Summary of PhD Thesis

SYNTHESIS OF POTENTIAL ANTIANDROGENS BY STRUCTURAL MODIFICATIONS OF THE A-RING OF DIHYDROTESTOSTERONE

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1. Introduction and aims

Androgenic hormones (testosterone, 5α-dihydrotestosterone - DHT) are an important group of natural carbon compounds. As transcription factors, they are involved in the regulation of many endonuclear processes, such as the growth and development of prostate cells. Increased androgen levels have been associated with the development of prostate cancer, making androgen deprivation therapy a first-line option for the treatment of metastatic prostate cancer. Drug resistance as a consequence of rapid mutations in cancer and the associated loss of efficacy, and undesirable side effects caused by agents that are not selective for cancer cells have led to a continuous need for the development of new types of anticancer agents. By semi-synthetically modifying the androgen receptor (AR) binding functional groups of the A and D rings of natural hormones, the hormonal effect can be suppressed and a new main effect, different from the one previously observed, can be obtained.

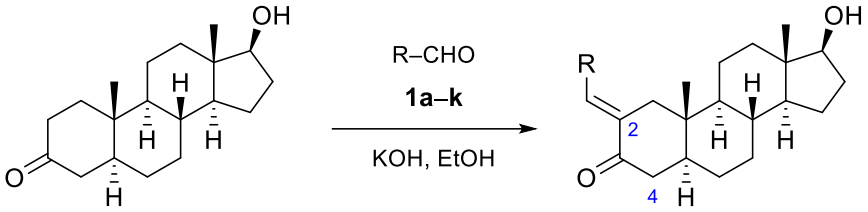
Based on the preliminary results of the Steroid Chemistry Research Group and the international literature, the aim of my Ph.D. thesis was the synthesis of new heterocyclic derivatives with different numbered rings fused to the A ring of DHT with a potential AR antagonist activity. We aimed to study the structure-activity relationships involved in the modification of the sterane backbone, in all cases aiming at optimizing the conditions of the transformations and confirming the structure of all obtained products via spectroscopic methods. Collaborations have also aimed at confirming the solid phase structure of certain representative derivatives by single crystal X-ray diffraction. *In vitro* pharmacological studies on AR binding of the synthesised compounds were to be carried out with the help of our foreign collaborators.

2. Experimental methods

During the synthetic work, most of the transformations were carried out in millimole quantities, and the starting materials were prepared on a gram scale. In some cases, microwave (MW) irradiation was used in a closed system, and the reactions were monitored by thin layer chromatography (TLC). The synthesized derivatives were purified by column chromatography and recrystallization, their structure was confirmed via spectroscopic methods (^{1}H- and ^{13}C-NMR, HSQC, HMBC, NOESY, ESI-MS), and the solid phase structure of certain compounds was confirmed by with the help of our collaborating partners.

3. Novel scientific results*

3.1. The *Claisen-Schmidt* condensation of DHT with benzaldehyde (**1a**) in alkaline ethanol at room temperature afforded the desired 2-benzylidene-DHT derivative (**2a**) in excellent yield (92%) (*Scheme 1*). It was found that the use of a higher temperature or MW heating technique favoured the formation of the undesired 4-benzylidene derivative.



DHT **2a–l**

R-CHO	R	Temperature	Time	Product	Yield (%)
1a	Ph	reflux	30 min	**2a**	74
1a	Ph	25 °C	3 h	**2a**	92
1a	Ph	80 °C (MW)	10 min	**2a**	69
1b	*p*-CH_3-C_6H_4	25 °C	4 h	**2b**	87
1c	*m*-CH_3-C_6H_4	25 °C	4 h	**2c**	89
1d	*p*-MeO-C_6H_4	25 °C	4 h	**2d**	89
1e	*p*-F-C_6H_4	25 °C	3 h	**2e**	91
1f	*p*-Cl-C_6H_4	0 °C	3 h	**2f**	90
1g	*p*-Br-C_6H_4	0 °C	3 h	**2g**	86
1h	furan-2-yl	0 °C	1 h	**2h**	84
1i	tiophen-2-yl	0 °C	3 h	**2i**	83
1j	pyridin-2-yl	0 °C	3 h	**2j**	69
1k	*p*-OH-C_6H_4	reflux	16 h	**2k**	47
1l	CH_3	-10 °C	3,5 h	**2l**	70

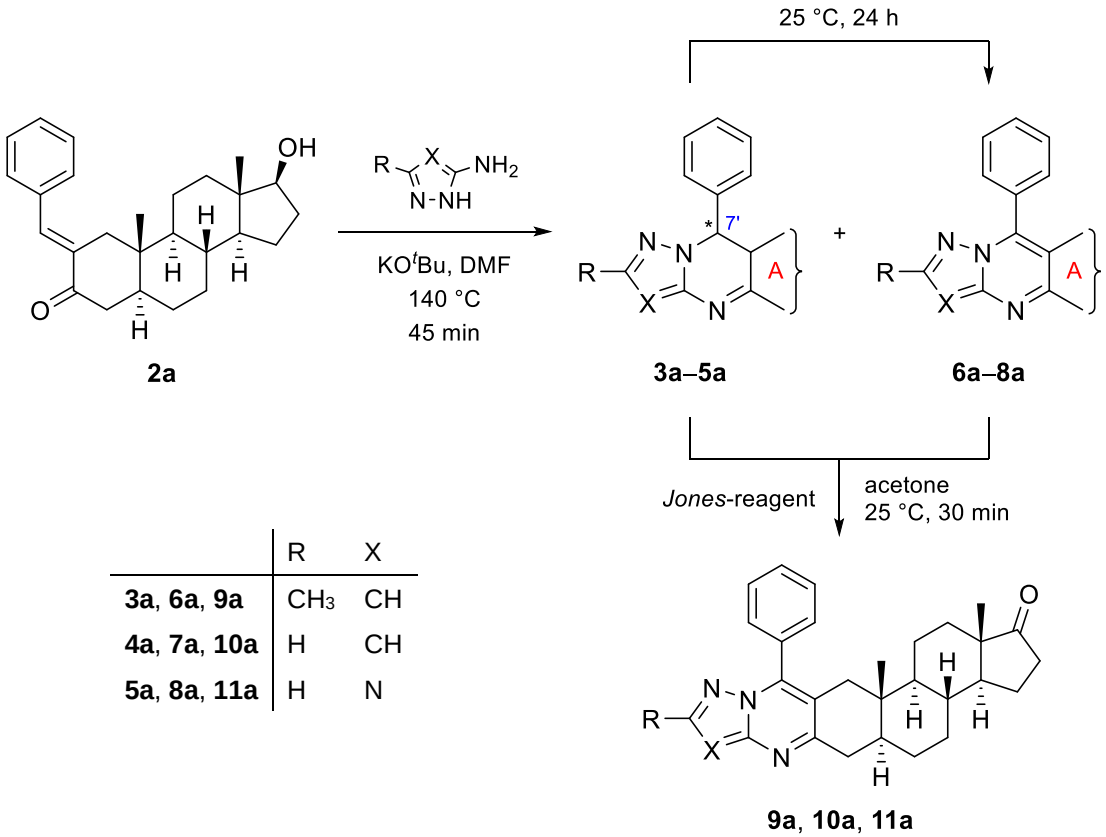
Scheme 1

3.2. By extending the *Claisen-Schmidt* reaction to other reactants, we found that the different electronic nature of the (hetero)arylaldehydes (**1b**–**k**) required various reaction conditions. For arylaldehydes (**1b**–**g**), reaction times depended on the quality of the substituent on the aromatic ring; for electron donating groups (CH_3, OMe), we found that longer reaction times were required at room temperature for the regioselective formation of the desired products (**2b**–**d**). For the reagents containing electron-withdrawing chlorine (**1f**) and bromine (**1g**) atoms, as well as for heteroaryl aldehydes **1h**–**j**, the increased reactivity necessitated the use of lower temperatures.

* The numbering of the compounds follows the numbering in the dissertation.

3.3. Our attempts to prepare the *p*-hydroxybenzylidene derivative (**2k**) in a similar manner were unsuccessful. We found, however, that the desired product could be obtained by protecting the aldehyde used with a methoxymethyl (MOM) group and then removing the protecting group with hydrochloric acid in aqueous methanol after the condensation reaction. The structure of the 2-(hetero)arylidene-DHT products was confirmed by ^{1}H- and ^{13}C-NMR measurements after purification by column chromatography, and the solid phase structure of **2a** was confirmed by single crystal X-ray diffraction (SXRD).

3.4. As model reactions, 2-benzylidene-DHT (**2a**) was then further converted in ring closure reactions using different aminoazole (3-aminopyrazole, 3AP, 3-amino-5-methylpyrazole, 3A5MP and 3-amino-1,2,4-triazole, 3AT) reagents. The optimized reaction conditions for the heterocyclizations were pointed out; in *N*,*N*-dimethylformamide (DMF) at 140 °C using potassium *tert*-butylate as a base, full conversion was observed within 45 min. The appearance of two new spots belonging to compounds more polar than **2a** was observed (TLC). In all three cases, the spot of to the less polar material belonged to the desired product (**6a**–**8a**) and the more polar one belonged to a mixture of two non-oxidized epimers of the latter (**3a**–**5a**) (*Scheme 2*).



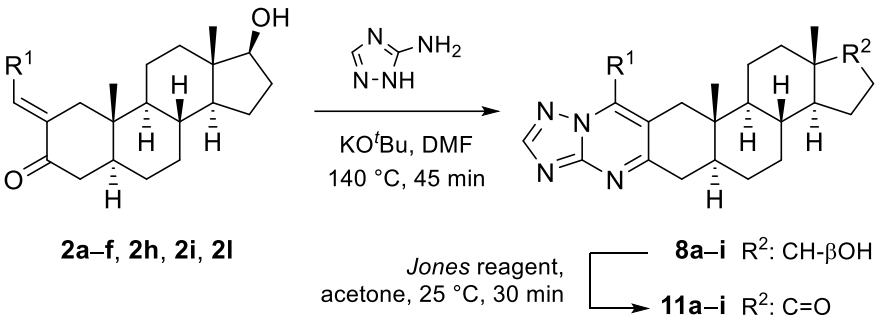
	R	X
3a, **6a**, **9a**	CH_3	CH
4a, **7a**, **10a**	H	CH
5a, **8a**, **11a**	H	N

Scheme 2

3.5. We have shown that stirring the reaction mixtures for a further 24 hours at room temperature results in the complete oxidation of the epimer mixture. We have pointed out that the treatment of the crude reaction mixtures with *Jones* reagent in acetone results in the oxidation of – in addition to the dihydropyrimidine ring – the 17β-hydroxyl group, and the corresponding 17-ones (**9a**–**11a**) were formed in moderate yields.

3.6. Attempts were also made to prepare the **8a** triazolo[1,5-*a*]pyrimidine in a one-pot, tricomponent reaction directly from DHT, but due to the approximately equal, in some cases inferior yields and the potential pharmacological activity of the α,β-enone products (**2a**–**k**) described previously, our studies on multicomponent reactions were discarded.

3.7. The (hetero)arylidene derivatives (**2a**–**f**, **2h**, **2i**, **2l**) were then used to prepare A-ring fused triazolo[1,5-*a*]pyrimidines under the optimized reaction conditions. In the reaction of **2f** carrying an electron-withdrawing chlorine atom on the benzene ring, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) was used as an oxidizing agent. The compound series was completed by the treatment of the crude reaction mixtures containing both **5** and **8** with *Jones* reagent, yielding 17-one derivatives (**11b**–**i**).

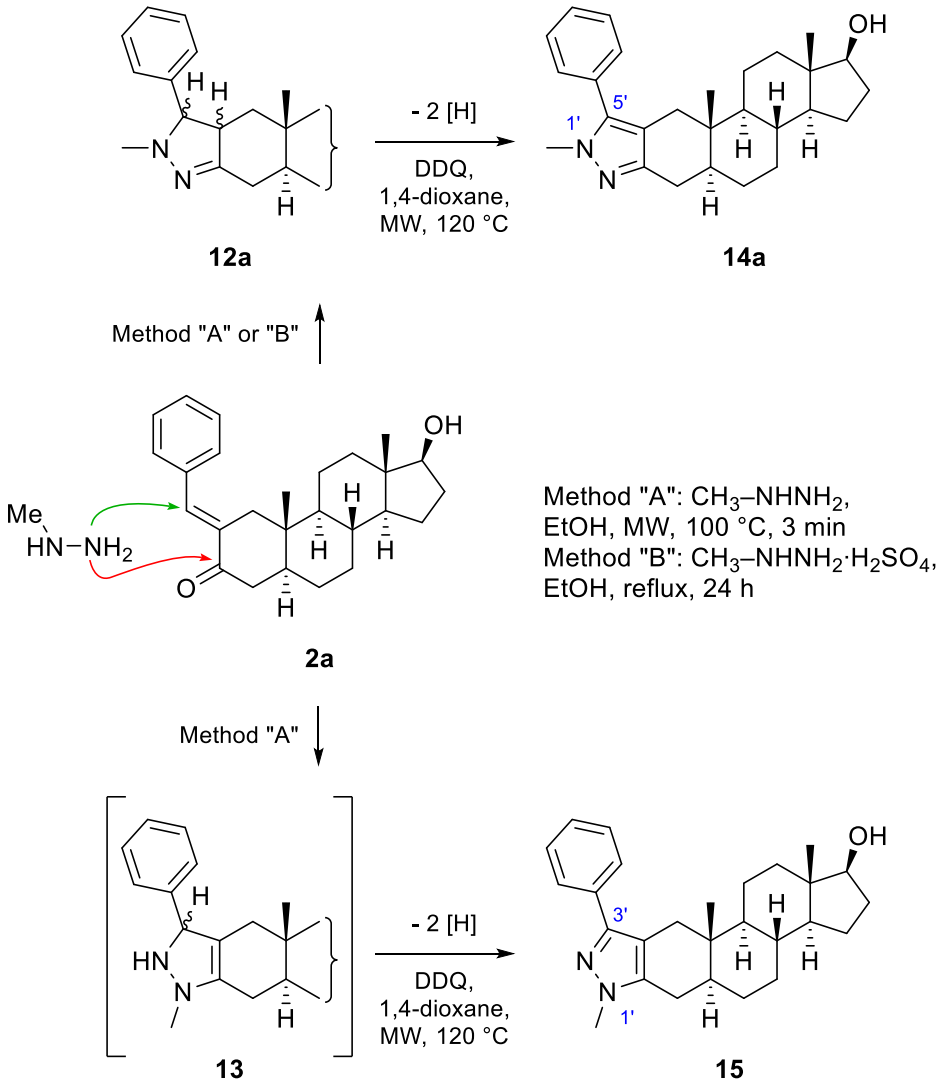


Enone	R^1	Product	Yield (%)	Product	Yield (%)
2a	Ph	**8a**	72	**11a**	59
2b	*p*-CH_3-C_6H_4	**8b**	76	**11b**	62
2c	m-CH_3-C_6H_4	**8c**	77	**11c**	66
2d	*p*-MeO-C_6H_4	**8d**	71	**11d**	59
2e	*p*-F-C_6H_4	**8e**	73	**11e**	57
2f	*p*-Cl-C_6H_4	**8f**	65	**11f**	62
2h	furan-2-yl	**8g**	59	**11g**	55
2i	tiophen-2-yl	**8h**	62	**11h**	57
2l	CH_3	**8i**	69	**11i**	52

Scheme 3

3.8. The solid phase crystal structure of a representative derivative bearing a thiophene ring (**8h**) was also confirmed by SXRD with the help of our collaborating partners. The single crystal was obtained by controlled evaporation of a solution of the compound from CH_2Cl_2/Et_2O.

3.9. The synthesis of disubstituted pyrazoles – regioisomers of those that have been previously synthesized in our research group – fused to the A-ring of the sterane backbone was achieved in ring-closing reactions of derivative **2a** with methylhydrazine. In ethanolic medium, using the free base of the reagent, in a MW reactor with an irradiation time of 3 min, four new spots were observed (Method "A"). Two of the four products were pyrazole regioisomers (**14a** and **15**) formed during heterocyclization and subsequent autooxidation, and two were diastereomeric pairs of the pyrazoline precursor (**12a**) of the main heteroaromatic product **14a** (*Scheme 4*). The structure of the compounds was confirmed by 1D- and 2D-NMR spectroscopy.

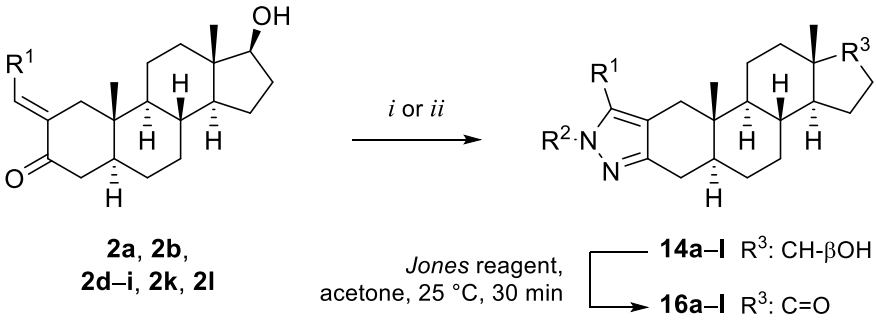


Scheme 4

3.10. To complete the partial spontaneous oxidation observed, an additional oxidation step was introduced before the purification of the reaction mixture. We have shown that the reaction with DDQ resulted in a mixture of the two possible pyrazole isomers (**14a** and **15**) with a ratio of about 2:1, which were easily separable by column chromatography. The **14a** derivative was obtained in moderate yield (57%).

3.11. Carrying out the reaction with methylhydrazine sulfate under conventional heating resulted in the sole formation of the thermodynamically more stable 1',5'-disubstituted pyrazole (**14a**), without the appearance of the diastereomeric pair of the pyrazoline precursor (**12a**) and the **15** pyrazole regioisomer (*Scheme 4*, Method "B").

3.12. In addition to product **14a**, the ring-closure of further arylidene derivatives (**2b**, **2d**–**i**, **2k**) and 2-ethylidene-DHT (**2l**) was also achieved according to Method "B". The corresponding 1',5'-pyrazole regioisomers (**14b**–**i**) were obtained in moderate to good yields (*Scheme 5*).



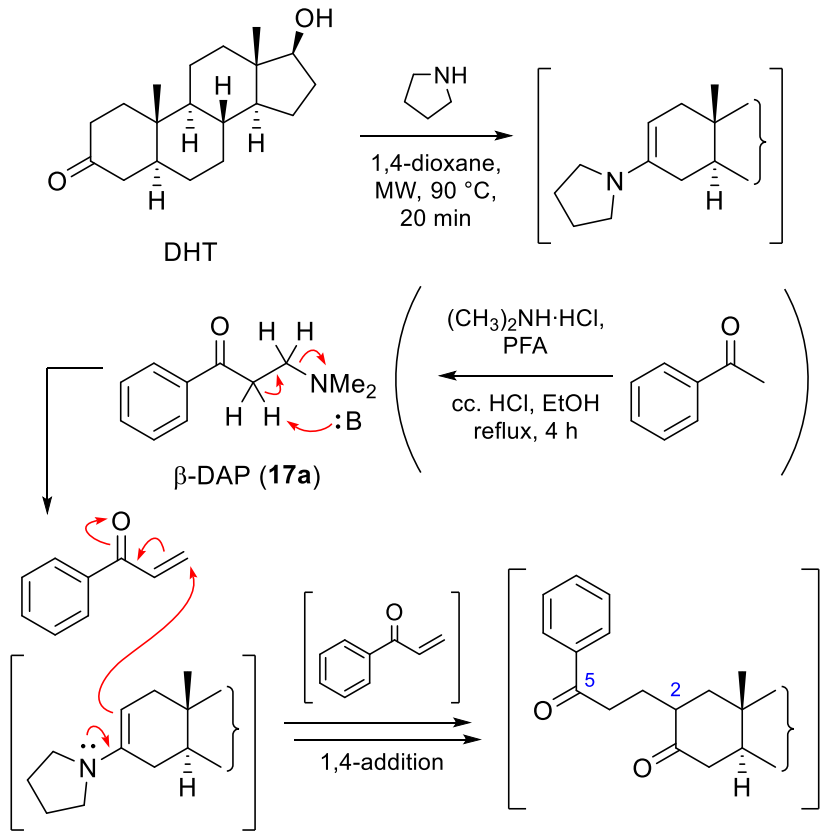
i) R_2–NH–NH_2·H_2SO_4, EtOH, reflux, 24 h (**14a–i**)
ii) R_2–NH–NH_2·HCl, I_2, EtOH, MW, 100 °C, 2 min (**14j–l**)

Enone	R^1	R^2	Product	Yield (%)	Product	Yield (%)
2a	Ph	CH_3	**14a**	80	**16a**	76
2b	*p*-CH_3-C_6H_4	CH_3	**14b**	81	**16b**	74
2d	*p*-MeO-C_6H_4	CH_3	**14c**	79	**16c**	74
2e	*p*-F-C_6H_4	CH_3	**14d**	66	**16d**	60
2f	*p*-Cl-C_6H_4	CH_3	**14e**	69	**16e**	64
2g	*p*-Br-C_6H_4	CH_3	**14f**	63	**16f**	57
2h	furan-2-yl	CH_3	**14g**	52	**16g**	46
2i	tiophen-2-yl	CH_3	**14h**	58	**16h**	53
2l	CH_3	CH_3	**14i**	60	**16i**	54
2a	Ph	Ph	**14j**	84	**16j**	95
2f	*p*-Cl-C_6H_4	Ph	**14k**	79	**16k**	91
2k	*p*-OH-C_6H_4	Ph	**14l**	90	**16l**	91

Scheme 5

3.13. Although spontaneous oxidation was observed in most cases, in the case of derivatives (**2e**–**g**) bearing halogen substituents on the benzene ring, oxidation was completed using DDQ. By treating the crude products with *Jones* reagent, we also added 17-ones (**16a**–**i**) to the compound library. The oxidative ring-closure reactions of three representative α,β-enones (**2a**, **2f**, **2k**) were also carried out with phenylhydrazine hydrochloride using MW irradiation.

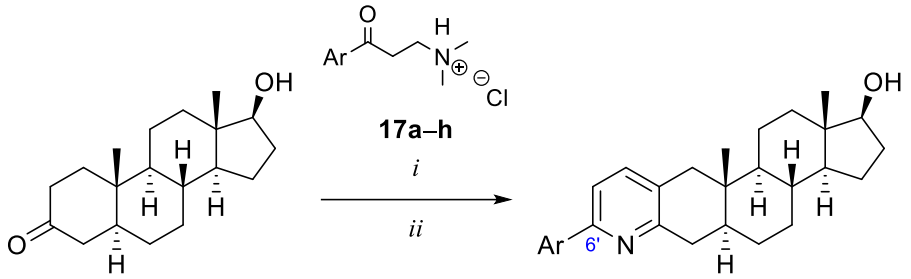
3.14. By the modification of the A-ring of DHT with 3-(dimethylamino)propyophenone hydrochloride (β-DAP, **17a**), a 1,5-diketone moiety was formed at the C-2 position regioselectively. The reaction parameters were optimized, and the desired product was prepared via an *in situ* formed pyrrolidine enamine in 1,4-dioxane under MW irradiation (*Scheme 6*).



Scheme 6

3.15. By the evaporation of the crude product, dissolving the residue in ethanol and carrying out the heterocyclization using MW irradiation, the 6'-phenylpyridine derivative (**18a**) was obtained in good yield (81%). Its structure was verified by ESI-MS, ^{1}H- and ^{13}C-NMR spectroscopy and single crystal X-ray diffraction using a single crystal obtained by controlled evaporation from dichloromethane.

3.16. *Mannich* salts (**17b**–**h**) were prepared from aryl methyl ketones bearing substituents with different electronic properties on the aromatic ring, and the compounds were converted to 1,5-diketone intermediates formed from DHT. In ring-closure reactions with hydroxylamine hydrochloride, 6'-monosubstituted pyridine derivatives were prepared in moderate to good yields, independently of the electronic nature of the substituent of the aromatic ring (**18a**–**h**, *Scheme 7*).

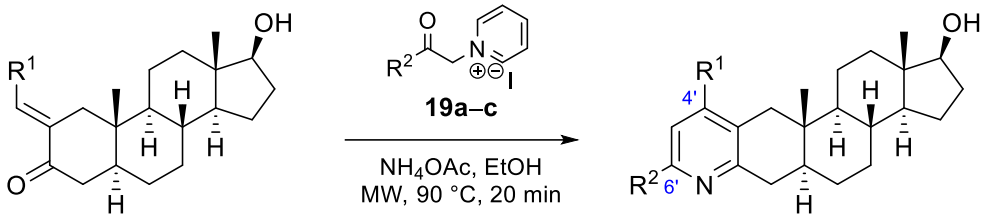


i) pyrrolidine, 1,4-dioxane, MW, 120 °C, 20 min
ii) HO–NH_2·HCl, EtOH, MW, 90 °C, 10 min

Mannich salt	Ar	Product	Yield (%)
17a	Ph	**18a**	81
17b	*p*-CH_3-C_6H_4	**18b**	70
17c	*p*-MeO-C_6H_4	**18c**	79
17d	*p*-NO_2-C_6H_4	**18d**	72
17e	*p*-F-C_6H_4	**18e**	80
17f	*p*-Cl-C_6H_4	**18f**	72
17g	*p*-Br-C_6H_4	**18g**	78
17h	*o*-OH-C_6H_4	**18h**	67

Scheme 7

3.17. Based on the preliminary pharmacological results, the synthesis of analogues substituted at both the C-6' and C-4' positions was also presented utilizing the 2-ethylidene (**2l**) and 2-benzylidene derivative (**2a**) and compounds bearing halogen substituents (**2e**–**g**). 1-(2-oxo-2-phenylethyl)pyridinium iodide salt (**19a**) and its analogues (**19b**, **19c**) were prepared by *Ortoleva-King* reactions. We found that by optimizing classical *Kröhnke* conditions, performing the heterocyclizations in ethanol, using a large excess of ammonium acetate and MW irradiation, reaction times could be reduced to 20 min. Systematically combining derivatives **2a**, **2e**–**g** and **2l** with *Kröhnke* salts (**19a**–**c**), 15 heterocyclic products – variously substituted at the C-6' and C-4' positions – were obtained in moderate to good yields, independently of the electronic nature of the reagents and reactants used (**20a**–**20o**, *Scheme 8*).

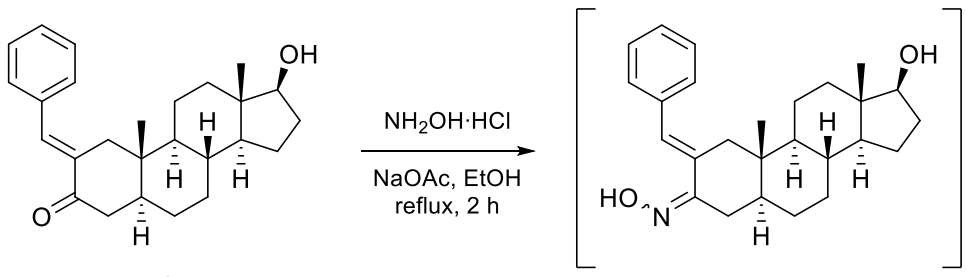


2a, **2e–g**, **2l** **20a–o**

Enone	R^1	*Kröhnke* salt	R^2	Product	Yield (%)
		19a	Ph	**20a**	72
2l	CH_3	**19b**	*o*-OH-C_6H_4	**20b**	65
		19c	pyridin-2-yl	**20c**	71
		19a	Ph	**20d**	77
2a	Ph	**19b**	*o*-OH-C_6H_4	**20e**	76
		19c	pyridin-2-yl	**20f**	82
		19a	Ph	**20g**	67
2e	*p*-F-C_6H_4	**19b**	*o*-OH-C_6H_4	**20h**	59
		19c	pyridin-2-yl	**20i**	68
		19a	Ph	**20j**	73
2f	*p*-Cl-C_6H_4	**19b**	*o*-OH-C_6H_4	**20k**	70
		19c	pyridin-2-yl	**20l**	77
		19a	Ph	**20m**	52
2g	*p*-Br-C_6H_4	**19b**	*o*-OH-C_6H_4	**20n**	51
		19c	pyridin-2-yl	**20o**	54

Scheme 8

3.18. 2-Benzylidene-DHT (**2a**) was reacted with hydroxylamine hydrochloride in ethanol in the presence of sodium acetate as a first step of forming isoxazole heterocycles fused to the A-ring of DHT at the 2,3-position. After two hours, complete conversion and the appearance of two new spots on the TLC was observed, presumably corresponding to isomers (*Z*) and (*E*) (*Scheme 9*). The isolation of the ketoxime intermediate was not carried out, and after the work-up, the residual oil was subjected to a tandem oxidative ring-closure reaction.

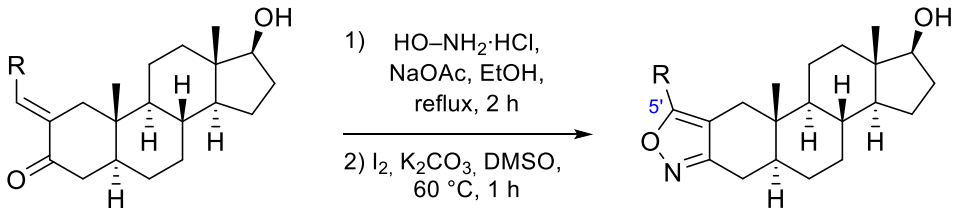


2a

Scheme 9

3.19. Oxidative cyclization was carried out using 1,2 equivalents of elemental iodine in dimethyl sulfoxide, using potassium carbonate as a base. Besides the disappearance of the ketoxime isomers, a new spot with a higher R_f value appeared on the TLC. We showed that the ring-closure reaction could be carried out within 1 h by stirring at 60 °C. After work-up, the final product was purified by column chromatography to give the 5'-substituted isoxazole derivative in two steps in moderate yield (**21a**, 62%, *Scheme 10*).

3.20. The iodine-mediated reaction pathway for the oxidative intramolecular C-O bond formation was further extended to nine additional α,β-enones (**2b**, **2d**–**j**, **2l**), and 5'-substituted isoxazole products (**21b**–**j**) were obtained in two steps without the purification of the ketoxime intermediates (*Scheme 10*).



2a, **2b**, **2d–j**, **2l** **21a–j**

Enone	R	Product	Yield (%)
2a	Ph	**21a**	62
2b	*p*-CH_3-C_6H_4	**21b**	67
2d	*p*-MeO-C_6H_4	**21c**	64
2e	*p*-F-C_6H_4	**21d**	68
2f	*p*-Cl-C_6H_4	**21e**	71
2g	*p*-Br-C_6H_4	**21f**	61
2h	furan-2-yl	**21g**	54
2i	tiophen-2-yl	**21h**	67
2j	pyridin-2-yl	**21i**	55
2l	CH_3	**21j**	55

Scheme 10

3.21. The antiandrogenic activity of the derivatives prepared was tested by our collaborators at the Palacký University in the Czech Republic. Some derivatives were shown to be able to suppress AR transactivation in a dose-dependent manner and to be able to inhibit the expression of AR-regulated proteins. Certain 5'-aryl-1'-methylpyrazoles were shown to be potent antagonists. D-ring oxidized analogues of these compounds were generally less potent than their 17β-OH analogues. The activity of 5'-(4"-bromophenyl)-1'-methylpyrazole (**16f**) was also tested in *ex vivo* cultures with promising results. For some representative derivatives, flexible docking studies were also carried out to describe the proposed binding mode.

4. Scientific publications directly related to the Ph.D. Thesis (MTMT identifier: 10068924)

1. **Márton A. Kiss**, Miroslav Peřina, Laura Bereczki, Ádám Baji, Jakub Bělíček, Radek Jorda, Éva Frank
   Dihydrotestosterone-based A-ring-fused pyridines: Microwave-assisted synthesis and biological evaluation in prostate cancer cells compared to structurally related quinolines
   The Journal of Steroid Biochemistry and Molecular Biology, **2023**, 231, 106315.

   IF = 4,100*

2. Miroslav Peřina, **Márton A. Kiss**, Gergő Mótyán, Eva Szczyrbová, Martin Eliáš, Vladimír Študent jr, Daniela Kurfürstová, Markéta Kovalová, Lukáš Mada, Jan Bouchal, Éva Frank, Radek Jorda
   A-ring-fused pyrazoles of dihydrotestosterone targeting prostate cancer cells via the downregulation of the androgen receptor
   European Journal of Medicinal Chemistry, **2023**, 249, 115086.

   IF = 6,700*

3. **Márton A. Kiss**, Miroslav Peřina, Václav Bazgier, Nóra V. May, Ádám Baji, Radek Jorda, Éva Frank
   Synthesis of dihydrotestosterone derivatives modified in the A-ring with (hetero)arylidene, pyrazolo[1,5-*a*]pyrimidine and triazolo[1,5-*a*]pyrimidine moieties and their targeting of the androgen receptor in prostate cancer
   The Journal of Steroid Biochemistry and Molecular Biology, **2021**, 211, 105904.

   IF = 5,011

Total IF = 15,811*

5. Other scientific publications

1. Yvette Szabó, **Márton A. Kiss**, Zoltán Kónya, Ákos Kukovecz, István Pálinkó, Pál Sipos, Éva Frank, Márton Szabados
   Microwave-induced base-catalyzed synthesis of methyl levulinate, a further improvement in dimethyl carbonate-mediated valorization of levulinic acid
   Applied Catalysis A: General, **2023**, 651, 119020.

   IF = 5,500*

2. Tatsiana V. Petrasheuskaya, Debora Wernitznig, **Márton A. Kiss**, Nóra V. May, Dominik Wenisch, Bernhard K. Keppler, Éva Frank, Éva A. Enyedy
   Estrone–salicylaldehyde *N*-methylated thiosemicarbazone hybrids and their copper complexes: solution structure, stability and anticancer activity in tumour spheroids
   Journal of Biological Inorganic Chemistry, **2021**, 26, 775–791.

   IF = 3,862

3. Éva A. Enyedy, Tatsiana V. Petrasheuskaya, **Márton A. Kiss**, Debora Wernitznig, Dominik Wenisch, Bernhard K. Keppler, Gabriella Spengler, Nóra V. May, Éva Frank, Orsolya Dömötör
   Complex formation of an estrone-salicylaldehyde semicarbazone hybrid with copper(II) and gallium(III): Solution equilibria and biological activity
   Journal of Inorganic Biochemistry, **2021**, 2230, 111468.

   IF = 4,336

4. Tatsiana V. Petrasheuskaya, **Márton A. Kiss**, Orsolya Dömötör, Tamás Holczbauer, Nóra V. May, Gabriella Spengler, Annamária Kincses, Ana Čipak Gašparović, Éva Frank, Éva A. Enyedy
   Salicylaldehyde thiosemicarbazone copper complexes: impact of hybridization with estrone on cytotoxicity, solution stability and redox activity
   New Journal of Chemistry, **2020**, 44, 12154–12168.

   IF = 3,591

5. Orsolya Dömötör, **Márton A. Kiss**, G. Tamás Gál, Nóra V. May, Gabriella Spengler, Márta Nové, Ana Čipak Gašparović, Éva Frank, Éva A. Enyedy
   Solution equilibrium, structural and cytotoxicity studies on Ru(η^6-*p*-cymene) and copper complexes of pyrazolyl thiosemicarbazones
   Journal of Inorganic Biochemistry, **2020**, 202, 110883.

   IF = 4,155

6. Gergő Mótyán, László Mérai, **Márton A. Kiss**, Zsuzsanna Schelz, Izabella Sinka, István Zupkó, Éva Frank
   Microwave-assisted synthesis of biologically relevant steroidal 17-*exo*-pyrazol-5'-ones from a norpregnene precursor by a side-chain elongation/heterocyclization sequence
   Beilstein Journal of Organic Chemistry, **2018**, 14, 2589–2596.

   IF = 2,595

Total IF = 24,039*

6. Lectures and posters related to the Ph.D. Thesis

1. **Márton A. Kiss**, Éva Frank
   Potenciális antiandrogének előállítása a dihidrotesztoszteron A-gyűrűjének szerkezetmódosításával
   MTA Szteroid- és Terpenoidkémiai Munkabizottsági ülés, online, 28 November 2022.

2. **Márton A. Kiss**, Éva Frank
   A DHT A-gyűrűjéhez kondenzált nitrogéntartalmú heterociklusok szintézise
   MTA Szteroid- és Terpenoidkémiai Munkabizottsági ülés, online, 6 December 2021.

3. **Márton A. Kiss**, Éva Frank
   Pirazolo- és triazolopirimidin szteroid hibrid vegyületek előállítása
   A Szegedi Ifjú Szerves Kémikusok Támogatásáért Alapítvány előadóülése, online, 18 May 2020.

7. Other lectures and posters

1. Tamás Pivarcsik, **Márton A. Kiss**, Uroš Rapuš, Hilda Kovács, Éva Frank, Iztok Turel, Éva A. Enyedy
   Complexes formed with $[Ru(\eta^6\text{-}p\text{-cymene})(Cl)_2]_2$, $[Rh(\eta^5\text{-}C_5Me_5)(Cl)_2]_2$ and $[Re(Cl)(CO)_5]$ organometallic cations of sterane-based ligands bearing (*N*,*N*) donor set
   3rd European NECTAR Conference, Ljubljana, Slovenia, 24–26 Augustus 2022. (poster presentation)

2. Tatsiana V. Petrasheuskaya, **Márton A. Kiss**, Nóra V. May, Gabirella Sengler, Peter Rapta, Éva Frank, Éva A. Enyedy
   Comparative solution study on the interactions of Cu(II), Fe(II/III) and Ni(II) with imidazole-derived thiosemicarbazones: impact of methylation, redox and anticancer activity
   16th European Biological Inorganic Chemistry Conference (EuroBIC-16), Grenoble, France, 17–21 July 2022. (poster presentation)

3. Tatsiana V. Petrasheuskaya, **Márton A. Kiss**, Debora Wernitznig, Dominik Wenisch, Bernhard K. Keppler, Nóra V. May, Éva Frank, Éva A. Enyedy
   Estrone-salicylaldehyde *N*-methylated-thiosemicarbazone hybrids and their copper complexes: solution study and anticancer activity in tumor spheroids
   International Symposium Thermodynamics of Metal Complexes, *ISMEC*, Białystok, Poland, 16–18 June 2021. (poster presentation)

4. Tatsiana V. Petrasheuskaya, **Márton A. Kiss**, Orsolya Dömötör, Gabirella Spengler, Debora Wernitznig, Bernhard K. Keppler, Nóra V. May, Éva Frank, Éva A. Enyedy
   Rákellenes tioszemikarbazon – ösztron hibridvegyületek és rézkomplexeik
   54. Komplexkémiai Kollokvium és Koordinációs Kémiai Munkabizottsági ülés, online, 26–27 May 2021.

5. Tatsiana V. Petrasheuskaya, Debora Wernitznig, **Márton A. Kiss**, Nóra V. May, Dominik Wenisch, Bernhard K. Keppler, Éva Frank, Éva A. Enyedy
   Effects of stepwise terminal NH_2-methylation of estrone-salicylaldehyde-thiosemicarbazone and copper coordination, solution speciation, anticancer activity and redox activity
   26th International Symposium on Analytical and Environmental Problems, Szeged, Hungary, 23–24 November 2020. (poster presentation)

6. Tatsiana V. Petrasheuskaya, **Márton A. Kiss**, Orsolya Dömötör, Debora Wernitznig, Dominik Wenisch, Gabriella Spengler, Annamária Kincses, Nóra V. May, Bernhard K. Keppler, Éva Frank, Éva A. Enyedy
   Comparative solution study on estrone salicyladehyde (thio)semicarbazones and their copper complexes: impact of hbydridization and methylation
   XLIII. Chemistry Days, Szeged, Hungary, 27–28 October 2020.

7. Tatsiana V. Petrasheuskaya, **Márton A. Kiss**, Orsolya Dömötör, Gabriella Spengler, Annamária Kincses, Nóra V. May, Éva Frank, Éva A. Enyedy
Synthesis, solution stability and anticancer activity of copper complexes formed with salicylaldehyde thiosemicarbazone-estrone conjugates
MTA Steroid and Terpenoid Chemistry working group meeting, Szeged, Hungary, 22 November 2019.

8. Tatsiana V. Petrasheuskaya, Orsolya Dömötör, Gabriella Spengler, Annamária Kincses, Nóra V. May, **Márton A. Kiss**, Éva Frank, Éva A. Enyedy
Antitumor copper complexes of salicylaldehyde thiosemicarbazones: Solution chemistry and biological acitivity
XLII. Chemistry Days, Szeged, Hungary, 28–30 October 2019.

9. Orsolya Dömötör, G. Tamás Gál, Nóra V. May, Gabriella Spengler, **Márton A. Kiss**, Éva Frank, Éva A. Enyedy
Studies on copper(II) and organoruthenium(II) complexes of pyrazolo-thiosemicarbazones: anticancer activity, structure and stability
International Symposium of Metal Complexes 2019, Debrecen, Hungary, 11–14 June 2019. (poster presentation)

10. Tatsiana V. Petrasheuskaya, Orsolya Dömötör, Gabriella Spengler, Annamária Kincses, **Márton A. Kiss**, Éva Frank, Éva A. Enyedy
Copper(II) complexes of salicylaldehyde thiosemicarbazone and its sterane-based conjugate: solution stability, redox properties and cytotoxicity
International Symposium of Metal Complexes 2019, Debrecen, Hungary, 11–14 June 2019. (poster presentation)

11. Orsolya Dömötör, Tatsiana V. Petrasheuskaya, G. Tamás Gál, Nóra V. May, Márta Nové, Annamária Kincses, Gabriella Spengler, Ana Čipak Gašparović, **Márton A. Kiss**, Éva Frank, Éva A. Enyedy
Pirazolo- és szaliciladehid-tioszemikarbazon ligandumok Cu(II) és Ru(II)(*p*-cimol) komplexei: szintézis, rákellenes aktivitás, stabilitás és szerkezet
53. Komplexkémiai Kollokvium, Velence, Magyarország, 21–23 May 2019.

12. **Márton A. Kiss**, Éva Frank
Potenciálisan rákellenes hatású komplexképző (tio)szemikarbazon ligandumok szintézise
XXXIV. Országos Tudományos Diákköri Konferencia, Budapest, Magyarország, 23 March 2019.

13. **Márton A. Kiss**, Éva Frank
Potenciálisan rákellenes hatású komplexképző (tio)szemikarbazon ligandumok szintézise
XLI. Kémiai Előadói Napok, Szeged, 15–17 October 2018.

14. **Márton A. Kiss**, Ágnes Zsigmond
Metal-Free Organophotoredox Catalysis with Visible Light
1st Hungarian-Norwegian Summer School on Bioactive Substance Research, Tromsø, Norvégia, 11–26 July 2016.

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