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Synthetic Approaches in Obtaining Novel Biologically Active Quinones

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ABSTRACT

The properties of 1,4-quinoid compounds in reactions with electrophilic and nucleophilic agents were studied. Heterocyclization of 1,4-quinone derivatives with furan, 1-methyl-2-pirydon and 5-arylmethyliden-4-thioxo-2-thiazolidones by Diels-Alder reaction was carried out. New condensed polyheterocyclic compounds were synthesized through interaction of 2,3-dichloro-1,4-naphthoquinone with several heteroderivatives of hydrazine and with their subsequent cyclization. Quantum-mechanical calculations for compounds-substrates by means of computer modeling were carried out. By in silico studies the possibility of displaying biological activity of synthesized compounds was predicted.

Keywords: 1, 4-quinones, heterodienes, hydrazones, heterocyclization.

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INTRODUCTION

Quinones and their derivatives form a great interest for pharmacologists as it is known a group of chemotherapy drugs that contain the quinone nucleus. However, due to differences in the structure and the diversity of pharmacological effects that they show, quinones are not sufficiently studied.

Naphthoquinone derivatives have a wide range of pharmacological properties, they show antibacterial, antifungal, antiviral, insecticidal, anti-inflammatory and antipyretic properties. Naphthoquinones, isolated from plants and microorganisms, are widely used for the treatment of cancerous tumors and parasitic diseases.

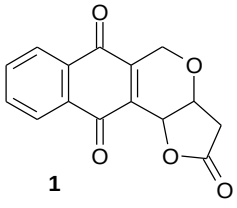
Interest in the synthesis of new compounds with a broad spectrum of activity is caused by a large number of existing drugs with significant side effects, which it is needed to minimize. For example, hydrazine sulfate, used in the treatment of cancer at the same time is highly toxic. So, the challenge of scientists is to synthesize active substances that will show maximum pharmacological activity and minor side effects.

Diels-Alder reaction is a cycloaddition between diene and dienophile, which have π-bond. If diene or dienophile has one or more heteroatoms, this reaction is called hetero-Diels-Alder reaction. The reaction is classified as $[_{\pi}4_s + _{\pi}2_s]$ cycloaddition. 4 and 2 means the number of π-electrons that are involved in electronic regrouping and the number of atoms that form a six-membered unsaturated ring [1].

Numerous monographs and reviews, which may explain the important processes that occur both in humans and in the environment and have photochemical nature, cover the scope of applying heterocyclic derivatives of 1,4-naphthoquinone in photochemistry [2].

Great number of natural quinones with heterocyclic ring system were isolated from bacteria, fungi, higher plants and animals. Their wide range of biological activity leads to develop new methods for the synthesis of the above mentioned systems. This is a significant class of compounds acting as powerful antibiotics, anticancer, antifungal and antimicrobial agents.

Compounds of naphthoquinone-pyran system **1,2** were isolated from plant Eleuteria bulbosa and from roots of the plant Ventilago medaraspatana [3].



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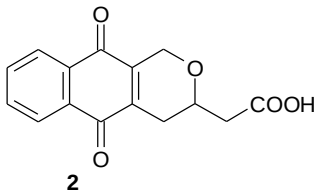

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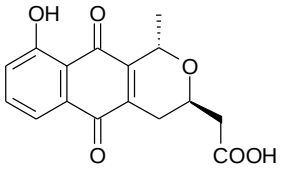
In 1974, heterocyclic derivatives of juglone **3,4** were isolated from bacteria Streptomyces rosa var. notoenses. Both compounds showed antimicrobial, antitumor and antifungal activities [3].



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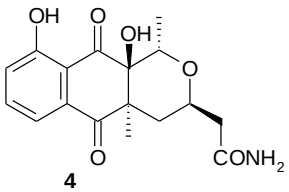

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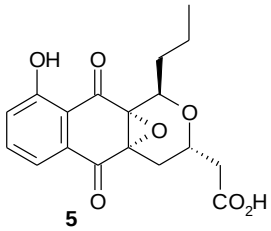
Other heterocyclic derivatives of juglone with antibiotic properties, namely frenocilin **5** and granaticin **6,** were isolated from cultures of Streptomyces roseofulvus and Streptomyces oliavaceus respectively [3].



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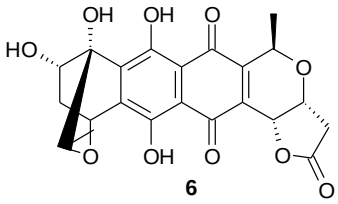

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A wide range of biological activity of described above compounds makes the development of methods of the synthesis of new similar heterocyclic derivatives.

RESULTS AND DISCUSSION

Analyzing literature sources concerning the chemistry of quinoid compounds we have developed a method of synthesis of new heterocyclic ensembles based on 1,4-quinoid systems.

Diels-Alder reaction of dienophiles **7-10** and heterodienes **a-k** was conducted in the medium of acetic acid at 115-118 ^{o}C. Products of [4+2] cycloaddition were formed by the interaction of quinones with heterodienes, were oxydated by excess of the corresponding quinone with obtaining of a series of polyheterocyclic derivatives of quinoid compounds. It was observed that the interaction of benzoquinone **7** with furan **a** was held with forming a mixture of products (TLC analysis), that cannot be separated.

Heterocyclic systems based on 1,4-naphthoquinone **8** with 5-arylmethyliden-4-thioxo-2-thiazolidones and 1-methyl-2-pirydone were previously synthesized and showed good results in antitumor activity [4]. Based on the above mentioned, we proposed to use as dienophiles 9,10-dihydroxyantra-1,4-dione and 5-hydroxy-1,4-naphthoquinone. These chemical transformations are shown in Scheme 1.

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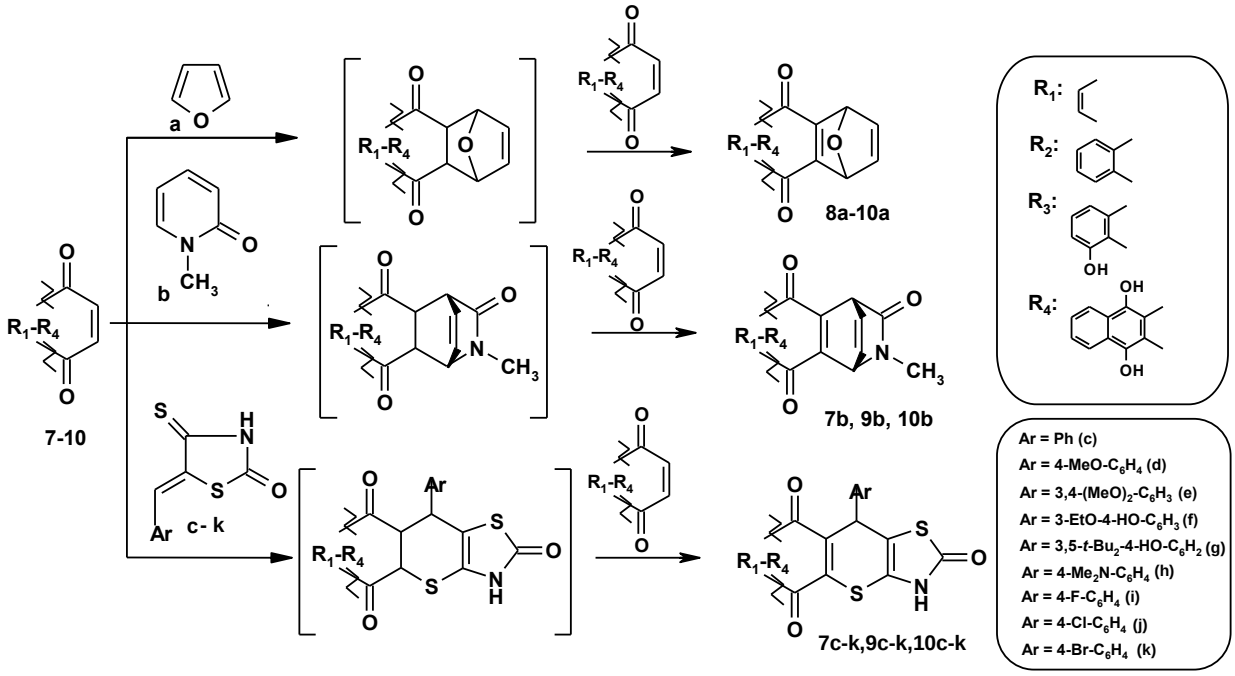
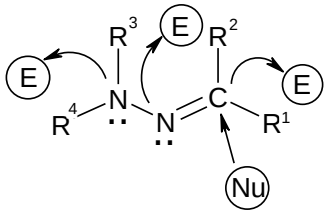
Scheme 1:



Hydrazones contain from two linked nitrogen atom of different nature and C-N double bond, which is conjugated with the lone pair of electrons of the terminal nitrogen atom. These structural fragments are mainly responsible for the physical and chemical properties of hydrazones. Both nitrogen atoms of hydrazone group are nucleophilic. The carbon atom of hydrazone group has both electrophilic and nucleophilic character [5,6].



With the ability to react with electrophilic and nucleophilic reagents, hydrazones are widely used in organic synthesis, especially in the synthesis of heterocyclic compounds. Introduction of functional groups in the hydrazone molecules expands scope of their applying in organic synthesis. In addition, the combination of hydrazone group with other functional groups leads to the formation of compounds with unique physical and chemical properties. Hydrazones containing halogen atoms in the α- or β-positions have been studied for years as a way of synthesis of nitrile amines [7,8] and 1,2-diazo-1,3-butadiene [9,10], which are active intermediates in cycloaddition chemistry. Amidrazones and thiosemicarbazones are well described due to their biological activity and applying in the synthesis of heterocyclic compounds [5,11,12].

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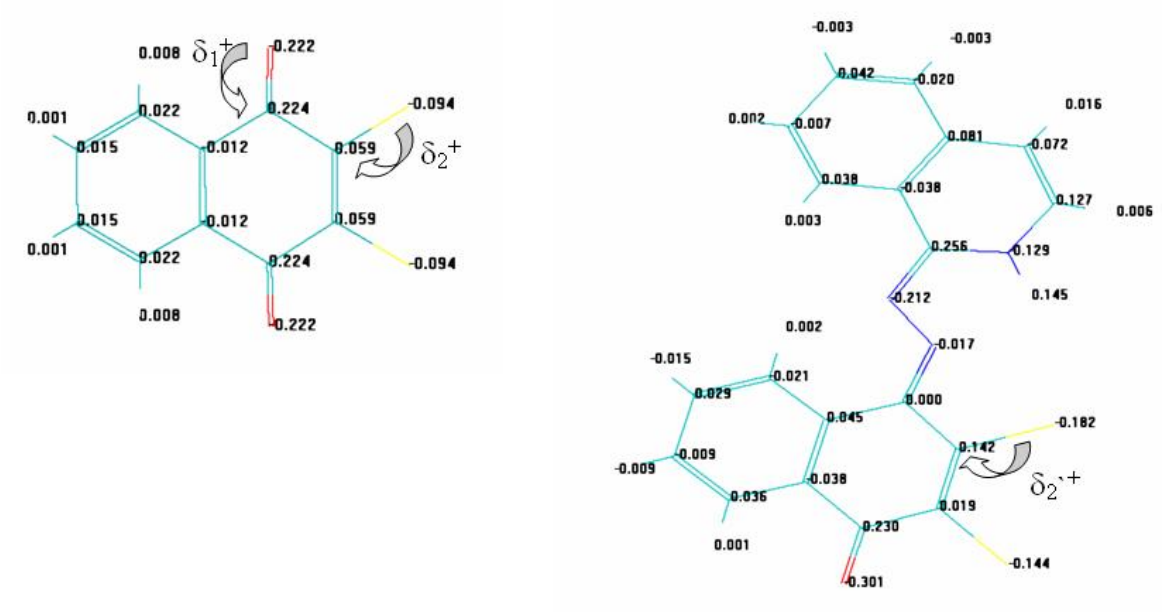
2,3-Dichloro-1,4-naphthoquinone is a promising reagent for the synthesis of multifunctional compounds, as it contains several active centers. Depending on the conditions of synthesis, interaction of 2,3-dichloro-1,4-naphthoquinone with N,N-binucleophiles can undergo on the alternative ways.

Using the computer modeling program HyperChem, a calculation of the location of charges in the molecule of 2,3-dichloro-1,4-naphthoquinone, that showed rather large positive charge on the atom of carbon in 1 and 4 positions, was carried out. Therefore, in the interaction with the studied hidrazines corresponding azomethines as the products will be formed. While carrying out quantum-chemical calculations of obtained azomethines was found that using as substituent hydrazide quinazoline, it is observed that positive charge at a nearby with azomethine group carbon atom increases.



So, we can confirm about the possibility of nucleophilic attack of the C^3-carbon atom by nucleophilic center of quinazoline nucleus.

Using nucleophilic substitution reactions we have obtained a number of heterocyclic derivatives of 1,4-naphthoquinone. The synthesis was carried out with the appropriate hydrazine **12 l-r** in the medium of acetic acid at the boiling point of the solvent. These chemical transformations are shown in Scheme 2.

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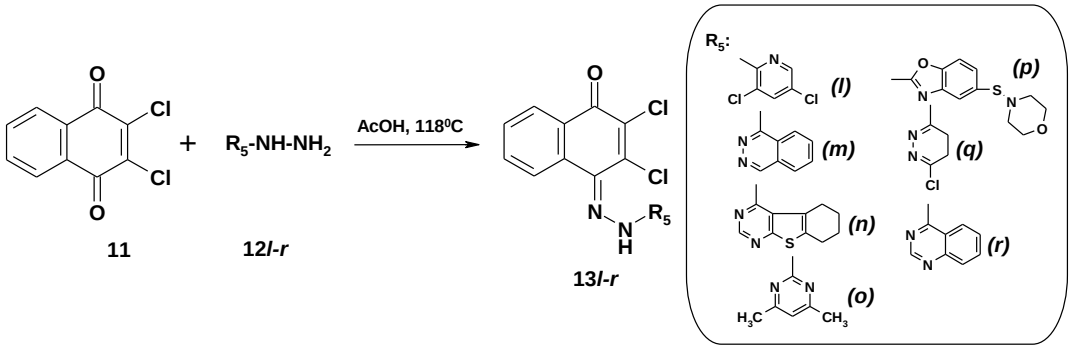
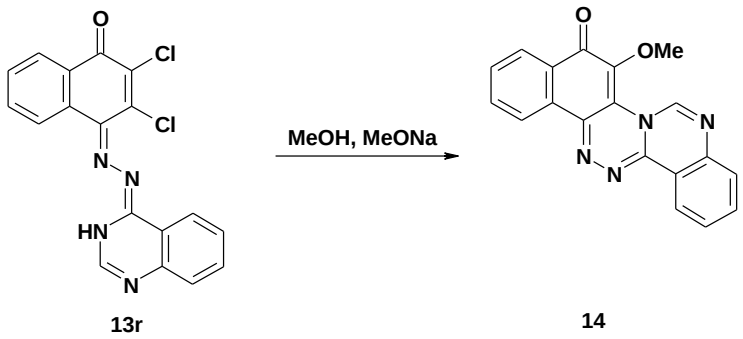
Scheme 2:



Exploring of the chemical properties of the obtained derivatives **13 l-r** was found, that the product **13r** is able to enter into heterocyclization reaction with forming of the corresponding product **14**. Heterocyclization was carried out in a mixture of sodium methylate and methanol.



Having carried out in silico studies by molecular docking, we could predict the possibility of showing the biological activity of compounds. As a result of docking studies the highest affinity of the studied compounds to a fragment of DNA was established. Accordingly, low levels of binding compounds with fragment tubulin, protein PPARγ were found. In Fig. 1,2 it is shown the compound-hit 13-(3,4-dimethoxy-phenyl)-6,11-dihydroxy-3,4a,12a,13-tetrahydro-1,4-dithia-3-aza-cyclopenta[b]naphthacene-2,5,12-trione **10e** in the field of DNA binding fragment (crystallographic model 2DES) and in compare with the selective inhibitor Morpholine-Doxorubicin. There is the possibility of π-π binding between the fragment of anthraquinone compound 13-(3,4-dimethoxy-phenyl)-6,11-dihydroxy-3,4a,12a,13-tetrahydro-1,4-dithia-3-aza-cyclopenta[b]naphthacene-2,5,12-trione **10e** and fragments of purine nucleotides, and also hydrophobic interactions of Morpholine-Doxorubicin and DNA fragment that duplicates side triazole-furyl fragment of the substance.

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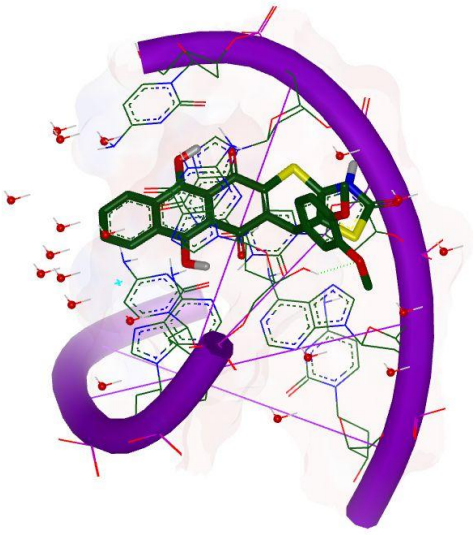

Fig.1. The compound-hit 13-(3,4-dimethoxy-phenyl)-6,11-dihydroxy-,4a,12a,13-tetra-hydro-1,4-dithia-3-aza-cyclopenta[b] naphthacene-2,5,12-trione **10e** in the field of binding fragment DNA (crystallographic model 2DES).

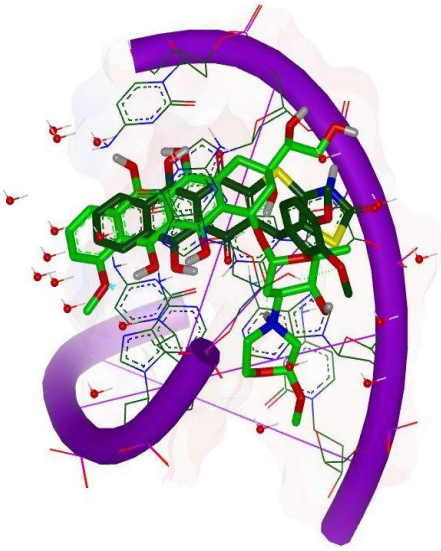

Fig.2. The compound-hit 13-(3,4-dimethoxy-phenyl)-6,11-dihydroxy-3,4a,12a,13-tetra-hydro-1,4-dithia-3-aza-cyclopenta[b] naphthacene-2,5,12-trione **10e** in the field of binding fragment DNA (crystallographic model 2DES) and in compare with selective inhibitor Morpholine-Doxorubicin.

Analyzing the results of obtained scoring functions we can talk about the highest binding of 13-(3,4-dimethoxy-phenyl)-6,11-dihydroxy-3,4a,12a,13-tetra-hydro-1,4-dithia-3-azacyclo-penta[b]naphthacene-2,5,12-trione **10e** with a fragment of DNA.

The high degree of affinity to the chosen biological target gives us a promising opportunity in displaying antitumor activity of these compounds.

EXPERIMENTAL

^{1}H NMR spectra of the products were recorded on spectrograph Varian VRX 300MHz. Monitoring the process of the reaction and the identity of substances were carried out by TLC on plates "Silufol UV-254" and "Merk Kieselgel 60 F254".

1, 4-Dihydro-1,4-epoxyanthracene-9,10-dione (8a)

To 0, 7g of 1, 4-naphthoquinone **8** (0.0044 mol) in 10 ml of acetic acid was added 0, 3g of furan (0.0044 mol) and a few crystals of hydroquinone. The reaction mass was refluxed for 1 hour, the resulting precipitate was filtered, recrystallized from heptane. Yellow-brown precipitate (68%) was obtained.

^{1}H NMR (300 MHz, DMSO-d6) δ, ppm: 8,10 (m, 2H); 7,82 (m, 2H); 6,80 (t, 2H); 5,83 (t, 2H).

Yield m = 68 %.
Calcd for $C_{14}H_8O_3$: C (75.00%); H (3.6%).
Found: C (74.43%); H (4.34%).

By the same method were obtained:

5-Hydroxy-1, 4-dihydro-1,4-epoxyanthracene-9,10-dione (9a)

^{1}H NMR (300 MHz, DMSO-d6) δ, ppm: 11,82 (s, 1H); 7,68 (d, 2H); 7,22 (m, 1H); 6,74 (m, 2H); 5,86 (m, 1H); 5,79 (m, 1H).

Yield m = 70 %
Calcd for $C_{14}H_8O_4$: C (70.00%) H (3.36%)
Found: C (69.45%); H (4.12%)

6, 11-Dihydroxy-1,4-dihydro-1,4-epoxytetracene-5,12-dione (10a)

^{1}H NMR (300 MHz, DMSO-d6) δ, ppm: 10,66 (s, 2H); 8,24 (m, 2H); 7,78 (m, 2H); 6,67 (t, 2H); 5,85 (t, 2H).

Yield m = 69 %.
Calcd for $C_{18}H_{10}O_5$: (70.59%) H (3.29%)
Found: C (70.18%) H (4,85%)

10-Methyl-1,4-dihydro-1,4-(epiminomethano)naphthalene-5,8,9-trione (7b)

^{1}H NMR (300 MHz, DMSO-d6) δ, ppm: 6,96 (m, 1H); 6,92 (m, 2H); 6,71 (m, 1H); 4,67 (dd, 1H); 4,52 (d, 1H); 2,89 (d, 3H).

Yield m = 63 %.
Calcd for $C_{12}H_9NO_3$: C (66.97%) H (4.22%) N (6.51%) O (22.30%)
Found: C (66.42%) H (5.06%) N (6.35%)

5-Hydroxy-12-methyl-1,4-dihydro-1,4-(epiminomethano)anthracene-9,10,11-trione (9b)

^{1}H NMR (300 MHz, DMSO-d6) δ, ppm: 11,82 (s, 1H); 7,72 (t, 1H); 7,65 (dd, 1H); 7,23 (m, 2H); 6,63 (m, 1H); 4,78 (dd, 1H); 4,74 (m, 1H); 2,89 (d, 3H).

Yield m = 69 %
Calcd for $C_{16}H_{11}NO_4$: C (68.32%) H (3.94%) N (4.98%)
Found: C (67.86%) H (4.61%) N (4.91%)

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6, 11-Dihydroxy-14-methyl-1,4-dihydro-1,4-(epiminomethano)tetracene-5,12,13-trione (10b)

^{1}H NMR (300 MHz, DMSO-d6) δ, ppm: 10,66 (s, 2H); 8,35 (m, 1H); 8,24 (m, 1H); 7,78 (m, 2H); 7,23 (m, 1H); 6,68 (m, 1H); 4,70 (m, 1H); 4,66 (dd, 1H); 2,90 (d, 3H).

Yield m = 75 %.
Calcd for $C_{20}H_{13}NO_5$: C (69.16%) H (3.77%) N (4.03%)
Found: C (68.77%) H (4.38%) N (3.98%)

9-Phenyl-3,9-dihydro-2H-thiochromeno[2,3-d][1,3]thiazole-2,5,8-trione (7c)

^{1}H NMR (300 MHz, DMSO-d6) δ, ppm: 10,79 (s, 1H); 7,29 (m, 2H); 7,25 (m, 1H); 7,18 (m, 2H); 6,92 (m, 2H); 5,33 (s, 1H).

Yield m = 68 %.
Calcd for $C_{16}H_9NO_3S_2$: C (58.70%) H (2.77%) N (4.28%) S (19.59%)
Found: C (58.37%) H (3.39%) N (4.35%) S (19.42%)

6-Hydroxy-11-phenyl-3,11-dihydro-2H-benzo[6,7]thiochromeno[2,3-d][1,3]thiazole-2,5,10-trione (9c)

^{1}H NMR (300 MHz, DMSO-d6) δ, ppm: 11,82 (s, 1H); 10,79 (s, 1H); 7,78 (dd, 1H); 7,37 (s, 1H); 7,25 (m, 1H); 7,24 (m, 2H); 7,23 (m, 1H); 7,16 (m, 2H); 5,61 (s, 1H).

Yield: m = 68 %.
Calcd for $C_{20}H_{11}NO_4S_2$: C (61.06%) H (2.82%) N (3.56%) S (16.30%)
Found: C (62.56%) H (3.25%) N (2.98%) S (13.81%)

6,11-Dihydroxy-13-phenyl-3,13-dihydro-2H-naphtho[2',3':6,7]thiochromeno[2,3-d][1,3] thiazole- 2, 5, 12-trione (10c)

^{1}H NMR (300 MHz, DMSO-d6) δ, ppm: 10,79 (s, 1H); 10,66 (s, 2H); 8,33 (m, 1H); 8,34 (m, 1H); 7,78 (m, 2H); 7,31 (m, 2H); 7,25 (m, 1H); 7,16 (m, 2H); 5,42 (s, 1H).

Yield m = 71 %.
Calcd for $C_{24}H_{13}NO_5S_2$: C (62.73%) H (2.85%) N (3.05%) S (13.96%)
Found: C (60.85%) H (3.23%) N (3.49%) S (16.19%)

9-(4-Methoxyphenyl)-3,9-dihydro-2H-thiochromeno[2,3-d][1,3]thiazole-2,5,8trione (7d)

^{1}H NMR (300 MHz, DMSO-d6) δ, ppm: 10,79 (s, 1H); 6,98 (m, 2H); 6,92 (m, 2H); 6,86 (m, 2H); 5,34 (s, 1H); 3,73 (s, 3H).

Yield m = 63 %.

Calcd for $C_{17}H_{11}NO_4S_2$: C (57.13%) H (3.10%) N (3.92%) S (17.94%)
Found: C (56.71%) H (3.63%) N (3.89%) S (17.74%)

6-Hydroxy-11-(4-methoxyphenyl)-3,11-dihydro-2H-benzo[6,7]thiochromeno[2,3-d][1,3] thiazole-2,5,10-trione (9d)

^{1}H NMR (300 MHz, DMSO-d6) δ, ppm: 11,82 (s, 1H); 10,79 (s, 1H); 7,78 (dd, 1H); 7,37 (t, 1H); 7,23 (dd, 1H); 6,99 (m, 2H); 6,82 (m, 2H); 5,62 (s, 1H); 3,73 (s, 3H).

Yield m = 71 %.
Calcd for $C_{21}H_{13}NO_5S_2$: C (59.56%) H (3.09%) N (3.31%) S (15.14%)
Found: C (59.29%) H (3.44%) N (3.27%) S (15.04%)

6,11-Dihydroxy-13-(4-methoxyphenyl)-3,13-dihydro-2H-naphtho[2',3':6,7]thiochromeno [2,3-d][1,3 thiazole-2,5,12-trione (10d)

^{1}H NMR (300 MHz, DMSO-d6) δ, ppm: 10,79 (s, 1H); 10,66 (s, 2H); 8,33 (s, 1H); 8,24 (s, 1H); 78 (m, 2H); 6,99 (m, 2H); 6,82 (m, 2H); 5,40 (s, 1H); 3,43 (s, 3H).

Yield m = 69 %
Calcd for $C_{25}H_{15}NO_6S_2$: C (61.34%) H (3.09%) N (2.86%) S (13.10%)
Found: C (61.14%) H (3.38%) N (2.74%) S (13.04%)

9-(3,4-Dimethoxyphenyl)-3,9-dihydro-2H-thiochromeno[2,3-d][1,3]thiazole-2,5,8-trione (7e)

^{1}H NMR (300 MHz, DMSO-d6) δ, ppm: 10,79 (s, 1H); 6,93 (m, 2H); 6,87 (m, 1H); 6,77 (m, H); 5,31 (s, 1H); 3,76 (s, 3H); 3,70 (s, 3H).

Yield m = 61 %.
Calcd for $C_{18}H_{13}NO_5S_2$: C (55.80%) H (3.38%) N (3.62%) S (16.55%)
Found: C (55.54%) H (3.78%) N (3.59%) S (16.42%)

11-(3,4-Dimethoxyphenyl)-6-hydroxy-3,11-dihydro-2H-benzo[6,7]thiochromeno[2,3-d][1,3] thiazole-2,5,10-trione (9e)

^{1}H NMR (300 MHz, DMSO-d6) δ, ppm: 11,82 (s, 1H); 10,79 (s, 1H); 7,78 (dd, 1H); 7,37 (t,1H); 7,23 (dd, 1H); 6,84 (d, 1H); 6,79 (dd, 1H); 6,73 (s, 1H); 5,52 (s, 1H); 3,76 (s , 3H); 3,70 (s, 1H).

Yield m = 70 %.
Calcd for $C_{22}H_{15}NO_6S_2$: C (58.27%) H (3.33%) N (3.09%) S (14.14%)
Found: C (58.02%) H (3.78%) N (3.04%) S (14.05%)

13-(3,4-Dimethoxyphenyl)-6,11-dihydroxy-3,13-dihydro-2H-naphtho[2',3':6,7]

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Thiochromeno [2,3-d][1,3]thiazole-2,5,12-trione (10e)

^{1}H NMR (300 MHz, DMSO-d6) δ, ppm: 10,79 (s, 1H); 10,66 (s, 2H); 8,33 (m, 1H); 8,24 (m, 1H); 7,78 (m, 2H); 6,85 (d, 1H); 6,79 (m, 2H); 5,26 (s, 1H); 3,76 (s, 3H); 3,70 (s , 3H).

Yield m = 64 %.
Calcd for $C_{26}H_{17}NO_7S_2$: C (60.11%) H (3.30%) N (2.70%) S (12.34%)
Found: C (59.88%) H (3.65%) N (2.66%) S (12.23%)

9-(3-Ethoxy-4-hydroxyphenyl)-3,9-dihydro-2H-thiochromeno[2,3-d][1,3]thiazole-2,5,8-trione (7f)

^{1}H NMR (300 MHz, DMSO-d6) δ, ppm: 10,79 (s, 1H); 6,97 (m, 1H); 6,90 (d, 1H); 6,76 (m, 1H); 73 (m, 1H); 6,69 (m, 1H); 5,22 (s, 1H); 4,15 (dd, 2H); 4,30 (m, 1H); 1,40 (t , 3H).

Yield m = 64 %.
Calcd for $C_{18}H_{13}NO_5S_2$: C (55.80%) H (3.38%) N (3.62%) S (16.55%)
Found: C (55.45%) H (3.85%) N (3.56%) S (16.46%)

11-(3-Ethoxy-4-hydroxyphenyl)-6-hydroxy-3,11-dihydro-2H-benzo[6,7]thiochromeno [2,3-d] [1,3] thiazole-2,5,10-trione (9f)

^{1}H NMR (300 MHz, DMSO-d6) δ, ppm: 11,82 (s, 1H); 10,79 (s, 1H); 8,86 (s, 1H); 7,79 (dd, 1H); 7,37 (t, 1H); 7,23 (dd, 1H); 6,76 (dd, 1H); 6,70 (m, 2H); 5,51 (s, 1H); 4,16 (dd , 2H); 1,40 (t, 3H).

Yield m = 71 %.
Calcd for $C_{22}H_{15}NO_6S_2$: C (58.27%) H (3.33%) N (3.09%) S (14.14%)
Found: C (58.03%) H (3.74%) N (3.03%) S (14.05%)

13-(3-Ethoxy-4-hydroxyphenyl)-6,11-dihydroxy-3,13-dihydro-2H-naphtho[2',3':6,7] thiochromeno [2,3-d][1,3]thiazole-2,5,12-trione (10f)

^{1}H NMR (300 MHz, DMSO-d6) δ, ppm: 10,79 (s, 1H); 10,66 (s, 2H); 8,86 (s, 1H); 8,33 (m, 1H); 24 (m, 1H); 7,78 (m, 2H); 6,77 (dd, 1H); 6,70 (m, 2H); 5,24 (s, 1H); 4,15 (dd , 2H); 1,40 (t, 3H).

Yield m = 69 %.
Calcd for($C_{26}H_{17}NO_7S_2$: C (60.11%) H (3.30%) N (2.70%) S (12.34%)
Found: C (59.85%) H (3.64%) N (2.58%) S (12.31%)

9-(3,5-Di-tert-butyl-4-hydroxyphenyl)-3,9-dihydro-2H-thiochromeno[2,3-d][1,3]thiazole-2,5,8-trione (7g)

^{1}H NMR (300 MHz, DMSO-d6) δ, ppm: 10,79 (s, 1H); 8,06 (s, 1H); 7,17 (s, 2H); 7,02 (d, 1H); 6,90 (d, 1H); 5,20 (s, 1H); 1,38 (s, 18H);

Yield m = 63 %.
Calcd for $C_{24}H_{25}NO_4S_2$: C (63.27%) H (5.53%) N (3.07%) S (14.08%)
Found: C (63.02%) H (5.93%) N (3.01%) S (13.99%)

11-(3,5-Di-tert-butyl-4-hydroxyphenyl)-6-hydroxy-3,11-dihydro-2H-benzo[6,7] thiochromeno [2,3-d] [1,3]thiazole-2,5,10-trione (9g)

^{1}H NMR (300 MHz, DMSO-d6) δ, ppm: 11,82 (s, 1H); 10,79 (s, 1H); 8,06 (s, 1H); 7,78 (dd, 1H); 7,37 (t, 1H); 7,23 (dd, 1H); 7,18 (s, 2H); 5,36 (s, 1H); 1,38 (s, 18H);

Yield m = 71 %.
Calcd for $C_{28}H_{27}NO_5S_2$: C (64.47%) H (5.22%) N (2.69%) S (12.29%)
Found: C (64.23%) H (5.56%) N (2.64%) S (12.21%)

13-(3,5-Di-tert-butyl-4-hydroxyphenyl)-6,11-dihydroxy-3,13-dihydro-2H-naphtho [2',3':6,7] thiochromeno[2,3-d][1,3]thiazole-2,5,12-trione (10g)

^{1}H NMR (300 MHz, DMSO-d6) δ, ppm: 10,79 (s, 1H); 10,66 (s, 2H); 8,33 (m, 1H); 8,24 (m, 1H); 8,06 (s, 1H); 7,78 (m, 2H); 7,23 (s, 2H); 5,08 (s, 1H); 1,38 (s, 18H).

Yield m = 65 %.
Calcd for $C_{32}H_{29}NO_6S_2$: C (65.40%) H (4.97%) N (2.38%) S (10.91%)
Found: C (65.19%) H (5.28%) N (2.29%) S (10.85%)

9-[4-(Dimethylamino)phenyl]-3,9-dihydro-2H-thiochromeno[2,3-d][1,3]thiazole-2,5,8-trione (7h)

^{1}H NMR (300 MHz, DMSO-d6) δ, ppm: 10,79 (s, 1H); 6,94 (m, 1H); 6,91 (m, 2H); 6,89 (m, 1H); 6,49 (m, 2H); 4,98 (s, 1H); 2,82 (s, 6H);

Yield m = 66 %.
Calcd for $C_{18}H_{14}N_2O_3S_2$: C (58.36%) H (3.81%) N (7.56%) S (17.31%)
Found: C (58.07%) H (4.32%) N (7.79%) S (17.20%)

11-[4-(Dimethylamino)phenyl]-6-hydroxy-3,11-dihydro-2H-benzo[6,7]thiochromeno[2,3-d] [1,3]thiazole-2,5,10-trione (9h)

^{1}H NMR (300 MHz, DMSO-d6) δ, ppm: 11,82 (s, 1H); 10,79 (s, 1H); 7,79 (dd, 1H); 7,37 (t, 1H); 7,23 (dd, 1H); 6,91 (d, 2H); 6,47 (d, 2H); 5,44 (s, 1H); 2,82 (s, 6H);

Yield m = 70 %.

Calcd for $C_{22}H_{16}N_2O_4S_2$: C (60.53%) H (3.69%) N (6.42%) S (14.69%)
Found: C (60.29%) H (4.13%) N (6.37%) S (14.63%)

11-[4-(Dimethylamino)phenyl]-6-hydroxy-3,11-dihydro-2H-benzo[6,7]thiochromeno[2,3-d] [1,3]thiazole-2,5,10-trione (10h)

^{1}H NMR (300 MHz, DMSO-d6) δ, ppm: 10,79 (s, 1H); 10,66 (s, 2H); 8,33 (m, 1H); 8,24 (m, 1H); 7,78 (m, 2H); 6,91 (d, 2H); 6,47 (d, 2H); 5,21 (s, 1H); 2,82 (s, 6H);

Yield m = 68 %.
Calcd for $C_{26}H_{18}N_2O_5S_2$: C (62.14%) H (3.61%) N (5.57%) S (12.76%)
Found: C (61.93%) H (4.01%) N (5.49%) S (12.70%)

9-(4-Fluorophenyl)-3,9-dihydro-2H-thiochromeno[2,3-d][1,3]thiazole-2,5,8-trione (7i)

^{1}H NMR (300 MHz, DMSO-d6) δ, ppm: 10,79 (s, 1H); 7,16 (m, 2H); 6,94 (m, 1H); 6,90 (m, 1H); 6,86 (m, 2H); 5,40 (s, 1H).

Yield m = 65 %.
Calcd for $C_{16}H_8FNO_3S_2$: C (55.64%) H (2.33%) F (5.50%) N (4.06%) S (18.57%)
Found: C (55.35%) H (2.89%) F (5.46%) N (4.01%) S (18.44%)

11-(4-Fluorophenyl)-6-hydroxy-3,11-dihydro-2H-benzo[6,7]thiochromeno[2,3-d][1,3]thiazole-2,5,10-trione (9i)

^{1}H NMR (300 MHz, DMSO-d6) δ, ppm: 11,82 (s, 1H); 10,79 (s, 1H); 7,78 (dd, 1H); 7,37 (t, 1H); 7,23 (dd, 1H); 7,12 (m, 2H); 6,84 (m, 2H); 5,66 (s, 1H).

Yield m = 69 %.
Calcd for $C_{20}H_{10}FNO_4S_2$: C (58.39%) H (2.45%) F (4.62%) N (3.40%) S (15.59%)
Found: C (58.12%) H (2.91%) F (4.61%) N (3.37%) S (15.41%)

13-(4-Fluorophenyl)-6,11-dihydroxy-3,13-dihydro-2H-naphtho[2',3':6,7]thiochromeno [2,3-d][1,3]thiazole-2,5,12-trione (10i)

^{1}H NMR (300 MHz, DMSO-d6) δ, ppm: 10,79 (s, 1H); 10,66 (s, 2H); 8,33 (m, 1H); 8,24 (m, 1H); 7,78 (m, 2H); 7,20 (m, 2H); 6,84 (m, 2H); 5,44 (s, 1H).

Yield m = 67 %.
Calcd for $C_{24}H_{12}FNO_5S_2$: C (60.37%) H (2.53%) F (3.98%) N (2.93%) S (13.3%)
Found: C (60.14%) H (2.92%) F (3.95%) N (2.90%) S (13.34%)

9-(4-Chlorophenyl)-3,9-dihydro-2H-thiochromeno[2,3-d][1,3]thiazole-2,5,8-trione (7j)

^{1}H NMR (300 MHz, DMSO-d6) δ, ppm: 10,79 (s, 1H); 7,25 (m, 2H); 7,18 (m, 2H); 6,94 (m, 1H); 6,90 (d, 1H); 5,48 (s, 1H).

Yield m = 62 %.
Calcd for $C_{16}H_8ClNO_3S_2$: C (53.11%) H (2.23%) Cl (9.80%) N (3.87%) S (17.72%)
Found: C (54.35%) H (2.89%) Cl (6.46%) N (4.01%) S (18.44%)

11-(4-Chlorophenyl)-6-hydroxy-3,11-dihydro-2H-benzo[6,7]thiochromeno[2,3-d][1,3]thiazole-2,5,10-trione (9j)

^{1}H NMR (300 MHz, DMSO-d6) δ, ppm: 11,82 (s, 1H); 10,79 (s, 1H); 7,79 (dd, 1H); 7,37 (t, 1H); 7,23 (dd, 1H); 7,21 (m, 2H); 7,16 (m, 2H); 4,72 (s, 1H).

Yield m = 76 %.
Calcd for $C_{20}H_{10}ClNO_4S_2$: C (56.14%) H (2.36%) Cl (8.29%) N (3.27%) S (14.51%)
Found: C (56.12%) H (2.91%) Cl (.61%) N (3.37%) S (15.41%)

13-(4-Chlorophenyl)-6,11-dihydroxy-3,13-dihydro-2H-naphtho[2',3':6,7]thiochromeno [2, 3-d] [1,3]thiazole-2,5,12-trione (10j)

^{1}H NMR (300 MHz, DMSO-d6) δ, ppm: 10,79 (s, 1H); 10,66 (s, 2H); 8,33 (m, 1H); 8,24 (m, 1H); 7,78 (m, 2H); 7,26 (m, 2H); 7,16 (m, 2H); 5,49 (s, 1H).

Yield m = 67 %.
Calcd for $C_{24}H_{12}ClNO_5S_2$: C (58.36%) H (2.45%) Cl (7.18%) N (2.84%) S (12.98%)
Found: C (60.14%) H (2.92%) Cl (3.95%) N (2.90%) S (13.34%)

9-(4-Bromophenyl)-3,9-dihydro-2H-thiochromeno[2,3-d][1,3]thiazole-2,5,8-trione (7k)

^{1}H NMR (300 MHz, DMSO-d6) δ, ppm: 10,79 (s, 1H); 7,55 (m, 2H); 7,34 (d, 2H); 6,94 (m, 1H); 6,90 (d, 1H); 5,40 (s, 1H).

Yield m = 61 %.
Calcd for $C_{16}H_8BrNO_3S_2$: C (47.30%) H (1.98%) Br (19.67%) N (3.45%) S(15.78%)
Found: C (57.35%) H (2.89%) Br (6.46%) N (4.01%) S (18.44%)

11-(4-Bromophenyl)-6-hydroxy-3,11-dihydro-2H-benzo[6,7]thiochromeno[2,3-d][1,3]thiazole-2,5,10-trione (9k)

^{1}H NMR (300 MHz, DMSO-d6) δ, ppm: 11,82 (s, 1H); 10,79 (s, 1H); 7,79 (dd, 1H); 7,50 (m, 2H); 7,37 (t, 1H); 7,23 (dd, 1H); 7,19 (d, 2H); 5,62 (s, 1H).

Yield m = 72 %.
Calcd for $C_{20}H_{10}BrNO_4S_2$: C (50.86%) H (2.13%) Br (16.92%) N (2.97%) S(13.58%)

Found: C (59.12%) H (2.91%) Br (3.61%) N (3.37%) S (15.41%)

13-(4-Bromophenyl)-6,11-dihydroxy-3,13-dihydro-2H-naphtho[2',3':6,7]thiochromeno [2,3-d][1,3]thiazole-2,5,12-trione (10k)

^{1}H NMR (300 MHz, DMSO-d6) δ, ppm: 10,79 (s, 1H); 10,66 (s, 2H); 8,33 (m, 1H); 8,24 (m, 1H); 7,79 (m, 2H); 7,50 (m, 2H); 7,08 (d, 2H); 5,38 (s, 1H).

Yield m = 65 %.
Calcd for $C_{24}H_{12}BrNO_5S_2$: C (53.54%) H (2.25%) Br (14.84%) N (2.60%) S (11.91%)
Found: C (61.14%) H (2.92%) Br (2.95%) N (2.90%) S (13.34%)

(4Z)-2,3-Dichloro-4-[2-(3,5-dichloropyridin-2-yl)hydrazinylidene]naphthalen-1(4H)-one (13l)

To 0.5866 g (0.0026 mol) of 2,3-dichloro-1,4-naphthoquinone in 30 ml of acetic acid is added 0.4599 g (0.0026 mol) of (3,5-dichloro-pyridin-2-yl)-hydrazine in 20 ml of acetic acid. The synthesis is carried out at the boiling temperature of the solvent and constant stirring. Reaction time - about 2 hours. The resulting product - sediment (4Z) -2,3-dichloro-4-[2 - (3,5-dichloropyridin-2-yl) hydrazinylidene] naphthalen-1 (4H)-one light brown color m = 0,43 g (43%).

1H NMR (300 MHz, DMSO-d6) δ, ppm: 8,58 (s, 1H); 8,30 (m, 2H); 8,08 (d, 1H); 7,78 (d, 1H); 7,68 (m, 2H).

Calcd for $C_{15}H_7C_{l4}N_3O$: C (46,6%) ; H (1,8%); Cl (36,6%); N (10,9%);
Found: C (45,7%); H (2,1%); Cl (4,5%); N (9,8%).

For given method were obtained following derivatives of 1,4-naphthoquinone **13m-r**:

(4Z)-2,3-Dichloro-4-[2-(phthalazin-1-yl)hydrazinylidene]naphthalen-1(4H)-one (13m)

1H NMR (300 MHz, DMSO-d6) δ, ppm: 11,30 (s, 1H); 9,42 (s, 1H); 8,30 (m, 2H); 8,11 (d, 1H); 7,65 (m, 5H).

Yield m = 48 %.
Calcd for $C_{18}H_{10}C_{l2}N_4O$: C (58,6%) ; H (2,7%); Cl (19,2%); N (15,2%);
Found: C (59, 2%); H (2,4%); Cl (19,8%); N (14,65%).

(4Z)-2,3-Dichloro-4-[2-(5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-4-yl) hydrazinylidene] naphthalen-1(4H)-one (13n)

1H NMR (300 MHz, DMSO-d6) δ, ppm: 11,11 (s, 1H); 8,30 (m, 3H); 7,68 (m, 2H); 2,77 (m, 2H); 2,56 (m, 2H); 1,81 (m, 4H).

Yield m = 50 %.
Calcd for $C_{20}H_{14}C_{l2}N_4OS$: C (56,0%); H (3,3%); Cl (16,5%); N (13,0%); S (7,5%).
Found: C (55,4%); H (3,7%); Cl (16,2%); N (13,5%); S (7,2%).

(4Z)-2,3-Dichloro-4-[2-(4,6-dimethylpyrimidin-2-yl)hydrazinylidene]naphthalen-1(4H)-one (13o)

1H NMR (300 MHz, DMSO-d6) δ, ppm: 11,46 (s, 1H); 8,28 (d, 2H); 7,68 (m, 2H); 7,11 (s, 1H); 2,58 (s, 6H).

Yield m = 53 %.
Calcd for $C_{16}H_{12}C_{l2}N_4O$: C (55,4%); H (3,5%); Cl (20,4%); N (16,1%);
Found: C (56,1%); H (3,9%); Cl (15,4%); N (4,2%).

(4Z)-2,3-Dichloro-4-{2-[5-(morpholin-4-ylsulfanyl)-1,3-benzoxazol-2-yl]hydrazinylidene} naphthalen-(4H)-one (13p)

1H NMR (300 MHz, DMSO-d6) δ, ppm: 10,06 (s, 1H); 8,35 (m, 2H); 7,79 (m, 4H); 7,13 (dd, 1H); 3,61 (m, 4H); 2,80 (m, 4H).

Yield m = 24 %.
Calcd for $C_{21}H_{16}C_{l2}N_4O_5S$: C (49,7%); H (3,2%); Cl (14,0%); N (11,0%); S (6,3%).
Found: C (48,9%); H (3,7%); Cl (13,6%); N (11,4%); S (5,8%).

(4Z)-2,3-Dichloro-4-[2-(6-chloro-4,5-dihydropyridazin-3-yl)hydrazinylidene]naphthalen-1(4H)-one (13q)

^{1}H NMR (300 MHz, DMSO-d6) δ, ppm: 10,33 (s, 1H); 8,30 (m, 2H); 7,91 (d, 1H); 7,68 (m, 2H); 7,60 (d, 1H).

Yield m= 28%.
Calcd for $C_{14}H_7Cl_3N_4O$: C (47,6%); H (2,0%); Cl (30,1%); N (15,8%); O (4,5%).
Found: C (48,1%); H (1,8%); Cl (31,6%); N (15,2%).

(4Z)-2,3-Dichloro-4-[(2Z)-quinazolin-4(3H)-ylidenehydrazinylidene]naphthalen-1(4H)-one (13r)

^{1}H NMR (300 MHz, DMSO-d6) δ, ppm: 9,80 (s, 1H); 8,73 (m, 1H); 8,48 (d, 1H); 8,38 (m, 1H); 8,16 (s, 1H); 7,84 (m, 1H); 7,74 (m, 1H); 7,68 (m, 1H); 7,52 (m, 2H).

Yield m= 54 %.
Calcd for $C_{18}H_{10}Cl_2N_4O$: C (58,6%); H (2,7%); Cl (19,2%); N (15,2%); O (4,3%).
Found: C (57,9%); H (3,1%); Cl (19,9%); N (14,7%).

8-Methoxy-9H-naphtho[2',1':5,6][1,2,4]triazino[4,3-c]quinazolin-9-one (14)

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1,0854 g (0,0030 mol) **(**4Z)-2,3-dichloro-4-[(2Z)-quinazolin-4(3H)-ylidenehydrazine ylidene]naphthalen-1(4H)-one (**13r**) was refluxed in a mixture of sodium methylate and methanol. The reaction was carried out at constant stirring. Reaction mixture was precipitated by acidified water and was filtered. The resulting product – dark brown sediment 8-methoxy-9H-naphtho[2',1':5,6][1,2,4]triazino[4,3-c]quinazoline-9-one, m=0,36 g (36%).

^{1}H NMR (300 MHz, DMSO-d6) δ, ppm: 9,01 (s, 1H); 8,50 (m, 2H); 8,36 (m, 1H); 8,03 (m, 1H); 7,89 (m, 1H); 7,78 (m, 2H); 7,61 (m, 1H); 3,82 (s, 3H).

Calcd for $C_{19}H_{12}N_4O_2$: C (69,5%); H (3,7%); N (17,0%); O (9,8%).
Found: C (68,9%); H (3,9%); N (16,5%).

REFERENCES

[1] Francesco Fringuelli. The Diels-Alder Reaction: Selected Practical Methods. – John Wiley &Sons 2002; 340.
[2] Yavor Kamdzhilov. A New Photoremovable Protecting Group – Synthesis and Reaction Mechanism– Basel 2005; 535.
[3] Wendell Peter Swigelaar. The synthesis of 3-allyl-4-ethyl-2-(1'-hydroxyethyl)-1-methoxynaphtalene and its behavior towards base- and palladium-promoted cyclisation under aerobic and anaerobic conditions. University of the Western Cape 2005; 214.
[4] D Atamanyuk, B Zimenkovsky, R Lesyk. Journal of Sulfur Chemistry 2008; 29(2):151–162.
[5] Kim S, Yoon JY. Sci Synth 2004; 27:671.
[6] Brehme R, Enders D, Fernandez R, Lassaletta JM. Eur J Org Chem 2007; 5629.
[7] Shawali AS, Parkanyi C. J Heterocycl Chem 1980; 17:833.
[8] Attanasi OA, De Crescentini L, Filippone P, Mantellini F. Arkivoc 2002; 9: 274.
[9] Attanasi OA, De Crescentini L, Favi G, Filippone P, Mantellini F, Perrulli FR, Santeusanio S. Eur J Org Chem 2009; 3109.
[10] Khafagy MM, El-Maghraby AA, Hassan SM, Bashandy MS, Phosphorus, Sulfur Silicon 2004; 179:2113.
[11] Aly AA, Nour-El-Din AM. Arkivoc 2008; 1: 153.
[12] Aly AA, Brown AB, El-Emary TI, Ewas AMM, Ramadan M. Arkivoc 2009; 1: 150.