Anti-tubercular Activity of Novel Indole and Indane Moiety Containing Derivatives: A Review

By

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A thesis submitted to the Department of Pharmacy in partial fulfillment of the requirements for the degree of
Bachelor of Pharmacy (Hons.)

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Brac University
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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Approval

The project titled "Anti-tubercular Activity of Novel Indole and Indane Moiety Containing Derivatives: A Review" submitted by Anik Roy - 14346001 of Summer 14, 2014 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy on 3rd October, 2019.

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Ethics Statement

The study does not involve any kind of animal trial and human trial.

Abstract

Tuberculosis (TB), a global epidemic, is creating critical situations like MDR, XDR or HIV TB which is causing death to millions of people. The demand of developing specific drugs who work through selective pathway and inhibit the mechanism of particular enzyme or bind with specific sites is not only what it needs to take drug discovery to another level, but also the solution to billions of mass people' problem. Through a vigorous study, impressive information was found about the anti-tubercular activity, *in vitro* and *in vivo* study results against various TB strains and clinical isolates by compounds who are indane and indole moiety containing derivatives. Moreover, these different classes of agents showed different working mechanisms with enhanced activity as compared to currently using standard drugs. Though some lacking were observed, further intensive study and analysis of certain molecules like indane-2-carboxamides can lead towards the next big thing in TB research.

Keywords: Tuberculosis; Resistance; Novel; Anti-tubercular

Dedication

Dedicated to my supervisor, Dr. Hasina Yasmin

Acknowledgement

In the beginning, I would like to thank Almighty God who has blessed me with immense strength. The gratefulness and assistance that Almighty God has provided throughout the journey of accomplishing this project was beyond mentioned. I am really grateful to some people for their constant guidance and supervision without which this project seemed very difficult to finish. That why, I am recognizing them here to convey my gratitude.

Firstly, I would like to express my deepest gratitude, dignity and admiration to Professor Dr. Eva Rahman Kabir, Chairperson and Professor, Department of Pharmacy, Brac University, one of the finest, kindest and elegant human being I have ever come in contact with.

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List of Acronyms

TB	Tuberculosis
WHO	World Health Organization
MIC	Minimum Inhibitory Concentration
MDR TB	Multi Drug Resistant Tuberculosis
XDR TB	Extensively Drug Resistant Tuberculosis
SI	Selectivity Index

Chapter 1

Introduction

1.1 Tuberculosis

Tuberculosis (TB), one of the oldest diseases of mankind, has co-evolved for a long period of times with humans (Hirsh, Tsolaki, DeRiemer, Feldman, & Small, 2004). To elaborate this, in a fossil of a Pleistocene bison which was radiocarbon dated at (17870±230) years, the earliest recognized molecular indication of TB was identified; and in case of human remains, it was retrieved in the Eastern Mediterranean from a Neolithic settlement which was 9000 years old (Rothschild et al., 2001; Hershkovitz et al., 2008). Although Dr. Richard Morton entrenched it as early as in 1689 that the pulmonary version was linked with "Tubercles", TB was not distinguished until the 1820s as a single disease because of the diversity of its symptoms and was eventually named in 1834 as "Tuberculosis" by J. L. Schönlein. Later, on March 24 of 1882, it was discovered by Robert Koch that TB is induced by airborne infection through a bacterium named *Mycobacterium tuberculosis* (Mtb) and as a result, in 1905, the Nobel prize in physiology or medicine was awarded to him (Sakula, 1982). To add with this, March 24 was nominated as "World TB Day" after a century, with a vision to aware the people about the impact TB is having around the world.

1.2 Epidemiology of TB: Global Scenario

TB, a global epidemic, is the dominant cause of death from a single contagious agent and one of the top 10 reasons of death worldwide. To enumerate this, in the Western Pacific and South-East Asia regions, the greatest number of new TB incidents with 62% occurred in 2017, chased by the African region with 25% of new incidents. In addition, among HIV-negative population in 2017, an approximated 1.3 million (m) fatalities and an additional 0.3 m fatalities from HIV-positive population was evoked by TB. Moreover, globally approximately 10.0 m population

has developed TB in 2017: 1.0 m children, 5.8 m men and 3.2 m women. Overall, 9% of them were living with HIV (72% population from Africa) and 90% of them were adults (≥15 years) and almost two third of this was in 8 countries: Bangladesh (4%), India (27%), Pakistan (5%), China (9%), Philippines (6%), Nigeria (4%), Indonesia (8%) and South Africa (3%). Furthermore, these and twenty-two other countries with 87% of global incidents are in World Health organization (WHO)s directory of 30 most TB concerned countries (Figure 1) (World Health Organization, 2018).

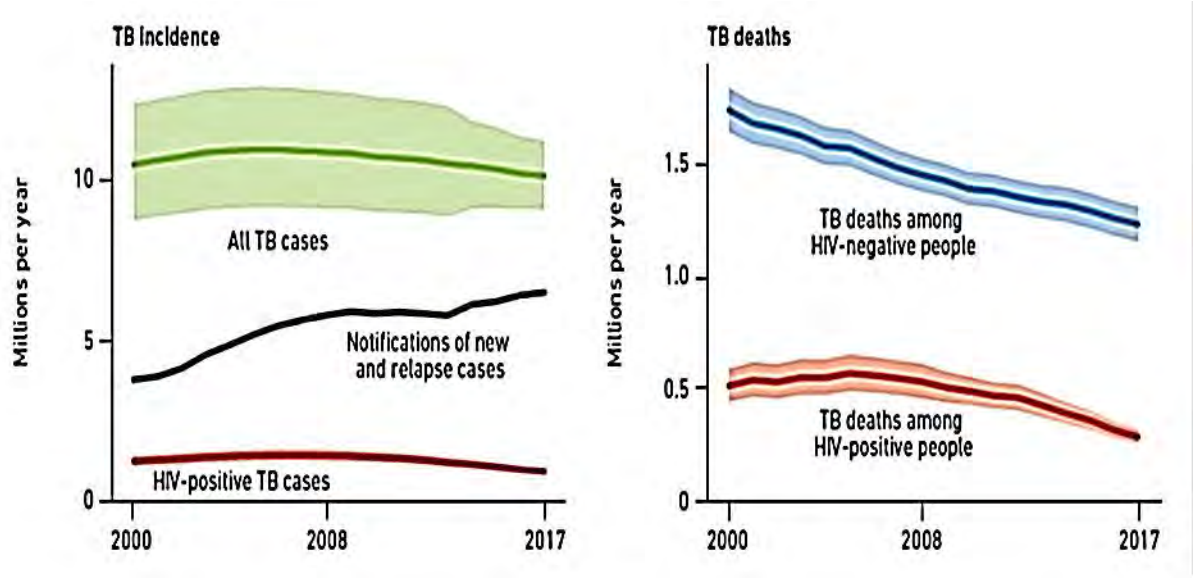


Figure 1: The Approximate Number of TB Incidents and Fatalities Globally; adopted from (World Health Organization, 2018)

1.3 Impact of TB in Bangladesh

In developing countries, TB stays as a top reason of mortality and morbidity, including Bangladesh. To enumerate this, with annual occurrence of 364,000 new cases, Bangladesh is one of the 30 most TB concerned countries. In addition, due to TB, about 59,170 people die annually (Figure 2) (World Health Organization, 2018).

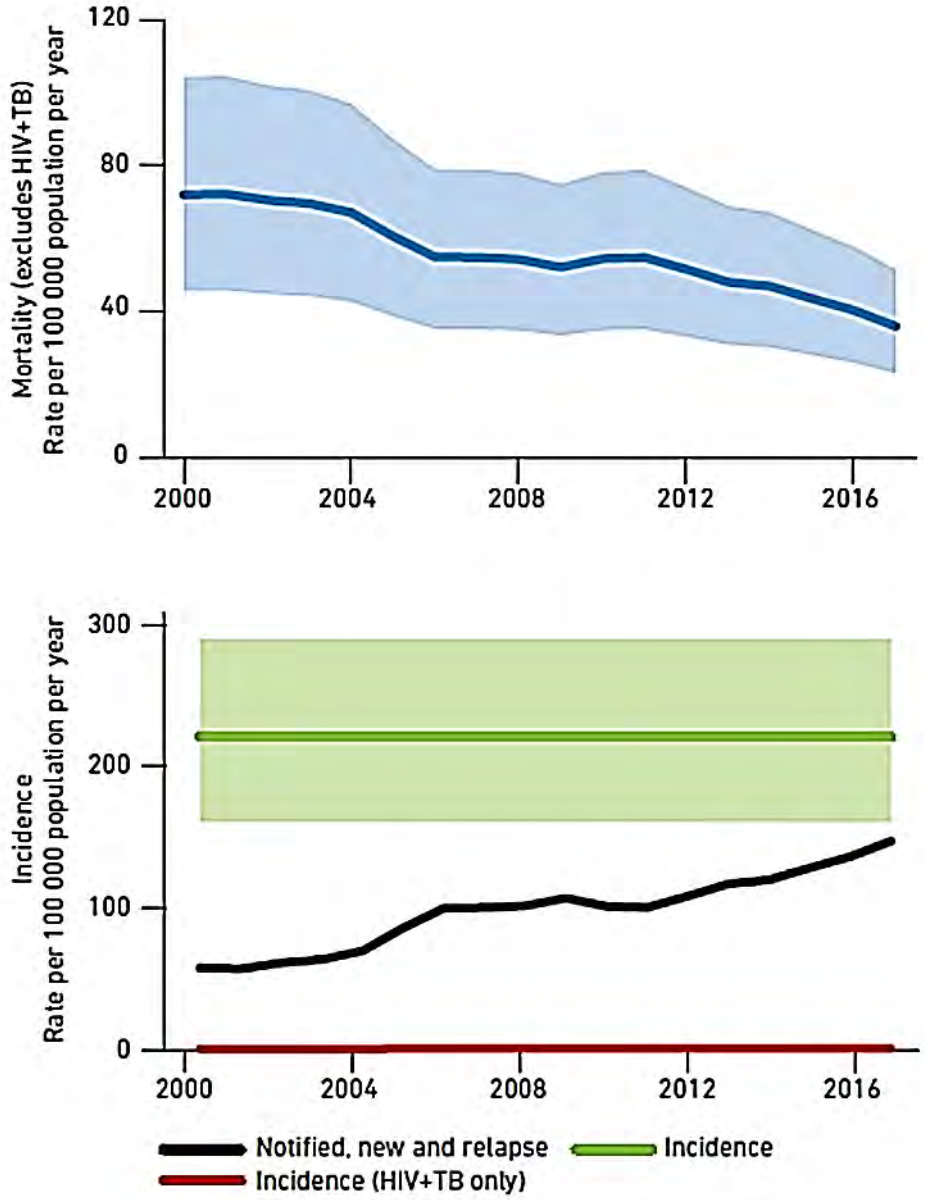


Figure 2: The Approximate Number of TB Mortality Rates and Incidents in Bangladesh; adopted from (World Health Organization, 2018)

1.4 Basic TB Facts

Though Mtb mainly attacks the lungs, it can spread to any part of a human body like spine, nervous system and kidney. To explain this, when people with TB in their lungs or throat sneeze, cough or speak, TB bacteria spread through the air in microscopic droplets and anyone can breathe in them. Moreover, body's natural defence, the immune system usually kills all of

them if someone breathes in TB bacteria and as a result, the person does not get ill. To add with this, it is called active TB, after someone breathes in TB bacteria and becomes sick which can happen during different period of times. On the other hand, it is latent TB, when the bacteria with an inferior level remain in the body as the immune system restricts them and thus that person won't get ill. If someone has active TB but it is not in the lungs or has latent TB, the person is not infectious. In addition, a person with latent TB infection has no symptoms and will need to get a blood or skin test to find out if he or she is infected. On the contrary, usually there are signs and symptoms if a person has the active version of the disease. They incorporate:

- A constant cough which remains for more than 3 weeks and brings out cloudy, thick and sometimes blood-stained sputum or phlegm from deep inside of the lungs
- Weight shrinkage and fatigue
- High temperature and perspiration during night times
- Chest burn and swelling in the neck

In case of latent infection, the infection starts when Mtb penetrates into the lungs to reach the alveolar arena and confront the tenant alveolar macrophages. Either by the pathogens which precisely affect the alveolar epithelium or through the tainted alveolar macrophages moving towards the lung parenchyma, Mtb invades the lung intestinal tissue if the primary line of the immunity fails to eradicate the bacilli. Subsequently, Mtb is transported by either dendritic cell or inflammatory monocytes for T cell priming to pulmonary lymph nodes. This incident leads to the enrollment of immune cells which includes T and B cells towards the lung parenchyma with a vision to formulate a granuloma. On the contrary, in case of active disease, within the growing granuloma, the bacteria replicate. In addition, to contain the infection, the granuloma will fail if the pathogenic haul becomes very large; and including brain, bacilli would disseminate eventually towards other organs (Lin et al., 2014). At this situation, the bacilli can penetrate into the blood stream or re-invade the respiratory system to be delivered. Moreover,

now the affected host is symptomatic, contagious and is believed to possess active TB disease (Figure 3) (Pai et al., 2016).

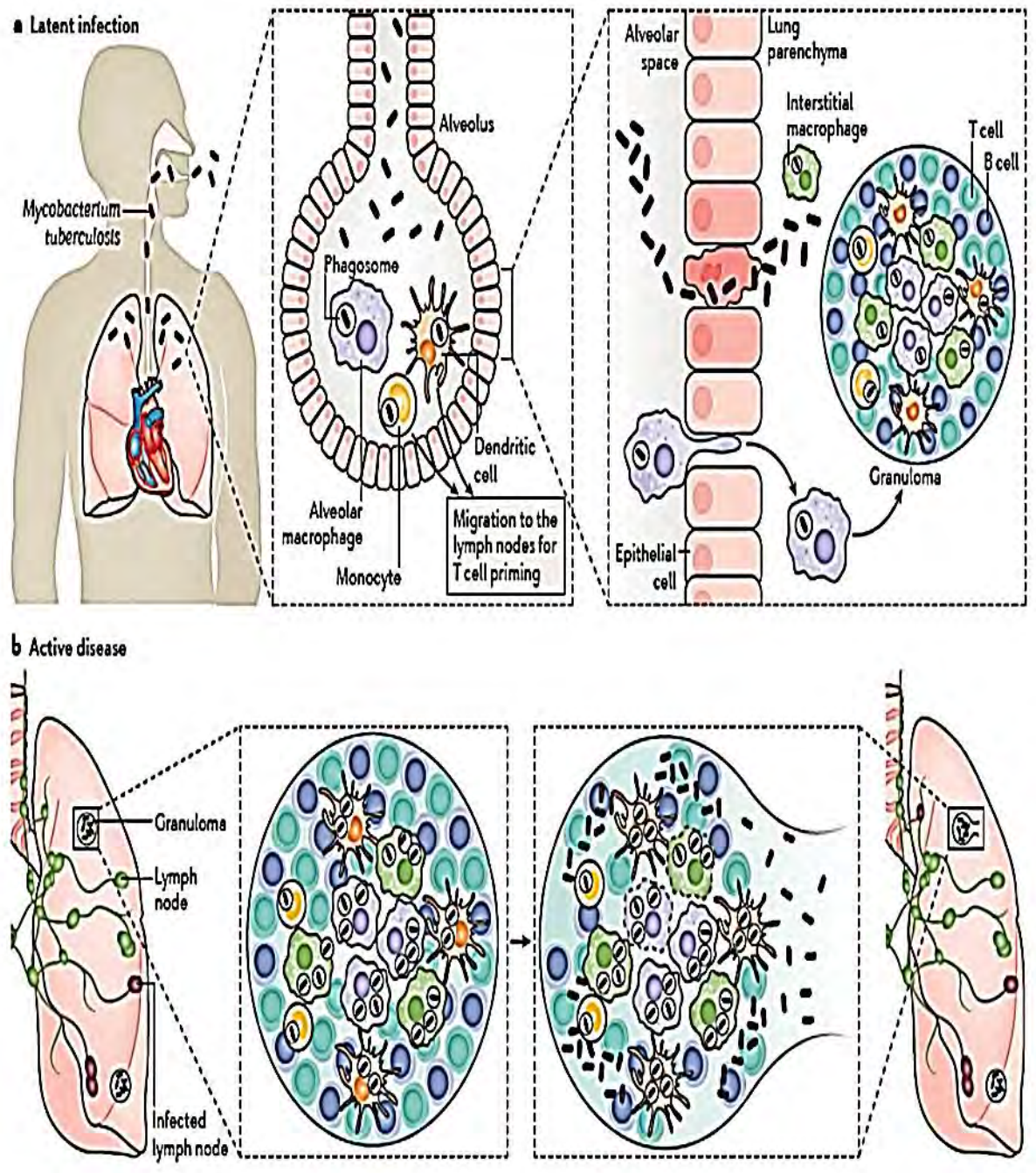


Figure 3: Mycobacterium tuberculosis Infection; adopted from (Pai et al., 2016)

1.5 Treatment of TB

TB is almost always curable through the help of proper treatment. To explain this, the dose and dosage of medications depends on which one works to eradicate the patient's TB condition. To add with this, latent TB can be re-active depending on the risk factors and as a result, can cause an active infection. That's why just in case to kill the inactive bacteria, the doctor might prescribe medication. There are 3 treatment pathways:

- Isoniazid (INH): This is the most prevailing anti-tubercular agent in case of latent TB. An INH antibiotic pill is typically taken by a person daily for around 9 months.
- Rifampin (RIF): A person normally takes this anti-tubercular drug every day for approximately 4 months. This can be an option when someone faces adverse effects or contraindications with INH.
- INH and Rifapentine (RPT): Under the doctor's supervision, a person takes both of these anti-tubercular agents once a week for around 3 months.

A person will need to take a number of antibiotics for around 6-9 months if that person has active TB. These four first-line anti-tubercular agents are most commonly used to treat it:

- Ethambutol (EMB)
- INH
- Pyrazinamide (PZA)
- RIF

The physician may direct to perform a test that analyzes which anti-tubercular agent would terminate that particular strain. In addition, for approximately 2 months, the patient would have around 3 or 4 medicines based on the assessment from the test. Afterwards, for around 4-7 months, that person will take two medications. After a few weeks of this treatment, the patient will probably start to feel better. If that person is still contagious or not, can only be told by a

doctor. Furthermore, the patient must tell the doctor right away if he or she has any of the following symptoms as these are the side effects of the treatment:

- Yellowing of the body surface and the white portion of the eyes
- An unexplained high temperature
- Burning, tingling or numbness of the hands and feet
- Brown or dark urine
- A rash or itchiness

Every dose of the anti-tubercular agent is important to take. If all the bacteria in the body are not killed, the remaining germs can adapt and become resistant to the drugs.

1.6 Drug-resistant TB

A leading public health problem, anti-tubercular drug resistance hampers the improvement made in the care and control of TB globally. To explain this, in 1948 during the early human trial of medications, the aspect of resistance to TB drugs was first mentioned (Daniels & Hill, 1952). Inaccurate use of anti-tubercular agents in the treatment of drug sensitive TB patients causes drug resistance. Moreover, person to person transmittance and negligence during TB therapy are 2 of the major reasons of multidrug resistance as it continues to emerge and escalate. In addition, a patient can transfer this to others when he or she develops the active form by a drug-resistant TB (DR TB) strain. To elaborate this, the bacilli, rebellious to at-least the two most effective first-line anti-tubercular agents, RIF and INH, cause multidrug-resistant TB (MDR TB). In fact, it is becoming more problematic to cure MDR TB in some regions as the patients face a lot of adverse effects, recommended medicines are not always available and paths of therapy are expensive and limited. In addition, extensively drug-resistant TB (XDR TB), a unique version of MDR TB, is defiant to RIF and INH along with any fluoroquinolone and one of the 3 injectable second-line anti-tubercular agents at-least; in other words, capreomycin, kanamycin and amikacin.

1.7 Mystery behind the Drug Resistance

Resistant Mtb strains can abide the anti-tubercular activity by a number of mechanisms, like enzymatic inactivation of anti-tubercular molecules, mutations in target genes, over interpretation of novel effluence pumps and poring modifications in the cell surface and trapping of agents and excess interpretation of proteins tangled in counterbalancing the activity of anti-tubercular drugs (Welch et al., 2005; Beauclerk & Cundliffe, 1987; S Magnet, Courvalin, & Lambert, 2001; Nikaido, 2003; Sophie Magnet, Smith, Zheng, Nordmann, & Blanchard, 2003; Sharma et al., 2016). To describe this, an illustrated schematic diagram has been provided which reflects the potential mechanism (s) of activity of first- and second-line anti-tubercular agents along with that of drug resistance, respectively.

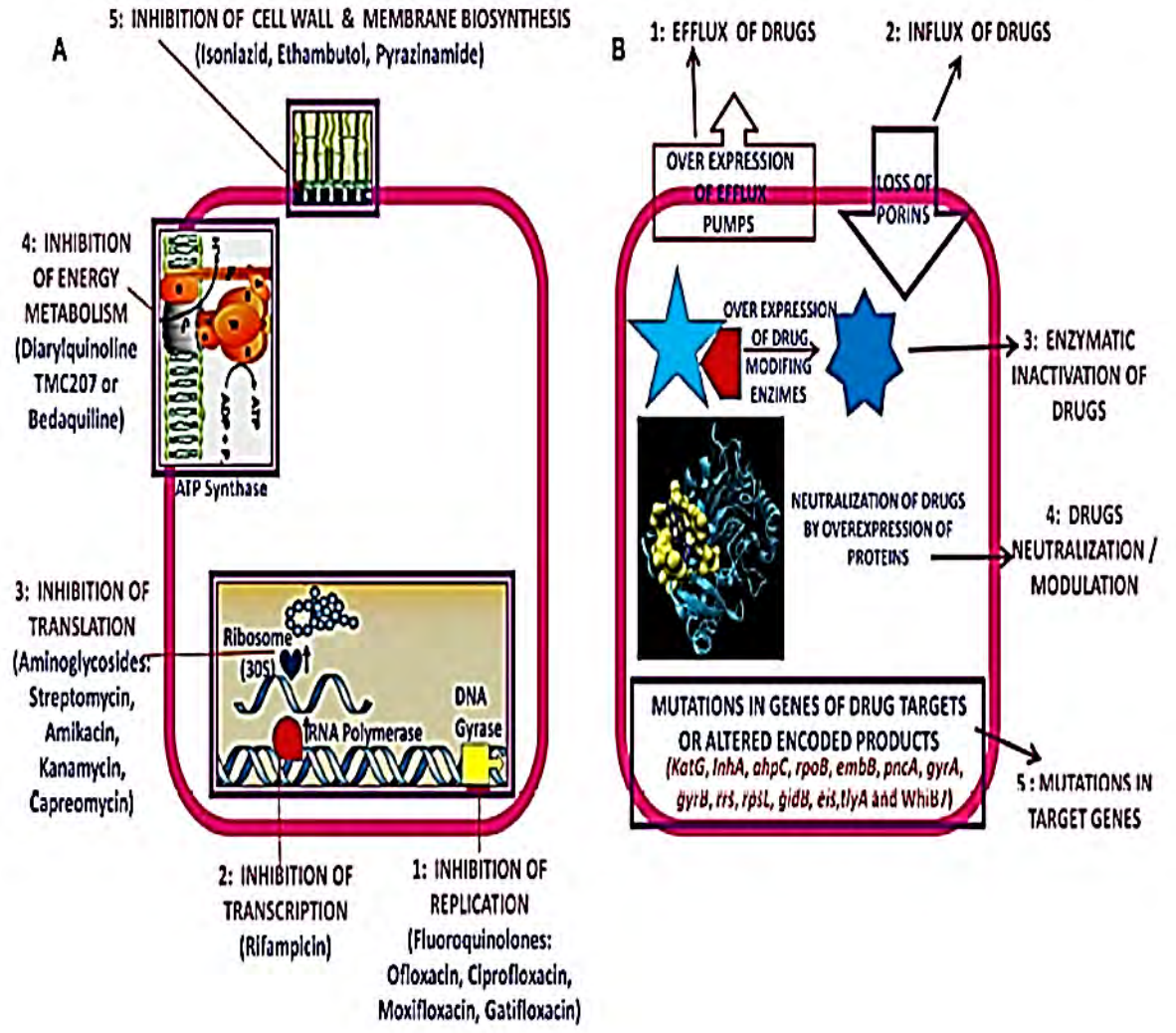


Figure 4: Mechanism (s) of Activity of Anti-tubercular Drugs and that of Drug Resistance in Mtb; adopted from (D. Sharma & Bisht, 2017)

To explain this, the 2 important mechanisms regarding drug resistance in the mutated genes are target modification or a damaged enzyme which turns a prodrug into an active agent. In fact, it is very important to understand the variety of the known mutation as diagnostic assessments constructed to identify resistance should be established on casual mutation only.

Latest surveillance data regarding anti-tubercular drug resistance reflects that 18% of the formerly treated incidents and 3.5% of fresh cases globally are predicted to possess MDR TB or rifampicin-resistant TB (RR TB). In addition, worldwide in 2017, an approximated 558,000 fresh incidents of MDR/RR TB have appeared. Moreover, nearly 8.5% of MDR TB incidents

contained XDR TB. In particular, estimated MDR/RR TB cases are around 5,800 per year in Bangladesh (World Health Organization, 2018). An illustration related to the global outcomes of TB treatment regarding MDR/RR TB has been provided (Figure 5).

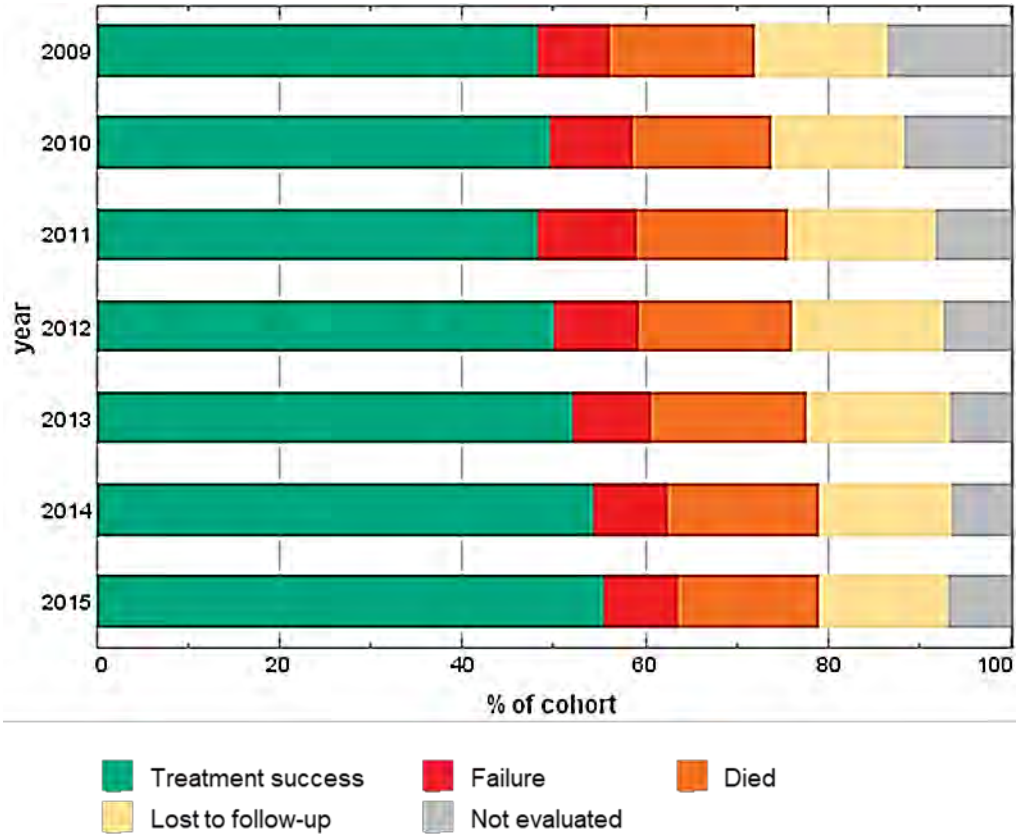


Figure 5: Global Outcomes of Treatment regarding MDR/RR TB; adopted from (World Health Organization, 2018)

1.8 Rationale of the Study

Available standard anti-tubercular drugs are not efficient enough to face current situations the world is facing for TB. To explain this, drug susceptible Mtb, MDR TB, XDR TB, HIV-TB etc. are just making things more and more complex. In addition, from the synthesis to the potential working mechanism of current available standard drugs, nothing is on par with the problems generating. However, through these novel scaffold containing indane or indole moiety, can surely be a solution if the current research and development goes on. Furthermore,

the molecular pathway to bind selectively as the activity against Mtb proved to be the major significance, forced to perform this study.

Chapter 2

Methodology

Diversified approaches and versatile measures were embraced and followed to create an ideal quality review regarded to novel anti-tubercular molecules from indane or indole scaffold. To begin with, a comprehensive pursue regarding peer-reviewed journals, related articles, official reports was performed through well-known and recognized databases, like PubMed, Science Direct, Google Scholar, Elsevier, Scopus etc. and key publications included were - ACS, Springer, Nature, Science etc. Moreover, articles from journals with high impact factor were considered as inclusion for the study. This process concluded with in-depth screening and narrowing down of most relevant 25 articles which were published within last 10 years.

Chapter 3

Results

3.1 Spiro-pyrrolothiazolyloxindoles

The spirocyclooxindole scaffold, whether it's of synthetic or natural origin, is equipped with a variety of pharmacological activities (Kitajima et al., 2006; Bacher et al., 2006; Mugishima et al., 2005; Ding et al., 2005; Ding et al., 2006; Raunak et al., 2005).

3.1.1 Synthesis of ATA 1

1,3-dipolar cycloaddition regarding azomethine ylides which were produced *in situ* through decarboxylative condensation in methanol containing 1,3-thiazolane-4-carboxylic acid with substituted isatins into 2-(arylmethylene)-2,3-dihydro-1H-inden-1-ones, generated novel spiro-pyrrolothiazolyloxindoles in decent yields (Figure 6). Furthermore, all the molecules were evaluated for their potency against Mtb and spiro[5.3′]-5′-nitrooxindole-spiro-[6.3″]-2,3-dihydro-1H-inden-1″-one-7-(2,3-dichlorophenyl)tetrahydro-1H-pyrrolo[1,2-c][1,3]thiazole (ATA 1) was found to be the most potent molecule (Prasanna, Balamurugan, Perumal, Yogeeswari, & Sriram, 2010).

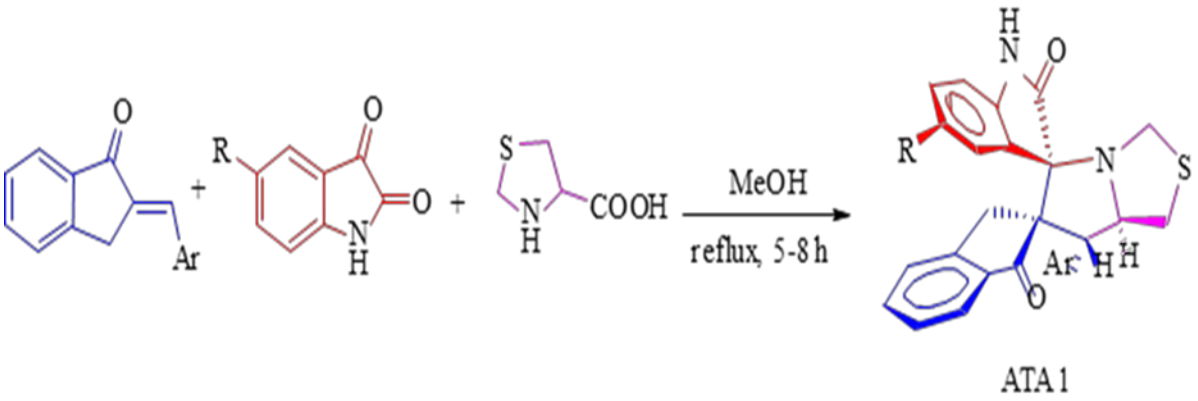


Figure 6: Synthesis of ATA 1; adopted from (Prasanna et al., 2010)

3.1.2 Anti-tubercular Activity of ATA 1

ATA 1 was evaluated for *in vitro* anti-tubercular potency against Mtb strain through Agar dilution method. To explain this, the MIC value is calculated as minimum concentration regarding the compounds which is required to restrain 99% of the pathogenic growth. In addition, MIC values of ATA 1 incorporated with those of common drugs are indexed (Table 1).

Table 1: Anti-tubercular Activity of ATA 1; adopted from (Prasanna et al., 2010)

Compound	Ar	R	Yield (%)	MIC (µM)
ATA 1	2,3-$Cl_2C_6H_3$	NO_2	85	2.8
R	-	-	-	0.1
INH	-	-	-	0.4
Ciprofloxacin	-	-	-	4.7
EMB	-	-	-	7.6

From the analysis, it was found that, the isatin nucleus contains a nitro group and that's why ATA 1 displayed elevated effectivity than others who have different structures. Moreover, with MIC of 2.8 µM, ATA 1 showed 2.70 and 1.67 times more potency than ethambutol (7.6 µM)

and ciprofloxacin (4.7 μM), reciprocally. However, it was not more effective than rifampicin and isoniazid.

3.2 Phaitanthrin congeners

Indole[2,1-b]quinazoline-6-12-dione or tryptanthrin shows a possible dimension for improved anti-tubercular agents since its synthetic derivatives reflect impressive effectivity against Mtb because of its different molecular mechanism (Pergola et al., 2012). To explain this, enoyl-acyl carrier-protein reductase (InhA) was validated as effective anti-microbial target as it is one of the key enzymes. As a result, the tryptanthrin based molecules was being designed in such a way that the keto group was replaced with other functional groups on the molecule core's 6^{th} position.

3.2.1 Synthesis of ATA 2

For the synthesis of β-hydroxyketones, through the existence of N-ethyl piperidine along with diisopropylcarbodiimide (DIC) maintaining 100 °C temperature in dry pyridine, isatin was treated by isatoic anhydride to get the intermediate product. In addition, in the existence of dimethyl amine, aldol condensation regarding that along with ketones produced the tittle compounds (Figure 7). To add with this, all the molecules were evaluated against Mtb strain and 2-aminophenacyl derivative (ATA 2) was found to be the better potent compound (Kamal et al., 2015).

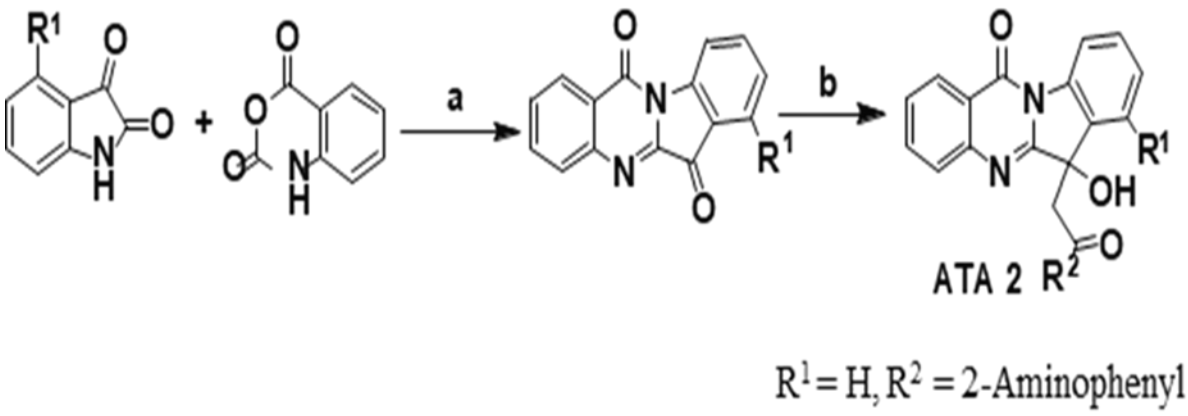


Figure 7: Synthesis of ATA 2; adopted from (Kamal et al., 2015)

3.2.2 Anti-tubercular Activity of ATA 2

Structure-Activity Relationship (SAR) conditions were analyzed based on the results listed (Table 2).

Table 2: Anti-tubercular Activity regarding ATA 2 against Mtb H37Rv (ATCC-27294); adopted from (Kamal et al., 2015)

Compound	Yield (%)	MIC (μM)
ATA 2	92	3.99
Ethambutol	-	15.3
Ciprofloxacin	-	12.6

The replacement found on the ring of ATA 2 reflected impressive effectivity on the anti-tubercular potency. Moreover, ATA 2 showed improved potency through MIC value of 3.99 μM which is better than ciprofloxacin (12.6 μM) and ethambutol (15.3 μM).

3.3 Dispiro-oxindolylpyrrolothiazole analogues

Through the cycloaddition reactions, the five-membered ring heterocycles are synthesized which were found to be very much efficient pharmacologically (Lown & Padwa, A., 1984;

Carruthers, 1990; Padwa & Pearson, 2002; Grigg & Sarker, 2006; Gomes, Nunes, Pais, Pinho e Melo, & Arnaut, 2006).

3.3.1 Synthesis of ATA 3

The tittle compounds were produced *in situ* through the reciprocation regarding 1,3-thiazolane-4-carboxylic acid along with isatin into 2-arylidene-1,3-indanediones which generated decent yields (Figure 8). Furthermore, these compunds were screened against Mtb and it was found that spiro[5.3′]-5′-nitrooxindolespiro-[6.3″]-1H-inden-1″,3″(2H)-dione-7-(4-bromophenyl)tetrahydro-1H-pyrrolo[1,2-c][1,3]thiazole (ATA 3) showed the better activity (Maheswari, Balamurugan, Perumal, Yogeeswari, & Sriram, 2010).

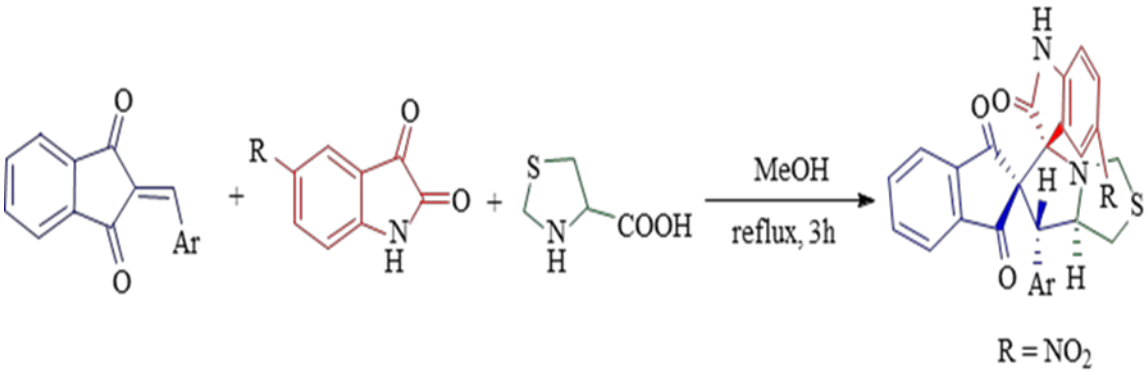


Figure 8: Synthesis of ATA 3; adopted from (Maheswari et al., 2010)

3.3.2 Anti-tubercular Activity of ATA 3

ATA 3 was evaluated for *in vitro* effectivity through Agar dilution method against Mtb H37Rv. To explain this, the MIC value of ATA 3 along with the common drugs were listed (Table 3).

Table 3: Anti-tubercular Activity of ATA 3; adopted from (Maheswari et al., 2010)

Compound	Ar	Yield (%)	Mtb (MIC) (μM)
ATA 3	4-BrC_6H_4	69	1.4
R	-	-	0.1
INH	-	-	0.4
Ciprofloxacin	-	-	4.7
EMB	-	-	7.6

ATA 3 showed improved activity with MIC value of 1.4 μM and it was found to be 5.4 and 3.4 times more effective than ethambutol and ciprofloxacin, reciprocally. To explain this, with respect to the SAR, the replacement into the isatin nucleus, NO_2 showed enhanced activity along with Br which was placed into the aryl ring.

3.4 Diarylpiperazine derivatives

B-carboline derivatives, both natural and synthetic, displayed impressive anti-mycobacterial activity (Rao et al., 2003; Rao et al., 2004). In addition, piperazine containing compounds also displayed wide range of anti-mycobacterial activates (Chetan et al., 2010; Wang et al., 2011).

3.4.1 Synthesis of ATA 4

The synthesis of titled analogues was performed through a course of reactions which started with DL-Tryptophan (Figure 9). Furthermore, these compounds were screened against Mtb and it was disclosed that (4-(2,3-dichlorophenyl)piperazin-1-yl)(9-methyl-1-phenyl-9H-pyrido[3,4-b]indol-3-yl)methanone (ATA 4) showed the maximum potency (Penta, Franzblau, Wan, & Murugesan, 2015).

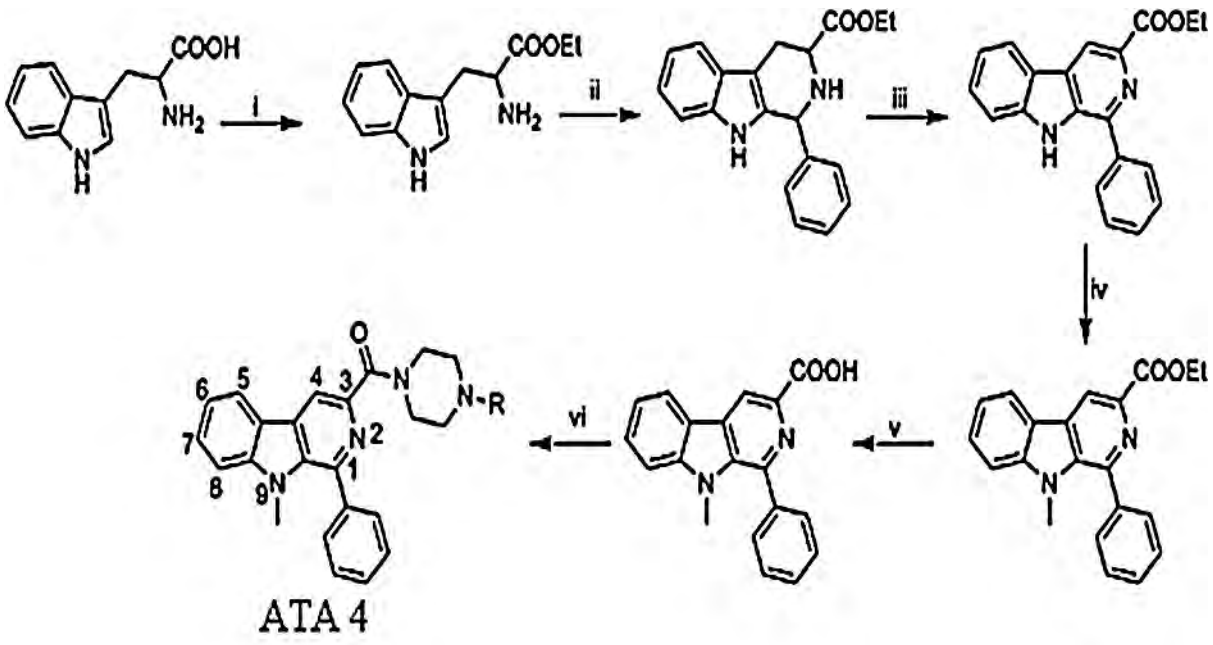


Figure 9: Synthesis of ATA 4; adopted from (Penta et al., 2015)

3.4.2 Anti-tubercular Activity of ATA 4

ATA 4 was screened utilizing Microplate-Alamar-Blue Assay (MABA) to evaluate the effectivity against Mtb H37Rv (L. Collins & Franzblau, 1997). Moreover, the MIC values of ATA 4 along with that of rifampicin were analyzed and listed (Table 4).

Table 4: Anti-tubercular Activity of ATA 4; adopted from (Penta et al., 2015)

Compound	R	Yield (%)	CC_{50} (µg/mL) Vero Cell	MIC (µg/mL)	MIC µM	Selectivity Index (SI)
ATA 4	-2,3-di-ClC_6H_3	74	>50	1.5	2.9	>33.3
Rifampicin	-	-	>150	0.11	0.13	>1363.4

ATA 4 contains 2,3-dichloro replacement on its phenyl ring which generated 8 folds' improvement in the effectivity. Moreover, SAR studies stated that, substitution through pyridyl moiety of phenyl group enhances anti-tubercular potency by 3 times. Furthermore, ATA 4 was screened for the cytotoxicity against Vero-cell lines (Falzari et al., 2005).

3.5 Amphiphilic Indole derivatives

The suggested target of phenothiazines, the desired site regarding NDH2, the mycobacterial membrane would be affected through accumulation which can occur when positively charged lipophilic moiety shows affinity towards negatively charged cellular-compartments (Dunn et al., 2014; Ross et al., 2008).

3.5.1 Synthesis of ATA 5

Synthesis of amphiphilic indole derivatives incorporated 1-bromooctane with the alkylation regarding fluoro or methoxyindole (Figure 10). Furthermore, all the compounds were screened against Mtb and it was stated that 8-[(6-Methoxy-1-octyl-1H-indol-3-yl)methyl]-1,4-dioxa-8-azaspiro[4.5]decane (ATA 5) showed the maximum potency (Yang et al., 2017).

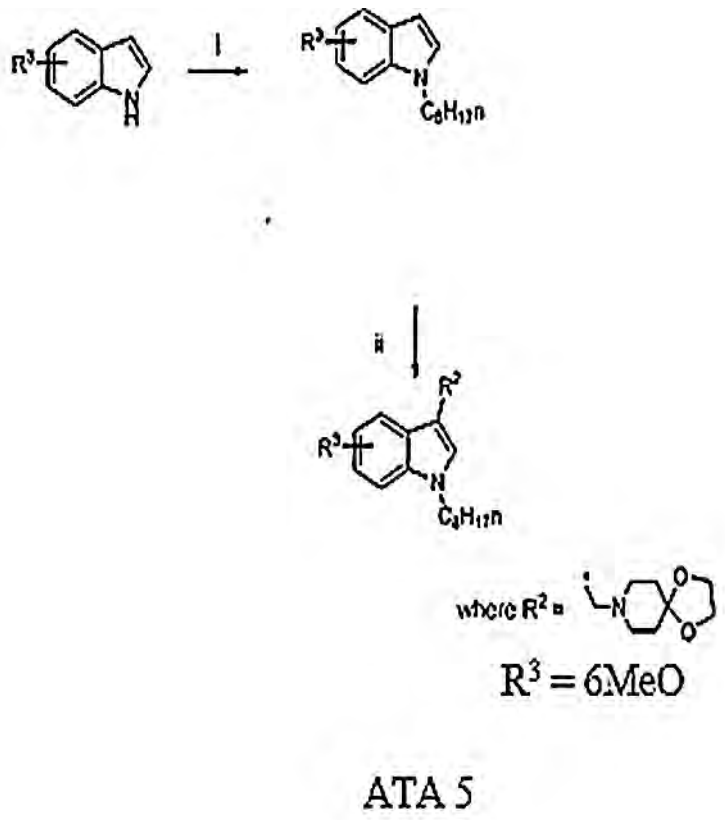


Figure 10: Synthesis of ATA 5; adopted from (Yang et al., 2017)

3.5.2 Anti-tubercular Activity of ATA 5

On the virulent tubercle bacillus, ATA 5 demonstrated potent anti-tubercular activity (Table 5). To explain this, the selective activity of ATA 5 was assessed on Vero and HepG2 cell lines.

Table 5: Anti-tubercular Activity of ATA 5; adopted from (Yang et al., 2017)

Compound	Yield (%)	MIC (μM) Mtb H37Rv (ATCC-27294)		Selectivity (HepG2)		Selectivity (Vero)	
		MIC_{50}	MIC_{90}	IC_{50}	SI	IC_{50}	SI
ATA 5	75	1.2	2.3	15.7 (± 0.5)	13.1	46.1 (± 3.3)	38.4

The lipophilic tail and aminomethyl side chain were predicted through SAR study as necessity for anti-tubercular activity which might not be sufficient. Moreover, by the insertion of H bonding, dioxa-azaspiro[4.5]decane at 2nd position or methoxy at 3rd position increased the selectivity and potency which were determined in ATA 5. In addition, isoniazid was used as the standard drug to analyze the potency.

3.6 Indole-pyridine derived Hydrazide-hydrazones

Indole derivatives were found effective against Mtb through pathogenic respiration and interceptions of cell surface biosynthesis. To add with this, inhibitors of MmpL3, CYP125A1, DprE1, indoleamine 2,3-dioxygenase (IDO), Mtb protein tyrosine phosphatase B enzymes, etc. (Ballell et al., 2013; Ouellet, Kells, Ortiz de Montellano, & Podust, 2011; Abdel-Magid, 2015).

3.6.1 Synthesis of ATA 6

The target compounds were produced through the reaction of pyridine-4-carbonhydrazide along with 2-ethoxycarbonyl/2-hydroxycarbonyl-indole-3-carboxaldehydes (Figure 11). Furthermore, all the molecules were evaluated against Mtb and it was disclosed that hydrazide-hydrazone derivative (ATA 6) showed maximum potency (Velezheva et al., 2016).

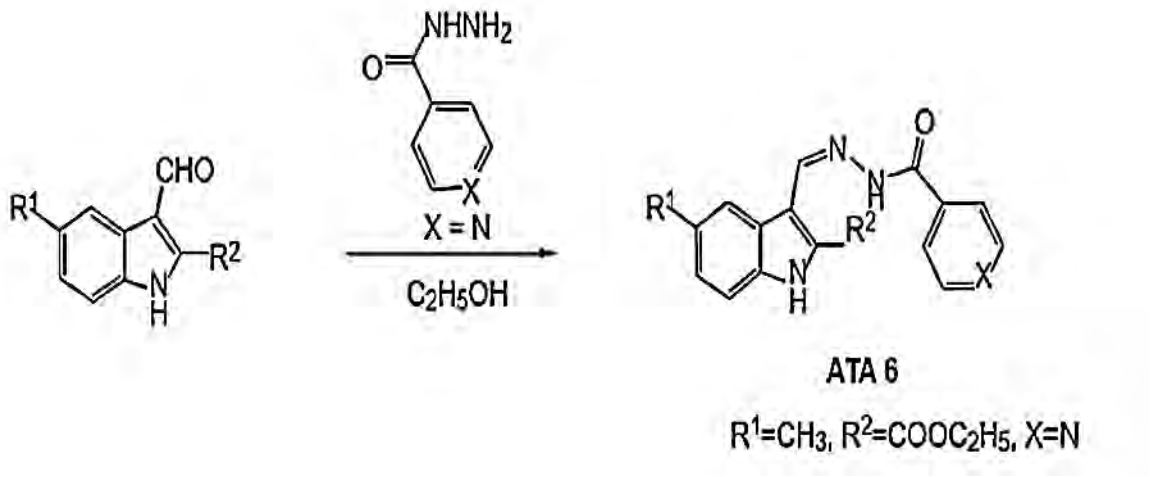


Figure 11: Synthesis of ATA 6; adopted from (Velezheva et al., 2016)

3.6.2 Anti-tubercular Activity of ATA 6

ATA 6 was evaluated *in vitro* for anti-tubercular effectivity against Mtb H37Rv strain and a clinical-isolate regarding INHR Mtb which is designated as CN-40 (Table 6).

Table 6: Anti-tubercular Activity of ATA 6; adopted from (Velezheva et al., 2016)

Compound	Yield (%)	MIC µg/mL against H37Rv	MIC µg/mL against CN-40
ATA 6	82	0.05	2-5

ATA 6 was analyzed with MIC value of 0.05 µg/mL which challenges that of INH. Moreover, the anti-tubercular effectivity of ATA 6 was found to be better than ethambutol (0.5 µg/mL) (Rastogi, Labrousse, & Goh, 1996). To add with this, against INHR strain Mtb CN-40, the MIC of ATA 6 was 2-5 µg/mL in comparison with that of INH (20 µg/mL).

ATA 6 was also evaluated for cytotoxicity as IC_{50} was calculated and thus SI was established in macrophages against Mtb H37Rv (Table 7) (Majorov et al., 2003).

Table 7: IC_{50} and SI value of ATA 6; adopted from (Velezheva et al., 2016)

Compound	IC_{50}	SI
ATA 6	15	300

ATA 6 displayed SI value of 300 and was nearly as potent as INH against Mtb H37Rv. However, contrasted to INH, ATA 6 displayed enhanced activity against CN-40 stain. To be specific, ATA 6 contains $COOC_2H_5$ at 2^{nd} position of indole ring which is in the vicinity

towards the azomethyne C=N aggregation and as result provides enhanced conditions for interception into the pathogenic cells (Zoubi, Kandil, & Chebani, 2014; S. Kumar, Dhar, & Saxena, 2009). To add with this, changes in the interception of the molecule may generate changes in the potency for the target and inflect molecular effectivity (Ballell et al., 2013). It can be speculated that improved anti-tubercular activity can be achieved through acquired synergism of INH-indole hybrids.

3.7 5,6-dimethoxy-1-oxo-2,5-dihydro-1H-2-indenyl-5,4-substituted Phenyl Methanone derivatives

Novel diketone scaffold contain a quite stable function which is behind the impressive anti-mycobacterial potency against INHR Mtb.

3.7.1 Synthesis of ATA 7

The synthesis of a course regarding substituted phenyl-5,6-dimethyl-1-oxo-2,5-dihydro-1H-2-indenylmethanone derivatives was performed (Figure 12). Furthermore, all the compounds were evaluated against Mtb along with INHR TB strain and it was stated that 5,6-dimethoxy-1-oxo-2,5-dihydro-1H-2-indenyl-4-fluorophenylmethanone (ATA 7) showed the maximum potency (Ali et al., 2009).

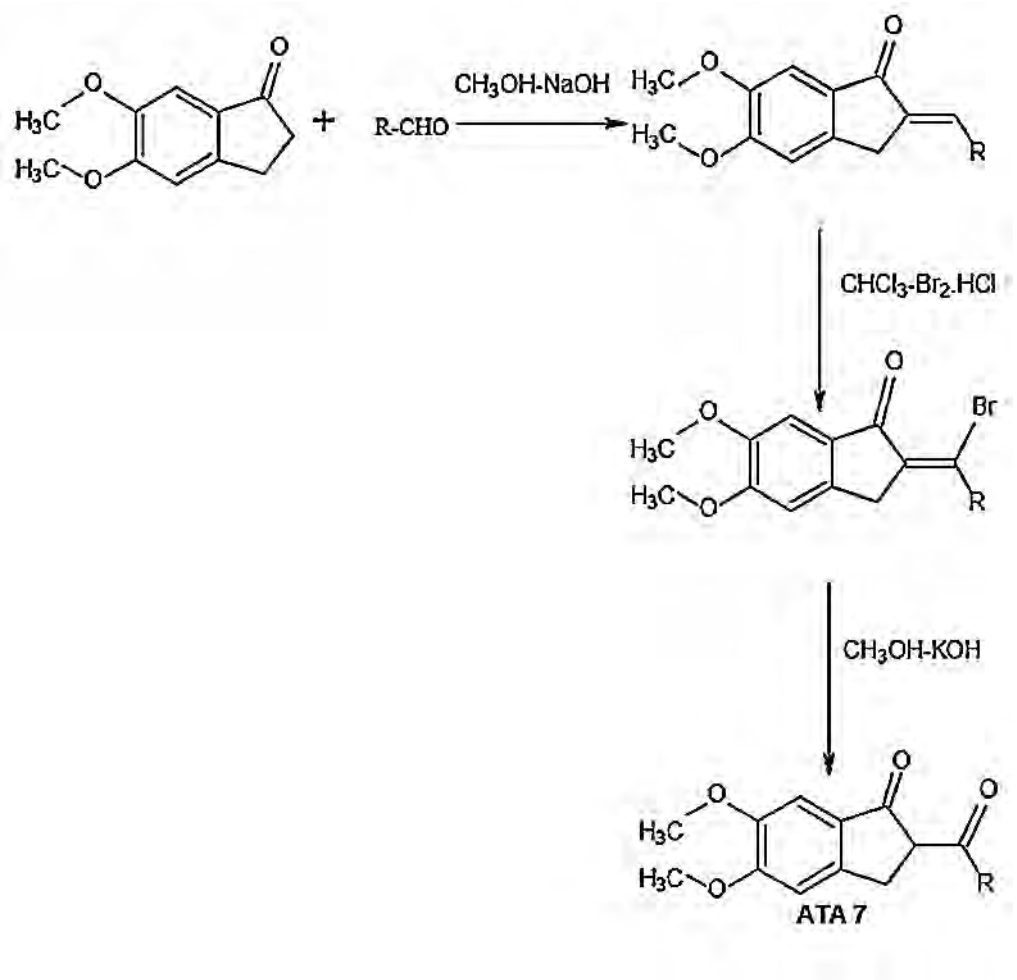


Figure 12: Synthesis of ATA 7; adopted from (Ali et al., 2009)

3.7.2 Anti-tubercular Activity of ATA 7

ATA 7 was evaluated *in vitro* for the anti-tubercular potency through Agar dilution method against Mtb along with INHR TB strain (Heifets, Flory, & Lindholm-Levy, 1989). To discuss this, the MIC value of ATA 7 was reported with that of INH for comparison (Table 8).

Table 8: Anti-tubercular Activity of ATA 7; adopted from (Ali et al., 2009)

Compound	R	Yield (%)	MIC (μM)	
			Mtb	INHR-Mtb
ATA 7	4-Fluoro phenyl-	92	0.10	0.10
INH	-	-	0.75	11.57

ATA 7 showed 115.7 and 9.12 times more effectivity versus INHR TB strain and Mtb, reciprocally. To explain this, the replacement of the election eliminating group caused impressive enhancement in anti-tubercular activity. Moreover, in Vero-cell lines, ATA 7 was screened for cytotoxicity where till 62.5 µg/mL, it showed to be non-toxic (Gundersen, Nissen-Meyer, & Spilsberg, 2002).

3.8 6,7-dimethoxy-3-(4-pyridyl)-2,3,3a,4-tetrahydroindeno[1,2-c]pyrazol-2-yl-4-substituted Phenylmethanone analogues

Substituted pyrazoline analogues displayed improved activity versus a variety of microbial species (Ali, Shaharyar, & Siddiqui, 2007; Ali, Samy, et al., 2009; Küçükgüzel & Rollas, 2002; Ali & Shaharyar, 2007; Shaharyar, Ali, Bakht, & Murugan, 2008; Ragavan, Vijayakumar, & Kumari, 2010).

3.8.1 Synthesis of ATA 8

The synthesis of tittle compounds was performed in room temperature by the help of condensation of isonicotinaldehyde along with 5,6-dimethoxy-1-indanone in 30% methanolic sodium hydroxide. Moreover, in the existence of glacial acetic-acid, the intermediate product was treated along with proper acid hydrazide to generate desired compounds (Figure 13). Furthermore, all the compounds were evaluated against Mtb and it was stated that 6,7-dimethoxy-3-(4-pyridyl)-2,3,3a,4-tetrahydroindeno[1,2-c]pyrazol-2-yl-4-pyridyl methanone (ATA 8) displayed the most potent activity versus Mtb along with INHR TB strain (Ali et al., 2012).

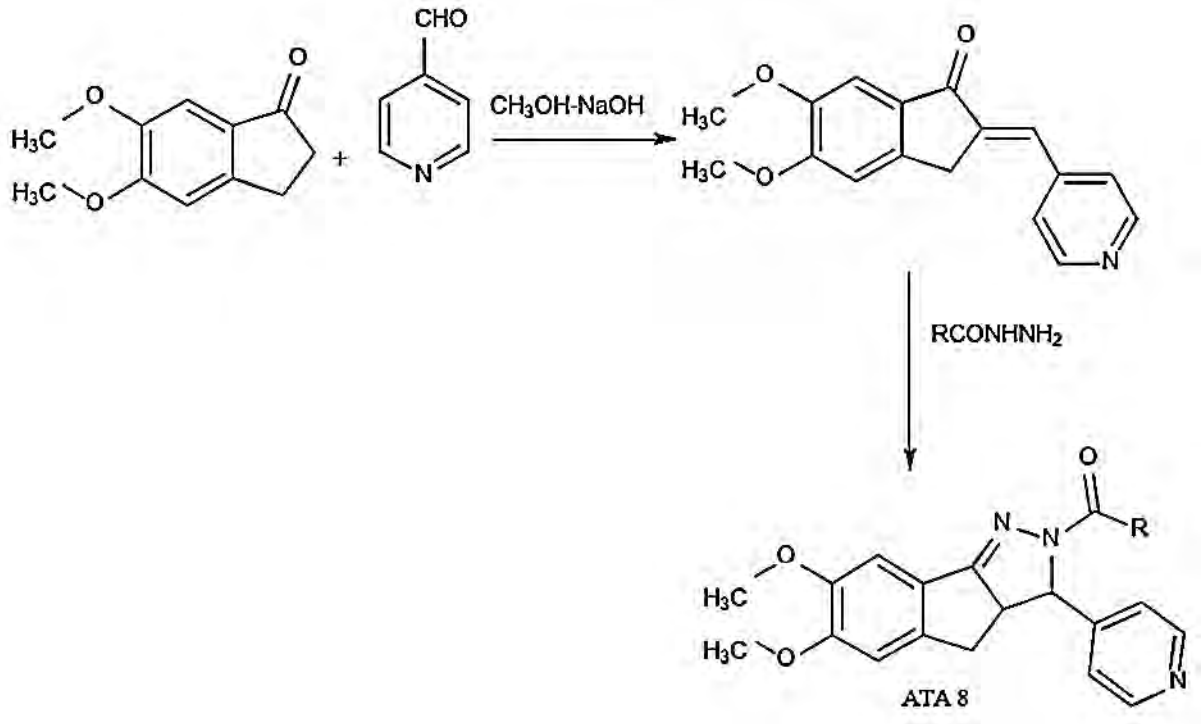


Figure 13: Synthesis of ATA 8; adopted from (Ali et al., 2012)

3.8.2 Anti-tubercular Activity of ATA 8

The MIC value of ATA 8 against Mtb was found to be 0.22 µM. To explain this, ATA 8 showed 15.7 and 3.12 times more effectivity in comparison with that of INH versus INHR TB strain along with Mtb, reciprocally. Furthermore, in Vero-cell lines, ATA 8 was also evaluated for cytotoxicity and it showed no toxicity till 62.5 µg/mL (Table 9) (Gundersen et al., 2002).

Table 9: Anti-tubercular Activity of ATA 8; adopted from (Ali et al., 2012)

Compound	R	Yield (%)	MIC (µM)		Cytotoxicity
			Mtb	INHR-Mtb	
ATA 8	Pyridyl-	65	0.22	0.72	>62.5
INH	-	-	0.73	11.37	>62.5

The first-line evaluation was conducted versus Mtb H37Rv (ATCC-27294) along with INHR TB strain through BACTEC 460 radiometric system (Heifets et al., 1989).

3.9 Dispiropyrrolidines

Heterocyclic compounds who possess 5 or 6 membered rings showed enhanced pharmacological activities (Amal Raj, Raghunathan, SrideviKumari, & Raman, 2003). Moreover, spiro molecules have displayed comparable or even improved potency than few of the standard anti-tubercular agents.

3.9.1 Synthesis of ATA 9

Preparation of substituted analogues was performed through a sequence of reaction (Figure 14). The synthesized compounds were screened utilizing Agar dilution method against Mtb along with INHR TB strain and it was stated that 4′-[5-(4-fluorophenyl)pyridin-3-yl]-1′-methyldispiro[indan-2,2′pyrrolidine-3′,2″-indan]-1,3,1″-trione (ATA 9) displayed better anti-tubercular activity (Wei, Ali, Choon, Arshad, & Razak, 2012).

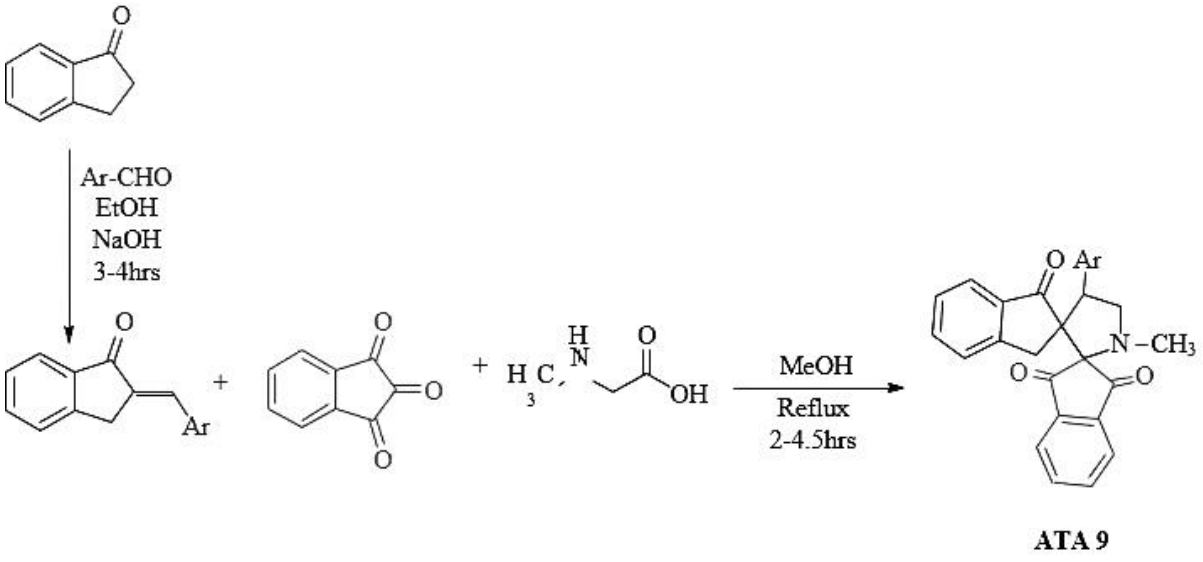


Figure 14: Synthesis of ATA 9; adopted from (Wei et al., 2012)

3.9.2 Anti-tubercular Activity of ATA 9

ATA 9 was evaluated *in vitro* for anti-tubercular effectivity utilizing Agar dilution method versus Mtb H37Rv along with INHR TB strain to determine the MIC value (L. A. Collins & Franzblau, 1997; Gundersen et al., 2002). Furthermore, at a concentration around 0.1215 µM and 5.121 µM, ATA 9 displayed >90% suppression versus Mtb along with INHR TB strain, reciprocally. To add with this, in Vero-cell lines, ATA 9 was screened for cytotoxicity and determined as non-toxic till 62.5 µg/mL (Table 10).

Table 10: Anti-tubercular Activity of ATA 9; adopted from (Wei et al., 2012)

Compound	Ar	Microwave irradiation (100 °C, 100 W)	MIC (µM)		Cytotoxicity (µg/mL)
		Yield (%)	Mtb H37Rv	INHR-Mtb	
ATA 9	5-[(4-Fluorophenyl)-pyridine	94	0.1215	5.121	>62.5
INH	-	-	0.73	11.23	>62.5

3.10 Thioridazine derivatives

Thioridazine (TZ) has lately been altered as anti-tubercular agent as it showed indications regarding the therapy of MDR TB (L. Amaral, Kristiansen, Viveiros, & Atouguia, 2001). To explain this, due to the adverse effects on CNS along with cardiovascular system, TZ is utilized as third-line anti-tubercular agent now (Leonard Amaral & Molnar, 2012). However, it intercepts the efflux pumps inside pathogens and thus changes the cell vesicle permeability of

Mtb (Rodrigues, Ramos, Couto, Amaral, & Viveiros, 2011; Machado et al., 2012; de Keijzer et al., 2016). Furthermore, it improves the capture regarding potassium ions along with spreading the acidification of phagolysomal germ and as a result it moves towards deterioration related to intramacrophagic Mtb (Martins et al., 2007). Therefore, phenothiazine core which is accountable for the fundamental adverse effects was substituted by another hetero-aromatic rings with the determination to lower the toxicity.

3.10.1 Synthesis of ATA 10

The synthesis of tittle compounds was performed which heterocycles contain ethyl-piperidine chain (Figure 15). Furthermore, these molecules were screened against Mtb strain and clinical isolates and it was disclosed that the indole derivative, 1-(2-(piperidin-2-yl)ethyl)-1H-indole (ATA 10) showed the maximum potency (Scalacci et al., 2017).

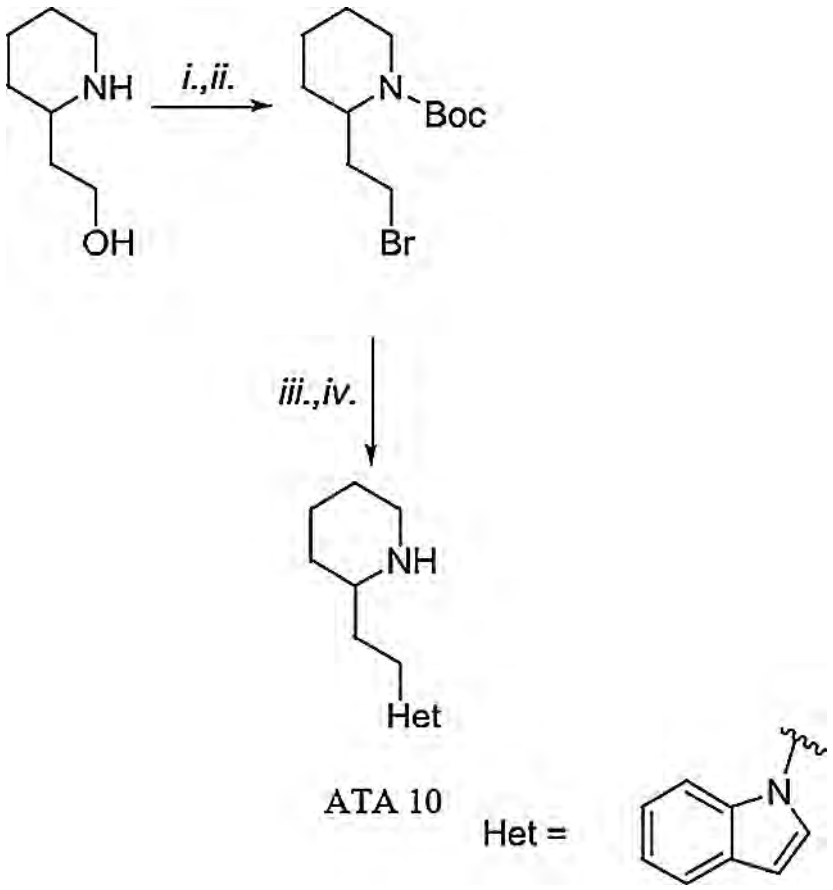


Figure 15: Synthesis of ATA 10; adopted from (Scalacci et al., 2017)

3.10.2 Anti-tubercular Activity of ATA 10

ATA 10 was screened versus Mtb strain, drug-susceptible and MDR clinical-isolates (Table 11).

Table 11: Anti-tubercular Activity of ATA 10; adopted from (Scalacci et al., 2017)

Compound	Yield (%)	MIC (µg/mL) Mtb		MIC (µg/mL) MDR-TB	
		H37Rv	Susc. (CF73)	CF104	CF81
ATA 10	94	2.9	1	10	4
INH	-	0.03	0.03	>25	>25
RIF	-	0.3	8	>25	>25

ATA 10 displayed an impressive anti-tubercular activity with MIC value of 1 and 2.9 µg/mL for drug-susceptible along with Mtb H37Rv strain, respectively. Moreover, the molecule displayed potential profile versus MDR TB strains with MIC value of 10 and 4 µg/mL. To explain this, on piperidine side-chain, the existence of secondary amine enhanced the anti-tubercular effectivity (Bhakta et al., 2016).

Finally, ATA 10 was screened for the cytotoxicity as it displayed SI value which was 15 times more than TZ (Table 12) (O'Brien, Wilson, Orton, & Pognan, 2000; Pavan et al., 2010).

Table 12: Cytotoxicity of ATA 10; adopted from (Scalacci et al., 2017)

Compound	IC_{50} J774	IC_{50} MRC-5	SI
ATA 10	7.3 µg/mL	15 µg/mL	15

The anti-tubercular activity of ATA 10 was determined utilizing Resazurin-Microtiter-Assay (REMA) method against Mtb H37Rv (ATCC-27294), drug-susceptible and MDR TB clinical-isolates (Palomino et al., 2002).

3.11 2-aryl-3,4-dihydro-2H-thieno[3,2-b]indole analogues

Indoles are with great significance in view of their wide ranging pharmacological activities (Somei & Yamada, 2003; Satoshi Hibino & Choshi, 2002; S Hibino & Choshi, 2001; Lounasmaa & Tolvanen, 2000; Gribble, 1996). In addition, improved pharmacological effectivities were also displayed by heterocycles which contain thiophene fused-nitrogen.

3.11.1 Synthesis of ATA 11

The tittle compounds were generated through a sequence of reactions with Fischer-indole synthesis (Figure 16). Moreover, all the molecules were evaluated against Mtb and it was stated that [2-(2,4-dichlorophenyl)-7-fluoro-3,4-dihydro-2H-thieno[3,2-b]indole] (ATA 11) showed better potency (Karthikeyan, Perumal, Shetty, Yogeeswari, & Sriram, 2009).

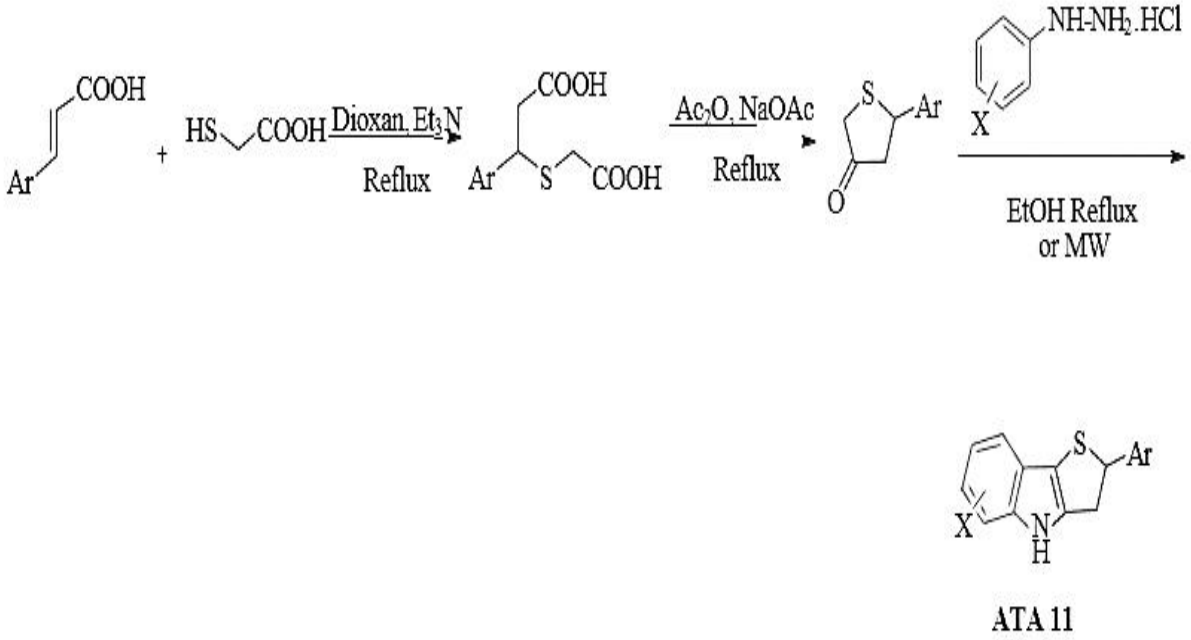


Figure 16: Synthesis of ATA 11; adopted from (Karthikeyan et al., 2009)

3.11.2 Anti-tubercular Activity of ATA 11

ATA 11 was tested *in vitro* for anti-tubercular efficacy and through Agar-dilution method, for both Mtb and MDR TB strains, the MIC value of ATA 11 was compared with those of common drugs (Table 13).

Table 13: Anti-tubercular Activity of ATA 11; adopted from (Karthikeyan et al., 2009)

Compound	Ar	X	Yield (%)		MIC (µg/mL)	
			Reflux	MW	Mtb	MDR-TB
ATA 11	2,4-$Cl_2C_6H_3$	7-F	95	97	0.40	0.40
R	-	-	-	-	0.10	3.13
INH	-	-	-	-	0.05	1.56
EMB	-	-	-	-	1.56	12.50
PZA	-	-	-	-	6.25	50.00

ATA 11 displayed MIC value of 0.4 µg/mL versus Mtb which is 16 and 4 fold more enhanced than PZA and EMB, respectively. To elaborate this, SAR study revealed that thienoidole scaffold contain halogens which improves the activity as fluoro derivatives showed better anti-tubercular activity from the chloro analogues. In addition, aryl ring which either contains disubstitution or propyl group, contributes to the improved activity.

3.12 Spiro-pyrrolothiazoles

Naturally occurring spiro molecules displayed improved anti-mycobacterial properties (Van Der Sar, Blunt, & Munro, 2006; James, Kunze, & Faulkner, 1991; Kobayashi et al., 1991; Longeon, Guyot, & Vacelet, 1990). To add with this, titled spiro heterocycles which consists of five membered nitrogen ring can be synthesized efficiently through the exocyclic bond

(Najera & Sansano, 2003; Waldmann, 1995; Fišera et al., 1994; Tsuge & Kanemasa, 1989; Vedejs & West, 1986).

3.12.1 Synthesis of ATA 12

Azomethine ylides were produced *in situ* through the reaction related to 1,3-thiozolane-4-carboxylic acid along with substituted isatins which underwent cycloaddition to generate tittle compounds (Figure 17). Furthermore, all the compounds were evaluated utilizing Agar dilution method *in vitro* versus Mtb along with MDR TB strain and it was stated that spiro[5.3″]-5″-nitrooxindole-spiro-[6.3′]-1′-methyl-5′-(2,4-di-chlorophenylmethylidene)-tetrahydro-4′(1H)-pyridinone-7-(2,4-dichlorophenyl)tetra-hydro-1H-pyrrolo[1,2-c][1,3]thiazole (ATA 12) displayed better potency (Karthikeyan et al., 2010).

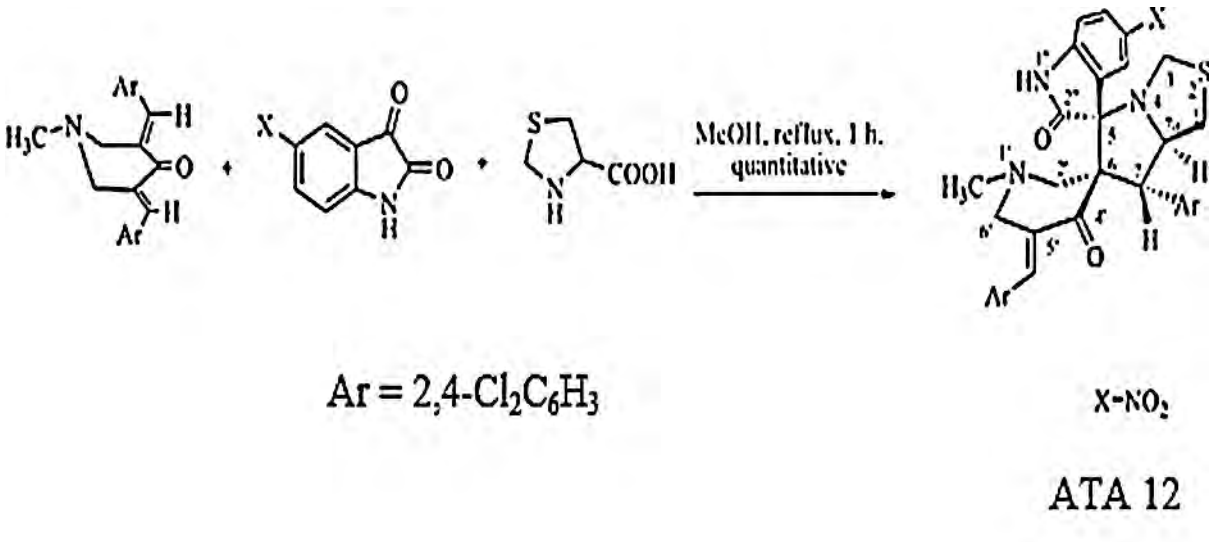


Figure 17: Synthesis of ATA 12; adopted from (Karthikeyan et al., 2010)

3.12.2 Anti-tubercular Activity of ATA 12

The clinical-isolate was resistant towards isoniazid, rifampicin, ethambutol and pyrazinamide. In addition, the MIC value of ATA 12 along with those of standard agents are listed (Table 14).

Table 14: Anti-tubercular Activity of ATA 12; adopted from (Karthikeyan et al., 2010)

Compound	Yield (%)	MIC (μM)	
		Mtb	MDR TB
ATA 12	96	0.6	0.6
INH	-	0.4	11.4
R	-	0.1	3.8
EMB	-	7.6	61.2
PZA	-	50.8	406.1

ATA 12 displayed impressive anti-tubercular activity with MIC value of 0.6 μM which is 85 and 13 fold more active than PZA and EMB, respectively; but offered lower effectivity than INH and rifampicin in case of Mtb. On the contrary, regarding MDR TB strain, ATA 12 offered enhanced activity than others. To explain this, as the isatin sub-structure contain Cl at 5th position, this offered improved anti-tubercular activity; while the existence of nitro group conferred elevated effectivity at 5th position. Similarly, the existence of two Cl related to phenyl rings provides better anti-tubercular potency.

3.13 Spiro-piperidin-4-ones

3.13.1 Synthesis of ATA 13

The synthesis of tittle compounds was performed through cycloaddition regarding azomethine which was produced *in situ* in combination related to R-amino acids along with isatins (Figure 18). Furthermore, all the compounds were screened versus Mtb along with MDR TB strain and it was stated that 4-(4-fluorophenyl)-5-phenylpyrrolo(spiro[2.3″]oxindole)spiro[3.3′]-1′-

methyl-5′-(4-fluorophenylmethylidene)piperidin-4′-one (ATA 13) showed better potency (R. R. Kumar, Perumal, Senthilkumar, Yogeeswari, & Sriram, 2008).

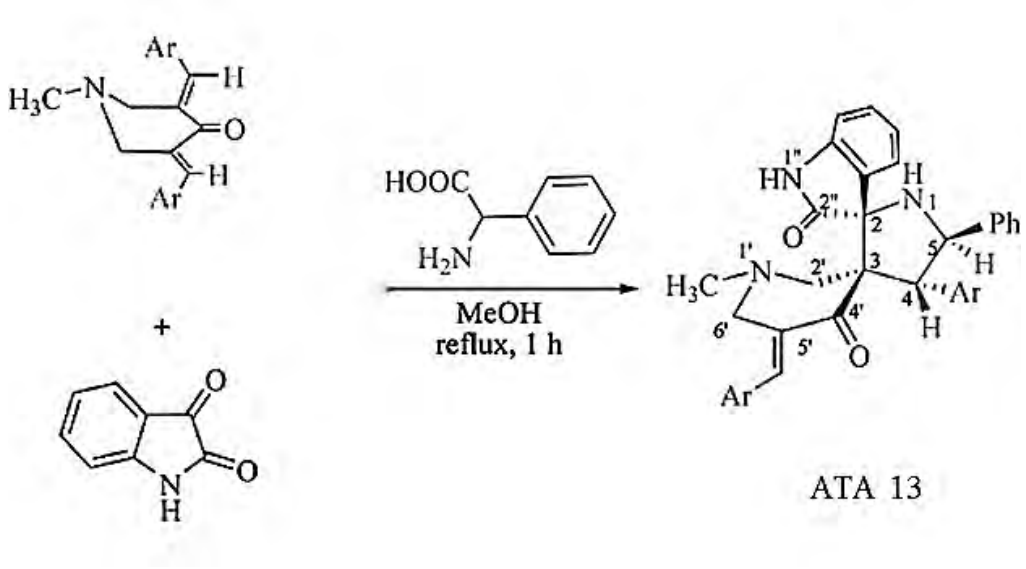


Figure 18: Synthesis of ATA 13; adopted from (R. R. Kumar et al., 2008)

3.13.2 Anti-tubercular Activity of ATA 13

ATA 13 was tested *in vitro* utilizing Agar dilution method versus Mtb along with MDR TB strain. To add with this, the clinical-isolate of MDR TB strain was resistant towards the common anti-tubercular agents. In particular, the MIC values of ATA 13 and the common drugs were listed (Table 15).

Table 15: Anti-tubercular Activity of ATA 13; adopted from (R. R. Kumar et al., 2008)

Compound	Aryl	IC_{50} (µM)	MIC (µg/mL)	
			Mtb	MDR TB
ATA 13	4-fluorophenyl	111.41	0.07	0.16
Isoniazid	-	-	0.36	45.57
Ciprofloxacin	-	-	4.71	37.73

ATA 13 displayed MIC value of 0.07 μM which was 67.2 and 5.1 fold more potent than ciprofloxacin and INH, reciprocally. To explain this, the aryl ring possessed para substitution which enhanced the anti-tubercular activity.

Afterwards, in CD-1 mice, the effectivity of ATA 13 was screened (Table 16).

Table 16: In vivo Activity of ATA 13; adopted from (R. R. Kumar et al., 2008)

Compound	spleen (log CFU ± SEM)	lungs (log CFU ± SEM)
Control	8.93 ± 0.20	7.31 ± 0.11
INH (25 mg/kg)	4.92 ± 0.15	5.61 ± 0.13
ATA 13 (25 mg/kg)	5.20 ± 0.13	6.01 ± 0.19

ATA 13 was determined as a promising molecule in reducing pathogenic count in spleen and lung tissues, though it displayed less potency than INH during same dose level. Furthermore, ATA 13 was screened for cytotoxicity utilizing serial dilution method and it was stated to be non-toxic till 62.5 μg/mL along with SI value of 1634.

3.14 Spiro-pyrido-pyrrolizines and pyrrolidines

The synthesis of tittle compounds was performed through the reaction of aromatic aldehydes along with 1-methyl-1-4-piperidone with the existence of pyrrolidine which was enhanced by microwave irradiation as it was solvent-free (Figure 19). Furthermore, all the compounds were tested utilizing Agar dilution method versus Mtb and MDR TB strain and it was disclosed that 1-methyl-4-(2,4-dichlorophenyl)pyrrolo(spiro[2.3″]oxindole)spiro[3.3′]-1′-methylpiperidin-4′-one (ATA 14) displayed better potency (Ranjith Kumar, Perumal, Senthilkumar, Yogeeswari, & Sriram, 2009).

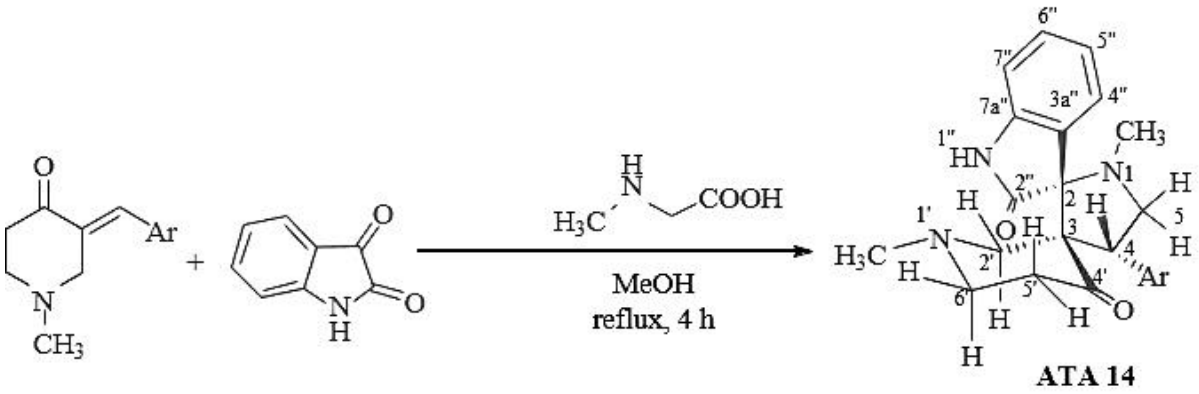


Figure 19: Synthesis of ATA 14; adopted from (Ranjith Kumar et al., 2009)

3.14.2 Anti-tubercular Activity of ATA 14

The clinical-isolate of MDR TB was resistant towards the common anti-tubercular agents. To explain this, MIC value of ATA 14 and those of common drugs are listed (Table 17).

Table 17: Anti-tubercular Activity of ATA 14; adopted from (Ranjith Kumar et al., 2009)

Compound	Yield (%)	MIC (µM)	
		Mtb	MDR TB
ATA 14	85	1.76	0.88
EMB	-	7.64	61.18
INH	-	0.39	11.38
PZA	-	50.77	406.13

ATA 14 displayed better potency with MIC of 0.88 and 1.76 µM versus MDR TB strain along with Mtb, reciprocally. To elaborate this, ATA 14 was found 13.0, 69.5 and 461.5 fold more active than INH, EMB and PZA, respectively.

3.15 *trans* 6-methoxy-1,1-dimethyl-2-phenyl-3-aryl-2,3-dihydro-1H-inden-4-yloxyalkylamine analogues

3.15.1 Synthesis of ATA 15-16

The synthesis of tittle compounds was performed through 2,2-dimethyl-3-phenyl-1-7-methoxy chromene (Figure 20; Table 18). Furthermore, all the compounds were screened against Mtb and it was disclosed that ATA 15-16 were the most potent compounds (Shailesh Kumar et al., 2013).

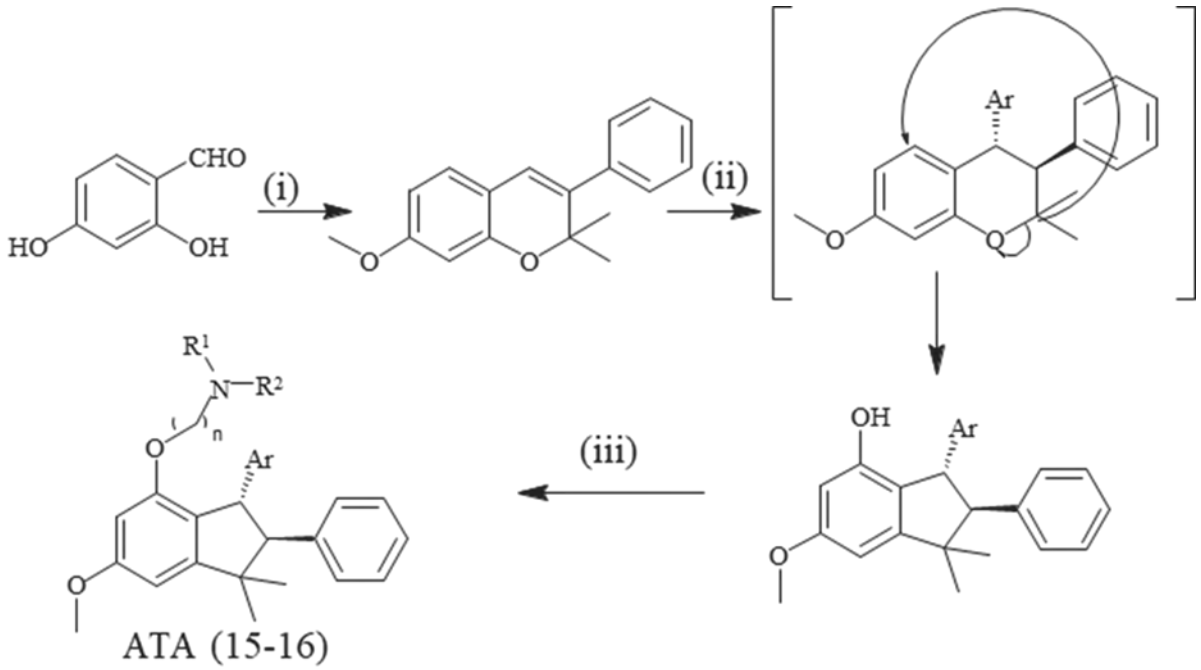
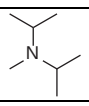
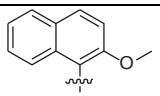


Figure 20: Synthesis of ATA 15-16; adopted from (Shailesh Kumar et al., 2013)

Table 18: Characteristics of ATA 15-16; adopted from (Shailesh Kumar et al., 2013)

Compound	Ar	n =	R^1R^2N- =
ATA 15	Ph	2	
ATA 16		2	

3.15.2 Anti-tubercular Activity of ATA 15-16

ATA 15-16 were evaluated for their MIC values and cytotoxicity by BACTEC radiometric method against Mtb H37Rv (Table 19) (Saquib et al., 2011; Kelly, Furney, Jessen, & Orme, 1996).

Table 19: Anti-tubercular Activity of ATA 15-16; adopted from (Shailesh Kumar et al., 2013)

Compound	MIC (µg/ml)	CC_{50} (µg/ml)	SI Value
ATA 15	3.125	49.16	15.73
ATA 16	1.56	23.98	15.37
ETB	0.5	38.51	77.02
RFM	0.39	62.46	160.1

ATA 15-16 contained 2 carbon-spacer which enhanced *in vitro* anti-tubercular activity. To add with this, utilizing Resazurin assay, the cytotoxicity of ATA 15-16 were determined in Vero-cell lines as it was marginally changed because of the aminoalkoxy side-chain which contains substituents on nitrogen.

Afterwards, ATA 15-16 was screened utilizing Agar dilution method and confirmed through BACTEC radiometric method versus MDR TB strain which exhibited resistance to rifampicin and INH (Table 20).

Table 20: In vitro Activity of ATA 15-16 against Drug Susceptible and MDR TB; adopted from (Shailesh Kumar et al., 2013)

Mtb Strains	Susceptibility or Resistance towards Anti-tubercular Agents	MIC (µg/ml)
Strain 2643 (MDR)	Rif^r INH^r	6.25 (ATA 15) 3.125 (ATA 16)
Strain 1678/05 (MDR)	Rif^r INH^r	6.25 (ATA 15) 3.125 (ATA 16)
Strain 2280	Drug Sensitive	3.125 (ATA 15) 1.56 (ATA 16)

ATA 15 was screened *in vivo* through murine TB model for acute infection (Kelly et al., 1996). To explain this, reduction of pathogenic CFU in lungs was observed as a result of utilizing ATA 15 (Table 21).

Table 21: In vivo efficacy of ATA 15; adopted from (Shailesh Kumar et al., 2013)

Treatment Regimen	Dose (mg/kg)	$\log_{10}$ CFU ± SE in lungs
Untreated	-	7.61 ± 0.37
ATA 15	100	6.25 ± 0.31
INH	25	4.83 ± 0.07

ATA 15 displayed 1.35 $\log_{10}$ reductions whereas 2.8 $\log_{10}$ reductions was achieved by INH which indicates the anti-tubercular identity of ATA 15.

3.16 Indole-2-carboxamides

The tittle compounds have been recognized as encouraging anti-tubercular molecules through phenotypic evaluation against Mtb.

3.16.1 Synthesis of ATA 17-18

The lead compounds were synthesized in a straight forward pathway through coupling of replaced indole-2-carboxylic acids along with corresponding amines with the existence of HATU and DIPEA into DMF (Kondo, Morohoshi, Mitsuhashi, & Murakami, 1999; Robinson, 1982; Sundberg, 1996; Babu, Chand, Kotian, & Kumar, 2011; Speckenback, Bisel, & Frahm, 1997). Furthermore, all the compounds were screened against Mtb and 4,6-dichloro-N-(4,4-dimethylcyclohexyl)-1H-indole-2-carboxamide (ATA 17) and 4,6-difluoro-N-(4,4-dimethylcyclohexyl)-1H-indole-2-carboxamide (ATA 18) showed better potency in comparison with common anti-tubercular agents (Figure 21) (S. P. S. Rao et al., 2013).

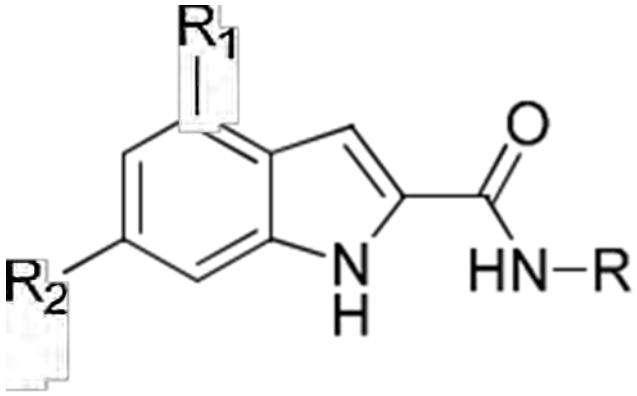
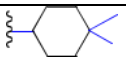
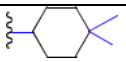


Figure 21: Chemical Structure of ATA 17-18; adopted from (S. P. S. Rao et al., 2013)

3.16.2 Anti-tubercular Activity of ATA 17-18

ATA 17-18 were evaluated for *in vitro* MIC value versus Mtb H37Rv and tested for cytotoxicity against HepG2 and THP-1 mammalian cell lines (Table 22) (Pethe et al., 2010).

Table 22: Anti-tubercular Activity of ATA 17-18; adopted from (S. P. S. Rao et al., 2013)

Compound	R_1	R_2	R	MIC_{50} (μM)	SI
ATA 17	Cl	Cl		0.015	>1000
ATA 18	F	F		0.023	>1000

Furthermore, ATA 17-18 were evaluated versus 9 different clinical isolates from MDR TB which were allocated into 6 clusters (Gutacker et al., 2006). Moreover, MIC of ATA 17-18 were in relevant range in consideration with the wild version of Mtb, analyzed through pellet formation method (Table 23).

Table 23: Anti-tubercular Activity of ATA 17-18 against MDR TB Clinical-isolates; M=moxifloxacin, I= isoniazid, PZA= pyrazinamide, R= rifampicin, S= streptomycin; adopted from (S. P. S. Rao et al., 2013)

Strains	Cluster	Resistance	MIC_{99} (μM)					
			ATA 17	ATA 18	M	R	I	S
MDR 1	I	SIR	<0.04	<0.04	0.31	>5	>20	>5
MDR 2	II	SIR	<0.04	0.08	0.16	>5	10	>5
MDR 3	II	SIRMP	<0.04	<0.04	>5	>5	>20	>5
MDR 4	IIA	SIRP	0.08	0.08	0.16	>5	>20	>5
MDR 5	IIA	SIR	<0.04	0.08	0.08	>5	>20	>5
MDR 6	III	SI	<0.04	0.08	0.31	0.02	>20	2.50
MDR 7	V	SIR	<0.04	0.08	0.16	>5	5	0.63
MDR 8	VI	IR	<0.04	0.08	0.31	>5	>20	>5
MDR 9	VI	SIRP	<0.04	<0.04	0.16	>5	>20	>5
H37Rv	VIII	None (wild Version)	0.02	0.02-0.04	0.16	0.02	0.62	0.31

The anti-tubercular activity of ATA 17-18 versus different MDR TB isolates varied from <0.04-0.08 μM which indicates the potency.

ATA 17-18 were screened *in vitro* for the pharmacokinetic (PK) studies (Table 24).

Table 24: In vivo Pharmacokinetics of ATA 17-18 in Mouse, Rat and Dog; adopted from (S. P. S. Rao et al., 2013)

Comp.	Species	Dose (mg /kg)	Intravenous PK parameters			Oral PK parameters			
			V_{ss} (L/kg)	CL (mL /min /kg)	Elim. $T_{1/2}$ (h)	C_{max} (µM)	AUC_{0-24} (µM*h)	T_{max} (h)	F %
ATA 17	Mouse	25 75	4.11	18.11	5.25	3.51 5.90	33.90 70.27	1.5 0.75	53 37
	Rat	50 300	2.32	6.02	6.49	16.65 (8.3) 26.64 (13.3)	241.40 (12.4) 290.62 (14.9)	7 3	76 15
	Dog	3 10	10.5	13.5	30.9	0.65 3.66	2.15 14.44	2 2	23.6 44.8
ATA 18	Mouse	25 75	2.24	18.74	4.47	4.21 9.30	35.48 118.98	1.5 3	51 55
	Rat	50 300	3.7	10.74	6	35.25 (15) 34.60 (14.7)	590.81 (23) 489.62 (19)	7 3	100 38
	Dog	3 10	7.6	16	13.4	0.54 3.49	4.36 28.77	3.3 3.3	45 98

The *in vivo* effectivity of ATA 17-18 were screened through established mouse model (Figure 22).

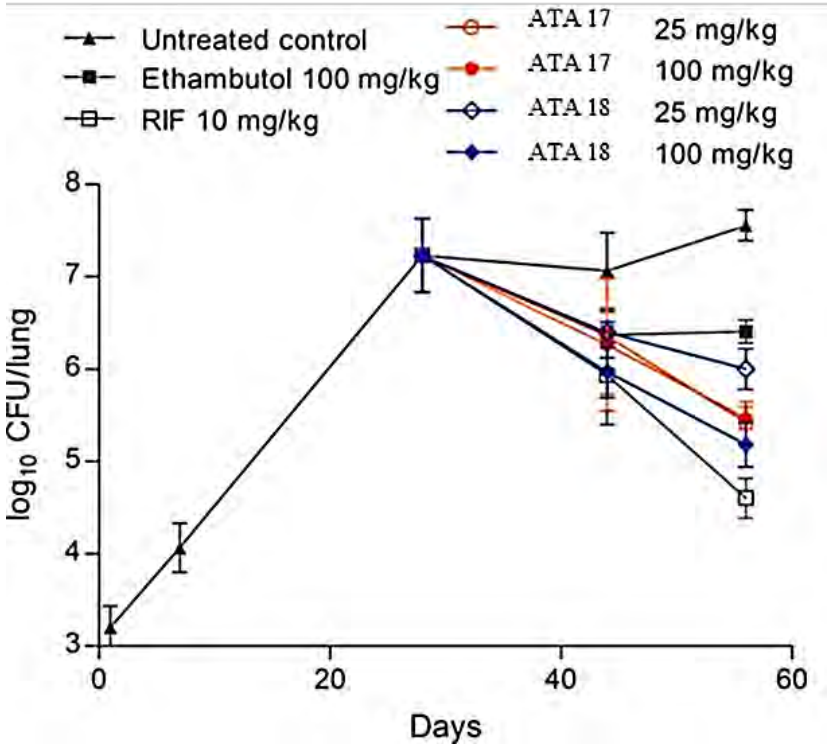
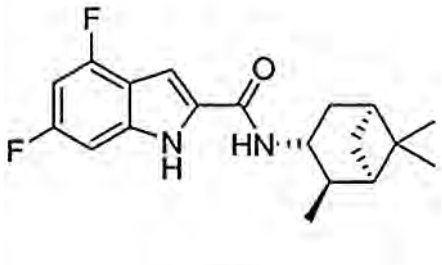


Figure 22: In vivo Efficacy of ATA 17-18; adopted from (S. P. S. Rao et al., 2013)

Test results through acute and chronic efficacy model suggest that ATA 17-18 possess enhanced *in vivo* potency against Mtb.

3.16.3 Synthesis of ATA 19

Under an argon condition, substituted indole-2-carboxylic acids acted with alkyl- or cycloalkylamine under the existence of coupling agents, EDC.HCl and HOBt along with base, trimethylamine to generate the tittle compounds. Furthermore, all the compounds were screened against Mtb and it was disclosed that 4,6-difluoro-N-((1R,2R,3R,5S)-2,6,6-trimethylbicyclo[3.1.1]-heptan-3-yl)-1H-indole-2-carboxamide (ATA 19) which displayed enhanced anti-tubercular activity (Figure 23) (Stec et al., 2016).



ATA 19

Figure 23: Chemical Structure of ATA 19; adopted from (Stec et al., 2016)

3.16.4 Anti-tubercular Activity of ATA 19

ATA 19 was evaluated against different isolates of Mtb collected through pulmonary TB patients (Table 25) (Ioerger et al., 2009).

Table 25: Anti-tubercular Activity of ATA 19; adopted from (Stec et al., 2016)

Compound	Mtb MIC (μM)						Vero cells IC_{50} (μM)	SI
	H37Rv/ DS	V4207/ DS	KZN494/ MDR	V2475/ MDR	TF274/ XDR	R506/ XDR		
ATA 19	0.012	0.023	0.012	0.047	0.006	0.012	≥192	≥16000

Moreover, ATA was screened against Vero-cell lines for cytotoxicity as the SI value was evaluated. To explain this, ATA 19 showed 2 times more potency in case of XDR TB isolates. The enhanced activity of ATA 19 portraits not only its effectivity against MDR and XDR TB isolates but also informs about the possibility that ATA 19 would not exhibit cross resistance. In addition, ATA 19 displayed higher IC_{50} value which reflects lower cytotoxicity against Vero-cell lines. ATA 19 was also screened against TSK54R, a mutant responsible for

identifying MmpL3 as a potential target. To explain this, a 16-32 times loss of activity versus the mutant through MIC value of 0.0625-0.125 µg/mL confirmed it as an important target.

It was predicted about the exposure of ATA 19 along with rifampin might reach the level to show real synergy rather than just being two individual effective agents. To elaborate this, Bliss independence model was utilized exclusively in testing pharmacologic drug-drug interactions (BLISS, 1939; Greco, Bravo, & Parsons, 1995). Furthermore, the synergy model was monitored through multiple combination of concentrations as highlighted (Table 26).

Table 26: In vitro Drug Combination of ATA 19 and Rifampin; adopted from (Stec et al., 2016)

	ATA 19								
RIF		0.0313	0.0625	0.125	0.25	0.5	1	2	4
	4								
	2								
	1								
	0.5	0.0	**0.1**	**0.1**	**0.1**	**0.1**			
	0.25	**0.1**	**0.1**	**0.4**	**0.6**	**0.6**			
	0.125	**0.1**	**0.0**	**0.1**	**0.8**	**1.0**			
	0.0625	0.0	0.0	0.0	**0.1**	**1.0**			
	0.0313	0.0	0.0	0.0	0.0	**1.0**			

The outcomes from the synergy between rifampin along with ATA 19 are very important as it raises opportunity about indole-2-carboxamide related therapeutic regimens connected with lower rifampin regimens which can be very much effective and efficient due to rifampin's identical attributes (Branch, Adedoyin, Frye, Wilson, & Romkes, 2000; Baciewicz, Chrisman, Finch, & Self, 2013; Acosta et al., 2007; Kirby et al., 2012).

3.16.5 Synthesis of ATA 20-21

In the existence of pTsOH, indole-2-carboxamide were produced through the reaction of ethyl pyruvate along with arylhydrazine generated ethyl indole-2-carboxylate and after the saponification, utilizing standard coupling agents, amines were coupled into indole-2-carboxylic acid. Furthermore, all the compounds were screened against Mtb and it was disclosed that N-cyclooctyl-4,6-dimethyl-1H-indole-2-carboxamide (ATA 20) and N-((1R,2R,3R,5S)-2,6,6-Trimethylbicyclo[3.1.1]heptan-3-yl)-4,6-dimethyl-1H-indole-2-carboxamide (ATA 21) were found to be the most potent compound (Figure 24) (Franz et al., 2017).

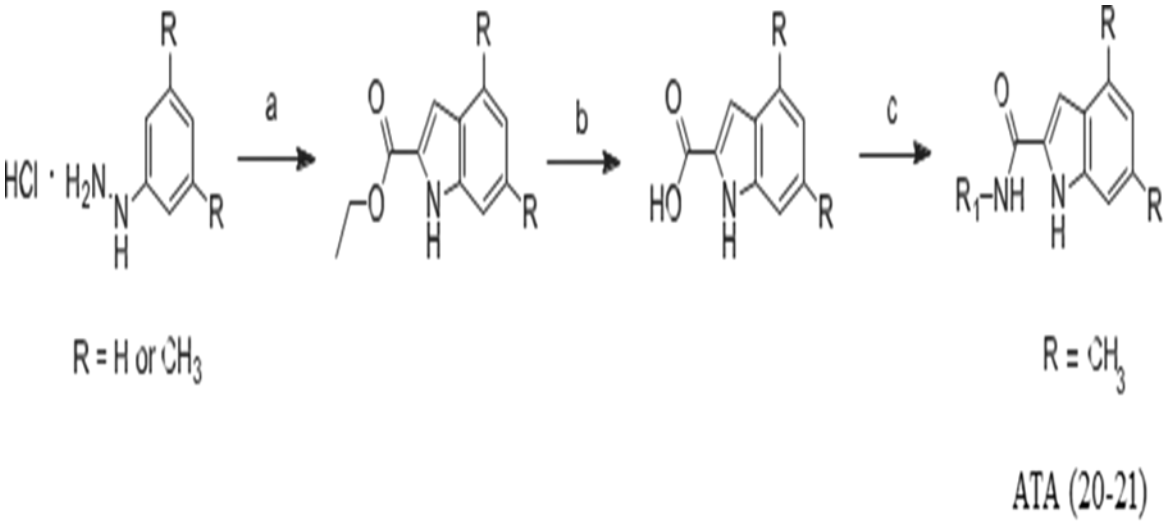


Figure 24: Synthesis of ATA 20-21; adopted from (Franz et al., 2017)

3.16.6 Anti-tubercular Activity of ATA 20-21

ATA 20-21 were screened for anti-tubercular activity which resulted in enhanced effectivity (Table 27).

Table 27: Anti-tubercular Activity of ATA 20-21; adopted from (Franz et al., 2017)

Compound	R_1	MIC values (µg/mL) Mtb H37Rv (Mc2-6206)	TD50 (µg/mL)	SI
ATA 20		0.0195	>14.9	>764
ATA 21		0.0195	>16.2	>830

ATA 20-21 displayed enhanced MIC value of 0.0195 µg/mL and were screened against THP-1 cell-lines for cytotoxicity.

Furthermore, ATA 20 was evaluated against XDR TB isolates (Table 28) (Ioerger et al., 2009).

Table 28: Anti-tubercular Activity of ATA 20 against Drug-susceptible and XDR TB isolates; adopted from (Franz et al., 2017)

Compound	MIC (µM)		
	V4207 (DS)	TF274 (XDR)	R506 (XDR)
ATA 20	0.026	0.026	0.0067

The MIC values were evaluated utilizing MABA through the average of 3 different measurements.

ATA 20 was tested *in vivo* through female mice of BALB/c which were affected by aerosol with Mtb strain and comparison was made with untreated mice as the pathogenic burden was decreased through dose-depended manner (Figure 25).

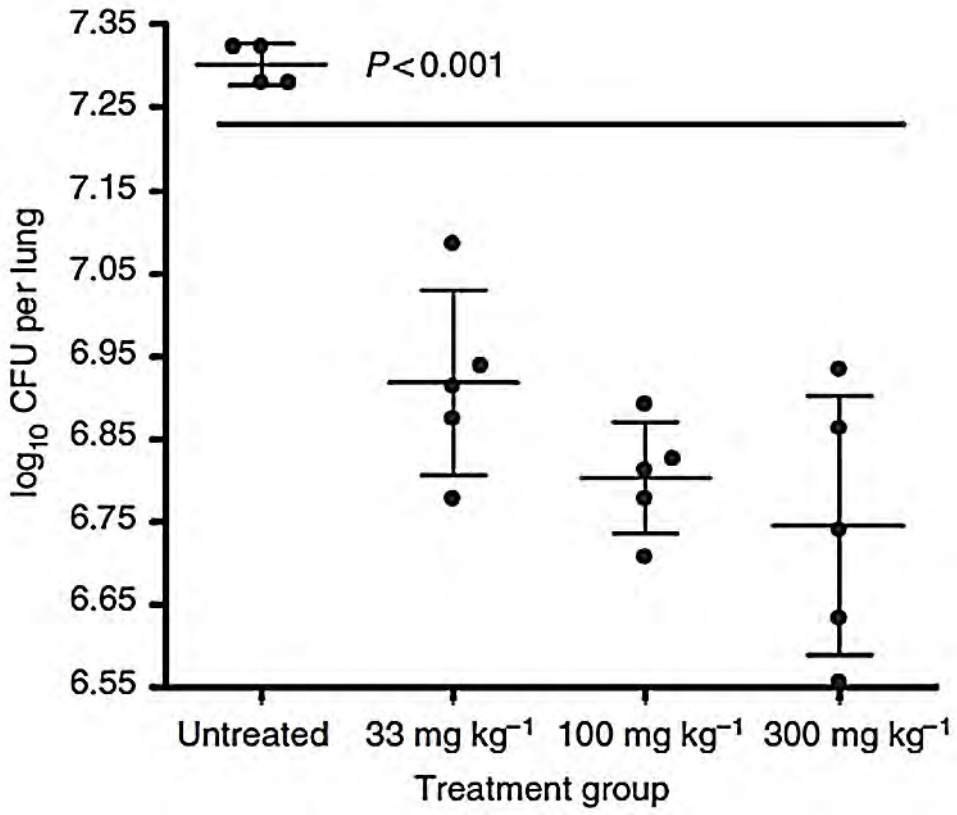


Figure 25: Activity of ATA 20 against Mtb during In vivo Infection; adopted from (Lun et al., 2013)

3.17 Benzoxazole analogues

3.17.1 Synthesis of ATA 22

The tittle compounds were synthesized through a reaction, controlled by EDC-mediated coupling which was occurred between corresponding benzylamines and imidazo[1,2-a]pyridine carboxylic acid (Figure 26). Furthermore, all the compounds were screened against Mtb and it was stated as 7-chloro-2-ethyl-N-((2-(4-(trifluoromethoxy)phenyl)benzo[d]oxazol-5-yl)methyl)imidazo[1,2-a]pyridine-3-carboxamide (ATA 22) was found to be the most potent compound (Kang et al., 2017).

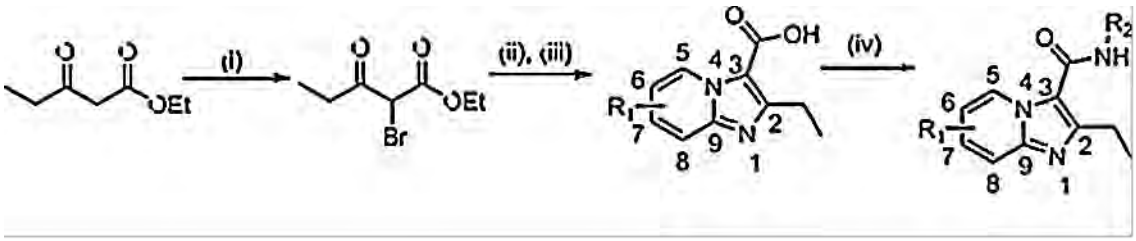
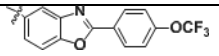


Figure 26: Synthesis of ATA 22; adopted from (Kang et al., 2017)

3.17.2 Anti-tubercular Activity of ATA 22

The anti-tubercular activity of ATA 22 was evaluated and listed (Table 29).

Table 29: Anti-tubercular Activity of ATA 22; adopted from (Kang et al., 2017)

Compound	R_1	R_2	Mtb H37Rv (µM)	
			Extracellular MIC_{80}	Intracellular MIC_{80}
ATA 22	7-Cl		0.009	<0.001
INH	-	-	0.49	0.20

ATA 22 was selected for PK evaluation *in vivo* and the test was performed with mice through oral and intravenous administration of 10 and 2 mg/kg, respectively (Table 30).

Table 30: In vivo PK Values of ATA 22; adopted from (Kang et al., 2017)

Compound	Pharmacokinetics (I. V.)			Pharmacokinetics (P. O.)				
	$T_{1/2}$ (h)	Cl (mL/min/kg)	Vd_{ss} (mL/kg)	C_{max} (ng/mL)	$T_{1/2}$ (h)	T_{max} (h)	$AUC_{0\text{-}inf}$ (ng.h/mL)	F (%)
ATA 22	18.0	0.6	1202	5557	36.3	1	116400	40.1

Within 1 hour, ATA 22 showed maximum concentration, reflected long half-life as after oral administration, lower systemic clearance resulted into higher drug-exposure elevation.

3.18 Isatinyl Thiosemicarbazone derivatives

The tittle molecules were hypothesized to bypass through PK interfaces regarding HIV-TB treatment to fight against the consequences developed as a result of immune reconstruction and lower the medication burden, thereby enhance patient compliance.

3.18.1 Synthesis of ATA 23-25

The synthesis of the tittle compounds was completed in 4 steps (Figure 27). Furthermore, all the compounds were screened against Mtb and it was disclosed that 1-Cyclopropyl-6-fluoro-7-[4-(3-{(Z)-2-[(hydroxyamino)carbothioyl]hydrazono}-5-fluoro-2-oxo-2,3-dihydro-1H-indol-1-yl)-3-methylhexahydropyrazin-1-yl]-8-(methyloxy)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (ATA 23); 1-Cyclopropyl-6-fluoro-7-[4-{[5-methyl-3-((Z)-2{[(methyloxy)amino]carbothioyl}hydrazono)-2-oxo-1H-indol-1(2H) yl]methyl}tetrahydropyrazin-1(2H)-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid and 1-Cyclopropyl-6-fluoro-7-[4-{[5-fluoro-3-((Z)-2-{[(methyloxy)amino]carbothioyl}hydrazono)-2-oxo-1H-indol-1(2H)-yl]methyl}-3-methyltetrahydropyrazin-1(2H)-yl]-8-(methyloxy)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (ATA 24-25) were stated as the most potent compounds (Banerjee et al., 2011).

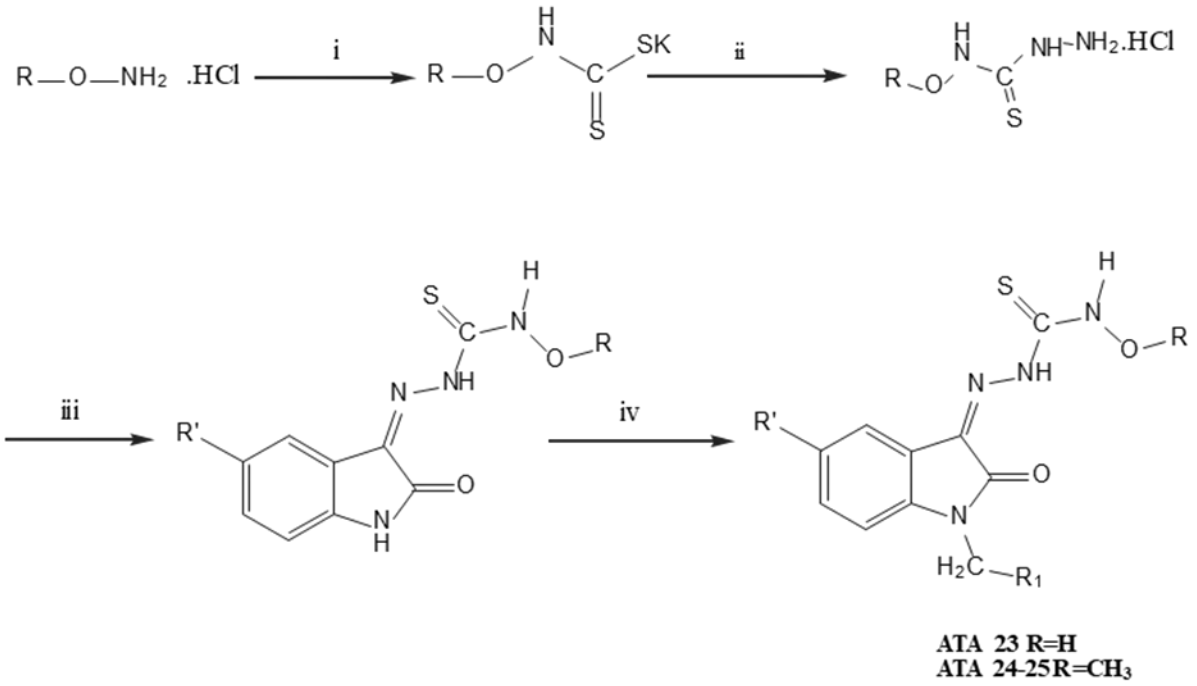


Figure 27: Synthesis of ATA 23-25; adopted from (Banerjee et al., 2011)

3.18.2 Anti-tubercular Activity of ATA 23-25

ATA 23-25 were evaluated against Mtb H37Ra and the MIC values were listed (Table 31).

Table 31: Anti-tubercular Activity of ATA 23-25; adopted from (Banerjee et al., 2011)

Compound	R′	R_1	Mtb in log phase (μM)	Dormant Mtb (μM)
ATA 23	F	-do-	0.16	9.74
ATA 24	CH3	-do-	0.66	18.44
ATA 25	F	-do-	0.15	9.17

Moreover, ATA 24 was evaluated for ICL suppression regarding Mtb as the comparison was outlined (Table 32).

Table 32: ICl suppresion of Mtb by ATA 24; adopted from (Banerjee et al., 2011)

Compound	MTB ICl % Inhibition
ATA 24	63.44 (10 μM)

3.19 Indoleketo derivatives

For both pathogens and mammals DHFR is a very important enzyme which also includes Mtb. To explain this, as inhibition regarding folate pathway leads towards cell death, selective site based molecular formation has gained a lot of attention in recent years and encouraged the discovery of anti-tubercular novel drugs.

3.19.1 Synthesis of ATA 26

The synthesis of tittle compounds was performed through different steps of reactions and in relation to that 4-((3-acetyl-1-benzyl-2-methyl-1H-indol-5-yl)oxy) butanoic acid (ATA 26) was obtained which showed maximum activity (Figure 28) (K. Sharma et al., 2018).

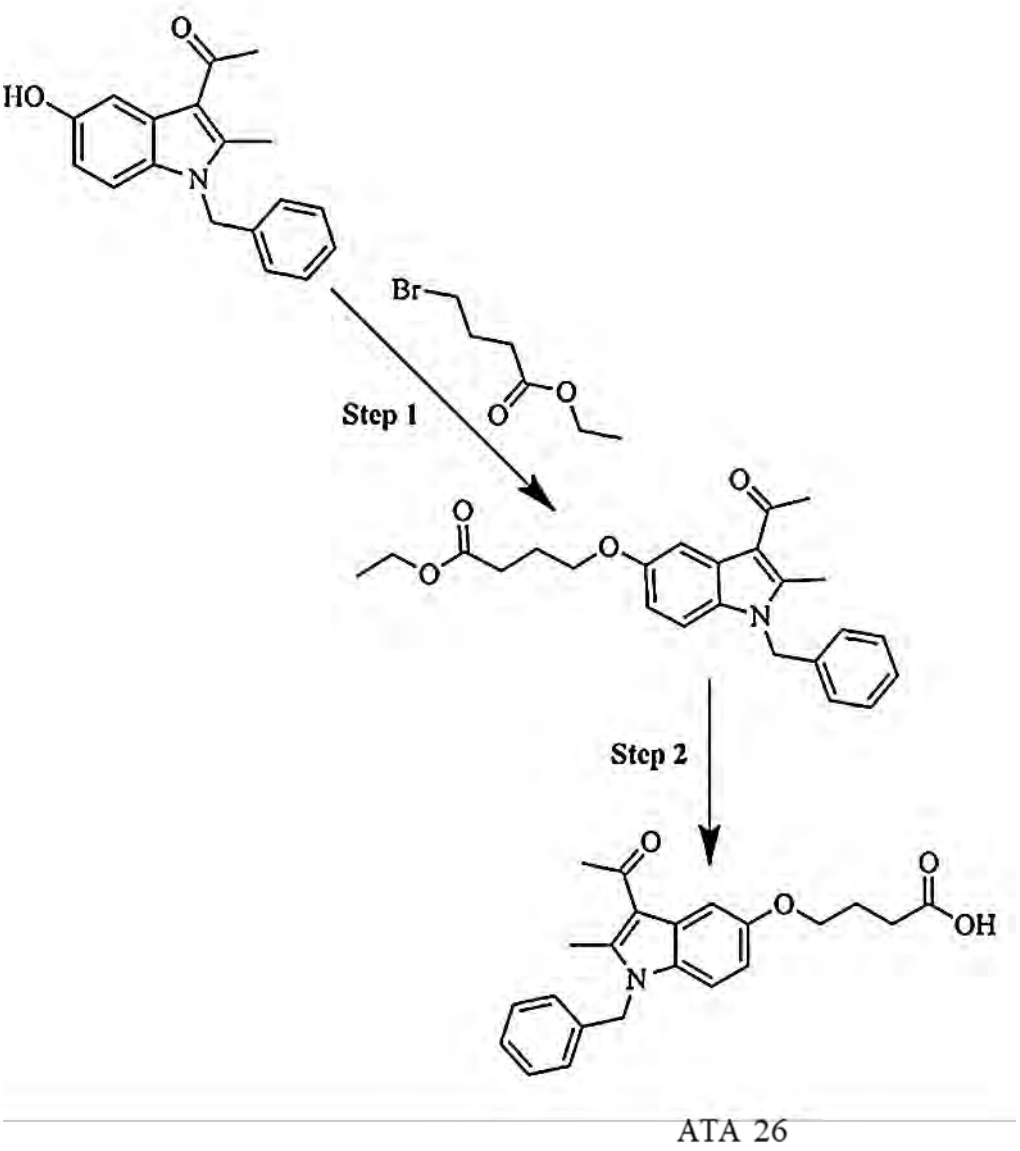


Figure 28: Synthesis of ATA 26; adopted from (K. Sharma et al., 2018)

3.19.2 Anti-tubercular Activity of ATA 26

ATA 26 was evaluated for the activity against Mtb H37Rv colonies (Figure 29) (Zelmer et al., 2012). Moreover, ATA 26 showed potential selectivity for Mtb-DHFR over h-DHFR and inhibited these 2 enzymes reflected through IC_{50} values of 150 and 980 μm, reciprocally. In addition, the SI value was evaluated at approximately 6.53.

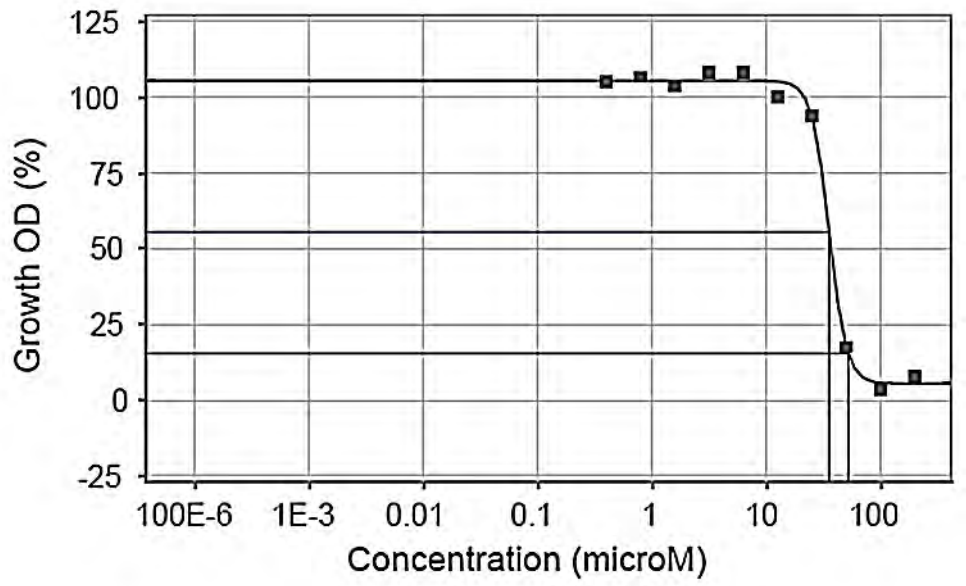


Figure 29: Dose Response Curve for ATA 26; adopted from (K. Sharma et al., 2018)

Chapter 4

Discussion

To control TB, a deadly disease, new anti-tubercular molecules, including those who possess enhanced activity against MDR and XDR TB, are hugely needed as global effort. To explain this, different assay methods along with screening procedures have been demonstrated to identify enhanced methods in order to discover novel lead molecules to fight against TB. However, notable limitations were observed as lack of information regarding target sites, tolerability and *in vivo* availability hampered the movement. While previous inadequate progress does not necessarily inhibit forward developments, knowledge about desired target (s) leads towards effective molecular optimization, which provides a molecular basis for SAR analysis which may indicate potential molecular pathways against Mtb. To add with this, demonstration of secured *in vivo* activity of a molecule is very essential for the continuous development of anti-tubercular agents.

To elaborate this, the substituent in the spiro-heterocycle ATA 1's isatin nucleus substantially affects the activity as apparent from the reality that a compound with a nitro group in the isatin nucleus exhibits greater activity as the compounds, carrying comparable substituents in the aryl rings that belong to other compound sequence. ATA 2 shows elevated affinity for the Mtb drug target Enoyl-acyl carrier protein reductase (InhA) in addition to this phaitanthhrin congener. Therefore, improved affinity of ATA 2 to InhA's binding site may result in the synthesis of anti-tubercular agents that are likely to be capable of fighting MTB's MDR strains. In addition, the substituent, NO2, present in the isatin nucleus, has a profound effect on the activity of dispiro-oxindolylpyrrolothiazole, ATA 3, in relation to the structure-Mtb activity relationship. Halogen existence, Br, also improved anti-mycobacterial activities in the aryl loop. In addition, the situation and shape of the substituent in the phenyl group connected to piperazine moiety,

ATA 4, has an important effect on anti-tubercular operation and the substitution of the phenyl group with pyridyl moiety increases three waves of anti-tubercular operation. Moreover, this indole compound, ATA 5's anti-mycobacterial action was heavily related to its cationic amphiphilic personality. For activity, a lipophilic side chain at R^1 and a strongly basic aminomethyl side chain at R^2 were compulsory features, and considerable leeway was permitted at other sites of the scaffold as far as both were retained. In addition, the Schiff base's synthetic layout, ATA 6, includes the existence of COOH or $COOC_2H_5$ clusters at place 2 of the indole ring, i.e. in the area of the azomethyne C= N cluster. Similar types of Schiff bases are usually regarded as quite excellent chelation ligands with different metal ions including those from Mtb's nutrient medium. The INH-indole hybrid, ATA 6, is linked to purchase synergism to solve INH strength. This phenomena may be explained by a notion of allosteric regulation of protein locations linked to putative metal ligands. Diketone derivative, ATA 7, also showed more anti-tubercular action with electron withdrawal band replaced phenyl group. To add with this, compound with electron rich groups substituted on the phenyl ring, ATA 8, was shown to have higher activity potentials. In addition, the derivative of pyridine4-fluoro phenyl group replacement (ATA 9) generally showed relatively higher inhibitory activity. Additionally, replacing the whole phenothiazine moiety with an indole nucleus as in ATA 10 led in an amazing anti-mycobacterial action compound. The results showed that the presence of halogens in the thienoindole moiety, ATA 11, enhances the activity with regard to the structure-MTB activity relationship. Fluoro derivatives are more active among halogens than chloro derivatives. With regard to the 2-aryl band, the behavior is enhanced by the aryl loop with halogen or propyl group. The activation is also amplified by disubstitution in the aryl chain similarly. Spiro-pyrrolothiazole, ATA 12, has resulted to further improvement of anti-tubercular behavior with nitro-substitution in the isatin loop. Anti-tubercular operation is also facilitated by para substitution at the aryl loop, ATA 13. The findings showed that the existence

of halogens in the thienoindole moiety enhances the exercise with regard to the structure-Mtb interaction connection. Fluoro derivatives are more active among halogens than chloro derivatives. With regard to the 2-aryl unit, the behavior is enhanced by the aryl loop with halogen or propyl group. In addition, it was noted from the SAR research that the location and size of the substituent on the phenyl group connected to piperazine moiety has an important effect on the anti-tubercular exercise and the substitution of the phenyl group with pyridyl moiety increases three curls of the anti-tubercular operation.

Potential mechanism(s) of intervention of the first and second row of anti-TB drugs illustrates that drugs such as isoniazid, ethambutol, and pyrazinamide operate through cell wall activation and membrane biosynthesis, while rifampicin operates through transcription inhibition. On the other side, the new anti-tubercular molecules studied are more flexible in their battle against the present TB situation that has circumstances such as drug-susceptible TB, MDR-TB, XDR-TB, HIV-TB, etc. To begin with, isocitrate lyase (ICL), a significant enzyme in glyoxalate shunt plays a crucial role in Mtb's persistence in the macrophages and escapes immunity, and this is one of the routes that these new molecules block to selectively work. In addition, these fresh lead compounds inhibit the biosynthetic pathway of mycolic acid in TB species. Specifically, they prevent the translocation of trehalose-monomycolate (TMM) to the outer membrane, suggesting Large 3 (MmpL3) activation of mycobacterial membrane protein. In addition, Mtb's Enoyl-acyl plant hormone reductase (InhA) is one of the main proteins with a fresh fashion of operation in which ATP output is inhibited by attacking the cytochrome bc1 complex within Mtb and validated by the fresh novel scaffold as an efficient anti-tubercular goal. In addition, Mtb-DHFR inhibition and efflux inhibition pumps in mycobacteria and alteration of Mtb's cell-envelope permeability are found as an impressive pathway to design the working mechanism of these new compounds. To explain the comparative studies of the available standard drugs and the studied upcoming compounds, it can be said that effective

binding sites or pathways which still work in a standard way like compounds as bacterial respiration and cell surface biosynthesis or by disrupting membrane function are present in the mechanism of the current studied molecules, but it is the new versatile mechanisms along with different selective pathways which can be very much efficient for the patients against the battle of current TB situation.

Chapter 5

Conclusion

Novel anti-tubercular agents were screened against different Mtb strains. To elaborate this, indane or indole identity containing scaffold were evaluated for the activity for H37Rv or H37Ra strains of Mtb, in some cases drug susceptible Mtb isolates, in serious concerns MDR TB isolates, also during extensive cases XDR TB isolates and critical situations like HIV-TB or selective enzyme related situations and opportunities. These molecules showed an impressive results with comparison to those standard drugs in different situations; sometimes in vitro, sometimes in vivo, again against strains from a certain part of the world, meanwhile working on different cells. To sum up all the potential molecules with their impressive results, these novel compounds contains the ability to solve the current available and potential situations related to TB.

Chapter 6

Future Work

To work with the finest findings in both dry and wet labs, so that this experience with the novel scaffold may reach a new dimension. Moreover, designing an anti-tubercular agent which may solve all the existing and potential situations related to TB is an option should be exercised if proper opportunity arises.

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