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Oxamic acid thiohydrazides and hydrazones based on them as convenient starting compounds for the synthesis of S- and N-containing heterocyclic products. A mini-review

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ABSTRACT

The chemistry of hydrazones is currently undergoing intensive development. For example, thioacylhydrazones, which are synthesized most often from thiosemicarbazides, have become very popular in recent years owing to impressive results of their extensive testing in medicinal chemistry. Their antiviral, insecticidal, antisclerotic, antioxidant, and antiparasitic activities have been demonstrated; thioacylhydrazones showed promise for the development of drugs against COVID-19 and HIV. The ligands based on these compounds with soft donor nitrogen and sulfur atoms are widely used in the creation of complexes with various bioactivities, including strong anticancer properties. Since the replacement of the oxygen atom with a sulfur atom may increase the biological activity of the compound, the desire to expand the spectrum of pharmacological action or to change the type of activity induces understandable interest in thio analogues of acylhydrazones that are known to have high bioactivity. At the same time, there are publications indicating that oxamic acid thiohydrazides containing thioamide and thiohydrazide moieties, due to their polyfunctional nature, can be effectively used in the synthesis of a wide variety of compounds, including bioactive products. This review describes the synthetic and applied potential of poorly investigated oxamic acid thiohydrazides and hydrazones based on them. A considerable benefit of these oxamic acid derivatives is the presence of an additional carboxamide group, which is itself significant for biological processes and can also be easily modified, thus providing a wealth of combinations for the synthesis of new promising products. The review describes convenient methods for the preparation of oxamic acid derivatives of this type and demonstrates their large synthetic potential, which opens up the way to new thiohydrazone analogues and to various heterocyclic compounds, including new-generation antibacterial drugs targeting the secretory system of bacteria, thus suppressing the infectious process and eliminating the pathogen from the body without affecting the proliferation of bacteria.

1. Introduction

The interest in hydrazones as efficient broad-spectrum anti-infective drugs is permanently increasing (Sharma et al., 2020; Boulebd et al., 2022; Liu et al., 2022; Tabbiche et al., 2022; Wang et al., 2023). Acylhydrazones containing the –CO–NH–N = CH– moiety in the molecule have proved to be a versatile class of compounds applicable in various fields of organic chemistry.

A variety of drugs derived from these compounds show antimicrobial, antiviral, anti-inflammatory, antifungal, antibacterial, antitumour, anti-infective, antidepressant, anti-hemorrhagic, myorelaxant, antitrichomonal, capillary-stabilizing, antiarrhythmic, and other types of activity (Mali et al., 2021; Popiołek, 2021; Belyaeva et al., 2022; Socea et al., 2022). Acylhydrazones are investigated for the treatment of Alzheimer's disease (Bozbey et al., 2020; Yang et al., 2023); their anticancer properties have been studied by molecular docking (Çakmak et al., 2022), and promising pesticide components have been reported (Wang et al., 2024). The bioactivity of natural compounds containing acylhydrazone moieties has been studied. It was found that echinopsine has high antiviral and fungicidal activities (Cui et al., 2022), quinolines show antituberculosis and anticancer properties (Mandewale et al., 2017), curcumin (Omidi and Kakanejadifard, 2020) and isatin (de Paiva et al., 2020) have antitumor activities; and chromones possess a high algicidal activity (Tu et al., 2013) and have anticancer and antioxidant

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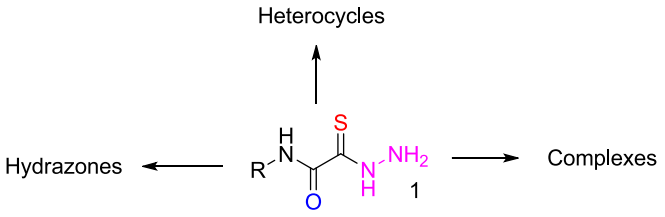
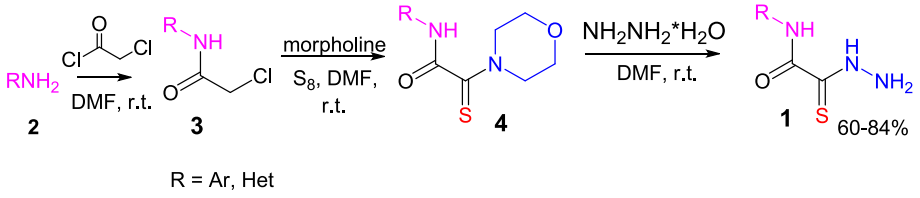


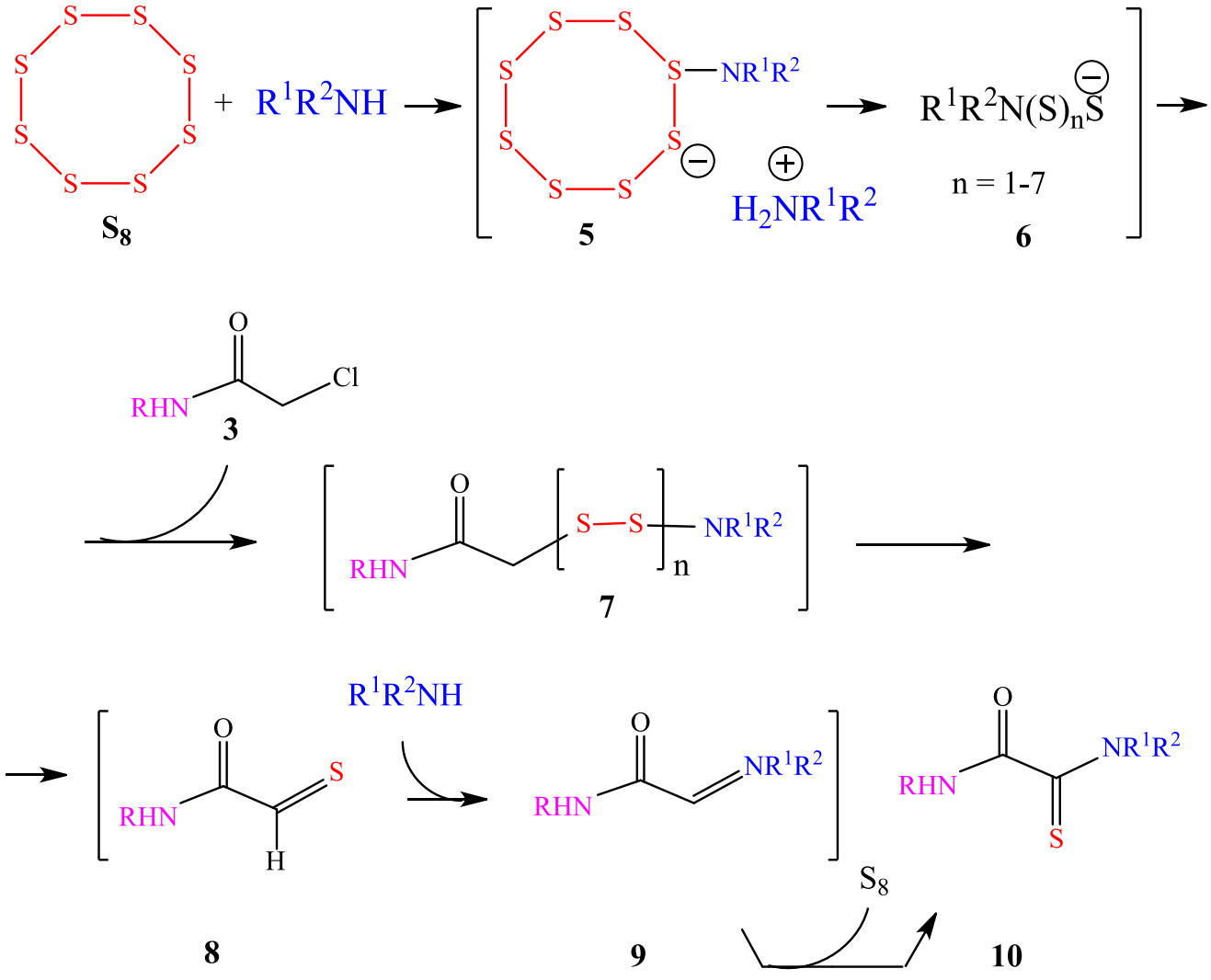
Scheme 1. Synthetic potential of OAT.

properties (Li et al., 2010). Acylhydrazones derived from vanillin were proposed as potential aldose reductase inhibitors (Demir et al., 2023). It is important that the properties of acylhydrazones are far from being limited to biological activity: they are successfully used for spectrophotometric determination of metals (Jabeen, 2022) and for the design of supramolecular complexes (Maiti et al., 2021); a review (Su and Aprahamian, 2014) describes the acylhydrazone-based molecular switches and sensors; and they have also been recommended (Meenatchi et al., 2021) for the design of high-quality nonlinear optical materials.

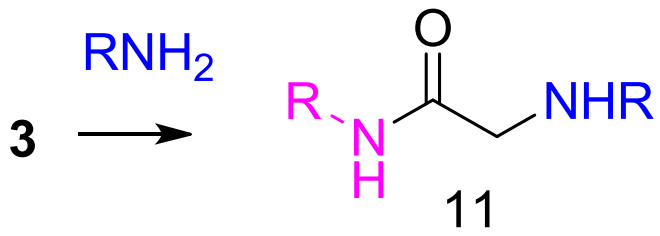
The thio analogues of reported acetylhydrazones, –C(=S)–NH–N = CH–, are of considerable interest since the replacement of the oxygen atom by sulfur may enhance the biological activity of the compound (for example, the piracetam thio analogues are more active than piracetam; Kadushkin et al., 1989; Soerensen and Smith, 1993), expand the range of pharmacological action (glycoluril thio analogues, Kravchenko et al., 2018), or change the type of activity, which is the case, for example, for purines and thiopurines (Bayoumy et al., 2021). Oxamic acid thiohydrazides containing proximate thioamide and thiohydrazide moieties are capable of a wide variety of transformations, owing to their polyfunctional nature and mutual influence of the moieties. Published works



Scheme 2. A convenient method for the preparation of monothiooxamides and OAT from amines.



Scheme 3. Scheme of the reaction of α-chloroacetamides with a mixture of amines and elemental sulfur prepared in advance.



Scheme 4. Side reaction in the synthesis of OAT.

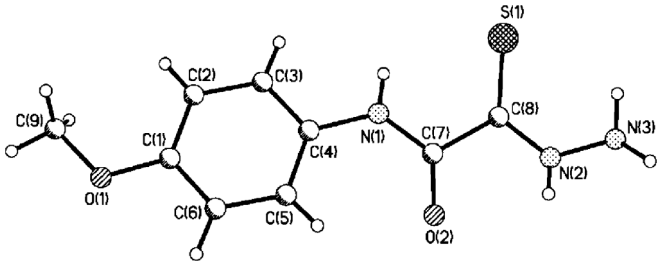
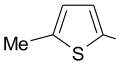
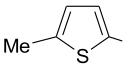


Fig. 1. Molecular structure of OAT 12 (Shirokov, 2005).

on oxamic acid thiohydrazides show their broad synthetic potential for creating original approaches to the synthesis of promising bioactive products such as rhodanine derivatives (Yarovenko et al., 2007), 1,3,4-thiadiazoles (Yarovenko et al., 2003), pyrazolines (Kamernitsky et al., 2007), pyridazines (Komkov et al., 2015), and thiadiazines (Komendantova et al., 2019).

The most studied derivatives are thiosemicarbazones obtained from thiosemicarbazides; they exhibit diverse bioactivity, including antiviral, insecticidal, antisclerotic, antioxidant, and antiparasitic activities, and have been used to synthesize anti-HIV agents (Acharya et al., 2021). Thiosemicarbazones were reported to exhibit anticancer activity (Shakya and Yadav, 2020; Acharya et al., 2021; Ahmed and Almalki, 2021; Dharmasivam et al., 2022) and antibacterial properties (Acharya et al., 2021; Li et al., 2021) and were studied against COVID-19 (Xu et al., 2022). A variety of biological properties were found for thiosemicarbazone metal complexes (Matesanz et al., 2021; Gupta et al., 2022; Khan et al., 2022). Their antibacterial properties have been reported (Souza et al., 2021; Scaccaglia et al., 2022); metal complexes have been tested as diagnostic radiopharmaceuticals (Parrilha et al., 2022) and anti-COVID-19 drugs (Ewert et al., 2022) and, what is especially important, they are effective against various types of tumours (He et al., 2021; Bai et al., 2022; Devi et al., 2022). The thiocarbonyl group of thioacylhydrazones is used for the design of heterocyclic compounds.

Table 1
Effect of substituents on the ratio of the hydrazone tautomers obtained from compounds **39a-h**.

Compounds*	R	R^1	**41**(%)	**40**(%)
39a	H	Ph	90	10
39b	3,4-Cl_2	Ph	0	100
39c	H		70	30
39d	H	4-NO_2-Ph	100	0
39e	3,4-Cl_2	4-NO_2-Ph	80	20
39f	3,4-Cl_2	2-NO_2-Ph	100	0
39 g	2,3-Me_2		60	40
39 h	3-Me		50	50

* The ^{1}H NMR spectra were recorded in DMSO-d_6 at T = 24°C.

It was shown that thiazolylhydrazone derivatives based on thioacylhydrazones are potent tyrosinase inhibitors (Djafarou et al., 2023). A review (Kostas and Steele, 2020) addresses the use of thiosemicarbazone complexes in catalyzed cross-coupling reactions. Oxamic acid thiohydrazides are also of undoubted interest as complex-forming structures, since they have donor atoms with both high (N,O) and low (S) electronegativity, due to which they are able to form fairly stable coordination compounds with both hard and soft Lewis acids (Yarovenko et al., 2005; Myannik et al., 2018a, 2018b).

All the foregoing attests to the relevance of investigating the synthetic and applied potential of poorly known thiohydrazides such as oxamic acid derivatives with a –NHC(O)–C(=S)–NH–N = CH– moiety. These compounds contain an additional carboxamide group, –NHC(O)–, which may be important for the formation of a particular type of bioactivity, complex formation, cyclization to form heterocycles, etc. Undoubtedly, the close proximity of the carboxamide and thiohydrazide moieties also affects the reactivity and applied properties of the compounds. Below we present the key methods for the synthesis of oxamic acid thiohydrazides (OAT) and OAT hydrazones (OATH), describe their reactivity, and give examples of synthesis of OAT- and OATH-based derivatives for biological purposes, including demonstrating the possibility of creating a new generation of drugs based on oxamic acid thiohydrazides for the treatment of chronic infections caused by pathogens.

2. Preparation and synthetic potential of oxamic acid thiohydrazides (OAT)

2.1. Synthesis of OAT

Owing to their polyfunctional nature, OAT **1** containing carboxamide and thiohydrazide moieties can undergo various transformations, some of which are depicted in Scheme 1.

Among the reported methods for OAT synthesis (Thiel and Mayer, 1989a, 1989b), a convenient method proposed in a review (Yarovenko et al., 2003) includes treatment of monothiooxamides **4** with hydrazine (Scheme 2). It is noteworthy that this reaction smoothly proceeds only for morpholine derivatives shown in the Scheme, while the use of other amides **4** results in markedly lower yields of products **1**.

In turn, these products and their various derivatives are obtained in good yields by the reactions of α-chloroacetamides with mixtures of elemental sulfur and amines prepared in advance (Yarovenko et al., 1998, 2002a, 2002b, 2007, 2009). It should be emphasized that OAT and monothiooxamides are easily obtained from amines, which makes it possible to design various heterocycles using a wide range of starting reactants, including numerous amino-containing natural compounds. In view of the simplicity of the method, it can be recommended, in particular, for the creation of extensive combinatorial libraries of potential bioactive carboxamide heterocycles based on various amines.

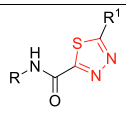
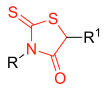
It is known (Daly and Brown, 1973) that the reaction of amines with elemental sulfur occurring in the solution as an eight-membered cyclic molecule is accompanied by accumulation of considerable amounts of polysulfide anions (Scheme 3). It was assumed (Yarovenko et al., 2003) that the polysulfide anions **6**, when present in a sufficiently high concentrations, react with chloroacetamides **4** via nucleophilic substitution of chlorine to give polysulfides **7**, in which amine molecules induce proton elimination simultaneously with sulfide bond cleavage, thus forming thioaldehyde moiety **8**. Thioaldehyde **8** reacts with amine to be converted to imine **9**, which is then oxidized with sulfur to give the corresponding thioamide moiety **10**.

Presumably the yield of monothiooxamides **10** considerably decreases due to the side reaction of amines with chloroacetamides **3**, which affords relatively unreactive α-aminoacetamides **11** (Shirokov, 2005) (Scheme 4).

This reaction can be prevented by keeping a mixture of elemental sulfur and amine for some time before the reaction.

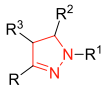
The structure of OAT was confirmed using X-ray diffraction in

Table 2
Bioactivity of compounds presented in the review.

Types and numbers of compounds, references	Bioactivity
1,3,4-Thiadiazoles	**Activity:** antibacterial anticancer
 **57** Kumar, D., Kumar, H., Kumar, V., Deep, A., Sharma, A., Marwaha, M.G., Marwaha, R.K., 2023. Mechanism-based approaches of 1,3,4-thiadiazole scaffolds as potent enzyme inhibitors for cytotoxicity and antiviral activity. Med Drug Discov 17, 100150. https://doi.org/10.1016/j.medidd.2022.100150.	anti-diabetic anti-epileptic antifungal antioxidant anti-parasitic diuretic **Commercial drugs:** Azetepa Acetazolamide Cefazedone Cefazolin Megazol Methazolamide Sulphamethizole
Rhodanine  **62** Chinchilli, K.K., Akunuri, R., Ghouse, S.M., Soujanya, D., Angeli, A., Parupalli, R., Arifuddin, M., Yaddanapudi, V.M., Supuran, C.T., Nanduri, S., 2023. Design, synthesis, and structure–activity studies of new rhodanine derivatives as carbonic anhydrase II, IX inhibitors. Arch. Pharm. 356, e2300205. https://doi.org/10.1002/ardp.202300205.	**Activity:** antibacterial anticancer antidepressant antifungal antimicrobial anti-leukemia **Inhibitors**: acetyl cholinesterase

(*continued on next page*)

Table 2 (*continued*)

	anti-apoptotic protein Bcl-2 carbonic anhydrase cholesterol esterase cholinesterase HCV NS3 protease HIV-1 integrase dengue virus protease lipoxygenase metallo-beta-lactamases MurD ligase mycobacterium tuberculosis tyrosinase
Pyrazolines  **75** Dash, B., Karim, S., 2021. Pyrazoline heterocyclic: a review. IJPSR, 12, 2570-2588; DOI: http://dx.doi.org/10.13040/IJPSR.0975-8232.12(5).2570-88. **76** Haider, K., Shafeeque, M., Yahya, S., Yar, M. S., 2022. A comprehensive review on pyrazoline based heterocyclic hybrids as potent anticancer agents. Eur. J. Med. Chem. 5, 100042. https://doi.org/10.1016/j.ejmcr.2022.100042.	**Activity:** analgesic antiamoebic antibacterial anticancer anticonvulsant antidepressant antidiabetic antifungal antihypertensive antimicrobial

(*continued on next page*)

Table 2 (*continued*)

	antioxidant antituberculosis anti-inflammatory **Commercial drugs:** Aminopyrine Axitinib Dipyrone Famprofazone Ibrutinib Morazone Phenylbutazone Ramifenazone
Pyridazines  **78** Sergeev, P.G., Nenajdenko, V.G., 2020. Recent advances in the chemistry of pyridazine - an important representative of six-membered nitrogen heterocycles. Russ. Chem. Rev. 89, 393-429. https://doi.org/10.1070/RCR4922. **79** Meanwell, N.A., 2023. The pyridazine heterocycle in molecular recognition and drug discovery. Med Chem Res 32, 1853-1921. https://doi.org/10.1007/s00044-023-03035-9.	**Activity:** anticancer antiproliferative antitumour g-secretase modulators PET imaging agents **Inhibitors**: tyrosine kinase LRRK2 kinase Trk receptors **Commercial drugs:**

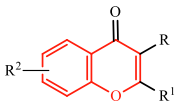
(*continued on next page*)

Table 2 (*continued*)

	Minaprine Relugolix Deucravacitinib
1,3,4-Thiadiazines  **81** Mamidala, S., Vangala, V., Peddi, S.R., Chedupaka, R., Manga, V., Vedula, R.R., 2021. A facile one-pot, three component synthesis of a new series of 1,3,4-thiadiazines: Anticancer evaluation and molecular docking studies. J. Mol. Struct. 1233, 130111. https://doi.org/10.1016/j.molstruc.2021.130111.	**Activity:** anticancer antibacterial antifungal antimicrobial antioxidant antiviral Coumarin based derivatives: anticancer anticholinesterase anticoagulant antidepressant antimicrobial anti-inflammatory antioxidant, antituberculosis antiviral **Inhibitors**: cholinesterase cyclic AMP phosphodiesterase

(*continued on next page*)

Table 2 (*continued*)

	Hepatitis C virus polymerase matrix metalloproteinase STAT3
Chromones  **91** Mohsin, N.u.A., Irfan, M., Hassan, S.u. 2020. Current Strategies in Development of New Chromone Derivatives with Diversified Pharmacological Activities: A Review. Pharm Chem J 54, 241-257. DOI:https://doi.org/10.1007/s11094-020-02187-x **92** Senobari, Z.S., Hosseini, M.M., Teimouri, M.B., Rezayan, A.H., Samarghandian, S., Hekmat, A., 2023. Chromone-embedded peptidomimetics and furopyrimidines as highly potent SARS-CoV-2 infection inhibitors: docking and MD simulation study. BMC Res Notes 16, 224. https://doi.org/10.1186/s13104-023-06508-7. **93** Kavitha, P., Reddy, K.L., 2016. Pd(II) complexes bearing chromone based Schiff bases: Synthesis, characterisation and biological activity studies. Arab. J. Chem. 9, 640-648. http://dx.doi.org/10.1016/j.arabjc.2013.06.018.	**Activity:** antiallergic anti-Alzheimer anticancer anti-diabetic anti-inflammatory antifungal antimalarial antimicrobial antioxidant antiulcer HIV inhibitory neuroprotective

relation to compound **12** (Shirokov, 2005) (Fig. 1).

The crystals of compound **12** refer to the monoclinic system with the unit cell parameters: $a = 24.910(6)$ Å, $b = 3.9567(11)$ Å, $c = 10.141(3)$ Å, $\beta = 91.589(11)^\circ$, $V = 999.1(5)$ Å^3, $Z = 4$, space group $P2_1/c$. The amide group in **12** is rotated relative to the benzene ring plane by 9.3° (C(5)-C(4)-N(1)-C(7). There is no conjugation in the O = C–C = S system, and the distance between the thiocarbonyl and carbonyl groups along the C(7)–C(8) bond is 1.532(3).

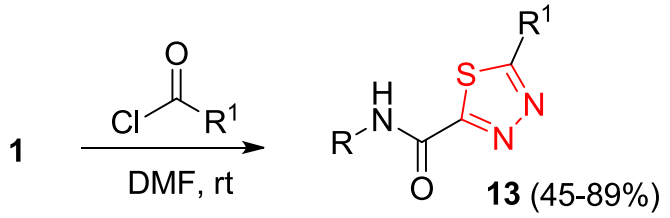
2.2. Synthetic potential of OAT

The following Sections present data demonstrating the extensive synthetic potential of OAT for the design of heterocyclic compounds.

2.2.1. Synthesis of 1,3,4-thiadiazoles

The synthesis of 1,3,4-thiadiazole derivatives is obviously a promising trend in the development of biologially active compounds (Kumar et al., 2023) (Table 2 Biological activity of the compounds). The preparation of 5-carbamoyl-1,3,4-thiadiazoles **13** under mild conditions by the reaction of OAT with acid chlorides has been reported (Yarovenko et al., 2003) (Scheme 5).

The resulting thiadiazoles contain reactive substituents capable of being further modified, in particular converted to heterocycles. For example, it was shown that the chloromethyl group of 5-chloromethyl-1,3,4-thiadiazole-2-carboxamides, synthesized by the reaction of OAT with chloroacetyl chloride (Yarovenko et al., 2003), can be converted to a dithiocarboxylic acid salt by treatment with sulfur and triethylamine. The subsequent treatment with methyl iodide gives dithiocarboxylic acid ester **14**, which smoothly reacts with ethylenediamine and 1,3-diaminopropane to give dihydroimidazoles **15a** and tetrahydropyrimidines **15b**, respectively (Shirokov, 2005). The reaction of OAT with carbon disulfide in the presence of bases furnishes N-aryl-5-thioxo-4,5-dihydro-1,3,4-thiadiazole-2-carboxamides **16**, which are converted to sulfides **17** upon alkylation. The oxidation of sulfides **17** with *m*-chloroperbenzoic acid yields products **18** with sulfoxide moieties, which are effective leaving groups in nucleophilic reactions. The oxidation of the thioamide group in thiadiazoles with $C(NO_2)_4$ leads to disulfides **19** (Yarovenko et al., 2003). Unsubstituted 5-carbamoyl-1,3,4-thiadiazoles **20** are formed in good yields by reactions of OAT with a new cyclization agent, a solution of diethyl chlorophosphate in DMF (Yarovenko et al., 2004). An OAT-involving synthesis of 3-(1,3,4-thiadiazol-2-yl) propanoic acids **21**, new agonists of free fatty acid receptors (GPR40), has been reported



Scheme 5. Synthesis of 5-carbamoyl-1,3,4-thiadiazoles.

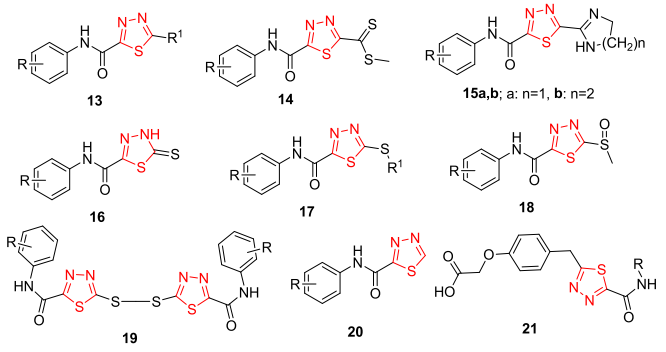


Fig. 2. 1,3,4-Thiadiazoles obtained by cyclization of OAT.

(Krasavin et al., 2017)(Fig. 2).

The reaction of OAT with chlorocarbonylsulfenyl chloride at room temperature affords 6-phenylcarbamoyl-5,6-dihydro (Sharma et al., 2020; Boulebd et al., 2022; Tabbiche et al., 2022; Wang et al., 2023) dithiazin-3-one **22**, which eliminates sulfur on heating and is thus converted to 5-phenylcarbamoyl-2-oxy-1,3,4-thiadiazole **23** (Yarovenko et al., 2003) (Scheme 6). The OAT cyclization on treatment with 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethylammonium tetrafluoroborate (TBTU) results in the formation of 2-dimethylamino-1.3.4-thiadiazoles **24** (Lukin et al., 2018).

2.2.2. *Synthesis of rhodanines*

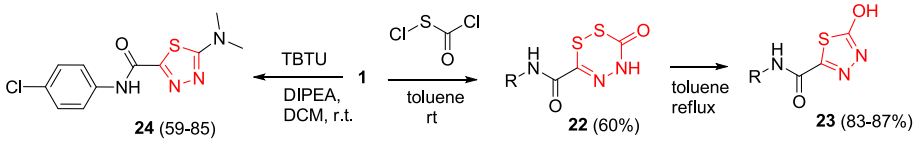
Rhodanines are important heterocycles possessing a wide range of biological activity, including anticancer, antibacterial and anti-mycobacterial properties (Chinchilli et al., 2023) (Table 2. Biological activity of compounds); they are utilized for the treatment of diabetes mellitus (Epalrestat drug).

It was shown that OAT react with trithiocarbonyl diglycolic acid in the presence of dicyclohexylcarbodiimide or carbonyldiimidazole to give 2-[(4-oxo-2-thioxo-1,3-thiazolidin-3-yl)amino]-N-(hetero)aryl-2-thioxamides **25** (Yarovenko et al., 2006) (Scheme 7).

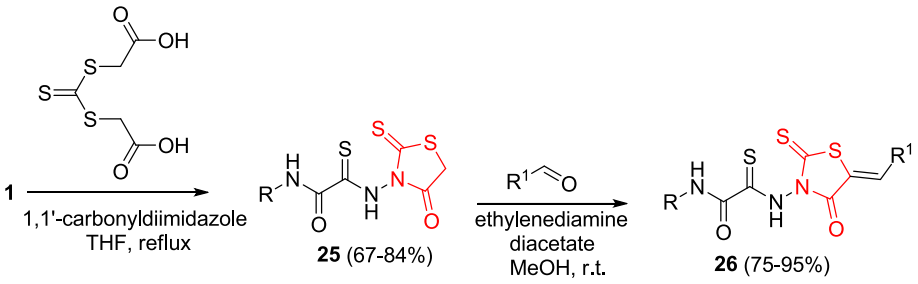
In view of the fact that functional rhodanine derivatives are widely used for the synthesis of various biologically active compounds, considerable attention is paid to the synthetic potential of rhodanine-containing OAT, modification of which can substantially extend the range of derivatives of this heterocycle. The reactions of 2-thioxo-1,3-thiazolidin-4-one **25** with aromatic aldehydes resulted in the formation of 5-arylidenerhodanines **26** (Yarovenko et al., 2007);some of these products inhibit endonuclease APE1 and have an antiproliferative effect against a cancer cell line; this makes them appropriate objects for the development of antiviral agents and anticancer drugs (Ramkumar et al., 2010). The reaction of rhodanines **25** with triethyl orthoformate affords ethoxy methylenerhodanines **27**, which are converted to enamines **28** on treatment with amines; the reactions of **25** with diazonium salts furnish 5-arylhydrazonorhodanines **29**; the acylation of rhodanines with benzoic acid chlorides produces 5-acylrhodanines **30**, while the bromination of rhodanines followed by amination gives arylaminorhodanines **31** (Yarovenko et al., 2007). The readily produced rhodanines **26**–**31** with OAT moieties were used in the synthesis of various fused heterocycles (Fig. 3).

Refluxing of rhodanine **25** with the Lawesson's reagent or with phosphorus pentasulfide in toluene gives N-aryl-5-thioxo[1.3]thiazolo[4,3-*b*] (Sharma et al., 2020; Liu et al., 2022; Tabbiche et al., 2022) thiadiazole-2-carbothioamides **32;** the condensation of rhodanines **26** with chloroacetic acid affords 2-thioxo-2,3-dihydrofuro[2,3-*d*] (Sharma et al., 2020; Liu et al., 2022)thiazol-6-ones **33**; when 5-benzylidenerhodanines **26** react with phenylhydrazine, tetrahydro-5H-pyrazolo[3,4-*d*] (Sharma et al., 2020; Liu et al., 2022)thiazole-5-thiones **34** are formed; refluxing of benzylidene rhodanine derivatives **26** with ethyl cyanoacetate in an acetic acid solution of ammonium acetate gives substituted 2-thioxothiazolopyridine-6-carbonitriles **35;** and the condensation of rhodanines **26** with malononitrile or the condensation of rhodanines **25** with benzylidenemalononitrile results in the formation of 3,7-dihydro-2H-pyrano[2,3-*d*] (Sharma et al., 2020; Liu et al., 2022)thiazole-6-carbonitriles **36**. It is important to note that microwave radiation has a pronounced effect on the formation of fused heterocycles (Yarovenko et al., 2007). For instance, the cycloaddition of arylidene rhodanines **26** to dienophiles can be successfully performed only under microwave irradiation. When these rhodanines react with maleic anhydride and with dimethyl acetylenedicarboxylate, pyrano[2,3-*d*]thiazoles **37a,b** and **38** are formed in 78—90 % yields, whereas this reaction without irradiation gives products in low yields, if at all (Yarovenko et al., 2008).

Oxamic acid thiohydrazide-hydrazones are successfully used in the synthesis of various heterocycles and complex structures. Although



Scheme 6. Reaction of OAT with chlorocarbonylsulfenyl chloride and TBTU.



Scheme 7. Synthesis of rhodanines and arylidenerhodanines.

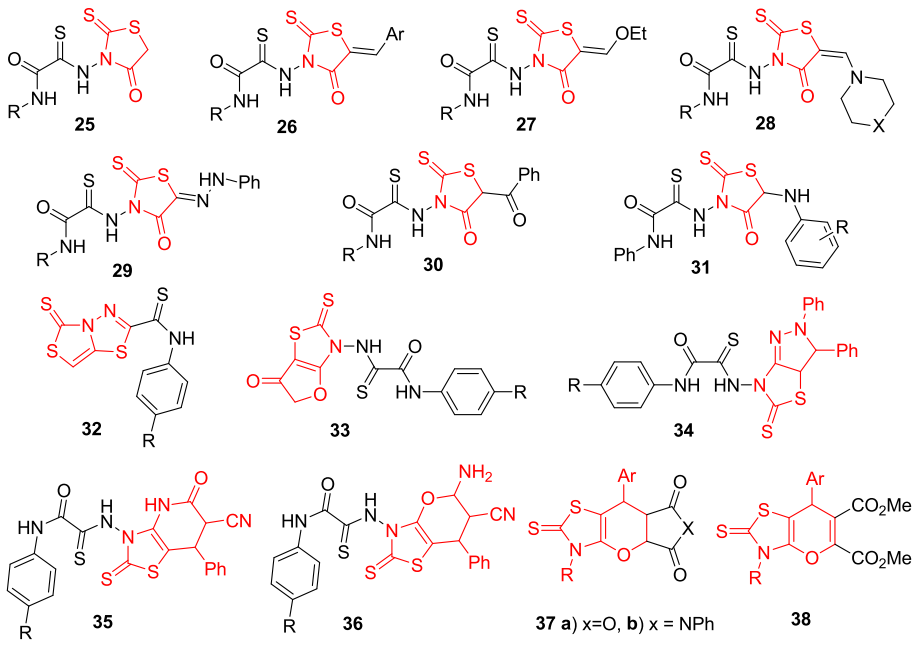


Fig. 3. Rhodanine derivatives based on OAT.

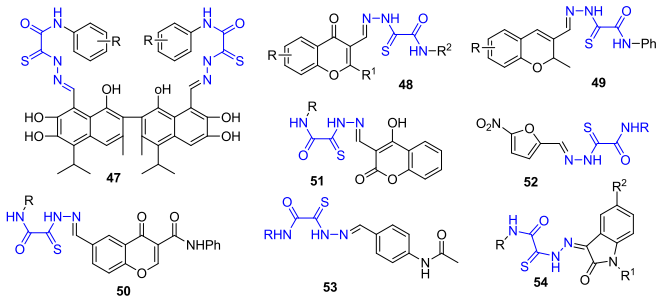
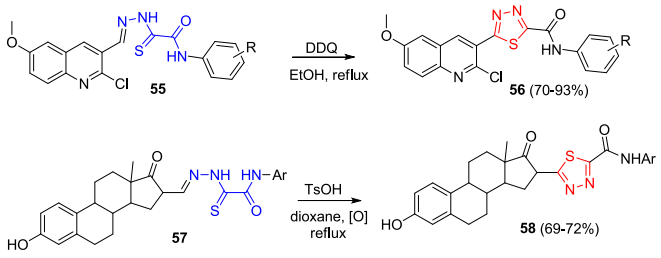


Fig. 4. Hydrazones resulting from reactions of OAT with various aldehydes.



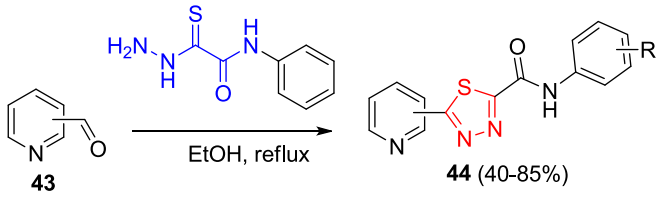
Scheme 9. Synthesis of quinolines and steroids containing 1,3,4-thiadiazole rings.

these compounds are products of OAT transformation, they are set out in a separate Section due to their exceptional importance.

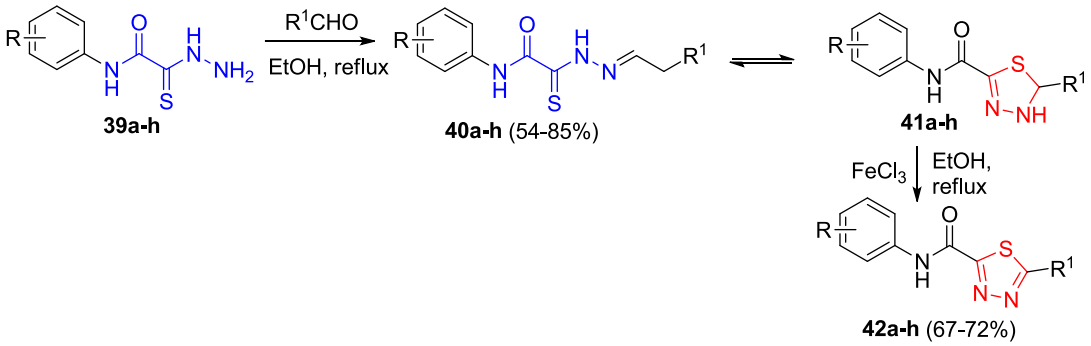
3. Oxamic acid thiohydrazide-hydrazones (OATH)

3.1. Synthesis and reactions of OATH

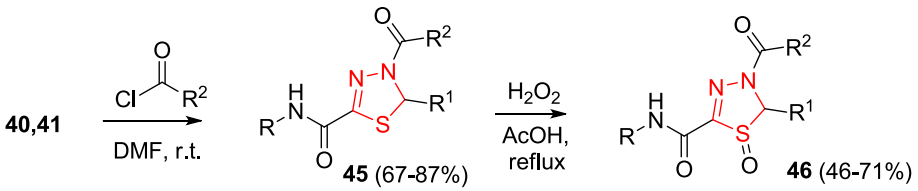
In the vast majority of cases, the synthesis of oxamic acid thiohydrazide-hydrazones (OATH) does not present any difficulty and is



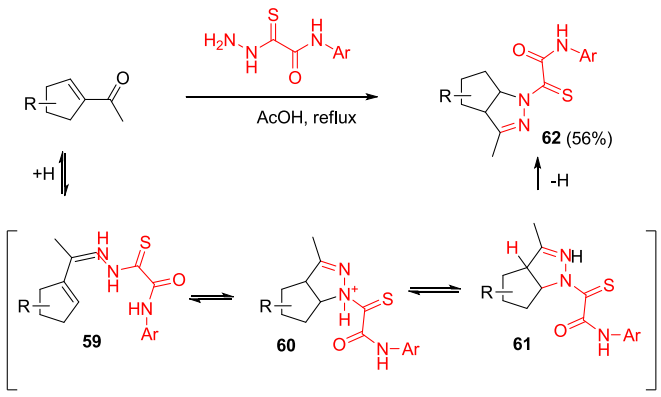
Scheme 10. Synthesis of pyridines containing 1.3.4-thiadiazole rings.



Scheme 8. Synthesis of N-aryl-1,3,4-thiadiazole-2-carboxamides.



Scheme 11. Synthesis of dihydro-1,3,4-thiadiazoles.



Scheme 12. Synthesis of pyrazolines.

traditionally carried out by the reaction of OAT with compounds containing aldehyde groups. For example, this approach was used to prepare the hydrazones of gossypol **47** (Stepanov et al., 2024), chromones **48**–**50**, which are of interest as antituberculosis agents (Myannik, 2018), coumarins **51** with high fungal toxicity (Milevsky et al., 2012), and formyl-nitrofuran **52** with antibacterial activity (Lukin et al., 2020). Analogues of the drugs thioacetazone **53** and metisazone **54** (Shirokov, 2005) exhibiting bactericidal activity have been obtained (Fig. 4).

OATH are convenient starting compounds for the synthesis of dihydro-1,3,4-thiadiazoles and 1,3,4-thiadiazoles. However, researchers may face a number of problems related to the identification of hydrazones. This is caused by both product tautomerism and the possibility of spontaneous conversion to heterocycles. For example, the reaction of aryl OAT derivatives **39a-h** with aldehydes yields hydrazones, which can exist in solutions as an equilibrium mixture of open- **40a-h** and closed-ring **41a-h** forms, which are converted to 2-carbamoyl-1,3,4-thiadiazoles **42a-h** on treatment with oxidants (Yarovenko et al., 2003; Shirokov, 2005) (Scheme 8).

The ratio of the tautomers depends on the substituents in both the aldehyde and thiohydrazide moieties of the molecule (Table 1) (Shirokov, 2005).

It can be seen from the Table that the presence of an electron-withdrawing group in the aldehyde shifts the equilibrium towards the cyclic product (compounds **41a** and **41d**), whereas electron-withdrawing substituents in OAT may have the opposite effect (compounds **40b** and **40e**). The position of substituents in the benzene rings of the reactants also plays a certain role (*cf*. data for derivatives of **39e** and **39f**).

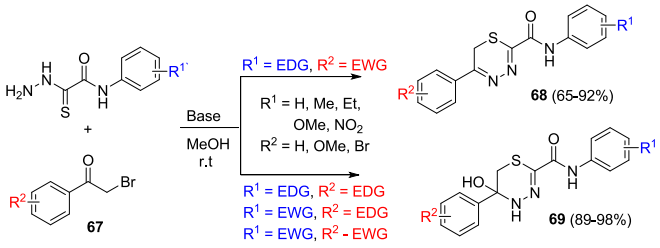
1,3,4-Thiadiazoles are synthesized using heterocyclic derivatives of OAT. For example, the oxidation of hydrazones **55** and **57** furnished quinolines **56** (Aksenov et al., 2021) and steroids **58** (Zavarzin et al., 2013) containing 1,3,4-thiadiazole rings (Scheme 9).

In some cases, it is impossible to isolate hydrazones, as their closed-ring form is immediately converted to 1.3.4-thiadiazoles upon auto-oxidation with air oxygen: for example, compounds **44** are formed in the reaction of OAT with formylpyridine isomers **43** (Myannik et al., 2017) (Scheme 10).

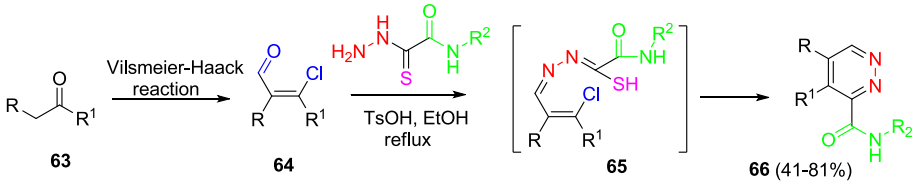
The treatment of hydrazones with acyl chloride may serve as a simple preparative method for the synthesis of dihydro-1,3,4-thiadiazoles and their derivatives. For example, the acylation of a mixture of hydrazones **40** and **41** affords 4-acetyl-2-carbamoyl-4,5-dihydro-1,3,4-thiadiazoles **45,** which are oxidized with hydrogen peroxide in acetic acid to give 4-acetyl- 2-carbamoyl-4,5-dihydro-1,3,4-thiadiazole 1-oxides **46** (Shirokov, 2005) (Scheme 11).

The diverse biological activity of pyrazolines (Table 2. Biological activity of compounds), formed upon the reaction of unsubstituted ketones with OAT thiohydrazides, is summarized in reviews (Dash and Karim, 2021; Haider et al., 2022). According to the authors (Kamernitsky et al., 2007) (Scheme 12), the reactions starts with the formation of hydrazones **59**; this is followed by NH-nucleophilic addition to the activated double bond to give pyrazolines **60**. The subsequent 1,3[H] rearrangement and deprotonation of intermediates **61** furnishes reaction products **62**. It was found that heterocyclization is promoted in the case of thiohydrazides with electron-donating substituents in the aryl moiety.

It is noteworthy that not only 5-membered but also 6-membered heterocycles, which are used in the synthesis of various biologically active compounds, can be obtained using OAT hydrazones. In particular, pyridazines were prepared as biologically active compounds (Sergeev



Scheme 14. Synthesis of thiadiazines.



Scheme 13. Synthesis of pyridazines.

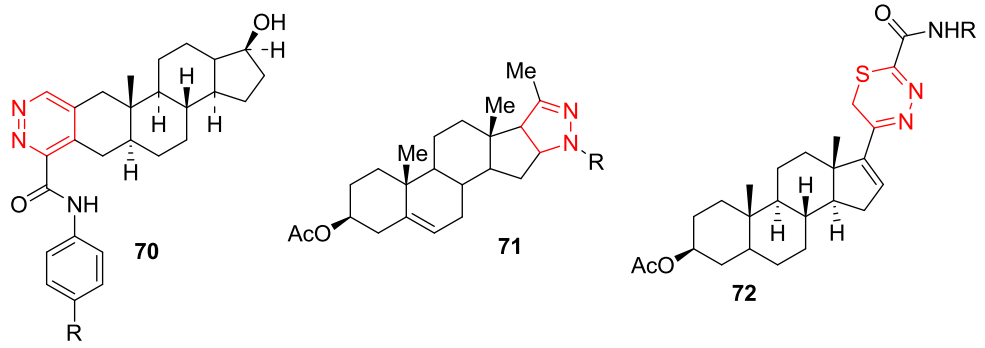
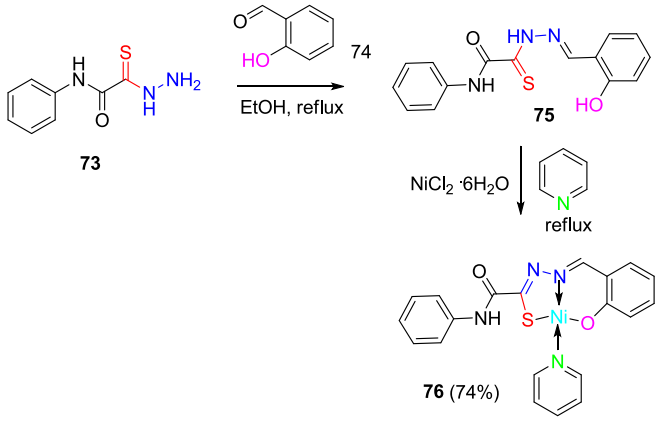


Fig. 5. Synthesis of steroids containing various heterocycles on the basis of OAT.

and Nenajdenko, 2020; Meanwell, 2023) (Table 2. Biological activity of compounds) from ketones and OAT according to Scheme 13, which includes Vilsmeier–Haack chloroformylation of enolyzable ketones **63** giving chlorides **64** followed by imination to give OAT hydrazones **65** and cascade electrocyclization/aromatization resulting in the formation of pyridazines **66** (Komkov et al., 2015).



Scheme 15. Synthesis of complex 76 in the presence of pyridine.

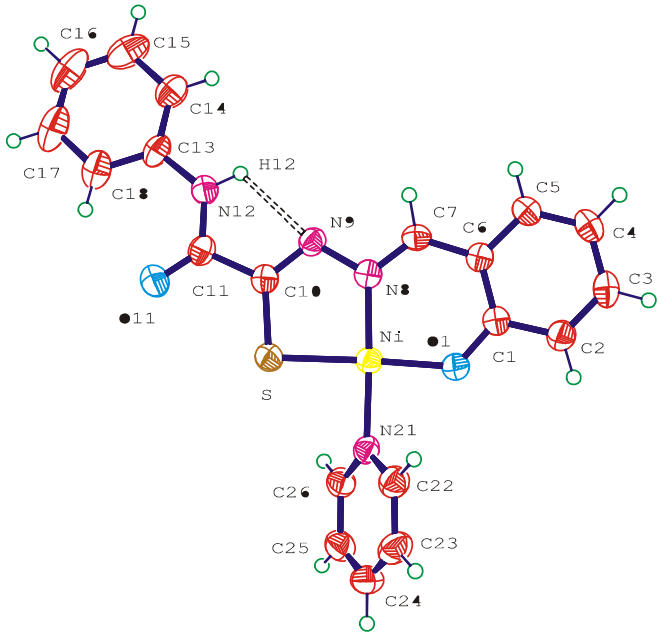


Fig. 6. Molecular structure of complex 76 (Yarovenko et al., 2005).

The reactions of OAT with phenacyl bromides **67** (Scheme 14), which affect the thione moiety and lead to 1,3,4-thiadiazines **68** and 5,6-dihydro-4H-1,3,4-thiadiazin-5-ols **69**, possessing a broad range of biological activity (Mamidala et al., 2021), have been reported (Komendantova et al., 2019) (Table 2. Bioloigal activity of compounds). The reaction was carried out using an equimolar mixture of OAT and α-bromoacetophenones under basic conditions. It was noted that the ratio of cyclocondensation products substantially depends on the substituents and conditions of the reaction.

The above transformations have been widely used in the chemistry of steroids possessing diverse pharmaceutical and bioactive properties (Schiffer et al., 2019; Birukova et al., 2023; Sharma et al., 2023). OAT hydrazones have been successfully used for the design of molecules containing pyridazine **70** (Volkova et al., 2016), pyrazoline **71** (Kamernitskii et al., 2006), and 1,3,4-thiadiazine moieties **72** (Chernoburova et al., 2019) (Fig. 5).

OAT are of obvious interest as complex forming agents, as they contain donor atoms both with high (N,O) and low (S) electronegativity; therefore, they can form fairly stable coordination bonds with both hard and soft Lewis acids.

3.2. *Complexes of OAT hydrazones*

It is known that metal complexes with thiosemicarbazones, resulting from reactions of salicylaldehyde with thiosemicarbazide and its derivatives, inhibit the growth of human leukemia cells and possess antibacterial and antifungal properties (Pahontu et al., 2013). Tridentate ligands based on OATH **75** were obtained. In particular, the complex [Ni($C_{15}H_{11}N_3O_2S$)(C_5H_5N)] (**76**) was synthesized by the reaction of OAT **73** (R = H) with salicylaldehyde and $NiCl_2$ in the presence of pyridine (Yarovenko et al., 2005) (Scheme 15).

The geometric parameters of the complex were studied by X-ray diffraction (Fig. 6), (Yarovenko et al., 2005). The needle-shaped dark red crystals of **76** crystallize in the monoclinic system with the unit cell parameters: a = 41.91(2), b = 3.952(3), c = 28.840(13)Å, β = 126.87 (4)°, V = 3821(4)Å^3, Z = 8, space group $C2/c$. The structure has an intramolecular hydrogen bond with N(12)–H(12) = 0.81(3)Å, H(12)…N (9) = 2.25(3)Å, N(12)…N(9) = 2.662(4)Å, and N(12)–H(12)…N(9) = 112(3)°. The deviation of atoms from the planes does not exceed 0.02 Å in any of the benzene rings. The square planar coordination of the central atom is typical of nickel. The deviation of the N(8), O(1), N(21), and S atoms from the plane does not exceed 0.1 Å. The six-membered N (21)/C(26) heterocycle is rotated relative to the plane of the above square by 58.5(1).

The square planar nickel coordination is completed by two additional atoms, S^{i}- (3.407(2)Å distance) and O^{ii} (3.451(4)Å distance; symmetry code i: x, y + 1, z and i: x, y-1, z) to give a distorted octahedron around the nickel atom. This gives rise to an infinite chain (Yarovenko et al., 2005) (Fig. 7).

Complex **77** containing the aminoadamantane drug as a ligand was

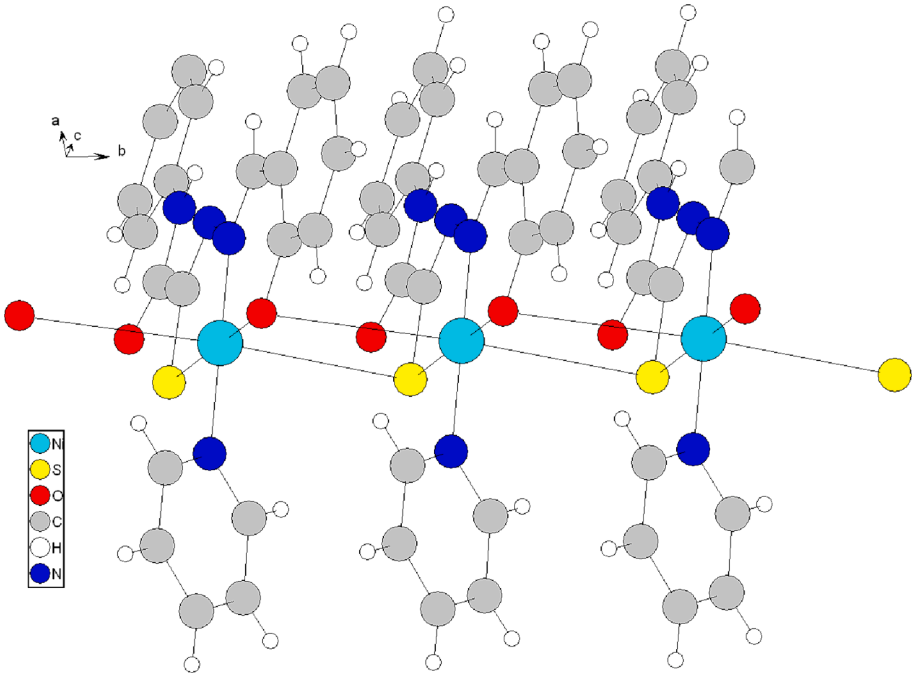
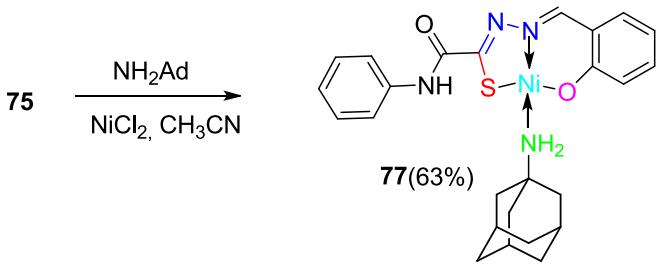
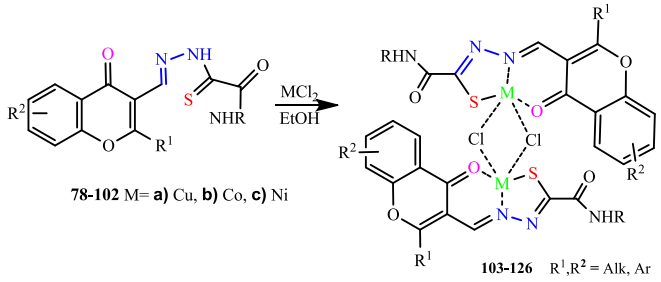


Fig. 7. Formation of polymer chains of complex 76 (Yarovenko et al., 2005).



Scheme 16. Synthesis of complex 77 containing aminoadamantane.



Scheme 17. Synthesis of binuclear complexes 103–126.

prepared by the reaction of the drug with hydrazone **75** and $NiCl_2$ in the presence of triethylamine (Shirokov, 2005)(Scheme 16).

Chromones are known to possess a broad range of biological activity, including anti-HIV (Mohsin et al., 2020) and anti-SARS-CoV-2 (Senobari et al., 2023) activities (Table 2. Biological activity of compounds); the unique ability of chromones to be compatible with various types of receptors was noted (Mohsin et al., 2020). It was shown that Pd complexes with Schiff bases based on formylchromones have antimicrobial properties (Kavitha and Reddy, 2016).

When metal chlorides (Cu^{II}, Co^{II}, Ni^{II}) react with hydrazones **78–102**, formed by the reaction of formylchromones with OAT, binuclear complexes $(L\text{-}H)_2M_2Cl_2$ **103–126** are produced (Scheme 17). The electrochemical behaviour of the ligands and the complexes was investigated by cyclic voltammetry (Myannik et al., 2018a, 2018b).

The structure of the Cu, Co, and Ni coordination compounds is almost the same for all of the ligands. The IR spectra of the complexes show significant shifts of the C = O, N-N, and C = N absorption bands to the 1620–1600 range, which confirms the coordination of the metal ion to the nitrogen atom. The C = S vibration band is missing, indicating that the ligand exists in the complex as the thioenol tautomer. One N–H band also disappears, which confirms the presented structure.

The absolute configuration of compound **103a** was established by X-ray diffraction analysis (Fig. 8). According to the results, complex **103a** consists of two tridentate moieties linked by two bridging chlorine atoms. The copper atom is coordinated to the carbonyl oxygen atom of the pyranone ring, aldimine nitrogen atom, and the sulfur atom of the thiolate group.

Note that the reactions of hydrazones **78–102** with copper chloride in ethanol give binuclear complexes, unlike their reported analogues containing carbonyl group in place of the thiocarbonyl group, which form mononuclear complexes. It is known that binuclear copper complexes have a higher catalytic activity in the azide–alkyne cycloaddition reaction giving triazoles than the corresponding mononuclear complex (Ye et al., 2017).

To summarize, we would like to conclude that the synthesis of complexes based on OAT hydrazones is not complicated, but the main challenges are related to determination of fine structure of the compounds.

4. Design of bioactive compounds based on OATH

Considerable progress was made in the development of promising bioactive compounds based on OATH. Below we present examples of synthesis of compounds of this type according to Scheme 18, which either proved to be efficient against model infections in animals, or were approved for clinical trials, or have already been registered. The purpose of these data is to extend information on the reactivity of OATH.

The key conclusion drawn from the years of experience in combating antibiotic resistance can apparently be formulated in the following way:

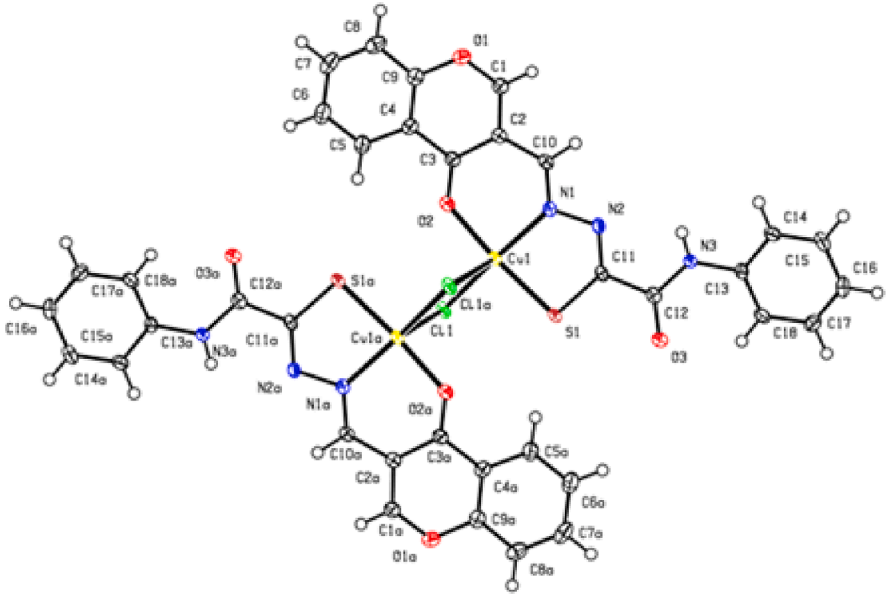
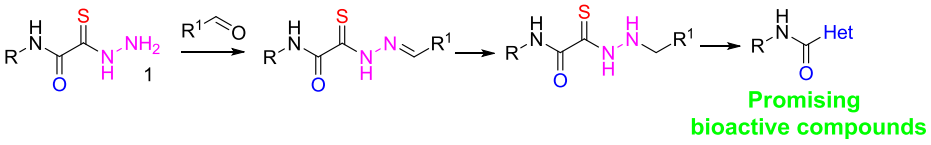


Fig. 8. Molecular structure of complex 103a (Myannik et al., 2018a, 2018b).



Scheme 18. Syntheses and transformations of OATH.

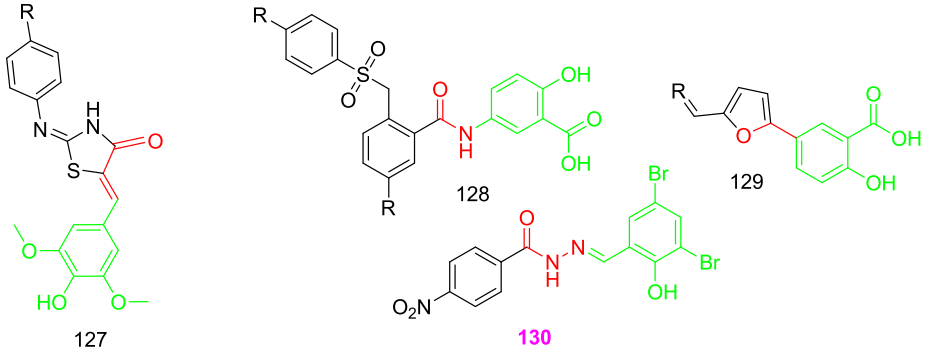
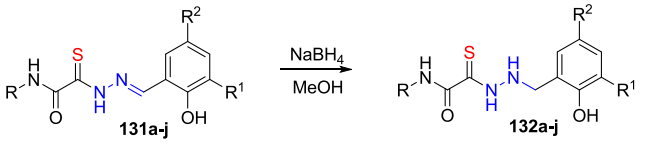


Fig. 9. Structures of T3SS inhibitors.



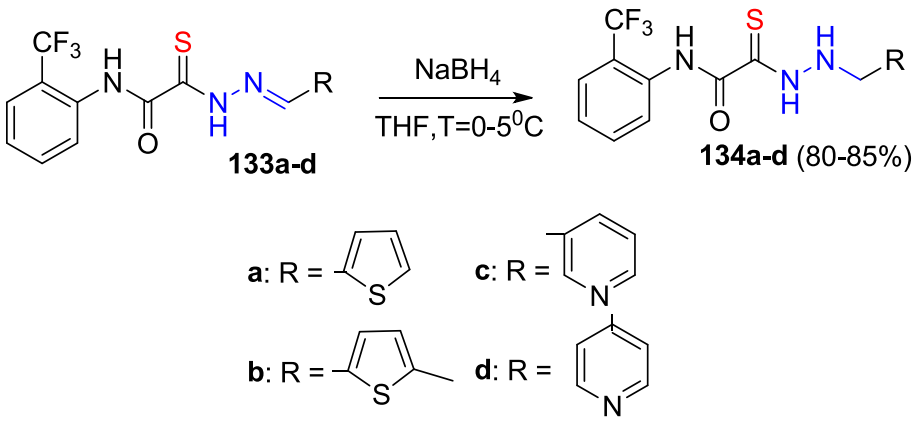
a: R=2-Me-C_6H_4, R^1=R^2=H
b: R=2-F-C_6H_4, R^1=OEt, R^2=H
c: R=3-F-C_6H_4, R^1=OEt, R^2=H
d: R=4-F-C_6H_4, R^1=OEt, R^2=H
e: R=4-F-C_6H_4, R^1=R^2=Br
f: R=2-CF_3-C_6H_4, R^1=OEt, R^2=H
g: R=3-CF_3-C_6H_4, R^1=OEt, R^2=H
h: R=4-CF_3-C_6H_4, R^1=OEt, R^2=H
i: R=Py, R^1=R^2=H
j: R^1=R^2=H, R=

Scheme 19. Reduction of OATH in methanol.

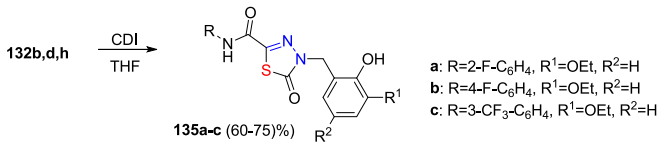
it is necessary to reduce the selective pressure of drugs on pathogens, i. e., the paradigm of treatment of infections should be changed: a drug should inhibit the bacterial virulence rather than kill the bacteria (Clatworthy et al., 2007; Czaplewski et al., 2016).We will consider this statement in relation to the effect of OATH on the type III secretion system (T3SS), a fairly attractive therapeutic target (Sheremet et al., 2020; Chen and Goldberg, 2023) for determining the bacterial virulence. Among known T3SS inhibitors (Zigangirova et al., 2012), the best studied compounds are hydrazones based on aromatic hydrazides of carboxylic acids and salicyladehydes **127**–**130**, which are depicted in Fig. 9.

Analogues of the well-known hydrazone **130** will be considered below in more detail. Thiohydrazones **131a-j** were synthesized (Zayakin, 2009; RU 2 402 531 C2, 2010; Zigangirova et al., 2012), and the imine bond in thiohydrazones **131a-j** was regioselectively reduced with sodium borohydride, with the carbonyl and thiocarbonyl groups remaining intact. This gave rise to N-(hetero)aryl-2-(2-arylhydrazino)-2-thioxoacetamides **132a-j** (Zayakin, 2009; RU 2 400 471 C1, 2010; Zigangirova et al., 2012)**1**(Scheme 19).

The reaction is sensitive to the structure of OAT hydrazones. The reduction of compounds **131a-j** was carried out in methanol; however,



Scheme 20. Reduction of OATH in THF.



Scheme 21. Reaction of OATH reduction products with carbonyldiimidazole.

an attempted reduction of thiohydrazones **133a-d** in the same solvent resulted in the formation of complex mixtures. Instead, compounds **133a-d** were smoothly reduced in THF (Zayakin, 2009) (Scheme 20).

A variety of heterocyclizations involving the OATH reduction products and giving five-, six-, and seven-membered heterocycles have been reported. It was shown that 4-arylmethyl-5-oxo-N-aryl-4,5-dihydro-1,3,4-thiadiazole-2-carboxamides **135a-c** can be obtained by treatment with 1,1′-carbonyldiimidazole (Zayakin, 2009; Zigangirova et al., 2012)(Scheme 21).

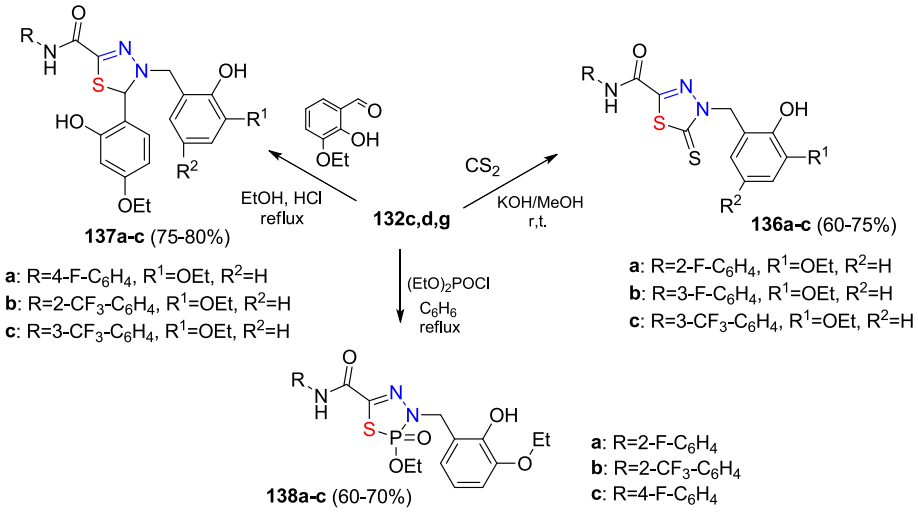
4-Arylmethyl-5-thioxo-N-aryl-4,5-dihydro-1,3,4-thiadiazole-2-carboxamides **136a-c**, thio analogues of compounds **135a-c**, were obtained by the reaction of thiohydrazides **132c,d,g** with carbon disulfide and an alkali in methanol. The reactions of thiohydrazide with 3-ethoxy-2-hydroxybenzaldehyde afford the corresponding 4,5-dihydro-1,3,4-thiadiazole-2-carboxamides **137a-c.** The reactions of thiohydrazide with diethyl chlorophosphate yield phosphorus-containing heterocycles, dihydrothiadiazaphospholane oxides **138a-c** (Zayakin, 2009) (Scheme 22).

Six-membered thiadiazinones **139** are formed in the reactions of thiohydrazides with chloroacetic acid in the presence of ammonium acetate. Traditionally, thiadiazinone modification involving the methylene group is performed by refluxing thiadiazinones with aldehydes in acetic acid and results in the formation of condensation products **141**. The interaction of thiohydrazides with oxalyl chloride in DMFA in the presence of triethylamine produces sulfoxide **140**; the reaction with aromatic alpha-bromoketones leads to thiadiazines **142**. Seven-membered tetrahydrothiadiazepines **143** are the products of reaction of thiohydrazides **132** with bromopropionic acid (Scheme 23) (Zayakin, 2009; RU 2 447 066 C2, 2012; Zigangirova et al., 2012).

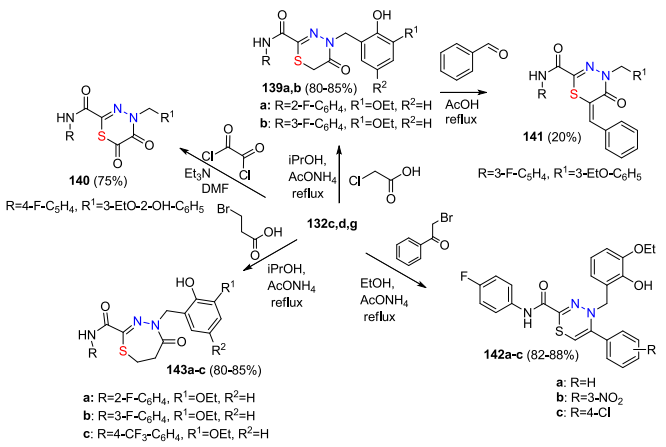
The synthesis of indole thiadiazinone derivatives **148** by the reaction of reduced hydrazone **147** with chloroacetic acid has been reported (Scheme 24) (RU 2 495 036 C1, 2013).

The biological activity assays (Zigangirova et al., 2012)of heterocyclic compounds based on the reduction products of OAT hydrazones and specifically targeting the Chlamydial type III secretion system revealed the most effective compound, thiadiazinone **152**, the synthesis of which is depicted in Scheme 25 (RU 2 447 066 C2, 2012).

Compound **152** was used for the subsequent, more advanced testing of biological properties, which showed that this compound is a low-molecular-weight inhibitor of type III secretion system and many gram-negative pathogenic bacteria. Product **152** exhibited *in vivo* and *in vitro* activity against *Chlamydia trachomatis*, *Salmonella enterica* serovar Typhimurium, and multidrug-resistant *Pseudomonas eruginosa* and



Scheme 22. Synthesis of five-membered heterocycles.

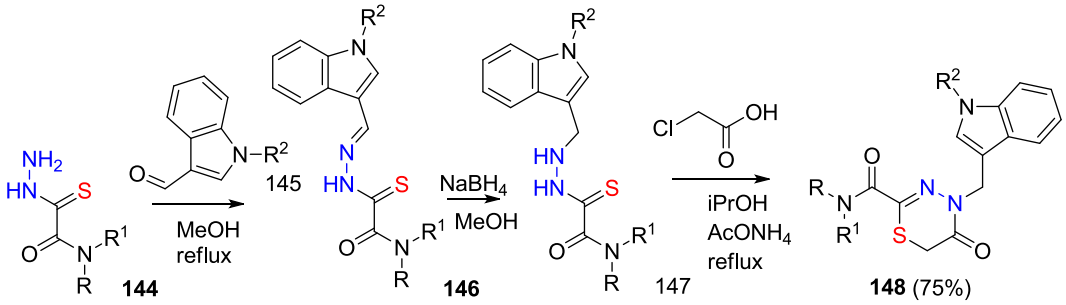


Scheme 23. Synthesis of six-membered heterocycles.

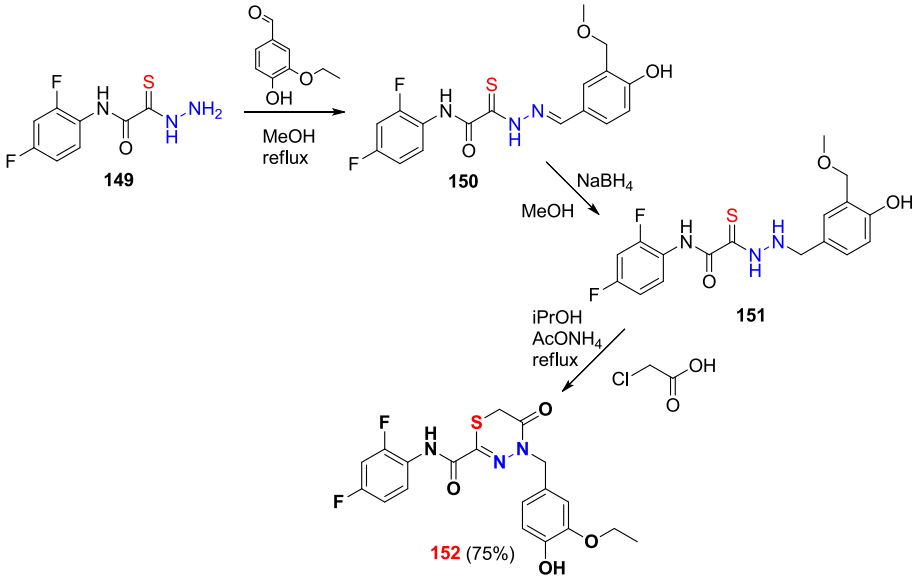
Acinetobacter baumannii. It was found that this agent easily penetrates into peripheral tissues, is retained in the body for a long time, and is mainly metabolized to fluorothiazinone glucuronide (Savitskii et al., 2023; Zigangirova et al., 2021; Tsarenko et al., 2023).

5. Conclusions

The interest in the synthesis of thiohydrazone-based compounds possessing a broad spectrum of bioactivity such as antiviral, insecticidal, antisclerotic, antioxidant, antiparasitic, anti-COVID-19, and anti-HIV activities has considerably increased in recent years. The ligands based on these compounds with soft donor nitrogen and sulfur atoms are widely used to obtain metal complexes with various bioactivities, including strong anticancer properties. There is a growing interest in oxamic acid thiohydrazides containing proximate thioamide and thiohydrazide moieties. Owing to their polyfunctional nature and mutual influence of the moieties, these compounds are capable of a wide variety of transformations. The review describes publications in this area, indicating good prospects of using poorly studied derivatives of oxamic acid thiohydrazides for the synthesis of new types of thioacylhydrazones as bioactive products. Convenient methods for the synthesis of oxamic acid thiohydrazides and related hydrazones are considered. Their high synthetic potential is demonstrated in relation to the design of diverse structures, including complexes and a plethora of heterocyclic compounds: pyridazines, pyrazolines, 1,3,4-thiadiazines, 1,3,4-thiadiazoles, thiadiazinones, dihydrothiadiazaphospholanes, thiadiazines, and tetrahydrothiadiazepines, in particular those prepared from natural compounds. Oxamic acid thiohydrazide-hydrazones were shown to function as innovative antivirulence drugs targeting the bacterial secretory system, thus suppressing the infectious process and eliminating the pathogen from the body without affecting the reproduction of bacteria. There are broad prospects for further research in this area owing to the sharp increase in the combinatorial opportunities via structural changes of the initial components and modification of carboxamide groups of oxamic acid derivatives.



Scheme 24. Synthesis of indole derivative of thiadiazinone 148.



Scheme 25. Synthesis of fluorothiazinone 152.

CRediT authorship contribution statement

M.M. Krayushkin: Writing – original draft. **V.N. Yarovenko:** Writing – original draft.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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