

The Cu(OTf)₂ catalysed microwave assisted synthesis of a new scaffold, 7-aryl-7,8-dihydropyrido[4,3-*c*]pyridazin-5(6*H*)-one

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Abstract

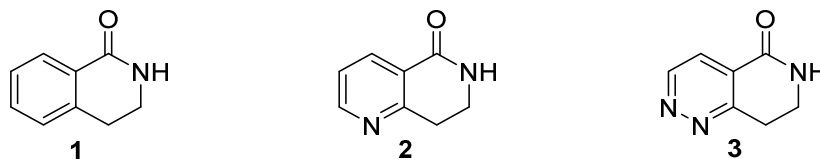
The synthesis of novel 7-aryl-7,8-dihydropyrido[4,3-*c*]pyridazin-5(6*H*)-ones is described including a one-step Mannich-type reaction followed by intramolecular ring closure of ethyl 3-methylpyridazine-4-carboxylate and aldimines, catalysed by the Lewis acid Cu(OTf)₂ under microwave heating. This synthesis opens up possibilities to access this unexplored scaffold for medicinal chemistry.

Keywords: Pyridopyridazinones, nitrogen heterocycles, microwave irradiation

Introduction

In the search for new biologically active compounds and drugs, extensive research is based on the synthesis of natural-like or small molecules. In this regard, the theory of privileged scaffolds, structures which can interact with high affinity to a broad range of (unrelated) receptors, provides new insights and hope for the synthesis of new active compounds.¹ They are typically rigid and polycyclic heteroatomic systems, able to orient numerous substituents in the three-dimensional space surrounding these scaffolds.² Because these privileged structures furnish activities towards different receptors, they are considered excellent lead compounds, especially when only little is known about the structure of the receptors. Because the amount of new drugs is declining, despite the large amount of sources and research that are invested in this research, new scaffolds need to be explored. Therefore, increasing the chemical diversity in the field of heterocyclic chemistry is of great interest for the pharmaceutical industry.

In the course of our research towards innovative heterocyclic scaffolds, our interests and efforts were guided towards the synthesis of 7-aryl-7,8-dihydropyrido[4,3-*c*]pyridazin-5(6*H*)-ones. Dihydroisoquinolinones and dihydronaphthyridinones (the benzo- and pyrido-analogues respectively) are widely reported and investigated. Dihydroisoquinolinones **1** for example can be used for the treatment of various disease conditions mediated by the regulation of 17 α -hydroxylase/C_{17,20}-lyase,³ whereas dihydronaphthyridinones **2** interact as mGluR5 allosteric modulators.⁴ 7,8-Dihydropyrido[4,3-*c*]pyridazin-5(6*H*)-ones **3** however, are only scarcely reported in scientific literature. The only references (which came up of a Scifinder search) disclose the scaffold with one or more extra aromatic rings annelated to the scaffold.^{5,6,7} The amide-reduced analogues 5,6,7,8-tetrahydropyrido[4,3-*c*]pyridazines are only reported in two references.^{8,9} The 7,8-dihydropyrido[4,3-*c*]pyridazin-5(6*H*)-one scaffold as such is still unknown in the scientific literature, leaving an opportunity towards the synthesis of a new possible privileged scaffold.



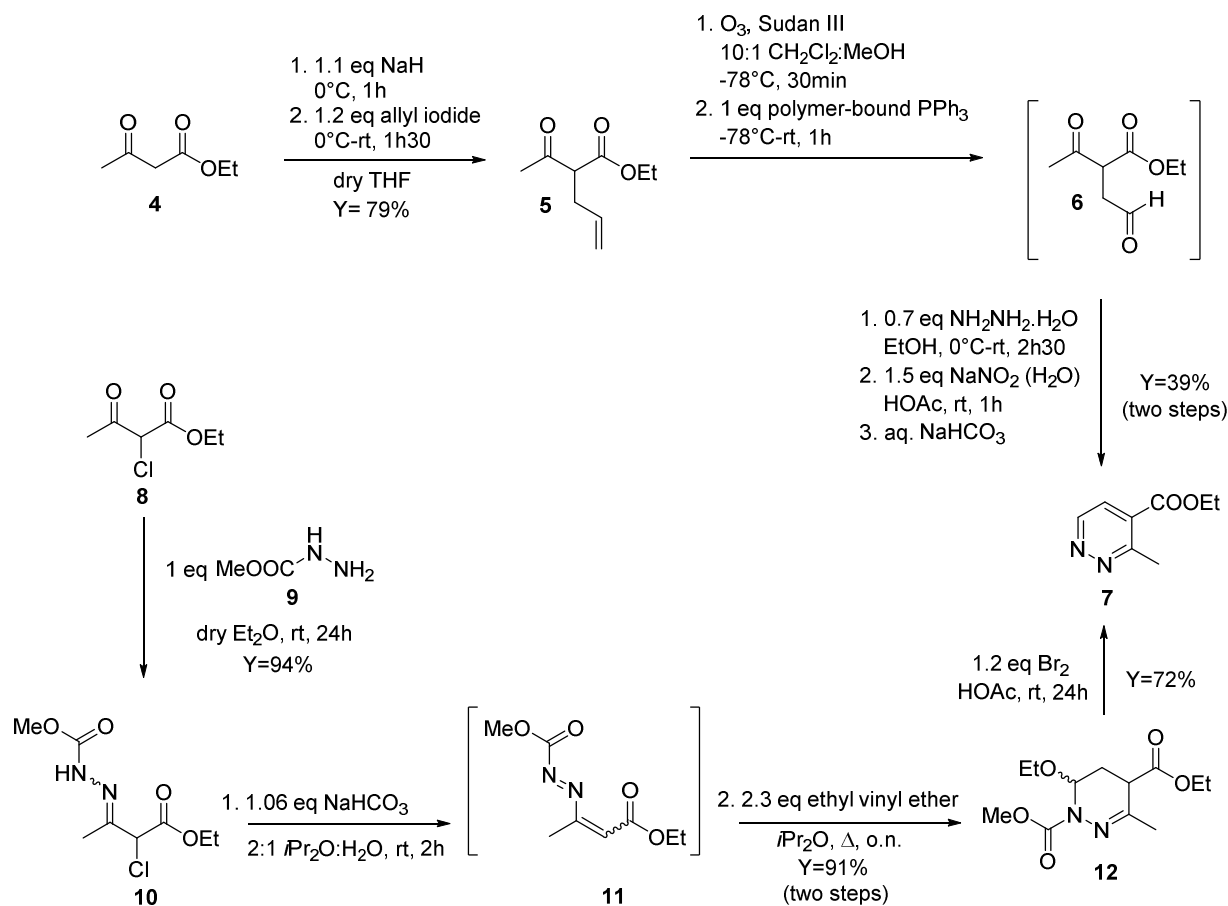
The synthesis of this new scaffold extends our research towards innovative bio-active heterocyclic scaffolds, in which small and natural-like molecules were discovered as anti-cancer chalcone derivatives,¹⁰ insect-repellant/antifeedant methanoproline analogues,^{11,12} or epibatidine-like nicotinic acetylcholine receptors inhibitors.^{13,14} Further, the synthesis of new previously unreported scaffolds, 4-(trifluoromethyl)-7,8-dihydroquinolin-5(6*H*)-ones and 4-(trifluoromethyl)-5,7,8,9-tetrahydro-6*H*-pyrido[3,2-*b*]azepin-6-ones,¹⁵ and 5,8-disubstituted 5,6,8,9-tetrahydro-4*H*,7*H*-2,5,6a,8,9a-pentaazaphenalene-1,3-diones were discovered,¹⁶ broadening the chemical diversity of possible privileged scaffolds.

In this paper, the synthesis of 7-aryl-7,8-dihydropyrido[4,3-*c*]pyridazin-5(6*H*)-ones is reported, synthesized by a one-step Mannich-type reaction followed by ring closure of ethyl 3-methylpyridazine-4-carboxylate and aldimines. The reactions were performed under Cu(OTf)₂ catalysis and microwave heating.

Results and Discussion

The synthesis started with the synthesis of ethyl 3-methylpyridazine-4-carboxylate **7** (Scheme 1). Two routes were explored, one starting from ethyl acetoacetate **4**, the other starting from ethyl 2-chloroacetoacetate **8**. In a first entry, ethyl acetoacetate was mono-allylated with 1.2 equivalents of allyl iodide and 1.1 equivalents of sodium hydride in dry THF for 1 hour 30

minutes at room temperature, leading to ethyl 2-allylacetate **5** by column chromatography in 79% yield.¹⁷ Allylation with allyl bromide and sodium hydride or a palladium catalyzed Trost-allylation with allyl bromide resulted in either diallylation or a mixture of mono- and diallylated product.



Scheme 1. Synthesis of ethyl 3-methylpyridazine-4-carboxylate (**7**).

Having the alkene in hand, an ozonolysis was performed to obtain the free aldehyde ethyl 2-acetyl-4-oxobutanoate **6**. This was performed by bubbling ozone through a solution of ethyl 2-allylacetate **5** in dichloromethane and methanol (ratio 10:1) at -78°C for 30 minutes, to which a trace amount of Sudan III was added as an indicator. An equimolar amount of polymer-bound PPh₃ was added for the reductive work-up of the intermediate ozonides and after 1 hour of slow stirring at room temperature, the reaction mixture was filtered and evaporated.¹⁸ Analysis of the reaction mixture by ¹H-NMR demonstrated a 52% conversion of the alkene towards the aldehyde. Because no full conversion of **5** and no pure aldehyde **6** could be obtained, the crude mixture of **5** and **6** was used as such in the next step for the synthesis of ethyl 3-methylpyridazine-4-carboxylate **7**.

The synthesis of ethyl 3-methylpyridazine-4-carboxylate **7** was performed by the reaction of crude **6** with hydrazine.¹⁸ A solution of the reaction mixture in ethanol was slowly treated with 0.7 equivalents of hydrazine monohydrate at 0°C. The reaction mixture was allowed to warm to room temperature and was stirred for 2 hours 30 minutes. Thereafter, 1.5 equivalents of sodium nitrite, dissolved in water, and acetic acid were added and the mixture was again stirred for 1 hour at room temperature. After column chromatography, the end product was obtained in 39% yield (two steps) as yellow-brownish crystals. Taken this low (overall) yield, the small scale and the troublesome synthesis of pyridazine **7** into account, this pathway was abandoned and a new pathway starting from ethyl 2-chloroacetoacetate was investigated.

The new synthesis pathway towards ethyl 3-methylpyridazine-4-carboxylate **7** started with the formation of ethyl 2-chloroacetoacetate *N*-methoxycarbonylhydrazone **10**.¹⁹ Ethyl 2-chloroacetoacetate **8** was dissolved in dry diethyl ether and 1 equivalent of methyl hydrazinocarboxylate **9** was added. After stirring for 24 hours at room temperature, the precipitate was filtered off and washed with petroleum ether, resulting in pure ethyl 2-chloroacetoacetate *N*-methoxycarbonylhydrazone **10** as a white powder in 94% yield.

The hydrazone **10** was subsequently converted into 4-ethyl 1-methyl 6-ethoxy-3-methyl-5,6-dihydropyridazine-1,4(4*H*)-dicarboxylate **12** via treatment with sodium bicarbonate and a subsequent inverse electron demand hetero Diels-Alder reaction.²⁰

Hydrazone **10** was dissolved in a 2:1 diisopropyl ether:water mixture and 1.06 equivalents of sodium bicarbonate were added. The reaction mixture discoloured immediately and release of gas was noticed and the 1,2-diaza-1,3-diene **11** was formed. After 2 hours of stirring at room temperature, the aqueous phase was discarded and the red organic phase was dried over magnesium sulfate. Because the isomeric mixture of **11** (of which the *E*-isomer is the major component) polymerises at room temperature and has explosive properties upon heating, thereby prohibiting purification by distillation, **11** was used as an unpurified mixture of isomers in diisopropyl ether in the next step.²¹

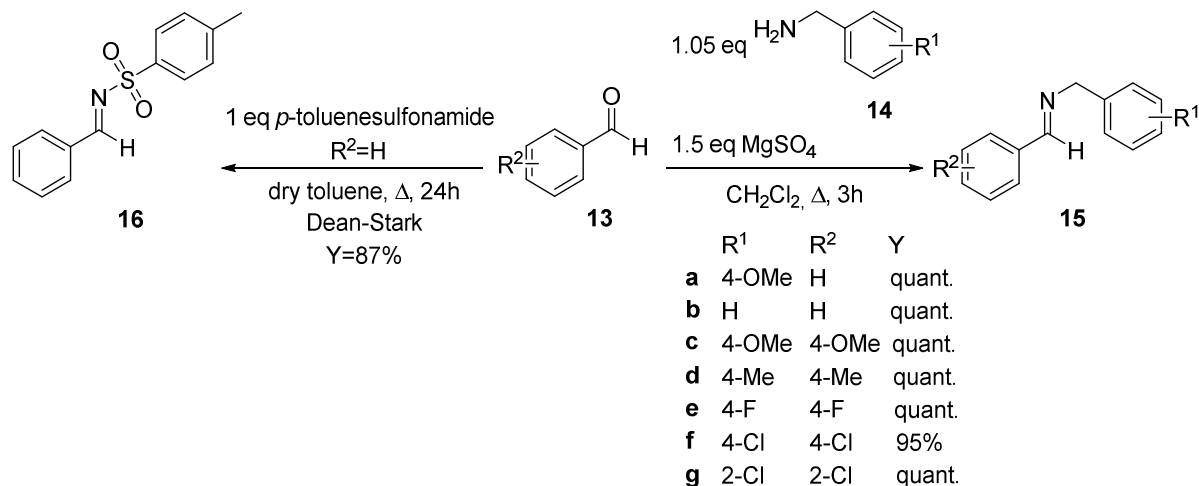
For the inverse electron demand hetero Diels-Alder reaction, 2.3 equivalents of ethyl vinyl ether were added to the dried solution of **11** in diisopropyl ether. The mixture was brought to reflux temperature and heated overnight. The reaction mixture was evaporated, resulting in a yellow oil of 4-ethyl 1-methyl 6-ethoxy-3-methyl-5,6-dihydropyridazine-1,4(4*H*)-dicarboxylate **12** in 91% yield over two steps. This Diels-Alder product **12** was obtained as a *cis-trans* mixture. Since **12** had to be converted to ethyl 3-methylpyridazine-4-carboxylate **7** in the next step, no purification nor separation of the isomers was necessary and **12** was used as such in the next step.

The last step in the synthesis of ethyl 3-methylpyridazine-4-carboxylate **7** is the oxidation of **12** with bromine in acetic acid.²⁰ The crude **12** was dissolved in acetic acid and 1.2 equivalents of bromine were slowly added. This resulted in the formation of a brown reaction mixture and the production of gas. After stirring for 24 hours at room temperature, diisopropyl ether was added, resulting in the formation of a precipitate which was filtered and washed with diisopropyl ether. Toluene was added and evaporated to remove residual acetic acid in an azeotropic

distillation. The residue was dissolved in water and trace amounts of small impurities were filtered off. The filtrate was neutralized by sodium bicarbonate and sodium chloride was added. The mixture was extracted with diisopropyl ether and the organic phase was dried over magnesium sulfate and evaporated, resulting in red-brown crystals of **7**. According to $^1\text{H-NMR}$ and LC-MS analysis, these crystals consisted of **7** in very high purity. Recrystallization from diethyl ether did not improve the purity. After column chromatography and subsequent recrystallization from diethyl ether, colorless crystals of **7** were obtained in 72% yield, having the same $^1\text{H-NMR}$ and LC-MS purity as the red-brown crystals.

The latter synthesis for ethyl 3-methylpyridazine-4-carboxylate was used starting from ethyl 2-chloroacetoacetate **8** because the first synthesis route, starting from ethyl acetoacetate **3**, did not offer satisfactory results. This second route not only comprised a more practical synthesis, it could also be executed on gram scale and in high (overall) yields.

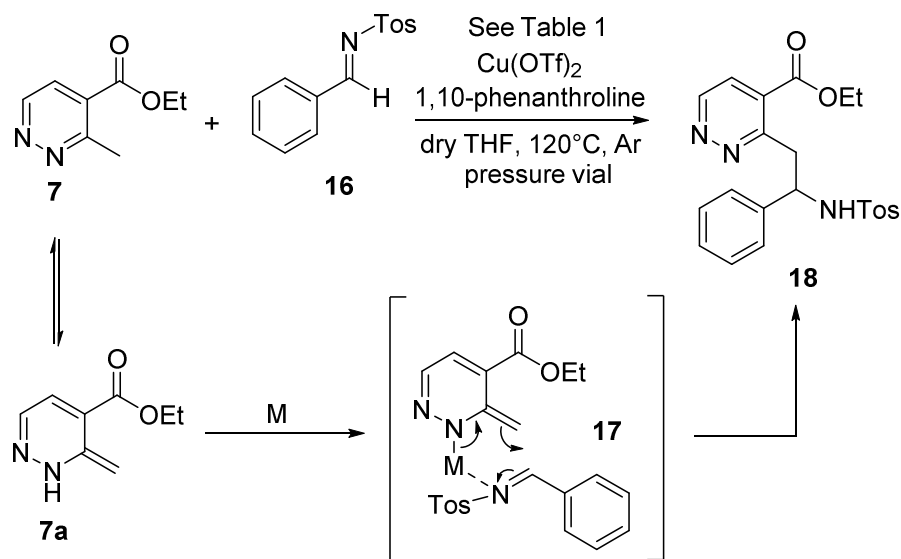
For the synthesis of the pyrido[4,3-*c*]pyridazines, ethyl 3-methylpyridazine-4-carboxylate **7** was reacted with aldimines. Different aldimines were synthesized via a straightforward procedure (Scheme 2).²² The appropriate aldehyde **13** was dissolved in dichloromethane and 1.05 equivalents of the corresponding amine **14** was added. After stirring at reflux temperature for 3 hours in the presence of 1.5 equivalents of magnesium sulfate, the precipitate was filtered and the aldimine **15** was obtained in almost always quantitative yield, without the need for purification. Also, the *N*-benzylidene-*p*-toluenesulfonamide **16** was synthesized by refluxing 1 equivalent of *p*-toluenesulfonamide and 1 equivalent of benzaldehyde under Dean-Stark conditions, resulting in 87% of **16** after recrystallization from diethyl ether.²³



Scheme 2. Synthesis of aldimines **15-16**.

The synthesized ethyl 3-methylpyridazine-4-carboxylate **7** and *N*-benzylidene-*p*-toluenesulfonamide **16** were used in a Mannich-type reaction to furnish the addition product **18** (Scheme 3, Table 1). Ethyl 3-methylpyridazine-4-carboxylate **7** and *N*-benzylidene-

p-toluenesulfonamide **16** were dissolved in dry THF in a pressure vial under an inert argon atmosphere and were heated at 120°C. Copper(II)triflate (9.4 mol%) was added, together with an equal amount of 1,10-phenanthroline as a ligand to solubilize the copper catalyst. This copper salt does not only activate imine **16** by acting as a Lewis acid, but also shifts the equilibrium between **7** and **7a** towards the enamine by the formation of a metal enamide species **17**.²⁴ In a first entry, an excess of **7** was used and the reaction was stirred for 1 hour 40 minutes, resulting in a conversion of 9% of **7** to **18**. When 5 mol% of catalyst was added and the reaction was performed for 24 hours, the conversion increased to 30% (entry 2). However, the isolated yield of **18** was very low, due to a very difficult purification by column chromatography. Increasing the equivalents of **16** did lead to an increase in yield after 20 hours (entry 3), while an extensive reaction time of 89 hours only offered a moderately improved yield (entry 4). Adding 1.5 equivalents of DIPEA to trap the expelled proton (entry 5) did not improve the reaction outcome as well.



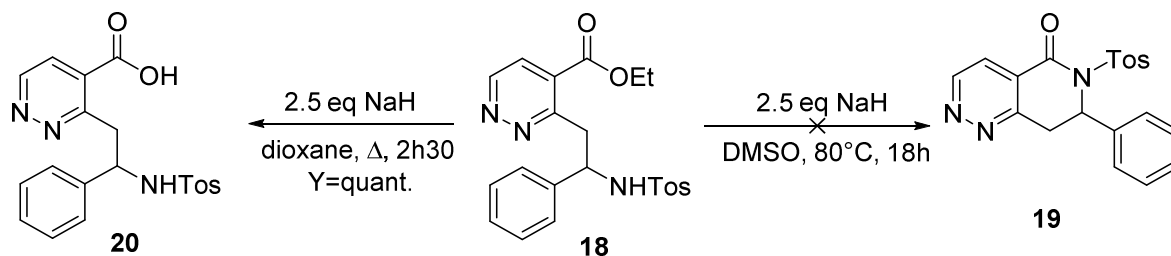
Scheme 3. Synthesis of **18**.

Table 1. Conditions for the synthesis of **18**

Entry	Eq 16	Eq Cu(OTf) ₂ Eq 1,10-phenanthroline	Time	Conversion (%) ^a	Yield (%)
1	0.4	0.094	1h40	9	-
2	0.4	0.05	24h	30	2
3	0.95	0.05	20h	-	33
4	0.95	0.05	89h	-	50
5	0.95	0.05 ; 1.5 eq DIPEA	70h	21	-

^aBased on NMR.

Nevertheless, having the Mannich-type addition product **18** in hand, the ring closure towards 7-phenyl-6-tosyl-7,8-dihydropyrido[4,3-*c*]pyridazin-5(6*H*)-one **19** could be attempted (Scheme 4). In a first attempt, **18** was dissolved in DMSO and this solution was added to a solution of 2.5 equivalents of sodium hydride in DMSO and was stirred at 80°C, but no cyclized product could be recovered.²⁵ When the solvent was changed to dioxane, no ring closure to **19** proceeded, but instead the saponification to 3-(2-(*N*-tosyl)-amino-2-phenylethyl)pyridazine-4-carboxylic acid **20** occurred. The last attempt comprised stirring **18** in a 10:1 dichloromethane:glacial acetic acid mixture overnight at room temperature. Also under these acidic reaction conditions, **19** could not be obtained.



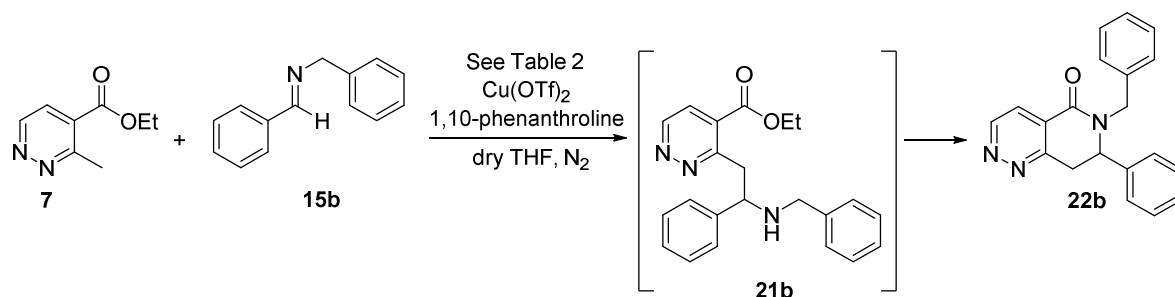
Scheme 4. Attempted synthesis of **19**.

The desired ring closure most probably did not occur due to the (too) strong electron withdrawing potency of the *N*-tosyl group. Therefore, alternative aldimines were used in the pursuit of 7,8-dihydropyrido[4,3-*c*]pyridazin-5(6*H*)-ones.

The copper(II) triflate-catalyzed Mannich-type reaction was repeated with *N*-benzylidene-benzylamine **15b** (Scheme 5, Table 2). Ethyl 3-methylpyridazine-4-carboxylate **7**, 0.95 equivalents of *N*-benzylidene-benzylamine **15b**, 5 mol% copper(II)triflate and 1,10-phenanthroline were dissolved in dry THF in a pressure vial under an inert nitrogen atmosphere. After 127 hours, the reaction mixture was filtered over a plug of silica involving washing with a large amount of ethyl acetate to remove the copper salts and the filtrate was evaporated. Purification by column chromatography yielded 6-benzyl-7-phenyl-7,8-dihydropyrido[4,3-*c*]pyridazin-5(6*H*)-one **22b** in 8% yield (entry 1). Interestingly, the Mannich-type addition and the direct ring closure occurred simultaneously, without the isolation of the Mannich-type adduct **21b**, which could not be observed in the reaction mixture.

An increase of the amounts of copper(II) triflate and 1,10-phenanthroline to 20 mol% and an increase in reaction temperature to 140°C resulted in a conversion of 44% (entry 2). The conversion could be enhanced by the use of 2 equivalents of **15b**, resulting in a conversion of 74% and a yield of 54% (entry 3). Because of the very slow reaction rate resulting in an extremely long reaction time, even at 120-140°C, the influence of microwave (MW) heating was evaluated in the next entries (entries 4-6). When microwave heating was applied at 165°C for 25 minutes, no reaction product could be isolated (entry 4). These conditions were too harsh for the microwave vial septum, resulting in the loss of the reaction mixture. When a temperature of

135°C was maintained for 9 hours, a conversion of 85% and the corresponding yield of 55% was obtained (entry 5). The reaction time could be reduced to 3 hours when 3 equivalents of imine **15b** were added (entry 6).



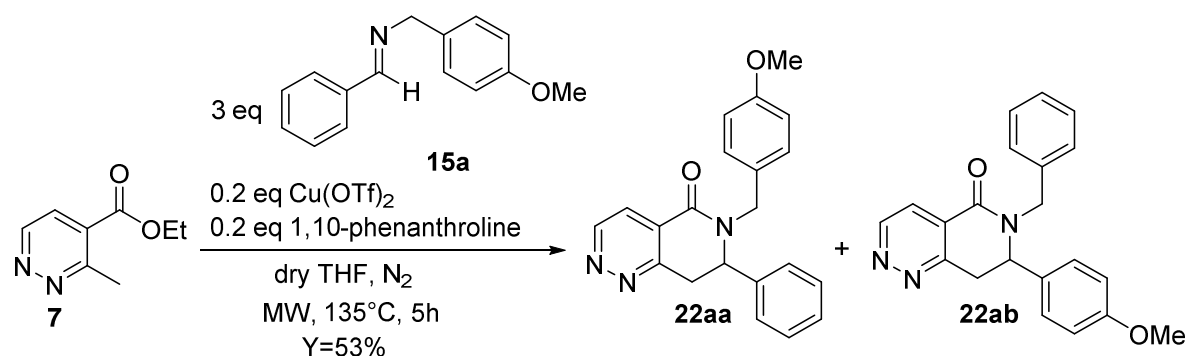
Scheme 5. Synthesis of **22b**.

Table 2. Conditions for the synthesis of **22b**

Entry	Eq 15b	Eq Cu(OTf) ₂ Eq 1,10-phenanthroline	Conditions	Conversion (%) ^a	Yield (%)
1	0.95	0.05	120°C, 127h pressure vial	-	8
2	0.95	0.2	120°C, 72h, 140°C, 144h pressure vial	44	-
3	2	0.2	120°C, 48h 140°C, 144h pressure vial	74	54
4	2	0.2	165°C, 25min, MW	-	-
5	2	0.2	135°C, 9h, MW	85	55
6	3	0.2	135°C, 3h, MW	82	48

^aBased on NMR.

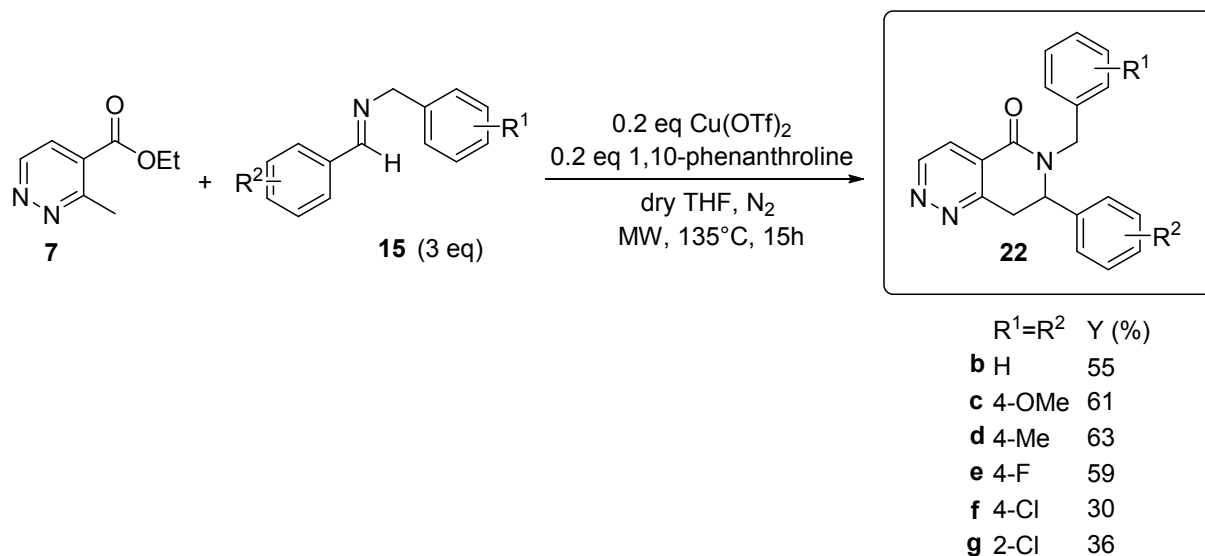
In an analogous reaction, *N*-benzylidene-(4-methoxybenzyl)amine **15a** was used as the aldimine. After purification, not only the desired 6-(4-methoxybenzyl)-7-phenyl-7,8-dihydropyrido[4,3-*c*]pyridazin-5(6*H*)-one **22aa** was obtained, but also 6-benzyl-7-(4-methoxyphenyl)-7,8-dihydropyrido[4,3-*c*]pyridazin-5(6*H*)-one **22ab** as an inseparable mixture (3:2 **22aa**:**22ab** or *vice versa*) in 53% total yield.



Scheme 6. Synthesis of **22a**.

These two isomers **22aa/22ab** were formed due to isomerization of **15a** to *N*-(4-methoxybenzylidene)-benzylamine via a [1,3]-proton shift under the prevailing reaction conditions. Therefore, only aldimines **15b-g** in which both aromatic moieties are substituted with the same R-group could be used in further reactions. In these cases, isomerization of the aldimine does not lead to a mixture of 7,8-dihydropyrido[4,3-*c*]pyridazin-5(6*H*)-one isomers.

To broaden the scope of the reaction towards the synthesis of 7-aryl-7,8-dihydropyrido[4,3-*c*]pyridazin-5(6*H*)-ones **22b-g**, different aldimines **15b-g** have been used. The reaction was performed overnight (15 hours) in order to obtain the highest possible yields of **22b-g**.



Scheme 7. Synthesis of **22b-g**.

After filtration of the reaction mixture over silica, pure compounds were only obtained after several consecutive purifications via column chromatography, due to the very similar retention factors of **22b-g** and the unreacted ethyl 3-methylpyridazine-4-carboxylate **7**. An alternative work-up procedure comprised stirring of the filtrate residue in a 1:2 2M aq. NaOH:THF solution

for 45 minutes. In this way, the unreacted ethyl 3-methylpyridazine-4-carboxylate **7** was hydrolyzed into the corresponding 3-methylpyridazine-4-carboxylate. When the organic phase was evaporated, **22b-g** could be extracted with dichloromethane, together with the excess of aldimine **15b-g**. The pure compounds **22b-g** were now easily obtained via column chromatography in moderate to good yields as yellow viscous oils. The chloro derivatives resulted in somewhat lower yields, probably due to the interaction of the chlorine atoms with the copper catalyst.

Attempts to further improve the yields were performed by a) the portion wise addition of the catalysts and aldimines, b) prolonging the reaction time up to 35 hours or c) using a dilute reaction mixture to increase the solubility of the starting ethyl 3-methylpyridazine-4-carboxylate **7**. Unfortunately, these attempts were not successful.

The conformational structure and spectroscopic data of the compounds **22b-g** did offer some intriguing results. Due to the steric interaction of the aryl groups positioned on the N₆ and C₇-position, the C₇-aryl group is forced into the pseudo-axial position (Figure 1).²⁶ Also, the geometrical conformation led to a difference in ¹H-NMR shift of around 2 ppm for the two diastereotopic geminal protons H_a and H_b in an AB-system from the amide-methylene group, due to the neighbouring amide carbonyl anisotropy.²⁷ By the use of a NOESY-¹H-NMR-experiment, proton H_a was assigned as the proton which is most closely positioned at H_{eq,c} ($\delta \approx 3.60$ ppm). Because of the anisotropy of the carbonyl group, proton H_b has a much higher chemical shift ($\delta \approx 5.60$ ppm).

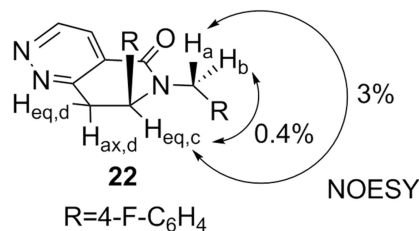


Figure 1. Conformational structure of **22b-g**.

This conformational structure was confirmed by the X-ray diffraction analysis of 6-(4-fluorobenzyl)-7-(4-fluorophenyl)-7,8-dihydropyrido[4,3-*c*]pyridazin-5(6*H*)-one **22e** of which the asymmetric unit and crystal unit cell are depicted in Figure 2 and Figure 3.

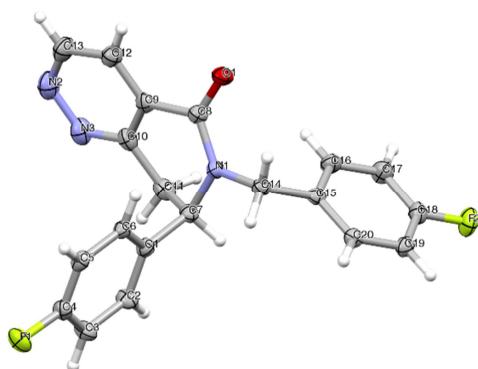


Figure 2. Asymmetric unit of the crystal structure of **22e**, showing thermal displacement ellipsoids at the 50% probability level and atom labeling scheme of the non-hydrogen atoms.

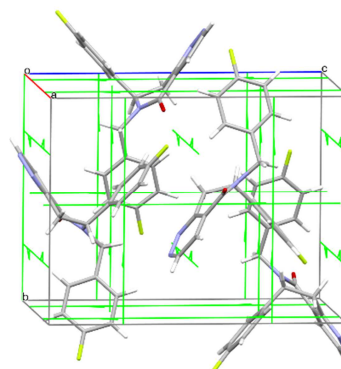


Figure 3. Crystal unit cell of **22e**, showing the non-centrosymmetrical spacegroup $P2_12_12_1$

Despite the difficult synthesis of the 7,8-dihydropyrido[4,3-*c*]pyridazin-5(6*H*)-ones **22**, requiring rather harsh conditions by microwave heating, we did succeed in the synthesis of this new scaffold.

Conclusions

In conclusion, a novel approach towards 7-aryl-7,8-dihydropyrido[4,3-*c*]pyridazin-5(6*H*)-ones **22b-g** is presented. The key step is a one-step Mannich-type reaction of ethyl 3-methylpyridazine-4-carboxylate **7** and aldimines **15b-g** followed by an intramolecular ring closure, catalysed by the Lewis acid $\text{Cu}(\text{OTf})_2$ under microwave heating. This ring closure occurred concomitantly with the Mannich-type reaction and the intermediate addition product could not be isolated nor observed. This new scaffold opens up new opportunities in the chemical space and in the field of heterocyclic chemistry for the pharmaceutical industry.

Experimental Section

General. High resolution NMR spectra were run on a Bruker Avance III Nanobay 400 MHz spectrometer ^1H -NMR (400 MHz), ^{13}C -NMR (100 MHz) and ^{19}F -NMR (376.5 MHz). Peak assignments were obtained with the aid of DEPT, 2D-HSQC, 2D-COSY spectra. The compounds were dissolved in deuterated solvents and the used solvent is indicated for each compound. Low resolution mass spectra were recorded on an Agilent 1100 Series VS (ES, 4000V) mass spectrometer. HRMS analysis was performed using an Agilent 1100 series HPLC

coupled to an Agilent 6210 TOF-Mass Spectrometer, equipped with ESI/APCI-multimode source. IR-spectra were obtained from a Perkin Elmer Spectrum One infrared spectrometer. The purification of reaction mixtures was performed by flash chromatography using a glass column with silica gel (Acros, particle size 0.035-0.070 mm, Pore diameter ca. 6 nm). All microwave reactions were performed in a CEM Discover Benchmate with a continuous power output from 0 to 300 watt and a self-adjusting, single mode MW cavity. The reactions were performed in 10 mL thick-walled Pyrex reaction vessels, closed with a 'snap-on' septa cap and equipped with a small stirring bar. A ramp time of maximum five minutes was used whereby the temperature was increased from room temperature to the desired one. This temperature was maintained during the course of the reaction for the indicated time. The temperature control system used a non-contact infrared sensor to measure the temperature on the bottom of the vessel and was used in a feedback loop with the on-board computer to regulate the temperature from 25 to 250 °C by adjusting the power output (1 Watt increments). Cu(OTf)₂ and 1,10-phenanthroline were dried at 60-80°C at 2-3 mbar for at least one hour before every use in the reactions. X-ray intensity data were collected on a Agilent Supernova Dual Source (Cu at zero) diffractometer equipped with an Atlas CCD detector using CuK α radiation ($\lambda = 1.54178 \text{ \AA}$) and ω scans. The images were interpreted and integrated with the program CrysAlisPro (Agilent Technologies). Using Olex2, the structure was solved by direct methods using the ShelXS structure solution program and refined by full-matrix least-squares on F² using the ShelXL program package. Non-hydrogen atoms were anisotropically refined and the hydrogen atoms in the riding mode and isotropic temperature factors fixed at 1.2 times U(eq) of the parent atoms. The amide and amine hydrogen atoms were located from a difference electron density map and were unrestrained refined. CCDC-1020668 contains the supplementary crystallographic data for this paper and can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44-1223-336033; or deposit@ccdc.cam.ac.uk).

Synthesis of ethyl 3-methylpyridazine-4-carboxylate (7) starting from ethyl 2-chloroacetoacetate (8)

Synthesis of ethyl 2-chloroacetoacetate *N*-methoxycarbonylhydrazone (10).¹⁹ Ethyl 2-chloroacetoacetate (8) (16.21 g, 1eq) and hydrazinocarboxylate(9) (8.90 g, 1eq) was dissolved in 100 ml of dry ethyl ether in a 250 ml round-bottomed flask. After stirring for 24 hours at room temperature, the precipitate was filtered off and washed with 2 times 50 ml petroleum ether, resulting in pure ethyl 2-chloroacetoacetate *N*-methoxycarbonylhydrazone **10** as a white powder in 94% yield (22.24 g).

Synthesis of 4-ethyl 1-methyl 6-ethoxy-3-methyl-5,6-dihydropyridazine-1,4(4*H*)-

dicarboxylate 12.²⁰ Ethyl 2-chloroacetoacetate-*N*-methoxycarbonylhydrazone (**10**) (5 g, 1 eq) was dissolved in a 2:1 diisopropyl ether:water mixture (35 ml:15 ml) and 1.06 equivalents (1.88 g) of sodium bicarbonate were added. The reaction mixture discoloured immediately and release of gas was noticed and methyl 2-(-4-ethoxy-4-oxobut-2-en-2-yl)diazene-1-carboxylate **11** was

formed. After 2 hours of stirring at room temperature, the aqueous phase was discarded and the red organic phase was dried over magnesium sulfate.

For the inverse electron demand hetero Diels-Alder reaction, 2.3 equivalents (4.69 ml) of ethyl vinyl ether were added to the dried solution of **11** in diisopropyl ether. The mixture was brought to reflux temperature and heated overnight. The reaction mixture was evaporated, resulting in 5.23 g of a yellow oil of 4-ethyl 1-methyl 6-ethoxy-3-methyl-5,6-dihydropyridazine-1,4(4*H*)-dicarboxylate **12** in 91% yield over two steps, without purification.

Synthesis of ethyl 3-methylpyridazine-4-carboxylate (7).²⁰ 4-Ethyl 1-methyl 6-ethoxy-3-methyl-5,6-dihydropyridazine-1,4(4*H*)-dicarboxylate (**12**) (18.48 g, 1eq) was dissolved in 250 ml of acetic acid in a 500 ml round-bottomed flask and 1.2 equivalents (4.05 ml) of bromine were slowly added. This resulted in the formation of a brown reaction mixture and the production of gas. After stirring for 24 hours at room temperature, 250 ml of diisopropyl ether was added, resulting in the formation of a precipitate which was filtered and washed with 2 times 50 ml of diisopropyl ether. 100 ml of toluene was added and evaporated to remove residual acetic acid in an azeotropic distillation. The residue was dissolved in 75 ml of water and trace amounts of small impurities were filtered off. The filtrate was neutralized by 7.3 g of sodium bicarbonate and 12 g of sodium chloride was added. The mixture was extracted with 3 times 75 ml diisopropyl ether and the organic phase was dried over magnesium sulfate and evaporated. After column chromatography with ethyl acetate ($R_f=0.38$) and subsequent recrystallization from diethyl ether, 8.03 g of colorless crystals of **7** were obtained in 72% yield.

General procedure for the synthesis of 7-aryl-7,8-dihydropyrido[4,3-*c*]pyridazin-5(6*H*)-ones (22b-g). The synthesis of 6-benzyl-7-phenyl-7,8-dihydropyrido[4,3-*c*]pyridazin-5(6*H*)-one **22b** is representative. 1 Equivalent (0.2 g) of ethyl 3-methylpyridazine-4-carboxylate **7**, 0.2 equivalent (0.043 g) of 1,10-phenanthroline and 0.2 equivalent (0.087 g) of $\text{Cu}(\text{OTf})_2$ are added to a flame-dried microwave vial with stirring bar. To this mixture, 3 ml of dry THF were added. 3 equivalents (0.705 g) of *N*-benzylidene-benzylamine **15b** is dissolved in 2 ml of dry THF and added to the mixture. The aldimine vial is rinsed with 1 ml of dry THF. The microwave vial is stirred at room temperature for 1 minute while flushing the headspace with a nitrogen flow, before closing the microwave vial with a septum. The mixture is heated during 15 hours at 135°C by the use of microwave irradiation.

After reaction, the mixture was filtered over a small plug of silica with the use of 50 ml of ethyl acetate and the filtrate was evaporated. The residue was dissolved in 20 ml: 40 ml 2M NaOH:THF solution and stirred for 45 minutes at room temperature. The organic phase was evaporated and the water phase extracted with 3 times 30 ml dichloromethane. The combined organic phases were dried over magnesium sulphate, filtrated and evaporated. The residue was coated on silica and purified by silica gel column chromatography using a solvent gradient from 1:1 Hexane:EtOAc to EtOAc.

6-Benzyl-7-phenyl-7,8-dihydropyrido[4,3-*c*]pyridazin-5(6*H*)-one (22b). ¹H-NMR (400MHz, CDCl_3): δ 3.61 (1H, dd, J 16.6, 2.3Hz, CHCH_aH_b), 3.73 (1H, d, J 16.6Hz, CHCH_aH_b); 3.74 (1H,

d, J_{AB} 14.8Hz, NCH_aH_b); 4.96 (1H, dd, J 6.8, 2.3Hz, $NCHCH_2$), 5.77 (1H, d, J_{AB} 4.8Hz, NCH_aH_b), 7.00-7.05 (2H, m, $2 \times CH_{arom}$), 7.25-7.39 (8H, m, $8 \times CH_{arom}$), 8.11 (1H, d, J 5.1Hz, $NCHCH$), 9.33 (1H, dd, J 5.1, 0.6Hz, $NCHCH$); ^{13}C -NMR (100MHz, $CDCl_3$): δ 36.4 ($CHCH_2$), 49.0 (NCH_2), 57.5 ($NCHCH_2$), 123.5 ($NCHCH$), 126.0 ($2 \times CH_{arom}$), 126.7 (COC_q), 128.1 (CH_{arom}), 128.2 ($2 \times CH_{arom}$), 128.3 (CH_{arom}), 129.0 ($2 \times CH_{arom}$), 129.2 ($2 \times CH_{arom}$), 136.4 (NCH_2C_q), 138.2 ($NCHC_q$), 152.0 ($NCHCH$), 155.8 (CO), 162.2 (NC_qCH_2). IR (ATR, cm^{-1}): ν_{max} 3030, 1654. HRMS (ES, pos. mode): m/z (%) calc: 316.1444, exp: 316.1459 (100) $[M+H^+]$. Chromatography: Hex/EtOAc 1/1 - EtOAc R_f 0.50 (EtOAc). Yield: 55%.

6-(4-Methoxybenzyl)-7-(4-methoxyphenyl)-7,8-dihydropyrido[4,3-c]pyridazin-5(6H)-one

(22c). 1H -NMR (400MHz, $CDCl_3$): δ 3.56 (1H, dd, J 16.5, 2.4Hz, $CHCH_aH_b$), 3.66 (1H, dd, J 16.5, 6.7Hz, $CHCH_aH_b$); 3.80 (1H, d, J_{AB} 14.6Hz, NCH_aH_b); 3.75 (3H, s, OMe), 3.82 (3H, s, OMe), 4.90 (1H, dd, J 6.7, 2.4Hz, $NCHCH_2$), 5.68 (1H, d, J_{AB} 14.6Hz, NCH_aH_b), 6.78 (2H, d, J 8.7Hz, $2 \times CHC_qO$), 6.88 (2H, d, J 8.7Hz, $2 \times CHC_qO$), 6.93 (2H, d, J 8.7Hz, $2 \times CHC_qCH$), 7.21 (2H, d, J 8.7Hz, $2 \times CH_2C_qCH$), 8.10 (1H, d, J 5.0Hz, $NCHCH$), 9.32 (1H, d, J 5.0Hz, $NCHCH$). ^{13}C -NMR (100MHz, $CDCl_3$): δ 36.6 ($CHCH_2$), 48.2 (NCH_2), 55.31 (OCH₃), 55.33 (OCH₃), 56.7 ($NCHCH_2$), 114.3 ($2 \times CHC_qO$), 114.5 ($2 \times CHC_qO$), 123.5 ($NCHCH$), 126.8 (COC_q), 127.2 ($2 \times CHC_qCH$), 128.4 (NCH_2C_q), 129.7 ($2 \times CH_2C_qCH$), 130.1 ($NCHC_q$), 151.9 ($NCHCH$), 155.9 (CO), 159.4 (C_qOCH_3), 159.5 (C_qOCH_3), 162.0 (NC_qCH_2). IR (ATR, cm^{-1}): ν_{max} 2930, 1654, 1510, 1244. HRMS (ES, pos. mode): m/z (%) calc: 376.1656, exp: 376.1653 (100) $[M+H^+]$. Chromatography: Hex/EtOAc 1/1 - EtOAc R_f 0.43 (EtOAc). Yield: 61%.

6-(4-Methylbenzyl)-7-(4-methylphenyl)-7,8-dihydropyrido[4,3-c]pyridazin-5(6H)-one (22d)

1H -NMR (400MHz, $CDCl_3$): δ 2.28 (3H, s, CH₃), 2.36 (3H, s, CH₃), 3.57 (1H, dd, J 16.6, 2.2Hz, $CHCH_aH_b$), 3.66 (1H, d, J_{AB} 14.7Hz, NCH_aH_b), 3.68 (1H, dd, J 16.6, 6.8Hz, $CHCH_aH_b$), 4.91 (1H, dd, J 6.8, 2.2Hz, $NCHCH_2$), 5.74 (1H, d, J_{AB} 14.7Hz, NCH_aH_b), 6.90 (2H, d, J 8.1Hz, $2 \times CHC_qCH$), 7.06 (2H, d, J 7.9Hz, $2 \times CHC_qCHCH$), 7.17 (4H, br. s, $2 \times CH_2C_qCHCH$), 8.10 (1H, d, J 5.0Hz, $NCHCH$), 9.31 (1H, dd, J 5.0, 0.6Hz, $NCHCH$). ^{13}C -NMR (100MHz, $CDCl_3$): δ 21.1 (CH₃), 21.2 (CH₃), 36.5 ($CHCH_2$), 48.6 (NCH_2), 57.0 ($NCHCH_2$), 123.5 ($NCHCH$), 125.9 ($2 \times CHC_qCH$), 126.8 (COC_q), 128.2 ($2 \times CH_2C_qCH$), 129.6 ($2 \times CHC_qCHCH$), 129.8 ($2 \times CH_2C_qCHCH$), 133.4 (CH_2C_qCH), 135.1 (CHC_qCH), 137.8 (CH_3C_q), 138.1 (CH_3C_q), 151.9 ($NCHCH$), 155.9 (CO), 162.0 (NC_qCH_2). IR (ATR, cm^{-1}): ν_{max} 2921, 1655. HRMS (ES, pos. mode): m/z (%) calc: 344.1757, exp: 344.1764 (100) $[M+H^+]$. Chromatography: Hex/EtOAc 1/1 - EtOAc R_f 0.47 (EtOAc). Yield: 63%.

6-(4-Fluorobenzyl)-7-(4-fluorophenyl)-7,8-dihydropyrido[4,3-c]pyridazin-5(6H)-one (22e)

1H -NMR (400MHz, $CDCl_3$): δ 3.58 (1H, dd, J 16.5, 2.4Hz, $CHCH_aH_b$), 3.72 (1H, dd, J 16.5, 6.7Hz, $CHCH_aH_b$), 3.70 (1H, d, J_{AB} 14.7Hz, NCH_aH_b), 4.93 (1H, dd, J 6.7, 2.4Hz, $NCHCH_2$), 5.55 (1H, d, J_{AB} 14.7Hz, NCH_aH_b), 6.92-7.07 (6H, m, $4 \times FC_qCH$, $2 \times FC_qCHCH$), 7.23-7.29 (2H, m, $2 \times FC_qCHCH$), 8.10 (1H, d, J 5.1Hz, $NCHCH$), 9.34 (1H, dd, J 5.1, 0.6Hz, $NCHCH$). ^{13}C -NMR (100MHz, $CDCl_3$): δ 36.5 ($CHCH_2$), 48.4 (NCH_2), 57.1 ($NCHCH_2$), 115.9 (d, J 21.7Hz, $2 \times FC_qCH$), 116.2 (d, J 21.9Hz, $2 \times FC_qCH$), 123.5 ($NCHCH$), 126.5 (COC_q), 127.7 (d, J 8.3Hz, $2 \times FC_qCHCH$), 130.0 (d, J 8.1Hz, $2 \times FC_qCHCH$), 132.0 (d, J 3.4Hz, FC_qCHCHC_q),

133.8 (d, J 3.1Hz, $\text{FC}_q\text{CHCHC}_q$), 152.1 (NCHCH), 155.5 (CO), 162.0 (NC_qCH_2), 162.50 (d, J 248.5Hz, FC_q), 162.53 (d, J 247.0Hz, FC_q). ^{19}F -NMR (376.5MHz, CDCl_3): δ -113.8 to -113.7 (F, m), -113.3 to -113.2 (F, m). IR (ATR, cm^{-1}): ν_{max} 2924, 1662, 1507, 1221, 1158. HRMS (ES, pos. mode): m/z (%) calc: 352.1256, exp: 352.1253 (100) $[\text{M}+\text{H}^+]$. Chromatography: Hex/EtOAc 1/1 - EtOAc R_f 0.50 (EtOAc). CDCC: 1020668. Yield: 59%.

6-(4-Chlorobenzyl)-7-(4-chlorophenyl)-7,8-dihydropyrido[4,3-c]pyridazin-5(6H)-one (22f).

^1H -NMR (400MHz, CDCl_3): δ 3.59 (1H, dd, J 16.6, 2.3Hz, CHCH_aH_b), 3.72 (1H, d, J 16.6Hz, CHCH_aH_b), 3.75 (1H, d, J_{AB} 15.0Hz, NCH_aH_b), 4.91 (1H, dd, J 6.7, 2.3Hz, NCHCH_2), 5.65 (1H, d, J_{AB} 15.0Hz, NCH_aH_b), 6.96 (2H, d, J 8.4Hz, $2 \times \text{CH}_{\text{arom}}$), 7.22 (2H, d, J 9.0Hz, $2 \times \text{CH}_{\text{arom}}$), 7.24 (2H, d, J 9.0Hz, $2 \times \text{CH}_{\text{arom}}$), 7.33 (2H, d, J 8.4Hz, $2 \times \text{CH}_{\text{arom}}$), 8.10 (1H, d, J 5.0Hz, NCHCH), 9.34 (1H, d, J 5.0, NCHCH). ^{13}C -NMR (100MHz, CDCl_3): δ 36.3 (CHCH_2), 48.5 (NCH_2), 57.2 (NCHCH_2), 123.6 (NCHCH), 126.4 (COC_q), 127.3 ($2 \times \text{CH}_{\text{arom}}$), 129.2 ($2 \times \text{CH}_{\text{arom}}$), 129.4 ($2 \times \text{CH}_{\text{arom}}$), 129.6 ($2 \times \text{CH}_{\text{arom}}$), 134.1 (CIC_q), 134.4 (CIC_q), 134.7 (NCH_2C_q), 136.5 (NCHC_q) 152.1 (NCHCH), 155.3 (CO), 162.1 (NC_qCH_2). IR (ATR, cm^{-1}): ν_{max} 2922, 2853, 1659, 1091. HRMS (ES, pos. mode): m/z (%) calc: 384.0665, exp: 384.0672 (100) $[\text{M}+\text{H}^+]$. Chromatography: Hex/EtOAc 1/1 - EtOAc R_f 0.42 (EtOAc). Yield: 30%.

6-(2-Chlorobenzyl)-7-(2-chlorophenyl)-7,8-dihydropyrido[4,3-c]pyridazin-5(6H)-one (22g).

^1H -NMR (400MHz, CDCl_3): δ 3.78 (2H, m, CHCH_2), 4.12 (1H, d, J_{AB} 15.0Hz, NCH_aH_b), 5.40-5.43 (1H, m, NCHCH_2), 5.53 (1H, d, J_{AB} 15.0Hz, NCH_aH_b), 6.75-6.78 (1H, m, CH_{arom}), 7.03-7.08 (1H, m, CH_{arom}), 7.17-7.22 (1H, m, CH_{arom}), 7.24-7.32 (2H, m, CH_{arom}), 7.36-7.42 (3H, m, CH_{arom}), 8.13 (1H, d, J 5.0Hz, NCHCH), 9.34 (1H, d, J 5.1, NCHCH). ^{13}C -NMR (100MHz, CDCl_3): δ 33.8 (CHCH_2), 47.3 (NCH_2), 55.6 (NCHCH_2), 123.5 (NCHCH), 126.2 (CH_{arom}), 126.4 (COC_q), 127.2 (CH_{arom}), 127.3 (CH_{arom}), 129.55 (CH_{arom}), 129.63 (CH_{arom}), 129.9 (CH_{arom}), 130.6 (CH_{arom}), 130.8 (CH_{arom}), 132.8 ($\text{C}_{q,\text{arom}}$), 133.4 ($\text{C}_{q,\text{arom}}$), 134.1 ($\text{C}_{q,\text{arom}}$), 135.1 ($\text{C}_{q,\text{arom}}$), 152.0 (NCHCH), 162.6 (CO), 162.6 (NC_qCH_2). IR (ATR, cm^{-1}): ν_{max} 2924, 1663, 1038. HRMS (ES, pos. mode): m/z (%) calc: 384.0665, exp: 384.0672 (100) $[\text{M}+\text{H}^+]$. Chromatography: Hex/EtOAc 1/1 - EtOAc R_f 0.49 (EtOAc). Yield: 36%.

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