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# Synthesis of 4-aryl-5-hydroxy- and 5-aryl-4-hydroxypyridazin-3(2*H*)-ones and their use in the preparation of 4,5-diarylpyridazin-3(2*H*)-ones and hitherto unknown isochromeno[3,4-*d*]pyridazinediones

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**Abstract**—Easily accessible 2-substituted 4-aryl-5-methoxy- and 2-substituted 5-aryl-4-methoxypyridazin-3(2*H*)-ones were transformed into the corresponding aryl-hydroxypyridazin-3(2*H*)-ones by alkaline hydrolysis. The use of these compounds in the synthesis of 2-substituted 4,5-diarylpyridazin-3(2*H*)-ones with two differently substituted aryl groups was investigated. Two aryl-hydroxypyridazin-3(2*H*)-ones, 2-(2-benzyl-5-hydroxy-3-oxo-2,3-dihydropyridazin-4-yl)benzaldehyde and 2-(1-benzyl-5-hydroxy-6-oxo-1,6-dihydropyridazin-4-yl)benzaldehyde, were transformed into 2-benzyl-1*H*-isochromeno[3,4-*d*]pyridazine-1,6(2*H*)-dione and 3-benzyl-3*H*-isochromeno[3,4-*d*]pyridazine-4,6-dione, respectively, via oxidation of the formyl group with $KMnO_4$ followed by lactonization. 

Recently, our laboratory described a smooth approach towards the synthesis of 2-substituted 4-aryl-5-methoxy- and 2-substituted 5-aryl-4-methoxypyridazin-3(2*H*)-ones via Suzuki arylation of the corresponding chloropyridazin-3(2*H*)-ones.[1a–c,2] Since a hydroxyl group allows further synthetic transformations, we decided to study the alkaline hydrolysis of the methoxy group of these arylated methoxy pyridazinones to the corresponding hydroxypyridazinones.[3]

5-Methoxy-2-methyl-4-(2-methylphenyl)pyridazin-3(2*H*)-one (**1**) was chosen as a test substrate. Attempts to hydrolyze the 5-methoxy group of **1** with 4 equiv. of KOH in water under reflux gave only a very slow reaction. More than 6 days were required to consume all the starting material. Using a larger excess of KOH (20 equiv. instead of 4 equiv., 0.57 M solution) increased the reaction rate and gave a complete hydrolysis after 24 h of reflux (Table 1). It seems that the presence of an aryl ring in the 4 position of the pyridazin-3(2*H*)-one is responsible for this slow hydrolysis rate since 4-chloro-5-methoxypyridazin-3(2*H*)-one can be hydrolyzed within 3 h of reflux using only 1.1 equiv. of KOH.[3d] Under the same conditions as used for the hydrolysis of **1**, the synthesis of other 2-substituted 4-aryl-5-hydroxypyridazin-3(2*H*)-ones was tried (Table 1). Due to the low solubility of several of the 2-substituted 4-aryl-5-methoxypyridazin-3(2*H*)-ones (**1**–**8**) in the hot aqueous KOH solution, often larger amounts of this 0.57 M KOH solution were required. Despite this drawback, the 4-aryl-5-hydroxypyridazin-3(2*H*)-ones (**9**–**16**) were obtained in good to excellent yields in reasonable reaction times. An analogous hydrolysis study on the isomeric 2-substituted 5-aryl-4-methoxypyridazin-3(2*H*)-ones (**17**–**20**) gave similar results (Table 2).

These new 2-substituted 4-aryl-5-hydroxy- and 2-substituted 5-aryl-4-hydroxypyridazin-3(2*H*)-ones seemed of particular synthetic interest. They can be transformed into the corresponding trifluoromethanesulfonyloxypyridazin-3(2*H*)-ones by reaction with trifluoromethanesulfonic anhydride in dichloromethane at −5°C using triethylamine as a base (Tables 3 and 4).[1e,4] A subsequent Suzuki arylation on these triflates yields 2-substituted 4,5-diarylpyridazin-3(2*H*)-ones (**25**–**29** and **30**–**32**) with two differently substituted aryl groups (Tables 3 and 4). Compounds of this type have recently been patented since they show interesting cyclo-oxygenase-2 inhibition properties.[1e] Theoretically, such 4,5-diarylpyridazin-3(2*H*)-ones can also be synthesized by performing a selective Suzuki reaction on 2-substituted 4,5-dichloro- or 2-substituted

*Keywords*: palladium; Suzuki reaction; pyridazinones; hydrolysis; coumarins.

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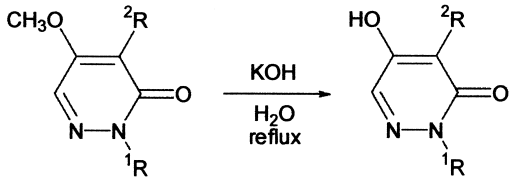
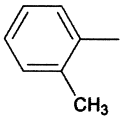
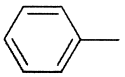
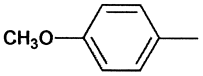
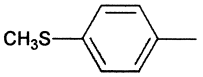
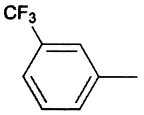
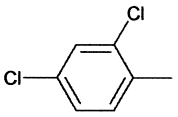
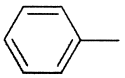
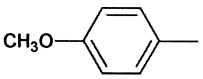
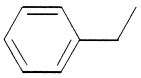
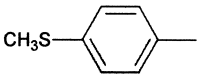
PII: S0040-4020(02)01285-1

**Table 1**. Hydrolysis of 2-substituted 4-aryl-5-methoxypyridazin-3(2*H*)-ones




**1-8** **9-16**

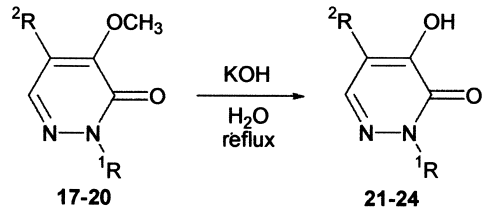
| Starting material | $^1$R | $^2$R | Time (h) | Reaction product | Yield (%) |
|---|---|---|---|---|---|
| **1** | $CH_3$ |  | 24 | **9** | 63[a] |
| **2** | $CH_3$ |  | 8 | **10** | 84[a] |
| **3** | $CH_3$ |  | 7 | **11** | 89[a] |
| **4** | $CH_3$ |  | 12 | **12** | 99[a] |
| **5** | $CH_3$ |  | 4 | **13** | 99[b] |
| **6** | $CH_3$ |  | 7.5 | **14** | 99[b] |
| **7** |  |  | 24 | **15** | 93[c] |
| **8** |  |  | 29 | **16** | 79[d] |

[a] Reaction conditions: **1**–**4** (1 mmol), 35 mL of a 0.57 M KOH solution, 110°C (oil bath).
[b] Reaction conditions: **5**, **6** (1 mmol), 85 mL of a 0.57 M KOH solution, 110°C (oil bath).
[c] Reaction conditions: **7** (1 mmol), 206 mL of a 0.57 M KOH solution, 110°C (oil bath).
[d] Reaction conditions: **8** (1 mmol), 175 mL of a 0.57 M KOH solution, 110°C (oil bath).

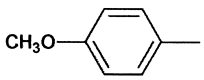
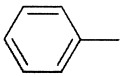
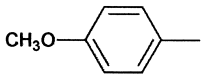
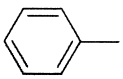
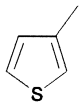
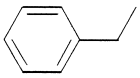
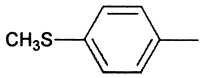
4,5-dibromopyridazin-3(2*H*)-ones followed by a second Suzuki reaction. However, such an approach is fairly unfavorable since we and others found only a poor regioselectivity (two monoaryl-isomers and diarylated product; ratios depending on the boronic acid used) when performing Suzuki arylations on 2-substituted 4,5-dichloro- and 2-substituted 4,5-dibromopyridazin-3(2*H*)-ones.[1a,e] In the above-mentioned patent a general alternative five-step methodology based on a selective Suzuki reaction on 2-benzyl-4-bromo-5-trifluoromethanesulfonyloxypyridazin-3(2*H*)-one is described (Fig. 1).[1e] However also in this case selectivity problems occur since a mixture of 2-benzyl-4-bromo-5-arylpyridazin-3(2*H*)-one and 2-benzyl-4,5-diarylpyridazin-3(2*H*)-one was obtained.[5] The new methodology (Fig. 2) we present in this paper, based on 2-benzyl-4-chloro-5-methoxypyridazin-3(2*H*)-one and its isomer, is a good alternative for the reported patent procedure since regioselectivity problems are avoided. The method based on 2-benzyl-4-chloro-5-methoxypyridazin-3(2*H*)-one is one step shorter than that based on the isomer since N-benzylation and substitution of the 5-chlorine of 4,5-dichloropyridazin-3(2*H*)-one can be performed in one step. Therefore 2-benzyl-4,5-diarylpyridazin-3(2*H*)-ones can be obtained in an equal number of synthetic steps as the patent protocol when 2-benzyl-4-chloro-5-methoxypyridazin-3(2*H*)-one is used. Furthermore, the 2-benzyl group of the 2-benzyl-4,5-diarylpyridazin-3(2*H*)-ones can be removed with $AlCl_3$ allowing further functionalization at the N-2 position.[6]

Recently, we described the synthesis of two isomeric pyridazino[4,5-*c*]isoquinolinones,[1c] 2-benzylpyridazino[4,5-*c*]isoquinolin-1(2*H*)-one and 3-benzylpyridazino[4,5-*c*]isoquinolin-4(3*H*)-one, by reaction of 2-(2-benzyl-5-methoxy-3-oxo-2,3-dihydropyridazin-4-yl)-benzaldehyde (**33**) or 2-(1-benzyl-5-methoxy-6-oxo-1,6-dihydropyridazin-4-yl)benzaldehyde (**35**), respectively, with ammonia. Alkaline hydrolysis of the methoxy group

**Table 2**. Hydrolysis of 2-substituted 5-aryl-4-methoxypyridazin-3(2*H*)-ones

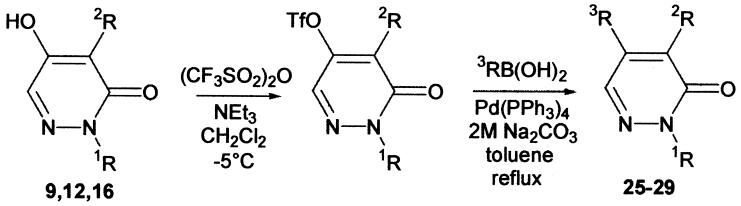



17-20 21-24

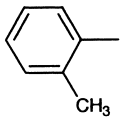
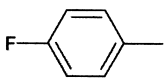
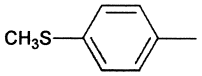
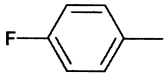
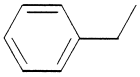
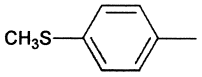
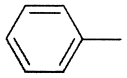
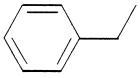
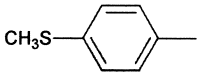
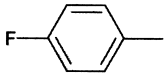
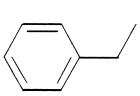
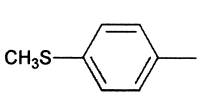
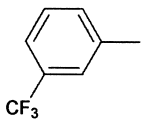
| Starting material | $^1$R | $^2$R | Time (h) | Reaction product | Yield (%) |
|---|---|---|---|---|---|
| **17** | $CH_3$ |  | 5 | **21** | 86[a] |
| **18** |  |  | 5 | **22** | 86[b] |
| **19** |  |  | 6 | **23** | 99[c] |
| **20** |  |  | 24 | **24** | 80[d] |

[a] Reaction conditions: **17** (1 mmol), 70 mL of a 0.57 M KOH solution, 110°C (oil bath).
[b] Reaction conditions: **18** (1 mmol), 170 mL of a 0.57 M KOH solution, 110°C (oil bath).
[c] Reaction conditions: **19** (1 mmol), 155 mL of a 0.57 M KOH solution, 110°C (oil bath).
[d] Reaction conditions: **20** (1 mmol), 140 mL of a 0.57 M KOH solution, 110°C (oil bath).

**Table 3**. Introduction of a second aryl group into 2-substituted 4-aryl-5-hydroxypyridazin-3(2*H*)-ones

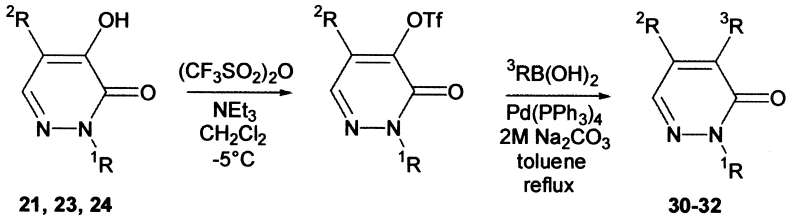



9,12,16 25-29

| Starting material | $^1$R | $^2$R | $^3$R | Time[a] (h) | Reaction product | Yield (%) |
|---|---|---|---|---|---|---|
| **9** | $CH_3$ |  |  | 8 | **25** | 72[b] |
| **12** | $CH_3$ |  |  | 4 | **26** | 73[c] |
| **16** |  |  |  | 2 | **27** | 72[c] |
| **16** |  |  |  | 3 | **28** | 73[c] |
| **16** |  |  |  | 3 | **29** | 54[c] |

[a] Reaction time for the synthesis of the triflate group: 0.5 h in all cases. Indicated reaction times refer to the Suzuki reaction.
[b] Reaction conditions: aryl-trifluoromethanesulfonyloxypyridazinone, boronic acid (3 equiv.), $Pd(PPh_3)_4$ (0.03 equiv.), $Na_2CO_3$ (2 M, 1 mL/mmol pyridazinone), toluene, 120°C (oil bath).
[c] Reaction conditions: aryl-trifluoromethanesulfonyloxypyridazinone, boronic acid (2 equiv.), $Pd(PPh_3)_4$ (0.03 equiv.), $Na_2CO_3$ (2 M, 1 mL/mmol pyridazinone), toluene, 120°C (oil bath).

**Table 4**. Introduction of a second aryl group into 2-substituted 5-aryl-4-hydroxypyridazin-3(2*H*)-ones




**21, 23, 24** **30-32**

| Starting material | $^1$R | $^2$R | $^3$R | Time[a] (h) | Reaction product | Yield (%) |
|---|---|---|---|---|---|---|
| **21** | $CH_3$ | $CH_3O$– | F– | 4 | **30** | 77[b] |
| **23** | | S | F– | 7 | **31** | 88[b] |
| **24** | | $CH_3S$– | F– | 3.5 | **32** | 88[b] |

[a] Reaction time for the synthesis of the triflate group: 0.5 h in all cases. Indicated reaction times refer to the Suzuki reaction.
[b] Reaction conditions: aryl-trifluoromethanesulfonyloxypyridazinone, boronic acid (2 equiv.), $Pd(PPh_3)_4$ (0.03 equiv.), $Na_2CO_3$ (2 M, 1 mL/mmol pyridazinone), toluene, 120°C (oil bath).

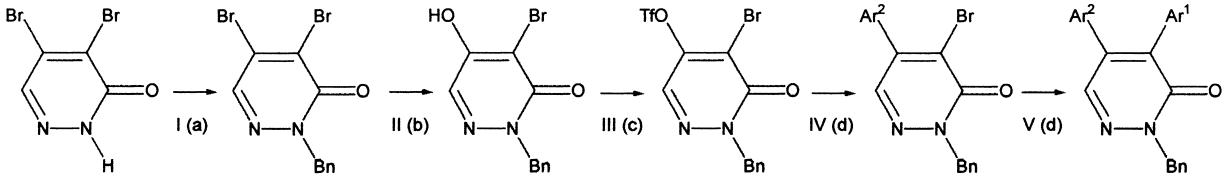



**Figure 1.** Synthesis of 2-benzyl-4,5-diarylpyridazin-3(2*H*)-ones: patented method. (a) Benzyl bromide, 8N KOH, DMF, 50°C; (b) 8N KOH, HMPA, 120–125°C; (c) trifluoromethanesulfonic anhydride, $Et_3N$, $CH_2Cl_2$, 0°C; (d) Suzuki arylation.

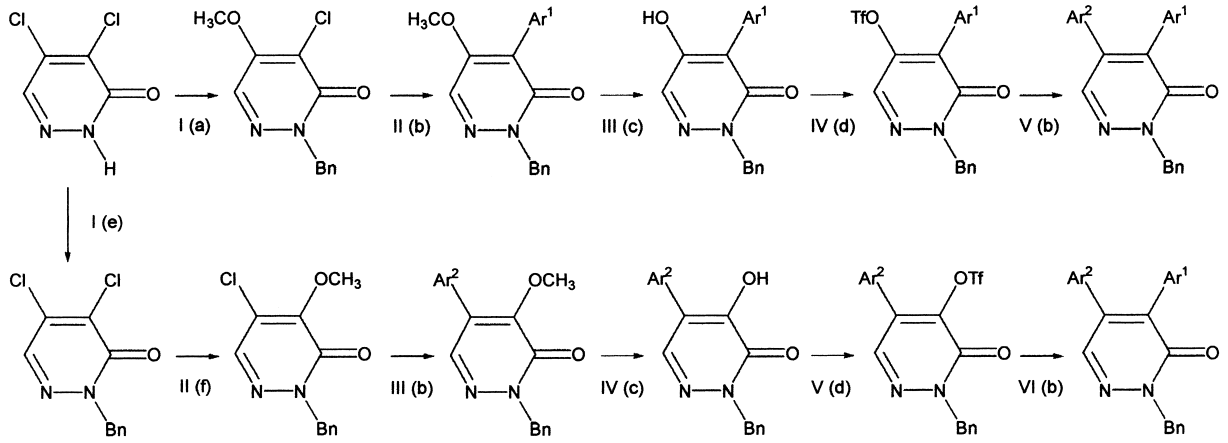
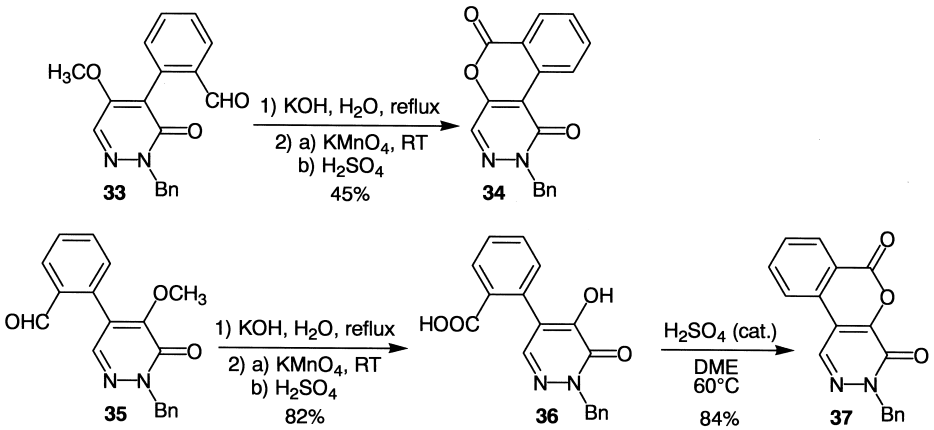



**Figure 2.** Synthesis of 2-benzyl-4,5-diarylpyridazin-3(2*H*)-ones: new method. (a) Benzyl bromide, $K_2CO_3$, $Bu_4NBr$, MeOH, reflux; (b) $Ar^xB(OH)_2$, $Pd(PPh_3)_4$, 2 M $Na_2CO_3$, toluene, reflux; (c) KOH, $H_2O$, reflux; (d) trifluoromethanesulfonic anhydride, $Et_3N$, $CH_2Cl_2$, −5°C; (e) benzyl bromide, $K_2CO_3$, $Bu_4NBr$, $CH_3CN$, reflux; (f) $NaOCH_3$, dioxane, rt.

of **33** with KOH in water as described above gives 2-(2-benzyl-5-hydroxy-3-oxo-2,3-dihydropyridazin-4-yl)benzaldehyde which was not isolated (scheme 1). After cooling down the reaction mixture, the aldehyde moiety of the hydroxypyridazin-3(2*H*)-one was oxidized by addition of $KMnO_4$. When the oxidation reaction was finished, the precipitated $MnO_2$ was filtered off. The obtained filtrate was subsequently acidified with concentrated $H_2SO_4$ leading to hitherto unknown 2-benzyl-1*H*-isochromeno[3,4-*d*]pyridazine-1,6(2*H*)-dione (**34**) in a one pot procedure (scheme 1). Surprisingly, attempts to use a similar protocol on the isomeric 2-(1-benzyl-5-methoxy-6-oxo-1,6-dihydropyridazin-4-yl)benzaldehyde (**35**) leads to the uncyclized 2-(1-benzyl-5-hydroxy-6-oxo-1,6-dihydropyridazin-4-yl)benzoic acid (**36**). Lactonization of **36** with a catalytic amount of concentrated $H_2SO_4$ in DME at 60°C leads to the desired




**Scheme 1.**

3-benzyl-3*H*-isochromeno[3,4-*d*]pyridazine-4,6-dione (**37**). The synthesis of the 5,6-dihydro-2*H*-pyrano[2,3-*d*]pyridazine-2,5-dione skeleton, a debenzo analogue of **34**, has already been described by Stanovnik, Kappe and Mátyus.[3e,7–9] However, the azabenzocoumarins of type **34** and **37** have not been reported before and are the first representatives of a new tricyclic ring system.

In conclusion, alkaline hydrolysis of the methoxy group of easily accessible 2-substituted 4-aryl-5-methoxy- and 5-aryl-4-methoxypyridazin-3(2*H*)-ones yields 2-substituted 4-aryl-5-hydroxy- and 5-aryl-4-hydroxypyridazin-3(2*H*)-ones. Transformation of the hydroxyl group of these compounds into a triflate and subsequent Suzuki arylation reaction on the aryl-trifluoromethanesulfonyloxypyridazin-3(2*H*)-ones gives 4,5-diarylpyridazin-3(2*H*)-ones with two different aryl groups in good yield without selectivity problems. Another illustration of the usefulness of the aryl-hydroxypyridazin-3(2*H*)-ones is provided by the synthesis of hitherto unknown azabenzocoumarins.

## 1. Experimental

NMR spectra were recorded on a Varian Unity 400 spectrometer with TMS as the internal standard. Chemical shifts are given in ppm and *J* values in Hz. The numbering used for the assignment of NMR-signals is as follows: pyridazinone ring simple figures, 4-substituents primed figures, 5-substituents double primed figures and N-substituents triple primed figures. $^{1}H$ and $^{13}C$ NMR assignments of compounds **9**–**16**, **21**–**32** are based on reference spectra; assignments of compounds **34** and **37** are based on 2D-NMR techniques. For mass-spectrometry analysis, samples were dissolved in $CH_3OH$ containing 0.1% formic acid and diluted to a concentration of approximately $10^{-5}$ mol/L. 1 μL injections were directed to the mass spectrometer at a flow rate of 5 μL/min $CH_3OH$ (0.1% formic acid), using the CapLC HPLC system (Waters, Millford). Product ion spectra and exact mass measurements were performed on a quadrupole-time-of-flight mass spectrometer (Q-Tof-2, Micromass, Manchester, UK) equipped with a standard electrospray ionisation (ESI) interface. Cone voltage (35 V) and capillary voltage (3.3 kV) were optimised on one compound and used for all others. Fragmentation was induced by low energy collisional activation using a collision energy of 30 eV (method 1). Alternatively, data dependant acquisition of product ion spectra was performed using an alternating collision energy of 20, 25 and 30 eV (method 2). Method 1 was used for compounds **9**–**15** and **21**–**23**, method 2 for compounds **16**, **24**–**32**, **34** and **37**. IR spectra were recorded on a Bruker Vector 22 spectrometer. The 4-aryl-5-methoxypyridazin-3(2*H*)-ones and 5-aryl-4-methoxypyridazin-3(2*H*)-ones were prepared as described earlier.[1a,c] Trifluoromethanesulfonic anhydride (Acros, Aldrich) and $Pd(PPh_3)_4$ (Acros) were purchased from commercial sources. Dioxane (Acros) was dried over sodium/benzophenone and freshly distilled before use. Flash column chromatography was performed on Kieselgel 60 (Merck), 0.040–0.063 mm.

### 1.1. General procedure for the synthesis of aryl-hydroxypyridazin-3(2*H*)-ones (9–16 and 21–24)

A mixture of the pyridazin-3(2*H*)-one (**1**–**8**, **17**–**20**: 1 mmol), KOH (**1**–**4**: 20 mmol; **17**: 40 mmol; **5**, **6**: 48.5 mmol; **20**: 80 mmol; **19**: 88.5 mmol; **18**: 97 mmol; **8**: 100 mmol; **7**: 119 mmol) and $H_2O$ (**1**–**4**: 35 mL; **17**: 70 mL; **5,6**: 85 mL; **20**: 140 mL; **19**: 155 mL; **18**: 170 mL; **8**: 175 mL; **7**: 206 mL) was stirred and heated under reflux (temperature of oil bath=110°C) until the starting material had disappeared as judged by TLC analysis. After cooling down, the reaction mixture was acidified with concentrated HCl (**1**–**4**: 4 mL; **17**: 8 mL; **5,6**: 10 mL; **20**: 16 mL; **19**: 18 mL; **18**: 19.5 mL; **8**: 20 mL; **7**: 23.5 mL) and placed in the refrigerator overnight. The precipitated hydroxypyridazin-3(2*H*)-one was filtered off, rinsed well with water and dried under vacuum.

The following compounds were prepared in this manner.

**1.1.1. 5-Hydroxy-2-methyl-4-(2-methylphenyl)pyridazin-3(2*H*)-one (9):.** Yield: 0.14 g, 63%; $\nu_{max}$ (KBr): 3068, 2959, 2698, 1629, 1551, 1381, 1303, 1157, 1055, 878, 746, 722, 685, 639, 474 $cm^{-1}$; $\delta_H$ (DMSO-$d_6$): 10.90 (br s, 1H, OH), 7.78 (s, 1H, H-6), 7.14–7.26 (m, 3H, H-3′,4′,5′), 7.07 (br d, 1H, H-6′), 3.62 (s, 3H, $NCH_3$); $\delta_C$ (DMSO-$d_6$): 160.48 (C-3), 154.43 (C-5), 136.82 (C-2′), 131.41 (C-6), 131.27 (C-1′), 130.26 (C-6′), 129.42 (C-3′), 127.56 (C-4′), 125.05

(C-5′), 117.78 (C-4), 39.32 ($NCH_3$); MS (ESI): 217, 142, 128, 117, 115, 105, 103; HRMS (ESI) for $C_{12}H_{13}N_2O_2$ $[M+H]^+$: calcd 217.0977, found 217.0970.

**1.1.2. 5-Hydroxy-2-methyl-4-phenylpyridazin-3(2*H*)-one (10).** Yield: 0.17 g, 84%; $\nu_{max}$ (KBr): 3061, 2677, 1616, 1579, 1412, 1373, 1313, 1150, 1058, 894, 761, 696, 573, 469, 422 $cm^{-1}$; $\delta_H$ (DMSO-$d_6$): 11.04 (br s, 1H, OH), 7.79 (s, 1H, H-6), 7.48 (br d, $J\approx7$ Hz, 2H, H-2′,6′), 7.37 (br t, $J\approx7$ Hz, 2H, H-3′,5′), 7.30 (br t, $J\approx7$ Hz, 1H, H-4′), 3.62 (s, 3H, $NCH_3$); $\delta_C$ (DMSO-$d_6$): 160.58 (C-3), 153.95 (C-5), 131.68 (C-6), 131.20 (C-1′), 130.22 (C-2′,6′), 127.36 (C-4′), 127.32 (C-3′,5′), 116.80 (C-4), 39.49 ($NCH_3$); MS (ESI): 203, 128, 91, 77; HRMS (ESI) for $C_{11}H_{11}N_2O_2$ $[M+H]^+$: calcd 203.0821, found 203.0821.

**1.1.3. 5-Hydroxy-4-(4-methoxyphenyl)-2-methylpyridazin-3(2*H*)-one (11).** Yield: 0.21 g, 89%; $\nu_{max}$ (KBr): 3066, 2974, 2699, 1626, 1610, 1581, 1551, 1371, 1295, 1252, 1178, 1150, 1057, 1024, 837, 797, 675, 615, 548 $cm^{-1}$; $\delta_H$ (DMSO-$d_6$): 10.91 (s, 1H, OH), 7.76 (s, 1H, H-6), 7.48 (d, $J$=8.9 Hz, 2H, H-2′,6′), 6.94 (d, $J$=8.9 Hz, 2H, H-3′,5′), 3.78 (s, 3H, $OCH_3$), 3.61 (s, 3H, $NCH_3$); $\delta_C$ (DMSO-$d_6$): 160.72 (C-3), 158.51 (C-4′), 153.55 (C-5), 131.64 (C-6), 131.54 (C-2′,6′), 123.17 (C-1′), 116.47 (C-4), 112.82 (C-3′,5′), 55.00 ($OCH_3$), 39.53 ($NCH_3$); MS (ESI): 233, 218, 217, 201, 190, 162, 161, 158, 147, 143, 133, 121, 119; HRMS (ESI) for $C_{12}H_{13}N_2O_3$ $[M+H]^+$: calcd 233.0926, found 233.0927.

**1.1.4. 5-Hydroxy-2-methyl-4-(4-methylthiophenyl)pyridazin-3(2*H*)-one (12).** Yield: 0.25 g, 99%; $\nu_{max}$ (KBr): 3061, 2683, 1617, 1572, 1547, 1494, 1411, 1365, 1301, 1151, 1095, 1052, 1011, 894, 762, 660, 590, 497, 475 $cm^{-1}$; $\delta_H$ (DMSO-$d_6$): 11.06 (br s, 1H, OH), 7.78 (s, 1H, H-6), 7.47 (d, $J$=8.6 Hz, 2H, H-2′,6′), 7.26 (d, $J$=8.6 Hz, 2H, H-3′,5′), 3.61 (s, 3H, $NCH_3$), 2.49 (s, 3H, $SCH_3$); $\delta_C$ (DMSO-$d_6$): 160.48 (C-3), 153.82 (C-5), 137.32 (C-4′), 131.56 (C-6), 130.66 (C-2′,6′), 127.60 (C-1′), 124.82 (C-3′,5′), 116.11 (C-4), 39.44 ($NCH_3$), 14.57 ($SCH_3$); MS (ESI): 234, 233, 201, 163, 57; HRMS (ESI) for $C_{12}H_{13}N_2O_2S$ $[M+H]^+$: calcd 249.0698, found 249.0692.

**1.1.5. 5-Hydroxy-2-methyl-4-(3-trifluoromethylphenyl)-pyridazin-3(2*H*)-one (13).** Yield: 0.27 g, 99%; $\nu_{max}$ (KBr): 3070, 2683, 1628, 1580, 1556, 1415, 1376, 1325, 1282, 1173, 1130, 1080, 889, 810, 764, 702, 662, 565, 474 $cm^{-1}$; $\delta_H$ (DMSO-$d_6$): 11.4 (br s, 1H, OH), 7.86 (br s, 1H, H-2′), 7.84 (s, 1H, H-6), 7.82 (br d, $J\approx7.7$ Hz, 1H, H-6′), 7.67 (br d, $J\approx7.7$ Hz, 1H, H-4′), 7.62 (br t, $J\approx7.7$ Hz, 1H, H-5′), 3.64 (s, 3H, $NCH_3$); $\delta_C$ (DMSO-$d_6$): 160.31 (C-3), 154.51 (C-5), 134.33 (C-6′), 132.34 (C-1′), 131.71 (C-6), 128.45 (C-5′), 128.31 (q, $J_{CF}$=31.5 Hz, C-3′), 126.74 (q, $J_{CF}$=3.8 Hz, C-2′), 124.26 (q, $J_{CF}$=272.4 Hz, $CF_3$), 124.04 (q, $J_{CF}$=3.8 Hz, C-4′), 114.97 (C-4), 39.53 ($NCH_3$); MS (ESI): 251, 231, 204, 203, 167; HRMS (ESI) for $C_{12}H_{10}N_2O_2F_3$ $[M+H]^+$: calcd 271.0694, found 271.0691.

**1.1.6. 4-(2,4-Dichlorophenyl)-5-hydroxy-2-methylpyridazin-3(2*H*)-one (14).** Yield: 0.27 g, 99%; $\nu_{max}$ (KBr): 3100, 2699, 1630, 1583, 1555, 1411, 1367, 1299, 1264, 1158, 1104, 1078, 1041, 1015, 872, 824, 601, 490 $cm^{-1}$; $\delta_H$ (DMSO-$d_6$): 11.33 (br s, 1H, OH), 7.79 (s, 1H, H-6), 7.67 (d, $J$=2.1 Hz, 1H, H-3′), 7.45 (dd, $J$=8.2 Hz, $J$=2.1 Hz, 1H, H-5′), 7.30 (d, $J$=8.2 Hz, 1H, H-6′), 3.62 (s, 3H, $NCH_3$); $\delta_C$ (DMSO-$d_6$): 159.82 (C-6), 155.21 (C-5), 134.59 (C-2′), 133.57 (C-6′), 133.24 (C-4′), 131.43 (C-6), 130.01 (C-1′), 128.53 (C-3′), 126.94 (C-5′), 114.64 (C-4), 39.25 ($NCH_3$); MS (ESI): 271, 235, 196, 159; HRMS (ESI) for $C_{11}H_9N_2O_2Cl_2$ $[M+H]^+$: calcd 271.0041, found 271.0040.

**1.1.7. 5-Hydroxy-4-(4-methoxyphenyl)-2-phenylpyridazin-3(2*H*)-one (15).** Yield: 0.27 g, 93%; $\nu_{max}$ (KBr): 3064, 2837, 2689, 1600, 1577, 1512, 1384, 1294, 1252, 1181, 1029, 840, 766, 696, 585 $cm^{-1}$; $\delta_H$ (DMSO-$d_6$): 7.89 (s, 1H, H-6), 7.34–7.56 (m, 7H, Ph+H-2′,6′), 6.93 (d, $J$=9.0 Hz, 2H, H-3′,5′), 3.78 (s, 3H, $OCH_3$); $\delta_C$ (DMSO-$d_6$): 160.64 (C-3), 159.54 (C-4′), 153.68 (C-5), 142.06 (C-1‴), 133.19 (C-6), 131.62 (C-2′,6′), 128.32 (C-3‴,5‴), 127.43 (C-4‴), 125.83 (C-2‴,6‴), 123.10 (C-1′), 116.98 (C-4), 112.82 (C-3′,5′), 55.01 ($OCH_3$); MS (ESI): 295, 176, 161, 147, 119, 93, 92; HRMS (ESI) for $C_{17}H_{15}N_2O_3$ $[M+H]^+$: calcd 295.1083, found 295.1074.

**1.1.8. 2-Benzyl-5-hydroxy-4-(4-methylthiophenyl)pyridazin-3(2*H*)-one (16).** Yield: 0.26 g, 79%; $\nu_{max}$ (KBr): 3438, 3062, 2915, 2719, 2360, 1625, 1572, 1495, 1410, 1377, 1303, 1265, 1154, 1093, 1055, 815, 748, 698, 592, 496 $cm^{-1}$; $\delta_H$ (DMSO-$d_6$): 11.29 (br s, 1H, OH), 7.87 (s, 1H, H-6), 7.48 (d, $J$=8.7 Hz, 2H, H-2′,6′), 7.35–7.28 (m, 5H, H-2‴,3‴,4‴,5‴,6‴), 7.26 (d, $J$=8.7 Hz, 2H, H-3′,5′), 5.23 (s, 2H, $CH_2$), 2.49 (s, 3H, $SCH_3$); $\delta_C$ (DMSO-$d_6$): 160.34 (C-3), 153.95 (C-5), 137.41(C-1‴ or C-4′), 137.20 (C-1‴ or C-4′), 132.35 (C-6), 130.75 (C-2′,6′), 128.33 (C-3‴,5‴), 127.75 (C-2‴,6‴), 127.59 (C-4‴), 127.27 (C-1′), 124.85 (C-3′,5′), 116.35 (C-4), 54.01 ($CH_2$), 14.61 ($SCH_3$); MS (ESI): 325, 91; HRMS (ESI) for $C_{18}H_{17}N_2O_2S$ $[M+H]^+$: calcd 325.1011, found 325.0995.

**1.1.9. 4-Hydroxy-5-(4-methoxyphenyl)-2-methylpyridazin-3(2*H*)-one (21).** Yield: 0.20 g, 86%; $\nu_{max}$ (KBr): 3192, 2843, 1635, 1598, 1519, 1371, 1302, 1255, 1186, 1140, 1030, 931, 842, 786, 750, 612, 522 $cm^{-1}$; $\delta_H$ (DMSO-$d_6$): 10.8 (br s, 1H, OH), 7.96 (s, 1H, H-6), 7.67 (d, $J$=8.9 Hz, 2H, H-3″,5″), 7.03 (d, $J$=8.9 Hz, 2H, H-2″,6″), 3.80 (s, 3H, $OCH_3$), 3.70 (s, 3H, $NCH_3$); $\delta_C$ (DMSO-$d_6$): 159.30 (C-4″), 157.36 (C-3), 148.40 (C-4), 138.14 (C-6), 129.84 (C-2″,6″), 124.51 (C-1″), 118.19 (C-5), 113.96 (C-3″,5″), 55.21 ($OCH_3$), 39.19 ($NCH_3$); MS (ESI): 233, 218, 217, 201, 190, 162, 133, 119, 91; HRMS (ESI) for $C_{12}H_{13}N_2O_3$ $[M+H]^+$: calcd 233.0926, found 233.0939.

**1.1.10. 4-Hydroxy-5-(4-methoxyphenyl)-2-phenylpyridazin-3(2*H*)-one (22).** yield: 0.25 g, 86%; $\nu_{max}$ (KBr): 3184, 2924, 1640, 1619, 1607, 1590, 1514, 1386, 1372, 1252, 1184, 1140, 1025, 835, 781, 763, 694, 521 $cm^{-1}$; $\delta_H$ (DMSO-$d_6$): 11.0 (br s, 1H, OH), 8.16 (s, 1H, H-6), 7.75 (d, $J$=8.7 Hz, 2H, H-2″,6″), 7.64 (br d, $J\approx7.9$ Hz, 2H, H-2‴,6‴), 7.53 (br t, $J\approx7.6$ Hz, 2H, H-3‴,5‴), 7.44 (br t, $J\approx7.2$ Hz, 1H, H-4‴), 7.06 (d, $J$=8.7 Hz, 2H, H-3″,5″), 3.82 (s, 3H, $OCH_3$); $\delta_C$ (DMSO-$d_6$): 159.30 (C-4″), 157.12 (C-3), 149.09 (C-4), 141.44 (C-1‴), 139.29 (C-6), 129.95 (C-2″,6″), 128.53 (C-3‴,5‴), 127.81 (C-4‴), 125.32 (C-2‴,6‴), 124.25 (C-1″), 117.71 (C-5), 113.94 (C-3″,5″), 55.17 ($OCH_3$); MS

(ESI): 174, 148, 146, 133, 92; HRMS (ESI) for $C_{17}H_{15}N_2O_3$ $[M+H]^+$: calcd 295.1083, found 295.1081.

**1.1.11. 4-Hydroxy-2-phenyl-5-(3-thienyl)pyridazin-3(2*H*)-one (23).** Yield: 0.27 g, 99%; $\nu_{max}$ (KBr): 3253, 3120, 3104, 1625, 1590, 1495, 1312, 1199, 1121, 852, 800, 772, 761, 687 $cm^{-1}$; $\delta_H$ (DMSO-$d_6$): 11.35 (br s, 1H, OH), 8.42 (s, 1H, H-6), 8.22 (br d, $J\approx3$ Hz, 1H, H-2″), 7.79 (br d, $J\approx5$ Hz, 1H, H-4″), 7.71 (br dd, $J\approx5$ Hz, $J\approx3$ Hz, 1H, H-5″), 7.64 (br d, $J\approx7.6$ Hz, 2H, H-2‴,6‴), 7.53 (br t, $J\approx7.6$ Hz, 2H, H-3‴,5‴), 7.46 (br t, $J\approx7.3$ Hz, H-4‴); $\delta_C$ (DMSO-$d_6$): 157.11 (C-3), 148.69 (C-4), 141.39 (C-1‴), 138.68 (C-6), 132.49 (C-3″), 128.53 (C-3‴,5‴), 127.80 (C-4‴), 127.15 (C-2″ or C-4″ or C-5″), 126.33 (C-2″ or C-4″ or C-5″), 126.09 (C-2″ or C-4″ or C-5″), 125.30 (C-2‴,6‴), 113.41 (C-5); MS (ESI): 150, 124, 122, 97, 92, 77; HRMS (ESI) for $C_{14}H_{11}N_2O_2S$ $[M+H]^+$: calcd 271.0541, found 271.0562.

**1.1.12. 2-Benzyl-4-hydroxy-5-(4-methylthiophenyl)pyridazin-3(2*H*)-one (24).** Yield: 0.26 g, 80%; $\nu_{max}$ (KBr): 3129, 1636, 1610, 1496, 1399, 1373, 1260, 794, 710 $cm^{-1}$; $\delta_H$(DMSO-$d_6$): 8.03 (s, 1H, H-6), 7.67 (d, $J$=8.6 Hz, 2H, H-2′,6′), 7.34 (d, $J$=8.6 Hz, 2H, H-3′,5′), 7.28–7.25 (m, 5H, Ph), 5.30 (s, 2H, $CH_2$), 2.51 (s, 3H, $SCH_3$); $\delta_C$ (DMSO-$d_6$): 157.06 (C-3), 149.14 (C-4), 138.79 (C-4″), 138.50 (C-6), 136.64 (C-1‴), 128.91 (C-2″,6″), 128.49 (C-1″), 128.37 (C-3‴,5‴), 127.89 (C-2‴,6‴), 127.46 (C-4‴), 125.57 (C-3″,5″), 117.93 (C-5), 54.24 ($CH_2$), 14.42 ($SCH_3$); MS (ESI): 325, 91; HRMS (ESI) for $C_{18}H_{17}N_2O_2S$ $[M+H]^+$: calcd 325.1011, found 325.1008.

### 1.2. General procedure for the synthesis of diarylpyridazin-3(2*H*)-ones (25–29 and 30–32)

A mixture of the pyridazin-3(2*H*)-one (**9**, **12**, **21**, **23**, **24**: 0.5 mmol; **16**: 1.4 mmol), $Et_3N$ (**9**, **12**, **21**, **23**, **24**: 0.093 mL; **16**: 0.26 mL), and dry dichloromethane (**9**, **12**, **21**, **23**, **24**: 3.5 mL; **16**: 7 mL) was placed in an ice-acetone bath (−5°C). Under magnetic stirring, trifluoromethanesulfonic anhydride (**9**, **12**, **21**, **23**, **24**: 0.093 mL (0.55 mmol); **16**: 0.26 mL (1.1 mmol)) was added dropwise to the cooled solution. The reaction mixture was stirred for 30 min at −5°C (the flask was equipped with a drying tube). The mixture was then poured into dilute HCl (**9**, **12**, **21**, **23**, **24**: 2.5 mL 1 M HCl; **16**: 7.3 mL 1 M HCl). Water (30 mL) was added, and the aqueous phase was extracted with $CH_2Cl_2$ (3×30 mL). The combined organic layers were washed with a $NaHCO_3$ solution (1%, 60 mL) and with brine (60 mL). After drying over $MgSO_4$, the organic phase was evaporated to dryness under reduced pressure.

To the crude triflated pyridazin-3(2*H*)-one the appropriate boronic acid (**12**, **16**, **21**, **23**, **24**: 2 equiv.; **9**: 3 equiv.), $Pd(PPh_3)_4$ (0.03 equiv.), $Na_2CO_3$ (2 M, 1 mL for 1 mmol of the crude pyridazinone) and toluene (7 mL) were added. The reaction mixture was flushed with $N_2$ for 5 min under magnetic stirring, and afterwards stirred and heated under reflux (oil bath temperature=120°C) under a $N_2$ atmosphere until the starting material had disappeared as judged by TLC and/or DCI-MS analysis. After cooling, the reaction mixture was evaporated to dryness under reduced pressure. EtOAc (40 mL) was added, and the suspension was placed in an ultrasonic bath for a few minutes. The mixture was filtered, washed thoroughly with EtOAc, and the filtrate was evaporated to dryness under reduced pressure. The residue was purified by flash column chromatography on silica gel.

The following compounds were prepared in this manner.

**1.2.1. 5-(4-Fluorophenyl)-2-methyl-4-(2-methylphenyl)-pyridazin-3(2*H*)-one (25).** Yield: 0.11 g, 72%; eluent for flash column chromatography: heptane–EtOAc (1:2); $\nu_{max}$ (KBr): 1630, 1597, 1579, 1509, 1481, 1339, 1233, 1162, 1104, 1011, 842, 792, 761, 711, 624 $cm^{-1}$; $\delta_H$ (DMSO-$d_6$): 8.05 (s, 1H, H-6), 7.19 (dd, $J_{HH}$=9.0, $J_{HF}$=5.5 Hz, 2H, H-2″,6″), 7.22–7.16 (m, 2H, H-3′ and H-4′), 7.11 (t, $J_{HH}$=$J_{HF}$=9.0 Hz, 2H, H-3″,5″), 7.09–7.04 (m, 1H, H-5′), 6.92 (br d, $J\approx7.8$ Hz, 1H, H-6′), 3.75(s, 3H, $NCH_3$), 2.02 (s, 3H, $CH_3$); $\delta_C$ (DMSO-$d_6$): 161.97 (d, $J_{CF}$=246.4 Hz, C-4″), 158.93 (C-3), 140.30 (C-5), 137.24 (C-6), 136.87 (C-2′ or C-4), 136.24 (C-2′ or C-4), 133.09 (C-1′), 130.95 (d, $J_{CF}$=3.8 Hz, C-1″), 130.84 (d, $J_{CF}$=8.4 Hz, C-2″,6″), 129.81 (C-6′ or C-3′), 129.63 (C-6′ or C-3′), 128.08 (C-4′), 125.32 (C-5′), 115.24 (d, $J_{CF}$=21.4 Hz, C-3″,5″), 40.01 ($NCH_3$), 19.18 ($CH_3$); MS (ESI): 295; HRMS (ESI) for $C_{18}H_{16}N_2OF$ $[M+H]^+$: calcd 295.1247, found 295.1238.

**1.2.2. 5-(4-Fluorophenyl)-2-methyl-4-(4-methylthiophenyl)pyrdidazin-3(2*H*)-one (26).** Yield: 0.12 g, 73%; eluent for flash column chromatography: heptane–EtOAc (1:2); $\nu_{max}$ (KBr): 2923, 1629, 1598, 1511, 1404, 1376, 1342, 1297, 1222, 1157, 848, 822, 591 $cm^{-1}$; $\delta_H$ (DMSO-$d_6$): 7.99 (s, 1H, H-6), 7.24 (dd, $J_{HH}$=8.9, $J_{HF}$=5.5 Hz, 2H, H-2″,6″), 7.17 (t, $J_{HH}$=$J_{HF}$=8.9 Hz, 2H, H-3″,5″), 7.15 (d, $J$=8.7 Hz, 2H, H-2′,6′), 7.09 (d, $J$=8.7 Hz, 2H, H-3′,5′), 3.74 (s, 3H, $NCH_3$), 2.44 (s, 3H, $SCH_3$); $\delta_C$ (DMSO-$d_6$): 161.92 (d, $J_{CF}$=246.4 Hz, C-4″), 159.30 (C-3), 139.33 (C-5 or C-4′), 138.48 (C-5 or C-4′), 137.72 (C-6), 135.52 (C-4), 131.29 (d, $J_{CF}$=9.2 Hz, C-2″,6″+C-1″), 130.83 (C-2′,6′), 129.04 (C-1′), 124.72 (C-3′,5′), 115.44 (d, $J_{CF}$=21.4 Hz, C-3″,5″), 40.12 ($NCH_3$), 14.20 ($SCH_3$); MS (ESI): 327, 279; HRMS (ESI) for $C_{18}H_{16}N_2OSF$ $[M+H]^+$: calcd 327.0967, found 327.0954.

**1.2.3. 2-Benzyl-4-(4-methylthiophenyl)-5-phenylpyridazin-3(2*H*)-one (27).** Yield: 0.39 g, 72%; eluent for flash column chromatography: heptane–EtOAc (8:2); $\nu_{max}$ (KBr): 3028, 2916, 2360, 1640, 1595, 1488, 1437, 1397, 1337, 1300, 1262, 1240, 1155, 1096, 1076, 939, 862, 817, 765, 740, 699, 635, 563, 514, 473 $cm^{-1}$; $\delta_H$ (DMSO-$d_6$): 8.04 (s, 1H, H-6), 7.43–7.29 (m, 8H, H-2‴,3‴,4‴,5‴,6‴+H-2″,6″ or H-3″,5″), 7.22–7.19 (m, 2H, H-2″,6″ or H-3″,5″), 7.13 (d, $J$=9.0 Hz, 2H, H-2′,6′), 7.09 (d, $J$=9.0 Hz, 2H, H-3′,5′), 5.33 (s, 2H, $CH_2$), 2.43 (s, 3H, $CH_3$); $\delta_C$ (DMSO-$d_6$): 159.11 (C-3), 140.20 (C-5), 138.41 (C-4′), 138.35 (C-6), 136.68 (C-1‴), 135.89 (C-4), 134.83 (C-1″), 130.89 (C-2′,6′), 129.12 (C-1′), 129.00 (C-2″), 128.46 (C-4″), 128.42 (C-3‴,5‴), 128.39 (C-3″), 128.18 (C-2‴,6‴), 127.55 (C-4‴), 124.63 (C-3′,5′), 54.78 ($CH_2$), 14.21 ($SCH_3$); MS (ESI): 385, 91; HRMS (ESI) for $C_{24}H_{21}N_2OS$ $[M+H]^+$: calcd 385.1370, found 385.1370.

**1.2.4. 2-Benzyl-5-(4-fluorophenyl)-4-(4-methylthiophenyl)pyridazin-3(2*H*)-one (28).** Yield: 0.41 g, 73%; eluent for flash column chromatography: heptane–EtOAc (8:2);

$\nu_{max}$ (KBr): 3034, 2920, 2360, 1645, 1594, 1509, 1489, 1435, 1348, 1234, 1160, 1096, 941, 861, 836, 823, 740, 696, 612, 583, 525, 500, 480, 456 $cm^{-1}$; $\delta_H$ (DMSO-$d_6$): 8.04 (s, 1H, H-6), 7.44–7.29 (m, 5H, H-2‴,3‴,4‴,5‴,6‴), 7.26 (dd, $J_{HH}$=9.0 Hz, $J_{HF}$=5.5 Hz, 2H, H-2″,6″), 7.16 (t, $J_{HH}$=$J_{HF}$=9.0 Hz, 2H, H-3″,5″), 7.14 (d, $J$=8.8 Hz, 2H, H-2′,6′), 7.10 (d, $J$=8.8 Hz, 2H, H-3′,5′), 5.32 (s, 2H, $CH_2$), 2.44 ($SCH_3$); $\delta_C$ (DMSO-$d_6$): 161.94 (d, $J_{CF}$=246.4 Hz, C-4″), 159.05 (C-3), 139.29 (C-5 or C-4′), 138.55 (C-5 or C-4′), 138.27 (C-6), 136.66 (C-1‴), 136.04 (C-4), 131.37 (d, $J_{CF}$=8.4 Hz, C-2″,6″), 131.22 (d, $J_{CF}$=3.8 Hz, C-1″), 130.89 (C-2′,6′), 128.98 (C-1′), 128.42 (C-3‴,5‴), 128.20 (C-2‴,6‴), 127.55 (C-4‴), 124.69 (C-3′,5′), 115.43 (d, $J_{CF}$=22.1 Hz, C-3″,5″), 54.78 (CH2), 2.44 ($SCH_3$); MS (ESI): 403, 91; HRMS (ESI) for $C_{24}H_{20}N_2OSF$ $[M+H]^+$: calcd 403.1280, found 403.1270.

**1.2.5. 2-Benzyl-4-(4-methylthiophenyl)-5-(3-trifluoromethylphenyl)pyridazin-3(2*H*)-one (29).** Yield: 0.34 g, 54%; eluent for flash column chromatography: heptane–EtOAc (8:2); $\nu_{max}$ (KBr): 3035, 2360, 2342, 1635, 1599, 1317, 1174, 1160, 1128, 1078, 819, 730, 704, 569, 503, 456 $cm^{-1}$; $\delta_H$ (DMSO-$d_6$): 8.12 (s, 1H, H-6), 7.67–7.64 (br. d, 1H, H-4″ or H-6″), 7.58–7.50 (m, 3H, H-2″,5″+H-4″ or H-6″), 7.44–7.29 (m, 5H, H-2‴,3‴,4‴,5‴,6‴), 7.14 (d, $J$=8.7 Hz, 2H, H-2′,6′), 7.10 (d, $J$=8.7 Hz, 2H, H-3′,5′), 5.35 (s, 2H, $CH_2$), 2.42 (s, 3H, $CH_3$); $\delta_C$ (DMSO-$d_6$): 159.01 (C-3), 138.85 (C-5 or C-4′), 138.81(C-5 or C-4′), 137.96 (C-6), 136.73 (C-1″ or C-1‴), 136.62 (C-1″ or C-1‴), 135.86 (C-4), 133.17 (C-6″), 130.84 (C-2′,6′), 129.46 (C-5″), 129.10 (q, $J_{CF}$=32.1 Hz, C-3″), 128.78 (C-1′), 128.44 (C-3‴,5‴), 128.22 (C-2‴,6‴), 127.59 (C-4‴), 125.97 (q, $J_{CF}$=3.8 Hz, C-4″ or C-2″), 125.09 (q, $J_{CF}$=3.8 Hz, C-4″ or C-2″), 124.92 (C-3′,5′), 123.72 (q, $J_{CF}$=272.4 Hz, $CF_3$), 54.82 ($CH_2$), 14.41 ($SCH_3$); MS (ESI): 453, 91; HRMS (ESI) for $C_{25}H_{20}N_2OSF_3$ $[M+H]^+$: calcd 453.1248, found 453.1264.

**1.2.6. 4-(4-Fluorophenyl)-5-(4-methoxyphenyl)-2-methylpyridazin-3(2*H*)-one (30).** Yield: 0.12 g, 77%; eluent for flash column chromatography: heptane–EtOAc (1:2); $\nu_{max}$ (KBr): 1637, 1607, 1530, 1514, 1501, 1469, 1457, 1378, 1342, 1295, 1250, 1233, 1221, 1180, 1157, 1023, 871, 838, 806, 607, 553, 540 $cm^{-1}$; $\delta_H$ (DMSO-$d_6$): 8.00 (s, 1H, H-6), 7.20 (dd, $J_{HH}$=9.0 Hz, $J_{HF}$=5.7 Hz, 2H, H-2′,6′), 7.11 (t, $J_{HH}$=$J_{HF}$=9.0 Hz, 2H, H-3′,5′), 7.10 (d, $J$=8.9 Hz, 2H, H-2″,6″), 6.86 (d, $J$=8.9 Hz, 2H, H-3″,5″), 3.73 (s, 6H, $OCH_3$ and $NCH_3$); $\delta_C$ (DMSO-$d_6$): 161.54 (d, $J_{CF}$=245.9 Hz, C-4′), 159.39 (C-3 or C-4″), 159.36 (C-3 or C-4″), 140.20 (C-5), 137.92 (C-6), 134.28 (C-4), 132.48 (d, $J_{CF}$=8.4 Hz, C-2′,6′), 130.52 (C-2″,6″), 129.57 (d, $J_{CF}$=3.8 Hz, C-1′), 126.64 (C-1″), 114.67 (d, $J_{CF}$=21.4 Hz, C-3′,5′), 113.94 (C-3″,5″), 55.11 ($OCH_3$), 40.03 ($NCH_3$); MS (ESI): 311, 267; HRMS (ESI) for $C_{18}H_{16}N_2O_2F$ $[M+H]^+$: calcd 311.1196, found 311.1202.

**1.2.7. 4-(4-Fluorophenyl)-2-phenyl-5-(3-thienyl)pyridazin-3(2*H*)-one (31).** Yield: 0.15 g, 88%; eluent for flash column chromatography: heptane–EtOAc (1:1); $\nu_{max}$ (KBr): 1637, 1606, 1504, 1229, 852, 835, 800, 782, 763, 696, 559 $cm^{-1}$; $\delta_H$ (DMSO-$d_6$): 8.34 (s, 1H, H-6), 7.75 (dd, $J$=2.9, 1.4 Hz, 1H, H-2″), 7.62 (br d, $J$≈8.4 Hz, 2H, H-2‴,6‴), 7.52 (br t, $J$≈7.9 Hz, 2H, H-3‴,5‴), 7.50 (br t, $J$≈7.4 Hz, 1H, H-4‴), 7.43 (dd, $J$=5.0, 2.9 Hz, 1H, H-5″), 7.31 (dd, $J_{HH}$=9.0 Hz, $J_{HF}$=5.7 Hz, 2H, H-2′,6′), 7.20 (t, $J_{HH}$=9.0 Hz, $J_{HF}$≈9.0 Hz, 2H, H-3′,5′), 6.67 (dd, $J$=5.0, 1.4 Hz, 1H, H-4″); $\delta_C$ (DMSO-$d_6$): 161.91 (d, $J_{CF}$=245.7 Hz, C-4′), 159.01 (C-3), 141.73 (C-1‴), 138.51(C-6), 135.31 (C-3″ or C-4 or C-5), 135.10 (C-3″ or C-4 or C-5), 134.76 (C-3″ or C-4 or C-5), 132.16 (d, $J_{CF}$=8.4 Hz, C-2′,6′), 129.73 (d, $J_{CF}$=3.8 Hz, C-1′), 128.51 (C-3‴,5‴), 127.89 (C-4‴ or C-2″ or C-4″ or C-5″), 127.76 (C-4‴ or C-2″ or C-4″ or C-5″), 127.63 (C-4‴ or C-2″ or C-4″ or C-5″), 126.78 (C-4‴ or C-2″ or C-4″ or C-5″), 125.54 (C-2‴ or C-6‴), 115.00 (d, $J_{CF}$=21.4 Hz, C-3′,5′); MS (ESI): 349; HRMS (ESI) for $C_{20}H_{14}N_2OSF$ $[M+H]^+$: calcd 349.0811, found 349.0801.

**1.2.8. 2-Benzyl-4-(4-fluorophenyl)-5-(4-methylthiophenyl)pyridazin-3(2*H*)-one (32).** Yield: 0.18 g, 88%; eluent for flash column chromatography: heptane–EtOAc (2:1); $\nu_{max}$ (KBr): 1639, 1597, 1229, 1157, 1120, 836, 700 $cm^{-1}$; $\delta_H$ (DMSO-$d_6$): 8.06 (s, 1H, H-6), 7.42–7.28 (m, 5H, Ph), 7.22 (dd, $J_{HH}$=9.0 Hz, $J_{HF}$=5.5 Hz, 2H, H-2″,6″), 7.16 (t, $J_{HH}$=$J_{HF}$=8.8 Hz, 2H, H-3″,5″), 7.15–7.08 (m, 4H, H-2′,3′,5′,6′), 5.32 (s, 2H, $CH_2$), 2.44 (s, 3H, $SCH_3$); $\delta_C$ (DMSO-$d_6$): 161.71 (d, $J_{CF}$=245.8 Hz, C-4′), 159.08 (C-3), 139.98 (C-5 or C-4″), 139.57 (C-5 or C-4″), 138.26 (C-6), 136.68 (C-1‴), 135.14 (C-4), 132.59 (d, $J_{CF}$=8.4 Hz, C-2′,6′), 130.92 (C-1″), 129.58 (C-2″,6″), 129.31 (d, $J_{CF}$=3.8 Hz, C-1′), 128.44 (C-3‴,5‴), 128.24 (C-2‴,6‴), 127.58 (C-4‴), 125.31 (C-3″,5″), 114.70 (d, $J_{CF}$=21.4 Hz, C-3′,5′), 54.80 ($CH_2$), 14.09 ($SCH_3$); MS (ESI): 403, 91; HRMS (ESI) for $C_{24}H_{20}N_2OSF$ $[M+H]^+$: calcd 403.1280, found 403.1275.

### 1.3. Synthesis of isochromeno[3,4-*d*]pyridazinediones (34 and 37)

**1.3.1. 2-Benzyl-1*H*-isochromeno[3,4-*d*]pyridazine-1,6(2*H*)-dione (34).** A mixture of 2-(2-benzyl-5-methoxy-3-oxo-2,3-dihydropyridazin-4-yl)benzaldehyde (**33**) (0.5 mmol), KOH (10 mmol) and $H_2O$ (18 mL) was stirred and refluxed for 24 h. The reaction mixture was cooled down to room temperature and a solution of $KMnO_4$ (0.55 mmol) in $H_2O$ (10 mL) was added dropwise. The mixture was stirred at room temperature for 7 h. Subsequently, the precipitated $MnO_2$ was filtered off and the filtrate was acidified with concentrated $H_2SO_4$ (1.1 mL) and cooled in ice for 30 min and then left overnight at room temperature. The precipitate was filtered off and purified by flash column chromatography on silica gel with dichloromethane as the eluent; yield: 0.07 g, 45%; $\nu_{max}$ (KBr): 2925, 2854, 1749, 1644, 1596, 1549, 1456, 1384, 1365, 1287, 1257, 1233, 1155, 1121, 1090, 1073, 1039, 1021, 836, 790, 740, 697, 686 $cm^{-1}$; $\delta_H$ ($CDCl_3$): 9.46 (ddd, $J$=8.2, 1.2, 0.5 Hz, 1H, H-10), 8.41 (ddd, $J$=7.9, 1.5, 0.5 Hz, 1H, H-7), 8.02 (s, 1H, H-4), 7.91 (ddd, $J$=8.2, 7.5, 1.5 Hz, 1H, H-9), 7.71 (ddd, $J$=7.9, 7.5, 1.2 Hz, 1H, H-8), 7.49–7.45 (m, 2H, $H_{Ph}$-2,6), 7.37–7.25 (m, 3H, $H_{Ph}$-3,4,5), 5.44 (s, 2H, $CH_2$); $\delta_C$ ($CDCl_3$): 159.19 (C-6), 158.64 (C-1), 150.87 (C-4a), 135.93 ($C_{Ph}$-1), 134.80 (C-9), 132.20 (C-10a), 130.72 (C-8), 130.19 (C-7), 130.10 (C-4), 128.75 and 128.73 ($C_{Ph}$-2,6 and $C_{Ph}$-3,5), 128.16 ($C_{Ph}$-4), 128.02 (C-10), 121.74 (C-6a), 111.62 (C-10b), 55.83 ($CH_2$); MS (ESI): 305, 91; HRMS (ESI) for $C_{18}H_{13}N_2O_3$ $[M+H]^+$: calcd 305.0926, found 305.0936.

**1.3.2. 3-Benzyl-3*H*-isochromeno[3,4-*d*]pyridazine-4,6-dione (37).** A mixture of 2-(1-benzyl-5-methoxy-6-oxo-1,6-dihydropyridazin-4-yl)benzaldehyde (**35**) (1 mmol), KOH (20 mmol) and $H_2O$ (35 mL) was stirred and refluxed for 24 h. The reaction mixture was cooled down to room temperature and a solution of $KMnO_4$ (1.1 mmol) in $H_2O$ (20 mL) was added dropwise. The mixture was stirred at room temperature for 7 h. Subsequently, the precipitated $MnO_2$ was filtered off and the filtrate was acidified with concentrated $H_2SO_4$ (2.2 mL) and cooled in ice for 30 min and then left overnight at room temperature. The precipitate was filtered off and dried in vacuo yielding 2-(1-benzyl-5-hydroxy-6-oxo-1,6-dihydropyridazin-4-yl)benzoic acid (**36**) in 82% (0.26 g) yield. A mixture of **36** (0.5 mmol) and concentrated $H_2SO_4$ (0.1 mL) in 1,2-dimethoxyethane (100 mL) was stirred and heated at 60°C for 48 h. The reaction mixture was poured on ice water (80 mL) and extracted with chloroform (3×100 mL). The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by flash column chromatography on silca gel using dichloromethane as the eluent; yield: 0.13 g, 84%; $\nu_{max}$ (KBr): 1750, 1663, 1617, 1455, 1343, 1315, 1260, 1224, 1059, 758, 747, 696, 689 $cm^{-1}$; $\delta_H$ (DMSO-$d_6$): 8.95 (s, 1H, H-1), 8.48 (br d, $J\approx$7.9 Hz, 1H, H-10), 8.33 (dd, $J\approx$7.9, 0.9 Hz, 1H, H-7), 8.06 (ddd, $J$=8.0, 7.4, 1.4 Hz, 1H, H-9), 7.87 (ddd, $J\approx$7.9, 7.4, 1.1, 1H, H-8), 7.37–7.34 (m, 4H, $H_{Ph}$-2,3,5,6), 7.34–7.27 (m, 1H, $H_{Ph}$-4), 5.38 (s, 2H, $CH_2$); $\delta_C$ (DMSO-$d_6$): 159.03 (C-6), 153.07 (C-4), 144.99 (C-4a), 136.34 ($C_{Ph}$-1), 135.64 (C-9), 132.44 (C-1), 131.66 (C-8), 130.64 (C-10a), 129.86 (C-7), 128.42 ($C_{Ph}$-3,5), 127.90 ($C_{Ph}$-2,6), 127.59 ($C_{Ph}$-4), 124.08 (C-10), 122.34 (C-6a), 115.76 (C-10b), 54.40 ($CH_2$); MS (ESI): 305; HRMS (ESI) for $C_{18}H_{13}N_2O_3$ $[M+H]^+$: calcd 305.0926, found 305.0938.

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