REVIEW ARTICLE

Cyclic imide derivatives: As promising scaffold for the synthesis of antimicrobial agents

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Cyclic imides as building blocks in the synthesis of natural products, drugs and polymers display a diverse of pharmacological activities such as antibacterial, antifungal, anticonvulsant, anticancer, and anti-inflammatory effects. This review summarizes recent findings on antimicrobial activities of cyclic imide derivatives and emphasis on the importance of cyclic imides for drug design and development of new antimicrobial compounds.

Key words: Antibacterial agents, antifungal agents, imides

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INTRODUCTION

Cyclic imides as a class of bioactive compounds possess several biological properties such as antibacterial, antifungal, antiviral,[1-4] analgesic,[1,5] antitumor,[6-9] androgen receptor antagonistic,[1] anti-inflammatory,[5] anxiolytic,[10] antidepressive, anticonvulsant, and muscle relaxant activities.[1,4]

Cyclic imides and their N-derivatives contain bisamide linkages with a general structure of [-CO-N(R)-CO-]. Their hydrophobicity and neutral structures can improve crossing them of the biological membranes.[1] Existence of oxygen and nitrogen atoms as donor sites can coordinate these ligands with the biological system and cause some pharmacological effects.[11,12] Some of these effects could be attributed to the size and electrophilic characteristics of substituent groups on the imide ring.[13] Cyclic imides with a para-sulfonamide group have been introduced as potential antitubercular agents.[12]

Cyclic imides are privileged pharmacophores and important building blocks for the synthesis of natural products, drugs, and polymers. Some of the important natural products with imide structure comprise migrastatin, lamprolobine, julocrotine, and cladoniamide A. The alkaloid phyllanthimide isolated from leaves of *Phyllanthus sellowianus* (Euphorbiaceae) has been used as a precursor for the synthesis of some of cyclic imides.[14] There are several approved drugs with cyclic imide structure such as phensuximide, buspirone, and thalidomide.[15]

Although cyclic imide derivatives show wide range of biological properties, in this review, we only provide an overview on the antimicrobial activities of this scaffold and present a summary of structure–activity relationship (SAR) in some areas.

CYCLIC IMIDES AS ANTIBACTERIAL AND ANTIFUNGAL AGENTS

Unfortunately, the efficacy of many antibacterial drugs has been reduced by the capacity of bacteria to develop

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resistance to nearly any antibacterial agent. Considerable researches necessitate on the synthesis of new compounds with potent antimicrobial activity.

Stiz *et al*. synthesized three different subfamilies of cyclic imides: methylphtalimides, carboxylic acid phtalimides, and itaconimides. The compounds were tested for their antifungal activity. The results exhibited that only the itaconimides have potent antifungal properties.[16] Dhivare and Rajput synthesized a series of N-phenyl glutarimides and N-phenylsuccinimides using bis-chalcones [Figure 1]. These compounds screened for *in vitro* antifungal activities at concentration of 100 µg/ml per disk. Almost all the synthesized compounds showed noticeable activities against *Candida albicans* and *Aspergillus niger* fungal strains in this concentration.[17,18]

Phthalimides, bicyclic imides, showed large range of applications. These compounds have been used as starting materials and intermediate for the synthesis of many types of alkaloids. Sultana *et al*. succeeded to synthesize 2-(2-methoxyphenyl)-1H-isoindole-1, 3 (2H)-dione ligand, and some of the metal complexes using the simple method. Synthesized complexes have exhibited enhanced antibacterial effects in comparison to their parent ligand [Figure 2].[11]

Mallesha *et al*. reported the synthesis of several isoindoline-1, 3-dione (phthalimide) derivatives. All compounds were evaluated for their *in vitro* antibacterial activities against clinically isolated strains, i.e., *Escherichia coli*, *Pseudomonas fluorescens*, *Micrococcus luteus*, and *Bacillus subtilis*. Compounds shown in Figure 3 exhibited significant antibacterial activities against Gram-positive and Gram-negative bacteria at 500 µg/mL concentration.[19]

Bisimide derivatives were studied and evaluated for their antimicrobial activities against bacteria, namely, *B. subtilis*, *Streptococcus lactis*, *E. coli*, *Pseudomonas* sp., and various fungi *A. niger*, *C. albicans*, and *Rhodotorula ingeniosa* at 10 µg/mL concentrations by Sabry *et al*. It was observed that thienyl derivative had remarkable antimicrobial activity comparable to positive controls [Figure 4].[20]

Al-azzawi and Al-Obiadi synthesized and screened antimicrobial activities of new cyclic imides, through molecular hybridization, with Schiff base, azetidinone, and acetyl oxadiazole derivatives. Azetidinone derivative with OH group on the phenyl ring showed high antibacterial activity against all tested bacteria and very high activity against *Candida krusei* [Figure 5].[3]

Naphthalimides, with strong hydrophobicity and π-conjugated structure, can interact with various active targets in biological system and show remarkable biological

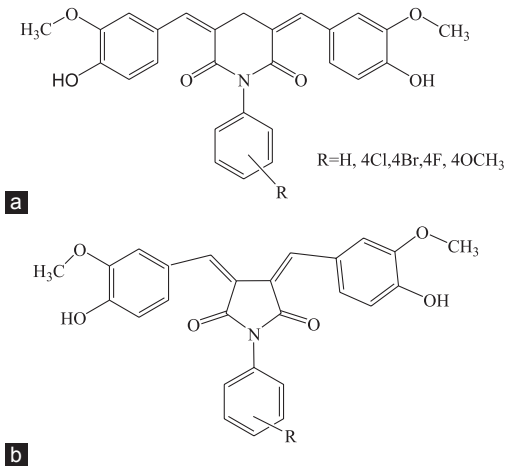

Figure 1: (a) 3,5-Bis((Z)-4-hydroxy-3-methoxybenzylidene)-1-phenylpiperidine-2, 6-dione and (b) 3,4-bis-4-hydroxy-3-methoxybenzylidene)-1-phenylpyrrolidine-2,5 dione

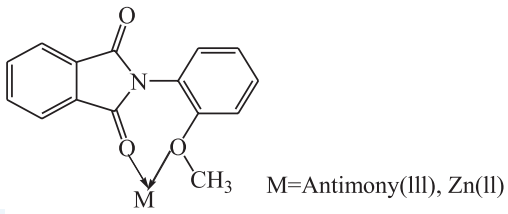

Figure 2: 2-(2-Methoxyphenyl)-1*H*-isoindole-1,3(2*H*)-dione

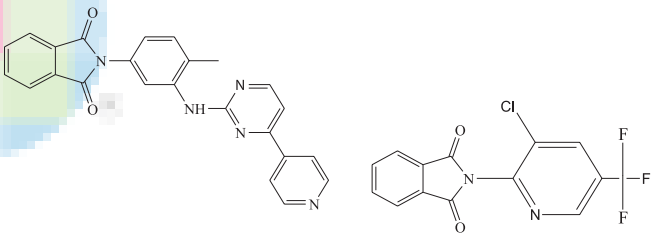

Figure 3: 2-(3-(4-(Pyridin-4-yl) pyrimidin-2-ylamino)-4-methylphenyl) isoindoline-1,3-dione and 2-(3-chloro-5-(trifluoromethyl)pyridin-2-yl)isoindoline-1,3-dione

activities including anticancer and antibacterial. Recent research revealed that the combination of naphthalimide with six-membered nitrogen heterocycles such as piperazinyl can improve antibacterial and antifungal activities.[21,22]

Al-Majidi *et al*. synthesized a series of 1,8-naphthalimides bearing five-membered ring substituents such as 1,3-oxazole, 1,3-thiazole, and 1,2,4-triazole moieties. These compounds were screened in three concentrations 25, 50, and 100 (mg/mL) using agar well diffusion method, against (*B. subtilis*, *Staphylococcus aureus*, *E. coli*, *and Pseudomonas aeruginosa*) bacterial and fungal (*C. albicans*) strains. These compounds exhibited good-to-moderate activity against the tested microorganisms [Figure 6].[23]

Guri *et al*. prepared a series of naphthalimide azoles (triazole, triazolium, and imidazole analogs) and tested

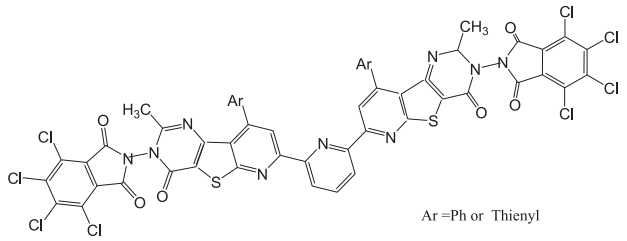

Figure 4: Bis-phthalimide derivatives

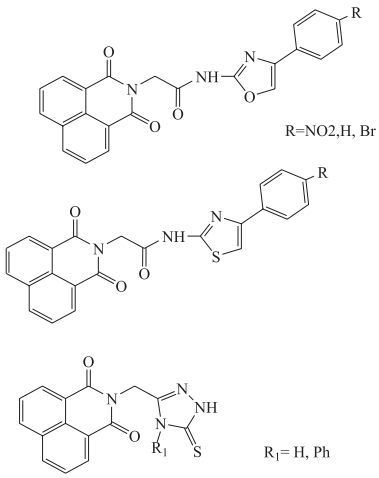

Figure 6: Naphthalimides linked to five-membered heterocyclic rings

them against Gram-positive (*S. aureus*, *B. subtilis*, and *M. luteus)* and Gram-negative bacteria (*Bacillus proteus*, *E. coli*, *P. aeruginosa*, and *Bacillus typhi*) and fungi *(C. albicans* and *Candida mycoderma*). The antimicrobial results manifested that the most naphthalimide triazoliums especially Compounds A and B with $(CH_2)_3$ as linker had better antimicrobial efficiency (minimum inhibitory concentration [MIC] = 2–16 μg/mL) than their corresponding azoles. Thio-triazoliums with 3,4-dichlorobenzyl and 2,4-difluorobenzyl substituents had potent efficacy against *M. luteus* and *B. typhi* with MIC values of 2 μg/mL.

The different substitution on azole ring and naphthalimide scaffold has considerable effect on antimicrobial activity [Figure 7].[22]

Several new naphthalimide-benzothiazole derivatives have been synthesized and evaluated for their antibacterial activities against a variety of bacterial strains such as *B. subtilis*, *S. aureus*, *Staphylococcus epidermidis*, *P. aeruginosa, E. coli,* and *Proteus vulgaris* by Kumari and Singh and Hamed separately. In researches down by Kumari and Singh, compound shown in Figure 8a exhibited the maximum antibacterial activity (MIC <0.65 μg/mL) against all tested bacterial strains.[24] In another study down by Hamed, derivatives shown in Figure 8b were introduced as highly active antimicrobial agents against all types of tested bacteria [Figure 8].[25]

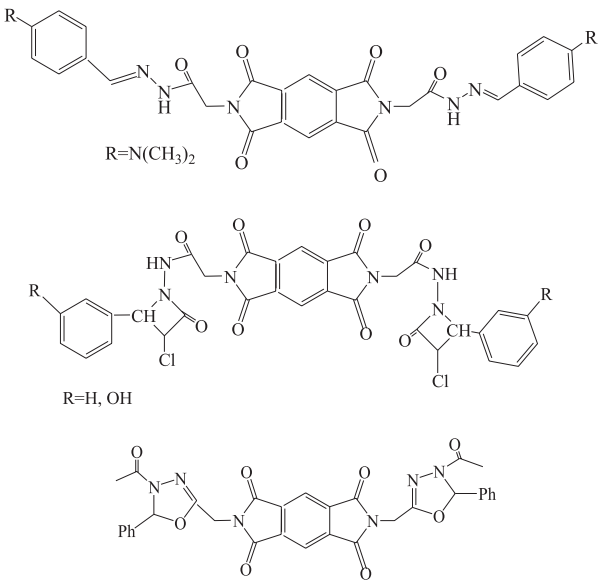

Figure 5: Schiff base, azetidinone, and acetyl oxadiazole derivatives of cyclic imides

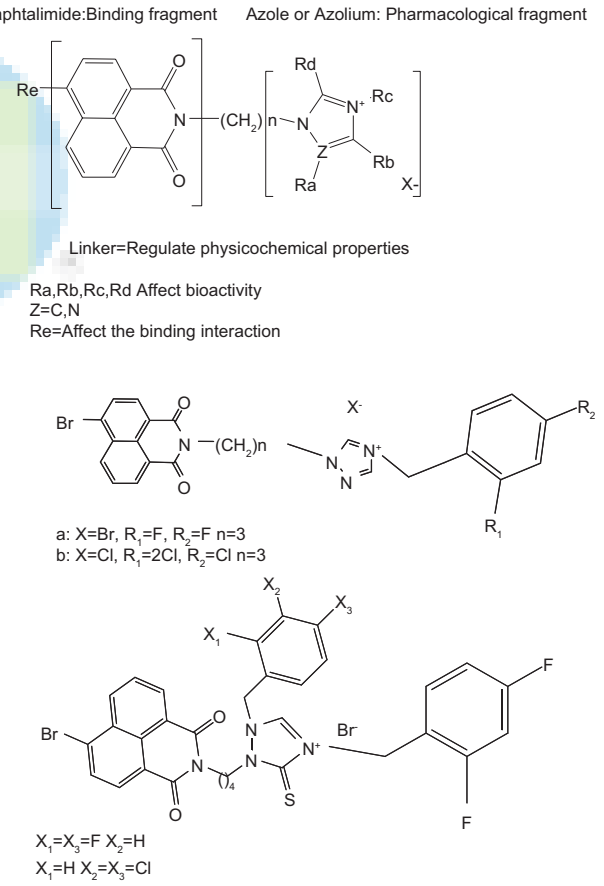

Figure 7: Naphthalimide-azole derivatives

Shaki *et al.* reported the synthesis of new cationic naphthalimide derivative and its intermediate with yellow-green fluorescence

and evaluated them for *in vitro* antimicrobial activity against *S. aureus*, *M. luteus*, *B. subtilis*, and *E. coli* bacteria and fungus *C. albicans*. Observed MIC values for compounds A and B against *S. aureus* were 62.5 μg/mL and 31.25 μg/mL, respectively. This results showed that compound with quaternary ammonium salt structure had higher antimicrobial activity than its corresponding intermediate. Furthermore, compounds exhibited better antimicrobial activity against Gram-positive bacteria [Figure 9].[26]

Jafari *et al*. synthesized and evaluated antimicrobial activity some cyclic imides derived from phthalic and succinic anhydrides which designed based on the glycinamide or 2-aminobenzylamine. According to the antimicrobial evaluations, phthalimide derived from benzylamine exhibited remarkable antimicrobial activity against *E. coli* at 16 (μg/mL) concentration [Figure 10].[27]

To investigate antifungal activity, Gayoso *et al*. synthesized some of the maleimide derivatives as stable cyclic unsaturated imide and screened them against fungal strains isolated from onychomycosis. The presence of two chloro atoms in compounds can improve antifungal activity. Reported MIC for antifungal activity was 100 μg/mL for 3,4-dichloro-N-phenyl-methyl-maleimide and 3,4-dichloro-N-phenyl-propilmaleimide and 200 μg/mL for 3,4-dichloro-N-phenyl-maleimide, 3,4-dichloro-N-phenyl-ethyl-maleimide, and 3,4-dichloro-N-phenyl-buthyl-maleimide, respectively [Figure 11].[28,29]

In addition, Sortino *et al*. synthesized a series of N-phenyl and N-phenylalkyl maleimide derivatives and performed a study on the time-dependent stability of each compound in the growth media to compare antifungal activity of opened and intact maleimide ring. All tested (intact ring) maleimide derivatives showed activities against *C. albicans* with MIC and minimum fungicidal concentrations 3.9 μg/mL and 7.8 μg/mL, respectively. According to this result, the length of alkyl chain did not influence on activity of these compounds. Furthermore, results indicated that maleamic acids did not possess any antifungal activity at concentrations up to 250 μg/mL [Figure 12].[30]

Al Azzawi and Mahdi reported the synthesis of new compounds containing maleimides linked to substituted benzothiazole. The presence of nitro group on benzothiazole moiety was found to greatly impact antimicrobial activity against *Klebsiella pneumoniae* as Gram-negative bacteria [Figure 13].[31]

To investigate antimicrobial activity of cyclic imides, Marulasiddaiah *et al*. synthesized a novel series of

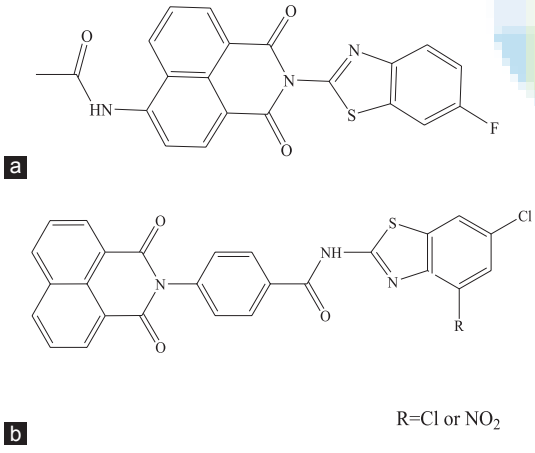

Figure 8: (a) N-[2-(6-Fluoro-benzothiazol-2-yl)-1,3-dioxo-2,3-dihydro-1Hbenzo[de]isoquinolin-6-yl]-acetamide. (b) 4-(N-naphthalimidyl)-N-(substitutedbenzothiazol-2-yl) benz- amide

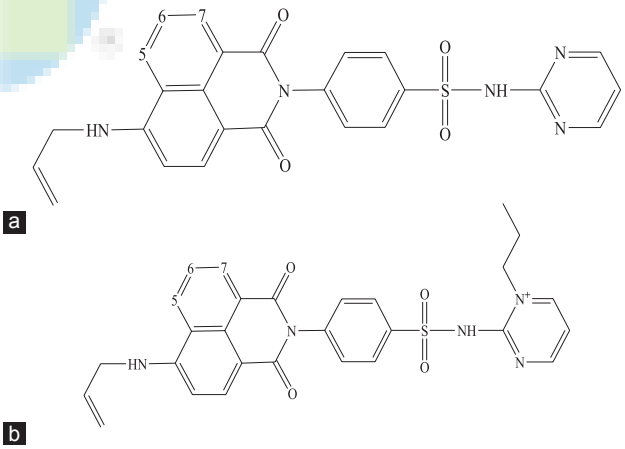

Figure 9: 4-allylamino-N-sulfadiazine-1, 8-naphthalimide (a) its quaterner derivative(b)

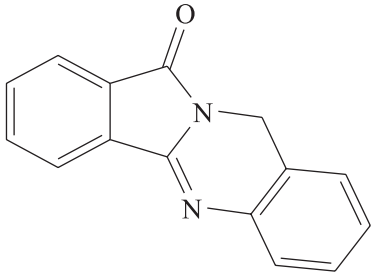

Figure 10: Phthalimide derived from 2-aminobenzylamine

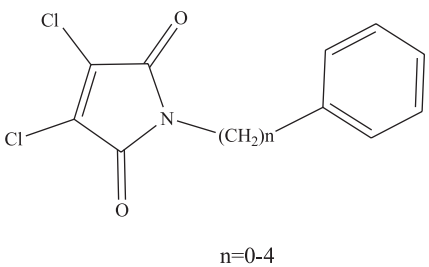

Figure 11: 3,4-Dichloro-N-phenylalkyl-maleimide derivatives

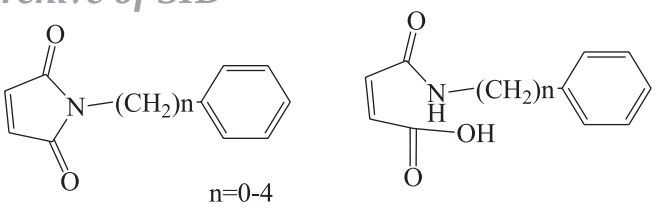

Figure 12: N-Phenyl and N-phenylalkyl maleimide

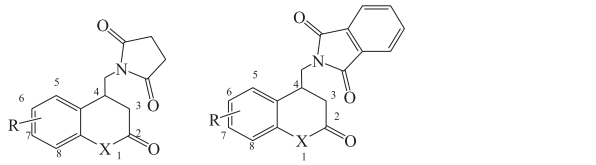

Figure 14: N-Substituted phthalimide or succinimide derivatives of coumarins and 1-azacoumarins

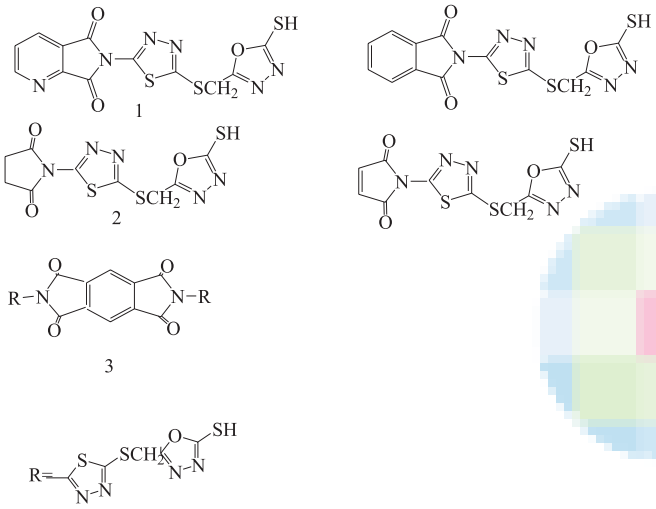

Figure 16: Cyclic imide derivatives containing both 1,3,4-thiadiazole and 1,3,4-oxadiazole cycles

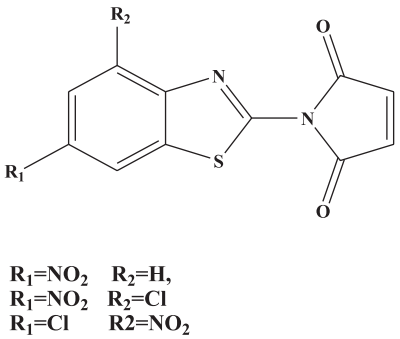

Figure 13: Maleimide-benzothiazole derivatives

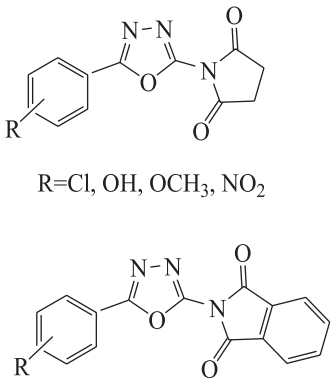

Figure 15: Phthalimide or succinimide-1,3,4-oxadiazole derivatives

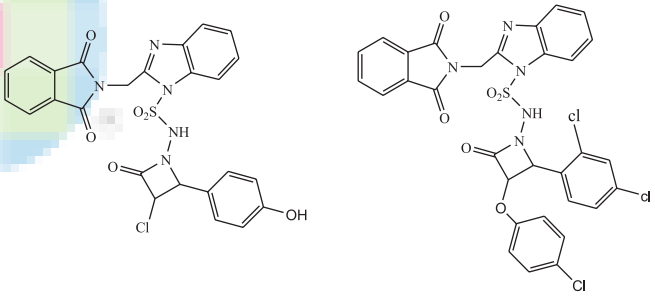

Figure 17: Chloro/p-chlorophenoxy substituted azetidinones bearing phthalimide-benzimidazole scaffold

N-substituted cyclic imides bearing coumarin and azacoumarin moiety. All the compounds were screened for their antibacterial and antifungal activities at three 100, 200, and 300 µg/ml concentrations. Antimicrobial results showed that N-substituted phthalimide derivatives of coumarins and 1-azacoumarins are relatively more active than N-substituted succinimide derivatives. SAR studies revealed that methyl substituent at the coumarin and 1-azacoumarin structure resulted in decreasing antibacterial activities, while compounds possessing chloro and methoxy groups at this backbone could increase activities [Figure 14].[12]

Al-Azzawi and Yaseen synthesized novel phthalimide or succinimide-1, 3, 4-oxadiazole derivatives and evaluated for their *in vitro* antimicrobial activities. The SARs showed that existence of chlorine or nitro group on the phenyl ring could probably improve antimicrobial effect against *E. coli* and slightly against *S. aureus*. Introduction of (OCH_3 and OH) groups on the phenyl ring only increased activity against *S. aureus* [Figure 15].[32]

Cyclic imide derivatives containing both 1, 3, 4-thiadiazole and 1, 3, 4-oxadiazole cycles were synthesized by Al-Azzawi and Hamd. Antimicrobial activities of all compounds were assessed against four types of bacteria *S. aureus*, *Streptococcus pyogenes*, *E. coli*, and *P. aeruginosa* and one fungus (*C. albicans)* at 100 µg/mL concentration. The results indicated that compounds 1, 2, and 3 are highly effective against all types of tested bacteria [Figure 16].[33]

Seth and Sah reported the synthesis of a new series of chloro/p-chlorophenoxy substituted azetidinones bearing phthalimide-benzimidazole scaffold at N-1 position.

Antimicrobial activity evaluation was performed against bacterial strains: *E. coli*, *Alcaligenes faecalis*, and *P. aeruginosa,* and *K. pneumoniae* and fungal strains: *Chaetomium globosum* and *Cochliobolus lunatus*. Structural activity relationship indicated that p-chlorophenoxy-substituted azetidinones had more antimicrobial activity than the chloro substituted azetidinones [Figure 17].[34]

CONCLUSION

Cyclic imides are fundamental backbone in a variety of active natural products and synthetic compounds. The aim of this review is to indicate antimicrobial activity of cyclic imide derivatives and try to emphasis on this scaffold as an effective antimicrobial agent.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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