Propargyl Anthranilate Derivatives and Their Application in the Synthesis of Rings Containing 1,2,3-Triazolo Motifs

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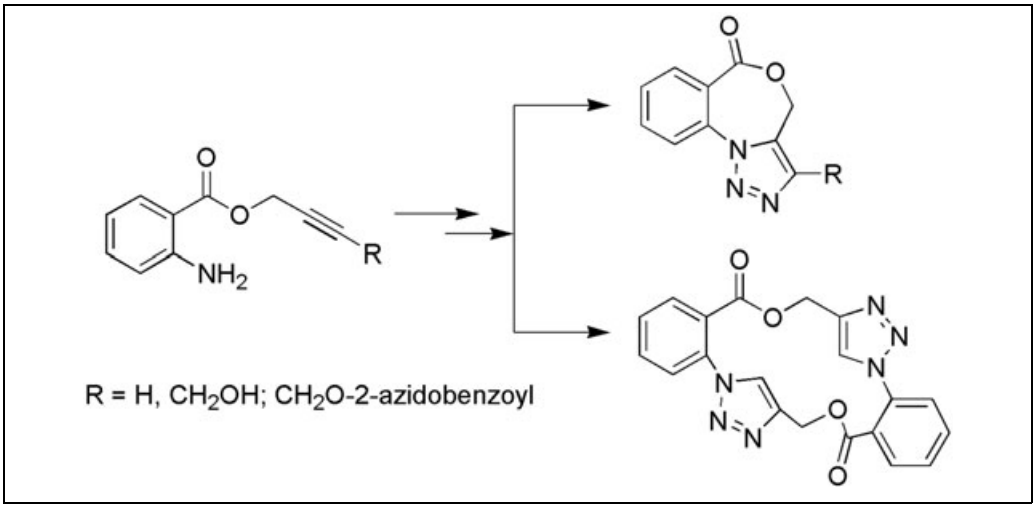

Propargyl anthranilate, a simple and less studied molecule with several reactive sites, is widely applicable in organic synthesis. An optimized synthesis of this compound and its derivatives and the preparation of azide derivatives are described. The optimized process of the known intramolecular cyclization is described, and the unknown intermolecular cyclizations of these azido derivatives and formation of a macrocycle are discussed.

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INTRODUCTION

Independent or annelated medium-sized heterocycles, especially compounds with seven-membered rings, have been receiving significant attention not only because of the existence of their structural units in some natural products [1] but also because this structural motif is common in pharmaceutically active compounds [2,3]. Of these, possibly the most popular is a group of thousands of compounds known as the "benzodiazepines." The most widely used benzodiazepine drug is diazepam. It is used as an anxiolytic, a sedative, a muscle relaxant, and also as a psychostimulant. It was observed that if the benzodiazepines are annelated with triazole, their activity increases, and hence, a lower dosage can be used. These structures are represented by compounds such as triazolam or alprazolam. Midazolam, a compound with an imidazole ring, is used as an intravenous anesthetic [2]. Some members of this group have also displayed antipsychotic activities [2,3]. Oxazepinone derivatives are much less frequent than diazepinone derivatives, mainly because of their low stability. Only the more stable dibenzooxazepinones are of considerable interest and are objects of patents of various pharmaceutical companies. The pharmacological activities of these compounds are variable and include antifungal activity, anti-HIV activity, and calcium channel activity; they also have applications as antidepressants or agents for the treatment of lipoprotein disorders [4–7].

While testing, we found that 4*H*,6*H*-[1,2,3]triazolo[1,5-*a*][4,1]benzoxaze-pin-6-on has a moderate cytostatic activity. This type of activity is unusual for similar types of compounds but is common for the 3-hydroxy-4(1*H*)-quinolinone derivatives. In most cases, the stability of the oxazepinone derivatives is limited. Moreover, as we have shown in the past, 3-hydroxy-4-(1*H*)-quinolinone derivatives were formed instead of the oxazepinone derivative [9,10]. Because the structure of 4*H*,6*H*-[1,2,3]triazolo[1,5-*a*][4,1]benzoxaze-pin-6-on was documented only with elemental analysis and ^{1}H-NMR [8], we decided to repeat the procedure described above and to perform more advanced NMR analysis to verify its structure.

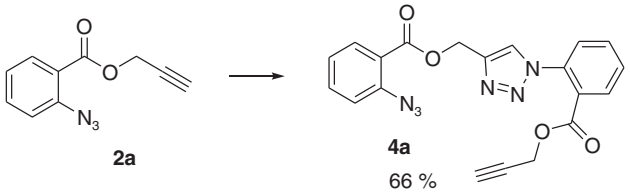
Therefore, we studied the synthesis of this compound and its derivatives, and our results are described here.

RESULTS AND DISCUSSION

The cyclization of compound **2a** into the oxazepinone derivative **3a** in boiling toluene was described recently [8]. Besides the azido derivative **2a**, we decided to also prepare some derivatives (Fig. 1) and to compare their reactivity during cyclization with the parent compound **2a**.

Better results were obtained, compared with the described procedure [8], for the synthesis of propargyl anthranilate **1a** if an excess of propargyl alcohol and only a catalytic amount of sodium hydride were used. Derivatives **1b** and **1c** were prepared in the same way by the reaction of isatoic anhydride and 1,4-butynediol in toluene, with sodium hydride as the catalyst. A mixture of these compounds was formed, their ratio depending on the ratio of the starting materials. Products **1a** and **1b** were separated by column chromatography. The best yield for compound **1b** was 55%, and the best yield for the compound **1c** was 48%. Derivative **1d** was prepared by catalytic oxidation of compound **1a** using copper acetate as the catalyst and hydrogen peroxide as an oxidation agent in the yield of 87%. The process was more reproducible than oxidation with atmospheric oxygen. Azido derivatives **2** were prepared through the reaction of the diazonium salts with sodium azide. The yield of the reaction was high (73 to 95%), and the reaction proceeded well. The products of this reaction are all in the form of a solid, except for compound **2b**. During the study of the behavior of compound **2a**, we found a deviation from the described procedure, and the formation of other compounds was observed. Later, we found that compound **2a** has limited stability and a new compound **4a** was formed during storage (Scheme 1). The reaction is quite slow, and only 50% of azide **2a** decomposed during 12 weeks at room temperature; thus, completion of this reaction takes more than 1 year. The maximum speed of dimerization for the preparation of compound **4a** was observed at 40°C. Under these conditions, 50% of azide **2a** reacted after 44 h. A large number of by-products were formed at higher temperatures, and the reaction is not applicable for the preparation of compound **4a** under these conditions. Compound **2a** was stable at −20°C for more than 1 year.

Scheme 1. Intermolecular dimerization of propargyl anthranilate.



By heating the transformed product **4a** in boiling toluene, a new macrocyclic compound **5a** was formed in low yield (Scheme 2).

New procedures for the cyclization of azido derivatives were developed, and older procedures were optimized. The use of DMF for the cyclization of derivative **2a** significantly reduced the reaction time, and the same method is applicable for the preparation of the substituted derivative **3b** (Scheme 3), where the final products are insoluble in toluene. Compound **3b** was prepared in 50% yield, and compound **3c** was prepared in the yield of 89%. This method is also applicable in the preparation of derivative **5a** from derivative **4a**. Macrocycle **5a** was prepared in the yield of 32%. Because the formation of a triazole ring from azide derivatives and a terminal alkyne group (known as a "click reaction") is performed in the presence of a copper catalyst, the influence of copper catalysis was also tested. Under these conditions, derivative **4a** reacted smoothly, and compound **5a** was formed in mild conditions in 50% yield. The cyclization of compound **2a** with copper catalysis was more complicated. The reaction was very fast, and a solid precipitate separated from the boiling solution in DMF within 20 min. The protonated molecule of the expected compound **3a** (*m*/*z* 202) was observed with very low intensity in the MS spectra. Besides this, a low intensity ion (*m*/*z* 403) corresponding to the protonated molecule **5a** was also observed. The NMR spectra also revealed a rich mixture of compounds.

The behavior of compound **2a** derivatives and their stability were also studied. It was found that the stability of compound **2b** is also limited, but a rich mixture of compounds is formed during its decomposition. The azido

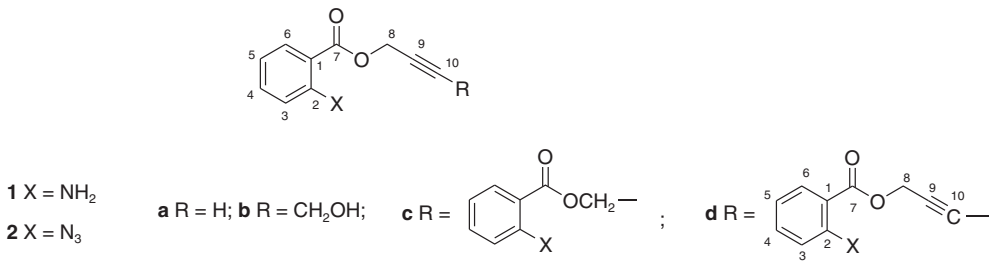
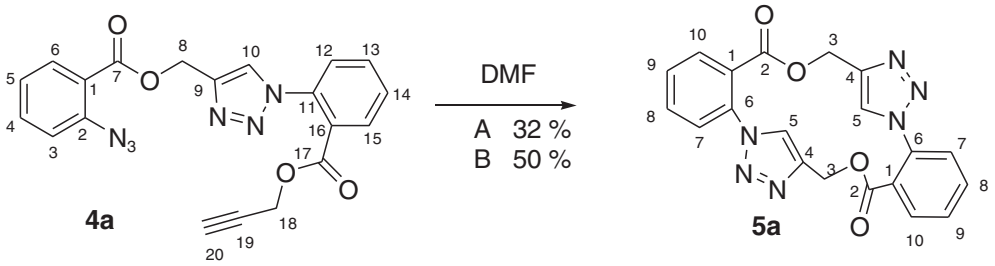
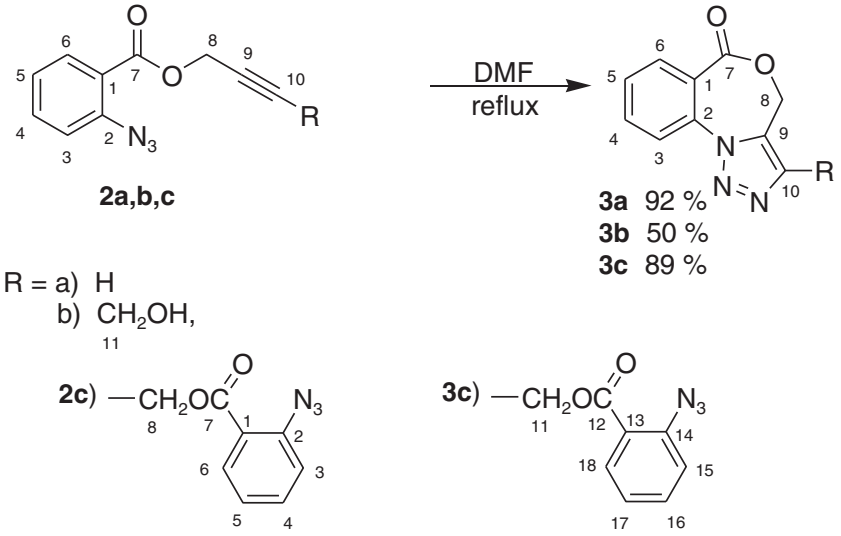


Figure 1. Some prepared derivatives besides the azido derivative **2a**.

Scheme 2. Formation of macrocycle **5a**.



Scheme 3. Optimized method for the formation of benzoxazepinones **3** from azido derivatives **2**.



derivatives **2c** and **2d** are stable, and they were unchanged during storage at room temperature for more than 1 year. Various routes for thermal cyclization were tested for these compounds.

Derivative **2c** reacted similarly as before, and derivative **3c** was formed. Conversely, during thermal cyclization of compound **2d**, the reaction was observed after 4 h, and a complex mixture was formed. Reaction with copper (as catalyst) was not effective for derivatives other than **1a**. Instead of cyclization, a reduction was observed, and the amount of catalyst (ascorbic acid and copper sulfate) had to be increased to complete the reaction. The mixture of aminoderivatives **1b**, **1c**, or **1d** was formed in this case.

Cytostatic activities of the newly prepared compounds were tested. Such an activity was not found for most of the compounds. Weak activity against the leukemia cell line K-562 was found only for compound **3c**, with an IC_{50} of 100 μM.

CONCLUSION

The structure of 4*H*,6*H*-[1,2,3]triazolo[1,5-*a*][4,1] benzoxazepin-6-on (**3a**), which was previously described [8], was verified with advanced NMR techniques. A modified procedure for the preparation of compounds **3a–3c** was described. The limited stability and unexpected intermolecular cyclization of propargyl 2-azidobenzoate **2a** was also found, and the formation of the new macrocycle **5a** was described.

EXPERIMENTAL

All reagents were of commercial quality (Fluka, Aldrich, Prague, Czech Republic) and were used as received. Reactions were monitored by thin layer chromatography on plastic plates coated with silica gel (Polygram Sil G/UV_{254}, Macherey-Nagel, Düren; Germany). Melting points were measured in a Köfler apparatus and are uncorrected. Elemental analysis was performed on an EA 1108 (Fisons Instruments, Waltham, USA).

NMR spectra of compound **1** was obtained on a Bruker AVANCE 300 (Rheinstetten, Germany) at 300.13 (^{1}H) and 75.47 MHz (^{13}C), whereas the NMR spectra of all other compounds were recorded on a Bruker AVANCE II 400 at 400.13 (^{1}H) and 100.62 MHz (^{13}C). The samples were dissolved in DMSO-d_6. ^{1}H and ^{13}C chemical shifts were in reference to the central signal of the solvent [$\delta = 2.55$ (^{1}H) and $\delta = 39.6$ (^{13}C)]. All 2D experiments [gradient-selected (gs)-COSY, gs-HMQC, gs-HMBC] were performed using the manufacturer's software (TOPSPIN 2.1). Proton spectra were assigned using gs-COSY. Protonated carbons were assigned by gs-^{1}H–^{13}C HMQC, and quaternary carbons were assigned by gs-^{1}H–^{13}C HMBC. The numbering of compounds for NMR purposes is given in Figure 1 and Schemes 2 and 3. NMR data for molecules **1–5** are summarized in Table 1.

MS characterization was carried out using the DEP–CI–MS (direct exposure probe–chemical ionization–mass spectrometry) technique with a quadrupole ion trap mass analyzer and isobutane as a CI reagent gas.

Preparation of propargyl anthranilate (1a). Sodium hydride (200 mg) was added to a suspension of isatoic anhydride (50 g, 0.307 mol) in propargyl alcohol (100 g, 1.78 mol), and the mixture was heated to reflux. The initial solid disappeared, and a clear solution was formed in 1.5 to 2 h. Afterward, the reaction was checked by TLC (AcOEt : *n*-hexane 7:3). If residual isatoic anhydride was present, the reaction was heated to reflux for another 30 min. The excess of propargyl alcohol was removed by distillation *in vacuo*.

The residue was cooled to 30°C and acidified with acetic acid (one to two drops). The reaction mixture was then diluted with water (200 mL), cooled to 0–5°C, and filtered. After letting the reaction mixture stand for 15 min, the solid was washed with water and dried *in vacuo*. The yield was 53.3 g (99.3%), mp 35–37°C. For analysis, the hydrochloride of **1a** was prepared by precipitation from a diethyl ether solution by the addition of an ethanolic solution of HCl, mp 165–168°C (lit [11] mp 176–177°C; lit [8] mp 169°C)

MS *m/z* (relative intensity) 232 (13) $[M + t\text{-butyl}]^+$, 218 (4) $[M + C_3H_7]^+$, 176 (40) $[M + H]^+$, 120 (100) $[H_2NC_6H_4CO]^+$, 92 (10), 79 (5). NMR data are given in Table 1.

Preparation of 4-hydroxybut-2-yn-1-yl anthranilate (1b) and but-2-yn-1,4-diyl dianthranilate (1c)

Procedure A. To a suspension of isatoic anhydride (10 g, 61.3 mmol) in toluene (100 mL), butynediol (5.3 g, 61.6 mmol) and sodium hydride (60 mg) were added. The reaction mixture was heated in a water bath at 60°C. The suspended solid dissolved in 20 min. After consumption of the starting material (confirmed by TLC) after approximately 1 h, an oily layer was separated. The reaction mixture was concentrated using a vacuum evaporator. The resulting residue was stirred with a saturated solution of sodium carbonate (100 mL) and extracted with ethyl acetate (3 × 70 mL). The organic extract was initially dried with sodium sulfate and finally on a vacuum evaporator. The final products were separated from the oily

Table 1

^{1}H and ^{13}C NMR data (δ, ppm) of compounds **2–5** in DMSO-d_6.

Compound		Position 1	2	3	4	5	6	7	8	9	10	11
1a	δ_H	–	–	6.76	7.25	6.52	7.67	–	4.86	–	3.55	
1b	δ_C	108.3	152.1	117.1	134.9	115.3	131.0	166.9	52.0	79.3	78.0	
	δ_H	–	–	6.76	7.25	6.52	7.67	–	4.91	–	–	4.10
1c	δ_C	108.4	152.0	117.1	134.9	115.3	131.0	167.0	52.2	79.3	87.0	49.4
	δ_H	–	–	6.76	7.25	6.52	7.67	–	4.96	–	–	
1d	δ_C	108.3	152.1	117.1	134.9	115.3	131.0	166.9	52.1	81.8		
	δ_H	–	–	6.76	7.25	6.51	7.66	–	5.02	–	–	
2a	δ_C		152.2	117.1	135.0	115.3	131.0	166.8	52.4	76.0	69.7	
	δ_H	–	–	7.44	7.70	7.33	7.83	–	5.01	–	3.31	
2b	δ_C	121.8	139.4	120.9	134.1	125.1	131.4	164.1	53.1	78.4	121.8	
	δ_H	–	–	7.44	7.70	7.33	7.93	–	5.01	–	–	4.19
2c	δ_C	121.8	139.4	120.9	134.1	125.1	131.4	164.1	53.1	78.4	87.3	49.2
	δ_H	–	–	7.41	7.65	7.28	7.77	–	5.01	–	–	
2d	δ_C	122.0	139.6	121.2	134.4	125.4	131.6	164.3	53.1	81.7		
	δ_H	–	–	7.42	7.65	7.28	7.78	–	5.07	–	–	
3a	δ_C	121.6	139.8	121.2	134.6	125.4	131.8	164.2	53.4	75.6	70.0	
	δ_H	–	–	8.11	7.76	7.99	8.11	–	5.54	–	8.15	–
3b	δ_C	122.9	132.7	122.4	129.5	125.0	133.9	166.8	55.8	133.8	133.0	–
	δ_H	–	–	8.10	7.76	7.97	8.10	–	5.56	–	–	7.78
3c[a]	δ_C	122.7	132.8	122.3	129.4	135.0	133.9	167.0	56.6	131.1	145.7	54.4
	δ_H	–	–	8.12	7.79	8.00	8.12	–	5.66	–	–	5.64
4a[b]	δ_C	122.7	132.7	122.4	129.7	135.0	134.0	166.7	56.3	133.0	140.0	57.1
	δ_H	–	–	7.48	7.70	7.34	7.87	–	5.51	–	8.75	–
5a	δ_C	122.2	139.2	120.9	133.8	125.0	131.3	164.4	58.1	142.0	126.5	135.5
	δ_H	–	–	5.22	–	8.44	–	7.65	7.90	7.84	8.15	–
	δ_C	127.0	165.0	58.1	141.4	127.1	135.5	127.3	133.7	130.6	131.5	–

[a] –/164.5 (12), –/139.2 (13), –/121.9 (14), 7.48/120.9 (15), 7.70/134.0 (16), 7.34/125.1 (17), 7.84/131.3 (18).
[b] 7.76/126.8 (12), 7.90/133.6 (13), 7.79/130.4 (14), 8.03/130.8 (15), –/126.4 (16), –/164.2 (17), 4.78/53.0 (18), –/78.3 (19), 3.61/77.6 (20).

residue by column chromatography on silica gel using a 1:1 mixture of *n*-hexane : AcOEt as the eluent.

The yield of compound **1b** was 6.9 g (55%), mp 65–69°C.

Calculated for $C_{11}H_{11}NO_3$ (205.21): 64.38% C; 5.40% H; 6.83% N; found: 64.05% C; 5.29% H; 6.98% N. MS *m/z* (relative intensity) 262 (8) $[M + t\text{-butyl}]^+$, 248 (4) $[M + C_3H_7]^+$, 206 (60) $[M + H]^+$, 188 (4) $[M + H - H_2O]^+$, 120 (100) $[H_2NC_6H_4CO]^+$, 92 (10). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.69 (1H, dd, J = 7.9; 1.3 Hz); 7.27 (1H, dt, J = 7.9; 1.5 Hz); 6.78 (1H, d, J = 8.4 Hz); 6.66 (2H, s); 6.54 (1H, t, J = 7.7 Hz); 5.23 (1H, t, J = 6.0 Hz); 4.93 (2H, t, J = 1.6 Hz); 4.12 (2H, td, J = 6.1; 1.6 Hz); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 166.4; 151.6; 134.4; 130.5; 116.6; 114.8; 107.8; 81.3; 51.6. NMR data are given in Table 1.

The yield of compound **1c** was 3.0 g (15%), mp 100–102°C.

Calculated for $C_{18}H_{16}N_2O_4$ (324.331): 66.66% C; 4.97% H; 8.64% N; found: 66.35% C; 4.80% H; 8.77% N. MS *m/z* (relative intensity) 381 (11) $[M + t\text{-butyl}]^+$, 367 (5) $[M + C_3H_7]^+$, 325 (90) $[M + H]^+$, 190 (10), 188 (25) $[M + H - \text{anthranilate}]^+$, 158 (5), 138 (17) $[H_2NC_6H_4COOH_2]^+$, 120 (100) $[H_2NC_6H_4CO]^+$, 92 (10). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 7.69 (2H, dd, J = 8.0; 1.3 Hz); 7.27 (2H, dt, J = 7.9; 1.5 Hz); 6.78 (2H, d, J = 8.3 Hz); 6.66 (4H, s); 6.54 (2H, dt, J = 7.5; 0.9 Hz); 4.98 (4H, s); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 166.4; 151.6; 134.4; 130.5; 116.6; 114.8; 107.8; 81.3; 51.6. NMR data are given in Table 1.

Procedure B. The same procedure as Procedure A was applied with the following modifications: isatoic anhydride (10 g, 61.3 mmol), butynediol (2.6 g, 30 mmol). The yield of compound **1b** was 1.4 g (12%), and the yield of compound **1c** was 8.6 g (48%).

Hexa-2,4-diyn-1,6-diyl dianthranilate (1d). Propargyl anthranilate **1a** (3 g; 17.12 mmol) was dissolved in DMF (30 mL). Copper acetate (0.5 g, 2.75 mmol) and ferrous chloride (0.1 g; 0.79 mmol) were added, and the reaction mixture was heated to 80°C. Then, hydrogen peroxide (35%; 2 mL, 20.5 mmol) was slowly added. The reaction time was approximately 2–2.5 h. If the reaction still contained starting material **1a**, a new portion of hydrogen peroxide (1 mL) was added. After the starting material was completely converted, the reaction was filtered with charcoal (0.2 g), the filter cake was washed with hot DMF (5 mL), the filtrate was concentrated on a vacuum evaporator, and the residue was diluted with water (50 mL). Afterward, AcOEt (100 mL) and charcoal (0.5 g) were added, and the reaction mixture was filtered. The organic layer was separated, and the water layer was extracted twice with AcOEt (50 mL). Then, the organic layer was separated, dried over sodium sulfate, and filtered through a layer of silica gel. The AcOEt was then evaporated, and the solid was dissolved in acetone (3 mL). Then, ethanol (30 mL) was added, and the acetone was evaporated *in vacuo*. The precipitated solid was filtered, and the yield of product **1d** was 2.6 g (87%), mp 139-142°C.

Calculated for $C_{20}H_{16}N_2O_4$ (348.35): 68.96% C; 4.63% H; 8.04% N; found: 68.75% C; 4.51% H; 8.14% N. MS *m/z* (relative intensity) 405 (5) $[M + t\text{-butyl}]^+$, 391 (3) $[M + C_3H_7]^+$, 349 (50) $[M + H]^+$, 214 (8), 212 (18) $[M + H - \text{anthranilate}]^+$, 196 (9), 194 (7), 168 (5), 138 (35) $[H_2NC_6H_4COOH_2]^+$, 120 (100) $[H_2NC_6H_4CO]^+$, 92 (15), 79 (5). NMR data are given in Table 1.

General procedure for the preparation of azido derivatives 2a–2d.

Caution! *Although no problems were observed during the handling of the azido derivatives, these compounds may be explosive and are potentially dangerous!*

Anthranilates **1** (3 mmol) were dissolved in ethanol or acetone (5 mL), concentrated hydrochloric acid (0.8 mL) was added dropwise, and a solution of sodium nitrite (0.207 g, 3 mmol) in water (0.5 mL) was added at −10 to 0°C. The reaction mixture was stirred for 15 min at this temperature, and then a solution of sodium azide (0.195 g, 3 mmol) in water (1 mL) was added in drops. During the reaction, the solids were precipitated. After consumption of the starting material (monitored by TLC; approximately 1 h), water was added (15 mL), and the precipitated solid was filtered off, washed with water or extracted with AcOEt (3 × 25 mL) in the case of oily azides. The isolated azides were used in the next reaction step without further purification.

Propargyl 2-azidobenzoate (2a). The preparation of this compound was performed in ethanol with **1a** (10 g, 57.08 mmol). The yield of product **2a** was 10.7 g (93%), mp 63–66°C (lit [8] mp 65°C).

Calculated for $C_{10}H_7N_3O_2$ (201.18): 59.70% C; 3.51% H; 20.89% N; found: 59.48% C; 3.39% H; 21.05% N. MS *m/z* (relative intensity) 230 (20) $[M - N_2 + t\text{-butyl}]^+$, 216 (4) $[M - N_2 + C_3H_7]^+$, 202 (3) $[M + H]^+$, 174 (100) $[M + H - N_2]^+$, 156 (45), 146 (44), 144 (20), 132 (16), 130 (22), 128 (21), 120 (53) $[H_2NC_6H_4CO]^+$, 103 (23), 92 (10), 89 (10). NMR data are given in Table 1.

2-Azido-benzoic acid 4-hydroxy-but-2-ynyl ester (2b). This procedure was performed with **1b** (0.5 g, 2.44 mmol) in ethanol. The yield of the yellow–red oily product **2b** was 0.4 g (71%).

Calculated for $C_{11}H_9N_3O_3$ (231.207): 57.14% C; 3.92% H; 18.17% N; found: 57.48% C; 4.13% H; 17.91% N. MS *m/z* (relative intensity) 260 (18) $[M - N_2 + t\text{-butyl}]^+$, 247 (4) $[M - N_2 + C_3H_7]^+$, 232 (2) $[M + H]^+$, 204 (45) $[M + H - N_2]^+$, 186 (35), 177 (33), 176 (32), 158 (100), 146 (10), 130 (77), 120 (61) $[H_2NC_6H_4CO]^+$, 103 (18), 92 (15), 65 (5). NMR data are given in Table 1.

2-Azido-benzoic acid 4-(2-azido-phenoxy)-but-2-ynyl ester (2c). This procedure was performed with **1c** (1 g; 3.08 mmol) in acetone. The yield of product **2c** was 1.1 g (95%) mp 59–62°C.

Calculated for $C_{18}H_{12}N_6O_4$ (376.326): 57.45% C; 3.21% H; 22.33% N; found: 57.30% C; 3.06% H; 22.51% N. MS *m/z* (relative intensity) 405 (3) $[M - N_2 + t\text{-butyl}]^+$, 377 (2) $[M + H]^+$, 349 (9) $[M + H - N_2]^+$, 321 (100) $[M + H - N_2 - N_2]^+$, 303 (10), 277 (7), 275 (8), 261 (7), 259 (7), 253 (10), 251 (21), 247 (12), 237 (9), 233 (8), 214 (8), 209 (11), 188 (8), 186 (11), 170 (7), 158 (7), 138 (8), 130 (7), 120 (39) $[H_2NC_6H_4CO]^+$, 92 (13), 65 (5). NMR data are given in Table 1.

Hexa-2,4-diyn-1,6-diyl bis(2-azidobenzoate) (2d). This procedure was performed with **1d** (0.5 g, 1.44 mmol) in acetone. The yield of product **2d** was 0.54 g (95%), mp 79–81°C.

Calculated for $C_{20}H_{12}N_6O_4$ (400.35): 60.00% C; 3.02% H; 20.99% N; found: 59.86% C; 2.95% H; 21.13% N. MS *m/z* (relative intensity) 429 (4) $[M - N_2 + t\text{-butyl}]^+$, 401 (<2) $[M + H]^+$, 373 (4) $[M + H - N_2]^+$, 345 (15) $[M + H - N_2 - N_2]^+$, 327 (10), 315 (7), 301 (14), 299 (15), 273 (8), 271 (10), 256 (7), 210 (10), 194 (9), 148 (7), 138 (38) $[H_2NC_6H_4COOH_2]^+$, 120 (100) $[H_2NC_6H_4CO]^+$, 92 (35), 79 (10), 65 (8). NMR data are given in Table 1.

General procedure for the cyclization of azido derivatives 2 or 4a. Azides **2** or **4a** (2.5 mmol) were dissolved in DMF (10 mL). The reaction mixture was refluxed for 30 min and then checked for completion of reaction by TLC. If the starting material was not present (TLC control), the reaction mixture was cooled and

poured into water. The precipitated solid was filtered off, dried *in vacuo*, and recrystallized from acetone.

Preparation of 4*H*,6*H*-[1,2,3]triazolo[1,5-*a*][4,1]benzoxazepin-6-on (3a). This was performed according to the general procedure with azido derivative **2a** (10 g, 49.71 mmol) in DMF (25 mL), with a reaction time of 45–60 min. The yield of product **3a** was 9.2 g (92%), mp 210–212°C (lit [8] mp 194°C).

Calculated for $C_{10}H_7N_3O_2$ (201.181): 59.70% C; 3.51% H; 20.89% N; found: 59.55% C; 3.42% H; 20.96% N. MS *m/z* (relative intensity) 258 (15) $[M + t\text{-butyl}]^+$, 244 (4) $[M + C_3H_7]^+$, 202 (100) $[M + H]^+$, 174 (4) $[M + H - CO]^+$, 146 (7) $[M + H - CO\ N_2]^+$, 118 (4). NMR data are given in Table 1.

3-(Hydroxymethyl)-4*H*,6*H*-[1,2,3]triazolo[1,5-*a*][4,1]benzoxazepin-6-one (3b). This was performed according to the general procedure with **2b** (0.5 g, 2.16 mmol), with a reaction time of 20 min. The yield of product **3b** was 0.25 g (50%), mp 191–195°C.

Calculated for $C_{11}H_9N_3O_3$ (231.21): 57.14% C; 3.92% H; 18.17% N; found: 57.27% C; 4.01% H; 18.05% N. MS *m/z* (relative intensity) 288 (6) $[M + t\text{-butyl}]^+$, 274 (4) $[M + C_3H_7]^+$, 232 (100) $[M + H]^+$, 204 (6) $[M + H - CO]^+$, 188 (5), 186 (7) $[M + H\ CO - H_2O]^+$, 158 (20) $[M + H - CO - H_2O - N_2]^+$, 132 (4), 120 (6) $[H_2NC_6H_4CO]^+$, 104 (4), 81 (3), 79 (7), 67 (4). NMR data are given in Table 1

4*H*,6*H*-[1,2,3]Triazolo[1,5-*a*][4,1]benzoxazepin-6-one-3-methyl 2-azidobenzoate (3c). This was performed according to the general procedure with **2c** (1 g, 2.66 mmol), with a reaction time of 45 min. The yield of product **3c** was 0.89 g (89%), mp 177–180.5°C.

Calculated for $C_{18}H_{12}N_6O_4$ (376.33): 57.45% C; 3.21% H; 22.33% N; found: 57.31% C; 3.09% H; 22.49% N. MS *m/z* (relative intensity) 433 (9) $[M + t\text{-butyl}]^+$, 419 (3) $[M + C_3H_7]^+$, 415 (5) $[M + C_3H_3]^+$, 377 (60) $[M + H]^+$, 349 (100) $[M + H - N_2]^+$, 321 (3) $[M + H - N_2 - CO]^+$, 320 (5), 275 (5), 263 (15), 247 (5), 232 (7), 230 (14), 216 (4), 204 (4), 186 (50), 174 (4), 158 (15), 146 (5), 138 (5), 132 (5), 130 (12), 120 (15) $[H_2NC_6H_4CO]^+$, 94 (4), 92 (10), 79 (3). NMR data are given in Table 1.

Preparation of prop-2-yn-1-yl 2-(4-{[(2-azidophenyl)carbonyloxy] methyl}-1*H*-1,2,3-triazol-1-yl)benzoate (4a). The solid compound **2a** was allowed to stand at laboratory temperature for 1 year. Compound **4a** was formed. The dimer was purified by column chromatography on silica gel. The yield of product **4a** was 0.66 g (66%), mp 131–133°C.

Calculated for $C_{20}H_{14}N_6O_4$ (402.36): 59.70% C; 3.51% H; 20.89% N; found: 59.58% C; 3.46% H; 21.08% N. MS *m/z* (relative intensity) 459 (3) $[M + t\text{-butyl}]^+$, 403 (10) $[M + H]^+$, 375 (4) $[M + H - N_2]^+$, 293 (3), 258 (7), 242 (4), 239 (4), 230 (4), 202 (50), 174 (100), 156 (8), 148 (6), 146 (18), 138 (6), 130 (10), 120 (25) $[H_2NC_6H_4CO]^+$, 92 (5), 79 (3). NMR data are given in Table 1.

Preparation of 9,22-Dioxa-1,12,13,14,25,26-hexaazapentacyclo [22.2.1.1^{11,14}.0^{2,7}.0^{15,20}]octacosa-2,4,6,11(28),12, 15,17,19,24 (27),25-decaene-8,21-dione(5a)

Procedure A. This was performed according to the general procedure with **4a** (1 g, 2.5 mmol) in DMF (30 mL), with a reaction time of 1.5 h. The wet product was washed in warm acetone (200 mL), and the yield of product **5a** was 0.32 g (32%), mp 328–331°C.

Calculated for $C_{20}H_{14}N_6O_4$ (402.36): 59.70% C; 3.51% H; 20.89% N; found: 59.78% C; 3.63% H; 21.01% N. MS *m/z* (relative intensity) 459 (3) $[M + t\text{-butyl}]^+$, 445 (3) $[M + C_3H_7]^+$, 443 (3) $[M + C_3H_5]^+$, 441 (5) $[M + C_3H_3]^+$, 403 (100) $[M + H]^+$, 375 (15) $[M + H - CO]^+$, 301 (3), 204 (3), 174 (10), 156 (10), 146 (5), 130 (4), 120 (4) $[H_2NC_6H_4CO]^+$, 79 (4), 74 (6). NMR data are given in Table 1.

Procedure B. Azido derivative **4a** (1 g, 2.5 mmol) was dissolved in DMF (30 mL). A solution of copper sulfate heptahydrate (0.1 g, 0.40 mmol) in water (3 mL) and a solution of ascorbic acid (0.15 g, 0.85 mmol) in water (3 mL) were added. The reaction mixture was stirred at room temperature. The starting material was not observed by TLC after 15 min, after which a solid compound was precipitated and the reaction mixture was stirred for 3 h. Then, the reaction mixture was poured into a mixture of water and ice (200 g). The precipitate was filtered off and washed with water. The solid compound was then dried and dissolved in hydrochloric acid (10 mL). This solution was dispersed onto silica gel, and the column was washed with a mixture of toluene (500 mL), ethyl acetate (500 mL), and formic acid (20 mL). In this first rinse, the impurities were removed. Then, the column was washed with a mixture of ethyl acetate (500 mL) and formic acid (20 mL). This part of the eluent was evaporated *in vacuo*; a solid white product was isolated, washed with a solution of ammonium bicarbonate, and recrystallized from DMF. The yield of product **5a** was 0.5 g (50%), mp 328–330°C.

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