Short thesis for the degree of doctor of philosophy

(PhD)

Domino Knoevenagel-cyclization reactions for the preparation of chiral heterocycles with antiproliferative activity

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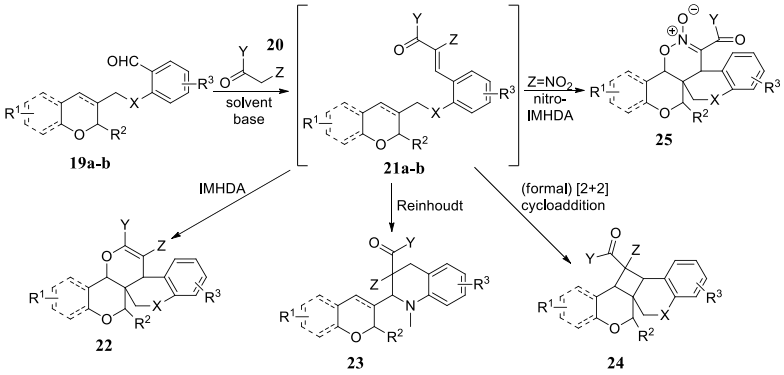
1. Introduction and objectives

The heterocyclic pyran ring is a common motif in natural products, often as part of a condensed ring system with benzene or other heterocycles. These heterocycles show a wide range of biological activities and the most common one is the anticancer effect. Their bioactivity may justify to find new and effective synthetic methods for the preparation of complex condensed heterocyclic ring systems. One of the possible routes is to use a partially unsaturated dihydropyran or 2*H*-chromene derivative in an intramolecular cycloaddition reaction, with the participation of the endocyclic double bond. However, there are only a handful of synthetic methods reported in the literature, where a dihydropyran or 2*H*-chromene moiety acts as the dienophile in a cycloaddition reaction. The efficiency of the synthesis can be improved by the use of domino reaction sequences, which allows us to prepare complex structures from relatively simple starting materials in several steps.



Scheme 1. Different domino Knoevenagel-cyclization pathways with substrates containing a pyran subunit.

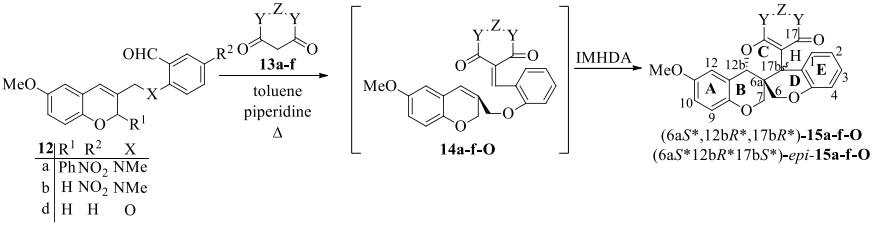
During my M.Sc. thesis research work, we already studied the intramolecular hetero Diels-Alder (IMHDA) reactions of 2*H*-chromene derivatives, which afforded a novel, condensed heterocyclic ring system diastereoselectively. During my doctoral thesis work, we aimed to expand the scope of this reaction in respect of substrates (**19a-b**) and active methylene reagents (**20**) having versatile substitution pattern. We planned to study the effect of different heteroatoms in the linker connecting the benzaldehyde and the chromene units (X = NMe or X = O) and the conjugation of the dienophile double bond (2*H*-chromene or dihydropyran) in the substrate. We also wanted to study the effect of the electron withdrawing groups (Y and Z) in the active methylene reagents (**20**) on the mechanism of the cyclization (Scheme 1.).

2. Applied methods

During the synthetic work, the macro-, semi-micro- and micro-methods of modern preparative organic chemistry were used. Thin-layer chromatography was used to monitor the reactions and to control the purity of the products. The reactions were purified by column chromatography and/or crystallization. The prepared novel compounds were characterized by classical analitical methods (melting point, retention factor), and their structures were elucidated by 1D- and 2D-NMR methods, infrared and mass spectroscopy and single-cystal X-Ray diffraction measurements. The relative configuration of the products were assigned using their characteristic NOE effects. The antiproliferative activities were tested on A2780 (ovarian carcinoma) and WM35 (melanoma) cell lines using MTT method.

3. New scientific results of the dissertation

3.1. Domino Knoevenagel-intramolecular hetero Diels-Alder reactions of 2H-chromene derivatives bearing an ortho-formylphenyl-ether moiety with cyclic 1,3-dicarbonyls afforded condensed heterocycles possessing three 2H-3,4-dihydropyran rings, of which several showed low μM IC_{50} values in in vitro antiproliferative assays.



Scheme 2. Domino Knoevenagel-IMHDA reactions of 2*H*-chromene derivative **12a**, **b**, **d** and cyclic active methylene reagents **13a-f**.

Entry	**13a-f**	Y	Z	Product	Yield[a]	**15**/*epi*-**15**[b]
1	**13a**	Me	C=O	**15a-O**	76%	100:0
2	**13b**	Et	C=S	**15b-O**	88%	100:0
3	**13c**	CH_2	CH_2	**15c-O,** *epi*-**15c-O**	83%	77:23
4	**13d**	CH_2	CH-Ph	**15d-O**, *epi*-**15d-O**	82%	85:15
5	**13e**	CH_2	-	**15e-O**, *epi*-**15e-O**	46%	60:40
6	**13f**[c]	1,2-phenylene[c]		**15f-O**	42%	100:0

a) isolated yield b) ratio of epimers from isolated yields c) 1,3-indanedione reagent.

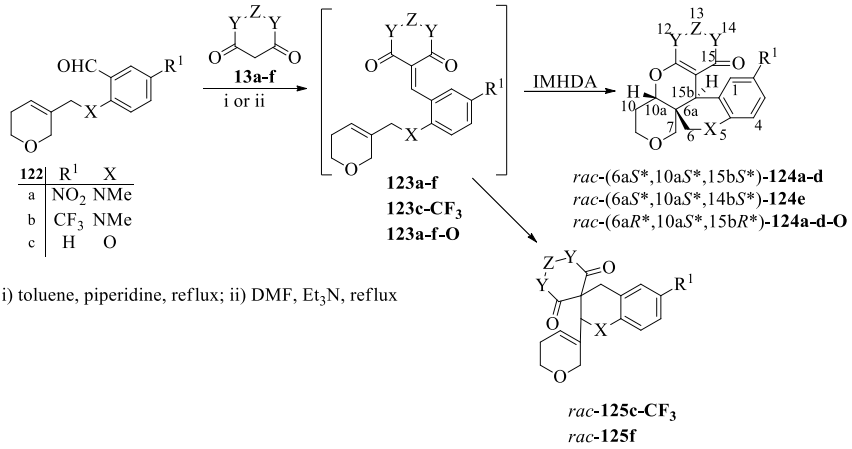
The reactions of *o*-formylaryl-amine derivatives **12a**,**b** were previously studied in our group. Thus, in order to expand the scope of the reaction and prepare additional analogues, the **12d** ether derivative was reacted with active methylene reagents **13a-f** (Scheme 2). In accordance

with previous results, the diastereoselectivity was affected by the structure of both the reagent (**13**) and the benzaldehyde derivative **12**.

The relative configuration of the products was determined in each case by their characteristic NOE correlations, which was corroborated by the single crystal X-ray diffraction study of **15f-O**. In the reaction of **12b** and **13e**, DFT calculation was used to show that the formation of both isolated isomers is feasible and the computed relative energy of the major product was found lower. The bioactivity study of products **15a-f-O** revealed that several of them showed promising antiproliferative activity, with **15a-O** being the most active, having an IC_{50} value of 1.62 and 6.29 uM on A2780 and WM35 cell lines, respectively.

3.2. The domino Knoevenagel-cyclization reactions were extended to the 5,6-dihydro-2H-pyran derivatives, where besides the usual hetero Diels-Alder reaction, a Reinhoudt cyclization took place in two cases.

The effect of the condensed benzene ring „A", conjugating with the dienophile double bond, was studied by the reactions of the dihydropyran derivatives **122a-c**. Both the (*o*-formylaryl)-amine (**122a-b**) and -ether (**122c**) derivatives showed decreased reactivity in the domino reaction, compared to the corresponding 2*H*-chromenes (**12a-d**). This was illustrated well by the reaction between **122a** and the indan-1,3-dione **13f**, where the IMHDA reaction proved to be unfavourable, and instead a Reinhoudt-reaction took place, which was not observed for the reactions of 2*H*-chromenes (entry 12). The two competing reaction mechanisms can be influenced by the substitution pattern, since the reaction of **122a** and **13c** afforded only the IMHDA product **124c**, while the trifluoromethyl-analogue **122b** gave both the **124c-CF_3** IMHDA and the **125c-CF_3** Reinhoudt products. The oxygen analogue **122c** afforded only the **123-O** Knoevenagel intermediates under identical conditions and underwent cyclization only under harsher conditions when refluxing in DMF, affording the products with lower yields than the respective amine derivatives (entry 7 and 9). The cyclization reactions yielded a single diastereomer in each case, the relative configuration of which was the same as the configuration of the respective 2*H*-chromene analogues. From these derivatives, **124d** showed the best antiproliferative activity, having an IC_{50} value of 3.15 and 2.99 μM on the two tested cell lines (A2780 and WM35).



i) toluene, piperidine, reflux; ii) DMF, Et_3N, reflux

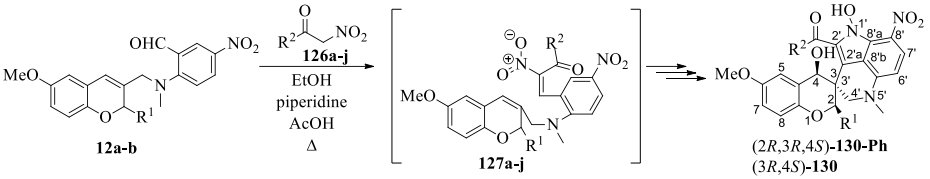
Scheme 3. Domino Knoevenagel-IMHDA and Knoevenagel-Reinhoudt reactions of 5,6-dihydropyran derivatives **122a-c** and cyclic active methylene reagents **13a-f**.

Entry	**122a-c**	**13a-f**	Y	Z	Product	Yield[a]
7	**122a**	**13c**	CH_2	CH_2	**124c**	82%
8	**122b**	**13c**	CH_2	CH_2	**124c-CF$_3$**	48%
					125c-CF$_3$	30%
9	**122c**	**13c**	CH_2	CH_2	**124c-O**	18%
10	**122a**	**13d**	CH_2	CH-Ph	**124d**	89%
11	**122c**	**13d**	CH_2	CH-Ph	**124d-O**	19%
12	**122a**	**13f**[b]	1,2-phenylene[b]		**123f→125f**[c]	53%
13	**122c**	**13f**[b]	1,2-phenylene[b]		**123f-O**	88%

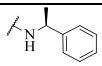
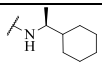
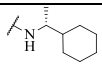
a) isolated yield, b) **13f**: 1,3-indanedione reagent, c) MW, 150°C, toluene.

3.3. A domino Knoevenagel-nitro-IMHDA-ring-opening-S_EAr reaction sequence was identified in the reaction of nitroacetic acid and nitroacetamide derivatives for the synthesis of hydroxyindole derivatives and a possible reaction mechanism was proposed.

Due to their decreased reactivity, the reactions of acyclic reagents were carried out in ethanol, using a piperidine/acetic acid buffer. Reagents containing a nitro group afforded intermediate **127** containing two different heterodienes; an α,β-unsaturated-carbonyl and -nitro moieties. The reaction did not afford any of the expected condensed heterocycles, but instead condensed spirocyclic hydroxyindoles **130a-j** were isolated (Scheme 4). The structure of the products were elucidated by using HSQC and ^{13}C-HMBC measurements, and in one case a ^{15}N-HMBC experiment and ^{13}C-NMR DFT calculations were carried out.



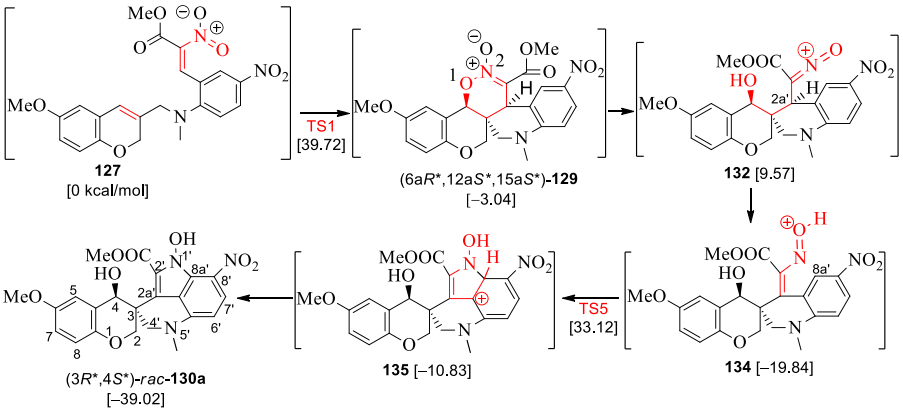
Scheme 4. Domino Knoevenagel-nitro-IMHDA-ring-opening-S_EAr reaction of 2*H*-chromenes and nitro compounds.

Entry	**12a-b**	**126a-i**	R^2	Product (yield)[a]
14	**12b**	**126a**	OMe	**130a**[b] (55%)
15	**12b**	**126b**	Ph	**130b**[b,c] (70%)
16	(*rac*)-**12a**	**126a**	OMe	**130a-Ph**[d] (49%)
17	(*rac*)-**12a**	**126b**	Ph	**130b-Ph**[d] (34%)
18	**12b**	**126c**	NH_2	**130c**[b] (65%)
19	**12b**	**126d**	1-pyrrolidinyl	**130d**[b] (74%)
20	**12b**	**126e**	1-piperidinyl	**130e**[b] (58%)
21	**12b**	**126f**	1-morpholinyl	**130f**[b] (91%)
22	**12b**	(*S*)-**126g**		(3*R*,4*S*,3"*S*)-**130g** (3*S*,4*R*,3"*S*)-*dia*-**130g** (68%)
23	**12b**	(*R*)-**126g**		(3*R*,4*S*,3"*R*)-**130g** (3*S*,4*R*,3"*R*)-*dia*-**130g** (36%)
24	**12b**	(*S*)-**126i**		(3*R*,4*S*,3"*S*)-**130i** (3*S*,4*R*,3"*S*)-*dia*-**130i** (40%)
25	**12b**	(*R*)-**126i**		(3*R*,4*S*,3"*R*)-**130i** (3*S*,4*R*,3"*R*)-*dia*-**130i** (54%)

a) isolated yield b) (3*R**,4*S**) diastereomer as a racemic mixture c) ^{1}H-NMR signal duplication in 54:46 ratio due to the rotation of the acyl group d) (2*R**,3*S**,4*S**) diastereomer as a racemic mixture

We proposed a possible reaction pathway on the basis of analogous reactions from the literature, which was supported by our DFT calculations of the reaction mechanism. Based on these results, the initial Knoevenagel condensation is followed by a nitro-Diels-Alder reaction, affording a nitrone derivative (**129**). The protonation of the heterocyclic oxygen (O-1) leads to spontaneous ring-opening by a heterolytic cleavage of the N-2−O-1 bond. According to our computational results, the aromatic electrophilic substitution can only take place after deprotonation at C-2a' and protonation of the nitroso oxygen (**132**→**134**). The pentacyclic hydroxyindole **130a** is then formed by rearomatization of the intermediate **135** (Scheme 5). The

overall reaction, and specifically the cyclization step involving a nitro group, shows similarity to the Cadogan reaction but deoxygenation takes place through a nitro-IMHDA-ring-opening sequence, and cyclization takes place on the benzene ring instead of an alkene subunit. The calculations also justified the formation of the hydroxyindole: the relative energy of **130a** is ~39 kcal mol^{-1} lower than that of the Knoevenagel intermediate **127a**. This multistep domino sequence is a novel, mild method for the transformation of nitro derivatives to hydroxyindoles. The spirocyclic ring system also represents a novel structure, and several of the products showed antiproliferative activity in low μM concentrations. The product **130i** showed the best activity with an IC_{50} value of 3.96 and 2.28 μM on the A2780 and WM35 cell lines, respectively.

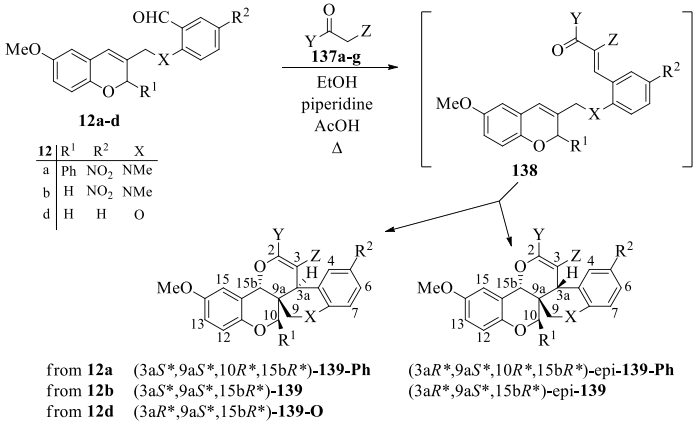


Scheme 5. Proposed reaction mechanism for the formation of (3*R**,4*S**)-*rac*-**130a** (ΔG_{rel} energies in kcal mol^{-1}).

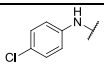
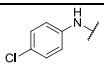
3.4. A series of novel pentacyclic O- and O,N-heterocycles were prepared in a domino Knoevenagel-IMHDA reaction using acyclic active methylene reagents.

In the absence of a nitro group, the α,β-unsaturated carbonyl moiety acts as the heterodiene in the cyclization reaction, similarly to the reaction of the cyclic reagents (Scheme 6). Acetoacetic ester (**137a**) afforded the product as a single diastereomer with **12a** (entry 22), but the reaction with **12b** produced two epimers with low selectivity (entry 23). In both cases, the ketone carbonyl group took part in the cyclization with full chemoselectivity. In the reactions of 4'-chloroacetoacetanilide (**137b**), a single diastereomer was isolated in both cases, and surprisingly the amide carbonyl group reacted as part of the dienophile (entry 24-25). This is caused by the intramolecular H-bond between the amide N-H and the oxygen of the ketone carbonyl, which forced the ketone carbonly into an s-*trans* conformation, preventing it from acting as part of the

heterodiene. Similar hetero Diels-Alder reactions involving acyclic amides is not known in the literature. Benzoyl-acetonitrile (**137d**) showed an interesting selectivity; in the reaction with **12b**, a ~1:1 mixture of the two epimers was isolated (entry 27), while **12a** and **12d** afforded a single diastereomeric product, with different relative configurations. The configuration of **139d-O** is identical to those of the major products from previous reactions (3a-H/C-9 *trans*) (entry 28), while **139d-Ph** had the same configuration as the minor epimers (3a-H/C-9 *cis*) (entry 26). The ester derivative (**137e**) showed similar selectivity but with **139e-Ph** being a mixture of epimers (entry 29), and **139e** isolated as a single diastereomer (entry 30).

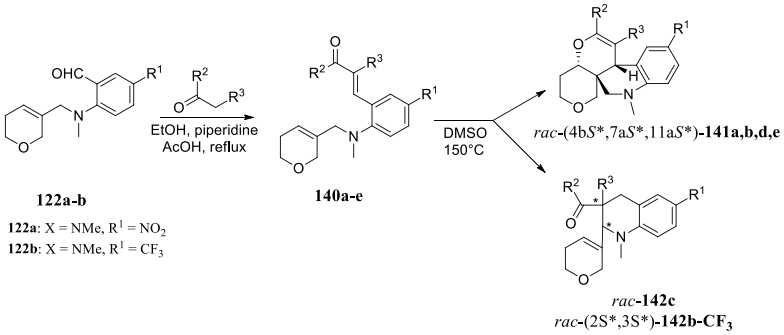


Scheme 6. Domino Knoevenagel-IMHDA reaction of 2*H*-chromene derivatives with acyclic active methylene reagents.

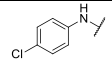
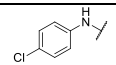
Entry	**12a-d**	**137a-e**	Y	Z	Product (yield)[a]	**139**/*epi*-**139**[b]
22	(*rac*)-**12a**	**137a**	CH_3	COOMe	**139a-Ph** (67%)	100:0
23	**12b**	**137a**	CH_3	COOMe	**139a**, *epi*-**139a** (30%)	64:36[c]
24	(*rac*)-**12a**	**137b**		Ac	**139b-Ph** (52%)	100:0
25	**12b**	**137b**		Ac	**139b** (47%)	100:0
26	(*rac*)-**12a**	**137d**	Ph	CN	*epi*-**139d-Ph** (77%)	0:100
27	**12b**	**137d**	Ph	CN	**139d**, *epi*-**139d** (92%)	51:49[c]
28	**12d**	**137d**	Ph	CN	**139d-O** (53%)	100:0
29	(*rac*)-**12a**	**137e**	OEt	CN	**139e-Ph**, *epi*-**139e-Ph** (63%)	51:49[c]
30	**12b**	**137e**	OEt	CN	**139e** (88%)	100:0

a) isolated yield b) ratio of epimers from isolated yields c) isolated as a mixture, ratio from NMR.

The cyclizacion reactions were also carried out with the **122a-b** pyran derivatives but due to their decreased reactivity, only the Knoevenagel intermediates **140a-e** formed except for one case (entry 35). The cyclization was achieved by heating the intermediates to 150°C in DMSO. Similarly to the cyclic derivatives, both IMHDA and Reinhoudt-reactions could occur and the cyclization mechanism was governed by the substitution of both the substrate and reagent (Scheme 7). The acetoacetic ester derivative underwent IMHDA reaction with the ketone carbonyl group, analogously to the 2*H*-chromene derivative (entry 31). With diethyl malonate, the Reinhoudt-reaction was preferred, due to the lower reactivity of the ester carbonyl group (entry 34. sor). In the reactions of amide derivatives **140b** and **140b-CF$_3$**, the substitution of the benzaldehyde ring influenced the cyclization: **141b** and **142b-CF$_3$** were isolated exclusively, formed in an IMHDA and Reinhoudt-reaction, respectively. (entry 32-33). The relative configuration of (2*S**,3*S**)-**142b-CF$_3$** was assigned using the characteristic NOE effects, which showed that the dihydropyran and acetyl groups are *trans*-diaxial.



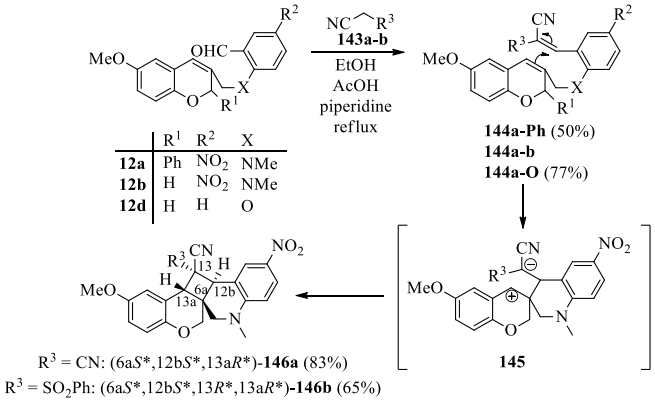
Scheme 7. Knoevenagel-cyclization reactions of dihydropyran derivatives with acyclic active methylene reagents.

Entry	**122a-b**	**137a-e**	R^2	R^3	Product	Yield[a]
31	**122a**	**137a**	CH_3	COOMe	**141a**	55%
32	**122a**	**137b**		Ac	**141b**	41%
33	**122b**	**137b**		Ac	**142b-CF$_3$**	40%
34	**122a**	**137c**	OEt	COOEt	**142c**	50%
35	**122a**	**137d**	Ph	CN	**141d**	84%
36	**122a**	**137e**	OEt	CN	**141e**	25%

a) overall yield for the two steps

The condensed heterocyclic products obtained from both the 2*H*-chromene (**139**) and dihydropyran derivatives (**141**) showed promising antiproliferative activity. The best activity was identified for **139e** and **141e** nitrile derivatives with IC_{50} values of 4.48 and 9.57 μM for the former, and 3.17 and 30.7 μM for the latter (on A2780 and WM35cell lines, respectively).

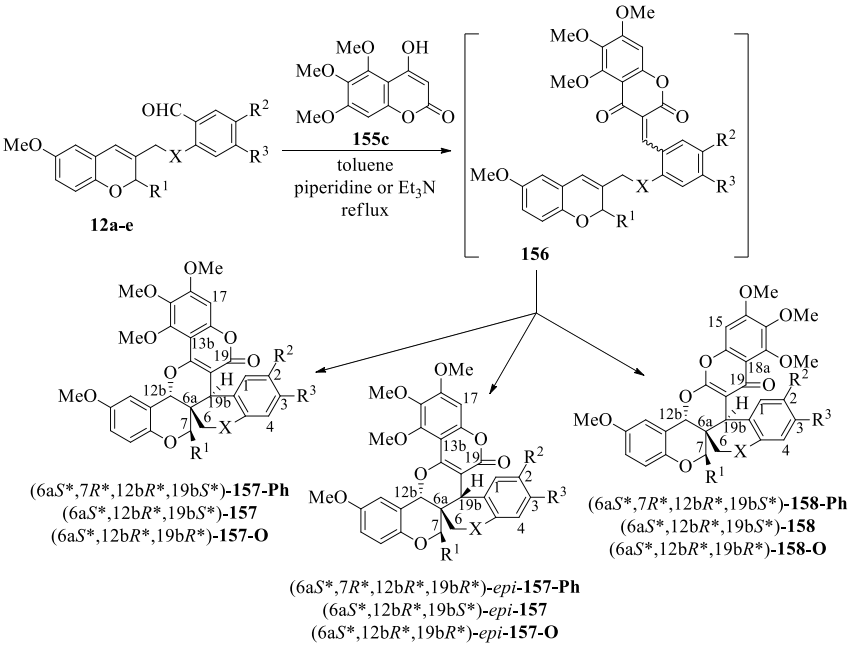
3.5. Condensed cyclobutane derivatives were prepared in a domino Knoevenagel-stepwise [2+2]-cycloaddition reaction using active methylene reagents lacking the carbonyl group.



Scheme 8. Formation of condensed cyclobutane derivatives in a stepwise [2+2] cycloaddition.

If the active methylene reagent lacks a suitable heterodiene for the IMHDA reaction (α,β-unsaturated nitro or carbonyl), the condensation reaction is followed by a stepwise formal [2+2] cycloaddition through a zwitterionic intermediate (**145**). Only **12b** afforded the condensed cyclobutane derivatives, the reactions of **12a** and **12d** gave the Knoevenagel intermediates (**144a-Ph** and **144a-O**), which did not undergo further cyclization reactions, even under harsher conditions. **146a** and **146b** possess a novel heterocyclic ring system with three and four contigous stereogenic centers, formed diastereoselectively in the reaction (Scheme 8). The relative configuration was determined by using NOE correlations, and it was confirmed by the single-crystal X-ray diffraction analysis of **146a**. The antiproliferative effect of **146a** was tested on A2780 and WM35 cell lines, and IC_{50} values of 5.9 and 23.7 μM were determined, respectively.

3.6. Domino Knoevenagel-IMHDA reactions were carried out with 4-hydroxycoumarin derivatives, and the regio- and diastereoselectivity was studied.



Scheme 9.Domino Knoevenagel-IMHDA reaction of 2*H*-chromene derivatives (**12a-e**) with 4-hydroxycoumarin **155c**.

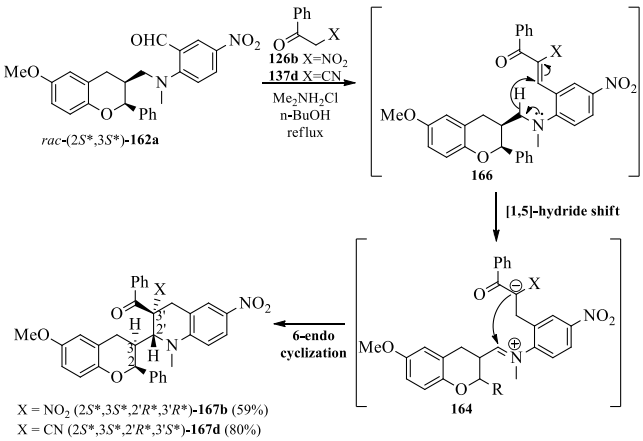
Entry	**12**	R^1	R^2	R^3	X	Product (yield)[b]
37	*rac*-**12a**	Ph	NO_2	H	NMe	**157c-Ph** (19%) *epi*-**157c-Ph** (10%)
38[a]	*rac*-**12a**	Ph	NO_2	H	NMe	**157c-Ph** (12%) *epi*-**157c-Ph** (34%)
39	**12b**	H	NO_2	H	NMe	**157c** (49%) **158c** (25%) *epi*-**157c** (16%)
40[a]	**12b**	H	NO_2	H	NMe	**157c** (21%) **158c** (13%) *epi*-**157c** (10%)
41	**12c**	H	H	CF_3	NMe	**157c-CF_3** (42%)
42	**12e**	H	H	H	NMe	**157c-H** (32%)
43	**12d**	H	H	H	O	**157c-O** (34%) **158c-O** (12%) *epi*-**157c-O** (13%)

a) reaction was carried out at room temperature b) isolated yield.

In the reactions with 4-hydroxycoumarin and related non-symmetric cyclic 1,3-dicarbonyl derivatives, the Knoevenagel intermediate **156** possesses two different heterodiene moieties. Unlike the reactions with acyclic reagents, the reactions did not take place with full chemoselectivity. The IMHDA reaction could afford four different products, two different regioisomers, both as a pair of diastereomers. The reactions afforded a maximum of three isomers with varying selectivities. Both the diastereo- and chemoselectivity were affected by the substitution of the substrate and the reagent as well (Scheme 9).

In a few cases, the effect of the reaction temperature on the selectivity was studied. The chemoselectivity was largely unaffected by it but the diastereoselectivity changed drastically in the reactions of *rac*-**12a** (entry 37-38), while it did not change in the reactions of **12b** (entry 39-40). In the reactions with dihydropyran **122a**, a single product was isolated, and the reactions were fully diastereo- and chemoselective.

3.7. A substrate of the domino cyclization containing a chroman moiety was prepared, and in the absence of the dienophile double bond, domino Knoevenagel-Reinhoudt reactions were carried out, affording products with a chroman and a tetrahydroquinoline ring linked through a C-3-C-2' sigma bond.



Scheme 10. Domino Knoevenagel-[1,5]-hydride shift-6-endo cyclization reaction with chroman derivatives.

In the reactions of 2*H*-chromene derivatives **12a-d**, we never observed that Reinhoudt-cyclizations would compete with the IMHDA (or stepwise [2+2] cycloadditions) reactions. In order to verify that this cyclization mechanism is viable, chroman derivative *rac*-**162a**, lacking the Δ^3 double bond, was prepared and its domino Knoevenagel-cyclization reactions with the

previously used active methylene reagents were studied. After the condensation step, cycloaddition pathways can not take place, and thus the product formed by a [1,5]-hydride-shift, followed by a 6-endo-cyclization of the zwitterionic intermediate (**164**) with full diastereoselectivity. This selectivity is due to the C-2 substituent of the chroman ring, since in the absence of this substituent, the product formed with a very low diastereoselectivity and a mixture of diastereomers was isolated.

4. Possible applications of the results

During our research work, the domino Knoevenagel-cyclization reactions of 2*H*-chromene and 5,6-dihydro-2*H*-pyran derivatives were studied, for which there are only a few remote examples in the literature. Four different cyclization pathways were identified resulting in four series of condensed heterocycles, from which three represent novel condensed heterocyclic ring systems. The scope and limitations of the reactions were extensively studied by modifying the substitution pattern of both the reagent and the substrate, and we identified the structural features that are required for each reaction mechanism. The multi-step domino reaction with nitro derivatives is a novel pathway, which provides a route for the mild conversion of nitroalkenes to hydroxyindoles.

Several of the more than one hundred prepared derivatives showed antiproliferative activity at low micromolar concentrations on human cancer cell lines. Further modification of the substitution pattern or further derivatization might lead to better activities and/or selectivities in the future.

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List of publications related to the dissertation

Foreign language scientific articles in international journals (2)

1. **Király, S. B.**, Tóth, L., Kovács, T., Bényei, A., Lisztes, E., Tóth, I. B., Bíró, T., Kiss-Szikszai, A., Kövér, K. E., Mándi, A., Kurtán, T.: Multifaceted Domino Knoevenagel-Cyclization Reactions; Four Movements for 2H-Chromenes and Chromans.
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5. List of publications

Publications in the subject of the thesis

1. Király, Sándor Balázs; Bényei, Attila; Lisztes, Erika; Bíró, Tamás; Tóth, Balázs István; Kurtán, Tibor: Knoevenagel-Cyclization Cascade Reactions of Substituted 5,6-Dihydro-2*H*-Pyran Derivatives; *Eur. J. Org. Chem.*; **2021**, 45 pp. 6161-6170. IF: 3,021.

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1. Vasas, Andrea; Lajter, Ildikó; Kúsz, Norbert; Király, Sándor Balázs; Kovács, Tibor; Kurtán, Tibor; Bózsity, Noémi; Nagy, Nikolett; Schelz, Zsuzsanna; Zupkó, István; Krupitza, Georg; Frisch, Richard; Mándi, Attila; Hohmann, Judit: Isolation, Structure Determination of Sesquiterpenes from Neurolaena lobata and Their Antiproliferative, Cell Cycle Arrest-Inducing and Anti-Invasive Properties against Human Cervical Tumor Cells; *Pharmaceutics*, **2021**, 13(*12*), 2088. IF: 6.525.

2. Yang, Sui-Qun; Mándi, Attila; Li, Xiao-Ming; Liu, Hui; Li, Xin; Balázs Király, Sándor; Kurtán, Tibor; Wang, Bin-Gui: Separation and configurational assignment of stereoisomeric phenalenones from the marine mangrove-derived fungus Penicillium herquei MA-370; *Bioorg. Chem.*; **2021**; 106; pp. 104477. IF: 5,275.

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Lectures in the subject

1. Király Sándor Balázs, Kajtár Mihály, Mándi Attila, Kovács Tibor, Antus Sándor, Kurtán Tibor: 3-Formil-2*H*-kromén származékok átalakításai. MTA Alkaloid- és Flavonoidkémiai mb. Ülése (Mátrafüred, 2016.04.14-15).

2. Király Sándor Balázs, Kurtán Tibor: Domino Knoevenagel-gyűrűzárási reakciók vizsgáltata *O,N*-heterociklusok előállítására. Tavaszi Szél Konferencia (Budapest, 2016.04.15-17).

3. Király Sándor Balázs, Kajtár Mihály, Mándi Attila, Kovács Tibor, Antus Sándor, Kurtán Tibor: 3-Formil-2*H*-kromén származékok átalakításai. Heterociklusos és Elemorganikus kémiai mb. Ülése (Balatonszemes, 2016.05.18-20).

4. Király Sándor Balázs, Kovács Tibor, Mándi Attila, Kajtár Mihály, Antus Sándor, Kurtán Tibor: Kondenzált O,N-heterociklusok előállítása domino reakcióval. Alkaloid- és Flavonoidkémiai mb. ülése (Mátrafüred, 2017.04.06-07).

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6. Király Sándor Balázs, Kajtár Mihály, Kovács Tibor, Mándi Attila, Antus Sándor, Kurtán Tibor: Domino Knoevenagel reakciók kondenzált *O,N*-heterociklusok előállítására. Gyógyszerkémiai és Gyógyszertechnológiai Szimpózium (Szeged, 2017.09.11-12.).

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8. Király Sándor Balázs, Antus Sándor, Kovács Tibor, Mándi Attila, Kurtán Tibor: Királis *O,N*-heterociklusok előállítása sztereoszelektív domino gyűrűzárási reakciókkal. Heterociklusos és Elemorganikus Kémiai Munkabizottság ülése (Balatonszemes, 2018.06.06-08).

9. Sándor Balázs Király: Domino cyclization reactions for the preparation of condensed *O,N*-heterocycles. Chemistry towards Biology (Budapest, 2018. 09. 24-27.).

10. Király Sándor Balázs, Kovács Tibor, Mándi Attila, Antus Sándor, Kurtán Tibor: Domino Knoevenagel-gyűrűzárási reakciók 2*H*-kromén és dihidrokinolin származékokon. Alkaloid- és Flavonoidkémiai mb. ülése (Mátrafüred, 2019.04.11-12).

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12. Sándor Balázs Király, Attila Mándi, Tibor Kurtán: Synthesis and stereochemical study of condensed heterocycles. Pan-Balkan Alliance of Natural Products and Drug Discovery Associations (Shanghai, 2019. 09. 24-28.).

13. Király Sándor Balázs, Kurtán Tibor: Domino iminképzés-gyűrűzárási reakciók vizsgálata primer aminokkal. Alkaloid- és Flavonoidkémiai mb. ülése (Mátrafüred, 2020.10.01-02).

14. Király Sándor Balázs, Kajtár Mihály, Mándi Attila, Kovács Tibor, Kurtán Tibor: Domino gyűrűzárási reakciók új alapvázat képviselő kondenzált heterociklusok előállítására. Gyógyszerkémiai és Gyógyszertechnológiai Szimpózium (Herceghalom, 2021.09.20-21.).

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