SYNTHESIS AND CONVERSION OF NEW POTENTIALLY BIOLOGICALLY ACTIVE 4-THIAZOLIDINONE DERIVATIVES WITH A TRIAZINOINDOLE FRAGMENT IN THE MOLECULES

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Abstract: A wide spectrum of biological activity and the possibility of diverse chemical modification of isatin derivatives prompts the search for new highly active compounds as potential drugs among condensed and non-condensed heterocyclic systems containing the specified molecular "matrix". Studies of 1,2,4-triazino[5,6-b]indoles, the chemical precursors of which are isatins, have shown the prospect of their use in the treatment of oncological diseases. In addition, potential antifungal, antiviral, antihypertensive agents have been identified among these derivatives.

Adhering to the main synthetic strategy of our research, which is based on the "hybrid-pharmacophoric" approach in the synthesis of new heterocyclic derivatives of 4-thiazolidinone, in our opinion, the combination of the main scaffold (4-thiazolidinone) and the structural "imitator" is interesting and promising of the isatin "matrix" - triazinoindole fragment, as well as the synthesis of new polyheterocyclic ensembles, including those with a pharmacologically attractive pyrazoline fragment. Under the conditions of the S-alkylation reaction of 3-mercapto-5H-1,2,4-triazino[5,6-b]indoles, 2-chloro-1-(3,5-diaryl-4,5-dihydropyrazole- 1-yl)ethanones, which made it possible to obtain 1,2,4-triazino[5,6-b]indole-pyrazolines with preparative yields. By hydrazinolysis of 3-mercapto-5H-1,2,4-triazino[5,6-b]indoles, corresponding hydrazines were obtained, which were successfully used for the first time in the Holmberg reaction, and derivatives of the triazinoindole-thiazolidinone system were obtained – 3-(1,2 ,4-triazino[5,6-b]indol-3-ylamino-2-thioxothiazolidin-4-ones Chemical modification of methylene-active compounds was carried out under the conditions of the Kniovenagel reaction with aromatic aldehydes and isatin derivatives, which was substantiated by the results of biological studies of structurally related heteryl-substituted 5-ylidenerhodanines. The synthesis of derivatives of the 4-thiazolidinone-thiadiazinoindole system, which is based on the interaction of N-(1,3,4-thiadiazinoindol-2-yl)-2-chloroacetamides with ammonium thiocyanate in an acetone medium, was carried out. The obtained conjugates are methylene-active compounds, which made it possible to synthesize a series of 5-arylidene derivatives under the conditions of the Kniovenagel reaction. The purpose of the work is to experimentally confirm or refute the feasibility of chemical modification of isatin into the triazine-indoline system and its combination with 4-thiazolidinone biophore for the search of new biologically active compounds, including highly active antitumor agents. The structure of the synthesized compounds was confirmed by NMR spectroscopy. To study the structure in the solid state, the IR spectra of the key compounds in KBr tablets were studied.

Keywords: isatin, synthesis, 4-thiazolidinone

1. INTRODUCTION

4-thiazolidinone and 2-oxo-1,3-dihydroindole molecular fragments are structural "matrixes" of numerous drugs and biologically active compounds. Their use in the modern process of drug discovery allows to achieve a high percentage of "hit structures" and "leader compounds" with diverse pharmacological activity, among which antitumor activity stands out. Progress in molecular biology has made it possible to explain the anticancer potential of 4-thiazolidinones by their ability to inhibit the anti-apoptotic complex Bcl-XL-BH3, necroptosis, tumor necrosis factor TNF, tyrosine phosphatase SHP-2, etc. In turn, the antitumor effect of 2-oxo-1,3-dihydroindole derivatives is associated with affinity for tyrosine kinase, cyclin-dependent kinase, and carbonic anhydrase. Previous studies have provided a number of arguments in favor of the effectiveness of using the "hybrid-pharmacophore approach" strategy in the modeling of heterocyclic structures based on thiazolidine and 2-oxo-1,3-dihydroindole fragments, which allows to achieve a new pharmacological profile of "drug-like molecules", potentiation of their action and reducing toxicity. Therefore, the targeted search for new chemotherapeutic agents from the given group of heterocycles is a justified and promising direction of pharmaceutical chemistry.

2. MATERIALS AND METHODS

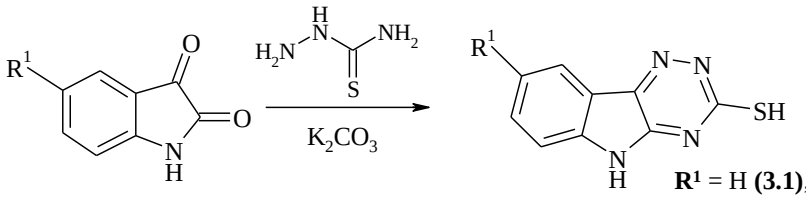
The purpose of the work is to experimentally confirm or refute the feasibility of chemical modification of isatin into the triazine-indoline system and its combination with 4-thiazolidinone biophore for the search of new biologically active compounds, including highly active antitumor agents. To achieve this goal, the following tasks were set:

- to synthesize a group of isatin derivatives with aromatic and heterocyclic fragments by the interaction of 5-R-2,3-dioxo-1,3-dihydroindoles (5-R-isatins) with 2-chloro-N-aryl(heteryl)acetamides under the conditions of the reaction of N- alkylation;
- to obtain previously undescribed thiazolidinone-indoline conjugates by the Kniovenagel reaction of 2-(2,3-dixo-1,3-dihydroindol-1-yl)-N-aryl(heteryl)acetamides and 4-thiazolidinones;
- to propose alternative methods of synthesis of new thiazolidinone-indoline systems based on 1,3-dihydroindol-2-ones as starting compounds;
- synthesize 1,2,4-triazino[5,6-b]indole derivatives and carry out their chemical modification in S-alkylation, hydrazinolysis and [2+3]-cyclocondensation reactions;

The objects of the research were N- and S-alkylation, heterocyclization, hydrazinolysis, and Kniovenagel reactions.
The subject of research was indolin-substituted 4-thiazolidinones and structurally related heterosystems as potential biologically active compounds.
Research methods: organic synthesis, NMR and IR spectroscopy, chromatography-mass spectrometry, elemental analysis, pharmacological screening, molecular docking, COMPARE analysis.

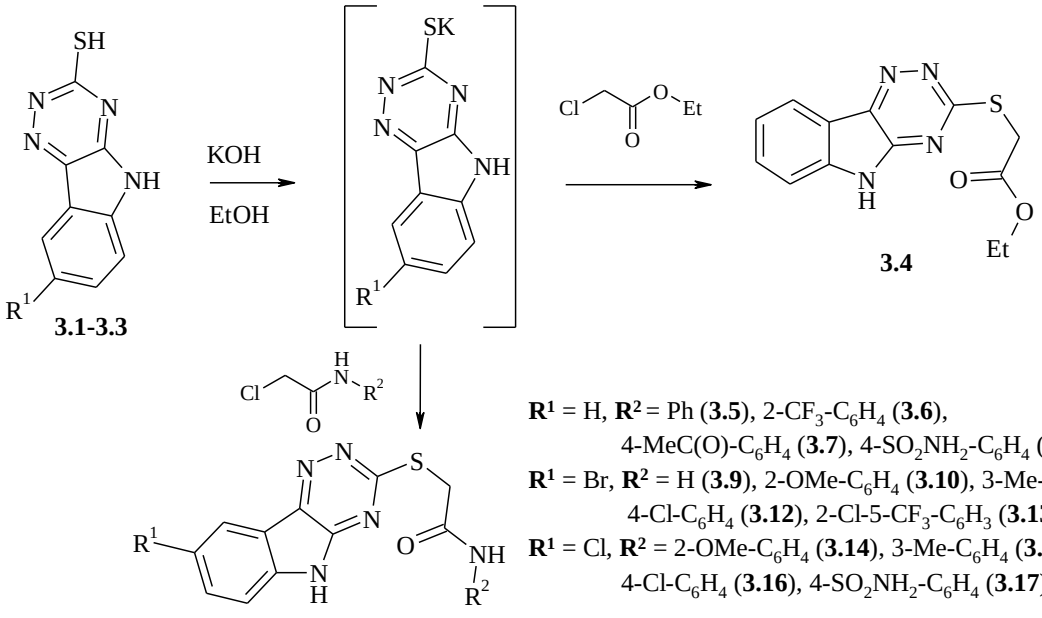
3. RESULTS

The synthesis of starting 3-mercapto-5H-1,2,4-triazino[5,6-b]indoles 3.1-3.3 was carried out according to the known method by reacting isatin, 5-bromoisitin, or 5-chloroisatin with thiosemicarbazide in aqueous environment in the presence of potassium carbonate.



R¹ = H **(3.1)**, Br (**3.2**), Cl (**3.3**)

In order to synthesize potential biologically active S-substituted derivatives by the interaction of S-potassium salts of 3-mercapto-5H-1,2,4-triazino[5,6-b]indoles 3.1-3.3 obtained in situ with ethyl chloroacetate or N-arylchloroacetamides compounds 3.4-3.17 were synthesized in ethanol medium. The rationale for obtaining these derivatives was the previously established fact of the importance of acetamide and carbethoxymethyl fragments for the manifestation and enhancement of the antitumor activity of some sulfur- and nitrogen-containing heterocyclic derivatives.



3.1-3.3

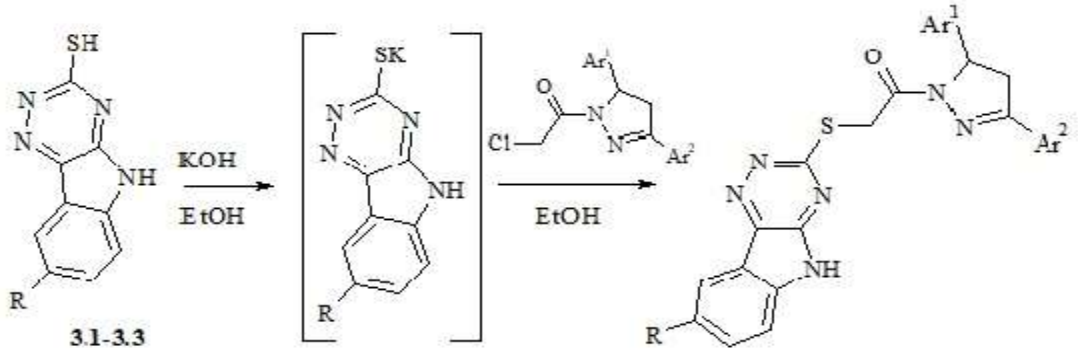
3.4

R¹ = H, **R²** = Ph (**3.5**), 2-CF_3-C_6H_4 (**3.6**),
4-MeC(O)-C_6H_4 (**3.7**), 4-SO_2NH_2-C_6H_4 (**3.8**),
R¹ = Br, **R²** = H (**3.9**), 2-OMe-C_6H_4 (**3.10**), 3-Me-C_6H_4 (**3.11**),
4-Cl-C_6H_4 (**3.12**), 2-Cl-5-CF_3-C_6H_3 (**3.13**),
R¹ = Cl, **R²** = 2-OMe-C_6H_4 (**3.14**), 3-Me-C_6H_4 (**3.15**),
4-Cl-C_6H_4 (**3.16**), 4-SO_2NH_2-C_6H_4 (**3.17**)

The obtained products 3.4-3.17 are orange crystalline powders soluble in DMF when cold, in acetic acid when heated, insoluble in alcohols, water and ether.

Com-pound	Results ,%	$T_{heating}$, °C	Formula	Calculated, %		Found, %	
				N	S	N	S
1	2	3	4	5	6	7	8
3.4	78	242-244	$C_{13}H_{12}N_4O_2S$	19,43	11,12	19,64	11,33
3.5	83	300-302	$C_{17}H_{13}N_5OS$	20,88	9,56	21,09	9,77
3.6	86	254-261	$C_{18}H_{12}F_3N_5OS$	17,36	7,95	17,68	8,27
3.7	76	250-252	$C_{19}H_{15}N_5O_2S$	18,56	8,50	18,78	8,73
3.8	80	294-296	$C_{17}H_{14}N_6O_3S_2$	20,28	15,47	20,03	15,22
3.9	88	>340	$C_{11}H_8BrN_5OS$	20,71	9,48	20,95	9,72
3.10	85	260-262	$C_{18}H_{14}BrN_5O_2S$	15,76	7,22	15,53	6,99
3.11	88	312-314	$C_{18}H_{14}BrN_5OS$	16,35	7,49	16,54	7,68
3.12	77	324-326	C17H11BrClN5OS	15,61	7,15	15,29	6,83
3.13	75	258-260	C18H10BrClF3N5OS	13,55	6,21	13,18	5,84
3.14	78	256-258	C18H14ClN5O2S	17,51	8,02	17,84	8,35
3.15	85	268-270	C18H14ClN5OS	18,24	8,35	18,57	8,68
3.16	81	280-282	C17H11Cl2N5OS	17,32	7,93	17,53	8,14
3.17	86	290-292	C17H13ClN6O3S2	18,72	14,29	18,51	14,08

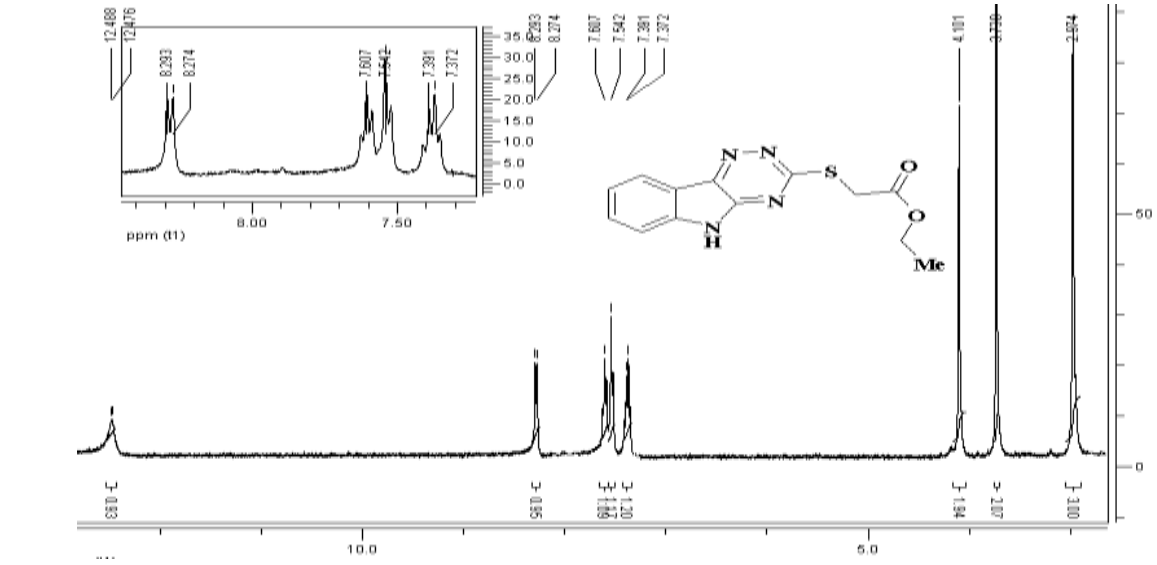
In order to establish the influence of the nature of the N-substituted acetamide fragment on the manifestation of the antitumor effect, a group of 3-mercapto-5H-1,2,4-triazino[5,6-b]indole with a 3,5-diarylpyrazoline substituent in the molecules was obtained. The reaction was carried out under conditions similar to those given above by generating in situ S-potassium salts of 3-mercapto-5H-1,2,4-triazino[5,6-b]indoles 3.1-3.3 for further interaction with 2-chloro-1 -(3,5-diaryl-4,5-dihydropyrazol-1-yl)ethanones as alkylating agents in an ethanol medium. As a result of synthetic transformations with satisfactory yields, a group of 1,2,4-triazino[5,6-b]indole-pyrazolines 3.18-3.22 was obtained according to the scheme:

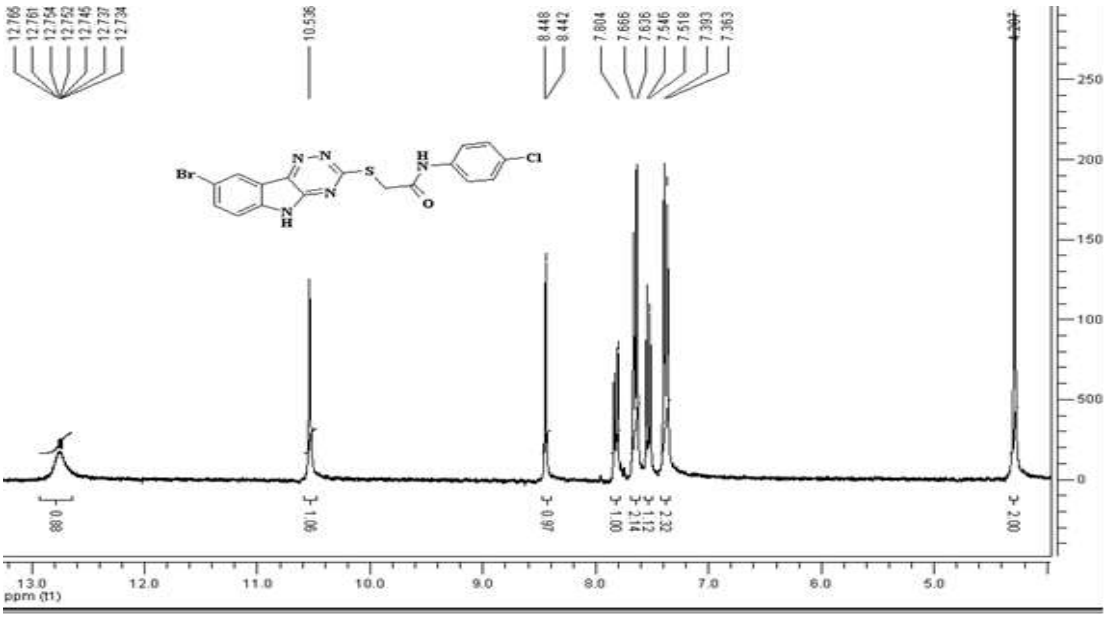


3.18 R = H, Ar^1 = 4-Cl-C_6H_4, Ar^2 = Ph
3.19 R = Br, Ar^1 = 4-Cl-C_6H_4, Ar^2 = Ph
3.20 R = H, Ar^1 = 4-F-C_6H_4, Ar^2 = naphtalene-2-yl
3.21 R = Br, Ar^1 = 4-F-C_6H_4, Ar^2 = naphtalene-2-yl
3.22 R = Cl, Ar^1 = 4-F-C_6H_4, Ar^2 = naphtalene-2-yl

The obtained products 3.18-3.22 are orange crystalline powders, soluble when heated in DMF, insoluble in acetic acid, alcohols, water, and ether. Purification of the synthesized compounds was carried out by recrystallization from a mixture of DMF - ethanol (1:2).

Com-pound	Results, %	$T_{heating}$, °C	Formula	Calculated, %		Found, %	
				N	S	N	S
3.18	84	254-256	$C_{26}H_{19}ClN_6OS$	16,84	6,43	16,61	6,21
3.19	79	265-266	$C_{26}H_{18}BrClN_6OS$	14,54	5,55	14,32	5,33
3.20	85	>270	$C_{30}H_{21}FN_6OS$	15,78	6,02	15,99	6,23
3.21	75	250-251	$C_{30}H_{20}BrFN_6OS$	13,74	5,24	13,95	5,45
3.22	80	278-280	$C_{30}H_{20}ClFN_6OS$	14,82	5,65	15,04	5,87





4. DISCUSSIONS

In the NMR spectra of the synthesized compounds, the protons of the indole fragment form a subspectrum of multiplets in the region ~7.37-8.28 ppm. Protons of the methylene group of compounds 3.3-3.17 resonate in the form of a singlet at 4.10-4.34 ppm., and compounds 3.18-3.20 form two doublets at ~4.60 and ~4.90 m.h. with spin-spin interaction constants of ~16.0 Hz. The CH2-CH protons of the pyrazoline fragment of compounds 3.18-3.20 form a characteristic subspectrum of the AMX system in the form of three doublets-doublets at ~3.23, ~4.96, and ~5.65 ppm. with the corresponding spin-spin interaction constants on the example of compound 3.18 JAM = 18.4 Hz, JMX = 11.8 Hz and JAX = 4.9 Hz. The arylacetamide fragment of compounds 3.5-3.17 is characterized by a singlet amide proton at 9.6-10.8 ppm. and the characteristic picture of aromatic protons in the area 7.0-8.3 m.h. with classical splitting of the signals, which confirms the passage of the alkylation reaction.

5. CONCLUSIONS

1. The synthesis of 3-mercapto-5H-1,2,4-triazino[5,6-b]indoles was carried out, the chemical precursors of which are isatin and its derivatives. In the subsequent modification of compounds 3.1-3.3 under the conditions of the S-alkylation reaction, the ethyl ester of (1,2,4-triazino[5,6-b]indol-3-ylsulfanyl)-acetic acid and the group (1,2, 4-triazino[5,6-b]indol-3-ylsulfanyl)-N-arylacetamides (3.5-3.17) for pharmacological screening for antitumor activity.
2. Under the conditions of the S-alkylation reaction of 3-mercapto-5H-1,2,4-triazino[5,6-b]indoles, 2-chloro-1-(3,5-diaryl-4,5-dihydropyrazole- 1-yl)ethanones, which made it possible to obtain 1,2,4-triazino[5,6-b]indole-pyrazolines 3.18-3.22 with preparative yields.
3. The structure of the synthesized compounds was confirmed by NMR spectroscopy.

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