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SYNTHESIS AND CHEMICAL POTENTIAL OF HYBRID STRUCTURES WITH OXADIAZOLE NUCLEI OF PYRAZOLE AND THIOPHENE

СИНТЕЗ ТА ХІМІЧНИЙ ПОТЕНЦІАЛ ГІБРИДНИХ СТРУКТУР З ОКСАДІАЗОЛЬНИМИ ЯДРАМИ ПІРАЗОЛУ ТА ТІОФЕНУ

Panasenko N. V. / Панасенко Н.В.
Ph.D., Associate Professor/ к.х.н.
Panasenko N. Yu. / Панасенко Н.Ю.
student/ студентка
Bukovinian State Medical University, 58000 Chernivtsi, Ukraine

Annotation *By cyclocondensation of 4-pyrazolylamidooximes with N-cyanoacetyl-3,5-dimethylpyrazole 3-(4-pyrazolyl)-5-(1,2,4-oxadiazolyl)acetonitriles were synthesized. By interaction of these compounds with sulfur and cycloalkanones in the conditions of Gewald reaction hybrid structures with pyrazole, 1,2,4-oxadiazole and aminothiophene nuclei were produced.*

Key words*: hybrid structures, 3-(4-pyrazolyl)-5-(1,2,4)-oxadiazolyl acetonitriles, 4-pyrazolyl-5-(1,2,4)-oxadiazolyl-3-thienylamines, cyclocondensation*

I. Introduction

Combination of several covalently bound structure fragments into one compound often modulates their characteristics or leads to emergence of new properties. This approach is attractive because it provides a significant quantity of variants of generation of wide range of new molecules for medical research and materials chemistry. It is customary to call compounds produced in this way 'hybrid', and in the recent years they were effectively used for design of bioactive scaffolds [1, 2].

II. Formulation of the problem

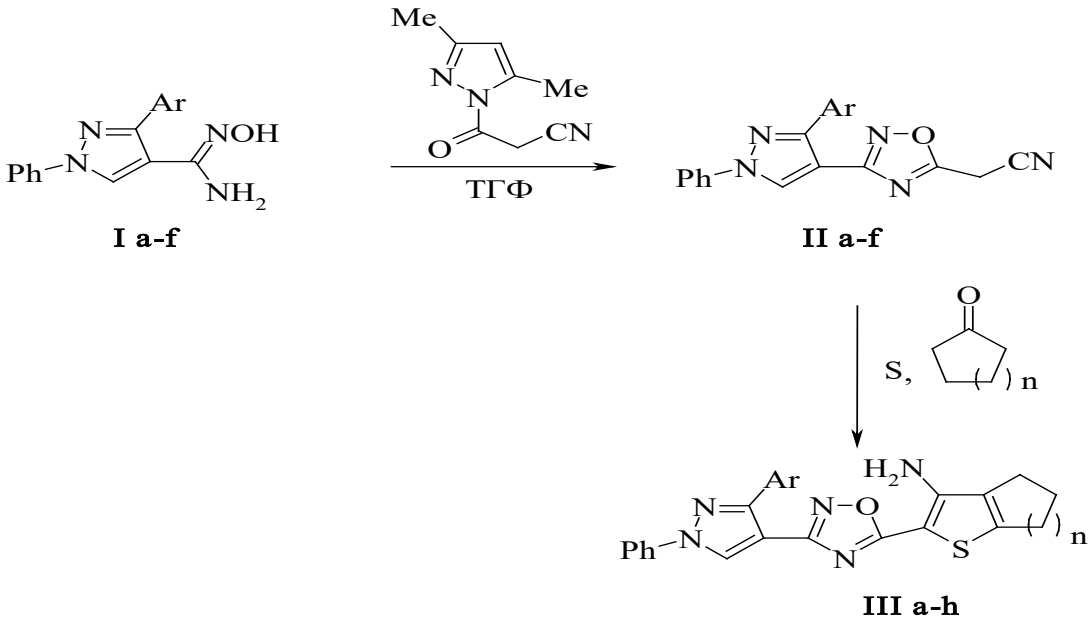
For the foregoing reasons it is desirable to combine three pharmacophores in one hybrid structure: pyrazole [3-5], 1,2,4-oxadiazole [6,7] and thiophene [8-11].

4-Pyrazolylamidooximes that we recently synthesized were chosen as key objects for building of systems of this kind **Ia-f** [12]. Their 3 hour interaction with 2,5-dimethyl-1-cyanoacetylpyrazole (as an equivalent of one-carbon electrophilic synthon) in boiling tetrahydrofurane allows to form 1,2,4-oxadiazole nucleus and to produce 3-(4-pyrazolyl)-5-(1,2,4-oxadiazolyl)acetonitriles **IIa-f** with yields of 63-76 %. As a side note, previously we performed successful synthesis of 5-substituted 1,2,4-oxadiazoles [12] by condensation of amidooximes, type **I**, with anhydrides of carboxylic acids.

It is known that 1,2,4-oxadiazole fragment is often used in the design if leading compounds as an important bio-isostere of esters and amides to achieve targeted pharmacokinetic parameters [13]. Derivatives of 1,2,4-oxadiazole are proposed as agonists of muscarinic [14,15] and benzodiazepine [16] receptors, and also as antagonists of histamine H_3 receptors [17]. Detailed patent search [18-20] demonstrated high inhibitory action of 1,2,4-oxadiazoles, exo-functionalized with aminothiophenol fragment, towards protein binding fatty acids. That's why further structural modification of the 5th position of 3-pyrazolyl 1,2,4-oxadiazole nucleus of this type with a group seems to be a convenient approach to new tricyclic hybrid structures.

III. Results

In view of this acetonitriles **IIa-f** were entered into Gewald reaction with cycloalkanones and sulfur in the presence of morpholine. As a result of this 4-pyrazolyl-5-(1,2,4-oxadiazolyl)-3-thienylamines **IIIa-h** were produced with the yields of 71-92 %.



I a-f **II a-f** **III a-h**

I, II, Ar = 3-$MeOC_6H_4$ (a), 4-ClC_6H_4 (b), 4-BrC_6H_4 (c), 4-EtC_6H_4 (d), 4-$F_2HCOC_6H_4$ (e), thienyl-2 (f);
III, Ar = 3-$MeOC_6H_4$, n=2 (a); 4-ClC_6H_4, n=2 (b); 4-BrC_6H_4, n=1 (c), 2 (d); 4-EtC_6H_4 n=1 (e), 2 (f); 4- $F_2HCOC_6H_4$, n=2 (g); thienyl-2, n=2 (h)

Composition and structure of the synthesized compounds (table 1-3) were confirmed by the measured results of their chromato-mass-, IR-, and NMR spectra. IR-spectra of intermediate acetonitriles **IIa-f** in particular are characterized by the absorption bands of CN groups with low intensity in the 2192-2197 cm^{-1} range. In the ^1H NMR spectra singlets of exocyclic methylene group are present in the 4.78-4.82 ppm range. In the IR spectra of the target products **IIIa-h** wide absorption bands of amino groups are recorded at 3435-3445 cm^{-1}. The presence of 1,2,4-oxadiazole and thienyl nuclei in their structure agrees with ^{13}C NMR spectra with corresponding signals of carbon atoms: 149-150 ppm ($C^3_{oxadiazole}$), 171 ppm ($C^5_{oxadiazole}$), 93-96 ppm ($C^3_{thiophene}$), 108-109 ppm ($C^4_{thiophene}$), 117-118 ppm ($C^5_{thiophene}$), 161-162 ppm $C^2_{thiophene}$

Experimental part

IR-spectra of the compounds in the KBr tablets were recorded in the UR-20 device. The ^1H and ^{13}C NMR spectra were measured using spectrometer Varian VXR-400 (399.97 and 100.613 MHz respectively) in DMSO-d_6, internal standard – TMS. Chromato-mass spectra were recorded using Agilent 1100/DAD MSD/VL G119562 device by direct injection of sample, ionization energy – 70 eV.

3-(4-Pyrazolyl)-5-(1,2,4-oxadiazolyl)acetonitriles (II a-f). Mixture of 0.01 mole of amidoxime **(I a-f)** and 1.63 g (0.01 mole) of 2,5-dimethyl-1-cyanoethylpyrazole in 15 ml THF was boiled for 3 hours. The reaction mixture was cooled down, the solvent was evaporated, and the residue was crystallized out of ethanol.

4-Pyrazolyl-5-(1,2,4-oxadiazolyl)-3-thienylamines (III a-h). Mixture of 0.001 mole of acetonitrile **(II a-e)**, 0.001 mole of corresponding cycloalkanone, 0.05 g (0.0015 mole) of sulfur and 0.5 ml of morpholine in 10 ml of ethanol were mixed for 1 hour at 50°C, and then 2 hours at 20-22°C. The resulting precipitate was filtrated and crystallized out of ethanol.

Table 1 - Characteristics of the compounds II a-f and III a-h

Compound	Formula	$[M+1]^+$	Found, % / Calculated, %			T_{melt}, ºC	Yield, %
			C	H	N		
II a	$C_{20}H_{15}N_5O_2$	358	66.92 / 67.22	4.13 / 4.23	19.78 / 19.60	103-104	74
II b	$C_{19}H_{12}ClN_5O$	362	62.84 / 63.08	3.25 / 3.34	19.60 / 19.36	131-133	68
II c	$C_{19}H_{12}BrN_5O$	407	55.91 / 56.18	3.09 / 2.98	17.47 / 17.24	135-137	76
II d	$C_{21}H_{17}N_5O$	356	71.24 / 70.97	4.93 / 4.82	19.47 / 19.71	108-109	71
II e	$C_{20}H_{13}F_2N_5O_2$	394	61.36 / 61.07	3.21 / 3.33	17.56 / 17.80	112-113	67
II f	$C_{17}H_{11}N_5OS$	334	61.55 / 61.25	3.25 / 3.33	21.18 / 21.01	123-125	63
III a	$C_{26}H_{23}N_5O_2S$	470	66.32 / 66.51	4.85 / 4.94	15.16 / 14.91	187-189	83
III b	$C_{25}H_{20}ClN_5OS$	474	63.64 / 63.35	4.16 / 4.25	14.54 / 14.78	182-184	89
III c	$C_{24}H_{18}BrN_5OS$	505	56.87 / 57.15	3.68 / 3. 60	14.09 / 13.88	173-175	81
III d	$C_{25}H_{20}BrN_5OS$	519	58.18 / 57.92	3.77 / 3.89	13.69 / 13.51	191-193	87
III e	$C_{26}H_{23}N_5OS$	454	68.56 / 68.85	5.20 / 5.11	15.21 / 15.44	165-167	92
III f	$C_{27}H_{25}N_5O_2S$	484	67.24 / 67.06	5.29 / 5.21	14.27 / 14.48	156-158	71
III g	$C_{26}H_{21}F_2N_5O_2S$	506	61.56 / 61.77	4.28 / 4.19	13.62 / 13.85	164-166	85
III h	$C_{23}H_{19}N_5OS_2$	446	61.71 / 62.00	4.38 / 4.30	15.51 / 15.72	148-149	79

Table 2

IR and ^{1}H NMR spectra of the compounds II a-f

Compound	IR spectra, ν, cm^{-1}		^{1}H NMR spectra, δ, ppm (*J* Hz)
	C≡N	NH_2	
IIa	2192		3.80 с (3H, CH_3), 4.79 с (2H, CH_2), 7.00-7.55 м (7H$_{arom}$), 8.02 д (2H$_{arom}$, *J* 7.6), 9.18 с (1H, H^5)
IIb	2197		4.78 с (2H, CH_2), 7.39-7.57 м (5H$_{arom}$), 7.82 д (2H$_{arom}$, *J* 8.6), 8.03 д (2H$_{arom}$, *J* 8.6), 9.21 с (1H, H^5)
IIc	2196		4.78 с (2H, CH_2), 7.38-7.51 м (3H$_{arom}$), 7.65 д (2H$_{arom}$, *J* 8.4), 7.77 д (2H$_{arom}$, *J* 8.4), 8.02 д (2H$_{arom}$, *J* 7.6), 9.21 с (1H, H^5)
IId	2195		1.20 т (3H, CH_3, *J* 7.2), 2.66 к (2H, CH_2, *J* 7.2), 4.78 с (2H, CH_2), 7.29 д (2H$_{arom}$, *J* 8.0), 7.39 т (1H$_{arom}$, *J* 8.0), 7.55 т (2H$_{arom}$, *J* 7.8), 7.72 д (2H$_{arom}$, *J* 7.6), 8.02 д (2H$_{arom}$, *J* 7.6), 9.16 с (1H, H$^5_{pyrazole}$)
IIe	2195		4.78 с (2H, CH_2), 7.27 д (2H$_{arom}$, *J* 8.1), 7.33 т (1H, CHF_2, *J* 7.6), 7.39 т (1H$_{arom}$, *J* 7.6), 7.55 т (2H$_{arom}$, *J* 7.6), 7.87 д (2H$_{arom}$, *J* 8.0), 8.02 д (2H$_{arom}$, *J* 8.0), 9.19 с (1H, H$^5_{pyrazole}$)
IIf	2194		4.82 с (2H, CH_2), 7.17-7.65 м (4H$_{arom}$), 7.95-8.07 м (3H$_{arom}$), 9.20 с (1H, H^5)
IIIa		3435	1.71-1.75 м (4H, 2CH_2), 2.53-2.58 м (2H, CH_2), 2.71-2.73 м (2H, CH_2), 3.80 с (3H, CH_3O), 7.01 д (1H$_{arom}$, *J* 8.0), 7.36-7.62 м (8H, 6H$_{arom}$ +NH_2), 8.01 д (2H$_{arom}$, *J* 7.6), 9.36 с (1H, H$^5_{pyrazole}$)
IIIb		3438	1.70-1.73 м (4H, 2CH_2), 2.54-2.58 м (2H, CH_2), 2.70-2.73 м (2H, CH_2), 7.38 т (1H$_{arom}$, *J* 7.8), 7.52-7.59 м (4H$_{arom}$), 7.65 с (2H, NH_2), 7.92 д (2H$_{arom}$, *J* 7.6), 8.01 д (2H$_{arom}$, *J* 7.6), 9.39 с (1H, H$^5_{pyrazole}$)
IIIc		3445	2.29-2.33 м (2H, CH_2), 2.67-2.71 м (2H, CH_2), 2.78-2.82 м (2H, CH_2), 7.39 т (1H$_{arom}$, *J* 7.8), 7.52-7.68 м (6H, 4H$_{arom}$ +NH_2), 7.86 д (2H$_{arom}$, *J* 7.6), 8.00 д (2H$_{arom}$, *J* 7.6), 9.38 с (1H, H$^5_{pyrazole}$)
IIId		3440	1.72-1.76 м (4H, 2CH_2), 2.53-2.57 м (2H, CH_2), 2.69-2.73 м (2H, CH_2), 7.40 т (1H$_{arom}$, *J* 7.8), 7.52-7.70 м (6H, 4H$_{arom}$ +NH_2), 7.85 д (2H$_{arom}$, *J* 7.6), 8.01 д (2H$_{arom}$, *J* 7.6), 9.39 с (1H, H$^5_{pyrazole}$)
IIIe		3442	1.05 т (3H, CH_3, *J* 7.2), 2.30-2.34 м (2H, CH_2), 2.62-2.69 м (4H, 2CH_2), 2.82-2.86 м (2H, CH_2), 7.30 д (2H$_{arom}$, *J* 7.4), 7.39 т (1H$_{arom}$, *J* 7.6), 7.56-7.64 м (4H, 2H$_{arom}$ +NH_2), 7.80 д (2H$_{arom}$, *J* 7.6), 8.01 д (2H$_{arom}$, *J* 7.6), 9.35 с (1H, H$^5_{pyrazole}$)
IIIf		3444	1.25 т (3H, CH_3, *J* 7.2), 1.70-1.75 м (4H, 2CH_2), 2.51-2.55 м (2H, CH_2), 2.65-2.72 м (4H, 2CH_2), 7.28 д (2H$_{arom}$, *J* 7.6), 7.38 т (1H$_{arom}$, *J* 7.8), 7.51-7.63 м (4H, 2H$_{arom}$ +NH_2), 7.79 д (2H$_{arom}$, *J* 7.8), 8.00 д (2H$_{arom}$, *J* 7.8), 9.34 с (1H, H$^5_{pyrazole}$)
IIIg		3442	1.71-1.75 м (4H, 2CH_2), 2.54-2.58 м (2H, CH_2), 2.70-2.74 м (2H, CH_2), 7.13-7.38 м (3H, $OCHF_2$+2H$_{arom}$), 7.40 т (1H$_{arom}$, *J* 7.6), 7.50-7.66 м (4H, 2H$_{arom}$ +NH_2), 7.94 д (2H$_{arom}$, *J* 8.4), 8.01 д (2H$_{arom}$, *J* 8.4), 9.39 с (1H, H$^5_{pyrazole}$)
IIIh		3440	1.74-1.79 м (4H, 2CH_2), 2.54-2.58 м (2H, CH_2), 2.75-2.79 м (2H, CH_2), 7.18 д (1H $_{thiophene}$, *J* 6.8), 7.41 т (1H$_{arom}$, *J* 7.6), 7.55-7.64 м (3H$_{arom}$), 7.69 с (2H, NH_2), 7.98 д (2H$_{arom}$, *J* 7.8), 8.20 с (1H$_c$), 9.39 с (1H, H$^5_{pyrazole}$)

Table 3

^{13}C NMR spectra of the compounds III a-h

Compound	δ, ppm										
	CH_2	$C^3_{thiophene}$	$C^4_{thiophene}$	$C^5_{thiophene}$	$C^4_{pyrazole}$	$C^5_{pyrazole}$	$C^3_{oxadiazole}$	$C^3_{pyrazole}$	$C^2_{thiophene}$	$C^5_{oxadiazole}$	Ar
III a	25.75, 26.50 30.81, 31.97	96.86	109.03	117.25	129.56	129.86	150.50	160.34	161.23	171.82	55.09 (OCH_3), 114.06, 114.44, 118.82, 121.14, 122.08, 129.04, 131.57, 133.43, 138.21
III b	22.14, 22.68 23.76,25.02	96.87	109.08	117.26	129.83	131.03	149.43	160.42	161.06	171.86	118.74, 127.08, 127.93, 129.50, 130.60, 131.74, 133.33, 138.82
III c	26.81, 27.95, 29.05	93.72	109.15	117.31	128.47	129.88	150.27	159.61	161.17	171.54	117.48, 126.57, 127.84, 129.14, 130.62, 131.87, 133.89, 137.94
III d	22.13, 22.67, 23.75, 25.01	96.87	109.05	117.26	129.50	129.82	149.47	160.40	101.05	171.63	118.76, 121.98, 127.13, 130.84, 130.90, 131.37, 131.70, 138.80
III e	26.95,28.53, 29.50	93.29	108.99	118.70	128.83	129.56	150.74	161.70	162.41	171.28	15.50 (CH_2), 28.01 (CH_2), 121.68, 126.97, 127.31 131.52, 132.07, 138.93, 139.65, 144.23
III f	22.15, 22.69, 23.73, 25.03	96.91	108.91	117.72	129.54	129.73	150.78	160.29	161.27	171.80	15.49 (CH_3), 28.00 (CH_2), 118.71, 126.97, 127.29 128.83, 129.85, 131.37, 138.93, 144.21
III g	22.13, 22.68, 23.75, 25.61	96.88	109.01	117.26	129.58	129.83	151.15	160.37	161.11	171.83	116.24 т (CHF_2, *J* 22.45 Hz), 118.03, 118.83, 127.05, 129.14, 130.57, 131.54, 138.85, 149.72
III h	22.17, 22.70, 23.78, 25.66	96.78	109.27	117.28	129.65	129.87	150.64	160.55	161.04	171.83	118.47, 126.96, 127.13, 128.58, 132.43, 134.04, 138.60, 144.77

IV. Conclusions

1. A preparatively convenient method of 4-pyrazolyl-5-(1,2,4-oxadiazolyl)-3-thienylamines synthesis was developed. It includes consecutive transformation of 4-pyrazolylamidooximes into 3-(4-pyrazolyl)-5-(1,2,4-oxadiazolyl)acetonitriles.
2. Their interaction with sulfur and cycloalkanones in conditions of Gewald reaction was studied.

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