Medicinal Chemistry & Drug Discovery

Sacubitril-Based Urea and Thiourea Derivatives as Novel Inhibitors for Anti-Tubercular against Dormant *Tuberculosis*

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In the present study, we have attempted to identify Sacubitril derivatives as lead compounds for dormant tuberculosis. A total of twenty-one compounds belongs to a series of the Sacubitril derivatives **5(a–u)** were synthesized using (*2R,4S*)-5-([1,1′-biphenyl]-4-yl)-4-(amino)-2-methylpentanoic acid ethyl ester hydrochloride with different isocyanates and isothiocyanates. All the compounds structures were determined by ^{1}H & ^{13}C NMR spectroscopy, mass spectrometry, and CHN analysis. Compound, **5r**, the structure confirmed by single-crystal X-ray diffraction analysis (**SXRD**). The newly synthesized compounds were screened for their *in vitro* antituberculosis activity (anti-TB) against dormant *Mycobacterium tuberculosis* H37Rv (ATCC27294). Among the twenty-one compounds, **5p** and **5q** were exhibited good potent anti-TB activity compared to the standard drug Ethambutol. Further, the anti-TB activities of the compounds (**5p** and **5q**) were evaluated against *M. tuberculosis* (***Mtb***) using the nutrient starvation model (NSM). Moreover, these two compounds, **5p** and **5q** have shown significant inhibition of growth of *Mtb* as compared to the control. To determine the toxicity nature, the potent anti-TB active compounds were evaluated against RAW 264.7 cells. Further, the anti-TB activities of all these compounds have shown a good correlation to their in-silico molecular docking analysis by exhibiting strong interactions with the inhibitor Mur-B.

1. Introduction

Tuberculosis (TB) is a contagious bacterial infection caused by the *Mycobacterium tuberculosis*[1] that usually affects the lungs (primary sites), followed by spreading through the circulatory and lymphatic system to the liver, joints, bones and spleen (secondary sites).[2] Tuberculosis is one of the most threatening human health problems because of 8.7 million new tuberculosis (TB) cases and 1.4 million mortalities per annum in the world.[3] TB became more alarming with the multidrug-resistant-TB (MDRTB), extensively drug-resistant-TB (XDR-TB), totally drug-resistant-TB (TDR) strains and longer treatment time (6–12 months). In fact, usually, the longer period of treatment associated with side effects and the complication of the drug regimen.[4,5] Therefore, there is an essential need for the development of new anti-TB drug candidates in order to overcome the above-mentioned problems. Hence, the discovery and development of novel anti-TB agents that can display less toxicity and specified mechanism of action have become an essential endeavour.

Sacubitril is an α-methyl-*c*-amino-*d*-biphenyl valeric acid derivative is also known as AHU-377[6] containing two stereocenters. Sacubitril is an important active pharmaceutical compound mainly used for the treatment of heart failure with a combination of Valsartan.[7] In fact, this combination (Sacubitril/Valsartan) composed of two molecular moieties in a single crystalline complex called supramolecular complex LCZ696, which is marketing as Entresto[8,9] by Novartis. This supramolecular hybrid LCZ696 complex identified to lower the risk of cardiovascular death of chronic heart failure in patients. Moreover, it approved as the first dual inhibitor of AT1 receptors for angiotensin II and neutral endopeptidase (NEP) by the FDA in 2015.[10]

On the other hand, urea and thiourea are, the more polar, metabolically stable important precursors and are also known to possess potent anti-mycobacterial activity.[11–16] Several derivatives of these compounds have been potentially identified to possess potent antituberculosis activity in the literature.[17,18] For instance, the amide derivative such as Pyrazinamide is already used as a first-line anti-TB drug.[19] Similarly, the thiourea derivative such as thiocarlide has exhibited potent antituberculosis activity against *Mtb* H37Rv through the inhibition of the mycolic acid synthesis.[20] Apart

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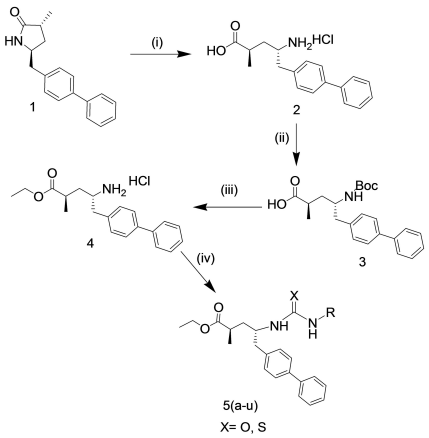
from this, urea and thiourea based heterocyclic derivatives display anticancer, antimicrobial, anthelmintic and insecticidal activities.[21–26] The new approach to drug discovery is the incorporation of various biologically active molecules in a single hybrid framework may allow changes in the biological properties of the hybrid molecule when compared to the parent molecule.[27] In continuation of our ongoing interest,[15,16,23–25] in the present study, we are amalgamating the urea and thiourea precursors with pharmaceutical important Sacubitril moiety and further explored their anti-TB activity.

1. Results and Discussion

1.1. Synthesis

The synthetic route for the synthesis of the Sacubitril based derivatives, **5(a–u)** has outlined in Scheme 1. The ethyl (*2R*,*4S*)-5-([1,1′-biphenyl]-4-yl)-4-amino-2-methylpentanoate derivatives (**2**) were synthesized from (*3R*,*5S*)-5-([1,1′-biphenyl]-4-ylmethyl)-3-methylpyrrolidin-2-one (**1**). Initially, we performed the reaction of (*3R*,*5S*)-5-([1,1′-biphenyl]-4-ylmethyl)-3-methylpyrrolidin-2-one with acetic acid and HCl in EtOAc afforded the (*2R*,*4S*)-5-([1,1′-biphenyl]-4-yl)-4-amino-2-methylpentanoic acid hydrochloride **2** in 94% yield. The copound **2**, which in turn reacted with Boc anhydride to afford the corresponding (*2R*,*4S*)-5-([1,1′-biphenyl]-4-yl)-4-((tert-butoxycarbonyl)amino)-2-methylpentanoic acid **3**. Later, the compound **3**, reacted with $SOCl_2$ in the presence of EtOH offered scaffold **4**. In the final step, compound, **4**, reacted with different isocyanate and isothiocyanate reagents to yield corresponding urea and thiourea derivatives, **5(a–u)** (Scheme 1).

Further, in this present study, we have synthesized twenty-one compounds by changing the various substitutions at R and X positions for optimizing the antituberculosis activity (Scheme 1). The compounds **5(a–u)**, were achieved in 6 h with yields ranging from 78–96%. All the twenty-one substituted (R and X) analogs with yields and their respective melting points of the compounds **5(a–u)** were summarized in table 1. The



Scheme 1. Synthesis of the title compounds, **5(a–u)**. Reagents and conditions: (i) Acetic acid, HCl, EtOAc, 90 °C, 15 h: (ii) Boc-anhydride, DIPEA, DCM, RT, 6 h; (iii) $SOCl_2$, EtOH, reflux, 18 h; (iv) RNCO/RNCS, TEA, DCM, 10 °C, RT.

Table 1. Physical data for Sacubitril derivatives **5(a–u)**.

Compound code	R	X	Yield (%)	M.P. (°C)
5a	4-Fluorophenyl	O	92	246
5b	4-Methylphenyl	O	93	228
5c	Allyl	O	87	195
5d	4-Methoxyphenyl	O	91	214
5e	4-Bromophenyl	O	95	231
5f	4-Nitrophenyl	O	83	263
5g	3,4-Dichlorophenyl	O	89	284
5h	Ethyl	O	91	259
5i	Propyl	O	84	247
5j	4-Fluorophenyl	S	89	235
5k	4-Methylphenyl	S	85	208
5l	Allyl	S	92	199
5m	4-Methoxyphenyl	S	86	230
5n	Isopropyl	S	96	241
5o	4-Bromophenyl	S	78	184
5p	4-Nitrophenyl	S	91	256
5q	3,4-Dichlorophenyl	S	86	212
5r	Ethyl	S	89	184
5s	Propyl	S	94	198
5t	3-Bromophenyl	S	86	234
5u	4-Chlorophenyl	S	93	220

synthesized compounds, **5(a–u)** were confirmed by ^{1}H and ^{13}C NMR spectroscopy, MASS spectrometry and elemental analysis (see, supporting information (S.I) for all the spectral data).

1.2. X-ray crystal structure

All the compounds **5(a–u)**, were characterized by ^{1}H & ^{13}C NMR spectroscopy, CHN analysis and MASS spectrometry (S.I). The structures determined by the spectroscopic techniques were also confirmed by single-crystal X-Ray diffraction (**SXRD**) analysis. The single crystals suitable for **SXRD** analysis were grown using dichloromethane/*n*-hexane solvent combination using the diffusion method. The **SXRD** structure (ORTEP) diagram of compound **5r**, is shown in figure 1 (**SXRD** data table provided in table S1, S.I). The ORTEP diagram clearly indicated that the structures determined by spectral data agree with the **SXRD** structure and confirmed two chiral carbons (C14 and C16). Compound, **5r**, crystallizes in an orthorhombic crystal system with a space group, $P2_12_12_1$ (No.19). In the **SXRD** structure, the asymmetric unit contains one formula unit ($C_{23}H_{30}N_2O_2S$), without any solvent of crystallization. Moreover, it exhibits an interesting intermolecular H-bond between O(1)–H(27)–N(2) with a value of 2.960 Å (Figure 1).

1.3. Antituberculosis activity

All the newly synthesized twenty-one Sacubitril-based derivatives, **5(a–u)** were studied for *in vitro* antituberculosis activity against *Mycobacterium tuberculosis* (*Mtb*) H37Rv (ATCC27294) using the microplate Alamar blue assay (MABA) method (See S.I for the detailed experimental details).[28–30] Ethambutol was used as a reference drug for this study and experiments were carried out in triplicate. The MIC values determined for each

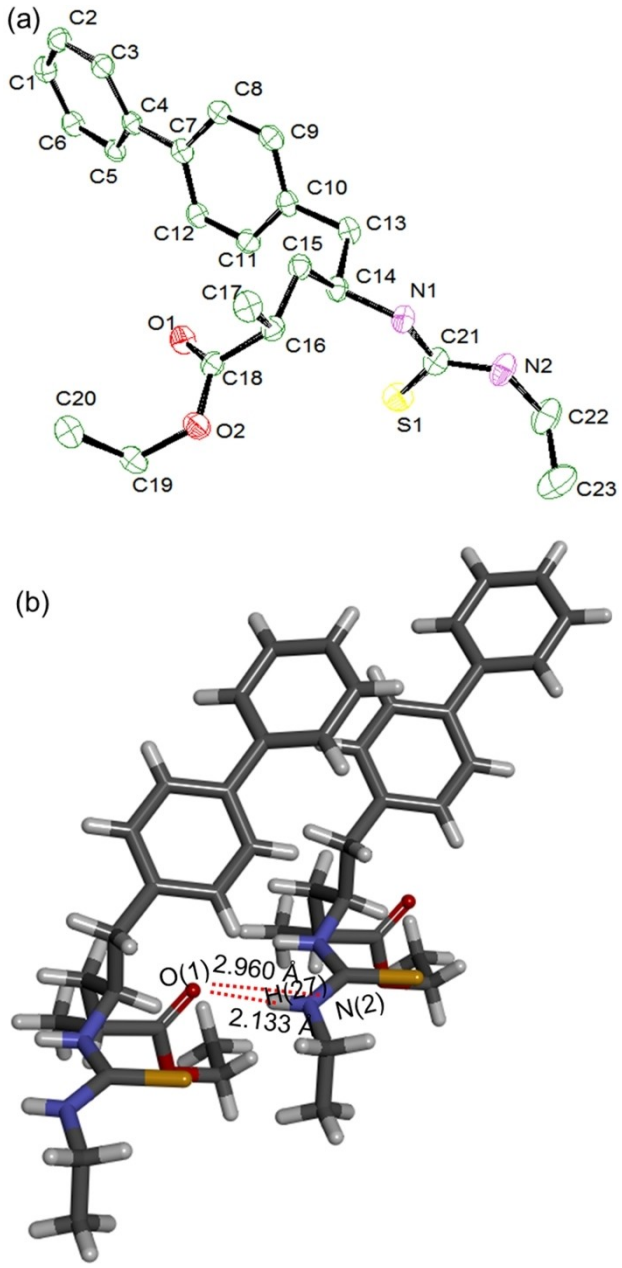


Figure 1. X-ray crystal structure ORTEP (50% probability) digram (a) (hydrogen atoms were excluded for clarity), and showing intermolecular H-bonding (b) of compound **5r**.

compound of **5(a–u)**, which were indicated in μg/mL in table 2. All the compounds exhibited good to poor anti-TB activity with MIC values in the range of 6.25 to > 25 μg/mL. Among all the compounds, **5(a–u)**, the compounds **5p** and **5q**, exhibited the same potent anti-TB activity with the MIC values of 6.25 μg/mL (Table 2). Similarly, the other two compounds, **5r** and **5s**, have also displayed the significant anti-Tb activity by exhibiting same MIC value, 12.50 μg/mL (Table 2). The remaining compounds have shown poor anti-TB activity (Table 2).

Table 2. Anti-TB activity of selected compounds **5(a–u)**.

Compound code[a]	X	R	Anti-TB Activity MIC (μg/mL)	Cytotoxicity (% of inhibition) against RAW264.7
5p	S	4-Nitrophenyl	6.25	24.6
5q	S	3,4-Dichloro-phenyl	6.25	20.9
5r	S	Ethyl	12.5	16.2
5s	S	Propyl	12.5	15.9
5t	S	3-Bromophen-yl	> 25	–
5u	S	4-Chlorophen-yl	> 25	–
Ethambutol	–	–	1.56	–

[a] Compounds **5a–5o, 5t** and **5u**, exhibited Anti-TB Activity MIC > 25 (μg/mL).

1.4. Nutrient Starved model (NSM) assay for Antituberculosis activity

In this study, the *Mtb* (H37Rv) culture draws successfully undernourished in PBS (phosphate buffered saline) for six week span of time culture was used for the assay study.[31] The test compounds (**5p** and **5q**) for their activity for 7 days at a concentration of 10 μg/mL was tested relative to standard against the Dormant stage attained bacteria. The test plates were kept for incubation at 37 °C over a period of four weeks and wells with illusory bacterial gathering were counted as positive. The most probable number (MPN) values were calculated using standard statistical methods as described previously.[32] Further, we have screened the selected two compounds **5p** and **5q** against the nutrient-starved dormant TB model. In the nutrient starvation model, the compounds **5p** and **5q** have displayed 1.9 and 2.2 log reduction in bacterial count equipotent to standard drugs Isoniazid and Rifampicin (Figure 2). These results suggest that compounds **5p** and **5q** are in good combat active stages, but also dormant forms of *Mtb*. In fact, this is very crucial in lowering the duration of therapy as designed the titled compounds.

1.5. Toxicity assay

The promising anti-TB active compounds such as **5p**, **5q**, **5r** and **5s** have been tested for their safety profile by the evaluation of cytotoxicity on normal RAW 264.7 cells at 25 μg/mL.[33] The results of four lead compounds of the present study, cytotoxicity inhibition (%) on RAW 264.7 cells have shown in figure 2. The cytotoxic inhibition (%) for the compounds **5p**, **5q**, **5r** and **5s** are 24.60, 20.90, 16.20 and 15.90%, respectively. These results clearly indicated that the cytotoxic inhibition percentage is low and hence these lead compounds do not affect the normal human immunity system.

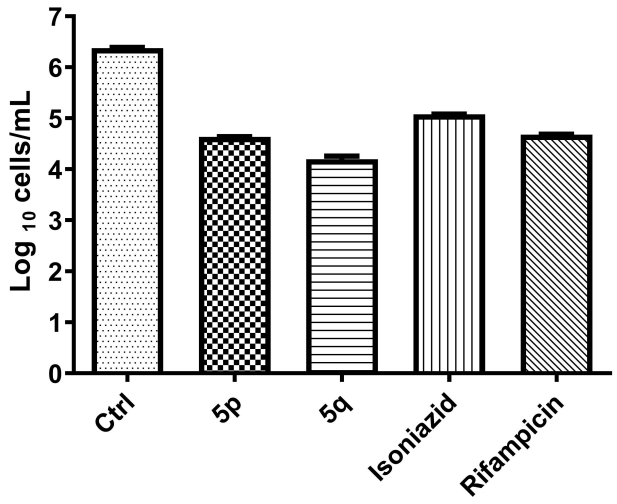


Figure 2. Biological activities of the active compounds against *Mtb* in the nutrient starvation model (NSM). The bacterial count estimated (Mean ± S.D., n = 3) for the control and treated groups, using the MPN assay. Two compounds have shown good inhibition of growth against *Mtb* in this model as compared to the control growth ($p < 0.0001$, two way ANOVA using "GraphPad" prism software).

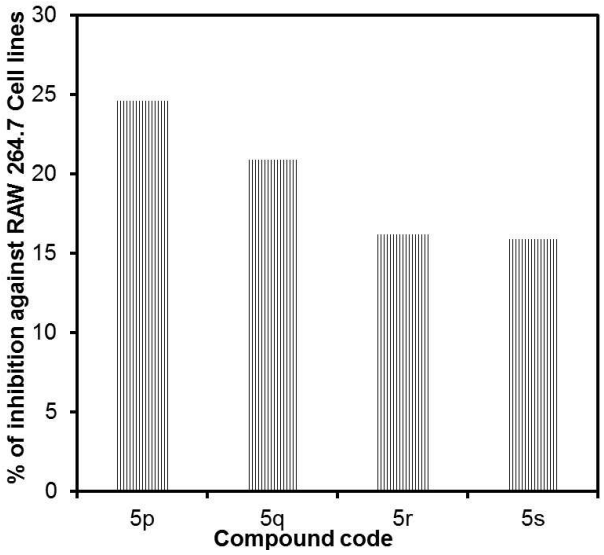


Figure 3. Percentage of inhibition on RAW 264.7 cell line at 25 μg/mL of the promising anti-TB compounds, **5p**, **5q**, **5r** and **5s**.

1.6. Molecular docking study

The molecular in-silico docking studies for all the twenty-one compounds, **5(a–u)** carried out using S. Areus MurB enzyme.[34] It is well known that, Mur proteins family (Mur A–F, Y and G) could be involved in the formation of the peptidoglycan layer of the cell walls of bacteria as a catalyst in more than ten biosynthetic transformations. UDP–N-acetylglucosamine-enol-pyruvate reductase (MurB) also plays an important part in the binding of the EP-UDPGlcNAc or NADPH in E. coil MurB.[34] Due to this reason, we choose to use the MurB enzyme as a target receptor for our docking study. The interactive results as shown in Table 3, indicated that compound, **5p**, exhibits the highest binding energy −10.28 Kcal/mol, shown H-bonding with five amino acid residues such as GLY140, SER254 (3), THR252 (Figure 4), which is in good agreement with its anti-TB activity MIC value of 6.25 (μg/mL). Similarly, compounds **5q** and **5e** also shown good binding energies of −10.12 and −10.09 Kcal/mol, H-bonded with two amino acids (GLU361, ARG238) and one amino acid (SER70) residues, respectively. Moreover, other

Table 3. Binding energies of **5(a–u)** substituted inhibitors against receptor UDP–N-acetylglucosamine-enol pyruvate reductase *Mtb* **MurB**.

S.No	Compound	Binding Energies *Mtb* **MurB** (PDB ID:5JZX) Binding energy (Kcal mol^{-1})	No. of H-bonds	Amino acid residues involved in bonding
1	**5a**	−9.56	03	GLY140, GLY69, GLY68
2	**5b**	−9.41	03	ARG176, PRO128, GLY140
3	**5c**	−8.28	03	SER70, ASN71, GLY69
4	**5d**	−9.65	02	ARG238, SER70
5	**5e**	−10.09	01	SER70
6	**5f**	−9.63	04	GLY242(2), SER254, SER70
7	**5g**	−9.95	01	SER70
8	**5h**	−8.28	02	SER130, GLY69
9	**5i**	−8.12	02	ARG238, GLY140
10	**5j**	−9.04	02	SER70, ALA67
11	**5k**	−9.00	02	SER(2)
12	**5l**	−6.78	02	VAL65, ALA67
13	**5m**	−8.16	03	ASP184, ASN71, LEU180
14	**5n**	−8.61	01	PRO128
15	**5o**	−9.85	01	SER70
16	**5p**	−10.28	05	GLY140, SER254 (3), THR252
17	**5q**	−10.12	02	GLU361, ARG238
18	**5r**	−9.97	02	GLU361, ASN71
19	**5s**	−9.87	03	HIS182 (2), VAL65
20	**5t**	−9.52	01	SER70
21	**5u**	−9.01	02	ARG238 (2)

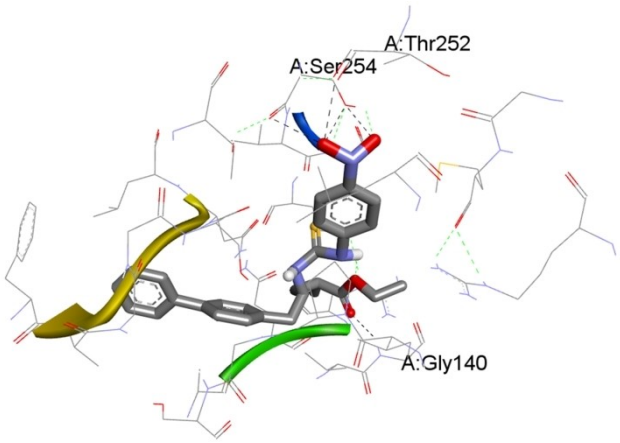


Figure 4. Molecular docking interactive profiles of the compound, **5p** (ball and stick model) showing its interactive H-bonding (black dotted lines) with the receptor UDP–N-acetylglucosamine-enol pyruvate reductase (**MurB**) protein amino acid residues (stick model).

compounds also shown good hydrogen-bonding interactions caused binding energies with the protein receptor found in the molecular docking analysis were reasonably good correlation with their respective anti-mycobacterial activity results.

The structure-activity correlation (**SAC**) of the titled compounds, **5(a–u)**, could be explained as follows. Overall, the thiourea based compounds, **5(a–i)** shown better ant-Tb activity compared with urea derivatives, **5(j–u)**. Among these compounds, the structural changes caused by various donor and acceptor ability driven substituted moieties on the heterocyclic scaffolds are very crucial in their different anti-Tb activity. Especially, compounds **5p** and **5q** shown good anti-Tb activity due to the presence of electron acceptor groups on the substituted phenyl moiety such as nitro- and chloro- groups. The electron acceptor moieties increase the polarity of the heterocyclic skeleton which might be the reason for high anti-Tb activities for these compounds. The in-silico molecular docking analysis also shown these compounds interact better with the inhibitors, **MurB**. Moreover, our cytotoxicity determination of lead compounds such as **5p** and **5q** indicated that, they are non-toxic to human cells. So these compounds could be potential candidates for new anti-Tb drugs.

2. Conclusion

A total of twenty-one compounds belongs to a series of the Sacubitril derivatives, **5(a–u)**, synthesized and well-characterized by ^{1}H & ^{13}C NMR spectroscopy, elemental analysis and MASS spectrometry. One compound, **5r**, structure also characterized by **SXRD** and confirmed with the structure obtained by spectroscopic study. All the newly synthesized compounds were evaluated for their *in vitro* anti-TB activity against *Mycobacterium tuberculosis* H37Rv (ATCC27294). Among these twenty-one compounds, two compounds, **5p** and **5q** exhibited potent anti-TB activity. Similarly, the other two compounds, **5r** and **5s** are also exhibited significant anti-TB activity. Further, the biological activities of the active compounds (**5p** and **5q**) were evaluated against *M. tuberculosis* in the nutrient starvation model and the two compounds gave significant inhibition of growth of *M. tuberculosis* in this model as compared to the control. The potent anti-TB active compounds **5p**, **5q**, **5r** and **5s** have exhibited lower toxicity (against RAW 264.7 cells) which could be promising hits for antituberculosis. Further, anti-TB activities of all the compounds have shown a good correlation with in-silico molecular docking analysis and some compounds exhibiting strong interactions with the inhibitors Mur-B. This study could provide a roadmap to design and synthesize new anti-TB drugs to overcome various problems associated with the available drugs in the market.

3. X-ray crystallography

Crystallographic information files (CIFs) for 5r, CCDC-2050579, contain(s) the supplementary crystallographic data for this paper. This data is provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures Service www.ccdc.cam.ac.uk/structures.

Supporting information Summary

The synthetic procedure of the compounds 1, 2, 3, 4, and 5(a-u) and spectral copies of all the compounds of the present study, ^{1}H NMR, ^{13}C NMR, MASS were shown in the supporting information (S.I). Experimental procedures for the biological assays (MABA, MMT and Nutrient Starved model assay), SXRD and docking study also provided in S.I.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Anti-TB activity · Cytotoxicity · Molecular docking study · NMR spectroscopy · Nutrient Starvation Model · Sacubitril derivatives

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