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A mild, efficient and improved protocol for the synthesis of novel indolyl crown ethers, di(indolyl)pyrazolyl methanes and 3-alkylated indoles using $H_4[Si(W_3O_{10})_3]$

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Abstract—Efficient electrophilic substitution reactions of indoles with various aldehydes proceed smoothly in acetonitrile using heteropoly acid ($H_4[Si(W_3O_{10})_3]$) to afford the corresponding new indolyl crown ethers and di(indolyl)pyrazolyl methanes. $H_4[Si(W_3O_{10})_3]$ is also found to catalyze the Michael addition of indoles to α,β-unsaturated compounds for the synthesis of 3-alkylated indoles.

1. Introduction

The synthesis and the reactions of indoles have received much interest for over a century because a number of their derivatives occur in nature and possess a variety of biological activities.[1] Pyrazole derivatives have been found to have anticancer,[2] antiviral[3] and antihyperglycemic activity.[4] Our efforts here are to synthesize the di(indolyl)-pyrazolyl methanes which might exert high antimicrobial activity.[5] Crown ethers are heteromacrocycles in which the framework is typically comprised of repeating ethylene oxy[–(CH_2CH_2O)–] units. Nitrogen and sulfur commonly replace oxygen in this framework leading to a great variety of compounds that have been used in molecular recognition studies and supramolecular chemistry.[6] Alkali metal cation–π interactions have recently received considerable attention due to their biological importance.[7]

The electrophilic substitution reactions of indoles with aromatic aldehydes afford corresponding bis(indolyl)-methanes. Lewis acids,[8] protic acids,[9] ionic liquids,[10] iodine,[11] clays,[12] LPDE,[13] amberlyst-15[14] and $RE(PFO)_3$[15] are known to promote these reactions. However, many Lewis acids are deactivated or sometimes decomposed by nitrogen containing reactants. Even when the desired reactions proceed, more than stoichiometric amounts of Lewis acids are required because the acids are trapped by nitrogen.[16]

The 3-position of indole is the preferred site for the electrophilic substitution reactions, 3-alkyl or acyl indoles are versatile intermediates for the synthesis of a wide range of indole derivatives.[17] A simple and direct method for the synthesis of 3-alkylated indoles involves the conjugate addition of indoles to α,β-unsaturated compounds in the presence of either protic[18] or Lewis acids.[19] However, the acid catalyzed conjugate addition of indoles requires careful control of acidity to prevent side reactions such as dimerization or polymerization. Many of these procedures involve strongly acidic conditions, expensive reagents and long reaction times, give low yields of the products and involve cumbersome experimental product isolation procedures. The lanthanide triflates and gold catalysts[20] though less acidic are rather expensive which limits their use in large scale synthesis. For this reason, cheaper acid catalysts that secure catalytic activity, low toxicity, moisture and air tolerance are desirable. In this paper, we wish to introduce $H_4[Si(W_3O_{10})_3]$ as mild, highly efficient moisture tolerant catalyst for the preparation of indole derivatives under mild conditions.

Heteropolyacids are remarkable catalysts that are used in both homogenous and heterogeneous conditions. Their application as acid catalysts has been already reviewed.[21] $H_4[Si(W_3O_{10})_3]$ is a solid heteropolyacid that has been used

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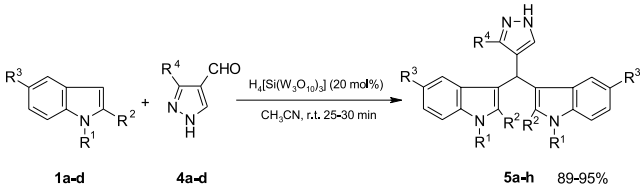
for the synthesis of trioxanes,[22] polymerization and for estimating nicotine and radioactive cesium in some derivatives.[23] Its efficiency as an acid catalyst in condensation and Michael addition in indoles is explored in this report.

2. Results and discussion

Di(indolyl)pyrazolylmethanes have been synthesized via $H_4[Si(W_3O_{10})_3]$ catalyzed condensation of indole (2 equiv) and pyrazolyl aldehydes (1 equiv). The reaction is facile and is complete within 30 min at room temperature. The method reported is favorable as good yields (89–95%) are obtained (Scheme 1). The procedure finds easy applicability because of the solubility of $H_4[Si(W_3O_{10})_3]$ in acetonitrile.



Scheme 1.

The catalytic activity of $H_4[Si(W_3O_{10})_3]$ is found to vary with different solvents (Table 1). The reaction of indole **1** with pyrazolyl aldehyde **4a** using $H_4[Si(W_3O_{10})_3]$ (20 mol%) as a catalyst was chosen as a model for optimization. Acetonitrile was found to give maximum yield followed by THF. The catalyst was found to be only mildly effective in dichloromethane. The effect of different ionic liquids on the $H_4[Si(W_3O_{10})_3]$ (20 mol%) catalyzed reaction was also examined. Butyl methyl imidazolium chloride [bmim][Cl] was found to be better than the other ionic liquids, but it could not compete with the effectiveness of the catalyst in acetonitrile.

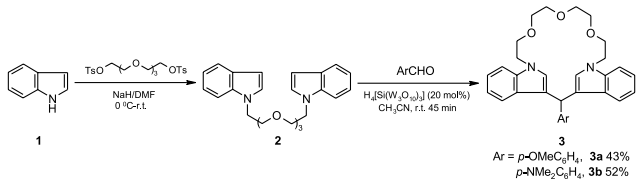
Table 1. Effect of solvent on the conversion to di(indolyl)pyrazolyl methane (**5a**)

Entry	Solvents	Time (min)	Yield (%)[a]
a	EtOH	60	75
b	THF	60	87
c	CH_2Cl_2	60	20
d	CH_3CN	25	95
e	[pmim][Br]	60	56
f	[ppy][Br]	60	41
g	[bmim][Cl]	60	72

[a] Isolated yields.

New indolyl crown ethers have been synthesized (Scheme 2) via $H_4[Si(W_3O_{10})_3]$ (20 mol%) catalyzed condensation of indole **2** (1 equiv) and aldehyde (1 equiv) under mild conditions. The reaction is facile and complete within 45 min at room temperature. The structure of **3a**[24] was further confirmed by single crystal X-ray crystallography (Fig. 1).

The efficacy of Lewis acids, such as CuI, $ZnCl_2$, $FeCl_3$, $CeCl_3$ and $InCl_3$ in acetonitrile was studied for the synthesis of di(indolyl)pyrazolylmethane **5a**. In comparison,



Scheme 2.

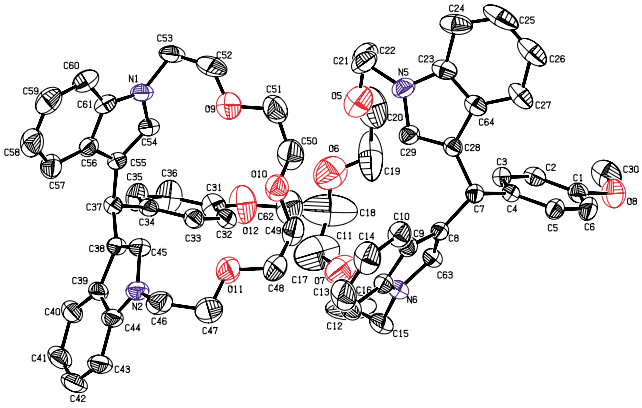


Figure 1. X-ray crystal structure of **3a**.

$H_4[Si(W_3O_{10})_3]$ was found to be an excellent acid catalyst in terms of conversion and reaction time (Table 2).

The maximum yield was 95% for **5a**. In fact, all the pyrazolyl aldehyde condensed with indoles giving di(indolyl)pyrazolylmethanes **5a–h** in high yields (89–95%). The catalytic activity of $H_4[Si(W_3O_{10})_3]$ was explored for the Michael addition of indole with α,β-unsaturated carbonyl compounds (Scheme 3). Methyl vinyl ketone reacted with indole and 2-methyl indole in the presence of a catalytic amount of $H_4[Si(W_3O_{10})_3]$ to give the 3-alkylated indoles (**7a**, **7c**) in excellent yields (Table 3).

The reaction was found to proceed smoothly at ambient temperature with high selectivity. Other electron deficient olefins like phenyl vinyl ketone **6b** afforded the product in good yield (87%). The same reaction was attempted with β-nitro styrene **6d** with indole in the presence of $H_4[Si(W_3O_{10})_3]$. The corresponding 3-alkylated indole **7f** was obtained in 90% yield without any side reactions thereby emphasizing the mild catalytic activity of $H_4[Si(W_3O_{10})_3]$.

The reactions were clean and the products were obtained in high yields (85–93%) without the formation of any side products such as dimers or trimers, which are normally observed under the influence of strong acids. Furthermore, no aqueous work-up was required after completion of the reaction. The reaction mixture was directly charged into a column after removing the solvent under vacuum.

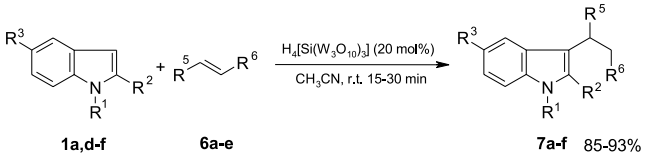
3. Conclusions

In conclusion, we report $H_4[Si(W_3O_{10})_3]$ as a highly efficient catalyst for the synthesis of new indolyl crown ethers, di(indolyl)pyrazolylmethanes and Michael addition

Table 2. $H_4[Si(W_3O_{10})_3]$ catalyzed synthesis of di(indolyl)pyrazolyl methanes[a]

Entry	Substituents				Time (min)	Yield (%)[b]
	R^1	R^2	R^3	R^4		
a	H	H	H	C_6H_5 **5a**	25	95
b	H	H	H	*m*-$OMeC_6H_4$ **5b**	30	94
c	H	H	H	*p*-$OMeC_6H_4$ **5c**	30	91
d	H	H	H	*p*-ClC_6H_4 **5d**	25	90
e	H	Me	H	C_6H_5 **5e**	30	93
f	H	H	OMe	C_6H_5 **5f**	30	89
g	Me	H	H	C_6H_5 **5g**	30	94
h	Me	H	H	*p*-ClC_6H_5 **5h**	30	91

[a] All products were characterized by IR, NMR and mass spectra.
[b] Isolated yields after purification.



Scheme 3.

Table 3. $H_4[Si(W_3O_{10})_3]$ catalyzed synthesis of 3-alkylated indoles[a]

Entry	Substituents					Product	Time (min)	Yield (%)[b]
	R^1	R^2	R^3	R^5	R^6			
a	H	H	H	H	COMe **6a**	**7a**	15	85
b	H	H	H	H	COPh **6b**	**7b**	15	87
c	H	Me	H	H	COMe **6a**	**7c**	10	91
d	H	H	H	*p*-$OMeC_6H_4$	COPh **6c**	**7d**	25	89
e	Me	H	H	*p*-$OMeC_6H_4$	COPh **6c**	**7e**	15	93
f	H	H	H	Ph	NO_2 **6d**	**7f**	15	90
g	*n*-Pr	H	H	*p*-$OMeC_6H_4$	COPh **6c**	**7g**	20	92
h	*n*-Bu	H	H	*p*-$OMeC_6H_4$	COPh **6c**	**7h**	15	90
i	H	H	OH	Ph	NO_2 **6d**	**7i**	25	90
j	H	H	H	CO_2Me	NO_2 **6e**	**7j**	20	93

[a] All products were characterized by IR, NMR and mass spectra.
[b] Isolated yields after purification.

of indoles with α,β-unsaturated carbonyl compounds. The reactions were successfully carried out in the presence of a catalytic amount of $H_4[Si(W_3O_{10})_3]$ in acetonitrile. $H_4[Si(W_3O_{10})_3]$ offers several advantages including mild reaction conditions, cleaner reactions, shorter reaction times, and high yields of products. This simple experimental procedure, offers an alternative route to the synthesis of biologically active indole derivatives.

4. Experimental

4.1. General

Melting points were recorded on a CONCORD melting point apparatus and are uncorrected. Analytical TLC was performed on precoated sheets of silica gel G of 0.25 mm thickness containing PF254 indicator (Merck, Darmstadt). $H_4[Si(W_3O_{10})_3]$ was purchased from Sisco Research Lab, India and used as such. Column chromatography was performed with silica gel (100–200 mesh, s.d fine). Mass spectra were recorded on JEOL-JMS DX 303HF mass spectrometer. IR spectra were recorded on a Perkin–Elmer FTIR spectrometer. NMR spectra were obtained on a JEOL ECA-500 MHz spectrometer. NMR was recorded at 500 MHz in $CDCl_3$ and DMSO-d_6 and the chemical shifts are given in δ. X-ray diffraction data were made on a Bruker SMART CCD area detector with monochromated Mo Kα radiation.

4.1.1. 1-[2-(2-{2-[2-(1*H*-Indol-1-yl)ethoxy]ethoxy}ethoxy)-ethyl]-1*H*-indole (2). Indole **1a** (500 mg, 4.27 mmol) was added to a suspension of NaH (60% in oil, 256 mg, 6.41 mmol washed with dry *n*-hexane [3×10 mL] by syringe) in dry DMF (30 mL), was stirred at 0 °C under nitrogen atmosphere. After the evolution of hydrogen gas had ceased, a dry DMF (10 mL) solution of tetraethylene glycol ditosylate (1.07 g, 2.14 mmol) was added dropwise to the suspension with stirring for 50 min at room temperature. After the reaction was complete, the organic solution was filtered and evaporated in vacuum, extracted with EtOAc (3×20 mL) washed with water, the brine then dried over anhydrous Na_2SO_4 and purified by column chromatography (Merck, 100–200 mesh, EtOAc–hexane, 2:8) to afford the pure product **2** in 85% yield (1.42 g) as a light yellow oil; [Found: C, 73.41; H, 7.15; N, 7.12. $C_{24}H_{28}N_2O_3$ requires C, 73.44; H, 7.19; N, 7.14%]; ν_{max} (neat) 3301, 1610, 1464, 1101, 754 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.70 (2H, d, J=8.0 Hz, ind *H*), 7.40 (2H, d, J=9.1 Hz, ind *H*), 7.27 (2H, t, J=7.4 Hz, ind *H*), 7.21 (2H, t, J=3.4 Hz, ind *H*), 7.17 (2H, t, J=7.4 Hz, C=C*H*N), 6.55 (2H, d, J=2.9 Hz, C*H*=CHN), 4.30 (4H, t, J=5.7 Hz, CH_2N), 3.79 (4H, t, J=5.7 Hz, OCH_2CH_2N), 3.53–3.49 (8H, m, OCH_2-CH_2O); δ_C (125 MHz, $CDCl_3$) 136.2, 128.8, 128.7, 121.6,

121.1, 119.5, 109.5, 101.3, 70.9, 70.7, 70.3, 46.3; *m/z* 392 (M^+).

4.2. Typical experimental procedure 3

A mixture of indole **2** (510 mg, 1.30 mmol), 4-(dimethylamino)benzaldehyde (194 mg, 1.30 mmol) and $H_4[Si(W_3O_{10})_3]$ (20 mol%) in acetonitrile (10 mL) was stirred at room temperature for 45 min. After complete conversion, as indicated by TLC, the reaction mixture was concentrated in vacuum, and purified by column chromatography on silica gel (Merck, 100–200 mesh, EtOAc–hexane, 3:7) to afford the pure product **3b** in 52% yield (354 mg).

4.2.1. 3-[1-[2-(2-{2-[2-(1*H*-Indolyl-1-yl)ethoxy]ethoxy}-ethoxy)ethyl](4-methoxyphenyl)methyl]-1*H*-indole (3a). Orange crystal (280 mg, 43%), mp 140–142 °C; [Found: C, 75.25; H, 6.68; N, 5.51. $C_{32}H_{34}N_2O_4$ requires C, 75.27; H, 6.71; N, 5.49%]; ν_{max} (KBr) 2865, 1609, 1465, 1350, 1103, 740 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.42 (2H, d, $J=8.4$ Hz, ind *H*), 7.31 (2H, d, $J=7.6$ Hz, ind *H*), 7.28 (2H, d, $J=8.4$ Hz, Ph), 7.19 (2H, t, $J=7.6$ Hz, ind *H*), 7.01 (2H, t, $J=7.6$ Hz, ind *H*), 6.85 (2H, d, $J=8.4$ Hz, Ph), 6.75 (2H, s, C═C*H*N), 5.87 (1H, s, Ar_3CH), 4.27–4.23 (2H, m, CH_2N), 4.15–4.12 (2H, m, CH_2N), 3.81 (3H, s, OCH_3), 3.74–3.66 (4H, m, OCH_2), 3.46–3.43 (2H, m, OCH_2), 3.37–3.30 (6H, m, OCH_2CH_2O); δ_C (125 MHz, $CDCl_3$) 157.9, 136.8, 136.7, 129.8, 129.7, 128.6, 127.7, 121.3, 120.1, 118.8, 113.6, 109.1, 72.0, 71.1, 70.0, 55.3, 46.3, 39.1; *m/z* 510 (M^+); λ_{max} (UV, MeOH) 309.6 nm.

4.2.2. 3-[1-[2-(2-{2-[2-(1*H*-Indolyl-1-yl)ethoxy]ethoxy}-ethoxy)ethyl](4-*N*,*N*-dimethylaminophenyl)methyl]-1*H*-indole (3b). Pink crystal (354 mg, 52%), mp 162–164 °C; [Found: C, 75.65; H, 7.11; N, 7.99. $C_{33}H_{37}N_3O_3$ requires C, 75.69; H, 7.12; N, 8.02%]; ν_{max} (KBr) 2865, 1611, 1517, 1466, 1350, 1123, 729 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.41 (2H, d, $J=8.0$ Hz, ind *H*), 7.29 (2H, d, $J=8.6$ Hz, Ph), 7.21–7.14 (4H, m, ind *H*), 6.98 (2H, t, $J=7.4$ Hz, ind *H*), 6.74 (2H, s, C═C*H*N), 6.70 (2H, d, $J=8.6$ Hz, ind *H*), 5.81 (1H, s, Ar_3CH), 4.27–4.20 (2H, m, CH_2N), 4.15–4.09 (2H, m, CH_2N), 3.73–3.64 (4H, m, OCH_2CH_2N), 3.45–3.40 (2H, m, OCH_2), 3.35–3.25 (6H, m, OCH_2CH_2O), 2.92 (6H, s, $N(CH_3)_2$); δ_C (125 MHz, $CDCl_3$) 156.3. 136.6, 129.4, 128.5, 127.8, 121.1, 120.3, 119.2, 118.6, 112.9, 109.0, 105.4, 72.0, 71.1, 70.0, 55.7, 46.3, 41.0; *m/z* 523 (M^+); λ_{max} (UV, MeOH) 309.0 nm.

4.3. Typical experimental procedure 5

A mixture of indole **1a** (200 mg, 1.71 mmol), 3-phenyl-1*H*-pyrazole-4-carbaldehyde **4a** (147 mg, 0.85 mmol) and $H_4[Si(W_3O_{10})_3]$ (20 mol%) in acetonitrile (10 mL) was stirred at room temperature for 25 min. After complete conversion, as indicated by TLC, the solvent was evaporated under vacuum and the product purified by column chromatography on silica gel (100–200 mesh, EtOAc–hexane, 3:7). The product obtained was analyzed and the yield was found to be (630 mg, 95%). The same procedure was followed for all the reactions (Table 2).

4.3.1. 3-[1*H*-Indol-3-yl(3-phenyl-1*H*-pyrazol-4-yl)methyl]-1*H*-indole (5a). Light orange solid (630 mg, 95%), mp 206 °C; [Found: C, 80.38; H, 5.16; N, 14.40. requires $C_{26}H_{20}N_4$ C, 80.39; H, 5.19; N, 14.42%]; ν_{max} (KBr) 3410, 3048, 1627, 1462, 1420, 1339, 1095, 745 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 12.52 (1H, br s, pyr N*H*), 10.78 (2H, s, ind N*H*), 7.56 (2H, d, $J=7.6$ Hz), 7.44 (1H, s, pyr C═C*H*N), 7.35–7.27 (5H, m, Ph), 7.17 (2H, d, $J=7.6$ Hz, ind *H*), 6.99 (2H, t, $J=7.6$ Hz, ind *H*), 6.86 (2H, s, ind C═C*H*N), 6.81 (2H, t, $J=7.7$ Hz, ind *H*), 5.83 (1H, s, Ar_3CH); δ_C (125 MHz, DMSO-d_6) 170.9, 137.2, 134.3, 132.4, 129.2, 127.9, 126.8, 123.9, 121.4, 119.3, 118.8, 114.3, 112.1, 111.2, 56.6, 30.2; *m/z* 388 (M^+).

4.3.2. 3-[1*H*-Indol-3-yl(3-(3-methoxyphenyl)-1*H*-pyrazol-4-yl)methyl]-1*H*-indole (5b). Orange solid (672 mg, 94%), mp 202–204 °C; [Found: C, 77.45; H, 5.32; N, 13.36. $C_{27}H_{22}N_4O$ requires C, 77.49; H, 5.30; N, 13.39%]; ν_{max} (KBr) 3418, 3037, 1620, 1462, 1431, 1250, 1088, 1037, 745 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 12.80 (1H, br s, pyr N*H*), 10.76 (2H, s, ind N*H*), 7.31 (2H, d, $J=8.4$ Hz, Ph), 7.27 (1H, s, pyr C═C*H*N), 7.24–7.17 (4H, m, Ph and ind *H*), 7.03 (1H, s, Ph), 7.00 (3H, t, $J=7.6$ Hz, ind *H*), 6.85 (2H, s, ind C═C*H*N), 6.81 (2H, t, $J=7.7$ Hz, ind *H*), 5.83 (1H, s, Ar_3CH), 3.37 (3H, s, OCH_3); δ_C (125 MHz, DMSO-d_6) 159.7, 137.2, 130.1, 129.4, 126.9, 125.3, 123.9, 122.0, 121.4, 119.9, 119.4, 119.1, 118.7, 116.2, 114.0, 112.6, 112.0, 55.0, 30.4; *m/z* 418 (M^+).

4.3.3. 3-[1*H*-Indol-3-yl(3-(4-methoxyphenyl)-1*H*-pyrazol-4-yl)methyl]-1*H*-indole (5c). Brown solid (650 mg, 91%), mp 207–209 °C; [Found: C, 77.46; H, 5.28; N, 13.41. $C_{27}H_{22}N_4O$ requires C, 77.49; H, 5.30; N, 13.39%]; ν_{max} (KBr) 3414, 3034, 1612, 1427, 1415, 1338, 1238, 1088, 1018, 745 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 12.83 (1H, br s, pyr N*H*), 10.80 (2H, s, ind N*H*), 7.50 (2H, d, $J=8.0$ Hz, Ph), 7.42 (1H, s, pyr C═C*H*N), 7.32 (2H, t, $J=7.6$ Hz, ind *H*), 7.20 (2H, d, $J=7.7$ Hz, ind *H*), 7.02 (2H, t, $J=7.6$ Hz, Ph), 6.91 (2H, t, $J=7.6$ Hz, ind *H*), 6.88 (2H, s, ind C═C*H*N), 6.85 (2H, t, $J=7.7$ Hz, ind H), 5.83 (1H, s, Ar_3CH), 3.73 (3H, s, OCH_3); δ_C (125 MHz, DMSO-d_6) 162.8, 159.1, 137.2, 130.2, 128.9, 126.9, 123.8, 121.3, 119.4, 119.2, 118.6, 114.5, 112.5, 111.9, 110.0, 55.5, 30.2; *m/z* 418 (M^+).

4.3.4. 3-[1*H*-Indol-3-yl(3-(4-chlorophenyl)-1*H*-pyrazol-4-yl)methyl]-1*H*-indole (5d). Orange solid (649 mg, 90%), mp 227–228 °C; [Found: C, 73.80; H, 4.53; N, 13.19. $C_{26}H_{19}ClN_4$ requires C, 73.84; H, 4.53; N, 13.25%]; ν_{max} (KBr) 3417, 1623, 1454, 1416, 1099, 737 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 12.85 (1H, br s, pyr N*H*), 10.80 (2H, s, ind N*H*), 7.61 (2H, d, $J=8.2$ Hz, Ph), 7.39 (3H, t, $J=7.6$ Hz, Ph), 7.35 (1H, t, $J=7.6$ Hz, ind *H*), 7.34 (1H, s, pyr C═C*H*N), 7.22 (2H, d, $J=8.0$ Hz, ind *H*), 7.03 (2H, t, $J=7.7$ Hz, ind *H*), 6.88 (2H, s, ind C═C*H*N), 6.85 (2H, t, $J=7.6$ Hz, ind *H*), 5.86 (1H, s, Ar_3CH); δ_C (125 MHz, DMSO-d_6) 160.1, 137.2, 134.4, 128.7, 126.6, 126.2, 124.0, 121.1, 119.5, 118.5, 116.6, 116.1, 115.9, 111.8, 109.2, 33.5; *m/z* 422 (M^+).

4.3.5. 2-Methyl-3-[(2-methyl-1*H*-indol-3-yl)(3-phenyl-1*H*-pyrazol-4-yl)methyl]-1*H*-indole (5e). Brownish orange solid (591 mg, 93%), mp 194–196 °C; [Found: C, 80.71; H, 5.80; N, 13.42. $C_{28}H_{24}N_4$ requires C, 80.74; H,

5.81; N, 13.45%]; ν_{max} (KBr) 3422, 3298, 1656, 1472, 1113, 1042, 756 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 12.75 (1H, br s, pyr N*H*), 10.64 (2H, s, ind N*H*), 7.50 (2H, d, J=7.6 Hz, Ph), 7.23 (3H, t, J=6.9 Hz, Ph), 7.17 (2H, d, J=7.6 Hz, ind *H*), 7.14 (1H, s, pyr C=C*H*N), 6.92 (2H, d, J=7.6 Hz, ind *H*), 6.86 (2H, t, J=7.6 Hz, ind *H*), 6.68 (2H, t, J=7.6 Hz, ind *H*), 5.78 (1H, s, Ar_3CH), 2.04 (6H, s, CH_3); δ_C (125 MHz, DMSO-d_6) 170.8, 160.9, 135.5, 131.9, 128.9, 128.6, 127.3, 121.5, 120.1, 118.7, 118.5, 113.4, 112.5, 111.8, 110.9, 60.3, 30.3; *m/z* 416 (M^+).

4.3.6. 5-Methoxy-3-[(5-methoxy-1*H*-indol-3-yl)(3-phenyl-1*H*-pyrazol-4-yl)methyl]-1*H*-indole (5f). Orange solid (615 mg, 90%), mp 118–120 °C; [Found: C, 74.94; H, 5.33; N, 12.48. $C_{28}H_{24}N_4O_2$ requires C, 74.98; H, 5.39; N, 12.49%]; ν_{max} (KBr) 3417, 3300, 1620, 1482, 1211, 1054, 772 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 12.70 (1H, br s, pyr N*H*), 10.59 (2H, s, ind N*H*), 7.54 (2H, d, J=7.6 Hz, Ph), 7.34 (2H, t, J=6.9 Hz, Ph), 7.27 (1H, t, J=7.6 Hz, Ph), 7.21 (1H, s, pyr C=C*H*N), 7.19 (2H, s, ind *H*), 6.85 (2H, s, ind C=C*H*N), 6.65 (2H, dd, J=2.3, 8.4 Hz, ind *H*), 6.57 (2H, s, ind *H*), 5.67 (1H, s, Ar_3CH), 3.51 (6H, s, OCH_3); δ_C (125 MHz, DMSO-d_6) 170.5, 153.1, 135.6, 130.6, 130.0, 129.4, 129.1, 127.9, 127.3, 124.5, 121.6, 118.7, 112.6, 111.0, 101.6, 55.7, 30.3; *m/z* 448 (M^+).

4.3.7. 1-Methyl-3-[(1-methyl-1*H*-indol-3-yl)(3-phenyl-1*H*-pyrazol-4-yl)methyl]-1*H*-indole (5g). Brown solid (561 mg, 94%), mp 142 °C; [Found: C, 80.72; H, 5.78; N, 13.44. $C_{28}H_{24}N_4$ requires C, 80.74; H, 5.81; N, 13.45%]; ν_{max} (KBr) 3432, 3059, 2926, 1616, 1473, 1329, 1097, 1013, 740 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 12.84 (1H, br s, pyr N*H*), 7.55 (2H, d, J=8.4 Hz, Ph), 7.35 (2H, d, J=8.5 Hz, Ph), 7.33 (3H, d, J=3.9 Hz, Ph and ind *H*), 7.31 (1H, s, pyr C=C*H*N), 7.18 (2H, d, J=7.6 Hz, ind *H*), 7.05 (2H, t, J=7.6 Hz, ind *H*), 6.85 (2H, t, J=7.6 Hz, ind *H*), 6.83 (2H, s, C=C*H*N), 5.80 (1H, s, Ar_3CH), 3.64 (6H, s, CH_3); δ_C (125 MHz, DMSO-d_6) 164.2, 149.4, 137.6, 132.2, 129.4, 129.1, 128.3, 127.1, 122.1, 121.5, 119.5, 118.9, 118.2, 116.5, 110.2, 32.8, 29.9; *m/z* 416 (M^+).

4.3.8. 1-Methyl-3-[(1-methyl-1*H*-indol-3-yl)(3-(4-chloro phenyl)-1*H*-pyrazol-4-yl)methyl]-1*H*-indole (5h). Orange solid (625 mg, 91%), mp 138 °C; [Found: C, 74.56; H, 5.11; N, 12.39. $C_{28}H_{23}ClN_4$ requires C, 74.57; H, 5.14; N, 12.42%]; ν_{max} (KBr) 3431, 3056, 2928, 1617, 1470, 1326, 1097, 745 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 12.85 (1H, br s, pyr N*H*), 7.54 (2H, d, J=8.4 Hz, Ph), 7.35 (2H, d, J=8.5 Hz, Ph), 7.33 (2H, d, J=7.6 Hz, ind *H*), 7.31 (1H, s, pyr C=C*H*N), 7.18 (2H, d, J=8.5 Hz, ind *H*), 7.05 (2H, t, J=7.7 Hz, ind *H*), 6.85 (2H, t, J=7.6 Hz, ind *H*), 6.82 (2H, s, ind C=C*H*N), 5.79 (1H, s, Ar_3CH), 3.64 (6H, s, CH_3); δ_C (125 MHz, DMSO-d_6) 161.5, 152.1, 129.4, 129.1, 128.3, 127.1, 122.1, 121.5, 119.5, 118.9, 118.2, 117.1, 115.2, 111.1, 110.2, 89.7, 32.1; *m/z* 450 (M^+).

4.4. Typical experimental procedure 7

To a mixture of 1-propyl indole (200 mg, 1.26 mmol) and (2*E*)-3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one **4g** (299 mg, 1.26 mmol) in acetonitrile (10 mL), $H_4[Si(W_3O_{10})_3]$ (20 mol%) was added and the reaction stirred for 20 min at room temperature. After complete conversion, as indicated by TLC, the solvent was evaporated under vacuum and the product purified by column chromatography on silica gel (100–200 mesh, EtOAc–hexane, 2:8) and the product was obtained (458 mg, 92% yield, Table 3).

4.4.1. 4-(1*H*-Indol-3-yl)butan-2-one (7a).[19a] Light brown solid (272 mg, 85%), mp 70–72 °C; [Found: 76.95; H, 7.02; N, 7.45. $C_{12}H_{13}NO$ requires C, 76.98; H, 7.00; N, 7.48%]; ν_{max} (KBr) 3409, 2928, 1709, 1165, 1067, 745 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 8.01 (1H, s, ind N*H*), 7.38 (1H, d, J=7.6 Hz, ind *H*), 7.28 (1H, d, J=7.6 Hz, ind *H*), 7.17 (1H, t, J=7.1 Hz, ind *H*), 7.10 (1H, t, J=7.0 Hz, ind *H*), 7.02 (1H, s, C=C*H*N), 3.05 (2H, t, J=6.8 Hz, ind CH_2), 2.80 (2H, t, J=6.8 Hz, CH_2C=O), 2.13 (3H, s, CH_3); δ_C (125 MHz, $CDCl_3$) 201.9, 136.7, 128.7, 126.4, 122.1, 121.5, 119.4, 118.5, 111.4, 110.8, 39.5, 8.9; *m/z* 187 (M^+).

4.4.2. 3-(1*H*-Indol-3-yl)-1-phenylpropan-1-one (7b).[19a] Brown solid (370 mg, 87%), mp 126–127 °C; [Found: C, 82.94; H, 6.03; N, 5.59. $C_{17}H_{15}NO$ requires C, 82.90; H, 6.06; N, 5.62%]; ν_{max} (KBr) 3410, 3055, 2928, 1683, 1335, 1205, 1097, 742 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 8.05 (1H, s, ind N*H*), 7.64–7.53 (2H, m, ind *H*), 7.48–7.32 (5H, m, Ph), 7.19–7.05 (3H, m, ind *H*), 3.51 (2H, t, J=7.6 Hz, ind CH_2), 3.26 (2H, t, J=7.6 Hz, CH_2C=O); δ_C (125 MHz, $CDCl_3$) 201.0, 138.2, 136.2, 132.9, 128.6, 128.1, 126.8, 121.9, 121.5, 118.9, 118.4, 111.7, 110.8, 39.5, 19.9; *m/z* 249 (M^+).

4.4.3. 4-(2-Methyl-1*H*-indol-3-yl)butan-2-one (7c).[19a] Colorless oil (313 mg, 91%); [Found: C, 77.55; H, 5.57; N, 6.92. $C_{13}H_{15}NO$ requires C, 77.58; H, 7.51; N, 6.96%]; ν_{max} (neat) 3415, 3028, 1714, 1457, 1371, 1226, 1035, 748 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 8.01 (1H, s, ind N*H*), 7.35 (1H, d, J=7.1 Hz, ind *H*), 7.15 (1H, t, J=7.1 Hz, ind *H*), 7.10 (1H, t, J=7.0 Hz, ind *H*), 6.95 (1H, d, J=2.1 Hz, ind *H*), 3.05 (2H, t, J=6.8 Hz), 2.80 (2H, t, J=6.8 Hz, CH_2C=O), 2.41 (3H, s, CH_3C=O), 2.13 (3H, s, ind CH_3); δ_C (125 MHz, $CDCl_3$) 201.8, 136.2, 128.5, 126.4, 123.9, 121.6, 119.7, 118.9, 110.4, 78.3, 38.5, 19.7, 12.4; *m/z* 201 (M^+).

4.4.4. 3-(1*H*-Indol-3-yl)-3-(4-methoxy phenyl)-1-phenyl propan-1-one (7d). Brown solid (540 mg, 89%), mp 128–130 °C; [Found: C, 81.07; H, 5.93; N, 3.95. $C_{24}H_{21}NO_2$ requires C, 81.10; H, 5.96; N, 3.94%]; ν_{max} (KBr) 3425, 3300, 2925, 1675, 1508, 1465, 1035, 739 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 8.09 (1H, s, ind N*H*), 7.95 (2H, d, J=7.5 Hz, Ph), 7.55 (1H, t, J=7.5 Hz, Ph), 7.45–7.41 (3H, m, Ph), 7.28 (3H, dd, J=2.3, 10.9 Hz, Ph), 7.16 (1H, t, J=8.0 Hz, ind *H*), 7.05 (1H, t, J=6.9 Hz, ind *H*), 6.93 (1H, s, C=C*H*N), 6.82 (2H, d, J=11.4 Hz, Ph), 5.06 (1H, t, J=6.9 Hz, Ar_2CH), 3.79–3.74 (2H, m, CH_2), 3.73 (3H, s, OCH_3); δ_C (125 MHz, $CDCl_3$) 199.9, 158.1, 137.3, 136.8, 136.5, 133.2, 128.9, 128.7, 128.3, 126.7, 122.2, 121.5, 119.7, 119.6, 119.5, 113.9, 111.4, 55.3, 45.5, 37.6; *m/z* 355 (M^+).

4.4.5. 3-(1-Methyl-1*H*-indol-3-yl)-3-(4-methoxyphenyl)-1-phenylpropan-1-one (7e). Brown solid (523 mg, 93%), mp 112 °C; [Found: C, 81.25; H, 6.24; N, 3.81. $C_{25}H_{23}NO_2$ requires C, 81.27; H, 6.27; N, 3.79%]; ν_{max} (KBr) 3420, 3302, 2925, 1505, 1035, 745 cm^{-1}; δ_H (500 MHz, $CDCl_3$)

7.95 (2H, d, J=7.6 Hz, Ph), 7.54 (1H, t, J=6.9 Hz, Ph), 7.47–7.42 (3H, m, Ph), 7.28 (3H, t, J=8.6 Hz, Ph), 7.20 (2H, t, J=7.4 Hz, ind *H*), 7.03 (1H, s, C=C*H*N), 6.83 (2H, t, J=8.5 Hz, ind *H*), 5.04 (1H, t, J=6.9 Hz, Ar_2CH), 3.82–3.78 (2H, dd, J=6.3, 16.6 Hz, CH_2), 3.75 (3H, s, OCH_3), 3.72 (3H, s, NCH_3); δ_C (125 MHz, $CDCl_3$) 198.9, 158.0, 137.5, 137.3, 136.6, 133.1, 128.9, 128.7, 128.2, 127.1, 126.3, 121.8, 120.4, 119.7, 118.9, 118.3, 113.9, 109.3, 55.3, 45.5, 37.6; *m/z* 369 (M^+).

4.4.6. 3-(2-Nitro-1-phenylethyl)-1*H*-indole (7f).[19a] Colorless oil (409 mg, 90%); [Found: C, 72.11; H, 5.27; N, 10.54. $C_{16}H_{14}N_2O_2$ requires C, 72.17; H, 5.30; N, 10.58%]; ν_{max} (neat): 3417, 3030, 2925, 1456, 1223, 1015, 745 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 8.01 (1H, s, ind N*H*), 7.42 (1H, d, J=7.6 Hz, Ph), 7.33–7.24 (6H, m, Ph and ind *H*), 7.21 (1H, t, J=7.6 Hz, ind *H*), 7.08 (1H, t, J=7.6 Hz, ind *H*), 6.97 (1H, d, J=2.5 Hz, ind *H*), 5.20 (1H, t, J=7.6 Hz, Ar_2CH), 4.81 (2H, m, CH_2); δ_C (125 MHz, $CDCl_3$) 139.2, 136.5, 128.9, 127.6, 127.4, 125.9, 123.4, 121.6, 119.8, 118.8, 114.1, 111.4, 79.4, 40.9; *m/z* 266 (M^+).

4.4.7. 3-(1-Propyl-1*H*-indol-3-yl)-3-(4-methoxyphenyl)-1-phenylpropan-1-one (7g). Brown oil (459 mg, 92%); [Found: C, 81.53; H, 6.84; N, 3.50. $C_{27}H_{27}NO_2$ requires C, 81.58; H, 6.85; N, 3.52%]; ν_{max} (neat) 3425, 3300, 2925, 1504, 1463, 1035, 742 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 8.13 (2H, d, J=8.0 Hz, Ph), 8.11 (1H, d, J=8.1 Hz, Ph), 7.74 (1H, d, J=8.1 Hz, Ph), 7.61–7.45 (5H, m, Ph), 7.38 (1H, t, J=7.4 Hz, ind *H*), 7.24 (1H, t, J=7.4 Hz, ind *H*), 7.15 (1H, s, C=C*H*N), 7.00 (2H, d, J=8.5 Hz, ind *H*), 5.34 (1H, s, Ar_2CH), 4.06 (2H, t, J=6.9 Hz, CH_2N), 3.99 (2H, dd, J=6.3, 20.6 Hz, CH_2C=O), 3.80 (3H, s, OCH_3), 1.95–1.88 (2H, m, CH_2), 1.02 (3H, t, J=7.4 Hz, CH_3); δ_C (125 MHz, $CDCl_3$) 199.0, 158.4, 137.6, 137.1, 137.0, 133.3, 129.2, 128.9, 128.4, 127.6, 125.7, 121.9, 120.1, 118.3, 119.1, 114.2, 109.9, 55.3, 48.1, 45.8, 37.9, 23.8, 11.8; *m/z* 397 (M^+).

4.4.8. 3-(1-Butyl-1*H*-indol-3-yl)-3-(4-methoxyphenyl)-1-phenylpropan-1-one (7h). Brown oil (442 mg, 93%); [Found: C, 81.69; H, 7.12; N, 3.41. $C_{28}H_{29}NO_2$ requires C, 81.72; H, 7.10; N, 3.40%]; ν_{max} (neat) 3420, 3307, 2922, 1675, 1465, 1037, 740 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 8.08 (2H, d, J=8.0 Hz, Ph), 7.76 (2H, d, J=8.0 Hz, Ph), 7.64–7.47 (5H, m, Ph), 7.39 (1H, d, J=7.6 Hz, ind *H*), 7.25 (2H, t, J=7.4 Hz, Ph), 7.17 (1H, d, J=6.9 Hz, ind *H*), 7.03 (1H, s, C=C*H*N), 5.05 (1H, s, Ar_2CH), 4.07 (2H, t, J=7.6 Hz, NCH_2), 4.01–3.95 (2H, m, CH_2C=O), 3.82 (3H, s, OCH_3), 1.97–1.85 (4H, m, CH_2), 0.89 (3H, t, J=7.6 Hz, CH_3); δ_C (125 MHz, $CDCl_3$) 199.9, 159.0, 137.2, 136.6, 133.2, 129.2, 128.7, 128.2, 127.6, 126.3, 121.8, 120.4, 119.7, 119.5, 119.1, 118.3, 113.7, 110.4, 55.3, 48.1, 45.8, 38.0, 24.0, 11.8; *m/z* 411 (M^+).

4.4.9. 3-(2-Nitro-1-phenylethyl)-1*H*-indol-5-ol (7i). Brown solid (319 mg, 90%), mp 124 °C; [Found: C, 68.01; H, 4.95; N, 9.88. $C_{16}H_{14}N_2O_3$ requires C, 68.07; H, 5.00; N, 9.92%]; ν_{max} (KBr) 3406, 3030, 1745, 1376, 1035, 742 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 8.05 (1H, s, ind N*H*), 7.32–7.20 (5H, m), 7.18 (1H, d, J=8.4 Hz), 6.98 (1H, d, J=2.6 Hz), 6.83–6.73 (2H, m), 5.11–4.80 (4H, m); δ_C (125 MHz, $CDCl_3$) 155.6, 148.7, 134.4, 132.9, 132.5, 127.4, 124.8, 124.1, 117.1, 108.1, 104.8, 102.3, 85.0, 37.5; *m/z* 282 (M^+).

4.4.10. Methyl-2-(1*H*-indol-3-yl)-3-nitropropanoate (7j). Light yellow oil (335 mg, 90%); [Found: C, 58.00; H, 4.85; N, 11.27. $C_{12}H_{12}N_2O_4$ requires C, 58.06; H, 4.87; N, 11.29%]; ν_{max} (neat) 3409, 3035, 1747, 1374, 745 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 8.02 (1H, s, ind N*H*), 7.64 (1H, d, J=8.4 Hz), 7.40–7.35 (1H, m), 7.32–7.13 (3H, m), 5.28–5.19 (1H, m), 4.81–4.60 (2H, m, CH_2), 3.73 (3H, s, CH_3); δ_C (125 MHz, $CDCl_3$) 172.0, 136.4, 125.9, 123.3, 123.1, 120.6, 118.7, 111.9, 76.3, 53.0, 39.1; *m/z* 248 (M^+).

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24. Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC Nos. 278106 for compound **3a**. Structural parameters for **3a**: data collection: Bruker SMART CCD area detector; radiation: Mo Kα wavelength: 0.71073 Å; crystal size: $0.22\times 0.20\times 0.18$ Å^3; crystal system: triclinic; space group: $P\bar{1}$ (#4); unit cell: $a=10.4646(9)$ Å, $b=15.3530(13)$ Å, $c=18.8220(16)$ Å, $\alpha=101.008(1)^\circ$, $\beta=106.060(1)^\circ$, $\gamma=98.345(1)^\circ$.