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Review Article

A Review on Biological and Chemical Potential of Phthalimide and Maleimide Derivatives

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Abstract

Phthalimide and maleimide derivatives have been reported as biologically compounds. In view of broad biological activities of phthalimide and maleimide derivatives, we herein plan to study of various phthalimide and maleimide derivatives, their chemistry, synthesis and biological activities. Diverse biological activities of phthalimide and maleimide and its derivatives have been exhibited such as antibacterial, antifungal, antiviral, analgesic, antiinflamatory, anticancer, anxiolytic, herbicides, insecticides and some other activities. The article also focuses on synthetic methods of phthalimides and maleimide having significant biological activities.

Keywords: Phthalimides; Maleimide; Biological Activities; Synthesis

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 "-C(=O)-NH-C(=O)-". 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 (or one dicarboxylic acid) [1].

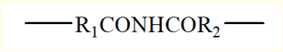
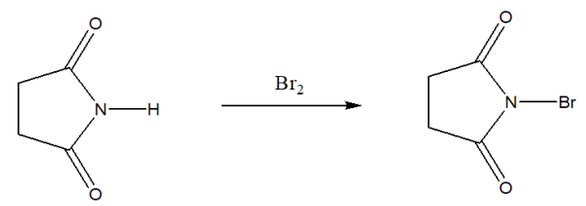


Figure 1: Imide.

The unsubstituted cyclic imide is an important functionality which has been found to maintain significant biological activity. The synthesis of unsubstituted cyclic imides either by conventional methods or microwave irradiation is often carried out under harsh conditions there by increasing byproduct formation. Many conventional synthesis of unsubstituted cyclic imides use the reaction of cyclic anhydrides with reactants including ammonia, urea, formamide, and lithium nitride. Additional microwave synthesis use the reaction of cyclic anhydrides with urea or thiourea, formamide, benzonitrile, cyanate, thiocyanate, DMAP/ammonium chloride, and ammonium acetate [2].

Uses of imides

Utilized in the preparation of pesticides and herbicides, to control diseases in fruits and vegetables. Used to give a fresh and bright look to many fruits. In the preparation of polyimides. N-bromosuccinimide is a good brominating agent [3].



Succinimide N- Bromosuccinimide

Scheme 1: Bromination of succinimide.

Maleimide

Chemistry of maleimide: Maleimide and its derivatives are prepared from maleic anhydride by treating with amines followed by dehydration [4].

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

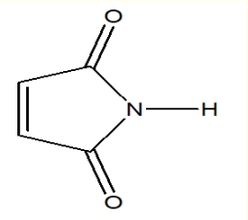


Figure 2: Maleimide.

unsaturated imide is an important building block in organic synthesis. Maleimide also describes a class of derivative of the potent maleimide where the NH group is replaced with alkyl or aryl group such as a methyl or phenyl respectively. Meanwhile, the vinylene group of a maleimide moiety having 1,2-disubstituted ethylene structure can be polymerized with radical or anionic initiators to yield the polymer having high thermostability or heat resisting property and can be copolymerization with vinyl acetate [5].

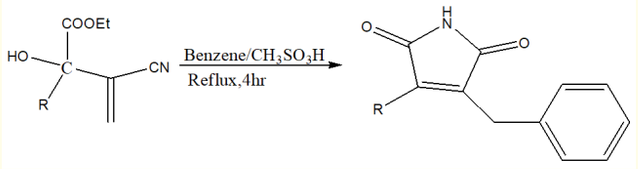
Biological activities and other uses of maleimide: Maleimide compounds in specific have shown antifungal and antibacterial properties, ability to inhibit Protein Kinase C (PKC), antitumor property and analgesic activity [6]. Polymaleimide (PMAI) is a type of polymer with high reactivity, often used as the polymeric skeleton of many functional materials with excellent thermal stability. For example, Polymaleimide was used to prepare nonlinear optical materials as liquid crystals to improve their thermal properties [7].

Natural products of maleimide

- **Maleimide-polyethylene glycol:** It is a molecule created by artificially modifying human hemoglobin. It can be used as a substitute for blood and so has applications in medical operation and transfusions [8].
- **Farinomalein:** Farinomalein was isolated maleimide from entomopathogenic fungus Paecilomyces farinosus [9].
- **Cytotoxic showdomycin:** It is isolated from Streptomycin showdoenesis [10].
- **Pencolide:** Pencolide is obtained from Pencolide multicolor [4].

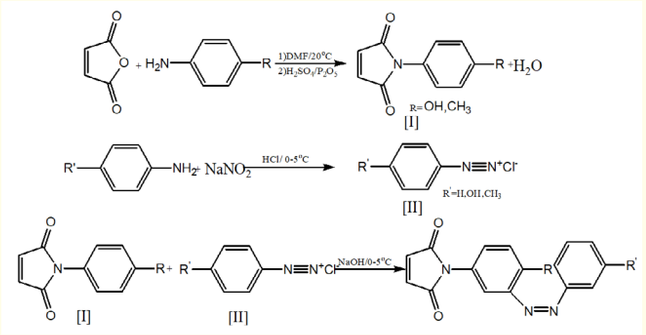
Reactions of Maleimide

Friedel- crafts reaction of B-H adducts maleimide



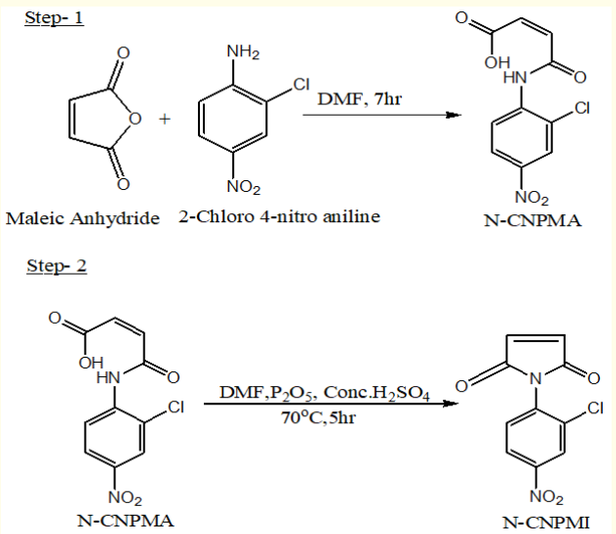
Scheme 2: Friedel- crafts reaction of B-H adducts maleimide.

Synthesis of N-(4-hydroxyphenyl)maleimide [I], N-(4-methylphenyl)maleimide [II]



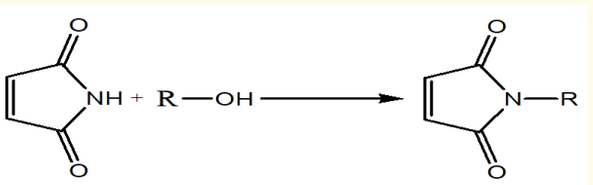
Scheme 3: Synthesis of N-(4-hydroxyphenyl)maleimide [I], N-(4-methylphenyl) maleimide [II].

Synthesis of N-CNMPA and N-CNMPI



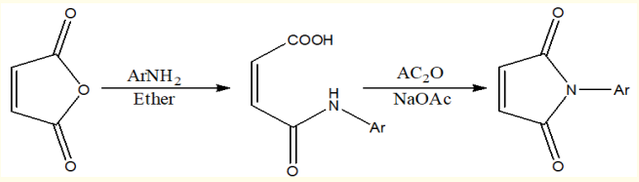
Scheme 4: Synthesis of N-CNMPA and N-CNMPI.

Synthesis of N- Alkylmaleimide



Scheme 5: Synthesis of N-Alkylmaleimide.

Synthesis of N- Alkylmaleimide



Scheme 6: Synthesis of N-aryl maleimides.

Phthalimide

Chemistry of phthalimide: Phthalimide possess a structural feature $C_8H_5NO_2$ and an imide ring which help them to be biologically active and pharmaceutically useful [11]. Among bicyclic non-aromatic nitrogen heterocycles, phthalimides are an interesting class of compounds. Phthalimides have served as starting materials and intermediates for the synthesis of many types of alkaloids and pharmacophores [12]. The structural diversity and biological importance of nitrogen containing heterocycles have prepared them important targets for synthesis over many years [13].

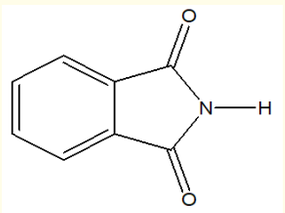


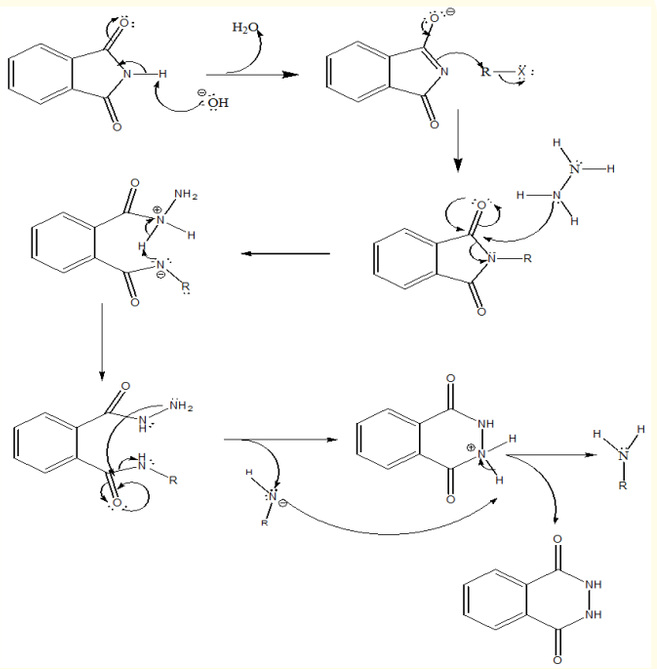
Figure 3: Isoindole-1,3-dione (Phthalimide).

Phthalimide is an imido derivative of phthalic acid. In organic chemistry, imide is a functional group consisting of two carbonyl groups bound to nitrogen. They are hydrophobic and neutral, and can therefore cross biological membranes *in vivo*. These compounds are structurally related to acid anhydrides [11].

Biological activity and other uses of phthalimide

Phthalimide and some of its derivatives proved to have received awareness due to their antibacterial, antifungal, analgesic, antitumour, anxiolytic and anti-HIV-1 activities. When phthalimide is subjected to Mannich condensation, it may yield Mannich bases which may display more potent biological activities. The present research focuses on novel synthesized phthalimides having significant biological activities [12] Amongst heterocyclic scaffolds, phthalimides are of particular biological interest and have been reported as herbicides, insecticides and anti-inflammatory agents. Phthalimide are an important class of drugs exhibiting anxiolytic, antimicrobial, antituberculosis, hypolipidemic, analgesic, anticancer, acetylcholinesterase inhibitors and inhibitor of human neuronal nitric oxide synthase [13]. Isoindole-1,3(2H)-dione is an aromatic imide, contains isoindole moiety, which is motif in nature. In the combined form with maleimides and succinimides, isoindole-1,3(2H)-diones used as plastic modifiers to improve heat resistance, antioxidant and anti-foulant properties [14].

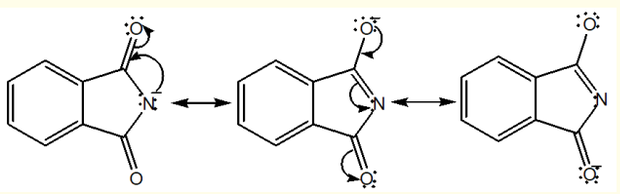
Name reaction of phthalimide [15]



Scheme 7: Gabriel synthesis.

Reactions of phthalimide

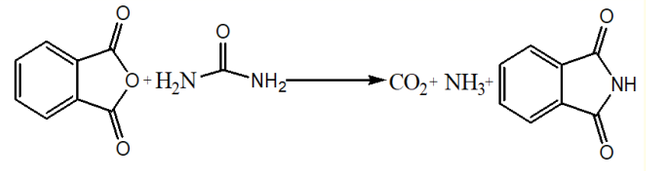
Phthalimide have resonance stabilized structures:



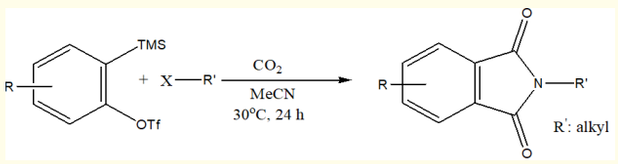
Scheme 8: Resonance stabilization of phthalimide.

Reaction between phthalic anhydride and urea resulted in the formation of phthalimide:

Transition-metal-free multicomponent reactions involving arynes, isocyanides, and CO_2 as the third component resulted in the formation of N-substituted phthalimides

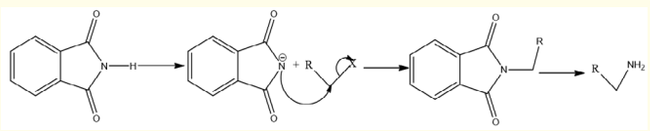


Scheme 9: Reaction between phthalic anhydride and urea.



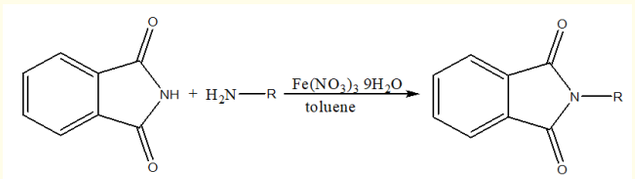
Scheme 10: Transition-metal-free multicomponent reactions.

Name reaction of phthalimide (Gabriel synthesis)



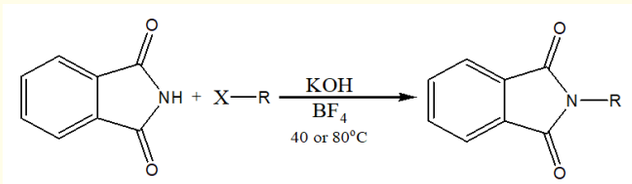
Scheme 11: Name reaction of phthalimide.

A highly efficient transamidation of several primary, secondary, and tertiary amides with aliphatic and aromatic amines (primary and secondary)



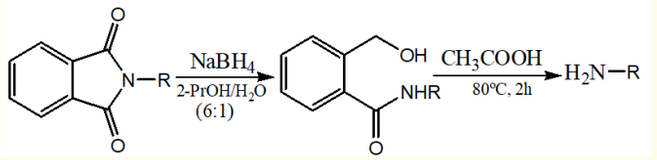
Scheme 12: Transamidation of several 1º, 2º and 3º amides.

A convenient, efficient, and selective N-Alkylation of N-acidic heterocyclic compounds with alkyl halides



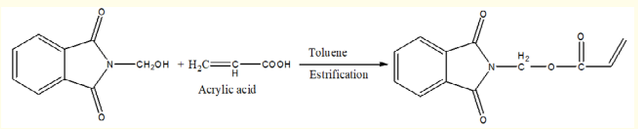
Scheme 13: N-Alkylation of N-acidic heterocyclic compounds with alkyl halides.

Phthalimides are converted to primary amines



Scheme 14: Ring cleavage of phthalimide derivatives.

N-hydroxy methyl phthalimide when reacted with acrylic acid to produce N-methyl acrylate phthalimide :

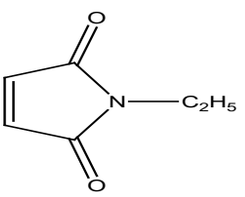
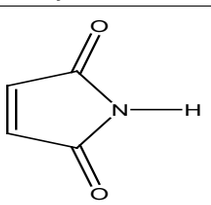
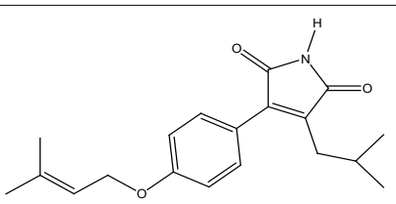


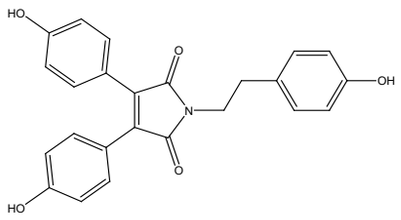
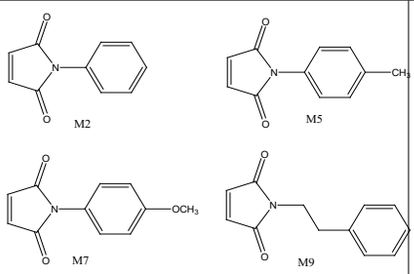
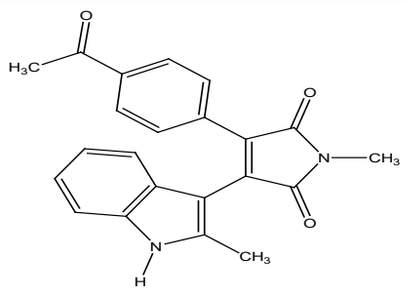
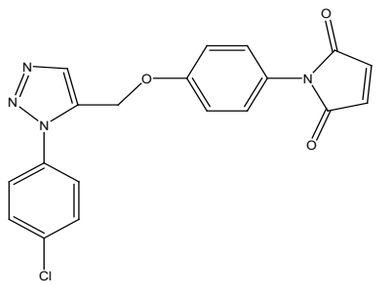
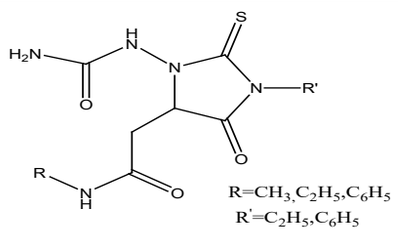
Scheme 15: Esterification of phthalimide derivatives.

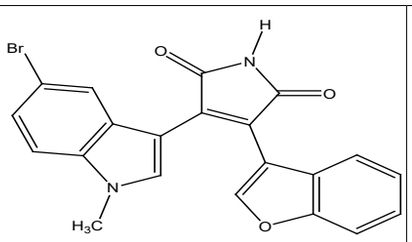
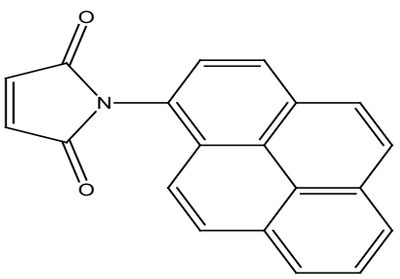
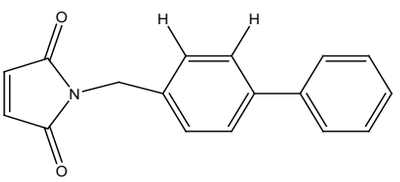
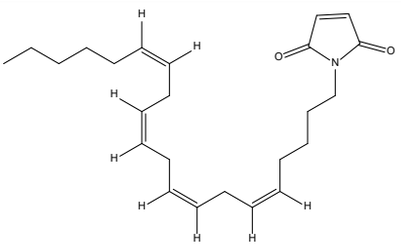
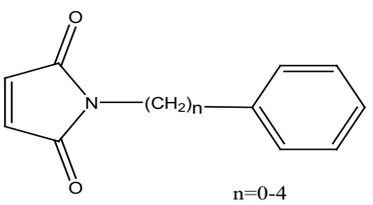
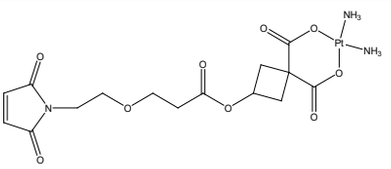
Pharmacological activities

Phthalimide and maleimide derivatives have been shown diverse biological activities such as antibacterial, antifungal, antiviral, analgesic, antiinflamatory, anticancer, anxiolytic, herbicides, insecticides and some other activities.

Pharmacological activity of maleimide

S. No.	Chemical structure	Biological activities
1	 N-ethyl maleimide	Nematicidal activity [15]
2	 Unsubstituted maleimide	Anti-microbial activity [6]
3	 Camphorataimide B	Anti-tumor activity in breast cancer cells [16]

4	 Denigrine A	Anti-tubercular agent [17]
5	 N-Phenylmaleimide derivatives	Antitumor and antimetastatic effects [18]
6	 Arylindolyl maleimide PDA-66	Anti-proliferative and Anti-leukemic activity [19]
7	 1-(4-((1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)-1H-pyrrole-2,5-dione	Antitumour activity [20]
8	 2-thioxo imidazolidinones	*In vitro* Anti-bacterial activity [21]

9	 Maleimide-based GSK-3β	Anxiolytic effect [22]
10	 N-(1-pyrenyl)maleimide	Anti-cancer drug [23]
11	 1-biphenyl-4-ylmethylmaleimide	Monoglyceride lipase inhibitor [24]
12	 N-Arachidonyl maleimide	Monoacylglycerol lipase inhibitor [25]
13	 N-phenylalkylmaleimide	Fungicidal activity [26]
14	 Diamineplatin(II)-[3-(6-maleimido-4-oxocaproyl)-cyclobutane-1,1-dicarboxylate]	Anti-tumor activity [27]

Pharmacological activity of phthalimide

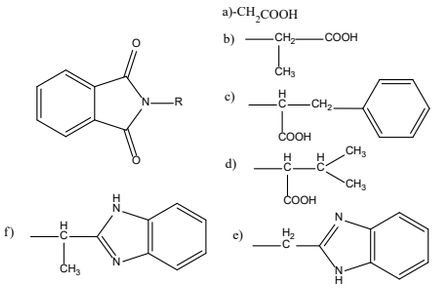
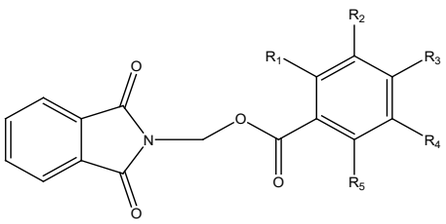
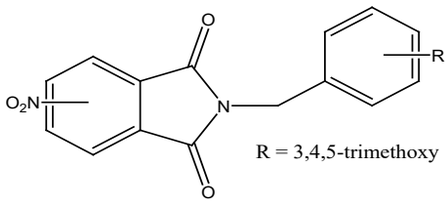
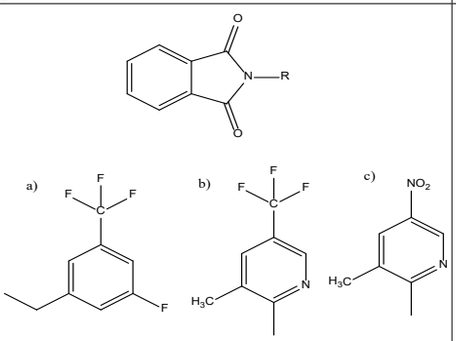
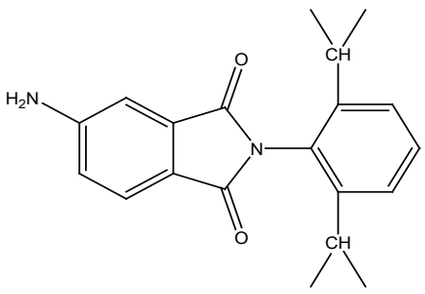
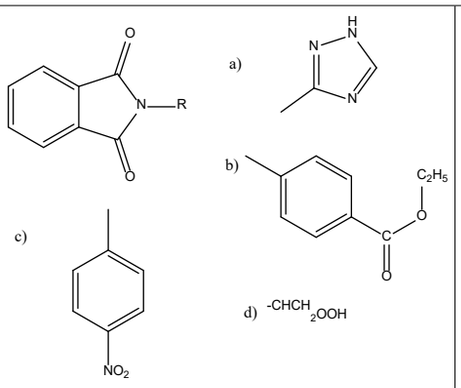
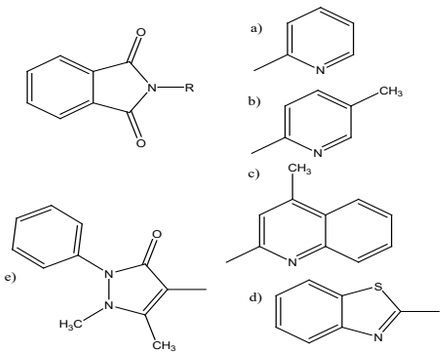
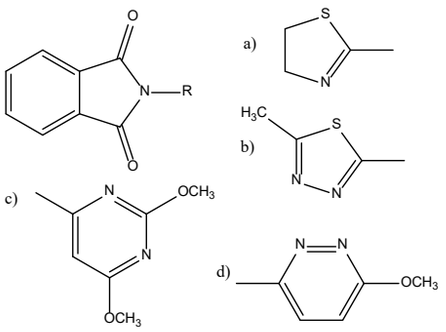
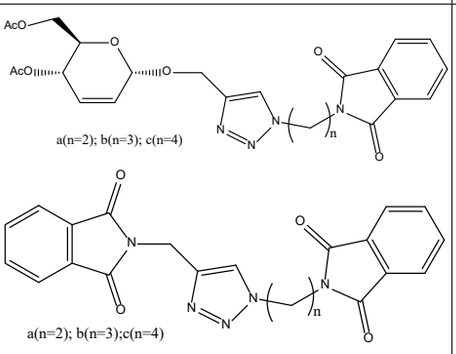
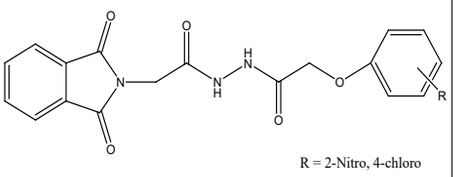
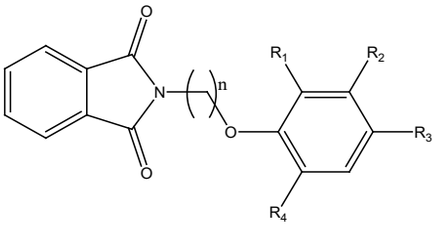
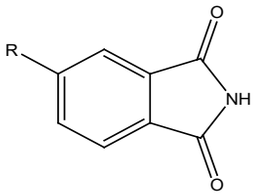
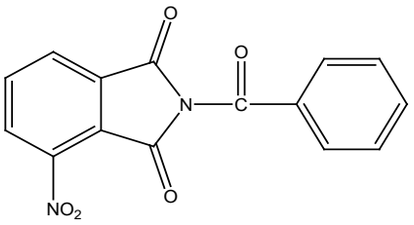
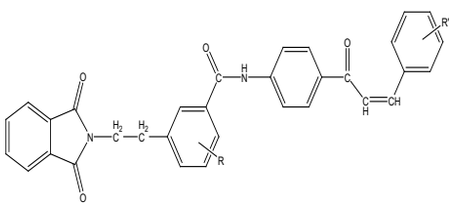
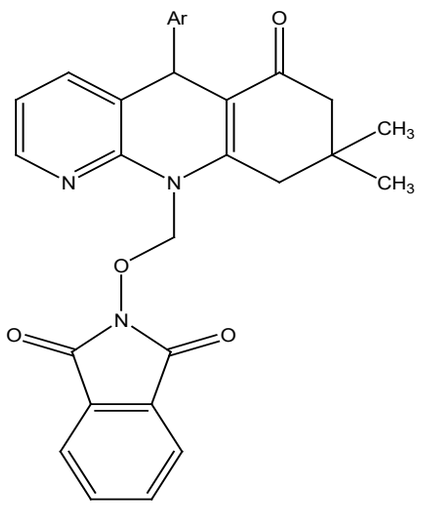
S. No.	Chemical structure	Biological activities
1.	 N-substituted phthalimide derivative	Antimicrobial activity [28]
2.	 N-ethyl phthalimide ester derivative	Antioxidant [29]
3.	 5-nitro-2-(3,4,5-trimethoxybenzyl) phthalimide	Anti-inflammatory and analgesic activity [30]
4.	 Isoindoline-1,3-dione derivatives	Anti-oxidant [31]
5.	 TC11	To treat multiple myeloma and osteoclasts [32]
6.	 N-substituted phthalimide derivative	Analgesic activity [33]
7.	 Phthalimide derivative	Antibacterial and Anticorrosion activity [34]
8.	 Phthalimide derivative	Antimycobac-terial activity [35]
9.	 1,2,3-triazol phthalimide derivative	Anti-inflammatory activity [36]
10.	 Substituted phenoxy acetyl hydrazine acetyl phthalimide	Anti-microbial activity [37]

Table 1

11.	 N-(phenoxyalkyl) phthalimide derivative	**α -** Glucosidase inhibitory activity [38]
12.	 R= H,C_6H_5HCHO,$C_6H_5CH_2HCHO$,$C_6H_5(CH_2)_3O$ C_5^- substituted phthalimide analogues	Anti-depressant (MAO-Inhibitor) [39]
13.	 N-benzoyl-3-nitro-phthalimide	Anxiolytic activity [40]
14.	 3-(phthalimidoethyl)-4-substituted cinnamoyl substituted benzanilides	Hypoglycemic activity [41]
15.	 Naphthyridine alkoxy phthalimide	Antibacterial and antifungal activity [42]

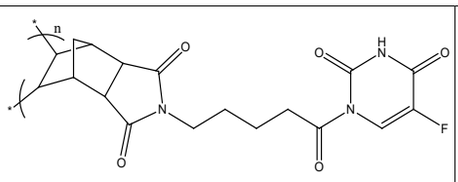
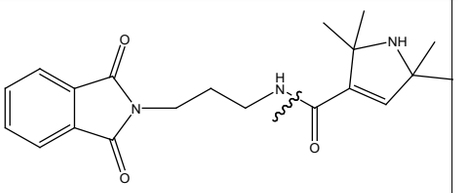
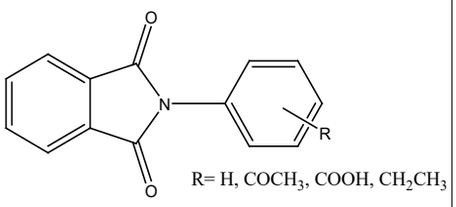
16.	 Poly(3,6-endo-methylene-1,2,3,6-tetra-hydrophthalimidopentanoyl-5-fluorouracil)	Antitumour activity [43]
17.	 2,2,5,5-tetramethyl-3-pyrroline-3-cabox-amide amine	Prevent Post-ischemic myocardial injury [44]
18.	 N-phenyl phthalimide	Hypolipid-emic activity [45]

Table 2

Maleimide: Chemical and biological activities were reported

S No.	Chemical and biological activities	Year	References
1	A new method for the rapid analysis of 1H-Pyrrole-2,5-diones (maleimides) in environmental samples by two-dimensional gas chromatography time-of-flight mass spectrometry	2016	Naeher., *et al.* [46]
2	Maleimide-bearing nanogels as novel mucoadhesive materials for drug delivery	2016	Tonglair-oum., *et al.* [47]
3	Effects of novel maleimide derivatives on cell cultures with different properties	2016	Ostrovska., *et al.* [48]
4	Maleimide-functionalized closo-dodecaborate albumin conjugates (MID-AC): Unique ligation at cysteine and lysine residues enables efficient boron delivery to tumor for neutron capture therapy	2016	Kikuchi., *et al.* [49]
5	Synthesis and Biological Activity of N-Aminoethyl-terpinene-maleimidebased Thiourea Compounds	2016	Lu-zhi., *et al.* [50]
6	2-(Maleimidomethyl)-1,3Dioxanes (MD): a Serum-Stable Self-hydrolysable Hydrophilic Alternative to Classical Maleimide Conjugation	2016	Dovgan., *et al.* [51]

7	Synthesis and antimicrobial activities of eleven N-substituted maleimide	2016	Chin., *et al.* [6]
8	Potent Nematicidal Activity of Maleimide Derivatives on Meloidogyne incognita	2016	Eloh., *et al.* [15]
9	Functionalization of a Triazine Dendrimer Presenting Four Maleimides on the Periphery and a DOTA Group at the Core	2016	Lee., *et al.* [52]
10	Protease-degradable PEG-maleimide coating with on-demand release of IL-1Ra to improve tissue response to neural electrodes	2016	Gutowsk., *et al.* [53]
11	Camphorataimide B, a maleimide in mycelium of Antrodia camphorate, inhibits progression of human MDA-MB-231 breast cancer cells	2016	Lee., *et al.* [16]
12	Cross-Linked Hydrogels Formed through Diels–Alder Coupling of Furan- and Maleimide-Modified Poly(methyl vinyl ether-*alt*-maleic acid)	2016	Stewart., *et al.* [54]
13	Grafting of polypropylene with P-hydroxy-N-phenyl maleimide to use it as a coupling agent in preparation of polypropylene/layered silicates nanocomposites	2016	Eid., *et al.* [55]
14	Stability of eosin-5'-maleimide dye used in flow cytometric analysis for red cell membrane disorders	2015	Mehra., *et al.* [56]
15	Synthesis and screening of new maleimide derivatives as potential anti-tubercular agents	2015	Sahooa., *et al.* [17]
16	Cytotoxicity of N-phenylmaleimide Derivatives and Inhibition of Melanoma Growth in a Preclinical Mouse Melanoma Model	2015	Noldin., *et al.* [18]
17	A biotin-PEAC5-maleimide labeling assay to detect electrophiles	2015	Abiko., *et al.* [57]
18	3D-QSAR study of maleimide analogues as glycogen synthase kinase-3(GSK-3) inhibitors using CoMSIA approach	2014	Crisan., *et al.* [58]
19	Development of Novel Maleimide Reagents for Protein Modification	2014	Marculescu., *et al.* [59]
20	Insights into the Interactions between Maleimide Derivates and GSK3b Combining Molecular Docking and QSAR	2014	Quesada-Romero., *et al.* [60]
21	The noval arylindolylmaleimide PDA-66 displays pronounced antiproliferative effects in acute lymphoblastic leukemia cells	2014	Christin., *et al.* [61]
22	Aryl maleimides as apoptosis inducers on L5178-Y murine leukemia cells (in silico, in vitro and ex vivo study)	2014	Andrade-Jorge., *et al.* [62]
23	PEG–Maleimide Hydrogels for Protein and Cell Delivery in Regenerative Medicine	2014	Garcia., *et al.* [63]
24	Synthesis of maleimide derivatives via CuAAC click chemistry and biological evaluation of their antitumor activity against cancer cell lines	2014	Xu., *et al.* [64]
25	Long-term stabilization of maleimide-Thiol conjugates	2014	Fontaine., *et al.* [65]
26	Synthesis and study the Biological Activity of some new bis Maleimide derivatives containing 1 ,3 ,4-oxadiazole ring	2013	Ahmad., *et al.* [66]
27	Molecular structure and modeling studies of azobenzene derivatives containing maleimide group	2013	Corneliu., *et al.* [67]
28	Characterization of Maleimide-Based Glycogen Synthase Kinase-3 (GSK-3) Inhibitors as Stimulators of Steroidogenesis	2013	Gunose-woyo., *et al.* [22]
29	Erythrocyte Flow Cytometric Analysis in Congenital Dyserythropoietic Anemia Type III-Evaluation of Eosin-5´-Maleimide, CD55, and CD59	2013	Liljeholm., *et al.* [68]
30	An efficient conversion of maleimide derivatives to 2-thioxo imidazolidinones	2013	Salhi., *et al.* [21]
31	A novel application of maleimide for advanced drug delivery: in vitro and in vivo evaluation of maleimide-modified pH-sensitive liposomes	2013	Li., *et al.* [69]
32	Selective Detection of the Reduced Form of Glutathione (GSH) over the Oxidized (GSSG) Form Using a Combination of Glutathione Reductase and a Tb(III)-Cyclen Maleimide Based Lanthanide Luminescent 'Switch On' Assay	2012	McMahon., *et al.* [70]
33	Dual inhibition of MAGL and type-II topoisomerase by N-phenylmaleimide as a potential strategy to reduce neuroblastoma cell growth	2012	Matuszak., *et al.* [71]
34	The study of terminated PEG maleimide synthesis and modification of hemoglobin	2012	Lei., *et al.* [72]
35	Maleimide-functionalised organoruthenium anticancer agents and their binding to thiol-containing biomolecules	2012	Hanif., *et al.* [73]
36	Synthesis and characterization of maleimide- functionalized polystyrene- SiO_2/TiO_2 hybrid nanocomposites by sol- gel process	2012	Sivalingam., *et al.* [74]
37	*N*-(1-Pyrenyl) maleimide inhibits telomerase activity in a cell free system and induces apoptosis in Jurkat cells	2012	Huang., *et al.* [23]

38	Maleimide activation of photon upconverting nanoparticles for bioconjugation	2012	Liebherr., *et al.* [75]
39	C–H bond addition and copolymerization reactions of *N*-arylmaleimides: Fundamentals of coagent-assisted polymer cross-linking	2012	Shanmugam., *et al.* [76]
40	Synthesis and free radical polymerization of N[4-fluoro phenyl] maleimide and study of properties of polymers	2012	Jain., *et al.* [77]
41	Synthesis of substituted maleimide derivatives using the Baylis–Hillman adducts	2011	Basavaiah., *et al.* [78]
42	N-phenylmaleimide derivatives as mimetic agents of the pro-inflammatory process: myeloperoxidase activation	2011	Noldin., *et al.* [79]
43	Investigation on the thermal properties of new thermo-reversible networks based on poly(vinyl furfural) and multifunctional maleimide compounds	2011	Gaina., *et al.* [80]
44	Chemical reactivity and antimicrobial activity of *N*-substituted maleimides	2011	Salewska., *et al.* [81]
45	Synthesis and free radical homopolymerization of 2-chloro-4-nitro (phenyl) maleimide and thermal study	2011	Hiran., *et al.* [82]
46	Copolymerization of Methyl Acrylate with N-4-Methyl phenyl maleimide and characterization of of the polymers	2011	Hiarn., *et al.* [83]
47	Synthesis of New Azo Compounds Based on N-(4Hydroxypheneyl) maleimide and N-(4-Methyl-pheneyl)maleimide	2010	Mohammed., *et al.* [84]
48	Synthesis and properties of N-substituted maleimides conjugated with 1,4-phenylene or 2,5-thienylene polymers	2010	Onimura., *et al.* [85]
49	*N*-Arachidonyl Maleimide Potentiates the Pharmacological and Biochemical Effects of the Endocannabinoid 2-Arachidonylglycerol through Inhibition of Monoacylglycerol Lipase.	2009	Burston., *et al.* [25]
50	Effects of maleimide-polyethylene glycol- modified human hemoglobin(MP4) on tissue necrosis in SKH1–HR hairless mice	2009	Goertzl., *et al.* [86]
51	Synthesis and in Vitro Evaluation of N-Substituted Maleimide Derivatives as Selective Monoglyceride Lipase Inhibitors	2009	Matuszak., *et al.* [24]
52	*N*-Phenyl and *N*-phenylalkyl-maleimides acting against *Candida* spp.: Time-to-kill, stability, interaction with maleamic acids	2008	Sortino., *et al.* [26]
53	Analysis of functionalization of methoxy-PEG as maleimide-PEG	2007	Ananda., *et al.* [87]
54	Hydrogel formation by photocrosslinking of dimethylmaleimide functionalized polyacrylamide	2007	Seiffert., *et al.* [88]
55	A concise synthesis of maleic anhydride and maleimide natural products found in *Antrodia camphorate*	2007	Stewart., *et al.* [89]
56	Antimicrobial Effectiveness of Maleimides on Fungal Strains Isolated from Onychomycosis	2006	Gayoso., *et al.* [90]
57	Synthesis and Biological Activity of Water-Soluble Maleimide Derivatives of the Anticancer Drug Carboplatin Designed as Albumin-Binding Prodrugs	2004	Warnecke., *et al.* [27]
58	Single Molecule Observation of Liposome-Bilayer Fusion Thermally Induced by Soluble N-Ethyl Maleimide Sensitive-Factor Attachment Protein Receptors (SNAREs)	2004	Bowen., *et al.* [91]
59	Synthesis, characterization, and biological activity of *N*-(4-acetylphenyl)maleimide and its oxime, carbazone, thiosemicarbazone derivatives and their polymers	2003	Soykan., *et al.* [92]
60	Maleimides stimulate oxygen reduction in illuminated thylakoids	2002	Ivanov., *et al.* [93]
61	The Michael Reaction of Enaminones with N-(p-tolyl)-maleimide: Synthesis and Structural Analysis of Succinimide-enaminones	2002	Cunha., *et al.* [94]
62	Maleimide Is a Potent Inhibitor of Topoisomerase II in Vitro and in Vivo: A New Mode of Catalytic Inhibition	2002	Jensen., *et al.* [95]
63	Evaluation of N-Aromatic Maleimides as Free Radical Photoinitiators: A Photophysical and Photopolymerization Characterization	2001	Miller., *et al.* [96]
64	Phenolic Resins Bearing Maleimide Groups: Synthesis and Characterization	1999	Bindu., *et al.* [97]
65	A new one step synthesis of maleimides by condensation of glyoxylate esters with acetamides	1999	Faul., *et al.* [98]
66	Synthesis of new maleimide derivatives of daunorubicin and biological activity of acid labile transferrin conjugates	1997	Kartz., *et al.* [99]
67	A mild conversion of maleic anhydrides into maleimides	1990	Davis., *et al.* [100]
68	Novel enzyme immunoassay for thyrotropin-releasing hormone using N-(4-diazophenyl)maleimide as a coupling agent	1986	Fujiwara., *et al.* [101]

69	Selective labeling of beef heart cytochrome oxidase subunit III with eosin-5-maleimide	1985	Miiller and Azzi [102]
71	Effect of maleimide derivatives, sulfhydryl reagents, on stimulation of neutrophil superoxide anion generation with concanavalin A	1983	Yamashita [103]
72	Characterization of sulphydryl groups of the mitochondrial phosphate translocator by a maleimide spin label	1983	Houstek., *et al.* [104]
73	Differential effect of N-ethyl maleimide on muscarinic agonist binding in rat and bovine brain membranes	1980	Carson [105]
74	The action of lipophilic maleimides in mitochondrial energy transduction	1976	Kiehl., *et al.* [103]
75	Structural alterations in the 30 S ribosomal subunit of *Escherichia coli* observed with the fluorescent probe N-(3-pyrene) maleimide	1975	Schechter., *et al.* [107]

Table 3

Phthaleimide

S. No.	Chemical and biological activities	Year	References
1	Recent Advances and Future Prospects of Phthalimide Derivatives	2016	Kushwaha., *et al.* [11]
2	Synthesis and antimicrobial activity of some new phthalimide derivatives	2015	Talal and Omran [108]
3	Synthesis of some N-phthalimide amino acids derivatives and Evaluation their Biological Activity	2015	Ahmad and Amer [28]
4	Phthalimide analogs as probable 15-lipoxygenas-1 inhibitors: synthesis, biological evaluation and docking studies	2015	Alireza., *et al.* [109]
5	Selective Target Protein Degradation via Phthalimide Conjugation	2015	Winter., *et al.* [110]
6	Synthesis, structural and antioxidant studies of some novel N-ethyl phthalimide esters	2015	Chidan Kumar., *et al.* [29]
7	Design, Synthesis and Evaluation of Novel Phthalimide Derivatives as in Vitro Anti-Microbial, Anti-Oxidant and Anti-Inflammatory Agents	2015	Lamie., *et al.* [111]
8	Phthalimide-based p-conjugated small molecules with tailored electronic energy levels for use as acceptors in organic solar cells	2015	Hendsbee., *et al.* [112]
9	Investigation of Antioxidant Properties of Phthalimide Derivatives	2015	Karthik., *et al.* [30]
10	Synthesis of New Bis-Phthalimide and Thalidomide Ester Derivatives, and Evaluation of their Cytotoxic Activity	2015	Ahmed Osman., *et al.* [113]
11	A novel phthalimide derivative, TC11, has preclinical effects on high-risk Myeloma cells and Osteoclasts	2014	Matsushita., *et al.* [32]
12	Structure-based design of phthalimide derivatives as potential cyclooxygenase-2 inhibitors: Anti-inflammatory and analgesic activity	2014	Alanazi., *et al.* [31]
13	Synthetic of Phthalimides via the reaction of phthalic anhydride with amines and evaluating of its biological and anti corrosion activity	2014	Hamak [34]
14	Cytotoxic and toxicological effects of phthalimide derivatives on tumor and normal murine cells	2014	Ferreira., *et al.* [114]
15	Synthesis, characterization and analgesic activity of several new N-substituted phthalimide analogues	2014	Fhid., *et al.* [33]
16	Docking Studies of Phthalimide Pharmacophore as a Sodium Channel Blocker	2013	Iman., *et al.* [115]
17	Comparative theoretical studies on natural atomic orbitals and simulated UV-visible spectra of N-(methyl)phthalimide and N-(2 bromoethyl)phthalimide	2013	Balachandran., *et al.* [116]
18	Synthesis,characterization and biological evaluation of acetazolamide, cycloserine and isoniazid condensed some noval phthalimide derivatives	2013	Elumalai., *et al.* [117]
19	Synthesis of phthalimide and succinimide copolymers and their evaluation as flow improvers for an Egyptian waxy crude oil	2013	Al-Sabagh., *et al.* [118]
20	Synthesis, characterization and antibacterial screening of new Schiff bases linked to phthalimide	2013	Al-Azzawi., *et al.* [119]
21	Synthesis and *in Vitro* antimycobacterial activity determination of phthalimide derivatives	2013	Paraiso., *et al.* [35]
22	2D-QSAR analysis of phthalimide derivatives as potent hypoglycemic agents	2013	Nain., *et al.* [120]
23	Synthesis and antimicrobial activity of substituted Phenoxyacetyl Hydrazino Acetyl-Phthalimides	2013	Sinha., *et al.* [36]
24	Eco-friendly Synthesis of Phthalimide Derivatives, their Analgesic Activity and QSAR Studies	2012	Gajare. and Mahajan [121].

25	QSAR Studies of phthalimide derivatives for their potent anxiolytic	2012	Gajare., *et al.* [122]
26	Synthesis and pharmacological evaluation of N-[4-(t-amino)-2butynyloxy] phthalimides	2012	Muhi-eldeen., *et al.* [123]
27	3D-QSAR for α-glucosidase inhibitory activity of N-(phenoxyalkyl)phthalimide derivatives	2012	Mbarki., *et al.* [38]
28	Synthesis and Anti-Inflammatory Activity of New Alkyl-Substituted Phthalimide 1H-1,2,3-Triazole Derivatives	2012	Oliveira Assis., *et al.* [37]
29	Studies of antibacterial activity of some new N-alkyl and N-alkyloxy phthalimides	2011	Pawar., *et al.* [124]
30	Synthesis and Evaluation of the Anxiolytic Activity of Some Phthalimide Derivatives in Mice Model of Anxiety	2011	Hassanza-deh., *et al.* [40]
31	Inhibition of monoamine oxidase by C5-substituted phthalimide analogues	2011	Manley-King., *et al.* [39]
32	Inhibitory effects of phthalimide derivatives on the activity of the hepatic cytochrome P450 monooxygenases CYP2C9 and CYP2C19	2010	Kolukisao-glu., *et al.* [125]
33	Synthesis and hypoglycemic activity of some phthalimide derivatives	2010	Mahapatra., *et al.* [41]
34	Synthesis and antimicro-bial evaluation of some alk-oxyphthalimide derivatives of naphthyridine	2009	Bhambi., *et al.* [42]
35	Phthalimide-N-oxyl (PINO) Radi-cal, a Powerful Catalytic Agent: Its Generation and Versatility Towards Various Organic Sub-strates	2009	Coseri [126]
36	Reactions of phthalimide with 1-methylethylamine: analgesic and anti-inflammatory proper-ties of resulting carboxamides	2006	Okunrobo., *et al.* [127]
37	Hypolipidemic activity of phthalimide derivatives IV: Further chemical modification and investigation of the hypolip-idemic activity of N-substituted imides	2006	James., *et al.* [128]
38	Design, synthesis and antiin-flammatory activity of novel phthalimide derivatives, struc-turally related to thalidomide	2005	Machado., *et al.* [129]
39	3D-QSAR Studies on Phthalimide Derivatives as HIV-1 Reverse Transcriptase Inhibitors	2004	Samee., *et al.* [130]
40	Synthesis and biological activity of phthalimide-based polymers containing 5-fluorouracil	2002	Lee., *et al.* [42]
41	Quantitative Structure-Ac-tivity Relationship Study on Phthalimide Derivatives as HIV-1 Reverse Transcriptase Inhibitors	2001	Ungwitaya-torn., *et al.* [131]
42	Targeted Antioxidant Proper-ties of N-[(Tetramethyl-3-pyr-roline3-carboxamido)propyl] phthalimide and Its Nitroxide Metabolite in Preventing Post-ischemic Myocardial Injury	1999	Shankar., *et al.* [44]
43	Novel biological response modifiers: phthalimides with TNF-alpha production regulating activity	1997	Miyachi., *et al.* [132]
44	The hypolipidemic activity of N-phenylphthalimide derivatives: a QSAR study	1993	Coutinho Neto., *et al.* [41]

Conclusion

On the basis of the previous study we concluded that the Phthalimide and maleimide compounds have considerable biological activities. Phthalimide and maleimide are an important class of drugs exhibited anxiolytic, antimicrobial, analgesic, antibacterial, antituberculosis, anticancer, hypolipidemic, antiproliferative, acetylcholinesterase inhibitors etc. Various phthalimide and maleimide derivatives will design and develop by incorporating new pharmacophores at various positions with the hope to get new and more potent therapeutically active compounds. Thus, it may be concluded that the various synthesized compound effectively used in the treatment of various diseases and disorders.

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