Full Paper

2-Aryl-3-(1*H*-Azol-1-yl)-1*H*-Indole Derivatives: A New Class of Antimycobacterial Compounds – Conventional Heating in Comparison with MW-Assisted Synthesis

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2-Aryl-3-(1*H*-imidazol-1-yl and 1*H*-1,2,4-triazol-1-yl)-1*H*-indole derivatives were synthesized and tested for their *in-vitro* antifungal and antimycobacterial activities. These indole derivatives were devoid of antifungal activity against the tested strains of *Candida* spp. Yet, they exhibited an interesting antitubercular activity against *Mycobacterium tuberculosis* reference strain H_{37}Rv.

Keywords: Antifungal activity / Antimycobacterial activity / Indole / MW-assisted synthesis

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Introduction

Considering the increased incidence of severe opportunistic fungal infections in immunocompromised patients together with the development of drug resistance among pathogenic strains of *Candida* spp., there is a great need for new antifungal compounds. On the other hand, the increase of tuberculosis due to emergence of MDR (multiple-drug resistant) strains of *Mycobacterium tuberculosis* [1 – 4] together with the increased incidence of severe disseminated infections produced by mycobacteria other than tuberculosis (MOTT), particularly *Mycobacterium avium* [5] in immunocompromised patients, has prompted the search for new antimycobacterial drugs.

Antifungal azole derivatives synthesized by us [6 – 8] inhibited the fungal cytochrome P450-dependent 14α-demethylase (P450 14DM CYP51) but exhibit also antitubercular activity which was attributed to a similar inhibitory interaction with the corresponding mycobacterial cytochrome. Using genomic DNA from a strain of *Mycobacterium tuberculosis* (MT), it was established that a CYP51-like gene encodes a bacterial sterol 14α-demethylase [9] (MT P450 14DM CYP51-like) which acts on 14α-methylsterols and binds azole antifungal drugs [1, 10, 11]. On the basis of these considerations and because many imidazole and triazole derivatives showed potent antifungal activity associated with good antimycobacterial activity [6, 7, 12, 13], we synthesized a series of 2-aryl-3-(1*H*-imidazol-1-yl- and 1*H*-1,2,4-triazol-1-yl)-1*H*-indole derivatives **3a – j** in which the azole moiety is linked at the 3-position of the indole nucleus. The indole moiety is present in only few derivatives already described for their antifungal activity [14 – 16] but none of these compounds has been studied to evaluate their potential antimycobacterial activity. As a possible precursor in the synthesis of the corresponding indole derivatives we also synthesized the 1-[2-(1*H*-imidazol-1-yl)- and (1*H*-1,2,4-triazol-1-yl)-1-arylethylidene]-2-phenylhydrazine derivatives **2a – j**; their features resemble typical azole antifungal drugs. All the synthesized compounds were tested *in vitro* for their antifungal and antitubercular activity towards *Candida spp.* and *Mycobacterium tuberculosis* H_{37}Rv. The phenylhydrazone derivatives **2a – j** showed a moderate antifungal and antimycobacterial

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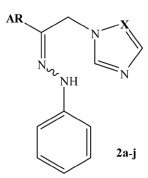
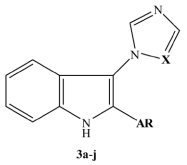
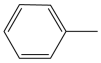
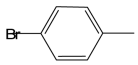
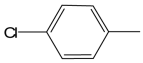
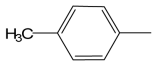
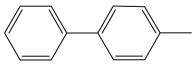
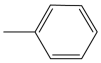
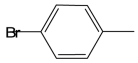
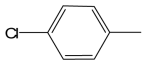
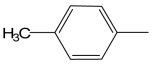
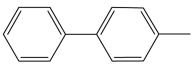
Abbreviations: microwave irradiation (MW); multiple-drug resistant (MDR); mycobacteria other than tuberculosis (MOTT); *Mycobacterium tuberculosis* (MT)

* A preliminary account of this work was presented at XIX Joint Meeting on Medicinal Chemistry, Verona (IT), September 14-18, 2008.

Table 1. Antifungal and antimycobacterial activities of compounds **2a – j** and **3a – j**.





Comp.	X	Ar	*C.A.* 685 MIC (μg/mL)	*C.G.* 66 MIC (μg/mL)	*M.tuberculosis* $H_{37}Rv$ MIC (μg/mL)
Miconazole			0.06 – 0.12	resistant	
Amphotericin B			1 – 1	2 – 4	
Rifampicin				–	0.5
2a	CH		8	>32	32
3a			>64	>64	8
2b	CH		8	32	16
3b			>64	>64	4
2c	CH		8	32	16
3c			>64	>64	8
2d	CH		16	>32	>64
3d			>64	>64	8
2e	CH		8	32	16
3e			>64	>64	2
2f	N		16	32	16
3f			64	64	8
2g	N		16	32	32
3g			>64	>64	4
2h	N		8	32	32
3h			>64	>64	8
2i	N		16	32	32
3i			>64	>64	8
2j	N		16	>32	32
3j			>64	>64	4

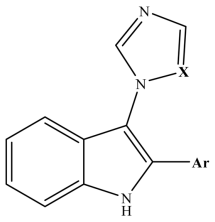
activity. On the other hand, indole derivatives **3a – j** exhibited a remarkable antimycobacterial activity but were devoid of antifungal activity (Table 1).

Moreover, we compare two synthetic methods to obtain the indole compounds **3a – j**: reflux heating and microwave irradiation (MW). The use of a microwave reactor ensures a significant increase in reaction yields and an easier work-up as well as a decrease in reaction time (Table 2).

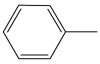
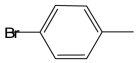
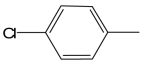
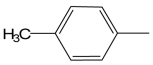
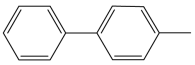
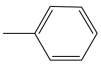
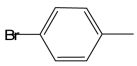
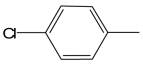
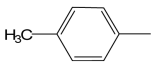
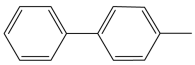
Results and discussion

The indole derivatives **3a – j**, characterized by the presence of imidazole or triazole substituents at the position 3 of the indole moiety, have been synthesized by Fischer indole synthesis using two synthetic procedures namely, conventional reflux synthesis and microwave irradiation (MW). Fischer indole synthesis is well known and largely described, as well as the use of a microwave oven for this kind of reaction. Several solvents and catalyst can be

Table 2. Yields of compounds **3a–j** under reflux (method A) or using MW irradiation (method B).



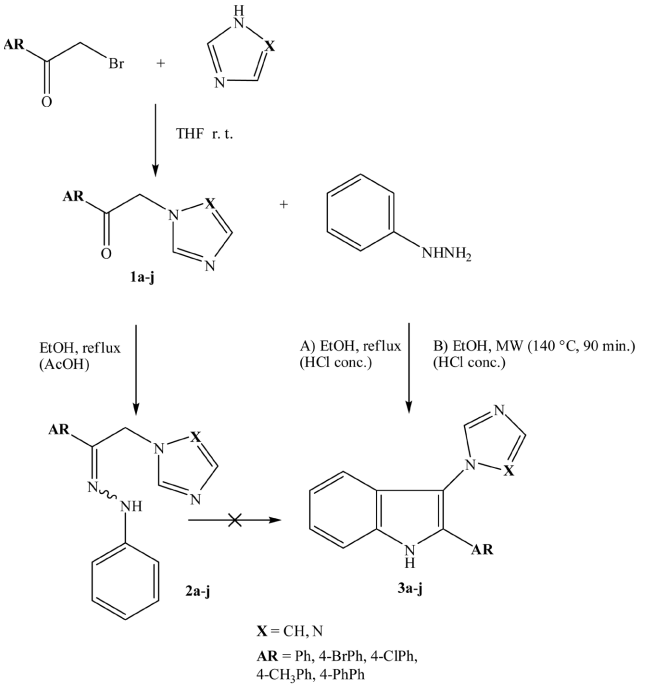
3a-j

Comp	X	Ar	Time (Reflux) (h)	Purification (Reflux)	Yield (Reflux) (%)	Time (MW) (h)	Purification (MW)	Yield (MW) (%)
3a	CH		22	AcOEt[a)]	2.4	1	AcOEt[a)]	43.4
3b	CH		10	AcOEt[a)]	8.0	1	AcOEt[a)]	38.0
3c	CH		20.5	AcOEt / EtOH 9.5 : 0.5[a)]	2.0	1	AcOEt / EtOH 9.5 : 0.5[a)]	35.3
3d	CH		24	AcOEt/Hexane 10 : 10[a)]	3.4	1	AcOEt/Hexane 10 : 10[a)]	39.3
3e	CH		18.5	AcOEt[a)]	4.3	1	AcOEt[a)]	47.3
3f	N		20	Hexane[b)]	12	1	Ethyl ether[b)]	57.6
3g	N		13.5	AcOEt/Hexane 4 : 6[a)]	3.9	1	Ethyl ether[b)]	68.2
3h	N		9.5	AcOEt[a)]	14.7	1	Ethyl ether[b)]	67.2
3i	N		21	AcOEt/Hexane 8 : 2[a)]	3.6	1	Ethyl ether[b)]	58.3
3j	N		46	AcOEt/Hexane 4 : 6[a)]	2.0	1	Ethyl ether[b)]	72.3

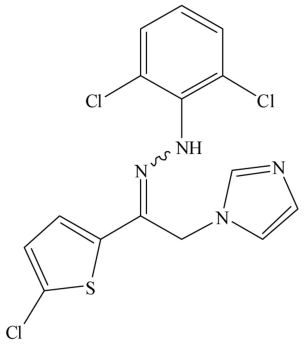
[a)] Dry-flash chromatography.
[b)] Crystallization.

used but absolute ethanol and HCl (conc.) seems to be the optimal combination with an easier work-up. The use of MW-irradiation ensures a significant increase in reaction yields and a decrease in reaction time. In Table 2, we reported the comparison between two synthetic methods to obtain compounds **3a–j**. Reaction time was drastically decreased and yields were strongly enhanced (from 2 to 15% of traditional heating, to 35 to 72% with MW). Moreover, the use of MW-irradiation reduces the formation of by-products, as documented by TLC.

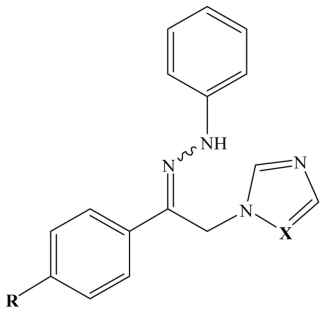
The indole derivatives **3a–j** have been tested for their antifungal and antimycobacterial activity. Target of azole antifungal drugs are enzymes involved in the biosynthesis of ergosterol, specifically the lanosterol 14α-demethylase P450-dependent (P450 14DM, CYP 51). The tertiary nitrogen of the imidazole cycle or the nitrogen atom at position 4 of the triazole ring bind the sixth coordination position of the heme iron of the lanosterol 14α-demethylase and the N1-linked moiety binds the amino acid sequence of the enzyme. The inhibition of P450



Scheme 1. Synthesis of compounds **3a–j**.



Zinoconazole



2a-j

Figure 1. Zinoconazole and compounds **2a–j**.

14DM increases the normal levels of methylated sterols, ergosterol depletion, and inhibition of cellular growth [17].

From the obtained results, however, the indole derivatives **3a–j** (Table 1), containing azole residues, were devoid of antifungal activity against the tested strains of *Candida* spp. Surprisingly, compounds **3a–j**, in which azole moieties are present, were characterized by a very interesting antimycobacterial activity (Table 1) against *Mycobacterium tuberculosis* H_{37}Rv, with MIC values ranging from 2 to 8 μg/mL. The higher antimycobacterial activity was exhibited by the indole derivatives **3b** and **3e** and by the triazole derivatives **3g** and **3j**, both characterized by the higher level of lipophilicity.

The antitubercular activity of the compounds may be due to the inhibition of the *Mycobacterium* sterol 14α-demethylase P450 dependent (MT P450 14DM, CYP 51-like) [9], whereas the lack of antifungal activity may be due to the incapacity of the indole component to bind the enzymatic protein of fungal P450 DM, even if *Candida albicans* CYP-51 and MT CYP 51-like share a sequence homology of 40% with 22% identical residues [18]. However, it is possible that the antimycobacterial activity of compounds **3a–j** depends on a mechanism which does not involve a coordination bond of the azole nitrogen atom with the heme iron of mycobacterial P450 DM. A preliminary molecular modeling of compounds and MT P450 complexes is in progress. Phenylhydrazone derivatives **2a–j** (Scheme 1) have been synthesized as possible intermediates in the synthesis of the corresponding indole derivatives **3a–j**. However, it was impossible to obtain compounds **3a–j** with a reasonable yield through this synthetic approach. In compounds **2a–j**, the 1-aryl-2-(1*H*-azol-1-yl)-ethane moiety, present in many azole antifungal drugs, is linked through an azomethyne linkage to phenylhydrazine. These features characterize the antifungal drug zinoconazole (Fig. 1), which exhibits antifungal activity against some strains of *Candida albicans*, with MIC values in the range of 6.2 - 12.5 μg/mL [19]. The phenylhydrazone derivatives **2a–j** exhibit a similar antifungal activity towards a strain of *Candida albicans* 685, with MIC values of 8 and 16 μg/mL (Table 1). The activity against a strain of *Candida glabrata* 66 miconazole-resistant was moderate, revealing MIC values of 32 μg/mL for almost all the compounds. The antimycobacterial activity of derivatives **2a–j** against *Mycobacterium tuberculosis* resembles their activity towards *C. albicans* 685 (Table 1), with MIC values of 16 and 32 μg/mL, suggesting that the mechanism of action may be dependent on the coordination of the azole nitrogen atom with heme iron of the fungal 14α-demethylase (P450 14DM-CYP 51) and myco-

bacterium 14α-demethylase (MT P450 14DM-CYP 51-like), respectively.

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The authors have declared no conflict of interest.

Experimental

Chemistry

Melting points were determined with a Büchi 510 capillary apparatus, and are uncorrected (Büchi, Switzerland). Infrared spectra in nujol mulls were recorded on a Jasko FT 200 spectrophotometer Jasko, Tokyo, Japan. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were determined on a Varian Gemini 200 spectrometer (Varian, Palo Alto, CA, USA), chemical shifts are reported as δ (ppm) in $CDCl_3$ solution (0.05% v/v TMS), DMSO-d_6 and CD_3OD. Reaction courses and product mixtures were routinely monitored by thin-layer chromatography (TLC) on silica gel precoated F_{254} Merck plates (Merck, Germany). Column chromatography and flash-dry chromatography were performed using silica gel 70–230 mesh and 15–40 mesh, respectively. ESI-MS spectra were obtained on a PE-API I spectrometer (Applied Biosystems, Inc. USA) by infusion of a solution of the sample in MeOH. Elemental analyses (C, H, N) were performed on a Carlo Erba analyzer (Carlo Erba, Milan, Italy) and were within ± 0.3 of the theoretical value. Microwave irradiations were performed using a CEM® (Discover®-Labmate"; CEM SRL, Italy) reactor.

The synthesis of compounds **3a–j** (Scheme 1), was carried out via a two-steps reaction which involved a *N*-alkylation of imidazole or 1,2,4-triazole with *para*-substituted 2-bromoacetophenones to afford the corresponding 1-aryl-2-(1*H*-imidazol-1-yl) or (1*H*-1,2,4-triazol-1-yl)-ethanones **1a–j** in accordance with the literature procedure [6, 8]. The indole derivatives **3a–j** were obtained through the classical Fischer cyclization (Scheme 1) by reacting compounds **1a–j** and phenylhydrazine in ethanol with acid catalyst (HCl) under reflux or using the microwave reactor. The simple condensation of compounds **1a–j** with phenylhydrazine gave the corresponding intermediate phenylhydrazone derivatives **2a–j**. The attempt to obtain the indole derivatives **3a–j** from the corresponding phenylhydrazone **2a–j** was unsuccessful.

*N-[2-(1H-Imidazol-1-yl)-1-phenylethylidene]-N′-phenyl-hydrazine **2a***

A solution of 1-phenyl-2-(1*H*-imidazol-1-yl)-ethanone (2.0 g, 11.0 mmol) in 50 mL of ethanol, was treated with a few drops of acetic acid. To the stirred solution, phenylhydrazine (1.19 g, 11.0 mmol) in 20 mL of absolute ethanol was added dropwise and the reaction mixture was heated at reflux for 7 h. Thereafter, the solvent was removed under reduced pressure and the residue was extracted with $CHCl_3$ (3 × 100 mL) and the organic phase was washed with distilled water. The collected organic phases were dried over sodium sulphate, filtered, and evaporated under reduced pressure. The residue was crystallized from absolute ethanol.

Yield: 35%; m.p.: 174–177°C; I.R.(nujol, cm^{-1}): 3222; ^{1}H-NMR ($CDCl_3$ / TMS) δ: 5.30 (s, 2H, CH_2), 6.90–8.00 (m, 13H, arom. and imidazole), 8.45 (broad sign., 1H, NH disappearing on deuteration); MS *m/z*: 277 [M + H$^+$]. Anal. calcd. for $C_{17}H_{16}N_4$ (MW: 276.34): C, 78.89: H, 5.84; N, 20.27. Found: C, 73.72; H, 5.67; N, 20.10.

Compounds **2b–j** have been prepared in an analogous way.

*N-[1-(4-Bromophenyl)-2-(1H-imidazol-1-yl)ethylidene]-N′-phenyl-hydrazine **2b***

Yield: 34%; m.p.: 185–189°C; I.R.(nujol, cm^{-1}): 3206; ^{1}H-NMR ($CDCl_3$ / TMS) δ: 5.28 and 5.42 (s, 2H, CH_2), 6.88–8.04 (m, 12H, arom. and imidazole), 8.50 (broad sign., 1H, NH disappearing on deuteration); MS *m/z*: 355 [M + H$^+$], 357 [M + H$^+$ + 2]. Anal. calcd. for $C_{17}H_{15}N_4Br$ (MW: 355.23): C, 57.48: H, 4.26; N, 15.77. Found: C, 57.44; H, 4.22; N, 15.73.

*N-[1-(4-Chlorophenyl)-2-(1H-imidazol-1-yl)ethylidene]-N′-phenyl-hydrazine **2c***

Yield: 40%; m.p.: 188–191°C; I.R.(nujol, cm^{-1}): 3213; ^{1}H-NMR ($CDCl_3$ / TMS) δ: 5.42 (s, 2H, CH_2), 6.84–8.00 (m, 12H, arom. and imidazole), 10.30 (broad sign., 1H, NH disappearing on deuteration); MS *m/z*: 311 [M + H$^+$], 313 [M + H$^+$ + 2]. Anal. calcd. for $C_{17}H_{15}N_4Cl$ (MW: 310.77): C, 65.70: H, 4.86; N, 18.03. Found: C, 65.48; H, 4.64; N, 17.81.

*N-[2-(1H-Imidazol-1-yl)-1-(4-methylphenyl)ethylidene]-N′-phenyl-hydrazine **2d***

Yield: 47%; m.p.: 197–203°C; I.R.(nujol, cm^{-1}): 3222; ^{1}H-NMR ($CDCl_3$ / TMS) δ: 2.40 (s, 3H, CH_3), 5.20 (s, 2H, CH_2), 6.94–7.81 (m, 12H, arom. and imidazole), 8.90 (broad sign., 1H, NH disappearing on deuteration); MS *m/z*: 291 [M + H$^+$]. Anal. calcd. for $C_{18}H_{18}N_4$ (MW: 290.36): C, 74.46: H, 6.25; N, 19.30. Found: C, 74.34; H, 6.43; N, 19.18.

*N-[1-(2-Biphenyl-4-yl)-2-(1H-imidazol-1-yl)ethylidene]-N′-phenyl-hydrazine **2e***

Yield: 57%; m.p.: 195–199°C; I.R.(nujol, cm^{-1}): 3222; ^{1}H-NMR (DMSO-d_6) δ: 5.49 (s, 2H, CH_2), 6.88–7.92 (m, 17H, arom. and imidazole), 10.30 (broad sign., 1H, NH disappearing on deuteration); MS *m/z*: 353. Anal. calcd. for $C_{23}H_{20}N_4$ (MW: 352.43): C, 78.38: H, 5.72; N, 15.90. Found: C, 78.18; H, 5.52; N, 15.70.

*N-[1-Phenyl -2-(1H-1,2,4-triazol-1-yl)-ethylidene]-N′-phenyl-hydrazine **2f***

Yield: 44%; m.p.: 168–170°C; I.R.(nujol, cm^{-1}): 3220; ^{1}H-NMR ($CDCl_3$ / TMS) δ: 5.44 (s, 2H, CH_2), 7.00–7.87 (m, 10H, arom.), 8.05 (s, 1H, H_5 triazole), 8.21 (s, 1H, H_3 triazole), 9.76 (broad sign., 1H, NH disappearing on deuteration); MS *m/z*: 278 [M + H$^+$]. Anal. calcd. for $C_{16}H_{15}N_5$ (MW: 277.32): C, 69.29: H, 5.45; N, 25.25. Found: C, 69.04; H, 5.20; N, 25.00.

*N-[1-(4-Bromophenyl)-2-(1H-1,2,4-triazol-1-yl) ethylidene]-N′-phenyl-hydrazine **2g***

Yield: 56%; m.p.: 187–190°C; I.R.(nujol, cm^{-1}): 3216; ^{1}H-NMR ($CDCl_3$ / TMS) δ: 5.25 (s, 2H, CH_2), 6.90–7.66 (m, 9H, arom.), 7.94 (s, 1H, H_5 triazole), 8.10 (s, 1H, H_3 triazole), 9.82 (broad sign., 1H, NH disappearing on deuteration); MS *m/z*: 356 [M + H$^+$], 358 [M + H$^+$ + 2]. Anal. calcd. for $C_{16}H_{14}N_5Br$ (MW: 356.23): C, 53.95: H, 3.96; N, 19.66. Found: C, 54.05; H, 4.06; N, 19.76.

*N-[1-(4-Chlorophenyl)-2-(1H-1,2,4-triazol-1-yl) ethylidene]-N′-phenyl-hydrazine **2h***

Yield: 54%; m.p.: 165 – 170°C; I.R.(nujol, cm^{-1}): 3232; ^{1}H-NMR ($CDCl_3$ / TMS) δ: 5.40 (s, 2H, CH_2), 6.97 – 7.78 (m, 9H, arom.), 8.05 (s, 1H, H_5 triazole), 8.20 (s, 1H, H_3 triazole), 9.77 (broad sign., 1H, NH disappearing on deuteration); MS *m/z*: 312 [M + H^+], 314 [M + H^+ + 2]. Anal. calcd. for $C_{16}H_{14}N_5Cl$ (MW: 311.77): C, 61.64: H, 4.53; N, 22.46. Found: C, 61.77; H, 4.66; N, 22.59.

*N-[1-(4-Methylphenyl)-2-(1H-1,2,4-triazol-1-yl) ethylidene]-N′-phenyl-hydrazine **2i***

Yield: 54%; m.p.: 110 – 112°C; I.R.(nujol, cm^{-1}): 3217; ^{1}H-NMR ($CDCl_3$ / TMS) δ: 2.41 (s, 3H, CH_3), 5.29 and 5.46 (s, 2H, CH_2), 6.87 – 7.90 (m, 9H, arom.), 7.98 and 8.05 (s, 1H, H_5 triazole), 8.30 and 8.36 (s, 1H, H_3 triazole), 9.80 (broad sign., 1H, NH disappearing on deuteration); MS *m/z*: 292 [M + H^+]. Anal. calcd. for $C_{17}H_{17}N_5$ (MW: 291.35): C, 70.08: H, 5.88; N, 24.04. Found: C, 70.03; H, 5.83; N, 23.99.

*N-[1-(2-Biphenyl-4-yl)-2-(1H-1,2,4-triazol-1-yl) ethylidene]-N′-phenyl-hydrazine **2j***

Yield: 52%; m.p.: 180 – 184°C; I.R.(nujol, cm^{-1}): 3235; ^{1}H-NMR ($CDCl_3$ / TMS) δ: 5.46 (s, 2H, CH_2), 6.98 – 7.94 (m, 14H, arom.), 8.06 (s, 1H, H_5 triazole), 8.23 (s, 1H, H_3 triazole), 9.76 (broad sign., 1H, NH disappearing on deuteration); MS *m/z*: 354 [M + H^+]. Anal. calcd. for $C_{22}H_{19}N_5$ (MW: 353.42): C, 74.77: H, 5.42; N, 19.82. Found: C, 74.94; H, 5.59; N, 19.99.

*General procedure for the synthesis of derivatives **3a – j***

- Method A: To an ethanolic solution of ethanone derivatives **1a – j** (200 mg), few milliliter of HCl conc. and a slight excess of phenylhydrazine were added. The reaction mixture was heated under reflux for several hours (Table 2). The cooled solution was evaporated under reduced pressure and the residue was treated with water, then neutralized with NaOH solution, and filtered. The residue obtained was dissolved in the minimum amount of ethyl acetate and purified by dry-flash chromatography.
- Method B: The same procedure but using an equimolar amount of phenylhydrazine was followed by carrying out the reaction in a sealed tube with the use of microwave oven. The reaction was performed at 120 – 140°C (300 W and 5 bar) with a complete cycle of 1 hour. The compounds were purified by dry-flash chromatography or by crystallization from diethyl ether and the yields of derivatives **3a – j** were greatly improved and reaction times were reduced (Table 2).

*3-(1H-Imidazol-1-yl)-2-phenyl-1H-indole **3a***

M. p.: 160 – 162°C; I.R.(Nujol, cm^{-1}): 3146; ^{1}H-NMR (CD_3OD / TMS) δ: 7.08 – 7.51 (m, 12H, 3H imid., 8H arom.); 7.72 (s, 1H, NH disappearing on deuteration); MS *m/z*: 260 [M + H^+]. Anal. calcd. for $C_{17}H_{13}N_3$ (MW: 259.31): C, 78.74; H, 5.05; N, 16.20. Found: C, 78.87; H, 5.19; N, 16.08.

*2-(4-Bromophenyl)-3-(1H-imidazol-1-yl)-1H-indole **3b***

M.p.: 230 – 232°C; I.R.(Nujol, cm^{-1}): 3142; ^{1}H-NMR (CD_3OD / TMS) δ: 7.18 – 7.76 (m, 11H, 3H imid., 8H arom.); 9.04 (s, 1H, NH disappearing on deuteration); MS *m/z*: 338 [M + H^+], 340 [M + H^+ + 2]. Anal. calcd. for $C_{17}H_{12}BrN_3$ (MW: 338.20): C, 60.37; H, 3.58; N, 12.42. Found: C, 60.45; H, 3.42; N, 12.51.

*2-(4-Chlorophenyl)-3-(1H-imidazol-1-yl)-1H-indole **3c***

M.p.: 220 – 222°C; I.R.(Nujol, cm^{-1}): 3151; ^{1}H-NMR (CD_3OD / TMS) δ: 7.09 – 7.51 (m, 11H, 3H imid., 8H arom.); 7.74 (s, 1H, NH disappearing on deuteration); MS *m/z*: 294 [M + H^+], 296 [M + H^+ + 2]. Anal. calcd. for $C_{17}H_{12}ClN_3$ (MW: 293.75): C, 69.51; H, 4.12; N, 14.30. Found: C, 69.40; H, 4.35; N, 14.17.

*3-(1H-Imidazol-1-yl)-2-(4-methylphenyl)-1H-indole **3d***

M.p.: >235°C; I.R.(Nujol, cm^{-1}): 3145; ^{1}H-NMR (CD_3OD / TMS) δ: 2.36 (s, 3H, CH_3); 7.12 – 7.63 (m, 11H, 3H imid., 8H arom.); 8.59 (s, 1H, NH disappearing on deuteration); MS *m/z*: 274 [M + H^+]. Anal. calcd. for $C_{18}H_{15}N_3$ (MW: 273.33): C, 79.10; H, 5.53; N, 15.37. Found: C, 79.02; H, 5.35; N, 15.27.

*2-(Biphenyl-4-yl)-3-(1H-imidazol-1-yl)-1H-indole **3e***

M.p.: >235°C; I.R.(Nujol, cm^{-1}): 3139; ^{1}H-NMR (CD_3OD / TMS) δ: 7.20 – 7.87 (m, 16H, 3H imid., 13H arom.); 9.29 (s, 1H, NH disappearing on deuteration); MS *m/z*: 336 [M + H^+]. Anal. calcd. for $C_{23}H_{17}N_3$ (MW: 335.40): C, 82.36; H, 5.11; N, 12.53. Found: C, 82.14; H, 5.37; N, 12.58.

*2-Phenyl-3-(1H-1,2,4-triazol-1-yl)-1H-indole **3f***

M.p.: 188 – 190°C; I.R.(Nujol, cm^{-1}): 3141; ^{1}H-NMR (CD_3OD / TMS) δ: 47.10 – 7.60 (m, 9H arom.); 8.08 (s, 1H, NH disappearing on deuteration); 8.30 (s, 1H, H_3 triaz.); 8.54 (s, 1H, H_5 triaz.); MS *m/z*: 261 [M + H^+]. Anal. calcd. for $C_{16}H_{12}N_4$ (MW: 260.29): C, 73.83; H, 4.65; N, 21.52. Found: C, 73.96; H, 4.88; N, 21.41.

*2-(4-Bromophenyl)-3-(1H-1,2,4-triazol-1-yl)-1H-indole **3g***

M.p.: 200 – 202°C; I.R.(nujol, cm^{-1}): 3149; ^{1}H-NMR (CD_3OD / TMS) δ: 7.10 – 7.55 (m, 9H, 8H arom., 1H, NH disappearing on deuteration); 8.31 (s, 1H, H_3 triaz.); 8.56 (s, 1H, H_5 triaz.); MS *m/z*: 339 [M + H^+], 341 [M + H^+ + 2]. Anal. calcd. for $C_{16}H_{11}N_4Br$ (MW: 339.19): C, 56.66; H, 3.27; N, 16.52. Found: C, 56.55; H, 3.40; N, 16.41.

*2-(4-Chlorophenyl)-3-(1H-1,2,4-triazol-1-yl)-1H-indole **3h***

M.p.: 205 – 207°C; I.R.(Nujol, cm^{-1}): 3142; ^{1}H-NMR (CD_3OD / TMS) δ: 7.13 – 7.55 (m, 9H, 8H arom., 1H, NH disappearing on deuteration); 8.57 (s, 1H, H_3 triaz.); 9.46 (s, 1H, H_5 triaz.); MS *m/z*: 295 [M + H^+], 297 [M + H^+ + 2]. Anal. calcd. for $C_{16}H_{11}N_4Cl$ (MW: 294.74): C, 65.20; H, 3.76; N, 19.01. Found: C, 65.35; H, 3.90; N, 18.91.

*2-(4-Methylphenyl)-3-(1H-1,2,4-triazol-1-yl)-1H-indole **3i***

M.p.: 185 – 187°C; I.R.(nujol, cm^{-1}): 3146; ^{1}H-NMR (CD_3OD / TMS) δ: 2.35 (s, 3H, CH_3); 7.09 – 7.51 (m, 9H, 8H arom., 1H, NH disappearing on deuteration); 8.31 (s, 1H, H_3 triaz.); 8.53 (s, 1H, H_5 triaz.); MS *m/z*: 275 [M + H^+]. Anal. calcd. for $C_{17}H_{14}N_4$ (MW: 274.32): C, 74.43; H, 5.14; N, 20.42. Found: C, 74.30; H, 5.20; N, 20.25.

*2-(Biphenyl-4-yl)-3-(1H-1,2,4-triazol-1-yl)-1H-indole **3j***

M.p.: 219 – 221°C; I.R.(nujol, cm^{-1}): 3152; ^{1}H-NMR (CD_3OD / TMS) δ: 7.10 – 7.66 (m, 14H, 13H arom., 1H, NH disappearing on deuteration); 8.32 (s, 1H, H_3 triaz.); 8.59 (s, 1H, H_5 triaz.); MS *m/z*: 337 [M + H^+]. Anal. calcd. for $C_{22}H_{16}N_4$ (MW: 336.39): C, 78.55; H, 4.79; N, 16.66. Found: C, 78.33; H, 4.66; N, 16.78.

Microbiology

Both series of derivatives **2a–j** and **3a–j** were evaluated for their antifungal activity against *Candida albicans* 685 and *Candida glabrata* 66, both clinical isolates; their antitubercular activity was evaluated against the reference strain *Mycobacterium tuberculosis* H_{37}Rv. Stock solutions of chemicals were prepared in DMSO at a concentration of 2 mg/mL. Antifungal activity was always evaluated by reference methods (NCCLS, 1997); miconazole and amphotericin B were chosen as a standard in antifungal activity measurements, each MIC was determined twice in duplicate experiments after 24 and 48 h incubation time. Antitubercular activity was evaluated by MRA, a recently developed, one-week duration, micro-dilution Resazurin assay [20]. The minimum inhibitory concentration, MIC, was defined as the lowest drug concentration that prevented Resazurin colour change from blue to pink and was determined by visual inspection twice in duplicate experiments; viable counting from control wells and from test wells performed onto agar plates confirmed bactericidal and bacteriostatic activity of the compounds. Rifampicin was used as a standard in antitubercular activity measurements, having a MIC of 0.5 μg/mL; DMSO was also evaluated and was always devoid of inhibiting activity up to the concentration of 2% (v/v). The antimicrobial activity of the compounds **2a–j** and **3a–j** is reported in Table 1.

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