Parallel Liquid-Phase Synthesis of 5-(1*H*-4-Pyrazolyl)-[1,2,4]oxadiazole Libraries

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Combinatorial libraries of substituted 3-(methylthio)-5-(amino)-4-([1,2,4]oxadiazol-5-yl)-1*H*-pyrazoles **6**, **10**, **13**, **15** (395 members, yields 32−87%), 4-([1,2,4]oxadiazol-5-yl)-1*H*-3,5-pyrazolediamines **8**, **11** (571 members, yields 25−83%), 2-(methylthio)-3-([1,2,4]oxadiazol-5-yl)pyrazolo[1,5-*a*]pyrimidin-7(4*H*)-ones **17** (85 members, yields 56−95%), and 2-(amino)-3-([1,2,4]oxadiazol-5-yl)pyrazolo[1,5-*a*]pyrimidin-7(4*H*)-ones **18** (110 members, yields 56−95%) were synthesized by the parallel liquid-phase synthesis method.

Introduction

The extensive use of [1,2,4]oxadiazoles in medicinal chemistry[1−5] has led to the elaboration and to the optimization methods of their synthesis. In particular, the synthesis of the molecules where isoxadiazole ring linked with another heterocyclic molecule attracts significant interest among researchers. Combination of various moieties in a structure has led to the extension of biological activity spectra. Our attention was attracted to the compounds, in which isoxadiazole cycle linked with pyrazole ring.

[1,2,4]Oxadiazole derivatives are known in the literature as bioisosteres for esters and amides,[6−8] and they exhibit a wide range of biological activity as dipeptidomimetics,[8] highly potent muscarinic agonists,[9] benzodiazepine receptor antagonists,[10,11] antirhinovirals,[12] antitussives,[13,14] anthelmintics,[15,16] inhibitors of the tyrosine kinase ZAP-70,[17] nonpeptidic angiotensin-II receptor antagonists;[18] and selective histamine H3-receptor antagonists;[19] they also show a variety of other physiological activities.[20−22] Pyrazoles in their turn, attract much attention as inhibitors of cyclin-dependent and integrin-linked kinases inhibitors with antiproliferative activity,[23] PPARγ partial agonists.[24]

There are several synthetic methods to construct heterocyclic systems contaning [1,2,4]oxadiazole and pyrazole cycles was found. It should be notice, it is possible to obtain 5-(4-pyrazolyl)-[1,2,4]oxadiazoles with different substitutions into pyrazole ring, such as amino-, alkoxy- and alkylsulfanyl groups.[25−27]

Initially, *N*-benzyl-4-[5-(1-phenyl-5-propyl-1*H*-pyrazol-4-yl)-[1,2,4]oxadiazol-3-yl]benzamide synthezed by the multistep reaction, between 4-cyano-benzoyl chloride, 1-phenyl-5-propyl-1*H*-pyrazole-4-carbonyl chloride and benzylamine.[25] Series of 2-{5-amino-4-[3-[1,2,4]oxadiazol-5-yl]-1*H*-pyrazol-3-yloxy}ethanoles were obtained by the reaction of [1,3]dioxolan-2-ylidene-[3-[1,2,4]oxadiazol-5-yl]-acetonitriles with hydrazines.[26] 2-(2,6-Dichloro-4-trifluoromethyl-phenyl)-4-(3-methyl-[1,2,4]oxadiazol-5-yl)-5-methylsulfanyl-2*H*-pyrazol-3-ylamine was obtained by the reaction of 2-(2,6-dichloro-4-trifluoromethylphenyl)-4-iodo-5-methylsulfanyl-2*H*-pyrazol-3-ylamine with 3-methyl-[1,2,4]oxadiazol-5-yl stannane in a present of palladium catalyst.[27] However the described above reaction can not be carried out in high-throughput format which was used for fast generation of combinatorial libraries.

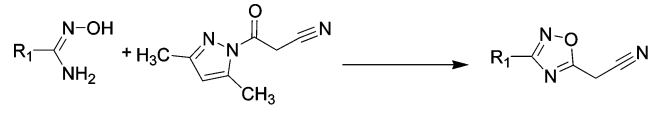
Results and Discussion

From our point of view, methylenactive nitriles 5-cyanomethyl-3-aryl-[1,2,4]oxadiazoles **3**{*1*−*9*} are prospective synthons for the construction of combinatorial libraries of the above-described heterocyclic system that contains [1,2,4]oxadiazole ring. So, we decided to use compounds **3**{*1*−*9*} as the starting materials for further synthetic manipulations. Their synthesis were carry out by the reaction between arylamidoximes **1**{*1*−*9*}[28] and 1-(cyanoacetyl)-3,5-dimethyl-1*H*-pirazole **2** in dioxane[29] (Scheme 1).

The 3-R_1-5-cyanomethyl-3-aryl-[1,2,4]oxadiazoles **3**{*1*−*9*} were characterized by HPLC spectroscopy as individual compounds. In the ^{1}H NMR spectra of **3**, the signal of the methylene group is observed at 4.72−4.76 ppm. All other proton signals are observed in their usual resonance areas.

3-R_1-5-[1-cyano-2,2-bis(methylthio)vinyl]-[1,2,4]oxadiazoles **4** were obtained by the reaction of **3** with CS_2 and CH_3I. Corresponding 3-R_1-5-[1-cyano-2-(R_{2a}(R_{2b})amino)-2-

Scheme 1. Synthesis of 5-Cyanomethyl-3-aryl-[1,2,4]oxadiazoles **3**{*1*−*9*}



1*{1-9}* **2** **3***{1-9}* Yields: 66-89%

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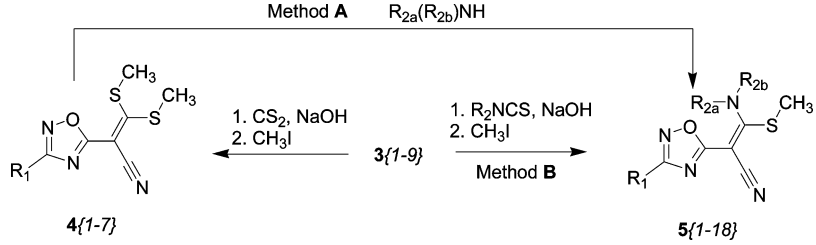
Scheme 2. Synthesis of *S*,*S*- and *S*,*N*-Acetales **4**{*1*−*7*} and **5**{*1*−*18*}



Scheme 3. Synthesis of the Corresponding Aminopyrazoles **6**{*1*−*7*} and **8**{*1*−*18*}

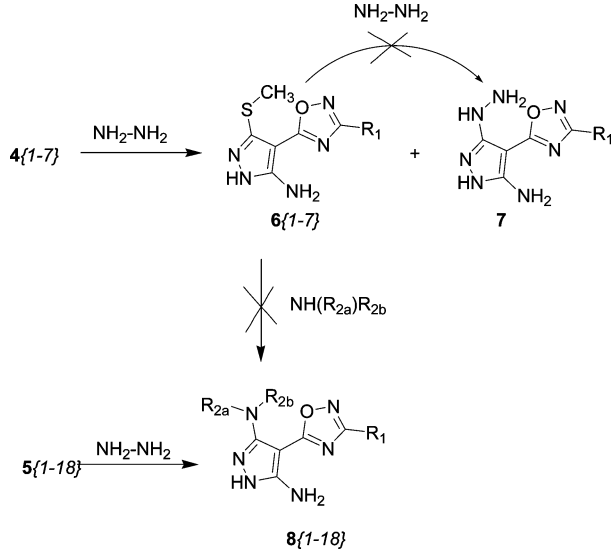


Table 1. Diversity of Nitriles **3**{*1*−*9*}

entry	R_1	yield, %
3{*1*}	C_6H_5	56
3{*2*}	3-CH_3-C_6H_4	64
3{*3*}	4-CH_3-C_6H_4	71
3{*4*}	4-CH_3O-C_6H_4	75
3{*5*}	3,4-di-(CH_3O)-C_6H_3	72
3{*6*}	3,4-CH_2O_2-C_6H_3	86
3{*7*}	4-Cl-C_6H_4	81
3{*8*}	3-Cl-C_6H_4	89
3{*9*}	2-CH_3-C_6H_4	60

Table 2. Diversity of *S*,*S*-Acetales **4**{*1*−*7*}

entry	R_1	yield, %
4{*1*}	C_6H_5	90
4{*2*}	3-CH_3-C_6H_4	87
4{*3*}	4-CH_3-C_6H_4	92
4{*4*}	4-CH_3O-C_6H_4	97
4{*5*}	3,4-di-(CH_3O)-C_6H_3	97
4{*6*}	3,4-CH_2O_2-C_6H_3	91
4{*7*}	4-Cl-C_6H_4	93

(methylthio)vinyl]-[1,2,4]oxadiazoles **5** were obtained by two synthetic ways: reaction of compounds **4** with amines (method **A**)[30] or reaction of **3** with isothiocyanates in a present of NaOH with further addition of CH_3I (method **B**)[31] (Scheme 2).

Method **A** has several advantages over method **B**: it make possible obtain corresponding **5** with wide diversity of amine moiety, included secondary amines, and exclude toxic isothiocyanates. But method **B** allows obtaining of *S*,*N*-acetales **5** directly from starting methylenactive nitriles **3**.

Table 3. Diversity of *S*,*N*-Acetales **5**{*1*−*18*}

entry	R_1	R_2	Yield, %
5{*1*}	C_6H_5	Me	89^A, 91^B
5{*2*}	C_6H_5	Et	89^A, 88^B
5{*3*}	C_6H_5	C_6H_5	71^A
5{*4*}	C_6H_5	morfolin	75^A
5{*5*}	4-CH_3-C_6H_4	Me	72^B
5{*6*}	4-CH_3-C_6H_4	Et	86^B
5{*7*}	4-CH_3-C_6H_4	i-Pr	81^B
5{*8*}	3-CH_3-C_6H_4	Me	81^B
5{*9*}	2-CH_3-C_6H_4	Me	76^B
5{*10*}	2-CH_3-C_6H_4	Et	73^B
5{*11*}	4-CH_3O-C_6H_4	Me	97^B
5{*12*}	4-CH_3O-C_6H_4	Et	89^B
5{*13*}	4-Cl-C_6H_4	Me	98^B
5{*14*}	4-Cl-C_6H_4	Et	96^B
5{*15*}	4-Cl-C_6H_4	Allyl	98^B
5{*16*}	4-Cl-C_6H_4	*i*-Pr	82^B
5{*17*}	3-Cl-C_6H_4	Me	94^B
5{*18*}	3-Cl-C_6H_4	Et	90^B

Table 4. Obtained Aminopyrazoles **6**{*1*−*7*}

entry	R_1	yield, %
6{*1*}	C_6H_5	90
6{*2*}	3-CH_3-C_6H_4	87
6{*3*}	4-CH_3-C_6H_4	92
6{*4*}	4-CH_3O-C_6H_4	97
6{*5*}	3,4-di-(CH_3O)-C_6H_3	97
6{*6*}	3,4-CH_2O_2-C_6H_3	91
6{*7*}	4-Cl-C_6H_4	93

Table 5. Obtained Diaminopyrazoles **8**{*1*−*18*}

entry	R_1	R_2	yield, %
8{*1*}	C_6H_5	Me	89
8{*2*}	C_6H_5	Et	89
8{*3*}	C_6H_5	C_6H_5	71
8{*4*}	C_6H_5	morfolin	75
8{*5*}	4-CH_3-C_6H_4	Me	72
8{*6*}	4-CH_3-C_6H_4	Et	86
8{*7*}	4-CH_3-C_6H_4	*i*-Pr	81
8{*8*}	3-CH_3-C_6H_4	Me	81
8{*9*}	2-CH_3-C_6H_4	Me	76
8{*10*}	2-CH_3-C_6H_4	Et	73
8{*11*}	4-CH_3O-C_6H_4	Me	97
8{*12*}	4-CH_3O-C_6H_4	Et	89
8{*13*}	4-Cl-C_6H_4	Me	98
8{*14*}	4-Cl-C_6H_4	Et	96
8{*15*}	4-Cl-C_6H_4	allyl	98
8{*16*}	4-Cl-C_6H_4	*i*-Pr	82
8{*17*}	3-Cl-C_6H_4	Me	94
8{*18*}	3-Cl-C_6H_4	Et	90

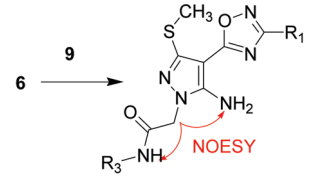
Parent ([1,2,4]oxadiazol-5-yl)-1*H*-pyrazoles **6** and **8** were obtained by the reaction of described above *S*,*S* and *S*,*N*-acetales **4** and **5** with hydrazine hydrate in the refluxing isopropyl alcohol (Scheme 3, Table 4, 5).

In ^1H NMR spectra of compounds **6** singlet NH group of the pyrazol ring is observed at 11.95−12.15 ppm, NH_2 group at 6.50−6.55 ppm, but in case of compounds **8** signal of

Table 6. Diversity of Chloroacetamides **9**{*1*−*60*}

entry	R_3	entry	R_3	entry	R_3
9{*1*}	C_6H_5	**9**{*21*}	3,4-di-CH_3-C_6H_3	**9**{*41*}	3-C_2H_5-C_6H_4
9{*2*}	4-[$(CH_3)_2CH$]-C_6H_4	**9**{*22*}	2,4-di-CH_3O-C_6H_3	**9**{*42*}	3-Cl-6-CH_3O-C_6H_3
9{*3*}	3-Cl-4-CH_3O-C_6H_3	**9**{*23*}	3,6-di-CH_3O-C_6H_3	**9**{*43*}	3-Cl-4,6-di-CH_3O-C_6H_2
9{*4*}	3-Cl-C_6H_4	**9**{*24*}	3,4-di-CH_3O-C_6H_3	**9**{*44*}	3-Cl-4-F-C_6H_3
9{*5*}	2-Cl-C_6H_4	**9**{*25*}	3,4-di-F-C_6H_3	**9**{*45*}	3-CH_3-C_6H_4
9{*6*}	4-Cl-C_6H_4	**9**{*26*}	4-CH_3O-C_6H_4	**9**{*46*}	2-C_2H_5O-C_6H_4
9{*7*}	3-Cl-6-CH_3-C_6H_3	**9**{*27*}	3-F-4-CH_3-C_6H_3	**9**{*47*}	2,4,6-tri-CH_3-C_6H_2
9{*8*}	2,4-di-CH_3-C_6H_3	**9**{*28*}	4-CH_3-C_6H_4	**9**{*48*}	4-Cl-2-F-C_6H_3
9{*9*}	2,4-di-F-C_6H_3	**9**{*29*}	3-CH_3S-C_6H_4	**9**{*49*}	4-Br-C_6H_4
9{*10*}	2−F-C_6H_4	**9**{*30*}	3-CH_3O-C_6H_4	**9**{*50*}	3-Cl-2-CH_3-C_6H_3
9{*11*}	3,5-diCH_3-C_6H_3	**9**{*31*}	4-C_2H_5-C_6H_4	**9**{*51*}	3-CH_3CO-C_6H_3
9{*12*}	3,5-diCH_3O-C_6H_3	**9**{*32*}	3-Cl-4-F-C_6H_3	**9**{*52*}	4-CH_3CO-C_6H_3
9{*13*}	3-F-C_6H_4	**9**{*33*}	2-CF_3-C_6H_4	**9**{*53*}	C_6H_5-CH_2
9{*14*}	4-C_2H_5O-C_6H_4	**9**{*34*}	2,6-di-CH_3−C_6H_3	**9**{*54*}	3-CH_3O-C_6H_4-CH_2
9{*15*}	2-C_2H_5-C_6H_4	**9**{*35*}	3-F-6-CH_3-C_6H_3	**9**{*55*}	4-F-C_6H_4-CH_2
9{*16*}	3,4-(CH_2O_2)-C_6H_3	**9**{*36*}	4-F-C_6H_4	**9**{*56*}	4-Cl-C_6H_4-CH_2
9{*17*}	3,4-($C_2H_4O_2$)-C_6H_3	**9**{*37*}	3-Cl-4-CH_3-C_6H_3	**9**{*57*}	C_6H_5-$CH_2CH_2CH_2$
9{*18*}	2-CH_3O-5-CH_3-C_6H_3	**9**{*38*}	3-CF_3-C_6H_4	**9**{*58*}	C_6H_5-$CH_2CH_2CH(CH_3)$
9{*19*}	2,5-di-F-C_6H_3	**9**{*39*}	2-CH_3O-C_6H_4	**9**{*59*}	$(CH_3)_2CH$
9{*20*}	2-CH_3-C_6H_4	**9**{*40*}	2-Cl-4-CH_3-C_6H_3	**9**{*60*}	$(CH_3)_3C$

Scheme 4. Selective Alkylation of **6** and **8**



NH_2 superimposed with NH-R_2 and observed at 5.80−6.0 ppm, NH signal of the pyrazole ring observed at 10.95−11.0 ppm. All other proton signals are observed in their usual resonance areas.

It should be noted that excess of hydrazine hydrate led to impurities of 3-hydrazino-4-(3-R_1-[1,2,4]oxadiazol-5-yl)-1*H*-pyrazol-5-amine **7** in crude 3-(methylthio)-4-(3-R_1-[1,2,4]oxadiazol-5-yl)-1*H*-pyrazol-5-amines**6**. But when we reflux isolated pure ([1,2,4]oxadiazol-5-yl)-1*H*-pyrazoles **6** with hydrazine hydrate or amine derivative reaction of substitution of the methylthio-group not occur. So, this side reaction occur possible only when two molecules of the hydrazine hydrate react with 3-R_1-5-[1-cyano-2,2-bis(methylthio)vinyl]-[1,2,4]oxadiazoles **4** before the pyrazole cycle formation. Described above impurities **7** can be easy separated by crystallization from hot isopropyl alcohol. The mother liquor consists of pure desired product **6**.

First combinatorial stage was based on selective alkylation of ([1,2,4]oxadiazol-5-yl)-1*H*-pyrazoles **6** and **8** by 2-chloracetamides **9** with K_2CO_3 in DMF. In our case we obtained only one isomer - alkylation by N1 atom near NH_2 group in both cases **6** and **8** (scheme 4). Thereby a combinatorial library of 5-[5-amino-1-{2-[R_3-amino]-2-oxoethyl}-3-(me-

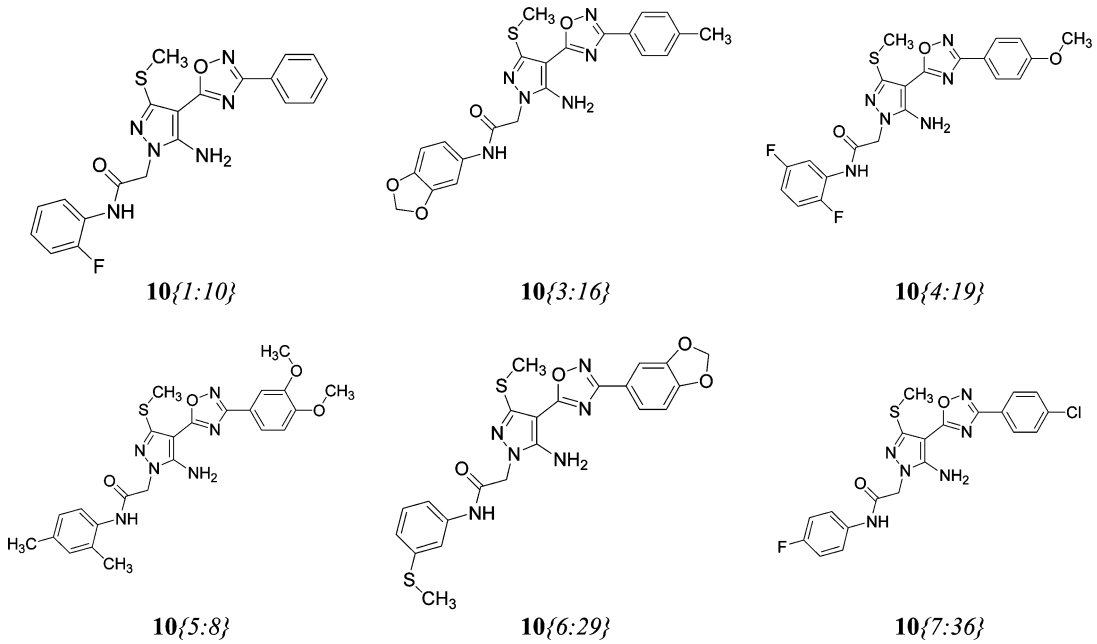


Figure 1. Examples of synthesized **10**.

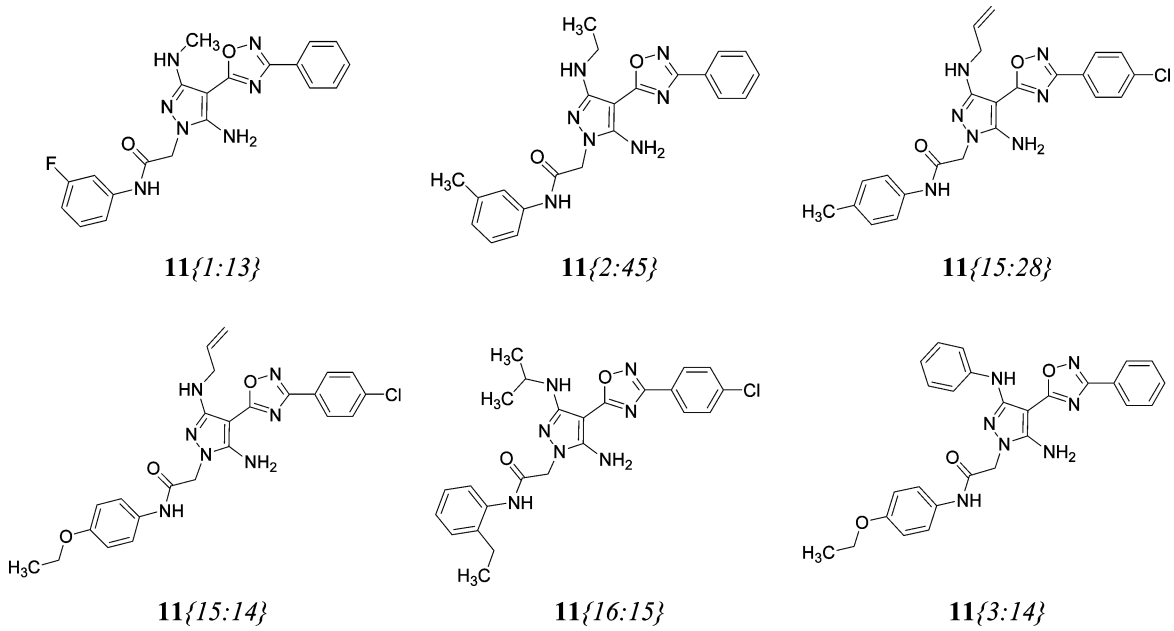


Figure 2. Examples of synthesized **11**.

Scheme 5. Scheme of Acetylating 5-[5-Amino-1-{2-[R_3-amino]-2-oxoethyl}-3-(methylthio)-1*H*-pyrazol-4-yl]-3-R_1-[1,2,4]oxadiazoles **10**

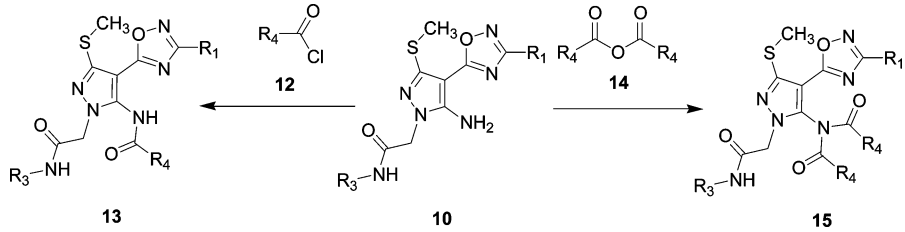


Table 7. Diversity of Acetyl Chlorides **12**{*1*−*3*} and **14**{*1*,*2*}

entry	R_4
12{*1*}	CH_3
12{*2*}	CH_2CH_3
12{*3*}	CH_2Cl
14{*1*}	CH_3
14{*2*}	CH_2CH_3

thylthio)-1*H*-pyrazol-4-yl]-3-R_1-[1,2,4]oxadiazoles **10** and 5-(5-amino-3-[R_{2a}(R_{2b})amino]-1-{2-[R_3-amino]-2-oxoethyl}-1*H*-pyrazol-4-yl)-3-R_1-[1,2,4]oxadiazoles **11** were prepared (Scheme 4, Figure 1, and Figure 2).

This fact was proved by NOESY spectra of **10**{*3:26*} by observing cross-coupling between CH_2-protons of the acetamide fragment at 4.88 ppm and amino group at 6.83 ppm, for **11**{*13*:*56*} between CH_2-protons at 4.55 ppm and unsubstituted amino group at 6.58 ppm (Scheme 4). Interaction between CH_2-protons of the acetamide fragment and substitutes at third position of the pyrazole ring was absent in both cases.

Obtained compounds **10** can be easy acetylated by acetyl chlorides **12** with formation of corresponding monoacetylderivatives **13**, but in case of acetic anhydride **14** the formation of diacetylderivatives **15** were observed (Scheme 5, Table 7, Figure 3, 4).

In a case of monoacetyl derivatives **13**, in the ^{1}H NMR spectra NH-proton is observed near 10.20 ppm. In a case of diacetyl derivatives **15**, in the ^{1}H NMR spectra NH-proton is absent and signal of acetyls protons was observed at 2.40−2.50 ppm with double integral intensity.

Next combinatorial diversification of the ([1,2,4]oxadiazol-5-yl)-1*H*-pyrazoles **6**, **8** was carried out by their reaction with substituted acetyl acetates **16** in acetic acid media (Scheme 6).

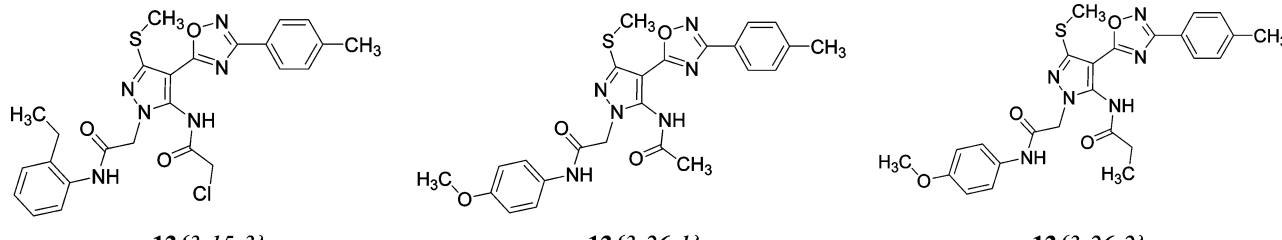
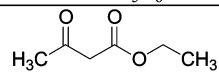
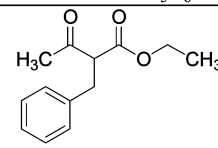
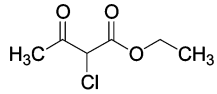
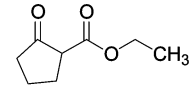
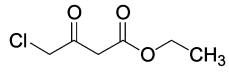
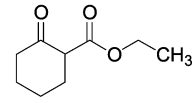
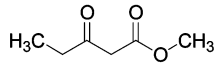
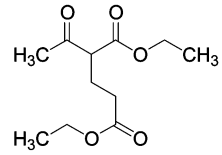
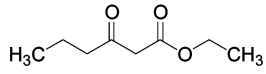
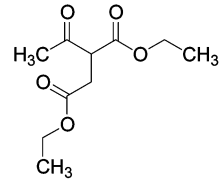
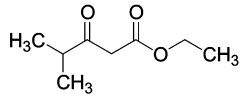
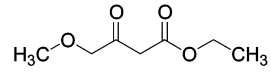
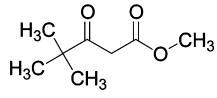
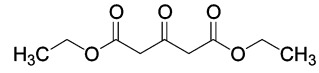
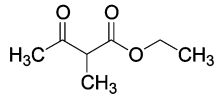
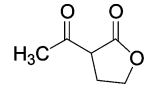
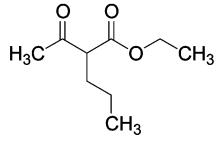
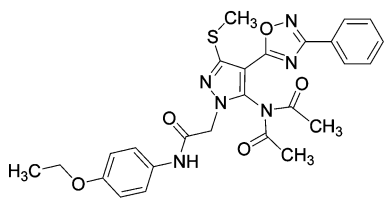


Figure 3. Examples of monoacetyl derivative **13**.

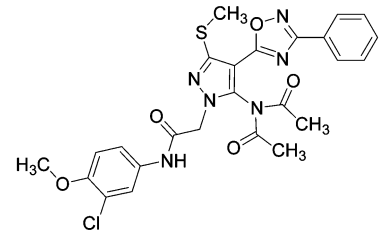
Table 8. Diversity of Acetates **16**

Entry	R_5R_6	Entry	R_5R_6
16*{1}*		**16***{10}*	
16*{2}*		**16***{11}*	
16*{3}*		**16***{12}*	
16*{4}*		**16***{13}*	
16*{5}*		**16***{14}*	
16*{6}*		**16***{15}*	
16*{7}*		**16***{16}*	
16*{8}*		**16***{17}*	
16*{9}*			

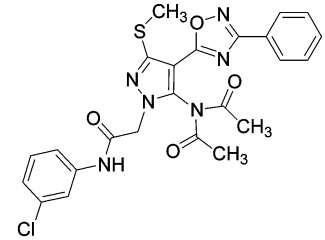
Reaction lead to 5-R_5-6-R_6-2-(methylthio)-3-(3-R_1-[1,2,4]oxadiazol-5-yl)pyrazolo[1,5-*a*]pyrimidin-7(4*H*)-ones **17** and 5-R_5-6-R_6-2-[R_{2a}(R_{2b})amino]-3-(3-R_1-[1,2,4]oxadiazol-5-yl)pyrazolo[1,5-*a*]pyrimidin-7(4*H*)-ones **18** correspondingly, with high yield and short time. Reaction of the ([1,2,4]oxadiazol-5-yl)-1*H*-pyrazoles **6** or **8** with **16**{*17*} occurs through opening tetrahydrofuranone ring, and *O*-acetyl derivative **17**{*1*,*3*,*6*:*17*} and **18**{*1*,*13*:*17*} were isolated. Thus, in case of **16***{17}* the structure of the final products depend on reaction media.



15*{1:14:1}*

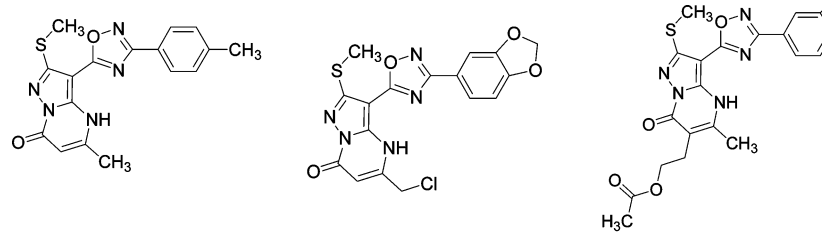


15*{1:37:1}*



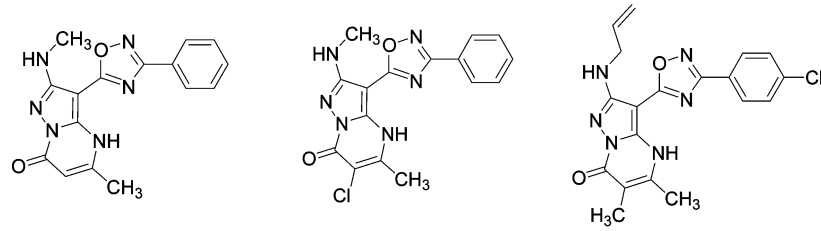
15*{1:4:1}*

Figure 4. Examples of diacetyl derivative **15**.



17*{3:1}* **17***{6:3}* **17***{6:17}*

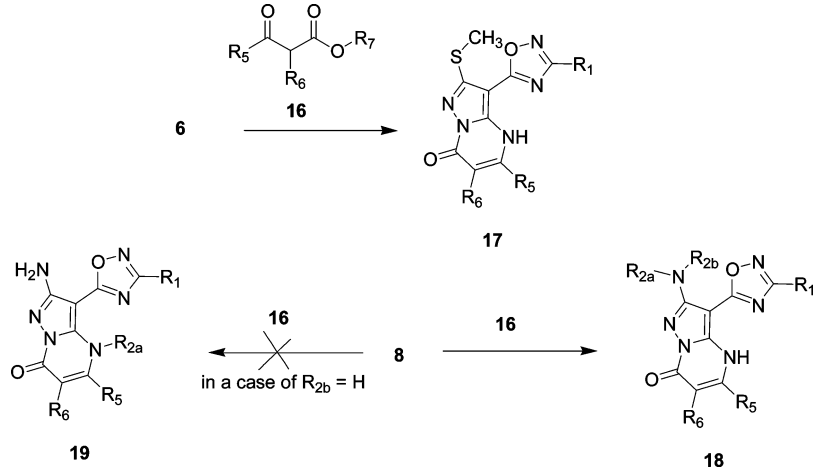
Figure 5. Examples of synthesized 5-R_5-6-R_6-2-(methylthio)-3-(3-R_1-[1,2,4]oxadiazol-5-yl)pyrazolo[1,5-*a*]pyrimidin-7(4*H*)-ones **17**.



18*{1:1}* **18***{1:2}* **18***{15:8}*

Figure 6. Examples of synthesized 5-R_5-6-R_6-2-[R_{2a}(R_{2b})amino]-3-(3-R_1-[1,2,4]oxadiazol-5-yl)pyrazolo[1,5-*a*]pyrimidin-7(4*H*)-ones **18**.

Scheme 6. Reaction of **6** and **8** with Substituted Acetyl Acetates **16**



The formation of isomeric pyrazolo[1,5-*a*]pyrimidin-7(4*H*)-ones **19** was not observed in NMR spectra. After the reaction of **8** with corresponding **16** in ^{1}H NMR spectra observed NH signal of pyrimidine moiety at 11.9−12.4 ppm and duplet of NH-signal at 6.30−6.45 ppm coupled on alkyl moiety, which proved formation of isomer **18.**

Conclusion

An efficient synthetic route for solution-phase parallel synthesis of diverse 5-[1*H*-pyrazol-4-yl]-1,2,4-oxadiazole and 1,2,4-oxadiazolyl-5-pyrazolo[1,5-a]pyrimidin-7(4*H*)-one libraries was developed. All the proposed reactions allowed us to obtain products with low levels of impurities, using a simple isolation procedure.

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Supporting Information Available. Experimental procedures, ^{1}H NMR, ^{13}C NMR, and NOESY data for obtained compounds. This materials are available free of charge via the Internet at http://pubs.acs.org.

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