3.1. Antimicrobial Resistance:

Antimicrobial resistance is a universal problem. New types of antimicrobial resistance can annoy international borders and blowout amongst continents easily. Many types of resistance blowout significantly fast. World health frontrunners have termed antimicrobial-resistant microbes as “nightmare bacteria” that “have a catastrophic hazard” to public of every country of the world. Every year in world, lots of people get severe infections with bacterial strains having resistance to one or more antibiotics used to cure those infections. Thousands of individuals die every year due to infections of antibiotic-resistant microbes. Many more die from other conditions that were complicated by an antibiotic-resistant infection. Antibiotic-resistant adds substantial and unnecessary costs to previously overstretched healthcare structure. In maximum cases, antibiotic-resistant need elongated and/or expensive treatments demand extra doctor visits, and consequence in larger incapacity and death\textsuperscript{196}.

The overuse of antibiotics is solitary most significant cause leading to antibiotic resistance. Antibiotics are amongst most regularly recommended drugs for human beings. Though, up to 50% of all antibiotics recommended are not required or are not quite effective. Modern regulation from U.S. Food and Drug Administration
(FDA) defines a pathway to control the overuse of antibiotics to diminish the antimicrobial resistance\textsuperscript{197}.

Second major cause in development of antibiotic resistance is blowout of resistant strains of bacteria amongst peoples, or from non-human to environment, together with food.

There are 4 essential activities that will support in fighting these lethal infections:

- Inhibiting infections and inhibiting blowout of resistance.
- Hunt down resistant bacteria.
- Humanizing usage of today’s antibiotics.
- Endorsing development of novel antibiotics and emerging new diagnostic tests.

Bacteria will certainly develop habits of resisting antibiotics we discover, so aggressive action is required to stop new resistance from emerging and to inhibit resistance already exists\textsuperscript{198}.

In 2012, antibiotic improvement lasts to go stale. Two systemic antibacterial drugs have been permitted for use by U.S. FDA from 2008 for human beings. In particular, we have not discovered new antibiotics to treat Gram-negative bacilli (GNB) for about 40 years, wonderfully; fluoroquinolones were last antibiotics to treat GNB. In the intervening time, antibiotic resistance stays to blowout like wildfire, predominantly among GNB. The U.S. and worldwide healthcare systems are meeting on a regular basis extensively drug-resistant (XDR) organisms (exceptionally colistin, a highly toxic agent of questionable efficacy). More badly, we are longsighted pan drug-resistant (PDR) organisms, resistant to all available
antibiotics, including colistin. Examples of XDR and PDR bacteria are plague and carbapenem-resistant bacteria, such as KPC Klebsiella and Acinetobacter. These infections grounds high death rates regardless of existing therapy. They will carry on killing infected patients till new prevention and cure techniques develop.

12 years ago, “The future of humanity and microbes will likely evolve…as episodes of our wits versus their genes” was written by Nobel Laureate Dr. Joshua Lederberg. During this period, we have seen a constant development of antibiotic resistant pathogens. Incredibly, we appear to have stopped our efforts to use our intellects to keep up. Because of this there are three reasons of failure of antibiotic market. First is scientific: Drug screens for novel antibiotics are apt to re-discover the identical lead all over again. Each new generation has outstretched the bar for what is needed to discover and develop next generation. Therefore, discovery of antibiotics has converted scientifically more difficult, more costly, and slow process over time. Second reason is economic: antibiotics signify a underprivileged return on investment comparative to other drugs. Third reason is regulatory: the regulations for antibiotic approval by U.S. FDA have become confusing, normally infeasible. The scientific and regulatory contests evidently raise the cost and timeline of development, which significantly intensifies economic difficulties of antibiotics. Since antibiotics are likely to sell much less than a billion dollars each year, there is as an alternative low acceptance for scientific and regulatory obstructions. The most evident is that antibiotics are petite course therapies, and companies identify that they will earn more money selling a drug that are used every day for the rest of your life. There is correspondingly unfair drug valuing in society. We can pay $50,000 for cancer chemotherapy that extends life by 3 months, but we can’t pay about $100 for antibiotics that cure infection.
The aim here is to develop new drugs with unmet medical need and to extend beneficial lives of critically required new drugs. Without knowing why the FDA has reformed rules leading antibacterial clinical trials, consequence has been a stuffy of novel antibiotic pipeline. Time has come to acknowledge that ways we have used earlier to develop antibiotics have failed. Time for innovative and bold resolutions has arrived to speed up development of novel antibiotics²⁰⁴-²⁰⁵.

3.2. Antimicrobial Resistance in selected Bacteria²⁰⁶:

1. *Escherichia coli*: confrontation to 3rd generation cephalosporins, comprising resistance conveyed by stretched spectrum beta-lactamases and fluoroquinolones.

2. *Staphylococcus aureus*: confrontation to methicillin, methicillin-resistant *S. aureus* [MRSA].

3. *Streptococcus pneumoniae*: confrontation or no susceptibility to penicillin (or both).

4. *Shigella* species: confrontation to fluoroquinolones.

5. *Neisseria gonorrhoeae*: reduced susceptibility to 3rd generation cephalosporins.


7. *Klebsiella pneumoniae*: confrontation to 3rd generation cephalosporins, as well as resistance conveyed by beta-lactamases and carbapenems.

There are some factors which can help to improve the antimicrobial research for academics as well as for industries:

1. All parties should formally acknowledge that the current initiatives under which antibacterial drug discovery and development fall are not working. There needs to
be a move to collaborative working across agencies.

2. Agencies worldwide should examine and promote new approaches that promote the improved and increased role of biotech collaboration with industry, academia and philanthropy.

3. Increased funding for research in the area is required, as are imaginative approaches for identifying such funding outside of Government funded research; this cannot be relied on in the current economic climate.

4. When funding is available, it should be for scientific excellence whether within industry or academia.

5. Academic translational research may benefit from external advisors with industrial experience as demonstrated by the Welcome Trust SDDI management structure.

6. Models for academic/industrial collaboration should be further explored – the Welcome Trust initiative is an excellent one but more are needed – perhaps even more imaginative ones.

7. The role of new chemistry in identifying new compounds should be further explored.

8. Antibacterials are undervalued and there is an urgent need to demonstrate the true cost of both success and failure to develop antibacterial agents.

9. There are a number of economic models that have the potential for estimating the societal costs; however no single model exists that can adequately measure the full spectrum of societal costs (lives lost, productivity lost, excess medical care costs,
etc.) of rising resistance and inaction in discovery and development of antibacterial agents.

10. There needs to be a shift in market perception to realise the true value, and subsequent required market price, of antibacterial agents.

**PLAN OF WORK:**

1. **Literature survey** to identify the available antibiotics (as available drugs are generally natural products and their derivatives) and what kind of synthetic molecules are found active against bacteria and fungus.

2. **Synthesis selection** on the basis of literature survey with the help of Scifinder and Science-direct, it was found that pyrazole and indole derivatives show some antibacterial and antifungal activity. So I choose to synthesize the derivatives of pyrazole and indole to find some molecules of desired activity. Selected molecules general structures are as follows:

   ![Pyrazole Derivatives](image1)
   ![Indole Derivatives](image2)

3. **Selection of scheme of synthesis** the tentative schemes for the synthesis of target molecules are as follows:
Scheme 1

Het NN
N O R2
X
O
R3
Het OH
O
H.HCl
N
O
Het N
O
O
Het Me
OMe MgCl Het
O
N
N O

Scheme 2

X & Y = electonegative atoms
R1, R2 & R3 = substituents

4. Synthesis and physicochemical characterization of designed compounds

a) Synthesis of designed novel compounds

b) Melting point determination

c) Thin layer chromatography (TLC) and column chromatography

d) Spectral studies: MASS, and NMR, IR.
5. **Biological Evaluation of Synthesized Compounds** against gram positive and gram negative strains for antibacterial and antifungal studies to find out the minimum inhibitory concentration (MIC) against few standard drugs available in market.

6. **Compilation of Results** to conclude the work done during complete tenure of research to find good result so that we can render the beneficiary services to the humanity.