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An eco-friendly procedure for the efficient synthesis of bis(indolyl)methanes in aqueous media

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ABSTRACT

A new, convenient and high yielding procedure for the preparation of bis(indolyl)methanes in water by electrophilic substitution reaction of indoles with different carbonyl compounds in the presence of a catalytic amount of [Cu(3,4-tmtppa)]$(MeSO_4)_4$ (1 mol%) as a highly stable and reusable catalyst is described. This procedure has also been applied successfully for the preparation of bis(pyrazole-5-ols) and dipyrromethanes.

1. Introduction

Use of aqueous media as a reaction solvent has attracted much attention in synthetic organic chemistry for several reasons [1,2]. In comparison with organic solvents, water is cheap, safe and reduces the use of harmful organic solvents and leads to the development of environmentally friendly chemical processes [3]. In addition, reactions in aqueous media illustrate unique reactivities and selectivities that are not usually observed in organic media [4–6]. However, organic solvents are still used instead of water for mainly two reasons. First, most organic substrates are not soluble in water and as a result, water cannot function as a reaction medium. Second, many reactive substrates, reagents and catalysts are sensitive towards water and are decomposed or deactivated in aqueous media. Therefore, efforts to carry out organic reactions in water pose an important challenge in the area of reaction design.

Indole derivatives are known for their vast applications in material sciences [7], agrochemicals [8] and pharmaceuticals [9,10]. Among these compounds, the substrates including bis(indolyl)methane moieties, such as secondary metabolites [11] and marine-sponge alkaloids [12], are important classes of bioactive metabolites. Thus, the synthesis of bis(indolyl)methanes has received an increasing attention in recent years. The simple method for the synthesis of this class of compounds involves the electrophilic substitution reaction of indoles with carbonyl compounds in the presence of protic [13] or Lewis acids [14–16]. However, these procedures suffer from certain limitations when acid sensitive substrates are used. On the other hand, many Lewis acids are deactivated or some times decomposed by nitrogen-containing reactants. Even when the desired reactions proceed, more than stoichiometric amounts of Lewis acids are required. Many attempts have been done by organic chemists to circumvent this problem [17–22]. However, most of the reported methods suffer from one or more of the following drawbacks: using large amounts of solid supports or un-recyclable catalysts which would eventually result in the generation of a large amount of toxic waste, long reaction times, moderate yields of the products, amenable only for aldehydes as carbonyl compounds and requiring an additional microwave or ultrasound irradiation. Therefore, it is necessary to further develop an efficient and convenient method for the synthesis of such significant scaffolds.

Metallophthalocyanines (Mpc), which are structurally similar to metal porphyrins, are easily accessible, more stable to degradation and cost effective than porphyrins. They have been extensively used as efficient catalysts in a variety of organic reactions [23–29]. Tetrapyridinoporphyrazines (tppa) are heterocyclic phthalocyanine (pc) derivatives in which benzene rings are replaced with electron-withdrawing pyridine rings. The presence of pyridine rings in these compounds not only increases the reactivity of tppa compared with pc, but also allows the facile quaternarization processes. The N,N',N'',N'''-tetramethylated quaternized form of tetrapyridinoporphyrazine can be prepared easily by its reaction with dimethyl sulfate in dimethyl formamide [30]. The resulting tetramethyl-

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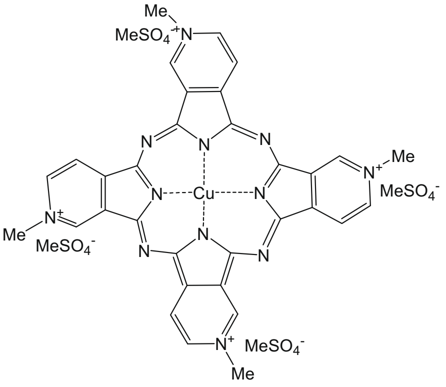


Fig. 1. [Cu(3,4-tmtppa)]$(MeSO_4)_4$ (**1**).

Table 1
Synthesis of bis(indolyl)methanes (**5**–**7**) by electrophilic substitution reaction of indoles (**2**–**4**) with carbonyl compounds catalyzed by [Cu(3,4-tmtppa)]$(MeSO_4)_4$ in water at 90 °C.

Entry	*R*^{1}	*R*^{2}	Indole	Product	Time (h)	Yield[a] (%)
1	C_6H_5	H	**2**	**5a**	2	92
2	C_6H_5	H	**3**	**6a**	1.5	94
3	C_6H_5	H	**4**	**7a**	2	90
4	4-O_2N–C_6H_4	H	**2**	**5b**	0.5	97
5	2-O_2N–C_6H_4	H	**2**	**5c**	0.75	96
6	2-Cl–C_6H_4	H	**2**	**5d**	2	90
7	4-Cl–C_6H_4	H	**2**	**5e**	0.5	90
8	2,6-Cl_2–C_6H_3	H	**2**	**5f**	0.25	95
9	4-Me–C_6H_4	H	**2**	**5g**	1	92
10	4-MeO–C_6H_4	H	**2**	**5h**	1.5	90
11	$C_6H_5CH{=}CH$	H	**2**	**5i**	1.25	80
12	2-Thienyl	H	**2**	**5j**	2.5	94
14	2-Furyl	H	**2**	**5k**	2	90
15	3-Indolyl	H	**2**	**5l**	3	71
16	C_6H_5CHMe	H	**2**	**5m**	3	75
17	*n*-Pentyl	H	**2**	**5n**	1.5	90
18	*n*-Hexyl	H	**2**	**5o**	2	92
19	4-OHC-C_6H_4	H	**2**[b]	**5p**	2.5	70
20	–$(CH_2)_5$–		**2**	**5q**	1.5	74
21	–$(CH_2)_4$–		**2**	**5r**	2	80
22	Me	CO_2Me	**2**	**5s**	0.5	84

[a] Yields refer to those of pure isolated products characterized by spectral data.
[b] Conditions: indole/terephetaldehyde: 4/1.

tetra-3,4-pyridinoporphyrazinato copper(II) methyl sulfate [Cu(3,4-tmtppa)]$(MeSO_4)_4$ (**1**) (Fig. 1) is a water soluble compound and has considerable low solubility in common organic solvents. Unlike for metallophthalocyanine, the reports on catalytic activity of metallotetrapyridinoporphyrazine in organic reactions are rare in the literature [31–33].

In continuation of our ongoing interest on the discovery of new applications of [Cu(3,4-tmtppa)]$(MeSO_4)_4$ as a catalyst in organic transformations, we have recently reported efficient synthesis of 1-aminophosphonates in the presence of [Cu(3,4-tmtppa)]$(MeSO_4)_4$ [34].

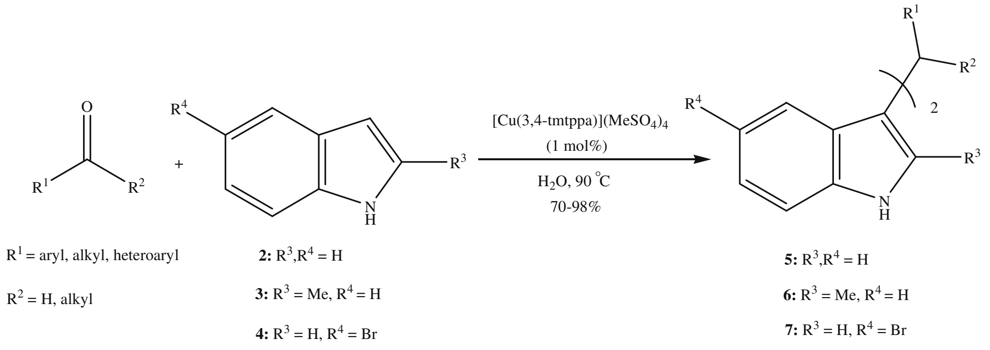
Herein, we report successful application of [Cu(3,4-tmtppa)]$(MeSO_4)_4$ as a recyclable catalyst for the synthesis of various types of bis(indolyl)methanes by electrophilic substitution reaction of indoles with aldehydes and ketones in water.

2. Results and discussion

The electrophilic substitution reaction of indole and benzaldehyde in water with different catalytic amounts of [Cu(3,4-tmtppa)]$(MeSO_4)_4$ and at different reaction temperatures have investigated in order to optimize the reaction conditions. The best yield of the corresponding bis(indolyl)methane was obtained in the presence of 1 mol% of [Cu(3,4-tmtppa)]$(MeSO_4)_4$ and at 90 °C. To show the generality and scope of this synthetic method, the electrophilic substitution reaction of indoles (**2**–**4**) with different carbonyl compounds was studied in the presence of [Cu(3,4-tmtppa)]$(MeSO_4)_4$ in water, using optimized reaction conditions (Scheme 1, Table 1).

As shown in Table 1, the catalytic electrophilic substitution reaction of benzaldehyde proceeded well with different substituted indoles (Entries 1–3). Substituted benzaldehydes with electron-donating and electron-withdrawing groups underwent electrophilic substitution reaction with indole **2,** and gave the corresponding bis(indolyl)methanes in 90–97% yields (Entries 4–10). Acid-sensitive aldehydes, such as cinnamaldehyde, thiophene-2-carbaldehyde, furfural and indol-3-carbaldehyde underwent smooth reactions without any decomposition or polymerization under the present reaction conditions producing the corresponding bis(indolyl)methanes in 71–94% yields (Entries 11–15). Moreover, aliphatic aldehydes were all effective substrates to successfully execute the electrophilic substitution reaction with indole catalyzed by [Cu(3,4-tmtppa)]$(MeSO_4)_4$ (Entries 16–18). Tetrakis-indolyl methane (**5p**) was also prepared successfully by the presented method in good yield from terephthaldehyde (Entry 19). In addition to aldehydes, some ketones were also screened to carry out the electrophilic substitution reaction by [Cu(3,4-tmtppa)]$(MeSO_4)_4$ in aqueous media. The results showed that the reactions involved acyclic dialkyl ketones and cyclic ketones worked well and the expected products could be smoothly achieved in 74–84% yields (Entries 20–22). However, no product was obtained when aryl ketones such as benzophenone and acetophenone were involved in this reaction under the same conditions.

The ability to recycle and reuse of [Cu(3,4-tmtppa)]$(MeSO_4)_4$ (**1**) was studied in this system. For this purpose, after performing the



Scheme 1.

preparation reaction of bis(indolyl)methane **5a** under the conditions described in Table 1, the reaction mixture was washed with ethyl acetate. The separated aqueous layer containing the catalyst was re-used for a consecutive run under the same reaction conditions. The average isolated yield for ten consecutive runs was 88.7%, which clearly demonstrates the practical reusability of this catalyst (Fig. 2). This reusability demonstrates the high stability and turnover of [Cu(3,4-tmtppa)]$(MeSO_4)_4$ under the employed conditions. It is worth to note that the recyclability test was stopped after ten runs.

The effect of reaction media on the electrophilic substitution reaction of indole **2a** with benzaldehyde catalyzed by **1** was also studied (Table 2). A survey of solvents revealed that the reaction media had a significant effect on this process. The results showed that the use of water as reaction media was superior to the others. In this solvent the highest yield of the desired product (**5a**) was obtained after shorter reaction time (Table 2, Entry 1). Under the same reaction conditions, when one equivalent of indole was used, the desired product (**5a**) was obtained in lower yields (Table 2, Entry 2).

Re-usability of the catalyst, easy work-up along with the high yields of the products encouraged us to study the applicability of this method for other electron-rich aromatic compounds (**8–15**) (Scheme 2, Table 3).

According to Table 3, the best results were obtained when pyrazolone (**8**) and pyrrole (**9**) were used as electron-rich aromatic compounds. Subsequently, the reactions of pyrazolone (**8**) and pyrrole (**9**) with a variety of aldehydes were investigated under the same reaction conditions. The results are depicted in Table 4.

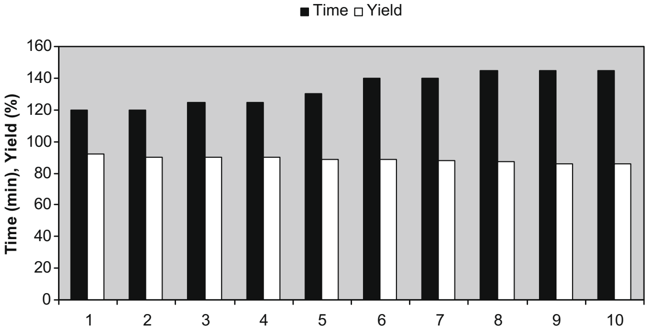
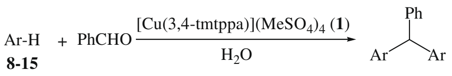


Fig. 2. Reusability of [Cu(3,4-tmtppa)]$(MeSO_4)_4$ as a catalyst for the preparation of bis(indolyl)methane **5a**.

Table 2
Effect of reaction media on the preparation of **5a** from the electrophilic substitution reaction of indole **2a** with benzaldehyde catalyzed by **1**.

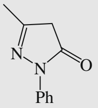
Entry	Solvent	Time (h)	Yield[a] (%)
1	Water[b]	2	92
2	Water[b,d]	1	48
3	CH_3CN[c]	24	45
4	DMSO[b]	24	5
5	THF[c]	24	30
6	CH_3OH[c]	24	70
7	*iso*-Propanol[c]	24	75
8	Benzene[c]	24	45
9	Toluene[b]	24	30
10	–[b]	24	50

[a] Yields refer to those of pure isolated products. Conditions: **2a**/benzaldehyde: 2/1 (except for Entry 2); catalyst **1** (1 mol%).
[b] Conditions: 90 °C.
[c] Conditions: reflux.
[d] Conditions: **2a**/benzaldehyde: 1/1.



Scheme 2.

Table 3
Results of the reaction of electron-rich aromatic compounds with benzaldehyde in the presence of catalyst **1**.

Entry	Electron-rich aromatic compound	Time (h)	Yield[a] (%)
1	 **8**	0.5	95[b]
2	Pyrrole (**9**)	0.5	70[c]
3	*N,N*-diethylaniline (**10**)	24	0
4	2-Methylthiophene (**11**)	24	0
5	Anisole (**12**)	24	0
6	Phenol (**13**)	24	0
7	Mesitylene (**14**)	24	0
8	*p*-Xylene (**15**)	24	0

[a] Yields refer to those of pure isolated products. Conditions: **8–15**/benzaldehyde: 2/1; catalyst **1** (5 mol%, except for Entries 1 and 2); 90 °C (except for Entry 2).
[b] Catalyst **1** (3 mol%).
[c] Catalyst **1** (1 mol%), room temperature.

As shown in Table 4, treatment of pyrazolone (**8**) or pyrrole with different aldehydes in water in the presence of [Cu(3,4-tmtppa)]$(MeSO_4)_4$ (**1**) gave bis(pyrazol-5-ols) (**10**) and dipyrromethanes (**11**) (Scheme 3) in good to high yields.

In conclusion, we have found that [Cu(3,4-tmtppa)]$(MeSO_4)_4$ can be used as a new, re-usable and efficient catalyst for the preparation of a variety of bis(indolyl)methanes by electrophilic substitution reaction of indoles with aldehydes/ketones in water. This reaction system not only provides a novel method for the synthesis of bis(indolyl)methanes, but also extends the applicability of [Cu(3,4-tmtppa)]$(MeSO_4)_4$ in organic synthesis in water which leads to environmentally friendly chemical processes. This property combined with ease of recovery and catalyst re-usability makes this method an economic, benign and waste-free chemical process for the synthesis of bis(indolyl)methanes. This procedure has also successfully applied for the preparation of bis(pyrazole-5-ols) and dipyrromethanes.

3. Experimental

3.1. Materials and physical measurements

Chemicals were purchased from Merck and Fluka Chemical Companies. Melting points were determined by Buchi 510 apparatus and are uncorrected. IR spectra were run on a Perkin–Elmer 780 instrument. NMR spectra were recorded on a Bruker Avance DPX-250. The purity of the products and the progress of the reactions were accomplished by TLC on silica-gel polygram SILG/UV_{254} plates.

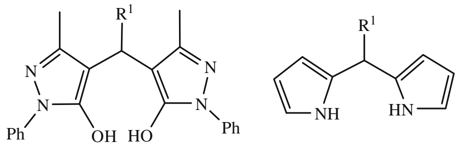
*3.2. Typical procedure for the synthesis of bis(indolyl)methanes (**5a**)*

Benzaldehyde (1.06 g, 10 mmol) and indole **2** (2.34 g, 20 mmol) was added to a stirring solution of [Cu(3,4-tmtppa)]$(MeSO_4)_4$ (0.108 g, 0.1 mmol) in water (20 mL). The mixture was heated in an oil bath at 90 °C for an appropriate time (Table 1). Water (20 mL) was added to the cooled reaction mixture. Then the reaction mixture was washed with EtOAc (3 × 20 mL) and the organic

Table 4
Results of the reaction of pyrazolone (**8**) and pyrrole (**9**) with aldehydes in the presence of [Cu(3,4-tmtppa)]$(MeSO_4)_4$ (**1**) in water.

Entry	R^1	Electron-rich aromatic compound	Product	Time (min)	Yield[a] (%)
1	C_6H_5	**8**	**10a**	30	95[b]
2		**9**	**11a**	30	70[c]
3	4-O_2N–C_6H_4	**8**	**10b**	5	98[b]
4		**9**	**11b**	–[b]	98[c]
5	2-Cl–C_6H_4	**8**	**10d**	5	90[b]
6	4-Cl–C_6H_4	**8**	**10e**	60	98[b]
7		**9**	**11e**	–[b]	98[c]
8	4-Me–C_6H_4	**8**	**10g**	30	95[b]
9		**9**	**11g**	–[b]	84[c]
10	4-MeO–C_6H_4	**8**	**10h**	45	93[b]
11	2-OH–C_6H_4	**8**	**10t**	15	95[b]
12	4-Br–C_6H_4	**9**	**11u**	–[b]	97[c]
13	2-Furyl	**8**	**10k**	30	90[b]

[a] Yields refer to those of pure isolated products characterized by comparison of their spectral data and physical properties with those of authentic samples [35–38].
[b] Conditions: catalyst (3 mol%); 90 °C.
[c] Conditions: catalyst (1 mol%); room temperature.



10 **11**

Scheme 3.

layer was separated and washed with H_2O (3 × 10 mL). Then the separated organic phase dried over Na_2SO_4 and concentrated under reduced pressure to give the crude product. The crude product was purified by chromatography on silica-gel eluted with *n*-hexane/EtOAc (5/1). Separated aqueous layer containing the catalyst was combined and concentrated to appropriate volume (20 mL) and reused for the preparation of bis(indolyl)methane (**5a**) following the above procedure.

*3.3. Typical procedure for the synthesis of bis(pyrazole-5-ols) (**10a**)*

Benzaldehyde (1.06 g, 10 mmol) and pyrazolone **8** (3.48 g, 20 mmol) was added to a stirring solution of [Cu(3,4-tmtppa)]$(MeSO_4)_4$ (0.324 g, 0.3 mmol) in water (20 mL). The mixture was heated in an oil bath at 90 °C for an appropriate time (Table 4). Water (20 mL) was added to the cooled reaction mixture. Then the reaction mixture was washed with EtOAc (3 × 20 mL) and the organic layer was separated and washed with H_2O (3 × 10 mL). Then the separated organic phase dried over Na_2SO_4 and concentrated under reduced pressure to give the crude product. The crude product was purified by recrystallization from ethanol (95%).

*3.4. Typical procedure for the synthesis of dipyrromethane (**11a**)*

Benzaldehyde (1.06 g, 10 mmol) and pyrrole **9** (1.34 g, 20 mmol) was added to a stirring solution of [Cu(3,4-tmtppa)]$(MeSO_4)_4$ (0.108 g, 0.1 mmol) in water (20 mL). The mixture was stirred at room temperature for an appropriate time (Table 4). Water (20 mL) was added to the reaction mixture. Then the reaction mixture was washed with EtOAc (3 × 20 mL) and the organic layer was separated and washed with H_2O (3 × 10 mL). Then the separated organic phase dried over Na_2SO_4 and concentrated under reduced pressure to give the crude product. The crude product was purified by chromatography on silica-gel eluted with *n*-hexane/EtOAc (3/1).

3.5. Spectral data for bis(indolyl)methanes

Compound **5a**: mp 140–142 °C; IR (KBr): 3402 (N–H) cm^{-1}; ^1H NMR ($CDCl_3$, TMS): δ 5.86 (s, 1 H), 6.66 (s, 2 H), 7.11 (t, 2 H, *J* = 6.9 Hz), 7.14–7.22 (m, 3 H), 7.28–7.31 (m, 2 H), 7.35–7.42 (m, 6 H), 7.93 (br s, NH) ppm; ^{13}C NMR ($CDCl_3$, TMS): δ 31.6, 110.9, 111.9, 118.4, 119.5, 121.2, 124.0, 126.3, 127.1, 128.5, 128.6, 137.0, 145.2 ppm.

Compound **5b**: mp 217–219 °C; IR (KBr): 3423 (N–H) cm^{-1}; ^1H NMR ($CDCl_3$, TMS): δ 6.01 (s, 1 H), 6.72 (s, 2 H), 7.02–7.08 (m, 4 H), 7.36 (d, 2 H, *J* = 8.1 Hz), 7.41 (d, 2 H, *J* = 8.1 Hz), 7.49 (d, 2 H, *J* = 8.6 Hz), 8.05 (br s, NH), 8.17 (d, 2 H, *J* = 8.6 Hz) ppm.

Compound **5c**: mp 139–141 °C; ^1H NMR ($CDCl_3$, TMS): δ 6.12 (s, 1 H), 6.91 (s, 2 H), 7.08–7.17 (m, 4 H), 7.29 (d, 2 H, *J* = 7.8 Hz), 7.47 (d, 2 H, *J* = 7.9 Hz), 7.57–7.66 (m, 2 H), 7.79–7.90 (m, 2 H), 8.21 (d, 2 H, *J* = 8.6 Hz) ppm.

Compound **5d**: mp 74–76 °C; IR (KBr): 3412 (N–H) cm^{-1}; ^1H NMR ($CDCl_3$, TMS): δ 6.32 (s, 1 H), 6.67 (s, 2 H), 7.02 (t, 2 H, *J* = 7.8 Hz), 7.10–7.22 (m, 6 H), 7.38–7.43 (m, 4 H), 7.98 (br s, NH) ppm.

Compound **5e**: mp 78–80 °C; IR (KBr): 3412 (N–H) cm^{-1}; ^1H NMR ($CDCl_3$, TMS): δ 5.86 (s, 1 H), 6.65 (s, 2 H), 6.85–7.96 (m, 12 H), 8.00 (br s, NH) ppm.

Compound **5f**: mp 108 °C; IR (KBr): ν 3440 (N–H) cm^{-1}; ^1H NMR ($CDCl_3$, TMS): δ 6.58 (s, 1 H), 6.68 (s, 2 H), 6.86–7.03 (m, 7 H), 7.09 (d, 2 H, *J* = 7.8 Hz), 7.41 (d, 2 H, *J* = 7.8 Hz), 7.71 (br s, NH) ppm; ^{13}C NMR ($CDCl_3$, TMS): δ 37.2, 110.7, 114.4, 119.3, 119.6, 121.4, 121.8, 124.7, 127.2, 128.2, 128.6, 136.3, 138.7 ppm.

Compound **5g**: mp 95–97 °C; IR (KBr): ν 3411 (N–H) cm^{-1}; ^1H NMR ($CDCl_3$, TMS): δ 2.33 (s, 3 H), 5.87 (s, 1 H), 6.69 (s, 2 H), 7.04 (t, 2 H, *J* = 7.1 Hz), 7.12 (d, 2 H, *J* = 7.1 Hz), 7.23–7.28 (m, 6 H), 7.41 (d, 2 H, *J* = 7.2 Hz), 7.94 (br s, NH) ppm.

Compound **5h**: mp 186–188 °C; IR (KBr): ν 3410 (N–H) cm^{-1}; ^1H NMR ($CDCl_3$, TMS): δ 3.76 (s, 3 H), 5.85, (s, 1 H), 6.68 (s, 2 H), 6.91 (d, 2 H, *J* = 8.2 Hz), 7.02 (t, 2 H, *J* = 7.3 Hz), 7.16 (t, 2 H, *J* = 7.3 Hz), 7.20 (m, 2 H), 7.35–7.41 (m, 4 H), 7.95 (br s, NH) ppm.

Compound **5i**: mp 100–102 °C; ^1H NMR ($CDCl_3$, TMS): δ 5.22 (m, 1 H), 6.19 (m, 1 H), 6.57 (d, 1 H, *J* = 15.4 Hz), 6.89 (s, 2 H), 7.02–7.09 (m, 4 H), 7.26–7.32 (m, 7 H), 7.49 (d, 2 H, *J* = 7.9 Hz), 7.92 (br s, NH) ppm.

Compound **5j**: mp 147–149 °C; IR (KBr): ν 3410 (N–H) cm^{-1}; ^1H NMR ($CDCl_3$, TMS): δ 6.08 (s, 1 H), 6.86 (s, 2 H), 6.97–7.45 (m, 11 H), 7.94 (br s, NH) ppm; ^{13}C NMR ($CDCl_3$, TMS): δ 35.9, 110.3, 111.5, 119.3, 120.0, 121.8, 122.6, 123.5, 125.3, 126.3, 128.9, 136.7, 145.5.

Compound **5k**: mp 318–319 °C; IR (KBr): ν 3410 (N–H) cm^{-1}; ^1H NMR ($CDCl_3$, TMS): δ 5.97 (s, 1 H), 6.90 (s, 2 H), 7.08–7.43 (m, 11 H), 8.00 (br s, NH) ppm; ^{13}C NMR (CDCl$_3$, TMS): δ 34.8, 106.5, 110.2, 111.3, 112.2, 118.0, 119.3, 119.7, 121.7, 124.3, 126.3, 135.9, 142.0 ppm.

Compound **5l**: mp 162 °C (dec.); IR (KBr): ν 3400 (N–H) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 6.11 (s, 1 H), 6.86–6.91 (m, 6 H), 7.05 (m, 3 H), 7.35 (d, 3 H, J = 7.9 Hz), 7.52 (d, 3 H, J = 7.9 Hz), 10.59 (s, 3 H, NH) ppm; ^{13}C NMR (DMSO-d_6): δ 136.4, 126.6, 123.0, 120.5, 119.1, 118.1, 117.8, 111.2, 30.8 ppm.

Compound **5m**: mp 165–167 °C; ^{1}H NMR (CDCl$_3$, TMS): δ 1.37 (d, 3 H, J = 7.0 Hz), 4.12 (m, 1 H), 4.78 (d, 1 H, J = 10.5 Hz), 6.52 (s, 2 H), 7.04–7.17 (m, 13 H), 7.90 (br s, NH) ppm.

Compound **5n**: mp 71–73 °C; IR (KBr): ν 3426 (N–H) cm^{-1}; ^{1}H NMR (CDCl$_3$, TMS) δ: 0.89 (t, 3 H, J = 6.7 Hz), 1.27–1.33 (m, 6 H), 1.52 (m, 2 H), 4.79 (t, 1 H, J = 6.6 Hz), 6.91 (s, 2 H), 6.99–7.07 (m, 4 H), 7.30 (d, 2 H, J = 7.8 Hz), 7.55 (d, 2 H, J = 7.8 Hz), 7.94 (br s, NH) ppm.

Compound **5o**: mp 66–68 °C; IR (KBr): ν 3414 (N–H) cm^{-1}; ^{1}H NMR (CDCl$_3$, TMS): δ 0.83 (t, 3 H, J = 6.8 Hz), 1.23–1.36 (m, 8 H), 2.19 (m, 2 H), 4.66 (t, 1 H, J = 7.2 Hz), 7.00–7.04 (m, 4 H), 7.13 (t, 2 H, J = 8.0 Hz), 7.31 (d, 2 H, J = 8.0 Hz), 7.57 (d, 2 H, J = 7.2 Hz), 7.90 (br s, NH) ppm.

Compound **5p**: mp 191 °C (dec.); IR (KBr): ν 3405 (N–H) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 5.87 (s, 2 H), 6.54 (s, 4 H), 7.09–7.18 (m, 8 H), 7.28–7.41 (m, 12 H), 8.14 (br s, NH) ppm. ^{13}C NMR (CDCl$_3$, TMS): δ 30.7, 111.8, 117.9, 118.1, 119.4, 121.1, 124.0, 126.6, 127.9, 137.0, 142.7 ppm.

Compound **5q**: mp 163–165 °C; IR (KBr): ν 3442 (N–H) cm^{-1}; ^{1}H NMR (CDCl$_3$, TMS): δ 1.61 (m, 2 H), 1.69 (m, 4 H), 2.54–2.57 (m, 4 H), 6.91 (s, 2 H), 7.05–7.12 (m, 4 H), 7.34 (d, 2 H, J = 7.8 Hz), 7.58 (d, 2 H, J = 7.5 Hz), 7.94 (br s, NH) ppm.

5r: mp 72–74 °C; IR (KBr): ν 3475 (N–H) cm^{-1}; ^{1}H NMR (CDCl$_3$, TMS): δ 1.75 (m, 4 H), 2.45 (m, 4 H), 6.75 (t, 2 H, J = 8.0 Hz), 6.95 (m, 4 H), 7.20 (d, 2 H, J = 8.0 Hz), 7.45 (d, 2 H, J = 8.0 Hz), 7.90 (br s, NH) ppm.

Compound **5s**: mp 158 °C; IR (KBr): ν 3400 (N–H), 1721 (C=O) cm^{-1}; ^{1}H NMR (CDCl$_3$, TMS): δ 1.96 (s, 3 H, CO$_2$CH$_3$), 3.47 (s, 3 H, CH$_3$), 6.71 (s, 2 H), 6.76–6.82 (m, 2 H), 6.90–6.96 (m, 2 H), 7.24 (d, 2 H, J = 7.5 Hz), 7.31 (d, 2 H, J = 7.5 Hz), 9.38 (br s, NH) ppm; ^{13}C NMR (CDCl$_3$, TMS): δ 25.0, 45.2, 51.0, 110.6, 117.7, 118.1, 119.8, 120.2, 122.4, 125.0, 136.0, 175.3 ppm.

Compound **6a**: mp 245–247 °C; IR (KBr): ν 3405 (N–H) cm^{-1}; ^{1}H NMR (CDCl$_3$, TMS): δ 2.05 (s, 6 H), 5.88 (s, 1 H), 6.78–7.01 (m, 6 H), 7.14–7.22 (m, 5 H), 7.28–7.31 (m, 2 H), 8.02 (br s, NH) ppm.

Compound **7a**: mp 251 °C; IR (KBr): ν 3418 (N–H) cm^{-1}; ^{1}H NMR (CDCl$_3$, TMS): δ 5.78 (s, 1 H), 6.65 (s, 2 H), 7.20–7.29 (m, 11 H), 8.00 (br s, NH) ppm.

3.6. Spectral data for selected bis(pyrazole-5-ols)

Compound **10b**: mp 219–220 °C; IR (KBr): ν 3056 (O–H) cm^{-1}; ^{1}H NMR (DMSO-d_6, TMS): δ 2.35 (s, 6 H), 5.13 (s, 1 H), 7.25–7.27 (m, 2 H), 7.44 (t, 4 H, J = 7.0 Hz), 7.52 (d, 2 H, J = 8.1 Hz), 7.71 (d, 4 H, J = 7.6 Hz), 8.17 (d, 2 H, J = 8.2 Hz) ppm; ^{13}C NMR (DMSO-d_6, TMS): δ 12.5, 34.1, 121.5, 124.2, 126.6, 129.5, 129.8, 146.8, 147.2, 151.2 ppm.

Compound **10e**: mp 230–231 °C; IR (KBr): ν 3044 (O–H) cm^{-1}; ^{1}H NMR (DMSO-d_6, TMS): δ 2.32 (s, 6 H), 4.97 (s, 1 H), 7.26 (d, 4 H, J = 8.2 Hz), 7.34 (d, 2 H, J = 8.0 Hz), 7.44 (t, 4 H, J = 7.1 Hz), 7.71 (d, 4 H, J = 7.6 Hz) ppm.

3.7. Spectral data for a selected dipyrromethane

Compound **11a**: mp 100–101 °C; IR (KBr): ν 3334 (N–H) cm^{-1}; ^{1}H NMR (CDCl$_3$, TMS): δ 5.49 (s, 1 H), 5.92 (s, 2 H), 6.14–6.18 (m, 2 H), 6.70–6.72 (m, 2 H), 7.21–7.36 (m, 5 H), 7.94 (br s, NH) ppm; ^{13}C NMR (CDCl$_3$, TMS): δ 43.9, 107.3, 108.4, 117.3, 126.9, 128.4, 128.7, 132.6, 142.1 ppm.

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