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AN OVERVIEW ON CURRENT AND FUTURE PROSPECTS OF PHTHALIMIDE DERIVATIVES

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ABSTRACT

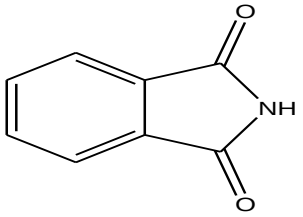
Currently, phthalimide derivatives widelyemployed in therapeutic perpose owning to have very potent due to their antimicrobial, anti-angiogenic, anticonvulsant, anxiolytics, Antioxidant, Tyrosinase inhibition, cytotoxic and toxicological effect, anti-inflammatory, anti proliferative, and HIV-I RT inhibitor. This review article affords highly relevant information on the synthesis, chemistry and biological activity such as antimicrobial and antitumor activity and toxicity status on aryl phthalimides. The established documentation of great-exertions toward phthalimide derivatives with a powerful therapeutic outline would be the vital key todevelop potential molecules for the handling of various diseases and thesemolecules can exposed innovative interest andprospects for investigators to design and develop novel therapeutic agentsof phthalimideframework.

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=Omoieties and it is further bound to nitrogen within the bicycle non aromatic heterocycle. Phthalimide was used as an initial material as pharmacophore[1]. Recently, Phthalimide and their compounds exhibited activity as antimicrobial[2], anti-angiogenic[3], anticonvulsant[4], anxiolytics[5], Antioxidant[6],Tyrosinase inhibition[7], Toxicological effect[8], anti-inflammatory[9], antiproliferative[10], and HIV-I RT inhibitor[11]. This review highlights antimicrobial and anticancer activity shown by various phthalimide derivatives. Several reports have revealed that some novel phthalimide derivatives containing amino acid analogues showed the potent antimicrobial activity[12]. Keeping in view, the above antimicrobial activity an attempt has been made to design phthalimide derivatives comprising of TNF-modulators and NSAID as therapeutic agent in inflammatory diseases in EUROPEAN patent application[13].

Structure of Phthalimide: Phthalic acid is comprised of an imido derivative to form phthalimide. Phthalimide is a lipophilic and neutral, and hence crosses biological

membranes *in vivo*.Phthalimide mainly Contribute in hydrogen bonding[14-15].



Dihedral -74.2(1)^0, planer,

Effect of -C=O on acidity of neighbouring of N-Bond

Phthalimide is readily soluble in aq.Alkaline solution. Amines are less acidic then imines. Phthalimides are more acidic due to presence of easily donating proton i.e. N-H and phthalimide form water soluble salt with strong bases such as sodium hydroxide[16]shown in figure no 1. Most of the phthalimides are synthesised by the conventional synthesis method in past. In recent period, the Heba S.R *et al.,* reported the synthesis bycarbonyl linker or using acetylbyheteroarylcompound containing sulphur, Nitrogen and halogen atoms [17].scheme 2 and table 1. OmranF et *al*.,synthesize the novel N-Substituted phthalimide analogues by using phthalates anhydrite with various amines in reflex synthesis. AsgharD et *al.*,have been synthesis of 2- substituted phthalimide pharmacophore by the condensation of a respective aromatic amine with the phthalic anhydrite & acetic acid at refluxtemperature [18]. FarshidH, et *al.,* was reported the synthesis of 3-nitroPhthalimide and the researcher did the reaction with the nitrated of phthalic anhydrite and treated with urea to 3-nitrophthalimide[19]. Chimatahalli SK*et al.*,Rizwan A*et al*and Sunil GS*et al* also synthesis the phthalimide by using phthalic anhydrite and differentamines [20-21].Ahmand H*et al.,* was synthesis the N-Phthalimide of amino acids through cyclo-condensations under the influence of organic solvents. The solvents having a high boiling point such as acetic acid, water and toluene were commonly used but those solvent were also replaced by the ionic liquid such as [bmim] [BF4] with the acceptable yield at room temperature. The Microwave irradiation has also been working in the presence or absence of organic solvents. Microwave mediated synthesis has given the high yield of phthalimide[21]. ShaguftaP*et al.,* reported the catalyticsynthesis under the influence of L-Proline.The optimization of reaction was done by using various catalysts(shown in table no 2)and has given promising phthalimide derivatives[9]. Suvarna P G *et al.,* was reported the eco-friendly synthesis of phthalimide derivative derivatives. In the background of green chemistry phthalimide derivatives were done by the microwave irradiation methods, where catalyst montmorillonite-KSF is a naturally occurring clay which having the advantage of reusable, non-toxic, non corrosive and economic as the green clay catalyst [23] showed in the scheme 4.

Mathews' reaction: IN Mathews' reaction, nitriles are going 'dry' hydrolysis of phthalic acid ortertiary amides by phthalic anhydride to obtain carboxylic acid and phthalimide scheme 5.[24].

Therapeutic potential of phthalimide analogues: Pharmaceutical innovation having the great advancement intreating the most diverse diseases. Phthalimides fused with heterocyclic derivatives present in several biological activities which are mention in literatures.

Antimicrobial: Keepingin view on the differing metabolic activity of phthalimide derivatives, the antimicrobial tests have the right to be featured by the broadness of activity and their greater potency against pathogenic microorganisms. Numerous infection by infectious, microscopic organisms, protozoa, parasites, etc. tranquilize mixed drinks, including intense medications that bring the client a few adverse effects in addition to requiring the long term and multidrug treatments [25]. Heba SR*et al.,*designed and developed anti-mycobacterial agents with multiple target affinity ,comprising of N-aryl or alkynyl phthalimide moiety. The resulting data information demonstrates that, a large portion of the novel compounds have potent antibacterial and antimycobacterialpotency. Their inhibition zones spread a decent scope of action, 18-25 mm with comparing MIC about equivalent to 0.49 to 31.25 µg/ml. They have worked on docking and SAR analysis with respective ENR enzymes and DNA-gyrase targets affinity. They predicted molecular properties such as % ABS, Topological polar surface area, Number of hydrogen bond doners,

logS, Solubility Coeffeicent, Lipinski parameters and ADME through the docking experiment were done[26] . Omran R*et al.,* synthesised the N-substituted phthalimide derivatives 2-5 were studied in vitro studies onS.aureus, E.coli at conc. 100µg using phenol as reference standard. All the phthalimide derivative showed high broad-spectrum inhibitory activity against the gram-positive organism[2]. Shown in the table 3. Phoebe Fl*et al.,*reported that sixteen novel phthalimide subtenants were synthesised and evaluvated for the antimicrobial activity in-vitro. (ZE)-2-[4-(1-Hydrazono-ethyl)-phenyl] isoindoline-1,3-dione exhibited more anti-microbial potency[27]. Ahmad h*et al.,*reported that, they have been performed research on N-phthalimides of amino acid and compounds were evaluvated for their antimicrobial activity. All the amino acid derivative have shown good results . The all compounds are tested for antimicrobial and Anti-mycobacterial activity in vitro determination. Compounds exhibited good inhibitory activity against tested pathogenic microorganism and data [28]showed in the table number 4.

Balaj K*et al.,*have beensynthesis of few Mannich base molecules of 2,5-amino - thiadiazoleswith primary amines/phthalimide and formaldehyde expecting tremendous as antimicrobial agents.Amongthese compounds have nitro group confirmed the most activity observed through phthalimide ,chloro and methyl group[29].

ArifR*et al.,* synthesised, NewBis-phthalimide derivatives & were screened for Antioxidant activitiesand antibacterial activity against Streptococcus mutons, was evaluated vitro studies by the agar well diffusion method. Among that compound and 1 & 2 having the significant activity[30]. Rizwan A*et al.,*reportedmolecular docking studies and carried out *In vitro*hemolytic, antibacterial and antioxidant activity. Here2-(-(2-(2-(2-(1,3dioxoisoindoline-2-yl-ethylamino) ethylamino) ethyl) isoindoline-1,3-dione (DEEI) and its copper (II) complex with N-Phthalimide have been synthesised. The antibacterial evaluation of derivatives evaluated against bacterial strains. The results have been found that the N-phthalimde-copper (II) complex have potent antibacterial comparable withDEEI and standard drug [31]. AhlamMA*et al.,*reported Schiff bases linked to phthalimidesbearing 2-[2-(biphenyl-4-yl)-2-iminoethyl]-1*H*-isoindole-1,3(2*H*)-dione derivatives having shown therapeutic value against microorganism[32]. Pattan SN *et al.,*reported molecular docking against antibacterial activity with phthalimide derivatives. The compound having the potential antibacterial activities against selective bacterias. Molecular docking studies were done &evaluated[33]. Pramod SP*et al.,* reported that antitubercularevaluation of phthalimide link with 1,2,3-triazoles. They were synthesis the novel substituted 2-(4-((1,3-dioxoisoindolin-2-yl) methyl)-1H-1,2,3-triazol-1-yl)-Nphenylacetamides (5a–l). 2,3-triazoles compounds have more potent antitubercular activity against mycobacteria H37Rv. Molecular docking study shows that everyone the molecules measure binding to the Mycobacterium tuberculosis [34]. Nilesh SP*et al.,* reported the antibacterial and antifungal activity of modified various N-Substituted phthalimides derivatives and exhibited high potency of antibacterial activity against Bacillus japonecum. and antifungal activity against Aspergillus Niger, Aspergillus flavous, Alternaria[35]. Anu R*et al.,*reported Anti-Tubercular Evaluation of 4-Aminoquinoline-Phthalimide Conjugates[36]have been synthesized and tested towards M. tuberculosis and showed considerable values of Minimum Inhibitory Concentration, cytotoxicity, and selectivity index to macrophages. Fluorinated phthalimide derivatives have been additionally examined &observed that the fluorinated phthalimide hybrid molecules had comparable anti-mycobacterial activity with sulphonamide drugs. In some other study, in which 12 phthalimide derivatives with fluorinated radicals have been synthesized, the compounds confirmed potent antimicrobial activities. The analogsacquired of N- [triethoxysilylpropyl] phthalimide have been tested for potentantimicrobial. The drugs examined have been viewed to be positive antimicrobials against all examined microorganisms, and the compounds with the phthalimidic structure confirmed a considerably greater result[37].

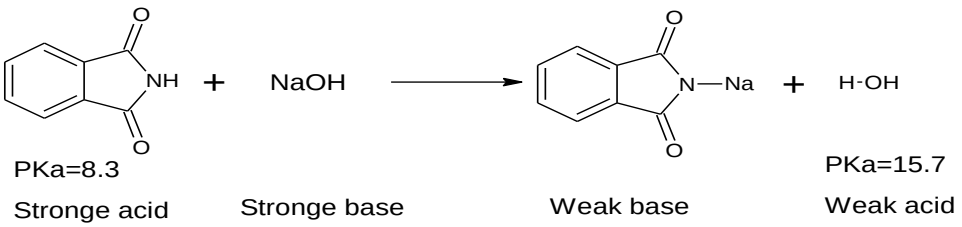
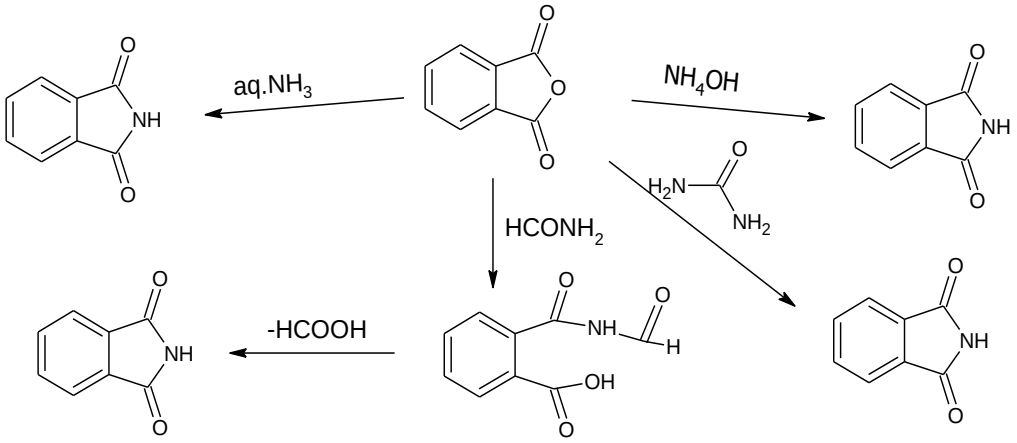


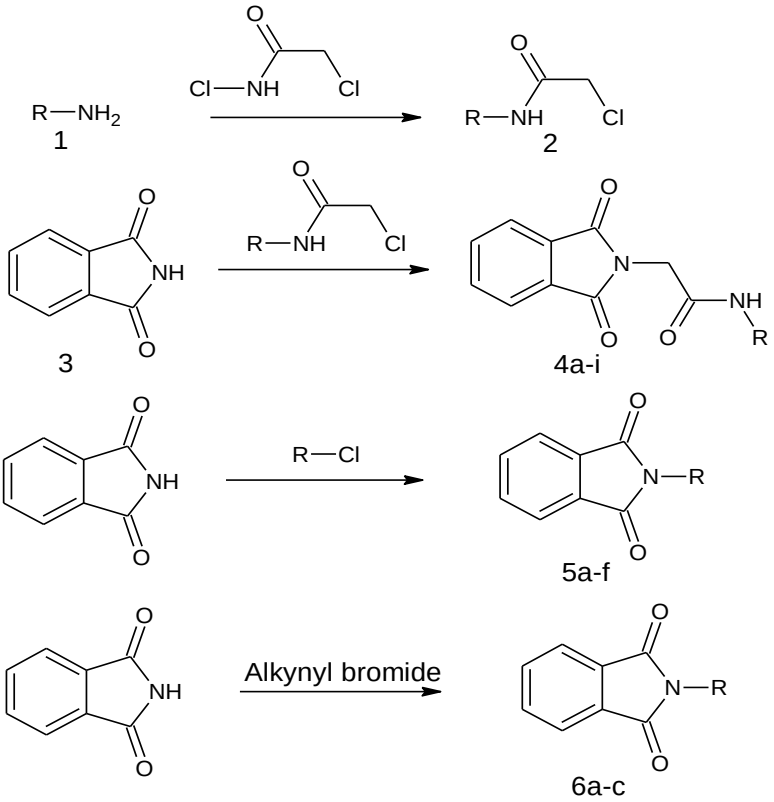
Figure 1: Phthalimide form water soluble salt with strong bases

Synthesis of phthalimide:

The synthetic rough for synthesis of phthalimide moiety in scheme 1



Scheme 1.



Scheme 2: [(4a-i), (5a-f) and (6a-c)].

Table 1: Rationale design of target compounds

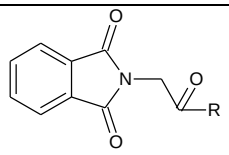
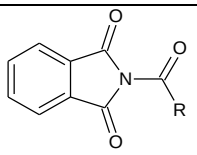
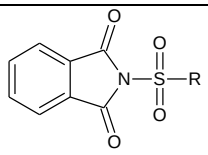
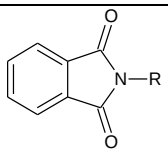
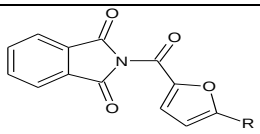
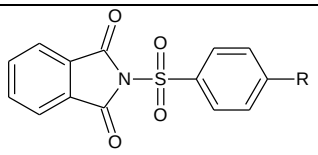
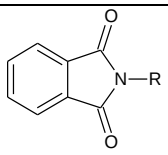
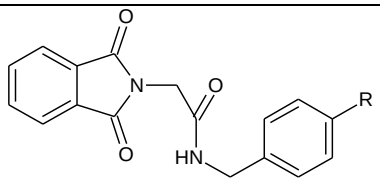
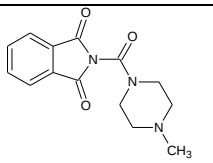
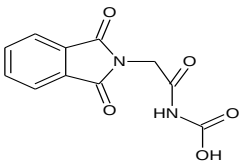
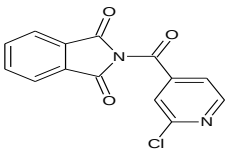
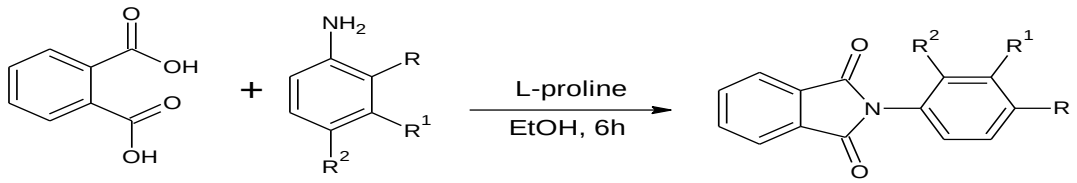
4a-i	s5a-f		6a-c
			
			
			
			

Table 2: Percentage yield of phthalimide with respective to catalysts

Sl no	Catalysts	Percentage yield
	AlCl3	8%
	CH3COOH	7%
	BBr3	7%
	CF3COOH	6%
	L-serine	10%
	6 L-arginine	12%
	L-lysine	15%
	L-proline	98%

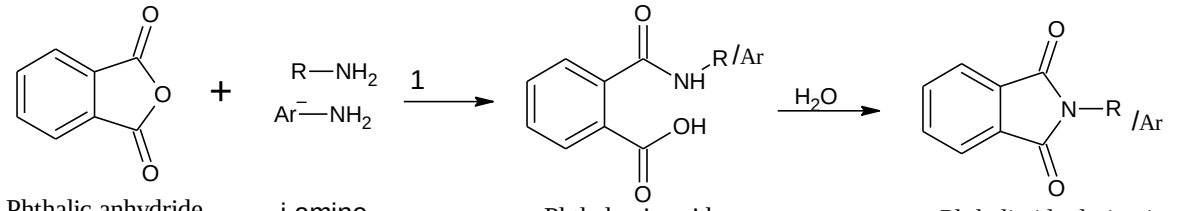
L-proline. The L-proline catalysed synthesis shown in the below scheme3.



1-7

1R=OCH_3,R^1=H, R^3=H; 2R=H, R^1=H, R^3=H; 3R=Cl, R^1=H, R^3=H; 4R=NO_2, R^1=H, R^3=H; 5R=CH_3, R^1=H, R^3=H; 6R=H, R^1=H, R^3=CH ; 7R=OCH_3,R^1=Cl, R^3=H

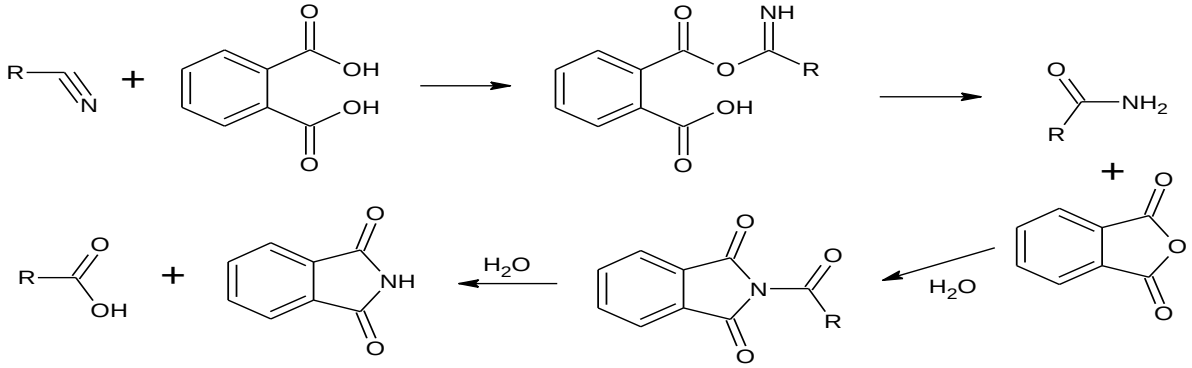
Scheme 3.



Phthalic anhydride i amine Phthalamic acid Phthalimide derivatives

Where 1=montmorillonite,KSF MW 700w

Scheme 4.



Scheme 5: Synthesis of phthalimide by Mathew reaction

Table 3: phthalimide derivative showed high broad-spectrum inhibitory activity against the gram-positive organism

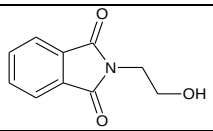
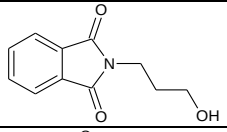
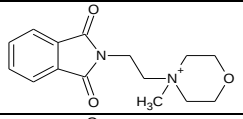
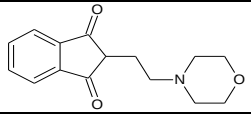
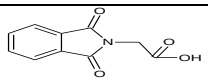
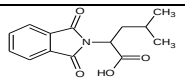
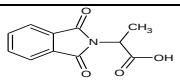
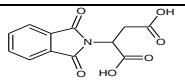
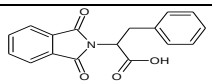
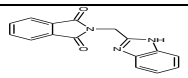
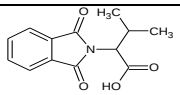
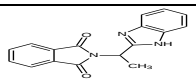
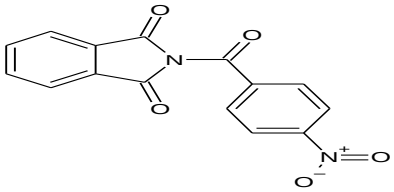
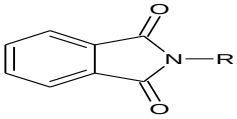
Comp no	Structure	Zone inhibition (mm)	
		S. aureus	E. coli
2		2.2	-
3		3	1.3
4		3.2	-
5		2.9	-
Phenol		1	2

Table 5: Compound numbers with their structure

Compound no	Structure	Compound no	Structure
IIIa		IIIe	
IIIb		IIIf	
IIIc		Va	
IIId		Vb	



N-nitro benzoyl phthalimide



N-substituted phthalimide derivatives

The compounds, 8- [4- [phthalimid2-yl] butyloxy] quinoline and N-vinylphthalimide, phthalimide derivatives shown excellent fungicidal agents. Synthetic analogues have been examined against phytopathogens, Among the compounds obtained, 12-acetyl-N, N-phthaloylhydroabietylamine confirmed remarkable activity towards the protozoan with EC [antiplasmodic activity] = 0.086 μM and SI [selectivity index] => 290, confirming that compounds with phthalimide grouping are promising promising in the therapy of intracellular protozoal infections [38].

Antitumor activity

Research with phthalimides with antitumor activity has developed fundamentally, principally in light of the fact that a few kinds of cancer may develop the resistance to medications already effectively utilized, which strengthens the need to look for new antimitotic atoms. Blockage of tumour development may occur in at least one of the six phenotypes of the malignant growth cell that give unpredictable proliferative limit. Numerous phthalimides have been proposed as the promising chemotherapeutic agent block cell development by signalling pathway [39].

Paulo MPF *et al.,* reported toxicological andCytotoxic effects of phthalimide compounds on tumour and normal murine cells[8]. Selvum*et al.,*have been reported few novel N-substituted Phthalimide and N-p-nitrobenzoylphthalimidederivatives synthesized by condensation. Synthesized derivatives weresubjected for HIV-I and IIduplication in MT-4 cells. Cytotoxicity was additionallyexplored in un-infected MT-IV cells. All the incorporated mixes displayed cytotoxicity in MT-IV cells [40]. Magdy AHZ*et al.,*reported series of novel phthalimideand thalidomideester derivatives and efficiently screened for antitumor activity of human liver and breast cancer cells, and the phthalimide ester i.e (1-methylidene-3-oxo-1,3-dihydro-2H-isoindol-2-yl)methyl (1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)acetate was the best cytotoxic compound against MCF7cells ,while remaining compounds were non-cytotoxic effect against HepG2 cells. Few of the synthesised derivatives, which contain two phthalimide moieties, shows greater immunosuppressant action. Derivatives having nicotinyl and indole moieties showed an immunostimulatoryaction [41]. Mohammed HM *et al.,* evaluated anticancer activity of 5-Fluorouracil-Phthalimide conjugated derivatives. They were worked on the basis of molecular hybridisation and the combination of

moieties of two pharmacologically active compounds results in a new hybrid derivative with better affinity and efficacy by comparing to the parent drugs. The following derivatives 5-fluoro-4-oxo-1,4-dihydropyrimidin-2-yl2-(1,3-dioxoisoindolin-2-ylamino) acetate [IV] and 2-(2-(5fluoro-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-oxoethylamino) isoindoline-1,3-dione [V] were synthesised and the synthesised derivatives have been studied for the preliminary cytotoxicity study that evaluated by crystal violet assay using a target breast cancer cell, murine mammary adenocarcinoma cell line indicates that the compounds have considerable anticancer activity which have been compare with the lead one[42]. Ismail MMO*et al.*,reported the new phthalimide based analogues comprising ofimidazopyrozole nucleus and evaluatedfor anti-microbial and anticancer activity. The anti-proliferative studies was tested for all synthesised derivatives against human liver [Hep G-2] cell line in contrastof reference vinblastine. The newly synthesised compound was calculated by using Insilco studies for drug liking and toxicity risk parameter. Further recommended that, phthalimide connecting with 3-aminopyrazolone dreivatives shows the potent antimicrobial and antitumor activity .Compared to the vinblastine,2-[(2E)-2-(3-amino-5-oxo-1,5-dihydro-4H-pyrazol-4-ylidene) hydrazinyl]-1H-isoindole-1,3(2H)-dione was more potent in cytotoxic assay with hepatic cancer cell line (HepG-2) [43]. Phthalimide derivatives have additionally been proposed as anticancer therapeutic agents in mixture with chemotherapeutics already used in antimitotic therapies. A learn about with Oprozomib [OPZ] a protease inhibitor and Pomalidomide [Pom] a phthalimidic by-product of thalidomide has proven that phthalimide in a learn about of antiangiogenic action on choroalanoid membrane towards the improvement of multiple myolaemic. This study confirmed that oprozomib was once in a position to significanctly decreased neoangiogenesis and expression of genes associated to endothelial protein synthesis. The study then observed that when Oprozomib was combined with dexamethasone [Dex] or with Pomalidomide the results have been even greater widespread when in contrast with monotherapy. There was even greater therapeutic importance, when the three molecules [OPZ + Pom + Dex] have been used, demonstrating that the pharmacological combinations might also make contributions to a higher therapeutic efficacy against cancer. In addition, this study have been used animal model permits to inspect other types of phthalimide derivatives, such as the tumor microenvironment, the transition of the mensenchymal epithelium and usually the angiogenesis process, which are no longer analyzed in cell culture analyzes[44].

Toxicity: Studies ofphthalimide and their derivatives have shown low toxic effects. In an exceedingly study with aryl phthalimidesofhypolipidemic and anti-inflammatory activity, a therapeutic safety test was performed to see its acute toxicity [LD50]. It is observed that, incontestable and the therapeutic dose for the biological activities tested [250 mg / kg] was safe, even at the tested dose of two g / weightand there was no lethality and neither did the animals show signs of adverse reactions like activity changes like twitching, respiration shortness of breath, palpitations, and belittled rate of respiration [45].

CONCLUSION

According to WHO infectious and cancer diseases are the one of mainlead of death in the worldwide. Many diseases are tough to treat due to the drug resistance. To overcome on resistances, we require to develop the drug by derivatizing them in to more potent**.**Despite the numerous advances in trendy medication, several diseases in heterogeneous nature still cause numerous complications and deaths. Bicyclic aromatic heterocyclic phthalimides are in remarkable category which has outsized applications. Recently, phthalimides and a few of its derivatives showed vital biological effects similar or perhaps over acknowledged pharmacologic mol ecules . In biomedical research, Phthalimideshave been uses as a potent molecule due to their potency towards various disease. This article mainly focusing an important class of phthalimide derivatives which is able show the better

effectivityon antimicrobial and anticancer activity.

Thus, the phthalimide moiety plays a huge role in medicinally activeand represents a stimulating model for therapeutic chemistry.

The established documentation having the information about phthalimide moities with a powerful therapeutic profile which is used design & develop potential molecules andprovide interest and opportunities for researchers work on phthalimide scaffold.

Conflict of interest: No Interest

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