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Synthesis of new pyrazolo[1,2,3]triazines by cyclative cleavage of pyrazolyltriazenes

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Abstract

We describe the synthesis of so far synthetically not accessible 3,6-substituted-4,6-dihydro-3H-pyrazolo[3,4-d][1,2,3]triazines as nitrogen-rich heterocycles. The target compounds were obtained in five steps, including an amidation and a cyclative cleavage reaction as key reaction steps. The introduction of two side-chains allowed a variation of the pyrazolo[3,4-d][1,2,3]triazine-core with commercially available building blocks, enabling the extension of the protocol to gain other derivatives straightforwardly. Attempts to synthesize 3,7-substituted-4,7-dihydro-3H-pyrazolo[3,4-d][1,2,3]triazines, the regio-isomers of the successfully gained 3,6-substituted-4,6-dihydro-3H-pyrazolo[3,4-d][1,2,3]-3H-triazines, were not successful

under similar conditions due to the higher stability of the triazene functionality in the regio-isomeric precursors and thus the failure of the removal of the protective group.

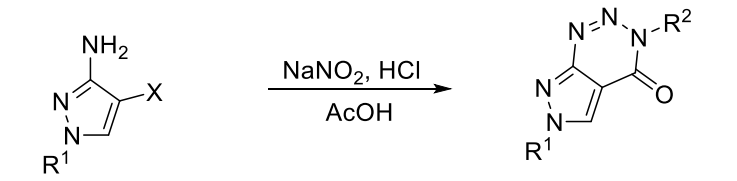
Keywords

Triazenes, Triazines, Pyrazoles, Diazonium chemistry, Cyclization

Introduction

The structural motif of pyrazolotriazines, in particular the pyrazolotriazinones, has drawn attention in regards to a possible application as therapeutic agents due to manifold biological activities. Amongst other known constitutional isomers such as pyrazolo[4,3-e][1,2,4]triazines [1-3] and pyrazolo[1,5-a][1,3,5]triazines [4-6], pyrazolo[3,4-d][1,2,3]triazines [7-34] and their derivatives are literature known and subject of different biological studies. Pyrazolo[3,4-d][1,2,3]triazines and their derivatives, for example, were reported to function as anticancer compounds [28, 29, 32], herbicides [19-21], antimicrobials[18], and pest control agents.[35]

There are several possibilities to gain the scaffold of pyrazolo[3,4-d][1,2,3]triazines synthetically and successful syntheses of manifold different isomers have been reported. 3,6-Dihydro-4H-pyrazolo[3,4-d][1,2,3]triazin-4-ones (**2**), as one example of the diverse compound class, can be gained via diazotization of 3-amino-1H-pyrazole-4-carboxamides (**1a**) or 3-amino-1H-pyrazole-4-carbonitriles (**1b**) and subsequent cyclization of the intermediate diazo-compounds under acidic conditions.[22]



1a: X = CONHR^2
1b: X = CN

2a (R^2 = H, alkyl)
2b (R^2 = H)

Scheme 1. Synthesis of 3,6-dihydro-4H-pyrazolo[3,4-d][1,2,3]triazin-4-ones (**2a**, **2b**) by diazotization of 3-amino-1H-pyrazole-4-carboxamides (**1a**) or 3-amino-1H-pyrazole-4-carbonitriles (**1b**) [22].

Structurally related 3,7-dihydro-4H-pyrazolo[3,4-d][1,2,3]triazin-4-ones (**3**) (Figure 1) which are substituted in position N-7 can be obtained in the same manner as described in Scheme 1 if the substitution position R^1 in 3-amino-1H-pyrazole-4-carboxamides (**1a**) or 3-amino-1H-pyrazole-4-carbonitriles (**1b**) is altered.[26] Furthermore, several 2,7-dihydro-3H-imidazo[1,2-c]pyrazolo[4,3-e][1,2,3]triazines (**4**) were described. However, while 3,6-substituted-3,6-dihydro-4H-pyrazolo[3,4-d][1,2,3]triazin-4-ones (**2**) and 3,7-substituted-3,7-dihydro-4H-pyrazolo[3,4-d][1,2,3]triazin-4-ones (**3**) are reported in several references dealing with their synthesis, modification and application,[36] their non-oxidized derivatives **5** and **6** are yet, to the best of our knowledge, unknown in literature.

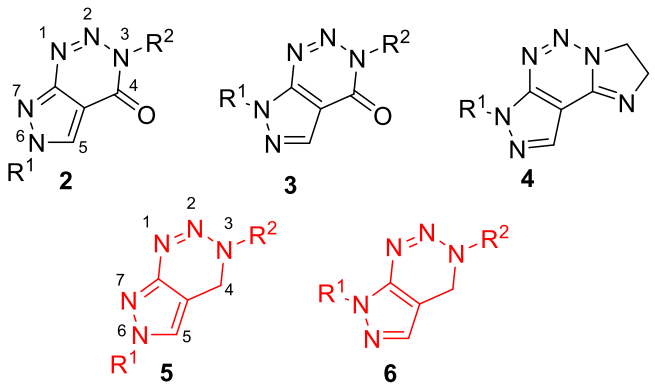
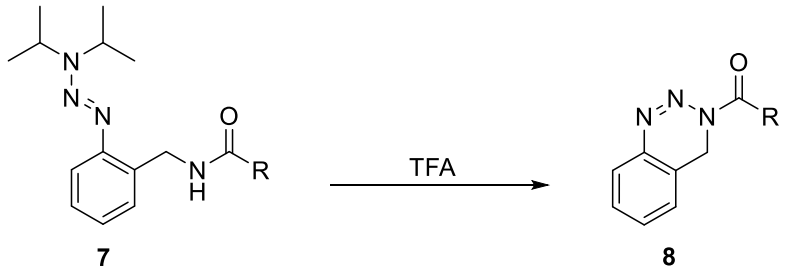


Fig 1. Structural differences of several known (**2**-**4**) and so far unknown (**5**, **6**) pyrazolo[3,4-d][1,2,3]-3H-triazine-derivatives.

In the past, it was shown that ortho-methylamide-substituted aryltriazenes (**7**) can be efficiently converted into 3,4-dihydrobenzo[d][1,2,3]triazine-derivatives (**8**).[37]



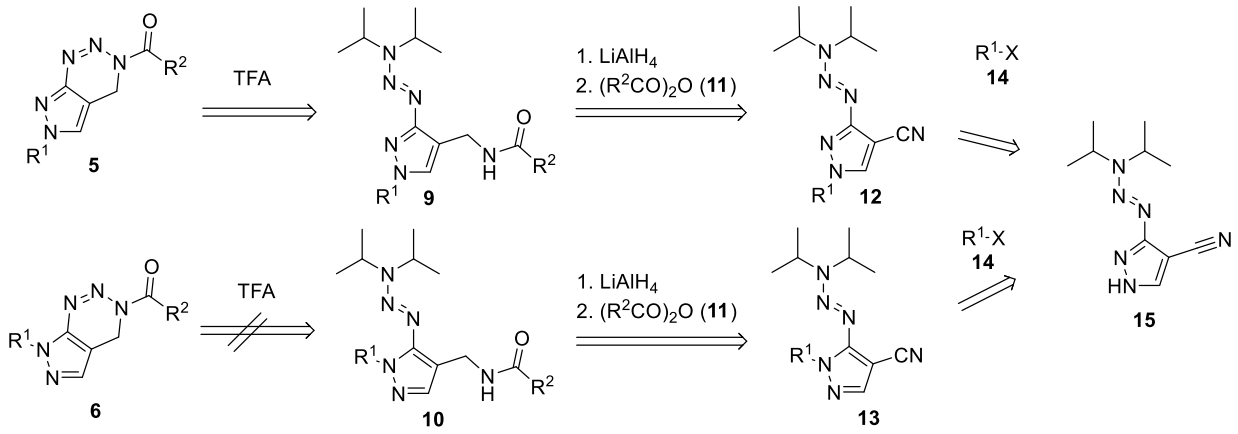
7 **8**

Scheme 2. Synthesis of 3,4-dihydrobenzo[d][1,2,3]triazine-derivatives (**8**) from triazene-containing precursors **7** .[37]

In this context, triazenes have shown beneficial properties as they can be used as protected diazonium species which can be handled and converted in various transformations without decomposition.[37-43] In the herein presented study, we apply the cyclative cleavage reaction to pyrazolyltriazenes instead of aryltriazenes, which results in the synthesis of diverse pyrazolo[3,4-d][1,2,3]-3H-triazine-derivatives (**5**).

Results and Discussion

According to the literature-known synthetic access to benzotriazines **8**, we designed a retrosynthetic route consisting of five steps to gain 4,6-dihydro-pyrazolo[3,4-d][1,2,3]-3H-triazines (**5**) and 4,7-dihydro-pyrazolo[3,4-d][1,2,3]-3H-triazines (**6**) starting from pyrazolyltriazenes **15** (Scheme 3).



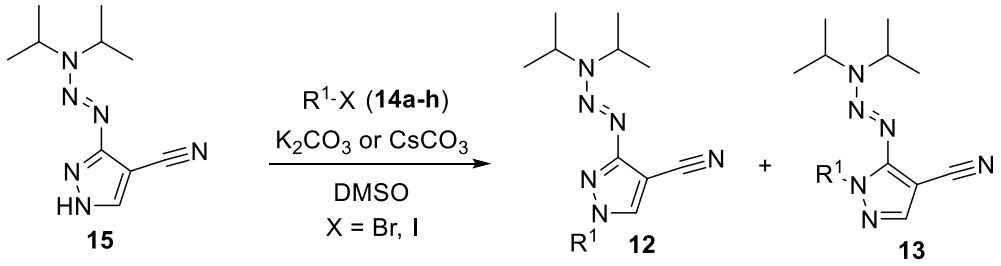
Scheme 3. Planned retrosynthesis to obtain 4,6-dihydro-pyrazolo[3,4-d][1,2,3]-3H-triazines (**5**) and 4,7-dihydro-pyrazolo[3,4-d][1,2,3]-3H-triazines (**6**) from pyrazolyltriazenes **15**.

The sequence contains two key steps that have a major influence on the outcome of the reaction: (1) the addition of side-chains R^1 to the core pyrazole ring system, which can occur in position N-6 or N-7, and (2) the cyclative cleavage of the triazene group of compounds **9** and **10** which should lead to the target compounds **5** and **6**. To carry out the designed synthetic route, 3-(3,3-diisopropyltriaz-1-en-1-yl)-1H-pyrazole-4-carbonitrile (**15**) was synthesized in a first step using the commercially available 3-amino-1H-pyrazole-4-carbonitrile. Thus, the aminopyrazole was diazotized in aqueous media using hydrochloric acid and sodium nitrite. Diisopropylamine and an aqueous solution of potassium carbonate were added to the in-situ generated diazonium salt according to literature-known protocols.[44] The resulting 3-(3,3-diisopropyltriaz-1-en-1-yl)-1*H*-pyrazole-4-carbonitrile (**15**) was used as starting material for the attempts to add different side-chains to the pyrazole moiety.

The addition of several aliphatic bromides or iodides (**14**) in combination with potassium or cesium carbonate in DMSO gave a mixture of the regio-isomeric

compounds **12** and **13** as a result of the addition of the alkyl substituents to one of the both pyrazole-nitrogen atoms. As shown in Table 1, the alkylation protocol did not give a selective conversion in favor of one of the generated isomers. The protocol was not changed or adapted to gain a higher selectivity of one of the isomers, as both regio-isomers were used in the subsequent syntheses.

Table 1. Synthesis of *N*-substituted-pyrazoles **12** and **13.**

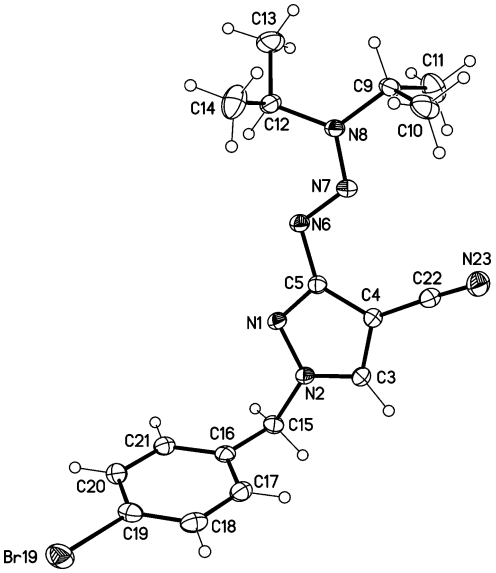


Entry[a]	**14** (equiv.)	**R^1**	**X**	**12 (yield)**	**13 (yield)**
1	**14a** (2.0)	Bn	Br	**12a** (54%)	**13a** (36%)
2	**14b** (1.5)	Tolyl-CH_2	Br	**12b** (59%)	**13b** (40%)
3	**14c** (2.0)	3,5-Difluorobenzyl	Br	**12c** (48%)	**13c** (42%)
4[b]	**14d** (1.2)	Ethyl	I	**12d** (34%)	**13d** (57%)
5[b]	**14e** (1.2)	Cyclopentyl	Br	**12e** (39%)	**13e** (52%)
6	**14f** (1.2)	^{i}Butyl	Br	**12f** (28%)	**13f** (47%)
7[c]	**14g** (1.1)	EtO_2COCH_2	Br	**12g** (54%)	**13g** (15%)
8	**14h** (2.0)	4-Bromobenzyl-	Br	**12h** (51%)	**13h** (42%)

[a]Typical conditions for the conversion are: **15**, Cs_2CO_3 or K_2CO_3 (1.2 equiv.), **14** (1.1 – 2.0 equiv.), DMSO, room temperature. [b]The conditions were varied in temperature (reactions with entries 4 and 5 were reacted at 80 °C, **8** at 40 °C). [c]0.95 equiv. of K_2CO_3 were used.

For the derivatives **12h** and **13c**, we were able to exemplarily determine the molecular structure by X-Ray crystallography proving also the regioisomer that was obtained in the alkylation reaction.

2a



2b

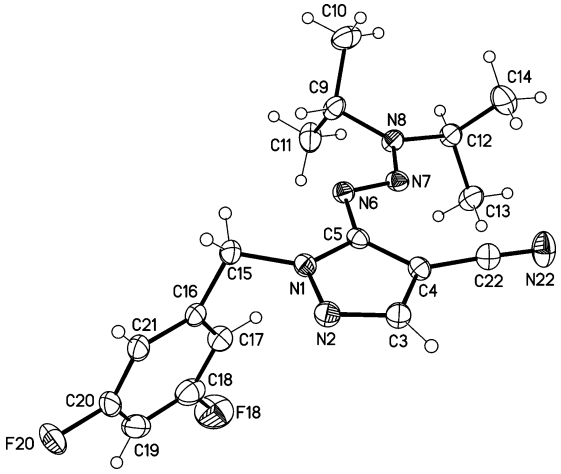


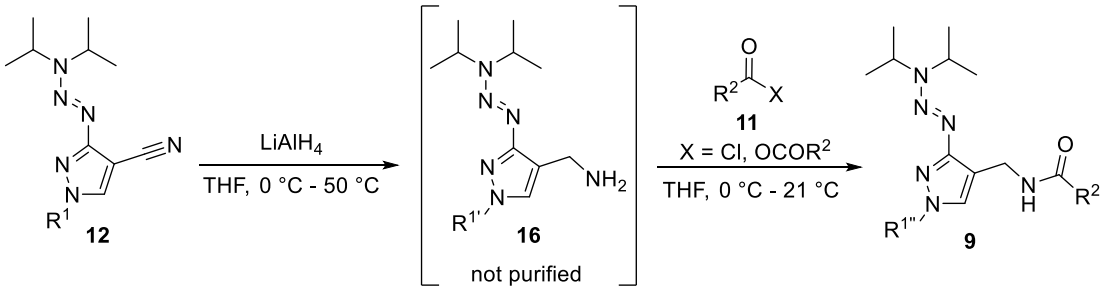
Fig 2. Molecular structures of compounds **12h** (Fig. 2a) and **13c** (Fig. 2b) representing both possible regio-isomers of the alkylation reaction (displacement parameters are drawn at 50% probability level).

While isomer **12** was used for the synthesis of pyrazolo[3,4-d][1,2,3]-3H-triazine-derivatives of general structure **5,** isomer **13** was intended to deliver pyrazolo[3,4-d][1,2,3]-3H-triazine-derivative of general structure **6**. The synthetic sequence to compounds **5** is described in detail in the following sections. The synthesis of the precursors to compound **6** derived from **13** are shifted to the Supporting Information of this manuscript as the cyclative cleavage to **6** failed in the last step of the synthesis.

The conversion of **12** to the reduced aminomethyl compounds **16** was challenging. While the reduction with $LiAlH_4$ in THF gave good results (shown via TLC and LCMS-

analysis), the isolated products were not stable and degraded quickly which made a full characterization impossible. Therefore, the crude aminomethyl compounds **16a-g** were directly converted to the corresponding amides **9a-i** using different anhydrides or acid chlorides **11a-c**. The resulting amides were stable and were gained in mediocre to good yields with exception of amide **9a** and **9d** (Table 2). The yield of **9d** was found to be very low due to a reductive replacement of the fluoro-atoms of the benzyl ring during the reduction of the nitrile with $LiAlH_4$. Only a small amount (5% yield) of the desired compound was isolated. Also, a reductive replacement was observed during the conversion of **12h**, yielding the intermediate **16a** with R^1 = Bn instead of R^1 = bromobenzyl. Depending on the nature of the side chain R^1 in compounds **12a-g**, the reduction to compounds **16a-g** leads to a change of R^1 to a different side-chain $R^{1'}$ which can be used for further transformation to $R^{1''}$ by conversion with electrophiles. This was shown with compound **12g** (R^1 = $-CH_2CO_2Et$), being reduced to compound **16g** ($R^{1'}$ = $-(CH_2)_2OH$) and acylated to **9i** with $R^{1''}$ = $-(CH_2)_2OCOMe$.

Table 2: Synthesis of amides **9a-i** via reduction of nitriles **12a-g** to pyrazolo-ortho-methylamines and subsequent conversion with aliphatic anhydrides or chlorides **11a-c**.

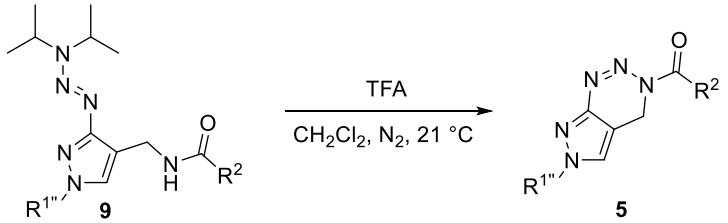


Entry[a]	12	R^1 (12)	16	11	9	$R^{1''}$ (9)	R^2	Yield 9 (%)

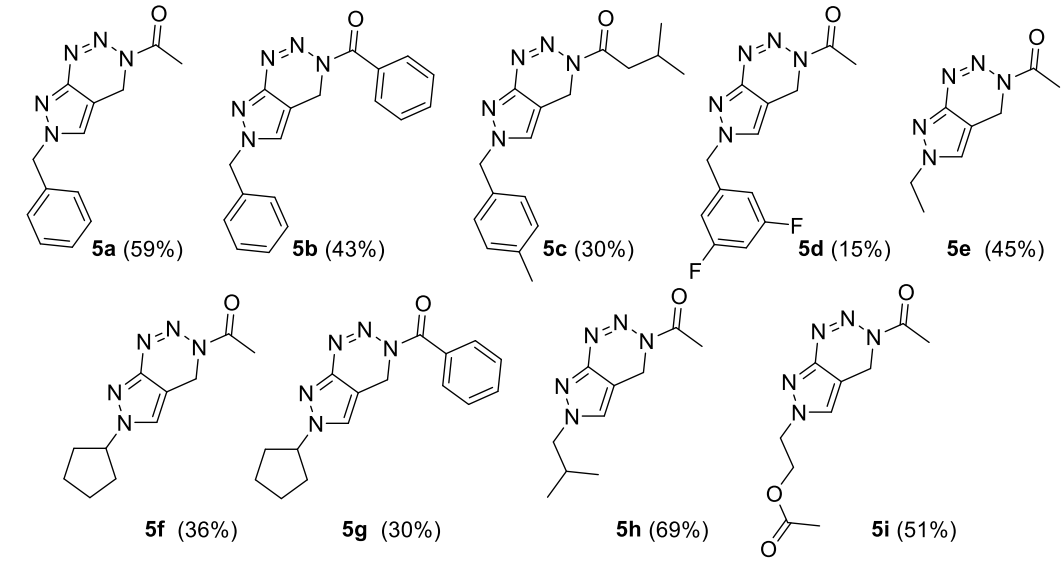
1	**12a**	Bn	**16a**	**11a**	**9a**	Bn	Me	23
2[b]	**12a**	Bn	**16a**	**11b**	**9b**	Bn	Ph	41
3	**12b**	Tolyl-CH_2	**16b**	**11c**	**9c**	Tolyl-CH_2	iBu	61
4[b]	**12c**	3,5-Difluorobenzyl	**16c**	**11a**	**9d**	3,5-Difluorobenzyl	Me	5
5	**12d**	Ethyl	**16d**	**11a**	**9e**	Ethyl	Me	59
6	**12e**	Cyclopentyl	**16e**	**11a**	**9f**	Cyclopentyl	Me	74
7	**12e**	Cyclopentyl	**16e**	**11b**	**9g**	Cyclopentyl	Ph	63
8	**12f**	*i*Butyl	**16f**	**11a**	**9h**	*i*Butyl	Me	52
9	**12g**	$EtCO_2CH_2$	**16g**	**11a**	**9i**	$MeCO_2(CH_2)_2$	Me	72

[a]The reaction consists of two steps. The intermediate compound **16** was isolated but not purified and used as obtained. Conditions: first step: **12**, $LiAlH_4$ (3.0 equiv.), THF, 0 °C to 21 °C, then 50 °C. Second step: **11** (X = $OCOR^2$) (1.5 equiv.), THF, 0 °C to 21 °C. [b]In a modified protocol, acid chlorides were used instead of anhydrides to introduce R^2. The second step was altered as follows: **11** (X = Cl) (1.5 equiv.), THF, NEt_3 (3.0 equiv.), 0 °C to 21 °C.

The last step to the synthesis of the target compounds **5a-5i** included the cleavage of the triazene unit of the amides **9** with subsequent cyclization to the final pyrazolo[3,4-d][1,2,3]triazine compounds **5** (Scheme 4). The successful cyclizations gave the desired pyrazolo[3,4-d][1,2,3]triazines **5** in moderate to good yields. Not all cyclization products were air-stable. While compounds **5a** to **5d** with a benzylic side chain in $R^{1"}$ were stable and a full characterization was possible, especially pyrazolotriazines with an aliphatic substituent on the pyrazole-nitrogen (**5e**-**5i**) degraded rapidly in contact with air/moisture.



$R^{1"}$ = Bn, 4-methylbenzyl, 3,5-difluorobenzyl, ethyl, isobutyl, cyclopentyl, -$CH_2CH_2OC(O)Me$
R^2 = Me, Ph, ^{i}Bu



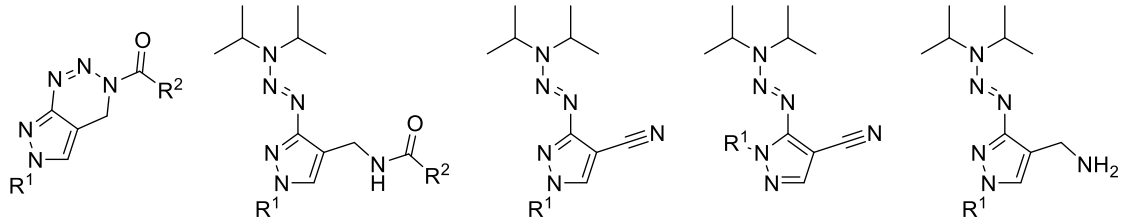
Scheme 4. Cleavage of the triazene protective group and cyclization of the resulting diazonium intermediate yielding pyrazolo[3,4-d][1,2,3]-3H-triazine-derivatives **5a-5i**.

The conversion of the region-isomeric compounds **10** to **6** failed under the conditions described in Scheme 4. The triazene protective group could not be cleaved even under harsh conditions (temperatures up to 100 °C in dichloroethane and use of H_2SO_4 as acid) and the starting material was recovered in all of the reactions.

Selected final compounds **5** and intermediates **9**, **12**, **13** and **16** obtained in this work were tested for their cytotoxicity. We conducted standardized MTT-assays [45] to evaluate, if the newly accessible compounds of type **5** and their precursors could become interesting target molecules for biological investigations or if the compounds show high toxicity which might prevent their use. We monitored cytotoxicity at six different concentrations ranging from 0.5 µM to 50 µM (for detailed results, see supporting information). It was found that the exemplarily chosen compounds of type

5, namely **5a**, **5d-f** and **5h**, did not reduce the viability of the human epithelial cervix carcinoma (HeLa) cells at every concentration tested. Those three derivatives of the target compound class 5 were chosen as they were available in sufficient amounts and showed no decomposition during storage and dilution in DMSO. Also most of the intermediates showed no reduction of cell viability, however, compounds **9b**, **12b-c**, **13a-b** and **13f-h** showed some cytotoxic effects at high concentrations (see Table 3 and supporting information, Table S1).

Table 3. Selected pyrazolo[1,2,3]triazines **5** and intermediates **9**, **12**, **13** and **16** and their calculated IC_{50}-values after treatment of HeLa cells with different concentrations of the respective compounds.



5 **9** **12** **13** **16**

Entry	Compound	R^1	R^2	IC_{50} [µM]
1	**5a**	Bn	Me	>50
2	**5d**	3,5-Difluorobenzyl	Me	>50
3	**5e**	Ethyl	Me	>50
4	**5f**	Cyclopentyl	Me	>50
5	**5h**	*i*Butyl	Me	>50
6	**9a**	Bn	Me	>50
7	**9b**	Bn	Ph	17
8	**9c**	Tolyl-CH_2	*i*Butyl	>50
9	**9d**	3,5-Difluorobenzyl	Me	>50
10	**9e**	Ethyl	Me	>50
11	**9f**	Cyclopentyl	Me	>50
12	**9g**	Cyclopentyl	Me	>50

13	**9h**	*i*Butyl	Ph	>50
14	**9i**	$MeCO_2(CH_2)_2$	Me	>50
15	**12a**	Bn	–	>50
16	**12b**	Tolyl-CH_2	–	41
17	**12c**	3,5-Difluorobenzyl	–	49
18	**12d**	Ethyl	–	>50
19	**12e**	Cyclopentyl	–	>50
20	**12f**	*i*Butyl	–	>50
21	**12g**	$EtCO_2CH_2$	–	>50
22	**12h**	4-Bromobenzyl	–	>50
23	**13a**	Bn	–	47
24	**13b**	Tolyl-CH_2	–	45
25	**13c**	3,5-Difluorobenzyl	–	>50
26	**13d**	Ethyl	–	20
27	**13e**	Cyclopentyl	–	>50
28	**13f**	*i*Butyl	–	46
29	**13g**	$EtCO_2CH_2$	–	21
30	**13h**	4-Bromobenzyl	–	29
31	**16f**	*i*Butyl	–	>50

Interestingly, no common structural motif promoted an increase of the *in vitro* cytotoxicity. However, by comparison of the IC_{50}-values of the compound classes **12** and **13**, regio-isomerism seems to play a decisive role: while compounds **12a** and **12d-h** had no influence on the viability of HeLa-cells, their regio-isomers **13a** and **13d-h** decreased the viability at high micormolar concentrations. A slightly increased cytotoxicity of some derivatives of compound class **12** compared to **13** was observed for **12b** and **12c**. The amides **9** had no influence on the viability except of derivate **9b**, characterized by two aromatic moieties at both variable positions R^1 and R^2.

As the IC_{50}-value of every compound tested lies above the concentration range that is interesting for biological applications, we consider our novel molecules as feasible

for further biological screenings. We will continue our studies with the search of potential targets for the versatile pyrazolo[1,2,3]triazine library presented herein.

Conclusion

In analogy to literature-known acid-induced conversions of triazene-benzyl acetamides to 3,4-dihydrobenzo[d][1,2,3]triazines, so far not described pyrazolo[3,4-d][1,2,3]-3H-triazines **5** were successfully synthesized. Altogether nine derivatives **5a**-**5i** were synthesized in five steps starting from the commercially available 3-(3,3-diisopropyltriaz-1-en-1-yl)-1H-pyrazole-4-carbonitrile. The herein given examples were generated by the introduction of two side-chains, one on the pyrazole-core and the other as a side-chain added to a methylamine intermediate in step 2 and step 4 of the reaction sequence. Depending on the introduced side-chain, further modifications were obtained (shown for compound **9g**). The triazene protective group tolerates the reaction conditions used for the herein described processes and is probably compatible with many others that are described in the literature, but limitations are given to acidic reaction media which tend to cleave the protective group. So far, the attempts to synthesize compounds of general structure **6**, a regio-isomer of the successfully gained pyrazolo[3,4-d][1,2,3]-3H-triazines **5**, failed under similar procedures.

Supporting Information

The Supporting Information contains detailed descriptions of the reactions and protocols as well as the characterization of all target compounds. Further, information on the synthesis of compounds **10** from **13**, which are not part of the main manuscript, is given (SI_File 1). It contains information on the availability of the

research data in the repository chemotion including direct links to the datasets and the reference numbers of the target compounds deposited in the Molecule Archive (SI_File 2) to be requested for further investigation or clarification if desired. CCDC 2054633 (**12h**), and 2054634 (**13c**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgments

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Abbreviations

TFA, trifluoroacetic acid; DMSO, dimethylsulfoxide; THF, tetrahydrofurane, TLC, thin layer chromatography, LCMS, liquid chromatography / mass spectrometry.

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