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ZVEAGHINȚEVA MARINA

SYNTHESIS AND STUDY OF 1-(1*H*-1,2,4-TRIAZOL-1-YL)ETHAN-2-ONES

143.01 – ORGANIC CHEMISTRY

Summary of the doctoral dissertation in chemical sciences

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Doctoral adviser:

MACAEV Fliur – habilitated doctor of chemical sciences, professor, corresponding member of the ASM

Members of the specialized scientific council:

ARÎCU Aculina	habilitated doctor of chemical sciences, associate professor, Institute of Chemistry, Moldova State University – *chairman*
GORINCIOI Elena	doctor of chemical sciences, associate professor, Institute of Chemistry, Moldova State University – *scientific secretary*
UNGUR Nicon	habilitated doctor of chemical sciences, associate professor, Institute of Chemistry, Moldova State University – *member*
STURZA Rodica	habilitated doctor of chemical sciences, professor, corresponding member of the ASM, Technical University of Moldova – *member*
KULCIȚKI Veaceslav	habilitated doctor of chemical sciences, associate professor, Institute of Chemistry, Moldova State University – *member*
CIOCÂRLAN Alexandru	doctor of chemical sciences, associate professor, Institute of Chemistry, Moldova State University – *member*
GUȚU Iacob	habilitated doctor of chemical sciences, professor, Moldova State University – *referent*
GUREV Angela	doctor of chemical sciences, associate professor, Technical University of Moldova – *referent*

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The doctoral thesis and summary can be consulted in the Central Scientific Library „*Andrei Lupan*” and on the website of the ANACEC (http://www.cnaa.md/) and on the USM website (http://usm.md/).

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Doctoral adviser:
MACAEV Fliur, habilitated doctor of chemical sciences,
professor, corresponding member of the ASM

Author:

Zveaghintseva Marina:

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CONCEPTUAL FRAMEWORK OF THE RESEARCH

The actuality and significance of the topic.

It is known that during the formation of a structural combination of organic substances involving heterocyclic compounds, various types of molecular interactions arise. These interactions determine unique properties that manifest both in their specific reactivity and in the realm of practical applications. Studies of 1,2,4-triazoles are due to their wide distribution among both synthetic and natural substances. One notable aspect of the chemistry of substituted 1*H*-1,2,4-triazoles is the wide range of structures they exhibit, leading to diverse properties, which also encompass biological effects. In this context, it is necessary to develop convenient and efficient methods for the synthesis of both known 1*H*-1,2,4-triazoles and new derivatives. The uniqueness of these compounds is associated with the presence of several reaction centers in their molecule, which allows their involvement in numerous transformations leading to a wide range of polyfunctional products of aliphatic and heterocyclic series. In addition to broad synthetic and applied prospects, alkyl/aryl substituted (1*H*-1,2,4-triazol-1-yl)ethan-2-ones can be considered as convenient objects for studying a number of theoretical problems: mutual influence of the substituted group and 1*H*-1,2,4-triazole cycle, reactivity and chemoselectivity, substitution, rearrangement and addition reactions. This underscores the significance of the subject matter being investigated in the current study.

The goal of the work:

The goal of this work is to develop methods for the synthesis of new (1*H*-1,2,4-triazol-1-yl)ethan-2-ones, and to study their structure and properties.

The main tasks of the work:

In accordance with the aim of the thesis the following tasks were defined: development of simple and efficient schemes for the synthesis of new alkyl/aryl-substituted (1*H*-1,2,4-triazol-1-yl)ethanones based on 1*H*-1,2,4-triazole and 2-halogen-1-(alkyl/aryl)ethan-2-ones;

study of the interaction reaction of synthesized alkyl/aryl-substituted (1*H*-1,2,4-triazol-1-yl)ethan-2-ones with aromatic aldehydes under Knoevenagel reaction conditions;

development of synthesis routes and study of properties of salts of alkyl/aryl-substituted (1*H*-1,2,4-triazol-1-yl)ethan-2-ones;

determination of optimal conditions for the preparation of unsaturated compounds with a given configuration of double bonds and the use of the latter for the construction of the carbon-heteroatom bond of cyclic derivatives in reactions of addition, elimination and salt formation;

preparation of hybrid materials with participation of 2-tret-butyl-3-(1*H*-1,2,4-triazol-1-yl)-2H-chromen-2-ol, dehydroabietinic acid and *β*-cyclodextrin;

evaluation of the "structure-bioactivity" relationship in a series of synthesized alkyl/aryl substituted (1*H*-1,2,4-triazol-1-yl)ethan-2-ones.

The research hypothesis.

The studies of this work were based on the supposed possibility of selective preparation of alkyl/aryl substituted derivatives of (1*H*-1,2,4-triazol-1-yl)ethan-2-ones, with the notable structural characteristic of having an activated methylene group in conjugation with a carbonyl function. Upon interaction with alcohols, it can lead to the formation of semiketals, causing asymmetry in the carbon atom of the carbonyl group. On the other hand, the interaction of quaternary salts of (1*H*-1,2,4-triazol-1-yl)ethan-2-ones with deprotonated 3-(2-oxo-2-phenylethylidene)indolin-2-one can lead to the formation of reactive pinacolin or NH_2^+ carbocations, eventually opening a new route to substituted indolin-2-ones. The reaction of conjugated addition of hydrazine hydrate, depending on the medium can lead to cycloaddition products and be accompanied by a cleavage reaction by the mechanism of bimolecular elimination E_2 to form the most substituted alkene (Zaitsev's rule) or cleavage of quaternary ammonium salts to form the least substituted alkene (Hoffman's rule).

Selected research methods review and justification.

Fine organic synthesis techniques were employed in this study, guided by the specific aims of investigating the selectivity of the alkylation reaction of 1H-1,2,4-triazole to produce related derivatives containing alkyl/arylethane-2-one fragments. Additionally, a strategy was developed for the single-reactor synthesis of new polycyclic heterosystems using these derivatives, utilizing the conditions of the Knoevenagel reaction. Expanding the application of *β*-cyclodextrin and dihydroabietinic acid, in combination with synthesized (1*H*-1,2,4-triazol-1-yl)ethan-2-ones, for the preparation of micro- and nanoscale hybrid materials in order to study the relationship between structure and biological activity.

TLC was used to monitor the progress of the reaction and the purity of the products. The synthesized alkyl/aryl substituted (1*H*-1,2,4-triazol-1-yl)ethan-2-ones were isolated by column chromatography and recrystallization. A number of physicochemical analytical methods such as infrared spectroscopy, NMR spectroscopy, X-ray diffraction analysis, elemental analysis, and high-performance liquid chromatography were used to establish the structure and determine the purity of the chemical compounds.

PAPER SUMMARY

INTRODUCTION includes the justification of the research topic relevance, the research purpose and main tasks, the research hypothesis, an overview and justification of the selected research methods, as well as paper summary.

1. ANALYSIS OF KNOWN METHODS OF SYNTHESIS OF SUBSTITUTED 1*H*-1,2,4-TRIAZOLES AND PATHWAYS OF THEIR TRANSFORMATIONS

This chapter is devoted to the literature data review on the preparation of substituted 1*H*-1,2,4-triazoles and the routes of their transformations. It describes the main methods of synthesis of substituted 1*H*-1,2,4-triazoles: cyclization of precursors and modern methods of alkylation of 1,2,4-triazoles and its derivatives.

2. SYNTHESIS OF SUBSTITUTED 1-(1*H*-1,2,4-TRIAZOL-1-YL)ETHAN-2-ONES OF LINEAR STRUCTURE

A notable aspect of the chemistry of substituted 1,2,4-triazoles is the remarkable diversity in their structurs. In the current phase, the objective is to establish effective methods for synthesizing substituted 1-(1H-1,2,4-triazol-1-yl)ethan-2-ones. These methods offer a significant advantage, as they capitalize on the accessibility of precursor compounds such as 1H-1,2,4-triazole, 4-amino-1H-1,2,4-triazole [1-4], and alkylating reagents.

2.1 Synthesis and properties of 4-amino-1*H*-1,2,4-triazole salts

Five-membered heterocycles containing nitrogen or oxygen atoms are known to be structural fragments of a number of natural and synthetic compounds and biologically active substances. Of interest are compounds containing fragments of several biologically active classes such as oxindoles and furans. The task was set to investigate the possibility of obtaining salts of 4-amino-1*H*-1,2,4-triazole and use them as a reagent for the synthesis of oxindole derivatives under the conditions of 1,3-dipolar cycloaddition reaction [5,6].

To this end, 4-amino-1-(3,3-dimethyl-2-oxobutyl)-4*H*-1,2,4-triazole-1-ium chloride **2**, 4-amino-1-methyl-4*H*-1,2,4-triazole-1-ium iodide **3** were prepared by interaction of 4-amino-1,2,4-triazole **1** with 1-chloropinacolone and methyl iodide in 86% and 64% yield, respectively (Figure 2.1.) [7-11].

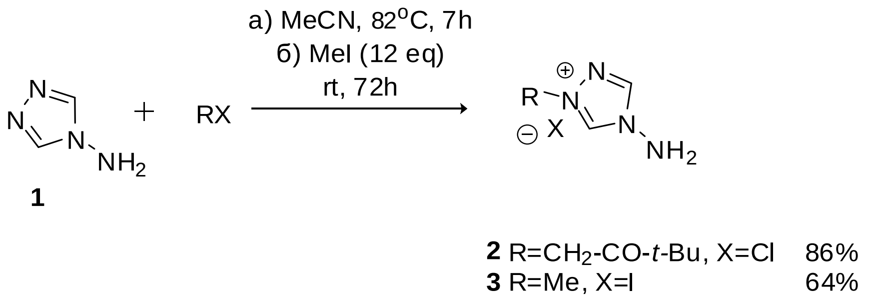


Fig. 2.1 Scheme for obtaining of 4-amino-1,2,4-triazole salts

In this work, the possibility of using the first synthesized salts **2** and **3** for functionalization of biologically active phenocylidene oxindoles **4a**, **b** [12,13] was investigated.

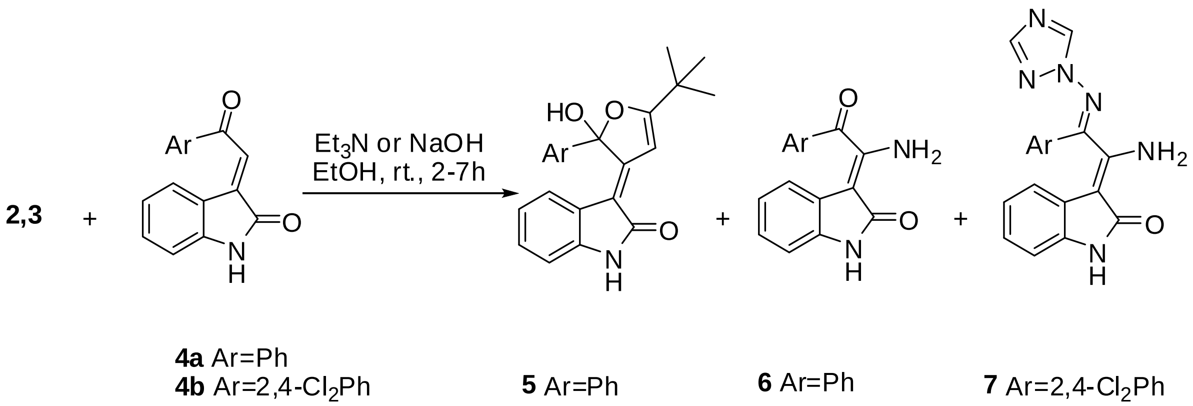
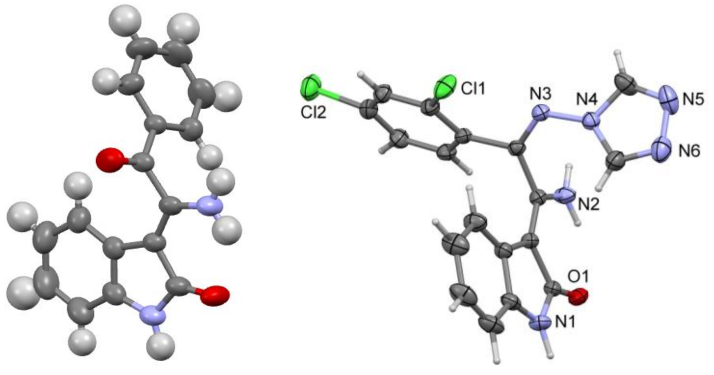


Fig. 2.2 Scheme for obtaining of 3-pyrrole functionalized oxindoles

Upon stirring an ethanol solution containing a combination of enone **4a** and salt **2** with triethylamine, a mixture of products was generated. Through chromatographic separation, compounds **5** and **6** were successfully isolated, yielding 14% and 5%, respectively (Fig. 2.2). By substituting chloride 2 with iodide 3 and Et_3N with NaOH, the yield of amine **6** increased to 20%. The interaction between iodide **3** and compound **4b** similarly yielded a complex mixture of difficult to separate substances, ultimately leading to the isolation of crystalline compound **7** with a yield of 20%.

The crystal and molecular structures of compounds **6**,**7** are shown in Figure 2.3.



6 7

Fig. 2.3 Crystal structure of compounds 6 and **7**

Thus, it is shown that within the suggested reaction conditions (Fig. 2.4) compounds of the oxindole series containing in their molecules a substituted dihydrofuran cycle substance **5**, amino derivative **6** or triazolylimine group substance **7** are formed. The formation of these compounds likely arises from the initial deprotonation of the oxindole fragment with the formation of a negative charge on the nitrogen atom, which is transferred to the methyl carbon of 3-phenocylidene-oxindole through a conjugated system of double bonds.

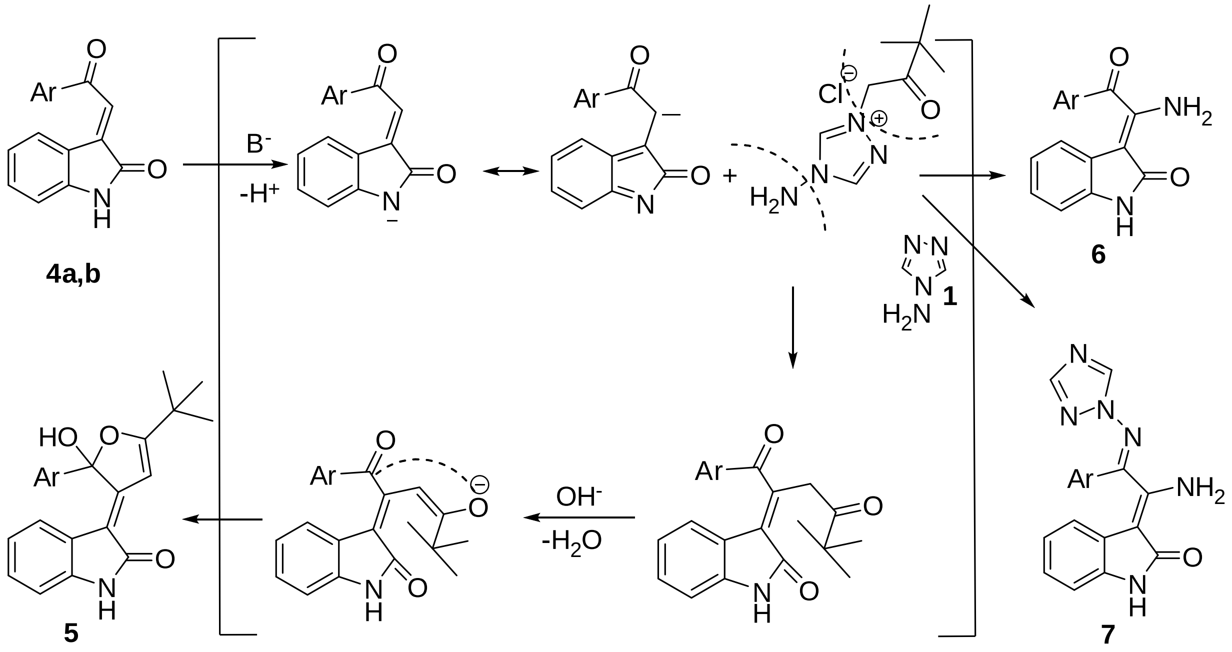
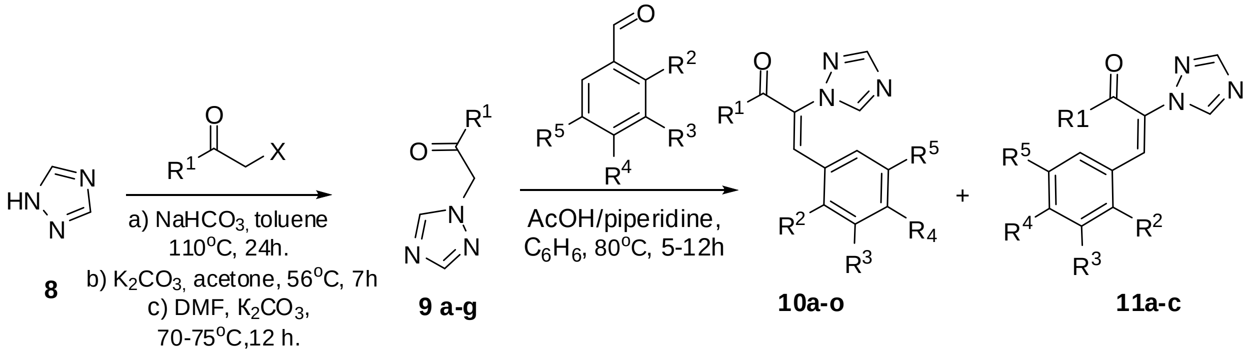


Fig.2.4 Possible reaction mechanism

When the "anion" attacks the triazolium salt, the carbcation of the pinacolinic group or the NH_2^+ cation is detached and the above-mentioned derivatives are formed. In the case of the pinacolinic group, the product of the addition is a ketone, which in alkaline medium is enolized to form a five-membered oxygen-containing cycle.

2.2 Synthesis of 1-substituted (1*H*-1,2,4-triazol-1-yl)ethan-2-on

A distinctive feature of 1-(1*H*-1,2,4-triazol-1-yl)ethan-2-ones is the presence of an activated CH_2-group, which makes the chemical transformations and synthetic possibilities of these substances very diverse, whereas in the reviewed period of time the main focus was on reactions involving the keto group. In this section, emphasis was placed on the transformations of commercially available 1-*H*-1,2,4-triazole **8** into versatile 1-(1*H*-1,2,4-triazol-1-yl)ethan-2-ones **9a**,**b**.



9a R^1=*t*-Bu, X=Cl, 99%
9b R^1=*i*-Bu, X=Br, 53%
9c R^1= Ph
9d R^1=2-Cl-Ph
9e R^1=4-Cl-Ph
9f R^1=4-Me-Ph
9g R^1=2.4-Cl_2-Ph

10a R^1= *t*-Bu, R^4= 4-NO_2-Ph, R^2-R^3=R^5=H 70%
10b R^1=*i*-Bu, R^4= 4-NO_2-Ph, R^2=R^3=R^5=H 54%
10c R^1= *t*-Bu, R^2= R^4=Cl, R^3=R^5=H 66%
10d R^1=Ph, R^2= OH, R^3=R^4=R^5=H 60%
10e R^1=Ph, R^2= OH, R^3=R^4=H, R^5=NO_2 92%
10f R^1=2-Cl-Ph, R^2= OH, R^3=R^4=H, R^5=NO_2 74%
10g R^1=4-Cl-Ph, R^2= OH, R^3=R^4=R^5=H 71%
10i R^1=4-Cl.-Ph, R^2=OH, R^3=R^4=H, R^5=$NO_{2,}$ 76%
10j R^1=4-Cl-Ph, R^2=OH, R^3=R^5=H, R^4=Ph 51%
10k R^1=4-Me-Ph, R^2=OH, R^3=R^4=H, R^5=NO_2 62%
10l R^1=2,4-Cl_2Ph, R^2=OH, R^3=R^4=R^5=H 58%
10m R^1=2,4-Cl_2Ph, R^2=OH, R^3=R^4=H, R^5=NO_2 65%
10n R^1=2,4-Cl_2Ph, R^2=OH, R^3=R^4=H, R^5=*t*-Bu 74%
10o R^1=2,4-Cl_2Ph, R^2=H, R^3=R^5=*t*-Bu, R^4=OH 82%
11a R^1=*t*-Bu R^4=4-MeO-Ph, $R^{2-}R^3$=R^5=H 85%
11b R^1=*t*-Bu R^4=4-Me_2N-Ph, R^2=R^3=R^5=H 60%
11c R^1=2,4-Cl_2Ph, R^2=OH, R^3=R^4=H, R^5=Cl 25%

Fig. 2.5 Synthesis scheme of *N*-vinyl-1,2,4-triazoles

Previously, 3,3-dimethyl-1-(1H-1,2,4-triazol-1-yl)butan-2-one **9a** was proposed as a precursor of powdery mildew inhibitors on barley *Erysiple gramins* and brown rust inhibitors on wheat *Puccinia recondite* [14]. The alkylation reaction of triazole **8** with pinacolon chloride in boiling toluene in the presence of $NaHCO_3$ proceeds with the formation of substance **9a** (65%

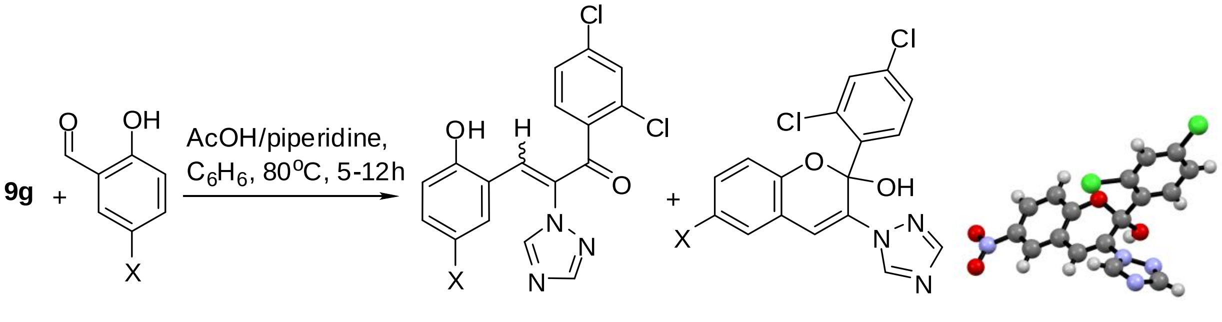
yield, fig. 2.5(a)) [15,16]. It was found that the most optimal option for alkylation of triazole **8** is boiling of equimolar mixture of reagents with K_2CO_3 in acetone, which provides efficiency and simplicity of the process to obtain ethan-2-one **9a** (99% yield, fig. 2.5(b)). The homologue **9b** was obtained in 53% yield (Fig. 2.5(c)) [17].

Further transformations of the obtained alkyl-substituted (1*H*-1,2,4-triazol-1-yl)ethan-2-ones as well as commercially available aryltriazolyl ketones are related to the investigation of their potential under Knoevenagel reaction conditions.

It was found that boiling of ketones **9a-g** with aromatic aldehydes in benzene solution in the presence of catalytic amounts of piperidine-acetic acid mixture leads to the formation of *N*-vinyl-1,2,4-triazoles in good yields [18-20].

It was shown that the configuration of the obtained *N*-vinyl-1,2,4-triazoles depends both on the nature of the substituent of the starting ketone and the substituent of the aromatic aldehyde. The configuration of the double bond was established on the basis of NOESY spectrum and X-ray diffraction analysis for compound **10b**. According to the data obtained, the *Z*-isomer is the predominant product under these conditions, giving compounds **10a-o**, while compounds **11a-c** were isolated as *E*-isomers.

The interaction of substance **9g** with 5-nitrosalicylic aldehyde proceeds with the formation of a mixture of ketone **10m** and semiketal **12a**, the structure of which was also confirmed by X-ray analysis (Fig. 2.6.).



12a

10m X=NO_2 65%
11c X=Cl 25%

12a X=NO_2 25%
12b X=Cl 75%

Fig. 2.7 General scheme of ketalization reaction of ketone 9g

The reaction of interaction of triazolyl methyl ketone **9g** with 5-chlorosalicylic aldehyde proceeds quite differently, and the nature of the formed products depends on the time of the reaction. After five hours of boiling a mixture of substances was formed, from which only one compound **11c** was isolated in individual form. If the reaction is carried out under the same conditions only by increasing the reaction time to 10 hours, the main product is the product **12b** (75% yield).

2.3 Conclusions to Chapter 2.

1. The reaction of interaction of oxindole compounds with 4-amino-1,2,4-triazole salts has been studied. It is shown that under the proposed conditions compounds containing substituted dihydrofuran cycle, amino and triazolylimine groups are formed.

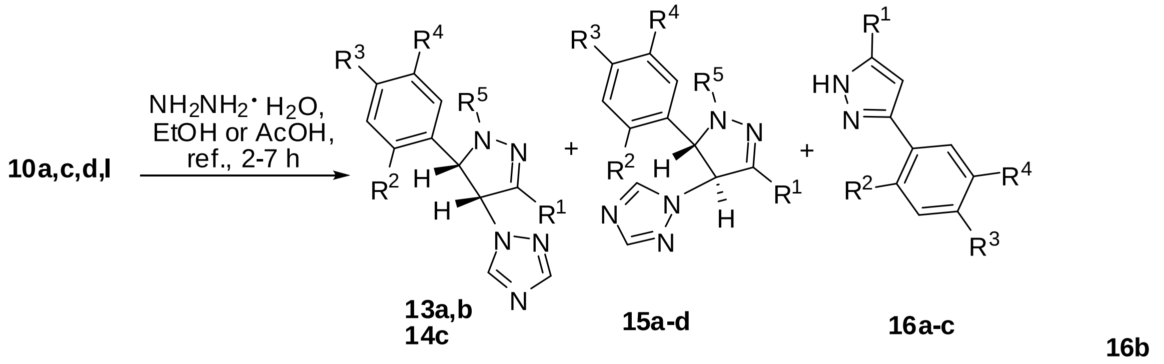
2. It is shown that during the interaction of substituted (1*H*-1,2,4-triazol-1-yl)ethan-2-ones with salicylic aldehyde derivatives under Knoevenagel reaction conditions, the nature of the reaction products formed and their qualitative ratio depend essentially on the nature of the substituent of the initial triazolylmethyl ketones and aromatic aldehydes, as well as on the reaction time. It was noted that the interaction of 1-(2,4-dichlorophenyl)-2-(1*H*-1,2,4-triazol-1-yl)ethanone with salicylic aldehyde derivatives in solution also involves the ketalization reaction of triazolylvinylketones, with the formation of stable compounds of cyclic form with a fragment of 2*H*-chromen-2-ol [14-16, 21]. Further research of the thesis work was aimed at extending the scope of the discovered approach of constructing 2H-chromen-2-ols combining 1*H*-1,2,4-triazole, aromatic or alkyl substituents in their molecule, and the results are presented in the next chapter.

3. SYNTHESIS OF FUNCTIONALIZED SUBSTANCES BY HETEROCYCLIZATION OF SUBSTITUTED (1*H*-1,2,4-TRIAZOL-1-YL)PROP-2-EN-1-ONES WITH HYDRAZINE HYDRATE

As it was shown in the previous chapter, vinyltriazoles containing halogen, carbonyl, nitro or alkyl groups as a second function are available substances. Our interest in the chemistry of this group of substances is related to the investigation of the possibility of introducing a pyrazoline or pyrazolone fragment into their molecules, which represent important classes of biologically active five-membered heterocyclic compounds.

3.1 Synthesis of 3,5-disubstituted-4,5-dihydro-(1*H*-pyrazol-4-yl)-1*H*-1,2,4-triazoles

Within the framework of this work it was found that the nature of the formed reaction products of the interaction of enone **10a** with hydrazine hydrate depends on the nature of the solvent.



13a	R^1= *t*-Bu, R^3=NO_2, R^2=R^4=R^5=H	50%
13b	R^1=2,4-Cl_2Ph, R^2=OH, R^3=H, R^4=NO_2, R^5=H	66%
14c	R^1= *t*-Bu, R^3=NO_2, R^2=R^4=H, R^5=Ac	1.4%
15a	R^1= *t*-Bu, R^3=NO_2, R^2=R^4=H, R^5=Ac	18%
15b	R^1= *t*-Bu, R^2=R^3=Cl, R^4=H, R^5=Ac	45%
15c	R^1= Ph, R^2=OH, R^3=R^4=H, R^5=Ac	11%
15d	R^1=2,4-Cl_2-Ph, R^2=OH, R^3=R^4=H,R^5=Ac	13%
16a	R^1= *t*-Bu, R^3=NO_2, R_2=R_4=H	19%
16b	R^1= Ph, R^2=OH, R^3=R^4=H	29%
16c	R^1=2,4-Cl_2Ph, R^2=OH, R^3=H, R^4=NO_2	27%

Fig. 3.1 Scheme of heterocyclization reaction involving hydrazine hydrate

In boiling ethanol only 4,5-dihydro-1*H*-pyrazolinfunctionalized 1*H*-1,2,4-triazole **13a,b** is formed, whereas in acetic acid along with the formation of a pair of diastereomeric substances of 4,5-dihydro-1*H*-pyrazoline series **14c**, **15a-d** the cyclization product is acylated or the fragment of 1*H*-1,2,4-triazole is cleaved off to form 3,5-disubstituted pyrazole **16a**. In order to study the possibility of obtaining pyrazoline derivatives based on vinyltriazoles **10a**,**c**,**d**,**l**, acetic acid was used as a solvent. The structures and yields of the synthesized compounds **15a-d**, **16a-c** are shown in Figure 3.1. The structure of compound **16b** was confirmed by X-ray analysis.

3.2 Conclusions to Chapter 3.

1) An approach to the synthesis of hard-to-find 3,5-disubstituted-4,5-dihydro-1*H*-pyrazol-4-yl)-1*H*-1,2,4-triazoles and 3,5-disubstituted pyrazoles with potential biological activity has been proposed. On the basis of the obtained data it can be concluded that a selective method of heterocyclization of nitro-substituted triazolylvinylketones in boiling ethanol to form stable 4,5-dihydro-(1*H*-pyrazol-4-yl)-1H-1,2,4-triazoles has been developed.

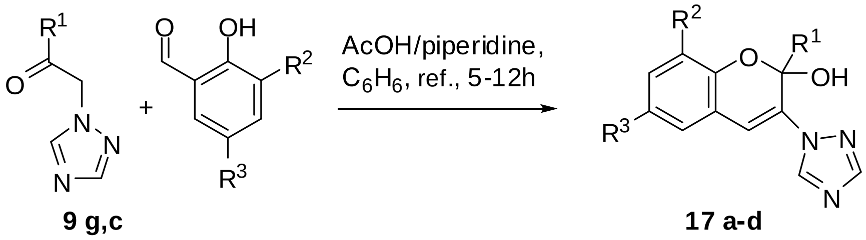
2) It is shown that in acetic acid along with the process of heterocyclization the formation of acetamides or cleavage of the triazole substituent with isomerization of the NH-group position takes place, which opens the way to specifically constructed substances of the pyrazole series.

4. SYNTHESIS OF 1*H*-1,2,4-TRIAZOLE-FUNCTIONALIZED 2*H*-CHROMEN-2-OLS

To explore potential biologically active compounds in the series of 2*H*-chromen-2-ol derivatives [24-32], we have synthesized a series of heterocyclic compounds containing a chromenol fragment and a triazole fragment in their molecular structures. Thus, hybrid molecules contain not one but several structural fragments with potential biological activity [33-35].

4.1. Synthesis of alkyl/aryl substituted (1*H*-1,2,4-triazol-1-yl)chromenols

As a follow-up to our work on the synthesis of functionalized 2*H*-chromen-2-ols **17a-d** based on 1-aryl-2-(1*H*-1,2,4-triazol-1-yl)ethanones **9c**,**g**, we performed a comparable study of the heterocyclization process involving salicylic aldehyde derivatives with substituents in the third and fifth positions (Fig. 4.1.).



17a R^1=2,4-Cl_2Ph, R^2=H, R^3= Me 75%

17b R^1=2,4-Cl_2Ph, R^2=Me, R^3=H 99%

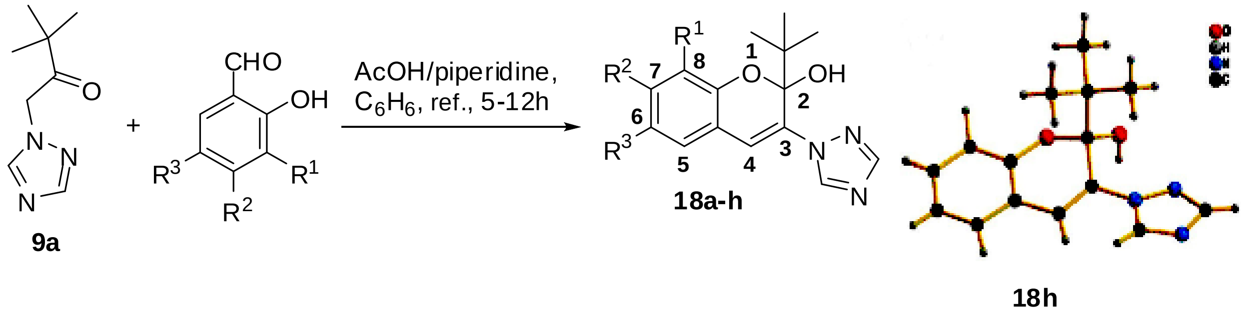
17c R^1= Ph, R^2=H R^3= OMe 60%

17d R^1= Ph, R^2=Me R^3= H 57%

Fig. 4.1 Scheme for preparation of aryl-functionalized 2*H*-chromen-2-ols

The highest yield of the dichloro derivative **17b** was obtained from 3-methylsalicylic aldehyde, whereas that of the derivative of 5-methoxysalicylic aldehyde was 75%. It was found that the interaction of 5-methoxysalicylic aldehyde with ethanone **9c** produced 2*H*-chromen-2-ol **17c**, while the reaction with 3-methylsalicylic aldehyde yielded **17d** yield changed little.

In the present work, a series of derivatives at C-6, C-7 and C-8 atoms of *tert*-butyl-functionalized 2*H*-chromen-2-ols have also been synthesized.



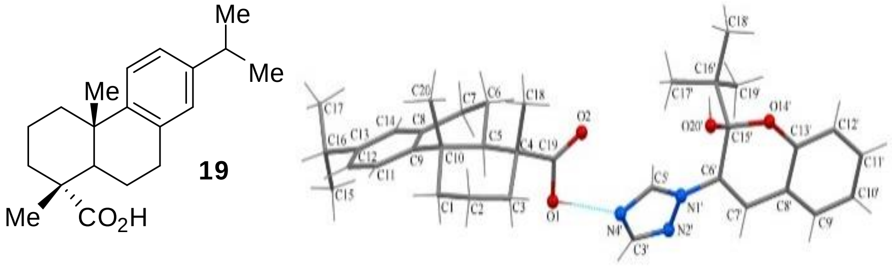
18a R^1=R^2=H, R^3=NO_2 40%
18b R^1=R^2=H, R^3=Cl 56%
18c R^1=R^2=H, R^3=Br 70%
18d R^1=R^3=H, R^2=Ph 67%
18e R^1=R^2= H, R_3=Me 55%
18f R_1=R_2= H, R_3=OMe 61%
18g R^1=Me, R^2=R^3=H 58%
18h R^1=R^2=R^3=H 70%

Fig. 4.2 Scheme for for preparation *tert*-butyl-substituted 2*H*-chromen-2-ones.

Five derivatives were obtained in position C-6: nitro-, chloro-, bromo-, methoxy-, and methyl. It was found that the presence of the nitro group in the molecule of the initial salicylic aldehyde negatively affected the course of the investigated reaction with 3,3-dimethyl-1-(1*H*-1,2,4-triazol-1-yl)butan-2-one **9a** (Fig. 4.2.). Substitution of the NO_2 group with Cl in the starting salicylic aldehyde resulted in a 16% higher yield of 2-*tret*-butyl-6-chloro-3-(1*H*-1,2,4-triazol-1-yl)-2*H*-chromen-2-ol **18b**. The interaction of 4-phenylsalicylic aldehyde with triazolyl methyl ketone **9a** was found to lead to the C-7 derivative of phenyl-substituted 2*H*-chromen-2-ol **18d**. The interaction with 3-methylsalicylic aldehyde was carried out under similar conditions to give C-8 methyl substituted 2*H*-chromen-2-ol **18g**. The best yield was obtained in the reaction with unsubstituted and 6-bromosalicylic aldehyde (Fig.4.2.).

The method for the preparation of racemic chromenol **18h**, the structure of which was also confirmed by X-ray diffraction analysis, was patented [30]. Considering that both epimers of racemate **18h** have opposite configuration at the stereogenic center C-2, one of them can form more stable systems with enantiomerically pure reagents, for example, dehydroabietinic acid **19**.

In the present part of the work, the conditions for cleavage of racemic **18h** using natural acid **19** were selected (Fig. 4.3).



19

20

Fig. 4.3 Dehydroabietic acid and the co-crystal structure of 20

It was found that incubation at room temperature of an acetonitrile solution of an equimolar mixture of chromenol **18h** and acid **19** leads to the formation of a new crystalline substance. The molecular structure and intermolecular interactions between the ingredients of the co-crystal **20** were characterized by single crystal X-ray diffraction analysis and are presented in Figure 4.3. According to the analysis data of the crystalline substance **20**, an S-configuration was assigned to the asymmetric chromenol atom.

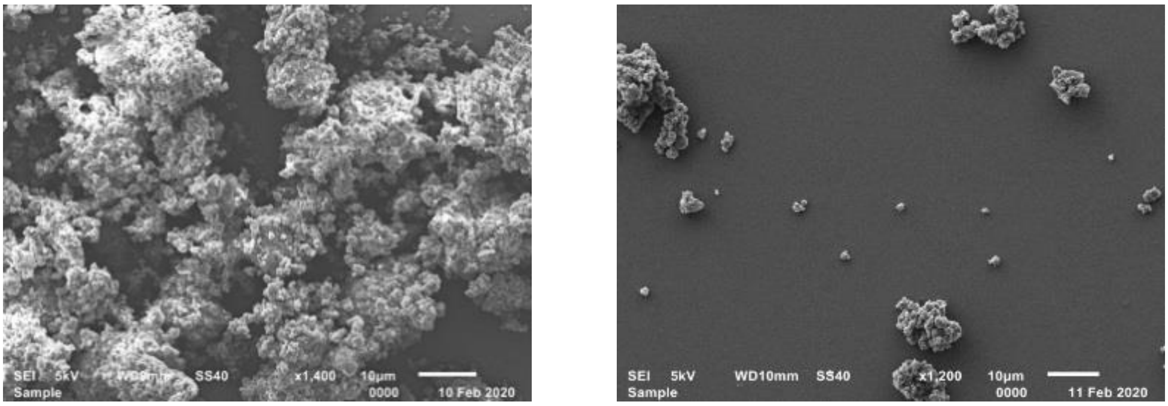
In the present study, various systems **21-24** based on diterpene acid **19**, chromenol-triazole hybrid **18h** and β-cyclodextrin (β-CD) have been studied in order to determine the shape, size, solubility and biological properties.

System **21** was obtained using the kneading method and co-mixing equimolar amounts of hybrid **18h**, acid **19** followed by addition of H_2O, rubbing to a powdery state and then drying. The binary system **22** was obtained by rubbing β-CD and the hybrid **18h**. The three-component system **23** was obtained by adding a methanolic solution of dehydroabietinic acid **19** and chromenol-triazole hybrid **18h** to a 50% aqueous methanolic solution of β-CD, stirring for 24 hours, evaporating the solvents under vacuum and drying at a temperature not exceeding 60ºC. The three-component system **24** was prepared similarly to systems **21**, **22**.

Determination of the shape, size of the **21-24** systems by scanning electron microscopy (SEM), and solubility was carried out in collaboration with Dr. Alexandru Brinzanu from the Institute of Biology, Romanian Academy of Sciences, Bucharest.

In vitro solubility studies of the synthesized systems compared to pure phosphate buffer in water (pH= 6.8) showed an increased dissolution rate of the chromenoltriazole hybrid in inclusion complexes compared to the free form in the following order: system **24** > system **23** > system **22** > system **21**.

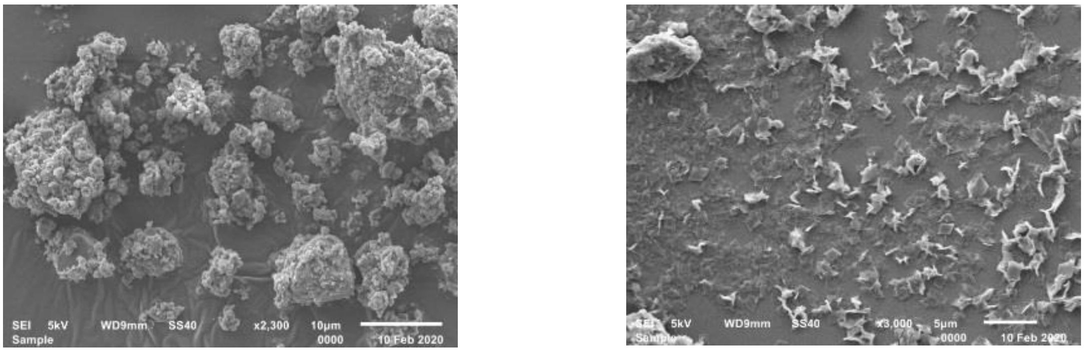
The scanning electron microscopy (SEM) image in Figure 4.4 showed that the diameter of system **21** is approximately 50-100 μm, and such data indicates the homogeneity of the prepared system. The morphology of the system after dissolution studies is characterized by the formation of solid matter with the main size range of particles obtained being between 0.1-50 μm.



(a) **(b)**

Fig. 4.4 SEM micrographs for dry (a) and wet (b) particles of system 21.

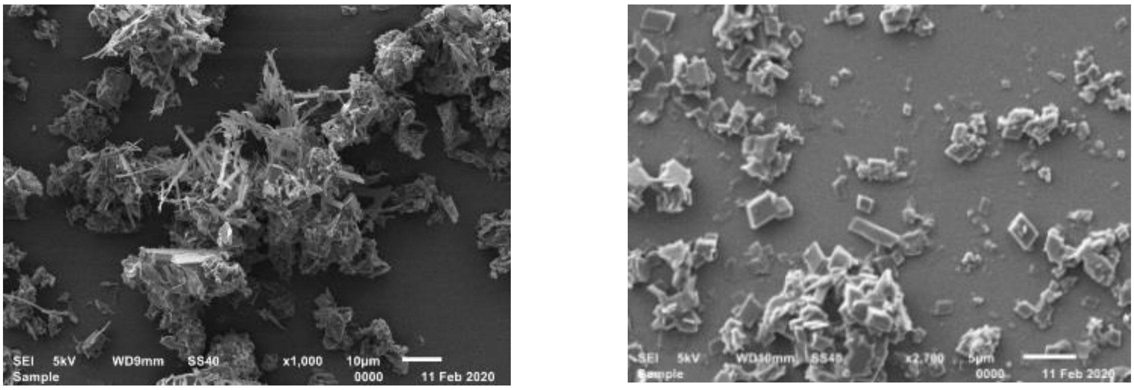
System **22** consists of a mixture of micro- and nanoparticles of irregular shape with predominance of the former (Fig. 4.5). The particles of system **22** after solubility study are characterized by the formation of solid gel and solid plates. The main size ranges of the obtained needle-shaped particles are approximately 0.1-250 μm. Thus, it can be concluded that *β*-CD is a solubilizer and promotes the solubility of chromenol-triazole hybrid **18h**.



(a) **(b)**

Fig. 4.5 SEM micrographs for dry (a) and wet (b) particles of system 22.

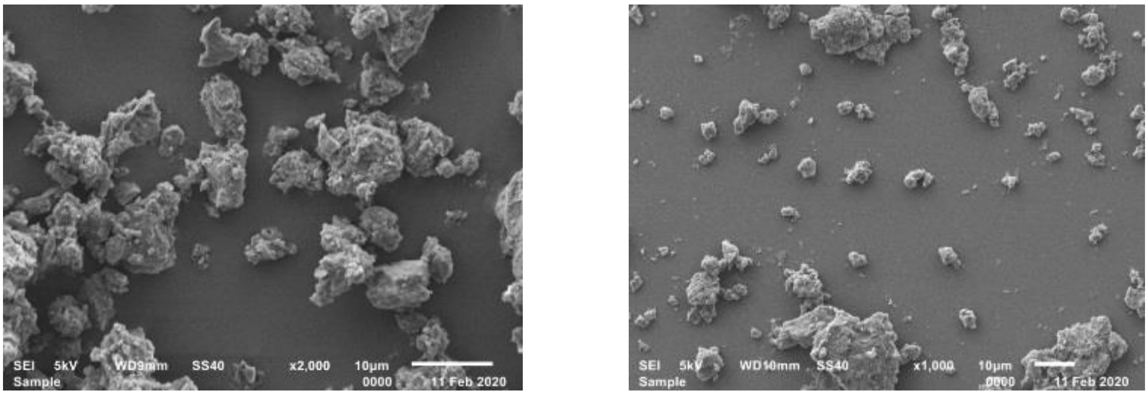
The surface of the particles of system **23** is smooth compared to the particles of systems **21-22** which have many roughnesses. Examination of the acquired images reveals that dehydroabietinic acid **19**, chromenol-triazole hybrid **18h** and *β*-CD are in close contact with each other and are sufficiently dispersed, indicating that the system **23** was successfully obtained. Visualized particle sizes showed that the particles of system **23** had homogeneous morphology and did not form aggregated structures after solubility study (Figure 4.6).



(a) (b)

Fig. 4.6 SEM micrographs for dry (a) and wet (b) particles of system 23.

SEM images of system **24** presented in Figure 4.7 show that the average particle sizes range from 0.4 μm to 3.9 μm, respectively, and no solid gel was formed. The particles of system **24** after dissolution in phosphate buffer are characterized by the formation of solid particles in the size range of approximately 0.1-250 μm (Figure 4.7).



(a) (b)

Fig. 4.7 SEM micrographs for dry (a) and wet (b) particles of system 24.

The particle surface of systems **24** is almost similar to that of dry systems **22-23**, which have many roughnesses, probably due to the presence of β-cyclodextrin adhering to the surface of chromenol-triazole **18h**.

4.2 Conclusions to Chapter 4.

1. A new method for the synthesis of substituted 2*H*-chromen-2-ols by interaction of alkyl/aryl-substituted (1*H*-1,2,4-triazol-1-yl)ethan-2-ones with salicylic aldehydes under Knoevenagel reaction conditions was proposed.

2. The example of racemic 2-tret-butyl-3-(1*H*-1,2,4-triazol-1-yl)-2*H*-chromen-2-ol shows a convenient method for the preparation of enantiomerically enriched substances of the investigated series.

3. Methods for the preparation of systems with microparticle size of 0.1-250 μm from *β*-cyclodextrin, dehydroabietinic acid and chromenol-1,2,4-triazole hybridomers have been developed. *In vitro* dissolution studies of the synthesized compounds in phosphate buffer (pH = 6.8) showed an increase in the solubility and antifungal activity (chapter 5, p. 18-19) of chromenoltriazole hybrid in inclusion complexes compared to the free form.

5. EVALUATION OF STRUCTURE-BIOACTIVITY RELATIONSHIP IN A SERIES OF SYNTHESIZED ALKYL/ARYL-SUBSTITUTED (1*H*-1,2,4-TRIAZOL-1-YL)ETHAN-2-ONES

The synthesized compounds were tested by the group of Prof. Athena Geronikaki from the the School of Pharmacy of the Aristotle University of Thessaloniki, Greece for their ability to inhibit the microorganisms *Aspergillus fumigatus, Aspergillus versicolor, Aspergillus ochramensis, A. niger, Trichoderma viride, Penicillium funiculosum, P. ochrochloron, P. verrucosum* var. *cyclopium,* respectively. Among alkyl-substituted (1*H*-1,2,4-triazolyl)ethanones **9a**, **9b**, **9c**, *iso*-butyl-4-nitro derivative **9b** showed the highest activity against *A. fumigatus* with MIC 0.02 mM, whereas the inhibition level *tert*-butyl homologues **10a**,**10c** was MIC 0.25 mM and MIC 0.14 mM, respectively. All the tested compounds showed good antibacterial activity with MIC and MIC values ranging from 0.0002 to 0.0069 mM. The antibacterial activity can be summarized as follows: **10a**>**10b** >**10c**. Compound **10b** was the most active among all tested with MIC 0.0002-0.0033 mM and MIC 0.0004-0.0033 mM, followed by compounds **10a** and **10c**. The activity against *A. ochramensis* in the series of tert-butyl substituted 2*H*-chromen-2-ols increased in the following order **18d → 18a → 18c → 18b → 18h** and amounted to MIC 0.431 mM, MIC 0.316 mM, MIC 0.199 mM, MIC 0.163 mM, MIC 0.92 mM. It should be noted that against *A. ochramensis*, the activity increased from MIC 0.201 mM in the row **18d → 18h →18b →18a** to MIC 0.071 mM and MFC 0.142 mM. The level of inhibition of *A. niger* decreased in the series of tested substances **18a →18d →18b →18c →18h** with MIC 0.316 mM, MIC 0.143 mM, MIC 0.081 mM, MIC 0.071 mM, MIC 0.022 mM and MFC 0.632 mM, MFC 0.287 mM, MFC 0.327 mM, MFC 0.142 mM, MFC 0.046 mM, respectively.

The obtained complexes of *β*-cyclodextrin with dehydroabietinic acid and chromenol-triazole showed good activity against *Candida albicans, Saccharomyces cerevisiae. Aspergillus fumigatus, A. versicolor, A. ochramensis* and *Trichoderma viride* compared to reference preparations with ketoconazole (MIC and MIC values of 0.28-1.88 mM and 0.38-2.82 mM, respectively), bifonazole (MIC and MIC values of 0.32-0.64 mM and 0.64-0.81 mM) and nystatin (MIC and MIC values of 0.55-0.65 mM and 0.65-0.79 mM). In this work, the structure-inhibitory activity relationship was evaluated in a series of systems based on chromenol-triazole derivative **18h**, co-crystal **20**, diterpene acid **19** and *β*-cyclodextrin. Co-crystal **20**, derived from chromenol **18h** with diterpene acid **19**, was 4-fold more active against *A.s fumigatus* (MIC 0.08 mM) than acid (MIC 0.35 mM) and three-fold chromenol **18h**. The activity of co-crystal **20** on inhibition of *A. versicolor* was 0.02 mM, and with respect to *A. ochramensis* was equal to 0.14 mM, which is higher than that of the initial ones. An interesting activity relationship was established for system **21**, obtained by rubbing chromenol **18h**, diterpene acid **19** with a small amount of water. The level of activity towards *A. fumigatus* (MIC 0.10 mM) and *A. ochramensis* (MIC 0.13 mM) remained practically at the same level as that of system **20**, whereas towards *A. versicolor* it was 11 times lower.

The activity of the synthesized substances against wheat root rot pathogens was evaluated by the group of Prof. Galina Lupascu from the Institute of Genetics, Physiology and Plant Protection of the Republic of Moldova. It was found that compounds **10a**, **10b** and **10c** showed inhibitory activity against the fungus *Fusarium oxysporum* causing inhibition of colony growth. A pronounced inhibitory effect was recorded at concentrations of 0.005 and 0.01 %. Thus, on the 6th day of growth the average diameter of colonies varied within 39...52 % and 39...68 % in relation to the control, respectively, at concentrations of 0.005 and 0.01 %. At concentrations of 0.00125 % and 0.0025 %, the analyzed index was 56...82 % and 68...104 % relative to the control, respectively, and compound **10c** exhibited the most pronounced antifungal activity against F. oxysporum. With respect to the fungus *Drechslera sorokiniana* a similar trend was revealed as in the case of *F. oxysporum* - higher inhibitory activity at high concentrations, but in contrast to *F. oxysporum* the efficiency of the compounds is greater *F.* oxysporum the efficiency of the compounds to a greater extent decreased or even caused stimulation of fungal growth: at concentrations of 0.005 and 0.01 % the diameter of colonies in relation to the control varied within 78...88 % and 86...143 %, respectively. It should be noted that the culture filtrate of *F. oxysporum* had a suppressive effect on all organs of growth and development of wheat, except for germination of grains. Compound **10a** stimulated the accumulation of dry weight in the plant at concentrations of 0.01% and 0.005% in the interaction of wheat with *F. oxysporum* by 64 and 44%, respectively. Compounds **10b** and **10c** in the range of concentrations investigated contributed to a significant increase in growth vigor and plant dry weight. It was found that **10b** increased the growth force and plant dry weight by 70-99% and 54-65%, while **10c** increased them from 49-88 and 42-71%, respectively. Regarding the effect of *D. sorokiniana on* wheat, the negative effect of the fungus on biomass accumulation in plants was revealed. In grain treatment, dry biomass per seedling decreased by 18% compared to the control. For this trait, increases of 19%, 56% and 10% were observed under the influence of compounds **10a** (concentration 0.005%), **10b** (concentration 0.0025%) and **10c** (concentration 0.0025%).

In cooperation with the group of Prof. Robert Reynolds from the Southern Research Institute, USA, it was shown that the patented product **10a** as well as the comparison drug rifampicin at a concentration of 6.25 mg/mL, inhibits 100% of the development of *Mycobacterium tuberculosis* H37Rv and leprosy, also known as Hansen's disease .

5.1. Conclusions to Chapter 5.

1. *N*-vinyl-1,2,4-triazoles have been shown to exhibit good antimicrobial activity, and compound **10a** is active against *Mycobacterium tuberculosis* and is promising for further in-depth studies [22].

2. The fungicidal activity of compound **18h** was found to be 7...20 times more active than ketoconazole against fungi *Aspergillus fumigatus, A. niger, Penicillium chrochloron and Trichoderma viride* [29].

3 Based on the obtained data on integral characteristics of plants - growth force index and dry weight per plant, it is possible to recommend as means of wheat protection against the fungus *F. oxysporum*, substances **10a** in the form of a mixture of *F. oxysporum* and *F. oxysporum* substances **10a** in concentrations of 0.005%, 0.01%, **10b** in concentrations of 0.00125-0.01%, **10c** in concentrations of 0.00125-0.01%, and in case of *D. sorokiniana* fungus - **10a** in concentration of 0.005%, **10b** in concentration of 0.0025% and **10c** in concentration of 0.0025%.

GENERAL CONCLUSIONS AND RECOMMENDATIONS

1. Original approaches to the construction of alkyl/aryl-substituted (1*H*-1,2,4-triazol-1-yl)ethanones and their transformation pathways have been proposed, allowing the synthesis of 50 derivatives of linear and cyclic structures.
2. The conditions for using the firstly synthesized 4-amino-1-(3,3-dimethyl-2-oxobutyl)-4*H*-1,2,4-triazol-1-ium chloride and 4-amino-1-methyl-4*H*-1,2,4-triazol-1-ium iodide for functionalization of 3-phenocylidene-oxindoles with potential biological activity were studied (paragraph 2.3, p.1).
3. A stereoselective method for the synthesis of trisubstituted triazole olefins under Knoevenagel reaction conditions has been developed. It is shown that the nature of the formed products and their qualitative ratio depend essentially on the nature of the substituent in the initial triazolylmethyl ketones and aromatic aldehydes, as well as on the

reaction time (paragraph 2.3, p.2).

4. The isomeric 4,5-dihydro-1*H*-pyrazol-1-yl)ethanones were synthesized by varying the nature of the solvent (paragraph 3.2)
5. It was found that condensation of alkyl/aryl-substituted (1*H*-1,2,4-triazol-1-yl)ethanones with salicylic aldehydes can serve as a convenient method for the preparation of compounds with the 2*H*-chromen-2-ol fragment (paragraph 4.2, p.1).
6. On the example of synthesis of racemic 2-*tret*-butyl-3-(1*H*-1,2,4-triazol-1-yl)-2*H*-chromen-2-ol and dehydroabietinic acid, a convenient method for preparation of optically active substances of the investigated series is shown (paragraph 4.2, p.2)
7. The obtained complexes of *β*-cyclodextrin with dehydroabietinic acid and chromenol-triazolium hybrid with microparticle size of 0.1-0.250 μm showed changes in physicochemical properties, increased solubility and fungicidal activity compared to the parent compounds (paragraph 4.2, p.3).
8. The following *tert*-butyl triazolyl ketone derivatives can be recommended for use in agriculture as fungicidal agents, based on the results of biological tests: (*Z*)-4,4-dimethyl-1-(4-nitrophenyl)-2-(1H-1,2,4-triazol-1-yl)pent-1-en-3-one **10a,** (*Z*)-5-метил-1-(4-nitrophenyl)-2-(1*H*-1,2,4-triazol-1-yl)hex-2-en-1-one **10b** and (*Z*)-1-(2,4-dichlorophenyl)-4,4-dimethyl-2-(1*H*-1,2,4-triazol-1-yl)pent-1-en-3-one **10c**. *Tert*-butyl triazolyl ketone derivatives **10a-c**; *tert*-butyl triazolyl 2*H*-chromenol derivatives **18c** and **18h**; two- and three-component systems of chromenol with dehydroabietinic acid and *β*-cyclodextrin are promising for further in-depth studies for their application in medicine as antifungal agents, and compound **10a** also as an antituberculosis agent (paragraph 5.1, p.1-2).

The results obtained within the framework of this paper made it possible to formulate the following **recommendations:**

1. The established regularities of organic synthesis of alkyl/aryl-substituted (1*H*-1,2,4-triazol-1-yl)ethan-2-ones open new possibilities for their directed structural modification and expand theoretical ideas about the chemical properties of functionally substituted 1*H*-1,2,4-triazoles. The obtained new data on the dipolar cycloaddition reaction complement theoretical ideas about the reactivity of triazolylmethyl ketones, including under conditions of cross-aldol condensation and can be used for the synthesis of similarly constructed substances with given properties.
2. The application of the developed method for the synthesis of optically active co-crystal (1*H*-1,2,4-triazol-1-yl)-2*H*-chromen-2-ol can serve as an approach to enantiomerically enriched organic substances with desired properties.

3. The developed and patented methods formed the basis for the selective synthesis of a series of heterocyclic compounds, the analysis of structure-property relationship showed that they have diverse bioactivity, exceeding the known preparations rifampicin, ketoconazole, bifinazole, ampicilin and are of practical interest for medicinal chemistry and agrochemistry for protection against wheat root rot pathogens with the property of growth stimulant.

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“Достижения молодых ученых: химические науки”, Всероссийская молодежная конференция, 17-20 мая 2017, г. Уфа, Россия, с.89.

14) **ZVEAGHINȚEVA**, **M**. Isomerizarea *N*-viniltriazolului sub acțiunea solventului, În: *Conferinta "Tendințe contemporane ale dezvoltării științei: viziuni ale tinerilor cercetători",* ediția a VII-a, 15 iunie 2018, Chișhinău, raport oral. pp. 114-118. ISBN 978-9975-108-45-4.

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23) **ЗВЯГИНЦЕВА, М.М**., СТЫНГАЧ, Е.П., МАКАЕВ, Ф.З. Синтез нового соединения 2-(2,4-дихлорфенил)-5-метил-3-(*1h*-1,2,4-триазол-1-ил)-*2H*-хромен-2-ол. В: *XXVIII Всероссийская конференция молодых учёных с международным участием «Актуальные проблемы биомедицины -2022»*. 24-26 марта, 2022, Санкт-Петербург, Россия, с. 374-375. ISBN 978-5-88999-775-7.

ANNOTATION

Zveaghintseva Marina, "Synthesis and study of 1-(1*H*-1,2,4-triazol-1-yl)ethan-2-ones". Dissertation for the degree of Doctor of Chemical Sciences. Chisinau, Republic of Moldova, 2023.

Dissertation contents: the thesis includes an introduction, 5 chapters, general conclusions and recommendations, a bibliography of 175 titles, 2 annexes, 120 pages of the main text, 84 figures and 4 tables. The results are published in 23 scientific publications.

Keywords: 1*H*-1,2,4-triazole, 1-(1*H*-1,2,4-triazol-1-yl)ethan-2-one, 2*H*-chromen-2-ol, 4,5-dihydro-1H-pyrazole, condensation, quaternization, 3-phenocylidene oxindole.

The goal of the scientific work: study of selective synthesis of new (1*H*-1,2,4-triazol-1-yl)ethan-2-ones, study of their structure and properties

The research objectives: development of simple and efficient schemes for the synthesis of new alkyl/aryl-substituted (1*H*-1,2,4-triazol-1-yl)ethanones based on 1*H*-1,2,4-triazole and 2-halo-1-(alkyl /aryl)ethanones and the study of the properties of triazolium salts; determination of the optimal conditions for obtaining unsaturated compounds with a given configuration of double bonds and the use of the latter to build a carbon-heteroatom bond of cyclic derivatives; evaluation of the "*structure-bioactivity*" relationship in the series of synthesized alkyl/aryl-substituted (1*H*-1,2,4-triazol-1-yl)ethanones

The novelty and the scientific originality of the work the conditions for the use of the first synthesized 4-amino-1-(3,3-dimethyl-2-oxobutyl)-4*H*-1,2,4-triazol-1-ium chloride and 4-amino-1-methyl-4*H*-1,2,4-triazol-1-ium iodide for the functionalization of 3-phenocylidene oxindoles were studied. A stereoselective method for the synthesis of trisubstituted olefins of the triazole series under the conditions of the Knoevenagel reaction has been developed and patented.

The solved scientific problem . An approach to a series of previously unknown nitrogen- and oxygen-containing polycyclic compounds has been developed, which opens up opportunities for their directed structural modification and expands the field of application of (1*H*-1,2,4-triazol-1-yl)ethanone derivatives in medicine and agriculture.

Theoretical significance of the dissertation. The obtained data on the dipolar cycloaddition reaction and the elimination reaction complement the new theoretical ideas about the reactivity of α,β-unsaturated ketones. The developed new effective method for the one-pot preparation of compounds with a 2*H*-chromen-2-ol fragment and isomeric 4,5-dihydro-(1*H*-pyrazol-1-yl)ethanones is a significant contribution to the development of the fundamentals of organic chemistry.

Applicative value of the dissertation: : The developed methods formed the basis for the selective synthesis of a large series of (1*H*-1,2,4-triazol-1-yl)ethanone derivatives. Using racemic 2-*tert*-butyl-3-(1*H*-1,2,4-triazol-1-yl)-2*H*-chromen-2-ol as an example, a convenient method for obtaining enantiomerically enriched substances is shown. Analysis of the "*structure-property*" dependence showed that for the first time the synthesized substances have anti-tuberculosis, antibacterial, fungicidal activity exceeding the known drugs and are of practical interest for the treatment of a number of pathologies, as well as agrochemistry for the protection of cereals with the property of a growth stimulator.

Implementation of the scientific results: Patented methods for the selective synthesis of derivatives of (1*H*-1,2,4-triazol-1-yl)ethanone have found application in the research activities of the Laboratory of Organic Synthesis of the Institute of Chemistry, Moldova, the School of Pharmacy of the Aristotle University of Thessaloniki, Greece, Southern Scientific research institute, USA. The data on bioactivity revealed promising substances for further in-depth studies at the USMF"*Nicolae Testemitanu*", the IGFPP and the Scientific and Practical Institute of Horticulture, Viticulture and Food Technologies of Moldova.

ADNOTARE

Zveaghințeva Marina, „Sinteza și cercetarea 1-(1*H*-1,2,4-triazol-1-il)etan-2-onelor”. Teză de doctor în științe chimice. Chișinău, Republica Moldova, 2023.

Structura tezei: Teza constă din introducere, 5 capitole, concluzii generale și recomandări, bibliografie ce include 175 de titluri, 2 anexe, 120 de pagini de text de bază, 84 de figuri și 4 tabele. Rezultatele cercetărilor efectuate sunt expuse în 23 lucrări științifice.

Cuvinte cheie: 1*H*-1,2,4-triazol, 1-(1*H*-1,2,4-triazol-1-il)etan-2-onă, 2*H*-cromen-2-ol, 4,5-dihidro-1*H*-pirazol, condensare, cuaternizare, 3-fenocylidene oxindole.

Scopul lucrării constă în: cercetarea modalităților de sinteză selectivă a unor noi (1*H*-1,2,4-triazol-1-il)etan-2-one, studiul structurii și proprietăților acestora.

Obiectivele cercetării: elaborarea unor scheme de sinteză simple și eficiente pentru obținerea noilor (1*H*-1,2,4-triazol-1-il)etanone alchil/aril-substituite pe baza de 1*H*-1,2,4-triazol și 2- halo-1-(alchil/aril)etanone și studiul proprietăților sărurilor de triazoliu; determinarea condițiilor optime pentru obținerea compușilor nesaturați cu o anume configurație a dublei legături și utilizarea acestora din urmă pentru a construi o legătură carbon-heteroatom a derivaților ciclici; evaluarea relației „*structură-bioactivitate*” în seria de (1*H*-1,2,4-triazol-1-il)etanone sintetizate alchil/aril-substituite.

Noutatea și originalitatea științifică a lucrării- Au fost studiate condițiile de utilizare a clorurii de 4-amino-1-(3,3-dimetil-2-oxobutil)-4*H*-1,2,4-triazol-1-iu și a iodurii de 4-amino-1-metil-4*H*-1,2,4-triazol-1-iu pentru funcționalizarea 3-fenociliden-oxindolilor. A fost dezvoltată și brevetată o metodă stereoselectivă pentru sinteza olefinelor trisubstituite din seria triazolilor în condițiile reacției Knoevenagel.

Problema științifică soluționată. A fost dezvoltată o abordare a unei serii de compuși policiclici cu conținutul de azot și oxigen necunoscuți anterior, care deschide posibilități de modificare structurală dirijată a acestora și extinde domeniul de aplicare a (1*H*-1,2,4-triazol-1-il)etanone în medicină și agricultură.

Valoarea teoretică a lucrării. Datele obținute pentru reacția de cicloadiție dipolară și reacția de eliminare completează noile idei teoretice despre reactivitatea cetonelor α,β-insaturate. O nouă metodă eficientă pentru prepararea într-un singur reactor a compușilor care conțin fragmentul 2*H*-cromen-2-ol și a 4,5-dihidro-(1*H*-pirazol-1-il)etanonelor izomere este o contribuție importantă la chimia organică.

Valoarea aplicativă a lucrării. Metodele dezvoltate au constituit baza pentru sinteza selectivă a unei serii mari de derivați (1*H*-1,2,4-triazol-1-il)etanonei. Folosind 2-*tert*-butil-3-(1*H*-1,2,4-triazol-1-il)-2*H*-cromen-2-olul racemic ca exemplu, este prezentată o metodă convenabilă pentru obținerea de substanțe îmbogățite enantiomeric. Analiza dependenței „*structură-proprietate*” a arătat că pentru prima dată substanțele sintetizate au activitate antituberculoză, antibacteriană, fungicidă care depășește medicamentele cunoscute și prezintă un interes practic pentru tratarea unui număr de patologii, precum și pentru agrochimie în protecția cerealelor cu proprietăți de stimulator de crestere.

Implementarea rezultatelor științifice: Metodele brevetate de sinteză selectivă a derivaților (1*H*-1,2,4-triazol-1-il)etanonei și-au găsit aplicație în activitățile de cercetare ale Laboratorului de Sinteză Organică al Institutului de Chimie, Moldova, Școala de Farmacie a Universității Aristotel din Salonic, Grecia, Institutul de Cercetare Științifică de Sud, SUA. Datele privind bioactivitatea au scos la iveală substanțe promițătoare pentru studii ulterioare aprofundate la Centrul de Cercetare a Produselor Medicamentale al Universității de Medicină și Farmacie „*Nicolae Testemițanu*”, Institutul de Genetică, Fiziologie și Protecția Plantelor și Institutul Științific și Practic de Horticultură, Viticultura și Tehnologii Alimentare din Moldova.

АННОТАЦИЯ

Звягинцева Марина Михайловна, «Синтез и исследование 1-(1*H*-1,2,4-триазол-1-ил)этан-2-онов». Диссертация на соискание ученой степени доктора химических наук. Кишинёв, Республика Молдова, 2023.

Структура диссертации: диссертация включает введение, 5 глав, общие выводы и рекомендации, библиографию из 175 наименований, 2 приложения, 120 страниц основного текста, 84 рисунков, 4 таблицы. Результаты опубликованы в 23 научных публикациях.

Ключевые слова: 1*H*-1,2,4-триазол, 1-(1*H*-1,2,4-триазол-1-ил)этан-2-он, 2*H*-хромен-2-ол, 4,5-дигидро-1*H*-пиразол, конденсация, кватернизация, 3-феноцилиден-оксиндол.

Цель научной работы: исследование селективного синтеза новых (1*H*-1,2,4-триазол-1-ил)этан-2-онов, изучение их строения и свойств.

Задачи исследования: разработка простых и эффективных схем синтеза новых алкил/арилзамещённых (1*H*-1,2,4-триазол-1-ил)этанонов на основе 1*H*-1,2,4-триазола и 2-галоген-1-(алкил/арил)этанонов и изучение свойств триазолиевых солей; определение оптимальных условий получения непредельных соединений с заданной конфигурацией двойных связей и использование последних для построения связи углерод-гетероатом циклических производных; оценка взаимосвязи «*структура-биоактивность*» в ряду синтезированных алкил/арилзамещённых (1*H*-1,2,4-триазол-1-ил)этанонов.

Новизна и научная оригинальность работы - изучены условия использования впервые синтезированных 4-амино-1-(3,3-диметил-2-оксобутил)-4*H*-1,2,4-триазол-1-иум хлорида и 4-амино-1-метил-4*H*-1,2,4-триазол-1-иум йодида для функционализации 3-феноцилиден-оксиндолов. Разработан и запатентован стереоселективный метод синтеза тризамещенных олефинов триазольного ряда в условиях реакции Кнёвенагеля.

Решенная важная научная проблема - разработан подход к серии ранее неизвестных азот- и кислородсодержащих полициклических соединений, что открывают возможности направленной их структурной модификации, расширяют область применения производных (1*H*-1,2,4-триазол-1-ил)этанонов в медицине и сельском хозяйстве .

Теоретическая значимость работы - полученные данные по реакции диполярного циклоприсоединения и реакции элиминирования дополняют новые теоретические представления о реакционной способности *α,β*-ненасыщенных кетонов. Разработанный новый эффективный метод однореакторного получения соединений с фрагментом 2*H*-хромен-2-ола и изомерных 4,5-дигидро-(1*H*-пиразол-1-ил)этанонов является существенным вкладом в развитие основ органической химии.

Прикладная значимость работы - разработанные методы легли в основу селективного синтеза большой серии производных (1*H*-1,2,4-триазол-1-ил)этанона. На примере рацемического 2-*трет*-бутил-3-(1*H*-1,2,4-триазол-1-ил)-2*H*-хромен-2-ола показан удобный метод получения энантиомернообогащенных веществ. Анализ зависимости «*структура-свойство*» показал, что впервые синтезированные вещества обладают антитуберкулезной, антибактериальной, фунгицидной активностью превышающей известные препапараты и представляют практический интерес для терапии ряда патологий, так и агрохимии для защиты колосовых со свойством стимулятора роста.

Внедрение научных результатов. Запатентованные методы селективного получения производных (1*H*-1,2,4-триазол-1-ил)этанона нашли применение в научно-исследовательской деятельности Лаборатории Органического Синтеза Института Химии, Молдовы, Школы Фармации Университета Аристотеля Салонники, Греция, Южного научно-исследовательского института, США. Данные по биоактивности выявили перспективные вещества для дальнейших углубленных исследований в Центре Исследования Медицинских Препаратов Университета Медицины и Фармации «*Николае Тестемицану*», Института Генетики, Физиологии и Защиты Растений и Научно-практического Института Садоводства Виноградарства и Пищевых Технологий Молдовы.

ZVEAGHINTSEVA MARINA

SYNTHESIS AND STUDY OF 1-(1H-1,2,4-TRIAZOL-1-YL)ETHAN-2-ONES

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