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BRONSTED ACID PROMOTED FOR THE SIMPLE AND EFFICIENT BIOACTIVE SYNTHESIS OF BIS (INDOLYL) METHANE DERIVATIVES.

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ABSTRACT

This work presents a highly an efficient and simple method for the synthesis of bis(indolyl)methanes employing an efficient, mild and inexpensive methane sulfonic acid catalyst was used for the synthesis of derivatives of 3, 3′- (Phenyl methylene)bis (1*H*-indole)from indole and substituted aromatic aldehydes in protic solvent under reflux condition. The titled compounds confirmed by advanced spectral data (^{1}HNMR, ^{13}NMR & LCMS) and also structure of the compounds determined by elemental analysis.This method is an environmentally benign, efficient reaction, requires shorter reaction time and simple experimental and workup procedures.

KEYWORDS: Indole, substituted aromatic aldehydes, methane sulfonic acid, derivatives of 3, 3′- (Phenyl ethylene) bis (1*H*-indole).

INTRODUCTION

Functionalized nitrogen-heterocyclic compounds play a significant role in medicinal chemistry and they have been intensively used as scaffolds for development of drug moiety. Indole and its derivatives showed an important role in synthetic chemistry as well as Medical chemistry. These compounds having fused ring system and also nitrogen class of heterocyclic compound. Hence, these are most attracting significant synthetic interest due to their agrochemicals and pharmaceuticals properties. Synthesis of bis (indolyl) alkane has been developed considerable interest in organic synthesis due to their in different natural products having biological potent activity.[1] and usefulness for drug design.[2] The main focus of Indoles and their derivatives used as antibiotics in the field of pharmaceuticals.[3] It was particularly affectedon the central nervous system and alsois used as tranquilizers. Its effect in the cure of the cancer due to its ability to modulate certain cancer causing estrogen metabolites.[4] Bis (indolyl) alkane and their derivatives having an important moiety of bioactive metabolites of terrestrial. Substituted bis (indolyl) alkane and their derivatives focused mainly in feature widely in Pharmacology, medicinal and biochemistry. The indole ring system is present in many natural products, pharmaceuticals, agrochemicals, and other compounds of importance. They are known to exhibit various biological activities including antibacterial, cytotoxicity, antioxidative and insecticidal activities.[5-16] The feasibility of electrophonic substitution at the 3-position of indole is such that it is widely used in organic synthesis3. Bis (indolyl)methanes have been obtained by reactions of indoles with various aldehydes via azafulvenium salt as intermediate form in the presence of several Bronsted. These compounds can be synthesized from the reaction of indoles with different functionalized aromatic aldehydes and ketones. several number of producers have been reported in the literature for the preparation of bis(indolyl)methane in which protic acids,[6] as well as Lewis and other acids, such as $LiClO_4$[17] Lewi'sacid catalysts as.[18] hexamethylenetetramine–bromine,[19] $ZrOCl_2$[20] Silica-bonded S-sulfonic acid,[21] Cellulose sulfuric acid.[22] polystyrene-supported aluminum chloride (PS-$AlCl_3$).[23] N,N,N,N-Tetrabromobenzene-1,3-disulfonamide (TBBDA) andpoly(N-bromobenzene-1,3-disulfonamide) (PBBS),[24] FeCl3.6H2O.[25] CeCl3.7H2O.[26] CuBr.[27] Ionic liquid 3-methyl-1-sulfonic acid imidazolium chloride.[28] Tetra butyl ammonium hydrogen sulfate.[29] Silica supported sodium hydrogen sulfate and amberlyst-15.[20] RuCl3•3H2O.[21] Heteropoly acids.[30,31] A-Chymotrypsin.[24] antimony Trichlorate.[32] phase-transfer catalytic (PTC)[33] [Et3NH][H2PO4][34] 1,3-dibromo-5,5-dimethylhydantoin(DDH)[35] Polymersupported dichlorophosphate (PEG-$OPOCl_2$)[36] Potassium tert-Butanolate.[37] fruit juice of Citrus lemon.[38] One of the alternative goals for organic synthesis is to minimize the use of harmful organic solvents. For this causes, over the last few two decades enormous advances have been made to achieve the environment friendly chemical processes. One way for this purpose is carrying out the reactions in solvent-free conditions.[39] In the present article, we report a facile

route using methane sulphonic acid as an efficient catalyst for the synthesis of widespread range ofbis (indolyl) methanes derivatives. It is non-explosive, easy handling, eco-friendly, stable and commercially available acid catalyst.

METHODS AND MATERIALS

All aldehydes and other regents, solvents required for the reactions and catalysts are commercially available, and were purchased and used without further purification solvents required for the reactions and they were procured from Sigma-Aldrich. The melting points of the newly obtained derivatives were measured by using a Agrawal 535 melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a 400 MHz NMR Bruker spectrometer, and ^{13}CNMR spectra were recorded on 100 MHz NMR Bruker spectrometer, respectively, using $CDCl_3$ as solvent at ambient temperature. Purity of the compounds checked by TLC. Merck recoated silica gel plates (60 F254). Chemical shifts are given in ppm. Methane sulphonic acid is commercially available and was purchased and used without further purification; water and other solvents were distilled before use. Although methane sulphonic acid has been known as a commercially available as an organic acid, this acid itself has attracted little attention from the synthetic community, mainly due to it's extremely solubility in organic solvents. Recently, some groups have developed a new Bronsted acid from the acid scaffold, which has been successfully used in organic synthesis of the titled product.

General procedure

Take clean and dry four necks 50mL RBF.A mixture of substituted aromatic aldehydes (2.125mmol.), indole (4mmol.) and methane sulphonic acid (10mL) introduced in a RBF and reaction mixture was stirred at room temperature for appropriate period of time on magnetic stirrer. After completion of the reaction, checked by TLC as a mobile phase (Ethylacetate:n: n-hexane = 4:6).The mixture of crude was taken in Ethylacetate:n as a solvent and added to the reaction mixture with aqueous solution of saturated sodium carbonate solution and separated the organic layer. The organic layer was distilled off under vacuum; get desired product and compound purified by column chromatography pure bis (indolyl) alkane which was characterized by spectral methods.

The spectral data of some of the bis (indolyl) methane summarized below

1) 1).3,3′-(Phenyl methylene)bis(1*H*-indole)(3a)

palepinksolid;Rf=0.43(EtOAc;n-hexane=4:6); **^{1}HNMR(400MHz,$CDCl_3$)**δppm:10.098(s,2H,NH), 7.634-7.426 (m,4H,Ar-CH), 7.245—7.179(m,4H,Ar-CH),7.148(t,J=8.0Hz, 1H, Ar-CH), 7.104(t,J=7.6 Hz, 2H, Ar-CH), 6.884(t, J=6.8 Hz, 2H, Ar-CH), 6.782(d,J=7.6 Hz, 2H, Ar-CH), 5.204(s, 1H, CH); **^{13}CNMR(100MHz,$CDCl_3$)** δppm:143.58,136.76,128.98,128.25, 127.44,125.54,122.59,121.86, 120.10,118.95,117.87, 112.58, 42.87.LCMS(m/z): 321.46 (M-H); Molecularformula:$C_{23}H_{18}N_2$. Elemental analysis: Calculated: C-85.68,H- 5.63, N- 8.69, Obtained: C-85.60, H-5.61, N- 8.76.

2) 3,3'-((4-Hydroxylphenyl) methylene) bis (1H-indole)(3b)

Pale red solid, Rf=0.47 (EtOAc; n-hexane =4:6); ^{1}H-NMR (400 MHz, $CDCl_3$) δppm: 10.025 (s, 2H,NH), 8.889 (s, 1H,-OH),7.452 (d, J = 6.8 Hz, 2H,Ar-H), 7.294 (d,J = 8.0 Hz, 2H,Ar-H), 7.196 (d, J = 7.2 Hz, 2H,Ar-H), 7.104 (t, J = 7.6 Hz, 2H,Ar-H), 6.928 (t, J = 5.6 Hz, 2H,Ar-H), 6.782 (s, 2H,Ar-H), 6.658 (d, J = 8.4 Hz, 2H,Ar-H), 5.248 (s, 1H,CH). 13C NMR (100MHz,CDCl3),δppm:146.23,141.45,136.53,130.56,129.22,128.65,126.44,125.54,123.08, 121.95, 120.53, 119.06, 118.41,115.57,112.28,48.96 .LCMS(m/z):337.33 (M-H): Molecular formula:$C_{23}H_{18}N_2O$: Elemental analysis: Calculated: C-81.63 ,H-5.36 , N-8.28 , Obtained : C-81.55 ,H-5.34, N-8.34.

3) 3, 3'-(4-methylphenyl) methylene) bis (1*H*-indole)(3c)

Bricked solid.;Rf=0.45 (EtOAc ; n-hexane =5:5); **^{1}HNMR(400 MHz,$CDCl_3$) δppm**: 10.146(s, 2H,NH),7.894 (d,J =6.8 Hz,2H,Ar-H), 7.656 (dd, J = 4.6 Hz, 2H,Ar-H), 7.436 (d, J = 8.8 Hz,2H,Ar-H), 7.118 (d, J = 7.6 Hz, 2H,Ar-H), 7.078 (d, J = 7.2 Hz, 2H,Ar-H),6.780(d,J=4.8Hz,2H,Ar-H),),5254(s,1H,CH), 1.587(s,3H,CH3);**^{13}CNMR(100MHz, $CDCl_3$)δppm:**144.67,141.12,137.59,128.87,128.45, 127.25,124.87,122.88,121.46,120.08,119.02,112.22,52.14,22.04;LCMS(m/z);337.63(M+H).$C_{24}H_{20}N_2$.Elemental analysis: Calculated: C-85.68, H-5.99, N-8.33, Obtained: C- 85.61,H-5.98, N-8.40.

4)33′-[(4-Fluorophenyl) methylene] bis (1*H*-indole)(3d):

paleredsolid,Rf=0.45(EtOAc;n-hexane=5:5);**^{1}HNMR**(400MHz,$CDCl_3$)δppm:10.124(s,2H,NH), 7.544(d,J=7.6Hz, 2H),7.259-7.148(m,4H,Ar-H),7.111-6.898(m,6H,Ar-H),5.450(s.2H,pyrrole ring),4.809(s,1H,CH-);**^{13}CNMR** (100MHz,$CDCl_3$)δppm: 155.87,143.25,133.88,130.57,128.93, 128.11,125.02, 122.49, 120.37,118.61, 117.27, 114.53, 110.88; LCMS(m/z):342.23(M+2).Molecularformula:$C_{23}H_{17}FN$. Elemental analysis: Calculated: C-85.16, H-5.03, N-8.23,Obtained: C-81.11, H-5.01, N-8.29.

5).3, 3′-[(4-Bromophenyl) methylene] bis (1*H*-indole)(3e)

Pink red solid, Rf-0.45 (EtOAc/n-hexane = 3:7). **^{1}H-NMR ($CDCl_3$)**δppm: 10.589 (s, 2H, N–H), 7.948 (d, J = 8.0 Hz,1H, Ar–H), 7.646 (d, J = 8.8 Hz, 2H, Ar–H), 7.478 (d, J = 7.6 Hz, 2H, Ar–H), 7.384–7.282 (m, 4H, Ar–H),7.183 (dt, J = 6.8, Hz, 1H, Ar–H), 7.112 (dt, J=8.0Hz,2H,Ar–H),6.957(dd,J=7.6,Hz,2H,Ar–H),5.244(s,CH,1H).^{13}C-NMR ($CDCl_3$) δppm:148.96, 138.66,132.79,130.18,128.84,128.24,127.52,126.51,124.85,122.64,121.59,119.46,

118.84,111.58,40.75.LCMS(m/z)=402.18(M+2),Molecularformula:$C_{23}H_{17}N_2Br$;Elemental analysis: Calculated:C-68.83, H-5.02, N-6.97, Obtained: C-68.76, H-5.01, N-7.09.

6).3,3'-((2,5-dimethoxyphenyl)methylene)bis(1H-indole) (3f).
Pale red Solid; Rf=0.45 (EtOAc ; n-hexane =5:5); **^{1}H NMR(400 MHz, $CDCl_3$)** δppm:8.547 (s,2H, NH), 7.431–6.864 (m, 6H, Ar-H), 6.759 (s,Ar-H,2H), 5.147 (s, IH, Ar-CH-), 3.628 (s, 3H, OCH3), 3.562 (s, 3H,OCH3); 13C NMR (100 MHz, CDCl3) δppm:152.74, 150.53, 136.06, 134.96, 128.92, 124.64, 122.67, 121.09, 119.78,118.23, 116.56, 112.77, 110.48, 108.96, 56.35, 55.74,31.82;LCMS(*m/z)*:383.41(M+H);
Molecularformulae:$C_{25}H_{22}N_2O_2$: Elementalanalysis: Calculated: C-78.51; H- 5.80; N- 7.32; Obtained: C,-78.45, H- 5.78; N-7.95.

7).4-(Di (1H-indol-3-yl) methyl) benzonitrile (3g):
White Solid;.Rf=0.45 (EtOAc ; n-hexane =5:5);**^{1}H NMR (400MHz, $CDCl_3$)**: 10.715 (s,NH,2H), 7.759 (d,J = 7.6 Hz, 2H,Ar-H),7.546 (d,J = 8.4Hz,2H,Ar-H),7.417-6.984 (m,8H,Ar-H),6.854 (s,2H,Ar-H),4.575(s,1H,Ar-H).^{13}C NMR (100MHz,$CDCl_3$): ppm:144.15, 135.57, 132.06, 129.34, 128.67,124.77,122.66,120.80,119.53, 118.82,117.47,110.9, 108.9, 40.8. ; LCMS (m/z): 348.08 [M + H]: Molecular formula: $C_{24}H_{17}N_3$.Elemental analysis: Calculated: C-82.95; H-4.92; N- 12.10; Obtained: C,-82.88, H-4.90; N-12.19.

Antibacterial assay
The antibacterial activities of the newly synthesized derivatives were determined by the well diffusion method. Three to five identical colonies from each agar plate were lifted with a sterile wire loop and transferred into a tube containing 5 ml of nutrient agar. The turbidity of each bacterial suspension was adjusted to reach an optical comparison to that of a 0.5McFarland standard; resulting in a suspension containing approximately 1–2 108CFU/ml. Nutrient agar plates were inoculated by streaking the swab over the entire sterile agar surface. This procedure was repeated by streaking two more times, rotating the plate approximately each time to ensure uniform distribution of the inoculums. As a final step, the rim of the agar was also swabbed. After allowing the inoculums dry at room temperature, 6 mm diameter wells were prepared in the agar with the help of sterilized cork borer. The different concentrations of the test compounds (100–150mg/ml) were prepared by dissolving in dimethyl sulphoxide (DMSO) and introduced into duplicate wells. The plates were incubated at 37C for24 h. Subsequently, the plates were examined for bacterial growth inhibition and the inhibition zone diameter measured to the nearest millimeter. The standard antibiotic (streptomycin) was used as positive control, whereas, the equivalent amount of solvent (DMSO) did not exhibit any activity in the assay.

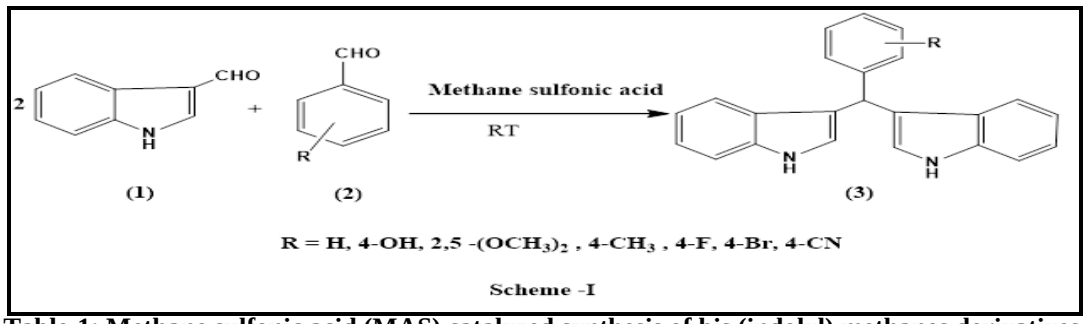
Antifungal assay
The method followed for antifungal bioassay of newly synthesized compounds is similar to that followed for antibacterial assay, where the mediums PDA 39 g/l. All the test compounds were examined for their antifungal activity at concentration 100–150mg/ml using DMSO as a solvent. The solvent did not exhibit any activity at the concentrations used. The treated and the controls were kept in an incubator at 28^0C for 48 h and inhibition zones were measured to the nearest millimeter. Three replicates were maintained for each treatment. Ketonozole was used as standard drug for this activity.

RESULTS AND DISCUSSION

As a part of our research work, we aimed to improve this methodology for yield and short reaction time by using methane sulphonic acid as the reaction catalyst or by performing organic transformations under solvent-free conditions at RT .We observed the use of novel small organic acid catalysts which is able to capable of promoting electrophilic substitution reactions of indole derivatives with different substituted aromatic aldehydes.

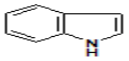
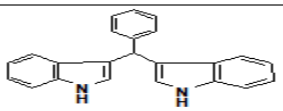
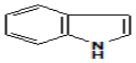
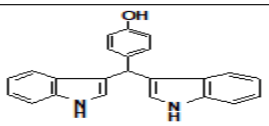
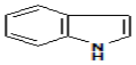
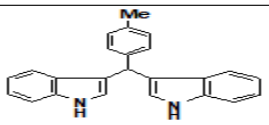
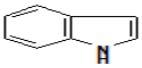
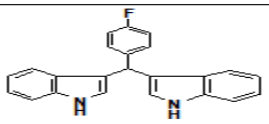
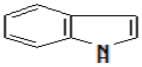
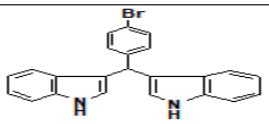
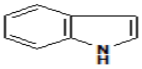
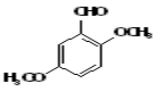
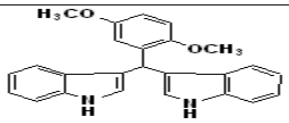
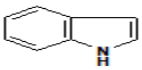
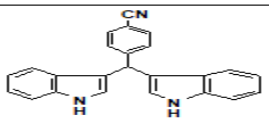
As a model of this reaction, substituted aromatic aldehydes were reacted with indole with different loadings of starting material, solvent and catalyst. It was observed that by simple mixing of substituted aromatic aldehydes (1 mmol) and indole (2 mmol), in the presence of methane sulphonic acid (10 mL), the desired product was obtained maximum yield 92%. (Scheme - 1).Encouraged by these successful results, we studied different aromatic aldehydes under optimized conditions to better understand the scope and generality of this simple procedure.

(Table-1)
A series of substituted aromatic aldehydes underwent an electrophilic substitution reaction with indole to afford a wide range of substituted bis (indolyl) methanes in good to excellent yields. This method is equally effective for substituted aromatic aldehydes containing electron withdrawing or donating groups. Furthermore, acid sensitive aldehydes worked well without any decomposition or polymerization under these reaction conditions.



Scheme -I

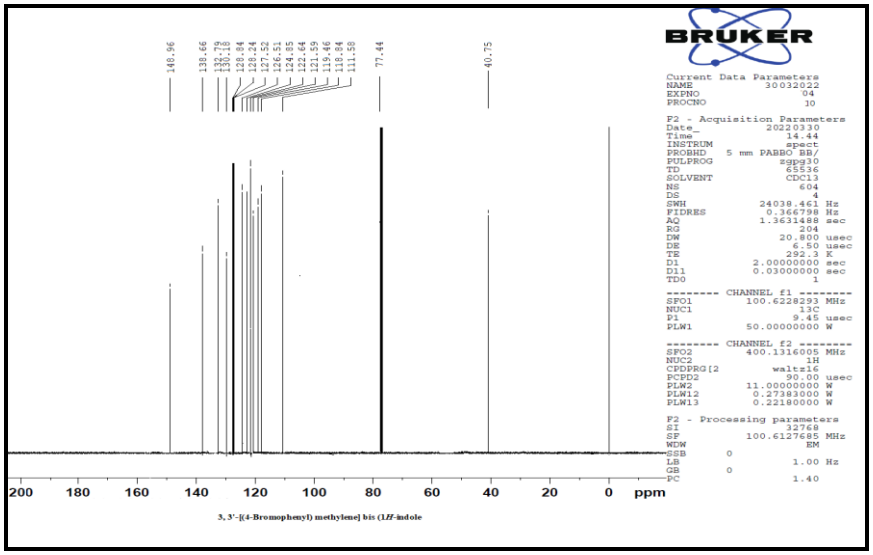
Table-1: Methane sulfonic acid (MAS) catalyzed synthesis of bis (indolyl) methanes derivatives.

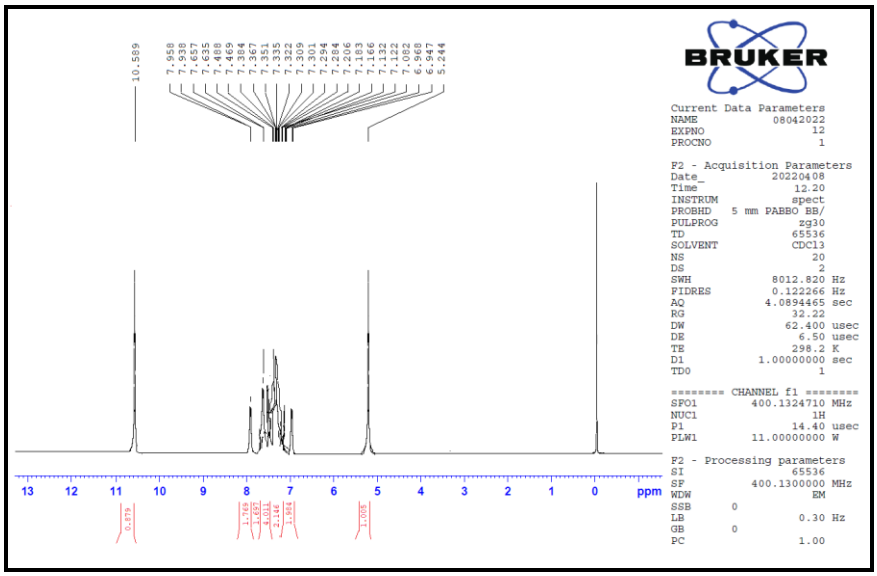
Entry	Indole	Aryl aldehyde	Product	Time (min)	Yield (%)	mp ^{0}C
1				40	86	144-146
2				30	91	124–126
3				10	90	189-191
4				45	90	236-238
5				75	89	258-260
6				75	92	245-247
7				90	87	212-214

Antibacterial activity

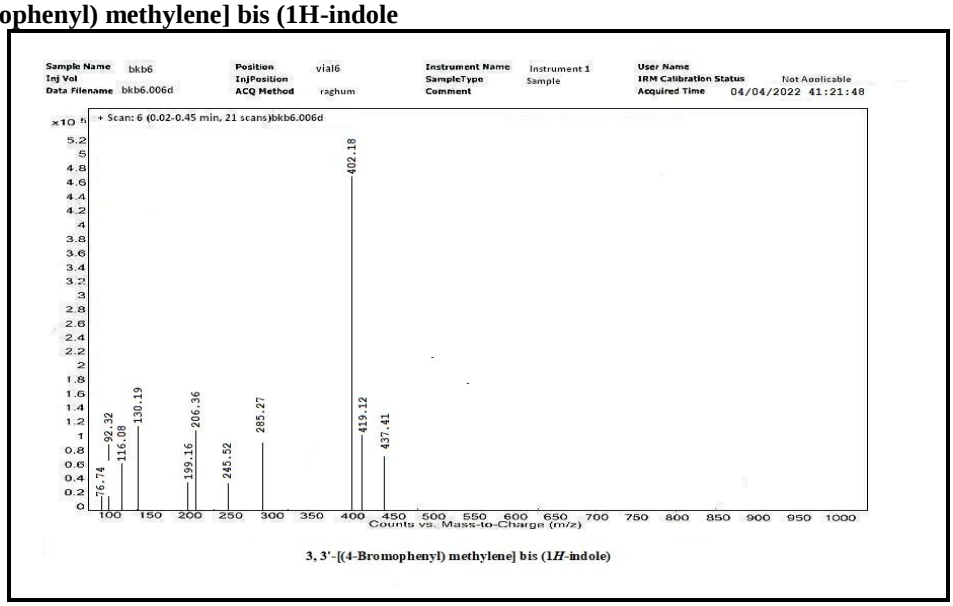
Table-I: Antimicrobial activity screening activity synthesized scaffold.

Comound Code	*Zone of inhibition in (mm)					
	Bacteria				Fungi	
	P.aeruginsa	E.coli	S. typhi	B.substills	A. niger	C. albicans
3a	07	09	06	07	08	07
3b	20	21	18	20	18	17
3c	17	20	18	19	16	15
3d	24	21	23	20	17	21
3e	22	20	20	23	17	14
3f	20	19	18	18	15	15
3g	16	07	04	06	04	06
Streptomycin	30	30	28	28	NA	NA
Ketoconazole	NA	NA	NA	NA	25	25
DMSO	---	----	---	---	---	---





3, 3′-[(4-Bromophenyl) methylene] bis (1H-indole



Amongst all the synthesized compounds were screened for their antibacterial activity against *P.seudomona aeruginosa*, *Escherichia coli*, as Gram-negative bacteria, *Bacillus subtilis Staphylococcus aureus* as Gram-positive bacteria and the antifungal activity was evaluated against yeast *Candida albicans*, *Aspergillus Niger*.The inhibitory zones(in mm) were evaluated by using agar well method(cup plate method). Antibiotic, streptomycin and Ketonozole were used as standard drug controls against bacteria and fungi, respectively. In all tests were performed and determined in duplicate and results were reports submitted as mean of at least three determinations. Table II showed that all the tested compounds showed moderated to good antibacterial activity. Compounds 3e and 3f showed significant inhibition against all the bacteria tested. In compounds 3a and 3g were no effect of activating or deactivating substituent's on the aryl ring in their inhibitory activity and observed to be less potent than the other compounds tested. Moreover, these derivatives such as 3a and 3g were low active against the tested bacteria. The incorporation of 5-cyano aromatic aldehydes **(3g)** group in BIM retarded the activity in all the strains except P. Aeruginosa than the corresponding rest of the bacterial strains. Similarly,5-Fluorophenyl derivative (3g) and 5-bromo phenyl derivatives was found to be more potent activity than the corresponding "3b and 3c" derivative. The significant inhibition showed by the compounds 3b and 3c might be due to the presence of bromo and flouro group on the fifth position of their corresponding.

Antifungal activity

The investigation of antifungal activity newly derivatives were examined data from Table III represented that the all tested compound screened moderate to good fungal inhibition. Compounds 3q and 3s were active against all the fungal species. The 5-fluro and 5-bromophenyl derivatives exhibited excellent inhibitory activity against all the two fungal strains than the corresponding 3b,3c derivatives.

3. CONCLUSION

In summary, we have developed an efficient synthetic protocol for the synthesis of BIMs from different functionalized aromatic aldehydes and indoles using 0.5 mol% methane sulphonic acid under mild conditions. This simple protocol has the advantages of environmental friendliness, higher yields, shorter reaction times and convenient operation, which only requires stirring the reaction mixture at ambient temperature. the synthesized compounds using this method have been evaluated for their antibacterial and antifungal activities. Almost all the compounds showed moderate to good antibacterial and antifungal activities.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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