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Expedited Synthesis and Comprehensive Characterization of Oxomorpholine-Imidazole Derivatives: Unraveling their Remarkable Antimicrobial Activity

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Abstract

This research focuses on synthesizing aromatic or heteroaromatic compounds with potential pharmaceutical and medicinal applications. Imidazole derivatives have garnered significant attention due to their versatile therapeutic potential, encompassing a broad spectrum of diseases, including cancer, bacterial infections, fungal infections, and malaria. To accomplish this, we have developed an efficient synthetic route to explore a diverse array of 2-((1,4-diphenyl-1H-imidazol-2-yl)thio)-N-(4-(3-oxomorpholino)phenyl) acetamide derivatives. The structural elucidation of the synthesized compounds was carried out using advanced techniques, including ^{1}H and ^{13}C NMR, FT-IR spectroscopy, mass spectroscopy, and elemental analysis. Furthermore, the oxo morpholino-imidazole derivatives synthesized in this study were further employed to produce diverse chemotherapeutic agents with significant potential for clinical applications.

Keywords: Heteroaryl compounds; Oxomorpholine; 1,4-Diaryl imidazoles; Biological implications.

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1. Introduction

The imidazole moiety, a nitrogenous heterocycle with a five-membered ring, plays a significant role in heterocyclic chemistry. It consists of three carbon atoms, two nitrogen atoms, four hydrogen atoms, and two double bonds. The general molecular formula for imidazole is $C_3H_4N_2$. Notably, the nitrogen atoms are positioned at the first and third positions of the ring, which are non-adjacent to each other [1]. Imidazole exhibits amphoteric characteristics, functioning as both an acid and a base. It is prone to nucleophilic and electrophilic reactions. Imidazole is typically observed as a colorless or pale-yellow solid, possessing an odor reminiscent of amines. Structurally, it is classified as an aromatic heterocycle in the 1,3-diazole category [2]. The synthesis of imidazole was initially accomplished by Heinrich Debus in 1858 through a chemical process. Debus

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employed a combination of glyoxal, formaldehyde, and ammonia to produce imidazole, marking a significant milestone in the scientific understanding of this compound [3].

The imidazole nucleus serves as the central framework for several important components in human organisms. These include histidine, a vital amino acid, Vitamin B12, DNA base structures and purines, histamine, and biotin. The imidazole nucleus plays a critical role in various biological processes, underscoring its significance in human biology [4]. Nitrogen-containing heterocycles, including imidazole and benzimidazole rings, possess a wide array of biological activities owing to their structural resemblance to various natural and synthetic compounds known for their biological effects. These heterocycles have served as privileged scaffolds in developing pharmaceutical or biologically relevant therapeutic molecules. Notably, nitrogen-containing heterocycles have demonstrated diverse biological activities, a characteristic attributed partly to their structural similarities with biologically active molecules found in nature or created synthetically. The utilization of imidazole and benzimidazole rings as privileged scaffolds underscores their significance in developing therapeutically relevant compounds in the pharmaceutical and biological sciences [5]. Imidazole and its derivatives have garnered significant attention in medicine due to their multifaceted therapeutic potential. These compounds exhibit a remarkable array of medicinal activities, extending beyond traditional applications. They have shown promising effects as analgesics, antifungal agents [6], antihypertensives [9,10], anticancer agents [11], antivirals [16,17], antitubercular agents [18,19], antiulcer [20], anti-inflammatory agents [21-23], antidepressants [24,25], antidiabetic drugs [26-28], antiasthmatics [29], antimalarial [30-32]. The broad spectrum of therapeutic activities displayed by imidazole-based compounds paves the way for innovative drug development and potential treatment breakthroughs in various medical domains. Numerous instances exist where commercially available pharmaceuticals incorporate the imidazole nucleus. These drugs have been developed, tested, and approved for clinical use. Their availability in the commercial market underscores the practical application and relevance of imidazole-based compounds in medicinal contexts [1].

The current study focuses on synthesizing and comprehensively characterizing a heteroaryl 1,4-diaryl-imidazole compound incorporating 4-(4-aminophenyl)morpholin-3-one motifs. The compound was subjected to rigorous analysis using diverse analytical techniques. Moreover, the synthesized compound underwent lead discovery and optimization to explore its potential biological activities. The findings of this research contribute to advancing our understanding of the compound's characteristics and its potential for further development in the context of biological applications [33].

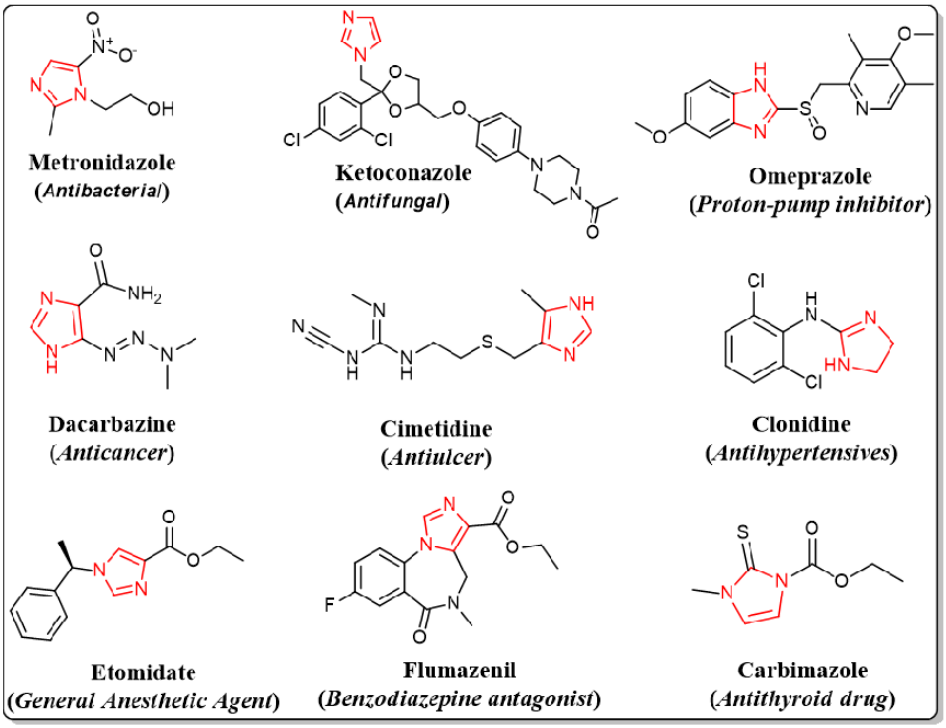

Fig. 1. Imidazole-based commercially available drugs.

2. Materials and Methods

The chemicals utilized for the synthesis were procured from reputable suppliers, namely Sigma-Aldrich, Spectrochem, Loba Chemie, and Merck, and were used as received. Reaction progress was monitored through Thin Layer Chromatography (TLC) using pre-coated silica gel GF254 plates. The IR spectra of the compounds were recorded using a Shimadzu-FTIR-8400 instrument, employing the KBr pellet technique. Mass Spectra were obtained using a Shimadzu GCMS-QP-2010 instrument, employing the Direct Injection Probe method. ^{1}H NMR and ^{13}C NMR spectra were recorded using a Bruker Avance-III 400MHz spectrometer, with trimethyl silane (TMS) as an internal standard.

3. General Reaction Scheme

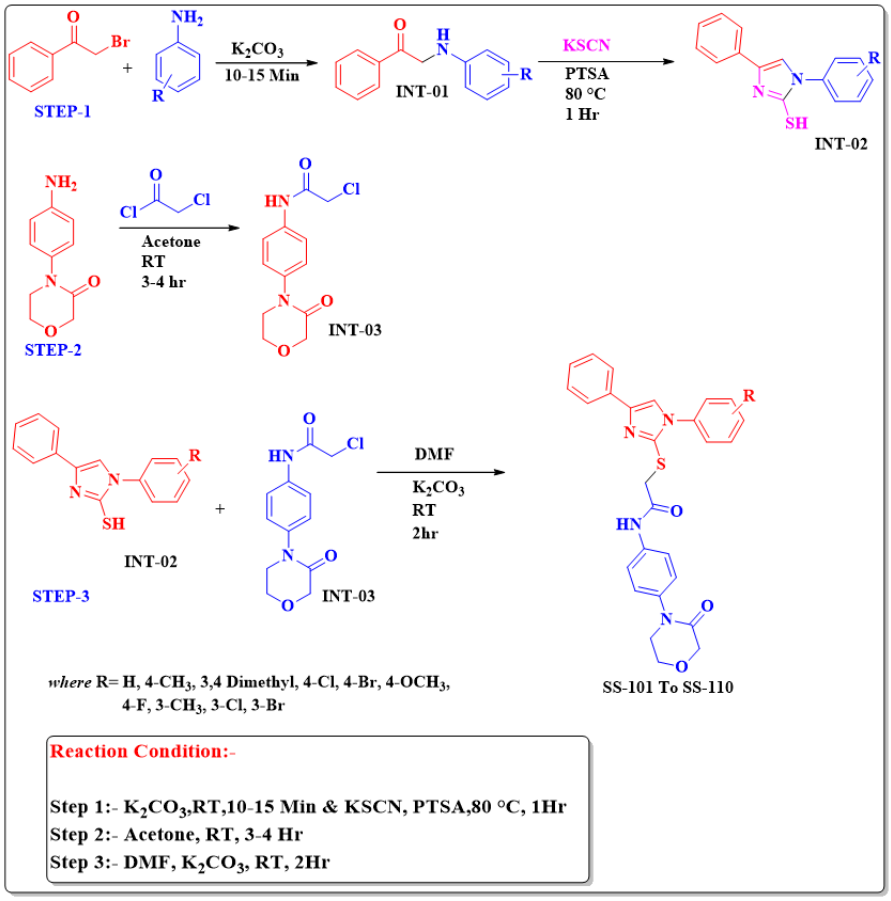

Fig. 2. General reaction scheme.

4. Experimental

4.1. *Synthesis of substituted 1-phenyl-2-(phenylamino)ethanone (INT-01)*

A mixture consisting of 1 mmol of phenacyl bromide and 1.1 mmol of the respective aniline derivative was prepared in a dry pestle and mortar. Anhydrous Na_2CO_3 or K_2CO_3 in a small quantity was added to the mixture. The components were meticulously ground until a homogeneous blend was obtained. During this process, an exothermic reaction took place, resulting in a temperature increase to approximately 45 °C within 2-3 min. The resulting solid, characterized by its yellow color, was thoroughly washed with ice-cold water to remove any remaining Na_2CO_3 or K_2CO_3. The solid was subsequently dried and, if necessary, subjected to recrystallization from ethanol.

4.2. *Synthesis of substituted 1,4-diphenyl-1H-imidazole-2-thiol (INT-02)*

A mixture containing 1 mmol of substituted 1-phenyl-2-(phenylamino)ethanone, 5 mmol of potassium thiocyanate, and 5 mmol of p-toluenesulphonic acid was vigorously ground using a pestle and mortar. The resulting mixture was then transferred to a conical flask and heated at 80-90 °C for 5-10 min. During the heating process, a yellow-colored solid precipitated. The solid was subsequently washed with water, filtered, and dried. Finally, the dried solid was subjected to crystallization from ethanol to obtain the desired product.

4.3. *Synthesis of 2-chloro-N-(4-(3-oxomorpholino)phenyl)acetamide (INT-03)*

An equivalent amount of amine was dissolved in acetone to prepare the amine solution. Then, chloroacetyl chloride was added dropwise to the solution using 1.1 equivalents. The resulting mixture was stirred at room temperature for 3-4 h. After the specified reaction time, the mixture was poured onto crushed ice, causing a solid intermediate product to form. The solid was isolated by filtration, washed with water, and dried. The solid intermediate product was subsequently employed in the subsequent synthesis step without undergoing additional purification.

4.4. *Synthesis of substituted 2-((1,4-diphenyl-1H-imidazol-2-yl)thio)-N-(4-(3-oxomorpholino)phenyl)acetamide (SS 101-110)*

A well-stirred solution of DMF (N, N-dimethylformamide) and K_2CO_3 (potassium carbonate) was prepared. INT-02 was added to this solution, and the resulting mixture was stirred for an additional 15 min at room temperature (R. T.). After this, INT-03 was introduced to the mixture and stirred for 2-3 h at room temperature to allow the reaction to proceed. Once the reaction was deemed complete, the reaction mixture was poured onto crushed ice, resulting in the formation of a solid precipitate. The solid product was isolated by filtration and purification using column chromatography employing an ethyl acetate and hexane solvent system.

5. Physical and Analytical Data

Table 1. Physical and analytical data.

Code	M. F.	R	M. W.	M. P. °C	% Yield
SMS-101	$C_{27}H_{24}N_4O_3S$	H	484.57	210-212	84
SMS-102	$C_{28}H_{26}N_4O_3S$	4-CH3	498.60	244-246	86
SMS-103	$C_{29}H_{28}N_4O_3S$	3,4 Dimethyl	512.62	252-254	89
SMS-104	$C_{27}H_{23}ClN_4O_3S$	4-Cl	519.01	276-278	87
SMS-105	$C_{27}H_{23}BrN_4O_3S$	4-Br	563.47	268-270	83
SMS-106	$C_{28}H_{26}N_4O_4S$	4-OCH3	514.60	222-224	79
SMS-107	$C_{27}H_{23}FN_4O_3S$	4-F	502.56	192-194	85
SMS-108	$C_{28}H_{26}N_4O_3S$	3-CH3	498.60	236-238	76
SMS-109	$C_{27}H_{23}ClN_4O_3S$	3-Cl	519.01	254-256	84
SMS-110	$C_{27}H_{23}BrN_4O_3S$	3-Br	563.47	236-238	81

6. Spectral Data of Some Synthesized Compounds

6.1. *2-((1-(3,4-dimethylphenyl)-4-phenyl-1H-imidazol-2-yl)thio)-N-(4-(3-oxo-morpholino)phenyl)acetamid(SMS-103)*

Off White solid, Yield: 89 %, Rf Value 0.21(9:1, DCM, MeOH), M.F: $C_{29}H_{28}N_4O_3S$, FT-IR :(KBr, $V_{max,}$ cm^{-1}): 3635 (-NH, str. amide), 1608 (C=O, amide), 1486 (-NH-, bend, sec. amine), 1368-1327 (C=C, str., aromatic), 1056 (C-H, bend, aromatic), 749 (o-disubs. aromatic ring), MS: (m/z): 513(M^+), ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.41 (s, 1H, NH-Amide), 7.82-7.80 (d, *J* = 8.0 Hz, 2H), 7.57–7.55 (d, *J* = 8.0 Hz, 2H), 7.42 (s,3H), 7.32–7.30 (m,1H), 7.18–7.12 (m,5H), 4.30(s,2H), 3.98(s,2H), 3.89(s,2H), 3.68(s,2H), 2.32 (s,6H) ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.40, 165.90, 141.34, 140.88, 137.84, 136.97, 134.29, 130.29, 128.49, 126.68, 125.88, 122.30, 119.33, 67.72, 63.48, 49.04, 37.66, 19.34, 19.02 Ele. Ana: Cal. C; 67.95 %, H; 5.51 %, N; 10.93 %, found C; 67.52 %, H; 5.14 %,N; 10.28 %.

6.2. *2-((1-(4-chlorophenyl)-4-phenyl-1H-imidazol-2-yl)thio)-N-(4-(3-oxo-morpholino) phenyl)acetamide(SMS-104)*

Cream solid, Yield: 87 %, Rf Value 0.23(9:1, DCM, MeOH), M.F: $C_{27}H_{23}ClN_4O_3S$, FT-IR :(KBr,$V_{max,}$$cm^{-1}$): 3420 (-NH, str. amide), 1625 (C=O, Amide), 1544 (-NH-, bend, sec. amine), 1347-1308 (C=C, str., aromatic), 1017 (C-H, bend, aromatic),835 (p-disubs. aromatic ring), MS: (m/z): 519(M^+), ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.23 (s, 1H, NH-Amide), 7.81-7.80 (d, *J* = 4.0 Hz, 2H), 7.56–7.48 (m, 4H), 7.45–7.43 (m, 3H), 7.37–7.30 (m, 3H), 7.18-7.16 (d, *J* = 8.0 Hz, 2H), 4.30 (s, 2H) 3.99 (t, 2H), 3.91(t, 2H), 3.68 (t, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.25, 165.9, 141.25, 137.08, 136.89, 135.44, 133.33, 129.56, 128.53, 126.99, 124.35, 119.37, 67.72, 63.47, 49.04, 37.92, Ele. Ana: Cal. C; 62.48 %, H; 4.47 %, Cl; 6.83 % N; 10.79 %, found C; 62.14 %, H; 4.18 %, Cl; 6.28 %, N; 10.34 %.

7. Results and Discussion

We have elucidated a straightforward and cost-effective method for synthesizing oxo-morpholine clubbed imidazole derivatives, yielding excellent results in terms of product yield. The synthesis of substituted 2-((1,4-diphenyl-1H-imidazol-2-yl)thio)-N-(4-(3-oxo-morpholino)phenyl)acetamide can be described as follows: In the first step, Phenacyl bromide is reacted with a substituted amine in the presence of Na_2CO_3 or K_2CO_3 as a base. This reaction leads to substituted 1-phenyl-2-(phenylamino)ethanone derivatives. Subsequently, these derivatives are treated with KSCN in the presence of PTSA (p-toluenesulfonic acid) to yield the substituted 1,4-diphenyl-1H-imidazole-2-thiol. In the second step, 4-(4-aminophenyl)morpholin-3-one is subjected to a reaction with chloroacetyl chloride. This reaction results in the formation of 2-chloro-N-(4-(3-oxo-morpholino)phenyl)acetamide. Finally, the synthesized substituted 1,4-diphenyl-1H-

imidazole-2-thiol is mixed with a well-stirred solution of DMF (N,N-dimethylformamide) and K_2CO_3 (potassium carbonate) for approximately 15 min. Then, 2-chloro-N-(4-(3-oxo-morpholino)phenyl)acetamide is added to the reaction mixture, and stirring is continued at room temperature for 2-3 h. Once the reaction is complete, the mixture is poured onto crushed ice, precipitating a solid product. The solid compound is isolated by filtration and further purified using column chromatography employing an ethyl acetate and hexane solvent system. All synthesized compounds were obtained with satisfactory to excellent yields. The structural confirmation of the compounds was conducted using various spectroscopic techniques, ensuring their accurate characterization.

7.1. *Antimicrobial evaluation*

All synthesized compounds (SMS-101 to SMS-110) were subjected to in vitro evaluation for their antibacterial and antifungal activity using the broth dilution method. The antimicrobial assays were conducted against two Gram-positive bacteria, namely *Staphylococcus aureus* MTCC-96 and *Streptococcus pyogenes* MTCC 442, as well as two Gram-negative bacteria, *Escherichia coli* MTCC 443 and *Pseudomonas aeruginosa* MTCC 424. Additionally, three fungal species, including *Candida albicans* MTCC 227, *Aspergillus niger* MTCC 282, and *Aspergillus clavatus* MTCC 1323, were employed for the antifungal evaluation. In order to compare the effectiveness of the synthesized compounds, standard drugs such as Ampicillin, Chloramphenicol, Ciprofloxacin, Norfloxacin, Nystatin, and Griseofulvin were utilized. The standard strains used in the experiments were obtained from the Institute of Microbial Technology's Microbial Type Culture Collection (MTCC) and Gene Bank in Chandigarh, India.

The minimum inhibitory concentration (MIC) values of the newly synthesized compounds were determined following the microdilution broth method by the standards set by the National Committee for Clinical Laboratory Standards (NCCLS) [35-38]. The MIC is defined as the lowest concentration of the component that inhibits visible growth. For the experiments, serial dilutions of the test compounds and reference drugs were prepared on Muellere-Hinton agar. The drugs, weighing 10 mg each, were dissolved in 1 mL of dimethylsulfoxide (DMSO) as the solvent. These solutions were then subjected to the serial dilution process to achieve different concentrations for testing. By employing the microdilution broth method, the MIC values were determined based on the lowest concentration of the compounds that prevented observable growth.

Additional serial dilutions were performed using melted Muellere-Hinton agar to obtain the required concentrations. The synthesized drugs were evaluated at 1000, 500, and 250 µg/mL concentrations in the primary screening phase. The compounds that exhibited significant activity in the primary screening were further tested against all microorganisms in a second set of dilutions at concentrations of 125, 100, 75, 62.5, 50, 25, 12.5, and 6.25 µg/mL. The culture tubes were inoculated with 108 colony-forming units per milliliter (cfu/mL) and incubated for 24 h at 37 °C to allow for bacterial growth and assessment of the inhibitory effects of the synthesized drugs.

The MIC was determined as the lowest concentration of the tested compound, resulting in no observable growth or turbidity on the agar plate. A control experiment was conducted to ensure that the solvent used (DMSO) did not impact bacterial growth. The control involved using the test medium supplemented with DMSO at the same dilutions as employed in the actual experiment. The results of the control experiment confirmed that DMSO did not affect the growth of microorganisms at the concentrations studied. This control ensured that any observed effects were due to the synthesized compounds and not influenced by the solvent.

Table 1. Antibacterial and antifungal activity of the synthesized compound.

Compounds	MIC (μg mL^{-1})						
	Gram-positive		Gram-negative		Fungal species		
	S. a.	*S. p.*	*E. c.*	*P. a.*	*C. a.*	*A. n.*	*A. c.*
SMS-101	100	100	250	250	250	125	250
SMS-102	62.5	100	75	62.5	100	100	125
SMS-103	75	100	62.5	62.5	125	100	125
SMS-104	100	100	62.5	62.5	125	100	100
SMS-105	62.5	62.5	125	125	100	250	125
SMS-106	100	100	75	75	100	125	100
SMS-107	75	62.5	100	75	250	125	250
SMS-108	100	100	250	250	100	125	125
SMS-109	100	75	100	100	100	125	125
SMS-110	62.5	75	100	100	125	100	125
Ampicillin	250	100	100	100	-	-	-
Chloramphenicol	50	50	50	50	-	-	-
Ciprofloxacin	50	50	25	25	-	-	-
Norfloxacin	10	10	10	10	-	-	-
Nystatin	-	-	-	-	100	100	100
Griseofulvin	-	-	-	-	500	100	100

Where S. a. = Staphylococcus aureus, S. p. = Streptococcus pyogenes, E. c. = Escherichia coli, P.a. = Pseudomonas aeruginosa, C. a. = Candida albicans, A. n. = Aspergillus Niger, A. c. = Aspergillus clavatus

8. Conclusion

In conclusion, this research has successfully presented a novel and innovative method for the synthesis of a series of substituted 2-((1,4-diphenyl-1H-imidazol-2-yl)thio)-N-(4-(3-oxo-morpholino)phenyl)acetamide compounds. The developed method offers distinct advantages over existing approaches, including reduced reaction conditions, higher yields, cost-effectiveness, improved safety, and environmental sustainability. The utilization of milder reaction conditions simplifies the synthetic process and enhances safety, making it more accessible and viable for implementation. Moreover, the method demonstrates increased yields, resulting in efficient production of the desired compounds and contributing to its cost-effectiveness. The extensive characterization of the synthesized compounds ensures their structural integrity and purity, providing a solid foundation for future investigations and applications in various fields. Notably, evaluating the compounds' antimicrobial potency against a range of microbial strains, including both

Gram-positive and Gram-negative bacteria, reveals promising results, highlighting their potential as effective agents in combating bacterial infections. These findings hold great significance in the medical field, where developing new therapeutic options for microbial control is highly sought after. Overall, this research showcases the advantages and potential of the developed method, paving the way for further research and development in the quest for more effective and targeted therapeutic interventions against microbial infections.

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