IJPSR (2023), Volume 14, Issue 8 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 03 November 2022; received in revised form, 09 January 2023; accepted 05 May 2023; published 01 August 2023

AN UPDATED STATUS OF *ALANINE RACEMASE* INHIBITORS: A REVIEW

P. Rathee [1], S. Saini [1] and A. Khatkar [*2]

SBMN Institute of Pharmaceutical Sciences and Research, B.M.U. [1], Rohtak, Haryana, India
Department of Pharmaceutical Sciences, M. D. University [2], Rohtak - 124001, Haryana, India.

Keywords:

In-situ gel, Acyclovir, Anti-viral, HPMC E50 LV, Pluronic F-127

Correspondence to Author:
Dr. Anurag Khatkar

Associate Professor,
Department of Pharmaceutical Sciences, M. D. University, Rohtak - 124001, Haryana, India.

E-mail: anuragpharmacy@gmail.com

ABSTRACT: Enzyme *Alanine racemase* is well known for performing the predominating role in mycobacterium cell wall synthesis. D-alanine provided by *Alanine racemase* serves as a peptidoglycan precursor, utterly vital for maintaining the growth and integrity of the cell wall. The lipid-rich mycobacterium cell wall is prevalent amidst prokaryotes with immense potential of becoming a therapeutic target for new drug discovery. The imperative role of *Alanine racemase* in mycobacterium cell wall synthesis implies that its inhibition is of utmost priority in dealing with various pathogenic infections. Interference with metabolic processes, lack of specificity, and cellular toxicity caused by several known inhibitors prompted renewed efforts by researchers to discover new and improved inhibitors with better therapeutic indexes. This paper provides an overview of the updated status of reported *Alanine racemase* inhibitors based on shreds of evidence in literature so that more precise inhibitors could be explored, designed, and identified to rationalize the overall drug discovery process, which will be true serendipity for the mankind.

INTRODUCTION: Microorganisms are defined as infectious agents of microscopic size, including bacteria, fungi, protozoan and viruses, responsible for causing various types of infections. To deal with infectious agents, there is an urgent need for an antimicrobial agent that antagonizes the action of infection-causing microbe [1]. The discovery of antimicrobial drugs conferred huge benefits on human health and changed the fate of mankind dramatically. Penicillin was the first antibiotic discovered by Alexander Fleming, which proved to be a boon in curing infectious diseases.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.14(8).3611-18

This article can be accessed online on www.ijpsr.com

DOI link: http://doi.org/10.13040/IJPSR.0975-8232.14(8).3611-18

As a result, antibiotics were regarded as wonder drugs and generally used to manage infection caused by pathogens. However, a large number of people are reliant on antibiotics for the maintenance and improvement of health. Antibiotics have become one of the most commonly prescribed pharmaceutical drugs for curing various infections. This ultimately leads to the development of drug resistance that may often associate with careless use and overconsumption, which is a key issue of concern for the researchers [2].

Now the greatest challenge of the twenty-first century is the development of drug resistance responsible for causing immense human suffering. The resistance problem urges iterated effort to strive for antibacterial agents efficacious against pathogenic bacteria rebellious to commercial antibiotics [3, 4].

This highlights the immediate call for upgraded antibacterial agents with advanced mechanisms for clinical application [5, 6].

Potential Target Sites for the Search of Futuristic Antimicrobials: The treatment of infectious diseases becomes knotty as microbial resistance shoots up at odds with antimicrobial agents. Drugs that destroy microbes prevent their proliferation, and pathogenic actions have dissimilar structures, inconsistent affinity towards the target site, and disparate spectrum of activity with various mechanisms of action. The advancement in bacterial genomics has greatly altered the antimicrobial therapeutic environment, and many potential targets stand by [7, 8].

Attempts have been made to reveal unhackneyed antimicrobial agents, and many researchers have taken steps to disclose ultra-modern drugs acting *via* advanced mechanisms or against the latest target sites from natural sources [9]. The probable targets for searching for new antimicrobial compounds may be focused on the following mechanisms 8, which are depicted in **Fig. 1** as follows.

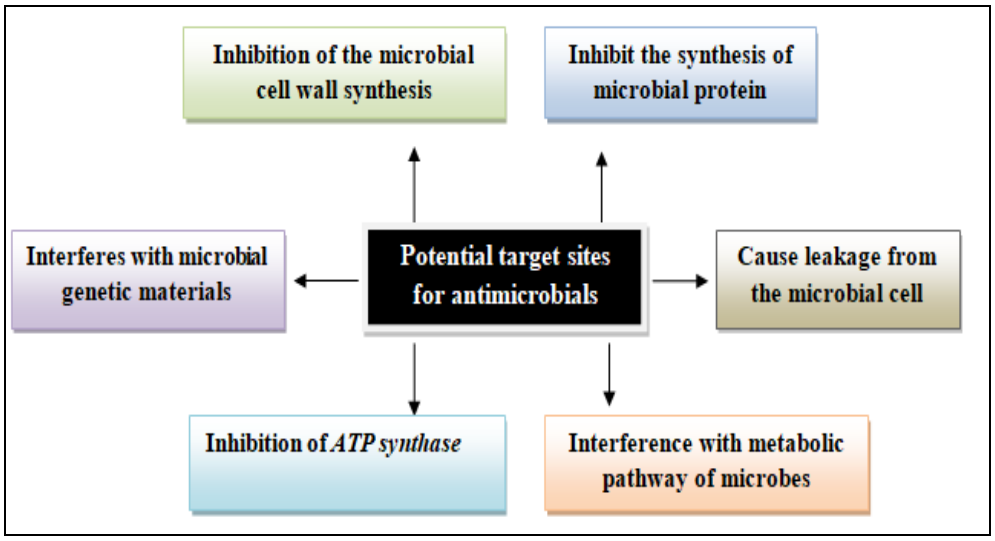


FIG. 1: POTENTIAL TARGET SITES FOR ANTIMICROBIAL AGENTS

Inhibition of Microbial Cell Wall Synthesis: Bacterial cells are surrounded by a cell wall made of a peptidoglycan network constitutes an essential component of the cell wall, serves as a perfect site for drug design since corresponding biosynthetic process are lacking in mammalian hosts. Blockage of bacterial cell wall synthesis is of paramount importance for the action of antimicrobials. The probable target sites [10-13, 8] in cell wall synthesis are summarized in **Fig. 2** may be.

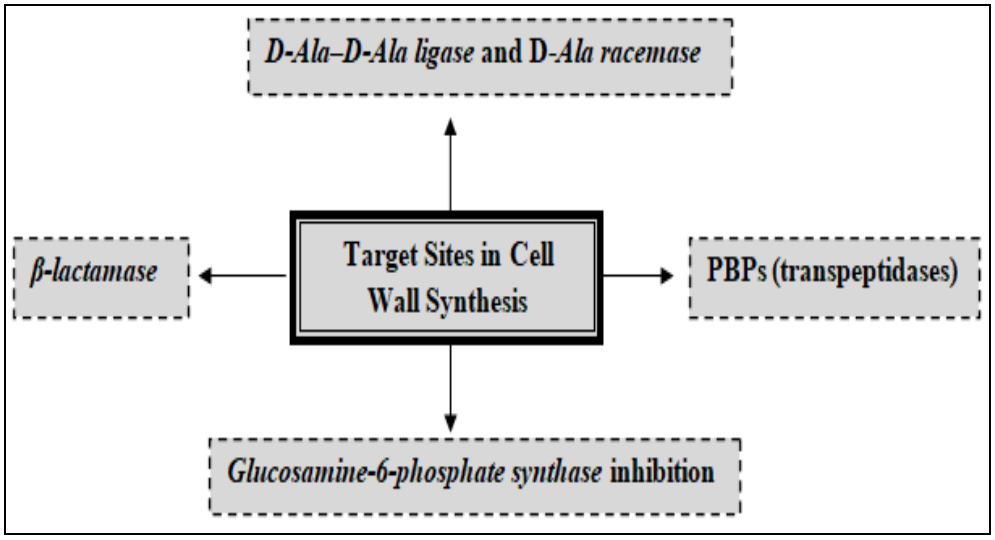
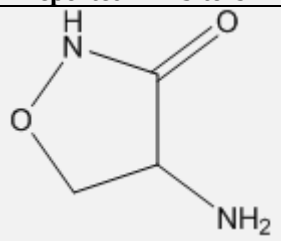
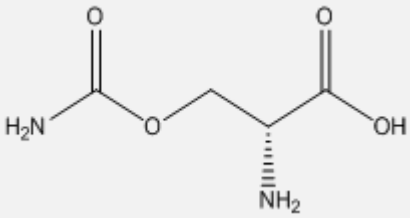
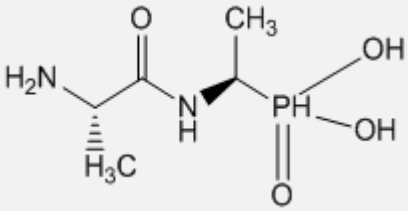
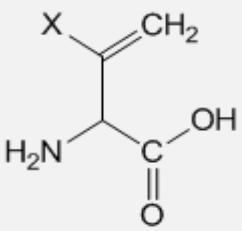
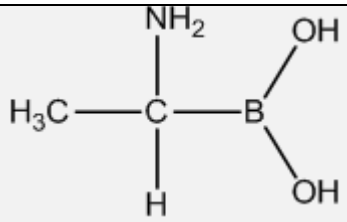
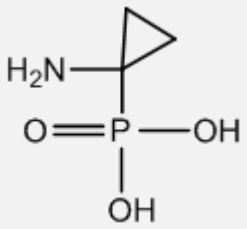
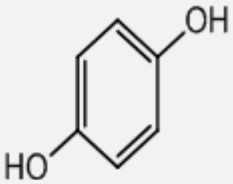
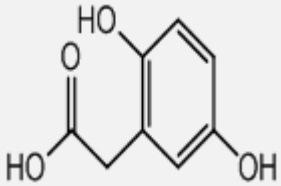
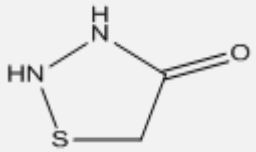
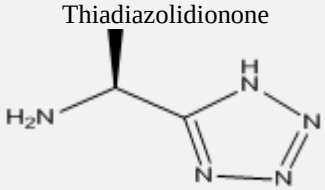
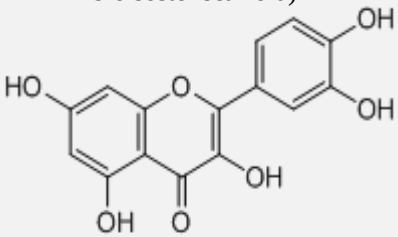
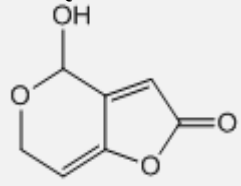


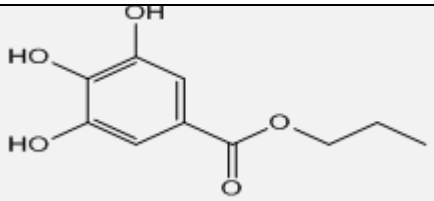
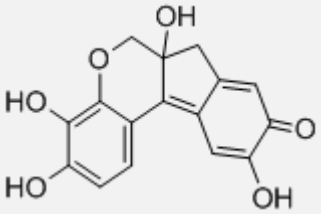
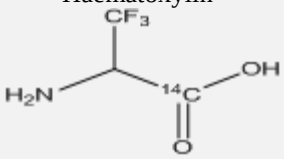
FIG. 2: TARGET SITES IN CELL WALL SYNTHESIS

***Alanine racemase* Promising Target for Antimicrobial agents:** *Alanine racemase* (Alr, EC 5.1.1.1) is a pyridoxal-5- phosphate (PLP) dependent homodimeric enzyme that brings about reversible racemization of L- alanine and D-alanine. This bacterial enzyme execute predominating role in cell wall synthesis of bacteria [14, 15] by providing D- alanine (D-ala) which serve as a key molecule for the biosynthesis of peptidoglycan network of mycobacterial cell wall; hence its inhibition has been reported to be fatal to pathogen viability in the deprivation of D-alanine supplementation [16, 17]. The lipid-rich mycobacterial cell wall is common amidst prokaryotes, making *Alanine racemase* a putative target for the design and development of pharmacologically active drug [18-21]. D-alanine provided by *Alanine racemase* is vital for maintaining cell wall growth and integrity. D-alanine acts as a pivotal precursor for peptidoglycan biosynthesis in bacterial cell walls *via* D-ala-D-ala formed by the enzyme D-ala-D-ala ligase [22]. This manifests how the inhibition of *alanine racemase* is importunate. This paper provides an overview of the updated status of reported Alanine racemase inhibitors based on shreds of literature. The products derived from natural sources have been recognized to play a significant role by being the lead molecules to be selected as potential candidates for drug development. Various researchers have synthesized derivatives of different scaffolds and evaluated them for *Alanine racemase* properties, summarized in **Table 1.**

TABLE 1: REPORTED INHIBITORS OF ENZYME *ALANINE RACEMASE*

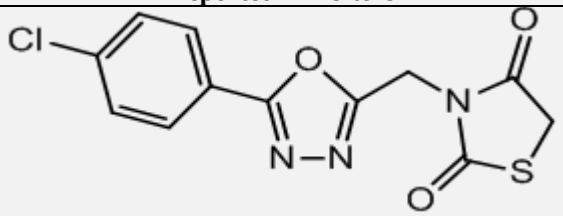
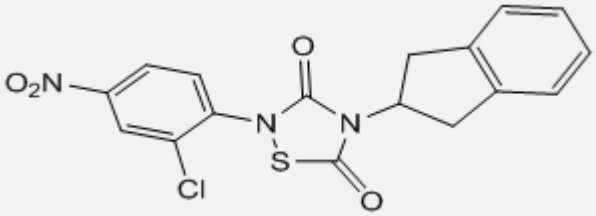
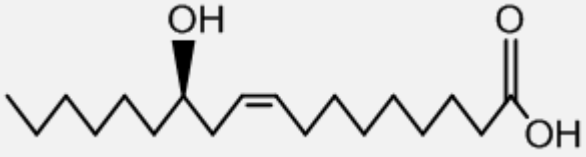
Sr. no.	Reported Inhibitors	Research Findings
1.	 D-cycloserine (DCS)	Sources: *Streptomyces garyphalus* or *S. orchidaceus*. Dissociation followed by subsequent rearrangement of DCS with substituted oxime unriddle *alanine racemase* reactivation in cellular pool. DCS, earlier proved to be an effective competitive inhibitor of enzyme, unfit for *S. aureus* Alr due to the absence of conformation essential for the molecule to bound with substrate region [23-25]. Enzyme kinetics- Km= 4.6 * 10^{-4} M (D-alanine) Km= 9.7 * 10^{-4} M (L-alanine)
2.	 *O*-carbamyl-D-serine	Sources: *Streptococcus faecalis* Determination of primary site of action of *O*-carbamyl-D-serine on Alr on the basis of UDP-NAC muramyl-L-ala-D-glu-L-lys accumulation and in the absence of D-ala-O-carbamyl-D-serine [26, 27] Enzyme kinetics- Km= 4.8 * 10^{-4} M (D-alanine), Km= 6.8 * 10^{-3} M (L-alanine)
3.	 Alafosfalin	Sources : Synthetic L-alanine analog Contains two parts-AlaR inhibitor fosfalin and carrier alanine moiety Based upon alafosfalin formation of external aldimine with PLP cofactor, phosphonate group rendered catalytic residues inaccessible for catalysis. Variable activity against gram positive and negative bacterial strains. Phosphonodipeptide with antibacterial properties [27-29].
4.	 X= Cl, F Halovinylglycine	Sources: synthesized from *N*-(benzyloxycarbonyl)-vinylglycine methyl ester which in turn obtained from methionine. Irreversible inhibitor of Alr obtained from *E.coli.* [27,30] D-chlorovinylglycine: MIC value- 32 µg/mL (*S.aureus*) 64 µg/mL (*S.faecalis*)

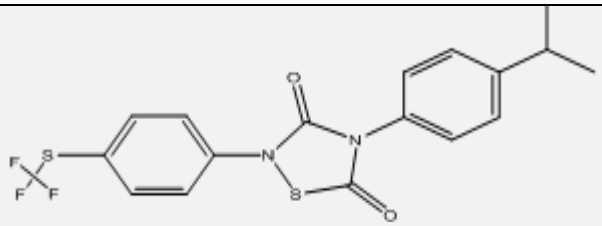
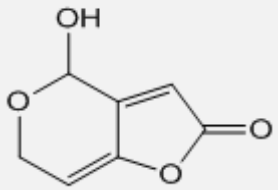
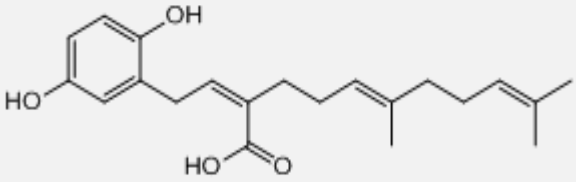
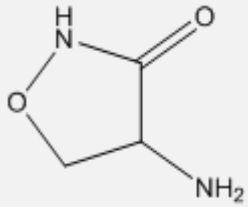
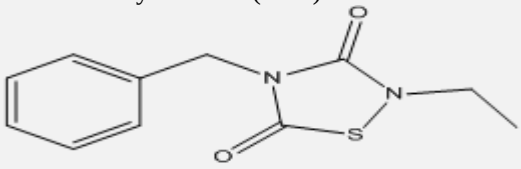
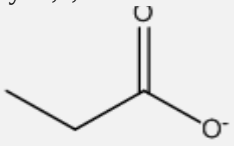
5.	 (1-aminoethyl) boronic acid	Structural analog of alanine Showed time-dependent inhibitory activity towards Alr isolated from *B. stearothermophillus* Competitive inhibitor of D-alanine at D-alanine binding sites [27, 31]
6.	 1-aminocyclopropane phosphonate	Slow but potent inhibitor of Alr obtained from *B. stearothermophillus* strain. Second order rate constant: $<150 M^{-1}S^{-1}$ K_m/K_i ratio: 2000[27,32]
7.	 Hydroquinone	Sources: Blueberry, pears, broccoli, onions, tea, coffee, beer, red wine, wheat and cereals etc. Alr-2 inhibitors found to be active against *Aeromonas hydrophila* IC_{50} value= 11.39 µM MIC value= 25 µg/mL Potent inhibitor of Alr isolated from *Streptococcus iniae* HNM-1[18,33]
8.	 Homogentisic acid	Sources: Aebutus unedo (strawberry-tree), honey, *Xanthomonas campestris* pv. Phaseoll, Yarrownia lipolytica Alr-2 inhibitors found to be active against *Aeromonas hydrophila* IC_{50} value= 0.2 µM MIC value= 1.73 µg/mL Potent inhibitor of Alr isolated from *Streptococcus iniae* HNM-1[18,33,34]
9.	 Thiadiazolidionone	Inhibitory activity against *M. tuberclosis* and *M. smegmatis* Alr with IC_{50} value ranging from <0.03 to 28 µM and 23 to >150 µM respectively [35].
10.	 1-aminoethyltetrazole (Tetrazole containing bioisoster scaffold)	C-terminal 1-aminoethyltetrazole containing di and oligopeptides synthesized by solid phase peptide coupling technique were identified as novel and potential *alanine racemase* inhibitors [29].
11.	 Quercetin	Sources: Apples, berries, broccoli, grapes, citrus fruits, cherries, green tea, coffee, red wine, onions and capers etc. M.W= 302.24 IC_{50} value= 0.33 µM Docking score= -102.489kcal/mol Potent inhibitor of AlaR Effective drug in the treatment of pulmonary tuberculosis [18,36]
12.	 Patulin	Sources: Apple, peach, grapes, fruit juices, several species of Aspergillus, Pencillium and Byssochlamys [18,37-39] M.W= 154.12 IC_{50} value= 14.7(0.27) µM MIC value= 20(0.89) µg/mL

13.	 Propyl gallate	M.W= 212.2 IC_{50} value=8.6(0.5) µM [18]
14.	 Haematoxylin	Sources: Heartwood of the logwood tree Haematoxylum campechianum [40] M.W= 302.29 IC_{50} value=15.6(0.23) µM
15.	 β, β, β-triflouroalanine	Exhibited time-dependent inhibition of against AlaR obtained from *S. typhimurium* and *B. stearothermophillus* [27] K_i values = 65 ±10 and >100mM K_{inact} = 0.08± 0.02 and >2.0min^{-1}

In drug discovery, computer-aided drug design (CADD) offers effective and reliable methodologies for lead optimization, virtual screening, and designing new drug candidates. Molecular docking is a computational drug design approach that provides insights into molecular recognition [41]. In an attempt to conduct wet laboratory experiments smoothly and effectively, this method is useful for predicting the compound architecture, preferred orientation and con-formation (binding pose), interaction, and binding geometry of small ligands into the catalytic pockets of biomolecular targets based on docking score function [42]. Based on literature evidence, molecular docking studies of some reported *Alanine racemase* Inhibitors have been presented in **Table 2.**

TABLE 2: REPORTED MOLECULAR DOCKING-BASED STUDIES OF *ALANINE RACEMASE* INHIBITORS

Sr. no.	Reported Inhibitors	Research Findings
1	 3-((5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl) methyl) thiazolidine-2,4-dione	PDB code: 1XFC Docking software- Schrodinger [43] IC_{50} value =13.1µM Number of H-bonds- 6 Salt bridge interaction- Arg228
2	 2-(2-chloro-4-nitrophenyl)-4-(2,3-di hydro-1H-inden-2-yl)-1,2,4-thiadiazo- lidine-3,5-dione	PDB code: 1XFC IC_{50} value=0.05µM Number of H-bonds-3 π-π stacking- His172, Tyr175 [43]
3	 Ricinoleic acid	PDB code: 3E5P Docking software- AutoDock Docking score: -7.81, Number of H-bonds-5 Amino acid residues – Ser207, Val225, Tyr356, Tyr267. Bioavailability score: 0.56 with high GI absorption [44]

4	 4-[4-(propan-2-yl)phenyl]-2-{4-[(trifluoromethyl) sulfanyl]phenyl}-1,2,4-thiadiazolidine-3,5-dione	PDB code: 1XFC, Resolution: 1.9 Å Docking software- Schrodinger Induced fit docking- Desmond Induced fit docking results revealed that Lys42, Tyr46, Tyr175 and Tyr364 residues were responsible for the stabilization of inhibitor-protein complexes [45]. Binding energy value = -38.88 kcal/mol IC_{50} value=0.17 µM
5	 Patulin	PDB code: 2rjh.1.A Docking software: AutoDock Compound possessed inhibitory activity against *Aeromonas hydrophilla* [18] IC_{50} value=0.62 µM against Caco-2 cells Also exhibits strong cytotoxic effects and reduce the viability of HeLa cells upto 99% at 6.25 µg/ml.
6	 Ganomycin B	PDB code: 2RJG Docking software: AutoDock4 Predicted Xscore Ki = 0.15 µM Compound forms H-bonds with residues Arg280, Tyr274 and prosthetic group PLP. Compound had narrow access to the active site [46]
7	 D-cycloserine (DCS) scaffold  4-benzyl-2-ethyl-1,2,4-thiadiazolidine-3,5-dione	PDB code: 1XFC-A (Mtb-Alr) Software: MODELLER (Homology modelling) Docking software: AutoDock Vina [15] Molecular Volume: 205.03
8	 Propionate	PDB code: 1SFT Program: LigBuilder (to generate phrmacophore model) Non-covalent inhibitor fits only two features of the dynamic pharmacophore model with no excluded volumes, made the compound insufficient in order to be oriented on to the model with excluded volumes [47]

CONCLUSION: The imperative role of *alanine racemase* in mycobacterium cell wall synthesis implies that its inhibition is of utmost priority in dealing with various pathogenic infections. This paper provides an overview of structural information on variously reported inhibitors of *alanine racemase* based on convincing shreds of evidence from literature so that more precise inhibitors could be explored, designed and identified to rationalize the overall drug discovery process which will be true serendipity for the mankind.

Ethics Approval and Consent to Participate: Not applicable.

Consent for Publication: Not applicable.

Funding: None.

ACKNOWLEDGEMENT: We would like to acknowledge and express our obligations to our Dean, Faculty of Pharmaceutical Sciences, Baba Mastnath University, Asthal Bohar, Rohtak and Department of Pharmaceutical Sciences, Maharshi

Dayanand University, Rohtak, for providing necessary help.

CONFLICT OF INTEREST: The authors declare no conflict of interest, financial or otherwise.

REFERENCES:

1. Eichenberger EM and Thaden JT: Epidemiology and mechanisms of resistance of extensively drug resistant Gram-negative bacteria. Antibiotics 2019; 8(2): 37.
2. Culp EJ, Waglechner N, Wang W, Fiebig-Comyn AA, Hsu YP, Koteva K, Sychantha D, Coombes BK, Van Nieuwenhze MS, Brun YV and Wright GD: Evolution-guided discovery of antibiotics that inhibit peptidoglycan remodelling. Nature 2020; 578(7796): 582-7.
3. Dadgostar P: Antimicrobial resistance: implications and costs. Infection and drug resistance. 2019; 12:3903.
4. Belete TM: Novel targets to develop new antibacterial agents and novel alternatives to antibacterial agents. Hum. Microbiome J 2019; 11(2): 100052.
5. Tassoni R, van der Aart LT, Ubbink M, Van Wezel GP and Pannu NS: Structural and functional characterization of the alanine racemase from Streptomyces coelicolor A3 (2). Biochem Biophys Res Commun 2017; 483(1): 122-8.
6. Breijyeh Z, Jubeh B, and Karaman R: Resistance of gram-negative bacteria to current antibacterial agents and approaches to resolve it. Molecules 2020; 25(6): 1340.
7. Paul RK, Dutta D, Chakraborty D, Nayak A, Dutta PK, and Nag M: Antimicrobial agents from natural sources: An overview. Adv Pharm J 2019; 4(2): 41-51.
8. Prestinaci F, Pezzotti P and Pantosti A: Antimicrobial resistance: a global multifaceted phenomenon. Pathog. Glob. Health 2015; 109(7): 309–318.
9. Monserrat-Martinez A, Gambin Y and Sierecki E: Thinking outside the bug: molecular targets and strategies to overcome antibiotic resistance. International Journal of Molecular Sciences 2019; 20(6): 1255.
10. Theuretzbacher U, Bush K, Harbarth S, Paul M, Rex JH, Tacconelli E and Thwaites GE: Critical analysis of antibacterial agents in clinical development. Nature Reviews Microbiology 2020; 18(5): 286-98.
11. Shahi G, Kumar M, Skwarecki AS, Edmondson M, Banerjee A, Usher J, Gow NA, Milewski S and Prasad R: Fluconazole resistant *Candida auris* clinical isolates have increased levels of cell wall chitin and increased susceptibility to a glucosamine-6-phosphate synthase inhibitor. The Cell Surface 2022; 8: 100076.
12. Abrahams KA and Besra GS: Mycobacterial cell wall biosynthesis: a multifaceted antibiotic target. Parasitology 2018; 145(2): 116-33.
13. Khameneh B, Iranshahy M, Soheili V and Fazly Bazzaz BS: Review on plant antimicrobials: a mechanistic viewpoint. Antimicrobial Resistance & Infection Control 2019; 8(1): 1-28.
14. Tassoni R, van der Aart LT, Ubbink M, Van Wezel GP and Pannu NS: Structural and functional characterization of the alanine racemase from Streptomyces coelicolor A3 (2). Biochem Biophys Res Commun 2017; 483(1): 122-8.
15. Jiang Q, He X, Shui Y, Lyu X, Wang L, Xu L, Chen Z, Zou L, Zhou X, Cheng L and Li M: D-Alanine metabolic pathway, a potential target for antibacterial drug designing in Enterococcus faecalis. Microbial Pathogenesis 2021; 158:105078.
16. Muhammad M, Li Y, Gong S, Shi Y, Ju J, Zhao B and Liu D: Purification, Characterization and Inhibition of Alanine Racemase from a Pathogenic Strain of Streptococcus iniae. Polish J Micro 2019; 68(3): 331–341.
17. Cook R, Barnhart R and Majumdar S: Effect of pH on the kinetics of alanine racemase from Mycobacterium tuberculosis. Journal of Young Investigators 2019; 36(1).
18. Wang Y, Yang C, Xue W, Zhang T, Liu X, Ju J, Zhao B, Liu D: Selection and characterization of alanine racemase inhibitors against *Aeromonas hydrophila*. BMC Microbiol 2017; 17(1): 122.
19. Kawakami R, Ohshida T, Sakuraba H and Ohshima T: A novel plp dependent alanine/serine racemase from the hyperthermophilic archaeon *Pyrococcus horikoshii* ot-3. Front Microbiol 2018; 9: 1481.
20. Van Wieren A, Durrant J and Majumdar S: Computational and experimental analyses of alanine racemase suggest new avenues for developing allosteric small-molecule antibiotics. bioRxiv 2022; 1.
21. Dong H, Han Q, Guo Y, Ju J, Wang S, Yuan C, Long W, He X, Xu S and Li S: Enzymatic characterization and crystal structure of biosynthetic alanine racemase from *Pseudomonas aeruginosa* PAO1. Biochemical and Biophysical Research Communica 2018; 503(4): 2319-25.
22. Marshall DD, Halouska S, Zinniel DK, Fenton RJ, Kenealy K, Chahal HK and Powers R: Assessment of metabolic changes in Mycobacterium smegmatis wild-type and alr mutant strains: evidence of a new pathway of d-alanine biosynthesis. J Proteo Res 2017; 16(3): 1270-79.
23. Evangelopoulos D, Prosser GA, Rodgers A, Dagg BM, Khatri B, Ho MM, Gutierrez MG, Cortes T and de Carvalho LP: Comparative fitness analysis of D-cycloserine resistant mutants reveals both fitness-neutral and high-fitness cost genotypes. Nature Communications 2019; 10(1): 1-1.
24. de Chiara C, Homšak M, Prosser GA: D-Cycloserine destruction by alanine racemase and the limit of irreversible inhibition. Nat Chem Biol 2020; 16: 686–694.
25. Deshpande D, Alffenaar JW, Köser CU, Dheda K, Chapagain ML, Simbar N, Schön T, Sturkenboom MG, McIlleron H, Lee PS and Koeuth T: d-Cycloserine pharmacokinetics/pharmacodynamics, susceptibility, and dosing implications in multidrug-resistant tuberculosis: a Faustian deal. Clinical Infecti Dise 2018; 67(3): 308-16.
26. Jayaram U and Azam MA: Computational Molecular Modeling Studies of Some Mycobacterium Tuberculosis Alanine Racemase Inhibitors. Acta Chimica Slovenica. 2022.
27. Azam MA and Jayaram U: Inhibitors of alanine racemase enzyme: a review. J Enzyme Inhib Med Chem 2016; 31(4): 517-526,
28. Nowak MG, Skwarecki AS and Milewska MJ: Amino acid based antimicrobial agents–synthesis and properties. Chem Med Chem 2021; 16(23): 3513-44.
29. Kondacs LA, Orenga S, Anderson RJ, Emma CL, Marrs ECL, Perry JD and Gray M: C-Terminal 1-Aminoethyltetrazole-Containing Oligopeptides as Novel Alanine Racemase Inhibitors. Molecul 2020; 25(6): 1315.
30. Kim WE, Patel A, Hur GH, Tufar P, Wuo MG, McCammon JA and Burkart MD: Mechanistic probes for the epimerization domain of nonribosomal peptide synthetases. Chem Bio Chem 2019; 20(2): 147-52.
31. Nowak MG, Skwarecki AS and Milewska MJ: Amino acid based antimicrobial agents–synthesis and properties. Chem Med Chem 2021; 16(23): 3513-44.
32. Muhammad M, Li Y, Gong S, Shi Y, Ju J, Zhao B and Liu D: Cloning, Biochemical Characterization and Inhibition of *Alanine racemase* from Streptococcus iniae. BioRxiv 2019; 611251.

33. Muhammad M, Li Y, Gong S, Shi Y, Ju J, Zhao B and Liu D: Purification, Characterization and Inhibition of Alanine Racemase from a Pathogenic Strain of. Polish Journal of Microbiology 2019; 68(3): 331-41.
34. Lloyd MD, Yevglevskis M, Nathubhai A, James TD, Threadgill MD and Woodman TJ: Racemases and epimerases operating through a 1, 1-proton transfer mechanism: reactivity, mechanism and inhibition. Chemical Society Reviews 2021; 50(10): 5952-84.
35. Harshaw NS, Meyer MD, Stella NA, Lehner KM, Kowalski RP and Shanks RM: The short chain fatty acid propionic acid activates the Rcs stress response system partially through inhibition of D-alanine racemase. bioRxiv 2022; 1.
36. Rahman M, Kaiser F, Jamshidi S, Freitas Monteiro M, Rahman KM, Mullany P and Roberts AP: Integron gene cassettes harboring novel variants of d-alanine-d-alanine ligase confer high-level resistance to d-cycloserine. Scientific Reports 2020; 10(1): 1-6.
37. Mahato DK, Kamle M, Sharma B, Pandhi S, Devi S, Dhawan K, Selvakumar R, Mishra D, Kumar A, Arora S and Singh NA: Patulin in food: A mycotoxin concern for human health and its management strategies. Toxicon 2021; 198: 12-23.
38. Zbyňovská K, Petruška P, Kalafová A, Capcarová M: Patulin-a Contaminant of Food and Feed: a review, Acta Fytotechnica Zootechnica 2016; 19(2): 64-67.
39. Zhong L, Carere J, Zhaoxin L, Fengxia L and Zhou T: Patulin in Apples and Apple-Based Food Products: The Burdens and the Mitigation Strategies 2018; 10(11): 475.
40. Ali F and Orchard GE: Hematoxylin in history – the heritage of histology. JAMA Dermatol 2017; 153(3): 328.
41. Jakhar R, Dangi M, Khichi A and Chhillar AK: Relevance of molecular docking studies in drug designing. Current Bioinformatics 2020; 15(4): 270-8.
42. Fan J, Fu A and Zhang L: Progress in molecular docking. Quantitative Biol 2019; 7(2): 83-9.
43. Jayaram U and Azam MA: Computational Molecular Modeling Studies of Some Mycobacterium Tuberculosis Alanine Racemase Inhibitors. Acta Chim Slov 2022; 69: 393–404.
44. Kumari R, Mishra RC, Yadav S and Yadav JP: Exploring Molecular Docking Studies of Alanine Racemase Inhibitors from *Elettaria cardamomum*. Curr Enzyme Inhib 2019; 15(2): 91-102.
45. Azam MA and Jayaram U: Induced fit docking, free energy calculation and molecular dynamics studies on Mycobacterium tuberculosis alanine racemase inhibitor. Mol Simulation 2018; 44(5): 424-32.
46. Bhardwaj SV: Antimicrobial Activity and Molecular Docking Studies of a Sesquiterpenoid Alcohol from Leaf Solvent Extracts of *Juniperus communis* L. International Journal of Green Pharmacy (IJGP) 2018; 12(02).
47. Harshaw NS, Meyer MD, Stella NA, Lehner KM, Kowalski RP and Shanks RM: The short chain fatty acid propionic acid activates the Rcs stress response system partially through inhibition of D-alanine racemase. bioRxiv 2022.

How to cite this article:
Rathee P, Saini S and Khatkar A: An updated status of alanine racemase inhibitors: a review. Int J Pharm Sci & Res 2023; 14(8): 3611-18. doi: 10.13040/IJPSR.0975-8232.14(8).3611-18.