Biologically Active Small Molecules

Modern Applications and Therapeutic Perspectives

Debarshi Kar Mahapatra
Sanjay Kumar Bharti
EDITORS

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Edited by
Debarshi Kar Mahapatra, PhD
Sanjay Kumar Bharti, PhD

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Abbreviations

ABAP	2,2'-azo-bis(2-amidino-propane)hydrochloride
ACE	angiotensin converting enzyme
Ach	acetylcholine
AGE	advanced glycation end
AhR	aryl hydrocarbon receptor
AP	alkaline phosphatase
ASA	acetyl salicylic acid
AUC	area under curve
BAC	boronate affinity chromatography
BP	blood pressure
CAR	constitutive androstane receptor
Cmax	peak plasma level
COPD	chronic obstructive pulmonary disease
COX	cyclooxgenase
CRE	carbonyl reducing enzymes
CYP	cytochrome P450
DHEA	dihydro epiandrosterone
DMPD	*N*, *N*-dimethyl-p-phenylenediamine dihydrochloride
DMSO	dimethyl sulphoxide
DNA	deoxyribonucleic acid
DPPH	1,1-diphenyl-2-picryl hydrazyl
*d*Tc	*d*-tubocurarine
ECMDB	E. coli metabolome database
EGF	epidermal growth factor
FRAP	ferric reducing ability of plasma
FRET	fluorescence resonance energy transfer
FXR	farnesoid X receptor
GA	general anesthetics
GDT	global distance test
GDTTS	global distance test total score
GI	gastrointestinal
GSH	glutathione
GST	glutathione transferases
HMDB	human metabolome database

HO-2-dG	β-hydroxy-2-deoxyguanosine
HPETE	hydroperoxy eicosatetraenoic
HTRF	homogeneous time-resolved fluorescence
HTS	high-throughput screening
IBD	inflammatory bowel disease
Iκκ	IκBα kinase
IL-1	interleukin-1
LOX	lipoxygenase
LPS	lipopolysaccharide
LXR	liver X receptor
LT	leukotriene
MAC	minimum alveolar concentration
MAO	monoamine oxidase
MAOI	monoamine oxidase inhibitor
NAR	nucleic acid research
NAT	*N*-acetyltransferase
NBT	nitroblue tetrazolium
NCBI	national center for biotechnology information
NF-κB	nuclear factor kappa B
NLM	national library of medicine
NMR	nuclear magnetic resonance
NrF2	nuclear factor erythroid 2-related factor 2
NSAIA	non-steroidal anti-inflammatory agent
NSAIC	non-steroidal anti-inflammatory candidate
NSAID	non-steroidal anti-inflammatory drug
ORAC	oxygen radical absorbance capacity
PAF	platelet activating factor
PC	prostacyclin
PDB	protein data bank
PG	prostaglandin
P-gp	P-glycoprotein
PPAR	peroxisome proliferator-activated receptor
PXR	pregnane X receptor
RA	rheumatoid arthritis
RMSD	root mean square deviation
RNA	ribonucleic acid
RNS	reactive nitrogen species
ROS	reactive oxygen species
SAR	structure-activity relationship

SPA	scintillation proximity assays
SULT	sulfotransferase
TDI	time-dependent inhibition
TG	thymidine glycol
TNF	tumor necrosis factor
TPTZ	2,4,6-tri-(pyridyl)-s-triazine
TRAP	total radical-trapping
TX	thromboxane
UGT	uridine diphosphate-glucuronosyltransferase
UHTS	ultra high-throughput screening
YMDB	yeast metabolome database

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Foreword

It is a moment of pleasure for me to write the foreword for this amazing book, *Biologically Active Small Molecules: Modern Applications and Therapeutic Perspectives,* edited by Debarshi Kar Mahapatra, PhD, and Sanjay Kumar Bharti, PhD. With the unprecedented progress in drug discovery techniques, the emergence of low molecular weight ligands remains a burning topic. In the modern day, when the world is moving toward "nano," the chemical entities are becoming smart. The structure-based drug design (SBDD)-based approach has revolutionized the screening of low molecular weight ligands in the rational development through the knowledge of biological targets.

There are 15 interdisciplinary and multidisciplinary chapters included in the book that highlight the latest developments, modern concepts, innovations in synthetic routes, natural products, biological targets, pharmacological advances, drug-design techniques, screening methods, metabolic transformations, etc., in a very concise, complete manner. The chapters are thoroughly edited and written in an easy-to-understand language, along with figures, diagrams, and illustrations for a better understanding.

I undoubtedly recommend this edited book to undergraduate students, postgraduate students and research scholars, faculty members at colleges, institutes, and universities, researchers and scientists of research laboratories, and industry research and development.

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Preface

Biologically Active Small Molecules: Modern Applications and Therapeutic Perspectives is a new book that concentrates only on a hot subject in pharmacology. With advances in drug discovery and design, creating therapeutically advantageous compounds based on the understanding of biomolecular targets (receptors, enzymes, channels, and others) is the most important field and the future of contemporary pharmacotherapeutics.

Low-mass compounds have an important role in a wide range of pharmacological actions. They have become universally popular due to their simple chemistry, fatigue-free separation techniques, versatile acceptance for computational studies, a large number of places for the substitution of active chemical moieties by well-established synthetic routes with less effort, better quality attributes, and ability to demonstrate a wide range of biological activities.

There was a period, many decades ago, when large molecules were thought to be superior to the low-mass components. Using morphine as an example, the bond disconnection method produced many notable centrally acting analgesics that are much more powerful and have fewer adverse effects than morphine. Natural goods and their semisynthetic derivatives, which often exhibit low-mass features, have received considerable attention in our contemporary age as a result of advances in rational design. This book is intended to provide the most up-to-date information and multidimensional advancements of certain recently discovered therapeutically active low molecular weight compounds, following the research route.

This edited book contains essential information for postgraduate and research students, college and university faculty, scientists at various levels, research laboratories, and industry personnel, and is written in an easy-to-understand language by eminent authors from reputable institutions around the world. The book is divided into five sections comprising 15 chapters that are up-to-date, concise, and comprehensive. The material includes categorization, structures, chemical synthesis, medicinal chemistry, pharmacology, biochemical pathways, mechanism of action, side effects, and adverse effects, among other things.

While editing the contents, the World Health Organization (WHO), the United States Food and Drug Administration (USFDA), and the United States Pharmacopeia (USP) used the most recent therapeutic regulations. The book provides a comprehensive overview of the subject by emphasizing advancements in medicine, chemical sciences, and pharmaceuticals from a multidisciplinary and interdisciplinary perspective. The flowcharts, figures, drawings, and diagrams will offer sufficient information while also piquing the readers' attention.

A multidimensional approach has been taken in the selection of the chapters. Chapter 1 focuses on the advances of bedaquiline, a low molecular weight ligand known to exhibit tremendous antitubercular activity. Chapter 2 highlights the role of volatile hydrocarbon gases used for operative surgical procedures. Chapter 3 stressed on the role of nuclear factor-kappa B (NF-κβ), a new molecular target involved in inflammation and their inhibition by very small molecules of natural and semisynthetic origin called "chalcone." Chapters 4 and 5 present in-depth details with classification, structures, biochemical pathways, pharmacology, mechanism of actions, side effects, adverse effects of low molecular weight adrenergic agonists, and antagonists. Chapter 6 corresponds to the role of small-sized skeletal muscle relaxants in neuromusculoskeletal pharmacotherapeutics. Chapter 7 represents the necessary concepts, developments, and latest innovations in the area of nonsteroidal anti-inflammatory agents.

Chapter 8 underlines the low molecular mass natural products of varied origin having noteworthy antihyperglycemic activity. Chapter 9 is a concise chapter briefing the methods and models for screening the antioxidant activity of small size ligands of both natural and synthetic origin. Chapter 10 is a very interesting chapter highlighting metabolism and enzymatic transformation of the ligands after administration. Chapter 11 is a generalized content on the possible interactions of a biologically privileged small compound with another drug, food, herb, and other components, which will be an appealing matter for the prescribers. Chapter 12 provides essential information of the numerous online databases which are of vital interest for the researchers in selecting and duly screening the low-mass ligands and the possible biological targets. Chapter 13 throws light on the high-throughput screening technique, an emerging technique for rapid virtual screening and speeding up drug discovery process of therapeutically active ligands of low mass. Chapter

14 provides the basic role of homology modeling technique for the rational design of low molecular weight ligand.

Chapter 15 is based on the current coronavirus pandemic situation (COVID-19). The molecular modeling and docking studies of potential drug candidates against various drug targets of the virus are comprehensively highlighted.

—Debarshi Kar Mahapatra, PhD
Sanjay Kumar Bharti, PhD

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PART I

Small Molecules as Active Pharmacological Agents

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CHAPTER 1

Bedaquiline: The New Antituberculosis Drug on the Horizon

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ABSTRACT

Multidrug-resistant tuberculosis (MDR-TB) is tuberculosis that is resistant to at least rifampicin and isoniazid, which threatens to erode the current progress in the global control of TB. Drug resistance may further worsen with the appearance of drug resistance to at least one of the injectable agents (amikacin, capreomycin, and kanamycin) or to fluoroquinolones (pre-extensively drug-resistant (pre-XDR)-TB) or both (extensively drug-resistant (XDR)-TB). Bedaquiline, a diarylquinoline compound with a novel mechanism of anti-TB action, has been granted accelerated or conditional approval in the US (2012) and Europe (2014) for use in MDR-TB, with interim guidance provided for its use by the World Health Organization (WHO). Recently, it was included in the revised WHO classification of second-line antituberculosis drugs in the management for drug resistant TB. It has a potential to reduce the current long duration of treatment of MDR-TB and XDR-TB, which is, as of now, adversely affecting the observance of these patients. The accessibility of this relatively new drug can revolutionize the therapeutics of TB today. This chapter deals with the development, pharmacology, clinical trials, and other essential aspects of bedaquiline.

Biologically Active Small Molecules: Modern Applications and Therapeutic Perspectives.
Debarshi Kar Mahapatra, & Sanjay Kumar Bharti (Eds.)

1.1 INTRODUCTION

Multidrug-resistant tuberculosis (MDR-TB) is tuberculosis that is resistant to at least isoniazid and rifampicin, which threatens to erode the current progress in the global control of TB.[1] Drug resistance may worsen further with the emergence of resistance to at least one of the injectable agents (amikacin, kanamycin, and capreomycin) or to fluoroquinolones (pre-extensively drug-resistant (pre-XDR)-TB) or both (extensively drug-resistant (XDR)-TB),[2,3] Diarylquinoline, bedaquiline (trade name Sirturo, code names TMC207 and R207910), is a new TB drug discovered by Koen Andries and colleagues. This drug has been granted accelerated or conditional approval in the US (2012) and Europe (2014) for use in MDR-TB, with interim guidance provided for its use by the World Health Organization (WHO).[4] In a span of almost 40 years, bedaquiline is the first new drug with a novel mechanism of action to appear on the horizon of antituberculosis treatment.

Adding bedaquiline to a favored environment schedule for 24 weeks results in a faster culture alteration and appreciably higher frequency of culture conversions at 120 weeks in comparison to the placebo. Udwadia et al. reported striking improvement in the first case series of five patients from India on the use of bedaquiline with the individualized optimal background regimen (MDR/XDR-TB) based on their drug sensitivity testing (DST) results.[5] In a recent study by Skrahina et al. from Belarus, the use of bedaquiline in XDR, pre-XDR, and MDR- pulmonary TB cases has been reported to achieve sputum culture conversion in 94% of such patients in 6 months.[6]

Bedaquiline probably kills both dormant and semidormant bacilli also along with the actively replicating mycobacteria by inhibiting mycobacterial ATP synthase, an essential membrane-bound enzyme by interfering with energy production and disrupting intracellular metabolism. This potential action of bedaquiline on dormant and semidormant bacilli has the potential to decrease both the duration of therapy as well as the risk of relapse. Both these aspects are much needed in the current management strategies of drug-resistant TB. This is an area of focus for future research with bedaquiline-based regimes.[7]

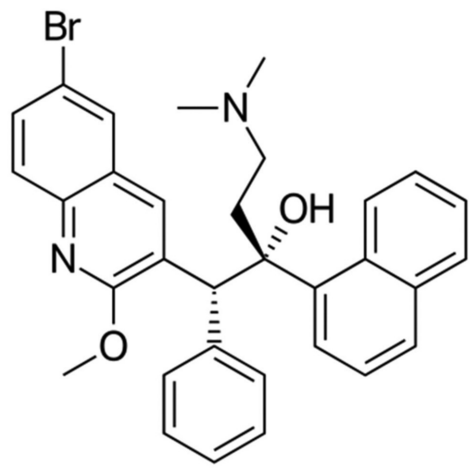
Recently, off-label use of bedaquiline has shown to have a potential role in the management of nontuberculous mycobacterial (NTM) lung disease with 50% patients showing culture conversion at 6 months. However, at present, bedaquiline is not recommended for use in NTM lung disease.[8]

1.2 PHARMACOLOGY

Bedaquiline is a diarylquinoline antimycobacterial with a novel mechanism of action. The drug inhibits adenosine 5'-triphosphate synthase present in mycobacteria. It is an enzyme that is necessary for the energy production in *M. tuberculosis*. It specifically binds to the c subunit and probably also to the ε subunit of the mycobacterial F-ATP synthase.[9–12]

Bedaquiline (Sirturo) for oral administration is available as 100 mg strength tablets. Each tablet contains 120.89 mg of bedaquiline fumarate drug substance, which is equivalent to 100 mg of bedaquiline.[13] The recommended dosage of bedaquiline is:

- Weeks 1–2: 400 mg (four tablets of 100 mg) once daily with food.
- Weeks 3–24: 200 mg (two tablets of 100 mg) 3 times per week with food (with at least 48 h between doses) for a total dose of 600 mg per week.



This novel anti-TB drug contains a central quinolinic heterocyclic nucleus with amine side chains and alcohol functional groups which are principally accountable for anti-infective response. It is a new class where the molecule directly targets the mycobacterial ATP synthase thereby crippling mycobacteria energy metabolism. Bedaquiline does not act exclusively against drug-resistant *M. tuberculosis* isolates, but also against drug-susceptible strains. Its effective half-life is >24 h (Table 1.1).[9–12]

TABLE 1.1 Pharmacodynamic and Pharmacokinetic Profile of Bedaquiline.

Parameters	Information
Group	Diarylquinoline antimycobacterial
Available as	Bedaquiline fumarate
IUPAC name	(1*R*,2*S*)-1-(6-bromo-2-methoxyquinolin-3-yl)-4-(dimethylamino)-2-naphthalen-1-yl-1-phenylbutan-2-ol
Molecular formula	$C_{32}H_{31}BrN_2O_2$
Molecular weight	555.516 g/mol
Metabolism	Primarily hepatic by CYP3A4, metabolized to M2 4–6 times less active in terms of antimycobacterial potency compared with parent drug) and M3
Elimination	Primarily excreted in the feces; renal elimination (<0.001%)
Half-life	5.5 months
Protein binding	>99%
T_{max}	~5 h

1.3 DRUG–DRUG INTERACTION

CYP3A4 inducers coadministration with bedaquiline reduces bedaquiline exposure whereas CYP3A4 inhibitors coadministration with bedaquiline increases the bedaquiline level.[14–16]

1.3.1 RIFAMPIN (STRONG CYP3A4 INDUCER)

Administration of bedaquiline (300 mg once daily) and rifampin (600 mg once daily) for 3 weeks leads to the reduction in the exposure by 52%. Decrease in the systemic exposure occurs when rifamycin is coadministered with bedaquiline, or systemic application of strong CYP3A4 inducers results. The application of bedaquiline as a first-line drug is a major concern where rifampicin remains a main-line component of the therapeutic schedule.

1.3.2 KETOCONAZOLE (STRONG CYP3A4 INHIBITOR)

Bedaquiline (400 mg once daily) administration for 14 days and ketoconazole (400 mg once daily) for 4 days results in an enhancement of exposure by 22%. As a result of adverse reactions with bedaquiline such as prolonged systemic exposure, coadministration of bedaquiline with systemically strong

CYP3A4 inhibitors for >14 days must be avoided, until the ratio of benefit/risk is greater than 1. When nevirapine was coadministered with bedaquiline, no dose adjustment was required.

1.4 SAFETY

At present, bedaquiline carries a black box warning alerting healthcare professionals to an augmentation in all-cause mortality and to a prolongation of the QT interval (QTcF) in patients receiving bedaquiline in contrast to controlled or placebo group. Currently, the only concern with bedaquiline is its safety. However, in a recently published study by Skrahina et al., it has been shown that the safety profile of this drug should not be a limitation to its efficacy potential of yielding a good culture conversion in advanced drug-resistant TB cases also.[6] Most of the side effects of this drug in their study were mild–to-moderate severity and could be managed. Overall, the following side effects may be observed during bedaquiline therapy.

1.4.1 CARDIAC RHYTHM DISTURBANCES

An electrocardiogram (ECG) should be obtained as a part of pretreatment evaluation, then daily for the first 2 weeks, subsequently every 2 weeks for 3 months, and then after every 30 days. QTcF is calculated by Fridericia's formula as QT interval divided by the cube-root of RR interval, where RR is the interval from the onset of one QRS complex (the graphical deflections seen on an ECG that correspond to the depolarization of the right and left ventricle with each heartbeat) to the onset of the next QRS complex, measured in milliseconds.[17] Coadministration of other QT interval prolonging drugs in the regime warrant at least weekly ECG monitoring throughout the bedaquiline therapy. QT prolongation can produce ventricular arrhythmias (Torsades de Pointes) and may cause unexpected deaths. Reports of major studies on the efficacy and safety of bedaquiline are summarized in Table 1.2.

1.4.2 HOW DOES ONE APPROACH PROLONGED QT INTERVAL DURING BEDAQUILINE THERAPY?[18]

- A QTc of >440 ms is deemed to be prolonged but no specific action is required awaiting >450 ms.

TABLE 1.2 Clinical Studies on Bedaquiline.

Group, Year	Type of study	Subjects	Efficacy findings	Tolerability findings	QTc effect
DIACON, 2009	Phase IIb, randomized, multicenter, double-blind, placebo-controlled study	23	Bedaquiline reduced the time to conversion to a negative sputum culture. Bedaquiline increased the proportion of patients with the conversion by sputum culture.	Most AEs were mild-to-moderate; only nausea occurred significantly more frequently in the bedaquiline group.	QT interval prolongation was observed in the bedaquiline and the placebo group (more pronounced in the bedaquiline group), with intergroup differences ranging from 1.0 to 10.8 ms ($p>0.05$). None of the absolute values for the corrected QT interval exceeding 500 ms, and no adverse events were associated with ECG changes.
DIACON, 2014	Phase IIb, randomized, multicenter, double-blind, placebo-controlled study	79	Bedaquiline reduced the median time to culture conversion from 125 days to 83 days	Bedaquiline had similar rates of AEs, treatment-related AEs, and AEs leading to study discontinuation than placebo The most frequent AEs were nausea, arthralgia, and vomiting. The severity of most adverse events was grade 1 or 2.	At study week 24, the mean change from baseline in the QTcF was an increase of 15.4 ms in the bedaquiline group and an increase of 3.3 ms in the placebo group ($p<0.001$). After bedaquiline treatment ended, the QTcF gradually decreased, and the mean value was similar to that in the placebo group by study week 60.
GUGLIELMETTI, 2015	Retrospective cohort study	35	Culture conversion rate was 97% after 6 months of therapy	Mild liver enzyme elevation (≥two-fold from baseline) was reported in 14% of patients, and a ≥five-fold increase occurred in two additional patients (6%). The confounding effect of concomitant drugs was mentioned.	QTc prolongation was greater in individuals exposed to bedaquiline and fluoroquinolones, or clofazimine

TABLE 1.2 *(Continued)*

Group, Year	Type of study	Subjects	Efficacy findings	Tolerability findings	QTc effect
NDJEKA, 2015	Interim cohort analysis	91 (54 HIV+)	In total, 48 (76%) out of 63 patients with 6 months of follow-up either achieved culture conversion or remained culture-negative 6 months after initiation of bedaquiline	Good profile	Clofazimine use and not HIV infection were associated with QTc increase. (ART based on either lopinavir/ ritonavir or nevirapine)
PYM, 2015	Phase 2, multicenter, multinational, open-label, noncompara-tive, single-arm trial	233	Culture conversion was 72.2% at 120 weeks, and 73.1%, 70.5% and 62.2% in MDR-TB, pre-XDR-TB and XDR-TB patients, respectively	The commonest AEs were similar to those generally reported in MDR-TB treatment cohorts; most were grade 1 or 2. Hyperuricemia and increased aspartate aminotransferase was the most frequent grade ≥3 AEs. The incidence of AEs was highest during the first 12 weeks. Serious AEs were reported in 47 (20.2%) patients: respiratory infections/ disorders were the most common	Prolongation of the QTcF interval was reported infrequently. Two patients had an increase in QTcF interval >500 ms; they were both taking clofazimine, and one had concurrent hypokalemia. No episode of clinically significant dysrhythmia was reported. Two deaths were considered doubtfully related to bedaquiline.
SKRAHINA, 2016	Interim cohort analysis	197	96% patients showed culture conversion at 6 months.	The most adverse events were mild or moderate in severity and reversible. One death was possibly related to MDR-TB therapy	41% patients had cardiac disorders (abnormal electrocardiogram and arrhythmia being the most common)

- A QTc value between 450 and 480 ms requires other causes of prolonged QTc interval to be ruled out before deciding to withhold bedaquiline.
- If the QTc value of >480 ms reaches, then following steps must be taken immediately:
  - Confirm the QTc prolongation by repeating the ECG.
  - Check the body electrolytes level. If found abnormal, therapy by bedaquiline should be terminated.
  - If the patient is quite stable and the electrolyte levels are normalized enough, however, the QTc interval is ranged between 480 and 500 ms, then repeat the ECG weekly to ascertain that the interval is stable.
  - If the ECG displays QTc interval of >500 ms, subsequently all the QTc prolonging medicines must be immediately stopped.
  - Bedaquiline and all QTc prolonging medicines must be stopped immediately, if ventricular arrhythmia is clinically diagnosed.
  - Because of the long half-life of bedaquiline, if the ECG has QTc prolongation, weekly monitoring of ECG should take place until the QTC interval normalizes even if the bedaquiline therapy is no longer being given.

1.4.3 MISCELLANEOUS ISSUES

1.4.3.1 AST AND/OR ALT ELEVATION

If the elevation is >3 times the upper limit of the normal, then the hepatotoxic drugs (e.g., pyrazinamide, ethionamide, PAS) of the regime may be withheld, and if levels do not return to normal, then bedaquiline needs to be withdrawn till the levels are normalized.[19]

1.4.3.2 AMYLASE AND OR LIPASE ELEVATION

Acute pancreatitis may rarely occur. If lipase is >2 times and/or amylase is >5 times the upper limit of normal, then bedaquiline should be immediately stopped.

1.4.3.3 MUSCULOSKELETAL SYSTEM–MYALGIA

Muscle tenderness at the site other than injection site, marked impairment of activity due to muscle involvement, or frank myonecrosis require bedaquiline to be stopped.

1.4.3.4 GASTROINTESTINAL SYSTEM DISORDERS

Nausea, Vomiting.

1.5 ISSUES OF DRUG RESISTANCE

The mutation in the target gene atpE of mycobacteria leads to bedaquiline resistance. Not all isolates with increased minimum inhibitory concentrations (MICs) have atpE mutations, suggesting the existence of at least one other resistance mechanisms.[20]

1.5.1 CROSS-RESISTANCE

The mutation in the gene transcriptional repressor, Rv0678, which encodes for efflux pump system (MmpS5-MmpL5) remains the prime nontarget-based bedaquiline resistance. The cross-resistance of bedaquiline with clofazimine is also reported. Provided the diversity of resistance-associated variants (RAVs) in the gene transcriptional repressor and their inconsistent consequences on the MIC, only the drug-susceptibility phenotypic methods can presently be promoted to evaluate the bedaquiline vulnerability.[21]

1.5.2 PRINCIPLES FOR FORMULATING A REGIME FOR DRUG-RESISTANT TB[22–23]

- At least a minimum of five different drugs (pyrazinamide and four s-line TB medicines must be chosen from category A – 1 drug / B – 1 drug / C – 2 drugs / D2 or D3 if needed) are strictly recommended for patients having multidrug-resistant TB or have developed resistance to rifampicin.
- Patients suffering from MDR-TB or rifampicin-resistant TB are recommended to continue high-dose ethambutol or high-dose isoniazid.
- Bedaquiline may classically be obligatory in the these conditions as stated by the WHO:
  - When an effectual therapeutic schedule involves 4 second-line anti-TB medicines in addition to pyrazinamide, it cannot be intended.
  - If resistance or multidrug resistance is reported for any fluoroquinolone class of drug.

- The most effective treatment regimen for multidrug-resistant TB as recommended by WHO includes pyrazinamide along with four second-line drugs. The drug resistance surveillance data and drug-susceptibility testing has indicated toward the use of a late-generation fluoroquinolone, a second-line injectable drug, and bacteriostatic drugs (ethionamide or prothionamide with cycloserine).
- Bedaquiline is primarily recommended if the antitubercular therapy is not practicable due to:
  - drug resistance
  - poor tolerance, adverse drug reactions, or contraindication to some specific constituent of the multidrug therapy, or
  - nonavailability of the drug from the supplier.

1.5.3 IMPORTANT ASPECTS OF THE BEDAQUILINE THERAPY OF THE WHO RECOMMENDATIONS[24]

- It needs a close observation.
- The application to HIV-affected patient, patients with comorbidities (especially cardiac, diabetes, and liver disease), and people addicted to habit-forming components must be in a state of adequate caution.
- A maximum dose of 400 mg daily for the first 2 weeks is recommended which is followed by 400 mg daily for the first 2 weeks of 200 mg dose for the remaining duration with a maximum duration of 6 months.
- It should not be appended to an unresponsive state as a sole agent.
- Continuous monitoring of cardiac parameters is essential to detect any kind of arrhythmia (specifically QT prolongation).
- Active pharmacovigilance systems must be kept in place among the patient groups before the commencement of therapy to report the spontaneously arising adverse drug reactions.
- The drug resistance should be determined by assessing the MICs, in those conditions when specific drug-susceptibility tests are absent.

Considering all these factors an effective background regime is very important in designing a bedaquiline-based regime as bedaquiline if used with a potentially weak/ineffective regime will be exposed to the risk of developing drug resistance.

1.6 THE CURRENT CHALLENGES AND WAY FORWARD WITH BEDAQUILINE

There are a few areas regarding bedaquiline which need to be focused on future avenues for potential research on this novel drug. At present, the WHO classification of medicines have been into application for managing the evidence-based drug-resistant tuberculosis at present. With the emergence of more evidence regarding the efficacy and safety of these medicaments, additional changes are expected to happen in this classification. One such possible future evolution of the current WHO classification has been predicted by Tiberi S et al. considering the current trend of recent emerging evidence (Table 1.3).[25] As seen from the proposed table of the possible future evolution of classification of anti-TB drugs, bedaquiline has the potential to be elevated to a higher group from its current status in the classification (i.e., elevated to future group B from current group D2). The possible inclusion of bedaquiline as a core drug of a regime to tackle drug-resistant TB cases will surely increase the overall efficacy of the regime.

TABLE 1.3 Possible Future Evolution of Classification of Anti-TB Drugs.

GROUP A (fuoroquinolones)	Levofloxacin, moxifloxacin, gatifloxacin
GROUP B (other core) Second-line agents	**Bedaquiline,** delamanid, ethionamide/ Prothionamide, cycloserine/terizidone, linezolid clofazimine
GROUP C (second-line injectable agents)	Amikacin, capreomycin, kanamycin, meropenem/ clavulanate
GROUP D (add-on agents) (not core MDR-TB regimen components)	Pyrazinamide, ethambutol, high-dose isoniazid, p-amino salicylic acid, amoxicillin-clavulanate, rifabutin

The introduction of bedaquiline in the pharmacotherapeutics of tuberculosis has validated adenosine triphosphate (ATP) synthase as an attractive target to kill *Mycobacterium tuberculosis*. Future research on this novel target may be the way forward.[26] Recently, the discovery of imidazo[1,2-a]pyridine ethers and squaramides as selective and potent inhibitors of mycobacterial ATP production has been reported by Tantry et al. signifying that research on these lines has already begun.[27] Bedaquiline has paved the way for opening up a whole new dimension to the future research in TB.

1.7 CONCLUSION

To conclude, bedaquiline is a novel molecule that has arrived in the field of tuberculosis. It needs to be utilized to its full potential in the most efficient possible way. A rationale and judicious use of this molecule are advisable to prevent resistance to this new and potentially lethal weapon in our armory against *Mycobacterium tuberculosis*.

KEYWORDS

- **bedaquiline**
- ***Mycobacterium tuberculosis***
- **antitubercular**
- **clinical studies**
- **drug resistance**
- **drug interactions**

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CHAPTER 2

Plant-Derived Natural Products as Antiglycating Agents

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ABSTRACT

In this era of endless possibilities, we are continually challenged by several lifelong chronic diseases like diabetes, making it difficult to lead a healthy life. Diabetes has been described as a process for dysregulation of glucose metabolism, resulting in its toxic levels in circulation. This, in turn, results in the modification of biomolecules, especially proteins, with the help of several mechanisms including glycation. Glycation is a direct expression of the reductive nature of glucose, unlike other glucose-induced protein modifications. It is a nonenzymatic process where carbonyl groups of the sugar part exclusively react with the amino group of the proteins and the nucleic acids resulting in the formation of advanced glycation end products. These products are difficult to eliminate and keep accumulating inside the cell altering the normal function and structure of biomolecules. Currently, antidiabetic therapies include the use of recombinant or artificial insulin taken in intravenous form and synthetic hypoglycemic agents taken orally. However, many antidiabetic agents are known to cause severe side effects which also add to the problems of diabetes-related complications. The screening of plants for antidiabetic and antiglycation activity can provide a safer alternative to the problems related to glucotoxicity. This chapter

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