Nitroimidazoles make a group of compounds of great commercial and chemotherapeutic importance. Clinical trials have shown that many of them have a remarkably broad spectrum of antimicrobial properties including antibacterial activity. The introduction of metronidazole which acts against anaerobic bacteria and additionally has antiprotozoal activity, has stimulated much synthetic chemistry on nitroimidazoles (1). A series of bicyclic nitroimidazo[2,1-b][1,3]oxazines, originally investigated as radiosensitizers for use in cancer chemotherapy, have been found to be active against culture replication of Mycobacterium tuberculosis (M. tuberculosis) (2, 3). Compounds containing the imidazo[2,1-b][1,3]oxazine ring system have been shown to be active against tuberculosis as well. The most promising compound of this series, PA-824 (Figure 1), has the MIC of 0.06 µg/mL against Mycobacterium bovis BCG and high activity against Mycobacterium tuberculosis H37Rv (4, 5).

Mycobacterium tuberculosis is the greatest single infectious cause of mortality worldwide. Estimates indicate that one-third of the world population is infected with latent M. tuberculosis (6). According to the World Health Organization (WHO) report, M. tuberculosis currently infects over 2 billion people worldwide. Each year, 30 million of new cases are reported. Tuberculosis (TB) kills roughly two million people annually (7). In most parts of the world people who suffer from TB are restricted to combinations of only five drugs for effective treatment of this disease. These are rifampicin, isoniazid, ethambutol, streptomycin and pyrazinamide (8, 9).

Hitherto, a series of 2,3-dihydro-6-nitroimidazo[2,1-b]oxazoles has been tested as to antitubercular properties. One of these compounds – CGI 17341 has been found particularly promising in clinical trials (10). This compound was originally discovered in the search for novel dinitroimidazoles that might be used as radiosensitizers. The reaction between 2,4-dinitroimidazoles and oxiranes unexpectedly gave the products of intramolecular cyclization and simultaneous loss of the 2-nitro group (2). However, the activity of 2,3-dihydro-7-nitroimidazo[5,1-b]oxazoles obtained from 4,5-dinitroimidazoles, was not discovered then.

In continuation of our work on the syntheses of pharmacologically active nitroimidazole derivatives, an effort was made at synthesis of bicyclic 2,3-dihydro-7-nitroimidazo[5,1-b]oxazoles. Some of newly obtained and some of previously described (11, 12) nitroimidazooxazoles from [2,1-b] and [5,1-b] series were tested in vitro as to their tuberculostatic activity.

**EXPERIMENTAL**

**Chemistry**

All compounds were crystallized from water or 40% ethanol. Melting points were measured on a Kofler’s apparatus and are uncorrected.
\[ \text{1H-NMR spectra were recorded on a Varian Gemini 300 VT and Mercury 300 spectrometers at 300 MHz in the DMSO-d}_6 \text{ solutions using TMS as internal standard. The mass spectra were recorded on a 402 AMD INTECTRA apparatus by the electron impact technique, operating at 75 eV. The HRMS were recorded on the same spectrometer. Analytical TLC was performed on Merck silica gel 60F254 plates using a mixture of methylene chloride and methanol (9:1, v/v) as eluent. The spots were observed in the ultraviolet light (\( \lambda = 254 \text{ nm} \)).} \]

The syntheses of a series of eight 2,3-dihydro-7-nitroimidazo[5,1-b]oxazoles were performed. These compounds were synthesized in a one-pot reaction by treating 4,5-dinitroimidazole or 2-methyl-4,5-dinitroimidazole with appropriate oxiranes (Scheme 1). This type of intramolecular cyclization was possible in the presence of a base and in alcohol as a solvent. In the syntheses of bicyclic derivatives of 4,5-dinitroimidazole, ethanol was the most satisfactory solvent. In the similar reactions of 2-methyl-4,5-dinitroimidazole, \( n \)-propanol was the optimal choice. In the preliminary experiment, sodium hydroxide was used as a base, however, it caused some decomposition reactions. Then, potassium carbonate was tested and proved to be smooth in activity and to lead to target compounds. Bromination with bromine in acetic acid solution in the presence of sodium acetate of compounds \( 7a \) and \( 8a \) gave two new derivatives as the products of electrophilic substitution reaction with the bromine atom only in the 2 position of aromatic imidazole ring. The structures of compounds \( 4a-8b \) were determined on the basis of their \( ^1\text{H-NMR}, \text{MS and HRMS spectra. The mass spectra of nitroimidazo-} \]

\[ \text{Zmoxazoles obtained in general showed highly abundant molecular ions which fragmented by the loss of O, then NO, followed by other groups or atoms such as Cl, Br to form an N-alkylimidazole radical. The subsequent loss of CH}_4 \text{ led to imidazolyl radical cation (m/z 67). In the 'H-NMR spectra of the compounds obtained the signals of the characteristic groups showed similar chemical shifts. For instance, the chemical shifts of the methyl groups at position 2 of the imidazole ring in compounds 4b-8b were in the range of 1.86-2.23 ppm, whereas in the spectra of compounds 4a and 4b, the doublets at 1.60-1.62 ppm were assigned to the methyl group at the oxazole moiety. In the case of ethyl group in the same position in oxazole ring (compounds 5a, 5b) there were two signals: triplets assigned to CH\(_2\) at 0.98-1.00 ppm and multiplets assigned to CH\(_2\) in the range of 1.86-2.06 ppm. The signals assigned to the CH\(_3\)Cl and CH\(_3\)Br groups appeared as fragment of multiplets in the range of 3.99-4.20 ppm in the 'H-NMR spectra of compounds 7a, 7b (11) and 8a, 8b. One singlet at 7.45 ppm with integral intensity for one proton was characteristic of the hydrogen atom at C-2 position in the imidazole ring (compounds 4a, 5a, 6a and 8a).} \]

**General procedures**

Nitroimidazoles, dinitroimidazoles (13) and compounds \( 7a, 7b \) (1 from 4,5-dinitroimidazole series), \( 10a \) (14), \( 11a, 11b \) (12) (from 2,4-dinitroimidazole series) were synthesized according to known procedures.

Compounds \( 4a-6b \)

In a typical experiment, compound \( 3a \) or \( 3b \) (1 equiv.) and the corresponding oxirane (3 equiv.) were dissolved in 10 mL of ethanol or \( n \)-propanol, respectively. One equiv. of anhydrous K\(_2\)CO\(_3\) was then added and the mixtures were heated under reflux for about 2 h. After cooling, the mixtures were diluted with five times quantity of water, then were transferred to a separatory funnel and extracted three times with methylene chloride. The organic extracts were dried with MgSO\(_4\) and concentrated in vacuum. The orange solid residues were crystallized from water with charcoal to afford pure products as white needles. Spectral and analytical data of the products obtained are as follows:

\[ \text{4a. Yield 25\%, m.p. 141-143°C, R}_f = 0.66; \]
\[ \text{'H-NMR } \delta \text{ (ppm): 7.43 (s, 1H, H}_{\text{arom}}\text{), 5.90-5.78 (m, 1H, CH\(_{-}\)CH\(_{3}\)), 4.51 (dd, J = 8.2; 10.2 Hz, 1H, N-CH\(_{2}\)), 4.00 (dd, J = 7.9; 10.3 Hz, 1H, N-CH\(_3\)), 1.62 (d, J = 6.3 Hz, 3H, CH\(_3\)). MS m/z (%): 169.0 (M\(^+\); 83.7); HRMS (ES): calcd. for C\(_6\)H\(_7\)O\(_3\)N\(_3\): 169.04874, found: 169.04848.} \]
4b. Yield 28%, m.p. 130-131°C, R f = 0.68; 1H-NMR δ (ppm): 5.89-5.78 (m, 1H, C-H-CH3), 4.42 (dd, J = 8.0; 9.9 Hz, 1H, N-CH2), 3.93 (dd, J = 7.7; 10.0 Hz, 1H, N-CH2), 2.20 (s, 3H, CH3 in the imidazole ring), 1.60 (d, J = 6.3 Hz, 3H, CH3). MS m/z (%): 183.1 (M+; 43.4); HRMS (ES): calcd. for C7H9O3N3: 183.16046, found: 183.16107.

5a. Yield 15%, m.p. 162-163°C, R f = 0.74; 1H-NMR δ (ppm): 7.45 (s, 1H, Harom.), 5.75-5.65 (m, 1H, C-H-C2H5), 4.54 (dd, J = 8.1; 10.0 Hz, 1H, N-CH2), 4.00 (dd, J = 8.1; 10.0 Hz, 1H, N-CH2), 2.06-1.87 (m, 2H, C2H2-CH3), 1.00 (t, J = 7.4 Hz, 3H, CH3). MS m/z (%): 183.1 (M+; 43.4); HRMS (ES): calcd. for C7H9O3N3: 183.16046, found: 183.16107.

6a. Yield 20%, m.p. 137-139°C, R f = 0.48; 1H-NMR δ (ppm): 7.52-7.28 (m, 6H, Ph (5H) and imidazole C-2 (1H)), 5.93 (dd, J = 8.5 Hz, 1H, CH2-Ph), 5.77 (t, J = 8.8 Hz, 1H, C-H-Ph), 5.24 (dd, J = 6.0; 9.2 Hz, 1H, N-CH2). MS m/z (%): 231.0 (M+; 50.2); HRMS (ES): calcd. for C11H9O3N3: 231.20746, found: 231.20767.

5b. Yield 26%, m.p. 91-92°C, R f = 0.77; 1H-NMR δ (ppm): 5.75-5.65 (m, 1H, CH2-C,H3), 4.40 (dd, J = 8.1; 10.0 Hz, 1H, N-CH3), 4.01 (dd, J = 7.8; 10.0 Hz, 1H, N-CH2), 2.21 (s, 3H, CH3 in the imidazole ring), 2.04-1.86 (m, 2H, CH2-C,H3), 0.98 (t, J = 7.4 Hz, 3H, CH2-C,H3). MS m/z (%): 197.0 (M+; 23.0); HRMS (ES): calcd. for C8H11O3N3: 197.08005, found: 197.08031.

6b. Yield 23%, m.p. 138-140°C, R f = 0.68; 1H-NMR δ (ppm): 7.51-7.27 (m, 5H, Ph) and imidazole C-2 (1H), 5.92 (dd, J = 6.1; 8.5 Hz, 1H, N-CH2), 5.76 (t, J = 8.8 Hz, 1H, C-H-Ph), 5.22 (dd, J = 6.0; 9.1 Hz, 1H, N-CH2), 1.86 (s, 3H, CH3 in the imidazole ring). MS m/z (%): 245.0 (M+; 52.4); HRMS (ES): calcd. for C12H11O3N3: 245.23404, found: 245.23435.
Compounds 8a, 8b
In a typical experiment compound 3a or 3b (1 equiv.) and epibromohydrin (3 equiv.) were dissolved in 10 mL of ethanol or n-propanol, respectively. One equiv. of anhydrous K$_2$CO$_3$ was then added and the mixtures were heated under reflux for 25 min. After cooling, the mixtures were diluted with five times quantity of water. The light brown precipitates were filtered off and washed with cold water. The products were crystallized from 40% ethanol with charcoal to give pure crystals as white needles. Spectral and analytical data are as follows:

8a. Yield 60%, m.p. 155-157°C, R$_f$ = 0.60; 1H-NMR δ (ppm): 7.45 (s, 1H, H$_{\text{amino}}$), 6.05-5.97 (m, 1H, CH$_2$-CH$_2$Br), 4.54 (dd, J = 8.9; 10.7 Hz, 1H, N-CH$_3$), 4.18-3.99 (m, 3H, N-CH$_2$ (1H) and CH$_2$Br (2H)). MS m/z (%): 247.0 (M +; 53.9); HRMS (ES): calcd. for C$_7$H$_8$O$_3$N$_3$Br: 282.9 (M +; 33.2); HRMS (ES): calcd. for C$_7$H$_8$O$_3$N$_3$ClBr: 282.8 (M +; 33.2); HRMS (ES): calcd. for C$_7$H$_8$O$_3$N$_3$Br: 282.9 (M +; 33.2); HRMS (ES): calcd. for C$_7$H$_8$O$_3$N$_3$Br: 282.9 (M +; 33.2).

8b. Yield 76%, m.p. 162-165°C, R$_f$ = 0.43; 1H-NMR δ (ppm): 6.04-5.96 (m, 1H, CH$_2$-CH$_2$Br), 4.53 (dd, J = 8.9; 10.7 Hz, 1H, N-CH$_3$), 4.20-3.99 (m, 3H, N-CH$_3$ (1H), CH$_2$Br (2H)), 2.23 (s, 3H, CH$_3$ in the imidazole ring). MS m/z (%): 261.0 (M +; 62.4); HRMS (ES): calcd. for C$_7$H$_8$O$_3$N$_3$Br: 260.97491, found: 260.97425.

Compounds 9a, 9b
In a typical experiment compound 7a or 8a (1 equiv.) and sodium acetate (3.6 equiv.) were dissolved in 10 mL of glacial acetic acid and the small excess of bromine (1.5 equiv.) was then added. After 24 h the light yellow solid was precipitated. The precipitate was filtered off and washed with cold water. To obtain the pure product, the solid was dissolved in DMSO and water was then dropped until 24 h the light yellow solid was precipitated. The majority of the compound precipitated; then, the precipitate was filtered off and washed with cold water. To obtain the pure product, the solid was dissolved in DMSO and water was then dropped until 24 h the light yellow solid was precipitated. The majority of the compound precipitated; then, the precipitate was filtered off and washed with cold water. To obtain the pure product, the solid was dissolved in DMSO and water was then dropped until 24 h the light yellow solid was precipitated. The majority of the compound precipitated; then, the precipitate was filtered off and washed with cold water. To obtain the pure product, the solid was dissolved in DMSO and water was then dropped until 24 h the light yellow solid was precipitated. The majority of the compound precipitated; then, the precipitate was filtered off and washed with cold water. To obtain the pure product, the solid was dissolved in DMSO and water was then dropped until 24 h the light yellow solid was precipitated. The majority of the compound precipitated; then, the precipitate was filtered off and washed with cold water. To obtain the pure product, the solid was dissolved in DMSO and water was then dropped until 24 h the light yellow solid was precipitated. The majority of the compound precipitated; then, the precipitate was filtered off and washed with cold water. To obtain the pure product, the solid was dissolved in DMSO and water was then dropped until 24 h the light yellow solid was precipitated. The majority of the compound precipitated; then, the precipitate was filtered off and washed with cold water. To obtain the pure product, the solid was dissolved in DMSO and water was then dropped until 24 h the light yellow solid was precipitated. The majority of the compound precipitated; then, the precipitate was filtered off and washed with cold water. To obtain the pure product, the solid was dissolved in DMSO and water was then dropped until 24 h the light yellow solid was precipitated. The majority of the compound precipitated; then, the precipitate was filtered off and washed with cold water. To obtain the pure product, the solid was dissolved in DMSO and water was then dropped until 24 h the light yellow solid was precipitated. The majority of the compound precipitated; then, the precipitate was filtered off and washed with cold water. To obtain the pure product, the solid was dissolved in DMSO and water was then dropped until 24 h the light yellow solid was precipitated. The majority of the compound precipitated; then, the precipitate was filtered off and washed with cold water. To obtain the pure product, the solid was diss...
Table 1. Antimycobacterial activity of the investigated compounds, as MIC values (µg/mL).

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<td></td>
<td>H&lt;sub&gt;2&lt;/sub&gt;R&lt;sub&gt;2&lt;/sub&gt;</td>
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<td>INH</td>
<td>RMP</td>
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<tr>
<td>4a</td>
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The distances between essential groups or atoms:

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<th></th>
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Figure 2. The molecular structure of isomeric compounds 11b and 5a.

REFERENCES


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