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An efficient water-mediated synthetic route for the alkylation of heteroarenes

Pınar SEYİTDANLIOĞLU, Essam Hamied Ahmed HANASHALSHAHABY, Canan ÜNALEROĞLU*

Department of Chemistry, Faculty of Science, Hacettepe University, Ankara, Turkey

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Abstract: An efficient synthetic route has been described for the alkylation of 1*H*-indole, 1*H*-benzimidazole, and 1*H*-benzotriazole. This approach features the alkylation of heteroaromatics through in situ generated enones from ketonic Mannich bases under metal-free conditions. A series of alkylated heteroaromatics have been synthesized via the K10 catalyzed alkylation reactions of these heteroaromatics with a variety of ketonic Mannich bases. Environmentally benign K10 catalyst, water-mediated mild reaction conditions, and the efficient synthesis of alkylated products are the advantages of this alkylation method.

Key words: Mannich base, alkylation reaction of 1*H*-indole 1*H*-benzimidazole and 1*H*-benzotriazole, K10, environmentally friendly synthesis

1. Introduction

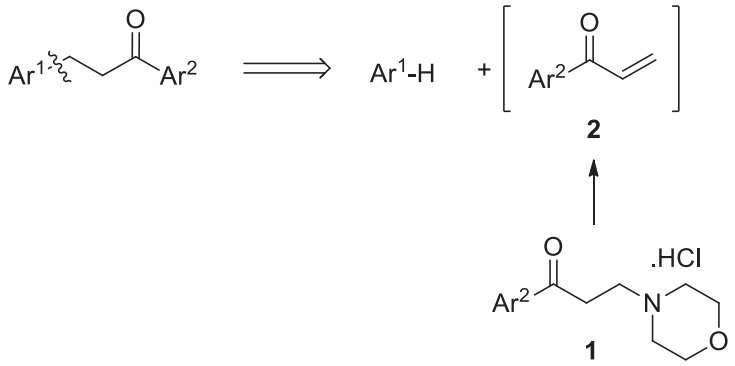
Indole, benzimidazole, and benzotriazole derivatives appear in a wide range of biologically active compounds on both the synthetic and the natural basis. These heteroaromatics exhibit biological activities such as antiparasitic,[1] antimicrobial,[2] antiviral,[3] antiserotonergic, antiadrenergic, antihistaminic, and analgesic.[4] Omeprazole, lansoprazole, rabeprazole, and pantoprazole as proton pump inhibitors or H_2 receptor blockers are market drugs of benzimidazole derivatives,[5] and nonsteroidal aromatase inhibitor vorozole[6] and antiemetic drug alizapride[7] are examples of commercially used benzotriazole derivatives. Moreover, alkyl functionalized indole, benzimidazole, and benzotriazole derivatives show such bioactivities.[8–10] Given the importance of these functionalized heteroaromatics in medicinal chemistry, development of an environmentally friendly synthetic route to these heteroaromatics is of high importance.

To date, various synthetic methods have been applied to the alkylation of these heteroaromatics; however, very limited studies have been reported on the synthesis of carbonyl functionality bearing alkyl substituted indoles, benzimidazoles, and benzotriazoles. Acid catalyzed Mannich reaction of 1*H*-benzimidazole with acetophenone and formaldehyde[9] or substitution reaction of alkyl halides with 1*H*-benzimidazole[8] in organic solvents is used for the alkylation of benzimidazole. Another approach for the alkylation of heteroaromatics was reported by Roman with the use of Mannich bases to reach alkyl substituted benzimidazoles,[11] in which Mannich bases provide a good opportunity to form new C-C and C-N bonds through the substitution or elimination-addition reactions.[12] Recently, syntheses of alkyl substituted benzotriazoles have been reported via Mannich-type coupling of ketones and benzotriazoles in the presence of Selectfluor catalyst in DMSO[13] or from the reaction of enones in the presence of $Sc(OTf)_3$.[14] Alkylated indole syntheses were handled from the reaction

*Correspondence: canan@hacettepe.edu.tr

of indoles with quite expensive and unstable enones in various organic solvents by using Br_2[15] or different metal catalysts such as Al(III), Pd(II)/Sn(II), Fe(II), Cu(II), and Ru(I)/Ag(I).[16–20]

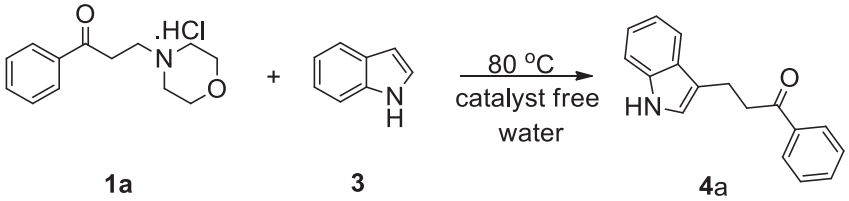
In the present work, it is aimed to achieve the metal-free alkylation of 1*H*-indole, 1*H*-benzimidazole, and 1*H*-benzotriazole from the reaction of these heteroaromatics with Mannich bases in water. In this approach, Mannich base **1** serves as an enone precursor for **2** as given in Scheme 1.



Scheme 1. Retrosynthetic strategy of alkylated heteroaromatics.

2. Results and discussion

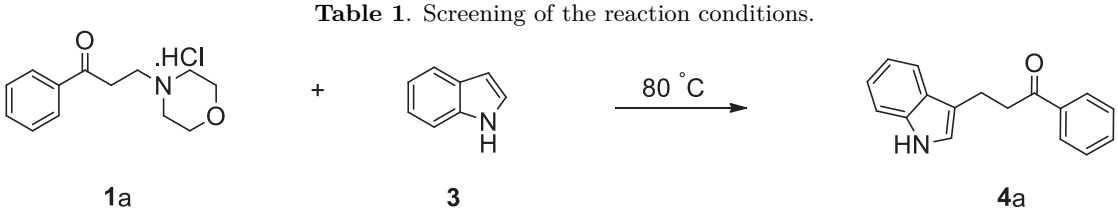
Vinyl ketones are generally unstable and high-cost starting materials; therefore, we previously used Mannich bases as enone precursors.[21] Here, our strategy began with the reaction of 1*H*-indole (**3**) with Mannich base **1a** in water (Scheme 2). The reaction furnished target molecule **4a** with quite a high yield (50%) under catalyst-free conditions.



Scheme 2. Alkylation of 1*H*-indole.

To improve the product yield, reaction conditions were optimized on the model reaction given in Scheme 2. In catalyst-free conditions, the highest yield was obtained in water (Table 1, entries 1–3.) We next tested a variety of catalysts to improve the yield but $Cu(OTf)_2$, $Ce(OTf)_3$, CAN, and KSF gave the product with lower yields (20%–40%) (Table 1, entries 5–8). When the reaction was performed with K10, the yield of **4a** increased from 50% to 75% (Table 1, entry 4). We then screened the effect of ratios of 1*H*-indole to Mannich base as shown in Table 1, entries 9–11. The same result was obtained with the optimum ratio of 1:1.5 (Table 1, entry 10). Compound **4a** has been previously obtained from the reaction of 1*H*-indole (**3**) with 1-phenylprop-2-en-1-one (**2a**) in the presence of different metal catalysts in yields between 72% and 95% in organic solvents.[16–20] With this strategy, we achieved a water-mediated environmentally friendly K10 catalyzed reaction starting from a Mannich base instead of unstable enones and compound **4a** was obtained with yields comparable to metal catalyst reaction systems.

Table 1. Screening of the reaction conditions.



1a **3** **4a**

Entry	Solvent	1*H*-Indole:mannich base	Catalyst	Yield (%)[a]
1	H_2O	1:3	-	50
2	EtOH	1:3	-	32
3	AcOH	1:3	-	10
4	H_2O	1:3	K-10	75
5	H_2O	1:3	$Cu(OTf)_2$	25
6	H_2O	1:3	$Ce(OTf)_3$	20
7	H_2O	1:3	CAN	20
8	H_2O	1:3	KSF	40
9	H_2O	1:1.2	K-10	45
10	H_2O	1:1.5	K-10	75
11	H_2O	1:2	K-10	75

[a]Isolated yields.

To extend the scope of the alkylation reactions of 1*H*-indole (**3**), we next used the synthesized Mannich bases **1a**–1**g** shown in the Figure in the optimized reaction condition.

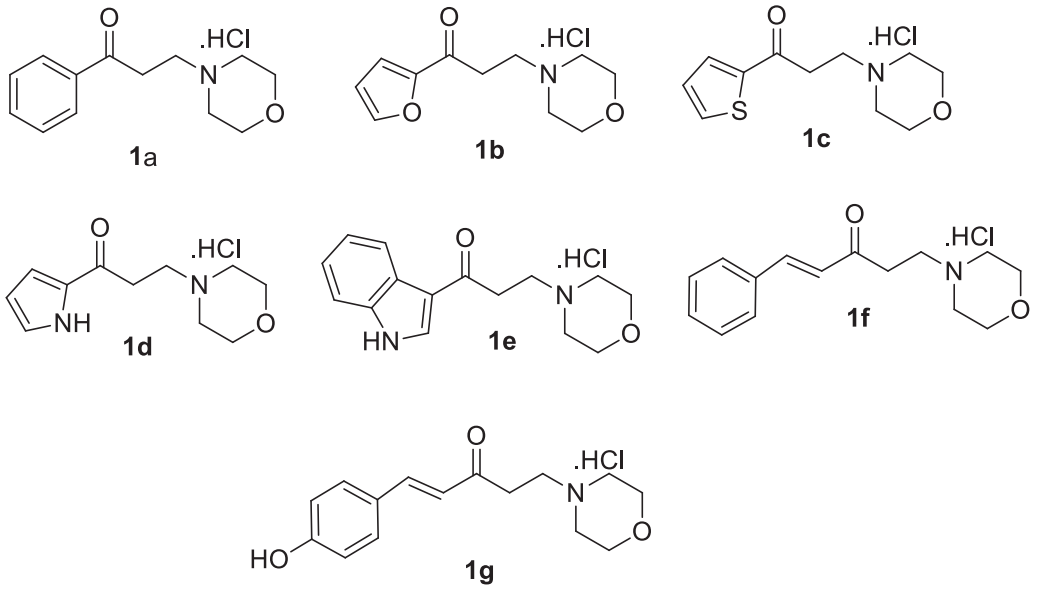
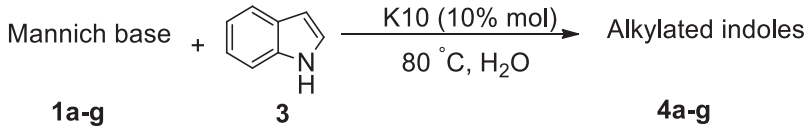


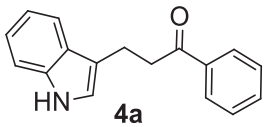
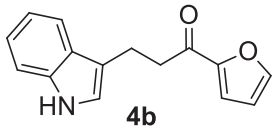
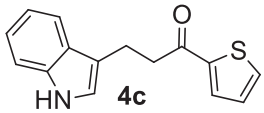
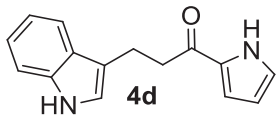
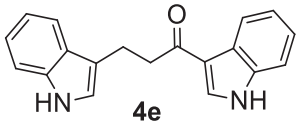
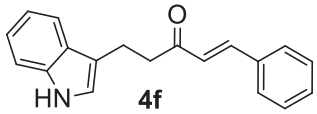
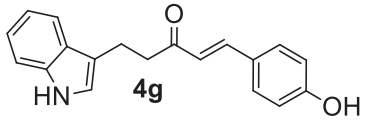
Figure. Mannich bases.

Reactions of 1*H*-indole with Mannich bases **1d** and **1e** formed products **4d** and **4e** with low yields (20% and 42%, respectively) (Table 2, entries 4 and 5). **4e** was previously obtained by condensation of *N*,*N*-

dimethylacrylamide/trifluoromethanesulfonic anhydride complex with indole in a lower yield.[22] Mannich bases **1b** and **1c**, respectively, yielded corresponding alkylated products **4b** and **4c** with moderate yields (72%, 65%) (Table 2, entries 2 and 3). The novel alkylated indole **4g** was obtained with high yield (85%) (Table 2, entry 7) and the highest yield (90%) was obtained for alkylated product **4f** from the reaction of Mannich base **4f** and 1*H*-indole (**3**) (Table 2, entry 6).

Table 2. Synthesis of alkylated indoles.



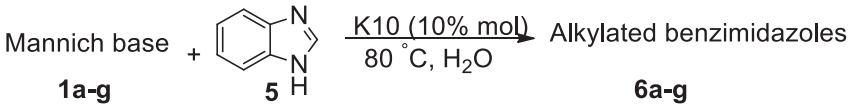
Entry	Mannich Base	Product	Time (h)	Yield (%)[a]
1	1a	 **4a**	12	75
2	1b	 **4b**	9	72
3	1c	 **4c**	8	65
4	1d	 **4d**	16	20
5	1e	 **4e**	12	42[b]
6	1f	 **4f**	9	90
7	1g	 **4g**	12	85

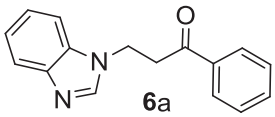
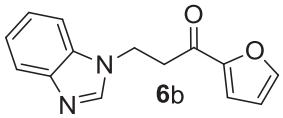
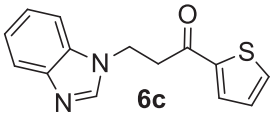
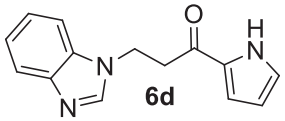
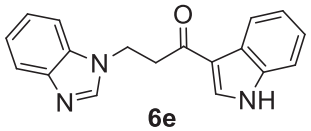
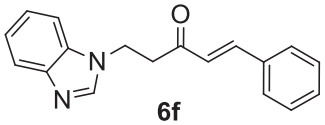
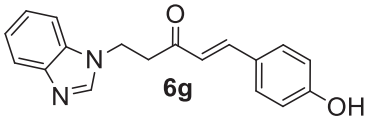
[a]Isolated yields [b]At reflux

With the optimum conditions in hand, we next expanded the reaction to the alkylation of 1*H*-benzimidazole (**5**) and 1*H*-benzotriazole (**7**). K10 catalyzed reactions of 1*H*-benzimidazole with Mannich bases **1a**–**1d**, **1f**–**1g** were generated in water and the corresponding 3-alkylated benzimidazoles **6a**–**6d**, **6f**–**6g** were obtained with

moderate to high yields (Table 3, entries 1–4, 6, 7). 3-Alkylated benzimidazoles **6a** and **6c** have been previously obtained with 61% and 77% yields, respectively, in ethanol/water.[11] K10 catalyzed reactions of 1*H*- benzimidazole with Mannich bases **1a**, **1c**, and **1f** formed the corresponding products **6a** (89%), **6c** (80%), and **6f** (80%). Moreover, reactions with Mannich bases **1b**, **1d**, and **1g** yielded the novel products **6b**, **6d**, and **6g** with moderate to high yields (67%–80%). The results indicate that this environmentally friendly reaction protocol is very applicable for the alkylation of 1*H*-benzimidazole. 3-Alkylated benzimidazole **6e** formed; however, the isolation of the product failed due to the low solubility of this product in organic solvents. Formation of **6e** was proved by mass analysis (Table 3, entry 5).

Table 3. Synthesis of alkylated benzimidazoles.



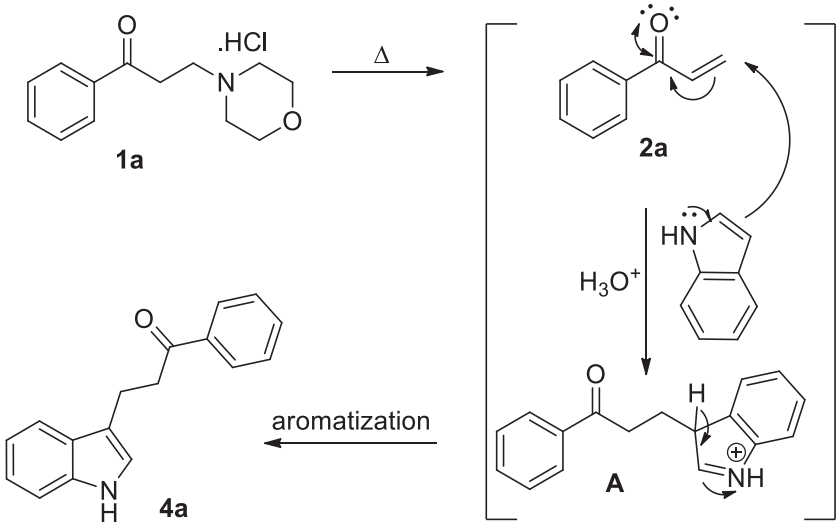
Entry	Mannich Base	Product	Time (h)	Yield (%)[a]
1	1a	 **6a**	6	89
2	1b	 **6b**	6	78
3	1c	 **6c**	6	80
4	1d	 **6d**	6	67
5	1e	 **6e**	6	-[b]
6	1f	 **6f**	3	80
7	1g	 **6g**	3	80

[a]Isolated yields [b]Not isolated

In the next step, the K10 catalyzed reactions of 1*H*-benzotriazole (7) with Mannich bases **1a**–**1g** were investigated. The reaction of 1*H*-benzotriazole with Mannich base **1a** was carried out and the reaction resulted in the formation of 3-alkylated benzotriazole **8a** as the major product with 65% yield and 2-alkylated benzotriazole **9a** as a minor product with 8% yield due to the two resonance forms of benzotriazole (Table 4, entry 1). 3-Alkylated benzotriazoles **8b**, **8c**, and **8f** were obtained with moderate to high yields (55%–79%) and 2-alkylated benzotriazoles **9b**, **9c**, and **9f** formed with low yields (3%–20%) from the reactions of benzotriazole and Mannich bases **1b**, **1c**, and **1f**, respectively (Table 4, entries 2, 3, and 6). From the reaction of Mannich base **1g**, 3-alkylated benzotriazole **8g** was obtained with 65% yield as the only product (Table 4, entry 7). Compounds **8d**, **9d**, **8e**, and **9e** were formed; however, they could not be isolated due to their low solubility in organic solvents. Formation of **8d**, **9d**, **8e**, and **9e** was proved by mass analysis (Table 4, entries 4 and 5). With these results, hitherto unknown compounds **8b**, **8f**, **8g**, **9b**, **9c**, and **9f** were described in this study. All the synthesized compounds were characterized by ^{1}H NMR, ^{13}C NMR, and HRMS-TOF-MS techniques.

To investigate the reaction mechanism, we performed a series of reactions of 1*H*-indole (**3**) and Mannich base **1a**. When the reactions were performed at 50 °C and room temperature, product yields decreased from 75% to 42% and 2%, respectively. These results showed that the formation of essential enone intermediate is highly temperature-dependent.

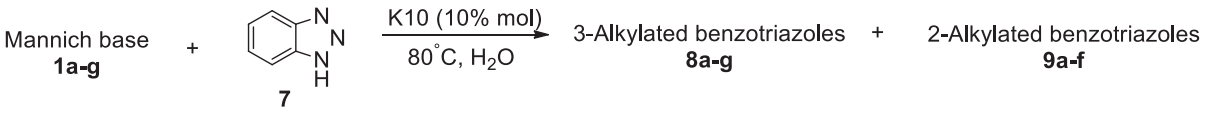
Independently isolated key structure enone **2a** was used in a separate reaction of 1*H*-indole (**3**), and the product was obtained in 80% yield, similar to the prior result (75%). In light of the foregoing findings, we suggest the reaction mechanism in Scheme 3. In this mechanism, Mannich base **1a** in situ forms enone **2a** at 80 °C and the addition of 1*H*-indole (**3**) to enone **2a** forms intermediate A, and the following aromatization gives target molecule **4a**.

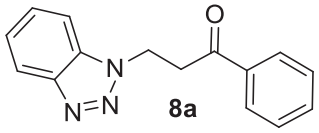
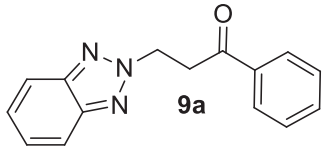
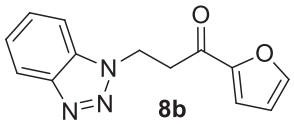
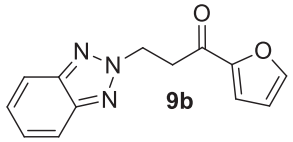
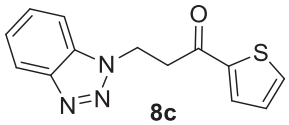
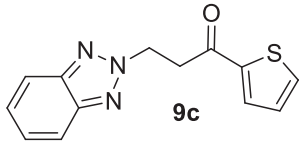
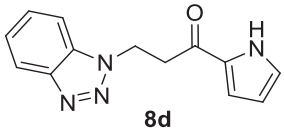
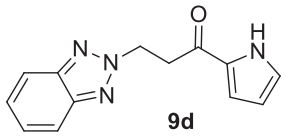
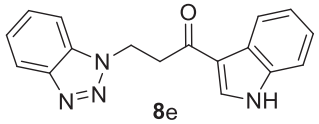
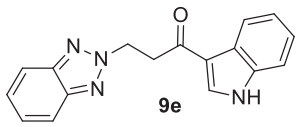
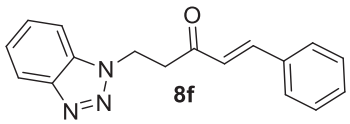
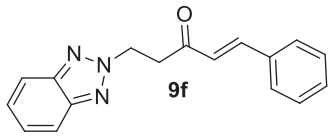
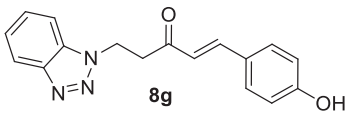


Scheme 3. Proposed reaction mechanism.

In conclusion, an environmentally friendly and simple method has been established to alkylate 1*H*-indole, 1*H*-benzimidazole, and 1*H*-benzotriazole. All alkylation reactions were performed under metal-free conditions in water. In this strategy, target molecules were efficiently obtained with moderate to highest yields via environmentally friendly K10 catalyzed reactions of ketonic Mannich bases, as enone precursors, with 1*H*-indole, 1*H*-benzimidazole, or 1*H*-benzotriazole. Our method exemplifies the fact that the Mannich bases

Table 4. Synthesis of alkylated benzotriazoles.



Entry	Mannich Base	3-Alkylated Benzotriazole	Yield (%)[a]	2-Alkylated Benzotriazole	Yield (%)[a]	Time (h)
1	1a	 **8a**	65	 **9a**	8	8
2	1b	 **8b**	55	 **9b**	5	6
3	1c	 **8c**	71	 **9c**	3	7
4	1d	 **8d**	-[b]	 **9d**	-[b]	8
5	1e	 **8e**	-[b]	 **9e**	-[b]	8
6	1f	 **8f**	79	 **9f**	20	5
7	1g	 **8g**	65	-		5

[a]Isolated yields [b]Not isolated

are effective reagents in alkylation reactions of these heterocyclic systems. This study provides a beneficial method for the further alkylation reactions of such heteroaromatics in water-mediated environmentally friendly moderate reaction conditions.

3. Experimental

All reagents were purchased from Acros Organics, Sigma-Aldrich, or Fischer Scientific and were used without further purification. Reactions were monitored by TLC using precoated silica plates (Kieselgel 60, F254, Merck) and visualized by an UV lamp. Flash column chromatography was performed using silica gel (0.05–0.63 nm, 230–400 mesh ASTM, Merck). ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) data were recorded on a Bruker DPX-400-Ultra Shield FT-NMR spectrometer using $SiMe_4$ as an internal reference. Coupling constants are expressed as J values in hertz (s = singlet, d = doublet, t = triplet, bs = broad singlet, m = multiplet). Melting points were determined with a Gallenkamp electrothermal digital melting point apparatus and are uncorrected. High-resolution mass spectra (HRMS) were recorded with an Agilent 1200/6210 high resolution mass time-of-flight (TOF) LC/MS spectrometer.

3.1. General procedure for synthesis of Mannich bases

Mannich bases were synthesized according to the given literature procedure.[23] A mixture of paraformaldehyde (1.80 g, 1.2 eq., 60.0 mmol), ketone (1.0 eq., 50.0 mmol), morpholine (4.35 g, 1.0 eq., 50.0 mmol), and hydrochloric acid (1.0 eq., 50.0 mmol) in ethanol was stirred at reflux. The reaction was monitored by TLC. After the completion of the reaction, crude product was filtered and recrystallized in ethanol.

3-Morpholino-1-phenylpropan-1-one hydrochloride (1a): White solid; mp 177–178 °C (lit. 175–178 °C); yield: 75%.[24]

1-(Furan-2-yl)-3-morpholinopropan-1-one hydrochloride (1b): White solid; mp 191–192 °C (lit. 191–192 °C); yield: 60%.[25]

3-Morpholino-1-(thiophen-2-yl)propan-1-one hydrochloride (1c): White solid; mp 193–194 °C (lit. 194 °C); yield: 70%.[26]

3-Morpholino-1-(1*H*-pyrrol-2-yl)propan-1-one hydrochloride (1d): Light brown solid; mp 206–207 °C (lit. 206–207 °C); yield: 20%.[27]

1-(1*H*-Indol-3-yl)-3-morpholinopropan-1-one hydrochloride (1e): Pink solid; mp 229–230 °C; yield: 50%.[21]

(*E*)-5-Morpholino-1-phenylpent-1-en-3-one hydrochloride (1f): White solid; mp 158–159 °C (lit. 158–159 °C); yield: 40%.[28]

(*E*)-1-(4-Hydroxyphenyl)-5-morpholinopent-1-en-3-one hydrochloride (1g): Yellow solid; mp 195–196 °C (lit. 195–196 °C); yield: 65%.[28]

3.2. General procedure for the alkylation of 1*H*-indole, 1*H*-benzimidazole, and 1*H*-benzotriazole

A mixture of 1*H*-indole, 1*H*-benzimidazole, or 1*H*-benzotriazole (1.0 eq., 0.49 mmol), ketonic Mannich base (1.5 eq., 0.75 mmol), and montmorillonite K10 (0.15 eq., 75 mg) in 2 mL of water was heated to 80 °C. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature and extracted with EtOAc (3 ×10 mL) and then dried over $MgSO_4$. Solvent was removed under reduced pressure and the crude product was purified by column chromatography (EtOAc:hexane, 1:3; EtOAc).

3-(1*H*-Indol-3-yl)-1-phenylpropan-1-one (4a): White solid; mp 127–128 °C (lit.[29] 126–127 °C); yield 75%; R_f = 0.34 (EtOAc-hexane, 1:3); ^{1}H NMR (400 MHz, DMSO) δ 3.04 (t, J = 7.4 Hz, 2H), 3.42 (t,

J = 7.4 Hz, 2H), 6.97 (t, J = 7.4 Hz, 1H), 7.06 (t, J = 7.0 Hz, 1H), 7.16 (bs, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.49–7.56 (m, 3H), 7.63 (t, J = 6.8 Hz, 1H), 8.00 (d, J = 7.8 Hz, 2H), 10.78 (s, 1H); ^{13}C NMR (100 MHz, DMSO) δ = 19.9, 39.2, 111.8, 114.1, 118.7, 118.8, 121.4, 122.8, 127.5, 128.4, 129.2, 133.5, 136.7, 137.2, 200.2; HRMS (ESI): m/z calculated for $C_{17}H_{16}NO$ $[M+H]^+$: 250.1226; found: 250.1235.

1-(Furan-2-yl)-3-(1*H*-indol-3-yl)propan-1-one (4b): White solid; mp 105–106 °C; yield 72%; R_f = 0.40 (EtOAc-hexane, 1:3); ^{1}H NMR (400 MHz, DMSO) δ 3.01 (t, J = 7.4 Hz, 2H), 3.19 (t, J = 7.4 Hz, 2H), 6.67 (bs, 1H), 6.96 (t, J = 7.4 Hz, 1H), 7.05 (t, J = 7.1 Hz, 1H), 7.12 (bs, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.45 (d, J = 3.5 Hz, 1H), 7.53 (d, J = 7.7 Hz, 1H), 7.95 (bs, 1H), 10.77 (bs, 1H); ^{13}C NMR (100 MHz, DMSO) δ = 19.8, 38.9, 111.8, 112.9, 113.8, 118.7, 118.8, 121.4, 122.9, 127.4, 136.7, 148.0, 152.4, 188.7; HRMS (ESI): m/z calculated for $C_{15}H_{14}NO_2$ $[M+H]^+$: 240.1019; found: 240.1026.

3-(1*H*-Indol-3-yl)-1-(thiophen-2-yl)propan-1-one (4c): White solid; mp 104–105 °C (lit.[30] 105 °C); yield 65%; R_f = 0.20 (EtOAc-hexane, 1:3); ^{1}H NMR (400 MHz, DMSO) δ 3.09 (t, J = 7.4 Hz, 2H), 3.38 (t, J = 7.4 Hz, 2H), 7.02 (t, J = 7.4 Hz, 1H), 7.10 (t, J = 7.5 Hz, 1H), 7.19 (bs, 1H) 7.25 (t, J = 4.3 Hz, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.59 (d, J = 7.8 Hz, 1H), 7.99 (bs, 1H), 8.01 (bs, 1H), 10.82 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO) δ = 20.1, 40.6, 111.8, 113.9, 118.7, 118.8, 121.4, 122.9, 127.5, 129.2, 133.6, 135.0, 136.7, 144.4, 193.3; HRMS (ESI): m/z calculated for $C_{15}H_{14}NOS$ $[M+H]^+$: 256.0791; found: 256.0809.

3-(1*H*-Indol-3-yl)-1-(1*H*-pyrrol-2-yl)propan-1-one (4d): White solid; mp 167.5–168.0 °C; yield 20%; R_f = 0.27 (EtOAc-hexane, 1:3); ^{1}H NMR (400 MHz, DMSO) δ 3.05 (t, J = 7.4 Hz, 2H), 3.15 (t, J = 7.4 Hz, 2H), 6.16–6.23 (m, 1H), 6.68–7.02 (m, 2H), 7.05–7.13 (m, 2H), 7.16 (bs, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.57 (d, J = 7.8 Hz, 1H), 10.79 (s, 1H), 11.81 (s, 1H); ^{13}C NMR (100 MHz, DMSO) δ = 20.6, 38.5, 110.1, 111.8, 114.2, 116.8, 118.7, 118.8, 121.4, 122.8, 125.6, 127.4, 132.2, 136.6, 189.7; HRMS (ESI): m/z calculated for $C_{15}H_{15}N_2O$ $[M+H]^+$: 239.1179; found: 239.1193.

1,3-Di(1*H*-indol-3-yl)propan-1-one (4e): Pink solid; mp 200–201 °C; yield 42%; R_f = 0.30 (EtOAc-hexane, 1:3); ^{1}H NMR (400 MHz, DMSO) δ 3.09 (t, J = 7.5 Hz, 2H), 3.27 (t, J = 7.5 Hz, 2H), 6.99 (t, J = 7.3 Hz, 1H), 7.08 (t, J = 7.4 Hz, 1H), 7.14–7.25 (m, 3H), 7.34 (d, J = 8.0 Hz, 1H), 7.47 (d, J = 6.9 Hz, 1H), 7.59 (d, J = 7.8 Hz, 1H), 8.25 (d, J = 7.4 Hz, 1H), 8.35 (bs, 1H), 10.77 (bs, 1H), 11.91 (gt, 1H); ^{13}C NMR (100 MHz, DMSO) δ = 20.6, 111.8, 112.5, 114.6, 116.9, 118.6, 118.8, 121.3, 121.9, 122.1, 122.8, 123.2, 125.9, 127.6, 134.3, 136.7, 137.1, 195.4; HRMS (ESI): m/z calculated for $C_{19}H_{17}N_2O$ $[M+H]^+$: 289.1385; found: 289.13512.

(E)-5-(1*H*-Indol-3-yl)-1-phenylpent-1-en-3-one (4f): White solid; mp 126–127 °C (lit.[31] 127 °C); yield 90%; R_f = 0.37 (EtOAc-hexane, 1:3); ^{1}H NMR (400 MHz, DMSO) δ 3.09 (t, J = 7.6 Hz, 2H), 3.17 (t, J = 7.6 Hz, 2H), 7.00 (d, J = 16.3 Hz, 1H), 7.06 (t, J = 7.9 Hz, 1H), 7.15 (t, J = 7.6 Hz, 1H), 7.22 (bs, 1H), 7.42 (d, J = 8.0 Hz, 1H), 7.45–7.52 (m, 3H), 7.64 (d, J = 7.7 Hz, 1H), 7.70 (d, J = 16.3 Hz, 1H), 7.73–7.79 (m, 2H), 10.86 (bs, 1H); ^{13}C NMR (100 MHz, DMSO) δ = 19.9, 41.2, 111.8, 114.1, 118.7, 118.8, 121.4, 122.8, 127.0, 127.5, 128.9, 129.4, 130.8, 135.0, 136.8, 142.5, 200.2; HRMS (ESI): m/z calculated for $C_{19}H_{18}NO$: $[M+H]^+$: 276.1383; found: 276.1372.

(E)-1-(4-Hydroxyphenyl)-5-(1*H*-indol-3-yl)pent-1-en-3-one (4g): Yellow solid; mp 198–199 °C; yield 85%; R_f = 0.14 (EtOAc-hexane, 1:3); ^{1}H NMR (400 MHz, DMSO) δ 2.97–3.02 (m, 4H), 6.70 (d, J = 16.2 Hz, 1H), 6.77 (d, J = 7.8 Hz, 2H), 6.96 (t, J = 7.4 Hz, 1H), 7.05 (t, J = 7.5 Hz, 1H), 7.09 (bs, 1H), 7.31

(d, J = 8.0 Hz, 1H), 7.49–7.54 (m, 4H), 9.99 (bs, 1H), 10.73 (bs, 1H); ^{13}C NMR (100 MHz, DMSO) δ = 20.0, 40.9, 111.8, 114.2, 116.3, 118.6, 118.8, 121.3, 122.7, 123.7, 125.9, 127.5, 130.8, 136.8, 142.8, 160.3, 199.9; HRMS (ESI): m/z calculated for $C_{19}H_{18}NO_2$: $[M+H]^+$: 292.1332; found: 292.1325.

3-(1*H*-Benzo[d]imidazol-1-yl)-1-phenylpropan-1-one (6a): White solid; mp 80–81 °C (lit.[9] 80–81 °C); yield 89%; R_f = 0.29 (EtOAc); ^{1}H NMR (400 MHz, acetone) δ 3.74 (t, J = 6.7 Hz, 2H), 4.73 (t, J = 6.7 Hz, 2H), 7.24–7.30 (m, 2H), 7.48–7.53 (m, 2H), 7.59–7.67 (m, 3H), 8.00–8.03 (m, 2H), 8.16 (bs, 1H); ^{13}C NMR (100 MHz, DMSO) δ = 38.5, 42.8, 111.0, 119.8, 121.9, 122,7, 128.4, 129.2, 134.0, 134.2, 136.6, 143.8, 144.7, 198.3; HRMS (ESI): m/z calculated for $C_{16}H_{15}N_2O$ $[M+H]^+$: 251.1179; found: 251.1179.

3-(1*H*-Benzo[d]imidazol-1-yl)-1-(furan-2-yl)propan-1-one (6b): White solid; mp 84.5–85.5 °C; yield 78%; R_f = 0.26 (EtOAc); ^{1}H NMR (400 MHz, DMSO) δ 3.46 (t, J = 6.7 Hz, 2H), 4.58 (t, J = 6.7 Hz, 2H), 6.68 (bs, 1H), 7.19 (t, J = 7.0 Hz, 1H), 7.25 (t, J = 7.0 Hz, 1H), 7.47 (bs, 1H), 7.57–7.72 (m, 2H), 7.97 (bs, 1H), 8.20 (bs, 1H); ^{13}C NMR (100 MHz, DMSO) δ = 38.2, 111.0, 113.0, 119.5, 119.8, 121.9, 122.8, 134.1, 143.8, 144.7, 148.5, 152.0, 186.4; HRMS (ESI): m/z calculated for $C_{14}H_{13}N_2O_2$ $[M+H]^+$: 241.0971; found: 241.0969.

3-(1*H*-Benzo[d]imidazol-1-yl)-1-(thiophen-2-yl)propan-1-one (**6c**): Colorless viscous oil; yield 80%; R_f = 0.28 (EtOAc); ^{1}H NMR (400 MHz, acetone) δ 3.62 (t, J = 6.7 Hz, 2H), 4.60 (t, J = 6.7 Hz, 2H), 7.16–7.23 (m, 2H), 7.25 (t, J = 7.1, 1H), 7.62–7.68 (m, 2H), 7.91–8.03 (m, 2H), 8.24 (bs, 1H); ^{13}C NMR (100 MHz, DMSO) δ 38.9, 111.0, 119.8, 122.0, 122.8, 129.3, 134.1, 134.3, 135.7, 143.7, 143.8, 144.7, 191.2; HRMS (ESI): m/z calculated for $C_{14}H_{13}N_2OS$ $[M+H]^+$: 257.0743; found: 257.0744.

Spectroscopic data are in agreement with literature values.[11]

3-(1*H*-Benzo[d]imidazol-1-yl)-1-(1*H*-pyrrol-2-yl)propan-1-one (**6d**): White solid; mp 164–165 °C; yield 67%; R_f = 0.22 (EtOAc); ^{1}H NMR (400 MHz, acetone) δ 4.58 (t, J = 6.0 Hz, 2H, CH_2), 6.14 (bs, 1H), 6.97 (bs, 1H), 7.06 (s, 1H), 7.18 (t, J = 8.0 Hz, 1H), 7.24 (t, J = 8.0 Hz, 1H), 7.60–7.67 (m, 2H), 8.20 (bs, 1H), 11.86 (bs, 1H); ^{13}C NMR (100 MHz, DMSO) δ = 37.6, 110.4, 110.9, 117.6, 119.8, 122.1, 122.6, 126.2, 131.9, 133.9, 143.5, 144.7, 187.1; HRMS (ESI): m/z calculated for $C_{14}H_{14}N_3O$ $[M+H]^+$: 240.1131; found: 240.1125.

3-(1*H*-Benzo[d]imidazol-1-yl)-1-(1*H*-indol-3-yl)propan-1-one (6e): HRMS (ESI): m/z calculated for $C_{18}H_{16}N_3O$ $[M+H]^+$: 290.1288; found: 290.1267.

(E)-5-(1*H*-Benzo[d]imidazol-1-yl)-1-phenylpent-1-en-3-one (**6f**): White solid; mp 153–154 °C; yield 80%; R_f = 0.65 (EtOAc) ; ^{1}H NMR (400 MHz, acetone) δ 4.55 (t, J = 6.8 Hz, 2H), 6.88 (d, J = 16.4 Hz, 1H), 7.19 (t, J = 8.0 Hz, 1H), 7.26 (t, J = 7.6 Hz, 1H), 7.38–7.45 (m, 3H), 7.57–7.72 (m, 5H), 8.22 (s, 1H); ^{13}C NMR (100 MHz, DMSO) δ = 40.6, 111.0, 119.8, 121.9, 122.7, 126.7, 129.0, 129.4, 131.1, 134.7, 143.5, 143.8, 144.7, 198.3; HRMS (ESI): m/z calculated for $C_{18}H_{17}N_2O$ $[M+H]^+$: 277.1335; found: 277.1315.

(E)-5-(1*H*-Benzo[d]imidazol-1-yl)-1-(4-hydroxyphenyl)pent-1-en-3-one (6g): White solid; mp 214–215 °C; yield 80%; R_f = 0.9 (EtOAc); ^{1}H NMR (400 MHz, DMSO) δ 3.29 (t, J = 6.8 Hz, 2H), 4.53 (t, J = 6.8 Hz, 2H), 6.66 (d, J = 16.0 Hz, 1H), 6.79 (d, J = 8.5 Hz, 2H), 7.19 (t, J = 7.5 Hz, 1H), 7.26 (t, J = 7.5 Hz, 1H), 7.51–7.56 (m, 3H), 7.62–7.67 (m, 2H), 8.21 (s, 1H), 10.10 (s, 1H); ^{13}C NMR (100 MHz, DMSO) δ = 40.6, 111.0, 116.3, 119.8, 121.9, 122.7, 123.4, 125.7, 125.8, 131.0, 134.1, 143.9, 144.6, 160.5, 197.8; HRMS (ESI): m/z calculated for $C_{18}H_{17}N_2O$: $[M+H]^+$: 293.1285; found: 293.1282.

3-(1*H*-Benzo[d][1,2,3]triazol-1-yl)-1-phenylpropan-1-one (8a): White solid; mp 62–63 °C (lit.[9] 62–63 °C); yield 65%; ^{1}H NMR (400 MHz, DMSO) δ 3.88 (t, J = 6.6 Hz, 2H), 5.05 (t, J = 6.6 Hz, 2H), 7.38–7.43 (m, 1H), 7.50–7.65 (m, 4H), 7.90–8.10 (m, 4H); ^{13}C NMR (100 MHz, DMSO) δ = 37.8, 42.8, 111.5, 119.1, 124.2, 127.4, 128.3, 129.2, 133.1, 133.7, 136.3, 145.4, 197.7; HRMS (ESI): m/z calculated for $C_{15}H_{14}N_3O$ $[M+H]^+$: 252.1131; found: 252.1143.

3-(2*H*-Benzo[d][1,2,3]triazol-2-yl)-1-phenylpropan-1-one (9a): White solid; mp 114–115 °C; yield 8%; ^{1}H (400 Hz, DMSO) δ 3.98 (t, J = 6.6 Hz, 2H), 5.12 (t, J = 6.6 Hz, 2H), 7.39–7.44 (m, 2H), 7.55 (t, J = 8.0 Hz, 2H), 7.67 (t, J = 8.0 Hz, 1H), 7.87–7.92 (m, 2H), 8.02 (d,J = 8.0 Hz, 2H); ^{13}C (100 MHz, DMSO) δ 37.5, 51.4, 118.2, 126.0, 128.5, 129.3, 134.0, 136.5, 144.0, 197.3; HRMS (ESI): m/z calculated for $C_{15}H_{14}N_3O$ $[M+H]^+$: 252.1131; found: 252.1141.

3-(1*H*-Benzo[d][1,2,3]triazol-1-yl)-1-(furan-2-yl)propan-1-one (8b): Colorless viscous oil; yield 55%; ^{1}H NMR (400 MHz, acetone) δ 3.67 (t, J = 6.5 Hz, 2H), 5.06 (t, J = 6.5 Hz, 2H), 6.62–6.67 (m, 1H), 7.37–7.44 (m, 2H), 7.56 (t, J = 8.0 Hz, 1H), 7.83 (bs, 1H), 7.90 (d, J = 8.3 Hz, 1H), 7.98 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, acetone) δ = 37.6, 42.3, 110.4, 112.3, 117.7, 119.2, 123.6, 127.0, 133.3, 145.8, 147.3, 152.3, 185.1; HRMS (ESI): m/z calculated for $C_{13}H_{12}N_3O$ $[M+H]^+$: 242.0924; found: 242.0924.

3-(2*H*-benzo[d][1,2,3]triazol-2-yl)-1-(furan-2-yl)propan-1-one (9b): Colorless viscous oil; yield 5%; ^{1}H (400 Hz, DMSO) δ 3.74 (t, J = 6.6 Hz, 2H), 5.09 (t, J = 6.6 Hz, 2H), 6.74 (bs, 1H), 7.37–7.48 (m, 2H), 7.56 (bs, 1H), 7.88–7.91 (m, 2H), 8.02 (bs, 1H); ^{13}C (100 MHz, DMSO) δ 37.2, 51.1, 113.1, 118.2, 119.5, 126.8, 144.0, 148.5, 185.4; HRMS (ESI): m/z calculated for $C_{13}H_{12}N_3O$ $[M+H]^+$: 242.0924; found: 242.0920.

3-(1*H*-Benzo[d][1,2,3]triazol-1-yl)-1-(thiophen-2-yl)propan-1-one (8c): White solid; mp 97–98 °C (lit.[32] 94–95 °C); yield 71%; R_f = 0.12 (EtOAc-hexane, 1:2); ^{1}H NMR (400 MHz, DMSO) δ 3.79 (t, J = 6.4 Hz, 2H), 5.03 (t, J = 6.4 Hz, 2H), 7.21 (bs, 1H), 7.39 (t, J = 7.2 Hz, 1H), 7.55 (t, J = 7.2 Hz, 1H), 7.95 (d, J = 8.1 Hz, 1H), 7.99–8.03 (m, 3H); ^{13}C NMR (100 MHz, DMSO) δ = 38.4, 43.2, 111.4, 119.5, 124.4, 127.6, 129.3, 133.4, 134.4, 135.7, 143.6, 145.6, 190.7; HRMS (ESI): m/z calculated for $C_{13}H_{12}N_3OS$: $[M+H]^+$: 258.0696; found: 258.0688.

3-(2*H*-Benzo[d][1,2,3]triazol-2-yl)-1-(thiophen-2-yl)propan-1-one (9c): Colorless viscous oil; yield 3%; R_f = 0.14 (EtOAc-hexane, 1:2); ^{1}H (400 Hz, DMSO) δ 3.89 (t, J = 6.6 Hz, 2H), 5.09 (t, J = 6.6 Hz, 2H), 7.25 (t, J = 4 Hz, 1H), 7.40–7.43 (m, 2H), 7.87–7.90 (m, 2H), 8.02–8.07 (m, 2H); ^{13}C (100 Hz, DMSO) δ = 37.9, 51.3, 118.2, 126.8, 129.3, 134.3, 135.7, 144.1, 190.3; HRMS (ESI): m/z calculated for $C_{13}H_{12}N_3OS$ $[M+H]^+$: 258.0696; found: 258.0683.

3-(1*H*-Benzo[d][1,2,3]triazol-1-yl)-1-(1*H*-pyrrol-2-yl)propan-1-one (8d) /

3-(2*H*-benzo[d][1,2,3]triazol-2-yl)-1-(1*H*-pyrrol-2-yl)propan-1-one (9d):

HRMS (ESI): m/z calculated for $C_{13}H_{13}N_4O$ $[M+H]^+$: 241.1084; found: 241.1073.

3-(2*H*-Benzo[d][1,2,3]triazol-2-yl)-1-(1*H*-indol-3-yl)propan-1-one (8e) /

3-(2*H*-benzo[d][1,2,3]triazol-2-yl)-1-(1*H*-indol-3-yl)propan-1-one (9e):

HRMS (ESI): m/z calculated for $C_{17}H_{15}N_4O$ $[M+H]^+$: 291.1240; found: 291.1241.

(E)-5-(1*H*-Benzo[d][1,2,3]triazol-1-yl)-1-phenylpent-1-en-3-one (8f): Colorless viscous oil; yield 79%; R_f = 0.59 (EtOAc-hexane, 1:1); ^{1}H (400 MHz, DMSO) δ 3.63 (t, J = 6.5 Hz, 2H), 5.05 (t, 6.5 Hz, 2H), 6.95 (d, J = 16.4 Hz, 1H), 7.35–7.46 (m, 4H), 7.57(t, J = 8.0, 1H), 7.59–7.76 (m, 3H), 7.97 (d, J =

8.4 Hz, 1H), 8.03 (d, J = 8.4 Hz, 1H); ^{13}C (100 MHz, DMSO) δ = 43.2, 111.4, 119.5, 124.4, 126.6, 127.6, 129.0, 129.4, 131.1, 133.4, 134.7, 143.5, 145.6, 197.7; HRMS (ESI): m/z calculated for $C_{17}H_{16}N_3O$ $[M+H]^+$: 278.1288; found: 278.1271.

(E)-5-(2*H*-Benzo[d][1,2,3]triazol-2-yl)-1-phenylpent-1-en-3-one (9f): Colorless viscous oil; yield 20%; R_f = 0.75 (EtOAc-hexane, 1:1); ^{1}H (400 Hz, DMSO) δ 3.63 (t, J = 6.6 Hz, 2H), 5.05 (t, J = 6.6 Hz, 2H), 6.95 (d, J = 16.0 Hz, 1H), 7.41–7.44 (m, 5H), 7.67–7.71 (m, 3H), 7.88–7.91 (m, 2H); ^{13}C (100 Hz, DMSO) δ = 51.4, 118.2, 126.5, 126.6, 129.1, 129.5, 131.1, 134.8, 143.4, 144.0, 197.2; HRMS (ESI): m/z calculated for $C_{17}H_{16}N_3O$: found $[M+H]^+$: 278.1288; found: 278.1288.

(E)-5-(1*H*-Benzo[d][1,2,3]triazol-1-yl)-1-(4-hydroxyphenyl)pent-1-en-3-one (8g): Brown solid; mp 183–184 °C; yield 65%; ^{1}H NMR (400 MHz, acetone) δ 3.48 (t, J = 6.6 Hz, 2H), 4.97 (t, J = 6.6 Hz, 2H), 6.70 (d, J = 16.3 Hz, 1H), 6.80 (d, J = 8.6 Hz, 2H), 7.40 (t, J = 7.3 Hz, 1H), 7.48–7.62 (m, 4H), 7.96 (d, J = 8.1 Hz, 1H), 8.03 (d, J = 8.4 Hz, 1H), 10.90 (bs, 1H, OH); ^{13}C (100 MHz, acetone) δ = 39.2, 42.8, 110.6, 115.8, 119.2, 123.1, 123.6, 126.2, 126.9, 130.4, 133.3, 143.2, 145.9, 159.9, 196.2; HRMS (ESI): m/z calculated for $C_{17}H_{16}N_3O_2$ $[M+H]^+$: 294.1237; found: 294.1233.

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