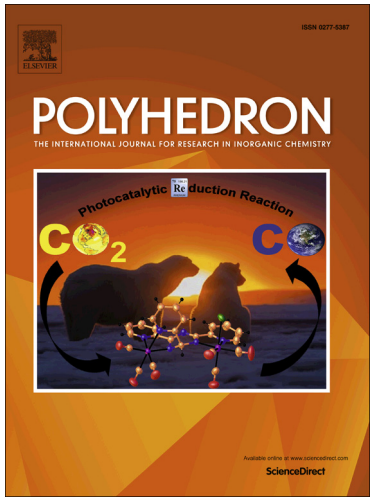

Molecular design and the optimum synthetic route of the compounds with multi-pyrazole and its derivatives and the potential application in antibacterial agents

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Molecular design and the optimum synthetic route of the compounds with multi-pyrazole and its derivatives and the potential application in antibacterial agents

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Abstract

Molecular design and efficient synthetic procedures have been developed for pyrazole and its derivatives with different linkers. In particular, twelve compounds with –I or $–NO_2$ substituted groups on the pyrazole ring were synthesized for the first time. These compounds are characterized by element analysis, IR, HNMR, M.P. and X-ray diffraction. In addition, some compounds and corresponding complexes were also assayed in vitro for their ability to inhibit the growth of representative Gram-positive bacteria, Gram-negative bacteria and the fungus. It was worthwhile to note that some compounds could be used as potential antibacterial agents.

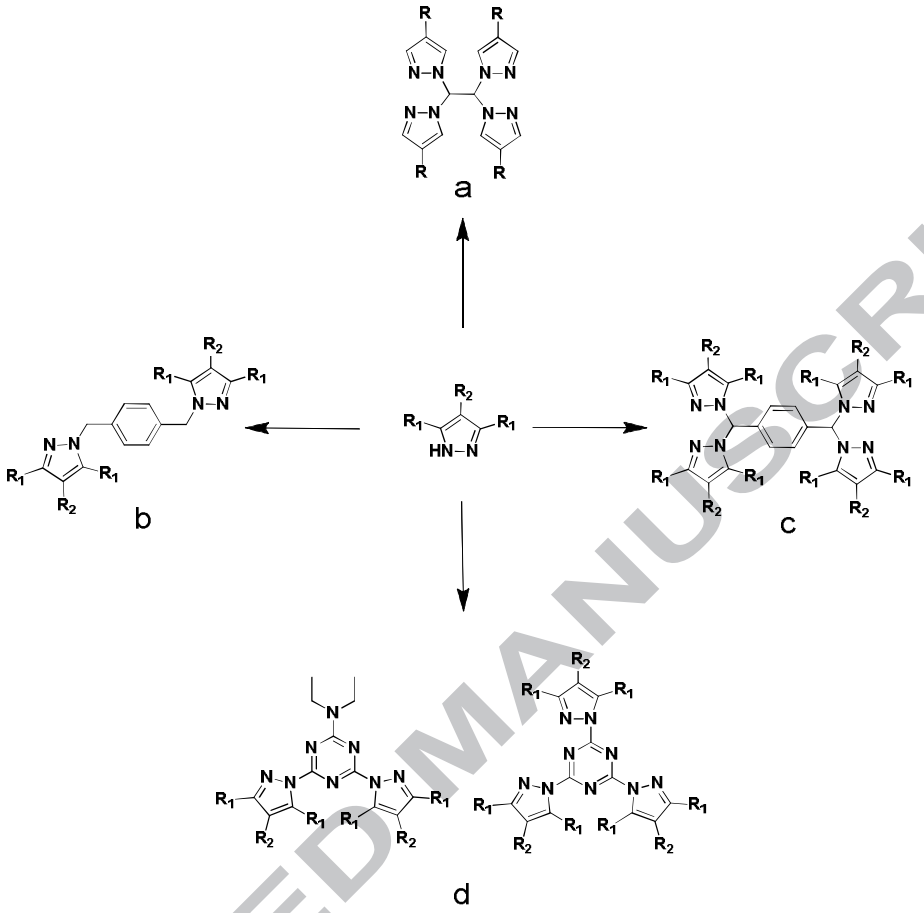
Keywords: Pyrazole and its derivatives; N-heterocyclic ligands; Antibacterial activity; Crystal structure

1 Introduction

Pyrazole and its derivatives as a crucial family member of N-heterocyclic ligands are used as pesticides and medicinal preparations because of their high biological activities[1-4]. In the mean time, it is also found widespread applications in the fields of supramolecular chemistry, crystal engineering, materials sciences, sensors, biochemistry, catalysis etc.[5-12]. In the recent years, with the further study of multidentate ligands, there is a growing interest in molecular design of multi-pyrazole compounds and its derivatives due to larger π-conjugated system, good planarity and stable structure[13-17]. During the past two decades, some complexes with multi-pyrazolyl compound as ligands have been reported, for instance, $[Zn(L_2)(SCN)_2]$ (L_2= 1,4-bis((3,5-dimethyl-1H-pyrazol-1-yl)methyl)benzene), $Co(bpz^*eaT)(SCN)_2$ (bpz*eaT: 2,4-dimethyl-1H-pyrazol-1-yl)-6-diethylamino-1,3,5-triazine), $[Ag_2(Lp)_{1.5}(NO_3)](NO_3)$ $[Cu_2(\mu\text{-}Lp)(H_2O)_6](SiF_6)_2\cdot(H_2O)_4$ $Ag(\mu\text{-}Lp)NO_3$ (Lp= p−$[CH(pz)_2]_2C_6H_4$), $Hg(TpzT)(SCN)_2\cdot H_2O$ (TPzT: 2,4,6-tri(pyrazole-1-yl)-1,3,5-triazine), etc.[18-22]. Most of the complexes were reported about their characteristics, including spectrum, structures, thermal properties, luminescent properties and synthesis. However, there are few investigations about biological activity for the complexes with multi-pyrazole and its derivatives as ligands. Obviously,

it became a hot issue that efficiently synthesizing of multi-pyrazole and its derivatives compounds for exploring the application of the complexes in the field of biochemistry.

Here, we have synthesized firstly twelve multi - pyrazolyl compounds with -I or -NO_2 substituted groups and explored a series of optimization synthetic procedures for preparing multi - pyrazolyl compounds by the reaction of pyrazole and its derivatives with different linkers in two kinds of solvents: dimethylsulfoxide (DMSO)-potassium hydroxide (KOH) and tetrahydrofuran (THF). Compared with traditional procedures[23-30], we have achieved the goals of maximizing reaction efficiency and minimizing chemical wastes. We have developed four types synthetic system, including multi - pyrazolyl compounds (scheme 1): alkane –pyrazole derivatives, benzene – dipyrazole derivatives and benzene – tetrapyrazole derivatives in the superbasic DMSO-KOH medium; triazine – pyrazole derivatives in the THF. In addition, in long time for exploring synthetic procedures, we found that steric hindrance, substituted groups and the condition of the reaction play a vital role in the targets of separating high yield and purity compounds. At the same time, some new compounds and the complexes reported by our group are assayed in vitro for their biological activity and some of them exhibit excellent ability of antibacterial activity.



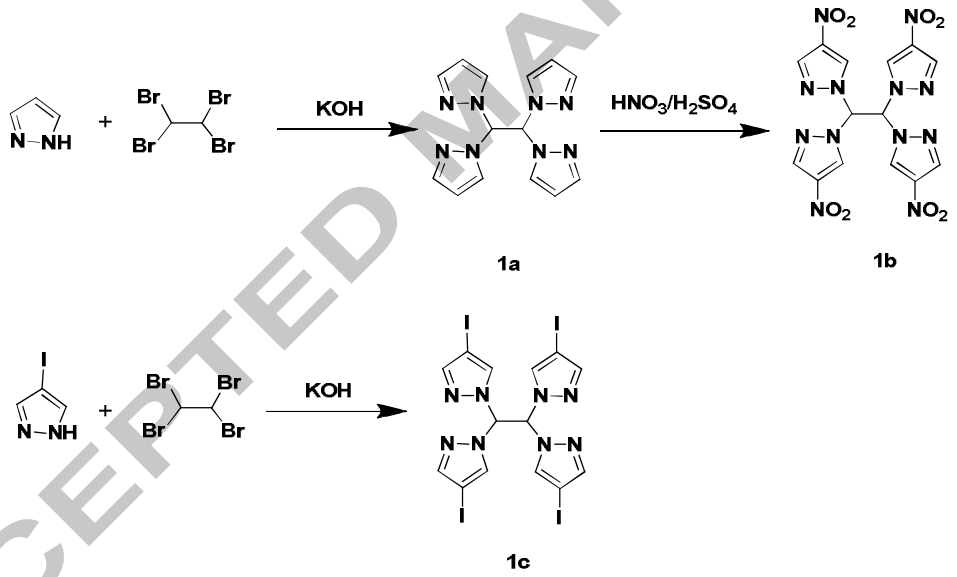
Scheme 1: Four kinds of pyrazole and its derivatives: (a) alkane –pyrazole derivatives; (b) benzene – dipyrazole derivatives; (c) benzene – tetrapyrazole derivatives; (d) triazine – pyrazole derivatives

2. Results and discussion

2.1 Synthesis

We began to explore the optimum synthetic route of alkane – pyrazole derivatives by controlling the reaction of pyrazole, 1,1,2,2 – tetrabromoethane (TBE) and potassium hydroxide (KOH) in 4:1:4 molar ratios and prolonging deprotonation reaction time in the mixed system of pyrazole and KOH in dimethylsulfoxide (DMSO) at 80 °C. That is the

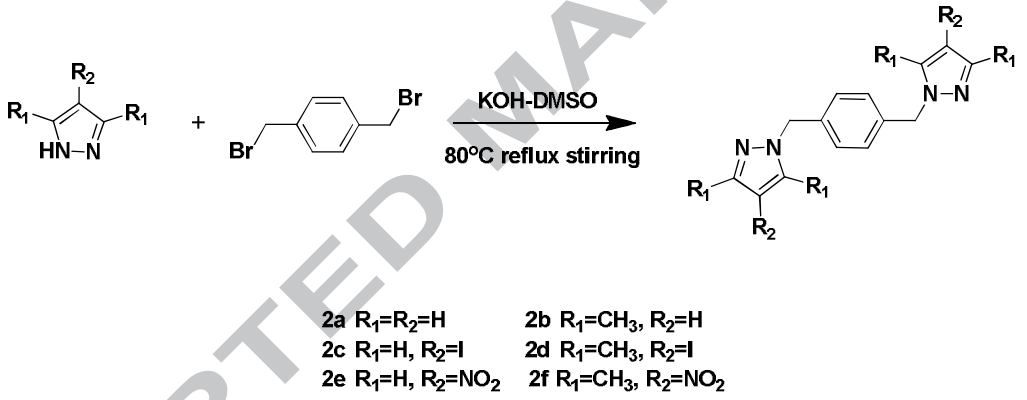
solution of TBE in DMSO was added dropwise into mixed solution and stirred continuously for 5 h. Through a series of follow-up treatments, the target product **1a** was obtained in 71.4 %, which was much higher yield and low side reactions with TBE than that reported in literature [24]. To obtain high yield and reduce reaction time of compound **1c**, we attempted to choose 4-iodo-*1H*-pyrazole as nucleophile to replace starting material "**1a"** in the literature[23] to synthesize "**1c**", and the synthetic condition was similar to that of compound **1a**, the result found that we have obtained successfully target product **1c** and achieved expected yield.



Scheme 2. The synthetic route of the compounds with alkane – pyrazole derivatives **1a**-**1c**

In addition, we have also studied the optimum synthetic method of benzene – dipyrazole derivatives and corresponding complexes[31]. That is the mixture of pyrazole (or its derivatives) and KOH in DMSO was vigorous stirred for making pyrazole complete deprotonation and then

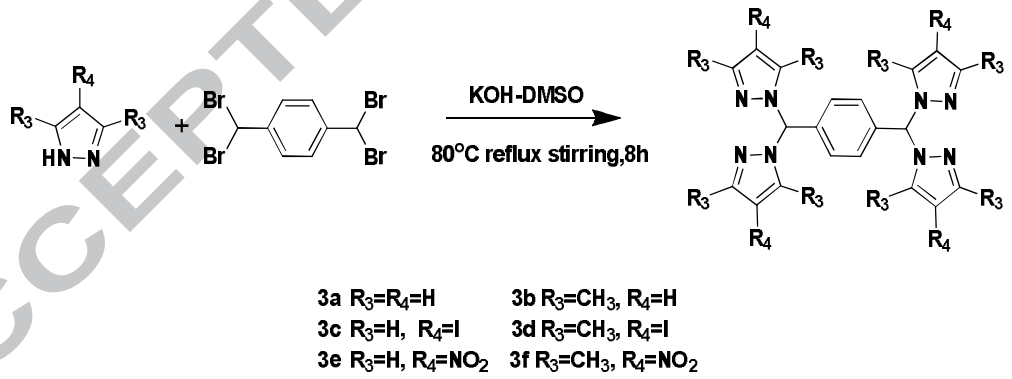
reacted with the solution of 1,4-bis(bromomethyl)benzene in DMSO. After a series of following steps, we obtained compounds **2a** and **2b**. It was considered that 1H-pyrazole occurs readily iodination (nitration) substituted reaction on the C4 atom and coordination modes of the compounds would be varied via introduction of different substituents onto the pyrazole rings, we choose pyrazole derivatives with iodination or nitration group as nucleophile and synthesized successfully four new compounds **2c** - **2f** with -I and NO_2 groups by the similar synthetic method of the compounds **2a** - **2b**.



Scheme 3 The synthetic route of the compounds with benzene – tetrapyrazole derivatives **2a**-**2f**

The facile methods of synthesizing benzene – tetrapyrazole derivatives were shown in **Scheme 4**. The optimization route ideology was similar to that of alkane – pyrazole derivatives: that is controlling primary materials molar ratio and prolonging completely deprotonation reaction time. We obtained higher yields and the products, which were readily isolated by dilution with water and filtration. The additional advantages

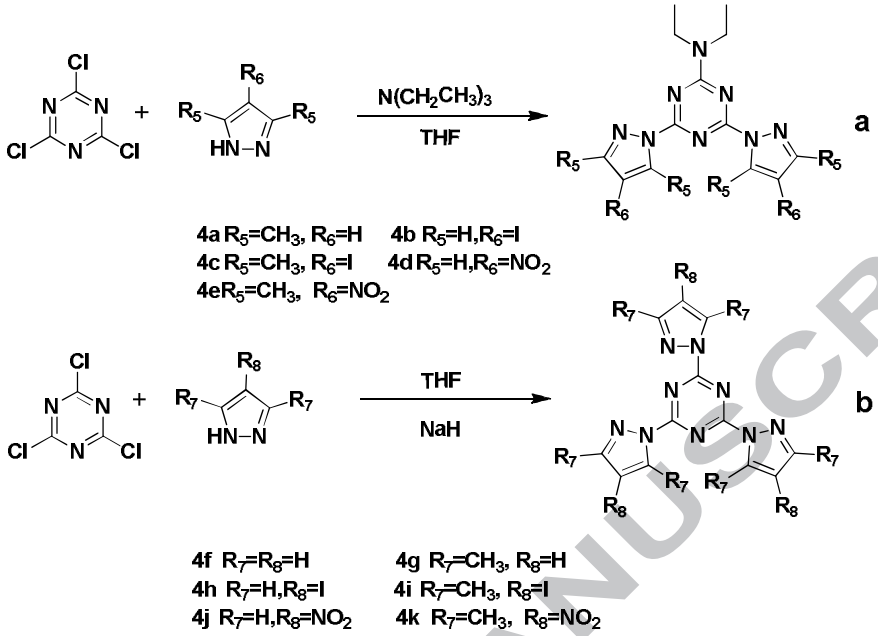
was avoiding the use of toxic phosgene in the traditional route, shortening the reaction time of pyrazole with 1,4-bis(dibromomethyl)benzene and the procedure was more benign from the ecological viewpoint. In addition, we also chosen pyrazole derivatives with -I and NO_2 groups as nucleophile to synthesize successfully a series of new compounds **3c** – **3f**. Through a lot of experimental results, we found that substituted groups and steric hindrance from different substituted groups on the pyrazole ring play a vital role in synthesizing benzene– dipyrazole/tetrapyrazole derivatives. So, synthesizing of the corresponding compounds with CH_3 group on the pyrazole ring would be more difficult than the other compounds and need more time. In addition, it needed more time to synthesize benzene – tetrapyrazole derivatives compounds due to the increasing number of pyrazole and its derivatives.



Scheme 4. The synthetic route of the compounds with benzene – tetrapyrazole derivatives **3a**-**3f**

In order to further investigate synthetic method and explore new compounds, we have also studied the synthetic procedures of 1,3,5-triazine – pyrazole derivatives. The triazine – pyrazole derivatives

were prepared by using a mild, convenient, timesaving and general method with high yield of the product (**Scheme 5**). We adjusted adding sequence of raw materials and modified reaction condition to obtain **4a**: that is 3, 5-dimethylpyrazol was added gradually into the stirring completely the THF solution with cyanuric chloride at room temperature, then, triethylamine was added dropwise to a mixture solution of 3,5-dimethylpyrazole and cyanuric chloride in the THF at room temperature. After stirring for 1 h at room temperature, the solution was refluxed at 80 °C for 5 h and then filtered to get desired compound. We attempted to change 3,5-dimethylpyrazole into pyrazole derivatives for obtaining new compounds and synthesized successfully **4b** – **4e** for the first time with the same reaction condition. In the mean time, we used the similar optimum reaction condition to obtain **4f – 4g**. For completely deprotonation of the pyrazole, the pyrazole in the anhydrous THF was added dropwise into completely mixed solution of NaH in the anhydrous THF at room temperature for 1 h. Subsequently, the anhydrous THF with cyanuric chloride was added dropwise into the refluxing mixture and the mixture refluxed at 70 °C for 5 h, at last, we obtained successfully a series of novel compounds **4h** – **4k** with the similar reaction route. In the exploration of synthetic routes, both the adding order of raw materials and different reaction temperature during the synthesizing process were essential factors.



Scheme 5. The synthetic route of the compounds with triazine – pyrazole derivatives **4a**-**4k**

2.2 Structural description

The complexes with multi - pyrazole and its derivatives were reported in many literatures, but few compounds with – I and -NO_2 substituted groups were studied. Here, we reported mainly some compounds with the multi - pyrazole of the - I and -NO_2 substituted groups. Crystallographic data and the structure refinement were given in **Table 1**. The selected bond lengths and bond angles were listed in **Table S1**.

$C_{14}H_{10}N_{12}O_8 \cdot 2DMSO$ (**1b**). Compound **1b** is crystallized in the triclinic system with *P-1* space group. X-ray single crystal analysis indicates that the asymmetric unit of the compound **1b** consists of an half of the compound **1b** molecule and one free DMSO molecule (Fig. 1a).

Four 4-nitro-pyrazolyl moieties are linked by the "-CH-CH-" moiety to form a N-heterocyclic compound which has trans-symmetrical molecular configuration. There are three kinds of hydrogen bondings among the carbon atoms from pyrazole or CH-CH moiety and the oxygen atom from the lattice DMSO molecule to form a trifurcated hydrogen bond (Fig. 1b): C2-H2···O5$^{\#1}$, C4-H4···O5$^{\#1}$ and C5-H5···O5$^{\#1}$[C2-H2···O5$^{\#1}$, 3.123(7) Å, 131.1°; C4-H4···O5$^{\#1}$, 3.076(6), 139.7°; C5-H5···O5$^{\#1}$, 3.188(7), 130.5°, #1: 2-x, 1-y, 1-z.].

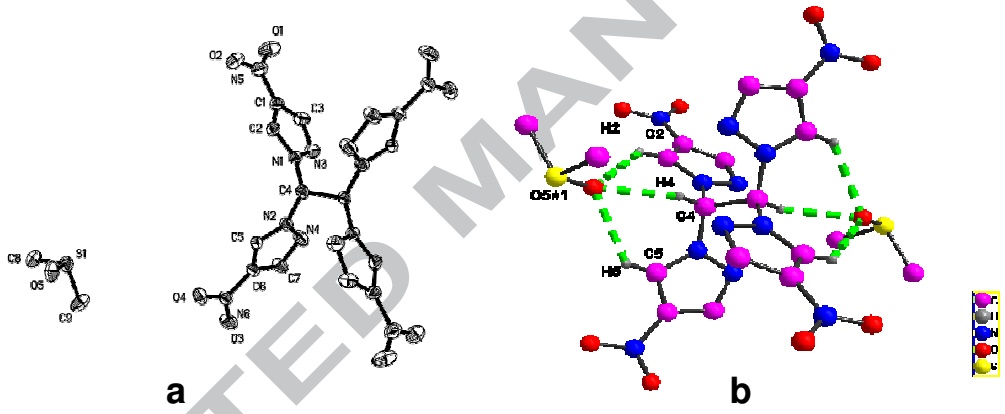


Fig.1 (a) molecular structure of compound **1b**; (b) a view of hydrogen bonds in **1b**. (a part of hydrogen atoms are omitted for clarity) (#1: 2-x, 1-y, 1-z).

$C_{14}H_{10}N_8I_4 \cdot 2DMF$ (**1c**). Single crystal X-ray diffraction analysis reveals that compound **1c** crystallizes in the monoclinic, space group $P2_1/n$. Similarly, the asymmetric unit of compound **1c** contains half a **1c** molecule and one lattice DMF molecule (Fig. 2a). Four 4-iodo-pyrazole moieties are linked by the "-CH-CH-" moiety to form a N-heterocyclic compound which has trans-symmetrical molecular configuration. In

addition, in the molecular packing of the compound **1c**, there are hydrogen bondings to occur, as illustrated in Fig. 2b: hydrogen bonding between the carbon from the pyrazole and the oxygen from the lattice DMF molecule, C5-H5A···O5$^{\#2}$ (C5-H5A···O5$^{\#2}$: 3.214(7) Å, 167.0°, #2: 1-x, 1-y, 2-z.).

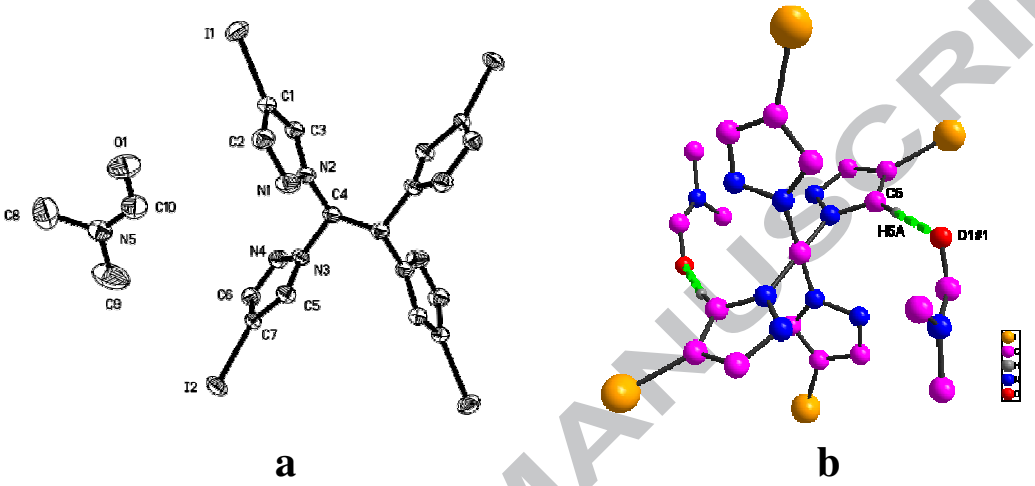


Fig.2 (a) molecular structure of compound **1c**; (b) a view of hydrogen bonds in **1c**. (a part of hydrogen atoms are omitted for clarity) (#2: 1-x, 1-y, 2-z).

$C_{14}H_{10}N_8I_4$·2DMF (**1c-1**). We obtained compound **1c-1** which is different from compound **1c** in crystal system and space group, temperature re-crystallized for the two compounds is distinct. **1c-1** is crystallized in the triclinic system with *P-1* space group. The asymmetric unit of the compound **1c-1** is made up of an half of the **1c-1** molecule and one lattice DMF molecule (Fig.3). The -CH-CH- moiety links four 4-iodo-pyrazole moieties to form a N-heterocyclic compound with trans-symmetrical molecular configuration.

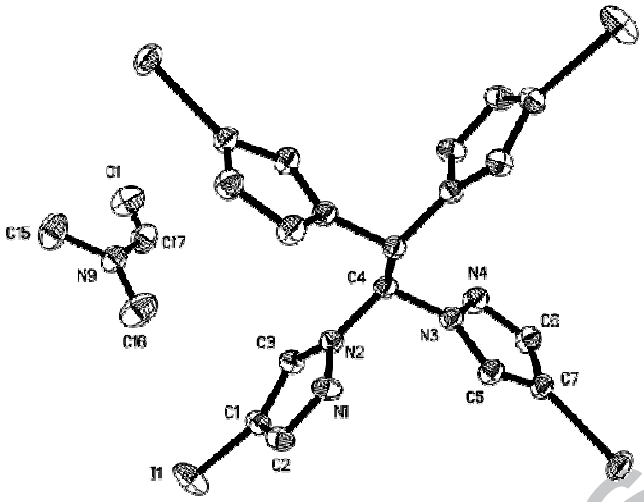


Fig.3 molecular structure of compound **1c-1**.(a part of hydrogen atoms are omitted for clarity)

$C_{14}H_{12}N_4I_2$ (**2c**). Single crystal X-ray diffraction analysis reveals that compound **2c** crystallizes in the monoclinic, space group $P2_1/n$. The asymmetric unit of compound **2c** contains an half of **2c** molecule (Fig. 4a). Two 4-iodo-pyrazole moieties are linked by the para-xylene moiety to form a N-heterocyclic compound with the structural feature of chair conformation. The dihedral angle between benzene ring and pyrazole ring is 76.51(34)°.

$C_{18}H_{20}N_4I_2$ (**2d**). Compound **2d** is crystallized in the monoclinic system with $P2_1/c$ space group. X-ray single crystal analysis indicates that the asymmetric unit of the compound **2d** consists an half of **2d** molecule (Fig. 4b). The para-xylene moiety links two 4-iodo-3,5-dimethyl-pyrazole moieties to form a N-heterocyclic compound which has the structural of tensional chair conformation. The

dihedral angle between benzene ring and pyrazole ring is 84.56(0.41)°.

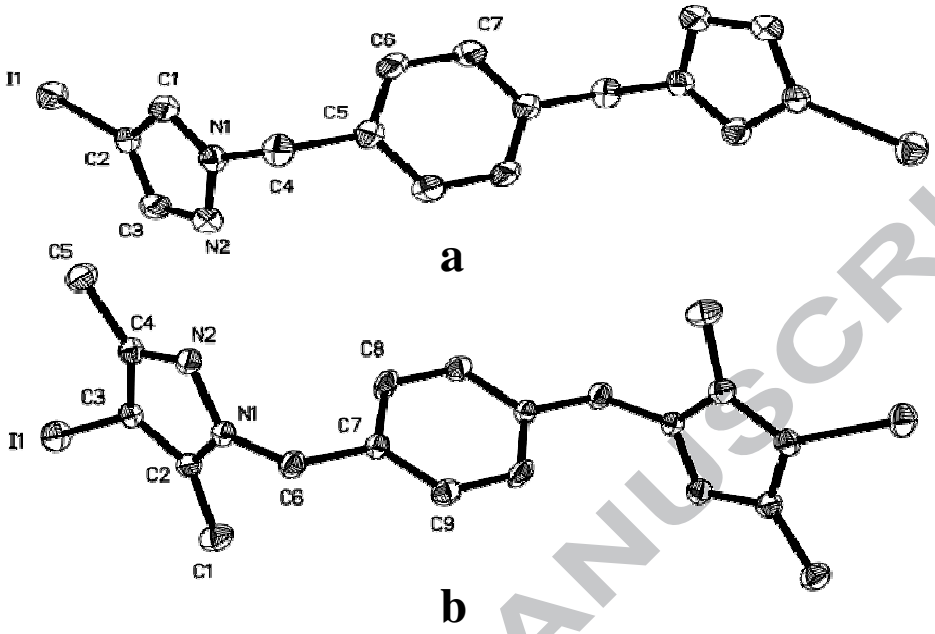


Fig.4 (a) molecular structure of compound **2c**; (b) molecular structure of compound **2d** (a part of hydrogen atoms are omitted for clarity)

$C_{14}H_{12}N_6O_4$ (**2e**) Single crystal X-ray diffraction analysis reveals that compound **2e** crystallizes in the monoclinic system with space group $P2_1/c$. Structural analysis shows that there is an half of the **2e** molecule in the asymmetric unit (Fig. 5a). Two 4-nitro-pyrazole moieties are linked by para-xylene moiety to form a N-heterocyclic compound which has the structural of chair conformation. The dihedral angle between benzene ring and pyrazole ring is 74.69(16)°. In addition, the adjacent molecules are further linked by intermolecular weak hydrogen bonding interactions between carbon atom from the pyrazole ring and oxygen atom of the nitro group (C7–H7···O2$^{\#3}$, 3.220(4) Å, 162.6°, #3: 1-x, 1-y, -z) to afford a zigzag chain along ac plane (Fig. 5b).

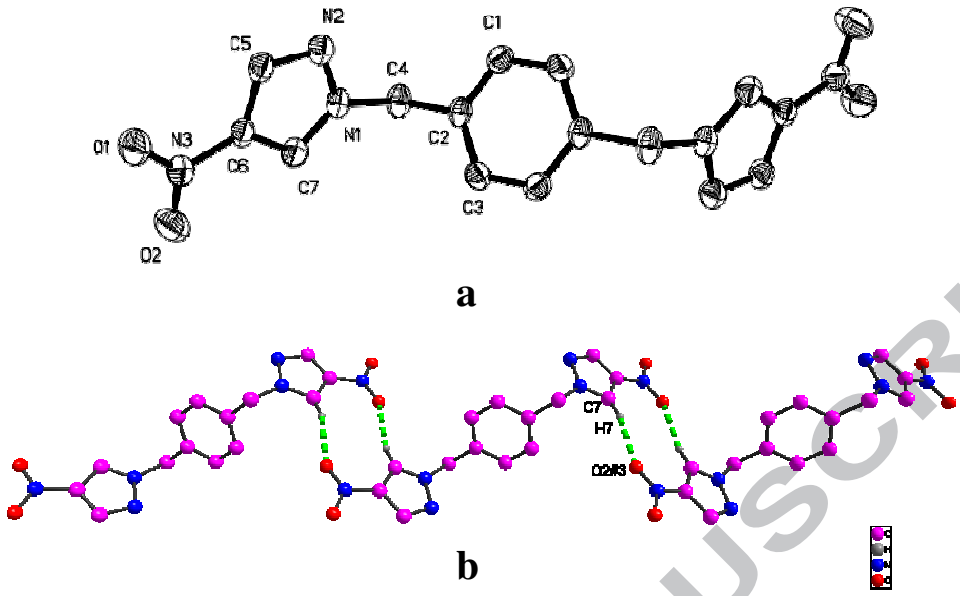


Fig.5 (a) molecular structure of compound **2e** (b) a view of hydrogen bonds in **2e**. (a part of hydrogen atoms are omitted for clarity) (#3: 1-x, 1-y, -z).

$C_{20}H_{14}N_8I_4$ (**3c**) Single crystal X-ray diffraction analysis reveals that compound **3c** crystallizes in the triclinic, space group *P1*. The asymmetric unit of compound **3c** contains an half of **3c** molecule (Fig. 6(a)). Four 4-iodo-pyrazole moieties are linked by a para-xylene moiety to form the N-heterocyclic compound with the trans-symmetrical structure. The dihedral angles between benzene ring and pyrazole ring are 72.07(54)° and 75.12(53)°, the dihedral angle between pyrazole ring with pyrazole ring is 68.93(32)°.

$C_{13}H_{14}N_8I_2$. (**4b**) Compound **4b** is crystallizing in monoclinic, space group $P2_1/c$. The asymmetric unit of compound **4b** consists an half of the **4b** molecule (Fig. 6(b)). The triazine moity links two 4-iodo-pyrazole moieties to form a N-heterocyclic compound. The dihedral angles between triazine ring and pyrazole ring are 3.51(28)° and

10.81(29)°.

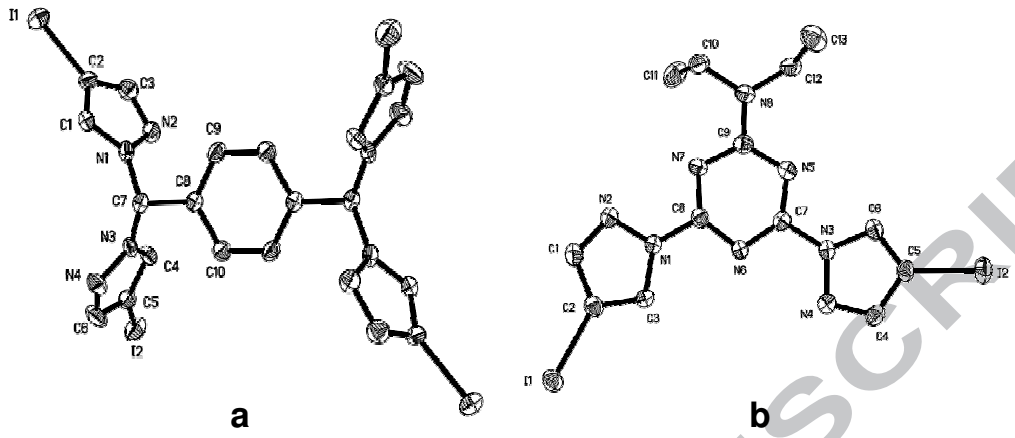


Fig. 6 (a) molecular structure of compound **3c** (b) molecular structure of compound **4b** (a part of hydrogen atoms are omitted for clarity)

By comparison of these structural characterization, it is found that the pyrazole ring and linkers are not in the same plane: (i) for the alkane – pyrazole derivatives and benzene – pyrazole derivatives, the pyrazole rings are linked by the linkers easily to form the N-heterocyclic compound of multi-coordination sites, which has trans-symmetrical structure or the characteristic of chair conformation; (ii) the small dihedral angle between triazine ring and pyrazole ring is formed easily in triazine – pyrazole derivatives. By comparison of corresponding bond lengths on the pyrazole ring (**Table 2**), it is found that the bond lengths of C-N and C-C are in the close range in the corresponding compounds, especially, the distances of C_{pz} – I and C_{pz} - N_{nitro} are close very much.

Table1 Crystallographic data for compounds

compounds	**1b**	**1c**	**1c-1**	**2c**	**2d**	**2e**	**3c**	**4b**
formula	$C_{18}H_{22}N_{12}O_{10}S_2$	$C_{20}H_{24}I_4N_{10}O_2$	$C_{20}H_{24}I_4N_{10}O_2$	$C_{14}H_{12}I_2N_4$	$C_{18}H_{20}I_2N_4$	$C_{14}H_{12}N_6O_4$	$C_{20}H_{14}I_4N_8$	$C_{13}H_{14}I_2N_8$
M (g mol^{-1})	630.60	944.09	944.09	490.08	546.18	328.30	873.99	536.12
Crystal system	Triclinic	Monoclinic	Triclinic	Triclinic	Monoclinic	Monoclinic	Triclinic	Monoclinic
Space group	*P-1*	*P2$_1$/c*	*P1*	*P-1*	*P2$_1$/c*	*P2$_1$/c*	*P1*	*P2$_1$/c*
a/Å	8.6812(17)	8.9094(11)	5.6438(8)	4.5306(10)	7.5347(11)	11.151(2)	5.4245(8)	8.644(2)
b/Å	9.5183(19)	11.0749(13)	9.6032(14)	8.2058(18)	14.945(2)	4.5954(9)	11.6688(18)	16.631(4)
c/Å	10.382(2)	16.5832(16)	14.003(2)	11.009(2)	8.7180(12)	14.707(3)	12.4309(19)	12.285(3)
α(°)	89.222(2)	90	76.079(2)	73.492(2)	90	90	99.592(2)	90
β(°)	67.749(2)	115.053(5)	83.613(2)	82.107(3)	95.782(2)	106.20(3)	91.753(2)	91.006(3)
γ(°)	64.594(2)	90	83.802(2)	75.042(3)	90	90	98.072(2)	90
V (Å^3)	705.7(2)	1482.3(3)	729.48(18)	378.22(14)	976.7(2)	723.7(2)	767.0(2)	1765.9(7)
Z	1	2	1	1	2	2	1	4
D_{calc} (g cm^{-3})	1.484	2.115	2.149	2.152	1.857	1.507	1.892	2.017
crystal size (mm)	0.31×0.23×0.19	0.64x0.55x0.49	0.55x0.25x0.09	0.67x0.19x0.17	0.53x0.21x0.15	0.46x0.31x0.26	0.45x0.37x0.22	0.46x0.14x0.07
F(000)	326	884	442	230	524	340	402	1016
μ(Mo-Kα)/mm^{-1}	0.261	4.240	4.308	4.153	3.227	0.115	4.083	3.573
θ (°)	2.15 to 27.03	2.28 to 24.00	2.19 to 26.00	2.66 to 25.00	2.72 to 25.00	3.81 to 27.45	2.22 to 25.00	2.06 to 26.65
Reflections collected	4155	6651	3786	1875	4795	6409	3705	9666
Independent reflections (I>2σ(I))	2995(1937)	2329(2075)	2784(2303)	1299(1224)	1706(1527)	1641(961)	2654(2272)	3637(2631)
Parameters	192	167	175	91	111	109	152	210
Δ(ρ) (e Å^{-3})	2.796, -0.682	0.510, -1.063	0.978, -1.169	0.844, -1.384	0.425, -1.879	0.156, -0.221	1.832, -1.229	0.464, -0.720

Goodness of fit	1.070	1.083	1.084	1.266	1.210	1.053	1.084	1.041
R^a	0.0997(0.1366)[b]	0.0311(0.0359)[b]	0.0382(0.0470)[b]	0.0342(0.0359)[b]	0.0412(0.0449)[b]	0.0582(0.1053)[b]	0.0521(0.0593)[b]	0.0351(0.0572)[b]
$wR_2{}^a$	0.2837(0.3225)[b]	0.0707(0.0731)[b]	0.0926(0.0978)[b]	0.1060(0.1071)[b]	0.1043(0.1070)[b]	0.1198(0.1371)[b]	0.1891(0.1970)[b]	0.0734(0.0828)[b]

*[a] $R = \Sigma||Fo|-|Fc||/\Sigma|Fo|$, $wR_2 = \{\Sigma[w(F_o^2-F_c^2)^2]/\Sigma[w(F_o^2)^2c^{1/2}$; $[F_o > 4\sigma(F_o)]$.

[b] Based on all data

Table 2. Comparison of related bond lengths (Å) for compounds

compounds	C_{pz}-C_{pz}	C_{pz}=C_{pz}	C_{pz}-N_{pz}	C_{pz}=N_{pz}	N_{pz}-N_{pz}	C_{pz}-I	C_{pz}-N_{nitro}
1b	1.403(8), 1.386(7)	1.370(8), 1.366(7)	1.340(6), 1.342(6)	1.317(7), 1.327(7)	1.366(6), 1.363(6)		1.432(7),1.437(6)
1c	1.391(8), 1.393(7)	1.359(7), 1.363(6)	1.344(6), 1.344(6)	1.322(7), 1.318(6)	1.359(5), 1.363(5)	2.080(5), 2.067(5)	
1c-1	1.395(7), 1.400(7)	1.369(7), 1.359(7)	1.348(6), 1.355(6)	1.320(7), 1.318(7)	1.365(5), 1.358(6)	2.068(5), 2.071(5)	
2c	1.383(8)	1.379(8)	1.343(8)	1.328(8)	1.360(7)	2.066(6)	
2d	1.403(7)	1.369(7)	1.349(6)	1.337(7)	1.362(5)	2.073(5)	
2e	1.384(3)	1.373(3)	1.321(3)	1.321(3)	1.365(3)		1.417(3)
3c	1.383(13),1.381(12)	1.374(12),1.373(14)	1.350(10),1.358(10)	1.321(12),1.358(13)	1.359(9), 1.329(10)	2.087(8),2.058(9)	
4b	1.404(6), 1.394(7)	1.342(6), 1.344(6)	1.370(5), 1.357(6)	1.314(6), 1.328(6)	1.363(5), 1.376(5)	2.077(5), 2.068(5)	

2.3 Antibacterial activity of the compounds and complexes 1-5

Antibacterial activity of the compounds and the complexes[31] were assayed in vitro for their ability to inhibit the growth of representative Gram-positive bacteria (Staphyloccocus aureus and Bacillus subtilis), Gram-negative (Escherichia coli and Pseudomonas aeruginosa) bacteria and the fungus Candida albicans. The susceptibilities of certain strains of bacteria and a fungus to the compounds and their complexes were evaluated by measuring the area of the bacteria-inhibiting ring: $S = \pi (R^2 - r^2)$ (R: radius of the bacteria-inhibiting ring; r: the radius of one piece of the filter paper). The results are given in **Table 3** and **Table S2** for the compounds and complexes.

In our work, we observed that compound **2b** and complexes **1** - **5** have varying degrees of antibacterial activities for all the bacteria and fungus. Most of them were found to be more active against Gram-positive bacteria than Gram-negative bacteria. Compounds **3a** and **3e** exhibited only the inhibiting effect to the Gram-positive bacteria and compound **3b** displayed better inhibiting effect to the Bacillus subtilis. In the experiments, it was worthwhile to note that (i) all of the compounds and complexes with antibacterial activities demonstrated the inhibiting effect in a dose-dependent manner; (ii) all of them showed the inhibiting effect to the Staphyloccocus aureus, their inhibitory effect was ordered as: **5** > **3e** > **2** > **4** > **1** > **3** > **2b** > **3a** > **3b**.

Based on the data in the **Table 3**, it was found that 3- and 5- positions of the pyrazole ring were substituted by electron-donating $-CH_3$ group, which would make the electron cloud density of pyrazole ring increasing, resulting in compounds exhibiting antibacterial activity in the benzene–dipyrazole derivatives. In which $-NO_2$ group was a withdrawing electron group and -I group was the cation with large ion

radius. Both reduced the electron density of the pyrazole ring. The benzene-tetrapyrazole derivatives showed only antibacterial activity against Gram-positive bacteria and their inhibitory effect was ordered as: **3e > 3a > 3b** (the substituted groups on the pyrazole ring for **3e** was NO_2, for **3b** was $-CH_3$ and no substituted group for **3a**). According to the structure of the compound, it was found that the antibacterial activity enhanced with the electron cloud density decreasing in the benzene - tetrapyrazole derivatives. The larger steric hindrance could result in low antibacterial activity of the compounds (**3c**, **3d** and **3f**). While the complexes exhibited common antibacterial activity against all the four bacteria and fungus. It was interesting to find that metal ions can improve inhibitory ability of the compound or made the compound to exhibit better antibacterial activity. At the same time, we also found that the kind of the metal ion would affect the result for the antibacterial activity. Complexes **2** and **3** were of similar structures with different central metal ions, but they exhibited respective excellence of the antibacterial activity against Gram-positive bacteria, Gram-negative bacteria and the fungus. The analysis result of antibacterial activity for some triazine – pyrazole derivatives found they have not any antibacterial activity (**Table S2**).

Table 3. Antibacterial activities for some the compounds and related complexes **1**-**5**

compound	Dose (μg)	Area of the zone (mm^2)				
		S. aureus	*B. subtilis*	*E. coil*	*P. aeruginosa*	*C. albicans*
2a	480	0.00	0.00	0.00	0.00	0.00
	240	0.00	0.00	0.00	0.00	0.00
	120	0.00	0.00	0.00	0.00	0.00
	60	0.00	0.00	0.00	0.00	0.00
2b	480	160.37	79.51	19.63	19.63	71.72
	240	79.51	40.84	12.78	19.63	33.45
	120	0.00	33.45	0.00	19.63	26.67
	60	0.00	15.58	0.00	0.00	0.00
2c	480	0.00	0.00	0.00	0.00	0.00
	240	0.00	0.00	0.00	0.00	0.00
	120	0.00	0.00	0.00	0.00	0.00
	60	0.00	0.00	0.00	0.00	0.00
2d	480	0.00	0.00	0.00	0.00	0.00

	240	0.00	0.00	0.00	0.00	0.00
	120	0.00	0.00	0.00	0.00	0.00
	60	0.00	0.00	0.00	0.00	0.00
	480	0.00	0.00	0.00	0.00	0.00
2e	240	0.00	0.00	0.00	0.00	0.00
	120	0.00	0.00	0.00	0.00	0.00
	60	0.00	0.00	0.00	0.00	0.00
	480	0.00	0.00	0.00	0.00	0.00
2f	240	0.00	0.00	0.00	0.00	0.00
	120	0.00	0.00	0.00	0.00	0.00
	60	0.00	0.00	0.00	0.00	0.00
	480	131.85	108.57	0.00	0.00	19.63
3a	240	104.89	63.62	0.00	0.00	0.00
	120	87.96	48.41	0.00	0.00	0.00
	60	55.70	0.00	0.00	0.00	0.00
	480	71.72	867.80	0.00	0.00	0.00
3b	240	12.78	517.70	0.00	0.00	0.00
	120	0.00	222.14	0.00	0.00	0.00
	60	0.00	141.37	0.00	0.00	0.00
	480	0.00	0.00	0.00	0.00	0.00
3c	240	0.00	0.00	0.00	0.00	0.00
	120	0.00	0.00	0.00	0.00	0.00
	60	0.00	0.00	0.00	0.00	0.00
	480	0.00	0.00	0.00	0.00	0.00
3d	240	0.00	0.00	0.00	0.00	0.00
	120	0.00	0.00	0.00	0.00	0.00
	60	0.00	0.00	0.00	0.00	0.00
	480	431.81	222.14	0.00	0.00	0.00
3e	240	255.38	123.05	0.00	0.00	0.00
	120	180.67	71.72	0.00	0.00	0.00
	60	79.51	40.84	0.00	0.00	0.00
	480	0.00	0.00	0.00	0.00	0.00
3f	240	0.00	0.00	0.00	0.00	0.00
	120	0.00	0.00	0.00	0.00	0.00
	60	0.00	0.00	0.00	0.00	0.00
	480	244.35	190.47	141.37	123.05	160.37
1	240	122.87	104.89	104.89	87.96	123.05
	120	71.56	71.72	66.93	63.62	55.70
	60	26.53	19.63	40.84	26.67	25.63
	480	473.97	267.04	48.41	79.51	79.51
2	240	244.57	185.55	26.67	48.41	48.41
	120	141.37	87.96	0.00	12.78	0.00
	60	87.96	19.63	0.00	0.00	0.00
	480	201.06	201.06	233.26	131.85	211.83
3	240	123.05	141.37	160.37	104.89	104.89
	120	87.96	87.96	19.63	87.96	26.67
	60	26.67	0.00	0.00	0.00	0.00
	480	290.19	201.06	87.96	87.96	79.51
4	240	201.06	104.89	40.84	40.84	40.84
	120	141.37	87.96	40.84	26.67	40.84
	60	79.51	40.84	40.84	0.00	26.67
	240	563.00	487.79	211.83	201.06	326.57
5	120	391.22	445.13	141.37	180.67	222.14
	60	364.52	314.75	104.89	79.51	180.67
	30	290.19	302.38	123.05	63.62	79.51

3. Conclusions

We have developed a practical and efficient route for synthesizing compounds with multi - pyrazole and its derivatives and successfully synthesized twelve novel pyrazole compounds with -I or -NO_2 substituted group. In the mean time, antibacterial activities of the some compounds and complexes are assayed. It is found that some of them could be used as potential antibacterial agents.

4. Experimental section

4.1 Materials and General procedure

All chemicals purchased were of reagent grade or better and were used without further purification. Biological reagent: Staphyloccocus aureus, Bacillus subtilis, Escherichia coli, Pseudomonas aeruginosa and Candida albicans were obtained from Dalian Medical University, Department of Biochemistry. The tryptone and yeast extract were purchased from OXOID. The gelatine was purchased from BIOSHARP. The complexes **1** – **5** were synthesized by the method of the literature[31]. The infrared spectra were recorded on a JASCO FT/IR-480 PLUS Fourier Transform spectrometer with pressed KBr pellets in the range 200–4000 cm^{-1}. Melting points were determined by *X*-5 precision melting point apparatus. The ^{1}H NMR and ^{13}C NMR spectra were recorded on BrukerAV-500 apparatus ($CDCl_3$ or DMSO-d_6 as solvent, TMS internal standard). Elemental analyses for C, H, and N were carried out on a Perkin Elmer 240C automatic analyzer.

4.2 X-ray single crystal structural determinations

Suitable single crystals of compounds were mounted on glass fibers for X-ray measurement, respectively. Reflection data were collected at room temperature on a Bruker AXS SMART APEX II CCD diffractermeter with graphite-monochromatized Mo-Ka radiation (λ= 0.71073 Å) and a ω scan mode. All the measured independent

reflections ($I>2\sigma(I)$) were used in the structural analyses, and semi-empirical absorption corrections were applied using SADABS program[32]. The structures were solved by the direct method using SHELXL-97 program[33].

4.3 Antibacterial activity methods

The bacteria-inhibiting ring method was applied to measure the anti-bacterial effects of benzene - pyrazole derivatives, a part of triazine - pyrazole derivatives and complexes **1** - **5** on the growths of the bacterium strains of Staphyloccocus aureus, Bacillus subtilis, Escherichia coli, Pseudomonas aeruginosa and Candida albicans. The five types of strains were made into bacterial culture plates by the four section line method and the plates were incubated at 37 °C for 17 h. The single colony was shook cultivation (37 °C, 160 r/min) in 5 mL of the LB liquid medium for 17 h. The bacterial suspensions were measured the absorbance at 600nm and diluted to OD_{600} = 0.1 (8.5×10^9 CFU/L). Then, 100 μL of the suspensions were coated evenly on the LB solid plate surface and put one piece of filter paper (diameter = 6mm) with autoclave and drying on the center of the plate. 10 μL of DMSO was added into the filter paper as negative control and four pieces of the filter paper were pasted evenly around it in the periphery. The four pieces of the filter paper were added respectively 10μL of different concentrations samples from high to low in clockwise. The plate was incubated at 37 °C in the incubator for 17 h, and then measured the diameter of the bacteria-inhibiting ring (accurate to 1 mm).

4.4 Preparation of alkane – pyrazole derivatives 1a - 1c

4.4.1 ***1,1,2,2-tetra(1H-pyrazol-1-yl)ethane*** (**1a**). A mixture of 13.88 g (0.2 mol) of pyrazole, 13.66 g (0.2 mol) of finely powdered potassium hydroxide, and 50 ml of DMSO was stirred at 80 °C. After 1 h, a

solution of 5.83 mL (0.05 mol) of TBE in 50 mL of DMSO was added dropwise to the resulting suspension, the mixture continue to stir for 5 h. Then, the reaction mixture was allowed to cool then diluted with 1000 mL of ice water. The precipitate was filtered off, washed with water and dried under reduced pressure. Obtaining as a white solid in 71.4 % (10.50 g), m. p.: 271 – 273 °C. IR (KBr, ν/cm^{-1}): 3136, 3117, 2994, 1521, 1310, 1052. ^{1}HNMR (500 MHz, $CDCl_3$, δ/ppm): 6.13 (t, 4H, 4-H-pz), 7.47 (d, 4H, 3-H-pz), 7.65 (d, 4H, 5-H-pz), 7.83 (s, 2H). Calc. for $C_{14}H_{14}N_8$: C, C, 57.13; H,4.79; N, 38.07. Found: 57.09; H, 4.67; N, 38.26 %.

4.4.2 ***1,1,2,2-tetrakis(4-nitro-1H-pyrazol-1-yl)ethane*** (**1b**). A mixture of 0.29 g (1.00 mmol) of compound **1a**, 1.3 ml of 68% nitric acid (20.0 mmol of HNO_3), and 6 ml of 98% sulfuric acid was kept for 24 h at room temperature. The mixture was then diluted with an ice–water mixture (150 mL). The precipitate was filtered off, washed with water and dried under reduced pressure. Compound **1b** was dissolved in 5 mL DMSO at room temperature and the crystals for X-ray measurement were obtained after 3 days. Obtaining as a white solid in 81 % (0.33 g), m. p.: > 280 °C. IR (KBr, ν/cm^{-1}): 3141, 3109, 3012, 1514, 1313, 1003, 1542, 1329. ^{1}HNMR (500 MHz, DMSO-d_6, δ/ppm): 9.22(s, 4H, 5-H-pz), 8.77(s, 2H, CH), 8.44(s, 4H, 3-H-pz). ^{13}CNMR (125 MHz, DMSO-d_6, δ/ ppm): 137.55, 135.99, 131.85, 71.69. Calc. for $C_{14}H_{10}N_{12}O_8$: C, 35.45; H,2.13; N, 35.44. Found: C, 35.37; H, 2.07; N, 35.61 %.

4.4.3 ***1,1,2,2-tetrakis(4-iodo-1H-pyrazol-1-yl)ethane*** (**1c**). A mixture of 3.88 g (0.02 mol) of 4-iodo-*1H*-pyrazole, 1.37 g (0.02 mol) of finely powdered potassium hydroxide, and 15 mL of DMSO was stirred at 80 °C. After 30 min, a solution of 0.58 mL (0.005 mol) of TBE in 10 mL of DMSO was added dropwise to the resulting suspension, the

mixture was stirred for 2 h. The reaction mixture was allowed to cool then diluted with 1000 mL of ice water. The precipitate was filtered off, washed with water and dried under reduced pressure. We obtained single crystals **1c** and **1c-1** for X-ray measurement with different recrystallization condition. Compound **1c** was dissolved in 10 mL DMF at room temperature to obtain single crystals **1c** for X-ray measurement after 5 days. Compound **1c** was dissolved in 10 mL DMF at 50 °C for 2h and then the solution was stored at room temperature to obtain single crystals **1c-1** for X-ray measurement after 5 days. Obtaining as a white solid in 86.7 % (3.46 g), m. p.: ＞280 °C. IR (KBr, ν/cm^{-1}): 3125, 3112, 2987, 1510, 1310, 1107, 611. ^{1}HNMR (500 MHz, DMSO-d_6, δ/ppm): 8.28(s, 2H, CH), 8.27(s, 4H, 5-H-pz), 7.57(s, 4H, 3-H-pz). ^{13}CNMR (125 MHz, DMSO-d_6, δ/ppm): 145.39, 135.95, 71.62, 59.05. Calc. for $C_{14}H_{10}N_8I_4$: C, 21.07; H,1.26; N, 14.04 Found: C, 21.16; H, 1.15; N, 14.31.%.

4.5 General experimental procedures for preparation of benzene – dipyrazole derivatives 2a-2f

4.5.1 ***1,4-bis((1H-pyrazol-1-yl)methyl)benzene*** (**2a**). A mixture of 1.02 g (15 mmol) of pyrazole, 1.02 g (15 mmol) of finely powdered potassium hydroxide, and 10 ml of DMSO was stirred at 80 °C. After 1 h, a solution of 1.98 g (7.5 mmol) of 1,4-bis(bromomethyl)benzene in 10 mL of DMSO was added dropwise to the resulting suspension, the mixture was stirred for 5 h. The reaction mixture was allowed to cool then diluted with 200 mL of water. The precipitate was filtered off, washed with the mixture of ethanol and water, dried under reduced pressure. Obtaining as a white powder in 68.9 % (1.23 g), m. p.: 111.5-112.1°C. IR (KBr, ν/cm^{-1}): 3116, 3090, 2934, 2857, 1611 1516, 1451, 1516 1285, 1051, 808,. ^{1}HNMR (500 MHz, $CDCl_3$, δ/ppm): 7.53(d, 2H, H^5-pz, J=1.7Hz), 7.36(d, 2H, H^3-pz, J=2.2Hz), 7.17(s, 4H, ph), 6.27(t, 2H, H4-pz,

J=2.1Hz), 5.30(s, 4H, CH_2). ^{13}CNMR (125 MHz, $CDCl_3$, δ/ppm): 139.62, 136.55, 129.24, 128.04, 106.02, 55.52. Calc. for $C_{14}H_{14}N_4$: C,70.57; H,5.92; N, 23.51. Found: C, 70.49; H, 5.88; N, 23.63%.

4.5.2 ***1,4-bis((3,5-dimethyl-1H-pyrazol-1-yl)methyl)benzene*** (**2b**). A mixture of 1.47 g (15 mmol) of 3,5-dimethylpyrazole, 1.02 g (15 mmol) of potassium hydroxide, and 10 ml of DMSO was stirred at 80 ℃ for 1 h. A solution of 1.98 g (7.5 mmol) of 1,4-bis(dibromomethyl)benzene in 10 ml of DMSO was added dropwise, the mixture was stirred for 8 h at 80 ℃, diluted with 200 ml of water, and the precipitate was filtered off ,washed with the mixture of ethanol and water, dried under reduced pressure. Obtaining a white powder in 61.2 % (1.35 g), m. p.: 101-102℃. IR (KBr, ν/cm^{-1}): 3123, 3030, 2934, 2860, 1610 1548, 1461, 1511 1308, 1026,797. ^{1}HNMR (500 MHz, $CDCl_3$, δ/ppm): 7.00(s, 4H, ph), 5.82(s, 2H, H^4-pz), 5.16(s, 4H, CH_2), 2.22(s, 6H, 5-CH_3-pz), 2.12(s, 6H, 3-CH_3-pz). ^{13}CNMR (125 MHz, $CDCl_3$, δ/ppm): 147.58, 139.11, 136.68, 126.92, 105.54, 52.23, 13.48, 11.07. Calc. for $C_{18}H_{22}N_4$: C, 73.44; H, 7.53; N, 19.03. Found: C, 73.57; H,7.32; N, 19.11 %.

4.5.3 ***1,4-bis((4-iodo-1H-pyrazol-1-yl)methyl)benzene*** (**2c**). Compound **2c** could be obtained by the similar synthetic procedures as compound **2a**, but the starting material 4-iodo-1H-pyrazol (2.19 g, 15 mmol) instead of pyrazole. The single crystals **2c** for X-ray measurement were obtained from methanol at room temperature after 3 days. Obtaining a white solid in the yield of 76.5 % (2.81 g), m. p.: 157-158℃. IR (KBr, ν/cm^{-1}): 3121, 2986, 2946, 1594, 1515, 1438, 1505, 1279, 1108, 801. ^{1}HNMR (500 MHz, $CDCl_3$, δ/ppm): 7.53(s, 2H, H^5-pz), 7.40(s, 2H, H^3-pz), 7.20(s, 4H, ph), 5.28(s, 4H, CH_2). ^{13}CNMR (125 MHz, $CDCl_3$, δ/ppm): 144.76, 136.10, 133.67, 128.37, 56.62, 56.01. Calc. for $C_{14}H_{12}N_4I_2$: C, 34.31; H, 2.47; N, 11.43. Found: C, 34.23; H, 2.55; N, 11.38 %.

4.5.4 ***1,4-bis((4-iodo-3,5-dimethyl-1H-pyrazol-1-yl)methyl)benzene*** (**2d**). Compound **2d** could be obtained by the similar synthetic procedures as compound **2b**, but the starting material 4-iodo-3,5-dimethyl-1*H*-pyrazole (3.33 g, 15 mmol) instead of 3,5-dimethylpyrazole. The single crystals **2d** for X-ray measurement were obtained from methanol at room temperature after 3 days. Obtaining a white solid with yield of 88.4 % (3.63 g), m. p.: 188-191°C. IR (KBr, ν/cm^{-1}): 3015, 2986, 2946, 1638, 1529, 1473, 1516, 1311, 1060, 799. ^{1}HNMR (500 MHz, $CDCl_3$, δ/ppm): 7.02(s, 4H, ph), 5.23(s, 4H, CH_2), 2.23(s, 6H, 5-CH_3-pz), 2.16(s, 6H, 3-CH_3-pz). ^{13}CNMR (125 MHz, $CDCl_3$, δ/ppm): 149.55, 140.68, 136.29, 127.16, 63.27, 53.59, 14.04, 12.04. Calc. for $C_{18}H_{20}N_4I_2$: C, 39.58; H, 3.69; N, 10.26. Found: C, 39.46; H, 3.55; N, 10.31 %.

4.5.5 ***1,4-bis((4-nitro-1H-pyrazol-1-yl)methyl)benzene*** (**2e**). Compound **2e** could be obtained by the similar synthetic procedures as compound **2a**, but the starting material 4-nitro-1*H*-pyrazole (1.70 g, 15 mmol) instead of pyrazole. The single crystals **2e** for X-ray measurement were obtained from methanol at room temperature after 3 days. Obtaining a yellow solid in 65.4 % (1.61 g), m. p.: 269.9-271°C. IR (KBr, ν/cm^{-1}): 3139, 3119, 2923, 2852, 1605, 1530, 1435, 1498, 1306, 1004, 824. ^{1}HNMR (500 MHz, DMSO-d_6, δ/ppm): 9.02(s, 2H, H^5-pz), 8.25(s, 2H, H^3-pz), 7.34(s, 4H, ph), 5.39(s, 4H, CH_2). ^{13}CNMR (125 MHz, DMSO-d_6, δ/ppm): 135.91, 135.68, 135.04, 130.58, 128.36, 55.37. Calc. for $C_{14}H_{12}N_6O_4$: C, 51.22; H, 3.68; N, 25.60. Found: C, 51.18; H, 3.59; N, 25.68 %.

4.5.6 ***1,4-bis((4-nitro-3,5-dimethyl-1H-pyrazol-1-yl)methyl)benzene*** (**2f**). Compound **2f** could be obtained by the similar synthetic procedures as compound **2b**, but the starting material 4-nitro-3,5-dimethyl-1*H*-pyrazol (2.12 g, 15 mmol) instead of 3,5-dimethylpyrazole. Obtaining a yellow solid in 61.8 % (1.78 g), m. p.: 188-191°C. IR (KBr, ν/cm^{-1}):

3041(=CH); 2991, 2851(CH_3); 1630, 1561, 1443(ph); 1488, 1308, 999(pz); 813(=CH). ^{1}HNMR (500 MHz, DMSO-d_6, δ/ppm): 7.13(s, 4H, ph), 5.24(s, 4H, CH_2), 2.55(s, 6H, 5-CH_3-pz), 2.52(s, 6H, 3-CH_3-pz). ^{13}CNMR (125 MHz, DMSO-d_6, δ/ppm): 146.38, 140.29, 135.26, 127.67, 53.20, 14.14, 11.69. Calc. for $C_{18}H_{20}N_6O_4$: C, 56.24; H, 5.24; N, 21.86. Found: C, 56.18; H, 5.17; N, 21.94 %.

4.6 General experimental procedures for preparation of benzene – tetrapyrazole derivatives 3a-3f

4.6.1 ***1,4-bis(di(1H-pyrazol-1-yl)methyl)benzene*** **(3a).** A mixture of 1.02 g (15 mmol) of pyrazole, 1.02 g (15 mmol) of finely powdered potassium hydroxide, and 10 ml of DMSO was stirred at 80 °C. After 1 h, a solution of 1.98 g (3.75 mmol) of 1,4-bis(dibromomethyl)benzene in 10 mL of DMSO was added dropwise to the resulting suspension, the mixture was stirred for 8 h. The reaction mixture was allowed to cool then diluted with 200 mL of water. The precipitate was filtered off, washed with the mixture of ethanol and water, dried under reduced pressure. Obtaining a yellow solid in 78 % (1.08 g), m. p.: 168-169°C. IR (KBr, ν/cm^{-1}): 3132, 3017, 2963, 2939, 1622, 1513, 1431, 1513, 1360, 1043, 797. ^{1}HNMR (500 MHz, DMSO-d_6, δ/ppm): 7.72(s, 2H, CH), 7.62(d, 4H, H^5-pz, J=1.6Hz), 7.54(d, 4H, H^3-pz, J=2.4Hz), 7.02(s, 4H, ph), 6.33(t, 4H, H^4-pz, J_1=2.15, J_2=2.05Hz). ^{13}CNMR (125 MHz, $CDCl_3$, δ/ppm): 140.90, 137.52, 129.78, 127.50, 106.79, 77.36. Calc. for $C_{20}H_{18}N_8$: C, 64.85; H, 4.90; N, 30.25. Found: C, 64.77; H, 5.05; N, 30.18 %.

4.6.2 ***1,4-bis(bis(3,5-dimethyl-1H-pyrazol-1-yl)methyl)benzene*** **(3b)**. Compound **3b** could be obtained by the similar synthetic procedures as compound **3a**, but the starting material 3,5-dimethylpyrazole (1.47 g 15 mmol) instead of pyrazole. Obtaining a yellow solid in 86.7 % (1.16 g), m. p.: 102-103 °C. IR (KBr, ν/cm^{-1}): 3132, 3024, 2946, 2922, 1619,

1557, 1464, 1514, 1301, 1033, 837. ^{1}HNMR (500 MHz, $CDCl_3$, δ/ppm): 7.60(s, 2H, CH), 6.89(s, 4H, ph), 5.83(s, 4H, H^4-pz), 2.19(s, 24H, CH_3). ^{13}CNMR (125 MHz, $CDCl_3$, δ/ppm): 148.80, 141.02, 137.12, 127.14, 106.91, 73.64, 13.70, 11.84. Calc. for $C_{28}H_{34}N_8$: C, 69.68; H, 7.10; N, 23.22. Found: C, 69.61; H, 7.23; N, 23.16 %.

4.6.3 ***1,4-bis(bis(4-iodo-1H-pyrazol-1-yl)methyl)benzene*** (**3c**). Compound **3c** could be obtained by the similar synthetic procedures as compound **3a**, but the starting material 4-iodo-1H-pyrazol (2.19 g, 15 mmol) instead of pyrazole. The single crystals **3c** for X-ray measurement were obtained from ethyl acetate at room temperature after 3 days. Obtaining a white solid in 87.0 % (2.85 g), m. p.: 154-155 °C. IR (KBr, ν/cm^{-1}): 3125, 3090, 2960, 1594, 1514, 1432, 1318, 1022, 795. ^{1}HNMR (500 MHz, DMSO-d_6, δ/ppm): 8.10(s, 2H, CH), 8.04(s, 4H, H^5-pz), 7.71(s, 4H, H^3-pz), 7.18(s, 4H, ph). ^{13}CNMR (125 MHz, DMSO-d_6, δ/ppm): 145.19, 136.99, 134.64, 127.50, 75.77, 59.04. Calc. for $C_{20}H_{14}N_8I_4$: C, 27.48; H, 1.61; N, 12.82. Found: C, 27.61; H, 1.48; N, 12.71 %.

4.6.4 ***1,4-bis(bis(4-iodo-3,5-dimethy-1H-pyrazol-1-yl)methyl)benzene*** (**3d**). Compound **3d** could be obtained by the similar synthetic procedures as compound **3a**, but the starting material 4-iodo-3,5-dimethyl-1*H*-pyrazole (3.33 g, 15 mmol) instead of pyrazole. Obtaining a white solid in 85% (3.13 g), m. p.: 186-189 °C. IR (KBr, ν/cm^{-1}): 3101, 2954, 2922, 1617, 1538, 1471, 1515, 1300, 1060, 781. ^{1}HNMR (500 MHz, $CDCl_3$, δ/ppm): 7.67(s, 2H, CH), 6.92(s, 4H, ph), 2.24(s, 12H, 5-CH_3-pz), 2.20(s, 12H, 3-CH_3-pz). ^{13}CNMR (125 MHz, $CDCl_3$, δ/ppm): 150.66, 142.38, 136.30, 127.28, 75.14, 66.00, 14.29, 12.98. Calc. for $C_{28}H_{30}N_8I_4$: C, 34.10; H, 3.07; N, 11.36. Found: C, 34.16; H, 2.89; N, 11.27 %.

4.6.5 ***1,4-bis(bis(4-nitro-1H-pyrazol-1-yl)methyl)benzene*** (**3e**).

Compound **3e** could be obtained by the similar synthetic procedures as compound **3a**, but the starting material 4-nitro-1*H*-pyrazole (1.70 g, 15 mmol) instead of pyrazole. Obtaining a yellow solid in 78 % (1.63 g), m. p.: 241.2-241.4 °C. IR (KBr, ν/cm^{-1}): 3131, 2923, 2852, 1611, 1539, 1513, 1488, 1409, 1003, 824. ^{1}HNMR (500 MHz, DMSO-d_6, δ/ppm): 9.04(s, 4H, H^{5}-pz), 8.47(s, 4H, H^{3}-pz), 8.32(s, 2H, CH), 7.44(s, 4H, ph). ^{13}CNMR (125 MHz, $CDCl_3$, δ/ppm): 137.03, 135.88, 134.72, 131.38, 128.36, 76.80. Calc. for $C_{20}H_{14}N_{12}O_8$: C, 43.64; H, 2.56; N, 30.54. Found: C, 43.58; H, 2.54; N, 30.62 %.

4.6.6 ***1,4-bis(bis(4-iodo-3,5-dimethy-1H-pyrazol-1-yl)methyl)benzene*** (**3f**). Compound **3f** could be obtained by the similar synthetic procedures as compound **3a**, but the starting material 4-nitro-3,5-dimethyl-1*H*-pyrazol (2.12 g, 15 mmol) instead of pyrazole. Obtaining a white solid in 75 % (2.12 g), m. p.: ＞280 °C. IR (KBr, ν/cm^{-1}): 3133, 2966, 2928, 1606, 1570, 1500, 1368, 1302, 1001, 813. ^{1}HNMR (500 MHz, $CDCl_3$, δ/ppm): 7.75(s, 2H, CH), 7.10(s, 4H, ph), 2.64(s, 12H, 5-CH_3-pz), 2.51(s, 12H, 3-CH_3-pz). ^{13}CNMR (125 MHz, $CDCl_3$, δ/ppm): 147.44, 142.53, 142.27, 134.90, 130.04, 127.58, 123.5, 74.64. Calc. for $C_{28}H_{30}N_{12}O_8$: C, 50.75; H, 4.56; N, 25.37. Found: C, 50.69; H, 4.48; N, 25.47 %.

4.7 General experimental procedures for preparation of triazine – pyrazole derivatives 4a-4k

4.7.1

2,4-bis(3,5-dimethy-1H-pyrazol-1-yl)-6-diethylamino-1,3,5-triazine (**4a**). A solution of 1.85 g (0.01 mol) of 2,4,6-trichloro-1,3,5-triazine in the 50 mL THF was stirred at room temperature for 1 h. Then, 3,5-dimethylpyrazole (2.94 g, 0.03 mmol) were added into the solution in batches. 5mL of triethylamine was added dropwise whilst stirring at

room temperature. After 1 h, the mixture was heated at 80 °C for 1 h. After cooling and filtering off, the filtrate evaporated on a steam bath and then washed with hot - water. Obtaining a white solid in 85 % (2.88 g), m. p.: 99.6-100.6°C. IR (KBr, ν/cm^{-1}): 3108, 2970, 2930, 1601, 1517, 1399, 1030, 808. ^{1}HNMR (500 MHz, $CDCl_3$, δ/ppm): 6.02(s, 2H, H^4-pz), 3.67(q, 4H, CH_2, NCH_2CH_3, J_1=J_2=7.1Hz), 2.69(s, 6H, 5-CH_3-pz), 2.32(s, 6H, 3-CH_3-pz), 1.25(t, 6H, CH_3, NCH_2CH_3, J_1=J_2=7.1Hz). ^{13}CNMR (125 MHz, $CDCl_3$, δ/ppm): 167.78, 163.68, 151.78, 143.33, 110.98, 42.29, 15.63, 13.64, 12.86. Calc. for $C_{17}H_{24}N_8$: C, 59.98; H, 7.11; N, 32.92. Found: C, 59.87; H, 7.08; N, 32,96 %.

4.7.2 ***2,4-bis(4-iodo-1H-pyrazol-1-yl)-6-diethylamino-1,3,5-triazine*** (**4b**). Compound **4b** could be obtained by the similar synthetic procedures as compound **4a**, but the starting material 4-iodo-1H-pyrazol (4.85 g, 0.025 mol) instead of 3,5-dimethylpyrazole. The single crystals **3c** for X-ray measurement were obtained from ethyl acetate at room temperature after 3 days. Obtaining a white solid in 84 % (4.50 g), m. p.: ＞280 °C. IR (KBr, ν/cm^{-1}): 3144, 2978, 2931, 1605, 1514, 1383, 1034, 808. ^{1}HNMR (500 MHz, $CDCl_3$, δ/ppm): 9.06 (s, 2H, H^5-pz), 7.99(s, 2H, H^3-pz), 3.72(q, 4H, CH_2, NCH_2CH_3), 1.21(t, 6H, CH_3, NCH_2CH_3). Calc. for $C_{13}H_{14}N_8I_2$: C, 29.12; H, 2.63; N, 20.90. Found: C, 29.04; H, 2.58; N, 20.86 %.

4.7.3

2,4-bis(4-iodo-3,5-dimethy-1H-pyrazol-l-yl)-6-diethylamino-1,3,5-triazine (**4c**). Compound **4c** could be obtained by the similar synthetic procedures as compound **4a**, but the starting material 4-iodo-3,5-dimethyl-1*H*-pyrazole (5.55 g, 0.025 mol) instead of 3,5-dimethylpyrazole. Obtaining a white solid in 87 % (5.15 g), m. p.: 212.6-214.5 °C. IR (KBr, ν/cm^{-1}): 2969, 2930, 1596, 1514, 1404, 1012,

807. ^{1}HNMR (500 MHz, $CDCl_3$, δ/ppm): 3.70(q, 4H, CH_2, NCH_2CH_3), , 2.77(s, 6H, 5-CH_3, pz), 2.34(s, 6H, 3-CH_3-pz) 1.26(t, 6H, CH_3, NCH_2CH_3). Calc. for $C_{17}H_{22}N_8I_2$: C, 34.48; H, 3.74; N, 18.92. Found: C, 34.40; H, 3.68; N, 18.89 %.

4.7.4 ***2,4-bis(bis(4-nitro-1H-pyrazol-1-yl)-6-diethylamino-1,3,5-triazin*** **(4d)**. Compound **4d** could be obtained by the similar synthetic procedures as compound **4a**, but the starting material 4-nitro-1*H*-pyrazole (2.83 g, 0.025 mol) instead of 3,5-dimethylpyrazole. Obtaining a white solid in 81 % (3.03 g), m. p.: 178.4-179.1°C. IR (KBr, ν/cm^{-1}): 3148, 3103, 2974, 1608, 1517, 1404, 1004, 815. ^{1}HNMR (500 MHz, $CDCl_3$, δ/ppm): 8.60(s, 2H, H^5-pz), 8.57(s, 2H, H^3-pz), 3.73(q, 4H, CH_2, NCH_2CH_3), 1.22(t, 6H, CH_3, NCH_2CH_3). Calc. for $C_{13}H_{14}N_{10}O_4$: C, 41.71; H, 3.77; N, 17.10. Found: C, 41.65; H, 3.68; N, 17.09 %.

4.7.5

2,4-bis(bis(4-nitro-3,5-dimethyl-1H-pyrazol-1-yl)-6-diethylamino-1,3,5-triazine (**4e**). Compound **4e** could be obtained by the similar synthetic procedures as compound **4a**, but the starting material 4-nitro-3,5-dimethyl-1*H*-pyrazol (3.53 g, 0.025 mol) instead of 3,5-dimethylpyrazole. Obtaining as a white solid in 81 % (3.57 g), m. p.: 180-182 °C. IR (KBr, ν/cm^{-1}): 2981, 2934, 1597, 1509, 1377, 1001, 811. ^{1}HNMR (500 MHz, $CDCl_3$, δ/ppm): 3.72(q, 4H, CH_2, NCH_2CH_3), 3.01(s, 6H, 5-CH_3-pz), 2.94(s, 6H, 3-CH_3-pz), 1.23(t, 6H, CH_3, NCH_2CH_3). Calc. for $C_{17}H_{22}N_{10}O_4$: C, 47.44; H, 5.15; N, 32.54. Found: C, 47.35; H, 5.06; N, 32.50 %.

4.7.6 ***2,4,6-tri(1H-pyrazol-1-yl)methyl)-1,3,5-triazine*** (**4f**). A solution of pyrazole (2.04 g, 0.03 mol) in freshly distilled THF (20 mL) was added to a stirred suspension of sodium hydride (60 %, 2.04 g, 0.03 mol) in 20 mL THF at room temperature. After 1 h, Cyanuric chloride (1.85 g, 0.01 mol) in THF (15 mL) was added to the above solution and white

precipitate was formed. After being stirred and heating at 70 ℃ for 5 h, the solution was filtered off, the filtrate evaporated on a steam bath, and then washed with hot - water. *2,4,6-tri(1H-pyrazol-1-yl)methyl)-1,3,5-triazine*. Obtaining a white solid in 84 % (2.34 g), m. p.: 228.2-229.0 ℃. IR (KBr, ν/cm^{-1}): 3215, 3090, 2924, 2853, 1578, 1532, 1459, 1038, 807. ^{1}HNMR (500 MHz, $CDCl_3$, δ/ppm): 8.81(d, 3H, H^5-pz, J=2.5Hz), 7.97(d, 3H, H^3-pz, J=0.5Hz), 6.61(t, 3H, H^4-pz, J_1=J_2=1.5Hz). ^{13}CNMR (125 MHz, $CDCl_3$, δ/ppm): 163.78, 146.11, 130.77, 110.44. Calc. for $C_{12}H_9N_9$: C, 51.61; H, 3.25; N, 45.14. Found: C, 51.08; H, 3.17; N, 45.09 %.

4.7.7 ***2,4,6-tri(3,5-dimethylpyrazol-1-yl)-1,3,5-triazine*** (**4g**). Compound **4g** could be obtained by the similar synthetic procedures as compound **4f**, but the starting material 3,5-dimethylpyrazole (2.94 g, 0.03 mol) instead of pyrazole. Obtaining a white solid in 83 % (3.01 g), m. p.: 250.7-251.9 ℃. IR (KBr, ν/cm^{-1}): 2980, 2928, 1595, 1556, 1416, 1028, 810. ^{1}HNMR (500 MHz, $CDCl_3$, δ/ppm): 6.09(s, 3H, H^4-pz,), 2.08(s, 9H, 5-CH_3-pz), 2.33(s, 9H, 3-CH_3-pz). ^{13}CNMR (125 MHz, $CDCl_3$, δ/ppm): 164.37, 153.45, 144.35, 111.95, 15.54, 13.93. Calc. for $C_{18}H_{21}N_9$: C, 59.49; H, 5.82; N, 34.69. Found: C, 59.37; H, 5.78; N, 34.60 %.

4.7.8 ***2,4,6-tri(4-iodo-1H-pyrazol-1-yl)-1,3,5-triazine*** (**4h**). Compound **4h** could be obtained by the similar synthetic procedures as compound **4f**, but the starting material 4-iodo-1H-pyrazol (5.82 g, 0.03 mol) instead of pyrazole. Obtaining a white solid in 80 % (5.26 g), m. p.: ＞290 ℃. IR (KBr, ν/cm^{-1}): 3134, 2963, 1574, 1524, 1389, 959, 806. ^{1}HNMR (500 MHz, DMSO-d_6, δ/ppm): 9.22(s, 3H, H^5-pz), 8.08(s, 3H, H^3-pz). ^{13}CNMR (125 MHz, DMSO-d_6, δ/ppm): 159.58, 149.60, 135.43, 134.04. Calc. for $C_{12}H_6N_9I_3$: C, 21.94; H, 0.92; N, 19.19. Found: C, 21.87; H,

0.89; N, 19.14 %.

4.7.9 ***2,4,6-tri(4-iodo-3,5-dimethyl-1H-pyrazol-1-yl)-1,3,5-triazine*** (**4i**). Compound **4i** could be obtained by the similar synthetic procedures as compound **4f**, but the starting material 4-iodo-3,5-dimethyl-1*H*-pyrazole (6.67 g, 0.03 mol) instead of pyrazole. Obtaining a white solid in 78 % (5.78 g), m. p.: ＞290 °C. IR (KBr, ν/cm^{-1}): 2953, 2924, 1579, 1544, 1412, 1005, 806. ^{1}HNMR (500 MHz, $CDCl_3$, δ/ppm): 2.61(s, 9H, 5-CH_3-pz), 2.25(s, 9H, 3-CH_3-pz). Calc. for $C_{18}H_{18}N_9I_3$: C, 29.17; H, 2.45; N, 17.01. Found: C, 29.09; H, 2.38; N, 16.97 %.

4.7.10 ***2,4,6-tri(4-nitro-1H-pyrazol-1-yl)-1,3,5-triazine*** (**4j**). Compound **4j** could be obtained by the similar synthetic procedures as compound **4f**, but the starting material 4-nitro-1*H*-pyrazole (3.39 g, 0.03 mol) instead of pyrazole. Obtaining a white solid in 70 % (2.90 g), m. p.: ＞280 °C. IR (KBr, ν/cm^{-1}): 3148, 3106, 2924, 2853, 1579, 1519, 1412, 1032, 823. ^{1}HNMR (500MHz, DMSO-d6, δ/ppm)：9.41 (s, 3H, H5-pz)，8.72(s, 3H, H3-pz). ^{13}C NMR (125 MHz; DMSO-d_6, δ/ppm)：149.79，135.39，129.71. Calc. for $C_{12}H_6N_{12}O_3$: C, 34.79; H, 1.46; N, 40.57. Found: C, 34.72; H, 1.43; N, 40.71 %.

4.7.11 ***2,4,6-tri(4-nitro-3,5-dimethyl-1H-pyrazol-1-yl)-1,3,5-triazine*** (**4k**). Compound **4k** could be obtained by the similar synthetic procedures as compound **4f**, but the starting material 4-nitro-3,5-dimethyl-1*H*-pyrazol (4.23 g, 0.03 mol) instead of pyrazole. Obtained as a white solid in 76 %, mp: 251.3-252.8 °C. IR (KBr, ν/cm^{-1}): 3215, 3071, 2925, 1592, 1512, 1412, 1001, 807. ^{1}HNMR (500 MHz, $CDCl_3$, δ/ppm): 2.94(s, 9H, 5-CH_3-pz), 2.51(s, 9H, 3-CH_3-pz). Calc. for $C_{18}H_{18}N_{12}O_6$: C, 43.31; H, 3.69; N, 19.19. Found: C, 43.38; H, 3.64; N, 19.26 %.

Supplementary material

Tables of atomic coordinates, an isotropic thermal parameters, and complete bond distances and angles have been deposited with the Cambridge Crystallographic Data Center. Copies of this information may be obtained free of charge, by quoting the publication citation and deposition numbers CCDC: 1035902 for **1b**, 1035903 for **1c**, 1035904 for **1c-1**, 1035905 for **2c**, 1035906 for **2d**, 1035907 for **2e**, 1035908 for **3c** and 1035909 for **4b**, from the Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44–1223–336033; E–mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

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Highlights:

1 The optimum synthetic route of the compounds with multi-pyrazole and its derivatives was developed.

2 Twelve new compounds were synthesized

3 Some multi - pyrazole compounds and the corresponding complexes were assayed in vitro for their biological activity.

Molecular design and the optimum synthetic route of the compounds with multi-pyrazole and its derivatives and the potential application in antibacterial agents

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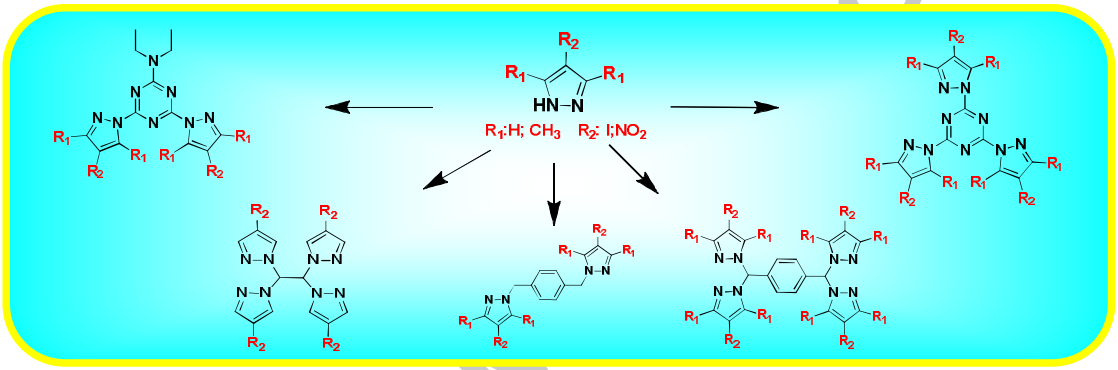

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The optimum synthetic route for a series of compounds with multi-pyrazole and its derivatives were developed, and twelve of theses compounds were synthesized for the first time. All the compounds were characterized by element analysis, IR, HNMR, M.P. and X-ray diffraction. Some compounds and corresponding complexes were assayed in vitro for their biological activity.