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Antitubercular and Cheminformatic Study of Substituted Benzofuran C-2 Coupled Quinoline Carboxylate Analogous

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ABSTRACT

Coupled heterocycles are becoming interesting biological targets in bringing out potent pharmaceuticals for the treatment of various diseases. In view of this a series of 2-(1-benzofuran-2-yl)-quinoline-4-carboxylic acids and their resultant esters were evaluated for their antitubercular activity against H37Rv strain by Microplate Alamar Blue Assay (MABA) method. *In silico* cheminformatics studies on bioactivity prediction was carried out using mole information. The results revealed that the analogues 4a, 5b-c and 6a-b exhibited excellent antitubercular potential at concentration of 1.6 µg/ml. The compounds 4b-c and 7c exhibited good activity at 6.25 µg/ml and compounds 5a, 6c, and 7a-b showed significant activity at 12.5 µg/ml when compared with standard drugs pyrazinamide, streptomycin and ciprofloxacin. Benzofuran coupled quinoline moieties are vital for activity as they possess excellent drug-like characteristics, suggesting being potentially best inhibitor of H37Rv strain. The *in silico* bioactivity study also revealed that the compounds have significant interaction with the drug targets.

Keywords: Cinchophen, Quinoline-4-carboxylic acid, H37Rv, MABA, ADMET

INTRODUCTION

Tuberculosis (TB) is one of the infectious diseases and remains a major health problem with two million deaths and eight million new cases annually [1-3]. Due to Multi Drug Resistant (MDR) strains of mycobacterium tuberculosis in patients who have acquired Human Immuno Deficiency Syndrome (AIDS) the number of patients infected with the disease is increasing worldwide [4-6]. The clinical management of TB has relied on a limited number of drugs such as isonicotinic acid hydrazide, rifampicin, ethambutal, streptomycin, ethionamide, pyrazinamide, fluoroquinolones etc. [7,8]. Currently, patients require 6-9 months of treatment. The long period leads to the lack of compliance, which in turn, can be responsible for the relapse and emergence of resistant strains [9]. There are several reasons that justify the need to search for new drugs for TB, like improvement of current treatment by shortening its duration, to achieve efficient treatment for MDR TB. So, the improvement of new drugs for shortening the duration of the treatment and to fight against multidrug resistant tuberculosis strains is urgent [10]. Some of the enzymes which are involved in antitubercular activity such as malate synthase work together with isocitrate lyase in the glyoxylate cycle to bypass two oxidative steps of the Krebs cycle and permit carbon incorporation from acetate or fatty acids in many microorganisms [11]. DNA gyrase is a validated target for antitubercular drug discovery, inhibitors of the enzyme were found to be active against non-replicating, persistent mycobacteria, which might be important for shortening the duration of TB therapy. A novel inhibitor of *M. tuberculosis* DNA gyrase would also be effective against MDR TB and will likely to be effective against fluoroquinolone resistant *M. tuberculosis* [12]. Catalase and peroxidase play an important role in mycobacterial resistance by killing mycobacteria in alveolar macrophages with Reactive Nitrogen Intermediate (RNI) [13]. The recent reports have shown that *M. tuberculosis* acquiring resistance to RNI and are due to the presence of iron in catalase involving detoxification process [14,15].

Benzofuran and its analogues has attracted due to their biological activities and their potential applications as pharmacological agents. Most of the benzofuran derivatives possess antitubercular, antimicrobial, sedative, hypnotic, antitumor, antiinflammatory, fungicidal and anticonvulsant activities [16-20]. Similarly, the quinoline nucleus is an important class of heterocyclic compounds found in many synthetic and natural products with a wide range of pharmacological activities [21-33]. In spite of its broad spectrum activity, very few activity studies have been reported against tuberculosis in comparison with other classes [34]. Quinoline analogues have been examined for different mycobacterial infections [35], as a result gatifloxacin and moxifloxacin are in the last stage of antitubercular drug discovery pipeline, FDA approved gatifloxacin and moxifloxacin as antitubercular agents [36].

In the present scenario, due to the emergence of MDR-TB and the association with HIV and TB, Directly Observed Treatment Short-course (DOTS) is becoming rapidly ineffective in controlling TB [37]. In such circumstances, the second line drugs are prescribed in combination with DOTS. The combination of drugs is very expensive, has to be administered for a longer duration which causes significant side effects.

The long duration therapy makes patient compliance difficult, and such patients become potent source of drug-resistant strains [38]. There is an urgent need to develop new antimycobacterium therapeutics to treat this deadly disease and shorten duration of treatment for better medication.

The literature survey reveals that when one biodynamic heterocyclic system coupled with another, a hybridized molecule with pronounced biological activity is formed [39]. Encouraged by these observations and in continuous our research work on biologically active hybridized heterocycles [40-42], benzofuran and quinoline carboxylate moieties were coupled and considered to evaluate their antitubercular potential of the compounds reported earlier from our laboratory [40].

METERIALS AND METHODS

Antitubercular activity

The antitubercular screening of the molecules was carried on *M. tuberculosis* H37Rv strain, by Microplate Alamar Blue Assay (MABA) method [43], using nontoxic and thermally stable reagent. In comparison to fluorometric MABA and BACTEC methods, visual MABA is an inexpensive, alternative, providing identical and rapid results without the use of specialized equipment.

The procedure for assay involves by taking 200 µl of sterile deionized water and was introduced into all outer perimeter wells of sterile 96-well plate to avoid evaporation of medium in test wells during incubation. The 96-well plate received 100 µl of the Middle brook 7H9 broth and serial dilutions of the compounds. The final drug concentrations tested were of 100-0.8 µg/ml and incubated at 37°C for 5 days. After incubation, 25 µl of freshly prepared 1:1 mixture of almar blue reagent and 10% tween-80 was added to the plate and further incubated for 24 h. After 24 h, the change in color was observed and the concentrations of the compounds inhibited were recorded. The drugs pyrazinamide, streptomycin and ciprofloxacin were used as positive standard for comparison.

In silico studies

Calculation of pharmacokinetic parameters and toxicity potential

Chemical structures and Simplified Molecular Input Line Entry System (SMILES) notations of the title compounds were obtained by using Advanced Chemistry Development (ACD) labs ChemSketch version and the derivatives were then fed in the online free Molinspiration Software to calculate various molecular properties and to predict the bioactivity score for drug targets including enzymes and nuclear receptors, kinase inhibitors, G-protein Coupled Receptors (GPCRs) ligands and ion channel modulators. Molecular properties such as the Partition Coefficient (LogP), Topological Polar Surface Area (TPSA), hydrogen bond donors and acceptors, rotatable bonds, number of atoms, molecular weight, and violations of Lipinski's rule of five were calculated to evaluate the drug likeness of the synthesized compounds [44]. The bioactivity score and drug likeness properties of the title compounds were compared with the standard drugs pyrazinamide, streptomycin and ciprofloxacin. Osiris property explorer, an online cheminformatics tool, was used to determine pharmacokinetics parameters such as toxicity potential, solubility and overall drug-likeness of synthesized analogues.

RESULTS AND DISCUSSION

In vitro antitubercular activity

The title compounds were further tested for *in vitro* anti-mycobacterial screening against *M. tuberculosis* H37Rv, using MABA, according to the reported method [43] taking pyrazinamide, streptomycin and ciprofloxacin as standard for comparison. The substituted methyl/ethyl/n-butyl-2-(1-benzofuran-2-yl) quinolone-4-carboxylates (4a-c, 5a-c, 6a-c, 7a-c and 8a-c) showed antitubercular activity with Minimum Inhibitory Concentration (MIC) value ranging from 1.6-12.5 µg/ml and the results are reported in Table 1.

Among the tested compounds, 4a, 5b-c and 6a-b showed excellent activity with a MIC value 1.65 µg/ml, which showed good activity as compared with standard drugs. While the molecules such as 4b-c and 7c exhibited activity with a MIC value 6.25 µg/ml and the molecules 5a, 6c and 7a-b display activity with a MIC value 12.5 µg/ml, which showed moderate activity as compared with standard drugs. Overall whole series of molecules were found to be possessing very good activity and prompt for further in depth investigation.

Table 1: MIC values of antitubercular activity against H37Rv strain

Code	MIC µg/ml
4a	1.6
4b	6.25
4c	6.25
5a	12.5
5b	1.6
5c	1.6
6a	1.6
6b	1.6
6c	12.5
7a	12.5
7b	12.5
7c	6.25
8a	50.0
8b	25.0
8c	12.5

Note: Strain used: *M. tuberculosis* (H37Rv strain); Standard drugs: Pyrazinamide-3.125 µg/ml, streptomycin-6.25 µg/ml, ciprofloxacin-3.125 µg/ml

Pharmacokinetics properties

Drug likeness score and bioactivity score of entitled compounds

Lipinski's rule of five is commonly used by pharmaceutical chemists in drug design and discovery to predict oral bioavailability of potential lead or drug molecules [44]. The molecular properties of methyl/ethyl/propyl/n-butyl-2-(1-benzofuran-2-yl)-quinolone-4-carboxylates were calculated and are presented in Table 2. The title compounds did not violate any of the Lipinski's rules of five; compounds showed zero violations and are expected to be orally active. Molecular weight of twenty one intermediate and Benzofuroquinoline Derivatives (BFQD) was found to be less than 500 and thus these molecules are likely to be easily transported, diffused and absorbed as compared to large molecules. Number of hydrogen bond acceptors (O and N atoms) and number of hydrogen bond donors (NH and OH) in the synthesized compounds were in accordance with the Lipinski's rule of five. The topological polar surface area is very much correlated with the hydrogen bonding of a molecule and is a very good indicator of the bioavailability of drug molecule. TPSA of synthesized derivatives was observed in the range of 81.15-121.53 Å and is well below the limit of 160 Å. The bioactivity scores of the title compounds for drug targets and are presented in Table 3. A molecule having bioactivity score more than 0.00 is most likely to exhibit considerable biological activities, while values 0.50-0.00 are expected to be moderately active and if the score is less than 0.50 it is presumed to be inactive [45]. The results clearly reveal that the physiological actions of synthesized analogues might involve multiple mechanisms and could be due to the interactions with GPCR ligands, nuclear receptor ligands, and inhibit protease and other enzymes. The bioactivity score of compounds is suggestive of significant interaction with all drug targets. The identified compounds showed a better bioactivity score than standard drugs (Table 3).

Table 2: Drug likeness score for the synthesized 2-(1-benzofuran-2-yl) quinoline-4-carboxylate derivatives using Molinspiration Cheminformatics software

Compounds	miLog P[a]	TPSA[b]	n-Atoms	n-ON[c]	n-OHNH[d]	n-violation	n-rotb[e]	MW[f]
4a	4.34	52.34	23	4	0	0	3	303.32
4b	5	52.34	24	4	0	0	3	278.91
4c	4.46	52.34	24	4	0	0	3	321.31
5a	4.72	52.34	24	4	0	0	4	317.34
5b	5.38	52.34	25	4	0	1	4	351.79
5c	4.84	52.34	25	4	0	0	4	335.33
6a	5.78	52.34	26	4	0	1	6	345.4
6b	6.44	52.34	27	4	0	1	6	379.84
6c	5.9	52.34	27	4	0	1	6	363.39
7a	5.22	52.34	25	4	0	1	5	331.37
7b	5.88	52.34	26	4	0	1	5	365.82
7c	5.34	52.34	26	4	0	1	5	349.36
8a	5.08	52.34	25	4	0	1	4	331.37
8b	5.74	52.34	26	4	0	1	4	365.02
8c	5.2	52.34	26	4	0	1	4	349.36
Streptomycin	-4.87	324.42	40	18	15	3	9	580.59
Pyrazinamide	-0.71	68.88	9	4	2	0	1	123.11
Ciprofloxacin	-0.7	74.57	24	6	2	0	3	331.35

[a]Logarithm of partition coefficient between n-octanol and water (miLogP); [b]Topological polar surface area (TPSA); [c]Number of hydrogen bond acceptors (n-ON); [d]Number of hydrogen bond donors (n-OHNH); [e]Number of rotatable bonds (n-rotb); [f]Molecular weight (MW)

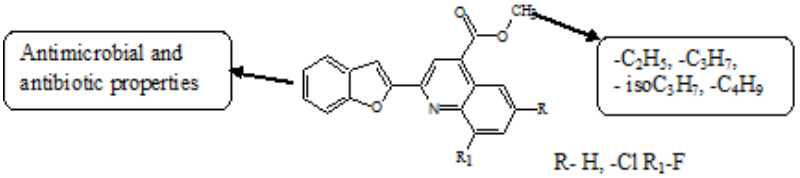
Table 3: Bioactive score of the synthesized 2-(1-benzofuran-2-yl) quinoline-4-carboxylate according to Molinspiration Cheminformatics software

Compounds	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
4a	-0.15	-0.29	-0.08	-0.07	-0.35	0
4b	-0.14	-0.28	-0.09	-0.07	-0.35	-0.03
4c	-0.11	-0.27	-0.15	-0.12	-0.41	0.03
5a	-0.18	-0.27	-0.14	-0.03	-0.36	-0.04
5b	-0.17	-0.26	-0.15	-0.05	-0.36	-0.06
5c	-0.14	-0.25	-0.21	-0.09	-0.42	-0.01
6a	-0.07	-0.22	-0.1	-0.01	-0.25	0.05
6b	-0.07	-0.22	-0.1	-0.01	-0.26	0.02
6c	-0.04	-0.21	-0.16	-0.05	-0.32	0.07
7a	-0.12	-0.25	-0.13	-0.02	-0.3	0.02
7b	-0.12	-0.25	-0.13	-0.04	-0.31	-0.01
7c	-0.09	-0.24	-0.19	-0.08	-0.37	0.04
8a	-0.15	-0.26	-0.13	-0.02	-0.3	-0.01
8b	-0.14	-0.25	-0.14	-0.4	-0.32	-0.04
8c	-0.12	-0.24	-0.2	-0.08	-0.37	0.01
Streptomycin	0.15	-0.14	-0.15	-0.02	0.64	0.42
Pyrazinamide	-1.97	-1.45	-1.71	-2.87	-1.84	-1.43
Ciprofloxacin	0.12	-0.04	-0.07	-0.19	-0.21	0.28

Structural Activity Relationship (SAR)

The compounds tested are limited, a few key features regarding structural requirements for these benzofuran quinoline carboxylate hybrids (4a-c, 5a-c, 6a-c, 7a-c and 8a-c) to exert their antitubercular activity was determined. Our strategy was to identify the key sub unit required for activity such as, either benzofuran (influence both the antimicrobial and antibiotic properties of drugs) [17,18], quinoline (antimalarial and antitubercular gents) [29,30] and carboxylates (active pharmacophore, which allows its derivatives to readily interact with diversity of enzymes, receptors in organisms and acts as a prodrug).

Further substituent's like, -Cl and -F (electron withdrawing) groups varied at 6th and 8th position on quinoline ring to enhance their lipophilicity properties is studied.



(4a)

The results demonstrated the following assumptions about the SAR: it is evident, that in a carboxylate groups having hydrocarbon length of -CH_3, -C_2H_5 and -C_4H_9 compounds (4a, 5b-c and 6a-b) substituents on quinoline ring influencing the antitubercular activity and was found to be most active. The antitubercular potential of these compounds methyl, ethyl and butyl functionality may be due to the ability to penetrate the lipid membrane of the mycobacterial cell, there by weakening the integrity of the cell membrane and allowing the cellular component to drain and subsequently cell death. Whereas, propyl derivatives found to be less active compared to the other derivatives, indicating the influence of the length of ester group which determine the logP value. The branched -C_3H_7 side chain exhibited less activity might be because of change in the structural feature which might not fit among the receptor active site to elicit bioactivity. The introduction of electron withdrawing groups namely the chloro and fluoro groups has greater influence in the bioactivity score of the compounds. Whereas the absence of electron withdrawing functions on the 6th and 8th position has less influence on biological activity which was observed with compounds (5a, 7a and 8a). Hence, over all the influence of esters as well as electron withdrawing groups has recommended their importance to be an active leads for further study.

CONCLUSION

In the present study, an attempt is made to predict cheminformatics properties; molecules are in acceptable range and further investigated for antitubercular activity. The present investigation indicated that the benzofuran quinoline carboxylates were found to possess good antitubercular activity (4a, 5b-c and 6a-b). The potent esters will be further taken up for in-depth study by varying the functionalities on the aromatic rings with various electron withdrawing and electron donating groups, which were reference to the commercially available antitubercular drugs. Further examination is required for modification of lead to increase the antitubercular potency. The results indicate that the core moieties benzofuran and quinoline carboxylates are essential for antitubercular activity. The obtained information is useful for operating as a positive reinforcement of the tendency to use antitubercular properties as a guideline for the drug design.

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