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## Microwave Assisted Synthesis of 1,3,5-Triazine Derivative Containing Isoxazole Analogue as an Antibacterial Agent

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## ABSTRACT

This work describes the synthesis and biological evaluation of *s*-triazine derivatives containing isoxazole, prepared using hydroxylamine hydrochloride via a microwave irradiation (MWI) method. The synthetic route began with substituted triazine chalcones, which subsequently reacted with NH<sub>2</sub>OH to yield isoxazole analogues derived from 1,3,5-triazine aniline. Compared to conventional methods, the use of microwave irradiation afforded shorter reaction times, higher yields, and improved purity. The synthesized compounds were characterized using spectroscopic techniques, and their antibacterial activities were systematically evaluated.

## 1. Introduction

Isoxazole was significant heterocycles with diverse biological actions. Heterocyclic compound such as these can function as immunosuppressive agent. These compounds have antibacterial [1], antifungal [2], analgesic [3], anticancer [4] and anti-tumour properties [5]. Organic researcher is exploring the synthesis of isoxazole framework, which has significant application in medicine, industry and modern organic chemistry. It is crucial to investigate methods for creating and synthesizing different isoxazole scaffolds that include heterocyclic rings and finding uses for them in domain of therapeutic chemistry. Isoxazole is one of many heterocyclic compounds that have shown promise as pharmacophores due to the extensive research into its pharmacological effects [6-9]. Over the past 30 years, there has been an increase in the employment of ultrasound as well as Microwave method used for the formation of compound. The ultrasonic irradiation accelerates catalytic processes in both homogeneous and heterogeneous systems [10]. Ultrasounds are used may lead to chemical reactions due to the collapse of cavitations during sound waves, bubbles are produced at specified areas in the liquid solution. Those have modest levels of dissolved gas. When reactants become stuck in a micro bubble and implode, they are subjected to extreme pressure and temperature. This fractures the molecules, resulting in highly susceptible species that can react with the adjacent particles [11].

The generation of organic materials under radiation from microwaves was primarily reliant on the capacity of the medium used for the reaction to successfully absorb microwave energy, along with the selection of natural solvents for complete chemical synthesis. Consequently, microwave-induced synthesis becomes more favorable as a result of constant heating, homogeneity, more substantial pace of chemical reactions, an enhancement in end product yield, and better simpler conditions for reactions. Based on this concept, the isoxazole derivatives are synthesized via chalcones under microwave irradiated heating method to reduce the by-products formation so that the yield of the final product can be improved in lesser reaction time<sup>12</sup>

Here, a lot of Researcher's achieve method for the synthesis of isoxazole derivative by ultrasound assisted medium using amine modified montmorillonite nanoclay [12], heterogeneous catalyst as Sn(II) Mont K-10 [13], ceric ammonium nitrate [13], copper sulphate pentahydrate [14],

absolute ethanol [15], pyridine [16], hydroxylamine hydrochloride in presence of ethanol [17] and conventional synthesis using the copper nano-crystal give the 3,5-disubstituted isoxazole [18]. Microwave assisted synthesis of isoxazole derivative have been prepared using Cu(I) catalysed [19], phase transfer catalyst includes polystyrene, polyamide, polyethyl eneglycol polyacrylamide (PEGA resin), silica etc. [20], also through 1,3 dipolar addition with oxime gives high yield [21], MW synthesized aryl isoxazole using NH<sub>2</sub>OH and chalcone, MW synthesis of substituted isoxazole ring containing pyrazolone moiety using SiO<sub>2</sub> as a catalyst [22], iso-oxazole derivative using sodium acetate [23], isoxazole derivative using NH<sub>2</sub>OH and ethanolic sodium hydroxide under MW irradiation at 210 watt [24], synthesis of trihalomethyl-3-arylisoxazoles using Py-MeOH [25], hydroxylamine hydrochloride with water [26].

Therefore, this present work approach was to synthesis of N<sub>2</sub>,N<sub>4</sub>-bis(4-substitutedphenyl)-N<sub>6</sub>-(4-(5-(4-substituted phenyl)isoxazol-3-yl)phenyl)-1,3,5-triazine-2,4,6-triamine (**6**) by using 1-(4-(4,6-bis(substituted phenylamino)-1,3,5-triazin-2-ylamino)phenyl)-3-(Substitutedphenyl) prop-2-enone (**5**) with hydroxylamine hydrochloride (General scheme). This work is had to prepare the given product by using different method such as a) conventional method (conv.) reflux at 110 °C and b) microwave method at certain temperature. Every synthetic chemical was examined for its ability to inhibit bacterial growth. Also, this work includes a comparison between microwave assisted and traditional methods.

## 2. Experimental Methods

## 2.1 Materials and Testing

Starting materials and solvents used for each reaction is of synthetic grade procured from S.D. Fine, and the products obtained were assessed for purity by physical constant determination, All the reactions were monitored using thin layer chromatography on pre-coated TLC plates (silica gel 60-120) using solvent system toluene : ethylacetate [8:2] for series-1 compounds and dichloromethane : ethyl acetate [9:1] for series-2 compounds. TLC was performed by ascending development in a chamber previously saturated with the solvent system. TLC plates were observed under long UV lamp in UV chamber for detection of spots. Final reactions were carried out on sonicator made by Dakshin, Mumbai.

The synthesized compounds were purified by recrystallization and their structures were characterized by Physical constant and IR. They have shown single spot-on TLC plate when observed under UV light. Melting points were taken in open capillaries on melting point apparatus and were

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uncorrected. Infrared spectroscopy was carried out using potassium bromide (KBr) pellet method on the SHIMADZU IR Affinity-1. The characterization with IR and <sup>1</sup>HNMR spectra of the synthesized compounds, confirmed the anticipated structure. IUPAC names were confirmed with ChemDraw Ultra 8.0 (Cambridge Soft, and Cambridge, USA) [27].

## 2.2 Conventional Synthesis (Scheme 1)

In 30 mL of pure methanol, a combination of hydroxylamine hydrochloride (40 mmole) and 3.24 grams of sodium methoxide (3.24, 40 mmoles) was swirled for 10 minutes (Table 1). After adding compound 2.28 D<sub>1</sub>-D<sub>5</sub> (0.004 moles), the mixture was refluxed for 5 hours. The methanol was diluted with ice water after most of it evaporated under decreased pressure. To get the dark chocolate-colored compound, the product was filtered, washed with diethyl ether, and re-crystallized from ethanol after being left overnight 2.36F<sub>1</sub>-F<sub>5</sub> (Table 2).

**Table 1** Optimization of NaOCH<sub>3</sub> as a catalyst

Entry	Catalyst	Quantity (g)	Time (min)	Yield (%)
1		3.22	300	75
1		3.24	300	80
1	NaOCH <sub>3</sub>	3.30	300	76
1		3.28	300	77
1		3.26	300	78

**Table 2** Synthesis of tri-substituted isoxazole derivatives under optimized condition using conventional

Compound	R	Observed M.P (°C)	% Yield	R <sub>f</sub> Value
2.36 F <sub>1</sub>	H	247	76	0.95
2.36 F <sub>2</sub>	P-OCH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	256	79	0.91
2.36 F <sub>3</sub>	P-NO <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	267	73	0.90
2.36 F <sub>4</sub>	P-OH C <sub>6</sub> H <sub>5</sub>	248	75	0.92
2.36 F <sub>5</sub>	P-Cl C <sub>6</sub> H <sub>5</sub>	253	77	0.93

**Table 3** IR Spectral data for conventional synthesis

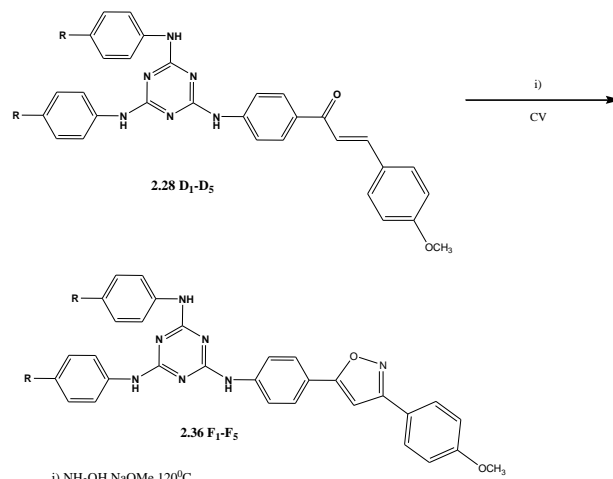
Compound	Name of Compound	IR (cm <sup>-1</sup> )
2.36 F <sub>1</sub>	N2-(4-(3-(4-methoxyphenyl)isoxazol-5-yl)phenyl)-N4,N6-diphenyl-1,3,5-triazine-2,4,6-triamine	3405 (N-H), 1615 (C=N), 2998 (Ar-CH), 785 (C-N, s-triazine), 1176 (isoxazole C-N str.), 1615 (isoxazole C=N), 827 (isoxazole N-O)
2.36 F <sub>2</sub>	N2,N4-bis(4-methoxyphenyl)-N6-(4-(3-(4-methoxyphenyl)isoxazol-5-yl)phenyl)-1,3,5-triazine-2,4,6-triamine	3416 (N-H), 1615 (C=N), 2998 (Ar-CH), 785 (C-N, s-triazine), 1176 (isoxazole C-N str.), 1615 (isoxazole C=N), 827 (isoxazole N-O)
2.36 F <sub>3</sub>	N2-(4-(3-(4-methoxyphenyl)isoxazol-5-yl)phenyl)-N4,N6-bis(4-nitrophenyl)-1,3,5-triazine-2,4,6-triamine	3410 (N-H), 1620 (C=N), 3015 (Ar-CH), 785 (C-N, s-triazine), 1180 (isoxazole C-N str.), 1620 (isoxazole C=N), 830 (isoxazole N-O)
2.36 F <sub>4</sub>	N2-(4-(3-(4-hydroxyphenyl)isoxazol-5-yl)phenyl)-N4,N6-bis(4-nitrophenyl)-1,3,5-triazine-2,4,6-triamine	3411 (N-H), 1620 (C=N), 3015 (Ar-CH), 785 (C-N, s-triazine), 1180 (isoxazole C-N str.), 1625 (isoxazole C=N), 834 (isoxazole N-O)
2.36 F <sub>5</sub>	N2,N4-bis(4-chlorophenyl)-N6-(4-(3-(4-methoxyphenyl)isoxazol-5-yl)phenyl)-1,3,5-triazine-2,4,6-triamine	3420 (N-H), 1620 (C=N), 3015 (Ar-CH), 785 (C-N, s-triazine), 1185 (isoxazole C-N str.), 1615 (isoxazole C=N), 825 (isoxazole N-O)

<sup>1</sup>H NMR spectral Data: 2.36 F<sub>2</sub>: δ=6.87-7.89 (m, 12H, Ar-H), δ=3.84 (S,6H,Ar-OCH<sub>3</sub>), δ=7.1 (d,1H,Ar-H), δ=7.7 (d,1H,Ar-H), δ=3.42 (S,1H,Ar-OCH<sub>3</sub>). 2.36 F<sub>3</sub>: δ=6.92-7.5 (m,12H, Ar-H), δ=3.75 (S,6H,Ar-OCH<sub>3</sub>), δ=7.2 (d,1H,Ar-H), δ=7.7 (d,1H,Ar-H), δ=3.45 (S,1H,Ar-OCH<sub>3</sub>). 2.36 F<sub>4</sub>: δ=6.67-7.88 (m,12H, Ar-H), δ=3.85 (S,6H,Ar-OCH<sub>3</sub>), δ=7.1 (d,1H,Ar-H), δ=7.6 (d,1H,Ar-H), δ=4.9 (S,1H,Ar-OH), 2.36 F<sub>5</sub>: δ=6.87-7.89 (m,12H,Ar-H), δ=3.8 (S,6H,Ar-OCH<sub>3</sub>), δ=7.0 (d,1H,Ar-H), δ=7.6 (d,1H,Ar-H).

<sup>13</sup>C NMR spectral Data: 2.36F<sub>2</sub>: δ=164.0, 126,125, 114, 113.5, 55.18, 40, 39, 2.36 F<sub>3</sub>: δ=164.6, 125,127, 115.5, 114, 39.29,57,98, 2.36 F<sub>4</sub>: δ=163.9, 124, 126, 117, 116, 115, 39.7, 38.8, 2.36 F<sub>5</sub>: δ=163.8, 123, 126, 113, 116, 120, 55.16, 40.13.

Mass spectrum analysis: It shows m/z Peak at 587, (m+1) peak at 588, (m-1) peak at 586. Table 3 gives the FTIR spectral data.

<https://doi.org/10.30799/jacs.S101.26120201>



**Scheme 1** Synthesis of N2,N4-bis(4-substitutedphenyl)-N6-(4-(3-(4-substituted phenyl)isoxazol-5-yl)phenyl)-1,3,5-triazine-2,4,6-triamine (2.36F<sub>1</sub>-F<sub>5</sub>) derivatives using NaOCH<sub>3</sub> as a Catalyst

## 2.3 Microwave Synthesis (Scheme 2)

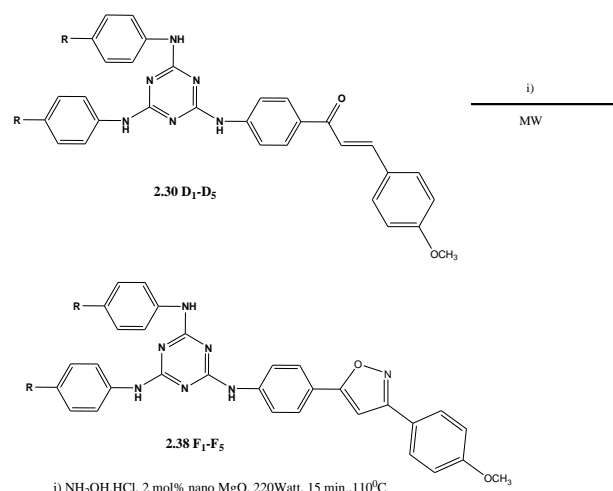
An equimolar combination of triazole substituted chalcones (2.30 D<sub>1</sub>-D<sub>5</sub>) (2 mmol) and hydroxylamine hydrochloride (2 mmol) and nano-MgO (2 mol%) in 5 mL distilled water (Table 4), the whole mixture was stirred at room temperature for 5 min. Then it was subjected to reflux under microwave irradiation at 220W for 15 minutes and temperature at 110 °C. The reaction progress completeness was monitored by using silica coated TLC plate. After completion of the reaction, the reaction mixture was filtered and hot residue taken in ethanol, this catalyst again used to prepare further derivative. The purification process was done by using column chromatography. The product 2.38 F<sub>1</sub>-F<sub>5</sub> was obtained in high purity (Table 5).

**Table 4** Optimization of nano-MgO catalyst

Entry	Catalyst	Mole%	Time (min)	Temp. (°C)	Yield (%)
1		0.5	12	110	78
1		1.0	14	110	80
1	nano-MgO	1.5	16	110	76
1		2.0	15	110	90
1		2.5	15	110	85

**Table 5** Synthesis of tri-substituted chalcone using microwave method

Compound	R	Observed M.P (°C)	Reported M.P (°C)	% Yield	R <sub>f</sub> Value
2.38 F <sub>1</sub>	H	246	248	85	0.96
2.38 F <sub>2</sub>	P-OCH <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	258	258	87	0.90
2.38 F <sub>3</sub>	P-NO <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	269	268	88	0.89
2.38 F <sub>4</sub>	P-OH C <sub>6</sub> H <sub>5</sub>	251	250	89	0.90
2.38 F <sub>5</sub>	P-Cl C <sub>6</sub> H <sub>5</sub>	255	254	90	0.91



**Scheme 2** Microwave Synthesis of N2, N4-bis (4-substitutedphenyl)-N6-(4-(3-(4-substitutedphenyl) isoxazol-5-yl)phenyl)-1,3,5-triazine-2,4,6-triamine (2.38F<sub>1</sub>-F<sub>5</sub>) using nano-MgO catalyst

**Table 6** IR Spectral data for microwave synthesis

Compound	Name of Compound	IR (cm <sup>-1</sup> )
2.38 F <sub>2</sub>	N2,N4-bis(4-methoxyphenyl)-N6-(4-(3-(4-methoxyphenyl)isoxazol-5-yl)phenyl)-1,3,5-triazine-2,4,6-triamine	3416 (N-H), 1615 (C=N), 2998 (Ar-CH), 785 (C-N, s-triazine), 1176 (isoxazole C-N str.), 1615 (isoxazole C=N), 827 (isoxazole N-O)
2.38 F <sub>3</sub>	N2-(4-(3-(4-methoxyphenyl)isoxazol-5-yl)phenyl)-N4,N6-bis(4-nitrophenyl)-1,3,5-triazine-2,4,6-triamine	3400 (N-H), 1620 (C=N), 3015 (Ar-CH), 785 (C-N, s-triazine), 1180 (isoxazole C-N str.), 1620 (isoxazole C=N), 830 (isoxazole N-O)
2.38 F <sub>4</sub>	N2-(4-(3-(4-hydroxyphenyl)isoxazol-5-yl)phenyl)-N4,N6-bis(4-nitrophenyl)-1,3,5-triazine-2,4,6-triamine	3400 (N-H), 1620 (C=N), 3015 (Ar-CH), 785 (C-N, s-triazine), 1180 (isoxazole C-N str.), 1625 (isoxazole C=N), 834 (isoxazole N-O)
2.38 F <sub>5</sub>	N2,N4-bis(4-chlorophenyl)-N6-(4-(3-(4-methoxyphenyl)isoxazol-5-yl)phenyl)-1,3,5-triazine-2,4,6-triamine	3400 (N-H), 1620 (C=N), 3015 (Ar-CH), 785 (C-N, s-triazine), 1185 (isoxazole C-N str.), 1615 (isoxazole C=N), 825 (isoxazole N-O)

<sup>1</sup>H NMR Spectral Data: 2.38F<sub>2</sub>: δ=6.87-7.89 (m,12H, Ar-H), δ=3.84 (S,6H,Ar-OCH<sub>3</sub>), δ=7.1 (d,1H,Ar-H), δ=7.7 (d,1H,Ar-H), δ=3.42 (S,1H,Ar-OCH<sub>3</sub>), 2.38F<sub>3</sub>: δ=6.92-7.5 (m,12H, Ar-H), δ=3.75 (S,6H,Ar-OCH<sub>3</sub>), δ=7.2 (d,1H,Ar-H), δ=7.7 (d,1H,Ar-H), δ=3.45 (S,1H,Ar-OCH<sub>3</sub>), 2.38F<sub>4</sub>: δ=6.67-7.88 (m,12H, Ar-H), δ=3.85 (S,6H,Ar-OCH<sub>3</sub>), δ=7.1 (d,1H,Ar-H), δ=7.6 (d,1H,Ar-H), δ=4.9 (S,1H,Ar-OH), 2.38F<sub>5</sub>: δ=6.87-7.89 (m,12H, Ar-H), δ=3.8 (S,6H,Ar-OCH<sub>3</sub>), δ=7.0 (d,1H,Ar-H), δ=7.6 (d,1H,Ar-H).

<sup>13</sup>C NMR: 2.38 F<sub>2</sub>: δ=164.0, 126,125, 114, 113.5, 55.18, 40, 39, 2.38F<sub>3</sub>: δ=164.6, 125,127, 115.5, 114, 39.29,57,98, 2.38 F<sub>4</sub>: δ=163.9, 124, 126, 117, 116, 115, 39.7, 38.8, 2.38 F<sub>5</sub>: δ=163.8, 123, 126, 113, 116, 120, 55.16, 40.13.

Mass spectrum Analysis: It shows m/z Peak at 587, (m+1) peak at 588, (m-1) peak at 586. Table 6 gives the FTIR spectral characteristics.

#### 2.4 Biological Activity of Synthesized Compounds

Autoclaving the medium, adding it to sterile petri dishes, and letting it harden under aseptic circumstances are the steps needed to make nutritional agar plates for testing the antibacterial activity of test chemicals or substances using the agar well diffusion technique. Used a sterile glass spreader or cotton brush to uniformly distribute a bacterial active suspension that has been incubated for 24 hours and is compatible with a 0.5 McFarland standard over the agar surface; this will inoculate the plates. Then made holes in the hardened agar with a sterilized cork borer. After that added 50-100 μL of the test chemical to every well in an aseptic manner. The plates were sat at 8 °C for half an hour to let the test chemical diffuse into the agar. While turned upside down, incubated the plates at 37 °C for 18 to 24 hours [28]. The sizes of the clear zones surrounding the wells were measured in millimeters after incubation and given in Table 7.

**Table 7** Antimicrobial spectrums of (2.38 F<sub>1</sub>-F<sub>5</sub>) against human pathogenic bacteria sp.±SD (all values are mean of three replicates)

Comp. No	Test compounds (Dissolved in DMSO) Concentration in μg/mL	Zone of Inhibition (mm) Against <i>Staphylococcus aureus</i>	Zone of Inhibition (mm) Against <i>E. coli</i>	Zone of Inhibition (mm) Against <i>Bacillus sp.</i>	Zone of Inhibition (mm) Against <i>Pseudomonas aeruginosa</i>
2.38F <sub>1</sub>	20	*	*	*	*
2.38F <sub>2</sub>	40	08 ±0.02	*	07±0.11	*
2.38F <sub>3</sub>	60	11 ±0.05	7 ±0.09	9 ±0.04	6 ±0.08
2.38F <sub>4</sub>	80	13 ±0.08	9 ±0.05	11 ±0.07	9 ±0.05
2.38F <sub>5</sub>	100	16±0.03	12±0.02	14±0.05	11±0.31

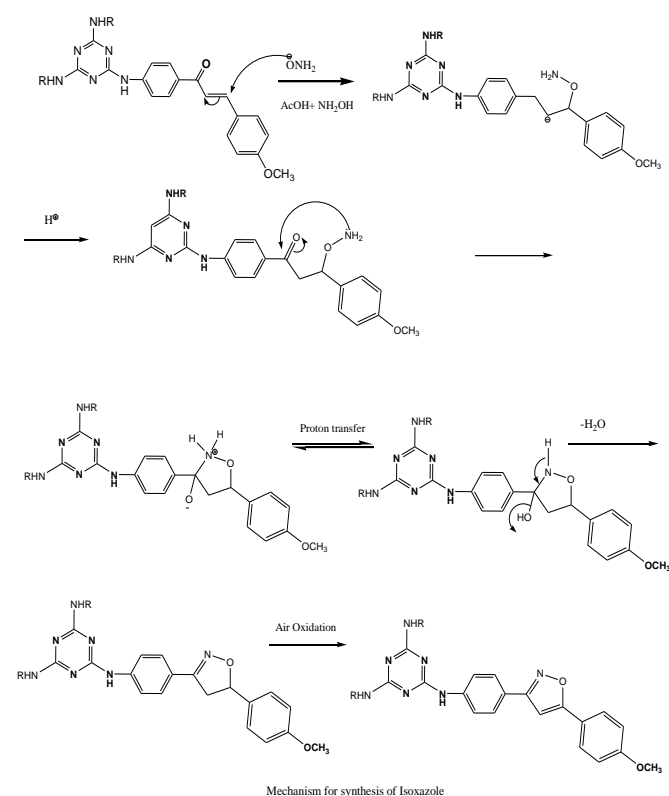
\*Note: Compounds shows antibacterial activity but not significant  
<https://doi.org/10.30799/jacs.S101.26120201>

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### 3. Results and Discussion

The nano crystalline MgO employed in the synthesis of S-triazine derivative containing isoxazole (2.38F<sub>1</sub>-F<sub>5</sub>). The best reaction condition was investigated using s-triazine chalcone (2.30D<sub>1</sub>-D<sub>5</sub>) (2 mmole) using microwave irradiation in presence of different solvent. Several solvent including water, ethanol, water, DMF, pet ether and n-hexane were used to perform model reaction. It was also carried out under circumstances without solvent, with different concentration of nano-MgO serving as the catalyst. Also, the reaction may proceed even when no catalyst was present. It was found that the 90% yield was obtained when the reaction one in presence of aq. condition using 2 mole% nano crystalline magnesium oxide (MgO) catalyst. The optimum temperature of reaction was set up at 110 °C. It was not giving any satisfactorily result for other temperature. The procedure includes varying the substrate molar ratio, temperature and different solvent,

Hence, the best result that the reaction was 1:1 mole ratio of s-triazine chalcone and hydrazine hydrochloride in presence of 2 mole% MgO in 4-5 mL aqueous solvent at 110 °C temperature was done in presence of microwave irradiation for 15-20 min. Present approach for synthesizing s-triazine derivative containing isoxazole was straight forward, efficient and takes less time than others. The similar process when performed under traditional condition took too much longer and produced lower yield but the reaction were accomplished out using microwave irradiation it completed in 15 minutes. Thus, microwave assisted synthesis provides cleaner and less expensive compare to traditional heating method. Also microwave assisted irradiation helped molecules become more polar, which speed up reaction and produce better yield. Because of its polarity, water plays an important role as a solvent in microwave organic synthesis. Water boosts heating efficiency and causes reaction effectively. In-contrast poor yield achieved using traditional approach, the current analysis found that microwave irradiation increased product yield by 80-90% (Scheme 3).

**Scheme 3** Mechanism for the synthesis of isoxazole

### 4. Conclusion

This present work has been synthesized the compound N2,N4-bis (4-substitutedphenyl)-N6-(4-(3-(4-substitutedphenyl)isoxazol-5-yl)phenyl)-1,3,5-triazine-2,4,6-triamine from substituted triazine containing chalcone and hydroxylamine hydrochloride with different ways as conventional, and microwave method. Nano-crystalline MgO (2 mole) has been used as a catalyst. The reaction time was completed in 15 minutes using aqueous solvent. From the data it was concluded that microwave assisted reaction shows good yield, cleaner approach, less expensive and less time required than traditional approach.

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