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Synthesis of N-Mannich bases from 5-((4-methylpiperazin-1-yl)methyl)-1,3,4-oxadiazole-2-thiol

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Abstract Methyl (4-methylpiperazin-1-yl)acetate (**2**) were synthesized by the condensation of compound (**1**) with ethyl bromoacetate in basic media. The synthesis of acid hydrazide derivatives (**3**) was brought about as a result of the reaction between compound (**2**) aand hydrazine hydrate. In the presence of basic conditions, the reaction of 2-(4-methylpiperazin-1-yl)acetohydrazide (**3**) with carbon disulfide resulted in the formation of 5-((4-methylpiperazin-1-yl)methyl)-1,3,4-oxadiazole-2-thiol (**4**). The reactions of (**4**) with different primary and secondary amines in the presence of formaldehyde ledato the formation of the corresponding Mannich bases (**5a-f**).

1. Introduction

In the synthesis of a broad range of bioactive components, the Mannich reaction is an essential stage in the process of synthesis. In the development of secondary and tertiary amine derivatives [1–3], it is an extremely important step in the process. The *N*-Mannich bases that are synthesized from NH-heterocycles and other compounds that are structurally linked to them have the potential to display a diverse range of pharmacological activities. Antimicrobial treatment is one example of these behaviors [4–6], antifungal [7], anti-HIV [8], antitubercular [9], neuroprotection [10], and anticancer activity. In a recent publication [11], the amazing biological activity associated with N-substituted isoindolin-1,3 diones was investigated.

These diones are members of an important group of compounds. It has been demonstrated that they are efficient against a number of different types of fungi [12], as well as inflammation and pain [13], convulsions [14], and bacteria [15], in addition to being antioxidants and hemolysers. N-Mannich bases of isoindolin-1,3-dione (phthalimide) and Mannich bases containing a phthalimide moiety have been discovered to be highly effective antibacterial, anthelmintic, and insecticidal agents [16,17]. These compounds are significant from a synthetic as biologically active compound.

Therefore, the use of the 5-((4-methylpiperazin-1-yl)methyl)-1,3,4-oxadiazole-2-thiol 4 in the N-Mannich process is going to be the primary focus of this investigation. The general schematic representation of the synthesis of N-Mannich Bases from 5-((4-methylpiperazin-1-yl)methyl)-1,3,4-oxa diazole-2-thiol **(4)** is given in the fig 1.

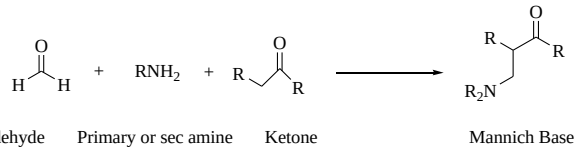

Fig. 1- The general schematic representation of Mannich reaction

2. Experimental Section

2.1. Chemistry

All of the chemicals were obtained from Fluka Chemie AG Buchs, which is located in Buchs, Switzerland, and utilized in its original form. The

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melting points of the synthetic compounds were determined using a Büchi B-540 melting point instrument and open capillaries. The results have not been adjusted for accuracy. A technique known as thin-layer chromatography (TLC) was performed on silica gel 60 F254 aluminum sheets in order to monitor the reactions. To locate the peaks, ultraviolet light was employed in conjunction with a mobile phase that was composed of ethyl acetate and ethyl ether in a ratio of 1:1. When recording FT-IR spectra, a spectrometer from at he 1600 series of Perkin Elmer's FTIR was used. ^{1}H NMR and ^{13}C NMR spectra were registered in DMSO-*d6* on a BRUKER AVENE II 400 MHz NMR Spectrometer (400.13 MHz for ^{1}H and 100.62 MHz for ^{13}C) or Varian-Mercury 200 MHz NMR Spectrometer (200 MHz for ^{1}H and 50 MHz for ^{13}C). Chemical shifts are given in ppm with respect to Me_4Si as an internal standard.

2.1.1 Ethyl 2-(4-methylpiperazin-1-yl)acetate (2)

To a solution of compound 1 (10 mmol) in tetrahydrofuran, triethylamine (20 mmol) was added, and after stirring for a period at room temperature, ethyl bromoacetate (10 mmol) was added dropwise; the mixture was then stirred for 24 hours at room temperature. Then, the solution was evaporated until it was completely dry, and the resulting white solid was filtered out.

Yield: % 89, m.p: 85-87°C. FT IR (υ_{max}, cm^{-1}): 1734 (C=O). ^{1}H NMR (DMSO-d_6, δ ppm): 1.17-1.20 (3H, m, CH_3), 1.99 (2H, s, CH_2), 2.14 (2H, s, CH_2), 2.30 (2H, s, CH_2), 3.17 (2H, s, CH_2), 3,40 (2H, d, *J*= 4,0 Hz, CH_2), 4,08 (3H, t, *J*= 16,0 Hz, CH_3). ^{13}C NMR (DMSO-d_6, δ ppm): 14.57 (CH_3), 46.17 (CH_3), 53.24 (CH_2), 55.06 (CH_2), 58.98 (CH_2), 60.20 (CH_2), 63.93 (CH_2), 170.36 (C=O). EI MS *m/z* (%): 173.25 ($[M+1]^+$, 100), 195.40 ($[M+Na]^+$, 70).

2.1.2. 2-(4-methylpiperazin-1-yl)acetohydrazide (3)

Compound 2 (10 mmol) was dissolved in ethanol, and then hydrazine hydrate (25 mmol) was added to the mixture, which was then refluxed for 15 hours. After a night in the fridge, the white solid was filtered off, and the crude product was crystallized in ethanol/water (2:1).

Yield: % 85, m.p: 134-136 ^{0}C. FT IR (υ_{max}, cm^{-1}): 1734 (C=O). ^{1}H NMR (DMSO-d_6, δ ppm): 2. 14 (3H, s, CH_3), 2.30 (2H, s, CH_2), 2.40 (4H, s, $2CH_2$), 2.88 (4H, s, $2CH_2$), 3.75 (2H, brs, NH_2), 8.84 (1H, s, NH). ^{13}C NMR (DMSO-d_6, δ ppm): 46.20 (CH_3), 53.21 ($2CH_2$), 55.01 ($2CH_2$), 60.37 (CH_2), 168.69 (C=O). EI MS *m/z* (%): 173.89 ($[M+1]^+$, 100), 195.75 ($[M+Na]^+$, 75).

2.1.3. 5-((4-methylpiperazin-1-yl)methyl)-1,3,4-oxadiazole-2-thiol (4)

The mixture of compound 3 (10 mmol) and carbon disulfide (20 mmol) in absolute ethanol was refluxed in the presence of dried potassium hydroxide (10 mmol) for 14 h. Then, the resulting solution was cooled to room temperature and acidified with acetic acid. The precipitate formed was filtered off, washed with water, and recrystallized from ethyl acetate:petroleum ether (1:3) Yield 72 %. M.p: 210–212^{0}C. FT IR (υ_{max}, cm^{-1}): 2755 (SH), 1596 (C=N), 1172 (C=S). ^{1}H NMR (DMSO-d_6, δ ppm): 2.44 (3H, s, CH_3), 2.65 (2H, s, CH_2), 2.88 (2H, s, CH_2), 3.10 (2H, s, CH_2), 3.48 (2H, s, CH_2), 3.78 (2H, s, CH_2) 13.95 (1H, s, SH). ^{13}C NMR (DMSO-d_6, δ ppm): 15.20 (CH_3), 50.51 (CH_2), 52.10 (CH_2), 53.69 (CH_2), 54.12 (CH_2), 55.12 (CH_2), 166.20 (C), 185.36 (C=S). EI MS *m/z* (%): 215.63 ($[M+1]^+$, 100), 189.52 (75), 110.23 (51).

2.2. General Method for the Synthesis of Compounds 5a-f

Following adding appropriate amine (10 mmol) to a solution of the corresponding compound 4 (10 mmol) in dimethyl formamide, the mixture was stirred for 24 hours at room temperature in the presence of formaldehyde (30 mmol). To obtain the required chemical, the solid precipitate was first filtered out, then washed with water, and finally recrystallized from a mixture of 1:1 dimethyl sulfoxide and water.

2.2.1 5-((4-methylpiperazin-1-yl)methyl)-3-(morpholinomethyl)-1,3,4-oxadiazole-2(3H)-thione (5a)

Yield 80 %. M.p: 198-200^{0}C. FT IR (υ_{max}, cm^{-1}): 1585 (C=N). ^{1}H NMR (DMSO-d_6, δ ppm): 2.28 (3H, s, CH_3), 2.43 (2H, s, CH_2), 2.45 (2H, s, CH_2), 2.49 (2H, s, CH_2), 2.60 (2H, s, CH_2), 2.78 (t, *J*=4.45, 4H, CH_2-N-CH_2), 3.58 (t, *J*=4.40, 4H, CH_2-O-CH_2), 5.16 (s, 2H, N-CH_2-N).

^{13}C NMR (DMSO-d_6, δ ppm): 46.05 (CH_3), 49.24 (CH_2), 52.85 (CH_2), 53.47 ($2CH_2$), 54.48 ($2CH_2$), 64.86 ($2CH_2$), 66.82 ($2CH_2$), 156.80 (C), 183.84 (C=S). EI MS *m/z* (%): 313.85 ($[M+1]^+$, 100), 247.52 (85), 178.12 (71), 113.65 (53).

2.2.2. 5-((4-methylpiperazin-1-yl)methyl)-3-(thiomorpholinomethyl)-1,3,4-oxadiazole-2(3H)-thione (5b)

Yield 82 %. M.p: 202-204^{0}C. FT IR (υ_{max}, cm^{-1}): 1578 (C=N). ^{1}H NMR (DMSO-d_6, δ ppm): 2.30 (3H, s, CH_3), 2.45 (2H, s, CH_2), 2.47 (2H, s, CH_2), 2.52 (2H, s, CH_2), 2.63 (2H, s, CH_2), 2.67 (2H, s, CH_2) 2.70 (2H, s, CH_2), 3.73 (2H, s, CH_2), 3.81 (2H, s, CH_2), 4.22 (2H, s, CH_2), 5.10 (2H, s, CH_2). ^{13}C NMR (DMSO-d_6, δ ppm): 46.10 (CH_3), 49.57 (CH_2), 52.78 (CH_2), 53.41 ($2CH_2$), 54.40 ($2CH_2$), 64.78 ($2CH_2$), 66.80 ($2CH_2$), 156.85 (C), 183.90 (C=S). EI MS *m/z* (%): 330.52 ([M+1]$^+$, 100), 279.02 (85), 245.36 (70), 198.52 (54).

2.2.3. 3,5-bis((4-methylpiperazin-1-yl)methyl)-1,3,4-oxadiazole-2(3H)-thione (5c)

Yield 84 %. M.p: 189-191^{0}C. FT IR (υ_{max}, cm^{-1}): 1598 (C=N). ^{1}H NMR (DMSO-d_6, δ ppm): 2.27 (3H, s, CH_3), 2.28 (3H, s, CH_3), 2.40 (4H, s, $2CH_2$), 2.42 (2H, s, CH_2), 2.50 (2H, s, CH_2), 2.58 (2H, s, CH_2), 2.60 (2H, s, CH_2) 2.61 (2H, s, CH_2), 3.82 (2H, s, CH_2), 4.23 (2H, s, CH_2), 5.07 (2H, s, CH_2).^{13}C NMR (DMSO-d_6, δ ppm): 30.12 (CH_3), 32.89 (CH_3), 48.37 (CH_2), 51.70 (CH_2), 53.92 ($2CH_2$), 54.49 ($2CH_2$), 64.65 ($2CH_2$), 66.89 ($2CH_2$), 156.12 (C), 183.88 (C=S). EI MS *m/z* (%): 327.90 ([M+1]$^+$, 100), 270.19 (73), 190.52 (59), 171.30 (48).

2.2.4. 3-((furan-2-ylmethylamino)methyl)-5-((4-methylpiperazin-1-yl)methyl)-1,3,4-oxadiazole-2(3H)-thione (5d)

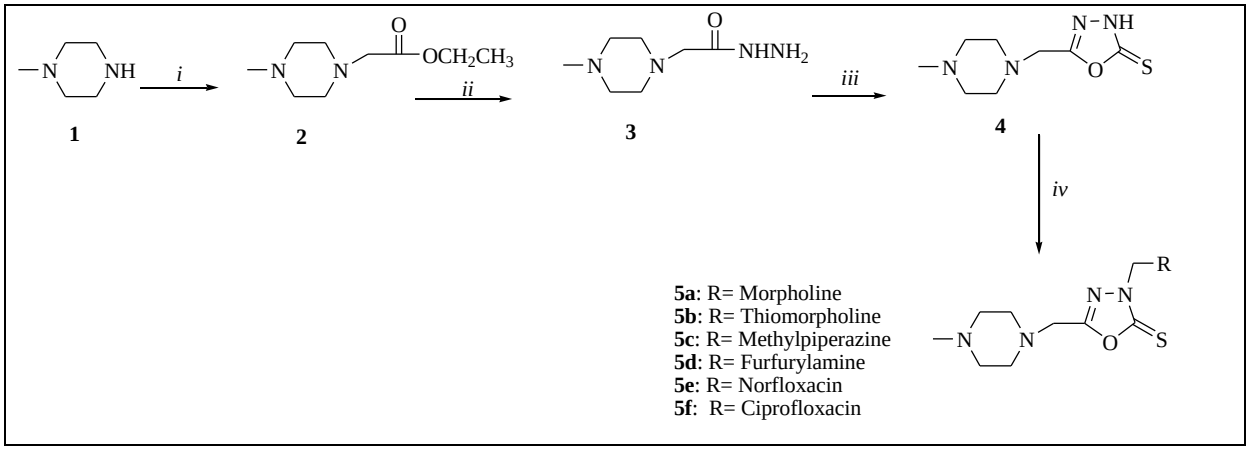
Yield 86 %. M.p: 178-180^{0}C. FT IR (υ_{max}, cm^{-1}): 3215 (NH), 1581 (C=N). ^{1}H NMR (DMSO-d_6, δ ppm): 2.39 (3H, s, CH_3), 2.39 (2H, s, CH_2), 2.44 (2H, s, CH_2), 2.59 (2H, s, CH_2), 2.61 (2H, s, CH_2), 2.67 (2H, s, CH_2) 2.75 (2H, s, CH_2), 4.22 (2H, s, CH_2), 4.63 (2H, s, CH_2), 5.14 (1H, s, NH). 6.19 (1H, s, furf), 6.24 (1H, s, furf), 7.28 (1H, s, furf). ^{13}C NMR (DMSO-d_6, δ ppm): 32.12 (CH_3), 47.71 (CH_2), 56.63 ($2CH_2$), 63.79 ($2CH_2$), 65.97 ($2CH_2$), 119.52 (CH), 120.12 (CH), 122.67 (CH), 155.29 ©, 157.12 ©, 181.20 (C=S). EI MS *m/z* (%): 324.63 ([M+1]$^+$, 100), 198.30 (77), 170.12 (51), 152.39 (43).

2.2.5. 1-ethyl-6-fluoro-7-(4-((5-((4-methyl piperazin-1-yl)methyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)methyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (5e)

Yield 91 %. M.p: 232-235 ^{0}C. FT IR (υ_{max}, cm^{-1}): 3385 (OH), 1593 (C=N), 1723 (C=O), 1741 (C=O). ^{1}H NMR (DMSO-d_6, δ ppm): 1.20 (3H, s, CH_3), 1.47 (3H, s, CH_3), 2.43 (2H, s, CH_2), 2.49 (2H, s, CH_2), 2.63 (2H, s, CH_2), 2.80 (2H, s, CH_2), 2.87 (2H, s, CH_2) 3.56 (2H, s, CH_2), 3.62 (2H, s, CH_2), 3.90 (2H, s, CH_2), 4.09 (2H, s, CH_2), 4.73 (2H, s, CH_2), 5.31 (2H, s, CH_2), 6.34 (1H, s, arH), 7.49 (1H, s, arH), 8.08 (1H, s, arH), 12.14 (1H, s, OH).^{13}C NMR (DMSO-d_6, δ ppm): 19.20 (CH_3), 24.52 (CH_3), 48.23 (CH_2), 54.89 ($2CH_2$), 61.70 ($2CH_2$), 63.49 ($2CH_2$), 65.55 (CH_2), 66.10 (CH_2), 67.35 (CH_2), 68.43 (CH_2), arC: [114.12 (CH), 116.98 (CH), 126.58 (C), 127.37 (C), 128.30 (C)] 131.89 (C), 136.89 (C), 148.73 (quinolone CH), 175.12 (C=O), 176.52 (C=O), 181.20 (C=S). EI MS *m/z* (%): 546.52 ([M+1]$^+$, 100), 198.12 (78), 170.36 (55).

2.2.6. 1-cyclopropyl-6-fluoro-7-(4-((5-((4-methyl piperazin-1-yl)methyl)-2-thioxo-1,3,4-oxa diazol-3(2H)-yl)methyl)piperazin-1-yl)-4-oxo-1,4-di hydroquinoline-3-carboxylic acid (5f)

Yield 93 %. M.p: 237-239 ^{0}C. FT IR (υ_{max}, cm^{-1}): 3324 (OH), 1593 (C=N), 1713 (C=O), 1739 (C=O). ^{1}H NMR (DMSO-d_6, δ ppm): 1.41 (3H, s, CH_3), 2.38 (2H, s, CH_2), 2.45 (2H, s, CH_2), 2.57 (2H, s, CH_2), 2.79 (2H, s, CH_2), 2.96 (2H, s, CH_2), 3.57 (2H, s, CH_2), 3.69 (2H, s, CH_2), 3.83 (2H, s, CH_2), 4.12 (2H, s, CH_2), 4.64 (2H, s, CH_2), 5.26 (2H, s, CH_2), 5.70 (2H, s, CH_2), 6.98 (1H, s, arH), 7.10 (1H, s, arH), 8.20 (1H, s, CH), 9.21 (1H, s, CH), 15.03 (1H, s, OH). ^{13}C NMR (DMSO-d_6, δ ppm): 17.13 (CH_3), 40.23 (CH_2), 51.89 ($2CH_2$), 57.96 ($2CH_2$), 61.10 ($2CH_2$), 63.79 (CH_2), 64.07 (CH_2), 65.10 (CH_2), 66.53 (CH_2), 67.27 (CH_2), 107.12 (CH), arC: [112.03 (CH), 113.79 (CH), 124.79 (C), 126.81 (C), 129.41 (C), 145.12 (C)] 134.10 (C), 137.90 (C), 148.12 (quinolone CH), 177.23 (C=O), 179.15 (C=O), 181.66 (C=S). EI MS *m/z* (%): 558.10 ([M+1]$^+$, 100), 340.12 (76), 210.12 (63), 198.13 (40).



Scheme 1: *i*. $BrCH_2COOEt$, EtOH; *ii*. NH_2NH_2, EtOH; *iii*: CS_2, KOH, EtOH, *iv*: dimethyl formamide, seconder amine, room temperature, 24 h.

3. Results and Discussion

During the research process, we made an attempt to synthesize various new 1,3,4-oxadiazoles mannich derivates. The structure of the target products was determined by using data from ^{1}H NMR, ^{13}C NMR, FT IR, and EI-MS. The synthetic procedures that were applied in order to obtain the compounds of interest are presented in Scheme 1.

By using a wide variety of amines in the synthesis process, research were able to successfully produce a variety of N-Mannich bases of 1,3,4-oxadiazole 4, with yields ranging anywhere from 80% to 93%. Compound (**2**) IR spectra showed pronounced absorption at 1734 cm^{-1} (C=O), while its ^{1}H-NMR spectra displayed five singlets (-CH_2) between 1.99 and 3.39 ppm. Compound (**3**) ^{1}H NMR spectra didn't have any signals that belonged to the -OCH_2CH_3 group, hence this can be concluded. Instead, new signals were created from the hydrazide structure, and these signals indicated between 3.75 ppm (–$NHNH_2$) and 8.84 ppm (–$NHNH_2$) when integrating for two proton and one proton, respectively (controlled by changing with D_2O). As seen in our previous studies, nh-nh2 peaks are observed in these intervals [18]. The infrared spectra of acid hydrazides (**3**) showed the occurrence of a novel peak at 1734 cm^{-1}, which was determined by their chemical composition. Compound (**4**) was made as a result of the treatment of compound (**3**) with carbon disulfide in basic media. Because of this treatment, the hydrazide side chain was converted into the 1,3,4-thiadiazole ring, which led to the synthesis of compound (**4**). The fact that 1,3,4-oxadiazoles can exist in their mercapto-thioxo tautomeric forms [19-21] is common knowledge. The infrared spectra of compound (**4**) revealed two stretching bands as a result of this tautomerism. Another of these bands, seen at 2755 cm^{-1}, corresponds to the –SH group, and the other band, recorded at 1172 cm^{-1}, reflects the presence of the -C=S group. As seen in the literature studies, the -SH peak is observed in these intervals [22]. When these bands were seen, they were found to be stretching in directions that were diametrically opposed to one another. In addition, the outcomes of the NMR, mass, and elemental tests performed on compound (**4**) were satisfactory. Compounds (**5a-f**) were produced by carrying out the Mannich reaction on compound (**4**) with a number of different amines in the presence of a solution of formaldehyde. During the process of creating compounds (**5a-f**), this reaction was one of the steps that was carried out. In the ^{1}H NMR and ^{13}C NMR spectra of compounds, additional signals coming from amine moieties were observed at the attended chemical ranges. These signals were observed at the molecular ranges that were being addressed to. The spectra of the molecules revealed the presence of these signals. There is no evidence that shows the presence of the NH band on the ^{1}H NMR or FT-IR spectra of any of the products (**5a-f**). On the other hand, in the spectra of the molecules' ^{1}H NMR and ^{13}C NMR, additional signals that came from amine moieties were found at the concerned chemical ranges. These signals were observed at the chemical ranges that were under investigation. This suggests that the NH band is absent from the spectrum. Recordings of mass spectrum data showed that these molecules displayed information that was in line with their structures.

3. Conclusion

In this study, methyl piperazine was first converted to an ester derivative and then to a hydrazide derivative. Then the hydrazide compound was converted to the

oxadiazole derivative compound. By reacting the 1,3,4-oxadiazole derivative compound with different amines, some Mannich derivative compounds were formed. For the characterization of all synthesized compounds, melting point determination, Infread spectrum, ^{1}H-NMR spectrum and ^{13}C-NMR measurements were made. As a result of all the characterization studies, the structures of the synthesized compounds were confirmed.

Statement of Research and Publication Ethics

The study is complied with research and publication ethics

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