EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 8
Issue: 3
434-438
Year: 2021

MICROWAVE SYNTHESIS OF NOVEL IMIDE DERIVATIVES AND THEIR ANTIOXIDANT POTENTIAL

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DOI: https://doi.org/10.17605/OSF.IO/CUYGJ

Article Received on 17/01/2021 **Article Revised on 07/02/2021** **Article Accepted on 27/02/2021**

ABSTRACT
Microwaves are in the form of electromagnetic energy which lie in electromagnetic spectrum corresponds to wavelength of 1cm to 1m and frequency of 30GHz to 300MHz. Imide is the form of amide in which the nitrogen atom is attached to two carbonyl group. Imide refers to any compound which contains the divalent radical. These compounds are derived from ammonia or primary amine, where two hydrogen atoms are replaced by a bivalent acid group or two monovalent acid groups, resulting in consisting of two carboxylic acid groups. Thus, the present communication utilized the technology beautifully for the synthesis, identification and characterization of some novel derivatives by the reaction of maleic anhydride with urea, glycine, aniline, sulphanilic acid to yield various maleimide derivatives using domestic microwave by getting percentage yield 92.86%, 90.64%, 86.70% and 55.53% of synthesized compound A_1,A_2,A_3 and A_4 respectively. The compound A_1 (92.86%) showed higher percentage practical yield. All synthesized compound(s) were subjected to melting point determination, TLC analysis, column chromatography (for purification), ^{1}H-NMR and Mass Spectrometry. All synthesized derivatives were subjected for DDPH scavenging activity, in which compound A_3 was found to have high anti-oxidant potential (91.85%) when ascorbic acid was taken as standard. All the chemicals used were of highly pure and purchased from Central Drug House (New Delhi).

KEYWORDS: Microwaves, Imide, Maleimide, Green chemistry, DDPH, Antioxidant.

INTRODUCTION
Imide is the form of amide in which the nitrogen atom is attached to two carbonyl group. Imide refers to any compound which contains the divalent radical. These compounds are derived from ammonia or primary amine, where two hydrogen atoms are replaced by a bivalent acid group or two monovalent acid groups, resulting in consisting of two carboxylic acid groups.[1]

Maleimide and its derivatives are prepared from maleic anhydride by treating with amines followed by dehydration.[2] Maleimide derivatives are very attractive compound in terms of chemical reactivity. They give rise to some interesting reactions such as Diels – Alder reaction with dienes and the nucleophilic Michael – type addition of thiols or amines to the vinylene moiety. The unsaturated imide is an important building block in organic synthesis.[3] Maleimide compounds in specific have shown antifungal and antibacterial properties, ability to inhibit Protein Kinase C (PKC), antitumor property and analgesic activity.[4]

Microwaves are in the form of electromagnetic energy which lie in electromagnetic spectrum corresponds to wavelength of 1cm to 1m and frequency of 30GHz to 300MHz. Microwave energy consist of both electric as well as magnetic field.[5] Just because of microwave chemistry does not produce any hazardous material like gas, fumes or heating using external energy source, it is also called as green chemistry.[6]

Green chemistry efficiently utilizes (preferably renewable) raw materials, eliminates waste and avoids the use of toxic and/or hazardous reagents and solvents in the manufacture and application of chemical products. The term 'Green Chemistry' was coined by Anastas of the US Environmental Protection Agency (EPA).[7] This technology opens up new opportunities to the synthetic chemist, in the form of new reactions that are not possible using conventional heating.[8]

Antioxidants are reducing agents which are added to the drug or other pharmaceuticals to prevent their oxidation through oxidative process. Antioxidants are the substances, which inhibit oxidation by free radicals. Antioxidants include detoxification enzymes, such as superoxide dismutase, vitamins including beta-carotene and other carotenoids, vitamin C & E and nutritional

supplements such as coenzyme Q_{10}, cysteine, glutathione, lipoic acid, polyphenols and melatonin.[9]

The aim of the present study is to synthesizemaleimide derivatives by using microwave assisted synthesis method and compare the activity of the synthesized molecules.

MATERIALS

Phthalic anhydride, Urea, Glycine, Sulphanilic acid, Aniline, Chloro form & DPPH were received from Central Drug House Ltd. New Delhi, India. Methanol, Ethyl acetate & n-Hexane were received from Himedia Pvt. Ltd. and Maleic anhydride was received from LOBA Chemie, Mumbai, India.

METHOD AND METHODOLOGY

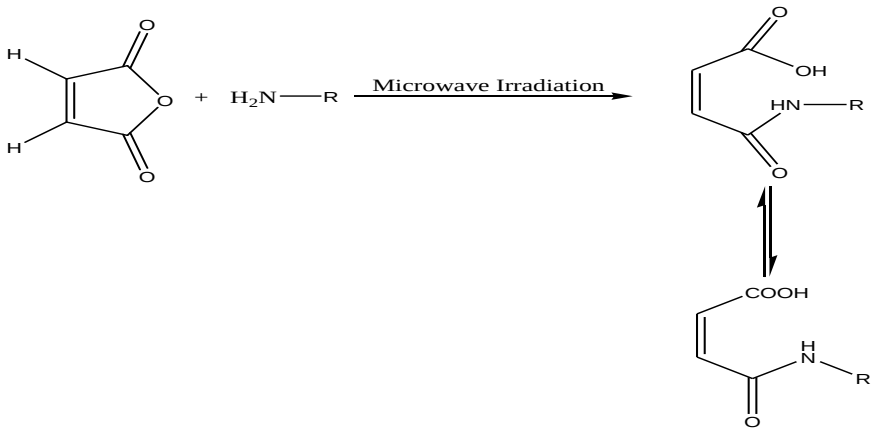
Thus, the present communication utilized the technology beautifully for the synthesis, identification and characterization of some novel derivatives by the reaction of maleic anhydride with urea, glycine, aniline, sulphanilic acid to yield various maleimide derivatives using domestic microwave by getting percentage yield 92.86%, 90.64%, 86.70% and 55.53% of synthesized compound A_1,A_2,A_3 and A_4 respectively. All synthesized compound(s) were subjected to melting point determination, TLC analysis, column chromatography (for purification), ^{1}H-NMR and Mass Spectrometry.

RESULT AND DISCUSSION

We developed new synthetic methodologies for the synthesis of maleimide derivatives. The starting material maleic acid was reacted with amino acids to give maleimide, the addition reaction was takes place:

Mechanism of synthesis

1.1 For maleimide derivatives



Scheme 1: Mechanism of synthesis of Maleimide.

1.2 Percentage yield

Table 1: Percentage yield of maleimide compounds.

S.No.	Compounds	% yield
1.	A_1	92.86
2.	A_2	90.64
3.	A_3	86.70
4.	A_4	55.53

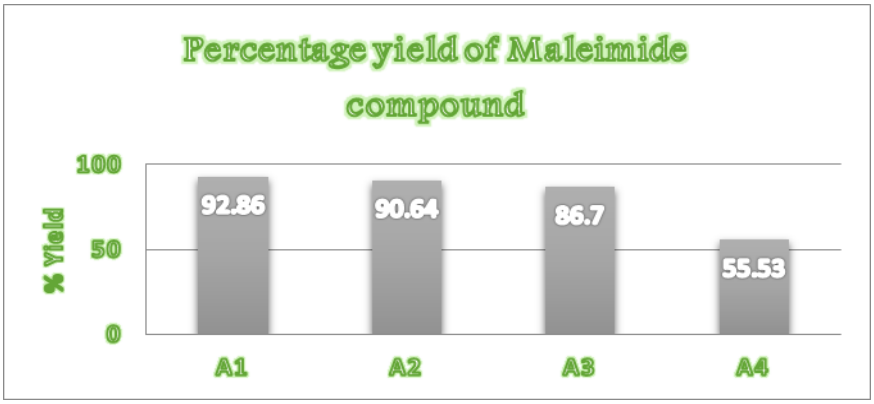


Diagram 1: Bar diagram of different Maleimide derivatives.

1.3 PHYSICOCHEMICAL PROPERTIES

Table 2: Physicochemical properties of various Maleimide derivatives (A_1-A_4)

Compound	Molecular formula	Molecular weight	Appearance	Percentage yield
A_1	$C_5H_4O_3N_2$	140.1	Brown powder	92.86
A_2	$C_6H_5O_4N$	155.11	Brown crystals	90.64
A_3	$C_{10}H_7O_2N$	173.17	Brown powder	86.70
A_4	$C_{10}H_7O_5NS$	253.23	Off White crystals	55.53

1.4 MELTING POINT

Table 3: Melting Point of Maleimide derivatives.

S.No	Compound	Melting Point Range(^{0}C)
1.	2,5-dioxo-2*H*-pyrrol-1(5*H*)-carboxamide(A_1)	268±2
2.	2-(2,5-dioxo-2*H*-pyrrol-1(5*H*)-yl) acetic acid(A_2)	239±2
3.	1-phenyl-1*H*-pyrrole-2,5-dione (A_3)	243±2
4.	4-(2,5-dioxo-2*H*-pyrrol-(5*H*)-yl)benzenesulfonic acid(A_4)	256±2

1.5 SOLUBILITY

Table 4: Solubility of Maleimide derivatives.

S.No.	COMPOUND	SOLUBILITY
1.	2,5-dioxo-2*H*-pyrrol-1(5*H*)-carboxamide(A_1)	Water, Methanol
2.	2-(2,5-dioxo-2*H*-pyrrol-1(5*H*)-yl) acetic acid(A_2)	Water, Methanol
3.	1-phenyl-1*H*-pyrrole-2,5-dione (A_3)	Water
4.	4-(2,5-dioxo-2*H*-pyrrol-(5*H*)-yl) benzenesulfonic acid(A_4)	Water, Acetone

1.6 pH

Table 5: pH of Maleimide compounds.

S.No.	COMPOUND	OBSERVATION
1.	2,5-dioxo-2*H*-pyrrol-1(5*H*)-carboxamide(A_1)	8.54
2.	2-(2,5-dioxo-2*H*-pyrrol-1(5*H*)-yl) acetic acid(A_2)	10.20
3.	1-phenyl-1*H*-pyrrole-2,5-dione (A_3)	9.25
4.	4-(2,5-dioxo-2*H*-pyrrol-(5*H*)-yl) benzenesulfonic acid(A_4)	8.86

1.7 Ultraviolet Spectroscopy

Table 6: Wavelength of Maleimide derivatives.

S.No.	COMPOUND	SOLVENT	WAVELENGTH (nm)
1.	2,5-dioxo-2*H*-pyrrol-1(5*H*)-carboxamide(A_1)	Water	292nm
2.	2-(2,5-dioxo-2*H*-pyrrol-1(5*H*)-yl) acetic acid(A_2)	Water	242nm
3.	1-phenyl-1*H*-pyrrole-2,5-dione (A_3)	Water	239nm
4.	4-(2,5-dioxo-2*H*-pyrrol-(5*H*)-yl) benzenesulfonic acid(A_4)	Water	249nm

1.8 Thin Layer Chromatography

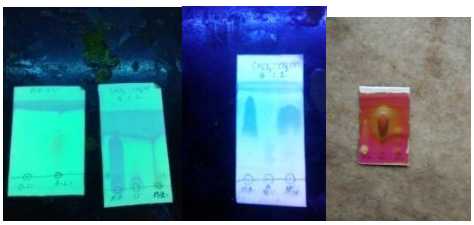


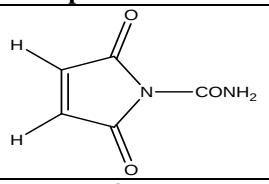
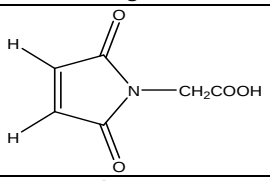
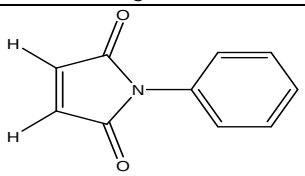
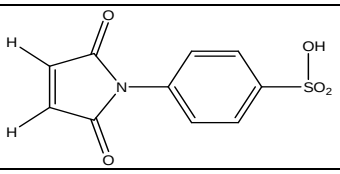
Figure 1: Spots of derivatives of Maleimide visualized in UV.

Table 7: Retention factor of Maleimide compounds.

S.No.	COMPOUND	Rf value
1.	2,5-dioxo-2*H*-pyrrol-1(5*H*)-carboxamide(A_1)	0.51
2.	2-(2,5-dioxo-2*H*-pyrrol-1(5*H*)-yl) acetic acid(A_2)	0.56
3.	1-phenyl-1*H*-pyrrole-2,5-dione (A_3)	0.46
4.	4-(2,5-dioxo-2*H*-pyrrol-(5*H*)-yl)benzenesulfonic acid(A_4)	0.73

1.9 The characteristic ^{1}H NMR data and interpretation of synthesized compounds

Table 8: ^{1}H NMRdata and interpretation of synthesized compounds.

Compound No.	Compound structure	δ (ppm)	Group	No. of H
A_1		6.45 5.47 4.88-4.90	H H NH_2	1 1 2
A_2		7.10-7.26 6.09 2.50 8.44	H H CH_2 OH	1 1 2 1
A_3		6.55-6.76 7.00-7.67 10.06-10.25	H Ar-H Ar-H	2 4 1
A_4		6.85-6.88 7.38-7.36 2.26-2.27	H Ar-H OH	2 4 1

1.10ELEMENTAL ANALYSIS

Table 9: Elemental analysis of different Maleimide compounds.

Comp.	Mol. Formula	Mol. Weight	Compound Name	Calculated % found				
				C%	H%	N%	O%	S%
A_1	$C_5H_4O_3N_2$	140.1	2,5-dioxo-2*H*-pyrrol-1(5*H*)-carboxamide(A_1)	42.87%	02.88%	20.00%	34.26%	_
A_2	$C_6H_5O_4N$	155.11	2-(2,5-dioxo-2*H*-pyrrol-1(5*H*)-yl) 0acetic acid(A_2)	46.46%	03.25%	09.03%	41.26%	_
A_3	$C_{10}H_7O_2N$	173.17	1-phenyl-1*H*-pyrrole-2,5-dione (A_3)	69.36%	04.07%	08.09%	18.48%	_
A_4	$C_{10}H_7O_5NS$	253.23	4-(2,5-dioxo-2*H*-pyrrol-(5*H*)-yl)benzenesulfonic acid(A_4)	42.67%	12.53%	04.98%	28.42%	11.39%

1.11ANTIOXIDANT ACTIVITY

- **In vito antioxidant activity by using DPPH scavenging method**

Table 10: DPPH scavenging activity of different Maleimide derivatives.

Concentration (mg/ml)	% inhibition				
	A_1	**A_2**	**A_3**	**A_4**	**Ascorbic acid**
0	0.0	0.0	0.0	0.0	0.0
0.02	64.94	61.95	74.89	66.65	84.02
0.04	74.79	67.28	84.09	68.05	86.35
0.06	78.14	70.88	85.59	68.69	86.57
0.08	79.71	71.6	89.23	70.42	86.92
0.10	87.46	77.86	91.85	72.95	87.45

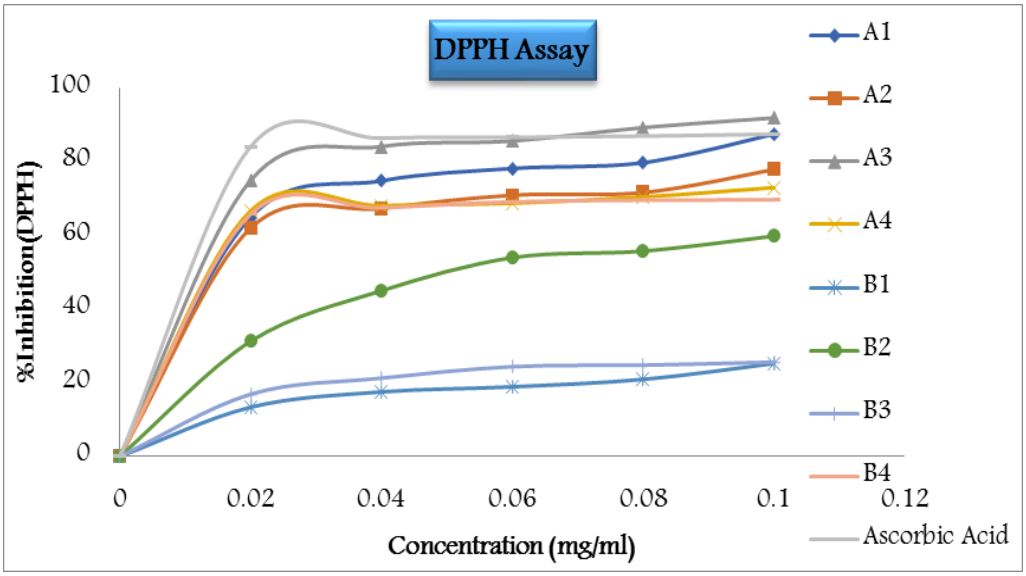


Diagram 2: Bar diagram of different Maleimide derivatives.

CONCLUSION

On the basis of the previous results, the study concluded that the synthesis of the designed compound has been successfully achieved. Purity and characterization of the synthesized compounds were confirmed by determination of physical properties (melting point, pH and R_f values), elemental analysis and 1H-NMR spectra. The compound A_1 of maleimide shows higher percentage practical yield. The *in-vitro* antioxidant activity of all synthesized compound was tested by using DDPH scavenging activity. The compounds were screened at different concentration from 0.02-0.10mg/ml in order to check the percentage inhibition of compounds. From the result in table (9) compound A_3 showed highly significant activity against DPPH. The result shows that as the concentration of compound increase, the compound showed high significant activity against DPPH. The other entire tested compound showed low to moderate activity. Thus, the study could be concluded as the compounds have considerable antioxidant activity. Thus, it may be concluded that the synthesized compound effectively can be further used in the treatment of above-mentioned element.

ACKNOWLEDGEMENT

The authors are grateful to the Himalayan Institute of Pharmacy & Research, Dehradun, Uttarakhand, India for helping us to carry out the study. We are grateful to the Uttarakhand technical university for their support in characterization studies. All the teaching staff of Himalayan Institute of Pharmacy & Research, Dehradun for their silent contribution in particular.

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