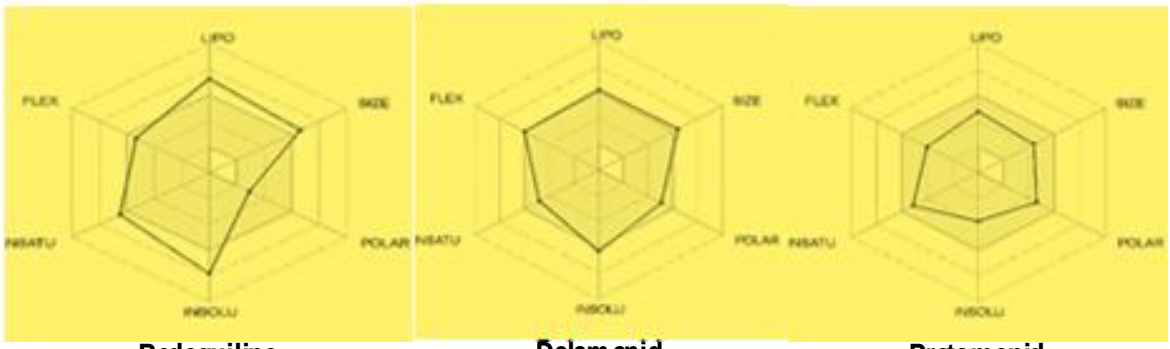
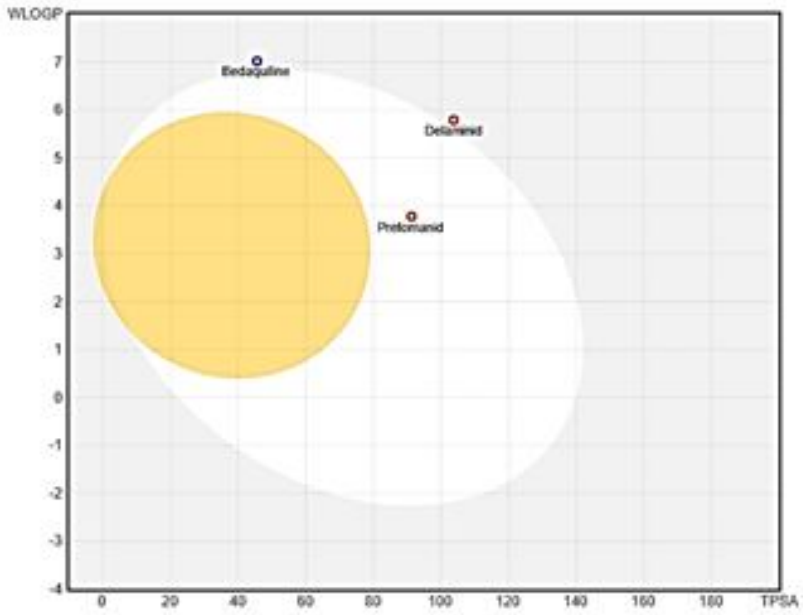
ISSN:0971-1260
Vol-22-Issue-12-November-2019



Bedaquiline **Delamanid** **Pretomanid**



Graphical abstract

THINK INDIA JOURNAL

ISSN:0971-1260
Vol-22- Issue-12-November-2019

Prediction of New TB Drugs Properties by SwissADME

Shubham, Somi, Makam Parameshwar*

Division of Research and Development, Lovely Professional University, Phagwara- 144411, India

* Corresponding author: Tel: +91-7095624914; *E-mail address*: makam.22764@lpu.co.in

Abstract: The Bedaquiline, Delamanid and Pretomanid are the anti-tuberculosis molecules approved in the last five years. The prediction and analysis of physico-chemical properties and brain access and gastrointestinal absorption properties of these molecules have been carried out using Swiss ADME, a free online software tool. From the prediction of these properties, the parameters need to be considered for designing the new chemical entities library has been discussed. These research findings will pave the way for the medicinal chemists to understand and rationalize the properties in design and development of the new chemical entities with quinolone and bicyclic 4-nitroimidazoles.

Keywords: *Mycobacterium tuberculosis*, tuberculosis, Bedaquiline, Delamanid, Pretomanid, SwissADME

ISSN:0971-1260
Vol-22- Issue-12-November-2019

1. Introduction

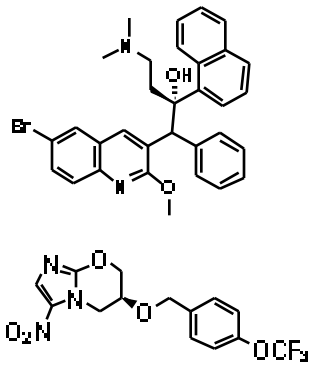
The infectious diseases are caused by the microbes or pathogens have been affecting mankind by immense misery from the prehistoric era to the modern era by re-evolving over the ages and by gaining the antimicrobial resistance (AMR). Among these infectious diseases, the 'Big Three' diseases - Tuberculosis (TB), malaria and HIV/AIDS have been the biggest threats to the present human health and especially in the high-burden countries. The *Mycobacterium tuberculosis (Mtb),* bacteria of *Mycobacterium* genus is the contributing agent of the TB. The TB has been known from the ages and postulated to be the disease of 150 million years[1] and whereas, *Mtb* existence was determined older than 3 million years.[2] TB remained to be impregnable although it a preventable and curable disease due to worldwide spread of the *Mtb* infections. Globally by claiming the lives of the millions, TB still stands leading public health issue. As per the estimation of WHO, in 2018 TB claimed 10 million infections and 1.5 million deaths which includes 0.25 million people died of HIV – TB synergy which accounts that TB is responsible for 1 in 4 HIV deaths. Another aggravating situation is development of *Mtb* drug-resistant strains which includes, multidrug-resistant (MDR), extensively drug-resistant (XDR) and totally drug-resistant (TDR) strains. In 2018, it is estimated that 0.48 million people were diagnosed with MDR-TB.[3] The most alarming situation with *Mtb* infections includes in the regions- South-East Asia (44%), African Region (25%) and Western Pacific Region (18%). From 2000 onwards, the TB incidence has been dropped to 18% with an average drop of 2% per year and an optimistic 37% of decline death rate were recorded. The positive developments in diagnosis and treatment of TB also aided to save 58 million lives. [3-4] More specifically the eight high-burden countries are accountable for the two-thirds of the total global infections. The

ISSN:0971-1260
Vol-22- Issue-12-November-2019

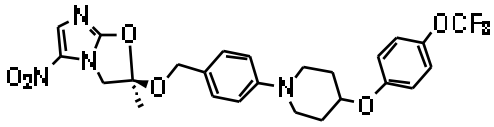
contributions of India, China, Indonesia, Philippines, Pakistan, Nigeria Bangladesh, South Africa is accountable for 27%, 9%, 8%, 6%, 5%, 4%, 4% and 3% respectively.

The last decade was a promising period in the development of chemotherapeutic agents for TB. It has been found that the magnitude of success has been achieved globally in declining the epidemic by massive funds, commitment, resources and innovations. There were many novel scaffolds, molecules and existing drugs were repurposed to identify the chemotherapeutic agents to treat TB. Amongst the Diarylquinoline (DARQs) derivatives and 4-Nitroimidazole derivatives have emerged as potent anti-TB chemotherapeutic agents.

The approved molecule of DARQs is Bedaquiline, a derivative of quinoline as the central structure with extended groups of side-chain *Viz.* are a tertiary amine and tertiary alcohol. On 28th December 2012, Bedaquiline got approved by the U.S. Food and Drug Administration (FDA) for its 24 weeks usage in combination therapy for treating adults (≥ 18 years) MDR-TB patients.[5] The Bedaquiline has exhibited MIC_{50} = 0.03 µg/ml values and in combination with pyrazinamide or fluoroquinolones and the Pretomanid, enhanced early bactericidal activity (EBA) has been observed against *Mtb*.[5-6] The Bedaquiline's mechanism of action includes the inhibition of the energy metabolism by targeting the adenosine 5'-triphosphate (ATP) synthase. [7]



(a)



(b) **(c)**

ISSN:0971-1260
Vol-22- Issue-12-November-2019

Figure 1. Our molecules of study: Anti-TB drugs which were approved in the last five years *Viz.* are (a) Bedaquiline, (b) Delamanid and (c) Pretomanid.

Amongst 4-Nitroimidazole derivatives, Delamanid and Pretomanid are the approved molecules for the treatment of TB. Delamanid, a nitro-dihydro-imidazooxazole derivative has been approved for treating the patients with MDR-TB and XDR-TB in a combination regimen by European Union in 2014.[8] The MICs of the Delamanid are in the range of 0.001 - 0.05 μg/mL.[9] The Delamanid is a prodrug and gets activated by the biotransformation mycobacterial F_{420} coenzyme system and deazaflavin dependent nitroreductase.[10] Delamanid essentially exerts antimycobacterial action by inhibiting the biosynthesis of mycolic acid, an essential constituent of the bacterial cell wall.[10b] Similarly 4-Nitroimidazole derivative, the Pretomanid has got approved by the US FDA on 14th August 2019 to co-administer with Linezolid and BDQ to treat pulmonary forms of nonresponsive MDR, XDR and pulmonary TB. [11] The Pretomanid is also a prodrug which again gets activated by the nitroreductase enzyme metabolical action. In anaerobic conditions Pretomanid acts by generating nitric oxide, a bacterial respiratory poison leading to bactericidal activity.[12] Whereas in the case of aerobic conditions bactericidal activity is exerted by the inhibiting the biosynthesis of mycolic acids and thus disturbing the formation of cell wall.

2. Results and Discussion

2.1. Physico-chemical properties analysis:

The physicochemical properties are the principal attributes that administrate the drug-like molecule (DLM) character of the molecule. The physicochemical properties further exert the profound impact on retaining Absorption, Distribution, Metabolism, Excretion and Toxicity (ADMET) properties in the drug or molecule.[13] This relationship was introduced by

ISSN:0971-1260
Vol-22- Issue-12-November-2019

the Lipinski *et al.,* as a revolutionary rule as 'rule of 5' (Ro5) or 'Lipinski's rule'.[14] This played an immense role in minimizing the failure rate to 15% for developing candidates from 1991 to 2000.[15] The Ro5 summarizes that the molecule with a Log *P* not greater than 5, molecular mass less than 500, hydrogen bond donors and acceptors less than 5 and 10 respectively could lead to good DLM character. The Veber *et al.* studied the oral bioavailability of 1100 drug candidates in rats and revealed that the molecules containing rotatable bonds, polar surface area and H-bond donors and acceptors equal to or less than 10, 140 Å and 12 respectively found to possess better oral bioavailability.[16] The works of Leeson *et al.,* identified 16 to 23% increase in the number of rings, hydrogen bonding groups, a number of rotatable bonds and molecular mass in the molecules approved from 1983 to 2002.[17] In addition to these, the patented pharmaceutical molecules have an increase in the size and lipophilicity.[18]

The aforementioned review of the literature demonstrates that the key modulations in the physicochemical properties are vital information for successful influence of the ADMET characteristics into the drug molecules. Hence, the physicochemical properties evaluation becoming a rapid and prerequisite for medicinal in design the DLMs. The SwissADME is a free online tool for the medicinal chemists. It aids medicinal chemists to design multiple small molecules by enabling them to know the properties of the molecule *Viz.* are physicochemical properties, lipophilicity, drug-likeness, bioavailability radar and pharmacokinetics, *etc*. in graphical output. In addition, SwissADME helps to predict the impact of structural and functional variations in the molecule with respect to the above-said properties. This paves the way for medicinal chemists to decide the pre-requisites for the design of molecules and directs for the preference of the molecules to be synthesized and evaluated for their biological properties and to validate the target.[19]

ISSN:0971-1260
Vol-22- Issue-12-November-2019

The balanced blend of usage of predictive online resources and synthesis and biology would lead to the reduction in the number molecules to be synthesised and analysed, which in turn reduces in the cost, time and utilisation of manpower and resources. We propose the application of SwissADME tool to predict the properties of anti-TB drugs which were approved in the last five years *Viz.* are Bedaquiline, Delamanid and Pretomanid and the data have been summarized in table 1. This interesting information paves for the medicinal chemists to understand and rationalizing the properties in the design and development of the new chemical entities with quinolone and bicyclic 4-nitroimidazoles.

Table 1 Properties of Bedaquiline, Delamanid, Pretomanid*

Property	Bedaquiline	Delamanid	Pretomanid
Physicochemical Properties			
Formula	$C_{32}H_{31}BrN_2O_2$	$C_{25}H_{25}F_3N_4O_6$	$C_{14}H_{12}F_3N_3O_5$
Molecular weight	555.50 g/mol	534.48 g/mol	359.26 g/mol
Heavy atoms	37	38	25
Arom. heavy atoms	26	17	11
Fraction Csp^3	0.22	0.40	0.36
H-bond acceptors	4	10	9
H-bond donors	1	0	0
Rotatable bonds	8	9	6
Molar Refractivity	155.36	134.06	78.56
Consensus Log $P_{o/w}$	6.24	3.71	2.20
TPSA	45.59 Ä²	103.80 Ä²	91.33 Ä²
Water Solubility			
Log S (SILICOS-IT)	-11.59	-6.28	-3.37
Solubility	1.44e-09 mg/ml ; 2.59e-12 mol/l	2.81e-04 mg/ml ; 5.26e-07 mol/l	1.52e-01 mg/ml ; 4.24e-04 mol/l
Class	Insoluble	Poorly soluble	Soluble

ISSN:0971-1260
Vol-22- Issue-12-November-2019

Pharmacokinetics			
GI absorption	Low	Low	High
BBB permeant	No	No	No
P-gp substrate	Yes	No	No
CYP1A2 inhibitor	Yes	No	Yes
CYP2C19 inhibitor	No	Yes	Yes
CYP2C9 inhibitor	No	Yes	Yes
CYP2D6 inhibitor	Yes	Yes	No
CYP3A4 inhibitor	Yes	Yes	No
Log K_p (skin permeation)	-4.57 cm/s	-5.72 cm/s	-6.52 cm/s
Drug likeness			
Lipinski	No; **2 violations**: MW>500, MLOGP>4.15	Yes; **1 violation**: MW>500	Yes; 0 violation
Ghose	No; **3 violations**: MW>480, WLOGP>5.6, MR>130	No; **3 violations**: MW>480, WLOGP>5.6, MR>130	Yes
Veber	Yes	Yes	Yes
Egan	No; **1 violation**: WLOGP>5.88	Yes	Yes
Muegge	No; **1 violation**: XLOGP3>5	No; **1 violation**: XLOGP3>5	Yes
Bioavailability Score	0.17	0.55	0.55
Medicinal Chemistry			
PAINS	0 alert	1 alert: anil_di_alk_E	0 alert
Brenk	0 alert	**2 alerts:** nitro group, oxygen-nitrogen single bond	**2 alerts:** nitro group, oxygen-nitrogen single bond
Lead likeness	No; **3 violations**: MW>350, Rotors>7, XLOGP3>3.5	No; **3 violations**: MW>350, Rotors>7, XLOGP3>3.5	No; **1 violation**: MW>350
Synthetic accessibility	4.39	4.76	3.63

*Calculated by Swiss ADME, a free online software tool accessed at http://www.swissadme.ch/help.php.

ISSN:0971-1260
Vol-22-Issue-12-November-2019

The Lipinski rule of the five has been evaluated and found that the molecular weight order for three compounds Bedaquiline >Delamanid > Pretomanid. Where Bedaquiline and Delamanid have a molecular weight of 555.50 g/mol and 534.48 g/mol and violated the rule of five with molecular weight more than 500. With respect to the number of H-bond acceptors, Delamanid is having the highest of 10 followed by the Pretomanid with 9 and least one is Bedaquiline with 4. But with number of H-bond donors, Bedaquiline has the 1 whereas in Delamanid and Pretomanid has none. The molar refractivity order is Bedaquiline > Delamanid > Pretomanid. Due to the high hydrophilicity and low lipophilicity of Pretomanid, the water solubility of it is higher than the Delamanid. The Bedaquiline is exhibiting the lowest water solubility. Bedaquiline is insoluble, Delamanid is poorly soluble whereas, Pretomanid is soluble in nature with water. Similarly, the Bioavailability Score is almost equal between Pretomanid and Delamanid but found low in Bedaquiline. The Delamanid found to be with highest Synthetic accessibility followed by the Bedaquiline and Pretomanid. These properties are summarised in the web diagrams shown in figure 2.

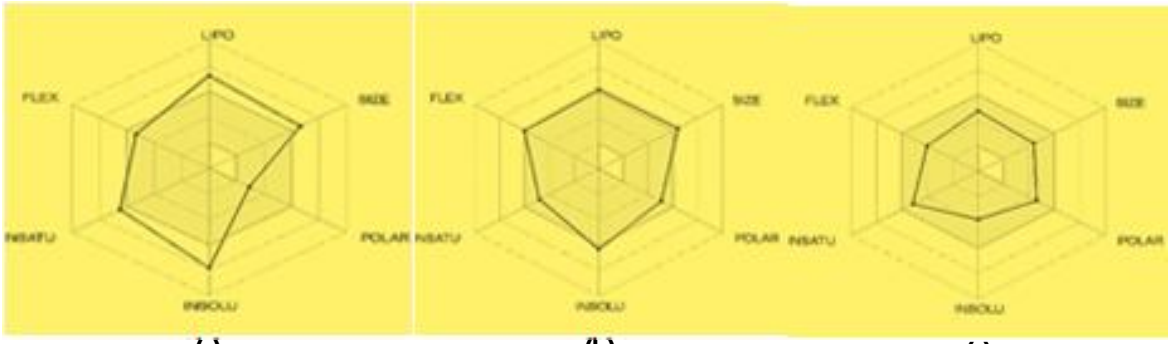


Figure 2. The summarised view of Bedaquiline, Delamanid, Pretomanid Properties.

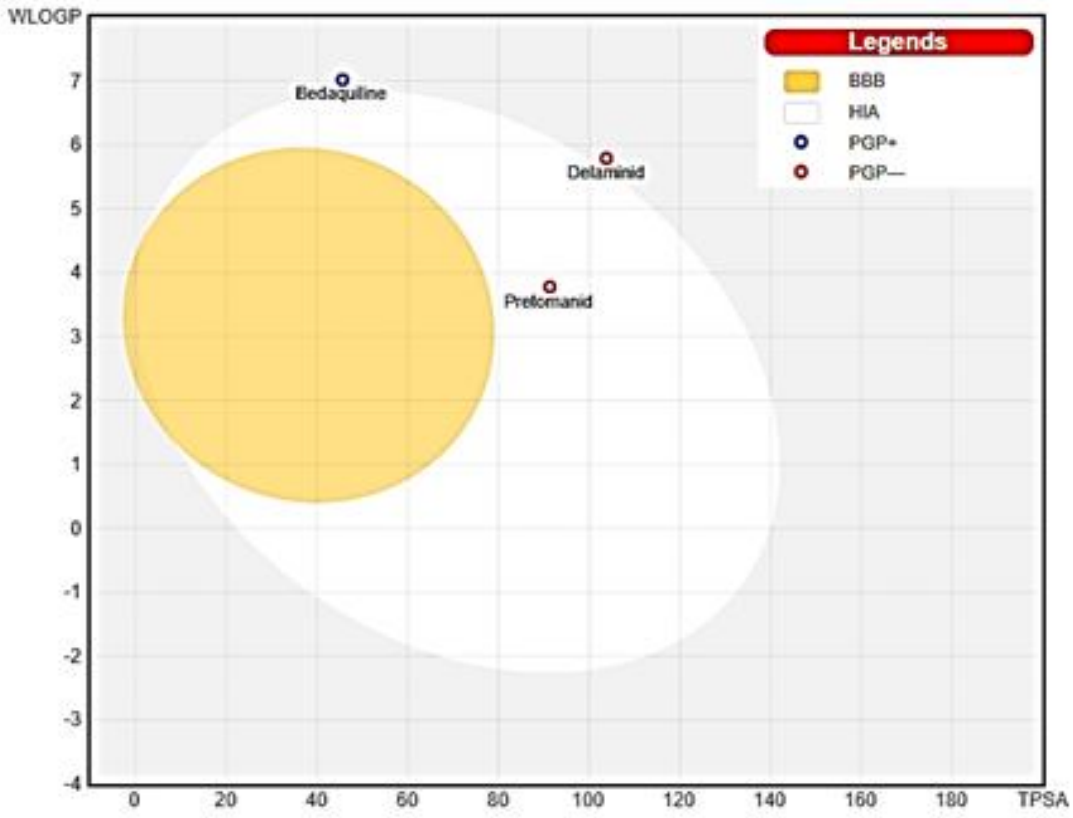
The success of molecules to become a drug not only depends on the efficacy and toxicity but also on demonstration of other key parameters, pharmacokinetics and bioavailability. The two pharmacokinetic properties that play a vital role in many phases of the drug include brain access and gastrointestinal absorption. To estimate these parameters,

ISSN:0971-1260
Vol-22- Issue-12-November-2019

SwissADME provides the Brain Or IntestinaL EstimateD permeation method (BOILED-Egg) model. The BOILED-Egg model takes polarity and lipophilicity of small molecules into account to compute and predict both brain and intestinal permeation parameters. This provides an ease of conceptual simplicity in designing chemical libraries. Using this BOILED-Egg method, the brain access and gastrointestinal absorption properties of Bedaquiline, Delamanid, and Pretomanid are analysed and represented in the graphics in figure 3.

ISSN:0971-1260
Vol-22-Issue-12-November-2019

Figure 3 consists of not mutually exclusive yolk and white areas. The white region in the diagram represents the gastrointestinal tract absorption area. The molecules with required physicochemical properties for better absorption fall in this area. Similarly, the yellow region (yolk) represents the brain permeation of the molecules with the characteristic



physicochemical space. The Pretomanid is the molecule which is falling in the white region whereas, Bedaquiline and Delamanid are almost crossing the white region. It clearly indicates that the Pretomanid is having all the physicochemical properties which can influence the better absorption and distribution in the gastrointestinal tract than the Delamanid and Bedaquiline. None of these molecules is in the yellow region, indicating poor brain permeation. The Delamanid and Bedaquiline are falling in the grey area indicating the poor brain access and gastrointestinal absorption properties.

ISSN:0971-1260
Vol-22- Issue-12-November-2019

Figure 3. BOILED-Egg model representing the brain access and gastrointestinal absorption properties of Bedaquiline, Delamanid, and Pretomanid.

3. Conclusion:

The analysed properties of Bedaquiline, Delamanid and Pretomanid indicate that the new chemical entities (NCEs) can de be designed to overcome the violations of these molecules especially in reduction of the molecular weights and lipophilicity values. By proper blending of the physico-chemical properties in the NCEs, the efficacy of the molecules can be enhanced with the better profiles of pharmacokinetics and bioavailability- brain access and gastrointestinal absorption properties. The SwissADME is a recommended free online software for medicinal chemists for designing the molecules with required attributes.

References:

1. Hayman, J., *Mycobacterium ulcerans*: An infection from jurassic time? *The Lancet* **1984,** *324* (8410), 1015-1016.

2. Gutierrez, M. C.; Brisse, S.; Brosch, R.; Fabre, M.; Omaïs, B.; Marmiesse, M.; Supply, P.; Vincent, V., Ancient origin and gene mosaicism of the progenitor of *Mycobacterium tuberculosis*. *PLoS Pathog*. **2005,** *1* (1), e5.

3. WHO *Tuberculosis: WHO global tuberculosis report 2017*; World Health Organization: World Health Organization, Geneva, 2017.

4. WHO *Tuberculosis: WHO global tuberculosis report, 2018*; World Health Organization: World Health Organization, Geneva, 2018.

5. Li, Y.; Sun, F.; Zhang, W., Bedaquiline and delamanid in the treatment of multidrug-resistant tuberculosis: Promising but challenging. *Drug Develop Res* **2019,** *80* (1), 98-105.

ISSN:0971-1260
Vol-22- Issue-12-November-2019

6. Niccolò, R.; Filippo Del, P.; Federica, M.; Lucia, T.; Antonio Di, B., Bedaquiline: A New Hope for Shorter and Better Anti-Tuberculosis Regimens. *Recent Patents on Anti-Infective Drug Discovery* **2018,** *13* (1), 3-11.

7. (a) Koul, A.; Dendouga, N.; Vergauwen, K.; Molenberghs, B.; Vranckx, L.; Willebrords, R.; Ristic, Z.; Lill, H.; Dorange, I.; Guillemont, J.; Bald, D.; Andries, K., Diarylquinolines target subunit c of mycobacterial ATP synthase. *Nat Chem Biol.* **2007,** *3* (6), 323-324; (b) Andries, K.; Verhasselt, P.; Guillemont, J.; Göhlmann, H. W. H.; Neefs, J.-M.; Winkler, H.; Van Gestel, J.; Timmerman, P.; Zhu, M.; Lee, E.; Williams, P.; de Chaffoy, D.; Huitric, E.; Hoffner, S.; Cambau, E.; Truffot-Pernot, C.; Lounis, N.; Jarlier, V., A Diarylquinoline Drug Active on the ATP Synthase of *Mycobacterium tuberculosis*. *Science* **2005,** *307* (5707), 223.

8. (a) Ryan, N. J.; Lo, J. H., Delamanid: First global approval. *Drugs* **2014,** *74* (9), 1041-5; (b) Lee, S. F. K.; Laughon, B. E.; McHugh, T. D.; Lipman, M., New drugs to treat difficult tuberculous and nontuberculous mycobacterial pulmonary disease. *Curr Opin Pulm Med.* **2019,** *25* (3), 271-280; (c) Hafkin, J.; Hittel, N.; Martin, A.; Gupta, R., Compassionate use of delamanid in combination with bedaquiline for the treatment of multidrug-resistant tuberculosis. *Eur Respir J.* **2019**, Jan 10 ;53(1). pii: 13993003.01154-2018. doi: 10.1183/13993003.01154-2018. Print 2019 Jan; (d) Yuan, T.; Sampson, N. S., Hit Generation in TB Drug Discovery: From Genome to Granuloma. *Chem Rev* **2018,** *118* (4), 1887-1916.

9. Stinson, K.; Kurepina, N.; Venter, A.; Fujiwara, M.; Kawasaki, M.; Timm, J.; Shashkina, E.; Kreiswirth, B. N.; Liu, Y.; Matsumoto, M.; Geiter, L., MIC of Delamanid (OPC-67683) against *Mycobacterium tuberculosis*; Clinical Isolates and a Proposed Critical Concentration. *Antimicrob. Agents Chemother.* **2016,** *60* (6), 3316.

ISSN:0971-1260
Vol-22- Issue-12-November-2019

10. (a) Lewis, J. M.; Sloan, D. J., The role of delamanid in the treatment of drug-resistant tuberculosis. *Ther Clin Risk Manag* **2015,** *11*, 779-91; (b) Szumowski, J. D.; Lynch, J. B., Profile of delamanid for the treatment of multidrug-resistant tuberculosis. *Drug Des Devel Ther* **2015,** *9*, 677-82.

11. (a) *PRETOMANID tablets, for oral use*; 2019; (b) Xu, J.; Li, S. Y.; Almeida, D. V.; Tasneen, R.; Barnes-Boyle, K.; Converse, P. J.; Upton, A. M.; Mdluli, K.; Fotouhi, N.; Nuermberger, E. L., Contribution of Pretomanid to Novel Regimens Containing Bedaquiline with either Linezolid or Moxifloxacin and Pyrazinamide in Murine Models of Tuberculosis. *Antimicrob Agents Chemother* **2019,** *63* (5), 00021-19.

12. Manjunatha, U.; Boshoff, H. I.; Barry, C. E., The mechanism of action of PA-824: Novel insights from transcriptional profiling. *Commun Integr Biol* **2009,** *2* (3), 215-8.

13. (a) Gleeson, M. P.; Hersey, A.; Montanari, D.; Overington, J., Probing the links between in vitro potency, ADMET and physicochemical parameters. *Nat. Rev. Drug Discov.* **2011,** *10* (3), 197-208; (b) Khojasteh, S.; Wong, H.; Hop, C. C. A., ADME properties and their dependence on physicochemical properties. In *Drug metabolism and pharmacokinetics quick guide*, Springer New York: 2011; pp 165-181.

14. (a) Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J., Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv Drug Deliver Rev.* **1997,** *23* (1–3), 3-25; (b) Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J., Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv Drug Deliver Rev* **2001,** *46* (1–3), 3-26.

15. Kola, I.; Landis, J., Can the pharmaceutical industry reduce attrition rates? *Nat Rev Drug Discov.* **2004,** *3* (8), 711-716.

ISSN:0971-1260
Vol-22- Issue-12-November-2019

16. Veber, D. F.; Johnson, S. R.; Cheng, H.-Y.; Smith, B. R.; Ward, K. W.; Kopple, K. D., Molecular properties that influence the oral bioavailability of drug candidates. *J Med Chem*. **2002,** *45* (12), 2615-2623.

17. Leeson, P. D.; Davis, A. M., Time-related differences in the physical property profiles of oral drugs. *J Med Chem*. **2004,** *47* (25), 6338-6348.

18. (a) Leeson, P. D.; Springthorpe, B., The influence of drug-like concepts on decision-making in medicinal chemistry. *Nat Rev Drug Discov.* **2007,** *6* (11), 881-890; (b) Leeson, P. D.; St-Gallay, S. A.; Wenlock, M. C., Impact of ion class and time on oral drug molecular properties. *Med Chem Comm*. **2011,** *2* (2), 91-105.

19. (a) Daina, A.; Michielin, O.; Zoete, V., SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. *Scientific Reports* **2017,** *7* (1), 42717; (b) Daina, A.; Michielin, O.; Zoete, V., iLOGP: A Simple, Robust, and Efficient Description of n-Octanol/Water Partition Coefficient for Drug Design Using the GB/SA Approach. *J Chem Inf Model* **2014,** *54* (12), 3284-3301; (c) Daina, A.; Zoete, V., A BOILED-Egg To Predict Gastrointestinal Absorption and Brain Penetration of Small Molecules. *Chem Med Chem* **2016,** *11* (11), 1117-1121.