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# Enoyl Acyl Carrier Protein Reductase Inhibitors: An Emerging Target

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**Abstract :** The evolution of drug resistant strains of important human pathogens has created an urgent necessity to find new targets and novel anti-infective agents such as anti-mycobacterial, anti-malarial and anti-fungal agents. Enoyl acyl carrier protein reductase is one of the most upcoming powerful target. Enoyl ACP reductase enzyme plays most determinant role in Fatty acid synthase II (FAS II) cycle. This review deals with the development made in the design of enoyl acyl carrier protein reductase inhibitors and the role played by 3D structure of the enzyme in drug design process. This review summarized on the recent advances made in the current understanding of enoyl acyl carrier protein reductase (ENR). The review focuses its potential as a promising drug target for future drug development against most anti-infective diseases.

**Keywords:** Fatty acid synthesis, Enoyl acyl carrier protein reducatse, Anti-tubercular, Anti-malarial, Anti-fungal.

## Introduction:

Bacterial fatty acid biosynthesis is an essential process that supplies precursors for the assembly of important cellular components including phospholipids, lipoproteins, lipopolysaccharides, mycolic acids and cell envelope. It is a multifunctional enzyme system that catalyzes the formation of fatty acids from acetyl-CoA, malonyl- CoA and NADPH and plays a central role in lipid biosynthesis.[(1)]Fatty acid synthesis is a vital process for both prokaryotic and eukaryotic cell, two distinct enzymatic systems are existing, i.e. FAS I in animal and fungi, and FAS II in plants and bacteria. FAS-I is typical for eukaryotes. FAS II is a complex system of functionally dependent separate enzyme where each catalytic enzyme function is conducted by a standalone enzyme. FAS II is typical for prokaryotic cells namely mycobacterium, corny bacteria, in these microorganism FAS I produces fatty acid up to length of palmitic acid ($C_{16}$) which then carry forward to FAS II to produce longer and structurally more diverse fatty acid. where FAS II system is a useful potential target for anti-infective drugs.[(2)]Although this final step in the fatty acid biosynthesis pathway is conserved amongst diverse organism the enzymes involved in this step differ substantially in the terms of structure and organization for instance in human cells, a large multifunctional protein. FAS I conducts all enzymatic activities in the pathway,



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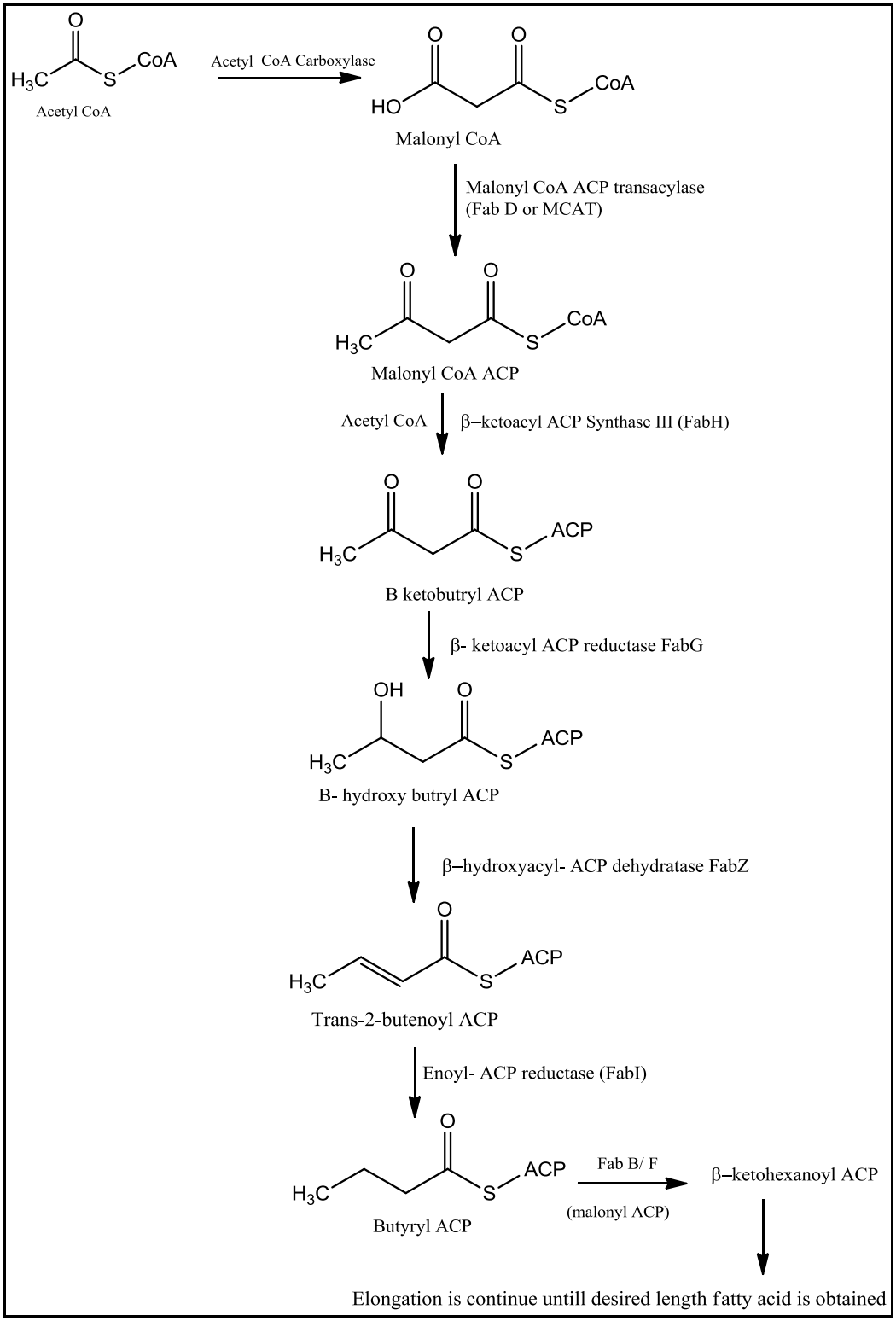
however in bacteria and protozoa monofunctional protein carry out each reaction separately (i.e. FAS II) therefore bacterial and protozoal ENRs are considered as good drug target because they are essential for micro-organism survival and can be targeted selected without harming the human FAS I protein.[3] The difference in organism between prokaryotes and eukaryotes makes bacterial fatty acid biosynthetic enzymatic pathway more potential and more selective for anti-infective targets. The enzyme of the fatty acid biosynthesis pathway (FAS II) in bacteria represent interesting target for antimicrobial drug design because their mammalian counterpart FAS I use a single multifunctional enzyme with low sequence similarity. This provides an opportunity to selective target interfering with mammalian enzymes. [4]

**Diagrammatic representation of fatty acid synthase cycle.**



**Enoyl ACYL Carrier Protein Reductase (ENRs):**

Enoyl- acyl carrier protein reductase (ENRs) are a group of enzymes that catalyzes the last step in the elongation of fatty acid biosynthesis cycle, it is a rate controlling enzyme in the FAS II pathway, which makes an ideal target among the other FAS II enzymes namely reduction of the substrate enoyl thioester (enoyl ACP) to an acyl moiety (acyl- ACP) which is catalyzed by Enoyl ACP reductase. Tyr-156 and Lys-163 amino acid considered crucial for fatty acid elongation to the assistance of bound NADH or NADPH as a hybrids source to accomplish the reduction. [(3)] Due to its essential role in metabolism and sequence conservation across many bacterial species. ENRs is promising target for anti-microbial drug discovery. It is a member of short chain alcohol dehydrogenase/ reductase (SDR) super family characterized by a catalytic trial of key tyrosine, lysine and serine residue that reduce a double bond in a enoyl substrate with $NAD^+$ / $NADP^+$ as an acceptor a key step in bacterial production of fatty acids. The systematic name of this enzyme class is acyl – [acyl carrier- protein] NADP+ oxidoreductase.[(3)]

**Mechanism of Action of ACP Reductase**

The mechanism of the reduction of ENRs is similar for most bacterial strains, for instance in *E. coli.* ENRs catalyze the last step of fatty acid elongation cycle in which FabI uses NADH to reduce the $C_2$-$C_3$ carbon-carbon double bond generated by the prior dehydratase enzymes to complete the synthesis of the acyl chain. Fatty acid is elongated by two carbons and that malonyl ACP is the source of this two-carbon fragment. The reduction mechanism involves the transfer of a hydride to the $C_3$ carbon of the $C_2$-$C_3$ double bond and the development of an enolate anion on the $C_1$ carbonyl oxygen, which accepts a proton from hydroxyl of the tyrosine 156. Two conserved residues of tyrosine (Tyr-156) and lysine (Lys-163) are crucial for catalytic activity. The resulting enol then undergoes tautomerize to the final product. The key lysine 163 plays the primary role to stabilize the binding of the cofactor through hydrogen bond interactions with the hydroxyl groups on the nicotinamide ribose. [(5)]The double bond reduction occurs by conjugate the reaction addition of a hydride ion from NADH (or NADPH) to C3of trans-2-butenoyl-ACP. The hydrogen added to $C_3$ is the pro-shydrogen of the coenzyme. The Tyr156 proton is replenished by aproton relay system through Lys163 and the hydroxyls of the coenzyme ribose moiety plus a chain of water molecules that provide access to solvent. [(5)]

**Superfamily of Enoyl ACYL Carrier Protein Reductase:**

Enoyl acyl carrier protein reductases can be classified into short chain dehydrogenase ENR [(eg- FabI) InhA, FabL, and FabV] which are NADH or NADPH containing protein and secondly non- short chain dehydrogenation ENRs (eg- FabK) which are FMN containing protein.

**1) SDR Family:**

The crystal structures or SDR superfamily ENRs are available, they are as follows *E. coli* (FabI), *Mycobacterium tuberculosis* (InhA,) indicate that all homo tetramers are essentially same structure. The former type of ENRs enzymes is the dominant form in microorganisms and is known to have a conserved tried in the catalytic site a tyrosine residue which acts as a proton donor, a lysine residue which has no direct role in catalysis but rather serves in stabilizing the binding of the co-factor and finally a phenylalanine or tyrosine residue located near the nicotinamide ring of NAD+ which guides the adoption of U shaped confirmatory by the fatty acyl substrate with the rise of resistance to existing therapies the search for new anti-bacterial and anti-malarial agents, it's become increasingly urgent hence ENRs are potentially attractive targets for new chemotherapeutics agents.[(6)]

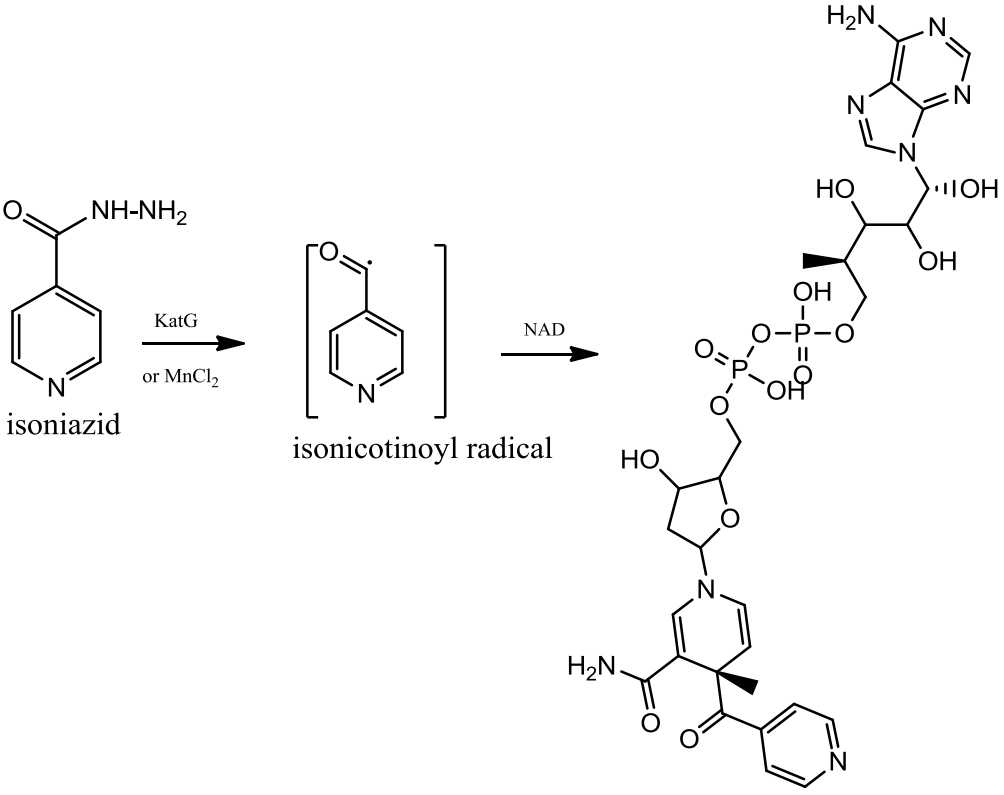
**2) MDR Family:**

ENRs are mostly present in bacteria and plants of the SDR superfamily are probably the dominate form in biology other protein catalyze this reaction. The most popular eg- Streptococcus pneumonia FabK. In this enzyme NADH is the reductant but acts indirectly by reducing the tightly bound flavin cofactor the reduced flavin then reduced the double bond unlike the SDR enzyme, FabK has a TIM barrel structure and is an FMN dependent oxidoreductase of NAD(P)H dependent family.[(6)]

**Synthetic Inhibitors of Enoyl ACYL Carrier Protein Reductase:**

**1) Isoniazid:**

The front-line drug isoniazid (INH) is one of the most efficient medicines to treat tuberculosis, but it is increasingly challenged by resistant Mtb strain. although INH has been used as an anti-tubercular agent since1952. INH interferes with the biosynthesis of mycolic acids, essential long α-alkylated and β-hydroxylated fatty acids, present in the mycobacterial cell wall. It inhibits the enoyl-ACP reductase (InhA), a NADH-dependent enzyme of the type II fatty acid synthase system (FAS II) that catalyzes the last reductive step of fatty acid elongation. InhA is a member of short chain dehydrogenase/reductase superfamily of enzyme.Inhibition of InhA disrupts the biosynthesis of the mycolic acids that are central constituents of the mycobacterial cell wall. As a prodrug, INH must first be activated by the mycobacterial catalase-peroxidase KatG into its acyl radical active form. The adduct resulting from covalent binding of the activated INH to the InhAcosubstrate NADH, or its oxidation product NAD+, function as a potent InhA inhibitor.[7]




Chemical structure of isoniazid and mechanism of formation of the INH-NADH adduct

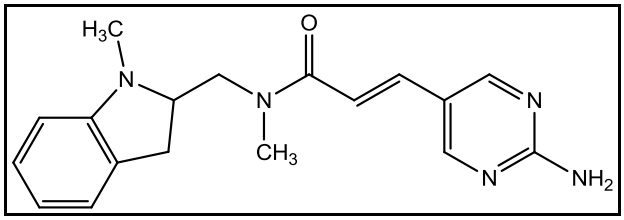
**2) Diazaborines:**

Diazaborines are a class of heterocyclic boron containing compound that inhibits FabI by the formation of covalent bond between the boron atom and the 2'- hydroxyl of the NAD+ ribose moiety. While both isoniazid and diazoborines form covalent adducts with the NAD-bound form of ENR the point of attachment is different and the interaction of the two drugs with the target enzyme differs. Diazoborines seems to have been medically useful set of compounds due to their undesirable inhibition of RNA processing in eukaryotic cell. [6]

**3) Aminopyridine Derivatives:**

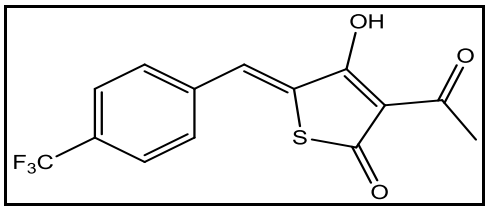
William H. Miller *et al*, (GlaxoSmithKline Pharmaceuticals) described that the aminopyridine based derivatives as a novel small molecule inhibitor of bacterial enoyl ACP reductase. They synthesized some molecules in which one derivatives shows activity at low micromolar inhibitor of FabI from *S. aureus* ($IC_{50}$) 2.4 µM) and *Haemophilus influenzae* ($IC_{50}$) 4.2 µM). it having very good narrow spectrum *in vitro* antibacterial activity against several organisms, including *S. aureus* (MIC) 0.5 µg/mL), and is effective *in vivo* in a *S. aureus* infection model in rats. Hence from mechanism of action and cytotoxicity studies it confirmed that the

antibacterial activity is due to inhibition of fatty acid biosynthesis through inhibition of FabI. Taken together, these results support FabI as a valid antibacterial target and demonstrate the potential of small-molecule FabI inhibitors for the treatment of bacterial infections.[8]



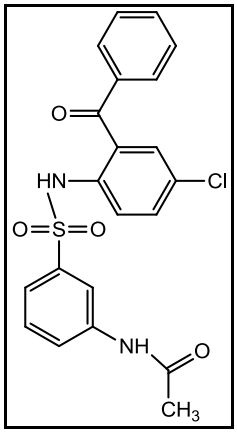

**4) 3- ACYL Thiotetronic Acid Derivatives:**

Rimao Hua *et al*, designed and synthesized twenty-six novel 3-acyl thiotetronic acid derivatives and evaluated for biological activities against *Valsamali, Curvularialunata, Fusarium graminearum, Fusarium oxysporum f. sp. lycopersici.* Among this one compound was the most effective against *V.mali, C. lunata, F. graminearum, and F. oxysporum f. sp. Lycopersici* with $EC_{50}$ of 4.1, 3.1, 3.6 & 4.1 µg/mL resp. while corresponding 0.14, 6.7, 22.4, & 4.3 µg/mL of fungicide azoxystrobin. The inhibitory potency against *V. mali* fatty acid synthase agreed well with the *in vitro* antifungal activity. The molecular docking suggested that the 3-acylthiotetronic acid derivatives targeted the C171Q KasA complex. The findings help understanding the mode of action and design and synthesis of novel potent fungicides. [9]



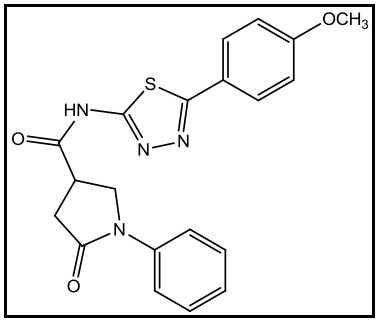

**5) Benzophenone Derivavtives:**

M. M. V. Ramana *et al* can conclude that ACP reductase is one of the receptor protein used in drug discovery for anti-leprosy agents.Molecules show good docking values in between range -7.95 to -10.25 with standard ligand score is -12.1.The docking scores indicate that some molecules are well docked molecules and their H-bond interactions reflect the possibilities of anti-leprosy drug-likeness. Also, the drug likeness can be supported by ADME properties of molecules like partition coefficient is 2.752 to 6.797, its crossing blood brain barrier is from (-3) to 1.2. further prediction percentage human oral all molecules ranged from 88.64 to 100% which are in acceptable range and better than the standard ligand. It can be concluded that the designed benzophenone class of molecules are positively interacting with Enoyl-ACP reductase protein and hence can be further processed as anti-leprosy drug candidates.[10]



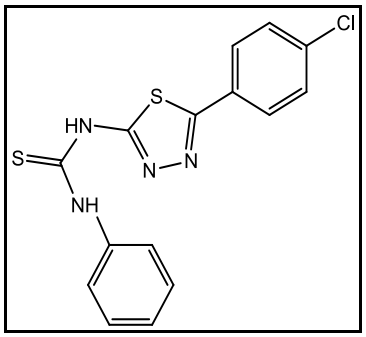
**6) Thiadiazolyl Pyrrolidine Carboxamide Derivavtives:**

Sonia George *et al* gives an insight view about the development of new direct Mtb enoyl ACP reductase (InhA) inhibitors, the synthesized derivatives characterized by UV, IR,[1]HNMR & Mass, its confirmed that they show anti-tubercular activity with MIC value 25 µg/mL.Thus,they were promising candidate as MtbInhAinhibitors. [(11)]



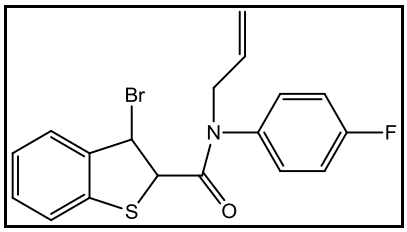

**7) Thiadiazolo Thiourea Derivatives:**

Sonia George *et al*, conclude that, the research focused on the design of enoyl ACP reductase inhibitors of *E. coli* has resulted in the development of novel thiourea linked 1,3,4-thiadiazole derivatives, highest binding energies observed in between -8.67 to -6.56 Kcal/mol. The antibacterial results revealed that the derivatives,showed a zone of inhibition of 28 mm when compared to the standard, ciprofloxacin (30 mm) at 250 µg/mL.The activity profile of the designed compounds indicated that the new 1,3,4-thiadiazolyl thiourea derivatives are excellent candidates in antibacterial drug discovery.[(12)]




**8) Benzothiophene Carboxamide Derivatives:**

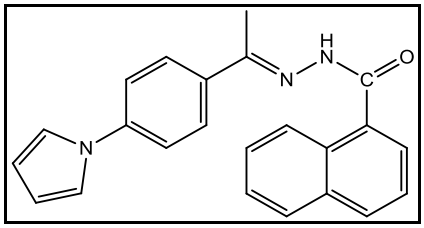
Tanushree Banerjee *et al*, frame that bromo-benzothiophene carboxamide derivatives ismost potent slow-tight binding inhibitors of Plasmodium acp reductase (PfENR). 3-Bromo-N-(4-fluorobenzyl)-benzothiophene-2-carboxamide inhibitor found with $IC_{50}$ of 115 nM for purified PfENR. The inhibition constant (Ki) was found to 18 nM with respect to the cofactor and 91 nM with respect to crotonoyl-CoA. These inhibitors showed competitive kinetics with cofactor and uncompetitive kinetics with the substrate. Thus, these compounds hold promising for the development of potent antimalarials. [(13)]




**9) Pyrrole Hydrazine Derivatives:**

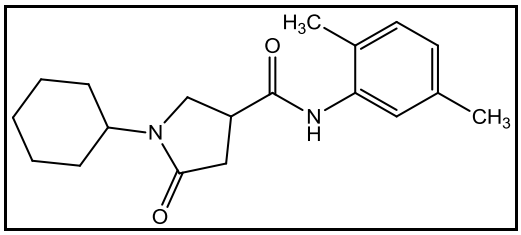
UttamA.More *et al* elobrate on a series of 52 novel pyrrole hydrazine derivatives, which is synthesized and screened for targeted enoyl ACP reductase, as anti-tubercular agents.These pyrrole hydrazones compounds

were explored as a new chemical entity in the search for tuberculosis drug treatment. Compound shows highly activity with MIC 0.2µg/mL. it also shows H- bonding interaction with Tyr 158 and $NAD^+$ with Enoyl ACP reductase.(14)



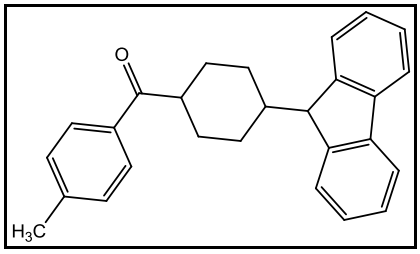

**10) Pyrrolidine Carboxamides Derivatives:**

Xin He *et al*, reported the on the basis of the preliminary SAR studies discovery through HTS of a series of pyrrolidine carboxamides as a novel class of potent InhA inhibitors. The newely identified compound showed as promising candidates for the development of second generation InhA inhibitor with improved bioavailability properties with the best inhibitor showing an IC50 of 62 nM. A 160-fold gain in potency was thus realized through library optimization. These newly identified compounds serve as promisingcandidates for the development of a second generation InhA inhibitors with improved bioavailability properties. (15)



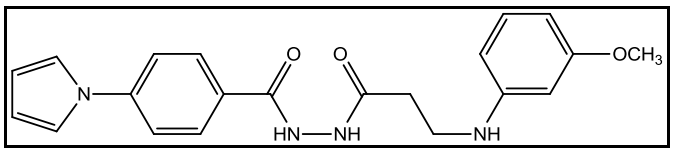

**11) Arylamide Derivatives:**

Xin He *et al*, has identified arylamide as a novel class of InhA inhibitors through HTS on the basis of preliminary SAR studies and the crystal structure of one InhA inhibitor complex. The best inhibitor exhibited as Ic50 of 90 nm a 34-fold in potent over inhitial lead compound.(16)



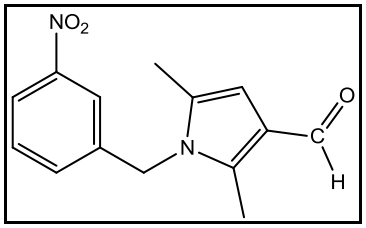

**12) Pyrrolyl Benzohydrazide Derivatives:**

Shrinivas D. Joshi *et al*, reported ACP inhibitors on the basis of molecular modelling studies of 35 novel pyrrole derivatives. These pyrrole hydrazides were explored as a new entry in the search of new tuberculostatics, identifying several hydrazides with reasonable inhibitory activities against M. tuberculosis. This docking study stated that the active site of the enzyme the amino acid residue Tyr 158 and co-factor NAD 500 plays an important role in binding with the ligand.(17)



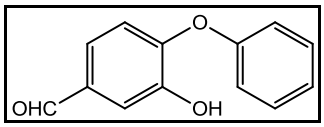
**13) Pyrrole Carbaldehyde Derivatives:**

Shrinivas Joshi *et al*, designed some compounds which showed H- bonding interaction similar triclosan with enoyl ACP enzyme and with better docking score 8.81 which stated that pyrrole carbaldehyde as powerful template for enoyl ACP reductase inhibitors.[18]



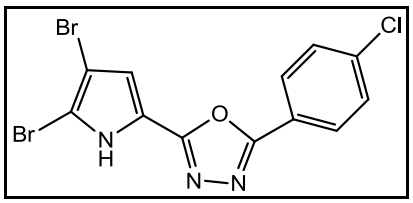

**14) Diphenyl Ether Derivatives:**

Manmohan Chhibber *et al*, designed and synthesized some novel diphenyl ether analogue and determining their binding energies for Enoyl ACP reductase of Plasmodium falciparum and Escherichia coli. The compounds show nanomolar inhibition of PfENR and low micromolar inhibition of EcENR from 40.04µM to 0.8 µM.[19]



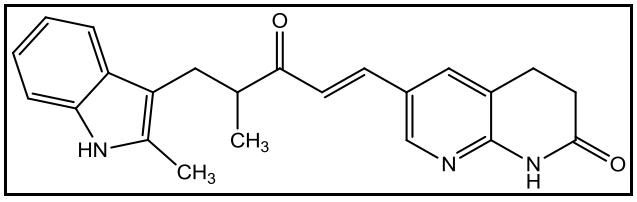

**15) Oxadiazole Pyrrole Derivatives:**

Kalyani asgaonkar *et al*, reported that the development of potential compound contains the pyrrole ligated oxadiazole analogue with anti-tubercular activity using 2D & 3D QSAR studies. The 2D designed compounds also showed a good binding interaction with the enoyl-ACP (CoA) reductase enzyme. The correctness of the rationale behind these dry lab studies can be further validated by carrying out the synthesis and antitubercular activity of the designed NCEs.[20]



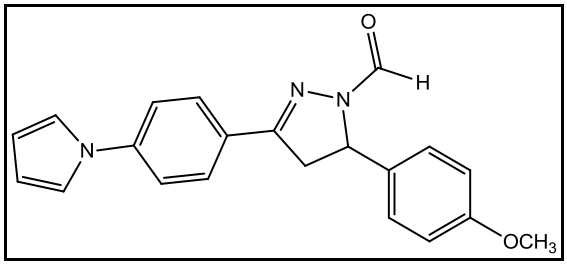

**16) Indole Naphthyridinones Derivatives:**

William H. Miller *et al* stated that the series of indole naphthyridinones derivatives displays excellent oral *in-vivo* efficacy against *S. aureus* also low micromolar inhibitor of fabKMIC-90s >500-fold and it also act as dual (fabI/fabK) inhibitor having broad spectrum activity.[21]



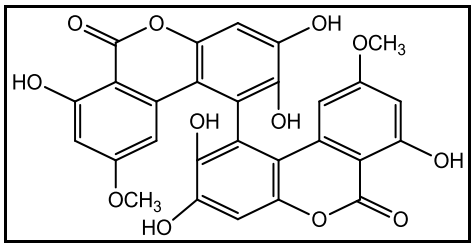

**17) Pyrrolyl Pyrazoline Carbaldehydes Derivavtives:**

Sheshagiridixit *et al*, design and synthesized some compounds and evaluated its anti-tubercular activity.in this some compounds show good anti-tubercular activity. Best MIC value was found to be 6.25 micro gm/ ml; it's also stated that due to presence of pharmacologically active hetero aryl pyrazoline ring with formyl group. It also shown very good inhibition with Enoyl ACP reductase enzyme.[22]




**18) Dibenzo-A-Pyrones Derivatives:**

Alternariol and its simple derivatives like alternariol methyl ether possessteratogenic, genotoxic and mutagenic effects. In the course of ongoing screening for new enoyl-ACP reductase inhibitors from microbial resources, isolated two new dimeric compounds of alternariol class, named verrulactones A–D form the culture broth of the fungal strain *Penicillium verruculosum*. Compound verrulactones A and B exhibited potent antibacterial activity as well as FabI-inhibitory are symmetric and asymmetric, respectively dimers of a new 1-demethyl-2-hydroxy-alternariol 9-O-methyl ether.[23]




**Activity of Enoyl ACYL Carrier Protein Reductase Inhibitors:**

**A) As Anti-Bacterial Agents:**

*Streptococcus pneumonia* is the main causative pathogen of respiratory tract infections such as community acquired pneumonia and acute otitis media. In this regard, fatty acid biosynthesis is an attractive target. Bacterial fatty acid biosynthesis (type II FAS) provides fatty acids which are used in the assembly of essential cellular components of bacteria. In bacteria different monofunctional enzymes catalyze each of the reactions and intermediates are carried through the cytosol as thioesters of the small acyl carrier protein (ACP).[25] various compounds including isoniazid, diazoborines, triclosan, indole naphthyridinones and thiopyridine reported as bacterial enoyl ACP inhibitors.[24]

**B) As Antitumor Agents:**

Human type-I FAS has been proposed as a chemotherapeutic target for the treatment of breast cancer based on the inactivation of human β-ketoacyl synthase activity by cerulenin. Triclosan functions by inhibiting the enoyl-reductase enzymes of type II FAS in susceptible bacteria. If triclosan is an inhibitor of human FAS and if inhibition of FAS is toxic to breast cancer cell lines, triclosan could prove to be a lead compound for the treatment of breast cancer. Consequently, the inhibitory activity of triclosan against vertebrate type I fatty acid synthases and its effects on breast cancer lines in cell culture were investigated. The results collaborate the hypothesis that fatty acid synthase may be a target of breast cancer chemotherapy and inhibitors of the enoyl-reductase partial activity of fatty acid synthase may have chemotherapeutic potential. [25]

**C) As Anti-Mycobacterial Agents:**

Increase in the incidence of TB in the recent years has also been attributed to the co-infection with HIV.This underlines the urgent need to develop new classes of antimycobacterial drugs. Increasing resistance, many studies targeting the mycobacterial cell wall and particularly the biosynthesis of mycolic acid has been reported. InhA is an essential enzyme of mycolic acidbiosynthesispathway.FAS II synthetase of mycobacteriais also an attractive target for the development of new antimycobacterial.Recently search several series of direct InhA inhibitors, including pyrazole derivative, indole-5-amides and alkyl diphenyl ethers, pyrrolidine carboxamides, and derivative of 4-pyridone and 4-pyrone derivative are also use to treat tuberculosis. [26]

**D) As Anti-Malarial Agents:**

Along with tuberculosis and AIDS, Malaria is one of the three most dangerous and wide spread parasitic of human infectious disease with a high rate of resistance and there is constant need for the discovery of novel anti- malarial drug targets.(28) Traditionally antimalarial drugs such as quinine, chloroquine, quinidine, mefloquine sulfadoxine-pyrimethamine and artemisinin derivatives are effective and work quickly, unfortunately the chronic use of these drugs may lead to resistant in *P. falciparum*. Rendering the drugs much less effective and ultimately resulting in treatment failure. however, the problem the world is facing today is parasite resistance to anti-malarial drugs. (29) Current insights on the Plasmodium metabolism have uncovered different targets for the development of novel antimalarials. Also, fatty acids biosynthesis enzymes are one of the important targets. Fatty acids play an important role in providing metabolic precursors of biological membrane represent in form of metabolic energy, making their biosynthetic pathway a promising target for antimalarial agents. Because it has been proposed to play an important role in membrane construction and energy production in the parasite and does not have any human analogues. (27)

**E) As Anti-Fungal Agents:**

Emerging fungal phytodiseases are increasingly becoming a food security threat, therefore Fatty acid synthesis in fungi is also play derteminant role in inhibiting ENRs. Various organisms are involved against enoyl acpreducatse are *Toxoplasma gondii, Staphylococcus aureus, Streptococcus pneumoniae, Francisella tularensis* etc.(28)

## Conclusion:

The large volume of research on structural classes of various anti-infective agents such as anti-tuberculosis, anti-malarial, anti-fungal agents indicates that the enoyl acyl carrier protein reductase is most potential target for enzyme inhibition studies as well as studies in drug design.

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