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Synthesis and Characterized of New Mannich Bases of Piperazine Derivative with Phenoxy Acetic Acid/ Butyric Acid Hydrazides

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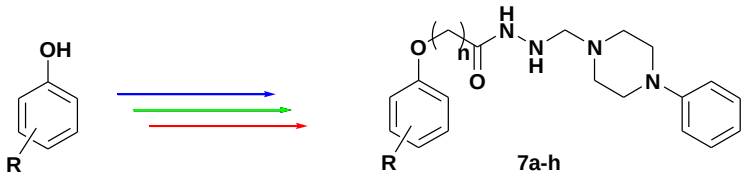
ABSTRACT

A new series of Mannich base by phenoxy-acetic/butyric acids N'-[(4-phenyl-piperazin-1-yl)-o-tolyl-methyl]-hydrazides (7a-h) were synthesized and characterized by IR, NMR and mass spectroscopy. The reaction of compounds 3a-h with hydrazine hydrate led to the formation of phenoxy-acetic/ butyric acid hydrazides 4a-h. The reaction of compound 4a-h with phenyl piperazine in the presence of formaldehyde afforded compounds 7a-h in good yields.

Graphical Abstract



a: R=4-Cl, n=1 e: R=2-CH_3, n=1
b: R=4-Cl, n=3 f: R=2-CH_3, n=3
c: R=3-NO_2,n=1 g: R=4-OCH_3, n=1
d: R=3-NO_2,n=3 h: R=4-OCH_3, n=3

Highlights

- A series of novel Mannich bases of phenyl piperazine bearing phenoxy acetic acid/ butyric acid hydrazides 7a-h were synthesized.
- Synthesized compounds were were characterized by IR, Mass, and NMR spectral data.

Keywords: Piperazine, Mannich base, Synthesis, Characterization.

INTRODUCTION

Piperazine nucleus and their derivatives had constituted an attractive pharmacological scaffold present in various potent marketed drugs.[1-5] Piperazine is a class of heterocyclic compounds that has attracted the interest of medicinal chemists due to their synthetic feasibility and their incorporation into variety of therapeutically active agents [6,8].

Mannich bases are known to play a vital role in the development of synthetic pharmaceutical chemistry. The literature studies revealed that Mannich bases are very reactive and can be easily converted to other compounds, for example, reduced to form physiologically active amino alcohols [9], and a powerful C-C bond formation of diverse amino alkyl derivatives. It involves the condensation of a compound capable of supplying one or more active hydrogen atoms with aldehyde and primary or secondary amine [10]. Mannich bases have several applications in pharmaceutical chemistry [11, 12], they have been encountered with anticancer [13], analgesic and anti-inflammatory [14], antibacterial [15], anticonvulsant [16], antimalarial [17], antiviral [18], and CNS depressant activities [19]. In view of these observations, we have synthesized new Mannich bases of phenyl piperazine bearing phenoxy acetic acid/ butyric acid hydrazides and the newly synthesized compounds were characterized by IR, Mass, and NMR spectral data.

MATERIALS AND METHODS

All materials used were of commercial grade without purification. Melting points were determined with a Thomas Hoover capillary melting point apparatus with a digital thermometer. IR spectra were determined on FT-IR Shimadzu 8300 spectrophotometer. All nuclear magnetic resonance (NMR) experiments were carried out a Bruker 400 MHz spectrometer using dimethyl sulfoxide-d_6 (DMSO-d_6) or $CDCl_3$-d_6 as the solvent. Chemical shifts were reported in ppm (δ) downfield from tetramethylsilane. Mass spectra were recorded in either positive or negative ion mode using electrospray ionization (ESI). High resolution LC-MS (HRMS) was carried out by a VG70-70H Spectrophotometer. The elemental analysis of the compounds was performed on a Perkin Elmer 2400 Elemental Analyzer. The results of elemental analyses were within ±0. 4%.

General synthetic procedure for phenoxy acetic/ butyric acid ethyl ester derivatives (3a-h): A mixture of substituted phenols **1a-d** (0.05mol) and **2a-b** (0.075mol) in dry acetone (40 mL) with anhydrous potassium carbonate (0.075mol) was refluxed for 8-10 h. The reaction mixture was cooled and solvent removed by distillation. The residual mass was triturated with cold water to remove potassium carbonate, and extracted with ether (3×30 mL). The ether layer was washed with 10% sodium hydroxide solution (3×30 ml) followed by water (3×30 mL) and then dried over anhydrous sodium sulphate and evaporated to afford compounds **3a-h.**

(4-Chloro-phenoxy)-acetic acid ethyl ester (3a): Yield; 90%; FT-IR (cm^{-1}): 1738 (C=O); ^{1}H NMR ($CDCl_3$): δ 1.35 (t, 3H, CH_3 of ester), 4.21 (q, 2H, CH_2 of ester), 5.01 (s, 2H, CH_2), 7.32-7.49 (m, 4H, Ar-H). LC-MS m/z 214 (M+) and 216 (M+2); Anal. Calc. for $C_{10}H_{11}ClO_3$: C, 55.96; H, 5.17 Found: C, 56.02; H, 5.10%.

4-(4-Chloro-phenoxy)-butyric acid ethyl ester (3b): Yield 83%; FT-IR (cm^{-1}): 1738 (C=O), 1281 (C-O-C); ^{1}H NMR ($CDCl_3$): δ1.35 (t, 3H, CH_3 of ester), 2.26 (m, 2H, CH_2), 2.75 (t, 2H, $COCH_2$), 4.07 (t, 2H, OCH_2), 4.31 (q, 2H, CH_2 of ester), 6.88-7.27 (m, 4H, Ar-H); LC-MS m/z 242 (M^+) and 242 (M+2). Anal. Calc. for $C_{12}H_{15}ClO_3$: C, 59.39; H, 6.23. Found: C, 59.50; H, 6.16%.

(3-Nitro-phenoxy)-acetic acid ethyl ester (3c): Yield 80%; FT-IR (cm^{-1}): 1742 (C=O), 1284 (C-O-C); ^{1}H NMR ($CDCl_3$): δ 1.34 (t, 3H, CH_3 of ester), 4.30 (q, 2H, CH_2 of ester), 5.04 (s, 2H, CH_2), 6.84-7.45 (m, 4H, Ar-H); LC-MS m/z 226 (M+1). Anal. Calc. for $C_{10}H_{11}NO_5$: C, 53.33; H, 4.92. Found: C, 53.47; H, 5.06%.

4-(3-Nitro-phenoxy)-butyric acid ethyl ester (3d): Yield 82%; FT-IR (cm^{-1}): 1742 (C=O), 1284 (C-O-C); ^{1}H NMR ($CDCl_3$): δ 1.34 (t, 3H, CH_3 of ester), 2.23 (m, 2H, CH_2), 2.73 (t, 2H, $COCH_2$), 4.05 (t, 2H, OCH_2), 4.29 (q, 2H, CH_2 of ester), 6.84-7.62 (m,4H, Ar-H); LC-MS m/z 254 (M+1). Anal. Calc. for $C_{12}H_{15}NO_5$: C, 56.91; H, 5.97. Found: C, 56.80; H, 5.91%.

o-Tolyloxy acetic acid ethyl ester (3e): Yield 83%; FT-IR (cm−1): 1735 (C=O), 1279 (C-O-C); ^{1}H NMR ($CDCl_3$): δ 1.35 (t, *J* = 7.0 Hz, 3H, CH_3 of ester), 2.16 (s, 3H, CH_3), 4.31 (q, 2H, CH_2 of ester), 5.01 (s, 2H, CH_2), 6.82-7.54 (m, 4H, Ar-H); LC-MS m/z 195 (M+1). Anal. Calc. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.14; H, 7.16%.

4-o-Tolyloxy-butyric acid ethyl ester (3f): Yield 84%; FT-IR (cm^{-1}): 1735 (C=O), 1279 (C-O-C); ^{1}H NMR ($CDCl_3$): δ 1.35 (t, 3H, CH_3 of ester), 2.16 (s, 3H, CH_3), 2.26 (m, 2H, CH_2), 2.75 (t, 2H, $COCH_2$), 4.07 (t, 2H, OCH_2), 4.31 (q, 2H, CH_2 of ester), 6.82-7.54 (m, 4H, Ar-H); LC-MS m/z 223 (M+1). Anal. Calc. for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.16; H, 8.25%.

(4-Methoxy-phenoxy)-acetic acid ethyl ester (3g): Yield 87%; FT-IR (cm^{-1}): 1740 (C=O), 1274 (C-O-C); ^{1}H NMR ($CDCl_3$): δ 1.32 (t, 3H, CH_3 of ester), 3.22 (s, 3H, OCH_3), 4.33 (q, 2H, CH_2 of ester), 5.04 (s, 2H, CH_2), 6.81-7.05 (d, 4H, Ar-H), LC-MS m/z 211(M+1). Anal. Calc. for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71. Found: C, 62.73; H, 6.65%.

4-(4-Methoxy-phenoxy)-butyric acid ethyl ester (3h): Yield 82%; FT-IR (cm^{-1}): 1740 (C=O), 1274 (C-O-C); ^{1}H NMR ($CDCl_3$): δ 1.32 (t, 3H, CH_3 of ester), 2.23 (m, 2H, CH_2), 2.76 (t, 2H, $COCH_2$), 3.22 (s, 3H, OCH_3), 4.04 (t, 2H, OCH_2), 4.33 (q, 2H, CH_2 of ester), 6.81-7.05 (d, 4H, Ar-H), LC-MS m/z 239 (M+1). Anal. Calc. for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.40; H, 7.52%.

General synthetic procedure for Phenoxy-acetic acid/ butyric acid hydrazide derivatives (4a-h): Hydrazine hydrate (0.045 mol) was added to the solution of compounds **3a-h** (0.03 mol) in ethanol (20 mL) and stirred the reaction mixture at room temperature for 5 h. Reaction completion was monitored by thin layer chromatography using hexane: ethylacetate (2:1) as the mobile phase and allowed to stand overnight. The white crystals **4a-h** formed were filtered, washed and after drying recrystalized from ethanol.

(4-Chloro-phenoxy)-acetic acid hydrazide (4a): Yield 92%; mp 115-117°C; FT-IR (KBr, cm^{-1}): 3315 (NH_2), 3220 (NH), 1672 (C=O); ^{1}H NMR ($CDCl_3$): δ 4.12 (bs, 2H, NH_2), 4.46 (s, 2H, CH_2), 6.91-7.28 (m, 4H, Ar-H), 9.24 (bs,1H, NH), LC-MS m/z 200 (M^+) and 202 (M+2). Anal. Calc. for $C_8H_9ClN_2O_2$: C, 47.89; H, 4.52; N, 13.96. Found: C, 47.78; H, 4.56; N, 14.08 %.

4-(4-Chloro-phenoxy)-butyric acid hydrazide (4b): Yield 90%; mp 85-87 °C; FT-IR (KBr, cm^{-1}): 3315 (NH_2), 3220 (NH), 1672 (C=O); ^{1}H NMR ($CDCl_3$): δ 2.26 (m, 2H, CH_2), 2.75 (t, 2H, $COCH_2$), 3.85 (bs, 2H, NH_2),4.07 (t, 2H, OCH_2), 6.88-7.27 (m, 4H, Ar-H), 8.40 (bs, 1H, NH); LC-MS m/z 228 (M+) and 230 (M+2). Anal. Calc. for $C_{10}H_{13}ClN_2O_2$: C, 52.52; H, 5.73; N, 12.25. Found: C, 52.43; H, 5.75; N, 12.39%.

(3-Nitro-phenoxy)-acetic acid hydrazide (4c): Yield 86%; mp 117-119°C;FT-IR (KBr, cm^{-1}): 3309 (NH_2), 3228 (NH), 1676 (C=O); ^{1}H NMR ($CDCl_3$): δ 3.91 (bs, 2H, NH_2),5.06 (s, 2H, CH_2), 6.84-7.62 (m, 4H, Ar-H), 8.46 (bs, 1H, NH); LC-MS m/z 212 (M+1). Anal. Calc. for $C_8H_9N_3O_4$: C, 45.50; H, 4.30; N, 19.90. Found: C, 45.56; H, 4.42; N, 19.86%.

4-(3-Nitro-phenoxy)-butyric acid hydrazide (4d): Yield 88%; mp 90-92°C;FT-IR (KBr, cm^{-1}): 3309 (NH_2), 3228 (NH), 1676 (C=O); ^{1}H NMR ($CDCl_3$): δ 2.27 (m, 2H, CH_2), 2.79 (t, 2H, $COCH_2$), 3.91 (bs, 2H, NH_2),4.05 (t, 2H, OCH_2), 6.84-7.62 (m, 4H, Ar-H), 8.46 (bs, 1H, NH); LC-MS m/z 240 (M+1). Anal. Calc. for $C_{10}H_{13}N_3O_4$: C, 50.21; H, 5.48; N, 17.56. Found: C, 50.23; H, 5.35; N, 17.62%.

o-Tolyloxy acetic acid hydrazide (4e): Yield 81%; mp 116-118 °C; FT-IR (KBr, cm^{-1}): 1672 (C=O), 3310 (NH_2), 3217 (NH); ^{1}H NMR ($CDCl_3$): δ 2.16 (s, 3H, CH_3), 4.20 (bs, 2H, NH_2), 4.83 (s, 2H, CH_2),

6.82-7.54 (m, 4H, Ar-H), 8.41 (bs, 1H, NH); LC-MS m/z 181 (M+1). Anal. Calc. for $C_9H_{12}N_2O_2$: C, 59.99; H, 6.71; N, 15.55. Found: C, 60.07; H, 6.65; N, 15.62%.

4-o-Tolyloxy-butyric acid hydrazide (4f): Yield 85%; mp 82-84^{o}C;FT-IR (KBr, cm^{-1}): 3310 (NH_2), 3217 (NH), 1672 (C=O); ^{1}H NMR ($CDCl_3$): δ 2.16 (s, 3H, CH_3), 2.24 (m, 2H, CH_2), 2.75 (t, 2H, $COCH_2$), 3.83 (bs, 2H, NH_2),4.07 (t, 2H, OCH_2), 6.82-7.54 (m, 4H, Ar-H), 8.41 (bs, 1H, NH); LC-MS m/z 209 (M+1). Anal. Calc. for $C_{11}H_{16}N_2O_2$: C, 63.44; H, 7.74; N, 13.45. Found: C, 63.56; H, 7.63; N, 13.42%.

(4-Methoxy-phenoxy)-acetic acid hydrazide (4g): Yield 86%; mp 115-117^{o}C;FT-IR (KBr, cm^{-1}): 3323 (NH_2), 3228 (NH), 1675 (C=O); ^{1}HNMR ($CDCl_3$): δ 3.22 (s, 3H, OCH_3), 3.85 (bs, 2H, NH_2), 5.08 (s, 2H, CH_2), 6.89-7.05 (d, 4H, Ar-H), 8.44 (bs, 1H, NH); LC-MS m/z 197 (M+1). Anal. Calc. for $C_9H_{12}N_2O_3$: C, 55.09; H, 6.16; N, 14.28. Found: C, 55.04; H, 5.95; N, 14.24%.

4-(4-Methoxy-phenoxy)-butyric acid hydrazide (4h): Yield 82%; mp 84-86^{o}C;FT-IR (KBr, cm^{-1}): 3323 (NH_2), 3228 (NH), 1675 (C=O); ^{1}H NMR ($CDCl_3$): δ 2.26 (m, 2H, CH_2), 2.75 (t, 2H, $COCH_2$), 3.22 (s, 3H, OCH_3), 3.85 (bs, 2H, NH_2),4.07 (t, 2H, OCH_2), 6.89-7.05 (d, 4H, Ar-H), 8.44 (bs, 1H, NH); LC-MS m/z 225 (M+1). Anal. Calc. for $C_{11}H_{16}N_2O_3$: C, 58.91; H, 7.19; N, 12.49. Found: C, 58.94; H, 7.34; N, 12.58%.

Substituted phenoxy-acetic/butyric acids N'-[(4-phenyl-piperazin-1-yl)-o-tolyl-methyl]-hydrazide (7a–h): A mixture of the solution of phenoxy-acetic acid/ butyric acid hydrazide derivatives (**4a-h**)(0.015mol) in absolute ethanol was treated with formaldehyde (0.07mol). Then, phenylpiperazine (0.015mol) in absolute ethanol (10 mL) was added with stirring and the reaction mixture was stirred overnight. The precipitated Mannich base was collected by filtration and dried. Recrystalization was done from methanol to give compounds **7a**–**h**.

(4-Chloro-phenoxy)-acetic acid N'-(4-phenyl-piperazin-1-ylmethyl)-hydrazide (7a): Yield 87%; mp 114-116 ^{o}C; FT-IR (KBr, cm^{-1}): 1650 (C=O), 3250–3400 (NH–NH);^{1}H NMR (DMSO-d_6): δ 2.72 (s, 2H, CH_2), 3.04(bs, 4H, piperazine ring), 3.65(bs, 4H, piperazine ring), 4.33 (s, 2H, OCH_2), 6.84-7.48 (m, 9H, Ar-H), 8.25-8.95 (d, 2H, 2NH); ^{13}C NMR (DMSO-d_6): δ 43.6, 70.4, 83.6, 114.4, 118.5, 123.7, 126.5, 128.8, 131.2, 136.3, 145.6, 151.8, 164.1, 175.7. LC-MS m/z 376(M^+) and 377 (M+2). Anal. Calc. for $C_{19}H_{23}ClN_4O_2$: C, 60.88; H, 6.18. Found: C, 60.74; H, 6.11%.

4-(4-Chloro-phenoxy)-butyric acid N'-(4-phenyl-piperazin-1-ylmethyl)-hydrazide (7b): Yield 82%; mp 109-111^{o}C; FT-IR (KBr, cm^{-1}): 1635 (C=O), 3135–3345 (NH–NH); ^{1}H NMR (DMSO-d_6): δ 2.24 (s, 2H, CH_2), 2.32 (m, 2H, CH_2), 2.64 (t, 2H, $COCH_2$), 2.70 (bs, 4H, piperazine ring), 3.89 (bs, 4H, piperazine ring), 4.20 (t, 2H, OCH_2), 6.68-7.92 (m, 9H, Ar-H), 8.48-9.10 (d, 2H, 2NH); ^{13}C NMR (DMSO-d_6): δ 27.9, 35.5, 47.3, 72.7, 77.67, 79.6, 109.3, 122.7, 124.8, 128.4, 130.5, 136.1, 145.2, 151.1, 158.3, 178.2. LC-MS m/z 403 (M^+) and 405 (M+2). Anal. Calcd. for $C_{21}H_{27}ClN_4O_2$: C, 62.60; H, 6.75. Found: C, 62.46; H, 6.63%.

(3-Nitro-phenoxy)-acetic acid N'-(4-phenyl-piperazin-1-ylmethyl)-hydrazide (7c): Yield 89%; mp 111-113^{o}C; FT-IR (KBr, cm^{-1}): 1660 (C=O), 3140–3355 (NH–NH); ^{1}H NMR (DMSO-d_6): δ 2.32 (s, 2H, CH_2), 2.88 (bs, 4H, piperazine ring), 3.36 (bs, 4H, piperazine ring), 4.16 (s, 2H, CH_2), 6.85-8.32 (m, 9H, Ar-H), 8.43-9.21 (d, 2H, 2NH); ^{13}C NMR (DMSO-d_6): δ 41.3, 73.7, 90.4, 111.8, 119.6, 124.6, 125.7, 128.2, 131.6, 136.5, 146.1, 151.8, 160.5, 172.4. LC-MS m/z 386(M+1). Anal. Calc. for $C_{19}H_{23}N_5O_4$: C, 59.21; H, 6.01. Found: C, 59.16; H, 5.89%.

4-(3-Nitro-phenoxy)-butyric acid N'-(4-phenyl-piperazin-1-ylmethyl)-hydrazide (7d): Yield 79%; mp 106-108 ^{o}C; FT-IR (KBr, cm^{-1}): 1654 (C=O), 3150–3365 (NH–NH); ^{1}H NMR (DMSO-d_6): δ 2.26 (s, 2H, CH_2), 2.31 (m, 2H, OCH_2), 2.63 (t, 2H, $COCH_2$), 2.69 (bs, 4H, piperazine ring), 3.87 (bs, 4H, piperazine ring), 4.16 (t, 2H, OCH_2), 6.85-8.30 (m, 9H, Ar-H), 8.43-9.37 (d, 2H, 2NH); ^{13}C NMR (DMSO-d_6): δ 17.9,

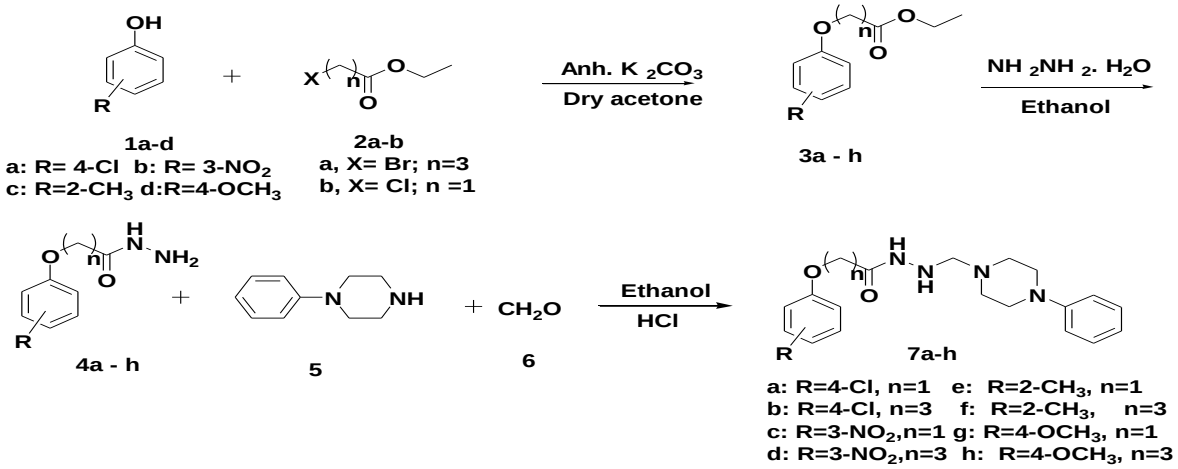
28.1, 39.5, 43.8, 73.5, 86.9, 118.7, 119.3, 124.7, 125.8, 123.2, 130.5, 136.2, 143.2, 154.2, 160.3, 170.4. LC-MS m/z 414(M+1). Anal. Calc. for $C_{21}H_{27}N_5O_4$: C, 61.00; H, 6.58. Found: C, 61.04; H, 6.32%.

o-Tolyloxy acetic acid N'-(4-phenyl-piperazin-1-ylmethyl)-hydrazide (7e): Yield 85%; mp 117-119 ^oC; FT-IR (KBr, cm^{-1}): 1660 (C=O), 3145–3370 (NH–NH); ^1H NMR (DMSO-d_6): δ 2.52 (s, 3H, CH_3), 2.65 (s, 2H, CH_2), 2.86 (bs, 4H, piperazine ring), 3.94 (bs, 4H, piperazine ring), 4.45 (s, 2H, CH_2), 6.76-8.22 (m, 9H, Ar-H), 8.68-9.45 (d, 2H, 2NH); ^{13}C NMR (DMSO-d_6): δ 21.5, 45.1, 57.9, 74.4, 80.5, 116.3, 120.3, 125.5, 126.7, 128.0, 131.2, 135.3, 144.4, 155.6, 160.6, 173.7. LC-MS m/z 355(M+1). Anal. Calc. for $C_{20}H_{26}N_4O_2$: C, 67.77; H, 7.39. Found: C, 67.53; H, 7.28 %.

4-o-Tolyloxy-butyric acid N'-(4-phenyl-piperazin-1-ylmethyl)-hydrazide (7f): Yield 82%; mp 110-112 ^oC; FT-IR (KBr, cm^{-1}): 1645 (C=O), 3145–3375 (NH–NH); ^1H NMR (DMSO-d_6): δ 2.56 (s, 2H, CH_2), 2.62 (m, 2H, CH_2), 2.77 (t, 2H, $COCH_2$), 2.88 (bs, 4H, piperazine ring), 3.54 (bs, 4H, piperazine ring), 4.46 (t, 2H, OCH_2), 6.97-8.23 (m, 9H, Ar-H), 8.76-9.56 (d, 2H, 2NH); ^{13}C NMR (DMSO-d_6): δ 25.5, 35.5, 43.5, 70.2, 84.5, 115.3, 119.7, 124.7, 126.1, 128.4, 130.5, 138.2, 144.5, 150.4, 160.5, 175.3. LC-MS m/z 383(M+1). Anal. Calc. for $C_{22}H_{30}N_4O_2$: C, 69.08; H, 7.91. Found: C, 68.87; H, 7.84 %.

(4-Methoxy-phenoxy)-acetic acid N'-(4-phenyl-piperazin-1-ylmethyl)-hydrazide (7g): Yield 88%; mp 113-115 ^oC; FT-IR (KBr, cm^{-1}): 1650 (C=O), 3155–3370 (NH–NH); ^1H NMR (DMSO-d_6): δ 2.65 (s, 2H, CH_2), 2.87 (bs, 4H, piperazine ring), 3.35 (s, 3H, OCH_3), 3.80 (bs, 4H, piperazine ring), 4.08 (s, 2H, CH_2), 6.95-8.09 (m, 9H, Ar-H), 8.53-9.65 (d, 2H, 2NH); ^{13}C NMR (DMSO-d_6): δ 28.9, 45.3, 53.6, 69.9, 80.5, 114.4, 118.5, 122.0, 126.3, 127.9, 129.1, 133.6, 141.0, 148.7, 157.6, 172.8. LC-MS m/z 371(M+1). Anal. Calc. for $C_{20}H_{26}N_4O_3$: C, 64.84; H, 7.07. Found: C, 64.71; H, 7.11 %.

4-(4-Methoxy-phenoxy)-butyric acid N'-(4-phenyl-piperazin-1-ylmethyl)-hydrazide (7h): Yield 83%; mp 106-108 ^oC; FT-IR (KBr, cm^{-1}): 1640 (C=O), 3140–3365 (NH–NH); ^1H NMR (DMSO-d_6): δ 2.58 (s, 2H, CH_2), 2.65 (m, 2H, CH_2), 2.67 (t, 2H, $COCH_2$), 2.78 (bs, 4H, piperazine ring), 3.30 (s, 3H, OCH_3), 3.85 (bs, 4H, piperazine ring), 4.47 (t, 2H, OCH_2), 6.95-8.16 (m, 9H, Ar-H), 8.58-9.60 (d, 2H, 2NH); ^{13}C NMR (DMSO-d_6): δ 25.8, 33.3, 48.1, 70.3, 88.1, 118.6, 120.7, 124.6, 126.3, 127.9, 130.1, 135.6, 148.0, 150.7, 159.6, 175.8. LC-MS m/z 399(M+1). Anal. Calc. for $C_{22}H_{30}N_4O_3$: C, 66.31; H, 7.59. Found: C, 66.26; H, 7.23%**,** as shown in scheme 1.



Scheme 1. Synthesis of phenoxy-acetic/butyric acids N'-[(4-phenyl-piperazin-1-yl)-o-tolyl-methyl]-hydrazides (7a-h)

RESULTS AND DISCUSSION

We report herein the Mannich nucleophilic addition reaction of phenylpiperazine 5 with phenoxy-acetic/ butyric acid hydrazide derivatives 4a-h and in the presence of formaldehyde6 (Scheme 1). As key reaction intermediates, eight phenoxy-acetic/ butyric acid hydrazide derivatives 4a-h were prepared in two steps from the commercially available phenols 1a-d by refluxed with 2a-b in the presence of K_2CO_3 in acetone yielded phenoxy acetic/ butyric acid ethyl ester derivatives 3a-h, the structure of compounds 3a-h have confirmed by the disappearance of OH stretching and appearance of carbonyl stretching band for the ester group in the IR absorption spectra. The proton NMR observations revealed that, broad singlet for OH proton was disappeared and a triplet and quartet for CH_3 and CH_2 protons respectively were appeared. The compounds 3a-h on treatment with hydrazine hydrate in ethanol afforded phenoxy-acetic/ butyric acid hydrazides 4a-h, which were established by the appearance of NH_2 stretching band of amide in the IR spectra. In proton NMR, the appearance of NH_2 and NH protons and disappearance of triplet and quartet peaks for CH_3 and CH_2 protons, respectively has confirmed the formation of the product. New Mannich bases (7a-h) were obtained by the reaction of phenylpiperazine 5with phenoxy-acetic/ butyric acid hydrazide derivatives 4a-h in the presence of formaldehyde6 in good yields. In IR spectra of compounds 7awas confirmed by the appearance of one more NH and disappearance of the NH_2 absorption peak. In addition, ^{1}H NMR spectra showed disappearance of NH_2 protons and an increase in one more NH proton peaks, as well as by the appearance of two characteristic bands corresponding to eight protons of piperazine ring which clearly evidence the formation of compound 7a. Further, all the target compounds 7a-h were clearly confirmed by ^{13}C NMR and mass spectra.

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