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# α-Sulfonamidophosphonates as new anti-mycobacterial chemotypes: Design, development of synthetic methodology, and biological evaluation

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ABSTRACT

Tuberculosis (TB) is the leading cause of death worldwide due to bacterial infection. The scarcity of effective drugs to treat the disease and the compounded problems due to the development of resistance to the available therapeutics and TB-HIV synergism drive medicinal chemists to search for new anti-Mtb chemotypes. Towards this endeavor, the α-sulfonamidophosphonate moiety has been identified as new anti-Mtb chemotype through the scaffold hopping as the design strategy, development of an effective synthetic methodology using green chemistry tools, and evaluation of anti-TB activity of the synthesized compounds against Mtb (*Mycobacterium tuberculosis*) H37Rv. Out of the sixteen compounds, five have been found to have MIC values of 1.56 μg/mL and one 3.125 μg/mL. The five most active compounds are non-cytotoxic to RAW 264.7 (mouse leukemic monocyte macrophage) cell lines. The compounds are found to possess acceptable values of the various parameters for drug likeness in accordance with the Lipinski rule with the topological surface area (tPSA) of > 70 that suggest eligibility of these new molecular entities for further consideration as potential drug candidates.

## 1. Introduction

Tuberculosis (TB), caused by the bacteria *Mycobacterium tuberculosis* (Mtb), is the ninth leading cause of deaths of humans worldwide and the leading cause of death due to single infection. An estimated 10.4 million new TB cases (occurring in every part of the world with 30 countries having the highest burden) and 1.7 million deaths due to TB were reported in 2016 [1]. The inadequacy of the existing drugs to treat the disease, the emergence of drug resistant strains of Mtb, and the TB-HIV synergism press the need to discover new drugs to combat with this deadly pathogenic mycobacteria [2]. The year 2017 marked the 24th anniversary of the declaration of tuberculosis as the global health emergency by World Health Organization (WHO) made in 1993 [3].

The first line drugs such as isoniazid (INH), rifampicin (R), pyrazinamide (Z), streptomycin (S), and ethambutol (E) are associated with one or more serious side effects [4]. For the drug-sensitive TB, patients are treated with the four first-line drugs (INH, R, Z, and E) for 2 months followed by the treatment with INH plus R for 4 months through directly observed treatment short course strategy (DOTS) that has the cure rate of > 95%. However, drug resistant TB patients require treatment with the more toxic and costly second-line medicines such as ciprofloxacin (Cfx), para-amino salicylic acid (Pas), kanamycin (Km), cycloserine (Dcs), ethionamide (Eto), amikacin (Amk), capreomycin (Cm), thioacetazone (Thz) for 18–24 months or for longer time [5]. The emergence of multi-drug resistant (MDR) and extensively drug resistant (XDR) strains of Mtb triggered efforts to find new therapeutic agents which might have novel mode of action [6–8]. This led to the discovery of bedaquiline [9] and delamanid [10] as new structural classes approved to treat MDR-TB patients as combination therapy with other drugs in the United States and European countries, respectively. However, the use of bedaquiline is associated with side effects of QT prolongation and hepatotoxicity [11,12]. Its use further necessitates special precaution with CYP3A4 inhibitors [13] due to drug-drug interaction (that also relates to QT prolongation). On the other hand, QT prolongation and CNS toxicity [14] are prominent side effects of the use of delamanid. Thus, exploration of new anti-TB chemotypes is an active area of research in the quest of effective therapeutic agents to combat the menace of this harmful disease [15].

## 2. Results and discussion

In continuation of our efforts to search for new anti-Mtb scaffolds [16–19] we realised that adopting the scaffold hopping strategy [20,21] to build new chemotypes through import of the critical structural features of structurally different anti-TB compounds would generate a novel class of anti-TB compounds. Towards this initiative, we were

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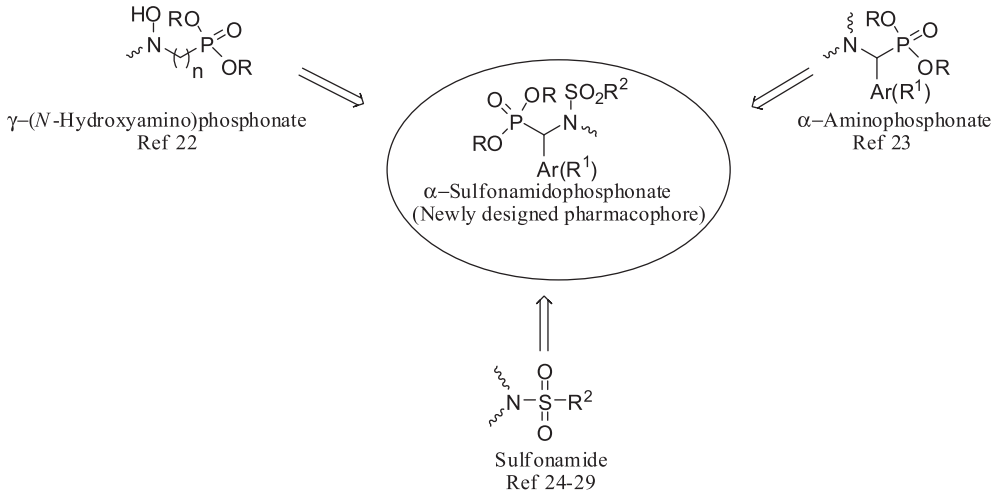



**Fig. 1.** Design of α-sulfonamidophosphonate as new anti-TB scaffold.

attracted by the recent reports on the anti-TB activity of γ-(*N*-hydroxyamino)phosphonates [22] and α-aminophosphonates [23] suggesting the α-aminophosphonate moiety to be a pharmacophoric feature for ant-TB activity. However, as the polarity of γ-(*N*-hydroxyamino)phosphonates diminish their ability to penetrate the lipophilic Mtb cell wall these compounds do not exhibit reasonable anti-TB potency (the most active compound with a Mtb MIC value of 9.4 μg/mL) [22]. On the other hand, the poor MIC values (100 μg/mL against Mtb H37Ra) [23] suggests that the α-aminophosphonate moiety alone may not be the critical pharmacophoric feature for anti-TB activity. We further took into the consideration the reports on the anti-TB activity of compounds bearing the sulphonamide [24–29] moiety and adopted the scaffold hopping approach to construct the α-sulfonamidophosphonate moiety as a novel anti-TB chemotype (Fig. 1). We report herein a new method of synthesis of α-sulfonamidophosphonates and demonstrate their potential as new anti-Mtb chemotype through biological evaluation against Mtb H37Rv.

## 3. Chemistry

We realised that the strategy of multiple component reaction (MCR) involving an amine, an aldehyde, and a di/trialkyl phosphite, known as Kabachnik-Fields reaction [30–34], would be a convenient approach for synthesis of the designed α-sulfonamidophosphonates (Fig. 2) due to the advantages of MCR [35–38] and its implication in drug discovery [39,40].

Hence, the catalytic efficiency of various Lewis acids, solid supported protic acids, ionic liquids, etc. was assessed for the model reaction involving 4-methoxybenzaldehyde **1a** (as a less electrophilic carbonyl partner), 4-methylbenzenesulphonamide **2**, and dimethyl phosphite (DMP) **3a** to form the corresponding α-sulfonamidophosphonate **4a** (SI: Table S1).

Performing the model reaction in the presence of these reported catalysts either at room temperature for 24 h or under heating at 100 °C for 8 h led to the formation of **4a** either in trace amount or in poor yield (Method A). As the use of microwave heating often proves to be advantageous in promoting organic reactions, including Kabachnik-Fields reaction, [41–45] and has emerged as an important component in green chemical technologies [46,47], the model reaction was performed under microwave irradiation in open vessel at 150 °C (Method B).

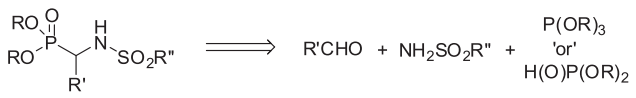



**Fig. 2.** Synthesis of α-sulfonamidophosphonates.

Charring of the reaction mixture was observed when the reaction was performed under MW-irradiation at 150 °C in closed vessel resulting in the decrease of the product yields.

The best result was obtained in performing the reaction under microwave irradiation in open vessel condition in the presence of anh Mg $(ClO_4)_2$ used as the catalyst.

The use of solvent, in general, was found to be detrimental to the product yield for both Method A and Method B (SI: Table S2). Out of the various solvents such as hydrocarbon (e.g., PhMe), halogenated hydrocarbon (e.g., DCE), ethereal (THF, 1,4-dioxane, and DME), weakly polar (EtOAc), protic polar (MeOH, EtOH, TFE, and water), and aprotic polar (MeCN and DMF) used, MeOH, EtOH, TFE, and DMF were effective providing the product in 61–78% yields. Herein also, performing the reaction under microwave gave better results compared to those obtained under classical heating.

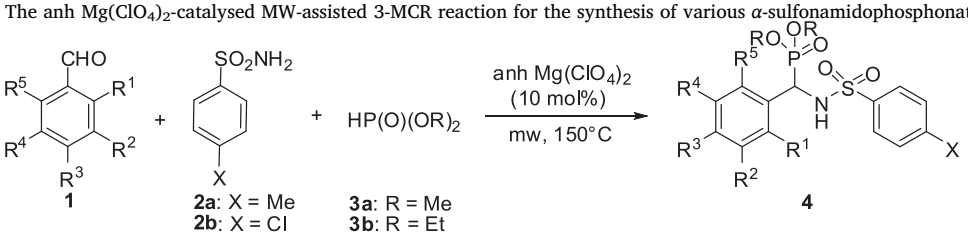
To establish the generality and the scope of the optimized reaction condition, various aromatic aldehydes and aryl sulphonamides were subjected to 3-MCR with DMP and diethyl phosphite (DEP) under MW irradiation at 150 °C in an open vessel under solvent free condition in the presence 10 mol% of anh $Mg(ClO_4)_2$ as the catalyst to afford the desired products in 81–95% yields (Table 1). The reaction works well with various aromatic aldehydes bearing electron donating/withdrawing substituents and halogens. The reaction condition is tolerant with sensitive substituents such as an acetoxy group and afforded the desired product without any competitive reaction at the acetoxy group (entry 15, Table 1) that are prone to undergo deprotection in the presence of nucleophilic agents [48–50]. In case of cinnamaldehydes used as the substrate (entries 11 and 15, Table 1) no competitive aza-Michael addition [51] took place. These demonstrate the chemoselectivity of this methodology that represents a new addition to the green chemistry tool box [52,53] of synthetic organic/medicinal chemists.

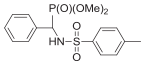
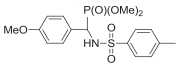
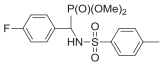
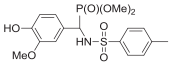
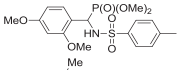
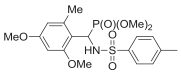
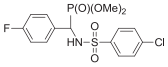
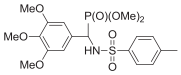
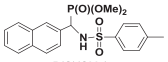
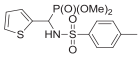
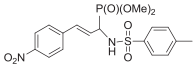
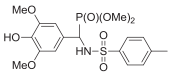
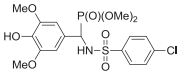
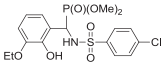
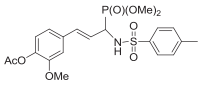
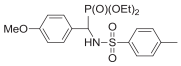
## 4. Biological evaluation

### 4.1. Anti-Mtb activity evaluation

All the synthesized sixteen α-sulfonamidophosphonates were first subjected to *in vitro* anti-TB activity against *M. tuberculosis* H37Rv (ATCC 27294 strain) [54]. The minimum inhibitory concentration (MIC; μg/ mL) values of all the synthesized compound along with the standard drugs isoniazid (INH), rifampicin (R), ethambutol (E), pyrazinamide (Z), and ciprofloxacin (Cfx) were determined in triplicate at pH 7.4 (Table 2). All the synthesized compounds exhibited MIC's in the micromolar range, varying from 1.56 to 50 μg/ mL.

**Table 1**
The anh $Mg(ClO_4)_2$-catalysed MW-assisted 3-MCR reaction for the synthesis of various α-sulfonamidophosphonates (4a-p).[a]




| Entry | 1 | 2 | 3 | 4 | Structure of 4 | Time (min) | Yield (%)[b] |
|---|---|---|---|---|---|---|---|
| 1 | $R^1 = R^2 = R^3 = R^4 = R^5 = H$ | 2a | 3a | 4a |  | 10 | 88 |
| 2 | $R^1 = R^2 = R^4 = R^5 = H$; $R^3$ = OMe | 2a | 3a | 4b |  | 10 | 91 |
| 3 | $R^1 = R^2 = R^4 = R^5 = H$; $R^3$ = F | 2a | 3a | 4c |  | 10 | 83 |
| 4 | $R^1 = R^4 = R^5 = H$; $R^2$ = OH: $R^3$ = F | 2a | 3a | 4d |  | 10 | 82 |
| 5 | $R^2 = R^4 = R^5 = H$; $R^1 = R^3$ = OMe | 2a | 3a | 4e |  | 10 | 92 |
| 6 | $R^2 = R^4 = H$; $R^1 = R^3$ = OMe; $R^5$ = Me | 2a | 3a | 4f |  | 10 | 91 |
| 7 | $R^1 = R^2 = R^4 = R^5 = H$; $R^3$ = F | 2b | 3a | 4g |  | 10 | 94 |
| 8 | $R^1 = R^5 = H$; $R^2 = R^3 = R^4$ = OMe | 2a | 3a | 4h |  | 10 | 95 |
| 9 | 2-Naphthaldehyde | 2a | 3a | 4i |  | 20 | 94 |
| 10 | Thiophene-2-carboxaldehyde | 2a | 3a | 4j |  | 5 | 93 |
| 11 | (*E*)-4-Nitrocinnamaldehyde | 2a | 3a | 4k |  | 2 | 92 |
| 12 | $R^1 = R^5 = H$; $R^2 = R^4$ = OMe; $R^3$ = OH | 2a | 3a | 4l |  | 5 | 82 |
| 13 | $R^1 = R^5 = H$; $R^2 = R^4$ = OMe; $R^3$ = OH | 2b | 3a | 4m |  | 15 | 84 |
| 14 | $R^1$ = OH; $R^2$ = OEt;$R^3 = R^4 = R^5 = H$ | 2b | 3a | 4n |  | 10 | 81 |
| 15 | (*E*)-4-Acetoxy-3-methoxycinnamaldehyde | 2a | 3a | 4o |  | 10 | 82 |
| 16 | $R^1 = R^2 = R^4 = R^5 = H$; $R^3$ = OMe | 2a | 3b | 4p |  | 10 | 86 |

[a] The 3-MCR of the **1** (1 mmol), **2** (1.1 mmol), and **3** (1.5 mmol) was performed in the presence of anh $Mg(ClO_4)_2$ (10 mol%) under MW irradiation under neat condition in open vessel at 150 °C.
[b] The isolated yield of **4** (characterized by IR, $^1H$ & $^{13}C$ NMR, and MS).

### 4.2. Cytotoxicity evaluation

Out of these, five compounds exhibited MIC value of 1.56 μg/mL and one compound showed MIC of 3.125 μg/mL and are more potent than the standard drug pyrazinamide (Z) (MIC of 6.25 μg/mL). The in vitro cell viability of the active phosphonates (MIC ≥ 6.25 μg/mL) was evaluated against RAW 264.7 (mouse leukemic monocyte macrophage) cell lines at a concentration of 50 μg/mL using the [(3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide)] MTT assay and were found to be non-toxic (Table 2).

The graphical representation of the relative antitubercular activity of α-sulfonamido phosphonates with the standard drugs is provided in Fig. 3.

## 5. Assessment for drug likeness

In order to assess the drug likeness, all these compounds were subjected to the amenability to the Lipinski rule [55] (Table 3). According to this rule, drug likeliness of the molecule to be an orally active drug ought to show not more than one violation of the following four criteria: not more than five hydrogen bond donors, not more than 10 hydrogen bond acceptors, molecular weight not more than 500 Da, not have an octanol-water partition coefficient (cLogP) greater than five and it was recently suggested that to secure good oral bioavailability, the number of rotatable bonds in a given molecule should be kept below 10. These properties were computed by Drug Discovery Studio 2.5

**Table 2**
The anti-TB (H37Rv) activity of the synthesized α-sulfonamidophosphonates 4a–p, the standard anti-TB drugs, and cytotoxicity of a few selected α-sulfonamidophosphonates exhibiting MIC values of ≤6.25 μg/mL.

| Compound | MIC[a] (μg/mL) | MIC (μM) | Cytotoxicity against RAW 264.7[b] (μM) |
|---|---|---|---|
| **4a** | 12.5 | 3.12 | ND[c] |
| **4b** | 12.5 | 3.39 | ND[c] |
| **4c** | 12.5 | 3.23 | ND[c] |
| **4d** | 1.56 | 3.76 | 28.62 |
| **4e** | 1.56 | 3.64 | 31.40 |
| **4f** | 25 | 5.64 | ND[c] |
| **4g** | 1.56 | 3.83 | 22.16 |
| **4h** | 12.5 | 2.72 | ND[c] |
| **4i** | 25 | 5.97 | ND[c] |
| **4j** | 50 | | ND[c] |
| **4k** | 1.56 | 3.55 | 30.81 |
| **4l** | 1.56 | 3.51 | 19.56 |
| **4m** | 3.125 | 6.71 | 16.73 |
| **4n** | 25 | 5.57 | ND [c] |
| **4o** | 50 | 1.04 | ND[c] |
| **4p** | 50 | 1.07 | ND[c] |
| **INH** | 0.098 | – | ND[c] |
| **R** | 0.197 | – | ND[c] |
| **E** | 1.56 | – | ND[c] |
| **Z** | 6.25 | – | ND[c] |

[a] 99% inhibition of growth of *M. tuberculosis* H37Rv (ATCC 27294 strain). Minimum inhibitory concentration (MIC) is the minimum concentration of the compound required to inhibit 99% of bacterial growth.
[b] % inhibition of RAW 264.7 cells lines at 50 μg/mL. cND: Not determined.

(Table 3) and all compounds followed the Lipinski rule and showed no violation of the above criteria except **4o**. It has been reported [56–58] that the topological surface area (tPSA) of a safe drug should be > 70. All of the molecules have the tPSA values greater than 70 indicating that the active compounds are likely to have the potential to be drug candidate. Since lipophilicity plays an important role in passage of compounds through the high lipid containing mycobacterium cell wall [59] therefore, cLogP values for all the synthesized compounds are significant although no direct correlation could be established between the activity and CLogP data of compounds **4a–4p**. Comparison of the cLogP data of many synthesised phosphonates with those of the standard drugs reveal that the synthetic analogues are more lipophilic in nature compared to the first line drugs i.e., INH (−0.668), E (0.1188), and Z (−0.67632). Therefore, the lipophilicity of the newly found compounds would enable them to pass more easily through lipid-rich cell wall and would provide further scope for lead optimization.

## 6. Conclusion

The α-sulfonamidophosponate moiety has been identified as a new pharmacophoric feature for exhibiting anti-TB activity. A new and effective catalytic procedure for the synthesis of the designed compounds with excellent chemoselectivity has been developed adopting the 3-MCR strategy under microwave irradiation and solvent-free condition in compliance with some of the principles of green chemistry that represents a new addition to the medicinal chemist tool box. Five compounds exhibited anti-TB activity (MIC 1.56 μg/mL) better than that of the standard drugs ethambutol (E) and pyrazinamide (Z) and were also found to be non-toxic. The favourable estimated Lipinski parameters and topological surface area support their drug likeness and further consideration as new candidates for anti-TB drug development.

## 7. Experimental section

Chemicals and all solvents were commercially available (Aldrich Chemical, Merck AG, Fluka, Alfa Aesar and SD Fine Chemicals) and used without further purification. $^{1}$H NMR and $^{13}$C NMR spectra were recorded on Bruker Advance DX spectrometer at 400 and 100 MHz, respectively, with TMS as an internal standard and using $CDCl_3$/MeOD/DMSO as solvent. Coupling constants were reported in hertz (Hz). $^{13}$C NMR spectra were fully decoupled. For analysis of the results of NMR, Topspin software was used. The abbreviations used to characterize the signals are as follows: s = singlet, m = multiplet, d = doublet, dd = doublet of doublet, dt = doublet of triplet, t = triplet, q = quartet, br s = broad singlet, br d = broad doublet,br m = broad multiplet, ArH = aromatic proton. Mass spectra were measured in the APCI mode at an ionization potential of 70 eV with LCMS MSD (Hewlett Packard) and on a GCMS-QP 5000 (Shimadzu) (for EI) mass spectrometers; Infra-red spectra were recorded on Perkin Elmer FT-IR spectrometer in the range of 4000–600 $cm^{-1}$ either as neat samples or using KBr for preparing pellets for solid samples or in solvent. Compounds were routinely checked for their purity on the silica gel GF-254 and visualized under UV at wavelength 254 nm. Melting points were measured with Labindia digital melting point apparatus. Evaporation of solvent was performed at reduced pressure, using a Buchi rotary evaporator. Crude sample was purified using with flash chromatography Biotage (Sweden) (isolera).

## 8. Experimental procedure

Representative general experimental procedure for the synthesis of α-sulfonamidophosphonate. Dimethyl [(4-methoxyphenyl) (4′-

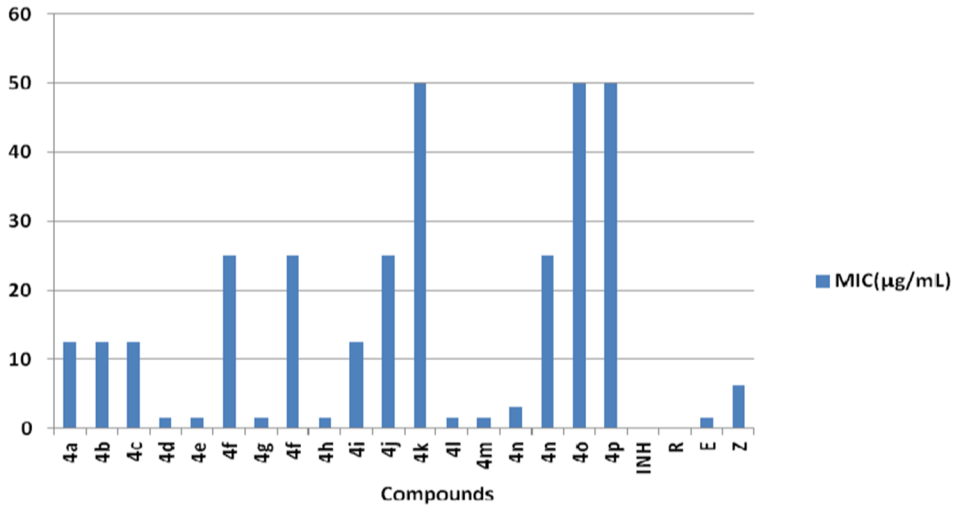



**Fig. 3.** Graphical representation of the anti-TB activity and cytotoxicity of the synthesized compounds in comparison with those of the standard anti-TB drugs.

**Table 3**
The assessment of drug likeness of α-sulfonamidophosphonates **4a–p** in view of the Lipinski rule.

| Entry | Compd No. | nViol[b] | cLogP[c,d] | Mol. Wt.[c,e] | No. of HBA[f,g] | No. of HBD[f,h] | No. of RB[f,i] | tPSA |
|---|---|---|---|---|---|---|---|---|
| Acceptable Range: | | | ≤5 | ≤500 | ≤10 | ≤5 | < 10 | > 70 |
| 1 | **4a** | 0 | 2.1084 | 399.40 | 7 | 1 | 8 | 90.93 |
| 2 | **4b** | 0 | 2.1894 | 369.37 | 6 | 1 | 7 | 81.7 |
| 3 | **4c** | 0 | 2.3324 | 387.36 | 6 | 1 | 7 | 81.7 |
| 4 | **4d** | 0 | 1.3716 | 415.40 | 8 | 2 | 8 | 111.16 |
| 5 | **4e** | 0 | 2.1974 | 429.42 | 8 | 1 | 9 | 100.16 |
| 6 | **4f** | 0 | 2.6464 | 443.45 | 8 | 1 | 9 | 100.16 |
| 7 | **4g** | 0 | 2.8488 | 407.78 | 6 | 1 | 7 | 81.7 |
| 8 | **4h** | 0 | 1.4895 | 459.45 | 9 | 1 | 10 | 109.39 |
| 9 | **4i** | 0 | 3.3634 | 419.43 | 6 | 1 | 7 | 81.7 |
| 10 | **4j** | 0 | 1.8354 | 375.40 | 6 | 1 | 7 | 81.7 |
| 11 | **4k** | 0 | 2.4744 | 440.41 | 9 | 3 | 9 | 133.51 |
| 12 | **4l** | 0 | 1.15467 | 445.42 | 9 | 2 | 9 | 120.39 |
| 13 | **4m** | 0 | 1.67107 | 465.84 | 9 | 2 | 9 | 120.39 |
| 14 | **4n** | 0 | 2.367 | 449.84 | 8 | 2 | 9 | 111.16 |
| 15 | **4o** | 1 | 1.8194 | 483.47 | 9 | 1 | 11 | 117.23 |
| 16 | **4p** | 0 | 2.9764 | 427.45 | 7 | 1 | 10 | 90.93 |

[a]99% inhibition of growth of *M. tuberculosis* $H_{37}Rv$ (ATCC 27294 strain).
[b] nViol, no. of violations.
[c] Calculated using ChembioDraw Ultra 11.0.1.
[d] cLog P, octanol-water partition co-efficient.
[e] MW, molecular weight.
[f] Calculated using Accelrys Discovery Studio 2.5.
[g] HBA, no. of hydrogen bond acceptors.
[h] HBD, no. of hydrogen bond donors.
[i] RB, no. of rotatable bonds.

methylphenylsulfonamido)methyl]phosphonate (**4a**): The mixture of 4-methoxybenzaldehyde **1a** (136 mg, 1 mmol, 0.12 mL), 4-methylbenzenesulfonamide **2a** (188 mg, 1.1 mmol), dimethylphosphite (DMP) **3a** (165 mg, 1.5 mmol, 0.14 mL), anh $Mg(ClO_4)_2$ (22 mg, 0.1 mmol, 10 mol %) in an open glass vessel was subjected to microwave irradiation at 150 °C for 10 min (TLC) under neat condition. The cooled reaction mixture was diluted with EtOAc (10 mL) and was passed through a plug of cotton (to filter the catalyst). The cotton plug was washed with EtOAc (2 × 5 mL) and the combined EtOAc extracts were washed with water (2 × 5 mL), to remove the unreacted alkyl phosphite, dried (anh $MgSO_4$), filtered, and concentrated under vacuum. The residue was dissolved in minimum volume of EtOAc (~1.0 mL), absorbed on chromatographic silica-gel (2.0 g), concentrated under vacuum, the resultant free flowing solid material was loaded on to the flash chromatography column, and eluted with EtOAc-hexane (80:20) to afford **4a** (361 mg, 91%). The remaining α-sulfonamidophosphonates (**4b–4p**) were prepared following this general procedure (Table 1). The physical data [IR, NMR, MS, and HRMS] for all new compounds are provided below.

*Dimethyl [(4-hydroxy-3-methoxyphenyl)(4-methylphenylsulfonamido) methyl]phosphonate* (**4d**): Yield 340 mg (82%, yellow solid), mp 146–147 °C; IR (KBr) $\nu$ ($cm^-$): 3524, 3453, 3125, 2956, 2880, 1606, 1519; $^1H$ NMR (400 MHz, $CDCl_3$) δ (ppm): 2.28 (s, 3H), 3.44 (d, $J$ = 10.6 Hz, 3H), 3.53 (s, 3H), 3.91 (d, $J$ = 10. 6 Hz, 3H), 4. 76 (dd, $J$ = 10.08 Hz and 24.12 Hz, 1H), 5.7 (brs, 1H, OH), 6.64 (s, 2H, ArH), 6.73 (s, 1H), 6.97 (d, $J$ = 8.08 Hz), 7.27–7.30 (brm, –NH), 7.46 (d, $J$ = 8.2 Hz); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ (ppm): 146.39, 145.58, 142.87, 138.03, 128.85, 127.1, 124.8, 121.5, 113.9, 110.1, 55.5, 54.7, 53.9, 53.81, 22.6; MS (APCI) $m/z$: 438.11 $[M + Na]^+$. HRMS (ESI): calcd for $C_{17}H_{22}NO_7PSNa$ $[M + Na]^+$ 438.0752, found: 438.0772.

*Dimethyl [(2,4-dimethoxyphenyl)(4-methylphenylsulfonamido)methyl]* phosphonate (**4e**): Yield 395 mg (92%, yellow solid), mp 153–154 °C; IR (KBr) $\nu$ ($cm^{-1}$): 3144, 2958, 1611, 1586, 1503, 1458; $^1H$ NMR (400 MHz, $CDCl_3$) δ (ppm): 2.28 (s, 3H), 3.45 (d, $J$ = 10.5 Hz, 3H), 3.71 & 3.72 (2 s, 6H), 3.85 (d, $J$ = 10.5 Hz, 3H), 5.17 (dd, $J$ = 10.3, 23.28 Hz, 1H), 6.17 (d, $J$ = 1.75 Hz, 1H, ArH), 6.23 (m,1H), 6.61 (brd, $J$ = 10.2 Hz, NH), 6.61–7.49 (5H, ArH); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ (ppm): 160.83, 157.4, 142.6, 137.5, 130.2, 128.7, 127.0, 114.2, 104.7, 98.2, 55.5, 54.3, 53.7, 49.3, 47.6, 21.3; (APCI) $m/z$: 452.10 $[M + Na]^+$. HRMS (ESI): calcd for $C_{18}H_{24}NO_7PSNa$ $[M + Na]^+$ 452.0908, found 452.0923.

*Dimethyl[(2,4-dimethoxy-6-methylphenyl)(4-methylphenylsulfonamido]methylphosphonate* (**4f**): Yield 403 mg (91%, yellow solid), mp 157–158 °C; IR (KBr) $\nu$ ($cm^{-1}$): 3164, 2924, 2852, 1604; $^1H$ NMR (400 MHz, $CDCl_3$) δ (ppm): 2.26 (s, 3H), 2.28 (s, 3H), 3.51 (d, $J$ = 12.5 Hz, 3H), 3.71 (s, 6H,), 3.75 (d, $J$ = 10.6 Hz, 3H), 4.99 (dd, $J$ = 10.6 & 26.04 Hz, 1H), 5.99 (s, 1H, NH), 6.17 (s, 1H, ArH), 6.29 (d, $J$ = 10.6 Hz, 1H, ArH), 6.98 (d, $J$ = 7.28 Hz, 2H, ArH), 7.42 (d, $J$ = 7.64 Hz, 2H, ArH); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ (ppm): 160.3, 158.7, 142.9, 138.9, 137.3, 128.8, 126.8, 126.5, 121.0, 107.5, 96.8, 55.6, 55.2, 53.9, 53.3, 51.1, 49.4, 21.3, 20.4; MS (APCI) $m/z$: 466.11 $[M + Na]^+$.

*Dimethyl (4-chlorophenylsulfonamido)(4-fluorophenyl)methylphosphonate* (**4g**): Yield 383 mg (94%, white solid), mp 146–147 °C; IR (KBr) $\nu$ ($cm^{-1}$): 3099, 2894, 1603, 1508; $^1H$ NMR (400 MHz, $CDCl_3$) δ (ppm): 3.39 (d, $J$ = 10.6 Hz, 3H), 3.94 (d, $J$ = 10.8 Hz, 3H), 4.83 (dd, $J$ = 9.76 & 24.28 Hz, 1H), 6.80 (d, $J$ = 8.4 Hz, 2H), 7.17–7.25 (m, 4H, ArH), 7.52 (d, $J$ = 8.6 Hz, 2H) 7.73 (brm, –NH); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ (ppm): 163.7, 161.3, 139.4, 138.7, 129.9, 129.0, 128.4, 115.5, 115.2, 55.0, 54.7, 54.0, 53.4; HRMS (ESI): calcd for $C_{15}H_{16}ClFNO_5PSNa$ $[M + Na]^+$ 430.0057, found 430.0077.

*Dimethyl (4-methylphenylsulfonamido)(3,4,5-trimethoxyphenyl)methylphosphonate* (**4h**): Yield 436 mg (95%, yellow solid), mp 146–147 °C; IR (KBr) $\nu$ ($cm^{-1}$): 3143, 2951, 2852, 1595, 1508; $^1H$ NMR (400 MHz, $CDCl_3$) δ (ppm): 2.27 (s, 3H), 3.49 (d, $J$ = 10.6 Hz, 3H), 3.61 (s, 6H), 3.75 (s, 3H), 3.96 (d, $J$ = 10.7 Hz, 3H), 4.78 (dd, $J$ = 10.08 & 24.36 Hz, 1H), 6.4 (s, 1H), 6.99 (d, $J$ = 8.0 Hz, 2H), 7.47 (d, $J$ = 8.2 Hz, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ (ppm): 153.3, 152.9, 142.9, 138.0, 137.5, 129.5, 128.7,128.4, 127.2, 105.3, 104.8, 60.7, 58.7, 56.2, 55.8, 55.0, 54.5, 53.9, 53.7, 21.3; $^{31}P$ NMR (162 MHz, $CDCl_3$-$H_3PO_4$ proton decoupled) δ (ppm): 21.47 (t, $J$ = 11.3 Hz); MS (APCI) $m/z$: 482.14 $[M + Na]^+$. HRMS (ESI): calcd for $C_{19}H_{26}NO_8PSNa$ $[M + Na]^+$ 482.1014, found 482.1030.

*(E)-Dimethyl 1-(4-methylphenylsulfonamido)-3-(2-nitrophenyl)allylphosphonate* (**4k**): Yield: 404 mg (94%, yellow solid), mp 145–146 °C; IR (KBr) $\nu$ ($cm^{-1}$): 3111, 2958, 2924, 1596, 1512; $^1H$ NMR (400 MHz,

$CDCl_3$) δ (ppm): 2.27 (s, 3H), 3.80 (d, $J$ = 10.7 Hz, 3H), 3.88 (d, $J$ = 10.7 Hz, 3H), 4.43 (m, 1H, –CHP–), 5.89 (m, 1H, CH = C<u>H</u>-CHP-), 6.86–7.46 (m, 7H, ArH and NH), 7.77 (d, $J$ = 7.8 Hz, 2H), 7.87 (d, $J$ = 8 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ (ppm): 147.3, 143.5, 137.7, 133.0, 131.4, 129.8, 129.5, 128.8, 127.4, 126.5, 124.4, 55.0, 54.0, 53.9, 52.3, 21.4; $^{31}$P NMR (162 MHz, $CDCl_3$-$H_3PO_4$) δ (ppm): 21.06 (s); HRMS (ESI): calcd for $C_{18}H_{21}N_2O_7PSNa$ $[M + Na]^+$ 463.0704, found 463.0722.

*Dimethyl (4-hydroxy-3,5-dimethoxyphenyl)(4-methylphenylsulfonamido)methylphosphonate* (**4l**): Yield: 365 mg (82%, white solid), mp 147–148 °C; IR (KBr) ν ($cm^{-1}$): 3520, 3413, 3135, 2956, 1622, 1523, 1467; $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm):2.27(s, 3H), 3.43 (d, $J$ = 10.6 Hz, 3H), 3.63 (s, 3H), 3.93 (d, $J$ = 10.7 Hz, 3H), 4.74 (dd, $J$ = 10.2 & 24.2 Hz, 1H,-CHP-), 6.4 (d, $J$ = 1.7 Hz, 2H), 6.96 (d, $J$ = 8.0 Hz, 2H), 7.45 (d, $J$ = 8.2 Hz, 2H), 7.53 (m, NH); $^{13}$C NMR (100 MHz, $CDCl_3$) δ (ppm): 146.7, 142.9, 138.1, 134.5, 128.7, 127.1, 123.9, 105.2, 56.0, 54.8, 54.4, 53.8, 21.2; HRMS (ESI): calcd for $C_{18}H_{24}NO_8PSNa$ $[M + Na]^+$ 468.0857, found 468.0856.

*Dimethyl (4-chlorophenylsulfonamido)(4-hydroxy-3,5-dimethoxyphenyl) methylphosphonate* (**4m**): Yield: 365 mg (82%, white solid), mp 193–194 °C; IR (KBr) ν ($cm^{-1}$): 3529, 3103, 2959, 2885, 1624, 1521, 1470; $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.44 (d, $J$ = 10.9 Hz, 3H), 3.65 (s, 3H), 3.95 (d, $J$ = 10.8 Hz, 3H), 4.76 (dd, $J$ = 10.2 & 23.7 Hz, 1H, –CHP–), 5.54 (brs, OH), 6.4 (d, $J$ = 1.7 Hz, 2H), 7.1 (d, $J$ = 8.0 Hz, 2H), 7.51 (d, $J$ = 8.2 Hz, 2H), 7.72 (brm, NH); $^{13}$C NMR (100 MHz, $CDCl_3$) δ (ppm): 146.8, 139.6, 138.6, 134.8, 128.5, 128.3, 123.6, 105.3, 56.1, 54.8, 54.4, 54.0, 53.9; MS (APCI) *m/z*: 488.25 $[M + Na]^+$.

*Dimethyl (4-chlorophenylsulfonamido)(3-ethoxy-2-hydroxyphenyl)methylphosphonate* (**4n**): Yield: 364 mg (81%, white solid), mp 147–148 °C; IR (KBr) ν ($cm^{-1}$): 3446, 3111, 2941, 2890, 1587, 1477, 1397; $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.42 (t, 3H, $J$ = 7.0 Hz), 3.52 (d, $J$ = 10.6 Hz, 3H), 3.65 (s, 3H), 3.90 (d, $J$ = 10.7 Hz, 3H), 4.00 (m, 2H), 5.10 (dd, $J$ = 9.7 & 24.5 Hz, 1H, –CHP–), 6.08 (brs, OH), 6.57–6.77 (m, 3H, ArH), 7.10 (d, $J$ = 11.2 Hz, 2H), 7.53 (d, $J$ = 11.2 Hz, 2H), $^{13}$C NMR (100 MHz, $CDCl_3$) δ (ppm): 145.81, 143.1, 138.5, 128.4, 128.2, 121.2, 120.1, 118.6, 111.2, 64.5, 54.6, 54.0, 14.8; MS (APCI) *m/z*: 472.24 $[M + Na]^+$, 474.25 $[(M + 2) + Na]^+$.

*(E)-4-(3-(Dimethoxyphosphoryl)-3-(4-methylphenylsulfonamido)prop-1-en-1-yl)-2-methoxyphenyl acetate* (**4o**): Yield: 396 mg (81%, white solid), mp 183–184 °C; IR (KBr) ν ($cm^{-1}$): 3127, 2959, 1770. 1599, 1509, 1465; $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.26 (s, 3H), 2.30 (s, 3H), 3.73 (d, $J$ = 10.7 Hz, 3H), 3.78 (s, 3H), 3.82 (d, $J$ = 10.6 Hz, 3H), 4.39 (m, 1H, –CHP–), 5.80 (m, 1H, CH = C<u>H</u>-CHP-), 6.27–6.32 (dd, J = 4.1 & 15.8 Hz, 1H), 6.55–6.68 (m, 2H including NH), 6.73 (s, 1H), 6.89 (d, $J$ = 8.1 Hz, 1H), 7.15 (d, 8.2 Hz, 2H), 7.74 (d, $J$ = 8.3 Hz, 2H); HRMS (ESI): calcd for $C_{21}H_{26}NO_8PSNa$ $[M + Na]^+$ 506.1014, found 506.1023.

## Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bioorg.2018.09.023.

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