Synthesis of [3,3′(4*H*,4′*H*)-Bi-2*H*-1,3-oxazine]-4,4′-diones and Their Hydrolysis

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The [3,3′(4*H*,4′*H*)-bi-2*H*-1,3-oxazine]-4,4′-diones **3a**–**3i** were obtained by [2+4] cycloaddition reactions of furan-2,3-diones **1a**–**1c** with aromatic aldazines **2a**–**2d** (*Scheme 1*). So, new derivatives of bi-2*H*-1,3-oxazines and their hydrolysis products, 3,5-diaryl-1*H*-pyrazoles **4a**–**4c** (*Scheme 3*), which are potential biologically active compounds, were synthesized for the first time.

Introduction. – The development of novel synthetic methods for the construction of new analogs of bioactive heterocyclic compounds represents a major challenge in synthetic organic and medicinal chemistry [1][2]. The bi-2*H*-1,3-oxazine ring systems are core structures present in a number of biologically active heterocycles. They are pivotal intermediates for the synthesis of pharmaceutical molecules. Increasing interest towards the synthesis of bi-2*H*-1,3-oxazine derivatives is mainly due to their potential biological and pharmacological actions such as analgesic, antitubercular, anticancer, anti-HIV, antihypertensive, antithrombotic, and antiulcer activities. In addition, certain of their members are of interest as photochromic compounds [3–9]. The 3,5-diaryl-1*H*-pyrazoles obtained by hydrolysis of bi-2*H*-1,3-oxazines have also been evaluated as cytotoxic or as potential antitumor agents [10–12]. Due to our interest in bi-2*H*-1,3-oxazines and 3,5-diaryl-1*H*-pyrazoles, we investigated the reactivity and synthetic applications of these compounds [13].

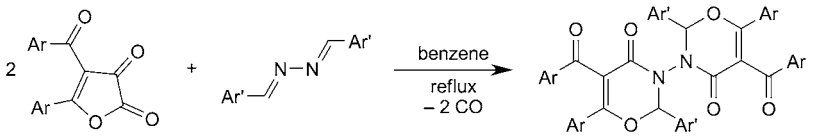
Furandiones are versatile starting materials for a variety of reactions, *e.g.*, generation of diacyl ketenes by thermolysis, cycloaddition of heterocumulenes, photochemical reactions, as well as addition of nucleophiles, leading to a number of heterocyclic systems [14–18]. Thermal decomposition of the furan-2,3-diones leads to formation of reactive α-oxoketene (acylketene) intermediates. α-Oxoketenes are versatile intermediates in organic synthesis; they not only react with various nucleophiles but also undergo cycloaddition reactions with unsaturated compounds [18–26]. On the other hand, azines (=alkylidenehydrazones) have attracted attention because of their ability to be used in the synthesis of a wide variety of heterocyclic compounds such as 1*H*-pyrazoles, purines, and pyrimidines. These compounds can be employed for useful synthetic transformations and possess some unexpected biological activities [27–31]. It was surprising to find that there have been very few reports on [2+4] cycloaddition reactions with azines as dienophiles. We have focused our interest on arylaldazines because, to the best of our knowledge, the dienophilic reactivity of

these compounds have gone unnoticed; nevertheless, they could be excellent systems for exploring the potential of our way of proceeding as well as for investigating the scope of azines in [2 + 4] cycloadditions.

Herein, we report the first synthesis of [3,3′(4*H*,4′*H*)-bi-2*H*-1,3-oxazine]-4,4′-diones **3** by [2 + 4] cycloaddition reactions of some furan-2,3-diones **1** with arylaldazines (= 1,2-dibenzylidenehydrazines) **2** as dienophiles (*Scheme 1*). The result of these experiments is discussed in this study. Our investigation also deals with new 3,5-diaryl-1*H*-pyrazoles **4**, formed by hydrolysis of some [3,3′(4*H*,4′*H*)-bi-2*H*-1,3-oxazine]-4,4′-diones and the acylation of **4** to derivatives **5** (*Scheme 3*). The synthesis of 3,5-diphenyl-1*H*-pyrazole has first been achieved by the reaction of hydrazine and dibenzoylmethane [10][13]. Later, the synthesis of 3,5-diaryl-1*H*-pyrazoles, *e.g.*, 3,5-bis(4-methoxyphenyl)-1*H*-pyrazole, from chalcones by using H_2O_2 in alkaline media (→ epoxychalcones) fallowed by treatment with hydrazine and dehydration has been reported by *Bhat* and co-workers [11].

Results and Discussion. – The substituted furan-2,3-diones **1a** – **1c** and azine derivatives **2a** – **2d**, which were used in the synthesis of the target [3,3′(4*H*, 4′*H*)-bi-2*H*-1,3-oxazine]-4,4′-diones **3a** – **3i**, were prepared by literature procedures [19 – 25][27]. The reaction of aldazine **2a** (1 mol-equiv.) with **1a** (2 mol-equiv.) in benzene proceeded smoothly to afford the target compound **3a** in 51% yield (*Scheme 1*). Similarly, the reaction between **1a** – **1c** and aldazine derivatives **2a** – **2d**, gave the diones **3b** – **3i** in 18 – 37% yield. Compounds **3a** – **3i** are stable solids whose structures were established by IR, ^{1}H- and ^{13}C-NMR spectroscopy (see also below), and elemental analyses. When this cycloaddition reaction was carried out with ketazines instead of aldazines **2a** – **2d**, such as that derived from benzophenone, TLC and ^{1}H-NMR analyses of the reaction mixtures indicated a mixture of starting materials and numerous products in poor amounts.

Scheme 1. *Reaction of Furan-2,3-diones* **1** *with Aromatic Aldazines* **1**



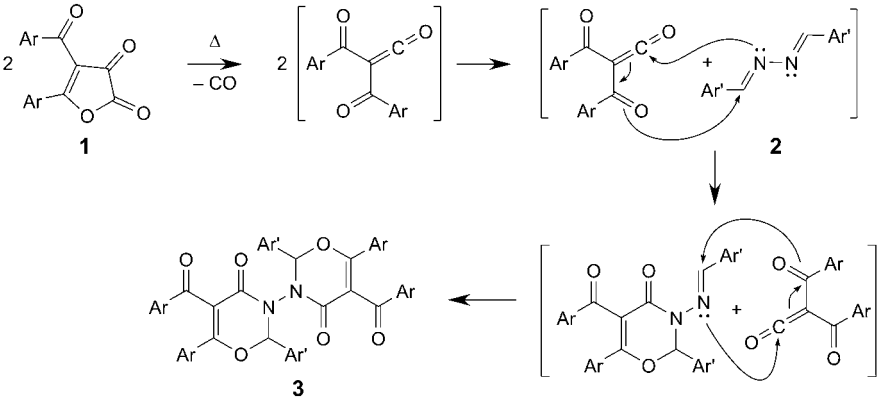
1a Ar = Ph
1b Ar = 4-MeO–C_6H_4
1c Ar = 4-Me–C_6H_4

2a Ar' = Ph
2b Ar' = Pyridin-3-yl
2c Ar' = 4-Me–C_6H_4
2d Ar' = 4-MeO–C_6H_4

	Ar	Ar'
3a	Ph	Ph
3b	4-MeO–C_6H_4	Ph
3c	4-Me–C_6H_4	Ph
3d	Ph	Pyridin-3-yl
3e	4-MeO–C_6H_4	Pyridin-3-yl
3f	Ph	4-Me–C_6H_4
3g	4-MeO–C_6H_4	4-Me–C_6H_4
3h	Ph	4-MeO–C_6H_4
3i	4-MeO–C_6H_4	4-MeO–C_6H_4

The formation of diones **3** can be explained by the thermal decomposition of the 4-acylfurandiones **1** by loss of CO leading to the diacylketenes as intermediates which can undergo [2 + 4] cycloaddition reactions with C=O, C=N, and C=S dienophiles [32]. Thus, reacting twice with aldazines **2** yields the diones **3** (*Scheme 2*).

Scheme 2. *Formation of [3,3′(4*H*,4′*H*)-Bi-2*H*-1,3-oxazine]-4,4′-diones* **3**



The cycloadition monitoring by TLC revealed a pronounced substituent effect on the overall reaction time. Electron-donating substituents at the aromatic ring of aldazine **2** accelerated the reaction, whereas electron-withdrawing substituents completely prevented the reaction. Because the products **3a** – **3i** contain two chiral centers, they were expected to be the racemic mixtures of the enantiomers and the *meso*-form (*Fig. 1*). The ^{1}H-NMR spectrum of **3a** revealed a 1:1 ratio of the *meso* to the (*R*)/(*S*) adducts by the integrals of the two H–C(2,2′) *s* of the bi-2*H*-1,3-oxazine moieties at δ(H) 5.97 and 5.65 [33][34]. The ^{13}C-NMR spectrum of **3a** showed signals at δ 192.23, and 191.70 (Ph–*C*=O), and 165.72, 164.92 (C(6), C(6′)), 164.40, and 161.46 (C(4)=O, C(4′)=O), 137.84 – 127.00 (arom. C), 111.98 and 110.71 (C(5), C(5′)), and 92.87 and 92.01 (C(2), C(2′)). Also the optical rotations of the [bi-2 H-1,3-oxazine]-

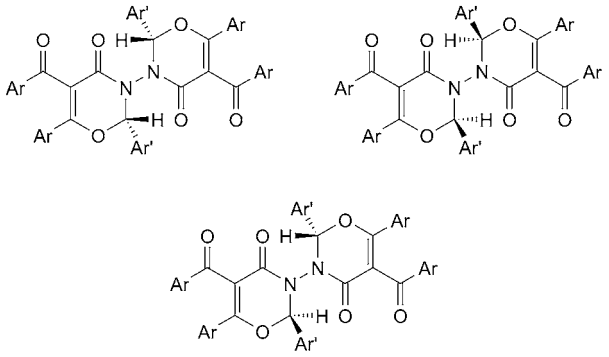
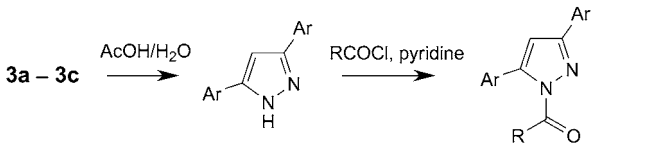


Fig. 1. *The three possible isomers* (50% *meso* and 50% (*R*)/(*S*)) *of* **3a** – **3i**

diones **3a**–**3i** in $CHCl_3$ solution were measured but no optical activity was observed. The ^{1}H- and ^{13}C-NMR spectra of **3b**, **3c**, **3e**, **3g**, and **3i** were similar to those of **3a**, except for the characteristic resonance of the Me groups and the correspondingly substituted aromatic rings. On the other hand, in the ^{1}H-NMR spectra of **3d**, **3f**, and **3h**, H–C(2,2′) gave rise to only one *s*, and these compounds melted sharply at a constant temperature, indicating that **3d**, **3f**, and **3h** were *meso* forms.

We also investigated the hydrolysis of [3,3′(4*H*,4′*H*)-bi-2*H*-1,3-oxazines]-4,4′-diones **3a-3c** in refluxing H_2O/AcOH, wich furnished as single products the corresponding 3,5-diaryl-1*H*-pyrazoles **4a**–**4c** (*Scheme 3*).

Scheme 3. *Hydrolysis of* **3a**–**3c**, *and Acylations of* **4a**–**4c**



4a Ar = Ph
4b Ar = 4-MeO–C_6H_4
4c Ar = 4-Me–C_6H_4

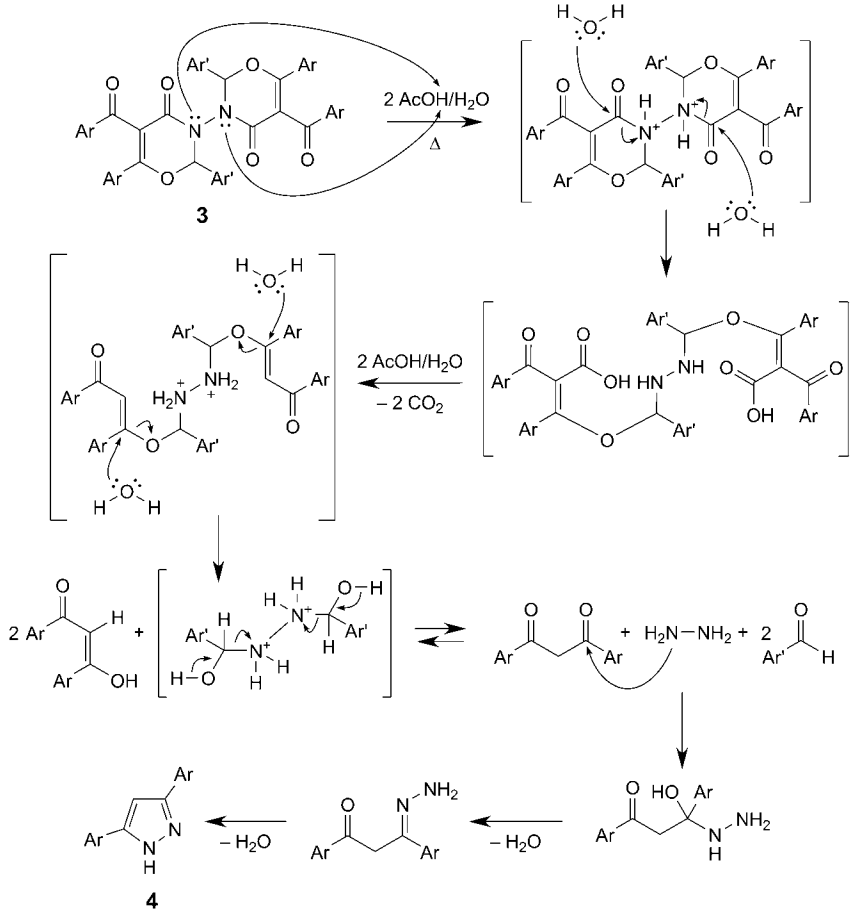
	Ar	R
5a	Ph	Me
5b	4-MeO–C_6H_4	Me
5c	4-Me–C_6H_4	Me
5d	4-MeO–C_6H_4	Ph
5e	4-Me–C_6H_4	Ph

In acidic solution, the same 1*H*-pyrazoles **4a** and **4b** were also always obtained on hydrolysis of [bi-oxazine]diones **3d**–**3i**. The spectral and analytical data of **4c**–**4c** were in good agreement with the proposed structures. In the IR spectrum of **4c**, *e.g.*, the characteristic absorption band for the NH group at 3139 cm^{-1}, and the skeleton bands of benzene or pyrazole rings at 1510–1440 cm^{-1} (C–C, C–N) were observed. The ^{13}C-NMR signals of **4c** were found at δ(C) 147.70 (C(5)), 123.47 (4 C_o), 137.46 (C(3)), 99.39 (C(4)), 129.78 (2 C_p), 129.47 (2 C_{ipso} and 4 C_m), and 21.21 (2 Me), and the ^{1}H-NMR signals at δ(H) 13.42 (exchangeable with D_2O, NH), 8.30–7.01 (arom. H), and 2.36 and 2.22 (2 Me) [35].

A reasonable mechanism for the formation of (*Scheme 4*) would involve protonation of **3** followed by ring opening *via* nucleophilic attack of H_2O to the antibonding (π^*) orbital at the CO C-atoms C(4,4′) of the bi-oxazine moiety to give a highly reactive intermediate β-keto carboxylic acid. The latter would then decarboxylate to give a 1,3-diketone, hydrazine, and an aromatic aldehyde. Nucleophilic attack of the hydrazine at the 1,3-diketone followed by intramolecular cyclization and dehydration would yield the 1*H*-pyrazole **4**.

After the successful synthesis of 3,5-diaryl-1*H*-pyrazoles **4**, the next step was their *N*-acylation to the corresponding 1-acyl-1*H*-pyrazoles by using acetyl or benzoyl chloride. The acylation was carried out in toluene under reflux to give the 1-acyl-1*H*-pyrazoles **5** in 91–85% yield without opening the 1*H*-pyrazole ring. The structures of **5a**–**5e** were elucidated by analysis of their NMR data, as exemplified with **5b**. The ^{1}H-NMR spectrum of **5b** exhibited one *s* at δ 2.85 for the Me group, two *s* at δ 4.04 and 3.88 for the MeO groups, and a *m* at δ 7.87–6.70 (two *AA′BB′* systems) for the aromatic

Scheme 4. *Formation of 3,5-Diary-1*H*-pyrazoles* **4**



H-atoms. ^{13}C-NMR and DEPT Spectra of **5b** confirmed the presence of one Me and two MeO groups, six quaternary C-atoms in the aromatic region, and one CO group.

We wish to dedicate this article to *Yunus Akçamur*, who passed away in 2007, and to *Gert Kollenz*. The authors are grateful to the *Technology Research and Application Centre* for the use of the NMR spectrometer and to the *Scientific Research Projects Chairmanship of Erciyes University* for financial support.

Experimental Part

General. Compounds **1** and azines **2** were prepared according to [13][21][27][36]. Reagents and solvents were purchased from *Merck*, *Fluka*, and *Sigma*, used without further purification. TLC: *Merck* precoated silica gel plates *60* F_{254}. M.p.: *Electrothermal-9200* apparatus; uncorrected. Optical rotations: *Perkin-Elmer-241-MC* polarimeter, at 589 nm. IR Spectra: *Shimadzu-8400-FT-IR* spectrometer; ATR = allenuated total reflectance; in cm^{-1}. ^{1}H- and ^{13}C-NMR spectra: *Bruker-Avance-III-Ultrashield*

spectrometer; at 400.13 (^{1}H) and 100.61 MHz (^{13}C) in (D_6)DMSO and/or $CDCl_3$; δ in ppm, coupling constants *J* in Hz; when necessary to identify all C-atoms, COSY and APT (attached-proton test) experiments were performed. Elemental analyses: *Leco-932-CHNS-O* analyzer.

*Substituted [3,3′(4*H*,4′*H*)-Bi-2*H*-1,3-oxazine]-4,4′-diones* **3**: *General Procedure 1* (*G.P.1*). Furandione **1** (2 mmol) and azine **2** (1 mmol) were dissolved in dry benzene (30 ml) and heated under reflux for 16–23 h. After cooling to r.t., the white precipitate was filtered off and recrystallized from EtOH: **3** as colorless crystals.

*5,5′-Dibenzoyl-2,2′,6,6′-tetraphenyl-[3,3′(4*H*,4′*H*)-bi-2*H*-1,3-oxazine]-4,4′-dione* (**3a**). According to the *G.P.1* (19 h reflux): 0.36 of **3a** (51%). M.p. 167–171°. IR (ATR): 3064*w* (arom. C–H), 2893*w* (aliph. C–H), 1671*s*, 1657*s* (C=O), 1598*s*, 1574*m*, 1493*m*, 1450*s* (C–C). ^{1}H-NMR ($CDCl_3$): 8.06–6.97 (*m*, 30 arom. H); 5.97, 5.65 (2*s*, H–C(2), H–C(2′)). ^{13}C-NMR ($CDCl_3$): 192.23, 191.70 (Ph–*C*=O); 165.72, 164.92 (C(6), C(6′)); 164.40, 161.46 (C(4)=O, C(4′)=O); 137.84, 133.67, 132.98, 130.12, 129.66, 129.43, 129.09, 128.75, 128.43, 128.34, 127.55, 127.14, 127.00 (arom. C); 111.98, 110.71 (C(5), C(5′)); 92.87, 92.01 (C(2), C(2′)). Anal. calc. for $C_{46}H_{32}N_2O_6$ (708.76): C 77.95, H 4.55, N 3.95; found: C 78.01, H 4.51, N 3.97.

*5,5′-Bis(4-methoxybenzoyl)-6,6′-bis(4-methoxyphenyl)-2,2′-diphenyl-[3,3′(4*H*,4′*H*)-bi-2*H*-1,3-oxazine]-4,4′-dione* (**3b**). According to the *G.P.1* (23 h reflux): 0.31 g of **3b** (37%). M.p. 155–159°. IR (ATR): 3057*w* (arom. C–H), 2838*w* (aliph. C–H), 1675*s* (C=O), 1599*s*, 1575*m*, 1509*s*, 1459*s* (C–C). ^{1}H-NMR ($CDCl_3$): 7.92–6.80 (*m*, 26 arom. H); 6.69, 6.66 (2*s*, H–C(2), H–C(2′)); 3.79, 3.71 (2*s*, 4 MeO). ^{13}C-NMR ($CDCl_3$): 190.67 (Ph–*C*=O); 165.49, 165.42 (C(6), C(6′)); 163.96, 162.65 (C(4)=O, C(4′)=O); 132.96, 132.36, 131.41, 130.95, 130.50, 128.61, 128.39, 123.42, 114.00, 113.97 (arom. C); 109.41 (C(5), C(5′)), 91.74 (C(2), C(2′)), 55.66, 55.58 (2 MeO). ^{15}N-NMR (40.5 MHz, $CDCl_3$): 199.99. Anal. calc. for $C_{50}H_{40}N_2O_8$ (828.86): C 72.45, H 4.86, N 3.38; found: C 71.98, H 4.59, N 3.36.

*5,5′-Bis(4-methylbenzoyl)-6,6′-bis(4-methylphenyl)-2,2′-diphenyl[3,3′(4*H*,4′*H*)-bi-2*H*-1,3-oxazine]-4,4′dione* (**3c**). According to the *G.P.1* (22 h reflux): 0.23 g of **3c** (30%). M.p. 180–186°. IR (ATR): 3034*w* (arom. C–H), 2966*w* (aliph. C–H), 1707*s*, 1678*s*, 1657*s* (C=O), 1610*m*, 1600*m*, 1554*m*, 1467*m* (C–C). ^{1}H-NMR ($CDCl_3$): 8.01–6.88 (*m*, 26 arom. H); 5.91, 5.61 (2*s*, H–C(2), H–C(2′)); 2. 25, 2.37 (2*s*, 4 *Me*–Ar). ^{13}C-NMR ($CDCl_3$): 191.26 (Ar–*C*=O); 165.93 (C(6), C(6′)); 164.80 (C(4)=O, C(4′)=O); 144.18, 142.50, 135.24, 132.32, 130.32, 129.86, 129.85, 129.21, 129.07, 128.48, 128.24, 128.09 (arom. C); 110.14 (C(5), C(5′)); 91.55 (C(2), C(2′)); 21.71, 21.42 (2 *Me*–Ar). Anal. calc. for $C_{50}H_{40}N_2O_6$ (764.86): C 78.52, H 5.27, N 3.66; found: C 77.98, H 4.98, N 3.65.

*5,5′-Dibenzoyl-6,6′-diphenyl-2,2′-dipyridin-3-yl[3,3′(4*H*,4′*H*)-bi-2*H*-1,3-oxazine]-4,4′-dione* (**3d**). According to the *G.P.1* (19 h reflux): 0.24 g of **3d** (33%). M.p. 250°. IR (ATR): 3057*w* (arom. C–H), 2974*w* (aliph. C–H), 1703*s*, 1689*s*, 1647*s* (C=O), 1608*s*, 1596*w*, 1577*w*, 1448*s* (C–C). ^{1}H-NMR ($CDCl_3$): 8.85–7.03 (*m*, 28 arom. H); 6.65 (*s*, H–C(2), H–C(2′)). ^{13}C-NMR ($CDCl_3$): 191.13 (Ar–*C*=O); 166.27 (C(6), C(6′)); 163.82 (C(4)=O, C(4′)=O); 152.21, 149.28, 137.33, 135.79, 134.55, 132.87, 130.77, 129.65, 129.53, 129.20, 129.07, 129.00, 128.74, 128.30, 124.14 (arom. C); 110.65, 111.72 (C(5), C(5′)); 90.02 (C(2), C(2′)). Anal. calc. for $C_{44}H_{30}N_4O_6$ (710.73): C 74.36, H 4.25, N 7.88; found: C 73.98, H 4.70, N 8.02.

*5,5′-Bis(4-methoxybenzoyl)-6,6′-bis(4-methoxyphenyl)-2,2′-dipyridin-3-yl[3,3′(4*H*,4′*H*)-bi-2*H*-1,3-oxazine]-4,4′-dione* (**3e**). According to the *G.P.1* (24 h reflux): 0.26 g of **3e** (31%). M.p. 233–236°. IR (ATR): 3057*w* (arom. C–H), 2943*w* (aliph. C–H), 1695*s*, 1670*s*, 1647*s* (C=O), 1597*s*, 1506*m*, 1478*m*, 1460*m* (C–C). ^{1}H-NMR ($CDCl_3$): 8.91–6.92 (*m*, 24 arom. H); 6.85, 6.77 (2*s*, H–C(2), H–C(2′)); 3.92, 3.67 (2*s*, 4 MeO). ^{13}C-NMR ($CDCl_3$): 189.72 (Ar–*C*=O); 170.89 (C(6), C(6′)); 164.80 (Ar–*C*=O); 164.22, 164.15 (MeO–*C*); 162.82 (C(4)=O, C(4′)=O); 151.48, 148.43, 143.00, 136.21, 134.44, 132.58, 131.06, 129.76, 127.36, 115.3, 114.61 (arom. C); 109.40 (C(5), C(5′)); 89.55 (C(2), C(2′)); 56.10, 55.92 (2 MeO). Anal. calc. for $C_{48}H_{38}N_4O_{10}$ (830.84): C 69.39, H 4.61, N 6.74; found: C 68.67, H 4.45, N 6.71.

*5,5′-Dibenzoyl-2,2′-bis(4-methylphenyl)-6,6′-diphenyl[3,3′(4*H*,4′*H*)-bi-2*H*-1,3-oxazine]-4,4′-dione* (**3f**). According to the *G.P.1* (18 h reflux): 0.16 g of **3f** (21%). M.p. 195°. IR (ATR): 3060*w* (arom. C–H), 2920*w* (aliph. C–H), 1697*s*, 1660*s* (C=O), 1610*m*, 1595*m*, 1512*m*, 1447*m* (C–C). ^{1}H-NMR ($CDCl_3$): 7.94–6.88 (*m*, 28 arom. H); 5.61 (*s*, H–C(2), H–C(2′)); 2.44 (*s*, 2 Me). ^{13}C-NMR ($CDCl_3$): 191.44 (Ar–*C*=O); 166.06 (C(6), C(6′)); 163.93 (C(4)=O, C(4′)=O); 140.59, 137.42, 134.35, 132.61, 131.10, 130.05, 129.50, 129.25, 129.10, 128.85, 128.71, 128.51 (arom. C); 110.61 (C(5), C(5′)); 92.02 (C(2), C(2′)); 21.42 (Me). Anal. calc. for $C_{48}H_{36}N_2O_6$ (736.81): C 78.24, H 4.92, N 3.80; found: C 77.83, H 4.51, N 3.53.

*5,5′-Bis(4-methoxybenzoyl)-6,6′-bis(4-methoxyphenyl)-2,2′-bis(4-methylphenyl)[3,3′(4*H*,4′*H*)-bi-2*H*-1,3-oxazine]-4,4′dione* (**3g**). According to the G.P.1 (21 h reflux): 0.27 g of **3g** (31%). M.p. 195–200°. IR (ATR): 3057*w* (arom. C–H), 2951*w* (aliph. C–H), 1711*s*, 1670*s* (C=O), 1593*m*, 1506*m*, 1487*m*, 1450*m* (C–C). ^{1}H-NMR ((D$_6$)DMSO): 7.96–6.87 (4 *AA′BB′*, 24 arom. H); 6.80, 6.70 (2*s*, H–C(2), H–C(2′)); 3.89–3.70 (*m*, 4 MeO); 2.44 (2*s*, 2 Me). ^{13}C-NMR ((D$_6$)DMSO): 190.12 (Ar–*C*=O); 164.65 (C(6), C(6′)); 164.37, 164.10 (MeO–*C*); 162.63 (C(4)=O, C(4′)=O); 140.40, 136.00, 132.11, 131.06, 130.54, 130.35, 129.12, 128.50, 126.55 (arom. C); 114.62, 114.52 (C(5), C(5′)); 91.69 (C(2), C(2′)); 56.07, 55.88 (2 MeO); 21.41 (2 Me). Anal. calc. for $C_{52}H_{44}N_2O_{10}$ (856.90): C 72.88, H, 5.18, N 3.27; found: C 72.84, H 5.38, N 3.19.

*5,5′-Dibenzoyl-2,2′-bis(4-methoxyphenyl)-6,6′-diphenyl[3,3′(4*H*,4′*H*)-bi-2*H*-(1,3-oxazine)]-4,4′dione* (**3h**). According to the G.P.1 (16 h reflux): 0.15 g of **3h** (21%). M.p. 177°. IR (ATR): 3073*w* (arom. C–H), 2942*w* (aliph. C–H), 1700*s*, 1678*s*, 1663*s* (C=O), 1600*m*, 1589*m*, 1502*m*, 1447*m* (C–C). ^{1}H-NMR ($CDCl_3$): 8.07–6.89 (*m*, 28 arom. H); 5.63 (*s*, H–C(2), H–C(2′)); 3.89 (*s*, 2 MeO). ^{13}C-NMR ($CDCl_3$): 191.58 (Ar–*C*=O); 166.50 (C(6), C(6′)); 164.75 (MeO–*C*); 161.14 (C(4)=O, C(4′)=O); 137.59, 133.37, 133.37, 131.87, 130.98, 130.77, 130.17, 129.89, 129.63. 128.93, 128.30, 113.46 (arom. C); 92.55 (C(5), C(5′)); 91.22 (C(2), C(2′)); 55.36 (2 MeO). Anal. calc. for $C_{48}H_{36}N_2O_8$ (768.81): C 74.99, H 4.72, N 3.80; found: C 75.49, H 4.74, N 4.36.

*5,5′-Bis(4-methoxybenzoyl)-2,2′,6,6′-tetrakis(4-methoxyphenyl)[3,3′(4*H*,4′*H*)-bi-2*H*-1,3-oxazine]-4,4′-dione* (**3i**). According to the *G.P.1* (20 h reflux): 0.21 g of **3i** (23%). M.p. 176–182°. IR (ATR): 3080*w* (arom. C–H), 2860*w* (aliph. C–H), 1703*m*, 1670*s* (C=O), 1608*m*, 1589*m*, 1506*m*, 1460*m* (C–C). ^{1}H-NMR ($CDCl_3$): 7.97–6.88 (6 *AA′BB′*, 24 arom. H); 6.75, 6.70 (2*s*, H–C(2), H–C(2′)); 3.91, 3.80, 3.73 (3*s*, 6 MeO). ^{13}C-NMR ($CDCl_3$): 190.50 (Ar–*C*=O); 165.23 (C(6), C(6′)); 163.71, 163.50, 162.95 (MeO–*C*); 160.96 (C(4)=O, C(4′)=O); 132.13, 131.97, 131.15, 130.83, 129.85, 129.77, 125.12, 123.36, 114.31, 113.75, 113.71, 113.42 (arom. C); 109.27 (C(5), C(5′)); 91.88, 91.53 (C(2), C(2′)); 55.57, 55.46, 55.38, 55.32 (6 MeO). Anal. calc. for $C_{52}H_{44}N_2O_{12}$ (888.92): C 70.26, H 4.99, N 3.15; found: C 70.31, H 4.99, N 3.25.

*Disubstituted 1*H*-Pyrazoles* **4**: *General Procedure 2.* Compound **3** was dissolved in AcOH (20 ml) and H_2O (4 ml) and heated under reflux for 12 h. After evaporation of the solvent, the residue was crystallized from EtOH: pure **4**.

*3,5-Diphenyl-1*H*-pyrazole* (**4a**): Colorless crystals. M.p. 198° ([11]: 200°) from MeOH. ^{1}H- and ^{13}C-NMR: identical with those reported in the literature.

*3,5-Bis(4-methoxyphenyl)-1*H*-pyrazole* (**4b**): From **3b** (0.83 g): 0.08 g (30%) of **4b**. M.p. 224°. IR (ATR): 3416*m* (N–H), 3022*w* (arom. C–H), 2957*w* (aliph. C–H), 1610*m*, 1501*m*, 1439*m* (C–C, C–N), 1247*m* (C–O). ^{1}H-NMR ($CDCl_3$): 8.50 (*s*, NH); 7.75 (*d*, $J = 8.4$, 4 H$_o$); 6.95 (*d*, $J = 8.4$, 4 H$_m$); 6.73 (*s*, H–C(4)); 3.80 (2*s*, 2 MeO). ^{13}C-NMR ($CDCl_3$): 159.58 (2 C$_p$); 148.48 (C(3), C(5)); 131.00 (4 C$_o$); 126.95 (C$_{ipso}$ at C(3)); 124.01 (C$_{ipso}$ at C(5)); 114.15 (4 C$_m$); 98.84 (C(4)); 55.24 (MeO). Anal. calc. for $C_{17}H_{16}N_2$ (267.30): C 72.84, H 5.75, N 9.99; found: C 73.00, H 5.70, N 9.96.

*3,5-Bis(4-methylphenyl)-1*H*-pyrazole* (**4c**). From **3c** (0.77 g): 0.17 g (59%) of **4c**. M.p. 238°. IR (ATR): 3142*m* (N–H), 3015*w* (arom. C–H), 2920*w*, 2860*w* (aliph. C–H), 1510*m*, 1443*m*, 1440*m* (C–C, C–N). ^{1}H-NMR ((D$_6$)DMSO): 12.42 (*s*, NH); 7.77 (*d*, $J = 8.30$, 4 H$_o$); 7.15 (*d*, $J = 8.30$, 4 H$_m$); 6.95 (*s*, H–C(4)); 2.36, 2.22 (2*s*, 2 Me). ^{13}C-NMR ((D$_6$)DMSO): 147.70 (C(3)); 137.46 (C(5)); 129.78 (2 C$_p$); 129.47 (2 C$_{ipso}$, 4 C$_m$); 123.47 (4 C$_o$); 99.39 (C(4)); 21.21 (2 Me). Anal. calc. for $C_{17}H_{16}N_2O_2$ (280.32): C 82.22, H 6.49, N 11.28; found: C 82.27, H 6.54, N 11.34.

*Trisubstituted 1*H*-Pyrazoles* **5**. *General Procedure 3.* To a stirred mixture of **4** (1 mmol) and AcCl or BzCl (1 mmol) in toluene (20 ml) was added pyridine (cat. amount). The mixture was heated under reflux on a steam bath for 3–5 h with stirring. The solvent was evaported, the residue treated with petroleum ether, and the solid filtered off, recrystallized from the proper solvent and dried (P_2O_5): **5**.

*1-(3,5-Diphenyl-1*H*-pyrazol-1-yl)ethanone* (**5a**): From **4a** (0.22 g): 0.24 g (91%) of **5a**. M.p. 88° (MeOH). IR (ATR): 3044*w* (arom. C–H), 2993*w* (aliph. C–H), 1748*s* (C=O), 1578*m*, 1554*m*, 1483*m*, 1452*m* (C–C, C–N). ^{1}H-NMR ($CDCl_3$): 7.94–7.24 (*m*, 10 arom. H); 6.75 (*s*, H–C(4)); 2.85 (*s*, Me). ^{13}C-NMR ($CDCl_3$): 170.59 (C=O); 153.40 (C(5) or C(3)); 148.73 (C(3) or C(5)); 147.22, 131.77, 130.97, 129.21, 128.94, 128.48, 127.90, 125.70 (arom. C); 109.87 (C(4)); 23.78 (Me). Anal. calc. for $C_{17}H_{14}N_2O$ (262.31): C 77.84, H 5.84, N 10.68; found: C 77.83, H 5.88, N 10.67.

*1-[3,5-bis(4-methoxyphenyl)-1*H*-pyrazol-1-yl]ethanone* (**5b**): From **4b** (0.28 g): 0.28 g (87%) of **5b**. M.p. 94° (MeOH). IR (ATR): 3051*w* (arom. C–H), 2847*w* (aliph. C–H), 1739*s* (C=O), 1610*m*, 1493*m*, 1435*m*, 1425*m* (C–C, C–N), 1285*s*, 1246*s* (C–O–C). ^{1}H-NMR ($CDCl_3$): 7.84 (*dd*, $^3J = 8.6$, $^4J = 2.6$, 2 H_o near C(3)); 7.42 (*d*, $^3J = 8.6$, 2 H_o near C(5)); 7.00 (*d*, $^3J = 8.6$, 2 H_m near C(3)); 7.43 (*dd*, $^3J = 8.6$, $^4J = 2.6$, 2 H_m near C(3)); 6.70 (*s*, H–C(4)); 4.04, 3.88 (2*s*, 2 MeO), 2.75 (*s*, Me). ^{13}C-NMR (APT, 100 MHz, $CDCl_3$): 170.62 (−); 160.52 (−); 159.95 (−); 153.40 (−); 148.73 (−); 133.79 (+); 130.33 (+); 129.44 (+); 124.76 (−); 121.45 (−); 114.23 (+); 110.94 (+); 56.30 (+); 55.35 (+); 55.30 (+); 23.83 (+). Anal. calc. for $C_{19}H_{18}N_2O_3$ (322.36): C 70.79, H 5.63, N 8.69; found: C 71.00, H 5.64, N 8.72.

*1-[3,5-Bis(4-methylphenyl)-1*H*-pyrazol-1-yl]ethanone* (**5c**): From **4c** (0.25 g): 0.25 g (85%) of **5c**. M.p. 85° (MeOH). IR (ATR): 3030*w* (arom. C–H), 2928*w* (aliph. C–H), 1742*s* (C=O), 1610*w*, 1501*m*, 1485*m*, 1441*m* (C–C, C–N), 1279*s* (C–O–C). ^{1}H-NMR ($CDCl_3$): 7.83 (*d*, $^3J = 8.1$, 2 H_o near C(3)); 7.40 (*d*, $^3J = 8.0$, 2 H_o near C(5)); 7.29 (*d*, $^3J = 8.0$, 2 H_m near C(5)); 7.23 (*d*, $^3J = 8.1$, 2 H_m near C(3)); 6.75 (*s*, H–C(4)); 2.85 (*s*, Me); 2.45, 2.35 (2*s*, 2 *Me*–C_6H_4). ^{13}C-NMR ($CDCl_3$): 170.61 (C=O); 153.41 (C(3)); 147.26 (2 C_o near C(5)); 139.15 (2 C_p near C(3)); 138.72 (C(5)); 129.52 (C_{ispo} near C(3)); 128.88 (2 C_m near C(5)); 128.41 (2 C_o near C(3)); 128.25 (2 C_m near C(3)); 126.39 (2 C_o near C(5)); 126.14 (C_{ispo} near C(5)); 109.61 (C(4)); 23.85 (Me); 21.42 (2 *Me*–C_6H_4). Anal. calc. for $C_{19}H_{18}N_2O$ (290.36): C 78.59, H 6.25, N 9.65; found: C 78.63, H 6.24, N 9.64.

*[3,5-Bis(4-methoxyphenyl)-1*H*-pyrazol-1-yl]phenylmethanone* (**5d**): From **4b** (0.28 g): 0.33 g (85%) of **5d**. M.p. 118° (EtOH). IR (ATR): 3059*w* (arom. C–H), 2964*w* (aliph. C–H), 1664*s* (C=O), 1598*m*, 1569*m*, 1450*m* (C–C, C–N), 1259*s* (C–O–C). ^{1}H-NMR ($CDCl_3$): 8.00 (*dd*, $^3J = 7.8$, $^4J = 1.2$, 2 H_o og Ph); 7.82 (*d*, $^3J = 8.4$, 2 H_o near C(3)); 7.60 (*tt*, $^3J = 7.8$, $^4J = 1.2$, H_p of Ph); 7.54 (*td*, $^3J = 7.8$, $^4J = 1.2$, 2 H_m of Ph); 7.48 (*d*, $^3J = 8.3$, 2 H_o near C(5)); 7.20 (*d*, $^3J = 8.3$, 2 H_m at C(5)); 7.15 (*d*, $^3J = 8.4$, 2 H_m near C(3)); 6.75 (*s*, H–C(4)); 3.77, 3.75 (2*s*, 2 MeO). ^{13}C-NMR (APT, 100 MHz, $CDCl_3$): 190.68 (−); 164.15 (−); 135.91 (−); 133.91 (−); 133.81 (+); 131.23 (+); 128.91 (+); 128.76 (+); 127.45 (−); 119.00 (−); 114.22 (+); 114.17 (+); 113.69 (+); 66.56 (+); 55.57 (+). Anal. calc. for $C_{24}H_{20}N_2O_3$ (384.43): C 74.98, H 5.24, N 7.29; found: C 74.96, H 5.20, N 7.27.

*[3,5-Bis(4-methylphenyl)-1*H*-pyrazol-1-yl]phenylmethanone* **5e**: From **4c** (0.25 g): 0.32 g (89%) of **5e**. M.p. 134° (EtOH). IR (ATR): 3024*w* (arom. C–H), 2980*w* (aliph. C–H), 1705*s* (C=O), 1595*s*, 1501*m*, 1447*m* (C–C, C–N), 1265*s* (C–O–C). ^{1}H-NMR ($CDCl_3$): 8.17 ('*dd*', $^3J = 7.2$, $^4J = 1.1$, 2 H_o of Ph); 7.80 (*d*, $^3J = 7.5$, 2 H_o near C(3)); 7.65 (*tt*, $^3J = 7.3$, $^4J = 1.1$, H_p of Ph); 7.54 (*td*, $^3J = 7.2$, $^4J = 1.1$, 2 H_m of Ph); 7.43 (*d*, $^3J = 8.1$, 2 H_o near C(5)); 7.27 (*d*, $^3J = 8.1$, 2 H_m near C(5)); 7.26 (*d*, $^3J = 7.5$, 2 H_m near C(3)); 6.85 (*s*, H–C(4)); 2.55, 2.45 (2*s*, 2 Me). ^{13}C-NMR ($CDCl_3$): 167.50 (C=O); 153.62 (C(3)); 139.06 (C_p near C(3)); 138.75 (C_p near C(5)); 133.08 (C(3)); 132.65 (C_{ipso} of Ph); 129.46, 129.08, 129.02, 128.38, 128.23, 128.00, 126.27 (arom. C); 108.68 (C(4)); 21.42 (2Me). Anal. calc. for $C_{24}H_{20}N_2O$ (352.43): C 81.79, H 5.72, N 7.95; found: C 81.77, H 5.70, N 7.98.

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