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N-Alkylation of benzimidazoles with ketonic Mannich bases and the reduction of the resulting 1-(3-oxopropyl)benzimidazoles*

Research Article

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Abstract: Benzimidazole, benzimidazoles diversely substituted at position 2, and 5,6-dimethylbenzimidazole have been alkylated at N^1 with ketonic Mannich bases derived from acetophenones, acetylnaphthalenes, 2-acetylthiophene and 1-tetralone to afford a series of novel 1-(3-oxopropyl)benzimidazoles. The reduction of these transamination products with $NaBH_4$ in methanol produced the corresponding 1-(3-hydroxypropyl)benzimidazoles in excellent yields.

Keywords: *Benzimidazole • Mannich bases • N-alkylation • Reduction*

1. Introduction

The ability of Mannich bases to alkylate structurally diverse substrates is a feature of particular interest in the chemistry of these compounds [2,3]. For instance, Mannich bases derived from ketones, phenols, or indoles have been shown to *C*-alkylate ketones, phenols, or heterocycles such as furan, pyrrole, indole, whereas thiols and thiocarbamates can act as sulfur-containing substrates in an *S*-alkylation reaction by Mannich bases. *N*-Alkylation of amines or *NH*-heterocycles with Mannich bases (also known as amine exchange reaction, or transamination) is also well documented. In particular, *N*-alkylation of *NH*-heterocycles (especially azoles and their benzo-fused congeners) with ketonic Mannich bases, phenolic Mannich bases, or indole Mannich bases represents an effective approach for the synthesis of heterocycles **1**, **2**, or **3** having at the nitrogen atom a 3-oxopropyl group, or a 2-hydroxybenzyl group, or a indol-3-ylmethyl group, respectively (Scheme 1).

Despite the fact that the scope and the limitation of this reaction were examined briefly by Tramontini *et al.* over 40 years ago [4], a close inspection of the literature revealed that more comprehensive studies on this topic are still scarce. A couple of studies presenting the *N*-alkylation of benzimidazole with Mannich bases derived from cycloalkanones, α,β-unsaturated ketones and acetophenones in ethanol reported modest yields of β-keto *N*-substituted benzimidazoles as reaction products [5,6]. Analogous *N*-alkylated benzimidazoles were described in patent literature and were claimed to posses interesting biological activities [7,8]. In continuation of our work on the *N*-alkylation of *NH*-heterocycles with Mannich bases [9,10], the current paper reports the transamination of ketonic Mannich bases and benzimidazoles and their subsequent reduction of the resulting to the corresponding alcohols. In addition, these ketones with an azole moiety have a huge potential as intermediates for the synthesis of novel heterocycles such as benzisoxazoles [11] or isoxazoles and pyrazoles [12], or may present interesting biological activities [13,14].

2. Experimental procedure

Melting points were taken on a Mel-Temp II apparatus and are uncorrected. Elemental analysis was conducted in-house on a PerkinElmer 2400 Series II CHNS/O system. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 MHz spectrometer. The signals owing

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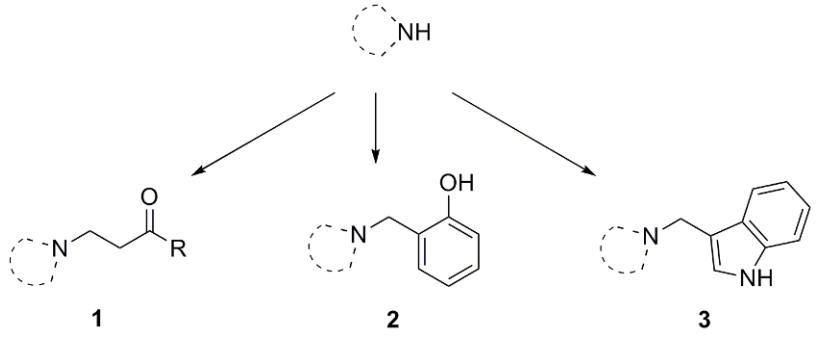
** This communication is Part 22 in the series "Synthesis and reactivity of Mannich bases"; for Part 21, see [1]*



Scheme 1. *N*-Alkylation of NH-azoles with ketonic, phenolic or indole Mannich bases.

to residual protons in the deuterated solvents were used as internal standards for the ^{1}H NMR spectra. The chemical shifts for the carbon atoms are given relative to deuteriochloroform (δ = 77.16 ppm) or dimethyl sulfoxide d_6 (δ = 39.52 ppm).

2-Ethylbenzimidazole [15], 2-benzylbenzimidazole [16], 2-(1-naphthylmethyl)benzimidazole [17] and 2-(phenoxymethyl)benzimidazole [18] were prepared through the Phillips benzimidazole synthesis involving the condensation of the appropriate carboxylic acid and *ortho*-phenylenediamine in 4N HCl. The ketonic Mannich bases required in this study were synthesized from the corresponding ketone through an adaptation of the procedure reported [19] for the direct aminomethylation of acetophenone with paraformaldehyde and dimethylamine hydrochloride, and the identity of compounds **4**–**14** was confirmed by comparing their melting point and NMR data with those reported in the literature [20-31]. All other chemical reagents were obtained from Sigma–Aldrich and were used without prior purification.

General procedure for the *N*-alkylation of benzimidazoles with hydrochlorides of ketonic Mannich bases. The solution of Mannich base hydrochloride (5 mmol) and benzimidazole (5 mmol) in a mixture of ethanol–water (12 mL, 1:1 v/v) was heated under reflux for 1 h. The reaction mixture was cooled in an ice–water bath under vigorous stirring until crystallization occurred. The resulting solid was filtered, washed with a mixture of ethanol–water, and recrystallized from the appropriate solvent(s). In the case of compound **50**, the supernatant was removed with a pipette at the end of the reaction time, and the remaining oil was dissolved in ethyl acetate (15 mL). The organic solution was washed with water (30 mL), dried over anhydrous Na_2SO_4, and then the solvent was removed under reduced pressure. Subsequent column chromatography of the oily residue afforded the pure compound **50**.

3-(1*H*-Benzimidazol-1-yl)-1-phenyl-1-propanone (15). Colorless crystals (2-propanol), yield 760 mg (61%), mp 104–105°C (lit. mp 102–103°C [4]); ^{1}H NMR ($CDCl_3$): *δ* 3.51 (t, *J* = 6.4 Hz, 2H), 4.66 (t, *J* = 6.4 Hz, 2H), 7.25–7.34 (m, 2H), 7.40–7.46 (m, 3H), 7.53–7.58 (m, 1H), 7.78–7.82 (m, 1H), 7.88 (d, *J* = 7.6 Hz, 2H), 8.04 (s, 1H); ^{13}C NMR ($CDCl_3$): *δ* 38.2, 39.5, 109.4, 120.7, 122.3, 123.1, 128.1, 128.9, 133.6, 133.9, 136.2, 143.8, 144.0, 196.8; *Anal.* Calcd. for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.54; H, 5.81; N, 11.36.

3-(2-Methyl-1*H*-benzimidazol-1-yl)-1-phenyl-1-propanone (16). Off-white crystals (2-propanol–hexanes), yield 605 mg (46%), mp 99–100°C; ^{1}H NMR ($CDCl_3$): *δ* 2.67 (s, 3H), 3.47 (t, *J* = 7.2 Hz, 2H), 4.60 (t, *J* = 7.2 Hz, 2H), 7.20–7.26 (m, 2H), 7.30–7.37 (m, 1H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.54–7.60 (m, 1H), 7.65–7.72 (m, 1H), 7.88 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$): *δ* 14.1, 38.0, 38.8, 109.1, 119.4, 122.1, 122.3, 128.1, 128.9, 133.9, 134.9, 136.2, 143.0, 151.7, 197.1; *Anal.* Calcd. for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60. Found: C, 76.92; H, 5.84; N, 10.50.

3-(5,6-Dimethyl-1*H*-benzimidazol-1-yl)-1-phenyl-1-propanone (17). Tan crystals (2-propanol–hexanes), yield 710 mg (51%), mp 114–115°C; ^{1}H NMR ($CDCl_3$): *δ* 2.37 (s, 3H), 2.40 (s, 3H), 3.50 (t, *J* = 6.8 Hz, 2H), 4.61 (t, *J* = 6.8 Hz, 2H), 7.20 (s, 1H), 7.40–7.48 (m, 2H), 7.53–7.60 (m, 2H), 7.86–7.94 (m, 3H); ^{13}C NMR ($CDCl_3$): *δ* 20.3, 20.7, 38.4, 39.5, 109.6, 120.7, 128.1, 128.9, 131.1, 132.1, 132.2, 133.8, 136.3, 142.7, 143.0, 196.9; *Anal.* Calcd. for $C_{18}H_{18}N_2O$: C, 77.67; H, 6.52; N, 10.06. Found: C, 77.49; H, 6.31; N, 10.27.

3-(1*H*-Benzimidazol-1-yl)-1-(4-chlorophenyl)-1-propanone (18). Colorless crystals (ethanol), yield 955 mg (67%), mp 132–133°C; ^{1}H NMR ($CDCl_3$): δ 3.48 (t, *J* = 6.4 Hz, 2H), 4.66 (t, *J* = 6.4 Hz, 2H), 7.26–7.36 (m, 2H), 7.38–7.47 (m, 3H) 7.77–7.86 (m, 3H), 8.03 (s, 1H); ^{13}C NMR ($CDCl_3$): *δ* 38.2, 39.4, 109.3, 120.7, 122.4, 123.1, 129.2, 129.4, 133.5, 134.4, 140.4, 143.8, 144.0, 195.6; *Anal.* Calcd. for $C_{16}H_{13}ClN_2O$: C, 67.49; H, 4.60; N, 9.84. Found: C, 67.72; H, 4.40; N, 10.04.

1-(4-Chlorophenyl)-3-(2-methyl-1*H*-benzimidazol-1-yl)-1-propanone (19). Colorless

crystals (ethanol), yield 925 mg (62%), mp 157–158°C; ^{1}H NMR ($CDCl_3$): *δ* 2.66 (s, 3H), 3.43 (t, *J* = 7.2 Hz, 2H), 4.58 (t, *J* = 7.2 Hz, 2H), 7.20–7.26 (m, 2H), 7.29–7.35 (m, 1H), 7.41 (dd, *J* = 2.0 and 8.8 Hz, 2H), 7.65–7.71 (m, 1H), 7.81 (dd, *J* = 1.8 and 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$): *δ* 14.1, 37.9, 38.7, 109.0, 119.4, 122.2, 122.3, 129.2, 129.5, 134.5, 134.8, 140.4, 143.0, 151.7, 195.9; *Anal.* Calcd. for $C_{17}H_{15}ClN_2O$: C, 68.34; H, 5.06; N, 9.38. Found: C, 68.55; H, 4.89; N, 9.62.

1-(4-Chlorophenyl)-3-(5,6-dimethyl-1*H*-benzimidazol-1-yl)-1-propanone (20). Tan crystals (ethanol), yield 1330 mg (85%), mp 162–163°C; ^{1}H NMR ($CDCl_3$): *δ* 2.36 (s, 3H), 2.40 (s, 3H), 3.46 (t, *J* = 6.6 Hz, 2H), 4.60 (t, *J* = 6.6 Hz, 2H), 7.18 (s, 1H), 7.40 (d, *J* = 8.8 Hz, 2H), 7.55 (s, 1H), 7.82 (d, *J* = 8.8 Hz, 2H), 7.90 (s, 1H); ^{13}C NMR ($CDCl_3$): *δ* 20.3, 20.7, 38.4, 39.4, 109.5, 120.7, 129.2, 129.5, 131.2, 132.1, 132.3, 134.6, 140.4, 142.6, 143.0, 195.7; *Anal.* Calcd. for $C_{18}H_{17}ClN_2O$: C, 69.12; H, 5.48; N, 8.96. Found: C, 69.38; H, 5.30; N, 9.11.

3-(1*H*-Benzimidazol-1-yl)-1-(4-bromophenyl)-1-propanone (21). Tan crystals (ethanol), yield 1250 mg (76%), mp 145–146°C; ^{1}H NMR ($CDCl_3$): *δ* 3.48 (t, *J* = 6.8 Hz, 2H), 4.66 (t, *J* = 6.8 Hz, 2H), 7.26–7.35 (m, 2H), 7.41–7.46 (m, 1H), 7.57 (d, *J* = 8.8 Hz, 2H), 7.74 (d, *J* = 8.8 Hz, 2H), 7.78–7.83 (m, 1H), 8.04 (s, 1H); ^{13}C NMR ($CDCl_3$): *δ* 38.3, 39.4, 109.3, 120.8, 122.4, 123.2, 129.2, 129.6, 132.2, 133.5, 134.9, 143.8, 144.0, 195.8; *Anal.* Calcd. for $C_{16}H_{13}BrN_2O$: C, 58.38; H, 3.98; N, 8.51. Found: C, 58.61; H, 4.19; N, 8.28.

1-(4-Bromophenyl)-3-(2-methyl-1*H*-benzimidazol-1-yl)-1-propanone (22). Off-white crystals (ethanol), yield 1305 mg (76%), mp 172–173°C; ^{1}H NMR ($CDCl_3$): *δ* 2.67 (s, 3H), 3.43 (t, *J* = 7.0 Hz, 2H), 4.58 (t, *J* = 7.2 Hz, 2H), 7.21–7.26 (m, 2H), 7.30–7.35 (m, 1H), 7.58 (dd, *J* =1.8 and 8.4 Hz, 2H), 7.66–7.71 (m, 1H), 7.74 (dd, *J* =2.4 and 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$): *δ* 14.1, 37.9, 38.7, 109.0, 119.5, 122.2, 122.3, 129.2, 129.6, 134.8, 134.9, 143.0, 151.7, 196.1; *Anal.* Calcd. for $C_{17}H_{15}BrN_2O$: C, 59.49; H, 4.41; N, 8.16. Found: C, 59.22; H, 4.66; N, 7.92.

1-(4-Bromophenyl)-3-(5,6-dimethyl-1*H*-benzimidazol-1-yl)-1-propanone (23). Tan crystals (ethanol), yield 1465 mg (82%), mp 174–175°C; ^{1}H NMR ($CDCl_3$): *δ* 2.37 (s, 3H), 2.40 (s, 3H), 3.46 (t, *J* = 6.6 Hz, 2H), 4.61 (t, *J* = 6.6 Hz, 2H), 7.18 (s, 1H), 7.52–7.61 (m, 3H), 7.74 (d, *J* = 8.8 Hz, 2H), 7.90 (s, 1H); ^{13}C NMR ($CDCl_3$): *δ* 20.4, 20.8, 38.3, 39.4, 109.5, 120.7, 129.1, 129.6, 131.3, 132.0, 132.2, 132.3, 135.0, 142.6, 143.0, 196.0; *Anal.* Calcd. for $C_{18}H_{17}BrN_2O$: C, 60.52; H, 4.80; N, 7.84. Found: C, 60.80; H, 5.03; N, 8.05.

3-(1*H*-Benzimidazol-1-yl)-1-(biphenyl-4-yl)-1-propanone (24). Colorless crystals (ethanol), yield 1270 mg (78%), mp 160–161°C; ^{1}H NMR ($CDCl_3$): *δ* 3.56 (t, *J* = 7.0 Hz, 2H), 4.70 (t, *J* = 7.0 Hz, 2H), 7.26–7.36 (m, 2H), 7.37–7.50 (m, 4H), 7.57–7.62 (m, 2H), 7.66 (d, *J* = 8.8 Hz, 2H), 7.79–7.84 (m, 1H), 7.96 (d, *J* = 8.4 Hz, 2H), 8.07 (s, 1H); ^{13}C NMR ($CDCl_3$): *δ* 38.4, 39.6, 109.4, 120.8, 122.3, 123.1, 127.4, 127.5, 128.6, 128.7, 129.1, 133.7, 134.9, 139.7, 143.8, 144.1, 146.6, 196.4; *Anal.* Calcd. for $C_{22}H_{18}N_2O$: C, 80.96; H, 5.56; N, 8.58. Found: C, 80.70; H, 5.78; N, 8.39.

1-(Biphenyl-4-yl)-3-(2-methyl-1*H*-benzimidazol-1-yl)-1-propanone (25). Colorless crystals (ethanol), yield 1325 mg (78%), mp 141–142°C; ^{1}H NMR ($CDCl_3$): *δ* 2.69 (s, 3H), 3.50 (t, *J* = 7.2 Hz, 2H), 4.62 (t, *J* = 7.2 Hz, 2H), 7.21–7.28 (m, 2H), 7.33–7.50 (m, 4H), 7.57–7.63 (m, 2H), 7.63–7.73 (m, 3H), 7.96 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$): *δ* 14.1, 38.0, 38.9, 109.1, 119.4, 122.1, 122.3, 127.4, 127.5, 128.6, 128.7, 129.1, 134.9, 135.0, 139.7, 143.0, 146.6, 151.7, 196.7; *Anal.* Calcd. for $C_{23}H_{20}N_2O$: C, 81.15; H, 5.92; N, 8.23. Found: C, 81.34; H, 6.20; N, 8.03.

1-(Biphenyl-4-yl)-3-(5,6-dimethyl-1*H*-benzimidazol-1-yl)-1-propanone (26). Tan crystals (ethanol), yield 1345 mg (76%), mp 188–189°C; ^{1}H NMR ($CDCl_3$): *δ* 2.38 (s, 3H), 2.41 (s, 3H), 3.54 (t, *J* = 6.6 Hz, 2H), 4.64 (t, *J* = 6.6 Hz, 2H), 7.22 (s, 1H), 7.36–7.50 (m, 3H), 7.55–763 (m, 3H), 7.66 (d, *J* = 8.4 Hz, 2H), 7.93 (s, 1H), 7.96 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$): *δ* 20.3, 20.7, 38.5, 39.6, 109.6, 120.7, 127.4, 127.5, 128.5, 128.7, 129.1, 131.2, 132.2, 132.3, 135.0, 139.7, 142.7, 143.0, 146.5, 196.5; *Anal.* Calcd. for $C_{24}H_{22}N_2O$: C, 81.33; H, 6.26; N, 7.90. Found: C, 81.09; H, 6.15; N, 8.14.

3-(1*H*-Benzimidazol-1-yl)-1-(naphthalen-1-yl)-1-propanone (27). Colorless crystals (ethanol–hexanes), yield 1125 mg (75%), mp 106–107°C; ^{1}H NMR ($CDCl_3$): *δ* 3.61 (t, *J* = 6.4 Hz, 2H), 4.72 (t, *J* = 6.4 Hz, 2H), 7.23–7.35 (m, 2H), 7.36–7.62 (m, 4H), 7.76 (dd, *J* = 1.0 and 7.4 Hz, 1H), 7.79–7.88 (m, 2H), 7.98 (d, *J* = 8.0 Hz, 1H), 8.09 (s, 1H), 8.62 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR ($CDCl_3$): *δ* 39.9, 41.2, 109.5, 120.7, 122.3, 123.1, 124.3, 125.7, 126.8, 128.4, 128.5, 128.6, 130.2, 133.6, 133.8, 134.1, 134.4, 143.8, 144.1, 200.4; *Anal.* Calcd. for $C_{20}H_{16}N_2O$: C, 79.98; H, 5.37; N, 9.33. Found: C, 80.21; H, 5.09; N, 9.17.

3-(2-Methyl-1*H*-benzimidazol-1-yl)-1-(naphthalen-1-yl)-1-propanone (28). Colorless crystals (2-propanol–hexanes), yield 925 mg (59%), mp 113–114°C; ^{1}H NMR ($CDCl_3$): *δ* 2.70 (s, 3H), 3.57 (t, *J* = 6.8 Hz, 2H), 4.66 (t, *J* = 6.8 Hz, 2H), 7.20–7.26 (m, 2H), 7.34–7.45 (m, 2H), 7.50–7.63 (m, 2H), 7.67–7.76 (m, 2H), 7.86 (dd, *J* = 1.2 and 8.4 Hz, 1H), 7.99 (d, *J* = 8.4 Hz, 1H), 8.65 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$): *δ* 14.1, 39.2, 40.9, 109.2, 119.4, 122.1, 122.3, 124.4,

125.7, 126.8, 128.5, 128.6, 128.7, 130.2, 133.8, 134.1, 134.5, 134.9, 143.0, 151.7, 200.6; *Anal.* Calcd. for $C_{21}H_{18}N_2O$: C, 80.23; H, 5.77; N, 8.91. Found: C, 80.01; H, 5.98; N, 9.14.

3-(5,6-Dimethyl-1*H*-benzimidazol-1-yl)-1-(naphthalen-1-yl)-1-propanone (29). Tan crystals (2-propanol), yield 675 mg (41%), mp 151–152°C; ^{1}H NMR ($CDCl_3$): *δ* 2.37 (s, 3H), 2.40 (s, 3H), 3.60 (t, *J* = 6.4 Hz, 2H), 4.68 (t, *J* = 6.4 Hz, 2H), 7.21 (s, 1H), 7.40–7.46 (m, 1H), 7.50–7.62 (m, 3H), 7.77 (dd, *J* = 1.2 and 7.2 Hz, 1H), 7.85 (d, *J* = 8.4 Hz, 1H), 7.94–8.01 (m, 2H), 8.62 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR ($CDCl_3$): *δ* 20.3, 20.7, 39.9, 41.3, 109.7, 120.7, 124.4, 125.7, 126.8, 128.3, 128.5, 128.6, 130.2, 131.2, 132.2, 132.3, 133.7, 134.1, 134.6, 142.7, 143.0, 200.6; *Anal.* Calcd. for $C_{22}H_{20}N_2O$: C, 80.46; H, 6.14; N, 8.53. Found: C, 80.71; H, 6.33; N, 8.40.

3-(1*H*-Benzimidazol-1-yl)-1-(naphthalen-2-yl)-1-propanone (30). Tan crystals (ethanol), yield 1195 mg (80%), mp 160–161°C; ^{1}H NMR ($CDCl_3$): *δ* 3.67 (t, *J* = 6.6 Hz, 2H), 4.73 (t, *J* = 6.6 Hz, 2H), 7.24–7.38 (m, 2H), 7.46–7.63 (m, 3H), 7.79–7.92 (m, 4H), 7.97 (dd, *J* = 2.0 and 8.4 Hz, 1H), 8.12 (s 1H), 8.37 (s, 1H); ^{13}C NMR ($CDCl_3$): *δ* 38.4, 39.8, 109.5, 120.7, 122.4, 123.2, 123.5, 127.1, 127.9, 128.9, 129.0, 129.7, 130.0, 132.5, 133.5, 133.6, 135.9, 143.7, 143.8, 196.7; *Anal.* Calcd. for $C_{20}H_{16}N_2O$: C, 79.98; H, 5.37; N, 9.33. Found: C, 80.18; H, 5.56; N, 9.11.

3-(2-Methyl-1*H*-benzimidazol-1-yl)-1-(naphthalen-2-yl)-1-propanone (31). Colorless crystals (2-propanol–hexanes), yield 925 mg (59%), mp 130–131°C; ^{1}H NMR ($CDCl_3$): *δ* 2.69 (s, 3H), 3.61 (t, *J* = 7.2 Hz, 2H), 4.65 (t, *J* = 7.2 Hz, 2H), 7.21–7.30 (m, 2H), 7.36–7.42 (m, 1H), 7.51–7.64 (m, 2H), 7.67–7.74 (m, 1H), 7.83–7.90 (m, 3H), 7.97 (dd, *J* = 2.4 and 4.8 Hz, 1H), 8.34 (s, 1H); ^{13}C NMR ($CDCl_3$): *δ* 14.1, 38.0, 39.0, 109.2, 119.4, 122.2, 122.3, 123.5, 127.2, 127.9, 128.9, 129.0, 129.7, 130.1, 132.5, 133.6, 134.9, 135.9, 143.0, 151.7, 197.1; *Anal.* Calcd. for $C_{21}H_{18}N_2O$: C, 80.23; H, 5.77; N, 8.91. Found: C, 80.47; H, 5.55; N, 9.16.

3-(1*H*-Benzimidazol-1-yl)-1-(4-hydroxyphenyl)-1-propanone (32). Off-white crystals (2-butanone), yield 880 mg (66%), mp 233–234°C; ^{1}H NMR (d_6-DMSO): *δ* 3.56 (t, *J* = 6.8 Hz, 2H), 4.58 (t, *J* = 6.8 Hz, 2H), 6.82 (d, *J* = 8.8 Hz, 2H), 7.15–7.28 (m, 2H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.84 (d, *J* = 8.8 Hz, 2H), 8.24 (s, 1H), 10.39 (s, 1H); ^{13}C NMR (d_6-DMSO): *δ* 37.4, 39.6, 110.5, 115.2, 119.3, 121.4, 122.2, 127.9, 130.5, 133.7, 143.3, 144.2, 162.3, 195.7; *Anal.* Calcd. for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 71.93; H, 5.39; N, 10.39.

1-(4-Hydroxyphenyl)-3-(2-methyl-1*H*-benzimidazol-1-yl)-1-propanone (33). Off-white crystals (acetone), yield 590 mg (42%), mp 239–240°C; ^{1}H NMR (d_6-DMSO): *δ* 2.58 (s, 3H), 3.46 (t, *J* = 7.2 Hz, 2H), 4.50 (t, *J* = 7.2 Hz, 2H), 6.81 (d, *J* = 8.8 Hz, 2H), 7.08–7.19 (m, 2H), 7.49 (d, *J* = 7.2 Hz, 1H), 7.54 (d, *J* = 7.2 Hz, 1H), 7.83 (d, *J* = 8.8 Hz, 2H), 10.39 (br s, 1H); ^{13}C NMR (d_6-DMSO): *δ* 13.5, 37.0, 38.7, 110.0, 115.2, 118.1, 121.1, 121.3, 127.9, 130.6, 134.9, 142.4, 151.8, 162.2, 195.8; *Anal.* Calcd. for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.55; H, 5.92; N, 10.12.

1-(4-Hydroxyphenyl)-3-(5,6-dimethyl-1*H*-benzimidazol-1-yl)-1-propanone (34). Tan crystals, yield 1075 mg (73%), mp 268–269°C; ^{1}H NMR (d_6-DMSO): *δ* 2.29 (s, 3H), 2.33 (s, 3H), 3.52 (t, *J* = 6.8 Hz, 2H), 4.51 (t, *J* = 6.8 Hz, 2H), 6.82 (d, *J* = 8.8 Hz, 2H), 7.39 (s, 1H), 7.42 (s, 1H), 7.84 (d, *J* = 8.8 Hz, 2H), 8.06 (s, 1H), 10.37 (s, 1H); ^{13}C NMR (d_6-DMSO): *δ* 19.8, 20.1, 37.4, 39.7, 110.5, 115.2, 119.4, 127.9, 129.6, 130.5, 130.8, 132.2, 142.0, 143.3, 162.3, 195.7; *Anal.* Calcd. for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.16; H, 5.95; N, 9.26.

3-(1*H*-Benzimidazol-1-yl)-1-(2-hydroxyphenyl)-1-propanone (35). Colorless crystals (methanol–water), yield 1115 mg (84%), mp 133–134°C; ^{1}H NMR ($CDCl_3$): *δ* 3.48 (t, *J* = 6.4 Hz, 2H), 4.57 (t, *J* = 6.4 Hz, 2H), 6.76–6.80 (m, 1H), 6.90–6.93 (m, 1H), 7.22–7.42 (m, 5H), 7.51–7.53 (dd, *J* = 1.5 and 8.0 Hz, 1H), 7.76–7.78 (dd, *J* = 1.5 and 7 Hz, 1H); 7.99 (s, 1H); 11.94 (s, 1H); ^{13}C NMR ($CDCl_3$): *δ* 37.5, 38.8, 109.1, 118.4, 118.8, 119.0, 120.3, 122.1, 122.9, 129.3, 133.2, 136.8, 143.5, 143.6, 162.1, 202.2; *Anal.* Calcd. for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.33; H, 5.61; N, 10.66.

1-(2-Hydroxyphenyl)-3-(2-methyl-1*H*-benzimidazol-1-yl)-1-propanone (36). Off-white crystals (methanol–water), yield 1150 mg (82%), mp 145–146°C; ^{1}H NMR ($CDCl_3$): *δ* 2.65 (s, 3H), 3.48 (t, *J* = 6.8 Hz, 2H), 4.56 (t, *J* = 6.8 Hz, 2H), 6.78–6.89 (m, 1H), 6.90–7.02 (m, 1H), 7.16–7.25 (m, 2H), 7.30–7.74 (m, 4H), 11.97 (s, 1H); ^{13}C NMR ($CDCl_3$): *δ* 14.3, 37.9, 38.8, 109.3, 119.1, 119.4, 119.6, 119.7, 122.5, 122.7, 129.9, 135.0, 137.4, 143.2, 151.9, 162.8, 203.1; *Anal.* Calcd. for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 73.08; H, 5.42; N, 10.21.

1-(2-Hydroxyphenyl)-3-(5,6-dimethyl-1*H*-benzimidazol-1-yl)-1-propanone (37). Off-white crystals (acetone), yield 1160 mg (79%), mp 186–187°C; ^{1}H NMR ($CDCl_3$): *δ* 2.36 (s, 3H), 2.39 (s, 3H), 3.53 (t, *J* = 6.6 Hz, 2H), 4.59 (t, *J* = 6.6 Hz, 2H), 6.82–6.86 (m, 1H), 6.96 (dd, *J* = 0.7 and 8.4 Hz, 1H); 7.18 (s, 1H), 7.43–7.47 (m, 1H), 7.55 (s, 1H), 7.59 (dd, *J* = 1.5 and 8 Hz, 1H), 7.90 (s, 1H), 11.97 (s, 1H); ^{13}C NMR ($CDCl_3$): *δ* 20.2, 20.6, 37.8, 39.0, 109.3, 118.6, 118.9, 119.1, 120.5, 129.4, 131.1, 131.8, 132.2, 136.9, 142.4, 142.7,

162.3, 202.5; *Anal.* Calcd. for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.69; H, 5.99; N, 9.77.

1-(2-Hydroxyphenyl)-3-(2-phenoxymethyl-1*H*-benzimidazol-1-yl)-1-propanone (38). Colorless crystals (methanol), yield 1545 mg (83%), mp 131–132°C; ^{1}H NMR ($CDCl_3$): δ 3.54 (t, J = 7.3 Hz, 2H), 4.74 (t, J = 7.3 Hz, 2H), 5.46 (s, 2H), 6.77–6.81 (m, 1H), 6.95–7.06 (m, 4H), 7.24–7.34 (m, 4H), 7.39–7.50 (m, 3H), 7.80–7.82 (m, 1H), 12.02 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 37.9, 39.1, 63.3, 109.4, 114.6, 118.5, 118.8, 119.1, 120.3, 121.7, 122.5, 123.4, 129.5, 129.7, 135.0, 136.8, 142.3, 149.2, 157.6, 162.3, 203.0; *Anal.* Calcd. for $C_{23}H_{20}N_2O_3$: C, 74.18; H, 5.41; N, 7.52. Found: C, 73.92; H, 5.59; N, 7.30.

3-(1*H*-Benzimidazol-1-yl)-1-(2-hydroxy-5-methylphenyl)-1-propanone (39). Colorless crystals (ethanol), yield 1305 mg (93%), mp 172–174°C; ^{1}H NMR ($CDCl_3$): δ 2.21 (s, 3H), 3.52 (t, J = 6.4 Hz, 2H), 4.62 (t, J = 6.4 Hz, 2H), 6.83–8.01 (m, 8H), 11.77 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 20.4, 37.7, 39.1, 109.2, 118.4, 118.5, 120.6, 122.2, 123.0, 129.0, 133.3, 138.1, 143.6, 143.8, 160.3, 202.2; *Anal.* Calcd. for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.66; H, 5.87; N, 10.18.

1-(2-Hydroxy-5-methylphenyl)-3-(2-methyl-1*H*-benzimidazol-1-yl)-1-propanone (40). Colorless crystals (methanol–water), yield 1280 mg (87%), mp 134–135°C; ^{1}H NMR ($CDCl_3$): δ 2.16 (s, 3H), 2.60 (s, 3H) 3.43 (t, J = 7 Hz, 2H), 4.50 (t, J = 7 Hz, 2H), 6.83 (d, J = 8.4 Hz, 1H), 7.19–7.32 (m, 5H), 7.65–7.67 (m, 1H), 11.82 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 13.7, 20.2, 37.3, 38.3, 108.8, 118.1, 118.5, 119.0, 121.9, 122.0, 128.2, 129.0, 134.4, 137.9, 142.6, 151.3, 160.0, 202.4; *Anal.* Calcd. for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.21; H, 6.37; N, 9.64.

1-(2-Hydroxy-5-methylphenyl)-3-(5,6-dimethyl-1*H*-benzimidazol-1-yl)-1-propanone (41). Tan crystals (acetone), yield 1245 mg (81%), mp 184–185°C; ^{1}H NMR ($CDCl_3$): δ 2.23 (s, 3H), 2.36 (s, 3H), 2.40 (s, 3H), 3.52 (t, J = 6.6 Hz, 2H), 4.60 (t, J = 6.6 Hz, 2H) 6.87 (d, J = 8.4 Hz, 1H) 7.19 (s, 1H), 7.26 (dd, J = 1.5 and 8.8 Hz, 1H), 7.35 (d, J = 1.5 Hz, 1H), 7.56 (s, 1H), 7.91 (s, 1H), 11.80 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 20.2, 20.4, 20.6, 37.9, 39.1, 109.4, 118.4, 118.6, 120.5, 128.3, 129.1, 131.1, 131.8, 132.2, 138.0, 142.8, 160.3, 202.4; *Anal.* Calcd. for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.08. Found: C, 73.81; H, 6.33; N, 9.29.

1-(2-Hydroxy-5-methylphenyl)-3-(2-phenoxymethyl-1*H*-benzimidazol-1-yl)-1-propanone (42). Colorless crystals (methanol), yield 1735 mg (90%), mp 148–149°C; ^{1}H NMR ($CDCl_3$): δ 2.19 (s, 3H), 3.53 (t, J = 7.3 Hz, 2H), 4.73 (t, J = 7.3 Hz, 2H), 5.46 (s, 2H), 6.88 (d, J = 8.4 Hz, 1H), 6.97–7.06 (m, 3H), 7.24–7.32 (m, 6H), 7.40–7.43 (m, 1H), 7.80–7.82 (m, 1H), 11.86 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 20.2, 37.9, 39.0, 63.2, 109.4, 114.6, 118.2, 118.5, 120.2, 121.6, 122.5, 123.4, 128.2, 129.2, 129.6, 135.0, 137.9, 142.3, 149.2, 157.6, 160.2, 202.8; *Anal.* Calcd. for $C_{24}H_{22}N_2O_3$: C, 74.59; H, 5.74; N, 7.25. Found: C, 74.83; H, 5.48; N, 7.47.

3-(2-Ethyl-1*H*-benzimidazol-1-yl)-1-(2-hydroxy-5-methylphenyl)-1-propanone (43). Colorless crystals (methanol), yield 1340 mg (87%), mp 160–161°C; ^{1}H NMR ($CDCl_3$): δ 1.45 (t, J = 7.5 Hz, 3H), 2.16 (s, 3H), 2.90 (q, J = 7.5 Hz, 2H), 3.43 (t, J = 7.1 Hz, 2H), 4.52 (t, J = 7.1 Hz, 2H), 6.84 (d, J = 8.4 Hz, 1H), 7.21–7.32 (m, 5H), 7.70–7.73 (m, 1H), 11.83 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 11.6, 20.5, 20.2, 37.5, 38.0, 108.8, 118.2, 118.5, 119.2, 121.8, 122.9, 128.2, 129.1, 134.5, 137.9, 142.6, 155.8, 160.1, 202.6; *Anal.* Calcd. for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.08. Found: C, 73.74; H, 6.28; N, 9.31.

3-(1*H*-Benzimidazol-1-yl)-1-(thiophen-2-yl)-1-propanone (44). Colorless crystals (2-propanol), yield 995 mg (77%), mp 114–115°C; ^{1}H NMR ($CDCl_3$): δ 3.35 (t, J = 6.4 Hz, 2H), 4.64 (t, J = 6.4 Hz, 2H), 7.07 (dd, J = 4.0 and 4.8 Hz, 1H), 7.24–7.35 (m, 2H), 7.44 (dd, J = 1.2 and 7.6 Hz, 1H), 7.60 (dd, J = 1.0 and 4.0 Hz, 1H), 7.63 (dd, J = 1.0 and 4.8 Hz, 1H), 7.79 (dd, J = 1.2 and 7.2 Hz, 1H), 8.01 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 38.9, 39.5, 109.4, 120.7, 122.3, 123.1, 128.4, 132.4, 133.6, 134.6, 143.3, 143.7, 144.0, 189.5; *Anal.* Calcd. for $C_{14}H_{12}N_2OS$: C, 65.60; H, 4.72; N, 10.93. Found: C, 65.33; H, 4.98; N, 11.08.

3-(2-Methyl-1*H*-benzimidazol-1-yl)-1-(thiophen-2-yl)-1-propanone (45). Colorless crystals (2-propanol–hexanes), yield 945 mg (70%), mp 100–101°C; ^{1}H NMR ($CDCl_3$): δ 2.65 (s, 3H), 3.39 (t, J = 7.0 Hz, 2H), 4.57 (t, J = 7.2 Hz, 2H), 7.07 (dd, J = 4.0 and 4.8 Hz, 1H), 7.19–7.27 (m, 2H), 7.31–7.38 (m, 1H), 7.57 (dd, J = 0.8 and 4.0 Hz, 1H), 7.64 (dd, J = 0.8 and 4.8 Hz, 1H), 7.63–7.71 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 14.0, 38.6, 38.8, 109.1, 119.4, 122.1, 122.3, 128.5, 132.5, 134.7, 134.8, 143.0, 143.4, 151.7, 189.8; *Anal.* Calcd. for $C_{15}H_{14}N_2OS$: C, 66.64; H, 5.22; N, 10.36. Found: C, 66.91; H, 5.02; N, 10.58.

3-(5,6-Dimethyl-1*H*-benzimidazol-1-yl)-1-(thiophen-2-yl)-1-propanone (46). Tan crystals (ethanol), yield 1035 mg (73%), mp 147–148°C; ^{1}H NMR ($CDCl_3$): δ 2.36 (s, 3H), 2.40 (s, 3H), 3.43 (t, J = 6.4 Hz, 2H), 4.59 (t, J = 6.4 Hz, 2H), 7.08 (t, J = 8.4 Hz, 1H), 7.19 (s, 1H), 7.54 (s, 1H), 7.60 (d, J = 3.6 Hz, 1H), 7.63 (d, J = 4.8 Hz, 1H), 7.88 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 20.3, 20.7, 39.0, 39.5, 109.6, 120.6, 128.4, 131.2, 132.0, 132.3, 132.4, 134.6, 142.6, 142.9, 143.4, 189.7; *Anal.* Calcd. for $C_{16}H_{16}N_2OS$: C, 67.58; H, 5.67; N, 9.85. Found: C, 67.85; H, 5.48; N, 10.04.

3-(2-Phenylmethyl-1*H*-benzimidazol-1-yl)-1-(thiophen-2-yl)-1-propanone (**47**). Off-white crystals (ethanol), yield 1160 mg (64%), mp 131–132°C; ^{1}H NMR (d_6-DMSO): δ 3.26 (t, J = 7.2 Hz, 2H), 4.37 (s, 2H), 4.50 (t, J = 7.2 Hz, 2H), 7.13–7.23 (m, 4H), 7.26–7.32 (m, 4H), 7.54–7.61 (m, 2H), 7.73 (dd, J = 1.2 and 3.6 Hz, 1H), 7.98 (dd, J = 1.0 and 5.0 Hz, 1H); ^{13}C NMR (d_6-DMSO): δ 33.0, 37.9, 38.5, 110.2, 118.5, 121.3, 121.7, 126.5, 128.5, 128.6, 128.7, 133.4, 134.9, 135.0, 136.9, 142.4, 143.1, 153.3, 190.5; *Anal.* Calcd. for $C_{21}H_{18}N_2OS$: C, 69.59; H, 5.01; N, 7.73. Found: C, 69.34; H, 4.79; N, 7.97.

3-(2-(Naphthalen-1-ylmethyl)-1*H*-benzimidazol-1-yl)-1-(thiophen-2-yl)-1-propanone (**48**). Tan crystals (ethanol), yield 1210 mg (61%), mp 183–184°C; ^{1}H NMR (d_6-DMSO): δ 3.34 (t, J = 7.2 Hz, 2H), 4.58 (t, J = 7.2 Hz, 2H), 4.84 (s, 2H), 7.11–7.23 (m, 3H), 7.33 (d, J = 6.8 Hz, 1H), 7.39–7.45 (m, 1H), 7.47–7.55 (m, 3H), 7.60 (d, J = 8.0 Hz, 1H), 7.74 (d, J = 3.6 Hz, 1H), 7.82 (d, J = 8.0 Hz, 1H), 7.90–7.96 (m, 1H), 7.99 (d, J = 5.2 Hz, 1H), 8.18–8.25 (m, 1H); ^{13}C NMR (d_6-DMSO): δ 31.0, 38.0, 38.7, 110.2, 118.5, 121.3, 121.8, 124.3, 125.5, 125.8, 126.1, 126.9, 127.3, 128.4, 128.7, 131.8, 133.1, 133.4, 133.6, 135.0, 135.1, 142.3, 143.2, 153.2, 190.7; *Anal.* Calcd. for $C_{25}H_{20}N_2OS$: C, 75.73; H, 5.08; N, 7.07. Found: C, 75.50; H, 4.91; N, 6.96.

2-(1*H*-Benzimidazol-1-ylmethyl)-3,4-dihydronaphthalen-1(2*H*)-one (49). Off-white crystals (2-propanol), yield 925 mg (67%), mp 144–145°C; ^{1}H NMR ($CDCl_3$): δ 1.77–1.91 (m, 1H), 2.03–2.13 (m, 1H), 2.88–3.08 (m, 3H), 4.43 (dd, J = 7.2 and 14.8 Hz, 1H), 4.88 (dd, J = 4.8 and 14.8 Hz, 1H), 7.21 (d, J = 7.6 Hz, 1H), 7.25–7.36 (m, 3H), 7.41–7.51 (m, 2H), 7.79–7.84 (m, 1H), 7.99 (s, 1H), 8.06 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 27.4, 28.8, 44.9, 48.2, 109.8, 120.7, 122.3, 123.2, 127.1, 127.7, 128.9, 132.1, 134.1, 134.2, 143.9, 144.0, 144.1, 197.3; *Anal.* Calcd. for $C_{18}H_{16}N_2O$: C, 78.24; H, 5.84; N, 10.14. Found: C, 78.04; H, 6.02; N, 10.31.

2-(2-Methyl-1*H*-benzimidazol-1-ylmethyl)-3,4-dihydronaphthalen-1(2*H*)-one (50). Yellowish oil after column chromatography (silicagel, ethyl acetate), yield 1145 mg (79%), R_f 0.23 (ethyl acetate); ^{1}H NMR ($CDCl_3$): δ 1.85–2.02 (m, 2H), 2.64 (s, 3H), 2.85–2.95 (m, 2H), 3.00–3.11 (m, 1H), 4.18 (dd, J = 9.6 and 15.2 Hz, 1H), 4.99 (dd, J = 4.4 and 15.2 Hz, 1H), 7.19–7.26 (m, 3H), 7.28–7.38 (m, 2H), 7.46–7.53 (m, 1H), 7.67–7.74 (m, 1H), 8.07 (dd, J = 1.2 and 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 14.3, 27.4, 28.8, 44.0, 47.9, 109.4, 119.4, 122.1, 122.3, 127.1, 127.6, 129.0, 132.1, 134.1, 135.4, 142.9, 143.9, 152.0, 197.5; *Anal.* Calcd. for $C_{19}H_{18}N_2O$: C, 78.59; H, 6.25; N, 9.65. Found: C, 78.25; H, 5.97; N, 9.93.

2-(5,6-Dimethyl-1*H*-benzimidazol-1-ylmethyl)-3,4-dihydronaphthalen-1(2*H*)-one (51). Tan crystals (2-propanol–hexanes), yield 1005 mg (66%), mp 144–145°C; ^{1}H NMR ($CDCl_3$): δ 1.75–1.89 (m, 1H), 1.97–2.08 (m, 1H), 2.89–2.97 (m, 2H), 2.97–3.07 (m, 1H), 4.33 (dd, J = 8.0 and 14.8 Hz, 1H), 4.86 (dd, J = 4.4 and 14.8 Hz, 1H), 7.17–7.24 (m, 2H), 7.33 (t, J = 7.0 Hz, 1H), 7.45–7.52 (m, 1H), 7.57 (s, 1H), 7.86 (s, 1H), 8.07 (d, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 20.4, 20.8, 27.2, 28.7, 44.8, 48.0, 110.0, 120.6, 127.0, 127.6, 128.9, 131.2, 132.1, 132.4, 132.6, 134.0, 142.6, 143.3, 143.9, 197.5; *Anal.* Calcd. for $C_{20}H_{20}N_2O$: C, 78.92; H, 6.62; N, 9.20. Found: C, 78.68; H, 6.45; N, 9.46.

General procedure for the reduction of benzimidazole–ketones. To the solution of benzimidazole–ketone (3 mmoles) in methanol (20 mL), $NaBH_4$ (342 mg, 9 mmoles) was added in small portions, under good stirring, at room temperature. The reaction mixture was then stirred at room temperature overnight. The solvent was removed under reduced pressure, and the residue was partitioned between water (30 mL) and ethyl acetate (15 mL). The aqueous phase was further extracted with ethyl acetate (15 mL), then the organic phases were combined and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give a residue that was crystallized from the appropriate solvent.

(±)-3-(1*H*-Benzimidazol-1-yl)-1-(4-chlorophenyl)-1-propanol (52). Colorless crystals (2-propanol–hexanes), yield 455 mg (53%), mp 168–169°C; ^{1}H NMR ($CDCl_3$): δ 2.10–2.28 (m, 2H), 4.25–4.34 (m, 1H), 4.38–4.46 (m, 2H), 4.49–4.60 (m, 1H), 7.19–7.32 (m, 6H), 7.40 (d, J = 8.0 Hz, 1H), 7.57 (d, J = 7.6 Hz, 1H), 7.93 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 38.3, 41.7, 69.3, 109.9, 120.3, 122.4, 123.2, 127.2, 128.8, 133.5, 133.6, 143.1, 143.6; *Anal.* Calcd. for $C_{16}H_{15}ClN_2O$: C, 67.02; H, 5.27; N, 9.77. Found: C, 67.25; H, 5.08; N, 9.98.

(±)-1-(4-Chlorophenyl)-3-(5,6-dimethyl-1*H*-benzimidazol-1-yl)-1-propanol (53). Colorless crystals (2-propanol–hexanes), yield 547 mg (58%), mp 130–131°C; ^{1}H NMR ($CDCl_3$): δ 2.06–2.26 (m, 2H), 2.26 (s, 3H), 2.35 (s, 3H), 4.17–4.27 (m, 1H), 4.31 (dd, J = 3.6 and 10.0 Hz, 1H), 4.46–4.57 (m, 1H), 4.98 (br s, 1H), 7.13 (s, 2H), 7.21 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 8.4 Hz, 2H), 7.84 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 20.2, 20.7, 38.1, 41.6, 68.9, 110.0, 120.2, 127.3, 128.7, 131.3, 132.0, 132.4, 133.3, 142.1, 143.0, 143.5; *Anal.* Calcd. for $C_{18}H_{19}ClN_2O$: C, 68.67; H, 6.08; N, 8.90. Found: C, 68.90; H, 5.83; N, 9.22.

(±)-3-(1*H*-Benzimidazol-1-yl)-1-(4-bromophenyl)-1-propanol (54). Colorless crystals (2-propanol), yield 845 mg (85%), mp 175–176°C; ^{1}H NMR ($CDCl_3$): δ 2.10–2.23 (m, 2H), 4.25–4.34 (m, 1H), 4.40 (dd, J = 4.0

and 10.0 Hz, 1H), 4.48 (br s, 1H), 4.48–4.60 (m, 1H), 7.16 (d, *J* = 8.4 Hz, 2H), 7.20–7.25 (m, 1H), 7.26–7.31 (m, 1H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.93 (s, 1H); ^{13}C NMR ($CDCl_3$): *δ* 38.2, 41.7, 69.3, 109.9, 120.3, 121.6, 122.4, 123.2, 127.5, 131.8, 133.6, 143.5, 143.6; *Anal.* Calcd. for $C_{16}H_{15}BrN_2O$: C, 58.02; H, 4.56; N, 8.46. Found: C, 57.81; H, 4.69; N, 8.60.

(±)-1-(4-Bromophenyl)-3-(5,6-dimethyl-1*H*-benzimidazol-1-yl)-1-propanol (55). Colorless crystals (2-propanol), yield 646 mg (60%), mp 154–155°C; ^{1}H NMR ($CDCl_3$): *δ* 2.03–2.29 (m, 2H), 2.25 (s, 3H), 2.34 (s, 3H), 4.18–4.31 (m, 2H), 4.47–4.59 (m, 1H), 7.08 (s, 1H), 7.12 (s, 1H), 7.15 (d, *J* = 8.4 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.85 (s, 1H); ^{13}C NMR ($CDCl_3$): *δ* 20.2, 20.7, 38.0, 41.6, 68.8, 110.0, 120.1, 121.3, 127.7, 131.3, 131.6, 131.9, 132.4, 142.0, 143.0, 144.1; *Anal.* Calcd. for $C_{18}H_{19}BrN_2O$: C, 60.18; H, 5.33; N, 7.80. Found: C, 59.95; H, 5.55; N, 8.02.

(±)-3-(1*H*-Benzimidazol-1-yl)-1-(naphthalen-1-yl) propan-1-ol (56). Colorless crystals (2-propanol), yield 752 mg (83%), mp 173–174°C; ^{1}H NMR (d_6-DMSO): *δ* 2.04–2.16 (m, 1H), 2.26–2.38 (m, 1H), 4.39–4.49 (m, 1H), 4.52–4.63 (m, 1H), 5.23 (d, *J* = 9.6 Hz, 1H), 5.69 (d, *J* = 3.6 Hz, 1H), 7.19–7.35 (m, 3H), 7.42–7.53 (m, 2H), 7.58 (dd, *J* = 1.2 and 8.0 Hz, 1H), 7.68 (d, *J* = 8.0 Hz, 2H), 7.79 (d, *J* = 8.4 Hz, 1H), 7.80 (d, *J* = 8.4 Hz, 1H), 8.27 (s, 1H); ^{13}C NMR (d_6-DMSO): *δ* 38.4, 41.7, 66.3, 110.4, 119.5, 121.5, 122.3, 122.7, 125.4, 125.5, 125.8, 127.2, 128.7, 129.6, 133.2, 133.8, 141.0, 143.6, 144.2; *Anal.* Calcd. for $C_{20}H_{18}N_2O$: C, 79.44; H, 6.00; N, 9.26. Found: C, 79.69; H, 5.78; N, 9.50.

(±)-3-(2-Methyl-1*H*-benzimidazol-1-yl)-1-(naphthalen-1-yl)propan-1-ol (57). Colorless crystals (2-propanol), yield 758 mg (80%), mp 176–177°C (softening at 165°C); ^{1}H NMR ($CDCl_3$): *δ* 1.95–2.07 (m, 1H), 2.19–2.31 (m, 1H), 2.56 (s, 3H), 4.30–4.40 (m, 1H), 4.45–4.55 (m, 1H), 5.23 (d, *J* = 9.6 Hz, 1H), 5.68 (d, *J* = 3.6 Hz, 1H), 7.11–7.19 (m, 2H), 7.26–7.33 (m, 1H), 7.39–7.57 (m, 4H), 7.64 (d, *J* = 8.8 Hz, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.79 (d, *J* = 8.4 Hz, 1H), 7.89 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$): *δ* 13.4, 38.0, 40.5, 66.1, 109.8, 118.2, 121.1, 121.4, 122.6, 122.7, 125.4, 125.5, 125.7, 127.2, 128.7, 129.5, 133.2, 135.0, 141.1, 142.5, 151.8; *Anal.* Calcd. for $C_{21}H_{20}N_2O$: C, 79.72; H, 6.37; N, 8.85. Found: C, 79.44; H, 6.14; N, 9.09.

(±)-3-(1*H*-Benzimidazol-1-yl)-1-(naphthalen-2-yl)propan-1-ol (58). Colorless crystals (2-propanol–hexanes), yield 660 mg (73%), mp 123–124°C; ^{1}H NMR (d_6-DMSO): *δ* 2.10–2.31 (m, 2H), 4.30–4.47 (m, 2H), 4.64–4.74 (m, 1H), 5.69 (d, *J* = 2.8 Hz, 1H), 7.17–7.29 (m, 2H), 7.43–7.53 (m, 3H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.82 (s, 1H), 7.84–7.91 (m, 3H), 8.24 (s, 1H); ^{13}C NMR (d_6-DMSO): *δ* 38.8, 41.4, 69.6, 110.3, 119.5, 121.4, 122.2, 123.9, 124.4, 125.6, 126.1, 127.5, 127.7, 132.3, 132.8, 133.8, 142.9, 143.5, 144.1; *Anal.* Calcd. for $C_{20}H_{18}N_2O$: C, 79.44; H, 6.00; N, 9.26. Found: C, 79.61; H, 6.17; N, 9.03.

(±)-3-(2-Methyl-1*H*-benzimidazol-1-yl)-1-(naphthalen-2-yl)propan-1-ol (59). Colorless crystals (2-propanol), yield 625 mg (66%), mp 179–180°C; ^{1}H NMR ($CDCl_3$): *δ* 2.01–2.23 (m, 2H), 2.53 (s, 3H), 4.23–4.40 (m, 2H), 4.69–4.77 (m, 1H), 5.71 (d, *J* = 4.8 Hz, 1H), 7.09–7.20 (m, 2H), 7.42–7.54 (m, 5H), 7.83 (s, 1H), 7.84–7.91 (m, 3H); ^{13}C NMR ($CDCl_3$): *δ* 13.4, 38.4, 40.3, 69.6, 109.7, 118.2, 121.1, 121.4, 123.9, 124.4, 125.6, 126.1, 127.5, 127.7, 132.3, 132.8, 135.0, 142.4, 142.9, 151.7; *Anal.* Calcd. for $C_{21}H_{20}N_2O$: C, 79.72; H, 6.37; N, 8.85. Found: C, 79.94; H, 6.60; N, 8.61.

(±)-3-(1*H*-Benzimidazol-1-yl)-1-(thiophen-2-yl)-1-propanol (60). Colorless crystals (2-propanol), yield 465 mg (60%), mp 127–128°C; ^{1}H NMR ($CDCl_3$): *δ* 2.32–2.45 (m, 2H), 4.11 (s, 1H), 4.30–4.38 (m, 1H), 4.47–4.57 (m, 1H), 4.80 (dd, *J* = 5.6 and 8.0 Hz, 1H), 6.94 (d, *J* = 3.6 Hz, 1H), 6.97 (dd, *J* = 3.6 and 4.8 Hz, 1H), 7.26–7.32 (m, 3H), 7.44 (d, *J* = 7.6 Hz, 1H), 7.72 (d, *J* = 7.6 Hz, 1H), 7.92 (s, 1H); ^{13}C NMR ($CDCl_3$): *δ* 38.6, 41.6, 66.1, 109.9, 120.3, 122.4, 123.2, 123.9, 124.8, 126.9, 133.7, 143.5, 143.7, 148.5; *Anal.* Calcd. for $C_{14}H_{14}N_2OS$: C, 65.09; H, 5.46; N, 10.84. Found: C, 65.32; H, 5.19; N, 11.07.

(±)-3-(2-Methyl-1*H*-benzimidazol-1-yl)-1-(thiophen-2-yl)-1-propanol (61). Colorless crystals (2-propanol–hexanes), yield 555 mg (68%), mp 146–147°C; ^{1}H NMR ($CDCl_3$): *δ* 2.31–2.38 (m, 2H), 2.58 (s, 3H), 3.64 (br s, 1H), 4.24–4.33 (m, 1H), 4.35–4.45 (m, 1H), 4.95 (t, *J* = 6.4 Hz, 1H), 6.94–7.01 (m, 2H), 7.20–7.31 (m, 3H), 7.33–7.40 (m, 1H), 7.62–7.68 (m, 1H); ^{13}C NMR ($CDCl_3$): *δ* 13.8, 38.9, 40.4, 66.8, 109.4, 119.0, 122.1, 122.2, 124.1, 125.1, 127.0, 135.2, 142.6, 148.0, 151.8; *Anal.* Calcd. for $C_{15}H_{16}N_2OS$: C, 66.15; H, 5.92; N, 10.29. Found: C, 66.39; H, 6.09; N, 10.08.

4-(3-(2-Methyl-1*H*-benzimidazol-1-yl)-1-hydroxypropyl)phenol (62). A suspension of benzimidazole–ketone **33** (840 mg, 3 mmol) in methanol (20 mL) was treated with $NaBH_4$ (570 mg, 15 mmol) in small portions under efficient stirring. The mixture is stirred at room temperature overnight, and then the solvent is removed under reduced pressure to give a sticky residue. Upon treatment with an excess of 10% HCl, this residue gradually dissolves in water (30 mL). The solution is filtered, cooled in an ice-bath, and treated dropwise with 28% NH_4OH under efficient stirring until pH reaches 8. The solid is filtered, washed thoroughly with water, air-dried, and recrystallized from 2-propanol

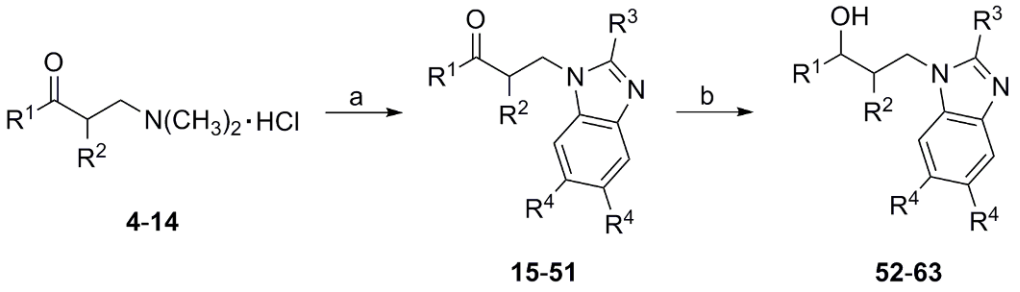
to give colorless crystals (565 mg, 67%), mp 200–201°C; ^{1}H NMR (d_6-DMSO): δ 1.91–2.07 (m, 2H), 2.52 (s, 3H), 4.17–4.31 (m, 2H), 4.41–4.49 (m, 1H), 5.35 (d, J = 4.4 Hz, 1H), 6.72 (d, J = 8.4 Hz, 2H), 7.09–7.21 (m, 4H), 7.42 (d, J = 7.2 Hz, 1H), 7.52 (d, J = 7.2 Hz, 1H), 9.30 (br s, 1H); ^{13}C NMR (d_6-DMSO): δ 13.3, 38.6, 40.3, 69.2, 109.7, 114.8, 118.2, 121.1, 121.4, 126.9, 135.0, 135.7, 142.4, 151.7, 156.3; *Anal.* Calcd. for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.11; H, 6.09; N, 10.20.

2-(3-(1*H*-Benzimidazol-1-yl)-1-hydroxypropyl)-4-methylphenol (63). The solution of benzimidazole–ketone **39** (840 mg, 3 mmol) in methanol (20 mL) was treated with $NaBH_4$ (570 mg, 15 mmol) in small portions under vigorous stirring at room temperature, and then the reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure and the residue was dissolved in water (30 mL). Dropwise addition of 10% acetic acid until pH reaches 7 yielded a colorless solid, which was removed by filtration, washed thoroughly with water, air-dried, and recrystallized from ethanol to afford colorless crystals (755 mg, 89%), mp 169–170°C; ^{1}H NMR ($CDCl_3$): δ 1.96–2.05 (m, 1H), 2.13–2.24 (m, 1H), 2.20 (s, 3H), 3.76 (br s, 1H), 4.38 (t, J = 7.2 Hz, 2H), 4.85–4.87 (m, 1H), 6.66 (d, J = 8.0 Hz, 1H); 6.84 (d, J = 8.0 Hz, 1H), 7.18–7.28 (m, 3H), 7.55 (d, J = 7.6 Hz, 1H), 7.67 (d, J = 7.6 Hz, 1H), 8.26 (s, 1H), 9.20 (br s, 1H); ^{13}C NMR ($CDCl_3$): δ 20.5, 37.4, 41.6, 64.4, 110.4, 114.8, 119.4, 121.6, 122.3, 126.7, 127.2, 127.8, 131.2, 133.9, 143.2, 144.0, 151.2. *Anal.* Calcd. for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.59; H, 6.22; N, 10.12.

3. Results and discussions

The aim of this study is to explore extensively the amine exchange reaction between benzimidazoles and ketonic Mannich bases derived from several common alkyl aryl ketones. Commercially available acetophenones substituted in the aromatic ring were the typical substrates in the synthesis of these ketonic Mannich bases, and 1- and 2-acetylnaphthalene, 2-acetylthiophene and 1-tetralone were chosen as substrates for aminomethylation with the aim to illustrate the behavior of structurally more diverse ketonic Mannich bases in the *N*-alkylation reaction of *NH*-azoles. The ketonic Mannich bases **4**–**14** required as intermediates in this study were obtained through the direct aminoalkylation of an alkyl aryl ketone in ethanol or 2-propanol [19]. The standard reaction time was 4 hours; however, the reaction time was shortened to 2 hours for the sparingly soluble Mannich base **10** derived from 4′-hydroxyacetophenone, owing to its rapid separation from the reaction mixture while being heated under reflux. Reaction times longer than 4 hours were preferred for the synthesis of Mannich base **8** derived from 1-acetylnaphthalene, as an attempt to improve the low yields reported in literature [23]. Additionally, the aminomethylation of 4′-phenylacetophenone in ethanol was revisited, despite previous reports of failure [22]. In contrast to this, the classical procedure ensured good yields of the desired compound **7** after 48 h, and a pure sample, in which the corresponding acrylophenone by-product could not be detected, was obtained after one recrystallization of the crude product.

Two experimental approaches for the amine exchange reaction involving ketonic Mannich bases and *NH*-azoles are available in the literature [4]. The difference between the two sets of conditions rests with the nature of the solvent employed (aprotic or protic), which in turn determines the form of the Mannich base (free base or salt, respectively) used in the reaction. Because there appears to be no significant difference between the yields for the isolated reaction products in both sets of conditions for ketonic Mannich bases as substrates in the amine exchange reaction [4], and because the intermediate ketonic Mannich bases are usually isolated as hydrochlorides, the approach employing protic solvents has been favored in this study. Provided that both reactants are water-soluble, the replacement of the amine moiety in Mannich bases with an *NH*-azole in a protic medium is best conducted in water. Besides being an environmentally friendly solvent, water also presents the advantage of a simple separation of the transamination product, which is usually water-insoluble. However, a mixture of water and ethanol is desirable as protic medium in the amine exchange reaction leading to the benzimidazole-derived compounds, owing to the limited solubility of some benzimidazoles in water at low temperatures. In this case, the resulting benzimidazole–ketones separate from the cold reaction mixtures in most cases as almost pure solids, and they can be subsequently isolated by filtration. Commercially available benzimidazole, 2-methyl-1*H*-benzimidazole, and 5,6-dimethyl-1*H*-benzimidazole were commonly employed for the displacement of the amine moiety in the ketonic Mannich base **4**–**14**; 2-ethyl-1*H*-benzimidazole, 2-benzyl-1*H*-benzimidazole, 2-phenoxymethyl-1*H*-benzimidazole, and 2-(naphthalen-1-ylmethyl)-1*H*-benzimidazole were the *NH*-azole counterpart in the amine exchange reaction in a limited number of examples only (Scheme 2). The benzimidazoles **15**–**51** alkylated at N^1 with residues derived from ketonic Mannich bases were generally obtained in good to excellent yields using this



4-14 **15-51** **52-63**

Scheme 2. Synthesis of benzimidazole–ketones **15–51** and their reduction to the corresponding alcohols **52–63**. Reagents and conditions: a) substituted benzimidazoles, ethanol–water (1:1, v/v), reflux, 1 h; b) $NaBH_4$, methanol, rt, overnight.

approach. It is worth mentioning that compounds derived from 2-methylbenzimidazole and 2-ethylbenzimidazole were frequently difficult to purify by recrystallization, as they have a tendency to separate as oils from their concentrated solutions, even upon slow cooling. Also, the purification of benzimidazoles *N*[1]-alkylated with a moiety derived from the Mannich base of 1-tetralone was often troublesome, and 2-(2-methyl-1*H*-benzimidazol-1-ylmethyl)-3,4-dihydronaphthalen-1(2*H*)-one **50** was the only benzimidazole derivative in this study that could not be obtain as a solid.

The reduction of selected 1-(3-oxopropyl) benzimidazoles with $NaBH_4$ in methanol at room temperature occurred at the carbonyl function to produce 1-(3-hydroxypropyl)benzimidazoles **52–63** (Scheme 2). The reducing agent (an excess of three equivalents) was added in small portions to the solution of the benzimidazole–ketone, and then the reaction mixture was stirred overnight. The isolation of the reaction product involves the removal of the solvent under reduced pressure, followed by addition of water with the view to dissolve the inorganics. The resulting secondary alcohol usually solidifies after some time, and is filtered off; in a small number of cases, extraction with ethyl acetate was necessary in order to isolate the reaction products, owing to their reluctance to crystallize even after having been stirred for up to one day. Under these experimental conditions, the isolated benzimidazole–alcohols are devoid of any starting material, and the yields are almost quantitative. The analytical samples were however purified by recrystallization, usually accompanied by filtration to remove small amounts of fine particles (presumably inorganics incorporated within the crystals upon solidification). Because these benzimidazole–alcohols are quite soluble in inferior alcohols, the solvent of choice for purification was either 2-propanol or its mixture with hexanes, but, even under these conditions, the recovery was sometimes poor.

The reduction of benzimidazole–ketones **33** and **39** derived from hydroxyacetophenones is particular due to the presence of the phenolic group. First of all, compound **33** has a very low solubility in cold methanol. Whereas all other benzimidazole–ketones are reduced swiftly and quantitatively in a homogenous system by three equivalents of $NaBH_4$, the reduction of benzimidazole–ketone **33** is limited by the rate of dissolution of the substrate, which is in turn determined by the formation of the corresponding more soluble sodium salt. Because the sodium salt of the substrate is formed slowly and gradually in the reaction with sodium methoxide resulted from the methanolysis of the reducing agent, it is conceivable that significant amounts of $NaBH_4$ are consumed without any actual reduction of the substrate taking place. Indeed, when compound **33** was reduced using three equivalents of reducing agent, a TLC analysis showed the presence of the starting material at the end of the reaction time, and the NMR analysis of an aliquot confirmed the presence of approximately 30% unreacted benzimidazole–ketone **33** in the reaction mixture. However, when 5 equivalents of $NaBH_4$ were used, the conversion of the starting material **33** into benzimidazole-alcohol **62** was complete. The isolation of compound **62** required also particular attention, due to the presence of an acidic phenolic group and a benzimidazole moiety capable of forming water-soluble salts in the presence of acids. The sticky semi-solid resulted after the removal of methanol, presumably a mixture of the sodium salt of **63** and inorganic by-products of the reaction, did not dissolve well in water, but formed readily a solution upon treatment with dilute HCl. The solution was filtered, cooled in an ice-bath, and rendered basic with concentrated NH_4OH, when benzimidazole-alcohol **62** precipitated as a crystalline solid. Despite its significantly higher solubility in methanol compared to compound **33**, five equivalents of $NaBH_4$ were employed also in the case of benzimidazole–ketone **39**, and the TLC analysis proved the complete reduction of the substrate at the end of the reaction time. The isolation of benzimidazole–alcohol **63** was straightforward, as the residue obtained after the removal of methanol was completely soluble in water. Careful treatment with dilute acetic acid under strict monitoring of pH provided the compound **63** as

a crystalline solid; at lower pH, the amount of isolated precipitate decreased, as benzimidazole–alcohol **63** dissolved partially in the acidic solution.

All of the synthesized compounds were characterized by NMR spectroscopy. The representative feature in the ^{1}H NMR spectra of benzimidazole–ketones **15**–**48** is the pair of well-defined triplets at approximately 3.5 and 4.5 ppm, which are associated with the protons of the methylene groups in the linker between the benzimidazole moiety and the aromatic ring originating from the initial Mannich base. In the case of benzimidazole–ketones **49**–**51** derived from 1-tetralone, the substitution at the carbon atom adjacent to the carbonyl group destroys the pattern observed in aliphatic region of proton spectra of their analogs **15**–**48** and creates two diastereotopic protons. Consequently, the typical feature in the ^{1}H NMR spectra of benzimidazole–ketones **49**–**51** is the pair of double doublets around 4.5 ppm engendered by the protons in the methylene group attached to the benzimidazole ring. The transformation of the carbonyl group into a secondary alcohol function through reduction also alters significantly the appearance of the aliphatic region of the proton spectra of benzimidazole–alcohols **52**–**63**. The protons in the methylene group adjacent to the hydroxyl function appear as two multiplets between 2 and 2.5 ppm that overlay one another to some extent in several cases. The remaining protons (two from the methylene group next to the benzimidazole moiety and one attached to the carbon atom of the secondary alcohol function) usually give three multiplets in the range of 4 to 5 ppm whose peaks are often superimposed. A broad singlet or a doublet with a coupling constant within the range of 3 to 5 Hz that can be associated with the proton of the hydroxyl group is noticeable also in the proton spectra of benzimidazole–alcohols **52**–**63**.

The transformation of benzimidazole–ketones into benzimidazole–alcohols is reflected also in the ^{13}C NMR spectra. Again, the carbon atoms in the linker bridging the two aromatic moieties in the structures of these compounds are responsible for the distinctive features in their carbon spectra. Aside from other peaks produced by the occasional aliphatic carbon atoms present in the structure of benzimidazole–ketones **15**–**51**, two signals, falling in the range from 37 to 41 ppm, are detectable always in the aliphatic region of the carbon spectra of these compounds; these signals are correlated with the carbon atoms in the two methylene groups of the linker. Upon reduction of benzimidazole–ketones to benzimidazole–alcohols, the chemical shift of these two carbon atoms does not change much, but the presence of a third signal at about 65–70 ppm, and the absence of the signal appearing at about 190–200 ppm in the carbon spectra of benzimidazole–ketones are indicative for the conversion of the carbonyl group into a hydroxyl function.

4. Conclusions

The exploration of the scope of the *N*-alkylation of benzimidazoles with ketonic Mannich bases has shown that azole substrates having various substitution patterns and a wide range of the aforementioned alkylating agents derived from acetophenones, acetonaphtones, 2-acetothienone or 1-tetralone are amenable to this reaction. The use of a variety of benzimidazoles and ketonic Mannich bases allowed the facile creation of a small library of structurally diverse 1-(3-oxopropyl)benzimidazoles that were fully described and characterized. This library was used to generate a second set of compounds that comprises 1-(3-hydroxypropyl)benzimidazoles by means of the reduction of the carbonyl group with $NaBH_4$. The antimicrobial activity of selected compounds from these collections will be investigated.

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