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Synthesis, antimicrobial and antioxidant evaluation of quinolines and bis(indolyl)methanes

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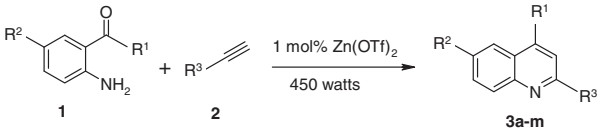
ABSTRACT

An improved and practical synthesis of substituted quinolines and bis(indolyl)methanes was achieved under microwave condition using $Zn(OTf)_2$ as catalyst. The synthesized compounds have been screened for antimicrobial and antioxidant activities.

Quinolines[1] display a wide range of biological properties, which includes antimalarial, antiinflammatory, antineoplastic, antifungal, antiseptic/anti-infective and analgesic applications.[2] They have generally been synthesized by various reactions like Skraup,[3] Doebner-von Miller,[4] Friedlander,[5] Pfitzinger,[6] Conrad-Limpach,[7] and Combes[8] synthesis. These classical syntheses are still frequently used for the preparation of pharmaceutical agents and lead molecules. However, current methods for quinoline synthesis often do not allow for adequate diversity and substitution on the quinoline ring system.[9] Recent revelation in the synthesis of quinoline derivatives has revealed that metal-catalyzed coupling cyclizations of appropriate precursors could compete with classical synthesis in terms of efficacy and rapidity of the quinoline construction.[10] On the other hand, bis(indolyl)methanes[11] display diverse pharmacological activities.[12] They are known to promote significant estrogen metabolism and induce apoptosis in human cancer cells.[13] Moreover, the exceptional capability of transition metal catalysis has led to an increase of transition metal assisted preparative methods for various heterocyclic scaffolds.[14] In our continuing effort in discovering new synthetic methodologies for heterocycles[15] under microwave condition,[15i–k] we herein report $Zn(OTf)_2$ catalyzed preparative method for substituted quinolines under microwave condition. The synthesized compounds were evaluated for their antimicrobial activities.

Recently, Lekhok et al. disclosed the $In(OTf)_3$ catalyzed synthesis of 2,4-disubstituted quinolines under microwave condition.[16] However, this reaction was limited to specific substrate class. In order to explore the feasibility of this reaction, we sought $Zn(OTf)_2$[17] as an effective catalyst for the synthesis of quinolines. We first investigated the reaction of 2′-aminoacetophenone and phenylacetylene using 5 mol % of $Zn(OTf)_2$ at a microwave irradiation of 450 W for 10 min. To our delight the reaction led to the formation of the expected quinoline **3g** in good yield (85%). Upon decreasing the catalyst amount to 1 mol %, the reaction shown good progress and resulted in the same amount of product formation. Decreasing the irradiation power from 450 to 300 W resulted in product formation, albeit in moderate yield (70%). Since, 1 mol % of $Zn(OTf)_2$ at a power level of 450 W was effective for the synthesis of quinoline **3g**, this reaction condition was applied for other substrates (Scheme 1, Table 1).[18]

All reactions were completed within 30 min. The yield of the products was independent of the nature of substrates used. The advantage of protocol is that the reaction is amenable to alkynes containing alkyl, aromatic and heteroaromatic groups, whereas the indium procedure uses only phenylacetylene as the alkyne source.[16] The ^1H NMR spectra of compounds (**3a–3k**) in $CDCl_3$ consisted of a characteristic singlet due to the C3–H proton in the region of 7.2–7.8 ppm, which ascertained the product formation.



Scheme 1. Microwave synthesis of quinolines (**3a–m**).

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Table 1
$Zn(OTf)_2$ catalyzed microwave synthesis of quinolines[a]

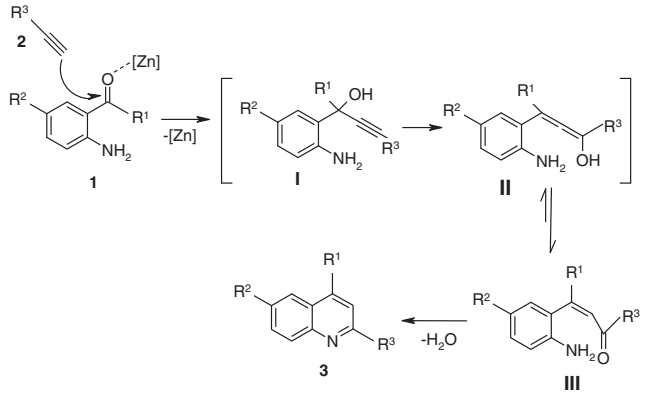
Entry	R^1	R^2	R^3	Product[b]	Yield[c] (%)
1	Ph	H	Bu	**3a**	85
2	Ph	H	Ph	**3b**	84
3	Ph	H	*p*-Tolyl	**3c**	89
4	Ph	H	*o*-Tolyl	**3d**	75
5	Ph	H	2-Pyridyl	**3e**	79
6	Ph	Cl	Ph	**3f**	82
7	Me	H	Ph	**3g**	85
8	Ph	H	*o*-Tolyl	**3h**	90
9	Ph	H	3-Br-phenyl	**3i**	81
10	Ph	Me	3-Br-phenyl	**3j**	82
11	Ph	H	3-Anisyl	**3k**	92
12	Ph	Cl	*p*-Tolyl	**3l**	86
13	Me	H	4-Pentylphenyl	**3m**	91

[a] All reactions were carried out using 1.0 mmol of 2′-aminocarbonyl ketone, 1.5 mmol of terminal alkyne and 1 mol % of $Zn(OTf)_2$ under microwave irradiation (450 W) for 10 min.
[b] All products were characterized by IR, ^1H NMR, ^{13}C NMR and mass spectroscopy.
[c] Isolated yield.

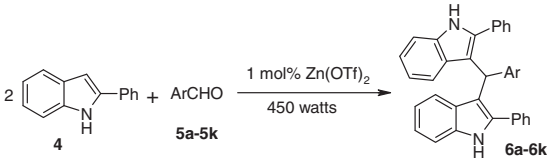
A tentative mechanism for the formation of quinolines was given in Scheme 2. According to which, the oxophilic $Zn(OTf)_2$ coordinates with the carbonyl group[19] of **1**, thus leading to the nucleophilic attack of the terminal alkyne **2** to the carbonyl carbon to form intermediate **I**, which undergoes Meyer Schuster rearrangement to the corresponding allenol intermediate **II**. The later undergoes tautomerism to form 2′-aminochalcone **III**, which upon cyclocondensation leads to the formation of 2,4-disubstituted quinoline **3**.

On the basis of the above results, coupled with the fact that, bis(indolyl)methanes are often associated with important biological properties, we explored the same reaction condition for the synthesis of bis(indolyl)methanes from 2-phenylindole and structurally diverse aldehydes. Thus microwave irradiation (450 W) of indoles with structurally diverse aldehydes in the presence of 5 mol % of $Zn(OTf)_2$ resulted in the formation of bis(indolyl)methanes within 10 min. The results revealed that all the substrates gave good to excellent yield of the products (Scheme 3, Table 2).[20] The ^1H NMR spectra of all compounds **(6a–6k)** exhibited a singlet at δ_H 5.8–6.7 ppm, characteristic of the methine proton (–C*H*–), thus confirming the formation of bis(indolyl)methanes. These findings were in excellent agreement with the literature report.[15e]

All the synthesized compounds (**3a–3m** and **6a–6k**) were screened for their in vitro antibacterial[21] and antifungal[22] activities by CUP plate method. Antibacterial activity of the quinolines (**3a–3m**) were performed against Gram(+)Ve and Gram(−)Ve bacterial strains namely *Staphylococcus aureus* (ATCC 25923) and *Escherichia coli* (ATCC 25922), respectively. Compounds possessing *p*-tolyl **3c** and 3-bromo **3j** groups showed similar activity with the standard drug *Amoxiclav* against *S. aureus*. Compounds possessing 3-bromo **3j** and 5-Cl, *p*-tolyl **3l** groups showed similar activity with *Amoxi-*

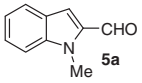
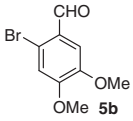
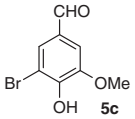
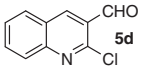
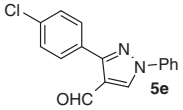
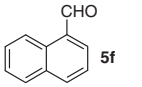
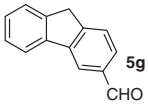
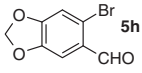
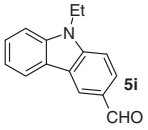
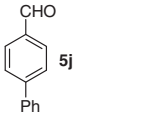
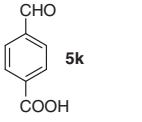


Scheme 2. Tentative mechanism for the formation of quinolines.



Scheme 3. Microwave synthesis of bis(indolyl)methanes (**6a–k**).

Table 2
Synthesis of bis(indolyl)methanes (**6a–6k**)[a]

S. No.	Aldehyde	Product[b]	Yield[c] (%)
1		**6a**	75
2		**6b**	80
3		**6c**	79
4		**6d**	74
5		**6e**	89
6		**6f**	78
7		**6g**	88
8		**6h**	81
9		**6i**	80
10		**6j**	90
11		**6k**	79

[a] All reactions were carried out using 1.0 mmol of 2-phenylindole, 0.55 mmol of aldehyde and 1 mol % of $Zn(OTf)_2$ under microwave irradiation (450 W) for 10 min.
[b] All products were characterized by IR, ^1H NMR, ^{13}C NMR and mass spectroscopy.
[c] Isolated yield.

Table 3
Antibacterial[a] and antifungal[b] evaluation of quinolines (**3a–3m**) by CUP plate method[c]

S. No.	Product and reference drug	Zone of inhibition[d] (mm)		
		S. aureus	*E. coli*	*C. albicans*
1	**3a**	20	19	15
2	**3b**	18	17	13
3	**3c**	**24**	17	19
4	**3d**	15	18	15
5	**3e**	23	18	18
6	**3f**	21	18	16
7	**3g**	14	20	16
8	**3h**	23	18	15
9	**3i**	14	12	10
10	**3j**	**24**	**22**	**21**
11	**3k**	21	**23**	14
12	**3l**	22	**22**	**23**
13	**3m**	21	18	18
14	*Amoxiclav*	24	22	NA
15	*Amphotericin-B*	NA	NA	20

NA—not applicable.
[a] Nutrient agar was employed as culture media.
[b] Sabouroud dextrose agar was employed as culture media.
[c] Test concentration of 1000 μg/mL was used with DMSO as solvent control.
[d] The bold values of zone of inhibition indicates the maximum antimicrobial activity than the reference drugs, *Amoxiclav* and *Amphotericin-B*.

Table 4
Antibacterial[a] and antifungal[b] evaluation of bis(indolyl)methanes (**6a–6k**) by CUP plate method[c]

S. No.	Product and reference drug	Zone of inhibition[d] (mm)		
		S. aureus	*E. coli*	*C. albicans*
1	**6a**	13	16	14
2	**6b**	12	14	16
3	**6c**	22	**24**	**26**
4	**6d**	18	15	18
5	**6e**	19	15	12
6	**6f**	23	16	10
7	**6g**	**24**	18	18
8	**6h**	**25**	**23**	**24**
9	**6i**	**24**	**23**	**24**
10	**6j**	**26**	**26**	**25**
11	**6k**	24	19	16
12	*Amoxiclav*	24	22	NA
13	*Amphotericin-B*	NA	NA	20

NA—not applicable.
[a] Nutrient agar was employed as culture media.
[b] Sabouroud dextrose agar was employed as culture media.
[c] Test concentration of 1000 μg/mL was used with DMSO as solvent control.
[d] The bold values of zone of inhibition indicates the maximum antimicrobial activity than the reference drugs, *Amoxiclav* and *Amphotericin-B*.

clav against *E. coli* (Table 3, entries 10 and 12) and compound having 3-anisyl **3k** group showed better activity than the reference drug (Table 3, entry 11). Antifungal activity of the synthesized compounds were performed against *Candida albicans* (ATCC 10231). Compounds 3-bromo **3j** and 5-Cl, *p*-tolyl **3l** showed better activity than the standard drug *Amphotericin-B* against *C. albicans* (Table 3, entries 10 and 12).

Antibacterial activity of bis(indolyl)methanes (**6a–6k**) were performed against Gram(+)Ve and Gram(−)Ve bacterial strains namely *S. aureus* and *E. coli*, respectively. Compounds having fluorenyl **6g** and carbazolyl **6i** groups showed similar activity (Table 4, entries 7 and 9) and compounds having 6-bromo piperanol **6h** and biphenyl **6j** groups showed better antibacterial activity with the standard drug *Amoxiclav* against *S. aureus* (Table 4, entries 8 and 10). Compounds having 3-bromo-4-hydroxy-5-methoxy **6c**, piperanol **6h**, carbazole **6i** and biphenyl **6j** groups showed better antibacterial and antifungal activities towards *E. coli* and *C. albicans*, respectively, than their standard drugs (Table 4, entries 3 and 8–10).

In the present study, DPPH radical scavenging method and hydrogen peroxide method were chosen to evaluate the antioxidant potential of the bis(indolyl)methanes (**6a–6k**). DPPH (1,1-diphenyl-2-picryl-hydrazil) radical scavenging activity[23] of bis(indolyl)methanes was determined by spectrophotometrically[24a] according to Blois's method.[24b] All compounds were tested for their interaction with the stable free radical DPPH.[25] This interaction indicates their radical scavenging activity. The percentage of inhibition was given in Table 5 and compared with that of standard L-ascorbic acid. The results in percentage, are expressed as the ratio of absorbance decrease at 517 nm, and the absorbance of DPPH solution in the absence of bis(indolyl)methanes. The analysis of Table 5 leads to conclude that the radical scavenging activity of bis(indolyl)methanes on DPPH radicals increases with the increase in concentration. Compounds possessing pyrazole **6e**, fluorene **6g** and 4-benzoic **6k** groups showed maximum activity at a concentration of 1000 μg/mL. The radical scavenging activity of compounds possessing quinoline **6d** and piperanol **6h** groups was less potent than the standard.

Hydrogen peroxide radical scavenging activity[26] was performed by using a solution of bis(indolyl)methanes in a mixture of phosphate buffer and a solution of H_2O_2 by spectrophotometric method.[27] Butylated hydroxy toluene (BHT) was used as standard. The absorbance value (230 nm) of the reaction mixture was recorded at 10 min intervals between 0 and 40 min. For each concentration, blank sample was used for background substraction. The absorbance values for bis(indolyl)methanes was given in Table 6, which revealed that compound possessing pyrazole ring **6e** exhibited maximum antioxidant potential after 40 min. However, the antioxidant property of compounds possessing indole **6a**, piperanol **6h** and

Table 5
DPPH radical scavenging activity of bis(indolyl)methanes (**6a–6k**)

S. No.	Sample	Concentration (μg/mL)					
		Absorbance (50 μg)	%	Absorbance (500 μg)	%	Absorbance (1000 μg)	%
1	L-Ascorbic acid[a]	0.035	96	0.026	97	0.008	99
2	**6a**	0.721	19	0.329	63	0.213	76
3	**6b**	0.704	21	0.427	52	0.276	69
4	**6c**	0.650	27	0.320	64	0.267	70
5	**6d**	0.873	02	0.784	12	0.579	35
6	**6e**	0.704	21	0.311	65	0.115	87
7	**6f**	0.668	25	0.374	58	0.213	76
8	**6g**	0.721	19	0.302	66	0.133	85
9	**6h**	0.802	10	0.686	23	0.516	42
10	**6i**	0.757	15	0.516	42	0.240	73
11	**6j**	0.695	22	0.401	55	0.222	75
12	**6k**	0.739	17	0.463	48	0.178	80
13	Control	0.8913					

[a] Reference drug used for antioxidant evaluation.

Table 6
Hydrogen peroxide radical scavenging activity of bis(indolyl)methanes (**6a–6k**)

S. No.	Sample	Time (min)									
		Abs (0 min)	%	Abs (10 min)	%	Abs (20 min)	%	Abs (30 min)	%	Abs (40 min)	%
1	BHT	0.072	92	0.126	86	0.153	83	0.162	82	0.180	80
2	**6a**	0.514	43	0.586	35	0.712	21	0.799	20	0.757	16
3	**6b**	0.126	86	0.135	85	0.234	74	0.252	72	0.279	69
4	**6c**	0.162	82	0.171	81	0.234	74	0.261	71	0.315	65
5	**6d**	0.144	84	0.153	83	0.180	80	0.243	73	0.288	68
6	**6e**	0.153	83	0.162	82	0.171	81	0.180	80	0.189	79
7	**6f**	0.063	93	0.144	84	0.162	82	0.207	77	0.261	71
8	**6g**	0.108	88	0.135	85	0.216	76	0.243	73	0.270	70
9	**6h**	0.387	57	0.514	43	0.550	39	0.631	30	0.712	21
10	**6i**	0.135	85	0.180	80	0.162	82	0.225	75	0.315	65
11	**6j**	0.117	87	0.153	83	0.225	75	0.270	70	0.369	59
12	**6k**	0.360	60	0.487	45	0.541	45	0.586	35	0.685	24
13	Control	0.9022									

4-benzoic **6k** groups were much lower. Other compounds exhibited comparable inhibition values with that of the standard, BHT.

In summary, a safe and practical synthesis of substituted quinolines and bis(indolyl)methanes was achieved under solvent free condition. Operational simplicity, low catalyst loading, wide substrate scope, were screened for their antimicrobial activities. Most good yield and short reaction time are the significant advantages from synthetic viewpoint. All the compounds of the compounds were identified to be active, with an efficacy comparable to those of the standard drugs. Most of the bis(indolyl)methanes showed good antioxidant potential. Further studies on the activity of these compounds in an expanded panel of organisms and in vivo efficacy models will be reported in due course.

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References and notes

1. (a) Michael, J. P. *Nat. Prod. Rep.* **2007**, *24*, 223; (b) Michael, J. P. *Nat. Prod. Rep.* **2005**, *22*, 627; (c) Michael, J. P. *Nat. Prod. Rep.* **2004**, *21*, 650; (d) Larsen, R. D.; Corley, E. G.; King, A. O.; Carrol, J. D.; Davis, P.; Verhoeven, T. R.; Reider, P. J.; Labelle, M.; Gauthier, J. Y.; Xiang, Y. B.; Zamboni, R. J. *J. Org. Chem.* **1996**, *61*, 3398; (e) Chen, Y. L.; Fang, K. C.; Sheu, J. Y.; Hsu, S. L.; Tzeng, C. C. *J. Med. Chem.* **2001**, *44*, 2374; (f) Roma, G.; Braccio, M. D.; Grossi, G.; Mattioli, F.; Ghia, M. *Eur. J. Med. Chem.* **2000**, 1021; (g) Kalluraya, B.; Sreenivasa, S. *Farmaco* **1998**, *53*, 399; (h) Dube, D.; Blouin, M.; Brideau, C.; Chan, C. C.; Dermarsis, S.; Ethier, D.; Falgueyret, J. P.; Friesen, R. W.; Girard, M.; Girard, Y.; Guay, J.; Riendeau, D.; Tagari, P.; Young, R. N. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1255; (i) Kouznetzov, V. V.; Mendez, L. Y. V.; Gomez, C. M. M. *Curr. Org. Chem.* **2005**, *9*, 141; (j) Arcadi, A.; Marinelli, F.; Rossi, E. *Tetrahedron* **1999**, *55*, 13233.
2. Kleeman, A.; Engel, J.; Kutscher, B.; Reichert, D. *Pharmaceutical Substances. Synthesis, Patents, Applications*; Thieme: Stuttgart, 2001.
3. Manske, R. H. F.; Kukla, M. *Org. React.* **1953**, *7*, 59.
4. Bergstrom, F. W. *Chem. Rev.* **1944**, *35*, 153.
5. Cheng, C.-C.; Yan, S.-J. *Org. React.* **1982**, *28*, 37.
6. Jones, G. In *The Chemistry of Heterocyclic Compounds*; Weissberger, A., Taylor, E. C., Eds.; John Wiley and Sons: Chichester, 1977; Vol. 32, pp 93–318. Part I.
7. Reitsema, R. H. *Chem. Rev.* **1948**, *43*, 47.
8. Bergstrom, F. W. *Chem. Rev.* **1944**, *35*, 156.
9. Jones, G. In *Heterocyclic Comprehensive Chemistry*; Katritzky, A. R., Rees, C. W., Scriven, E. E., Eds.; Pergamon Press: Oxford, 1996; Vol. 5, p 167. Chapter 5.05.
10. (a) Horn, J.; Marsden, S. P.; Nelson, A.; House, D.; Weingarten, G. G. *Org. Lett.* **2008**, *10*, 4117; (b) Sakai, N.; Annaka, K.; Konakahara, T. *J. Org. Chem.* **2006**, *71*, 3653; (c) Xiao, F.; Chen, Y.; Liu, Y.; Wang, J. *Tetrahedron* **2008**, *64*, 2755; (d) Isobe, A.; Takagi, J.; Katagiri, T.; Uneyama, K. *Org. Lett.* **2008**, *10*, 2657; (e) O'Dell, D. K.; Nicholas, K. M. *J. Org. Chem.* **2003**, *68*, 6427; (f) Taguchi, K.; Sakaguchi, S.; Ishii, Y. *Tetrahedron Lett.* **2005**, *46*, 4539; (g) Jacob, J.; Jones, W. D. *J. Org. Chem.* **2003**, *68*, 3563; (h) Abbiati, G.; Arcadi, A.; Canevari, V.; Capezzuto, L.; Rossi, E. *J. Org. Chem.* **2005**, *70*, 6454; (i) Amii, H.; Kishikawa, Y.; Uneyama, K. *Org. Lett.* **2001**, *3*, 1109; (j) Korivi, R. P.; Cheng, C.-H. *J. Org. Chem.* **2006**, *71*, 7079.
11. Shiri, M.; Zolfigol, M. A.; Kruger, H. G.; Tanbakouchian, Z. *Chem. Rev.* **2010**, *110*, 2250.
12. (a) Bradfield, C. A.; Bjeldanes, L. F. *J. Toxicol. Health* **1987**, *21*, 311; (b) Dashwood, R. H.; Uyetake, L.; Fong, A. T.; Hendricks, J. D.; Bailey, G. *Environ. Food Chem. Toxicol.* **1987**, *27*, 385.
13. Zeligs, M. A. *J. Med. Food* **1998**, *1*, 67.
14. (a) Eilbracht, P.; Bärfacker, L.; Buss, C.; Hollmann, C.; Kitsos-Rzychon, B. E.; Kranemann, C. L.; Rische, T.; Roggenback, R.; Schmidt, A. *Chem. Rev.* **1999**, *99*, 3329; (b) Simoes, J. A. M.; Beauchamp, J. L. *Chem. Rev.* **1990**, *90*, 629.
15. (a) Praveen, C.; Kumar, K. H.; Muralidharan, D.; Perumal, P. T. *Tetrahedron* **2008**, *64*, 2369; (b) Praveen, C.; Sagayaraj, Y. W.; Perumal, P. T. *Tetrahedron Lett.* **2009**, *50*, 644; (c) Praveen, C.; Kiruthiga, P.; Perumal, P. T. *Synlett* **2009**, 1990; (d) Praveen, C.; Jegatheesan, S.; Perumal, P. T. *Synlett* **2009**, 2795; (e) Praveen, C.; Karthikeyan, K.; Perumal, P. T. *Tetrahedron* **2009**, *65*, 9244; (f) Praveen, C.; Kalyanasundaram, A.; Perumal, P. T. *Synlett* **2010**, 777; (g) Praveen, C.; Parthasarathy, K.; Perumal, P. T. *Synlett* **2010**, 1635; (h) Praveen, C.; Iyyappan, C.; Perumal, P. T. *Tetrahedron Lett.* **2010**, *51*, 4767; (i) Kumar, K. H.; Muralidharan, D.; Perumal, P. T. *Synthesis* **2004**, 63; (j) Shanthi, G.; Subbulakshmi, G.; Perumal, P. T. *Tetrahedron* **2007**, *63*, 2057; (k) Selvam, N. P.; Shanthi, G.; Perumal, P. T. *Can. J. Chem.* **2007**, *84*, 989; (l) Karthikeyan, K.; Seelan, T. V.; Lalitha, K. G.; Perumal, P. T. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3370; (m) Damodiran, M.; Muralidharan, D.; Perumal, P. T. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3611; (n) Sujatha, K.; Shanthi, G.; Selvam, N. P.; Manoharan, S.; Perumal, P. T.; Rajendran, M. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4501.
16. Lekhok, K. C.; Prajapati, D.; Boruah, R. C. *Synlett* **2008**, 655.
17. For reactions involving $Zn(OTf)_2$ as catalyst, see: (a) Chiacchio, U.; Rescifina, A.; Saita, M. G.; Iannazzo, D.; Romeo, G.; Mates, J.; Tejero, T.; Merino, P. *J. Org. Chem.* **2005**, *70*, 8991; (b) Murakata, M.; Tsutsui, H.; Hoshino, O. *Org. Lett.* **2001**, *3*, 299; (c) Ishimaru, K.; Kojima, T. *J. Org. Chem.* **2003**, *68*, 4959; (d) Zhu, X.; Ganesan, A. *J. Org. Chem.* **2002**, *67*, 2705.
18. Representative procedure for the $Zn(OTf)_2$ catalyzed synthesis of quinoline (**3i**) under microwave condition: 2′-aminobenzophenone (1.0 mmol), 3-bromophenylacetylene (1.5 mmol) and $Zn(OTf)_2$ (1 mol %) was stirred for 5 min for uniform mixing and was then transferred to a glass tube and inserted in an alumina bath (100 g, 60 G_{254}, Fischer scientific bath (6.8 cm diameter)) and was irradiated in a domestic microwave oven (BPL, India) at 450 W for 10 min. The temperature of the alumina bath (90 °C) was measured after 1 min of the reaction. On completion, the reaction mixture was directly charged on a small silica gel column and eluted with a mixture of EtOAc/hexane to afford the pure quinoline product (**3i**) as yellow liquid; IR (film): 701, 773, 793, 878, 1073, 1545, 1588, 3062 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ_H 7.36 (t, J = 7.8 Hz, 1H), 7.44–7.58 (m, 7H), 7.70–7.73 (s, 1H),7.75 (s, 1H), 7.90 (dd, J = 0.75, 8.11 Hz, 1H), 8.09 (dt, J = 0.72, 7.8 Hz, 1H), 8.21–8.24 (m, 1H), 8.38 (t, J = 1.7 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 118.9, 123.0, 125.6, 125.8, 126.0, 126.6, 128.4, 128.6, 129.4, 129.6, 130.11, 130.2, 130.5, 132.1, 138.1, 141.5, 148.6, 149.42, 155.0. MS (ESI): m/z = 360 $[M+H]^+$, 362 $[M+H]^+$.[2] Anal. Calcd for $C_{21}H_{14}BrN$: C, 70.02; H, 3.92; N, 3.89. Found: C, 70.41; H, 4.00; N, 3.75. This procedure was followed for all the substrates.
19. For the reaction of $Zn(OTf)_2$ assisted nucleophilic addition of terminal alkyne with carbonyl group, see: (a) Boyall, D.; Frantz, D. E.; Carreira, E. M. *Org. Lett.* **2002**, *4*, 2605; (b) Yamashita, M.; Yamada, K.-i.; Tomioka, K. *Adv. Synth. Catal.* **2005**, *347*, 1649.
20. Representative procedure for the $Zn(OTf)_2$ catalyzed synthesis of bis(indolyl)methane (**6i**) under microwave condition: 2-Phenylindole (**4**) (1.0 mmol), aldehyde (**5i**) (0.55 mmol) and $Zn(OTf)_2$ (1 mol %) was stirred for 5 min for uniform mixing and was then transferred to a glass tube and inserted in an alumina bath (100 g, 60 G_{254}, Fischer scientific bath (6.8 cm diameter)) and was irradiated in a domestic microwave oven (BPL, India) at 450 W for 10 min. The temperature of the alumina bath (90 °C) was measured after 1 min of the reaction. On completion, the reaction mixture was directly charged on a small silica gel column and eluted with a mixture of EtOAc/hexane to afford the pure bis(indolyl)methane (**6i**) product as a pale yellow solid; mp 278–280 °C; R_f = 0.23 (AcOEt/petroleum ether 20%). IR (KBr): 3401, 1483, 1457, 1340, 1233, 743 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ_H 1.26 (t, 3H, J = 7.6 Hz, $-NCH_2CH_3$), 4.33 (q, 2H, J = 6.8 Hz, $-NCH_2CH_3$), 6.17 (s, 1H, $-CH$-Ar), 6.58 (t, 2H, J = 8.4 Hz,

Ar-H), 6.88 (d, 2H, *J* = 7.6 Hz, Ar-H), 6.94–7.00 (m, 3H, Ar-H), 7.15–7.16 (m, 6H, Ar-H), 7.27 (d, 1H, *J* = 7.6 Hz, Ar-H), 7.31–7.37 (m, 7H, Ar-H), 7.44 (d, 1H, *J* = 8.4 Hz, Ar-H), 7.48 (d, 1H, *J* = 7.6 Hz, Ar-H), 7.79 (d, 1H, *J* = 7.6 Hz, Ar-H), 7.85 (s, 1H, carbazolyl-H), 11.33 (s, 2H, –N*H*). ^{13}C NMR (75 MHz, DMSO-d_6) δ_C 13.7, 37.0, 39.4,108.5, 108.9, 111.3, 115.1, 118.4, 119.8, 120.2, 120.8, 122.0, 122.1, 125.5, 126.8, 127.1, 128.0, 128.2, 128.4, 132.8, 135.1, 136.1, 136.3, 138.1, 139.8. MS (ESI): *m*/*z* = 591 [M$^+$]. Anal. Calcd for $C_{43}H_{33}N_3$: C, 87.28; H, 5.62; N, 7.10. Found: C, 87.41; H, 5.70; N, 7.17. This procedure is followed for all the substrates.

21. Experimental for antibacterial activity of compounds (**3a–3m**) and (**6a–6k**): Sterile nutrient broth was prepared and inoculated with different species of bacteria (*E. coli* and *S. aureus*) and incubated at 37 °C for overnight. From this overnight culture, 1% stock culture was prepared (99 mL of sterile nutrient broth + 1 mL of overnight culture). 25 mL of nutrient agar was poured in sterile Petri plates and allowed to cool. Each agar plates were inoculated with 200 μL of 1% bacterial culture and spreaded by spreader. Using a sterile cork borer, 6 mm diameter of holes were made in the solidified agar plates containing 1% of respective bacterial culture. A total volume of 20 μL of test sample (**3a–3m and 6a–6k**) was poured into the well with the concentration of 1000 μg/mL. One well was poured with 1000 μg/mL of *Amoxiclav* and incubated at 37 °C for 24 h. After 24 h of incubation, zone of Inhibition was measured in millimeter.
22. Experimental for antifungal activity of compounds (**3a–3m**) and (**6a–6k**): Saborauds dextrose broth was prepared and inoculated with *C. albicans* spores and incubated at 28 °C for overnight. From this overnight culture 1% stock culture was prepared (99 mL of sterile saborauds dextrose broth + 1 mL of overnight culture). 25 mL of saborauds dextrose agar was poured in sterile Petri plates and allowed to cool. Each agar plates were inoculated with 200 μL of 1% different species of fungus and spreaded by spreader. Using a sterile cork borer, 6 mm diameter of holes were made in the solidified agar plates containing fungal culture (1%). A total volume of 20 μL of test sample (**3a–3m** and **6a–6k**) was poured into the well with the concentration of 1000 μg/mL. One well was poured with 1000 μg/mL of *Amphotericin-B* and incubated at 28 °C for 24 h. After 24 h of incubation, zone of inhibition was measured in millimeter.
23. (a) Sanchez-Moreno, C.; Larrauri, J. A.; Saura-Calixto, F. J. *Sci. Food Agric.* **1998**, *76*, 270; (b) Brand-Williams, W.; Cuvelier, M. E.; Berst, C. *Lebensm.-Wiss. u.-Technol.* **1995**, *28*, 25; (c) Bondel, V.; Brand-Williams, W.; Benset, C. *Lebensm.-Wiss. u.-Technol.* **1997**, *30*, 609; (d) Soares, J. R.; Dinis, T. C. P.; Cunha, A. P.; Ameida, L. M. *Free Radical Res.* **1997**, *26*, 469; (e) Duh, P. D.; Tu, Y. Y.; Yen, G. C. *Lebensm.-Wiss. u.-Technol.* **1999**, *32*, 269.
24. (a) Hatano, T.; Kagawa, H.; Yasuhara, T.; Okuda, T. *Chem. Pharm. Bull.* **1988**, *36*, 2090; (b) Blois, M. S. *Nature* **1958**, *26*, 1199.
25. General procedure for the determination of radical scavenging activity of bis(indolyl)methanes (**6a–6k**) by DPPH method: To a 3 mL ethanolic solution of DPPH (200 μM), 0.05 mL of different concentration (50, 500, 1000 μg/mL) of test samples and 20 μg of ascorbic acid were added. The solutions were incubated at 37 °C for 30 min. The absorbance was measured at 517 nm using Systronics 118 model spectrophotometer. The percentage inhibition of DPPH radical was calculated by comparing the results of the test with those of the control using the formula: % inhibition = $(A_C - A_T)/A_C \times 100$, where A_C is the absorbance of control and A_T is the absorbance of test.
26. Shon, M.-Y.; Lee, J.; Choi, J.-H.; Choi, S.-Y.; Nam, S. H.; Seo, K., II; Lee, S.-W.; Sung, N.-J.; Park, S.-K. J. *J. Food Compos. Anal.* **2007**, *20*, 113.
27. *General procedure for the hydrogen peroxide radical scavenging activity of bis(indolyl)methanes* (**6a–k**): Hydrogen peroxide radical scavenging activity was done by using 10 μg of bis(indolyl)methanes (**6a–k**), each was dissolved in 3.4 mL of 0.1 M Phosphate buffer (pH 7.4) and mixed with 600 μL of 43 mM solution of H_2O_2. BHT (20 μg) was used as standard and the stock solution was prepared in the same buffer. The absorbance value (230 nm) of the reaction mixture was recorded at 10 min intervals between zero and 40 min. For each concentration blank sample was used for background substraction. The percentage inhibition of was calculated by comparing the results of the test with those of the control using the formula: % inhibition = $(A_C - A_T)/A_C \times 100$, where A_C is the absorbance of control and A_T is the absorbance of test.