**In Silico and in Vitro Studies of Fluorinated Chroman-2-Carboxilic Acid Derivatives as an Anti-tubercular Agent**

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**Background:** Despite the use of traditional method, Ugi reaction currently is a well-established multicomponent reaction. Chromane motif itself possesses a variety of biological functions. In order to improve its anti-tubercular activity, it is necessary to modify it accordingly.

**Aim:** To ensure relation between in silico and in vitro study, we have carried out in vitro screening against H37Rv anti-tubercular agent.

**Materials and methods:** Ugi four-component condensation (U-4CCRs) between 6-fluorochroman-2-carboxylic acid, various aryl aldehyde, 3,4,5-trimethoxy amine and tert-butyl isocyanide, gave N-(tert-butylcarbamoyl)(4-substitutedphenyl)methyl)-6-fluoro-N-(3,4,5-trimethoxyphenyl) chroman-2-carboxamide. The molecular level insight of all compounds was carried out by molecular docking study against the receptor tyrosine phosphatase PtpB. All these newly synthesized compounds were screened for their anti-microbial activity against Mycobacterium tuberculosis H37Rv to determine the MIC, IC50 and IC90 of the compound.

**Results:** The compound 5d also shows large hydrophobic surface contact on the face of the α7–α8 (Ile 207, Phe 211, Met 206, Ile203, Phe161, Phe80, Met126, Tyr130, Val231 and Leu101) that lines one side of the entrance to the active site of the receptor. The compound 5d bind with tyrosine phosphatase PtpB with predicted docking geometric score of 4664, whereas a score of rifampicin was 6586 determined.

**Conclusion:** From the docking studies, compound 5d, was considered to be the potent inhibitor, which gave strong supportive coordinate with the in vitro study. It is highly active against H37Rv, having MIC and IC50 value of was 70 μM and 53 μM respectively in in vitro study.

**BACKGROUND**

Tuberculosis (TB) is an airborne disease caused by Mycobacterium tuberculosis (M. tuberculosis). M. tuberculosis and seven very closely related mycobacterial species together comprise what is known as the M. tuberculosis complex. Most, but not all, of these species have been found to cause disease in humans and extensively drug-resistant. TB is the major causes of death from infectious diseases worldwide. According to WHO, tuberculosis mostly affects young adults, in their most productive years. However, all age groups are at risk. Over 95% of cases and deaths are in developing countries.2,3 Recently, in 2012 FDA approved drug, bedaquiline is introduced as an anti-tuberculosis drug, specifically approved for the treatment in multi-drug-resistant tuberculosis.

Since last decades, an important progress in the field of molecular biology together with the development of high-throughput drug screening methodologies has led to an ever-increasing demand for finding a new drug candidate. In these perspective multicomponent reactions (MCRs), because of their efficiency, ease of automation along with their chemical diversity-generating power, subtraction of byproducts, have attracted much attention in the field of academic as well as industrial research community.5,6 Within the class of MCRs, based on the irregular reactivity of isocyanides, and in particular the Ugi reaction, have been among the most widely used pathway.7,8 The combination of MCRs with transition-metal-catalysis gives access
to complex molecules in few steps as compared to traditional multistep processes. Typically, Ugi four component reactions (U-4CR) provide access to carboxamide-like derivatives by a one pot condensation of aldehyde, amine, carboxylic acid and isocyanide.

An analogous of chromane scaffolds were well studied compounds and known for their considerable biological awareness in last few decades i.e. anti-tuberculosis, anti-viral and many more. On the other side in the field of medicinal chemistry many other heterocycles containing fluorinated motif were also known for their prominent impediment against H37Rv. The pharmacological active motif were also known for their prominent impediment of many other heterocycles containing fluorinated isocyanide.

desination of aldehyde, amine, carboxylic acid and to carboxamide-like derivatives by a one pot component reactions (U-4CR) provide access to traditional multistep processes. Typically, Ugi multicomponent reaction as an anti-tubercular scaffold.

MATERIALS AND METHODS

General

Chemicals and solvents were purchased from the Sigma-Aldrich Chemical Co., Merck chemical, Finar Chemicals and solvents were purchased from the Sigma-Aldrich Chemical Co., Merck chemical, Finar Chemicals and solvents were purchased from the Sigma-Aldrich Chemical Co., Merck chemical, Finar Chemicals and solvents were purchased from the Sigma-Aldrich Chemical Co., Merck chemical, Finar Chemicals and solvents were purchased from the Sigma-Aldrich Chemical Co., Merck chemical, Finar.

Yield: 68%, mp 220°C. IR (cm⁻¹): 3323.35 (NH-stretching), 2937.59 (C-H stretching), 1672.28 (Ketonic carbonyl stretching), 1645.28 (Amide C=O stretching), 1492.90, 1548.84 (Aromatic ring skeleton), 1319.31 (C-H bending), 1257.59 (C-O bending), 1115.75 (C-F stretching), 997.20 (p-di substitution), 798.53 (C-Cl stretching). ¹H NMR (CDCl₃): δ 7.52 (2H), 7.29 (2H), 7.03 (m, 2H), 6.43 (s, 1H), 5.98 (s, 2H), 5.72 (m, 1H), 5.90 (s-broad, 1H), 4.49 (t, J = 6.3 Hz, 1H), 3.74 (s-broad, 1H), 2.95 (t, J = 6.1Hz, 2H), 2.58 (q, J = 6.3 Hz, 2H), 1.29 (s, 9H). ¹³C NMR (CDCl₃): δ 170.46, 162.76, 160.95, 158.45, 155.68, 152.08 (d), 140.29, 136.73, 135.32, 130.62, 128.65, 127.94, 122.60 (d), 114.71 (d), 113.18, 112.97, 111.26, 111.06, 106.35, 77.95, 62.36, 60.57, 56.13, 51.35, 28.86, 27.21 (d), 22.80. m/z [M+1] found in Molecular Formula: C₃₁H₃₄ClF₂N₂O₆ 585.

N-((tert-Butylcarbamoyl)(3-(cyclopropylmethoxy)phenyl)methyl)-6-fluoro-N-(3,4,5-trimethoxyphenyl) chroman-2-carboxamide (5a)

Yield: 68%, mp 220°C. IR (cm⁻¹): 3323.35 (NH-stretching), 2937.59 (C-H stretching), 1672.28 (Ketonic carbonyl stretching), 1645.28 (Amide C=O stretching), 1492.90, 1548.84 (Aromatic ring skeleton), 1319.31 (C-H bending), 1257.59 (C-O bending), 1115.75 (C-F stretching), 997.20 (p-di substitution), 798.53 (C-Cl stretching). ¹H NMR (CDCl₃): δ 7.52 (2H), 7.29 (2H), 7.03 (m, 2H), 6.43 (s, 1H), 5.98 (s, 2H), 5.72 (m, 1H), 5.90 (s-broad, 1H), 4.49 (t, J = 6.3 Hz, 1H), 3.74 (s-broad, 1H), 2.95 (t, J = 6.1Hz, 2H), 2.58 (q, J = 6.3 Hz, 2H), 1.29 (s, 9H). ¹³C NMR (CDCl₃): δ 170.46, 162.76, 160.95, 158.45, 155.68, 152.08 (d), 140.29, 136.73, 135.32, 130.62, 128.65, 127.94, 122.60 (d), 114.71 (d), 113.18, 112.97, 111.26, 111.06, 106.35, 77.95, 62.36, 60.57, 56.13, 51.35, 28.86, 27.21 (d), 22.80. m/z [M+1] found in Molecular Formula: C₃₁H₃₄ClF₂N₂O₆ 585.

N-((tert-Butylcarbamoyl)(3-(cyclopropylmethoxy)phenyl)methyl)-6-fluoro-N-(3,4,5-trimethoxyphenyl) chroman-2-carboxamide (5b)

Yield: 62%, mp 198°C. IR (cm⁻¹): 3344.57 (NH-stretching), 2970.38 (C-H stretching), 1681.93 (Ketonic carbonyl stretching), 1643.35 (Amide C=O stretching), 1490.97, 1543.05 (Aromatic ring skeleton), 1362.17 (C-H bending), 1257.59 (C-O binding), 1115.75 (C-F stretching), 997.20 (p-di substitution), 798.53 (C-Cl stretching). ¹H NMR (CDCl₃): δ 7.52 (2H), 7.29 (2H), 7.03 (m, 2H), 6.43 (s, 1H), 5.98 (s, 2H), 5.72 (m, 1H), 5.90 (s-broad, 1H), 4.49 (t, J = 6.3 Hz, 1H), 3.74 (s-broad, 1H), 2.95 (t, J = 6.1Hz, 2H), 2.58 (q, J = 6.3 Hz, 2H), 1.29 (s, 9H). ¹³C NMR (CDCl₃): δ 170.46, 162.76, 160.95, 158.45, 155.68, 152.08 (d), 140.29, 136.73, 135.32, 130.62, 128.65, 127.94, 122.60 (d), 114.71 (d), 113.18, 112.97, 111.26, 111.06, 106.35, 77.95, 62.36, 60.57, 56.13, 51.35, 28.86, 27.21 (d), 22.80. m/z [M+1] found in Molecular Formula: C₃₁H₃₄ClF₂N₂O₆ 585.
Ugi Adducts as an Anti-Tubercular Agents

1. \[ J = 6.2 \text{ Hz}, 1H) \]
2. \[ J = 7.5 \text{ Hz}, 2H) \]
3. \[ J = 3.70 \text{ Hz}, (s, 9H) \]
4. \[ J = 2.94 \text{ Hz}, (t, J = 6.1 \text{ Hz}, 2H) \]
5. \[ J = 2.54 \text{ Hz}, (q, J = 6.2 \text{ Hz}, 2H) \]
6. \[ J = 1.30 \text{ Hz}, (s, 9H) \]
7. \[ J = 1.32 \text{ Hz}, (m, 1H) \]
8. \[ J = 0.66 \text{ Hz}, (m, 2H) \]
9. \[ J = 0.41 \text{ Hz}, (m, 2H) \]

10. \[ \delta 170.46, 162.76, 161.96, 158.44, 155.68, 152.08 (d), 151.08, 144.59 (t), 136.73, 135.32, 127.65, 124.54, 122.60 (d), 122.15, 121.24, 118.56, 117.92, 115.88, 114.71 (d), 113.17, 112.97, 111.26, 111.06, 106.35, 77.95, 74.00, 63.16, 60.57, 56.13, 51.35, 28.86, 27.21 (d), 22.80, 10.70, 7.85. \]

11. \[ m/z [M+1] \text{ found in Molecular formula: C}_{36}H_{41}F_{3}N_{2}O_{8} 686.} \]

12. \[ N-((\text{tert-Butylcarbamoyl})(2\text{-methoxyphenyl})methyl)-6\text{-fluoro-N-(3,4,5-trimethoxy phenyl)chroman-2-carboxamide} \]

13. \[ R_1 = (\text{yield}) \]
14. \[ 4\text{-CF}_2, 3\text{-OCH}_2\text{CP} \]
15. \[ 2\text{-OCH}_3 \]
16. \[ 3\text{-CP}, 4\text{-OCH}_2\text{CP} \]
17. \[ 3,4,5\text{-Tri OCH}_3 \]
18. \[ 3\text{-OPh} \]
19. \[ 4\text{-NO}_2 \]
20. \[ 4\text{-Br} \]
21. \[ 4\text{-CH}_3 \]
22. \[ 3,4\text{-Di OCH}_3 \]
23. \[ 2\text{-Cl} \]
24. \[ 3,4\text{-Di OH} \]
25. \[ @2-\text{Furan} \]
26. \[ @3-\text{Pyridine} \]
27. \[ @2-\text{Thiophene} \]

28. \[ CP= \text{Cyclopropyl} \]

**Reaction condition:** (a) Methanol, RT, 12.0 h

**Reaction Scheme 1:** Synthetic pathway for the Ugi 4-component condensation reaction (5a-o)

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J = 6.2 Hz, 1H), 3.96 (d, J = 7.5 Hz, 2H), 3.70 (s, 9H), 2.94 (t, J = 6.1 Hz, 2H), 2.54 (q, J = 6.2 Hz, 2H), 1.30 (s, 9H), 1.32 (m, 1H), 0.66 (m, 2H), 0.41 (m, 2H). \[ ^{13} \text{C NMR (CDCl}_3; \delta 170.46, 162.76, 160.96, 158.44, 155.68, 152.08 (d), 151.08, 144.59 (t), 136.73, 135.32, 127.65, 124.54, 122.60 (d), 122.15, 121.24, 118.56, 117.92, 115.88, 114.71 (d), 113.17, 112.97, 111.26, 111.06, 106.35, 77.95, 74.00, 63.16, 60.57, 56.13, 51.35, 28.86, 27.21 (d), 22.80, 10.70, 7.85. m/z [M+1] \text{ found in Molecular formula: C}_{36}H_{41}F_{3}N_{2}O_{8} 686.}

\[ N-((\text{tert-Butylcarbamoyl})(2\text{-methoxyphenyl})methyl)-6\text{-fluoro-N-(3,4,5-trimethoxy phenyl)chroman-2-carboxamide} \]

Yield: 69%, mp 210 °C. IR (cm\(^{-1}\)): 3307.92 (NH-stretching), 2968.45 (C-H stretching), 1734.01 (Ketonic carbonyl stretching), 1734.01 (Ketonic carbonyl stretching), 2968.45 (C-H stretching), 1734.01 (Ketonic carbonyl stretching), 1653.00 (Amidic C=O stretching), 1490.97, 1543.05 (Aromatic ring skeleton), 1323.17 (C-H bending), 1217.08 (C-O...
bending), 1116.10 (C-F stretching), 812.03 (α-di substitution). $^1$H NMR (CDCl$_3$):$\delta$ 7.14 (m, 2H), 7.02 (m, 3H), 6.85 (d, $J$ = 7.4, Hz, 1H), 6.32 (s, 2H), 6.21 (s, 1H), 6.02 (s-broad, 1H), 5.74 (d, $J$ = 7.5 Hz, 1H), 4.57 (t, $J$ = 6.3 Hz, 1H), 3.74 (s, 9H), 3.76 (s, 3H), 2.95 (t, $J$ = 6.1Hz, 2H), 2.62 (q, $J$ = 6.3 Hz, 2H), 1.31 (s, 9H). $^{13}$C NMR (CDCl$_3$):$\delta$ 170.46, 162.43, 160.96, 159.87, 158.44, 155.68, 152.08 (d), 136.73, 135.32, 129.06, 127.14, 122.60 (d), 121.98, 121.48, 114.65 (m), 113.18, 112.97, 111.26, 111.06, 106.35, 77.95, 61.69, 60.57, 56.13, 51.35, 28.86, 27.21 (d), 22.80. m/z [M+1] found in Molecular formula: C$_{32}$H$_{37}$FN$_2$O$_7$ 580.6.

IN SILICO STUDIES

In-silico studies were conducted by comparing the synthesized molecule with rifampicin which is the standard drug used against tyrosine phosphatase PtpB protein (PDB ID: 1YWF, 296 amino acid containing) of Mycobacterium tuberculosis.$^{15}$ Ligands were generated by the online portal of UNM Biocomputing- University of New Mexico (http://pasilla.health.unm.edu/tomcat/biocomp/convert) and docking studies were performed by PatchDock software with clustering root mean square deviation (RMSD) value of 4.0.$^{16}$ Finally the predicted protein-ligand bindings were visualized with PyMOL software (https://pymol.org/).$^{17}$

RESULTS AND DISCUSSION

CHEMISTRY

Synthetic Optimization

As mentioned earlier, it was a condensation between four components, i.e. 6-flourochromane-2-carboxilic acid (1), 3,4,5-Trimethoxyaniline (2), Various aromatic aldehydes (3a-o) and tert-butyl isocyanide (4), gives racemic products in analytically comparable yield (5a-o) (Reaction Scheme 1). The Reaction was adopted by using greener solvent and reaction condition, i.e. it was carried out at room temperature by stirring without any catalyst. The purification of this new type of carboxamide compounds can be accomplished by column chromatography on silica (Mesh Size: 60-120; Hexane: Ethyl acetate as an eluent) to provide better yield (describe in experimental section). The first approach has the benefit that, besides removal of unreacted components and chemical impurities, single enantiomers can be isolated in a single step purification process. A reaction mechanism similar to that suggested by Ugi$^{18}$ has been followed in the proposed work. Confirmation of single isomer was carried out by an X-ray structure determination technique of compound 5a. ORTEP diagram of compound 5a exhibited in Figure 1 which can exactly identify spatial arrangements of atoms as well as chiral geometry (CCDC No. 1402956).

Figure 1. ORTEP diagram for compounds 5a.
Among the solvents tested, methanol was the only solvent in which the reaction led to the formation of the target compound in reasonably higher yields (Table 1).

Table 1. Optimization of the reaction conditions for the synthesis of 5a by selective condition of solvents vs. yield

| Entry | Solvent                   | Time [Hours]a | Yield [%] |
|-------|---------------------------|---------------|-----------|
| 1     | Ethanol                   | 48-64         | 50        |
| 2     | Methanol                  | 10-15         | 55-75     |
| 3     | Toluene                   | 5 days        | -         |
| 4     | Dimethyl formamide        | 4 days        | 5-22      |
| 5     | Duterated methanol        | 3 days        | 23-25     |

*Rifampicin*  

*5d*

**Figure 2.** Predicted 3-dimensional structures and ligand binding sites of tyrosine phosphatase PtpB protein (PDB ID: 1YWF. **A** (20 Å sphere) and **C** (12 Å sphere) represents binding of rifampicin whereas **B** (20 Å sphere) and **D** (12 Å sphere) represents the binding of ligand **5d** with PtpB protein.*
Table 2. Crystal data and parameters for structure refinement of title compound 5a

| Compound ID | 5a |
|-------------|----|
| CCDC Deposition Number | 1402769 |
| Empirical formula | C_{31}H_{34}ClF_{2}N_{2}O_{6} |
| Formula weight | 585.07 |
| Crystal color, habit | colorless, chip |
| Crystal dimensions (mm) | 0.760 × 0.620 × 0.300 mm |
| Crystal system | triclinic |
| Lattice type | Primitive |
| Lattice parameters | a = 10.704(2) Å, b = 12.843(2) Å, c = 13.179(2) Å, α = 116.968(4)°, β = 103.203(4)°, γ = 95.788(5)°, V = 1527.8(4) Å³ |
| Space group | P-1 (#2) |
| Z value | 2 |
| D_{calc} | 1.272 g/cm³ |
| F(000) | 616.00 |
| μ(MoKα) | 1.753 cm⁻¹ |
| Diffractometer | SCX mini |
| Radiation | MoKα (λ = 0.71075 Å) graphite monochromated |
| ω oscillation range | -120.0 - 60.0° |
| Exposure rate | 10.0 sec./Degree |
| Detector position | -30.80° mm |
| 2θ_{max} | 55.0° |
| No. of reflections measured | Total: 15580; Unique: 6966 |
| Corrections | Lorentz-polarization Absorption (trans. factors: 0.645 - 0.949) |
| R_{int} | 0.054 |
| R₁ (I > 2.00 σ(I)) | 0.0602 |
| R (All reflections) | 0.0976 |
| WR₂ (All reflections) | 0.2450 |
| Largest diff. peak and hole (e/Å³) | 0.26, -0.27 |
| Goodness of fit | 0.782 |
Crystal of compound 5a was performed with a Rigaku SCX mini diffractometer using graphite monochromated Mo-Kα radiation. All the calculations were performed using the crystal structure crystallographic software package except for refinement, which was performed using SHELXL-97. All the hydrogen atoms were located in difference Fourier maps, and their coordinates were refined with isotropic displacement parameters.

Table 2 summarizes the crystallographic data for compound 5a.

**Antitubercular Assay**

Anti-tubercular screening was carried out at the National Institute of Allergy and Infectious Diseases (NIAID), an agency of the National Institute of Health (NIH), Bethesda, USA.

**MIC under Aerobic Conditions**

The MIC, IC_{50} and IC_{90} of compound 5a-5o (Table 3) were determined by measuring bacterial growth after 5 days in the presence of test compounds. Dose response curves were generated using the Levenberg-Marquardt algorithm and the concentrations that resulted in 50% and 90% inhibition of growth were determined (IC_{50} and IC_{90} respectively).

Rifampicin (100 μM) was chosen as the standard drugs for the comparison of antitubercular activity. The drug was dissolved in DMSO and diluted and tested as described above. The bottles were incubated at 75-80°C for 3 days for solidification and sterilization.

From the results of preliminary antimycobacterial screening of compounds 5a-5o (Table 3), it has been observed that compounds 5d, 5i and 5j shows comparative higher minimum inhibition concentration than other synthesized compounds, may be due to the presence of donating influence at 3 and 4 positions of aromatic nucleus but IC_{50} and IC_{90} value for the same compounds show that it is required in a reasonably higher concentration. Other compounds give moderate inhibitory value, which might be possible due to the withdrawing as well as steric hindrance of the substituents.

**Docking Study**

To obtain molecular insight, all ligands were further subjected to molecular docking study to obtain molecular interaction and generate the supportive coordination between *in silico* and *in vitro* results. By taking the “tyrosine phosphatase PtpB, a member of protein tyrosine phosphatases (PTP) superfamily “as the protein target, molecular docking study was performed with the synthesized lead compounds. Ribbon diagram of PtpB protein represents 44% helical (15 helices; 133 residues), 6% beta sheet (5 strands; 18 residues) and a P loop. A docking geometric score of 4664 with an interface area size of 614, desolvation energy -156.68 and transformation values of (0.53, -0.79, 1.08, -2.02, 47.52 and 19.52) were observed for compound 5d. The compound 5d also shows large hydrophobic surface contact on the face of α7–α8 (Ile 207, Phe 211, Met 206, Ile203, Phe161, Phe80, Met126, Tyr130, Val231 and Leu101) hairpin that lines one side of the entrance to the active site of the receptor. Whereas rifampicin has a docking geometric score of 6586 with an interface area size of 614, desolvation energy -156.68 and transformation values of (0.53, -0.79, 1.08, -2.02, 47.52 and 19.52) were observed for compound 5d. The compound 5d also shows large hydrophobic surface contact on the face of the α7–α8 (Ile 207, Phe 211, Met 206, Ile203, Phe161, Phe80, Met126, Tyr130, Val231 and Leu101) hairpin that lines one side of the entrance to the active site of the receptor. Whereas rifampicin has a docking geometric score of 6586 with an interface area size of 877.80, desolvation energy -308.05 and transformation values of (-0.76, 0.34, 2.67, 18.98, 56.81, -22.02). This study highly coordinates with the *in vitro* results. Moreover, it was observed, that the top-ranked ligands occupied, to a great extent, the same binding space and exhibited similar binding orientation in the active site as of rifampicin.

**Table 3. In vitro antitubercular activity of compounds 5a–5o against the Mtb strains H37Rv**

| Compounds ID | MIC (μM) | IC_{50} (μM) | IC_{90} (μM) |
|-------------|---------|-------------|-------------|
| 5a          | >200    | >200        | >200        |
| 5b          | >200    | >200        | >200        |
| 5c          | >200    | >200        | >200        |
| 5d          | 79      | 53          | >100        |
| 5e          | >200    | >200        | >200        |
| 5f          | >200    | >200        | >200        |
| 5g          | >200    | >200        | >200        |
| 5h          | >200    | >200        | >200        |
| 5i          | >200    | 93          | >200        |
| 5j          | >200    | 64          | >100        |
| 5k          | >200    | >200        | >200        |
| 5l          | >100    | >200        | >100        |
| 5m          | >200    | >200        | >200        |
| 5n          | >100    | >100        | >200        |
| 5o          | >200    | >200        | >200        |
| Rifampicin  | 0.04    | 0.02        | 0.03        |
Finally, considering \textit{in vitro} and \textit{in silico} molecular docking results, among these newly synthesized molecules, 5d gave the best result and was considered as the best inhibitor of tyrosine phosphatase PtpB and can be an effective anti-tubercular drug.

\textbf{CONCLUSIONS}

A new series of chromane-2-carboxamide derivatives (5a-5o) were synthesized from 6-flourochroman-2-carboxilic acid via the Ugi reaction and characterized by spectral and elemental analyses. These new chemical entities were evaluated for their \textit{in vitro} antituberculosis activities against different pathogenic strains. Among the tested compounds, compound 5d displayed considerable antimycobacterial activities against \textit{H37Rv} as a MIC, IC\textsubscript{50} and IC\textsubscript{90}. A lead molecule 5d implements better scoring based on binding surface with reference to rifampicin. Entire study shows that the docking was rigid for compounds other than 5d. The utilization of the remaining synthesized molecules were enabled us to permit more binding towards amino acids.

\textbf{CONFLICT OF INTEREST}

The authors declare they have no conflict of interest.

\textbf{ACKNOWLEDGMENTS}

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In silico and in vitro investigation of chroman-2-carboxylic acid derivatives as anti-tubercular agents

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Introduction: In the current study, an in vitro screening of a homocyclic reaction was performed using the antitubercular agent H37Rv.

Materials and methods: A four-component condensation reaction (U-4CCRs) between 6-fluorochroman-2-carboxylic acid derivatives, other aryl aldehydes, 3,4,5-trimethoxymethylamine and 2-butyli isocyanide was used to synthesize a new series of 6-fluorochroman-2-carboxamides. The molecular level was determined by molecular docking with the receptor tyrosine phosphatase PTPb. All these newly synthesized compounds were screened for their antitubercular activity.

Results: Compound 5d showed the highest contact surface area (7-8) (Ille 207, Phe 211, Met 206, Ile 203, Phe 161, Phe 80, Met 126, Tyr 130, Val 231 and Leu 101), which is the most active compound in the active site of the receptor. Compound 5d interacts with the tyrosine phosphatase PTPb with the predicted docking geometry of 4664, whereas the interaction with rifampicin is 6586.

Conclusion: According to the docking study, compound 5d is a good inhibitor and is comparable to the results of the in vitro study. It is very active against H37Rv, with MIC and IC50 values of 70 μM and 53 μM, respectively.