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Original article

# Synthesis and characterization of new *N*-(4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyphenyl)amide/sulfonamide derivatives as possible antimicrobial and antitubercular agents

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ABSTRACT

In this paper we report the SAR studies of a series of *N*-(4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyphenyl)amide and *N*-(4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyphenyl)sulfonamide derivatives **6**(**a**–**o**) and **7**(**a**–**o**), were synthesized in good yields and characterized by $^1$H NMR, $^{13}$C NMR and mass spectral analyses. The preparation of the key intermediate highlights an optimized palladium catalyzed ($Pd_2(dba)_3$/RuPhos) Buchwald cross-coupling of intermediate **2** and **3**. The newly synthesized compounds were evaluated for their in vitro antibacterial activity against *Staphylococcus aureus*, (Gram-positive), *Escherichia coli* and *Klebsiella pneumoniae* (Gram-negative), antifungal activity against *Candida albicans*, *Aspergillus flavus* and Rhizopus sp. and antitubercular activity against *Mycobacterium tuberculosis H37Rv*, *Mycobacterium smegmatis*, *Mycobacterium fortuitum* and MDR-TB strains. The synthesized compounds displayed interesting antimicrobial activity. The compounds **7d**, **7f**, **7h** and **7n** displayed significant activity against *Mycobacterium tuberculosis* H37Rv strain.

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## 1. Introduction

There are certain diseases that take a long time to develop; these diseases are called chronic germ diseases. Tuberculosis is a specific communicable disease caused by *Mycobacterium tuberculosis*. It affects both the pulmonary and non pulmonary tissues. This disease may be acute or chronic, general or local. These bacilli are microscopic and were first discovered in 1882. Due to the heterogeneous bacterial populations in the tuberculosis lesions and perhaps also to insufficient host immunity, treatment with a combination of drugs must be given for extended periods of time to prevent reactivation of disease by persisting bacilli. Tuberculosis is a devastating worldwide problem, whose control is complicated by a number of confounding factors including development of multi-drug-resistant (MDR) strains to commonly used drugs, substantially long course of therapy, and lack of affordable cheap drugs in the cases involving patients suffering due to MDR tuberculosis [1–3]. The increasing problem of MDR-TB has focused attention on developing new drugs that are not only active against drug resistant TB, but also shorten the lengthy therapy [4]. In developing new TB drugs, it is crucial to think about which target in the tubercle bacillus are good targets. Several reviews on this topic are readily available [5,6]. Literature review shows that imidazole based compounds were reported to possess antimicrobial activities [7]. In recent years [8], the high therapeutic properties of the imidazole related drugs have been attracting the attention of medicinal chemists to synthesize a large number of novel chemotherapeutic agents. Medicinal properties of imidazole containing compounds include anticancer [9], antimicrobial [8,10–12], antioxidant [13,14], antiviral [15], antitubercular [16] activities. Keeping in view of the overall statistics, there is an urgent requirement of developing new drugs with a unique structure and different mechanism of action than the existing drug. The present study highlights the recently synthesized series of imidazole derivatives possessing important biological activities. In this communication, we describe the synthesis of *N*-(4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyphenyl)amide, *N*-(4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyphenyl)sulfonamide derivatives and evaluation of their in vitro antibacterial activity against three representative bacterial species viz., *Staphylococcus aureus*, (Gram-

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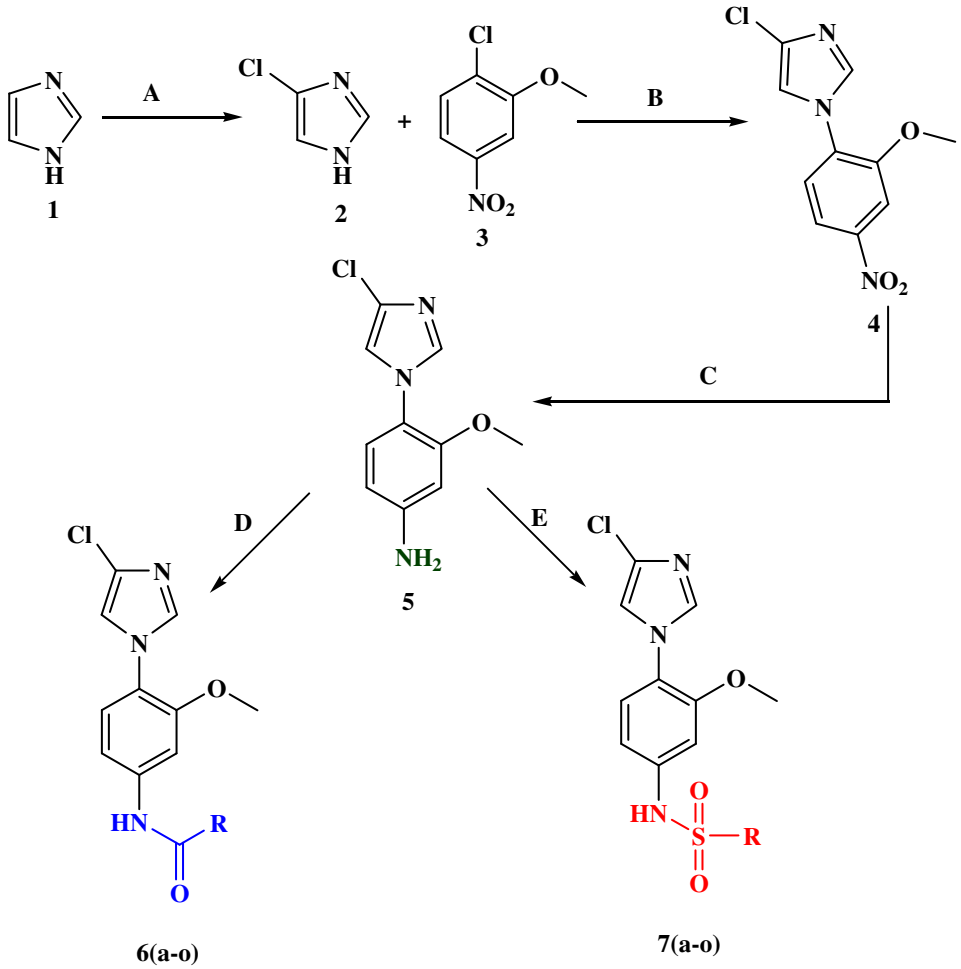
positive), *Escherichia coli* and *Klebsiella pneumoniae* (Gram-negative) using ciprofloxacin as reference and in vitro antifungal activity against three representative fungal species viz., *Candida albicans*, *Aspergillus flavus* and *Rhizopus* sp. using Amphotericin B as reference, In addition, the anti-tuberculosis activity against *M. tuberculosis* H37Rv ATCC 27294, and non-tubercular mycobacterial (NTM) species like *Mycobacterium smegmatis* (MC2) ATCC 19420, *Mycobacterium fortuitum* ATCC 19542 and MDR-TB strains were also carried out.

As a part of our research work on the development of useful synthetic molecules [17] and for new antitubercular agents [18] it has been planned to introduce 4-chloro substituted imidazole amides and sulfonamides. In this communication, we report the synthesis of newly designed *N*-(4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyphenyl)amide, *N*-(4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyphenyl)sulfonamide derivatives **6**(**a**–**o**) and **7**(**a**–**o**) (Scheme 1) and evaluated these compounds for the antimicrobial and antitubercular activities.

## 2. Results and discussion

### 2.1. Chemistry

The synthetic pathway that leads to the formation of the title compounds **6**(**a**–**o**) and **7**(**a**–**o**) are sketched in Scheme 1. 4-Chloroimidazole (**2**) was prepared by reacting simple imidazole with sodium hypochlorite and sodium hydroxide at ambient temperature. Microwave assisted palladium catalyzed Buchwald cross-coupling reactions were employed on the chloroimidazole, (**2**) with 1-chloro-2-methoxy-4-nitrobenzene (**3**) in dioxane at 120 °C. Palladium catalyst and different ligand combinations (Table 1) were tried in this step to find an appropriate catalyst that would enhance the coupling. Table 2 shows the different bases that were explored in order to find an effective base that would enhance the coupling yield. From the table it is clear that $Cs_2CO_3$ was found to be an effective base among all the bases explored. Among the solvents, dioxane (Table 3) was found to be a better choice and Table 3 shows the effect of solvents on the cyclization reactions. Surprisingly, $Pd_2(dba)_3$/RuPhos was found to give better conversions to product compared to other catalytic systems. The key intermediate (**5**) which is formed by reducing intermediate (**4**) by using $NH_4Cl$ in presence of Zinc powder in THF at ambient temperature. The title compounds **6**(**a**–**o**) were synthesized by coupling the key intermediate **5** with different substituted phenyl acids in presence of *N*-(3-dimethylaminopropyl)-*N*′-ethyl-carbodiimide hydrochloride (EDC·HCl) and hydroxybenzotriazole (HOBt) [19] in dichloromethane at ambient temperature. The title compounds **7**(**a**–**o**) were synthesized by coupling the key intermediate **5** with different substituted phenyl sulfonyl chlorides in presence of (EDC·HCl) and dimethylaminopyridine (DMAP) in dichloromethane at ambient temperature. The newly synthesized compounds were characterized by $^1$H NMR, $^{13}$C NMR and LCMS. The formation of 4-chloroimidazole (**2**) was confirmed by its $^1$H NMR spectrum where the disappearance of the doublet aromatic proton




**Scheme 1.** (A) NaOH, NaOCl, ambient temperature (B) $Pd_2(dba)_3$/RuPhos, dioxane, microwave, $Cs_2CO_3$, 120 °C (C) Zn, $NH_4Cl$, THF, ambient temperature (D) RCOOH, EDCl, HOBt, TEA, Dichloromethane, ambient temperature (E) $RSO_2Cl$, EDCl, DMAP, dichloromethane, ambient temperature.

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**Table 1**
Effect of catalyst on the Buchwald coupling of **2** and **3**.[a]

| Entry | Ligand | % Yield[b] |
|---|---|---|
| **1** | $PPh_3$ | Traces |
| **2** | Xanthphos | Traces |
| **3** | X-Phos | 25 |
| **4** | S-Phos | 45 |
| **5** | RuPhos | 60 |

[a] Reaction conditions: Intermediate **2** (0.01 mol), Intermediate **3** (0.011 mol), $K_3PO_4$ (0.02 mol), $Pd_2(dba)_3$ (5 mol %), Ligand (10 mol%), DMF. microwave irradiated at 120 °C for 30 min.
[b] Isolated yield after column purification.

**Table 3**
Effect of solvent on Buchwald coupling of **2** and **3**.[a]

| Entry | Solvent | % Yield |
|---|---|---|
| 1 | Toluene | 21 |
| 2 | THF | 39 |
| 3 | DME | 32 |
| 4 | DMF | 62 |
| 5 | Dioxane | 79 |

[a] *Reaction conditions*: Intermediate **2** (0.01 mol), intermediate **3** (0.011 mol), $Cs_2CO_3$ (0.02 mol), $Pd_2(dba)_3$ (5 mol %), RuPhos (10 mol%), solvent, microwave irradiated at 120 °C for 30 min.

peak at δ7.21 ppm. The formation of intermediate **4** [20] was confirmed by the disappearance of −NH peak at δ12.42 ppm and was also evidenced by LCMS spectral data. The formation of the key intermediate **5** was confirmed by its $^1$H NMR spectrum. In its spectrum appearance of singlet ($-NH_2$) peak at δ 5.47 ppm and was also evidenced by LCMS spectral data. The title compound formation was confirmed by its $^1$H NMR spectrum, where the absence of $NH_2$ proton at δ 5.47 ppm and was also evidenced by its LCMS spectral data. The spectral data is discussed in experimental section and the characterization data of **6**(**a**–**o**) and **7**(**a**–**o**) are tabulated in Table 4.

### 2.2. Structure activity relationship

In this study we have mainly concentrated at the region 2 (Fig. 1) of the synthesized molecules. When we screened an in house collection of compounds for antibacterial activity, sulfonamide derivative (**7l**) was identified as a moderate inhibitor to the tested organisms. Surprisingly the amide derivative (**6l**) showed less activity against the tested organisms. In view of its novel structural template we were interested to study further SAR of the related class of compounds. Thus with compound **7l** as the starting point, we developed a novel series of imidazole derivatives and investigated their biological actions as potential antimicrobial and antitubercular agents. Lipophilicity of compounds plays a major part in studying the biological activity of a compound [21,22]. These properties are seen as an important parameter related to membrane permeation in biological system. It has been well established that halogenated and particularly $CF_3$ substituted molecules have got a significant place in modern medicinal chemistry [23,24]. The $-NH_2$ group of the key intermediate was coupled with different carboxylic acids and sulfonyl chlorides which lead to the formation of amide and sulfonamide respectively. Biological results indicate that compound **7d**, **7f** and **7h** displayed good activity and this might be due to the presence of halogen and $-CF_3$ group attached to the aryl ring increases the lipophilic nature of the compound, there by making the molecule more cell permeable. One of the other reasons could be the sulfonamide group present in the molecule. The biological results indicated that the sulfonamide derivatives with electron withdrawing group at the ring at the region 2 of the molecules were more active (**7a**, **7d**, **7f**, **7g** and **7h**), where as amide derivatives with electron withdrawing group at the ring at the region 2 of the molecules were less active (**6a**, **6d**, **6f**, **6g**, **6h** and **6n**). On the other hand benzyl substituted sulfonamides (**7b** and **7k**) at the region 2 of the molecule showed less activity, which shows aromatic ring which is directly attached to the sulfonamide group are more active. Surprisingly electron donating substituent at the region 2 reduces the activity (**7e**, **7m** and **7o**). For instance, after methyl substitution at the region 2 the activity has been lowered for compound **7i** compared to compound **7d**. Furthermore biological results showed that the heterocyclic substitution at the region 2 of the molecule (**7c** and **7j**) is slightly active. The SAR studies of the synthesized molecules show that sulfonamide linkage at the region 2 of the molecule is more active than amide linkage at the region 2 and electron withdrawing substituent at the region 2 of the sulfonamide derivatives are more active. Electron donating substituent at the region 2 of the sulfonamide derivatives decreases the activity.

**Table 2**
Effect of base on the Buchwald coupling of **2** and **3**.[a]

| Entry | Base | % Yield |
|---|---|---|
| 1 | $CH_3COOK$ | NR |
| 2 | $Na_2CO_3$ | NR |
| 3 | $K_2CO_3$ | 57 |
| 4 | $Cs_2CO_3$ | 62 |

[a] *Reaction conditions*: Intermediate **2** (0.01 mol), Intermediate **3** (0.011 mol), base (0.02 mol), $Pd_2(dba)_3$ (5 mol%), RuPhos (10 mol%), DMF, microwave irradiated at 120 °C for 30 min.

From the obtained results (Table 5), it has been noticed that tested compounds exhibited moderate to good inhibition (4–256 μg/mL in DMSO) against the tested two Gram-negative and one Gram-positive bacteria except **6c**, **6e**, **6h**, and **6m** against *S. aureus*, **6e**, **6g**, **6i**, **6n**, **6o** and **7e** against *E. coli* and **6a**, **6c**, **6n** and **7c** against *K. pneumoniae*. Some of the compounds exhibited significant activity against *S. aureus* as exemplified by compounds **7a**, **7b**, **7d**, **7f**, **7g**, **7h** and **7l**. Surprisingly, the inhibitory activity of the compound **7b**, **7d**, **7f** and **7h** against *S. aureus*, exhibiting MIC value about one fold times lower than the reference Ciprofloxacin. Similarly, the inhibitory activity of the compound **7a**, **7d** and **7h** against *E. coli* were found to be same as that of reference. The inhibitory activity of the compounds **7d** and **7f** and **7h** against *Klebsiella pneumonia* exhibiting MIC value about one fold times and the compound **7b** exhibiting MIC value about two fold times lower than the reference Ciprofloxacin. Investigation of antifungal screening data has shown that few of the compounds produced considerable and varied results. It is apparent from Table 5 compounds **6e**, **6i**, **6k** and **6n** failed to exert activity against all the three pathogenic strains at MIC 256 μg/ml except **6b** and **6g** against *C. albicans* (for which MIC was noticed at 128 μg/ml) and **6c**, **6m** and **7e** against *A. flavus* (for which MIC was noticed at 128 μg/ml). Thus against *C. albicans* compounds **7d**, **7f** and **7h** and against *A. flavus* compound **7d** showed equivalent potency in comparison with reference Amphotericin B, whilst all other compounds exhibited MIC between 16 and 256 μg/ml. Although compounds **6b**, **6c**, **6e**, **6g**, **6i**, **6k**, **6m**, **6n**, **7c**, **7e**, **7g**, **7i** and **7o** did not exert antifungal activity against *Rhizopus* sp. up to 256 μg/ml, interestingly compounds **7d**, **7f** and **7h** exhibited the same potency (MIC 16 μg/ml) compared to the reference drug. Further, the preliminary antimycobacterial screening of the title compounds were carried out at 1, 10 and 100 μg/mL concentrations against three different TB strains and also against MDR-TB strain. From the result, it was noticed that the compounds **6a**, **6b**, **6d**, **6f**, **6g**, **6j**, **6k**, **7c**, **7d**, **7f**, **7g**, **7h**, **7j**, **7l** and **7n** were active between 1 and 10 μg/mL concentrations against *M. tuberculosis* H37Rv strain. The active compounds from the preliminary investigation were further subjected to second level of

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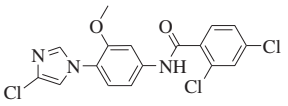
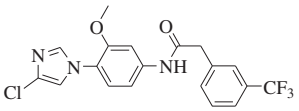
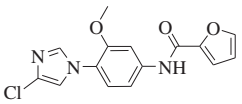
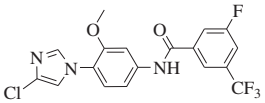
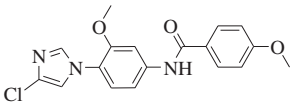
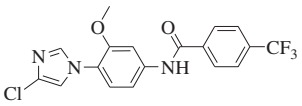
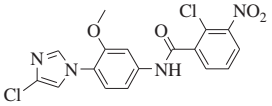
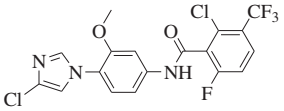
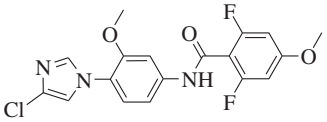
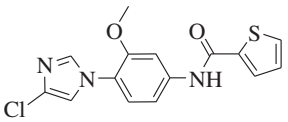
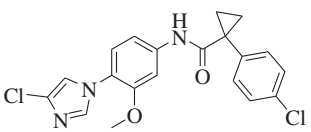
**Table 4**
Characterization data of synthesized compounds **6**(**a**–**o**) and **7**(**a**–**o**).

| Compound | Structure | Mol. formula<br>M. wt | M.P. °C | Yield[a] (%) |
|---|---|---|---|---|
| **6a** |  | $C_{17}H_{12}Cl_3N_3O_2$<br>396.7 | 178–180 | 84 |
| **6b** |  | $C_{19}H_{15}ClF_3N_3O_2$<br>409.8 | 164–166 | 89 |
| **6c** |  | $C_{15}H_{12}ClN_3O_3$<br>317.7 | ND | 85 |
| **6d** |  | $C_{18}H_{12}ClF_4N_3O_2$<br>413.8 | 180–182 | 80 |
| **6e** |  | $C_{18}H_{16}ClN_3O_3$<br>357.8 | 173–175 | 90 |
| **6f** |  | $C_{18}H_{13}ClF_3N_3O_2$<br>395.8 | 162–164 | 72 |
| **6g** |  | $C_{17}H_{12}Cl_2N_4O_4$<br>407.2 | 208–210 | 63 |
| **6h** |  | $C_{18}H_{11}Cl_2F_4N_3O_2$<br>448.2 | 182–184 | 68 |
| **6i** |  | $C_{18}H_{14}ClF_2N_3O_3$<br>393.8 | ND | 62 |
| **6j** |  | $C_{15}H_{12}ClN_3O_2S$<br>333.8 | 196–198 | 81 |
| **6k** |  | $C_{20}H_{17}Cl_2N_3O_2$<br>402.3 | ND | 68 |

(*continued on next page*)

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**Table 4** (*continued*)

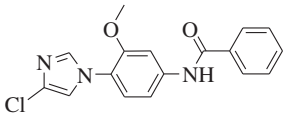
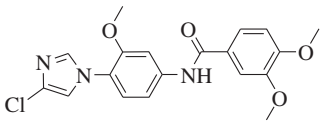
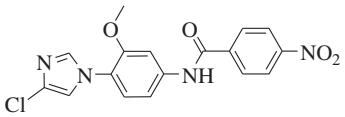
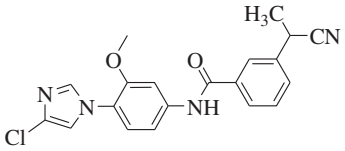
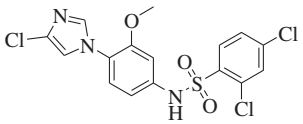
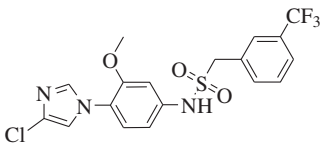
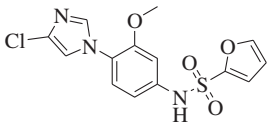
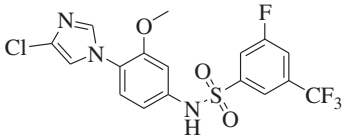
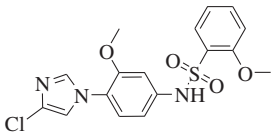
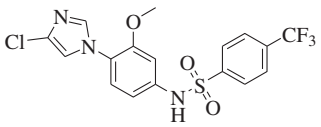
| Compound | Structure | Mol. formula<br>M. wt | M.P. °C | Yield[a] (%) |
|---|---|---|---|---|
| **6l** |  | $C_{17}H_{14}ClN_3O_2$<br>327.8 | 169–171 | 68 |
| **6m** |  | $C_{19}H_{18}ClN_3O_4$<br>387.8 | 173–175 | 85 |
| **6n** |  | $C_{17}H_{13}ClN_4O_4$<br>372.8 | 216–218 | 62 |
| **6o** |  | $C_{20}H_{17}ClN_4O_2$<br>380.8 | ND | 59 |
| **7a** |  | $C_{16}H_{12}Cl_3N_3O_3S$<br>432.7 | 149–151 | 84 |
| **7b** |  | $C_{18}H_{15}ClF_3N_3O_3S$<br>445.8 | ND | 80 |
| **7c** |  | $C_{14}H\ ClN_3O_4S$<br>353.8 | ND | 76 |
| **7d** |  | $C_{17}H_{12}ClF_4N_3O_3S$<br>449.8 | ND | 72 |
| **7e** |  | $C_{17}H_{16}ClN_3O_4S$<br>393.8 | ND | 82 |
| **7f** |  | $C_{17}H_{13}ClF_3N_3O_3S$<br>431.8 | ND | 70 |

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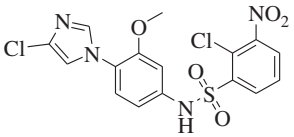
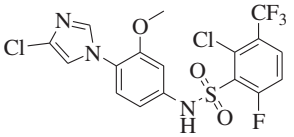
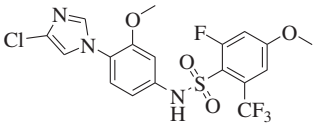
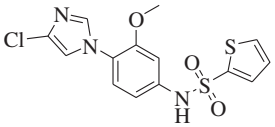
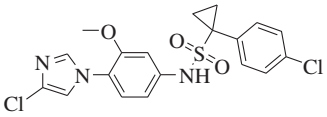
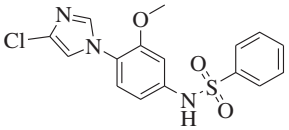
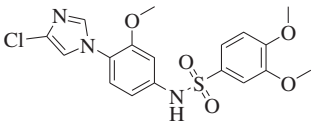
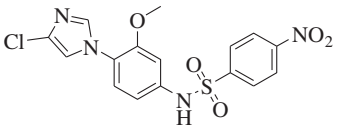
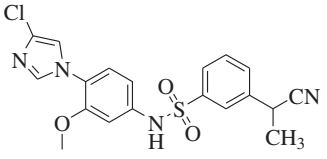
**Table 4** (*continued*)

| Compound | Structure | Mol. formula<br>M. wt | M.P. °C | Yield[a] (%) |
|---|---|---|---|---|
| **7g** |  | $C_{16}H_{12}Cl_2N_4O_5S$<br>443.3 | 192–194 | 84 |
| **7h** |  | $C_{17}H_{11}C_{l2}F_4N_3O_3S$<br>484.3 | 154–156 | 73 |
| **7i** |  | $C_{18}H_{14}ClF_4N_3O_4S$<br>479.8 | ND | 70 |
| **7j** |  | $C_{14}H_{12}ClN_3O_3S_2$<br>369.8 | 142–144 | 68 |
| **7k** |  | $C_{19}H_{17}Cl_2N_3O_3S$<br>438.3 | ND | 62 |
| **7l** |  | $C_{16}H_{14}ClN_3O_3S$<br>363.8 | 138–140 | 66 |
| **7m** |  | $C_{18}H_{18}ClN_3O_5S$<br>423.9 | 144–146 | 64 |
| **7n** |  | $C_{16}H_{13}ClN_4O_5S$<br>408.8 | 184–186 | 79 |
| **7o** |  | $C_{19}H_{17}ClN_4O_3S$<br>416.9 | ND | 74 |

[a] Isolated yield after column chromatography.

testing. The compounds which were active at 100 μg/mL concentration were not taken for further studies. The second level testing was carried out at concentrations 0.3125, 0.625, 1.25, 2.5, and 5 μg/mL. Amongst the tested compounds **7d**, **7f**, **7h** and **7n** are active at 0.625 μg/mL concentrations against *M. tuberculosis* H37Rv strain and compounds **6f**, **6g**, **6n**, **7b**, **7e**, **7j**, **7k** and **7m** are active at 1.25 μg/mL concentrations. Similarly the target molecules **6g**, **6j**, **7e**, **7f**, **7h**, **7j** and **7m** displayed significant activity at 1.25 μg/mL against *M. smegmatis* (ATCC 19420). It is interesting to note that most of the compounds showed either enhanced activity or activity in line with the reference compound isoniazid against *M. fortuitum* (ATCC 19542). Further, the compounds **7d**, **7f**, **7h** and **7n** showed promising

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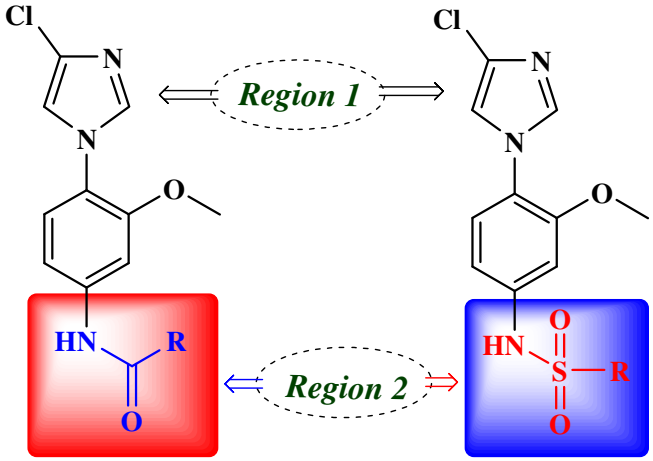


**Fig. 1.** Selected regions for the study.

activity against the MDR-TB strain at 6.25 μg/mL. These are just initial screening results to check the antimicrobial potential, since this is established and further work would be done to understand their mechanism of action.

### 2.3. Pharmacology

Antimycobacterial activity of the synthesized compounds **6**(**a**–**o**) and **7**(**a**–**o**) were evaluated against M. tuberculosis-H37Rv and non-tubercular mycobacterial (NTM) species by Resazurin Assay method. Antibacterial and antifungal activities of the synthesized compounds **6**(**a**–**o**) and **7**(**a**–**o**) were assessed in vitro against each three-representative bacterial species viz., *S. aureus*, (Gram-positive), *E. coli* and *K. pneumoniae* (Gram-negative) and fungal species viz., *C. albicans*, *A. flavus* and *Rhizopus* sp. by serial plate dilution method. Ciprofloxacin and Amphotericin B were used as positive controls for bacteria and fungi respectively while the solvent, dimethylsulfoxide (DMSO) served as negative control. DMSO used for the preparation of compounds did not show inhibition against the tested organisms. Table 5 displays antimicrobial activity of final compounds **6**(**a**–**o**) and **7**(**a**–**o**) in terms of minimum inhibitory concentrations (MIC in μg/ml). Based on the encouraging results from the antibacterial screening, title compounds were further tested for their in vitro antimycobacterial activity against *M. tuberculosis H37Rv*, *M. smegmatis* (ATCC 19420), *M. fortuitum* (ATCC 19542) and *MDR-TB* strains using isoniazid and rifampicin as standards. The screening results of in vitro antimycobacterial activity of the final compounds are tabulated in Table 6.

**Table 5**
Antimicrobial activity data of the synthesized compounds **6**(**a**–**o**) and **7**(**a**–**o**).

| Entry | Minimum inhibitory concentration (MIC in μg/mL)[a] | | | | | |
|---|---|---|---|---|---|---|
| | Bacterial strains | | | Fungal strains | | |
| | *S. aureus* | *E. coli* | *K. pneumoniae* | *C. albicans* | *A. flavus* | *Rhizopus* sp. |
| **6a** | 128 | 64 | >256 | >256 | 128 | 128 |
| **6b** | 128 | 256 | 64 | 128 | 256 | >256 |
| **6c** | >256 | 128 | >256 | >256 | 128 | >256 |
| **6d** | 128 | 128 | 64 | 64 | 256 | 128 |
| **6e** | >256 | >256 | 256 | >256 | 256 | >256 |
| **6f** | 128 | 64 | 64 | 32 | 128 | 64 |
| **6g** | 128 | >256 | 128 | 128 | 256 | >256 |
| **6h** | >256 | 128 | 256 | 128 | >256 | 128 |
| **6i** | 256 | >256 | 128 | 256 | 256 | >256 |
| **6j** | 128 | 128 | 64 | 256 | 64 | 32 |
| **6k** | 64 | 128 | 256 | >256 | 256 | >256 |
| **6l** | 128 | 256 | 128 | 256 | 256 | 128 |
| **6m** | >256 | 256 | 256 | >256 | 128 | 256 |
| **6n** | 256 | >256 | >256 | >256 | >256 | 256 |
| **6o** | 256 | >256 | 128 | 128 | 256 | 128 |
| **7a** | 8 | 4 | 64 | 128 | 64 | 128 |
| **7b** | 4 | 64 | 4 | 64 | 32 | 128 |
| **7c** | 128 | 64 | >256 | 128 | 64 | 256 |
| **7d** | 4 | 4 | 8 | 8 | 8 | 16 |
| **7e** | 128 | >256 | 128 | 256 | 128 | >256 |
| **7f** | 4 | 16 | 8 | 8 | 16 | 16 |
| **7g** | 8 | 128 | 32 | 64 | 128 | 256 |
| **7h** | 4 | 4 | 8 | 8 | 16 | 16 |
| **7i** | 64 | 128 | 32 | 128 | 128 | 256 |
| **7j** | 128 | 64 | 256 | 64 | 256 | 128 |
| **7k** | 128 | 64 | 128 | 128 | 64 | 128 |
| **7l** | 8 | 64 | 128 | 128 | 128 | 64 |
| **7m** | 256 | 128 | 256 | 128 | 256 | 128 |
| **7n** | 128 | 128 | 64 | 256 | 128 | 64 |
| **7o** | 64 | 128 | 64 | 64 | 128 | 256 |
| **Cfn** | 8 | 4 | 16 | – | – | – |
| **Am B** | – | – | – | 8 | 8 | 16 |

[a] MIC values were evaluated at concentration ranging between 4 and 256 μg/mL. The figures in the table show the MIC values in μg/mL; MIC (μg/mL) = minimum inhibitory concentration, i.e., lowest concentration to completely inhibit bacterial growth.

## 3. Conclusion

We herein report the successful synthesis of *N*-(4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyphenyl)amide, *N*-(4-(4-chloro-1*H*-imidazol-1-yl)-3-methoxyphenyl)sulfonamide derivatives **6**(**a**–**o**) and **7**(**a**–**o**). They have been characterized by spectral studies. The

**Table 6**
Antitubercular activity data of the synthesized compounds **6**(**a**–**o**) and **7**(**a**–**o**).

| Compound | Preliminary in vitro screening results, MIC (μg/mL) | | | | Second level screening results, MIC (μg/mL) | | | |
|---|---|---|---|---|---|---|---|---|
| | MTB[a] | MS[b] | MF[c] | %[d] | MTB | MS | MF | MDR-TB |
| **6a** | 10 | 10 | >100 | <90 | 5 | 10 | – | 25 |
| **6b** | 10 | 10 | 10 | <90 | 2.5 | 10 | 10 | >50 |
| **6c** | >100 | 10 | >100 | <90 | 5 | – | – | >50 |
| **6d** | 10 | >100 | 10 | 90 | 10 | – | 10 | >50 |
| **6e** | >100 | >100 | >100 | 0 | – | – | – | – |
| **6f** | 1 | 1 | 10 | 90 | 1.25 | 2.5 | 1.25 | >50 |
| **6g** | 1 | 1 | 10 | 90 | 1.25 | 1.25 | 1.25 | >50 |
| **6h** | 10 | 10 | >100 | <90 | 2.5 | 2.5 | – | 25 |
| **6i** | >100 | 10 | >100 | <90 | 5 | – | – | >50 |
| **6j** | 1 | 1 | 10 | 90 | 5.0 | 1.25 | 2.5 | >50 |
| **6k** | 10 | 10 | >100 | <90 | 2.5 | 2.5 | – | 25 |
| **6l** | >100 | >100 | 10 | <90 | 5 | 10 | – | 25 |
| **6m** | >100 | >100 | >100 | 0 | – | – | – | – |
| **6n** | >100 | 10 | >100 | <90 | 1.25 | 2.5 | 1.25 | >50 |
| **6o** | >100 | 10 | 10 | 90 | 2.5 | – | 10 | >50 |
| **7a** | >100 | 10 | >100 | <90 | 5 | – | – | >50 |
| **7b** | >100 | 10 | 10 | 90 | 1.25 | – | 10 | >50 |
| **7c** | 10 | 10 | >100 | <90 | 5 | 10 | – | 25 |
| **7d** | 1 | 10 | 10 | 95 | 0.625 | 10 | 10 | 6.25 |
| **7e** | >100 | 1 | 10 | 90 | 1.25 | 1.25 | 1.25 | >50 |
| **7f** | 1 | 1 | 10 | 95 | 0.625 | 1.25 | 10 | 6.25 |
| **7g** | 10 | 10 | 1 | <90 | 2.5 | 2.5 | – | 25 |
| **7h** | 1 | 1 | 10 | 90 | 0.625 | 1.25 | 10 | 6.25 |
| **7i** | >100 | 10 | >100 | <90 | 5 | 10 | – | 25 |
| **7j** | 1 | 1 | 10 | 90 | 1.25 | 1.25 | 1.25 | >50 |
| **7k** | >100 | 10 | 10 | 90 | 1.25 | – | 10 | >50 |
| **7l** | 10 | 10 | >100 | <90 | 5 | 10 | – | 25 |
| **7m** | >100 | 1 | 10 | 90 | 1.25 | 1.25 | 1.25 | >50 |
| **7n** | 1 | 1 | 10 | 90 | 0.625 | 10 | 1.25 | 6.25 |
| **7o** | >100 | 10 | 1 | <90 | 2.5 | 2.5 | – | 25 |
| Isoniazid | 0.7 | 50 | 12.5 | 95 | 0.7 | 50 | 12.5 | 12.5 |
| Rifampicin | 0.5 | 1.5 | 1.5 | 95 | 0.5 | 1.5 | 1.5 | 25 |

'–' Not detected.
[a] *Mycobacterium tuberculosis* H37Rv.
[b] *Mycobacterium smegmatis* (ATCC 19420).
[c] *Mycobacterium fortuitum* (ATCC 19542).
[d] Percentage of inhibition against *M. tuberculosis* H37Rv.

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preparation of the key intermediate highlights an optimized palladium catalyzed (Fig. 2) ($Pd_2(dba)_3$/RuPhos) Buchwald cross-coupling of 4-chloroimidazole and 1-chloro-2-methoxy-4-nitrobenzene. All the title compounds have been investigated for their antibacterial and antimycobacterial activities, the investigation of antibacterial screening revealed that all the newly synthesizes compounds showed moderate to good inhibition at 4–256 μg/mL in DMSO. Compounds **7d**, **7f** and **7h** exhibited comparatively good activity against the tested bacterial strains. Further, the compounds **7d**, **7f**, **7h** and **7n** displayed significant activity against *M. tuberculosis* H37Rv strain. Furthermore, the target molecules **6g**, **6j**, **7e**, **7f**, **7h**, **7j** and **7m** displayed significant activity at 1.25 μg/mL against *M. smegmatis* (ATCC 19420). Similarly the compounds **7d**, **7f**, **7h** and **7n** showed substantial activity against the MDR-TB strain at 6.25 μg/mL. The halogen and trifluoro substituted aromatic compounds will improve the lipophilic nature of the compound at the same time methyl or methoxy substituted compound would act as an electron donors. In addition the presence of a sulfonamide group would be the essential element for the enhanced activity of the synthesized compounds. The above mentioned properties of these pharmacophores would be responsible for the promising activities of the title compounds. The scaffold synthesized in the research work can be taken for further derivatization in order to find the lead in these series.

## 4. Experimental

### 4.1. General

All reagents were purchased from Aldrich. Solvents used were extra dried. Final purifications were carried out using Quad biotage Flash purifier (A Dyax corp. Company). Microwave-assisted syntheses were performed in Biotage initiator. TLC experiments were performed on alumina backed silica gel 40 F254 plates (Merck, Darmstadt, Germany). The plates were illuminated under UV (254 nm) and molesybidinic acid. All $^1H$ and $^{13}C$ NMR spectra were recorded on a Bruker AM-300 (300.12 MHz) and AM-400 (400.13 MHz), Bruker Biospin Corp., Germany. Molecular weights of unknown compounds were checked by LCMS 6200 series Agilent Technology. Chemical shifts are reported in ppm ($\delta$) with reference to internal standard TMS. The signals are designated as follows: s, singlet; d, doublet; t, triplet; m, multiplet.

### 4.2. Procedure for the preparation of 4-chloroimidazole (**2**)

Imidazole (10 g, 0.150 mol) and sodium hydroxide (29.4 g, 0.74 mol) were charged to the reaction flask containing water (250 mL) and stirred vigorously for 15 min at ambient temperature. Cooled the reaction mass to 10 °C and charged sodium hypochlorite (16.7 g, 0.225 mol) to the reaction mixture, during the addition temperature was maintained at 10 °C. Stirred the reaction mass for 6 h at ambient temperature, the reaction completion was monitored by TLC. After the completion of the reaction cooled the reaction mass to 10 °C and slowly charged concentrated HCl solution to bring the reaction pH to 6 to 7. Charged dichloromethane (2 × 200 mL) and stirred for 10 min, separated the organic layer and was washed with saturated brine solution. The organic layer was dried over sodium sulfate and concentrated the dichloromethane and the crude obtained was purified by column chromatography on a silica gel (230–400 mesh) using ethyl acetate (10–35%) in petroleum ether as eluant to afford 4-chloroimidazole.

Appearance: Pale yellow solid; Yield = 52%; M.P. = 118–119 °C; $^1H$ NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm = 7.09 (s, 1H, ArH), 7.39 (s, 1H, ArH), 12.42 (s, 1H, NH); $^{13}C$ NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm = 126.7, 128.2, 140.2; LC/MS (ESI-MS) $m/z$ = 103.6 (M + 1).

### 4.3. Procedure for the preparation of 4-chloro-1-(2-methoxy-4-nitrophenyl)-1H-imidazole (**4**)

4-Chloroimidazole (1.0 g, 0.01 mol), in dioxane (15 mL) was added $Pd_2(dba)_3$ (5 mol%), RuPhos (10 mol%). The solution was purged with nitrogen and stirred at room temperature for 5 min and 1-chloro-2-methoxy-4-nitrobenzene (2.0 g, 0.011 mol), $Cs_2CO_3$ (0.02 mol), were added. The reaction mixture was again purged with nitrogen and heated in the microwave at 120 °C for 30 min. Reaction was monitored by TLC. After the completion, reaction mixture was cooled to room temperature and water was added to the reaction mixture. It was then extracted with ethyl acetate (25 mL × 2) and separated organic layer was dried over $Na_2SO_4$.

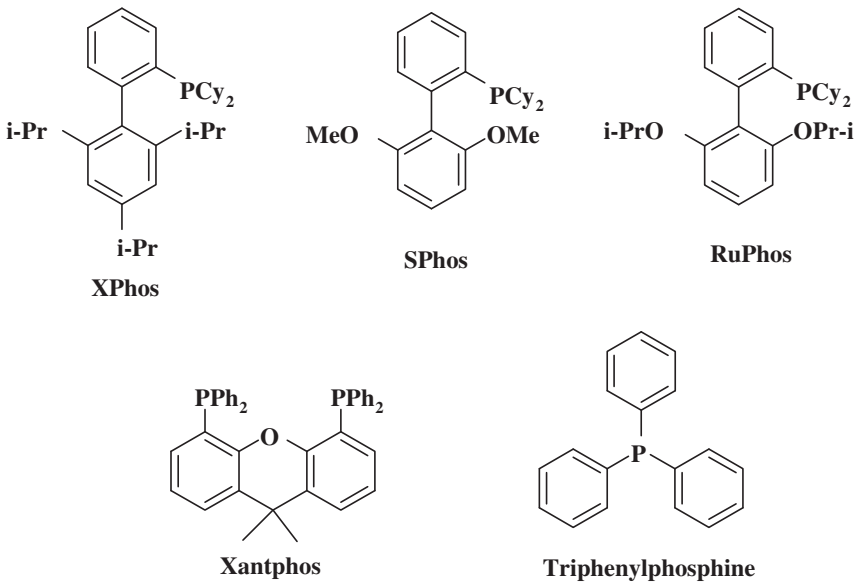


**Fig. 2.** Structures of ligands used for the Buchwald coupling.

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Organic layer was filtered and concentrated under vacuum, and the residue was purified by flash column chromatography on silica gel.

Appearance: Off white solid; yield = 79%; M.P. = 251–252 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm = 3.83 (s, 3H, $CH_3$), 7.34 (d, 1H, ArH), 7.48 (s, 1H, ArH), 7.59 (d, 1H, ArH), 7.72 (s, 1H, ArH), 7.83 (s, 1H, ArH); $^{13}$C NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm = 55.9, 113.5, 117.8, 125.9, 126.4. 127.6, 131.8, 136.4, 148.7, 152.3; LC/MS (ESI-MS) $m/z$ = 254.7 (M + 1).

### 4.4. Procedure for the preparation of 4-(4-chloro-1H-imidazol-1-yl)-3-methoxy benzenamine (**5**)

The intermediate 4-chloro-1-(2-methoxy-4-nitrophenyl)-1*H*-imidazole (1.0 g, 0.004 mol), $NH_4Cl$ (0.42 g, 0.008 mol) and Zinc powder (0.25 g, 0.008 mol) in methanol (15 mL) were stirred at ambient temperature and stirred for 12 h. Reaction completion was monitored by TLC. After completion, reaction mass was filtered through celite. The filtrate concentrated under reduced pressure. The crude obtained was dissolved in ethyl acetate (25 mL) and the organic layer was washed with water (2 × 20 mL). The organic layer was dried over sodium sulfate and concentrated under reduced pressure to afford (**5**) an off white solid. Appearance: Off white solid; M.P. = 219–221 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm = 3.70 (s, 3H, $CH_3$), 5.47 (s, 2H, $NH_2$), 6.19 (d, 1H, ArH), 6.38 (s, 1H, ArH), 6.99 (d, 1H, ArH), 7.32 (s, 1H, ArH), 7.64 (s, 1H, ArH); $^{13}$C NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm = 54.7, 101.2, 101.7, 108.2, 113.2, 120.6, 124.2, 127.8, 132.9, 142.4, 146.8; LC/MS (ESI-MS) $m/z$ = 224.9 (M + 1).

### 4.5. General procedure for the preparation of compounds **6**(**a**–**o**)

A mixture of phenyl acid (0.001 mol), EDCl (0.003 mol), HOBt (0.002 mol), Triethylamine (0.006 mol) and dichloromethane (5.0 mL) was stirred vigorously for 10 min at ambient temperature. Then amine (**5**) (0.0022 mol) in dichloromethane was added slowly to the reaction mixture. The reaction mass was stirred at ambient temperature for 4 h. The reaction completion was monitored by TLC. After completion, the reaction mass was diluted with dichloromethane, washed with 10% $NaHCO_3$ (10 mL), brine solution. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified on a Biotage parallel column purifier using ethyl acetate: petroleum ether (3:1) as eluant to methanol: methylene chloride (2–6%). The spectral data of compounds **6**(**a**–**o**) are given below.

#### 4.5.1. 2,4-Dichloro-N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)benzamide (**6a**)

Appearance: off white solid; M.P. = 178–180 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm = 3.74 (s, 3H, $CH_3$), 6.75 (d, 1H, ArH), 6.82 (d, 1H, ArH), 6.94 (s, 1H, ArH), 7.55 (s, 1H, ArH), 7.61 (s, 1H, ArH), 7.77 (d, 1H, ArH), 7.98 (s, 1H, ArH), 8.05 (d, 1H, ArH), 11.01 (s, 1H, NH); $^{13}$C NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm = 54.7, 103.2, 112.6, 117.9, 120.9, 123.8, 124.7, 127.1, 130.3, 130.9, 131.6, 134.2, 136.8, 139.5, 151.3, 165.9; LC/MS (ESI-MS) $m/z$ = 397.8 (M + 1).

#### 4.5.2. N-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-2-(3-(trifluoromethyl)phenyl) acetamide (**6b**)

Appearance: brown solid; M.P. = 164–166 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm = 3.28 (s, 2H, $CH_2$), 3.85 (s, 3H, $CH_3$), 7.44 (s, 1H, ArH), 7.49 (d, 2H, ArH), 7.55 (s, 1H, ArH), 7.73 (s, 1H, ArH), 7.88 (s, 1H, ArH), 7.92 (m, 3H, ArH), 10.72 (s, 1H, NH); $^{13}$C NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm = 38.2, 54.7, 103.2, 112.6, 117.9, 120.9, 123.8, 124.1, 124.5, 124.7, 128.2, 129.1, 131.0, 131.6, 135.7, 137.2, 139.5, 151.3, 168.4; LC/MS (ESI-MS) $m/z$ = 410.7 (M + 1).

#### 4.5.3. N-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)furan-2-carboxamide (**6c**)

Appearance: brown solid; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm = 3.73 (s, 3H, $CH_3$), 7.14 (d, 1H, ArH), 7.23 (d, 1H, ArH), 7.58 (s, 1H, ArH), 7.62 (t, 1H, ArH), 7.75 (s, 1H, ArH), 7.88 (s, 1H, ArH), 7.96 (d, 1H, ArH), 8.12 (d, 1H, ArH), 10.84 (s, 1H, NH); $^{13}$C NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm = 54.7, 103.2, 110.9, 112.6, 114.8, 117.9, 120.9, 123.8, 124.7, 131.6, 139.5, 144.2, 148.5, 151.3, 164.6; LC/MS (ESI-MS) $m/z$ = 319.0 (M + 1).

#### 4.5.4. N-((4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-3-fluoro-5-trifluoromethyl) benzamide (**6d**)

Appearance: brown solid; M.P. = 180–182 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm = 3.85 (s, 3H, $CH_3$), 7.44 (s, 1H, ArH), 7.49 (d, 2H, ArH), 7.55 (s, 1H, ArH), 7.73 (s, 1H, ArH), 7.88 (s, 1H, ArH), 8.02 (s, 1H, ArH), 8.17 (s, 1H, ArH), 10.72 (s, 1H, NH); $^{13}$C NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm = 54.7, 103.2, 112.6, 115.2, 116.2, 117.9, 119.0, 120.9, 122.2, 123.8, 124.7, 131.6, 134.6, 137.5, 139.5, 151.3, 164.7, 165.9; LC/MS (ESI-MS) $m/z$ = 415.0 (M + 1).

#### 4.5.5. N-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-methoxybenzamide (**6e**)

Appearance: gray solid; M.P. = 173–175 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm = 2.43 (s, 3H, $CH_3$), 3.67 (s, 3H, $CH_3$), 6.78 (s, 1H, ArH), 6.88 (d, 1H, ArH), 6.99 (d, 1H, ArH), 7.41 (s, 1H, ArH), 7.50 (s, 1H, ArH), 7.61 (d, 2H, ArH), 7.70 (s, 1H, ArH), 10.94 (s, 1H, NH); $^{13}$C NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm = 54.7, 61.3, 103.2, 112.6, 115.2, 117.9, 120.9, 123.8, 124.7, 125.6, 129.5, 131.6, 139.5, 151.3, 162.8, 165.9; LC/MS (ESI-MS) $m/z$ = 358.9 (M + 1).

#### 4.5.6. N-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(trifluoromethyl)benzamide (**6f**)

Appearance: off white solid; M.P. = 162–164 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm = 3.70 (s, 3H, $CH_3$), 6.71 (d, 1H, ArH), 6.78 (d, 1H, ArH), 7.12 (s, 1H, ArH), 7.70 (s, 1H, ArH), 7.84 (s, 1H, ArH), 8.17 (d, 2H, ArH), 8.31 (d, 2H, ArH), 10.94 (s, 1H, NH); $^{13}$C NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm = 54.7, 103.2, 112.6, 117.9, 120.9, 123.8, 124.3, 124.7, 128.2, 128.9, 131.6, 135.6, 137.6, 139.5, 151.3, 167.9; LC/MS (ESI-MS) $m/z$ = 397.1 (M + 1).

#### 4.5.7. 2-Chloro-N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-3-nitrobenzamide (**6g**)

Appearance: yellow solid; M.P. = 208–201 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm = 3.91 (s, 3H, $CH_3$), 7.06 (m, 3H, ArH), 7.21 (d, 1H, ArH), 7.29 (d, 1H, ArH), 7.37 (s, 1H, ArH), 7.51 (s, 1H, ArH), 7.82 (s, 1H, ArH), 11.08 (s, 1H, NH); $^{13}$C NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm = 54.7, 103.2, 112.6, 117.9, 120.9, 123.8, 124.7, 126.4, 128.6, 129.1, 131.6, 136.0, 136.7, 139.5, 145.2, 151.3, 168.4; LC/MS (ESI-MS) $m/z$ = 408.5 (M + 1).

#### 4.5.8. 2-Chloro-N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-6-fluoro-3-(trifluoro methyl) benzamide (**6h**)

Appearance: white solid; M.P. = 182–184 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm = 3.87 (s, 3H, $CH_3$), 7.09 (d, 1H, ArH), 7.18 (s, 1H, ArH), 7.23 (d, 2H, ArH), 7.50 (d, 1H, ArH), 7.78 (s, 1H, ArH), 7.98 (s, 1H, ArH), 10.92 (s, 1H, NH); $^{13}$C NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm = 54.7, 103.2, 112.6, 113.6, 115.2, 117.9, 120.9, 121.6, 123.8, 124.7, 126.3, 127.9, 129.9, 131.6, 139.5, 151.3, 162.8, 165.9; LC/MS (ESI-MS) $m/z$ = 449.7 (M + 1).

#### 4.5.9. N-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-2,6-difluoro-4-methoxy benzamide (**6i**)

Appearance: semisolid; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm = 2.56 (s, 3H, $CH_3$), 3.67 (s, 3H, $CH_3$), 6.80 (s, 1H, ArH), 7.11 (d, 1H, ArH), 7.48 (s, 1H, ArH), 7.59 (s, 1H, ArH), 7.64 (d, 2H, ArH), 7.82

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(s, 1H, ArH), 11.08 (s, 1H, NH); $^{13}$C NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm = 54.7, 60.2, 94.6, 103.2, 107.4, 112.6, 117.9, 120.9, 123.8, 124.7, 131.6, 139.5, 151.3, 161.8, 165.2, 169.4; LC/MS (ESI-MS) $m/z$ = 395.1 (M + 1).

#### 4.5.10. N-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl) thiophene-2-carboxamide (**6j**)

Appearance: off white solid; M.P. = 196–198 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm = 3.81 (s, 3H, $CH_3$), 7.23 (d, 1H, ArH), 7.37 (d, 1H, ArH), 7.47 (s, 1H, ArH), 7.51 (t, 1H, ArH), 7.69 (s, 1H, ArH), 7.82 (s, 1H, ArH), 7.89 (d, 1H, ArH), 8.05 (d, 1H, ArH), 10.41 (s, 1H, NH); $^{13}$C NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm = 54.7, 103.2, 112.6, 117.9, 120.9, 123.8, 124.7, 129.3, 131.6, 134.4, 136.9, 138.5, 139.5, 151.3, 164.5; LC/MS (ESI-MS) $m/z$ = 335.2 (M + 1).

#### 4.5.11. N-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-1-(4-chlorophenyl) cyclo propanecarboxamide (**6k**)

Appearance: colorless oil; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm = 1.14 (t, 2H, $CH_2$), 1.47 (t, 2H, $CH_2$), 3.74 (s, 3H, $CH_3$), 7.39 (d, 2H, ArH), 7.46 (d, 4H, ArH), 7.51 (s, 1H, ArH), 7.77 (s, 1H, ArH), 7.79 (s, 1H, ArH), 10.99 (s, 1H, NH); $^{13}$C NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm = 14.2, 28.6, 54.7, 103.2, 112.6, 117.9, 120.9, 123.8, 124.7, 125.4, 128.6, 130.2, 131.6, 139.5, 144.6, 151.3, 170.1; LC/MS (ESI-MS) $m/z$ = 403.9 (M + 1).

#### 4.5.12. N-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl) benzamide (**6l**)

Appearance: white solid; M.P. = 169–171 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm = 3.74 (s, 3H, $CH_3$), 6.72 (s, 1H, ArH), 6.86 (d, 1H, ArH), 7.06 (d, 1H, ArH), 7.32 (s, 1H, ArH), 7.47 (s, 1H, ArH), 7.65 (d, 2H, ArH), 7.82 (s, 1H, ArH), 11.08 (s, 1H, NH); $^{13}$C NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm = 54.7, 103.2, 112.6, 117.9, 120.9, 123.8, 124.7, 127.5, 129.4, 131.6, 132.9, 135.8, 139.5, 151.3, 166.1; LC/MS (ESI-MS) $m/z$ = 329.2 (M + 1).

#### 4.5.13. N-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-3,4-dimethoxybenzamide (**6m**)

Appearance: brown solid; M.P. = 173–175 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm = 2.51 (s, 6H, $CH_3$), 3.69 (s, 3H, $CH_3$), 6.83 (s, 1H, ArH), 6.94 (d, 1H, ArH), 7.01 (d, 1H, ArH), 7.48 (s, 1H, ArH), 7.56 (s, 1H, ArH), 7.64 (d, 2H, ArH), 7.75 (s, 1H, ArH), 11.01 (s, 1H, NH); $^{13}$C NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm = 54.7, 63.2, 103.2, 112.6, 114.5, 115.6, 117.9, 120.9, 122.2, 123.8, 124.7, 128.9, 131.6, 139.5, 144.6, 151.3, 155.6, 166.8; LC/MS (ESI-MS) $m/z$ = 389.1 (M + 1).

#### 4.5.14. N-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-nitrobenzamide (**6n**)

Appearance: pale yellow solid; M.P. = 216–218 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm = 3.75 (s, 3H, $CH_3$), 6.76 (d, 1H, ArH), 6.82 (d, 1H, ArH), 6.98 (s, 1H, ArH), 7.62 (s, 1H, ArH), 7.71 (s, 1H, ArH), 8.00 (d, 2H, ArH), 8.10 (d, 2H, ArH), 11.07 (s, 1H, NH); $^{13}$C NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm = 54.7, 103.2, 112.6, 117.9, 120.9, 121.6, 123.8, 124.7, 126.8, 131.6, 139.5, 148.5, 151.3, 153.4, 166.9; LC/MS (ESI-MS) $m/z$ = 373.8 (M + 1).

#### 4.5.15. N-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-3-(1-cyanoethyl)benzamide (**6o**)

Appearance: yellow oil; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm = 1.62 (s, 3H, $CH_3$), 3.84 (s, 3H, $CH_3$), 4.45 (m, 1H, CH), 7.41 (d, 1H, ArH), 7.52 (d, 1H, ArH), 7.59 (s, 1H, ArH), 7.62 (s, 1H, ArH), 7.83 (m, 1H, ArH), 7.96 (d, 2H, ArH), 7.99 (s, 1H, ArH), 8.05 (s, 1H, ArH), 10.59 (s, 1H, NH); $^{13}$C NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm = 16.4, 25.8, 54.7, 103.2, 112.6, 117.9, 118.6, 120.9, 123.8, 124.7, 126.4, 128.4, 129.4, 130.4, 131.6, 133.5, 136.8, 139.5, 151.3, 168.5; LC/MS (ESI-MS) $m/z$ = 381.9 (M + 1).

### 4.6. General procedure for the preparation of **7**(**a**–**o**)

The intermediate (**5**) (0.002 mol), EDCl (0.0032 mol), DMAP (0.0028 mol) were stirred in dichloromethane (10 mL) at 0 °C, and the substituted sulfonyl chloride (0.002 mol) were dissolved in (4 mL) of dichloromethane and charged to the reaction mixture and stirred at ambient temperature for 6 h. The reaction completion was monitored by TLC. After completion, the reaction mixture was diluted with (10 mL) of dichloromethane, and was washed with 10% $NaHCO_3$ (10 mL). Separated the organic layer and was washed with saturated brine solution (10 mL). The organic layer was dried over sodium sulfate and concentrated the organic layer under reduced pressure. The crude obtained was recrystallized in ethyl acetate/hexane to afford compounds **7**(**a**–**o**). The spectral data of compounds **7**(**a**–**o**) are given below.

#### 4.6.1. 2,4-Dichloro-N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)benzene sulfonamide (**7a**)

Appearance: white solid; M.P. = 149–151 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm = 3.73 (s, 3H, $CH_3$), 6.01 (d, 1H, ArH), 6.22 (d, 1H, ArH), 6.30 (s, 1H, ArH), 7.43 (s, 1H, ArH), 7.58 (s, 1H, ArH), 7.69 (d, 1H, ArH), 7.92 (s, 1H, ArH), 8.10 (d, 1H, ArH), 8.34 (s, 1H, NH); $^{13}$C NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm = 54.2, 102.1, 112.6, 117.4, 119.5, 123.2, 124.0, 127.9, 129.4, 130.0, 132.4, 134.2, 135.2, 138.7, 150.7; LC/MS (ESI-MS) $m/z$ = 433.9 (M + 1).

#### 4.6.2. N-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-2-(3-(trifluoromethyl)phenyl) methanesulfonamide (**7b**)

Appearance: colorless oil; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm = 3.24 (s, 2H, $CH_2$), 3.80 (s, 3H, $CH_3$), 6.85 (s, 1H, ArH), 6.92 (d, 2H, ArH), 7.05 (s, 1H, ArH), 7.64 (s, 1H, ArH), 7.94 (s, 1H, ArH), 7.99 (m, 3H, ArH), 8.38 (s, 1H, NH); $^{13}$C NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm = 37.6, 53.4, 102.8, 113.0, 118.4, 121.2, 122.6, 123.9, 124.2, 125.8, 127.9, 128.4, 131.0, 131.6, 134.2, 136.3, 138.4, 150.8; LC/MS (ESI-MS) $m/z$ = 447.1 (M + 1).

#### 4.6.3. N-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)furan-2-sulfonamide (**7c**)

Appearance: semisolid; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm = 3.54 (s, 3H, $CH_3$), 6.38 (d, 1H, ArH), 6.42 (d, 1H, ArH), 6.69 (s, 1H, ArH), 7.50 (t, 1H, ArH), 7.62 (s, 1H, ArH), 7.95 (s, 1H, ArH), 8.05 (d, 1H, ArH), 8.35 (d, 1H, ArH), 8.74 (s, 1H, NH); $^{13}$C NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm = 53.8, 102.8, 108.7, 111.6, 113.6, 116.8, 119.4, 122.8, 125.4, 133.6, 136.8, 146.4, 147.4, 149.8; LC/MS (ESI-MS) $m/z$ = 355.1 (M + 1).

#### 4.6.4. N-((4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-3-fluoro-5-trifluoromethyl) benzene sulfonamide (**7d**)

Appearance: semisolid; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm = 3.80 (s, 3H, $CH_3$), 6.62 (s, 1H, ArH), 6.89 (d, 2H, ArH), 7.01 (s, 1H, ArH), 7.52 (s, 1H, ArH), 7.93 (s, 1H, ArH), 8.22 (s, 1H, ArH), 8.29 (s, 1H, ArH), 9.03 (s, 1H, NH); $^{13}$C NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm = 53.8, 102.7, 113.4, 114.8, 116.8, 118.2, 119.1, 120.7, 122.8, 123.8, 126.1, 132.8, 135.2, 137.9, 140.6, 152.6, 159.4; LC/MS (ESI-MS) $m/z$ = 451.3 (M + 1).

#### 4.6.5. N-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-methoxybenzenesulfonamide (**7e**)

Appearance: semisolid; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm = 2.30 (s, 3H, $CH_3$), 3.54 (s, 3H, $CH_3$), 6.38 (s, 1H, ArH), 6.46 (d, 1H, ArH), 6.72 (d, 1H, ArH), 7.18 (s, 1H, ArH), 7.48 (s, 1H, ArH), 7.68 (d, 2H, ArH), 7.84 (s, 1H, ArH), 9.07 (s, 1H, NH); $^{13}$C NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm = 52.8, 60.1, 104.7, 113.4, 115.2, 118.3, 119.4, 123.8, 124.2, 127.4, 129.9, 134.7, 138.5, 156.4, 160.1; LC/MS (ESI-MS) $m/z$ = 394.9 (M + 1).

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*4.6.6. N-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-(trifluoromethyl)benzene sulfonamide (**7f**)*

Appearance: colorless oil; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm = 3.84 (s, 3H, $CH_3$), 6.82 (d, 1H, ArH), 6.94 (d, 1H, ArH), 6.99 (s, 1H, ArH), 7.12 (s, 1H, ArH), 7.42 (s, 1H, ArH), 8.64 (d, 2H, ArH), 8.92 (d, 2H, ArH), 9.35 (s, 1H, NH); $^{13}$C NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm = 53.4, 102.7, 113.4, 118.2, 121.4, 122.5, 124.3, 125.9, 128.2, 130.4, 131.2, 136.3, 137.2, 142.3, 153.4; LC/MS (ESI-MS) $m/z$ = 432.9 (M + 1).

*4.6.7. 2-Chloro-N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-3-nitrobenzenesulfon amide (**7g**)*

Appearance: off white solid; M.P. = 192–194 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm = 3.72 (s, 3H, $CH_3$), 6.91 (m, 3H, ArH), 7.01 (d, 1H, ArH), 7.20 (d, 1H, ArH), 7.24 (s, 1H, ArH), 7.48 (s, 1H, ArH), 7.80 (s, 1H, ArH), 8.34 (s, 1H, NH); $^{13}$C NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm = 53.2, 102.4, 113.4, 116.8, 119.9, 122.4, 125.6, 126.9, 128.6, 129.9, 133.4, 136.0, 137.4, 140.4, 146.2, 153.3; LC/MS (ESI-MS) $m/z$ = 444.3 (M + 1).

*4.6.8. 2-Chloro-N-(4-(4-chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-6-fluoro-3-(trifluoro methyl) benzene sulfonamide (**7h**)*

Appearance: white solid; M.P. = 154–156 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm = 3.72 (s, 3H, $CH_3$), 6.68 (d, 1H, ArH), 6.87 (s, 1H, ArH), 6.99 (d, 2H, ArH), 7.46 (d, 1H, ArH), 7.70 (s, 1H, ArH), 7.82 (s, 1H, ArH), 8.39 (s, 1H, NH); $^{13}$C NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm = 50.7, 101.4, 110.7, 112.4, 115.9, 116.5, 120.1, 121.4, 123.6, 125.2, 126.3, 128.2, 129.4, 133.2, 142.8, 153.4, 161.5; LC/MS (ESI-MS) $m/z$ = 486.2 (M + 1).

*4.6.9. N-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-2,6-difluoro-4-methoxybenzene sulfonamide (**7i**)*

Appearance: semisolid; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm = 2.62 (s, 3H, $CH_3$), 3.75 (s, 3H, $CH_3$), 6.24 (s, 1H, ArH), 6.92 (d, 1H, ArH), 7.36 (s, 1H, ArH), 7.64 (s, 1H, ArH), 7.83 (d, 2H, ArH), 7.89 (s, 1H, ArH), 8.49 (s, 1H, NH); $^{13}$C NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm = 52.7, 64.3, 92.7, 102.9, 108.3, 113.4, 118.6, 121.4, 123.2, 126.4, 133.4, 141.6, 153.4, 160.1, 163.4; LC/MS (ESI-MS) $m/z$ = 480.8 (M + 1).

*4.6.10. N-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl) thiophene-2-sulfonamide (**7j**)*

Appearance: brown solid; M.P. = 142–144 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm = 3.75 (s, 3H, $CH_3$), 6.72 (d, 1H, ArH), 6.89 (d, 1H, ArH), 7.07 (s, 1H, ArH), 7.48 (t, 1H, ArH), 7.76 (s, 1H, ArH), 7.94 (s, 1H, ArH), 8.03 (d, 1H, ArH), 8.17 (d, 1H, ArH), 9.02 (s, 1H, NH); $^{13}$C NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm = 53.8, 102.8, 112.6, 1184, 119.8, 124.9, 125.5, 130.2, 132.5, 133.5, 137.4, 138.9, 140.1, 151.8; LC/MS (ESI-MS) $m/z$ = 371.0 (M + 1).

*4.6.11. N-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-1-(4-chlorophenyl)cyclo propane sulfonamide (**7k**)*

Appearance: semisolid; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm = 1.63 (t, 2H, $CH_2$), 1.82 (t, 2H, $CH_2$), 3.95 (s, 3H, $CH_3$), 6.67 (d, 2H, ArH), 6.89 (d, 4H, ArH), 7.17 (s, 1H, ArH), 7.48 (s, 1H, ArH), 7.87 (s, 1H, ArH), 8.56 (s, 1H, NH); $^{13}$C NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm = 13.5, 24.5, 42.9, 99.4, 108.6, 114.5, 119.7, 122.6, 124.1, 126.3, 127.4, 129.8, 133.8, 137.8, 140.6, 149.7; LC/MS (ESI-MS) $m/z$ = 439.5 (M + 1).

*4.6.12. N-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl) benzenesulfonamide (**7l**)*

Appearance: off white solid; M.P. = 138–140 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm = 3.25 (s, 3H, $CH_3$), 6.25 (s, 1H, ArH), 6.57 (d, 1H, ArH), 6.89 (d, 1H, ArH), 7.21 (s, 1H, ArH), 7.37 (s, 1H, ArH), 7.79 (d, 2H, ArH), 8.02 (s, 1H, ArH), 8.49 (s, 1H, NH); $^{13}$C NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm = 46.8, 99.2, 109.7, 113.8, 119.6, 122.4, 125.7, 126.9, 130.2, 132.5, 133.8, 136.8, 142.6, 153.9; LC/MS (ESI-MS) $m/z$ = 364.9 (M + 1).

*4.6.13. N-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-3,4-dimethoxybenzene sulfonamide (**7m**)*

Appearance: brown solid; M.P. = 144–146 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm = 2.35 (s, 6H, $CH_3$), 3.48 (s, 3H, $CH_3$), 6.26 (s, 1H, ArH), 6.57 (d, 1H, ArH), 6.84 (d, 1H, ArH), 7.29 (s, 1H, ArH), 7.74 (s, 1H, ArH), 7.89 (d, 2H, ArH), 8.01 (s, 1H, ArH), 8.64 (s, 1H, NH); $^{13}$C NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm = 49.4, 59.6, 99.8, 107.4, 111.5, 114.8, 118.6, 120.1, 121.5, 123.8, 126.9, 128.0, 135.6, 142.5, 146.9, 153.4, 157.3; LC/MS (ESI-MS) $m/z$ = 425.6 (M + 1).

*4.6.14. N-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-4-nitrobenzenesulfonamide (**7n**)*

Appearance: yellow solid; M.P. = 184–186 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm = 2.69 (s, 3H, $CH_3$), 5.98 (d, 1H, ArH), 6.17 (d, 1H, ArH), 6.49 (s, 1H, ArH), 7.54 (s, 1H, ArH), 7.99 (s, 1H, ArH), 8.14 (d, 2H, ArH), 8.21 (d, 2H, ArH), 9.21 (s, 1H, NH); $^{13}$C NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm = 45.6, 99.8, 108.6, 114.5, 117.9, 120.4, 121.9, 125.6, 128.4, 133.6, 139.0, 147.6, 152.9, 156.7; LC/MS (ESI-MS) $m/z$ = 409.9 (M + 1).

*4.6.15. N-(4-(4-Chloro-1H-imidazol-1-yl)-3-methoxyphenyl)-3-(1-cyanoethyl)benzene sulfonamide (**7o**)*

Appearance: colorless oil; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ ppm = 1.48 (s, 3H, $CH_3$), 3.28 (s, 3H, $CH_3$), 4.08 (m, 1H, CH), 6.38 (d, 1H, ArH), 6.64 (d, 1H, ArH), 6.96 (s, 1H, ArH), 7.48 (s, 1H, ArH), 7.59 (m, 1H, ArH), 7.87 (d, 2H, ArH), 8.14 (s, 1H, ArH), 8.29 (s, 1H, ArH), 8.98 (s, 1H, NH); $^{13}$C NMR (300 MHz, DMSO-$d_6$) $\delta$ ppm = 14.8, 24.8, 50.2, 98.7, 108.9, 116.4, 117.5, 119.5, 121.6, 125.9, 127.4, 129.0, 130.2, 132.6, 133.2, 134.7, 136.1, 140.2, 153.5; LC/MS (ESI-MS) $m/z$ = 418.2 (M + 1).

### 4.7. Antibacterial studies

The synthesized compounds were screened for their antibacterial activity against one Gram positive and two Gram negative bacterial species viz., *S. aureus* (ATCC-25923), *E. coli* (ATCC-25922) and *K. pneumoniae* (ATCC-13883) bacterial strains by serial plate dilution method [25,26]. Serial dilutions of the drug in Mueller-Hinton broth were taken in tubes and their pH was adjusted to 5.0 using phosphate buffer. A standardized suspension of the test bacterium was inoculated and incubated for 16–18 h at 37 °C. The minimum inhibitory concentration (MIC) was noted by seeing the lowest concentration of the drug at which there was no visible growth. A number of antimicrobial discs are placed on the agar for the sole purpose of producing zone of inhibition in the bacterial lawn. Twenty milliliters of agar media was poured into each Petri dish. Excess of suspension was decanted and plates were dried by placing in an incubator at 37 °C for an hour. Using an agar punch, wells were made on these seeded agar plates and minimum inhibitory concentration of the test compounds in dimethylsulfoxide (DMSO) were added into each labeled well. A control was also prepared for the plates in the same way using solvent DMSO. The Petri dishes were prepared in triplicate and maintained at 37 °C for 3–4 days. DMSO used for the preparation of compounds did not show inhibition against the tested organisms. Antibacterial activity was determined by measuring the diameter of the inhibition zone. Activity of each compound was compared with ciprofloxacin as standard [27,28]. MIC (μg/mL) and corresponding results are summarized in Table 5.

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### 4.8. Antifungal studies

Newly prepared compounds were screened for their antifungal activity against *C. albicans, A. flavus* and *Rhizopus* sp in DMSO by serial plate dilution method [29,30]. Sabourands agar media was prepared by dissolving peptone (1 g), D-glucose (4 g) and agar (2 g) in distilled water (100 mL) and adjusting the pH to 5.7. Normal saline was used to make a suspension of spore of fungal stain for lawning. A loopful of particular fungal strain was transferred to 3 mL saline to get a suspension of corresponding species. Twenty milliliters of agar medis was poured into each Petri dish. Excess of suspension was decanted and plates were dried by placing in incubator at 37 °C for 1 h. Using a punch, wells were made on these seeded agar plates minimum inhibitory concentrations of the test compounds in DMSO were added into each labeled well. A control was also prepared for the plates in the same way using solvent DMSO. The Petri dishes were prepared in triplicate and maintained at 37 °C for 3–4 days. DMSO used for the preparation of compounds did not show inhibition against the tested organisms. Antifungal activity was determined by measuring the diameter of the inhibition zone. Activity of each compound was compared with Amphotericin B as standard. MIC (μg/mL) and Zone of inhibition (mm) were determined for all the synthesized compounds and their corresponding results are summarized in Table 5.

### 4.9. Antituberculosis study

The compounds were screened for their in vitro antimycobacterial activity against *M. tuberculosis H37Rv* ATCC 27294 and non-tubercular mycobacterial (NTM) species like *M. smegmatis* (MC2) ATCC 19420, and *M. fortuitum* ATCC 19542 by Resazurin Assay method [31] and their MIC values were determined. The standard drugs, viz. isoniazid and rifampicin were used for comparison. *M. tuberculosis* strains were grown in Middlebrook 7H9 broth (Difco BBL, Sparks, MD, USA) supplemented with 10% OADC (Becton Dickinson, Sparks, MD, USA). The culture was diluted to McFarland 2 standard with the same medium. From this, 50 μL of this culture was added to 150 μL of fresh medium in 96 well microtitre plates. Stock solutions (2 mg/mL) of the test compounds were prepared in dimethyl formamide (DMF). The compounds were tested at 1, 10 and 100 μg/mL concentrations. Further the second level testing was carried out at concentrations 0.3125, 0.625, 1.25, 2.5, and 5 μg/mL. Control tubes had the same volumes of DMF without any substrate. Rifampicin and isoniazid were used as the reference compounds. After incubation at 37 °C for 7 days, 20 μL of 0.01% Resazurin (Sigma, St. Louis. MO, USA) in water was added to each tube. Resazurin, a redox dye, is blue in the oxidized state and turns pink when reduced by the growth of viable cells. The control tubes showed a color change from blue to pink after 1 h at 37 °C. Compounds which prevented the change of color of the dye were considered to be inhibitory to *M. tuberculosis* and the corresponding results are summarized in Table 6.

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