REVIEW ARTICLE

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

Farshid Hassanzadeh, Elham Jafari[1]

Department of Medicinal Chemistry, Isfahan Pharmaceutical Sciences Research Center, School of Pharmacy and Pharmaceutical Sciences, Isfahan University of Medical Sciences, [1]Department of Medicinal Chemistry, Bioinformatics Research Center, School of Pharmacy and Pharmaceutical Sciences, Isfahan University of Medical Sciences, Isfahan, Iran

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

How to cite this article: Hassanzadeh F, Jafari E. Cyclic imide derivatives: As promising scaffold for the synthesis of antimicrobial agents. J Res Med Sci 2018;23:53.

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

Access this article online

Quick Response Code:

Website: www.jmsjournal.net

DOI: 10.4103/jrms.JRMS_539_17

Address for correspondence: Dr. Elham Jafari, Department of Medicinal Chemistry, Bioinformatics Research Center, School of Pharmacy and Pharmaceutical Sciences, Isfahan University of Medical Sciences, Isfahan, Iran. E-mail: jafari@pharm.mui.ac.ir

Received: 25-06-2017; **Revised:** 19-02-2018; **Accepted:** 19-03-2018

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

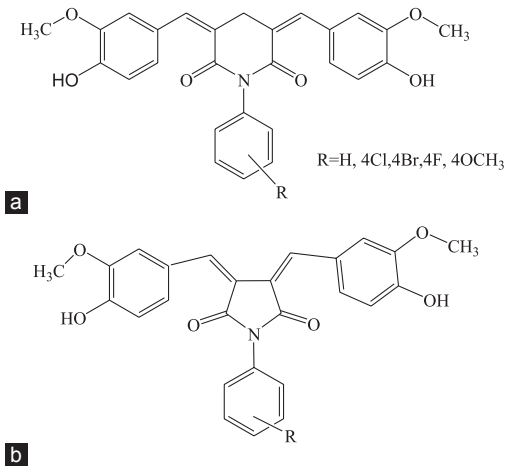


Figure 1: (a) 3,5-Bis((Z)-4-hydroxy-3-methoxybenzylidene)-1-phenylpiperidine-2, 6-dione and (b) 3,4-bis-4-hydroxy-3-methoxybenzylidene)-1-phenylpyrrolidine-2,5 dione

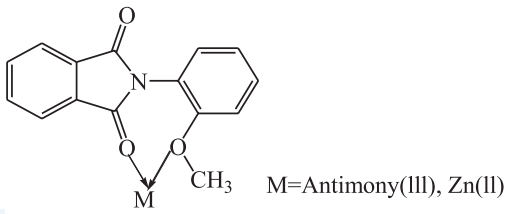


Figure 2: 2-(2-Methoxyphenyl)-1*H*-isoindole-1,3(2*H*)-dione

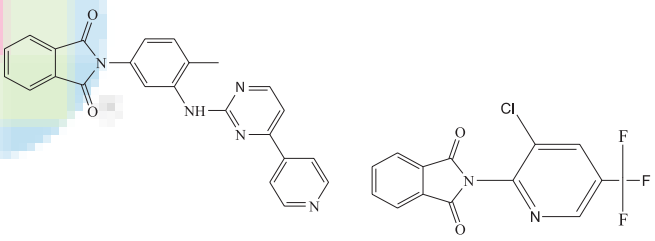


Figure 3: 2-(3-(4-(Pyridin-4-yl) pyrimidin-2-ylamino)-4-methylphenyl) isoindoline-1,3-dione and 2-(3-chloro-5-(trifluoromethyl)pyridin-2-yl)isoindoline-1,3-dione

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

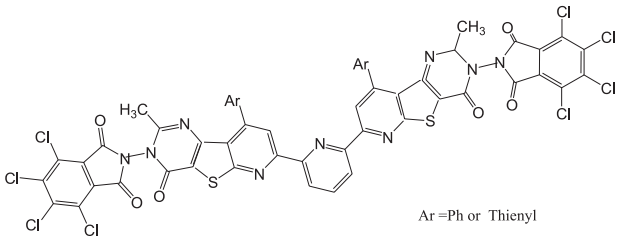


Figure 4: Bis-phthalimide derivatives

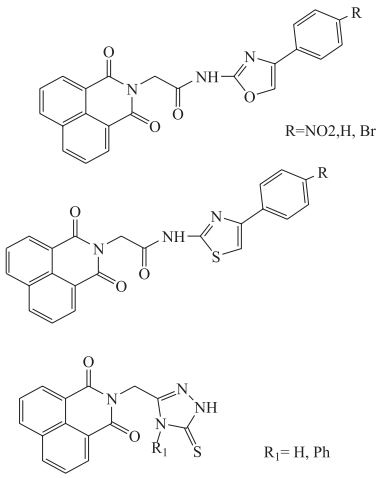


Figure 6: Naphthalimides linked to five-membered heterocyclic rings

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]

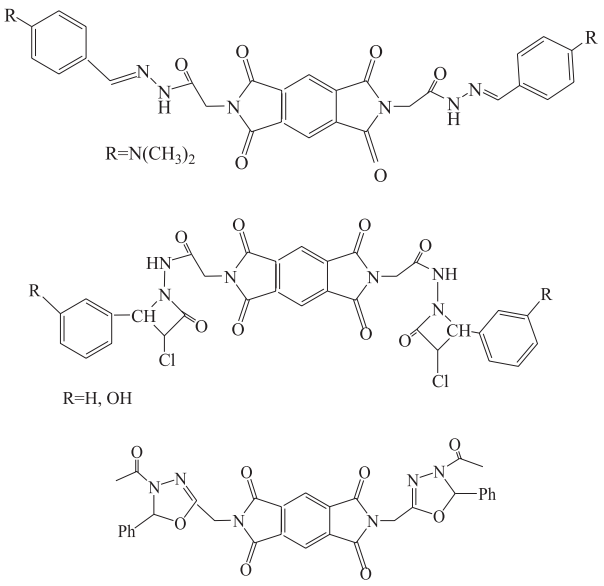


Figure 5: Schiff base, azetidinone, and acetyl oxadiazole derivatives of cyclic imides

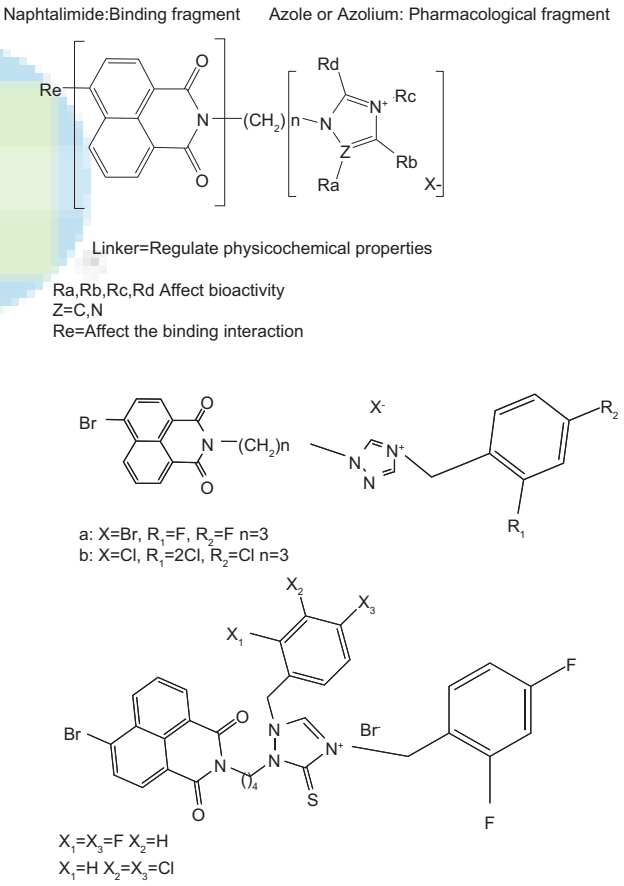


Figure 7: Naphthalimide-azole derivatives

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

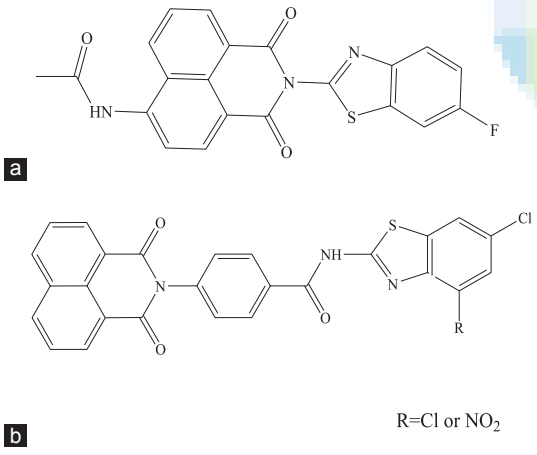


Figure 8: (a) N-[2-(6-Fluoro-benzothiazol-2-yl)-1,3-dioxo-2,3-dihydro-1Hbenzo[de]isoquinolin-6-yl]-acetamide. (b) 4-(N-naphthalimidyl)-N-(substitutedbenzothiazol-2-yl) benz- amide

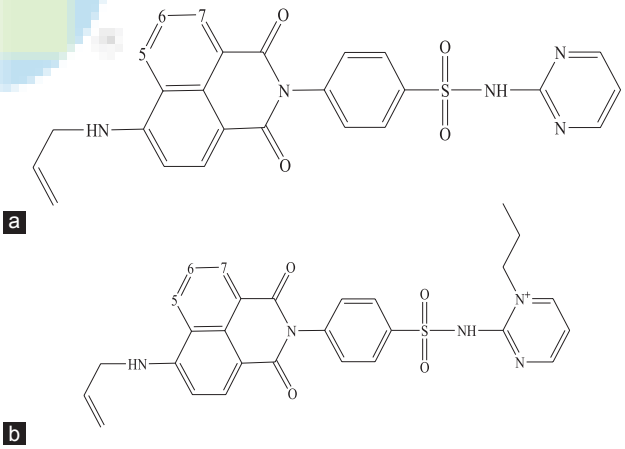


Figure 9: 4-allylamino-N-sulfadiazine-1, 8-naphthalimide (a) its quaterner derivative(b)

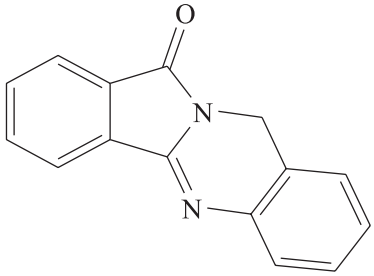


Figure 10: Phthalimide derived from 2-aminobenzylamine

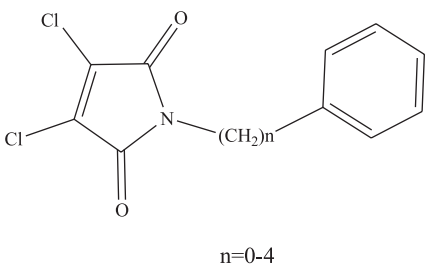


Figure 11: 3,4-Dichloro-N-phenylalkyl-maleimide derivatives

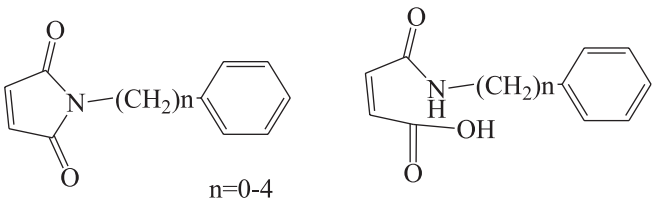
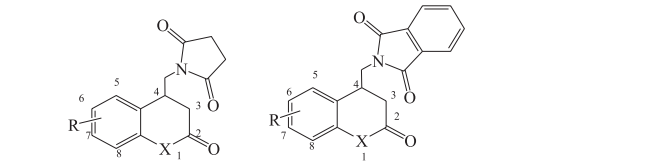


Figure 12: N-Phenyl and N-phenylalkyl maleimide



X=O, R=6-CH_3, 7CH_3, 7,8-diMe, 7-Cl, 6-OMe, **X=NH**, R= H,7-Cl,5,8-diMe,8-Me

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

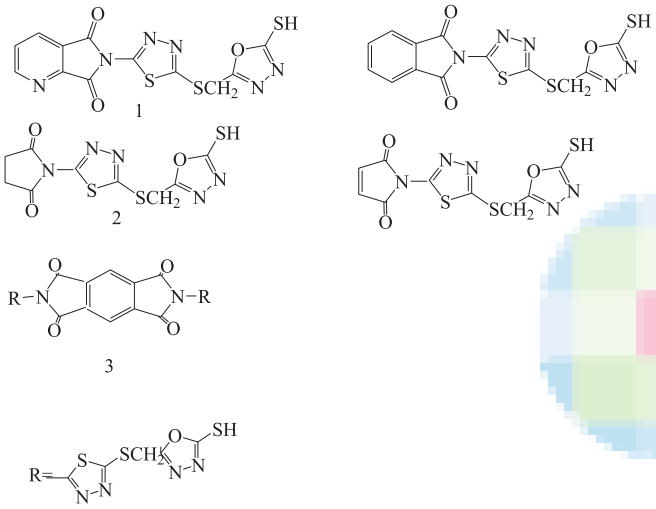
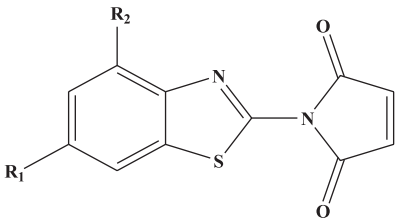
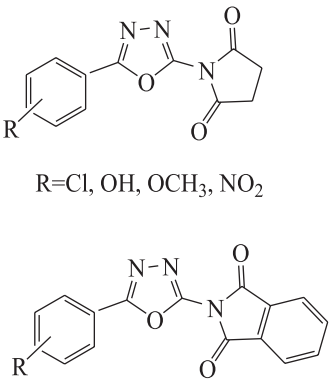


Figure 16: Cyclic imide derivatives containing both 1,3,4-thiadiazole and 1,3,4-oxadiazole cycles



R_1=NO_2 R_2=H,
R_1=NO_2 R_2=Cl
R_1=Cl R2=NO_2

Figure 13: Maleimide-benzothiazole derivatives



R=Cl, OH, OCH_3, NO_2

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

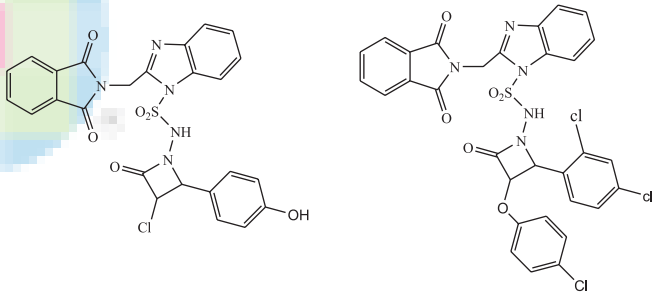


Figure 17: Chloro/p-chlorophenoxy substituted azetidinones bearing phthalimide-benzimidazole scaffold

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.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Patil MM, Rajput SS. Succinimides: Synthesis, reaction, and biological activity. Int J Pharm Sci 2014;6:8-14.
2. Khalil AE, Berghot MA, Gouda MA. Synthesis and study of some new N-substituted imide derivatives as potential antibacterial agents. Chem Paper 2010;64:637-44.
3. Azzawi AM, Al-Obiadi KK. Synthesis and antimicrobial screening of new bis schiff bases and their acetyl oxadiazole azetidinone derivatives from pyromellitic diimid. Int J Res Pharm Chem 2016;6:1-8.
4. Dhivare RS, Rajput SS. Synthesis and antimicrobial activity of five membered cyclic imide derivatives of mono, di and tri substituted aromatic amines and napthyl amine. World J Pharm Res 2015;4:1650-8.
5. de Campos F, Corrêa R, de Souza MM, Yunes RA, Nunes RJ, Cechinel-Filho V, *et al.* Studies on new cyclic imides obtained from aminophenazone with analgesic properties. Potent effects of a 3,4-dichloromaleimide derivative. Arzneimittelforschung 2002;52:455-61.
6. Yunesa JA, Cardoso AA, Yunes RA, Corrêa R, de Campos-Buzzi F, Filho VC, *et al.* Antiproliferative effects of a series of cyclic imides on primary endothelial cells and a leukemia cell line. Z Naturforsch C 2008;63:675-80.
7. Noldin VF, Locatelli C, Cordova CA, Noldin AT, Vanzin F, fae JD, *et al*. Citotoxicity of N-phenylmaleimide derivatives and inhibition of melanoma growth in a preclinical mouse melanoma model. Res Rev J Pharm Sci 2015;4:32-42.
8. Hassanzadeh F, Jafari E, Hakimelahi GH, Khajouei MR, Jalali M, Khodarahmi GA, *et al.* Antibacterial, antifungal and cytotoxic evaluation of some new quinazolinone derivatives. Res Pharm Sci 2012;7:87-94.
9. Wang Y, Zhang J, Li M, Li M, Xie S, Wang C, *et al.* Synthesis and evaluation of novel amonafide-polyamine conjugates as anticancer agents. Chem Biol Drug Des 2017;89:670-80.
10. Hassanzadeh F, Rabbani M, Khodarahmi GA, Fasihi A, Hakimelahi GH, Mohajeri M. Synthesis of phthalimide derivatives and evaluation of their anxiolytic activity. Res Pharm Sci 2007;2:35-41.
11. Sultana K, Khan NH, Shahid K. Synthesis, characterization and *in vitro* antibacterial evaluation of Sn, Sb, and Zn coordination complexes of 2-(2-methoxyphenyl)-1H-isoindole-1, 3 (2h)-dione. Int J Pharm Sci Rev Res 2014;28:1-5.
12. Marulasiddaiah R, Kalkhambkar RG, Kulkarni MV. Synthesis and biological evaluation of cyclic imides with coumarins and azacoumarins. Open J Med Chem 2012;2:89-97.
13. Prado SR, Cechinel-Filho V, Campos-Buzzi F, Corrêa R, Cadena SM, de Oliveira MB, *et al.* Biological evaluation of some selected cyclic imides: Mitochondrial effects and *in vitro* cytotoxicity. Z Naturforsch C 2004;59:663-72.
14. Garad DN, Tanpure SD, Mhaske SB. Radical-mediated dehydrative preparation of cyclic imides using (NH4) 2S2O8-DMSO: Application to the synthesis of vernakalant. Beilstein J Org Chem 2015;11:1008-16.
15. Kuran B, Krawiecka M, Rosolowski S, Kossakowski J, Szymanek K, Mlynarczyk G. Synthesis and biological activity of derivatives of 1-bromo-17-zapentacyclononadeca-2,4,6,9,11,13heksaen -16,18 dione. Curr Issues Pharm Med Sci 2010;23:19-27.
16. Stiz D, Corrêa R, D'Auria FD, Simonetti G, Cechinel-Filho V. Synthesis of cyclic imides (Methylphtalimides, carboxylic acid phtalimides and itaconimides) and evaluation of their antifungal potential. Med Chem 2016;12:647-54.
17. Dhivare RS, Rajput SS. Synthesis and antimicrobial evaluation of some novel bis-heterocyclic chalcones from cyclic imides under microwave irradiation. Chem Sci Rev Lett 2015;4:937-44.
18. Dhivare RS, Rajput SS. Microwave assisted solvent free synthesis and antifungal evaluation of 3, 5-bis-(4-hydroxy-3-methoxybenzylidene)-nphenylpiperidine-2, 6-dionederived from N -phenyl glutarimides. Int J Chem Tech Res 2016;9:325-31.
19. Mallesha L, Karthik CS, Mallu P, Patil V. Synthesis, characterization and antibacterial activity of isoindoline-1,3-dione derivatives. Sop Trans Organic Chem 2014;1:21-8.
20. Sabry NM, Flefel EM, Al-Omar MA, Amr AE. Synthesis and antimicrobial activities of some new synthesized imide and schiff's base derivatives. J Chem 2013;2013:1-6.
21. Kamal A, Satyanarayana M, Devaiah V, Rohini V, Yadav JS, Mullick B, *et al*. Synthesis and biological evaluation of coumarin linked fluoroquinolones, phthalimides and naphthalimides as potential DNA gyrase inhibitors. Lett Drug Des Discov 2006;3:494-502.
22. Guri D, QingPeng W, HuiZhen Z, YiYi Z, Song LV, ChengHe Z. A series of naphthalimide azoles: Design, synthesis and bioactive evaluation as potential antimicrobial agents. Sci China Chem 2013;56:952-69.
23. Al-Majidi SM, Ahmad MR, Kareem Khan A. Synthesis and characterization of novel 1,8-naphthalimide derivatives containing 1,3-oxazoles, 1,3-thiazoles, 1,2,4-triazoles as antimicrobial agents. J Al-Nahrain Univ 2013;16:55-66.
24. Kumari G, Singh RK. Green synthesis, antibacterial activity, and SAR of some novel naphthalimides and allylidenes. Med Chem Res 2015;24:171-81.
25. Hamed AS. Synthesis, characterization, and antibacterial evaluation of new N-phenylnaphthalimides linked to benzothiazole moiety. Al-Anbar J Vet Sci 2014;7:44-9.
26. Shaki H, Khosravi A, Gharanjig K, Mahboubi A. Synthesis and biological properties of novel cationic fluorescent dye. Int J Tec Res Appl 2015;29:103-6.
27. Jafari E, Jarah-Najafabadi NT, Jahanian-Najafabadi A, Poorirani S, Hassanzadeh F, Sadeghian-Rizi S, *et al.* Synthesis and evaluation of antimicrobial activity of cyclic imides derived from phthalic and succinic anhydrides. Res Pharm Sci 2017;12:526-34.

28. Filho VC, Corrêa FC. Aspectos quimicos e potencial terapeutico de imidas ciclicas: Uma revisao d literatura. Quim Nova 2003;26:230-41.
29. Gayoso CW, Lima EO, Souza EL, Filho VC, Trajano VN, Pereira FO, *et al*. Antimicrobial effectiveness of maleimides on fungal strains isolated from onychomycosis. Braz Arch Bio Tech 2006;49:661-4.
30. Sortino M, Cechinel Filho V, Corrêa R, Zacchino S. N-phenyl and N-phenylalkyl-maleimides acting against candida spp.: Time-to-kill, stability, interaction with maleamic acids. Bioorg Med Chem 2008;16:560-8.
31. Al-Azzawi AM, Mahdi SA. Synthesis and evaluation of antimicrobial activity of several new maleimides to benzothiazole moiety. J Baghdad Sci 2013;10:658-72.
32. Al-Azzawi AM, Yaseen HK. Synthesis and characterization of new phthalimides and succinimides substituted with 1,3,4-oxadiazole ring. J Uni anbar Pure Sci 2011;5:1-2.
33. Al-Azzawi AM, Hamd AS. Synthesis, characterization and antimicrobial activity evaluation of new cyclic imides containing 1,3,4 – Thiadiazole and 1,3,4-oxadiazole moities. Int J Res Pharm Chem 2013;3:890-7.
34. Seth M, Sah P. Synthesis and antimicrobial activity of 2 – Azetidinones derived from benzimidazole. J Chem Pharm Res 2012;4:146-53.