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Research Article

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Synthesis and biological evaluation of amino alcohol derivatives of 2-methylbenzimidazole as antitubercular and antibacterial agents

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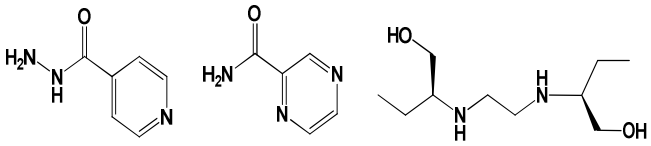
ABSTRACT

*We report synthesis of novel series of amino alcohol derivatives of 2-methyl benzimidazole. These compounds have been synthesized by epoxide ring opening of 2-methyl benzimidazole with different substituted cyclic amines. These synthesized compounds have been characterized using IR, ^{1}H NMR and ES-MS spectral data together with their melting point. These compounds **(4a-4o)** were evaluated for their preliminary in-vitro antibacterial activity against Gram +ve (Staphylococcus aureus) and Gram -ve (Escherichia coli) pathogens. Out of all tested compounds, the compounds **4c, 4j, 4n** and **4o** showed moderate to good activity compared to standard drugs Ciprofloxacin and Norfloxacin. Further, these compounds were screened for their antitubercular activity against Mycobacterium tuberculosis H37Rv strain by MABA method. The compound **4c** and **4o** were found to exhibit moderate antimycobacterial activity compared to standard Isoniazid.*

Keywords: 2-methyl benzimidazole, epoxide, H37Rv strain, antituberculosis, antibacterial.

INTRODUCTION

Tuberculosis (TB), a contagious infection caused by the airborne transmission of *Mycobacterium tuberculosis* (MTB), still remains the leading cause of the worldwide death among the infectious disease [1]. It was estimated that in year 2011, about 8.7 million new cases of TB continue to occur each year and about 1.4 million peoples died of this disease annually [2]. This is also a leading cause of death amongst people who are HIV-positive (13 % of death worldwide) [3]. The current threat in TB treatment lies in the emergence of strains resistant to the best anti-tubercular drugs, Isoniazid (INH), Pyrazinamide (PZA), Rifampicin (RIF) and Ethambutol (EMB). Ethambutol is synthetic amino alcohol.



The current TB treatment comprises of 3-4 drugs for a period of 6-9 months [4]. Novel drugs are urgently required, which can shorten this long-treatment period and target multi-drug-resistant strains of TB.

Infectious microbial disease remains a pressing problem worldwide, because microbes have resisted prophylaxis or therapy longer than any other form of life. In recent decades, the prevalence of drug resistant bacteria is growing at an alarming rate in both developing and developed countries [5]. The increase in bacterial resistance has attracted considerable interest in the discovery and development of new classes of anti-bacterial agents.

As we know that, Heterocyclic species like benzimidazole derivatives have received much interest in the field of medicinal chemistry because of its synthetic utility and broad spectrum of pharmacology activity. Various benzimidazole moieties are known to have varied biological activities such as antitumor [6, 7], anticancer [8, 9], anti-HIV-1 [10, 11], antibacterial [12, 13], proton pump inhibitor [14], antihypertensive [15], antifungal [16] and antituberculosis [17-20]. Literature survey reveals that, N-substituted benzimidazoles are found to be more potent and hence the design and synthesis of N-substituted benzimidazole derivatives is the potential area of research. Along with this, Nitrogen containing heterocyclic compound played a vital role in biological processes and are wide spread as natural products. They are widely found in nature particularly in nucleic acids, plants alkaloids, anthocycnins and flavones as well as in haem and chlorophyll. Additionally some vitamins, proteins, hormones contain aromatic heterocyclic system. Synthetically produced heterocycles are used for instance as agrochemicals and pharmaceutical and play an important role in human life. Heterocycles have enormous potential as the most promising molecules as lead structures for the design of new drugs.

In continuation with our research work [21-23], we herein report the synthesis of new amino alcohol derivatives of 2-methyl benzimidazole.

EXPERIMENTAL SECTION

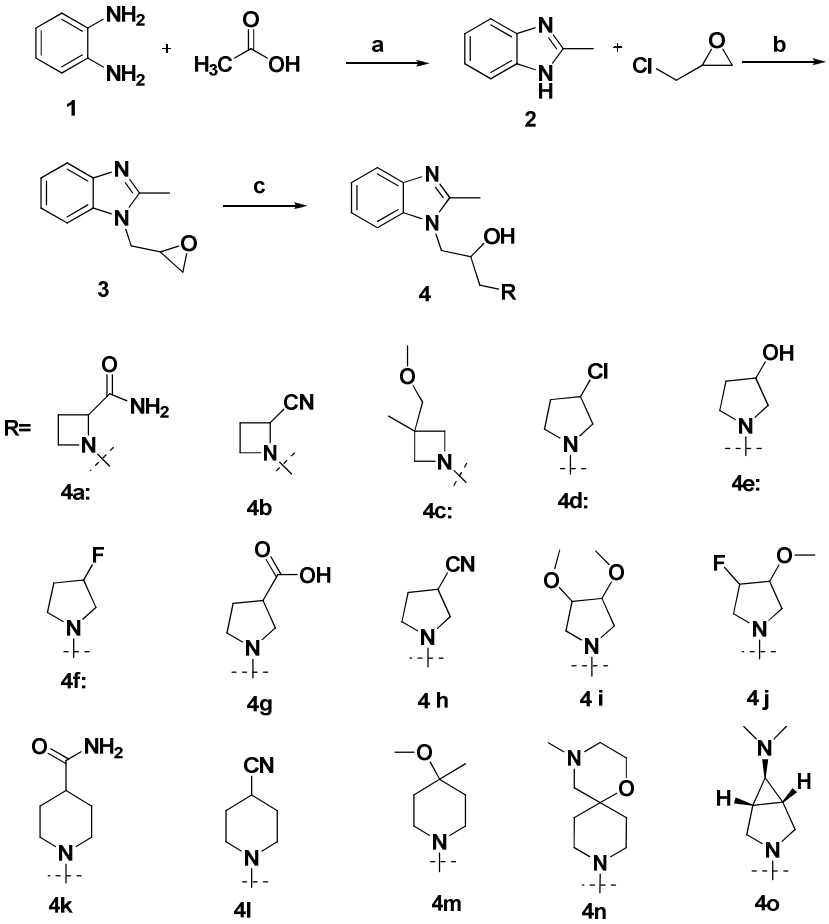
The reagents o-phenylenediamine, epichlorohydrin and cesium carbonate used for reaction were commercially available. Reagent grade substituted cyclic and bicyclic amines were used. Melting points were determined on a Veego apparatus and are uncorrected. Infrared spectra were recorded on a Bruker spectrophotometer in a KBr disc, and the absorption bands are expressed in cm^{-1}. ^1H NMR spectra were recorded on a Varian AS 400 MHz spectrometer in $CDCl_3$/DMSO-d_6, chemical shifts (δ) are in ppm relative to TMS and coupling constants (*J*) are expressed in Hertz (Hz). Mass spectra were taken by electrospray ionization method (ES-MS). Progress of reaction was monitored by TLC using TLC sheets precoated with UV fluorescent silica gel MERCK 60 F 254 that were visualized by UV lamp. The synthetic route of corresponding 2-Methyl benzimidazole amino alcohol derivatives is shown in scheme 1.

General procedure:

Synthesis of 2-methyl-1*H*-benzo[*d*]imidazole (2): Concentrated Hydrochloric acid (36 %) (132 ml) and o-phenylenediamine (25 gm, 231 mmol) was charged and it was stirred for 10 minutes. Acetic acid (42 ml) was charged and it was heated to 95-98 °C and stirred for 45 minutes. After complete conversion by TLC, reaction mixture was cooled to 0-5 °C and basified using ammonium hydroxide solution. Precipitated product was filtered, washed and recrystallized using 10 % aqueous ethanol as a grayish solid. Yield 65%. mp 175-176 °C. IR (KBr, cm^{-1}): 3450, 3030, 1112, 928; ^1H NMR: (400 MHz, DMSO-*d6*): δ 12.7 (s, 1H, NH), 7.48-7.43 (m, 2H), 7.15-7.07 (m, 2H), 2.51 (s, 3H). ES-MS *m/z* 133 [M+1].

Synthesis of 2-methyl-1-(oxiran-2-ylmethyl)-1*H*-benzo[*d*]imidazole (3):

2-methyl-1*H*-benzo[*d*]imidazole (10 gm, 75 mmol), DMF (100 ml) and cesium carbonate (30.8 gm, 94 mmol) were charged and it was heated to 75 °C, stirred for 15 minutes, reaction mixture was cooled to 0 °C. Epichlorohydrin (11.9 ml, 151 mmol) was slowly added. Allow to attain at room temperature and stirred for 24 hr at room temperature. TLC showed complete conversion. Reaction mixture was slowly poured into chilled water (500 ml) and stirred for 15 minutes. Reaction mixture was filtered to remove precipitates. Filtrate was extracted with DCM (3x100 ml). DCM was concentrated on rotary evaporator to obtain crude compound. It was purified by using DCM: Methanol, silica 60-120. gives brownish semi solid, yield 53%. IR (KBr, cm^{-1}): 3028, 1132, 928; ^1HNMR ($CDCl_3$, 400 MHz): δ 7.67-7.65 (m, 1H), 7.30-7.27 (m, 1H), 7.22-7.20 (m, 2H), 4.45-4.40 (dd, 1H), 4.11-4.06 (m, 1H), 3.22 (m, 1H), 2.77-2.75 (m, 1H), 2.58 (s, 3H), 2.41-2.40 (m, 1H). ES-MS *m/z* 189 [M+1].



Scheme-1: Synthetic route of amino alcohol derivetives of 2-methyl benzimidazole (4a-4o). Reagents and conditions: (a) Conc.HCl, 95-98 °C, 45 min; (b) Cs_2CO_3, DMF, 25 °C, 24 h; (c) Substituted cyclic and bicyclic amine.HCl, triethyl amine, ethanol, 80°C.

Synthesis of compounds 4a-4o:

In a pre-cooled solution of 2-methyl-1-(oxiran-2-ylmethyl)-1*H*-benzo[*d*]imidazole (500 mg) and triethyl amine (1.5 eq. for mono hydrochloride and 3.0 eq. for di hydrochloride) in ethanol (5 ml), substituted cyclic amine mono or di hydrochloride (1.25 eq.) was added and reaction mass was heated to 80 °C, progress of reaction was monitored by TLC. After complete conversion ethanol was distilled out on rotary evaporator. To the concentrated mass, water (5 ml) was charged and it was extracted with dichloromethane (2x5 ml), organic layer was washed with water (2x5 ml) and brine (1x5 ml), dried on sodium sulphate, concentrated on rotary evaporator. Crude compound was column purified using DCM: Methanol, silica 60-120 to afford a title compounds **(4a-4o)** with good to better yields.

The physical and spectral data of compounds **(4a-4o)** are given below,

1-(2-hydroxy-3-(2-methyl-1H-benzo[d]imidazol-1-yl) propyl) azetidine-2-carboxamide (4a):

White solid. Yield 68 %, mp 138-142 °C; IR (KBr, cm^{-1}): 3490 (O-H), 3028, 1685 (C=O), 1110; ^{1}H NMR: (400 MHz, DMSO-*d6*): δ 7.48-7.43 (m, 2H), 7.15-7.07 (m, 2H), 6.92 (br, 2H), 5.13 (br, 1H), 4.21-4.16 (dd, *J* =3.2 Hz, 1H), 4.04-3.99 (dd, *J* = 7.6 Hz, 1H), 3.80-3.78 (t, 1H), 3.75 (m, 1H), 3.48-3.38 (m, 2H), 2.63 (m, 2H), 2.52 (s, 3H), 2.40-2.34 (m, 2H), ES-MS *m/z* 289 [M+1].

1-(2-hydroxy-3-(2-methyl-1H-benzo[d]imidazol-1-yl)propyl)azetidine-2-carbonitrile (4b):

White solid, Yield 75 %, mp 155-157 °C; IR (KBr, cm^{-1}): 3560 (O-H), 3030, 2265 (C≡N), 1116; ^{1}H NMR: (400 MHz, DMSO-*d6*): δ 7.48-7.43 (m, 2H), 7.15-7.07 (m, 2H), 5.11 (br, 1H), 4.23-4.18 (dd, *J* =3.2 Hz, 1H), 4.04-3.99

(dd, *J* =7.6 Hz, 1H), 3.86-3.83 (t, 1H), 3.75 (m, 1H), 3.48-3.39 (m, 2H), 2.63 (m, 2H), 2.51 (s, 3H), 2.40-2.34 (m, 2H), ES-MS *m/z* 271 [M+1].

1-(3-(methoxymethyl)-3-methylazetidin-1-yl)-3-(2-methyl-1H-benzo[d]imidazol-1-yl)propan-2-ol (4c):
Semi solid, Yield 65 %. IR (KBr, cm^{-1}): 3570 (O-H), 3028, 1684, 1110; ^{1}H NMR: (400 MHz, DMSO-*d6*): δ 7.48-7.43 (m, 2H), 7.15-7.07 (m, 2H), 5.11 (br, 1H), 4.23-4.18 (dd, *J* = 3.2 Hz, *J* = 3.6 Hz, 1H), 4.04-3.99 (dd, *J* = 7.6 Hz, *J* = 7.6 Hz, 1H), 3.75 (br, 1H), 3.30 (s, 2H), 3.27 (s, 3H), 3.19 (s, 2H), 3.00 (s, 2H), 2.59 (s, 1H), 2.51 (s, 3H), 2.48 (s, 1H), 1.18 (s, 3H), ES-MS *m/z* 304 [M+1].

1-(3-chloropyrrolidin-1-yl)-3-(2-methyl-1H-benzo[d]imidazol-1-yl)propan-2-ol (4d):
Yellowish solid, Yield 72 %, mp 110-112 °C; IR (KBr, cm^{-1}): 3515 (O-H), 3032, 1667, 1122; ^{1}H NMR: (400 MHz, DMSO- *d6*): δ 7.49-7.43 (m, 2H), 7.15-7.07 (m, 2H), 5.11 (br, 1H), 4.49-4.46 (m, 1H), 4.23-4.18 (dd, *J* = 3.2 Hz, 1H), 4.04-3.99 (dd, *J* = 7.6 Hz, 1H), 3.75 (m, 1H), 3.65-3.60 (m, 1H), 3.41-3.23 (m, 3H), 2.63 (m, 2H), 2.51 (s, 3H), 2.37-2.31 (m, 1H), 2.20-2.14 (m, 1H). ES-MS *m/z* 294 [M+1].

1-(2-hydroxy-3-(2-methyl-1H-benzo[d]imidazol-1-yl)propyl)pyrrolidin-3-ol (4e):
Semi solid, Yield 69 %. IR (KBr, cm^{-1}): 3450 (O-H), 3350, 2810, 1115; ^{1}H NMR: (400 MHz, $CDCl_3$): δ 7.58-7.57 (m, 1H), 7.18-7.16 (m, 3H), 4.32 (s, 1H), 4.17-4.14 (m, 1H), 4.14-4.08 (m, 2H), 2.98-2.83 (m, 2H), 2.78-2.75 (m, 1H), 2.67-2.62 (m, 2H), 2.57 (s, 3H), 2.52-2.46 (m, 1H), 2.32-2.28 (m, 1H), 2.13-2.10 (m, 1H), 1.72 (m, 1H),1.28-1.24 (m, 1H). ES-MS *m/z* 276 [M+1].

1-(3-fluoropyrrolidin-1-yl)-3-(2-methyl-1H-benzo[d]imidazol-1-yl)propan-2-ol (4f):
White solid, Yield 78 %, mp 135-137 °C; IR (KBr, cm^{-1}): 3460 (O-H), 3032, 1667, 1115; ^{1}H NMR: (400 MHz, DMSO-*d6*): δ 7.49-7.42 (m, 2H), 7.15-7.07 (m, 2H), 5.11 (br, 1H), 4.38-4.36 (m, 1H), 4.24-4.18 (dd, *J* = 3.2 Hz, 1H), 4.04-3.99 (dd, *J* = 7.6 Hz, 1H), 3.75 (m, 1H), 3.65-3.60 (m, 1H), 3.42-3.23 (m, 3H), 2.63 (m, 2H), 2.51 (s, 3H), 2.37-2.31 (m, 1H), 2.20-2.14 (m, 1H). ES-MS *m/z* 278 [M+1].
1-(2-hydroxy-3-(2-methyl-1H-benzo[d]imidazol-1-yl)propyl)pyrrolidine-3-carboxylic acid (4g):
White solid, Yield 72 %, mp 187-189 °C; IR (KBr, cm^{-1}): 3440 (O-H), 2812, 2551, 1310 ; ^{1}H NMR: (400 MHz, DMSO-*d6*): δ 11.3 (s, 1H), 7.48-7.43 (m, 2H), 7.15-7.07 (m, 2H), 5.11 (br, 1H), 4.49-4.46 (m, 1H), 4.23-4.18 (dd, *J* = 3.2 Hz, 1H), 4.04-3.99 (dd, *J* = 7.6 Hz, 1H), 3.75 (m, 1H), 3.65-3.60 (m, 1H), 3.41-3.23 (m, 3H), 2.63 (m, 2H), 2.51 (s, 3H), 2.37-2.31 (m, 1H), 2.20-2.14 (m, 1H). ES-MS *m/z* 304 [M+1].

1-(2-hydroxy-3-(2-methyl-1H-benzo[d]imidazol-1-yl)propyl)pyrrolidine-3-carbonitrile (4h):
Off white solid, Yield 72 %, mp 165-167 °C; IR (KBr, cm^{-1}): 3440 (O-H), 3010, 2239(C≡N), 1115; ^{1}H NMR: (400 MHz, DMSO-*d6*): δ 7.49-7.42 (m, 2H), 7.17-7.09 (m, 2H), 5.11 (br, 1H), 4.30-4.28 (m, 1H), 4.23-4.18 (dd, *J* = 3.2 Hz, 1H), 4.04-3.99 (dd, *J* = 7.6 Hz, 1H), 3.76 (m, 1H), 3.65-3.60 (m, 1H), 3.42-3.23 (m, 3H), 2.63 (m, 2H), 2.51 (s, 3H), 2.37-2.31 (m, 1H), 2.20-2.14 (m, 1H). ES-MS *m/z* 285 [M+1].

1-(3,4-dimethoxypyrrolidin-1-yl)-3-(2-methyl-1H-benzo[d]imidazol-1-yl)propan-2-ol (4i):
Semi solid, Yield 55.2%. IR (KBr, cm^{-1}): 3440 (O-H), 3010, 2812, 1117; ^{1}H NMR: (400 MHz, $CDCl_3$): δ 7.62-7.58 (m, 1H), 7.30-7.25 (m, 1H), 7.21-7.15 (m, 2H), 4.21-4.09 (m, 2H), 4.07-4.03 (m, 1H), 3.73-3.66 (m, 2H), 3.33 (s, 3H), 3.30 (s, 3H), 3.01-2.97 (q, 1H), 2.85-2.82 (q, 1H), 2.66-2.63 (m, 1H), 2.59 (s, 3H), 2.57-2.50 (m, 2H), 2.50-2.45 (m, 1H). ES-MS *m/z* 320 [M+1].

1-(3-fluoro-4-methoxypyrrolidin-1-yl)-3-(2-methyl-1H-benzo[d]imidazol-1-yl) propan-2-ol (4j):
Semi solid, Yield 62 %. IR (KBr, cm^{-1}): 3462 (O-H), 3010, 1670, 1114; ^{1}H NMR: (400 MHz, DMSO-*d6*): δ 7.49-7.44 (m, 2H), 7.14-7.09 (m, 2H), 5.05 (br, 1H), 4.26-4.23 (m, 1H), 4.06-4.00 (m, 2H), 3.87 (m, 2H), 3.56 (s, 1H), 3.35 (s, 3H), 3.29-3.26 (m, 1H), 3.10-3.09 (m, 1H), 2.96-2.94 (m, 2H), 2.61-2.56 (m, 1H), 2.53 (s, 3H). ES-MS *m/z* 308 [M+1].

1-(2-hydroxy-3-(2-methyl-1H-benzo[d]imidazol-1-yl)propyl)piperidine-4-carboxamide (4k):
White solid, Yield 78 %, mp 147-149 °C; IR (KBr, cm^{-1}): 3610 (O-H), 2810, 1680 (C=O), 1110 ; ^{1}H NMR: (400 MHz, DMSO-*d6*): δ 7.42-7.39 (m, 2H), 7.20 (br, 1H), 7.16-7.10 (m, 2H), 6.92 (br, 1H), 4.90 (br, 1H), 4.29-4.26 (m, 1H), 4.02-3.98 (m, 1H), 3.90 (m, 1H), 2.63-2.60 (m, 1H), 2.52 (s, 3H), 2.42-2.40 (m, 1H), 2.36-2.29 (m, 3H), 2.20 (m, 2H), 1.79-1.75 (m, 2H), 1.52-1.46 (m, 2H). ES-MS *m/z* 317 [M+1].

1-(2-hydroxy-3-(2-methyl-1H-benzo[d]imidazol-1-yl)propyl)piperidine-4-carbonitrile (4l):
White solid, Yield 73 %, mp 132-135 °C; IR (KBr, cm^{-1}): 3617 (O-H), 2810, 2253 (C≡N), 1112 ; ^{1}H NMR: (400 MHz, DMSO-*d6*): δ 7.43-7.41 (m, 2H), 7.17-7.13 (m, 2H), 4.90 (br, 1H), 4.29-4.25 (m, 1H), 4.04-3.00 (m, 1H), 3.90 (m, 1H), 2.63-2.60 (m, 1H), 2.60-2.57 (m, 1H), 2.52 (s, 3H), 2.34-2.26 (m, 3H), 2.20 (m, 2H), 1.78-1.75 (m, 2H), 1.51-1.49 (m, 2H). ES-MS *m/z* 299 [M+1].

1-(4-methoxy-4-methylpiperidin-1-yl)-3-(2-methyl-1H-benzo[d]imidazol-1-yl)propan-2-ol (4m):
White solid, Yield 57 %, mp 137-139 °C; IR (KBr, cm^{-1}): 3440 (O-H), 3010, 2812, 1113; ^{1}H NMR: (400 MHz, DMSO-*d6*): δ 7.48-7.44 (m, 2H), 7.14-7.09 (m, 2H), 4.90 (br, 1H), 4.29-4.25 (m, 1H), 4.04-4.00 (m, 1H), 3.87 (m, 1H), 3.34 (s, 3H), 2.51-2.44 (m, 4H), 2.63-2.56 (m, 2H), 2.52 (s, 3H), 1.82-1.78 (m, 4H), 1.30 (s, 3H). ES-MS *m/z* 318 [M+1].

1-(2-methyl-1H-benzo[d]imidazol-1-yl)-3-(4-methyl-1-oxa-4,9-diazaspiro[5.5]undecan-9-yl)propan-2-ol (4n):
White solid, Yield 76 %, mp 140-142 °C; IR (KBr, cm^{-1}): 3460 (O-H), 3010, 1679, 1110; ^{1}H NMR: (400 MHz, DMSO-*d6*): δ 7.48-7.43 (m, 2H), 7.15-7.07 (m, 2H), 4.90 (br, 1H), 4.29-4.25 (dd, *J* = 2.8 Hz, *J* = 2.4 Hz, 1H), 4.04-3.98 (dd, *J* = 8.4 Hz, 1H), 3.90 (br, 1H), 3.57-3.55 (m, 2H), 2.52 (s, 3H), 2.43-2.41 (m, 1H), 2.36-2.26 (m, 4H), 2.20 (br, 3H), 2.09 (s, 5H), 2.09-1.75 (m, 2H), 1.52-1.46 (m, 2H). ES-MS *m/z* 359 [M+1].

1-((1R,5S,6s)-6-(dimethylamino)-3-azabicyclo[3.1.0]hexan-3-yl)-3-(2-methyl-1H-benzo[d]imidazol-1-yl)propan-2-ol (4o):
White solid, Yield 65 %, mp 158-160 °C; IR (KBr, cm^{-1}): 3455 (O-H), 3012, 1680, 1115; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68-7.66 (m, 1H), 7.31-7.28 (m, 1H), 7.26-7.20 (m, 2H), 4.20-4.05 (dd, *J* = 4 Hz, *J* = 6 Hz, 2H), 3.99-3.97 (m, 1H), 3.05-2.95 (dd, *J* = 8.8 Hz, *J* = 8.4 Hz, 2H), 2.62 (s, 3H), 2.62-2.59 (m, 1H), 2.55-2.50 (t, 1H), 2.42-2.31 (m, 1H), 2.32-2.29 (m, 1H), 2.28 (s, 6H). ES-MS *m/z* 315 [M+1].

RESULTS AND DISCUSSION

Chemistry:

2-methyl benzimidazole was synthesized by refluxing o-phenylenediamine, Conc. HCl and acetic acid. It was treated with epichlorohydrin in presence of cesium carbonate in DMF. The epoxide ring opened with different substituted cyclic and bicyclic amines in ethanol at high temperature give amino alcohol derivatives of 2-methyl benzimidazole.

Table 1: Antibacterial activity of amino alcohol derivatives of 2-methyl benzimidazole

Compound no.	Zone of Inhibition (in mm)					
	Staphylococcus aureus			*Escherichia coli*		
	20 µg/ml	40 µg/ml	60 µg/ml	20 µg/ml	40 µg/ml	60 µg/ml
4a	08	12	16	07	12	16
4b	09	14	18	10	13	16
4c	14	18	23	15	18	22
4d	07	12	14	07	09	11
4e	--	15	18	--	14	17
4f	10	12	15	08	12	16
4g	--	09	11	--	07	11
4h	09	13	17	10	12	14
4i	--	07	11	--	08	12
4j	13	19	23	14	18	22
4k	08	11	15	06	11	15
4l	09	12	16	08	12	14
4m	06	08	13	07	11	13
4n	13	18	22	14	20	24
4o	14	18	23	13	18	22
Ciprofloxacin	15	20	24	16	22	25
Norfloxacin	16	22	26	15	20	23

Biology:

Antibacterial activity:

All newly synthesized compounds were evaluated for their antibacterial activity against *Staphylococcus aureus* (NCIM 2079) and *Escherichia coli* (NCIM 2065) at 20, 40 and 60 µg/ml concentrations, using cup-plate method. *Ciprofloxacin* and *Norfloxacin* where used as standard drugs. Antibacterial activities of newly synthesized compounds are mentioned in **Table 1**. The compounds **4c, 4j, 4n** and **4o** were found to be moderate to good antibacterial agent.

Antitubercular activity:

The encouraging results from the antibacterial activity prompted us to opt for preliminary screening of these titled compounds for their *in-vitro* antitubercular activity. This antitubercular study was conducted using MABA assay method [24] and data of the same was mentioned in **Table 2**. Isoniazid was used as a competitor drug. In this study we found that, the compound **4c** and **4o** showing moderate antituberculosis activity, while remaining compounds of this series exhibited poor antituberculosis activity.

Table 2: Antitubercular activity of amino alcohol derivatives of 2-methyl benzimidazole

Compound no.	*Mycobacterium tuberculosis* (H37Rv) MIC in µg/ml
4a	12.5
4b	12.5
4c	6.25
4d	25
4e	50
4f	25
4g	25
4h	12.5
4i	25
4j	50
4k	25
4l	25
4m	25
4n	50
4o	6.25
Isoniazid	0.05

Structure activity relationship study reveals that, the first step towards lead optimization was epoxide ring opening by using nitrogen containing four membered substituted cyclic amines. The compound having 3-(methoxymethyl)-3-methylazetidine showing good antibacterial activity against Gram +ve and Gram -ve microorganism. It was found that there was no major change by using electron withdrawing group –CN and $–CONH_2$ at position 2 of azetidine ring. The next structural change was made by using five membered cyclic amines, 3 and 3, 4 substituted pyrrolidine. We have introduced electron withdrawing groups like -Cl, -F, -COOH, -CN at 3-postion of pyrrolidine ring. It was found that there was no improvement in biological activity. Further we have introduced two electron withdrawing groups $–OCH_3$ and –F at 3, 4 positions. The compound having $-OCH_3$ and -F substitution showed remarkable improvement in biological activity. On the basis of above biological data, we have opened the epoxide ring by using six memberd piperidine and bicyclic amine compound. The compound **4n** and **4o** showed substantial improvement in biological activity as compare to other compounds.

Based upon antibacterial activity data, we have submitted these titled compounds for antitubercular activity using MABA method. Surprisingly, we found that, some of the compounds **4c** and **4o** which have shown effective antibacterial activity have shown effective antitubercular activity and some of the compounds **4j** and **4n** completely loss their antituberculosis activity. So, we say that the compound **4c** and **4o** were satisfactory antituberculosis activity against *Mycobacterium tuberculosis* H37Rv.

CONCLUSION

We have synthesized amino alcohol derivatives of 2-methyl benzimidazole and evaluated for their antibacterial and antituberculosis activity. The compounds **4c, 4j, 4n** and **4o** were found to be moderate to good antibacterial agent. When these titled compounds submitted for antituberculosis study, the compound **4c** and **4o** found to have

reasonably moderate antituberculosis activity against *Mycobacterium tuberculosis* H37Rv. It was also observed that the promising antibacterial have proved to be better antimycobacterial.

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