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Isomeric thiazole derivatives as ligands for the neuropeptide Y5 receptor

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Abstract—Sets of isomeric thiazole derivatives **1** and **2** have been synthesised in a parallel iterative solution-phase synthesis approach guided by the SAR analysis derived from biological results and computer-aided design and analysis. This synergistic and streamlined working procedure led to highly active isomeric NPY5 receptor ligands. However, a 10-fold difference at least in their respective binding affinities was consistently found for all isomeric pairs **1** and **2**. The analysis of conformational differences due to heteroatom interactions in **1** and **2** revealed a favourable C=O···S interaction in **1**, whereas thiazoles **2** showed a repulsive C=O···N interaction.

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Neuropeptide Y is a 36 amino acid peptide that is widely distributed in the central and peripheral nervous systems. This peptide mediates a number of physiological effects through its various receptor subtypes. Studies on animals have shown that neuropeptide Y is a powerful stimulus of food intake, and it has been demonstrated that activation of neuropeptide Y Y5 receptors results in hyperphagia and decreased thermogenesis. Therefore, the compounds that antagonise neuropeptide Y at the Y5 receptor subtype represent an approach to the treatment of eating disorders such as obesity and hyperphagia.[1–3] In the course of a medicinal chemistry programme aimed towards the identification of novel NPY5 receptor ligands, thiazole derivatives have been previously described as interesting scaffolds.[4,5] A versatile procedure was developed towards the synthesis of isomeric aminothiazole derivatives **1** and **2**, thus allowing for maximum flexibility in the design of new NPY5 ligands having three main vectors of diversity. The parallel iterative solution-phase synthesis of the series of compounds of **1** and **2** demonstrates a streamlined working procedure in which the latest biological results were combined with the results from modelling activities. Any derived SAR was synergistically integrated into the design and synthesis of new thiazole derivatives in new synthetic rounds.[6] Both synthetic routes started from the common thiourea intermediate **3**, which already defines the first vector of diversity. Pursuing the first synthetic route, four subsequent steps were required to arrive at the desired aminothiazole derivatives **1**. The C1 elongation of thiourea **3** by the reaction with *N*,*N*-dimethylamino dimethylformamide gave access to the iminourea **4** in 90% yield. The thiazole ring was formed from the reaction of **4** with α-bromoketones, in this particular case 2-methylphenacyl bromide, in acceptable 77% yield.[7] Obviously, this vector of diversity may easily be altered by use of various α-bromoketones to arrive at a structure activity relationship with respect to substitution patterns and electronic properties. Deprotection of the amino functionality in **4** was followed by derivatisation with electrophiles (sulfonylchlorides, acid chlorides and isocyanates) to add a third vector of diversity. In total, 50 thiazoles **1** with this particular sub-structure were synthesised in synthetically useful yields depending on the reactivity of the respective electrophile (Scheme 1). twenty-nine sulfonamide thiazole derivatives **1** were obtained, from which a preliminary SAR was derived. However, to further improve our knowledge about related thiazoles, the isomeric counterparts of **1** seemed to be interesting. Aminothiazole derivatives **2** were obtained from a similarly versatile synthetic sequence. The common starting thiourea **3** was reacted with 3-bromo-1-*o*-tolyl-propane-1,2-dione[8] to access the *N*-Boc protected thiazole derivative **5** in 71% yield. Again, a

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Keywords: Conformational analysis; Neuropeptide Y5; Iterative parallel solution-phase chemistry; SAR; Thiazoles.

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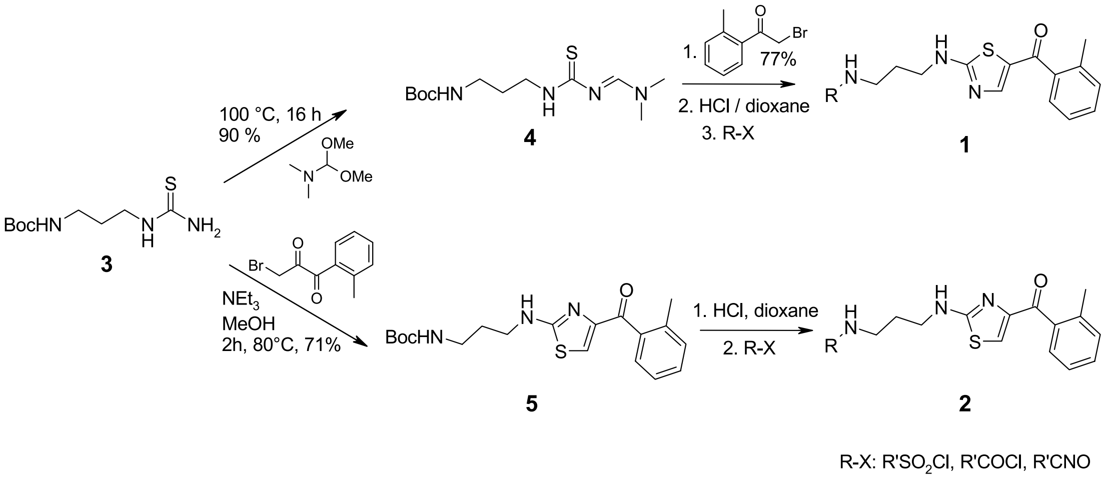
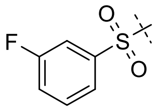
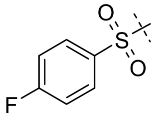
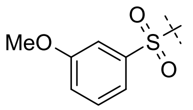
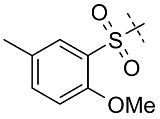
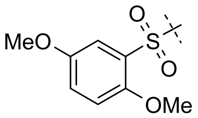
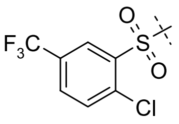
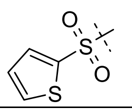


Scheme 1. Synthetic route towards isomeric thiazole derivatives **1** and **2**.

variation of the bromo propanedione led to the introduction of further diversity. Further manipulation through cleavage of the Boc group with HCl and subsequent reaction with electrophiles gave access to 35 amino thiazoles **2** in synthetically useful yields. A set of 11 sulfonamide thiazole derivatives **2** was synthesised and could be conveniently compared to their isomeric counterparts **1**.

All compounds synthesised were tested for their binding affinity at the mouse NPY5 receptor. Ureas and amide derivatives **1** and **2** were, in general, less potent than the sulfonamide derivatives **1** and **2**. In Table 1, the IC_{50} values and, respectively, the % inhibition data at 1 μM are shown for some pairs of isomeric sulfonamide derivatives **1** and **2**. With these sets of

Table 1. Inhibition data of selected sulfonamide derivatives **1** and **2** at the mNPY5 receptor

No	mNPY5 IC_{50} or inhibition at 1 μM	R	mNPY5 IC_{50} or inhibition at 1 μM	No
1a	5.5 nM		64 nM	**2a**
1b	9.9 nM		16%	**2b**
1c	11 nM		12%	**2c**
1d	0.71 nM		6 nM	**2d**
1e	1.6 nM		17 nM	**2e**
1f	0.85 nM		9 nM	**2f**
1g	1.0 nM		11 nM	**2g**

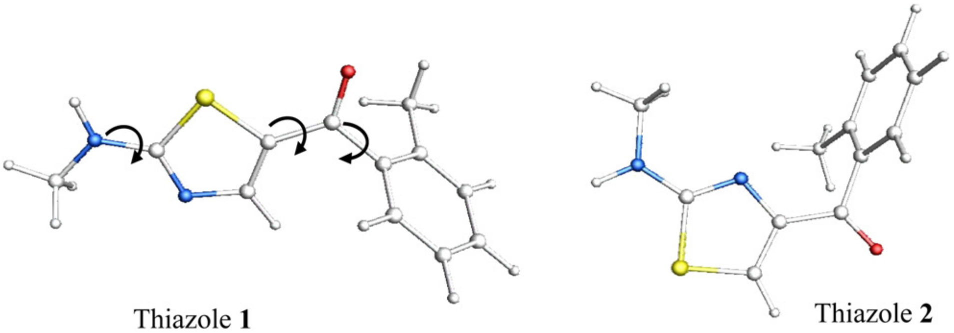


Figure 1. Conformations corresponding to the minimum energies for the thiazole isomers **1** and **2**. The arrows represent the torsional angles sampled in both isomers.

compounds the general SAR trend is nicely illustrated.

In general, thiazoles **1** show low nanomolar binding affinities for the mouse receptor. The nature of the substituents influenced the inhibition potential. Electron withdrawing and pushing (e.g., **1a–1c**) substituents show similar IC_{50} values and also the positioning of the substituents seemed to have a minor influence. The combination of two substituents led to thiazoles (e.g., **1d–1f**) with IC_{50} values in the picomolar range. In general, heteroaromatic substitution is allowed as well (e.g., **1g**). The isomeric counterparts **2** showed, in general, at least a 10-fold lower binding affinity, however, still producing compounds in the nanomolar range. The SAR trends for thiazoles **1** and **2** are very similar (e.g., **2a–2g**).

To understand the origin of the 10-fold shift of the binding affinity between thiazoles **1** and **2**, a conformational analysis was performed using MacroModel 8.6.[9] For this analysis, thiazole isomers have been reduced to their core scaffolds since the shift is consistent over the whole sulfonamide SAR (see Fig. 1). Three torsional angles have been sampled with 5000 steps of Monte Carlo search (MCMM), followed by 1000 steps of energy minimization (PRCG). The solvent effect has been modelled either with a dielectric constant (CDIE) of 4 or with a Generalized Born/Surface Area (GB/SA) water model. The results are similar in both models.

Figure 1 displays the energy minima for the thiazole isomers **1** and **2**. They both have in common a rotation of the phenyl ring with respect to the carbonyl function of ±58° induced by the methyl substituent, but the two structures differ in the torsional angle between the carbonyl function and the heterocycle. On the one hand, the more potent thiazole **1** series displayed a favourable interaction between the carbonyl oxygen and the sulfur stabilising an extended conformation. This type of $C{=}O\cdots S$ interaction, with a distance significantly below the sum of van der Waals radii (<3.3 Å), is highly favourable as explored both statistically and theoretically by Iwaoka et al.[10] This is further corroborated by more than 100 molecules with a similar atom arrangement, which can be found in the Cambridge Structural Database.[11] On the other hand, the thiazole **2** series favours a bent conformation due to the repulsive interaction between the thiazole nitrogen and the carbonyl oxygen. The potential energy difference between the bent minimum and the extended conformation of thiazole **2** is 10 kJ/mol with the CDIE model and 7 kJ/mol with the GB/SA model, which is in agreement with the 10-fold IC_{50} shift, corresponding to a free energy difference of 5.7 kJ/mol. Of course, the change in potential energies is only a fraction of the observed free energy difference, which also includes the interaction energy and entropy. Nevertheless, this comparison clearly shows that an extended conformation is preferred for the binding to the NPY5 receptor. The results of this analysis will be further pursued and integrated in the design of new NPY5 receptor ligands.

In conclusion, sets of isomeric thiazole derivatives **1** and **2** have been synthesised in a parallel iterative solution-phase synthesis approach guided by the SAR analysis derived from biological results and computer-aided design and analysis. This synergistic and streamlined working procedure led to highly active isomeric ligands for the NPY5 receptor. However, a 10-fold difference at least in their respective binding affinities was consistently found for all isomeric pairs **1** and **2**. The analysis of conformational differences due to heteroatom interactions in **1** and **2** revealed a favourable $C{=}O\cdots S$ interaction in **1**, whereas thiazoles **2** showed a repulsive $C{=}O\cdots N$ interaction. In the design of new NPY5 receptor ligands, this result will be incorporated in the quest towards new compounds with preferable biological and pharmacokinetic profiles. The variation of the bis-amino linker moiety needs to be further explored. This is currently under investigation in our laboratories and will be reported in due course.

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