The Preparation of Various New Heterocyclic Compounds via Cyclization of Substituted Derivatives of Phenacyl Esters of Hydrazonoacetic Acid

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Abstract: A procedure for the preparation of derivatives of phenacyl hydrazonopropanoates and their application in the synthesis of various heterocycles has been developed. Not only is the preparation of indole derivatives described, but also a new method for the preparation of previously unknown pyridazine derivatives.

Key words: phenacyl esters, hydrazone, cyclization, indoles, pyridazine

Heterocycles are an important class of biologically active compounds that have enormous potential in medicine. New synthetic methods for the preparation of these compounds are crucial for the development of new drugs. We decided to test the applicability of our recently developed method for the synthesis of 2-aryl-3-hydroxyquinolin-4(1*H*)-ones **1** (Figure 1).[1–5] This reaction was shown to have general applicability in the synthesis of different scaffolds, including naphthyridines,[6] and in the preparation of 3-amino derivatives.[7] All these compounds can be considered as aza analogues of flavones and they are promising biologically active compounds. These compounds exhibit, in particular, anticancer activity, but also antiviral and antiprotozoal effects have been observed.[8] Based on the interesting biological results from previously prepared molecules, we wanted to prepare new compounds with one ring. Therefore, we also attempted to apply this synthetic method to the preparation of pyridazine derivatives **2**.

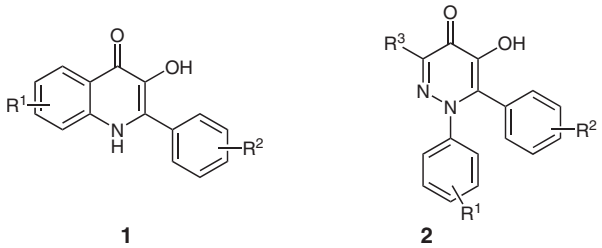

Figure 1 Original preparation of heterocycle **2**

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We selected hydrazones **3** as the starting materials, which are isosteric with the phenacyl esters of anthranilic acid **4** (Figure 2). Various methods of cyclization have been reported for the preparation of quinolones **1**;[1] these methods were also tested for the cyclization of hydrazones **3**.

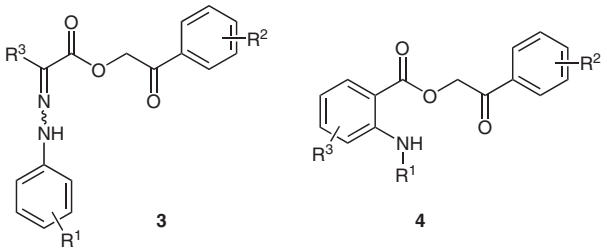
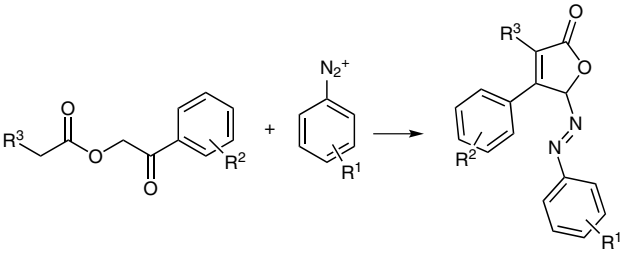


Figure 2

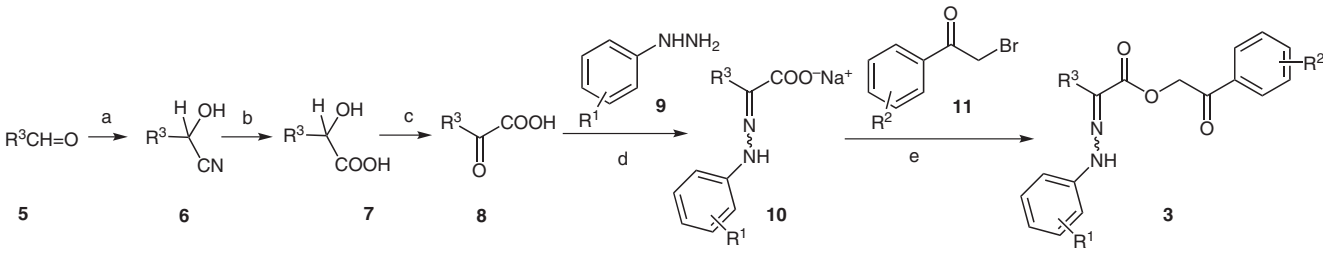
Because the starting materials **3** are relatively complex and contain several reactive functional groups, the reactions and reaction conditions need to be carefully chosen. Phenacyl malonates react with diazonium salts to produce furan derivatives (Scheme 1);[9] thus, a different synthetic route had to be selected.



Scheme 1

Keto acids **8** were selected as the key starting materials. Compounds **8a–c** are commercially available, and phenylglyoxalic acids **8d–g** were prepared by the oxidation of the corresponding cyanohydrins **6d–g** as previously described (Scheme 2, Table 4).[10,11]

The phenacyl esters of hydrazones **3a–x** (Scheme 2, Table 1) were synthesized in the next step by reaction of the sodium salts of hydrazones **10a–l** with phenacyl bromide



5–8
a R^3 = Me[a]
b R^3 = Bn[a]
c R^3 = Et[a]
d R^3 = Ph
e R^3 = 4-MeOC_6H_4
f R^3 = 4-MeC_6H_4
g R^3 = 2-MeOC_6H_4

9
a R^1 = H
b R^1 = 4-Cl
c R^1 = 2,4-$(NO_2)_2$
d $R^1C_6H_4$ = 6-chloropyridin-2-yl
e R^1 = 3-MeO
f R^1 = 4-Et
g R^1 = 2-MeO

11
a R^2 = H
b R^2 = 4-F
c R^2 = 4-NO_2
d R^2 = 4-NH_2-3,5-Cl_2
e R^2 = 3-NO_2
f R^2 = 4-Br
g R^2 = 4-MeO
h R^2 = 4-Me
i R^2 = 3-HO-4-MeO

Scheme 2 *Reagents and conditions:* (a) NaCN, H_2O, $Na_2S_2O_5$; (b) HCl; (c) NaOH, $KMnO_4$; (d) Na_2CO_3, EtOH, 25 °C, 1–8 h; (e) DMF, 5–70 °C, 0.5–20 h. [a] Synthesis started from commercially available compound **8**.

derivatives **11a**–**i** in *N*,*N*-dimethylformamide (Scheme 2, Table 5). In another method, the triethylammonium salts of hydrazone **10** react with phenacyl bromide derivatives **11** in boiling acetone.

The formation of geometrical isomers was observed in these reactions. Some isomers were obtained as the by-product, mostly in low yield, to the major isomers: (*Z*)-**3c** (2%), (*Z*)-**3h** (2%), (*Z*)-**3i** (6%), (*Z*)-**3j** (55%), and (*Z*)-**3l** (19%). Cyclization was not observed on heating (*Z*)-**3m** and (*Z*)-**3r** in trifluoroacetic acid or polyphosphoric acid, instead quantitative formation of isomers (*E*)-**3m** and (*E*)-**3r** was observed. Also the quantitative transformation of isomers (*E*)-**3m** and (*E*)-**3r** was observed on standing in ethanolic solution to give isomers (*Z*)-**3m** and (*Z*)-**3r**.

The structure of the isomers was proven by X-ray crystallography (Figures 3–6) and can also be determined from the NMR data.

Crystal data were collected on a Nonius Kappa CCD diffractometer using graphite monochromated MoKα radiation (λ = 0.7107 Å) at room temperature (295 K). The data sets were integrated with the Denzo-SMN package[12] and corrected for Lorentz polarization effects. The structures were solved by direct methods (SIR97)[13] and refined by full-matrix least square methods with all non-hydrogen atoms anisotropic and hydrogens isotropic. All calculations were performed using SHELXL-97[14] and PARST[15] implemented in the WINGX[16] system of programs.

The most common method for the preparation of quinolones **1** is the cyclization of phenacyl ester **4** in the presence of various acids, typically trifluoroacetic acid or polyphosphoric acid.[3]

The cyclization of hydrazones **3** is more complicated because various reaction pathways are possible, especially the hydrolysis of either the hydrazone or the ester bond. In the cases of compounds **3a**–**i**,**k**,**l**, there is a possibility of the formation of indole derivatives **12**. In fact, all of these

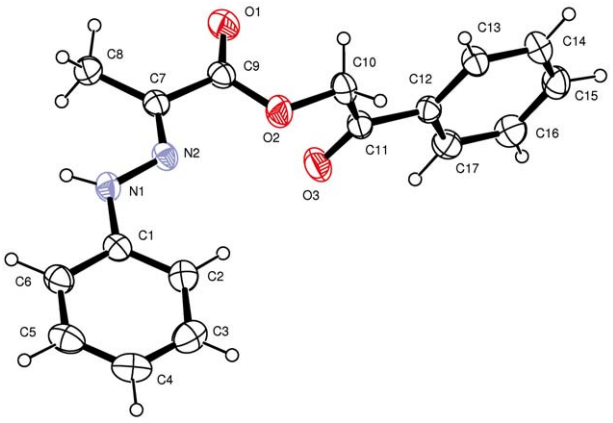


Figure 3 ORTEP[17] views of compound (*E*)-**3a** displaying the thermal ellipsoids at 30% probability

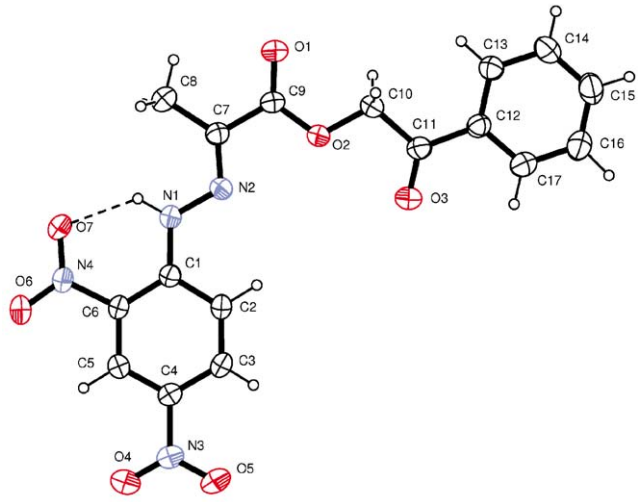


Figure 4 ORTEP[17] views of compound (*E*)-**3j** displaying the thermal ellipsoids at 30% probability

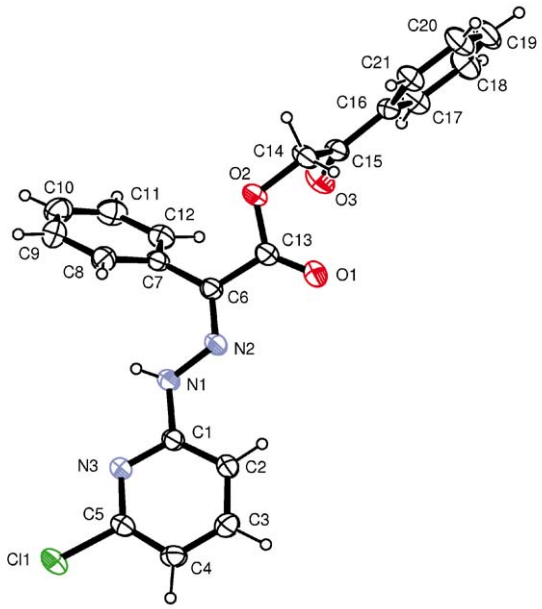


Figure 5 ORTEP[17] views of compound (*E*)-**3r** displaying the thermal ellipsoids at 30% probability

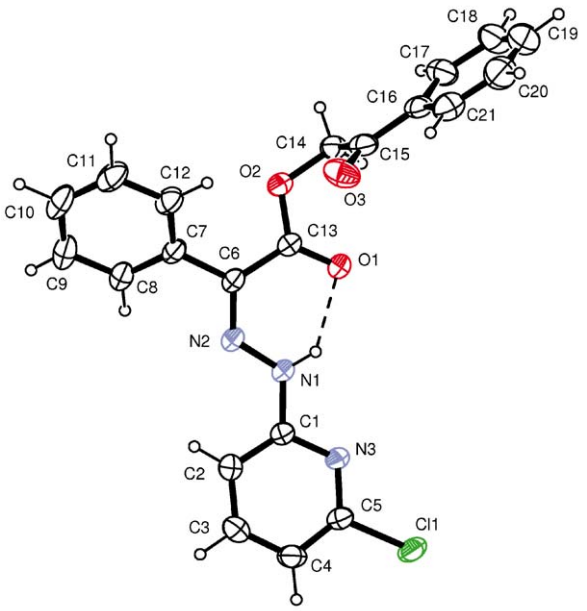


Figure 6 ORTEP[17] views of compound (*Z*)-**3r** displaying the thermal ellipsoids at 30% probability

reactions were observed (Scheme 3). The final product and course of the reaction depends especially on the substitution of the starting compound. The R^3 substituents are critically important in determining the course of the reaction and formation of individual heterocyclic systems.

When we started our research, various acids were used as cyclization agents. Fisher's type of cyclization was preferred for compounds **3a**–**i**,**k**,**l**. Indole derivatives **12** were formed at first as the major products after a few minutes of reflux in trifluoroacetic acid (Scheme 3, Table 2). Lactones **13** and **14** were isolated as the main products if the reaction time was prolonged. Similar reaction pathways as observed in the cyclization using trifluoroacetic acid were also observed in the cyclization of compounds **3a** and **3b** using polyphosphoric acid or boron trifluoride–diethyl ether complex in toluene.

The structures of compounds **12**, **13**, and **14** were confirmed by NMR, and compound **14a** was also confirmed by X-ray crystallography (Figure 7). Using similar cyclization conditions for the cyclization of compounds (*Z*)-**3m** and (*Z*)-**3r** produced only (*E*)-**3m** and (*E*)-**3r**.

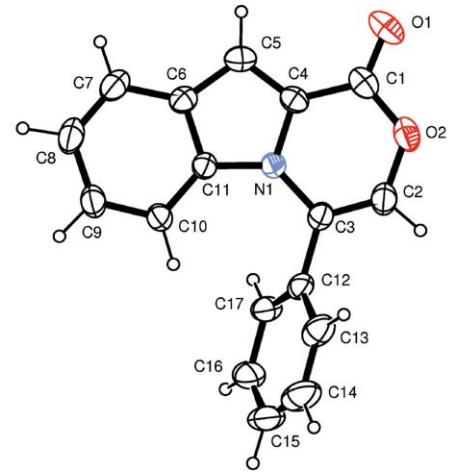
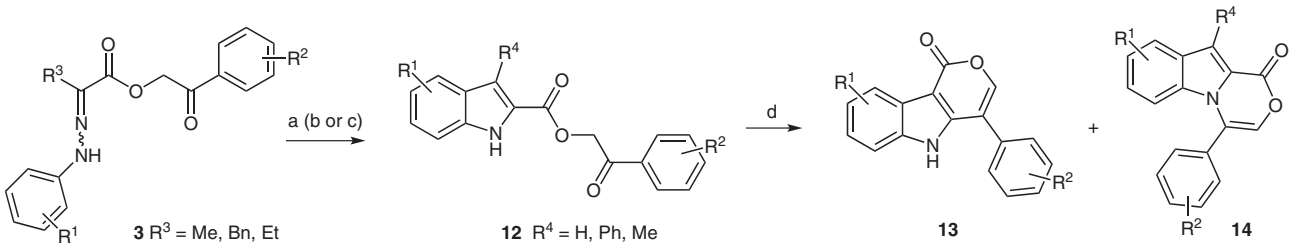


Figure 7 ORTEP[17] views of compound **14a** displaying the thermal ellipsoids at 30% probability

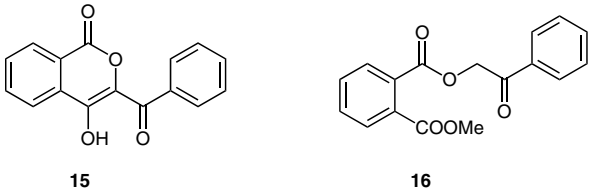


Scheme 3 *Reagents and conditions:* (a) TFA, reflux, 5–30 min; (b) PPA, 90 °C, 35 min; (c) $BF_3{\cdot}OEt_2$, reflux, 30 min; (d) TFA, reflux, 5–320 h.

In addition to using acids, different methods for the cyclization of phenacyl ester **4** are known. In particular, thermal cyclization affords high yields in the cyclization of acetonyl derivatives.[5] Unfortunately, the formation of tar-like product was observed in our case.

A complex mixture of compounds was also observed if the reaction of compound **3** was performed in boiling phosphoryl chloride or warm 1-methylpyrrolidin-2-one.

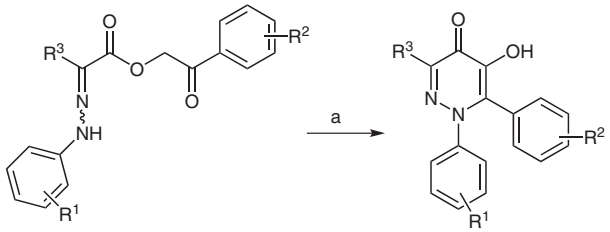
The preparation of quinolone derivatives **1** from anthranilates **4** via cyclization in alkali medium is also known. The best results were observed if the reaction was performed in *N*,*N*-dimethylformamide, 1-methylpyrrolidin-2-one, dimethyl sulfoxide or similar solvents with sodium or potassium hydroxide, but the yields of quinolones **1** were low, most likely due to the limited stability of quinolones **1** in alkali medium. Because the acid cyclization conditions lead to nearly quantitative product yields, cyclization in alkali medium is not used for the preparation of quinolone **1**. Nevertheless, this method was successfully used for the preparation of isocoumarins **15** from phenacyl phthalates **16** (Figure 8), whereas other methods failed.[18]



15 **16**

Figure 8

The expected compounds **2** were prepared by the cyclization of derivatives **3m**–**q**,**s**–**x** in alkali conditions (Scheme 4, Table 3). The best results were obtained using 1-methylpyrrolidin-2-one in the presence of potassium hydroxide at 110 °C. At lower temperatures, only hydrolysis of the ester was observed.



3m–q,s–x **2m–q,s–x**

Scheme 4 *Reagents and conditions:* (a) KOH, NMP, 110 °C, 5–35 min.

Products **2** were only obtained in low yields, hence, other reaction conditions were explored including catalytic potassium *tert*-butoxide in various solvents, the combination of potassium hydroxide with alcohols, diglyme, or toluene, and microwave catalysis. However, all of these reaction conditions failed, and only hydrolysis products were observed.

Only the combination of sodium, potassium, or lithium hydroxide in *N*,*N*-dimethylformamide, 1-methylpyrrolidin-2-one, or dimethyl sulfoxide was successful.

Moreover, other conditions were examined including potassium *tert*-butoxide in tetrahydrofuran at 25 °C, potassium *tert*-butoxide in 1-methylpyrrolidin-2-one under microwave catalysis, potassium hydroxide in methanol and *tert*-butyl alcohol, and potassium *tert*-butoxide in diglyme. All of these conditions led to hydrolyzed products. This reaction did not proceed when the R^1 and R^2 substituted derivatives had electron-withdrawing groups, e.g. NO_2; in these cases only hydrolysis was observed. At higher temperatures, decarboxylation is possible.

The structure of 5-hydroxy-1,3,6-triphenylpyridazin-4(1*H*)-one (**2a**) was confirmed by X-ray (Figure 9).

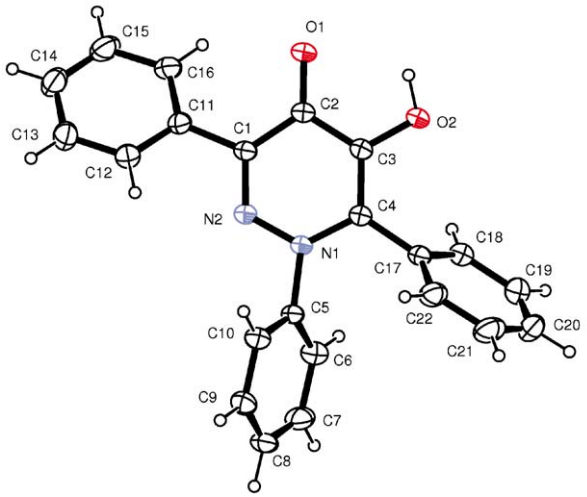


Figure 9 ORTEP[17] views of compound **2a** displaying the thermal ellipsoids at 30% probability

In conclusion, we verified that synthetic method used for the synthesis of 2-aryl-3-hydroxyquinolin-4(1*H*)-ones **1** fail for the synthesis of 5-hydroxy-1,3,6-triarylpyridazin-4(1*H*)-one **2**. A new method for the synthesis of these molecules was developed. Beside these compounds, also new indole derivatives **12**–**14** were prepared.

Table 1 Preparation of Hydrazone Derivatives **3**

Entry	Product (colored solid)	R^1	R^2	R^3	Temp, time	Yield	Mp (°C) (R_f)[a]	HRMS found (calcd)
1	(*E*)-**3a** (light yellow)	H	H	Me	25 °C, 2 h	2.53 g (54%)	147–148 (0.331)	295.1082 (295.1077)
2	(*E*)-**3b** (light yellow)	H	4-F	Me	25 °C, 0.67 h	4.35 g (88%)	138–140 (0.346)	313.0989 (313.0983)
3	(*E*)-**3c** (yellow)	H	4-NO_2	Me	5 °C, 3.5 h	3.86 g (72%)	175–178 (0.278)	340.0932 (340.0928)
4	(*Z*)-**3c** (brown)	H	4-NO_2	Me	5 °C, 3.5 h	0.1 g (2%)[b]	151–153 (0.586)	340.0927 (340.0928)
5	(*E*)-**3d** (light yellow)	H	4-NH_2-3,5-Cl_2	Me	5 °C, 1.5 h	5.12 g (86%)	172–174 (0.293)	378.0412 (378.0407)
6	(*E*)-**3e** (yellow)	H	3-NO_2	Me	5 °C, 1 h	3.66 g (68%)	132–134 (0.195)	340.0931 (340.0928)
7	(*E*)-**3f** (beige)	H	4-Br	Me	5 °C, 1.5 h	4.73 g (80%)	181–183 (0.383)	373.0187 (373.0182)
8	(*E*)-**3g** (beige)	4-Cl	H	Me	5 °C, 0.5 h	3.57 g (69%)	145–147 (0.299)	329.0693 (329.0686)
9	(*E*)-**3h** (beige)	4-Cl	4-Br	Me	25 °C, 1 h	4.89 g (76%)	176–179 (0.328)	408.9948 (408.9949)
10	(*Z*)-**3h** (yellow)	4-Cl	4-Br	Me	25 °C, 1 h	0.12 g (2%)[b]	161–166 (0.704)	408.9949 (408.9949)
11	(*E*)-**3i** (yellow)	4-Cl	4-NO_2	Me	25 °C, 1 h	3.46 g (59%)	183–186 (0.196)	374.0543 (374.0538)
12	(*Z*)-**3i** (yellow)	4-Cl	4-NO_2	Me	25 °C, 1 h	0.33 g (6%)[b]	172–176 (0.545)	374.0541 (374.0538)
13	(*E*)-**3j** (yellow)	2,4-$(NO_2)_2$	H	Me	25 °C, 3 h	2.34 g (39%)	122–124 (0.290)	385.0781 (385.0779)
14	(*Z*)-**3j** (yellow)	2,4-$(NO_2)_2$	H	Me	25 °C, 3 h	3.33 g (55%)	212-215 (0.333)	385.0780 (385.0779)
15	(*E*)-**3k** (brown)	H	H	Bn	70 °C, 2 h	0.45 g (8%)[b]	153–155 (0.493)	373.1551 (373.1547)
16	(*E*)-**3l** (beige)	H	H	Et	25 °C, 1.5 h	3.62 g (74%)	140–143 (0.364)	309.1240 (309.1233)
17	(*Z*)-**3l** (yellow)	H	H	Et	25 °C, 1.5 h	0.91 g (19%)[b]	110–114 (0.678)	311.1388 (311.1390)
18	(*Z*)-**3m** (yellow)	H	H	Ph	25 °C, 5.5 h	4.78 g (84%)	114–117 (0.386)	359.1389 (359.1390)
19	(*E*)-**3m** (yellow)	H	H	Ph	25 °C, 3 h	4.29 g (86%)[c]	184–186 (0.546)	359.1391 (359.1390)
20	(*Z*)-**3n** (yellow)	H	4-NH_2-3,5-Cl_2	Ph	25 °C, 20 h	6.69 g (96%)	142–145 (0.370)	440.0567 (440.0563)
21	(*Z*)-**3o** (yellow)	H	4-OMe	Ph	25 °C, 8 h	5.18 g (84%)	111–113 (0.348)	389.1493 (389.1496)
22	(*Z*)-**3p** (brown)	H	4-Me	Ph	25 °C, 16 h	3.12 g (53%)	114–115 (0.500)	373.1544 (373.1547)
23	(*Z*)-**3q** (yellow)	H	3-OH-4-OMe	Ph	70 °C, 16 h	2.72 g (43%)	150–152 (0.196)	403.1290 (403.1289)

Table 1 Preparation of Hydrazone Derivatives **3** (continued)

Entry	Product (colored solid)	R^1	R^2	R^3	Temp, time	Yield	Mp (°C) (R_f)[a]	HRMS found (calcd)
24	(*Z*)-**3r** (yellow)	–[d]	H	Ph	25 °C, 8 h	5.55 g (89%)	152–154 (0.420)	394.0950 (394.0953)
25	(*E*)-**3r** (beige)	–[d]	H	Ph	70 °C, 5.5 h	4.34 g (79%)[e]	144–148 (0.304)	394.0958 (394.0953)
26	(*Z*)-**3s** (yellow)	3-OMe	H	Ph	25 °C, 2 h	5.04 g (82%)	117–120 (0.590)	389.1500 (389.1496)
27	(*Z*)-**3t** (brown)	4-Et	H	Ph	25 °C, 1.5 h	4.51 g (74%)	123–126 (0.676)	387.1699 (387.1703)
28	(*Z*)-**3u** (yellow)	2-OMe	H	Ph	25 °C, 1.5 h	5.36 g (87%)	150–155 (0.589)	389.1494 (389.1496)
29	(*Z*)-**3v** (yellow)	H	H	4-$MeOC_6H_4$	25 °C, 3 h	5.08 g (83%)	120–124 (0.568)	389.1494 (389.1496)
30	(*Z*)-**3w** (brown)	H	H	4-MeC_6H_4	25 °C, 0.6 h	4.17 g (71%)	110–114 (0.653)	373.1545 (373.1547)
31	(*Z*)-**3x** (yellow)	H	H	2-$MeOC_6H_4$	25 °C, 8 h	0.66 g (11%)[b]	90–95 (0.474)	389.1495 (389.1496)

[a] TLC solvent system: toluene–EtOAc (9:1).
[b] Purified by column chromatography (toluene–EtOAc, 9: 1).
[c] Obtained from (*Z*)-**3m** (TFA).
[d] $R^1C_6H_4$ = 6-chloropyridin-2-yl.
[e] Obtained from (*Z*)-**3r** (PPA).

Table 2 Preparation of Indole Derivatives **12**, **13**, and **14**

Entry	Product (colored solid)	R^1	R^2	R^4	Temp, time	Yield	Mp (°C) (R_f)	HRMS found (calcd)
1	**12a** (beige)	H	H	H	90 °C, 35 min	0.42 g (26%)	197–201 (0.100)[a]	278.0816 (278.0812)
2	**13a** (beige)	H	H	–	73 °C, 9 h	0.75 g (47%)	226–232 (0.294)[b]	260.0713 (260.0706)
3	**14a** (yellow)	H	H	H	73 °C, 9 h	0.68 g (43%)	153–156 (0.673)[b]	262.0861 (262.0863)
4	**12b** (light pink)	H	4-F	H	126 °C, 30 min	0.52 g (30%)	208–211 (0.123)[a]	296.0724 (296.0718)
5	**13b** (white)	H	4-F	–	73 °C, 32 h	0.29 g (17%)	251–253 (0.292)[b]	280.0768 (280.0768)
6	**14b** (beige)	H	4-F	H	73 °C, 32 h	0.58 g (34%)	153–155 (0.670)[b]	280.0767 (280.0768)
7	**12c** (brown)	H	4-NO_2	H	73 °C, 35 min	1.76 g (93%)	222–226 (0.069)[a]	323.0668 (323.0663)
8	**13c** (yellow)	H	4-NO_2	–	73 °C, 36 h	0.12 g (7%)	332–336 (0.258)[b]	305.0562 (305.0557)
9	**14c** (yellow)	H	4-NO_2	H	73 °C, 36 h	0.81 g (44%)	266–270 (0.587)[b]	307.0711 (307.0713)
10	**12d** (light yellow)	H	4-NH_3-3,5-Cl_2	H	73 °C, 30 min	0.92 g (44%)	224–227 (0.077)[a]	361.0146 (361.0141)

Table 2 Preparation of Indole Derivatives **12**, **13**, and **14** (continued)

Entry	Product (colored solid)	R^1	R^2	R^4	Temp, time	Yield	Mp (°C) (R_f)	HRMS found (calcd)
11	**13d** (beige)	H	4-NH_3-3,5-Cl_2	–	73 °C, 28 h	0.36 g (17%)	261–264 (0.292)[b]	345.0192 (345.0192)
12	**14d** (light yellow)	H	4-NH_3-3,5-Cl_2	H	73 °C, 28 h	0.56 g (27%)	190–193 (0.647)[b]	345.0192 (345.0192)
13	**12e** (light yellow)	H	3-NO_2	H	73 °C, 25 min	1.29 g (68%)	174–176 (0.069)[a]	323.0668 (323.0663)
14	**13e** (yellow)	H	3-NO_2	–	73 °C, 26 h	0.22 g (12%)	280–282 (0.253)[b]	305.0562 (305.0557)
15	**14e** (yellow)	H	3-NO_2	H	73 °C, 26 h	0.90 g (48%)	223–225 (0.560)[b]	307.0711 (307.0713)
16	**12f** (beige)	H	4-Br	H	73 °C, 40 min	0.88 g (42%)	218–221 (0.200)[a]	355.9922 (355.9917)
17	**13f** (beige)	H	4-Br	–	73 °C, 28 h	0.40 g (20%)	291–296 (0.303)[b]	339.9970 (339.9968)
18	**14f** (beige)	H	4-Br	H	73 °C, 28 h	0.91 g (44%)	195–198 (0.707)[b]	339.9969 (339.9968)
19	**12g** (white)	5-Cl[c]	H	H	73 °C, 40 min	0.55 g (30%)	205–209 (0.130)[a]	312.0428 (312.0422)
20	**13g** (beige)	8-Cl[d]	H	–	73 °C, 55 h	0.22 g (12%)	276–280 (0.275)[b]	294.0324 (294.0316)
21	**14g** (beige)	8-Cl[e]	H	H	73 °C, 55 h	0.36 g (20%)	203–205 (0.707)[b]	296.0472 (296.0473)
22	**12h** (light yellow)	5-Cl[c]	4-Br	H	73 °C, 20 min	0.50 g (22%)	240–245 (0.212)[a]	389.9531 (389.9527)
23	**13h** (beige)	8-Cl[d]	4-Br	–	73 °C, 320 h	0.24 g (10%)	317–318 (0.275)[b]	373.9578 (373.9578)
24	**14h** (beige)	5-Cl[c]	4-Br	H	73 °C, 320 h	0.35 g (15%)	185–188 (0.747)[b]	373.9578 (373.9578)
25	**12i** (light yellow)	5-Cl[c]	4-NO_2	H	73 °C, 30 min	0.58 g (28%)	218–220 (0.083)[a]	357.0279 (357.0273)
26	**13i** (yellow)	8-Cl[d]	4-NO_2	–	73 °C, 190 h	0.23 g (11%)	336–339 (0.225)[b]	341.0323 (341.0324)
27	**14i** (beige)	8-Cl[e]	4-NO_2	H	73 °C, 190 h	0.52 g (25%)	275–279 (0.588)[b]	341.0321 (341.0324)
28	**12k** (white)	H	H	Ph	73 °C, 20 min	0.48 g (23%)	162–163 (0.144)[a]	356.1283 (356.1281)
29	**14k** (yellow)	H	H	Ph	73 °C, 3.5 h	0.35 g (17%)	189–191 (0.700)[b]	338.1174 (338.1176)
30	**12l** (beige)	H	H	Me	73 °C, 5 min	0.18 g (11%)	181–188 (0.159)[a]	294.1124 (294.1125)
31	**14l** (yellow)	H	H	Me	73 °C, 15 min	1.45 g (86%)	148–150 (0.760)[b]	276.1017 (276.1019)

[a] TLC solvent system: *n*-hexane–EtOAc (7:3).
[b] TLC solvent system: toluene–EtOAc (9:1).
[c] Position 5 of the indole system.
[d] Position 8 of the 4-substituted pyrano[4,3-*b*]indol-1-one.
[e] Position 8 of the 4-substituted 1*H*-[1,4]oxazino[4,3-*a*]indol-1-one.

Table 3 Preparation of Pyridazine Derivatives **2**

Entry	Product (colored solid)	R^1	R^2	R^3	Temp, time	Yield	Mp (°C) (R_f)[a]	HRMS found (calcd)
1	**2m** (beige)	H	H	Ph	20 min, 110 °C	0.13 g (15%)	274–275 (0.157)	341.1289 (341.1285)
2	**2n** (beige)	H	4-NH_2-3,5-Cl_2	Ph	20 min, 110 °C	0.15 g (13%)	245–250 (0.183)	424.0611 (424.0614)
3	**2o** (white)	H	4-OMe	Ph	20 min, 110 °C	0.28 g (29%)	242–243 (0.099)	371.1396 (371.1390)
4	**2p** (white)	H	4-Me	Ph	35 min, 110 °C	0.21 g (23%)	267–269 (0.155)	355.1439 (355.1441)
5	**2q** (white)	H	3-OH-4-OMe	Ph	5 min, 110 °C	0.11 g (11%)	174–180 (0.099)	387.1326 (387.1339)
6	**2s** (beige)	3-OMe	H	Ph	15 min, 110 °C	0.19 g (19%)	230–232 (0.147)	371.1396 (371.1390)
7	**2t** (beige)	4-Et	H	Ph	30 min, 110 °C	0.07 g (7%)	203–205 (0.324)	369.1591 (369.1596)
8	**2u** (beige)	2-OMe	H	Ph	15 min, 110 °C	0.22 g (22%)	288–292 (0.077)	371.1392 (371.1390)
9	**2v** (brown)	H	H	4-$MeOC_6H_4$	20 min, 110 °C	0.08 g (9%)	247–255 (0.139)	371.1392 (371.1390)
10	**2w** (beige)	H	H	4-MeC_6H_4	25 min, 110 °C	0.16 g (17%)	271–273 (0.111)	355.1436 (355.1441)
11	**2x** (white)	H	H	2-$MeOC_6H_4$	30 min, 110 °C	0.14 g (15%)	245–249 (0.028)	371.1393 (371.1390)

[a] TLC solvent system: *n*-hexane–EtOAc (7:3).

Table 4 Preparation of Phenylglyoxalic Acid Derivatives **8**

Enry	Product[a]	R^3	Yield[b]
1	**8d**	Ph	27.0 g (90%)
2	**8e**	4-$MeOC_6H_4$	7.9 g (22%)
3	**8f**	4-MeC_6H_4	19.0 g (58%)
4	**8g**	2-$MeOC_6H_4$	11.2 (31%)

[a] **8d**–**g** were all yellowish oils.
[b] Yield was calculated based on compound **5**.

Table 5 Preparation of Sodium Salts **10**

Enry	Product[a]	R^1	R^3	Time (h)	Yield
1	**10a**	H	Me	1	8.9 g (98%)
2	**10b**	4-Cl	Me	1.5	10.4 g (98%)
3	**10c**	2,4-$(NO_2)_2$	Me	1	11.9 g (98%)
4	**10d**	H	Bn	1	10.4 g (90%)
5	**10e**	H	Et	1.5	5.5 g (63%)
6	**10f**	H	Ph	2	7.0 g (64%)
7	**10g**	3-MeO	Ph	1.5	5.6 g (46%)
8	**10h**	4-Et	Ph	1	8.2 g (67%)
9	**10i**	2-MeO	Ph	1	6.4 g (52%)
10	**10j**	H	4-$MeOC_6H_4$	1	6.9 g (56%)
11	**10k**	H	4-MeC_6H_4	8	10.8 g (94%)
12	**10l**	H	2-$MeOC_6H_4$	1.5	3.8 g (31%)

[a] Products **10a**–**l** were all yellow solids.

NMR measurements: ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 500 spectrometer (500.13 MHz for ^1H, 125.76 MHz for ^{13}C) in DMSO-d_6. The central signals of the solvent [δ = 2.55 (^1H) and δ = 39.6 (^{13}C)] were used as the reference signals. All 2D experiments (gradient-selected (gs)-COSY, gs-TOCSY, gs-HMQC, gs-HMBC) were performed using the manufacturer's software.

LCMS measurements: LCMS were measured with a Thermo Exactive instrument (Thermo Scientific, USA). The chromatographic apparatus consisted of an Accela 1250 LC pump, autosampler, and column thermostat. The separation was performed using the follow-

ing conditions: (1) Luna C18, 3 um, 50 × 2 mm i.d. column (Phenomenex, USA), isocratic elution; mobile phase: MeCN–H_2O (50:50) + 0.1% HCO_2H; flow rate: 250 μL/min; column temperature: 30 °C. (2) Luna C18, 3 um, 4 × 2 mm i.d. column (Phenomenex, USA), isocratic elution; mobile phase: MeCN–H_2O (70:30) + 0.1% HCO_2H; flow rate: 150 μL/min; column temperature: 30 °C. The samples were prepared using the following procedure: sample (1 mg) was dissolved in MeCN–H_2O (1:1, 10 mL) (1 min sonication), and then a portion of this soln (30 μL) and MeCN–H_2O (1:1, 970 μL) were added to a vial and mixed as a final dilution before injection of 5 μL.

HRMS measurements: An Exactive spectrometer with an orbitrap mass analyzer was equipped with heated electrospray ionization (HESI) or atmospheric pressure chemical ionization (APCI). The spectrometer was tuned to obtain a maximum response for *m*/*z* 70–1000. The source parameters were set to the following values: HESI temperature: 250 °C; spray voltage: ±3.5 kV; transfer capillary temperature: 300 °C; sheath gas/auxiliary gas (N_2) flow rates: 35/10. APCI temperature: 400 °C; spray voltage: ±3.5 kV; transfer capillary temperature: 330 °C; sheath gas/aux gas (N_2) flow rates: 25/10. The separated compounds were observed by recording the TIC (total ion current)/time signal. The HRMS spectra of target peaks allowed for evaluation of their elemental composition due to high intensities of their protonated/deprotonated molecules. The identification of the respective structures was performed with less than 3 ppm difference between the experimental and theoretically calculated values.

1,3,6-Triaryl-5-hydroxypyridazin-4(1*H*)-ones 2; General Procedure

Acetates **3m**–**q** and **3s**–**x** (2.65 mmol) were dissolved in NMP (6.0 mL). The mixture was heated to 110–120 °C, and KOH (31.9 mmol, 12 equiv) was added. The mixture was stirred at this temperature for 5–35 min (Table 3, entries 1–11). When the starting material was not observed by TLC (*n*-hexanes–EtOAc, 7:3), the mixture was poured onto ice (100 g). The mixture was acidified by HCl to pH 1. The crude solid product was filtered off, washed with H_2O, and dried in a vacuum drier at 60 °C. Then, the solid product **2** was suspended in EtOAc and heated to reflux for 5 min, and the undissolved product was filtered off. The filter cake was washed with EtOAc and dried in vacuo at 60 °C. If the crude product **2** was soluble in EtOAc, then it was crystallized (EtOH), see Table 3.

2m
Beige solid; yield: 0.13 g (15%).

^{1}H NMR: δ = 8.25 (m, 2 H), 7.37–7.54 (m, 13 H).

^{13}C NMR: δ = 162.3, 147.8, 147.2, 143.8, 136.9, 134.5, 130.0 (all C), 130.4 (2 C), 128.9, 128.8, 128.7 (2 C), 128.4, 128.3, 128.0 (2 + 2 C), 126.8 (2 C) (all CH).

2n
Beige solid; yield: 0.15 g (13%).

^{1}H NMR: δ = 8.24 (m, 2 H), 7.37–7.52 (m, 8 H), 7.25 (s, 2 H), 5.84 (s, NH_2).

^{13}C NMR: δ = 162.3, 148.1, 147.1, 143.9, 141.6, 135.1, 134.6, 117.9, 117.1 (2 C) (all C), 130.1 (2 C), 128.9 (2 C), 128.6, 128.3 (2 C), 128.1 (2 C), 126.9 (2 C) (all CH).

2o
White solid; yield: 0.28 g (29%).

^{1}H NMR: δ = 8.25 (m, 2 H), 7.28–7.54 (m, 10 H), 6.91 (m, 2 H), 3.77 (s, OCH_3).

^{13}C NMR: δ = 162.2, 159.4, 148.0, 144.0, 143.9, 136.8, 134.6, 122.0 (all C), 131.9 (2 C), 128.8, 128.7 (2 C), 128.3 (2 C), 128.0 (2 C), 126.8 (2 C), 113.5 (all CH), 55.2 (OCH_3).

2p
White solid; yield: 0.21 g (23%).

^{1}H NMR: δ = 8.24 (m, 2 H), 7.49 (m, 3 H), 7.43 (m, 2 H), 7.35 (m, 3 H), 7.25 (m, 2 H), 7.16 (m, 2 H), 2.29 (s, CH_3).

^{13}C NMR: δ = 162.3, 147.9, 147.1, 144.0, 137.0, 134.6, 127.0 (all C), 130.3 (2 C), 128.9, 128.8 (2 C), 128.6 (2 C), 128.4, 128.3 (2 C), 128.0 (2 C), 126.9 (2 C) (all CH), 20.9 (CH_3).

2q
White solid; yield: 0.11 g (11%).

^{1}H NMR: δ = 8.23 (m, 2 H), 7.33–7.52 (m, 8 H), 6.86 (d, *J* = 1.9 Hz, 1 H), 6.82 (dd, *J* = 8.1, 1.9 Hz, 1 H), 6.74 (d, *J* = 8.1 Hz, 1 H), 3.56 (s, OCH_3).

^{13}C NMR: δ = 162.3, 147.9, 147.1, 147.0, 144.3, 137.2, 134.6, 120.5 (all C), 128.9, 128.7 (2 C), 128.3 (2 C), 128.2, 128.1 (2 C), 126.8 (2 C), 123.7, 115.1, 114.8 (all CH), 55.7 (OCH_3).

2s
Beige solid; yield: 0.19 g (19%).

^{1}H NMR: δ = 8.24 (m, 2 H), 7.50 (m, 3 H), 7.37 (m, 5 H), 7.25 (t, *J* = 8.1 Hz, 1 H), 7.05 (m, 1 H), 7.00 (dd, *J* = 7.9, 1.9 Hz, 1 H), 6.90 (dd, *J* = 8.4, 2.5 Hz, 1 H), 3.67 (s, OCH_3).

^{13}C NMR: δ = 162.4, 159.2, 147.8, 147.2, 144.8, 136.9, 134.6, 130.1 (all C), 130.4 (2 C), 129.5, 128.9, 128.8, 128.3 (2 C), 128.1 (2 C), 119.1, 114.3, 112.9 (all CH), 55.5 (OCH_3).

2t
Beige solid; yield: 0.07 g (7%).

^{1}H NMR: δ = 8.25 (m, 2 H), 7.49 (m, 3 H), 7.34 (d, *J* = 8.5 Hz, 7 H), 7.18 (m, 2 H), 2.58 (q, *J* = 7.6 Hz, CH_2), 1.15 (t, *J* = 7.6 Hz, CH_3).

^{13}C NMR: δ = 162.3, 147.9, 147.2, 144.1, 141.7, 137.0, 134.6, 130.1 (all C), 130.4, (2 C), 128.9, 128.8, 128.3 (2 C), 128.1 (2 C), 128.0 (2 C), 126.7 (2 C) (all CH), 27.7 (CH_2), 15.4 (CH_3).

2u
Beige solid; yield: 0.22 g (22%).

^{1}H NMR: δ = 8.19 (m, 2 H), 7.61 (m, 1 H), 7.46–7.53 (m, 3 H), 7.31–7.37 (m, 6 H), 7.00 (t, *J* = 7.7 Hz, 1 H), 6.96 (d, *J* = 8.4 Hz, 1 H), 3.64 (s, OCH_3).

^{13}C NMR: δ = 162.5, 153.2, 147.6, 147.4, 138.4, 134.5, 132.4, 129.6 (all C), 130.9, 129.9 (2 C), 129.0, 128.9, 128.8, 128.3 (2 C), 128.1 (2 C), 127.6 (2 C), 120.4, 112.2 (all CH), 55.6 (OCH_3).

2v
Brown solid; yield: 0.08 g (9%).

^{1}H NMR: δ = 8.27 (m, 2 H), 7.29–7.42 (m, 10 H), 7.06 (m, 2 H), 3.85 (s, OCH_3).

^{13}C NMR: δ = 162.3, 159.9, 147.4, 146.9, 143.9, 136.8, 130.1, 127.0 (all C), 130.5 (2 C), 129.8 (2 C), 128.9, 128.8 (2 C), 128.4, 128.1, 126.9 (2 C), 113.5 (all CH), 55.3 (OCH_3).

2w
Beige solid; yield: 0.16 g (17%).

^{1}H NMR: δ = 8.16 (m, 2 H), 7.30–7.43 (m, 12 H), 2.40 (s, CH_3).

^{13}C NMR: δ = 162.4, 147.7, 147.2, 143.9, 138.5, 136.9, 131.8, 130.1 (all C), 130.5 (2 C), 128.9, 128.8 (2 C), 128.7 (2 C), 128.4, 128.2 (2 C), 128.1 (2 C), 126.9 (2 C) (all CH), 21.1 (CH_3).

2x
White solid; yield: 0.14 g (15%).

^{1}H NMR: δ = 7.48 (m, 1 H), 7.27–7.39 (m, 11 H), 7.18 (d, *J* = 8.3 Hz, 1 H), 7.07 (t, *J* = 7.4 Hz, 1 H), 3.76 (s, OCH_3).

^{13}C NMR: δ = 162.2, 157.9, 150.5, 146.4, 143.7, 137.1, 130.1, 124.4 (all C), 130.9, 130.5 (2 C), 130.2, 128.9, 128.8 (2 C), 128.3, 128.1 (2 C), 126.9 (2 C), 120.3, 111.8 (all CH), 55.7 (OCH_3).

2-Aryl-2-oxoethyl (2*E*)-(2-Arylhydrazono)propanoates and 2-Aryl-2-oxoethyl (2*Z*)-(2-Arylhydrazono)propanoates 3; General Procedure

Sodium (2*E*)-(2-arylhydrazono)propanoate **10–c** (17.5 mmol) or sodium (2*Z*)-aryl(arylhydrazono)acetate **10d–g** (17.5 mmol) was dissolved in DMF (30 mL). 1-Aryl-2-bromoethanone **11a–i** (15.8 mmol, 0.9 equiv) was added, and the mixture was stirred for 0.5–20 h at 5–70 °C (TLC monitoring, toluene–EtOAc, 9:1). The mixture was poured onto ice (300 g). The product was filtered off, washed with H_2O, and dried to give **3a–x** in 40–90% yields.

The crude product was purified by dissolving it in acetone and filtering it over charcoal. The acetone was evaporated, and EtOH was added. The mixture was cooled to 0 °C, and the precipitated product was filtered off and dried in a vacuum drier, see Table 1 and Table 6 (Supporting Information).

The isomers of esters **3** were isolated as impurities from the mother liquor by crystallization (**3j**) or by column chromatography (toluene–EtOAc, 9:1) (**3c**,**h**,**i**,**k**,**l**,**x**).

2-Oxo-2-phenylethyl (2*E*)-Phenyl(phenylhydrazono)acetate [(*E*)-3m]

2-Oxo-2-phenylethyl (2*Z*)-phenyl(phenylhydrazono)acetate [(*Z*)-**3m**, 13.9 mmol] was dissolved in TFA (50.0 mL). The mixture was stirred for 3 h at 25 °C (Table 1, entry 19). Then, the mixture was poured into a mixture of ice and H_2O (500 g). The precipitated solid was filtered off, washed with H_2O, and dried. The isolated product was recrystallized (EtOH), see Table 1 (entry 19) and Table 6 (Supporting Information).

2-Oxo-2-phenylethyl (2*E*)-[(6-Chloropyridin-2-yl)hydrazono]phenylacetate [(*E*)-3r]

2-Oxo-2-phenylethyl (2*Z*)-[(6-chloropyridin-2-yl)hydrazono]phenylacetate [(*Z*)-**3r**, 13.9 mmol] was dissolved in PPA (50.0 g). The mixture was stirred for 5.5 h at 70 °C (Table 1, entry 25). Then, the mixture was poured into a mixture of ice and H_2O (500 g). The precipitated solid was filtered off, washed with H_2O, and dried. The isolated product was recrystallized (EtOH), see Table 1 (entry 25) and Table 6 (Supporting Information).

Arylglyoxalic Acid Derivatives 8d–g; General Procedure[9,10]

NaCN (9.8 g, 200 mmol) was dissolved in H_2O (34 mL). Aldehyde derivative **5d–g** (200 mmol) and ice (50.0 g) were added, and the mixture stirred for 5 min at r.t. Then, a mixture of sodium disulfite (19.0 g, 200 mmol) in H_2O (50 mL) was added, and the mixture stirred for 1 h at this temperature. Cyanohydrin derivatives **6d–g** were filtered off or the organic layer was separated, and the derivatives were used in the next step without purification. Cyanohydrin **6d–g** was dissolved in aq 36% HCl (120.0 mL) and stirred for 12 h at 25 °C. Then, the mixture was concentrated in vacuo. The residue was extracted into hot toluene (3 × 100 mL). The toluene layer was evaporated in vacuo, and the oily residue containing hydroxy acid derivative **7d–g** was used in the next step without purification. The oily residue was suspended in H_2O (18.0 mL), and NaOH (3.95 g, 98.75 mmol) in H_2O (18 mL) and ice (70.0 g) were added. The mixture was cooled in an ice–salt bath and $KMnO_4$ (31.6 g, 200 mmol) was added in small portions over a period of 0.5 h at –4 to –2 °C. Then, the reaction was kept at 0 °C for 1.5 h. At the end of the reaction, the excess $KMnO_4$ was destroyed with sodium sulfite. The mixture was filtered off, and the filtrate was acidified to pH 1 using aq 36% HCl. The filtrate was extracted into Et_2O (3 × 100 mL), dried (Na_2SO_4) and concentrated using a rotary evaporator. Phenylglyoxalic acids **8d–g** were obtained as yellowish oils and were used in the next step without purification (Table 4).

Sodium (2*E*)-(2-Arylhydrazono)propanoates 10a–e and (2*Z*)-Sodium Aryl(arylhydrazono)acetates 10f–l; General Procedure

Derivatives **8a–g** (45.4 mmol) were dissolved in EtOH (30.0 mL). Arylhydrazine derivatives **9a–g** (45.4 mmol) were added, and the mixture was stirred at 25 °C for 1–8 h (Table 5) (TLC monitoring, *n*-hexanes–EtOAc, 7:3). Then Na_2CO_3 (2.4 g, 22.7 mmol) was added and the mixture was stirred at 25 °C for 2 h. The solid precipitate was filtered off, washed with EtOH, and dried in a vacuum drier. Compounds **10a–g** were obtained as yellow solids and used in the next step without purification.

2-Aryl-2-oxoethyl 1*H*-Indole-2-carboxylates 12; General Procedure

2-Aryl-2-oxoethyl (2*E*)-(2-arylhydrazono)propanoate **3a–i**,**k**,**l** (5.86 mmol) was dissolved in TFA (20 mL), PPA, or $BF_3{\cdot}OEt_2$ in toluene. The mixture stirred at 100 °C for 20–40 min. When the reaction was complete (TLC monitoring, *n*-hexanes–EtOAc, 7:3), the mixture was poured onto ice (500 g). The precipitated solid was filtered off, washed with H_2O, and dried in vacuo at 60 °C. The isolated compounds **12a–i**,**k**,**l** were purified by crystallization (EtOH) or by column chromatography (*n*-hexanes–EtOAc, 7:3), see Table 2 and Table 7 (Supporting Information).

4-Arylpyrano[4,3-*b*]indole-1(5*H*)-ones 13 and 4-Aryl-1*H*-[1,4]oxazino[4,3-*a*]indole-1-ones 14; General Procedure

Propanoate **3a–i**,**k**,**l** (6.1 mmol) was dissolved in TFA (40.0 mL), and the mixture was heated to reflux until consumption of the starting material (HPLC monitoring). When the reaction was complete, the mixture was poured onto ice (500 g). The precipitated solid was filtered off, washed with H_2O, and dried. The products were separated by column chromatography (silica gel, toluene–EtOAc, 9:1). The isolated products **13** and **14** were then crystallized (EtOH), see **13a–i** and **14a–i**,**k**,**l** (Table 2), and **13a–i** (Table 8) and **14a–i**,**k**,**l** (Table 9) (Supporting Information).

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

References

(1) Hradil, P.; Vaněček, J.; Hlaváč, J.; Ševčík, J. *Collect. Czech. Chem. Commun.* **1999**, *64*, 257.
(2) Hradil, P.; Krejčí, P.; Hlaváč, J.; Wiedermannová, I.; Lyčka, A.; Bertolasi, V. *J. Heterocycl. Chem.* **2004**, *41*, 375.
(3) Hradil, P.; Jirman, J. *Collect. Czech. Chem. Commun.* **1995**, *60*, 1375.
(4) Soural, M.; Hlaváč, J.; Hradil, P.; Fryšová, I.; Hajdúch, M.; Bertolasi, V.; Maloň, M. *Eur. J. Med. Chem.* **2006**, *41*, 467.
(5) Hradil, P.; Hlaváč, J.; Lemr, K. *J. Heterocycl. Chem.* **1999**, *36*, 141.
(6) Lopez, S. E.; Rosales, M. E.; Salazar, J.; Urdaneta, N.; Ferrer, R.; Angel, J. E. *Heterocycl. Commun.* **2003**, *9*, 345.
(7) Hradil, P.; Grepl, M.; Hlavac, J.; Soural, M.; Malon, M.; Bertolasi, V. *J. Org. Chem.* **2006**, *71*, 819.
(8) Hradil, P.; Hlaváč, J.; Soural, M.; Hajdúch, M.; Kolář, M.; Večeřová, R. *Mini-Rev. Med. Chem.* **2009**, *9*, 696.
(9) Mělnický, R.; Kvapil, L.; Šlézar, P.; Grepl, M.; Hlaváč, J.; Lyčka, A.; Hradil, P. *J. Heterocycl. Chem.* **2008**, *45*, 1.

(10) Corson, B. B.; Dodge, A.; Harris, S. A.; Yeaw, J. S. *Org. Synth. Coll. Vol. I*; John Wiley & Sons: London, **1941**, 336.
(11) Corson, B. B.; Dodge, A.; Harris, S. A.; Yeaw, J. S. *Org. Synth. Coll. Vol. I*; John Wiley & Sons: London, **1941**, 241.
(12) Otwinowski, Z.; Minor, Z. In *Methods in Enzymology*; Vol. 276, Part A; Carter, C. W.; Sweet, R. M., Eds.; Academic Press: London, **1977**, 307–326.
(13) Altomare, A.; Burla, M. C.; Camalli, M.; Cascarano, G. L.; Giacovazzo, C.; Guagliardi, A.; Moliterni, A. G.; Polidori, G.; Spagna, R. *J. Appl. Crystallogr.* **1999**, *32*, 115.
(14) Sheldrick, G. M. *SHELXL97, Program for Crystal Structure Refinement*; University of Göttingen: Göttingen, **1997**.
(15) Nardelli, M. *J. Appl. Crystallogr.* **1995**, *28*, 659.
(16) Farrugia, L. J. *J. Appl. Crystallogr.* **1999**, *32*, 837.
(17) Burnett, M. N.; Johnson, C. K. *ORTEP-III: Oak Ridge Thermal Ellipsoids Plot Program for Crystal Structure Illustrations, Oak Ridge National Laboratory Report ORNL-6895*; Oak Ridge National Laboratory: Oak Ridge (TN, USA), **1996**.
(18) Hradil, P.; Mělnický, R.; Grepl, M.; Koristek, K.; Hlaváč, J.; Bertolasi, V. *Heterocycles* **2006**, *68*, 9.