Short thesis for the degree of doctor of philosophy (PhD)

Preparation and stereochemical analysis of chiral isochroman and acridan derivatives

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Doctoral School of Chemistry

Debrecen, 2023.

1. Introduction and objectives

O-heterocycles can be found in the skeletal structure of several pharmacologically significant families of natural compounds, such as flavonoids, isoflavanoids, alkaloids, antibiotics, and have fundamental roles in *in vivo* biochemical processes.

Benzene-fused *O*-heterocycles include 3,4-dihydro-1*H*-2-benzopyran, also known as the isochroman skeleton, which contain a 3,6-dihydro-2*H*-pyran heterocycle. Many of the natural and synthetic substituted isochroman derivatives exhibit antimicrobial, antitumor, antioxidant, antihypertensive and anti-inflammatory activity. They may also affect the central nervous system.

One of the goals of my doctoral work was to prepare optically active 1,3-disubstituted isochroman derivatives (**1**) for pharmacological and stereochemical studies. To achieve this objective, we intended to use ring closure reactions in accordance with the retrosynthetic scheme shown in Figure 1.

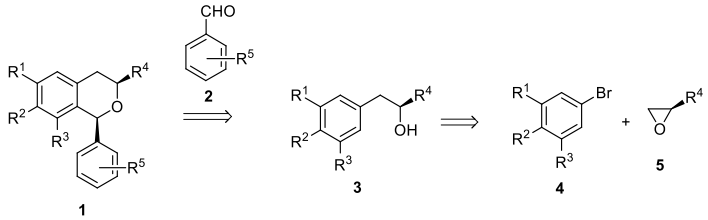


Figure 1. Retrosynthetic scheme of the synthesis of optically active, 1,3-substituted isochroman derivatives.

The preparation of 1,3-substituted isochromans (**1**) from 1-aryl-propan-2-ol derivatives (**3**) with different substitution patterns can be realized with aromatic aldehydes (**2**) in an acid-catalyzed oxa-Pictet-Spengler reaction. In this case, a water molecule is elimnated and intramolecular aromatic isochromic skeleton is formed by electrophilic substitution. Different optically active 1-aryl-propan-2-ol derivatives (**3**) required for the ring closure reaction that can be prepared from aryl halides (**4**) and optically active epoxide derivatives (**5**). The reaction proceeds via the regioselective ring opening of the epoxide.

We intended to perform the stereoselective synthesis of an optically active isochromane-2*H*-chromene hybrid molecule (**10**) via the coupling reaction of optically active 1-aryl-propan-2-ol and 2*H*-chromene derivatives. In addition, we wished to explore the stereochemistry and neuroprotective effect of the product (Figure 2) in designated experiments.

Assuming that the neuroprotective effect can be proved, we also planned to develop a synthesis route (**6→7→8→9**) that would make possible to synthesize the target compound at a gram-scale level for *in vivo* studies.

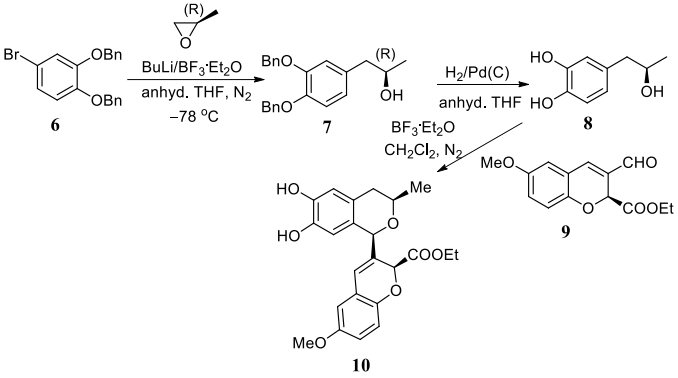


Figure 2. Preparation of the **10** isochromane-2*H*-chromene hybrid molecules.

We also aimed to synthesize additional structural analogs of hybrid molecule **10** from bromobenzene derivatives featuring different substituents (**4**) and optically active epoxides (**11a,b**). Our further goal was the synthesis and stereochemical analysis of 1-arylisochromane (**14**) derivatives (Figure 3), which contain naphthyl and aryl chromophores at the C-1 position.

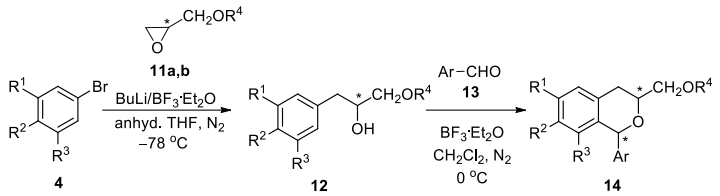


Figure 3. Route of the preparation of 1,3-disubstituted isochroman derivatives and 1-aryl isochromans (**14**) analogous to isochroman derivative **10**.

In the second part of my doctoral work, an *N*-aryl-1,5-benzoxazepine derivative (**22**) was prepared to explore the possibility of producing substituted acridane (**24**) or condensed 1,5-benzoxazepine (**23**) derivatives by utilizing the domino Knoevenagel ring-closure reaction (Figure 4).

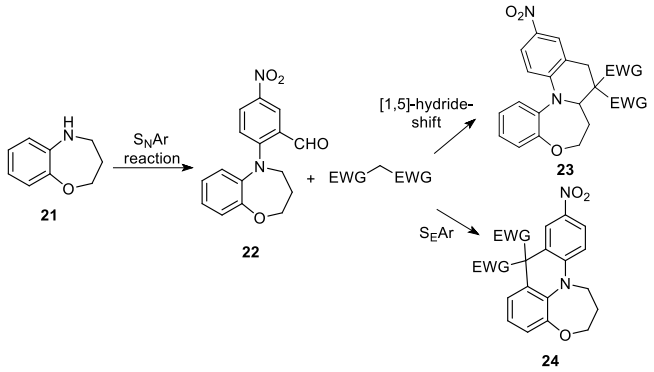


Figure 4. The preparation of *N*-aryl-1,5-benzoxazepine derivatives (**22**) and its domino ring closure reactions with active methylene reagents.

2. Applied methods

Thin-layer chromatography was used for monitoring the reactions and testing the purity of the products. The crude products were purified by column chromatography, crystallization or preparative thick layer chromatography. The melting point of the produced solid crystalline derivatives was determined. The planar structure and

stereochemistry of the final products were verified by 1D- and 2D-NMR, IR HRMS, specific rotation, ECD and single-crystal X-ray diffraction methods.

3. New scientific results

3.1. An optically active isochromane-2H-chromene hybrid target compound (142) containing the 6,7-dihydroxyisochromane skeleton, which is the building block of natural materials, and a 2H-chromene unit were prepared for neuroprotective effect studies from the benzyl-protected optically active aryl-propan-2-ol compound.

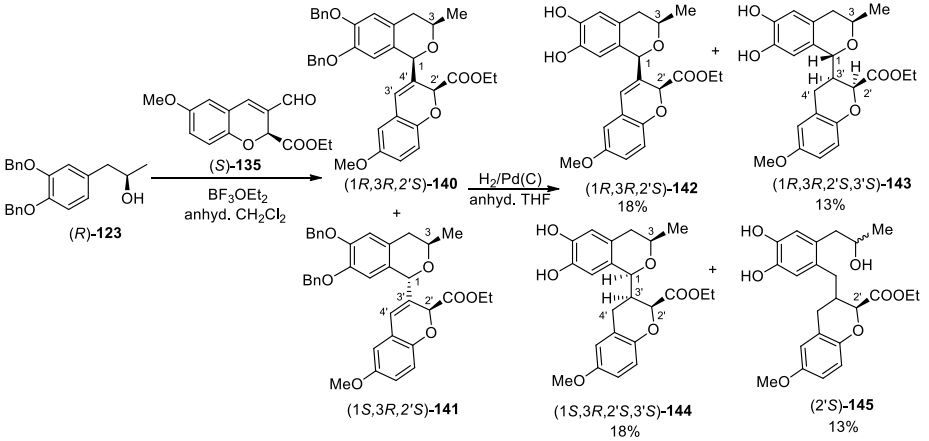


Figure 5. Preparation of derivative (1*R*,3*R*,2'*S*)-**142**.

The 3-formyl-2*H*-chromene derivative (*S*)-**135** was prepared on the basis of literature data and reacted with the protected optically active aryl-propan-2-ol compound (*R*)-**123** in a Lewis acid catalyzed oxa-Pictet-Spengler reaction (Figure 5). The diastereomeric products *trans*-(1*S*,3*R*,2'*S*)-**141** and *cis*-(1*R*,3*R*,2'*S*)-**140** formed in a ratio of 1:5. The isomers could not be separated by column chromatography. The removal of the benzyl groups was thus carried out with the diastereomeric mixture by catalytic hydrogenation, and the formation of four products (**142-145**) was observed (Figure 5). Our target

compound was the (1*R*,3*R*,2'*S*)-**142** derivative, in which the C-1 and C-3 substituents of the isochromic unit have a *cis* relative configuration and the absolute configuration was found to be (1*R*,3*R*,2'*S*). We also isolated three additional derivatives as side products, which were also tested in neuroprotective effect studies. In the case of compounds **143** and **144**, the reduction of the $\Delta^{3',4'}$ double bond in the chromene ring was also achieved in addition to the removal of the benzyl protecting groups. In the case of compound (2'*S*)-**145**, the opening of the isochroman ring also took place at the reactive, benzyl or allyl C-1 position of the isochroman unit (Figure 5).

3.2. In order to test the neuroprotective derivative 142 in vivo, we developed a gram-scale synthesis, in which the ring closure was performed from an optically active alcohol derivative containing free phenolic hydroxyl groups.

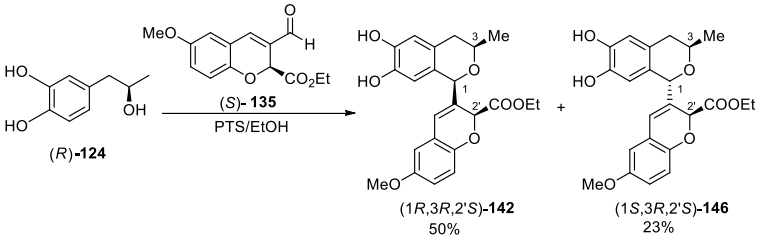


Figure 6. Stereoselective synthesis of (1*R*,3*R*,2'*S*)-**142** hybrid molecule.

Initial studies revealed such a promising neuroprotective activity for compound **142** that was worthwhile to test in further *in vivo* animal experiments. Our collaborating research group at the Shanghai Institute of Materia Medica required 2.0 g sample for such purpose. The original synthetic route would not have been suitable for providing compound **142** in gram quantities, because non-separable diastereomeric products formed during the ring closure, and the removal of the benzyl protecting group also resulted in three by-products.

Therefore, the benzyl protecting groups of the starting alcohol were removed before the ring closure reaction, and the oxa-Pictet-Spengler ring closure reaction was performed with derivative (*R*)-**124** containing free hydroxyl groups. In the oxa-Pictet-Spengler ring

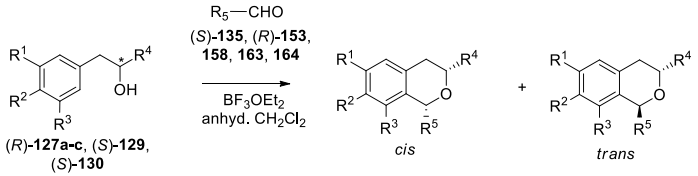
closure reaction, using *p*-toluenesulfonic acid (PTS) acid catalysis, the target compound (1*R*,3*R*,2'*S*)-**142** was obtained as the main product, which was efficiently separated from the diastereomer by-product by column chromatography (Figure 6).

3.3. The in vitro neuroprotective effect of the (1R,3R,2'S)-142 derivative against H_2O_2-induced neurotoxicity was identified in human SH-SY5Y neurons and rat primary cortical neurons. Based on the corresponding pharmacological study, we have concluded that this molecule exerts its neuroprotective activity by a dual mechanism.

Pretreatment with the isochroman derivative (1*R*,3*R*,2'*S*)-**142** resulted in neuroprotective activity against H_2O_2-induced toxicity in human SH-SY5Y cells and rat primary cortical neurons. Upon treatment with H_2O_2, the survival rate of human SH-SY5Y neurons showed clear dependence on the concentration of (1*R*,3*R*,2'*S*)-**142** . At 10 μM concentration, it provided better survival in human SH-SY5Y neurons than *N*-acetylcysteine (positive control) applied at 100 μM concentration. We confirmed that (1*R*,3*R*,2'*S*)-**142** exerts its neuroprotective effect, activates cell survival, and inhibits apoptotic changes through a double regulatory mechanism. MAPK signaling, especially ERK and P38, has a potential role in the neuroprotective effect against oxidative stress-induced cell damage, while blocking the PI3K/Akt signaling pathway with the known PI3K inhibitor LY294002 flavone derivative, (1*R*,3*R*,2'*S*)-**142**, this effect is significantly reduced.

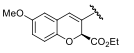
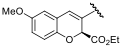
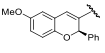
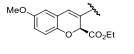
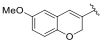
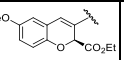
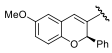
3.4. Structural analogues of the lead molecule, (1R,3R,2'S)-142, were prepared. They contain phenyl or hydrogen instead of the C-2' ethoxycarbonyl group, do not contain the condensed benzene ring of the 2H-chromene unit, or carry a new chirality center in the 2H-chromene after reduction of the $\Delta^{3',4'}$ double bond. We modified the C-3 substituent on the isochroman unit and the substitution pattern of the benzene ring of the isochroman skeleton.

To investigate the structure – effect relationships, analogs of the lead molecule, (1*R*,3*R*,2'*S*)-**142**, were prepared with different substitution patterns.



	R^1	R^2	R^3	R^4
(*R*)-**127a**	OMe	OMe	H	CH_2OMe
(*R*)-**127b**	OMe	H	OMe	CH_2OMe
(*R*)-**127c**	OMe	OMe	OMe	CH_2OMe
(*S*)-**129**	OMe	OMe	H	CH_2OBn
(*S*)-**130**	OMe	OMe	H	CH_2OH

Figure 7. Preparation of analogues of the hybrid molecule, (1*R*,3*R*,2'*S*)-**142**.

No	Alcohol	Aldehyde	R^5	*cis*-product (yield)	*trans*-product (yield)
1	(*R*)-**127a**	(*S*)-**135**		(1*S*,3*R*,2'*S*)-**148** (61%)	(1*R*,3*R*,2'*S*)-**149** (17%)
2	(*R*)-**127b**	(*S*)-**135**		(1*R*,3*R*,2'*S*)-**155** (14%)	(1*S*,3*R*,2'*S*)-**154** (64%)
3	(*R*)-**127b**	(*R*)-**153**		(1*R*,3*R*,2'*R*)-**157**	(1*S*,3*R*,2'*R*)-**156** (sum 85%)
4	(*R*)-**127b**	**158**		(1*S*,3*R*)-**160** (13%)	(1*R*,3*R*)-**159** (68%)
5	(*R*)-**127c**	(*S*)-**135**		(1*R*,3*R*,2'*S*)-**166** (16%)	(1*S*,3*R*,2'*S*)-**165** (54%)
6	(*R*)-**127c**	**163**		(1*R*,3*R*)-**167** (70%)	–
7	(*R*)-**127c**	**164**		(1*R*,3*R*)-1**68** (80%)	–
8	(*R*)-**127c**	**158**		(1*S*,3*R*)-**169** (87%)	–
9	(*S*)-**129**	(*S*)-**135**		(1*R*,3*S*,2'*S*)-**170** (84%)	–
10	(*S*)-**129**	(*R*)-**153**		(1*R*,3*S*,2'*R*)-**171** (75%)	–
11	(*S*)-**130**	**164**		(1*R*,3*S*)-**176** (63%)	(1*R*,3*S*)-**175** (29%)

The starting materials, i.e., the secondary alcohols [(*R*)-**127a-c**, (*S*)-**129**, (*S*)-**130**], for the oxa-Pictet-Spengler ring-closing reactions were obtained by regioselective ring-opening of commercially available, optically active epoxides. In these reactions, aryllithium nucleophiles were used, which were obtained in the Lewis acid activated reactions of aryl bromide derivatives with butyllithium. The substitution pattern of the secondary alcohols was varied by changing the substituents of the aryl bromide and the optically active propylene oxide derivatives.

The ring closure of the optically active secondary alcohols [(*R*)-**127a-c**, (*S*)-**129** and (*S*)-**130**] was achived with various aldehydes [(*S*)-**135**, (*R*)-**153**, **158**, **163**, **164**] in Lewis acid catalyzed oxa-Pictet-Spengler reaction (Figure 7). The diastereoselectivity of the products depends on the structure of the optically active alcohol and the aldehyde.

We reduced the C-3' and C-4' double bonds in the 2*H*-chromene unit of derivative *cis*-(1*S*,3*R*,2'*S*)-**148,** and the removed the benzyl protecting group of derivatives (1*R*,3*S*,2'*R*)-**170** and (1*R*,3*S*,2*R*)-**171** by catalytic hydrogenation. In each case, the relative configuration of the final products was determined based on their characteristic NOE cross-peaks. In all cases, ECD measurements were also performed for distinguishing the resulting epimers.

3.5. Optically active 1-aryl isochroman derivatives are produced, which contain 1-naphthyl, 2-naphthyl or substituted phenyl carbon units on the C-1 carbon atom of isochroman and feature different substitution patterns on the isochroman condensed benzene ring and carbon atom C-3. The corresponding stereoisomers and structural isomers were investigated by ECD spectroscopy.

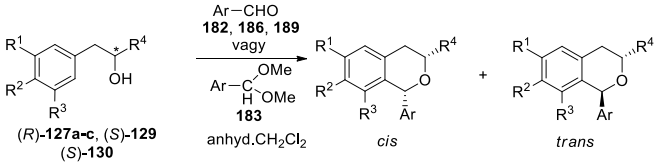
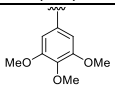
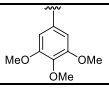
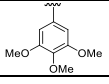


Figure 8. Preparation of optically active 1,3-disubstituted-1-aryl-isochromans.

Entry	Alcohol	Aldehyde	Ar	*cis*-product (yield)	*trans*-product (yield)
1	(*R*)-**127a**	**183**		(1*R*,3*R*)-**184** (59%)	(1*S*,3*R*)-**185** (17%)
2	(*R*)-**127a**	**186**		(1*S*,3*R*,)-**187**	(1*R*,3*R*,)-**188** (sum 91%)
3	(*R*)-**127a**	**189**		(1*R*,3*R*)-**190** (72%)	–
4	(*R*)-**127b**	**182**		–	(1*S*,3*R*)-**191** (96%)
5	(*R*)-**127b**	**186**		(1*R*,3*R*)-**193** (6%)	(1*S*,3*R*)-**192**(72%)
6	(*R*)-**127b**	**189**		–	(1*S*,3*R*)-**194** (78%)
7	(*R*)-**127c**	**182**		–	(1*S*,3*R*)-**195** (77%)
8	(*R*)-**127c**	**186**		(1*R*,3*R*)-**197** (56%)	(1*S*,3*R*)-**196** (14%)
9	(*R*)-**127c**	**189**		–	(1*S*,3*R*)-**198** (84%)
10	(*S*)-**129**	**182**		(1*S*,3*S*)-**199** (64%)	(1*R*,3*S*)-**200** (11%)
11	(*S*)-**129**	**32**		(1*R*,3*S*)-**201** (17%)	(1*S*,3*S*)-**202** (59%)
12	(*S*)-**130**	**182**		(1*S*,3*S*)-**203**	(1*R*,3*S*)-**204** (sum 79%)
13	(*S*)-**130**	**182**		(1*R*,3*S*)-**205** (60%)	(1*S*,3*S*)-**206** (35%)
14	(*S*)-**130**	**183**		(1*S*,3*S*)-**207** (88%)	–

The optically active alcohols [(*R*)-**127a-c**, (*S*)-**129** and (*S*)-**130]** were reacted with naphthalene-1-carbaldehyde (**186**), naphthalene-2-carbaldehyde (**182**), 3,4,5-trimethoxybenzaldehyde (**189**) and the dimethyl acetal derivative **183** in an oxa-Pictet-Spengler reaction. We have investigated the diastereoselectivity of the ring closure and prepared several optically active isochroman derivatives containing an aryl group at the

C-1 position. The ratio of the epimeric products depends both on the structure of the starting optically active alcohol and the aromatic aldehyde. In most cases, the C-1 epimers were separated by column chromatography and characterized as a single compound by spectroscopic methods.

3.6. ***An N-aryl-1,5-benzoxazepine derivative was prepared by using the Buchwald-Hartwig reaction for N-arylation. During the ring closure of active methylene reagents, the reaction proceeds via the domino Knoevenagel-S_EAr reaction instead of the domino Knoevenagel-[1,5]-hydride migration-ring closure sequence seen with 1,4-benzoxazepine derivatives. A derivative containing an acridane backbone forms that shows AChE inhibitory activity.***

The *N*-aryl-1,5-benzoxazepine derivative **211** was prepared in a four-step sequence including the crucial Buchwald-Hartwig *N*-arylation reaction. Compound **211** was reacted with 1,3-dimethylbarbituric acid, and the acridane derivative **221** formed via the S_EAr reaction of the carbocationic precursor **220** yielding the Knoevenagel intermediate. The domino Knoevenagel-[1,5]-hydride migration-ring closure sequence observed in 1,4-benzoxazepine derivatives did not take place. This can be interpreted by considering that the S_EAr reaction of the carbocationic precursor is favored on the highly activated aromatic ring.

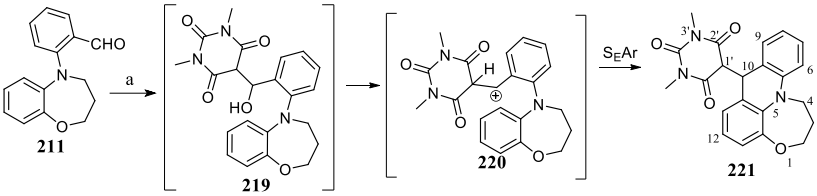


Figure 9. Preparation of acridan derivative **221**; a: 1,3-dimethylbarbituric acid, $MgSO_4$, $CHCl_3$, room temperature (64%).

In the AChE inhibition tests, the performance of the acridane derivative **221** was characterized by $IC_{50} = 6.98x10^{-6}$ mol/L.

4. Possible applications of the results

During this research work, we developed a gram-scale stereoselective synthesis for the hybrid molecule (1*R*,3*R*,2'*S*)-**142** that contains 2*H*-chromene and isochromane units. The molecule shows neuroprotective activity against H_2O_2-induced toxicity in human SH-SY5Y cells. *In vivo* studies revealed that it has anti-inflammatory effect in microglial cells. We also achieved the production of several structural analogs of target compound **142**, which can be potential neuroprotective derivatives. A large number of optically active 1,3-disubstituted-1-aryl-isochroman derivatives were prepared utilizing a similar reaction scheme.

Ring closure of our *N*-aryl-1,5-benzoxazepine derivative with 1,3-dimethylbarbuturic acid resulted in an AChE inhibitory acridan derivative.

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Subject: PhD Publication List

Candidate: Dóra Vargáné Szalóki
Doctoral School: Doctoral School of Chemistry
MTMT ID: 10080016

List of publications related to the dissertation

Foreign language scientific articles in international journals (2)

1. Tao, L., Ji, S. s., **Vargáné Szalóki, D.**, Kovács, T., Mándi, A., Antus, S., Ding, X., Kurtán, T., Zhang, H. Y.: An optically active isochroman-2H-chromene conjugate potently suppresses neuronal oxidative injuries associated with the PI3K/Akt and MAPK signaling pathways.
Acta Pharmacol. Sin. 42 (1), 36-44, 2021. ISSN: 1671-4083.
DOI: http://dx.doi.org/10.1038/s41401-020-0391-9
IF: 7.169

2. **Vargáné Szalóki, D.**, Tóth, L., Buglyó, B., Kiss-Szikszai, A., Mándi, A., Mátyus, P., Antus, S., Chen, Y., Li, D., Tao, L., Zhang, H. Y., Kurtán, T.: [1,5]-Hydride Shift-Cyclization versus C(sp2)-H Functionalization in the Knoevenagel-Cyclization Domino Reactions of 1,4- and 1,5-Benzoxazepines.
Molecules. 25 (6), 1-19, 2020. ISSN: 1420-3049.
DOI: http://dx.doi.org/10.3390/molecules25061265
IF: 4.411

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További közlemények

Idegen nyelvű tudományos közlemények külföldi folyóiratban (1)

3. Lihi, N., May, N. V., Udvardy, A., Najóczki, F., Bonczidai-Kelemen, D., Diószegi, R., **Vargáné Szalóki, D.**, Sánta, S. O., Fábián, I.: Complexes of 1,10-phenanthroline-mono-N-oxides with copper(II) and nickel(II) in aqueous solution and solid phase.
Inorg. Chim. Acta. 557, 1-11, 2023. ISSN: 0020-1693.
DOI: http://dx.doi.org/10.1016/j.ica.2023.121715
IF: 2.8 (2022)

A közlő folyóiratok összesített impakt faktora: 14,38
A közlő folyóiratok összesített impakt faktora (az értekezés alapjául szolgáló közleményekre): 11,58

A DEENK a Jelölt által az iDEa Tudóstérbe feltöltött adatok bibliográfiai és tudománymetriai ellenőrzését a tudományos adatbázisok és a Journal Citation Reports Impact Factor lista alapján elvégezte.

Debrecen, 2023.09.08.

DEBRECENI EGYETEM * Egyetemi és Nemzeti Könyvtár *

5. List of publications

Publications in the subject of the thesis

1. D. Szalóki Vargáné, L. Tóth, B. Buglyó, A. Kiss-Szikszai, A. Mándi, P. Mátyus, S. Antus, Y. Chen, D. Li, L. Tao, H. Zhang, Tibor Kurtán; [1,5]-Hydride shift-cyclization versus C(sp^2)-*H* functionalization in the Knoevenagel-cyclization domino reactions of 1,4- and 1,5-benzoxazepines, *Molecules* **2020**, *25*, 1265; (2020 IF: 4.411)

2. L.-X. Tao, S.-S. Ji, D. Szalóki, T. Kovács, A. Mándi, S. Antus, X. Ding, T. Kurtán, H.-Y. Zhang; An optically active isochroman-2*H*-chromene conjugate potently suppresses neuronal oxidative injuries associated with the PI3K/Akt and MAPK signaling pathways, *Acta Pharmacol. Sin.*, **2021**, *42*, 36; (2021 IF: 7.169)

3. Lingxue Tao, Weicheng Yu, Ziyi Liu, Sijing Lin, Dóra Szalóki, Máté Kicsák, Tibor Kurtán[c] and Haiyan Zhang[: JE-133 suppresses LPS-induced microglial neuroinflammation by dual regulation of JAK/STAT and Nrf2 signaling pathways, közlésre beküldve

Publications in other subjects

Lihi, N.; May, N. V.; Udvardy, A.; Najóczki, F.; Bonczidai-Kelemen, D.; Diószegi, R.; Szalóki, D.; Sánta, S. O.; Fábián, I., Complexes of 1, 10-phenanthroline-mono-n-oxides with copper (ii) and nickel (ii) in aqueous solution and solid phase. *Inorg. Chim. Acta* **2023**, 121715; DOI: https://doi.org/10.1016/j.ica.2023.121715 (2023 IF: 2.8)

Lectures in the subject

1) Szalóki Dóra, Tóth László, Antus Sándor és Kurtán Tibor: N-Aril-1,5-benzoxazepin származékok előállítása és gyűrűzárási reakcióik (szóbeli előadás); *MTA Alkaloid- és Flavonoid kémiai munkabizottság ülése, Balatonalmádi, 2013. május 13-14,*

2) Szalóki Dóra, Antus Sándor, Kurtán Tibor: Kondenzált 1,5-benzoxazepin és 1-arilizoindolin származékok vizsgálata (szóbeli előadás); *Heterociklusos és Elemorganikus Kémiai Munkabizottság ülése, Balatonszemes, 2013. június 5-7,*

3) Szalóki Dóra: O,N-heterociklusok előállítása (dolgozat és szóbeli előadás, III helyezett); *TDK, Debrecen, 2013. november 22,*

4) Szalóki Dóra, Illyés Tünde Zita, Antus Sándor, Kurtán Tibor: Kondenzált 1,5-benzoxazepinek és szubsztituált hexahidro-2,7-metano-1,5-benzoxazonin származékok előállítása (szóbeli előadás); *MTA Alkaloidkémiai és Flavonoidkémiai munkabizottság ülése, Balatonalmádi, 2014. május 12-13,*

5) Szalóki Dóra, Illyés Tünde Zita, Antus Sándor, Kurtán Tibor: Kondenzált 1,5-benzoxazepinek és szubsztituált hexahidro-2,7-metano-1,5-benzoxazonin származékok előállítása (szóbeli előadás); *Heterociklusos és Elemorganikus Kémiai Munkabizottság ülése, Balatonszemes, 2014. május 21-23,*

6) Szalóki Dóra, Mándi Attila, Tóth László, Antus Sándor, Kurtán Tibor: Izokromán, hexahidro-2,7-metano-1,5-benzoxazonin és dihidroakridin származékok vizsgálata (szóbeli előadás); *MTA Alkaloidkémiai és Flavonoidkémiai munkabizottság ülése, Balatonalmádi, 2015. május 18-19,*

7) Szalóki Dóra, Mándi Attila, Tóth László, Antus Sándor, Kurtán Tibor: Izokromán, hexahidro-2,7-metano-1,5-benzoxazonin és dihidroakridin származékok vizsgálata (szóbeli előadás); *Heterociklusos és Elemorganikus Kémiai Munkabizottság ülése, Balatonszemes, 2015. május 27-29,*

8) Szalóki Dóra, Mándi Attila, Kovács Tibor, Tóth László, Antus Sándor, Kurtán Tibor: Optikailag aktív izokromán származékok előállítása és sztereokémiai vizsgálata (szóbeli előadás); *MTA Alkaloid- és Flavonoidkémiai Munkabizottság ülése, Mátrafüred, 2016. április 14-15.*