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Investigations on 5,6,7,8-tetrahydro-[1,2,4]triazolo[1,2-*a*]pyridazin-1-amines and related compounds: synthesis, chemical behaviour, structure elucidation and iNOS inhibitory activity[#]

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[#] N,N-Coupled heterobicycles from cyclic hydrazine derivatives. Part 17; Part 16: Schulz U, Großmann A, Wilde F, Freitag M, Lemmerhirt C, Schulzke C, Link A, Morgenstern O (2017) Investigations on synthesis, chemical behavior, structure elucidation and iNOS inhibitory activity of 1-substituted 3-methylsulfanyl-5,6,7,8-tetrahydro-1H-[1,2,4]-triazolo[1,2-a]pyridazines. Pharmazie 72: 371 – 382.

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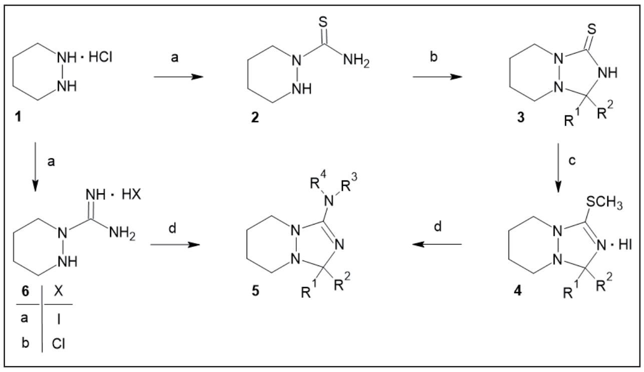
The present work reports on the preparation of the hitherto unknown title compounds **5,** with various synthetic routes described. The initially pursued concept of S-N exchange with varioius 1-substituted 3-methylsulfanyl-5,6,7,8-tetrahydro-1*H*-[1,2,4]triazolo[1,2-*a*]pyridazines **4** by using nitrogen nucleophiles was only marginally successful. The reactions proceeded slowly and the yields were low, mainly because of the pronounced formation of 5,6,7,8-tetrahydro-[1,2,4]triazolo[1,2-*a*]pyridazin-1-imines **7** by oxidation of the heterocyclic amines **5** initially formed. The integration of the synthesis of 3-acylsulfanyl analogues with the more reactive leaving groups also failed. On the other hand, the cyclization of the hydrohalides of hexahydropyridazine-1-carboximidamide with aromatic aldehydes and some low molecular weight ketones gives significantly better results in the synthesis of the title compounds **5**. The use of the hydrochloride **6b** proved to be advantageous in comparison to the hydroiodide **6a** because the yields were significantly better and the imines **7** formed at the same time only to a small extent. In addition, the starting compound **6b** can be prepared in a single-step synthesis in very good yield from hexahydropyridazine hydrochloride **1** and cyanamide. The cyclization of *N'*-phenylhexahydropyridazine-1-carboximidamide hydrochloride **6c** with substituted benzaldehydes gives the 3-aryl-substituted 2-phenyl-2,3,5,6,7,8-hexahydro-*1H*-[1,2,4]triazolo[1,2-*a*] pyridazin-1-imines **8**. In the context with the study of the reaction of hexahydropyridazine-1-carboximidamide hydroiodide **6a** with cyclohexanone, the hexahydropyridazine-1-carboxamide **9** was specifically synthesized. This can be reacted with aromatic aldehydes to give the 5,6,7,8-tetrahydro-1*H*-[1,2,4]triazolo[1,2-*a*]pyridazin-1-ones **10** in very good yields. The results of the biological testing of representatives of the synthesized 5,6,7,8-tetrahydro-[1,2,4] triazolo[1,2-a]pyridazine-1-amines **5** show, in comparison to the already examined thions **3** and 3-methylsulfanyl derivatives **4,** significantly less inducible nitric oxide synthase (iNOS) inhibitory activity.



Scheme 1: **a:** Morgenstern et al. 2004; **b:** Schulz et al. 2013, 2014; **c:** Schulz, et al. 2017; **d:** reported in this publication

1. Introduction

We have previously reported on investigations in preparation and inducible nitric oxide synthase (iNOS) inhibitory activity of 2,3,5,6,7,8-hexahydro-1*H*-[1,2,4]triazolo[1,2-*a*]pyridazine-1-thiones (**3**) (Schulz et al. 2013, 2014) and those derived from it the 3-methylsulfanyl products (**4**) (Schulz et al. 2017). As the most effective synthesis route for the thiones **3** the cyclization of hexahydropyridazine-1-carbothioamide (**2**) (Morgenstern et al. 2004) was found with carbonyl compounds. The products **4** were achieved as their hydroiodides by alkylation of the sulfur atom of the thiones **3,** taking into account the sensitivity of these compounds to oxidation (Scheme 1).

A formal S-N exchange with the compounds **4** leads to the heterobicycles **5,** possessing an aminoguanidine partial structure, which bears in an advantageous manner more sp^3 hybridizid skeletal atoms (Wilde and Link 2013). Aminoguanidine (preferred IUPAC name – PIN: hydrazinecarboximidamide) itself as well as a number of known bioactive substances posessing an aminoguanidine substructure, integrated in very different patterns, show a wide spectrum of biological activities. Examples for 2-monosubstituted aminoguanidine derivatives are guanabenz (antihypertensive), icergustat (potential drug in multiple sclerosis), and sardomozide (antiproliferative) while tegaserod (serotonin agonist) represents a 2,*N*-disubstituted aminoguanidine derivative. However, in comparision to the totality of bioactive molecules, these represent only a small fraction of structures.

Like aminoguanidine itself, among such substances are also those that inhibit the formation of nitric monoxide *via* different pathways. Examples for this are semapimod (four 2-monosubstitued aminoguanidine subunits) and zevaquenabant (pyrazole-1-carboximidamide derivative). Likewise, pyrazolo[4,3-*d*]pyrimidin-7-amines have been recently reported as inhibitors of inducible nitric oxide synthase which, like the title compounds described here, have the structure of heterobicyclic amines. With regard to the inhibitory activity of these investigated compounds, a substituent in position 7 with a vinyl spacer between the heterocyclic system and a (hetero)aryl substituent (2-phenylethenyl or 2-(furan-2-yl)ethenyl substituent) appears to be advantageous (Shi et al. 2019). Consistent with this finding, various 3-substituted 2,3,5,6,7,8-hexahydro-1*H*-[1,2,4]triazolo[1,2-*a*]pyridazine-1-thiones previously investigated by us, the 2-phenylethenyl derivative showed the best iNOS inhibitory activity (Schulz et al. 2013, listed there as compound **2d**).

This work reports on the synthesis and biological evaluation of a new class of the title compounds as potential inhibitors of iNOS activity. One aim of the present work was to investigate the possiblities of S-N exchange reactions with the sensitive compounds **4**. Utilizing ammonia, amines and related nitrogen nucleophiles, we planned a synthesis route to the desired 5,6,7,8-tetrahydro-3*H*-[1,2,4]triazolo[1,2-*a*]pyridazin-1-amines **5** (Scheme 1). On the other hand, the synthesis of the **5** in a one-step procedure was taken into account by starting from the hexahydropyridazine-1-carboximidamide salts **6** because of the sensitivity of the 3-methylsulfanyl-5,6,7,8-tetrahydro-1*H*-[1,2,4]triazolo[1,2-*a*]pyridazines **4** (Schulz et al. 2017). The synthesis of the hydroiodide **6a**, starting from hexahydropyridazine hydrochloride **1**, has already been reported (Morgenstern et al. 2004). Therefore the related investigations should be started with compound **6a** (Scheme 1). We also investigated the iNOS inhibitory activity of the newly synthesized title compounds **5** in a cell-based assay and compared these results with those of the known iNOS inhibitor, aminoguanidine.

2. Investigations, results and discussion

2.1. Synthesis and chemical behavior

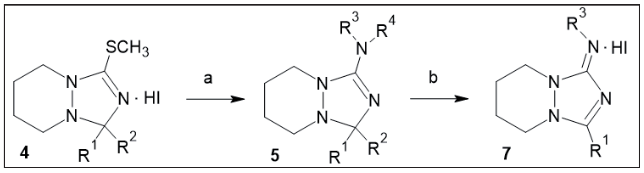
2.1.1. S-N Exchange at 5,6,7,8-tetrahydro-1H-[1,2,4]-triazolo[1,2-a]pyridazines

2.1.1.1. Reaction of 3-methylsulfanyl-5,6,7,8-tetrahydro-1H-[1,2,4]triazolo[1,2-a]pyridazines **4** with nitrogen nucleophiles

Because the 3-methylsulfanyl-1-phenyl derivative **4b** ($R^1 = C_6H_5$, $R^2 = H$) (Schulz et al. 2013, 2017) (Scheme 1) was easily accessible, its reaction was first investigated by using propylamine and pyrrolidine as nitrogen nucloephiles, respectively. Hereby the fact that both of these nucleophiles are anhydrous and are liquids at room temperature was also an advantage. To prevent undesirable side-reactions, the investigations were carried out under mild conditions and in the absence of water. Although evolution of methanthiol was quickly verified in both reactions, **4b** reacted slowly and uncompleatly [several days; TLC control – mobile phase: propan-1-ol/acetic acid/water (3:1:1, volume parts), solid phase: silica gel GF_{254}, MERCK, detection: UV radiation $\lambda = 254$ nm, subsequent spraying with MUNIER reagent (Munier 1953)]. As expected, the observed differences in the reaction times correlated with the nucleophilicity of the nitrogen nucleophiles. After further progress of the reaction could no longer be verified, the batches were worked up. In this way, the first representatives of the 5,6,7,8-tetrahydro-3*H*-[1,2,4]triazolo[1,2-*a*]pyridazin-1-amines were obtained as their hydroiodides **5m,o** (Table 1). However, only compound **5o** was isolated in a satisfactory yield. All variations of the reaction conditions to complete the reaction of **4b** with propylamine by using a larger excess of the amine, by gentle heating and/or by removing the methanethiol formed under reduced pressure or by passing air through did not improve yields. As a result of these investigations, however, the didehydro product of **4b**, methyl-(3-phenyl-5,6,7,8-tetrahydro-1*H*-[1,2,4]triazolo[1,2-*a*]pyridazine-1-ylidene)sulfonium iodide, was isolated, which we have already characterized (Schulz et al. 2017). Comparable with the observations with the monosubstituted **3** ($R^2 = H$) and **4** ($R^2 = H$) (Schulz et al. 2013, 2017), the corresponding didehydro product **7j** is also formed when a solution of **5m** in DMSO was allowed to stand for a longer period of time (Scheme 2, Table 2).

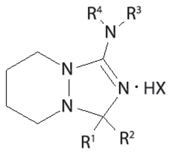
Analogously, **4b** ($R^1 = C_6H_5$, $R^2 = H$) was subjected the action of piperidine and morpholine, respectivly, but only the reaction product with morpholine (compound **5p**) (Table 1) could be isolated but in a relatively poor yield. Instead of the desired reaction product with piperidine, the didehydro product of **4b** was obtained. Obviously, the nucleophilic attack is clearly hindered by the higher molecular flexibility of piperidine than that of morpholine, so that the oxidation of the starting compound occurs on a larger scale under the applied reaction conditions (Scheme 2).

That the related didehydro products of type **7** (Table 2) could also be formed from the 5,6,7,8-tetrahydro-3*H*-[1,2,4]triazolo[1,2-*a*]pyridazin-1-amines **5** was found for the first time with the product



Scheme 2: for **5e,l,m,o,p,v,w** – corresponding anhydrous nitrogen nucleophile, organic solvent, room temperature, 2 – 6 weeks; **a** and **b**: for **7f** - dry ammonia, ethanol, room temperature, 6 weeks, further oxidation of the intermediate **5a**

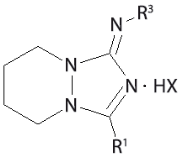
Table 1: 5,6,7,8-Tetrahydro-3*H*-[1,2,4]triazolo[1,2-*a*]pyridazin-1-amine salts 5



Nr.	R^1	R^2	R^3	R^4	X
5a	C_6H_5	H	H	H	I
5b	C_6H_5	H	H	H	Cl
5c	2-CH_3-C_6H_4	H	H	H	Cl
5d	4-CH_3-C_6H_4	H	H	H	Cl
5e	2-Cl-C_6H_4	H	H	H	I
5f	2-Cl-C_6H_4	H	H	H	Cl
5g	4-Cl-C_6H_4	H	H	H	Cl
5h	2-NO_2-C_6H_4	H	H	H	I
5i	2-NO_2-C_6H_4	H	H	H	Cl
5j	4-NO_2-C_6H_4	H	H	H	Cl
5k	4-CH_3O-C_6H_4	H	H	H	Cl
5l	2-Cl-C_6H_4	H	CH_3	H	I
5m	C_6H_5	H	C_3H_7	H	I
5n	3-C_6H_5O-C_6H_4	H	C_3H_7	H	I
5o	C_6H_5	H	-$(CH_2)_4$-		I
5p	C_6H_5	H	-$(CH_2)_2$-O-$(CH_2)_2$-		I
5q	CH_3	CH_3	H	H	I
5r	CH_3	CH_3	H	H	Cl
5s	CH_3	C_2H_5	H	H	tosyl
5t	CH_3	C_6H_5	H	H	Cl
5u	C_2H_5	C_2H_5	H	H	tosyl
5v	CH_3	CH_3	C_3H_7	H	I
5w	CH_3	CH_3	C_4H_9	H	I

isolated from the reaction of **4b** with ammonia. Instead of the desired **5a** (Table 1) the base of the related didehydro product **7f** (**7f** base) (Table 2) was obtained (Scheme 2).

Table 2: 5,6,7,8-Tetrahydro-1*H*-[1,2,4]triazolo[1,2-*a*]pyridazin-1-imine hydrohalides 7



Nr.	R^1	R^3	X
7a	H	H	Cl
7b	H	C_4H_9	I
7c	C_2H_5	H	I
7d	C_3H_7	H	I
7e	C_6H_5	H	Cl
7f	C_6H_5	H	I
7g	2-Cl-C_6H_4	H	I
7h	4-Cl-C_6H_4	H	I
7i	C_6H_5	CH_3	I
7j	C_6H_5	C_3H_7	I

These didehydro products were also isolated in the experiments of the cyclization of hexahydropyridazine-1-carboximidamide **6a** (Morgenstern et al. 2004) with aldehydes (see 2.1.2.1). The NMR spectra recorded from the batches of **4a** (R^1, R^2 = H) (Schulz et al. 2014) with propylamine and butylamine, respectively, indicated the formation of the related oxidation products.

From the reaction utilizing butylamine as a reactant, a small amount of a substance identified as **7b** could be isolated. Compound **7i** was obtained in a better yield from the reaction of **4b** ($R^1 = C_6H_5$, R^2 = H) with methylamine (Scheme 2).

However, in the two reactions with the 1-(2-chlorophenyl) derivative **4c** (R^1 = 2-Cl-C_6H_4, R^2 = H) the formation of the didehydro compounds **7** was not observed. In fact, in both cases the desired amino derivatives **5e** and **5l**, respectively, (Table 1) were isolated.

All efforts to react various other 1-monosubstituted methylsulfanyl derivatives **4** (Schulz et al. 2017) with propylamine under comparable reaction conditions usually yielded mixtures of the base of the respective compound **4** and their related didehydro product **7** (Schulz et al. 2017). Only with one of the corresponding 1-substituted 3-methylsulfanyl-5,6,7,8-tetrahydro-1*H*-[1,2,4]-triazolo[1,2-*a*]pyridazine hydroiodide could the N-propyl derivative **5n** (table 1) be obtained in a good yield. The starting compound for this reaction was a non-crystalline mass, obtained by allowing iodomethane (Schulz et al. 2017) to react with 3-(3-phenoxyphenyl)-2,3,5,6,7,8-hexahydro-1*H*-[1,2,4]triazolo[1,2-*a*]pyridazine-1-thione as reported by Schulz et al. 2014 (listed there as compound **2t**).

In the cases of the investigated 1,1-disubstituted methylsulfanyl compounds **4** (R^1, R^2 = aryl, alkyl) (Schulz et al. 2017), the exposure to nitrogen nucleophiles under the above reported mild conditions did not lead to the desired amino derivatives **4**. Normally, the respective bases of **4** were isolated from these reactions. Even after reacting for several weeks, only in a few cases did monitoring the reaction indicate the formation of any new products. This was the case with the 1,1-dimethyl derivative **4d** (R^1, $R^2 = CH_3$) when it was allowed to react with propylamine and butylamine, respectively. The NMR spectra of the respective products, obtained in very low amounts, were in accordance with the anticipated structures of **5v** and **5w**, respectively (Table 1).

Presumably, the substitution with two spatially demanding moieties in position 1 of the compounds **4** hinders the formation of a sp^3 hybridized C(3) atom at the transition state in the S_N2 attack. This assumption is supported by the results of the attempts of the direct transformation of the thiones **3** (Schulz et al. 2014) (Scheme 1) with amines in the presence of lead(II) acetate. In none of the cases was it possible to achieve the S-N exchange.

These findings suggested that the initially pursued concept of the S-N exchange with 1,1-disubstituted compounds **4** is not a suitable synthesis route for the desired amino derivatives **5**. In contrast, for the 1-monosubstituted representatives of the methylsulfanyl derivatives **4** could be shown that the 5,6,7,8-tetrahydro-3*H*-[1,2,4]-triazolo[1,2-*a*]pyridazin-1-amines in principle are accessable in this way. However, as a simple and general applicable method for the synthesis of the amino derivatives **5**, the S-N exchange with the methylsulfanyl compounds **4** is only marginally suitable.

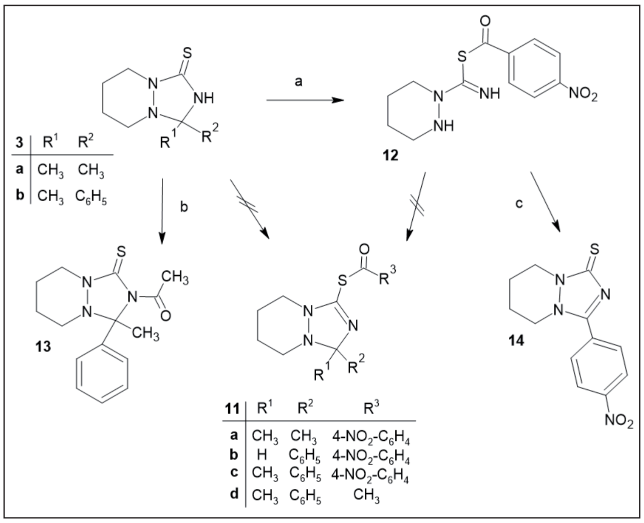
2.1.1.2. Investigations on the synthesis of 3-acylsulfanyl-5,6,7,8-tetrahydro-1H- [1,2,4]triazolo[1,2-a]pyridazines from the respective thiones 3

The previous results suggested that more suitable leaving groups were needed in the 1,1-disubstituted compounds **4**. For this reason the synthesis of the 3-(4-nitrobenzoylsulfanyl)-[1,2,4]-triazolo[1,2-*a*]pyridazines **11a,c** was investigated starting from the related compounds **3a** ($R^1 = CH_3$, $R^2 = CH_3$) and **3b** ($R^1 = CH_3$, $R^2 = C_6H_5$), respectively (Scheme 3). While no reaction at all was observed with **3a**, the action of an equimolar amount of 4-nitrobenzoyl chloride on **3b** in dichloromethane at room temperature led to the rapid evolution of hydrogen chloride and the formation of a new product which was isolated. The analytical investigations showed, however, that the (hexahydropyridazine-1-carboximidothioic acid) (4-nitrobenzenecarboxylic acid) anhydride **12** was formed with opening of the 1,2,4-triazole ring of the heterobicyclic starting compound. The TLC control of the reaction gave no indication of the suspected intermediate stage **11c**.

The addition of various auxiliary bases suppressed or delayed the formation of **12** without the formation of the desired **11c**. Interestingly, various attempts to subject compound **12** to an S-N exchange with amines or to (re)cyclize it with benzaldehyde to **11b** each gave the same reaction product, which could be identified as the 5,6,7,8-tetrahydro-1*H*-[1,2,4]triazolo[1,2-*a*]pyridazine-1-thione **14**. Formally, this compound represents the didehydro product of the already synthesized 3-(4-nitrophenyl)-2,3,5,6,7,8-hexahydro-1*H*-[1,2,4]triazolo[1,2-*a*]pyridazine-1-thione (Schulz et al. 2013) which has not yet been isolated. Similarely as described by Kaválek et al. 1985, this product was formed directly from **12** under the reaction conditions used (heating; proton and base catalysis, respectively) in a first step by rearrangement of the 4-nitrobenzoyl group from the sulfur atom towards the adjacent exocyclic nitrogen atom, followed by a cyclocondensation reaction as the second step.

Next, the S acetylation of **3b** was investigated with the expectation that the comparatively lower reactivity of acetyl chloride and acetic anhydride would not result in a ring cleavage. This expectation was confirmed but at room temperature no acetylation was observed with either reagent. The use of acetyl chloride also proved unsuitable even when heated (only very little conversion of **3b**). Acetic anhydride reacted under these conditions, probably because of its better polarizability of the C=O bond, much more easily with **3b** in a very uniform reaction. Unfortunately, **11d** (Scheme 3) was not obtained. The product isolated in very good yield was identified as the N-acetyl derivative **13**. Obviously, the latter was formed via attack of the acetic anhydride to the N(2) atom of the heterocycle which is more electronegative and more basic than the sulfur atom.

The results obtained up to this point made clear that the strategy of S-N exchange on the 5,6,7,8-tetrahydro-1*H*-[1,2,4]triazolo[1,2-*a*]-pyridazines for the preparation of the heterocyclic amines **5** was not going to be successful. In addition to the low reactivity of the 3-methylsulfanyl heterocycles, this is also due to the oxygen



Scheme 3: **a:** with **3b**, 4-nitrobenzoyl chloride, room temperature, 24 hours; **b**: with **3b**, acetic anhydride, reflux, 30 minutes; **c**: benzaldehyde, 155 °C, 1 hour; also: anhydrous nitrogen nucleophiles, dichloromethane, room temperature, 1 – 3 days

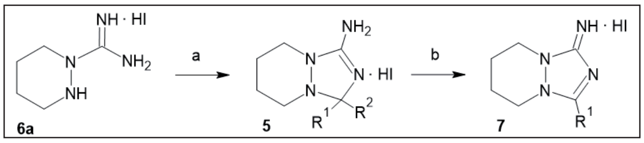
sensitivity of the hydroidides used and the problems associated in isolating the reaction products **5** and oxidation of the latter to the didehydro compounds **7**.

2.1.2. Synthesis and cyclization of hexahydropyridazine-1-carboximidamides with carbonyl compounds

2.1.2.1. Investigations on the unsubstituted hexahydropyridazine-1-carboximidamides **6a,b**

Hexahydropyridazine-1-carboximidamide hydroiodide **6a.** In analogy to the synthesis of the thiones **3** from the carbothioamide **2** another possible synthesis route to the title compounds **5** was seen in the cyclization of hexahydropyridazine-1-carboximidamides **6** with carbonyl compounds (Scheme 1). First, the behaviour of the hydroiodide **6a** obtainable from hexahydropyridazine hydrochloride in a two step synthesis in a total yield of approx. 20% (Morgenstern et al. 2004) was investigated.

To begin the investigations on the cyclization, **6a** was reacted in a acid-catalyzed reaction at approx. 100 °C with different aromatic aldehydes without a solvent (Scheme 4). In each case, a complete conversion of the starting compound was observed, which took place relatively quickly compared to the S-N exchange (see 2.1.1.1). However, reaction work-up caused problems, mainly as a result of partial oxidation of the iodide to iodine. For this reason crystallization was more difficult, leading to the formation of didehydro products **7** and reducing the yields of **5**. Although the compounds **5a,e,h** (Table 1) could be obtained in this way, the yields were not satisfactory.



Scheme 4: **a:** for **5a,e,h** – corresponding aldehyde, p-toluenesulfonic acid monohydrate, 100 °C, 3 – 5.5 hours; **a** and **b**: 1) for **7f,g** – corresponding aromatic aldehyde, p-toluenesulfonic acid monohydrate, 150 – 155 °C, 3 – 4 hours, via the oxidation pathway of the related intermediates **5**; 2) for **7c,d** – corresponding aliphatic aldehyde, 100 °C, 6 hours, via the oxidation pathway of the related intermediates **5**

Moreover, in the reactions with benzaldehyde or 2-chlorobenzaldehyde, the corresponding didehydro products **7f,g** (Table 2) were formed in such large amounts that they could be isolated and characterized (Scheme 4).

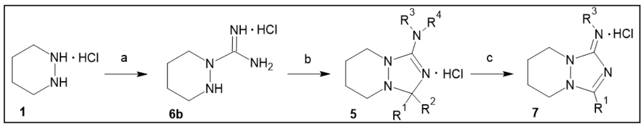
When aliphatic aldehydes (unbranched with 1 to 4 carbon atoms and paraformaldehyde or paraldehyde or acetaldehyde dimethyl acetal, respectively) were allowed to react with **6a** under various conditions, the starting compound was always completely consumed. The NMR investigations of the reaction mixtures also provided indications of the formation of the desired **5**, but the isolation of crystalline reaction products proved to be difficult, mainly because of their low tendency to crystallize. In analogy with the formation of the corresponding didehydro compounds **7** observed with the 3-aryl derivatives **5**, the work-up of the reactions (pressure reactor) with propionaldehyde and butyraldehyde, respectively, only resulted in the isolation of the corresponding 3-alkyl derivatives **7c,d** (Table 2) (Scheme 4). That the compounds **7** can, in principle, also be formed directly from the unsubstituted hexahydropyridazine-1-carboximidamides **6** could be shown on the basis of the (parent) compound **7a** unsubstituted in position 3 (Table 2). **7a** was to obtain in very good yield by the action of formic acid on **6a**. As was found in preliminary experiments, it should be possible to obtain the parent compound of the amino derivatives **5** ($R^1 – R^4$ = H) (Scheme 1) by pressure hydrogenation of **7a** (3.5 bar hydrogen pressure, Adams catalyst, room temperature).

The work-up of the reactions also caused problems when **6a** was subjected to the presence of ketones, although the formation of didehydro compounds **7** was not to be expected in these cases and was actually not observed. On the one hand, the acid-catalyzed reaction in boiling acetone led to complete conversion of the starting compound. The purification of the product obtained in good yield and characterized as the first representative of the 3,3-disubstituted 5,6,7,8-tetrahydro-3*H*-[1,2,4]triazolo[1,2-*a*]pyridazin-1-amines (**5q,** R^1,R^2 = CH_3) (Table 1) was unsatisfactory, however, and gave a substance with a very broad melting range. Nonetheless, the comparison of the mid infrared (MIR) and NMR data with the hydrochloride **5r** (Table 1) obtained later from **6b** showed a very substantial similarity. Nevertheless, although **5q** were not available in the desired purity, for possible reference purposes the analytical data are also given in the experimental section. **6a** also reacted completely with cyclohexanone at approx. 150 °C in the presence of *p*-toluenesulfonic acid. Although the product was also not satisfactorily purified, the analytical data suggest the formation of an amino derivative **5** [R^1,R^2 = $-(CH_2)_5-$], in which the C(3) atom of the heterocyclic ring system represents a part of a spiro system.

In order to shorten the reaction time, which is longer compared to the aromatic aldehydes, tests were carried out in addition to conventional heating of the reactants as well as investigations on the reaction of **6a** with aliphatic, cycloaliphatic, and araliphatic ketones in the pressure reactor or in the microwave apparatus. By refluxing **6a** with acetophenone and diethyl ketone, respectivly, products were formed which could only be isolated as non-crystalline and impured masses in a relatively poor yield; however, analytical data indicated the formation of the desired products. While the hydroiodide **6a** was usually recovered from the attempts when the pressure reactor was used (with the exception of the attempt with cyclohexanone from which was obtained the hexahydropyridazine-1-carboxamide **9,** see 2.1.3), the hoped-for advantages of using a microwave apparatus only partially came into effect when the reaction was carried out with acetophenone. On the one hand, a reduction of the reaction time from 32 h (refluxing; see above) to 3 min with an improvement of the yield from 29% to 41% was achieved by microwaves. On the other hand, the formed product, which analytical data indicated to be the assumed structure, was only obtainable as a non-crystalline and rather impured mass.

Particularities were observed when using alicyclic ketones. While the formation of a reaction product could not be observed with cyclopentanone, **6a** reacts even under mild conditions when exposed to cyclohexanone. However, the expected 3,3-pentamethylene derivative **5** could not be obtained. As could be confirmed by TLC by counter-synthesis (see 2.1.3.), the detected hexahydropyridazine-1-carboxamide **9** (Scheme 7) is formed as a further intermediate.

Hexahydropyridazine-1-carboximidamide hydrochloride **6b.** In order to avoid the difficulties mentioned above, the hydrochloride **6b**, which has not yet been described, was considered as the starting compound. By melting hexahydropyridazine hydrochloride **1** with cyanamide (Scheme 5), its preparation succeeded similar to the known reaction of 1,2,3,4-tetrahydrophthalazine (formally a hydrogenated benzo[*d*]pyridazine) (Panneman 1970) but whithout a solvent in very good yields. In addition, when working up the attempt, the formation of oxidation products was only observed when the concentrated mother liquors were repeatedly taken up again in the solvent and concentrated. In this way, **7e** (Table 2) could be obtained, for example, from the reactions with benzaldehyde.



Scheme 5: **a:** cyanamide, 100 °C, 2 hours; **b**: for **5b-d,f,g,i-k** – corresponding aldehyde, *p*-toluenesulfonic acid, 100 °C, 2 – 20.5 hours; **b** and **c**: for **7e** – work-up the batch of **5b** (benzaldehyde, *p*-toluenesulfonic acid, 100 °C, 2 hours): second fraction of fractional crystallization of the mother liquor

All eight aromatic aldehydes used reacted smoothly and uniformly on heating with cyclization to the respective amino heterocycles **5b-d**,**f**,**g**,**i-k** within a short time (Table 1). In this way, **7e** (Table 2) could be obtained, for example, from the reactions with benzaldehyde.

As expected, the ketones used for the cyclization reaction with **6b** showed a clearly different behavior. Among the aliphatic ketones used, acetone converted the starting compound relatively slowly (2 days) but completely under reflux; indeed, the product isolated in good yield could be characterized as the desired amino derivative **5r** (Table 1). When using ethyl methyl ketone or diethyl ketone, a reaction of **6b** – also under reflux – was only found when larger amounts of *p*-toluenesulfonic acid monohydrate were added and the time of exposure was significantly longer (> 10 days). Only when using diethyl ketone was there a complete conversion of **6b**. When working up the two reaction mixtures, TLC monitoring showed pure but non-crystalline products, while MIR and NMR data was consistent with the *p*-toluenesulfonates **5s** (ethyl methyl ketone) and **5u** (diethyl ketone) (Table 1).

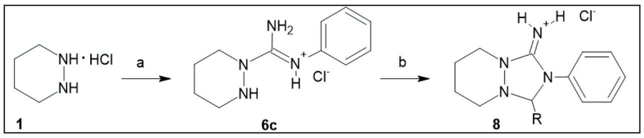
On the other hand, the diaryl ketones benzophenone as well as 2- and 4-chlorobenzophenone, respectively, did not react with **6b** when melted at 150 °C, even when a larger amount of *p*-toluenesulfonic acid monohydrate was added. When using 1,8-diazabicyclo[5.4.0]undec-7-en (DBU) as an auxiliary base, a larger number of products was formed, none of which could be isolated and thus were not characterized.

In contrast to the diaryl ketones, acetophenone, an araliphatic ketone, reacted with **6b** in the presence of acid at 150 °C, whereby the reaction did not proceed uniformly. In this case as well, work-up of the reaction proved difficult. However, it was possible to isolate a compound in a very small amount which was indicated by TLC to be uniform and could be identified as the desired **5t** (Table 1).

The results of the investigations on the cyclization of the hydrochloride **6b** with carbonyl compounds showed that this route to the title compounds **5** (in particular also to the 3,3-disubstituted **5**) is much more suitable than the S-N exchange at the 3-methylsulfanyl-5,6,7,8-tetrahydro-1*H*-[1,2,4]triazolo[1,2-*a*]pyridazines **4**. The use of the hydrochloride of the hexahydropyridazine-1-carboximidamide (**6b**) rather than the initially used hydroiodide **6a** provided the expected advantages in the work-up of all reactions. Moreover, when the reactions with the hydrochloride **6b** and (aromatic) aldehydes were worked up, the didehydro products **7** were formed from the **5** to a significantly smaller extent.

2.1.2.2. Investigations with N‘-phenylhexahydropyridazine-1-carboximidamide hydrochloride **6c**

The preparation of the hydroiodide, which base corresponds to that of the hydrochloride **6c**, we have already reported (Morgenstern et al. 2004). In addition to the multi step synthesis of this starting compound the expected oxidation reactions (see above) were disadvantageous for the planned investigations. Therefore, a one-step synthesis of **6c** was developed in analogy to that of the hydrochloride **6b**. In this **6c**, starting from hexahydropyridazine hydrochloride **1** and phenyl cyanamide (synthesized according to Kumar et al. 2008), is obtained directly in a very good and thus in significantly better yield than the related hydroiodide described previously (Morgenstern et al. 2004) (Scheme 6). Moreover, **6c** was not mentioned yet by other authors and the related substructure in larger molecules appears very seldom (e. g. at Liepa et al. 2011).

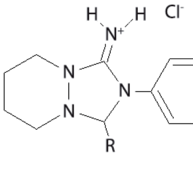


Scheme 6: **a:** phenylcyanamide, 100 °C, 6 hours; **b**: corresponding aldehyde, *p*-toluenesulfonic acid, 100 °C, 3 – 6 hours

As could be shown with the synthesis by using benzyl cyanide (Kumar et al. 2008) which provided the not yet reported *N*‘-benzyl-hexahydropyridazine-1-carboximidamide hydrochloride **6d** (see *Experimental*, 3.2.1.4.), in principle, further N‘-substituted **6** should be accessible as precursors for cyclization rections.

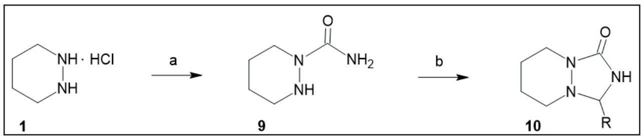
The investigations on the cyclization of **6c** with aldehydes and ketones were carried out, as with the N,N‘-unsubstituted hydrochloride **6b**, under comparable conditions (heating without a solvent at 100 °C, proton catalysis). *N*‘-Phenyl-hexahydropyridazine-1-carboximidamide hydrochloride **6c**, too, reacted with the ten aldehydes used to give corresponding cyclization products, as the data from the NMR and LCMS investigations of the respective attempts showed (see *Structural investigations*). But, the isolation of the products caused greater problems because of its extremely low tendency to crystallize. However, it was possible to isolate four of the reaction products, namely from the chloro- and nitro-substituted benzaldehydes used, in acceptable yields. As the structural analysis of these products revealed, they were in all cases not the expected *N*-phenyl-5,6,7,8-tetrahydro-3*H*-[1,2,4]triazolo[1,2-*a*]pyridazin-1-amines **5** (R^1 = aryl; R^3 = phenyl; R^2, R^4 = H) (Scheme 1). Instead, the isomeric 2-phenyl-2,3,5,6,7,8-hexahydro-1*H*-[1,2,4]triazolo[1,2-*a*]pyridazine-1-imines were obtained in the form of their hydrochlorides (compounds **8**) (Scheme 6, Table 3). This indicates that the ring closure with the carbonyl carbon atom of the respective aldehyde preferably proceeds via the N‘ atom of the carboximidamide group bearing the phenyl ring, which is obviously more polarizable due to resonance effects.

Table 3: 2,3,5,6,7,8-Hexahydro-1*H*-[1,2,4]triazolo[1,2-*a*]pyridazin-1-imine hydrochlorides 8



Nr.	R
8a	2-Cl-C_6H_4
8b	4-Cl-C_6H_4
8c	2-NO_2-C_6H_4
8d	4-NO_2-C_6H_4

In contrast, attempts to convert **6c** into the corresponding cyclization products with ketones (acetone, acetophenone, benzophenone) were even less successfully than when **6b** was used. When heated with acetone, only a partial conversion of **6c** was observed even after one week. The LCMS check of the non-crystalline product mixture showed that, in addition to the starting compound, a small amount of a cyclization product with the expected relative molecular mass was present. In the experiments with acetophenone and benzophenone, respectively, no conversion of **6c** was observed at all, even after heating for several days.



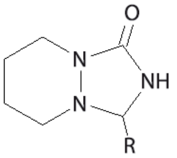
Scheme 7: **a:** potassium cyanate 100 °C, 2 hours; **b**: corresponding aldehyde, *p*-toluenesulfonic acid, 100 °C, 0.75 – 1 hour

*2.1.3. Synthesis and cyclization of hexahydropyridazine-1-carboxamide **9** with aromatic aldehydes*

During the investigations on the reaction of the hydroiodide **6a** with cyclohexanone (see 2.1.2.1.), the hexahydropyridazine-1-carboxamide **9** was purposefully synthesized for the first time by melting **1** together with potassium cyanate. With this easily accessible compound, which can be obtained in large quantities, it was of interest whether this could be cyclize in analogy to the hexahydropyridazine-1-carbothioamides **2** (Schulz et al. 2013; Morgenstern et al. 2004) (Scheme 1) with aldehydes in order to obtain the corresponding 2,3,5,6,7,8-hexahydro-1*H*-[1,2,4]triazolo[1,2-*a*]pyridazin-1-ones **10** (Scheme 7). The cyclization of **9** to the heterobicycles **10** was initially investigated by using aromatic aldehydes, because these reacted easily in the cyclization of the related carbothioamide **2** to the thiones **3** in good yields (Schulz et al. 2013). It was found that the reaction of **9** with a 40% excess of the respective aldehyde at a reaction temperature of 100 °C in the presence of *p*-toluenesulfonic acid monohydrate was completed in all cases after a relatively short time (45 to 60 min) (compare **6a,b**).

In this way, the synthesis of the reported 2,3,5,6,7,8-hexahydro-1*H*-[1,2,4]triazolo[1,2-*a*]pyridazin-1-ones **10** succeeded for the first time (Table 4), although 2,3-disubstituted **10** occurs occasionally as a partial structure in larger molecules (Kilama 1994 and 1997). The analytical data of the compounds clearly confirmed the isolation of the desired products. Interestingly, no indications of the formation of didehydro products of **10** during work-up of the batches were found.

Table 4: 2,3,5,6,7,8-Hexahydro-1*H*-[1,2,4]triazolo[1,2-*a*]pyridazin-1-ones 10



Nr.	R
10a	C_6H_5
10b	2-Cl-C_6H_4
10c	4-Cl-C_6H_4
10d	2-NO_2-C_6H_4
10e	4-NO_2-C_6H_4

2.2. Structural investigations

General. The elemental compositions and purity (high resolution MS, elemental analysis) were determined for all compounds; these are consistent with the specified structures. Their constitution was verified by using one-dimensional ^{1}H NMR and ^{13}C NMR spectroscopy as well as 2D NMR techniques such as ^{1}H,^{1}H COSY, ^{1}H,^{13}C HSQC, ^{1}H,^{13}C HMBC. In addition, the specified structures were confirmed by further informations from the MIR spectra, from the melting behavior and from the TLC behavior (*RF* value) and, in the case of compounds **7**, also by countersynthesis. The following exemplary explanations relate in particular to the characteristic NMR spectroscopic data which, above all, make it possible to reliably assign the structure of the compounds obtained. In this context obtaining confirmation on the intact heterobicyclic system of the **5**, **7**, **8** and **10**, the formation of possible didehydro compounds **7** from the amines **5**, the tautomeric forms and the protonation sites in amines **5** and imines **7** and **8** were of particular interest.

*2.2.1. (Hexahydropyridazine-1-carboximidothioic acid) (4-nitrobenzenecarboxylic acid) anhydride **12***

When examining the compound initially assumed to be **11c** (Scheme 3), it could already be seen from the values of the elemental analysis and in the ^{1}H NMR spectrum that it was characterized by the presence of only one aromatic ring with four protons. The characteristic position and the splitting pattern of the signals of the aromatic protons (7.73 ppm, 7.78 ppm and 8.25 ppm, 8.29 ppm) indicated a 1,4-substituted phenyl ring. Also, the MIR spectrum of the compound showing a band for the nitro group at 1528 cm^{-1} spoke in favor of a 4-nitrophenyl substituent. In the ^{1}H NMR and in the ^{13}C NMR spectrum no signals could be detected for a further phenyl ring or a methyl group, as should occur in the case of **11c**. However, two signals (8.46 ppm, 8.58 ppm) each for one proton on nitrogen atoms could be assigned in the ^{1}H NMR spectrum. In addition, the expected bands for NH stretching vibrations (3270 cm^{-1} and 3324 cm^{-1}) were found in the MIR spectrum. The position and the shape of these NH bands indicated two separate NH partial structures, consistent with the ^{1}H NMR spectrum. For the C=NH partial structure bands were found at 1600 cm^{-1} (NH deformation vibration) and 1644 cm^{-1} (C=N stretching vibration). The ^{13}C NMR spectrum also provides corresponding indications with a peak at 169.93 ppm, which is in the expected range for the C atom of the C=N partial structure, and with a peak at 182.89 ppm, which is to assigne to the C atom of the C=O group. These facts clearly indicate that a reaction of the thione **3b** with 4-nitrobenzoyl chloride had taken place at the expected position, but also with opening of the triazole ring and extrusion of the C(3) atom with its two substituents.

Waly and Abou Dobara (2009) reported products that are structurally very similar to compound **12**. The authors obtained these among other related compounds from piperidine and morpholine, respectively, by the action of S-benzoyl isothiocyanate on different N-nucleophiles. They also specifically used the high reactivity of the carbonyl groups of the S-benzoyl intermediates formed from 4,6-dimethyl-pyrimidin-2-amine and S-benzoyl isothiocyanate for cyclization reactions, in which pyrimido[1,2-*a*][1,3,5]triazinethiones are obtained.

*2.2.2. 1-(3-Methyl-3-phenyl-1-sulfanylidene-2,3,5,6,7,8-hexahydro-1H-[1,2,4]triazolo[1,2-a]pyridazin-2-yl)-ethanone) **13***

Both the mass spectrum and the ^{1}H NMR spectrum of the product obtained by acetylation of the thione **3b** indicated the formation of either the desired **11d** or its 2-acetyl isomer **13** (Scheme 3). The ^{13}C NMR spectrum provided further informations for clarifying which of the two compounds had been isolated. In the case of an S-acylation with the formation of an endocyclic C=N double bond (**11d**), there would be a shift in the signal position for the C1 of the bicyclic ring system (compare: $\underline{C}$=S at **3b** at 176.63 ppm in $CDCl_3$ (Schulz et al. 2014) *vs.* $\underline{C}$=N expected in the S-methylation product of **3b** at 162.99 ppm in DMSO-d_6 (Schulz et al. 2017) towards higher field. If **11d** was present, the carbon signal for the S-$\underline{C}$=N partial structure should appear well below 170 ppm (Schulz et al. 2017), while if the N-acetyl product **13** was present, the corresponding carbon signal (S=$\underline{C}$-N) should appear above 170 ppm (Schulz et al. 2013, 2014). In addition, in the case of S-acetylation, due to the heavy atom effect of sulfur, the position of the signal of the carbon atom of the acetyl group should appear even at lower field as found so for the *S*-(4-nitrobenzoyl) product **12**. From the available ^{13}C NMR spectrum, assigning the signals for the C atoms of the acetyl group (171.36 ppm) and for the C=S partial structure (172.56 ppm), the isolation of **13** (Scheme 3) can be verified with high probability. The assignment of the ^{13}C NMR peaks for the carbon atoms of the two methyl groups of **13** [$\underline{C}H_3$-C=O: 26.99 ppm; $\underline{C}H_3$-C(3): 20.75 ppm] was carried out both by evaluating the DEPT-135 spectrum and by comparing with the signal position of comparable methyl groups at position 3 of [1,2,4]triazolo[1,2-*a*]-pyridazines (20 ppm – 25 ppm, Schulz et al. 2014).

2.2.3. 3-(4-Nitrophenyl)-5,6,7,8-tetrahydro-1H-[1,2,4]-triazolo[1,2-a]pyridazine-1-thione 14

In all attempts to react the *S*-(4-nitrobenzoyl) derivative **12** with benzaldehyde or amines, the same product was repeatedly obtained (see 2.1.1.2). The structural analysis investigations showed that the starting compound **12** was subjected to an intramolecular reaction. The relative molecular mass determined with the high-resolution ESI MS indicated an elimination of water. In the NMR spectra, there were no indications of any part of the molecule that could have been added by reaction with other reagents of the respective batch. Also, no signals for NH groups could be found in the ^{1}H NMR spectrum. However, the characteristic signals for the carbon atoms of the intact hexahydropyridazine ring [19.03 ppm and 19.11 ppm for C(6) and C(7); 45.40 ppm and 47.49 ppm for C(8) and C(5)] appear in the ^{13}C NMR spectrum. The hydrogen atoms bonded in each case can be found in the ^{1}H NMR spectrum and can be assigned to the associated carbon atoms. The typical splitting pattern and the position of the peaks in the ^{1}H NMR spectrum (8.07 ppm and 8.42 ppm) could be assigned to a 1,4-substituted phenyl radical. The latter could be verified by the related signals of the ^{13}C NMR and the ^{1}H,^{13}C correlation spectrum. The peak occurring at 148.41 ppm is in the expected range for a nitro-substituted carbon atom and can be assigned to the C(4) of the aromatic ring. In the MIR spectrum the band for the nitro group appears at 1518 cm^{-1}. These facts spoke in favor of the presence of the 4-nitrophenyl radical. In the ^{13}C NMR spectrum, there are also peaks at 153.52 ppm ($\underline{C}$=N) and 174.07 ppm ($\underline{C}$=S), which are in accordance with the findings for previously obtained 3-phenyl substituted 5,6,7,8-tetrahydro-1*H*-[1,2,4]triazolo[1,2-*a*]pyridazine-1-thiones (Schulz et al. 2013) were assigned to the carbon atoms of the partial structures in question. The presence of the endocyclic imine partial structure was additionally supported by a band occurring at 1598 cm^{-1} in the MIR spectrum. The results of these structural investigations suggested that after previous S-N migration (Pratt and Bruice 1971) of the 4-nitrobenzoyl group of the compound **12** under formation of a reactive intermediate [presumably *N*-(4-nitrobenzoyl)-hexahydropyridazine-1-carbothioamide], the isolated **14** is formed from this by intramolecular cyclocondensation. In addition, the analytical data of compound **14** are similar to the previously characterized didehydro products of the corresponding 2,3,5,6,7,8-hexahydro-1*H*-[1,2,4]triazolo[1,2-*a*]pyridazine-1-thiones.

2.2.4. 5,6,7,8-Tetrahydro-3H-[1,2,4]triazolo[1,2-a]pyridazin-1-amine salts 5

Both the replacement of the methylsulfanyl group of the **4** with nitrogen nucleophiles and the cyclization of **6a** and **6b**, respectively, with carbonyl compounds enabled the access to the amino derivatives **5**, as is shown below by way of example on **5a** and **5q**. A first indication of the formation of **5a** from 3-methylsulfanyl-1-phenyl-1*H*-[1,2,4]triazolo[1,2-*a*]pyridazine hydroiodide **4b** (R^1 = C_6H_5, R^2 = H) (Scheme 1), the structure of which has been verified (Schulz et al. 2017), and ammonia under mild conditions led to the formation of methanethiol (characteristic odour). The thermal cyclization of the hexahydropyridazine-1-carboximidamide hydoiodide **6a**, the structure of which has also been elucidated (Morgenstern et al. 2004), with benzaldehyde gave the same product, namely the amino derivative **5a**. Therefore, it was to be expected that the product would have an intact heterobicyclic parent structure. The NMR spectra provided clear indications for this. In the ^{13}C NMR spectrum, comparable to that of **4b** (81.60 ppm), also appears a signal for a tertiary carbon atom [C(3)] between the N(2) and the N(4) atom of the heterobicyclic system at 78.21 ppm. The C(3)H proton appears in the ^{1}H NMR spectrum at 5.45 ppm as a singlet (**4b**: 5.88 ppm). In all NMR spectra of the amino derivatives **5** monosubstituted in position 3, these signals appear usually in the ranges between 5 ppm and a little over 6 ppm in the ^{1}H NMR spectra and between 74 ppm and a little over 78 ppm in the ^{13}C NMR spectra. The lack of these signals in various spectra of the supposed compounds **5** indicated the formation of the corresponding didehydro products **7** (see below). Indications of a failure of the cyclization of **6a** or a cracking of the heterobicyclic system in **4b**, such as additional signals or strong deviations from the expected signal positions, were not found in the NMR spectra. The (advantageous) use of hexahydropyridazine-1-carboximidamide hydochloride **6b** for the cyclization with benzaldehyde yielded the hydrochloride **5b**, the NMR spectra of which are (almost) identical to those of the hydroiodide **5a**. Although the structure of **6b** could be confirmed by a direct comparison with **6a**, this was a further indication for the formation of **6b** from hexahydropyridazine hydrochloride **1** and cyanamide.

Comparable results were obtained in the structural investigations of the 3,3-disubstituted amino derivatives **5q-w**. This way the 3,3-dimethyl-1*H*-[1,2,4]triazolo[1,2-*a*]pyridazin-1-amine hydroiodides **5v,w** are formed analogously to **5a** by the action of propylamine or butylamine on the corresponding methylsulfanyl derivative **4d** (R^1, R^2 = CH_3) (Scheme 1). The thermal cyclization of **6a,b** with acetone yielded products (the hydroiodide **5q** and the hydrochloride **5r**) whose bases were identical even according to the NMR spectroscopic data. The NMR spectra of the 3,3-disubstituted amino derivatives **5q-w** show similarities to those of the 3-monosubstituted **5a-p**. Here, however, all ^{1}H NMR spectra lack the singlet for a proton in the range from approx. 5 ppm to 6 ppm, which is characteristic of the monosubstituted derivatives, due to the two-fold substitution at the sp^3 hybridized carbon atom of the triazole ring part. However, in the ^{13}C NMR spectrum for the quaternary carbon atom, the respective signal is found as expected at lower filed in the range from slightly below 78 ppm (**5q**, 3,3-dimethyl) to well above 82 ppm (**5u**, 3,3-diethyl). These facts speak for the intact heterobicyclic system of **5q-w** and there were also no indications in the ^{1}H and ^{13}C NMR spectra that contradict the structure assignment made.

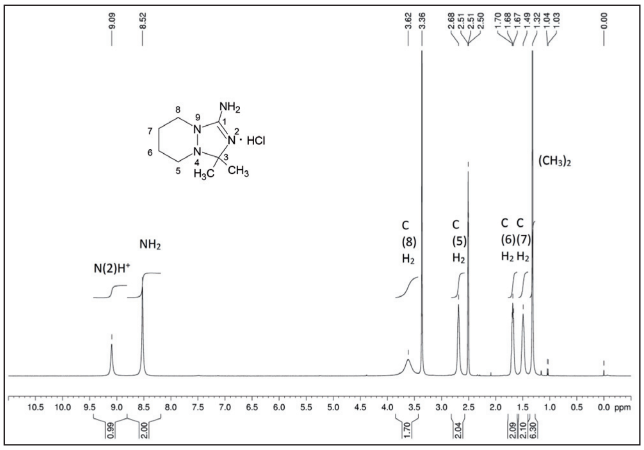


Fig. 1: ^{1}H NMR spectrum (400.20 MHz) of 3,3-dimethyl-5,6,7,8-tetrahydro-3*H*-[1,2,4]triazolo[1,2-*a*]pyridazin-1-amine hydrochloride **5r** in DMSO-d_6.

An important point in the structure assignment concerned the clarification of the tautomeric chartacteristics in the compounds **5**. Since in the *3,3-disubstituted derivatives* the formation of a 2,3-double bond in the triazole ring part could be excluded for structural reasons, their presence in the amino or imino form was of particular interest here.

In the case of the latter, the double bond would not be oriented between the C(1) and the N(2) atoms of the ring system, but rather from the C(1) to the exocyclic N atom. In the case of the 3,3-dimethyl derivative **5r**, which is unsubstituted at the exocyclic nitrogen atom, the ^{1}H NMR spectrum (solvent: DMSO-d_6) shows two signals for NH protons, each of which appears as a singlet (Fig. 1). The integral of the singlet at 8.52 ppm represents the two chemically equivalent protons of the amino group, while the singlet at a lower field (9.09 ppm) with the integral for one proton represents the proton of the N(2)$^+$H structure and indicates the protonation of the N(2) atom. The occurrence of this typical signal pattern is also observed for all the other obtained 3,3-disubstituted compounds of type **5**. When changing the solvent from DMSO-d_6 to CDCl$_3$, the signals for the N(2)$^+$H proton are often no longer observed (poorer solvation of the cation), which provides an additional argument for the protonation site in the molecules.

In the case of the *3-monosubstituted derivatives* **5**, the presence of a 2,3 double bond in the triazole ring part could already be excluded because the relevant C(3)H signals in all ^{1}H NMR spectra of these compounds (solvent: DMSO-d_6) appear in the range between 5 ppm and 6 ppm. The assignment of these protons to the respective C(3) atoms could be made unequivocally using two-dimensional ^{1}H,^{13}C NMR correlation spectra (HSQC, HMBC). In addition for these tertiary carbon atoms of the compounds **5** the corresponding signals in the ^{13}C NMR spectra appear in the range from approx. 74 ppm to approx. 78 ppm. In contrast, the signals of the carbon atoms of the C(3)=N(2) double bond in the didehydro compounds **7** appear at a significantly lower field (approx. 155 pm to approx. 158 ppm). Related to the NH protons, the ^{1}H NMR spectra of all 3-monosubstituted compounds **5** always show the signal pattern that has already been described for the corresponding 3,3-disubstituted derivatives (a singlet with an integral for two protons in the range of approx. 8 ppm to approx. 9 ppm and a singlet with an integral for one proton in the range from approx. 9 ppm to approx. 10 ppm). An additional argument for their presence in the amino form is provided by the four obtained derivatives **8** in which the imino form is fixed. In the ^{13}C NMR spectra of the compounds **8**, the signals for the C(1) atoms appear in a fairly narrow range from approx. 153.1 ppm to approx. 153.5 ppm, whereas those of the C(1) atoms of the amino derivatives **5** also appear in a narrow range, but clearly at lower field above 154.5 ppm. In addition, the respective singlets of the two $^+$NH$_2$ protons comparatively appear in the NMR spectra of the derivatives **8** consistently at even lower field (approx. 8.8 ppm to 9 ppm for the compounds **7** *vs.* approx. 8 to approx. 8.8 ppm for the compounds **5**). Thus, for all compounds **5** the presence of the amino form (at least under the investigation conditions) also in accordance with the numbers and positions of the NH vibration bands in the MIR spectra can be considered certain.

2.2.5. *2-Phenyl-2,3,5,6,7,8-hexahydro-1H-[1,2,4]triazolo[1,2-a]pyridazin-1-imine hydrochlorides* 8

The structure of the *N'*-phenyl-hexahydropyridazine-1-carboximidamide hydrochloride **6c** used as the starting compound for the compounds **8** was confirmed by the MS and spectroscopic data (see *Experimental*) as well as by the data of the related hydroiodide already obtained by the autors (Morgenstern et al. 2004; there listed as compound **4i**). For all the compounds **8** obtained, the formation of the desired [1,2,4]triazolo[1,2-*a*]pyridazine parent are again to be verified by the appearence of ^{13}C NMR signals caused by the tertiary C(3) atoms in the range from 80.30 (**8c**) to 83.96 (**8b**). These appear at a significantly lower field than in the case of the amino derivatives **5**. The ^{1}H NMR signals of the corresponding protons at C(3), which were clearly identified by means of ^{1}H,^{13}C HSQC, also appear in comparison to those of the compounds **5** at more lower field (approx. 6 ppm to approx. 6.5 ppm). For the desired ring closure *via* the phenyl substituted N' atom of **6c** speak, in addition to mechanistic aspects, the NH signals in all ^{1}H NMR spectra of the compounds **8**. In these spectra, a singlet caused by two equivalent protons is always found in the range between 8.8 ppm and 9 ppm, which indicates the presence of a protonated N-unsubstituted imino structure at position 1. In the case of cyclization via the unsubstituted N atom, there should be a phenylimino radical at position 1, which would be protonated in the course of salt formation with the formation of an energetically favorable cation. Consequently, two NH signals for one proton each would be expected in the ^{1}H NMR spectra of the compounds **8**, but these could not be observed. In addition, there was no evidence of the presence of a 1-phenylimino substituent among the other analytical data.

2.2.6. *5,6,7,8-Tetrahydro-1H-[1,2,4]triazolo[1,2-a]pyridazin-1-imine hydrohalides* 7

These compounds were obtained repeated in attempts either to synthesize the 3-monosubstituted 5,6,7,8-tetrahydro-3*H*-[1,2,4]-triazolo[1,2-*a*]pyridazin-1-amines **5** or were isolated as by-products in the synthesis of the amines **5**. Indications for the formation of the compounds **7** (by oxidation of the analogous amines **5**) resulted in particular from the ^{1}H and ^{13}C NMR spectra and from the mass spectra of the products obtained. In all ^{1}H NMR spectra of the **7**, initially the absence of singlet signals in the range from approx. 5 ppm to 6 ppm was noticeable. However, these occure in a characteristic manner for the protons at the respective C(3) atom of the monosubstituted amines **5**. In addition, the integrals indicated two protons fewer in the molecules of the **7** than in the **5**, which could be verified by the MS in all cases. The assumption that the didehydro compounds **7** are formed by direct oxidation of the **5** initially formed in the synthesis was very close based on the behavior of the 2,3,5,6,7,8-hexahydro-1*H*-[1,2,4]triazolo[1,2-*a*]-pyridazine-1-thiones **3** (Schulz et al. 2013) and the analogous methylsulfanyl derivatives **4** (Schulz et al. 2017). In fact, in no case was it possible to detect a signal for a sp^3-hybridized tertiary C(3) atom, which occurs in the amines **5** in the range from approx. 74 ppm to approx. 78 ppm. Instead, in each case in the range from approx. 154 ppm to approx. 158 ppm a new signal was found in the ^{13}C NMR spectra of the **7**, which spoke in favor of a sp^2-hybridized C(3) atom. In the case of the 3-substituted compounds **7**, the signal assignment could be carried out unequivocally by means of ^{1}H,^{13}C HMBC spectra and in the case of **7a,b** in each case utilizing the ^{1}H,^{13}C HSQC spectrum. The remaining ^{13}C signal for a sp^2-hybridized carbon atom, which appears at slightly lower field, was to assign unceremoniously to the C(1) atom of the imino group. **7a,b** are 3-unsubstituted derivatives, for which the C(3) signals occur at a significantly higher field (**7a**: 147.92 ppm; **7b**: 147.2 ppm). Their C(1) signal positions, however, correspond to those of the other didehydro compounds **7**. In addition, the analytical data of compound **7a**, which was specifically synthesized from hexahydropyridazine-1-carboximidamide hydrochloride **6b** and formic acid, further support the proposed structure for all products **7**.

All the compounds **7** are present as hydrohalides and are protonated at the exocyclic N atom. In all ^{1}H NMR spectra recorded in DMSO-d_6 or CDCl$_3$, singlets between approx. 8 ppm and 9 ppm appear for the protonated N atom: for **7a** and **7c-h** with an integral for two protons (-$^+$NH$_2$ group), for **7b,i,j** for one proton each (-$^+$NH group). With **7b,i,j** the possible coupling with neighbouring protons of R^3 is not observed (relatively high acidity of $^+$NH leads to rapid proton exchange). Moreover, all other analytical data obtained for the compounds **7** are in agreement with the proposed structure.

2.2.7. *2,3,5,6,7,8-Hexahydro-1H-[1,2,4]triazolo[1,2-a]-pyridazin-1-ones* 10

These compounds were obtained by cyclizing the hexahydropyridazine-1-carboxamide **9** (Scheme 7). For compound **9**, no experimentally determined data were known so far. The structure of this compound closely related to the analogous carbothioamide **2** (Scheme 1) (Morgenstern et al. 2004), which is reflected in the ^{1}H and ^{13}C NMR spectra, was ensured by means of a series of analytical data (see experimental section). For the cyclization of **9** with the aromatic aldehydes *via* the N atom of the carboxamide and the N(2) atom of the hexahydropyridazine ring their ^{1}H and ^{13}C NMR spectra spoke in particular. These show signals already found to be characteristic of the thiones **3** (Scheme 1) (Schulz et al. 2013). At all the obtained compounds **10** were found ^{13}C signals between 71 ppm and 77 ppm, which indicate the presence of the tertiary C(3) atom. In correlation with this, the signals between 4.8 ppm and 5.7 ppm for the C(3)H protons are detected in the ^{1}H NMR spectra. The signals appearing between 158.7 ppm and 159.2 ppm in the ^{13}C NMR spectra could be assigned unequivocally to the respective atoms C(1), although these are at a relatively high field for a carbon atom of a C=O group. The very intense bands, which are characteristic for C=O stretching vibrations, in the MIR spectra of the compounds **10** (less intense at compound **10e**) in the range of 1689 cm^{-1} up to 1711 cm^{-1} speak against an endocyclic C=N double bond (and at the same time against a possible cyclization with the formation of an imino-oxadiazole partial structure). The peaks appearing in the ^{1}H NMR spectra in the range from 7.6 ppm to 8 ppm are in accordance with the assigned structure for the **10** and represent the NH signals of the cyclic amide structure.

2.3. Biological testing of the [1,2,4]triazolo[1,2-a]pyridazin-1-amines 5

We have already reported on the results of studies on the iNOS inhibitory activity of the thiones **3** (Schulz et al. 2013, 2014) and the 3-methylsulfanyl derivatives **4** (Scheme 1) (Schulz et al. 2017). Of interest was the iNOS inhibitory activity of the new amino derivatives **5**, which in the series of [1,2,4]triazolo[1,2-*a*]pyridazines we synthesized, because they have the greatest structural similarity to the reference inhibitor aminoguanidine. For these investigations, the easily accessible and water-soluble [1,2,4]triazolo[1,2-*a*]pyridazin-1-amine hydrochlorides **5** were chosen for testing in the screening assay that we have already utilized previously (Schulz et al. 2013, 2014, 2017). The key parameters are described in section *3.3. Biological tests*.

However, the results show that with the integration of an aminoguanidine partial structure into the bicyclic ring system, as in the case of compounds **5**, no better inhibitory activity against iNOS (Fig. 2) was achieved compared to the already tested representatives of **3** and **4**.

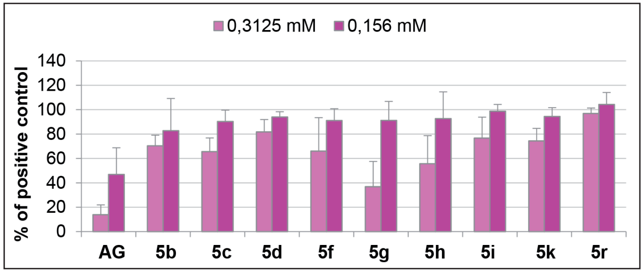


Fig. 2: Concentration-dependent inhibition of iNOS of RIN5F cells by the amino derivatives **5** using aminoguanidine (AG) as a reference inhibitor; NO measured as nitrite by GRIESS reaction; presented as % of positive control; mean ± SD; n = 7-11 (AG > 30, as a control on each plate).

The amino derivatives **5** are only slightly active (**5g**), but above all notably less active than aminoguanidine or not active at all (**5d**) (Table 5). In addition, they show some cytotoxicity, which is pronounced for **5c** and **5h** (Fig. 3).

Despite the lower inhibitory activity of **5**, it is noteworthy that the relations already observed between structure and iNOS inhibitiory activity in the thions **3** (Schulz et al. 2013, 2014) and the methylsulfanyl derivatives **4** (Schulz et al. 2017) are also present in these compounds. The 3,3-dialkyl substituted representative **5r** shows almost no activity, while the 3-(4-chlorophenyl) derivative **5g** gave the best result.

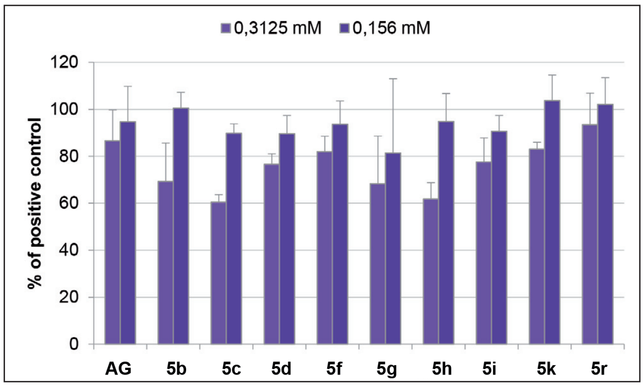


Fig. 3: Concentration-dependent cytotoxicity of amino derivatives **5** on RIN5F cells using aminoguanidine (AG) as a reference inhibitor; viability determined using MTT; presented as % of positive control; mean ± SD; n = 7-11 (AG > 30, as a control on each plate).

3. Experimental

3.1. Chemistry – General

The reported melting temperature ranges were determined on a Kofler-Boëtius apparatus type PHMK 81/3035 (VEB Wägetechnik Rapido) and are uncorrected. Elemental analyses were done with the LECO CHNS-932 (Leco Corporation) for the compounds **5q**, **13** and **14** and with the 2400 CHN Elemental Analyzer (Perkin-Elmer) for the compounds **5l,m,o,p**, **7i**, and **12** and with the vario MICRO cube analyzer (Elementar Analysensysteme GmbH, Hanau) for the compounds **5a-k,r**, **6b**, **7a,f**, **8a-d**, **9**, and **10a-e**. For the microwave-assisted attempts for synthesis of the compounds **5** the Discover LabMate with the IntelliVent™ Pressure Control System, circular, single-mode-self-tuning-system, frequency 2.45 GHz, and CEM's SynergyT software (CEM Kamp-Lintfort) was used. The high pressure syntheses of compounds **7c-e** were done with the laboratory reactor BR-300, System Highpreactor™, Fa. Berghof, Tübingen (Germany). The spectra were recorded with the following instruments and conditions: MIR spectra: IR 200 FT-IR (Thermo Electron Corporation Nicolet), ATR technique (diamond) for the compounds **5a-k,n,r-w**, **6b-d**, **7a-g,j**, **8a-d**, **9**, and **10a-e**; FT-IR 1600 (Perkin-Elmer), transmission technique (KBr discs) for the compounds **5l,m,o-q**, **7h,I**, **12**, **13** and **14**. NMR spectra (both FT NMR spectrometers from Bruker Analytische Messtechnik GmbH): AVANCE DPX 200 (^{1}H; ^{1}H,^{1}H-COSY; DEPT-135; ^{13}C) with the operating frequencies for ^{1}H at 200.11 MHz and for ^{13}C at 50.32 MHz for the compounds **5l,m,o-q**, **7h,I**, **12**, **13** and **14**; AVANCE III™ 400 (^{1}H; ^{1}H,^{1}H-COSY; DEPT-135; ^{13}C; ^{1}H,^{13}C HSQC; ^{1}H,^{13}C HMBC) with the operating frequencies for ^{1}H at 400.20 MHz and for ^{13}C at 100.63 MHz for the compounds **5a-k,n,r-w**, **6b-d**, **7a-g,j**, **8a-d**, **9**, and **10a-e**; temperature 25 °C, solvents used are specified in the data of the related compound; internal standard tetramethylsilane; chemical shift δ in ppm. To verify the signal assignments 2D NMR techniques as ^{1}H,^{13}C HSQC, ^{1}H,^{13}C HMBC, and ^{1}H,^{1}H COSY were used. Mass spectra:, M 40 AMD (Intectra GmbH), electron impact (EI-MS), energy 70 eV, (with the exception of the molecular ion peaks normally only peaks > 10% are listed) for the compounds **5e,o-q**, **7h,I**, **12**, **13** and **14**. High Resolution Mass Spectra (HR-MS) for the compounds **5a-k,r,u**, **6b-d, 7a,c-g,j**, **8a-d**, **9**, and **10a-e**: ESI, Shimadzu High Performance Liquid Chromatograph/Mass Spectrometer LCMS-IT-TOF with the system characterized as following: solvent delivery module LC-20AD Prominence, autosampler SIL-20AC HT Prominence, column oven CTO-20A Prominence, system controller CBM-20A Prominence, UV/VIS photodiode array detector SPD-M20A Prominence, evaporative light scattering detector ESD-LT II, spectrometric detector RF-10A XL, LCMS-IT-TOF workstation, software LCMS solution Version 3.41; column Chromolith® SpeedRod RP-18 endcapped, 50 mm; mobile phases (m. ph.) used and specified in the data of the related compound: m. ph. VIII was methanol/water 1:1 (0.1% HCOOH in H_2O) (v/v), flow rate: 0.2 mL·min^{-1} and m. ph. IX was methanol/water 7:3 (0.1% HCOOH in H_2O) (v/v), flow rate: 0.2 mL·min^{-1}. High Resolution Mass Spectra for compounds **7h** and **14**: ESI, Bruker Daltonics MicroOTOF-LC (ESI-TOF); external calibration (Agilent ESI TuneMix); column Zorbax RP-C18; 2.1 x 30 mm, 3.5 µm; mobile phase (m. ph. XI): gradient propan-2-ol/water 20% Ba' 50% B.; flow rate: 0.3 mL·min^{-1}.

For TLC silica gel aluminum foil covered with silica gel 60 F_{254} (Merck) was utilized as stationary phase. The running distance for the front of the mobile phase was 6.5 cm. The following mixtures were used as mobile phases:

m. ph. I:	propan-1-ol/acetic acid/water 3:1:1 (v/v/v)
m. ph. II:	propan-1-ol/acetic acid/water 8:2:1 (v/v/v)
m. ph. III:	hexane/ethyl acetate 1:1 (v/v)
m. ph. IV:	hexane/ethyl acetate/acetic acid 5:5:1 (v/v/v)
m. ph. V:	cyclohexane/ethyl acetate/triethylamine 3:3:1 (v/v/v)
m. ph. VI:	methanol/acetic acid 95:5 (v/v)
m. ph. VII:	dichloromethane/acetone 1:1 (v/v)

Each mobile phase (m. ph.) used is specified in the data of the related compound. The substances were detected with UV radiation (λ = 254 nm), iodine gas or Munier spray reagent (Munier 1953) and iodine azide reagent (Awe 1948).

The HPLC investigations were done under the following conditions: system – LaChrom (Merck Hitachi) consisting of pump L-7100, autosampler L-7200, column thermostat L-7350, solvent degasser L-7612, interface D-7000, and diode array detector L-7450 (λ = 220 nm or 240 nm); stationary phase – RP columns (given in the HPLC data of the compounds); the dead time *t0* was determined with uracil; mobile phase (m. ph. X): acetonitrile/water 7:3 (v/v). The values for the dead time *t0* and the retention times *tR* are specified in the data of the related compound.

Table 5: Percentual inhibition of the iNOS in RIN5F cells by aminoguanidine (AG) and the amino derivatives 5 as a proportion of the remaining NO production compared to the untreated control (RIN5F stimulated with cytokines but without added inhibitor).

Inhibitor	0,3125 mM			0,156 mM		
	% Untreated Control	SD	Significance	% Untreated Control	SD	Significance
AG	13,83	8,092	-	46,79	21,98	-
5b	70,27	8,84	***	82,70	26,48	***
5c	65,57	11,25	***	90,28	9,35	***
5d	81,74	10,18	***	93,95	4,39	***
5f	65,99	27,51	**	91,04	9,75	***
5g	36,80	20,75	*	91,14	15,66	***
5h	55,66	23,07	**	92,62	21,99	**
5i	76,67	17,23	***	98,74	5,55	***
5k	74,37	10,31	***	94,41	7,25	***
5r	96,83	4,54	***	104,28	9,80	***

mean ± SD; n = 5 (AG > 30, as a control on each plate); statistical significance *versus* AG: *** p < 0,001 / ** p < 0,01 / *p < 0,05 / n. s. not significant

3.2. Chemistry – Syntheses

3.2.1. Hexahydropyridazine-1-carboximidamides 6

3.2.1.1. Hexahydropyridazine-1-carboximidamide hydroidide **6a**

Compound **6a** was obtained according the multistep procedure described by Morgenstern et al. (2004).

3.2.1.2. Hexahydropyridazine-1-carboximidamide hydrochloride **6b**

A mixture of 2 mmol of hexahydropyridazine hydrochloride **1** and 3 mmol of cyanamide was melted together at 100 °C (metal bath). After the reaction was completed (TLC control, about 2 h) the cooled melt was treated with hot acetone. The crystals formed were separated by filtration under reduced pressure. The pure product was obtained by recrystallization from propan-2-ol. Yield: 84 %.
Colourless crystals. M.r.: 193-197 °C (propan-2-ol).
TLC (m. ph. II): R_F = 0.40. MIR (cm^{-1}): $\tilde{\nu}$ = 1444 (CH_2); 1491 and 1518 (NH); 1603 and 1619 (NH_2); 1653 (C=N); 2852, 2940 and 2958 (CH_2); 3122, 3200, 3236 and 3325 (NH). ^{1}H NMR (400.20 MHz, DMSO-d_6, ppm): δ = 1.56–1.64 (m, 4 H, C(4)H_2 and C(5)H_2), 2.77–2.81 (m, 2H, C(3)H_2), 3.56 (s, 2 H, C(6)H_2), 5.25 (t, ^3J = 7.2 Hz, 1 H, N(2)H), 7.50 (s, 4 H, NH_2, NH_2^+). ^{13}C NMR (100.63 MHz, DMSO-d_6, ppm): δ = 23.34 and 23.50 (C4 and C5); 44.92 (C6); 46.49 (C3); 156.77(CN). MS [(ESI) m/z]: Calcd. for $[C_5H_{12}N_4+H]^+$: 129.1135. Found $[M+H]^+$: 129.1136. Elemental analysis [$C_5H_{13}ClN_4$ (164.64), %]: Calcd. C 36.48, H 7.96, N 34.03. Found C 36.41, H 7.69, N 33.29.

3.2.1.3. N‘-Phenyl-hexahydropyridazine-1-carboximidamide hydrochloride **6c**

A mixture of 2 mmol of hexahydropyridazine hydrochloride **1** and 3 mmol of phenyl cyanamide was melted together for 6 h at a temperature of 100 °C (metal bath). Subsequently the cooled melt was treated with 10 mL of ethyl acetate. The crystals formed were separated by filtration under reduced pressure, washed with a little ethyl acetate and dried at 95 °C under reduced pressure. Because the product is very hygroscopic, it has to store protected to moisture. Yield: 81 %.
Yellow crystals. M.r.: 139–146 °C (ethyl acetate).
TLC (m. ph. VI): R_F = 0.52. MIR (cm^{-1}): $\tilde{\nu}$ = 1437, 1496, 1580, 1597, 1635 (C=N), 2217; 2854, 2888, 2945, 3064, 3140, 3274, 3404 (peaks of a broad band). ^{1}H NMR (400.20 MHz, DMSO-d_6, ppm): δ = 1.63–1.72 (m, 4 H, C(4)H_2 and C(5)H_2), 2.88 (implied q, ^3J = 4.4 Hz, 2 H, C(3)H_2), 3.74 (s, 2 H, C(6)H_2), 5.49 (t, ^3J = 6.8 Hz, 1 H, N(2)H); 6.99–7.01 (m, 1 H), 7.25-7.29 (m, 2 H), 7.42-7.46 (m, 2 H) (arom. H); 7.68 (s, 2 H, NH_2), 9.81 (s, 1 H, NH^+).^{13}C NMR (100.63 MHz, DMSO-d_6, ppm): δ = 23.49 (C4 and C5), 46.16 (C6), 46.64 (C3), 112.21 (C4’), 125.12 (broad signal, 2 C), 129.55 (2C), 138.84 (C1’), 154.85 (C=N^+H). MS [(ESI) m/z]: Calcd. for $[C_{11}H_{16}N_4+H]^+$: 205.1448. Found $[M_{base}+H]^+$: 205.1442.

3.2.1.4. N‘-Benzyl-hexahydropyridazine-1-carboximidamide hydrochloride **6d**

A mixture of 2 mmol of hexahydropyridazine hydrochloride **1** and 3 mmol of benzyl cyanamide was melted together for 4 h at a temperature of 100 °C (metal bath). Subsequently the cooled melt was treated with 5 mL of ethyl acetate. The crystals formed were separated by filtration under reduced pressure, washed with a little ethyl acetate and dried at 80 °C under reduced pressure. Yield: 92 %.
Pale yellow crystals. M.r.: 116–121 °C (ethyl acetate).
TLC (m. ph. VI): R_F = 0.60. MIR (cm^{-1}): $\tilde{\nu}$ = 1451, 1495, 1570, 1614, 1648, 2940; 3132, 3191, 3270, 3448 (peaks of a brod band). ^{1}H NMR (400.20 MHz, DMSO-d_6, ppm): δ = 1.58–1.65 (m, 4 H, C(4)H_2 and C(5)H_2), 2.81 (implied q, ^3J = 4.4 Hz, 2 H, C(3)H_2), 3.65 (s, 2 H, C(6)H_2), 4.49 (d, ^3J = 6.8 Hz, 2 H, CH_2 of the benzyl group), 5.33 (t, ^3J = 7.2 Hz, 1 H, N(2)H), 7.28–7.36 (m, 5 H, arom. H), 7.77 (s, 2 H, NH_2); 8.36 (t, ^3J = 6.4 Hz, 1 H, C=NH^+). ^{13}C NMR (100.63 MHz, DMSO-d_6, ppm): δ = 23.43 (C4 and C5), 43.79 ($\underline{C}H_2$ of the benzyl group), 45.64 (C6), 46.49 (C3), 126.39 (C4’), 126.98 (C2’ and C6’), 128.36 (C3’ and C5’), 137.82 (C1’), 155.39 ($\underline{C}$=N^+H). MS [(ESI) m/z]: Calcd. for $[C_{12}H_{18}N_4+H]^+$: 219.1604. Found $[M_{base}+H]^+$: 219.1614

3.2.2. [1,2,4]Triazolo[1,2-a]pyridazin-1-amines 5 from hexahydropyridazine-1-carbox-imidamides 6

3.2.2.1. [1,2,4]Triazolo[1,2-a]pyridazin-1-amine hydroiodides **5a,e,h**

To a mixture of 0.5 mmol of hexahydropyridazine-1-carboximidamide hydroiodide **6a** and 1.5 mmol of the related aldehyde 3 mg of *p*-toluenesulfonic acid monohydrate were added. The batch was heated in a metal bath at 100 °C and at the same time the course of reaction was monitored by TLC. After the reaction was complete or when the respective oxidation product **7** began to form, the supply of heat was stopped and the cooled melt was taken up in acetone. The further work-up procedure was carried out as indicated for the respective compound.
In this way the following compounds were obtained:

3-Phenyl-5,6,7,8-tetrahydro-3H-[1,2,4]triazolo[1,2-a]pyridazin-1-amine hydroiodide 5a

With benzaldehyde. Reaction time: 3 hours. Work-up: After the solvent had been removed, the residue was triturated with hexane with the supply of heat and the supernatant was poured off. Subsequently the crystalline mass yielded was recrystallized from propan-2-ol. The oxidation by-product **7f** obtained in this way was separated off by vacuum filtration and the mother liquor was completely concentrated. **5a** and **7f** were still present in the residue of the mother liquor. To obtain the pure **5a** this residue was then triturated with diethyl ether and the ether phase was separated. The crystalline product remained was washed with ethyl acetate and dried. Yield: 23 %.
Colourless crystals. M.r.: 150–153 °C (propan-2-ol/diethyl ether/ethyl acetate).
TLC (m. ph. II): R_F = 0.68. MIR (cm^{-1}): $\tilde{\nu}$ = 1543 and 1582 (C=C), 1666 (C=N), 2842, 2927 and 2944 (CH_2), 3088 (CH), 3245 (NH). ^{1}H NMR (400.20 MHz, DMSO-d_6, ppm): δ = 1.44–1.79 (m, 4 H, C(6)H_2 and C(7)H_2), 2.70 (t, ^3J = 10.4 Hz, 1 H, C(5)H), 2.96 (d, ^3J = 10 Hz, 1 H, C(5)H), 3.20 (t, ^3J = 11.6 Hz, 1 H, C(8)H), 3.99 (d, ^3J = 12,4 Hz, 1 H, C(8)H), 5.45 (s, 1 H, C(3)H), 7.43–7.46 (m, 5 H, arom.), 8.44 (s, 2 H, NH_2), 9.45 (s, 1 H, N(2)H^+). ^{13}C NMR (100.63 MHz, DMSO-d_6, ppm): δ = 22.56 and 22.69 (C6 and C7); 43.67 (C8), 52.08 (C5), 78.21 (C3), 127.16 (C2’ and C6’), 128.54 (C3’ and C5’), 129.30 (C4’), 136.66 (C1’), 154.61 (C1). MS [(ESI) m/z]: Calcd. for $[C_{12}H_{16}N_4+H]^+$: 217.1448. Found $[M_{base}+H]^+$: 217.1450. Elemental analysis [$C_{12}H_{17}IN_4$ (344.20), %]: Calcd. C 41.87, H 4.98, N 16.28. Found C 41.66, H 5.04, N 15.99.

*3-(2-Chlorophenyl)-5,6,7,8-tetrahydro-3H-[1,2,4]triazolo[1,2-a]pyridazin-1-amine hydroiodide **5e***

With 2-chlorobenzaldehyde (unlike the general procedure 0.5 mmol only). Reaction time: 3 hours. Work-up: The resulting precipitate was separated off by vacuum filtration, dissolved in propan-2-ol and the insoluble residue (oxidation product **7g**) was filtered off. To obtain **5e** the filtrate was concentrated to dryness and the residue was digested with ethyl acetate were the pure product remained. Yield: 6 %.
Light yellow crystals. M.r.: 203–213 °C (acetone/propan-2-ol).
TLC (m. ph. II): R_F = 0.70. MIR (cm^{-1}): $\tilde{\nu}$ = 1034, 1052, and 1097 (C-Cl), 1540 and 1587 (C=C), 1657 (C=N), 2356 (NH^+), 2943 (CH_2), 3100 (CH), 3173 and 3244 (NH). ^{1}H NMR (400.20 MHz, DMSO-d_6, ppm): δ = 1.44–1.83 (m, 4 H, C(6)H_2 and C(7)H_2), 2.81 (bs, 1 H, C(5)H), 3.07 (d, ^3J = 9.6 Hz, 1H, C(5)H), 3.26 (bs, 1 H, C(8)H), 4.02 (d, ^3J = 12.8 Hz, 1 H, C(8)H), 5.78 (s, 1 H, C(3)H), 7.44–7.47 (m, 3 H, C(4’)H, C(5’)H and C(6’)H), 7.54–7.56 (m, 1 H, C(3’)H), 8.46 (s, 2 H, NH_2), 9.44 (s, 1 H, N(2)H^+). ^{13}C NMR (100.63 MHz, DMSO-d_6, ppm): δ = 22.76 and 22.86 (C6 and C7), 43.26 (C8), 52.83 (C5), 75.05 (C3), 127.46 and 127.65 (C5’ and C6’), 129.92 (C3’), 130.83 (C4’), 132.59 (C2’), 134.15 (C1’), 154.67 (C1). MS [(ESI) m/z]: Calcd. for $[C_{12}H_{15}ClN_4+H]^+$: 251.1058. Found $[M_{base}+H]^+$: 251.1068.

3-(2-Nitrophenyl)-5,6,7,8-tetrahydro-3H-[1,2,4]triazolo[1,2-a]pyridazin-1-amine hydroiodide ***5h***

With 2-nitrobenzaldehyde (unlike the general procedure 0.55 mmol only). Reaction time: 5.5 hours. Work-up: The small amount of the remaining solid was separated off and the solution was completely concentrated and the residue was taken up in ethyl acetate. After the addition of hexane the precipitate formed was aspirated off and then it was digested with propan-2-ol to supply the pure product **5h**. Yield: 24 %.

Yellow crystals. M.r.: 212–217 °C (hexane/propan-2-ol).

TLC (m. ph. II): R_F = 0.69. MIR (cm^{-1}): $\tilde{\nu}$ = 1348 and 1521 (N=O), 1557 and 1591 (C=C), 1649 (C=N), 2955 (CH_2), 3103 (CH), 3189, 3243 and 3288 (NH). ^{1}H NMR (400.20 MHz, DMSO-d_6, ppm): δ = 1.41–1.84 (m, 4 H, C(6)H_2 and C(7)H_2), 2.85 (t, ^3J = 10.6 Hz, 1 H, C(5)H), 3.01 (d, ^3J = 10.0 Hz, 1 H, C(5)H), 3.27 (t, ^3J = 12.4 Hz, 1 H, C(8)H), 4.02 (d, ^3J = 12.0 Hz, 1 H, C(8)H), 6.14 (s, 1 H, C(3)H), 7.69 (t, ^3J = 8.0 Hz, 2 H, C(4')H and C(6')H), 7.84 (t, ^3J = 6.8 Hz, 1 H, C(5')H), 8.12 (d, ^3J = 7.6 Hz, 1 H, C(3')H), 8.40 (s, 2 H, NH_2), 9.56 (s, 1 H, N(2)H^+). ^{13}C NMR (100.63 MHz, DMSO-d_6, ppm): δ = 22.75 and 22.93 (C6 and C7), 43.15 (C8), 53.07 (C5), 73.96 (C3), 125.24 (C3'), 127.71 (C6'), 130.43 (C4'), 132.49 (C1'), 134.09 (C5'), 147.74 (C2'), 154.48 (C1). MS [(ESI) m/z]: Calcd. for $[C_{12}H_{15}N_5O_2+H]^+$: 262.1299. Found $[M_{base}+H]^+$: 262.1310. Elemental analysis [$C_{12}H_{16}IN_5O_2$ (389.19), %]: Calcd. C 37.03, H 4.14, N 17.99. Found C 36.71, H 4.25, N 17.58.

3.2.2.2. 3,3-Dimethyl-5,6,7,8-tetrahydro-3H-[1,2,4]triazolo[1,2-a]pyridazin-1-amine hydroiodide **5q**

A mixture of 0.5 mmol of hexahydropyridazine-1-carboxamidimide hydroiodide **6a**, 10 mL of acetone and 8 mg of *p*-toluenesulfonic acid monohydrate was refluxed (bath temperature: 130 °C) for 5.5 h. Then the excess of acetone was evaporated and the residue was taken up in a small amount of propan-2-ol. After the solvent was removed the resulting brown unctuous product was digested with a little hexane, and a brownish semi-crystalline substance remained. Yield: 70 %.

TLC (m. ph. I) R_F = 0.63. MIR (KBr disc, cm^{-1}): = 1548, 1606 (NH); 1665 (C=N); 2858, 2922, 2962 (all aliph.H); 3087, 3250, 3333 (NH). ^{1}H NMR (200.11 MHz, DMSO-d_6, ppm): δ = 1.32 (s, 6 H, (2 x CH_3),1.49–1.50 (m, 2 H, C(6)H_2), 1.69 (m, 2 H, C(7)H_2), 2.69 (m, 2 H, C(5)H_2), 3.54 (m, 2 H, C(8)H_2), 8.21 (s, 2 H, NH_2), 8.88 (s, 1 H, N(2)H^+). ^{13}C NMR (50.32 MHz, DMSO-d_6, ppm): δ = 23.44, 23.73 (C6 and C7), 23.94 (C(3)($\underline{C}H_3)_2$), 44.71 (C8), 47.55 (C5), 78.74 (C3), 155.43 (C1). MS (EI, 70 eV, 310 °C) m/z (%): 167.9 (9.34) $[M_{base}^{+\cdot}]$, 152.4 (100) $[M_{base}^{+\cdot} - {}^{\cdot}CH_3]$, 127.7 (67), 126.7 (34), 70.8 (14), 55.2 (13), 43.0 (21), 42 (11), 41 (13). Elemental analysis [$C_8H_{17}IN_4$ (296,15), %]: Calcd. C 32.45, H 5.79, N 18.92. Found C 33.39, H 5.94, N 17.99.

3.2.2.3. 3-Monosubstituted [1,2,4]triazolo[1,2-a]pyridazin-1-amine hydrochlorides **5b-d,f,g,i-k**

To a mixture of 0.5 mmol of hexahydropyridazine-1-carboximidamide hydrochloride **6b** and 0.7 mmol of the related aldehyde 3 mg of *p*-toluenesulfonic acid monohydrate were added. The reaction was heated in a metal bath at 100 °C and at the same time the course of reaction was monitored by TLC. After the reaction was complete or when the respective oxidation product **7** began to form, the supply of heat was stopped and the cooled melt was taken up in acetone. The yielded crystals were aspirated off by filtration under reduced pressure, washed with acetone and dried.

In this way the following compounds were obtained:

3-Phenyl-5,6,7,8-tetrahydro-3H-[1,2,4]triazolo[1,2-a]pyridazin-1-amine hydrochloride ***5b***

With benzaldehyde (unlike the given procedure: 1.5 mmol). Reaction time: 2 hours. Yield: 73 %.

Colourless crystals. M.r.: 187–195 °C (acetone).

TLC (m. ph. II): R_F = 0.68. MIR (cm^{-1}): $\tilde{\nu}$ = 1542 and 1613 (C=C), 1678 (C=N), 2362 (NH^+), 2913 (CH_2), 2976 and 3001 (CH). ^{1}H NMR (400.20 MHz, DMSO-d_6, ppm): δ = 1.43–1.75 (m, 4 H, C(6)H_2 and C(7)H_2), 2.69 (t, ^3J = 10.2 Hz, 1 H, C(5)H), 2.95 (d, ^3J = 10.0 Hz, 1 H, C(5)H), 3.18 (bs, 1 H, C(8)H), 4.14 (d, ^3J = 11.2 Hz, 1 H, C(8)H), 5.44 (s, 1 H, C(3)H), 7.41–7.45 (m, 5 H, arom.), 8.69 (s, 2 H, NH_2), 9.62 (s, 1 H, N(2)H^+). ^{13}C NMR (100.63 MHz, DMSO-d_6, ppm): δ = 22.64 and 22.75 (C6 and C7), 43.77 (C8), 52.13 (C5), 78.17 (C3), 127.09 (C2' and C6'), 128.49 (C3' and C5'), 129.20 (C4'), 136.86 (C1'), 154.79 (C1). MS [(ESI) m/z]: Calcd. for $[C_{12}H_{16}N_4+H]^+$: 217.1448. Found $[M_{base}+H]^+$: 217.1438. Elemental analysis [$C_{12}H_{17}ClN_4$ (252.74), %]: Calcd. C 57.03, H 6.78, N 22.17. Found C 55.29, H 6.44, N 21.27.

3-(2-Methylphenyl)-5,6,7,8-tetrahydro-3H-[1,2,4]triazolo[1,2-a]pyridazin-1-amine hydrochloride ***5c***

With 2-methylbenzaldehyde. Reaction time: 5 hours. Yield: 68 %.

Colourless crystals. M.r.: 203–219 °C (acetone).

TLC (m. ph. II): R_F = 0.73. MIR (cm^{-1}): $\tilde{\nu}$ = 1541 and 1593 (C=C), 1662 (C=N), 2334 (NH^+), 2950 (CH_2), 3042 (CH), 3172 and 3203 (NH). ^{1}H NMR (400.20 MHz, DMSO-d_6, ppm): δ = 1.43–1.79 (m, 4 H, C(6)H_2 and C(7)H_2), 2.36 (s, 3 H, CH_3), 2.74 (bs, 1 H, C(5)H), 2.96 (bs, 1 H, C(5)H), 3.21 (bs, 1 H, C(8)H), 4.14 (bs, 1 H, C(8)H), 5.67 (s, 1 H, C(3)H), 7.23–7.32 (m, 4 H, arom.), 8.68 (s, 2 H, NH_2), 9.61 (s, 1 H, N(2)H^+). ^{13}C NMR (100.63 MHz, DMSO-d_6, ppm): δ = 18.71 (CH_3), 22.81 and 22.89 (C6 and C7), 43.50 (C8), 52.42 (C5), 75.63 (C3), 125.85, 128.85, and 130.75 (C3', C4', C5' and C6'), 134.48 (C2'), 136.64 (C1'), 155.10 (C1). MS [(ESI) m/z]: Calcd. for $[C_{13}H_{18}N_4+H]^+$: 231.1604. Found $[M_{base}+H]^+$: 231.1606. Elemental analysis [$C_{13}H_{19}ClN_4$ (266.77), %]: Calcd. C 58.53, H 7.18, N 21.00. Found C 58.03, H 7.02, N 20.95.

3-(4-Methylphenyl)-5,6,7,8-tetrahydro-3H-[1,2,4]triazolo[1,2-a]pyridazin-1-amine hydrochloride ***5d***

With 4-methylbenzaldehyde. Reaction time: 3 hours. Yield: 55 %.

Colourless crystals. M.r.: 180–192 °C (acetone).

TLC (m. ph. II): R_F = 0.73. MIR (cm^{-1}): $\tilde{\nu}$ = 1533 and 1614 (C=C), 1681 (C=N), 2362 (NH^+), 2852, 2914, and 2971 (CH_2), 3000 and 3052 (CH). ^{1}H NMR (400.20 MHz, DMSO-d_6, ppm): δ = 1.42–1.77 (m, 4 H, C(6)H_2 and C(7)H_2), 2.32 (s, 3 H, CH_3), 2.66 (t, ^3J = 10.2 Hz, 1 H, C(5)H), 2.92 (d, ^3J = 10.0 Hz, 1 H, C(5)H), 3.17 (bs, 1 H, C(8)H), 4.14 (d, ^3J = 10.4 Hz, 1 H, C(8)H), 5.38 (s, 1 H, C(3)H), 7.23 (d, ^3J = 8.0 Hz, 2 H, C(3')H and C(5')H), 7.34 (d, ^3J = 8.0 Hz, 2 H, C(2')H and C(6')H), 8.68 (s, 2 H, NH_2), 9.57 (s, 1 H, N(2)H^+). ^{13}C NMR (100.63 MHz, DMSO-d_6, ppm): δ = 20.78 (CH_3), 22.61 and 22.73 (C6 and C7), 43.84 (C8), 51.94 (C5), 78.20 (C3), 127.12 (C2' and C6'), 129.00 (C3' and C5'), 133.94 (C1'), 138.68 (C4'), 154.88 (C1). MS [(ESI) m/z]: Calcd. for $[C_{13}H_{18}N_4+H]^+$: 231.1604. Found $[M_{base}+H]^+$: 231.1598. Elemental analysis [$C_{13}H_{19}ClN_4$ (266.77), %]: Calcd. C 58.53, H 7.18, N 21.00. Found C 58.54, H 6.99, N 20.68.

3-(2-Chlorophenyl)-5,6,7,8-tetrahydro-3H-[1,2,4]triazolo[1,2-a]pyridazin-1-amine hydrochloride ***5f***

With 2-chlorobenzaldehyde. Reaction time: 3.5 hours. In difference to the general procedure, the resulting crystals were additionally washed with propan-2-ol. Yield: 41 %.

Colourless crystals. M.r.: 214–223 °C (acetone/propan-2-ol).

TLC (m. ph. II): R_F = 0.72. MIR (cm^{-1}): $\tilde{\nu}$ = 1034, 1049, and 1072 (C-Cl), 1546, 1575, and 1593 (C=C), 1663 (C=N), 2835, 2931, 2944, and 2961 (CH_2), 3055 (CH), 3163 and 3215 (NH). ^{1}H NMR (400.20 MHz, DMSO-d_6, ppm): δ = 1.43–1.82 (m, 4 H, C(6)H_2 and C(7)H_2), 2.81 (bs, 1 H, C(5)H), 3.07 (d, ^3J = 8.0 Hz, 1 H, C(5)H), 3.24 (bs, 1 H, C(8)H), 4.18 (d, ^3J = 10.8 Hz, 1 H, C(8)H), 5.77 (s, 1H, C(3)H), 7.43 (s, 3 H, C(4')H, C(5')H and C(6')H), 7.53 (d, ^3J = 4.8 Hz, 1 H, C(3')H), 8.76 (s, 2 H, NH_2), 9.61 (s, 1 H, N(2)H^+). ^{13}C NMR (100.63 MHz, DMSO-d_6, ppm): δ = 22.84 and 22.91 (C6 and C7), 43.35 (C8), 52.87 (C5), 75.11 (C3), 127.40 and 127.53 (C5' and C6'), 129.90 (C3'), 130.74 (C4'), 132.59 (C2'), 134.31 (C1'), 154.89 (C1). MS [(ESI) m/z]: Calcd. for $[C_{12}H_{15}N_4Cl+H]^+$: 251.1058. Found $[M_{base}+H]^+$: 251.1057. Elemental analysis [$C_{12}H_{16}Cl_2N_4$ (287.19), %]: Calcd. C 50.19, H 5.62, N 19.51. Found C 49.43, H 5.61, N 19.77.

3-(4-Chlorophenyl)-5,6,7,8-tetrahydro-3H-[1,2,4]triazolo[1,2-a]pyridazin-1-amine hydrochloride ***5g***

With 4-chlorobenzaldehyde. Reaction time: 5 hours. Yield: 62 %.

Colourless crystals. M.r.: 184–194 °C (acetone).

TLC (m. ph. II): R_F = 0.69. MIR (cm^{-1}): $\tilde{\nu}$ = 1056 and 1088 (C-Cl), 1541 and 1596 (C=C), 1677 (C=N), 2849, 2915, 2950, and 2965 (CH_2), 3025 and 3039 (CH). ^{1}H NMR (400.20 MHz, DMSO-d_6, ppm): δ = 1.42–1.79 (m, 4 H, C(6)H_2 and C(7)H_2), 2.70 (t, ^3J = 11.0 Hz, 1 H, C(5)H), 2.97 (d, ^3J = 10.4 Hz, 1 H, C(5)H), 3.19 (t, ^3J = 12.0 Hz, 1 H, C(8)H), 4.14 (d, ^3J = 12.0 Hz, 1 H, C(8)H), 5.49 (s, 1 H, C(3)H), 7.47–7.52 (m, 4 H, arom.), 8.71 (s, 2 H, NH_2), 9.66 (s, 1 H, N(2)H^+). ^{13}C NMR (100.63 MHz, DMSO-d_6, ppm): δ = 22.62 and 22.75 (C6 and C7), 43.72 (C8), 52.19 (C5), 77.27 (C3), 128.51 (C3' and C5'), 128.94 (C2' and C6'), 133.74 (C4'), 136.11 (C1'), 154.64 (C1). MS [(ESI) m/z]: Calcd. for $[C_{12}H_{15}N_4Cl+H]^+$: 251.1058. Found $[M_{base}+H]^+$: 251.1063. Elemental analysis [$C_{12}H_{16}Cl_2N_4$ (287.19), %]: Calcd. C 50.19, H 5.62, N 19.51. Found C 50.14, H 5.58, N 19.13.

3-(2-Nitrophenyl)-5,6,7,8-tetrahydro-3H-[1,2,4]triazolo[1,2-a]pyridazin-1-amine hydrochloride ***5i***

With 2-nitrobenzaldehyde. Reaction time: 20.5 hours. Deviating from the general procedure, the obtained crystals were additionally washed with propan-2-ol. Yield: 34 %.

Light yellow crystals. M.r.: 218–226 °C (acetone/propan-2-ol).

TLC (m. ph. II): R_F = 0.66. MIR (cm^{-1}): $\tilde{\nu}$ = 1357 and 1529 (N=O), 1607 (C=C), 1662 (C=N), 2901 (CH_2), 2975 (CH). ^{1}H NMR (400.20 MHz, DMSO-d_6, ppm): δ = 1.40–1.83 (m, 4 H, C(6)H_2 and C(7)H_2), 2.85 (t, ^3J = 11 Hz, 1 H, C(5)H), 2.99 (d, ^3J = 10.4 Hz, 1 H, C(5)H), 3.23 (t, ^3J = 12.2 Hz, 1 H, C(8)H), 4.15 (d, ^3J = 12.0 Hz, 1 H, C(8)H), 6.13 (s, 1 H, C(3)H), 7.67–7.70 (m, 2 H, C(4')H and C(6')H), 7.83 (t, ^3J = 7.6 Hz, 1 H, C(5')H), 8.10 (d, ^3J = 8.0 Hz, 1 H, C(3')H), 8.70 (s, 2 H, NH_2), 9.73 (s, 1 H, N(2)H^+). ^{13}C NMR (100.63 MHz, DMSO-d_6, ppm): δ = 22.79 and 22.96 (C6 and C7), 43.23 (C8), 53.05 (C5), 74.06 (C3), 125.21 (C3'), 127.67 (C6'), 130.36 (C4'), 132.66 (C1'), 134.00 (C5'), 147.79 (C2'), 154.70 (C1). MS [(ESI) m/z]: Calcd. for $[C_{12}H_{15}N_5O_2+H]^+$: 262.1299. Found $[M_{base}+H]^+$: 262.1301. Elemental analysis [$C_{12}H_{16}ClN_5O_2$ (297.74), %]: Calcd. C 48.41, H 5.42, N 23.52. Found C 47.70, H 5.42, N 23.34.

3-(4-Nitrophenyl)-5,6,7,8-tetrahydro-3H-[1,2,4]triazolo[1,2-a]pyridazin-1-amine hydrochloride ***5j***

With 4-nitrobenzaldehyde. Reaction time: 20 hours. Deviating from the general procedure, the obtained crystals were additionally washed with propan-2-ol. Yield: 47 %.

Light yellow crystals. M.r.: 198–213 °C (acetone/propan-2-ol).

TLC (m. ph. II): R_F = 0.58. MIR (cm^{-1}): $\tilde{\nu}$ = 1347 and 1519 (N=O), 1610 (C=C), 1679 (C=N), 2849, 2957, and 2986 (CH_2), 3067 (CH). ^{1}H NMR (400.20 MHz, DMSO-d_6, ppm): δ = 1.44–1.83 (m, 4 H, C(6)H_2 and C(7)H_2), 2.79 (t, ^3J = 10.6 Hz, 1 H, C(5)H), 3.05 (d, ^3J = 10.0 Hz, 1 H, C(5)H), 3.23 (t, ^3J = 12.4 Hz, 1 H, C(8)H), 4.18 (d, ^3J = 11.6 Hz, 1 H, C(8)H), 5.72 (s, 1 H, C(3)H), 7.74 (d, ^3J = 8.4 Hz, 2 H, C(2')H and C(6')H), 8.30 (d, ^3J = 8.4 Hz, 2 H, C(3')H and C(5')H), 8.81 (s, 2 H, NH_2), 9.85 (s, 1 H, N(2)H^+). ^{13}C NMR (100.63 MHz, DMSO-d_6, ppm): δ = 22.68 and 22.81 (C6 and C7), 43.60 (C8), 52.55 (C5), 76.63 (C3), 123.66 (C3' and C5'), 128.20 (C2' and C6'), 144.67 (C1'), 147.86 (C4'), 154.52 (C1). MS [(ESI) m/z]: Calcd. for $[C_{12}H_{15}N_5O_2+H]^+$: 262.1299. Found $[M_{base}+H]^+$: 262.1305. Elemental analysis [$C_{12}H_{16}ClN_5O_2$ (297.74), %]: Calcd. C 48.41, H 5.42, N 23.52. Found C 47.94, H 5.37, N 22.94.

3-(4-Methoxyphenyl)-5,6,7,8-tetrahydro-3H-[1,2,4]triazolo[1,2-a]pyridazin-1-amine hydrochloride ***5k***

With 4-methoxybenzaldehyde. Reaction time: 5 hours. Yield: 57 %.

Beige crystals. M.r.: 188–203 °C (acetone).

TLC (m. ph. II): R_F = 0.71. MIR (cm^{-1}): $\tilde{\nu}$ = 1508, 1543, and 1600 (C=C), 1665 (C=N), 2832 (OCH_3), 2919 and 2950 (CH_2), 3031 (CH), 3226 and 3285 (NH). ^{1}H NMR (400.20 MHz, DMSO-d_6, ppm): δ = 1.43–1.77 (m, 4 H, C(6)H_2 and C(7)H_2), 2.63 (t, ^3J = 10.4 Hz, 1 H, C(5)H), 2.90 (d, ^3J = 9.6 Hz, 1 H, C(5)H), 3.17 (bs, 1 H, C(8)H), 3.77 (s, 3 H, OCH_3), 4.11 (d, ^3J = 10.8 Hz, 1 H, C(8)H), 5.34 (s, 1 H, C(3)H), 6.98 (d, ^3J = 8.8 Hz, 2 H, C(3')H and C(5')H), 7.38 (d, ^3J = 8.4 Hz, 2 H, C(2')H and C(6')H), 8.63 (s, 2 H, NH_2), 9.50 (s, 1 H, N(2)H^+). ^{13}C NMR (100.63 MHz, DMSO-d_6, ppm): δ = 22.56 and 22.70 (C6 and C7), 43.90 (C8), 51.75 (C5), 55.24 (OCH_3), 78.20 (C3), 113.87 (C3’ and C5’), 128.38 (C1’), 128.68 (C2’ and C6’), 154.89 (C1), 160.02 (C4’). MS [(ESI) m/z]: Calcd. for $[C_{13}H_{18}N_4O+H]^+$: 247.1553. Found $[M_{base}+H]^+$: 247.1559. Elemental analysis [$C_{13}H_{19}ClN_4O$ (282.77), %]: Calcd. C 55.22, H 6.77, N 19.81. Found C 54.87, H 6.62, N 19.23.

3.2.2.4. 3,3-Disubstituted 5,6,7,8-tetrahydro-3H-[1,2,4]triazolo[1,2-a]pyridazin-1-amine hydrochlorides **5r,t**

3,3-Dimethyl-5,6,7,8-tetrahydro-3H-[1,2,4]triazolo[1,2-a]pyridazin-1-amine hydrochloride ***5r***

A mixture of 0.5 mmol of hexahydropyridazine-1-carboximidamide hydrochloride **6b**, 10 mL of acetone, and 8 mg of *p*-toluenesulfonic acid monohydrate was refluxed at 100 °C bath temperatur. After the reaction was completed (TLC monitoring) the heating was ended (about 2 days). The crystals formed on cooling were aspirated off, washed with a small amount of acetone and dried. Yield: 68 %.

Colourless crystals. M.r.: 181–185 °C (acetone).

TLC (m. ph. II): R_F = 0.52. MIR (cm^{-1}): ṽ = 1538 and 1602 (C=C), 1665 (C=N), 2850, 2903 and 2978 (CH_2), 3125 and 3219 (NH). ^{1}H NMR (400.20 MHz, DMSO-d_6, ppm): δ = 1.32 (s, 6 H, both CH_3), 1.49 (bs, 2 H, $C(7)H_2$), 1.68 (t, ^3J = 4.8 Hz, 2 H, $C(6)H_2$), 2.69 (bs, 2 H, $C(5)H_2$), 3.62 (bs, 2 H, $C(8)H_2$), 8.52 (s, 2 H, NH_2), 9.09 (s, 1 H, N(2)H$^+$). ^{13}C NMR (100.63 MHz, DMSO-d_6, ppm): δ = 22.61 and 22.87 (C6 and C7), 43.97 (C8), 46.63 (C5), 77.84 (C3), 154.70 (C1). MS [(ESI) m/z]: Calcd. for $[C_8H_{16}N_4+H]^+$: 169.1448. Found $[M_{base}+H]^+$: 169.1455. Elemental analysis [$C_8H_{17}ClN_4$ (204.70), %]: Calcd. C 46.94, H 8.37, N 27.37. Found C 45.90, H 7.97, N 25.85.

3-*Methyl-3-phenyl-5,6,7,8-tetrahydro-3H-[1,2,4]triazolo[1,2-a]pyridazin-1-amine hydrochloride* ***5t***

A mixture of 0.5 mmol of hexahydropyridazine-1-carboximidamide hydrochloride **6b**, 2 mmol of acetophenone, and 20 mg of *p*-toluenesulfonic acid monohydrate was heated at 150 °C in a metal bath for 3 days. Then the cooled melt was suspended in acetone and the formed solid was filtered off under reduced pressure. The filtrate was reduced to dryness and the resulting residue was digested with diethyl ether and subsequently treated with tetrahydrofuran. The crystalline solid thus formed was aspirated off, washed two times with a small amount of acetonitrile and dried. Yield: 2 %.

Beige crystals. M.r.: 220–224 °C (tetrahydrofuran/acetonitrile).

TLC (m. ph. II): R_F = 0.76. ^{1}H NMR (400.20 MHz, DMSO-d_6, ppm): δ = 1.44–1.79 (m, 4 H, $C(6)H_2$ and $C(7)H_2$), 1.63 (s, 3 H, CH_3), 2.58 (s, 1 H, C(5)H), 2.75 (bs, 1 H, C(5)H), 3.33 (s, 1 H, C(8)H), 3.79 (bs, 1 H, C(8)H), 7.35–7.43 (m, 3 H, C(3’)H, C(4’)H and C(5’)H), 7.53 (d, ^3J = 7.2 Hz, 2 H, C(2’)H and C(6’)H), 8.42 (s, 2 H, NH_2), 9.83 (s, 1 H, N(2)H$^+$). ^{13}C NMR (100.63 MHz, DMSO-d_6, ppm): δ = 22.18 (CH_3), 22.70 and 22.96 (C6 and C7), 43.61 (C8), 47.41 (C5), 81.13 (C3), 125.52 (C2’ and C6’), 128.24 (C3’, C4’, and C5’), 141.98 (C1’), 154.46 (C1).

3.2.2.5. [1,2,4]Triazolo[1,2-a]pyridazin-1-amine tosylates **5s,u**

3-Ethyl-3-methyl-5,6,7,8-tetrahydro-3H-[1,2,4]triazolo[1,2-a]pyridazin-1-amine tosylate **5s**

A mixture of 1 mmol of hexahydropyridazine-1-carboximidamide hydrochloride **6b**, 10 mL of ethyl methyl ketone, and 66 mg of *p*-toluenesulfonic acid monohydrate was refluxed at 100 °C bath temperature for twelve days. Subsequently the excess of ketone was evaporated at room temperature. The remained product was solved in some propan-2-ol and to the solution charcoal was added which was filtered off after few minutes. The filtrate was concentrated to dryness and the residue was digested firstly with a hexane/acetone mixture (same volume parts) and secondly with cyclohexane. A viscous, but TLC clean product remained which did not crystallize even after long time storage.

TLC (m. ph. II): R_F = 0.65. ^{1}H NMR (400.20 MHz, DMSO-d_6, ppm): δ = 0.85 (t, ^3J = 7.4 Hz, 3 H, $C(11)H_3$), 1.29 (s, 3 H, $C(12)H_3$), 1.38–1.44 (m, 2 H, $C(7)H_2$), 1.58–1.60 (m, 3 H, $C(10)H_2$ and C(6)H), 1.74–1.75 (m, 1 H, C(6)H), 2.29 (s, 3 H, CH_3), 2.57–2.63 (m, 1 H, C(5)H), 2.77–2.79 (m, 1 H, C(5)H), 3.22–3.28 (m, 1 H, C(8)H), 3.79–3.82 (m, 1 H, C(8)H), 7.12 (d, ^3J = 8.0 Hz, 2 H, C(3’)H and C(5’)H), 7.48 (d, ^3J = 8.0 Hz, 2 H, C(2’)H and C(6’)H), 8.17 (s, 2 H, NH_2), 8.96 (s, 1 H, N(2)H$^+$). ^{13}C NMR (100.63 MHz, DMSO-d_6, ppm): δ = 8.02 (C11), 18.92 (C12), 20.79 (CH_3), 22.61 and 23.01 (C6 and C7), 30.18 (C10), 43.80 (C8), 46.74 (C5), 80.38 (C3), 125.50 (C2’ and C6’), 128.08 (C3’ and C5’), 137.66 (C4’), 145.68 (C1’), 154.36 (C1).

3,3-Diethyl-5,6,7,8-tetrahydro-3H-[1,2,4]triazolo[1,2-a]pyridazin-1-amine tosylate ***5u***

A mixture of 0.5 mmol of hexahydropyridazine-1-carboximidamide hydrochloride **6b**, 10 mL of diethyl ketone, and 8 mg of *p*-toluenesulfonic acid monohydrate was refluxed at 120 °C bath temperature for nine days. At the sixth day an extra amount (50 mg) of *p*-toluenesulfonic acid monohydrate was added. The TLC monitoring showed the complete conversion of **6b** within the above given time range. After cooling the formed sticky brown product was removed and discarded. Then, the excess of diethyl ketone was evaporated from the solution. The remaining residue was digested at first with hexane and then with diethyl ether. Thereafter to the residue so treated some acetone was added to give a brown viscous but pure (TLC control) precipitate.

TLC (m. ph. II): R_F = 0.75. ^{1}H NMR (400.20 MHz, DMSO-d_6, ppm): δ = 0.86 (t, ^3J = 7.4 Hz, 6 H, $C(11)H_3$ and $C(13)H_3$), 1.49–1.51 (m, 2 H, $C(7)H_2$), 1.61–1.66 (m, 6 H, $C(6)H_2$, $C(10)H_2$ and $C(12)H_2$), 2.29 (s, 3 H, CH_3), 2.72 (t, ^3J = 5.2 Hz, 2 H, $C(5)H_2$), 3.52 (bs, 2 H, $C(8)H_2$), 7.13 (d, ^3J = 7.6 Hz, 2 H, C(3’)H and C(5’)H), 7.49 (d, ^3J = 8.4 Hz, 2 H, C(2’)H and C(6’)H), 8.14 (s, 2 H, NH_2), 9.12 (s, 1 H, N(2)H$^+$). ^{13}C NMR (100.63 MHz, DMSO-d_6, ppm): δ = 7.87 (C11 and C13), 20.77 (CH_3), 22.64 (C7), 23.13 (C6), 25.58 (C10 and C12), 43.96 (C8), 46.29 (C5), 82.66 (C3), 125.45 (C2’ and C6’), 128.12 (C3’ and C5’), 137.83 (C4’), 145.36 (C1’), 154.62 (C1). MS [(ESI) m/z]: Calcd. for $[C_{10}H_{20}N_4+H]^+$: 197,1761. Found $[M_{base}+H]^+$: 197.1763.

3.2.3. [1,2,4]Triazolo[1,2-a]pyridazin-1-amines 5 from 3-methylsulfanyl-1H-[1,2,4]triazolo[1,2-a]pyridazine hydroiodides 4

3.2.3.1. [1,2,4]Triazolo[1,2-a]pyridazin-1-amine hydroiodides **5e,l**

Into a solution of 0.33 mmol **4c** (Schulz et al. 2017) in 2 mL of ethanol dry ammonia (**5e**) and methylamine (**5l**), respectively, was bubbled for 3 minutes. The plugged reaction flask was allowed to stand at room temperature for six (**5e**) and five (**5l**) weeks, respectively (TLC reaction control). Following the solvent was removed and the residue was treated with a little propan-2-ol (**5e**) and propan-2-ol/diethyl ether (v/v, 2:1) (**5l**), respectively. The formed crystals were aspirated off, washed with a minimum of ethanol and dried under reduced pressure.

In this way the following compounds were obtained:

3-(2-Chlorophenyl)-5,6,7,8-tetrahydro-3H-[1,2,4]triazolo[1,2-a]pyridazin-1-amine hydroiodide ***5e***

Yield: 14 %.

Colourless crystals. M.r.: 215–217 °C (propan-2-ol).

TLC (m. ph. I): R_F = 0.34. MIR (KBr disc, cm^{-1}): ṽ = 1036 (Ar–Cl), 1585, 1661 (C=N), 2835, 2856, 2925, 2952 (CH); 3109, 3247 (NH). ^{1}H NMR (400.20 MHz, $CDCl_3$, ppm): δ = 1.71–1.89 (m, 4 H, $C(6)H_2$ and $C(7)H_2$), 2.92–3.40, 4.40 (m and d, 4 H, $C(5)H_2$ and $C(8)H_2$), 5.79 (s, 1 H, C(3)H), 7.32–7.56 (m, 4 H, arom. H), 7.84 (s, 2 H, NH_2), 8.22 (s, 1 H, N(2)H$^+$). ^{13}C NMR (100.63 MHz, $CDCl_3$, ppm): δ = 23.16, 23.45 (C6 and C7), 45.26 (C8), 53.54 (C5), 76.63 (C3),127.50, 127.89, 130.18, 130.96, 132.62, 133.44 (all arom. C), 154.45 (C1). MS (EI, 70 eV, 215 °C) m/z (%): 248.8 (17) [$M^{+\cdot}_{base}$], 139.0 (100) [$M^{+\cdot}_{base}$ – $^{\cdot}C_6H_4Cl$], 127.7 (26), 126.8 (14), 88.9 (12), 85.0 (19) [$C_4H_9N_2^+$], 56.3 (11), 55.2 (10), 41.0 (13), 31.9 (19), 30.0 (14), 27.9 (84). Elemental analysis [$C_{12}H_{16}ClIN_4$ (378.7), %]: Calcd. C 38.07, H 4.26, N 14.80. Found C 37.93, H 4.28, N 14.27.

3-(2-Chlorophenyl)-N-methyl-5,6,7,8-tetrahydro-3H-[1,2,4]triazolo[1,2-a]pyridazin-1-amine hydroiodide ***5l***

Yield: 51 %.

Colourless crystals. M.r.: 175–178 °C (propan-2-ol/diethyl ether).

TLC (m. ph. I): R_F = 0.31. MIR (KBr disc, cm^{-1}): ṽ = 1547, 1672 (C=N); 2850, 2948 (CH); 3120 (NH). ^{1}H NMR (200.11 MHz, $CDCl_3$, ppm): 1.71–1.85 (m, 4 H, $C(6)H_2$ and $C(7)H_2$), 2.86–3.19 (m, 2 H,$C(5)H_2$), 3.19 (3 H, N–CH_3), 4.47 (d, 2 H, $C(8)H_2$), 5.81 (s, 1 H, C(3)H), 7.28–7,51 (m, 4 H, arom. H), 7.68–8.15 (m, 2 H, C(1)–NH–CH_3 and N(2)H). ^{13}C NMR (50.32 MHz, $CDCl_3$, ppm) δ = 23.18, 23.20 (C6 and C7), 31.20 (CH_3), 45.67 (C5), 53.37 (C8), 75.87 (C3); 127.24, 128.20, 130.11, 130.8 4, 132.86, 133.70 (all arom. C); 155.18 (C(1)=N). MS (EI, 70 eV, 345 °C) m/z (%): 263.9 (42) [$M^{+\cdot}_{base}$], 208.8 (13), 206.8 (29), 178.8 (18),153.7 (19), 152.5 (100) [$M^{+\cdot}_{base}$ – $^{\cdot}C_6H_4Cl$], 151.1 (13), 137.9 (13), 127.8 (63), 126.9 (35),125.0 (22), 101.7 (13), 88.9 (15), 85.0 (13) [$C_4H_9N_2^+$], 57.3 (16), 56.3 (12), 55.2 (16), 41.9 (21), 41.0 (21), 30.0 (13), 28.0 (20). Elemental analysis [$C_{13}H_{18}ClIN_4$ (392.7), %]: Calcd. C 39.76, H 4.62, N 14.27. Found C 39.65, H 4.98, N 14.28.

3.2.3.2. [1,2,4]Triazolo[1,2-a]pyridazin-1-amine hydroiodides **5m,o**

To a solution of 0.33 mmol of 3-methylsulfanyl-1-phenyl-5,6,7,8-tetrahydro-1*H*-[1,2,4]triazolo[1,2-*a*]pyridazine hydroiodide **4b** (Schulz et al. 2017) in 2 mL of dichloromethane 0.66 mmol of the related nitrogen nucleophile was added and the mixture was allowed to stand for 15 days. Subsequently the solvent was removed and the residue was taken up with a little propan-2-ol. Then some diethyl ether was added whereupon crystals began to form. After standing about 4 hours the crystals were aspirated off, washed with a small amount of propan-2-ol and dried.

In this way the following compounds were obtained:

N-Propyl-3-phenyl-5,6,7,8-tetrahydro-3H-[1,2,4]triazolo[1,2-a]pyridazin-1-amine hydroiodide **5m**

With propylamine. Yield: 12 %.

Colourless crystals. M.r.: 191.5 – 194.5° C (propan-2-ol/diethyl ether).

TLC (m. ph. I): R_F = 0.40. MIR (KBr disc, cm^{-1}): ṽ = 1434, 1456, 1470 (CH), 1552, 1667 (C=N), 2845, 2869, 2930, 2957 (CH), 3041 (arom. H), 3222 (NH), 3450 (NH). ^{1}H NMR (200.11 MHz, $CDCl_3$, ppm): δ = 0.95 (t, 3 H, $C(\gamma)H_3$), 1.65-1.86 (m, 6 H, $C(6)H_2$/ $C(7)H_2$/ $C(\beta)H_2$), 2.61-2.71 (m, 1 H, C(5)H), 2.88-2.98 (m, 1 H, C(α)H), 3.21-3.33 (m, 1 H, C(α)H), 3.46-3.54 (m, 2 H, $C(8)H_2$), 4.47-4.58 (m, 1 H, C(5)H), 5.30 (s, 1 H, C(3)H), 7.38 (s, 3 H, arom. C(2)H, C(4)H, and C(6)H), 7.47-7.60 (m, 2 H, arom. C(3)H and C(5)H), 8.40 (s, 1 H, NH). ^{13}C NMR (50.32 MHz, $CDCl_3$, ppm): δ = 11.29 (Cγ), 22.65 (C7), 22.96 (C6), 23.12 (Cβ), 45.96 (C8), 46.18 (Cα), 52.34 (C5), 79.72 (C3), 127.75 (arom. C4), 128.72 (2 C. arom. C2 and C6), 129.78 (2 C, arom. C3 and C5), 135.18 (arom. C1), 154.69 (C(1)=N). Elemental analysis [$C_{15}H_{23}IN_4$ (386.3), %]: Calcd. C 46.64, H 6.00, N 14.50. Found C 48.73, H 6.17, N 15.17.

3-Phenyl-1-(pyrrolidin-1-yl)-5,6,7,8-tetrahydro-3H-[1,2,4]triazolo[1,2-a]pyridazine hydroidide **5o**

With pyrrolidine. Yield: 59 %.

Colourless crystals. M.r.: 180–182.5° C (propan-2-ol).

TLC (m. ph. I): R_F = 0.41. MIR (KBr disc, cm^{-1}): ṽ = 1433, 1446, 1481 (CH); 1640 (C=N); 2780, 2892, 2949, 2998 (CH); 3064 (arom. H); 3432 (NH). ^{1}H NMR (200.11 MHz, $CDCl_3$, ppm): δ = 1.64 (s), 1.71-2.02 (m), 2.05-2.13 (m): 8 H, $C(6)H_2$/ $C(7)H_2$/ $C(\beta)H_2$/ $C(\gamma)H_2$, 2.85-2.87 (m), 2.98 (m): 2 H, $C(8)H_2$, 3.41 (t, 1 H, C(5)H), 3.62-3.70 (m, 2 H, $C(\delta)H_2$), 3.95-4.15 (m, 2 H, $C(\alpha)H_2$), 5.50 (s, 1 H, C(3)H), 7.37-7.40 (m, 3 H, arom. C(2)H, C(4)H and C(6)H), 7.61-7.64 (m, 2 H, arom. C(3)H and C(5)H), 8.72 (s, 1 H, NH). ^{13}C NMR (50.32 MHz, $CDCl_3$, ppm): δ = 23.10 (C6), 24.09 (C7), 25.46 (2 C, Cβ/ Cγ), 47.80 (C8), 51.52 (2 C, Cα/ Cδ), 52.50 (C5), 79.13 (C3), 128.15 (arom. C4), 128.70 (2 C, arom. C2 and C6), 129.79 (2 C, arom. C3 and C5), 135.37 (arom. C1), 154.14 (C(1)=N). MS (EI, 70 eV, 345 °C) m/z (%): 269.0 (55) [$M^{+\cdot}_{base}$], 193.0 (100) [$M^{+\cdot}_{base}$ – $^{\cdot}C_6H_5$], 184.9 (17), 173.0 (36), 157.9 (18), 127.8 (37), 126.9 (16), 103.6 (17), 102.7 (17), 91.0 (17), 55.2 (22), 41.0 (20), 28.0 (13). Elemental analysis [$C_{16}H_{23}IN_4$ (398.3), %]: Calcd. C 48.25, H 5.82, N 14.07. Found C 47.90, H 5.63, N 13.91.

3.2.3.3. 1-(Morpholin-4-yl)-3-phenyl-5,6,7,8-tetrahydro-3*H*-[1,2,4]triazolo[1,2-*a*]-pyridazine hydroiodide **5p**

To a solution of 0.33 mmol of 3-methylsulfanyl-1-phenyl-5,6,7,8-tetrahydro-1*H*-[1,2,4]triazolo[1,2-*a*]pyridazine hydroiodide **4b** (Schulz et al. 2017) in 2 mL of ethanol 0.66 mmol of morpholine were added and the closed reaction vessel was allowed to stand at room temperature for three weeks (TLC monitoring). The solvent and the excess of morpholine were removed in an air flow and the residue was treated with a little propan-2-ol. The crystals formed were aspirated off, washed with a small amount of cold propan-2-ol and dried under reduced pressure. Yield: 18 %.

Colourless crystals. M.r.: 210–214 °C (propan-2-ol).

TLC (m. ph. I): R_F = 0.44. MIR (KBr disc, cm^{-1}): $\tilde{\nu}$ = 1640 (C=N); 2735, 2813, 2583, 2922 (CH); 2993 (Ar–H). ^{1}H NMR (200.11 MHz, DMSO-d_6, ppm): δ = 1.60–1.81 (m, 4 H, C(6)H_2 u. C(7)H_2), 2.78–3.09 (m, 2H, C(8)H_2), 3.33–3.72 (m, 8 H, morpholin-4-yl), 4.06 (d, 2 H, C(5)H_2), 5.51 (s, 1 H, C(3)H), 7.44–7.57 (m, 5 H, arom. H), 9.71 (s, 1 H, N(2)H). ^{13}C NMR (50.32 MHz, DMSO-d_6, ppm): δ = 22.97, 23.22 (C6 and C7), 48.06 (C3 and C5 of morpholin-4-yl), 48.29 (C5), 52.21 (C8), 64.16 (C2 and C6 of morpholin-4-yl), 78.14 (C3), 127.43, 128.54, 129.50, 136.64 (all arom. C), 155.75 (C1). MS (EI, 70 eV, 180 °C) m/z (%): 286.9 (37), 285.0 (41) [both $M^{+\cdot}_{base}$], 210.0 (13), 208.9 (100) [$M^{+\cdot}_{base}$ – $^{\cdot}C_6H_5$], 173.0 (49), 144.7 (19), 143.8 (16), 127.8 (27), 126.8 (14), 116.6 (26), 103.6 (15), 90.9 (16), 89.9 (11), 77.3 (12), 55.2 (15), 42.0 (15), 41.0 (18), 28.0 (25). Elemental analysis [$C_{16}H_{23}IN_4O$ (414.3), %]: Calcd. C 46.39, H 5.60, N 13.52. Found C 46.05, H 5.21, N 14.32.

3.2.3.4. [1,2,4]Triazolo[1,2-a]pyridazin-1-amine hydroiodides **5v,w**

A suspension of 0.25 mmol of 1,1-dimethyl-3-methylsulfanyl-[1,2,4]triazolo[1,2-*a*]-pyridazine hydroiodide **4d** (Schulz et al. 2017) in 100 µL of the respective amine was stand alone at room temperature until des reaction was completed (TLC monitoring). Following the batch was reduced to dryness in an air flow. After addition of some acetic acid to the residue it was reduced to dryness in an air flow again. The resulting residue was dissolved in a little propan-2-ol and than diethyl ether was dropwise added. The crystals which formed within some hours were isolated by centrifugation and subsequent decanting, and dried under reduced pressure.

In this way the following compounds were obtained:

3,3-Dimethyl-N-propyl-5,6,7,8-tetrahydro-3H-[1,2,4]triazolo[1,2-a]pyridazin-1-amine hydroiodide ***5v***

With propylamine. Reaction time: 4 days. Yield: < 1 %.

Colourless crystals (propan-2-ol/diethyl ether).

TLC (m. ph. I): R_F = 0.68. MIR (cm^{-1}): $\tilde{\nu}$ = 1553 (NH); 1648 (C=N); 2959 (CH); 3129 (NH). ^{1}H NMR (400.20 MHz, $CDCl_3$, ppm): δ = 0.99 (t, ^3J = 7.2 Hz, 3 H, C(γ)H_3), 1.53 (s, 6 H, C(3)$CH_3)_2$), 1.65 (m, 2 H, C(7)H_2), 1.74 (m, ^3J = 7.2 Hz, 2 H, C(β)H_2), 1.81 (m, ^3J = 4.8 Hz, 2 H, C(6)H_2), 2.72 (t, ^3J = 4.8 Hz, 2 H, C(5)H_2), 3.47 (t, ^3J = 7.2 Hz, C(α)H_2). ^{13}C NMR (100.63 MHz, $CDCl_3$, ppm): δ =11.2 (Cγ), 22.8 (Cβ), 23.2 (C6 and C7), 45.9 (C8 and Cα), 47.2 (C5), 79.2 (C3),154.4 (C1).

N-Butyl-3,3-dimethyl-5,6,7,8-tetrahydro-3H-[1,2,4]triazolo[1,2-a]pyridazin-1-amine hydroiodide ***5w***

With butylamine. Reaction time: 4 days. Yield: < 1 %.

Colourless crystals (propan-2-ol/diethyl ether).

TLC (m. ph. I): R_F = 0.75. MIR (cm^{-1}): $\tilde{\nu}$ = 1553 (NH), 1649 (C=N), 2870, 2954 (CH), 3125 (NH). ^{1}H NMR (400.20 MHz, $CDCl_3$, ppm): δ = 0.94 (t, ^3J = 7.2 Hz, 3 H, C(δ)H_3); 1.41 (m, 2 H, C(γ)H_2), 1.53 (s, 6 H, C(3)$(CH_3)_2$), 1.67 (m, 2 H, C(β)H_2), 1.68 (m, 2 H, C(7)H_2), 1.81 (m, 2 H, C(6)H_2), 1.72 (t, ^3J = 4.8 Hz, 2 H, C(5)H2), 3.51 (t, ^3J =7.2 Hz, 2 H, C(α)H_2). ^{13}C NMR (100.63 MHz, $CDCl_3$, ppm): δ = 13.9 (Cδ), 19.8 (Cγ), 23.2 (C6 and C7), 31.4 (Cβ), 44.4 (Cα), 45.9 (C8), 47.2 (C5), 79.2 (C3), 154.4 (C1).

3.2.4. [1,2,4]Triazolo[1,2-a]pyridazin-1-imine hydrohalides **7**

3.2.4.1. 5,6,7,8-Tetrahydro-1H-[1,2,4]triazolo[1,2-a]pyridazin-1-imine hydrochloride **7a**

A mixture of 6 mmol of hexahydropyridazine-1-carboximidamide hydrochloride **6b** and 12 mL of anhydrous formic acid was refluxed for 2 h. After the reaction was completed (TLC control) methanol was added until the acid was neutralized. Following the solution was concentrated under reduced pressure. The formed crystals were aspirated off, washed three times with each 10 mL of anhydrous diethyl ether and dried at 195 °C under reduced pressure. Yield: 82%.

Colourless crystals. M.r.: 257–262 °C (diethyl ether).

TLC (m. P. I): R_F = 0.11. MIR (cm^{-1}): $\tilde{\nu}$ = 1459; 1476, 1529, and 1591 (NH_2); 1656 (C=N); 2856 (aliph. CH); 3012 and 3090 (olefin. CH), 3126 and 3313 (NH). ^{1}H NMR (400.20 MHz, DMSO-d_6, ppm): δ = 1.90–2.01 (m, 4 H, C(6)H_2 and C(7)H_2), 4.10 (t, ^3J = 5.6 Hz, 2 H, C(8)H_2), 4.22 (t, ^3J = 5.6 Hz, 2 H, C(5)H_2), 8.21 (s, 2 H, NH_2^+), 8.69 (s, 1 H, C(3)H). ^{13}C NMR (100.63 MHz, DMSO-d_6, ppm): δ = 19.24 and 19.26 (C6 and C7), 44.97 (C8), 46.70 (C5), 147.92 (C3), 157.73 (C1). MS [(ESI) m/z]: Calcd. for [$C_6H_{10}N_4$+H]$^+$: 139.0978. Found [M_{base}+H]$^+$: 139.0984. Elemental analysis [$C_6H_{10}ClN_4$ (139.09), %]: Calcd. C 41.27, H 6.35, N 32.08. Found C 37.28, H 6.82, N 29.30.

3.2.4.2. N-Butyl-5,6,7,8-tetrahydro-1H-[1,2,4]triazolo[1,2-a]pyridazin-1-imine hydroiodide **7b**

A suspension of 0.25 mmol of 3-methylsulfanyl-[1,2,4]triazolo[1,2-*a*]pyridazine hydroiodide **4a** (Schulz et al. 2017) in 100 µL of butylamine was stand alone at room temperature for 39 days. Following the batch was reduced to dryness in an air flow. After addition of some acetic acid to the residue it was reduced to dryness in an air flow again. The resulting residue was solved in a little propan-2-ol and than diethyl ether was dropwise added. The crystals, which formed within some hours, were isolated by centrifugation and subsequent decanting, and dried under reduced pressure. Yield: < 1%.

Colourless crystals (propan-2-ol/diethyl ether).

TLC (m. ph. I): R_F = 0.38. MIR (cm^{-1}): $\tilde{\nu}$ = 1628 (C=N), 2870, 2929 and 2955 (CH), 3097 and 3210 (NH). ^{1}H NMR (400.20 MHz, $CDCl_3$, ppm): δ = 0.94 (t, ^3J = 7.6 Hz, 3 H, C(δ)H_3), 1.40 (m, ^3J = 7,6 Hz, 2 H, C(γ)H_2), 1.74 (m, ^3J = 7.6 Hz, 2 H, C(β)H_2), 2.13 (m, 2 H, C(7)H_2), 2.22 (m, 2 H, C(6)H_2), 3.53 (m, 2 H, C(α)H_2), 4.27 (t, ^3J = 6.0 Hz, 2 H, C(8)H_2), 4.65 (t, ^3J = 6.0, 2 H, C(8)H_2), 8.06 (s, 1 H, C(3)H), 8.45 (bs, 1 H, NH). ^{13}C NMR (100.63 MHz, $CDCl_3$, ppm): δ = 13.7 (Cδ), 19.9, 20.0, and 20.3 (Cγ, C6, and C7), 31.4 (Cβ), 43.0 (Cα), 47.6 (C5), 48.4 (C8), 147.2 (C3), 158.5 (C1).

3.2.4.3. [1,2,4]Triazolo[1,2-a]pyridazin-1-imine hydroiodides **7c,d**

A mixture of 0.3 mmol of hexahydropyridazine-1-carboximidamide hydroiodide **6a** and 4 mL of the respective aldehyde was heated at 100 °C for 6 hours (heating phase: 1 hour) in a pressure vessel under argon atmosphere. After cooling down the closed vessel overnight the excess of aldehyde was removed. The resiude was treated portionwise with hexane (hexane phase was discarded each) until the sticky product solidified. The further respective work-up is described below.

In this way the following compounds were obtained:

3-Ethyl-5,6,7,8-tetrahydro-1H-[1,2,4]triazolo[1,2-a]pyridazin-1-imine hydroiodide ***7c***

With propionaldehyde. Work-up: the solid was dissolved in a sufficient amount of dichloromethane. Some silica gel was added to the solution, which was filtered off after a few minutes. The filtrate was concentrated to dryness. The remaining solid was washed with a little dichloromethane, recrystallized from methanol and dried at 75 °C under reduced pressure. Yield: 43 %.

Colourless crystal R_F = 0.29. HPLC (m. ph. IX): RP-18e, t_0 = 2.42, t_R = 4.72, *k'* = 0.95. MIR (cm^{-1}): $\tilde{\nu}$ = 1535, 1589 (NH), 1661 (C=N), 2964, 2986 (CH_2), 3097, 3230, 3321 (NH). ^{1}H NMR (400.20 MHz, DMSO-d_6, ppm): δ = 1.17–1.24 (t, 3 H, CH_3), 1.88–1.99 (m, 4 H, C(6)H_2 and C(7)H_2), 2.69–2.72 (q, 2 H, CH_2), 3.94–3.96 (t, 2 H, C(5)H_2), 4.12–4.14 (t, 2 H, C(8)H_2), 7.97 (s, 2 H, =NH_2^+). ^{13}C NMR (100.63 MHz, DMSO-d_6, ppm): δ = 9.91 (CH_3), 18.46 (-CH_2-), 19.08, 19.26 (C6 and C7), 44.70 (C8), 45.17 (C5), 157.01, 161.12 ((C1)=NH). MS [(ESI) m/z]: Calced. for [$C_8H_{15}N_4$]$^+$: 167.1291. Found [M_{base}]$^+$: 167.1283.

3-Propyl-5,6,7,8-tetrahydro-1H-[1,2,4]triazolo[1,2-a]pyridazin-1-imine hydroiodide ***7d***

With butyraldehde. Work-up: the solid was taken up in sufficient dichloromethane. Some silica gel was added to the solution, which was filtered off after a few minutes. The filtrate was evaporated to dryness and the residue was taken up in ethanol. Following diethyl ether was added dropwise until an opalescence occurs. After 3 days the formed crystals were aspirated off, washed with propan-2-ol/diethyl ether (1 : 3, volume parts) an dried at 75 °C under reduced pressure. Yield: 14 %.

Colourless crystals. M.r.: 204–212 °C (ethanol/diethyl ether)

TLC (m. ph. I): R_F = 0.29. HPLC (m. ph. IX): RP-18e, t_0 = 4.96; t_R = 5.04; *k'* = 0.02. MIR (cm^{-1}): $\tilde{\nu}$ = 1508, 1529, 1560, 1589 (NH), 1656 (C=N); 2868, 2959, 2986 (CH); 3136, 3285 (NH). ^{1}H NMR (400.20 MHz, $CDCl_3$, ppm): δ = 1.14–1.10 (t, 3 H, -CH_3), 1.77–1.88 (q, 2 H, CH_2), 2.13–2.24 (m, 4 H, C(6)H_2 and C(7)H_2), 2.63–2.70 (t, 2 H, CH_2), 4.14–4.20 (t, 2 H, C(5)H_2), 4.59–4.65 (t, 2 H, C(8)H_2) 6.89 (s, 2 H, =NH_2^+). ^{13}C NMR (100.63 MHz, $CDCl_3$, ppm): δ = 13.93 (CH_3), 19.87, 20.31 (C6 and C7), 28.14, 29.93 (CH_2), 46.38 (C8), 48.58 (C5), 157.51, 161.64 ((C1)=NH). MS [(ESI) m/z]: Calcd. for [$C_9H_{17}N_4$]$^+$: 181.1448. Found [M_{base}]$^+$: 181.1451.

3.2.4.4. 3-Phenyl-5,6,7,8-tetrahydro-1H-[1,2,4]triazolo[1,2-a]pyridazin-1-imine hydrochloride **7e**

Method 1 - A mixture of 0.3 mmol of hexahydropyridazine-1-carboximidamide hydroiodide **6a** and 4 mL of benzaldehyde was heated at 100 °C for 6 hours (heating phase: 1 hour) in a pressure vessel under argon atmosphere. After cooling down the closed vessel overnight the excess of aldehyde was evaporated. The r was dissolved in dichloromethane. The solution was passed through a filter and the filtrate was concentrated to dryness. The residue was dissolved in a methanol/water mixture (1 : 5, volume parts) and small amounts of sodium hydroxide was added until pH 10 was reached. The solid was aspirated off using a sintered glass filter, washed with water and than dilute hydrochloric acid was allowed to pass through the residue. The filter cake obtained was recrystallized from a methanol/diethyl ether mixture (equal volume parts). The formed crystals were aspirated off, washed and dried at 75 °C under reduced pressure. Yield: 10%.

Method 2 - A mixture of 0.5 mmol of hexahydropyridazine-1-carboximidamide hydrochloride **6b,** 1.5 mmol of benzaldehyde and 3 mg of *p*-toluenesulfonic acid monohydrate was heated at 100 °C (metal bath) for 2 hours. Then the cooled melt was treated with acetone and the crystals formed (compound **5b**) were aspirated off. The filtrate was reduced to dryness and after addition of a small amount of acetone to the residue the crystals formed (second fraction of **5b**) were aspirated off again. By repeating the last mentioned procedure the compound **7e** (the didehydro product of **5b**) crystalized, which was aspirated off and dried. Yield: 4 %.

Colourless crystals. M.r.: 229–233 °C (propan-2-ol).

TLC (m. ph. II): R_F = 0.24. MIR (cm^{-1}): $\tilde{\nu}$ = 1593, 1672 (C=N), 3119, 3240, and 3258 (NH). ^{1}H NMR (400.20 MHz, DMSO-d_6, ppm): δ = 1.97–2.03 (m, 4 H, C(6)H_2 and C(7)H_2), 4.08 (t, ^3J = 5.6 Hz, 2 H, C(5)H_2), 4.30 (t, ^3J = 5.4 Hz, 2 H, C(8)H_2), 7.62–7.72 (m, 3 H, C(3')H, C(4')H and C(5')H), 7.82 (d, ^3J = 7.2 Hz, 2 H, C(2')H and C(6')H), 8.11 (s, 2 H, NH_2^+). ^{13}C NMR (100.63 MHz, DMSO-d_6, ppm): δ = 18.94 (C6), 19.55 (C7), 45.16 (C5), 47.93 (C8), 124.74 (C1'), 129.09 and 129.22 (C2', C3', C5' and C6'), 132.24 (C4'), 156.93 (C1 and C3). MS [(ESI) m/z]: Calcd. for [$C_{12}H_{14}N_4$+H]$^+$: 215.1291. Found: [M_{base}+H]$^+$: 215.1287.

3.2.4.5. 3-Phenyl-5,6,7,8-tetrahydro-3H-[1,2,4]triazolo[1,2-a]pyridazin-1-imine hydroiodide **7f**

Method 1 - Into a solution of 0.33 mmol of **4b** (Schulz et al. 2017) in 2 mL of ethanol dry ammonia was bubbled for 3 minutes. The plugged reaction flask was allowed to stand at room temperature for six weeks. Thereafter the reaction was reduced to dryness. Treating the residue with a little cold propan-2-ol resulted in the formation of crystals, which were aspirated off, washed with a minimum of ethanol and dried under reduced pressure. Yield: 16 %.

Method 2 - A mixture of 0.5 mmol of hexahydropyridazine-1-carboximidamide hydroiodide **6a,** 1.5 mmol of benzaldehyde and 3 mg of *p*-toluenesulfonic acid monohydrate was heated at 150–155 °C (metal bath) for 3 hours. Then the cooled melt was crushed and suspended in a little acetone. The solvent was removed in an air stream. To the residue some propan-2-ol was given whereby **7f** crystallized. The product was aspirated off and dried. Yield: 15 %.

Colourless crystals. M.r.: 260 – 264 °C (propan-2-ol).

TLC (m. ph. I): R_F = 0.44. MIR (cm^{-1}): $\tilde{\nu}$ = 1590, 1674 (C=N), 2940 and 2959 (CH$_2$), 3115, 3245, and 3267 (NH). ^{1}H NMR (400.20 MHz, DMSO-d_6, ppm): δ = 1.97–2.04 (m, 4 H, C(6)H$_2$ and C(7)H$_2$), 4.10 (t, ^3J = 5.8 Hz, 2 H, C(5)H$_2$), 4.30 (t, ^3J = 5.6 Hz, 2 H, C(8)H$_2$), 7.62–7.72 (m, 3 H, C(3')H, C(4')H and C(5')H), 7.81–7.83 (m, 2 H, C(2')H and C(6')H), 8.12 (s, 2 H, NH$_2^+$). ^{13}C NMR (100.63 MHz, DMSO-d_6, ppm): δ = 18.93 (C6), 19.54 (C7), 45.18 (C5), 47.93 (C8), 124.73 (C1'), 129.09 and 129.20 (C2', C3', C5' and C6'), 132.21 (C4'), 156.91 and 156.93 (C1 and C3). MS [(ESI) m/z]: Calcd. for [$C_{12}H_{14}N_4$+H]$^+$: 215.1291. Found [M$_{base}$+H]$^+$: 215.1294. Elemental analysis [$C_{12}H_{15}IN_4$ (342.18), %]: Calcd. C 42.12, H 4.42, N 16.37. Found C 40.84, H 3.99, N 15.37.

3.2.4.6. [1,2,4]Triazolo[1,2-a]pyridazin-1-imine hydroiodides ***7g,h***

A mixture of 0.5 mmol of hexahydropyridazine-1-carboximidamide hydroiodide **6a,** 0.5 mmol of the respective aldehyde and 3 mg of *p*-toluenesulfonic acid monohydrate was heated at 150–155 °C (metal bath) for the below given reaction time. Then the cooled melt was crushed and suspended in minimal acetone. The further work-up is described below.

In this way the following compounds were obtained:

3-(2-Chlorophenyl)-5,6,7,8-tetrahydro-1H-[1,2,4]triazolo[1,2-a]pyridazin-1-imine hydroiodide ***7g***

With 2-chlorobenzaldehyde. Reaction time: 4 hours. Work-up: The formed crystals were aspirated off, washed with propan-2-ol and dried. Yield: 3 %.

Light yellow crystals. M.r.: 284–288 °C (acetone/propan-2-ol).

TLC (m. ph. I): R_F = 0.44. MIR (cm^{-1}): $\tilde{\nu}$ = 1035, 1055, and 1073 (C-Cl), 1588 (NH), 1659 and 1667 (C=N), 2918 and 2969 (aliph. CH), 3105 (arom. CH), 3245 and 3307 (NH). ^{1}H NMR (400.20 MHz, DMSO-d_6, ppm): δ = 1.94–2.09 (m, 4 H, C(6)H$_2$ and C(7)H$_2$), 4.00 (s, 2 H, C(5)H$_2$), 4.15 (s, 2 H, C(8)H$_2$), 7.60–7.63 (m, 1 H, C(5')H), 7.69–7.76 (m, 3 H, C(3')H, C(4')H and C(6')H), 8.28 (s, 2 H, NH$_2^+$). ^{13}C NMR (100.63 MHz, DMSO-d_6, ppm): δ = 18.92 (C7), 19.22 (C6), 45.31 (C8), 46.86 (C5), 123.94 (C1'), 127.96 (C5'), 130.30 (C3'), 131.99 (C6'), 132.28 (C2'), 133.72 (C4'), 154.42 (C3), 157.09 (C1). MS [(ESI) m/z]: Calcd. for [$C_{12}H_{13}ClN_4$+H]$^+$: 249.0902. Found [M$_{base}$+H]$^+$: 249.0905.

3-(4-Chlorophenyl)-5,6,7,8-tetrahydro-1H-[1,2,4]triazolo[1,2-a]pyridazin-1-imine hydroiodide ***7h***

With 4-chlorobenzaldehyde. Reaction time: 14 hours. Work-up: The formed crystals were aspirated off, washed with a little acetone and dried under reduced pressure. Yield: 21 %.

Colourless crystals. M.r.: 283–284 °C (acetone).

TLC (m. ph. I): R_F = 0.45. MIR (KBr disc, cm^{-1}): = 745 (C–Cl), 1504, 1531 (NH), 1591, 1681 (C=N), 2864, 2937, 2960 (aliph. CH); 3121, 3240 (NH). ^{1}H NMR (200.11 MHz, DMSO-d_6, ppm): δ = 2.00 (m, 4 H, C(6)H$_2$ and C(7)H$_2$), 4.08 (t, 2 H, C(5)H$_2$), 4.27 (t, 2 H, C(8)H$_2$), 7.72 (d, ^3J = 8.74 Hz, 2 H, C(3)H and C(5)H of 4-chlorophenyl); 7.85 (d, ^3J = 8.72 Hz, 2 H, C(2)H and C(6)H of 4-chlororphenyl); 8.13 (s, 2 H, =NH$_2^+$). ^{13}C NMR (50.32 MHz, DMSO-d_6, ppm); δ = 18.77 (C6), 19.35 (C7), 45.11 (C8), 47.83 (C5); 123.51, 129.29, 130.88, 137.07 (arom. C); 155.83 (C(3)=N); 156.75 (C(1)=N). EI-MS (70 eV, 345 °C) m/z (%): 248 (7) [M$^{+\cdot}_{base}$]; 32.0 (30). MS [(ESI) m/z]: Found [M$_{base}$+H]$^+$: 249.1145.

3.2.4.7. N-Methyl-3-phenyl-5,6,7,8-tetrahydro-1H-[1,2,4]triazolo[1,2-a]-pyridazin-1-imine hydroiodide **7i**

Into a solution of 0.33 mmol of **4b** (Schulz et al. 2017) in 2 mL of ethanol dry methylamine was bubbled for 3 minutes. The stoppered reaction flask was allowed to stand at room temperature for five weeks (TLC reaction control). Next, the solvent was removed and the residue was treated with a little cold propan-2-ol/diethyl ether mixture (2 : 1, volume parts). The formed crystals were aspirated off, washed with a minimal ethanol and dried under reduced pressure. Yield: 19 %.

Colourless crystals. M.r.: 270–272 °C (propan-2-ol/diethyl ether).

TLC (m. ph. I): R_F = 0.37. MIR (KBr disc, cm^{-1}): = 1608, 1640 (C=N); 2869, 2926, 2961 (aliph. CH); 3128, 3170 (NH). ^{1}H NMR (200.11 MHz, CDCl$_3$, ppm): δ = 3.20 (m, 4 H, C(6)H$_2$ and C(7)H$_2$), 3.15 (s, 3 H, N–CH$_3$), 4.30 (hinted t, 2 H, C(5)H$_2$), 4.67 (t, ^3J = 5.6, 2 H, C(8)H$_2$), 7.59 – 7.77 (m, 5 H, arom. H), 8.31 (s, 1 H, N(2)H). ^{13}C NMR (50.32 MHz, CDCl$_3$), ppm): δ = 20.02 (C6), 20.89 (C7), 28.91 (N–$\underline{C}$H$_3$), 48.38 (C8), 48.55 (C5); 124.36, 129.26, 129.51, 132.89 (arom. C); 158.19 (C1), 159.68 (C3). MS (EI, 70 eV, 370 °C) m/z (%): 227.9 (0.37) [M$^{+\cdot}_{base}$]. Elemental analysis [$C_{13}H_{17}IN_4$ (356.2), %]: Calcd. C 43.83, H 4.81, N 15.73. Found C 43.33, H 3.54, N 14.89.

3.2.4.8. 3-Phenyl-N-propyl-5,6,7,8-tetrahydro-1H-[1,2,4]triazolo[1,2-a]-pyridazin-1-imine-hydroiodide **7j**

The substance was obtained from a solution of compound **5m** in DMSO-d_6, which was stored for about 11 months, by removing the solvent by gentle warming under reduced pressure. Crystallization from methanol yielded **7j**. Yield: Quantitative (determined by comparing the NMR spectra of **5m** and **7j**).

Colourless crystals. M.r.: 240–245 °C (methanol).

TLC (m. ph. II): R_F = 0.41. MIR (cm^{-1}): $\tilde{\nu}$ = 1462, 1627 (C=N); 2853, 2925 (aliph. CH); 3201, 3240, 3279 (NH). ^{1}H NMR (400.20 MHz, DMSO-d_6, ppm): δ = 0.92 (t, 3 H, ^3J = 6.4 Hz, , CH$_2$-CH$_2$-C$\underline{H3}$), 1.68 (q, 2 H, ^3J = 6.8 Hz, , CH$_2$-C$\underline{H2}$-CH$_3$), 1.97–2.01 (m, 4 H, C(6)H$_2$ and C(7)H$_2$), 3.45 (m, 2 H, C$\underline{H2}$-CH$_2$-CH$_3$, peak is superimposed with the peak of $\underline{H}$DO); 4.14 (t, 2 H, ^3J = 5.2 Hz) and 4.29 (t, 2 H, ^3J = 5.2 Hz) (C(8)H$_2$ and C(5)H$_2$); 7.61–7.69 (m, 3 H, arom. C(3)H, C(4)H and C(5)H), 7.82 (d, 2 H, ^3J = 7.6 Hz, arom. C(2)H and C(6)H), 8.49 (bs, 1 H, NH$^+$). ^{13}C NMR (100.63 MHz, DMSO-d_6, ppm): δ = 11.26 (CH$_2$-CH$_2$-$\underline{C}$H$_3$), 19.03 and 19.76 (C6 and C7), 22.33 (CH$_2$-$\underline{C}$H$_2$-CH$_3$), 44.26 ($\underline{C}$H$_2$-CH$_2$-CH$_3$), 45.50 and 48.00 (C5 and C8), 124.81 (arom. C1), 129.29 and 129.31 (arom. C2, C3, C5 and C6), 132.36 (arom. C4), 156.81 and 156.89 (C(1)=NH$^+$- and C3). MS [(ESI) m/z]: Calcd. for [$C_{15}H_{21}N_4$]$^+$: 257.1761. Found: M$^{+\cdot}_{base}$: 257.1768.

3.2.5. 2-Phenyl-2,3,5,6,7,8-hexahydro-1H-[1,2,4]triazolo[1,2-a]pyridazin-1-imine hydrochlorides ***8***

A mixture of 1 mmol of compound **6c**, 0.95 mmol of the corresponding benzaldehyde, and of 3 mg of *p*-toluenesulfonic acid monohydrate was heated at a temperature of 100 °C (metal bath) until the reaction was completed (TLC control). The cooled melt was covered with 2 mL of propan-2-ol and then diethyl ether was added dropwise until opalascence occurred. If there was not formed any crystalline product after longer standing or due to the complete dissolution of the solid, additional amounts of diethyl ether were added dropwise. The formed crystals were aspirated off, washed with diethyl ether and dried.

In this way the following compounds **8** were obtained:

3-(2-Chlorophenyl)-2-phenyl-2,3,5,6,7,8-hexahydro-1H-[1,2,4]triazolo[1,2-a]pyridazin-1-imine hydrochloride ***8a***

With 2-chlorobenzaldehyde. Reaction time: 6 hours. Yield: 43 %.

Pale beige crystals. M.r.: 217–221 °C (propan-2-ol/diethyl ether).

TLC (m. ph. VI): R_F = 0.56. MIR (cm^{-1}): $\tilde{\nu}$ = 1440, 1526, 1593, 1655 (C=N); 2934 (peak of a very broad band, aliphat. and arom. H, NH$_2^+$). ^{1}H NMR (400.20 MHz, DMSO-d_6, ppm): δ = 1.58–1.86 (m, 4 H, C(6)H$_2$ and C(7)H$_2$), 2.98 (t, ^3J = 10 Hz, 1 H, C(5)H$_2$), 3.12 (d, ^3J = 10.8 Hz, 1 H, C(5)H$_2$), 3.30 (mostly covered by signal of water, 1 H, C(8)H$_2$), 4.38 (d, ^3J = 12.8 Hz, 1 H, C(8)H$_2$), 6.25 (s, 1 H, C(3)H), 7.39–7.66 (m, 9 H, arom. H), 8.90 (s, 2 H, NH$_2^+$). ^{13}C NMR (100.63 MHz, DMSO-d_6, ppm): δ = 22.49 and 22.79 (C6 and C7), 44.49 (C8), 53.08 (C5), 81.57(C3), 126.53 (C2'' and C6'', 2-phenyl substituent); 127.74, 128.88, 129.55, (arom. C); 129.99 (C3'' and C5'', 2-phenyl substituent); 130.03, 131.48, 133.40, 133.89 (arom. C); 153.14 (C1). MS [(ESI) m/z]: Calcd. for [$C_{18}H_{19}ClN_4$+H]$^+$: 327.1371. Found [M $_{base}$ +H]$^+$: 327.1357. Elemental analysis [$C_{18}H_{20}Cl_2N_4$ (363.28), %]: Calcd. C 59.51, H 5.55, N 15.42. Found C 59.41, H 5.58, N 15.27.

3-(4-Chlorophenyl)-2-phenyl-2,3,5,6,7,8-hexahydro-1H-[1,2,4]triazolo[1,2-a]pyridazin-1-imine hydrochloride ***8b***

With 4-chlorobenzaldehyde. Reaction time: 3.5 hours. Yield: 51 %.

Pale beige crystals. M.r.: 205–216 °C (propan-2-ol/diethyl ether).

TLC (m. ph. VI): R_F = 0.72. MIR: (cm^{-1}): $\tilde{\nu}$ = 1491, 1523, 1594, 1668 (C=N), 2930 (peak of a very broad band, aliphat. and arom. H, NH$_2^+$). ^{1}H NMR (400.20 MHz, DMSO-d_6, ppm): δ = 1.60–1.85 (m, 4 H, C(6)H$_2$ and C(7)H$_2$), 2.85 (t, ^3J = 9.6 Hz, 1 H, C(5)H$_2$), 3.02 (d, ^3J = 10.8 Hz, 1 H, C(5)H$_2$), 3.30 (t, mostly covered by signal of water, 1 H, C(8)H$_2$), 4.36 (d, ^3J = 12.4 Hz, 1 H, C(8)H$_2$), 5.93 (s, 1 H, C(3)H), 7.29–7.46 (m, 9 H, arom. H), 8.82 (s, 2 H, NH$_2^+$). ^{13}C NMR (100.63 MHz, DMSO-d_6, ppm): δ = 22.39 and 22.66 (C6 and C7); 44.47 (C8); 52.32 (C5); 83.96 (C3); 126.94 (C2'' and C6''), 128.74 (C3'' and C5''), 128.97 (C4'') (2-phenyl substituent); 130.02 (C2' and C6'), 130.26 (C3' and C5') 3-(4-chlorophenyl) substituent); 133.23 (C1'') (2-phenyl substituent), 133.67 (C1'') 3-(4-chlorophenyl) substituent), 134.56 (C4', 3-(4-chlorophenyl) substituent), 153.25 (C1). MS [(ESI) m/z]: Calcd. for [$C_{18}H_{19}ClN_4$+H]$^+$: 327.1371. Found [M $_{base}$ +H]$^+$: 327.1374. Elemental analysis [$C_{18}H_{20}Cl_2N_4$ (363.28), %]: Calcd. C 59.51, H 5.55, N 15.42. Found C 58.36, H 5.60, N 15.06.

*3-(2-Nitrophenyl)-2-phenyl-2,3,5,6,7,8-hexahydro-1*H*-[1,2,4]triazolo[1,2-*a*]pyridazin-1-imine hydrochloride* ***8c***

With 2-nitrobenzaldehyde. Reaction time: 3.5 hours. Yield: 35 %.

Dark yellow crystals. M.r.: 236–243 °C (propan-2-ol/diethyl ether).

TLC (m. ph. VI): R_F = 0.65. MIR: (cm^{-1}): $\tilde{\nu}$ = 1443, 1525 (NO$_2$), 1604, 1661 (C=N); 2907 (peak of a very broad band, aliphat. and arom. H, NH$_2^+$). ^{1}H NMR (400.20 MHz, DMSO-d_6, ppm): δ = 1.57–1.87 (m, 4 H, C(6)H$_2$ and C(7)H$_2$), 2.99 (t, ^3J = 10.8 Hz, 1 H, C(5)H$_2$), 3.18 (d, ^3J = 10.8 Hz, 1 H, C(5)H$_2$), 3.26 (d, 12 Hz, 1 H, C(8)H$_2$), 4.33 (d, ^3J = 12.8 Hz, 1 H, C(8)H$_2$); 6.47 (s, 1 H, C(3)H), 7.41–7.50 (m, 5 H, 2-phenyl substituent), 7.68-7.84 (m, 3 H, C(4')H-C(6')H, 3-(2-nitrophenyl) substituent), 8.04 (d, 1 H, C(3')H 3-(2-nitrophenyl) substituent), 9.00 (s, 2 H, NH$_2^+$). ^{13}C NMR (100.63 MHz, DMSO-d_6, ppm): δ = 22.52 and 22.88 (C6 and C7); 44.29 (C8); 53.59 (C5); 80.30 (C3); 125.32 (C4''), 126.20 (C2'' and C6''), 130.02 (C3'' and C5''), 131.18 (C1'') (2-phenyl substituent); 128.73, 128.98, 130.02, 133.89 (C3'-C6', 3-(2-nitrophenyl) substituent); 134.16 (C1', 3-(2-nitrophenyl) substituent), 148.70 (C2', 3-(2-nitrophenyl) substituent), 153.19 (C1). MS [(ESI) m/z]: Calcd. for [$C_{18}H_{19}N_5O_2$+H]$^+$: 338.1612. Found [M$_{base}$+H]$^+$: 338.1606. Elemental analysis [$C_{18}H_{20}ClN_5O_2$ (363.28), %]: Calcd. C 57.83, H 5.39, N 18.73. Found C 57.48, H 5.46, N 18.45.

3-(4-Nitrophenyl)-2-phenyl-2,3,5,6,7,8-hexahydro-1H-[1,2,4]triazolo[1,2-a]pyridazin-1-imine hydrochloride ***8d***

With 4-nitrobenzaldehyde. Reaction time: 3 hours. Yield: 38 %.

Yellow crystals. M.r.: 205–210 °C (propan-2-ol/diethyl ether).

TLC (m. ph. VI): R_F = 0.69. MIR (cm^{-1}): $\tilde{\nu}$ = 1430, 1519 (NO$_2$) 1605, 1670 (C=N); 2931 (peak of a very broad band, aliph. and arom. H; NH$_2^+$); 3051 (CH). ^{1}H NMR (400.20 MHz, DMSO-d_6, ppm): δ = 1.58–1.86 (m, 4 H, C(6)H$_2$ and C(7)H$_2$), 2.95 (t, ^3J = 9.6 Hz, 1 H C(5)H$_2$), 3.09 (d, ^3J = 10.8 Hz, 1 H, C(5)H$_2$), 3.30 (bs, 1 H, C(8)H$_2$), 4.43 (d, 12.8 Hz, 1 H, C(8)H$_2$), 6.20 (s, 1 H, C(3)H), 7.34–7.45 (m, 5 H, 2-phenyl substituent), 7.74 (d, ^3J = 8.4 Hz, 2 H, C(2')H, C(6')H, 3-(4-nitrophenyl) substituent), 8.22 (d, ^3J = 8.4 Hz, 2 H, C(3')H, C(5')H, 3-(4-nitrophenyl) substituent), 8.97 (s, 2 H, NH$_2^+$). ^{13}C NMR (100.63 MHz, DMSO-d_6, ppm): δ = 22.44 and 22.71 (C6 and C7); 44.68 (C8); 53.59 (C5); 83.22 (C3); 123.83, 126.81, 129.01 (C2''-C6'', 2-phenyl substituent); 129.57, 130.10 (C2', C3', C5', C6', 3-(4-nitrophenyl) substituent), 133.64 (C1'', 2-phenyl substituent); 141.54 (C1', 3-(4-nitrophenyl) substituent), 148.32 (C4', 3-(4-nitrophenyl) substituent), 153.11 (C1). MS [(ESI) m/z]: Calcd. for [$C_{18}H_{19}N_5O_2$+H]$^+$: 338.1612. Found [M$_{base}$+H]$^+$: 338.1606. Elemental analysis [$C_{18}H_{20}ClN_5O_2$ (363.28), %]: Calcd. C 57.83, H 5.39, N 18.73. Found C 57.24, H 5.38, N 17.84.

3.2.6. *Hexahydropyridazine-1-carboxamide **9***

A mixture of 1 mmol of hexahydropyridazine hydrochloride **1** and 5 mmol of potassium cyanate was melted together at a temperature of 100 °C (metal bath). After the reaction was completed (TLC control, about 2 h) the reaction product was suspended in propan-2-ol. The undesired solid was separated by filtration under reduce pressure, the mother liquor was evaporated and the remaining residue was taken up with diethyl ether five times (each 10 mL). The diethyl ether fractions were collected, combined and finally evaporated to dryness. By doing so, compound **9** was obtained. Yield: 76 %.
Colourless crystals. M.r.: 85 – 92 °C (diethyl ether).
TLC (m. ph. II): R_F = 0.76. MIR (cm^{-1}): $\tilde{\nu}$ = 1423 and 1442 (NH), 1562 (CONH$_2$), 1632 (C=O), 2848 and 2922 (CH$_2$), 3222 and 3300 (NH), 3446 (NH$_2$). ^{1}H NMR (400.20 MHz, CDCl$_3$, ppm): δ = 1.58–1.72 (m, 4 H, C(4)H$_2$ and C(5)H$_2$), 2.90 (t, ^3J = 5.4 Hz, 2 H, C(3)H$_2$), 3.36 (bs, 1 H, N(2)H), 3.57 (bs, 2 H, C(6)H$_2$), 5.42 (bs, 2 H, NH$_2$). ^{13}C NMR (100.63 MHz, CDCl$_3$, ppm): δ = 24.01 (C5), 25.72 (C4), 43.20 (C6), 47.57 (C3), 159.02 (C=O). MS [(ESI) m/z]: Calcd. for [$C_5H_{11}N_3O$+H]$^+$: 130.0975. Found [M$_{base}$+H]$^+$: 130.0985.

3.2.7. *[1,2,4]Triazolo[1,2-a]pyridazin-1-ones **10***

A mixture of 0.5 mmol of hexahydropyridazine-1-carboxamide **9** and 0.7 mmol of the corresponding aldehyde, to which was added 4 mg of *p*-toluenesulfonic acid monohydrate under trituration, was melted together at 100 °C. After the reaction was completed (TLC control), heating was stopped and the cooled melt was taken up in hexane. The crystals obtained were separated by vacuum filtration and dried.
In this way the following compounds were obtained:

*3-Phenyl-2,3,5,6,7,8-hexahydro-1H-[1,2,4]triazolo[1,2-a]pyridazin-1-one **10a***
With benzaldehyde. Reaction time: 1 hour. Yield: 82 %.
Slightly orange coloured crystals. M.r.: 165–171 °C (hexane).
TLC (m. ph. IV): R_F = 0.78. MIR (cm^{-1}): $\tilde{\nu}$ = 1689 (C=O), 2840 and 2945 (CH$_2$), 3197 (NH). ^{1}H NMR (400.20 MHz, DMSO-d_6, ppm): δ = 1.32–1.68 (m, 4 H, C(6)H$_2$ and C(7)H$_2$), 2.47 (s, 1 H, C(5)H), 2.77 (bs, 2 H, C(5)H and C(8)H), 3.57 (bs, 1 H, C(8)H), 4.89 (s, 1 H, C(3)H), 7.37–7.42 (m, 3 H, C(3')H, C(4')H and C(5')H), 7.44–7.47 (m, 2 H, C(2')H and C(6')H), 7.67 (s, 1 H, NH). ^{13}C NMR (100.63 MHz, DMSO-d_6, ppm): δ = 22.93 and 23.27 (C6 and C7), 42.79 (C8), 51.23 (C5), 76.81 (C3), 127.71 and 128.23 (C2', C3', C5' and C6'), 128.82 (C4'), 137.99 (C1'), 159.21 (C1). MS [(ESI) m/z]: Calcd. for [$C_{12}H_{15}N_3O$+H]$^+$: 218.1288. Found [M +H]$^+$: 218.1288. Elemental analysis [$C_{12}H_{15}N_3O$ (217.27), %]: Calcd. C 66.34, H 6.96, N 19.34. Found C 65.34, H 6.69, N 18.18.

*3-(2-Chlorophenyl)-2,3,5,6,7,8-hexahydro-1H-[1,2,4]triazolo[1,2-a]pyridazin-1-one **10b***
With 2-chlorobenzaldehyde. Reaction time: 1 hour. Yield: 76 %.
Slightly orange coloured crystals. M.r.: 149–157 °C (hexane).
TLC (m. ph. IV): R_F = 0.81. MIR (cm^{-1}): $\tilde{\nu}$ = 1034, 1052 and 1077 (C-Cl), 1689 (C=O), 2845, 2918, and 2950 (CH$_2$), 3065 (CH), 3228 (NH). ^{1}H NMR (400.20 MHz, DMSO-d_6, ppm): δ = 1.29–1.69 (m, 4 H, C(6)H$_2$ and C(7)H$_2$), 2.64 (bs, 1 H, C(5)H), 2.81 (bs, 1 H, C(8)H), 2.90 (bs, 1 H, C(5)H), 3.61–3.65 (m, 1 H, C(8)H), 5.32 (s, 1 H, C(3)H), 7.37–7.42 (m, 2 H, C(5')H and C(6')H), 7.45–7.49 (m, 1 H, C(3')H), 7.51–7.55 (m, 1 H, C(4')H), 7.73 (s, 1 H, NH). ^{13}C NMR (100.63 MHz, DMSO-d_6, ppm): δ = 22.88 and 23.35 (C6 and C7), 42.00 (C8), 52.17 (C5), 72.55 (C3), 127.17 (C5'), 129.47 (C3' and C4'), 130.17 (C6'), 132.90 (C2'), 135.72 (C1'), 159.07 (C1). MS [(ESI) m/z]: Calcd. for [$C_{12}H_{14}ClN_3O$+H]$^+$: 252.0898. Found [M+H]$^+$: 252.0894. Elemental analysis [$C_{12}H_{14}ClN_3O$ (251.71), %]: Calcd. C 57.26, H 5.61, N 16.69. Found C 56.77, H 5.45, N 15.32.

*3-(4-Chlorophenyl)-2,3,5,6,7,8-hexahydro-1H-[1,2,4]triazolo[1,2-a]pyridazin-1-one **10c***
With 4-chlorobenzaldehyde. Reaction time: 1 hour. Yield: 86 %.
Slightly orange coloured crystals. M.r.: 140–148 °C (hexane).
TLC (m. ph. IV): R_F = 0.74. MIR (cm^{-1}): $\tilde{\nu}$ = 1036 and 1089 (C-Cl), 1597 (C=C), 1693 (C=O), 2845 and 2945 (CH$_2$), 3212 (NH). ^{1}H NMR (400.20 MHz, DMSO-d_6, ppm): δ = 1.30–1.69 (m, 4 H, C(6)H$_2$ and C(7)H$_2$), 2.46 (bs, 1 H, C(5)H), 2.78 (bs, 2 H, C(5)H and C(8)H), 3.58 (d, ^3J = 9.2 Hz, 1 H, C(8)H), 4.94 (s, 1 H, C(3)H), 7.44–7.49 (m, 4 H, arom.), 7.71 (s, 1 H, NH). ^{13}C NMR (100.63 MHz, DMSO-d_6, ppm): δ = 22.89 and 23.27 (C6 and C7), 42.68 (C8), 51.38 (C5), 75.78 (C3), 128.27 and 129.47(C2', C3', C5' and C6'), 133.31 (C4'), 137.33 (C1'), 159.05 (C1). MS [(ESI) m/z]: Calcd. for [$C_{12}H_{14}ClN_3O$+H]$^+$: 252.0898. Found [M+H]$^+$: 252.0905. Elemental analysis [$C_{12}H_{14}ClN_3O$ (251.71), %]: Calcd. C 57.26, H 5.61, N 16.69. Found C 56.62, H 5.35, N 14.84.

*3-(2-Nitrophenyl)-2,3,5,6,7,8-hexahydro-1H-[1,2,4]triazolo[1,2-a]pyridazin-1-one **10d***
With 2-nitrobenzaldehyde. In deviation from the general instruction the batch was transferred into the reaction vessel by using the methanolic solution of the components, since the solid starting materials in each case liquefied during the trituration. Reaction time: 45 minutes. Despite the addition of boiling stones there was a delay in boiling causing yield losses. Yield: 23 %.
Yellow crystals. M.r.: 169–178 °C (hexane).
TLC (m. ph. IV): R_F = 0.67. MIR (cm^{-1}): $\tilde{\nu}$ = 1345 and 1524 (N=O), 1701 (C=O), 2845 and 2950 (CH$_2$), 3202 (NH). ^{1}H NMR (400.20 MHz, DMSO-d_6, ppm): δ = 1.22–1.75 (m, 4 H, C(6)H$_2$ and C(7)H$_2$), 2.73–2.86 (m, 3 H, C(5)H$_2$ and C(8)H), 3.58–3.63 (m, 1 H, C(8)H), 5.66 (s, 1 H, C(3)H), 7.59–7.63 (m, 1 H, C(4')H), 7.71–7.79 (m, 2 H, C(5')H and C(6')H), 7.94 (s, 1 H, NH) , 7.99–8.01 (m, 1 H, C(3')H). ^{13}C NMR (100.63 MHz, DMSO-d_6, ppm): δ = 22.66 and 23.35 (C6 and C7), 41.43 (C8), 52.25 (C5), 71.09 (C3), 124.72 (C3'), 127.93 (C6'), 129.60 (C4'), 133.28 (C5'), 134.64 (C1'), 148.36 (C2'), 158.77 (C1). MS [(ESI) m/z]: Calcd. for [$C_{12}H_{14}N_4O_3$+H]$^+$: 263.1139. Found [M+H]$^+$: 263.1134. Elemental analysis [$C_{12}H_{14}N_4O_3$ (262.27), %]: Calcd. C 54.96, H 5.38, N 21.36. Found C 54.78, H 5.24, N 19.94.

*3-(4-Nitrophenyl)-2,3,5,6,7,8-hexahydro-1H-[1,2,4]triazolo[1,2-a]pyridazin-1-one **10e***
With 4-nitrobenzaldehyde. In deviation from the general instruction the starting materials were not triturated. Reaction time: 45 minutes. Yield: 67 %.
Orange crystals. M.r.: 173–183 °C (hexane).
TLC (m. ph. IV): R_F = 0.63. MIR (cm^{-1}): $\tilde{\nu}$ = 1347 and 1524 (N=O), 1711 (C=O), 2845 and 2944 (CH$_2$), 3244 (NH). ^{1}H NMR (400.20 MHz, DMSO-d_6, ppm): δ = 1.30–1.73 (m, 4 H, C(6)H$_2$ and C(7)H$_2$), 2.61 (t, ^3J = 10.2 Hz, 1 H, C(5)H), 2.81–2.85 (m, 2 H, C(5)H and C(8)H), 3.61 (d, ^3J = 10.4 Hz, 1 H, C(8)H), 5.16 (s, 1 H, C(3)H), 7.73 (d, ^3J = 8.8 Hz, 2 H, C(2')H and C(6')H), 7.89 (s, 1 H, NH), 8.26 (d, ^3J = 8.8 Hz, 2 H, C(3')H and C(5')H). ^{13}C NMR (100.63 MHz, DMSO-d_6, ppm): δ = 22.83 and 23.29 (C6 and C7), 42.37 (C8), 51.71 (C5), 74.94 (C3), 123.44 (C3' and C5'), 128.66 (C2' and C6'), 146.25 (C1'), 147.66 (C4'), 158.82 (C1). MS [(ESI) m/z]: Calcd. for [$C_{12}H_{14}N_4O_3$+H]$^+$: 263.1139. Found [M+H]$^+$: 263.1131. Elemental analysis [$C_{12}H_{14}N_4O_3$ (262.27), %]: Calcd. C 54.96, H 5.38, N 21.36. Found C 54.88, H 5.16, N 19.54.

3.2.8. *(Hexahydropyridazine-1-carboximidothioic acid) (4-nitrobenzencarboxylic acid) anhydride **12***

To a solution of 0.4 mmol of the thione **3b** (Schulz et al. 2014) in 3 mL of dichloromethane an equimolar amount of 4-nitrobenzoyl chloride was added. After allowing the reacton to stand for 24 h at room temperature, the formed crystals were aspirated off, washed with dichloromethane and dried under reduced pressure. Yield: 17 %.
Colourless crystals. M.r.: 211 – 214 °C (CH$_2$Cl$_2$).
TLC (m. ph. I) R_F = 0.85. MIR (KBr disc, cm^{-1}): = 1528 (NO$_2$), 1600, 1644 (C=N), 2936, 3011, 3052, 3072 (–CH–), 3160 (Ar–H), 3270, 3324 (NH). ^{1}H NMR (200.11 MHz, DMSO-d_6, ppm): δ = 1.62 – 1.71 (m, 4 H, C(4)H$_2$ and C(5)H$_2$), 2.87 (t, 2 H, C(3)H$_2$), 4.34 (d, ^3J = 13.6 Hz, 1 H of C(6)H$_2$), 4.90 (d, ^3J = 12.8 Hz, 1 H, of C(6) H$_2$), 7.76 (d, ^3J = 8.6 Hz, 2 H, C(2')H and C(6')H 4-nitrobenzoyl group), 8.27 (d, ^3J = 8.6 Hz, 2 H, C(3')H and C(5')H of 4-nitrobenzoyl), 8.46 (s, 1 H, N(2)H), 8.58 (s, 1 H, NH carbimidothioc group). ^{13}C NMR (50.32 MHz, DMSO-d_6, ppm): δ = 22.17 (C4 and C5), 42.67 (C3), 50.38 (C6); 123.14 (C3', C5'), 127.33 (C2', C6'), 141.41 (C1'), 148.12 (C4') (4-nitrobenzoyl group); 169.93 (S–C=N), 182.89 (C=O). Elemental analysis [$C_{12}H_{14}N_4O_3S$ (294.3), %]: Calcd. C 48.97, H 4.79, N 19.04. Found C 48.17, H 4.97, N 18.17.

3.2.9. *1-(3-Methyl-3-phenyl-1-sulfanylidene-2,3,5,6,7,8-hexahydro-1H-[1,2,4]triazolo-[1,2-a]pyridazine-2-yl)-ethanone **13***

Thione **3b** (0.24 mmol; Schulz et al. 2014) was heated under reflux for 30 minutes in 8 mL of acetic anhydride. Subsequently, the batch was evaporated to dryness, whereupon crystallization began. The crystals were collected, washed with a small amount of hexane, recrystallized from dichloromethane and dried at room temperature. Yield: 63 %.
Beige crystals. M.r.: 89–104 °C (decomp., CH$_2$Cl$_2$).
TLC (m. ph. I) R_F = 0.74. MIR (KBr disc, cm^{-1}): = 1600, 1644, 1681 (C=O); 2931, 2951, 2992 (CH$_3$– und –CH$_2$–); 3031, 3063 (Ar–H). ^{1}H NMR (200.11 MHz, CDCl$_3$, ppm): δ = 1.61 (bs, 2 H, C(6)H$_2$), 1.77 (bs, 2 H, C(7)H$_2$), 1.89 (s, 3 H, C(3)–C$\underline{H}_3$), 2.45 (m, 1 H, C(5)H), 2.60 (m, 1 H, C(8)H), 2.82 (s, 3 H, C$\underline{H}_3$ of the acetyl group), 3.59 (m, 1 H, C(8)H), 4.12 (m, 1 H, C(5)H), 7.27 – 7.31 (m, 5 H, arom. H). ^{13}C NMR (50.32 MHz, CDCl$_3$, ppm): δ = 20.75 (C(3)-$\underline{C}$H$_3$); 21.89, 22.84 (C6 and C7); 26.99 ($\underline{C}$H$_3$ of the acetyl group), 44.96 (C5), 47.55 (C8), 84.87 (C3), 124.91 – 127.35, 139.15 (all arom. C), 171.36 ($\underline{C}$O of acetyl), 172.56 (C1). MS (EI, 70 eV, RT) m/z (%): 289.0 (36) [M$^{+\cdot}$]:, 274.0 (21) [M$^{+\cdot}$ – $^{\cdot}$CH$_3$], 233.0 (13), 231.9 (100) [M$^{+\cdot}$ – $^{\cdot}$CH$_3$ – $^{\cdot}$COCH$_3$], 187.0 (11), 170.0 (35), 161.8 (24), 102.7 (14), 85.0 (41) [$C_4H_9N_2^{+\cdot}$], 77.3 (11), 43.0 (21), 27.9 (16). Elemental analysis [$C_{15}H_{19}N_3OS \cdot 3\ H_2O$ (343.45), %]: Calcd. C 52.46, H 5.58, N 12.23, S 9.34. Found C 52.12, H 6.17, N 12.15, S 9.09.

3.2.10. *3-(4-Nitrophenyl)-5,6,7,8-tetrahydro-1H-[1,2,4]triazolo[1,2-a]-pyridazine-1-thione **14***

Method 1 – To a solution of 0.3 mmol of **12** in 3 mL of dichloromethane 0.3 mmol of pyrrolidine were added. After standig the mixture for one day at room temperature the solvent was slowly removed. The formed crystals were collected, subsequently washed with a little ethanol and dried. Yield: 78 %.
Method 2 – To a solution of 0.3 mmol **12** in 3 mL of dichloromethane 0.3 mmol of propan-1-amine were added. After standig the mixture for three days at room temperature it was slowly and carefully reduced to dryness. The formed crystals were collected and washed with a small volume of acetone and dried. Yield: 84 %
Method 3 – To 0.3 mmol of compound **12** an equimolar amount of benzaldehyde was added and the mixture was heated in a metal bath at 155 °C for one hour. The formed yellow powdery product was suspended in a little acetone, collected, washed with a small amount of cold acetone and dried. Yield: 97 %.
Yellow crystals. M.r.: 243 – 248 °C (acetone).

TLC (m. P. VII) $R_F = 0.61$. MIR (KBr disc, cm^{-1}): = 1350, 1440, 1518 (NO$_2$), 1598 (C=N); 2882, 2925, 2963 (CH$_2$); 3020, 3083 (arom. H). ^{1}H NMR (200.11 MHz, DMSO-d_6, ppm): δ = 1.98 (m, 4 H, C(6)H$_2$ and C(7)H$_2$), 4.08 (t, 2 H, C(5)H$_2$), 4.25 (t, 2 H, C(8)H$_2$), 8.07 (d, $^3J_{HH}$ = 8.41 Hz, 2 H, C(2)H and C(6)H 4-nitrophenyl), 8.42 (d, $^3J_{HH}$ = 8.68 Hz, 2 H, C(3)H and C(5)H 4-nitrophenyl). ^{13}C NMR (50.63 MHz, DMSO-d_6, ppm): δ = 19.03, 19.11 (C6 and C7); 45.40 (C8), 47.49 (C5); 123.38 (C3', C5'), 130.03 (C2', C6'), 131.31 (C1'), 148.41 (C4') (arom. C); 153.52 (C3), 174.07 (N–C(1)=S). MS (EI, 70 eV, 345 °C) m/z (%): 275.8 (8) [M$^+$]: 31.9 (43); [(ESI) m/z]: Found [M+H]$^+$: 277.0999. Elemental analysis [$C_{12}H_{12}N_4O_2S \cdot H_2O$ (294.33), %]: Calcd. C 48.97, H 4.79, N 19.04, S 10.89. Found C 49.56, H 4.21, N 18.42, S 10.96.

3.3. *Biological tests*

Materials and methods are described in detail in a previous publication (Schulz et al. 2013). The key parameters are given in the following.

3.3.1. *Cell culture materials*

All chemicals as well as interleukin-1β, fetal calf serum and trypane blue were purchased from Sigma Aldrich. Cell culture plastics, PBS, trypsin/EDTA and interferon-γ were obtained from Biochrom AG, RPMI1640 and penicillin/streptomycin from Lonza.

3.3.2. *Cell line*

The insulin-producing rat insulinoma cell line RIN5F (ECACC catalogue No. 95090402) was used;the adherent cells were grown under standard conditions (95% humidity, 37 °C, 5% CO$_2$) in RPMI1640 supplemented with L-glutamine (2 mmol/L), 10% heat-inactivated FCS, penicillin (100 I.E.) and streptomycin (100 I.E.).

3.3.3. *iNOS expression and inhibition*

Tests were performed with 1×10^5 cells per well in 200 µL culture media in 96-well plates at standard culture conditions. Twenty-four hours after cells had been seeded out, iNOS was induced by adding 1 ng/mL IL-1β (human, recombinant) and 10 ng/mL IFN-γ (rat, recombinant). For the primary screening, test compounds were added to the cells at concentrations of 0.3125 mM and 0.156 mM along with 0.5% dimethyl sulfoxide (DMSO) as the solvent. The reference inhibitor aminoguanidine (AG) was tested at the same concentrations. DMSO in the same concentration was added to the untreated controls.

3.3.4. *NO assay*

Nitrite concentration, an indication for the degree of NO production, was determined from 50 µL cell-free supernatant (two samples from each cavity) by using the Griess reaction (Green et al. 1982; Griess 1879). For this, each 50 µM of a 0.1% sulfanilamide solution in 5% phosphoric acid and an aqueous 0.01% *N*-(1-naphthyl) ethylenediamine dihydrochloride solution were pipetted separately to the supernatant and incubated for 5 min in the dark. Afterwards, the absorption was measured in a plate reader at a wavelength of 550 nm. For calibration, a dilution series of nitrite (0 to 100 µM) was included on every plate.

3.3.5. *MTT assay*

The remaining cells in the test plates were used to perform the MTT assay as a test of cytotoxicity (Mosmann 1983). The medium was completely removed and replaced with 100 µL of fresh medium then 20 µL MTT in PBS (2.5 mg/mL) were added. After 4 h incubation at 37 °C the medium was carefully removed and 100 µL dimethyl sulfoxide were added. After dissolution of the formazan crystals the absorption was immediately measured at a wavelength of 570 nm.

3.3.6. *Statistics*

Normality was tested and if positive F- and t-test were performed. Otherwise the Mann-Whitney-test was executed. Statistical significance was assumed for $p < 0.05$ or lower (n = 5).

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