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Facile microwave-assisted synthesis and antitubercular evaluation of novel aziridine derivatives

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ABSTRACT

Novel 2-(aryloxymethyl)aziridines and 2-((3-aryl-1-phenylallyloxy)methyl)aziridine derivatives were prepared *via* ring-opening reaction of epoxides. The synthesized derivatives were characterized by using elemental analysis (EA), FT-IR, ^{13}C NMR, and ^{1}H NMR. The in vitro antitubercular activities of the synthesized compounds were evaluated against *Mycobacterium tuberculosis* H37Rv (MTB H37Rv) strain using MTT-MABA assay. All the aziridine derivatives exhibited improved persuasive antitubercular activity against MTB H37Rv in comparison with standard drugs. Among the tested compounds, 2-(naphthalene-1-yloxy) methyl aziridine (**5b**), 2-(naphthalene-2-yloxy)methylaziridine (**5c**), 2-(*m*-tolyloxymethyl)aziridine (**5e**), 2-(3-(4-methoxyphenyl)-1-phenylalloxy)methylaziridine (**12b**) and 2-(3-(2-chlorophenyl)-1-phenylallyloxy)methylaziridine (**12c**) revealed promising activity against MTB H37Rv. Specifically, compound **5b** and **12 b** showed three-times more active (MIC = 0.5 μg/mL) than the standard drugs ethambutol (MIC = 1.56 μg/mL) and ciprofloxacin (MIC = 1.56 μg/mL).

1. Introduction

Tuberculosis (TB) is one of the most contagious air-borne diseases caused by *Mycobacterium tuberculosis* (MTB), causing more deaths than any other infection worldwide [1]. Conferring to universal TB, Report-2018 TB is one of the topmost 10 reasons of human demise globally in 2017 [2]. The current therapy comprises of longstanding multi-drug combination that is non-compliant with treatment and leads to associated adverse side effects. Various studies led by the World Health Organization (WHO) divulge 10 million people suffer from MTB and 1.6 million dies from it (comprising 0.3 million in HIV patients) [3-5]. MTB is a prominent killer of HIV-positive patients and a vital cause of antimicrobial resistant-related death. TB is cured with complex therapeutic drugs, which comprises several antibiotics that target different cellular processes. According to the WHO, the global TB reports estimate that in 2017, women 3.2 million, men 5.8 million, and children 1.0 million suffer from TB and 2, 30,000 died from TB (comprising children with HIV-positive related TB, WHO, 2018). After a certain period, the pathogen resisted the two most powerful drugs, such as fluoroquinolones and rifampicin. Universally in 2017, 558,000 peoples were exposed to TB and 160,000 multidrug resistance (MDR-TB/RR-TB) and rifampicin resistance (RR-TB) [6,7]. However, there are many anti-tubercular drug molecules in the pipeline, but there is still an urgent necessity to scrutinize novel anti-tubercular drug molecules to battle the peril of TB [8].

Over the past two decades, almost enormous quantities of natural products and organic synthetic products have been studied for TB infections [9]. Of these, aziridines are of great interest due to the following facts: aziridines are a group of nitrogenous species related to epoxides and are natural and synthetic organic compounds that have a three-membered heterocyclic ring with one amine moiety [10-14]. The organic chemist considered the aziridine system to be well known because of its tremendous potential in both organic synthesis and medicinal chemistry [15-18]. Aziridine nucleus occurs in several natural and many synthetic compounds of biological and pharmacological interest [11,12].

From the multitude of contributions in the scientific literature [13], it is clear that aziridines can be regarded as cherished compounds from a clinical and synthetic point of view [14]. More-

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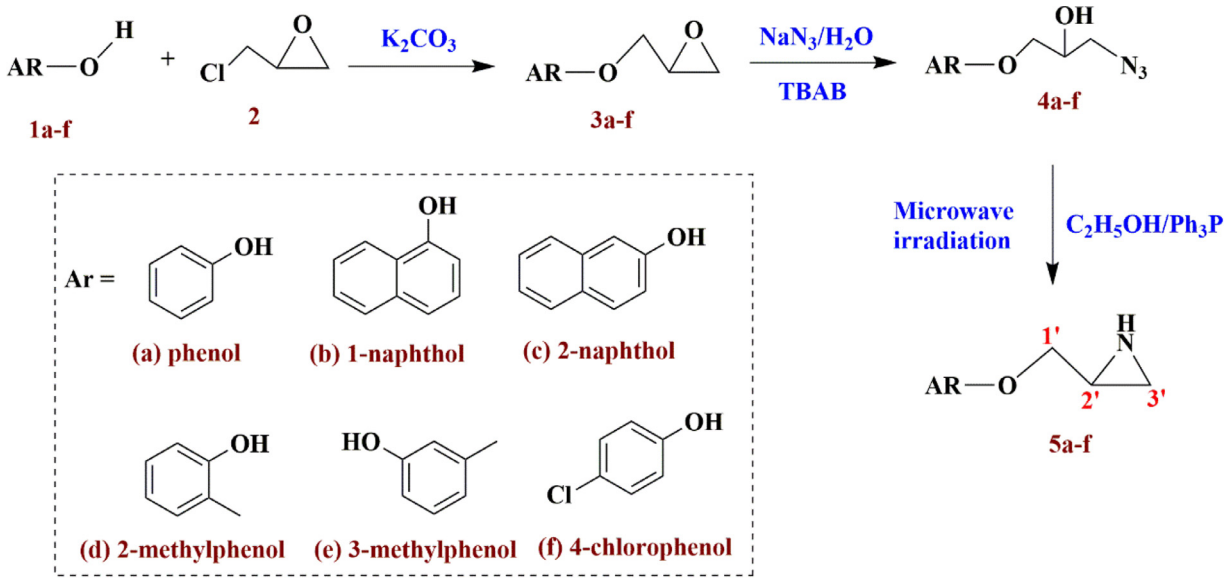
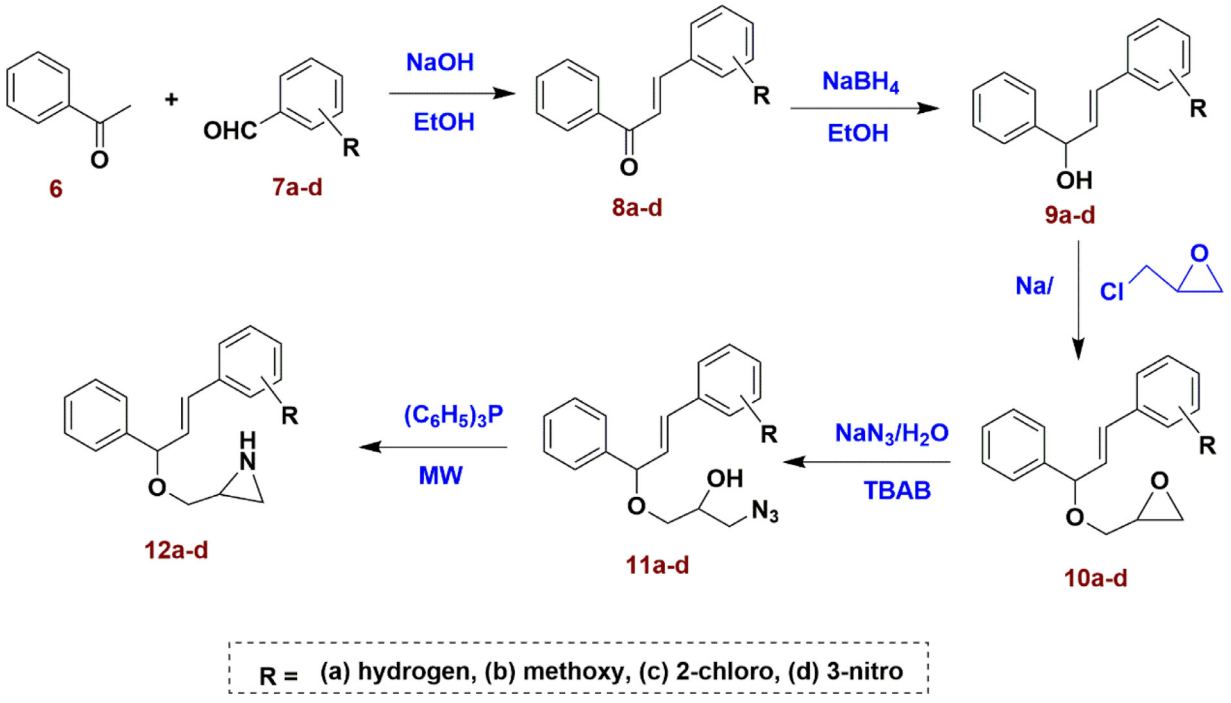


Scheme 1. Synthesis of 2-(aryloxymethyl) aziridines (5a-f).



Scheme 2. Synthesis of 2-((3-Aryl-1- phenylallyloxy)methyl)aziridine (12a-d).

over, the scope and application of aziridine compounds in chemistry have rapidly increased, as these classes of compounds have drawn substantial attention owing to their biological properties. It has been found that aziridine compounds play an important role as therapeutic activities such as cytotoxic [19], antiviral [20], antifungal [21], antimicrobial, antimalarial [22] and antitubercular properties [23] antiproliferative and antidiabetic activities [24]. Interestingly, the synthesized aziridine derivatives showed better performance than the conventional standard drugs. With this perspective, we have synthesized some novel compounds of aziridines and evaluated them for antitubercular activity by the facile microwave-assisted reaction method.

Important clinical compounds that are synthesized through facile steadfast reactions obtain the most fascinated attention. Non-conventional conditions and their approach to implementing novel synthetic organic reaction become very popular, mainly to avoid growing ecological concerns [25]. The literature shows that scientists have ultimately contributed to the fast development of novel chemical companies available for biological assessment. The microwave-assisted reaction is a priceless technology for the preparation of organic compounds over time because it reduces the reaction time with improved selectivity and yields [26,27].

Therefore, the present work reports a facile microwave-assisted synthesis of a new class of aziridine derivatives (**5a-f** and **12a-d**) *via* the ring-opening reaction of epoxides (Schemes 1 and 2). The synthesized aziridine compounds were characterized (elemental analysis, FT-IR, ^{1}H NMR, and ^{13}C NMR) and studied as antitubercular activity against MTB H37Rv strain.

2. Experimental

2.1. Measurements and reagents

All the starting materials and precursors were used in this work are analytical grade and are purchased from Sigma Aldrich. Fourier Transform InfraRed spectra (FT-IR) measurements were recorded on a Bruker Alpha FT-IR spectrophotometer with a frequency range of 4000cm^{-1}–500 cm^{-1} by the attenuated total reflection (ATR) method. Data were collected over 64 scans with a resolution of 4 cm^{-1}. Carbon and proton nuclear magnetic resonance spectra (^{13}C NMR and ^{1}H NMR) were recorded with a Bruker 500 MHz at 25 °C, with $CDCl_3$ or DMSO–d_6 as the solvent. Chemical shift (δ) and coupling constants (J) are uttered in part per million (ppm) and hertz, respectively. NMR data are given as several protons and multiplicity: singlet (s), doublet (d), triplet (t), multiplet (m). Mass spectra were performed on Shimadzu GCMS-QP 1000 EX mass spectrometer (EI; 70 eV model). The elemental analysis (EA) was performed on CHNS-932-LECO elemental analyzer.

2.2. Synthesis

2.2.1. General synthesis of 2-(aryloxymethyl)oxiranes (3a-f)

The general procedure for **3a-f** synthesis was as follows. Into a doubled-necked round-bottomed flask (100 mL) phenol compounds (**1a-f**, shown in Scheme 1) (0.01 mol) and 20 mL of epichlorohydrin (EPH) (**2**) were added, and the mixture was refluxed for 180 min in the presence of a mild base (K_2CO_3). Subsequently, the reaction mixture was cooled to ambient temperature and then the excess EPH was eliminated under vacuum. The achieved residue was poured into cold-water and mined with ethyl acetate. Finally, the obtained 2-(aryloxymethyl)oxiranes (**3a-f**) product was dried in an oven under a vacuum.

2.2.2. General synthesis of 1-azido-3-(aryl) propane-2-ol (4a-f)

NaN_3 (0.03 mol) and 2-(Aryloxymethyl)oxiranes (**3a-f**) (0.01 mol) were dissolved in ethanol and water mixture in the ratio of 50:50 vol% and stirred for 1 h. Subsequently, a pinch of tetrabutylammonium bromide (TBAB) was introduced to the above mixture to improve the completeness of the reaction. The obtained product was treated with ice-cold water and separated with ethyl acetate. Finally, the obtained 1-azido-3-(aryl) propan-2-ol (**4 a-f**) product was dried in an oven under a vacuum.

2.2.3. General synthesis of 2-(aryloxymethyl)aziridines (5a-f)

1-Azido-3-(aryl)propan-2-ols (**4a-f**) (0.01 mol) and triphenylphosphine (0.01 mol) were thoroughly mixed in ethanol, after which the reaction mixture was subjected to microwave irradiation yields 2-(aryloxymethyl) aziridines (**5a-f,** physical state: brown viscous gel).

2.2.3.1. 2-(Phenoxymethyl)aziridine (5a). Yield 70%. IR ($CHCl_3$) ν/cm^{-1}) = 3381, 2931, 2361, 2101, 1628, 1391, 1217, 1119, 1038, 959, 838. ^{1}H NMR (500 MHz, $CDCl_3$); δ (ppm) = 1.41, 1.67 (m, 2H, -CH_2 of aziridine ring), 2.11 (m, 1H, C1'–CH), 3.67, 3.42 (m, 2H, C2'–CH2), 6.99–7.34 (Ar–H). ^{13}C NMR (500 MHz, $CDCl_3$); δ (ppm) = 23.31, 28.83, 70.82 (C–C), 114.01 (*C* = *C*), 120.35 (*C* = *C*), 129.33 (*C* = *C*), 159.43 (Ar–C–O). MS (EI, 70 eV): *m/z (%)* = 149. Elemental Anal. Calcd. (%) for $C_9H_{11}NO$ = *C*, 72.46; H, 7.43; N, 9.39; O, 10.72; found = *C*, 72.28; H, 7.17; N, 9.13; O, 10.43.

2.2.3.2. 2-(Naphthalene-1-yloxy) methyl aziridine (5b). Yield 65%. IR ($CHCl_3$) ν/cm^{-1}) = 3386, 2936, 2880, 2366, 2106, 1633, 1396, 1222, 1124, 1043, 964 and 843. ^{1}H NMR (500 MHz, $CDCl_3$); δ (ppm) = 1.44, 1.71 (m, 2H, –CH_2 of aziridine ring), 2.11 (m, 1H, C'1–CH), 3.67, 3.45 (m, 2H, C2'–CH_2), 6.68–8.36 (Ar–H). ^{13}C NMR (500 MHz, $CDCl_3$); δ (ppm) = 18.23, 28.11, 28.71, 71.12 (C–C), 107.33, 120.84, 125.41, 126.05, 127.85, 128.54, 133.51, 133.63, 154.32. MS (EI, 70 eV): *m/z (%)* = 199. Elemental Anal.Calcd. (%) for $C_{13}H_{13}NO$ = *C*, 78.36; H, 6.58; N, 7.03; O, 8.03; found = *C*, 78.07; H, 6.29; N, 6.77; O, 7.78.

2.2.3.3. 2-(Naphthalene-2-yloxy) methylaziridine (5c). Yield: 65%. IR ($CHCl_3$) ν/cm^{-1}) = 3385, 2936, 2879, 2363, 2105, 1632, 1398, 1224, 1126, 1045, 966 and 845. ^{1}H NMR (500 MHz, $CDCl_3$); δ (ppm) = 1.41, 1.67 (m, 2H, –CH_2 of aziridine ring), 2.11 (m, 1H, C'1–CH), 3.77, 3.52 (m, 2H, C'2–CH_2), 7.48–7.97 (Ar-C). ^{13}C NMR (500 MHz, $CDCl_3$); δ (ppm) = 23.04, 28.84, 70.83 (C–C), 118.11, 124.02, 126.63, 126.70, 126.91, 129.50, 129.64, 155.66. MS (EI, 70 eV): *m/z (%)* = 199 (Fig. S1). Elemental Anal.Calcd. (%) for $C_{13}H_{13}NO$ = *C*, 78.36; H, 6.58; N, 7.03; O, 8.03; found = *C*, 78.08; H, 6.31; N, 6.75; O, 7.75.

*2.2.3.4. 2-(*ortho-*Tolyloxymethyl)aziridine (5d).* Yield: 70%. IR ($CHCl_3$) ν/cm^{-1}) = 3387, 2938, 2881, 2365, 2107, 1634, 1400, 1226, 1128, 1047, 968, 847. ^{1}H NMR (500 MHz, $CDCl_3$); δ (ppm) = 1.42, 1.65 (m, 2H, –CH_2 of aziridine ring), 2.11 (m, 1H, C1'–CH), 2.15 (s, 3H, –CH_3), 3.67, 3.42 (m, 2H, C2'–CH_2), 6.89- 7.12 (Ar–C). ^{13}C NMR (500 MHz, $CDCl_3$); δ (ppm) = 15.42, 23.00, 28.83, 70.81, 112.04, 120.24, 126.32, 126.78, 131.29, 155.47. MS (EI, 70 eV): *m/z (%)* = 163. Elemental Anal.Calcd. (%) for $C_{10}H_{13}NO$ = *C*, 73.59; H, 8.03; N, 8.58; O, 9.80; found = *C*, 73.34; H, 7.79; N, 8.35; O, 9.54.

*2.2.3.5. 2-(*meta-*Tolyloxymethyl)aziridine (5e).* Yield: 72%. IR ($CHCl_3$) ν/cm^{-1}) = 3389, 2940, 2883, 2363, 2109, 1630, 1402, 1228, 1130, 1049, 970, 849. ^{1}H NMR (500 MHz, $CDCl_3$); δ ppm = 1.41, 1.66 (m, 2H, –CH_2 of aziridine ring), 2.11 (m, 1H, C1′–CH), 2.34 (s, 3H, –CH_3), 3.67, 3.42 (m, 2H, C2′ –CH_2), 6.79–7.22 (Ar–C). ^{13}C NMR (500 MHz, $CDCl_3$); δ ppm = 21.60, 23.02, 28.89, 70.88, 111.47, 113.01, 120.66, 129.29, 139.05, 157.34. MS (EI, 70 eV): *m/z (%)* = 163. Elemental Anal. Calcd. (%) for $C_{10}H_{13}NO$ = *C*, 73.59; H, 8.03; N, 8.58; O, 9.80; found = *C*, 73.33; H, 7.77; N, 8.32; O, 9.52.

2.2.3.6. 2-((4-Chlorophenoxy)methyl)aziridines (5f). Yield: 60%. IR ($CHCl_3$) ν/cm^{-1}): 3394, 2944, 2887, 2366, 2112, 1634, 1406, 1232, 1134, 1053, 974, 853. ^{1}H NMR (500 MHz, $CDCl_3$); δ ppm = 1.46, 1.65 (m, 2H, –CH_2 of aziridine ring), 2.11 (m, 1H, C1′–CH), 3.67, 3.42(m, 2H, C2′ –CH_2), 7.03–7.38 (Ar–C). ^{13}C NMR (500 MHz, $CDCl_3$); δ (ppm) = 23.23, 28.85, 70.82, 117.50, 125.99, 130.54, 157.51. MS (EI, 70 eV): *m/z (%)* = 183. Elemental Anal. Calcd. (%) for $C_9H_{10}C_lNO$ = C, 58.86; H, 5.49; Cl, 19.31; N, 7.63; O, 8.71; found = *C*, 58.59; H, 5.23; N, 19.05; O, 8.43.

2.2.4. ***General synthesis of 3-aryl-1-phenylprop-2-en-1-one (8a-d)***

The general procedure for **8a-d** synthesis was as follows. To a stirred alcoholic solution of acetophenone (**6**) in 10 mL of 95% ethanol, aromatic aldehydes (**7a-d**) (0.01 mol) was added at room temperature. Afterward, 6 mL of 10% NaOH solution was introduced drop-wise to it. After stirring for 30 min, 20 mL of ice-cold water was added to it. Finally, the obtained product (**8a-d**) was filtered and recrystallized using aqueous ethanol.

2.2.5. General synthesis of 3-aryl-1-phenylprop-2-en-1-ol (9a-d)

Into a doubled-necked round-bottomed flask (100 mL) a suspension of 3-aryl-1-phenylprop-2-en-1-one (**8a-d**) (0.01 mol) and sodium borohydride (0.02 mol) in ethanol (10 mL) was added and refluxed for 180 min. Then, the reaction mixture was then poured into ice-cold water, and extracted with ethyl acetate. Lastly, the obtained product (**9a-d**) was dried in an oven under a vacuum.

2.2.6. General synthesis of 2-(1-phenyl-3-arylallyloxy)methyloxirane (10a-d)

To a solution of 1–chloro-2, 3-epoxypropane (5 mL), 3-aryl-1-phenylprop-2-en-1-ol (**9a-d**) (0.01 mol), and sodium metal (0.02 mol) were added into the round-bottomed flask and refluxed for 90 min. Afterward, the mixture was filtered, extracted and the solvent was eliminated under vacuum condition. The obtained residue was treated with cold water and extracted with diethyl ether. Finally, the achieved product (**10a-d**) was dried in an oven under a vacuum.

2.2.7. General synthesis of 1-azido-3-(3-aryl-1-phenylallyloxy) propan-2-ol (11a-d)

To a solution of 2-(1-phenyl-3-arylallyloxy)methyl oxirane (**10a-d**) (0.01 mol), a solution of sodium azide (0.03 mol) in 50:50 vol% of water and ethanol and a pinch of TBAB were added and the reaction mixture was constantly agitated for 60 min. Subsequently, the reaction mixture was poured into ice-cold water and extracted with ethyl acetate. Finally, the achieved product **11a-d** was dried in on over under a vacuum.

2.2.8. General synthesis of 2-((3-aryl-1-phenylallyloxy)methyl)aziridine (12 a-d)

Compounds **11a-d** (0.01 mol) and triphenylphosphine (0.01 mol) were thoroughly mixed in ethanol, after which the reaction mixture was subjected to microwave irradiation yields 12 a-d (physical state: brown viscous gel).

2.2.8.1. 2-(1, 3-Diphenylallyloxy)methylaziridine (12a). Yield: 70%. IR ($CHCl_3$) ν/cm^{-1} = 3376, 2931, 2361, 2078, 1628, 1391, 1176, 1119, 1038, 719 and 690. ^1H NMR (500 MHz, $CDCl_3$); δ (ppm) = 1.40, 1.68 (m, 2H, -CH_2 of aziridine ring), 1.93 (m, 1H, C1′–CH), 3.77, 3.52 (m,2H, C2′–CH_2), 4.31 (m, 1H, -CH of allyl), 6.64, 6.38 (m, 2H, –*C* = *H* of allyl, 7.27–7.44 (Ar–C). ^{13}C NMR (500 MHz,$CDCl_3$); δ (ppm) = 23.19, 29.67, 78.71, 81.11, 124.64, 127.28, 127.83, 129.04, 136.42, 139.87. MS (EI, 70 eV): *m/z (%)* = 265. Elemental Anal. Calcd. (%) for $C_{18}H_{19}NO$ = *C*, 81.47; H, 7.22; N, 5.28; O, 6.03; found = *C*, 81.22; H, 6.97; N, 5.02; O, 5.77.

2.2.8.2. 2-(3-(4-Methoxyphenyl)−1-phenylalloxy)methylaziridine (12b). Yield: 65%. IR ($CHCl_3$) ν/cm^{-1} = 3378, 3054, 2396, 2336, 2082, 1628, 1393, 1179, 1117, 1040, 721 and 695. ^1H NMR (500 MHz, $CDCl_3$); δ (ppm) = 1.69, 1.41 (m, 2H, –CH_2 of aziridine ring), 1.93 (m, 1H, C'1–CH), 3.77, 3.52 (m, 2H, C'2–CH_2), 3.81 (s,3H, –CH_3), 4.31 (m,1H, –CH of allyl), 6.66, 6.37 (m, 2H, –*C* = *H* of allyl, 7.48–7.97 (Ar–C). ^{13}C NMR (500 MHz, $CDCl_3$); δ (ppm) = 23.20, 29.60, 55.85, 78.74, 80.19, 81.13, 124.69, 127.44, 128.63, 128.78, 129.11 (*C* = *C*), 129.64, 130.25, 39.93, 159.80. MS (EI, 70 eV): *m/z (%)* = 283. Elemental Anal.Calcd. (%) for $C_{19}H_{21}NO_2$ = *C*, 77.26; H, 7.17; N, 4.74; O, 10.83; found = *C*, 77.02; H, 6.92; N, 4.48; O, 10.58.

2.2.8.3. 2-(3-(2-Chlorophenyl)−1-phenylallyloxy)methylaziridine (12c). Yield: 70%. IR ($CHCl_3$) ν/cm^{-1}): 3380, 3057, 2398, 2338, 2084, 1630, 1395, 1181, 1119, 1042, 723 and 697. ^1H NMR (500 MHz, $CDCl_3$); δ (ppm) = 1.46, 1.71 (m, 2H, –CH_2 of aziridine ring), 1.93 (m, 1H, C1′–CH), 3.58, 3.33 (m, 2H, C2′–CH_2), 4.31 (m,1H, –CH of allyl), 6.64, 6.48 (m, 2H, –*C* = *H* of allyl), 7.32–7.44 (Ar–C). ^{13}C NMR (500 MHz, $CDCl_3$); δ (ppm) = 23.44, 29.83, 78.79, 81.12, 126.61, 127.43, 127.85, 128.62, 129.18, 129.33, 129.91, 133.00, 134.95, 139.92. MS (EI, 70 eV): *m/z (%)* = 299. Elemental Anal. Calcd. (%) for $C_{18}H_{18}C_lNO$ = *C*, 72.11; H, 6.05; Cl, 11.83; N, 4.67; O, 5.34; found = *C*, 71.86; H, 5.79; Cl, 11.57; N, 4.43; O, 5.09.

2.2.8.4. 2-(3-(3-Nitrophenyl)−1-phenylallyloxy) methylaziridine (12d). Yield: 75%. IR ($CHCl_3$) ν/cm^{-1}) = 3384, 3060, 2877, 2400, 2344, 1634, 1399, 1187, 1123, 1046, 727 and 700. ^1H NMR (500 MHz, $CDCl_3$); δ (ppm) = 1.40 & 1.66 (m, 2H, –CH_2 of aziridine ring), 1.93 (m, 1H, C1′–CH), 3.58, 3.33 (m, 2H, C2′–CH_2), 4.31 (m, 1H, –CH of allyl), 6.91, 6.48 (m, 2H, –*C* = *H* of allyl), 7.48–8.31 (Ar–C). ^{13}C NMR (500 MHz, $CDCl_3$); δ (ppm) = 23.04, 29.61, 78.75, 81.14, 124.63, 127.48, 128.69, 129.57, 134.60, 136.16, 147.86. MS (EI, 70 eV): *m/z (%)* = 310. Elemental Anal. Calcd. (%) for $C_{18}H_{18}N_2O_3$ = *C*, 69.66; H, 5.85; N, 9.03; O, 15.47; found = *C*, 69.42; H, 5.59; N, 8.78; O, 15.21.

2.2.9. Antitubercular studies

Synthesized aziridine derivatives were screened against MTB H37Rv using MTT-MABA assay [28]. The inoculum was made by employing a new LJ medium re-suspended in the 7H9-S medium. Originally, the 7H9-S medium was prepared by 7H9 broth in 0.1% casitone, oleic acid, 0.5% glycerol, albumin, catalase [OADC], and dextrose. The prepared medium attuned to a McFarland tube No. 1 and it was diluted to 1:20; 100 µL and employed as inoculum. The prepared stock solution was defrosted and diluted in 7H9-S at four-fold the last uppermost concentration verified. A germ-free 96-well microliter plate using 100 µl 7H9-S was used to prepare the two-fold dilutions of each drug. Growth control comprising no antibiotic and a germ-free control were also fortified on each plate. To evade evaporation during incubation, germ-free water was employed in all the perimeter wells. Lastly, the resultant plates were covered, sealed in plastic bags, and incubated at 35 °C under normal conditions. After one week of incubation, 30 mL of alamarBlue solution was added to each well, and again the plate was subjected to re-incubation overnight. The variation in color from blue (oxidized state) to pink (reduced) exposed the growth of bacteria and the MIC value was well-defined as the lowermost concentration of drugs that avert this color alteration.

3. Results and discussion

3.1. Characterization

The synthetic pathway adopted for the construction of novel 2-(aryloxymethyl) aziridines (**5a-f**) was displayed in Scheme 1. The different phenols (**1a-f**) were refluxed with EPH in the existence of K_2CO_3 to yield their 2-(aryloxymethyl) oxiranes (**3a-f**). Aryloxymethyl)oxiranes (**3a-f**) were prepared by condensation of excess phenols or substituted phenols with epichlorohydrin. The obtained **3a-f** were further reacted with sodium azide to yield the azido alcohols (**4a-f**). During the above ring-opening reaction [29-31], the sodium azide attacks the oxirane species on less substituted methylene groups through an SN2 mechanism produces **4a-f**. Further, the reaction of **4a-f** with triphenylphosphine on microwave irradiation resulted in the formation of title compounds 2-(aryloxymethyl)aziridines (**5a-f**) by the condensation reaction. The obtained products are namely, 2-(phenoxymethyl)aziridine (**5a**), 2-(naphthalene-1-yloxy) methyl aziridine (**5b**), 2-(naphthalene-2-yloxy)methylaziridine (**5c**), 2-(o-tolyloxymethyl)aziridine (**5d**), 2-(*meta*-tolyloxymethyl)aziridine (**5e**), and 2-((4-chlorophenoxy)methyl)aziridines (**5f**) are in good yield.

The presence of the aziridine group in structures of **5a-f** was confirmed by the presence of the IR band at around 2931–2940 cm^{-1}. The compounds **5a-f** (Fig. S2-S7) showed two multiplet at δ 1.70 and 1.45 ppm due to the existence of CH_2 and CH of the aziridine ring. The presence of multiplet at δ 2.11 ppm due to the presence of methine (C1′-CH) group. Similarly, the presence of a methylene (C'2-CH_2) group in compound **5a-f** was confirmed by the presence of δ 3.67 and 3.42 ppm. Further, the existence of

Table 1
Antitubercular activity of the synthesized compounds 5a-f and 12 a-d (a; High potent antitubercular compounds).

Compound	MIC(μg/mL)	Compound	MIC(μg/mL)	Compound	MIC(μg/mL)
5a	13.7	**12a**	11.5	Isoniazid	0.1
5b	0.5[a]	**12b**	0.5 [a]	Rifampicin	0.2
5c	3.125[a]	**12c**	2.50[a]	Ethambutol	1.56
5d	7.25	**12d**	15.75	Ciprofloxacin	1.56
5e	1.25 [a]				
5f	25				

an aromatic ring in the manufactured compounds (**5a-f**) was indicated by the appearance of δ at 6.99 – 7.34 ppm region. ^{13}C NMR spectra analysis gave the signal at δ = 23.04 and 28.84 ppm which is indicative of aziridine ring carbon. Similarly, the presence of an aliphatic methylenic group whereas aromatic carbon group in compound **5a-f** were confirmed by the existence of δ = 114.4–159.7 ppm.

The title compounds, novel 2-((3-aryl-1-phenylallyloxy) methyl)aziridine (**12a-d**) have been prepared by the following multi-step pathway, starting from aromatic aldehydes (Scheme 2). The chalcones, 3-aryl-1-phenylprop-2-en-1-one (**8a-d**) was synthesized by digesting acetophenone and aromatic aldehydes by the addition of NaOH. 3-Aryl-1-phenylprop-2-en-1-one (**8a-d**) was then careful reduction with sodium borohydride in refluxed ethanol solution and achieved 3-aryl-1-phenylprop-2-en-1-ol (**9a-d**). A solution of 1–chloro-2, 3-epoxypropane, 3-aryl-1-phenylprop-2-en-1-ol (**9a-d**), and sodium metal mixture were refluxed for getting the respective 2-(1-phenyl-3-arylallyloxy)methyloxirane (**10a-d**). The obtained 2-(1-phenyl-3-arylallyloxy)methyloxirane (**10a-d**) were reacted with NaN_3 in the existence of TBAB to yield their 1-azido-3-(3-aryl-1-phenylallyloxy) propan-2-ol (**11a-d**).

When the microwave irradiation of the 1-azido-3-(3-aryl-1-phenylallyloxy) propan-2-ol (**11a-d**) with triphenylphosphine gave the title compounds, 2-((3-aryl-1-phenylallyloxy) methyl)aziridine (**12 a-d**) with moderate to better yield.The obtained product are namely, 2-(1, 3-diphenylallyloxy)methylaziridine (**12a**), 2-(3-(4-ethoxyphenyl)−1-phenylalloxy)methylaziridine (**12b**), 2-(3-(2-Chlorophenyl)−1-phenylallyloxy)methylaziridine (**12c**), 2-(3-(3-Nitrophenyl)−1-phenylallyloxy) methylaziridine (**12d**).

The IR spectra of the aziridine derivative (**12a-d**) specify the creation of products as it displays a typical absorption peak at around 2931–2940 cm^{-1}, which corresponds to the aziridine group. The ^{1}H NMR spectra (Fig. S8-S11) of aziridine derivative (**12a-d**) show chemical shift peaks, multiplets at around δ 1.66 & 1.46 ppm due to the -CH_2 of aziridine ring and the peak at δ 7.27–8.31 ppm region for aromatic protons, respectively. The presence of two characteristics of carbon signals is witnessed at around δ = 23.07 and 29.84 ppm in the ^{13}C NMR spectrum of **12a-d** owing to the signals of aziridine ring carbons, confirming the successful preparation of compounds **12a-d**.

3.2. Biological studies

The in vitro anti-TB activity of synthesized compounds **5a-f** and **12a-d** against MTB H37Rv using the MABA assay and was evaluated and their minimum inhibitory concentration (MIC) values are tabulated in Table 1 at μg/mL [32]. From the outcomes of anti-TB activity, all the synthesized compounds showed appreciable activity compared to the standard drugs rifamycin, ethambutol, and ciprofloxacin. However, compounds **5b** (MIC: 0.5 μg/mL), **5c** (MIC: 3.125 μg/mL), **5e** (MIC: 1.25 μg/mL), **12b** (MIC: 0.5 μg/mL), and **12c** (MIC: 2.50 μg/mL) showed the highest potent activity against MTB H37Rv in comparison with reference drugs. Compound **5b** and **12b** also showed the highest potent activity (MIC: 0.5 μg/mL) which is three-times highly active than standard drugs, ethambutol (MIC: 1.56 μg/mL), and ciprofloxacin (MIC: 1.56 μg/mL). The existence of phenyl groups in its aziridine moiety exhibits good anti-TB activity against MTB H37Rv. The role of phenyl groups in its aziridine moiety in improving anti-TB activities is supported by the studies of Zayane et al. [33].

3.3. Molecular docking studies

The anti-TB screening revealed that the compounds 5b, 5e, and 12b exhibited good activity against MTB H37Rv. Keep in mind that all the compounds obtained are newly synthesized, there is no literature information regarding their biological function. Prediction of Functional Spectrum for Material (PASS) was used to gain a sense of their potential activity online program. This instrument is invented to offer possible biological activity based on the compound's molecular structure. The receptor 5UHA was selected for docking studies. To determine whether the docking parameters were adequate, flexible ligand-rigid enzyme simulation was performed with 5UHA. The compound 5b interaction with 5UHA (Fig. 1) shows nitrogen atom of the aziridine moiety made a conventional H-bond with Gly538, and the pi-donor hydrogen

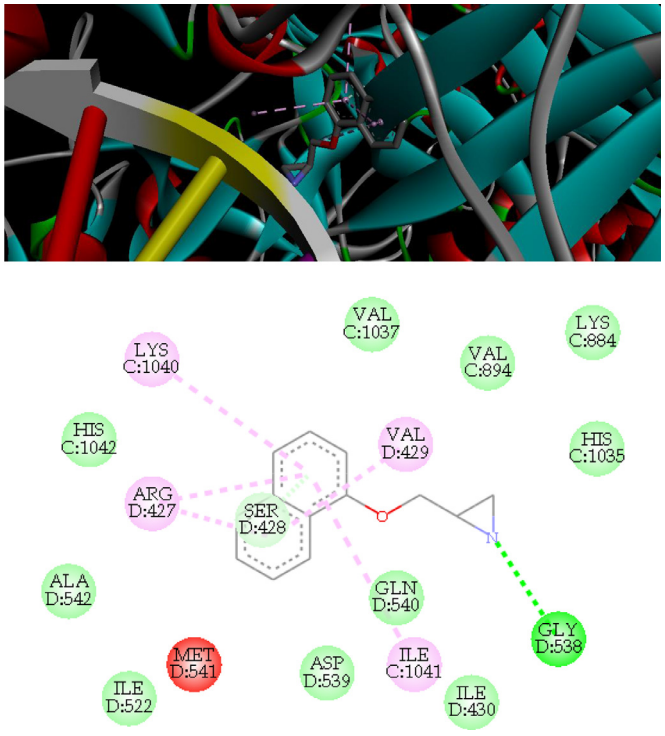


Fig. 1. Docking mode, hydrogen and non-hydeogen bonding interaction of the compound **5b** with 5UHA receptor.

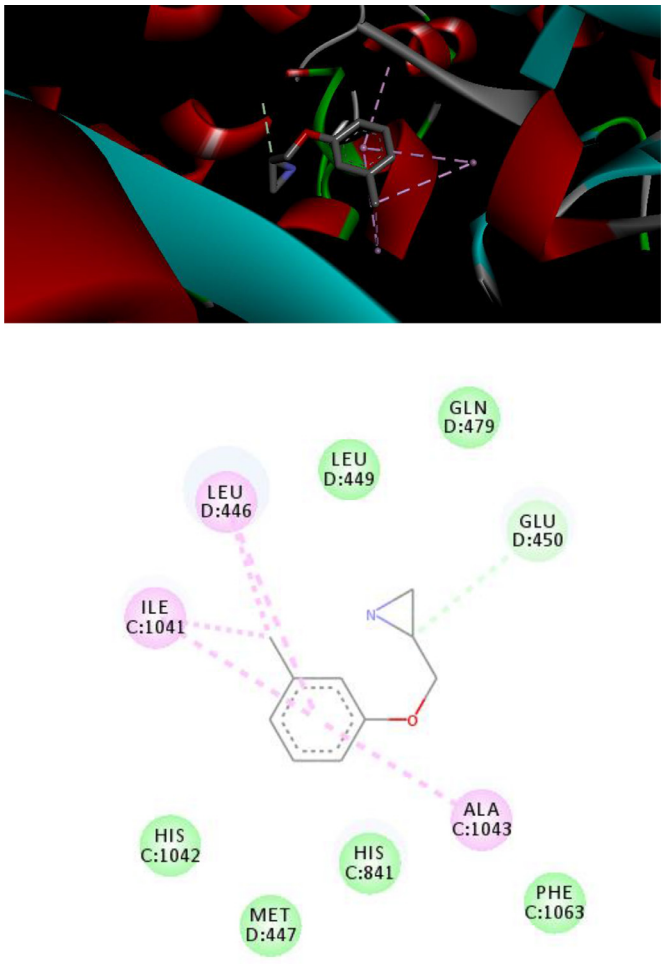


Fig. 2. Docking mode, hydrogen and non-hydrogen bonding interaction of the compound 5e with 5UHA receptor.

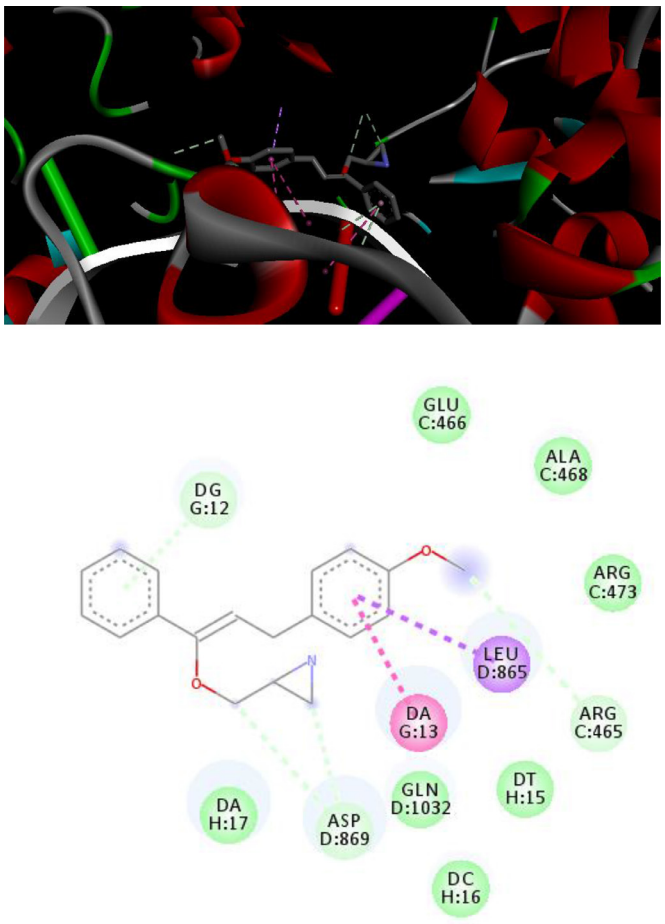


Fig. 3. Docking mode, hydrogen and non-hydrogen bonding interaction of the compound 12b with 5UHA receptor.

bond has a bond distance of 2.42425 and 2.37381 Å with ser428, respectively. The compound 5b is encapsulated in a hydrophobic cavity formed by lys1040, ile1041, arg427, and val429 with a bond length of 4.77356, 5.2971, 5.1705, 3.68931, and 5.43094, respectively.

In addition to this π-alkyl hydrophobic interaction was shown by lys1040, ile1041, arg427, and val429. In the second region of 5e and 5UHA (Fig. 2), three different types of interactions were shown. π-alkyl and alkyl hydrophobic interactions amid ile1041, ala1043, and leu446 have been shown. The interaction amid 5e and glu450 has weak H-bonding interactions. In the hydrophobic chamber, alkyl-alkyl interaction was shown between ile1041 and leu446 with a 5e compound. Weak H-bonding interaction is established between 5e and glu450. In the third region, hydrophobic activity formed by dg12, da13, dg13, and leu865 shows π-sigma interactions with a bond distance of 5.5442, 5.61401, 4.60537, 3.87417 Å, respectively. Weak hydrogen bond interaction occurs between arg465, arg869, and asp869 with a bond length of 3.69983, 3.48711, and 3.44505 Å, respectively. In the hydrophobic chamber (Fig. 3), aziridine moieties are situated via π donor-hydrogen bonding interaction between dg12 and dg13 with 3.14882 and 3.30779 Å respectively. It is vital to highlight that the examined compounds 5b, 5e, and 12b establish hydrogen bonds with the 5UHA receptor. These facts described the excellent anti-TB activity of aziridine compounds 5b, 5e, and 12b.

4. Conclusions

The present work describes a series of new 2-(aryloxymethyl)aziridines (**5 a-f)** and 2-((3-aryl-1-phenylallyloxy)methyl)aziridines (**12a-d**) derivatives that were synthesized by the ring-opening reaction of epoxides. The structures of the synthesized aziridine derivative **5a-f** and **12a-d** were confirmed by various spectroscopic techniques and elemental analysis. The synthesized compounds are screen for their in vitro anti-TB activity against MTB H37Rv using the MABA assay. Among these aziridine compounds, **5c, 5e**, and **12c** have displayed high potent anti-TB activity against MTB H37Rv. Out of these screened compounds, **5b** and **12b** were found to be the most potent inhibitor for MTB H37Rv. These compounds, **5b** and **12b** have shown 0.5 μg/mL MIC against MTB H37Rv which is three-time better than standard drugs. Therefore, it can be concluded from the above results that the prepared aziridine derivatives offer a fascinated foremost series for the invention of novel anti-TB agents.

Author statement

Our revised manuscript entitled **Facile microwave-assisted synthesis and antitubercular evaluation of novel aziridine derivatives**". "**Ms. Ref. No.: MOLSTRUC-d-20–02,638**" with the authors including "**Perumal Sarojini[a], Malaichamy Jeyachandran[b]*, Dharmarajan Sriram[c], Palraj Ranganathan[d], S**

Gandhimathi[b]", is the author done all the experimental, characterization, analysis, and wrote most part of the manuscript.

Declaration of Competing Interest

The authors declare no competing financial interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.molstruc.2021.130038.

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