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Is samoquasine A indeed benzo[*f*]phthalazin-4(3*H*)-one? Unambiguous, straightforward synthesis of benzo[*f*]phthalazin-4(3*H*)-one and its regioisomer benzo[*f*]phthalazin-1(2*H*)-one

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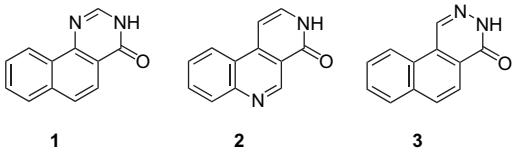
Abstract—In search for the structural elucidation of samoquasine A, a natural product isolated from the seeds of *Annona squamosa* L., two benzo[*f*]phthalazinone isomers have been synthesized. The synthetic pathway followed to build up these skeletons is based on the combination of two Suzuki reactions on a pyridazinone precursor and a ring closure reaction via a condensation reaction. ^{1}H NMR data of the synthesized compound allowed to establish that the structure of the natural product samoquasine A is not benzo[*f*]phthalazin-4(3*H*)-one, as previously suggested.

1. Introduction

The custard apple, *Annona squamosa* L. (Annonaceae), is a tropical fruit tree that grows mainly in America and South-East Asia. The seeds contain many polyketides (acetogenins) showing a wide variety of different biological activities as well as waxy substances containing long-chain fatty acids. In 2000 investigation on seed extracts by Japanese researchers resulted in the isolation of a new minor cytotoxic alkaloid, samoquasine A.[1a,2] A detailed spectroscopic analysis pointed benzo[*h*]quinazolin-4(3*H*)-one (**1**) as the chemical structure of samoquasine A (Fig. 1). Two years later, the same researchers stated, without further argumentation, the alkaloid perlolidine (**2**) to be identical with samoquasine A (Fig. 1), accordingly they withdrew the trivial name samoquasine A.[1b] In January 2003, a Taiwanese group reported a synthesis for benzo[*h*]quinazolin-4(3*H*)-one (**1**).[3] Comparison of the ^{1}H NMR spectral data of this compound with the reported data of samoquasine A clearly confirmed that the chemical structure of samoquasine A is not benzo[*h*]quinazolin-4(3*H*)-one (**1**). In the same paper Wu's group suggested samoquasine A to be benzo[*f*]phthalazin-4(3*H*)-one (**3**). The formal movement of the N-1 nitrogen in **1** from position 1 to 2 is still in agreement with the reported NMR data and observed long-range hydrogen–carbon correlations in the HMBC spectrum of samoquasine A. In November 2003, Chakrabarty and co-workers provided further confirmation for the non-identity of samoquasine A with **1**.[4] Moreover, they clearly showed on the basis of a difference in melting points, solubility data, and the absence of a signal in a specific region of the ^{13}C NMR spectrum of perlolidine that it is highly doubtful that the chemical structure of samoquasine A is identical to that of **2**.



1 2 3

Figure 1. Benzo[*h*]quinazolin-4(3*H*)-one (**1**), perlolidine (**2**), and benzo-[*f*]phthalazin-4(3*H*)-one (**3**).

In this manuscript, as a part of our studies on the synthesis of aza-heterocyclic compounds with biological activities, we

Keywords: Suzuki reaction; Condensation; Natural product; Benzophthalazine.
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now describe the first synthesis of benzo[*f*]phthalazin-4(3*H*)-one (**3**), in order to confirm or reject this chemical structure as the structure of the natural product, and to elaborate a new efficient and flexible approach to access this class of compounds. We followed our well-established strategy, in which we started from pyridazine precursors and utilized the combination of a palladium-catalyzed C–C bond forming process and a C–X (X=N, O) or another C–C bond forming reaction (for C–X: nucleophilic substitution, condensation, lactonization, nitrene C–H insertion, and Buchwald–Hartwig amination; for C–C: Pschorr reaction, Heck-type reaction) to obtain pyridazino-fused ring systems.[5] In this article, syntheses of benzophthalazinone regioisomers, as new examples of such an approach, are described by a combination of two Suzuki reactions (arylation, methylation) with an intramolecular condensation reaction.

2. Results and discussion

The retrosynthetic analysis opted for is shown in Figure 2. 2-Protected 5-(2-formylphenyl)-4-methylpyridazin-3(2*H*)-one (**10**) could be considered as a convenient precursor for **3** via a cyclization that could be achieved by a condensation reaction. The 4-methylpyridazinone should be accessible from a suitable pyridazinone precursor, which allows a regioselective Suzuki reaction.

To avoid regioselectivity problems in a Suzuki reaction on easily accessible 2-protected 4,5-dichloropyridazin-3(2*H*)-ones, a provisionally masked functionality was introduced in the 5-position of this compound.[5,6] As we have recently shown a methoxy group is optimal for this purpose since it can be regioselectively introduced in the 4- or 5-position of the pyridazin-3(2*H*)-one, depending on the solvent, and after the first Suzuki reaction the methoxy substituent can be easily transformed into a leaving group making an appropriate substrate for a second Suzuki reaction yielding the 5-substituted 4-methylpyridazinone (Schemes 1 and 2). For the N-2 protection of the commercially available 4,5-dichloropyridazin-3(2*H*)-one (**4**) benzyl and benzyloxymethyl groups were selected since these should be easily removable at the end of the planned reaction sequence (Scheme 1).[7,8]

The applicability of the Suzuki reaction for the introduction of aromatic rings in chloro-methoxypyridazin-3(2*H*)-ones has extensively been investigated by the Antwerp team, but it is well known that Suzuki reactions in general become more problematic when used for the introduction of aliphatic substituents.[9] Only a few publications about Suzuki methylations were published when we first started to work on this topic and during our study.[9–15] Moreover, there was only one report dealing with the specific methylation of a pyridazinone skeleton, namely 4,5-dichloro-2-methylpyridazin-3(2*H*)-one, by use of trimethylboroxine as methylating agent and an oxime-derived palladacycle as the catalyst.[13b] In this case, due to the presence of the two chlorine atoms, a mixture of 2,4,5-trimethylpyridazin-3(2*H*)-one and 4-chloro-2,5-dimethyl-pyridazin-3(2*H*)-one was formed. Unfortunately the isolated yield of 4-chloro-2,5-dimethylpyridazin-3(2*H*)-one was rather low (35%). Since our approach required a 4-methylpyridazin-3(2*H*)-one a different approach had to be followed. As a first test experiment the Suzuki methylation reaction of 2-benzyloxymethyl-4-chloro-5-methoxypyridazin-3(2*H*)-one (**6a**) with methylboronic acid was attempted under standard Gronowitz reaction conditions (Table 1, entry 1).[16] The reaction was finished after 24 h and produced the desired 2-benzyloxymethyl-5-methoxy-

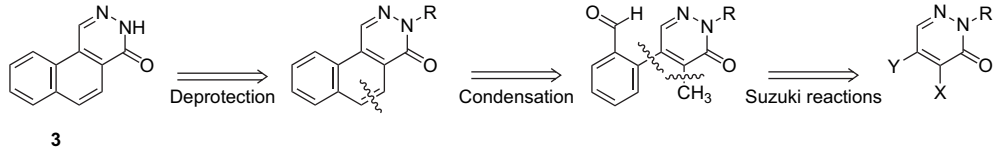
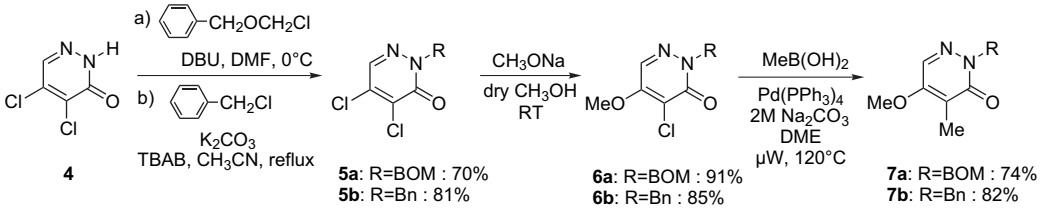
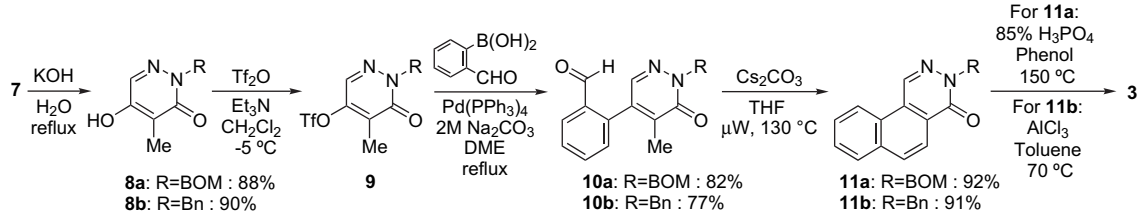


Figure 2. Retrosynthetic analysis of benzo[*f*]phthalazin-4(3*H*)-one (**3**).

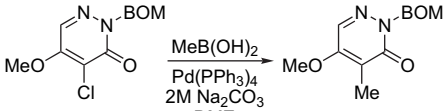


Scheme 1. Synthesis of 2-substituted 4-methyl-5-methoxypyridazin-3(2*H*)-one (**7**).



Scheme 2. Synthesis of benzo[*f*]phthalazin-4(3*H*)-one (**3**).

Table 1. Methylation of **6a** by Suzuki reaction



6a **7a**

Entry	Heating method	Temperature (°C)	Time (h)	Yield (%)
1	Oil bath (atm. pressure)	Reflux	24	71
2	μW	120	4	74
3	μW	120	2	—[a]
4	μW	160	1	80
5	Preheated oil bath (pressure tube)	120	4	77

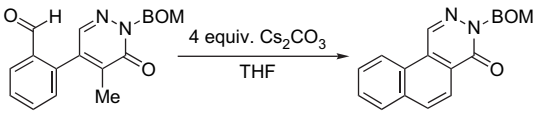
[a] No complete conversion of **6a**.

4-methylpyridazin-3(2*H*)-one (**7a**) in good yield. To examine whether the reaction time could be shortened by raising the reaction temperature we repeated the experiment in an 80 mL closed vessel at 120 °C in a single mode microwave apparatus (CEM, Discover). In this case complete conversion of substrate was obtained in less than 4 h (Table 1, entry 2). Since online monitoring of the microwave experiment (by taking aliquots) is not possible a similar experiment in a reaction time of 2 h was also attempted. The reaction time turned out to be insufficient for complete conversion of **6a** (Table 1, entry 3). By further increasing the reaction temperature to 160 °C, the reaction time could be further reduced to 1 h (Table 1, entry 4). Finally, a rough control experiment was carried out in which a sealed tube containing the reaction mixture was placed in a preheated oil bath. The inner temperature of the mixture was monitored by fiber optic temperature measurement and the temperature of the oil bath was adjusted so that the inner temperature of the mixture was 120 °C.[17] As in the case of microwave heating, the reaction was finished in 4 h and about the same yield of **7a** was obtained after work-up and purification (Table 1, entry 5). This rough comparison indicates that no (useful) special microwave effects have to be taken into account for this type of reaction. For the methylation of the 2-benzyl derivative **6b**, also standard oil bath heating at reflux and microwave irradiation at 120 °C were tested. Both gave good results, although in the case of the reflux experiment under conventional heating a substantially longer reaction time (5 days) was required. While our work was in progress an alternative procedure for the methylation of halopyridazinones has been published by Stevenson and co-workers, in which trimethylaluminum is used as the transmetalating agent with $Pd(PPh_3)_4$ as the catalyst.[18] Unfortunately, methylation of 2-substituted 4,5-dichloropyridazin-3(2*H*)-ones using 1 equiv of trimethylaluminum afforded 4,5-dimethylpyridazin-3(2*H*)-ones and no regioselectivity could be achieved.

Once the methylation reaction was optimized, the methoxy group on C-5 was converted to a triflate in two steps to obtain a leaving group for a Suzuki reaction at this position (Scheme 2). Our previously described reaction conditions for both the hydrolysis and the subsequent triflation reaction of methoxypyridazin-3(2*H*)-ones could be adopted without any problem.[19] Due to their potential instability, the triflates **9** were not purified but immediately subjected to a Suzuki reaction with 2-formylphenylboronic acid under Gronowitz reaction conditions (Scheme 2).

Having precursors **10** in hands we investigated their ring closure to benzo[*f*]phthalazin-4(3*H*)-ones **11**. For these reactions we used our experience in the ring closure reaction of 2′-methylbiphenyl-2-carbaldehydes to phenanthrenes.[20] Remarkably, Cs_2CO_3 as base in DMF at a temperature of 200 °C proved to be suitable for the phenanthrene synthesis. Due to the temperature dependence of pK_a, and carefully designed conditions, the intramolecular condensation of 2′-methylbiphenyl-2-carbaldehydes became feasible in the presence of a weak base at high temperature. When comparing the 2-substituted 5-(2-formylphenyl)-4-methylpyridazin-3(2*H*)-ones (**10**) to 2′-methylbiphenyl-2-carbaldehyde, the methyl groups of **10** clearly will be more acidic due to the electron withdrawing effect of the 4-pyridazinyl unit. Therefore the high-boiling solvent was replaced by THF and a reaction temperature of only 130 °C was selected. The results for the optimization of the ring closure reaction of 2-benzyloxymethyl-5-(2-formylphenyl)-4-methylpyridazin-3(2*H*)-one (**10a**) are summarized in Table 2. Again, microwave irradiation was utilized to heat up the reaction mixture. We changed to the Mars unit (multimode) since we earlier found that the heating efficiency of the Discover unit (single mode), using the 80 mL closed vessel filled with 20 mL of solvent with a low tan δ value (like THF), was low.[21] The Mars microwave apparatus is a multimode microwave oven with a maximum power output of 1200 W and more suitable for heating up larger volumes of poor microwave energy-heat converters. Entry 1 shows that the ring closure of **10a** took place very smoothly under the selected reaction conditions. The reaction is completed after only 45 min and the 3-benzyloxymethylbenzo[*f*]phthalazin-4(3*H*)-one (**11a**) could be isolated in excellent yield. Also in this case a rough comparative experiment was set up to have an indication if microwave effects have to be taken into account.[17] The reaction was thus repeated in a closed vessel in a preheated oil bath with fiber optic temperature measurement (Table 2, entry 2). The reaction gave the same result as the one in which microwave irradiation was used so also in this case only the temperature parameter in the Arrhenius equation is responsible for the fast reactions. Since the condensation proceeded so smoothly the question rose if a temperature of 130 °C is really essential for the reaction to proceed. Therefore, the ring closure reaction was also performed in refluxing THF. Although a 45 min reaction time turned out to be insufficient, a complete conversion of the substrate could be achieved after 2 h. The ring closure reaction of **10b** to 3-benzylbenzo[*f*]phthalazin-4(3*H*)-one (**11b**) was carried out

Table 2. Ring closure reaction of **10a**



10a **11a**

Entry	Heating method	Temperature (°C)	Time (min)	Yield (%)
1	μW	130	45	92
2	Preheated oil bath (pressure tube)	130	45	94

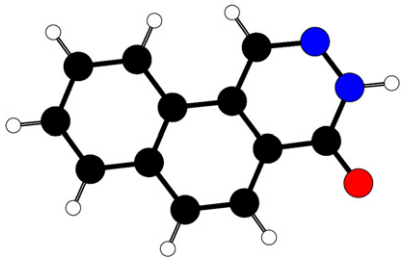


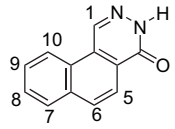
Figure 3. Powder X-ray diffraction confirms the structure of benzo[*f*]phthalazin-4(3*H*)-one (**3**).

under the same microwave conditions as described in entry 1 of Table 2 and also proceeded smoothly.

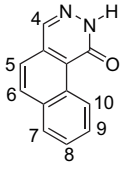
Finally, the last step to obtain benzo[*f*]phthalazin-4(3*H*)-one (**3**) consisted of the removal of the N-2 protecting group of the pyridazinone moiety. The deprotection of **11a** went smoothly in orthophosphoric acid in the presence of phenol,[7] and in the case of **11b** $AlCl_3$ was used as the deprotecting agent (Scheme 2).[8] Besides NMR, IR, and MS analysis also powder X-ray diffraction confirmed the structure of benzo[*f*]phthalazin-4(3*H*)-one (**3**) (Fig. 3).[22] When we compared the ^{1}H NMR data of benzo[*f*]phthalazin-4(3*H*)-one (**3**) with those reported for samoquasine A by Morita et al.,[1] it immediately turned out that there are major differences between both data sets (Table 3). Therefore we unambiguously proved that the structure of the natural product samoquasine A is not benzo[*f*]phthalazin-4(3*H*)-one (**3**).

Table 3. Comparison of the ^{1}H NMR data of samoquasine A, benzo[*f*]phthalazin-4(3*H*)-one (**3**) and benzo[*f*]phthalazin-1(2*H*)-one (**17**)

Samoquasine A



3

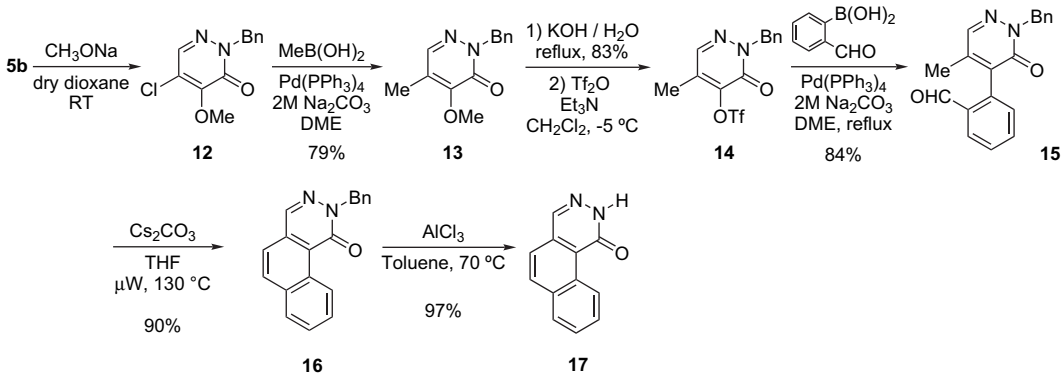


17

δ_H ($CDCl_3$)[1a]	δ_H ($CDCl_3$)		δ_H ($CDCl_3$)	
9.60 s	11.02 s	NH	10.36 s	NH
8.40 dd	9.01 s	H-1	10.10 dd	H-10
8.12 dd	8.56 m	H-10	8.28 s	H-4
7.87 dt	8.41 dd	H-5	8.24 d	H-6
7.71 dt	8.16 d	H-6	8.00 dd	H-7
7.55 d	8.03 m	H-7	7.83 ddd	H-9
7.30 d	7.81–7.75 m	H-8,9	7.77 ddd	H-8
			7.69 d	H-5

Since the identity of the structure of samoquasine A remains unsolved, it seemed worthwhile to synthesize also benzo[*f*]phthalazin-1(2*H*)-one (**17**), an isomer of benzo[*f*]phthalazin-4(3*H*)-one (**3**), which was also taken into consideration as a possible candidate for the chemical structure of samoquasine A. Moreover the strategy we applied for the synthesis of benzo[*f*]phthalazin-4(3*H*)-one (**3**), should only require a minor adaptation to give access to its regioisomer benzo[*f*]phthalazin-1(2*H*)-one (**17**). Indeed, by carrying out the methoxylation of 2-substituted 4,5-dichloropyridazin-3(2*H*)-ones (**5**) in dry dioxane as the solvent instead of dry methanol, the methoxy group is introduced at position 4 instead of position 5.[8] This small change allows to prepare the isomer while all the subsequent reactions can be carried out completely analogously to the above-described procedures (Scheme 3). For the methylation reaction again both conventional heating and microwave irradiation in a closed vessel were tested and gave also similar results. The same goes for the ring closure reaction, for which the microwave heated reaction as well as the reaction under conventional heating in a closed vessel and at reflux gave excellent yields, albeit that also in this case the reflux experiment required a longer reaction time. Since the earlier described deprotection reaction on benzo[*f*]phthalazin-4(3*H*)-one (**3**) showed that both a benzyloxymethyl and a benzyl group could be removed smoothly at the end of the sequence, only a benzyl group was chosen as the protective group for the synthesis of **17**. Comparison of the ^{1}H NMR data of **17** with those described for samoquasine A (Table 3) clearly revealed that also benzo[*f*]phthalazin-1(2*H*)-one could be excluded as the structure of samoquasine A. The structure of compound **17** was also confirmed by powder X-ray diffraction (Fig. 4).[23]

Although the procedure described for the synthesis of benzo[*f*]phthalazin-4(3*H*)-one (**3**) and benzo[*f*]phthalazin-1(2*H*)-one (**17**) is very efficient and allows complete regioselectivity it consists of a considerable number of steps. Therefore we also looked at a classical procedure in which the pyridazinone moiety is attached onto a carbocyclic skeleton by reaction of an *ortho*-dicarbonyl compound with hydrazine (Scheme 4). In the late sixties, Stanovnik and Tišler described a simple two-step synthesis of 1,4-dichlorobenzo[*f*]phthalazine (**20**) starting from commercially available 1,2-naphthalenedicarboxylic anhydride (**18**).[24] When



Scheme 3. Synthesis of benzo[*f*]phthalazin-1(2*H*)-one (**17**).

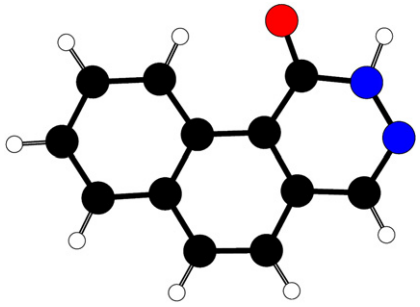


Figure 4. Powder X-ray diffraction confirms the structure of benzo[*f*]-phthalazin-1(2*H*)-one (**17**).

1,4-dichlorobenzo[*f*]phthalazine (**20**) is subjected to acidic hydrolysis, formation of two different regioisomeric reaction products is theoretically possible: 1-chlorobenzo-[*f*]phthalazin-4(3*H*)-one (**21**) and 4-chlorobenzo[*f*]phthalazin-1(2*H*)-one (**22**). 1-Chlorobenzo[*f*]phthalazin-4(3*H*)-one (**21**) is a direct precursor for benzo[*f*]phthalazin-4(3*H*)-one (**3**), while 4-chlorobenzo[*f*]phthalazin-1(2*H*)-one (**22**) can be converted to benzo[*f*]phthalazin-1(2*H*)-one (**17**). Since we expected a mixture of **21** and **22** in the hydrolysis reaction, and consequently possible purification problems of the isomers, this 'classical' route was not explored as a first approach for **3**. Interestingly, the acidic hydrolysis of compound **20** turned out to be very regioselective since mainly 4-chlorobenzo[*f*]phthalazin-1(2*H*)-one (**22**) (50%) and only a trace of 1-chlorobenzo[*f*]phthalazin-4(3*H*)-one (**21**) (6%) could be isolated.

The regioselectivity of the kinetically controlled nucleophilic substitution of a chlorine atom with an acetoxy group (under the experimental conditions the reaction is irreversible) can be well understood on the basis of some structural parameters obtained at semiempirical PM3 level. It was found that the atomic charges (derived from the electrostatic potential) on the relevant carbons differ significantly from each other: C1 (0.38) possesses a more positive charge than C4 (0.28) (Fig. 5), while the LUMO (ε=−1.3864 eV) coefficients on the same carbons are very close in their values (0.42 vs 0.44). Accordingly, substitution of 1-chloro is preferred (Fig. 6). The same conclusion can be drawn by the comparison of the heat of formation values of the respective Meisenheimer intermediates possessing a negative charge. Their thermodynamic stability difference (which according to the Hammond postulate reflects the stability

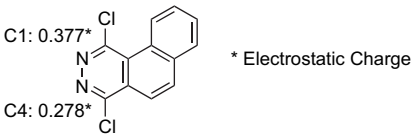


Figure 5. Electrostatic charge of 1,4-dichloro[*f*]phthalazine (**20**) calculated at semiempirical PM3 level.

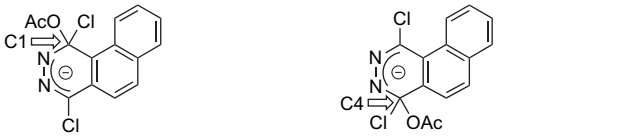


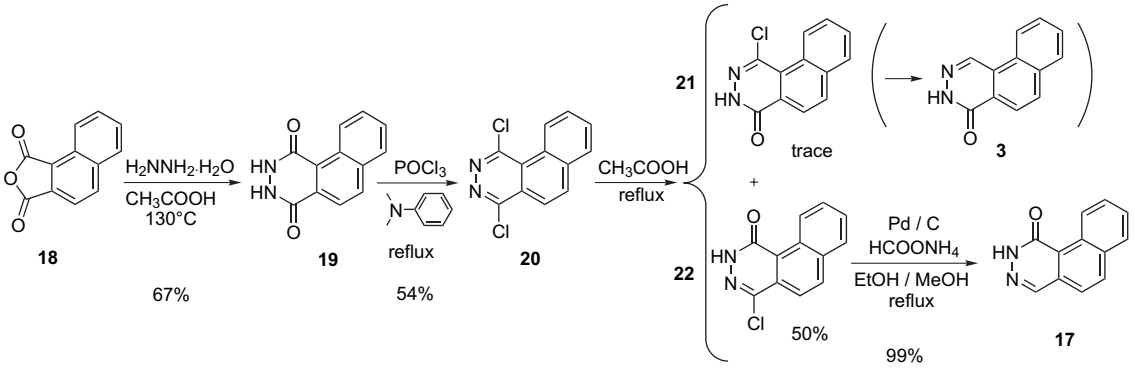
Figure 6. Calculated heat of formation for both Meisenheimer complexes.

difference between the respective transition states) also favors the substitution of 1-chloro group (Fig. 6). (Note: (a) Since the dipole moments of the Meisenheimer complexes are comparable their solvations are expected to be similar. (b) Since the reaction is performed in acetic acid it is possible that a neutral (protonated) intermediate is formed.)

Since the acidic hydrolysis of **20** gave only compound **22** in a practical yield, only the synthesis of benzo[*f*]phthalazin-1(2*H*)-one (**17**) from **22** was attempted. Conversion of 4-chlorobenzo[*f*]phthalazin-1(2*H*)-one (**22**) to benzo[*f*]-phthalazin-1(2*H*)-one (**17**) could be easily accomplished in good yield by classical catalytic transfer hydrogenolysis using Pd/C. Therefore the 'classical' approach starting from **18** is preferred for the synthesis of benzo[*f*]phthalazin-1(2*H*)-one (**17**) while a practical synthesis of benzo[*f*]phthalazin-4(3*H*)-one (**3**) can only be done following the double Suzuki—intramolecular condensation approach. It is important to mention that also for the synthesis of **17** the 'classical', naphthalene-based approach has an important drawback since the complete removal of the trace amount of **21** from **22** requires multiple purifications via column chromatography.

3. Conclusions

In summary, syntheses of two benzo[*f*]phthalazinone isomers, benzo[*f*]phthalazin-4(3*H*)-one (**3**) and benzo[*f*]-phthalazin-1(2*H*)-one (**17**), were accomplished in efficient and straightforward pathways with complete control of



Scheme 4. Classical heterocyclic approach for the synthesis of benzo[*f*]phthalazinone **17**.

regioselectivity. Comparison of their ^{1}H NMR data with those described by Morita for samoquasine A clearly shows that neither benzo[*f*]phthalazin-4(3*H*)-one nor its 1(2*H*)-one regioisomer is identical with the structure of the natural product.

4. Experimental

4.1. General

Melting points were determined on a Büchi apparatus and are uncorrected. The IR data were recorded on a Bruker Vector 22 spectrometer using potassium bromide pellets. The NMR spectra were recorded on one of the following spectrometers: a Bruker Avance II 400, a Bruker AM200, a Bruker Avance 500 or a Varian MP 400. TMS was used as internal standard. *J* values are given in hertz. The numbering used for the assignment of NMR-signals is as follows: pyridazinone ring simple figures, 5-substituents primed figures, 4-substituents double primed figures and N-substituents triple primed figures. For mass-spectrometric analysis, samples were dissolved in CH_3OH containing 0.1% formic acid and diluted to a concentration of approximately 10^{-5} mol/L. Injections of 1 μL were directed to the mass spectrometer at a flow rate of 5 μL/min (CH_3OH, 0.1% formic acid), using a CapLC HPLC system. Accurate mass data were acquired on a Q-TOF 2 mass spectrometer equipped with a standard electrospray ionization (ESI) interphase. Cone voltage (approx. 35 V) and capillary voltage (approx. 3.3 kV) were optimized on one compound and used for all others. For the determination of the accurate mass of the molecular ion $[M+H]^+$, a solution of polyethylene glycol 300 in CH_3OH/H_2O with 1 mmol ammonium acetate was added just before the mass spectrometer (at a rate of 1 μL/min) to the mobile phase. The calculated masses of PEG $[M+H]^+$and $[M+NH_4]^+$ions were used as lock mass. The microwave reactions were carried out in a CEM Mars (multimode microwave apparatus) or in a CEM Discover (single mode microwave apparatus), as specified. The following starting compounds and reagents were obtained from commercial sources: 4,5-dichloropyridazin-3(2*H*)-one, 1,8-diazabicyclo[5.4.0]undec-7-ene, tetrakistriphenylphosphinepalladium(0), benzyl chloromethyl ether, methylboronic acid, trifluoromethanesulfonic anhydride, 2-formylphenylboronic acid, cesium carbonate, phenol, orthophosphoric acid, aluminum trichloride, Pd/C, and ammonium formate. All commercial products were used without extra purification. Compounds **5b**,[8] **6b**,[8] **12**,[8] and **20**[24] were prepared according to literature procedures. Flash column chromatography was performed on Kieselgel 60 (ROCC, 0.040–0.063 mm). THF was freshly distilled from sodium. Semiempirical PM3 calculations were carried out by using the Spartan software package ('04 Mechanics Program; PC/x86; full geometry optimization: analytical gradient, MM/amide correction).

4.1.1. 2-Benzyloxymethyl-4,5-dichloropyridazin-3(2*H*)-one (5a). A solution of 4,5-dichloropyridazin-3(2*H*)-one **4a** (2 g, 12.12 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (2.3 mL) in DMF (40 mL) was cooled to 0 °C and benzyl chloromethyl ether (5.3 mL, purity: 60%) was added. The mixture was allowed to reach room temperature and stirred overnight. Then the solvent was removed under reduced pressure, water (100 mL) was added and the mixture was extracted with ether (3×100 mL), the combined organic layers were washed with water (100 mL), dried over Na_2SO_4, evaporated, and the residue was recrystallized from methanol. The mother liquid was purified by column chromatography on silica gel using dichloromethane as the eluent to yield the title compound **5a** (2.49 g, 70%) as white crystals. Mp: 74–74.5 °C (lit.,[25] 72–72.5 °C); (Found: C, 50.9; H, 3.7; N, 9.8%; Calcd for $C_{12}H_{10}Cl_2N_2O_2$: C, 50.55; H, 3.5; N, 9.8%); ν_{max} (KBr)/cm^{-1}: 1654, 1586, 1204, 1088, 1072, 946, 866, 750, 730, 702, and 610; δ_H (200 MHz, $CDCl_3$, Me_4Si): 4.73 (2H, s, C*H*$_2$Ph), 5.57 (2H, s, 2-N–C*H*$_2$), 7.20–7.40 (5H, m, Ph), 7.78 (1H, s, 6-H); δ_C (50 MHz, $CDCl_3$, Me_4Si): 72.4 (t), 80.4 (t), 127.7 (d, 2C), 127.9 (d), 128.3 (d, 2C), 134.8 (s), 136.0 (d), 136.9 (s), 137.0 (s), 160.0 (s).

4.1.2. 2-Benzyloxymethyl-4-chloro-5-methoxypyridazin-3(2*H*)-one (6a). 2-Benzyloxymethyl-4,5-dichloropyridazin-3(2*H*)-one **5a** (1.146 g, 4.02 mmol) was dissolved in anhydrous methanol (25 mL). It was slightly warmed to get solution in methanol and then cooled back to room temperature. NaOMe solution (5 M) (1.2 mL, 6 mmol) was added and the mixture was stirred at room temperature for 1 h in a flask equipped with a drying tube. The mixture was poured into water (150 mL), extracted with dichloromethane (3×100 mL), the organic layer was washed with water (1×100 mL), dried over Na_2SO_4, and evaporated to dryness. The crude product was purified by column chromatography on a short silica gel column with a mixture of ethyl acetate and dichloromethane (1:9) to yield the title compound **6a** (1.032 g, 91%) as white crystals. Mp: 109–110 °C; (Found: C, 55.3; H, 4.65; N, 9.9%; Calcd for $C_{13}H_{13}ClN_2O_3$: C, 55.6; H, 4.7; N, 10.0%); ν_{max} (KBr)/cm^{-1}: 2922, 1638, 1604, 1496, 1458, 1436, 1410, 1396, 1384, 1314, 1280, 1204, 1172, 1096, 1028, 998, 942, 904, 876, 830, 764, 734, 692, 652, 630, 568, 510, and 474; δ_H (200 MHz, $CDCl_3$, Me_4Si): 4.07 (3H, s, 5-OMe), 4.72 (2H, s, C*H*$_2$Ph), 5.59 (2H, s, 2-N–C*H*$_2$), 7.25–7.40 (5H, m, Ph), 7.84 (1H, s, 6-H); δ_C (50 MHz, $CDCl_3$, Me_4Si): 57.7 (q), 72.1 (t), 80.0 (t), 116.8 (s), 127.1 (d), 127.8 (d, 3C), 128.3 (d, 2C), 137.2 (s), 155.0 (s), 159.2 (s); MS (ESI): 281, 251; HRMS (ESI) calcd for $C_{13}H_{14}ClN_2O_3$ $[M+H]^+$: 281.0693, found 281.0683.

4.1.3. 2-Benzyloxymethyl-5-methoxy-4-methylpyridazin-3(2*H*)-one (7a).

4.1.3.1. Method 1: classic oil bath heating at reflux temperature. 2-Benzyloxymethyl-4-chloro-5-methoxypyridazin-3(2*H*)-one **6a** (471 mg, 1.68 mmol) was dissolved in 1,2-dimethoxyethane (10 mL) under an argon atmosphere. $Pd(Ph_3P)_4$ (101 mg, 5 mol %), methylboronic acid (151 mg, 1.5 equiv), and aqueous 2 M Na_2CO_3 solution (3.35 mL) were added. Then the mixture was refluxed for 24 h under argon atmosphere. After cooling, water (20 mL) was added and the mixture was extracted with dichloromethane (5×20 mL), dried over $MgSO_4$, evaporated to dryness, and purified by column chromatography on a silica gel column; eluent: ethyl acetate/toluene (1:4) to yield the title compound **7a** (310 mg, 71%) as white crystals.

4.1.3.2. Method 2: microwave heating in a closed vessel at 120 °C. 2-Benzyloxymethyl-4-chloro-5-

methoxypyridazin-3(2*H*)-one **6a** (471 mg, 1.68 mmol) was dissolved in 1,2-dimethoxyethane (10 mL) in an 80 mL microwave vessel under an argon atmosphere. $Pd(Ph_3P)_4$ (101 mg, 5 mol %), methylboronic acid (151 mg, 1.5 equiv), and 2 M aqueous Na_2CO_3 solution (3.35 mL) were added. The vessel was flushed with argon, closed, and placed into a microwave apparatus (CEM, Discover). The mixture was irradiated for 240 min at 120 °C with a set power of 150 W. After cooling, water (20 mL) was added and the mixture was extracted with dichloromethane (5×20 mL), dried over $MgSO_4$, evaporated to dryness, and purified by column chromatography on a silica gel column; eluent: ethyl acetate/toluene (1:4) to yield the title compound **7a** (325 mg, 74%) as white crystals.

Mp: 60–61 °C; (Found: C, 64.5; H, 6.2; N, 10.8%; Calcd for $C_{14}H_{16}N_2O_3$: C, 64.6; H, 6.2; N, 10.8%); ν_{max} (KBr)/cm^{-1}: 1646, 1635, 1610, 1467, 1380, 1337, 1278, 1229, 1161, 1099, 777, and 740; δ_H (400 MHz, $CDCl_3$, Me_4Si): 2.05 (3H, s, 4-Me), 3.96 (3H, s, 5-OMe), 4.71 (2H, s, C*H*$_2$Ph), 5.57 (2H, s, 2-N–CH$_2$), 7.27–7.37 (5H, m, Ph), 7.80 (1H, s, 6-H); δ_C (50 MHz, $CDCl_3$, Me_4Si): 8.5 (q), 56.8 (q), 71.7 (t), 79.3 (t), 119.9 (s), 127.5 (d), 127.6 (d), 127.7 (d, 2C), 128.2 (d, 2C), 137.5 (s), 155.6 (s), 163.0 (s); MS (ESI): 153, 91; HRMS (ESI) for $C_{14}H_{17}N_2O_3$ [M+1]: calcd 261.1239, found 261.1249.

4.1.4. 2-Benzyl-5-methoxy-4-methylpyridazin-3(2*H*)-one (7b).

4.1.4.1. Method 1: classic oil bath heating at reflux temperature. 2-Benzyl-4-chloro-5-methoxypyridazin-3(2*H*)-one **6b** (1.767 g, 7.05 mmol) was dissolved in 1,2-dimethoxyethane (42 mL) under an argon atmosphere. $Pd(Ph_3P)_4$ (408 mg, 5 mol %), methylboronic acid (634 mg, 1.5 equiv), and aqueous 2 M Na_2CO_3 solution (14.8 mL) were added. Then the mixture was refluxed for five days under argon atmosphere. After cooling, water (60 mL) was added and the mixture was extracted with dichloromethane (5× 50 mL), dried over Na_2SO_4, evaporated to dryness, and purified by column chromatography on a silica gel column with a mixture of ethyl acetate and toluene (2:8) as the eluent to yield the title compound **7b** (992 mg, 61%) as white crystals.

4.1.4.2. Method 2: microwave heating in a closed vessel at 120 °C. 2-Benzyl-4-chloro-5-methoxypyridazin-3(2*H*)-one **6b** (421 mg, 1.68 mmol) was dissolved in 1,2-dimethoxyethane (10 mL) in an 80 mL microwave vessel under an argon atmosphere. $Pd(Ph_3P)_4$ (101 mg, 5 mol %), methylboronic acid (151 mg, 1.5 equiv), and 2 M aqueous Na_2CO_3 solution (3.35 mL) were added. The vessel was flushed with argon, closed, and placed into a microwave apparatus (CEM, Discover). The mixture was irradiated for 240 min at 120 °C with a set power of 150 W. After cooling, water (20 mL) was added and the mixture was extracted with dichloromethane (5×20 mL), dried over Na_2SO_4, evaporated to dryness, and purified by column chromatography on a silica gel column with a mixture of ethyl acetate and toluene (2:8) as the eluent to yield the title compound **7b** (320 mg, 82%) as white crystals.

Mp: 89–91 °C; (Found: C, 68.0; H, 6.1; N, 12.3%; Calcd for $C_{13}H_{14}N_2O_2$: C, 67.8; H, 6.1; N, 12.2%); ν_{max} (KBr)/cm^{-1}: 1636, 1604, 1454, 1400, 1368, 1334, 1306, 1266, 1228, 1160, 1072, 980, 898, 870, 736, 702, 524, 508, and 490; δ_H (400 MHz, $CDCl_3$, Me_4Si): 2.04 (3H, s, 4-Me), 3.93 (3H, s, 5-OMe), 5.32 (2H, s, 2-N–CH$_2$), 7.23–7.34 (3H, m, 3‴-H, 4‴-H, and 5‴-H), 7.41 (2H, m, 2‴-H and 6‴-H), 7.76 (1H, s, 6-H); δ_C (100 MHz, $CDCl_3$, Me_4Si): 8.7 (q), 55.2 (t), 56.8 (q), 120.1 (s), 127.0 (d), 127.8 (d), 128.6 (d, 2C), 128.7 (d, 2C), 136.3 (s), 155.6 (s), 162.4 (s); MS (ESI): 91; HRMS (ESI) for $C_{13}H_{15}N_2O_2$ [M+1]: calcd 231.1138, found 231.1123.

4.1.5. 2-Benzyloxymethyl-5-hydroxy-4-methylpyridazin-3(2*H*)-one (8a).

2-Benzyloxymethyl-5-methoxy-4-methylpyridazin-3(2*H*)-one **7a** (1.004 g, 3.86 mmol) and KOH (11.8 g) in water (335 mL) was refluxed overnight (14 h). After cooling, the mixture was filtered on a glass filter under vacuum, cooled in an ice-water bath, and concentrated HCl (20 mL) was added. The precipitate was immediately filtered, washed till neutral, and dried in a drying gun. No further purification was needed. The title compound **8a** was isolated in 88% yield (833 mg) as white powder-like crystals. Mp: 159–160 °C; (Found: C, 63.45; H, 5.7; N, 11.45%; Calcd for $C_{13}H_{14}N_2O_3$: C, 63.4; H, 5.7; N, 11.4%); ν_{max} (KBr)/cm^{-1}: 3070, 3028, 3004, 2946, 1642, 1594, 1390, 1368, 1134, 1070, 748, 704, and 610; δ_H (200 MHz, DMSO-d_6, Me_4Si): 1.88 (3H, s, 4-Me), 4.59 (2H, s, C*H*$_2$Ph), 5.39 (2H, s, 2-N–CH$_2$), 7.20–7.40 (5H, m, Ph), 7.70 (1H, s, 6-H), 11.00 (1H, br s, 5-OH); δ_C (50 MHz, DMSO-d_6, Me_4Si): 8.3 (q), 70.5 (t), 78.7 (t), 114.7 (s), 127.5 (d, 3C), 128.2 (d, 2C), 132.1 (d), 137.8 (s), 154.8 (s), 162.5 (s); MS (ESI): 139, 111, 91; HRMS (ESI) for $C_{13}H_{15}N_2O_3$ [M+1]: calcd 247.1069, found 247.1077.

4.1.6. 2-Benzyl-5-hydroxy-4-methylpyridazin-3(2*H*)-one (8b).

2-Benzyl-5-methoxy-4-methylpyridazin-3(2*H*)-one **7b** (970 mg, 4.21 mmol) and KOH (13 g) in water (370 mL) was refluxed overnight (14 h). After cooling, the mixture was filtered on a glass filter under vacuum, cooled in an ice-water bath, and concentrated HCl (21 mL) was added. The precipitate was filtered, washed with water till neutral, and dried in a drying gun. No purification was needed. The title compound **8b** was isolated in 90% yield (816 mg) as white powder-like crystals. Mp: 235–237 °C; (Found: C, 66.5; H, 5.6; N, 13.0%; Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.6; N, 13.0%); ν_{max} (KBr)/cm^{-1}: 3066, 2960, 2924, 1642, 1564, 1394, 1266, 1222, 1146, 742, and 696; δ_H (400 MHz, DMSO-d_6, Me_4Si): 1.89 (3H, s, 4-Me), 5.19 (2H, s, 2-N–CH$_2$), 7.22–7.34 (5H, m, Ph), 7.69 (1H, s, 6-H), 10.82 (1H, br s, 5-OH); δ_C (100 MHz, DMSO-d_6, Me_4Si): 8.4 (q), 53.7 (t), 114.7 (s), 127.2 (d), 127.6 (d, 2C), 128.3 (d, 2C), 131.5 (d), 137.3 (s), 154.4 (s), 161.7 (s); MS (ESI): 91; HRMS (ESI) for $C_{12}H_{13}N_2O_2$ [M+1]: calcd 217.0977, found 217.0980.

4.1.7. 2-Benzyloxymethyl-5-(2-formylphenyl)-4-methylpyridazin-3(2*H*)-one (10a).

2-Benzyloxymethyl-5-hydroxy-4-methylpyridazin-3(2*H*)-one **8a** (464 mg, 1.88 mmol) was suspended in dry dichloromethane (14 mL) in a flask equipped with drying tube. Triethylamine (0.37 mL, 2.58 mmol) was added and the obtained solution was cooled to −5 °C on an ice–acetone bath. Trifluoromethanesulfonic anhydride (0.37 mL, 2.19 mmol) was added dropwise. The mixture

was stirred at this temperature for 30 min, then 1 M HCl (10 mL) and dichloromethane (50 mL) was added. The organic layer was separated, washed with 1% $NaHCO_3$ solution and brine, dried over Na_2SO_4, and evaporated to dryness. The crude product **9a** was used in the next step without further purification.

The crude triflate was dissolved in 1,2-dimethoxyethane (11 mL) under an argon atmosphere. $Pd(Ph_3P)_4$ (113 mg, 5 mol %), 2-formylphenylboronic acid (352 mg, 1.25 equiv), and aqueous 2 M Na_2CO_3 solution (2.25 mL) were added. Then the mixture was refluxed for 7 h under an argon atmosphere. After cooling, water (30 mL) was added and the mixture was extracted with $CHCl_3$ (3×30 mL), dried over Na_2SO_4, and evaporated to dryness. The obtained black oil was dissolved in ethyl acetate (40 mL), activated carbon was added, and the mixture was warmed to boiling. After filtration and evaporation, the obtained yellow oil was purified by column chromatography on a silica gel column with a mixture of ethyl acetate/chloroform (5:95) as the eluent yielding the title compound **10a** (520 mg, 82%) as a light yellow oil. (Found: C, 71.6; H, 5.5; N, 8.3%; Calcd for $C_{20}H_{18}N_2O_3$: C, 71.8; H, 5.4; N, 8.4%); ν_{max} (KBr)/cm^{-1}: 3064, 3032, 2926, 2856, 1698, 1652, 1610, 1596, 1570, 1560, 1496, 1454, 1378, 1340, 1296, 1276, 1260, 1222, 1198, 1162, 1092, 1028, 982, 966, 892, 840, 824, 770, 742, and 698; δ_H (400 MHz, $CDCl_3$, Me_4Si): 1.99 (3H, s, 4-Me), 4.81 (2H, s, C*H*$_2$Ph), 5.70 (1H, d, *J* 9.8) and 5.59 (1H, d, *J* 9.8): 2-N–CH_2, 7.26 (1H, dd, *J* 7.6 and 1.5, 6′-H), 7.28–7.42 (5H, m, Ph), 7.58 (1H, s, 6-H), 7.65 (1H, td, *J* 7.6 and 1.4, 4′-H or 5′-H), 7.72 (1H, td, *J* 6.0 and 1.5, 4′-H or 5′-H), 8.04 (1H, dd, *J* 7.6 and 1.5, H-3′), 9.90 (1H, s, 2′-CHO); δ_C (50 MHz, $CDCl_3$, Me_4Si): 13.9 (q), 72.1 (t), 80.0 (t), 127.7 (d, 3C), 128.2 (d, 2C), 129.7 (d), 129.9 (d), 130.6 (d), 133.2 (s), 134.3 (d), 136.8 (s), 137.3 (d), 137.6 (s), 138.0 (s), 139.5 (s), 161.3 (s), 190.4 (d); MS (ESI): 199, 170, 157, 129, 91; HRMS (ESI) for $C_{20}H_{19}N_2O_3$ [M+1]: calcd 335.1396, found 335.1392.

4.1.8. 2-Benzyl-5-(2-formylphenyl)-4-methylpyridazin-3(2*H*)-one (10b). 2-Benzyl-5-hydroxy-4-methylpyridazin-3(2*H*)-one **8b** (1.576 g, 7.29 mmol) was suspended in dry dichloromethane (50 mL) in a flask equipped with drying tube. Triethylamine (1.35 mL, 9.71 mmol) was added, and the obtained solution was cooled to −5 °C on an ice–acetone bath. Trifluoromethansulfonic anhydride (1.35 mL, 7.99 mmol) was added dropwise. The mixture was stirred at this temperature for 30 min and then 1 M HCl (46 mL) was added. The mixture was extracted with dichloromethane (3×50 mL). The organic layer was washed with 1% $NaHCO_3$ solution (2×50 mL) and brine (50 mL), dried over $MgSO_4$, and evaporated to dryness. The crude product **9b** (2.49 g light brown oil) was used in the next step without further purification.

The crude triflate was dissolved in 1,2-dimethoxyethane (43 mL) under an argon atmosphere. $Pd(Ph_3P)_4$ (415 mg, 5 mol %), 2-formylphenylboronic acid (1.340 g, 1.25 equiv), and aqueous 2 M Na_2CO_3 solution (7.90 mL) were added. Then the mixture was refluxed for 5.5 h under an argon atmosphere. After cooling, water (50 mL) was added and the mixture was extracted with $CHCl_3$ (3×50 mL), dried over $MgSO_4$, and evaporated to dryness. The obtained black oil was dissolved in ethyl acetate (40 mL), activated carbon was added, and the mixture was warmed to boiling. After filtration and evaporation, the obtained yellow oil was purified by column chromatography on a silica gel column with a mixture of ethyl acetate and dichloromethane (2.5:97.5) as the eluent yielding the title compound **10b** (1.709 g, 77%) as a light yellow oil. (Found: C, 74.7; H, 5.3; N, 9.1%; Calcd for $C_{19}H_{16}N_2O_2$: C, 75.0; H, 5.3; N, 9.2%); ν_{max} (KBr)/cm^{-1}: 3064, 3034, 2926, 1704, 1642, 1598, 1380, 1336, 1298, 1260, 1238, 1216, 1200, 894, 766, 730, and 700; δ_H (400 MHz, $CDCl_3$, Me_4Si): 1.99 (3H, s, 4-Me), 5.30 (1H, d, *J* 13.5) and 5.47 (1H, d, *J* 13.5): 2-N–CH_2, 7.24–7.40 (4H, m, 6′-H, 3‴-H, 4‴-H, and 5‴-H), 7.51 (2H, m, 2‴-H and 6‴-H), 7.60 (1H, s, 6-H), 7.62 (1H, td, *J* 7.4 and 1.5, 4′-H or 5′-H), 7.70 (1H, td, *J* 7.6 and 1.5, 4′-H or 5′-H), 8.03 (1H, dd, *J* 7.8 and 1.4, 3′-H), 9.92 (1H, s, 2′-CHO); δ_C (100 MHz, $CDCl_3$, Me_4Si): 14.1 (q), 55.7 (t), 128.0 (d), 128.6 (d, 2C), 128.9 (d, 2C), 129.6 (d), 130.0 (d), 130.2 (d), 133.4 (s), 134.2 (d), 136.3 (s), 137.0 (d), 137.3 (s), 137.9 (s), 139.0 (s), 160.6 (s), 190.3 (d); MS (ESI): 91; HRMS (ESI) for $C_{19}H_{17}N_2O_2$ [M+1]: calcd 305.1290, found 305.1290.

4.1.9. 3-Benzyloxymethylbenzo[*f*]phthalazin-4(3*H*)-one (11a).

4.1.9.1. Method 1: classic oil bath heating at reflux temperature. 2-Benzyloxymethyl-5-(2-formylphenyl)-4-methylpyridazin-3(2*H*)-one **10a** (250 mg, 0.75 mmol) was dissolved in dry tetrahydrofuran (5 mL) in a two-neck flask under an argon atmosphere and then Cs_2CO_3 (977 mg, 4 equiv) was added. The mixture was stirred and refluxed in an oil bath for 2 h. After cooling, the mixture was filtered, rinsed with tetrahydrofuran, and evaporated. The residue was purified by column chromatography on a short silica gel column with dichloromethane as the eluent to yield the title compound **11a** (187 mg, 79%) as white crystals.

4.1.9.2. Method 2: microwave heating in a closed vessel at 130 °C. 2-Benzyloxymethyl-5-(2-formylphenyl)-4-methylpyridazin-3(2*H*)-one **10a** (250 mg, 0.75 mmol) was dissolved in dry tetrahydrofuran (5 mL) in an 80 mL microwave vessel under an argon atmosphere. Cs_2CO_3 (977 mg, 4 equiv) was added and the vessel was flushed with argon, closed, and placed into a microwave apparatus (CEM, Mars). The mixture was irradiated for 45 min at 130 °C with a set power of 1200 W while stirring. After cooling, the mixture was filtered, rinsed with tetrahydrofuran, and evaporated. The residue was dissolved in dichloromethane (50 mL), washed with water (2×20 mL), and dried over $MgSO_4$. The solvent was evaporated and the crude product was purified by column chromatography on a short silica gel column with a mixture of ethyl acetate and dichloromethane (5:95) to yield the title compound **11a** (218 mg, 92%) as white crystals.

Mp: 107–108 °C; (Found: C, 76.1; H, 5.0; N, 8.9%; Calcd for $C_{20}H_{16}N_2O_2$: C, 75.9; H, 5.1; N, 8.9%); ν_{max} (KBr)/cm^{-1}: 1647, 1582, 1345, 1299, 1196, 1168, 1082, 921, 911, 845, 805, 762, 743, 710, and 694; δ_H (400 MHz, $CDCl_3$, Me_4Si): 4.80 (2H, s, C*H*$_2$Ph), 5.76 (2H, s, 3-N–CH_2), 7.23 (1H, m, 4‴-H), 7.30 (2H, m, 3‴-H and 5‴-H), 7.39 (2H, m, 2‴-H and 6‴-H), 7.73–7.81 (2H, m, 8-H and 9-H), 8.02 (1H, m, 7-H), 8.14 (1H, d, *J* 8.7, 6-H), 8.42 (1H, d, *J* 8.7, 5-H), 8.54 (1H, m, 10-H), 8.98 (1H, s, 1-H); δ_C (100 MHz, $CDCl_3$, Me_4Si): 71.8 (t), 79.4 (t), 122.3 (d),

123.1 (d), 127.06 (s), 127.14 (s), 127.6 (d), 127.72 (s), 127.78 (d, 2C), 128.28 (d, 2C), 128.33 (d), 129.1 (d), 129.2 (d), 132.5 (d), 133.9 (d), 135.2 (s), 137.7 (s), 160.3 (s); MS: (ESI) 209; HRMS (ESI) for $C_{20}H_{17}N_2O_2$ [M+1]: calcd 317.1290, found 317.1299.

4.1.10. 3-Benzylbenzo[*f*]phthalazin-4(3*H*)-one (11b).

4.1.10.1. Method 1: classic oil bath heating at reflux temperature. 2-Benzyl-5-(2-formylphenyl)-4-methylpyridazin-3(2*H*)-one **10b** (228 mg, 0.75 mmol) was dissolved in dry tetrahydrofuran (5 mL) in a two-neck flask under an argon atmosphere and then Cs_2CO_3 (977 mg, 4 equiv) was added. The mixture was stirred and refluxed in an oil bath for 10 h. After cooling, the mixture was filtered, rinsed with tetrahydrofuran, and evaporated. The residue was purified by column chromatography on a small silica gel column with dichloromethane as the eluent to yield the title compound **11b** (198 mg, 92%) as white crystals.

4.1.10.2. Method 2: microwave heating in a closed vessel at 130 °C. 2-Benzyl-5-(2-formylphenyl)-4-methylpyridazin-3(2*H*)-one **10b** (228 mg, 0.75 mmol) was dissolved in dry tetrahydrofuran (5 mL) in an 80 mL microwave vessel under an argon atmosphere. Cs_2CO_3 (977 mg, 4 equiv) was added and the vessel was flushed with argon, closed, and placed into a microwave apparatus (CEM, Mars). The mixture was irradiated for 45 min at 130 °C with a set power of 1200 W while stirring. After cooling, the mixture was filtered, rinsed with tetrahydrofuran, and evaporated. The residue was dissolved in dichloromethane (50 mL), washed with water (2×20 mL), and dried over $MgSO_4$. The solvent was evaporated and the crude reaction product was purified by column chromatography on a small silica gel column with dichloromethane to yield the title compound **11b** (196 mg, 91%) as white crystals.

Mp: 153–154 °C; (Found: C, 79.7; H, 4.95; N, 9.8%; Calcd for $C_{19}H_{14}N_2O$: C, 79.7; H, 4.9; N, 9.8%); ν_{max} (KBr)/cm^{-1}: 1644, 1620, 1580, 1342, 758, 696, and 494; δ_H (500 MHz, $CDCl_3$, Me_4Si): 5.51 (2H, s, 3-N–CH_2), 7.28 (1H, m, 4‴-H), 7.35 (2H, m, 3‴-H and 5‴-H), 7.52 (2H, d, *J* 7.3, 2‴-H and 6‴-H), 7.70–7.77 (2H, m, 8-H and 9-H), 7.98 (1H, m, 7-H), 8.09 (1H, d, *J* 8.7, 6-H), 8.39 (1H, d, *J* 8.7, 5-H), 8.48 (1H, m, 10-H), 8.95 (1H, s, 1-H); δ_C (125 MHz, $CDCl_3$, Me_4Si): 55.0 (t), 122.2 (d), 123.0 (d), 126.9 (s), 127.0 (s), 127.6 (s), 127.8 (d), 128.2 (d), 128.56 (d, 2C), 128.63 (d, 2C), 128.9 (d), 129.1 (d), 132.3 (d), 133.6 (d), 134.8 (s), 136.8 (s), 159.5 (s); MS (ESI): 106, 91, 88; HRMS (ESI) for $C_{19}H_{15}N_2O$ [M+1]: calcd 287.1171, found 287.1180.

4.1.11. Benzo[*f*]phthalazin-4(3*H*)-one (3).

4.1.11.1. Starting from 3-benzyloxymethylbenzo[*f*]-phthalazin-4(3*H*)-one (11a). A mixture of 3-benzyloxymethylbenzo[*f*]phthalazin-4(3*H*)-one **11a** (190 mg, 0.6 mmol), phenol (62 mg, 1.1 equiv), and 85% orthophosphoric acid (9 mL) was heated and stirred in an oil bath (150 °C) for 5 h. After cooling, the mixture was poured into ice-cold water (100 mL). The precipitate was filtered and washed with water. The filtrate was neutralized with NaOH and extracted with dichloromethane (6×20 mL). The combined organic layers were combined with the precipitate, evaporated, and purified on a short silica gel column using a mixture of ethyl acetate and dichloromethane (3:7) to yield the title compound **3** (104 mg, 88%) as white crystals.

4.1.11.2. Starting from 3-benzylbenzo[*f*]phthalazin-4(3*H*)-one (11b). 3-Benzylbenzo[*f*]phthalazin-4(3*H*)-one **11b** (100 mg, 0.35 mmol) was dissolved in dry toluene (10.5 mL), $AlCl_3$ (279 mg, 6 equiv) was added and the mixture was stirred, and heated in an oil bath (70 °C) for an hour (the condenser was equipped with a drying tube). After cooling, water (10 mL) was added, the mixture was extracted with dichloromethane (3×20 mL), washed with brine (20 mL), dried over $MgSO_4$, evaporated, and purified by column chromatography using a mixture of ethyl acetate and dichloromethane (3:7) to yield the title compound **3** (60 mg, 87%) as white crystals.

Mp: 251–252 °C; (Found: C, 73.3; H, 4.0; N, 14.1%; Calcd for $C_{12}H_8N_2O$: C, 73.5; H, 4.1; N, 14.3%); ν_{max} (KBr)/cm^{-1}: 3296, 3148, 3020, 2917, 2891, 1654, 1561, 1516, 1480, 1428, 1409, 1344, 1301, 1262, 1216, 1170, 1161, 1105, 1072, 1030, 948, 935, 884, 867, 837, 796, 755, 706, 670, 602, 567, 538, 494, 479, and 426; δ_H (400 MHz, $CDCl_3$, Me_4Si): 7.81–7.75 (2H, m, 8-H, 9-H), 8.03 (1H, m, 7-H), 8.16 (1H, d, *J* 8.6, 6-H), 8.41 (1H, dd, *J* 8.6 and 0.6, 5-H), 8.56 (1H, m, 10-H), 9.01 (1H, s, 1-H), 11.02 (1H, s, NH); δ_C (100 MHz, $CDCl_3$, Me_4Si): 121.72 (5-C), 123.28 (10-C), 127.19 (10a-C), 127.77 (4a-C), 127.84 (10b-C), 128.42 (9-C), 129.17 (8-C), 129.28 (7-C), 132.63 (6-C), 134.70 (1-C), 135.33 (6a-C), 160.76 (4-C); MS (ESI): 197, 154; HRMS (ESI) for $C_{12}H_9N_2O$ [M+1]: calcd 197.0715, found 197.0724. The structure was confirmed by NOESY, HMQC, and HMBC.

4.1.12. 2-Benzyl-4-methoxy-5-methylpyridazin-3(2*H*)-one (13).

4.1.12.1. Method 1: heating of the reaction mixture at 130 °C in a Berghof autoclave. 2-Benzyl-5-chloro-4-methoxypyridazin-3(2*H*)-one **12** (1.503 g, 6 mmol) was dissolved in 1,2-dimethoxyethane (36 mL) in a Teflon vessel of a Berghof autoclave under an argon atmosphere. $Pd(Ph_3P)_4$ (348 mg, 5 mol %), methylboronic acid (540 mg, 1.5 equiv), and 2 M aqueous Na_2CO_3 solution (12.6 mL) were added. The vessel was flushed with argon, closed, and heated for 270 min at 130 °C. After cooling, the mixture was poured into water (50 mL) and extracted with dichloromethane (5×20 mL). The combined organic layers were dried over Na_2SO_4, evaporated, and purified by column chromatography on silica gel using dichloromethane as the eluent to yield the title compound **13** (1.1 g, 79%) as white crystals.

4.1.12.2. Method 2: microwave heating in a closed vessel at 120 °C. 2-Benzyl-5-chloro-4-methoxypyridazin-3(2*H*)-one **12** (421 mg, 1.68 mmol) was dissolved in di methoxyethane (10 mL) in an 80 mL microwave vessel under an argon atmosphere. $Pd(Ph_3P)_4$ (101 mg, 5 mol %), methylboronic acid (151 mg, 1.5 equiv), and 2 M aqueous Na_2CO_3 solution (3.35 mL) were added. The vessel was flushed with argon, closed, and placed into a microwave apparatus (CEM, Discover). The mixture was irradiated for 240 min at 120 °C with a set power of 150 W. After cooling, water (20 mL) was added and the mixture was extracted with dichloromethane (5×20 mL), dried over $MgSO_4$, evaporated to dryness, and purified by column chromatography on a silica gel column

with a mixture of ethyl acetate and toluene (2:8) as the eluent to yield the title compound **13** (322 mg, 75%) as white crystals.

Mp: 43–45 °C; (Found: C, 68.05; H, 6.1; N, 12.2%; Calcd for $C_{13}H_{14}N_2O_2$: C, 67.8; H, 6.1; N, 12.2%); ν_{max} (KBr)/cm^{-1}: 1638, 1600, 1534, 1492, 1432, 1328, 1264, 1136, 1086, 1032, 986, 902, 794, 736, 696, 612, 582, and 518; δ_H (200 MHz, $CDCl_3$, Me_4Si): 2.07 (3H, s, 5-Me), 4.14 (3H, s, 4-OMe), 5.29 (2H, s, 2-N–CH_2), 7.25–7.45 (5H, m, Ph), 7.56 (1H, s, 6-H); δ_C (50 MHz, $CDCl_3$, Me_4Si): 12.5 (q), 54.9 (t), 59.7 (q), 126.9 (d), 127.8 (d), 128.5 (d, 4C), 136.4 (s), 140.0 (d), 152.5 (s), 157.7 (s); MS (ESI): 231, 153; HRMS (ESI) for $C_{13}H_{15}N_2O_2$ [M+1]: calcd 231.1134, found 231.1128.

4.1.13. 2-Benzyl-4-hydroxy-5-methylpyridazin-3(2*H*)-one (14). 2-Benzyl-4-methoxy-5-methylpyridazin-3(2*H*)-one **13** (1.1 g, 4.78 mmol) and KOH (14.72 g) in water (400 mL) was refluxed overnight (15 h). After cooling, the mixture was filtered on a glass filter under vacuum, cooled on an ice-water bath, and concentrated HCl (24 mL) was added. The obtained precipitate was filtered, washed with water till neutral, and dried in a drying gun. No further purification was needed. The title compound **14** was isolated in good yield (857 mg, 83%) as pink crystals. An analytical sample was obtained by recrystallization from toluene to get white crystals. Mp: 153–155 °C; (Found: C, 66.6; H, 5.6; N, 13.0%; Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.6; N, 12.95%); ν_{max} (KBr)/cm^{-1}: 3200, 1648, 1604, 1432, 1404, 1352, 1256, 746, and 700; δ_H (200 MHz, DMSO-d_6, Me_4Si): 2.00 (3H, s, 5-Me), 5.24 (2H, s, 2-N–CH_2), 7.00–7.50 (5H, m, Ph), 7.72 (1H, s, 6-H), 10.64 (1H, s, 4-OH); δ_C (50 MHz, DMSO-d_6, Me_4Si): 11.6 (q), 54.1 (t), 117.3 (s), 127.4 (d), 127.8 (d, 2C), 128.4 (d, 2C), 137.0 (s), 141.0 (d), 150.6 (s), 156.6 (s); MS (ESI): 217; HRMS (ESI) for $C_{12}H_{13}N_2O_2$ [M+1]: calcd 217.0977, found 217.0970.

4.1.14. 2-Benzyl-4-(2-formylphenyl)-5-methylpyridazin-3(2*H*)-one (15). 2-Benzyl-4-hydroxy-5-methylpyridazin-3(2*H*)-one **14** (805 g, 3.72 mmol) was suspended in dry dichloromethane (25 mL) in a flask equipped with drying tube. Triethylamine (0.69 mL, 4.96 mmol) was added and the obtained solution was cooled to −5 °C on an ice–acetone bath. Trifluoromethansulfonic anhydride (0.69 mL, 4.08 mmol) was added dropwise. The mixture was stirred at this temperature for 30 min and then 1 M HCl (23.5 mL) was added. The mixture was extracted with dichloromethane (3×25 mL). The organic layer was washed with 1% $NaHCO_3$ solution (2×25 mL) and brine (25 mL), dried over Na_2SO_4, and evaporated to dryness. The crude product (1.25 g, light brown oil) was used in the next step without further purification.

The crude triflate was dissolved in 1,2-dimethoxyethane (21.5 mL) under an argon atmosphere. $Pd(Ph_3P)_4$ (207 mg, 5 mol %), 2-formylphenylboronic acid (669 g, 1.25 equiv), and aqueous 2 M Na_2CO_3 solution (3.6 mL) were added. Then the mixture was refluxed for 3 h under an argon atmosphere. After cooling, water (40 mL) was added and the mixture was extracted with $CHCl_3$ (3×40 mL), dried over Na_2SO_4, and evaporated to dryness. The obtained black oil was dissolved in ethyl acetate (40 mL), activated carbon was added, and the mixture was warmed to boiling. After filtration and evaporation, the obtained yellow oil was purified by column chromatography on a silica gel column with a mixture of ethyl acetate and dichloromethane (5:95) as the eluent. Then a second column chromatography was applied with a mixture of toluene and ethyl acetate (9:1) as the eluent to yield the title compound **15** (957 mg, 84%) as a light yellow oil.

(Found: C, 74.7; H, 5.4; N, 9.1%; Calcd for $C_{19}H_{16}N_2O_2$: C, 75.0; H, 5.3; N, 9.2%); ν_{max} (KBr)/cm^{-1}: 1698, 1642, 1598, 1494, 1452, 1428, 1384, 1330, 1298, 1250, 1198, 826, 784, 764, 730, 700, and 620; δ_H (200 MHz, $CDCl_3$, Me_4Si): 1.97 (3H, s, 5-Me), 5.29 (1H, d, *J* 13.7) and 5.37 (1H, d, *J* 13.7): 2-N–CH_2, 7.14–7.72 (8H, m, 4″-H, 5″-H, 6″-H, and Ph), 7.74 (1H, s, 6-H), 7.98 (1H, d, *J* 7.6, 3″-H), 9.84 (1H, s, 2″-CHO); δ_C (50 MHz, $CDCl_3$, Me_4Si): 17.1 (q), 55.4 (t), 127.8 (d), 128.5 (d, 3C), 128.7 (d, 2C), 129.1 (d), 130.36 (d), 130.39 (s), 133.9 (d), 134.3 (s), 135.2 (s), 136.3 (s), 137.4 (s), 139.0 (d), 159.4 (s), 190.9 (d); MS (ESI): 305, 91; HRMS (ESI) for $C_{19}H_{17}N_2O_2$ [M+1]: calcd 305.1290, found 305.1281.

4.1.15. 2-Benzylbenzo[*f*]phthalazin-1(2*H*)-one (16).

4.1.15.1. Method 1: classic oil bath heating at reflux temperature. 2-Benzyl-4-(2-formylphenyl)-5-methylpyridazin-3(2*H*)-one **15** (228 mg, 0.75 mmol) was dissolved in dry tetrahydrofuran (5 mL) in a two-neck flask under an argon atmosphere and then Cs_2CO_3 (977 mg, 4 equiv) was added. The mixture was stirred and refluxed in an oil bath for 9.5 h. After cooling, the mixture was filtered, rinsed with tetrahydrofuran, and evaporated. The residue was purified by column chromatography on a short silica gel column with dichloromethane as the eluent to yield the title compound **16** (199 mg, 93%) as white crystals.

4.1.15.2. Method 2: microwave heating in a closed vessel at 130 °C. 2-Benzyl-4-(2-formylphenyl)-5-methylpyridazin-3(2*H*)-one **15** (228 mg, 0.75 mmol) was dissolved in dry tetrahydrofuran (5 mL) in an 80 mL microwave vessel under an argon atmosphere. Cs_2CO_3 (977 mg, 4 equiv) was added, and the vessel was flushed with argon, closed, and placed into a microwave apparatus (CEM, Mars). The mixture was irradiated for 45 min at 130 °C with a set power of 1200 W while stirring. After cooling, the mixture was filtered, rinsed with tetrahydrofuran, and evaporated. The residue was purified by column chromatography on a short silica gel column with dichloromethane to yield the title compound **16** (192 mg, 90%) as white crystals.

4.1.15.3. Method 3: heating of the reaction mixture to 130 °C in a closed vessel (oil bath temperature 150 °C). 2-Benzyl-4-(2-formylphenyl)-5-methylpyridazin-3(2*H*)-one **15** (228 mg, 0.75 mmol) was dissolved in dry tetrahydrofuran (5 mL) in a closed vessel under an argon atmosphere. Cs_2CO_3 (977 mg, 4 equiv) was added, and the vessel was flushed with argon, closed, and placed into an oil bath preheated to 150 °C. The mixture was stirred and heated for 4×45 min. After cooling, the mixture was filtered, rinsed with tetrahydrofuran, and evaporated. The residue was purified by column chromatography on a short silica gel column with dichloromethane to yield the title compound **16** (200 mg, 93%) as white crystals.

Mp: 157–158 °C; (Found: C, 79.7; H, 4.8; N, 9.8%; Calcd for $C_{19}H_{14}N_2O$: C, 79.7; H, 4.9; N, 9.8%); ν_{max} (KBr)/cm^{-1}: 1636, 1614, 1584, 1258, 1122, 1060, 818, 764, 748, 706, 610, and 510; δ_H (200 MHz, $CDCl_3$, Me_4Si): 5.54 (2H, s, 2-N–CH_2), 7.20–7.40 (3H, m, 3‴-H, 4‴-H, and 5‴-H), 7.45–7.58 (2H, m, 2‴-H and 6‴-H), 7.54 (1H, d, *J* 8.6, 5-H), 7.62–7.82 (2H, m, 8-H and 9-H), 7.90 (1H, d, *J* 8.2, 7-H), 8.10 (1H, d, *J* 8.6, 6-H), 8.22 (1H, s, 4-H), 10.14 (1H, d, *J* 8.4, 10-H); δ_C (50 MHz, $CDCl_3$, Me_4Si): 55.4 (t), 122.4 (d), 123.2 (s), 127.7 (d), 128.3 (d, 2C), 128.4 (d), 128.5 (d, 4C), 129.0 (d), 130.2 (s), 130.3 (s), 134.2 (s), 134.9 (d), 137.1 (s), 137.6 (d), 160.2 (s); MS (ESI): 270, 91; HRMS (ESI) for $C_{19}H_{15}N_2O$ [M+1]: calcd 287.1184, found 287.1194.

4.1.16. Benzo[*f*]phthalazin-1(2*H*)-one (17). 2-Benzylbenzo-[*f*]phthalazin-4(3*H*)-one **16** (180 mg, 0.63 mmol) was dissolved in dry toluene (19 mL), $AlCl_3$ (504 mg, 3.78 mmol, 6 equiv) was added and the mixture was stirred, and heated on an oil bath (70 °C) for an hour (the condenser was equipped with a drying tube). After cooling, water (25 mL) was added, the mixture was extracted with dichloromethane (3×40 mL) and $CHCl_3$ (3×40 mL), dried over Na_2SO_4, evaporated, and purified by column chromatography using first dichloromethane and then a mixture of ethyl acetate and dichloromethane (2:8) as the eluent to yield the title compound **17** (120 mg, 97%) as white crystals. Mp: 264–265 °C; (Found: C, 73.6; H, 4.0; N, 14.25%; Calcd for $C_{12}H_8N_2O$: C, 73.5; H, 4.1; N, 14.3%); ν_{max} (KBr)/cm^{-1}: 1632, 1594, 1548, 1504, 894, 818, 760, and 558; δ_H (400 MHz, $CDCl_3$, Me_4Si): 7.69 (1H, d, *J* 8.5, 5-H), 7.77 (1H, ddd, *J* 8.0, 7.0, and 1.3, 8-H), 7.83 (1H, ddd, *J* 8.6, 7.0, and 1.5, 9-H), 8.00 (1H, dd, *J* 8.0 and 1.5, 7-H), 8.24 (1H, d, *J* 8.5, 6-H), 8.28 (1H, s, 4-H), 10.10 (1H, dd, *J* 8.6 and 1.3, 10-H), 10.36 (1H, s, NH); δ_C (100 MHz, $CDCl_3$, Me_4Si): 122.73 (5-C), 123.77 (10b-C), 128.50 (10-C), 128.58 (7-C), 128.88 (8-C), 129.44 (9-C), 130.43 (10a-C), 131.04 (4a-C), 134.41 (6a-C), 135.59 (6-C), 139.13 (4-C), 161.47 (C-1); MS (ESI): 154, 140, 127; HRMS (ESI) for $C_{12}H_9N_2O$ [M+1]: calcd 197.0715, found 197.0716. The structure was confirmed by NOESY, HMQC, and HMBC.

4.1.17. 1-Chlorobenzo[*f*]phthalazin-4(3*H*)-one (21) and 4-chlorobenzo[*f*]phthalazin-1(2*H*)-one (22). 1,4-Dichlorobenzo[*f*]phthalazine **20** (250 mg, 1 mmol) was suspended in acetic acid (2 mL) and was refluxed on an oil bath (130 °C) for 2 h. After cooling, water was added (2 mL), the yellow precipitate was filtered, washed with water, dried on air, and subjected to column chromatography on silica gel using a mixture of ethyl acetate and dichloromethane (1:9) as the eluent. Repeating the column chromatography several times resulted in a complete separation.

4.1.18. 1-Chlorobenzo[*f*]phthalazin-4(3*H*)-one (21). Yield: 13 mg, 6%; Mp: 292–295 °C; δ_H (500 MHz, DMSO-d_6, Me_4Si): 7.87 (2H, m, 8-H and 9-H), 8.23 (1H, m, 7-H), 8.29 (1H, d, *J* 8.6, 5-H), 8.42 (1H, d, *J* 8.7, 6-H), 9.62 (1H, m, 10-H), 13.31 (1H, s, 3-H); δ_C (DMSO, Me_4Si): 121.7 (5-C), 125.5 (4a-C), 125.8 (10-C), 126.7 (10a-C), 128.3 (8-C or 9-C), 129.2 (8-C or 9-C), 129.3 (10b-C), 129.7 (7-C), 134.4 (6-C), 135.1 (1-C), 135.8 (6a-C), 159.0 (4-C); MS (ESI): 153, 140; HRMS (ESI) for $C_{12}H_8ClN_2O$ [M+1]: calcd 231.0325, found 231.0319. The structure was confirmed by NOESY, HSQC, and HMBC.

4.1.19. 4-Chlorobenzo[*f*]phthalazin-1(2*H*)-one (22). Yield: 115 mg, 50%; Mp: 275–277 °C (lit: 273–276 °C); δ_H (500 MHz, DMSO-d_6, Me_4Si): 7.90–7.83 (2H, m, 8-H and 9-H), 8.02 (1H, d, *J* 8.8, 5-H), 8.19 (1H, dd, *J* 7.0 and 2.3, 7-H), 8.51 (1H, d, *J* 8.8, 6-H), 10.06 (1H, dd, *J* 7.5 and 2.0, 10-H), 13.20 (1H, s, 2-H); δ_C (DMSO, Me_4Si): 121.4 (5-C), 123.6 (10b-C), 127.1 (10-C), 128.4 (7-C), 128.8 (10a-C), 129.2 (8-C or 9-C), 129.4 (8-C or 9-C), 129.5 (4a-C), 134.1 (6a-C), 136.0 (6-C), 137.4 (4-C), 160.3 (1-C); MS (ESI): 153, 140, 127; HRMS (ESI) for $C_{12}H_8ClN_2O$ [M+1]: calcd 231.0325, found 231.0319. The structure was confirmed by NOESY, HSQC, and HMBC.

4.1.20. Benzo[*f*]phthalazin-1(2*H*)-one (17). 4-Chlorobenzo[*f*]phthalazin-1(2*H*)-one **22** (104 mg, 0.45 mmol) was dissolved in a mixture of ethanol (50 mL) and methanol (10 mL) with heating. After cooling back to room temperature, Pd/C (20 mg) and ammonium formate (142 mg, 5 equiv) was added, and the mixture was refluxed for 1 h. The warm solution was filtered through Celite, washed with ethanol, and evaporated to dryness. Water was added (10 mL) and the mixture was vigorously stirred for 2 h, filtered, washed with water, and dried. The crude product was not further purified. Yield: 88 mg, 100%; Mp: 264–267 °C. The product is identical with the compound obtained from the earlier described method.

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22. Crystallographic data for the structure **3** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-631245. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0)1223 336 033 or e-mail: deposit@ccdc.cam.ac.uk).
23. Crystallographic data for the structure **17** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-631398. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0)1223 336 033 or e-mail: deposit@ccdc.cam.ac.uk).
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