GREEN ROUTE FOR THE SYNTHESIS OF OXADIAZOLE DERIVATIVE CONTAINING BENZIMIDAZOLE MOIETY AND ITS MANNICH BASES: IN-VITRO ANTIMICROBIAL ACTIVITY

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ABSTRACT

Green method is employed for the synthesis of 5-((1H-benzimidazol-2-ylthio) methyl)-3-(substituted)-1,3,4-oxadiazole-2(3H)-thione derivatives by Mannich reaction of 5-((1H-benzimidazol-2-ylthio)methyl)-3-(substituted)-1,3,4-oxadiazole-2(3H)-thione with formaldehyde and different secondary amines. The ¹H NMR, FT-IR and mass spectral studies were carried out to assign the structure of newly synthesized compounds. Amongst all tested new compounds, the antimicrobial assay of piperazinyl substituted oxadiazole derivatives showed good in vitro antibacterial activities.

Keywords: Mannich Bases, Oxadiazole, Benzimidazole, Microwave Irradiation, Antibacterial Activity.

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INTRODUCTION

Amines are an extremely important group in medicinal chemistry and are present in many drugs. Mannich reaction is a multicomponent condensation reaction in which an active substrate is amino methylated for synthesis and modification of biologically active compounds. As Mannich bases have amine groups, they are physiologically active. The most important use for the Mannich bases is in pharmaceutical industries as they possess antibacterial¹⁻⁴, antifungal⁵⁻⁶, anticancer⁷⁻¹⁰, antioxidant¹¹⁻¹², antimalarial¹³, anti-inflammatory¹⁴⁻¹⁵, anti-proliferative¹⁶ and anti-diabetic¹⁷ properties. Moreover, Mannich bases are important pharmacophores in treating thrombosis caused by antioxidants.¹⁸ Mannich bases have technological applications in polymer chemistry as paints and surface-active agents.¹⁹

Amongst heterocycles, benzimidazole is having immense importance. Benzimidazole is the constituent of Vitamin-B₁₂ and many pharmaceutical drugs. This heterocyclic ring system shows numerous biological activities such as antifungal²⁰, antibacterial²¹, antioxidant²²⁻²³, antiparasitic²⁴⁻²⁵, anti-inflammatory²⁶, antiproliferative²⁷, and anti-HIV²⁸. Oxadiazole nucleus is associated with a variety of pharmacological actions and shows prominent antibacterial²⁹, anticonvulsant³⁰, antifungal³¹⁻³², and antitubercular³³ activities.

We have adopted a non-conventional and greener approach for the synthesis of new biologically active compounds by incorporating different pharmacophores in the same unit. A new series of Mannich bases of oxadiazole derivative containing benzimidazole moiety was synthesized using microwave irradiation technique. This technique is a method of accelerated organic synthesis of the compounds in a short time with good yield and provides a greener alternative to the conventional methods. In this new series, the exchangeable hydrogen atom of the NH group in oxadiazole moiety is substituted with an amine through a methylene bridge by Mannich reaction under microwave radiation.

EXPERIMENTAL

Materials and Methods

Analytical grade reagents and solvents were used for the present work and were not purified further. The melting points of the synthesized compound **4** and **5a-g** were recorded using the melting point apparatus.

Precoated TLC plates (Merck) were used to confirm the completion of the reaction. The obtained TLC spots were visualized using iodine vapors. Crystallization was used as a technique for the purification of newly synthesized compounds. IR spectra ($\nu_{\max}$ cm^{-1}) were measured on the Shimadzu FT-IR spectrophotometer using solid KBr pellets. Bruker Advance II 400 MHz was used for recording ^1H NMR chemical shifts in ppm. CDCl_3 - $\text{DMSO } d_6$ was used as a solvent and tetramethylsilane (TMS) as an internal standard. A domestic microwave oven of output energy range from 140W to 900W was used for carrying out reaction under microwave irradiation.

General Procedure

Synthesis of Ethyl 2-(1H-benzimidazol-2-ylthio) acetate (2)

1.50 g of 1H-benzimidazole-2-thiol (0.01 mol) and 1.22 ml ethyl 2-chloroacetate (0.01 mol) in acetone along with 1g anhydrous K_2CO_3 were irradiated at 350W power for 3.5 minutes. When the reaction completed, checked by TLC, the reaction mixture was treated with water. The product obtained was recrystallized to give compound **2**; yield: 82%; M.P. 60°C.

Synthesis of 2-(1H-benzimidazol-2-ylthio) acetohydrazide (3)

2.36 g of ethyl 2-(1H-benzimidazol-2-ylthio) acetate (0.01 mol) and 0.9 ml of hydrazine monohydrate (0.01 mol) in ethanol was irradiated at 300W power for 4.0 minutes. The reaction mixture was kept at 8-10°C for about 1h, the separated solid was recrystallized with an appropriate solvent to furnish compound **3**; yield: 60%; M.P. 195°C

Synthesis of 5-((1H-benzimidazol-2-ylthio)methyl)-1,3,4-oxadiazole-2(3H)-thione(4)

Conventional Method

0.01 mol of 2-(1H-benzimidazol-2-ylthio) acetohydrazide was taken in a solution of 0.015 mol of KOH in 20 ml Ethanol. This was treated with 0.015 mol of CS_2 . This mixture was diluted with 15 ml of absolute ethanol. It was stirred at 30°-35°C for 14-16h. As the reaction completed (monitored by TLC), it was treated with dil HCl under cold condition. The precipitated yellow product was filtered. Recrystallization of the crude product with absolute ethanol gave compound **4**. M.P. 176-178°C

Microwave Method

10 mmol of 2-(1H-benzimidazol-2-ylthio) acetohydrazide was treated with 15 mmol of KOH and 15 mmol of CS_2 using a minimum amount of ethanol. The reaction mixture was irradiated at 400W power for nearly 4 minutes. When the reaction completed confirmed by TLC, it was just acidified with dil HCl under cold condition. The yellow product precipitated in high yield. The product was purified by crystallization with ethanol to obtain compound **4**.

M.P. 176-178°C; IR (KBr, $\nu_{\max}$): 3349.8, 3129(-NH-), 1672.5(C=N), 1523.8(Ar C=C), 1454(C=S), 1262 and 1109(C-O-C), 745. ^1H NMR (CDCl_3 , TMS): δ ppm 3.37(s, 2H, - CH_2 -), 5.335(s, 1H, -NH-), 7.1-7.3(m, 4H, Ar), 7.58(s, 1H, -NH-). MS: m/z 265[M+H] $^+$.

General Method for Synthesis of Mannich Bases (5a-g)

Conventional Method

1 mmol of 5-((1H-benzimidazol-2-ylthio)methyl)-1,3,4-oxadiazole-2(3H)-thione was dissolved in 10 ml of ethanol. To this 1.5 mmol of HCHO and 1 mmol of appropriate amine were added. On magnetic stirrer, the reaction mixture was stirred at 25-30°C for the required time given in table 1. The obtained crude products were recrystallized with absolute ethanol to get compounds **5a-g**.

Microwave Method

1 mmol of appropriate amine, 1.5 mmol of HCHO and 1 mmol of compound **4** were dissolved in the minimum amount of ethanol. The reaction mixture was irradiated in a microwave oven till completion of the reaction (1-4 min), confirmed by TLC. The separated products were recrystallized with absolute ethanol to get compounds **5a-g**.

Spectroscopic Data of Compound 5a-g**5-((1H-Benzimidazol-2-ylthio)methyl)-3-(morpholinomethyl)-1,3,4-oxadiazole-2(3H)-thione (5a)**

M.P. 158-160°C; IR (KBr, $\nu_{\max}$ cm^{-1}): 2957(Ar C-H), 2865(C-H), 1618(-C=N-), 1440(-C=S), 1323(-C-N-), 1161(-C-O-C-), 750. ^1H NMR (DMSO- d_6 , TMS): δ ppm 2.515(t, 4H, -CH₂-) 3.4(s, 2H, -CH₂-), 4.6(s, 2H, -CH₂-), 4.8(s, 2H, -CH₂-), 7.2-7.6(m, 4H, Ar). MS: m/z 364[M-H].

5-((1H-Benzimidazol-2-ylthio)methyl)-3-(pyrrolidin-1-ylmethyl)-1,3,4-oxadiazole-2(3H)-thione (5b)

M.P. 205-207°C; IR (KBr, $\nu_{\max}$ cm^{-1}): 3025(Ar C-H), 2962(C-H stretching), 1620(-C=N-), 1330(-C-N-), 1437(-C=S), 1202(C-O-C), 755, 739. ^1H NMR (DMSO- d_6 , TMS): δ ppm 1.6(t, 4H, -CH₂-), 2.20(t, 4H, -CH₂-), 4.5(s, 2H, -CH₂-), 5.01(s, 2H, -CH₂-), 7.27-7.65 (m, 4H, Ar). MS: m/z 348[M+H]⁺.

5-((1H-Benzimidazol-2-ylthio)methyl)-3-((dimethylamino)methyl)-1,3,4-oxadiazole-2(3H)-thione (5c)

M.P. 186-188°C; IR (KBr, $\nu_{\max}$ cm^{-1}): 3060(Ar -C-H), 2892(C-H stretching), 1650(C=N), 1600(C=C), 1440(C=S), 1335(C-N), 1221(C-O-C), 750. ^1H NMR (DMSO- d_6 , TMS): δ ppm 2.3(s, 6H, CH₃), 2.9(s, 4H, -CH₂-), 4.84(s, 2H, -CH₂-), 5.12(s, 2H, -CH₂-), 7.3-7.72(m, 4H, Ar). MS: m/z 322[M+H]⁺.

5-((1H-Benzimidazol-2-ylthio)methyl)-3-((diethylamino)methyl)-1,3,4-oxadiazole-2(3H)-thione (5d)

M.P. 230-232°C; IR (KBr, $\nu_{\max}$ cm^{-1}): 3220(Ar -C-H), 2924(C-H stretching), 2872(CH₃), 1623(-C=N-), 1588(-C=C-), 1437(-C=S), 1295(-C-N-), 1212(-C-O-C-), 740, 706. ^1H NMR (DMSO- d_6 , TMS): δ ppm 1.2(t, 6H, -CH₂-), 2.45(q, 4H, -CH₂-), 4.1(s, 2H, -CH₂-), 5.26(s, 2H, -CH₂-), 7.32-7.65(m, 4H, Ar). MS: m/z 350[M+H]⁺.

5-((1H-Benzimidazol-2-ylthio)methyl)-3-(piperidin-1-ylmethyl)-1,3,4-oxadiazole-2(3H)-thione (5e)

M.P. 256-258°C; IR (KBr, $\nu_{\max}$ cm^{-1}): 3236(Ar -C-H), 2854(-C-H stretching), 1633(-C=N-), 1488(-C=C-), 1397(-C=S), 1284(-C-N-), 1196(-C-O-C-), 738. ^1H NMR (DMSO- d_6 , TMS): δ ppm 1.5(t, 6H, CH₂), 2.24(t, 4H, -CH₂-), 4.34(s, 2H, -CH₂-), 5.3(s, 2H, -CH₂-), 7.4-7.7(m, 4H, Ar). MS: m/z 362[M+H]⁺.

5-((1H-Benzimidazol-2-ylthio)methyl)-3-((4-methylpiperazin-1-yl)methyl)-1,3,4-oxadiazole-2(3H)-thione (5f)

M.P. 245-247°C; IR (KBr, $\nu_{\max}$ cm^{-1}): 3105(Ar -C-H), 2806(-C-H stretching), 1658(-C=N-), 1560(-C=S), 1320(-C-N-), 1247(-C-O-C-), 748, 742, 723. ^1H NMR (DMSO- d_6 , TMS): δ ppm 2.27(t, 3H, CH₃), 2.46(t, 8H, -CH₂-), 4.67(s, 2H, -CH₂-), 4.86(s, 2H, -CH₂-), 7.33-7.82(m, 4H, Ar). MS: m/z 377[M+H]⁺.

5-((1H-Benzimidazol-2-ylthio)methyl)-3-((4-ethylpiperazin-1-yl)methyl)-1,3,4-oxadiazole-2(3H)-thione (5g)

M.P. 280-282°C; IR (KBr, $\nu_{\max}$ in cm^{-1}): 2980(Ar C-H), 2870(-C-H stretching), 1627(-C=N-), 1625(-C=C-), 1520(-C=S), 1311(C-N), 1232(-C-O-C-), 752. ^1H NMR (DMSO d_6 , TMS): δ ppm 1.2(t, 3H, CH₃), 2.46(t, 8H, -CH₂-), 2.40(q, 2H, -CH₂-), 4.9(s, 2H, -CH₂-), 5.59(s, 1H, -CH₂-), 7.25-7.79(m, 4H, Ar). MS: m/z 391[M+H]⁺.

Antimicrobial Activity

The in vitro antibacterial assay of newly synthesized compounds **4** and **5a-g** was carried out against different bacterial strains like *E. coli*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Bacillus Subtilis*, and *Pseudomonas aeruginosa* by well diffusion method. A lawn of an overnight grown broth culture was prepared on Muller Hinton agar plates. The well was created using a borer and filled with samples to be tested (app 100 $\mu\text{m}/\text{ml}$). The plates were kept in an incubator for 24 h. The zone of inhibition was measured around the well (in mm).

RESULTS AND DISCUSSION

In the present work a new series of Mannich bases (**5a-g**) of 5-(benzimidazol-2-ylthio) methyl)-1,3,4-oxadiazole-2(3H)-thione **4** was synthesized by Mannich reaction of an active substrate 5-(benzimidazol-2-ylthio) methyl)-1,3,4-oxadiazole-2(3H)-thione **4** with formaldehyde and different secondary amines as

described in the Scheme-1. The reaction steps to synthesize the target compounds are given in Scheme-1. The yield (%) and the time (h) required for both the microwave irradiation method and the conventional method is compared in Table-1. TLC was used at every step to confirm the completion of the reaction. The structures of synthesized compounds **4** and **5a-g** were subsequently evidenced by their FT-IR, ¹H NMR and mass spectral analysis. Newly synthesized 5-((1H-benzimidazol-2-ylthio)methyl)-1,3,4-oxadiazole-2(3H)-thione **4** and its Mannich bases **5a-g** were assessed for antibacterial activity against different bacterial strains. Ciprofloxacin was designated as a standard drug. The observed antibacterial activities are shown in Table-2.

Scheme-1: Synthesis of Oxadiazole Derivative and its Mannich Bases

The new Mannich bases of 5-((1H-benzimidazol-2-ylthio)methyl)-1,3,4-oxadiazole-2(3H)-thione were synthesized in four steps as depicted in Scheme-1.

In acetone with anhydrous K₂CO₃, commercially available 2-Mercaptobenzimidazole was condensed with ethyl chloroacetate to give compound ethyl 2-(1H-benzimidazol-2-ylthio) acetate (**2**) under microwave radiation by reported method³⁴.

Ammonolysis of ethyl 2-(1H-benzimidazol-2-ylthio) acetate (**2**) with hydrazine monohydrate solution in ethyl alcohol afforded 2-(1H-benzimidazol-2-ylthio) acetohydrazide (**3**) using microwave radiation by reported method³⁴.

Table-1: Comparative Study for Microwave and Conventional Technique 4 and 5a-g

Product	Conventional Method		Microwave Irradiation (MW)	
	Time (h)	^a Yield (%)	Condition	^a Yield (%)
			Power(W)/Time(min)	
4	16	60	400/4.0	88
5a	2	72	350/1.0	90
5b	3	70	350/1.5	86
5c	8	55	400/3.0	70
5d	9	54	400/3.5	72
5e	6	60	400/2.0	75
5f	4	68	350/2.0	85
5g	4.5	65	350/2.0	84

^aYield of isolated product

The alkaline solution of 2-(1H-benzimidazol-2-ylthio) acetohydrazide (**3**) in ethanol was treated with CS₂ by both the conventional method and the microwave method. The conventional method of vigorous stirring at 30-35°C to synthesize desired compound 5-((1H-benzimidazol-2-ylthio)methyl)-1,3,4-oxadiazole-2(3H)-thione (**4**) required long reaction time 14-16h and gave 60% yield. While the

microwave method gave 88% yield in just 4 minutes. The formation of compound **4** was evidenced by its mass (m/z) peak at 265[M+H⁺]. In ¹H NMR spectral analysis, the multiplets in the range δ 7.1-7.3 ppm revealed aromatic protons and the singlet at δ 5.33 ppm showed the presence of exchangeable NH proton in oxadiazole moiety. The absorption bands at 3349- 3129 cm⁻¹ in the IR spectra also supported the existence of exchangeable NH proton in oxadiazole moiety. While the bands at 1672.5 cm⁻¹, 1523.8 cm⁻¹, 1454 cm⁻¹ were observed due to -C=N-, -C=C-, -C=S and -C-H bonds.

One-pot multicomponent Mannich reaction of 5-((1H-benzimidazol-2-ylthio)methyl)-1,3,4-oxadiazole-2(3H)-thione (**4**) with formaldehyde and different secondary amine gave target compounds **5a-g** as mentioned in Scheme-1. The reactions performed using microwave radiations were completed within 1-4 minutes in high yield, while the conventional method required longer reaction time and gave low yield (Table 1). The formation of compounds **5a-g** was confirmed by the corresponding mass (m/z) peak. The IR absorption bands at 1618 cm⁻¹ were observed due to C=N bond. Absorption bands at 1440 cm⁻¹ and 1161 cm⁻¹ represented C-N and C-O-C bonds respectively. ¹H NMR spectral peaks around δ 7.2- 7.8 ppm, δ 4.8-5.3 ppm and peaks in the region δ 1-3 ppm affirmed the presence of aromatic protons, bridge CH₂ protons and the aliphatic protons of secondary amines in the target compounds **5a-g** respectively.

The newly synthesized compounds **4** and **5a-g** were checked for antibacterial activity against different bacterial strains. The zone of inhibition (mm) of all the synthesized compounds **4** and **5a-g** are presented in Table-2. Compound **5a** with morpholinyl substituent showed good antimicrobial activity while **5b-e** exhibited moderate activity. The presence of N-methyl and N-ethyl piperazinyl moiety in the target compounds showed much better inhibition activity. *E. coli*, *Staphylococcus aureus*, and *Bacillus Subtilis* were resistant against compound **5c**. Compound **5d** was inactive against *E. coli*, *Bacillus Subtilis* and *Pseudomonas aeruginosa*.

Table-2: Antibacterial Activity of Compounds 4 & 5a-g

Compound	Antimicrobial Activity (mm)				
	E. coli	Staphylococcus aureus	Klebsiella pneumoniae	Bacillus Subtilis	Pseudomonas Aeruginosa
4	15	13	14	12	14
5a	18	15	20	16	12
5b	16	11	15	10	16
5c	-	-	11	-	13
5d	-	15	10	-	-
5e	12	14	12	11	12
5f	20	16	21	15	18
5g	22	14	18	21	20
Ciprofloxacin	27	23	22	25	24

CONCLUSION

A new compound 5-((1H-benzimidazol-2-ylthio)methyl)-1,3,4-oxadiazole-2(3H)-thione **4** and its derivatives 5-((1H-benzimidazol-2-ylthio) methyl)-3-(substituted)- 1,3,4-oxadiazole-2(3H)-thione **5a-g** were successfully synthesized by the Mannich reaction under microwave irradiation with high yield and short reaction time. The spectroscopic investigations of compounds **4** and **5a-g** supported the proposed structures for these compounds. The compound **4** and its Mannich bases **5a-g** exhibited moderate to good antimicrobial activity.

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