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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF SOME NEW PHTHALIMIDE DERIVATIVES

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ABSTRACT

Infectious and parasitic diseases are responsible for 23% of percentage of worldwide deaths and the second ranking cause of death according to the World Health Organization. The other issue related to infectious diseases is their emerging resistance to the used antimicrobial agents. The aim of the study was to synthesize, and identification of novel anti-microbial agents that can potently target microbes.

KEY WORDS

Phthalimide, *N*-aminophthalimide, Antimicrobial activity, Microwave and Reflux synthesizer.

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INTRODUCTION

Isoindoline-[1, 3]-dione appears to function as the pharmacophoric structure of many agents having diverse biological activities, which include sedative hypnotic[1-4]. Phthalimide (isoindoline-1, 3-dione) is a cyclic imide in which two carbonyl groups bound to an amine moiety. It is an important starting material for organic synthesis and preparation of biologically active compounds. A Number of phthalimide derivatives has been synthesized with interesting pharmacological activities such as antibacterial, anti-inflammatory, anticonvulsant, antiviral and antitumor activities[5-9].Phthalimides also applied in agriculture as herbicides, fungicides and insecticides[9, 10]. Recently, phthalimide and some of its derivatives have proved to have important

biological effects similar or even higher than known pharmacological molecules and so their biological activity is being a subject of biomedical research.

MATERIALS AND METHODS

All commercial reagents were used as received. TLC analyses were performed using silica gel plates, using ultraviolet light (254 nm). The melting points were determined by open capillary method and were uncorrected. IR spectra were recorded using samples that were prepared in to KBr discs using FTIR Shimadzu.

General procedures for synthesis of phthalimide derivatives

Phethalic anhydride **1** (0.013 mol), an amine (0.14 mol) and sulphamic acid were added to glacial acetic acid (15 ml), the reaction was stirred at 110 °C for 10 minutes. The reaction mixture was poured into cold water and the solid was collected by filtration, washed with water and crystallized form ethanol.

Synthesis of N-aminophthalimide

Phthalimide**1** (14.7 g, 0.1mol) was dissolved in 100 ml of ethanol. The solution was cooled (ice bath) and stirred at 5 °C. Hydrazine (3.6 ml, 0.11 mol) was added drop wise and the mixture was stirred for 2 hours. An ice water (200 ml) was added and the product was filtered and crystallized from ethanol.

General procedure for synthesis of imine derivatives of N-aminophthalimide

Into a 100-mL, round-bottomed flask, equipped with magnetic stirring, and a reflux condenser was placed *N*-amino phthalimide (0.0062 mol) and aldehyde (0.0063 mol). Methanol (50 ml), and 1 drop of sulfuric acid were added and the mixture was refluxed for 30 minutes. The reaction mixture was poured into cold water, the solid was filtered off and crystallized from methanol.

Methods

We are reporting the synthesis of the new series of N-substituted phthalimide linked to different biologically active heterocycles. Preparation of the new phthalimide derivatives was performed via multistep synthesis. In the first step reaction of phthalimide with hydrazine under reflux condition producing *N*-aminophthalimide II. In the second step reaction of *N*-aminophthalimide with aldehydes or acid chloride under microwave and reflux conditions producing Schiff's base and amide derivatives respectively.

Results

The structures of the synthesized derivatives were confirmed by means of physical and spectral analysis. All the synthesized compounds were evaluated *in vitro* for their anti-microbial activity. The results indicated that some of them were found to exhibit good antimicrobial activity compared to the standard drugs.

Conclusion

Our results clearly demonstrate that some of N-substituted phthalimide derivatives exhibited good anti-bacterial and anti-fungal activities.

General procedure for synthesis of amide derivatives

Method A.

N-aminophthalimide (0.011 mol), zinc dust (0.13 g) and acid chloride (0.019 mol) were added and the mixture was stirred at room temperature for 4 minutes. The organic compounds were extracted with Chloroform (25 ml) and the chloroform layer was washed two times with saturated solution of sodium bicarbonate (10 ml) and once with water (10 ml). The chloroform extract was concentrated and the crude product was crystallized from methanol.

Method B.

N-aminophthalimide (0.0031 mol) and acid chloride (0.0032 mol) were placed in small vial. The mixture was subjected to microwave irradiation at 450 watt for 4 minutes. The crude product was crystallized from methanol.

RESULTS AND DISCUSSION

Chemistry

Different methods have been reported for the synthesis of *N*-phthalimides[16-20]. Following the method reported by Langade[19], for the synthesis of *N*-phethalimides, a number of these compounds were prepared as solids in a good yield by refluxing of phthalic anhydride with amine in the presence of sulphamic acid as catalyst Table No.1.

Lighter and coworkers[21] have prepared *N*-aminophthalimide by the reaction of hydrazine with *N*-phthalimide in methanol at low temperature (5

ºC). In our work we coupled *N*-amino phthalimide with different aldehydes and acid halides to form hydrazones and amides respectively. The results of these reactions are summarized in Table No.2 and 3. All the synthesized hydrazones and amide are obtained in a good yield and in a pure crystalline form.

Reaction of acyl chlorides with *N*-amino phthalimide to form amide derivatives are accomplished with two different methods. The microwave assisted method (method B) has advantages over using zinc dust method (Method A). Method B is a solvent free reaction (neat), one pot and it does not need workup procedure. More over the product crystallizes in the reaction vessel in a pure crystalline form and in a good yield. In comparison, method **A** needs purification from zinc and workup procedure to get the pure compound Table No.2.

BIOLOGICAL EVALUATION

All the prepared compounds in this work were screened for their antibacterial activity against MRSA methicillin-resistant *staphylococcus aureus*, E.Coli:- *Escherichia coli*, ESBL: Extended spectrum B-lactamase *Entero:-enterococcus faecalic*, *Strepto:-Streptococcus pyogenes* at 100 µg/disc using Ampicillin, Carbenocillin as the standard antibacterial drug, and for their antifungal activity *Candida albicans* (660, 669, 772, 1047, 1057) was used and nystatin was used as a standard antifungal agent. DMSO (3%) was used as a control. The zone of inhibition was recorded in mm after incubation of plates for 24 hrs (antibacterial) and 72 hrs (antifungal) at 37 ºC. The antibacterial and antifungal activity of the phthalimide derivatives is summarized in Table No.4.

The *N*-hydroxynaphthalene sulphonic acid phthalimide 8, thiophenephthalimide derivatives 15, phthalimide Schiff's base 17 and 18 have shown significant antifungal activity against Candida albicans compared to the standard antifungal drug. The antifungal data revealed that the compound 8, 15, 17 and 18 were more active than other compounds tested against the above microbes. Compound 8, 12, 17 and 18 exhibit good antibacterial activities compared to the ampicillin and carbenocillin. The synthesized compounds have found to be better antimicrobial activity than parent compound, while other compounds were near about equipotent in antibacterial and antifungal activity.

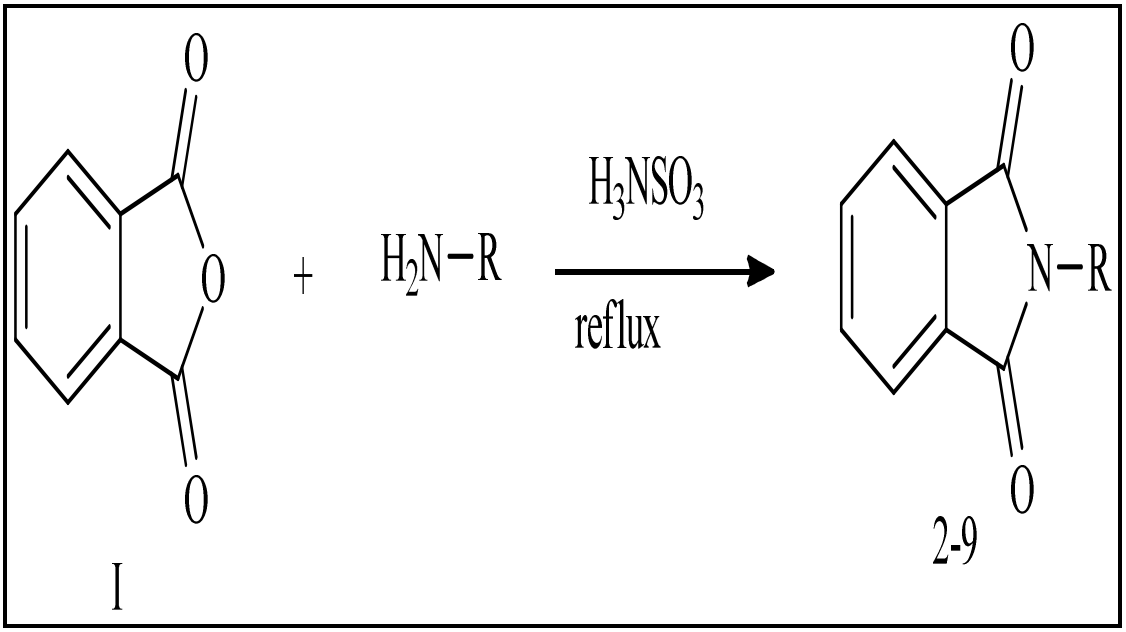
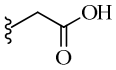
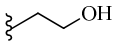
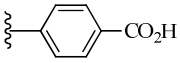
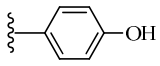
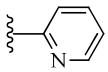
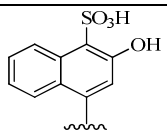
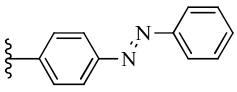


Table No.1: Newly Synthesized Phthalimide Derivatives

S.No	Compound and Yield	R	Y%	mp	IR-spectra
1	2-(1, 3-dioxoisoindolin-2-yl) acetic acid.		15	188	CO_2H 3567 C=O 1772 CO-N 1696 C=C 1424
2	2-(2-Hydroxyethyl) isoindolin-1, 3-dione.		4	160	O-H3200 C=O 1742 C=C 1424 C-O 1694
3	4-(1, 3-dioxoisoindolin-2-yl) benzoic acid.		48	280	CO_2H 3010 C=O 1690 CO-N 1654 C=C 1534
4	2-(4-Hydroxyphenyl) isoindoline-1, 3-dione.		82	298	OH 3413 C=O 1710 CO-N 1654 C=C 1517
5	2-(pyridine-2-yl) isoindoline 1, 3-dione.		41	288	C=O 1746 C=N 1734 CO-N 1673 C=C 1439
6	2-(thiazol-2-yl) isoindolin-1, 3-dione.		22	198	C=O 1731 C=N 1787 CO-N 1673 C=C 1448
7	4(1, 3-dioxisoindolin-2-yl)-2-hydroxynaphthalene-1-sulphonic acid.		86	300	OH 2654 C=O 1690 CO-N 1526
8	(*E*)-2-(4-(phenyldiazenyl) phenyl) isoindoline-1, 3-dione.		79	255	C=O 1705 CO-N 1690 C=C 1585

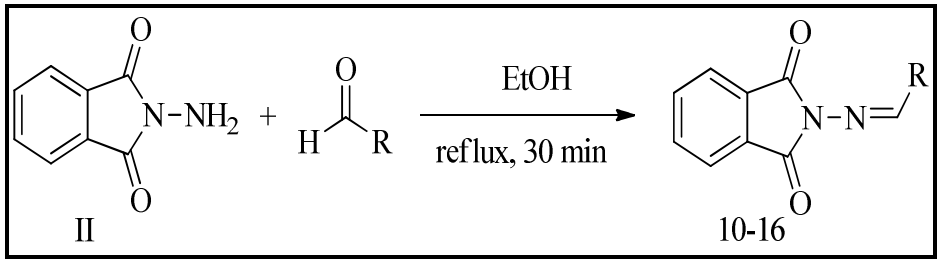
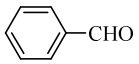
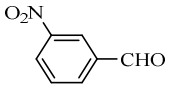
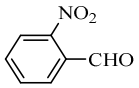
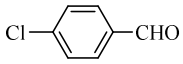
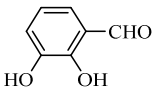
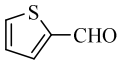
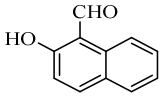


Table No.2: General synthesis of imine (Schiff s base)

S.No	Compound	R	Y%	mp	IR
1	2-(Benzylideneamino) isoindoline-1,3-dione.		10	156	C=N 1703 C=O 1590 C=C 1466
2	2-((3-Nitrobenzylidene)amino)isoindoline - 1,3-dione.		25	216	C=N 1716 C=O 1605 C=C 1468 NO_2 1380
3	2-((2-Nitrobenzylidene)amino)isoindoline - 1,3-dione.		31	221	C=N 1736 C=O 1564 C=C 1466 NO_2 1318
4	2-((4-chlorobenzylidene)amino)isoindoline- 1,3-dione		27	199	C=N 1703 C=O 1590 C=C 1466
5	2-((2,3-dihydroxybenzylidene)amino)isoindoline- 1,3-dione		12	219	OH 3672 C=N 1721 C=O 1610 C=C 1467
6	2-((thiophen-2-ylmethylene)amino)isoindoline-1,3-dione		13	151	C=N 1716 C=O 1582 C=C 1433
7	2-(((2-hydroxynaphthalen-1-yl)methylene)amino)isoindoline-1,3-dione		34	232	C=N 1710 C=O 1622 C=C 1465

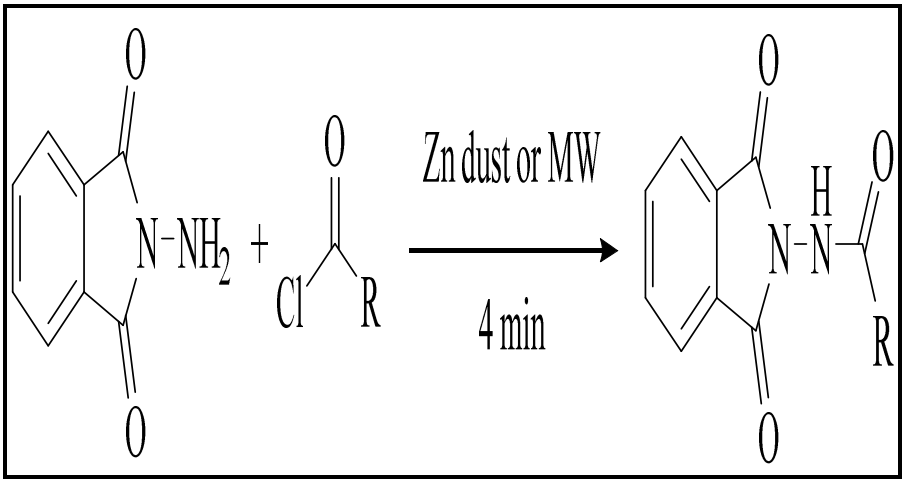


Table No.3: Two synthetic pathways for synthesized N-amide phthalimide derivatives

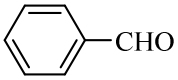
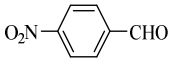
S.No	Compound	R	Y% Method A	B Method B	mp	IR
1	*N*-(1,3-dioxoisoindolin-2-yl)benzamide		30	70	192	NHCO 1666 C=O 1597 C=C 1448
2	*N*-(1,3-dioxoisoindolin-2-yl)-4-nitrobenzamide		-	20	198	C=O 1690 NHCO 1605 C=C 1482 NO_2 1386

Table No.4: Antimicrobial screening of synthesized compounds by hot plate diffusion method

Zone of inhibition in mm / Conc. 100µg																					
Number of compounds																					
S.No	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	AMP 20µg	AMP 25µg	CAR 100µg	NY 100µg
C.alb1057	6	6	6	6	6	6	25	10	10	10	10	6	6	20	-ve	15	14	15	-	-	20
C.alb660	10	11	10	11	11	12	25	10	10	10	10	6	6	15	-ve	20	20	13	-	-	19
C.alb1047	6	6	6	6	6	6	25	6	6	6	6	6	6	10	6	21	23	12	-	-	20
C.alb772	6	6	6	6	6	6	26	6	6	6	6	6	6	10	6	24	26	13	-	-	20
C.alb669	6	6	6	6	6	6	13	6	6	6	6	6	6	14	6	13	14	12	-	-	16
MRSA	6	6	6	6	6	6	26	6	6	6	15	6	6	9	6	25	26	-	12	6	-
E.coli12241	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6			6
E.coli11934	6	6	6	6	6	6	16	6	6	6	16	6	6	6	6	15	15	-	15	15	-
Entero12697	6	6	6	6	6	6	20	6	6	6	15	6	6	6	6	19	20	-	25	20	-
ESBL70	6	6	6	6	6	6	10	6	6	6	12	6	6	6	6	14	14	-	6	6	-
ESBL12	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	-	6	6	-
ESBL54	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	14	14	-	6	6	-
Strepto12696	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6

MRSA: methicillin-resistant staphylococcus Aure, E.Coli:-Escherichia coli, C.alb:- Candida aibicans , ESBL:- , Extended spectrum B-lactamase , Entero:-enterococcus faecalic , Strepto:-Streptococcus pyogenes, AMP: Ampicllin , CAR: Carbenocillin, NY: Nystatine

CONCLUSION

Microwave irradiation method is a practical and efficient method for the synthesis of *N*-phthalimide derivatives in a pure crystalline form. The presence of azomethine and phthalimide functional group is responsible for antimicrobial activity, which can be altered depending upon the type of substituent present on the aromatic rings. The basic N=C group believed to enhance antimicrobial activity. Nevertheless, some of the compounds were found to possess good antimicrobial activity. Therefore they may be used as lead compounds for further development.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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