Synthesis of new triazepine derivatives

PhD Thesis

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1. Introduction

2,3-Benzodiazepines are very important, biologically active compounds. The first representative was tofisopam, which was distributed with the name Grandaxin by Egis Pharmaceuticals in 1974. Tofisopam proved to be a good anxiolytic drug. It is a big advantage that tofisopam has no sedative, tranquilizer and nerve system dampening effects, besides this, no addiction is developed even by for a long-term usage. Research of the 2,3-benzodiazepines was continued, as a result of this, several derivatives of this compound family were pharmacologically tested. Among the synthesized derivatives, only nerisopam reached the clinical stage.\(^1\) The compound with number GYKI-52466 shows α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) antagonist activity, which feature could be useful to prevent the nervous system against damage caused by cerebral vascular occlusion.\(^2\) In this field, talampanel reached the clinical stage (Fig. 1.).\(^3\)

![Biologically active benzodiazepines](attachment:image)

Later, several fused tricyclic benzodiazepine derivatives were synthesized and examined. The imidazole-fused derivative GYKI-47261 showed antiparkinson effect beside the AMPA antagonist activity.\(^4\) Triazolone- (1), triazole- (2) and tetrazole-containing compounds (3) bear also improved anticonvulsant activities (Fig. 2.).\(^2,5\)

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The benzene ring and the five-membered heterocycles containing one heteroatom, e.g. thiophene, furane and pyrrole are bioisosteres to each other. Consequently, replacing the benzene ring with heterocycles and synthesizing new ring systems is an interesting and important field of medicinal chemistry.

During my PhD research our aim was the synthesis of three new pyrrolotriazepine derivatives condensed with an imidazole (5), a triazole (6), tetrazole (7), triazolone (8) and quinazolinone (9) ring, using the previously described and synthesized pyrrolotriazepinones (Fig. 3.).

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**Figure 2. Biologically active tricyclic benzodiazepine derivatives**

**Figure 3. Our first objective.**

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Our further objective was the synthesis of 1,4-diaryl-pyrrolotriazepines (10) (Fig. 4.), which can also be biologically active compounds.

![Diagram](image-url)

**Figure 4. Our second objective.**

Moreover, we also aimed at the synthesis of a new imidazoletriazepinone compound family (11) (Fig. 5.), which can be used for synthesis of new tricyclic ring systems with expected biological activities.

![Diagram](image-url)

**Figure 5. Our third objective.**

### 2. Experimental methods

The reaction mixtures were analysed by thin layer chromatography (TLC) and HPLC-MS. Purification of the crude products was carried out by flash chromatography (Isco CombiFlash Rf) and recrystallization. The products were identified and characterized by melting point, $^1$H and $^{13}$C NMR, high-resolution mass spectrometry or elemental analysis. The structures of the new compounds were confirmed by single crystal diffractometric measurements.
3. New scientific results

3.1. Forming an imidazole ring onto the pyrrolotriazepine core

Imidazo-pyrrolotriazepines 5 were synthesized by a two-step synthesis from starting materials 4 [1]. At the first step, the amide nitrogen atoms of 4 were alkylated with appropriate iodo-acetophenone derivatives in the presence of cesium carbonate base. The obtained dioxo compounds 12 were cyclized with ammonium acetate in boiling acetic acid (Scheme 6).

Scheme 6. Synthesis of imidazo-pyrrolotriazepines

3.2. Forming a triazole ring onto the pyrrolotriazepine core

Triazole derivatives 6 were also synthesized from 4 [1]. At first, an oxigen-sulfur exchange was carried out with Lawesson’s reagent in refluxing toluene, which procedure gave thio compounds 13. In the second step, thiones 13 were treated with various acyl hydrazides in boiling butanol to obtain the desired triazole derivatives (Scheme 7, Method A). Nevertheless, in a few cases the expected triazole compounds were not formed. In these cases we took a bypass: methylation of compounds 13 provided S-methyl derivatives 14, which could be transformed easily to the triazole derivatives in the presence of a catalitic amount of hydrochloric acid (Scheme 7, Method B).

Scheme 7. Synthesis of triazolo-pyrrolotriazepines
3.3. Synthesis of tetrazole and triazolone compounds

Tetrazole-bearing compounds 7 could be reached from thio derivatives 13 in a two-step synthesis [1]. At first, thiones 13 were treated with hydrazine hydrate in tetrahydrofurane, when hydrazones 15 were formed. Compounds 7 were prepared by treatment of 15 with sodium nitrite and hydrochloric acid (Scheme 8). Triazolone derivatives 8 were obtained from the reaction of hydrazone 15 and triphosgene (Scheme 8) [2].

![Scheme 8. Synthesis of tetrazole and triazolone compounds](image)

3.4. Synthesis of a quinazolinone-condensed new ring system

Seven members of a new tetracyclic ring system were prepared from S-methyl derivatives 14 and anthranilic acids under conditions of a modified Niemontowski-condensation [3] (Scheme 9). Single-crystal X-ray measurement was performed on one representative from this new compound family. The single crystal was growed from CDCl₃ (Scheme 10). On the perspective view, an interesting phenomenon could be observed: a molecule of CDCl₃ takes a typical hydrogen-bond position. The measured geometrical data (a) and calculated charge distribution (b) can be seen on Scheme 10. This type of hydrogen-bond is already known, but a rare phenomenon, therefore this experience is definitely worth mentioning.

![Scheme 9. Synthesis of quinazolinone-pyrrolotriazepines](image)

3.5. Synthesis of 1,4-diaryl-pyrrolotriazepines

Altogether 13 representatives of a new compound family, 1,4-diaryl-pyrrolotriazepines (10) were prepared by two diverse synthetic pathways [4]. At first, diketones (17) obtained from alkylating of 2-arylpurroles were treated with hydrazine hydrate to form the triazepine ring. Liebeskind-Srogl coupling reaction of thiones 13 and boronic acids also served triazepines 10 (Scheme 11.).

3.6. Synthesis of new imidazotriazepinone compound family

We planned to prepare the new series of triazepinones from imidazole in analogy to the previously described pyrrole-condensed derivatives, in four steps. At first, imidazole was acylated by appropriate acyl halides, then these compounds (18) were alkylated with ethyl bromoacetate. However, the reaction of ester 19 with hydrazine hydrate lead to formation of a non-desired product (21), reduction of formation of this compound could not be reached [5] (Scheme 12.).
Because of this finding, compounds 11 have been prepared in a different synthetic route. Alkaline hydrolysis of esters 19 gave carboxylic acids 22, which were coupled with tert-butyl carbazate using HATU coupling agent, and acid-catalized reaction of protected acyl hydrazides 23 afforded the desired products [5] (Scheme 13.).
4. Theses

I. I have synthesized novel imidazo[1,2-b]pyrrolo[1,2-e][1,2,5]triazepines from 3H-pyrrolo[2,1-d][1,2,5]triazepin-4(5H)-ones in two steps. 8 derivatives were prepared with this method [1].

II. I have prepared new 6-aryl-pyrrolo[1,2-e][1,2,4]triazolo[4,3-b][1,2,5]triazepines from 1-aryl-3H-pyrrolo[2,1-d][1,2,5]triazepin-4(5H)-ones. 24 derivatives were prepared [1].

III. I have synthesized new ring systems, 6-aryl-11H-pyrrolo[1,2-e]tetrazolo[1,5-b][1,2,5]triazepines and 6-aryl-2,11-dihydro-3H-pyrrolo[1,2-e][1,2,4]triazolo-[4,3-b][1,2,5]triazepin-3-ones from 1-aryl-3H-pyrrolo[2,1-d][1,2,5]triazepin-4(5H)-thiones. With these methods 7 and 6 representatives were prepared [1,2].

IV. I have synthesized 7 representatives of the new tetracyclic 14-aryl-[20,10:4,5][1,2,5]triazepino[7,1-b]quinazolin-11(5H)-ones by the reactions of anthranilic acids and 1-aryl-4-(methylsulfanyl)-5H-pyrrolo[2,1-d][1,2,5]triazepines [3].

V. I have prepared 13 representatives of the novel 1,4-diaryl-5H-pyrrolo[2,1-d][1,2,5]triazepines by two diverse strategies. Target compounds were reached either by cyclizing the corresponding diketones or by Liebeskind-Srogl cross-coupling reaction [4].

VI. I have elaborated a five-step total synthesis of the new 9-aryl-5H-imidazo[2,1-d][1,2,5]triazepin-6(7H)-ones from imidazole [5].
5. Application possibilities

During my PhD research seven new ring systems were synthesized and characterised. In these compounds the condensation of frequently biologically active rings may result in pharmacologically significant molecules, if it possess one or both constituent’s appropriate properties.

6. Publications

6.1. Full scientific publications related to the PhD Thesis


6.2. Other publications not related to the PhD Thesis


6.3. Oral presentations


