Facile Synthesis, Single-Crystal Structure, and Biological Evaluation of Novel Pyrazolo[5,1-*d*][1,2,5]triazepin-4-ones

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A facile ring-enlargement reaction of 2,6-diphenyl-4*H*-pyrazolo[5,1-*c*][1,4]oxazin-4-one is described, generating the pyrazolo[5,1-*d*][1,2,5]triazepin-4-ones in good yields. Structures of the prepared compounds were determined on the basis of IR, ^{1}H- and ^{13}C-NMR, and HR-MS data. Moreover, the molecular structure was confirmed by the X-ray crystal-structure analysis of one compound that was prone to crystallization. Preliminary biological evaluation showed that the compounds **2e**–**2h** promote the viability and inhibit the apoptosis of vascular endothelial cells at low concentration.

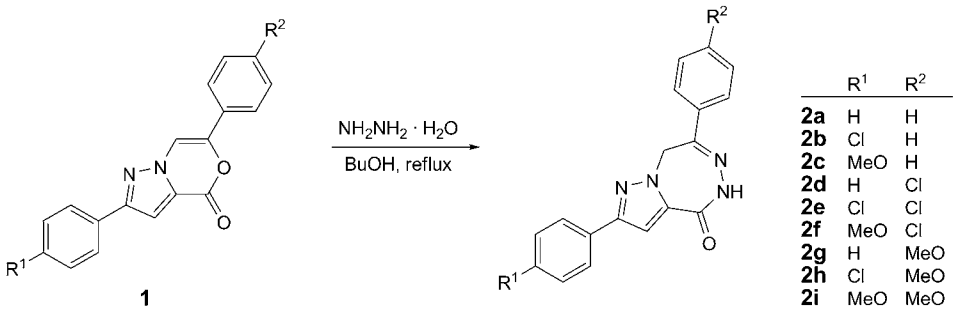
Introduction. – Small- and medium-sized N-containing heterocyclic skeletons, such as fused triazepines with a bridgehead N-atom in the molecule exhibit remarkable biological properties [1]. Although several methods for constructing 1,3,5-triazepine can be found in the literature [2], the 1,2,5-triazepin skeleton has only received scant attention [3].

It has been reported that the class of pyrazoles represents structurally diverse molecules with widespread and diverse pharmacological properties such as anticancer [4], antimicrobial [5], antiviral [6], antidepressant [7], antimycobacterial [8], anti-inflammatory [9], anti-angiogenic [10], and antiglaucoma activities [11]. Moreover, pyrazoles have found applications in drug development for the treatment of dyslipidemia [12], obesity [13], and neuropathic pain [14]. However, pyrazole-fused triazepin derivatives remain to be fully exploited, since most of them have not yet been found in nature or have not been synthesized, or its biological properties have not been evaluated.

We previously reported our efforts to identify novel potential agents, which inhibited human umbilical vein endothelial cell (HUVEC) apoptosis, based on pyrazole heterocycles [15]. More recently, we became interested in exploring pyrazole-fused heterocycles that contain more heteroatoms, ultimately discovering novel antithrombotic and anticancer agents [16]. In continuation of our search for biologically potent molecules, we hereby report the synthesis and structure characterization of pyrazolo[5,1-*d*][1,2,5]triazepin-4-one derivatives, which could inhibit endothelial cell apoptosis.

Results and Discussion. – The general synthetic strategy to obtain pyrazole-fused triazepin analogs is outlined in *Scheme 1*. Starting material **1** with various R^1 and R^2 substituents could be easily synthesized *via* cyclization of 3-aryl-1-(2-aryl-2-oxoethyl)-1*H*-pyrazole-5-carboxylic acid in the presence of Ac_2O [17]. Reaction of **1** with $NH_2NH_2 \cdot H_2O$ at reflux temperature in BuOH provided the desired pyrazolo[5,1-*d*][1,2,5]triazepin-4-one **2** in 68–82% yield.

Scheme 1. *Synthesis of 5,8-Dihydro-2,7-diphenyl-4*H*-pyrazolo[5,1-*d*][1,2,5]triazepin-4-ones*



	R^1	R^2
2a	H	H
2b	Cl	H
2c	MeO	H
2d	H	Cl
2e	Cl	Cl
2f	MeO	Cl
2g	H	MeO
2h	Cl	MeO
2i	MeO	MeO

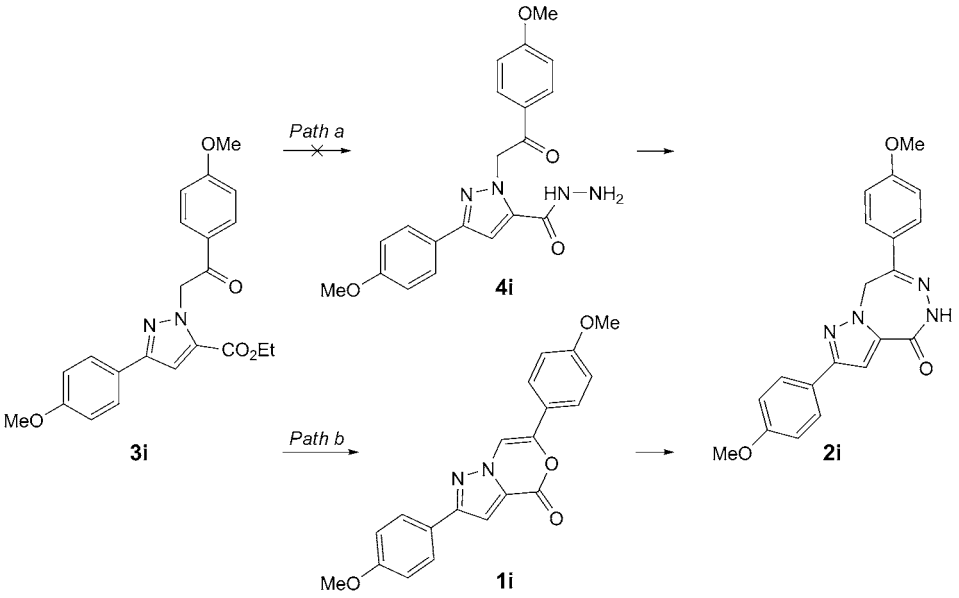
It was of interest to convert ethyl 3-aryl-1-(2-aryl-2-oxoethyl)-1*H*-pyrazole-5-carboxylate derivatives **3** to the corresponding pyrazolo[5,1-*d*][1,2,5]triazepine derivatives **2**. As an approach towards the construction of **2**, we initially chose a sequential process of condensation and ring-closure reaction between δ-keto esters and $NH_2NH_2 \cdot H_2O$ *via* the intermediate hydrazide **4** [18]. Thus, for example, we carried out the reaction of **3i** with 1 equiv. or excess $NH_2NH_2 \cdot H_2O$ in refluxing EtOH for 12 h to obtain the desired compound **2i**; however, our attempt unfortunately failed due to competitive reactions (*Scheme 2*, *Path a*).

We next attempted at another route as shown in *Scheme 2* (*Path b*). According to our previous report [17], basic hydrolysis of **3i**, followed by acidic treatment, afforded 3-(4-methoxyphenyl)-1-[2-(4-methoxyphenyl)-2-oxoethyl]-1*H*-pyrazole-5-carboxylic acid. Then, treatment of the latter with Ac_2O gave lactone **1i**, which reacted with $NH_2NH_2 \cdot H_2O$ in BuOH to afford **2i** and **4i** in 75 and 15% yields, respectively.

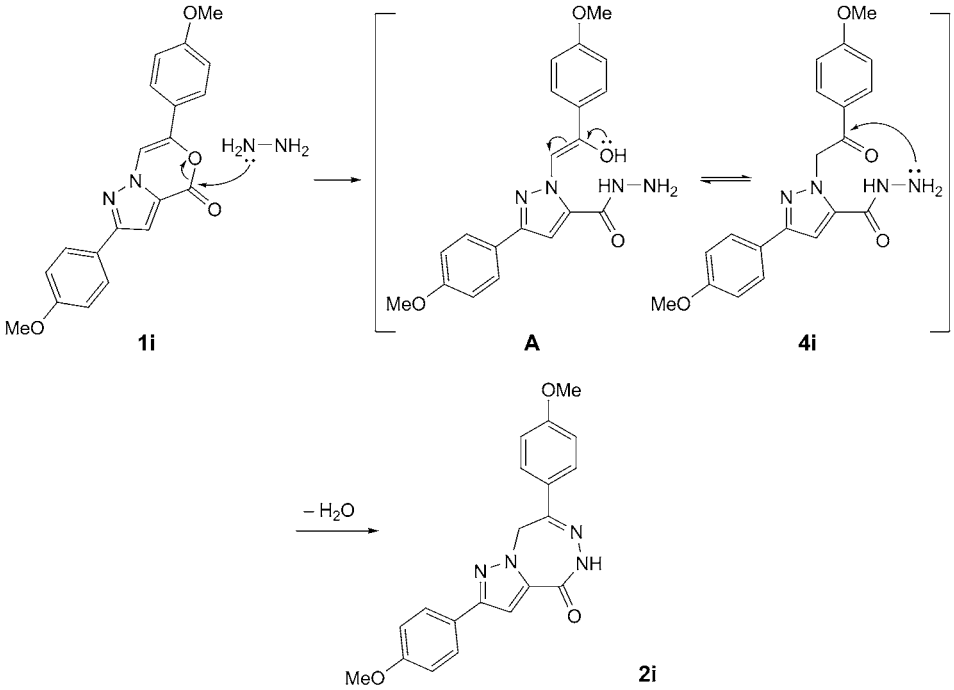
A proposed ring-enlargement mechanism is outlined in *Scheme 3*. In boiling BuOH, nucleophilic addition of NH_2NH_2 to the C=O group of lactone **1i** formed an enol intermediate **A** that should isomerize to the ketone **4i**. Although the enol **A** might be more stable because of the conjugated structure, ketone **4i** reacts *via* intramolecular reaction with NH_2 to result in the final cyclic hydrazide [19].

The structures of compounds **2a**–**2i** were established by IR, ^{1}H-NMR, HR-MS, and X-ray crystal diffraction of **2c** (*Fig. 1*). Moreover, the assignment of NH in the target compounds and C=O in the by-products of type **4** were accomplished by spectroscopic data. For example, IR spectra showed the characteristic stretching vibration at 1657 cm^{-1} for the C=O group of **2i**, along with the absorption band at 3203–2933 cm^{-1} due to the NH group. On the other hand, IR spectra of compound **4i** showed characteristic absorption bands at 1689 and 1668 cm^{-1} corresponding to the ketone C=O and hydrazide C=O group, respectively. The ^{1}H-NMR spectra of **2i** exhibited a signal corresponding to the CONH moiety at δ(H) 11.40 ppm as well as aromatic H-

Scheme 2



Scheme 3



atom signals in the range of 6.97 – 7.89 ppm. The significant feature of **4i** was the appearance of a *singlet* for NH_2 at δ(H) 4.45 ppm. The mass spectra of the two compounds **2i** and **4i** showed peaks for the $[M+H]^+$ ion at m/z 363.1454 and 381.1570, respectively, in full agreement with their assigned structures.

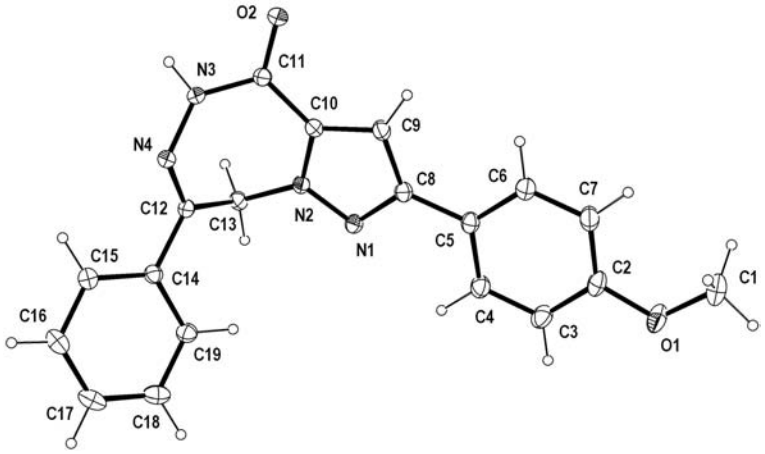


Fig. 1. *ORTEP View of compound* **2c***, including the atom numbering.* Displacement ellipsoids are drawn at the 25% probability.

Single crystals of **2c** suitable for X-ray single-crystal analysis were obtained at room temperature by partial evaporation of the solvent from AcOEt solution. The compound was constituted as pyrazolo[5,1-*d*][1,2,5]triazepine frame which is the core of the structure, and it has two phenyl rings attached at C(8) and C(12). All bond lengths and bond angles in the phenyl rings are in the normal range. In the triazepine ring, the bond length of C(11)=O(2) (1.2343(19) Å) is slightly longer than that in the corresponding reactant **1c** [18]. Moreover, the bond length C(11)–N(3) and bond angle C(11)–N(3)–N(4) are 1.366(2) Å and 130.24(14)°, respectively (*Table 1*). This implies delocalization of the lone pair of electrons on the N-atom over the pyrazole and benzylideneamine moiety in **2c**. All the aromatic rings are almost planar. Furthermore, the pyrazole ring and the attached substituted phenyl ring are almost coplanar with a

Table 1. *Selected Bond Lengths* [Å] *and Angles* [°] *of Compound* **2c**

N(4)–C(12)	1.284(2)	N(3)–N(4)	1.4025(19)
N(3)–C(11)	1.366(2)	C(11)–O(2)	1.2343(19)
C(10)–C(11)	1.467(2)	N(1)–N(2)	1.3439(18)
N(2)–C(13)	1.454(2)	C(10)–N(2)	1.354(2)
C(12)–N(4)–N(3)	119.28(15)	N(4)–N(3)–C(11)	130.24(14)
N(3)–C(11)–O(2)	119.33(15)	O(2)–C(11)–C(10)	120.93(15)
C(11)–C(10)–C(9)	130.72(15)	C(11)–C(10)–N(2)	122.78(15)
C(10)–N(2)–C(13)	124.72(14)	N(2)–C(13)–C(12)	109.11(14)
C(13)–C(12)–N(4)	122.68(15)	C(10)–N(2)–N(1)	112.80(13)
N(2)–N(1)–C(8)	104.59(13)	C(9)–C(10)–N(2)	106.49(15)

dihedral angle of 7.76(6)°. The two phenyl rings in compound **2c** were neither coplanar nor perpendicular, being close to 45° (47.91(6)°).

The triazepine ring adopts a twist-boat conformation, similar to those observed in the crystal structures of azepine [20]. The seven-membered ring consists of two coplanar halves (*Fig. 1*). The first is defined by atoms N(3), N(4), C(12), and C(13). The second half of the ring is composed of atoms C(13), N(2), C(10), and C(11), with the largest deviation from this plane not exceeding 0.007(2) Å. The dihedral angle between the two halves is 61.89(8)°, which is within the range of 57.74 – 63.93°, values found for this group of the similar compounds [21].

In the crystal lattice, the C=O group of the triazepinone interacts with the NH of the adjacent molecules through a pair of linear $N(3)–H(3)_A\cdots O(2)$ H-bonds to form an eight-membered $R_2^2(8)$ ring motif (*Table 2*). A C(15)–H(15)···O(1) H-bond leads to self-assembly of **2c** molecules into *C*(13) chains, and pairs of $C(1)–H(1)_A\cdots O(2)$ H-bonds join two **2c** molecules into centrosymmetric dimers of $R_2^2(24)$ type. Moreover, the $C(13)–H(13)_B\cdots O(2)$ H-bonds convert the mentioned chains to a 2D network. Furthermore, some other C–H···π interactions may supply further Coulombic stabilization and take part in formation of the three-dimensional structure (*Fig. 2*).

Table 2. *H-Bond Geometry for* **2c**

X–H···A/π[a])	d(X–H) [Å]	d(H···A/π) [Å]	d(X···A/π) [Å]	∠(X–H···A/π) [°]	Symmetry codes
$N(3)–H(3)_A\cdots O(2)$	0.90(2)	2.02(2)	2.908(2)	175(2)	$-x, 1-y, 2-z$
$C(1)–H(1)_A\cdots O(2)$	1.03(3)	2.47(3)	3.497(3)	172(2)	$-1-x, -y, 1-z$
$C(13)–H(13)_B\cdots O(2)$	0.98(2)	2.54(2)	3.168(3)	121.6(14)	$1+x, y, z$
C(15)–H(15)···O(1)	0.96(2)	2.49(2)	3.368(3)	151.1(16)	$1+x, 1+y, 1+z$
$C(1)–H(1)_C\cdots Cg2$	1.00(3)	2.80(2)	3.687(3)	148.0(19)	$-1-x, -1-y, 1-z$
C(17)–H(17)···*C*g1	0.95(2)	2.85(3)	3.609(3)	138(2)	$1-x, -y, 2-z$

[a]) *C*g1 and *C*g2 are the centriods of pyrazole ring and the substituted phenyl ring, respectively.

The sulforhodamine B (SRB) assay as described first by *Skehan et al.* was developed to be used in the disease-oriented, large-scale anticancer drug-discovery program of the *National Cancer Institute* (*NCI*) that was launched in 1985 [22]. Up to now, SRB protein staining has been widely used for cell proliferation and chemosensitivity testing, replacing tetrazolium-based assays.

Regulation of vascular endothelial cell (VEC) survival and apoptosis plays a crucial role during development, and in numerous physiologic and pathologic processes. First, we observed the morphological image of the VECs treated with compounds **2a** – **2i** under a phase-contrast microscope in this study. We found that there were no obvious morphological changes of the cells, even if the cells were treated with compounds at a concentration of 2.5 μM for 24 h. To evaluate the effects on the growth of VECs, we carried out the SRB assay with the compounds at 12 and 24 h, respectively. To our surprise, it was found that the quantities of the cells treated with the synthesized compounds were increased as shown in *Fig. 3*. Compounds **2c** and **2e** – **2h** promoted VEC growth by *ca.* 10% at 2.5 μM for 12 and 24 h compared with the control group. Compounds **2d** and **2i** could markedly promote the cell growth after the treatment for 12 h. Other compounds did not affect the growth of VECs (data not shown).

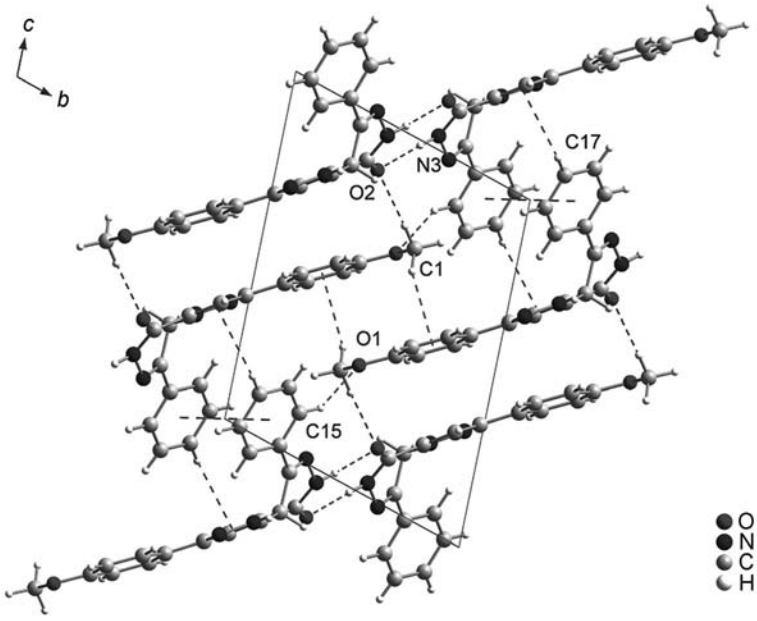


Fig. 2. *Molecular packing in compound* **2c**, *showing details of the H-bond connectivities*

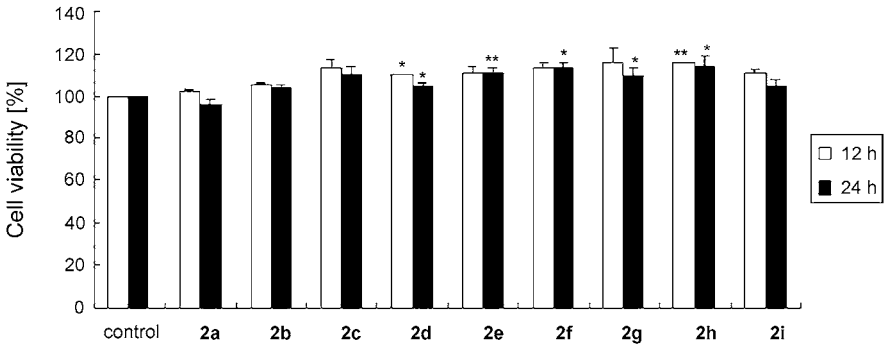


Fig. 3. *Effects of compounds* **2a**–**2i** *on cell viability of VECs at the concentration of 2.5* μM *for 12 and 24 h* (*: $p < 0.05$, **: $p < 0.01$ *vs.* control group, $n = 3$)

Analyzing endothelial apoptosis is necessary not only for the understanding of several physiologic and pathologic processes but also for evaluating treatments that inhibit endothelial cell apoptosis. To further demonstrate the apoptotic level, we examined the morphological changes induced by compounds **2a**–**2i** in VECs using *Hoechst 33258* staining. Granulation of the nucleus appeared as fluorescent blue in the detail of the *Hoechst 33258* stained cells (those in which vehicle was absent). Since nucleus granulation is a feature of the morphological change in apoptosis, these results indicate that **2e**–**2h** may inhibit partly apoptosis in VECs compared with the control group at the concentration of 2.5 μM after 12 h (*Fig. 4*), whereas the ratio of apoptotic

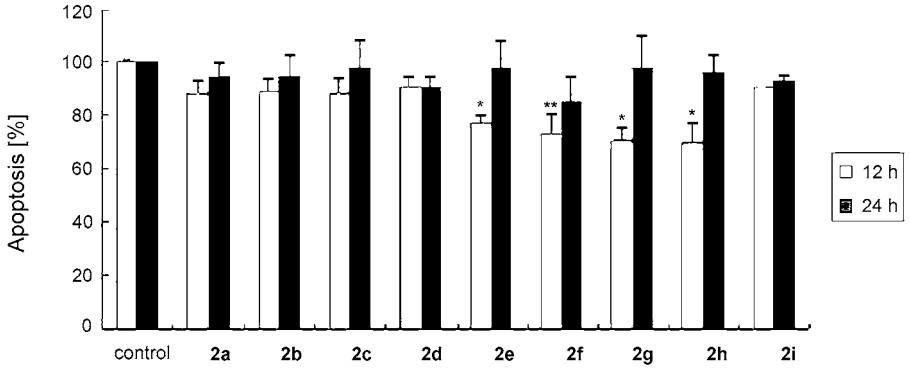


Fig. 4. *Inhibition of VEC apoptosis by compounds* **2a**–**2i** *at the concentration of 2.5* μM *for 12 and 24 h.* Ratio of apoptotic cells *vs.* control. Results are presented as mean ± SE ($n = 3$, *: $P < 0.05$ *vs.* control, **: $P < 0.01$ *vs.* control).

cells in the experimental groups treated with compounds **2e**–**2h** for 24 h was restored to their original level. These results suggested that the anti-apoptotic effects of compounds **2e**–**2h** at low concentration may be in accordance with the proliferation of the VECs.

Conclusions. – A series of novel pyrazolo[5,1-*d*][1,2,5]triazepin-4-ones were synthesized. The structures of the prepared compounds **2a**–**2i** were determined by spectroscopic methods. The representative X-ray single-crystal structure characterization of **2c** was also performed. The biological assay revealed that compounds **2e**–**2h** promoted the VEC growth and inhibited the apoptosis of VECs at the concentration of 2.5 μM.

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Experimental Part

General. The purity of the obtained compounds was checked by TLC on silica gel (SiO_2) *60* F_{254} plates (*Merck*) in AcOEt/petroleum ether 1:1 and 1:2, detection with UV light. M.p.: *XD-4* Digital micro melting point apparatus; uncorrected. IR Spectra: *Avatar 370 FT-IR* (*ThermoNicolet*) spectrophotometer in KBr disks; $\tilde{\nu}$ in cm^{-1}. ^1H- and ^{13}C-NMR spectra: *Bruker Avance 400* spectrometer at 400 (^1H) and 100 (^{13}C) MHz; in (D_6)DMSO solns.; δ in ppm rel. to Me_4Si as internal standard, J in Hz. HR-MS: *LTQ Orbitrap Hybrid* mass spectrometer; in *m*/*z*.

*5,8-Dihydro-2,7-diphenyl-4*H*-pyrazolo[5,1-*d*][1,2,5]triazepin-4-ones* **2**. To a soln. of *2,6-diphenyl-4*H*-pyrazolo[1,5-*a*][1,4]oxazin-4-one* (**1**; 1.0 mmol) in BuOH (25 ml), $NH_2NH_2 \cdot H_2O$ (1.2 mmol) was added. The mixture was stirred and heated to reflux for 2.5–6 h, until TLC indicated the end of the reaction. After cooling, a white solid was filtered off and washed with a small amount of EtOH. Pure products of **2** were obtained by column chromatography (SiO_2; AcOEt/petroleum ether 1:1) in good yields.

*5,8-Dihydro-2,7-diphenyl-4*H*-pyrazolo[5,1-*d*][1,2,5]triazepin-4-one* (**2a**). White solid. Yield: 248 mg (82%). M.p. 230–232°. IR: 3201–2946 (NH), 1658 (C=O). ^1H-NMR: 5.61 (*s*, CH_2); 7.34 (*t*, $J = 7.2$, 1 arom. H); 7.40 (*s*, 1 pyrazole H); 7.42 (*t*, $J = 7.2$, 2 arom. H); 7.50–7.54 (*m*, 3 arom. H); 7.86 (*d*, $J = 7.2$, 2

arom. H); 7.91 – 7.94 (*m*, 2 arom. H); 11.55 (*s*, CONH). HR-MS: 303.1234 ($[M+H]^+$, $C_{18}H_{15}N_4O^+$; calc. 303.1246).

*2-(4-Chlorophenyl)-5,8-dihydro-7-phenyl-4*H*-pyrazolo[5,1-*d*][1,2,5]triazepin-4-one* (**2b**). White solid. Yield: 230 mg (68%). M.p. 276 – 277°. IR: 3206 – 2916 (NH), 1663 (C=O). ^{1}H-NMR: 5.62 (*s*, CH_2); 7.46 (*s*, 1 pyrazole H); 7.48 (*d*, *J* = 8.6, 2 arom. H); 7.51 – 7.53 (*m*, 3 arom. H); 7.89 (*d*, *J* = 8.6, 2 arom. H); 7.91 – 7.93 (*m*, 2 arom. H); 11.59 (*s*, CONH). HR-MS: 337.0847 ($[M+H]^+$, $C_{18}H_{14}ClN_4O^+$; calc. 337.0856).

*5,8-Dihydro-2-(4-methoxyphenyl)-7-phenyl-4*H*-pyrazolo[5,1-*d*][1,2,5]triazepin-4-one* (**2c**). White solid. Yield: 245 mg (74%). M.p. 217 – 219°. IR: 3217 – 2936 (NH), 1668 (C=O). ^{1}H-NMR: 3.78 (*s*, MeO); 5.58 (*s*, CH_2); 6.97 (*d*, *J* = 8.8, 2 arom. H); 7.31 (*s*, 1 pyrazole H); 7.48 – 7.52 (*m*, 3 arom. H); 7.78 (*d*, *J* = 8.8, 2 arom. H); 7.90 – 7.92 (*m*, 2 arom. H); 11.52 (*s*, CONH). ^{13}C-NMR: 49.0; 55.6; 106.6; 114.6; 125.0; 127.2; 127.3; 129.4; 131.2; 134.8; 137.6; 150.5; 155.6; 158.2; 159.8. HR-MS: 333.1341 ($[M+H]^+$, $C_{19}H_{17}N_4O_2^+$; calc. 333.1352).

*7-(4-Chlorophenyl)-5,8-dihydro-7-phenyl-4*H*-pyrazolo[5,1-*d*][1,2,5]triazepin-4-one* (**2d**). White solid. Yield: 246 mg (73%). M.p. 280 – 282°. IR: 3196 – 2927 (NH), 1669 (C=O). ^{1}H-NMR: 5.61 (*s*, CH_2); 7.34 (*t*, *J* = 7.4, 1 arom. H); 7.41 (*s*, 1 pyrazole H); 7.42 (*t*, *J* = 7.4, 2 arom. H); 7.58 (*d*, *J* = 8.6, 2 arom. H); 7.65 (*d*, *J* = 7.4, 2 arom. H); 7.94 (*d*, *J* = 8.6, 2 arom. H); 11.60 (*s*, CONH). HR-MS: 337.0865 ($[M+H]^+$, $C_{18}H_{14}ClN_4O^+$; calc. 337.0856).

*2,7-Bis(4-chlorophenyl)-5,8-dihydro-4*H*-pyrazolo[5,1-*d*][1,2,5]triazepin-4-one* (**2e**). White solid. Yield: 304 mg (82%). M.p. 238 – 239°. IR: 3188 – 2936 (NH), 1665 (C=O). ^{1}H-NMR: 5.60 (*s*, CH_2); 7.45 (*s*, 1 pyrazole H); 7.48 (*d*, *J* = 8.6, 2 arom. H); 7.58 (*d*, *J* = 8.6, 2 arom. H); 7.88 (*d*, *J* = 8.6, 2 arom. H); 7.93 (*d*, *J* = 8.6, 2 arom. H); 11.61 (*s*, CONH). HR-MS: 371.0456 ($[M+H]^+$, $C_{18}H_{13}Cl_2N_4O^+$; calc. 371.0466).

*7-(4-Chlorophenyl)-5,8-dihydro-2-(4-methoxyphenyl)-4*H*-pyrazolo[5,1-*d*][1,2,5]triazepin-4-one* (**2f**). White solid. Yield: 289 mg (79%). M.p. 186 – 187°. IR: 3231 – 2932 (NH), 1653 (C=O). ^{1}H-NMR: 3.78 (*s*, MeO); 5.57 (*s*, CH_2); 6.97 (*d*, *J* = 8.3, 2 arom. H); 7.31 (*s*, 1 pyrazole H); 7.57 (*d*, *J* = 8.3, 2 arom. H); 7.78 (*d*, *J* = 8.3, 2 arom. H); 7.93 (*d*, *J* = 8.3, 2 arom. H); 11.57 (*s*, CONH). ^{13}C-NMR: 48.9; 55.6; 106.8; 114.6; 125.0; 127.2; 129.1; 129.5; 133.6; 136.0; 137.6; 150.6; 154.4; 158.1; 159.8. HR-MS: 367.0951 ($[M+H]^+$, $C_{19}H_{16}ClN_4O_2^+$; calc. 367.0962).

*5,8-Dihydro-7-(4-methoxyphenyl)-2-phenyl-4*H*-pyrazolo[5,1-*d*][1,2,5]triazepin-4-one* (**2g**). White solid. Yield: 242 mg (73%). M.p. 204 – 205°. IR: 3202 – 2938 (NH), 1664 (C=O). ^{1}H-NMR: 3.82 (*s*, MeO); 5.57 (*s*, CH_2); 7.06 (*d*, *J* = 8.9, 2 arom. H); 7.33 (*t*, *J* = 7.9, 1 arom. H); 7.38 (*s*, 1 pyrazole H); 7.42 (*t*, *J* = 7.9, 2 arom. H); 7.85 (*d*, *J* = 7.9, 2 arom. H); 7.89 (*d*, *J* = 8.9, 2 arom. H); 11.43 (*s*, CONH). HR-MS: 333.1351 ($[M+H]^+$, $C_{19}H_{17}N_4O_2^+$; calc. 333.1352).

*2-(4-Chlorophenyl)-5,8-dihydro-7-(4-methoxyphenyl)-4*H*-pyrazolo[5,1-*d*][1,2,5]triazepin-4-one* (**2h**). White solid. Yield: 267 mg (73%). M.p. 270 – 271°. IR: 3201 – 2939 (NH), 1663 (C=O). ^{1}H-NMR: 3.82 (*s*, MeO); 5.57 (*s*, CH_2); 7.06 (*d*, *J* = 8.8, 2 arom. H),7.42 (*s*, 1 pyrazole H); 7.47 (*d*, *J* = 8.5, 2 arom. H); 7.87 (*d*, *J* = 8.5, 2 arom. H); 7.89 (*d*, *J* = 8.8, 2 arom. H); 11.45 (*s*, CONH). HR-MS: 367.0972 ($[M+H]^+$, $C_{19}H_{16}ClN_4O_2^+$; calc. 367.0962).

*2,7-Bis(4-methoxyphenyl)-5,8-dihydro-4*H*-pyrazolo[5,1-*d*][1,2,5]triazepin-4-one* (**2i**). White solid. Yield: 272 mg (75%). M.p. 193 – 194°. IR: 3203 – 2933 (NH), 1657 (C=O). ^{1}H-NMR: 3.78 (*s*, MeO); 3.82 (*s*, MeO); 5.54 (*s*, CH_2); 6.97 (*d*, *J* = 8.8, 2 arom. H); 7.06 (*d*, *J* = 8.9, 2 arom. H); 7.28 (*s*, 1 pyrazole H); 7.77 (*d*, *J* = 8.8, 2 arom. H); 7.89 (*d*, *J* = 8.9, 2 arom. H); 11.40 (*s*, CONH). ^{13}C-NMR: 48.8; 55.6; 55.9; 106.4; 114.6; 114.8; 125.1; 126.9; 127.1; 129.1; 137.6; 150.4; 155.6; 158.3; 159.7; 161.8. HR-MS: 363.1454 ($[M+H]^+$, $C_{20}H_{19}N_4O_3^+$; calc. 363.1457).

*2,7-Bis(4-methoxyphenyl)-8*H*-pyrazolo[5,1-*d*][1,2,5]triazepin-4-ol:* White solid. Yield: 57 mg (15%). M.p. 190 – 192°. IR: 3332 – 3248 (NH), 1689 (C=O), 1668 (CONH). ^{1}H-NMR: 3.79 (*s*, MeO); 3.88 (*s*, MeO); 4.45 (*s*, NH_2); 6.08 (*s*, CH_2); 7.01 (*d*, *J* = 8.7, 2 arom. H); 7.10 (*d*, *J* = 8.8, 2 arom. H); 7.26 (*s*, 1 pyrazole H); 7.67 (*d*, *J* = 8.7, 2 arom. H); 8.03 (*d*, *J* = 8.8, 2 arom. H); 9.84 (*s*, CONH). HR-MS: 381.1570 ($[M+H]^+$, $C_{20}H_{21}N_4O_4^+$; calc. 381.1563).

X-Ray Crystal-Structure Analysis. Crystals suitable for X-ray analysis were grown by slow evaporation of the solvent from AcOEt soln. The diffraction measurement was carried out by graphite monochromated MoK_α radiation ($\lambda = 0.71073$ Å) on a *Bruker SMART CCD* diffractometer at r.t. The

structure was solved with direct methods using the *SHELXS*-97 program, and refined on F^2 by full-matrix least-squares with the *SHELXL*-97 package [23]. All data were corrected by multi-scan method using SADABS program [24]. The H-atoms were placed at calculated positions with 0.96 Å (Me) and 0.93 Å (aromatic CH) using a riding model. Molecular graphics were designed by using *XP* and *DIAMOND* 3.2 [25]. PLATON Program was also used for structure analysis [26]. The crystal data and details concerning data collection and structural refinement are collected in *Table 3*. CCDC-819054 contains the supplementary crystallographic data for this article. These data can be obtained free of charge *via* http://www.ccdc.cam.ac.uk/data_request/cif.

Table 3. *Crystallographic Data of Compound* **2c**

Empirical formula	$C_{19}H_{16}N_4O_2$
M_r	332.36
Crystal dimensions [mm]	$0.15 \times 0.15 \times 0.10$
Crystal system	triclinic
Space group	$P\bar{1}$
Z	2
Unit cell parameters:	
a [Å]	7.0499(9)
b [Å]	9.9557(12)
c [Å]	13.1850(17)
α [°]	102.526(2)
β [°]	104.162(2)
γ [°]	104.260(2)
D_x [g/cm^3]	1.328
μ [mm^{-1}]	0.090
$F(000)$	348
Reflection collected	4448
Data/restraints/parameters	3209/0/290
θ Range for data collection [°]	2.21 – 26.00
R(int)	0.0203
Ranges of indices h, k, l	$-8 \le h \le 8,\ -12 \le k \le 6,\ -11 \le l \le 16$
Absorption correction	multi-scan ($T_{min} = 0.987$, $T_{max} = 0.991$)
Refinement method	full-matrix least-squares on F^2
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0480$, $wR_2 = 0.1207$[a])
Goodness-of-fit on F^2	1.018
$\Delta\rho$ (max./min) [e Å^{-3}]	0.252; −0.346

a) Weighting scheme: $w = 1/[\sigma^2(F_o)^2 + (0.0806P)^2 + 0.0618P]$ where $P = (F_o^2 + 2F_c^2)/3$.

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