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SYNTHESIS OF BIOLOGICALLY ACTIVE COMPOUNDS BASED ON *o*-FERROCENYLBENZOIC ACID

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ABSTRACT

The article provides information on the importance of biologically active compounds derived from ferrocene, one of the important representatives of metallocenes, in the chemical industry, medicine, pharmacology, on the synthesis of an o-ferrocenylbenzoic acid derivative with amygdalin ([(6-O-β-D-glucopyranosyl -4-O-(o-ferrocenylbenzoyl)-β-D-glucopyranosyl) oxy]phenyl) acetonitrile), reaction with monomethylol-urea and reaction product (1-(2-carboxyphenyl)-1'-N-methyloxy-ferrocenylamide) , as well as the results of IR and mass spectral analysis and study of the biological activity of water-soluble salts of the obtained compounds.

KEYWORDS: *Ferrocene, П-Complex, Physiological Activity, O-Ferrocenylbenzoic Acid, 1-(2-Carboxyphenyl)-1'-N-Methyloxyferrocenamide, AKHM, IR Spectroscopy, Mass Spectrometry.*

INTRODUCTION

The use of biologically active substances that increase the productivity of agricultural crops will increase productivity and increase the ability to meet the growing needs of the population in goods derived from agricultural crops. The identification, synthesis and introduction of new types of sources of biologically active substances is one of the urgent tasks.

Currently, special attention is paid to the synthesis of chemical compounds that have a stimulating effect on the growth and development of crops, increasing the scale of their application. This indicates the need for efficient synthesis of compounds using available raw materials. In particular, it is important to synthesize new types of biostimulants based on compounds containing such trace elements as cobalt, manganese, iron, copper, zinc, and to study their biological activity by chemical and biological means. The synthesis and introduction of new

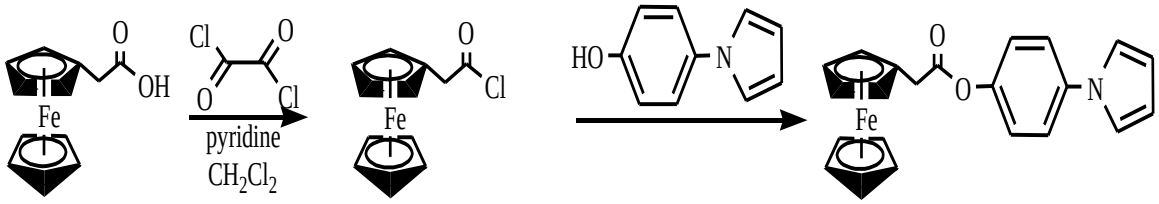
biologically active compounds for agricultural crops based on *o*-ferrocenylbenzoic acid is of great scientific and practical importance.

Literature review. In 1951, with the synthesis of ferrocene, the synthesis of π-complexes, a compound of the "sandwich" type, which is a specific type of organometallic compounds, and their comprehensive study began **[1].** The American chemist R. Woodward, based on the results of ferrocene acetylation, its stability and magnetic properties (ferrocene is a diamagnet), concluded that the iron atom in the ferrocene molecule is located between two mutually parallel cyclopentadienyl rings **[2].**

Since the discovery of ferrocene, many scientists have studied its properties and synthesized new derivatives. Biologically active products based on ferrocene are widely used in medicine, pharmacology, agriculture and other sectors of the national economy. One-dimensional polymers of p-ferrocenylbenzoic acid with Mn(OAc)2•2H2O and Cd(OAc)2•2H2O were synthesized by Chinese scientists and their structure and properties were studied **[3].**

The physiological activity and cheapness of ferrocene and its numerous derivatives make it possible to obtain great benefits from their use in various sectors of the national economy **[4].** The physiological activity of ferrocene derivatives is determined by the specific structure of its molecule and the properties of some functional groups in derivatives obtained by arylation, alkylation, acylation, and condensation reactions. In particular, physiologically active products that are supposed to be obtained on the basis of ferrocene must meet the following requirements: non-carcinogenicity, low toxicity, good solubility in water, the easiest splitting and excretion, chemical, biochemical and physiological inertness **[5].**

The synthesis and study of new derivatives of ferrocene lead to their widespread use. In particular, chemical sensors, catalysts, antidetanators, supramolecular compounds, and antidiabetic, antiproliferative, anti-inflammatory, antianemic, antibacterial and many other biologically active drugs and compounds with medicinal properties are used in the relevant fields. Biologically active compounds of ferrocene can be used as a drug in the treatment of certain cancers through chemotherapy. For example, 4-(1H-pyrrol-1-yl)phenylferrocenecarboxylate modified with a pyrrole group has a high biological activity and has an antiproliferative effect on breast cancer cells **[6].**



Compounds such as ferrocenium trichloroacetate, 1-[1-ferrocenyl(ethyl)]benzotriazole and ferrosifen have a high level of biological activity, but very low toxic properties. These compounds have been shown in clinical trials to resist the proliferation of cancer cells **[7, 8].** The anti-tuberculosis activity of the ferrocene derivative obtained by modification with quinoline showed effective results in vitro. The use of this quinoline-ferrocene hybrid in the amount of 2.5–5 μg/ml in the fight against tuberculosis microbacteria showed the highest results **[9].**

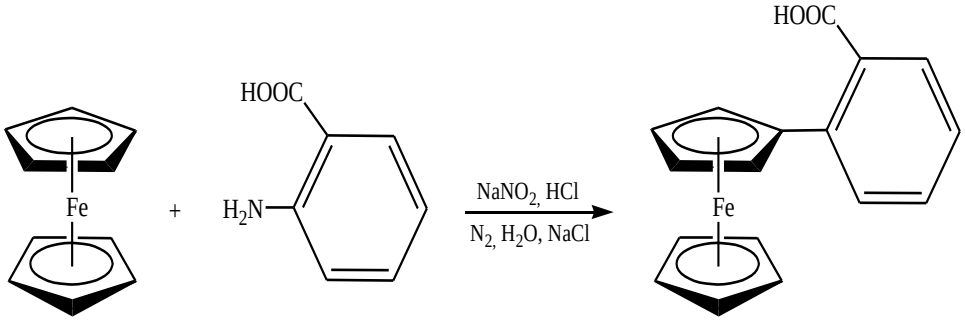
o-Ferrocenylbenzoic acid exhibits stronger acidic properties than *m*- and *p*-ferrocenylbenzoic acids, the acidic properties of which are almost the same; they are several times stronger than ferrocenecarboxylic acid **[10].**

Scientists from Andijan State University have synthesized a number of derivatives of ferrocenecarboxylic and ferrocenylbenzoic acids, which exhibit the properties of a biostimulator of agricultural crops **[10].**

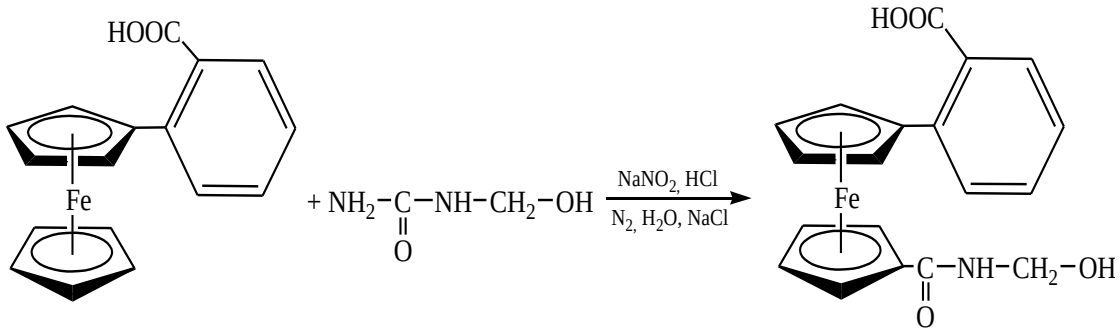
Experimental part.

IR spectra were taken on a Perkin Elmer Spectrum IR-Fourier spectrophotometer (Version 10.4.2) (Germany), mass spectra were obtained on a PerkinElmer AxION 2 TOF MS chromato-mass spectrometer (Germany).

Synthesis of *o*-ferrocenylbenzoic acid. 100 ml of distilled water, 50 g of ice, 2.74 g (0.02 mol) of *o*-aminobenzoic acid and 20 ml of concentrated hydrochloric acid are poured into a 500 ml round-bottom flask equipped with an auto-mixer. The reaction flask is placed in an ice bath. 3.45 g (0.05 mol) of sodium nitrite solution dissolved in 50 ml of water was added dropwise to the mixture over 1 hour with constant stirring. The ice bath is then replaced with a water bath. 3.72 g (0.02 mol) of ferrocene dissolved in 150 ml of diethyl ether are added to the resulting diazo solution. The mixture is stirred at 34°C for 3 hours. The mixture is then poured into a separating funnel. The ethereal and water parts are separated. The aqueous part is washed three times with diethyl ether. The ether parts are combined and washed three times with distilled water. An ethereal solution is then added and washed with 2% sodium hydroxide solution. Then the aqueous layer is separated and acidified with a 5% hydrochloric acid solution until the precipitation stops. This forms a reddish-brown precipitate. The precipitate is separated by filtration. Product weight 2.02 g (yield 33%). T.melt. = 120-121 ^{o}C. The reaction proceeds according to the following scheme:



Synthesis of 1-(2-carboxyphenyl)-1'-N-methyloxyferrocenamide. The synthesis of 1-(2-carboxyphenyl)-1'-N-methyloxyferrocenamide was carried out according to the above method. To a solution of 0.18 g of monomethylol urea was added 3.65 ml of concentrated hydrochloric acid, 1.38 g of sodium nitrite, 3.06 g of *o*-ferrocenylbenzoic acid dissolved in 150 ml of diethyl ether. Yield 1.97 g (52% based on *o*-ferrocenylbenzoic acid). T.melt. = 153-154 ^{o}C. The reaction proceeds according to the following scheme:



To determine the structure of the obtained compound, IR spectroscopy and mass spectrometry were used.

According to the results of the IR spectra, the intensity of the absorption band in the region of 760 sm^{-1}, the relatively low absorption in the region of 998 $sm^{-1}$and the absorption band in the region of 1584 sm^{-1}correspond to the characteristic absorption frequencies of the benzene ring. Vibration δ_{CH} of the cyclopentadienyl ring in the molecule is observed in the region of 810 sm^{-1}. The stretching vibration (ν_{CC}) of the carbon atoms of the substituted ring was found in the region of 1100 sm^{-1} in the exchange ring. It was also found that vibrations of carboxyl groups are characterized by absorption bands for $\nu_{(C\text{-}C\text{-}OH)}$ in the region of 1243 $sm^{-1}$and for $\nu_{(C=O)}$ in the region of 1553 sm^{-1}, respectively. The absorption band related to stretching vibrations of the -OH group is a broadened line in the region of 2500-4000 sm^{-1} (Fig. 1).

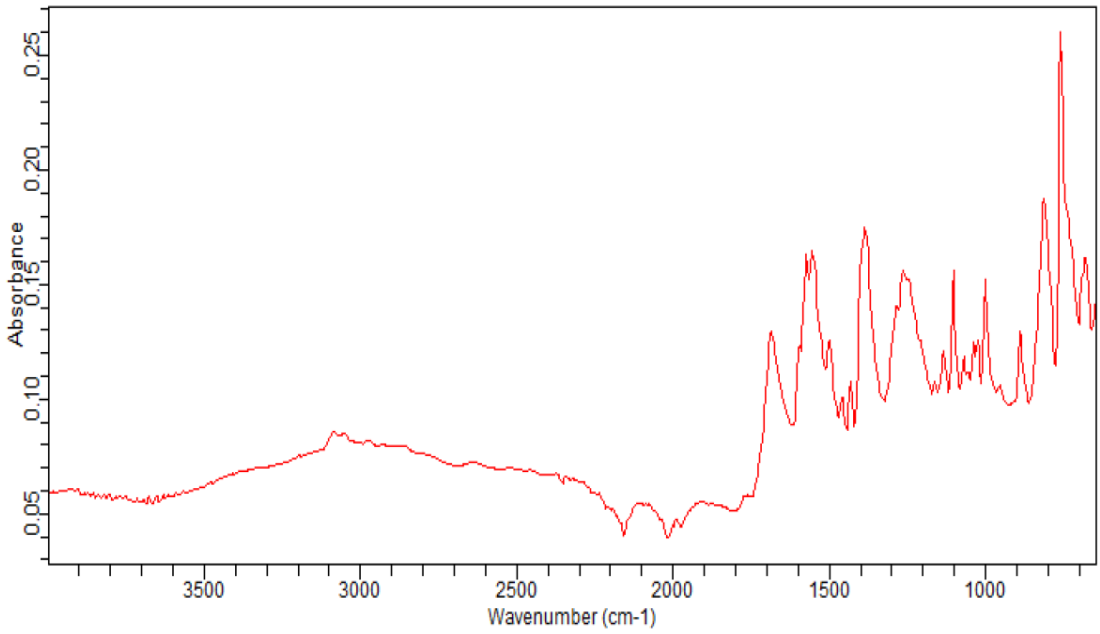


Fig. 1. IR spectrum of 1-(2-carboxyphenyl)-1'-N-methyloxyferrocenylamide.

To determine the specificity of the absorption spectrum of 1-(2-carboxyphenyl)-1'-N-methyloxyperrocenylamide, the experimental data were compared with the results of quantum-chemical calculations of the vibrational spectra of this molecule. The vibrational spectra of molecules of the synthesized compound were calculated using the Gaussian 98 program based on the DFT/B3LYP 6-311G (2G) method (Fig. 2).

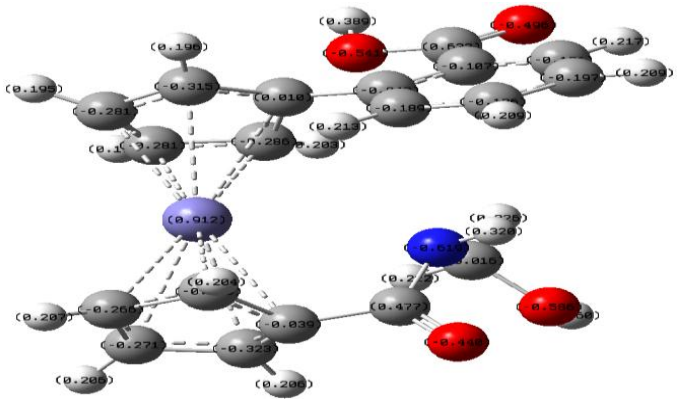


Fig.2. Molecular structure of 1-(2-carboxyphenyl)-1'-N-methyloxyferrocenylamide.

When comparing the results of the IR spectrum obtained in theoretical calculations with the results of the experimentally determined IR spectrum, it can be seen that they do not differ significantly (Table 1).

TABLE 1 CALCULATED AND FOUND VALUES OF THE WAVE NUMBERS OBSERVED IN THE IR SPECTRUM OF 1-(2-CARBOXYPHENYL)-1'-N-METHYLOXYFERROCENYLAMIDE

№	Oscillation type	Wave number of the maximum of the absorption region, sm-1	
		Calculated value	Found value
1.	$\delta_{s(C-H)(Cp)}$	660	675
2.	$\delta_{s\ (C-H)\ (Ar)}$	**760**	**760**
3.	$\nu_{s(CCC)\ (Cp)}$	807	810
4.	$\nu_{s(CCC)\ (Cp)}$	891	892
5.	$\delta_{(C-H)(Ar)}$	993	998
6.	$\delta_{(CCC)\ (Ar)}$	987	998
7.	$\nu_{s(C-C)\ (Cp)}$	**1100**	**1100**
8.	$\nu_{as(C-C-OH)(COOH)}$	1243	1257
9.	$\delta_{(NH)}$	1390	1393
10.	$\nu_{(C=O)\ (COOH)}$	**1553**	**1553**
11.	$\nu_{(C-H)}$	1560	1570
12.	$\delta_{(CCC)\ (Ar)}$	1588	1584
13.	$\delta_{\ (NH2)}$	1677	1682
14.	$\nu_{s(CH2)}$	3278	2500-4000 wideabsorptionarea
15.	$\nu_{as(CH2)}$	3327	
16.	$\nu_{as(CH)\ (Ar)}$	3353	
17.	$\nu_{s(CH)\ (Ar)}$	3359	
18.	$\nu_{s(C-H)(Cp)}$	3365	
19.	$\nu_{(NH)}$	3744	
20.	$\nu_{(O-H)}$	3914	
21.	$\nu_{(O-H)(COOH)}$	3940	

Mass spectrometric analysis of the synthesized 1-(2-carboxyphenyl)-1'-N-methyloxyferrocenamide was also carried out. The results are shown in Figure 3 and Table 2.

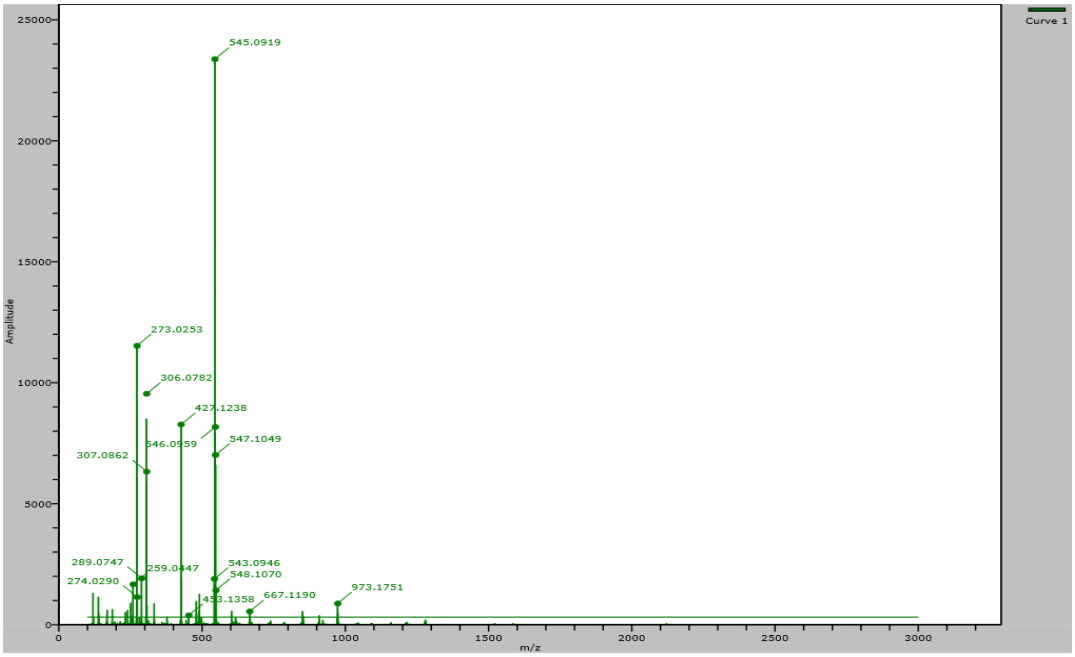


Fig. 3. Mass spectrum of 1-(2-carboxyphenyl)-1'-N-methyloxyferrocenylamide.

TABLE 2 MASS SPECTROMETRIC PARAMETERS OF 1-(2-CARBOXYPHENYL)-1'-N-METHYLOXYFERROCENYLAMIDE

№	Ion	m/z	Relative intensity, %
1	$[OOCC_6H_4FcCONHCH_2Fc]^+$	545	94±1
2	$[HOOCC_6H_4FcCONHCH_2Fc]^{2+}$	273	46±1
3	$FcC_6H_4COOH^+$	306	38±1
4	$FcC_6H_4COOHCONHCH_2Fc^+$	546	30±1
5	$[HOOCC_6H_4FcCONHCH_2Fc]^+$	547	28±1
6	$[FcC_6H_4COOH]^+$	307	25±1
7	$[FcCONHCH_2Fc]^+$	427	32±1

So, in the mass spectrum, the most intense peak belongs to the singly charged molecular ion of 1-(2-carboxyphenyl)-1'-N-methyloxyferrocenylamide, a less intense peak is observed for the doubly charged ion of this compound. This confirms that 1-(2-carboxyphenyl)-1'-N-methyloxyferrocenylamide is the main reaction product.

Sodium salt of 1-(2-carboxyphenyl)-1'-N-methyloxy-ferrocenylamide. 5.46 g (0.01 mol) of 1-(2-carboxyphenyl)-1'-N-methyloxy-ferrocenylamide was dissolved at room temperature with constant stirring in 0.1 M sodium bicarbonate solution until carbon dioxide evolution ceased. The resulting solution was filtered, poured into a beaker with 100 ml of acetone. The precipitate that formed was filtered off and dried at room temperature, then in an oven.Определение биологической активности 1-(2-карбоксифенил)-1'-N-метилоксиферроценамида.

To determine the biological activity of the sodium salt of 1-(2-carboxyphenyl)-1'-N-methyloxyferrocenylamide (symbol AKHM) in laboratory conditions, solutions of this substance with a concentration of 10^{-6}, 10^{-7} and 10^{-8} mol/l were prepared, as standard used succinic acid. Untreated wheat seeds served as control.

Research methods and materials. Studies to determine the biostimulating activity of the AKHM preparation, morphophysiological assessment was carried out according to GOST 12042-80 "Determination of the energy and germination of seeds" **[11].** Initially, samples of wheat seeds of the "Chillaki" variety were taken. Each sample was then treated with test and reference preparations. The tested seed samples were grown on moist filter paper 20x100 cm in size. Wheat samples treated with the AKHM preparation and the standard were checked every 24 hours. The ratio of water used to swell the grains to the weight of the grain was calculated in %. Root length and shoot length were measured and recorded after 24, 48 and 72 hours **[12].** The results of the experiments showed that wheat and barley treated with the AKHM preparation, in terms of yield, root length, growth and development of plants, are 24% more than the control variant (Table 3).

TABLE 3 INFLUENCE OF THE AKHM PREPARATION ON THE GERMINATION OF WHEAT SEEDS

Statistical indicators	Weight of zerg in one head mg	Weight of zerg in one head mg			Ratio of water spent on budding with grain weight, %	Root length, cm	Shoot length, cm	Germination, %
		24 hours	48 hours	72 hours				
	Control (water)							
Average	0,36 ±0.01	0,12 ±0.04	0,08 ±0.03	0,11 ±0.02	89,94±6.89	2,60 ±0.30	1,56 ±0.08	**63,66 ±1.20**
	AKHM							
10^{-6}	0,41	0,24	0,19	0,12	133,48	3,10	2,17	**76,00**
10^{-7}	0,42	0,24	0,16	0,12	126,33	3,17	2,07	**79,00**
10^{-8}	0,46	0,26	0,18	0,09	115,37	2,73	1,50	**71,00**
Average	**0,41 ±0.01**	**0,23 ±0.01**	**0,16 ±0.01**	**0,09 ±0.01**	**121,23 ±5.80**	**2,80 ±0.16**	**1,82 ±0.09**	**68,73 ±3.62**

The results presented in table 2 show that the weight of wheat seeds in the control variant before germination was 0.36 mg, after 24 hours the increase in weight was 0.12 mg, after 48 hours 0.08 mg and 0.11 mg after 72 hours . The ratio of germination water to grain weight was 89.94%. Then it was determined that the root length is 2.60 cm, the shoot length is 1.56 cm, and the germination rate is 63.66%.

When determining AKHM for wheat germination at these concentrations, after 24 hours the weight of seeds increased by 0.24, 0.24, 0.26 mg, after 48 hours by 0.19, 0.16, 0.18 mg and after 72 hours by 0.12, 0.12, 0.09 mg, respectively. The ratio of germination water to grain weight was respectively 133.48, 1.26.33, 115.37, root length 3.10, 3.17, 2.73 cm, shoot length 2.17, 2.07, 1, 50 cm, average germination 76.00, 79.00, 71.00%. Among the studied solutions, the greatest

effect was noted with a 10-7 M solution of AKHM, the germination of seeds was 24% higher than in the control variant.

CONCLUSION

Practical studies have shown that the AKHM preparation obtained by us on the basis of o-ferrocenylbenzoic acid in experiments on wheat exhibits high biostimulating activity. An increase in root length by 22%, shoot length by 32.7% and germination by 24% was noted than in the control variant. The data obtained allow us to conclude that the AKHM preparation can be widely used in grain growing.

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