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Original Article

Synthesis, Characterization, Anti-tubercular Evaluation, and Teratogenicity Studies of Novel 5-(4-fluorobenzoyl) tetrahydro benzamidazoquinazoline Derivatives

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ABSTRACT

Background: The largest infectious agent-related cause of death and the most common disease with a high contagiousness profile is tuberculosis. For the treatment of tuberculosis, various benzimidazole and quinazoline compounds have been developed in the past with effectiveness. In this example, our goal was to synthesise new compounds with enhanced activity by combining the moieties of benzimidazole and quinazoline. The present study was planned to synthesize novel 5-(4-flourobenzoyl)12-(substitutedphenyl)-3,3-dimethyl-3,4,5,12-tetrahydrobenzo [4,5] imidazo [2,1-*b*] quinazolin-1(2*H*)-one derivatives. **Materials and Methods:** A series of benzamidazo quinazoline derivatives were synthesized and characterized by using IR,[1]HNMR, [13]CNMR, and Mass spectroscopy. The antitubercular activity of the synthesised compounds was evaluated against the H37RV strain to determine their antitubercular potential. To examine the teratogenicity of the synthesised compounds, zebrafish larvae were utilised. **Results and Discussion:** At 3.25 µg/ mL, compounds R2, R3, R4 and R9 exhibited good efficacy against *Mycobacterium tuberculosis* strains. Most of the synthesized compounds were proved as safe at 0.5 µM without any abnormalities. **Conclusion:** Compounds containing Electron withdrawing groups at 4[th] position were found to possess excellent antitubercular activity.

Keywords: Benzimidazole, Quinazoline, Antitubercular activity, Teratogenicity, Zebra fish larvae.

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INTRODUCTION

An infectious disease known as tuberculosis (TB) is one of the world's leading causes of death and a significant contributor to poor health.[1] Prior to the coronavirus (COVID-19) pandemic, TB was the most common infectious disease to cause death, surpassing HIV/AIDS. Mycobacterium tuberculosis, the bacillus that causes tuberculosis, spreads when TB patients cough up bacteria into the air (e.g., by coughing). Although it can affect other areas, the disease primarily affects the lungs (pulmonary TB). About 90% of those who contract the illness do so as adults, and more males than women experience it. A quarter of the world's population has *M. tuberculosis* infection. The development of novel therapeutic approaches is an even more urgent need than the exploration of new pharmacological forms for the delivery of current antitubercular medications, which may help to improve patient compliance and stop the spread of the disease.[2,3] While drug-susceptible TB can be treated for 6–8 months on average with the present standard of care, multi- and extensively drug-resistant (MDR/XDR) infections require at least 20 months of therapy with poor results, posing a severe threat to human health.[4] The rapid spread of infections with treatment resistance and ongoing genetic adaptation have caused an expected decline in the therapeutic efficacy of the available anti-TB medications, posing significant difficulties for researchers who wish to find alternative molecular entities to address this problem. Therefore, the design of more efficient and quicker therapies depends on the discovery of novel drugs that target both reproducing and dormant Mtb bacilli.

The creation and development of drugs with broad applicability in the pharmaceutical industry nowadays heavily relies on heterocyclic molecules. The therapeutic effects of benzimidazole derivatives as antibacterial,[5,6] antitubercular,[7-9] antitumor,[10] anthelmintic,[11] antihistaminic,[12] proton pump inhibitors,[12] anti-inflammatory,[13] anticancer,[14] antioxidant,[15] and antihypertensive[16] drugs have generated a great deal of attention in the medical community. Quinazolines serve as the building blocks for creating a variety of biologically active compounds and have played significant roles in medicinal chemistry. Numerous substituted quinazoline derivatives have a variety of biological actions, including antitubercular,[17] anti-inflammatory,[18] anti-depressant, antifungal, antiviral, antiprotozoal, diuretic, antimalarial, anticancer, and antibacterial properties.[19] Due to the quinazoline nucleus extensive range of chemotherapeutic in vivo and in vitro efficacies, it has attracted a great deal of attention. There have been reports of potential bioactivities for benzimidazole when it is anchored with other heterocyclic substances, including triazole, thiadiazole, oxadiazole, morpholine, piperazine, or piperidine.[20] These findings boosted our interest in looking for benzimidazole anchored quinazoline possible pharmacologically active leads.

According to the literature review, the majority of them have synthesised 12-(substituted phenyl)-3,3-dimethyl-3,4,5,12-tetrahydrobenzo [4,5] imidazo[2,1-*b*] quinazolin-1(2*H*)-one derivatives[21-24] and we tried to synthesise new derivatives by reacting these with 4-floro benzoyl chloride to form 5-(4-fluorobenzoyl)-12-(substitutedphenyl)-3,3-dimethyl-3,4,5,

12-tetrahydrobenzo[4,5] imidazo[2,1-*b*] quinazolin-1(2*H*)-one derivatives (R1-10) to produce novel compounds with improved activity.

MATERIALS AND METHODS

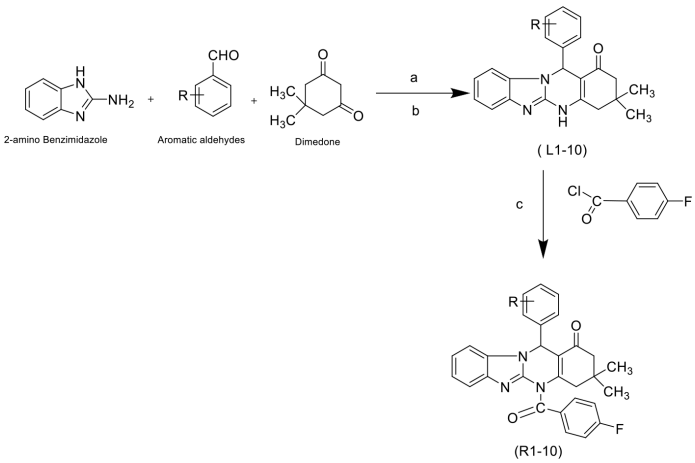
Experimental

S.D. Fine Chemicals Limited in Mumbai and Avra Chemicals Pvt Limited in New Delhi provided the materials for the reaction. We used thin layer chromatography (TLC) with E. Merck 0.25-mm silica gel plates, UV illumination (256 nm), and an iodine chamber to assess reaction completeness. Utilizing a single spot in TLC, the purity of the synthesised compounds was determined following recrystallization with methanol and aqueous ethanol. It took some trial and error before the TLC mobile phase was discovered. Their melting points were calculated using capillary tubes, and the outcomes were uncorrected. All ^{1}HNMR spectra were collected using DMSO-d6 as the solvent, with TMS serving as the internal standard. Shimadzu FT-IR spectrophotometer and discs containing 1 percent KBr were used to record FTIR spectra. An Agilent 1100 series mass spectrometer was used to record the compounds mass spectra.

General Procedure

Synthesis of 12-(substituted phenyl)-3,3-dimethyl-3,4,5,12-tetrahydrobenzo [4,5] imidazo[2,1-b] quinazolin-1(2H)-one derivatives (L1-10): Iodine (10 mol %) was added to a mixture of 2-amino benzimidazole (1.0 mmol), different aromatic aldehydes (1.0 mmol), dimedone (1.0 mmol), and acetonitrile (5 mL) are refluxed for 3-4h. The reaction mass was cooled to room temperature once the reaction was complete, as determined by TLC, and the solid that had been separated was filtered, water-washed, and dried under reduced pressure.

Synthesis of 5-(4-flourobenzoyl)12-(substitutedphenyl)-3,3-dimethyl-3,4,5,12-tetrahydrobenzo [4,5] imidazo[2,1-b] quinazolin-1(2H)-one derivatives (R1-10): Drop by drop, 0.001 mmol of 4-flouro benzoyl chloride was added to a solution of intermediate (L1-10) (0.001 mmol) in a THF: TEA (1: 3) solution. A magnetic stirrer was used to agitate the reaction mixture mentioned above for a full hour. The reaction mixture was then extensively washed with $NaHCO_3$ and poured onto crushed ice when the reaction was finished. The resulting solid was filtered and recrystallized from ethanol (Scheme1).



Compound code	R1	R2	R3	R4	R5	R6	R7	R8	R9	R10
R	C_6H_5	4-Br	4-NO_2	4-F	4-OCH_3	4CH_3	2-NO_2	2-Cl	4-Cl	3-Br

Scheme: Reagents and conditions; **a)** CH_3CN, **b**) i-PrOH 10% reflux for 3-4 h, **c)** THF, TEA, (1:3) stirring for 1-2 h.

- ***R1 5-(4-flourobenzoyl)-3,3-dimethyl-12-phenyl-3,4,5,12-tetrahydrobenzo [4,5] imidazo[2,1-b] quinazolin-1(2H)-one:*** IR(KBr): 3456, 2785, 1676, 1639, 1622, 1612, 1564, 771cm^{-1}; ^{1}H NMR: 8.05-7.02, (m,13H), 6.41(s, 1H), 2.61-2.51(d, 2H), 2.28-2.24 (d, 1H), 2.07 (d, 1H), 1.06 (s, 3H), 0.93 (s, 3H). ^{13}CNMR: 197.6, 168.1, 165.4, 140.1, 132.1, 128.6, 114.9, 55.1, 26.5. m/z [M+H]: 466.1
- ***R2 12-(4-bromophenyl)-5-(4-flourobenzoyl)-3,3-dimethyl-3,4,5, 12-tetrahydrobenzo [4,5] imidazo[2,1-b] quinazolin-1(2H)-one***: IR(KBr): 3425, 2689, 1680, 1642, 1621, 1609, 1559, 765cm^{-1}; ^{1}H NMR: 8.15-7.12, (m,12H), 6.28(s, 1H), 2.58-2.49 (d, 2H), 2.28-2.24 (d, 1H), 2.05 (d, 1H), 1.08 (s, 3H), 0.99 (s, 3H). ^{13}CNMR: 195.5, 167.1, 164.3, 141.4, 138.2, 126.7, 115.9, 54.6, 27.4. m/z [M+2H]: 546.3
- ***R3 5-(4-flourobenzoyl)-3,3-dimethyl-12-(4-nitrophenyl-3,4,5,12-tetrahydrobenzo [4,5] imidazo[2,1-b] quinazolin-1(2H)-one:*** 3458, 2686, 1678, 1641, 1628, 1605, 1558, 768cm^{-1}; ^{1}H NMR: 8.15-7.08, (m,12H), 6.30 (s, 1H), 2.62-2.58 (d, 2H), 2.29-2.26 (d, 1H), 2.09 (d, 1H), 1.00 (s, 3H), 0.99 (s, 3H). ^{13}CNMR: 196.6, 167.5, 165.5, 141.2, 135.6, 129.5, 114.5, 56.1, 28.5. m/z [M+H]: 511.5
- ***R4 5-(4-flourobenzoyl)-12-(4-flourophenyl-3,3-dimethyl-3,4,5, 12-tetrahydrobenzo [4,5] imidazo[2,1-b] quinazolin-1(2H)-one:*** 3448, 2682, 1684, 1639, 1620, 1610, 1560, 765cm^{-1}; ^{1}H NMR: 8.00-7.52, (m,12H), 6.56 (s, 1H), 2.59-2.49 (d, 2H), 2.28-2.25 (d, 1H), 2.01(d, 1H), 1.01(s, 3H), 0.97 (s, 3H). ^{13}CNMR: 194.5, 166.5, 165.3, 142.1, 133.2, 128.9, 115.2, 56.2, 27.8 m/z [M+H]: 484.12
- ***R5 5-(4-flourobenzoyl)-12-(4-methoxyphenyl-3,3-dimethyl-3,4,5, 12-tetrahydrobenzo [4,5] imidazo[2,1-b] quinazolin-1(2H)-one:*** 3398, 2684, 1676, 1642, 1628, 1609, 1559, 768cm^{-1}; ^{1}H NMR: 7.96-6.90, (m,12H), 6.00 (s, 1H), 3.94 (s, 3H), 2.69-2.58 (d, 2H), 2.27-2.26 (d, 1H), 2.05(d, 1H), 1.00(s, 3H), 0.95 (s, 3H). ^{13}CNMR: 196.6, 167.5, 163.2, 141.2, 138.1, 129.6, 114.2, 56.5, 55.2, 26.8. m/z [M+2H]: 496.20.
- ***R6 5-(4-flourobenzoyl)-3,3-dimethyl-12-(p-tolyl)-3,4,5,12-tetrahydrobenzo [4,5] imidazo[2,1-b] quinazolin-1(2H)-one:*** 3396, 2679, 1680, 1633, 1621, 1606, 1569, 782cm^{-1}; ^{1}H NMR: 8.00-7.94, (m,12H), 6.05 (s, 1H), 2.60-2.54 (d, 2H), 2.34 (s, 3H), 2.28-2.23 (d, 1H), 2.01(d, 1H), 0.99 (s, 3H), 0.94 (s, 3H). ^{13}CNMR: 195.6, 167.4, 164.5, 142.1, 138.5, 129.6, 113.5, 56.5, 26.9, 21.3.m/z [M+H]: 480.12.
- ***R7 5-(4-flourobenzoyl)-3,3-dimethyl-12-(2-nitrophenyl)-3,4,5, 12-tetrahydrobenzo [4,5] imidazo[2,1-b] quinazolin-1(2H)-one:*** 3459, 2678, 1682, 1639, 1626, 1606, 1552, 772cm^{-1}; ^{1}H NMR: 8.10-7.69, (m,12H), 6.29 (s, 1H), 2.63-2.57 (d, 2H), 2.28-2.24 (d, 1H), 2.04 (d, 1H), 1.04 (s, 3H), 0.97 (s, 3H). ^{13}CNMR: 198.36, 165.4, 162.1, 142.1, 136.5, 128.5, 115.6, 53.2, 26.9. m/z [M+H]: 511.5.

Antitubercular activity

Using MABA, synthesized drugs **(R1–10)** were evaluated against M. tuberculosis H37Rv strain. A sterile 96-well plate's perimeter wells were filled with 200µL of sterile deionized water to prevent media from drying up during incubation.[25] The 96-well plate was filled with diluted ingredients and 100µL of Middle Brook 7H9 broth. From 100 to 0.2 µg/mL were used as final samples. Five days were spent incubating coated, parafilm-sealed plates at 37°C. The next step was a 24 h incubation with 25 µL of newly made 1:1 Alamar blue reagent and 10% Tween 80. Pink indicated bacterial development, while blue denoted the absence of such growth. The lowest dose of a drug required to prevent a blue substance from becoming pink is known as the minimum inhibitory concentration (MIC).

Teratogenicity Assay

The teratogenicity of these final compounds was examined in zebrafish larvae, and findings were obtained.

Animals: Zebrafish that were adults were housed in a rectangular aquarium and fed conventional fish food. The fish were housed in their aquariums using a 14h light/dark cycle, and the water was kept at room temperature.

Collection of embryos: At 6:00 p.m., a breeding tank containing male and female zebra fish was fed. The embryos were taken out the next morning, cleaned with E3 medium three times, and incubated at 25–28°C in E3 medium.[26] The control group was given 1mL of vehicle, whereas the test group was given ten different test chemicals six hours after fertilisation. The following medication dosages (n = 10) were evaluated up until day 5: 50, 10, 5, 3, 1, 0.5, 0.25, and 0.01 µM. Five days after fertilization, the larvae were anaesthetized with tricaine methane sulfonate and examined under a microscope. We took photos and compared any morphological deviations to the control group.

RESULTS

Synthetic routes for the targeted compounds 5-(4-flourobenzoyl)12-(substitutedphenyl)-3,3-dimethyl-3,4,5,12-tetrahydrobenzo [4,5] imidazo [2,1-*b*] quinazolin-1(2*H*)-one derivatives is presented in scheme 1. Iodine was used as a catalyst for preparation of intermediates, and We attempted with several catalysts and solvents to create the target molecules, but we ultimately noticed a smooth reaction when we employed the TEA: THF (1:3) ratio (Table 1).

All the final compounds (R1-10) were tested against the *M. tuberculosis* H37Rv strain using positive drug standards as isoniazid, ethambutol, and pyrazinamide for the study. The compounds R2, R3, R4and R9 were shown to be equally effective compared to pyrazinamide (3.2 µg/mL) and to be very good inhibitors of *M. tuberculosis* growth at a concentration of 3.2 µg/mL. As per the results, the MIC values were found between 3.2 and 1.6 µg/mL. Whereas compounds R1 and R5 shown inhibition of bacterial growth at 6.25 µg/mL (Table 2). The fact that compounds R2, R3, R4 and R9 was found promising in exhibiting excellent antitubercular action against the TB strain.

Zebrafish larvae were used to test synthetic compounds teratogenicity (R1-10). Out of ten compounds, four were severely teratogenic for zebrafish larvae and R1, R2, R4, R5, R6, and R8 were safe at 0.5 µM without abnormalities. Teratogenicity assay results showed that majority of the compounds were found to be safer at 0.5 µM without exhibiting any abnormalities (Figure 1).

Table 1: Physical data of 5-(4-flourobenzoyl)12-(substitutedphenyl)-3,3-dimethyl-3,4,5,12-tetrahydrobenzo [4,5] imidazo[2,1-*b*] quinazolin-1(2*H*)-one derivatives (R1-10).

Compound	Mol.formula	Mol.wt	MP°C	Yield
R1	$C_{29}H_{24}FN_3O_2$	465	180-182	78
R2	$C_{29}H_{23}BrFN_3O_2$	544	176-178	72
R3	$C_{29}H_{23}FN_4O_4$	510	185-186	70
R4	$C_{29}H_{23}F_2N_3O_2$	483	162-163	68
R5	$C_{30}H_{26}FN_3O_3$	495	170-171	71
R6	$C_{30}H_{26}FN_3O_2$	479	158-160	69
R7	$C_{29}H_{23}FN_4O_4$	510	180-181	73
R8	$C_{29}H_{23}ClFN_3O_2$	500	157-158	69
R9	$C_{29}H_{23}ClFN_3O_2$	500	148-150	68
R10	$C_{29}H_{23}BrFN_3O_2$	544	173-174	70

Table 2: Antitubercular activity results of the synthesized compounds.

S.no	Sample	100 µg/ml	50 µg/ml	25 µg/ml	12.5 µg/ml	6.25 µg/ml	3.12 µg/ml	1.6 µg/ml
1	R1	S	S	S	S	S	R	R
2	R2	S	S	S	S	S	S	R
3	R3	S	S	S	S	S	S	R
4	R4	S	S	S	S	S	S	R
5	R5	S	S	S	S	S	R	R
6	R6	S	S	S	R	R	R	R
7	R7	S	S	S	R	R	R	R
8	R8	S	S	S	R	R	R	R
9	R9	S	S	S	S	S	S	R
10	R10	S	S	S	R	R	R	R
11	Isoniazid	S	S	S	S	S	S	S
12	Ethambutol	S	S	S	S	S	S	S
13	Pyrazinamide	S	S	S	S	S	S	R

S = Sensitive, R = Resistant

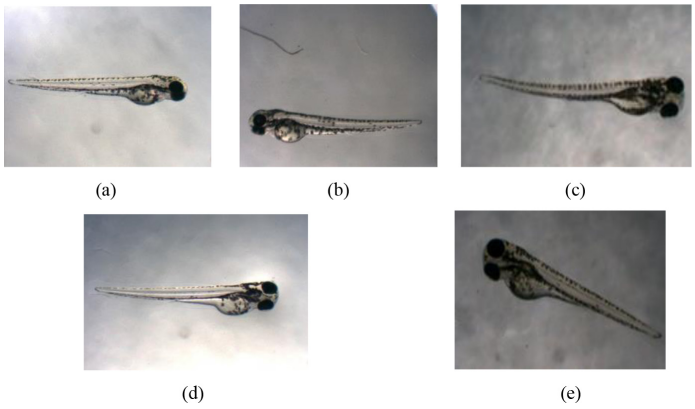


Figure 1: (a) control (b) R1 (0.5µM) (c) R2 (0.5µM) (d) R4 (0.5µM) (e) R8(0.5µM) – all the larvae had no abnormalities when compared to the control group.

DISCUSSION

Two steps were executed to make a series of 5-(4-flourobenzoyl)12-(substitutedphenyl)-3,3-dimethyl-3,4,5,12-tetrahydrobenzo [4,5] imidazo [2,1-*b*] quinazolin-1(2*H*)-one derivatives. The first step is one pot reaction between 2-maino benzimidazole, different aromatic aldehydes and dimedone were reacted in acetonitrile using iodine as a catalyst to produce 12-(substituted phenyl)-3,3-dimethyl-3,4,5,12-tetrahydrobenzo [4,5] imidazo[2,1-*b*] quinazolin-1(2*H*)-one derivatives (L1-10). In the next step these intermediate compounds were reacted with 4-flouro benzoyl chloride in TEA: THF (1:3) ratio to produce the target compounds (R1-10) in quantifiable yields (Table 1). The synthesised compounds were characterized by IR, ^{1}HNMR, ^{13}CNMR and ESI-MS spectral analysis.

The elucidation of the synthesis of the intermediate compounds (L1-10) was accomplished by the utilisation of spectral and elemental analysis. The formation of compound L1 was evident from the appearance of f [M+H] + peak at m/z 344.17 in mass spectrum (ESI), –C=O stretching at 1648 cm^{-1} in IR and the appearance of characteristic methine proton as a singlet at δ 6.35 in ^{1}H NMR. And also, the appearance of NH proton as a singlet at δ11.02 clearly indicating the smooth cyclization.[23] Similar to this, spectral analysis provided proof of the synthesis of the title

compounds (R1–10). In the ^{1}HNMR spectrum of R1, for example, the signal of -NH at around 11.02 ppm was missing, and the development of new signal as multiplet at about 8.05-7.02 ppm due to presence of extra aromatic protons corresponding to substituted benzoyl chloride supports the formation of the final product.

Additionally, the structures of compounds (R1–10) and their total proton counts are very well matched. Antitubercular activity was conducted by using Microplate alamar blue assay technique (MABA). The compounds R2, R3, R4and R9 were shown to be equally effective compared to pyrazinamide (Table 2). It could be explained by the following way that the presence of electron withdrawing group like bromo, nitro, flouro and chloro at the para position of the benzamidazoquinazoline nucleus. Besides the presence of Electron donating group like -OCH_3 at para position and unsubstituted derivative prone to have moderate biological activity. Surprisingly the presence of Electron withdrawing groups other than the para position showed weak activity. Teratogenicity assay results showed that majority of the compounds were found to be safer.

CONCLUSION

We created a library of novel hybrid compounds containing benzimidazole and quinazoline nucleus. The designed analogues were synthesized, their spectral characteristics determined, and their antitubercular potency evaluated. Among the synthesized compounds, R2, R3, R4, and R9, have demonstrated notable antitubercular action. A MIC value may be between 3.2 and 1.6 µg/mL. Zebrafish larvae were used in the teratogenicity assay for these compounds; four out of the ten compounds were extremely teratogenic. At 0.5 µM, R1, R2, R4, R5, R6, and R8 were shown to be safer without displaying any anomalies. For potential medicinal study, compounds having electron-withdrawing groups in the fourth position, such as flouro, bromo, nitro, and chloro, were promising lead molecules. Overall, the results suggest the molecular hybridization technique may be useful for lead optimization in the development of novel hybrid antitubercular drugs based on benzimidazole and quinazoline analogues.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

TLC: Thin layer chromatography; **THF:** Tetrahydro furan; **TEA:** Triethyl amine; IR: Infrared; **KBr:** Potassium bromide; **NMR:** Nuclear magnetic resonance; **MABA:** Microplate alamar blue assay; **µg/mL:** Microgram per millilitre.

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