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Meglumine as a green, efficient and reusable catalyst for synthesis and molecular docking studies of bis(indolyl)methanes as antioxidant agents

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ABSTRACT

An efficient and convenient Meglumine catalyzed procedure for the synthesis of bis(indolyl) methanes at ambient temperature under aqueous conditions in high yields. The catalytic reaction proceeds very smoothly. Clean reaction, ease of product isolation/purification, easily available reactants, metal free and environmentally friendly reaction conditions are the notable advantages of the present methodology. All the entitled compounds were characterized by IR, ^{1}H, ^{13}C NMR, mass spectra and evaluated for their antioxidant (DPPH, H_2O_2 and NO scavenging methods). They exhibited potent in vitro antioxidant activity dose-dependently. The binding interactions and molecular docking studies for entitled compounds were studied against 3MNG protein. **4d** exhibited marked binding affinity with excellent docking score of −7.6 K.cal/mol and emerged as a lead compound.

1. Introduction

Indoles represent an important group of *N*-heterocycles, which are known to have potent pharmaceutical and biological properties [1]. Indoles and their derivatives are one of the important classes of heterocyclic compounds that are present in various natural products, pharmaceuticals, agrochemicals and other compounds of importance [2]. Among them, bis(indolyl)methanes (BIMs) are frequently found in natural products, drugs and biological molecules (Fig. 1) [3] and also identified to possess wide range of applications in pharmacology, biochemistry and medicinal chemistry [4]. BIMs and their derivatives are found in terrestrial and marine metabolites [5]. In fact, bis(indolyl)alkanes exhibit a wide spectrum of biological activities viz., cytotoxic [6,7], antitumor, antiviral [8], antimicrobial [9], anti-inflammatory [10], and antioxidant [11,12]. The BIM is also a privileged scaffold in alkaloids including ramiflorine A and ramiflorine B, vibrindole A, streptindole, deoxytopsentin, bromodeoxytopsentin, and sponges. Because of the unique pharmacological activities and the prevalence of indole moiety in many natural products, a great deal of interest has been focused on the development of efficient synthetic protocols for the preparation of bis(indolyl)alkanes. A number of synthetic methods for their preparation have been reported [13–17]. Catalyst is an important aspect of green chemistry. The design and application of new catalysts and catalytic systems are playing a vital role in achieving goals of environmental defense and economic assistance. Reusability of the catalyst without any loss of activity is an indispensable fact of green chemistry. However, the use of toxic reagents, high temperature, and volatile organic solvents are among the drawbacks of most of these protocols [18]. Hence, there is a need for a new, efficient, and inexpensive synthetic methodologies based on green chemistry processes in organic synthesis. In the present communication, herein we report the use of meglumine as a catalyst for the synthesis of bis(indolyl)methane derivatives (Scheme 1).

2. Chemistry

Initially we focused on the development of an optimal reaction condition for the synthesis of bis(indolyl)methanes. We selected indole **1a** (1.0 mmol), benzaldehyde **2a** (0.5 mmol) for the model reaction (Table 1). The above reaction was carried out at room temperature in

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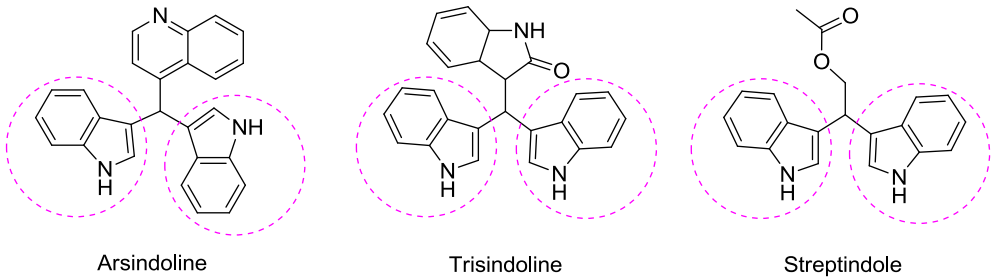
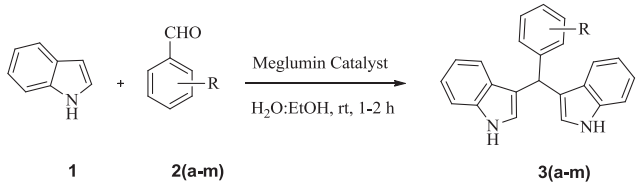


Fig. 1. Bio-active BIMs derivatives.



R = a) H
b) 4-CH_3
c) 4-CH_3O
d) 3,5-dimethoxy
e) 4-N,N-dimethyl
f) 4-F
g) 4-Cl
h) 2-Cl
i) 4-Br
j) 4-OH
k) 4-NO_2
l) 3-NO_2
m) 4-CN

Scheme 1. Synthesis of bis (indolyl) methane derivatives 3(a-m).

Table 1
Optimization of the reaction conditions for the synthesis of **3a.**

Entry	Catalyst	Solvent	Time (hrs)	Yield (%)
1	$KHSO_4$	H_2O	13	55
2	$FeCl_3$	H_2O	12	59
3	$LiClO_4$	H_2O	12	35
4	Sulfamic acid	H_2O	10	67
5	$Cu(OTf)_2$	H_2O	6	78
6	Meglumine	H_2O:EtOH (1:1)	0.25	96
7	Meglumine	No	5	16
8	Meglumine	MeOH	4	60
9	Meglumine	EtOH:H_2O (1 : 9)	4	65
10	Meglumine	THF	4	41
11	Meglumine	PEG 400	4	52

water with catalyst.. As shown in Table 1, it was observed that only a low yield of product was formed even after the reaction time was prolonged to 13 h (Table 1, entry **1**). Then, we tried to optimize the reaction conditions with different catalysts, which might be help to reduce the reaction time and improve the yield of the target product. After viewing several catalysts, it can be prominent that $Cu(OTf)_2$ exhibited a slight catalytic activity to give the product in a low yield (78%, Table 1, entry **5**). The improvement was observed when several catalist such as $KHSO_4$, $FeCl_3$, $LiClO_4$, Sulfamic acid were used, and the desired product was obtained in 35–67% yield (Table 1, entries **1–4**). Further experiments indicated that meglumine was the best catalyst for this transformation and afforded the desired product in 96% within 1 h (Table 1, entry **6**). Some solvents such as H_2O, MeOH, THF, PEG 400, and ethanol–water mixture was tested for the model reaction. It was observed that mixer of water and ethanol was the most effective solvent, and the present reaction proceeded efficiently giving the highest yield. It is distinguished that when the reaction was performed under solvent-free conditions, low yield of target product was obtained (Table 1, entry **7**). Then the effect of catalyst loading was evaluated in the model reaction at room temperature in H_2O.

Apart from these, to find out the influence of the catalyst concentration, the reaction of indole (**1**) and benzaldehyde (**2**) was carried out with different concentrations of catalyst in H_2O at room temperature. The results presented in Table 2 indicated that 10 mol% of meglumine is an optimum to achieve high yield in shorter reaction time. There is no effect by increasing the amount of catalyst on the product yield, on the other hand employing a lower percentage of meglumine resulted in a decreased yield of desired product (Table 2)

Table 2
Effect of concentration of meglumine on the reaction of indole (1) with benzaldehyde (2).

Entry	Mole % of Catalyst	Time (min)	Yield (%)
1	1	50	50
2	2.5	45	65
3	5	40	70
4	7.5	20	75
5	10	15	96
6	12.5	15	96
7	15	15	96

All the compounds were performed in open atmosphere and are not sensitive to air and moisture. All the synthesized compounds have been characterized by spectral data.

3. Biology

Peroxiredoxins (Prxs) are important peroxidases associated with both antioxidant protection and redox signaling. They are used as conserved Cys residue to reduce peroxide substrates. The Prxs have a remarkably high catalytic efficiency that makes them a dominant player in cell-wide peroxide reduction, but the origins of their high activity have been mysterious. We are extant here a novel structure of human PrxV at 1.45 A° resolution that has a dithiothreitol bound in the active site with its diol moiety mimicking the two oxygens of a peroxide substrate. This suggests diols and similar di-oxygen compounds as a novel class of competitive inhibitors for the Prxs. Common features of this and other structures containing peroxide, peroxide-mimicking ligands or peroxide-mimicking water molecules reveal hydrogen bonding and steric factors that promote its high reactivity by creating an oxygen track along which the peroxide oxygens move as the reaction proceeds. Key insights include how the active-site microenvironment activates both the peroxidatic cysteine side chain and the peroxide substrate and how it is exquisitely well suited to stabilize the transition state of the in-line SN_2 substitution reaction that is peroxidation.

3.1. Antioxidant activity

The compounds **3(a-m)** were screened for their antioxidant property by DPPH, H_2O_2 and NO methods at three different concentrations 50, 75 and 100 µg/mL. Ascorbic acid was used as standard drug to compare anti-oxidant activities.

Table 3
The in vitro antioxidant activity of 3(a-m) in DPPH method.

Compound	Concentration (μg/mL)			
	50 Mean ± SD	75 Mean ± SD	100 Mean ± SD	IC_{50} Mean ± SD
3a	51.14 ± 0.10	53.43 ± 0.18	57.61 ± 0.22	48.88
3b	70.29 ± 0.15	72.22 ± 0.24	74.15 ± 0.15	35.56
3c	58.15 ± 0.21	60.45 ± 0.16	62.23 ± 0.24	42.99
3d	74.32 ± 0.24	76.34 ± 0.23	78.67 ± 0.18	33.63
3e	68.25 ± 0.19	70.46 ± 0.19	72.46 ± 0.34	36.63
3f	73.46 ± 0.18	75.84 ± 0.34	77.35 ± 0.39	34.03
3g	55.54 ± 0.11	57.36 ± 0.38	59.64 ± 0.17	45.01
3h	72.82 ± 0.25	74.25 ± 0.26	76.40 ± 0.16	34.33
3i	63.51 ± 0.34	65.43 ± 0.17	67.10 ± 0.32	39.36
3j	60.91 ± 0.31	62.43 ± 0.16	64.27 ± 0.23	41.04
3k	66.03 ± 0.18	68.05 ± 0.13	70.43 ± 0.17	37.86
3l	64.64 ± 0.27	66.84 ± 0.10	68.07 ± 0.10	38.67
3m	62.37 ± 0.31	64.28 ± 0.15	66.63 ± 0.14	40.08
Ascorbic acid	75.64 ± 0.14	77.54 ± 0.11	78.91 ± 0.26	33.05

Values were the means of three replicates ± SD

4. Results and discussion

The compounds **3(a-m)** were tested for antioxidant property by 1,1-diphenyl-2-picrylhydrazyl (DPPH) [19,20], hydrogen peroxide (H_2O_2) [21], and nitric oxide methods (NO) [22,23]. The experimental data on the antioxidant activity of the compounds **3(a-m)** and control drug are presented in Tables 3–5, respectively. The mean antioxidant values are shown visually in Figs. 2–4. DPPH forms a stable molecule on accepting an electron or a hydrogen and thus found application in the determination of radical scavenging and antioxidant activity. According to our prophesied results, the bis(indolyl)methanes **3(a-m)** have ability to scavenge the DPPH radical by donating one electron. Amongst all the tested compounds **3d**, **3f**, **3 h** and **3b** showed good radical scavenging activity for all the three methods when compared with the standard drug ascorbic acid. Moreover, the remaining compounds **3a, 3c, 3e, 3 g, 3i, 3j, 3 k, 3 l, 3 m** the order is as follows **3e** > **3 k** > **4e** > **3 l** > **3i** > **3 m** > **3j** > **3c** > **3 g** > **3a**. Further, the analysis of the data presented in Tables 3, 4 and 5 indicates that radical scavenging activity in DPPH, hydrogen peroxide and nitric oxide methods increases with increase in concentration. The free radical scavenging activity of the compounds **3d** and **3f** was measured at different concentrations and monitored the change in absorbance at 10, 20 and 30 min in DPPH method (Table 6). At these 10 min intervals, the values are very close, and the results indicated that the antioxidant activity is independent of time.

Table 4
The in vitro antioxidant activity of 3(a-m) in H_2O_2 method.

Compound	Concentration (μg/mL)		
	50 Mean ± SD	75 Mean ± SD	100 Mean ± SD
3a	56.56 ± 0.12	58.10 ± 0.13	60.36 ± 0.14
3b	73.36 ± 0.21	75.66 ± 0.15	77.58 ± 0.25
3c	60.53 ± 0.34	62.44 ± 0.18	64.39 ± 0.17
3d	78.48 ± 0.37	80.76 ± 0.14	82.52 ± 0.28
3e	70.56 ± 0.24	72.43 ± 0.17	74.37 ± 0.13
3f	76.64 ± 0.26	78.78 ± 0.16	80.61 ± 0.21
3g	58.28 ± 0.17	60.43 ± 0.25	62.82 ± 0.19
3h	74.63 ± 0.16	76.88 ± 0.26	78.47 ± 0.27
3i	66.28 ± 0.26	68.38 ± 0.27	70.85 ± 0.31
3j	62.83 ± 0.22	64.89 ± 0.29	66.99 ± 0.37
3k	69.68 ± 0.19	71.50 ± 0.24	73.27 ± 0.29
3l	68.85 ± 0.11	70.42 ± 0.22	72.75 ± 0.11
3m	64.90 ± 0.10	66.23 ± 0.16	68.44 ± 0.10
Ascorbic acid	77.28 ± 0.19	77.29 ± 0.09	79.20 ± 0.12

Values were the means of three replicates ± SD

Table 5
The in vitro antioxidant activity of 3(a-m) in NO method.

Compound	Concentration (μg/mL)		
	50 Mean ± SD	75 Mean ± SD	100 Mean ± SD
3a	57.78 ± 0.14	59.22 ± 0.37	61.61 ± 0.29
3b	72.44 ± 0.28	74.13 ± 0.26	76.43 ± 0.26
3c	60.15 ± 0.19	62.52 ± 0.18	64.52 ± 0.18
3d	79.84 ± 0.27	81.20 ± 0.34	83.06 ± 0.34
3e	71.56 ± 0.34	73.46 ± 0.25	75.56 ± 0.19
3f	77.24 ± 0.15	79.21 ± 0.16	81.89 ± 0.27
3g	58.92 ± 0.36	60.35 ± 0.31	62.12 ± 0.30
3h	76.62 ± 0.24	78.18 ± 0.22	80.35 ± 0.21
3i	67.66 ± 0.38	69.28 ± 0.33	71.64 ± 0.16
3j	62.72 ± 0.26	64.78 ± 0.19	66.31 ± 0.10
3k	70.42 ± 0.18	72.34 ± 0.37	74.94 ± 0.17
3l	69.48 ± 0.16	71.34 ± 0.28	73.31 ± 0.31
3m	65.54 ± 0.11	67.91 ± 0.13	69.94 ± 0.29
Ascorbic acid	78.11 ± 0.31	79.86 ± 0.23	81.36 ± 0.14

Values were the means of three replicates ± SD

4.1. Experimental procedure for antioxidant activity of compounds 3(a-m)

4.1.1. 1,1-Diphenyl-2-picryl hydrazyl (DPPH) radical scavenging activity

This assay is based on the measurement of the scavenging ability of antioxidant substances toward the stable radical. The hydrogen atom or electron donation ability of the compounds was measured from the bleaching of the purple colored methanol solution of 1,1-diphenyl-2-picryl hydrazyl radical (DPPH). The spectrophotometric assay uses the stable radical DPPH as a reagent. To 4 mL of 0.004% w/v methanol solution of DPPH, 1 mL of various concentrations of the test compounds (50, 75 and 100 μg/mL) in methanol were added. After 30 min incubation period at room temperature, the absorbance was read against blank at 517 nm. Ascorbic acid was used as the standard. The percent of inhibition (I %) of free radical production from DPPH was calculated by the following equation

$$\%\ of\ scavenging = [(A_{control} - -A_{sample})\ /A_{control}]\ \text{X}\ 100$$

where $A_{control}$ is the absorbance of the control reaction (containing all reagents except the test compounds), A_{sample} is the absorbance of the test compound (containing methanolic DPPH and test compound). Tests were carried out in triplicate.

4.1.2. Hydrogen peroxide (H_2O_2) scavenging activity

Hydrogen peroxide (H_2O_2) is a biologically important, non-radical reactive oxygen species (ROS) that can influence several cellular processes. The H_2O_2 scavenging ability of the test compound was

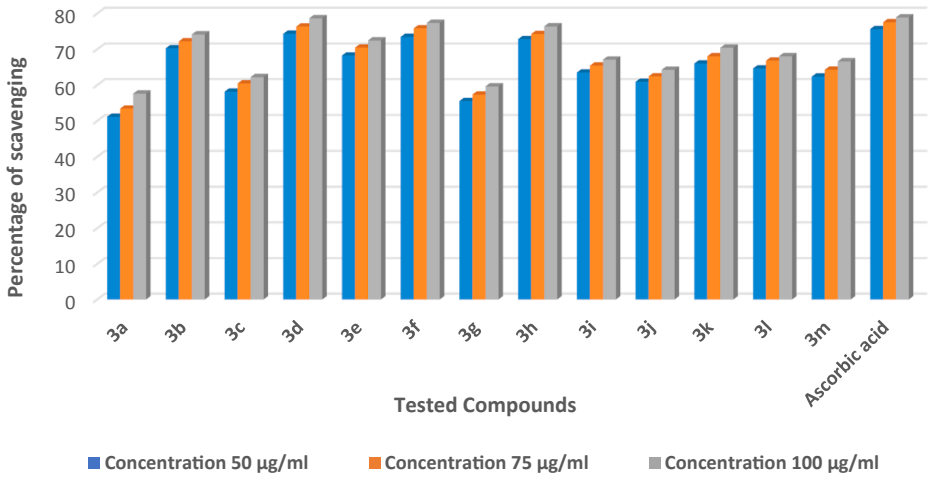


Fig. 2. The in vitro antioxidant activity of **3(a-m)** in DPPH method.

determined by a solution of H_2O_2 (40 mm) was prepared in phosphate buffer (pH 7.4). 50, 75 and 100 µg/mL concentrations of the test compounds in 3.4 mL phosphate buffer were added to H_2O_2 solution (0.6 mL, 40 mm). The absorbance value of the reaction mixture was recorded at 230 nm. Ascorbic acid was used as the standard. The percent scavenging of H_2O_2 was calculated by the following equation.

$$\%\ of\ \ scavenging\ \ =\ \ [(A_{control}\ -\ -A_{sample})\ /A_{control}]\ X\ \ 100$$

where $A_{control}$ is the absorbance of the control reaction (containing all reagents except the test compounds), A_{sample} is the absorbance of the test compound (containing all reagents and test compound). Tests were carried out in triplicate.

4.1.3. Nitricoxide (NO) scavenging activity

Sodium nitroprusside (5 µM) in phosphate buffer pH 7.2 was incubated with different concentrations (50, 75 and 100 µg/mL) of test compounds dissolved in a suitable solvent (methanol) and tubes were incubated at 25 °C for 2 h. The compound sodium nitroprusside is known to decompose in aqueous solution at physiological pH (7.2) producing NO. Under aerobic conditions, NO reacts with oxygen to produce stable products (nitrate and nitrite). The quantities of which can be determined using Griess reagent. Scavengers of nitric oxide compete with oxygen leading to reduced production of nitrite ions. Control experiment was conducted with equal amount of solvent in an identical manner. At intervals, 0.5 mL of incubation solution was taken and diluted with 0.5 mL of Griess reagent (1% Sulfanilamide, 0.1%*N*-naphthyl ethylene diamine di hydrochloride and 2% *o*-phosphoricacid dissolved in distilled water). The absorbance of the chromophore formed during diazotization of nitrite with sulfanilamide and subsequent *N*-naphthyl ethylene diamine di hydrochloride was read at 546 nm. The experiment was run in triplicate. Nitric oxide scavenging activity was calculated by the following equation.

$$\%\ \ of\ \ \ scavenging = [(A_{control}\ -\ A_{sample})/A_{control}] \times 100$$

where $A_{control}$ is the absorbance of the control reaction (containing all reagents except the test compounds), A_{sample} is the absorbance of the test compound (containing all reagents and test compound). Tests were carried out in triplicate.

5. Molecular docking analyses

To prove the reputation of our synthesized compounds, docking analysis was carried out for compounds **3(a-m)** with selective pharmacological target such as 3MNG protein of Human being which is a suitable target for anti-oxidant activity. The crystal structure of 3MNG protein (PDB id: 3MNG) was retrieved from the protein data bank, and the reference drugs such as DTT and BHT were from Pub Chem Drug bank. The docking results of the synthesized compounds such as **3a, 3b,**

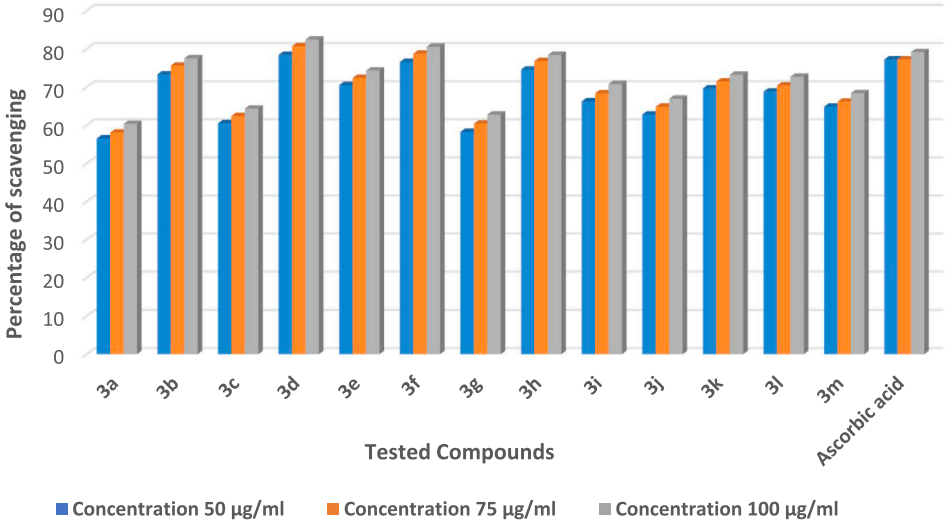


Fig. 3. The in vitro antioxidant activity of **3(a-m)** in H_2O_2 method.

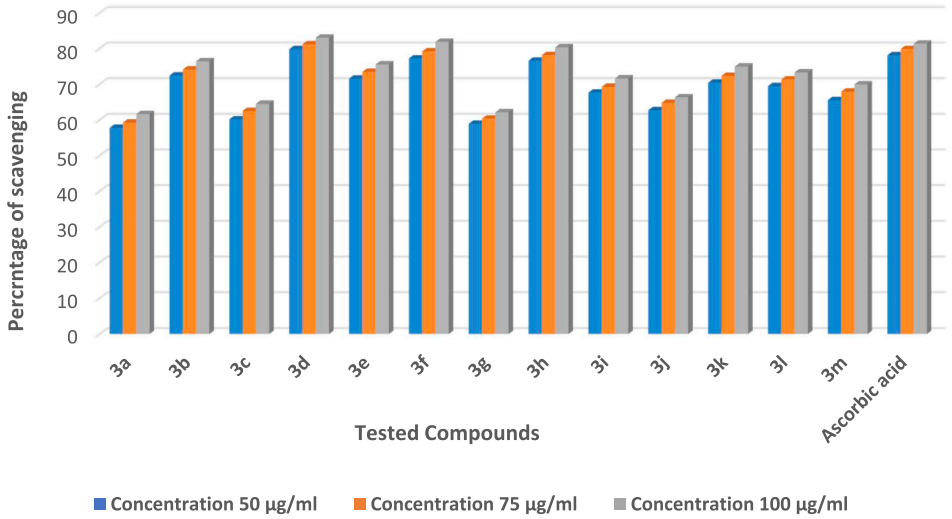


Fig. 4. The in vitro antioxidant activity of **3(a-m)** in NO method.

Table 6
Antioxidant activity of the compounds 3d and 3f at 10 min.

Compound	10 min	20 min	30 min
3d	74.41	74.50	74.61
3f	75.37	75.42	75.69

Time intervals by DPPH scavenging method.

3c, 3d, 3e, 3f, 3g, 3h, 3i, 3j, 3k, 3l, 3m have significant binding modes, with dock scores of **−6.6, −7.3, −6.9, −7.6, −7.2, −7.3, −6.8, −7.3, −7.1, −6.9, −7.2, −7.2 and −7.0** against 3MNG protein when compared with the control drugs, **DTT(-4.6)** and **BHT(-5.2)** respectively. The H-bonds, binding affinities and energy profiles of compounds **3(a-m)** along with reference drugs, towards the active site amino acids of the enzyme are summarized in Table 7. Based on the binding scores, the compounds **3(a-m)** are suggested that they fitted more stably into the 3MNG protein binding pocket. Hence, the present investigation demonstrate that the synthesised compounds will be the promising next generation drugs as effective anti-oxidative agents, which can be effectively used in the treatment of oxidative stress and other related disorders. Compounds **3c, 3d, 3m and BHT** have shown hydrophobic interaction against 3MNG Protein.

5.1. *In silico ADME prediction*

The synthesized compounds **3(a-m)** were subjected to prediction of ADME properties. The various ADME properties including topological polar surface area (TPSA), molecular weight, number of rotatable bonds, molecular volume, number of hydrogen bond donors, number of hydrogen bond acceptors, mi Log P and violations of Lipinski rule were calculated by the Molinspiration online property toolkit. % ABS was calculated by using the formula: % ABS = 109-(0.345 9 TPSA) [24]. ADME prediction properties like HIA%, $CaCO_2$ permeability, PPB%, and blood-brain barrier (BBB) were predicted by using pre-ADMET online server (http://preadmet.bmdrc.org/).

Table 7
Bonding characterization of synthesized compounds 3(a-m).

S. No	Compound	Rank	Binding energy (K calmol^{-})	Binding interaction	Bond Length(A^{O})	Bond Angle (^{o})	Bond Type
Std	**DTT**	R	− 4.6	Gly 82 CA….OH	2.5	137.7	H- don
				Gly 17 CA…..OC	2.7	113.6	H- acc
Std	**BHT**	R	− 5.2	Arg 86 CZ ….OC	2.1	113.2	H- acc
3a	**3a**	13	− 6.5	Val 94 CZ ….HN	2.0	114.8	H- don
3b	**3b**	4	− 6.7	Glu 16 CA ….HN	2.3	100.5	H- don
3c	**3c**	11	− 6.4	Asn 21 CZ ….OC	2.9	119.3	H- acc
				Val 94 CZ ….HN	2.1	120.9	H- don
3d	**3d**	1	− 6.4	Asn 21 CA ….OC	2.6	117.3	H- acc
				Arg 86 CB ….OC	2.1	87.7	H- acc
				Val 94 CB ….HN	2.6	103.7	H- acc
				Glu 91 CZ…..HN	2.5	120.0	H- don
3e	**3e**	5	− 6.5	Val 94 CA ….HN	2.1	131.7	H- don
3f	**3f**	2	− 6.4	Val 94 CA ….HN	1.9	118.7	H- don
3g	**3g**	12	− 6.4	Val 94 CA ….HN	1.9	126.6	H- don
3h	**3h**	3	− 6.5	Val 94 CA ….HN	2.0	108.7	H- don
3i	**3i**	8	− 6.5	Asn 21 CZ…..OH	2.7	112.7	H- acc
				Glu 91 CZ…..HN	2.8	136.8	H- don
3j	**3j**	10	−6.9	Asn 21 CZ…..ON	2.8	87.6	H- acc
				Asn 21 CZ…..ON	2.6	117.3	H- acc
				Val 94 CA ….HN	2.0	120.4	H- don
3k	**3k**	6	−7.6	Asn 21 CZ…..ON	2.6	121.6	H- acc
				Val 94 CA ….HN	2.1	130.0	H- don
3l	**3l**	7	−6.5	Val 94 CB…..HN	1.9	78.8	H- don
3m	**3m**	9	−6.3	Val 94 CB…..HN	1.9	103.7	H- don

Table 8
Physicochemical properties of compounds 3(a-m).

Compound	Mol. wt[a]	Mol. vol[b]	n- ROTB[c]	n- OHNH donor[d]	*n*-ON acceptor[e]	mi Log P[f]	TPSA (A° 2)[g]	Lipinski's violation	%ABS[h]
Rule	**≤ 500**			**≤ 5**	**≤ 10**	**≤ 5**		**≤ 1**	
3a	329.4	226.4	6	0	7	2.12	88.10	0	90.5
3b	366.6	314.6	5	0	7	3.33	80.46	0	92.2
3c	347.1	293.8	5	0	8	3.26	84.42	0	96.3
3d	443.6	262.0	6	0	8	3.18	82.21	0	92.5
3e	410.4	348.1	5	0	8	3.55	87.14	0	88.4
3f	377.1	368.5	6	0	7	3.24	90.22	0	92.4
3g	280.7	303.4	6	0	8	3.30	91.28	0	91.5
3h	381.6	389.6	4	0	6	3.96	88.13	0	93.3
3i	404.2	372.7	4	0	6	4.11	90.02	0	96.6
3j	398.8	322.0	5	0	7	3.66	92.22	0	94.2
3k	260.4	398.2	5	0	6	3.06	82.80	0	94.2
3l	244.8	368.1	5	0	8	2.86	90.14	0	94.4
3m	299.1	333.7	5	0	6	3.78	87.47	0	92.4

[a] Molecular weight
[b] Molecular volume
[c] Number of rotatable bonds
[d] Number of hydrogen bond donors
[e] Number of hydrogen bond acceptors
[f] Logarithmic ratio of the octanol-water partitioning coefficient
[g] Topological polar surface area
[h] Percentage of absorption. %ABS = 109 − (0.345 9 TPSA)

5.2. Bioavailability of compounds 3(a-m)

Nowadays, many potential drugs fail to reach the clinic because of ADMET liabilities. Adsorption, distribution, metabolism, excretion and toxicity (ADMET) processes play a pivotal role in defining the therapeutic efficacy of a drug. Drug likeness appears as a promising paradigm of a compound that optimizes their ADME in the human body [25]. With the aim of estimating the drug-likeness of the compounds, we have determined the compliance of the synthesized molecules to the Lipinski's 'rule of five'. According to this rule, poor absorption or permeation is more likely when there are more than five hydrogen bond donors, ten hydrogen bond acceptors, the molecular weight is > 500 and the calculated log p (logarithmic ratio of the octanol-water partitioning coefficient) is > 5. Molecules violating more than one of these parameters may have problems with bioavailability and a high probability of failure to display drug-likeness [26].

Further, the topological polar surface area (TPSA) which is another key property in estimating drug bioavailability was also calculated. Generally, compounds with a TPSA ≥ 140 A°, are thought to have low bioavailability [27]. As shown in Table 8, all the synthesized compounds comply with these rules. Moreover, the compounds exhibited a greater percentage of absorption (%ABS) ranging from 84.70 to 98.6%. Hence, theoretically, all of these compounds should have good passive oral absorption and drug likeness. In addition to this different ADME predictions, such as BBB penetration, percentage of human intestinal absorption (HIA%), $CaCO_2$ permeability and percentage of plasma protein binding (PPB%) were predicted for all compounds. Analyzing the ADME predictions Table 9, it was observed that all the compounds showed high HIA% values in the range of 96.14–99.98% and are well absorbed. The $CaCO_2$ cell permeability values are moderate, ranging from 20.14 to 28.24 nm/s. Furthermore, all the compounds were strongly bound to plasma proteins with %PPB penetration > 90.46%. In addition, they were found to have moderate penetration (0.102–0.412) to the CNS through the BBB. From all these parameters, it can be observed that, theoretically, all the compounds exhibited good absorption and bioavailability with reasonable permeability through the BBB. Here we represent the 3D modelled binding modes within the binding domain of Peroxiredoxins **(**Fig. 5**).**

Table 9
Prediction of pharmacokinetic properties of compounds 3(a-m).

Compound	$CaCO_2$[a] permeability	HIA[b] (%)	PPB[c] (%)	BBB[d](Cbrain/Cblood)
3a	21.63	98.18	90.22	0.221
3b	28.62	94.66	96.27	0.120
3c	20.12	96.36	93.33	0.110
3d	24.46	96.12	92.14	0.106
3e	26.66	98.30	92.78	0.127
3f	24.16	98.82	96.28	0.135
3g	20.88	92.14	99.46	0.347
3h	21.23	97.30	99.18	0.261
3i	28.12	97.10	94.66	0.244
3j	20.99	98.76	94.08	0.347
3k	25.16	96.27	95.07	0.245
3l	24.60	99.14	95.42	0.286
3m	20.46	98.46	94.96	0.226

[a] Colon adenocarcinoma
[b] Human intestinal absorption
[c] Plasma protein binding
[d] Blood-brain barrier

6. Conclusions

In conclusion, we have successfully developed competent methodology for the synthesis of bis(indolyl)methanes at room temperature under aqueous conditions in high yields by the combination of aldehydes with indoles in the presence of meglumine catalyst. The notable advantages of the present methodology are clean reaction, ease of product isolation/purification, easily accessible reactants, metal free and environmentally friendly reaction conditions. These features make this procedure a green synthetic protocol. We believe that our present methodology will open a new route for the synthesis of bis(indolyl) methane derivatives. All the entitled compounds were characterized by IR, ^1H, ^{13}C NMR, mass spectra and evaluated for their antioxidant (DPPH, H_2O_2 and NO scavenging methods) activity, they exhibited potent in vitro antioxidant activity dose-dependently. The binding interactions and molecular docking studies for entitled compounds were studied against 3MNG protein. **4d** exhibited marked binding affinity with excellent docking score of −7.6 K.cal/mol and emerged as a lead compound.

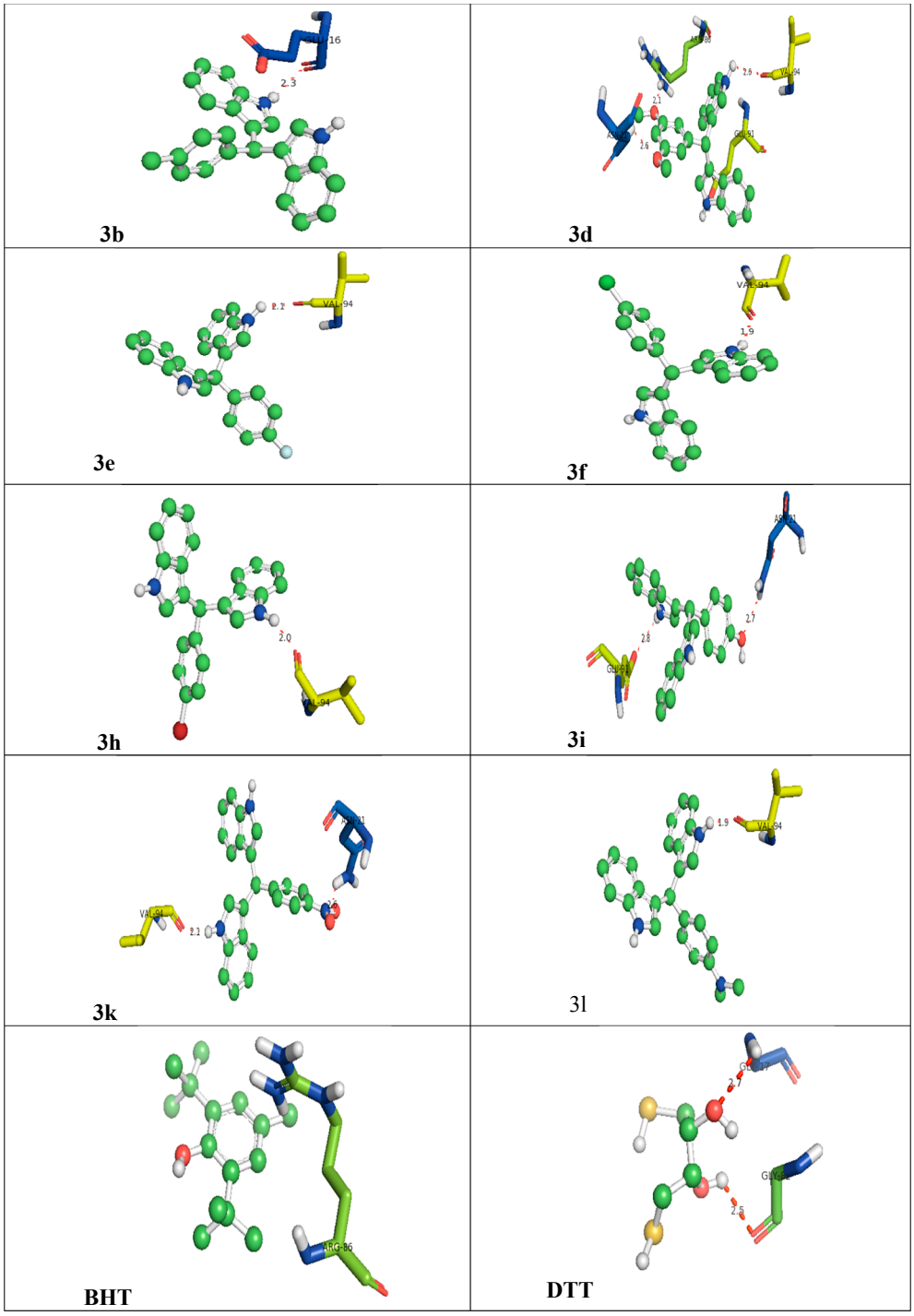


Fig. 5. Diagrammatic representation of the 3D modelled binding modes of compounds **3b, 3d, 3e, 3f, 3 h, 3i, 3 k, 3 l** and **DTT** (Native ligand) and **BHT** (Standard) within the binding domain of Peroxiredoxins.

7. Experimental

7.1. Chemistry

All the chemicals were purchased from commercial sources and used without further purification. Melting points were determined in open capillaries on a Mel-Temp apparatus and are uncorrected. The purity of the compounds was checked by thin-layer chromatography (TLC) (silica gel H, British Drug Houses (BDH), ethyl acetate/hexane, 1:3). Infrared (IR) spectra were recorded on a Thermo Nicolet IR 200 FT-IR spectrometer (Shimadzu Corporation, Kyoto, Japan) as KBr pellets, and the wave numbers are given in cm^{-1}. ^{1}H NMR spectra were recorded in $CDCl_3$/DMSO-d_6 on a Varian Mercury Plus spectrometer (Agilent Technology, California, USA) at 400 MHz. ^{13}C NMR spectra were recorded in $CDCl_3$/DMSO-d_6 on Varian Gemini spectrometer (Agilent Technology, California, USA) at 100 MHz. All chemical shifts are reported in δ (ppm) using tetramethylsilane as an internal standard. Mass spectra were recorded with PE Sciex model API 3000 spectrometer (Perkin Elmer, California, USA). The microanalyses were performed on a Perkin-Elmer 240C elemental analyzer (Massachusetts, USA). The progress of the reaction was monitored by TLC using silica gel plates (silica gel 60 F254 0.25 mm), and components were

visualized by observation under ultraviolet (UV) light (254 and 365 nm). Molecular docking studies [28] were carried against 3MNG protein and the reference drugs DTT and BHT, using the docking module implemented in Pyrx 2010.12 Initially the protein structures were protonated with the addition of polar hydrogens, followed by energy minimization with the MMFF94x force field, to get the stable conformer of the proteins. Flexible docking was employed, the inhibitor binding site residues were softened and highlighted through the "Site Finder" module implemented in the Pymol software. The grid dimensions were predicted as ° X: 28.27, Y: 27.13, Z: 28.51 for 3MNG respectively. The docking was carried out with the default parameters i.e., placement: triangle matcher, recording 1: London dG, refinement: force field and a maximum of 10 conformations of each compound were allowed to be saved in a separate database file in a mdb format. After the docking process, the binding energy and binding affinity of the protein–ligand complexes were calculated using Pymol viewer tool (www.pymol.org).The three-dimensional structure of Peroxiredoxins **(**PDB: 3MNG**)** and the reference drugs such as DTT (Pub Chem ID 446094) and BHT (Pub Chem ID 31404) were downloaded from the RCSB protein Data Bank and Pub chem. The atomic coordinates of the protein was estranged and geometry optimization was done using Argus Lab 4.0.1 [29]. The chemical structure of compounds were prepared using ChemBioDraw and converted all the ligands into Pdbqt file format and atomic coordinates were generated using Pyrx 2010.12. The active sites are the coordinates of the ligand in the original target protein grids, and these active binding sites of target protein were analysed using the Drug Discovery Studio version 3.0 and 3D Ligand Site virtual tools.

7.1.1. General procedure for the synthesis of bis(indolyl)methane derivatives 3(a-m)

To a stirred solution of substituted indole (**1**) (2.0 mmol) and carbonyl compound (**2**) (1 mmol) in H_2O (10 mL), meglumine (0.10 mmol) was added and continued the stirring at room temperature for 15 m and monitored by TLC. After completion of the reaction, precipitate was formed, filtered and washed with water. The resultant product was found to be pure enough for characterization.

7.1.1.1. 3,3′-(Phenylmethylene)bis(1H-indole) ***(3a)***. Red solid; Yield: 94%; mp: 140–142 °C; IR (KBr, cm^{-1}): 3315 (NH); ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 7.89 (s, 2H, NH), 7.28–6.62 (m, 15H, Ar—H), 5.91 (s, 1H, CH) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 144.4, 136.9, 129.7, 128.5, 127.4, 126.8, 123.4, 121.7, 120.3, 119.9, 118.6, 111.7 (aromatic carbons), 41.2 (CH) ppm. MS (EI) *m/z*: 322.4033 [M^+]; Anal. Calcd. for $C_{23}H_{18}N_2$: C, 85.68; H, 5.63; N, 8.69; Found: C, 85.78; H, 5.61; N, 8.90%.

7.1.1.2. 3,3′-(p-Tolylmethylene)bis(1H-indole) ***(3b)***. White solid; Yield: 96%; mp: 93–95 °C; IR (KBr, cm^{-1}): 3362 (NH); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.42 (s, 2H, NH), 7.41–6.97 (m, 14H, Ar—H), 5.91 (s, 1H, CH), 2.73 (s, 3H, CH_3) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 141.6, 136.6, 135.3, 130.8, 128.1, 127.6, 124.7, 121.3, 119.8, 119.4, 118.1, 111.9 (aromatic carbons), 41.5 (CH), 21.9 (CH_3) ppm. MS (EI) *m/z*: 336.4298 [M^+]; Anal. Calcd. for $C_{24}H_{20}N_2$: C, 85.68; H, 5.99; N, 8.33; Found: C, 85.81; H, 5.97; N, 8.56%.

7.1.1.3. 3,3′-((4-Methoxyphenyl)methylene)bis(1H-indole) ***(3c)***. Brown solid; Yield: 92%; IR (KBr, cm^{-1}): 3359 (NH); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.64 (s, 2H, NH), 7.73–7.14 (m, 14H, Ar—H), 5.71 (s, 1H, CH), 3.05 (s, 3H, OCH_3) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 158.3, 136.8, 135.4, 130.4, 127.5, 124.1, 122.5, 121.0, 120.6, 119.7, 113.9, 111.6 (aromatic carbons), 55.8 (OCH_3), 42.7 (CH) ppm. MS (EI) *m/z*: 352.1578 [M^+]; Anal. Calcd. for $C_{24}H_{20}N_2O$: C, 81.79; H, 5.72; N, 7.95; Found: C, 81.91; H, 5.74; N, 8.14%.

7.1.1.4. 3,3′-((3,5-dimethoxyphenyl)methylene)bis(1H-indole) ***(3d)***. Red solid; Yield: 89%; mp: 196–198 °C; IR (KBr, cm^{-1}): 3323 (NH); ^{1}H NMR (DMSO-d_6, 400 MHz) δ = 7.89 (s, 2H, NH), 7.19–6.68 (s, 16H, Ar-H), 5.85 (s, 1H, CH), 3.76 (s, 6H, 2-OCH_3) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz) δ = 161.4, 140.8, 136.3, 127.7, 123.9, 121.0, 119.7, 118.9, 116.5, 113.2, 111.8, 105.9, 97.6 (aromatic carbons), 55.8 (OCH_3), 42.4 (CH); MS (EI) *m/z*: 352.1578 [M^+]; Anal. Calcd. for $C_{25}H_{22}N_2O_2$: C, 78.51; H, 5.80; N, 7.32; Found: C, 78.62; H, 5.83; N, 7.57%.

7.1.1.5. 3,3′-((4-N,N-dimethylaniline)methylene)bis(1H-indole) ***(3e)***. Pink solid; Yield: 86%; mp 170–171 °C; IR (KBr, cm^{-1}): 3346 (NH); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.01 (s, 2H, NH), 7.61–6.68 (m, 14H, Ar-H), 5.88 (s, 1H, CH), 3.16 (s, 6H, CH_3) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 151.7, 137.5, 133.0, 130.2, 126.9, 123.7, 121.9, 118.5, 118.1, 117.3, 116.2, 111.1, 108.2 (aromatic carbons), 39.7 (CH), ppm. MS (EI) *m/z*: 365.4714 [M^+]; Anal. Calcd. for $C_{25}H_{23}N_3$: C, 82.16; H, 6.34 N, 11.50; Found: C, 82.28; H, 6.36; N, 11.75%.

7.1.1.6. 3,3′-((4-Fluorophenyl)methylene)bis(1H-indole) ***(3f)***. Red solid; Yield: 95%; IR (KBr, cm^{-1}): 3350 (NH); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.59 (s, 2H, NH), 7.20–6.83 (m, 14H, Ar—H), 5.75 (s, 1H, CH) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 162.5, 139.1, 136.2, 131.2, 128.1, 124.3, 123.1, 119.4, 119.1, 118.7, 116.0, 111.9 (aromatic carbons), 39.6 (CH) ppm. MS (EI) *m/z*: 340.3932 [M^+]; Anal. Calcd. for $C_{23}H_{17}FN_2$: C, 81.16; H, 5.03; N, 8.23; Found: C, 81.28; H, 5.05; N, 8.46%.

7.1.1.7. 3,3′-((4-Chlorophenyl)methylene)bis(1H-indole) ***(3 g)***. Red solid; Yield: mp: 74–76 °C, 88%; IR (KBr, cm^{-1}): 3328 (NH); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.94 (s, 2H, NH), 7.06–6.64 (m, 14H, Ar—H), 5.88 (s, 1H, CH) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 143.7, 137.4, 132.5, 131.6, 129.1, 128.9, 124.7, 123.3, 119.7, 119.1, 118.6, 111.2 (aromatic carbons), 39.6 (CH) ppm. MS (EI) *m/z*: 356.8479 [M^+]; Anal. Calcd. for $C_{23}H_{17}ClN_2$: C, 77.41; H, 4.80; N, 7.85; Found: C, 77.55; H, 4.81; N, 8.06%.

7.1.1.8. 3,3′-((2-Chlorophenyl)methylene)bis(1H-indole) ***(3 h)***. Pink solid; Yield: 91%; mp: 71–73 °C, IR (KBr, cm^{-1}): 3332 (NH); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.71 (s, 2H, NH), 7.19–6.54 (m, 14H, Ar—H), 6.52 (s, 1H, CH); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 141.3, 136.2, 134.1, 131.2, 129.5, 126.6, 126.1, 125.7, 124.6, 122.7, 119.7, 119.3, 118.4, 111.3 (aromatic carbons), 36.2 (CH) ppm. MS (EI) *m/z*: 356.8479 [M^+]; Anal. Calcd. for $C_{23}H_{17}ClN_2$: C, 77.41; H, 4.80; N, 7.85; Found: C, 77.54; H, 4.82; N, 8.09%.

7.1.1.9. 3,3′-((4-Bromophenyl)methylene)bis(1H-indole) (3i). Pink solid; Yield: 87%; mp: 111–113 °C, IR (KBr, cm^{-1}): 3341 (NH); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.88 (s, 2H, NH), 7.07–6.62 (m, 14H, Ar—H), 5.87 (s, 1H, CH); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 144.2, 137.8, 132.4, 131.6, 128.4, 124.8, 123.2, 120.7, 119.9, 119.5, 119.1, 111.2 (aromatic carbons), 39.9 (CH) ppm. MS (EI) *m/z*: 401.2979 [M^+]; Anal. Calcd. for $C_{23}H_{17}BrN_2$: C, 68.84; H, 4.27; N, 6.98; Found: C, 68.97; H, 4.29; N, 7.19%.

7.1.1.10. 3,3′-((4-Hydroxyphenyl)methylene)bis(1H-indole) ***(3j)***. Red solid; Yield: 84%; IR (KBr, cm^{-1}): 3318 (NH), 3554 (OH); mp: 121–123 °C, ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 10.8 (s, 2H, NH), 9.04 (s, 1H, OH), 7.06–6.71 (m, 14H, Ar—H), 5.92 (s, 1H, CH) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 156.1, 136.6, 135.4, 129.7, 126.3, 123.9, 120.8, 119.5, 118.2, 117.8, 114.3, 111.2 (aromatic carbons), 38.9 (CH) ppm; MS (EI) *m/z*: 338.4020 [M^+]; Anal. Calcd. for $C_{23}H_{18}N_2O$: C, 81.63; H, 5.36; N, 8.28; Found: C, 81.76; H, 5.38; N, 8.50%.

7.1.1.11. 3,3′-((4-Nitrophenyl)methylene)bis(1H-indole) ***(3 k)***. Yellow solid; Yield: 90%; mp: 218–220 °C, IR (KBr, cm^{-1}): 3366 (NH); ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 7.57 (s, 2H, NH), 7.09–6.87 (m, 14H, Ar—H), 5.91 (s, 1H, CH); ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 153.7,

146.7, 135.5, 128.4, 127.2, 122.2, 121.8, 120.9, 118.8, 118.2, 116.3, 114.2 (aromatic carbons), 40.1 (CH) ppm. MS (EI) *m/z*: 367.4006 [M^+]; Anal. Calcd. for $C_{23}H_{17}N_3O_2$: C, 75.19; H, 4.66; N, 11.44; Found: C, 75.33; H, 4.68; N, 11.65%.

7.1.1.12. 3,3′-((3-Nitrophenyl)methylene)bis(1H-indole) ***(3 l)***. Yellow solid; Yield: 93%; mp: 220–222 °C, IR (KBr, cm^{-1}): 3372 (NH); ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 7.83 (s, 2H, NH), 7.12–6.97 (m, 2H, Ar−H), 5.88 (s, 1H, CH); ^{13}C NMR (DMSO-d_6, 100 MHz): δ = 147.5, 145.4, 136.9, 133.9, 129.6, 126.7, 123.9, 124.6, 123.3, 122.5, 119.1, 119.4, 118.3, 111.3 (aromatic carbons), 40.1 (CH). MS (EI) *m/z*: 367.4035 [M^+]; Anal. Calcd. for $C_{23}H_{17}N_3O_2$: C, 75.19; H, 4.66; N, 11.44; Found: C, 75.29; H, 4.67; N, 11.64%.

7.1.1.13. 3,3′-((4-Phenylnitrile)methylene)bis(1H-indole) ***(3 m)***. Slight brown solid, Yield: 85%; mp 205–207 °C; IR (KBr, cm^{-1}): 3357 (NH), 1592 (C═N); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.96 (s, 2H, NH), 7.64–6.89 (m, 14H, Ar-H), 5.97 (s, 1H, CH) ppm; ^{13}C NMR (DMSO-d_6, 100 MHz): δ 150.9, 136.8, 132.7, 129.5, 126.4, 123.3, 121.5, 118.9, 118.8, 118.3, 116.7, 111.6, 108.9, 38.8 (CH), ppm (aromatic carbons). MS (EI) *m/z*: 347.4124 [M^+]; Anal. Calcd. for $C_{24}H_{17}N_3$: C, 82.97; H, 4.93; N, 12.10; Found: C, 83.06; H, 4.94; N, 12.33%.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bioorg.2019.03.005.

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