinolines was synthesized in five steps from 6-hydroxy-2,3-dihydro-1*H*-inden-1-one. Alkylation with 1-chloro-2-methylpropane afforded 6-isobutoxy-2,3-dihydro-1*H*-inden-1-one (**I**). This was condensed with 4-hydrazinyl-7,8-dimethylquinolin-2-ol to furnish 4-[2-(6-isobutoxy-2,3-dihydro-1*H*-inden-1-ylidene) hydrazinyl]-7,8-dimethylquinolin-2-ol (**II**). The compound (**II**) was subjected to intramolecular cyclization with dowtherm or diethylene glycol to give 10-isobutoxy-3,4-dimethyl-7,12-dihydroindeno [2′,1′:4,5] pyrrolo [3,2-*c*] quinolin-6-ol (**III**) which was converted to 6-chloro-10-isobutoxy-3,4-dimethyl-7,12-dihydroindeno [2′,1′:4,5] pyrrolo [3,2-*c*] quinoline (**IV**). The chloro compound (**IV**) was subjected to Suzuki-Miyaura cross-coupling reaction with different boronic acids to give 10-isobutoxy-6-(substituted phenyl)-3,4-dimethyl-7,12-dihydroindeno [2′,1′:4,5] pyrrolo [3,2-*c*] quinolines (**V**a-j). Reaction of the compound (**IV**) with various substituted aromatic amines furnished N-(substituted phenyl)-10-isobutoxy-3,4-dimethyl-7,12-dihydroindeno [2′,1′:4,5] pyrrolo [3,2-*c*] quinolin-6-amines (**Vi**a-h). The structures of the products obtained have been established by their spectral data.

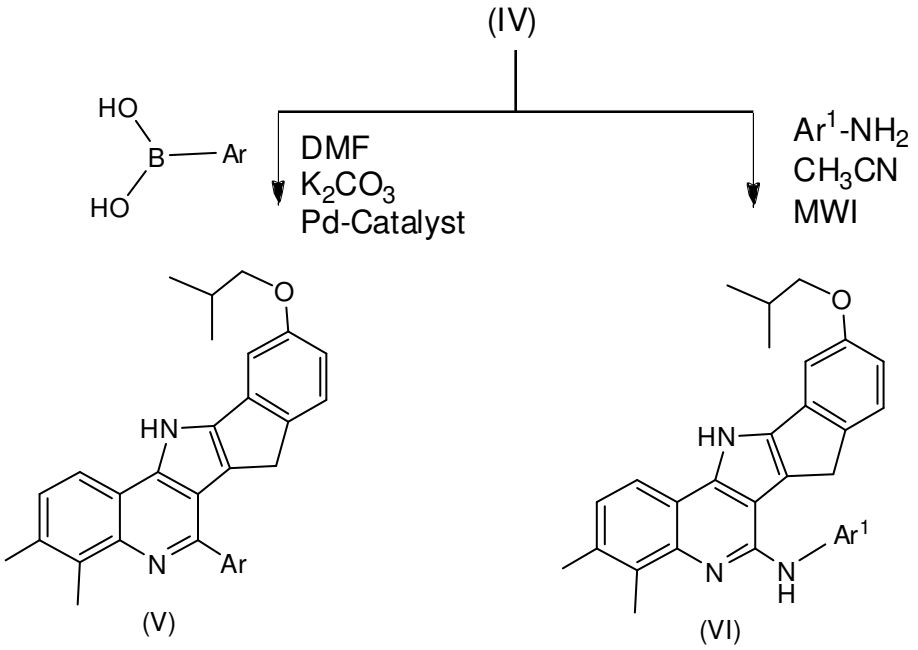
Polynuclear heterocycles derived from quinoline moiety represent an important class of compounds and have attracted a great deal of attention in recent years because of their wide range of pharmacological properties[1]. Quinoline derivatives represent the major class of heterocycles and a number of preparations have been known since the late 1800s. The quinoline ring system occurs in various natural products[2,3] especially in alkaloids. The quinoline skeleton is often used for the design of many synthetic compounds with diverse pharmacological properties[4-9].

The pyrrolo [3,2-*c*] quinoline ring system and its derivatives have been known for several years as the most important skeleton for their diverse biological activities such as antitumor[10], hypotensive[11] properties, gastric (H^+/K^+)-ATPase inhibition[12-14], anti-inflammatory activities[15] and 5-HT3 agonism[16-18].

Thus, within our program for the syntheses of quinoline derivatives, it was thought of interest to synthesise annulated quinoline derivatives based on the framework of pyrrolo [3,2-*c*] quinolines and study their biological activities. The pyrrolo [3,2-*c*] quinoline derivatives could be further transformed into various pyrrolo-quinoline derivatives by chlorination, substitution and coupling reactions. The novel pyrrolo [3,2-*c*] quinoline derivatives described herein were synthesized as shown in Scheme-1.

In the present work, alkylaton of 6-hydroxy-2,3-dihydro-1*H*-inden-1-one was performed using 1-chloro-2-methylpropane and potassium carbonate in N,N-dimethylformamide as solvent at 120^0 for 4 hours to give 6-isobutoxy-2,3-dihydro-1*H*-inden-1-one (**I**). 6-Isobutoxy-2,3-dihydro-1*H*-inden-1-one (**I**) was condensed with 4-hydrazinyl-7,8-dimethylquinolin-2-yl and refluxed for 20 hr in ethanol with a catalytic amount of glacial acetic acid to furnish 4-[2-(6-isobutoxy-2,3-dihydro-1*H*-inden-1-ylidene) hydrazinyl]-7,8-dimethylquinolin-2-ol (**II**). Compound (**II**) was subjected to Fischer-Indole synthesis with anhydrous zinc chloride as Lewis acid and glacial acetic acid. The reaction mixture was heated at 120^0 for 4 hr under nitrogen atmosphere and a un-expected product


HO
O
K2CO3
DMF
Cl
O
O
(I)
HN-NH2
N
OH
Ethanol
O
HN-N
N
OH
(II)
Diethylene glycol
2500
O
HN
N
OH
(III)
POCl3
O
HN
N
Cl
(IV)



Scheme-1

was obtained by cleavage of compound (**II**). We tried cyclization of 4-[2-(6-isobutoxy-2,3-dihydro-1*H*-inden-1-ylidene) hydrazinyl]-7,8-dimethylquinolin-2-ol (**II**) using different acids such as hydrochloric acid, sulfuric acid, polyphosphoric acid, glacial acetic acid and a mixture of different acids with Lewis acid as catalyst. Only a few milligrams of expected product (**III**) was isolated along with different by products and starting materials in these reactions.

4-[2-(6-Isobutoxy-2,3-dihydro-1*H*-inden-1-yldene) hydrazinyl]-7,8-dimethyl quinolin-2-ol (**II**) was subjected to intramolecular cyclization with dow therm or diethylene glycol under reflux condition and the desired 10-isobutoxy-3,4-dimethyl-7,12-dihydroindeno [2′,1′:4,5] pyrrolo [3,2-*c*] quinolin-6-ol (**III**) was isolated in good yield. Diethylene glycol gave better result as compared to dowtherm under identical reaction conditions. The conversion of 10-isobutoxy-3,4-dimethyl-7,12-dihydroindeno [2′,1′:4,5] pyrrolo [3,2-*c*] quinolin-6-ol (**III**) into 6-chloro-10-isobutoxy-3,4-dimethyl-7,12-dihydroindeno [2′,1′:4,5] pyrrolo [3,2-*c*] quinoline (**IV**) was achieved by heating the compound (**III**) with excess of phosphorous oxychloride at 120^0 for 7 hr. 6-Chloro-10-isobutoxy-3,4-dimethyl-7,12-dihydroindeno [2′,1′:4,5] pyrrolo [3,2-*c*] quinoline (**IV**) was subjected to Suzuki-Miyaura cross-coupling reaction with different boronic acids in N,N-dimethylformamide, 1M sodium carbonate solution and tetrakis (triphenyl phosphine) palladium (0) catalyst to afford 10-isobutoxy-6-(substituted phenyl)-3,4-dimethyl-7,12-dihydroindeno [2′,1′:4,5] pyrrolo [3,2-*c*] quinolines (**V**a-j). The reaction mixture was heated at 120^0 for 3 hr under nitrogen atmosphere in an oil bath, then filtered through selite-545 bed and washed with N,N-dimethylformamide. The organic layer was removed under reduced pressure and the residue obtained was diluted with ethyl acetate and 1N NaOH solution to remove residual boronic acid. The pure compound was isolated using flash chromatography (silica gel) eluting with chloroform. Similarly (**IV**) was reacted with different aromatic amines in presence of acetonitrile under microwave conditions. The reaction mixture was irradiated at 150^0 for 4-7 hr. After completion of the reaction, acetonitrile was removed under reduced pressure and the solid obtained was purified by flash chromatography (silica gel) eluting with chloroform to give N-(substituted phenyl)-10-isobutoxy-3,4-dimethyl-7,12-dihydroindeno [2′,1′:4,5] pyrrolo [3,2-*c*] quinolin-6-amines (**VI**a-h). The structures of the newly synthesized compounds were elucidated by their NMR, LC-MS and elemental analysis.

Table-1
Characterization of the compounds (**V**a-j) & (**VI**a-h)

Compd	Ar	M.P. (^{0}C)	Yield (%)
Va	Phenyl	332	72
Vb	4-Methoxyphenyl	328	75
Vc	Pyridin-3-yl	319	70
Vd	4-Methylphenyl	305	78
Ve	3-(Trifluoromethyl)-phenyl	298	68
Vf	4-(Trifluoromethyl)-phenyl	314	70
Vg	4-Fluorophenyl	297	72
Vh	6-Methylpyridin-3-yl	325	75
Vi	6-Methoxypyridin-3-yl	330	67
Vj	1-Methyl-1H-pyrazol-4-yl	292	65
VIa	Phenyl	314	65
VIb	4-Methylphenyl	303	60
VIc	4-Methoxyphenyl	298	62
VId	3,4-Dimethoxyphenyl	310	68
VIe	4-Chlorophenyl	289	58
VIf	4-(Trifluoromethyl)phenyl	321	55
VIg	4-Cyanophenyl	324	61
VIh	Fluorophenyl	285	66

Antibacterial activity

The compounds (**V** & **VI**) were screened *in vitro* for antibacterial activity against *Staphylococcus aureus, Escherichia coli, Bacillus subtilis* and *Salmonella typhosa* using concentrations of 2mg/cm^3 and 5mg/cm^3 by the ditch plate technique[19]. From the antibacterial activity data, it was found that the tested compounds have shown some activity against the selected microorganisms. It is clear that some compounds possessed significant antibacterial activity. Compounds **V**b, **V**e, **V**j and **VI**c possessed the highest degree of antibacterial activity as compared to other compounds.

Antifungal activity

The compounds (**V** & **VI**) synthesized were screened *in vitro* for antifungal activity against *Aspergillus niger, Candida albicans, Cryptococcus neoformans* and *Thielaviopsis paradoxa* by paper-disc diffusion method[20] at concentrations of 2 mg/cm^3 and 5 mg/cm^3. Nutrient agar was employed as culture media and N,N-dimethylformamide was used as solvent control for antifungal activity.

The known compounds such as ampicillin, amoxicillin, norfloxacin, penicillin and griseofulvin were used for comparison purpose. The diameter of zone of inhibition was measured in mm.

The antibacterial and antifungal screening data are recorded in Table-5 and Table-6.

Experimental

6-Hydroxy-2,3-dihydro-1*H*-inden-1-one, dichlorobis (triphenylphosphine) palladium (**II**) [Pd $(PPh_3)_2Cl_2$] catalyst and other chemicals were purchased from commercial sources and were used without additional purification. The reactions were monitored on TLC (silica gel) and column chromatographic purifications were performed on silica gel. Melting points were taken in open capillaries and are uncorrected. The IR spectra in KBr were recorded on a Perkin-Elmer 257 spectrophotometer. ^{1}H NMR spectra in DMSO-d_6 and $CDCl_3$ were recorded on VXR-300 MHz and Bruker AMX-300MHz Spectrophotometers using TMS as internal standard. Mass spectra were recorded on Agilent LCMS (ESI-MS) and Shimadzu Q-5050. The purity of the compounds was monitored by thin layer chromatography. Microwave irradiations were carried out in CEM discover. CHN analysis of all compounds was found to be satisfactory.

6-Isobutoxy-2,3-dihydro-1*H*-inden-1-one (I)

A mixture of 6-hydroxy-2,3-dihydro-1*H*-inden-1-one (1.0g, 6.75 mmol), 1-chloro-2-methylpropane (0.68g, 7.42 mmol) and potassium carbonate (1.39g, 10.12 mmol) was dissolved in N,N-dimethylformamide (30.0 cm^3). The reaction mixture was heated at 120^0 for 4 hr. After completion of the reaction, N,N-dimethylformamide was removed under reduced pressure. The reaction mass was poured in ice-water and extracted with ethyl acetate. The organic phase was dried over anhydrous sodium sulphate and removed under reduced pressure. The solid obtained

Table-2
Antibacterial activity of compounds

Compd	*S. aureus*		*E. coli*		*B. subtilis*		*S. typhosa*	
	2mg	5mg	2mg	5mg	2mg	5mg	2mg	5mg
Va	-	+	++	++	+	++	+	+
Vb	+	++	+	++	+	++	++	++
Vc	-	+	-	+	+	+	-	-
Vd	-	+	-	-	-	+	-	+
Ve	+	++	+	+	+	++	++	++
Vf	+	+	+	-	+	++	+	+
Vg	-	+	+	+	-	+	-	+
Vh	-	+	-	++	+	+	+	++
Vi	-	-	+	-	-	-	+	+
Vj	++	++	-	+	+	++	+	++
VIa	+	+	-	+	-	+	+	+
VIb	-	++	+	+	-	+	+	+
VIc	+	++	+	+	+	+	+	-
VId	+	+	+	+	-	+	-	+
VIe	-	-	-	+	+	+	+	+
VIf	+	+	+	-	+	+	-	-
VIg	-	-	+	+	-	-	+	+
VIh	-	+	+	++	-	+	+	+

Inhibition zone diameter in mm : (-) <11mm
(+) 11-14 mm
(++) 15-18 mm

Table-3
Antifungal activity of compounds

Compd	*A. niger*		*C. albicans*		*C. neoformans*		*T. paradoxa*	
	2mg	5mg	2mg	5mg	2mg	5mg	2mg	5mg
Va	+	+	+	+	-	+	-	-
Vb	-	-	-	+	-	+	-	+
Vc	-	+	+	-	-	-	-	+
Vd	+	++	+	+	+	+	-	-
Ve	+	+	-	++	-	++	+	+
Vf	+	-	+	-	-	++	+	+
Vg	-	++	+	+	+	+	+	+
Vh	-	+	+	-	+	+	+	++
Vi	-	-	+	-	-	-	+	-
Vj	+	+	-	+	+	+	-	+
VIa	+	+	-	+	-	-	+	-
VIb	-	+	+	+	+	+	+	+
VIc	+	++	+	+	+	+	-	-
VId	-	+	-	+	-	-	+	+
VIe	+	-	+	+	-	+	-	+
VIf	+	+	-	-	+	+	-	-
VIg	+	-	-	+	-	-	+	+
VIh	-	+	+	++	-	+	-	+

Inhibition zone diameter in mm : (-) <11mm
(+) 11-14 mm
(++) 15-18 mm

was recrystallized from a mixture of (40-60^0) petroleum ether : ethyl acetate (8:2) to give (**I**), yield (1.26g, 92%), m.p. 47^0. ^{1}H NMR (DMSO-d_6): δ 0.9 (d, 6H, $2CH_3$), 2.0 (m, 1H, CH), 2.6 (t, 2H, -CH_2,Ph), 3.0 (t, 2H, -CH_2.C=O), 3.7 (d, 2H, -OCH_2), 7.0-7.4 (m, 3H, ArH); Mass : m/z 205 (M^{+1}). [Found : C, 76.40, H, 7.87 $C_{13}H_{16}O_2$ requires C, 76.44, H, 7.90%].

4-[2-(6-Isobutoxy-2,3-dihydro-1*H*-inden-1-ylidene) hydrazinyl]-7,8-dimethylquinolin-2-ol (II)

6-Isobutoxy-2,3-dihydro-1*H*-inden-1-one (**I**) (1.1g, 5.41 mmol) and 4-hydrazinyl-7,8-dimethylquinolin-2-ol (1.0g, 4.92 mmol) were dissolved in ethanol (50.0 cm^3). A catalytic amount of glacial acetic acid (0.50 cm^3) was added and the reaction mixture was refluxed for 20 hr. After completion of reaction, the solvent was removed under reduced pressure. The solid obtained was filtered, washed with ethanol and recrystallized from a mixture of chloroform: methanol (7:3) to give (**II**), yield (1.61g, 77%), m.p. 289^0. ^{1}H NMR (DMSO-d_6): 1.0 (d, 6H, $2CH_3$), 2.0 (m, 1H, CH), 2.3 (s, 6H, $2CH_3$), 3.0 (t, 2H, -CH_2,Ph), 3.1 (t, 2H, -CH_2-C=O), 3.8 (d, 2H, -OCH_2), 6.3 (s, 1H, CH quinoline at C-3), 6.9-7.8 (m, 5H, ArH), 9.0 (s, 1H, -NH), 9.9 (s, 1H, -OJ). Mass : m/z 390 (M^{+1}). [Found : C, 73.99, H, 6.96, N, 10.77 $C_{24}H_{27}N_3O_2$ requires C, 74.01, H, 6.99, N, 10.79%].

10-Isobutoxy-3,4-dimethyl-7,12-dihydroindeno [2′,1′:4,5] pyrrolo [3,2-*c*] quinolin-6-ol (III)

4-[2-(6-Isobutoxy-2,3-dihydro-1*H*-inden-1-ylidene) hydrazinyl]-7,8-dimethylquinolin-2-ol (**II**) (0.50g, 1.28 mmol) was dissolved in diethylene glycol (5.0 cm^3) and refluxed at 250^0 for 3.0 hr. The reaction mixture was cooled and ice-water (20 cm^3) was added. The product obtained was filtered, washed with water and recrystallized from methanol to give (**III**), yield (0.320g, 67%), m.p. 321^0. ^{1}H NMR (DMSO-d_6): 1.0 (d, 6H, $2CH_3$), 2.0 (m, 1H, -CH). 2.3 (s, 6H, $2CH_3$), 3.6 (s, 2H, -CH_2), 3.8 (d, 2H, -OCH_2), 6.7-7.7 (m, 5H, ArH), 10.1 (s, 1H, -OH), 12.5 (s, 1H, -NH); Mass : m/z 373 (M^{+1}). [Found : C, 77.36, H, 6.48, N, 7.50 $C_{24}H_{24}N_2O_2$ requires C, 77.39, H, 6.49, N, 7.52%].

6-Chloro-10-isobutoxy-3,4-dimethyl-7,12-dihydroindeno [2′,1′:4,5] pyrrolo [3,2-*c*] quinoline (IV)

10-Isobutoxy-3,4-dimethyl-7,12-dihydroindeno [2',1':4,5] pyrrolo [3,2-*c*] quinolin-6-ol (**III**) (0.50g, 1.34 mmol) was refluxed with phosphorus oxychloride (4.0 cm^3) at 120^0 for 7 hr. The reaction mixture was cooled, poured into ice-water (20 cm^3) and triturated with an excess of saturated sodium bicarbonate solution. The solid obtained was extracted with ethyl acetate and purified by column chromatography to give (**IV**), yield (0.393g, 75%), m.p. 166^0. ^{1}H NMR (DMSO-d_6): 0.9 (d, 6H, $2CH_3$), 2.2 (m, 1H, -CH), 2.4 (s, 6H, $2CH_3$), 3.8 (d, 2H, -OCH_2), 3.6 (s, 2H, -CH_2), 6.9-7.9 (m, 5H, ArH), 12.4 (s, 1H, -NH). Mass : m/z 391 (M^{+1}). [Found : C, 73.71, H, 5.90, N, 7.14 $C_{24}H_{23}N_2O$ requires C, 73.74, H, 5.93, N, 7.17%].

10-Isobutoxy-6-(substituted phenyl)-3,4-dimethyl-7,12-dihydroindeno [2′,1′:4,5] pyrrolo [3,2-c] quinolines (Va-j)

6-Chloro-10-isobutoxy-3,4-dimethyl-7,12-dihydroindeno [2′,1′:4,5] pyrrolo [3,2-*c*] quinoline (**IV**) (0.10g, 0.26 mmol) and boronic acid (0.28 mmol) were dissolved in N,N-dimethylformamide (10 cm^3). 1M sodium carbonate solution (1.5 cm^3, 0.39 mmol) and tetrakis-(triphenylphosphine) palladium (0) catalyst (4.8 mg, 0.004 mmol) were added and the reaction mixture was heated at 120^0 for 3 hr in an oil bath under nitrogen atmosphere. After completion of reaction, the reaction mass was filtered through selite-545 bed and washed with N,N-dimethylformamide. The organic phase was removed under reduced pressure. The residue obtained was diluted with ethyl acetate and washed with 1N NaOH solution to remove residual boronic acid. The organic phase was separated and washed with water followed by brine and dried over anhydrous sodium sulphate. The product obtained was purified by column chromatography to give (**V**). (**V**b): ^{1}H NMR (DMSO-d_6): 1.0 (d, 6H, $2CH_3$), 2.0 (m, 1H, -CH), 2.3 (s, 6H, $2CH_3$), 3.6 (s, 2H, -CH_2), 3.8 (d, 2H, -OCH_2), 3.9 (s, 3H, -OCH_3), 6.6-7.9 (m, 9H, ArH), 12.1 (s, 1H, -NH); Mass : m/z 463 (M^{+1}). The compounds (**V**a-j) were obtained in a similar manner. The melting points, yields and analytical data are given in Table-1.

N-(Substituted phenyl)-10-isobutoxy-3,4-dimethyl-7,12-dihydroindeno [2′,1′:4,5] pyrrolo [3,2-*c*] quinolin-6-amines (VIa-h)

A mixture of 6-chloro-10-isobutoxy-3,4-dimethyl-7,12-dihydroindeno [2′,1′:4,5] pyrrolo [3,2-*c*] quinoline (**IV**) (0.10g, 0.26 mmol) and appropriate aromatic amine (1.82 mmol) was dissolved in acetonitrile (10.0

cm^3) and irradiated at 150^0 for 4-7 hr in a microwave oven at 250W. After completion of reaction, the solvent was removed under reduced pressure and the solid obtained was purified by flash chromatography (silica gel) eluting with chloroform to give (**VI**). (**VI**a) : ^{1}H NMR (DMSO-d_6): 0.9 (d, 6H, $2CH_3$), 2.0 (m, 1H, -CH), 2.4 (s, 6H, $2CH_3$), 3.6 (s, 2H, $-CH_2$), 3.7 (d, 2H, $-OCH_2$), 3.7-7.8 (m, 10H, ArH), 9.6 (s, 1H, -NH Ar), 12.2 (s, 1H, -NH pyrrole); Mass : m/z 448 (M^{+1}). The compounds (**VI**a-h) were prepared in an analogous way. The characterization data of compounds (**VI**a-h) are given in Table-2.

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