Syntheses, Characterization, and Antibacterial Activities of Four New Schiff Base Compounds Derived from 1-Phenyl-3-methyl-4-benzoyl-2-pyrazolin-5-one

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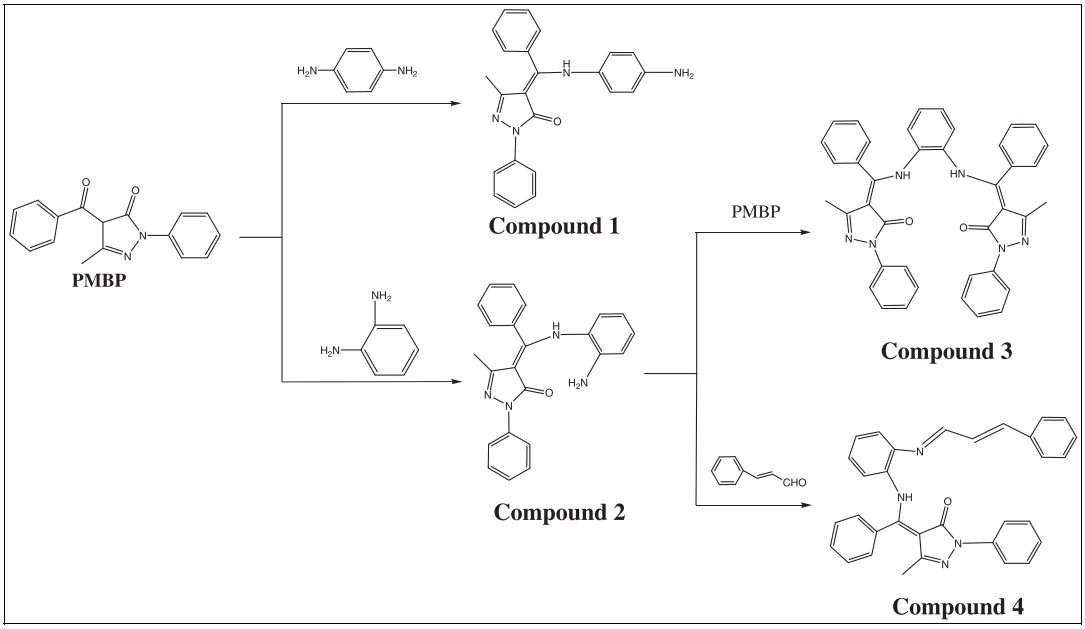

Four new Schiff bases were designed and synthesized. 5-Methyl-4-(4-aminophenylamino-phenyl-methylene)-2-phenyl-2,4-dihydro-pyrazol-3-one (compound **1**) and 5-methyl-4-(2-aminophenylamino-phenyl- methylene)-2- phenyl-2,4- dihydro-pyrazol-3- one (compound **2**) were synthesized by interaction of 1- phenyl -3- methyl - 4- benzoyl-2- pyrazolin -5- one (PMBP) with *o* - and *p*-phenylenediamine, respectively; 4,4′- (1,2 - phenylenebis(azanediyl)bis(phenylmethanylylidene))bis(3 - methyl -1- phenyl -1H - pyrazol - 5(4H) - one) (compound **3**) and 5 - methyl - 4 - (phenyl(2- ((3- phenylallylidene)amino)phenylamino)methylene)-2-phenyl-2,4-dihydro-pyrazol-3-one (compound **4**) were synthesized by interaction of compound **2** with PMBP and cinnamaldehyde in an ethanolic medium, respectively. The molecular structures of the title compounds were first characterized by single-crystal X-ray diffraction, mass spectrometry, and elemental analysis. The title compounds were tested for antibacterial activity (*Escherichia coli*, *Staphylococcus aureus*, and *Bacillus subtilis*) by disk diffusion method.

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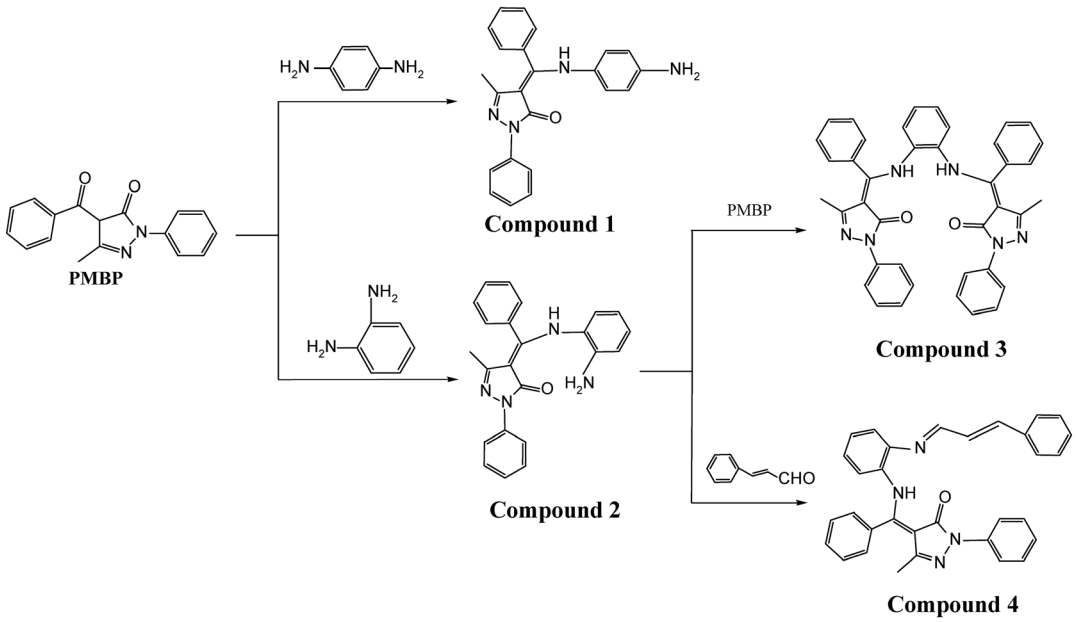
INTRODUCTION

Schiff bases are well known not only for thermochromism and photochromism in the solid state [1] but also for their pharmacological properties as antibacterial agents, antifungal bioactivities, and antitumor and inhibitory activities against viruses [2–12]. In particular, much attention has been paid on heterocyclic Schiff base because of its super biological activity [13,14]. 1-Phenyl-3-methyl-4-benzoyl-2-pyrazolin-5-one (PMBP) is a representative nitrogen heterocyclic diketone chelating agent [15], which has been extensively applied in the extraction of lanthanides, actinides, and radioactive chemical separation analysis early years [16,17]. Recently, Schiff bases derived from PMBP and their metal complexes have been widely studied in pharmaceutical activity and catalysis [18–22], although Schiff bases with PMBP and diamine were ignored. Taking into consideration all the features described above, we report the syntheses, structural characterization, and antibacterial activities of four new Schiff base compounds derived from PMBP and phenylenediamines (*o*- or *p*-phenylenediamine) in this work, the reaction sequence is outlined in Scheme 1.

RESULTS AND DISCUSSION

Crystal structure of compounds 1–4. The molecular structures of four compounds were determined from single-

Scheme 1. Syntheses of compounds **1**–**4**.



crystal X-ray studies. Experimental details for X-ray data collection of compounds **1**–**4** are presented in Table 1. Oak Ridge Thermal-Ellipsoid Plot Program (ORTEP) diagrams of compounds **1**–**4** with the atom numbering schemes are shown in Figure 1. In compound **1**, rings a, b, and c adopt "three lobe motorfan"-like conformation, the C7 atom is the "axis", and rings a, b, and c are "lobes", as shown in Figure 1(I). The following data may be responsible for the "motorfan" conformation. The angles of N3 C7 C14, C14 C7 C8, and N3 C7 C8 are 119.6°, 120.1°, and 120.2°, respectively, which are all close to 120°. In addition, the dihedrals between rings a and b, rings a and c, and rings b and c are 62.0°, 57.4°, and 62.1°, respectively, which are very similar. Two kinds of intramolecular hydrogen bonding interactions (N3—H3A···O1 and C23—H23···O1) exist in the molecule of compound **1** [Fig. 1(I) and Table 2], which favor the "motorfan" conformation. Similar to compound **1**, rings a, b, and c in compound **2** also adopt "three lobe motorfan"-like conformation with three angles all close to 120° (∠N2C7C8 = 120.0°, ∠N2C7C14 = 118.2°, and ∠C14C7C8 = 121.8°), and three dihedrals very similar (∠ab = 65.7°, ∠bc = 65.4°, and ∠ac = 63.6°). There are two intramolecular hydrogen bonding interactions within the molecule of compound **2** [Fig. 1(III) and Table 2], which favor the "motorfan" conformation. Compared with compounds **1** and **2**, neither rings a, b, and c nor rings a, b′, and c′ in compound **3** form a "three lobe motorfan" conformation with very different dihedrals of ∠ab = 65.2°, ∠bc = 63.4°, ∠ac = 89.5°; ∠ab′ = 78.1°, ∠b′c′ = 76.0°, ∠ac′ = 21.8°. There exists one kind of intramolecular C—H···O hydrogen bonding interaction and two kinds of intramolecular N—H···O hydrogen bonding interactions in compound **3**, the data are listed in Table 2. Compound **4** crystallizes in the *P*2/*n* space group with two crystallographically unique molecules in the asymmetric unit. The same as compound **3**, the molecules in compound **4** do not form "three lobe motorfan"-like conformation as the dihedrals of ∠ab, ∠bc, and ∠ac in molecule A with 77.8°, 78.1°, and 45.4°, respectively, and the dihedrals of ∠a′b′, ∠b′c′, and ∠a′c′ in molecule B with 72.7°, 71.7°, and 49.7°, respectively, are very different, as shown in Figure 1 (V). The molecules A and B are associated in pair by two kinds of C—H···O hydrogen bonds [Fig. 1(V)], the data of hydrogen bonding geometries are compiled in Table 2.

That acyl pyrazolone schiff bases often exist in different tautomeric forms such as inime-one, anime-ol, and anime-one forms (Scheme 2) in solid state, and thus, many studies have been made to establish the geometry of these derivatives [23–25]. The C—N distances of the imine moiety of compounds **1**–**4** except C23 N4 and C55 N8 in compound **4** are in the range 1.332–1.346 Å, which are significantly longer than the C=N distances of 1.298 Å [26] and 1.292 Å [27] in pyrazolone compounds, and comparable to C—N (1.342 Å) distance observed in similar pyrazolone compound [28]; and the bond length of C7—C14 in compound **1** and **2,** C10—C8 and C32—C30 in compound **3** and C10—C8 and C42—C38 in compound **4** are in the range 1.374–1.402 Å, which fall into the normal range of C=C double bond; in addition the C—O distances in the pyrazol moiety of compounds **1**–**4** are in the range 1.240–1.251 Å, which are significantly shorter than the distances found for C—O in some pyrazolone derivatives,

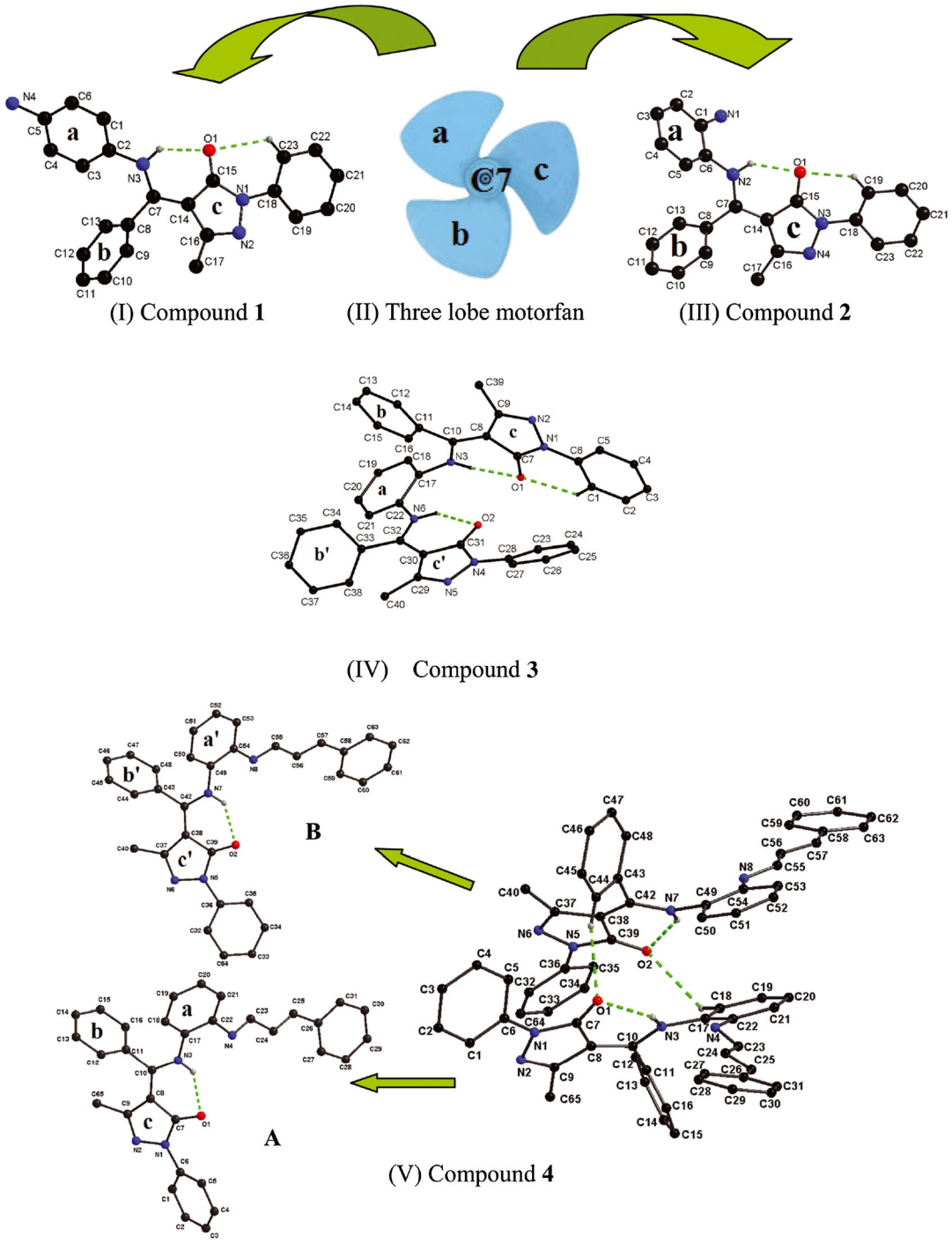


Figure 1. I, III, IV, and V: molecular structures of compounds **1**–**4** showing the atom numbering scheme, dashed lines indicate hydrogen bonds, H atoms not involved in hydrogen bonding have been omitted for clarity; II: scheme of three lobe motorfan conformation. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

1.341, 1.346 Å [29], and 1.331 Å [30], however, they are close to the distances found for C O in similar compounds, 1.262 Å [29] and 1.254 Å [27]. All the above data prove that compounds **1**–**4** exist in amine-one form.

Testing of biological activities. The biological activity of a particular substance relies on a complex sum of individual properties including compound structure, affinity for the target site, survival in the medium of application, survival within the biological system, transport properties, and state of the target organism [7]. In this study, we focused our attention on the structure–activity relationship.

The data of antibacterial activities are summarized in Table 3, which indicate that the synthesized compounds

Table 1

Crystal data for compounds **1**–**4**.

Compound	**1**	**2**	**3**	**4**
Empirical formula	$C_{23}H_{20}N_4O$	$C_{23}H_{20}N_4O$	$C_{40}H_{32}N_6O_2$	$C_{64}H_{52}N_8O_2$
Formula weight	368.43	368.43	628.72	965.14
T (K)	296(2)	296(2)	296(2)	296(2)
Crystal system	Monoclinic	Monoclinic	Triclinic	Monoclinic
Space group	*Cc*	*P*2(1)/*c*	*P*−1	*P*2/*n*
A (Å)	9.944(3)	9.203(2)	10.871(2)	17.097(2)
b (Å)	16.960(3)	21.683(5)	11.584(3)	11.5033(14)
c (Å)	11.172(4)	9.611(2)	13.574(3)	26.830(3)
α (°)	90	90	88.757(3)	90
β (°)	99.635(4)	97.880(3)	75.521(3)	96.028(2)
γ (°)	90	90	82.029(3)	90
V (Å^3)	1857.5(9)	1899.7(8)	1638.9(6)	5247.5(11)
Z	4	4	2	4
F (0 0 0)	776	776	660	2032
Dc (mg m^{-3})	1.317	1.288	1.274	1.222
Goodness-of-fit on F^2	0.987	1.048	0.995	1.121
Data/restraints/parameters	3915/2/255	3517/0/254	6060/0/435	9239/37/670
Final *R* indices [I > 2sigma(I)]	*R*1 = 0.0503	*R*1 = 0.0394	*R*1 = 0.0409	*R*1 = 0.0590
	*wR*2 = 0.0806	*wR*2 = 0.0995	*wR*2 = 0.0695	*wR*2 = 0.0667
R indices (all data)	*R*1 = 0.1416	*R*1 = 0.0535	*R*1 = 0.0861	*R*1 = 0.2080
	*wR*2 = 0.1074	*wR*2 = 0.1102	*wR*2 = 0.0777	*wR*2 = 0.0901
No. data collected	8121	13,995	12,796	38,240
No. unique data	3915	3517	6060	9239
Largest diff. peak and hole (e Å^{-3})	0.174 and −0.179	0.297 and −0.205	0.177 and −0.179	0.184 and −0.157

display antibacterial activities against the tested bacteria and the higher concentration of test samples, the more active against the tested bacteria. Compound **1** has more active against the tested bacteria than isomeric compound **2**, owing to amino group at different locations. As can be seen from Table 3 that symmetrical bis-Schiff base compound **3** is more active against the tested bacteria than compound **2-**single-Schiff base and compound **4**-asymmetrical bis-Schiff base. Compound **3** contains two pyrazole rings, and compounds **2** and **4** both have one pyrazole ring, which indicated that the activity of compounds against bacterial strains decreased when the number of pyrazole ring decreased. The results implied that *N*-heterocycle were helpful in the antibacterial activity of the compounds.

Table 2

Hydrogen-bonding geometries (Å,°) for the title compounds.

Compound	D–H···A	D–H	H···A	D–H···A	∠D–H···A
1	N3–H3a···O1	0.86	2.16	2.796(4)	131
	C23–H23···O1	0.93	2.39	2.960(5)	120
2	N2–H2d···O1	0.86	2.07	2.735(2)	133
	C19–H19···O1	0.93	2.28	2.912(2)	125
3	N3–H3a···O1	0.86	2.02	2.689(2)	135
	N6–H6···O2	0.86	1.92	2.659(2)	144
	C1–H1···O1	0.93	2.25	2.891(3)	125
4	N3–H3a···O1	0.86	2.03	2.733(4)	139
	N7–H7···O2	0.86	2.05	2.741(4)	137
	C18–H18···O2	0.93	2.59	3.230(5)	127
	C44–H44···O1	0.93	2.39	3.293(6)	164

CONCLUSIONS

In this study, four new compounds derived from PMBP were prepared and mainly structural characterized by X-ray diffraction. The molecular structures of the title compounds and intramolecular hydrogen bonding interactions were studied. Biological testing showed that the synthesized Schiff-base compounds displayed antibacterial activities to the three bacteria, and antibacterial activity increased with the increase of concentration. The study on structure–activity relationships of these Schiff base indicated that spatial position and the sum of *N*-heterocycle had influence on antibacterial activities of compounds **1**–**4**.

EXPERIMENTAL

Physical measurements. All reagents were commercially available and used without further purification. Melting points

Scheme 2. Tautomeric forms of acyl pyrazolone derivatives.

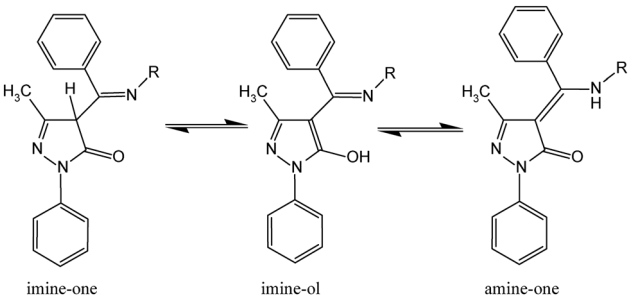


Table 3

Antibacterial activities data of compounds **1**–**4**.

	1	2	3	4
Escherichia coli				
1	0.83	0.68	0.72	–
5	1.21	0.74	0.91	–
10	1.29	0.80	1.10	0.62
15	1.34	0.82	1.15	0.64
20	1.40	0.83	1.20	0.74
25	1.43	0.90	1.23	0.83
Staphylococcus aureus				
1	1.1	–	0.63	–
5	1.15	0.62	1.21	–
10	1.28	0.74	1.32	0.75
15	1.47	0.80	1.48	1.01
20	1.51	0.97	1.55	1.13
25	1.57	1.01	1.62	1.19
Bacillus subtilis				
1	–	0.63	0.80	–
5	+	0.70	1.21	–
10	1.15	0.85	1.32	0.67
15	1.27	0.90	1.41	0.70
20	1.35	1.21	1.54	0.73
25	1.40	1.30	1.61	0.81

were determined on a Micromelting point apparatus and were not corrected. IR spectra were measured as KBr disks on a Nicolet Avatar 5700 FT-IR spectrometer. Elemental analyses were performed with an Elementar Vario EL analyzer. Mass spectra were taken on an Agilent Liquid chromatography–mass spectrometry 6340 series instrument in the electrospray ionization (positive electrospray ionization) mode.

Compound 1. PMBP (0.834 g, 3.0 mmol) and *p*-phenylenediamine (0.378 g, 3.5 mmol) were dissolved in ethanol (40 mL) and the solution was heated under reflux for several hours. The solvent was removed and yellow crystals obtained upon recrystallization from ethanol in about 78% yield. m.p. 209–212 °C. IR (KBr): 3430, 3042, 1626, 1599, 1475, 1421, 1362, 1300, 1250, 1185, 815, 750, 620, 570, 500 cm^{-1}. MS (ES^+) *m/z* 369.1866 [M+H]. Anal. calcd. for $C_{23}H_{20}N_4O$: C, 74.98; H, 5.47; N, 15.21. Found: C, 74.84; H, 5.22; N, 15.46.

Compound 2. The same synthetic procedure as that for compound **1** was used except *p*-phenylenediamine was replaced by *o*-phenylenediamine. The color of product is orange. Yield: 83%. m.p. 229–231 °C. IR (KBr): 3403, 1626, 1583, 1567, 1502, 1395, 1310w, 1050, 850, 750, 700, 660, 590 cm^{-1}. MS (ES^+) *m/z* 369.2342 [M+H]. Anal. calcd. for $C_{23}H_{20}N_4O$: C, 74.98; H, 5.47; N, 15.21. Found: C, 74.93; H, 5.35; N, 15.39.

Compound 3. Compound **2** (0.368 g, 1.0 mmol) and PMBP (0.417 g, 1.5 mmol) were dissolved in ethanol (30 mL) and the solution stirred under room temperature for several hours. The solvent volatilized under the temperature of about 5 °C and the yellow crystals were obtained in about 30% yield after 2 months. m.p. 197–199°C. IR (KBr): 3409, 1617, 1590, 1500, 1390, 1290, 1200, 1080, 1000, 750, 700, 670, 600 cm^{-1}. MS (ES^+) *m/z* 629.4896 [M+H]. Anal. calcd. for $C_{40}H_{32}N_6O_2$: C, 76.41; H, 5.13; N, 13.37. Found: C, 76.56; H, 5.42; N, 13.14.

Compound 4. The same synthetic procedure as that for compound **3** was used except PMBP (0.417 g, 1.5 mmol) was replaced by cinnamaldehyde (0.198 g, 1.5 mmol). The color of product is yellow. Yield: 76%. m.p. 181–183 °C. IR (KBr): 3408, 1626, 1595, 1585, 1505, 1384, 1050, 850, 790, 750, 695, 650, 590 cm^{-1}. MS (ES^+) *m/z* 483.3678 [M+H]. Anal. calcd. for $C_{32}H_{26}N_4O$: C, 79.64; H, 5.43; N, 11.61. Found: C, 79.46; H, 5.25; N, 11.87.

Crystallographic measurement. Single-crystal diffraction data were measured at room temperature in the ω/2θ mode on the Bruker APEX II area detector diffractometer using the graphite-monochromated Mo Kα radiation.

Antibacterial testing. Preliminary *in vitro* tests for antibacterial activity of all compounds have been carried out by disk diffusion method. Antibacterial activities of compounds **1**–**4** against *Escherichia coli*, *Staphylococcus aureus*, and *Bacillus subtilis* have been investigated at the dosages of 1, 10, 15, 20, and 25 mg mL^{-1}, respectively, with the solvent of DMF. The disks with tested substances and the blank (solvent) were added onto Petri dishes inoculated with the tested bacterial strains. After 24-h cultivation at 37°C, diameters of zones of inhibition were determined, DMF was inactive under the applied conditions.

Supplementary material. X-ray crystallographic files (CIF) have been deposited with the Cambridge Crystallographic Data Center, CCDC Nos. 803599–803602 for compound **1**–**4**, respectively. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44-1223-336-033; email: deposit@ccdc.cam.ac.uk or www:http://www.ccdc.cam. ac.uk).

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