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REVIEW ARTICLES

Telacebec (Q203): Is there a novel effective and safe anti--tuberculosis drug on the horizon?

Telacebek (Q203): Vynára sa na obzore nové efektívne a bezpečné antituberkulotikum?

Ivan Malík • Jozef Čižmárik • Gustáv Kováč • Mária Pecháčová • Lucia Hudecová

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Summary

High prevalence and stronger emergency of various forms of drug-resistant tuberculosis (DR-TB), including the multidrug-resistant (MDR-TB) as well as extensively drug-resistant (XDR-TB) ones, caused by variously resistant *Mycobacterium tuberculosis* pathogens, make first-line anti-tuberculosis (anti-TB) agents therapeutically more and more ineffective. Therefore, there is an imperative to develop novel highly efficient (synthetic) agents against both drug-sensitive-TB and DR-TB. The exploration of various heterocycles as prospective core scaffolds for the discovery, development and optimization of anti-TB drugs remains an intriguing scientific endeavour. **Telacebec** (**Q203**; **TCB**), a molecule containing an imidazo[1,2-*a*]pyridine--3-carboxamide (IPA) structural motif, is considered a novel very promising anti-TB agent showing a unique mechanism of action. The compound blocks oxidative phosphorylation by inhibiting a mycobacterial respiratory chain due to interference with a specific cytochrome *b* subunit (QcrB) of transmembrane *bc1* menaquinol-cytochrome *c* oxidoreductase as an essential component for transporting electrons across the membrane from menaquinol to other specific subunit, cytochrome *c* (QcrC). Thus, the ability of mycobacteria to synthesize adenosine-5´-triphosphate is limited and energy generating machinery is disabled. The **TCB** molecule effectively fights drug-susceptible, MDR as well as XDR *M. tuberculosis* strains. The article briefly explains a mechanism of an anti-TB action related to the compounds containing a variously substituted IPA scaffold and is focused on their fundamental structure-anti-TB activity relationships as well. Special consideration is paid to **TCB** indicating the importance of particular structural fragments for maintaining (or even improving) favourable pharmacodynamic, pharmacokinetic and/or toxicological properties. High lipophilicity of **TCB** might be regarded as one of the key physicochemical properties with positive impact on anti-TB effect of the drug. In January 2021, the **TCB** molecule was also involved in phase-II clinical trials focused on the treatment of Coronavirus Disease-19 caused by Severe Acute Respiratory Syndrome Coronavirus 2.

Key words: *Mycobacterium tuberculosis* • drug-resistant tuberculosis • imidazo[1,2-*a*]pyridine-3-carboxamides • telacebec (Q203) • respiratory chain

Súhrn

Vysoká prevalencia rôznych foriem rezistentnej tuberkulózy (drug-resistant tuberculosis – DR-TB), vrátane multirezistentnej tuberkulózy (multidrug-resistant tuberculosis – MDR-TB) a extenzívne rezistentnej tuberkulózy (extensively drug-resistant tuberculosis – XDR-TB), ktoré sú zapríčinené rezistentnými patogénmi *Mycobacterium tuberculosis*, rezultuje do silnejúcej hrozby terapeutickej neefektívnosti antituberkulotík (anti-TB) prvej línie. Imperatívom je preto projekcia nových vysokoúčinných (syntetických) liečiv proti senzitívnym a aj rezistentným kmeňom mykobaktérií spôsobujúcim TB. V tomto kontexte je mimoriadne

Assoc. Prof. PharmDr. Ivan Malík, PhD. (✉)
Department of Pharmaceutical Chemistry, Faculty of Pharmacy
Comenius University in Bratislava
Odbojárov 10, 832 32 Bratislava, Slovak Republic
Institute of Chemistry, Clinical Biochemistry and Laboratory Medicine, Faculty of Medicine
Slovak Medical University in Bratislava
e-mail: malik2@uniba.sk

J. Čižmárik, M. Pecháčová
Department of Pharmaceutical Chemistry, Faculty of Pharmacy
Comenius University in Bratislava, Slovak Republic

G. Kováč, L. Hudecová
Institute of Chemistry, Clinical Biochemistry and Laboratory Medicine, Faculty of Medicine
Slovak Medical University in Bratislava, Slovak Republic

zaujímavé vedecky skúmať rôzne heterocykly ako perspektívne kľúčové štruktúry pre projekciu, vývoj a optimalizovanie takýchto anti-TB-liečiv. **Telacebek** (**Q203**; **TCB**), molekula obsahujúca imidazo[1,2-*a*]-pyridín-3-karboxamidový (IPA) štruktúrny motív, je považovaný za veľmi sľubnú anti-TB-substanciu, ktorá sa vyznačuje unikátnym mechanizmom pôsobenia. Táto zlúčenina blokuje oxidatívnu fosforyláciu mykobaktérií inhibíciou ich dýchacieho reťazca tak, že interferuje so špecifickou podjednotkou, cytochrómom *b* (QcrB), ktorý je súčasťou transmembránovej *bc1* menachinol-cytochróm *c* oxidoreduktázy. Tento komplex je kľúčovým komponentom podieľajúcim sa na transmembránovom transporte elektrónov z menachinolu na ďalšiu špecifickú podjednotku, cytochróm *c* (QcrC). Schopnosť mykobaktérií syntetizovať adenozín-5´-trifosfát je potom limitovaná a súčasne sú významne obmedzené ich možnosti generovať energiu. **TCB** efektívne pôsobí proti susceptibilným, MDR- a aj XDR-kmeňom *M. tuberculosis*. V publikácii možno nájsť stručné vysvetlenie mechanizmu účinku zlúčenín obsahujúcich IPA-fragment a aj hodnotenie vzťahov medzi ich štruktúrou a anti-TB-aktivitou. Mimoriadna pozornosť je venovaná významu jednotlivých štruktúrnych častí **TCB** z pohľadu zachovania (alebo dokonca ďalšieho zlepšenia) výhodných farmakodynamických, farmakokinetických a/alebo toxikologických vlastností. Vysoká lipofilita **TCB** by mohla byť považovaná za jednu z kľúčových fyzikálno-chemických charakteristík, ktoré pozitívne ovplyvňujú anti-TB-pôsobenie tohto liečiva. V januári 2021 vstúpil **TCB** aj do fázy II klinického skúšania orientovaného na liečbu ochorenia COVID-19 (Coronavirus Disease-19), ktorého pôvodcom je koronavírus 2 vyvolávajúci ťažký akútny respiračný syndróm (Severe Acute Respiratory Syndrome Coronavirus 2).

Kľúčové slová: *Mycobacterium tuberculosis* • tuberkulóza rezistentná voči liečivám • imidazo[1,2-*a*]-pyridín-3-karboxamidy • telacebek (Q203) • dýchací reťazec

Introduction

Human tuberculosis (TB) is one of the oldest but still persistent diseases known to affect human lives. TB is not a disease caused by a single *bacterium*, but rather twelve closely related members of the *Mycobacterium* genus, termed the *Mycobacterium tuberculosis* complex (MTBC). The history of TB has been traced to the Stone Age Paleolithic Period, circa 3.3 million years ago. This airborne infectious-contagious and deadly disease, whose main cause is an obligate aerobic acid-fast *Mycobacterium tuberculosis* bacillus belonging into MTBC, reached epidemic levels in Europe and North America in the 18th–19th century[1, 2].

In 2019, TB claimed approximately 1.2 million deaths in HIV-negative individuals and additional 208 000 deaths among people suffering from HIV. Eight countries accounted for two thirds of the global total as follows: India (26.0%), Indonesia (8.5%), China (8.4%), Philippines (6.0%), Pakistan (5.7%), Nigeria (4.4%), Bangladesh (3.6%) and South Africa (3.6%)[3].

Many forms of resistance of strains from *Mycobacterium* sp., including *M. tuberculosis*, which is also known as Koch's bacillus, to activity of drugs have been developed and can be found worldwide. The drug-resistant form of TB (DR-TB) is caused by the mycobacteria resistant to at least one first-line anti-TB drug, i.e., **isoniazid** (**INH**), **rifampicin** (**RIF**), **pyrazinamide** (**PZA**), or **ethambutol** (**EMB**). Polydrug-resistant TB (PDR-TB) indicates the resistance of the mycobacterial organisms to more than one anti-TB drug, but not including both **INH** and **RIF**. The multidrug-resistant disease (MDR-TB) is caused by the mycobacterial pathogens resistant to at least **INH** and **RIF**. Original definition of extensively drug-resistant TB (XDR-TB) needs to be modified as all-oral regimens become standard of care. The cause of pre-extensively (pre-extremely) drug-resistant TB (pre-XDR-TB) is the existence of such MDR mycobacterial strains which are, in addition, resistant to any **fluoroquinolone** (**FQ**) or second-line injectable agent, i.e., **amikacin** (**AK**), **kanamycin** (**KAN**), or **capreomycin** (**CAP**). The XDR-TB form is caused by the mycobacteria, which show multidrug-resistance, and are resistant to any **FQ** and at least one of the second-line injectable anti-TB agents (**AK**, **KAN**, or **CAP**). The *M. tuberculosis* strains that possess resistance to all first-line anti-TB drugs as well as second-line anti-TB compounds are referred to as totally drug resistant (TDR-TB)[4–6].

Globally, the TB incidence rate is falling. However, the decline was much slower to reach a required milestone of 20% reduction between 2015 and 2020[3]. Moreover, the DR-TB disease continues to be a public health threat. The low success rates in the treatment of MDR-TB and XDR-TB, which account for 55% and 34%, respectively, led the World Health Organization (WHO) to conclude that MDR-/XDR-TB remained a very serious public health crisis[3, 7].

Evidently, the development of therapeutically effective anti-TB molecules is imperative. Regarding this aim, the attention was paid to the class of compounds containing an imidazo[1,2-*a*]pyridine-3-carboxamide (IPA) structural motif[8].

Those anti-TB agents showed excellent selective potency against MDR-TB and XDR-TB as well as encouraging pharmacokinetics. The data indicated discovery of the molecules with promising attributes of synthetic accessibility, no redox active moieties, impressive potency, unique mechanism of action and selectivity toward replicating MDR and XDR *M. tuberculosis* strains[9–11], including *M. tuberculosis* $H_{37}R_v$.

Besides, the imidazo[1,2-*a*]pyridine moiety is considered one of the most promising bicyclic 5–6-membered heterocyclic systems, which has been recognized as a "drug prejudice" scaffold due to its broad range of applications in medicinal chemistry. The moiety can be used for the design of anticancer, antimycobacterial, antileishmanial, anticonvulsant, antimicrobial, antiviral, antidiabetic, or insecticidal compounds[12].

Mechanism of anti-tuberculosis action of substituted imidazo[1,2-*a*]pyridine-3-carboxamides

Cellular respiration is the process, in which an energy source (e.g., sugars, fatty acids, or amino acids) is oxidized, simultaneously reducing an electron acceptor (e.g., oxygen, nitrate, sulfur, or sulfate) to produce chemical energy for the synthesis of adenosine-5´-triphosphate. In aerobic organisms, oxygen is the terminal electron acceptor. The entire system forms the electron transport chain (ETC) containing specific electron carriers[13].

Indeed, the *M. tuberculosis* pathogen strictly depends on oxygen to multiply, and terminal oxidases are a vital part of the oxidative phosphorylation pathway. Three very important druggable targets in a respiratory chain of *M. tuberculosis* have been identified, i.e., proton-pumping type II NADH dehydrogenase, cytochrome oxidase, and F_1F_0-ATP synthase, respectively[14].

Considering the second one, the bacterium possesses two aerobic respiratory branches, i.e., proton-pumping cytochrome *bc1-aa3* supercomplex consisting of a transmembrane *bc1* menaquinol-cytochrome *c* oxidoreductase (*bcc*/Qcr) and transmembrane *aa3* cytochrome *c* oxidase (CtaC-F) that are tightly associated, and bacteria-specific cytochrome *bd* type menaquinol oxidase. The *bc1* menaquinol-cytochrome *c* oxidoreductase transfers electrons from menaquinol to *aa3* cytochrome *c* oxidase *via* the QcrC domain. The oxidase pumps protons across the membrane[15]. In *M. tuberculosis*, the genetic knockout of a cytochrome *bc1-aa3* supercomplex resulted in slowed growth *in vitro* as well as partial attenuation *in vivo*[16, 17].

The cytochrome *bd* type menaquinol oxidase, an integral membrane protein complex, is not only involved in fundamental bioenergetic maintenance, but also enhances resistance to oxidative and nitrosative stress[18]. The expression of given oxidase in both *M. tuberculosis* and *M. smegmatis* is upregulated in response to hypoxia[19]. Comprehensive understanding of the protective role of a cytochrome *bd* type menaquinol oxidase in *M. tuberculosis* can be found in the recent paper of Mascolo and Bald (2020)[20].

Indeed, the respiratory chain of *M. tuberculosis* has attracted attention as a highly promising target for next-generation antimycobacterial agents. Some compounds containing an IPA scaffold (Fig. 1) inhibit *M. tuberculosis* growth *via* a unique mechanism. The molecules, including **telacebec** (**TCB**; **Q203**) (Fig. 2), target QcrB, which is a *b* subunit of the *bc1* menaquinol-cytochrome *c* oxidoreductase, as a part of ETC of the *Mycobacterium*[13, 21]. This subunit is regarded as a key player in the function of this *bc1* complex because being able to coordinate actions of all segments of the complex[22]. Besides, the cytochrome *b* subunit is known as a biological (pharmacological) target of antimalarial drug **atovaquone**[23].

If **TCB** will be successfully developed as an anti-TB drug, it might be therapeutically coupled with cytochrome *bd* type menaquinol oxidase inhibitors, as **aurachin D**, which invokes bactericidal activity of **TCB**[24]. For clarification, inhibition of the *bc1* menaquinol-cytochrome *c* oxidoreductase by **TCB** forces the mycobacteria to switch to less energetically efficient cytochrome *bd* type menaquinol oxidase, which generates a proton motive force due to the release of protons after quinol oxidation. Concerned oxidase also facilitates metabolic adaptation of certain *M. tuberculosis* laboratory strains, including the $H_{37}R_v$ one, to imidazopyridine-type cytochrome *bc1* menaquinol-cytochrome *c* oxidoreductase inhibitors[25].

Aurachins are myxobacterial 3-farnesyl-4(1*H*)-quinolone derived compounds initially described as respiratory chain inhibitors, more specifically as inhibitors of various cytochrome complexes[26].

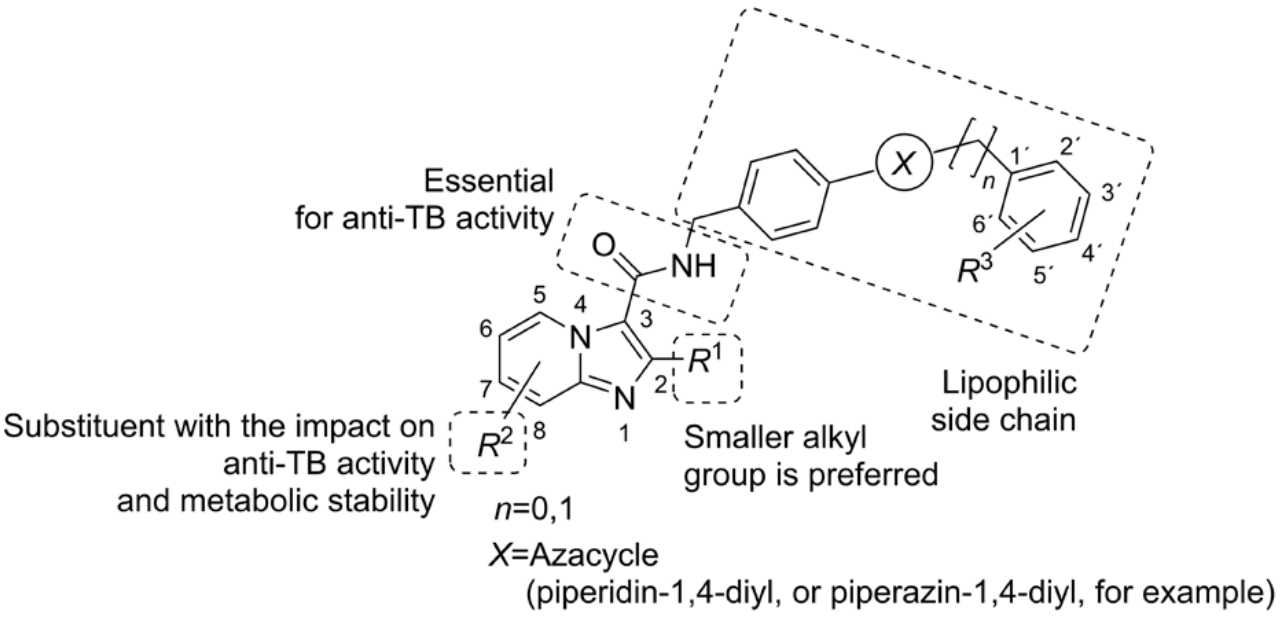

Fig. 1. Brief overview on structure–anti-TB activity relationships connected with imidazo[1,2-a]pyridine-3-carboxamides

Structure-anti-tuberculosis activity relationships connected with substituted imidazo[1,2-*a*]pyridine-3-carboxamides and telacebec (Q203)

In regard to optimize the chemical structure of lead compounds containing an IPA moiety in order to improve the efficiency of resulting derivatives against *M. tuberculosis* $H_{37}R_v$ replicating outside and inside macrophages as well as their pharmacokinetic properties, structure-anti-TB activity relationships (SAR) were investigated. Some of the key SAR findings might be summarized as follows (Fig. 1)[27–30]:

a) Presence of a small alkyl chain (R^1 substituent), especially a C_2H_5 group, appears to be the most favourable.
b) 6- or 7-Cl Atom (R^2 substituent) enhances both anti-TB activity and metabolic stability of the derivatives compared to an unsubstituted compound, i.e., the molecule containing R^2 = H, or the substances containing a highly lipophilic bulky substituent (R^2 = Br, for example).
c) Lipophilic side chain is pivotal for anti-TB efficiency, regardless of its length, or linearity.
d) Substituted *N*-benzyl moiety within a lipophilic side chain is important but not critical for anti-TB activity.
e) 4´-OCF_3-Phenylpiperidino group is the optimal choice regarding the selection of a substituent within a lipophilic side chain. Basic moiety (*X* substituent) might be replaced with other nitrogen-containing heterocycles in the effort to maintain pharmacodynamic properties and improve pharmacokinetic features of resulting derivatives.
f) Presence of a 3-C(O)NH group is essential for anti-TB activity, switching its position from 3 to 2 causes the decrease in anti-TB activity.

Further structural optimization of given IPA scaffold led to design[31], *in vitro* and *in vivo* investigation of **TCB** (Fig. 2), chemically 6-chloro-2-ethyl-*N*-[(4-{4-[4-(trifluoromethoxy)phenyl]piperidin-1-yl}phenyl)methyl]-imidazo[1,2-*a*]pyridine-3-carboxamide (CAS Registry Number: 1334719-95-7). The lack of chiral centre in the **TCB** molecule could be considered advantageous for the large-scale synthesis.

Motamen and Quinn reported[32] lipophilicity (CLOGP values calculated *in silico*, in fact) as a critical property, which showed the most difference between anti-TB drugs used clinically and anti-TB candidates in clinical trials. In addition, they observed a new TB space with more appropriate molecular weight (MW) values of the candidates (MW ≤ 500.00 Da), predicted lipophilicity (CLOGP) in an interval of –4.00 ≤ (compound's) CLOGP ≤ 3.00, as well as polar surface area (PSA) parameter varied as follows: 30.00 Å^2 ≤ (compound's) PSA ≤ 150.00 Å^2. The proposed TB space might be a useful and reliable guide to design new anti-TB compounds.

Regarding these *in silico* descriptors connected with a highly lipophilic **TCB**[32], there could be a space to optimize pharmacokinetic, or toxicological properties of its derivatives while maintaining (or even potentiating) their anti-TB activity.

Fundamental SAR related to **TCB** might be summarized briefly as follows[27, 28, 31, 33, 34]:

a) Modification of chlorine position attached to an aromatic ring, i.e., shift of the substituent from a 6-position to the 7-one, slightly improves efficiency against *M. tuberculosis* $H_{37}R_v$ replicating outside and inside macrophages. On the other hand, the designed positional isomer inhibits five different isozymes belonging into a cytochrome P450 enzymes class.
   Introduction of other less lipophilic R^1 and R^2 substituents into a structure of those potent anti-TB agents might be also possible (R^1 = R^2 = CH_3, for example) presuming quite extensive modification of a lipophilic side chain, i.e., an *N*-(2-[4-substituted] phenoxy)ethyl moiety can be incorporated (Fig. 1).
b) Introduction of an ionizable saturated ring between two aryl groups results in improved solubility under acidic conditions without anti-TB-activity loss. Eventual replacement of a cyclic piperidin-1,4-diyl moiety with a classical bioisosteric piperazin-1,4-diyl group

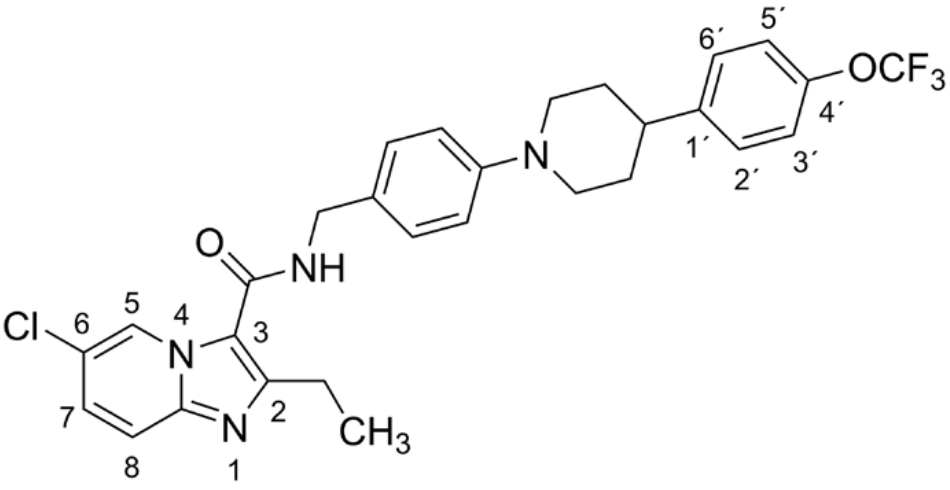

Fig. 2. Chemical structure of telacebec (TCB; Q203)

leads to a slightly more active derivative against *M. tuberculosis* $H_{37}R_v$, which shows, in addition, comparable stability in human microsomes. However, the CYP enzymes are inhibited more efficiently by given classical bioisostere.

The introduction of piperazin-1,4-diyl can be also considered in attempt to design effective and safe compounds presuming suitable modification of a lipophilic side chain. For example, acceptable pharmacokinetic and toxicological features of less lipophilic **TCB** derivatives, which might serve as promising lead compounds for further anti-TB drug discovery, development and optimization, can be achieved if an "original" 4´-OCF_3-phenylpiperidino group is replaced with the 4-(cyclohexylmethyl)piperazin-1-yl one. Other approaches how to design desired derivatives of **TCB** can be based on the incorporation of bicyclic structures containing nitrogen atoms – an octahydropyrrolo[3,4-*c*]pyrrole moiety can be taken into the consideration, for example.

c) Classical bioisosteric replacement of a 4´-OCF_3 group with a 4´-Cl, or 4´-F substituent provides slightly less potent derivatives, which, in addition, inhibit the CYP enzymes.
d) Insertion of an etheric bridge or OCH_2 group between a piperidin-1,4-diyl scaffold and phenyl moiety causes slight decrease in anti-TB efficiency. Replacement of a piperidin-1,4-diyl fragment with the piperazin-1,4-diyl one and simultaneous incorporation of a CH_2 chain between the basic group and aromate provides a similar conclusion.
e) Extensive modification of a linear lipophilic side chain might be also the alternative to find effective anti-TB compounds. The SAR related to the molecules containing shorter fused ring moieties can be found in a research paper of Kang et al. (2017)[28].

Optimising physicochemical properties of new anti-TB candidates is one of key aspects in their discovery to address the balance between anti-TB efficiency, favourable pharmacokinetics and minimisation of off-target effects. Regarding the properties connected with the first-line anti-TB drugs and clinical candidates, a diverse range of molecular size, lipophilicity, hydrogen bond donors, hydrogen bond acceptors, and calculated molar refraction can be found[35].

The principle of minimal lipophilicity, or strict agreement of compound's properties with very well-known Lipinski's Rule of 5 (Ro5), i.e., MW ≤ 500.00 Da, CLOGP ≤ 5.00, or MLOGP ≤ 5.14 (values *in silico* in both cases), hydrogen bond donors (n_{OHNH}) ≤ 5, and hydrogen bond acceptors (n_{ON}) ≤ 10, in order to achieve the improvement in solubility, metabolic profiles, and off-target effects[36] cannot be applied unconditionally to a highly anti-TB effective **TCB** molecule, as its MW = 557.01, CLOGP = 7.64, n_{OHNH} = 1, and n_{ON} = 6 clearly indicated[35].

Furthermore, Veber's rules add that the compounds with < 10 rotatable bonds (n_{rot}) and PSA < 140.00 Å^2 are more likely to be orally bioavailable[37]. Focusing on **TCB**[32, 38], the violations of these rules are not observed (n_{rot} = 8, PSA = 58.87 Å^2).

Indeed, the anti-TB agents do challenge established Ro5 that gives a rough evaluation of the potential of a small molecule to be absorbed passively after oral administration. The fact is that novel anti-TB compounds and promising clinical candidates are more lipophilic than first-line anti-TB drugs (**INH**, **PZA**, **EMB**), many antibiotics, or other antibacterial chemotherapeutics[35, 38]. This may be due to interference of these highly lipophilic molecules with waxy mycobacterial cell wall containing high amount of lipids, long chains of mycolic acids, and peptidoglycan. Thus, it is not surprising that the wall acts as an impermeable barrier for hydrophilic agents[35, 38].

High lipophilicity of **TCB**, an unattractive structure in terms of „classical" Ro5, allows for strong drug-mycobacterial membrane interactions altering stability and functional integrity of the membrane due to the disruption of proton motive force and/or mycobacterial efflux pumps[32, 38]. Thus, strict adherence to Ro5 may have resulted in the loss of opportunities in particularly for a difficult pathogen as *M. tuberculosis*.

Initial *in vitro* evaluations and clinical trials concerning telacebec (Q203)

The **TCB** molecule is an orally bioavailable substituted IPA that was invented at the Institute Pasteur Korea (Seongnam-si, Republic of Korea), a biotech company[39]. Following the results of initial *in vitro* screening, it was suggested that **TCB** might achieve good blood exposure in humans. As reported in early phases of the evaluation[21], **TCB** did not inhibit hERG potassium channel, thus indicating its low potential for cardiotoxicity. The molecule did not inhibit any of the cytochrome P450 isoenzymes tested (CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4), nor did it induce human pregnane X receptor activation. In addition, **TCB** was not a substrate or an inhibitor for the efflux transporter P-glycoprotein, indicating drug's low potential for drug-drug interactions. Concerned derivative showed the bioavailability of 90% and terminal half-life of 23.4 hrs (*in vivo* experimental models)[21].

In 2018, the compound was involved in an open-label randomized study (phase-IIa trial) under the ClinicalTrials.gov number NCT03563599 performed by Qurient Company (Qurient Co.) in Cape Town (Republic of South Africa) to evaluate early bactericidal activity, safety, tolerability, and pharmacokinetics of its multiple oral doses in treatment-naive patients with newly diagnosed **RIF**- and **INH**-sensitive sputum smear-positive pulmonary TB[40].

Increasing doses of **TCB** were associated with greater reductions in viable mycobacterial sputum load. The use of **TCB** was connected with acceptable adverse-event rates as well. In addition, there were observed no serious adverse drug reactions and no adverse drug reactions that might cause early withdrawal from the study[21, 41].

Infectex, a subsidiary biotech company of Maxwell Biotech Group (Moscow, Russian Federation) licensed **TCB** from Qurient Co. to develop and commercialize this drug in the Russian Federation, Armenia, Azerbaijan, Belarus, Kazakhstan, Kyrgyzstan, Moldova, Tajikistan, Turkmenistan, Uzbekistan, and Ukraine[42], as being announced at the beginning of February, 2014.

Infectex communicated the successful completion of a phase-I trial of **TCB** in the Russian Federation (June 2017) evaluating its safety, tolerability, and pharmacokinetic parameters when administered to healthy volunteers on a one-time basis. The study proved the safety and good tolerability of **TCB** in all tested doses. All adverse effects due to drug-taking were of mild severity and represented clinically insignificant laboratory abnormalities that did not require additional actions from physicians nor the prescription of medication[43, 44].

In January 2021, the **TCB** molecule was also involved in phase-II clinical trials[45] (Republic of South Africa) focused on the treatment of Coronavirus Disease-19 caused by Severe Acute Respiratory Syndrome Coronavirus 2.

Conclusions

The development of drug resistance and concurrence of TB in HIV-positive patients are major reasons why TB is so difficult to eradicate and has become a challenge to overcome. Particular forms of DR-TB, including MDR-TB, or XDR-TB, are considered the potential obstacles for elimination of TB globally. One can expected that novel anti-TB drugs will not only shorten and simplify the treatment duration but will also reduce the interruption/dropout rate of the treatment and improve the cure rate compared to the therapy primarily based on existing front-line anti-TB drugs. After decades of stagnation, the treatment of DR-TB is undergoing a breakthrough. In more detail, **bedaquiline** and **delamanid**, which showed a unique mechanism of anti-TB action, have been approved by stringent regulatory authorities and are recommended by the WHO. Innovation for the treatment of susceptible TB as well as DR-TB forms might be expected to come with approval and relevant clinical use of first-in-class **TCB**, a compound containing an imidazo[1,2-*a*]pyridine-3-carboxamide structural motif. The presence of an extended chain of aromatic and aliphatic rings characterized with a 4´-trifluoromethoxyphenyl substitution gives highly lipophilic nature to this compound as becomes standard in current anti-TB research. Despite of the fact that such approach is quite questionable in the light of „traditional" Lipinski's Ro5, high lipophilicity is a key parameter that should be taken into consideration very seriously when designing novel anti-TB drugs, or promising clinical candidates. Overall, the unique mechanism of **TCB**'s action based on very effective and selective inhibition of a mycobacterial respiratory chain, its convenient pharmacokinetic parameters and favourable toxicological properties open the door to this potentially first all-new pantuberculosis regimen of the 21st century.

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