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Chemistry

A SOLVENT-FREE GREEN ROUTE TO FLUORINATED ISOXAZOLIDINES AND THEIR BIOLOGICAL EVALUATION AS POTENT ALDOSE REDUCTASE INHIBITORS

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ABSTRACT A simple and environmentally benign method has been developed for the synthesis of fluorinated isoxazolidine derivatives from 1,3-dipolar cycloaddition reactions of azomethine *N*-oxides and fluoro substituted maleimide on montmorillonite K-10 clay as solid acid catalysts by microwave under solvent-free conditions and evaluate these compounds for their advanced glycation end (AGE) product formation inhibitory activity.

KEYWORDS : Eco-friendly; green chemistry; microwave; cycloaddition; antiglycation; pyrrolo-isoxazolidines.

1.INTRODUCTION

Among all the 1,3-dipole, azomethine *N*-oxides are the building blocks of 'Huisgen reactions' which undergo cycloaddition reactions with variously substituted dipolarophiles having activated double bonds like maleimides,[1,2] cinnamoyl piperidines,[3,4] chiral Lewis acids and metal catalysed substrates.[5-9]Azomethine *N*-oxides are remarkable key intermediates, behave as electrophiles toward organic synthesis and organometallic chemistry.[10] In recent times, metal derivatives promoted 1,3-dipolar cycloaddition reactions become an area of new research.[11]Besides, azomethine *N*-oxides are useful spin trapping reagent in biological studies[12] and have applications as therapeutics in age-related diseases.[13]Azomethine *N*-oxides are prepared commonly by direct condensation of aldehydes with hydroxylamine and oxidation of secondary amines.[8-10,14] Pyrrolo-isoxazolidine compounds are well known from past few decades for their antimicrobial and antioxidant behaviour. Pyrrolo-isoxazolidine derivatives are reported in pharmaceutical chemistry as broad spectrum antibiotic and highly active against various gram positive and gram negative bacteria. The antifungal activity has also been shown against various fungi or yeast.[15] Amino and chloro substituted pyrrolo-isoxazolidines have also been reported to be active against bacteria like *Vibrio parahaemolyticus, Streptococcus pyogenes, Proteus vulgaris, Shingellaflexneri, Salmonella typhi* and *Vibrio cholera.*[16] Synthesis of pyrrolo-isoxazolidine derivatives for their advanced glycation end (AGE) product formation inhibitory activity,[17] acetylcholinesterase inhibitors for the management of Alzheimer's disease and anti-amnestic agents,[18] antistress and antibacterial evaluations of isoxazolidine derivatives has also been reported.[19,20] Thus, herein, we report an highly efficient, eco-friendly synthesis of fluoroisoxazolidine derivatives under solvent-free conditions in microwave using solid clay catalyst. It is an improved alternative to other conventional methods of synthesis. The synthesized compounds are evaluated for their advanced glycation end (AGE) product formation inhibitory activity.

2.RESULTS AND DISCUSSION

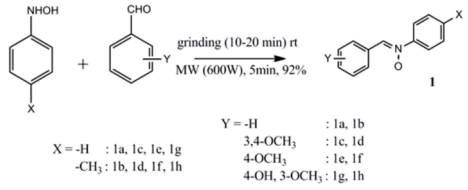
2.1. Chemistry

Montmorillonite (MMT) K-10 clay catalyzed microwave assisted 1,3-dipolar cycloaddition reactions of stable azomethine *N*-oxides **1a-h** with *N*-*p*-fluorophenylmaleimide **2** in solvent-free conditions resulted in the formation of a series of new fluoro-isoxazolidine derivatives **3a-h** with high yields, improved purity and very short reaction times in highly regioselective manner. It is noteworthy to mention that the enhanced reaction rates and better yields in short reaction time are the features obtained in 600W microwave radiations **(Table 1, entries 2, 3, 4)**. However, the same reaction in 450W microwave radiations did not give the satisfactory results **(Table 1, entry 1)**. On the other hand, the reaction was studied using NaOAc and NH_4OAc as a base (3 mmol per 1 mmol of substrate) **(Table 1, entries 2, 3)**. To evaluate the impact of base on the reaction rate but it was found that the difference was minimal. The results showed that the reaction undergoes simultaneously without any additive making this a highly atom-efficient method. Therefore, by employing the optimized conditions phenylhydroxylamine (1mmol) and aldehyde (1mmol) were ground at room temperature to 10-20 min afforded the corresponding azomethine *N*-oxide in 92% yield **(Table 1, entries 4, Scheme 1)**.

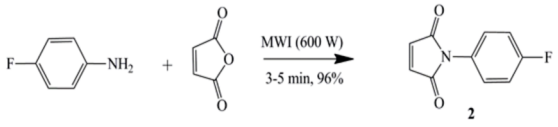
Table 1. Optimization of the reaction condition[a] for azomethine *N*-oxide 1a-h

Entry	MWI (W)	Δ C	Base	Time[b] (min)	Yield[b] (%)
1	450	-	NaOAc	15 min	72
2	600	-	NaOAc	5 min	85
3	600	-	NH_4OAc	7-8 min	82
4	600	-	-	<5	92
5	-	160	-	120 min	<50

[a]Phenylhydroxylamine (1 mmol), aldehyde (1 mmol), base (3 mmol), reactants were ground to 10-20 min, 353K; [b]Isolated yield

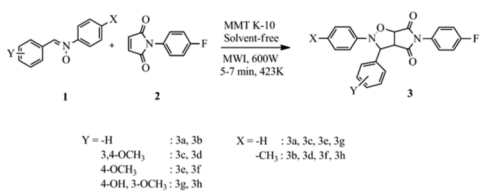


Scheme 1. Schematic diagram describing the synthesis of variously substituted azomethine *N*-oxide derivatives in microwave **1a-h**



Scheme 2. Schematic diagram describing the microwave assisted synthesis of *N*-*p*-fluorophenylmaleimide **2**

It was observed that under identical reaction conditions slightly higher yields were obtained at 5 mol% catalyst **(Table 2, entries 2,4,6,8,10,12)**, but lowering the amount of catalyst to 2 mol% led to lower yields **(Table 2, entries 1,3,5,7,9,11)**. The synthesis of variously substituted isoxazolidine derivatives from corresponding azomethine *N*-oxides (1 mmol) and maleimide (1 mmol) under 600W microwave radiations catalyzed by MMT K-10 clay (5 mol%) was very effective (95% yield) in short reaction time **(Table 2, entries 10)**. MMT K-10 clay formed a labile complex with azomethine *N*-oxide, lowered the transition state energy and reaction proceeded smoothly at much faster rates.



Scheme 3. Schematic diagram describing the solvent-free clay catalyzed green synthesis of fluorinated isoxazolidine derivatives **3a-h**

Table 2. Optimization of reaction condition[a] for isoxazolidines 3a-h in different solid acidic catalysts.

Entry	Catalyst	Catalyst mol%	Time (min)	Yield[b](%)
1	SiO_2/Al_2O_3	2	20-25	68
2		5	15	75
3	CrO_3-Sio_2	2	25	72
4		5	15	78
5	KF/Al_2O_3	2	15	80
6		5	12	84
7	MMT-KSF	2	10	82
8		5	7	87
9	MMT K-10	2	10	88
10		5	5	95
11	MMT K-30	2	10	87
12		5	8	90

[a]**1a-h** (1 mmol), **2** (1 mmol), 423K; [b] Isolated yield.

After optimizing the reaction conditions, the various substrates were subjected to solvent-free MMT K-10 catalysed microwave radiations to afford the corresponding products in excellent yields **(Table 3)**. The anticipated cycloadducts characterized through their melting point, elemental analysis, IR, ^{1}H-NMR, ^{13}C-NMR and mass spectral studies. All the compounds have given satisfactory elemental analysis.

Table 3. Characterisation data of 2,3-substituteddiphenyl-5-(4'-fluorophenyl)-4*H*-2,3,3a,5,6,6a hexahydropyrrolo[3,4-*d*]isoxazole-4,6-diones derivatives 3a-h

X		Y	Melting point	Time (min)	Yield[b](%)
3a	-H	-H	156-158	4	93
3b	$-CH_3$	-H	165-166	5	95
3c	-H	3,4-OCH_3	204-205	6	88
3d	$-CH_3$	3,4-OCH_3	198-199	7	82
3e	-H	4-OCH_3	200-202	5	85
3f	$-CH_3$	4-OCH_3	190-191	6	90
3g	-H	4-OH, 3-OCH_3	184-186	5	96
3h	$-CH_3$	4-OH, 3-OCH_3	202-204	5	92

1a-h (1 mmol), **2** (1 mmol), catalyst (5 mol%), 423K; [b]Isolated yield

In the IR spectrum of 2,3-Diphenyl-5-(4'-fluorophenyl)-4*H*-2,3,3a,5,6,6a-hexahydropyrrolo[3,4-*d*]isoxazole-4,6-dione **3a** revealed the presence of strong carbonyl stretching vibration band at 1777 cm^{-1} due to carbonyl group of succinimide ring while a shoulder band at 1722 cm^{-1} was assigned to the second carbonyl group of succinimide ring. Absorption band at 1600 cm^{-1} was assigned to the aromatic C=C skeletal stretching vibrations. In the ^{1}H-NMR spectrum, compound **3a** displayed two doublets at δ 4.95 with J = 9.2 Hz and δ 5.42 with J = 7.76 Hz, respectively, for protons C_3-H and C_{6a}-H on coupling with proton C_{3a}-H. Proton C_{6a}-H appeared downfield in comparison to proton C_3-H because of electronegative oxygen atom attached to C_{6a}-H. Aromatic protons appeared as multiplets in the range of δ 7.43–7.06 (equivalent to 14H). A double doublet at δ 4.20 (J = 7.80 Hz and J = 7.88 Hz) has been assigned to proton C_{3a}-H. In the ^{13}C-NMR spectrum, compound **3a** displayed the characteristic signals at δ 173.66 and δ 171.45, which have been assigned to two succinimide carbonyl carbons. The signals in the range of δ 146.03–115.70 has been assigned to aromatic carbons. Another two signals at δ 77.13 and δ 54.34 have been assigned to C_{6a} and C_{3a} carbon atoms, respectively. A signal at δ 70.65 has been assigned to C_3 carbon. Only one isomer has been obtained in all cases as evidenced by thin layer chromatography (TLC) analysis showing single spot in each case.

2.2. Advanced glycation end-product formation inhibitory activity

The data from **table 4** indicated that among all the synthesized compounds with *p*-CH_3 substituent on the *N*-phenyl ring of the azomethine *N*-oxide moiety **3d**, **3f** and **3h** were found to be exceedingly potent in comparison to the compound with no substitution on this ring **3c**, **3e** and **3g**. Furthermore, it was concluded that the dimethoxy substituted compound **3d** on the *C*-phenyl ring was the best anti-glycating agent **(see Table 4).** However, the introduction of hydroxy group with methoxy substituent on *C*- phenyl ring **3g** decrease the potency to inhibit advanced glycation end product formation.

Table 4. Advanced glycation end product formation inhibitory activity of 3a-h

Compounds	X	Y	IC_{50}(μM)
3a	-H	-H	90.36 ± 2.41
3b	$-CH_3$	-H	87.50 ± 0.97
3c	-H	3,4-OCH_3	50.03 ± 0.35
3d	$-CH_3$	3,4-OCH_3	4.17 ± 0.70
3e	-H	4-OCH_3	58.03 ± 1.83
3f	$-CH_3$	4-OCH_3	22.84 ± 2.63
3g	-H	4-OH, 3-OCH_3	116.71 ± 4.43
3h	$-CH_3$	4-OH, 3-OCH_3	83.61 ± 1.85
Aminoguanidine	-	-	40.54 ± 2.04

3.EXPERIMENTAL

3.1.Chemistry

3.1.1.General

All the reagents and the solvents used were of analytical grade. Melting points recorded were uncorrected. IR spectra were recorded on a Perkin Elmer RXIFT infrared spectrophotometer (manufactured at Buckinghamshire, England) using KBr pellets. ^{1}H-NMR was recorded at 400 MHz on BRUKER spectrometer (manufactured at Fallanden, Switzerland) using tetramethylsilane (TMS) as internal standard. The ^{13}C-NMR spectra were recorded at 400 MHz on BRUKER spectrometer using TMS as internal standard. Mass spectra were recorded on Waters Micromass Q-T of Micro (ESI) spectrometer (manufactured at Vernon Hills, USA). Elemental analysis was carried out using ElementarVario MICRO cube CHN analyser (Frankfurt, Germany). Thin-layer chromatography (TLC) analysis was carried out on glass plates coated with silica gel-G (LobaChemie) suspended in methanol-chloroform. Column chromatography was performed using silica gel (100-200 mesh, LobaChemie).

3.1.2. General procedure for the synthesis of *N-p*-fluorophe nylm aleimide under microwave conditions

The *N-p*-fluorophenylmaleinilic acid were dissolved in acetic anhydride and anhydrous sodium acetate and further irradiate the mixture under microwave conditions (600 W) for 15-17 minutes. The reaction mixture was then poured in ice cold water to afford the solid which was filtered and washed with water to give fine needle like *N-p*-fluorophenylmaleimide. The crude product was then recrystallised from petroleum ether to give shining crystals.

3.1.3. General procedure for synthesis of azomethine *N*-oxide under microwave conditions

The aldehyde, hydroxylamine hydrochloride (1 equiv) and sodium acetate (1.2 equiv) were placed in 20 mL glass tube equipped with septa. The reaction mixture were exposed to microwave oven at 600 W irradiation power at 80 ºC for appropriate time until the substrates were consumed as judged by thin layer chromatography. The reaction mixture was diluted with water, extracted with CH_2Cl_2, dried over anhydrous sodium sulphate, filtered and the solvent was removed under high vacuum and the crude product was purified by column chromatography using hexane-ethyl acetate (9:1) mixture.

3.1.4. General procedure for cycloaddition under various conditions

Method A: An oven-dried flask was cooled under a stream of nitrogen. The variously substituted *N-p*-fluorophenylmaleimide (0.01 mol) and azomethine *N*-oxide have been reacted in anhydrous toluene (30 mL). The contents in the flask were refluxed for 4-6 hour until the completetion of the reaction as indicated by TLC. Then it was cooled under the tap water. The crude product was filtered on precipitation then recrystallised from toluene-petroleum ether (8:2) to give corresponding cycloadduct.

Method B: A mixture of *N-p*-fluorophenylmaleimide (1.0 mmol) and azomethine *N*-oxide (1.0 mmol) were ground with 1g of silica gel (60-120 mesh) and exposed to microwave at 600 W irradiating power. After the completion of reaction as judged by TLC, the residue was purified by column chromatography using hexane-ethyl acetate (9:1) as eluent to afford fluoro-isoxazolidine derivatives.

Method C: A mixture of *N-p*-fluorophenylmaleimide (1.0 mmol) and azomethine *N*-oxide (1.0 mmol) were ground with CrO_3-silica (200 mg) in the ratio of 1:1 by weight and exposed to microwave at 600 W irradiating power. After completion of the reaction as judged by TLC, the reaction mixture was diluted with water, extracted with CH_2Cl_2,

dried over anhydrous sodium sulphate, filtered and the solvent was removed under high vacuum and the crude product was purified by column chromatography using hexane-ethyl acetate (9:1) as eluent to afford fluoro-isoxazolidine derivatives.

2,3-Diphenyl-5-(4'-fluorophenyl)-4*H*-2,3,3a,5,6,6a-hexahydropyrrolo[3,4-*d*]isoxazole-4,6-dione (3a). Compound obtained as a white solid (yield 69%), m.p. 156-158 ºC; **IR (KBr pellets, ν_{max}/cm^{-1}):** 1722.2, 1777.4 (C=O); **^{1}H-NMR (400 MHz, DMSO-d$_6$):δ_H** 7.43-7.06 (m, 14H, ArH), 5.42 (d, 1H, *J* = 7.76 Hz, H-6a), 4.95 (d, 1H, *J* = 9.2 Hz, H-3), 4.20 (dd, 1H, *J* = 7.80, 7.88 Hz, H-3a); **^{13}C-NMR (100 MHz, DMSO-d$_6$):δ** 173.6, 171.4, 146.0, 134.6-115.7, 128.4, 120.3, 77.1, 70.6, 54.3; **MS(ESI):m/z:** 387[M]$^+$; **Anal. Calc. for $C_{23}H_{16}N_2O_3F$:** C, 71.32; H, 4.13; N, 7.23, **Found:** C, 71.40; H, 4.23; N, 7.28.

5-(4'-Fluorophenyl)-3-(4'-methylphenyl)2-phenyl,-4*H*-2,3,3a,5,6,6a-hexahydropyrrolo[3,4-*d*]isoxazole-4,6-dione (3b). Compound obtained as a white solid (yield 67%), m.p. 165-166 ºC; **IR (KBr pellets, ν_{max}/cm^{-1}):** 1708.6, 1782.2 (C=O); **^{1}H-NMR (400 MHz, DMSO-d$_6$):δ_H** 7.43-7.06 (m, 13H, ArH), 5.42 (d, 1H, *J* = 7.76 Hz, H-6a), 4.95 (d, 1H, *J* = 9.2 Hz, H-3), 4.20 (dd, 1H, *J* = 7.80, 7.88 Hz, H-3a), 2.25 (s, 3H, -CH$_3$); **^{13}C-NMR (100 MHz, DMSO-d$_6$):δ** 176.6, 170.4, 156.0, 138.9-117.7, 124.4, 119.3, 76.1, 70.2, 56.3; **MS(ESI):m/z:** 401[M]$^+$; **Anal. Calc. for $C_{24}H_{19}N_2O_3F$:** C, 71.82; H, 4.74; N, 6.98, **Found:** C, 71.84; H, 4.69; N, 6.92.

3-(3',4'-Dimethoxyphenyl)-5-(4'-fluorophenyl)-2-phenyl-4*H*-2,3,3a,5,6,6a-hexahydropyrrolo[3,4-*d*]isoxazole-4,6-dione (3c). Compound obtained as a white solid (yield 68%), m.p. 204-205ºC; **IR (KBr pellets, ν_{max}/cm^{-1}):** 1693.9, 1777.1 (C=O), 1284 (C-O aromatics), 1037 (C-O aliphatics); **^{1}H-NMR (400 MHz, DMSO-d$_6$):δ_H** 7.45-7.21 (m, 12H, ArH), 5.40 (d, 1H, *J* = 7.76 Hz, H-6a), 4.87 (d, 1H, *J* = 9.2 Hz, H-3), 4.22 (dd, 1H, *J* = 7.80, 7.88 Hz, H-3a), 3.60 (s, 6H, -OCH$_3$); **^{13}C-NMR (100 MHz, DMSO-d$_6$): δ** 172.6, 170.2, 148.0, 132.7-114.9, 127.4, 119.3, 76.0, 70.5, ,63.3, 56.3; **MS(ESI):m/z:** 448[M]$^+$; **Anal. Calc. for $C_{25}H_{21}N_2O_5F$:** C, 66.96; H, 4.69; N, 6.25, **Found:** C, 66.94; H, 4.70; N, 6.22.

3-(3',4'-Dimethoxyphenyl)-5-(4'-fluorophenyl)-2-(4-methylphenyl)-4*H*-2,3,3a,5,6,6a-hexahydropyrrolo[3,4-*d*]isoxazole-4,6-dione (3d). Compound obtained as a white solid (yield 65%), m.p. 198-199 ºC; **IR (KBr pellets, ν_{max}/cm^{-1}):** 1694.1, 1778.2 (C=O), 1282 (C-O aromatics), 1031 (C-O aliphatics); **^{1}H-NMR (400 MHz, DMSO-d$_6$):δ_H** 7.33-7.00 (m, 11H, ArH), 5.32 (d, 1H, *J* = 7.76 Hz, H-6a), 4.99 (d, 1H, *J* = 9.2 Hz, H-3), 4.00 (dd, 1H, *J* = 7.80, 7.86 Hz, H-3a), 3.60 (s, 6H, -OCH$_3$), 2.18 (s, 3H, CH$_3$); **^{13}C-NMR (100 MHz, DMSO-d$_6$):δ** 172.4, 170.2, 145.8, 135.7-112.7, 127.6, 119.1, 76.4, 70.8, ,63.2, 53.3, 20.3; **MS(ESI):m/z:** 462[M]$^+$; **Anal. Calc. for $C_{26}H_{23}N_2O_5F$:** C, 67.53; H, 4.98; N, 6.07, **Found:** C, 67.52; H, 4.99; N, 6.02.

5-(4'-Fluorophenyl)-3-(4-methoxyphenyl)-2-phenyl-4*H*-2,3,3a,5,6,6a-hexahydropyrrolo[3,4-*d*]isoxazole-4,6-dione (3e). Compound obtained as a yellow solid (yield 78 %), m.p. 200-202 ºC; **IR (KBr pellets, ν_{max}/cm^{-1}):** 1713.4, 1784.4 (C=O), 1288 (C-O aromatics), 1033 (C-O aliphatics); **^{1}H-NMR (400 MHz, DMSO-d$_6$): δ_H** 7.47-7.20 (m, 13H, ArH), 5.41 (d, 1H, *J* = 7.77 Hz, H-6a), 4.94 (d, 1H, *J* = 9.2 Hz, H-3), 4.18 (dd, 1H, *J* = 7.80, 7.88 Hz, H-3a), 3.70 (s, 3H, -OCH$_3$); **^{13}C-NMR (100 MHz, DMSO-d$_6$):δ** 172.2, 171.1, 148.0, 133.9-113.7, 126.4, 118.5, 76.1, 71.6, , 54.6, 52.3; **MS(ESI):m/z:** 417[M]$^+$; **Anal. Calcd. for $C_{24}H_{18}N_2O_4F$:** C, 69.07; H, 4.32; N, 6.71, **Found:** C, 69.02; H, 4.29; N, 6.72.

5-(4'-Fluorophenyl)--3-(4-methoxyphenyl)-2-(4-methylphenyl)-4*H*-2,3,3a,5,6,6a-hexahydropyrrolo[3,4-*d*]isoxazole-4,6-dione (3f). Compound obtained as a yellow solid (yield 75 %), m.p. 190-191 ºC; **IR (KBr pellets, ν_{max}/cm^{-1}):** 1713.9, 1781.6 (C=O), 1285 (C-O aromatics), 1030 (C-O aliphatics); **^{1}H-NMR (400 MHz, DMSO-d$_6$):δ_H** 7.54-7.02 (m, 12H, ArH), 5.46 (d, 1H, *J* = 7.76 Hz, H-6a), 5.02 (d, 1H, *J* = 9.2 Hz, H-3), 4.18 (dd, 1H, *J* = 7.80, 7.87 Hz, H-3a), 3.59 (s, 3H, -OCH$_3$), 2.20 (s, 3H, -CH$_3$); **^{13}C-NMR (100 MHz, DMSO-d$_6$):δ** 172.6, 170.9, 148.0, 135.6-114.7, 126.4, 118.3, 76.0, 72.6, 56.3, 54.3, 20.4; **MS(ESI): m/z:** 431[M]$^+$; **Anal. Calc. for $C_{25}H_{26}N_2O_4F$:** C, 69.60; H, 6.03; N, 6.49, **Found:** C, 69.62; H, 5.59; N, 6.53.

5-(4'-Fluorophenyl)-3-(4-hydroxy-3-methoxyphenyl)-2-phenyl-4*H*-2,3,3a,5,6,6a-hexahydropyrrolo[3,4-*d*]isoxazole-4,6-dione (3g). Compound obtained as a white solid (yield 72%), m.p. 184-186 ºC; **IR (KBr pellets, ν_{max}/cm^{-1}):** 1715.1, 1788.7 (C=O), 1288 (C-O aromatics), 1032 (C-O aliphatics), 3370 (O-H); **^{1}H-NMR (400 MHz, DMSO-d$_6$):δ_H** 8.94 (s, 1H, -OH), **δ_H** 7.48-7.04 (m, 11H, ArH), 5.22 (d, 1H, *J* = 7.76 Hz, H-6a), 4.75 (d, 1H, *J* = 9.2 Hz, H-3), 4.12 (dd, 1H, *J* = 7.80, 7.88 Hz, H-3a), 3.49 (s, 3H, -OCH$_3$); **^{13}C-NMR (100 MHz, DMSO-d$_6$):δ** 172.8, 170.4, 149.0, 135.3-113.7, 127.4, 119.3, 77.2, 70.9, 56.3, 54.0; **MS(ESI): m/z:** 434[M]$^+$; **Anal. Calc. for $C_{24}H_{19}N_2O_5F$:** C, 66.36; H, 4.38; N, 6.45, **Found:** C, 66.42; H, 4.33; N, 6.72.

5-(4'-Fluorophenyl)-3-(4-hydroxy-3-methoxyphenyl)-2-(4-methylphenyl)-4*H*-2,3,3a,5,6,6a-hexahydropyrrolo[3,4-*d*]isoxazole-4,6-dione (3h). Compound obtained as a white solid (yield 74%), m.p. 202-204 ºC; **IR (KBr pellets, ν_{max}/cm^{-1}):** 1709, 1781 (C=O), 1283 (C-O aromatics), 1034 (C-O aliphatics), 3377 (O-H); **^{1}H-NMR (400 MHz, DMSO-d$_6$):δ_H** 8.91 (s, 1H, -OH), **δ_H** 7.99-6.74 (m, 12H, ArH), 5.34 (d, 1H, *J* = 7.68 Hz, H-6a), 4.74 (d, 1H, *J* = 9.08 Hz, H-3), 4.07 (dd, 1H, *J* = 8.84, 8.92 Hz, H-3a), 3.71 (s, 3H, -OCH$_3$), 2.56 (s, 3H, -CH$_3$); **^{13}C-NMR (100 MHz, DMSO-d$_6$):δ** 174.1, 171.6, 162.5, 147.3, 134.1-110.9, 127.9, 119.9, 76.7, 71.0, 55.3, 54.2, 20.3; **MS(ESI):m/z:** 448[M]$^+$; **Anal. Calc. for $C_{25}H_{21}N_2O_5F$:** C, 66.96; H, 4.68; N, 6.25, **Found:** C, 66.92; H, 4.53; N, 6.28.

4.CONCLUSION

A facile, convenient, economical, highly competent green chemistry protocol for the synthesis of biologically active novel fluorinated isoxazolidine derivatives has been established under MMT K-10 catalysed solvent-free microwave conditions. The attractive features of this protocol are high yield at ambient pressure in short reaction time, easy to work-up, economic efficiency, prevent waste, promote atom economy and clean reaction methodology. These fluorinated isoxazolidine derivatives may serve as template for the synthesis of potent aldose reductase inhibitors which are mainly influenced by the presence of electron withdrawing/donating substituents and their relative positions on *C*-phenyl ring.

5.ACKNOWLEDGMENT

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REFERENCES

1. Hamer, T. and Macaluso, A. (1974). Nitrones. Chem. Rev., 64, 473-495.
2. Singal, K. K. (1996). 1,3-Dipolar Cycloaddition Reactions of C-(2-Nitro)-styryl-N-phenyl Nitrone Leading to the Regiospecific and Stereospecific Synthesis of New Isoxazolidine Derivatives, Synth. Commun., 26(19), 3571-3580.
3. Banerji, A. Banerji, J. Haldar, S. Maiti, K. Basu, S. Prange, T.; Neumann, A. (1998). 1,3-Dipolar Cycloadditions - part-III - cycloaddition of C,N-diarylnitrones to N-cinnamoylpiperidines. Indian. J. Chem., 37(2), 105-119.
4. Jensen, K. B. Roberson, M. (2000). Catalytic enantioselective 1,3-dipolar cycloaddition reactions of cyclic nitrones: a simple approach for the formation of optically active isoquinoline derivatives J. Org. Chem., 65, 9080-9084.
5. Heravi, M. M. Tamimi, M. Yahyavi, H. Hosseinnejad, T. (2016). Huisgen's Cycloaddition Reactions: A Full Perspective Current Organic Chemistry., 20, 000-000.
6. Sibi, M. P. Ma, Z. Jasperse, C. P. J. (2005). Enantioselective Addition of Nitrones to Activated Cyclopropanes Am. Chem. Soc., 127(16), 5764-5765.
7. Carmona, D. Lamata, M. P. Viguri, F. Rodriguez, R. Oro, L. A. Balana, A. I. (2004). The Complete Characterization of a Rhodium Lewis Acid-Dipolarophile Complex as an Intermediate for the Enantioselective Catalytic 1,3-Dipolar Cycloaddition of C,N-Diphenylnitrone to Methacrolein. J. Am. Chem. Soc., 126, 2716-7.
8. Kaur, J. Singh, B. Singal, K. K. (2006). Huisgen reaction of nitrile oxides and nitrile imines leading to isoxazoline and pyrazole-4,6-diones. Chem. Heterocycl. Com. 42(6), 818-822.
9. Wang, B. Ahmed, M.N. Zhang, J. Chen, W. Wang, X. Hu, Y. (2013). Easy preparation of 1, 4, 5-trisubstituted 5-(2-alkoxy-1, 2-dioxoethyl)-1, 2, 3-triazoles by chemoselective trapping of copper (I)–carbon bond with alkoxalyl chloride. Tetrahedron Lett., 54(45), 6097-6100.
10. Merino, P. (2004). In Science of Synthesis; Padwa, A.; ed.; Thieme: Stuttgart, 27, 511-580.
11. Fruhauf, H.W. (1997). Metal-Assisted Cycloaddition Reactions in Organotransition Metal Chemistry. Chem. Rev. 97(3), 523-596.
12. Zhang, H. Joseph, J. Vasquez-Vivar, J. Karoui, H. Nsanzumuhire, C. Marta´sek, P. Tordo, P. Kalyanaraman, B. (2000). EPR spin trapping of superoxide from nitric oxide synthase. FEBS Lett., 473, 58-62.
13. Floyd, R. A. (2006). Nitrones as therapeutics in age-related diseases. Aging Cell, 5(1), 51-57.
14. Breuer, E. (1982). In The Chemistry of Amino, Nitroso and Nitro Compounds and Their Derivatives; Patai, S., ed.; Wiley & Sons: New York. (pp. 1-1393).
15. Kaur, M. Kaur, A. Singh, B. Singh, B. (2017). Synthesis and Evaluation of Novel 5-cyclohexyl-2-(4″-substitutedphenyl)-3-(2″-substitutedphenyl)4H-2,3,3a,5,6,6a-hexahydropyrrolo[3,4-d]isoxazole-4,6-dione Derivatives for Their In Vitro Antioxidant and Antibacterial Activities. J. Het. Chem. 54(1): 80-88.
16. Chakraborty, B. Sharma, P. K. Rai, N. Sharma, C.D. (2012). Solvent-free one-pot 1,3-Dipolar cycloaddition reactions of dihydropyran derived nitrone. J. Chem. Sci. 124(3), 679-685.
17. Kaur, A. Singh, B. Jaggi, A. S. (2013). Synthesis and evaluation of novel 2,3,5-triaryl-4H,2,3,3a,5,6,6a-hexahydropyrrolo[3,4-d]isoxazole-4,6-diones for advanced glycation end product formation inhibitory activity. Bioorg. Med. Chem. Lett., 23, 797-801.
18. Anand, P. Singh, B. (2012). Synthesis and evaluation of novel 4-[(3H,3aH,6aH)-3-

phenyl)-4,6-dioxo-2-phenyldihydro-2H-pyrrolo[3,4-d]isoxazol-5(3H,6H,6aH)
19. yl]benzoic acid derivatives as potent acetylcholinesterase inhibitors and anti-amnestic agents. Bioorg. Med. Chem., 20, 521-530.
20. Badru, R. Anand, P. Singh, B. (2012). Synthesis and evaluation of hexahydropyrrolo[3,4-d]isoxazole-4,6-diones as anti-stress agents. Eur. J. Med. Chem., 48, 81-91.
21. Kaur, A. Singh, B. (2013). Synthesis and Antibacterial Activity of New 2,5-Diaryl-3-styryl-4H,2,3,3a,5,6,6a-hexahydropyrrolo[3,4-d]isoxazole-4,6-diones J. Het. Chem., 51, 482-491.