A multicomponent and one pot synthesis of bis(indolyl)methane using bio-derived HMF

By

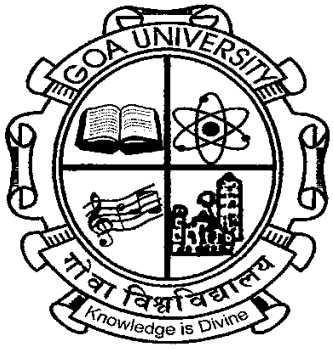
Minita Johnson Clement

A multicomponent and one pot synthesis of bis(indolyl)methane using bio-derived HMF

Dissertation submitted to Goa University in partial fulfilment of the requirement for the degree of Master of Science in Chemistry (2019-2020).

By

Miss. Minita Johnson Clement



School of Chemical Sciences

Goa University

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2019-2020

DECLARATION

This dissertation work entitled "**A multicomponent and one pot synthesis of bis(indolyl)methane using bio derived HMF**" being submitted to the school of chemical sciences Goa University, has been carried out by me under the supervision of Dr. Santosh G. Tilve, Professor, School of Chemical Sciences. The results compiled in this dissertation are original and has not previously formed the basis for the award of any degree or diploma.

Miss. Minita Johnson Clement

CH-18-010

MSc Part-II

Organic Chemistry

CERTIFICATE

This is to certify that Miss. Minita Johnson Clement has satisfactorily completed the dissertation entitled "**A multicomponent and one pot synthesis of bis(indolyl)methane using bio derived HMF**" being submitted to Goa University in partial fulfilment of the requirement for the degree of Master in Science in Chemistry Course in the academic year 2018-2020.

Miss. Minita Johnson Clement (Student)

Dr. Santosh G. Tilve (Research Guide)

Dr. V.S. Nadkarni

Dean

School of Chemical Sciences

Goa University

ACKNOWLEDGEMENTS

It gives me immense pleasure to present this project report entitled **'A multicomponent and one pot synthesis of bis(indolyl)methane using bio-derived HMF**'.

The success and final outcome of this project required lot of guidance and assistance from many people and I am extremely privileged to have got this all along the completion of my project. All that I have done is only due to such supervision and assistance and I would not forget to thank them.

Firstly, I would like to express my sincere gratitude to my guide Dr. Santosh G. Tilve. He guided and encouraged me during the entire study of the project work. I am indebted to the help rendered by him during the entire project period of my study.

I am highly obliged to Prof. V.S. Nadkarni (Dean of School of Chemical Sciences, Goa University) for permitting me to carry out my project in the provided schedule, for his encouragement and for providing all the necessary facilities during the project work.

I gratefully acknowledge Prof. V. M. S. Verenker for permitting to work in solid state laboratory and kindly allowing me to use Ball milling instrument without which this project would not be a success.

I would like to thank Dr. Sandesh T. Bugde for his valuable assistance and selfless attitude towards us.

I am grateful towards research students, Mr. Shashank Mhaldar and Mr. Ketan Mandrekar for helping me in flash column chromatography and for recording the NMR spectras of my compounds.

I am also grateful to research student Miss. Lima Rodrigues for helping me to determine the bio-activity of my compounds.

I would like to thank Organic Laboratory staff Mr. Mehul Shirodkar, Mr. Virendra Phadte and store in-charge, for their kind help in fulfilling my lab needs and supplies.

I profusely thank all my friends for being there as an helping hand for me during difficult times.

My endeavor would not be complete if it were not for the constant support and encouragement of my parents who have also rendered me financial assistance.

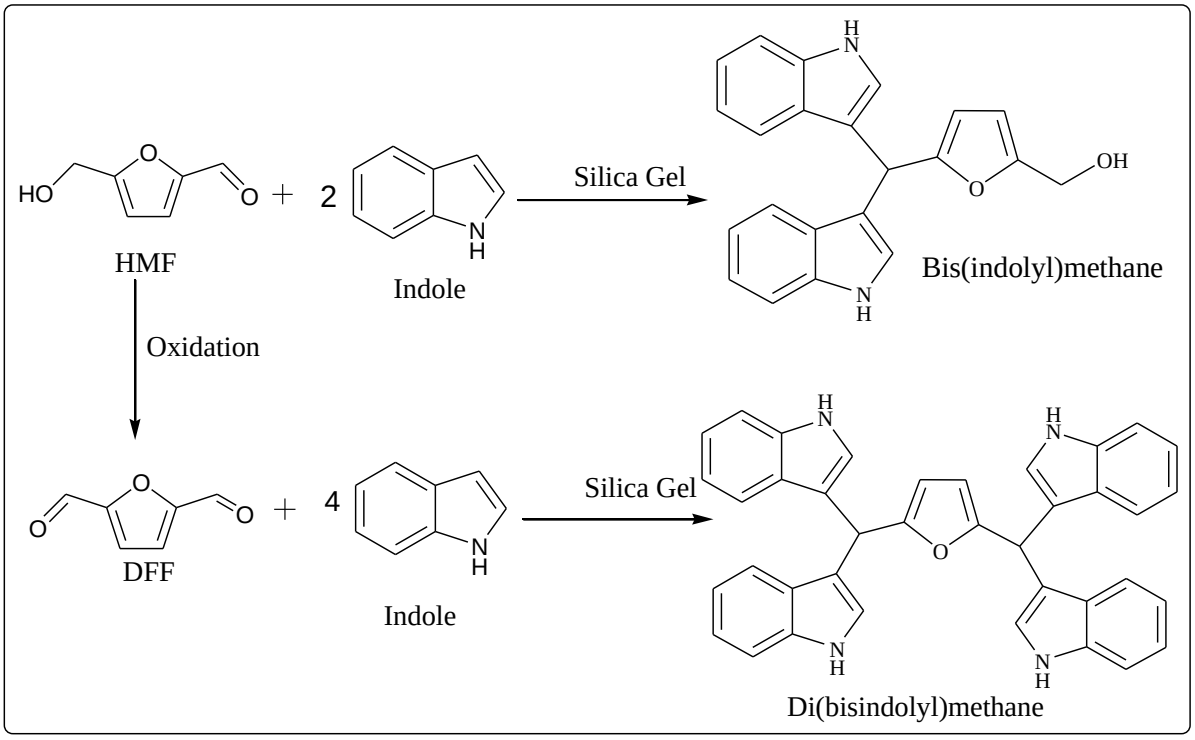
Above all I would like to thank Lord Almighty who I would turn to when things did not go as planned for making my dissertation the success that is today.

INDEX

Abstract

A one pot synthesis of bis(indolyl)methanes(BIMs) via electrophilic aromatic substitution reaction of bio-derived 5-hydroxymethylfurfural (HMF) with indoles have been studied. For this ball milling technique was employed which afforded an eco-benign and operationally simple synthesis, with a variety of indole substrates for the first time. Silica gel utilized for the synthesis not only acted as an acid catalyst but also functioned as a grinding medium. The ball milling technique used has several advantages such as simple procedure, mild conditions, reduced environmental consequences, which offered the novel synthesis of BIMs reported here. In addition, fewer examples of di(bis(indolyl)methanes) were also synthesized.

Graphical Abstract:



Introduction

The use of renewable resources (biomass) as an alternative to the dwindling fossil fuels and chemicals, is the need of the hour, to meet the increasing global demand. Sustainable resources like biomass which is cost effective and found abundantly, offer renewable source of organic molecules for the synthesis of value-added chemicals[1]. A considerable range of chemical building blocks have been derived from renewable resources[2].

One of them is 5-hydroxymethylfurfural (HMF), which is readily obtained from the acid catalyzed dehydration of sugars such as fructose, glucose, sucrose, cellulose and inulin[3].

- 5-Hydroxymethylfurfural:

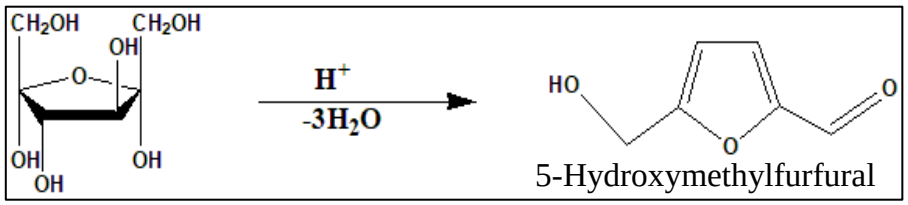


Figure 1. General scheme for synthesis of HMF.

It is an important platform molecule used as a precursor to synthesise high value-added chemicals, biofuels[3-6], polymers, plastic resins[4,7-8]. An application of this is the production of polyethylene terephthalate using 2,5-furandicarboxylic acid obtained from HMF instead of terephthalic acid[9]. Numerous methods have been reported for the synthesis of HMF[10-14].

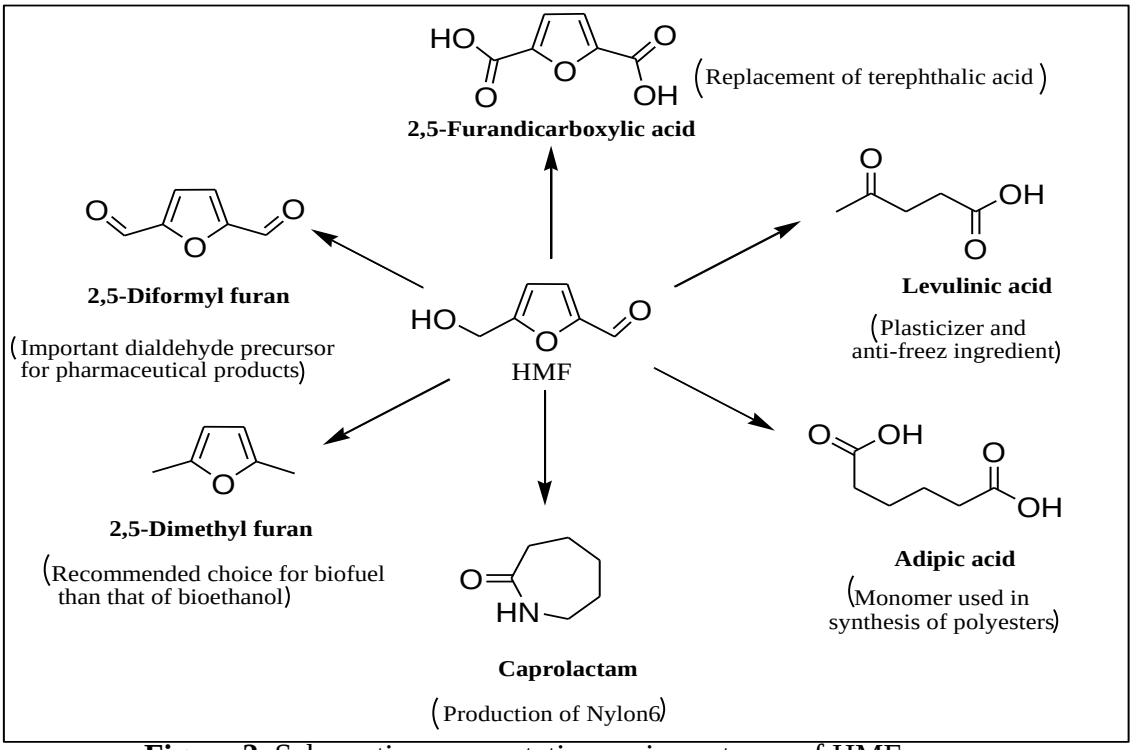


Figure 2. Schematic representation on importance of HMF.

- Multicomponent Reactions (MCR):

A multicomponent reaction is a one pot synthesis in which three or more reactants react to give a single product. It is a powerful synthetic tool which allows the straightforward formation of product directly from simple starting reactants[15]. It includes convenient and efficient strategies to synthesize highly functionalized compounds by one-pot procedures[16]. It has many advantages over stepwise reactions, such as high atom economy, less waste generation and high convergence[17].

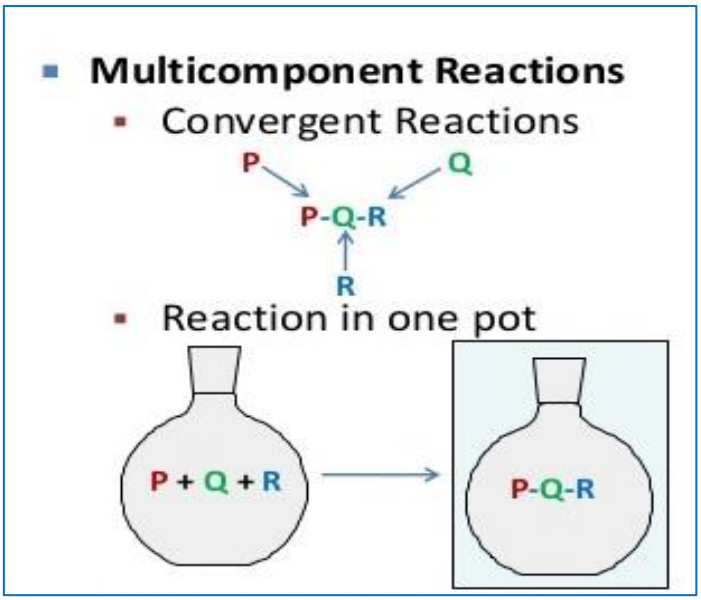


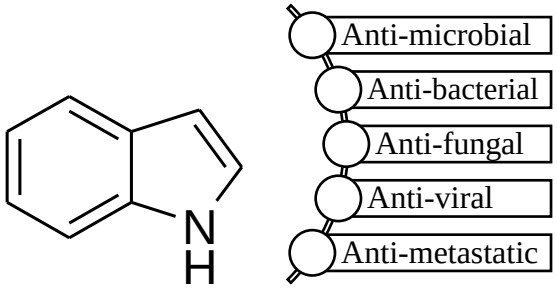
Figure 3. Schematic diagram illustrating MCR.

There are only few reports on the multicomponent reactions on HMF.

- Weigang Fan *et al.*[17] reported the first use of HMF in the 3-component Biginelli reactions, with 1,3-dicarbonyl compounds and urea building blocks.
- Weigang Fan, *et al.*[16] reported the first use of biomass-derived HMF in the one-pot Kabachnik–Fields reaction, using iodine as a non-metal catalyst and bio based 2-MeTHF as the solvent at room or moderate temperature.
- J. J. Matasi *et al.*[18] reported an adenosine receptor (A_{2A}) antagonist, HMF derivative, by a three-component reaction of HMF.
- Shinobu *et al.*[19]reported the synthesis of 3-((5-(hydroxymethyl)furan-2-yl) methylene)-N-acetyl-2-oxoindoline by using the reaction between HMF and N-acetyloxindole catalysed by piperidine.

- Indole:

Indole, a nitrogen heterocycle is widely distributed in nature[20]. It is present in many natural products, agrochemicals, pharmaceuticals and other important compounds[21]. Indole derivatives are of major interests due to their chemical diversity and broad biological activities[22]. They show many pharmaceutical properties such as anti-microbial, anti-bacterial, anti-fungal, anti-viral, anti-metastatic, analgesic, radical scavenging and anti-inflammatory activities[23-25].



Indole

Figure 4. Illustrating properties of Indole.

- Bisindolylmethanes (BIMs):

Bisindolylmethanes (BIMs) are commonly synthesised from two molecules of indole and one molecule of carbonyl compound. The indole unit forms the basis for general BIMs structure. It is found naturally in marine organisms and cruciferous plants[20]. Thus, they are widely isolated from terrestrial and marine sources. These natural products show a wide range of biological activities[26-33].

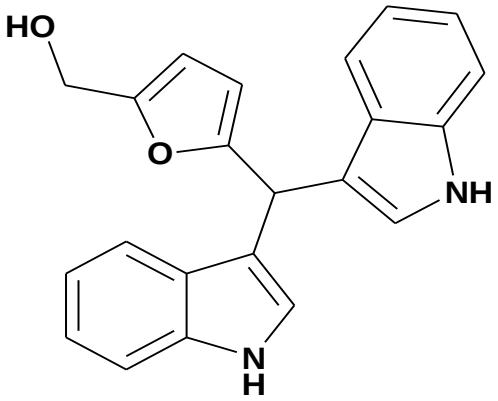


Figure 5. Structure of 3,3'-Bis(indolyl)methane.

➢ Drug-activity of BIMs:

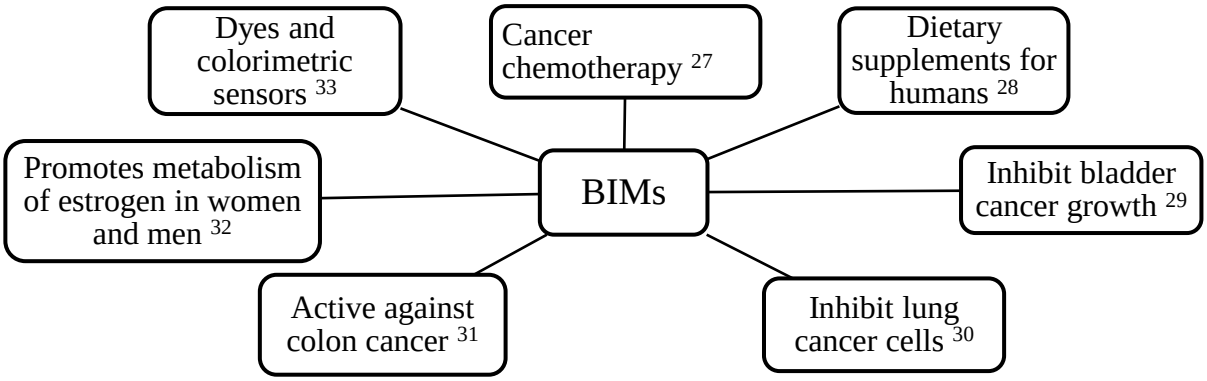
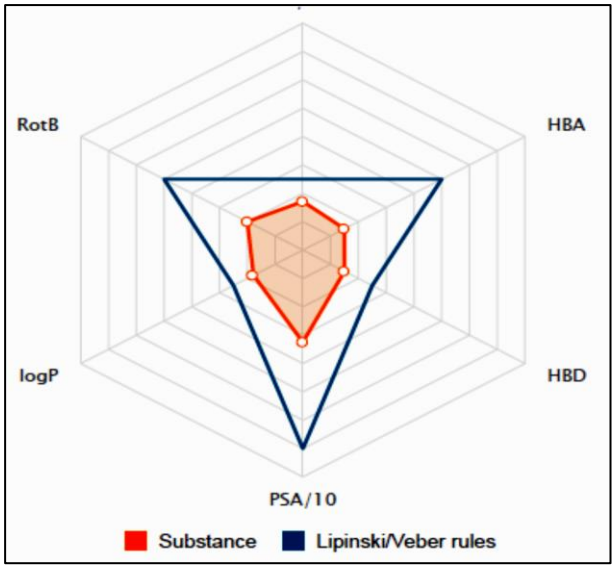


Figure 6. Applications of BIMs.

The drug likeness of some of the BIMs obtained from Reaxys website have shown below;



www.reaxys.com

(a)

Lipinski rules component	
Molecular weight	342.397
logP	3.556
HBA	3
HBD	3
Matching Lipinski rules	4

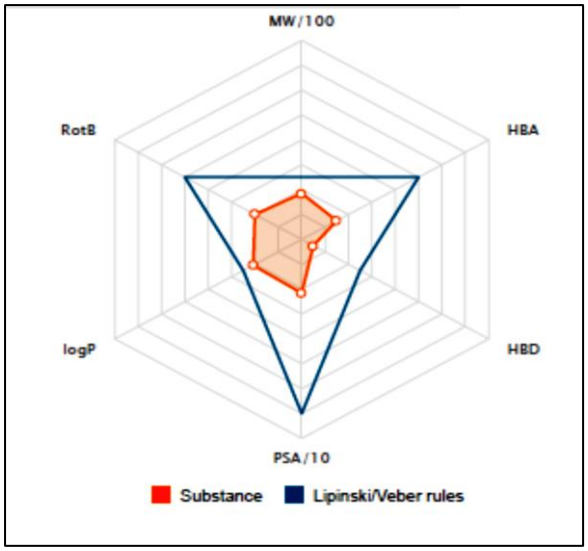
(b)

Verber rules component	
Polar surface area (PSA)	64.95
Rotatable bond (RotB)	4
Matching verber rules	2

(c)

Figure 7. Drug-likeness of II A- 3,3'-((5-Hydroxymethylfurfuryl)methylene)bis(1H-indole).

(a)Schematic representation. (b)Lipinski rules component. (c)Verber rules component.



(a)

Lipinski rules component	
Molecular weight	370.451
logP	4.164
HBA	3
HBD	1
Matching Lipinski rules	4

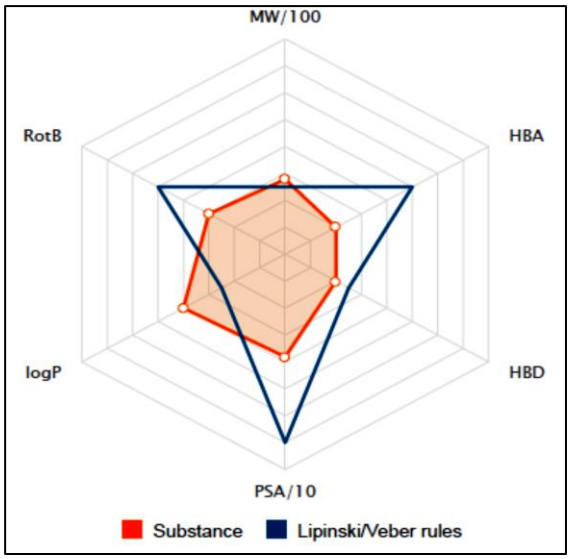
(b)

Verber rules component	
Polar surface area (PSA)	43.23
Rotatable bond (RotB)	4
Matching verber rules	2

(c)

Figure 8. Drug-likeness of II E - 3,3'-((5-Hydroxymethylfurfuryl)methylene)bis(N-methylindole)

(a)Schematic representation. (b)Lipinski rules component. (c)Verber rules component.



(a)

Lipinski rules component	
Molecular weight	556.667
logP	8.005
HBA	4
HBD	4
Matching Lipinski rules	2

(b)

Verber rules component	
Polar surface area (PSA)	76.3
Rotatable bond (RotB)	6
Matching verber rules	2

(c)

Figure 9. Drug-likeness of IV A - 2,5-Bis(di(1H-indol-3-yl)methyl)furan

(a)Schematic representation. (b)Lipinski rules component. (c)Verber rules component.

➢ Method of synthesis:

The simple and standard method of synthesis of BIMS is the Friedal crafts reaction between indoles and carbonyl compounds in the presence of an acid or base[20(a)]. Various protocols have been reported for the synthesis of BIMs involving protic acids[34], Lewis acids[35], N-bromosuccinimide[36], $NaHSO_4$/ amberlyst[37]. However, some of these have limitations like high cost of reagents, harsh conditions.

S. N. Mhalder *et al*.[38] have reported a green, simple, economical and efficient method for the synthesis of BIMs involving Ball-Milling technique. The same technique has been used in this study to synthesis BIMs.

- <u>Ball-milling:</u>

Ball-milling is a mechanical technique widely used to grind powders into fine particles and blend materials[39].

It is a simple, fast, cost-effective green technology with enormous potential[40], and have found wide applications in industry all over the world.

➢ Advantages:
  - cost-effectiveness
  - reliability
  - ease of operation
  - time efficiency
  - environment friendliness
  - reproducible results due to energy and speed control

Figure 10. Planetary ball milling machine (PULVERISETTE 7)

The multicomponent reactions on HMF has been scarcely explored. Herein we wish to report –

- the multicomponent reactions of HMF to synthesis BIMs using indole and HMF as the carbonyl source using solvent free, efficient and green procedure,
- and the bio-activity of the synthesized BIMs.

Materials and Methods

All the required solvents and chemicals were purchased from commercial suppliers and used without further purification. Synthesis of Bis(indolyl)methanes (BIMs) were carried out using planetary ball milling machine (PULVERISETTE 7) marketed by FRITSCH and reactions were monitored using thin layer chromatography (TLC). ^{1}H NMR experiments were performed on a 400 MHz Bruker Avance III instrument using $CDCl_3$ as a solvent with tetramethylsilane as an internal standard at room temperature. The coupling constants *J* are given in hertz and the multiplicity is designated as s-singlet, d-doublet, t-triplet, q-quartet, dd-doublet of doublet, m-multiplet. Flash column chromatography was performed using silica gel (230-400 mesh, sigma).

Commercially available 2-methyl indole was purified by column chromatography using silica gel (60-120 mesh) and was used for the reaction.

2-Phenyl indole and N-methyl indole were synthesized using the literature procedure[41].

- **Procedure for the synthesis of 5- hydroxymethyl furfural (HMF) from fructose:**

A mixture of fructose (5g), 10% NaCl solution (15 mL), dimethylsulfoxide (DMSO) (5mL), methyl isobutyl ketone (MIBK) (80 mL), and conc.HCl (1 mL) were heated in a 500 mL round bottom flask at 170 ºC for 3 hr. The reaction mixture was then filtered and the filtrate was neutralized using NaOH pellets and then the aqueous layer was extracted with ethyl acetate. The organic phase was dried over anhydrous Na_2SO_4 and evaporated to obtain the brown oil of crude HMF. The obtained crude HMF was purified by column chromatography (65.57%).

- **General procedure for the synthesis of Bis(indolyl)methanes:**

HMF (1.0 mmol), indole (2.0 mmol) and silica gel (60-120) (1g) were taken in a ball milling vessel with 10 balls and then milled in a ball mill with a speed of 500 rpm. The reaction was monitored using thin layer chromatography (TLC).

After the reaction was complete the product was purified by flash column chromatography (silica gel 230-400) using a mixture ethyl acetate and petroleum ether as an eluent.

Figure 11. Drying of compound using Rotatory evaporator.

- **Procedure for the synthesis of diformylfuran (DFF) from HMF: Oxidation of HMF:**

1g (7.92 mmol) of HMF and 30 mL DCM were taken in a 100 mL round bottom flask fitted with a guard tube and was kept in an ice bath. To this 1g of $NaHCO_3$ was added with stirring. After 20 mins. 5 g of Dess- martin periodinane (DMP) was added and stirring continued for 30 mins. The completion of reaction was monitored using TLC. After completion, 35 mL of sat. $Na_2S_2O_3$ was added to reaction mixture and stirred further for 15 mins. The organic layer was then separated and neutralized with conc.HCl. The extracted organic layer was then evaporated to obtain the solid DFF. (97%, m.p.-110^oC)

Figure 12. Purification of compound by Flash column chromatography.

- **General procedure for the synthesis of Di-Bis(indolyl)methanes:**

HMF (1.0 mmol), indole (4.0 mmol) and silica gel (60-120) (1g) were taken in a ball milling vessel with 10 balls and then milled in a ball mill with a speed of 500 rpm. The reaction was monitored using TLC. After the reaction was complete the product was purified by flash column chromatography (silica gel 230-400) using a mixture of ethyl acetate and petroleum ether as an eluent.

- **General procedure to check the bio-activity:**

Anti-oxidant activity (DPPH assay):

1 mg of compound was dissolved in 1mL methanol. To this 2 mL of 0.06 mM DPPH (2,2'-diphenyl-1-picrylhydrazyl) solution in methanol was added. The reaction mixture was shaken and kept in dark for 15 minutes at room temperature. After 15 minutes absorbance of each reaction mixture was recorded at 517nm. Butylated hydroxy toluene (BHT) was used as reference. The percent anti-oxidant activity was calculated as follows:

$$\% \text{ anti-oxidant activity} = [(A_{control} - A_{sample})/A_{control}] \times 100$$

Where, Acontrol is the absorbance without the sample

Asample is the absorbance with the sample

Anti-tyrosinase activity:

Compounds were dissolved in methanol to get final concentration of 400 µM. Kojic acid was used as reference. 20 µL of mushroom tyrosinase (1000 U/mL) and 120 µL test sample in 50 mM phosphate buffer (pH 6.8) was kept at 32 ± 2°C for 5 minutes. Then, 2 mM L-tyrosine (300 µL) was added to each reaction mixture and kept at 32 ± 2°C for 30 minutes. After 30 minutes absorbance of each reaction mixture was recorded at 475 nm. The % anti-tyrosinase activity was calculated as follows:

$$\% \text{ anti-tyrosinase activity} = [(A_{control} - A_{sample})/A_{control}] \times 100$$

Where, Acontrol is the absorbance without the test sample in methanol

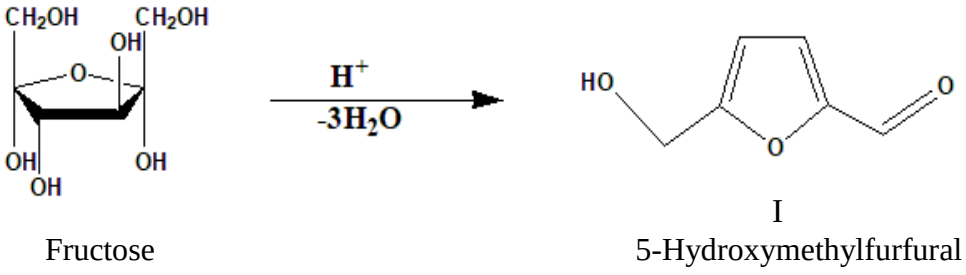
Asample is the absorbance with the test sample in methanol

Results and Discussion

- **Synthesis of 5-hydroxymethylfurfural (HMF):**

5-Hydroxymethylfurfural HMF was synthesized from fructose in presence of acid catalyst. Two different acids i.e. conc.HCl and conc.H_2SO_4 were used for the synthesis. Both sets of reaction gave similar yield of 65.57% and 63.80% respectively. A wide range of color change was observed during the course of reaction. The formation of product I was determined by TLC (1:1, Ethyl acetate: Pet. ether) using an authentic sample of HMF.

SCHEME 1:

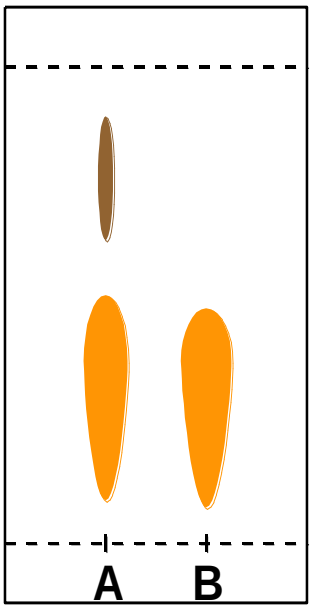


Fructose

I
5-Hydroxymethylfurfural

(a)

(b)



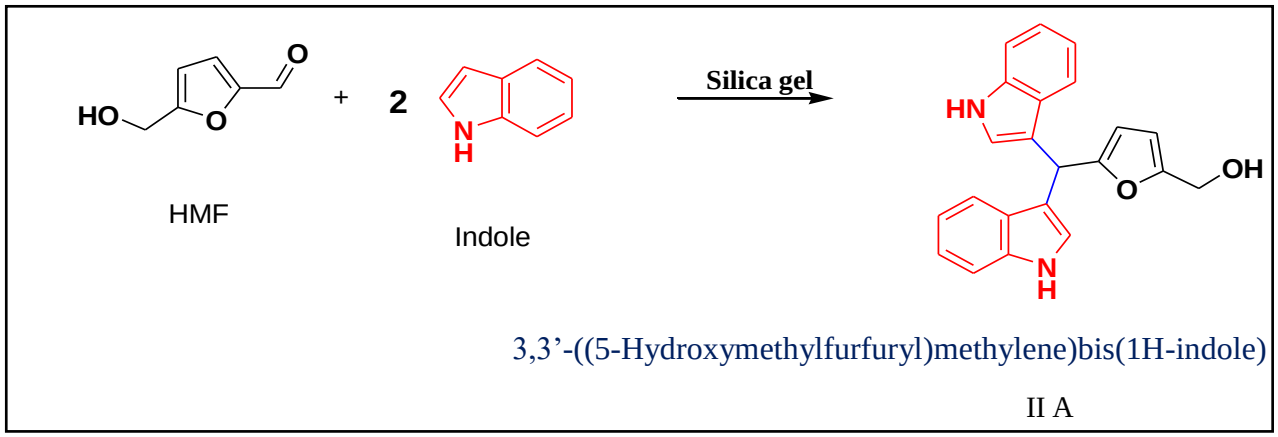
(c)

Figure 13. Synthesis of HMF. (a)Experimental set up. (b) Color change observed. (c) Reaction monitored by TLC. A- Crude product B- Authentic Sample

- **Synthesis of Bis(indolyl)methanes:**

To begin with we added 1equiv. of HMF and 2 equiv. of Indole with 1g silica gel in the vessel with 10 balls and milled in a ball milling machine. Silica gel added not only acted as a supporting material but also as a catalyst. The reaction was complete within 3 h. The crude product (sky blue color) was then subjected to flash column chromatography which gave the purified product as a yellow color solution which further on evaporation of solvent gave a dark red solid II A with a yield of 34% and melting point of 84-86ºC. The structure of the product formed was characterized by spectral analysis.

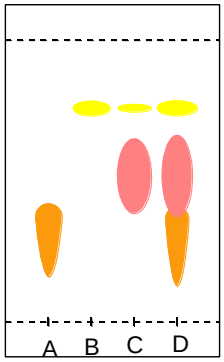
SCHEME 2:



(a)

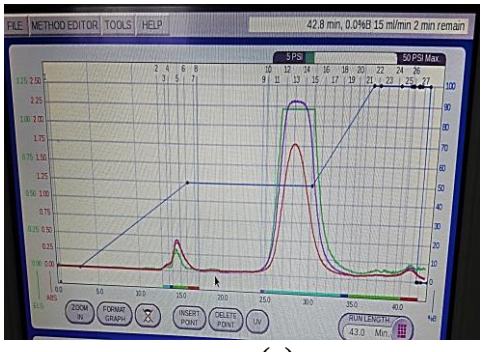
(b)

(c)



(d)

A - HMF
B - Indole
C - Crude Product
D - CO Spot



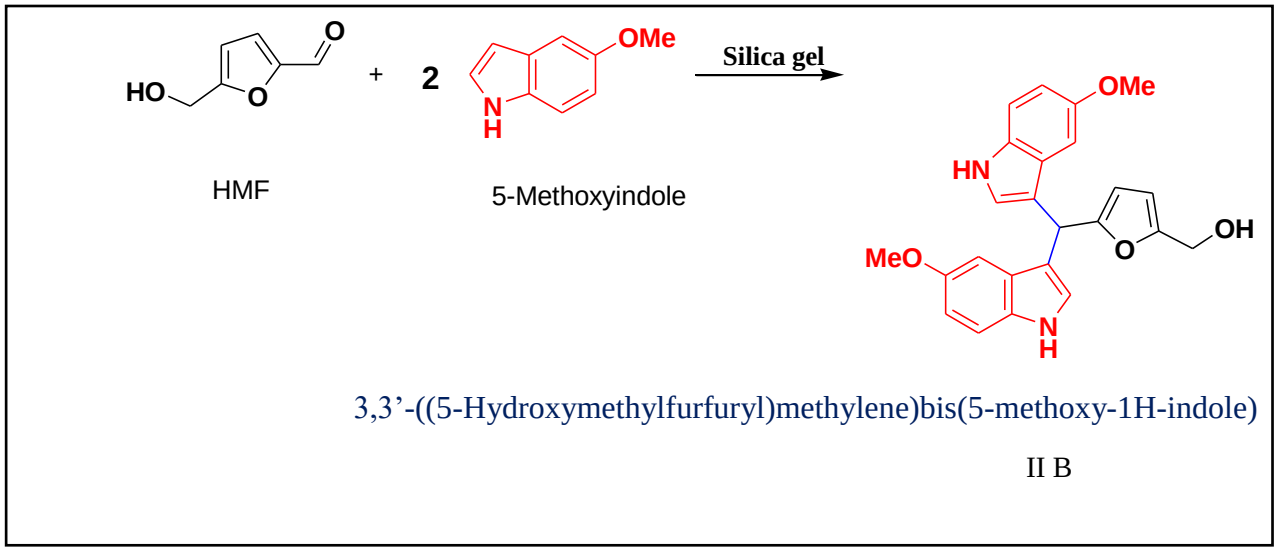
(e)

Figure 14. Synthesis of II A. (a) Crude sample. (b) Pure product. (c) Product in solvent. (d) Reaction monitored using TLC. (e) Graph showing elution of product during flash column chromatography.

➢ Further similar reactions were carried out using few more indoles;

With 2 equiv. of 5-methoxyindole: The reaction was completed within 2 h. The product was obtained from the crude (brown color) by flash column chromatography which gave a dark brown color solution which on further evaporation of solvent gave a dark red solid II B with a good yield of 82.45% and melting point of 88-90°C. The structure of the product was characterized by spectral analysis.

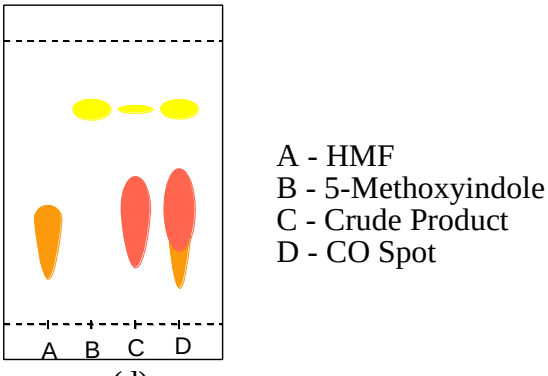
SCHEME 3:



(a)

(b)

(c)

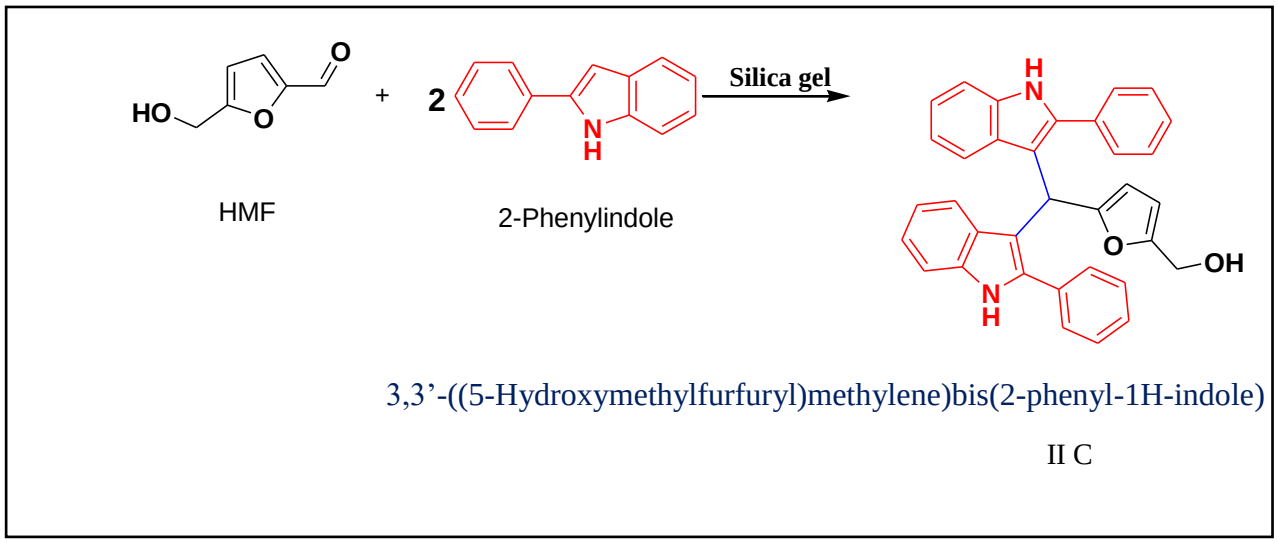


(d)

Figure 15. Synthesis of II B. (a) Crude sample. (b) Pure product. (c) Product in solvent. (d) Reaction monitored using TLC.

With 2 equiv. of 2-phenylindole: The reaction was carried out for 24 h but was not complete. Hence the reaction mixture was directly heated at 190°C for 10 h, but did not attain completion. However, the product formed was isolated from crude mixture (light brown) by flash column chromatography, forming a yellow color solution which on evaporation of solvent gave a dark brown color solid II C with a poor yield.

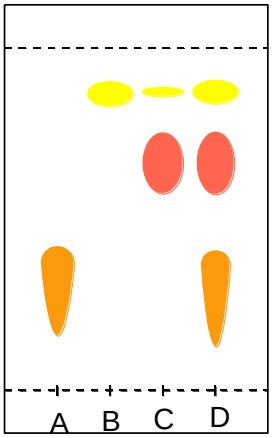
SCHEME 4:



(a)

(b)

(c)



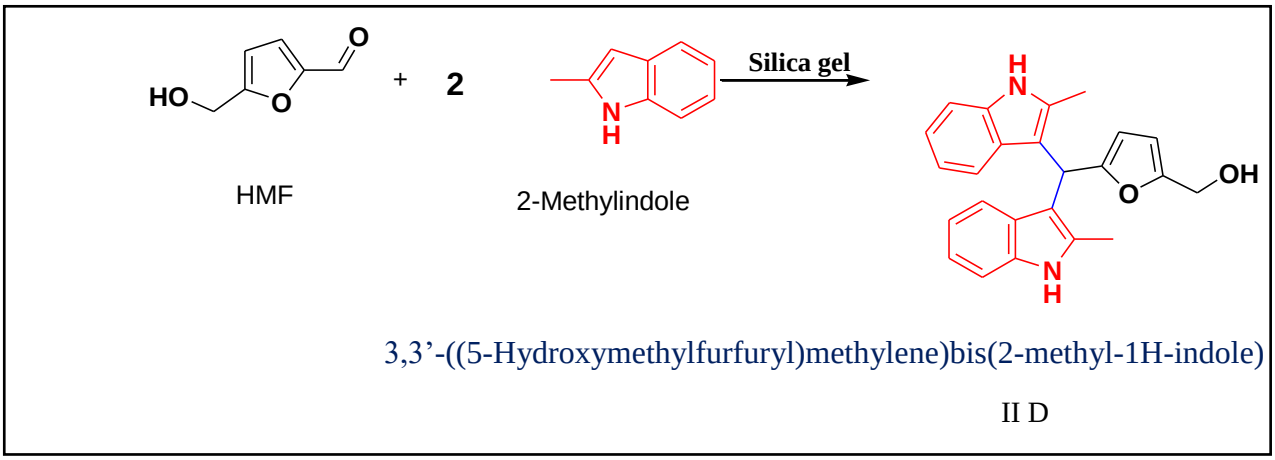
A - HMF
B - 2-Phenylindole
C - Crude Product
D - CO Spot

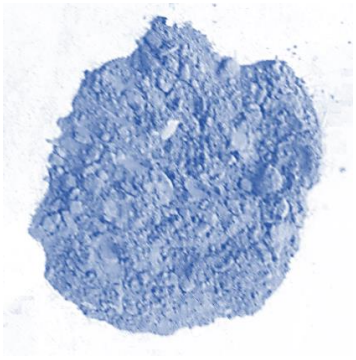
(d)

Figure 16. Synthesis of II C. (a) Crude sample. (b) Pure product. (c) Product in solvent. (d) Reaction monitored using TLC.

With 2 equiv. of 2-methylindole: The reaction was complete within 5 h. The crude product (sky blue color) was then subjected to flash column chromatography which gave the purified product as a yellow color solution which further on evaporation of solvent gave a dark red solid II D with a yield of 69%.

SCHEME 5:

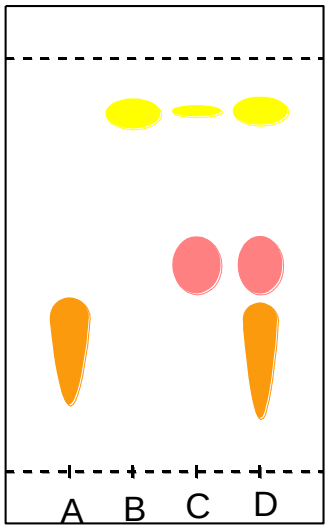




(a)

(b)

(c)



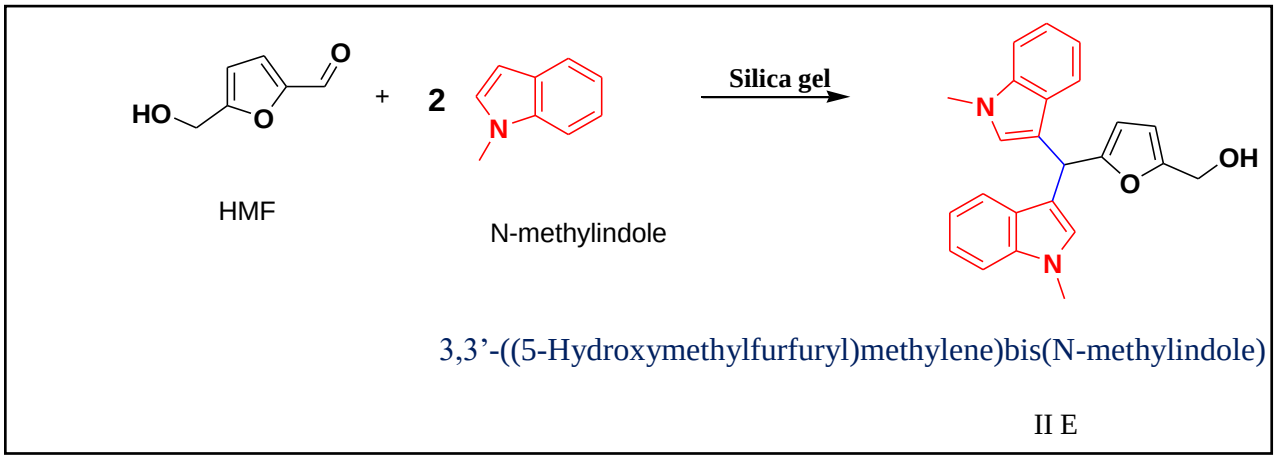
(d)

A - HMF
B - 2-Methylindole
C - Crude Product
D - CO Spot

Figure 17. Synthesis of II D. (a) Crude sample. (b) Pure product. (c) Product in solvent. (d) Reaction monitored using TLC.

With 2 equiv. of N-methyl indole: The reaction was complete within 7 h. giving a light pink color crude mixture. The product was then isolated by flash column chromatography giving a red color solution which on evaporation gave a yellow color solid II E with a poor yield.

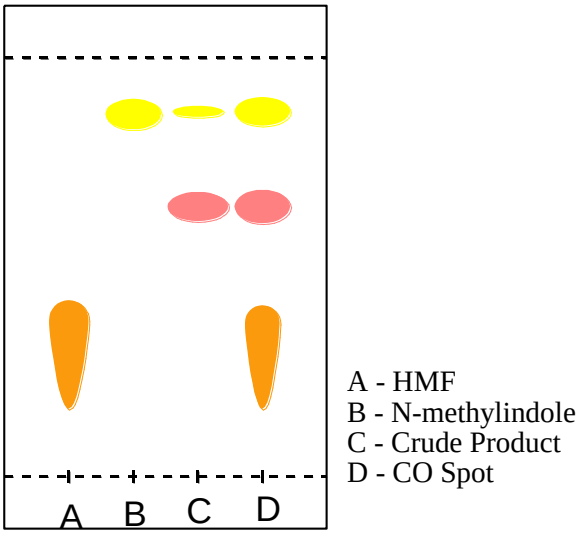
SCHEME 6:



(a)

(b)

(c)

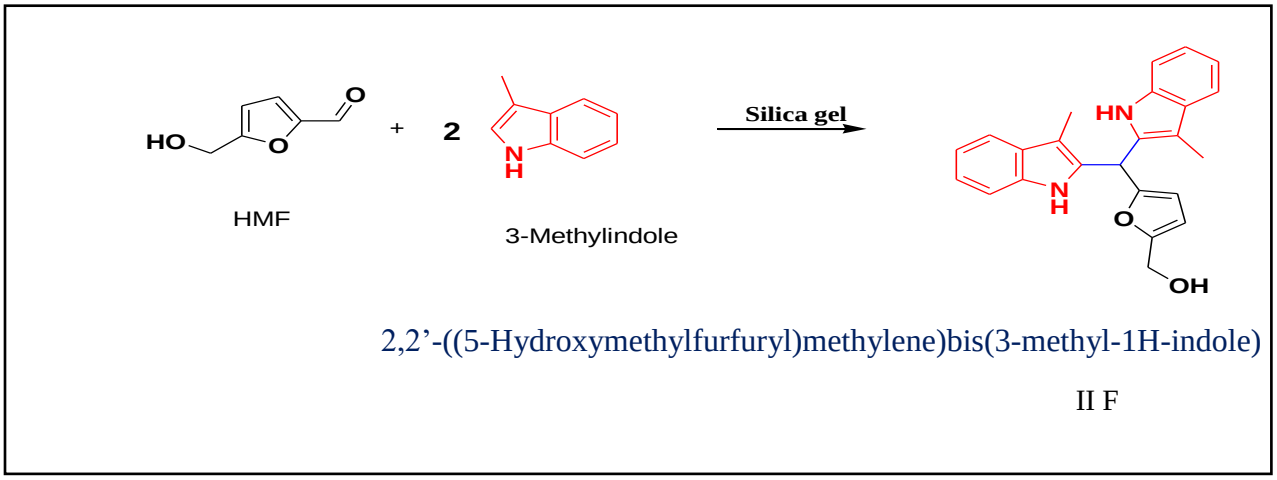


(d)

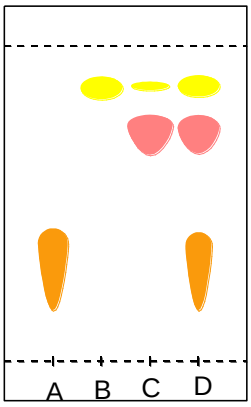
Figure 18. Synthesis of II E. (a) Crude sample. (b) Pure product. (c) Product in solvent. (d) Reaction monitored using TLC.

With 2 equiv. of 3-methylindole: The reaction was completed within 27 h. which gave a white color crude mixture. The product II F is required to be isolated.

SCHEME 7:



(a)



(b)

A - HMF
B - 3-Methylindole
C - Crude Product
D - CO Spot

Figure 19. Synthesis of II F. (a) Crude sample.
(b) Reaction monitored using TLC.

- **Synthesis of Di-bis(indolyl)methanes:**

For the synthesis of di bis(indolyl)methanes we first set up a similar reaction condition as mentioned above with 1: 4 equiv. of HMF and indole in presence of 2 equiv. of MnO_2 oxidizing agent for 24 h. but reaction was unsuccessful. Further we increased the amount of MnO_2 to 10 equiv. and then to 20 equiv. and continued the reaction for another 24 h. Still the reaction did not proceed to form di(bis(indolyl))methane.

Hence, we took the step to oxidize HMF first to diformylfuran (DFF) and then use in the synthesis.

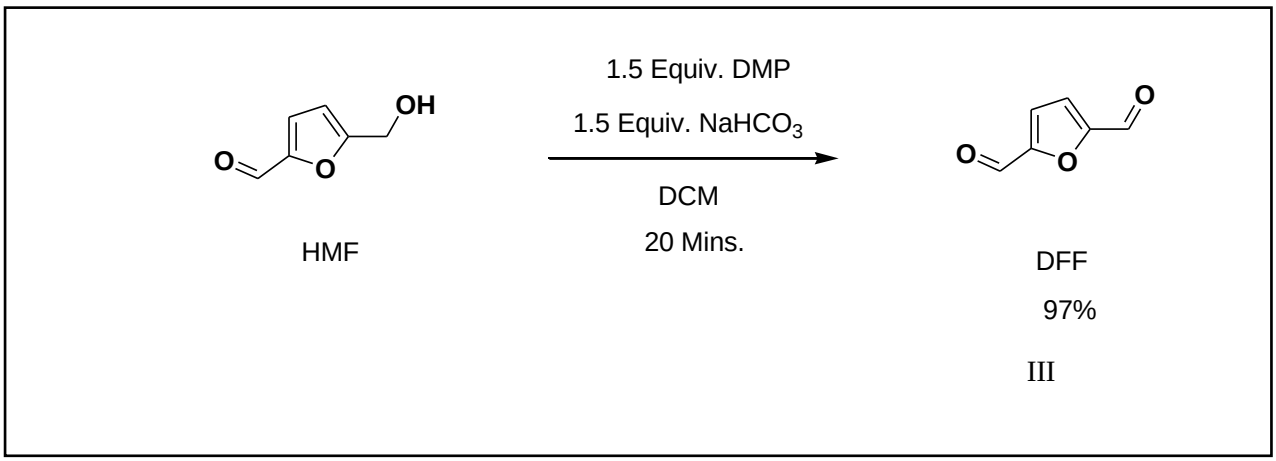
Oxidation of HMF:

For this 1 equiv. of HMF and 10 equiv. of MnO_2 was taken in DCM solvent and reaction was set up in a magnetic stirrer for 24 h and then to 8 days. But the reaction was unsuccessful.

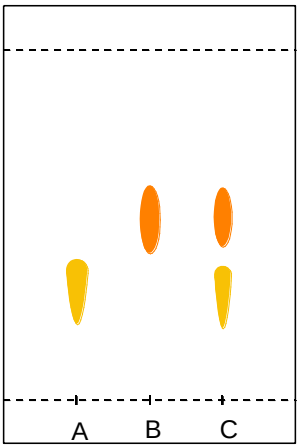
Further we tried the oxidation of HMF with magnetic catalyst 5% MnO_2-Fe_2O_3 in DCM solvent under oxygen atmosphere for 7 days. Due to the failure of this we evaporated DCM and refluxed the same mixture in acetonitrile solvent for 10 h. This procedure also did not work.

We then set up the reaction with Dess-Martin periodinane DMP oxidizing agent. For this 1 equiv. of HMF was treated with 1.5 equiv. of DMP to yield a yellow color solid product III DFF within a short time of 20 min. and an excellent yield of 97%.

SCHEME 8:



(a)



A - HMF
B- DFF
C- CO Spot

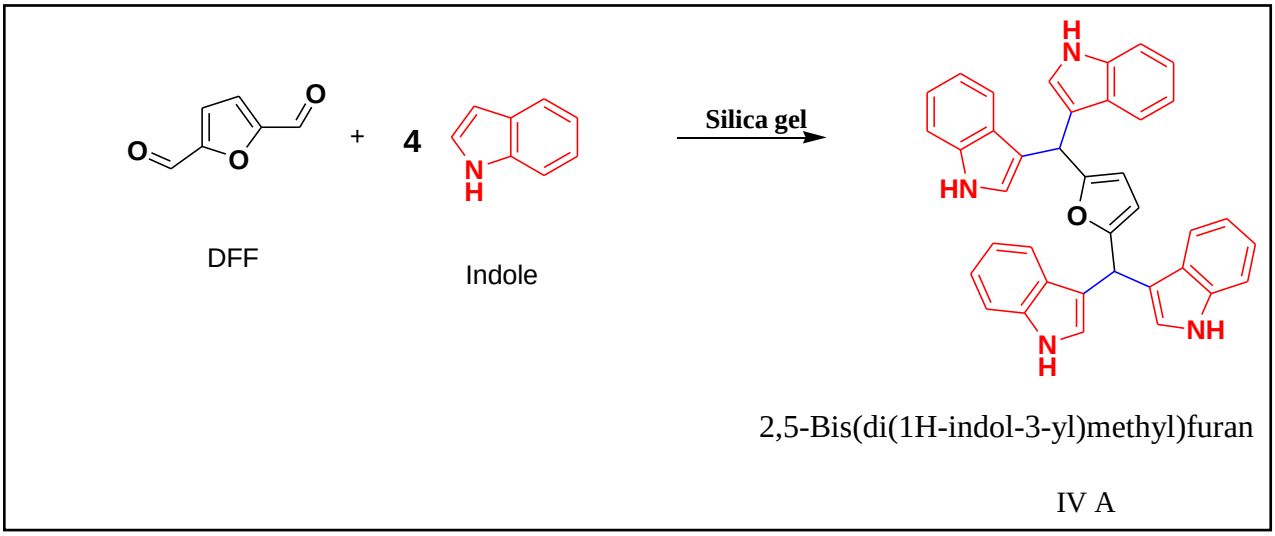
(b)

Figure 20. Synthesis of DFF. (a) Pure DFF (b) Reaction monitored using TLC

The DFF so synthesized was used for the following reactions.

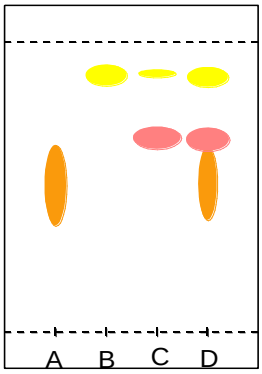
We began by adding 1 equiv. of DFF and 4 equiv. of indole with 1g of silica gel and milled in a ball milling vessel with 10 balls. The reaction was complete within 18 h. with the formation of coffee brown color crude product. The isolation of product from crude is under investigation.

SCHEME 9:



2,5-Bis(di(1H-indol-3-yl)methyl)furan

IV A



A - DFF
B - Indole
C - Crude Product
D - CO Spot

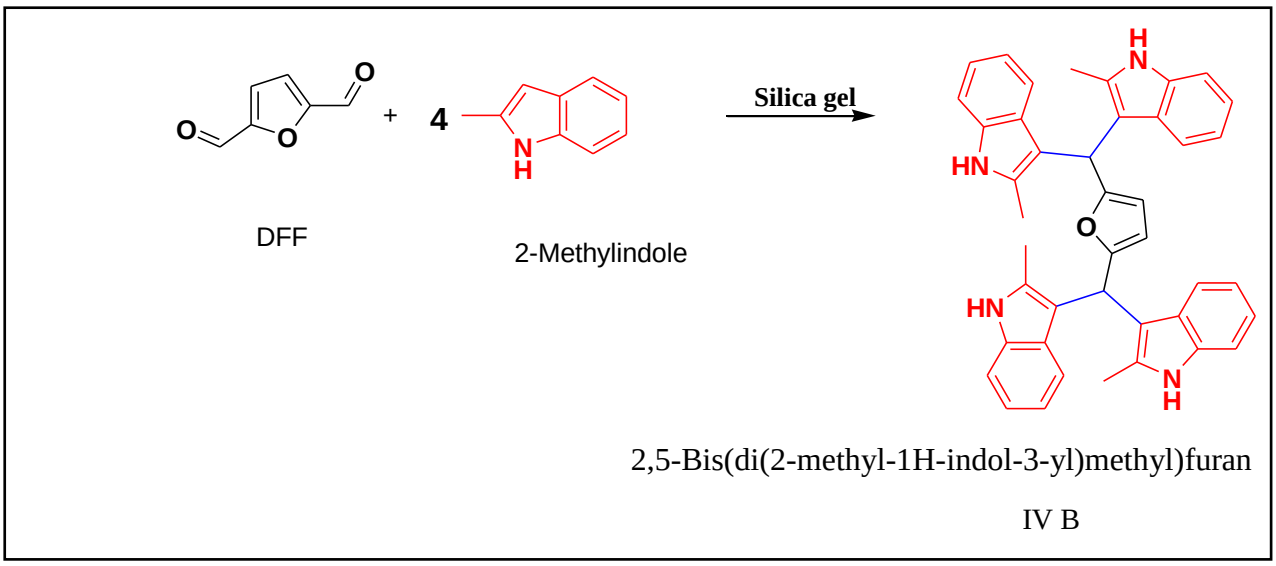
(a) (b)

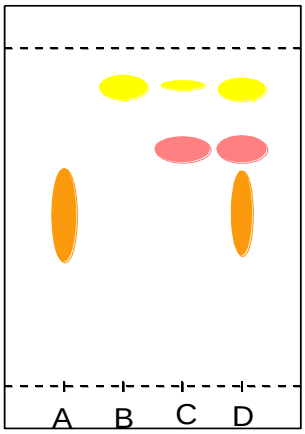
Figure 21. Synthesis of IV A. (a) Crude product. (b) Reaction monitored using TLC.

Next, we tried the same reaction with other derivative of indole.

With 4 equiv. of 2-methylindole: The reaction was completed within 16 h. and a white color crude product was obtained. Further purification of product IV B is under process.

SCHEME 10:





A - DFF
B - 2-Methylindole
C - Crude Product
D - CO Spot

Figure 22. Synthesis of IV B, reaction monitored using TLC.

- **Drug-likeness of compounds:**

Table 1. Showing the results of Bio-activity of compounds.

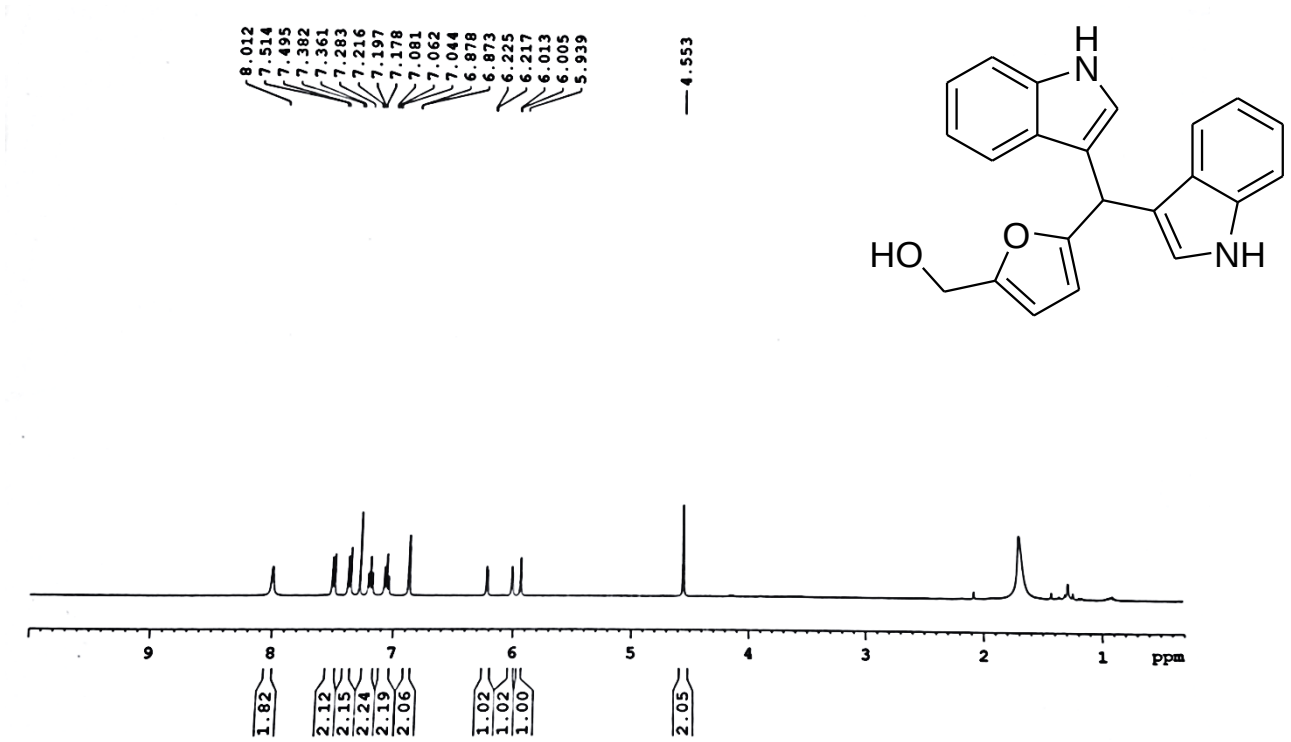
Compounds	% Anti-tyrosinase activity (Mushroom tyrosinase inhibition activity)	% Anti-oxidant activity (DPPH radical scavenging activity)
II A	15.00	69.20
II B	14.70	71.00
II C	14.69	74.80
II D	25.80	84.67

As can be seen from the above data all the compounds show a very low value of % of anti-tyrosinase activity. The % of anti-tyrosinase activity compound II D is higher than II A followed II B and II C which have almost similar value.

All the four compounds show a very good anti-oxidant activity. Among them compound II D shows the highest % of anti-oxidant activity that II C followed by II B and lastly II A.

It can be concluded that all four compounds show a very good anti-oxidant property than anti-tyrosinase activity.

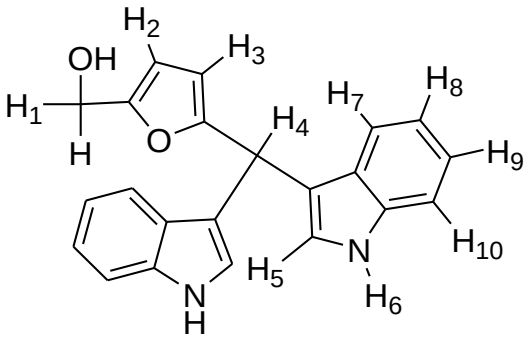
- **Spectral analysis:**



^{1}H NMR (400 MHz, $CDCl_3$):

Table 2. NMR data of II A - 3,3'-((5-Hydroxymethylfurfuryl)methylene)bis(1H-indole)

	δ	Multi plicity	*J* (Hz)	No. of Equiv. H
H1	4.553	s	-	2H
H2	6.009	d	3.2	1H
H3	6.221	d	3.2	1H
H4	5.939	s	-	1H
H5	6.878, 6.873	2 x s	-	2H
H6	8.012	s	-	2H
H7	7.37	d	7.6	2H
H8	7.062	t	7.6,	2H
H9	7.197	t	7.6,	2H
H10	7.50	d	7.6	2H



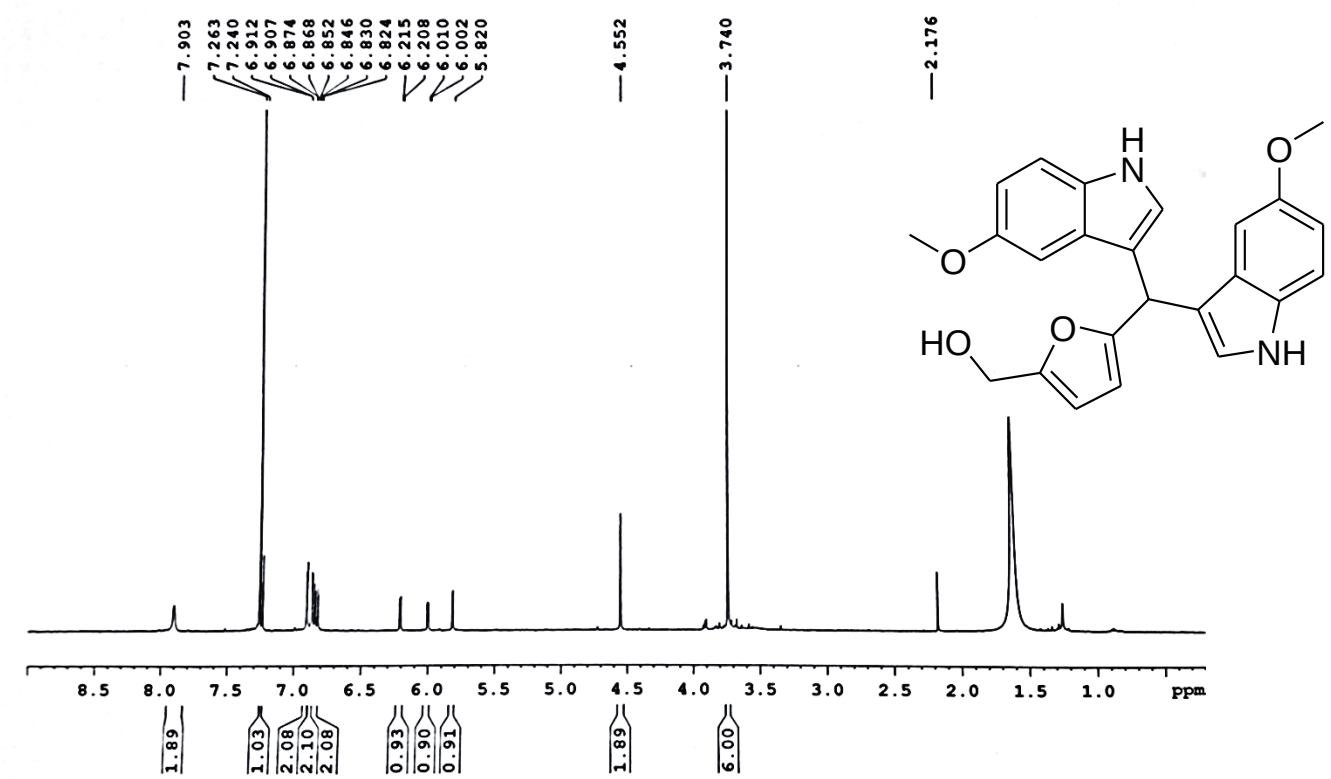
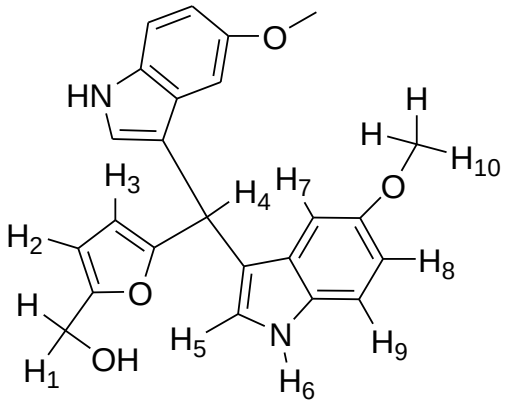


Table 3. NMR data of II B - 3,3'-((5-Hydroxymethylfurfuryl)methylene)bis(5-methoxy-1H-indole)

	δ	Multiplicity	*J* (Hz)	No. of Equiv. H
H1	4.552	s	-	2H
H2	6.006	d	3.2	1H
H3	6.211	d	2.8	1H
H4	5.820	s	-	1H
H5	6.871	d	2.4	2H
H6	7.903	s	-	2H
H7	6.910	d	2	2H
H8	6.838	dd	8.8 & 2.4	2H
H9	6. 251	d	9.2	2H
H10	3.740	s	-	6H



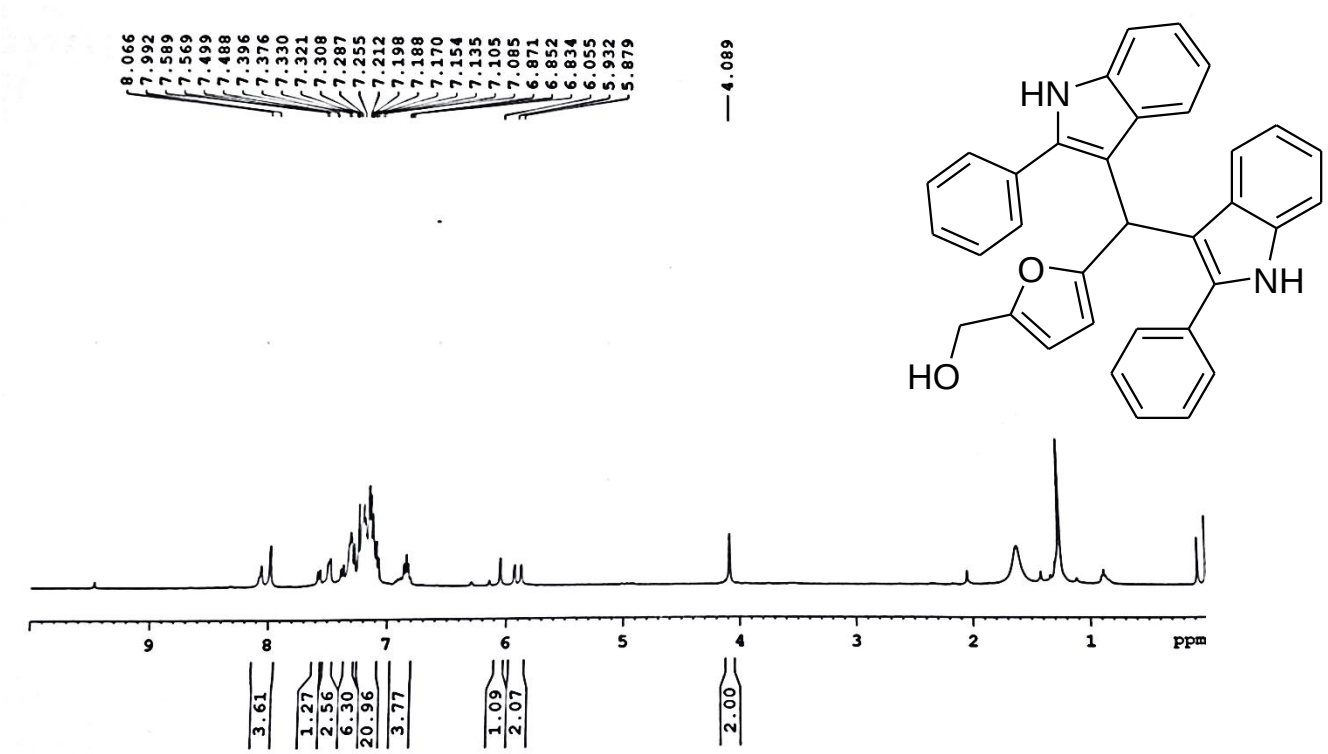
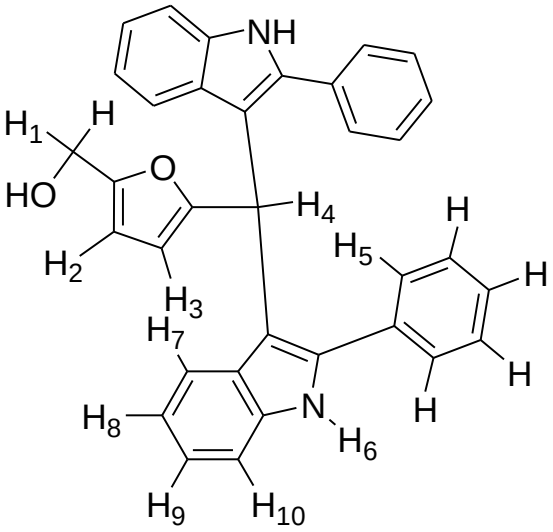


Table 4. NMR data of II C - 3,3'-((5-Hydroxymethylfurfuryl)methylene)bis(2-phenyl-1H-indole)

	δ	Multiplicity	No. of Equiv. H
H1	4.089	s	2
H2	5.932	s	1
H3	6.055	s	1
H4	5.879	s	1
H5	7.255-7.085	m	10
H6	8.066	s	2
H7	7.589-7.287	-	2
H8		-	2
H9		-	2
H10		-	2



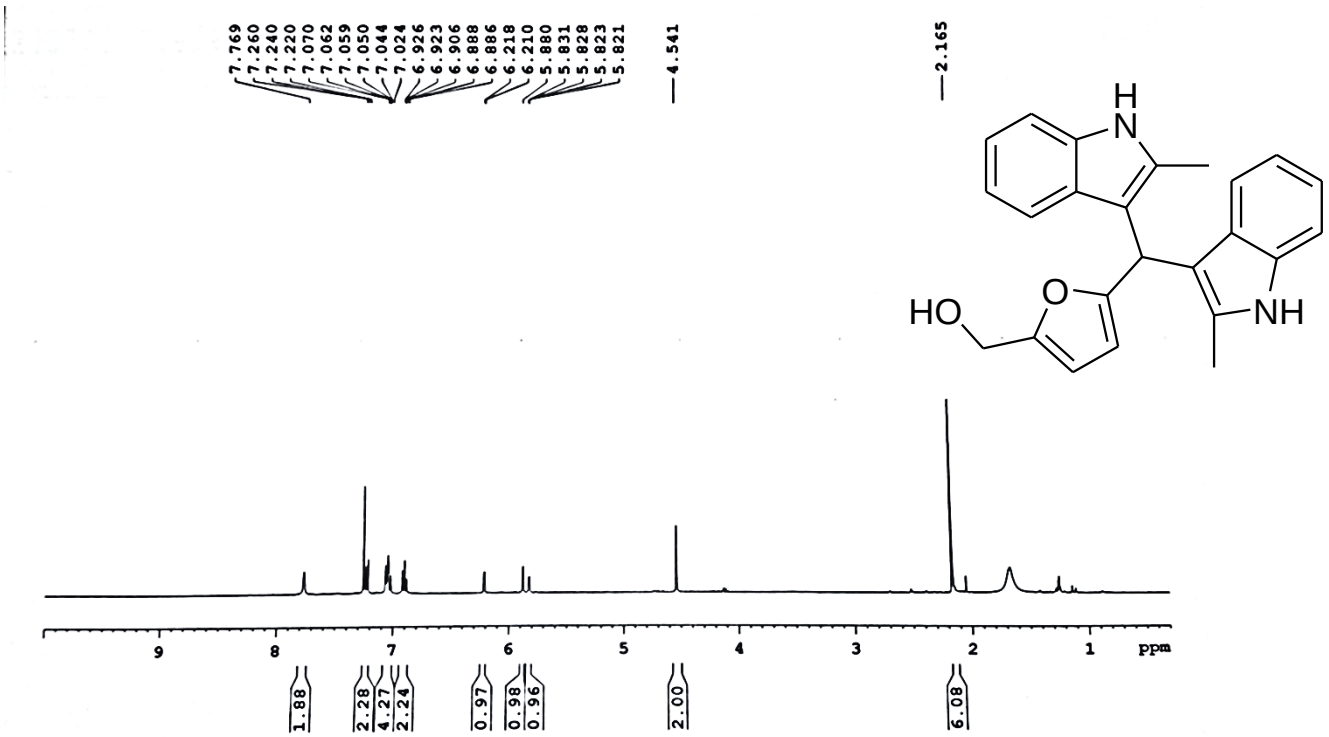
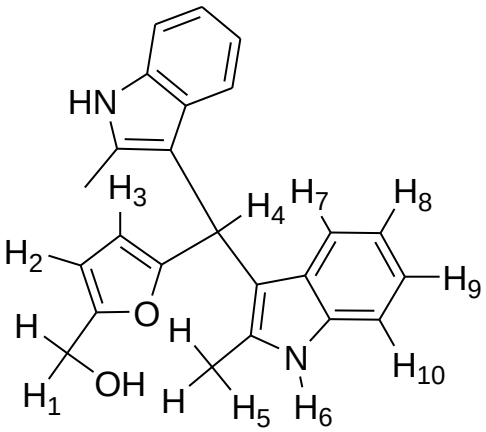


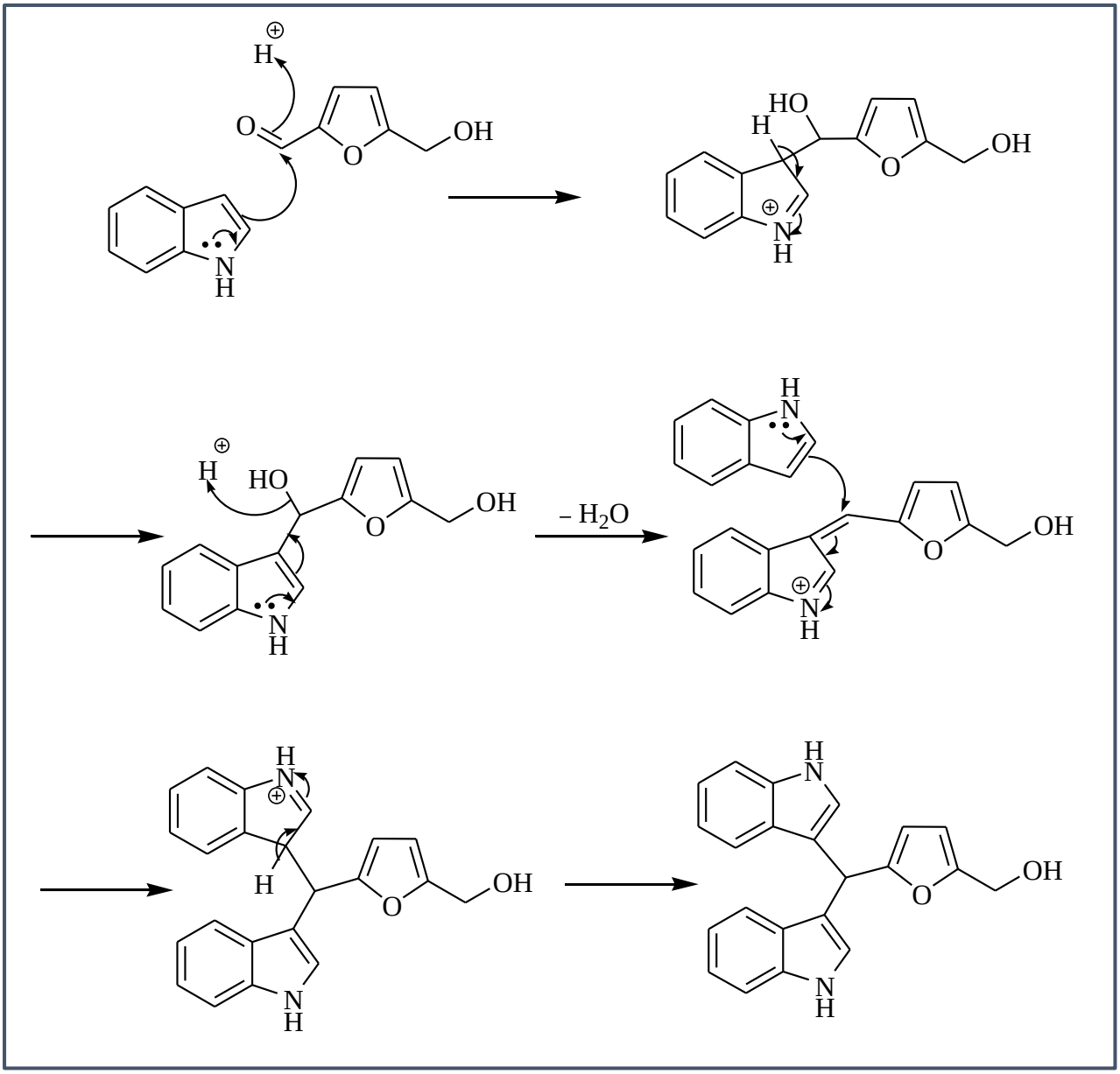
Table 5. NMR data of II D - 3,3'-((5-Hydroxymethylfurfuryl)methylene)bis(2-methyl-1H-indole)

	δ	Multi plicity	*J* (Hz)	No. of Equiv. H
H1	4.541	s	-	2H
H2	5.826	dd	3.2, 1.2, 0.8	1H
H3	6.214	d	3.2	1H
H4	5.880	s	-	1H
H5	2.165	s	-	6H
H6	7.769	s	-	2H
H7	7.034	d	8	2H
H8	6.90	2t	8, 7	2H
H9	7.357	dt	6.2, 3.6, 2.4, 3.2	2H
H10	7.230	d	8	2H



- **Plausible Mechanism:**

Scheme 11. Probable mechanism for the synthesis of BIMs.



Conclusion

In conclusion, we have studied the multicomponent reactions of HMF via a one pot synthesis of Bis(indolyl)methanes. All the 3,3'-bisindolylmethanes synthesized were novel molecule, except for II A which was found to be a patented molecule[42]. A novel 2,2'-BIMs was also synthesized with 3-substitued indole. Additionally, we could successfully synthesis two novel molecules of Di(bis(indolyl))methanes by oxidizing HMF. All BIMs and DI BIMs novel molecules undoubtedly extended the BIMs library. Following novel molecules synthesized were analyzed for their bio-activity.

1. II A - 3,3'-((5-Hydroxymethylfurfuryl)methylene)bis(1H-indole)
2. II B - 3,3'-((5-Hydroxymethylfurfuryl)methylene)bis(5-methoxy-1H-indole)
3. II C - 3,3'-((5-Hydroxymethylfurfuryl)methylene)bis(2-phenyl-1H-indole)
4. II D - 3,3'-((5-Hydroxymethylfurfuryl)methylene)bis(2-methyl-1H-indole)

The purification and analysis of the bio-activity of the remaining BIMs is under investigation.

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