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Research Article

Conventional and Microwave-assisted Synthesis of Fibric Acid Based 1,3,4-oxadiazole Derivatives and Evaluation of Their *in vivo* Anti-hyperglycemic Activity

Majda Batool[a,b,*], Munawar Ali Munawar[c], Muhammad Asim Raza Basra[a], Sumra Amanat[b], Shazia Amir[b], Hafiz Adnan Ahmad[b]

[a]*School of Chemistry, University of the Punjab, Lahore 54600, Pakistan*
[b]*Department of Chemistry, Government Graduate College, Township, Lahore 54700, Pakistan.*
[c]*Department of Chemistry, Faculty of Science, University of Central Punjab, Lahore 54700, Pakistan*

Abstract

Microwave assisted synthesis, a green synthetic method was applied to synthesize a series of oxadiazole based fibric acid derivatives **(3a-h)** resulted good to excellent yields (82-96%) and less reaction time in comparison to conventional methods and ultrasonic methods. The synthesized compounds were characterized by ^{1}H-NMR, EI/MS and ^{13}C-NMR and their postulated structures were in agreement with spectral data. In present study title compounds were further evaluated for their hypoglycemic potential and among them compounds **(3c)** showed the significant biological response. The hypoglycemic effect was compared with glibenclamide.

Keywords:
Fiberates, Green chemistry, Microwave, Oxadiazole derivatives, Carboxymethylcellulose, Glibenclamide, Body weight.

1. Introduction

Diabetes mellitus (DM), often referred as simply diabetes, is dysmetabolic syndrome that can have various causes, but is primarily characterized by consistently high blood sugar levels and abnormalities in the metabolism of carbohydrates, proteins, and fats. These abnormalities are typically caused by irregularities in the way insulin works in the body, including both insulin secretion and insulin action. Based on analysis, control and the clinical expressions DM can be classified into many types, each with its own specific causes and aspects. Diabetes type 1, for example, is an immunological disorder in which insulin producing cells are attacked and destroyed by body's immune system. While diabetes type 2, is generally caused by the combination of various genetic and lifestyle factors, that causes insulin resistance, in which body's cells response poorly to insulin. Regardless of the specific cause the end result of diabetes is a chronic state of high blood glucose levels that can lead to a lot of complications if not cared. These can include nerve destruction, kidney disorder, blindness, and an increased risk of cardiovascular disease [1, 2].

Hyperlipidemia and constant high levels of blood glucose are the main common symptoms in almost all the major types of DM [3].The ultimate effects of diabetes mellitus include cut away, retinopathy, cataract and joints disorder. Diabetic patients are also at higher risk of developing heart disease, which results in heart attacks, peripheral vascular disease that affects blood vessels of legs and feet and cerebrovascular disease that damage the blood vessels of brain. This increased scarring is due to the high blood sugar levels that ca lead to impairment of blood vessels and nerve of whole body [4].

The adverse effects of diabetes mellitus can be avoided with good glycemic control, regular screening for related issues and proper control of any existing complications. However if left untreated severe complications may arise in diabetic patients. These complications include oxidative stress, hyperlipidemia and enzymatic glycation of protein [5]. Fibric acid derivatives belong to a class of drugs known as fibrates, and they work by increasing the breakdown and elimination of triglycerides (TG) and cholesterol from the blood. Fiberates are an important class

*Corresponding Author:
majdabatool12@gmail.com (Majda Batool)

of lipid-lowering drugs. These reduces the risk of cardiovascular disease that is usually associated with high levels of blood lipids in body.

These drugs are most effective for the patients who have high levels of triglycerides (TG) that are the major cause for the development of cardiovascular disease. Gemfibrozil and fenofiberate are examples of fibric acid derivatives. Although these drugs effectively reduce the blood lipid levels but these are associated with many side effects such as liver disease, gastrointestinal problems and muscles fatigue [6].

Among patients with T2DM hyperlipidemia can increase the risk of cardiac arrest. It causes the deposition of fats (plaques) on the walls of blood vessels that results in atherosclerosis. Atherosclerosis can narrow the blood vessels and restrict blood supply to the heart, which can increase the risk of cardiac arrest. Moreover, patients with T2DM have more chances of developing cardiovascular disease, and hyperlipidemia can further promote the situation [7].

The diabetic hyperlipoproteinemia also known as atherogenic dyslipidemia is due to increased triglycerides TG, low density lipoproteins (LDL), and reduced levels of high density lipoproteins (HDL) cholesterol [8]. Compounds with five - membered rings having one or more heteroatoms are of great interest in drug design and medicinal chemistry due to their diverse pharmacological activities, high selectivity towards biological targets, and potential for the development of novel and effective drugs [9].

The 1,3,4-oxadiazole ring is a five-membered heterocyclic compound containing two nitrogen atoms and one oxygen atom. This ring system has gained attention from researchers as a potential replacement for carbonyl containing compounds e.g., carboxylic acids, esters, and amides in drug design. This substitution is known as a bioisostere, which means it has a similar shape and electronic properties to the original compound, allowing it to retain or improve upon the original compound's biological activity .In drug design, the oxadiazole ring is often used as an effective moiety of the pharmacophore. It can interact with the ligand, forming various chemical bonds that can influence the drug's affinity and selectivity for the target, as well as its pharmacokinetic properties. In some cases, the oxadiazole ring can act as a flat aromatic linker. This property makes it useful in drug design, where the linker can be tailored to optimize the molecule's properties, such as solubility, stability, and bio availability.

Overall, the 1,3,4-oxadiazole ring is a versatile and promising bioisostere that can improve the biological activity and pharmacokinetic properties of drug molecules. Its potential applications are vast and continue to be explored by researchers in the field of drug chemistry [10]. The compounds containing this characteristic oxadiazole moiety have been reported to exhibit diverse pharmachological activities such as antifungal [11], antibacterial [12], anti-mycobacterial [13], anticonvulsant [14], antidiabetic [15], anticancer, anti-inflammatory and analgesic [16]. So, it is an hour of need to have such a drug that have diversity and be able to spread its roots among all mechanisms and complications regarding diabetes mellitus.

The aim of our study is also centered to bring some drug with 1,3,4-oxadiazole moiety that is able to combat against frequently found complications. Previously we used ultrasonic method for the synthesis of 1,3,4-oxadiazole derivatives [17]. In continuation of our ongoing research, we have applied conventional and microwave-assisted synthetic strategies and achieved maximum yields of fibric acid 1,3,4-oxadiazole derivatives (3a-h) over shorter reaction times by microwave exposure. The titled compounds were further evaluated for their *in vivo* hypoglycemic potential.

2. Materials and Methods

2.1. Chemistry

Microwave-assisted synthesis was performed with a microwave apparatus Model EA-180M. Analytical grade chemicals were purchased from Sigma Aldrich and Alfa Aesar. Purity of synthesized compounds was checked by TLC G-25-UV254 plates by using ethylacetate : *n*-hexane (1:4) giving single spot. Griffin and George melting point apparatus were used for melting points by using open capillary tube method and reported as uncorrected. The synthesized scaffolds were recrystallized from 30% ethanol. 5-[2-(4-Chlorophenoxy) propan-2-yl]-1,3,4 - oxadiazol -2-thiol **(1)** [18] and aromatic *N*-substituted -2- bromoacetamides **(2a-h)** were synthesized by already reported protocol with slight modifications [19].

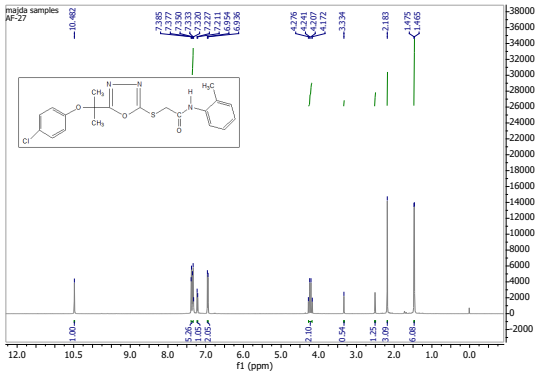

Figure 1. ^{1}H-NMR spectrum of compound **(3b)**

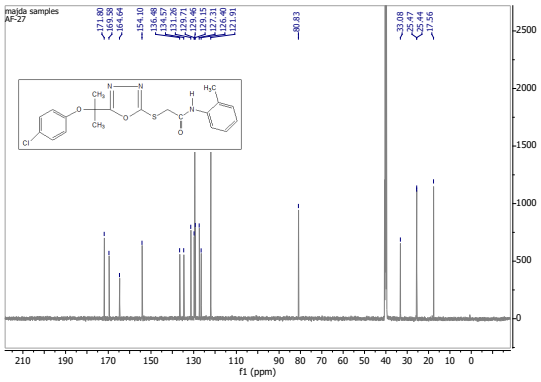

Figure 2. ^{13}C-NMR spectrum of compound **(3b)**

2.1.1. *Conventional method for synthesis of Fibric Acid 1,3,4-Oxadiazole Derivatives* ***(3a-h)***

To a solution of 5-[2 -(4-chloropropan-2-yl]-1,3,4 - oxadiazole - 2-thiol **(1)** (1 mmol) in DMF were added lithium hydride (2 mmol) as a catalyst and stirred at room temperature for half an hour. Then, *N*-substituted-2-bromoacetamide **(2a-h)** (1 mmol) was added as an electrophile, and the reaction mixture was further stirred at room temperature for 11-26 hours. The progress of reaction was monitored by TLC (using ethylacetate : n-hexane, 1:4) as mobile phase. On completion, the reaction mixture was poured over ice chilled water and the resulting precipitates were filtered, washed with distilled water, and dried to obtain the desired compounds **(3a-h)** in good yield (Table 3). The product **(3a-h)** was further recrystallized by using 30% ethanol.

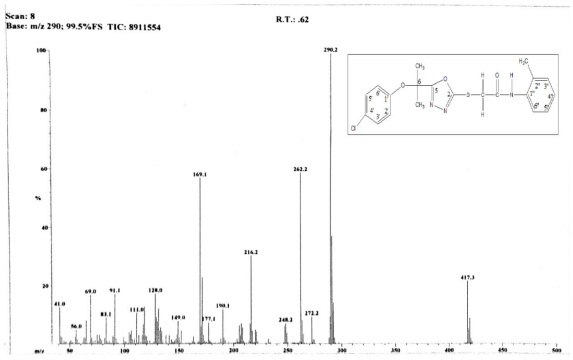

Figure 3. EI-MS of compound 3b

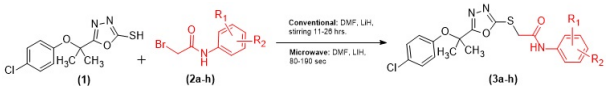

Figure 4. Scheme showing synthetic pathway for conventional / microwave assisted synthesis of acetamides (3a-h).

Table 1. Different substitutions in **(3 a-h)**

Codes	3a	3b	3c	3d	3e	3f	3g	3h
R^1	H	H	H	H	$2-CH_3$	$2-CH_3$	$2-CH_3$	$3-CH_3$
R^2	H	$2-CH_3$	$3-CH_3$	$4-CH_3$	$3-CH_3$	$4-CH_3$	$6-CH_3$	$4-CH_3$

2.1.2. *Microwave-assisted method for synthesis of Fibric Acid 1,3,4-Oxadiazole Derivatives* ***(3a-h)***

To a solution of 5-[2-(4-chloropropan-2-yl]-1,3,4 - oxadiazole - 2-thiol **(1)** (1 mmol) in DMF were added lithium hydride (2 mmol) as a catalyst and stirred at room temperature for half an hour. Then, *N*-substituted-2-bromoacetamide **(2a-h)** (1 mmol) was added as an electrophile and the reaction mixture was subjected to MW irradiations for 80-190 sec. The progress of reaction was monitored by TLC (using ethylacetate : n-hexane, 1:4) as the mobile phase. On completion, the reaction mixture was poured over ice chilled water and the resulting precipitates were filtered, washed with distilled water, and dried to obtain the desired compounds **(3a-h)** in good to excellent yield (Table 3) . The product **(3a-h)** was further recrystallized by using 30% ethanol.

2.2. *Biological Essay*

2.2.1. *Anti-hyperglycemic activity*

Experimental animals in this study were Sprague Dawley Albino rats weighing between 200-250 g. They were kept in an animal house at a controlled temperature of 25 ± 5°C and humidity of 50 ± 10%. The rats were given free access to pathogen-free feed and autoclaved tap water for 24 hours. All *in vivo* experiments were approved by the Institutional ethical committee (Approval No. D/017/Chem.) and followed international ethical guidelines to ensure the proper care and well-being of the rats in animal house.

2.2.2. *Oral glucose tolerance test in normal rats*

After 18 hours of starvation blood sugar level of each rat was measured by using a code-free glucometer. Rats with the blood sugar levels ranging between 80-100 mg/dL were grouped in sets of six. A single oral dose of the synthesized compounds (100 mg/kg body weight), was given to experimental group after emulsification in aqueous carboxymethyl cellulose (0.5%). Only aqueous CMC (0.5%) was given to control group. After exactly half an hour administration of vehicle/test sample, a glucose solution (2.0 g/kg body weight) was orally given to each rat. The blood sugar level of each rat was measured at 1, 3, and 5 hours intervals after the glucose administration [20].

3. Results and Discussion

3.1. *Chemistry*

Scheme of Microwave-assisted, a green synthetic technique that is environment friendly, economical, time saving affording excellent yield was adopted along with conventional method as shown in figure 4. The ultrasonic method of synthesizing the title compounds has been already reported [17] as affording fibric acid-oxadiazole derivatives **(3a-h)** in moderate to good (75-91%) yields. Purpose of the present study was to increase the yield and reduce the time for synthesis by applying the microwave-assisted approach to achieve the desired product as compared to conventional method. In conventional and microwave -assisted approach the scaffold 5-[2-(4-Chlorophenoxy) propan-2-yl] - 1,3,4-oxadiazole-2-thiol **(1)** was coupled with electrophiles, *N*-substituted-2-bromoacetamide **(2a-h)** to synthesize *N*-substituted 5 -[2-(4-chlorophenoxy) propan-2-yl]-1,3,4-oxadiazol-2-ylthio acetamides (**(3a-h)** Scheme shown in figure 4, Table 1). The ultrasonic technique yielded products of 75-91% in 60-90 minutes at room temperature as compared to conventional method that affords products of 41-69% in 11-26 hours at room temperature. The MW technique was much more efficient as the maximum yield of target compounds 82-96% in short period of time 80-190 seconds was obtained. The fibric acid derivative **(3h)** was obtained with maximum yield, while compound **(3a)** was achieved within least yield by all three synthetic protocols as mentioned in Table 3. The supposed

Table 2. Physical Parameters of *N*-substituted 5-[2-(4-chlorophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-ylthioacetamides **(3a-h)**

Code	Appearance	Mol. formula	EIMS: m/z
3a	white fluffy amorphous flakes	$C_{19}H_{18}N_3O_3SCl$	403 [M^+, 2 %], 405 [M^{+2}, 0.8 %], 276 (100), 248 (5), 202 (13), 183 (20), 166 (30), 128 (26), 123 (64), 106 (22), 93 (13), 77 (11), 65 (13), 55 (8), 41 (9).
3b	Light yellow color powder	$C_{20}H_{20}N_3O_3SCl$	417 [M^+, 22 %], 419 [M^{+2}, 9 %], 290 (100), 272 (9), 262 (59), 248 (7), 216 (30), 190 (12), 177 (7), 169 (57), 149 (8), 128 (17), 111(11), 91 (17), 83 (9), 69 (17), 56 (5), 41 (13).
3c	Lemon yellow color powder	$C_{20}H_{20}N_3O_3SCl$	417 [M^+, 12 %], 419 [M^{+2}, 4 %], 290 (100), 272 (4), 262 (18), 248 (3), 216 (25), 183 (35), 169 (24), 148 (12), 138 (35), 138 (25), 123 (71), 107 (16), 91 (17), 69 (10), 41 (7).
3d	Dirty white color powder	$C_{20}H_{20}N_3O_3SCl$	417 [M^+, 5 %], 419 [M^{+2}, 2 %], 290 (100), 262 (5), 216 (7), 183 (24), 148 (10), 138 (22), 123 (55), 91 (8), 55 (5), 41 (5).
3e	Creamy white color powder	$C_{21}H_{22}N_3O_3SCl$	431 [M^+, 38 %], 433 [M^{+2}, 14 %], 304 (100), 286 (12), 276 (88), 261 (8), 230 (15), 219 (13), 204 (32), 191 (11), 169 (72), 152 (8), 145 (17), 128 (15), 105 (12), 77 (7), 69 (16), 56 (6), 41 (14).
3f	Golden yellow color powder	$C_{21}H_{22}N_3O_3SCl$	431 [M^+, 17 %], 433 [M^{+2}, 7 %], 304 (100), 286 (7), 276 (13), 262 (2), 230 (24), 204 (4), 194 (32), 183 (41), 162 (21), 152 (37), 128 (32), 123 (81), 83 (11), 55 (7), 41 (10).
3h	Off-white color powder	$C_{21}H_{22}N_3O_3SCl$	431 [M^+, 11 %], 433 [M^{+2}, 5 %], 304 (100), 276 (9), 230 (12), 194 (23), 183 (42), 169 (14), 162 (20), 152 (37), 128 (22), 123 (84), 109 (10), 91 (9), 77 (10), 55 (6), 41 (9).

Table 3. Comparison of conventional, Ultrasonic and microwave-assisted methods

Compound	Reaction Yield (%)			Reaction Time			Melting Point (°C)	
	Conventional	Ultrasonic	Microwave	Conventional (hour)	Ultrasonic (minute)	Microwave (second)	Found	Reported [17]
3a	41	75	82	11	60	80	84	84-86
3b	62	87	93	23	80	155	141	140-142
3c	46	78	85	19	75	140	71	71-72
3d	55	84	89	12	60	84	68	68-70
3e	60	86	91	26	90	190	186	186-188
3f	52	81	88	24	80	160	79	78-80
3g	65	89	94	12	60	86	98	98-100
3h	69	91	96	17	70	124	80	80-82

structures of synthesized compounds **(3a-h)** were confirmed by spectral data [17].

The synthesized compound **(3b)** was obtained as light yellow color powder having yield 87% and m.p. 140-142°C. Molecular formula $C_{20}H_{20}N_2O_3SCl$ was confirmed by EI-MS showing molecular ion peak at 290 (Figure 3). In FTIR spectrum peaks for N−Hstretching appeared at 3339, for C−H stretching of aromatic ring 2981, C=O amide stretching 1667, C=C aromatic ring stretching at 1484. ^{1}H-NMR results show peak at 10.48 as a singlet for NH. A multiplet at 7.38-7.32 represents two aromatic protons of fibric acid moiety (H-3´, H-5´) and three aromatic protons of acetamide group (H-4´´, H-5´´ & H-6´´). Appearance of four doublets at 7.22, 6.94, 4.26 and4.19 confirm proton H-3´, H-2´´ & H-6´´, Ha and Hb respectively. Three singlets at 2.18, 1.47 and 1.48 represents three protons of aromatic CH_3 and six protons of fibric acid aliphatic region (Fig.1). These cumulative spectral evidences determine the structure as 2-5-[2-(4-Chlorophenoxy)propan-2-yl]-1,3,4-oxadiazol-2-ylthio-N-(2-methylphenyl)acetamide. All spectral results from FT-IR, ^{1}H-NMR, ^{13}C-NMR and EI-MS thoroughly confirm the structure of remaining fibric acid derivatives **(3a-h)**.

Table 4. OGTT in normal rats

Sr. No.	Compounds	Glucose level mg/dL			
		Fasting	1 hr	3 hr	5 hr
1	1	91	109	85	84
2	3a	74	102	84	72
3	3b	69	114	85	83
4	3c	80	119	96	89
5	3d	79	122	104	104
6	3e	82	128	104	103
7	3f	88	121	109	101
8	3g	75	89	81	78
9	3h	81	113	90	74
10	Control	99	100	79	75
11	Glibenclamide	93	76	49	42

3.2. Pharmacology

From the Table 4, it can be observed that compounds **(3a-h)** have varying effects on glucose levels as compared to the control group and glibenclamide. Compound **(3c)** has a slightly higher fasting glucose level than the control group, but it shows a reduction in glucose levels at 1 hour, 3 hours, and 5 hours after treatment. The glucose-lowering effect of **(3c)** is comparable to that of glibenclamide. However, compounds **(3d)**, **(3e)**, and **(3f)** show a reduction in glucose levels at 1 hour after treatment but do not maintain this effect at 3 hours and 5 hours after treatment. Compound **(3g)** shows a reduction in glucose levels at all time points after treatment but to a lesser extent than 3c and glibenclamide. Compound **(3h)** shows a reduction in glucose levels at 1 hour and 3 hours after treatment but not at 5 hours after treatment.

Overall, the above results suggest that compound **(3c)** has potential as an anti-diabetic agent as it shows a sustained glucose-lowering effect comparable to glibenclamide. However, further more studies are needed to assess the safety and efficacy of this compound in the treatment of diabetes.

4. Conclusion

Our results revealed that the Synthesis of titled compounds, **(3a-h)**, by microwave- assisted method resulted into high yield within 80-190 seconds with maximum yield of 82-96% as compared to ultrasonic and conventional techniques that afforded products of 75-91% in 60-90 minutes and 41-69% in 11-26 hours respectively (Table 3). The spectroscopic data well supported the supposed structures of synthesized compounds. The compound **(3c)** showed good anti-hyperglycemic activity in normal hyperglycemic rats. This may be due to methyl substitution at ortho position of phenyl ring of amide. On the basis of above results, it was concluded that the compounds **(3a-h)** may be used as drug candidates suitable for hypoglycemia and other related diseases.

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