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Ethambutol Analogues as Potential Antimycobacterial Agents

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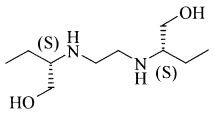
Abstract—A range of new ethambutol analogues was synthesised and their inhibitory potencies were probed with *Mycobacterium smegmatis*. Interestingly, apparently even minor deviation from the structure of the parent compound resulted in reduced antimycobacterial activity.

Ethambutol [(*S*,*S*)-2,2′-(ethylenediimino)-di-1-butanol, **1**], first reported by Wilkinson and co-workers[1] in the early 1960s, is one of the few long-known and reliable front-line antimycobacterial chemotherapeutic agents.[2] Recently, it could be shown that this activity is due to the inhibition of mycobacterial arabinofuranosyl transferases responsible for glycosylation steps in the biosynthesis of lipoarabinomannan (LAM) and arabinogalactan (AG) which are constituents of the mycobacterial cell wall.[3,4] Subsequently, an iminoalditol (**2**) mimicking the arabinofuranosyl motif was found to exhibit antimycobacterial properties in an infected macrophage model.[5]



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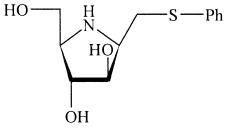
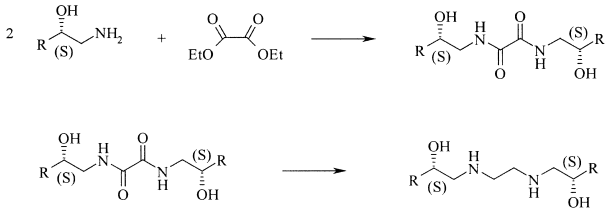


2

Other iminoalditols bearing the ethambutol partial structure were reported to be inactive.[6,7]

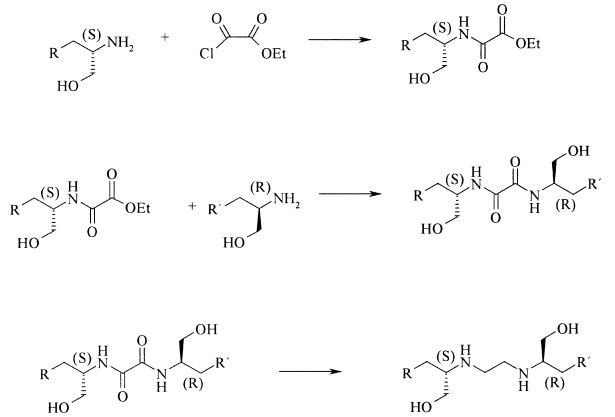
In context with a programme aimed at the synthesis of antibacterial iminoalditol derivatives, several derivatives of ethambutol were prepared to probe the minimal structural requirements for antimycobacterial activity in this type of chemotherapeutic agent.

Symmetrical ethambutol analogues were prepared by the reaction of selected amines with diethyl oxalate in toluene at ambient temperature and subsequent reduction of the resulting symmetrical diamides employing $LiAlH_4$ in refluxing THF according to Scheme 1.



Scheme 1.

For the synthesis of unsymmetrical derivatives of compound **1**, oxalic ester chloride was reacted with amine **1** in DMF/THF 1:3 at 0 °C followed by reaction with amine **2** in toluene at ambient temperature and subsequent $LiAlH_4$ reduction of the respective diamide thus obtained in THF at 50 °C (Scheme 2).



Scheme 2.

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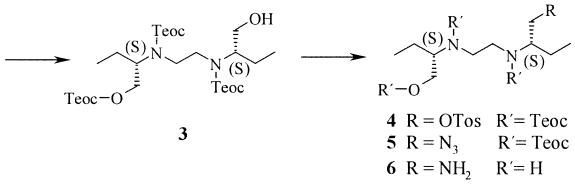
In a third type of approach, ethambutol was reacted with excess trichloroethoxycarbonyl chloride (slow addition) in aqueous sodium bicarbonate at pH 9 at ambient temperature to furnish new *N*,*N*,*O*-triprotected compound **3** in good yield. This could subsequently be modified at the remaining free hydroxy group.

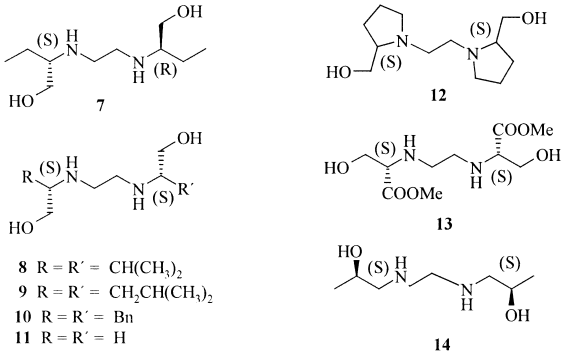
For example, employing standard methodology it was converted, via the corresponding *O*-sulfonate **4** and the azidodeoxy derivative **5**, into triamine **6** (Scheme 3).



Scheme 3.

The trichloroethoxycarbonyl groups were reductively removed employing Zn in glacial acetic acid at ambient temperature.

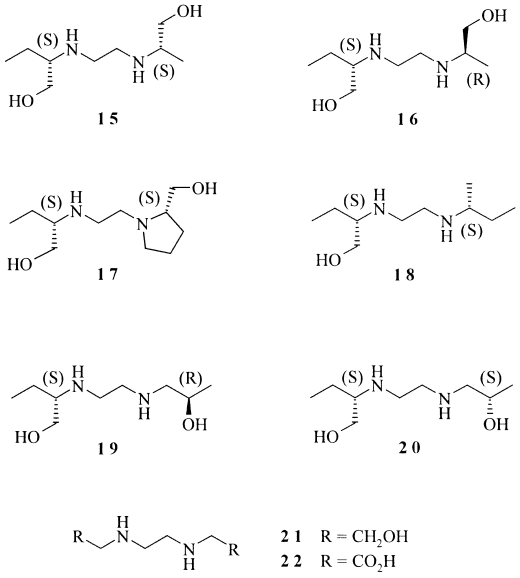
Antimycobacterial activities of these compounds were assessed by screening with *Mycobacterium smegmatis* employing the agar diffusion technique.[8] Inhibition zones were compared with that of ethambutol (**1**).



Neither of the new derivatives[9] nor any of the previously known analogues (**7**–**12**) synthesised for comparison to obtain a more complete set of structure–activity relationships was as active as ethambutol. 45% activity (as compared to standard compound **1**) was exhibited by the long-known (*RS*)-diastereomer **7**.

Any type of chain extension such as in compounds **8**–**10** was deleterious to the biological activity.

Furthermore, introduction of conformational constraint, such as in symmetrical prolinol derivative **12**,[10] abolished antimycobacterial activity against the bacterial strain under consideration whereas unsymmetrical relative **17** exhibited activity of about 10%. Removal of chiral properties by structural reduction (commercially available compound **21**) as well as oxidation of the hydroxyl groups (**13**) rendered these products inactive. How limited the 'allowed' alterations in this system are is also demonstrated by the chain-shortened derivatives **11**, **15** and **16**. Whereas previously reported[11] symmetrical derivative **11** exhibited 40% activity of the standard and the closely related analogue **15** showed 50% of the activity of compound **1**, the corresponding values for its (*R,S*)-configured diastereomer **16** were less than 10%. The ethambutol related complexing agents such as **22** as well as EDTA (not depicted) did not exhibit any activity.



Apparently, in light of the above, ethambutol is a structurally uniquely well-suited inhibitor of arabinofuranosyl transferase(s) of LAM biosynthesis but is not a good lead for the synthesis of analogues as has been shown in this study.

Acknowledgements

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References and Notes

1. Wilkinson, R. G.; Shepherd, R. G.; Thomas, J. P.; Baughn, C. *J. Am. Chem. Soc.* **1961**, *83*, 2212. Shepherd, R. G.; Wilkinson, R. G. *J. Med. Pharm. Chem.* **1962**, *5*, 823. Wilkinson, R. G.; Cantrall, M. B.; Shepherd, R. G. *J. Med. Pharm. Chem.* **1962**, *5*, 835. Brit. 961,317; *Chem. Abstr.* **1964**, *61*, 8191e. US 3,463,861; *Chem. Abstr.* **1970**, *72*, 89762g.
2. Wilson, T. M. *Chemotherapy* **1970**, *16*, 222.
3. Lee, R. E.; Mikušová Brennan, P. J.; Besra, G. S. *J. Am. Chem. Soc.* **1995**, *117*, 11829.
4. Lety, M. A.; Nair, S.; Berche, P.; Escuyer, V. *Antimicrob. Agents Chemother.* **1997**, *41*, 2629.
5. Maddry, J. A.; Bansal, N.; Bermudez, L. E.; Comber, R. N.; Orme, I. M.; Suling, W. J.; Wilson, L. N.; Reynolds, R. C. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 237.
6. Reynolds, R. C.; Bansal, N.; Rose, J.; Friedrich, J.; Suling, W. J.; Maddry, J. A. *Carbohydr. Res.* **1999**, *317*, 164.
7. Lee, R. E.; Smith, M. D.; Pickering, L.; Fleet, G. W. J. *Tetrahedron Lett.* **1999**, *40*, 8689.

8. *Mycobacterium smegmatis* MC^2: for drug susceptility testing see: Woods, L.; Washington, J. A. In *Manual of Clinical Microbiology*; Murray P. R., Baron, E. J., Pfaller, M. A., Tenover, F. C., Yolken, R. H., Eds.; ASM: Washington DC, 1995; p 1327. Griffith, M.; Barrett, M. L.; Bodily, H. L.; Wood, R. M. *Am. J. Clin. Path.* **1967**, *47*, 812.

9. Selected data: **6**: $[\alpha]_D^{20}$ +1 (*c* 1.3, MeOH); ^{13}C NMR (CD_3OD): δ 61.8, 58.1, 57.9, 41.7, 40.9, 38.3, 21.2, 20.6, 9.3, 8.1. **15**: $[\alpha]_D^{20}$ +12.3 (*c* 0.5, MeOH); ^{13}C NMR (CD_3OD): δ 66.8, 64.0, 62.0, 55.9, 50.3, 47.4, 24.9, 16.9, 10.8. **16**: $[\alpha]_D^{20}$ −6 (*c* 0.5, MeOH); ^{13}C NMR (CD_3OD): see **15**. **17**: $[\alpha]_D^{20}$ −16 (*c* 1.0, MeOH); ^{13}C NMR (CD_3OD): δ 67.1, 65.4, 63.6, 62.5, 55.7, 55.5, 46.6, 28.8, 24.6, 24.1, 10.8. **18**: $[\alpha]_D^{20}$ +8 (*c* 0.5, MeOH); ^{13}C NMR (DMSO-d_6): 60.3, 57.5, 54.8, 48.6, 40.3, 25.2, 20.4, 14.9, 9.8, 9.5. **19**: $[\alpha]_D^{20}$ −1 (*c* 0.6, MeOH); ^{13}C NMR (CD_3OD): δ 67.2, 64.0, 62.1, 58.0, 50.1, 47.2, 24.8, 21.6, 10.8. **20**: $[\alpha]_D^{20}$ +5.5 (*c* 0.7, MeOH); ^{13}C NMR (CD_3OD): see **19**.

10. Colombo, L.; Gennari, C.; Poli, G.; Scolastico, C. *Tetrahedron* **1982**, *38*, 2725.

11. Vannoorenberghe, Y.; Buono, G. *J. Am. Chem. Soc.* **1990**, *112*, 6142.