Original Article

SYNTHESIS, ANTIMICROBIAL, ANTITUBERCULAR AND CHEMINFORMATIC STUDIES OF 2-(1-BENZOFURAN-2-YL)-*N*'-[(3*Z*)-2-OXO-1, 2-DIHYDRO-3*H*-INDOL-3-YLIDENE] QUINOLINE-4-CARBOHYDRAZIDE AND ITS DERIVATIVES

S. SANTOSHKUMAR[1], N. D. SATYANARAYAN[*1], R. ANANTACHARYA[1] AND P. SAMEER[2]

[1]Department of Pharmaceutical Chemistry, Kuvempu University, Post Graduate Centre, Kadur 577548, Chikkamagalur Dist., Karnataka St. India, [2]Department of Post Graduate Studies and Research in Biochemistry, Jnana Sahyadri, Kuvempu University Shankaraghatta 577451, Shivamogga Dt., Karnataka State, India
Email: satya1782005@gmail.com

ABSTRACT

Objective: Synthesis of novel 2-(1-benzofuran-2-yl)-*N*'-[(3*Z*)-2-oxo-1, 2-dihydro-3*H*-indol-3-ylidene] quinoline-4-carbohydrazide and its derivatives for antimicrobial and antitubercular activity.

Methods: Synthesis was carried out using the general method and the structures were confirmed by IR, ^{1}H-NMR, ^{13}C-NMR and mass spectral analysis. The antibacterial activity was carried by agar well diffusion method, antifungal activity was performed by poison food technique and antitubercular activity was carried out by Microplate Alamar Blue Assay (MABA) method with the help of H37Rv. *In silico* absorption, distribution, metabolism, excretion, toxicity (ADMET) study of the drug, likeliness was carried out in ACD/lab-2.

Results: The results revealed that at 25 mg/ml concentration, compounds 3a and 5a showed good antibacterial activity at 3.5±0.1, 3.8±0.3, 3.6±0.2 respectively against *E. coli*, *K. pneumonia* and *S. typhimurium*, when compared with drug streptomycin with similar concentration. The percentage of inhibition found at 50 µg/ml concentration, compounds 2b and 6a exhibited good antifungal activity at 53±1.15, 57±1.52 against *A. flavus* and *C. neoformans,* compared with standard drug fluconazole. The increase in activity was found to be dose dependent. The analogue 2a showed good antitubercular activity at 12.5±0.5 µg/ml, compounds 2b, 3a, 4a-b, 5a-b and 6a-b exhibited significant activity at 25±0.57 µg/ml and compound 3b showed moderate activity at 50±0.57 µg/ml. The mean value of P<0.05 were considered to be statistically significant. The absorption, distribution, metabolism, excretion and toxicity studies of the entitled molecules were analyzed and found to be in acceptable range.

Conclusion: The study reveals that compounds containing benzofuran coupled nitrogen heterocycles are essential for activity as they possess excellent drug-like characteristics, suggesting to be potentially best inhibitor of H37Rv strain. The *in silico* ADME analysis also revealed that all the compounds were in acceptable range to obey the pharmacokinetic parameters.

Keywords: Benzofuran, Quinoline, Isatin, Antimicrobial, Antitubercular, ADMET and MABA method

INTRODUCTION

Tuberculosis (TB), an airborne infectious disease caused predominantly by *Mycobacterium tuberculosis (Mtb),* is a global health problem and a leading cause of death among adults in the developing world. According to the World Health Organization (WHO), one-third of the world's population is infected with *M. tuberculosis (Mtb)* [1]. The number of new cases arising each year is increasing globally, posting a continued health and financial burden in various parts of the world, particularly Asia and Africa [2]. When coupled with the emergence of multidrug-resistant strains of *M. tuberculosis* (MDR-TB)/the scale of the problem becomes clear, as it will inevitably become even more difficult to treat TB [3]. This has spurred new efforts to find new anti-tuberculosis drug candidates with novel modes of action, develop pipelines for drug discovery and try to find new regimens that can considerably shorten the duration of effective therapy which would improve patient compliance and slow down the emergence of drug resistant strains [4-9]. Benzofuran is widespread interest in the field of synthetic chemistry and natural products has attracted due to their biological activities and their potential applications as pharmacological agents. Several benzofuran ring systems bearing various substituents at the C-2 position are widely distributed in nature [10-12].

The quinoline nucleus occurs in numerous natural compounds (cinchona alkaloids) and pharmacologically active substances displaying a wide range of biological activity [13]. The biological activity of quinoline compounds has been found to possess antibacterial, antifungal antitubercular, antiasthmatic, anti-inflammatory and antihypertensive properties. In addition to the medicinal applications, quinolines have been employed in the study of bioorganic and bioorganometallic processes [14].

Schiff bases are characterized by the–N=CH–(imine) group, which is an important in elucidating the mechanism of transamination and racemization reactions in biological systems [15]. Due to the great flexibility and varied structural aspects, a wide range of Schiff bases have been synthesized from a variety of compounds such as aminothiazole, 2-hydroxy-1-napthalaniline, amino sugars, aromatic aldehydes, ketones, isatin, a triazole ring, thiosemicarbazides, amino acids and pyrazolone [16-18] etc. Antibacterial, antifungal, antitubercular, antitumor and anticancer activities of some Schiff bases have been reported, and they are active against a wide range of organisms [19]. Some Schiff bases bearing aryl groups or heterocyclic residues possessing excellent biological activities have attracted the attention of many researchers in recent years [20]. The Schiff bases formed from aromatic aldehydes, ketones and their derivatives are quite stable. Many Schiff bases are known to be medicinally important and are used to design medicinal compounds [21].

Recognizing these facts and in continuation to our research activities towards the development of anti-infective agents [22-24]. Multi-component reactions (MCRs) have been used to produce the large-scale production of drug candidates. The MCRs provides medicinal chemists with a powerful tool to create novel chemical diversity, matching the space of biological targets with relevant chemistry. The discovery of novel MCRs has become an increasingly active area of research, yielding novel chemical scaffolds for drug discovery efforts [25].

In the present work, we synthesised 2-(1-benzofuran-2-yl) quinoline-4-carboxylic acid by using 2-acetyl benzofuran and isatin. The carboxylic acid functionality of 2-(1-benzofuran-2-yl) quinoline-4-carboxylic acid was further used in the synthesis of methyl ester using methyl alcohol in acidic medium. The carboxylate treated with hydrazine hydrate it yields the carbohydrazide, which upon reaction with substituted isatins generates the title compounds for screening antimicrobial and antitubercular activity. Hence, the present study was initiated with the aim of investigating the antimicrobial and antitubercular activity. The preliminary *in silico* ADMET studies for the potential drug likeliness of the compounds were investigated.

MATERIALS AND METHODS

Materials

Chemicals used in the synthesis of compounds were from Alfa Aesar and Spectrochem Pvt. Ltd. The solvents were of reagent grade and when necessary, they were purified and dried by the standard methods. Melting points (M. Pt.) of the synthesized compounds were determined with the help of Raga digital melting point apparatus and are uncorrected; Infrared data were recorded on a Bruker spectrophotometer using KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AVANCE II 400 and 100 MHz instruments using DMSO-d6/CDCl$_3$ as a solvent and TMS as an internal standard; chemical shifts are expressed as δ values (ppm).

The J values are expressed in Hertz (Hz). Mass spectra (MS) were recorded in JEOL GCMATE II LC–Mass spectrometer using electron impact ionisation (EI) technique. Analytical thin-layer chromatography (TLC) was performed on precoated TLC sheets of silica gel 60 F254 (Merck, Darmstadt, Germany), visualized by long and short wavelength UV lamps. Column chromatographic purifications were performed on Merck silica gel (100-200 mesh).

Procedure for synthesis of 2-(1-benzofuran-2-yl) quinoline-4-carbohydrazide 1(a-b)

The compound 1(a-b) was synthesized by earlier reported method [26]. A mixture of methyl 2-(1-benzofuran-2-yl) quinoline-4-carboxylates (0.5 mmol) and hydrazine hydrate (1 mmol) was taken into 30 ml of dry ethanol in a 50 ml round bottom flask and refluxed for 4 h. After completion of the reaction the obtained white solid mass was filtered in the hot condition and washed with cold ethanol followed by recrystalized with methyl alcohol (Yield a)-80 % and b) 72 %, m. p. a) 260-264 °C and b) 317-320 °C).

General procedure for the synthesis of (1-benzofuran-2-yl)-*N'*-[(3*Z*)-2-oxo-1, 2-dihydro-3*H*-indol-3-ylidene] quinoline-4-carbo-hydrazide and its derivatives 2(a-b), 3(a-b), 4(a-b), 5(a-b) and 6(a-b)

Accurately weighed equimolar amount of 2-(1-benzofuran-2-yl) quinoline-4-carbohydrazide 1(a-b) 0.050 g (1.5 mmol) and substituted isatins (1.5 mmol) into the round bottom flask containing 10 ml of ethanol, then add catalytic amount of glacial acetic acid and the reaction mixture was refluxed for about 12 to 14 h. The progress of the reaction was monitored by TLC, after completion of the reaction the solid obtained was filtered, washed with water, dried and recrystalized using ethanol.

2-(1-benzofuran-2-yl)-*N'*-[(3*E*)-2-oxo-1, 2-dihydro-3*H*-indol-3-ylidene] quinoline-4-carbohydrazide (2a)

Mp: 305-308 °C; Yield: 79 %; IR (KBr: ν$_{max}$/cm^{-1}): 3305 (N-H Stretch of amide and isatin), 1705 (C = O Stretch of amide and isatin); ^{1}H-NMR (DMSO-d$_6$, δ, ppm, 400 MHz): 13.66 (s, 1H, N-H of amide), 11.32 (s, 1H, N-H of isatin), 8.44 (s, 1H, Ar-H), 8.26-8.32 (t, 1H, J = 24 Hz, Ar-H), 8.18-8.20 (d, 1H, J = 8, 4 Hz, Ar-H), 7.92 (s, 1H, Ar-H), 7.78-7.80 (d, 1H, J = 8 Hz, Ar-H), 7.73-7.75 (d, 1H, J = 8 Hz, Ar-H), 7.66-7.68 (d, 1H, J = 8 Hz, Ar-H), 7.41-7.45 (t, 2H, J = 16 Hz, Ar-H), 7.31-7.33 (t, 1H, J = 8 Hz, Ar-H), 7.14 (s, 1H, Ar-H), 6.87-6.95 (m, 2H, Ar-H). ^{13}C-NMR (DMSO-d$_6$, δ, ppm, 100 MHz): 161.47 (C=O carbon), 157.15, 155.51, 154.47, 153.68, 152.92, 150.09, 149.55, 148.34, 147.87, 146.47, 141.64, 137.69, 135.01, 131.53, 128.69, 126.87, 126.08, 124.71, 122.71, 118.66, 116.50, 112.14, 109.87 and 108.51; MS: m/z = 443(M+1).

2-(1-benzofuran-2-yl)-8-fluoro-*N'*-[(3*E*)-2-oxo-1, 2-dihydro-3*H*-indol-3-lidene] quinoline-4-carbohydrazide (2b)

Mp: 272-275 °C; Yield: 81 %; IR (KBr: ν$_{max}$/cm^{-1}): 3320 (N-H Stretch of amide and isatin), 1708 (C = O Stretch of amide and isatin); ^{1}H-NMR (DMSO-d$_6$, δ, ppm, 400 MHz): 13.65 (s, 1H, N-H of amide), 11.31 (s, 1H, N-H of isatin), 8.53 (s, 1H, Ar-H), 8.01 (s, 1H, Ar-H), 7.96 (s, 1H, Ar-H), 7.78-7.80 (d, 1H, J = 8 Hz, Ar-H), 7.74-7.76 (d, 2H, J = 8 Hz, Ar-H), 7.68-7.71 (d, 2H, J = 12 Hz, Ar-H), 7.42-7.46 (t, 2H, J = 8 Hz, Ar-H), 7.41-7.45 (t, 2H, J = 16 Hz, Ar-H), 7.31-7.33 (t, 1H, J = 8 Hz, Ar-H), 7.14 (s, 16H, Ar-H), 7.31-7.35 (t, 1H, J = 16 Hz, Ar-H), 7.13 (s, 1H, Ar-H), 6.88-6.93 (d, 2H, J = 20 Hz, Ar-H). ^{13}C-NMR (DMSO-d$_6$, δ, ppm, 100 MHz): 168.75 (C=O carbon), 163.05, 159.03, 155.60, 151.28, 148.58, 145.68, 143.31, 140.57, 135.45, 132.87, 128.61, 127.33, 126.96, 125.37, 124.22, 122.85, 121.61, 117.96, 115.56, 112.21, 111.73, 109.74, 108.81,104.58 and 102.07.

2-(1-benzofuran-2-yl)-*N'*-[(3*E*)-5-chloro-2-oxo-1, 2-dihydro-3*H*-indol-3-lidene] quinoline-4-carbohydrazide (3a)

Mp: 290-293 °C; Yield: 83 %; IR (KBr: ν$_{max}$/cm^{-1}): 3285 (N-H Stretch of amide and isatin), 1716 (C = O Stretch of amide and isatin); ^{1}H-NMR (DMSO-d$_6$, δ, ppm, 400 MHz): 13.55 (s, 1H, N-H of amide), 11.56 (s, 1H, N-H of isatin), 8.42 (s, 1H, Ar-H), 8.19-8.21 (d, 1H, J = 8 Hz, Ar-H), 7.92 (s, 3H, Ar-H),7.71-7.80 (m, 4H, Ar-H), 7.43-7.46 (t, 2H, J = 12 Hz, Ar-H), 7.32-7.36 (t, 1H, J = 16 Hz, Ar-H), 6.94-6.96 (d, 1H, J = 16 Hz, Ar-H) 7. ^{13}C-NMR (DMSO-d$_6$, δ, ppm, 100 MHz): 162.87 (C=O carbon), 155.53, 154.47, 148.33, 141.99, 135.14, 131.99, 131.46, 130.04, 128.68, 127.31, 126.70, 125.56, 124.16, 123.77, 122.71, 118.54, 117.14, 113.30, 112.14, 108.00 and 105.43; MS: m/z = 467 (M+1).

2-(1-benzofuran-2-yl)-*N'*-[(3*E*)-5-chloro-2-oxo-1, 2-dihydro-3*H*-indol-3-ylidene]-8-fluoroquinoline-4-carbohydrazide (3b)

Mp: 282-285 °C; Yield: 83 %; IR (KBr: ν$_{max}$/cm^{-1}): 3362 (N-H Stretch of amide and isatin), 1691 (C = O Stretch of amide and isatin); ^{1}H-NMR (DMSO-d$_6$, δ, ppm, 400 MHz): 13.70 (s, 1H, N-H of amide), 11.65 (s, 1H, N-H of isatin), 8.48 (s, 1H, Ar-H), 8.04 (s, 1H, Ar-H), 7.91 (s, 1H, Ar-H), 7.75-7.77 (d, 1H, J = 8 Hz, Ar-H), 7.72 (s, 1H, Ar-H), 7.68-7.70 (d, 2H, J = 8 Hz, Ar-H), 7.40-7.43 (t, 2H, J = 12 Hz, Ar-H), 7.28-7.32 (t, 1H, J = 16 Hz, Ar-H),6.91 (s, 1H, Ar-H). ^{13}C-NMR (DMSO-d$_6$, δ, ppm, 100 MHz): 162.80 (C=O carbon), 159.03, 156.48, 155.58, 154.13, 148.49, 141.91, 138.63, 132.05, 128.60, 127.34, 126.90, 125.34, 124.19, 122.81, 121.02, 118.12, 115.64, 115.45, 113.27, 112.17, 108.68 and 106.39; MS: m/z = 486 (M+1).

2-(1-benzofuran-2-yl)-*N'*-[(3*E*)-5-bromo-2-oxo-1, 2-dihydro-3*H*-indol-3-idene] quinoline-4-carbohydrazide (4a)

Mp: 220-223 °C; Yield: 85 %; IR (KBr: ν$_{max}$/cm^{-1}): 3296 (N-H Stretch of amide and isatin), 1708 (C = O Stretch of amide and isatin); ^{1}H-NMR (DMSO-d$_6$, δ, ppm, 400 MHz): 13.35 (s, 1H, N-H of amide), 11.65 (s, 1H, N-H of isatin), 10.01 (s, 1H, Ar-H), 8.13-8.20 (m, 3H, Ar-H), 7.49 (s, 1H, Ar-H), 7.90-7.94 (m, 1H, Ar-H), 7.88 (s, 1H, Ar-H), 7.81-7.86 (m, 1H, Ar-H), 7.70-7.79 (m, 5H, Ar-H), 7.30-7.35 (m, 1H, Ar-H). ^{13}C-NMR (DMSO-d$_6$, δ, ppm, 100 MHz): 165.98 (C=O carbon), 155.55, 154.67, 148.36, 148.28, 142.51, 131.07, 129.77, 128.72, 128.00, 126.56, 125.98, 124.38, 124.10, 122.65, 116.72, 112.11, and 107.57.

2-(1-benzofuran-2-yl)-*N'*-[(3*E*)-5-bromo-2-oxo-1, 2-dihydro-3*H*-indol-3-ylidene]-8-fluoroquinoline-4-carbohydrazide (4b)

Mp: 280-283 °C; Yield: 87 %; IR (KBr: ν$_{max}$/cm^{-1}): 3278 (N-H Stretch of amide and isatin), 1685 (C = O Stretch of amide and isatin); ^{1}H-NMR (DMSO-d$_6$, δ, ppm, 400 MHz): 13.64 (s, 1H, N-H of amide), 11.64 (s, 1H, N-H of isatin), 8.55 (s, 1H, Ar-H), 7.98 (s, 1H, Ar-H), 7.73-7.82 (m, 1H, Ar-H), 7.45-7.48 (t, 1H, J = 12 Hz, Ar-H), 7.34-7.37 (t, 1H, J = 12 Hz, Ar-H), 7.11 (s, 1H, Ar-H). ^{13}C-NMR (DMSO-d$_6$, δ, ppm, 100 MHz): 163.06 (C=O carbon), 159.03, 156.48, 155.61, 154.14, 142.31, 138.67, 135.07, 133.06, 128.61, 126.96, 125.36, 124.77, 124.23, 122.86, 121.61, 120.65, 118.21, 115.54, 112.19, 108.74 and 103.97; MS: m/z = 530 (M+1).

2-(1-benzofuran-2-yl)-*N'*-[(3*E*)-5-nitro-2-oxo-1, 2-dihydro-3*H*-indol-3-ylidene] quinoline-4-carbohydrazide (5a)

Mp: 300-303 °C; Yield: 83 %; IR (KBr: ν$_{max}$/cm^{-1}): 3308 (N-H Stretch of amide and isatin), 1691 (C = O Stretch of amide and isatin); ^{1}H-

NMR (DMSO-d$_6$, δ, ppm, 400 MHz): 8.40 (s, 1H, Ar-H), 8.17-8.19 (d, 1H, J = 8 Hz, Ar-H), 7.86 (s, 2H, Ar-H), 7.75-7.76(d, 1H, J = 4 Hz, Ar-H),7.67 (s, 2H, Ar-H), 7.40 (s, 1H, Ar-H), 7.30 (s, 1H, Ar-H), 7.13 (s, 1H, Ar-H); MS: m/z = 478 (M+1).

2-(1-benzofuran-2-yl)-*N*'-[(3*E*)-5-nitro-2-oxo-1, 2-dihydro-3*H*-indol-3-ylidene]-8-fluoroquinoline-4-carbohydrazide (5b)

Mp: 299-302 °C; Yield: 78 %; IR (KBr: ν$_{max}$/cm^{-1}): 3325 (N-H Stretch of amide and isatin), 1691 (C = O Stretch of amide and isatin); ^{1}H-NMR (DMSO-d$_6$, δ, ppm, 400 MHz): 13.45 (s, 1H, N-H of amide), 11.94 (s, 1H, N-H of isatin), 8.48 (s, 1H, Ar-H), 8.29 (s, 1H, Ar-H), 8.03 (s, 1H, Ar-H), 7.78 (s, 1H, Ar-H), 7.72-7.76 (d, 1H, J = 16 Hz, Ar-H), 6.94-7.10 (m, 7H, Ar-H). ^{13}C-NMR (DMSO-d$_6$, δ, ppm, 100 MHz): 163.21 (C=O carbon), 159.29, 159.03, 158.91, 158.54, 158.16, 156.47, 155.60, 154.09, 148.34, 143.35, 128.39, 126.93, 125.31, 124.21, 122.84, 121.52, 120.68, 118.18, 117.07, 115.67, 115.50, 114.19, 112.17, 112.04 and 108.70; MS: m/z = 496 (M+1).

2-(1-benzofuran-2-yl)-*N*'-[(3*E*)-5-fluoro-2-oxo-1, 2-dihydro-3*H*-indol-3-lidene] quinoline-4-carbohydrazide (6a)

Mp: 165-168 °C; Yield: 73 %; IR (KBr: ν$_{max}$/cm^{-1}): 3320 (N-H Stretch of amide and isatin), 1693 (C = O Stretch of amide and isatin); ^{1}H-NMR (DMSO-d$_6$, δ, ppm, 400 MHz): 13.60 (s, 1H, N-H of amide), 11.86 (s, 1H, N-H of isatin), 8.18-8.20 (d, 1H, J = 8Hz, Ar-H), 7.88-7.91 (m, 2H, Ar-H), 7.77-7.79 (d, 1H, J = 18 Hz, Ar-H), 7.72-7.74(d, 1H, J = 8Hz, Ar-H), 7.70 (s, 1H, Ar-H), 7.54 (s, 1H, Ar-H), 7.41-7.45 (t, 1H, J = 16Hz, Ar-H), 7.31-7.34 (t, 1H, J = 12Hz, Ar-H), 7.26 (s, 1H, Ar-H), 7.10 (s, 1H, Ar-H). ^{13}C-NMR (DMSO-d$_6$, δ, ppm, 100 MHz): 162.90 (C=O carbon), 155.51, 154.47, 148.60, 148.33, 146.17, 133.19, 131.48, 130.03, 128.69, 126.71, 125.56, 124.16, 123.76, 122.71, 119.08, 113.39, 112.14, and 108.00; MS: m/z = 451 (M+1).

2-(1-benzofuran-2-yl)-8-fluoro-*N*'-[(3*E*)-5-fluoro-2-oxo-1, 2-dihydro-3*H*-indol-3-ylidene] quinoline-4-carbohydrazide (5b)

Mp: 231-234 °C; Yield: 80 %; IR (KBr: ν$_{max}$/cm^{-1}): 3454 (N-H Stretch of amide and isatin), 1712 (C = O Stretch of amide and isatin); ^{1}H-NMR (DMSO-d$_6$, δ, ppm, 400 MHz): 8.49 (s, 1H, Ar-H), 8.03 (s, 2H, Ar-H), 7.19 (s, 2H, Ar-H), 7.76-7.78 (d, 1H, J = 8 Hz, Ar-H), 7.69-7.71 (d, 3H, J = 8 Hz, Ar-H), 7.51 (s, 1H, Ar-H), 7.40-7.44 (t, 1H, J = 16 Hz, Ar-H), 7.29-7.33 (t, 2H, J = 16 Hz, Ar-H), 7.14(s, 2H, Ar-H), 6.69 (s, 2H, Ar-H);MS: m/z = 469 (M+1).

Biological activities

Antibacterial activity

The antibacterial activity of the synthesized molecules were carried out by using different gram-ve bacteria such as *Escherichia coli* (ATCC No. 25922), *Klebsiella pneumonia* (ATCC No. 700603) and *Salmonella typhimurium* (ATCC No. 14028) (gram-negative), the bacterial strains were obtained from the Department of Microbiology, Kuvempu University, Karnataka India. The chemical stock solution of synthesized compounds was prepared at a different concentration of 25 and 50 mg/ml by using dimethyl formamide (DMF). The antibacterial activity was carried out by agar well diffusion method [27] which is a simple susceptibility screening method. Each microorganism was suspended in nutrient broth and diluted approximately colony forming unit (cfu)/ml. They were 'flood-inoculated' onto the surface of the nutrient agar and then dried. The 6 mm diameter wells were cut from the agar using a sterile cork borer, 0.1 ml of the test compound solution were delivered into the wells and were incubated for 24 h. at 37 °C. Antibacterial activity was evaluated by measuring the zone of inhibition against the test organism by using standard drug streptomycin.

Table 1: Physical constant of 2-(1-benzofuran-2-yl)-*N*'-[(3*Z*)-2-oxo-1, 2-dihydro-3*H*-indol-3-ylidene] quinoline-4-carbohydrazide and its derivatives 2(a-b), 3(a-b), 4(a-b), 5(a-b) and 6(a-b)

S. No.	Sample code	R	R^1	M. For.	M. Wt.	M. Pt. °C
1	2a	H	H	C$_{26}$H$_{16}$N$_4$O$_3$	432.43	305-308
2	2b	H	F	C$_{26}$H$_{15}$FN$_4$O$_3$	450.42	272-275
3	3a	H	H	C$_{26}$H$_{15}$ClN$_4$O$_3$	466.87	290-293
4	3b	H	F	C$_{26}$H$_{14}$ClFN$_4$O$_3$	484.86	282-285
5	4a	H	H	C$_{26}$H$_{15}$BrN$_4$O$_3$	511.32	220-223
6	4b	H	F	C$_{26}$H$_{14}$BrFN$_4$O$_3$	529.31	280-283
7	5a	H	H	C$_{26}$H$_{15}$N$_5$O$_5$	477.00	300-303
8	5b	H	F	C$_{26}$H$_{14}$FN$_5$O$_5$	495.41	299-302
9	6a	H	H	C$_{26}$H$_{15}$FN$_4$O$_3$	450.42	165-168
10	6b	H	F	C$_{26}$H$_{14}$F$_2$N$_4$O$_3$	468.41	231-234

M. For.**-**Molecular formula, M. Wt.**-**Molecular weight, M. Pt.**-**Melting point.

Antifungal activity

The antifungal activity of synthesized compounds was performed by poisoned food techniques against *Aspergillus flavus* and *Cryptococcus neoformans* by potato dextrose agar medium. The potato dextrose agar medium was sterilized by autoclave at 121 °C (15 lb/sq. inch), for 15 min. A 30 ml of molten potato dextrose agar medium is inoculated with respective fungus (5 mm disc of the fungus grown) was transferred, aseptically into each sterilized petri plate 10 cm diameter. The petridishes were incubated at a temperature of 28±1 °C. The zone of inhibition was measured by using 'antibiotic zone reader'. The diameter reading is noted to determine the minimum mycelial growth inhibition (MGI) [28].

Minimum mycelial growth inhibition (MGI) = [(Dc-Dt)/Dc] X 100

Where Dc and Dt are average diameters of the fungal colony of control and test samples respectively.

Antitubercular activity

The antitubercular screening of synthesized molecules was carried on *M. tb* H37RV strain, by Microplate Alamar Blue Assay (MABA) method [29], 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 to 0.8 μg/ml and incubated at 37 °C for five 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 minimum inhibitory concentration (MIC) is the lowest drug concentration that stopped a colour change from blue (no growth) to pink (growth). The drugs pyrazinamide, ciprofloxacin and streptomycin were used as a positive standard for comparison.

In silico studies

ADME-toxicity prediction

The molecular descriptors of synthesized compounds (2a-b, 3a-b, 4a-b, 5a-b and 6a-c) were predicted by pharmacokinetics parameter such as ADMET. The ADMET/SAR [30] helps to evaluate biologically

active molecules and eliminate a biologically poor molecule, an active lead molecule which contains undesirable functional groups based on Lipinski rule. The statistical calculation for lead molecules includes surface area, geometry and fingerprint properties which help to understand biologically important end points. Aqueous solubility (PlogS), Blood-brain barrier penetration (QlogBB), intestinal absorption (logHIA), hepatotoxicity, Caco-2 cell permeability (QPPCaco) also helps to predict the toxicity of lead molecules [31] with intraperitoneal, oral, intravenous and subcutaneous. The *in silico* study enables to decide the safety and efficacy of active molecules take up the molecule for in-depth studies.
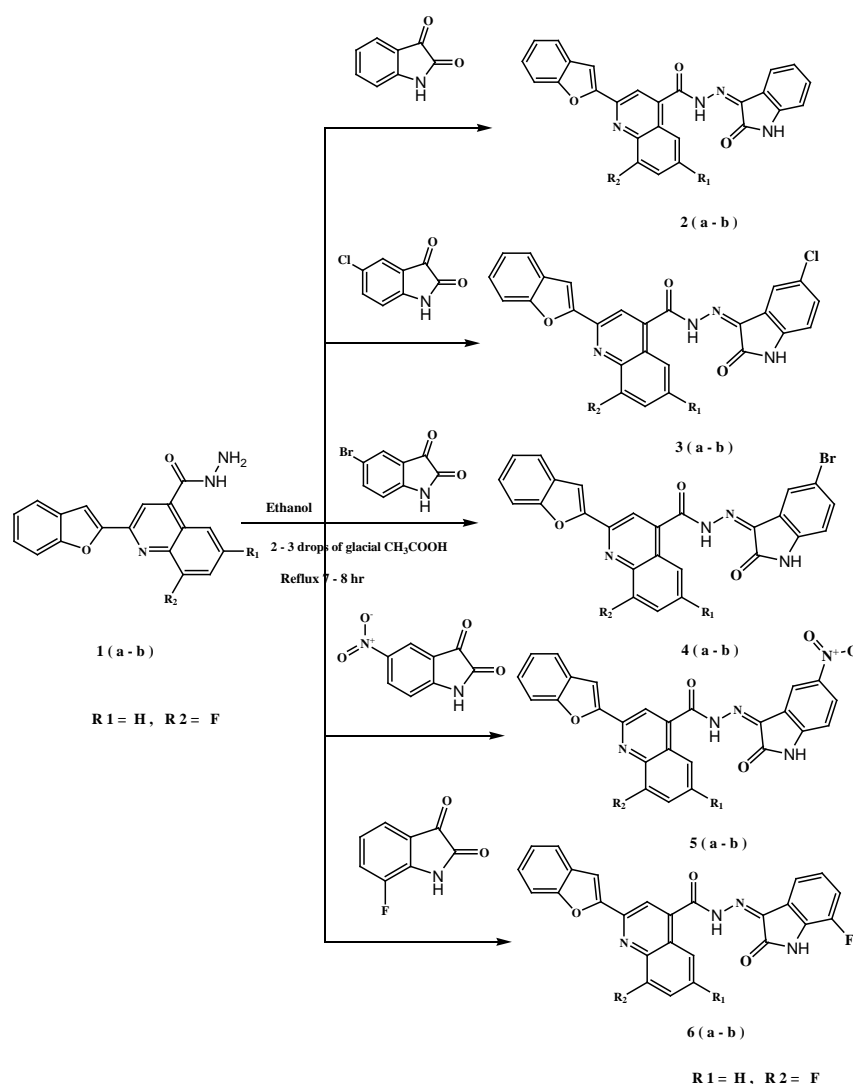
RESULTS AND DISCUSSION

Chemistry

(1-benzofuran-2-yl)-*N'*-[(3*Z*)-2-oxo-1, 2-dihydro-3*H*-indol-3-ylidene] quinoline-4-carbohydrazide and its derivatives 2(a-b), 3(a-b), 4(a-b), 5(a-b) and 6(a-b) were obtained by 2-(1-benzofuran-2-yl) quinoline-4-carbohydrazide 1(a-b) 0.050 g (1.5 mmol) and

substituted isatin (1.5 mmol) into the round bottom flask containing 10 ml of ethanol, then add catalytic amount of glacial acetic acid as presented in scheme-1.

The physical data of the compounds were presented in table-1. The structures of compounds were confirmed by IR, ^{1}H-NMR, ^{13}C-NMR and mass spectral analysis. The IR spectrum of 2a exhibited absorption band at 3305.99 cm^{-1} for NH stretching frequency of amide and isatin. The absorption band at 1705.07 cm^{-1} corresponds to C=O stretching of amide and isatin. In the ^{1}H NMR spectrum, the compound 2a showed a singlet peaks at δ 13.66 and 11.32 ppm due to NH protons of amide and isatin.

The peaks between δ 6.87-8.44 ppm corresponding to aromatic protons. Similarly, ^{13}C-NMR spectrum of compound 2a showed a peak at 161.47 ppm corresponding to the C=O carbon of amide and isatin, the peak between δ 157.15-108.51 ppm corresponding to aromatic carbons. Further, the mass spectrum of compound 2a showed a molecular ion peak M+1 at m/z 443, which confirms its molecular weight.

Scheme 1: Synthesis of 2-(1-benzofuran-2-yl)-*N'*-[(3*Z*)-2-oxo-1, 2-dihydro-3*H*-indol-3-ylidene] quinoline-4-carbohydrazide and its derivatives 2(a-b), 3(a-b), 4(a-b), 5(a-b) and 6(a-b)

Antibacterial activity

The *in vitro* antibacterial activity of synthesised entitled compounds was determined by the agar well diffusion method. In this study, *E. coli* (ATCC. 25922), *K. pneumonia* (ATCC. 700603) and *S. typhirium* (ATCC. 14028) (Gram negative) were selected because of its infectious nature. The test compounds were dissolved in dimethylformamide (DMF) at concentrations of 25 and 50 mg/ml as shown in table 2.

Table 2: Antibacterial activities (zone of inhibition in cm) of 2-(1 benzofuran-2-yl)-*N'*-[(3*Z*)-2-oxo-1, 2-dihydro-3*H*-indol-3-ylidene] quinoline-4 carbohydrazide and its derivatives 2(a-b), 3(a-b), 4(a-b), 5(a-b) and 6(a-b)

Samples code	E. coli		K. pneumonia		S. typhimurium	
	25 mg/ml	50 mg/ml	25 mg/ml	50 mg/ml	25 mg/ml	50 mg/ml
2a	2.3±0.1	3.2±0.1	3.4±0.2	3.5±0.15	3.5±0.2	4.0±0.1
2b	2.0±0.15	2.8±0.2	3.1±0.15	3.6±0.20	3.5±0.15	3.8±0.1
3a	3.5±0.1	3.7±0.15	3.0±0.1	3.6±0.20	3.4±0.26	3.8±0.15
3b	2.5±0.26	2.8±0.20	3.2±0.15	3.5±0.20	2.5±0.15	3.5±0.15
4a	1.7±0.55	2.7±0.1	2.6±0.15	3.4±0.1	3.2±0.1	3.8±0.15
4b	1.8±0.17	2.8±0.1	3.2±0.2	3.1±0.1	2.6±0.2	3.4±0.3
5a	2.4±0.15	3.5±0.15	3.8±0.3	4.2±0.23	3.6±0.20	4.0±0.15
5b	2.8±0.1	3.6±0.20	3.2±0.15	3.8±0.3	2.7±0.15	3.7±0.15
6a	3.2±0.15	3.4±0.32	2.7±0.11	3.2±0.20	3.1±0.25	3.6±0.25
6b	1.4±020	2.8±0.1	3.7±0.20	4.0±0.20	2.3±0.20	2.9±0.2
Streptomycin	2.5±0.26	3.6±0.3	3.2±0.3	3.8±0.15	3.0±0.15	3.5±0.20

Values are expressed as mean±SD (n=3). Values are significant with each other at P<0.05 (Duncan's multiple range test).

The molecule 5b (The molecule having fluoro substitution at 8th position of quinoline ring and nitro substitution at 5th position of the isatin ring) shown potent activity against all the tested bacterial species as compared with standard drug streptomycin. The molecules such as 3a (chloro substitution at 5th position of the isatin ring) and 6a (fluoro substitution at 7th position of isatin ring) displayed persuasive activity against *E. coli* compared with a standard drug. The molecules such as 5a (nitro substituted isatin) and 6b (fluoro substitution at 8th position of quinoline and 7th position of isatin) exhibited promising activity against *K. pneumonia* as compared with standard, while the molecules such as 2a (unsubstituted Schiff base), 2b (fluoro substitution at 8th position of quinoline ring), 3a (chloro substation at 5th position of isatin ring), 4a (bromo substation at 5th position of isatin ring), 5a (nitro substation at 5th position of isatin ring) and 6a (fluoro substation at 7th position of isatin ring) exhibited potent activity against *S. typhimurium* as compared with standard molecule. While the remaining molecules are good to moderate activity against all the tested bacterial species.

The above results indicate that coupled heterocyclic moieties are essential for antimicrobial activity. The isatin ring substituted with electron withdrawing groups (2a, 3a, 4a, 5a-b and 6a) were the most active against *Escherichia coli*, *Klebsiella pneumonia* and *Salmonella typhimurium*; this might be due to the presence of electron withdrawing nitro and halogen groups on the 5th and 7th position of the isatin ring. The lipophilic nature of nitro and halogen substituted molecules enables greater penetration into the cell membrane and or might be involved in the inhibition of certain enzymes responsible in the synthesis of cell membrane composition [32]. The other derivatives were found to be less potential even though the presence of halogen substitution on isatin might be because of the bulky nature in the case of bromine substitution and varying in the position of fluorine substitution which might not have significant contribution in interacting with proteins/enzymes involved in the synthesis of cell wall/membranes.

Antifungal activity

The *in vitro* antifungal activity was carried out against *A. flavus* and *C. neoformans*. The test compounds were dissolved in dimethyl sulphoxide (DMSO) and the activity was determined by the poisoned food technique at concentrations of 50 and 100 µg/ml. The antifungal result is shown in table 3.

Table 3: Antifungal activities of 2-(1 benzofuran-2-yl)-*N'*-[(3*Z*)-2-oxo-1, 2-dihydro-3*H*-indol-3-ylidene] quinoline-4 carbohydrazide and its derivatives 2(a-b), 3(a-b), 4(a-b), 5(a-b) and 6(a-b)

Samples code	A. flavus % inhibition		C. neoformans % inhibition	
	50 µg/ml	100 µg/ml	50 µg/ml	100 µg/ml
2a	25±0.57	68±1.5	42±1.5	83±1.15
2b	53±1.15	68±1.5	34±0.57	73±1.5
3a	35±1.5	57±0.9	41±0.57	68±0.57
3b	34±0.9	62±0.57	24±1.0	57±0.9
4a	52±0.57	68±057	42±1.5	63±1.0
4b	49±0.9	69±1.0	39±1.5	48±2.0
5a	18±1.5	37±1.5	32±0.57	72±2.08
5b	52±1.5	78±1.7	45±1.52	67±1.0
6a	32±1.5	58±1.15	57±1.52	88±1.0
6b	43±2.0	67±1.15	29±1.0	57±1.15
Fluconazole	31±2.0	68±0.57	43±1.0	72±1.5

Values are expressed as mean±SD (n=3). Values are significant with each other at P<0.05 (Duncan's multiple range test).

The molecules such as 2b (fluoro substitution at 8th position of the quinoline ring), 4a (bromo substitution at 5th position of the isatin ring), 4b (fluoro substitution at 8th position of the quinoline ring and bromo substitution at 5th position of the isatin ring) and 5b (fluoro substitution at 8th position of the quinoline ring and nitro substitution at 5th position of the isatin ring) are shown potent activity against *A. flavus* as compared with standard drug fluconazole.

While the molecule such as 6a (fluoro substitution at 7th position of the isatin ring) showed promising activity against *C. neoformans* as compared with a standard drug. While the other molecules are shown good to moderate activity against all the fungal species.

The results indicate that heterocycles coupled with isatin Schiff base moieties are vital for antifungal activity. The isatin substituted with electron withdrawing groups (2a, 2b, 4a, 5b and 6a) is the most active against *A. flavus* and *C. neoformans*; this might be due to the presence of electron withdrawing nitro and halogen groups on the 5th and 7th position of the isatin ring and also halogens which are present on the benzofuran coupled quinoline. The presence of these groups has a greater chance of disrupting the integrity of the cell

membrane which allows the loss of cell contents or by inhibition the synthesis of cell membrane precursor [32].

In vitro antitubercular activity

The title compounds were further tested for *in vitro* antimycobacterial screening against *Mycobacterium tuberculosis* H37Rv, using microplate alamar blue assay (MABA), according to the reported method [29] taking pyrazinamide, ciprofloxacin and streptomycin have standard for comparison.

The 2-(1 benzofuran-2-yl)-*N'*-[(3*Z*)-2-oxo-1, 2-dihydro-3*H*-indol-3-ylidene] quinoline-4 carbohydrazide and its derivatives 2(a-b), 3(a-b), 4(a-b), 5(a-b) and 6(a-b) showed antitubercular activity with MIC value ranging from 12.5 to 50 µg/ml and the results are reported in table 4.

Table 4: *In vitro* antitubercular activity of-(1 benzofuran-2-yl)-*N'*-[(3*Z*)-2-oxo-1, 2-dihydro-3*H*-indol-3-ylidene] quinoline-4 carbohydrazide and its derivatives 2(a-b), 3(a-b), 4(a-b), 5(a-b) and 6(a-b)

S. No.	Sample code	MIC (µg/ml)
1	2a	12.5±0.5
2	2b	25±0.57
3	3a	25±0.57
4	3b	50±0.57
5	4a	25±0.57
6	4b	25±0.57
7	5a	25±0.57
8	5b	25±0.57
9	6a	25±0.57
10	6b	25±0.57
Std–I Pyrazinamide		3.125±0.20
Std–II Ciprofloxacin		3.125±0.20
Std–III Streptomycin		6.250±0.12

Values are expressed as mean±SD (n=3). Values are significant with each other at P<0.05 (Duncan's multiple range test).

Among the tested compounds, 2a (un-substituted Schiff base) showed activity with a MIC value 12.5 µg/ml, which showed good activity as compared with standard drugs. While the molecules such a 2b, 3a, 4a, 4b, 5a, 5b, 6a, and 6b which exhibits activity with a MIC value 25 µg/ml, and the molecule 3b display activity with a MIC value 50 µg/ml, which showed moderate activity as compared with standard drugs.

The quinoline derivatives carrying benzofuran coupled at second position, carbohydrazide moiety and isatin Schiff bases, respectively, with the hope that newly designed molecules would exhibit enhanced activity. The only molecules having functionalities on isatin imparts lipophilic behaviours and their size and shape might be the best fit for the involvement in the inhibition of enzymes such as DNA gyrase, catalase-peroxidase, malate synthase and aryl amine transferase which are directly and indirectly involved in anti-TB action.

The other derivatives having halogen substitution (Br and F) have not shown a considerable degree of activity this might be because of their size and shape, which play an important role in drug binding and their effectiveness [33-37].

Statistical analysis

All quantitative measurements were expressed as mean±SD for standard drugs. The data were analyzed using one-way analysis of variance (ANOVA) followed by Duncan's Multiple Range Test (DMRT) by using statistical package of social science (SPSS) version 10.0 for Windows. A difference in the mean values of P<0.05 was considered to be statistically significant.

Pharmacokinetic properties

In silico ADMET results

The compounds with poor bioavailability show less efficiency against disease. To solve this problem, predicting bioavailability properties will be of great advantage for drug development. Hence, using computer-based methods like ADMET and SAR [30] tools the molecular descriptors and drug likeliness properties were studied. The pharmacokinetic properties are represented in table 5. The partition coefficient of blood/brain barrier penetration (logB/B) was computed and access with central nervous system (CNS). The CNS activity was computed on-2 (inactive) to+2 (active) which showed all the molecules are displayed within the acceptable range.

Table 5: LD$_{50}$ ADME-TOX Parameters of substituted (1 benzofuran-2-yl)-*N'*-[(3*Z*)-2-oxo-1, 2-dihydro-3*H*-indol-3-ylidene] quinoline-4 carbohydrazide and its derivatives 2(a-b), 3(a-b), 4(a-b), 5(a-b) and 6(a-b) using ACD/I-Lab 2.0

Ligands	Intraperitoneal	Oral	Intravenous	Subcutaneous
2a	830 (0.54)	1300 (0.13)	67(0.2)	160 (0.22)
2b	970(0.46)	1100(0.13)	69(0.18)	210(0.23)
3a	1200(0.41)	16000.17	87(0.22)	180(0.22)
3b	1400(0.35)	1300(0.17)	84(0.23)	220(0.2)
4a	1100(0.36)	1100(0.04)	86(0.23)	210(0.2)
4b	1300(0.32)	920(0.03)	100(0.17)	290(0.19)
5a	1000(0.4)	1200(0.22)	73(0.24)	150(0.17)
5b	1200(0.34)	1000(0.22)	81(0.22)	190(0.18)
6a	1000(0.48)	960(0.11)	62(0.19)	220(0.23)
6b	1200(0.38)	530(0.24)	62(0.17)	250(0.21)
Pyrazinamide	2000(0.83)	540(0.28)	170(0.56)	1000(0.71)
Ciprofloxacin	930(0.72)	3500(0.78)	120(0.86)	1400(0.58)
Streptomycin	310(0.76)	880(0.53)	110(0.67)	400(0.52)
Fluconazole	1200(0.73)	1000(0.51)	580(0.47)	2700(0.23)

Estimated LD$_{50}$-mouse value in mg/kg after Intraperitoneal, Oral, Intravenous and Subcutaneous administration, The drugs with a moderate effect on reliability index (>0.5), The drugs with borderline effect on reliability index (>0.3,<0.5).

The interpretation of test compounds with the reference molecule (pyrazinamide, ciprofloxacin, streptomycin and fluconazole) show that the compounds 2(a-b), 3(a-b), 4(a-b), 5(a-b) and 6(a-b) were in good, acceptable range and hence, they can be used to make an oral formulation for absorption and to carry by transport proteins and metabolizing by the enzymes to maintain homeostatic condition. The intestinal absorption (log_{HIA}) and Caco-2 cell permeability (PCaco-2) in between the range of-2 poor absorption and+2 more absorption show

that the compounds are more permeable in the intestine and helps for good transport of drug metabolic compounds [31].

The reference range of -5 (poor) to +1 (good) and substrate inhibitor from 0 to 1 in which the reference and test compounds 2(a-b), 3(a-b), 4(a-b), 5(a-b) and 6(a-b) showed good acceptable range. While the reference compound, as well as test compounds, came within the acceptable range as represented in table 6.

Table 6: ADME and pharmacological parameters prediction for the ligands (1 benzofuran-2-yl)-*N*'-[(3*Z*)-2-oxo-1, 2-dihydro-3*H*-indol-3-ylidene] quinoline-4 carbohydrazide and its derivatives 2(a-b), 3(a-b), 4(a-b), 5(a-b) and 6(a-b) by using ADMET/SAR toolbox

Ligand	PlogBB[a]	log_{HIA}[c]	PCac[b]	logpGI (substrate)[d]	logpGI (non-inhibitor)[e]	PlogS[f]	logpap[g]
2a	0.9179	0.9896	0.5983	0.8586	0.8211	-3.8048	0.8245
2b	0.9199	0.9911	0.6063	0.8590	0.8318	-3.9629	0.8685
3a	0.9004	0.9911	0.5972	0.8602	0.7685	-4.2350	0.9477
3b	0.9199	0.9957	0.6008	0.8571	0.8235	-4.1361	0.8988
4a	0.8970	0.9873	0.6056	0.8578	0.8300	-4.1580	0.8942
4b	0.9164	0.9939	0.6079	0.8548	0.8442	-4.0418	0.8508
5a	0.7529	0.8685	0.5692	0.8452	0.9139	-3.5226	0.7256
5b	0.7550	0.8885	0.5830	0.8403	0.8931	-3.7414	0.7363
6a	0.9199	0.9911	0.6063	0.8590	0.8318	-3.9629	0.8685
6b	0.9199	0.9911	0.6063	0.8590	0.8318	-3.9629	0.8685
Pyrazinamide	0.9745	0.7222	0.9813	0.8760	0.9731	-0.8476	1.3021
Ciprofloxacin	0.9655	0.8956	0.9795	0.9116	0.9231	-3.4638	0.8090
Streptomycin	0.9712	0.6968	0.8824	0.8177	0.9230	-2.0122	-0.5128
Fluconazole	0.9382	0.9894	0.8867	0.6008	0.8782	-1.8626	1.3598

[a]Predicted blood/brain barrier partition coefficient (1-high penetration, 2-medium penetration and 3-Low penetration). [b]Predicted Caco-2 cell permeability in nm/s (acceptable range: -1 is poor, 1is great). [c]Predicted Human intestinal absorption in nm/s (acceptable range: 0 poor,>1 great). [d]Predicted P-glycoprotein substrate in nm/s (acceptable range of-5 is poor, 1 is great). [e]Predicted P-glycoprotein inhibitor in nm/s (accepted range: 0 to 1), [f]Predicted aqueous solubility, (Concern value is 0-2 highly soluble). [g]Predicted probability of Caco-2 cell permeability in cm/s (Concern value is-1 to 1).

CONCLUSION

A simple and effective approach was described for the synthesis of (1 benzofuran-2-yl)-*N*'-[(3*Z*)-2-oxo-1, 2-dihydro-3*H*-indol-3-ylidene] quinolone-4 carbohydrazide and its derivatives 2(a-b), 3(a-b), 4(a-b), 5(a-b) and 6(a-b) in good yield. Analogues were made to predict ADMET/SAR *in silico,* the synthesized molecules are in the acceptable range were further screened for antimicrobial and antitubercular activity. The present work indicates that synthesized molecules were found to possess good antitubercular and potent antimicrobial activity. The above results indicate that the core moiety benzofuran, quinoline and isatin are essential for antimicrobial and antitubercular activity. The fluoro substitution at 8th position of the quinoline ring and nitro, bromo, fluoro substituted on isatin ring is essential for the activity. The results provide useful information for operating as a positive reinforcement of the tendency to use antimicrobial and antitubercular properties as a guideline of the rational design of this class of compounds.

AUTHORS CONTRIBUTION

Dr. N. D. Satyanarayan is the mentor involved in designing and in the generation of new benzofuran quinoline Schiff base analogues, he is the supervisor of the overall work. Mr. S. Santoshkumar was mainly involved in synthesis/characterization of entitled molecules, Mr. Anantacharya R. carried out *in silico* ADMET studies and their interpretation and Mr. Sameer P. Was instrumental in carrying out *in vitro* antimicrobial results.

ACKNOWLEDGEMENT

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

REFERENCES

1. Global tuberculosis control: surveillance, financing and planning. World Health Organization; 2015.
2. Blumberg HM, Burman WG, Chaisson RE, Daley CL, Etkind SC, Friedman LN, *et al.* American thoracic society/centers for disease control and prevention/infectious diseases society of America: treatment of tuberculosis. Am J Respir Crit Care Med 2003:167;603-62.
3. Goletti D, Weissman D, Jackson RW, Graham NM, Vlahov D, Klein RS, *et al.* Effect of Mycobacterium tuberculosis on HIV replication. Role of immune activation. J lmmunol 1996:157;1271-8.
4. Spigelman MK. New tuberculosis therapeutics: a growing pipeline. J Infect Dis 2007:196;S28-S34.
5. Mdluli K, Spigelman M. Novel targets for tuberculosis drug discovery. Curr Opin Pharmacol 2006:6;459-67.
6. Spigelman M, Gillespie S. Tuberculosis drug development pipeline: progress and hope. Lancet 2006:367;945-7.
7. Ginsberg AM, Spigelman M. Challenges in tuberculosis drug research and development. Nat Med 2007:13;290-4.
8. Duncan K. Progress in TB drug development and what is still needed. Tuberculosis (Edinb) 2003:83;201-7.
9. Duncan K. Identification and validation of novel drug targets in tuberculosis. Curr Pharm Des 2004:10;3185-9.
10. Komeilizadeh H. Does nature prefer heterocycles? Iranian J Pharm Res 2006:4;229-30.
11. Abdel-Wahab BF, Abdel-Aziz HA, Ahmed EM. Synthesis and antimicrobial evaluation of 1-(benzofuran-2-yl)-4-nitro-3-arylbutan-1-ones and 3-(benzofuran-2-yl)-4, 5-dihydro-5-aryl-1-[4-(aryl)-1,3-thiazol-2-yl]-1H-pyrazoles. Eur J Med Chem 2009:44;2632-5.
12. Koca M, Servi S, Kirilmis C, Ahmedzade M, Kazaz C, Özbek B, *et al*. Synthesis and antimicrobial activity of some novel derivatives of benzofuran: part 1. Synthesis and antimicrobial activity of (benzofuran-2-yl) (3-phenyl-3-methylcyclobutyl) ketoxime derivatives. Eur J Med Chem 2005:40;1351-8.

13. Chauhan PMS, Srivastava SK. Present trends and future strategy in chemotherapy of malaria. J Med Chem 2001:8;1535-42.
14. Sanjay SP, Shapi AS, Thomas D, Rajgopal JL, Kumar VS. Ionic liquid-promoted regiospecific friedlander annulation: a novel synthesis of quinolines and fused polycyclic quinolines. J Org Chem 2003:68;9371-8.
15. Lau KY, Mayr A, Cheung KK. Synthesis of transition metal isocyanide complexes containing hydrogen bonding sites in a peripheral location. Inorg Chim Acta 1999:285;223-32.
16. Raman N, Muthuraj V, Ravichandran S, Kulandaisamy A. Synthesis, characterisation and electrochemical behaviour of Cu(II), Co(II), Ni(II) and Zn(II) complexes derived from acetylacetone and *p*-anisidine and their antimicrobial activity. J Chem Sci 2003;115;161-7.
17. Sridhar SK, Ramesh A. Synthesis, characterization and pharmacological screening of some isatinoid compounds. J Indian Chem Soc 2002:41B;668-72.
18. Piotr P, Bogumil B. Spectroscopic studies and PM3 semiempirical calculations of schiff bases of gossypol with L-amino acid methyl esters. Biopolymers 2002:67;61-9.
19. Sari N, Arslan S, Logoglu E, Sakiyan I. Antibacterial activities of some new amino acid-schiff bases. G U J Sci 2003:16;283-8.
20. Holla BS, Rao BS, Shridhara K, Akberali PM. Studies on arylfuran derivatives. Part XI. Synthesis, characterisation and biological studies on some mannich bases carrying 2, 4-dichlorophenylfurfural moiety. Farmaco 2000:55;338-44.
21. Capdeville R, Buchdunger E, Zimmermann J, Matter A. Glivec (STI571, imatinib), a rationally developed, targeted anticancer drug. Nat Rev Drug Discovery 2002:1;493-502.
22. Anantacharya R, Manjulatha K, Satyanarayan ND, Santoshkumar S, Kaviraj MY. Antiproliferative, DNA cleavage, and ADMET study of substituted 2-(1-benzofuran 2 yl) quinoline-4-carboxylic acid and its esters. Cogent Chem 2016:2;1158382. https://doi.org/10.1080/23312009.2016.1158382
23. Manjunatha KS, Manjulatha K, Satyanarayan ND, Kaviraj MY, Adarsha HJ. Anti-proliferative and ADMET screening of novel 3-(1H-indol-3-yl) 1, 3-diphenylpropan1-one derivatives. Cogent Chem 2016:2;1172542. http://dx.doi.org/10.1080/23312009.2016.1172542
24. Satyanarayan ND, Santoshkumar S, Sheelavanth S, Yadav DB, Anantacharya R, Sandeep T. Antitubercular, antibacterial and molecular docking studies of new 2 (naphtha [2, 1-] furan-2-yl) quinoline-4-carboxylic acids and their esters. Inventi Impact: Med Chem 2016:3;75-83.
25. Lutz W. The application of multi-component reactions in drug discovery. Curr Med Chem 2002:9;1241-53.
26. Santoshkumar S, Manjulatha K, Satyanarayan ND, Anantacharya R, Harishkuar S, Harishkuar HN, *et al*. Antiproliferative, ADMET and potential *in silico* g6pdh

inhibitory activity of novel 2-(1-benzofuran-2-yl)-4-(5-phenyl-4h-1, 2, 4-triazol-3-yl) quinoline derivatives. Int J Pharm Pharm Sci 2016:8;313-9.
27. Saundane AR, Rudresh K, Satyanarayan ND, Hiremath SP. Pharmacological screening of 6H, 11H-indol [3,2-c] isoquinolin-5-ones and their derivatives. Indian J Pharm Sci 1998:60;379-83.
28. Pathak PD, Sharma KD. Determination of the antifungal activity of some organic chemicals. Def Sci J 1984:34;311-6.
29. Maria CSL, Marcus VN de Souza, Alessandra CP, Marcelle de LF, Raoni SBG, Thais Cristina MN, *et al*. Evaluation of the antitubercular activity of nicotinic and isoniazid analogues. ARKIVOC 2007:15;181-91.
30. Feixiong C, Weihua L, Yadi Z, Jie S, Zengrui W, Guixia L, *et al*. Classification of cytochrome p450 inhibitors and non-inhibitors using combined classifiers. J Chem Inf Model 2012:52;3099-105.
31. Lin JH, Yamazaki M. Role of P-glycoprotein in pharmacokinetics: clinical implications. Clin Pharmacokinet 2003:42;59-98.
32. Segura A, Duque E, Mosqueda G, Ramos JL, Junker F. Multiple responses of gram-negative bacteria to organic solvents. Environ Microbiol 1999:1;191-8.
33. Eswaran S, Adhikar AV, Chowdhury IH, Pal NK, Thomas KD. New quinoline derivatives: synthesis and investigation of antibacterial and antituberculosis properties. Eur J Med Chem 2010:45;3374-83.
34. Krieger IV, Freundlich JS, Gawandi VB, Roberts JP, Gawandi VB, Sun Q, *et al.*, the Structure-guided discovery of phenyl-diketo acids as potent inhibitors of *M. tuberculosis* malate synthase. Chem Biol 2012:19;1556-67.
35. Fu G, Wu J, Liu W, Zhu D, Hu Y, Deng J, *et al*. Crystal structure of DNA gyrase B' domain sheds lights on the mechanism for T-segment navigation. Nucleic Acids Res 2009:37;5908-16.
36. Gulten G, Sacchettini JC. Structure of the Mtb CarD/RNAP beta-lobes complex reveals the molecular basis of interaction and presents a distinct dna-binding domain for mtb card. Structure 2013:21;1859-69.
37. Sandy J, Holton S, Fullham E, Sim E, Noble MEM. Binding of the antitubercular drug isoniazid to the arylamine n-acetyltransferase protein from mycobacterium smegmatis. Protein Sci 2005:14;775-82.

How to cite this article