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Synthesis and Characterization of Several Mannich Bases Derived from 2-(4-methylpiperazin-1-yl)acetohydrazide

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Abstract
This study explores the transformation of 2-(4-methylpiperazin-1-yl)acetohydrazide (1) through its reaction with phenylisothiocyanate (2), resulting in the formation of a novel urea derivative (3). The synthesis involves an intramolecular ring closure, where the hydrazide functionality plays a crucial role, leading to the formation of a 1,2,4-triazole structure. The journey continues as the 1,2,4-triazole derivative undergoes a Mannich reaction, leveraging its active methylene group. By reacting Compound 3 with formaldehyde and a selection of primary or secondary amines, a β-aminocarbonyl compound is synthesized, showcasing a significant molecular transformation.
The structural elucidation of the synthesized compounds is carried out using a range of sophisticated analytical techniques, including mass spectrometry, infrared (IR) spectroscopy, and nuclear magnetic resonance (NMR) spectroscopy for both ^{1}H and ^{13}C nuclei. These methods provide deep insights into the molecular architecture, enabling the determination of atomic connectivity and the identification of functional groups, thus confirming the integrity and structure of the synthesized molecules.

1. Introduction

Heterocyclic compounds are integral to the field of chemistry, particularly in pharmaceutical development, due to their unique ability to incorporate heteroatoms like nitrogen, oxygen, or sulfur into their ring structures. These compounds exhibit a broad spectrum of biological activities, which makes them critical targets in medicinal chemistry [1]. The structural diversity of heterocycles has led to the discovery of new therapeutic agents, including antimicrobials, anti-inflammatory drugs, anticancer agents, and antioxidants [2,3]. Among these, five-membered heterocyclic rings such as triazoles and diazoles have gained significant attention due to their potent biological properties [4,5].
Triazoles, in particular, are heterocyclic compounds characterized by the presence of three contiguous nitrogen atoms [6]. Their exceptional stability and ability to form hydrogen bonds enhance their solubility and binding affinity for biomolecular targets [7]. These characteristics make triazoles attractive scaffolds for the development of bioactive molecules [8]. Triazole-containing drugs such as fluconazole, voriconazole, and ravuconazole are widely used antifungal agents in clinical practice, demonstrating the therapeutic potential of this functional group [9,10]. Beyond antifungal activity, triazoles have also shown antibacterial, antiviral, anticancer, and anti-inflammatory effects, making them versatile candidates in drug discovery [11,12].
Fluoroquinolones are another class of compounds with significant antibacterial efficacy. These drugs inhibit DNA replication and transcription in bacteria by stabilizing the complex between DNA and topoisomerases, specifically targeting enzymes such as DNA gyrase and topoisomerase IV [13,14]. While early quinolones like nalidixic acid exhibited limited activity due to their narrow spectrum [15], the introduction of fluorine atoms at the C6 position in fluoroquinolones led to a significant enhancement in antibacterial potency and pharmacokinetics [16]. This structural modification, along with further advancements in fluoroquinolone chemistry, has expanded their clinical utility against a broad range of bacterial infections (Figure 1) [17].

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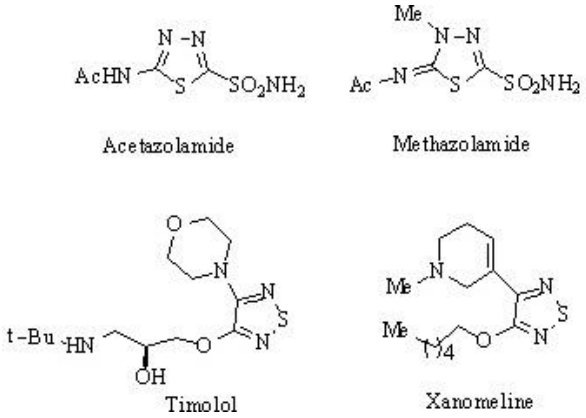


Figure 1: Some Selected Thiadiazole-Based Drugs

Research into bioactive heterocyclic compounds has consistently demonstrated the potential of these molecules in various therapeutic areas [18]. Triazoles and thiadiazoles, in particular, have emerged as critical components in the design of new drugs due to their diverse biological activities [19,20]. Compounds containing 1,2,4-triazole and 1,3,4-thiadiazole moieties have been reported to exhibit anticancer, antibacterial, antifungal, and antioxidant properties [21,22]. These heterocyclic structures are commonly incorporated into pharmaceuticals to enhance their biological efficacy [23]. Clinically used drugs like timolol, methazolamide, and acetazolamide highlight the medical importance of triazole and thiadiazole-containing compounds [24]. Their ability to interact with biological targets through hydrogen bonding and other interactions underpins their wide therapeutic applicability [25,26].

Triazoles are particularly noteworthy for their role as linker molecules in the design of hybrid drugs. By connecting two pharmacophores through a triazole moiety, researchers have been able to develop bifunctional drugs that target multiple biological pathways simultaneously, thereby enhancing therapeutic outcomes [27,28]. This strategy is exemplified by antifungal drugs like fluconazole and voriconazole, where the triazole group plays a critical role in improving drug-target interactions (Figure 2) [29]. Additionally, the triazole scaffold has been employed in the design of compounds with antibacterial, antiviral, and anticancer activities, broadening its application in drug development [30].

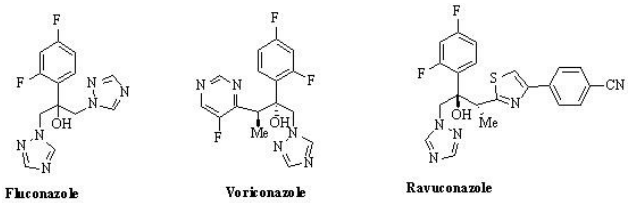


Figure 2: Some Selected Triazole-Based Drugs

Fluoroquinolones have also undergone substantial development over the years, particularly in addressing their limitations against Gram-positive bacteria [31]. Structural modifications, such as the introduction of nitrogen-containing heterocyclic rings at the C7 position, have expanded the antibacterial spectrum of fluoroquinolones and improved their pharmacokinetic profiles [32,33]. These modifications have resulted in the synthesis of widely used drugs like ciprofloxacin, norfloxacin, and ofloxacin, which exhibit broad-spectrum activity against a variety of bacterial pathogens [34]. Fluoroquinolones work by inhibiting DNA gyrase and topoisomerase IV, enzymes crucial for bacterial DNA replication [35]. This mode of action, combined with their ability to target both Gram-positive and Gram-negative bacteria, makes fluoroquinolones invaluable in clinical practice [36].

Recent studies have focused on further optimizing triazole and fluoroquinolone derivatives to enhance their biological activity and combat resistance mechanisms in pathogens [37]. For instance, fluoroquinolones have shown effectiveness against bacteria resistant to beta-lactam and aminoglycoside antibiotics, making them critical in treating drug-resistant infections [38]. Ongoing research in this area aims to develop new compounds that retain efficacy against resistant strains, thereby addressing one of the most pressing challenges in modern medicine [39,40]. Figure 3 showcases a selection of notable fluoroquinolone-containing compounds, highlighting their diverse applications and structural innovations.

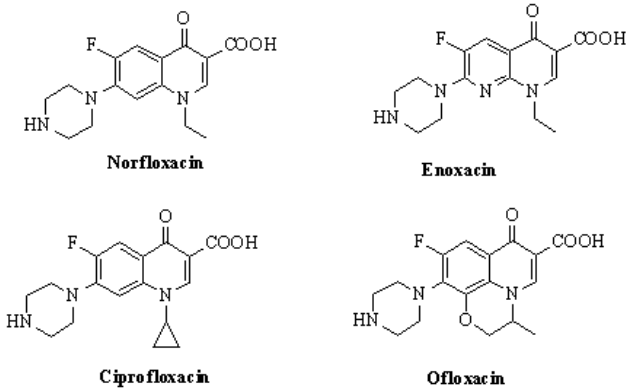


Figure 3: Chemical Structures of Selected Fluoroquinolones

Regarding their mechanism of action, FQs prevent bacteria from replicating and transcribing DNA by maintaining the stability of the complex formed between DNA and topoisomerases. Quinolones function by modifying the enzymes they specifically target, gyrase and topoisomerase IV, causing them to become detrimental and disrupt the

structure of the bacterial chromosome. Resistance related to the target is a widely observed and highly significant form of resistance in clinical settings. These mutations weaken the interactions between quinolones and enzymes like gyrase and topoisomerase IV, leading to the main cause of the issue [41]. Additional resistance mechanisms involve safeguarding the target, deactivating the drug through metabolism, and controlling drug entry and exit [42–44]. By developing novel quinolones that remain effective against these modified enzymes, the potential of this drug class could be significantly enhanced in clinical applications.

2. Material and Method

2.1. Chemistry

In this study, commercially available reagents were used without further purification. Melting points of the synthesized compounds were measured using a Büchi B-540 melting point apparatus. Thin-layer chromatography (TLC) was performed on silica gel 60 F254 plates, using ethyl acetate and diethyl ether in a 1:2 ratio as the mobile phase, and the reaction progress was monitored under UV light. Infrared (IR) spectra were recorded on a Perkin Elmer 1600 series FTIR spectrometer. Nuclear magnetic resonance (NMR) spectra were obtained using a BRUKER AVENE II 400 MHz spectrometer, with DMSO-d6 as the solvent. Chemical shifts (δ) were reported in ppm relative to tetramethylsilane (TMS), and coupling constants (J) were given in Hz.

2-(4-Methylpiperazin-1-yl)Acetohydrazide (1)

Hydrazine hydrate (25 mmol) was added dropwise to a solution of the precursor compound (10 mmol) in ethanol. The reaction mixture was refluxed for 8 hours. After cooling, the crude product was purified by column chromatography using silica gel and a hexane/ethyl acetate mixture (7:3). Yield: 85%, m.p.: 134-136°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, CH_2). ^{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).

***N*-Phenyl-2-[(4-Methylpiperazin-1-yl)Acetyl]Hydrazinecarbothioamide (2)**

A solution of phenylisothiocyanate (20 mmol) was added to the hydrazide compound 1 (10 mmol) in dichloromethane. The reaction was stirred at room temperature for 24 hours. The resulting solid was filtered and crystallized from ethanol to yield the pure product. Yield: 91%, m.p.: 152-154°C. FT IR (υ_{max}, cm^{-1}): 3217 (NH), 3254 (NH), 1703 (C=O), 2145 (C=S). ^{1}H NMR (DMSO-d_6, δ ppm): 1.89 (3H, s, CH_3), 2.42 (2H, s, CH_2), 2.62 (2H, s, CH_2), 2.72 (2H, s, CH_2), 3.11 (2H, s, CH_2), 3.11 (2H, s, CH_2), 5.76 (2H, s, CH_2), 7.16-7.65 (5H, m, arH), 9.56 (2H, s, 2NH), 9.87 (1H, s, NH). ^{13}C NMR (DMSO-d_6, δ ppm): 44.81 (CH_3), 51.81 ($2CH_2$), 54.22 ($2CH_2$), 59.68 (CH_2), arC: [117.35 (CH), 121.48 (CH), 128.61 (CH), 129.43 (CH), 129.52 (CH), 141.66 (C)] 156.16 (C=O), 181.05 (C=S). EI MS *m/z* (%): 308.26 ($[M+1]^+$, 100), 330.15 ($[M+Na]^+$, 72), 203.19 (51), 113.58 (30)

5-((4-Methylpiperazin-1-yl)Methyl)-4-Phenyl-4H-1,2,4-Triazole-3-Thiol (3)

The carboxamide derivative (2) was treated with sodium hydroxide in ethanol and refluxed for 8 hours. The reaction mixture was then acidified to pH 4-5 using hydrochloric acid, and the resulting precipitate was purified by filtration and recrystallized from ethyl acetate. Yield: 75%, m.p.: 162-164°C. FT IR (υ_{max}, cm^{-1}): 3067 (aromatic CH), 2558 (SH). ^{1}H NMR (DMSO-d_6, δ ppm): 2.10 (3H, s, CH_3), 3.35 (10H, s, $5CH_2$), 6.91-7.60 (5H, m, arH),13.35 (1H, s, SH). ^{13}C NMR (DMSO-d_6, δ ppm): 25.52 (CH_3), 53.89 ($2CH_2$), 54.85 ($2CH_2$), 57.23 (CH_2), arC: [129.09 (CH), 129.42 (CH), 129.87 (CH), 129.92 (CH), 133.15 (CH), 140.62 (C)], 148.72 (triazole C-3), 165.82 (triazole C-5). EI MS *m/z* (%): 290.36 ($[M+1]^+$, 100), 169.78 (69), 134.15 (37), 111.23 (20).

General Method for The Synthesis of Compounds 4a-d: Mannich bases were synthesized by reacting compound 3 (10 mmol) with formaldehyde (30 mmol) and various amines in dimethylamine at room temperature for 24 hours. The precipitate was filtered, washed with water, and recrystallized from a dimethylsulfoxide (1:1) mixture to yield the desired compounds.

5-((4-Methylpiperazin-1-yl)Methyl)-2-(Morpholinomethyl)-4-Phenyl-2H-1,2,4-Triazole-3(4H)-Thione (4a)

Yield: % 85, m.p: 178-180°C. FT IR (υ_{max}, cm^{-1}): 3088 (aromatic CH). ^{1}H NMR (DMSO-d_6, δ ppm): 2.15 (3H, s, CH_3), 3.40 (16H, s, $8CH_2$), 4.23 (2H, d, *J*= 4.0 Hz, CH_2), 5.46 (2H, s, CH_2), 7.28 (2H, d, *J*= 4.0 arH), 7.65 (1H, s, arH), 7.98 (2H, d, *J*= 8.0 Hz, arH). ^{13}C NMR (DMSO-d_6, δ ppm): 28.36 (CH_3), 46.12 ($2CH_2$), 47.63 ($2CH_2$), 48.69 ($2CH_2$), 49.79 ($2CH_2$), 50.10 (CH_2), 52.63 (CH_2), arC: [121.45 (CH), 122.87 (CH), 123.96 (CH), 124.60 (CH), 126.70 (CH), 139.50 (C)], 151.52 (triazole C-3), 159.63 (triazole C-5). EI MS *m/z* (%): 110.12 (100), 389.89 ($[M+1]^+$, 92), 214.63 (69), 143.56 (29).

5-((4-Methylpiperazin-1-yl)Methyl)-4-Phenyl-2-((4-Phenylpiperazin-1-yl)Methyl)-2H-1,2,4-Triazole-3(4H)-Thione (4b)

Yield: % 80, m.p: 181-183°C. FT IR (υ_{max}, cm^{-1}): 3075 (aromatic CH), 3089 (aromatic CH). ^{1}H NMR (DMSO-d_6, δ ppm): 1.24 (3H, s, CH_3), 2.01 (2H, s, CH_2), 2.11 (2H, s, CH_2), 3.40 (10H, s, $5CH_2$), 4.37 (2H, s, CH_2), 4.70 (2H, s, CH_2), 5.76 (2H, s, CH_2), 6.94-7.27 (7H, m, arH), 7.49 (2H, d, *J*= 8.0 Hz, arH), 8.07 (1H, s, arH). ^{13}C NMR (DMSO-d_6, δ ppm): 21.14 (CH_3), 47.71 ($2CH_2$), 48.88 ($2CH_2$), 50.12 ($2CH_2$), 51.98 ($2CH_2$), 53.43 (CH_2), 55.79 (CH_2), arC: [112.85 (CH), 113.97 (CH), 114.96 (CH), 115.37 (CH), 118.93 (CH), 119.63 (CH), 120.12 (CH), 121.53 (CH), 122.38 (CH), 123.49 (CH), 139.12 (C), 140.46 (C)], 153.96 (triazole C-3), 157.83 (triazole C-5). EI MS *m/z* (%): 464.89 ($[M+1]^+$, 100), 300.19 (78), 178.12 (55), 112.09 (31).

1-Ethyl-6-Fluoro-7-(4-((3-((4-Methylpiperazin-1-yl)Methyl)-4-Phenyl-5-Thioxo-4,5-Dihydro-1,2,4-Triazol-1-yl)Methyl)Piperazin-1-yl)-4-Oxo-1,4-Dihydroquinoline-3-Carboxylic Acid (4c)

Yield: % 89, m.p: 252-254°C. FT IR (υ_{max}, cm^{-1}): 3312 (OH), 3083 (aromatic CH), 1698 (C=O), 1712 (C=O). ^{1}H NMR (DMSO-d_6, δ ppm): 1.17 (3H, s, CH_3), 1.42 (3H, s, CH_3), 2.73 (2H, s, CH_2), 2.82 (2H, s, CH_2), 2.89 (2H, s, CH_2), 3.39 (14H, s, CH_2), 6.95-7.27 (3H, m, arH), 7.49-7.56 (3H, m, arH), 7.87-7.95 (1H, m, arH), 8.93 (1H, s, CH), 15.35 (1H, s, OH). ^{13}C NMR (DMSO-d_6, δ ppm): 17.23 (CH_3), 21.25 (CH_3), 48.52 ($2CH_2$), 49.12 ($2CH_2$), 51.10 ($2CH_2$), 52.23 ($2CH_2$), 53.96 (CH_2), 54.30 (CH_2), 57.23 (CH_2), arC: [112.52 (CH), 113.12 (CH), 117.60 (CH), 119.63 (CH), 124.89 (CH), 125.43 (CH), 126.30 (CH), 138.12 (C), 139.50 (C), 140.12 (C), 141.23 (C), 143.98 (C), 144.07 (C)], 148.12 (quinolone CH), 155.13 (triazole C-3), 159.96 (triazole C-5), 171.12 (C=O), 173.20 (C=O).EI MS *m/z* (%): 389.12 (100), 621.89 ($[M+1]^+$, 90), 643.30 ($[M+Na]^+$, 71), 187.12 (36).

1-Cyclopropyl-6-Fluoro-7-(4-((3-((4-Methyl piperazin-1-yl)Methyl)-4-Phenyl-5-Thioxo-4,5-Dihydro-1,2,4-Triazol-1-yl)Methyl)Piperazin-1-yl)-4-Oxo-1,4-Dihydroquinoline-3-Carboxylic Acid (4d)

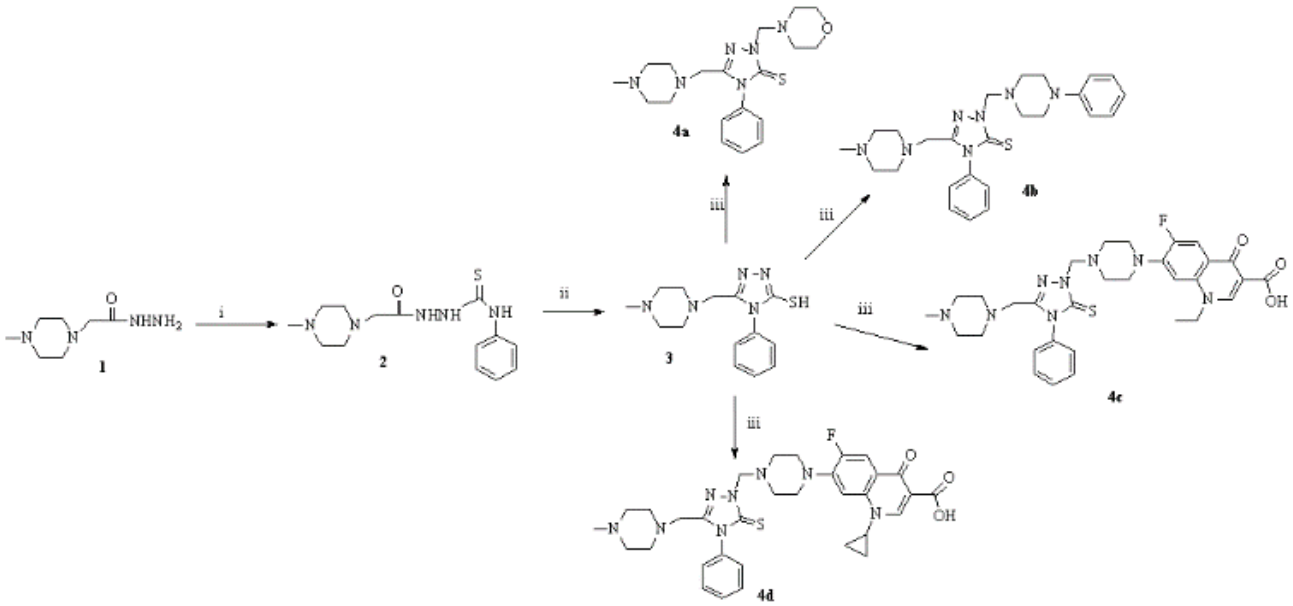
Yield: % 91, m.p: 250-252 °C. FT IR (υ_{max}, cm^{-1}): 3323 (OH), 3091 (aromatic CH), 1702 (C=O), 1723 (C=O). ^{1}H NMR (DMSO-d_6, δ ppm): 1.13 (3H, s, CH_2), 1.29 (3H, s, CH_2), 2.73 (3H, s, CH_3), 2.82 (2H, s, CH_2), 2.89 (2H, s, CH_2), 3.29 (2H, s, CH_2), 3.35 (8H, s, $4CH_2$), 4.33 (2H, d, *J*= 8.0 Hz, CH_2), 5.00 (2H, s, CH_2), 5.24 (2H, s, CH_2), 7.21-7.52 (7H, s, arH), 7.80 (1H, d, *J*= 12.0 Hz, CH), 8.65 (1H, s, CH), 15.23 (1H, s, OH). ^{13}C NMR (DMSO-d_6, δ ppm): 12.12 (CH_2), 14.78 (CH_2), 34.79 (CH_3), 37.98 (CH_2), 39.12 (CH_2), 40.65 (CH_2), 41.01 (CH_2), 43.50 (CH_2), 44.97 (CH_2), 45.32 (CH_2), 46.89 (CH_2), 47.81 (CH_2), 50.03 (CH_2), 103.12 (CH), arC: [115.12 (CH), 116.89 (CH), 121.20 (CH), 122.85 (CH), 126.50 (CH), 128.90 (CH), 130.41 (CH), 133.56 (C), 134.52 (C), 136.12 (C), 137.20 (C), 138.43 (C), 139.61 (C)], 148.34 (quinolone CH), 157.10 (triazole C-3), 160.12 (triazole C-5), 171.77 (C=O), 174.09 (C=O). EI MS *m/z* (%): 632.12 ($[M+1]^+$, 100), 498.12 (88), 346.98 (71), 219.52 (55).

3. Results and Discussion

3.1. Chemistry

This work involved the conversion of a carbox(thio)amide derivative (1) through an intramolecular cyclization reaction to produce 1,2,4-triazoles (2) as shown in Scheme 1. The molecule was identified by the presence of a signal at 13.35 ppm in the 1H NMR data, which was a singlet that could be exchanged with D2O. This confirmed the presence of a -SH group. The stretching band originating from these groups was observed at a wavenumber of 2558 cm-1 in the FT-IR data of this molecule.

Mannich bases are bioactive compounds [48–50]. Mannich bases (4a–d) were synthesized by reacting compound (3) with formaldehyde and several physiologically active amines (Scheme 1) [51, 52]. The hydroxyl (OH) peaks of molecules 4c and 4d, which belong to the fluoroquinolone ring, were observed with chemical shifts of 15.35 and 15.23 ppm, respectively, in the 1H NMR spectrum. The carbon-hydrogen (CH) peaks of molecules 4c and 4d, which belong to the fluoroquinolone ring, exhibited signals at 148.12 and 148.34 ppm in the 13C NMR spectrum.



Scheme 1: i: RNCS, EtOH, ii. NaOH, EtOH, H_2O; iii: dimethyl formamide, seconder amine, room temperature, 24

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4. Conclusion and Suggestions

In this study, the synthesis of a 1,2,4-triazole derivative was accomplished, starting from the precursor 2-(4-methylpiperazin-1-yl)acetohydrazide (1). Following the initial synthesis, a series of novel Mannich bases (4a-d) were obtained through a Mannich reaction with various amines, introducing structural diversity and potential for enhanced biological activity. The synthesized compounds are of significant interest due to their relevance in medicinal chemistry and widespread applications reported in the literature. Comprehensive structural characterization of these derivatives was carried out using a combination of advanced spectroscopic techniques, including infrared (IR) spectroscopy, proton nuclear magnetic resonance (^{1}H NMR), carbon-13 nuclear magnetic resonance (^{13}C NMR), and mass spectrometry, confirming their molecular frameworks and functional integrity. The successful synthesis and detailed structural validation of these compounds contribute valuable insights to the field, potentially paving the way for future studies on their pharmacological properties.

Statement of Research and Publication Ethics.

The study is complied with research and publication ethics

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