PARTIAL 5-HT2A RECEPTOR AGONISTS OF THE PHENYLETHANAMINE SERIES: EFFECT OF A TRIFLUOROMETHYL SUBSTITUENT

Heim, B., Pertz, H.H., Eltz, S.
Institut für Pharmazie, Fachbereich Biologie, Chemie, Pharmazie, Freie Universität Berlin, König-Luise-Str. 2-4, 14195 Berlin, Germany

Analogues of the hallucinogenic amphetamine derivatives DOB/DOB, e.g., 1, have recently been characterized as extremely potent partial agonists at rat 5-HT2A receptors.\(^1\) A report on potent CF3 analogues of DOB/DOB\(^2\) stimulated us to study the influence of CF3 substitution on affinity and agonist activity of 1-type derivatives.

<table>
<thead>
<tr>
<th>No.</th>
<th>X</th>
<th>R</th>
<th>rel. pot.</th>
<th>(\text{E}_{\text{max}})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Br</td>
<td>CH3</td>
<td>384</td>
<td>38±2</td>
</tr>
<tr>
<td>2</td>
<td>CF3</td>
<td>CH3</td>
<td>107</td>
<td>36±5</td>
</tr>
<tr>
<td>3</td>
<td>CF3</td>
<td>H</td>
<td>136</td>
<td>28±4</td>
</tr>
<tr>
<td>4</td>
<td>Br</td>
<td>CF3</td>
<td>n. d.</td>
<td>6±1</td>
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<tr>
<td>5</td>
<td>-</td>
<td>n. d.</td>
<td>&lt;10</td>
<td></td>
</tr>
<tr>
<td>6-HT</td>
<td>-</td>
<td>-</td>
<td>1 100</td>
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</tbody>
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New compounds were synthesized using reported methods\(^{1-3}\) and were studied on 5-HT2A receptors of isolated rat tail artery. Although being less potent than 1, 2 and 3 displayed nanomolar affinity and partial agonist activity. Replacement of the ortho-OCH3 substituent of 1 (\(\rightarrow 4\)) and of a related 5-methoxyindole derivative (\(\rightarrow 5\)) resulted in decreased affinity and almost complete loss of agonism. This result emphasizes the prominent role of an ortho-CH3 or -OCH3 group (as present in 1 - 3) for activating the 5-HT2A receptor protein.


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PLATE READER-BASED ASSAY FOR HISTONE DEACETYLASE ACTIVITY AND ITS INHIBITION

Heltweg, B., Jung, M.
Department of Pharmaceutical Chemistry, Westfälische Wilhelms-Universität Münster, Hittorfstr. 58-62, D-48149 Münster, Germany

The determination of histone deacetylase (HDAC) activity and its inhibition is receiving high interest as HDAC is a key regulator of transcription and has been linked to the pathogenesis of malignant disease. We have previously established a new assay for the determination of enzyme activity in protein purification and characterization and the screening of potential inhibitors that is able to replace existent isotopic assays. It is based on the HPLC analysis of the enzymatic conversion of the unnatural substrate 1 \(^{[1]}\) which is easily accessible from commercially available starting materials and is now distributed by Calbiochem.

Here we present a plate reader based assay which allows for higher throughput. Using a Titertek Fluoroscan II the limit of quantitation is 50 ng/mL (compared to 5 ng/mL with HPLC and fluorescence detection) which is still low enough for the determination of the remaining amount of substrate in the absence of an inhibitor.


RE-EVALUATION OF TRIMETHOPRIM DRUG SUBSTANCE

Hens, S.\(^1\), Röpe, D.\(^1\), Eger, K.\(^1\)
\(^1\)Institut für Pharmazie, Universität Leipzig, Brüderstrasse 34, D-04103 Leipzig
\(^1\)Bundesinstitut für Arzneimittel und Medizinprodukte, Sonnstrasse 10-11, D-13353 Berlin

Trimethoprim, in combination with sulfonamides, is one of the most widely used antibiotics. Therefore, drug manufacturers all over the world have a great interest in synthesizing generics such as trimethoprim. However, these drugs are often synthesized in a different way from the original, registered one. Therefore, so far unknown impurities occur and may not be identified with compendial methods. In order to guarantee high quality, it is necessary to identify new impurities and update analytical methods of the pharmacoepia.

Hence, we have developed a new HPLC-method in order to detect and quantify all impurities presently observed in TMP-batches. This HPLC-method was validated with all necessary parameters, including linearity, accuracy, precision, limit of detection, limit of quantification and ruggedness. Ethoxy-TMP could be identified as the major impurity of some batches from asiatic origin in concentrations of around 1%. In order to ensure the identity of all investigated impurities, they were synthesized in parallel synthesis. Additionally, we investigated trimethoprim batches of various producers with analytical methods, like FT-IR, thin-layer, HPLC, LC-MS, GC-MS and NMR. The results of these investigations were in accordance with the HPLC results.