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Graphical Abstract:

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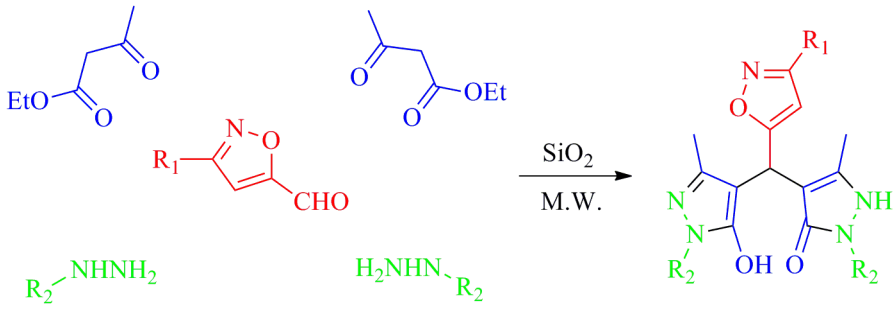

"Solvent-free, no catalyst"

An efficient synthesis of 4-substituted pyrazolone derivatives was developed *via* condensation starting from ethylacetoacetate, hydrazine and isoxazole-aldehyde over solid support SiO_2 under microwave-assisted solvent-free conditions in satisfactory yields.

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Abstract

An efficient synthesis of 4-substituted pyrazolone derivatives was developed. 4-Substituted pyrazolone derivatives were synthesized in 78–97% yields starting from various 3-substituted isoxazole-5-carbaldehydes, ethyl acetoacetate and hydrazine under microwave irradiation and solvent-free conditions, and were characterized by HRMS, FT-IR, ^{1}H NMR and ^{13}C NMR spectroscopy. SiO_2 was found to possess favorable catalytic activity and dispersancy for the condensation reaction. The merits of this method include the environmentally friendly reaction conditions, simple operation, broad substrate, satisfied yields and the reuse of the silica. Moreover, the crystal structure of the compound 2-(4-chlorophenyl)-4-((1-(4-chlorophenyl)-5-hydroxy-3-methyl-1*H*-pyrazol-4-yl)(3-phenylisoxazol-5-yl)methyl)-5-methyl-1*H*-pyrazol-3(2*H*)-one (**5a**) in the monoclinic space group *C2/c* was presented.

Keywords 3-methyl-1*H*-pyrazol-5-ol, 5-methyl-1*H*-pyrazol-3(2*H*)-one, isoxazole, microwave irradiation, solid support SiO_2, solvent-free.

1. Introduction

In recent years, focusing on green chemistry by using eco-friendly benign media and reaction conditions is one of the most fascinating developments in synthesis of organic compounds. Microwave irradiation as an unconventional energy source has been increasingly used in organic

synthesis. Microwave-assisted organic synthesis could obtain rapid, reproducible, and scalable processes to prepare new compounds in high yields compared with the traditional heating methods.[1] It is reported that the organic compound was easily polarized to generate electronic polarization, atom polarization, orientation polarization and interfacial polarization in the microwave irradiation. Also, electronic and atom polarization rates are much faster than the frequency of the microwave, and the other polarization rates are close to the frequency of the microwave. Thus, microwave irradiation resulting in the motion state of organic molecules was transformed from original thermal motion to alternating arrangement corresponding to the frequency of the microwave, oscillation intensifying, further generating thermal efficiency. As a result, microwave irradiation as dielectric heating is a process in which the organic compounds consume electromagnetic energy, which can accelerate the reaction rate for several times, 10 times or even tens of thousands of times compared with the conventional heating.[2]

Pyrazoles and isoxazoles are important classes of heterocyclic compounds and attractive targets both in medicinal chemistry and organic synthesis in recent years.[3–8] Pyrazoles, especially 1*H*-pyrazol-5(4*H*)-one derivatives including 4,4'-(arylmethylene)bis(1*H*-pyrazol-5-ols)s are not only a very useful synthetic intermediate, but also an important pharmacophore found in a large number of biologically active and potential therapeutic compounds.[9–11] These compounds have been widely used in significant antipyretic,[12] antidepressant,[13] antibacterial,[14] antiviral,[15] antitumor,[16] antiinflammatory.[17] Moreover, a number of these compounds have been considered as the chelating and extracting reagents for different metal ions.[18,19] Some of the pyrazolone derivatives are now included in many commercialized drugs for brain ischemia and myocardial ischemia.[20,21]

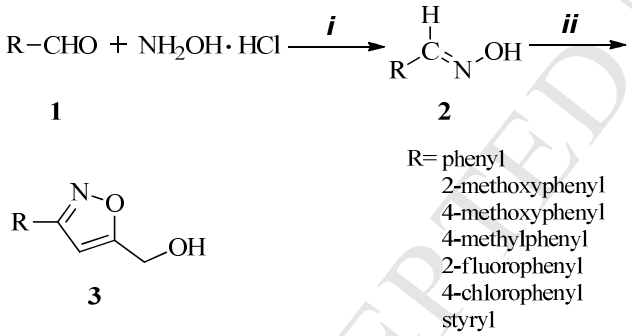
One-pot tandem Knoevenagel–Michael reaction is one of the most broadly used methods for preparing 4,4'-(arylmethylene)bis(1*H*-pyrazol-5-ol)s *via* three-component condensation of aldehydes with 2 equiv of 3-methyl-1-phenyl-5-pyrazolone. In the last few years, some catalysts have been applied to access these compounds, such as acetic acid or piperidine,[22] cesium fluoride (CsF),[23] 3-aminopropylated silica gel,[24] heteropolyacids,[25,26] sodium dodecyl sulfate (SDS),[27] ceric ammonium nitrate (CAN),[15] Na^+-MMT-[pmim]HSO_4,[28] 1,3,5-tris(hydrogensulfato) benzene (THSB),[29] benzyltriethylammonium chloride,[30] $ZnAl_2O_4$ nanoparticles,[31] silica-bonded S-sulfonic acid (SBSSA),[32] $LiOH\cdot H_2O$,[33] [Cu(3,4-tmtppa)]$(MeSO_4)_4$,[34] and so on. However, the synthesis of

4-substituted-((5-hydroxy-3-methyl-1*H*-pyrazol-4-yl)(3-aryl-isoxazol-5-yl)methyl)-5-methyl-1*H*-pyrazol-3(2*H*)-ones (4-substituted pyrazolone derivatives) was rarely reported using one-pot tandem Knoevenagel–Michael reaction, although few literature has reported about 4-substituted pyrazolone derivatives synthesized *via* the condensation reaction of aromatic aldehydes with 3-methyl-1-phenyl-5-pyrazolone.[35,36] It is known that many of the methods reported above suffer from one or more limitations such as long reaction time, strongly acidic or basic conditions, high solvent consumption, difficulty in handling and separation of catalyst, use of expensive catalysts and also occurrence of side reactions that restrict their usage in practical applications. Consequently, it is very significant to study and develop new, environmentally friendly scalable synthetic routes able to construct fused 4-substituted pyrazolone derivatives in high yields.

Recently, the applications of the solid support Al_2O_3 and silica gel (SiO_2) have drawn much attention as they are the inexpensive, non-toxic dispersant and catalyst for many organic transformations providing high yields. It is reported that Al_2O_3 and SiO_2 in a solvent-free process has greatly simplified the workup procedures.[37,38] Also, it is found that 4,4'-(arylmethylene)bis(1*H*-pyrazol-5-ol)s with benzene ring and/or furan ring, could be synthesized using different catalyst 2-HEAP,[39] or [Dsim]$AlCl_4$[40] under solvent-free and conventional heating condition. Nevertheless, solvent-free microwave-assisted method was not yet introduced into the synthesis of 4-substituted pyrazolone derivatives. Considering the above points, and in continuation of our interest in multi-component organic reactions, a convenient and eco-friendly strategy for the synthesis of 4-substituted pyrazolone derivatives was designed starting from 3-substituted isoxazole-5-carbaldehydes, ethylacetoacetate and hydrazine in microwave irradiation using SiO_2 as solid support under solvent-free condition. The structures of the synthesized compounds were characterized by HRMS, FT-IR, ^{1}H NMR and ^{13}C NMR spectroscopy. Moreover, the crystal structure of 2-(4-chlorophenyl)-4-((1-(4-chlorophenyl)-5-hydroxy-3-methyl-1*H*-pyrazol-4-yl)(3-phenylisoxazol-5-yl)methyl)-5-methyl-1*H*-pyrazol-3(2*H*)-one (**5a**) was described. It suggested that the used slovent and heating method in the process of reaction played an important role in the single crystal formation.

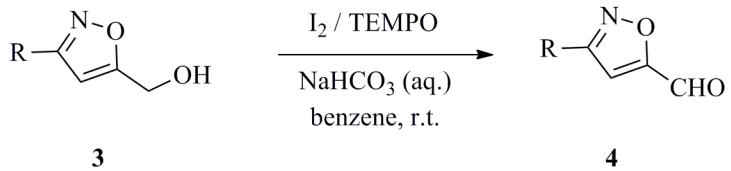
2. Results and discussion

It is known that isoxazole is a versatile scaffold for the synthesis of varieties of complex natural products, and functionalized isoxazole derivatives are active pharmacophores in many pharmacologically important molecules,[41–43] e.g. pyrazole derivatives with 3-substituted phenyl isoxazole-ring which may extend the application of pyrazole derivatives. In the present work, 3-substituted isoxazole-5-carbaldehydes were synthesized in three steps starting form substituted benzaldehyde according to the literature (Scheme 1).[37] Aldoximes (**2**), a kind of important intermediates for the whole synthetic process, were readily synthesized from aromatic aldehyde (**1**) and hydroxylamine and prepared in over 95% yield in accordance with the literature.[35] (3-Substituted phenylisoxazol-5-yl)methanols (**3**) were synthesized by one-pot method according to the reported procedures *via* 1,3-dipolar cycloaddition reaction where the aldoximes were subjected to successive reactions in just one reactor using $ZnCl_2$ as a catalyst in the literature (Scheme 1).[44] A series of 3-substituted isoxazole-5-carbaldehydes were prepared by employing intermediates **3** under I_2, TEMPO and $NaHCO_3$ (aq.) in 58%–93% yields (Table 1).



Scheme 1. Synthetic pathway of 3-substituted isoxazole-5-carbaldehydes: i) 6 M NaOH (aq.), EtOH, reflux; ii) a) NCS, DMF. b) propargyl alcohol, $ZnCl_2$, Et_3N.

Table 1. Synthesis and yields of 3-substituted isoxazole-5-carbaldehydes



Entry	Alcohol	R	Product	Time/h	Yield/% [a]	M.p./°C
1	3a	phenyl	4a	9	81	62–63

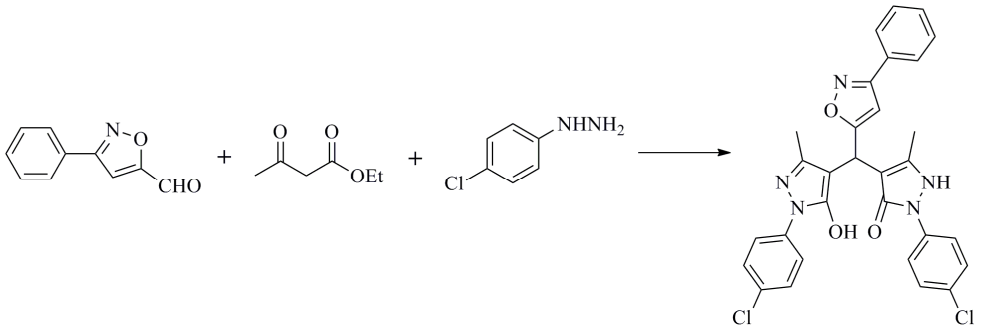
2	3b	2-methoxyphenyl	4b	14	58	74–76
3	3c	4-methoxyphenyl	4c	14	66	72–74
4	3d	4-methylphenyl	4d	10	81	70–72
5	3e	2-fluorophenyl	4e	9	88	71–73
6	3f	4-chlorophenyl	4f	9	82	126–128
7	3g	styryl	4g	8	92	102–103
8	3h	3-nitrophenyl	4h	8	93	222–224

[a] Isolated yields.

At the beginning of our investigation, referring to the previous literature,[39,40] the synthesis of 4,4'-(arylmethylene)bis(*1H*-pyrazol-5-ol) with 3-substituted phenyl isoxazole-ring was explored by employing 3-phenylisoxazole-5-carbaldehyde, ethyl acetoacetate and hydrazine using solid support SiO_2 under solvent-free condition. Michael addition and self-cycloaddition reaction among 3-phenylisoxazole-5-carbaldehyde (1 mmol), 4-chlorophenylhydrazine (2 mmol), ethyl acetoacetate (2 mmol) were readily carried out. The brown red product was obtained and characterized by HRMS, FT-IR, ^{1}H NMR and ^{13}C NMR spectroscopy. The characterized result showed: The band around 1732 cm^{-1} and 1701 cm^{-1} attributed to stretching vibration of C=O presented in IR spectrum. Also, the chemical shift δ=173.33 ascribed to the resonances of C=O was found using DMSO as solvent in ^{13}C NMR. It suggested that C=O group was found on the synthesized product molecule. Accordingly, the structure of the product was confirmed to 2-(4-chlorophenyl)-4-((1-(4-chlorophenyl)-5-hydroxy-3-methyl-1*H*-pyrazol-4-yl)(3-phenylisoxazol-5-yl)methyl)-5-methyl-1*H*-pyrazol-3(2*H*)-one. The possible reason about the reaction not obtaining 4,4'-(arylmethylene)bis(*1H*-pyrazol-5-ol) was related to the heating method and the solvent used in the course of reaction.

To find an appropriate reaction medium for the solid synthesis of **5a**, under otherwise similar experimental conditions, the effects of different heating conditions, solid support, and different reaction temperatures on the yield of the desired product in the presence/absence of solvent are summarized in Table 2.

Table 2. Synthesis of **5a** under different reaction conditions [a]



4a 5a

Entry	Media	Time	Temp./ °C	Yield [b]/ %
1	C_2H_5OH	4 h	Reflux	Trace
2	CH_3CN	5 h	Reflux	N. D.
3	C_7H_8	6 h	Reflux	N. D.
4	THF	4 h	Reflux	Trace
5	Solvent-free (M.W.)	10 min	70	42
6	SiO_2 (M.W.)	10 min	40	46
7	SiO_2 (M.W.)	10 min	60	77
8	SiO_2 (M.W.)	10 min	70	84
9	SiO_2 (M.W.)	10 min	80	83
10	SiO_2 (M.W.)	5 min	70	67
11	SiO_2 (M.W.)	8 min	70	81
12	SiO_2 (M.W.)	12 min	70	84
13	Al_2O_3 (M.W.)	10 min	70	74
14	Al_2O_3 (M.W.)	10 min	80	74
15	Al_2O_3 (M.W.)	12 min	70	75
16	SiO_2 (M.W.) (100–200 mesh)	10 min	70	76
17	SiO_2 (M.W.) (300–400 mesh)	10 min	70	85

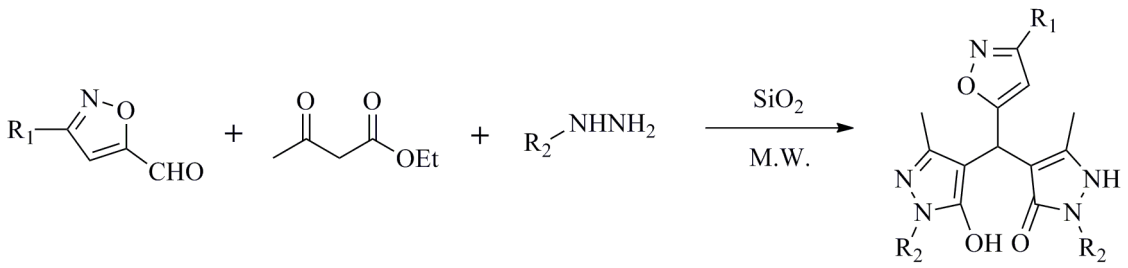
[a] The reaction was conducted with aromatic aldehyde (1 mmol), ethyl acetoacetate (2 mmol) and 4-chlorophenyl hydrazine hydrochloride (2 mmol). N.D. (not detected), [b] Isolated product yields.

As shown in Table 2, the desired **5a** was successfully synthesized with 42–84% yields in the different reaction condition. To our delighted, microwave irradiation as a green and convenient process, could accelerate the reaction and obtain the desired product in better yields (Table 2,

entries 5–15) compared with traditional method (Table 2, entries 1–4). The yield used Al_2O_3 or SiO_2 as solid support under microwave irradiation (entries 6–12) is higher than that of the product obtained both under conventional heating (Table 2, entries 1–4) and under microwave heating in the absence of solid support (Table 2, entry 5), respectively. Also, the yield of loading equal SiO_2 was higher than that of loading Al_2O_3. The reason might be SiO_2 possessing bigger specific surface area compared with the same loading Al_2O_3. To investigate the effect of specific surface area on the yield, the different particle sizes of SiO_2 were introduced into the reaction (Table 2, entry 16 and 17). The yield was gradually increased from 76% (100–200 mesh) to 84% (200–300 mesh, Table 2, entry 8), then basically remained unchanged (85%, 300–400 mesh) with the increase of the particle size of SiO_2, which proved that the particle sizes of SiO_2 assuredly affected the catalysis and dispersancy of SiO_2. Additionally, under conventional heating, the yields of the obtained product were trace or no reaction (Table 2, entries 1–3). Hence, solid support SiO_2 and microwave irradiation were chosen to synthesize the other 4-substituted pyrazolone derivatives.

Furthermore, the effect of microwave irradiation time and reaction temperature on the yields of product **5a** was investigated on solid support SiO_2 under solvent-free microwave radiation condition. It was observed that the yields of **5a** were gradually increased to 84% (70^{o}C), followed decrease (46%) with increasing reaction temperatures from 40^{o}C to 80^{o}C (Table 2, entries 6–9). As for the effect of microwave irradiation time on yields obtained similar law in which the highest yield obtained was microwave irradiation for 10 min (Table 2, entries 8, 10–12). Therefore, optimization for microwave reaction temperature and time revealed that the best yield could be obtained with solvent-free solid support SiO_2 at 70 ^{o}C for 10 min. (Table 2, entry 8, yield is 84%).

Table 3. Synthesis of 4-substituted pyrazolone derivatives **5a–h** and **6a–g** on SiO_2 solid support under microwave irradiation [a]



4 **5**

Entry	Aldehyde	R_1	R_2	Product	Time [b]/ min	T [c]/ °C	Yield [d]/ %
1	4a	phenyl	4-chlorophenyl	5a	10	70	84
2	4b	2-methoxyphenyl	4-chlorophenyl	5b	10	70	90
3	4c	4-methoxyphenyl	4-chlorophenyl	5c	10	70	87
4	4d	4-methylphenyl	4-chlorophenyl	5d	10	70	87
5	4e	2-fluorophenyl	4-chlorophenyl	5e	10	70	86
6	4f	4-chlorophenyl	4-chlorophenyl	5f	10	70	83
7	4g	styryl	4-chlorophenyl	5g	12	80	79
8	4h	3-nitrophenyl	4-chlorophenyl	5h	12	80	78
9	4a	phenyl	H	6a	8	60	90
10	4b	2-methoxyphenyl	H	6b	8	60	97
11	4c	4-methoxyphenyl	H	6c	8	60	95
12	4d	4-methylphenyl	H	6d	8	60	94
13	4e	2-fluorophenyl	H	6e	8	60	94
14	4f	4-chlorophenyl	H	6f	8	60	90
15	4g	styryl	H	6g	9	60	87

[a] The reaction was conducted with aromatic aldehyde (1 mmol), ethyl acetoacetate (2 mmol) and hydrazine (2 mmol). [b] Reaction time. [c] Reaction temperature. [d] Isolated product yields.

Having been optimized the reaction conditions for the model system (Table 2, entry 8) was chosen to explore the scope and limitations of this protocol (Table 3). As shown in Table 3, all scanned reactants afforded the corresponding 4-substituted pyrazolone derivatives in excellent yields (78–97%). It was relatively sensitive to isoxazole terminal aldehyde bearing varieties of functional groups. When benzene ring on isoxazole terminal aldehydes was substituted by ortho- and para-position directing group (Table 3, entries 1–6 and 9–14), the yields of the synthesized

compounds were higher than that of benzene ring substituted by meta-position directing group (Table 3, entries 7–8, 15). The reason might be that eletrophilicity of the aldehyde was diminished when benzene ring on isoxazole terminal aldehyde was substituted by meta-position directing group.

Finally, recyclability of solid support SiO_2 was examined through the reaction of 3-phenylisoxazole-5-carbaldehyde, ethyl acetoacetate and 4-chlorophenylhydrazine under microwave irradiation (Fig. 1). As showed in Fig. 1, solid support SiO_2 could be easily recovered and reused at least five times without any significant loss of yield. Besides, the satisfied result was also obtained when the reaction was circulated five times.

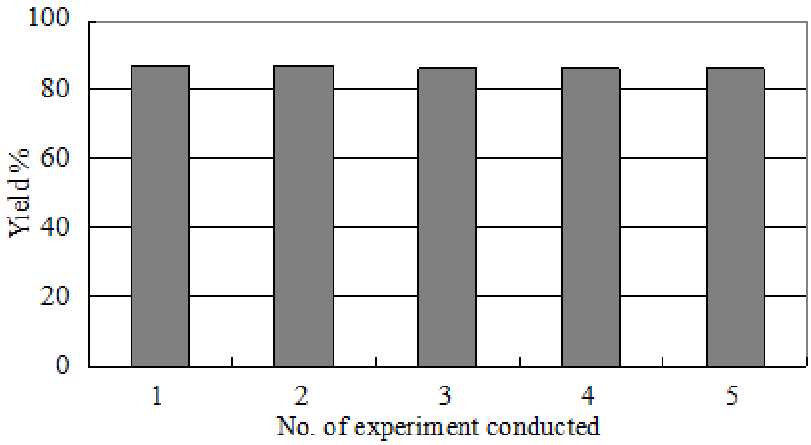
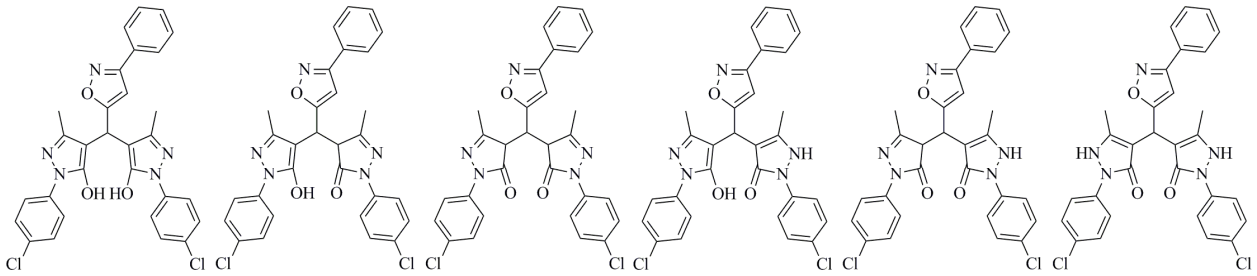


Fig. 1. Recycle of silica under microwave irradiation [a, b].

[a] The reaction was conducted with aromatic aldehyde (1 mmol), ethyl acetoacetate (2 mmol) and 4-chlorophenylhydrazine (2 mmol). [b] Isolated product yields.

The structures of 4-substituted pyrazolone derivatives were confirmed by FT-IR, ^{1}H and ^{13}C NMR and HRMS spectra analysis. With compounds **5b–5h** as examples, the $–CH_3$ protons on pyrazole ring and –CH– protons exhibited resonances at δ 2.34–2.36 ppm and δ 5.21–5.30 ppm using DMSO as solvent, while the resonances for the corresponding $–CH_3$ and –CH– carbon atom were observed peaks at δ 11.89–11.98 ppm and δ 27.85–28.04 ppm, respectively.

Besides, summarizing the previous work[35,45,46] found the structure of the synthesized compound **5a** have six conceivable structures (Scheme 2) due to bearing active hydroxyl group, carbonyl group, benzene ring and several heterocycle rings from the tandem Knoevenagel–Michael reaction.



I *II* *III* *IV* *V* *VI*

Scheme 2. Probable structures of compound **5a**

As shown in scheme 2, six possible structures (*I–VI*) of compound **5a** were proposed. To confirm the structure of **5a**, crystals of compound suitable for X-ray crystal structure determination were slowly grown from methanol at about 40^{o}C for three days. The structure of **5a** was determined by single crystal X-ray diffraction analysis. All non-hydrogen atoms were refined anisotropically. N−H hydrogen was located from difference electron density maps. Other hydrogen atoms were included in idealized position and were allowed to ride. The details of crystallographic collection and refinement data are given in Table 4. Hydrogen-Bond Geometries for **5a** are given in Table 5. The ORTEP drawing of molecule structure is shown in Fig 2.

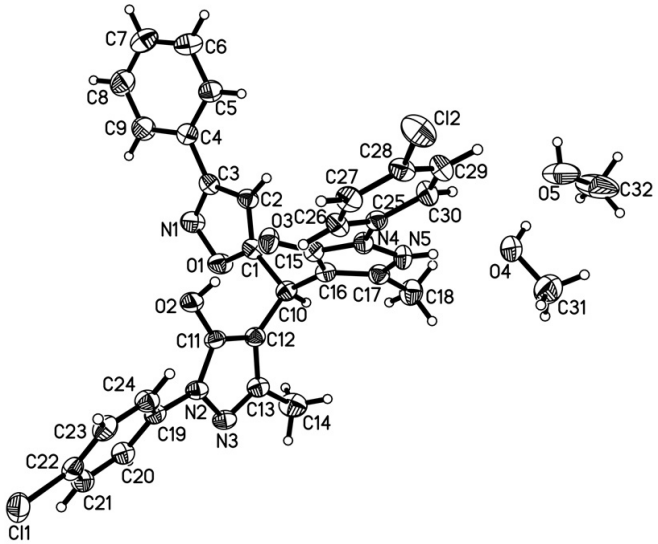


Fig. 2. Molecular structure of **5a**. The thermal ellipsoids are drawn at 30% probability levels.

Table 4. Crystal Data and Structure Refinement for Compound **5a**

Data	**5a**
Formula	$C_{32}H_{31}Cl_2N_5O_5$
Fw	636.52

Temperature / K	293(2)
Crystal system	Monoclinic
Space group	*C2/c*
a/ Å	28.207(6)
b/ Å	13.384(3)
c/ Å	16.643(3)
α/°	90
β/°	92.46(3)
γ/°	90
Volume(Å^3)	6277(2)
Z	8
D_{calcd} (Mg m^{-3})	1.347
F(000)	2656
range for data collection	3.00^o to 27.48^o
Limiting indices	–36 ≤ h ≤ 35, –17 ≤ k ≤17, –21≤ l ≤ 21
Data/restraints/parameters	7150 / 0 / 408
Goodness-of-fit on F^2	1.067
Final *R* indices [*I*>2(*I*)]	R_1[a] = 0.0568, wR_2[b] = 0.1733
R indices (all data)	R_1[a] = 0.0856, wR_2[b] = 0.1939
Largest diff. peak and hole/ e.A^{-3}	0.362 and –0.445

[a] $R_1 = \sum||F_o|-|F_c||/\sum|F_o|$. [b] $wR_2 = [\sum[\, w\,(F_o^2-F_c^2)^2] / \sum[\, w\,(F_o^2)^2]]^{1/2}$

Table 5. Hydrogen-Bond Geometries for **5a**

structure	D–H···A	*d*(D–H) (Å)	*d*(H···A) (Å)	*d*(D···A) (Å)	<(DHA) (deg)
5a	O(2)–H(2)···O(3)	0.82	1.71	2.531(3)	173.0
	O(4)–H(4)···O(5)	0.82	1.88	2.695(4)	175.5
	O(5)–H(5A)···N(3)#1	0.82	2.05	2.863(3)	172.1
	C(24)–H(24)···O(2)	0.93	2.54	2.977(4)	109.3

C(26)–H(26)···O(3)	0.93	2.38	2.915(3)	116.3
C(21)–H(21)···O(3)#2	0.93	2.71	3.579(3)	156.1
C(30)–H(30)···O(4)	0.93	2.71	3.520(4)	145.5
N(5)–H(100)···O(4)	0.76(3)	1.97(3)	2.713(3)	166(3)
C(30)–H(30)···Cl(1)#3	0.93	2.92	3.531(3)	124.4
C(29)–H(29)···Cl(1)#3	0.93	2.88	3.507(3)	126.1

Symmetry transformations used to generate equivalent atoms:

#1 x,-y+1,z+1/2; #2 x,-y,z-1/2; #3 -x+2,y+1,-z+1/2.

Compound **5a** crystallizes in the monoclinic space group *C2/c*. Due to the enol tautomerism, the two dihydral angles between the two five-membered rings and the two phenyl plane are different, being 142.5^{o} (the angle between the 1-(4-chlorophenyl)-3-methyl-1*H*-pyrazol-5-ol C11/C12/C13/N2/N3 and the phenyl ring C19/C20/C21/C22/C23/C24) and 25.5^{o} (the angle between the 2-(4-chlorophenyl)-5-methyl-1*H*-pyrazol-3(2*H*)-one C15/C16/C17/N4/N5 and the phenyl ring C25/C26/C27/C28/C29/C30), respectively. Meanwhile, the C10 atom becomes a chiral atom and has a distorted tetrahedral structure. The bond angles around the C10 atom being 112.75(19)^{o} (C(1)–C(10)–C(16)), 111.4(2)^{o} (C(1)–C(10)–C(12)), 113.3(2)^{o} (C(16)–C(10)–C(12)), 106.2^{o} (C(1)–C(10)–H(10)), 106.2^{o} (C(16)–C(10)–H(10)), 106.2^{o} (C(12)–C(10)–H(10)), respectively. The dihedral angles between the three five-membered rings are 117.0^{o} (C15/C16/C17/N4/N5 and C1/C2/C3/N1/O1), 85.6^{o} (C1/C2/C3/N1/O1 and C11/C12/C13/N2/N3), and 114.8^{o} (C15/C16/C17/N4/N5 and C11/C12/C13/N2/N3), respectively. The dihedral angle between the isoxazole ring (C1/C2/C3/N1/O1) and the phenyl ring (C4/C5/C6/C7/C8/C9) bonded to isoxazole ring is 14.7^{o}. The packing of **5a** was stabilized by intramolecular and intermolecular hydrogen bonds, shown in Figs 3–4. The hydrogen-bond geometries for **5a** are summarized in Table 5. In the pack of **5a**, the molecules form one-dimensioned chains through C30−H30···Cl1 and C29−H29···Cl1 hydrogen bonds with the graph-setmotifs $R_2^1(5)$,[47] as shown in Fig. 3. There also exist intramolecular C26−H26···O3 hydrogen bond with the graph-set motif S(6) and intramolecular O2−H2···O3 hydrogen bond with the graph-set motif S(8). The two methanol solvent molecules are linked together through intermolecular O4−H4···O5 hydrogen bond. There also exist intermolecular hydrogen bonds between the one-dimensioned chain and the solvent

molecules to form graph-set motifs $R_2^1(7)$ through N5−H100···O4 and C30−H30···O4 hydrogen bonds. The chains are further linked together through O5−H5A···N3 and C21−H21···O3 to form three-dimensioned network, shown in Fig. 4.

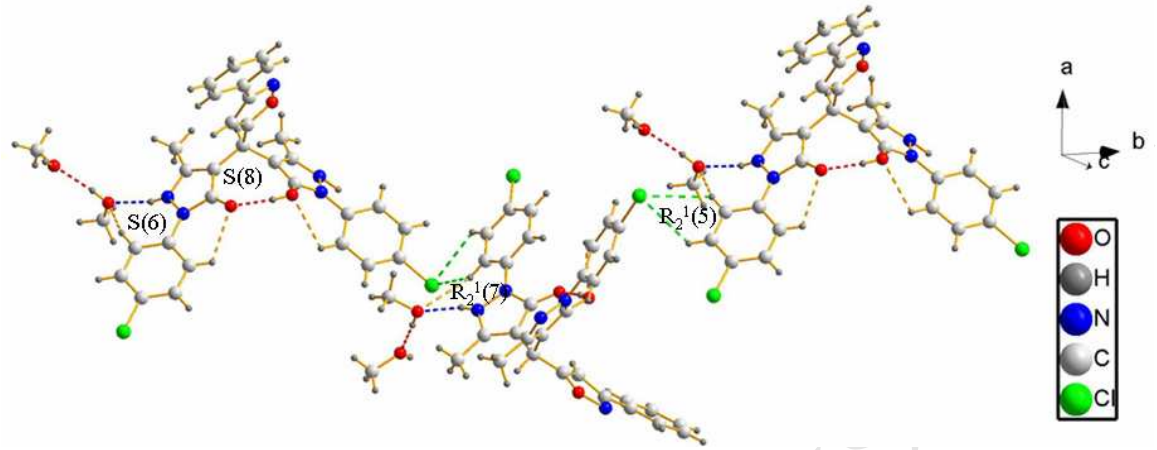


Fig. 3. 1-D chains formed by C–H···Cl hydrogen bonds. Green dashed lines: C–H···Cl hydrogen bonds ; Blue dashed lines: N–H···O hydrogen bonds; Red dashed lines: O–H···O hydrogen bonds; Yellow dashed lines: C–H···O hydrogen bonds.

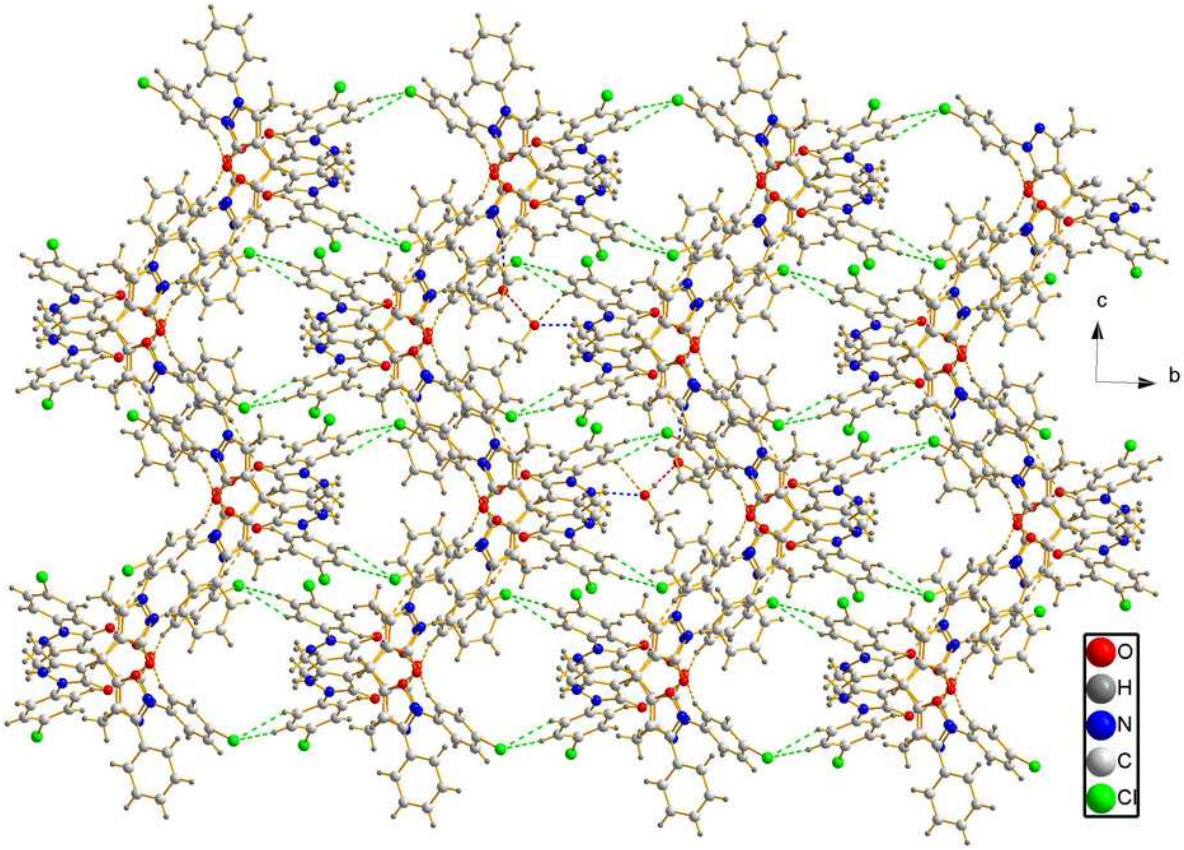
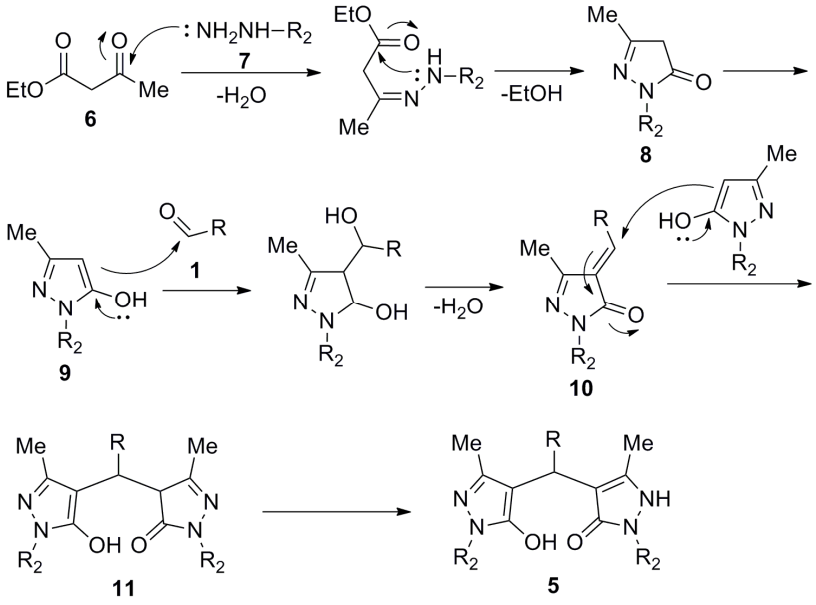


Fig. 4. Packing of **5a**. (Only two methanol molecules are shown for clarity.) Green dashed lines: C–H···Cl hydrogen bonds; Blue dashed lines: N–H···O hydrogen bonds; Red dashed lines: O–H···O hydrogen bonds;

Yellow dashed lines: C–H···O hydrogen bonds.

Therefore, it can be seen from single crystal structure analysis of **5a (**Table 4, Table 5, Fig. 3 and Fig. 4**)** that **5a** (Scheme 2d**)** from recrystallizing in methanol is stable, which was in accordance with the characterized structure by HRMS, FT-IR, ^{1}H NMR and ^{13}C NMR spectroscopy. As for the other structure compounds were not obtained mainly resulting from microwave heating. Thus, based on the structure of the obtained **5a** could infer the tentative reaction mechanism for the formation of 4-substituted pyrazolone derivatives is shown in Scheme 3. Firstly, compound **7** nucleophilicly attacked *β*-keto esters **6**, the intermediate hydrazone was obtained. Amino group on hydrazone subsequently nucleophilicly attacked itself carbonyl group to remove a molecular ethanol and cyclize to intermediate **8**. Then, intermediate **8** interconverted the stable intermediate **9**. Further, the formation of intermediate **10** by the nucleophilic addition of intermediate **9** to 3-substituted isoxazole-5-carbaldehydes **1** followed by dehydration.[48] The next step is a Michael addition of the second molecule intermediate **9** to intermediate **11**. Finally, the target product **5** is formed by tautomeric proton shift.



Scheme 3. Proposed mechanism for the one-pot pseudo-three-component synthesis of 4-substituted pyrazolone derivatives under microwave irradiation

3. Conclusions

In conclusion, a green method for the synthesis of 4-substituted pyrazolone derivatives under

solvent-free conditions using microwave irradiation has been presented. SiO_2 has been proved to be an efficient dispersant and a favorable catalyst for the reaction as it is inexpensive, easy-to-handle, commercially available and reusable. Fifteen desired 4-substituted pyrazolone derivatives bearing substituted isoxazole ring were obtained in 78–97% yields. Therefore, the method is an important contribution to the 4,4'-(arylmethylene)-(1*H*-pyrazol-5-ol and 1*H*-pyrazol-5-one) compounds synthesis pathways, and can be extended to the synthesis of the other heterocyclic compounds. Besides, the synthesis of more 4-substituted pyrazolone derivatives compounds and biological tests of the synthesized compounds are being studied in our laboratory. We believe that the synthesized 4-substituted pyrazolone derivatives bearing isoxazole ring compounds can be used for many practical application in sterilization, antiviral and anticancer fields.

4. Experimental

4.1. General Remarks

Various substituted benzaldehydes were of analytical-reagent grade from Aladdin reagent Co (China). and used without further purification. The other solvents and reagents used were supplied by Tianjin Tiantai Chemical Co. Ltd (China) and and Beijing Chemical Plant (China). All melting points were determined on an XT−4 melting point apparatus (China) and were uncorrected. ^{1}H and ^{13}C NMR spectra were measured using a Bruker AVANCE-500 NMR (Germany) spectrometer and with TMS as an internal standard. The chemical shift is given in δ relative to TMS. HRMS was collected using an Agilent 1290-micrOTOF Q II spectrometer (USA). FT-IR spectra were obtained as KBr pellets using an IRAffinity-1 instrument (Shimadzu, Japan) in the range of 500 – 4000 cm^{-1}. An MCL-3-type microwave reactor (200 W, single-mode) Sichuan University (China) with a thermometer for microwave application was used in all experiments.

4.2. General synthesis process for 3-substituted isoxazole-5-carbaldehydes

3-Substituted isoxazole-5-carbaldehydes were synthesized according to reported procedures.[37] (3-Phhenylisoxazol-5-yl)methanols (5.0 mmol) were dissolved into benzene (10 mL). An aqueous solution of sodium bicarbonate (13 mL, 1.2 mol/L) was added into the benzene slurry at room

temperature. Then, the mixed solid TEMPO (0.5 mmol) was added and solid iodine (10 mmol) dissolved in alcohol was added into the reaction mixture. The reaction mixture was then aged for 10–12 h at room temperature; the reaction was monitored by TLC. The crude product was diluted with ethyl acetate (15 mL). The batch was washed with $Na_2S_2O_3$ and transferred to a separatory funnel, and the aqueous layer was extracted with ethyl acetate (2 × 10 mL). The organic layers were mixed and dried over anhydrous sodium sulfate for 30 min, filtrated and evaporated under vacuum to give the crude product which was purified by column chromatography (silica gel, 200–300 mesh) using petroleum ether/ethyl acetate (φ_r = 5 : 1) to furnish the product. The yields of obtained 3-substituted isoxazole-5-carbaldehydes products were 58–92 %.

4.3. General synthesis process for 4-substituted-((5-hydroxy-3-methyl-1*H*-pyrazol-4-yl)(3-aryl-isoxazol-5-yl)methyl)-5-methyl-1*H*-pyrazol-3(2*H*)-ones

SiO_2 or Al_2O_3 (200–300 mesh, pH 6–7, 1.0 g) was added to a mixture of ethylacetoacetate (2.0 mmol) and hydrazine (2.0 mmol). The reaction mixture was irradiated in a microwave at 60 ^oC for 5–10 min. 3-substituted isoxazole-5-carbaldehydes (1.0 mmol) was added to a mixture. The reaction mixture was irradiated in a microwave at 70 ^oC for 5–10 min. The reaction was monitored by TLC. The crude products were directly purified by column chromatography using ethyl acetate/methanol (φ_r = 10 : 1) to afford **5a–h** and **6a–g**.

4.4 Crystal structure determination for compounds 5a

The single crystal X-ray diffraction data for compound **5a** was collected on a Rigaku R-AXIS RAPID IP diffractometer equipped with graphite-monochromated Mo-K_α radiation (λ = 0.71073 Å), operating at 293±2 K. The structure was solved by direct method[49] and refined by full-matrix least squares based on F^2 using the SHELXTL 5.1 software package.[50] CCDC–1440588 (**5a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/deposit or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44-1223-336-033; E-mail: deposit@ccdc.cam.ac.uk.

4.5 Spectroscopic data for the products

*4.5.1. 2-(4-chlorophenyl)-4-((1-(4-chlorophenyl)-5-hydroxy-3-methyl-1H-pyrazol-4-yl)(3-phenylisoxazol-5-yl)methyl)-5-methyl-1H-pyrazol-3(2H)-one (**5a**)*. Yield: 84%, mp 160–162 ^oC. IR (KBr) (ν/cm^{-1}) 3647, 3320, 3118, 3069, 3044, 2977, 2920, 2789, 2752, 1732, 1701, 1605,

1567, 1493, 1446, 1404, 1275, 1092, 1013, 920, 829, 692, 592; ^{1}H NMR (500 MHz, DMSO) δ: 13.89 (s, 1H), 7.87 – 7.83 (m, 2H), 7.77 (d, J = 8.9 Hz, 4H), 7.52 (d, J = 8.8 Hz, 4H), 7.49 – 7.45 (m, 3H), 6.80 (d, J = 0.9 Hz, 1H), 5.25 (s, 1H), 2.35 (s, 6H); ^{13}C NMR (126 MHz, DMSO) δ: 173.33, 165.13, 162.23, 148.72, 147.03, 134.14, 131.78, 130.48, 129.42, 129.33, 129.15, 127.03, 122.43, 100.80, 27.96, 14.52; HRMS (EI): calcd for $C_{30}H_{24}Cl_2N_5O_3$ $[M+H]^+$ 572.1256, $[M+H+2]^+$ 574.1256, found 572.1286, 574.1256.

*4.5.2. 2-(4-chlorophenyl)-4-((1-(4-chlorophenyl)-5-hydroxy-3-methyl-1H-pyrazol-4-yl)(3-(2-methoxyphenyl)isoxazol-5-yl)methyl)-5-methyl-1H-pyrazol-3(2H)-one (**5b**).* Yield: 90%, mp 209–211 ^{o}C. IR (KBr) (ν/cm^{-1}) 3626, 3343, 3137, 3096, 3013, 2974, 2940, 2835, 2790, 2758, 1742, 1701, 1605, 1573, 1497, 1468, 1402, 1275, 1174, 1088, 1022, 829, 773, 602; ^{1}H NMR (500 MHz, DMSO) δ: 13.96 (s, 1H), 7.78 – 7.74 (m, 4H), 7.70 (dd, J = 7.7, 1.7 Hz, 1H), 7.52 (d, J = 8.8 Hz, 4H), 7.48 – 7.43 (m, 1H), 7.16 (d, J = 8.4 Hz, 1H), 7.03 (t, J = 7.5 Hz, 1H), 6.61 (d, J = 0.9 Hz, 1H), 5.26 (d, J = 6.1 Hz, 1H), 3.80 (s, 3H), 3.18 (s, 2H), 2.36 (s, 6H); ^{13}C NMR (126 MHz, DMSO) δ: 171.98, 159.89, 157.30, 154.49, 147.07, 137.76, 135.52, 131.86, 129.36, 129.32, 122.37, 121.14, 117.84, 112.70, 103.53, 56.18, 49.03, 27.85, 11.93; HRMS (EI): calcd for $C_{31}H_{26}Cl_2N_5O_4$ $[M+H]^+$ 602.1362, $[M+H+2]^+$ 604.1362, found 602.1394, 604.1369.

*4.5.3. 2-(4-chlorophenyl)-4-((1-(4-chlorophenyl)-5-hydroxy-3-methyl-1H-pyrazol-4-yl)(3-(4-methoxyphenyl)isoxazol-5-yl)methyl)-5-methyl-1H-pyrazol-3(2H)-one (**5c**).* Yield: 87%, mp 151–153 ^{o}C. IR (KBr) (ν/cm^{-1}) 3647, 3346, 3076, 3001, 2930, 2831, 1723, 1701, 1609, 1573, 1493, 1429, 1254, 1173, 1092, 1013, 829, 611; ^{1}H NMR (500 MHz, DMSO) δ: 13.88 (s, 1H), 7.78 (dd, J = 8.6, 6.5 Hz, 6H), 7.52 (d, J = 8.8 Hz, 4H), 7.01 (d, J = 8.8 Hz, 2H), 6.71 (s, 1H), 5.22 (s, 1H), 3.80 (s, 3H), 2.34 (s, 6H); ^{13}C NMR (126 MHz, DMSO) δ: 172.95, 161.83, 161.04, 160.95, 156.20, 147.02, 130.13, 129.32, 128.51, 122.42, 121.56, 114.81, 100.49, 55.69, 27.92, 11.92; HRMS (EI): calcd for $C_{31}H_{26}Cl_2N_5O_4$ $[M+H]^+$ 602.1362, $[M+H+2]^+$ 604.1362, found 602.1391, 604.1365.

*4.5.4. 2-(4-chlorophenyl)-4-((1-(4-chlorophenyl)-5-hydroxy-3-methyl-1H-pyrazol-4-yl)(3-(p-tolyl)isoxazol-5-yl)methyl)-5-methyl-1H-pyrazol-3(2H)-one (**5d**).* Yield: 87%, mp 219–221 ^{o}C. IR (KBr) (ν/cm^{-1}) 3669, 3360, 3069, 3039, 2954, 2920, 2810, 1738, 1701, 1593, 1579, 1493, 1431, 1180, 1094, 1012, 826, 654; ^{1}H NMR (500 MHz, DMSO) δ: 13.89 (s, 1H), 7.77 (d, J = 8.9 Hz, 4H), 7.73 (d, J = 8.1 Hz, 2H), 7.52 (d, J = 8.8 Hz, 4H), 7.27 (d, J = 8.1 Hz, 2H), 6.74 (s, 1H),

5.23 (s, 1H), 2.34 (d, *J* = 2.6 Hz, 9H); ^{13}C NMR (126 MHz, DMSO) *δ*: 173.14, 167.66, 162.13, 147.04, 140.15, 129.99, 129.98, 129.33, 126.93, 126.36, 122.43, 119.97, 100.63, 27.95, 21.36; HRMS (EI): calcd for $C_{31}H_{26}Cl_2N_5O_3$ $[M+H]^+$ 586.1413, $[M+H+2]^+$ 588.1413, found 586.1431, 588.1416.

*4.5.5. 2-(4-chlorophenyl)-4-((1-(4-chlorophenyl)-5-hydroxy-3-methyl-1H-pyrazol-4-yl)(3-(2-fluorophenyl)isoxazol-5-yl)methyl)-5-methyl-1H-pyrazol-3(2H)-one (**5e**)*. Yield: 86%, mp 163–165 ^{o}C. IR (KBr) (*ν*/cm^{-1}) 3636, 3308, 3073, 3027, 2920, 2849, 2790, 2740,1730, 1711, 1618, 1572, 1495, 1458, 1404, 1267, 1180, 1092, 1013, 953, 831, 590; ^{1}H NMR (500 MHz, DMSO) *δ*: 13.96 (s, 1H), 7.87 (td, *J* = 7.7, 1.7 Hz, 1H), 7.76 (d, *J* = 8.9 Hz, 4H), 7.58 – 7.54 (m, 1H), 7.52 (d, *J* = 8.9 Hz, 4H), 7.35 (ddd, *J* = 15.2, 9.8, 4.8 Hz, 2H), 6.65 (d, *J* = 2.1 Hz, 1H), 5.30 (s, 1H), 2.36 (s, 6H); ^{13}C NMR (126 MHz, DMSO) *δ*: 173.40, 164.38, 160.88, 158.89, 157.86, 147.11, 132.73, 130.25, 129.73, 129.40, 125.54, 122.47, 117.10, 117.04, 102.66, 27.91, 11.96; HRMS (EI): calcd for $C_{30}H_{23}Cl_2FN_5O_3$ $[M+H]^+$ 590.1162, $[M+H+2]^+$ 592.1162, found 590.1191, 592.1168.

*4.5.6. 2-(4-chlorophenyl)-4-((1-(4-chlorophenyl)-5-hydroxy-3-methyl-1H-pyrazol-4-yl)(3-(4-chlorophenyl)isoxazol-5-yl)methyl)-5-methyl-1H-pyrazol-3(2H)-one (**5f**)*. Yield: 83%, mp 205–207 ^{o}C. IR (KBr) (*ν*/cm^{-1}) 3647, 3321, 3069, 3045, 2970, 2922, 2797, 2751, 1740, 1700, 1603, 1572, 1493, 1427, 1271, 1174, 1092, 1013, 949, 826, 590; ^{1}H NMR (500 MHz, DMSO) *δ*: 13.86 (s, 1H), 7.89 (d, *J* = 8.6 Hz, 2H), 7.77 (d, *J* = 8.9 Hz, 4H), 7.53 (t, *J* = 8.2 Hz, 6H), 6.84 (s, 1H), 5.25 (s, 1H), 2.35 (s, 6H); ^{13}C NMR (126 MHz, DMSO) *δ*: 173.65, 165.21, 161.31, 147.02, 135.17, 130.17, 129.52, 129.33, 128.83, 128.02, 122.43, 119.95, 100.87, 27.96, 11.91; HRMS (EI): calcd for $C_{30}H_{23}Cl_3N_5O_3$ $[M+H]^+$ 606.0866, $[M+H+2]^+$, 608.0866, found 606.0902, 608.0878.

*4.5.7. (E)-2-(4-chlorophenyl)-4-((1-(4-chlorophenyl)-5-hydroxy-3-methyl-1H-pyrazol-4-yl)(3-styrylisoxazol-5-yl)methyl)-5-methyl-1H-pyrazol-3(2H)-one (**5g**)*. Yield: 79%, mp 161–163 ^{o}C. IR (KBr) (*ν*/cm^{-1}) 3647, 3360, 3061, 3034, 2947, 2922, 2790, 2751, 1732, 1701, 1605, 1573, 1493, 1431, 1275, 1174, 1092, 1013, 829, 694, 592; ^{1}H NMR (500 MHz, DMSO) *δ*: 13.88 (s, 1H), 7.78 (d, *J* = 8.9 Hz, 4H), 7.64 (d, *J* = 7.4 Hz, 2H), 7.53 (d, *J* = 8.8 Hz, 4H), 7.38 (t, *J* = 7.4 Hz, 2H), 7.32 (dd, *J* = 13.5, 6.3 Hz, 1H), 7.18 (d, *J* = 16.6 Hz, 1H), 6.68 (s, 1H), 5.21 (s, 1H), 2.34 (s, 6H); ^{13}C NMR (126 MHz, DMSO) *δ*: 172.36, 167.08, 162.09, 159.16, 147.07, 136.69, 136.23, 130.17,

129.35, 129.20, 127.48, 122.41, 119.95, 116.19, 99.91, 27.85, 11.90; HRMS (EI): calcd for $C_{32}H_{26}Cl_2N_5O_3$ $[M+H]^+$ 598.1413, $[M+H+2]^+$ 600.1413, found 598.1403, 600.1378.

*4.5.8. 2-(4-chlorophenyl)-4-((1-(4-chlorophenyl)-5-hydroxy-3-methyl-1H-pyrazol-4-yl)(3-(3-nitrophenyl)isoxazol-5-yl)methyl)-5-methyl-1H-pyrazol-3(2H)-one (**5h**).* Yield: 78%, mp 207–209 °C. IR (KBr) (ν/cm^{-1}) 3649, 3308, 3080, 3052, 2974, 2922, 2790, 2758, 1732, 1701, 1605, 1566, 1493, 1403, 1274, 1174, 1092, 1013, 829, 731, 592; ^{1}H NMR (500 MHz, DMSO) δ: 13.86 (s, 1H), 8.65 – 8.62 (m, 1H), 8.32 (dd, J = 10.9, 5.0 Hz, 2H), 7.80 – 7.76 (m, 5H), 7.52 (d, J = 8.9 Hz, 4H), 7.07 (d, J = 1.1 Hz, 1H), 5.30 (d, J = 0.8 Hz, 1H), 2.36 (s, 6H); ^{13}C NMR (126 MHz, DMSO) δ: 174.29, 160.80, 153.67, 148.79, 147.05, 136.77, 133.40, 131.94, 131.19, 130.75, 130.16, 129.34, 125.10, 122.42, 121.45, 119.96, 101.27, 28.04, 11.98; HRMS (EI): calcd for $C_{30}H_{23}Cl_2N_6O_5$ $[M+H]^+$ 617.1107, $[M+H+1]^+$ 618.1107, found 617.1067, 618.1091.

*4.5.9. 4-((5-hydroxy-3-methyl-1H-pyrazol-4-yl)(3-phenylisoxazol-5-yl)methyl)-5-methyl-1H-pyrazol-3(2H)-one (**6a**).* Yield: 90%, mp 200–202 °C. IR (KBr) (ν/cm^{-1}) 3648, 3183, 3117, 3052, 2960, 2928, 1730, 1703, 1597, 1489, 1468, 1281, 1213, 1146, 1032, 928, 768, 600, 513; ^{1}H NMR (500 MHz, DMSO) δ: 11.34 (s, 2H), 7.81 (dd, J = 6.6, 3.0 Hz, 2H), 7.47 (dd, J = 5.0, 1.7 Hz, 3H), 6.52 (s, 1H), 5.07 (s, 1H), 2.11 (s, 6H); ^{13}C NMR (126 MHz, DMSO) δ: 175.04, 162.19, 161.90, 151.50, 130.37, 129.45, 129.35, 126.92, 101.74, 100.45, 27.66, 10.62; HRMS (EI): calcd for $C_{18}H_{18}N_5O_3$ $[M+H]^+$ 352.1410, found 352.1408.

*4.5.10. 4-((5-hydroxy-3-methyl-1H-pyrazol-4-yl)(3-(2-methoxyphenyl)isoxazol-5-yl)methyl)-5-methyl-1H-pyrazol-3(2H)-one (**6b**).* Yield: 97%, mp 177–179 °C. IR (KBr) (ν/cm^{-1}) 3648, 3177, 3116, 3002, 2956, 2934, 2836, 1732, 1705, 1603, 1509, 1472, 1432, 1281, 1252, 1117, 1024, 949, 758, 665; ^{1}H NMR (600 MHz, DMSO) δ: 11.43 (s, 2H), 7.70 (dd, J = 7.7, 1.8 Hz, 1H), 7.47 – 7.44 (m, 1H), 7.16 (d, J = 8.3 Hz, 1H), 7.05 – 7.02 (m, 1H), 6.47 (s, 1H), 5.06 (s, 1H), 3.81 (s, 3H), 2.12 (s, 6H); ^{13}C NMR (151 MHz, DMSO) δ: 173.59, 159.85, 159.62, 157.31, 145.73, 131.84, 129.29, 121.20, 118.05, 112.72, 103.59, 101.94, 56.22, 27.58, 10.68; HRMS (EI): calcd for $C_{19}H_{20}N_5O_4$ $[M+H]^+$ 382.1515, found 382.1509.

*4.5.11. 4-((5-hydroxy-3-methyl-1H-pyrazol-4-yl)(3-(4-methoxyphenyl)isoxazol-5-yl)methyl)-5-methyl-1H-pyrazol-3(2H)-one (**6c**).* Yield: 95%, mp 197–199 °C. IR (KBr) (ν/cm^{-1}) 3647, 3184, 3117, 3001, 2955, 2934, 2836, 1735, 1703, 1611, 1528, 1455, 1431, 1297, 1254, 1028, 835, 608; ^{1}H NMR (500 MHz, DMSO) δ: 11.33 (s, 2H), 7.74 (d, J = 8.8 Hz, 2H), 7.01 (d, J = 8.8 Hz, 2H),

399 6.45 (s, 1H), 5.03 (s, 1H), 3.80 (s, 3H), 2.11 (s, 6H); ^{13}C NMR (126 MHz, DMSO) δ: 174.67,
400 167.01, 161.51, 160.95, 156.13, 128.39, 121.77, 114.84, 101.79, 100.17, 55.70, 27.64, 10.62;
401 HRMS (EI): calcd for $C_{19}H_{20}N_5O_4$ $[M+H]^+$ 382.1515, found 382.1510.

402 *4.5.12. 4-((5-hydroxy-3-methyl-1H-pyrazol-4-yl)(3-(p-tolyl)isoxazol-5-yl)methyl)-5-methyl-1H-*
403 *pyrazol-3(2H)-one (**6d**)*. Yield: 94%, mp 206–208 ^{o}C. IR (KBr) (ν/cm^{-1}) 3647, 3183, 3117, 3026,
404 2955, 2924, 1732, 1704, 1601, 1526, 1460, 1429, 1279, 1141, 1042, 951, 822, 600; ^{1}H NMR (500
405 MHz, DMSO) δ: 11.36 (s, 2H), 7.69 (d, J = 8.1 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H), 6.48 (s, 1H),
406 5.04 (s, 1H), 2.34 (s, 3H), 2.11 (s, 6H); ^{13}C NMR (126 MHz, DMSO) δ: 174.84, 166.59, 161.80,
407 140.00, 130.00, 126.81, 126.55, 119.95, 101.78, 100.30, 27.64, 21.35, 10.61; HRMS (EI): calcd
408 for $C_{19}H_{20}N_5O_3$ $[M+H]^+$ 366.1566, found 366.1562.

409 *4.5.13. 4-((3-(2-fluorophenyl)isoxazol-5-yl)(5-hydroxy-3-methyl-1H-pyrazol-4-yl)methyl)-5-*
410 *methyl-1H-pyrazol-3(2H)-one (**6e**)*. Yield: 94%, mp 190–192 ^{o}C. IR (KBr) (ν/cm^{-1}) 3647, 3185,
411 3112, 3039, 2980, 2934, 1732, 1704, 1597, 1507, 1472, 1405, 1268, 1221, 1146, 1042, 953, 762,
412 662; ^{1}H NMR (600 MHz, DMSO) δ: 11.40 (s, 2H), 7.87 (td, J = 7.7, 1.7 Hz, 1H), 7.57 – 7.52 (m,
413 1H), 7.39 – 7.31 (m, 2H), 6.45 (d, J = 3.1 Hz, 1H), 5.10 (s, 1H), 2.13 (s, 6H). ^{13}C NMR (151
414 MHz, DMSO) δ: 175.10, 166.95, 160.77, 159.11, 157.47, 132.70, 129.55, 125.63, 117.16, 117.13,
415 102.64, 101.76, 27.64, 10.67. HRMS (EI): calcd for $C_{18}H_{17}FN_5O_3$ $[M+H]^+$ 370.1315, found
416 370.1318.

417 *4.5.14. 4-((3-(4-chlorophenyl)isoxazol-5-yl)(5-hydroxy-3-methyl-1H-pyrazol-4-yl)methyl)-5-*
418 *methyl-1H-pyrazol-3(2H)-one (**6f**)*. Yield: 90%, mp 204–206 ^{o}C. IR (KBr) (ν/cm^{-1}) 3648, 3190,
419 3112, 3052, 2980, 2923, 1735, 1704, 1603, 1507, 1455, 1427, 1273, 1219, 1145, 1092, 1015, 951,
420 835, 608; ^{1}H NMR (600 MHz, DMSO) δ: 11.33 (s, 2H), 7.86 (d, J = 8.6 Hz, 2H), 7.53 (d, J = 8.6
421 Hz, 2H), 6.57 (s, 1H), 5.07 (s, 1H), 2.11 (s, 6H); ^{13}C NMR (151 MHz, DMSO) δ: 175.09, 160.77,
422 159.11, 157.46, 152.24, 132.70, 129.53, 125.62, 117.21, 117.02, 102.64, 101.74, 27.64, 10.67;
423 HRMS (EI): calcd for $C_{18}H_{17}ClN_5O_3$ $[M+H]^+$ 386.1020, found 386.1034.

424 *4.5.15. (E)-4-((5-hydroxy-3-methyl-1H-pyrazol-4-yl)(3-styrylisoxazol-5-yl)methyl)-5-methyl-*
425 *1H-pyrazol-3(2H)-one (**6g**)*. Yield: 87%, mp 198–200 ^{o}C. IR (KBr) (ν/cm^{-1}) 3648, 3183, 3112,
426 3033, 2921, 1732, 1704, 1593, 1526, 1487, 1475, 1435, 1260, 1208, 1147, 1075, 1034, 964, 822,
427 754, 608; ^{1}H NMR (500 MHz, DMSO) δ: 11.34 (s, 2H), 7.67 – 7.64 (m, 2H), 7.39 (dd, J = 8.1,
428 6.7 Hz, 3H), 7.36 – 7.31 (m, 2H), 6.43 (s, 1H), 5.01 (s, 1H), 2.10 (s, 6H); ^{13}C NMR (126 MHz,

DMSO) δ: 174.09, 162.01, 161.72, 152.09, 136.28, 136.26, 129.18, 129.16, 127.47, 116.40, 101.73, 99.64, 27.56, 10.59; HRMS (EI): calcd for $C_{20}H_{20}N_5O_3$ $[M+H]^+$ 378.1566, found 378.1570.

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