Synthesis of Small Molecule Anti-Trypanosomal Drugs: A Brief SAR Study

Samuel Peter Anderson

Department of Chemistry, College of Arts and Sciences, University of Nebraska at Omaha, Omaha, NE 68182

Introduction

Human African Trypanosomiasis (HAT) is a debilitating tropical disease caused by the flagellar protozoan parasite Trypanosoma Brucei. Left untreated, trypanosomiasis parasites invade a patient’s brain and induce neurological changes such as sleep disorder, ataxia, psychosis, coma, and ultimately death. Fortunately, aggressive epidemiological intervention by the World Health Organization has limited the spread of the disease in recent years. However, approximately 70 million people distributed worldwide are estimated to be at differing levels of risk of contracting HAT. While current drug treatments—suramine, pentamidine, nitrofurazone, and melarsoprol—are effective, they are also costly, inconvenient, and toxic. Limitations of these current treatments are well described, with limited side effects, often modulate a specific and well understood process. Sadly, the pathways associated with disease. The best therapeutic compounds, potent with known efficacy. Systematically changing molecular shape, size, rigidity, or functional groups can identify patterns that correlate chemical structure to biological activity. Such experiments are called structure activity relationship (SAR) studies.

General Methods

(a) Nucleophilic Aromatic Substitution: K2CO3 (2 eq.), anhy. DMF, air free, 130 °C, 1 hr
(b) Cu(i) Bromide Oxidation: 70% TBuOOH (4 eq.), Cu(II)Br2 (0.1 eq.) acetonitrile, 23 °C, 1 hr
(c) Sodium Borohydride Reduction: NaBH4 (3 eq.), methanol, 23 °C, 1 hr
(d) Caddick Reduction: NaBH4 (8 eq.), NiCl2, 23 °C, 5 min.
(e) Acidic Precipitation: Anhydrous HCl in ethyl acetate, 23 °C, 5 min.
(f) K2CO3 (2 eq.), anhy. DMF, air free, 130 °C, 1 hr

Discussion

The derived compounds have a 3,4' substitution pattern whereas our previous work focused on 4,4' substituted compounds. The enhanced activity of 15 relative to AM272 suggests that 3,4' substituted compounds may be superior in general. However, at present, the claim is equivocal.

Another important finding is the apparent unsuitability of amides as side chain functional groups. The amide analog of 15, 13, is an order of magnitude less active. This emphasizes that cationic groups, such as the protonated amine, are important structural features of active HAT drugs.

Conclusion and Future Work

The preliminary findings of the SAR study support the notion of 3,4' substitution patterns in HAT drugs. Diphenyl ether amide derivatives, however, make poor drug compounds. Future work will complete the synthesis and assay of the best remaining candidates of the group (3-CH2NH3+, 4'-OH; 3-CH3NH2+, 4'- CH2NH3+). Subsequently, the starting materials made during the project will be applied to the rapid synthesis of other promising 3,4' analogs.

Results

Of the sixteen compounds prepared, four were sent to the Swiss TPHI for trypanosomal assay: 13 (3-OH; 4'-ONH2), 15 (3-OH; 4'-CH2NH3+), 31 (3-OH; 4'- OH), and 41 (3-ONH2; 4'-ONH2). The results are summarized in Table 1.

Table 1: Swiss TPHI in vitro Test Results

<table>
<thead>
<tr>
<th>Compound</th>
<th>IC50 Activity (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>35.62</td>
</tr>
<tr>
<td>15</td>
<td>1.35</td>
</tr>
<tr>
<td>31</td>
<td>45.89</td>
</tr>
<tr>
<td>41</td>
<td>43.46</td>
</tr>
</tbody>
</table>

References

(1) Khan, O. Drug Targets Insights. 2007, 2, 129-146.