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SYNTHESIS AND STUDY OF OPTICALLY ACTIVE OXINDOLS

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CONCEPTUAL FRAMEWORK OF THE RESEARCH

The actuality and significance of the topic.

The organic chemistry trends of recent decades, aimed at the disclosing of optically active substances potential, are associated with the well-known fact that the spatial structure of the chiral molecule significantly affects its properties, including biological ones.

There are two main methods for obtaining optically active substances - synthesis of chiral natural substances or using of the latter as catalysts. As such, the search for simple and effective synthetic methods for polyfunctionalized oxindoles selective obtaining based on available isatins is an urgent task, and one that offers practical advantages. The recent explosion of scientific articles about oxindoles shows the significance of this class of compounds, especially for pharmaceutical chemistry, with a significant potential, especially revealed in the light of recent discoveries. The works being carried out in this direction led to the implementation of innovating effective drugs into the therapy practice, in the treatment of a number of human diseases. The study of polyfunctionalized oxindoles chemical and stereochemical characteristics, its physicochemical properties and settlement patterns requires the development of simple and effective methods for the synthesis of its individual geometric isomers. The most accessible and universal strategy for the substituted oxindoles synthesis is the conversion of isatins into oxindole series 3-substituted derivatives, available for implementation with and without catalysts.

The goal of the work:

Investigation of the routes for selective synthesis of optically active substituted oxindoles on the basis of isatins, investigation of their structure and properties.

The main tasks of the work:

The elaboration of simple and effective synthetic schemes for obtaining the new substituted oxindoles starting from isatins; study of the regularities of cross-aldol reaction by using chiral catalysts; exploration of the synthetic routes towards the optically active *N*-substituted isatins; investigation of the reactions of obtaining spirooxindoles from isatin, natural amino acids and chalcones; evaluation of the "structure-bioactivity" relationship for a number of the synthesized substituted oxindoles based on the obtained data.

The research hypothesis.

The research of the abovementioned paper was based on the proposed possibility of obtaining geometric isomers of oxindole derivatives with high stereoselectivity using well-known methods of organic chemistry, such as aldol condensation reactions in the presence of chiral catalysts, [3+2]-dipolar cycloaddition, alkylation of isatins by nitrogen atom with optically active compounds, etc.

Selected research methods review and justification.

In the course of this paper, modern methods of organic synthesis have been used, determined by the goals laid down in the basis of this study, namely, to study the reaction of the stereoisomeric 3-hydroxy-3-substituted oxindoles formation with the involvement of primary and secondary amines; to study the prospects for obtaining *N*-glycosylated isatines by the Stolle and Sandmeyer method. Based on the literature data, to investigate the effect of synthesized substances substituents on the course of the reaction of [3+2]-dipolar cycloaddition and its stereo- and regioselectivity; to determine the relationship between the structure and biological activity of new optically active oxindoles.

To control the reaction progress, as well as the products purity, thin-layer chromatography has been used. The target substances were purified through recrystallization, column chromatography and preparative thin-layer chromatography. In order to establish the structure and determine the chemical compounds purity, modern physico-chemical analysis methods were used, such as infrared spectroscopy, NMR spectroscopy, X-ray diffraction analysis, elemental analysis, high-performance liquid chromatography, determination of the plane-polarized light rotation angle and melting point.

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 OXINDOLES AND WAYS OF ITS TRANSFORMATIONS

This chapter is devoted to the literature data review on the isatin preparation and its transformations into optically active derivatives of the oxindole series. It describes recently discovered methods for the isatin synthesis and oxindoles based on it, including 3-hydroxyoxindoles, spirooxindoles with various heterocycles in the molecule.

2. SYNTHESIS OF 3-SUBSTITUTED-2-OXINDOLES AND ITS TRANSFORMATIONS

In recent decades, the pharmaceutical chemistry has accumulated a number of examples in the development of natural substances hybrids with heterocyclic fragments, allowing to enhance the native biological activity. The study of the chemical and stereochemical features of polyfunctionalized oxindoles, its physicochemical properties and formation patterns requires the development of, if possible, simple and effective methods for the synthesis of such compounds individual geometric isomers. As mentioned before within the framework of the first chapter, the most accessible and universal strategy for various substituted oxindoles synthesis is a scheme using the isatins conversion reactions into oxindole series heterocyclic derivatives.

2.1 Synthesis of oxindolpyrroles

Azobenzenes have attracted a lot of attention due to the fact that they undergo photo-reversible chemical transformations into a *trans*- configuration from a thermodynamically unstable *cis*- configuration under the influence of visible light or heat, and the reverse reaction can be initiated by radiation in the UV spectrum [1]. In a biological context, the abovementioned photochromism can be used to obtain enzyme inhibitors in ion channels. Consequently, the search for synthetic methods for the selective production of optically active hybrid materials with isatin **1** fragments offered practical advantages, for example, for photodynamic therapy based on photosensitive substances use from the group of azobenzoloxindoles and certain wavelength [2] radiation.

Within the framework of this study, it has been established that 4-aminoacetophenone **4** diazotization with subsequent treatment of the reaction mixture with phenol (Fig. 2.1) led to azobenzene **5** derivative [3-6].

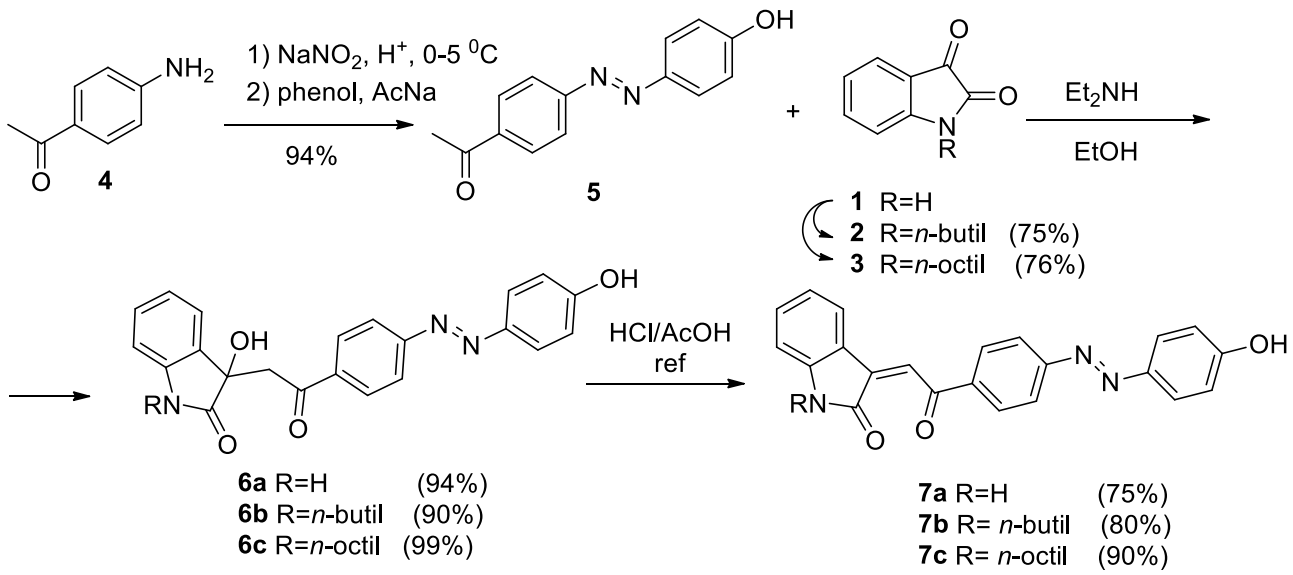


Fig. 2.1 Scheme for obtaining azobenzene adducts with isatins

Conditioning at room temperature of isatin 1 equimolar amounts with azobenzene **5** in the presence of 10 mol% Et_2NH in 96% ethanol gives the aldol **6a**. Alcohol **6a** refluxing in a mixture of HCl/AcOH proceeds with water elimination and enone **7a** formation. Isatin **1** alkylation was carried out with butyl bromide and octyl iodide within K_2CO_3/DMF system to form products **2** and **3**, which, along with isatin **1**, were involved in the reaction with azobenzene **5**. The substances **7b-c** have been formed after adducts **6b-c** dehydration.

Considering the well-known fact that natural and synthetic pyrroles possess a wide spectrum of biological activity, further molecule hybridization was associated with the pyrrole heterocycle construction.

By the beginning of our studies, there were no data on the synthesis of 2,3-dihydro-1H-3-indolyl-5-aryl-1H-3-pyrrol carboxylates functionalized with sesquiterpenes. A synthetic construction method for such oxindoles may involve enones **7a-c** acetoacetate **11** hybridization with a *cis*-articulated decalin fragment presented in the natural substance aureol molecule, exhibiting selective cytotoxicity against human tumor cells, including lung cancer A549, colon adenocarcinoma cells HT-29 [7], as well as activity against the influenza A virus [8]. While obvious progress has been made within the framework of this area, the chemistry of similarly constructed substances with anti-HIV activity remains a poorly studied area [9, 10], including those based on optically active sclareol, opening up the prospect for new biologically active compounds [11] synthesis.

The optically active acetoacetate **11** synthesis (Fig. 2.2) included the initial reduction of lactone **8** to diol **9a**, being commercially available, converted to ether **9b** under the influence of a

mixture of acetic anhydride with *N*,*N*-dimethylaminopyridine in pyridine. The interaction of substance **9b** with boron trifluoride etherate has been accompanied by a stereospecific rearrangement with product **10a** formation.

In processing of the ether **10a** KOH/MeOH, hydrolysis results in the formation of alcohol **10b**. It has been found that conditioning at room temperature within a benzene solution, an alcohol **10b** equimolar mixture with diketene in the presence of a catalytic amount of pyridine contributes to the acetyl acetate **11** formation.

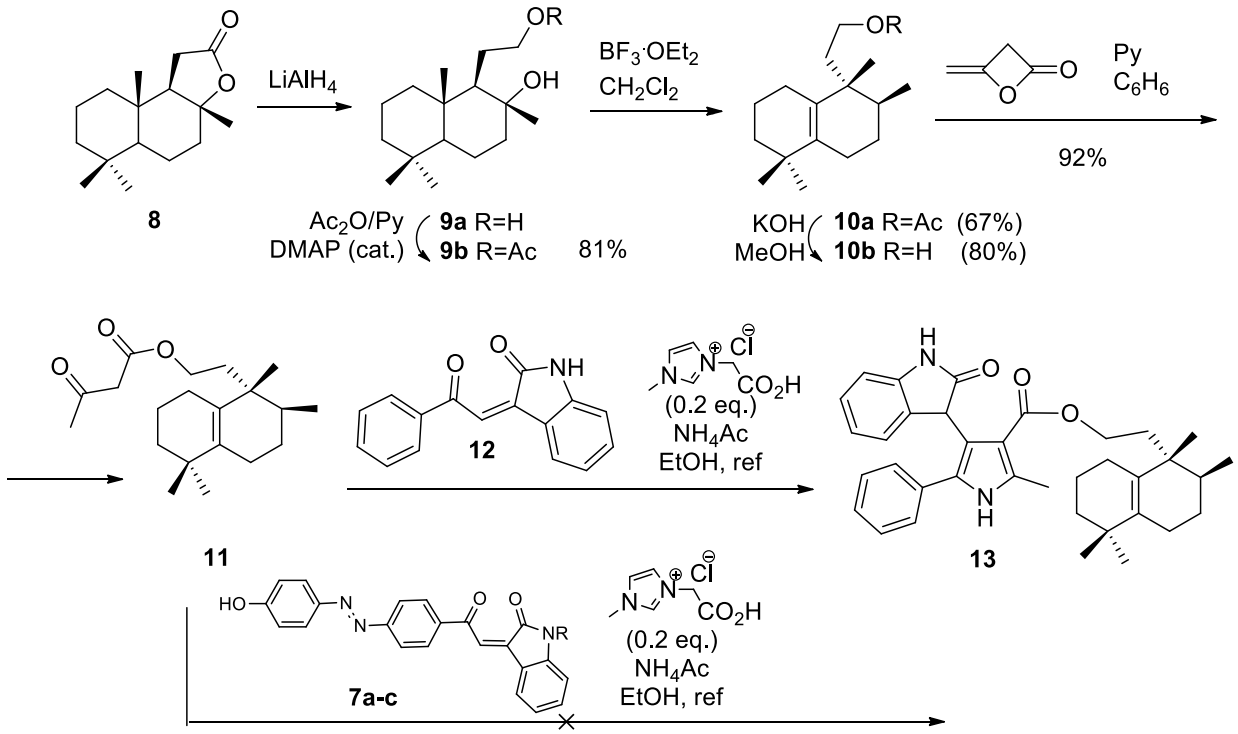


Fig. 2.1 Scheme of synthesis of 3-pyrrole functionalized oxindoles

The target pyrroles are not formed in the reaction of enones **7a-c**, ammonium acetate and acetylacetate **11** in the presence of a carboxy-functionalized ionic liquid. The enones **7a-c** substitution with substance **12** led to the product **13** formation.

The property of cyclopentyl ether derivatives of *L*-leucine **14** to easily penetrate into the cell is well-known, while it is hydrolyzed under the influence of intracellular esterase, whereas the substance with a free carboxyl group is not excreted from the cell, thereby increasing the bioactive substance concentration inside the cell.

The pyrrole functionalized oxindole synthesis with a leucine **16** fragment (Fig. 2.3) was carried out by condensation of enone **12**, cyclopentyl ether of leucine **14** and acetoacetic ether **15**.

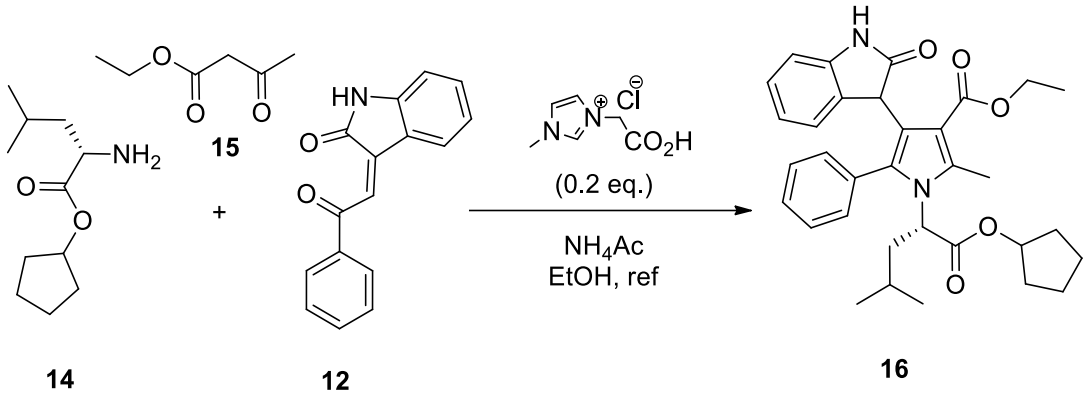


Fig. 2.2 Scheme of substance 16 synthesis

It should be noted that products **13** and **16** tautomerism in the abovementioned solutions has been established by NMR spectroscopy method, thus, they act as lactim or lactam.

2.2 Synthesis of 3-hydroxy-2-oxindoles

3-Substituted 3-hydroxy-2-oxindoles are fairly widely represented among biologically active substances [12,13]. For convolutamidine A **21c**, in which the 4,6-dibromo-3-hydroxyoxindole structural fragment at the C-3 carbon atom is linked with a 2-oxopropyl substituent, not only antitumor activity [14,15] has been established, but also an analgesic effect in comparison with its analogues **21a** and **21b** [16].

Structural hybridization is one of the methods for constructing potential drugs containing fragments of known biologically active substances [17]. This part of the research is devoted to the hybrid molecules synthesis based on oxindoles **21a-e** (Figure 2.4), in which the 3-hydroxy-2-oxindole fragment is linked via a 2-oxopropyl linker [18,19,20].

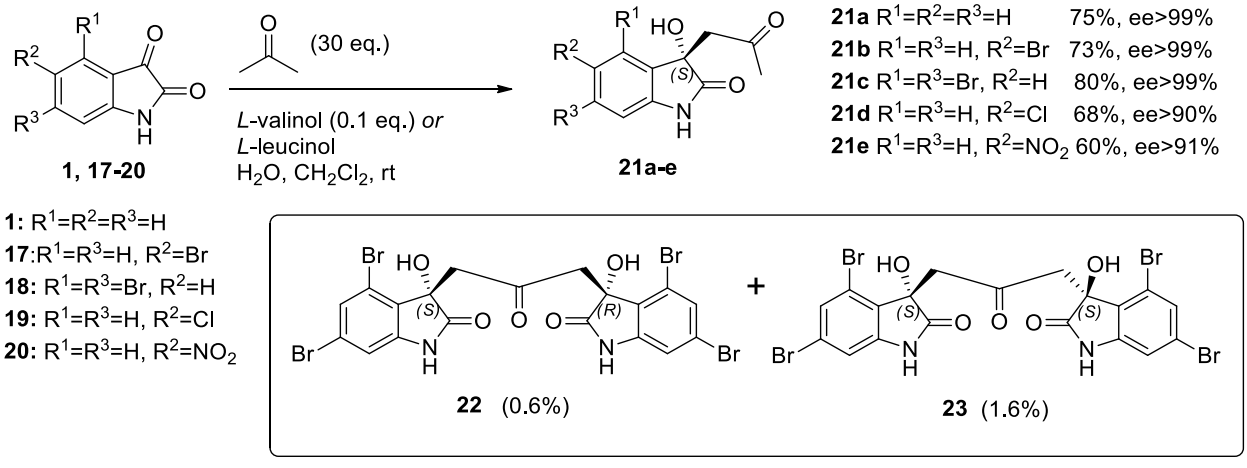


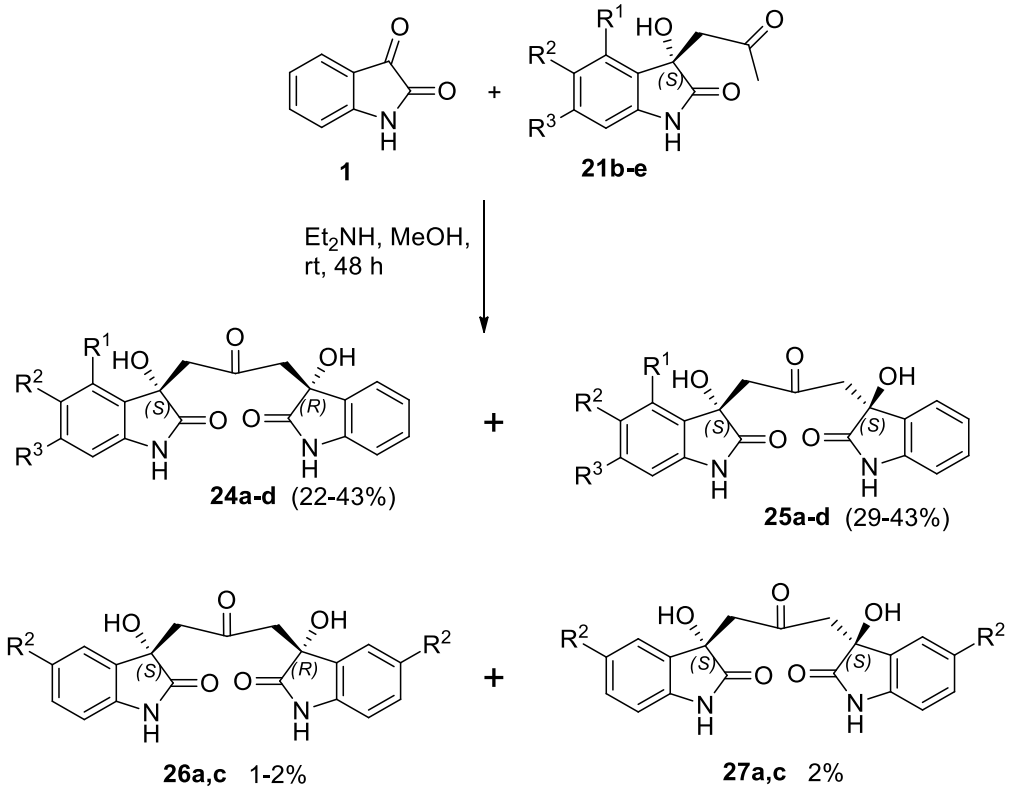
Fig. 2.3 Synthesis of convolutamidine A analogs

Well-known methods for the (-)-convolutamidine A **21c** synthesis include the *L*-leucinol

catalyzed interaction of 4,6-dibromisatin **18** with acetone [21, 22, 23]. We found out that a mixture of three compounds is formed under the described conditions [20]. In addition to compound **21c** (80% yield), bis-adducts **22** and **23** were isolated with yields of 1.6% and 0.6%, respectively.

Assuming the limiting factor for the cross-aldol condensation products formation is the poor solubility of adduct **21c** in the CH_2Cl_2-H_2O mixture, the latter was replaced by MeOH. Conditioning the reaction mixture under new conditions did not lead to an increase in products yield, whereas the main product **21c** was formed in the racemate form, consistent with the data [23] on the effect of solvent nature on the reaction enantioselectivity. The use of other primary amines, such as *L*-valinol, *L*-prolinol, *trans*-4-hydroxy-*L*-proline, as catalysts, was not successful. Only trace amounts of products were formed, both in the methylene chloride medium or methanol medium, using cinchonidine or DABCO. Many by-products were formed in the reaction mixture, in the case of piperidine, while the substances **22** and **23** formation was observed upon diethylamine catalysis, the yield was 40% and 37%, respectively. Thus, we have found that diethylamine is the most optimal catalyst in the reaction for the bis-adducts preparation.

The next stage of the research was (-)-convolutamidine A **21c** asymmetric derivatives synthesis and its analogues linked through a 2-oxopropyl linker (Fig. 2.5).



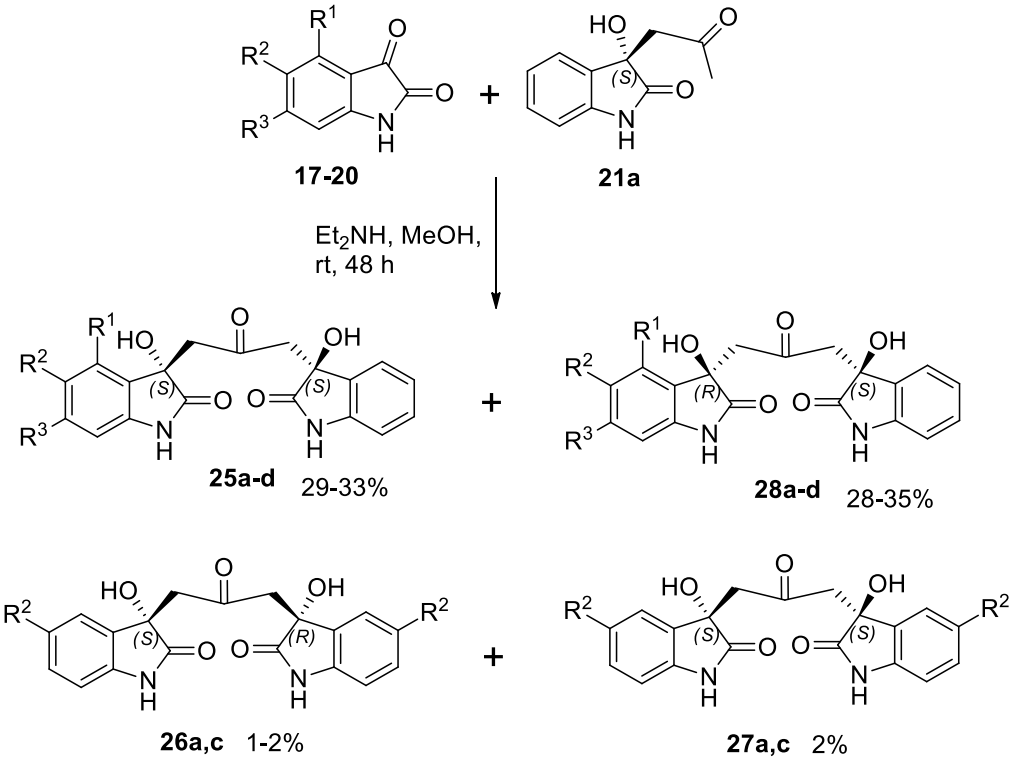
21-27a: R^1=R^3=H, R^2=Br **21-25b** R^1=R^3=Br, R^2=H **21-27c** R^1=R^3=H, R^2=Cl **21-25d** R^1=R^3=H, R^2=NO_2

Fig. 2.4 Synthesis of cross-aldol condensation bis-adducts

Using the optimal conditions revealed by us, analogues - substances **24a-d** and **25a-d** with yields of 22-43% were obtained from isatin **1** and substituted cross-aldoles **21b-e**. Symmetric bis-adducts of cross-aldol condensation **26 a,c** and **27a, c** have been found in trace amounts, as well.

In order to determine the obtained substances stereochemistry, a counter synthesis was carried out. In the reaction with unsubstituted cross-aldol **21a**, substituted isatines **17-20** have been used instead of isatin **1** (Fig. 2.6).

A common diastereomer **25a-d** has being formed in both reactions. The substances **24**, **25**, **28** stereochemistry was determined by the plane-polarized light rotation angle. The stereomer **25** had the same sign and value $[\alpha]_D^{25}$, in both syntheses, as well as the second substance **28** in the counter reaction has the same value $[\alpha]_D^{25}$ as **24**, but the opposite sign; notably, the substances **28** and **24** are enantiomers.



25-28a R^1=R^3=H, R^2=Br **25b,28b** R^1=R^3=Br, R^2=H **25-28c** R^1=R^3=H, R^2=Cl **25d,28d** R^1=R^3=H, R^2=NO_2

Fig. 2.5 Synthesis of cross-aldol condensation bis-adducts

2.3 Synthesis of isatin aldoles with cyclic ketones

Earlier studies [24, 25] reported the condensation cyclohexanone with isatin **1,** which formed a racemic mixture of oxindoles **29a-d**, which exhibited anticonvulsant activity.

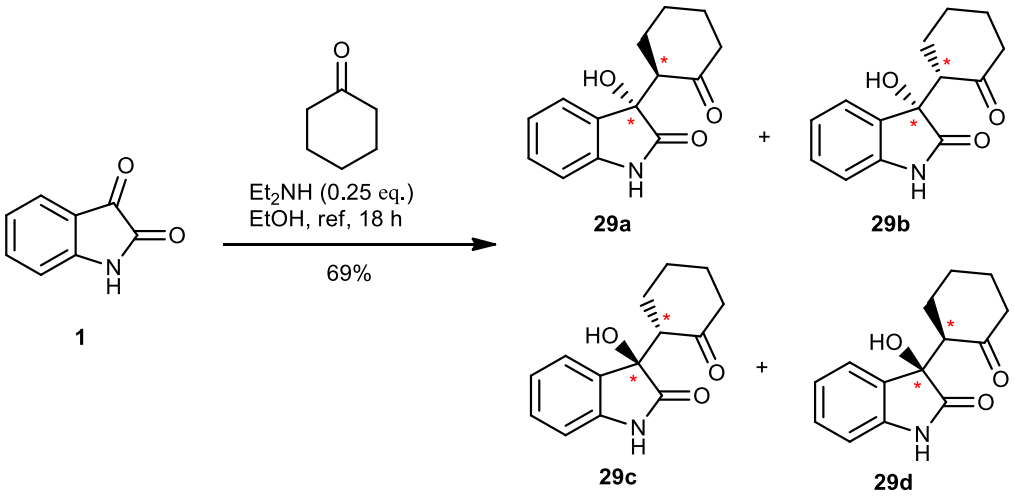


Fig. 2.6 Reaction of isatin interaction with cyclohexanone, catalyzed by Et_2NH

Under the conditions (25 mol% diethylamine in absolute ethanol during boiling), indicated by the authors [24], a products mixture was obtained by us, which contained, according to the chromatographic analysis on the chiral column, an equal mixture of compounds **29a**, **29b**, **29c**, **29d** (Fig. 2.7).

In order to develop a stereoselective method for the described compound synthesis, the solvent effect on the cyclohexanone cross-aldol condensation reaction with isatin **1** [26, 27, 28, 29] was investigated by us. It was found that replacing absolute ethanol with a mixture CH_2Cl_2-H_2O in this reaction in combination with a decrease in the amount of diethylamine catalyst to 10 mol% at room temperature for 48 hours leads to an increase in diastereoselectivity with a diastereomeric ratio of 87:13 and yield 63%.

It was found that the cyclohexanone cross-aldol condensation with isatin **1** in CH_2Cl_2-H_2O mixture is catalyzed by 10 mol.% (-)-valinol, whereas the isatin **1** complete conversion at room temperature took place within 48 hours (Fig. 2.8). Uniquely two out of four compounds are formed under these conditions with a diastereomer ratio of 98:2 and an enantioselectivity of 99%, with a yield of 65% of the total product.

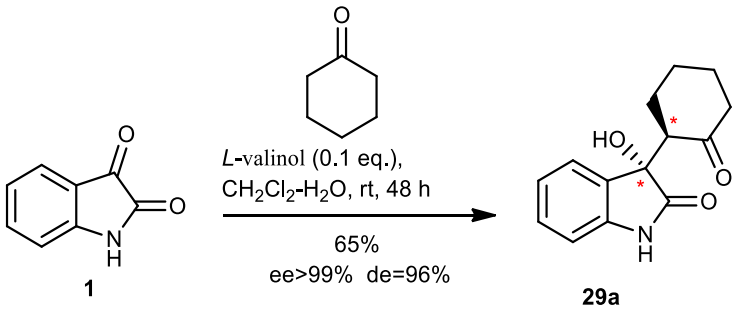


Fig. 2.7 Scheme of asymmetric synthesis of 3-hydroxy-3 - (2-oxocyclohexyl)indoline-2-one

The compound **29a** structure was determined by NMR method. Within the framework of the NOESY spectrum (Fig. 2.9), an interaction between the hydrogens of the OH (δ_H 5.83 ppm) and CH (δ_H 3.08 ppm) groups was observed, suggesting the following structure of (*S*)-3-hydroxy-3-[(*R*)-2-oxocyclohexyl]indoline-2-one **29a**. The absolute configurations were determined by comparing the NMR spectra $[\alpha]_D^{25}$ and the literature data [30, 31].

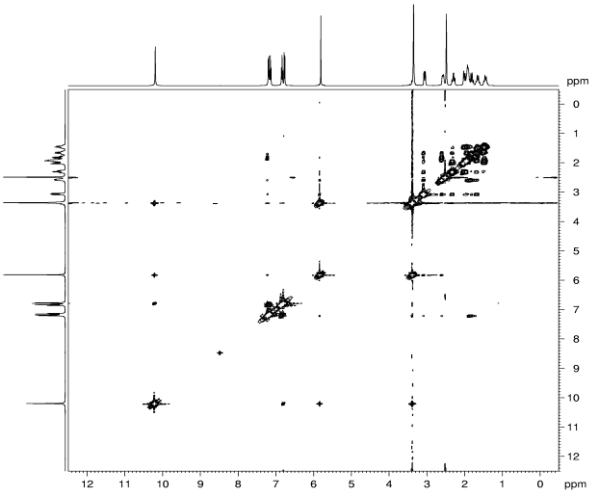
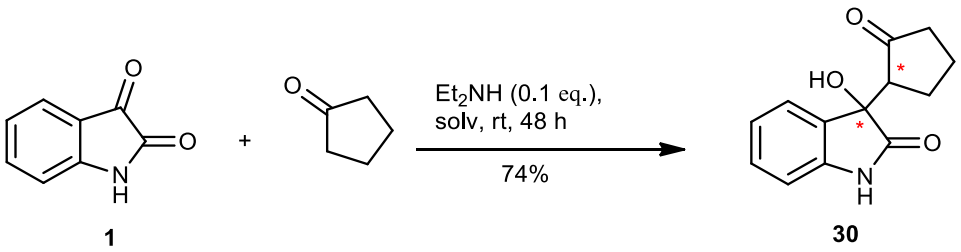


Fig. 2.8 NOESY spectrum of substance 29a

It was found that the MeOH substitution with CH_2Cl_2-H_2O within the framework of the cyclopentanone cross-aldol condensation reaction with isatin **1** also leads to diastereoselectivity increase. (Fig. 2.10).

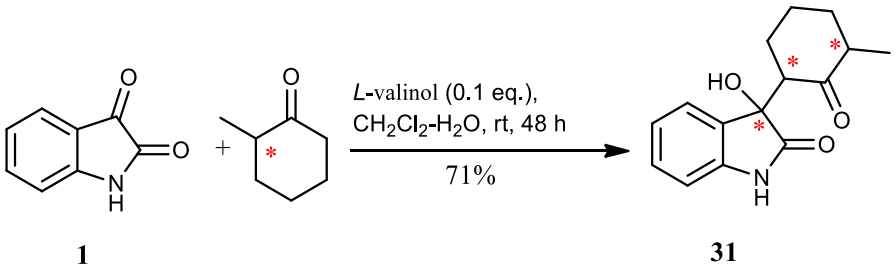


1 **30**

Fig. 2.9 Scheme of 3-hydroxy-3-(2-oxocyclopentyl)indoline-2-one synthesis

According to the data of the chiral column analysis, two out of four compounds **30** are formed with a diastereomer ratio of 94: 6.

2-Methylcyclohexanone has also been investigated as a nucleophile for cross-aldol condensation with isatin 1 (Fig. 2.11).



1 **31**

Fig. 2.10 Scheme of 3-hydroxy-3-(3 methyl-2-oxocyclohexyl)indoline-2-one synthesis

We have demonstrated that the racemic methylcyclohexanone condensation with isatin 1 in the dichloromethane - water solvent system is catalyzed by 10 mol.% of *L*-valinol for 2 days, uniquely three out of eight potential compounds are formed, with a total yield of 71%. These are diastereomers.

2.4 Bioassay results

The synthesized compounds were tested concerning the ability to inhibit the replication of HIV-1 (strain IIIB) and HIV-2 (strain ROD) in acutely infected MT-4 T-cell leukemia cells, with parallel determination of own cytotoxicity, in the same cells. Aldol **6a** and dehydration product **7a** exhibit different levels of cytotoxicity with CC_{50} values of 0.0301 and 0.0031 mM, respectively. Nitrogen-derived substance **5** exhibited the lowest cytotoxicity of all the studied azo compounds with a CC_{50} index value of 0.1878 mM. The sesquiterpene derivatives cytotoxicity increases compared to the initial lactone **8** (CC_{50} 0.2690 mM) when switching from five-membered cycle to diol **9a**, it increases while the bicyclic fragment structure is replaced to **10b**, and decreases when switching to a polyfunctionalized oxindole derivative with a pyrrole fragment. Concurrently, acetoacetate **11** (CC_{50} 0.0315 mM) has the highest cytotoxicity among sesquiterpene derivatives. Hybrid substance **16** with a *L*-leucine cyclopentyl ether fragment has a much higher cytotoxicity than compound **13**, with values 0.1602 and 0.0116 mM, respectively.

The bromine-substituted aldoles cytotoxicity is approximately the same and lies in the range of 0.1970-0.2470 mM. The cytotoxicity of enantiomers **24b** and **28b** (0.2050 and 0.2450 mM) is not radically different. The cross-aldol **21a** cyotoxicity is lower than bromine-substituted **21b** cyotoxicity and consists of 0.570 mM.

The inhibitory activity against HIV of all substances was equal or lower than cytotoxicity.

3. SYNTHESIS OF SPIROOXINDOLES

3.1 Preparation of *N*-glycosylated spiro[oxindolethiadiazoles]

The modification of the oxindole fragment substituent with a reactive amino group in the 1,3,4-

thiodiazoline molecule can lead to the formation of new compounds with antiviral activity. It was previously reported that spiro[oxindol-(1,3,4-thiodiazoline)] demonstrated good activity against the MT-4 cell colony and noticeable activity against HIV-1 [32, 33].

In order to obtain glycosylated isatins, the reaction of **5** methylisatin with glucose was studied in methanol, ethanol and water [34, 35, 36, 37]. At the same time, the reaction time, temperature, reagents concentration and pH medium were modified, however, the desired substances could not be obtained. Replacing glucose with mannose did not change the situation, suggesting that the presence of a free amino group, instead of an amide group, plays an important role in the molecule reactivity. To obtain the desired products, it had been decided to synthesize anilides firstly, which can subsequently be converted into *N*-glycosylated isatins by the Stolle method.

The study has demonstrated that boiling a methanol solution of 4-methylaniline **32a** with glucose for 24 hours and further proceeding by acetic anhydride in pyridine leads to adduct formation, isolated as tetraacetate **33a** (Fig. 3.1).

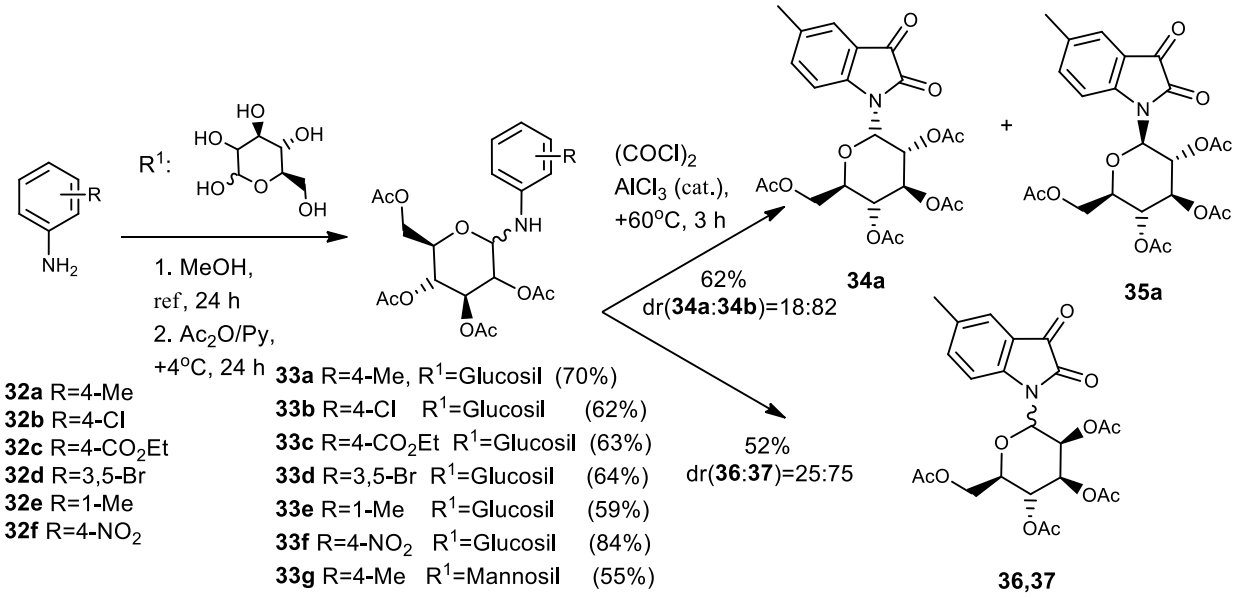


Fig. 3.1 Scheme for the production of glycosylated isatins by the Stolle method

To introduce two carbonyl groups into the aminoglycoside molecule, the nitrogen atom acylation was carried out with simultaneous electrophilic substitution by the Friedel-Crafts reaction. The compound **33a** mixture stirring with oxalyl chloride at 55-60 °C with $AlCl_3$ within 3 hours led to the cyclic products mixture formation, managed to divide into individual α- and β-anomers **34a** and **35a**. It should be noted that substances **33b**, **33c**, **33d**, **33e**, **33f** have been tarred after the catalyst $AlCl_3$ adding at 40 ℃ and the target reaction products were not detected even in trace amounts. The isatins anomeric glycosides **36** and **37** based on **33g** were obtained in

a moderate yield, and couldn't be separated.

Thus, it can be concluded that the stage of obtaining glycosidized isatins cannot be carried out by the Sandmeer method due to the glucose fragment presence in the molecule. However, the Stolle method also imposes restrictions on the reagent structure, in view of the fact that it should not contain iodine-, bromine-, chlorine-, ester-, carboxyl-, hydroxyl- groups, as well as primary amino group.

The interaction between thiosemicarbazide and isatin **35a** in 65% yield leads to the thiosemicarbazone **38** formation (Figure 3.2), turning into a derivative **39** while being treated with a NaOMe solution in MeOH.

We have discovered that heating thiosemicarbazone **38** in acetic anhydride for 6 hours leads to its heterocyclization with simultaneous acylation into stereoisomeric spiro[oxindoltiadiazoles] **40a** and **40b** individually isolated.

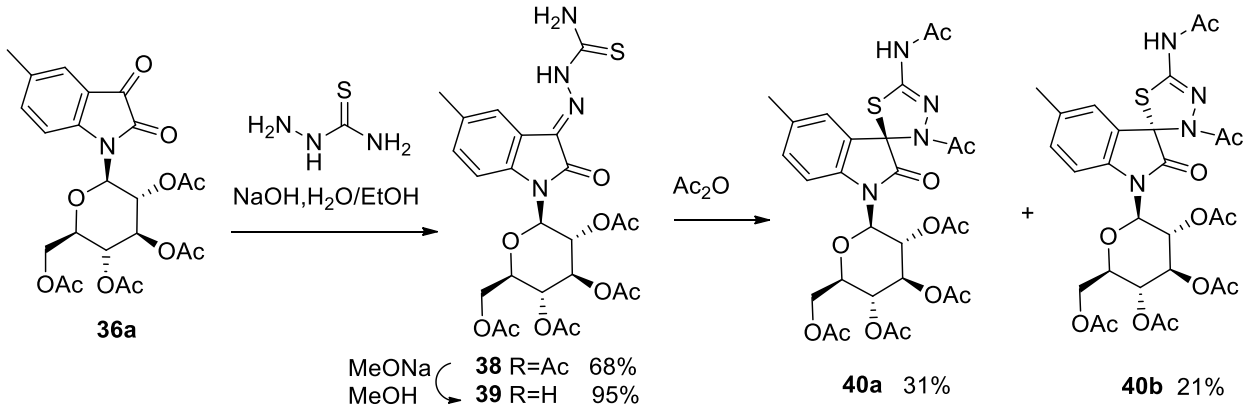


Fig 3.2 Scheme for the production of *N*-glycosylated spiro[oxindoltiadiazoles]

The compound **40a** absolute configuration was determined based on X-ray diffraction analysis data.

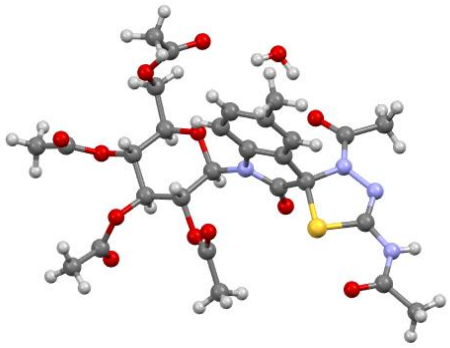
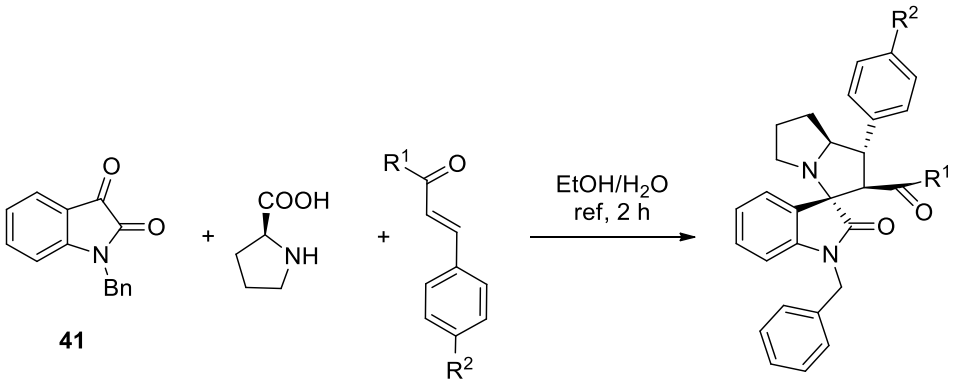


Fig. 3.3 Crystal structure of the substance 40a

3.2 Synthesis of spiro[oxindolpyrrolizidines]

Pyrrolizidine derivatives are widely represented among both biologically active alkaloids and among synthetic substances obtained by introducing an oxindole substituent. The 1,3-dipolar cycloaddition reaction is considered as one of the promising methods for spiro[oxindolpyrrolizidines] [38-42] preparation. The selectivity of reaction of the *L*-proline, isatin and chalcones was investigated aimed to develop this direction.

It was found that the reaction proceeds stereospecifically when reagents are boiled in an aqueous-alcohol solution for 2 hours (Fig. 3.4).



42a R^1=Me, R^2=H	**43a** R^1=Me, R^2=H (40%)
42b R^1=C_6H_5, R^2=H	**43b** R^1=C_6H_5, R^2=H (53%)
42c R^1=C_6H_5, R^2=$N(CH_3)_2$	**43c** R^1=C_6H_5, R^2=$N(CH_3)_2$ (50%)
42d R^1=4-$MeOC_6H_4$, R^2=$N(CH_3)_2$	**43d** R^1=4-$MeOC_6H_4$, R^2=$N(CH_3)_2$ (46%)
42e R^1=C_6H_5, R^2=F	**43e** R^1=C_6H_5,, R^2=F (60%)

Fig. 3.4 Scheme of synthesis of spiro[oxindolpyrrolizidines] 43a-e

The chalcones **42a-e** interaction with *L*-proline and isatin **41** leads to the spirooxindoles **43a-e** formation, isolated with yields of 40-60%. This reaction proceeds with high diastereoselectivity.

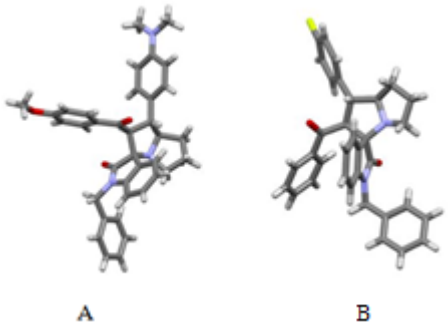


Fig. 3.5 Crystal structure of spirooxindoles 43d (A) and 43e (B)

We found that with the participation of *trans*-4-hydroxy-L-proline, α, β-unsaturated ketones 42b, 47 interact with isatins 1, 17, 41, 44, 45, 46 at room temperature for one day, or by boiling in ethanol for 15 min, i.e., the reaction proceeds faster than with *L*-proline with the

formation of only two of the 32 possible stereoisomers (Fig. 3.6). It is essential to emphasize that this is a simple method for obtaining easily separated optically active spirooxindoles **48a-h** and **49a-h**, finally allowing the investigation of biological properties.

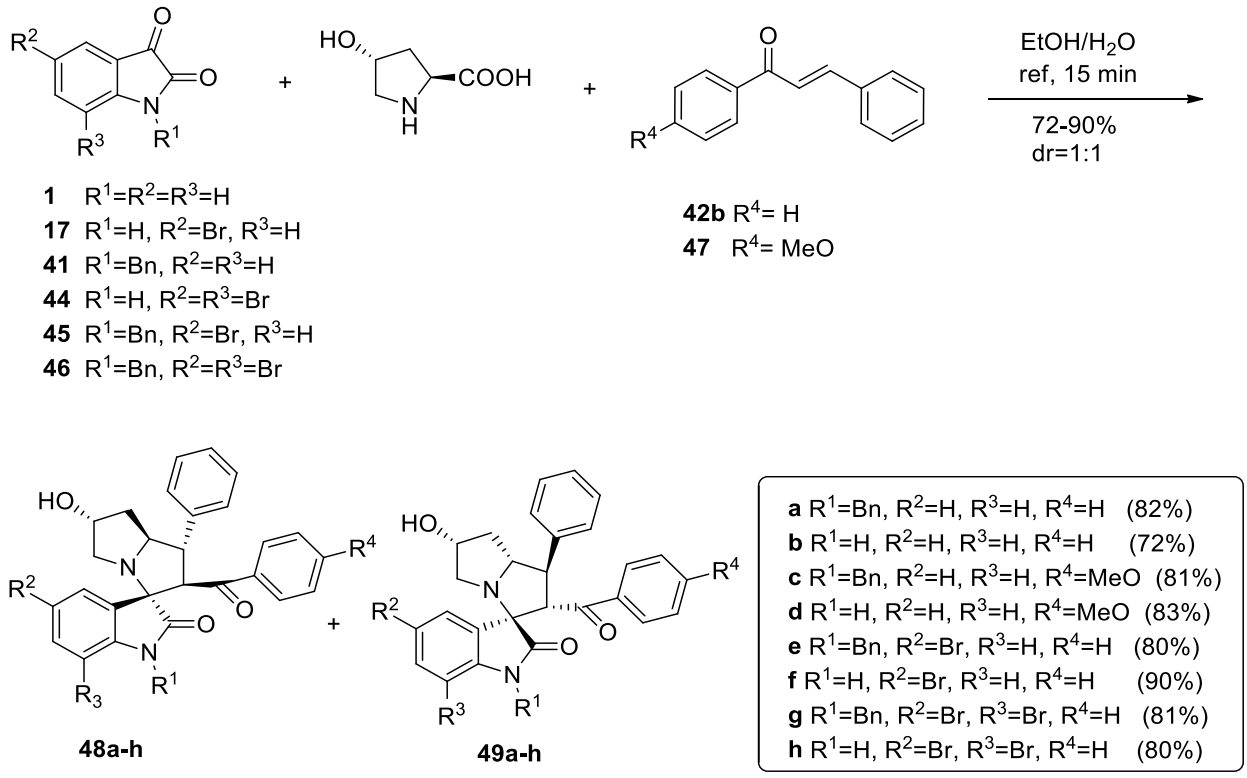
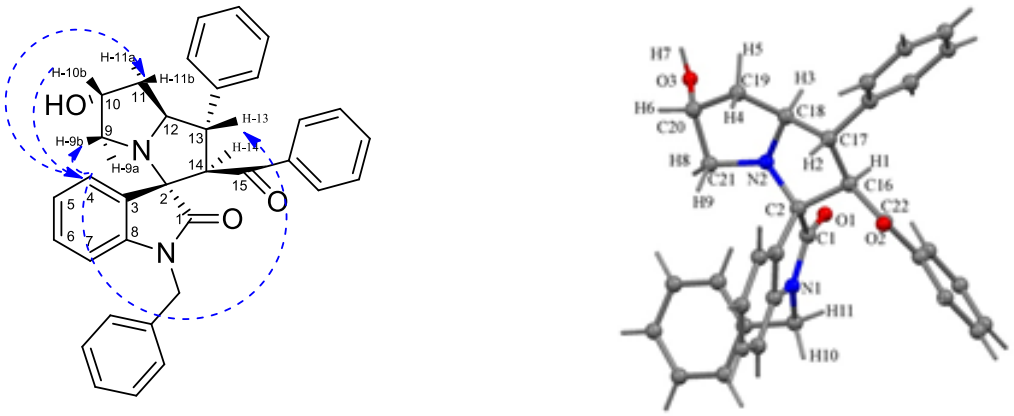


Fig. 3.6 Scheme of synthesis of spiro[oxindolpyrrolizidines] 48a-h, 49a-h

The absolute configuration of diastereomers **48a-h**, **49a-h** was established using the NOESY experiment, taking into account the stereochemistry of heminal hydrogen with a hydroxyl group. The chiral atoms of C-10, 12, 13, 14 absolute configurations were determined based on the well-known H-10 configuration. The C-2 stereochemistry was determined by the H-4 interaction with one of the hydrogens while C-9.

The substance **48a** configuration at C-10 is preserved during the reaction and it is well-known (Fig. 3.7). The hydroxyl group hydrogen is absent in the spectrum, but there is H-10 (4.54-4.49 m. d.), having an interaction with H-4 (7.22 m. d.) within the NOESY spectrum, interacting in turn with both H-9b (2.99 m. d.), H-11b (2.04 m. d.) and H-13 (4.00 m. d.). The isatin fragment has a flat structure and is perpendicular to the book-shaped pyrrolizidine cycle (N-C12 bond fold); the benzene ring is turned in the same direction as the hydrogens H-9b,10,11b,13, with which H-4 interacts.



A ***B***

A – hydrogens interaction through space, according to the substance **48a** NOESY spectrum,

B – substance **48a** crystal structure

Fig. 3.7 Determination the substance 48a structure

The absolute configuration of spiran **48a** chiral centers was confirmed using the X-ray diffraction analysis method.

3.3 Bioassay results

Glucopyranosylamines **33a-d**, **e, g** exhibit different cytotoxicity levels in relation to the MT-4 cell line with values (CC_{50} 0.0087-0.7430 mM). The substance **33b** has demonstrated the highest cytotoxicity of all the tested compounds. The lowest cytotoxicity has the 4-methyl derivative **33g**. Concerning the substance **33a** CC_{50} of 0.0469 mM, its cytotoxicity is around twice as high as that of **33c**. The substances **33d** and **33e** have the same cytotoxicity equal to CC_{50} 0.28 mM.

Further cytotoxicity changing is associated with changes in the hydrocarbon skeleton. It fluctuates in a small range of CC_{50} 0.11-0.31 mM in the anomers **36**, **37**, isatin **35a** and its thiosemicarbazones **38**, **39** derivatives, as well as spiro[oxindolthiodiazoles] **40a**, **40b**.

The cytotoxicity of spiro[oxindolpyrrolizidines] with a substituent in the benzene ring **43c,d,e** (CC_{50} 0.1633-0.2419 mM) is several times lower than that of substance **43b** (CC_{50} 0.0719 mM).

In the presence of OH- group in a pyrrolizidine fragment, the cytotoxicity of substances **48c,d,f,g,h** and **49g** increases several times and is CC_{50} 0.0185-0.0265 mM, the substituents in the oxindole fragment aromatic circle, as well as the benzyl group at the nitrogen atom, do not affect it in any way. The diastereomers **48g** and **49g** have similar cytotoxicity values. Compound **48e** has a lower cytotoxicity equal to 0.0821 mM.

These substances have also been tested for the ability to inhibit HIV replication, however,

it was found to be lower or equal to cytotoxicity.

In conclusion, it should be noted that studies have been carried out for antimicrobial activity against the bacteria *Xantomonas campestris*, *Bacillus subtilis*, and a yeast-like fungus-*Saccharomyces cerevisae*. The compounds **34a**, **35a**, **40a** and **40b** have not demonstrated any activity, while **38** inhibited the growth of *Xantomonas campestris*, *Bacillus subtilis* at MIC $2.5*10^{-5}$ mM concentration and *Saccharomyces cerevisae* at MIC $5*10^{-5}$ mM.

GENERAL CONCLUSIONS AND RECOMMENDATIONS

1. A certain cycle of studies was carried out concerning to organic synthesis selective pathways development for 75 compounds of the oxindole and spirooxindole series, including 58 previously unknown ones. Four compounds have been investigated by X-ray diffraction and their biological properties were studied, as well.
2. The prospects of using the diterpene alcohol sclareol optically active derivative has been illustrated, for the construction of a polyfunctionalized oxindole derivative with a pyrrole fragment.
3. The analysis of the dependence of the reaction course of cross-aldol condensation on the nature of the catalyst, solvent and substituent was carried out for the first time, both in prochiral indoldione-2,3 and in its adduct with acetone, in the directed synthesis of symmetric and unsymmetrical derivatives of (-)-convolutamidine A and analogs, in which the 3-hydroxy-2-oxindole moieties are linked through a 2-oxopropyl linker.
4. The possibility of regulating the regio- and enantioselectivity of the the solvent system CH_2Cl_2 - H_2O in the presence of 10 mol% (-)-valinol was demonstrated by the example of the isatin reaction with cyclic ketones. In the case of an isatin adduct with cyclohexanone, only (*S*)-3-hydroxy-3-((*R*)-2-oxocyclohexyl) indoline-2-one is formed, out of four potential compounds, with diastereoselectivity of 96% and enantioselectivity of 99%.
5. The optimal pathways for *N*-glycosilated isatins obtaining have been investigated. The possibility of synthesis has been shown for the first time, and the absolute *N*-glycosilated spiro[oxindoltiadiazoles] configuration based on 4-methylaniline has been established.
6. The optimization of the conditions for the isatin adducts synthesis with α,β-unsaturated ketones and proline has been carried out, leading to the spiro[oxindolpyrrolizidines] stereoselective formation. The use of *trans*-4-hydroxy-*L*-proline allows to synthesize enantiomerically pure hydroxyfunctionalized spiro[oxindolpyrrolizidines] with high diastereoselectivity.
7. Promising compounds for further in-depth studies of drugs with desired properties were

identified among the synthesized substances as a result of the bioassay for antiviral, antibacterial, antifungicidal activity and cytotoxicity.

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

1. The revealed patterns and features of synthetic indoline-2-ones transformations open up new opportunities for its directed structural modification and expand the theoretical understanding of the chemical properties of functionally substituted oxindoles. The new data obtained concerning the cross-aldol condensation reaction, as well as dipolar cycloaddition, complement the theoretical understanding of oxindoles reactivity and can be used to form similarly constructed substances with desired properties.
2. The utilization of patented (-)-valinol-CH_2Cl_2-H_2O system allows to synthesize optically active oxindole derivatives, and also, can be used to obtain other practically important hydroxyl functionalized organic substances.
3. The developed methods formed the basis for the heterocyclic compounds series selective synthesis. The structure-property relationship analysis has demonstrated its diverse bioactivity and potential for practical applications both for pharmaceutical chemistry and as a chemical protecting agent for agricultural plants in the Republic of Moldova.

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ANNOTATION

Bilan Dmitri Iaroslav, "Synthesis and study of optically active oxindoles". The doctor dissertation in chemical sciences. Chisinau, Republic of Moldova, 2022.

Dissertation contents: the thesis includes an introduction, 3 chapters, general conclusions and recommendations, a list of references of 144 titles, 108 pages of the main text, 76 figures, 3 tables. The results are published in 21 scientific papers.

Keywords: oxindole, isatin, chiral substance, cycloaddition, asymmetric synthesis.

The goal of the scientific work: investigation of the routes for selective synthesis of optically active substituted oxindoles on the basis of isatins, investigation of their structure and properties.

The research objectives: the elaboration of simple and effective synthetic schemes for obtaining the new substituted oxindoles starting from isatins; study of the regularities of cross-aldol reaction by using chiral catalysts; exploration of the synthetic routes towards the optically active *N*-substituted isatins; investigation of the reactions of obtaining spirooxindoles from isatin, natural amino acids and chalcones; evaluation of the "structure-bioactivity" relationship for a number of the synthesized substituted oxindoles based on the obtained data.

The novelty and the scientific originality of the work consists in the development of selective routes for the synthesis of previously unknown compounds belonging to the oxindole series, four of them being characterized by X-ray structural analysis, as well as study of their properties; the possibility of obtaining the potentially bioactive *N*-glycosylated isatins and spirooxindoles has been presented; the synthetic routes towards a series of new chiral hybrid molecules containing the pyrrolizidine fragment, found in alkaloids, have been investigated; a method was developed for the preparation of symmetrical and unsymmetrical derivatives of natural convolutamidine A and analogs, in which the 3-hydroxy-2-oxindole fragments are linked through an 2-oxopropyl linker.

The solved scientific problem consists in the determination of the optimal conditions for the synthesis of heterocyclic compounds of the oxindole series potentially endowed with biological activity and investigation of the "structure-bioactivity" relationship, as well. The optimal conditions for the synthesis of bis-adducts of isatins with acetone have been established. For the first time, a highly stereoselective method for the preparation of (*S*)-3-hydroxy-3-((*R*)-2-oxocyclohexyl) indolin-2-one has been proposed.

Theoretical significance of the dissertation. The perspective of using a derivative of the natural diterpenoid sclareol and the cyclopentyl ester of *L*-leucine for the construction of an optically active polyfunctionalized derivative of oxindole containing the pyrrole moiety, has been illustrated. The features have been revealed, regarding the α-aminoalcohols- catalyzed aldol condensation reaction of isatins with acetone. It was found, that the stereoselectivity of the aldol condensation of indolinedione with cyclic ketones is influenced by the nature of the solvent and catalyst.

Applicative value of the dissertation: The developed methods formed the basis for the selective synthesis of a series of heterocyclic compounds of oxindole series. The analysis of the "structure-property" relationship revealed the cytotoxicity of some compounds against the T-cell leukaemia MT-4, and fungicidal and bactericidal activity too, thus being of practical interest, including also photodynamic therapy.

Implementation of the scientific results: The patented method of diastereo- and enantioselective construction of optically active oxindoles has been applied in the scientific research activity of Laboratory of Organic Synthesis of the Institute of Chemistry. Data on the cytotoxicity pointed out the promising substances for further in-depth research.

ADNOTARE

Bilan Dmitri Iaroslav „Sinteza și studiul oxindolilor optic activi”.
Teză de doctor în științe chimice. Chișinău, Republica Moldova, 2022

Structura tezei. Teza constă din introducere, 3 capitole, concluzii generale și recomandări, bibliografie ce include 144 de titluri, 108 de pagini de text de bază, 76 de figuri, 3 tabele. Rezultatele cercetărilor efectuate sunt expuse în 21 de lucrări științifice.

Cuvinte cheie: oxindol, isatină, substanța chirală, cicloadiție, sinteză asimetrică.

Scopul lucrării constă în: cercetarea modalităților de sinteză selectivă a oxindolilor optic activi substituiți, pe bază de isatine, evaluarea structurii și proprietăților acestora.

Obiectivele cercetării: elaborarea unor scheme de sinteză simple și eficiente pentru obținerea noilor oxindoli substituiți din isatine; studierea regularităților parcurgerii reacției aldolice cu participarea catalizatorilor chirali; cercetarea căilor de sinteză a isatinelor *N*-substituite optic active; investigarea reacției de obținere a spirooxindolilor pe baza isatinei, aminoacizilor naturali și calconelor; evaluarea relației "structură-activitate" în seria oxindolilor sintetizați.

Noutatea și originalitatea științifică a lucrării constă în dezvoltarea căilor selective de sinteză a unei serii de compuși necunoscuți anterior din seria oxindolului, structura a patru dintre aceștia fiind demonstrată prin metoda difracției cu raze X, și studierea proprietăților acestora; a fost demonstrată posibilitatea obținerii noilor compuși cu potențial înalt de bioactivitate isatinici și spirooxindolici *N*-glicozilați; au fost studiate căi de sinteză a unei noi serii de compuși chirali hibrizi, conținând fragment pirolizidinic caracteristic pentru alcaloizi; a fost dezvoltată o metodă de preparare a derivaților simetrici și asimetrici ai convolutamidinei A naturale și analogilor, în care fragmentele 3-hidroxi-2-oxindolului sunt legate prin linkerul 2-oxipropil.

Soluționarea unei probleme științifice constă în determinarea condițiilor optime de sinteză a noilor compuși heterociclici din seria oxindolică cu potențial de activitate biologică, determinarea relației „structură-bioactivitate”. Au fost stabilite condițiile optime de sinteză a bis-aducților isatinei cu acetona. Pentru prima dată a fost propusă o metodă cu stereoselectivitate înaltă de obținere a (*S*)-3-hidroxi-3-((*R*)-2-oxociclohexil) indolin-2-onei.

Semnificația teoretică a lucrării. A fost demonstrată perspectiva utilizării derivatului diterpenoidei naturale sclareol și a esterului *L*-leucinei cu ciclopentanolul, pentru prepararea derivatului oxindolic polifuncționalizat chiral conținând fragmentul pirolului. Au fost relevate unele particularități, privind rolul catalitic al α-aminoalcoolilor în reacția aldolică cu participarea isatinelor și acetonei. A fost stabilit, că natura solventului și catalizatorului influențează stereoselectivitatea reacției aldolice cu participarea indolindionei și cetonelor ciclice.

Valoarea aplicată a lucrării. Metodele elaborate au servit pentru sinteza selectivă a câtorva serii de compuși heterociclici oxindolici. Analiza relației "structură-proprietăți" a demonstrat, că unii compuși manifestă citotoxicitate pentru leucemia cu celule T MT-4, activitate fungicidă și bactericidă și prezintă interes practic, inclusiv pentru terapia fotodinamică.

Implementarea rezultatelor științifice: Metoda brevetată de construire diastereo- și enantioselectivă a oxindolilor optic activi și-a găsit aplicare în cadrul activității științifice a Laboratorului de Sinteză Organică a Institutului de Chimie. Datele privind citotoxicitatea au identificat substanțe promițătoare pentru cercetări aprofundate ulterioare.

АННОТАЦИЯ

Билан Дмитрий Ярославович, «Синтез и исследование оптически активных оксиндолов». Диссертация на соискание ученой степени доктора химических наук. Кишинёв, Республика Молдова, 2022.

Структура диссертации: диссертация включает введение, 3 главы, общие выводы и рекомендации, библиографию из 144 наименований, 108 страниц основного текста, 76 рисунков, 3 таблицы. Результаты опубликованы в 21 научной публикации.

Ключевые слова: оксиндол, изатин, хиральное вещество, циклоприсоединение, асимметрический синтез.

Цель научной работы: исследование путей селективного синтеза оптически активных замещенных оксиндолов на основе изатинов, изучение их строения и свойств.

Задачи исследования: разработка простых и эффективных схем синтеза новых замещенных оксиндолов на основе изатинов; изучение закономерностей протекания кросс-альдольной реакции при участии хиральных катализаторов; исследование путей синтеза оптически активных *N*-замещенных изатинов; исследование реакции получения спирооксиндолов с участием изатина, природных аминокислот и халконов; на основании полученных данных, оценить взаимосвязь «структура-биоактивность» в ряду синтезированных оксиндолов.

Новизна и научная оригинальность работы заключается в разработке селективных путей синтеза серии ранее неизвестных соединений оксиндольного ряда, для четырех из которых структура была доказана методом РСА, а также изучении их свойств; показана возможность получения потенциально биоактивных *N*-гликозилированных изатинов и спирооксиндолов; изучены пути синтеза серии новых хиральных гибридных молекул с фрагментом пирролизидина, содержащегося в алкалоидах; разработан метод получения симметричных и несимметричных производных природного конволутамидина А и аналогов, у которых 3-гидрокси-2-оксиндольные фрагменты связаны через 2-оксопропильный линкер.

Решенная важная научная проблема заключается в определении оптимальных условий синтеза новых гетероциклических соединений оксиндольного ряда, с потенциальной биологической активностью, изучении взаимосвязи «структура-биоактивность». Выявлены оптимальные условия синтеза бис-аддуктов ацетона с изатинами. Впервые предложен высокостереоселективный метод получения (*S*)-3-гидрокси-3-((*R*)-2-оксоциклогексил)индолин-2-она.

Теоретическая значимость работы. Проиллюстрирована перспективность использования производного природного дитерпеноида склареола и циклопентилового эфира *L*-лейцина, для построения оптически активного полифункционализированного производного оксиндола с фрагментом пиррола. Выявлены особенности катализа *α*-аминоспиртами реакции альдольной конденсации изатинов с ацетоном. Установлено, что на стереоселективность реакции альдольной конденсации индолиндиона с циклическими кетонами влияет природа растворителя и катализатора.

Прикладная значимость работы. Разработанные методы легли в основу селективного синтеза нескольких серий гетероциклических соединений оксиндольного ряда. Анализ взаимосвязи «структура-свойство» показал, что некоторые соединения обладают цитотоксичностью в отношении к линии Т-клеточной лейкемии МТ-4, фунгицидной и бактерицидной активностью, и представляет практический интерес, в том числе для фотодинамической терапии.

Внедрение научных результатов. Запатентованный метод диастерео- и энантиоселективного построения оптически активных оксиндолов нашел применение в научно-исследовательской деятельности Лаборатории Органического Синтеза Института Химии. Данные по цитотоксичности выявили перспективные вещества для дальнейших углубленных исследований.

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BILAN DMITRI IAROSLAV

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143.01 – CHIMIE ORGANICĂ

Rezumatul tezei de doctor în științe chimice

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