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Balasubramanian Narasimhan

MEDICINAL CHEMISTRY OF HETEROCYCLIC/NATURAL COMPOUNDS

PREFACE TO THE BOOK

The idea of writing this book was conceived when my own students, found great difficulty in getting the recent literature regarding the biological profile of heterocycles. The current book is compilation of biological profile of heterocycles and the natural product, gallic acid in the past decade.

I gratefully acknowledge my teachers and students for their continuous inspiration and encouragement. My sincere thanks to my teachers, **Prof.A.S.Dhake,** Principal, SMBT College of Pharmacy, Nasik, India and **Prof.D.C. Sundaravelan,** College of Pharmacy, Sri Ramakrishna Institute of Paramedical Sciences, Coimbatore, India for their blessings.

My sincere thanks to my research scholar, **Mr.Pradeep Kumar**, for his help in the compilation of this book. I also like to thank my family members especially my beloved brother **Mr.B. Venkatesan,** who served as the back bone of my success.

To print what I want to say, requires lot of time, patience and most importantly a healthy family environment. I like to thank my beloved better half **Ms.Sapna** and daughter **Ms.Taniskaa Iyer** for their kind support and sacrifice while writing of this book.

Dr. Narasimhan B

Contents

A comprehensive review on biological activities of 2-azetidinone derivatives

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Abstract: β-Lactam antibiotics are the most commonly used antibiotics. The 2-carbonyl derivative of azetidine is designated as 2-azetidinone or, more commonly, β-lactam. 2-Azetidinone derivatives occupy a pivotal position in modern medicinal chemistry and its biological diversity has attracted the attention of many researchers to explore this skeleton. Apart from its antimicrobial activity, 2-azetidinone have also shown anticancer, antitubercular, anti-inflammatory, anticonvulsant, antidiabetic, antiviral, cholesterol absorption inhibitor, tryptase and chymase inhibitor, vasopressin V1a antagonist's and fatty acid amide hydrolase activities. The present review article focuses on the biological potential of 2-azetidinones.

Keywords: 2-Azetidinones • Chemistry of 2-azetidinone • Biological activities

Contents

1. Introduction

A large number of drugs and biologically relevant molecules contain heterocyclic systems. Often the presence of hetero atoms or groupings imparts preferential specificities in their biological responses. The chemistry and biological study of heterocyclic compounds has been interesting field for a long time due to medicinal and agricultural reasons. The number of heterocyclic derivatives containing nitrogen and sulfur atom possess broad spectrum of biological activities (Patel *et al.,* 2010). Even more than 70 years after the discovery of penicillin, β-lactam antibiotics remain as one of the most important contributions of science to humanity. The β-lactam skeleton is the common structural element of the widely used penicillins, cephalosporins, thienamycine, nocardicins, aztreonam and carumonam (Jarrahpour *et al.,* 2006). The 2-azetidinone derivatives have been reported to possess a wide range of biological activities *i.e.* antimicrobial, anticancer, antitubercular, anti-inflammatory, anticonvulsant, antidiabetic, antiviral, cholesterol absorption inhibitor, tryptase and chymase inhibitor, vasopressin V1a antagonists and fatty acid amide hydrolase.

2. Chemistry of 2-azetidinone

2-azetidinone is commonly known as β-lactam. A β-lactam ring is a four-membered lactam. It is named as such, because the nitrogen atom is attached to the β-carbon relative to the carbonyl. The name lactam is given to cyclic amides. The biological activity of the β -lactam skeleton is generally believed to be associated with the chemical reactivity of their β -lactam ring and on the substituents especially at nitrogen of the 2-azetidinone ring. The oxo group is at 2nd position *i.e.* 2-azetidinone. Substituents may be varied at N-1, C-3 and C-4 position as shown in Figure -1.

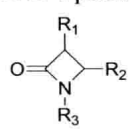


Figure-1

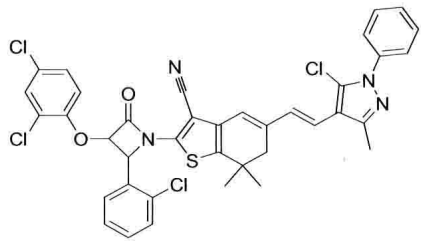
3. Biological activities of 2-azetidinone

Pharmacological interventions of 2-azetidinones derivatives are voluminous but this chapter covers the latest and most relevant ones.

3.1 Antimicrobial activity

Trivedi *et al.* synthesized a novel series of benzo[*b*]thiophene derivatives containing β-lactam nucleus and tested them *in vitro* for their antimicrobial activity

against *Escherichia coli, Pseudomonas aeruginosa, Bacillus subtilis, Staphylococcus aureus, Micrococcus luteus* bacteria and *Trichphyton longifusus, Candida albicans, Microsporum canis, Fusarium solani* fungal strains by the agar well diffusion method. DMSO was used as a control solvent and, chloramphenicol and cefixime as standard drugs. The preliminary *in vitro* biological activities of the title compounds 2-(3-(2,4-dichlorophenoxy)-2-(aryl)-4-oxoazetidin-1-yl)-5-(2-(5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)vinyl)-6,7-dihydro-7,7-dimethylbenzo[b]thiophene-3-carbonitriles revealed that compounds **1** and **2** exhibited significant antibacterial (*Bacillus subtilis* value 18.70 mm and 18.86 mm) and antifungal (*Candida albicans* value 94 mm and 91 mm) activities. The structure–activity relationship (SAR) shows that substitution at the 2-position (ortho) of the phenyl substituent enhanced the antibacterial action of the compounds (Trivedi *et al.*, 2012).



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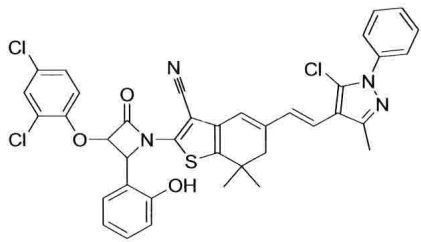


2

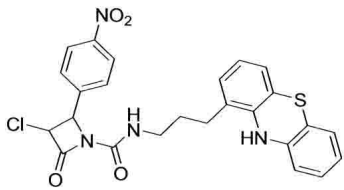
A new series of *N*-[3-(10*H*-phenothiazin-1-yl)propyl]-4-(substituted phenyl)-3-chloro-2-oxo-1-azetidinecarboxamide derivatives were synthesized by Sharma *et al.* and evaluated for its antibacterial, antifungal and antitubercular activities. The antibacterial, antifungal and antitubercular activity of synthesized compounds has been assayed *in vitro* against selected bacteria, *B. subtilis, E. coli, S. aureus, K. pneumoniae* and fungi *A. niger, A. flavus, F. oxisporium, C. albicans* and *M. tuberculosis* (H37Rv strain), respectively. Streptomycin and griseofulvin used as standard for antibacterial and antifungal activity, respectively and for antitubercular activity, isoniazid and rifampicin taken as standards. Nitro derivative (**3**) showed higher activity than chloro or bromo group containing compounds. Results are presented in Table 1. On the basis of SAR, concluded that the activity of compounds depends on electron withdrawing nature of the substituted groups. The sequence of the activity is as follows: NO2 > Cl > Br (Sharma *et al.*, 2012).

Table 1. Antibacterial and antifungal activities (minimum inhibition concentration, μg/mL) of compound **3**

Comp.	Antibacterial activity				Antifungal activity			
	B. subtilis	***E. coli***	***S. aureus***	***K. pneumoniae***	***A. niger***	***A. flavus***	***F. oxisporium***	***C. albicans***
3	3.25	3.25	3.75	3.25	12.50	13.50	12.25	14.50

The MIC values of standard streptomycin for all bacterial strain and griseofulvin for all fungi strain were in the range of 1.25–3.25 and 6.25–12.5 μg/ml, respectively

Patel *et al.* synthesized a series of 2-azetidinone derivatives and studied them against Gram positive bacteria (*Bacillus subtillies* and *Staphycoccus aureus)* and Gram negative bacteria (*Escherichia coli* and *Salmonella typhi*) at a concentration of 50μg/ml by agar cup method. The area of inhibition of zone is measured in percentage. Among the synthesized derivatives, compound **4** [3-chloro-4-(2-hydroxyphenyl)-1-(4-(naphthalen-2-yl)thiazol-2-yl)azetidin-2-one] was the most active one. This compound is equipotent and more potent against Gram positive bacteria *Bacillus subtillis* (85 %) and *Staphycoccus aureus* (70 %) and Gram negative bacteria *Escherichia coli* (70 %) and *Salmonella typhi* (80 %) as compared to the standard drug Penicillin (Patel and Mehta, 2006).



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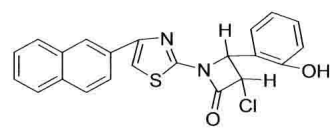
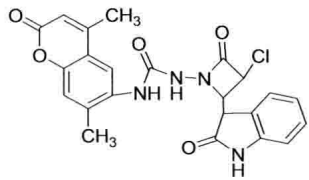


4

Mulwad *et al.* synthesized a series of *N*-[coumarin-6-yl] spiro-indoloazetidin-2-ones/thiazolidin-4-one derivatives and evaluated their antibacterial activity against four bacterial strains viz *Staphycoccus aureus*, *Bacillus subtilis, Pseudomonas aurignosa* and *Escherichia coli* by cup plate method. Among the tested derivatives, 1-(3-chloro-2-oxo-4-(2-oxoindolin-3-yl)azetidin-1-yl)-3-(4,7-dimethyl-2-oxo-2H-chromen-6-yl)urea **(5)** showed the maximum activity against *Staphycoccus aureus* (83%), *Bacillus subtilis* (87 %), *Pseudomonas aurignosa* (87%) and *Escherichia coli* (91%) as compared to standard drug norfloxacin. Rest of the compounds showed moderate to good biological activity (Mulwad *et al.,* 2008).

Shingade *et al.* synthesized a series of 3-chloro-1-{2-[4-(chloroacetyl)piperazin-1-yl]ethyl}-4-arylazetidin-2-one derivatives and screened their antimicrobial activity against the following bacterial strains: *Bacillus subtilis* ATCC 6633, *Staphylococcus epidermidis* ATCC 12228, *Micrococcus luteus* ATCC 4698, *Staphylococcus aureus* ATCC 25923, *Staphylococcus hominis* ATCC 27844, *Bacillus pumilus* ATCC 14884, *Bacillus cereus* ATCC 11778, *Proteus vulgaris* ATCC 13315, *Proteus mirabilis* ATCC 49565, *Salmonella typhi* ATCC 19430, *Klebsiella pneumonia* ATCC 13883, *Escherichia coli* ATCC 25922, *and Pseudomonas aeruginosa* ATCC 10145 and against the following fungal strains: *Aspergillus niger* ATCC 9142, *Aspergillus awamori* ATCC 22342, *Candida albicans* ATCC 10231, *Alternaria alternate* ATCC 66868, *Microsporum canis* ATCC 11622, *Rhizoctonia solani* ATCC 76131, *Trichophyton longiformis* ATCC 22397, *Aspergillus flavus* ATCC 15517, *Fusarium solani* ATCC 38136, and *Trichoderma viride* ATCC 52440. The activity data revealed that the compound **6** having electron releasing substitution at 4th position of the phenyl ring exhibited good antibacterial as well as antifungal activity as compared to the other derivatives. Results are presented in Table 2 (Shingade and Bari, 2013).



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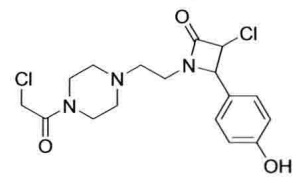


6

Table 2. Antibacterial activity (µg/ml) of most active compound (**6**)

Comp.	***B. subtilis***	***S. epidermidis***	***M. luteus***	***S. aureus***	***S. hominis***	***B. pumilus***	***B. Cereus***
6	9.37	9.37	9.37	9.37	9.37	9.37	9.37
Standard.	2.34	2.34	2.34	2.34	2.34	2.34	2.34
Comp.	***P. vulgaris***	***P. mirabilis***	***S. typhi***	***K. pneumonia***	***E. coli***	***P. aeruginosa***	
6	4.68	9.37	9.37	9.37	4.68	9.37	
Standard.	2.34	2.34	2.34	2.34	2.34	2.34	

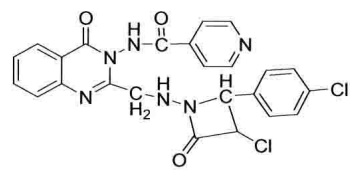
Myangar *et al.* synthesized a series of 2-[(4'-oxo-3'-chloro-2'-phenylazetidin- 1'-ylamino)-methyl]-3-[*N*-isonicotinamide-yl]-quinazolin-4-one clubbed with 2-

azetidinone and the minimal inhibition concentration (MIC) of synthesized compounds was carried out by broth dilution method against bacterial strains such as some Gram-positive bacteria *S. aureus* (MTCC 96), *S. pyogenus* (MTCC 442), *B. subtilis* (MTCC441) and Gram-negative bacteria *E. coli* (MTCC 443), *P. aeruginosa* (MTCC 1688), *Kl. pneumoniae* (MTCC109), *S. typhi* (MTCC 98), and fungal strain such as *C. albicans* (MTCC 227), *A. niger* (MTCC 282), *A. clavatus* (MTCC 1323). From *in vitro* antibacterial activity data, it is confirmed that compounds containing strong electron withdrawing, *i.e.* **7** (4-nitro) exhibited excellent antibacterial activities against the tested Gram-positive microorganisms while compound **8** (4-chloro) exhibited excellent antibacterial activities against tested Gram-negative strains. The evaluation of the *in vitro* antifungal activity demonstrated that compounds **9** (2-chloro) and **10** (4-OCH_3) displayed highest activity against the fungal strains tested. Results are presented in Table 3 (Myangar *et al.,* 2012).

Table 3. Minimal inhibition concentration (µg/ml) of **7**, **8**, **9** and **10**

Comp.	Gram –ve				Gram + ve			Fungi			Antitubercular activity	
	E.c.	*P.a.*	*Klp*	*S.t.*	*S.a.*	*S.p.*	*B.s.*	*C.A.*	*A.N.*	*A.C.*	*M. tuberculosis* (µg/ml)	% Inhibition
7	150	150	200	200	100	125	100	500	>1000	>1000	50	99
8	50	100	100	100	500	500	250	250	1000	1000	62.5	99
9	250	250	100	500	500	500	500	200	200	250	500	98
10	500	500	62.5	500	125	200	250	200	250	200	259	98
Gentamycin	0.05	1	0.05	1	0.25	0.5	-	-	-	-	40	98
Ampicillin	100	100	100	100	250	100	-	-	-	-	0.20	99
Chloramphenicol	50	50	50	50	50	50	-	-	-	-	-	-
Ciprofloxacin	25	25	25	25	50	50	-	-	-	-	-	-
Norfloxacin	10	10	10	10	10	10	-	-	-	-	-	-
Nystatin	-	-	-	-	-	-	-	100	100	100	-	-
Greseofulvin	-	-	-	-	-	-	-	500	100	100	-	-
Rifampicin	-	-	-	-	-	-	-	-	-	-	40	98
Isoniazid	-	-	-	-	-	-	-	-	-	-	0.20	99

7



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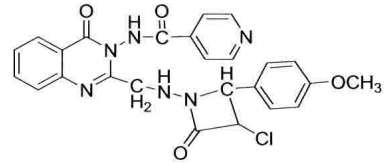
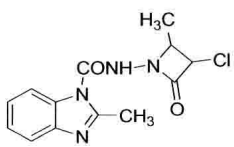


10

A number of *N*-substituted-2-methyl benzimidazole derivatives of 2-azetidione were synthesized by Ansari *et al.* and tested for their antimicrobial activities. Investigation of antimicrobial activity of the compounds was done by disc diffusion method using Gram-positive (*S. aureus, S. mutans and B. subtilis*), Gram-negative (*E. coli, S. typhi and P. aeruginosa*) bacteria and fungi (*C. albicans, A. flavus and A. niger*). Compounds **11** and **12** exhibited appreciable activity against *S. aureus* (38 mm) and *B. subtilis* (28 mm) comparable to reference compound, ampicillin and nalidixic acid. Compound **11** is also most active compound against fungal strain *Candida albicans* (26 mm) as compared to reference drug Amphotericin B (Ansari and Lal, 2009).

A novel series of azetidinones and thaizolidinones were synthesized by Meshram *et al.* and screened for their biological activities against the panel of nine bacterial strains (*E. coli (mixed), B. subtilis, Pseudomonas sp., S.aureus, P.vulageris, Salmonella sp., E. coli* (+ve strain), *Rhodococci, B. stearothermopelus*). It was observed that within the synthesized derivatives, 3-chloro-1-(4-(4-(2-hydroxyphenyl)-2,3,5,6-tetramethyl-1,7-diphenyl-1,2,7,7a-tetrahydro dipyrazolo-[3,4-*b*:4',3'-*e*]-pyridine-8(4*H*,6*H*,8*aH*)-yl)-phenyl)-4-(3-nitrophenyl) azetidin-2-one (**13**) showed good activity against all bacterial strains (Table 4) (Meshram *et al.*, 2011).



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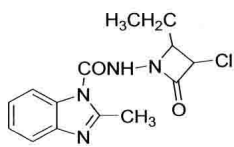

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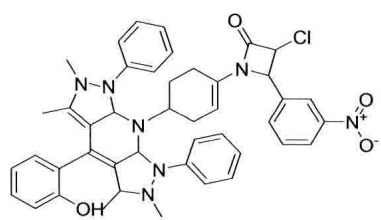

13

Table 4. Biological activities of compound **13**

Comp.	Zone of inhibition in mm								
	E. coli (mixed)	*B. subtilis*	*Pseudomonas sp.*	*S. aureus*	*P. vulageris*	*Salmonella sp.*	*E. coli (-ve)*	*Rhodococci*	*B. stearothermopelus*
13	15	4	10	5	12	12	-	3	4.5
Nystatin	17	6	12	9	17	19.1	11	6	7.2

Ceric *et al.* developed a simple and efficient procedure for the stereoselective synthesis of new azetidinone-isothiazolidinones. New compounds were tested *in vitro* on a panel of selected Gram-positive (*Staphylococcus aureus, Enterococcus faecalis* and *Streptococcus pneumoniae*) and Gram-negative (*Escherichia coli, Haemophilus influenzae* and *Moraxella catarrhalis*) bacterial strains. Compound **14** (trans form), with two aromatic substituents, showed the best inhibitory activity against selected Gram-positive strains with the best growth inhibition of *S. pneumoniae* (MIC 8 μg/mL) as compared to amoxicillin (MIC 4 μg/mL) (Ceric *et al.*, 2010).

Gilani *et al.* synthesized a series of novel thiazolidin-4-ones and azetidin-2-ones. All the synthesized compounds were tested for their *in vitro* antimicrobial activity against one Gram positive bacteria *Staphylococcus aureus* (ATCC-25923), three Gram-negative bacteria *Escherichia coli* (ATCC-25922), *Pseudomonas aeruginosa* (ATCC-27853) and *Klebsiella pneumoniae* (ATCC-700603) and five fungi *Candida albicans* (ATCC- 2091), *Aspergillus niger* (MTCC-281), *Aspergillus flavus* (MTCC-277), *Monascus purpureus* (MTCC 369) and *Penicillium citrinum* (NCIM-768). The investigation of antibacterial and antifungal screening data revealed that all the tested compounds showed moderate to good inhibition at 12.5–200 μg/mL in DMSO. It has been observed that azetidin- 2-one derivatives are found to be more active than thiazolidin-4-ones derivatives against all pathogenic bacterial and fungal strains by using serial plate dilution method as compared to the reference drugs ofloxacin and ketoconazole for bacterial and fungal activity, respectively. The compounds **15** and **16** showed comparatively good activity against all the bacterial strains. The good activity is attributed to the presence of pharmacologically active 2,4-dichlorophenyl (**15**) and phenoxy group (**16**) attached at the fourth position of the β-lactam moiety. Compounds **17** and **18** showed comparatively good activity against all the fungal strains. These compounds contain biologically active acetyl (**17**) and 4-nitrophenyl (**18**) groups attached at the fourth position of β-lactam ring, respectively (Table 5) (Gilani *et al.*, 2012).