

## SYNTHESIS, CHARACTERIZATION AND CRYSTAL STRUCTURES OF TWO NEW PHENOLIC MANNICH BASES

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**ABSTRACT.** Two new Mannich bases, 5-methyl-2-((4-(pyridin-2-yl)piperazin-1-yl)methyl)phenol (**I**) and 5-methyl-2-((4-(4-nitrophenyl)piperazin-1-yl)methyl)phenol (**2**), were prepared and characterized structurally with elemental analysis, IR, UV and NMR spectroscopic techniques as well as single crystal X-ray diffraction. Compound **I** crystallizes in the monoclinic space group P21/c with unit cell dimensions  $a = 6.6726(2) \text{ \AA}$ ,  $b = 17.0542(6) \text{ \AA}$ ,  $c = 13.3222(4) \text{ \AA}$ ,  $\beta = 100.832(1)^\circ$ ,  $V = 1489.00(8) \text{ \AA}^3$ ,  $Z = 4$ ,  $R_1 = 0.0408$ ,  $wR_2 = 0.1143$ . Compound **II** crystallizes in the monoclinic space P21 with unit cell dimensions  $a = 5.9519(2) \text{ \AA}$ ,  $b = 17.3315(8) \text{ \AA}$ ,  $c = 15.7237(7) \text{ \AA}$ ,  $\beta = 90.348(2)^\circ$ ,  $V = 1621.95(12) \text{ \AA}^3$ ,  $Z = 4$ ,  $R_1 = 0.0353$ ,  $wR_2 = 0.0965$ . Both compounds have their structures stabilized by hydrogen bonding and  $\pi \cdots \pi$  interactions.

**KEY WORDS:** Mannich base, Piperazine, X-ray diffraction, Hydrogen bonds

### INTRODUCTION

Mannich bases from phenols and acetophenones especially have shown significant corrosion inhibition, anticancer, antimalarial properties in addition to coordination potentials with metal ions of biological interests including biocatalysis [1, 2]. Our recent research focus has been on the catecholase activities of Cu(II) and Fe(III) complexes of specially designed Mannich bases and they have shown promising results in this regard [3-4]. A report on the synthesis and characterisation of two new phenolic Mannich bases with potentially beneficial properties in the field of coordination chemistry; 5-methyl-2-((4-(pyridin-2-yl)piperazin-1-yl)methyl)phenol (**I**) and 5-methyl-2-((4-(4-nitrophenyl)piperazin-1-yl)methyl)phenol (**II**), is presented herein.

### EXPERIMENTAL

#### *Materials and measurements*

Formaldehyde, 1-(2-pyridyl)piperazine, 1-(4-nitrophenyl)piperazine and *m*-cresol as well as solvents were purchased from Sigma-Aldrich and used as received. Micro analytical determinations (C, H and N) were obtained using Elementar Analysensysteme VarioMICRO V1.62 GmbH analysis System. NMR spectra (<sup>1</sup>H and <sup>13</sup>C NMR) were acquired in CDCl<sub>3</sub> using Bruker AMX 300 MHz spectrometer. Attenuated total reflection Fourier transform infrared (ATR-FTIR) spectra for all the samples were recorded on a PerkinElmer Spectrum400 spectrophotometer in the range 4000 to 650 cm<sup>-1</sup>. Electronic spectra were recorded for the solutions of the synthesized compounds in DMF on a Perkin Elmer UV-Vis spectrophotometer model Lambda 25. The melting points were determined on a Gallenkamp melting point apparatus.

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*Synthesis of 5-methyl-2-((4-(pyridin-2-yl)piperazin-1-yl)methyl)phenol (I)*

A mixture of *m*-cresol (6 mmol, 0.649 g), 1-(2-pyridyl)piperazine (6 mmol, 0.979 g) and (40 mmol, 3 mL) of formaldehyde solution (37%) were refluxed in 15 mL of ethanol for 24 h. White crystalline solids were obtained from the reaction mixture upon standing for about 3 days. These were collected, washed with ethanol and dried. Yield was 68%. Single crystals suitable for X-ray diffraction measurements were obtained by recrystallization of the product from chloroform: ethyl acetate mixture. Anal. calcd. (%) for C<sub>17</sub>H<sub>20</sub>N<sub>3</sub>O: C, 73.59; H, 8.03; N, 8.58; found (%): C, 73.55; H, 8.44; N, 8.70%. M.p. 270 °C. UV (λ): 288 and 305 nm. IR data (FT-IR, cm<sup>-1</sup>): 3412 (br), 2827 (s), 1592 (s), 1480 (s), 1436 (s), 1382 (w), 1252 (s), 1120 (s), 939 (w), 859 (w), 780 (s), 732 (s), 717 (w). <sup>1</sup>H NMR (300 MHz; CDCl<sub>3</sub>): δ 10.73 (s, 1H, OH), 6.68-8.08 (m, 7H, ArH), 3.72 (s, 2H, Ar-CH<sub>2</sub>), 3.60 (t, 4H, (CH<sub>2</sub>)<sub>2</sub>N-), 2.68 (t, 4H, (CH<sub>2</sub>)<sub>2</sub>N-), 2.30 (s, 3H, CH<sub>3</sub>-Ar). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 158.93, 157.33, 147.69, 138.76, 137.33, 128.28, 119.73, 117.66, 116.49, 113.45, 106.85, 61.00, 52.02, 44.83, 20.95.

*Synthesis of 5-methyl-2-((4-(4-nitrophenyl)piperazin-1-yl)methyl)phenol (II)*

A mixture of *m*-cresol (6 mmol, 0.649 g), 1-(4-nitrophenyl)piperazine (6 mmol, 1.243 g) and (40 mmol, 3 mL) formaldehyde solution (37%) in 15 mL of ethanol were refluxed for 24 h. Solid precipitates were obtained upon leaving the reaction mixture for about a week. This was collected and washed with ethanol. Yield was 70%. Single crystals suitable for X-ray diffraction were obtained by recrystallization of the product from chloroform: ethyl acetate mixture. Anal. calcd (%) for C<sub>18</sub>H<sub>21</sub>N<sub>3</sub>O<sub>3</sub>: C, 66.04; H, 6.47; N, 12.84; found (%): C, 65.57; H, 6.98; N, 12.81%. M.p. 217 °C. UV (λ): 277, 369 and 430 nm. IR data (FT-IR, cm<sup>-1</sup>): 3392 (b), 2828 (s), 1591 (s), 1494 (s), 1445 (w), 1325 (s), 1247 (s), 1118 (w), 1002 (s), 825 (s), 755 (s), 695 (w), 668 (w). <sup>1</sup>H NMR (300 MHz; CDCl<sub>3</sub>): δ 10.27 (s, 1H, OH), 6.63 - 6.91 (m, 7H, ArH), 3.75 (s, 2H, Ar-CH<sub>2</sub>), 3.47 (t, 4H, (CH<sub>2</sub>)<sub>2</sub>N-), 2.72 (t, 4H, (CH<sub>2</sub>)<sub>2</sub>N-), 2.30 (s, 3H, CH<sub>3</sub>-Ar). <sup>13</sup>C NMR (75 MHz; CDCl<sub>3</sub>): δ 157.19, 154.56, 139.44, 138.96, 128.74, 125.94, 116.94, 113.09, 61.08, 51.95, 47.09, 21.25.

*Data collection, structural determination and refinement*

The data were collected using a Bruker KAPPA APEX II single crystal X-ray diffractometer, with a 4-circle Kappa goniometer and sensitive CCD detector. The instrument used a Molybdenum fine focus sealed X-ray tube as an X-ray source and an Oxford Cryostream 700 system for sample temperature control. Bruker's APEX2 software [5] was used for instrument control. The structure was solved using SHELXT-2014 [6] and refined by least square procedures using SHELXL-2016 [7] with SHELXLE [8] as a graphical interface. Data were recorded for absorption effects using the numerical method implemented in SADABS [5]. The crystallographic data for the compounds are summarized in Table 1. Information on Hydrogen bonding is provided in Table 2.

**RESULTS AND DISCUSSION***Chemistry*

Compounds **I** and **II** were readily synthesized through the reaction of 1:1 molar ratio of *m*-cresol with 1-(2-pyridyl)piperazine and 1-(4-nitrophenyl)piperazine respectively by refluxing in ethanol, in moderately high yields (about 70 %) and high purity (Scheme 1). Both compounds are soluble in chloroform, DMF and DMSO. Single crystals suitable for X-ray diffraction were obtained by two-solvent recrystallization technique followed by slow evaporation in air. Various

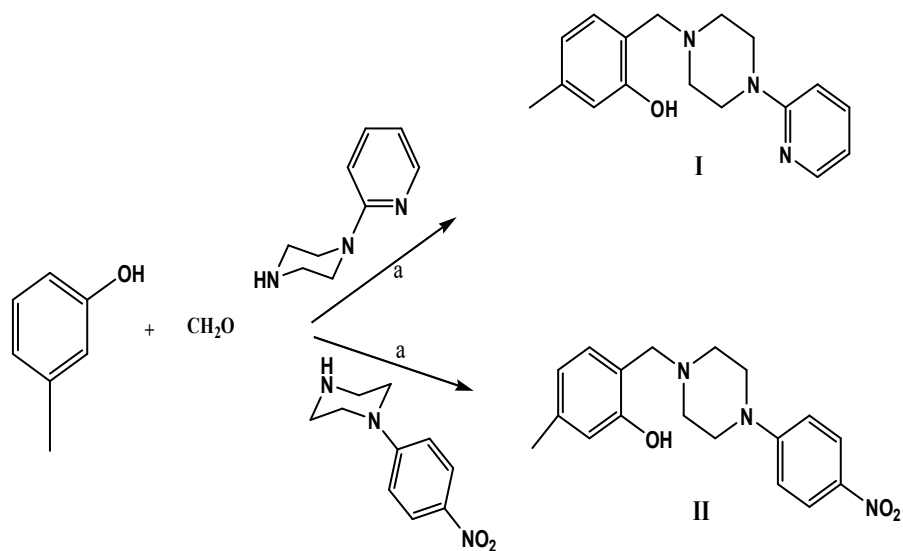
spectroscopic techniques in addition to single crystal X-ray crystallography were employed to characterise the compounds.

Table 1. Crystallographic and experimental data for the compounds.

Compound	I	II
Formula	C <sub>17</sub> H <sub>21</sub> N <sub>3</sub> O	C <sub>18</sub> H <sub>21</sub> N <sub>3</sub> O <sub>3</sub>
Mr	283.37	327.38
T (K)	200	200
Crystal shape/color	Block/white	Block/orange
Crystal size (mm <sup>3</sup> )	0.31 × 0.39 × 0.56	0.29 × 0.58 × 0.61
Crystal system	Monoclinic	Monoclinic
Space group	P21/c	P21
a (Å)	6.6726(2)	5.9519(2)
b (Å)	17.0542(6)	17.3315(8)
c (Å)	13.3222(4)	15.7237(7)
α (°)	90	90
β (°)	100.832(1)	90.348(2)
γ (°)	90	90
V (Å <sup>3</sup> )	1489.00(8)	1621.95(12)
Dc (g cm <sup>-3</sup> )	1.264	1.341
μ (Mo-Kα)	0.081	0.093
F (000)	608	696
Reflections collected	20944	23493
Unique reflections	3707	7948
Observed reflections (I ≥ 2σ)	2815	7011
Parameters	192	437
R <sub>1</sub> , wR <sub>2</sub>	0.0408, 0.1143	0.0353, 0.0965
θmax/deg	2.0/28.3	1.3/28.3
Rint	0.018	0.017
min/max	-0.16/0.21	-0.19/0.20

Table 2. Hydrogen bond distances (Å) and bond angles (°) for the compounds.

D-H...A	d(D-H)	d(H...A)	d(D...A)	Angle(D-H...A)
<b>I</b>				
O1-H1...N1	0.8400	1.98	2.72(13)	146.00
C1-H1E...O1	0.98	2.55	3.4345(17)	151.00
C22-H22A...N3	0.99	2.38	2.7702(16)	103.00
<b>II</b>				
O11-H11...N11	0.84	2.00	2.736(2)	145.00
O21-H21...N21	0.84	1.97	2.703(2)	146.00
C121-H12D...O13	0.99	2.41	3.024(3)	120.00
C21-H21A...O23	0.98	2.56	3.524(3)	169.00
C224-H22J...O23	0.99	2.40	3.095(3)	127.00
C235-H235...O11	0.95	2.58	3.478(2)	158.00



Scheme 1. Reagents and conditions (a) EtOH, 80 °C, 24 h.

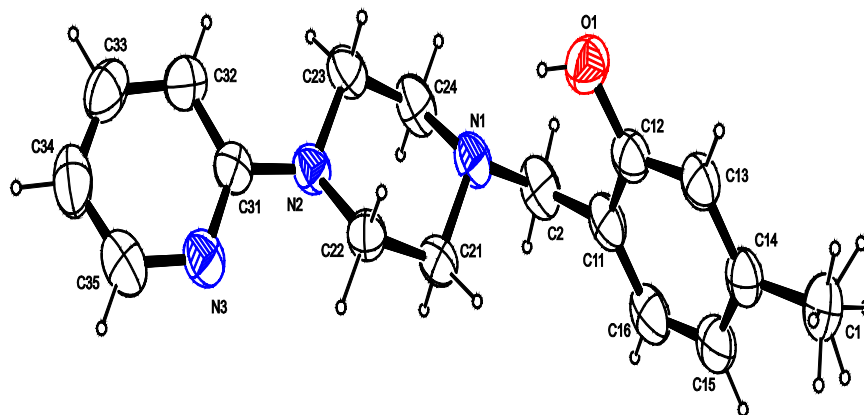


Figure 1. A perspective view of the molecular structure of **I** with the atom labelling scheme. Thermal ellipsoids are drawn at the 50% probability level.

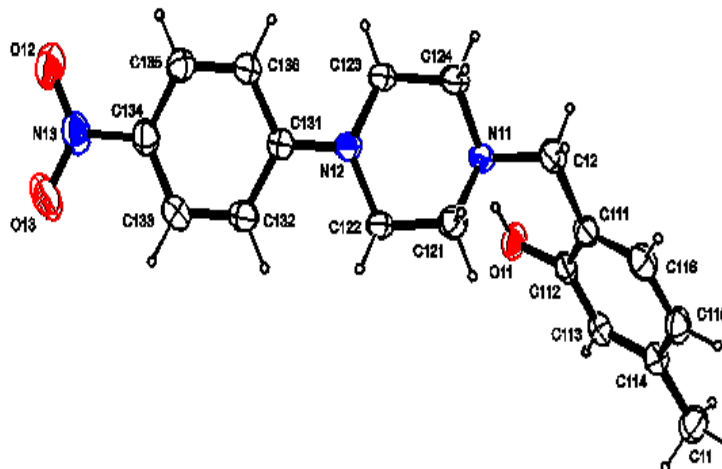


Figure 2. A perspective view of the molecular structure of **II** with the atom labelling scheme. Thermal ellipsoids are drawn at the 50% probability level.

#### *Spectral description*

UV spectra of the two Mannich bases are shown in Figure 5. Compound **I** displayed  $\pi-\pi^*$  and  $n-\pi^*$  transitions at 288 and 305 nm respectively [12] while compound **II** showed a intraligand transition attributed to the nitro group at 430 nm in addition to  $\pi-\pi^*$  and  $n-\pi^*$  transitions at 277 and 369 nm respectively [13, 14].

The FT-IR spectra of the compounds showed vibrations for hydrogen bonded OH protons around  $3300\text{ cm}^{-1}$  as broad bands while two strong bands for each compound were observed for the  $\nu(\text{C-N-C})$  vibrations of the piperazine units in the Mannich bases at about  $1320$  and  $1250\text{ cm}^{-1}$  [15].

The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of the compounds were recorded  $\text{CDCl}_3$ . In the  $^1\text{H}$  NMR spectra, the broad signal at about 10.5 ppm is attributed to the proton of the  $-\text{OH}$  groups in each case of the Mannich base. Formation of mono-Mannich bases is proven by singlet signals (of the methylene group that acted as a linker between the phenol and the secondary amine) at about 3.72 ppm and their integration for two protons in each case [16, 17]. The unsymmetrical nature of the piperazine units in the Mannich bases is supported by the observation of two signals of its protons in the range 2.68–3.60 ppm. The aromatic protons were observed as multiplets in the range 6.63–8.08 ppm while the aromatic carbons resonated in the range 107–160 ppm. The aromatic carbon carrying the hydroxyl group resonate around 153 ppm.

#### *Supporting information*

CCDC–1542043 for **I**, and 11542044 for **II** contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at <http://www.ccdc.cam.ac.uk/const/retrieving.html> or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0)1223-336033 or e-mail: [deposit@ccdc.cam.ac.uk](mailto:deposit@ccdc.cam.ac.uk).

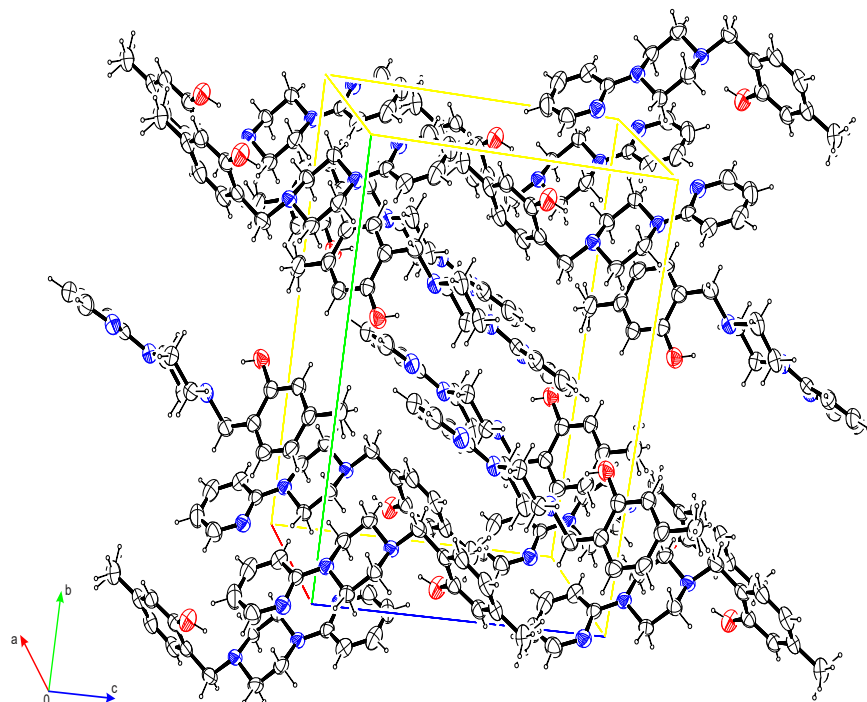


Figure 3. Packing of structure **I** with only the major disorder components showing. Ellipsoids drawn at 50 % probability level.

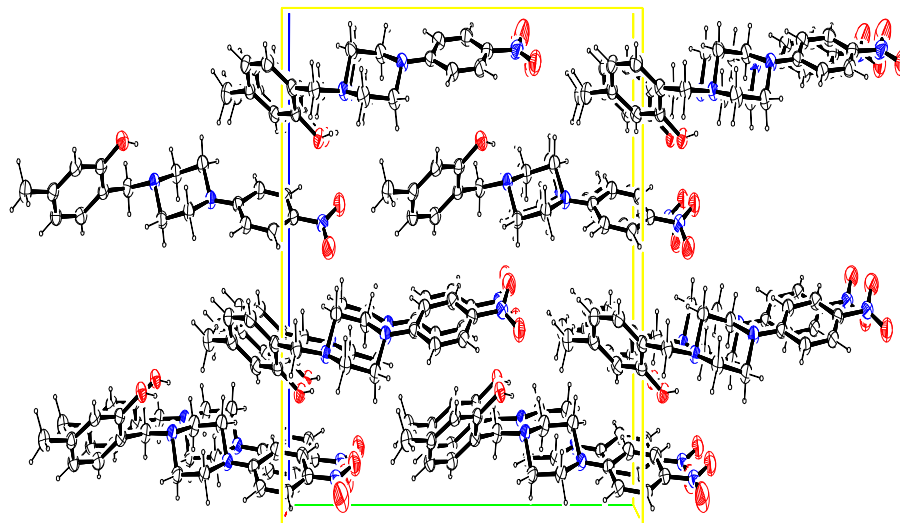


Figure 4. Molecular packing diagram of **II** viewed normal to (100). Ellipsoids drawn at 50 % probability level.

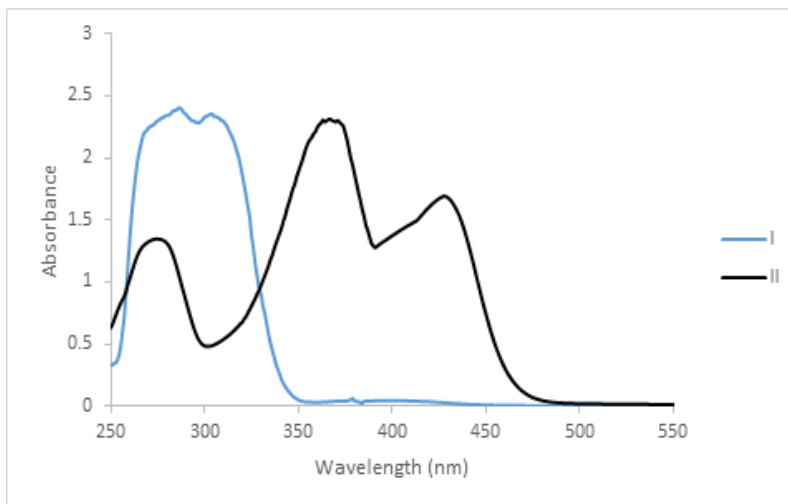


Figure 5. UV spectra of DMF solutions of the compounds I and II.

### CONCLUSION

Two phenolic Mannich bases, 5-methyl-2-((4-(pyridin-2-yl)piperazin-1-yl)methyl)phenol and 5-methyl-2-((4-(4-nitrophenyl)piperazin-1-yl)methyl)phenol, were prepared and characterized by spectroscopic techniques. The crystal structures of the compounds are described in details. Both compounds have their structures stabilized by hydrogen bonds and  $\pi \cdots \pi$  interactions.

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