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

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

Faculty of Pharmaceutical Sciences, B. M. University [1], Rohtak - 124001, Haryana, India.
Department of Pharmaceutical Sciences, M. D. University [2], Rohtak - 124001, Haryana, India.

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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 a 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 uttermost priority in order to deal 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. In an attempt 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. As a result, antibiotics were regarded as wonder drugs and used generally for managing 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].

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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 antibacterial agents efficacious against pathogenic bacteria rebellious to commercial antibiotics [3, 4].

This highlights the immediate call for upgraded antibacterial agents with an advanced mechanism 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 target site, and disparate spectrum of activity with various mechanism 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 for the revelation of unhackneyed antimicrobial agents, and many researchers have taken initiative steps intended to disclose ultra-modern drugs acting *via* advanced mechanisms or against the latest target sites from natural sources [9]. The probable targets for the search for new antimicrobial compounds may be focused on the following mechanisms [8] are depicted in **Fig. 1** as follows.

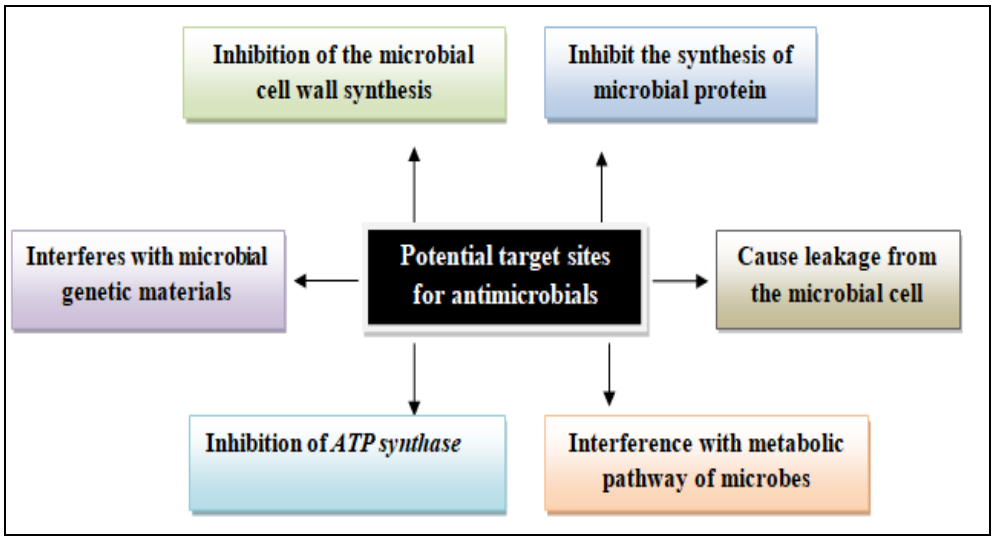


FIG. 1: POTENTIAL TARGET SITES FOR ANTIMICROBIAL AGENTS

Inhibition of Microbial Cell wall Synthesis: Bacterial cells are surrounded by a cell wall made of 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.

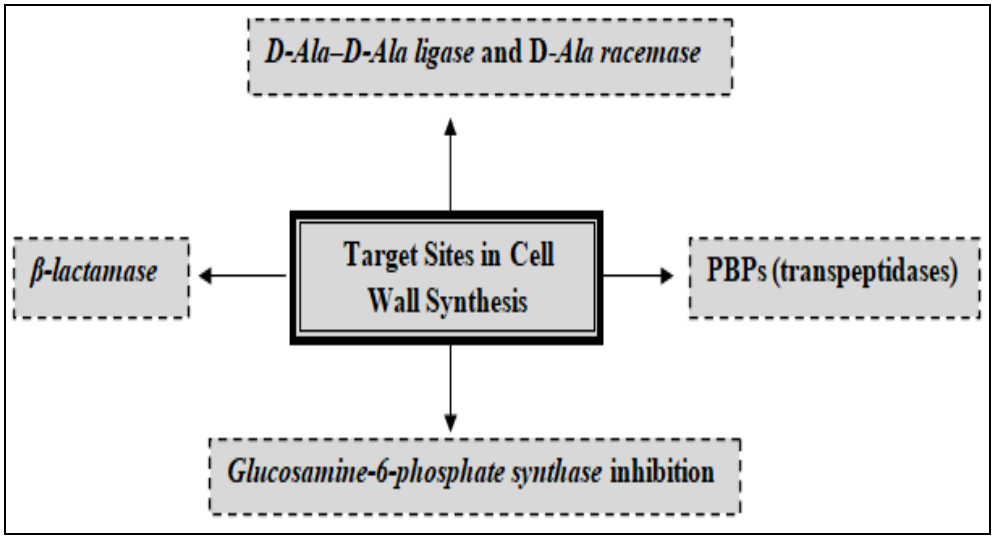
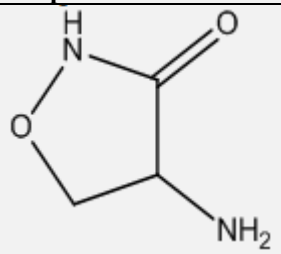
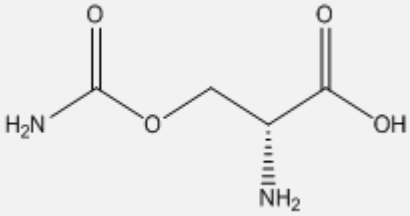
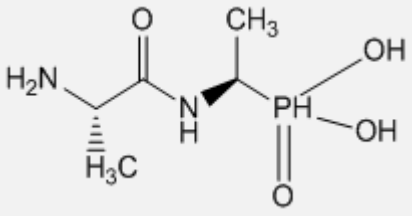
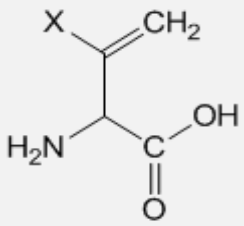
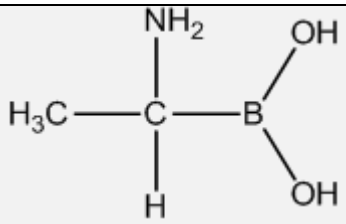
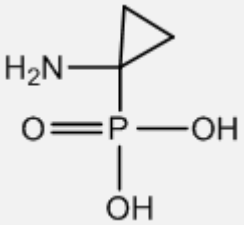
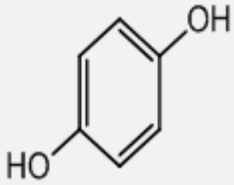
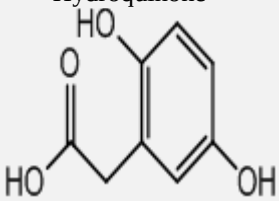
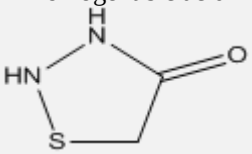
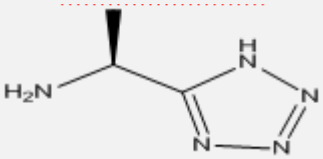
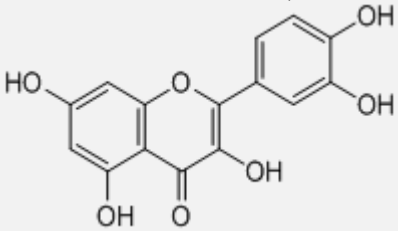
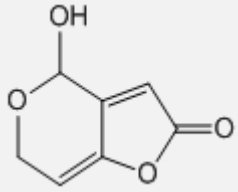


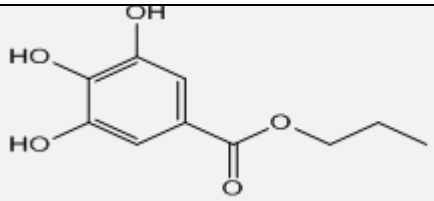
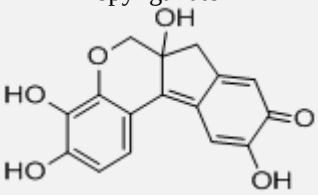
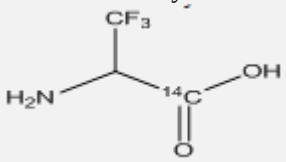
FIG. 2: TARGET SITES IN CELL WALL SYNTHESIS

***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 bring 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 drugs [18-21]. D-alanine provided by *Alanine racemase* is utterly vital for maintaining the growth and integrity of the cell wall. D-alanine acts as a pivotal precursor for peptidoglycan biosynthesis in bacterial cell walls *via* D-ala-D-ala formed by enzyme D-ala-D-ala ligase [22]. This manifests how the inhibition of *alanine racemase* is important. In this paper, an overview on the updated status of reported *Alanine racemase* inhibitors has been provided 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*

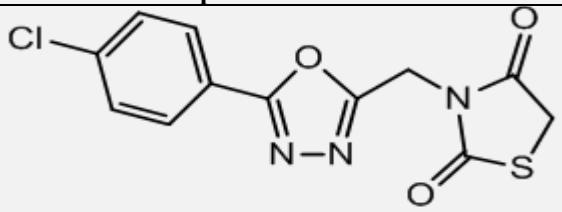
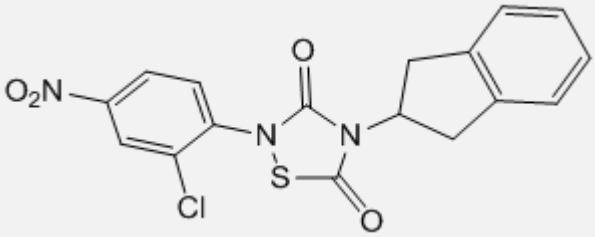
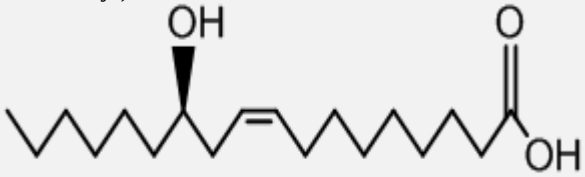
Sr. no.	Reported Inhibitors	Research Findings
1.	 D-cycloserine (DCS)	Sources: *Streptomyces garyphalus* or *S. orchidaceus*. Dissociation followed by subsequent rearrangement of DCS with substituted oxime unriddle *alanine racemase* reactivation in cellular pool. DCS, earlier proved to be an effective competitive inhibitor of enzyme, unfit for *S. aureus* Alr due to 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*)

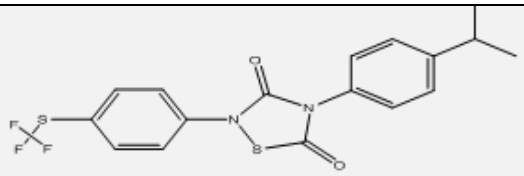
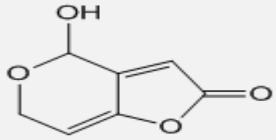
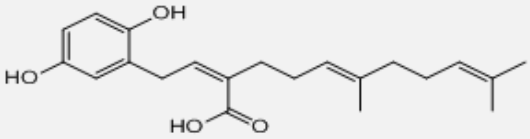
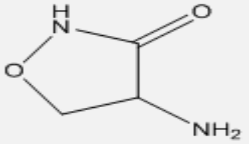
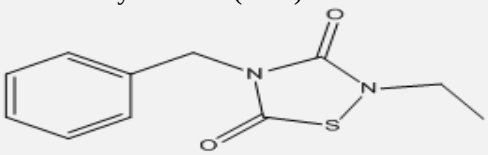
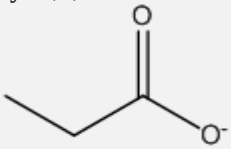
5.	 (1-aminoethyl) boronic acid	Structural analog of alanine Showed time-dependent inhibitory activity towards Alr isolated from *B. stearothermophillus* Competitive inhibitor of D-alanine at D-alanine binding sites [27, 31]
6.	 1-aminocyclopropane phosphonate	Slow but potent inhibitor of Alr obtained from *B. stearothermophillus* strain. Second order rate constant: $<150M^{-1}S^{-1}$ 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 of new drug candidates. Molecular docking is a computational drug design approach used for providing 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 the biomolecular target 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.

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