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Short communication

Synthesis and anti-mycobacterial activity of novel amino alcohol derivatives

Wilson Cunico [a,c,*], Claudia R.B. Gomes [a], Maria L.G. Ferreira [a], Thaís G. Ferreira [a], Danielle Cardinot [a], Marcus V.N. de Souza [a], Maria C.S. Lourenço [b]

[a] Instituto de Tecnologia em Fármacos – Farmanguinhos, FioCruz – Fundação Oswaldo Cruz, R. Sizenando Nabuco, 100, Manguinhos, 21041-250, Rio de Janeiro, RJ, Brazil
[b] Instituto de Pesquisas Clínicas Evandro Chagas, Departamento de Bacteriologia, FioCruz – Fundação Oswaldo Cruz, Av. Brazil, 4365, Manguinhos, Rio de Janeiro, Brazil
[c] NuQuiA – Núcleo de Química Aplicada, Departamento de Química Orgânica, UFPel, Campus Universitário s/n, 96010-900 Pelotas, RS, Brazil

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ABSTRACT

Thirteen new hydroxyethylamines have been synthesized from reactions of (2*S*,3*S*)Boc-phenylalanine epoxide, piperonylamine and arenesulfonyl chlorides in good yields. These compounds were evaluated as antibacterial agents against *Mycobacterium tuberculosis* H37Rv using the Alamar Blue susceptibility test and their activity expressed as the minimum inhibitory concentration (MIC) in μM. Two amino alcohols displayed significant activity when compared with first line drug ethambutol (EMB). Therefore this class of compounds could be a good starting point to develop new lead compounds in the treatment of tuberculosis.

1. Introduction

Amino alcohols are very important and versatile compounds with significant applications in many fields, such as in synthetic and medicinal chemistry. Different compounds containing the moiety amino alcohols have been synthesized to use in various diseases [1]. For example, compounds that present hydroxyethylamines core have the capacity to inhibit aspartic protease enzymes and are widely used as anti-HIV [2,3], antimalarial [4] and anti-leishmaniose [5] agents. Recently, we reported the synthesis and antimalarial activity against *Plasmodium falciparum* of hydroxyethypiperazines [6] and hydroxyethylsulfonamides derivatives [7]. The only amino alcohol used in the treatment of tuberculosis (TB) disease is Ethambutol (EMB). Despite its modest anti-tuberculosis activity, EMB is used in combination with other front-line anti-tuberculosis agents mainly owing to its synergy with the other drugs and also because it's low toxicity [8].

Lee et al. [9] reported that the 1,2-ethylenediamine moiety is the EMB pharmacophore due the possibility of chelate formation with divalent metal ions such copper, and that the best 1,2-diamine synthesized was 35-fold more active than EMB. However, results of advanced studies of this 1,2-ethylenediamine derivative for treatment of tuberculosis show that it does not have the same target as EMB [10]. It has also been reported that the presence of a hydroxyl group β to the amine results in an increase in antitubercular potency [8,9]. Moreover, the distance between oxygen atom and nitrogen atom in EMB is the same distance of both atoms in hydroxyethylamine structure suggesting good relationship between both structures (Fig. 1).

Tuberculosis (TB) is a chronic bacterial infection transmitted through the air. This disease is caused by the bacteria *Mycobacterium tuberculosis* and mainly affects the lungs (pulmonary TB), which is responsible for more than 75 percent of cases, but it may also affect different parts of the body, such as the brain, stomach, bones, skin, intestine, liver, kidneys, spinal cord and breasts [11,12]. Different factors are responsible for the resurgence of TB, such the AIDS epidemic, which emerged in the mid-1980s and immigration, war, famine, homelessness.

A serious problem worldwide in the fight against TB is the rapid spread of the multidrug-resistant (MDR) TB due to inconsistent or partial treatment, and the lack of new drugs in the market. Particularly worrisome is the super bacterium XDR-TB (extensively drug-resistant tuberculosis), which is resistant to all first and second line anti-TB drugs. Because of these problems, the World Health Organization (WHO) declared TB a global health emergency in 1993. According to statistical data, 9.27 million people worldwide develop active TB and almost 1.77 million die every year [13].

To overcome the problems with available treatments, new drugs to treat TB are urgently required, specifically more potent therapies,

* Corresponding author. Instituto de Tecnologia em Fármacos – Farmanguinhos, FioCruz – Fundação Oswaldo Cruz, R. Sizenando Nabuco, 100, Manguinhos, 21041-250, Rio de Janeiro, RJ, Brazil. Tel.: +55 53 3275 7358.
E-mail address: wjcunico@yahoo.com.br (W. Cunico).

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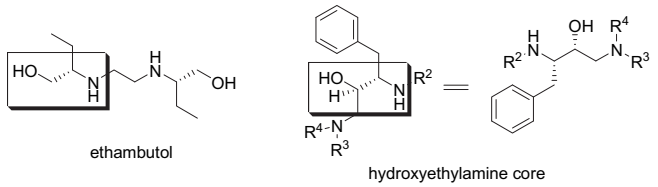
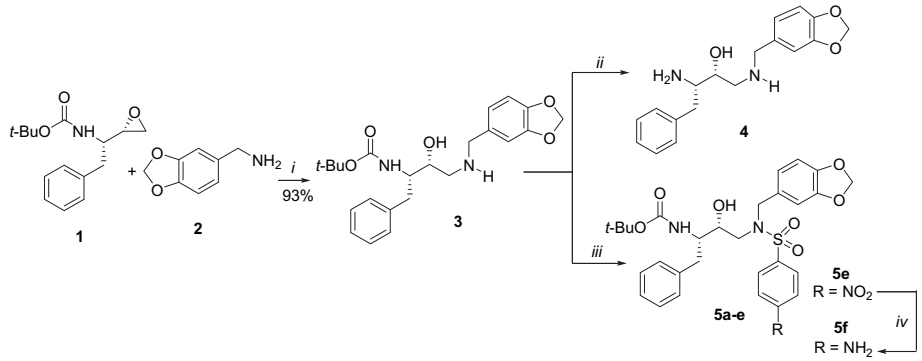


Fig. 1. Ethambutol and hydroxyethylamine-based structures.

for 4 h without any purification as an oil (Scheme 2). Table 1 shows the yields, melting points and LC–MS data for compounds **3**, **4**, **5a**–**f** and **6a**–**e**.

All the compounds were identified by ^{1}H, ^{13}C NMR and by LC–MS data. In the proton nuclear magnetic resonance spectra (^{1}H NMR), the signals of hydrogen for the synthesized compounds were verified on the basis of their chemical shifts, multiplicities and coupling constants (Table 2). 2D-NMR techniques (HMBQ, HMQC and COSY) helped us to assign the correct signals of compounds. For the hydroxyethylamine core, the protons H1 appears as two double-doublets more shielded than the protons H4, which also shows two double-doublets. The two multiplets in the ^{1}H NMR spectra in the range of δ 3.59 to 3.37 ppm were assigned to the H2 and H3 protons. The ^{13}C NMR spectra exhibited CH signals at δ 72–71 ppm for C3 (C–OH) and at δ 56–60 ppm for C2 (C–NH). The CH_2 signals for C4 and C1 appears at δ 49–55 ppm and 35–38 ppm, respectively.



Scheme 1. Reaction and conditions: i: IPA, reflux, 16 h; ii: TFA/CH_2Cl_2 (1/3), r.t., 4 h; iii: Et_3N, DMF, $ArSO_2Cl$, CH_2Cl_2, r.t., 4 h; iv: H_2, Pd/C 10%, EtOH, r.t., 16 h.

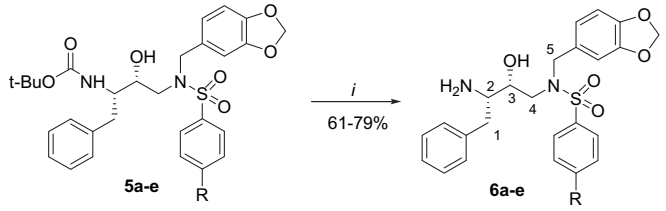
with fewer side effects, to be used in shorter treatment regimens and to be employed to treat MDR TB and latent disease. In this context and in the course of our investigations on hydroxyethylamine derivatives [6,7], the aim of this work is the synthesis and *in vitro* activity of novel hydroxyethylsulfonamide-based compounds, against *M. tuberculosis*.

2. Results and discussion

2.1. Chemistry

The target compounds **3**, **4**, **5a**–**f** and **6a**–**e** were prepared as outlined in Scheme 1 and Scheme 2. The selective ring-opening of the (2*S*,3*S*)Boc-phenylalanine epoxide **1** with piperonilamine **2** in reflux of isopropanol afforded the hydroxyethylamine intermediate **3**, which was coupled with arenesulfonyl chlorides by using triethylamine, CH_2Cl_2 and DMF (catalytic concentration) at room temperature to give the hydroxyethylsulfonamides **5a**–**e** in good yields (Scheme 1). The compound **5f** was prepared by reduction reaction of nitro group of compound **5e** with H_2 Pd/C 10% using ethanol in quantitative yield. We also synthesized the amino alcohol **4** after deprotection of *tert*-butoxycarbonil group with trifluoroacetic acid and CH_2Cl_2 (1/3) mixture at room temperature in quantitative yield (Scheme 1).

The amino alcohols **6a**–**e** were prepared in excellent yields from reaction of hydroxyethylsulfonamides **5a**–**e** with a solution of trifluoroacetic acid and methylene chloride (1/3) at room temperature



Scheme 2. Reaction and conditions: i: TFA/CH_2Cl_2 (1/3), r.t., 4 h.

2.2. Anti-mycobacterial activity

The results of anti-mycobacterial activity of all compounds **3**, **4**, **5a**–**f** and **6a**–**e** is shown in Table 3. The intermediates **3** and **4** showed poor activity suggesting that the sulfonamide moiety was important to activity. Clearly, the presence of amino alcohol moiety on hydroxyethylsulfonamides **6a**–**e** is crucial for anti-mycobacterial activity since the presence of the carbamate moiety (*tert*-butoxycarbonyl group) leads to loss of activity (**5a**–**f**). This information was in according with literature reported once reduced

Table 1
Yields and selected physical properties of compounds **3**, **4**, **5a**–**f** and **6a**–**e**.

Product	R	m.p.[a] (°C)	Yield[b] (%)	LC/MS *m/z* (%)
3	–	148–149	92	415.2 (M^+ + 1, 100)
4	–	oil	95	315.2 (M^+ + 1, 100)
5a	Br	189–190	93	673.0 (M^+ + K, 100)
5b	OMe	160–161	71	623.2 (M^+ + K, 51)
5c	Me	175–177	89	607.1 (M^+ + K, 100)
5d	F	159–161	72	611.2 (M^+ + K, 100)
5e	NO_2	194–195	76	638.2 (M^+ + K, 94)
5f	NH_2	oil	91	535.2 (M^+ + 1, 100)
6a	Br	oil	79	532.1 (M^+ + 1, 98)
6b	OMe	oil	66	484.2 (M^+ + 1, 100)
6c	Me	oil	68	473.1 (M^+ + 1, 100)
6d	F	oil	68	500.1 (M^+ + 1, 100)
6e	NO_2	oil	61	415.2 (M^+ + 1, 100)

[a] melting points are uncorrected.
[b] yields of purified compounds.

Table 2
Selected ^{1}H and ^{13}C NMR data of compounds **3**, **4**, **5a**–**f** and **6a**–**e**.

	δ (ppm) for ^{1}H NMR (J_{H}-H Hz) and ^{13}C NMR (J_{C}-F Hz)[a]
3	7.27–7.19 (m; 2H); 7.17–7.15 (m; 3H); 6.92 (s; 1H); 6.83 (d; 1H; J = 7.9); 6.75 (d; 1H; J = 7.8); 6,66 (d; 1H; J = 9.1; OH); 5.96 (s; 2H; OCH_2O); 4.79 (br; 1H; NH); 3.59 (s; 2H; H5); 3.59–3.56 (m; 1H; H2); 3.45–3.44 (m; 1H; H3); 2.97 (dd; 1H; J = 13.8; ^{2}J = 3.1H4a); 2.55 (dd; 1H; J = 13.6; ^{2}J = 3.5; H4b); 2.49 (dd; J = 11.9; ^{2}J = 6.5; H1a); 2.44 (dd; 1H; J = 11.9; ^{2}J = 7.4; H1b); 1.24 (s; 9H; $C(CH_3)_3$). 155.3 (C=O); 147.2, 145.8, 139.8, 134.9, 129.1, 127.9, 125.6, 121.0, 108.4, 107.8 (aryl); 100.6 (OCH_2O); 77.3 ($\underline{C}(CH_3)_3$); 72.0 (C3); 55.1 (C2); 52.8 (C5); 51.6 (C4); 36.1 (C1); 28.2 ($C(\underline{CH_3})_3$).
4	7.19–6.55 (m; 5H); 6.92 (s; 1H); 6.83 (d; 1H; J = 7.9); 6.75 (d; 1H; J = 7.8); 6.66 (d; 1H; J = 9.1; OH); 5.96 (s; 2H; OCH_2O); 4.79 (br; 1H; NH); 3.59 (s; 2H; H5); 3.59–3.55 (m; 1H; H2); 3.44–3.43 (m; 1H; H3); 2.97 (dd; 1H; J = 13.8; ^{2}J = 3.1H4a); 2.55 (dd; 1H; J = 13.6; ^{2}J = 3.5; H4b); 2.49 (dd; J = 11.9; ^{2}J = 6.5; H1a); 2.44 (dd; 1H; J = 11.9; ^{2}J = 7.4; H1a). 147.2, 145.8, 139.8, 134.9, 129.7, 129.2, 127.5, 121.0, 108.4, 107.8 (aryl); 100.6 (OCH_2O); 72.0 (C3); 55.1 (C2); 52.8 (C5); 51.6 (C4); 36.1 (C1).
5a	7.80–7.76 (m; 2H); 7.74–7.73 (m; 2H); 7.23–7.18 (m; 2H); 7.16–7.11 (m; 3H); 6.83 (d; 1H; J = 8.4); 6.77 (s; 1H) 6.76 (d; 1H; J = 7.1); 6.62 (d; 1H; J = 9.0; OH); 5.99 (d; 2H; J = 2.7; OCH_2O); 4.99 (d; 1H; J = 6.5; NH); 4.45 (d; 1H; J = 15.4; H5a); 4.29 (d; 1 H; J = 15.4; H5b); 3.50–3.42 (m; 2H; H2, H3); 3.01 (dd; 1H; J = 14.7; ^{2}J = 8.6; H4a); 2.90 (dd; 1H; J = 13.8; ^{2}J = 2.8; H4b); 2.51–2.48 (m; 1H; H1a); 2.44 (dd; 1H; J = 13.6; ^{2}J = 10.8; H1b); 1.21 (s; 9H; $C(CH_3)_3$). 155.2 (C=O); 147.2, 146.6, 139.6, 139.4, 132.1, 130.1, 129.1, 129.1, 128.9, 127.8, 126.4, 125.6, 121.8, 108.4, 107.9 (aryl); 100.9 (OCH_2O); 77.4 ($\underline{C}(CH_3)_3$); 71.5 (C3); 54.9 (C2); 50.9 (C5); 50.2 (C4); 35.3 (C1); 28.1 ($C(\underline{CH_3})_3$).
5b	7.76 (d; 2H; J = 8.8); 7.22 (t; 2H; J = 7.4); 7.17–7.13 (m; 3H); 7.09 (d; 2H; J = 8.8); 6.81 (d; 1H; J = 7.8); 6.76 (s; 1H); 6.75 (d; 1H; J = 7.9); 6.71 (d; 1H; J = 8.8; OH); 5.97 (d; 2H; J = 2.4; OCH_2O); 4.92 (d; 1H; J = 6.1; NH); 4.38 (d; 1H; J = 15.5; H5a); 4.26 (d; 1H; J = 15.4; H5b); 3.84 (s; 3H; OMe); 3.53–3.46 (m; 2H; H2, H3); 3.35–3.30 (m; 1H; H4a); 2.95–2.89 (m; 2H; H4b, H1a); 2.46 (dd; 1H; J = 13.5; ^{2}J = 10.6; H1b); 1.23 (s; 9H; $C(CH_3)_3$). 162.3 (aryl); 155.2 (C=O); 147.2, 146.4, 139.5, 131.6, 130.5, 129.2, 129.1, 127.8, 125.6, 121.7, 114.3, 108.5, 107.9 (aryl); 100.9 (OCH_2O); 77.4 ($\underline{C}(CH_3)_3$); 71.9 (C3); 55.6 (OCH_3); 54.8 (C2); 51.2 (C5); 50.4 (C4); 35.1 (C1); 28.1 ($C(\underline{CH_3})_3$).
5c	7.70 (d; 2H; J = 8.1); 7.38 (d; 2H; J = 8.0); 7.25–7.20 (m; 2H); 7.15–7.12 (m; 3H); 6.81 (d; 1H; J = 8.4); 6.75 (s; 1H); 6.74 (d; 1H; J = 7.8); 6.59 (d; 1H; J = 9.0; OH); 5.97 (d; 2H; J = 2.3; OCH_2O); 4.94 (d; 1H; J = 6.3; NH); 4.39 (d; 1H; J = 15.4; H5a); 4.27 (d; 1H; J = 15.4; H5b); 3.51–3.42 (m; 2H; H2, H3); 3.35–3.31 (m; 1H; H4a); 2.96–2.87 (m; 2H; H4b, H1a); 2.46 (dd; 1H; J = 13.8; ^{2}J = 10.5; H1b); 2.40 (s; 3H; CH_3); 1.22 (s; 9H; $C(CH_3)_3$). 155.2 (C=O); 147.3, 146.5, 143.0, 139.5, 137.1, 130.5, 129.7, 129.2, 127.9, 127.0, 125.7, 121.8, 108.5, 108.0 (aryl); 100.9 (OCH_2O); 77.5 ($\underline{C}(CH_3)_3$); 71.9 (C3); 54.9 (C2); 51.2 (C5); 50.5 (C4); 35.1 (C1); 28.1 ($C(\underline{CH_3})_3$); 21.0 (CH_3).
5d	7.89 (dd; 2H; J = 8.7; ^{2}J = 5.2); 7.41 (t; 2H; J = 8.8); 7.23–7.20 (m; 2H); 7.16–7.11 (m; 3H); 6.82 (d; 1H; J = 4.0); 6.76 (s; 1H); 6.75 (d; 1H; J = 7.4); 6.62 (d; 1H; J = 8.9; OH); 5.98 (d; 2H; J = 2.4; OCH_2O); 4.99 (d; 1H; J = 6.4; NH); 4.44 (d; 1H; J = 15.4; H5a); 4.29 (d; 1H; J = 15.4; H5b); 3.55–3.43 (m; 2H; H2 and H3); 2.99 (dd; 1H; J = 14.8; ^{2}J = 8.7; H1a); 2.90 (d; 1H; J = 13.5; J = = 3.0; H4a); 2.49–2.47 (m; 1H; H4b); 2.42 (dd; 1H; J = 14.8; ^{2}J = 9.8; H1b); 1.21 (s; 9H; $C(CH_3)_3$). 164.2 (d; J = 250.0; aryl)); 155.2 (C=O); 147.3; 146.6; 139.5; 136.7; 130.2; 130.0 (d; $^{3}J_{CF}$ = 9.0); 129.2; 127.9; 125.7; 121.8; 116.3 (d; ^{2}J = 22.3); 108.5; 108.0 (aryl); 101.0 (OCH_2O); 77.5 ($\underline{C}(CH_3)_3$); 71.6 (C3); 54.9 (C2); 50.9 (C5); 50.2 (C4); 35.3 (C1); 28.1 ($C(\underline{CH_3})_3$).
5e	8.37 (d; 2H; J = 8.8); 8.08 (d; 2H; J = 8.8); 7.23–7.21 (m; 2H); 7.15–7.11 (m; 3H); 6.85 (d; 1H; J = 7.9); 6.79 (s; 1H); 6.78 (d; 1H; J = 7.9); 6.62 (d; 1H; J = 9.0; OH); 5.99 (d; 2H; J = 3.3; OCH_2O); 4.99 (d; 1H; J = 6.6; NH); 4.56 (d; 1H; J = 15.3; H5a); 4.33 (d; 1H; J = 15.4; H5b); 3.52–3.38 (m; 2H; H2, H3); 3.11 (dd; 1H; J = 14.8; ^{2}J = 8.8; H4a); 2.90 (dd; 1H; J = 13.2; ^{2}J = 3.2; H4b); 2.50–2.48 (m; 1H; H1a); 2.43 (dd; 1H; J = 13,7; ^{2}J = 10.8; H1b); 1.21 (s; 9H; $C(CH_3)_3$). 155.2 (C=O); 149.5, 147.4, 146.7, 146.1, 139.4, 129.8, 129.8, 129.3, 129.1, 128.6, 127.9, 125.7, 124.4, 121.9, 108.5, 108.1 (aryl); 101.1 (OCH_2O); 77.5 ($\underline{C}(CH_3)_3$); 71.2 (C3); 54.9 (C2); 50.7 (C5); 50.1 (C4); 35.4 (C1); 28.1 ($C(\underline{CH_3})_3$).
5f	7.44 (d; 2H; J = 8.6); 7.23–7.18 (m; 2H); 7.16–7.13 (m; 3H); 6.80 (d; 1H; J = 7.7); 6.75 (s; 1H); 6.74 (d; 1H; J = 8.0). 6.61 (d; 2H); 6.55 (d; 1H; J = 9.0; OH); 5.99 (s; 2 H; NH_2); 5.97 (d; 2H; J = 2.4; OCH_2O); 4.83 (d; 1H; J = 6.0; NH); 4.29 (d; 1H; J = 15. 4; H5a); 4.18 (d; 1H; J = 15.3; H5b); 3.57–3.44 (m; 2H; H2, H3); 3.30 (dd; 1H; J = 14.6; ^{2}J = 3.2; H4a); 2.90 (dd; 1H; J = 13.8; ^{2}J = 2.6; H4b); 2.80 (dd; 1H; J = 14.4; ^{2}J = 8.0; H1a); 2.47–2.45 (m; 1H; H1b); 1.23 (s; 9H; $(C(CH_3)_3$); 1.10 (s; 2H; NH_2). 155.1 (C=O); 152.7, 147.1, 146.2, 139.5, 130.9, 129.0, 128.8, 127.7, 124.3, 121.5, 112.6, 112.6, 108.4, 107.7 (aryl); 100.7 (OCH_2O); 77.3 ($\underline{C}(CH_3)_3$); 72.1 (C3); 54.7 (C2); 51.4 (C5); 50.5 (C4); 34.9 (C1); 28.0 ($C(\underline{CH_3})_3$).
6a	7.77 (d; 2H; J = 8.7); 7.73 (d; 2H; J = 8.7); 7.28–7.23 (m; 2H); 7.19–7.16 (m; 3H); 6.85 (d; 1H; J = 7.4); 6.78 (s; 1H); 6.75 (d; 1H; J = 8.0); 5.99 (s; 2H; OCH_2O); 4.75 (d; 1H; J = 5.7; NH); 4.41 (d; 1H; J = 15.5; H5a); 4.34 (d; 1H; J = 15.4; H5b); 3,45 (dd; 1H; J = 14.5; ^{2}J = 2.4; H4a); 3.42–3.37 (m; 1H; H2); 3.12 (dd; 1H; J = 14.8; ^{2}J = 8.7: H1a); 2.71 (dd; 1H; J = 14.4; ^{2}J = 3.0; H4b); 2.30 (dd; 1H; J = 14.7; ^{2}J = 9.8; H1b); 1.27 (br; 2H; NH_2). 147.2, 146.5, 139.8, 139.5, 132.2, 130.4, 129.2, 128.9, 128.1, 126.3, 125.8, 121.7, 108.4, 107.9 (aryl); 100.9 (OCH_2O); 72.2 (C3); 56.1 (C2); 51.4 (C5); 49.9 (C4); 36.7 (C1).
6b	7.76 (d; 2H; J = 8.9); 7.27–7.24 (m; 2H); 7.20–7.14 (m; 3H); 7.09 (d; 2H; J = 8.9); 6.83 (d; 1H; J = 7.9); 6.74 (d; 1H; J = 7.9); 5.98 (s; 2H; OCH_2O); 4.70 (d; 1H; J = 5.6; NH); 4.32 (s; 2H; H5); 3.85 (s; 3H; OCH_3); 3.44–3.40 (m; 2H; H2, H3); 3.04 (dd; 1H; J = 13.9; ^{2}J = 8.0, H4a); 2.74–2.70 (m; 2H; H4b, H1a); 2.29 (dd; 1H; J = 14.1; ^{2}J = 9.6, H1b); 1.17 (br; 2H; NH_2). 162.3, 147.2, 146.4, 139.9, 131.5, 130.8, 129.2, 129.1, 128.0, 125.7, 121.6, 114.3, 108.4, 107.9 (aryl); 100.9 (OCH_2O); 72.5 (C3); 56.0 (OCH_3); 55.6 (C2); 51.6 (C5); 50.2 (C4); 36.3 (C1).
6c	7.70 (d; 2H; J = 8.2); 7.39 (d; 2H; J = 8.0); 7.27–7.24 (m; 2H); 7.20–7.17 (m; 2H); 6.75 (d; 1H; J = 7.9); 6.73 (s; 1H); 6.72 (dd; 1H; J = 6.9; ^{2}J = 1.2); 5.98 (s; 2H; OCH_2O); 4.78 (br; 1H; NH); 4.32 (s; 2H; H5); 3.46–3.41 (m; 2H; H2, H3); 3.04 (dd; 1H; J = 15.1; ^{2}J = 9.0; H4a); 2.79–2.76 (m; H4b, H1a); 2.40 (s; 3H; CH_3); 2.32 (dd; 1H; J = 14.3; ^{2}J = 8.6; H1b); 1.24 (br; 2H; NH_2). 147.4, 146.7, 143.3, 139.9, 137.1, 131.0, 129.9, 129.4, 128.4, 127.2, 126.1, 121.9, 108.7, 108.1 (aryl); 101.1 (OCH_2O); 72.5 (C3); 56.1 (C2); 51.9 (C5); 50.4 (C4); 38.7 (C1); 21.2 (CH_3).
6d	7.90–7.86 (m; 2H); 7.40 (t; 2H; J = 8.8); 7.27–7.22 (m; 2H); 7.19–7.14 (m; 3H); 6.83 (d; 1H; J = 7.9); 6.77 (s; 1H); 6.74 (d; 1H; J = 8.0); 5.99 (s; 2H; OCH_2O); 4.74 (d; 1H; J = 5.2; NH); 4.40 (d; 1H; J = 15.5; H5a); 4.35 (d; 1H; J = 15.4; H5b); 3.45 (dd; 1H; J = 14.5; ^{2}J = 2.7; H4a); 3.41–1.32 (m; 2H; H2, H3); 3.11 (d; 1H; J = 14.5; ^{2}J = 8.6; H4b); 2.76–2.69 (m, 1H; H1a); 2.30 (dd; 1H; J = 14.2; ^{2}J = 10.0; H1b); 1.28 (br; 2H; NH_2). 164.2 (d; J = 249.0), 147.2, 146.6, 139.8, 136.6, 130.5, 130.0 (d; ^{3}J = 9.1), 129.2, 128.1, 125.7, 121.6, 116.2 (d; ^{2}J = 22.2), 108.4, 107.9 (aryl); 100.9 (OCH_2O); 72.3 (C3); 56.1 (C2); 51.3 (C5); 49.9 (C4); 35.3 (C1)
6e	8.35 (d; 2H; J = 8.8); 8.06 (d; 2H; J = 8.8); 7.26–7.23 (m; 2H); 7.17–7.14 (m; 3H); 6.85 (d; 1H; J = 7.8); 6.81 (d; 1H; J = 1.3); 6.77 (dd; 1H; J = 6.0; ^{2}J = 1.3); 5.99 (d; 2H; J = 2.5; OCH_2O); 4.76 (d; 1H; J = 5.3; NH); 4.5 (d; 1H; J = 15.4; H5a); 4.39 (d; 1H; J = 15.4; H5b); 3.49 (dd; 1H; J = 14.4; ^{2}J = 1.9; H4a); 3.22 (dd; 1H; J = 14.5; ^{2}J = 9.0; H4b); 2.75–2.67 (m; 3H; H2, H3, H1a); 2.30 (dd; J = 14.4; ^{2}J = 10.3; H1b); 1.27 (br; 2H; NH_2). 149.4, 147.3, 146.6, 146.0, 139.7, 130.1, 129.2, 128.5, 128.1, 125.8, 124.3, 121.7, 108.4, 108.0 (aryl); 101.0 (OCH_2O); 71.9 (C3); 56.1 (C2); 51.2 (C5); 49.7 (C4); 38.8 (C1).

[a] NMR Spectra in DMSO-d_6/TMS.

basicity of amino group results in a loss of activity. [9] The amino alcohol moiety on hydroxyethylsulfonamides **6a**–**e** is more closely to ethambutol structure than carbamate moiety of hydroxyethylsulfonamides **5a**–**e**. The best results were obtained for amino alcohols **6a**, **6b** and **6c**, especially for amino alcohol **6a** (R = Br) that exhibit the highest activity (MIC = 23.5 μM). The compound with the strongly electron withdrawing nitro (**6e**) did not show activity, suggesting that the substituent in the phenyl ring is important for

Table 3
The *in vitro* activity of compounds **3**, **4**, **5a**–**f** and **6a**–**e** against *Mycobacterium tuberculosis* H37Rv strain (ATCC 27294, susceptible to ethambutol).

Comp.	R	MIC (μM)	logP
3	–	241	5.152
4	–	318	1.409
5a	Br	>500	7.114
5b	OMe	>500	6.362
5c	Me	>500	6.754
5d	F	>500	5.381
5e	NO_2	>500	6.264
5f	NH_2	>500	6.469
6a	Br	23.5	3.371
6b	OMe	51.6	2.619
6c	Me	106	3.010
6d	F	211	1.638
6e	NO_2	>500	2.521
EMB	–	15.9	0.35

the biological activity. Three other compounds (**3**, **4**, and **6d**) exhibited low activity (MIC up to 200 μM). The more active compounds are at least 1.5–6 times less active than EMB (MIC = 15.9 μM), their IC_{50} values are in the micromolar concentration range comparable to recently reported results [10] and could be a start point to find new compounds with better antitubercular activity. Lipophilicities of the compounds **3**, **4**, **5a**–**f**, **6a**–**e** and the standard drug EMB, which were expressed as logP values, were determined using logP method through online http://www.molinspiration.com/cgi-bin/properties site, as show in Table 3.

3. Experimental

3.1. Materials and methods

Unless otherwise indicated, common reagents and solvents were used as obtained from commercial suppliers without further purification. All melting points were determined on a Buchi Melting Point B-545 and are uncorrected. ^1H and ^{13}C NMR spectra were recorded using a Bruker DRX 400 spectrometer (^1H at 400.14 MHz and ^{13}C at 100.61 MHz) or with a Bruker Avance 500 spectrometer (^1H at 500.13 MHz and ^{13}C at 125.75 MHz) in DMSO-d_6 containing TMS as in internal standard. The low resolution LC/MS analyses were performed on an LC/MS micromass ZMD using chloroform/methanol 1:1 as mobile phase with flux of 0.3 mL/min. The analyses used Electrospray Ionization technique on positive ion mode. Samples were introduced by the standard direct insertion probe method.

3.2. General procedure for the preparation of compound 3

Epoxide **1** (1.6 mmol) and piperonylamine **2** (1.5 mmol) were dissolved in isopropanol (10 mL) and stirred under reflux for 16 h. After this period, the solvent was removed by evaporation and the crude product was purified by crystallization in methanol/water (7:3).

3.3. General procedure for the preparation of compounds *5a*–*e*

The compound **3** was dissolved in CH_2Cl_2 (10 mL) and then TEA (2.2 mmol) and DMF (0.2 mmol) were added. The mixture was stirred for 30 min over nitrogenous atmosphere, arenesulfonyl chloride (2.0 mmol) was added portion wise and stirred over 8 h. The organic layer was washed with 5% HCl aqueous solution, water, brine and dried over $MgSO_4$. The solvent was removed in high vacuum and the products **5a**–**e** were obtained after recrystalization in hot hexane.

3.4. General procedure for the preparation of compound *5f*

To a stirred solution of nitro compound **5e** (0.57 mmol) in absolute ethanol (15 mL) under a blanket of nitrogen was added 10% palladium on activated charcoal (5 mg). The reaction was evacuated, placed under a hydrogen atmosphere and stirred overnight. The reaction mixture was filtered through Celite and the solvent was removed under reduced pressure to yield brown oil. The residue was purified by chromatography on silica, eluting with 3:1 hexane/ethyl acetate.

3.5. General procedure for the preparation of compounds *4* and *6a*–*e*

Trifluoracetic acid (1.5 mL, 20 mmol) was added to a solution of the compounds **3** or **5a**–**e** (2 mmol) in CH_2Cl_2 (6 mL). After 4 h at room temperature, the solvent was removed in high vacuum. The residue was dissolved in EtOAc (20 mL), washed with 5% $NaHCO_3$ aqueous solution, H_2O, brine and dried over $MgSO_4$. The solvent was removed to afford the compounds **4** or **6a**–**e**, respectively, without any further purification.

3.6. Anti-mycobacterial activity

The anti-mycobacterial activities of compounds **3**, **4**, **5a**–**f** and **6a**–**e** have been assessed against *M. tuberculosis* ATTC 27294 using the micro plate Alamar Blue assay (MABA) [14] (Table 3). This methodology is nontoxic, uses a thermally-stable reagent and shows good correlation with proportional and BACTEC radiometric methods [15,16]. The method is described as follows: 200 ml of sterile deionized water was added to all outer-perimeter wells of 96 sterile well plates (falcon, 3072: Becton Dickinson, Lincoln Park, NJ) to minimize evaporation of the medium in the test wells during incubation. The 96 plates received 100 mL of the Middlebrook 7H9 broth (Difco laboratories, Detroit, MI, USA) and successive dilution of the compounds was made directly on the plate. The final drug concentrations tested were 0.01–20.0 μg/mL. Plates were covered and sealed with parafilm and incubated at 37 ° C for five days. 25 mL of a freshly prepared 1:1 mixture of Alamar Blue (Accumed International, WestlakeOhio) reagent and 10% tween 80 was then added to the plate and incubated for 24 h. A blue color in the well was interpreted as no bacterial growth, and a pink color was scored as growth. The minimal inhibition concentration (MIC) was defined as the lowest drug concentration, which prevented a color change from blue to pink.

4. Conclusion

In conclusion, the synthesis of thirteen hydroxyethylamines derivatives **3**, **4**, **5a**–**f** and **6a**–**e** were easily performed with good yields. All compounds were tested against *M. tuberculosis* and three of them (**6a**–**c**) exhibit significant activity when compared with first line drug ethambutol (EMB) with amino alcohol **6a** (R = Br) showing the best activity (MIC = 23.5 μM). It suggests that these amino alcohols could be a good start point to find new lead compounds.

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