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Original article

Synthesis and antifungal activity of new 1-halogenobenzyl-3-imidazolylmethylindole derivatives

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Abstract

A series of 1-benzyl-3-(imidazol-1-ylmethyl)indole derivatives **35**–**46** were prepared under mild reaction conditions and tested for their antifungal activity. Pharmacomodulation at N^1, C^2 and C^5 of the indole ring and at the level of the alkyl chain (R_1) was carried out starting from the corresponding 3-acylindoles **6**, **7** or 3-formylindoles **11**–**22**. Target imidazolyl compounds **35**–**46** were obtained in satisfactory yields by CO_2 elimination from the intermediate carbamates. All of the compounds were evaluated in vitro against two human fungal pathogens, *Candida albicans* (CA980001) and *Aspergillus fumigatus* (AF980003); amphotericin B, fluconazole and itraconazole were used as references. Seven out of 27 compounds (**35b**, **35e**, **35g**, **35h**, **36a**, **38a** and especially **40a**) exerted significant antifungal activity against *C. albicans*, with MIC in the range of 1–6 μg mL^{-1}. As regards inhibitory activity against *A. fumigatus*, the MIC figures of most of our compounds were in excess of 20 μg mL^{-1} in contrast to the reference drugs, amphotericin B and itraconazole, whose MIC_{90} and MIC_{80} values were 0.14 and 0.50 μg mL^{-1}, respectively. The most potent compound, **45a**, exhibited MIC value (8 ± 1 μg mL^{-1}) 16-fold higher than that of itraconazole.

Keywords: Imidazolylmethylindoles; Azoles; Antifungal activity; *Candida albicans*; *Aspergillus fumigatus*

1. Introduction

In recent years, fungal infection became an important complication and a major cause of morbidity and mortality in immunocompromised individuals such as those suffering from tuberculosis, cancer or AIDS and in organ transplant cases [1,2]. Amphotericin B has been widely used to treat fungal infections, but it can cause serious side effects notably due to its renal toxicity [3,4]. The conazoles, which include the imidazole and triazole compounds (Fig. 1) inhibit the synthesis of sterols in fungi by inhibiting cytochrome P450-dependent 14α-lanosterol demethylase ($P\text{-}450_{14DM}$), which removes the methyl group on C-14 of lanosterol [5,6], a key intermediate step in the formation of ergosterol in the fungal cell membrane. Among azoles, ketoconazole and itraconazole (Fig. 1) are currently used for both superficial and systemic fungal infections [7–11]. However, their clinical value has been limited by their relatively high risk of toxicity, the emergence of drug resistance, pharmacokinetic deficiencies, and/or insufficiencies in their antifungal activities. Despite recent developments [12], there is still a need for a genuinely broad-spectrum fungicidal agent.In the research field of conazole antifungal agents, investigations with an indole core have been few reported [13,14]. More recently, a new antifungal N-reverse prenylated indole alkaloid, isolated from the basidiomycete *Asporpium caryae*, and its derivative having a 2,3-dihydroxy-1,1-dimethylpropyl unit, have been studied for their interesting antifungal abilities [15,16]. In relation with these works, we synthesised new 1-benzyl-3-(1-imidazolylmethyl)indoles for investigating the importance of: (i) an alkyl substituent at the methylene bridge; (ii) a methyl group at position 2 on indole nucleus and a bromine atom at

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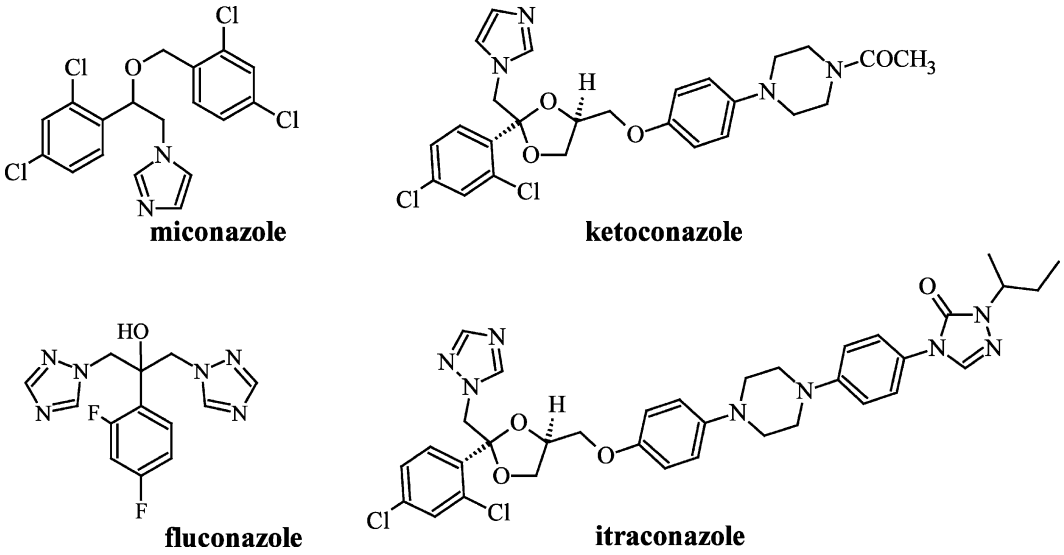


Fig. 1. Imidazole and triazole derivatives used in fungal infections.

position 5. The antifungal activity of the target compounds was then evaluated against *Candida albicans* and *Aspergillus fumigatus*, the two most clinically important fungi responsible for the majority of systemic fungal infections.

2. Chemistry

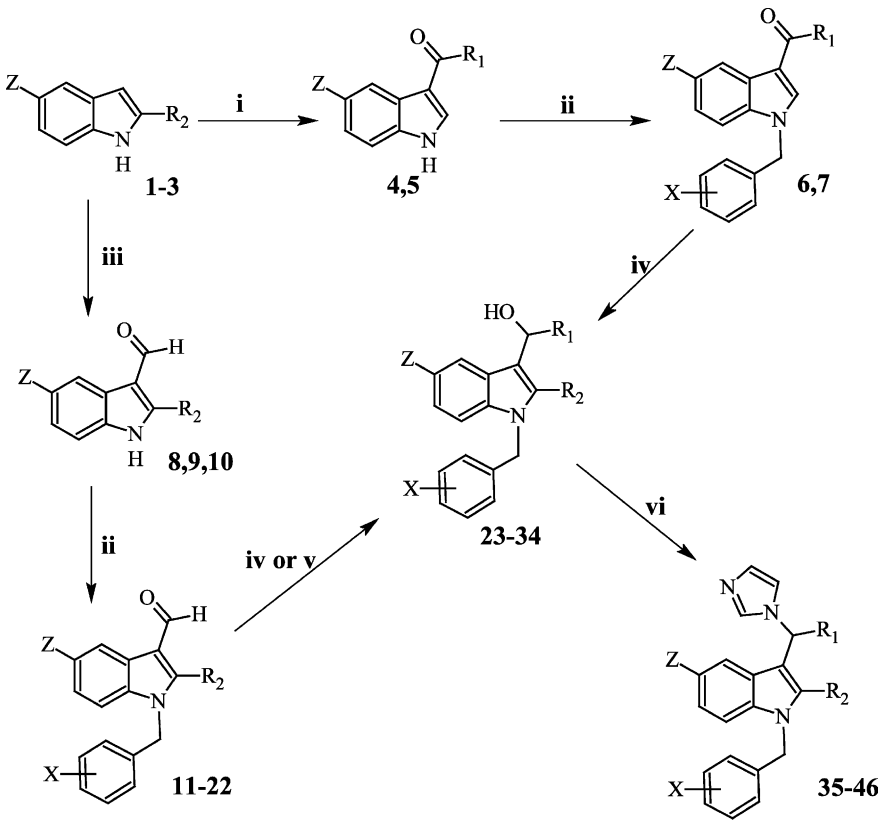
Preparation of the target 1-benzyl-3-(1-imidazolylmethyl)indoles **35**–**46** (Fig. 2) was carried out by two methods: (i) reduction of 1-benzyl-3-acylindoles **6**, **7** afforded the intermediate alcohols **23** and **34** which were condensed with 1,1-carbonyldiimidazole [17] leading to carbamates undergoing in situ decarboxylation to afford the expected compounds; (ii) an alternative pathway consisted in synthesising the alcohols **23**–**34** by Grignard reaction starting from the 1-benzyl-3-formylindoles **11**–**22**.

3-Acylindoles have been obtained by alkaline hydrolysis of 3-acetoacetylindole derivatives [18], under Vilsmeier–Haack conditions [19] involving dialkylamides and phosphorus oxychloride, by Cu_2O-catalyzed cyclisation of 2-acylmethylphenylisocyanides [20] or palladium-catalysed indole cyclisation of β-(2-haloanilino)-α,β-unsaturated ketones [21]. Selective 3-acylation of indole with acetic anhydride in the presence of aluminium chloride necessitates previous N-protection [22]. The reaction of the indole magnesium salt with acid chlorides gives often a mixture of N-1 and 3-substituted products; using the zinc salt of indole (obtained by exchange with the magnesium salt) and facilitating formation of the carbonyl ion complex by Lewis acid like $AlCl_3$, allowed selective 3-acylation in fair yields [23]. Direct acylation of indole, **1**, and 5-bromoindole, **3**, by this method afforded the 3-acylindoles **4b**, **d**, **e**, **g**, **h** and **5d**, **g** which were N^1-benzylated using the couple NaH–DMSO, and reduced by $LiAlH_4$ to give the corresponding 3-(1-hydroxyalkyl)indole derivatives **23** and **34**. In order to avoid the generally moderate or low yield of the acylation step, the Grignard reaction was applied to 3-formylindole **8**, 3-formyl-2-methylindole **9** and 5-bromo-3-formylindole **10**, obtained by Vilsmeier–Haack reaction [24]. Alcohols **23c**, **d**, **f** and **24**–**29** belonging to subseries **b** ($R_1 = CH_3$) were obtained by this sequence in overall yields ranging from 50 to 60%. The 1-benzyl-3-hydroxymethylindole derivatives **23**–**28** and **30**–**34** belonging to subseries **a** ($R_1 = H$) were obtained by $LiAlH_4$ reduction of the corresponding 1-benzyl-3-formylindoles **11**–**16** and **18**-**22**. The physicochemical properties of all these compounds are described in the experimental part and in Table 1 for **35**–**46**.

3. Pharmacology

The target 1-benzyl-3-imidazolylmethylindole derivatives **35**–**46** were tested for antifungal activity against *C. albicans* and *A. fumigatus*. The growth inhibition test for drug screening against *C. albicans* and *A. fumigatus* was carried out by the method based on the fluorometric properties of alamar Blue [25]. Amphotericin B, fluconazole and itraconazole were used as positive controls. The minimum inhibitory concentration (MIC) values (in $\mu g\ mL^{-1}$) of **35**–**46**, together with their structure, are gathered in Table 2.

Pharmacomodulation aimed at evaluating the influence of (i) the steric bulk and the lipophilicity resulting from alkyl substitution at R_1, (ii) the nature and position of halogen group(s) fixed at the benzyl unit



Z	R_2	X	N°
H	H	4-Cl	**11, 23, 35**
H	H	4-F	**12, 24, 36**
H	H	2,4-diF	**13, 25, 37**
H	H	2,4-diCl	**14, 26, 38**
H	CH_3	4-F	**15, 27, 39**
H	CH_3	4-Cl	**16, 28, 40**
H	CH_3	4-Br	**17, 29, 41**
H	CH_3	2,4-diCl	**18, 30, 42**
Br	H	2-F	**19, 31, 43**
Br	H	4-F	**20, 32, 44**
Br	H	2-Cl	**21, 33, 45**
Br	H	4-Cl	**22, 34, 46**

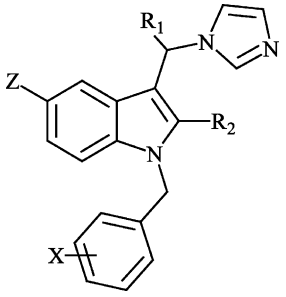
Fig. 2. Reagents: (i) $ZnCl_2$, EtMgBr, $AlCl_3$, CH_2Cl_2, r.t.; (ii) NaH, halogenated benzylchloride, DMSO; (iii) $POCl_3$, DMF; (iv) $LiAlH_4$, THF; (v) R_1MgX, THF, −78 °C; (vi) CDI, THF, reflux.

and (iii) a bromine atom at C^5 of indole and a methyl group at C^2 of indole.

The results of the MIC tests against *C. albicans* can be summarised as follows. SAR resulting from introduction of an alkyl group (R_1) were explored in the subseries of 1-(4-chlorobenzyl)indole derivatives **35**. Replacing hydrogen by methyl exerted a favourable effect: **35b** was 10-fold as active as **35a** (3 ± 0.1 and 27 ± 1 μg mL^{-1}) and this level of activity could be maintained with a bulky group, such as *i*-Pr, *n*- and *t*-Bu (**35e**, **g**, **h**), indicating that high lipophilicity did not prevent activity; astonishingly the propenyl derivative **34f** was a very moderate inhibitor and the *n*-propyl analogue **34d** was devoid of activity at 100 μg mL^{-1}.

Replacing the 4-chloro at the benzyl moiety of **35a** by a fluorine atom, leading to **36a**, exerted a positive effect and the same increase was observed after dihalogenation

Table 1
Physical constants of 3-imidazolylmethylindole compounds **35**–**46**



Number	Z	R_2	X	R_1	M.p. (°C)	Formula	Yield (%)
35a	H	H	4-Cl	H	55–57	$C_{19}H_{16}ClN_3$	83
35b	H	H	4-Cl	Methyl	Oil	$C_{20}H_{18}ClN_3$	52
35c	H	H	4-Cl	Ethyl	Oil	$C_{21}H_{20}ClN_3$	64
35d	H	H	4-Cl	*n*-Propyl	Oil	$C_{22}H_{22}ClN_3$	53
35e	H	H	4-Cl	*i*-Propyl	126–127	$C_{22}H_{22}ClN_3$	45
35f	H	H	4-Cl	Propenyl	Oil	$C_{22}H_{20}ClN_3$	43
35g	H	H	4-Cl	*n*-Butyl	Oil	$C_{23}H_{24}ClN_3$	47
35h	H	H	4-Cl	*t*-Butyl	142–145	$C_{23}H_{24}ClN_3$	62
36a	H	H	4-F	H	91–92	$C_{19}H_{16}FN_3$	17
36b	H	H	4-F	Methyl	Oil	$C_{20}H_{18}FN_3$	68
37a	H	H	2,4-diF	H	62–63	$C_{19}H_{15}F_2N_3$	30
37b	H	H	2,4-diF	Methyl	Oil	$C_{20}H_{17}F_2N_3$	62
38a	H	H	2,4-diCl	H	Oil	$C_{19}H_{15}Cl_2N_3$	40
38b	H	H	2,4-diCl	Methyl	Oil	$C_{20}H_{17}Cl_2N_3$	79
39a	H	CH_3	4-F	H	157–158	$C_{20}H_{18}FN_3$	30
39b	H	CH_3	4-F	Methyl	137–140	$C_{21}H_{20}FN_3$	45
40a	H	CH_3	4-Cl	H	147–148	$C_{20}H_{18}ClN_3$	51
41b	H	CH_3	4-Br	Methyl	Oil	$C_{21}H_{20}BrN_3$	54
42a	H	CH_3	2,4-diCl	H	157–160	$C_{20}H_{17}Cl_2N_3$	50
42b	H	CH_3	2,4-diCl	Methyl	Oil	$C_{21}H_{19}Cl_2N_3$	63
43a	Br	H	2-F	H	101–102	$C_{19}H_{15}BrFN_3$	26
44a	Br	H	4-F	H	123–124	$C_{19}H_{15}BrFN_3$	34
45a	Br	H	2-Cl	H	98–100	$C_{19}H_{15}BrClN_3$	50
46a	Br	H	4-Cl	H	145–147	$C_{19}H_{15}BrClN_3$	53
46d	Br	H	4-Cl	*n*-Propyl	Oil	$C_{22}H_{21}BrClN_3$	53
46g	Br	H	4-Cl	*n*-Butyl	Oil	$C_{23}H_{23}BrClN_3$	71

(2,4-dichloro or 2,4-difluoro) in **37a** and **38a**; but compared with the 1-(4-chlorobenzyl) subseries, the parent methyl (R_1) counterparts, **36b**, **37b** and **38b** were less active.

The presence of a bromine atom at C^5 of indole exerted a constant detrimental effect: **43a**, **44a**, **45a**, and **46a**, **d**, **g**. In the 2-methylindole series (**39**–**42**, $R_2 = CH_3$) comparison with the corresponding unsubstituted (R_2 = H) derivatives brought to the fore that this pharmacomodulation usually exerted a negative effect; nevertheless a clear-cut increase of activity was observed in the 1-(4-chlorobenzyl)-3-imidazolylmethylindole subseries: **40a** was about 30-fold as active as **35a**; this compound, with a MIC of 1 ± 0.2 μg mL^{-1}, was the most potent antifungal against *C. albicans* in the studied series. This encouraging result justified ongoing investigation.

Results of the MIC tests against *A. fumigatus* were not very promising; 13 compounds out of 26 displayed MIC in the range of about 15–30 μg mL^{-1}; although compounds issued from the 5-bromoindole series were generally inefficient (MIC > 100 μg mL^{-1}), 5-bromo-1-(2-chlorobenzyl)-3-(1H-imidazol-1-ylmethyl)indole **45a** exhibited the lightest activity with a MIC value of 8 ± 1 μg mL^{-1}.

First approach in the series of new imidazolylmethylindoles bearing different structural features on the indole moiety and the intercyclic methylene points out that the 1-(4-chlorobenzyl)-2-methyl-3-(1H-imidazol-1-ylmethyl)indole **40a** and the 5-bromo-1-(2-chlorobenzyl)-3-(1H-imidazol-1ylmethyl)indole **45a** exert significant in vitro antifungal activity against *C. albicans* and *A. fumigatus*, respectively. Although less potent than the reference drugs, they could represent new lead com-

Table 2
In vitro antifungal activity of 3-imidazolylmethylindole derivatives **35–46**

Number	Z	R_2	X	R_1	MIC	
					Candida albicans (CA980001) (μg mL^{-1})	*Aspergillus fumigatus* (AF980003) (μg mL^{-1})
35a	H	H	4-Cl	H	27±1	25±2
35b [a]	H	H	4-Cl	Methyl	3.0±0.1	24±2
35c [b]	H	H	4-Cl	Ethyl	15±4	24±5
35d[a]	H	H	4-Cl	*n*-Propyl	>100	>100
35e	H	H	4-Cl	*i*-Propyl	5.0±0.1	25±3
35f [a]	H	H	4-Cl	Allyl	34±1	29±1
35f [b]	H	H	4-Cl	Allyl	28±2	>100
35g [a]	H	H	4-Cl	*n*-Butyl	3.5±0.1	>100
35h	H	H	4-Cl	*t*-Butyl	6.1±0.2	>100
36a	H	H	4-F	H	4±1	13±1
36b [a]	H	H	4-F	Methyl	25±1	28±1
37a	H	H	2,4-diF	H	16±2	19±2
37b [b]	H	H	2,4-diF	Methyl	26±5	>100
38a	H	H	2,4-diCl	H	5±1	20±8
38b [a]	H	H	2,4-diCl	Methyl	15±3	31±1
39a	H	CH_3	4-F	H	>100	>100
39b	H	CH_3	4-F	Methyl	22±1	23±1
40a	H	CH_3	4-Cl	H	1.0±0.2	19±2
41b	H	CH_3	4-Br	Methyl	>100	>100
42a	H	CH_3	2,4-diCl	H	10±2	24±1
42b [b]	H	CH_3	2,4-diCl	Methyl	23±1	>100
43a	Br	H	2-F	H	>100	>100
44a	Br	H	4-F	H	>100	>100
45a	Br	H	2-Cl	H	32±14	8±1
46a	Br	H	4-Cl	H	>100	>100
46d [a]	Br	H	4-Cl	*n*-Propyl	>100	>100
46g [a]	Br	H	4-Cl	*n*-Butyl	45±2	>100
Amphotericin B					0.12±0.01	0.14±0.04
Fluconazole					0.02±0.001	–
Itraconazole					–	0.5±0.1

[a] Fumarate salt.
[b] Nitrate salt.

pounds for further pharmacomodulation in the series of indole-based imidazole or 1,2,4-triazole derivatives.

4. Experimental

4.1. Materials

Melting points, as determined in open tubes with a Tottoli–Büchi apparatus, are uncorrected. Infrared spectra were obtained on a Beckman IR 4230 spectrophotometer using KBr pellets or NaCl disk. The ^{1}H-NMR spectra were recorded on a Bruker AC-250 instrument (250 MHz); chemical shifts are expressed in δ units (ppm) using the solvent signal as reference. Elemental analyses of the target compounds, indicated by the element symbols, were within ±0.4% of the theoretical values.

The synthesis of 3-acetylindole **4b** [23], 3-*n*-butyrylindole **4d** [18], 3-isobutyrylindole **4e** [19], 3-valerylindole **4g** [24], 3-isovalerylindole [23] and 3-pivaloylindole **4h** [23] have been previously reported; 3-formylindole **8** and 5-bromo-3-formylindole **10** have been previously described [24].

4.2. Chemistry

4.2.1. General procedure for ketones 4, 5

To a suspension of indole **1** or 5-bromoindole **3** (4.3 mmol) and zinc chloride (1 M solution in diethyl ether, 8.6 mL) in 20 mL of CH_2Cl_2 was added dropwise a solution of EtMgBr (1M in THF, 4.3 mL) over 20 min. The mixture was stirred for 1 h and acyl chloride (5.4 mmol) was added. The suspension was stirred for another h and $AlCl_3$ (0.98 g) was added. The resultant mixture was stirred until the reaction was complete (1–4 h) and it was cautiously quenched with sat. NH_4Cl (20 mL). The organic layer was washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4 and filtered. The solvent was removed under vacuum. The product was treated with cold ether, filtered and dried to give **4** or **5** as a white powder.

*4.2.1.1. 3-Butyryl-5-bromo-1H-indole (**5d**).* White powder (16%), m.p. 160–161 °C; IR ν_{max} 3402, 2934, 2930, 1636 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 0.96 (t, $J = 7.30$ Hz, 3H, CH_3), 1.69 (m, 2H, CH_2), 2.85 (t, $J = 7.30$ Hz, 2H, CH_2), 7.37 (dd, $J = 8.55$ Hz, $J' = 1.85$ Hz, 1H, 6-CH), 7.48 (d, $J = 8.55$ Hz, 1H, 7-CH), 8.37 (d, $J = 1.85$ Hz, 1H, 4-CH), 8.42 (d, $J = 3.05$ Hz, 1H, 2-CH), 12.14 (d, $J = 3.05$ Hz, 1H, NH).

*4.2.1.2. 3-Valeryl-5-bromo-1H-indole (**5g**).* White powder (20%), m.p. 169–170 °C; IR ν_{max} 3394, 2897, 2802, 1657 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 0.96 (t, $J = 7.30$ Hz, 3H, CH_3), 1.37 (m, 2H, CH_2), 1.65 (m, 2H, CH_2), 2.86 (t, $J = 7.30$ Hz, 2H, CH_2), 7.36 (dd, $J = 8.55$ Hz, $J' = 1.80$ Hz, 1H, 6-CH), 7.47 (d, $J = 8.55$ Hz, 1H, 7-CH), 8.36 (d, $J = 1.80$ Hz, 1H, 4-CH), 8.42 (d, $J = 3.05$ Hz, 1H, 2-CH), 12.13 (d, $J = 3.05$ Hz, 1H, NH).

*4.2.2. General procedure for N^1-substituted ketones **6** and **7***

Sodium hydride (60% in dispersion, 1.5 g, 37.8 mmol) was added to a solution of **4** or **5** (34.4 mmol) in 200 mL of anhydrous DMSO at room temperature (r.t.) with stirring. After 1 h stirring at the same temperature, benzyl chloride (41.28 mmol) was added to the solution. The mixture was stirred at the same temperature for 2 h. After addition of water, the mixture was extracted with dichloromethane. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was chromatographed on a silica gel column using CH_2Cl_2: *n*-hexane (1:1) to give **6** or **7**.

*4.2.2.1. 3-Acetyl-1-(4-chlorobenzyl)-1H-indole (**6b**).* Brown powder (54%), m.p. 170–172 °C; IR ν_{max} 1659, 1299, 1090 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 2.50 (s, 3H, CH_3), 5.54 (s, 2H, CH_2), 7.24 (m, 2H, 5,6-CH), 7.35 (d, $J = 8.40$ Hz, 2H, Ph-H), 7.44 (d, $J = 8.40$ Hz, 2H, Ph-H), 7.55 (m, 1H, 7-CH), 8.23 (m, 1H, 4-CH), 8.58 (s, 1H, 2-CH).

*4.2.2.2. 3-Butyryl-1-(4-chlorobenzyl)-1H-indole (**6d**).* White powder (35%), m.p. 140–141 °C; IR ν_{max} 1625, 1256, 1088 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 1.05 (t, $J =$ 7.30 Hz, 3H, CH_3), 1.70 (m, 2H, CH_2), 2.76 (m, 2H, CH_2), 5.55 (s, 2H, CH_2), 7.22 (m, 2H, 5,6-CH), 7.34 (m, 2H, Ph-H), 7.43 (m, 2H, Ph-H), 7.53 (m, 1H, 7-CH), 8.23 (m, 1H, 4-CH), 8.61 (s, 1H, 2-CH).

*4.2.2.3. 3-iso-Butyryl-1-(4-chlorobenzyl)-1H-indole (**6e**).* White powder (79%), m.p. 119–120 °C; IR ν_{max} 1668, 1258, 1092 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 1.17 (d, $J = 6.00$ Hz, 6H, CH_3), 3.44 (m, 1H, CH), 5.53 (s, 2H, CH_2), 7.24 (m, 2H, 5,6-CH), 7.33 (m, 2H, Ph-H), 7.38 (m, 2H, Ph-H), 7.53 (m, 1H, 7-CH), 8.24 (m, 1H, 4-CH), 8.64 (s, 1H, 2-CH).

*4.2.2.4. 3-Valeryl-1-(4-chlorobenzyl)-1H-indole (**6g**).* Brown powder (90%), m.p. 103–104 °C; IR ν_{max} 1632, 1254, 1058 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 0.97 (t, $J =$ 7.30 Hz, 3H, CH_3), 1.39 (m, 2H, CH_2), 1.65 (tt, $J = 7.30$ Hz, 2H, CH_2), 2.88 (t, $J = 7.30$ Hz, 2H, CH_2), 5.53 (s, 2H, CH_2), 7.23 (m, 2H, 5,6-CH), 7.34 (d, $J = 8.50$ Hz, 2H, Ph-H), 7.43 (d, $J = 8.50$ Hz, 2H, Ph-H), 7.53 (m, 1H, 7-CH), 8.25 (m, 1H, 4-CH), 8.62 (s, 1H, 2-CH).

*4.2.2.5. 3-Pivaloyl-1-(4-chlorobenzyl)-1H-indole (**6h**).* White powder (15%), m.p. 118–120 °C; IR ν_{max} 1674, 1233, 1087 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 1.40 (s, 9H, CH_3), 5.56 (s, 2H, CH_2), 7.21 (m, 2H, 5,6-CH), 7.34 (d, $J = 8.40$ Hz, 2H, Ph-H), 7.44 (d, $J = 8.40$ Hz, 2H, Ph-H), 7.51 (m, 1H, 7-CH), 8.33 (m, 1H, 4-CH), 8.72 (s, 1H, 2-CH).

*4.2.2.6. 3-Butyryl-5-bromo-1-(4-chlorobenzyl)-1H-indole (**7g**).* White powder (65%), m.p. 124–126 °C; IR ν_{max} 1628, 1239, 1076 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 0.98 (t, $J = 7.30$ Hz, 3H, CH_3), 1.70 (m, 2H, CH_2), 2.86 (t, $J = 7.30$ Hz, 2H, CH_2), 5.54 (s, 2H, CH_2), 7.34 (d, $J = 8.50$ Hz, 2H, Ph-H), 7.37 (m, 1H, 6-CH), 7.44 (d, $J = 8.50$ Hz, 2H, Ph-H), 7.55 (m, 1H, 7-CH), 8.38 (d, $J = 1.50$ Hz, 1H, 4-CH), 8.67 (s, 1H, 2-CH).

*4.2.2.7. 3-Valeryl-5-bromo-1-(4-chlorobenzyl)-1H-indole (**7h**).* Yellow powder (88%), m.p. 127–128 °C; IR ν_{max} 1658, 1263, 1088 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 0.94 (t, $J = 7.30$ Hz, 3H, CH_3), 1.38 (m, 2H, CH_2), 1.65 (m, 2H, CH_2), 2.88 (m, 2H, CH_2), 5.54 (s, 2H, CH_2), 7.37 (m, 1H, 6-CH), 7.37 (m, 2H, Ph-H), 7.42 (m, 2H, Ph-H), 7.53 (m, 1H, 7-CH), 8.37 (d, $J = 1.50$ Hz, 1H, 4-CH), 8.67 (s, 1H, 2-CH).

*4.2.3. 3-Formyl-2-methyl-1H-indole (**9**)*

A solution of 1 g (7.62 mmol) of 2-methyl-1*H*-indole **2** in 5 mL of *N,N*-dimethylformamide was added at 5–10 °C over 1 h to a mixture of 0.79 mL (8.46 mmol) of phosphorus oxychloride and 2.6 mL of *N,N*-dimethylformamide. The orange solution was stirred at r.t. for 1 h. Ice (12 g) was added, followed by a solution of 3.38 g (84.5 mmol) of potassium hydroxide in 30 mL of water. The mixture was heated at 93 °C for 30 min and then stored at r.t. overnight. The precipitate was collected, washed with water, and dried to afford 1.1 g (90%) of **9** as a white powder, m.p. 202–203 °C. IR ν_{max} 1635, 1290, 1095 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 2.72 (s, 3H, CH_3), 7.17 (dd, $J = 8.80$ Hz, $J = 7.35$ Hz, 1H, 5-CH), 7.23 (dd, $J = 8.80$ Hz, $J' = 7.35$ Hz, 1H, 6-CH), 7.73 (d, $J = 8.80$ Hz, 1H, 7-CH), 8.08 (d, $J = 8.80$ Hz, 1H, 4-CH),10.09 (s, 1H, CHO), 12.02 (s, 1H, NH).

*4.2.4. General procedure for compounds **11–22***

The procedure is the same as that employed for compounds **6** and **7**.

*4.2.4.1. 1-(4-Chlorobenzyl)-3-formyl-1H-indole (**11**).* Brown powder (89%), m.p. 117–119 °C; IR ν_{max} 3389, 1650 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 5.59 (s, 2H, CH_2), 7.30 (m, 2H, 5,6-CH), 7.36 (d, $J = 8.60$ Hz, 2H, Ph-H), 7.45 (d, $J = 8.60$ Hz, 2H, Ph-H), 7.60 (m, 1H, 7-CH), 8.15 (m, 1H, 4-CH), 8.51 (s, 1H, 2-CH), 9.99 (s, 1H, CHO).

*4.2.4.2. 1-(4-Fluorobenzyl)-3-formyl-1H-indole (**12**).* Brown powder (76%), m.p. 116–117 °C; IR ν_{max} 3230, 1633 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 5.57 (s, 2H, CH_2), 7.27 (m, 4H, 5,6-CH and Ph-H), 7.42 (m, 2H, Ph-H), 7.64 (m, 1H, 7-CH), 8.15 (m, 1H, 4-CH), 8.52 (s, 1H, 2-CH), 9.98 (s, 1H, CHO).

*4.2.4.3. 1-(2,4-Difluorobenzyl)-3-formyl-1H-indole (**13**).* Brown powder (84%), m.p. 120–121 °C; IR ν_{max} 3256, 1658 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 5.61 (s, 2H, CH_2), 7.12 (m, 1H, Ph-H), 7.35 (m, 4H, Ph-H and 5,6,7-CH), 7.65 (m, 1H, Ph-H), 8.43 (s, 1H, 4-CH), 9.98 (s, 1H, CHO).

*4.2.4.4. 1-(2,4-Dichlorobenzyl)-3-formyl-1H-indole (**14**).* Brown powder (87%), m.p. 121–123 °C; IR ν_{max} 3400, 1628 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 5.57 (s, 2H, CH_2), 7.32 (m, 2H, 5,6-CH), 7.42 (d, $J = 8.35$ Hz, 1H, Ph-H), 7.45 (dd, $J = 8.35$ Hz, $J' = 2.10$ Hz, 1H, Ph-H), 7.56 (m, 1H, 7-CH), 8.19 (d, $J = 7.20$ Hz, 1H, 4-CH), 8.40 (s, 1H, 2-CH), 9.98 (s, 1H, CHO).

*4.2.4.5. 1-(4-Fluorobenzyl)-3-formyl-2-methyl-1H-indole (**15**).* White powder (75%), m.p. 121–123 °C; IR ν_{max} 3452, 1655 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 2.74 (s, 3H, CH_3), 5.61 (s, 2H, CH_2), 7.18 (m, 2H, 5,6-CH), 7.21 (m, 2H, Ph-H), 7.25 (m, 2H, Ph-H), 7.56 (m, 1H, 7-CH), 8.17 (m, 1H, 4-CH), 10.16 (s, 1H, CHO).

*4.2.4.6. 1-(4-Chlorobenzyl)-3-formyl-2-methyl-1H-indole (**16**).* Brown powder (80%), m.p. 116–118 °C; IR ν_{max} 3403, 1676 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 2.73 (s, 3H, CH_3), 5.59 (s, 2H, CH_2), 7.13 (d, $J = 8.45$ Hz, 2H, Ph-H), 7.26 (m, 2H, 5,6-CH), 7.43 (d, $J = 8.45$ Hz, 2H, Ph-H), 7.55 (m, 1H, 7-CH), 8.17 (m, 1H, 4-CH), 10.17 (s, 1H, CHO).

*4.2.4.7. 1-(4-Bromobenzyl)-3-formyl-2-methyl-1H-indole (**17**).* Brown powder (75%), m.p. 122–123 °C; IR ν_{max} 3400, 1659 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 2.74 (s, 3H, CH_3), 5.56 (s, 2H, CH_2), 7.12 (m, 2H, Ph-H), 7.20 (m, 2H, 5,6-CH), 7.43 (m, 2H, Ph-H), 7.51 (m, 1H, 7-CH), 8.10 (m, 1H, 4-CH), 10.17 (s, 1H, CHO).

*4.2.4.8. 1-(2,4-Dichlorobenzyl)-3-formyl-2-methyl-1H-indole (**18**).* White powder (80%), m.p. 165–166 °C; IR ν_{max} 3388, 1655 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 2.68 (s, 3H, CH_3), 5.60 (s, 2H, CH_2), 6.37 (d, $J = 8.55$ Hz, 1H, Ph-H), 7.28 (m, 2H, 5,6-CH), 7.33 (dd, $J = 8.55$ Hz, $J' = 2.10$ Hz, 1H, Ph-H), 7.46 (d, $J = 7.20$ Hz, 1H, 7-CH), 8.20 (d, $J = 7.60$ Hz, 1H, 4-CH), 10.19 (s, 1H, CHO).

*4.2.4.9. 5-Bromo-1-(2-fluorobenzyl)-3-formyl-1H-indole (**19**).* Brown powder (70%), m.p. 131–132 °C; IR ν_{max} 3392, 1649 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 5.65 (s, 2H, CH_2), 7.20 (m, 1H, Ph-H), 7.30 (m, 1H, Ph-H), 7.39 (dd, $J = 7.20$ Hz, $J' = 1.90$ Hz, 1H, Ph-H), 7.48 (dd, $J = 8.80$ Hz, $J' = 1.80$ Hz, 1H, 6-CH), 7.64 (d, $J = 8.80$ Hz, 1H, 7-CH), 8.28 (d, $J = 1.80$ Hz, 1H, 4-CH), 8.49 (s, 1H, 2-CH), 9.96 (s, 1H, CHO).

*4.2.4.10. 5-Bromo-1-(4-fluorobenzyl)-3-formyl-1H-indole (**20**).* Brown powder (76%), m.p. 132–133 °C; IR ν_{max} 3412, 1648 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 5.57 (s, 2H, CH_2), 7.21 (m, 2H, Ph-H), 7.40 (m, 2H, Ph-H), 7.46 (dd, $J = 8.75$ Hz, $J' = 1.85$ Hz, 1H, 6-CH), 7.65 (d, $J = 8.75$ Hz, 1H, 7-CH), 8.27 (d, $J = 1.85$ Hz, 1H, 4-CH), 8.56 (s, 1H, 2-CH), 9.96 (s, 1H, CHO).

*4.2.4.11. 5-Bromo-1-(2-chlorobenzyl)-3-formyl-1H-indole (**21**).* Brown powder (80%), m.p. 128–129 °C; IR ν_{max} 3375, 1644 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 5.68 (s, 2H, CH_2), 6.97 (dd, $J = 7.55$ Hz, $J' = 1.70$ Hz, 1H, Ph-H), 7.35 (m, 2H, Ph-H), 7.47 (dd, $J = 8.75$ Hz, $J' = 1.80$ Hz, 1H, 6-CH), 7.54 (d, $J = 8.75$ Hz, 1H, 7-CH), 8.30 (d, $J = 1.80$ Hz, 1H, 4-CH), 8.44 (s, 1H, 2-CH), 9.97 (s, 1H, CHO).

*4.2.4.12. 5-Bromo-1-(4-chlorobenzyl)-3-formyl-1H-indole (**22**).* Brown powder (55%), m.p. 200–201 °C; IR ν_{max} 3279, 1634 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 5.59 (s, 2H, CH_2), 7.35 (d, $J = 8.45$ Hz, 2H, Ph-H), 7.45 (d, $J = 8.45$ Hz, 2H, Ph-H), 7.48 (m, 1H, 6-CH), 7.61 (d, $J = 8.75$ Hz, 1H, 7-CH), 8.28 (d, $J = 1.80$ Hz, 1H, 4-CH), 8.36 (s, 1H, 2-CH), 9.97 (s, 1H, CHO).

*4.2.5. General procedure for alcohols **23** and **34** from ketones **6** and **7***

To a solution of **6** or **7** in anhydrous tetrahydrofuran (15 mL), $LiAlH_4$ (1.1 equiv.) was slowly added with vigorous stirring under nitrogen atmosphere at r.t. The reaction mixture was stirred for 30 min and then quenched with water. The mixture was extracted with CH_2Cl_2 and the organic layer was washed with brine, dried over Na_2SO_4 and evaporated under vacuum. The crude product was purified by chromatography.

*4.2.5.1. 1-(4-Chlorobenzyl)-3-(1-hydroxyethyl)-1H-indole (**23b**).* Green oil (97%); IR ν_{max} 3369, 1265, 1079 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 1.52 (d, $J = 6.30$ Hz, 3H, CH_3), 4.94 (d, $J = 4.65$ Hz, 1H, OH), 5.03 (m, 1H, CH), 5.39 (s, 2H, CH_2), 7.08 (m, 2H, 5,6-CH), 7.35 (d, $J =$

8.50 Hz, 2H, Ph-H), 7.44 (d, $J = 8.50$ Hz, 2H, Ph-H), 7.55 (m, 1H, 7-CH), 7.69 (d, $J = 7.80$ Hz, 1H, 4-CH), 8.25 (s, 1H, 2-CH).

*4.2.5.2. 1-(4-Chlorobenzyl)-3-(1-hydroxybutyl)-1H-indole (**23d**).* Yellow oil (96%); IR ν_{max} 3200, 1235, 1082 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 0.97 (t, $J = 7.10$ Hz, 3H, CH_3), 1.25 (m, 2H, CH_2), 1.90 (m, 2H, CH_2), 4.98 (d, $J = 4.70$ Hz, 1H, OH), 5.03 (m, 1H, CH), 5.40 (s, 2H, CH_2), 7.15 (m, 2H, 5,6-CH), 7.40 (d, $J = 8.55$ Hz, 2H, Ph-H), 7.47 (d, $J =$ 8.55 Hz, 2H, Ph-H), 7.52 (m, 1H, 7-CH), 7.64 (s, 1H, 2-CH), 7.69 (m, 1H, 4-CH).

*4.2.5.3. 1-(4-Chlorobenzyl)-3-(1-hydroxy-2-methylpropyl)-1H-indole (**23e**).* Light yellow oil (95%); IR ν_{max} 3250, 1237, 1075 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 0.81 (d, $J = 6.60$ Hz, 6H, CH_3), 1.80 (m, 1H, CH), 4.89 (m, 1H, CH), 4.99 (m, 1H, OH), 5.39 (s, 2H, CH_2), 7.06 (m, 2H, 5,6-CH), 7.25 (d, $J = 8.35$ Hz, 2H, Ph-H), 7.40 (d, $J = 8.35$ Hz, 2H, Ph-H), 7.45 (m, 2H, 4,7-CH), 7.76 (s, 1H, 2-CH).

*4.2.5.4. 1-(4-Chlorobenzyl)-3-(1-hydroxypentyl)-1H-indole (**23g**).* Yellow oil (98%); IR ν_{max} 3128, 1285, 1085 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 0.88 (t, $J = 6.60$ Hz, 3H, CH_3), 1.24 (m, 4H, CH_2), 1.83 (m, 2H, CH_2), 4.83 (m, 1H, CH), 4.91 (d, $J = 4.50$ Hz, 1H, OH), 5.40 (s, 2H, CH_2), 7.02 (dd, $J = 7.90$ Hz, $J' = 7.05$ Hz, 1H, 5-CH), 7.11 (dd, $J = 7.90$ Hz, $J' = 7.05$ Hz, 1H, 6-CH), 7.24 (d, $J = 8.40$ Hz, 2H, Ph-H), 7.36 (m, 2H, Ph-H), 7.68 (m, 1H, 7-CH), 8.15 (m, 1H, 4-CH), 8.51 (s, 1H, 2-CH).

*4.2.5.5. 1-(4-Chlorobenzyl)-3-(1-hydroxy-2,2-dimethylpropyl)-1H-indole (**23h**).* Light yellow oil (96%); IR ν_{max} 3255, 1255, 1079 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 1.00 (s, 9H, CH_3), 4.84 (d, $J = 4.60$ Hz, 1H, OH), 5.06 (m, 1H, CH), 5.44 (s, 2H, CH_2), 7.08 (m, 2H, 5,6-CH), 7.27 (d, $J = 8.40$ Hz, 2H, Ph-H), 7.38 (m, 2H, Ph-H), 7.43 (m, 1H, 7-CH), 7.58 (m, 1H, 4-CH), 7.60 (s, 1H, 2-CH).

*4.2.5.6. 5-Bromo-1-(4-chlorobenzyl)-3-(1-hydroxybutyl)-1H-indole (**34d**).* Yellow oil (96%); IR ν_{max} 3198, 1257, 1087 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 0.97 (t, $J = 7.00$ Hz, 3H, CH_3), 1.23 (m, 2H, CH_2), 1.74 (t, $J = 7.00$ Hz, 2H, CH_2), 4.87 (d, $J = 4.70$ Hz, 1H, OH), 5.15 (m, 1H, CH), 5.41 (s, 2H, CH_2), 7.30 (d, $J =$ 8.50 Hz, 2H, Ph-H), 7.31 (s, 1H, 2-CH), 7.40 (d, $J = 8.50$ Hz, 2H, Ph-H), 7.56 (m, 2H, 6,7-CH), 7.63 (m, 1H, 4-CH).

*4.2.5.7. 5-Bromo-1-(4-chlorobenzyl)-3-(1-hydroxypentyl)-1H-indole (**34g**).* Green oil (97%); IR ν_{max} 3258, 1237, 1072 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 0.90 (t, $J = 7.00$ Hz, 3H, CH_3), 1.30 (m, 4H, CH_2), 1.85 (m, 2H, CH_2), 4.99 (d, $J = 4.65$ Hz, 1H, OH), 5.11 (m, 1H, CH), 5.41 (s, 2H, CH_2), 7.37 (d, $J = 8.50$ Hz, 2H, Ph-H), 7.44 (d, $J = 8.50$ Hz, 2H, Ph-H), 7.49 (s, 1H, 2-CH), 7.64 (m, 2H, 6,7-CH), 7.70 (m, 1H, 4-CH).

*4.2.6. General procedure for compounds **23a**–**28a** and **30a**–**34a** from **11** to **16** and **18** to **22***

These compounds were prepared according to the procedure used ($LiAlH_4$ reduction) for ketones **6** and **7**.

*4.2.6.1. 1-(4-Chlorobenzyl)-3-(1-hydroxymethyl)-1H-indole (**23a**).* White powder (85%), m.p. 75–76 °C; IR ν_{max} 3385 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 4.68 (d, $J =$ 5.40 Hz, 2H, CH_2), 4.87 (t, $J = 5.40$ Hz, 1H, OH), 5.42 (s, 2H, CH_2), 7.08 (m, 2H, 5,6-CH), 7.25 (d, $J = 8.60$ Hz, 2H, Ph-H), 7.41 (m, 3H, 2-CH, Ph-H), 7.45 (d, $J = 7.45$ Hz, 1H, 7-CH), 7.64 (d, $J = 7.60$ Hz, 1H, 4-CH).

*4.2.6.2. 1-(4-Fluorobenzyl)-3-(1-hydroxymethyl)-1H-indole (**24a**).* Yellow powder (80%), m.p. 91–92 °C; IR ν_{max} 3385 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 4.85 (t, $J =$ 5.35 Hz, 1H, OH), 4.67 (d, $J = 5.35$ Hz, 2H, CH_2), 5.51 (s, 2H, CH_2), 7.05 (m, 2H, 5,6-CH), 7.18 (m, 2H, Ph-H), 7.33 (m, 2H, Ph-H), 7.43 (s, 1H, 2-CH), 7.47 (d, $J = 8.10$ Hz, 1H, 7-CH), 7.64 (d, $J = 7.60$ Hz, 1H, 4-CH).

*4.2.6.3. 1-(2,4-Difluorobenzyl)-3-(1-hydroxymethyl)-1H-indole (**25a**).* Yellow oil (97%); IR ν_{max} 3287 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 4.68 (m, 1H, CH_2), 4.77 (m, 1H, OH), 5.54 (s, 2H, CH_2), 7.09 (m, 2H, 5,6-CH), 7.12 (m, 1H, Ph-H), 7.35 (m, 1H, Ph-H), 7.40 (s, 1H, 2-CH), 7.44 (m, 1H, 7-CH), 7.60 (m, 1H, 4-CH), 7.65 (m, 1H, Ph-H).

*4.2.6.4. 1-(2,4-Dichlorobenzyl)-3-(1-hydroxymethyl)-1H-indole (**26a**).* Brown powder (98%); IR ν_{max} 3215 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 4.60 (m, 2H, CH_2), 4.68 (m, 1H, OH), 5.41 (s, 2H, CH_2), 6.18 (d, $J = 8.30$ Hz, 1H, Ph-H), 7.09 (m, 2H, 5,6-CH), 7.24 (m, 1H, Ph-H), 7.35 (s, 1H, 2-CH), 7.38 (m, 1H, 7-CH), 7.64 (d, $J = 7.60$ Hz, 1H, 4-CH), 7.70 (d, $J = 2.00$ Hz, 1H, Ph-H).

*4.2.6.5. 1-(4-Fluorobenzyl)-3-(1-hydroxymethyl)-2-methyl-1H-indole (**27a**).* Yellow oil (95%); IR ν_{max} 3198 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 2.36 (s, 3H, CH_3), 4.68 (m, 3H, CH_2 and OH), 5.46 (s, 2H, CH_2), 7.06 (m, 2H, 5,6-CH), 7.11 (m, 2H, Ph-H), 7.18 (m, 2H, Ph-H), 7.38 (m, 1H, 7-CH), 7.58 (m, 1H, 4-CH).

*4.2.6.6. 1-(4-Chlorobenzyl)-3-(1-hydroxymethyl)-2-methyl-1H-indole (**28a**).* Yellow powder (97%), m.p. 75–77 °C; IR ν_{max} 3362 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 2.35 (s, 3H, CH_3), 4.65 (m, 3H, CH_2 and OH), 5.46 (s, 2H, CH_2), 7.05 (m, 2H, 5,6-CH), 7.25 (m, 2H, Ph-H), 7.37 (m, 1H, 7-CH), 7.43 (m, 2H, Ph-H), 7.60 (d, $J =$ 7.85 Hz, 1H, 4-CH).

*4.2.6.7. 1-(2,4-Diclorobenzyl)-3-(1-hydroxymethyl)-2-methyl-1H-indole (**30a**).* White powder (96%), m.p. 110–112 °C; IR ν_{max} 3258 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 2.32 (s, 3H, CH_3), 4.67 (m, 2H, CH_2), 4.72 (m, 1H, OH), 5.46 (s, 2H, CH_2), 6.17 (d, $J = 8.55$ Hz, 1H, Ph-H), 7.06 (m, 2H, 5,6-CH), 7.28 (m, 2H, Ph-H and 7-CH), 7.77 (m, 2H, Ph-H and 4-CH).

*4.2.6.8. 5-Bromo-1-(2-fluorobenzyl)-3-(1-hydroxymethyl)-1H-indole (**31a**).* Yellow oil (97%); IR ν_{max} 3319 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 4.63 (d, $J =$ 5.40 Hz, 2H, CH_2), 4.94 (t, $J = 5.40$ Hz, 1H, OH), 5.46 (s, 2H, CH_2), 7.09 (m, 1H, Ph-H), 7.18 (m, 2H, Ph-H), 7.26 (dd, $J = 8.90$ Hz, $J'_{HF} = 8.90$ Hz, 1H, Ph-H), 7.42 (s, 1H, 2-CH), 7.48 (d, $J = 8.70$ Hz, 1H, 7-CH), 7.82 (d, $J = 1.80$ Hz, 1H, 4-CH).

*4.2.6.9. 5-Bromo-1-(4-fluorobenzyl)-3-(1-hydroxymethyl)-1H-indole (**32a**).* Yellow powder (95%), m.p. 70–73 °C; IR ν_{max} 3358 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 4.62 (d, $J = 5.40$ Hz, 2H, CH_2), 4.89 (t, $J = 5.40$ Hz, 1H, OH), 5.45 (s, 2H, CH_2), 7.21 (m, 2H, Ph-H), 7.33 (m, 1H, 6-CH), 7.40 (s, 1H, 2-CH), 7.41 (m, 2H, Ph-H), 7.44 (m, 1H, 7-CH), 7.78 (d, $J = 1.50$ Hz, 1H, 4-CH).

*4.2.6.10. 5-Bromo-1-(4-chlorobenzyl)-3-(1-hydroxymethyl)-1H-indole (**33a**).* Yellow oil (94%); IR ν_{max} 3356 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 4.65 (d, $J =$ 5.40 Hz, 2H, CH_2), 4.97 (t, $J = 5.40$ Hz, 1H, OH), 5.51 (s, 2H, CH_2), 6.74 (dd, $J = 7.50$ Hz, $J' = 1.50$ Hz, 1H, Ph-H), 7.25 (m, 2H, 6-CH and Ph-H), 7.35 (s, 1H, 2-CH), 7.40 (m, 1H, Ph-H), 7.53 (dd, $J = 7.80$ Hz, $J' =$ 1.50 Hz, 1H, Ph-H), 7.86 (d, $J = 1.80$ Hz, 1H, 4-CH).

*4.2.6.11. 5-Bromo-1-(4-chlorobenzyl)-3-(1-hydroxymethyl)-1H-indole (**34a**).* Yellow oil (95%); IR ν_{max} 3267 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 4.64 (d, $J =$ 5.40 Hz, 2H, CH_2), 4.95 (t, $J = 5.40$ Hz, 1H, OH), 5.41 (s, 2H, CH_2), 7.24 (m, 1H, 6-CH), 7.25 (d, $J = 8.40$ Hz, 2H, Ph-H), 7.41 (d, $J = 8.40$ Hz, 2H, Ph-H), 7.44 (m, 1H, 7-CH), 7.49 (s, 1H, 2-CH), 7.83 (d, $J = 1.75$ Hz, 1H, 4-CH).

*4.2.7. General procedure for alcohols **23**–**27**, **29**, **30** from **11** to **15**, **17** and **18***

A solution of **11**–**15**, **17** or **18** in tetrahydrofuran was cooled at −40 °C and then appropriate alkylmagnesium halogenide (1.2 equiv.) was added dropwise over a period of 15 min to the solution. The whole was stirred at the same temperature. A saturated aqueous solution of NH_4Cl (400 mL) and water was added and the resulting mixture was extracted with ethyl acetate. The extracts were combined, washed successively with water and brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel.

*4.2.7.1. 1-(4-Chlorobenzyl)-3-(1-hydroxypropyl)-1H-indole (**23c**).* Yellow oil (97%); IR ν_{max} 3386, 1263, 1078 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 0.88 (t, $J = 7.00$ Hz, 3H, CH_3), 1.93 (m, 2H, CH_2), 4.93 (m, 1H, CH), 4.95 (d, $J =$ 4.70 Hz, 1H, OH), 5.42 (s, 2H, CH_2), 7.07 (m, 2H, 5,6-CH), 7.36 (d, $J = 8.40$ Hz, 2H, Ph-H), 7.43 (d, $J = 8.40$ Hz, 2H, Ph-H), 7.50 (m, 1H, 7-CH), 7.77 (d, $J = 7.60$ Hz, 1H, 4-CH), 7.81 (s, 1H, 2-CH).

*4.2.7.2. 1-(4-Chlorobenzyl)-3-(1-hydroxybut-3-enyl)-1H-indole (**23f**).* Brown oil (96%); IR ν_{max} 3360, 1248, 1083 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 0.98 (m, 1H, CH), 1.61 (d, $J = 7.10$ Hz, 2H, CH_2), 4.95 (m, 1H, CH), 5.00 and 5.16 (d, $J_{cis} = 10.60$ Hz, $J_{trans} = 17.00$ Hz, 2H, CH_2), 5.08 (d, $J = 4.75$ Hz, 1H, OH), 5.40 (s, 2H, CH_2), 7.03 (dd, J = 7.60 Hz, $J' = 7.05$ Hz, 1H, 5-CH), 7.12 (dd, $J = 7.70$ Hz, $J' = 7.05$ Hz, 1H, 6-CH), 7.23 (d, $J = 8.35$ Hz, 2H, Ph-H), 7.40 (m, 2H, Ph-H), 7.43 (m, 1H, 7-CH), 7.51 (s, 1H, 2-CH), 7.69 (d, $J = 7.60$ Hz, 1H, 4-CH).

*4.2.7.3. 1-(4-Fluorobenzyl)-3-(1-hydroxyethyl)-1H-indole (**24b**).* Yellow oil (79%); IR ν_{max} 3369, 1286, 1154 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 1.52 (d, $J = 6.30$ Hz, 3H, CH_3), 4.95 (d, $J = 4.60$ Hz, 1H, OH), 5.03 (dd, $J = 6.30$ Hz, $J' = 4.60$ Hz, 1H, CH), 5.38 (s, 2H, CH_2), 7.02 (dd, $J = 7.70$ Hz, $J' = 7.00$ Hz, 1H, 5-CH), 7.13 (dd, $J = 8.20$ Hz, $J' = 7.00$ Hz, 1H, 6-CH), 7.19 (m, 2H, Ph-H), 7.30 (m, 2H, Ph-H), 7.38 (s, 1H, 2-CH), 7.68 (m, 1H, 7-CH), 7.69 (d, $J = 7.70$ Hz, 1H, 4-CH).

*4.2.7.4. 1-(2,4-Difluorobenzyl)-3-(1-hydroxyethyl)-1H-indole (**25b**).* Yellow oil (73%); IR ν_{max} 3299, 1248, 1155 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 1.51 (d, $J = 6.40$ Hz, 3H, CH_3), 4.96 (d, $J = 4.60$ Hz, 1H, OH), 5.03 (m, 1H, CH), 5.42 (s, 2H, CH_2), 7.02 (m, 1H, 5-CH), 7.05 (m, 1H, Ph-H), 7.10 (m, 1H, 6-CH), 7.20 (m, 2H, Ph-H), 7.31 (s, 1H, 2-CH), 7.48 (d, $J = 7.90$ Hz, 1H, 7-CH), 7.68 (m, 1H, 4-CH).

*4.2.7.5. 1-(2,4-Dichlorobenzyl)-3-(1-hydroxyethyl)-1H-indole (**26b**).* Yellow oil (98%); IR ν_{max} 3358, 1259, 1095 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 1.52 (d, $J = 6.30$ Hz, 3H, CH_3), 4.98 (d, $J = 4.60$ Hz, 1H, OH), 5.02 (m, 1H, CH), 5.48 (s, 2H, CH_2), 6.71 (d, $J = 8.35$ Hz, 1H, Ph-H), 7.32 (m, 2H, 5,6-CH), 7.41 (m, 1H, Ph-H), 7.45 (m, 1H, 7-CH), 7.75 (s, 1H, 2-CH), 7.77 (d, $J = 8.50$ Hz, 1H, Ph-H), 7.78 (m, 1H, 4-CH).

*4.2.7.6. 1-(4-Fluorobenzyl)-3-(1-hydroxyethyl)-2-methyl-1H-indole (**27b**).* Yellow oil (96%); IR ν_{max} 3288, 1269, 1160 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 1.50 (d, $J =$ 6.30 Hz, 3H, CH_3), 2.36 (s, 3H, CH_3), 4.87 (d, $J = 4.75$

Hz, 1H, OH), 5.12 (m, 1H, CH), 5.39 (s, 2H, CH_2), 6.98 (dd, $J,J' = 7.00$ Hz, 1H, 5-CH), 7.05 (m, 1H, 6-CH), 7.07 (m, 2H, Ph-H), 7.15 (m, 2H, Ph-H), 7.38 (d, $J = 7.00$ Hz, 1H, 7-CH), 7.75 (d, $J = 7.00$ Hz, 1H, 4-CH).

*4.2.7.7. 1-(4-Bromobenzyl)-3-(1-hydroxyethyl)-2-methyl-1H-indole (**29b**).* Yellow oil (96%); IR ν_{max} 3287, 1259, 1088 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 1.50 (d, $J = 6.20$ Hz, 3H, CH_3), 2.35 (s, 3H, CH_3), 4.88 (d, $J = 4.70$ Hz, 1H, OH), 5.12 (m, 1H, CH), 5.56 (s, 2H, CH_2), 6.99 (m, 2H, 5,6-CH), 7.01 (m, 2H, Ph-H), 7.35 (d, $J = 7.90$ Hz, 1H, 7-CH), 7.52 (d, $J = 8.00$ Hz, 1H, Ph-H), 7.75 (d, $J = 7.00$ Hz, 1H, 4-CH).

*4.2.7.8. 1-(2,4-Dichlorobenzyl)-3-(1-hydroxyethyl)-2-methyl-1H-indole (**30b**).* White powder (84%), m.p. 107–108 °C; IR ν_{max} 3179, 1237, 1094 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 1.53 (d, $J = 5.80$ Hz, 3H, CH_3), 2.31 (s, 3H, CH_3), 4.93 (d, $J = 4.65$ Hz, 1H, OH), 5.15 (m, 1H, CH), 5.43 (s, 2H, CH_2), 7.02 (m, 2H, 5,6-CH), 7.28 (m, 3H, Ph-H and 7-CH), 7.77 (m, 2H, Ph-H and 4-CH).

*4.2.8. General procedure for the preparation of 3-imidazolylmethylindole derivatives **35**–**46***

To a solution of **23**–**34** in anhydrous tetrahydrofuran (20 mL), 1,1′-carbonydiimidazole (1.2 equiv.) was added. The reaction mixture was refluxed with stirring for 5 h. The mixture was extracted with CH_2Cl_2 and the organic layer was washed with brine, dried over Na_2SO_4 and evaporated under vacuum. The residue was chromatographed with CH_2Cl_2: EtOH (20: 1).

*4.2.8.1. 1-(4-Chlorobenzyl)-3-(1H-imidazol-1-ylmethyl)-1H-indole (**35a**).* IR ν_{max} 1621, 1297 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 5.36 (s, 2H, CH_2), 5.45 (s, 2H, CH_2), 6.88 (s, 1H, imidazole-H), 7.10 (m, 2H, 5,6-CH), 7.20 (s, 1H, imidazole-H), 7.25 (d, $J = 8.30$ Hz, 2H, Ph-H), 7.41 (m, $J = 8.30$ Hz, 2H, Ph-H), 7.47 (m, 1H, 7-CH), 7.59 (d, $J = 7.55$ Hz, 1H, 4-CH), 7.63 (s, 1H, 2-CH), 7.79 (s, 1H, imidazole-H). Anal. $C_{19}H_{16}ClN_3$ (C, H, N).

*4.2.8.2. 1-(4-Chlorobenzyl)-3-[1-(1H-imidazol-1-yl)ethyl]-1H-indole (**35b**).* IR ν_{max} 1631, 1326 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 1.89 (d, $J = 7.00$ Hz, 3H, CH_3), 5.44 (s, 2H, CH_2), 5.88 (m, 1H, CH), 6.92 (s, 1H, imidazole-H), 6.99 (m, 2H, 5,6-CH), 7.27 (s, 1H, imidazole-H), 7.26 (m, 2H, Ph-H), 7.42 (m, 2H, Ph-H), 7.45 (m, 1H, 7-CH), 7.68 (m, 2H, 2,4-CH), 7.87 (s, 1H, imidazole-H). Anal. $C_{20}H_{18}ClN_3$ (C, H, N).

*4.2.8.3. 1-(4-Chlorobenzyl)-3-[1-(1H-imidazol-1-yl)propyl]-1H-indole (**35c**).* IR ν_{max} 1652, 1290 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 0.88 (t, $J = 7.20$ Hz, 3H, CH_3), 2.32 (m, 2H, CH_2), 5.45 (s, 2H, CH_2), 5.55 (t, $J = 7.40$ Hz, 1H, CH), 6.88 (s, 1H, imidazole-H), 7.00 (dd, $J,J' = 7.45$ Hz, 1H, 5-CH), 7.13 (dd, $J,J' = 7.45$ Hz, 1H, 6-CH), 7.22 (s, 1H, imidazole-H), 7.25 (d, $J = 8.40$ Hz, 2H, Ph-H), 7.42 (d, $J = 8.40$ Hz, 2H, Ph-H), 7.41 (m, 1H, 7-CH), 7.44 (m, 1H, 4-CH), 7.73 (s, 1H, 2-CH), 7.85 (s, 1H, imidazole-H). Anal. $C_{21}H_{20}ClN_3$ (C, H, N).

*4.2.8.4. 1-(4-Chlorobenzyl)-3-[1-(1H-imidazol-1-yl)butyl]-1H-indole (**35d**).* IR ν_{max} 1636, 1312 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 0.98 (t, $J = 7.25$ Hz, 3H, CH_3), 1.27 (m, 2H, CH_2), 2.28 (t, $J = 7.45$ Hz, 2H, CH_2), 5.47 (s, 2H, CH_2), 5.68 (t, $J = 7.60$ Hz, 1H, CH), 6.89 (s, 1H, imidazole-H), 7.03 (dd, $J = 7.40$ Hz, $J' = 7.35$ Hz, 1H, 5-CH), 7.14 (dd, $J,J' = 7.35$ Hz, 1H, 6-CH), 7.24 (s, 1H, imidazole-H), 7.27 (d, $J = 8.40$ Hz, 2H, Ph-H), 7.43 (d, $J = 8.40$ Hz, 2H, Ph-H), 7.45 (m, 1H, 7-CH), 7.49 (m, 1H, 4-CH), 7.76 (s, 1H, 2-CH), 7.88 (s, 1H, imidazole-H). Anal. $C_{22}H_{22}ClN_3$ (C, H, N).

*4.2.8.5. 1-(4-Chlorobenzyl)-3-[1-(1H-imidazol-1-yl)-2-methylpropyl]-1H-indole (**35e**).* IR ν_{max} 1653, 1305 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 0.80 and 0.99 (d, $J = 6.10$ Hz, 6H, CH_3), 2.71 (m, 1H, CH), 5.45 (s, 2H, CH_2), 6.29 (d, $J = 10.00$ Hz, 1H, CH), 6.86 (s, 1H, imidazole-H), 7.09 (m, 2H, 5,6-CH), 7.23 (d, $J = 8.20$ Hz, 2H, Ph-H), 7.28 (s, 1H, imidazole-H), 7.41 (d, $J = 8.20$ Hz, 2H, Ph-H), 7.43 (m, 1H, 7-CH), 7.67 (d, $J = 7.65$ Hz, 1H, 4-CH), 7.83 (s, 1H, 2-CH), 7.86 (s, 1H, imidazole-H). Anal. $C_{22}H_{22}ClN_3$ (C, H, N).

*4.2.8.6. 1-(4-Chlorobenzyl)-3-[1-(1H-imidazol-1-yl)but-3-enyl]-1H-indole (**35f**).* IR ν_{max} 1643, 1303 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 2.74 (m, 2H, CH_2), 3.04 (m, 1H, CH), 5.05 and 5.15 (d, $J_{cis} = 10.20$ Hz, $J_{trans} = 17.20$ Hz, 2H, CH_2), 5.45 (s, 2H, CH_2), 5.74 (m, 1H, CH), 6.86 (s, 1H, imidazole-H), 7.01 (dd, $J,J' = 7.35$ Hz, 1H, 5-CH), 7.15 (m, 1H, 6-CH), 7.24 (s, 1H, imidazole-H), 7.26 (d, $J = 8.50$ Hz, 2H, Ph-H), 7.42 (d, $J = 8.50$ Hz, 2H, Ph-H), 7.44 (m, 2H, 4,7-CH), 7.76 (s, 1H, 2-CH), 7.84 (s, 1H, imidazole-H). Anal. $C_{22}H_{20}ClN_3$ (C, H, N).

*4.2.8.7. 1-(4-Chlorobenzyl)-3-[1-(1H-imidazol-1-yl)pentyl]-1H-indole (**35g**).* IR ν_{max} 1655, 1295 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 0.89 (t, $J = 6.70$ Hz, 3H, CH_3), 1.22 (m, 4H, CH_2), 2.28 (m, 2H, CH_2), 5.45 (s, 2H, CH_2), 5.63 (t, $J = 7.35$ Hz, 1H, CH), 6.87 (s, 1H, imidazole-H), 7.00 (dd, $J,J' = 7.40$ Hz, 1H, 5-CH), 7.12 (dd, $J,J' = 7.40$ Hz, 1H, 6-CH), 7.22 (s, 1H, imidazole-H), 7.25 (d, $J = 8.50$ Hz, 2H, Ph-H), 7.40 (d, $J = 7.40$ Hz, 1H, 4-CH), 7.41 (d, $J = 8.50$ Hz, 2H, Ph-H), 7.43 (d, $J = 7.40$ Hz, 1H, 7-CH), 7.74 (s, 1H, 2-CH), 7.86 (s, 1H, imidazole-H). Anal. $C_{23}H_{24}ClN_3$ (C, H, N).

*4.2.8.8. 1-(4-Chlorobenzyl)-3-[1-(1H-imidazol-1-yl)-2,2-dimethylpropyl]-1H-indole (**35h**).* IR ν_{max} 1636,

1323 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 1.02 (s, 9H, CH_3), 5.47 (s, 2H, CH_2), 5.64 (s, 1H, CH), 6.88 (s, 1H, imidazole-H), 7.09 (m, 2H, 5,6-CH), 7.10 (s, 1H, imidazole-H), 7.26 (d, $J = 8.25$ Hz, 2H, Ph-H), 7.41 (d, $J = 8.25$ Hz, 2H, Ph-H), 7.42 (m, 1H, 7-CH), 7.74 (d, $J = 7.55$ Hz, 1H, 4-CH), 7.88 (s, 1H, imidazole-H), 8.08 (s, 1H, 2-CH). Anal. $C_{23}H_{24}ClN_3$ (C, H, N).

*4.2.8.9. 1-(4-Fluorobenzyl)-3-(1H-imidazol-1-ylmethyl)-1H-indole (**36a**).* IR ν_{max} 1646, 1362 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 5.36 (s, 2H, CH_2), 5.43 (s, 2H, CH_2), 6.88 (s, 1H, imidazole-H), 7.11 (m, 1H, 5-CH), 7.11 (m, 4H, 6-CH, Ph-H, imidazole-H), 7.30 (m, 2H, Ph-H), 7.50 (d, $J = 8.10$ Hz, 1H, 7-CH), 7.59 (d, $J = 7.59$ Hz, 1H, 4-CH), 7.63 (s, 1H, 2-CH), 7.82 (s, 1H, imidazole-H). Anal. $C_{19}H_{16}FN_3$ (C, H, N).

*4.2.8.10. 1-(4-Fluorobenzyl)-3-[1-(1H-imidazol-1-yl)ethyl]-1H-indole (**36b**).* IR ν_{max} 1638, 1285m^{-1}. ^{1}H-NMR (DMSO-d_6) δ 1.89 (d, $J = 6.90$ Hz, 3H, CH_3), 4.77 (m, 1H, CH), 5.43 (s, 2H, CH_2), 6.89 (s, 1H, imidazole-H), 6.99 (dd, $J,J' = 7.30$ Hz, 1H, 5-CH), 7.13 (dd, $J = 7.80$ Hz, $J' = 7.30$ Hz, 1H, 6-CH), 7.14 (s, 1H, imidazole-H), 7.20 (d, $J = 8.50$ Hz, 2H, Ph-H), 7.32 (m, 3H, Ph-H and 7-CH), 7.46 (m, 1H, 4-CH), 7.69 (s, 1H, 2-CH), 7.83 (s, 1H, imidazole-H). Anal. $C_{20}H_{18}FN_3$ (C, H, N).

*4.2.8.11. 1-(2,4-Difluorobenzyl)-3-(1H-imidazol-1-ylmethyl)-1H-indole (**37a**).* IR ν_{max} 1618, 1333 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 5.36 (s, 2H, CH_2), 5.47 (s, 2H, CH_2), 6.89 (s, 1H, imidazole-H), 7.08 (m, 2H, 5,6-CH), 7.19 (m, 2H, 7-CH, Ph-H), 7.20 (s, 1H, imidazole-H), 7.32 (t, $J = 9.00$ Hz, 1H, Ph-H), 7.53 (d, $J = 8.15$ Hz, 1H, Ph-H), 7.58 (s, 1H, 2-CH), 7.60 (d, $J = 7.35$ Hz, 1H, 4-CH), 7.82 (s, 1H, imidazole-H). Anal. $C_{19}H_{15}F_2N_3$ (C, H, N).

*4.2.8.12. 1-(2,4-Difluorobenzyl)-3-[1-(1H-imidazol-1-yl)ethyl]-1H-indole (**37b**).* IR ν_{max} 1650, 1299 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 1.88 (d, $J = 7.00$ Hz, 3H, CH_3), 5.48 (s, 2H, CH_2), 5.84 (q, $J = 7.00$ Hz, 1H, CH), 7.10 (m, 1H, Ph-H), 6.87 (s, 1H, imidazole-H), 7.00 (m, 1H, 5-CH), 7.18 (m, 1H, 6-CH), 7.19 (s, 1H, imidazole-H), 7.30 (m, 1H, Ph-H), 7.35 (m, 1H, Ph-H), 7.37 (m, 1H, 7-CH), 7.49 (d, $J = 8.20$ Hz, 1H, 4-CH), 7.62 (s, 1H, 2-CH), 7.80 (s, 1H, imidazole-H). Anal. $C_{20}H_{17}F_2N_3$ (C, H, N).

*4.2.8.13. 1-(2,4-Dichlorobenzyl)-3-(1H-imidazol-1-ylmethyl)-1H-indole (**38a**).* IR ν_{max} 1639, 1292 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 5.38 (s, 2H, CH_2), 5.52 (s, 2H, CH_2), 6.80 (s, 1H, imidazole-H), 6.90 (m, 1H, Ph-H), 7.16 (m, 2H, 5,6-CH), 7.20 (s, 1H, imidazole-H), 7.40 (m, 2H, Ph-H), 7.60 (m, 1H, 4,7-CH), 7.77 (s, 1H, 2-CH), 7.83 (s, 1H, imidazole-H). Anal. $C_{19}H_{15}Cl_2N_3$ (C, H, N).

*4.2.8.14. 1-(2,4-Dichlorobenzyl)-3-[1-(1H-imidazol-1-yl)ethyl]-1H-indole (**38b**).* IR ν_{max} 1663, 1368 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 1.88 (d, $J = 6.70$ Hz, 3H, CH_3), 5.54 (s, 2H, CH_2), 5.89 (q, $J = 6.70$ Hz, 1H, CH), 6.37 (d, $J = 8.30$ Hz, 1H, Ph-H), 6.88 (s, 1H, imidazole-H), 7.03 (dd, $J,J' = 7.70$ Hz, 1H, 5-CH), 7.15 (dd, $J,J' = 7.70$ Hz, 1H, 6-CH), 7.22 (s, 1H, imidazole-H), 7.38 (m, 2H, 4,7-CH), 7.39 (d, $J = 8.30$ Hz, 1H, Ph-H), 7.63 (s, 1H, 2-CH), 7.74 (d, $J = 2.10$ Hz, 1H, Ph-H), 7.82 (s, 1H, imidazole-H). Anal. $C_{20}H_{17}Cl_2N_3$ (C, H, N).

*4.2.8.15. 1-(4-Fluorobenzyl)-3-(1H-imidazol-1-ylmethyl)-2-methyl-1H-indole (**39a**).* IR ν_{max} 1662, 1290 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 2.48 (s, 3H, CH_3), 5.36 (s, 2H, CH_2), 5.45 (s, 1H, CH_2), 6.85 (s, 1H, imidazole-H), 7.05 (m, 2H, 5,6-CH), 7.15 (m, 4H, Ph-H), 7.12 (s, 1H, imidazole-H), 7.43 (d, $J = 7.63$ Hz, 1H, 7-CH), 7.58 (d, $J = 7.30$ Hz, 1H, 4-CH), 7.75 (s, 1H, imidazole-H). Anal. $C_{20}H_{18}FN_3$ (C, H, N).

*4.2.8.16. 1-(4-Fluorobenzyl)-3-[1-(1H-imidazol-1-yl)ethyl]-2-methyl-1H-indole (**39b**).* IR ν_{max} 1649, 1308 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 1.98 (d, $J = 7.30$ Hz, 3H, CH_3), 2.42 (s, 3H, CH_3), 5.44 (s, 2H, CH_2), 5.78 (q, $J = 7.30$ Hz, 1H, CH), 6.89 (s, 1H, imidazole-H), 7.02 (m, 2H, 5,6-CH), 7.08 (m, 2H, Ph-H), 7.13 (d, $J = 8.60$ Hz, 2H, Ph-H), 7.20 (s, 1H, imidazole-H), 7.42 (d, $J = 7.30$ Hz, 1H, 7-CH), 7.46 (d, $J = 7.00$ Hz, 1H, 4-CH), 7.76 (s, 1H, imidazole-H). Anal. $C_{21}H_{20}FN_3$ (C, H, N).

*4.2.8.17. 1-(4-Chlorobenzyl)-3-(1H-imidazol-1-ylmethyl)-2-methyl-1H-indole (**40a**).* IR ν_{max} 1649, 1334 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 2.46 (s, 3H, CH_3), 5.36 (s, 2H, CH_2), 5.46 (s, 2H, CH_2), 6.86 (s, 1H, imidazole-H), 7.08 (m, 4H, 5,6-CH, Ph-H), 7.04 (s, 1H, imidazole-H), 7.38 (d, $J = 8.00$ Hz, 2H, Ph-H), 7.38 (m, 2H, 7-CH, Ph-H), 7.58 (d, $J = 7.10$ Hz, 1H, 4-CH), 7.75 (s, 1H, imidazole-H). Anal. $C_{20}H_{18}ClN_3$ (C, H, N).

*4.2.8.18. 1-(4-Bromobenzyl)-3-[1-(1H-imidazol-1-yl)ethyl]-2-methyl-1H-indole (**41b**).* IR ν_{max} 1628, 1352 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 1.97 (d, $J = 7.00$ Hz, 3H, CH_3), 2.40 (s, 3H, CH_3), 5.43 (s, 2H, CH_2), 5.76 (m, 1H, CH), 6.88 (s, 1H, imidazole-H), 6.96 (m, 1H, 5-CH), 6.97 (d, $J = 8.20$ Hz, 2H, Ph-H), 7.07 (m, 1H, 6-CH), 7.21 (s, 1H, imidazole-H), 7.41 (m, 1H, 7-CH), 7.44 (m, 1H, 4-CH), 7.53 (d, $J = 8.20$ Hz, 2H, Ph-H), 7.76 (s, 1H, imidazole-H). Anal. $C_{21}H_{20}BrN_3$ (C, H, N).

*4.2.8.19. 1-(2,4-Dichlorobenzyl)-3-(1H-imidazol-1-ylmethyl)-2-methyl-1H-indole (**42a**).* IR ν_{max} 1660, 1320 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 2.43 (s, 3H, CH_3), 5.39 (s, 2H, CH_2), 5.49 (s, 2H, CH_2), 6.18 (d, $J = 8.25$ Hz,

1H, Ph-H), 6.87 (s, 1H, imidazole-H), 7.08 (m, 2H, 5,6-CH), 7.14 (s, 1H, imidazole-H), 7.31 (dd, $J = 8.25$ Hz, $J' = 2.00$ Hz, 1H, 7-CH), 7.33 (dd, $J = 7.30$ Hz, $J' = 1.85$ Hz, 1H, 4-CH), 7.61 (m, 1H, Ph-H), 7.76 (d, $J = 2.15$ Hz, 1H, Ph-H), 7.77 (s, 1H, imidazole-H). Anal. $C_{20}H_{17}Cl_2N_3$ (C, H, N).

*4.2.8.20. 1-(2,4-Dichlorobenzyl)-3-[1-(1H-imidazol-1-yl)ethyl]-2-methyl-1H-indole (**42b**).* IR ν_{max} 1646, 1291 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 2.00 (d, $J = 7.00$ Hz, 3H, CH_3), 2.86 (s, 3H, CH_3), 5.48 (s, 2H, CH_2), 5.80 (q, $J = 7.00$ Hz, 1H, CH), 6.19 (d, $J = 8.20$ Hz, 1H, Ph-H), 6.90 (s, 1H, imidazole-H), 7.01 (dd, $J = 7.90$ Hz, $J' = 7.00$ Hz, 1H, 5-CH), 7.10 (dd, $J = 7.60$ Hz, $J' = 7.00$ Hz, 1H, 6-CH), 7.24 (s, 1H, imidazole-H), 7.33 (m, 1H, Ph-H), 7.47 (d, $J = 7.60$ Hz, 1H, 7-CH), 7.77 (d, $J = 7.90$ Hz, 1H, 4-CH), 7.75 (d, $J = 1.80$ Hz, 1H, Ph-H), 7.78 (s, 1H, imidazole-H). Anal. $C_{21}H_{19}Cl_2N_3$ (C, H, N).

*4.2.8.21. 5-Bromo-1-(2-fluorobenzyl)-3-(1H-imidazol-1-ylmethyl]-1H-indole (**43a**).* IR ν_{max} 1599, 1324 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 5.35 (s, 2H, CH_2), 5.50 (s, 2H, CH_2), 6.88 (s, 1H, imidazole-H), 7.14 (s, 1H, imidazole-H), 7.22 (m, 5H, 6-CH, Ph-H), 7.50 (d, $J = 8.75$ Hz, 1H, 7-CH), 7.65 (s, 1H, 2-CH), 7.81 (s, 1H, 4-CH), 7.81 (s, 1H, imidazole-H). Anal. $C_{19}H_{15}BrFN_3$ (C, H, N).

*4.2.8.22. 5-Bromo-1-(4-fluorobenzyl)-3-(1H-imidazol-1-ylmethyl]-1H-indole (**44a**).* IR ν_{max} 1660, 1326 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 5.34 (s, 2H, CH_2), 5.43 (s, 2H, CH_2), 6.89 (s, 1H, imidazole-H), 7.17 (d, $J = 8.75$ Hz, 1H, 6-CH), 7.20 (s, 1H, imidazole-H), 7.20 (m, 2H, Ph-H), 7.28 (d, $J = 8.90$, $J_{HF} = 5.50$ Hz, 2H, Ph-H), 7.49 (d, $J = 8.75$ Hz, 1H, 7-CH), 7.70 (s, 1H, 2-CH), 7.81 (s, 1H, 4-CH), 7.81 (s, 1H, imidazole-H). Anal. $C_{19}H_{15}BrFN_3$ (C, H, N).

*4.2.8.23. 5-Bromo-1-(2-chlorobenzyl)-3-(1H-imidazol-1-ylmethyl]-1H-indole (**45a**).* IR ν_{max} 1623, 1353 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 5.36 (s, 2H, CH_2), 5.54 (s, 2H, CH_2), 6.79 (d, $J = 7.60$ Hz, Ph-H), 6.88 (s, 1H, imidazole-H), 7.19 (s, 1H, imidazole-H), 7.30 (m, 3H, 6-CH, Ph-H), 7.34 (d, $J = 7.60$, 1H, Ph-H), 7.43 (d, $J = 8.75$ Hz, 1H, 7-CH), 7.70 (s, 1H, 2-CH), 7.82 (s, 1H, 4-CH), 7.82 (s, 1H, imidazole-H). Anal. $C_{19}H_{15}BrClN_3$ (C, H, N).

*4.2.8.24. 5-Bromo-1-(4-chlorobenzyl)-3-(1H-imidazol-1-ylmethyl)-1H-indole (**46a**).* IR ν_{max} 1639, 1295 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 5.36 (s, 2H, CH_2), 5.44 (s, 2H, CH_2), 6.91 (s, 1H, imidazole-H), 7.22 (s, 1H, imidazole-H), 7.29 (d, $J = 8.80$ Hz, 1H, 6-CH), 7.33 (d, $J = 8.55$ Hz, 1H, Ph-H), 7.41 (d, $J = 8.55$ Hz, 1H, Ph-H), 7.47 (d, $J = 8.80$ Hz, 1H, 7-CH), 7.70 (s, 1H, 2-CH), 7.82 (s, 1H, imidazole-H) 7.83 (s, 1H, 4-CH). Anal. $C_{19}H_{15}BrClN_3$ (C, H, N).

*4.2.8.25. 5-Bromo-1-(4-chlorobenzyl)-3-[1-(1H-imidazol-1-yl)butyl]-1H-indole (**46d**).* IR ν_{max} 1644, 1329 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 0.95 (t, $J = 7.00$ Hz, 3H, CH_3), 1.22 (m, 2H, CH_2), 2.22 (t, $J = 7.00$ Hz, 2H, CH_2), 5.37 (m, 1H, CH), 5.45 (s, 2H, CH_2), 6.89 (s, 1H, imidazole-H), 7.21 (m, 4H, Ph-H), 7.40 (s, 1H, imidazole-H), 7.43 (m, 2H, 6,7-CH), 7.66 (s, 1H, 4-CH), 7.84 (s, 1H, 2-CH), 7.90 (s, 1H, imidazole-H). Anal. $C_{22}H_{21}BrClN_3$ (C, H, N).

*4.2.8.26. 5-Bromo-1-(4-chlorobenzyl)-3-[1-(1H-imidazol-1-yl)pentyl]-1H-indole (**46g**).* IR ν_{max} 1640, 1311 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 0.88 (t, $J = 7.00$ Hz, 3H, CH_3), 1.31 (m, 4H, CH_2), 2.25 (t, $J = 7.30$ Hz, 2H, CH_2), 5.45 (s, 2H, CH_2), 5.48 (m, 1H, CH), 6.89 (s, 1H, imidazole-H), 7.25 (m, 4H, Ph-H), 7.40 (s, 1H, imidazole-H), 7.43 (m, 2H, 6,7-CH), 7.66 (s, 1H, 4-CH), 7.84 (s, 1H, 2-CH), 7.90 (s, 1H, imidazole-H). Anal. $C_{23}H_{23}BrClN_3$ (C, H, N).

4.2.9. General procedure for preparation of fumarate and nitrate salts

Fumarate (**35b**, **35d**, **35f**, **35g**, **36b**, **38b**, **46d**, **46g**): The obtained 3-imidazolymethylindole derivative was dissolved in ethanol and a solution of fumaric acid (1 equiv.) in ethanol was added. The mixture was stirred for 5 h. After removal of ethanol under reduced pressure, a small amount of ether and then hexane were added to afford white crystals which were collected by filtration and recrystallised from ethyl acetate and hexane mixture.

Nitrate (**35c**, **35f**, **37b**, **42b**): The obtained 3-imidazolymethylindole derivative was dissolved in ether and nitric acid (1 equiv.) in ethanol was dropped slowly. The mixture was stirred for 30 min. The crystals were collected by filtration.

4.3. Pharmacology

4.3.1. Anti-Candida in vitro activity

C. albicans (CA980001) suspension was prepared in RPMI 1640 medium supplemented with 0.165 M morpholinopropanesulphonic acid (MOPS, Sigma), 2% glucose and antibiotics (medium A) and adjusted to give a final concentration of 10^3 cells mL^{-1}. A 96-well microplate (Nunc, Polylabo, Strasbourg, France) was seeded with 100 μL of *Candida* suspension. Molecules were first dissolved in dimethylsulfoxide and then diluted in medium A. Each concentration of molecule (100 μL) to be tested was added (in triplicate) and plates were incubated at 37 °C for 24 h. The cellular viability was evaluated on the Fluorolite 1000 (Dynatech) with an excitation at 550 nm and an emission at 590 nm after a 4 h incubation with 10 μL of alamar Blue® (Interchim, Montluçon, France) [25]. The minimal inhibitory concentration (MIC) is the concentration that inhibited 80

and 90% of the cell growth for azoles and amphotericin B, respectively; MICs were determined by linear regression analysis and expressed as the mean of the triplicate values.

4.3.2. Anti-Aspergillus in vitro activity

Conidia of *A. fumigatus* (AF980003) were microscopically counted and diluted in medium A. One hundred microliters of a 10^4 cells mL^{-1} suspension were inoculated in a 96-well microplate (Nunc). In order to use the hyphal forms of *A. fumigatus*, conidia were incubated for 4 h at 37 °C. Drugs were diluted in the same medium and 100 μL of the drug dilutions were added to the cell suspension. After an incubation time of 48 h at 37 °C, the cellular viability was evaluated as in *Candida* assay [25]. Activity of the studied and reference molecules was expressed as the MIC.

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