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STUDIES AN ANTIMICROBIAL ACTIVITY OF VARIOUS *N*-SUBSTITUTED PHTHALIMIDES DERIVATIVES

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ABSTRACT

Structural modification of various *N*-substituted phthalimides compounds through such simple, rapid and environment-friendly approach polymer support method has been taken to study the bioassay and their structure-activity relationships (SAR). Derivatization of phthalimide and *N*-hydroxy phthalimide exhibits good antibacterial efficacy and very less antifungal potency even though parent phthalimide moiety oriented compounds are potent fungicides.

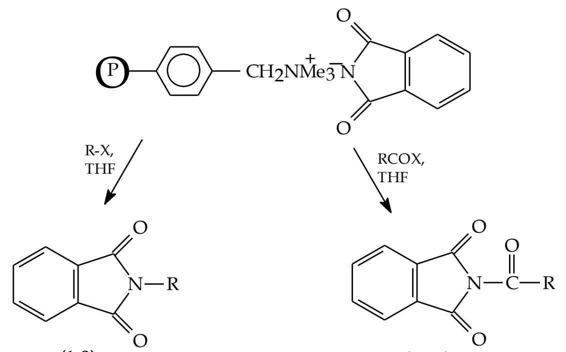
Key words: *N*-alkyl, *N*-acyl, *N*-alkyloxy, *N*-acyloxy, phthalimide, antibacterial, polymer support, etc.

INTRODUCTION

In heterocyclic chemistry, the compounds containing phthalimide moiety are distinguished by their potent fungicidal action[1-3]. The well known products namely, captan [*N*-(trichloromethyl-thio) tetrahydrophthalimide], folpet [*N*-(trichloromethyl-thio) phthalimide] and difolatan [*N*-1,1-2,2-(tetrachloroethyl-thio) phthalimide] are good synthetic commercial fungicides. Also it is one of industrial importance as the starting material for producing anthranilic acid by Hoffmann degradation and a large number of primary amines can be produced by the Gabriel synthesis. Phthalimide is an intermediate in the production of agricultural pesticides and also used in preservatives, pigments and pharmaceuticals.

The phthaloyl group is a well-established protective group for primary amines[7] in various types of compounds, particularly peptides[8], aminoglycosides[9], *β*-lactum antibiotics[10] and in aminoacylophosphonic derivatives[11]. Several methods exist for phthaloylation of amines[12-20].

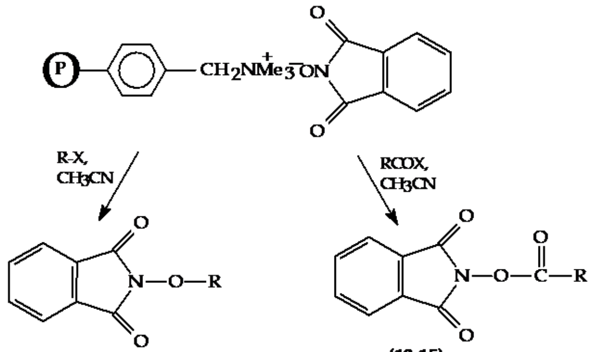
Synthesis of *N*-alkyl and *N*-acyl phthalimide



(1-8) (9-12)

Keeping in view the importance of phthalimides not only as fungicides in crop protection but also equally as protective group for primary amines, H_2NR and *O*-alkylhydroxylamines, H_2NOR, we have prepared *N*-alkyl and *N*-acyl[21] also *N*-alkyloxy and *N*-acyloxy[22] phthalimides in higher yields with higher purity under mild reaction conditions by polymer-support and tested their antimicrobial activities.

Synthesis of *N*-alkyloxy and *N*-acyloxy phthalimide



(1-11) (12-15)

METHODS AND MATERIALS

The synthesized *N*-alkyl and *N*-acyl and also *N*-alkyloxy and *N*-acyloxy phthalimides were characterized by their physical constants[23] and also by TLC through comparison with the products obtained by conventional methods[24]. The yield and purity of alkyl and acyl derivatives of phthalimides and *N*-hydroxy phthalimides were higher, which supports that the polymeric reagent seems to increase the nucleophilicity of the anions.

Antimicrobial Activity:
All the synthesized *N*-alkyl and *N*-acyl as well as *N*-alkyloxy and *N*-acyloxy phthalimides were tested for their pest control (antimicrobial) potency against various four fungi and four bacteria species. Bioassay is an important and crucial in evaluation of bioactivity of the compounds and helpful to establish structure-activity relationships (SAR).

The methodology for evaluation of antimicrobial activity has performed same as well known methods[25,26]. The results are summarized in Tables and Figures.

RESULTS AND DISCUSSION

Phthalimide and its derivatives:

Antifungal activity
N-alkyl and *N*-acyl phthalimides were tested for their antifungal potency against four fungi species, viz. *Aspergillus niger, Aspergillus flavous, Alternaria alternata,* and *Fusarium oxysporum* of 5000 ppm concentration. The results have been summarized in **Table 1.1** and represented in **Fig. 1.1**.

Only four derivatives of phthalimide, namely, butyl, allyl and carboxymethyl ethers and benzoate esters reflected antifungal action. Other derivatives including parent compound have not showed antifungal activity.

Antibacterial activity
N-alkyl and *N*-acyl phthalimides were evaluated for their antibacterial efficacy against four bacteria species, viz. *Bacillus mecarium, Bacillus japonecum, Pseudomonas fluorescence* and *Pseudomonas putida*. The results are summarized in **Table 1.2** and presented in **Fig. 1.2**.

All derivatives of phthalimides exhibited very good antibacterial potency against *Bacillus japonecum*. Only some derivatives have shown positive action against *Pseudomonas fluorescence*, however, no any bacterial effect was observed against *Bacillus mecarium* and *Pseudomonas putida*. Against *Bacillus japonecum*, butyl phthalimide showed the highest antibacterial potency followed among alkyl derivatives in decreasing order by propyl, ethyl, (methyl and benzyl), and allyl. Whereas among esters the activity decreasing order was phenyl acetate, benzoate and (acetate and cinnamate).

N-*Hydroxy phthalimide and its derivatives*
Antifungal activity
Antifungal efficacy of *N*-hydroxy phthalimide derivatives was evaluated against four fungi species viz. *Aspergillus niger, Aspergillus flavous, Alternaria alternata* and *Fusarium oxysporum*. The results are summarized in **Table 1.3** and presented in **Fig. 1.3**.

In general, derivatives of *N*-hydroxy phthalimide reflected better antifungal potency than that of

Table 1.1: Antifungal activity of phthalimides and its derivatives

Derivatives	*Aspergillus niger*	*Aspergillus flavous*	*Alternaria alternata*	*Fusarium oxysporum*
Parent Phthalimide	----	----	----	----
Alkyl				
Methyl	----	----	----	----
Ethyl	----	----	----	----
Propyl	----	----	----	----
Isopropyl	----	----	----	----
Butyl	21.0	----	----	----
Allyl	24.0	----	----	----
Benzyl	----	----	----	----
Carboxy methyl	23.0	----	----	----
Acyl				
Acetate	----	----	----	----
Benzoate	25.0	----	----	----
Cinnamate	----	----	----	----
Phenyl acetate	----	----	----	----

Zones of Inhibition (diameter, mm)

Table 1.2: Antibacterial activity of phthalimides and its derivatives

Derivatives	*Bacillus mecarium*		*Bacillus japonicum*		*Pseudomonas fluorescence*		*Pseudomonas putida*	
	Zones of Inhibition (dia., mm)	**% change in activity over parent**	**Zones of Inhibition (dia., mm)**	**% change in activity over parent**	**Zones of Inhibition (dia., mm)**	**% change in activity over parent**	**Zones of Inhibition (dia., mm)**	**% change in activity over parent**
Parent Phthalimide	----	----	13.0	---	10.0	----	----	----
Alkyl								
Methyl	----	----	23.0	76.9	14.0	40.0	----	----
Ethyl	----	----	25.0	92.3	10.0	00.0	----	----
Propyl	----	----	30.0	130.7	14.0	40.0	----	----
Isopropyl	----	----	28.0	115.3	10.0	00.0	----	----
Butyl	----	----	31.0	138.4	11.0	10.0	----	----
Allyl	----	----	20.0	53.8	14.	40.0	----	----
Benzyl	----	----	23.0	76.9	----	----	----	----
Carboxy methyl	----	----	22.0	69.2	----	----	----	----
Acyl								
Acetate	----	----	19.0	46.1	----	----	----	----
Benzoate	----	----	21.0	61.5	13.0	30.0	----	----
Cinnamate	----	----	19.0	46.1	12.0	20.0	----	----
Phenyl acetate	----	----	31.0	138.4	----	----	----	----

Table 1.3: Antifungal activity of *N*-Hydroxy phthalimides and its derivatives

Derivatives	*Aspergillus niger*	*Aspergillus flavous*	*Alternaria alternata*	*Fusarium oxysporum*
Parent *N*-Hydroxy Phthalimide	----	----	----	----
Alkyloxy				
Methyloxy	----	----	----	10.0
Ethyloxy	----	----	----	09.0
Propyloxy	----	----	----	10.0
Ethylacetoactyloxy	----	----	----	12.0
Butyloxy	----	----	----	----
Allyloxy	----	----	----	09.0
Benzyloxy	----	----	----	10.0
Carboxy methyloxy	----	----	----	----
Triphenyl methoxy	----	----	----	14.0
2,4-Dinitro benzyloxy	----	----	----	12.0
2,4,6-Trinitro benzyloxy	----	----	----	17.0
Acyloxy				
Acetyloxy	----	----	----	13.0
Benzoyloxy	----	----	----	25.0
Cinnamayloxy	----	----	----	11.0
Phenyl acetyloxy	----	----	----	10.0

Zones of Inhibition (diameter, mm)

Table 1.4: Antibacterial activity of *N*-Hydroxy phthalimides and its derivatives

Derivatives	*Bacillus mecarium*	*Bacillus japonicum*	*Pseudomonas fluorescence*	*Pseudomonas putida*
Parent *N*-Hydroxy Phthalimide	----	----	----	----
Alkyloxy				
Methyloxy	12.0	11.0	10.0	11.0
Ethyloxy	07.0	07.0	07.0	05.0
Propyloxy	11.0	13.0	13.0	11.0
Ethylacetoactyloxy	10.0	09.0	07.0	12.0
Butyloxy	08.0	09.0	10.0	10.0
Allyloxy	10.0	09.0	09.0	08.0
Benzyloxy	11.0	08.0	09.0	09.0
Carboxy methyloxy	15.0	14.0	09.0	11.0
Triphenyl methoxy	10.0	09.0	12.0	08.0
2,4-Dinitro benzyloxy	09.0	12.0	13.0	10.0
2,4,6-Trinitro benzyloxy	11.0	12.0	11.0	09.0
Acyloxy				
Acetyloxy	10.0	11.0	10.0	11.0
Benzoyloxy	09.0	12.0	09.0	12.0
Cinnamayloxy	12.0	16.0	14.0	12.0
Phenyl acetyloxy	15.0	13.0	10.0	14.0

Zones of Inhibition (diameter, mm)

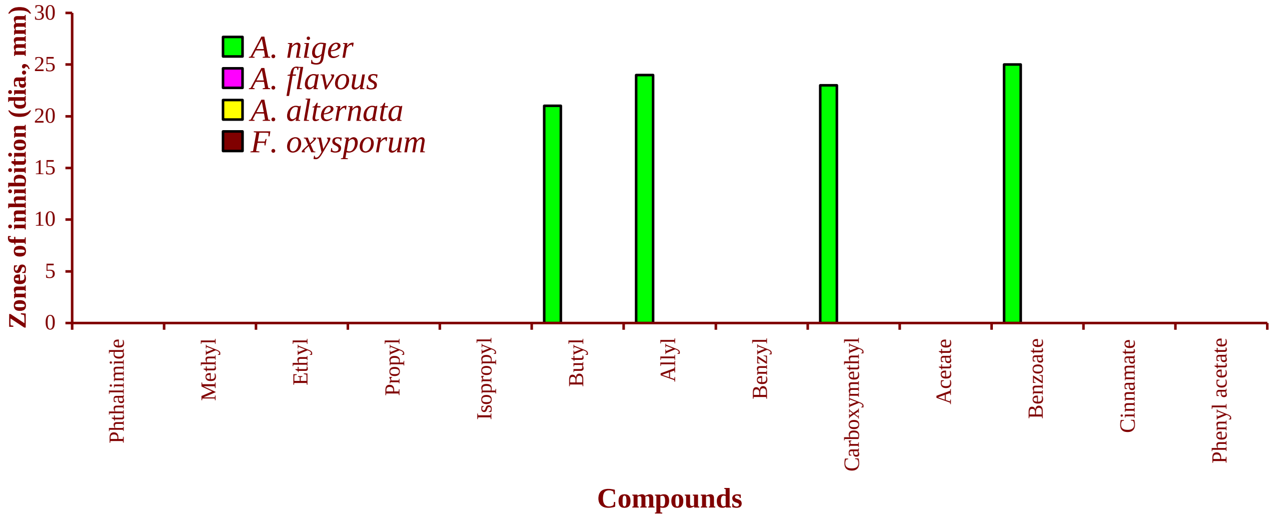


Fig 1.1: Antifunal activity of phthalimide and its derivatives

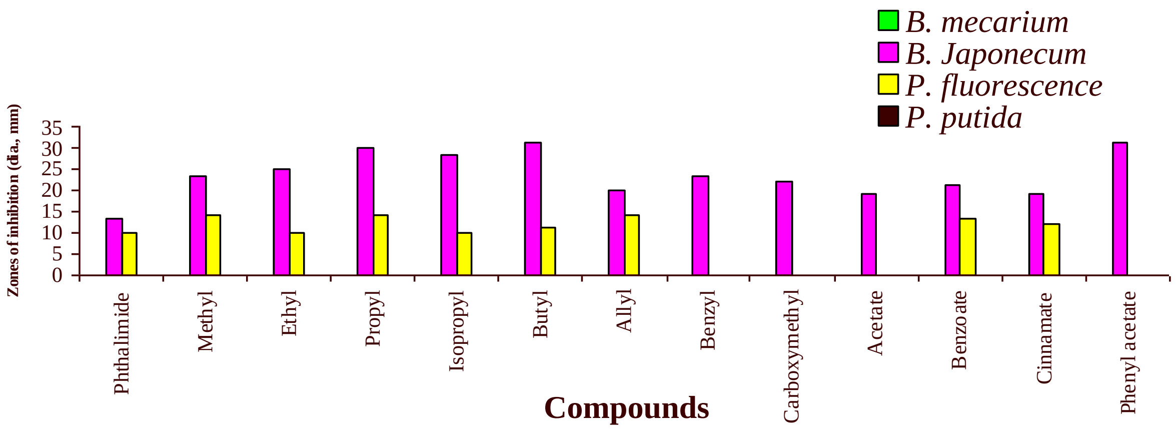


Fig. 1.2: Antibacterial activity of phthalimide and its derivatives

phthalimide against *Fusarium oxysporum*. Only, however all derivatives were found to be totally inactive against remaining fungi species viz. *Aspergillus niger*, *Aspergillus flavous* and *Alternaria alternata* even at 5000 ppm concentration.

Antibacterial activity

All derivatives of *N*-hydroxy phthalimide showed very good antibacterial potency against all four test bacteria species. The activity order among derivatives was found to be different for different test species, however, alkyl and acyl derivatives reflected averagely equal antibacterial efficacy. The results are summarized in **Table 1.4** and presented in **Fig. 1.4**.

In overall antimicrobial bioassay, derivatives of both phthalimide and *N*-hydroxy phthalimide found to be possess good antibacterial efficacy and very less antifungal potency. The parent compound phthalimide reflected antibacterial activity against only *Bacillus japonecum* and *Pseudomonas fluorescence* at test concentrations, whereas it was found to be totally inactive against other test bacteria as well as fungi species. The bioassay clearly reveals that the derivatization of phthalimide and *N*-hydroxy phthalimide will be beneficial in the field of pest management for designing the active molecules.

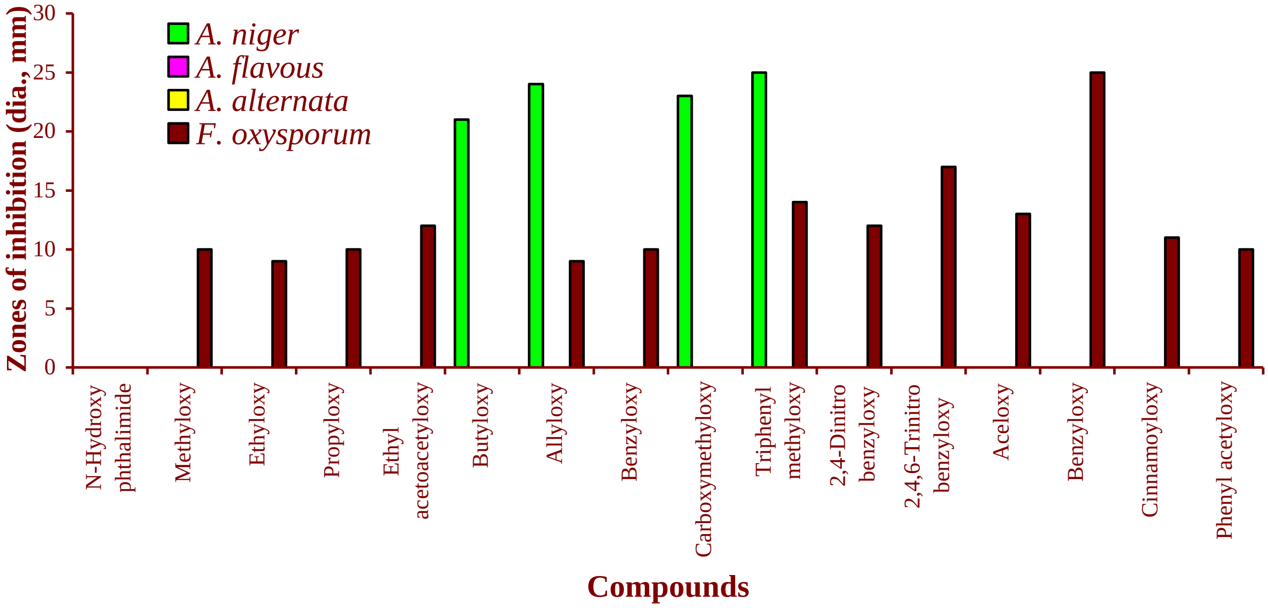


Fig 1.3: Antifunal activity of N-Hydroxy phthalimide and its derivatives

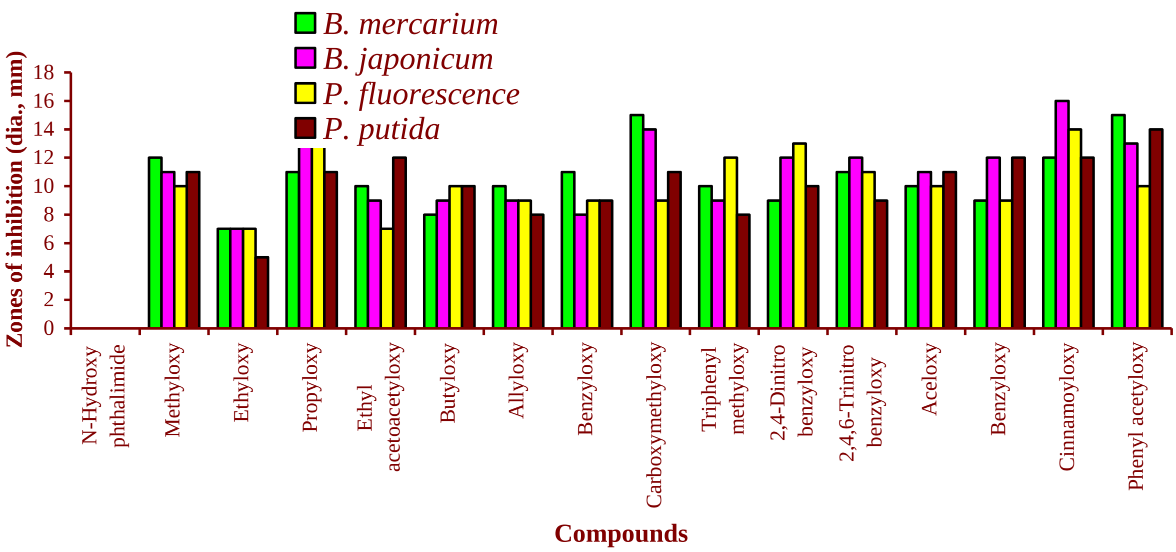


Fig 1.4: Antibacterial activity of N-Hydroxy phthalimide and its erivatives

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