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TFA PROMOTED FOR BIOACTIVE SYNTHESIS OF 3, 3′- (PHENYL METHYLENE) BIS (1*H*-INDOLE) DERIVATIVES.

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ABSTRACT

An efficient, mild and inexpensive TFA catalyst was used for the synthesis of derivatives of 3, 3′- (Phenyl methylene) bis (1*H*-indole). These derivatives synthesized from indole and substituted aromatic aldehyde in protic solvent under reflux condition. The characterization of the titled compounds evaluated by spectral data (1HNMR, 13NMR & LCMS). In addition to the compounds study in biological properties.

KEYWORDS: Indole, substituted aromatic aldehyde, TFA, derivatives of 3, 3′- (Phenyl methylene) bis (1*H*-indole), Antimicrobial activities.

1. INTRODUCTION

Nitrogen functionalized containing fused heterocycles compounds are play a predominant role in medicinal chemistry and synthetic organic chemistry. They have been intensively used as scaffolds for drug development in pharmacological properties. Hence, these are most attracting significant synthetic interest due to their pharmaceuticals and agrochemicals activities. Synthesis of bis (indolyl) alkane has been developed considerable interest in organic synthesis because of their in different natural products containing biological activity[1] and usefulness for drug design.[2] The utilities of Indoles and their derivatives in antibiotics in the field of pharmaceuticals.[3] These derivatives used as tranquilizers due to affect in the central nervous system Its effect in the prevention of cancer due to its ability to modulate certain cancer causing estrogen metabolites.[4] Bis (indolyl) alkane and their derivatives constitute an important group of bioactive metabolites of terrestrial. The feature of substituted indole derivatives have widely in Pharmacology, medicinal and biochemistry.[5] These compounds can be synthesized from the reaction of indoles with various substituted aromatic aldehydes and ketones. The several number of methods 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 $LiClO_4$[7], Lewis acid catalysts such as I_2[8], hexamethylenetetramine–bromine[9], $ZrOCl_2$[10], p-toluenesulfonicacid[11], [bnmim][HSO_4][12], NH_4Cl[13], $AlPW_{12}O_{40}$[14], TPA-ZrO_2[15], $Zr(DS)_4$[16], sulfamicacid[17], $ZrCl_4$[18], trichloro-1, 3, 5-triazine[19] and $ZrOCl_2$ $8H_2O$–silica gel.[20] Severalcatalystincluding lanthanide triflate[21] $Dy(OTf)_3$[22], $InCl_3$[23], PPh_3-$HClO_4$[24], montmoriloniteK-0[25], NBS[26], KHSO4[27], $RE(PFO)_3$ [28], InF_3[29], and acidic ionic liquid[30] were found to promote the reaction. Recently, Shingare and co-workers reported synthesis of few derivatives of bis(indolyl)methanes using cellulose sulfuric acid.[31] In the present article, we report a facile route using Cellulose Supported Perchloric Acid (CSPA) as an efficient catalyst for the synthesis of widespread range of bis(indolyl)methanes derivatives. It is non-explosive, easy handling, eco-friendly, stable and recoverable solid acid catalyst.

The present work, the synthesis of titled compounds in the presence of trifluoro acetic acid as catalyst and ethanol as solvent and uses the various aromatic aldehydes means both electron donating groups as well as electron withdrawing groups and also evaluated biological activities.

2. METHODS AND METIARLS

2.1. Experimental

All the synthetic grade reagents and analytical chemicals were procured from Meric and Fine chemicals. Organic solvent used as absolute alcohol. The melting point of the all newly synthesized compounds were find out using an Agrwal thermal apparatus and uncorrected. The NMR spectra of selective compounds were recorded on a Bruker for 400 1H NMR spectra and 100 MHz for 13C NMR spectra in CDCl3 solvent using TMS as internal standard. Chemical shifts (δ) are referred in terms of ppm and J -coupling constants are given in Hz. Abbreviations for multiplicity is as follows: s (singulet), d (doublet), t (triplet), q (quadruplet), m (multiplet). The reaction was monitored by thin layer chromatography using silica gel as an adsorbent and ethyl acetate-hexane in different ratios as eluent. All the synthesized compounds find the molecular weight using LCMS. All chemicals, reagents,

solvents and also starting materials required for the reactions were procured from Sigma-Aldrich with and used without further purification. The newly synthesized sized derivatives were characterized using ^{1}H NMR, 13C NMR spectra.

2.2. General procedure

A mixture of substituted aromatic aldehydes (2.15 equiv.), indole (4.0equiv.) and trifluoro acetic (l00mg) was stirred at room temperature for fixed period of time on magnetic stirrer. On completion of reaction, the progress of the reaction monitored by TLC (Ethylacetae: n-hexane). The crude was taken in Ethylacetae as a solvent and added to the reaction mixture with aqueous solution of sodium bi carbonate solution and separated the desired product. The compound purified by Coloumnchromotogrphy. Pure bis (indolyl) alkane which was characterized by spectral methods. The spectral data of some of the bis (indolyl) methanes i**s** summarized below.

Characterization of the Titled compounds

2.2.1. 3, 3′-(Phenyl methylene)bis(1*H*-indole) (3a)

Yield=85%;Paleredsolid;m.p-174—176°C:^{1}HNMR(400MHz, $CDCl_3$)δppm:10.245(s, 2H, N-H), 7.652-7.276(m, 4H, Ar-H), 7.255-7.167(m, 4H, Ar-H), 7.126(t, J=8.8 Hz, 1H, Ar-H), 7.066 (t, J=7.6 Hz, 2H, Ar-H), 6.943(t, J=7.2 Hz, 2H, Ar-H), 6.789(d, J=7.6 Hz, 2H, Ar-H), 5.118(s, 1H, CH); ^{13}C NMR(100 MHz, $CDCl_3$) δ ppm: 144.68, 135.26, 129.53, 128.55, 127.32, 125.84, 122.69, 122.44, 120.35, 119.85, 116.67, 112.48, 42.87. Molecular formula: $C_{23}H_{18}N_2$.LCMS(m/z):323.46(M+H).

2.2.2. 3, 3'-((4-Hydroxylphenyl) methylene) bis (1H-indole) (3b)

Yield=90%; Pale red solid, m.p: 190–192 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δppm: 10.149 (s, 2H, N-H), 9.026 (s, 1H, N-H), 7.328 (d, J = 7.2 Hz, 2H, Ar-H), 7.242 (d, J = 7.2 Hz, 2H, Ar-H), 7.186 (d, J = 8.8 Hz, 2H, Ar-H), 7.078 (t, J = 7.4 Hz, 2H, AR-H), 6.884 (t, J = 7.6 Hz, 2H, Ar-H), 6.882 (s, 2H, Ar-H), 6.758 (d, J = 8.4 Hz, 2H, Ar-H), 5.148 (s, 1H, -CH-). ^{13}C NMR (100 MHz, $CDCl_3$)δppm:147.93, 141.85, 135.83, 130.76, 128.89, 128.45, 127.74, 126.84, 123.68, 122.49, 121.83, 119.66, 118.81, 115.72, 112.88, 49.26. Molecularformule: $C_{23}H_{18}N_2O$. LCMS (m/z):337.08(M-H).

2.2.3. 3, 3'-(4-methylphenyl) methylene) bis (1*H*-indole) (3c)

Paleredsolid. Yeild:91 %; m.p- 245–247 °C; **^{1}HNMR(400 MHz, $CDCl_3$) δppm**: 10.278(s, 2H, -NH-), 7.844 (d, J = 6.8 Hz, 2H, Ar-H), 7.596 (dd, J = 9.0 Hz, 2H, Ar-H), 7.361 (d, J = 7.2 Hz, 2H, Ar-H), 7.188 (d, J = 8.0 Hz, 2H, Ar-H), 7.078 (d, J = 7.8 Hz, 2H, Ar-H), 6.856(d, J = 8.8 Hz, 2H, Ar-H), 5.155(s, 1H, -CH-), 1.785(s, 3H, CH_3);^{13}CNMR(100MHz, $CDCl_3$)δppm:143.44, 139.89, 135.48, 128.88, 128.38, 128.04, 125.71, 122.34, 121.63, 120.66, 118.74, 112.98, 50.47, 21.84;LCMS(m/z); 336.12(M^+). Molecularformule: $C_{24}H_{20}N_2$.

2.2.4. 3, 3′-[(4-Methoxyphenyl)methylene]bis(1*H*-indole)(3d):

Colorless solid; Yield-91%; m. p- 221-223°C; **^{1}H NMR (400 MHz, $CDCl_3$)** δppm*:* 10.145(s, 2H, NH), 7.462(d, J=8.4 Hz, 2H, Ar-H), 7.224-7.124 (m, 4H, Ar-H), 7.106(d, J=7.6 Hz, 2H, Ar-H), 7.045-6.884(m, 4H, Ar-CH), 6.826 (d, J=6.8 Hz, 2H, Ar-H), 5.124(s, 1H, -CH-), 3.648(s, 3H, $-OCH_3$);**^{13}CNMR($CDCl_3$, 100MHz)**δppm:156.27, 137.62, 134.37, 129.15, 128.46, 125.68, 122.58, 119.45, 118.66, 117.50, 114.62, 112.87, 53.56, 40.53.Molecularformulae :$C_{24}H_{20}N_2O$. LCMS (m/z) :352.50(M^+).

2.2.5. 3, 3′-[(4-Chlorophenyl) methylene]bis(1*H*-indole)(3e)

Yield-88%; redsolid;m.p-231-232°C;1HNMR(400MHz, $CDCl_3$)δppm:10.451(s, 2H, NH), 7.541- 7.314(m, 6H, Ar-H), 7.254(d, J=7.8Hz, 2H, Ar-H), 7.211-7.118(m, 2H, Ar-H), 7.108-6.893(m, 4H, Ar-H), 6.771(s, 2H, Ar-H), 4.45(s, 1H, CH);^{13}CNMR(100MHz, $CDCl_3$)δppm:143.56, 139.21, 136.54, 130.59, 129.22, 128.65, 125.27, 122.63, 120.58, 119.67, 118.30, 116.86, 113.54, 40.28;Molecular formula: $C_{23}H_{17}ClN_2$. LCMS (m/z):359.08(M+2).

2.2.6. 3, 3′-[(4-Bromophenyl) methylene] bis (1*H*-indole) (3f)

Yield-88%; Red solid, m.p: 234–236°C (EtOAc/ n-hexane- 1:4). **^{1}H-NMR ($CDCl_3$)**δppm: 10.526 (s, 2H, N–H), 7.724(d, J = 7.6 Hz, 1H, Ar–H), 7.426 (d, J = 7.2 Hz, 2H, Ar–H), 7.295 (d, J = 6.8 Hz, 2H, Ar–H), 7.254–7.147 (m, 4H, Ar–H), 7.104 (t, J = 5.8 Hz, 1H, Ar–H), 7.046(t, J = 10. 8 Hz, 2H, Ar–H), 6.984 (dd, J = 7.6 Hz, 2H, Ar–H), 5.546 (s, 1H, -CH-). ^{13}C-NMR ($CDCl_3$) δppm: 143.66, 138.32, 132.59, 128.88, 128.24, 127.98, 127.42, 126.21, 123.55, 122.34, 121.99, 119.26, 118.64, 112.08, 40.55. LCMS (m/z) = 402.27(M+2), Molecular formula $C_{23}H_{17}N_2Br$.

2.2.7. 4-(Di (1H-indol-3-yl) methyl) benzonitrile (3g)

Yield-87%; White Solid; m.p - 224–226 °C; **^{1}H NMR (400MHz, $CDCl_3$)**: 10.641 (s, 2H, NH), 7.659 (d, J = 8.0 Hz, 2H, Ar-H), 7.446 (d, J = 8.4Hz, 2H, Ar-H), 7.244-6.994 (m, 8H, Ar-H), 6.84 (s, 2H, Ar-H), 4.75 (s, 1H, -CH-).^{13}C NMR (100MHz, $CDCl_3$): 145.34, 136.29, 131.47, 130.71, 128.82, 1239.2, 122.76, 121.08, 119.53, 118.92, 117.17, 112.59, 108.59, 41.88.;LCMS(m/z):348.39 [M+H]: Molecular formula: $C_{24}H_{17}N_3$.

2.2.8.3, 3'-((4-nitrophenyl)methylene)bis(1H-indole) (3h)

Yield-85%;Red Solid;m.p- 225–227 °C; **^{1}H NMR (400 MHz, $CDCl_3$)** δppm: 10.691(s, 2H, NH), 8.346 (d, 2H, J = 8.0 Hz, Ar-H), 7.861 (d, 2H, J = 7.8 Hz, Ar-H), 7.445–6.988 (m, 8H, Ar-H), 6.772 (s, 2H, Ar-H), 5.204 (s, IH, -CH-); **^{13}C NMR (100 MHz, $CDCl_3$):** 147.66, 145.55,

138.21, 136.82, 129.77, 128.57, 127.59, 125.28, 123.11, 122.06, 121.26, 118.53, 41.14; LCMS(m/z): 367.61 [M + H]:Molecular formula: $C_{23}H_{17}N_3O_2$.

3. Biological Activity

3.1. Anti-Bacterial Activity

The *invitro* anti-bacterial activities of newly synthesized derivatives **(3a-h**) are examined against four pathogenic bacteria strains. The result of antibiotic activity evaluated for the titled compounds. The gram (-ve) bacteria screened were Escherichia Coli and Pseudomonas aeruginosa. The gram (+ve) bacteria screened were S-aureas and B.substill. The target compounds were used at the concentration of 250 µglml and 500 µglml using DMSO as a solvent the amoxylin 10 µglml disc were used as a standard. The rest of the compounds were found to be moderate active against the tested microorganism.

3.2. Anti-Fungal Activity

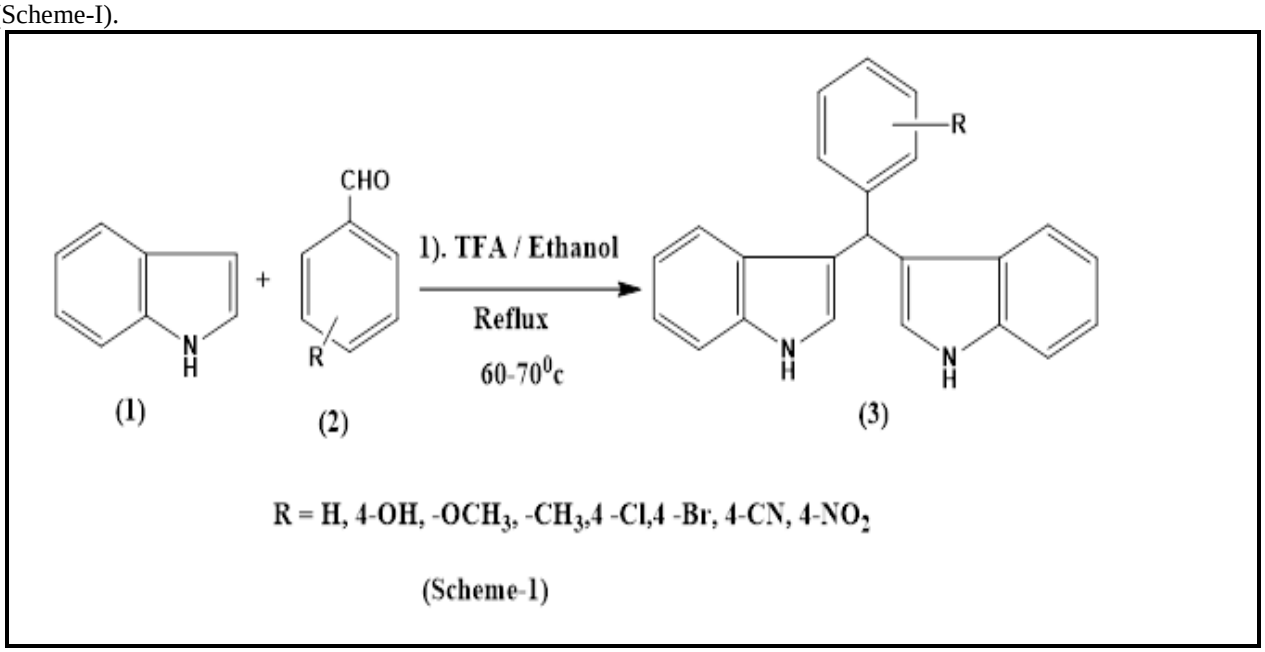
In vitro anti-fungal activity of new synthesized derivatives **(3a-h**) was examined by disc diffusion method against the organism of AspergillusNiger and Candida albicans. Compared were treated at the concentrations of 250 µglml and 500 µglml using DMSO as a solvent. The standard drug was used as ketoconazole 50 µglml against both organisms.

4. RESULT AND DISCUSSION

4.1. Chemistry

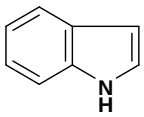
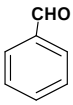
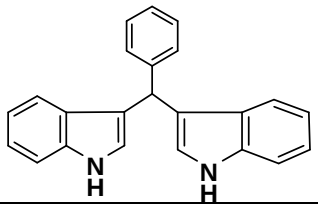
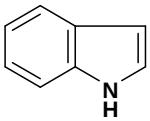
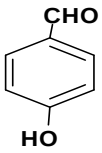
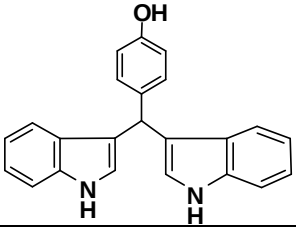
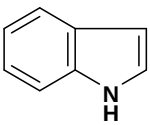
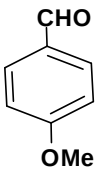
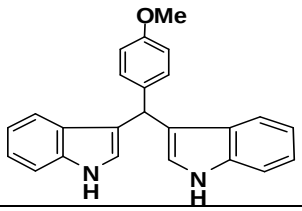
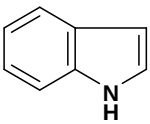
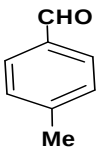
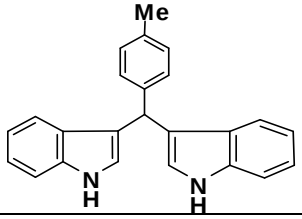
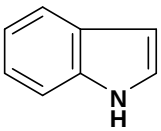
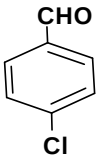
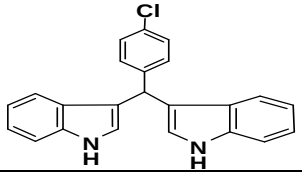
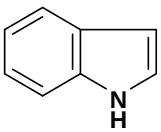
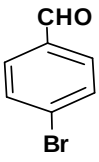
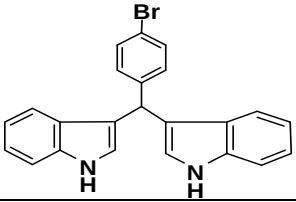
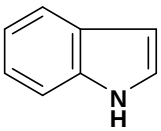
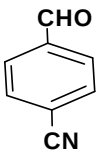
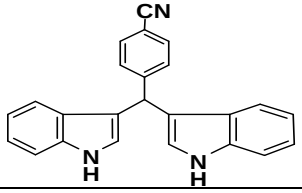
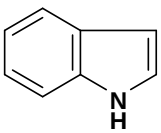
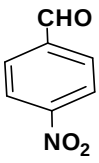
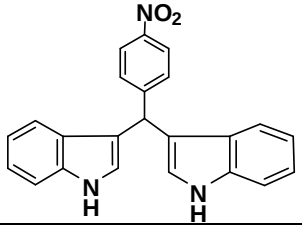
All titled compounds **(3a-h)** can be synthesized at room temperature and also obtained colored product. In this reaction, we got the percentage of the yield 85-92%.These titled compounds can be obtained, we used to TFA acid catalyst is Bronsted acid catalyst. This catalyst can be used to improve the reaction conditions and reaction is completed maximum 3 hours. The rate of reaction was developed by this catalyst. The catalyst used due to emerging as a powerful nature, inexpensive, ecofriendly, readily available, economical and water soluble compound. We applied various P-substituted aromatic aldehydes such as electron donating group of aromatic aldehydes and electron withdrawing group of aromatic aldehydes. Hence, electron donating group of aldehydes react with indole to give more yield and rate of reaction increases and completion of the reaction before 30 min compared to that of electron withdrawing group of aldehyde react with indole. We are using trifluoro acetic acid, the reaction workup is easily.

(Scheme-I).



(Scheme-1)

Table-1: Trifluoroacetic acid (TFA) catalyzed synthesis of bis (indolyl) methanes derivatives.

Entry	Indole	Substituted Aromatic aldehyde	Product	Time (min)	Yield (%)	m.p^{0}C
1				40	85	174-176
2				30	90	190-192
3				15	91	245-247
4				10	91	221-223
5				45	88	231-233
6				45	88	234-236
7				60	87	224-226
8				90	85	225–227

4.2. Biological Activity

All the tested derivatives were evaluated anti-bacterial activity as well as antifungal. The electron withdrawing group of compounds "3h" didn't show any active potent. Other hand electron withdrawing group of compounds exhibited poor active potent compared with electron donating groups. All halogen compounds exhibit excellent potent activity. The compound which possess electron donating group shows moderate activity as shown in **Table-I.**

Table I: Antimicrobial activity screening activity synthesized scaffold.

Entry	*Zone of inhibition in (mm)					
	Bacteria				Fungi	
	S.aureus	E.coli	S. typhi	B.substill	A. niger	C. albicans
3a	08	07	10	11	15	07
3b	11	10	12	18	06	08
3c	10	08	08	11	07	08
3d	18	18	17	19	11	13
3e	25	24	24	26	17	16
3f	24	25	24	26	16	15
3g	08	09	09	07	05	08
3h	0	0	0	0	10	09
Ciprafloxin	30	35	31	28	NA	NA
Ketoconazole	NA	NA	NA	NA	20	25
DMSO	---	----	---	---	---	---

CONCLUSION

The reaction condition carried at room temperature for all the newly synthesized derivatives. The yield of the titled compounds obtained from 85-92%. The compound possesses electron donating group gives maximum yield than that of the compound possesses electron withdrawing group and the rate of reaction enhanced by TFA catalyst. All the compounds tested by anti-microbial activity against gram positive, gram negative and fungal. The compound having halogen substituted group compounds exhibited excellent active potential. Otherwise the compounds having NO_2 group which did not show than that of the electron with drawing group.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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