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GYÖRGY OLÁH DOCTORAL SCHOOL

Synthesis of spiro[cycloalkane-pyridazinones] with favorable Fsp^3 character

Summary of PhD thesis

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1. INTRODUCTION

I started my research work on pyridazinones as an MSc student at Cominnex Zrt. The company's profile includes the development of new molecular scaffolds which can be important in the search for a lead molecule in the creation of new compound libraries. In the course of my work here I was concerned with the preparation of a molecular library of spiropyridazinone derivatives with high Fsp^3 character. During my doctoral studies I worked on the expansion of the compound library.

Already in the early stages of drug development much attention is paid to the physicochemical properties and ADME/T (adsorption, desorption, metabolism, excretion, toxicity) parameters of the drug candidates. After the introduction of Lipinski's Rule of 5,[1,2] the importance of several properties which affect oral bioavailability has been pointed out. These are the polar surface of the compounds or the number of rotatable bonds.[3] The Fsp^3 character of the compounds determined by the saturation of the molecules may also contribute to successful drug development. The higher molecular saturation means a better chance to become a clinical candidate.[4,5] Another influencing factor is the number of aromatic and heteroaromatic rings in the compounds, which determine the 2- and 3-dimensional structure of the compounds, respectively.[6] Another possible route for the further expansion of the chemical space is the introduction of spirocyclic compounds. The spirocyclic backbone generally has a high Fsp^3 character and can serve as a bioisostere of peripheral fragments, allowing for improved physicochemical properties and access to structures with better pharmacokinetic properties.[7] Another possibility to improve the physicochemical properties of the compounds and to expand the chemical space is to replace the phenyl and pyridyl rings with bioisostere pyridazine. This provides an opportunity to prepare a number of diaza analog compounds that allow for new interactions, lower logP values, and the appearance of better crystal salts.

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[1] Lipinski, C.A.; Lombardo, F.; Dominy, B.W.; Feeney, P.J. *Adv. Drug Deliv. Rev.,* **1997**, *23*, 3-25.

[2] Lipinski, C.A. *Drug Discov. Today: Tech.,* **2004**, *1*(4), 337–341.

[3] Veber, D.F.; Johnson, S.R.; Cheng, H.Y.; Smith, B.R.; Ward, K.W.; Kopple, K.D. *J. Med. Chem*. **2002**, *45*, 2615-2623.

[4] Lovering, F.; Bikker, J.; Humblet, C. Escape from Flatland: *J. Med. Chem.* **2009**, *52*, 6752-6756.

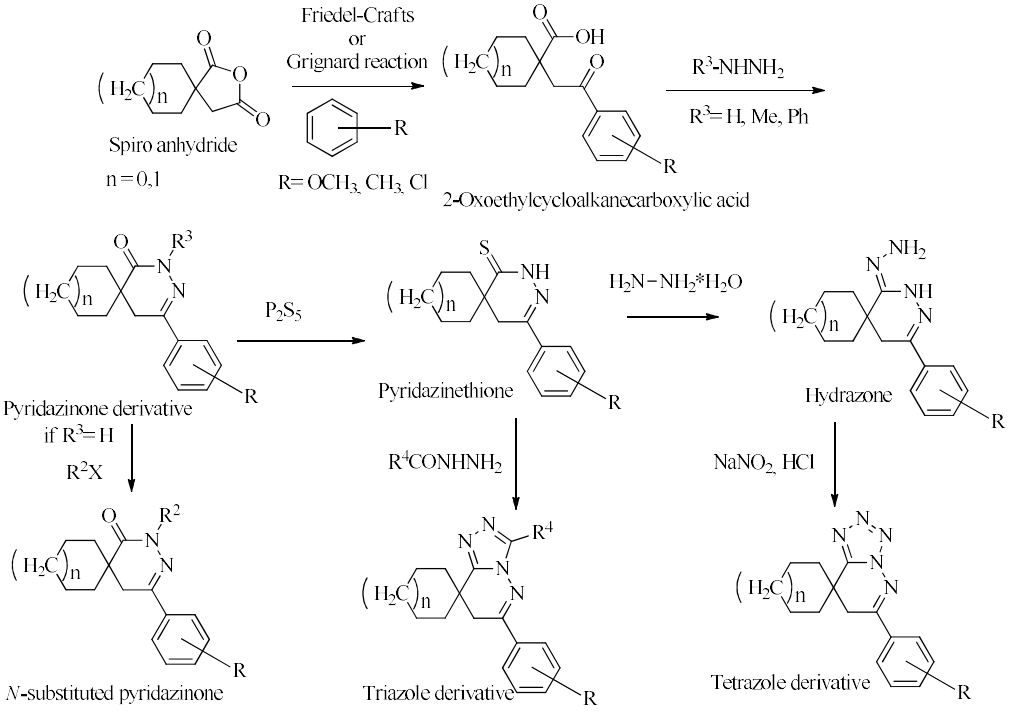
[5] Lovering, F. *Med. Chem. Commun*. **2013**, *4*, 515-519.

[6] Ritchie, T.J.; Macdonald, S.J.F. *Drug Discov. Today,* **2009**, *14*(21-22), 1011-1020.

[7] Zheng, Y.; Tice, C.M.; Singh, S.B. *Bioorg. Med. Chem. Lett.,* **2014**, *24*, 3673-3682.

Another advantage is that the replacement of the phenyl ring with pyridazine may result in a better water solubility of highly lipophilic molecules.[8] Over the past decades, many papers and patents were reported on bioactive pyridazines and pyridazinones affecting almost all therapeutic fields with various mechanisms of action.

Taking into consideration the above, our research has focused on the nowadays popular spiro compounds, in our case spiro[cycloalkane-pyridazinones] which have high Fsp^3 values and favorable physicochemical parameters. First we planned the preparation of the corresponding 2-oxoethylcycloalkanecarboxylic acid derivatives from the starting 2-oxaspiro[4.5]decane-1,3-dione or 2-oxaspiro[4.4]nonane-1,3-dione and the variously substituted benzene derivatives by Friedel-Crafts and Grignard reactions, respectively. We planned the cyclization reaction from the obtained 2-oxoethylcycloalkanecarboxylic acids with hydrazine and its derivatives (*N*-methyl and *N*-phenyl hydrazine) to obtaine the corresponding spiro[cycloalkane-pyridazinone]. Another possibility for the preparation of *N*-substituted pyridazinone derivatives is provided by *N*-alkylation/aralkylation reactions. Furthermore, our plans included the conversion of the pyridazinones into pyridazinethiones, which opens the way for the formation of new ring systems (tetrazole, triazole) (***Figure 1.***).



1. Figure. The planned synthetic route for the preparation of spiro[cycloalkane-pyridazinones]

8 Wermuth, C.G. *Med. Chem.Comm*., **2011**, *2*, 935-941.

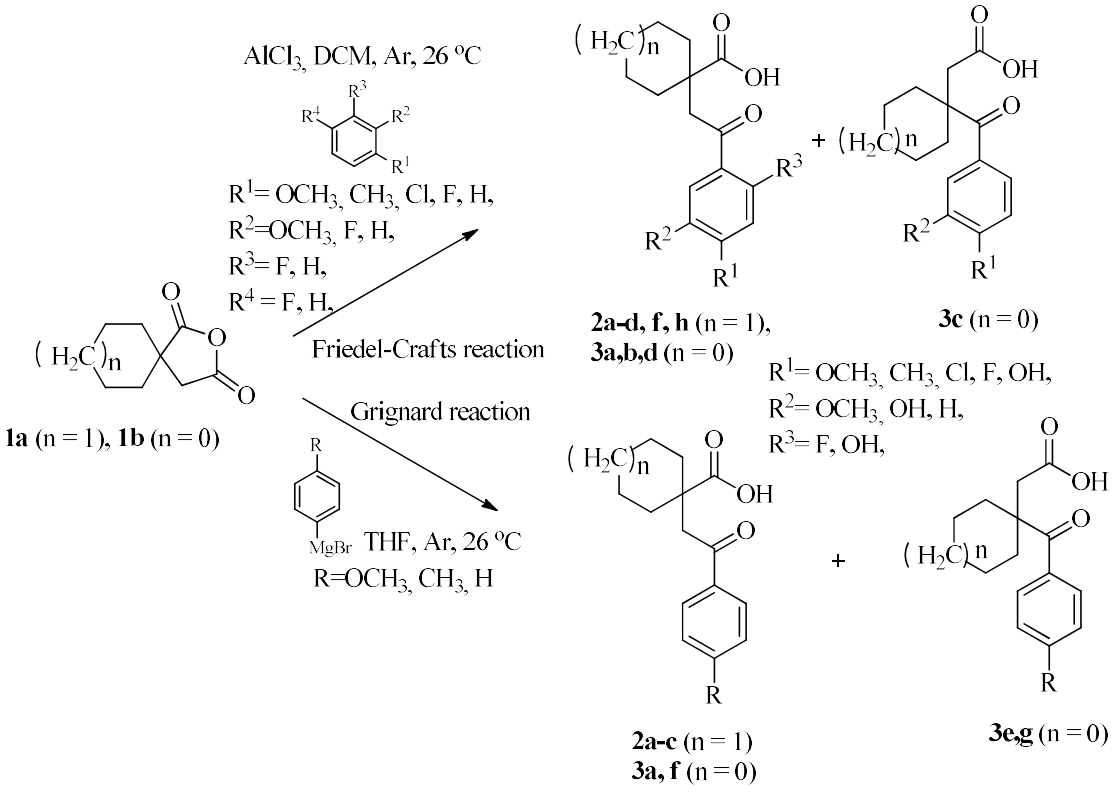
2. EXPERIMENTAL METHODS

The reactions were monitored by thin layer chromatography. Column chromatography and preparative thin layer chromatography were used to purify the crude products and reaction mixtures. The new compounds were characterized by IR spectra, ^{1}H- and ^{13}C-NMR spectra and high-resolution mass spectrometry measurements.

3. RESULTS

3.1. Preparation of 2-oxoethylcycloalkanecarboxylic acids by Friedel-Crafts and Grignard reactions

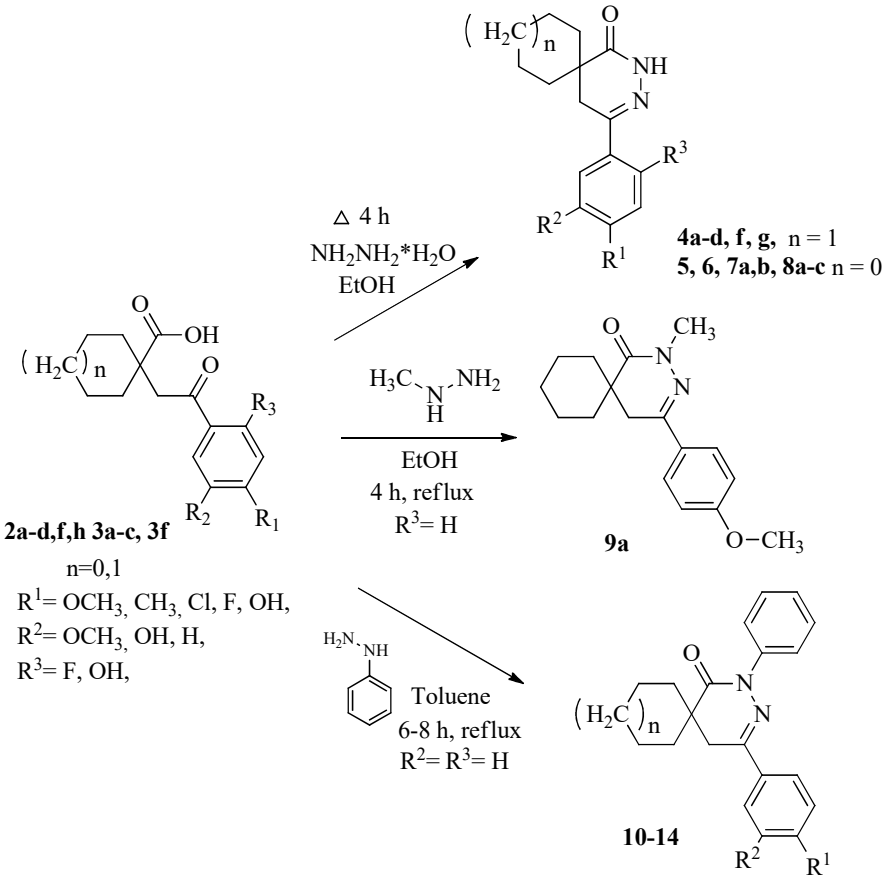
The synthesis of the 2-oxoethylcycloalkanecarboxylic acids was performed in two ways by Friedel-Crafts and Grignard reactions, in which the starting 2-oxaspiro[4.5]decane-1,3-dione (**1a**) and 2-oxaspiro[4.4]nonane-1,3-dione (**1b**) was reacted with variously substituted benzene derivatives. 11 new 2-oxoethylcycloalkanecarboxylic acids (**2a–d, 3a–g**) with Fsp^3 values ranging from 0.47 to 0.53 were prepared. In case of the fluorinated derivatives (**2f, h**), the crude product was carried on to the next step without isolation and purification. (***Figure 2.***).



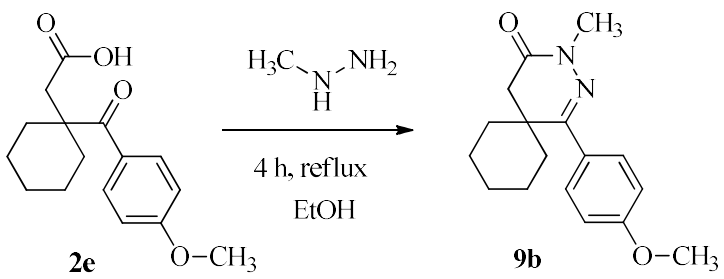
2. Figure. Preparation of 2-oxoethylcycloalkanecarboxylic acids (2a-d,f,h and 3a-g) by Friedel-Crafts and Grignard reactions

3.2. Preparation of pyridazinone derivatives

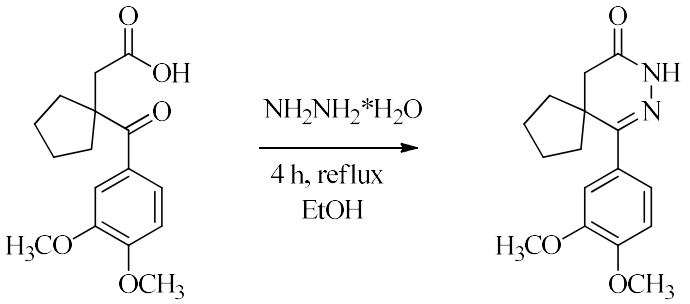
Starting from the prepared 2-oxoethylcycloalkanecarboxylic acids (**2a–d, f, h, 3a–c, f**) the corresponding pyridazinones (**4a–g, 5, 6, 7a–c, 8a–c**) were formed with reaction with hydrazine. 14 new pyridazinone derivatives with high Fsp^3 values and favorable physicochemical parameters were prepared. *N*-substituted pyridazinone derivatives were formed with methyl- and phenyl hydrazine, respectively, to give seven new *N*-substituted pyridazinones (**9a, 9b, 10–14**) (***Figure 3.***). In two cases pyridazinone with an isomeric structure (**9b** and **7c**) was also isolated (***Figure 4., Figure 5.***).



3. Figure. Preparation of pyridazinone (4a-d,f,g, 5, 6, 7,a,b, 8a-c, 9a, and 10-14) derivatives



4. Figure. Preparation of N-methyl pyridazinone (9b) derivative with isomeric structure

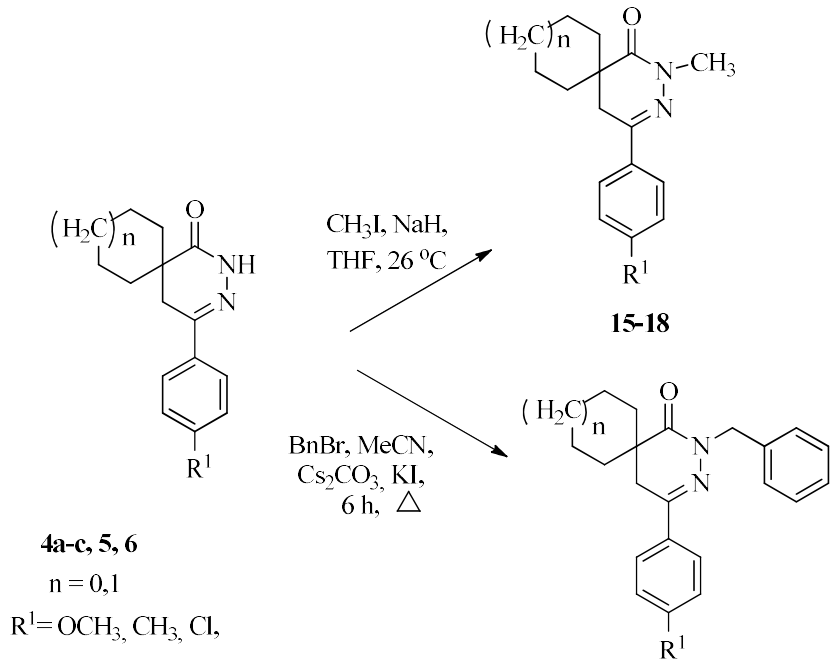


3c **7c**

5. Figure. Preparation of spiro[cyclopentane-pyridazinone] (7c) derivative with isomeric structure

3.3. *N*-alkylation/aralkylation reactions

Starting from the previously isolated pyridazinones (**4a–c, 5, 6**), alkylation with methyl iodide in tetrahydrofuran in the presence of sodium hydride resulted in the *N*-methylated derivatives in medium yields (49–64%) (**15–18**). The *N*-benzylated derivatives were prepared in the presence of cesium carbonate in acetonitrile. In this way, after purification, the desired *N*-benzylated pyridazinones (**19–23**) were isolated in medium yields (42–56%) (***Figure 6.***).



4a-c, 5, 6
n = 0,1
R^1= OCH_3, CH_3, Cl,

15-18

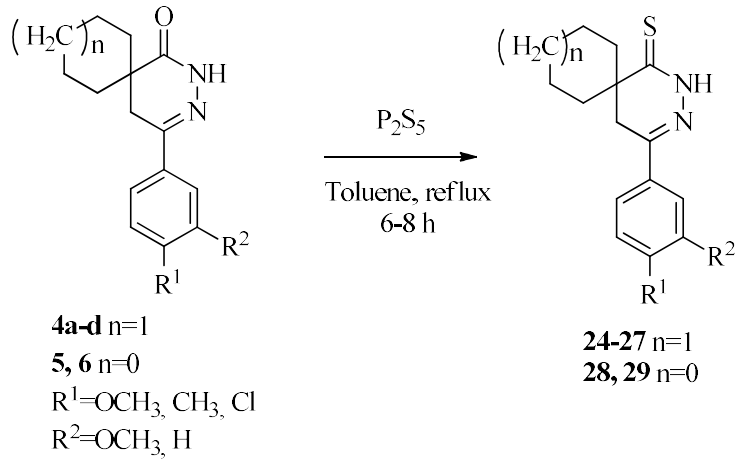
19-23

6. Figure. Preparation of N-methyl- (15-18) and N-benzylpyridazinones (19-23)

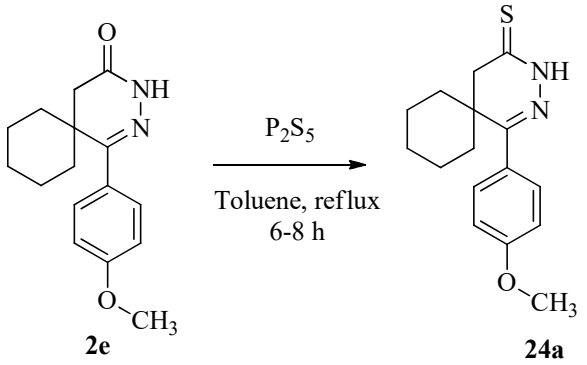
3.4. Preparation of thioxo derivatives

Thioxo derivatives are essential intermediates for the formation of further new ring systems. Previously prepared spiro[cycloalkane]pyridazinones (**4a-d, 5** and **6**) were reacted

with phosphorus pentasulfide in refluxing toluene. According to TLC, the starting material was consumed after 6-8 hours. After the workup and preparative TLC purification, the products (**24-27**, **28** and **29**) were isolated in yields of 40-89%. The new compounds (**24-27, 28** and **29**) were characterized by ^{1}H and ^{13}C NMR, as well as HRMS. During the preparation of the *p*-methoxyphenyl[spirocyclohexane]pyridazinone (**2a**), the isomeric pyridazinone derivative (**2e**) was isolated as a by-product. The thionation reaction with phosphorus pentasulfide led to the corresponding pyridazinethione (**24a**) in a yield of 14% (***Figure 7., Figure 8.***).



7. Figure. Preparation of the thioxo derivatives (24-29)

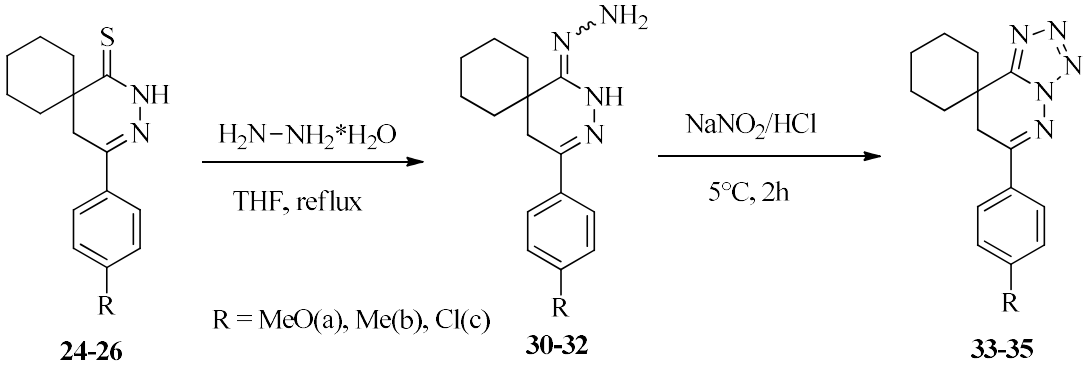


8. Figure. Preparation of the 1-(4-methoxyphenyl)-2,3-diazaspiro[5.5]undec-1-ene-4-thione (24a)

3.5. Preparation of hydrazone derivatives, formation of the tetrazole ring

We have planned the development of new ring systems to expand the compound library with hopefully biologically active and patentable new scaffolds. Reacting the thioxo derivatives (**24–26)** with hydrazine hydrate, the corresponding hydrazones (**30–32**) were isolated in 48–61% yields. The 4-(phenyl)-2,3-diazaspiro[5.5]undec-3-ene-1-thiones (**24–26**) and hydrazine hydrate in THF had to be stirred at reflux for 5 h. Intermediates **30–32** were reacted further in a diazotization reaction. The tetrazolo-pyridazinones (**33–35**) were obtained in 45–77% yields

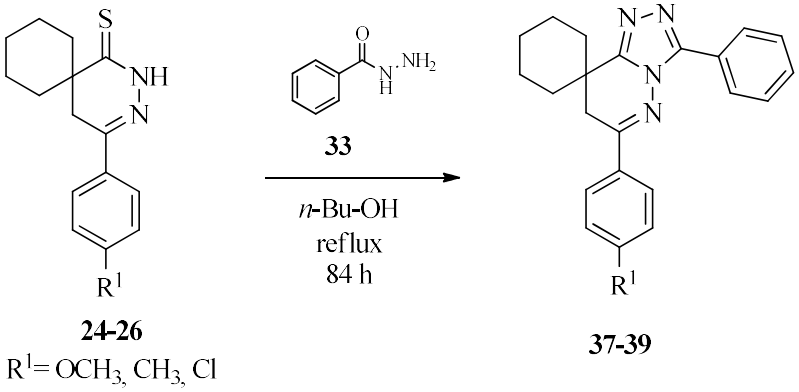
(***Figure 9.***) after a preparative TLC purification. Compounds **30**–**32** and **33**–**35** were new and were characterized by ^{1}H and ^{13}C NMR, as well as HRMS.



9. Figure. Formation of the tetrazole ring (33-35)

3.6. Formation of a triazole ring from thioxo pyridazinone derivatives

The thioxo compounds (**24**–**26**) were refluxed with benzoic acid hydrazide (**33**) in *n*-butanol. After evaporation and chromatographic purification, the triazole-pyridazinone derivatives (**37**–**39**) were isolated in yields of 14–42% (***Figure 10.)***. The introduction of an additional aromatic ring increased the logP and clogP values and decreased the Fsp^3 character.



10. Figure. Formation of a triazole ring (37-39)

4. THESES

1. Studying the Friedel-Crafts reaction of 2-oxaspiro[4.5]decane-1,3-dione or 2-oxaspiro[4.4]nonane-1,3-dione with anisole and veratrole I prepared five 2-oxoethylcycloalkanecarboxylic acids with high Fsp^3 character which are not known in the literature; they are important intermediates in the synthesis of spiro[cycloalkane-pyridazinone] derivatives. [**SFC-1, IF: 1,169, Author's share: 90%, SFC-3, IF: -, Author's share: 100%, SFC-4, IF: -, Author's share: 100%, SFC-6, IF: -, Author's share: 90%**]
2. Starting from 2-oxaspiro[4.5]decane-1,3-dione or 2-oxaspiro[4.4]nonane-1,3-dione and *p*-tolylmagnesium bromide or (4-chlorophenyl)magnesium bromide by Grignard reaction, I also prepared six 2-oxoethylcycloalkanecarboxylic acids with high Fsp^3 character which are also important intermediates in the synthesis of spiro[cycloalkane-pyridazinone] derivatives. [**SFC-2, IF: 0.779, Author's share: 90%, SFC-3, IF: -, Author's share: 100%, SFC-4, IF: -, Author's share: 100%, SFC-6, IF: -, Author's share: 90%**]
3. Reaction of the prepared 2-oxoethylcycloalkanecarboxylic acids with hydrazine derivatives (hydrazine, methylhydrazine, phenyl hydrazine) gave 21 new spiro[cycloalkane-pyridazinones] which have favorable physical-chemical parameters due to their high Fsp^3 values. They can be good starting points for drug research projects. [**SFC-1, IF: 1.169, Author's share: 90%; SFC-2, IF: 0.779, Author's share: 90%, SFC-3, IF: -, Author's share: 100%, SFC-4, IF: -, Author's share: 100%, SFC-6, IF: -, Author's share: 90%**]
4. To expand the compound library, additional *N*-methyl- and *N*-benzyl-spiro[cycloalkane-pyridazinone] derivatives were obtained from the earlier prepared spiro[cycloalkane-pyridazinones] by the *N*-alkylation and *N*-aralkylation reactions. The *N*-methyl derivatives further increased, while the introduction of phenyl and benzyl groups decreased the Fsp^3 character of the compounds. I added nine new compounds to the compound library. [**SFC-1, IF: 1.169, Author's share: 90%; SFC-2, IF: 0.779, Author's share: 90%, SFC-3, IF: -, Author's share: 100%, SFC-4, IF: -, Author's share: 100%, SFC-6, IF: -, Author's share: 90%**]
5. By reacting spiro[cycloalkane pyridazinones] with phosphorus pentasulfide, I prepared seven new pyridazinethiones, also with favorable Fsp^3 values, from which I formed three new hydrazone derivatives. I also prepared two additional ring systems containing new triazole and tetrazole rings (6 new compounds). [**SFC-5, IF: 3,267, Author's share: 90%;**]

5. POSSIBLE APPLICATIONS

During my doctoral work I created a small molecular library with 57 new compounds with high Fsp^3 character which, due to their favorable physicochemical parameters can be good starting points for drug research projects.

6. PUBLICATION

6.1. Publications related to the PhD thesis:

- [**SFC-1**] **Sepsey Für, Cs**.; Riszter, G.; Gerencsér, J.; Szigetvári, A., Dékány, M., Hazai, L.; Keglevich, G.; Bölcskei, H. Synthesis of Cycloalkyl Pyridazinones with High Fsp^3 Character – *Lett. in Drug Design and Discov.*, **2020**, *17*(6), 731-744. https://doi.org/10.2174/1570180816666190710130119 [**IF: 1,169, Author's share: 90%**]
- [**SFC-2**] **Sepsey Für, Cs**.; Horvát, E.J.; Szigetvári, A.; Dékány, M.; Hazai, L.; Keglevich, G.; Bölcskei, H. Synthesis of Cycloalkyl Pyridazinones with High Fsp^3 Character Part 2. *Lett. in Org. Chem.,* **2021**, *18*(5), 373-381. DOI: 10.2174/1570178617999200728214211 [**IF: 0,779, Author's share: 90%**]
- [**SFC-3**] **Sepsey Für, Cs.;** Bölcskei, H.; - Kedvező Fsp^3 karakterrel rendelkező spiro-cikloalkán-piridazinon-származékok szintézise, *Magyar Kémiai Folyóirat, Kémiai Közlemények*, **2020**, *126*(2), 47–53. DOI: 10.24100/MKF.2020.02.47 [**IF: -, Author's share: 100%**]
- [**SFC-4**] **Sepsey Für, Cs.;** Bölcskei, H. New Spiro[cycloalkane-pyridazinone] Derivatives with Favorable Fsp^3 Character. *Chemistry,* **2020**, *2*(4), 837–848; DOI: 10.3390/chemistry2040055 [**IF: -, Author's share: 100%**]
- [**SFC-5**] **Sepsey Für, Cs.;** Riszter, G.; Szigetvári, A.; Dékány, M.; Keglevich, Gy.; Hazai, L.; Bölcskei, H. Novel ring systems: Spiro[cycloalkane] derivatives of Triazolo- and Tetrazolo-pyridazines. *Molecules*, **2021**, *26*(8), 2140-2151. https://doi.org/10.3390/molecules26082140 [**IF: 3,267, Author's share: 90%**]
- **[SFC-6] Sepsey Für, Cs**.; Herczeg, B.; Gerencsér, J.; Makara, G.; Szigetvári, A.; Dékány, M.; Hazai, L.; Keglevich, Gy.; Bölcskei, H. Cikloalkil piridazinonok szintézise, *KEN kiadvány*, **2017**, 209-213. ISBN: 978-963-3970-830 [**IF: -, Author's share: 90%**]

6.2. Other publications:

- Sepsey Für, Cs.; Keglevich, P.; Bölcskei, H.; Ilkei V.; Hazai, L. Eredmények a természetes szerves anyagok kutatásában - Új *Vinca* alkaloid származékok előállítása és flavon alkaloidok szintézise. *Magyar Kémiai Folyóirat, Kémiai Közlemények*, **2018**, *124(*1-2*)*, 71-77. https://doi.org/10.24100/MKF.2018.01.71 [**IF: -, Author's share: 50%**]
- Mayer, Sz.; Keglevich, A.; Sepsey Für, Cs.; Bölcskei, H., Ilkei, V.; Keglevich, P.; Hazai, L. Results in Chemistry of Natural Organic Compounds. Synthesis of New Anticancer Vinca Alkaloids and Flavone Alkaloids. *Chemistry*, **2020**, *2*(3), 714-726; DOI: 10.3390/chemistry2030046 [**IF: -, Author's share: 16%**]

6.3. Presentations related to the topics of the PhD thesis:

- **Sepsey Für Csilla,** Bölcskei Hedvig, Makara Gergely, Gerencsér János, Keglevich György: Spiro-piridazinon-származékok szintézise – Fiatal Kutatók Fóruma – Budapest, BME, 2014. november 28.
- Bölcskei Hedvig, **Sepsey Für Csilla**, Herczeg Barbara, Makara Gergely, Gerencsér János, Keglevich György: Spiro-piridazinon-származékok szintézise – MTA Heterociklusos és Elemorganikus Kémiai Munkabizottság, Balatonszemes, 2015. május 27-29.
- **Sepsey Für Csilla,** Riszter Gergő, Szigetvári Áron, Dékány Miklós, Herczeg Barbara, Gerencsér János, Makara Gergely, Keglevich György, Hazai László, Bölcskei Hedvig: Cikloalkil- és piperidil piridazinon-származékok szintézise – MTA Alkaloid- és Flavonoid Kémiai Munkabizottság, Mátrafüred 2017. április 6-7.
- **Sepsey Für Csilla,** Herczeg Barbara, Gerencsér János, Makara Gergely, Szigetvári Áron, Dékány Miklós, Hazai László, Keglevich György, Bölcskei Hedvig: Cikloalkil piridazinonok szintézise – XL. Kémiai Előadói Napok, Szeged, 2017. október 16-18.
- **Sepsey Für Csilla,** Szigetvári Áron, Dékány Miklós, Herczeg Barbara, Gerencsér János, Makara Gergely, Hazai László, Keglevich György, Bölcskei Hedvig: Spiro[cikloalkil-piridazinonok] szintézise – XXIV. Nemzetközi Vegyészkonferencia, Szovátafürdő, 2018. október 24-27.
- **Sepsey Für Csilla**, Riszter Gergő, Szigetvári Áron, Dékány Miklós, Gerencsér János, Hazai László, Keglevich György, Bölcskei Hedvig - Magas Fsp^3 karakterű

piridazinonok szintézise – Oláh György Doktori Iskola XVI. Konferencia – 2019. január 31.

- **Sepsey Für Csilla,** Riszter Gergő, Szigetvári Áron, Dékány Miklós, Hazai László, Keglevich György, Bölcskei Hedvig: Spiro[cikloalkán-piridazinonok] és piridazintion-származékok előállítása - MTA Alkaloid- és Flavonoid Kémiai Munkabizottság, Mátrafüred 2019. április 11-12.