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Multi Component One Pot Synthesis of 3-((1, 3-Bis (Phenyl)-1H-Pyrazol-4-Yl) (1H-Indol-3-Yl) Methyl)-1H-Indole and Their Derivatives by Using Zro_2/SBA-15 Nano Catalyst

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Abstract : The synthesis of 3-((1,3-bis(phenyl)-1H-pyrazol-4-yl)(1H-indol-3-yl)methyl)-1H-indole and their derivatives has been prepared through the reaction of 1,3-diphenyl-1H-pyrazole-4-carbaldehyde and1H-indole using low cost, easily seperable and recyclable nano ZrO2/SBA-15 catalyst through the simple one pot synthesis. This method is very efficient and eco friendly. The synthesized 3-((1,3-bis(phenyl)-1H-pyrazol-4-yl)(1H-indol-3-yl)methyl)-1H-indole derivative's characteristics are assigned by NMR, C^{13} NMR, IR and Mass spectroscopy.

Keywords: one pot synthesis, 3-((1,3-bis(phenyl)-1H-pyrazol-4-yl)(1H-indol-3-yl)methyl)-1H-indole, recyclable nano ZrO2/SBA-15 catalyst.

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I. INTRODUCTION

The multi component reactions clearly have evolved from being a chemical curiosity towards a powerful tool for synthesis in organic chemistry in the past few years. Most of the multi component reactions are proceeds through three or more components those are reacted in a single reactor to form a product retaining all the reactants in this method the desired product with high yield and completed in short time[1&2]. The multi component reactions play an important role in synthesis of heterocyclic compounds [3]. And also the MCRs have been known for over 150 years with the strecker synthesis of α- amino cyanides[4]. Its importance lies mainly in medicinally potent compounds and its convenient preparation[5-7].

In recent times, the heterocyclic compounds continue to drive the field of synthesis in organic chemistry. Organic chemists have been engaged in extension of produce heterocyclic compounds by developing new and efficient synthetic transformation. Pyrazolyl compounds and their derivatives have shown interesting biological activities such as estrogenic activity[8], antipyretic[9], anti-inflommatory[10,11], anticancer[12, 13], antiviral[14, 15] antibiotic[16],anti microbial [17] and analgesic[18]. 1,3-diphenyl-1H-pyrazole-4-carbaldehyde , one of the starting materials is synthesized in our lab as per the procedure[19].

From the literature survey, pyrazolyl methylenebis indoles provide novel lead structures for drug discovery. However, only a few synthetic strategies have been reported for the synthesis of pyrazolyl methelene bis indoles. Farhanullah *et al* reported Amberlyst 15 catalyzed synthesis of indole-pyrazole based tri(hetero) arylmethanes[20]. Sivaprasad G at al using phosphotungestic acid [21]. From the mesoporous Lewis acidic ZrTUD-1 Kandasamy Karthikeyan et al reported[22]. After several methods have been reported to synthesis of bis indoles indole and its derivatives being a key moiety of physiological properties[23-25]. Bis indolyl metabolites affect the central nervous system [26&27]. Various indolyl derivatives display diverse pharmacological activities and are useful in treatment of fibromyalgia, chronic fatigue and irritable bowel syndrome [28-30]. Vibrindole a bisindolylmethane was known to exhibit anti-bacterial activity [31].

Herein, in order to achieve a more efficient synthetic process, minimize by-products, decrease the number of separate reaction steps, improving the yields and reaction times and also in extending our research on the application of nanocatalysts in MCRs, in this we report a clean and environmentally friendly approach to the synthesis of Bis phenyl pyrazolyl methyl bis indoles, via multi-component reaction in the presence of silica coated zerconia nano catalyst (ZrO2/SBA-15). SBA-15 mesoporous silica was prepared according to literature described elsewhere [32-31]. ZrO2/SBA-15 catalyst was prepared by wet impregnation method with zirconium acetyl acetonate as zirconia precursor and SBA-15 [38]

II. EXPERIMENTAL

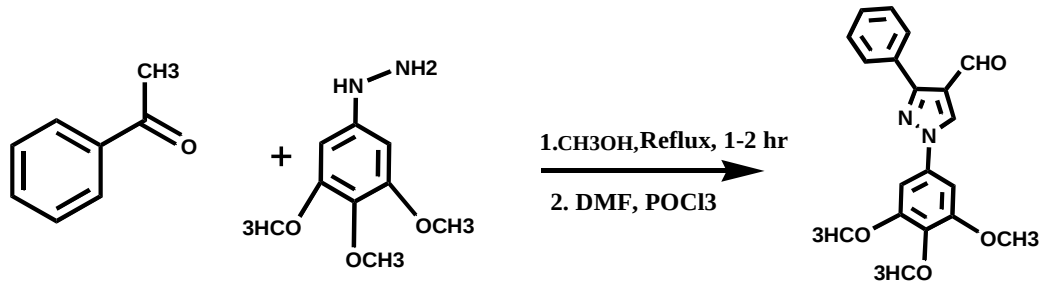
Materials and methods

All the chemicals were used in sigma Aldrich aldehedes and indoles purified by distillation prior. 1HNMR and 13C NMR spectra were recorded on Bruker 300 MHz spectrometer, and 75 MHz, using TMS as an internal standard (chemical shifts in d). Peak multiplicitiesof NMR signals were designated as s (singlet), bs (broad singlet), d (doublet), dd (doublet of doublet), t (triplet), m (multiplet) etc. The HRMS spectra were recorded as ESI-HRMS on a Q-TOF LC-MS/MS mass spectrometer. All experiments were monitored by thin layer chromatography (TLC) performed on pre-coated silica gel plates. After elution, plate was visualized under UV illumination at 254nm for UV active materials. Further visualization was achieved by staining with KMnO4 and charring on a hot plate. Column chromatography was performed on silica gel (100-200 mesh) by standard techniques.

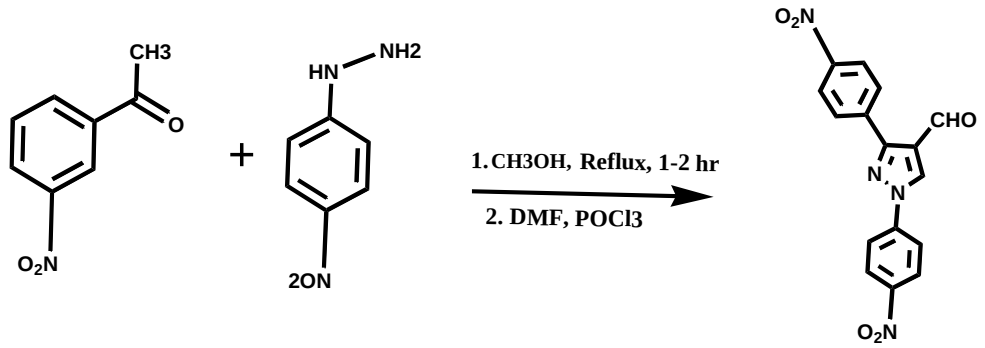
Scheme-1&2 Synthesis of 3-phenyl-1-(3,4,5-trimethoxyphenyl)-1H-pyrazole-4-carbaldehyde and 1,3-bis(4-nitrophenyl)-1H-pyrazole-4-carbaldehyde[19]

Substituted phenyl hadrazones were prepared by heating substituted acetophenone with different hydrazines in methanol under for 1-2hrs. phosphorous oxychloride (0.02 mol) was added drop wise to a mixture of dmf (0.1mol) and phenyl hydrazone (0.01mol) under cold condition.

After the addition, the reaction mixture was stirred at 60-70^{0}C for 1-2 hrs. Solution was cooled and poured into ice cubes and neutralize the solid obtained under the suction and recrystalized from methanol.



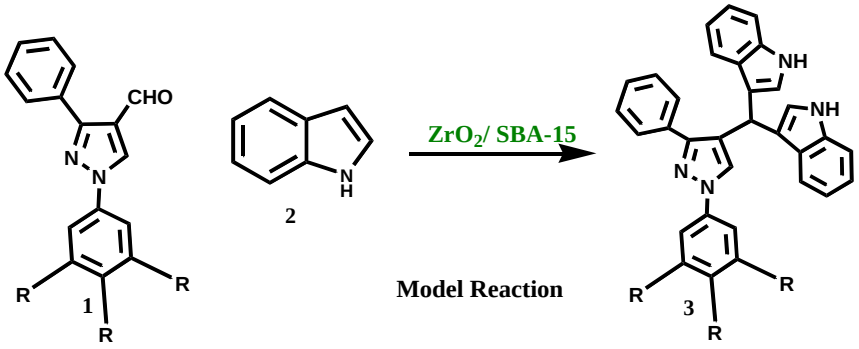
Scheme -1



Scheme -2

Scheme- 3 General experimental procedure for synthesis of 3-((1,3-bis(phenyl)-1H-pyrazol-4-yl)(1H-indol-3-yl)methyl)-1H-indole

The one pot synthesis of 3-((1,3-bis(phenyl)-1H-pyrazol-4-yl)(1H-indol-3-yl)methyl)-1H-indole And derivatives carried out in 100ml round bottomed flask taking 1,3-diphenyl-1H-pyrazole-4-carbaldehyde(1 mmol), indole (2mmol), 15mol% ZrO2/SBA-15 and water as solvent the reaction was stirred for 1hr at 100^0 C. the progress of the reaction was monitored by TLC. After the completion of the reaction, the catalyst was separated and mixture was cooled, filtered. The obtained solid product is washed with ethyl acetate the desired 3-((1,3-bis(phenyl)-1H-pyrazol-4-yl)(1H-indol-3-yl)methyl)-1H-indole were obtained with high yields. The identify and purity of the products were confirmed by H NMR, C NMR and mass spectra recorded on a perkin elmer spectra-880 spectrophotometer by using KBr pellets in the Region 400-4500 recorded on a (Perkin Elmer Spectra-880) spectrophotomet cm−1 and 1H NMR spectra was characterized by 400 MHz-(Bruker Avance) in CDCl3 solvent and MASS spectra was recorded at 70 eV (MASPEC low resolution mass spectrometer).

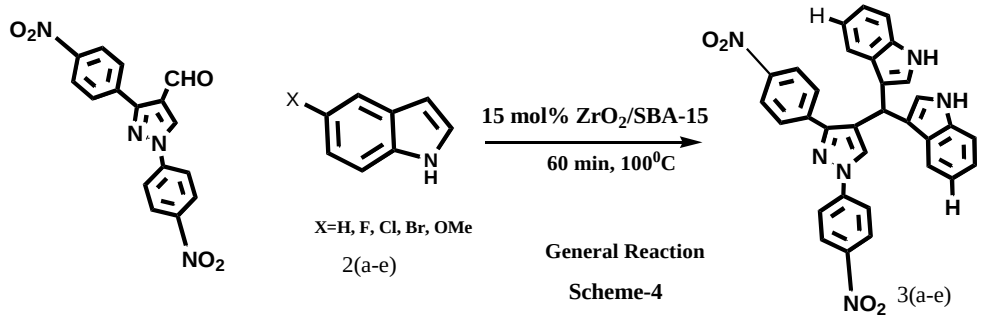


Model Reaction

R= NO2, OCH3

From this model reaction procedure new methodology for one pot synthesis of 3-((1,3-bis(phenyl)-1H-pyrazol-4-yl)(1H-indol-3-yl)methyl)-1H-indole taking into consideration avoiding Solvents, long reaction time the usage of a new and efficient catalyst with high catalytic activity and easy work up reo the synthesis of 3-((1,3-bis(phenyl)-1H-pyrazol-4-yl)(1H-indol-3-yl)methyl)-1H-indole and their derivatives.

Scheme – 4&5 Synthesis of 3-((1,3-bis(phenyl)-1H-pyrazol-4-yl)(1H-indol-3-yl)methyl)-1H-indole and their derivatives



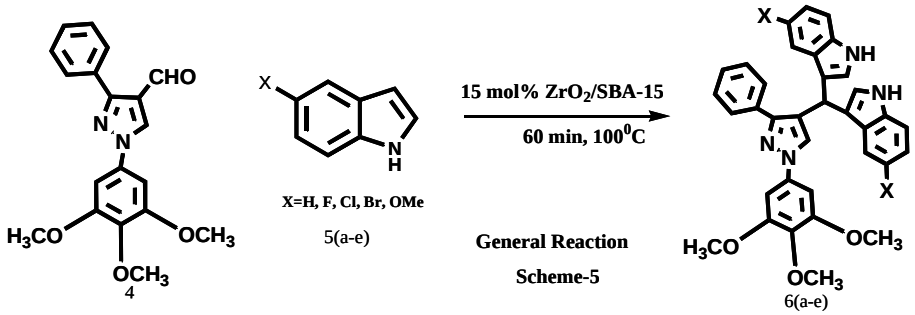


Table:1 Optimised conditions of synthesis of 3-((1,3-bis(phenyl)-1H-pyrazol-4-yl)(1H-indol-3-yl)methyl)-1H-indole

Entry	Solvent	Tempertature (^{0}C)	Catalyst (mol %)	Time (min)	Yield %
1	--	--	--	120	--
2	Water	RT	--	120	---
3	Methanol	RT	--	120	--
4	DMSO	RT	--	120	--
5	CH3CN	RT	--	120	--
6	Water	50	5	60	<10
7	Methanol	50	5	60	<12
8	DMSO	50	5	60	--
9	CH3CN	50	5	60	<05
10	Water	90	10	40	42
11	Methanol	90	10	40	<10

12	DMSO	90	10	40	<15
13	CH3CN	90	10	40	<20
14	Water	100	15	60	98
15	Water	100	20	60	98
16	Water	100	25	60	98

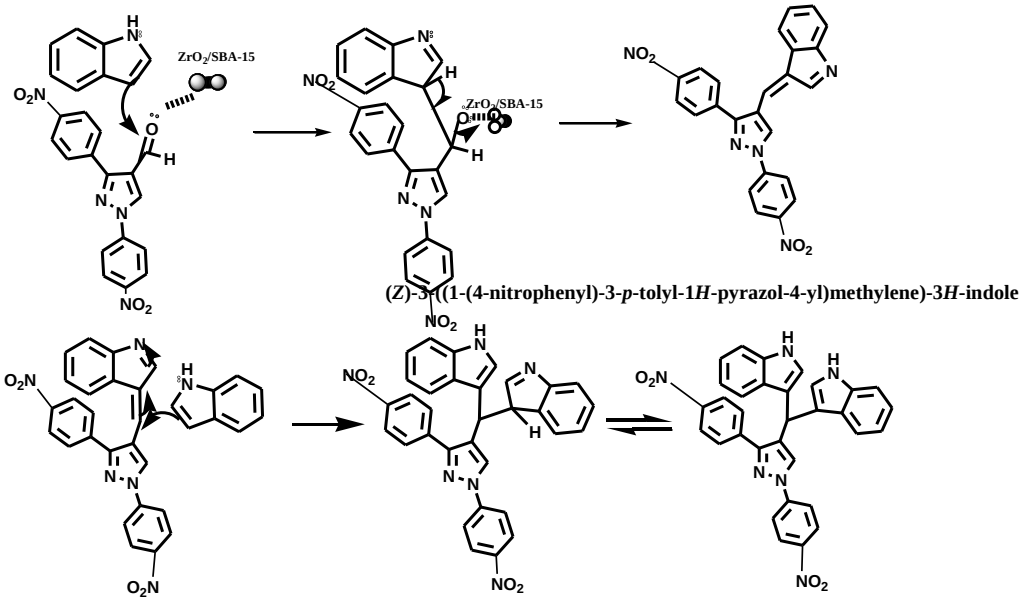
Table- 2 Table 2: Synthesis of 3-((1,3-bis(phenyl)-1H-pyrazol-4-yl)(1H-indol-3-yl)methyl)-1H-indole and their derivatives

Code	Aldehydes (R=)	Indoles (X=)	Time (min)	Yield (%)
3a	NO_2	H	60	98
3b	NO_2	F	45	86
3c	NO_2	Cl	60	91
3d	NO_2	Br	55	93
3e	NO_2	OMe	60	98
6a	OCH_3	H	60	87
6b	OCH_3	F	55	79
6c	OCH_3	Cl	45	83
6d	OCH_3	Br	40	84
6e	OCH_3	OMe	50	87

III. RESULT AND DISCUSSION

in present work involves the multi components in one reactor to synthesize 3-((1,3-bis(phenyl)-1H-pyrazol-4-yl)(1H-indol-3-yl)methyl)-1H-indole and their derivatives the reaction between 1,3-diphenyl-1H-pyrazole-4-carbaldehyde(1) and indole (2) is taken as model substrates in presence of reusable nano ZrO_2/SBA-15 catalyst is shown in scheme 3. In this investigation the effects of catalytic amount, temperature changes and solvents on the yield of model reaction were shown in table.1. Obviously it was clearly observed that no yield of product was obtained without solvent and catalyst at room temperature even after 2hrs(table .1 entry .1) we have investigated the same reaction by using various solvents without catalyst at room temperature even after 2 hrs no new spots observes on TLC plate (table.1 entry 2-5). When added 5 mol % of ZrO_2/SBA-15 catalyst in water and methanol at 50 ^{0} C after 1hr trace amount of yields observed (table.1 entry 6&7). No products observed with the same catalyst loading and temperature in solvents of DMSO and CH_3CN (table. 1 entry 8&9). The reaction proceeds with 10 mol % of ZrO_2/SBA-15 at 100^0 C greater yield was observed in the solvent of water (table.1 entry .10) water than other solvents low yield observed (table.1entries 11-13). Greater percentage of yield observed with 15 mol % of catalyst at 100^0 C in water (table. 1 entry 14). No increase of yield observed in increasing of ZrO_2/SBA-15(table .1 entries 15 & 16).

Successfully optimize the model reaction condition follows the synthesis of 3-((1,3-bis(phenyl)-1H-pyrazol-4-yl)(1H-indol-3-yl)methyl)-1H-indole in presence of 15 mol% of ZrO_2/SBA-15 at 100^0 C in water. After finding the reaction condition the model reaction is performed with various aldehydes and indoles were observed yields are summarized in table. 2. Greater amount of yields obtained from nitro substituted aldehydes than methoxy substituted aldehydes (3a-3e) and also observed better yields in without electron releasing grouped indoles (3a, 6a, 3e&6e). These synthesized 3-((1,3-bis(phenyl)-1H-pyrazol-4-yl)(1H-indol-3-yl)methyl)-1H-indole derivatives were analyzed through proton nuclear magnetic resonance, carbon nuclear magnetic resonance and mass spectral analysis. The plausible mechanism for the synthesized 3-((1,3-bis(phenyl)-1H-pyrazol-4-yl)(1H-indol-3-yl)methyl)-1H-indoleby using reusable ZrO_2/SBA-15 is shown in figure .1. the reaction proceeds by the formation of highly reactive , not isolated Z)-3-((1, 3-diphenyl-1H-pyrazol-4-yl) methylene)-3H-indole.



Plausible Mechanism

We need to examine the reusability of the ZrO_2/SBA-15 catalyst by the synthesis of 3-((1,3-bis(phenyl)-1H-pyrazol-4-yl)(1H-indol-3-yl)methyl)-1H-indole. From this investigation the catalyst can be re used upto 5 cycles (table.3) the catalyst was seperated by simple filtration after the reaction, washed with pure double distilled water followed by ethylacetate, dried at 100^0 and reused for the next cycle.

Table -3 Reusability of nanocatalyst

Reaction cycle	1	2	3	4	5
Yield (%)	98	96	95	92	90

Spectral analysis data

3a. 3-(1,3-bis (4-nitrophenyl)-1H-pyrazol-4-yl)(1H-indol-3-yl)methyl)-H-indole

Pale red solid. M.P: 175- 177 ^{0}C; HNMR (300MH$_z$, DMSO-d$_6$) : δ 5.95(1H, s), 6.86- 6.91(2H,m), 7.05-7.09(2H,t, J= 7.742), 7.20-7.43(10H, m) , 7.67-7.75(5H,m) 7.83(1H,s),10.4(2H,s).^{13}C NMR (75MH$_z$, DMSO-d$_6$) : δ 30.0; 111.3; 117.9; 118.1; 118.1; 120.8; 123.4; 125.4; 127.5; 128.1; 129.1; 129.1; 133.3; 133.3; 136.7; 139.5; 150.0.HRMS (ESI) *m/z*: calc. for [M+H$^+$] $C_{32}H_{22}N_6O_4$: 555.55; found: 555.98

3b. 3-(1,3-bis (4-nitrophenyl)-1h-pyrazol-4-yl)(5-fluoro 1H-indol-3-yl)methyl)-5-fluoro-1H-indole

Pale yellow Solid . M.P: 267- 269 ^{0}C; ^{1}H NMR (300MH$_z$, DMSO-d$_6$) : δ 5.87(1H,s) , 6.90(2H,d,J=1.88),7.057.08(1H,dd,J$_1$=1.88&J$_2$=6.798),7.247.46(9H,m),7.647.74(5H,m),10.49(2H,s) ; ^{13}C NMR (75MH$_z$, DMSO-d$_6$) : δ 27.6; 110.2; 115.3; 115.8; 118.8; 121.3; 122.2; 122.7; 123.4; 124.8; 125.1; 125.8; 126.7; 130.7; 132.9; 137.2; 147.9.HRMS (ESI) *m/z*: calc. for [M+H$^+$] $C_{32}H_{20}F_2N_6O_4$: 591.54; found: 591.89

3c. 3-(1,3-bis (4-nitrophenyl)-1h-pyrazol-4-yl)(5-chloro1H-indol-3-yl)methyl)-5-chloro -1H-indole

Pale red Solid . M.P: 203- 206^{0}C; ^{1}H NMR (300MH$_z$, DMSO-d$_6$) : δ 5.87(1H,s) , 6.85(2H,d,J= 1.88), 7.20-7.48(11H,m), 7.68-7.75(4H, m), 1.015(2H,s); ^{13}C NMR (75MH$_z$, DMSO-d$_6$) : δ 29.0; 110.6; 112.0; 116.8; 117.4; 120.4; 123.0; 123.6; 126.6; 127.0; 127.3; 128.1; 132.2; 134.6; 138.7; 149.4.HRMS (ESI) *m/z*: calc. for [M+H$^+$] $C_{32}H_{20}Cl_2N_6O_4$: 624.45; found: 624.83

3d. 3-(1,3-bis (4-nitrophenyl)-1h-pyrazol-4-yl)(5-bromo 1H-indol-3-yl)methyl)-5-bromo -1H-indole

Pale pink Solid . M.P: 254- 258 ^{0}C; ^{1}H NMR (300MH$_z$, DMSO-d$_6$) : δ 5.85(1H,s) 6.83-6.91(4H,m) 7.23-7.45 (7H,m), 7.54(1H,d,J=3.021), 7.66-7.75(5H,m) 1.15(2H, broad singlet) ; ^{13}C NMR (75MH$_z$, DMSO-d$_6$) : 31.2; 104.6; 104.9; 110.2; 110.5; 112.9; 113.0; 119.3; 125.7; 126.7; 127.4; 127.6; 128.5; 129.2; 130.0; 134.2; 134.4; 140.7; 151.4; 156.3; 159.4.HRMS (ESI) *m/z*: calc. for [M+H$^+$] $C_{32}H_{20}Br_2N_6O_4$: 713.35; found: 713.76

3e. 3-(1,3-bis (4-nitrophenyl)-1h-pyrazol-4-yl)(5-methoxy 1H-indol-3-yl)methyl)-5-methoxy -1H-indole

Pale pink Solid . M.P: 194- 198 ^{0}C; ^{1}H NMR (300MH$_z$, DMSO-d$_6$) : δ 2.48(6H,s-OCH$_3$), 4.72(1H,s) 5.56-5.64(4H,m), 5.91(2H, d, J=2.077), 6.18(3H,t,J= 7.931) 6.29-6.40(5H,m), 6.61(2H, dd, J$_1$= 1.700,J$_2$= 6.421) 6.75(2H, d, J= 7.742) ,7.11(1H,s), 9.62(2H,s).; ^{13}C NMR (75MH$_z$, DMSO-d$_6$) : δ 30.0; 55.5; 101.1; 111.0; 112.5; 118.; 118.4; 124.7; 126.0; 126.3; 127.0; 128.1; 128.3; 128.8; 129.8; 132.2; 133.7; 139.9; 150.5; 153.1.HRMS (ESI) *m/z*: calc. for [M+H$^+$] $C_{34}H_{26}N_6O_6$ 615.61; found: 615.92

6a. 3-((1H-indol-3yl)(3-phenyl-1-(3,4,5-trimethoxyphenyl)-1H-pyrazol-4-yi)methyl)-1Hindole
White solid. M.P: 236-238^{0}C. ^{1}H NMR (300MH$_z$, DMSO-d$_6$): δ 2.60(6H,t,J= 1.70), 3.75(3H,s), 5.96(1H,s), 6.92-696(8H,m), 7.072-7.11(3H,t,J= 70176), 7.36-7.45(6H,m), 10.54(2H,s).; ^{13}C NMR (75MH$_z$, DMSO-d$_6$) : δ 30.5; 55.4; 60.3; 111.8; 105.0; 118.3; 118.6; 119.1; 121.3; 124.1; 125.5; 126.1; 126.5; 128.2; 129.0; 129.6; 137.2; 137.5; 139.8; 150.0; 153.0; HRMS (ESI) *m/z*: calc. for [M+H$^+$] $C_{35}H_{28}N_4O_3F_2$: 555.64; found: 555.55

6b. 3-fluoro-3-((5-fluoro-1H-indole-3-yl)(3-phenyl-1-(3,4,5-trimethoxyphenyl)-1H-pyrazol-4-yl) methyl)-1H-indole
Pale pink Solid. M.P: 286 - 288^{0}C; ^{1}H NMR (300MH$_z$, DMSO-d$_6$) : δ 3.44(6H,s), 3.83(3H,s) 5.87(1H,s), 6.91-6.96(4H,m), 7.08-7.11(2H,dd,J_1=1.88,J_2=6.60) 7.23-7.47(7H,m) 7.57(1H,s), 7.70(2H,d,J=7.742), 10.1892H,s).; ^{13}C NMR (75MH$_z$, DMSO-d$_6$) : δ 28.6; 53.6; 55.5; 58.8; 103.1; 111.2; 116.2; 116.7; 119.8; 122.3; 122.9; 123.9; 124.3; 125.7; 126.1; 127.1; 127.6; 133.9; 135.7; 138.1; 148.4; 151.2; HRMS (ESI) *m/z*: calc. for [M+H$^+$] $C_{35}H_{28}F_2N_4O_3$: 591.54; found: 591.62

6c. 5-chloro-3-((5-chloro-1H-indole-3-yl)(3-phenyl-1-(3,4,5-trimethoxyphenyl)-1H-pyrazol-4-yl) methyl)-1H-indole
White Solid. M.P: 216- 288^{0}C; ^{1}H NMR (300MH$_z$, DMSO-d$_6$) : δ 3.45(6H,s), 3.82(3H,s), 5.86(1H,s), 6.93(4H,m), 7.19-7.35(5H,m), 7.41-747(4H,s). 7.58(1H,s), 7.70(2H,d,J=7.742), 10.46(2H,s).; ^{13}C NMR (75MH$_z$, DMSO-d$_6$) : δ 29.3; 54.4; 59.5; 103.9; 110.7; 112.6; 116.8; 117.5; 120.2; 123.1; 123.7; 124.6; 125.1; 126.9; 127.2; 127.9; 128.4; 134.9; 136.5; 138.8; 149.1; 152.0; HRMS (ESI) *m/z*: calc. for [M+H$^+$] $C_{35}H_{28}N_4O_3Cl_2$: 624.53; found: 624.62.

6d. 5-bromo-3-((5-bromo -1H-indole-3-yl)(3-phenyl-1-(3,4,5-trimethoxyphenyl)-1H-pyrazol-4-yl) methyl)-1H-indole
Pale pink Solid. M.P: 154- 156^{0}C; ^{1}H NMR (300MH$_z$, DMSO-d$_6$) : 53.43(6H,s), 3.81(3H,s), 5.84(1H,s), 6.84-7.01(8H,m), 7.22-7.45(5H,m) 7.54(1H,s), 7.61(1H,s) 7.69(2H,d,J=7.742) 10.20(2H,s).;^{13}C NMR (75MH$_z$, DMSO-d$_6$) : δ30.2; 54.9; 60.1; 103.2; 103.5; 104.3; 109.0; 109.4; 111.8; 117.9; 124.1; 125.4; 127.4; 128.4; 128.8; 133.3; 136.9; 139.4; 149.8; 152.5; 155.1; 158.2. HRMS (ESI) *m/z*: calc. for [M+H$^+$] . $C_{35}H_{28}N_4O_3Br_2$: 713.43; found: 713.53.

6e.5-methoxy-3-((5-methoxy-1H-indole-3-yl)(3-phenyl-1(3,4,5trimethoxyphenyl)1Hpyrazol-4-yl) methyl)-1H-indole
WhiteSolid. M.P: 204- 208 ^{0}C; ^{1}H NMR (300MH$_z$, DMSO-d$_6$) : 3.42(6H,s), 3.76(6H,s), 3.80(3H,s)5.85(1H,s), 6.77-6.90(6H,m), 7.01(2H,s), 7.22-7.34(3H,m), 7.42(2H,t,J=7.554) 7.60-7.72(3H,m), 10.01(2H,s).;^{13}C NMR (75MH$_z$, DMSO-d$_6$) : δ 284; 53.1; 53.6; 58.4; 99.4; 102.6;108.9; 109.9; 115.9; 116.2; 122.5; 122.9; 123.7; 124.7; 125.8; 126.9; 127.0; 130.2; 135.1; 137.7; 148.1; 150.7; 151.0; HRMS (ESI) *m/z*: calc. for [M+H$^+$]. $C_{37}H_{34}N_4O_5$: 615.69; found: 615.86.

IV. SUMMARY & CONCLUSION

In this present study, we concluded that the synthesis of 3-((1,3-bis(phenyl)-1H-pyrazol-4-yl)(1H-indol-3-yl)methyl)-1H-indole and their derivatives by using easily separable and reusable ZrO_2/SBA-15 nano catalyst. This method offers so many advantages including simplicity of operation, low cost, cleaner and short time reaction and being good to excellent yields.

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