Tetrahedron Letters 53 (2012) 2189–2194

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis and biological evaluation of 3-aryltyramines as fragments binding to BACE-1 and BACE-2

Stefanie K. Fehler [a], Gerald Pratsch [a], Walter Huber [b], Alain Gast [b], Remo Hochstrasser [b], Michael Hennig [b,*], Markus R. Heinrich [a,*]

[a] Department für Chemie und Pharmazie, Pharmazeutische Chemie, Friedrich-Alexander-Universität Erlangen-Nürnberg, Schuhstraße 19, 91052 Erlangen, Germany
[b] F. Hoffmann-La Roche Ltd., Discovery Technologies, 4070 Basel 65/319, Switzerland

ARTICLE INFO

Article history:
Received 18 January 2012
Revised 9 February 2012
Accepted 14 February 2012
Available online 21 February 2012

Keywords:
Radical reactions
Tyramine
BACE
Biaryl
Arylation

ABSTRACT

3-Aryltyramines were prepared in one single step from tyramine and various arenediazonium salts by radical arylation. Binding as well as enzyme inhibition data of the 14 compounds do not prove true interaction with BACE-1. In contrast, with BACE-2 inhibition and binding could be confirmed indicating that 3-aryltyramines are potential starting points for a drug discovery effort.

Tyramine[1] and tyrosine[2] derivatives structurally modified by ring-arylation have recently become of interest as new building blocks for pharmaceutical research. In fragment screening experiments, Kuglstatter et al.[1] observed that compounds possessing a (2-hydroxybiphen-5-yl)ethylamine substructure bind to the β-site amyloid precursor protein cleavage enzyme 1 (BACE-1) and act as inhibitors. Due to its essential role in the amyloid cascade hypothesis, BACE-1 today represents one of the most attractive drug targets for the treatment of Alzheimer's disease. According to the hypothesis, BACE-1 is the enzyme responsible for the formation of the pathological 40 or 42 amino acid containing β-amyloid peptides. The cerebral plaques resulting from the deposition of β-amyloid peptides are considered to be responsible for Alzheimer's disease and the related symptoms of dementia.[3,4] To show activity in vivo, potential BACE-1 inhibitors have to be able to pass the blood–brain barrier. For this purpose, molecular properties like low molecular weight and positive charge are beneficial. Both requirements are fulfilled by tyramine (**1**) and its arylated derivatives **2a** and **2b**, which have so far been identified as inhibitors for BACE-1 (Fig. 1).[1] BACE-2, which is structurally a close homolog of BACE-1,[5] is expressed in beta cells and involved in the cleavage of TMEM27. Consequently, inhibition of BACE-2 could be of therapeutic use for the treatment of diabetes.

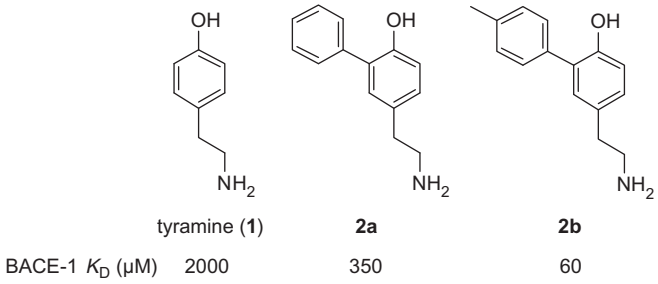


Figure 1. 3-Aryltyramines **2a** and **2b** acting as BACE-1 inhibitors.

Based on the crystal structure of the enzyme,[6] in silico docking experiments have been performed with a number of substituted tyramines.[7] Among the compounds investigated, especially those tyramines bearing a *meta*-substituted aromatic phenyl group as substituent show a good interaction with the active site of BACE-1 with the potential to reach out to the S3 pocket (Fig. 2). This structure based molecular design study encouraged us to synthesize a number of such compounds and test their binding as well as biological activity to BACE-1 and BACE-2.

Our interest in 3-aryltyramines such as **2a** and **2b** was further driven by recent developments in the field of radical arylation of

* Corresponding authors. Tel.: +49 9131 85 24115; fax: +49 9131 85 22585 (M.R.H.); tel.: +41 616886046 (M.H.).
E-mail addresses: michael.hennig@roche.com (M. Hennig), Markus.Heinrich@medchem.uni-erlangen.de (M.R. Heinrich).

0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2012.02.070

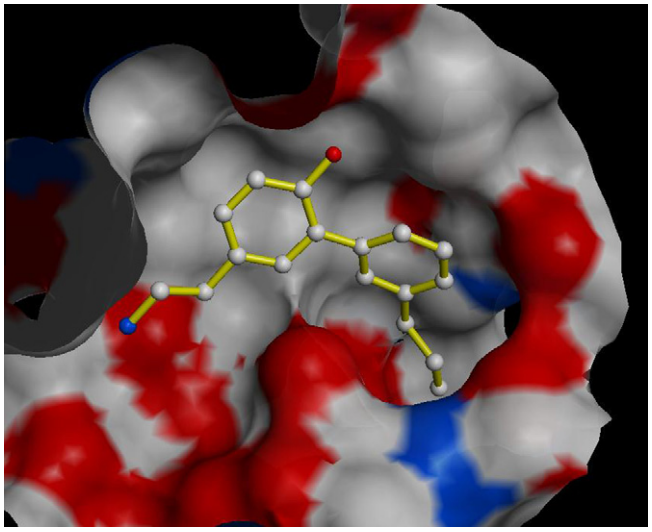


Figure 2. Tyramine derivative with *meta*-substituted phenyl substituent docked to the active site of BACE-1.

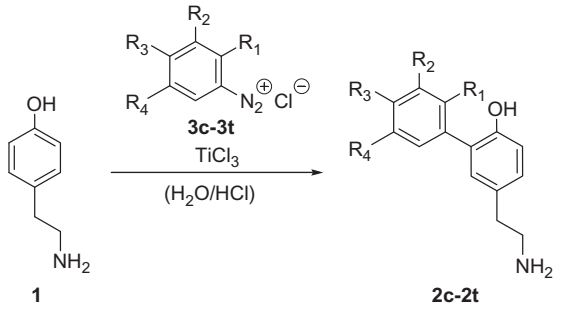
non-protected phenols and anilines.[8–10] Especially through the use of arenediazonium salts,[11] such as **3c**, as aryl radical source, tyramine (**1**) can be converted into its 3-aryl derivative **2c** in a single step without the need for protecting groups (Scheme 1).[10b,12,13] The existing access, which has been exploited for the synthesis of the BACE-1 inhibitors **2a** and **2b**, comprises four steps with a Suzuki coupling as the key reaction.[1]

With the perspective of applying radical arylation reactions in automated parallel syntheses, we decided to evaluate the scope of this new methodology by preparing a small library of 3-aryltyramines in combination with biological testing as BACE-1 and BACE-2 inhibitors. The radical reactions for the library synthesis were carried out using titanium(III)-chloride as the reductant in diluted hydrochloric acid and acetonitrile. Diazonium salts were prepared as chlorides and were added to a solution containing tyramine (**1**) and $TiCl_3$. Since the 3-aryltyramines **2c**–**2t** are less polar than tyramine (**1**), product separation from excess **1** was largely possible by simple extraction of the basified aqueous reaction mixture with diethyl ether.[14] The compounds synthesized through the radical arylation reactions are summarized in Table 1.

Aryltyramines **2c–2k** were accessible without any complications. Products **2l** and **2m** were obtained in lower yields, which are most probably due to the steric hindrance caused by their *ortho*-substituents. In addition, we were unable to fully separate **2l** and **2m** from their regioisomers by HPLC.

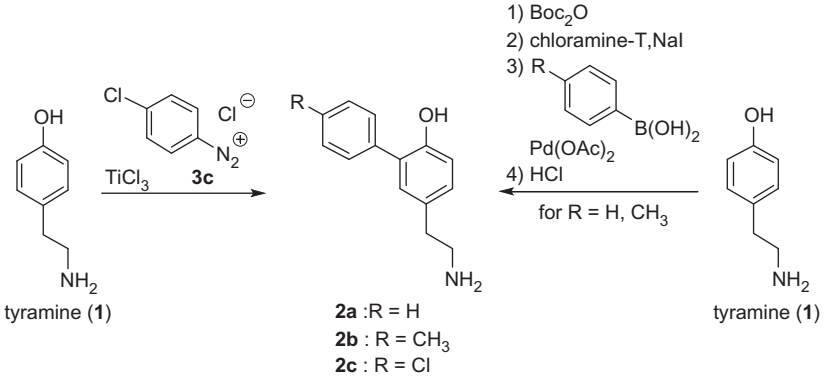
The syntheses starting from the diazonium salts **3n**–**3t** gave the desired products in lower yields, since they were complicated by different side-reactions. Due to its electron-donating substituent, the diazonium salt **3n** was reduced too slowly to effectively give aryl radicals at ambient temperature.[15] In the cases of **3h**, **3k**, **3o**, **3p**, **3r,** and **3s**, additional acetonitrile had to be added to achieve solubility in the diazotization step. Larger amounts of this solvent usually lead to increased hydrogen abstraction.[16,17] The radical arylations with the iodinated diazonium salts **3o** and **3q** gave 1,3- and 1,4-diiodobenzene as by-products, which suggest the occurrence of intramolecular iodine transfer reactions.[18] Significant homocoupling, which means the addition of aryl radicals to their original diazonium salts, was observed in the arylation with salt **3t**. Due to the fact that especially well stabilized cyclohexandienyl radicals (captodative effect) arise from the addition step,[19]

Table 1
3-Aryltyramines **2c–2t** prepared by radical arylation of tyramine (**1**)



Product (diazonium salt)	R^1	R^2	R^3	R^4	Yield[a,b] (%)
2c (**3c**)	H	H	Cl	H	42
2d (**3d**)	H	H	F	H	43
2e (**3e**)	H	Cl	H	H	41
2f (**3f**)	H	F	H	H	40
2g (**3g**)	H	H	Br	H	46
2h (**3h**)	H	Br	H	H	61
2i (**3i**)	H	CN	H	H	35
2j (**3j**)	H	F	F	F	39
2k (**3k**)	H	CF_3	H	H	40
2l (**3l**)	Cl	H	H	H	40[c]
2m (**3m**)	Br	H	H	H	27[c]
2n (**3n**)	H	H	OMe	H	10[d]
2o (**3o**)	H	I	H	H	41[d]
2p (**3p**)	H	Cl	Cl	H	41[d]
2q (**3q**)	H	H	I	H	26[d]
2r (**3r**)	H	H	COMe	H	14[d]
2s (**3s**)	H	H	COOMe	H	7[d]
2t (**3t**)	H	OMe	H	H	22[d]

[a] For reaction conditions, see Experimental section.
[b] Yield after extraction with Et_2O (corrected for minor amounts of **1**, regioisomer and by-products, extraction not quantitative).
[c] Separation of regioisomer not possible by HPLC.
[d] 3-Aryltyramines accompanied by further by-products (see text).



Scheme 1. Radical and organometallic access to 3-aryltyramines **2a**–**2c**.