Synthesis of new heterocyclic compounds based on 1,4-naphthoquinones and azomethines of α-amino acids

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Abstract – Analysed the literature sources to establish the basic "skafolds ", necessary for the design of "drugs-like molecules." Created the combinatorial library of new heterocyclic derivatives of 1,4-naphthoquinone. A docking study for determining structure leaders was conducted, ways of optimization the chemical structures to enhance the biological activity were determined. Designed by methods of obtaining a new heterocyclic derivatives based on 1,4-naphthoquinone and conducted search including effective anti-cancer agents.

Key words – heterocyclic compounds, 1,4-naphthoquinones, azomethines of α-amino acids, anticancer agents, "drug-like" compounds, 1,3-dypolar cycloaddition reaction.

I. Introduction

In the modern society one of the main items is the system of health care. On the background of adverse social and environmental conditions etiologic and pathogenic factors, arise to the development and evolution of various diseases. This situation requires modernization treatments, the most common of which is chemotherapy (therapy by medicinal products).

Mentioned above requires continuous updating and improvement of drugs for the treatment of pathological conditions, contributing to the development of synthetic chemistry, namely in the synthesis of new biologically active compounds. [1,2]

Heterocyclic Compounds (mainly derivatives of heterocycles) is extremely widespread in wildlife and perform a variety of biological functions. These compounds account for about 50% of natural substances, including biologically active compounds (it's a part of chlorophyll, hemoglobin, vitamins, alkaloids, nucleic acids, enzymes, etc.).. Also exhibit moderate antitumor, aperient, astringent, anti-inflammatory and bactericidal action. [3-9]

Most of these compounds are used as medicines or as starting materials for the synthesis. Due to heterocyclic compounds the arsenal of synthetic drugs is continuously replenished.

II. Result and Discussion

In recent decades, a lot of attention is paid to obtain new heterocyclic compounds with a wide range of biological activity.

A promising research direction of modern organic and pharmaceutical chemistry is directed synthesis and investigation of chemical, physico-chemical and biological properties of new heterocyclic compounds based on 1,4- naphthoquinone.

Research in the field of quinoid compounds made significant contribution to the theoretical basis of organic chemistry, and made it possible to detect many substances that exhibit different biological activities (biocide, antibiotic, antioxidant, etc.). [10-16]

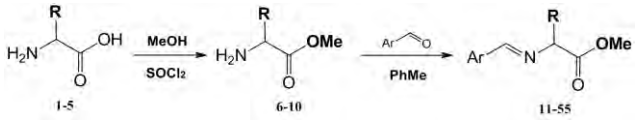
Also, the presence in the structure of compound fragment of quinone provides a high degree of bioavailability.

Important is to develop a method of constructing conjugate of one or more heterocyclic rings with the quinoid fragment, as most ligands for biological targets are compounds of heterocyclic structure. Therefore, in our opinion, the combining in one molecule quinoid and heterocyclic rings will lead to the formation of new heterocyclic systems based on 1,4-naphthoquinone – potential biologically active substances.

The aim of this work was the synthesis of new heterocyclic derivatives of 1,4-naphthoquinone with substituted pyrrole moiety. The task was implemented using 1,3-dypolar cycloaddition reaction by reacting the corresponding of azomethines α-amino acids with 1,4-naphthoquinone molecules in the medium of toluene in the presence of silver acetate and the base. Obtaining of the product was carried out in three stages.

The first step was to obtain methyl esters of α-amino acids. The reaction was carried out in methanol in the presence of thionyl chloride, which form an acidic medium and is used as degidrating agent. Using of esters avoid polymerization of amino acids in the synthesis of azomethines.

The next stage was to obtain azomethines in toluene with azeotropic stripping of water, formed in the reaction (1):



The third stage was carried for obtaining target product by dipolar cycloaddition of azomethines of α-amino acids with 1,4-naphthoquinone in toluene, in the presence of silver acetate and triethylamine (2):

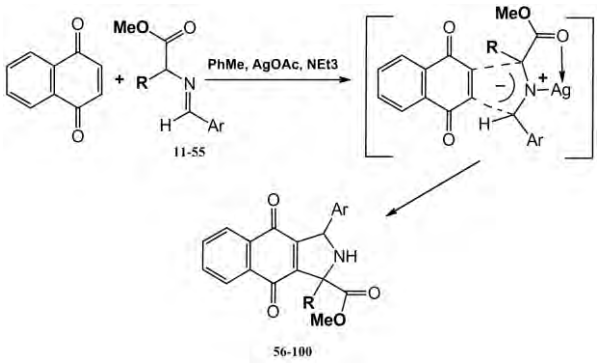


TABLE I

STRUCTURE OF THE SYNTHESIZED COMPOUNDS

№	Ar	R	№	Ar	R
56	Ph	H	79	3,5-Bu_2-4-HO-C_6H_2	CH_2CHME_2
57	Ph	Me	80	3,5-Bu_2-4-HO-C_6H_2	CH(Me)Et
58	Ph	$CHMe_2$	81	4-Me_2N-C_6H_4	H
59	Ph	CH_2CHME_2	82	4-Me_2N-C_6H_4	Me
60	Ph	CH(Me)Et	83	4-Me_2N-C_6H_4	$CHMe_2$
61	4-MeO-C_6H_4	H	84	4-Me_2N-C_6H_4	CH_2CHME_2
62	4-MeO-C_6H_4	Me	85	4-Me_2N-C_6H_4	CH(Me)Et
63	4-MeO-C_6H_4	$CHMe_2$	86	4-F-C_6H_4	H
64	4-MeO-C_6H_4	CH_2CHME_2	87	4-F-C_6H_4	Me
65	4-MeO-C_6H_4	CH(Me)Et	88	4-F-C_6H_4	$CHMe_2$
66	3,4-$(MeO)_2$-C_6H_3	H	89	4-F-C_6H_4	CH_2CHME_2
67	3,4-$(MeO)_2$-C_6H_3	Me	90	4-F-C_6H_4	CH(Me)Et
68	3,4-$(MeO)_2$-C_6H_3	$CHMe_2$	91	4-Cl-C_6H_4	H
69	3,4-$(MeO)_2$-C_6H_3	CH_2CHME_2	92	4-Cl-C_6H_4	Me
70	3,4-$(Me)_2$-C_6H_3	CH(Me)Et	93	4-Cl-C_6H_4	$CHMe_2$
71	3-EtO-4-HO-C_6H_3	H	94	4-Cl-C_6H_4	CH_2CHME_2
72	3-EtO-4-HO-C_6H_3	Me	95	4-Cl-C_6H_4	CH(Me)Et
73	3-EtO-4-HO-C_6H_3	$CHMe_2$	96	4-Br-C_6H_4	H
74	3-EtO-4-HO-C_6H_3	CH_2CHME_2	97	4-Br-C_6H_4	Me
75	3-EtO-4-HO-C_6H_3	CH(Me)Et	98	4-Br-C_6H_4	$CHMe_2$
76	3,5-Bu_2-4-HO-C_6H_2	H	99	4-Br-C_6H_4	CH_2CHME_2
77	3,5-Bu_2-4-HO-C_6H_2	Me	100	4-Br-C_6H_4	CH(Me)Et
78	3,5-Bu_2-4-HO-C_6H_2	$CHMe_2$			

The structure of the synthesized compounds was confirmed by PMR-spectroscopy, TLC (thin layer chromatography). Also, a preliminary virtual screening was held by using the program PASS (Table II).

TABLE II

LIST OF PREDICTED BIOLOGICAL ACTIVITY BY PROGRAM PASS

Compound	P_a	P_i	Activity
11a	0,830	0,002	Antibiotic Glycopeptide-like
	0,765	0,023	CYP2H substrate
11d	0,799	0,036	CYP2C12 substrate
	0,756	0,019	Membrane permeability inhibitor
12d	0,758	0,019	Membrane permeability inhibitor
	0,771	0,043	CYP2C12 substrate
13a	0,757	0,024	CYP2H substrate
	0,708	0,035	Membrane permeability inhibitor
13c	0,733	0,039	Gluconate 2-dehydrgenase (acceptor)inhibitor
	0,710	0,035	Membrane permeability inhibitor
14b	0,730	0,030	CYP2H substrate
	0,710	0,051	Gluconate 2-dehydrogenase (acceptor) inhibitor
15d	0,820	0,007	Membrane permeability inhibitor
	0,719	0,054	CYP2C12 substrate

Conclusion

The article describes the main ways of synthesis of potentially biologically active compounds from 1,4-naphthoquinones. A docking study for determining structure leaders was conducted, ways of optimization the chemical structures to enhance the biological activity were determined. Designed by methods of obtaining a new heterocyclic derivatives based on 1,4-naphthoquinone and conducted search including effective anti-cancer agents.

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