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Synthesis of novel 1-methyl-1*H*-pyridazino[3,4-*b*]indoles

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Cordially dedicated to Professor András Lipták on the occasion of his 70th birthday.

Abstract—New synthetic pathways have been elaborated to 1-methyl-1*H*-pyridazino[3,4-*b*]indoles starting from halopyridazin-3(2*H*)-ones. Suzuki cross-coupling reaction of chloro, iodo, dichloro, and dibromo substituted pyridazin-3(2*H*)-ones with 2-pivaloylaminophenylboronic acid followed by hydrolysis of the amide and subsequent ring closure via condensation gave fused indoles. Some of these compounds showed biological activity as antitrypanosomal agents.

1. Introduction

As a continuation of our earlier investigations, novel efficient pathways were developed for substituted 1-methyl-1*H*-pyridazino[3,4-*b*]indoles starting from halopyridazin-3(2*H*)-ones.[1] The area of these methylated pyridazino-fused indoles seemed particularly interesting as we have noticed some structural similarity between neocryptolepine (**A**) and the 1-methyl-1*H*-pyridazino[3,4-*b*]indole (**B**) ring system (Fig. 1).

Naturally occurring tetracyclic indolo[3,2-*b*]quinoline alkaloid cryptolepine as well as its [2,3-*b*] fused isomer neocryptolepine, isolated from a decoction of the root of *Cryptolepis sanguinolenta*,[2a,b] showed antitrypanosomal and antiplasmodial activity and have been used as lead compounds for new therapeutic agents.[2c] Introduction of halogen or nitro substituents has resulted in more active and/or more selective antiplasmodial agents.[3] Importantly, the 'debenzo' derivative of cryptolepine, that is, 1-methyl-δ-carboline, showed a much better selectivity index (cytotoxicity/antiplasmodial activity) than cryptolepine itself.[4] This finding prompted us to make efforts to synthetize substituted 1-methyl-1*H*-pyridazino[3,4-*b*]indoles and to investigate their antiplasmodial and antitrypanosomal activity.

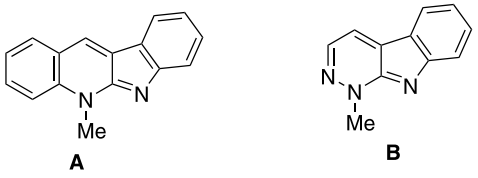

Figure 1. The structural similarity of neocryptolepine (**A**) and 1-methyl-1*H*-pyridazino[3,4-*b*]indole (**B**) ring systems.

2. Discussion

Earlier we found that 2-substituted 4,5-dichloropyridazin-3(2*H*)-ones undergo non-selective Suzuki cross-coupling reaction with arylboronic acids under classical Suzuki conditions resulting in a mixture of mono- and diaryl-substituted pyridazin-3(2*H*)-ones.[5] Recently, on 4,5-dichloro-2-methylpyridazin-3(2*H*)-one (**1**) a C-5 selectivity was observed in the coupling reaction with phenylboronic acid using $Pd(PEt_3)_2Cl_2$ as precatalyst and 1 M Na_2CO_3 as base in DMF.[6] Unfortunately, the general applicability of

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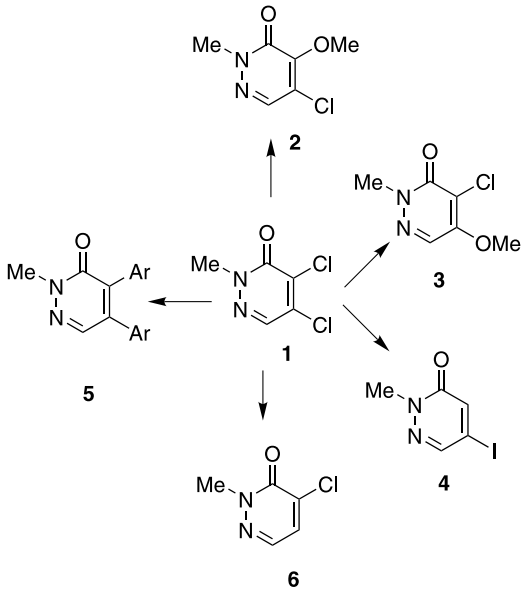
these optimized reaction conditions remain unknown. Alternatively, in order to achieve selective arylation we earlier introduced the strategy of 'provisionally masked functionalities' (PMFs).[1] For this purpose **1** was converted into chloro-methoxy substituted pyridazin-3(2*H*)-ones (**2**, **3**)[7] by nucleophilic substitution and into 5-iodo-2-methyl-pyridazin-3(2*H*)-one (**4**)[8] by halogen exchange followed by hydrodeiodination (Scheme 1).



Scheme 1.

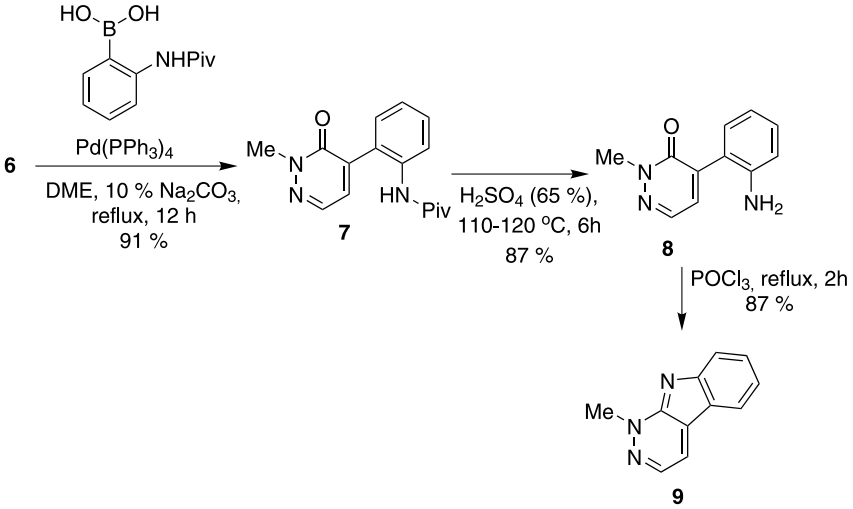
In this paper our efforts towards the synthesis of substituted 1-methyl-1*H*-pyridazino[3,4-*b*]indoles starting from (substituted) mono- and dihalopyridazin-3(2*H*)-ones are summarized. To the best of our knowledge, only very limited literature data are available for derivatives of the 1*H*-pyridazino[3,4-*b*]indole ring system.[9]

First, we attempted the synthesis of the unsubstituted 1-methyl-1*H*-pyridazino[3,4-*b*]indole (**9**) starting from 4-chloro-2-methylpyridazine-3(2*H*)-one (**6**). Compound **6**[10a] was synthesized from **1** via reaction with hydrazine followed by hydrodehydrazination of 4-chloro-5-hydrazino-2-methyl-pyridazin-3(2*H*)-one with $CuSO_4$, a procedure that has successfully been applied for the analogous demethyl derivative.[10b] This compound reacted with 2-pivaloylaminophenylboronic acid under the Gronowitz reaction conditions,[11] that is, in a mixture of dimethoxyethane and 10% aqueous sodium carbonate solution using tetrakis(triphenylphosphine)palladium as catalyst. The cross-coupling reaction afforded the pivaloyl protected compound **7**[12] in high yield (91%). Compound **7** was hydrolyzed to the aminophenyl derivative **8** under reaction conditions previously reported by us.[13] This compound—due to the proximity of the amino and oxo functions—underwent smooth condensation reaction in boiling phosphoryl chloride yielding the desired 1-methyl-1*H*-pyridazino[3,4-*b*]indole (**9**) as red crystals (Scheme 2).[13]

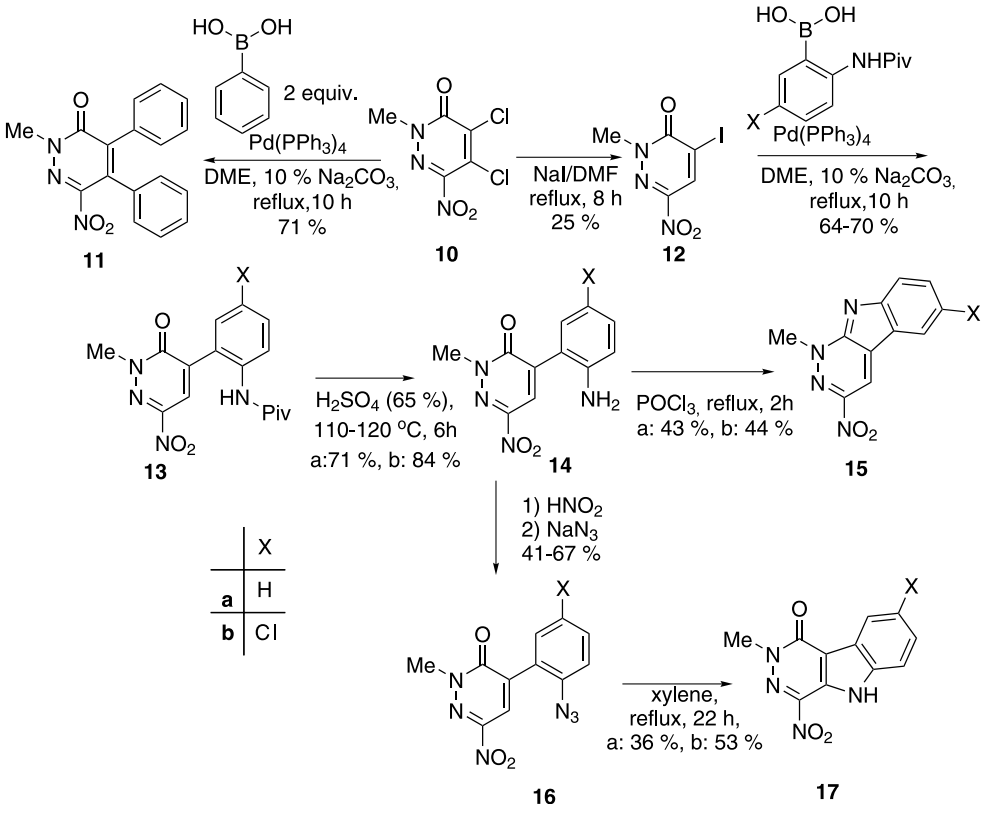
4,5-Dichloro-2-methylnitropyridazin-3(2*H*)-one (**10**) was synthesized from **1** by a nitration reaction.[14] Also on this substrate we observed that cross-coupling reaction with phenylboronic acid gave some diphenyl-substituted pyridazin-3(2*H*)-one (**11**) indicating the non-selective nature of the reaction. In order to realize the desired C-4 selective phenylation we used 4-iodo-2-methyl-6-nitropyridazin-3(2*H*)-one (**12**) which can be simply prepared from 4,5-dichloro-2-methyl-6-nitropyridazin-3(2*H*)-one (**10**) by reaction with sodium iodide in refluxing DMF.[8b]

When **12** was subjected to cross-coupling with 2-pivaloylaminophenylboronic acid and 5-chloro-2-pivaloylaminophenylboronic acid, 2-methyl-4-(2-pivaloylaminophenyl)-6-nitropyridazin-3(2*H*)-one (**13a**) and 2-methyl-4-(5-chloro-2-pivaloylaminophenyl)-6-nitropyridazin-3(2*H*)-one (**13b**), respectively, were obtained in good yield (Scheme 3). After hydrolytic removal of the pivaloyl protecting group the corresponding anilino compounds (**14a**,**b**) were obtained. These compounds were cyclized by the procedure described above for the synthesis of derivative **9** to yield 1-methyl-3-nitro-1*H*-pyridazino[3,4-*b*]indole (**15a**) and 6-chloro-1-methyl-3-nitro-1*H*-pyridazino[3,4-*b*]indole (**15b**).

Interestingly, 2-methyl-2,5-dihydro-1*H*-pyridazino[4,5-*b*]indol-1-ones (**17a**,**b**) could also be prepared starting



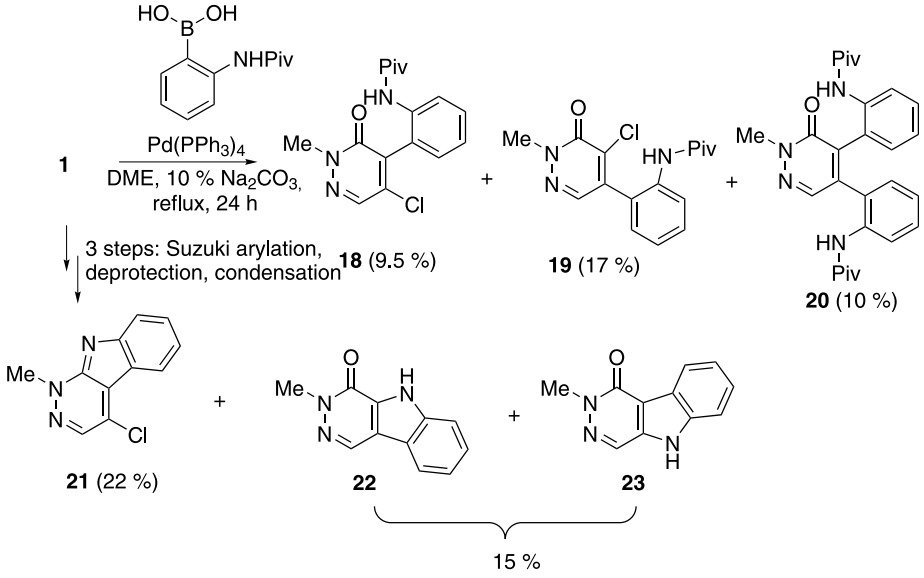
Scheme 2.



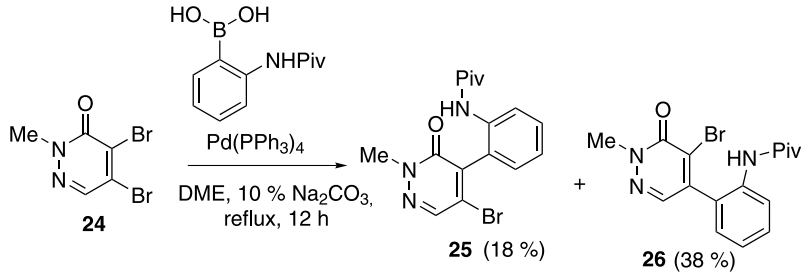
Scheme 3.

from **14a**,**b** using our earlier developed method for the synthesis of isomeric 3-methyl-3,5-dihydro-4*H*-pyridazino[4,5-*b*]indol-4-ones:[15] (i) first azides **16a**,**b** were prepared from the corresponding anilines **14a**,**b** (ii) upon heating of these compounds in xylene the desired ring closed products (**17a**,**b**) were obtained via formation of an electrophilic nitrene. It is remarkable that the pyrrole ring formation occurs so smoothly taking into account the electron deficient nature of C-5 of **16a**,**b**. This is due to the fact that C-5 is part of an α,β-unsaturated lactam system, and the inductive effect of the nitro group.

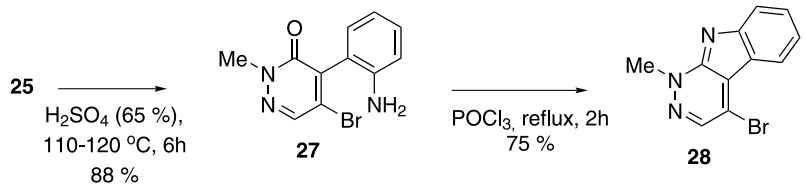
From a medicinal chemistry point of view, synthesis of derivatives having halogen substituents on the pyridazine ring are of interest and further efforts on 4,5-dihalo-2-methylpyridazin-3(2*H*)-one substrates seemed desirable. Therefore, we tried to follow a reaction pathway for the synthesis of 1*H*-pyridazino[3,4-*b*]indole **21** starting from **1** (Scheme 4). However, as could be expected Suzuki arylation of **1** with 2-pivaloylaminophenylboronic acid was not selective. After tedious column chromatography on silicagel some fractions of pure compounds **18**, **19** and **20** could be obtained. Structures of regioisomers **18** and **19**



Scheme 4.



Scheme 5.



Scheme 6.

were proven by COSY, HETCOR and long-range HETCOR measurements.

Because of the purification problems experienced with the reaction mixture from the Suzuki reaction on **1**, the crude reaction mixture (i.e., the mixture of **18**, **19**, and **20**) was subjected to two subsequent reaction steps (deprotection and ring closure) without isolation of the respective intermediates. Although the final reaction mixture was fairly complex, separation of 4-chloro-1-methyl-1*H*-pyridazino[3,4-*b*]indole (**21**) by chromatography was greatly facilitated by its bright orange-red colour. The overall yield of the three steps was 22%.

Furthermore, two unexpected ring closure products (**22** and **23**) were also detected and a mixture of these pyridazinoindoles was isolated in 15%. The ^{1}H NMR spectrum (H-6 signals of the pyridazin-3(2*H*)-one moiety) of this mixture indicated that the ratio of **22** and **23** was 4:1, respectively. Both regioisomers could easily be identified since these compounds (**22** and **23**) have already previously been synthesized by us via an independent route,[15] and their NMR-spectra were therefore available for comparison. Their formation can be rationalized by intramolecular nucleophilic substitution (addition–elimination reaction) of the corresponding anilines formed by deprotection of **18** and **19**.

In contrast to the difficulties experienced with the dichloro compound **1**, more favourable results have been obtained with the analoguous 4,5-dibromo-2-methylpyridazin-3(2*H*)-one **24**.[16] Coupling of **24** with 2-pivaloylaminophenylboronic acid under the same condition as applied with the synthesis of **7**, **13**, and **18** yielded a mixture of two regioisomeric aryl-bromopyridazin-3(2*H*)-ones (**25** and **26**) which, could be easily separated by a simple treatment with diethyl ether. When diethylether was added precipitation of only one of the two isomers namely 4-bromo-2-methyl-5-(2-pivaloyl-aminophenyl)pyridazin-3(2*H*)-one (**26**) occured. Chromatography on silicagel of the mother liquor yielded regioisomeric 5-bromo-2-methyl-4-(2-pivaloyl-aminophenyl)pyridazin-3(2*H*)-one (**25**) in pure form (Scheme 5). Its structure was identified by HETCOR and long-range HETCOR measurements (a long-range coupling of both H-6 and H-6′[12] with the quaternary C-4 was observed).

The further transformation of **25** was carried out in a similar way as used for the synthesis of **9**, **15**, and **21**. Thus, hydrolysis of the pivaloyl group of **25** gave the anilino substituted derivative **27** in good yield (Scheme 6). This compound smoothly underwent condensation reaction in boiling phosphoryl chloride yielding 4-bromo-1-methyl-1*H*-pyridazino[3,4-*b*]indole (**28**) as bright orange crystals.

Compounds **9**, **15a**, **21** and **28** were selected for biological tests. Antiprotozoal activities against *Trypanosoma brucei rhodesiense*, *Trypanosoma cruzi*, *Leishmania donovani*, *Plasmodium falciparum* (chloroquine-resistant), and cytotoxicity on human L6 cells, are listed in Table 1. Compound

Table 1. Antitrypanosomal, antileishmanial, antiplasmodial and cytotoxic (L6 cells) activity (IC_{50}, μg/ml)

	Trypanosoma brucei rhodesiense	*Trypanosoma cruzi*	*Leishmania donovani* (axenic amastigotes)	*Plasmodium falciparum* K1	*Cytotoxicity* (L6 cells)
28	0.83±0.10	8.2±1.2	15.87±1.05	3.22±0.95	4.80±0.75
15a	2.47±0.11	0.24±0.05	6.1±3.0	4.49±0.10	29.5±4.2
21	0.20±0.01	23.4	0.71[a]	>5	2.41±0.50
9	26.1	>90	>30	>5	nt[b]
Positive control[c]	0.0023	0.39	0.25	0.065	0.003

[a] Antileishmanial activity of compounds showing an $IC_{50}<1$ μg/ml in the assay on axenic amastigotes is confirmed in an assay on infected macrophages. However, for **21** this determination was not possible due to cytotoxicity on the host cells.
[b] nt, not tested.
[c] Positive controls used were: Melarsoprol for *T. b. rhodesiense*, benznidazole for *T. cruzi*, miltefosine for *Leishmania donovani*, chloroquine for *P. falciparum* and podophyllotoxin for L-6 cells.

9 shows no significant biological activity in the assays used. Introduction of a nitro-substituent in position 3, as in **15a**, results in a pronounced increase of the antitrypanosomal activity, especially against *T. cruzi* ($IC_{50}<1$ μg/ml). Introduction of a halo-substituent in position 4 on the other hand, as in **21** or **28**, leads to a high antitrypanosomal activity against *T. b. rhodesiense* ($IC_{50}<1$ μg/ml). In case of the chloro-derivative **21** also antileishmanial activity is observed against *L. donovani* axenic amastigotes. In an assay in infected macrophages, however, the antileishmanial activity could not be confirmed. From this limited and preliminary structure–activity relationship study it appears that this class of compounds deserves further attention as potential antitrypanosomal agents.

3. Conclusion

The obtained results reveal that the easily accessible 2-methyl-4,5-dichloropyridazin-3(2*H*)-ones (**1**, **10**) can serve as suitable precursors for the synthesis of 4-monoarylated pyridazin-3(2*H*)-ones by using Suzuki arylation in two ways: (i) via the 2-methyl-4-chloropyridazin-3(2*H*)-one (**6**) and (ii) via the 4-iodo-2-methyl-6-nitropyridazin-3(2*H*)-one (**12**). When 2-methyl-4,5-dihalopyridazin-3(2*H*)-ones (**1**, **10**, **24**) are directly used in Suzuki arylation reactions under Gronowitz conditions, using a small excess of arylboronic acid, at least a mixture of two monoarylated pyridazin-3(2*H*)-ones is obtained (also often diarylated pyridazin-3(2*H*)-one is formed). If an *ortho* amino group is present on the phenyl ring in position 4 of the pyridazin-3(2*H*)-one cyclization can take place upon heating with $POCl_3$ yielding 1-methyl-1*H*-pyridazino[3,4-*b*]indole derivatives. This reaction pathway represents a new approach to the parent tricyclic ring system. The antiprotozoal screening results show that 1-methyl-1*H*-pyridazino[3,4-*b*]indoles deserve further attention as potential antitrypanosomal agents.

4. Experimental

Melting points were determined on a Büchi apparatus and are uncorrected. The IR data were obtained with a Thermo Nicolet AVATAR 320 FT-IR or a Bruker Vector 22 spectrometer. The NMR spectra were recorded on a Varian spectrometer (200 or 400 MHz for ^1H and 50 or 100 MHz for ^{13}C) and a Bruker Avance-500 instrument (500 MHz for ^1H and 125 MHz for ^{13}C). 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. One micro-litre injection was directed to the mass spectrometer at a flow rate of 5 μL/min (CH_3OH, 0.1% formic acid), using a CapLC HPLC system (Waters, Millford). Accurate mass data were acquired on a quadrupole-time-of-flight mass spectrometer (Q-Tof-II, Micromass, Manchester, UK) equipped with a standard electrospray ionisation (ESI) interface. 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.

Antiprotozoal evaluation and determination of cytotoxicity was carried out as described before.[17] Only compounds showing $IC_{50}<1$ μg/ml were tested in duplicate or triplicate (mean ± SD).

4.1. General procedure for the synthesis of arylpyridazin-3(2*H*)-ones (7, 13a, 13b, 18, 19, 20, 25, 26)

A mixture of the appropriate halogen substituted 2-methylpyridazin-3(2*H*)-one (2 mmol, **1**: 0.358 g, **6**: 0.289 g, **12**: 0.562 g, **24**: 0.536 g) and tetrakis(triphenylphosphine)palladium(0) (0.10 mmol, 0.116 g) in dimethoxyethane (12 mL) was stirred for 30 min at room temperature under argon. Then, 2-pivaloylaminophenylboronic acid (2.4 mmol, 0.532 g) or 5-chloro-2-pivaloylaminophenylboronic acid (2.4 mmol, 0.612 g) and aqueous sodium carbonate solution (4 mL, 10%) was added and the mixture was refluxed (oil bath temp. 97 °C) under an argon atmosphere for 6–24 h. The reaction mixture was cooled and poured onto ice-water (20 mL) and extracted with chloroform (3×20 mL). The combined organic fractions were dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The purification of the crude reaction mixtures is indicated below.

4.1.1. 2-Methyl-4-(2-pivaloylaminophenyl)pyridazin-3(2*H*)-one (7). The evaporated crude product was purified by column chromatography (eluent: EtOAc–CH_2Cl_2 1:9).

Yield: 0.525 g, 92%; mp: 142–144 °C; IR (KBr) ν_{max}: 3290, 2962, 1666, 1638, 1606, 1590, 1512, 1476, 1448, 1400, 1368, 1296, 1270, 1240, 1170, 876, 754, 610 cm^{-1}; δ_H ($CDCl_3$, 400 MHz): 9.20 (br s, 1H, NH), 7.92 (d, 1H, $J=$ 4.2 Hz, H-6), 7.78 (d, 1H, $J=8.0$ Hz, H-3′ or H-6′), 7.47 (m, 1H, H-4′ or H-5′), 7.31 (d, $J=4.2$ Hz, H-5), 7.24 (m, 2H, H-3′ or H-6′, H′-4 or H-5′), 3.95 (s, 3H, CH_3), 1.22 (s, 9H, $C(CH_3)_3$); δ_C ($CDCl_3$, 100 MHz): 177.4, 160.8, 140.8, 137.0, 136.8, 131.9, 130.6, 130.1, 128.5, 126.3, 125.4, 41.3, 39.4, 27.5. MS (ESI): 185, 202; HRMS (ESI) Calcd for $C_{16}H_{19}N_3O_2$ 285.1447, found: 285.1459.

4.1.2. 2-Methyl-6-nitro-4-(2-pivaloylaminophenyl)pyridazin-3(2*H*)-one (13a). Recrystallization from acetonitrile yielded 0.462 g of product (70%); mp 187–188 °C; IR (KBr) ν_{max}: 3568, 3424, 3242, 2966, 2934, 2870, 1682, 1638, 1580, 1534, 1516, 1476, 1442, 1360, 922, 788, 750 cm^{-1}; δ_H ($CDCl_3$ 200 MHz): 8.60 (s, 1H, NH), 8.19 (s, 1H, H-5), 7.75 (m, 1H, H-3′ or H-6′), 7.58–7.49 (m, 1H, H-4′ or H-5′), 7.32–7.26 (m, 2H, H-4′ or H-5′, H-3′ or H-6′), 4.04 (s, 3H, CH_3), 1.21 (s, 9H, $C(CH_3)_3$); δ_C ($CDCl_3$ 50 MHz): 171.3 ($OCC(CH_3)_3$), 160.4 (C-3), 146.2 (C-6), 142.7 (C-2′), 136.9 (C-4), 131.4 and 130.8 (C-4′,6′), 127.5 (C-1′), 127.0, 126.1, 125.9 (C-5, 3′,5′), 42.3 (CH_3), 39.5 ($C(CH_3)_3$), 27.5 ($C(CH_3)_3$). Anal. Calcd for $C_{16}H_{18}N_4O_4$ (330.34): C, 58.17; H, 5.49; N, 16.96. Found: C, 58.12; H, 5.48; N, 17.02. MS (ESI): 146, 185, 233, 234, 261; HRMS (ESI) Calcd for $C_{16}H_{18}N_4O_4$ $[M+H]^+$331,1406, found 331,1407.

4.1.3. 4-(5-Chloro-2-pivaloylaminophenyl)-2-methyl-6-nitropyridazin-3(2*H*)-one (13b). Recrystallization from acetonitrile yielded 0.467 g of product (64%); mp 180–181 °C; IR (KBr) ν_{max}: 3568, 3436, 3274, 2964, 2932, 2872, 1682, 1644, 1586, 1500, 1480, 1402, 1362, 928, 788, 754 cm^{-1}: δ_H ($CDCl_3$ 200 MHz): 8.53 (s, 1H, NH), 8.19 (s, 1H, H-5), 7.71 (d, 1H, $J_{3',4'}=8.6$ Hz, H-3′), 7.48 (dd, $J_{3',4'}=8.6$ Hz, $J_{4',6'}=2.4$ Hz, 1H, H-4′), 7.31 (d, $J_{4',6'}=2.4$ Hz, 1H, H-6′), 4.04 (s, 3H, CH_3), 1.20 (s, 9H, $C(CH_3)_3$); δ_C ($CDCl_3$ 50 MHz): 177.3 ($OCC(CH_3)_3$), 160.1 (C-3), 146.0 (C-6), 141.1 (C-2′), 135.6 (C-4), 131.3 (C-5′), 131.2 and 130.3 (C-4′, and −6′), 128.8 (C-1′), 128.2 and 126.2 (C-3′, and -5), 42.3 (CH_3), 39.5 ($C(CH_3)_3$), 27.4 ($C(CH_3)_3$). HRMS (ESI) Calcd for $C_{16}H_{18}ClN_4O_4$ $[M+H]^+$365.1017, found 365.1024.

4.1.4. 5-Chloro-2-methyl-4-(2-pivaloylaminophenyl)pyridazin-3(2*H*)-one (18). The crude reaction mixture was purified by flash column chromatography on silica using a CH_2Cl_2–MeOH 100:0.5 mixture as the eluent.

Yield: 0.063 g, 9.8%; mp: 120–124 °C; IR (KBr) ν_{max}: 3487, 3335, 2967, 1670, 1637, 1605, 1515, 1486, 1447, 1370, 1295, 1255, 1210, 1170, 1016, 957, 779, 752, 743, 712, 635 cm^{-1}; δ_H ($CDCl_3$, 400 MHz): 8.16 (br s, 1H, NH), 7.91 (s, 1H, H-6), 7.80 (dd, 1H, $J=8.7$, 1.1 Hz, 1H, H-3′ or H-6′), 7.45 (ddd, 1H, $J=7.8$, 7.5, 1.7 Hz, H-4′ or H-5′), 7.31 (dd, 1H, $J=7.8$, 1.7 Hz, H-3′ or H-6′), 7.23 (ddd, 1H, $J=8.7$, 7.6, 1.2 Hz, H-4′ or H-5′), 3.87 (s, 3H, CH_3), 1.18 (s, 9H, C-$(CH_3)_3$); δ_C ($CDCl_3$, 100 MHz):176.9, 159.4, 138.0, 137.5, 136.9, 136.8, 130.8, 130.4, 126.1, 125.2, 124.9, 40.9, 39.4, 27.4. MS (ESI): 322, 320, 304, 284, 228, 200, 57; HRMS (ESI) Calcd for $C_{16}H_{19}ClN_3O_2$ $[M+H]^+$320.1166, found 320.1158.

4.1.5. 4-Chloro-2-methyl-5-(2-pivaloylaminophenyl)pyridazin-3(2*H*)-one (19). The crude reaction mixture was purified by flash column chromatography on silica using a CH_2Cl_2–MeOH 100:0.5 mixture as the eluent.

Yield: 0.110 g, 17%; mp: >150 °C (decomposition); IR (KBr) ν_{max}: 3340, 1682, 1646, 1579, 1520, 1479, 1442, 1284, 1156, 1025, 873, 768, 755, 728, 674 cm^{-1}; δ_H ($CDCl_3$, 400 MHz): 7.80 (dd, 1H, $J=8.7$, 1.2 Hz, H-3′ or H-6′), 7.69 (s, 1H, H-6), 7.52 (br s, 1H, NH), 7.50 (dd, 1H, $J=7.7$, 7.6 Hz, H-4′ or H-5′), 7.32 (ddd, 1H, $J=8.7$, 7.6, 1.2 Hz, H-4′ or H-5′), 7.24 (dd, 1H, $J=7.7$, 1.3 Hz, H-3′ or H-6′), 3.83 (s, 3H, CH_3), 1.18 (s, 9H, $C(CH_3)_3$); δ_C ($CDCl_3$, 100 MHz): 176.9, 157.3, 140.1, 137.1, 134.8, 133.7, 130.6, 128.9, 127.4, 125.9, 125.6, 41.0, 39.4, 27.4. MS (ESI): 322, 320, 304, 302, 246, 238, 236, 200, 85, 58, 57; HRMS (ESI) Calcd for $C_{16}H_{19}ClN_3O_2$ $[M+H]^+$320.1166, found: 320.1156.

4.1.6. 2-Methyl-4,5-bis(2-pivaloylaminophenyl)pyridazin-3(2*H*)-one (20). The crude reaction mixture was purified by flash column chromatography on silica using a CH_2Cl_2–MeOH 100:0.5 mixture as the eluent.

Yield: 0.095 g, 10%; mp: >215 °C (decomposition); IR (KBr) ν_{max}: 3325, 2962, 2926, 1675, 1616, 1601, 1576, 1505, 1479, 1444, 1368, 1298, 1262, 1161, 1019, 771, 747 cm^{-1}; δ_H ($CDCl_3$, 400 MHz): 8.44 (br s, 1H, N–H), 7.82 (s, 1H, H-6), 7.65 (br d, $J=8.1$ Hz, 1H), 7.59 (br d, $J=8.2$ Hz, 1H), 7.36 (br s, 1H, N–H), 7.24 (br m, 2H), 7.05 (br d, $J=7.6$ Hz, 1H), 6.95 (br t, $J=7.1$ Hz, 1H), 6.89 (br t, $J=7.6$ Hz, 1H), 6.75 (br d, $J=7.5$ Hz, 1H), 3.94 (s, 3H, CH_3), 1.29 (s, 9H, $C(CH_3)_3$), 1.21 (s, 9H, $C(CH_3)_3$); δ_C ($CDCl_3$, 100 MHz): 177.4, 176.7, 160.6, 141.6, 138.2, 137.9, 137.7, 134.9, 131.6, 130.9, 129.8, 128.6, 128.2, 127.0, 126.3, 125.5, 125.3, 124.7, 41.0, 39.6, 39.3, 27.6, 27.5. MS (ESI): 377, 359, 304, 303, 293, 57; HRMS (ESI) Calcd for $C_{27}H_{33}N_4O_3$ $[M+H]^+$461.2553, found: 461.2534.

4.1.7. 5-Bromo-2-methyl-4-(2-pivaloylaminophenyl)pyridazin-3(2*H*)-one (25). The crude reaction mixture was suspended with diethyl ether (5 mL), the white precipitated solid was removed by filtration. This etheral mother liquor was subjected to column chromatography (silica, eluent: chloroform-methanol 100:1 mixture) and the product was recrystallized from an ether–hexane mixture.

Yield: 0.131 g, 18%; mp: 114–116 °C; IR (KBr) ν_{max}: 3338, 3065, 3032, 2966, 1674, 1639, 1604, 1507, 1486, 1463, 1435, 930, 756 cm^{-1}; δ_H ($CDCl_3$, 400 MHz): 8.06 (br s, 1H, NH), 8.02 (s, 1H, H-6), 7.79 (dd, $J=8.2$, 1.1 Hz, 1H, H-3′), 7.45 (ddd, $J=7.8$, 7.5, 1.5 Hz, 1H, H-4′), 7.30 (dd, $J=7.8$, 1.5 Hz, 1H, H-6′), 7.24 (ddd, $J=7.8$, 7.6, 1.2 Hz, 1H, H-5′), 3.82 (s, 3H, CH_3), 1.18 (s, 9H, $C(CH_3)_3$); δ_C ($CDCl_3$, 100 MHz):176.8 (CO), 159.0 (C-3), 139.6 (C-4), 139.4 (C-6), 136.4 (C-2′), 130.6, 130.4 (C-5′,6′), 129.2 (C-5), 127.1 (C-1′), 125.9 (C-3′), 124.9 (C-4′) 40.8 (CH_3), 39.4 ($C(CH_3)_3$), 27.4 ($C(CH_3)_3$). Anal. Calcd for $C_{16}H_{18}BrN_3O_2$ (364.24): C, 52.76; H, 4.98; N, 11.54. Found: C, 52.65; H, 5.12; N, 11.45.

4.1.8. 4-Bromo-2-methyl-5-(2-pivaloylaminophenyl)pyridazin-3(2*H*)-one (26). The crude reaction mixture was suspended with diethyl ether (5 mL) and the white precipitated product was filtered off and recrystallized from acetonitrile.

Yield: 0.277 g, 38%; mp: 181–186 °C; IR (KBr): ν_{max}: 3340, 3048, 2975, 1682, 1643, 1579, 1519, 1441, 1282, 1155, 769, 755, 644, cm^{-1}; δ_H ($CDCl_3$, 200 MHz): 7.78 (dd, $J=8.1$, 1.2 Hz, 1H, H-3′ or H-6′), 7.61 (s, 1H, H-6), 7.50 (dd, $J=8.1$, 7.3 Hz, 1H, H-4′ or H-5′), 7.34 (ddd, $J=8.1$, 7.5, 1.2 Hz, 1H, H-4′ or H-5′), 7.25 (br s, 1H, NH), 7.22 (dd, $J=7.5$, 1.8 Hz, 1H, H-3′ or H-6′), 3.89 (s, 3H, CH_3), 1.17 (s, 9H, $C(CH_3)_3$); δ_C ($CDCl_3$, 50 MHz): 176.7, 157.4, 143.4, 136.8, 134.8, 134.2, 130.5, 128.4, 127.6, 125.9, 125.1, 41.3, 39.4, 27.3. Anal. Calcd for $C_{16}H_{18}BrN_3O_2$ (364.24): C, 52.76; H, 4.98; N, 11.54. Found: C, 52.88; H, 5.08; N, 11.65.

4.1.9. 2-Methyl-6-nitro-4,5-diphenylpyridazin-3(2*H*)-one (11). 4,5-Dichloro-2-methyl-6-nitropyridazin-3(2*H*)-one (**10**, 17.50 mmol, 3.92 g) and tetrakis(triphenylphosphine)-palladium(0) (0.88 mmol, 1.01 g) as catalyst were dissolved in anhydrous toluene (90 mL) and the mixture was stirred at room temperature under argon for 30 min. Phenylboronic acid (36.0 mmol, 4.39 g) and a solution of sodium carbonate (2 M, 35 mL) were then added and the mixture was refluxed for 10 h. The cold mixture was poured onto ice-water (200 mL), extracted with chloroform (3× 120 mL), and dried over anhydrous sodium sulphate.

Evaporation of the organic layer gave a crude product which was suspended in diethyl ether. The precipitated yellow crystals were filtered off and recrystallized from ethanol.

Yield: 3.83 g (12.4 mmol), 71%; mp 190.5–191 °C; IR (KBr) ν_{max}: 1662, 1592, 1540, 1445, 1372, 1332, 876, 744, 698 cm^{-1}; δ_H ($CDCl_3$ 200 MHz): 7.24–6.98 m, 10H, Ar-H), 3.86 (s, 3H, CH_3); δ_C ($CDCl_3$ 50 MHz): 159.5 (C-3), 149.2 (C-6), 141.2, 135.5, 131.3, 130.9 (C-4,-5,-1′,-1″), 129.9–127.8 (C-2′,3′,4′,5′,6′,2″,3″,4″,5″,6″), 40.91 (CH_3). Anal. Calcd for $C_{17}H_{13}N_3O_3$ (307.30): C, 66.44; H, 4.26; N, 13.67. Found: C, 66.60; H, 4.16; N, 13.72. MS (ESI): 170, 247; HRMS (ESI) Calcd for $C_{17}H_{13}N_3O_3$ $[M+H]^+$308.1035, found 308.1034.

4.2. General procedure for the preparation of aminophenyl substituded pyridazin-3(2*H*)-ones by hydrolysis (8, 14a, 14b, 27)

A mixture of the appropriate pivaloylaminophenyl pyridazinone (2 mmol, **7**: 0.57 g, **13a**: 0.66 g, **13b**: 0.73 g, **25**: 0.72 g) and sulphuric acid (65%, 10 mL) was heated at 110–120 °C for 6 h. The reaction mixture was cooled down to c. and diluted with water (50 mL) and the pH of the mixture was adjusted to 8 by addition of aqueous (25%) ammonia. It was extracted with dichloromethane (3×40 mL), and the organic layer was dried over Na_2SO_4 and evaporated. The crude product was suspended with ether (10 mL) and the yellow or orange crystals were filtered off.

4.2.1. 4-(2-Aminophenyl)-2-methylpyridazin-3(2*H*)-one (8). Yield: 0.35 g, 87%; mp: 123–126 °C; IR (KBr) ν_{max}: 3442, 3346, 3086, 3042, 2986, 2946, 2892, 1646, 1610, 1568, 1492, 1452, 1402, 1364, 1342, 1310, 1286, 1240, 1156, 1142, 1120, 1002, 872, 788, 752, 616, 594, 542, 520, 470 cm^{-1}; δ_H ($CDCl_3$, 400 MHz): 7.83 (d, 1H, J=4.2 Hz, H-6), 7.27 (d, 1H, J=4.2 Hz, H-5), 7.23–7.10 (m, 2H, H-3′, H-4′), 6.86–6.74 (m, 2H, H-5′, H-6′), 4.73 (br s, 2H, NH_2), 3.90 (s, 3H, CH_3); δ_C ($CDCl_3$, 100 MHz): 160.2, 146.6, 141.7, 136.2, 131.1 (2C), 130.6, 121.8, 119.0, 117.8, 41.1. MS (ESI): 114, 128, 130, 185; HRMS (ESI) Calcd for $C_{11}H_{12}N_3O$ $[M+H]^+$202.0980, found: 202.0988.

4.2.2. 4-(2-Aminophenyl)-2-methyl-6-nitropyridazin-3(2*H*)-one (14a). Yield: 0.35 g, 71%; mp 217–218 °C (acetonitrile); IR (KBr) ν_{max}: 3446, 3366, 1648, 1624, 1598, 1586, 1566, 1524, 1488, 1356, 1114, 758 cm^{-1}; δ_H (DMSO-d_6, 500 MHz): 8.11 (s, 1H, H-5), 7.13 (t, 1H, $J_{3',4'}=J_{4',5'}$=7.0 Hz, H-4′), 7.10 (d, 1H, $J_{5',6'}$=8.0 Hz, H-6′), 6.74 (d, 1H, $J_{3',4'}$=7.0 Hz, H-3′), 6.62 (dd, 1H, $J_{5',6'}$= 8.0 Hz, $J_{4',5'}$=7.0 Hz, H-5′), 5.16 (s, 2H, NH_2), 3.82 (s, 3H, CH_3); δ_C (DMSO-d_6, 125 MHz): 159.2 (C-3), 146.6 (C-2′), 145.8 (C-6), 140.0 (C-4), 130.3 (C-4′), 130.2 (C-6′), 125.0 (C-5), 117.4 (C-1′), 115.7 (C-5′), 115.6 (C-3′), 41.3 (CH_3). MS (ESI): 115, 142, 144, 170, 201, 247; HRMS (ESI) Calcd for $C_{11}H_{11}N_4O_3$ $[M+H]^+$ 247.0831, found 247.0820.

4.2.3. 4-(2-Amino-5-chlorophenyl)-2-methyl-6-nitropyridazin-3(2*H*)-one (14b). Yield: 0.47 g, 84%; mp 249–249.5 °C (acetonitrile); IR (KBr) ν_{max}: 3420, 3362, 3068, 1654, 1628, 1582, 1526, 1486, 1360, 1260, 834 cm^{-1}; δ_H (DMSO-d_6, 500 MHz): 8.17 (s, 1H, H-5), 7.16 (dd, 1H, $J_{3',4'}$=8.6 Hz, $J_{4',6'}$=2.2 Hz, H-4′), 7.12 (d, 1H, $J_{4',6'}$= 2.2 Hz, H-6′), 6.75 (d, 1H, $J_{3',4'}$=8.6 Hz, H-3′), 5.35 (s, 2H, NH_2), 3.81 (s, 3H, N–H_3); δ_C (DMSO-d_6, 125 MHz): 159.0 (C-3), 145.7 (C-6), 145.6 (C-2′), 138.3 (C-4), 129.9 (C-4′), 129.3 (C-6′), 125.5 (C-5), 118.7 (C-5′), 118.3 (C-1′), 116.9 (C-3′), 41.3 (CH_3). Anal. Calcd for $C_{11}H_9ClN_4O_3$ (280.67): C, 47.07; H, 3.23; N, 19.96; Cl, 12.63. Found: C, 46.94; H, 3.08; N, 20.00; Cl, 12.69. MS (ESI): 176, 178, 204; HRMS (ESI) Calcd for $C_{11}H_9ClN_4O_3$ $[M+H]^+$281.0437, found 281.0433.

4.2.4. 4-(2-Aminophenyl)-5-bromo-2-methylpyridazin-3(2*H*)-one (27). Yield: 0.49 g, 88%; mp 173–179 °C (ethanol); IR (KBr) ν_{max}: 3425, 3344, 1647, 1604, 1491, 1453, 1307, 926, 757 cm^{-1}; δ_H ($CDCl_3$, 200 MHz): 8.00 (s, 1H, H-6), 7.25 (ddd, 1H, J=7.4, 6.0, 1.6 Hz, H-4′), 7.08 (dd, J=8.0, 1.4 Hz 1H, H-3′), 6.85 (ddd, 1H, J=7.6, 7.2, 1.0 Hz, H-5′), 6.82 (d, 1H, J=8.0 Hz H-6′), 3.82 (s, 3H, CH_3), 3.82 (s, 2H, NH_2); δ_C ($CDCl_3$, 50 MHz): 158.3, 144.7, 138.7, 135.0, 130.5, 130.4, 129.0, 118.7, 117.3, 115.6, 40.6. Anal. Calcd for $C_{11}H_{10}BrN_3O$ (280.12): C, 47.16; H, 3.60; N, 15.00. Found: C, 47.04; H, 3.72; N, 15.11.

4.3. General procedure for ring closure reaction by phosphoryl chloride (9, 15a, 15b, 28)

A mixture of the appropriate aminophenyl compound (1 mmol, **8**: 0.21 g, **14a**: 0.25 g, **14b**: 0.28 g, **27**: 0.28 g) and phosphoryl chloride (10 mL) was refluxed at 110 °C for 2 h. The reaction mixture was evaporated, the residue was mixed with ice-cool water (50 mL) and the pH of the mixture was adjusted to 8 by addition of aqueous (25%) ammonia. The mixture was extracted with dichloromethane (3×20 mL) and the extract was dried over Na_2SO_4. Evaporation of the solvent gave a crude product which was suspended with ether (5 mL). The red precipitated crystals were filtered off to give the ring closed product.

4.3.1. 1-Methyl-1*H*-pyridazino[3,4-*b*]indole (9). Yield: 0.130 g; 71%; mp:172–173 °C; IR (KBr) ν_{max}: 3446, 1630, 1600, 1540, 1492, 1462, 1436, 1416, 1342, 1322, 1262, 1200, 1128, 1108, 1040, 1010, 998, 872, 862, 776, 762, 738 cm^{-1}; δ_H ($CDCl_3$, 400 MHz): 8.34 (d, 1H, J= 4.6 Hz, H-3), 8.13–8.09 (m, 2H, H-4 and H-8) 7.84 (d, 1H, J=8.2 Hz, H-5), 7.68 (ddd, 1H, J=8.2, 7.2, 1.2 Hz, H-6), 7.27 (ddd, 1H, J=8.2, 7.2, 1.2 Hz, H-7), 4.54 (s, 3H, CH_3); δ_C ($CDCl_3$, 100 MHz): 155.9, 153.2, 133.9, 133.2, 131.4, 122.4, 121.1, 119.7, 118.5, 118.4, 42.7. MS (ESI): 114, 128, 130, 140, 142, 169, 184; HRMS (ESI) Calcd for $C_{11}H_{10}N_3$ $[M+H]^+$184.0875, found 184.0867.

4.3.2. 1-Methyl-3-nitro-1*H*-pyridazino[3,4-*b*]indole (15a). Yield: 0.10 g (0.44 mmol), 43%; mp 209–210 °C; IR (KBr) ν_{max}: 3430, 2924, 1652, 1622, 1554, 1528, 1508, 1356, 1330, 1296, 764 cm^{-1}; δ_H (DMSO-d_6, 400 MHz): 9.49 (s, 1H, H-4), 8.52 (dd, 1H, $J_{5,6}$=6.8 Hz, $J_{5,7}$=1.0 Hz, H-5), 7.80 (dd, 1H, $J_{7,8}$=7.0 Hz, $J_{6,8}$=1.0 Hz, H-8), 7.75 (td, 1H, $J_{7,8}=J_{6,7}$=7.0 Hz, $J_{5,7}$=1.0 Hz H-7), 7.38 (ddd, 1H, $J_{6,7}$=7.0 Hz, $J_{5,6}$=6.8 Hz, $J_{6,8}$=1.0 Hz H-6), 4.55 (s, 3H, CH_3); δ_C (DMSO-d_6, 100 MHz): 157.0 (C-9a), 152.7 (C-3), 145.6 (C-8a), 134.2 (C-4a), 132.4 (C-7), 124.3 (C-5), 122.9 (C-4b), 121.3 (C-6), 119.1 (C-8), 115.3 (C-4), 43.5 (CH_3). MS (ESI): 229, 183, 156; HRMS (ESI) Calcd for $C_{11}H_9N_4O_2$ $[M+H]^+$229.0726, found 229.0714.

4.3.3. 6-Chloro-1-methyl-3-nitro-1*H*-pyridazino[3,4-*b*]indole (15b). Yield: 0.115 g, 44%); mp 224–225 °C; IR (KBr) ν_{max}: 3068, 1556, 1502, 1432, 1352, 1332, 1296, 832, 690 cm^{-1}; δ_H (DMSO-d_6, 200 MHz): 9.49 (s, 1H, H-4), 8.59 (d, 1H, $J_{5,7}=3.0$ Hz, H-5), 7.78 (d, 1H, $J_{7,8}=7.5$ Hz, H-8), 7.71 (dd, 1H, $J_{7,8}=7.5$ Hz, $J_{5,7}=3.0$ Hz, H-7), 4.51 (s, 3H, CH_3); δ_C (DMSO-d_6, 50 MHz): 155.2, 152.8 (C-3, 9a), 145.5 (C-8a), 133.2 (C-6), 132.0 (C-4), 125.2, 123.7 (C-4a, 4b), 123.5, 120.4, 116.3 (C-5, 7, 8), 43.4 (CH_3). MS (ESI): 263, 217, 190; HRMS (ESI) Calcd for $C_{11}H_8ClN_4O_2$ $[M+H]^+$263.0336, found 263.0328.

4.3.4. 4-Bromo-1-methyl-1*H*-pyridazino[3,4-*b*]indole (28). Yield: 0.196 g, 75%; mp: 130–133 °C; IR (KBr) ν_{max}: 3045, 2942, 1627, 1598, 1536, 1495, 1463, 1438, 1405, 1338, 1262, 1117, 1093, 968, 756, 727 cm^{-1}; δ_H ($CDCl_3$, 200 MHz): 8.38 (dd, 1H, $J=7.7$, 0.9 Hz, H-8), 8.25 (s, 1H, H-3), 7.84 (dd, 1H, $J=8.2$, 0.8 Hz, H-5), 7.71 (dd, 1H, $J=8.2$, 6.9 Hz, H-6), 7.33 (dd, 1H, $J=7.7$, 6.9 Hz, H-7), 4.50 (s, 3H, CH_3), δ_C ($CDCl_3$, 50 MHz): 155.5, 153.1, 134.5, 132.0, 131.9, 129.9, 124.4, 121.1 120.7, 118.6, 42.8. MS (ESI): 218, 203, 155, 154; Anal. Calcd for $C_{11}H_8BrN_3$ (262.11): C, 50.41; H, 3.08; N, 16.03. Found: C, 50.54; H, 3.12; N, 15.91.

4.3.5. Procedure for the synthesis of 4-chloro-1-methyl-1*H*-pyridazino[3,4-*b*]indole (21). Reaction of **1** with 2-pivaloylaminophenylboronic acid was carried out as described above. Column chromatography of the crude reaction product was omitted and, instead, the mixture was lyophilized during 3 h. Subsequently 40% H_2SO_4 (5 mL) was added and this mixture was refluxed (temperature of the oil bath: 110 °C) overnight (17 h). Then, the reaction was cooled to rt and 20 mL H_2O was added. Concentrated aqueous ammonium hydroxide was added until pH=8, and the mixture was extracted with dichloromethane (3× 30 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. After this manipulation, $POCl_3$ (3 mL) was added and the mixture was refluxed (temperature of the oil bath: 117 °C) for 3 h. After cooling down, $POCl_3$ was removed by evaporation under reduced pressure, and ice-water (20 mL) was added. The mixture was adjusted to pH=8 using concentrated aqueous ammonium hydroxide and was extracted with dichloromethane (3×30 mL). The combined organic extract was dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The crude reaction mixture was purified by flash column chromatography on silica using a EtOAc–EtOEt 4:1 mixture as the eluent.

Yield: 0.099 g, 22%; mp: 102–104 °C; IR (KBr) ν_{max}: 2924, 2854, 1626, 1598, 1536, 1493, 1462, 1438, 1399, 1336, 1261, 1238, 1226, 1210, 1197, 1120, 1093, 967, 758, 744, 730, 638 cm^{-1}; δ_H ($CDCl_3$, 400 MHz): 8.37 (ddd, 1H, $J=$ 7.9, 1.2, 0.8 Hz, H-8), 8.22 (s, 1H, H-3), 7.83 (ddd, 1H, $J=$ 8.2, 0.9, 0.7 Hz, H-5), 7.70 (ddd, 1H, $J=8.2$, 7.2, 1.2 Hz, H-6), 7.32 (ddd, 1H, $J=7.9$, 7.1, 0.9 Hz, H-7), 4.49 (s, 3H, CH_3), δ_C ($CDCl_3$, 100 MHz): 156.0, 153.2, 134.4, 132.1, 129.9, 129.5, 124.5, 121.3, 120.7, 118.8, 42.8. MS (ESI): 218, 203, 155, 154; HRMS (ESI) Calcd for $C_{11}H_9ClN_3$ $[M+H]^+$218.0485, found: 218.0483.

4.4. General procedure for the azidation of aminopyridazin-3(2H)-ones 14a,b

The appropriate aminopyridazin-3(2*H*)-one (5.0 mmol) was dissolved in 37% hydrochloric acid (100 mL) and was cooled to 0 °C with stirring. Aqueous sodium nitrite solution (0.73 g (10.62 mmol) of sodium nitrite in 27 mL of water) was added dropwise at such a rate that the temperature of the reaction mixture did not exceed 5 °C. The mixture was stirred at this temperature for 1.5 h.

A solution of sodium azide (0.664 g, 10.62 mmol) and anhydrous sodium acetate (5.744 g, 70.02 mmol) in water (24 mL) was then added at 0–5 °C and the mixture was stirred for an additional 1 h at this temperature. Then the mixture was neutralized with a saturated solution of sodium carbonate and extracted with dichloromethane (3× 100 mL). The organic layer was evaporated under reduced pressure (without heating) and the residue was suspended with diethyl ether to yield red-brown crystals which were filtered off. The product decomposed on air and was therefore stored under an argon atmosphere in a refrigerator.

4.4.1. 4-(2-Azidophenyl)-2-methyl-6-nitropyridazin-3(2*H*)-one (16a). Starting from **14a** (0.29 g, 1.18 mmol), 0.13 g of the crude product (0.48 mmol, 41%) was obtained; R_f (chloroform–ethyl acetate 95:5): 0.67; IR (KBr) ν_{max}: 3420, 2924, 2140, 2100, 1668, 1586, 1572, 1520, 1490, 1360, 1300, 830, 784, 768 cm^{-1}; δ_H ($CDCl_3$, 500 MHz): 8.16 (s, 1H, H-5), 7.53 (t, 1H, $J_{3',4'}=J_{4',5'}=7.8$ Hz, H-4′), 7.47 (d, 1H, $J_{5',6'}=7.5$ Hz, H-6′), 7.31 (d, 1H, $J_{3',4'}=$ 7.8 Hz, H-3′), 7.26 (dd, 1H, $J_{4',5'}=7.8$ Hz, $J_{5',6'}=7.5$ Hz, H-5′), 3.98 (s, 3H, CH_3); δ_C ($CDCl_3$, 125 MHz): 159.2 (C-3), 145.1 (C-6), 139.0 (C-4), 138.5 (C-2′), 131.5 (C-4′), 130.9 (C-6′), 125.2 (C-5), 124.9 (C-5′), 124.2 (C-1′), 118.9 (C-3′), 41.8 (CH_3).

4.4.2. 4-(2-Azido-5-chlorophenyl)-2-methyl-6-nitropyridazin-3(2*H*)-one (16b). Starting from **14b** (0.68 g, 2.42 mmol) 0.50 g of the crude product (1.63 mmol, 67%) was obtained; R_f (chloroform–ethyl acetate 95:5): 0.69; IR (KBr) ν_{max}: 3420, 2926, 2142, 1674, 1582, 1522, 1484, 1358, 1346, 1314, 826, 784, 760 cm^{-1}; δ_H ($CDCl_3$, 200 MHz): 8.16 (s, 1H, H-5), 7.48 (m, 1H, H-4′), 7.46 (m, 1H, H-6′), 7.25 (m, 1H, H-3′), 3.97 (s, 3H, CH_3); δ_C ($CDCl_3$, 50 MHz): 158.8 (C-3), 145.2 (C-6), 137.5 (C-4), 137.1 (C-2′), 131.4 (C-4′), 130.8 (C-6′), 130.3 (C-5′), 125.6 (C-5), 125.4 (C-1′), 120.1 (C-3′), 41.9 (CH_3).

4.5. General procedure for ring closure reaction of 16a,b

A solution of the appropriate azide (1.00 mmol) in dry xylene (5 mL) was refluxed for 22 h and the solvent was then removed under reduced pressure. The residue was purified by column chromatography and recrystallization from ethanol yielded pale yellow crystals.

4.5.1. 2-Methyl-4-nitro-2,5-dihydro-1*H*-pyridazino[4,5-*b*]indol-1-one (17a). Compound **16a** (0.09 g, 0.33 mmol) gave the ring closed title compound **17a** (0.03 g, 0.12 mmol, 36%); mp 314–316 °C; R_f (chloroform–ethyl acetate 95:5): 0.33; IR (KBr) ν_{max}: 3276, 1654, 1592, 1544, 1436, 1342, 1322, 760 cm^{-1}; δ_H (DMSO-d_6, 500 MHz): 12.65 (s, 1H,

NH), 8.23 (d, 1H, $J_{8,9}$=7.8 Hz, H-9), 7.82 (d, 1H, $J_{6,7}$=8.3 Hz, H-6), 7.59 (t, 1H, $J_{7,8}$=7.7 Hz, H-7), 7.42 (t, 1H, $J_{7,8}$=7.7 Hz, $J_{8,9}$=7.8 Hz, H-8), 3.92 (s, 3H, CH_3); δ_C (DMSO-d_6, 125 MHz): 158.0 (C-1), 139.0 (C-5a), 136.9 (C-4), 129.1 (C-4a), 127.5 (C-7), 122.6 (C-8), 121.9 (C-9a), 121.2 (C-9), 113.5 (C-6), 112.7 (C-9b), 40.7 (CH_3). MS (ESI): 245, 199, 169, 144; HRMS (ESI) Calcd for $C_{11}H_9N_4O_3$ $[M+H]^+$ 245.0675, found 245.0675.

4.5.2. 8-Chloro-2-methyl-4-nitro-2,5-dihydro-1*H*-pyridazino[4,5-*b*]indol-1-one (17b). Compound **16b** (0.25 g, 0.81 mmol) gave the ring closed title compound **17b** (0.12 g, 0.43 mmol, 53%); mp 354–354.5 °C; R_f (chloroform–ethyl acetate 95:5): 0.48; IR (KBr) ν_{max}: 3258, 1652, 1590, 1550, 1440, 1338, 1232, 800 cm^{-1}; δ_H (DMSO-d_6, 500 MHz): 8.15 (d, 1H, $J_{7,9}$=2.1 Hz, H-9), 7.81 (d, 1H, $J_{6,7}$=8.8 Hz, H-6), 7.61 (dd, 1H, $J_{6,7}$=8.8 Hz, $J_{7,9}$=2.1 Hz, H-7), 3.91 (s, 3H, CH_3); δ_C (DMSO-d_6, 125 MHz): 157.5 (C-1), 137.4 (C-5a), 136.5 (C-4), 129.7 (C-4a), 127.2 (C-7), 126.8 (C-8), 122.7 (C-9a), 119.8 (C-9), 114.8 (C-6), 111.7 (C-9b), 39.5 (CH_3). MS (ESI): 279, 233, 207, 203, 198, 152, 149, 121, 57; HRMS (ESI) Calcd for $C_{11}H_8ClN_4O_3$ $[M+H]^+$ 279.0285, found 279.0298.

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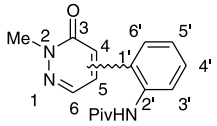
12. Although IUPAC nomenclature is used preferentially, in this paper compounds **7**, **13a**, **13b**, **18**, **19**, **20**, **25** and **26** are regarded as 2-pivaloylaminophenyl substituted pyridazin-3(2*H*)-ones rather than as 2-substituted *N*-phenylpivaloylamides. In this way the names and NMR assignments of these compounds can more easily be compared with those of the corresponding 2-aminophenyl- and 2-azidophenylpyridazin-3(2*H*)-ones.



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