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Way of Administrating Supramolecular Drug Associates Against Multidrug-Resistant Bacteria in Improving Multidrug Therapy

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Abstract

The development of new drugs to combat bacterial virulence and target specific locations is a major challenge in the pharmaceutical industry. Multidrug resistance in bacteria can occur through the accumulation of drug-resistive parts in multiple genes or increasing genetic expression for multidrug efflux pumps. Multidrug-resistant bacteria can be tackled with a combination of antibacterial drugs, known as multidrug therapy. An important drawback of this method is that administering each drug separately can lead to an incremental increase in drug resistance once the target bacterial cell is reached. Now, if we can develop the cocrystals of multiple drug molecules with tabletability and plasticity, we can administrate the sustainable multidrug to a target bacterium and ensure the killing, just after checking potential efficacy. The drug molecule selection process should involve considerations of crystal engineering principles for sustainable drug delivery to each bacteria cell, and complementary drug activities to ensure the killing bacteria. Now the multidrug will not raise the drug resistance step-by-step and the philosophy of multidrug therapy will be properly justified. We are bringing attention to the antituberculosis multidrug cocrystal therapy as a means to combat the impending tuberculosis epidemic, which is being overlooked due to the focus on Covid-19 treatment.

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1. Introduction

Wide ranges of antibiotics used in human, farm animal, pets, and aquarium fish results in developing immunity against multiple drugs in the bacteria. Bacteria-antimicrobial resistance of 88 pathogen-drug combinations in 204 countries estimated the death of 4.95 million people in 2019.[1] Multidrug resistivity (MDR) occurs in every single cell in two ways, accumulation of different drug-resistive parts in multiple genes or by increasing genetic expression for multidrug efflux pumps.[2] Thus, killing each single multidrug resistive bacteria by administrating different drugs is a major challenge in medical science as we need to ensure reaching multiple drugs together. As there is no chemical bonding between the multiple drug molecules, the individual drug molecules reach different bacteria separately and help enhance the resistance against the drug molecule in conventional multidrug therapy. This major drawback in multidrug therapy significantly increases the treatment time against the multiple drug resistive bacteria and often promotes multidrug resistivity. Increased treatment duration also raises the risk of a multidrug-resistant infection spreading in society, potentially leading to an epidemic.

For addressing multidrug-resistant bacteria, a new protocol is proposed here, ensuring simultaneous delivery of all drug components to the targeted bacteria. Conventionally, co-crystals[3] are formed by a drug molecule with a coformer to enhance solubility, permeability, and thermal stability and reduce brittleness.[4,5] The co-crystals can be formed by different supramolecular bondings like H bonding, π-π stacking, halogen bonding, vender Walls' Interaction *etc*. By

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forming co-crystals of different drugs for the same kind of bacteria, we will be able to administrate all the drug molecules at the same time to a single bacterium. The various drug molecules can work on a single bacterium more effectively after reaching the targeted bacteria collectively than in the conventional multidrug therapy protocol. Various crystallization techniques, such as slow evaporation, hydrothermal synthesis, solvent diffusion, etc., can be employed to crystalize multiple drug molecules, which can effectively target and eliminate multidrug-resistant bacteria cells in a complementary manner (Scheme 1). The six leading pathogens like *Escherichia coli, Staphylococcus aureus, Klebsiella pneumonia, Streptococcus pneumoniae, Acinetobacter baumannii*, and *Pseudomonas aeruginosa* were responsible for around 929000 deaths in 2019.[1]

After Covid-19, tuberculosis (short TB) becomes a potential threat as an epidemic for the scarcity of medicines in remote places. Other chronic diseases like TB and malignancies were ignored to prioritize the treatment against the immediate threat of Covid-19. During this time, TB drugs were not administered to the patients regularly, which promoted multidrug resistivity to the TB bacteria. In this perspective, the cocrystal formation of multidrug for TB treatment will be focused mainly. More people have died from TB than any other infectious disease in the last 2000 years.[6] Rather than synthesizing the TB drug endlessly, we can minimize the scientific effort and time once we start preparing cocrystals of available drug molecules. The formation of cocrystals can increase the solubility and plasticity of drug molecules, while also eliminating the need for pharmaceutical excipients. Excipients used in pharmaceuticals are essential for safely delivering medication molecules to certain organs. To boost solubility, plasticity, or tabletability, we can combine necessary pharmacological molecules with their complementary counterparts, which would completely replace the necessity for excipients in certain cases like multidrug cocrystallization. By employing this tactic, we hope to improve patient outcomes by increasing the potency of our medication against bacterial infections.

2. Spreading paths of multidrug resistive bacteria

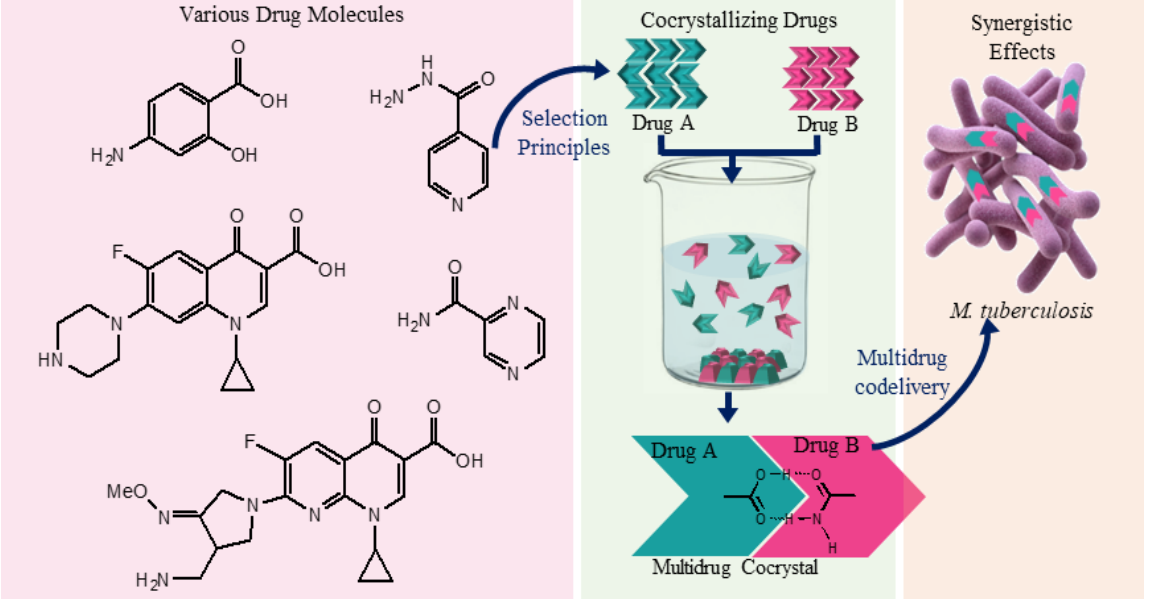
Several studies since 2010 demonstrated that international traveling introduces a major threat to acquiring multidrug-resistant Enterobacteriaceae.[7]

When deployed in war or crisis zones, soldiers are prone to acquire multidrug-resistant bacteria at their military medical camps. Awkward hygiene environments stimulate their war injuries into infection and colonization of multidrug-resistant bacteria. Precisely, the Gram-negative bacteria exacerbate wound infections. Despite frequently cleaning the host from colonizing strains at reintegration (after returning from crisis zones), transmission occurs to their close contacts. An effort for worldwide resistance investigation can demonstrate a brief resistance distribution pattern and spreading style at deployment sites. As bacteria-culture-based diagnoses are usually unavailable at the deployment site, molecular rapid diagnostic systems are a very useful option for transmission control.[8] The situation even does not improve far at a sophisticated medical facility-based US hospital, as patients come from different societies.[9] Among 41.6 million hospitalized people (>20% annually) in 2017, pathogens infection was estimated for 622,390 patients. Among them, onset in the community was 517,818 (83%) and onset in the hospital was 104,572 (17%). In a separate study in an Indian Hospital at Hariyana for 45 months, 5615 isolates (19.38%) from 28971 cultures showed culture yield. Among them, the Gram-negative load was 80.8% and the Gram-positive was 19.9%.[10]

MDR pathogens are also present in the surface water and recreational water centres, which serve as reservoirs for MDR bacteria and hot spots in the community.[11] The MDR pathogen *Mycobacterium tuberculosis* can spread when a patient with TB disease of the throat or lungs speaks, sings, laughs, coughs or sneezes near a normal person. TB germs in such cases pass through the air. However, TB cannot pass through a patient's clothes, eating utensils, drinking glass, handshake, toilet, or other used surfaces.

3. Range of bacteria and other pathogens to be covered

Gram-negative pathogens acquire different ranges of drug resistivity like pandrug-resistivity (PDR) multidrug-resistivity (MDR), and extensive drug-resistivity (XDR) which make them deadly in raising epidemic situations.[12] To standardize such terminologies, the Centers for Disease Control and Prevention (CDC) and the European Centre for Disease Prevention and Control (ECDC) worked together and defined them as follows. XDR is denoted as non-susceptible to one among the two or fewer antimicrobial classes. MDR is denoted when drug resistivity appears in at least one agent among three or more antimicrobial groups. We denote PDR when drug resistivity appears in every antimicrobial class (*i.e.* no agents appear as vulnerable to that organism). Infections bacteria like *Acinetobacter baumannii, Pseudomonas aeruginosa, Escherichia coli*, and *Klebsiella pneumonia* are Gram-negative in nature and cause alarming mortality. Billions of dollars are consumed behind the prolonged treatments with utmost proper medical care and infection prevention. Better care for critically sick patients comes from



Scheme 1 Various complementary tuberculosis drugs can be cocrystallized by exploiting certain synthons to target the tuberculosis bacterium cells together.

understanding the geographical patterns of resistance and individual resistance factors. Despite global efforts to discover new treatments for MDR Gram-negative infections, only a little progress is made. To address the MDR criticalities, we depend on the new combinations of ongoing antibiotics. Nonetheless, *β*-lactamase inhibitors like vibactam, relebactam or vaborbactam, are combined with conventional antibiotics cephalosporins or carbapenems to enhance the bioactivities against targeted bacteria.[13] HIV-infected people are very vulnerable to mycobacterial disease.[14] Once we understand the complete bacterial defense mechanism and can address them by complementary drug molecules, we can select the drugs for developing cocrystals.

3.1 Pseudomonas aeruginosa

P. aeruginosa is a multidrug-resistant gram-negative bacteria in the soil, water, and hospitals and causes nosocomial infections. It infects the bloodstream, urinary tract and, ventilators (to cause pneumonia).[15] It is resistant to various antimicrobials as it is highly efficient in acquiring new genes to resist different drugs. The low permeability of their cell wall restricts the intake of antibiotics. Carbapenems are used here as the 1st line drug, but resistance may appear for the action of efflux pumps, loss of porin, and impermeability to the drug.[16] *P*. aeruginosa resistant to Carbapenems becomes one of the major threats to hospitals and outbreaks in several countries.[17] Presently new drugs like Cefiderocol, Ceftolozane-tazobactam, and Ceftazidime-avibactam are getting used against the *Pseudomonas* species.[18]

3.2 Staphylococcus aureus

S. aureus is a multidrug-resistant gram-positive bacteria that live in an open environment (air, water and soil) and also exist in the nose and skin of humans and causes endocarditis, pneumonia, septicemia, meningitis, systemic infections, with risk of death.[10] In the beginning, *S. aureus*-driven infections were straightforwardly controlled by penicillin but received a beta-lactamase with plasmid-encoded instructions shortly after penicillin was introduced for clinical practice. To address this issue, a semisynthetic beta-lactamase-resistant antibiotic methicillin was produced and employed in 1959 for the penicillin-resistant strains, but methicillin resistivity arose quickly.[19] In 1961, methicillin-resistant *S. aureus* spread globally in an outbreak and comes among the top three threatening infectious diseases for human health.

Over 80,000 diseases and 11,000 deaths were caused by Methicillin-resistant *S. aureus*, as reported by the Center for Disease Control and Prevention, the USA in 2011.[20] Up to the 1990s, methicillin-resistant *S. aureus* was restricted inside hospital premises but thereafter it appears in communities. Some strains infect pet animals like chicken, cattle, horses, and pork causing endocarditis, pneumonia, and necrotizing fasciitis since 1975.[21,22] At present, daptomycin and Vancomycin are commonly used as antibiotics for *S. aureus* infections.[23]

Some Oxacillin narrow-spectrum beta-lactam antibiotics of penicillin, like cloxacillin, dicloxacillin, flucloxacillin, oxacillin, Methicillin, nafcillin can be used for treating *S. aureus* and cocrystallized for treating the multidrug-resistant bacteria.

3.3 Acinetobacter baumannii

Acinetobacter is a gram-negative nonfermenting genus that exists in water, soil, various animals, vegetables, and human hosts. It lives in the commensal flora of mucous membranes and human skin. The utmost infections in the community and hospital are driven by *A. calcoaceticus-A. baumannii* complex.[24] In the USA, *A. baumannii* causes yearly 12,000 health-associated infections, among which 7,200 appear as multidrug-resistant cases and result in 500 deaths.[25] Hospitals instruments like mechanical ventilation systems, dialysis machines, and water sources are often infected by *A. baumannii*, even if it lives in the mucous membranes and the skin of health professionals or patients.[26] It was long been considered an opportunistic entity with low pathogenicity. Acinetobacter was formerly thought to be an opportunistic agent with little pathogenicity. Recently, the WHO announce that this is a first-priority pathogen, for which antibiotics should be developed on an urgent basis.[27] *A. baumannii* is regarded as a high risk of morbidity and a life-threatening agent. This bacterium often shows high resistance against antimicrobials. The multi-drug resistant *A. baumannii* strains often worsen patient situations due to insufficient initial therapy, inadequate treatment options, and the high toxicity of existing therapies. Drug resistance can be acquired or intrinsic, facilitated by different factors like damage to membrane permeability or the creation of betalactamases, which break down beta-lactam antibiotics. The most significant contributor to bacterial resistance, particularly in gram-negative bacilli, is betalactamases.[28] The resistance to carbapenems occurs for the efflux pump and the affinity change in penicillin-binding proteins. Some very recent drugs like cefiderocol, eravacycline, ETX2514[29] and some effective drugs like piperacillin/tazobactam, polymyxins E and B, carbapenems, sulbactam, tigecycline and aminoglycosides[30] can be taken together for making co-crystals.

3.4 Mycobacterium tuberculosis

M. tuberculosis is a type of pathogenic bacterium that is classified as weakly Gram-positive,[31] and it can be found in a variety of animals such as humans, cats, dogs, goats, rabbits, deer, pigs, and badgers.[14] Identification of the bacterium can be done through the use of acid-fast stains such as Ziehl-Neelsen or fluorescent stains like auramine.[32] The bacteria have the potential to infect various parts of the body including the brain, spine, and kidneys. It is worth noting that M. tuberculosis can be asymptomatic in some individuals, resulting in the condition known as latent TB.

Continuous research efforts are being made to develop new drug molecules to combat multidrug-resistant Tuberculosis (TB) bacteria. Recently, Chrysomycin A has been developed, which targets the topoisomerase I enzyme of TB.[33] Its 33 new analogues have demonstrated significant activity against MDR TB bacteria.[34] Another compound, 3′-hydroxy-5′-[4-isobutyl-1-piperazinyl] benzoxazino Kang A, has shown antibacterial activity against Staphylococcus aureus and Mycobacterium tuberculosis.[35] This semisynthetic compound is particularly promising due to its ability to combat two different types of bacteria. Furthermore, 2-aminothiazoles and their 2-aminooxazole analogous compounds[36] have been found to possess anti-tuberculosis activity. Additionally, the natural product nargenicin has been discovered to act as a genotoxin by damaging DNA in Mycobacterium tuberculosis. Nargenicin works by bonding with the DNA of the bacterium, ultimately leading to its destruction.[37] The cocrystal of multidrug preparation is discussed in detail in section 8.

4. Multidrug resistive mechanism

A wide range of antibiotics is used for killing bacteria in humans, pet animals, and aquatic fishes, which promotes multi-drug resistivity in bacteria. Multidrug resistivity arises through three paths.[38] In the first case, bacteria accumulate multiple drug-resistive genes through horizontal transfer of plasmid in bacterial conjugation. In the second case, the increased genetic expression, coded with multidrug efflux pumps, promotes multi-drug resistivity. At the cell wall, multidrug efflux pumps extrude a wide range of drug molecules.[2] In the 3rd case, the modification of enzymes also helps raise drug-resistivity in bacteria.[39]

1) Horizontal transfer of plasmid: Gram-positive bacteria do not contain the outer membrane, a permeability barrier to certain antibiotics and drugs.[40] Herein, the gram-negative bacteria is advanced in preventing antibiotics. The presence of porins at the outer membrane, on the other hand, renders it permeable to basic needs such as nutrition, water, food, or iron in Gram-negative bacteria. Furthermore, the coevolution of host-plasmid pairs assists the multidrug resistance in Gram-negative and Gram-positive bacteria.[41] The MDR bacteria introduce their drug resistivity to their neighbor bacteria through the horizontal transfer of plasmid, containing the antibiotic resistance genes. The stabilizing factors of plasmids in bacterial conjugation even increase the multi-drug resistivity, as bacteria get a new kind of drug-resistive plasmid along with its own plasmid (Fig. 1).[42] One of the stabilizing factors is the coevolution of host-plasmid under antibiotic selection that promoted the emergence of MDR through two different plasmids from different bacteria (Escherichia coli and Klebsiella pneumonia) after removing the antibiotics. In such a case, evolution supported the higher stability of a plasmid.

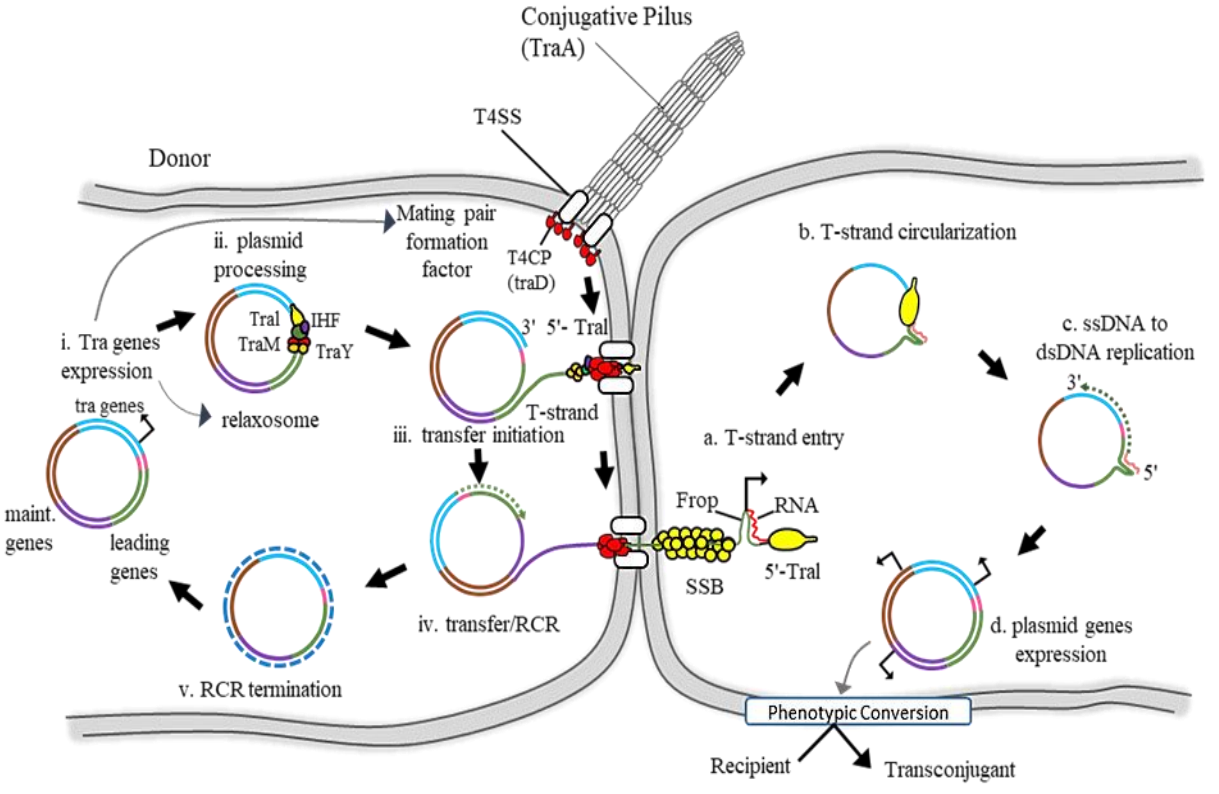


Fig. 1 The conjugational transfer of the F plasmid is presented here schematically. In the backbone of the F plasmid, *tra* sections encode every gene involved in conjugational transmission (light blue), the source of transfer *oriT* (red); the leading region (olive), which is the earliest to be transferred into the acceptor cell; and the maintenance region (purple) replicates and partition the plasmid. (i) The *tra* genes' expression is necessary for the start of conjugation. The conjugative pilus and the T4SS, which employ the recipient cell and facilitate mating pair stabilization, are formed by some of the generated Tra proteins. (ii) TraI, TraM, and TraY are additional Tra proteins that make up the relaxosome. Together with the integration host factor (IHF), they attach to the *oriT* and make the plasmid for transmission by initiating the nicking reaction through TraI relaxase. (iii) The T-strand transfer by the T4SS is started by the interactivity between Type IV Coupling Protein (T4CP) and the relaxosome. (iv, v) The transformation of the ssDNA towards dsDNA by Rolling Circle Replication (RCR) in the donor occurs concurrently with the transmission of the T-strand, attached to TraI-bound in the recipient. (a) The single-stranded Frpo develops a stem-loop conformation that is recognised by the RNA polymerase host to start the biosynthesis of RNA primers after the single-stranded DNA T-strand is covered by the host chromosomal SSB upon entry into the recipient. (b) The fully internalised T-strand is circularised by TraI. (c) The host DNA polymerase recognizes the RNA-DNA duplex and starts its complementary strand synthesis process. (d) After the single-stranded DNA (ssDNA) plasmid has been converted into double-stranded DNA (dsDNA), plasmid gene expression causes the recipient cell to phenotypically change into a transconjugant cell.[42]

2) Efflux pumps: Efflux pumps (Fig. 2)[38] are located at the cell membrane and besides extruding the antibiotics can also extrude toxic compounds like heavy metals, pollutants, and antimicrobials generated by competitors.[43] The cell membrane of both Gram-positive and Gram-negative bacteria are compared in Fig. 3. The multidrug efflux pumps also contribute to acquired, intrinsic, and phenotypic resistance to bacterial pathogens. Expression of the efflux pumps is generally strongly down-regulated, implying that high-level transient expression can be achieved by the right effectors which infer the biological activities.

3) Bacterial enzymes: Besides genetic evolution against certain drugs and efflux pumps, bacterial enzymes also promote the emergence of drug resistance. These enzymes can be classified by their biochemical mechanisms[39] as i) modifying enzymes as an antibiotic target[44] ii) modification of enzymes for intracellular targets, iii) enzymatic transformation of antibiotics and, iv) the employment of cellular metabolic reactions. Modification of the enzymes that act as antibiotic targets, enzymatic modification of intracellular targets, the enzymatic transformation of antibiotics, and the implementation of cellular metabolism reactions. The group of all antibiotic-resistant genes is called a resistome. The chromosomal gene-encoded enzymes protect

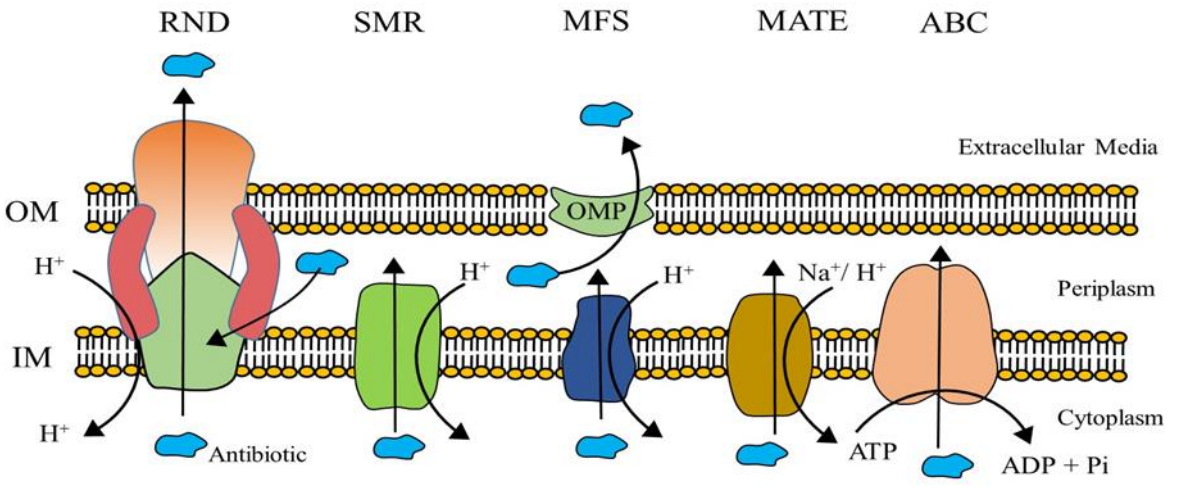


Fig. 2 The schematic presentation of the five major families of efflux pumps i) resistance-nodulation-division (RND), ii) small multidrug resistance (SMR), iii) major facilitator superfamily (MFS), iv) multidrug and toxic compound extrusion (MATE) and v) ATP-binding cassette (ABC) superfamily, observed at the bacterial membrane. The full forms of the abbreviations used here are as follows-ATP: Adenosine triphosphate, ADP: Adenosine diphosphate, OM: Outer membrane, IM: Inner membrane, OMP: Outer membrane protein.

pathogens creating antibiotics against modifying their potential targets.[39]

5. Drug resistance in tuberculosis

The drug resistance mechanism should be thoroughly investigated to control TB before it reaches the epidemic stage. We will be better able to understand how to prevent drug resistance by using this information, as well as discover the proteins and genes those are responsible for drug resistance. Unlike common bacterial pathogens, *M. tuberculosis* lacks horizontal transfer of "resistance genes" to gain drug resistance. Drug resistance instead entirely results from mutations in mycobacterial housekeeping genes that code for proteins involved in drug absorption, prodrug activation or efflux pump. The successive accumulation of these mutations during unsuccessful chemotherapy appears to be the cause of multi-drug resistance.[45] To overcome this issue, we propose the use of a cocrystal-based multidrug approach, which can attack bacteria using different mechanisms at the same time.

The cell wall of *M. tuberculosis* contains complex lipids that create a permeability barrier against drug molecules attempting to enter the cell. However, this barrier is not always effective, as spontaneous mutations in the bacterium's genome can result in changes to its enzymes or proteins that allow it to become resistant to the drug. The level of resistance depends on the drug's mode of action. Treatment of tuberculosis involves the use of first-line, second-line or third-line drugs, which must be accurately categorized to achieve effective treatment outcomes. The rate of spontaneous *M. tuberculosis* gene mutations that can lead to drug resistance is reported to be 3.5×10^{-6} for Isoniazid, 1.10×10^{-7} for Ethionamide, 2.29×10^{-8} for streptomycin, and 3.1×10^{-8} for Rifampicin.[46] The biological effects and causes of resistance of some TB drugs are provided bellow. Only the first-line drugs with their activities and causes behind the resistance are discussed here just to demonstrate the designing strategy (Vide infra).

5.1 Isoniazid

It is a widely used 1st line TB drug. Passive diffusion allows it to enter *M. tuberculosis* cells.[47] A catalase-peroxidase enzyme with the *katG* gene is responsible for its activation. The enzyme's peroxidase activity is crucial for converting INH into a toxic molecule in the bacterial cell. This toxic substance impacts intracellular targets, such as inhibiting the formation of mycolic acid, a crucial component of the mycobacterial cell wall.[48] It results in morphological changes of mycobacteria cells through surface bulging, wrinkles formation and destroying the internal structure. The alternation in the target genes like *ahpC, ndh, katG, kasA*, and *inhA* causes isoniazid resistance.

5.2 Rifampicin

This 1st line drug is semi-synthetically produced from *Streptomyces mediterranei* and extremely useful for short-course chemotherapy. The crucial *rpoB* gene, a product of DNA-dependent RNA polymerase activity, acts early in transcription and can be inhibited by Rifampicin.[49] Rifampicin's binding to the ß-subunit shuts the RNA/DNA channel and prevents the passage of an expanding RNA chain. Rifampicin drug resistance is mostly linked to mutations in the

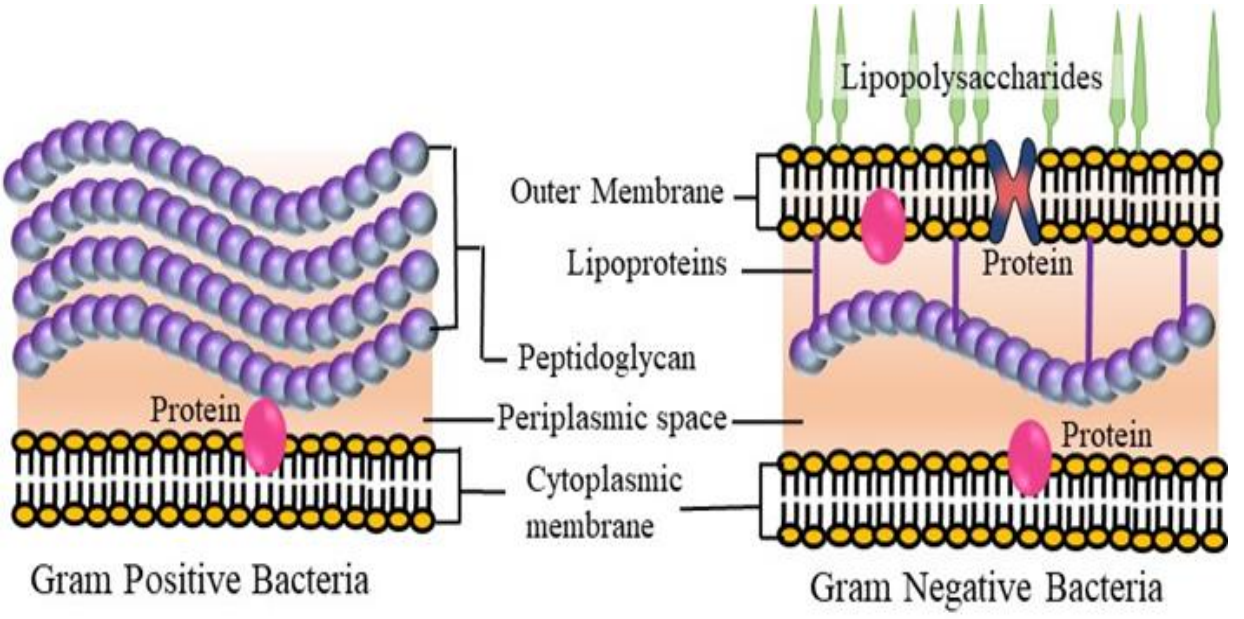


Fig. 3 The schematic presentation of the cell membranes of Gram-positive and Gram-negative bacteria.

rpoB gene. This results in conformational changes that impair drug binding and, as a result, resistance.

5.3 Pyrazinamide

It is a bactericidal molecule that works at acidic pH. The mechanism of Pyrazinamide is poorly understood. The mechanism is just opposite to the common antibiotics. It does not show activity against the developing tubercle bacilli but is mainly active against non-growing persisters.[50,51] At the initial state of chemotherapy, it kills persistent tuberculosis bacilli by targeting an enzyme involved in the production of fatty acids.[52] Pyrazinamidase (PZAase), which is encoded by *pncA*, converts pyrazinamide into pyrazinoic acid after passively diffusing into bacteria. A crucial target enzyme, such as fatty acid synthase (FAS-I), is inactivated when pyrazinoic acid builds up and the pH falls to an unfavourable level.[53] Pyrazinamide drug resistance in M. tuberculosis is driven by *pncA* gene mutations.[54]

5.4 Ethambutol

It is a bacteriostatic antibiotic exhibiting activity against growing bacilli[55] through inhibiting cell-wall synthesizing arabinosyl-transferases (*embB*) involved in cell-wall biosynthesis.[56] The drug resistance to ethambutol appears from the mutations of *embB*.

5.5 Streptomycin

The soil actinomycetes *Streptomyces griseus* developed the first aminoglycoside antibiotic streptomycin, a first-line TB drug. It interferes with the initiation and elongation phases of protein synthesis by binding to the 30S ribosomal subunit.[57] The ribosomal alterations in the ribosomal protein S12 (rpsL) and 16S rRNA (rrs) that cause misreading of the mRNA and suppression of protein synthesis in M. tuberculosis are linked to drug resistance mechanisms.[58]

6. Pramaceuticle cocrystal in multidrug therapy

Crystallization is a technique that can boost the bioactivities of APIs. In addition, incorporating a coformer to aid in the formation of cocrystals can enhance the water solubility, tabletability, and plasticity of the API, rendering it more commercially feasible.[59] Therefore, it is crucial to design cocrystals to introduce these desirable characteristics. However, by substituting a coformer with different drug molecules, cocrystals can be utilized to treat various diseases or combat multidrug-resistant bacteria. Pharmaceutical excipients carry the drug molecules to a targeted organ and leave the place ideally without damaging the body. Once we can increase the solubility, plasticity or tabelatibility by combining a required drug molecule with its complementary drug, we can exclude the pharmaceutical excipients. It benefits the patients in two ways, 1) administrating complementary drugs through cocrystals and 2) avoiding probable side effects of excipients. This strategy would be particularly helpful for treating MDR pathogens. By employing this method, we hope to enhance the virulence of our treatment against bacterial infections and improve patient outcomes.

6.1 Supramolecular bonding in sustaining drugs as a supramolecular associate for co-delivery

The supramolecular bonding has the potential to carry the drug molecules together up to a targeted cell. Formation of cocrystals improves important physicochemical characteristics of the pharmaceutical compounds like solubility, bioavailability and stability inside the patients[60] and plasticity, tabletability inside the pharmaceutical aluminium foil.[59] Cocrystal preparation has the advantage of being environmentally friendly. To form a cocrystal, two or more drug molecules should be dissolved in a solvent or solvent mixture and allowed to evaporate slowly. The selection of drug molecules should be based on the supramolecular synthon formation strategy mentioned earlier. However, the resulting cocrystal must be soluble in water, as it will be used as a drug. In the case of ammonium carboxylate synthons, a Δ pKa value of less than 3.5 can make the cocrystal unstable in the presence of any protic solvent,[61] such as water in the human body. The number of hydrogen (or other supramolecular) bonds increases the strength of the bonding between the conjugate drug molecules, ensuring that they reach the multidrug at a bacterial cell. If a plasmid shows resistance to a particular drug component of the multidrug cocrystal, the bacteria can be killed by the second drug. If the bacteria do not have resistance to both drugs, they will attack the bacteria cell simultaneously. The use of supramolecular bonds to combine pharmaceutical molecules and attack bacteria together has never been employed before, and it improves the quality of multidrug therapy by preventing the bacteria from developing resistance to synergistic attack.[62] Through supramolecular bonding, even supramolecular gel[63] and metal-organic frameworks (MOFs)[64] can be exploited for drug delivery purposes.

6.2 Exploiting supramolecular synthon for developing cocrystals

Supramolecular synthons are the spatial arrangement of intermolecular noncovalent interactions to build the predictable robust architecture. It can be exploited for MOFs,[65] self-healing crystals,[66] supramolecular gels,[67-72] pharmaceutical cocrystals,[59] pheromone containers,[61,73] or some other supramolecular materials. Cocrystals, composed of a coformer and specific drug molecule, are commonly utilized in the pharmaceutical industry to improve plasticity, solubility, and reduce the brittleness of drugs. The concept of supramolecular synthon can also be applied to replace a coformer with a complementary drug to intensify the medicinal effect. Using supramolecular interactions, two or more drug molecules can be combined and simultaneously delivered to a pathogenic cell, which can modify the multidrug therapy process. Various supramolecular synthones, such as acid-amide synthon,[74] acid-pyridine dimers, and acid-aminopyrimidine trimer, as well as carboxylic acid-amino pyrimidine synthon,[75] can be explored for this purpose. For the development of a drug using cocrystal formation or pharmaceutical cocrystal,[76] the cocrystal should be able to dissolve in water and have the ability to form tablets to make them usable as medicine. To achieve this, the crystal structure should have a 2D sheet that exhibits shearing behaviour in the presence of mechanical stress, reducing brittleness[59] and increasing the plasticity of the active pharmaceutical ingredient (API). When the pharmaceutical crystal becomes twistable, it may exhibit exceptional tabletability.[77] Conventionally, a co-former[78] is used to produce pharmaceutical co-crystals, which is not essentially a drug molecule and does not treat the patient's illness, despite it is administered with the medicine. However, if a drug molecule is used as a co-former[79,80] and maintains the tabletability and solubility, it can significantly improve the drug's effectiveness. Even supramolecular gels can be used as a matrix to develop pharmaceutical cocrystals.[81] Some examples of well-studied supramolecular synthons for developing tuberculosis drug cocrystals are presented in Fig. 4.

6.3 Cocrystallizing multidrug for multiple disorders

It is possible to create cocrystals by combining several drug molecules,[3] which has become a common practice in the medical field. For disorders that involve multiple diseases, cocrystals can be used to administer multiple drugs at once. Although there are other methods of administering several medicines, such as mesoporous complexes, salts, coamorphous, systems,[83] surface-engineered nanocargos,[84] the key advantages of cocrystals are their effectiveness in targeting numerous receptors and their low cost of production.[3] Cocrystals that contain multiple drugs are more advantageous compared to coamorphous materials because they have improved solubility, at least for one of the components.[85,86] They also have lower payloads, improved bioavailability,[87] better stability,[88,89] increased flowability, and enhanced mechanical strength.[59]

Multidrug cocrystal (MDC) can be created to improve or decrease the solubility of a specific drug. In situations where certain drugs are not adequately soluble in water, cocrystal formation can be used to improve solubility. For instance, the cocrystallization of ethenzamide and gentisic acid, or Meloxicam and aspirin has been shown to enhance solubility.[90] On the other hand, cocrystals of lamotrigine and phenobarbital have been prepared to reduce solubility, allowing the drugs to be administered at the proper rate.[91] While crystal engineering can assist in the identification and

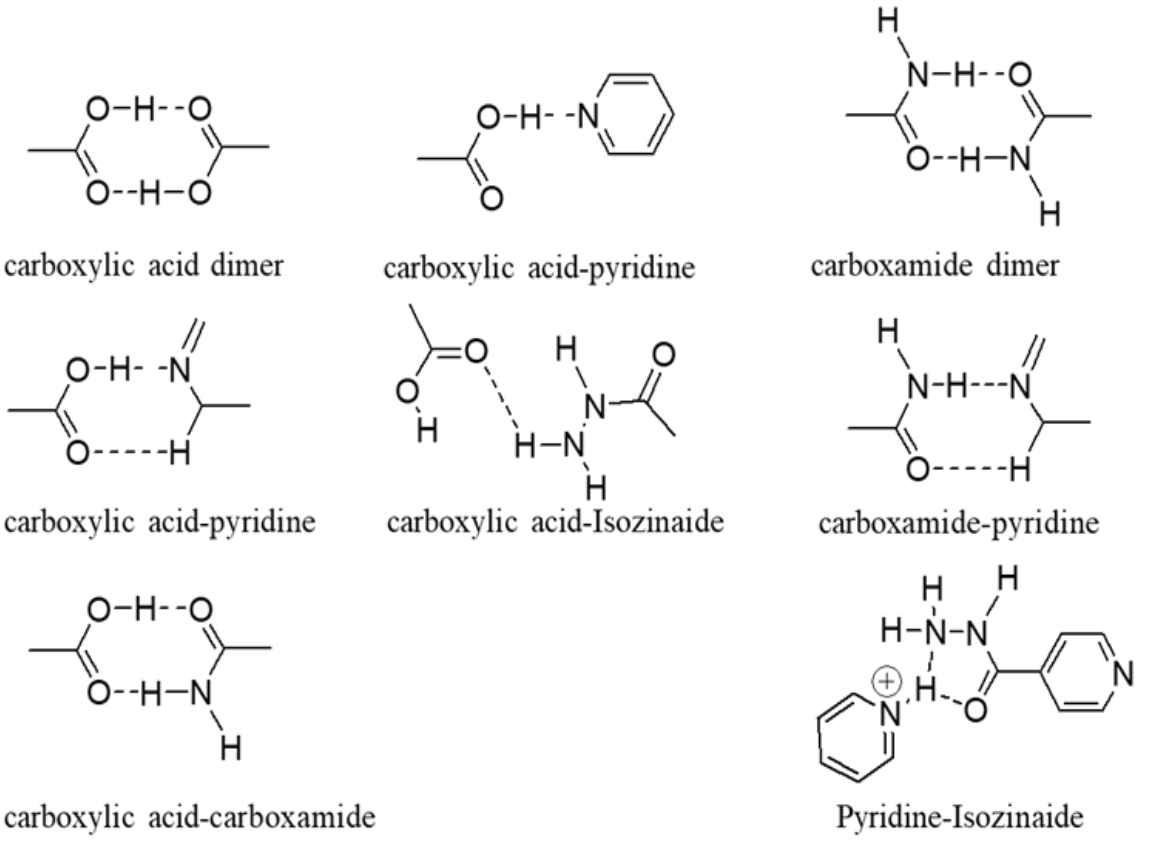


Fig. 4 Various Supramolecular synthons for developing drug-drug cocrystals based on Cambridge Structure Database (CSD).[59,82]

formulation of cocrystals, a computational approach to this process is yet to be developed.

6.4 Gradually introducing drugs inside the solid structure

Multicomponent supramolecular solids are recently developed, where different molecules are crystallized together. In a quaternary cocrystal, resorcinol, tetramethylpyrazine, phenazine and pyrene crystalized together by forming an unusual supramolecular synthone.[92] Similarly, a six-component solid ABC$[D_{1-(x+y)}E_xF_y]_2$ was also reported. In both cases, the process was initiated by designing and developing stoichiometric quaternary cocrystals. A molecule becomes labile in a lower-order cocrystal when it is placed in two different crystallographic environments and the weakly bonded site can be replaced by a new molecule. However, it should also be enthalpically favorable. In this way, a binary system can be grown step by step to ternary, quaternary and so on.[93] This is the first report on developing higher-order multicomponent supramolecular systems. Such a strategy can also be adopted in developing multidrug systems for addressing multidrug resistive pathogens.

7. Selection of multiple drugs for targeting MDR tuberculosis

Covid-19 introduces several indirect effects on our society. Consumption of estrogenic pills during the lockdown period ultimately passes to the environment and presently threatens biodiversity.[94] It also hampered the tuberculosis treatment, which is appearing to be a post covid epidemic.[95] So synthesizing one more new drug will provide doctors one more option of killing a tuberculosis bacteria until it develops resistance again. However, a new drug cannot make the bacteria full forever. We have sufficient drugs, but the process of administration is questionable. In multidrug therapy, we administrate multiple individual drugs separately. We can never ensure that all the drug molecules of different drugs can reach every individual bacteria together. Thus, bacteria in reality get the opportunity to raise the drug resistance one by one and after a few months, new multiple drugs are administered again. The process continues by reducing the bacteria and raising the drug resistivity among the remaining living pathogens. As there is no established alternative to replace multidrug therapy, the practice is continued. If we can take the principle of using multiple drugs to fight against the bacteria before raising drug resistance and engineering the drug molecules to reach a single bacterium together, the philosophy of multidrug therapy will be properly justified. By cocrystallizing multiple drug molecules, we can ensure the multiple drugs together reach to every single bacterium. For designing the cocrystals of multiple drugs, the

supramolecularsynthons[96,97] will be exploited, so that the cocrystal development strategy can be presented. Selecting coformers is only for introducing plasticity, and tabletability will not be worth designing pharmaceutical co-crystals.[45] A coformer must be a drug molecule so that it can fight TB. While selecting the drug molecules, we may also need to select multipurpose drugs, which can cure some additional diseases besides TB, so that, a patient suffering from some other diseases with TB can also be cured without taking any additional drugs. A huge effort is going on to develop new drugs for killing *Mycobacterium tuberculosis* bacteria.[6] Li *et al*. synthesized a series of compounds, where an adamantyl or aromatic headgroup is connected with ethylenediamine or analogous linkers with cationic, protonatable, and neutral backbones to a geranyl tail.[98]

Wide ranges of organic molecules are explored for their anti-tuberculosis property and some of them show potency. According to a study based on 68 approved medicines, it takes approximately 14 years and 800 million US dollars to bring only one new drug to market.[99] A separate study shows that the development of a new regimen of 3-4 drugs takes 15-20 years.[100] Thus, from laboratory to regimen, a drug molecule takes a long time and a series of compounds are in a pipeline as anti-TB candidates. To address such an issue, a noble pan-TB regimen development gained momentum in the last decade and a quest is already started for universal drug therapy.[101] Finding a few complementary drugs for developing universal drug therapy is debatable, as again, one-by-one reaching of drug molecules to a bacteria will enhance the drug resistance slowly. To develop the universal therapy, a proper combination of complementary drug molecules will not be enough but needs to develop cocrystals of such complementary candidates.

8. Developing principle of multidrug cocrystallization

The treatment of tuberculosis typically involves the use of first-line drugs, including isoniazid, rifamycin, pyrazinamide, and ethambutol, while second and third-line drugs such as moxifloxacin, high-dose levofloxacin, linezolid, delamanid, and bedaquiline are also employed in multidrug therapy (Fig. 5).[102] Novel drugs, such as bedaquiline, delamanid, pretomanid, SQ109, and Q203, have been developed based on phenotype treatment.[103] In cases where bacteria develops resistance to a drug molecule, alternative drugs must be used. Co-crystals, solely consisting of TB-treating drug molecules and lacking external co-formers, can provide plasticity and tabletability, ensuring that targeted bacteria receive multiple drug molecules. Supramolecular bonding can group drug molecules together, impeding the development of bacterial resistance. When preparing multidrug therapy, the selection of drug molecules should be guided by the following principles.[104]

i) When selecting drug molecules, it is crucial to choose those with different mechanisms of action to enhance virulence and complement each other. For instance, isoniazid and ethambutol both damage the cell wall through different biochemical mechanisms. By cocrystallizing either of these drugs with rifampicin, pyrazinamide, or streptomycin, the drugs can damage the cellular organelles to destroy the bacteria cells more quickly. Pyrazinamide, relatively smaller than rifampicin and streptomycin, is easier to cocrystallize. By cocrystallizing complementary isoniazid, ethambutol, and pyrazinamide, the medicine can work even faster.

ii) When a bacterium becomes resistant to a particular drug, creating cocrystals using drug molecules with similar biological activity becomes challenging. This is because bacteria can quickly develop resistance to comparable antibiotic compounds. Therefore, when preparing cocrystals, avoiding using similar antibiotic compounds is essential. Moreover, since antibiotic molecules are larger, it is difficult for two or more of them to crystallize together. In such cases, small suitable molecules should be used for crystallization.

iii) To prepare cocrystals, the drug molecules selected based on medicinal considerations should undergo a second screening based on crystal engineering principles. The molecules should be able to form one or more supramolecular synthons when combined. For instance, isoniazid and pyrazinamide are anticipated to form carboxamide dimer or pyridine-isozinaide synthon (as depicted in Fig. 4). Once the appropriate components have been identified, the cocrystals should be prepared using one of the techniques like conventional slow evaporation, diffusion, hydrothermal synthesis.

iv) To preserve the effectiveness of individual drug components, it is recommended to externally add additional amounts of less potent components to the co-crystal.

It is advisable to use established drug regimens for cocrystallization in order to achieve better results with proven potency. A recently useful combination is ceftazidime-avibactam, which works as a cephalosporin-β-lactamase inhibitor. Avibactam is a new type of β-lactamase inhibitor, similar to diazabicyclooctanes (DBO), that binds reversibly to β-lactamase enzymes and enables recycling and rebinding of broad-spectrum β-lactamases. This can enhance the ceftazidime's activity by over a thousand-fold. Avibactam can treat pyelonephritis, complicated intra-abdominal infections (cIAI), and complicated urinary tract infections (cUTI)[13] and provides coverage for Ambler Classes A, C, and D.[105,106]

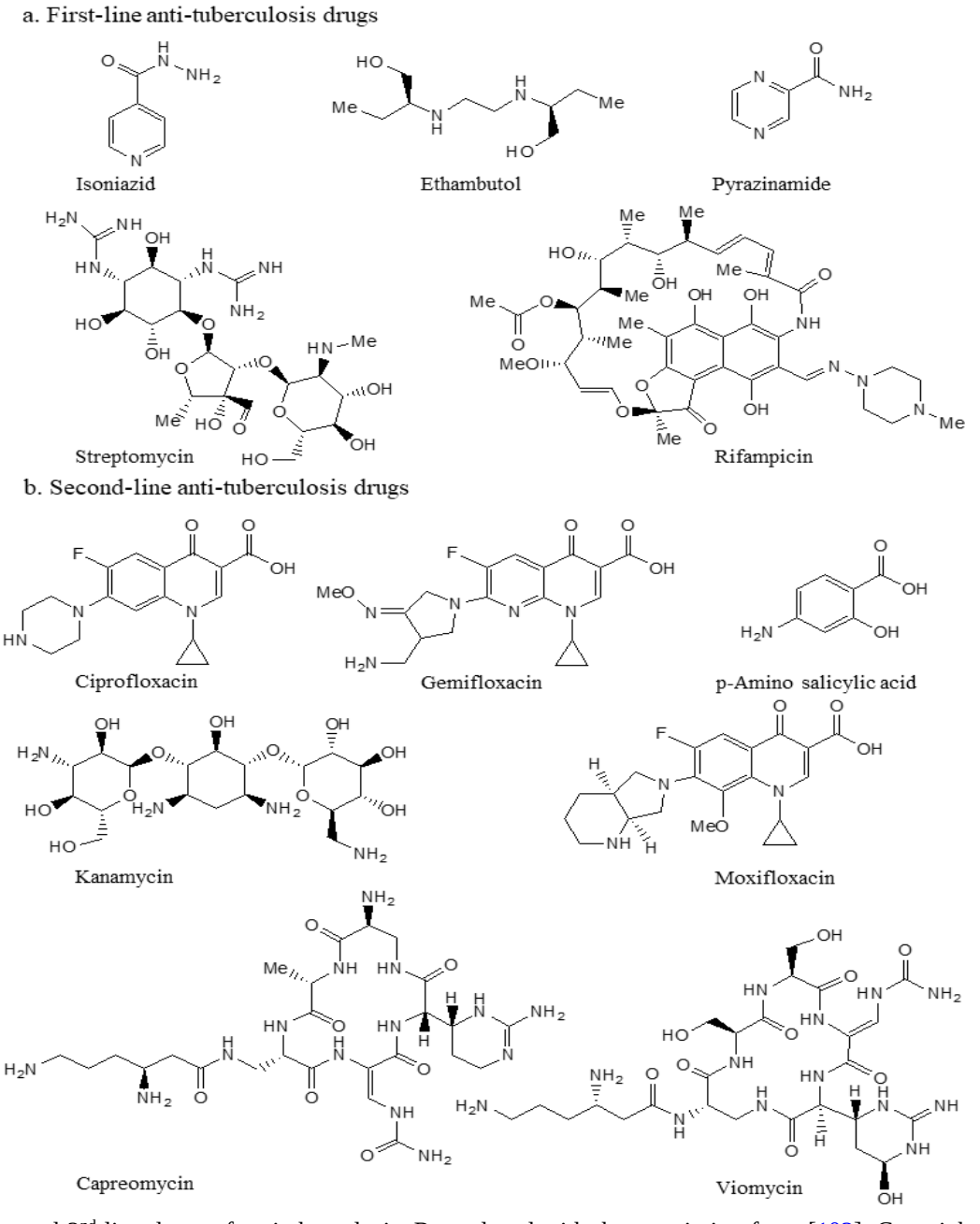


Fig. 5 Few 1st line and 2nd line drugs of antituberculosis. Reproduced with the permission from [102], Copyright 2021 American Chemical Society.

In June of 2019, Ceftolozane-Tazobactam, a newly approved combination of β-lactamase and cephalosporin inhibitors, was introduced as a treatment option for a wide range of infections including hospital-acquired pneumonia (HAP), complicated intra-abdominal infections (cIAI), complicated urinary tract infections (cUTI), and ventilator-associated pneumonia (VAP). This medication is particularly beneficial in treating multidrug-resistant Enterobacteriaceae and Ambler Classes pathogens that have the potential to produce extended-spectrum beta-lactamases (ESBLs). One of the key advantages of Ceftolozane-Tazobactam is that it remains effective against bacterial resistance mechanisms such as efflux pumps, AmpC overproduction, and porin alteration. This makes it significantly harder for bacteria to develop resistance against the drug combination, thereby increasing its effectiveness in managing the aforementioned infections.[107]

The newly developed β-lactamase inhibitor, Relebactam, is used to manage the release of carbapenemase by Gram-negative bacteria.[108] When combined with imipenem-colistatin, the clinical response rate is almost the same as imipenem-relebactam, which is 71.4% and 70.0%, respectively. For optimal clinical response, imipenem-relebactam should be combined with HAP or VAP.[13]

To reduce the duration of treatment, expenses, and mortality rate, it is recommended to employ a suitable supramolecular synthon when creating drug-drug cocrystal. However, if such a synthon is unavailable, co-formers with antibacterial properties, such as salicylic acid and p-aminosalicylic acid, can be used as alternatives.

8.1 Harmonization of drug components in cocrystals

The development of innovative strategies for tuberculosis (TB) therapeutics[109,110] is currently gaining momentum, necessitating effective communication amongst the upcoming generation of TB drug trial researchers, controllers, and policymakers.[100] Typically, it takes 15-20 years to develop a new regimen of 3-4 drugs. However, the past five to ten years have witnessed a surge in the development of pan-TB regimens, due to the growing pipeline of anti-TB drugs with unique modes of action. This upsurge in drug options has made it feasible to develop new regimens that can effectively treat multi-drug-resistant (MDR), extensively drug-resistant (XDR), and drug-susceptible *M. tuberculosis* infections. The development of universal regimens could significantly accelerate global TB control efforts. Nevertheless, predicting the most effective regimens remains a challenge, given the vast array of three, four, or five drug combinations that may be utilized from ten critical drug classes.[101] The ranking of regimens is currently influenced by limited preclinical data and could be improved with more robust clinical trials.[111] As cocrystals are formed with a fixed stoichiometric ratio and work synergistically at the molecular level in the bacterial cell, the potency of individual drug components cannot be determined by their intrinsic potencies alone. Instead, the harmonization ratio of cocrystal formation should be considered, and the effective potency should be experimentally determined. It is expected that cocrystal-based drug systems will require a lower amount of drug components for their enhanced individual potency, which is expected to result from the synergistic effect at the molecular level.

8.2 Preventing mortality, time loss and financial damage

In conventional multi-drug therapy, individual drug molecules are administered separately, which may not guarantee the simultaneous delivery of all drug molecules to each bacterial cell. This therapy's drawback is that it fails to reach all bacterial cells simultaneously, increasing drug resistance during treatment. Consequently, drug molecules often need to be changed during treatment, which prolongs treatment time, increases treatment cost, and may result in health complications, including death. However, supramolecular bonding between multidrug molecules can be utilized to ensure simultaneous delivery to bacterial cells, preventing drug resistance development. This approach can ultimately reduce drug resistance in bacteria. Unlike fixed dose combination therapy, where different drug molecules are not bound to reach target cells to show their synergistic effect, cocrystals can ensure simultaneous delivery to target cells, resulting in better efficacy. Consequently, cocrystals are expected to reduce drug dosage, treatment duration, and treatment cost.

8.3 Potential use of multidrug cocrystals in other sectors

In healthcare facilities specializing in treating bacterial infections such as tuberculosis, it is common for the surfaces of walls, ceilings, and furniture to become contaminated with bacteria. Although it is not feasible to frequently sterilize the entire facility with antibacterial solutions, the transmission of bacteria from inanimate objects can be prevented by applying a coating of multidrug co-crystals to surfaces such as walls, ceilings, doors, windows, and furniture. Coating objects with multi-drug cocrystal powder can be achieved by spreading the powder over a thin layer of adhesive.

9. Conclusions and perspectives

Bacteria possess a range of defensive mechanisms that enable them to resist drug molecules. The outer membrane's porin channels and efflux pumps assist in the removal of foreign substances, including drugs and antibiotics, from bacterial cells. Furthermore, the limited permeability of bacterial cell wall restricts antibiotic uptake. However, if a drug can enter a cell disguised as a beneficial peptide molecule, it will be identified and trigger the production of drug-resistant mechanisms. To address the issue of bacteria developing resistance to a single drug, a new approach called multidrug therapy has been developed, where multiple drugs are administered simultaneously. Nevertheless, administering multiple drugs to a bacteria cell one-by one at a time in the multidrug therapy process frequently promotes drug resistance in bacteria. Once a bacteria cell develops resistance to a single drug molecule and is given time before the second drug molecule's attack, it can transfer the plasmid in bacterial conjugation to other bacteria and acquire resistance against the first drug molecule. This defensive mechanism in bacteria frequently renders several drugs ineffective one by one, leading to increased treatment time, cost, and mortality. Therefore, even slight carelessness can result in fatal consequences for patients.

This scientific review proposes a novel protocol to tackle the issue of multidrug-resistant bacteria. The proposed protocol involves the formation of co-crystals using various

types of supramolecular bonding, including H bonding, π-π stacking, halogen bonding, and Van der Waals' interaction. The co-crystals of different drugs specific to the same type of bacteria can be administered simultaneously, ensuring that all drug components reach the targeted bacteria. The simultaneous delivery of the drugs enhances their effectiveness compared to the ongoing multidrug therapy protocol. The emergence of Covid-19 has exacerbated the issue of multidrug-resistant bacteria, including tuberculosis, which is expected to become the next epidemic after Covid-19. Therefore, the perspective suggests developing several co-crystals of 1st line, 2nd line, and 3rd line tuberculosis drug molecules. This approach will ensure that the crystallized drug molecules reach every single tuberculosis bacteria simultaneously, preventing the development of multidrug resistance and securing the killing of the bacterial cell.

In order to administer multiple drugs to tuberculosis (TB) patients, it is possible to co-crystallize traditional TB medications such as Isoniazid, Rifampin, Ethambutol, and Pyrazinamide. Furthermore, the spread of TB bacteria can be prevented by coating hospital walls, furniture, and ceilings. This technique can also be utilized for other types of multidrug-resistant bacteria. It is imperative to crystallize drugs with complementary bio-mechanisms at bacterial cells and the ability to form appropriate supramolecular synthons from an appropriate solution using one of the conventional crystallization techniques. By developing a series of co-drug co-crystals for multidrug therapy, a range of multidrug-resistant bacteria can be addressed. The distribution patterns of multidrug-resistant bacteria can be analyzed to determine potential threat regions for initiating co-crystal-based multidrug therapy.

Authors Contribution

PS conceptualize the work and prepared the manuscript. IC modified and SR reviewed the work.

Conflict of Interest

There is no conflict of interest.

Supporting Information

Not applicable.

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