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DIVERSITY-ORIENTED SYNTHESIS OF SUBSTITUTED PYRAZOLO-[4,3-*d*][1,2,3]TRIAZIN-4-ONES

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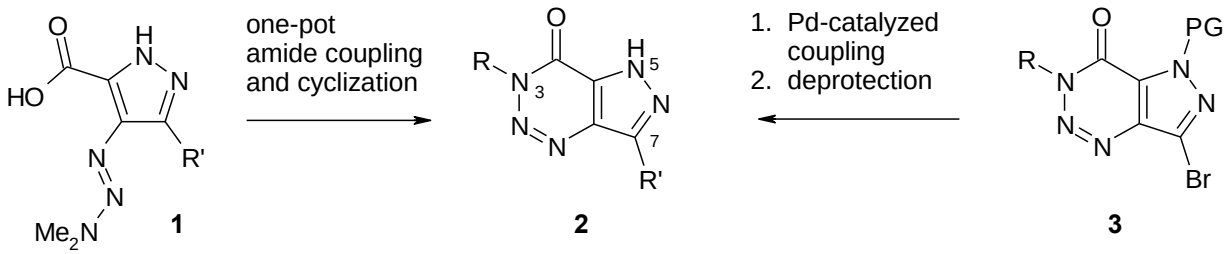
Abstract – An efficient synthesis of 3,7-disubstituted 3,5-dihydro-4*H*-pyrazolo-[4,3-*d*][1,2,3]triazin-4-ones (**2**), especially suited for late-stage decoration, is described. Diverse 3-benzyl analogs were obtained by amidation-cyclization in one pot and various pyrazolotriazinone-7-bromides were employed in Suzuki and Sonogashira cross-coupling reactions.

INTRODUCTION

In medicinal chemistry heterocyclic scaffolds represent building blocks of paramount importance, since they provide an assorted selection of varying geometries, polarities, and hydrogen-bonding properties, useful for the elaboration of structure-activity relationships and the optimization of pharmacokinetic and physicochemical parameters. In this respect and also in terms of intellectual property, underutilized heterocyclic systems such as the pyrazolotriazinones offer a variety of new opportunities.

Purine base analogs have been the subject of numerous medicinal chemistry programs as their structure inherently bears the key to many beneficial biological properties.[1,2] Surprisingly, only rare literature precedent exists on pyrazolo[4,3-*d*][1,2,3]triazin-4-ones. For example, Baraldi et al. have described them as adenosine A_1- and A_{2a}-receptor antagonists[3] and Manfredini *et al*. showed pyrazolotriazinone nucleosides to display cytostatic properties.[4] Previously, these heterocycles were accessed by a six-step linear sequence.[3,4,5,6] However, for elaboration of structure-activity relationships, this approach is hampered by the early introduction of substituents R and R'. A recent medicinal chemistry program required a general, straightforward, and diversity-oriented synthesis of 3,7-disubstituted 3,5-dihydro-4*H*-pyrazolo[4,3-*d*][1,2,3]triazin-4-ones **2** (Scheme 1). Herein, we report two novel synthetic strategies to pyrazolotriazinones **2,** designed for rapid and convenient "analoging" allowing the late-stage introduction of substituents R or R'.

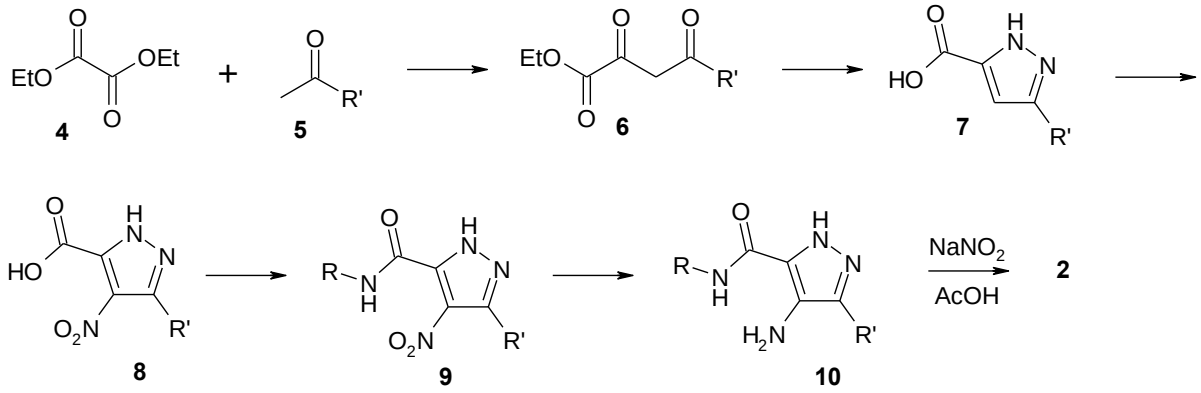
Scheme 1



RESULTS AND DISCUSSION

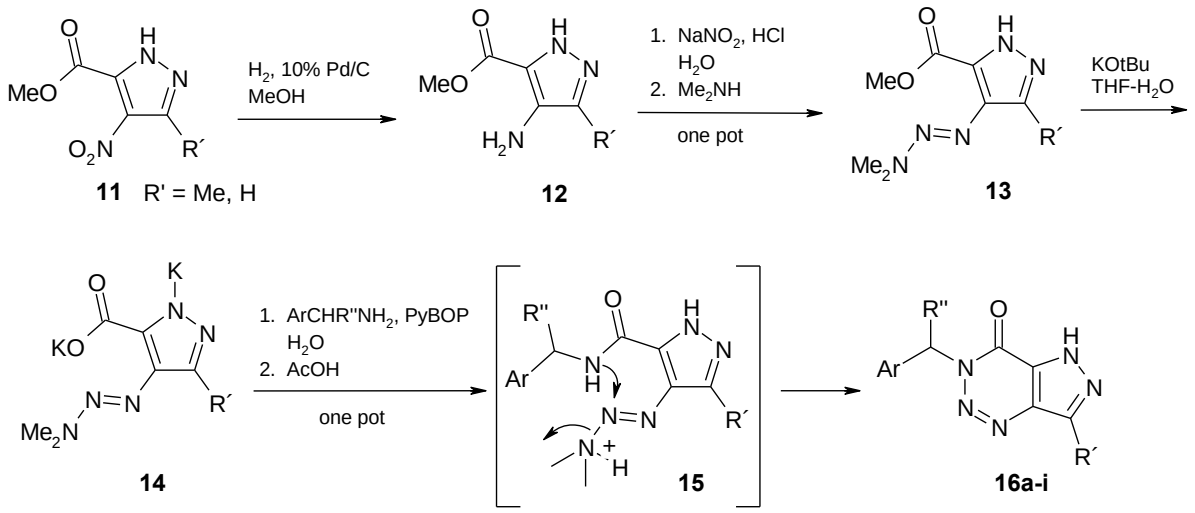
Published syntheses of 3,7-disubstituted 3,5-dihydro-4H-pyrazolo[4,3-d][1,2,3]triazin-4-ones **2**, followed a diazonium mediated ring closing strategy starting from pyrazole carboxamides of type **10**[7,8] (Scheme 2).

Scheme 2



Accordingly, the incorporation of a new substituent R at position 3 required a three-step sequence starting from nitrocarboxylic acid **8**. Efforts to establish a convenient and chemically feasible one pot procedure failed as reactants and solvents were incompatible for this purpose. As a consequence, the isolation and purification of all intermediates was required. In our search for an improved method we got inspired by the proficient work of Braese et al.,[9] who converted a resin-bound 2-carboxy-phenyltriazene into a benzotriazinone by amide coupling followed by TFA-mediated cleavage and simultaneous cyclization. We adapted Braese's solid-phase methodology to our needs for producing a solution-phase library, using triazene carboxylate **14** as a key intermediate (Scheme 3). In this route, the *N*,*N*-dimethyltriazene was acting as a protected form of the diazonium ion intermediate. This route was readily amenable to parallel synthesis.

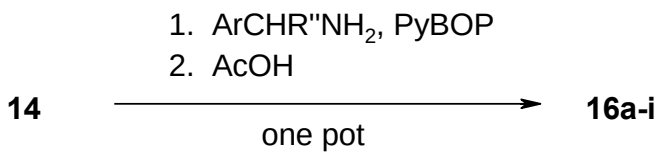
Scheme 3



PyBOP: (Benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate

Esters **11** were prepared according to literature procedures[10,11] from commercially available starting materials **7**. Hydrogenation of **11** yielded the amines **12** which were treated with sodium nitrite. The intermediate diazonium ions could be captured by addition of dimethylamine to form the stable triazenes **13**. Saponification of **13** gave the dipotassium salts **14** on a multi-gram scale. Triazenes **14** reacted with a broad variety of primary amines under standard amide coupling conditions with (Benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyBOP) as the coupling reagent. The triazene amides could be isolated, however, subsequent addition of acetic acid to the reaction mixture induced clean cyclization to the desired pyrazolotriazinones **16a-i** in one pot from triazenes **14**, conceivably via the intermediate **15**. Starting from esters **11** the complete sequence required just a single final chromatography to obtain the pyrazolotriazinones **16a-i** in acceptable yields (Table 1).

Table 1. 3-Benzylpyrazolotriazinones **16a-i** from triazenes **14**



Nr.	**Ar**	**R''**	**R'**	**Yield [%]**
16a	3-MePh	H	Me	26
16b	3-NO_2Ph	H	Me	42
16c	4,6-Me_2-2-pyrimidinyl	H	Me	39
16d[a]	Ph	CH_2OH	Me	24

Nr.	Ar	R''	R'	Yield [%]
16e[a]	3-Pyridyl	CH_2CO_2Me	Me	17
16f	p-ClPh	H	H	30
16g	3,5-F_2Ph	H	H	28
16h	4-MeSPh	H	H	28
16i[a]	6-MeO-3-Pyridyl	Me	H	21

a) racemate

Aromatic as well as heterocyclic benzylic amines with different substitution patterns have successfully been utilized following the amidation-cyclization-procedure (Table 1). In addition, branched substrates with R'' = alkyl could be employed. In all, by the procedure sketched in Scheme 3, we rapidly prepared over one hundred structurally diverse analogs.[12]

Position 7 in the pyrazolotriazinone-scaffold could successfully be addressed by Pd-catalyzed methodologies starting from bromo derivatives of type **18** (Scheme 4) or **22** (Scheme 5). The novel bromides **17** and **21** were synthesized in good yield by heating **16f** or **20** with NBS in acetonitrile. The same procedure could be employed for the preparation of iodo- or chloro-substituted congeners by using NIS (Scheme 7) or NCS[12] instead of NBS. Suzuki and Sonogashira cross-coupling reactions were readily feasible (Scheme 4, Scheme 5, Table 2, Table 3). However, attempts to perform coupling reactions with N-5 H-pyrazolotriazinones failed due to decomposition of starting material. Representative examples selected from about 70 diverse analogs synthesized by a Suzuki protocol are listed in Table 2. Low yields were observed in the cases **19a-h** where unpurified starting material was employed.

Scheme 4

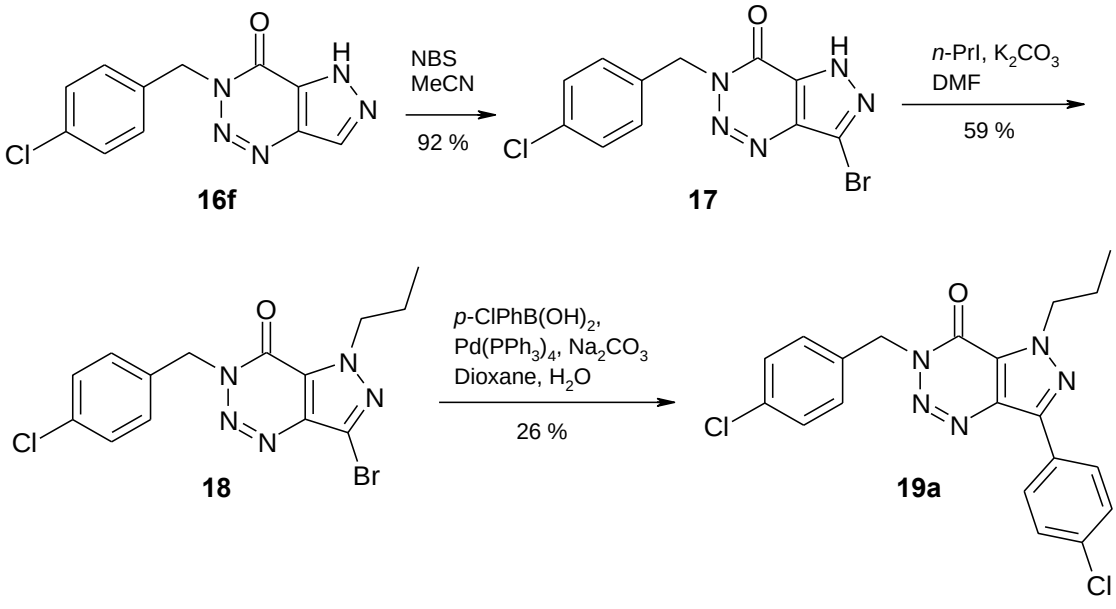
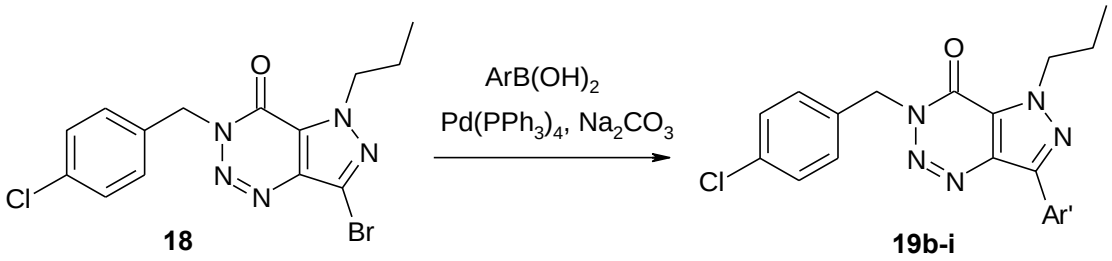


Table 2. 7-Arylpyrazolotriazinones **19b-i** from bromide **18**

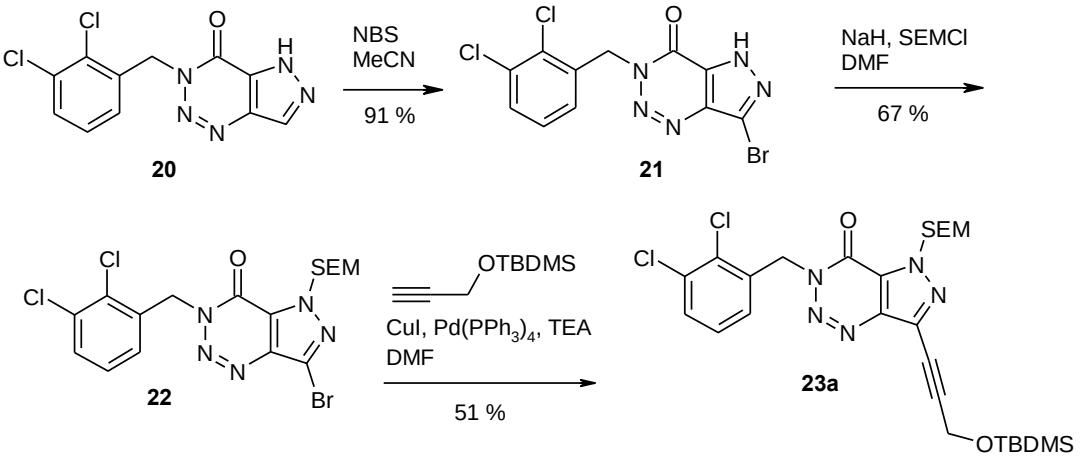


18 **19b-i**

Nr.	**Ar'**	**Yield [%]**
19b	4-VinylPh	18
19c	4-($HOCH_2$)Ph	10
19d	4-Pyridyl	27
19e	Benzothiophen-3-yl	20
19f	2-CF_3Ph	19
19g	3,5-Me_2-isoxazolin-4-yl	29
19h	N-Isobutyl-pyrazolin-4-yl	29
19i	3-NO_2Ph	49

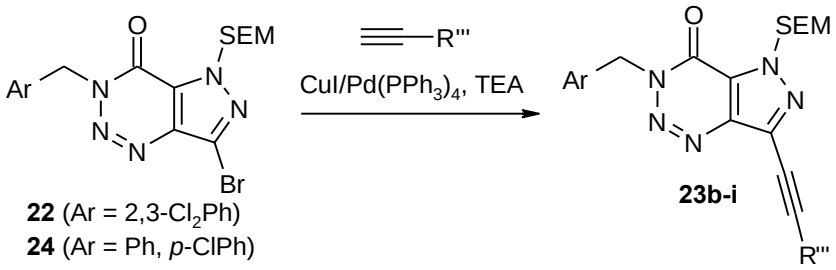
Sonogashira couplings were preferentially performed on SEM-protected substrates such as **22** and **24** (Scheme 5, Table 3). Compounds **24** were obtained analogously to the procedure sketched in Scheme 5 (see experimental section). The reactions reproducibly gave the desired products in moderate to good yield (Table 3). In some cases Glaser-type alkynyl homo coupling products were isolated along the target compounds. Functionalities like esters of benzoic acid, ether-, dialkylamino- and silyl-groups were tolerated while the conversion of alkynylesters met with failure.

Scheme 5



SEM: 2-Trimethylsilylethoxymethyl; TBDMS: *tert*-butyldimethylsilyl

Table 3. 7-Alkynylpyrazolotriazinones **23b-i** from bromides **22** and **24**



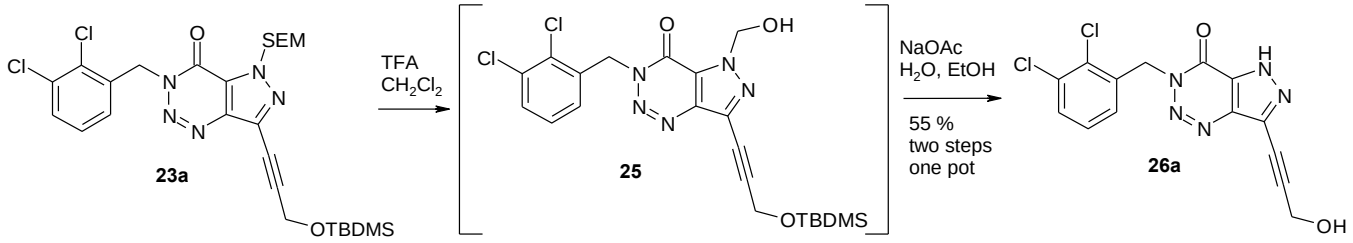
22 (Ar = 2,3-Cl_2Ph)
24 (Ar = Ph, *p*-ClPh)

Nr.	**Ar**	**R'''**	**Yield [%]**
23b	Ph	Ph	42
23c	Ph	TMS	61
23d	Ph	$TBDMSOCH_2$	56
23e	4-ClPh	4-MeOPh	50
23f	4-ClPh	Cyclohexyl	93
23g	4-ClPh	2-($MeCO_2$)Ph	61
23h	2,3-Cl_2Ph	2-($MeCO_2$)Ph	62
23i	4-ClPh	Me_2NCH_2	63

SEM: Trimethylsilylethoxymethyl; TBDMS: *tert*-butyldimethylsilyl

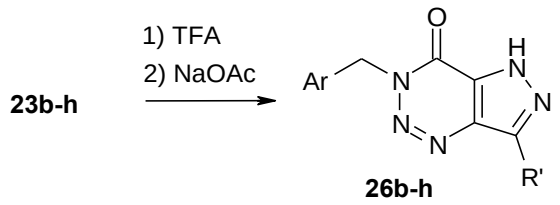
The deprotection of the pyrazole nitrogen was achieved in a stepwise manner (Scheme 6). Treatment of **23a** with trifluoroacetic acid yielded mixtures of hemiaminal **25**[13] and the desired NH-pyrazolotriazinone **26a**. However, pure **26a** could be obtained by treatment of the intermediate mixture under basic conditions. Yields varied considerably when this procedure was transferred to other substrates (Table 4). Attempts to achieve complete deprotection with tetrabutylammonium fluoride failed due to decomposition of the starting material.

Scheme 6



SEM: 2-Trimethylsilylethoxymethyl; TBDMS: *tert*-butyldimethylsilyl

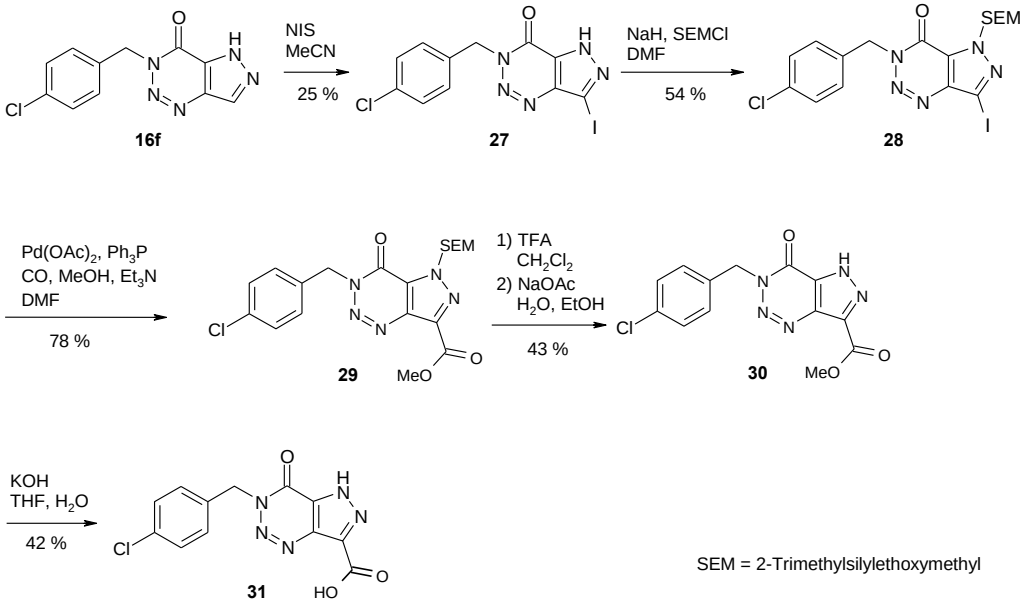
Table 4. 7-Acetylenylpyrazolotriazinones **26b-h** from **23b-h**



Nr	Ar	R’	Yield [%]
26b	Ph	Ph—	70
26c	Ph	TMS—	53
26d	Ph	$HOCH_2$—	62
26e	4-ClPh	Cyclohexyl—	14
26f	4-ClPh	2-($MeCO_2$)Ph—	39
26g	2,3-Cl_2Ph	2-($MeCO_2$)Ph—	67
26h	4-ClPh	4-MeOPh—	20

In an alternative approach to introduce structural diversity in the 7-position we were able to capitalize of iodide **28** by applying a palladium catalyzed methoxycarbonylation using carbon monoxide under atmospheric pressure (Scheme 7). In two consecutive steps the acid **31** was prepared from ester **29**. Building blocks of type **31** open the door to a wide variety of drug like compounds (e.g. amides) by applying standard protocols.

Scheme 7



In summary, we have designed an efficient late-stage decorating procedure for the pyrazolotriazinone core **2**. A one pot amidation-cyclization procedure was applied in broad scope and gave access to diverse analogs with benzylic substituents in the 3-position. Furthermore, pyrazolotriazinone-7-bromides were employed in a series of Suzuki and Sonogashira cross-coupling reactions. Likewise, also Stille or Heck-type Pd-catalyzed cross-couplings should be feasible with these valuable novel halogenated building-blocks.

EXPERIMENTAL

Methods and materials:

Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. Flash chromatography was done on silica gel (0.063 - 0.200 mm) from Merck KgaA, Darmstadt, Germany. Preparative HPLC chromatography was done on a 250 mm x 30 mm column packed with YMC gel ODS-AQ S-5 / 15 µM, with MeCN / water as eluent and UV detection. Spin multiplicities of NMR spectra are given as s (singlet), d (doublet), t (triplet), q (quartet) m (multiplet) as well as br (broad).

LC-MS method 1 for Table 1, 2, a and b: instrument MS Waters ZQ 2000; Instrument HPLC Agilent 1100, 2-column-circuit, autosampler HTC PAL; column YMC-ODS-AQ, 50 mm x 4.6 mm, 3.0 µm; eluent A: water + 0.1% formic acid, eluent B: MeCN + 0.1% formic acid; gradient: 0.0 min 100%A → 0.2 min 95%A → 1.8 min 25%A → 1.9 min 10%A → 2.0 min 5%A → 3.2 min 5%A → 3.21 min 100%A → 3.35 min 100%A; oven: 40 °C; flow: 3.0 mL/min; UV-detection: 210 nm.

LC-MS method 2: instrument MS Micromass ZQ; instrument HPLC Waters Alliance 2795; column Phenomenex Synergi 2µ Hydro-RP Mercury 20 mm x 4 mm; eluent A: 1 l water + 0.5 mL 50% formic acid, eluent B: 1 l MeCN + 0.5 mL 50% formic acid; gradient: 0.0 min 90%A → 2.5 min 30%A → 3.0 min 5%A → 4.5 min 5%A; flow: 0.0 min 1 mL/min, 2.5 min/3.0 min/4.5 min 2 mL/min; oven: 50 °C; UV-detection: 210 nm.

LC-MS method 3: Instrument Micromass Quattro LCZ with HPLC Agilent series 1100; column Phenomenex Synergi 2 µ Hydro-RP Mercury 20 mm x 4 mm; eluent A: 1 l water + 0.5 mL 50% formic acid, eluent B: 1 l MeCN + 0.5 mL 50% formic acid; gradient: 0.0 min 90% A → 2.5 min 30% A → 3.0 min 5% A → 4.5 min 5% A; flow: 0.0 min 1 mL/min, 2.5 min/3.0 min/4.5 min 2 mL/min; oven: 50 °C; UV-detection: 208- 400 nm..

LC-MS method 4: Instrument MS Micromass ZQ; Instrument HPLC HP 1100 Series; UV DAD; column Phenomenex Synergi 2 µ Hydro-RP Mercury 20 mm x 4 mm; eluent A: 1 l water + 0.5 mL 50% formic acid, eluent B: 1 l MeCN + 0.5 mL 50% formic acid; gradient: 0.0 min 90% A → 2.5 min 30% A → 3.0 min 5% A → 4.5 min 5% A; flow: 0.0 min 1 mL/min, 2.5 min/3.0 min/4.5 min. 2 mL/min; oven: 50 °C;

UV-detection: 210 nm.

HPLC method 1: Instrument HP 1100 with DAD-detection; column Kromasil 100 RP-18, 60 mm x 2.1 mm, 3.5 µm; eluent: A = 5mL $HClO_4$ (70 %)/L H_2O, B = MeCN, gradient: 0 min 2% B → 0.5 min 2% B → 4.5 min 90% B → 6.5 min 90% B → 6.7 min 2% B → 7.5 min 2 % B, flow: 0.75 mL/min, column temperature: 30 °C, detection: UV 210 nm.

HPLC method 2: Instrument: HP 1100 with DAD-detection; column Kromasil 100 RP-18, 60 mm x 2.1 mm, 3.5 µm; eluent: A = 5 mL $HClO_4$ (70 %ig)/L H_2O, B = MeCN; gradient: 0 min 2% B → 0.5 min 2% B → 4.5 min 90% B → 15 min 90% B → 15.2 min 2% B → 16 min 2 % B, flow: 0.75 mL/min, column temperature: 30 °C, detection: UV 210 nm.

HPLC method 3: Instrument HP 1100 with DAD-detection; column Kromasil 100 RP-18, 60 mm x 2.1 mm, 3.5 µm; eluent: A = 5 mL $HClO_4$ (70 %ig)/L H_2O, B = MeCN; gradient: 0 min 2% B → 0.5 min 2% B → 4.5 min 90% B → 9 min 90% B → 9.2 min 2% B → 10 min 2 % B, flow: 0.75 mL/min, column temperature: 30 °C, detection: UV 210 nm.

Synthetic procedures:

4-[3,3-Dimethyltriaz-1-en-1-yl]-3-methyl-1H-pyrazol-5-carboxylic acid methyl ester (13) (R' = Me)

3-Methyl-4-nitro-1*H*-pyrazol-5-carboxylic acid methyl ester **11** (13.10 g, 71 mmol) was dissolved in MeOH (150 mL) and hydrogenated (4 bar H_2) for 2 h using 10 % palladium on charcoal (1.00 g) as catalyst. The resulting suspension was filtered through Celite, the solvent was removed in vacuo and the residue was taken up in water (40 mL) and concentrated hydrochloric acid (18 mL). After cooling to 0 °C a solution of sodium nitrite (4.90 g, 71 mmol) in water (10 mL) was added dropwise. The reaction was stirred for 10 min at 0 °C. Then a 40 % aqueous solution of dimethylamine was added dropwise until pH = 9 was reached. The ice bath was removed and the reaction mixture was stirred for additional 10 min. The product was collected by suction, washed with water and dried overnight at 60 °C under vacuum. 7.32 g (48%) of the target compound were obtained as a solid.

MS (ESIpos): m/z = 212 $(M+H)^+$.

^{1}H-NMR (300 MHz, DMSO-d_6): 2 sets of signals in a ratio of 1.5:1. Signal set 1: δ = 2.23 (s, 3H), 3.0 - 3.4 (s br, 6H), 3.72 (s, 3H), 13.03 (s br, 1H). Signal set 2: δ = 2.20 (s, 3H), 3.0 - 3.4 (s br, 6H), 3.78 (s, 3H), 13.24 (s br, 1H).

4-[3,3-Dimethyltriaz-1-en-1-yl]-1H-pyrazol-5-carboxylic acid methyl ester (13) (R' =H) was synthesized analogously.

Dipotassium 4-[3,3-dimethyltriaz-1-en-1-yl]-3-methyl-1H-pyrazol-1-yl-5-carboxylate (14) (R'=Me)

Water (330 µL) was added dropwise to a suspension of potassium *tert*-butylate (2.06 g, 18 mmol) in dry

THF (20 mL). Then the mixture was stirred for 10 min at rt. 4-[3,3-Dimethyltriaz-1-en-1-yl]-3-methyl-1*H*-pyrazol-5-carboxylic acid methyl ester (1.29 g, 6.0 mmol) was added and stirring was continued for additional 10 min. The solvent was evaporated, and the resulting product was used without further purification.

Dipotassium 4-[3,3-dimethyltriaz-1-en-1-yl]-1H-pyrazol-1-yl-5-carboxylate (14) (R' = H) was synthesized analogously.

3-(4-Chlorobenzyl)-3,5-dihydro-4H-pyrazolo[4,3-d][1,2,3]triazin-4-one (16f)

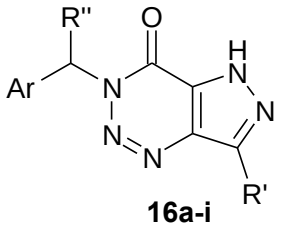
Dipotassium 4-[3,3-dimethyltriaz-1-en-1-yl]-1*H*-pyrazol-1-yl-5-carboxylate (32 mg, 0.1 mmol) and triethylammonium chloride (41 mg, 3.0 mmol) were dissolved in DMF (0.8 mL) and the mixture was stirred for 15 min. PyBOP (62 mg, 0.12 mmol) was added followed by 1-(4-chlorophenyl)methanamine (42 mg, 0.3 mmol) and the solution was stirred for 2 h at rt. Acetic acid (0.5 mL) was added, and the reaction mixture was stirred for additional 16 h at ambient temperature. The suspension was diluted with DMF, filtered and purified by preparative HPLC. The target compound was obtained as a solid: 8 mg (30 %).

LC/MS method 4: R_t = 2.13 min, m/z = 262 $(M+H)^+$.

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 5.58 (s, 2H), 7.37 (d, 2H), 7.41 (d, 2H), 8.81 (s br, 1H), 15.01 (s br, 1H).

All examples in Table a were prepared analogously and characterized by LC/MS method 1.

Table a. 3-Benzylpyrazolotriazinones



16a-i

Nr.	Ar	R''	R'	Mass detected $[M+H]^{+}$. [a]	Retention Time [min][a]	Yield [%]
16a	3-MePh	H	Me	256	1.74	26
16b	3-NO_2Ph	H	Me	287	1.63	42
16c	4,6-Me_2-2-pyrimidinyl	H	Me	272	1.34	39
16d[a]	Ph	(CH_2OH	Me	272	1.46	24
16e[a]	3-Pyridyl	CH_2CO_2Me	Me	315	1.13	17
16g	3,5-F_2Ph	H	H	264	1.63	28

Nr.	Ar	R''	R'	Mass detected $[M+H]^{+\cdot}$ [a]	Retention Time [min][a]	Yield [%]
16h	4-MeSPh	H	H	274	1.69	28
16i	6-MeO-3-Pyridyl	Me	H	273	1.47	21

a = racemate

7-Bromo-3-(4-chlorobenzyl)-3,5-dihydro-4H-pyrazolo[4,3-d][1,2,3]triazin-4-one (17)

3.5 g (13.3 mmol) 3-(4-chlorobenzyl)-3,5-dihydro-4H-pyrazolo[4,3-d][1,2,3]triazin-4-one **16f** and 2.6 g (14.6 mmol) *N*-bromosuccinimid were suspended in 50 mL anhydrous MeCN and the reaction mixture was stirred for 1 h at 60 °C. The reaction was quenched by addition of 25 mL water and the solvent was removed in vacuo partially causing the product to crystallize. The solid was filtered off and washed with water. 4.16 g (92%) of the target compound was obtained.

LC/MS method 2: R_t = 2.16 min, m/z = 341 $(M+H)^+$.

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 5.60 (s, 2H), 7.34 - 7.44 (m, 4H), 15.40 (s br, 1H).

7-Bromo-3-(4-chlorobenzyl)-5-propyl-3,5-dihydro-4H-pyrazolo[4,3-d][1,2,3]triazin-4-one (18)

7-Bromo-3-(4-chlorobenzyl)-3,5-dihydro-4H-pyrazolo[4,3-d][1,2,3]triazin-4-one (97 mg, 0.3 mmol), 1-iodopropane (49 mg, 0.3 mmol) and potassium carbonate (79 mg, 0.6 mmol) were stirred overnight in DMF (4 mL) at rt. The reaction mixture was separated by preparative HPLC. 65 mg (59%) of the target compound were obtained as a solid.

LC/MS method 2: R_t = 2.77 min, m/z = 384 $(M+H)^+$.

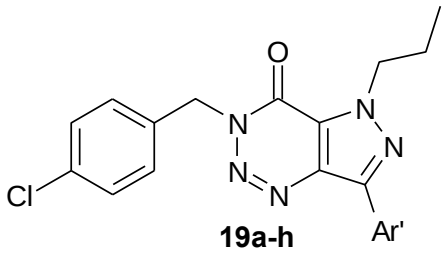
^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.42 (d, 2H), 7.39 (d, 2H), 5.57 (s, 2H), 4.51 (t, 2H), 1.86 (d tr, 2H), 0.84 (t, 3H).

7-(3-Nitrophenyl)-3-(4-chlorobenzyl)-5-propyl-3,5-dihydro-4H-pyrazolo[4,3d][1,2,3] triazin-4-one (19i)

7-Bromo-3-(4-chlorobenzyl)-5-propyl-3,5-dihydro-4*H*-pyrazolo[4,3-*d*][1,2,3]triazin-4-one (151 mg, 0.394 mmol), 3-nitrophenylboronic acid (82 mg, 0.493 mmol), tetrakis(triphenylphosphino)palladium (28.5 mg, 0.025 mmol) and sodium carbonate (104 mg, 0.985 mmol) were mixed in dioxane (2.5 mL) and water (0.5 mL). The reaction mixture was stirred overnight at 85 °C. Yield according to LC/MS method 2 49 %.

All examples in Table b were prepared analogously and characterized by LC/MS method 1.

Table b. 7-Arylpyrazolotriazinones



19a-h

Nr.	**Ar'**	**Mass detected $[M+H]^{+}$.** [a]	**Retention time [min]**[a]	**Yield [%]**
19a	4-ClPh	414	2.42	26
19b	4-VinylPh	406	2.42	18
19c	4-($HOCH_2$)Ph	410	2.36	10
19d	4-Pyridyl	381	2.42	27
19e	Benzothiophen-3-yl	435	2.42	20
19f	2-CF_3Ph	448	2.51	19
19g	3,5-Me_2-isoxazolin-4-yl	399	2.42	29
19h	N-Isobutyl-pyrazolin-4-yl	426	2.42	29

3-(2,3-dichlorobenzyl)-3,5-dihydro-4H-pyrazolo[4,3-d][1,2,3]triazin-4-one (20)

9.97 g (63.5 mmol) 4-nitro-1*H*-pyrazole-5-carboxylic acid, 10.16 g (57.7 mmol) 1-(2,3-dichlorophenyl)-methanamine, 14.38 g (75.0 mmol) *N*-[3-(dimethylamino)propyl]-*N*'-ethylcarbodiimide hydrochloride and 9.36 g (69.2 mmol) 1*H*-benzotriazol-1-ol were dissolved in 380 mL of anhydrous DMF. The reaction was stirred over night before the solvent was removed in vacuo. After the residue has been taken up with water, the resulting suspension was poured onto a mixture of ice in water acidified by concentrated hydrochloric acid. The suspension was allowed to reach rt, then the solid was collected by filtration. After washing with water, recrystallization from EtOH and washing with Et_2O, 16.34 g (89 %) of *N*-(2,3-dichlorobenzyl)-4-nitro-1*H*-pyrazole-5-carboxamide was obtained.

1.167 g 10 % palladium on charcoal was suspended in 86 mL water and cooled with an ice bath before being treated with a suspension of 3.924 g (103.7 mmol) sodium borohydride in 86 mL water and 86 mL MeOH. 16.34 g (51.9 mmol) *N*-(2,3-dichlorobenzyl)-4-nitro-1*H*-pyrazole-5-carboxamide were added portionwise over a period of 10 min to the reducing mixture. The reaction was slowly allowed to reach rt, stirred for 1 h then again cooled to 0 °C. 1.962 g (51.9 mmol) sodium borohydride was added and the ice bath was removed. After the mixture has reached rt, it was filtered through celite. The solvent of the

filtrate was removed in vacuo and the residue was washed with water. 10.87 g (74 %) 4-amino-*N*-(2,3-dichlorobenzyl)-1*H*-pyrazole-5-carboxamide was obtained.

10.87 g (38.1 mmol) 4-amino-*N*-(2,3-dichlorobenzyl)-1*H*-pyrazole-5-carboxamide was dissolved in 61 mL DMF, 61 mL water and 122 mL acetic acid before being cooled to 0 °C. 3.288 g (47.7 mmol) sodium nitrite was added and the reaction was stirred over night at ambient temperature. The solvent was removed in vacuo and the residue was taken up with water. The solid was collected by filtration and washed with water. 10.23 g (91 %) of the title compound was obtained.

HPLC method 1: R_t = 4.31 min

MS (CIpos): m/z = 313 $(M+NH_4)^+$.

^{1}H-NMR (400 MHz, DMSO-d_6): 4.85 (s, 2H), 6.25 (d, 1H), 6.45 (t, 1H), 6.74 (d, 1H), 7.93 (s br, 1H)

7-Bromo-3-(2,3-dichlorobenzyl)-3,5-dihydro-4H-pyrazolo[4,3-d][1,2,3]triazin-4-one (21)

9.00 g (30.4 mmol) 3-(2,3-dichlorobenzyl)-3,5-dihydro-4*H*-pyrazolo[4,3-*d*][1,2,3]triazin-4-one and 5.95 g (33.4 mmol) *N*-bromosuccinimid were suspended in 115 mL anhydrous MeCN and the reaction mixture was stirred for 2 h at 60 °C. The reaction was quenched by addition of 57 mL water and the solvent was removed in vacuo. The solid was filtered off and washed with water. 10.4 g (91%) of the target compound was obtained.

HPLC method 1: R_t = 4.75 min

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 5.70 (s, 2H), 7.17 (d, 1H), 7.31 (t, 1H), 7.63 (d, 1H), 15.46 (s br, 1H).

7-Bromo-3-(2,3-dichlorobenzyl)-5-{[2-(trimethylsilyl)ethoxy]methyl}-3,5-dihydro-4H-pyrazolo[4,3-d]-[1,2,3]triazin-4-one (22)

1.00 g (2.67 mmol) 7-bromo-3-(2,3-dichlorobenzyl)-3,5-dihydro-4*H*-pyrazolo[4,3-*d*][1,2,3]triazin-4-one **21** and 1.39 g (8.36 mmol) [2-(chloromethoxy)ethyl](trimethyl)silane were dissolved in 8.40 mL anhydrous DMF followed by a portionwise addition of 304 mg (7.60 mmol) sodium hydride (60% w/w) at 0 °C. The reaction mixture was then stirred at rt for 30 min before being quenched with saturated aqueous sodium hydrogen carbonate solution. EtOAc was added, the organic phase was separated, washed with water and brine, dried over magnesium sulfate, and evaporated in vacuum. Purification by preparative HPLC yielded 904 mg (67%) of the target compound.

MS (CIpos): m/z = 521 $(M+NH_4)^+$.

^{1}H-NMR (300 MHz, DMSO-d_6): δ = -0.11 (s, 9H), 0.82 (t, 2H), 3.60 (t, 2H), 5.71 (s, 2H), 5,80 (s, 2H), 7.22 (dd, 1H), 7.30 (t, 1H), 7.62 (dd, 1H).

7-(3-{[tert-Butyl(dimethyl)silyl]oxy}prop-1-in-1-yl)-3-(2,3-dichlorobenzyl)-5-{[2(trimethylsilyl)-ethoxy]-methyl}-3,5-dihydro-4H-pyrazolo[4,3-d][1,2,3]triazin-4-one (23a)

500 mg (0.99 mmol) 7-bromo-3-(2,3-dichlorobenzyl)-5-{[2-(trimethylsilyl)ethoxy]methyl}-3,5-dihydro-4*H*-pyrazolo[4,3-*d*][1,2,3]triazin-4-one **22** were dissolved in 6.20 mL of anhydrous DMF together with 75 mg (0.40 mmol) copper(I) iodide and successively treated with 1.69 g (9.90 mmol, 2.01 mL) *tert*-butyl(dimethyl)(prop-2-in-1-yloxy)silane, 200 mg (1.98 mmol, 0.28 mL) triethylamine and 229 mg (0.20 mmol) tetrakis(triphenylphosphin)palladium(0). The mixture was stirred for 6 days at rt before being quenched with water and diluted with EtOAc. The organic phase was separated, washed with brine, dried over magnesium sulfate, filtered and evaporated to dryness. Purification by preparative HPLC yielded 301 mg (51%) of the target compound.

MS (ESIpos): m/z = 594 $(M+H)^+$.

^{1}H-NMR (300 MHz, DMSO-d_6): δ = -0.13 (s, 9H), 0.15 (s, 6H), 0.81 (t, 2H), 0.89 (s, 9H), 3.60 (t, 2H), 4.69 (s, 2H), 5.71 (s, 2H), 5.81 (s, 2H), 7.20 (dd, 1H), 7.30 (t, 1H), 7.62 (dd, 1H).

3-Benzyl-7-(phenylethynyl)-5-{[2-(trimethylsilyl)ethoxy]methyl}-3,5-dihydro-4H-pyrazolo[4,3-d][1,2,3]-triazin-4-one (23b)

Preparation as in the case of **23a**. 43 mg (42%) of the target compound were obtained.

MS (CIpos): m/z = 458 $(M+H)^+$.

HPLC method 2: R_t = 5.99 min

^{1}H-NMR (300 MHz, DMSO-d_6): δ = -0.01 (s, 9H), 0.94 (t, 2H), 3.73 (t, 2H), 5.74 (s, 2H), 5.95 (s, 2H), 7.38 - 7.49 (m, 5H), 7.57 - 7.61 (m, 3H), 7.76 - 7.81 (m, 2H).

3-Benzyl-5-{[2-(trimethylsilyl)ethoxy]methyl}-7-[(trimethylsilyl)ethinyl]-3,5-dihydro-4H-pyrazolo-[4,3-d][1,2,3]triazin-4-one (23c)

Preparation as in the case of **23a**. 370 mg (61%) of the target compound were obtained.

MS (CIpos): m/z = 454 $(M+H)^+$.

HPLC method 2: R_t = 5.88 min

^{1}H-NMR (300 MHz, DMSO-d_6): δ = -0.12 (s, 9H), 0.29 (s, 9H), 0.81 (t, 2H), 3.58 (t, 2H), 5.60 (s, 2H), 5.80 (s, 2H), 7.26 - 7.34 (m, 5H).

3-Benzyl-7-(3-{[tert-butyl(dimethyl)silyl]oxy}prop-1-yn-1-yl)-5-{[2-(trimethylsilyl)ethoxy]methyl}-3,5-dihydro-4H-pyrazolo[4,3-d][1,2,3]triazin-4-one (23d)

Preparation as in the case of **23a**. 1.35 g (56%) of the target compound were obtained.

HPLC method 2: R_t = 6.20 min

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 0.00 (s, 9H), 0.28 (s, 6H), 0.93 (t, 2H), 1.02 (s, 9H), 3.73 (t, 2H), 4.81 (s, 2H), 5.73 (s, 2H), 5.93 (s, 2H), 7.42 - 7.47 (m, 5H).

3-(4-Chlorobenzyl)-7-[(4-methoxyphenyl)ethinyl]-5-{[2-(trimethylsilyl)ethoxy]methyl}-3,5-dihydro-4H-pyrazolo[4,3-d][1,2,3]triazin-4-one (23e)

Preparation as in the case of **23a**. 276 mg (50%) of the target compound were obtained.

LC/MS method 3: R_t = 3.44 min, m/z = 521

^{1}H-NMR (400 MHz, DMSO-d_6): δ = -0.12 (s, 9H), 0.82 (t, 2H), 3.60 (t, 2H), 3.82 (s, 3H), 5.61 (s, 2H), 5.82 (s, 2H), 7.05 (d, 2H), 7.39 (s, 4H), 7.62 (d, 2H).

3-(4-Chlorobenzyl)-7-(cyclohexylethinyl)-5-{[2-(trimethylsilyl)ethoxy]methyl}-3,5-dihydro-4H-pyrazolo[4,3-d][1,2,3]triazin-4-one (23f)

Preparation as in the case of **23a**. 491 mg (93%) of the target compound were obtained.

MS (MSES+): m/z = 499 $(M+H)^+$.

HPLC method 2: R_t = 6.80 min

^{1}H-NMR (300 MHz, DMSO-d_6): δ = -0.14 (s, 9H), 0.80 (t, 2H), 1.25 - 1.84 (m, 11H), 3.56 (t, 2H), 5.58 (s, 2H), 5.77 (s, 2H), 7.38 (s, 4H).

Methyl 2-{[3-(4-chlorobenzyl)-4-oxo-5-{[2-(trimethylsilyl)ethoxy]methyl}-4,5-dihydro-3H-pyrazolo-[4,3-d][1,2,3]triazin-7-yl]ethinyl}benzoate (23g)

Preparation as in the case of **23a**. 354 mg (61%) of the target compound were obtained.

LC/MS method 4: R_t = 3.44 min, m/z = 549

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 0.00 (s, 9H), 0.95 (t, 2H), 3.73 (t, 2H), 4.03 (s, 3H), 5.74 (s, 2H), 5.96 (s, 2H), 7.51 (s, 4H), 7.75 (dt, 1H), 7.83 (dt,1H), 7.94 (d br, 1H), 8.11 (d br, 1H).

Methyl 2-{[3-(2,3-dichlorobenzyl)-4-oxo-5-{[2-(trimethylsilyl)ethoxy]methyl}-4,5-dihydro-3H-pyrazolo-[4,3-d][1,2,3]triazin-7-yl]ethinyl}benzoate (23h)

Preparation as in the case of **23a**. 270 mg (62%) of the target compound were obtained.

LC/MS method 3: R_t = 3.46 min, m/z = 583

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 0.00 (s, 9H), 0.95 (t, 2H), 3.74 (t, 2H), 4.02 (s, 3H), 5.84 (s, 2H), 5.97 (s, 2H), 7.33 (d br, 1H), 7.41 (t, 1H), 7.75 (dt, 2H), 7.81 (dt, 1H), 7.93 (d br, 1H), 8.10 (d br, 1H).

3-(4-chlorobenzyl)-7-[3-(dimethylamino)prop-1-yn-1-yl]-5-{[2-(trimethylsilyl)ethoxy]methyl}-3,5-dihydro-4H-pyrazolo[4,3-d][1,2,3]triazin-4-one (23i)

Preparation as in the case of **23a**. 317 mg (63%) of the target compound were obtained.

MS (CIpos): m/z = 473.

HPLC method 2: R_t = 4.74 min

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 0.12 (s, 9H), 0.92-1.01 (m, 2H), 2.41 (s, 6H), 3.67 - 3.74 (m, 2H), 3.75 (s, 2H), 5.72 (s, 2H), 5.92 (s, 2H), 7.51 (s, 4H).

7-Bromo-3-benzyl-5-{[2-(trimethylsilyl)ethoxy]methyl}-3,5-dihydro-4H-pyrazolo[4,3-d][1,2,3]triazin-4-one (24) (Ar = Ph)

6g (38.2 mmol) commercially available 4-nitro-3-pyrazolcarboxylic acid and 19.887 g (38.2 mmol) PyBOP were dissolved in 100 mL DMF before being treated with 4.1 g (38.2 mmol) benzylamine and *N*,*N*-diisopropylethylamine. The reaction was stirred over night, concentrated in vacuo and poured on a mixture of concentrated HCl, ice and water. The precipitate was collected and washed with water. Recrystallization from ethanol afforded 7.83 g (77%) of *N*-benzyl-4-nitro-1*H*-pyrazole-5-carboxamide.

0.715 g 10 % palladium on charcoal was suspended in 50 mL water and cooled with an ice bath before being treated with a suspension of 2.4 g (63.4 mmol) sodium borohydride in 50 mL water and 50 mL MeOH. 7.8 g (31.7 mmol) *N*-benzyl-4-nitro-1*H*-pyrazole-5-carboxamide were added portionwise over a period of 10 minutes to the reducing mixture. The reaction was slowly allowed to reach rt, stirred for 1.5 h and filtered through celite. The solvent of the filtrate was removed in vacuo and the residue was washed with water. 7.55 g of the residue were obtained which were taken in the subsequent reaction without further drying. 7.55 g (34.914 mmol) of the solid were taken up with a mixture of 30 mL of water, 30 mL of DMF and 60 mL of acetic acid before being cooled to 0°C. 3.011 g (43.6 mmol) sodium nitrite was added and the reaction was stirred for 30 min. The ice bath was removed and stirring continued for 3 h at rt. The solvent was removed in vacuo and the residue was taken up with water. The solid was collected by filtration and washed with water. 6.6 g (81 %) 3-benzyl-3,5-dihydro-4*H*-pyrazolo[4,3-*d*][1,2,3]triazin-4-one was obtained.

6.72 g (29.6 mmol) 3-benzyl-3,5-dihydro-4*H*-pyrazolo[4,3-*d*][1,2,3]triazin-4-one and 5.8 g (32.5 mmol) *N*-bromosuccinimid were suspended in acetonitrile and heated to 60 °C for 45 min. Water was added and solvents were reduced in vacuo until precipitation occurs. The precipitate was collected, washed with water and dried at 60 °C in vacuo. 7.67 g (85 %) of 7-Bromo-3-benzyl-3,5-dihydro-4*H*-pyrazolo-[4,3-*d*][1,2,3]triazin-4-one were obtained.

2.67 g (8.72 mmol) 7-bromo-3-benzyl-3,5-dihydro-4*H*-pyrazolo[4,3-*d*][1,2,3]triazin-4-one and 4.8 g (28.8 mmol) [2-(chloromethoxy)ethyl](trimethyl)silane were dissolved in 29 mL anhydrous DMF followed by a portionwise addition of 1.05 g (26.2 mmol) sodium hydride (60% w/w) at 0 °C. The reaction mixture was then stirred at rt for 30 min before being quenched with saturated aqueous sodium

hydrogen carbonate solution at 0 °C. EtOAc was added, the organic phase was separated, washed with water and brine, dried over magnesium sulfate, and evaporated in vacuum. Purification by preparative HPLC yielded 2.74 g (72%) of the target compound.

MS (CIpos): m/z = 436 $(M+NH_4)^+$.

^{1}H-NMR (300 MHz, DMSO-d_6): δ = -0.11 (s, 9H), 0.82 (t, 2H), 3.60 (t, 2H), 5.60 (s, 2H), 5.80 (s, 2H), 7.23 – 7.43 (m, 5H).

7-Bromo-3-(4-chlorobenzyl)-5-{[2-(trimethylsilyl)ethoxy]methyl}-3,5-dihydro-4H-pyrazolo[4,3-d]-[1,2,3]triazin-4-one (24) (Ar = *p*-ClPh)

3.5 g (8.72 mmol) 7-bromo-3-(4-chlorobenzyl)-3,5-dihydro-4*H*-pyrazolo[4,3-*d*][1,2,3]triazin-4-one **17** and 5.65 g (33.9 mmol) [2-(chloromethoxy)ethyl](trimethyl)silane were dissolved in 34 mL anhydrous DMF followed by a portionwise addition of 1.233 g (30.8 mmol) sodium hydride (60% w/w) at 0 °C. The reaction mixture was then stirred at rt for 30 min before being quenched with saturated aqueous sodium hydrogen carbonate solution at 0 °C. EtOAc was added, the organic phase was separated, washed with water and brine, dried over magnesium sulfate, and evaporated in vacuum. Purification by preparative HPLC yielded 3.66 g (76%) of the target compound.

MS (CIpos): m/z = 487 $(M+NH_4)^+$.

^{1}H-NMR (300 MHz, DMSO-d_6): δ = -0.12 (s, 9H), 0.81 (t, 2H), 3.58 (t, 2H), 5.59 (s, 2H), 5.79 (s, 2H), 7.38 (s, 4H).

3-(2,3-Dichlorobenzyl)-7-(3-hydroxyprop-1-in-1-yl)-3,5-dihydro-4H-pyrazolo[4,3-d][1,2,3]triazin-4-one (26a)

293 mg (0.49 mmol) 7-(3-{[*tert*-butyl(dimethyl)silyl]oxy}prop-1-in-1-yl)-3-(2,3-dichlorobenzyl)-5-{[2(trimethylsilyl)ethoxy]methyl}-3,5-dihydro-4*H*-pyrazolo[4,3-*d*][1,2,3]triazin-4-one **23a** were dissolved in 4.10 mL CH_2Cl_2 at 0 °C and treated with 4.10 mL trifluoroacetic acid. The mixture was stirred overnight at rt before being evaporated to dryness. A solution of 202 mg (2.46 mmol) sodium acetate in 0.75 mL water and 7.5 mL EtOH was added to the residue. The mixture was again stirred overnight, reduced and purified by preparative HPLC. 95 mg (55%) of the target compound were obtained.

MS (ES+): m/z = 351 $(M+H)^+$.

HPLC method 3: R_t = 4.21 min

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 4.44 (d, 2H), 5.59 (t, 1H), 5.70 (s, 2H), 7.14 (d, 1H), 7.31 (t, 1H), 7.62 (d, 1H).

3-Benzyl-7-phenylethinyl-3,5-dihydro-4H-pyrazolo[4,3-d][1,2,3]triazin-4-one (26b)

For preparation see example **26a**. 112 mg (70%) of the target compound were obtained.

MS (CIpos): m/z = 345 $(M+NH_4)^+$.

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 5.62 (s, 2H), 7.27 - 7.39 (m, 5H), 7.47 - 7.56 (m, 3H), 7.65 - 7.70 (m, 2H), 15.44 (s br, 1H).

3-Benzyl-7-trimethylsilylethinyl-3,5-dihydro-4H-pyrazolo[4,3-d][1,2,3]triazin-4-one (26c)

For preparation see example **26a**. 95 mg (53%) of the target compound were obtained.

MS (ES+): m/z = 324 $(M+H)^+$.

HPLC method 2: R_t = 5.02 min

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 0.30 (s, 9H), 5.60 (s, 1H), 7.30 - 7.40 (m, 5H), 15.39 (s br, 1H).

3-Benzyl-7-(3-hydroxyprop-1-in-1-yl)-3,5-dihydro-4H-pyrazolo[4,3-d][1,2,3]triazin-4-one (26d)

For preparation see example **26a**. 300 mg (62%) of the target compound were obtained.

MS (ES+): m/z = 282 $(M+H)^+$.

HPLC method 1: R_t = 3.73 min

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 4.44 (d, 2H), 5.58 (t, 1H), 5.60 (s, 2H), 7.25 - 7.39 (m, 5H), 15.33 (s br, H).

3-(4-Chlorobenzyl)-7-cyclohexylethinyl-3,5-dihydro-4H-pyrazolo[4,3-d][1,2,3]triazin-4-one (26e)

For preparation see example **26a**. 50 mg (14%) of the target compound were obtained.

MS (ES+): m/z = 368 $(M+H)^+$.

HPLC method 3: R_t = 5.03 min

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 1.30 – 1.46 (m, 3H), 1.46 – 1.62 (m, 3H), 1.63 – 1.78 (m, 2H), 1.82 – 1.94 (m, 2H), 2.82 (tt, 1H), 5.57 (s, 2H), 7.32 - 7.44 (AA'BB'-system, 4H), 15.18 (s br, 1H).

Methyl 2-{[3-(4-chlorobenzyl)-4-oxo-4,5-dihydro-3H-pyrazolo[4,3-d][1,2,3]triazin-7-yl]ethinyl}-benzoate (26f)

For preparation see example **26a**. 102 mg (39%) of the target compound were obtained.

MS (ES+): m/z = 420 $(M+H)^+$.

HPLC method 3: R_t = 4.92 min

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 3.92 (s, 3H), 5.62 (s, 2H), 7.36 - 7.46 (AA'BB'-system, 4H), 7.64 (td, 1H), 7.73 (td, 1H), 7.83 (dd, 1H'), 8.01 (dd, 1H), 15.49 (s br, 1H).

Methyl 2-{[3-(2,3-dichlorobenzyl)-4-oxo-4,5-dihydro-3H-pyrazolo[4,3-d][1,2,3]triazin-7-yl]ethinyl}-benzoate (26g)

For preparation see example **26a**. 135 mg (67%) of the target compound were obtained.

MS (ES+): m/z = 456 $(M+2H)^+$.

HPLC method 3: R_t = 5.04 min

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 3.93 (s, 3H), 5.72 (s, 2H), 7.18 (d, 1H), 7.63 (d, 1H), 7.63 (t, 1H), 7.73 (t, 1H), 7.83 (d, 1H), 8.01 (d, 1H), 15.53 (s br, 1H).

3-(4-Chlorobenzyl)-7-(4-methoxyphenylethinyl)-3,5-dihydro-4H-pyrazolo[4,3-d][1,2,3]triazin-4-one (26h)

For preparation see example **26a**. 41 mg (20%) of the target compound were obtained.

MS (ES+): m/z = 392 $(M+H)^+$.

HPLC method 1: R_t = 4.96 min

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 3.83 (s, 3H), 5.61 (s, 2H), 7.06 (d, 2H), 7.36 - 7.44 (AA'BB'-System, 4H), 7.62 (d, 2H), 15.38 (s br, 1H).

7-Iodo-3-(4-chlorobenzyl)-3,5-dihydro-4H-pyrazolo[4,3-d][1,2,3]triazin-4-one (27)

500 mg (1.911 mmol) 3-(4-chlorobenzyl)-3,5-dihydro-4*H*-pyrazolo[4,3-*d*][1,2,3]triazin-4-one **16f** and 1.12 g (4.97 mmol) *N*-iodosuccinimide were suspended in 68 mL anhydrous MeCN, and the reaction mixture was stirred overnight at 80 °C. The solvent was evaporated and the residue was taken up in EtOAc. The solution was washed with water and brine before being concentrated in vacuo. Purification of the solid by preparative HPLC yielded 183 mg (25%) of the target compound.

LC/MS method 2: R_t = 2.01 min, m/z = 388 $(M+H)^+$.

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 5.60 (s, 2H), 7.39 (s, 4H).

7-Iodo-3-(4-chlorobenzyl)-5-{[2-(trimethylsilyl)ethoxy]methyl}-3,5-dihydro-4H-pyrazolo[4,3-d][1,2,3]-triazin-4-one (28)

750 mg (1.94 mmol) 7-iodo-3-(4-chlorobenzyl)-3,5-dihydro-4*H*-pyrazolo[4,3-*d*][1,2,3]triazin-4-one **27** and 720 mg (4.26 mmol) [2-(chloromethoxy)ethyl](trimethyl)silane were dissolved in 6.3 mL anhydrous DMF followed by a portionwise addition of 155 mg (3.87 mmol) sodium hydride (60% w/w) at 0 °C. The reaction mixture is then stirred at rt for 30 min before being quenched with saturated aqueous sodium hydrogen carbonate solution. EtOAc and water were added. The organic phase was separated and extracted additional twice with EtOAc. The combined organic extracts were washed with brine, dried over magnesium sulfate, and the solvent was distilled off under reduced pressure. Purification of the

crude product by preparative HPLC yielded 540 mg (54%) of the target compound.

MS (ES+): m/z = 518 $(M+H)^+$.

HPLC method 3: R_t = 5.88 min

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 0.00 (s, 9H), 0.93 (t, 2H), 3.70 (t, 2H), 5.71 (s, 2H), 5.92 (s, 2H), 7.51 (s, 4H).

Methyl 3-(4-chlorobenzyl)-4-oxo-5-{[2-(trimethylsilyl)ethoxy]methyl}-4,5-dihydro-3H-pyrazolo[4,3-d]-[1,2,3] triazine-7-carboxylate (29)

160 mg (0.309 mmol) 7-iodo-3-(4-chlorobenzyl)-5-{[2-(trimethylsilyl)ethoxy]methyl}-3,5-dihydro-4*H*-pyrazolo[4,3-*d*][1,2,3]triazin-4-one **28**, 188 mg (1.85 mmol) *N*,*N*-diethylethanamine, 1.19 g (37.0 mmol) dry MeOH, 6 mg (0.028 mmol) palladium(II) acetate and 15 mg (0.056 mmol) triphenylphosphine were dissolved in 1.3 mL anhydrous DMF. Carbon monoxide was bubbled slowly through the mixture for 2 min before a balloon containing carbon monoxide was put on the reaction vessel. The mixture was stirred overnight, evaporated to dryness and purified by preparative HPLC. 108 mg (78%) of the target compound was obtained.

MS (ES+): m/z = 450 $(M+H)^+$.

HPLC method 2: R_t = 5.39 min

^{1}H-NMR (400 MHz, DMSO-d_6): δ = -0.13 (s, 9H), 0.81 (t, 2H), 3.59 (t, 2H), 3.96 (s, 3H), 5.62 (s, 2H), 5.89 (s, 2H), 7.39 (s, 4H).

Methyl 3-(4-chlorobenzyl)-4-oxo-4,5-dihydro-3H-pyrazolo[4,3-d][1,2,3]triazine-7-carboxylate (30)

102 mg (0.227 mmol) methyl 3-(4-chlorobenzyl)-4-oxo-5-{[2-(trimethylsilyl)ethoxy]methyl}-4,5-dihydro-3*H*-pyrazolo[4,3-*d*][1,2,3]triazine-7-carboxylate **29** were dissolved in 1.9 mL CH_2Cl_2 and 1.9 mL trifluoroacetic acid at 0 °C. The mixture was stirred for 2 h at rt before being concentrated in vacuo. The residue was taken up with a solution of 93 mg (1.1 mmol) sodium acetate in 3.6 mL EtOH and 0.36 mL water. After stirring overnight the reaction was purified by preparative HPLC. 31 mg (43%) of the target compound were obtained.

MS (MSES+): m/z = 319 $(M+H)^+$.

HPLC method 1: R_t = 4.19 min

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 3.11 (s, 3H), 4.76 (s, 2H), 6.54 (s, 4H).

3-(4-Chlorobenzyl)-4-oxo-4,5-dihydro-3H-pyrazolo[4,3-d][1,2,3]triazine-7-carboxylic acid (31)

15 mg (0.047 mmol) Methyl 3-(4-chlorobenzyl)-4-oxo-4,5-dihydro-3*H*-pyrazolo[4,3-*d*][1,2,3]triazine-7-carboxylate **30** were dissolved in 0.4 mL THF and 0.3 mL water. After addition of 12 mg (0.206 mmol)

potassium hydroxide the mixture was stirred overnight, diluted with water, acidified with 2N HCl to pH = 2 and chromatographed by preparative HPLC. 6 mg (42%) of the target compound was obtained.

HPLC method 3: R_t = 3.83 min

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 5.59 (s, 2H), 7.39 (s, 4H).

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REFERENCES

1. C. C. Cheng and R. K.-Y. Zee-Cheng, *Drugs of the future*, 1986, **11**, 121.
2. P. G. Baraldi, D. Simoni, V. Periotto, S. Manfredini, M. Guarneri, R. Manservigi, E. Cassai, and V. Bertolasi, *J. Med. Chem.*, 1984, **27**, 986.
3. P. G. Baraldi, B. Cacciari, A. Dalpiaz, S. Dionisotti, C. Zocchi, M. J. Pineda de las Infantas, G. Spalluto, and K. Varani, *Drug Res.*, 1996, **46**, 365.
4. S. Manfredini, R. Bazzanini, P. G. Baraldi, M. Guarneri, D. Simoni, M. E. Marongiu, A. Pani, E. Tramontano, and P. La Colla, *J. Med. Chem.*, 1992, **35**, 917.
5. P. G. Baraldi, A. Casolari, M. Guarneri, S. Manfredini, G. P. Pollini, D. Simoni, and V. Zanirato, *Synthesis*, 1988, **1**, 78.
6. P. G. Baraldi, L. Garuti, and M. Roberti, *Synthesis*, 1994, **12**, 1437.
7. R. A. Long, J. F. Gerster, and L. B. Townsend, *J. Heterocycl. Chem.*, 1970, **7**, 863.
8. J. G. Buchanan, A. Stobie, and H. Wightman, *J. Chem. Soc., Perkin Trans. 1*, 1981, 2374.
9. C. Gil, A. Schwoegler, and S. Braese, *J. Comb. Chem.*, 2004, **6**, 38.
10. P. Hrelia, C. Fimognari, F. Maffei, B. Brighenti, L. Garuti, S. Burnelli, and G. Cantelli-Forti, *Mutation Research*, 1998, **397**, 293.
11. P. G. Baraldi, B. Cacciari, A. Leoni, M. Recanatini, M. Roberti, M. Rossi, S. Manfredini, V. Periotto, and D. Simoni, *Il Farmaco*, 1991, **46**, 1337.
12. N. Svenstrup, C. Freiberg, E. Lohrmann, M. Bauser, D. Meibom, H. Meier, and G. Schiffer, DE 10 2005 021 963 A1, 2005.
13. S. Bartlett and A. Nelson, *Org. Biomol. Chem.*, 2004, **2**, 2874.