WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 12, Issue 13, 737-757. Review Article ISSN 2277–7105

AN OVERVIEW ON VERSATILE PHARMACOPHORE OF PHTHALIMIDE DERIVATIVES

Sathish Annadurai[1]*, Dr. S. K. Senthilkumar[2], Sanjay Babu[3], Sandhiya Uralliappan[3], Santhanam Sambath[3], Sethupathi Rajamani[3] and Shahithabanu Ameer[3]

[1*]Assistant Professor, Department of Pharmaceutical Chemistry, Arunai College of Pharmacy, Tiruvannamalai, Tamilnadu, India.

[2]Professor, Department of Pharmaceutics, Arunai College of Pharmacy, Tiruvannamalai, Tamilnadu, India.

[3]B. Pharmacy Final Year Students, Arunai College of pharmacy, Tiruvannamalai, Tamilnadu, India.

Article Received on
15 June 2023,

Revised on 05 July 2023,
Accepted on 25 July 2023

DOI: 10.20959/wjpr202313-29210

***Corresponding Author**
Sathish Annadurai
Assistant Professor, Department of Pharmaceutical Chemistry, Arunai College of Pharmacy, Tiruvannamalai, Tamilnadu, India.

ABSTRACT

Currently, phthalimide derivatives widely employed in therapeutic perpose owning to have very potent due to their antimicrobial, anti-angiogenic, anticonvulsant, anxiolytics, Antioxidant, Tyrosinase inhibition, cytotoxic and toxicological effect, anti-inflammatory, anti proliferative, and HIV-I RT inhibitor activity. This review article is intended to provide highly relevant information on the biological activities of these compounds and their mechanisms of systemic action that have already been elucidated. The phthalimides and their derivatives studied in this study presented individual molecules, but also conjugated with other pharmacophoric groups, in order to improve their pharmacokinetic and pharmacodynamic aspects and thus generate better therapeutic response. The established documentation having the information about phthalimide moities with a powerful therapeutic profile which is used design & develop potential molecules and provide interest and opportunities for researchers work on phthalimide scaffold.

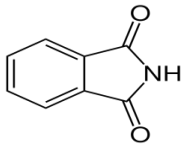
KEYWORDS: Phthalimide derivatitves, phthalic anhydride, phthalic acid, imide.

INTRODUCTION

Phthalimides are the group of cyclic imides which having the chemical feature of -CO-N(H)-

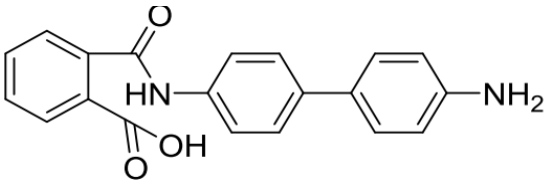
CO- and having a chemical feature of two C=O moieties and it is further bound to nitrogen within the bicycle non aromatic heterocycle. Phthalimide was used as an initial material as pharmacophore. Recently, Phthalimide and their compounds exhibited activity as antimicrobial[1], Antioxidant[2], Anti-inflammatory[3], Analegesic[4], Anti-mycobacterial[5], Anti depressant[6], Anxiolytics[7], Hypoglycemic activity[8], Antitumour[9] and Hypolipidimic activity[10]…etc. Phthalimide have served as starting materials and intermediates for the synthesis of many types of alkaloids and pharmacophores.

STRUCTURE OF PHTHALIMIDE

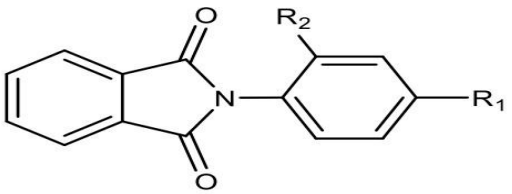


Phthalimide is an imido derivative of phthalic acid. In organic chemistry, imide is a functional group consisting of two carbonyl groups bound to nitrogen. They are hydrophobic and neutral, and can therefore cross biological membranes in vivo. These compounds are structurally related to acid anhydrides. In N-Benzyl phthalimide the benzene and imide groups are planar and make a dihedral angle with one another. There are three weak C-H O hydrogen bonds, forming a two dimensional network structure. Most of the imides are cyclic compounds derived from dicarboxylic acids and their names reflect the parent acid. Examples are succinimide derived from succinic acid and phthalimide derived from phthalic acid. As imide has the formula NH, being highly polar, imides exhibit good solubility in polar media. The N-H centre for imides derived from ammonia is acidic and can participate in hydrogen bonding.

Hussniya A.Aldifar et al (2023) synthesized the benzimidazole and phthaloylamino acid derivatives and antibacterial activity. In the presence of acetic acid, the pthalic anhydride reacted with benzidine in a cyclization reaction to obtain the biphenyl of 7 products. When phthalic anhydride react with D-glycine, D- alanine, D-valine under solventless and fusion condition using an oil bath the N-pthaloyamino acids 2-(1,3 dioxoisoindolin-2-yl) acetic acid and 2-(1,3-dioxoisoindolin-2-yl) succinic acid were obtained. A high yield was found for 7 products and it was found between 60% and 80%. The biological activity of the products was examined and the result show good inhibitory activity against used bacteria.[11]



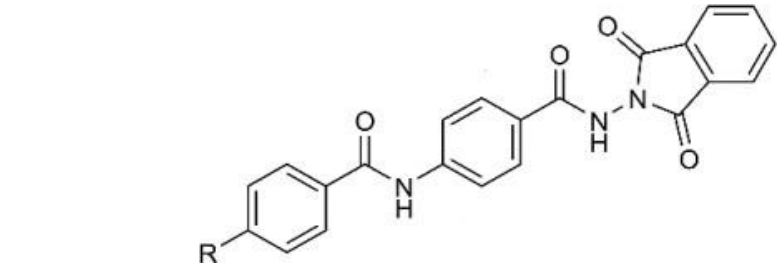
Najeeb Ur Rehman et al (2023) phthalimide have diverse bioactivities and are attractives molecule of drug discovery and development. Here, explored new synthesized pthalimide derivatives 2-(2,4 dimethylphenyl) isoindoline-1,3-dione in improving memory impaiments associated with Alzheimer's disease(AD) using invitro and invivo acetylcholinesterase (AChE) and butyryl cholinesterase (BuChE) inhibition and in vivo models including Y-maze test and novel object reconition test (NORT). Pthalimide derivatives 2-(2,4 dimethylphenyl) isoindoline -1,3-dione possess anti-oxidants effects and inhibit choline esterase enzyme invitro complemented by molecular docking studies. They could be useful leads for the development of novel therapeautics agents memory impairments in alzheimers disease.[12]



Compounds **1-3**

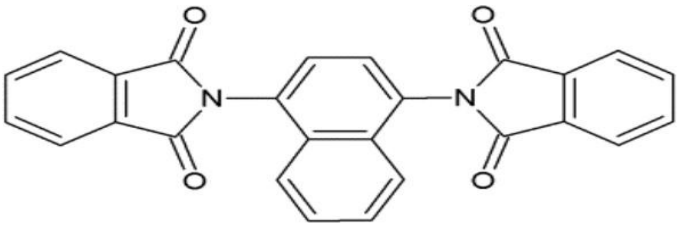
1:R_1=CF_3, R_2=H
2:R_1=Br, R_2=H
3:R_1= R_2= CH_3

Bedia Kocyigit-Kaymakcioglu et al (2023) In this study 13 pthalimide derivatives were designed and synthesized. All these synthesized compounds were evaluated to determine their potential for inhibitory activities against females of the Caribbean fruit fly, *Anastrephasuspensa* (loew) (Diptera: Tephritidae). These efforts led to be the discovery of three compounds 4-Benzamido-N-(1,3-dioxoisoindolin-2yl)benzamide, N-(1,3 Dioxoisoindolin-2-yl)-4-(4-cholrobenzamido)benzamide, N-(1,3-Dioxoisoindolin-2 yl)4(4methylbenzamido)benzamide with potent insecticidalactivity (LD50 range from 0.70to 1.91 fly). In addition to the fact that the phthalimide structure is environmentally friendly compound, the synthesized compound were thought to be promising compound due to their better bioconcentration factor and IGC50 values compared to the precursor compounds. 4-Benzamido-N-(1.3 dioxoisoindolin -2yl) benzamide has strong potential as a candidate component for developing and novel environment.[13]



R: -H, 4-F, 4-Cl, 4-CH_3, 4-OCH_3, 4-Br, 4-SCF_3, 4-OCF_3, 2-CF_3, 3-CF_3, 3-CH_3, 4-CN, 4-NO_2

Mieczyslaw Lapkowski et al (2023) in this study naphthalene phthalimide derivatives as model compounds for electrochromic materials. Development of efficient, cathodic electrochromic mzterials is challenging due to the worse stability of electron accepting materials compared with electron donating ones. Neverthless, designing stable cathodic coloring organic materials is highly desired among other reasons to increase the coloration performance. Hence four pthalimide derivatives named 1,5-PhDI,1,4-PhDI,2,6-PhDI and 3,3'-PhDI were synthesized and analysed in depth. In the case of imide derivatives, adsorption bands related to both reduced and neutral forms are located in the UV region. However, importantly, the introduction of the 3,3'-dimethylnapthtidine bridges leads to an noticeable bathochromic shift of the reduced form absorption band of 3-3'PhDI. This also shows that there is no interaction between the imide/diimide unit and N-substituents. The optimisation of the pthalimide structure allows as to obtain stable, cathodic elactochromic material.[14]

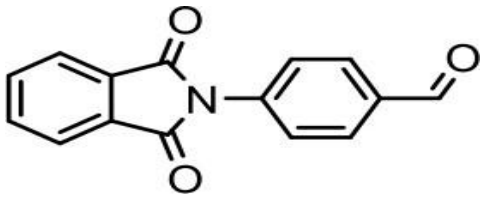


Krzysztof Z.Lackowski etal (2023), Nine pthalimide thiazoles 2-(2-(2-(4-Fluro phenylamino)thiazol-4-yl)ethyl)isoindoline-1,3-dione and 2- (2-(2-(4-Acetylphenylamino) thiazol-4-yl) ethyl) isoindolin-1,3-dione were synthesized and investigated as new human neutrophil elastae (HNE) inhibitors using spectroflurometric and computational methods. The pthalimide - thiazole derivatives with various substituents in the phenyl ring have been synthesized to explore their role in human neutrophil elastase inhibition and anti proliferative activity. The most active compound containing 4-trifluoromethyl, 4-naphthyl and 2,4,6-trichloro substituents exibit high HNE inhibitory activity with IC50 values of 12.98-16.62 M.

Additionaly, compound with 4,trifluromethyl group showed mixed mechanism of action, some compounds showed high antiproliferative activity against leukemia, lung, breast and urinary bladder human cancer cells lines with IC50 values of 8.21 to 25.57M. Spectoscopic analysis showed that the most active compounds demonstrated high stability under physiological conditions 4-trifluoromethyl, 4-naphthyl and 2,4,6,-trichloro substituents may serve as lead steuctures to design highly potent HNE inhibitors with good antiproliferative property.[15]

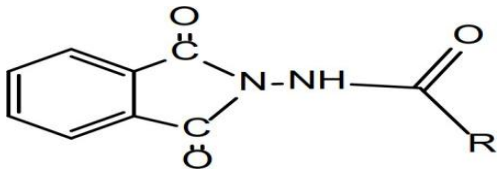
Compound	$IC_{50} \pm SD$ [μM]
4a	29.35 ± 3.13
4b	46.51 ± 4.85
4c	12.89 ± 0.98
4d	22.92 ± 1.59
4e	15.58 ± 0.16
4f	49.88 ± 0.98
4g	64.89 ± 7.75
4h	16.62 ± 2.06
4i	25.60 ± 1.78
Ursolic acid	5.32 ± 0.68

Halah A.Sahib and Mohammed H.Mohammed etal (2020), was synthesised a new series of bases of Schiff (2-(4- (1,3-dioxoisoindolin-2-yl) benzylidene)amino)3-(4-hydroxy phenyl) proponoate) (N'(4-(1,3-dioxoisonidolin-2-yl) benzylidene) isonicotinohydrazide) derived from pthalic anhydride were synthesised. These Schiff base were prepared by the reaction of different amines (tyrosine methyl ester, phenylamine methyl ester, and isoniazid) with the pthalimide derived aldehyde with the aid of glacial acetic acid or triethylamime as catalysts. New Schiff bases derivatives containing pthalimide core were successfully synthesized and their structure were characterised by "IR and HNMR spectral" methods. All the synthesized compounds showed no activity at all against Gram positive bacteria, for Gram negative bacteria and fungi they showed moderate or no activity except compound (4-(1,3-dioxoisonidolin -2-yl) benzaldehyde) revealed high antifungal activity against Candida tropicalisat concentrations 125 and 250 ml.[16]



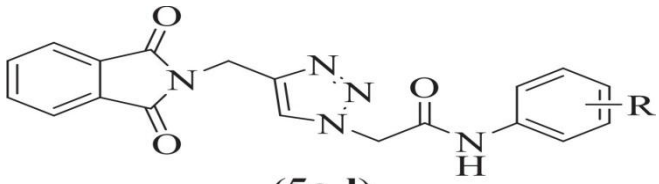
Nebras M.Jamel etal (2019), was synthesized the Pthalimide anhydride with various amines using microwave or without a method with the difference of the catalyst used in a prepared Pthalimide, either structure general are C6H4CONRCO and used as starting material in

synthesis several compounds derivative pthalimide are an important compounds because spectrum wide biological activities including Antimicrobial activity, anticonvulsant activity, Anti-inflamatory activity, Analgesic activity, Anti-influenza activity and Thromboxane inhibitory activity.[18]



$R=C_6H_5$ CHO,4-$NO_2C_6H_4$CHO

Krishan P.Haval etal (2019), was synthsised the synthesis, antitubercular evaluation and molecular docking studies of pthalimide bearing 1,2,3-triazoles. In a search for safer and potent antitubrcular agents, here a library of newly substituted dioxoisoindolinylmethyl-triazolyl-N-phenylacetamide derivatives (5a-I) has been synthesized2-(4-((1,3 -dioxoisoindolin-2-yl)methyl) -1H-1,2,3-triazol 1-yl) N-phenylacetamides. Had reported a series of newly substituted dioxoisoindolinylmethyl-triazolyl-N-phenylacetamide derivatives by 1,3-dipolar cyclo addition of the alkyene and substituted phenyl acetamide. Molecular docking study indicates that all the molecules are binding to the enoylreductase of the Mycobacterium tuberculosis the result obtained herein will provide a strong platform for structure based optimization of these newly identified 1,4 disubstituted 1,2,3-triazole derivatives as antitubercular agents.[19]

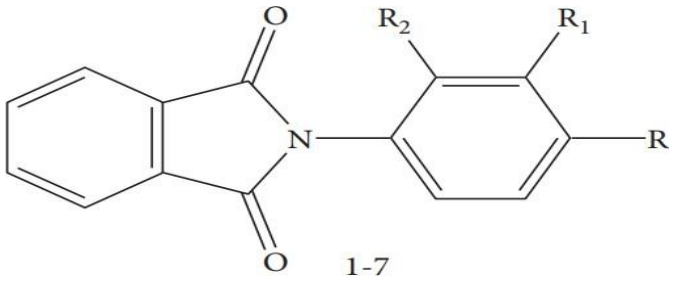


(5a-l)

5a : R = 4-CH_3, **5b** : R = 4-Cl, **5c** : R = H, **5d** : R = 4-Br,
5e : R = 3-NO_2, **5f** : R = 3-OCH_3, **5g** : R = 2-Cl, **5h** : R = 4-F,
5i : R = 2-OCH_3, **5j** : R = 3-Cl, **5k** : R = 3-OCH_3, **5l** : R = 2-CH_3

Shagufta Perveen et al(2018) to synthesize the pthalimide derivatives, initially the reaction was optimized with various catalyst and L-proline was found to be best catalyst as it provided excellent yield. A series of pthalimide derivatives was synthesized by facile one top reaction of phthalic acid with aryl amine under mild reaction conditions in the presence of l-proline as catalyst. Product were obtained in excellent yield and structurally characterized by H,C NMR and mass spectral data. Product N-(4-methoxyphenyl) isoindoline -1,3dione and N-(2-chloro-4-methoxyphenyl) isoindolidoline-1,3-dione were evaluated for antioxidant activity, anti

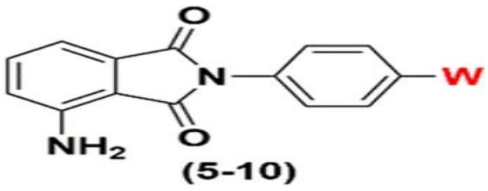
inflammatory and lipoxygenase enzyme inhibition activities. Through the optimization of reaction, pthalimide derivatives were obtained in excellent yield and all the product showed weak to moderate antioxidant potential whereas compound N-(4-methoxyphenyl)isoindoline 1,3-dione and N-(4-nitro) isoindoline -1,3 dione. Showed outstanding and potent antioxidant and lipoxygenase enzyme inhibition potential as compared to the standard drug used.[20]



1-7

1 R = OCH_3, R_1 = H, R_2 = H
2 R = H, R_1 = H, R_2 = H
3 R = Cl, R_1 = H, R_2 = H
4 R = NO_2, R_1 = H, R_2 = H
5 R = CH_3, R_1 = H, R_2 = H
6 R = H, R_1 = H, R_2 = CH_3
7 R = OCH_3, R_1 = Cl, R_2 = H

Rafael Victorio Carvalho Guido and Vanderlan Silva Bolzani et al (2018) was synthesized the design and synthesize of N-phenyl pthalimide derivatives with inhibitory activities against plasmodium falciparum (sensitive and resistant strains) in the lower micromolar range and noticeable selectivity indices against human cells. The best inhibitor, 4-amino-2-(4-methoxyphenyl) isoindoline-1,3 dione showed as slow actind mechanism similar to that atovaquone. The modelled binding mode of 4-amino-2-(4-methoxyphenyl) isiondoline-1,3 dione suggested the molecular determinant that might be related to the inhibitory activity of thus series. Therefore,our finding indicate that 4-amino-2-(4-methoxyphenyl)-isoindoline-1,3 dione is a new hit for the development of lead compounds with superior properties.[21]



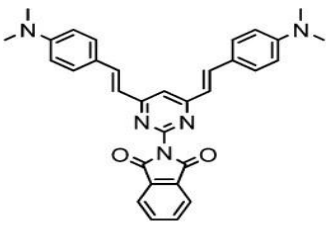
(5-10)

(5) R = H, **W** = NO_2
(6) R = H, **W** = CF_3
(7) R = H, **W** = Cl
(8) R = H, **W** = H
(9) R = H, **W** = Me
(10) R = H, **W** = OMe

Hiba Kadhim Yaseen et al (2015) was synthesized the characterization of several new poly (Allyloxy phenyl) bearing pendenttetarchloropthalimides. Synthesis of these polymers was

performed by many steps in the first step your N-(hydroxyphenyl) tetrachloropthalamic acids were prepared via reaction of ortho, meta and p-amino phenols with tetra chlorophthalic anhydride. Dehydration of these amic acids by fusion in the second step afforded the corresponding N-(hydroxy phenyl)(allyloxy phenyl) were introduced in reaction with ally chloride in basic medium in the third step producing N-(allyloxy phenyl) tetra chloro pthalimides which introduce in free radical homopolymerization affording the target polymers. The presence of allyoxy groups in repeating units of the new polymers exihibit them flexibility leading to better solubility and processability with keeping good thermal stability.[17]

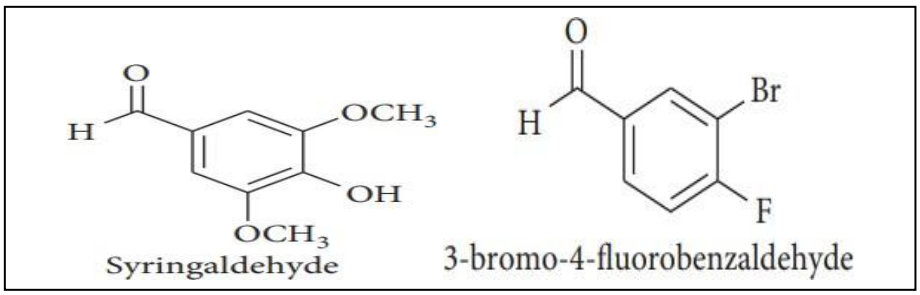
Shusheng Ge and Yun Lu et al (2017) molecules with D-A structures that is connecting electron donating (D) and electron acceptin (A) group via conjugated linker have attracted increasing attention since they can serve as electroactive and photoactive materials in biochemical fluroscent technology, efficient non linear optical (NLO) applications electrogenerted chemiluminescence organic lightening diodes OLEDS solar cells. In this work two new chromophores PB and NPB consisting of phthalimide and pyrimide based derivatives were synyhesized. The reaction was carried out under refluxing conditions in toluene and the products were readily obtained by recrystallization in good yield. Two new atypical AIE chromophores PB and NPB werte designed and synthesized also characterized by IR, H NMR, C NMR and HRMS. The novel pyrimidine pthalimide derivatives with sensitive response to pH both in water solution and in the gas phase may hold great potential for applications in the material science fields.[22]



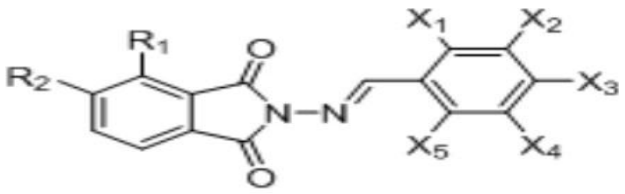
NPB

Hayman Sardar Abdukrahman et al (2020) they developed the phthalimide based derivatives as potential new drugs. Displaying different types of functionalities and at alternating positions and explore possible differential biological effects as antioxidants and anticancer agents. A total sixteen compounds were synthesized and each was verified by FT-IR, H NMR, C NMR and MS production routes. The active functional group namely the methoxy group and ortho position is expected to increase the compound activity against the cancer cell

environment. The presence of phenolic acid and methoxy substitution at aromatic amines that improves the antioxidant activity of phthalimide, while the presence of meta bromo and para fluoro substituted imines will improve the anticancer activity.[23]



Girish Kumar Sinha et al (2017) an innovative protocol to the synthesis of this material emerged on exploring the potential of the various form of N-aminophthalimides on its reaction with a number of aromatic aldehydes. New series of biologically active substituted Schiff bases with general formula, R1N=CHR2 where R1=3-nitro-N-aminophthalimide,3-bromo-N-aminophthalimide, 4-nitro-n-aminophthalimide, 4-bromo-N-aminophthalimide, R2=2,6-dichlorobenzaldehyde, o-anisaldehyde and o-vanilin were synthesized by the reaction of substituted N-aminophthalimides and substituted aldehydes in ethanol. 4a-4p (C15H7N3O4CL2-C16H11N2O4Br) were found to be effective against bacterial and fungal activities to a greater extent. 4a-4d (C15H7N3O4CL2-C16H11N3O6) & 4i-4l (C15H7N3O4CL2-C16H11N3O6).[24]

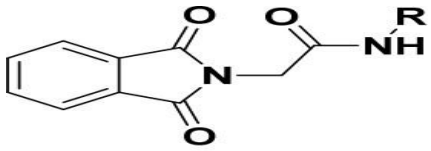


4(a-p)

4a. $R_1 = NO_2$, $R_2 = H$, $X_1 = Cl$, $X_2, X_3, X_4 = H$, $X_5 = Cl$
4b. $R_1 = NO_2$, $R_2 = H$, $X_1 = OCH_3$, $X_2, X_3, X_4, X_5 = H$
4c. $R_1 = NO_2$, $R_2 = H$, $X_1, X_2, X_3, X_5 = H$, $X_4 = Br$
4d. $R_1 = NO_2$, $R_2 = H$, $X_1 = OH$, $X_2 = OCH_3$, $X_3, X_4, X_5 = H$
4e. $R_1 = Br$, $R_2 = H$, $X_1 = Cl$, $X_2, X_3, X_4 = H$, $X_5 = Cl$
4f. $R_1 = Br$, $R_2 = H$, $X_1 = OCH_3$, $X_2, X_3, X_4, X_5 = H$
4g. $R_1 = Br$, $R_2 = H$, $X_1, X_2, X_3, X_5 = H$, $X_4 = Br$
4h. $R_1 = Br$, $R_2 = H$, $X_1 = OH$, $X_2 = OCH_3$, $X_3, X_4, X_5 = H$
4i. $R_1 = H$, $R_2 = NO_2$, $X_1 = Cl$, $X_2, X_3, X_4 = H$, $X_5 = Cl$
4j. $R_1 = H$, $R_2 = NO_2$, $X_1 = OCH_3$, $X_2, X_3, X_4, X_5 = H$
4k. $R_1 = H$, $R_2 = NO_2$, $X_1, X_2, X_3, X_5 = H$, $X_4 = Br$
4l. $R_1 = H$, $R_2 = NO_2$, $X_1 = OH$, $X_2 = OCH_3$, $X_3, X_4, X_5 = H$
4m. $R_1 = H$, $R_2 = Br$, $X_1 = Cl$, $X_2, X_3, X_4 = H$, $X_5 = Cl$
4n. $R_1 = H$, $R_2 = Br$, $X_1 = OCH_3$, $X_2, X_3, X_4, X_5 = H$
4o. $R_1 = H$, $R_2 = Br$, $X_1, X_2, X_3, X_5 = H$, $X_4 = Br$
4p. $R_1 = H$, $R_2 = Br$, $X_1 = OH$, $X_2 = OCH_3$, $X_3, X_4, X_5 = H$

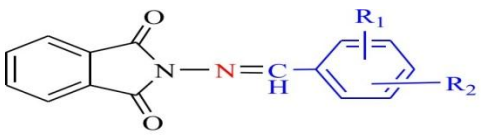
Hany E.A.Ahmed et al (2016) In continuation of our endeavour towards the design and development of potent and effective antimicrobial agents, three series of phthalimide derivatives (4a-I,5a-f 7 6a-c) were synthesized fully characterised and evaluated potential antibacterial, antifungal and antimycobacterial activities. Molecular modelling studies were

done to explore the binding mode of the most active derivates to M.tuberculosis enoyl reductase (InhA) and DNA gyrase B. The study showed the importance of both hydrogen bonding and hydrophobic interactions as a key interaction with the target enzymes. Different synthetic routes to these novel N-aryl or alkynyl phthalimide derivatives (4a-I,5a-f&6a-c) have been successfully carried out. The activity data shows that most of the novel compounds have potent antibacterial and antimycobacterial activities compared to reference drugs. Finally, ceratin N-phthalimide derivatives of various structures were synthesized and offered good antimicrobial and antimycobacterial activities with good DNA-gyrase and ENRenzymes targets affinity.[25]



4a-i

Pattan Sirajuddin Nyab et al (2016) Investigated new phthalimide - based Schiff base molecules as promising DNA-binding and free radical scavenging agents. physiochemical properties of these molecules were demonstrated on the basis of elemental analysis, ultraviolet-visible (UV-VIS), infra-red (IR), 1H and 13C Nuclear magnetic resonanace (NMR)spectroscopy. The two novel phthalimide derivative as promising DNA binding and antioxidant agents. The interaction of 2a(2-(4-ISOpropylbenzylideneamino)-isoindoline-1,3-dione) and 2b[2-(3,4- dihydroxybenylideneamino)- isoindoline-1,3-dione] with Ct-DNA was determined by means of spectroscopic, thermal denaturation and hydrodynamic studies. The antioxidant capabilities for synthesized compounds were found to be 2b>2a, demonstrating that the compound 2b displayed greater scavenging activity against DPPH and H2O2 radicals compared to reference ascorbic acid. The presence of phenolic group causes 2b to be more effective antioxidant than 2a.[26]

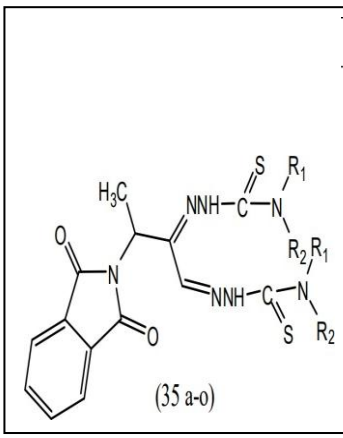


2a-2b

2a: $R_1 = H$; $R_2 = CH(CH_3)_2$
2b: $R_1 = 3\text{-}OH$; $R_2 = 4\text{-}OH$

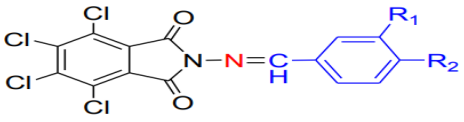
Neelottama Kushwaha et al (2016) among bicyclic non-aromatic nitrogen heterocycles, phthalimides are an interesting class of compounds with a large range of applications.

Phthalimide contains an imide functional group and maybe considerd as nitrogen analogues of anhydrides or as diacyl derivatives of ammonia. They are liphophilic and neutral compounds and can therefore easily cross biological membranes in vivo and showing different pharmacological activities. New prototypes drug candidates with different biological activities and are used in different diseases as, for example AIDS, tumour, diabetes, convulsion, inflammation, pain, bacterial infection among others. The established track record of significant efforts toward phthalimide scaffolds with impressive therapeutic profile would be the important step to a possible drug development for treatment of many diseases and these comprehensive endeavors will open up new opportunities for reseachers to design invaluable therapeutic agents phthalimide scaffold.[27]



Compound	R_1	R_2
35 a	Me	Me
35 b	H	i-Pr
35 c	H	Cyclohexyl
35 d	H	Allyl
35 e	H	Bn
35 f	H	4-Cl-Bn
35 g	H	Ph
35 h	H	2-F-Ph
35 i	H	4-Br-Ph
35 j	H	4-F-Ph
35 k	H	4-Cl-Ph
35 l	H	3,4-Cl, Cl-Ph
35 m	H	3,5-CF3,F3-Ph
35 n	H	4-Me-Ph
35 o	H	4-MeO-Ph

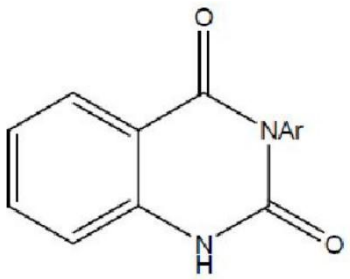
Pattan Sirajuddin Nayab et al (2023) A new series of N substituted phthalimide derivatives were prepared by condensation of appropriate amount of n-amino tetrachlorophthalimide with respective aldehyde in glacial acetic acid. The structural investigation of the synthesized compounds was done by spectroscopic methods (UV-Vis,IR,H and C NMR) and elemental analysis. The antibacterial screening of these compounds was performed against *Escherichia Coli* and *Staphyloccocus mutans.* The synthesized compounds were evaluated for their antioxidant potential using 2,2-diphenyl -1- picrylhydrayl (DPPH) as a scavenging agent. Two compounds were showing remarkable antibacterial activity against the selected bacteria. The presence of methoxy group at *para* position cause compound 2-(4-methoxybenzylideneamino)-4,5,6,7,- tetrachloro isoindoline-1,3-dione be more active, which gives it a higher potential for cellular uptake, and inhibits the growth of bacteria. The results obtained indicate that 2-(4-methoxybenzylideneamino)-4,5,6,7-tetrachloro-isoindoline-1,3-dione can bind to DNA more strongly than 2-(3-ethoxy-4-hydroxybenzylidenemino)-4,5,6,7-tetrachloroisoindoline-1,3-dione.[28]



3a-d

3a: $R_1 = OC_2H_5$; $R_2 = OH$
3b: $R_1 = H$; $R_2 = OCH_3$
3c: $R_1 = H$; $R_2 = CH_3$
3d: $R_1 = H$; $R_2 = Cl$
3e: $R_1 = H$; $R_2 = Br$

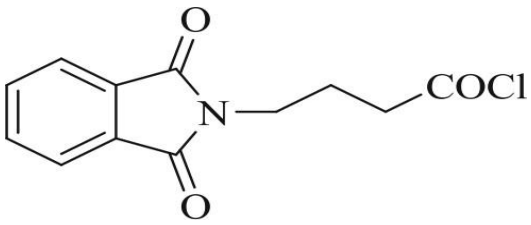
M.M.Hemdan et al (2015) A versatile highly accelerated, efficient and environmentally friendly microwave assisted synthesis of pthalimides, pthalazines, and quinazolines is described. This shows the advantages of good substrate, tolerance, clean and rapid conversion to these important heterocycles. Quinazolinone derivatives attract a widespread interest due to the diverse biological activities associated with them. Cyclic imides pthalazinediones and quinazolinones were prepared by applying a simple, fast and highly efficient procedure under microwave irradiation. The products are fully examined by their melting point mixed melting, TLC, IR spectroscopy with authentic samples. All yields correspond to isolated pure compounds.[29]



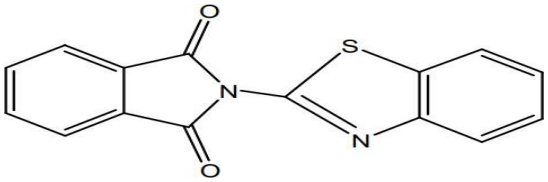
9a-d

Priya Ahuja. Asif Husain. Nadeem Siddiqui et al (2014) A series of novel N-(2-benzlamino)-1-substituted-2-oxoethyl)-4-(1,3-dioxoisoindolin-2-yl) butanamide derivatives were synthesized unifying the functionalized amino acid unit and GABA phthalimide moiety with essential amino acid substituted on it with a view to explore prospective anticonvulsant candidates. The initial screening was performed using the intraperitoneal (i.p)maximal electro shocl test and subcutaneous pentylenetetrazole (scPTZ)test in mice. These result encourage our future investigation on the rational modification of this basic framework for better potency. The empirical blueprint of the functinalized amino acids (lacosamide and valrocemide) unit applied to the phthalimide moiety through the integral linkers GABA (gabapentin) form the basis tenets of spectancular activity attained in these analogues. The

difference activity of the three hallmarks N (1-benzylamino)-3-(1H-imidazole-4-yl)-1-oxopropan-2-yl)-4-(1,3-dioxoisoindolin-2-yl) butanamide, N-benzyl-2-(4-(1,3-dioxoisoindolin-2-yl) butanamido)-4-(methylthio) butanamide, and N-benzyl-2-(4-(1,3-dioxoisoindolin-2-yl) butanamido)-3-hydroxybutanamide obtained in this unprecedented study maybe due to variable pharmacokinectics, different routes of administration or novel molecular targetinteraction.[30]

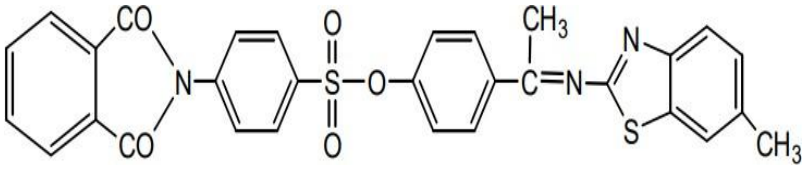


Khuluod Fahed Hamak et al (2014) A series of phthalimide were prepared in satisfactory yields by reaction of phthalic anhydride with amines (amino pyridine, 5-methy amino pyridine, 4-methyl amino quinoline, aminobenzotiazol, 4-amino antipyrines, fluoren-9(9aH)-ylidene)hydrazine). The structure of synthesized has been established on the basis of their spectral data (FT-IR, MASS, H,C-NMR, elemental analysis) data. The purity of compound was confirmed by TLC. The synthesized compound were screened for their antibacterial activity against four microorganisms **staphylococcus aureus, Bacillus subtilis, Escherichia Coli** and **klebsiella pneumonia.** And they were found tp exihibit good to moderate antibacterial activity. Compounds (C13H8N2O2-C15H10N2O2S) which contain functional moiety is most potent against bacterial its showed good antimicrobial activity.[31]

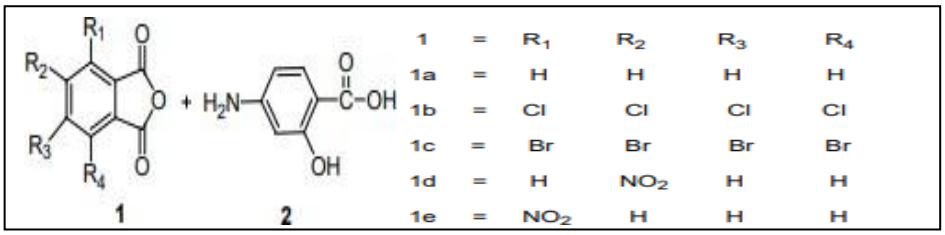


Ahlam M.AL-Azzawi et al (2014) A series of Schiff bases linked to phthalimidyl phenyl sulfonate moiety have been synthesized. The first step involved reaction of phthalic anhydride with aniline producing N- phenyl pthalamic acid and treatment with acetic anhydride and anhydrous sodium acetate. The synthesized imide was treated with chlorosulfonic acid in the third step producing 4-(N-pthalimidyl)phenyl sulfonyl chloride which was introduced in reaction with 4-hydroxy acetophenone in the fourth step producing 4-(4-(N-pthalimidyl) phenyl sulfonate acetophenone. The newly synthesized compound were characterized through spectral data including (FTIR,HNMR,CNMR). Antimicrobial activity of the prepared Schiff base was evaluated against two types of bacteria and one type of fungi.

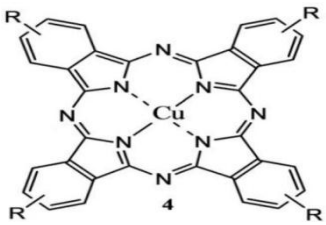
The presence of the two active functionalities phthalimide and Schiff base in the new synthesized molecules exihibit them biological activity. The presence of the known biologically active benzothiazole moiety in the compound 4-(4-N-phthalimidyl) phenyl sulfonate) methyl benzylidene increased the activity of this compound among the others.[32]



Y.Dathu Reddy et al (2014) Green synthesis of novel compounds 4-(2- carboxy benzamido) -2-hydroxybenzoic acids and 4-(1,3-dioxoisoindolin-2-yl)-2-hydroxybenzoic acids have been developed in good yields which were analogues of P- amino salicyclic acid (used as anti tuberculosis agent). Pthalic anhydride were treated with 4-amino salicylic acid in glycerol at 40C for 10 mins to yield monoacid monoamide derivatives I.e 4-(2-carboxy benzamido)-2-hydroxybenzoic acid respectively.[33]

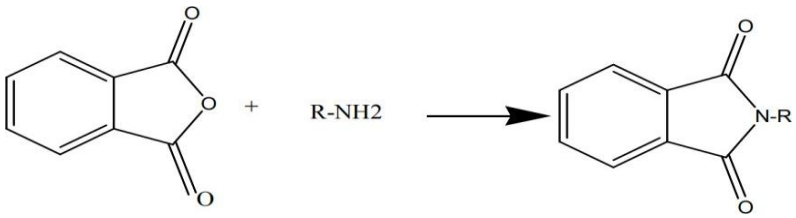


A. Yahyazadeh et al (2013) were synthesized the copper phthalocyanine and 2,9,16,23 tetrakisnitro copper phthalocyanine has been synthesized respectively from phthalonitrile and 3-nitro phthalonitrile. 4-nitro pththalonitrile synthesized from phthalimide in three steps.b The newly prepared compounds have been characterized by IR, UV-VIS, H NMR and MS spectra. The low activity of HB, a small pore bidirectional nano dimensional zeotile, is probably related to diffusional limitations of the pores and geometrical consraints for the formation of the intermediats inside the pores. The amount of product reactants and adsorbed products should decrease, decreasing the catalust decay.[34]

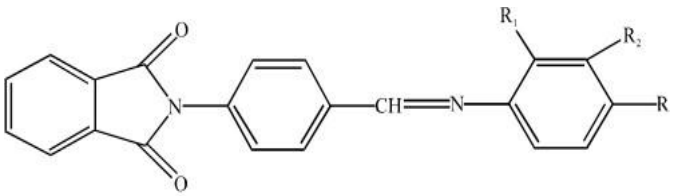


R: H **4a**
R: -NO_2 **4b**

Veena Kathuria et al (2012) A series of N-substituted phthalimide were synthesized for the purpose of determining the anticonvulsant activities of these compounds. The compounds were synthesized using phthalic anhydride and various amines in microwave synthesizer. The synthesized derivatives were confirmed by means of IR.1H-NMR. The anticonvulsant activity of all compounds were evaluated by subcutaneous pentylenetetrazole-induced seizures test. N-substituted-1,3-isoindoline dione derivatives were synthesized. The derivatives were prepared from phthalic anhydride and amine derivatives via direct fusion in microwave synthesizer at temperature 150-250 c. The purity of these compounds was determined byTLC and their structures were confirmed by IR, H-NMR.[35]



Sharma.S et al (2012) The novel Schiff bases of imides moiety have been synthesized which showed analgesic activities and anti-inflammatory activities. First step involves in the reaction of phthalic anhydride with 4-amino benzaldehyde in the presence of dichloromethane which results in the formation of 4-(1,3-dioxoisoindolin-2-yl) benzaldehyde. The synthesized compounds were screened for their anti-inflammatory activity potential using carrageenan induced rat paw edema model and analgesic activity by tail immersion and hot plate methods in mice at different concentrations i.e 100,200 and 300 mg kg. The results showed that the Schiff bases of imide moiety possess significant therapeutic potential and can be used as analgesic and anti-inflammatory agents.[36]

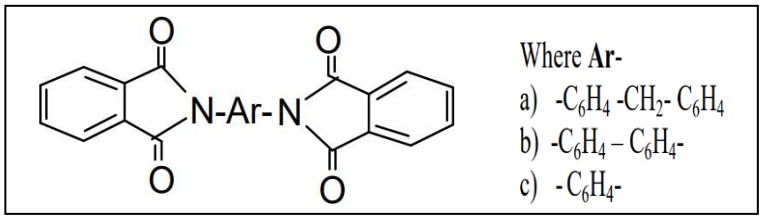


2-(4-((phenylamino)methyl)phenyl)isoindoline-1,3-dione

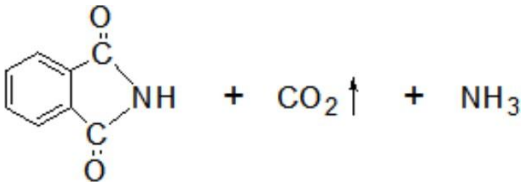
$R = NO_2, R_1 = H, R_2 = H$ (3) $R = OH, R_1 = H, R_2 = H$ (4)
$R_1 = CH_3, R = H, R_2 = H$ (5) $R_2 = Cl_2, R = H, R_1 = H$ (6)

Nilesh S.pawar et al (2012) microwave induced organic reaction enhancement (MORE) chemistry has received considerable attention due to several advantages. Various N-substituted phthalimide compounds have been synthesized by microwave irradiation as well as conventional methods. The conclusion of simple, efficient and cost effective method is

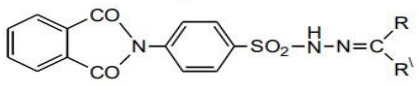
described for the synthesis of phthalimido compounds. This protocal is adoptable to parallel synthesis and generation of combinatorial library of potentially biological active phthalimido compounds.[37]



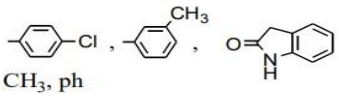
Yan-Hua-Cai et al (2012) the synthesis of phthalimide had been developed under solvent free microwave irradiation condition and the structures of the synthesized compounds had been characterized by FTR, H NMR. Further investigated by scanning electron microscopy (SEM) and TGA thermal analyser. Phthalimide was simply and effectively synthesized from urea and phthalic anhydride by solvent free reaction using microwave irradiation. The thermal stability of the phthalimide showed that the decomposition temperature significantly increased with increasing of heating rate and decomposition rate was fast during heating. The result of TGA indicated that 10^0 C/min, phthalimide showed good thermal stability of phthalimide under 150^0C and that decomposition completed at 250^0C. Finally the synthesized compound phthalimide was used to successfully modify the suface of talc.[38]



Ahlam Marouf AL-Azzawi et al (2011) the novel schiff bases linked to phthalimide moiety have been synthesized via various steps. The first step involved the reaction of phthalic anhydride with aniline producing N-phenyl phthalamic acid. The imide was treated with chlorosulfonic acid in the third step producing 4-(N-phthalimide) phenyl sulfonyl chloride. which on amination with hydrazine hydrate in the fourth step afforded 4(N-phthalimide) phenyl sulfonyl hydrazine. The compound 4-(N-phthalimidyl phenyl sulfonyl hydrazine showed very high activity against *S.aureus*, E.coli and showed good to moderate antibacterial activity.[39]

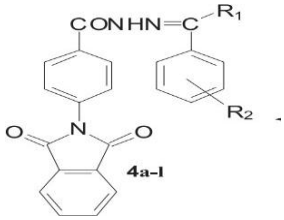


R= (o, m, p-nitrophenyl),  , (o, m, p-hydroxyphenyl),  ,



R\ = H, CH_3, ph

Mashooq A.Bhat et al (2011) A series of Schiff bases of phthalimide 4-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-N'-[(substituted phenyl) methylene] benzohrdrazides were prepared in satisfactory yields and evaluated for their anticonvulsant activities and neurotoxicity. All the compounds were active in MES screen and less neurotoxic than phenytoin. Compounds 4-(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)-Ní[(4- hydroxyphenyl) methylene]benzohydrazide,4-(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)-Ní-(3,4-dimethoxyphenyl)methylenebenzohydrazide,4-(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)-Ní-1-(4-methylphenyl)ethylidene]benzohydrazide, Ní-1-(4-chlorophenyl)ethylidene]-4-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)benzohydrazide,4-(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)-Ní-1-(4-methoxyphenyl) ethylidene]benzohydrazide,Ní-1-(2,4-dichlorophenyl) ethylidene] -4-(1,3-dioxo1,3-dihydro-2H-isoindol-2 yl)benzohydrazide and 4-(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)-Ní-1-(2 nitrophenyl)ethylidene]benzohydrazide showed neurotoxicity only upto o.5h. All thecompounds showed were less neurotoxic than phenytoin. Compound 4-(1,3-Dioxo-1,3-dihydro-2H-isoindol-2-yl)-Ní-1- (2-nitrophenyl) ethylidene] benzohydrazidehaving nitro substitution at ortho position of the distal aryl ring emerged as most promising anticonvulsant agent with low neurotoxicity.[40]



4a: R_1 = H, R_2 = 4-OH; **4b**: R_1 = H, R_2 = 3,4 $(OCH_3)_2$; **4c**: R_1 = H, R_2 = 3-NO_2; **4d**: R_1 = CH_3, R_2 = 2-OH; **4e**: R_1 = CH_3, R_2 = 4-OH; **4f**: R_1 = CH_3, R_2 = 4-CH_3; **4g**: R_1 = CH_3, R_2 = 4-Cl; **4h**: R_1 = CH_3, R_2 = 4-NO_2; **4i**: R_1 = CH_3, R_2 = 4-OCH_3; **4j**: R_1 = CH_3, R_2 = 2,4-$(Cl)_2$; **4k**: R_1 = CH_3, R_2 = 2-OH, 3-OCH_3; **4l**: R_1 = CH_3, R_2 = 2-NO_2

CONCLUSION

Despite the many advances in modern medicine, many diseases of a diversified nature still cause various health complications and deaths. Among the various classes of organic synthesis molecules, phthalimides are distinguished by their extremely pharmacological effects and often pleiotropic, acting on more than one front in the same organisms. Recently,

phthalimides and a few of its derivatives showed vital biological effects similar or perhaps over acknowledged pharmacologic molecules. The established documentation has the information about phthalimide moieties with a powerful therapeutic profile which is used to design & develop potential molecules and provide interest and opportunities for researchers work on phthalimide scaffold.

REFERENCE

1. Ahmad H and Amer K. "Synthesis of some N-phthalimide amino acids derivatives and evaluation their biological activity". *The Pharmaceutical and Chemical Journal,* 2015; 2.3: 33-41.
2. Chidan Kumar CS., *et al*. "Synthesis, structural and antioxidant studies of some novel N-ethyl phthalimide esters". *PLOS ONE,* 2015; 10.3: 1-8.
3. Karthik CS., *et al*. "Investigation of Antioxidant Properties of Phthalimide Derivatives". *Canadian Chemical Transactions,* 2015; 3.2: 199-206.
4. Fhid O., *et al*. "Synthesis, characterization and analgesic activity of several new N-substituted phthalimide analogues". *International Journal of Pharmaceutical Sciences and Research,* 2014; 5.8: 3199-3203.
5. Paraiso W K. and Alea G. "Synthesis and in Vitro antimycobacterial activity determination of phthalimide derivatives". *The Manila Journal of Science,* 2013; 8.2: 27-34.
6. Manley King CI., *et al*. "Inhibition of monoamine oxidase by C5-substituted phthalimide analogues". *Bioorganic Medicinal Chemistry,* 2011; 19.16: 162-192.
7. Hassanzadeh F., *et al*. "Synthesis and Evaluation of the Anxiolytic Activity of Some phthalimide derivatives in mice model of anxiety". *Iranian Journal of Pharmaceutical Research,* 2011; 11.1: 109-115.
8. Mahapatra S P., *et al*. "Synthesis and hypoglycemic activity of some phthalimide derivatives". *Journal of Pharmaceutical Sciences and Research,* 2010; 2.9: 567-578.
9. Lee N., *et al*. "Synthesis and biological activity of phthalimidebased polymers containing 5-fluorouracil". *Polymer International,* 2002; 51.7: 569-576.
10. Coutinho Neto M D., *et al*. "The hypolipidemic activity of Nphenylphthalimide derivatives: a QSAR study". *Journal of The Brazilian Chemical Society,* 1993; 4.3: 139-141.
11. Hussniya A.AlDifar, Basma S.Baaiu, Khalid M. A. Darwish, Mohamad F.Ali, Othman O.Dakhil, Mansour Abd-Alsalam, Haneen Al Difar. Synthesis of Benzimidazole and Phthaloylamino Acid derivatives and Antibacterial Activity. J. Med. Chem. Sci, 2023;

6(9): 1975-1984. DOI:https://doi.org/10.26655/JMCHEMSCI.2023.9.6.

12. Nasiara Karim, Inbisat Khan, Imran Khan, Sobia Ahsan Halim, Asaad Khalid, Ashraf N. Abdalla, Najeeb Ur Rehman, Ajmal Khan, and Ahmed Al-Harrasi. Antiamnesic Effects of Novel Phthalimide Derivatives in Scopolamine-Induced Memory Impairment in Mice: A Useful Therapy for Alzheimer's Disease. ACS Omega, 2023; 8(8): 8052-8065. https://doi.org/10.1021/acsomega.2c07951.
13. Tok, F.; Yang, X.; Tabanca, N.; Koçyi ˘git-Kaymakçıo ˘glu, B. Synthesis of Phthalimide Derivatives and Their Insecticidal Activity against Caribbean Fruit Fly, Anastrepha suspense(Loew). Biomolecules, 2023; 13: 361. https://doi.org/10.3390/biom13020361
14. Zawadzka, M.; Nitschke, P.; Musioł, M.; Siwy, M.; Pluczyk-Małek, S.; Honisz, D.; Łapkowski, M. Naphthalene Phthalimide Derivatives as Model Compounds for Electrochromic Materials. Molecules, 2023; 28: 1740. https://doi.org/10.3390/molecules28041740.
15. Donarska Beata, Świtalska Marta, Wietrzyk Joanna, Płaziński Wojciech, Łączkowski Krzysztof Z.: Spectrofluorimetric and computational investigation of new phthalimide derivatives towards human neutrophil elastase inhibition and antiproliferative activity, International Journal of Molecular Sciences, 2023; 24(1): 1-17. DOI:10.3390/ijms24010110
16. Halah A. Sahib, Mohammed H. Mohammed. Synthesis and Preliminary Biological Activity Evaluation of New N- Substituted Phthalimide Derivatives, Iraqi J Pharm Sci, 2020; 29(1). DOI:https://doi.org/10.31351/vol29iss1pp247-252.
17. Ahlam Marouf Al-Azzawi, Hiba Kadhim Yaseen. Synthesis and Characterization of Several New Poly (Allyloxy Phenyl) Bearing pendenttetrachlorophthalimides, Volume 6 Issue 11, November 2017. www.ijsr.net. DOI: 10.21275/ART20177801.
18. Nebras M.Jamel, Kawther Abdu Al-Hammed, Basma j.Ahmed. Methods of Synthesis Phthalimide Derivatives and Biological Activity-Review. Nebras M.Jamel et al /J. Pharm. Sci. & Res, 2019; 11(9): 3348-3354.
19. Pramod S. Phatak, Rajubai D. Bakale, Sambhaji T. Dhumal, Lalita K. Dahiwade, Prafulla Choudhari, Vagolu Siva Krishna, Dharmarajan Sriram & Kishan P. Haval (2019) Synthesis, antitubercular evaluation and molecular docking studies of phthalimide bearing 1,2,3-triazoles, Synthetic Communications, 49: 16, 2017-2028. DOI:https://doi.org/10.1080/00397911.2019.1614630.
20. Shagufta Perveen, Raha Orfali, "L-Proline-Catalyzed Synthesis of Phthalimide Derivatives and Evaluation of Their Antioxidant, Anti-Inflammatory, and Lipoxygenase

Inhibition Activities", Journal of Chemistry, vol. 2018, Article ID 5198325, 6 pages, 2018. DOI:https://doi.org/10.1155/2018/5198325.

21. Celso Yassuo Okada-Junior, Gustavo Claro Monteiro, Anna Caroline Campos Aguiar, Victor Sousa Batista, Juliana Oliveira de Souza, Guilherme Eduardo Souza, Renata Vieira Bueno, Glaucius Oliva, Nailton M. Nascimento-Júnior, Rafael Victorio Carvalho Guido, and Vanderlan Silva Bolzani. Phthalimide Derivatives with Bioactivity against Plasmodium falciparum: Synthesis, Evaluation, and Computational Studies Involving bc1 Cytochrome Inhibition, ACS Omega, 2018; 3(8): 9424-9430. DOI: 10.1021/acsomega.8b01062.
22. Han Yan, Xinlei Meng, Baoyan Li, Shusheng Ge and Yun Lu. Design, synthesis, photophysical properties and pH-sensing application of pyrimidine-phthalimide derivatives, J. Mater. Chem. C, 2017; 5: 10589--10599. DOI:https://doi.org/10.1039/C7TC03472E.
23. Hayman Sardar Abdulrahman, Mohamed Hassan Mohammed, Lina A. Al-Ani, Mohd Hafiz Ahmad, Najihah M. Hashim, Wageeh A. Yehye, "Synthesis of Phthalimide Imine Derivatives as a Potential Anticancer Agent", Journal of Chemistry, vol. 2020, Article ID 3928204, 13 pages, 2020. DOI:https://doi.org/10.1155/2020/3928204.
24. Girish Kumar Sinha, Akanksha Priya, Sonal Priya, Satyendra Narayan. "Synthesis and Biological Activity of Some Schiff Bases from Phthalimides," Universal Journal of Chemistry(CEASE PUBLICATION), 2017; 5(2): 36-42. DOI: 10.13189/ujc.2017.050202.
25. Heba S. Rateb, Hany E. A. Ahmed, Sahar Ahmed, Saleh Ihmaid, Tarek H Afifi. Discovery of Novel Phthalimide Analogs: Synthesis, Antimicrobial and Antitubercular Screening With Molecular Docking Studies. Excli Journal, 2016; 15: 781-796 – ISSN 1611-2156. DOI:http://dx.doi.org/10.17179/excli2016.
26. Nayab PS, Akrema, Ansari IA, Shahid M and Rahisuddin. New phthalimide-appended Schiff bases: studies of DNA binding, molecular docking and antioxidant activities. Luminescence, 2016. DOI:https://doi.org/10.1002/bio.3259.
27. Kushwaha N, Kaushik D. Recent Advances and Future Prospects of Phthalimide Derivatives. J App Pharm Sci, 2016; 6(03): 159-171. DOI: 10.7324/JAPS.2016.60330.
28. Nayab PS, Pulaganti M, Chitta SK, Oves M, Uddin R. Synthesis, spectroscopic studies of novel N-substituted phthalimides and evaluation of their antibacterial, antioxidant, DNA binding and molecular docking studies. Bangladesh J Pharmacol, 2015; 10: 703-713. DOI: 10.3329/bjp.v10i3.23637.

29. Hemdan M., Fahmy A., El-Sayed A. Microwave-assisted synthesis of phthalimides, phthalazines and quinazolines. Chem Xpress, 2015; 8(1): 31-36.
30. Ahuja, P., Husain, A. & Siddiqui, N. Essential aminoacid incorporated GABA–phthalimide derivatives: synthesis and anticonvulsant evaluation. Med Chem Res, 2014; 23:4085–4098. DOI:https://doi.org/10.1007/s00044-014-0949-5.
31. Hamak K.F. Synthetic of Phthalimides via the reaction of phthalic anhydride with amines and evaluating of its biological and anti corrosion activity.International Journal of ChemTech Research, 2014; 6(1): 324-333.
32. Azzawi AMA., Razzak MSA. Synthesis, Characterization and Antimicrobial Screening of New Schiff Bases Linked to Phthalimidyl Phenyl Sulfonate Moiety. Baghdad Science Journal, 2014; 11(2): 438-446.
33. Y. Dathu Reddy, P. Praveen Kumar, B. Rama Devi, Ch. Venkata Ramana Reddy and P. K. Dubey. Green Synthesis of Novel Phthalimide Derivatives of P-Aminosalicylic Acid As Potential Anti- Tuberculosis Agents, Eur.Chem. Bull, 2014; 3(5): 460-462.
34. A. Yahyazadeh et al.: Synthesis of phthalocyanine derivatives by synergistic effect of catalysts over nanodimensional zeolites under solvent-free conditions. Int. J.Nano Dimens, 5(1): 35-39, Winter 2014. ISSN: 2008-8868.
35. Veena Kathuria, D. P. Pathak. Synthesis And Anticonvulsant Activity Of Some N-Substituted-Phthalimide Analogs, The Pharma Innovation, 2012; 1(10): 2277- 7695.
36. S. Sharma, A.D.K. Jain, A. Aggarwal and N.S. Gill, 2012. Synthesis, Characterization and Pharmacological Evaluation of Novel Schiff Bases of Imide Moiety. Journal of MedicalSciences, 12: 61-69. DOI: 10.3923/jms.2012.61.69.
37. Nilesh S. Pawar, Sunil L. Garud and Vasant S. Patil. Microwave Mediated Synthesis of Biologically Active Various N-Substituted Phthaloyl Derivatives, Der Pharmacia Lettre, 2012; 4(4): 1129-1136, ISSN 0975-5071.
38. YAN-HUA CAI et al: Solvent-Free Synthesis of Phthalimide Under Microwave Irradiation and Modification of Talc with Synthesized Phthalimide, Asian Journal of Chemistry, 2012; 24(2): 481-484.
39. Ahlam Marouf Al-Azzawi and Marwa Shawqi Abdul Razzak et al: Synthesis, Characterization and antibacterial activity of Several New Schiff Bases Linked to Phthalimide Moiety, Kerbala J. Pharm. Sci, 2011 - iasj.net.
40. Bhat MA, Al-Omar MA. Synthesis characterization and in vivo anticonvulsant and neurotoxicity screening of Schiff bases of phthalimide. Acta Pol Pharm, 2011 May-Jun; 68(3): 375-80. PMID: 216.